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In this second edition of this Atlas, firstly published in 2009, the introductory chapter has been partially rewritten to better understand the new scenario designed by technological and cultural changes appeared in the last few years.

**From the Monocular to the Binocular Vision, from Analogical to Digital Imaging: The Revolution of Hybrid Machines**

The twentieth-century diagnostic imaging scenario has been based for almost its entire duration on two separate universes: (1) the morphostructural, where information on anatomy and structures is acquired, having pathology as gold standard, and (2) the functional, where normal and altered functions are analyzed, with pathophysiology as reference individuating disease.

In the “old medicine” these universes are separately observed, as in a monocular vision having the capability to see only half of the whole view; therefore, using a single eye, an incomplete information is achievable. To overcome this handicap, the traditional diagnostic imaging may complement individual images, acquired at different times, through a visual comparison; but this approach is affected by many limitations, mainly due to a subjective analysis.

In the last decades the development of technology and computers determined a revolution that killed the analogical imaging, creating a new world only occupied by digital data. In this scenario, a major improvement has been obtained with the so-called fusion imaging, based on the overlap of digital scans acquired, at the beginning separately, by different techniques. As the main consequence, overlapping PET or SPECT scans on digital spatially coincident data, obtained with CT or MRI, it has been possible to produce new implemented images containing either the morphostructural or the functional content.

An even greater revolution has been determined when hybrid tools, containing in the same gantry a PET or a SPECT machine coupled with a CT scanner, have been produced and commercialized. More recently, a further technological improvement has been obtained with the construction of PET/MRI hybrid systems which have further increased quality and wideness of results achievable with hybrid machines.

Using these new tools an information containing the sum of advantages and the subtraction of disadvantages of the single procedures taken alone has become available, allowing a significantly higher diagnostic accuracy: furthermore, new capabilities, as the definition of “viable” tumor target in radiotherapy or a guided biopsy directed to the most malignant part of the neoplasm, have become feasible. Referring the readers to other texts for indications and information achievable by SPECT/CT and PET/MRI, we will discuss in this Atlas exclusively PET/CT with FDG.

In the last few years, PET stand-alone is almost completely disappeared. It has been demonstrated beyond any reasonable doubt the absolute superiority of hybrid machines with respect to PET scanners alone, widely justifying their higher cost. Today the achievement of functional PET images nonimplemented by CT contribution may be considered unethical and no more cost effective.

Using hybrid tools, a major improvement with respect to individual nuclear medicine’s machines has been reached in a higher precise anatomical accuracy of fused image (with an error averaging 1 mm with respect to 1 cm, typically present when using a software-based fusion approach); this upgrading is obtained because the two studies are (almost) simultaneously acquired, with the patient immobile on the same bed. Moreover, a measured attenuation correction, and therefore a more accurate quantitative analysis, may be calculated with the coupled CT. All these advantages are obtained with a faster duration of the diagnostic course, allowing an earlier diagnosis and lower costs of the whole clinical track.

It has to be pointed out that some minor technical problems continue to exist also using hybrid machines, mainly due to differences in acquisition’s time and spatial resolution between CT and nuclear medicine (NM) techniques; nevertheless, many solutions, as the respiratory gating, are already in the clinical practice and many implementations are arriving to further improve the whole system in optimizing the final result. Significant progresses have been obtained either in hardware and software, permitting a more rigorous correction of problems,
such as those determined by scatter and random radiations, field’s inhomogeneities, a too slow time of PET scanning, and so on. Actual PET machines are highly performing, showing a significantly higher sensitivity and spatial resolution with respect to the past. Concerning hardware components, an important evolution has been determined by the introduction of time-of-flight (TOF) systems, which allow improved performances and faster scans, with a better contrast, more evident in obese patients, because of a higher signal-to-noise ratio, furthermore more homogeneous in the whole field of view. A more recent improvement may be connected with the commercial diffusion of completely digitalized PET systems, allowing the achievement of previously unreachable performances.

In parallel with technological evolution of PET scanners, innovative solutions have also been introduced in the CT component, actually allowing not only better performances, but also a reduced radiation charge to the patients.

Finally, with respect to 2009, when the first edition of this Atlas was published, a further major change occurred at cultural level.

In the last few years the professional lecture of the fused image has changed because of the greater relevance associated with the evaluation of its morphostructural content. In other words, while previously CT was mainly utilized to localize pathological uptake seen by PET or to better understand the anatomical context, today it is a fundamental part of the diagnostic information, the morphostructural content being considered essential as the functional data in acquiring the final diagnosis. The CT’s contribution is further increased when contrast media are used to improve diagnostic accuracy.

As a consequence, the “professional” interpreter of fused image is no more a nuclear physician educated with only a basic knowledge of anatomy and pathology, but an expert lecturer of CT scans, having the capability to recognize pathological data also in the absence of an increased uptake at PET. The next step, already actively operating in many institutions, is connected with a further evolution in which nuclear physician and radiologist will act together in a single practitioner having the capability to extract the whole content of the fused image by alone. This new “diagnostic imager” must have the competence to see and understand either morphostructural or functional data. In this way we will reach a goal where the final result will be no more the sum of two images, but a new image with an implemented content, which may give the opportunity to significantly improve the accuracy in all the fields where diagnostic imaging is a fundamental part of the clinical course.

Therefore, with respect to the first edition, this widely renewed publication wants to improve and stimulate the readers not only in individuating all the incredible wealth of knowledge contained in a PET image, but also in significantly enriching their ability to understand and productively interpret CT images.

**PET/CT: The Radiologist Point of View**

The understanding by a nuclear physician of the CT’s role in the combined PET/CT system requires the knowledge of facts about CT technology and CT contrast media.

**The Choice of Slice Number**

The choice of slice number should really be considered a “nonproblem” matter in an oncologic field. Even an old and simple four-slice CT is able to perform a whole-body examination in an acceptable time allowing the study of every portion of the body with the appropriate timeframe. Increasing the number of slices reduces, of course, the examination time but the diagnostic improvement is especially evident in vascular studies and 64 or more slices are really mandatory only for cardiac exams. For this reason, 8- or 16-slice machines should be considered absolutely adequate for a PET/CT scanner if heart studies are not planned.

**CT Contrast Agents**

To perform a correct diagnostic CT examination, it is necessary to have a good knowledge of main issues concerning contrast agents. Essentially there are two different kinds of contrast: oral contrast and intravenous contrast.
Oral Contrast
If your CT experience is outperforming probably oral contrast is unnecessary; otherwise oral contrast allows to easily distinguish bowel loops from lymph nodes or other normal and abnormal abdominal structures. It is possible to choose between positive and neutral endo-luminal contrast agents.

(a) **Positive contrasts** are barium sulfate – 1.5 g/100 mL –1000 cc, meglumine diatrizoate –3%–1000 cc. Positive contrast agents allow better delineation of gastrointestinal tract organs from their surrounding structures, but exhibit potential PET attenuation artifacts.

(b) **Neutral oral contrasts** are water or low-density barium sulfate suspension; they are less evident than positive contrast agents, but exhibit some important advantages: better delineation of the gastrointestinal tract mucosa and intravenous contrast mucosal enhancement (normally obscured by positive oral contrast), without potential PET/CT attenuation artifacts. Which neutral contrast would be more useful? Water is cheap, but quickly absorbed and only good for stomach and proximal small bowel. Low-density barium sulfate suspension is more expensive, but allows better distension of small/ large bowel.

Intravenous (IV) Contrast Agents
Intravenous contrast agents allow better anatomic detail, delineate vascular structures, and improve overall CT contrast. Iodine is a temporal and spatial variable introduced in the vascular circulation, allowing better pathophysiological evaluation of the entire body. It permits to study tissue enhancement patterns with improved diagnostic accuracy and confidence, by supporting lesion detection and characterization, especially in tumors with only mild or absent increase in FDG’s uptake. Furthermore, a separate “diagnostic” contrast-enhanced CT (CECT) scan is not required, with a consequent reduced radiation dose to the patient. IV iodine contrast agents are different in concentration and iodine content; with multiple options being available, different protocols beforehand have to be chosen. Iodine’s content is variable from 200 to 400 mg/mL. Higher concentrations (350–400) are suitable for abdominal (especially liver) or vascular studies; lower concentrations (300) are used in lung parenchymal exams.

(a) **Protocols:** Specific organs and whole body protocols are partially dependent on the used scanner and a complete explanation of the matter is out of the aims of this chapter.

(b) **Iodine pharmacokinetic:** Iodine performs as macro- and microvascular enhancer during the first minutes after the IV injection, allowing an easy recognition of normal and abnormal vascularization patterns of organs and tissues. Minimal dimensions of iodine contrast agents determine also some other kinds of different behaviors. The agent is filtered by kidneys and excreted with urine in the excretory system few minutes after the injection; the agent is also extracted by hepatocytes and excreted with the bile up to many hours after the administration. A consistent portion of iodine contrast agent leaves the vessels throw the spaces between the endothelial cells, determining a late interstitial extravascular enhancement.

Contrast Enhancement of CT in PET/CT
(PET-CECT)
The CT part of the combined PET/CT imaging is often applied as a whole-body low-dose scan without application of IV contrast agent (PET-LDCT); this approach is primarily utilized for attenuation correction and for anatomic localization of tracer’s uptake in PET. However, in some clinical conditions the contrast enhancement of CT in PET/CT (PET-CECT) may be added to increase diagnostic accuracy and certainty.

The optimal PET-CECT scanning protocol is still a point of debate. If you plan to use intravenous contrast agents, the injection can be performed in a single-step procedure, during the acquisition of whole-body CT data used for attenuation correction, or in a two-step approach, after completion of the whole-body low-dose CT and PET data acquisition. The latter approach may be preferred, because a multiphase contrast-enhanced CT can be acquired in the region of interest, avoiding unnecessary radiation exposure if the standard PET/CT procedure,
performed with a low-dose CT (PET-LDCT), doesn’t show any pathologic or doubtful finding or if it identifies a systemic disease.

The benefit of PET-CECT compared to PET-LDCT is more pronounced in those diseases in which a surgical intervention or a radiation therapy, as single therapeutic approach, is the most commonly used treatment. It has already been shown that combined PET-CECT is the best available diagnostic modality for staging of patients with localized central bronchial tumors. PET imaging warrants a high sensitivity for detection of distant metastases and CECT allows the exact delineation of mediastinal and chest wall invasion by the primary tumor as well as the exact demarcation of involved juxtaposed lymph nodes and vessels. Comprehensive information regarding tumor delineation is a precondition for planning both a radiotherapeutic treatment and surgical treatments. This procedure manifests a clear benefit, including changes in management as well as in diagnostic confidence.

PET imaging’s results can be optimized if doubtful findings are judged on the basis of a CECT assessment. This is particularly true when an area of focal increased uptake cannot be attributed univocally to an anatomical structure only on the basis of low-dose CT (as it may happen in pancreatic malignancies or in benign duodenum inflammatory lesions); similarly, a significant improvement is achieved when a lesion shows only a mild or absent FDG’s uptake. In these cases, a CECT on the region of interest allows lesion’s detection and characterization.

A full-dose contrast-enhanced CT should also be performed if small lesions in the liver or spleen are suspected by US and no pathologic findings are identified by PET-LDCT. The lack of sensitivity in detection of such small lesions by PET-LDCT could be due to its lower contrast resolution compared to full-dose CECT.

As negative counterpart, a fully diagnostic PET-CECT examination results in an increased radiation dose compared to a standard PET-LDCT examination. Therefore, patient referral for PET-CECT studies should be justified in each case to avoid repeated exposures or overexposures. A PET-CECT scanning should be avoided in patients primarily under consideration for systemic therapy, in individuals with recently performed state-of-the-art whole-body CT and in subjects referred for therapy monitoring. When the use of an intravenous contrast is planned, a further disadvantage connected with CECT is determined by the need of the onsite presence of a physician, for monitoring and dealing with potential allergic reactions/extravasations. Before the injection it is mandatory to be aware of IV contrast contraindications, as poor renal function, myeloma, diabetes, and so on. In particular, it is obligatory to pre-assess the renal function.

Oral contrast is strongly suggested when a correct diagnostic examination in patients with pelvic or abdominal cancers or in patients with suspected peritoneal metastases is requested. Oral contrast allows to better delineate gastrointestinal organs from surrounding structures, improving diagnostic accuracy and confidence. When planning the use of oral contrast, the patient needs to arrive earlier with respect to the scan time’s schedule: contrast drinking starts 90 min before the study, 1 cup every 25 min, and it is important to monitor drinking timetable. To obtain an optimal contrast also in the stomach, a last cup of contrast solution is swallowed just before patient’s positioning on the table. Oral contrast media should be omitted when PET/CT imaging is used for radiotherapy planning, because of interference with densitometry in the field of radiation.

**F-18 Fluorodeoxyglucose (FDG)**

Although partially reduced in percentage with respect to few years ago, because of introduction and diffusion in the clinical practice of a growing number of other radiotracers labeled with positron emitters, F-18 fluorodeoxyglucose (FDG) still remains the most utilized radiopharmaceutical for PET. Today more than 90% of PET procedures worldwide are performed with FDG, mostly used for oncologic indications, although its clinical use is becoming more diffuse in evaluating other pathological conditions such as neuropsychiatric and cardiovascular diseases, inflammation, and infection.

This dominance 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 min) with respect to shorter lived C-11, N-13, and O-15, F-18 is the only one in this series that can be distributed without difficulty also to PET centers nonequipped with cyclotrons. Therefore, it can be used in a wider geographic area covering, in more developed countries, all the national territory. From the chemical point of view, fluorine is a halogen allowing a very stable binding nonaffecting 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.

**Physiology and Pathophysiology of Glucose and FDG’s Biodistribution**

Glucose is an essential biomolecule in living organisms, being the most important carbon supplier in energy-producing metabolic processes, depending largely on its availability. At cerebral level it is the only source of energy.

For a correct reading of PET-FDG images, based on the interpretation of all the involved molecular events, we have at first to analyze the normal glucose distribution, starting from the knowledge of its pathophysiological behavior.

Devoting a deeper analysis of FDG as “molecular tracer” of glucose transporters (many GLUT isoforms have been identified so far) to more extensive and/or specialized publications, it is important to remember that glucose uptake in human cells can take place through two main mechanisms: facilitated diffusion and active transport.

The first one is a carrier-mediated intracellular transfer, 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. Because FDG utilizes the same transporters of the native molecule, there is a strong interference on FDG’s 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’s distribution, it is crucial to define some major issues as a fasting time (at least 4–6 h), a serum glucose range and, in diabetes, the timing after insulin injection. Although chronic hyperglycemia is less disturbing with respect to the acute one, PET scans have to be 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, with the analysis of PET-FDG in patients being critical and more restrictive showing values >150 ng/dL. In some of the cases with higher glucose values, when possible, the studies have to be rescheduled trying to reach lower glucose levels before the FDG’s injection. Similarly, a warning has to be defined in the presence of hyperinsulinemia, reducing diagnostic accuracy because of a strong interference on Biodistribution.

Glucose’s active transport, occurring against an electrochemical gradient, is less diffuse functioning only in certain special epithelial cells specifically adapted for active absorption, as those present in gastrointestinal membranes or at the level of renal tubules. Only in exceptional cases the cellular glucose uptake may also be determined by a passive diffusion.

**FDG “Trapping”**

While glucose and FDG are transported in the large majority of cells through a similar mechanism, their intracellular metabolism is significantly different.

The biochemical fate of glucose starts with phosphorylation, occurring 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 quickly progresses in its metabolic route, after a dephosphorylation mediated by glucose-6-phosphatase, undergoing glycolysis (and/or storage of glycogen and/or conversion to lipids or proteins). Conversely, FDG-6-phosphate is no further metabolized in the glycolytic pathway, remaining “intracellularly trapped,” because of the lack of significant amounts of FDG-6-phosphatase to reverse its phosphorylation. This is the most significant difference between native glucose and FDG, which determine a major advantage for FDG imaging: while radiolabeled “native” glucose has a too fast metabolism to easily permit a PET study, the “trapped” FDG can reliably “in vivo” trace glucose concentration up to two and more hours. Nevertheless, although this is
not strictly correct from a metabolic point of view, because glucose transport and metabolism are strongly correlated, we can consider FDG as a glucose analogue reliably tracing glucose metabolism in humans.

FDG reflects glucose metabolism in all the organisms, 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 bladder. 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 at times more distant from the injection. It has to be pointed out that in individuals with normal renal function, 50% of the radioactivity reaches the bladder up to 2 h. In this sense the patient has to be invited to urinate before the scan to reduce the pelvic background and dosimetry, because of the consequent lower effective half-life. Conversely, to define a major contraindication, it has to be remembered that FDG crosses the placenta, being distributed mainly in fetal brain and excreted by fetal kidneys. With a high percentage of the total dose of a PET-FDG study derived by CT, in the exceptional cases in which a PET study may be however considered cost effective in a pregnant woman, the choice of a PET/MRI, when available, and a lower FDG's dosage have to be absolutely preferred.

Breastfeeding is contraindicated up to 10 h after IV injection of FDG.

Physiological and Para-Physiological Distribution 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 premise to the normal whole-body FDG's pattern.

The patient is IV injected, fasting from at least 4–6 h, in the presence of a good hydration. During the injection and the following uptake's phase preceding the scan (about 40 min after the administration), the individual has to be at rest, in a quiet room, comfortable and relaxed. In particular, he/she has to try to avoid actions as chewing, eating, running, and any other exercise and/or sensorial activation affecting FDG distribution, mainly increasing muscular or regional cerebral uptake. Being impossible to avoid swallowing, mainly for patients undergoing a PET scan for head and neck tumors, the effect on the FDG's uptake in the vocal cords has to be remembered when talking. Then the patient is invited to urinate and the scan starts generally 45–60 min after the IV injection.

In a standard condition the highest FDG's activity is seen at cerebral level (mainly in gray matter), with the brain being the only organ using exclusively glucose as 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 and to the intraluminal 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, myelo-hyoid muscles, and, only in young patients, thymus, adenoidal tissue, and testicles. No uptake is normally seen at the level of lungs, with a slight activity being sometimes present in posterior and inferior segments. The skeletal muscle's uptake, being low at rest, increases as specific response to stress and/or exercise in the involved muscular cells. An increased uptake can be determined by many conditions as hyperventilation, hiccupping, 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 background at renal and vesical level, can create difficulties in evaluating FDG's pathological uptake mainly in kidneys, bladder, and prostate. Small localized areas of ureteric stasis may
simulate lymph adenopathy. The presence of anomalous locations of kidneys and ureters has to be known, to avoid mistakes in PET image interpretation. Thyroid uptake can be occasionally observed in clinically normal patients, being more frequently caused by thyroiditis or hyperthyroidism, also not clinically evident. In premenopausal women (and/or in women taking estrogens) breast tissue may often demonstrate moderate symmetrical FDG's concentration. Intense uptake is showed 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 lower body mass index. Increasing this uptake when the patient is injected and/or is stationed in a cold room, it is important to guarantee the injection and the stationing in a warm environment.

With the lesion's detectability in nuclear medicine being dependent on lesion/background ratio, it is evident that major difficulties in PET-FDG's analysis 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 when analyzed with the help of morphostructural information obtained by CT. To reduce errors, some authors also suggest the administration of muscle relaxants, cleansing bowel preparations, and placement of a Foley's catheter. However, because of difficulties in standardizing these procedures and because of the impossibility to reliably avoid possible pitfalls, a strategy of “keep it simple” is more frequently adopted, but in individual particular situations.

**Pathophysiology of FDG Uptake in Cancer (and Benign Diseases)**

Generally, cancer cells present an increased metabolism, requiring a higher amount of glucose (and therefore of FDG) with respect to normal cells. In particular, malignancy is frequently associated with the appearance of 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, as a fuel necessary to answer to new requests of energy, produced mainly through anaerobic glycolysis. FDG's uptake and its Biodistribution in tumors are influenced by many parameters such as increased glucose turnover, expression of glucose transporters, and hexokinase activity, being also dependent (through nonspecific mechanisms, independent of neoplastic transformation) on the increased number of cell divisions, a relative hypoxia, and a functional activation. Therefore, although cancer cells may concentrate more FDG with respect to activated normal cells growing at the same rate, an increased FDG's uptake is nonpathognomonic of cancer, being possible also in some benign conditions. Conversely, a low or null increase of FDG's uptake may be observed in well-differentiated or slow-growing tumors, in which pathophysiological conditions described above are absent.

Devoting a deeper analysis of molecular mechanisms to wider and/or specialized publications, we define here some general behaviors and consequent suggestions helpful in the analysis of PET-FDG images in oncology and other benign diseases to be taken into account for differential diagnosis.

**FDG Uptake in Tumors**

For the reasons described in the previous paragraph, the large majority of malignant tumors show an increased FDG's uptake. As it has been anticipated, this pathological concentration is influenced by the “biological malignancy,” i.e., by issues as growing rate, hypoxia, histopathology concerning both histotype and grading, and presence and extension of neo-angiogenesis. Intense uptake is more frequently observed in lymphoma, melanoma, colorectal, esophageal and head/neck cancer, non-small cell lung cancer (NSCLC), bone tumors, cervical cancer and seminoma, gastric and pancreatic cancer, sarcoma, and, more generally, high-grade tumors. Many American and European reports describe PET-FDG-appropriate indications for each neoplastic disease, in the different clinical scenario.

Nevertheless, a minority of tumors can present low or absent FDG's uptake. This pattern is mainly
dependent on a preserved differentiation and/or on slow-growing neoplasm, as evident 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 lower FDG uptake, in tumors characterized by a low growing rate, as prostate cancer, in tumors characterized by functional features as the mucinous production, or by a particular tumor morphology, as it can be observed in primary ovarian cancer, frequently consisting of large cystic portions.

**FDG’s Uptake in Benign Diseases (and Other Pitfalls)**

FDG is not a tumor-specific tracer, although the probability of malignancy grows in the presence of a “hot spot,” with the percentage of benign lesions being high which doesn’t concentrate glucose. Nevertheless, a minority of nonneoplastic lesions may be positive at PET-FDG. Although the degree of inflammatory uptake is usually less than the one within neoplastic tissues, there is clearly an overlap between the two conditions and, in some cases, the uptake could even exceed the neoplastic concentration.

FDG accumulates in normal and benign reactive cells, as white cells and macrophages, when functionally stimulated or activated. As example, the FDG’s uptake grows in cerebral cells after specific stimulation, as it happens at the level of calcarine cortex when opening the eyes, or in the muscles under physical stress. With respect to pathological conditions, FDG concentrates at the level of active inflammatory processes either infectious or noninfectious. This uptake may be present either in acute condition or in chronic diseases, where the hyperconcentration is also dependent on the increased quota of anaerobic glycolysis.

False-positive results can create problems more in diagnosis (and in staging of patients with cancer), than in restaging, for the comparison with the previous scan and an already known diagnosis. The implemented support given by CT significantly increases diagnostic accuracy.

For the reasons reported above, it is necessary to be very careful when utilizing PET-FDG for a primary diagnosis, mainly in patients with a high prevalence of inflammatory or granulomatous conditions, such as tuberculosis or sarcoidosis. Furthermore, FDG’s uptake can be present at the level of wound healing (in general up to 6 months) and in many benign conditions such as inflammatory reaction after radiotherapy, associated benign lymph adenopathies or infections, lung atelectasis and pleural effusion, and reactive thymus hyperplasia (sometimes appearing in young patients after chemotherapy). Dubious images can also be due to torticollis and other muscle contractions, laryngeal nerve palsy, gastritis, colitis, adenomatous colon’s polyps, gastroesophageal reflux, diverticulitis, inflammatory bowel disease, abscess, hiatal hernia, bladder diverticulum, benign uterine fibroids, atherosclerotic plaque, and autoimmune diseases such as Graves’ disease. Possible mistakes in diagnosing bone metastases may be determined by an uptake in benign healing fractures or arthropathy, with a FDG’s concentration being also possible associated with an occult bone infarction or a skeletal fibrous dysplasia. A diffuse increase at the level of bone marrow (and/or spleen) can be observed after the administration of granulocyte colony-stimulating factor. Pitfalls may also be due to physiological or para-physiological conditions as brown adipose tissue and even ovulation and normal menstrual cycle. Radioactivity in bowel loops, urinary system, blood vessels, pelvic kidney, and a slight uptake in bone marrow can similarly lead to false-positive interpretations.

However, many of these causes of misinterpretation described above can be easily recognized. Proper patient preparation and scanning protocol are needed for accurate PET/CT imaging. Four to six hours fasten time prior to PET scanning is necessary and oral hydration is recommended. Muscle stress, tension, and movement during the FDG’s concentration phase after the IV administration should be minimized to decrease muscle uptake. It is also important to reduce FDG accumulation within the urinary bladder, mainly if pelvic malignancies are studied. Patients should void completely immediately prior to the start of scanning and the pelvis has to be imaged as early as possible in the
study. Metallic objects (keys and wallets, etc.) should be removed and patient movements during the PET scanning should be avoided.

Some potential causes of false-positive results like bowel or tonsil uptake or activity in blood vessels can be easily interpreted only by recognizing the normal FDG uptake distribution: in these cases, the experience of the PET reader is clearly crucial. Many of the pitfalls that have plagued FDG-PET imaging, like correct identification of brown fat and interpretation of focal bone uptake due to nonmalignant processes or of areas of FDG uptake in the bowel, can be avoided carefully analyzing associated CT images, significantly improving diagnostic accuracy and confidence. Finally, a clinical history correctly collected before PET scanning may help to avoid many causes of false-positive results like recent fractures, phase of ovulation or menstrual cycle, recent surgery or radiation therapy, presence of benign thyroid or lung diseases, or many other nonneoplastic pathologic conditions (for example acute or chronic infection), already known or highly suspicious. The interpretation of PET scans is improved when relevant studies, with a major emphasis for other diagnostic radiologic investigations, together with clinical and hematochemical data are considered and carefully reviewed.

**PET/CT in Oncology**

Referring to the following chapters, concerning different organs and apparatus, a wider analysis of indications of PET-FDG in specific territories, we want here to synthesize some of the most important general issues.

**Pre-therapeutic Evaluation: Diagnosis and Staging**

As general information, the role of PET-FDG is typically justified in restaging of tumors, less frequently in staging, and only rarely in differential diagnosis.

At present the diagnostic use of PET may be suggested for the characterization of solitary pulmonary nodules (SPN), for the identification of cancer of unknown primary (CUP) and of the cause of fever of unknown origin (FUO).

With respect to the first indication, its role is dependent on the capability to increase a diagnostic accuracy in patients who previously underwent CT; this improvement is only present when excluding categories with a high a priori probability of benign diseases determining false-positive results, as sarcoidosis and tuberculosis. It is important to remember that PET-FDG may increase or decrease the probability of neoplasm, but that it is not sufficient to define alone a final diagnosis, however requiring a pathological analysis.

Whole-body PET/CT with FDG has been successfully used for identifying CUP of the most common histology, namely adenocarcinomas, squamous cell carcinoma, and poorly differentiated carcinoma, and/or in individuating an oncologic cause, frequently due to lymphomas, in patients affected with a FUO.

Despite its limited role in diagnosis, a “pre-therapeutic” use of PET-FDG may be suggested, in the presence of a high probability of cancer, for many motivations as follows: (1) a more accurate staging with respect to a traditional approach; (2) when the use of PET-FDG is provided in follow-up, with the aim to detect metastases and/or to diagnose local recurrence, because it is important to demonstrate a basal positive scan to justify the use of PET in follow-up; (3) for a prognostic evaluation, helping in better defining therapeutic strategies; (4) as basal examination to evaluate tumor response; (5) to guide a biopsy; and (6) to design a biological target in radiotherapy.

The indication to the use of PET imaging for staging is definitely supported by literature for few tumors, in particular NSCLC and in selected cases of head and neck and esophageal cancer, as well as in some cases of melanoma and lymphoma. Nevertheless, a pre-therapeutic inclusion of PET-FDG in the toolbox may be justified in many patients, for the reasons described above. Being however the inclusion of PET-FDG in a pre-therapeutic course a clinical responsibility of the oncologist and of the diagnostic imager who have to make a cost-effective evaluation in comparison with alternative procedures, PET-FDG cannot be justified in patients with suspicion of tumors highly differentiated (as thyroid carcinomas or NET), in women with an early primary breast cancer, being more effective the traditional approach and the sen-
tinel node (SLN) procedure for staging, in subjects with a melanoma, where it is also suggested the SLN technique for staging.

**FDG Uptake as Guide to Biopsy and/or to Define the Target in Radiotherapy**

In structurally inhomogeneous tumors FDG's uptake is higher in the most malignant part of the lesion, being lower in differentiated components and absent in necrotic or fibrotic areas. Therefore, PET-FDG can guide a biopsy to the most malignant part of the tumor, when associated to CT, which gives spatial coordinates to correctly reach the tissue that has to be biopsied.

For the same reason, PET-FDG allows a better definition of “biological target” in radiotherapy. This is a very important achievement in oncologic therapy, because, thanks to PET-FDG, it has been possible to significantly reduce the target’s extension, excluding areas without neoplastic tissue. Today, mainly in the presence of the so-called tomotherapeutic systems, strictly connecting PET/CT with radiotherapeutic tools (also including a shared respiratory gating system), PET/CT with FDG image can guide to design a tailored therapeutic plan, giving a higher dosage to the most malignant part of the tumor, saving as much as possible normal tissues. Another major contribution of PET-FDG in defining biological target is given by the increased diagnostic accuracy achievable with respect to CT alone. As example, in a patient with lung cancer, a mediastinal target may be avoided although there is the presence of enlarged lymph nodes, as detected by CT, which suggests a neoplastic involvement requiring the inclusion of this field in treatment’s plan. Using FDG, the radiotherapeutic target may be restricted excluding mediastinum, if the enlarged lymph nodes don’t show glucose’s concentration. In fact, in this case, the probability of absent neoplastic disease is very high, strongly justifying the design of a more favorable treatment plan. Finally, with the therapeutic response to radiotherapy being faster with respect to the morphostructural one, evaluable by CT, PET/CT with FDG could help to sequentially redesign biological target on the basis of the reduced area of FDG’s uptake observed at controls.

**FDG Uptake as Prognostic Indicator**

As general evidence, when a FDG’s uptake at the level of a lesion is not observed we can reliably make a diagnosis in agreement with a benign disease, being also possible in the presence of a malignant tumor with a favorable prognosis. In other words, as described above, a slight or absent uptake may be observed in a little group of malignancies, when characterized by issues as high differentiation’s grade or slow growing rate, as it happens in the majority of thyroid cancers or in NET. In this group of neoplasm PET-FDG may play a prognostic role when a dedifferentiation is suspected, as it may happen in restaging. It means that we don’t have to propose PET-FDG in the evaluation of a patient undergoing surgery for a differentiated thyroid cancer. Conversely, a justified indication for PET-FDG is present in the same patient when, in follow-up, an increased plasmatic value of thyroglobulin is accompanied by a negative result at a whole-body scan with radioiodine.

A relevant prognostic information may also be found in comparing neoplastic patients bearing the same histotype. In this homogeneous category, a higher uptake individuates a worst fate, therefore supporting the choice of more aggressive therapeutic strategies. In fact, as previously described, FDG’s uptake in cancer tissue is determined, among other factors, by tumor proliferation rates, aggressiveness, and rate of neo-angiogenesis. This relationship is however nonlinear, mainly in rapidly growing tumors, being dependent on many parameters, including a various percentage of anaerobic metabolism and presence of necrosis.

**Post-therapeutic Evaluation: Restaging**

Routine oncologic follow-up includes clinical evaluation, laboratory tests, morphological imaging, and tumor markers. In most cases, cancer relapse is suggested by an increase in serum tumor markers, while traditional imaging modalities may remain negative for a long time. In the presence of increased markers and negative or inconclusive conventional imaging, FDG-PET is frequently able to find a locoregional relapse and/or distant metastases, thus
changing the clinical management in a large number of patients.

The usefulness of FDG-PET in restaging has been reported in a wide number of tumors, including breast, ovarian, testicle, non-small cell lung cancer, melanoma, head and neck, pancreas, esophagus, stomach, and others. In all these tumors, in case of inconclusive findings or of discordance between conventional imaging techniques and hematocinical data, FDG-PET has to be proposed for identifying early recurrent cancer. For a fewer number of malignancies, as lymphoma and colorectal cancer, FDG-PET has been suggested as a systematic tool in follow-up.

PET-FDG is effective in restaging of patients with all the cancers showing a high FDG's uptake at pre-therapeutic scan. Although a higher sensitivity is generally observed in detecting distant metastases with respect to alternative procedures, the diagnosis of recurrence may be more difficult. Mainly at an early evaluation, a differentiation from post-therapeutic outcomes is not ever easy determining pathological and functional changes similar to those connected with the persistence of a little amount of residual tumor or with an early appearance of relapse. PET-FDG should be used in the search of a local recurrence only in patients showing a FDG's uptake before therapy. In this sense, although it is not mandatory, a pre-therapeutic PET-FDG scan should be suggested, at least in patients having a high probability of using PET-FDG in follow-up, as in lymphoma. Recurrent disease, because of the tendency to lose differentiated features, is in general characterized by a higher FDG's uptake with respect to the primary tumor. Therefore, because of its greater malignancy, a recurrent tumor should be individuated also when of little size; nevertheless, its evidence may be conditioned by unfavorable conditions, such as an increased background also determined by physiologic and para-physiologic conditions associated with increased permeability, wound-healing process, and benign inflammatory reaction.

Even more than in pre-therapeutic phase, the reliability of a diagnosis of recurrence has to be reinforced by the complementary contribution given by CT. The diagnostic accuracy grows with the time, becoming more reliable starting 6 months after surgery or other therapeutic major interventions.

When needed, i.e., in the presence of a high probability of relapse, PET-FDG could be performed also before 6 months, mainly because of a high negative predictive value. In fact, there is no FDG's uptake in the absence of viable cancer cells, i.e., in necrosis and/or fibrosis. In cancer patients, showing a FDG's uptake at pre-therapeutic control, a negative PET scan in follow-up can reliably exclude relapse. On the contrary, as it has been several times repeated, the opposite is not ever true: in restaging FDG's uptake is not necessarily determined by recurrence, because of possible false-positive results, decreasing when carefully evaluating complementary CT data.

Response to Therapy

Chemotherapy is currently the treatment of choice in many patients affected with oncologic diseases such as lymphomas or various metastatic solid tumors, including breast, colorectal, ovarian, lung cancer, and others; chemotherapy is frequently in combination with surgery and/or radiotherapy, being also used alone in several cases, mainly when they are with a more advanced stage.

Traditionally, structural changes in tumor volume are used to assess therapeutic action as a surrogate endpoint for other measures of clinical benefit, such as disease-free period and overall survival. Moreover, in routine practice, clinicians are keen to use volume changes, as evidenced by CT, MRI, and US, to modify therapeutic approach. Since tissue metabolism changes occur before morphological modifications, variations in FDG's uptake are evermore frequently used to evaluate tumor response to therapy.

A typical example is in malignant lymphomas, where anatomical imaging after completion of therapy often reveals residual masses that could represent either persistent disease or fibrotic tissue. Identification of residual disease after radio- or chemotherapy is clearly influencing further treatment options. Positive FDG-PET findings after therapy completion in patients affected by lymphoma are a strong predictor of relapse, while a negative PET study has been demonstrated to be an excellent predictor of a favorable prognosis. Several studies have already demonstrated the utility of FDG-PET for
response’s evaluation during the treatment. Early identification of chemotherapy-resistant lymphoma patients provides a basis for alternative treatment strategies. Multi-trial experiences and strict interaction between some of the most authoritative international experts in onco-hematology allowed the proposal and the clinical utilization of shared protocols, defined by consensus, using interim PET as an effective marker to be performed after a defined number of courses.

Unfortunately, either because of a wider histotype variation and number of therapeutic strategies, or probably for difficulties in reaching an international consensus, a shared strategy has not yet been found in defining standardized protocols for interim PET in evaluating early tumor response in solid tumors. Nevertheless, being evident that response assessment by changes in tumor size (using conventional imaging) requires a longer period and is frequently less accurate than changes in metabolism, as demonstrated by PET, FDG has been proposed and is evermore widely used for an early individualization of nonresponders.

PET can predict the tumor response after few cycles of chemotherapy in several solid tumors. Helpful results have been achieved in metastatic breast cancer, making PET-FDG also a valid tool for prognostic stratification, in patients with stage III and IV NSCLC, usually treated with chemotherapy or chemoradiotherapy, in the management of locally advanced rectal cancer, undergoing chemoradiotherapy before surgery.

The importance of FDG-PET in assessing neo-adjuvant chemoradiotherapy response, due to its intrinsic capacity to precociously identify changes in tumor behavior, has been underlined in many papers. FDG-PET has been reported to be superior to CT and MRI in early predicting pathologic response to preoperative treatment. Useful results, although sometimes more difficult to be interpreted, because of a possible early reactive benign increase in FDG’s uptake, may also be obtained in evaluating tumor response in patients undergoing radiotherapy.

The usefulness of PET in this setting is likely to be further increased by the diffusion of targeted therapy. As example, one of the principal mechanisms of communication between cells is the binding of polypeptide ligands to cell surface receptors possessing tyrosine kinase (TK) activity. Though many actions of these receptors involve physiological processes, perturbation of TK signaling can result in malignant transformation. During the last few decades, these signaling networks have been studied in detail and finally agents targeted at key molecules have been produced. These pharmacological tools have rapidly become part of standard care for common tumors like breast, colorectal, ovarian, lung, and head and neck cancers. Actually many multi-target agents have been introduced and yielded promising results; newer and probably even more effective agents for a tailored therapy are being developed. Until now, no predictor of response to target therapy has been fully validated; yet the selection of patients who are likely to benefit from TK inhibitors is mandatory not only for clinical but also for economic reasons: being very expensive, this therapy has to be reserved only to patients in which an early evaluation of effective tumor response may be demonstrated. In this sense molecular imaging with PET could be proposed as a tool to recruit these individuals.

Although many positive results have already been achieved, some issues, as those concerning an early prediction of a “complete response,” have to be further studied. This problem seems more difficult to be solved in patients affected with solid tumors; the difficulty increases in case of polyclonal and/or dedifferentiated neoplasm, showing different targets and therefore a heterogeneous tumor response. In this sense, the definition of multicenter trials shared by leading groups is important in individuating specific strategies in which PET/CT could give reliable answers in evaluating tumor response. In parallel with studies analyzing patients undergoing chemotherapy, a further evaluation is also needed to define protocols useful in evaluating tumor response to radiotherapy and/or to newer target therapies.

**Usefulness of FDG in Benign Diseases**

We will not discuss in this publication the clinical usefulness of PET/CT with FDG in cardiology, with this issue being out of the aims of this Atlas. Similarly, we will not analyze in this chapter metabolic and pathophysiological issues concerning the brain, with the clinical role of PET-FDG in
neuropsychiatry being described in the following pages of this book.

Conversely we will briefly analyze the possible usefulness of PET-FDG in evaluating benign diseases, where many indications may be individuated.

At first, PET-FDG is a first-line procedure in diagnosis of fever of unknown origin (FUO), because of the need in these patients of the highest sensitivity to detect occult lesions, not negatively counterbalanced by a reduced specificity. It has to be remembered that occult lesions determining fever may be individuated either as neoplasm, including frequently lymphoma or head and neck cancers, or as inflammatory diseases, often in an active chronic phase.

Other useful information may be provided by PET-FDG in defining the activity in many inflammatory diseases, as Crohn’s disease or sarcoidosis, to detect activated atherosclerotic plaques in great vessels, to determine the presence of an inflammatory reaction in the area surrounding prosthetic devices, in autoimmune diseases, and so on.

**Differential Diagnosis with PET-FDG in Oncology**

Although a FDG’s uptake is “probably” connected with the presence of neoplastic cells, this event is non-pathognomonic of malignancy, because of the possible presence of false-positive results. Similarly, the absence of uptake cannot exclude the presence of neoplasm, because of the possibility of false negatives due to many parameters as histologic type (low or absent uptake in differentiated neoplasm), size (under 0.5 mm or even more in some territories), and location (difficult detection for cerebral metastases).

Therefore, a differential diagnosis cannot be based exclusively on PET-FDG, requiring an implementation at first based on clinical and hematocellular data and on the relevant complementary contribution given by CT, mainly when implemented with the use of contrast media.

Nevertheless, in many cases a certain diagnosis is difficult to be obtained and therefore many procedures trying to increase the diagnostic accuracy have been developed and proposed in clinical routine.

**Dual-Time Imaging**

For PET-FDG, two main approaches have been developed, based on the rationale that malignant lesions have a higher uptake with respect to the benign ones and on different kinetics. With respect to the latter approach, dual-time procedures have been suggested on the basis of the observation that in the first few hours after iv injection, while FDG's uptake tends to grow or remain stationary in cancer, at the opposite it decreases in benign lesions. This differential diagnostic strategy didn't find at the moment a wide diffusion, either because of the lack of a full and wide evidence in all the kind of pathological lesions and because of the high cost (not yet justified on the basis of clinical data acquired up to now) of a second scan, which clearly may significantly reduce the number of patients that can be daily studied with a PET scanner.

**Role of Quantification**

More applicable is the use of a quantitative approach. Although it has been demonstrated that neoplastic cells may concentrate more glucose with respect to normal cells growing at the same rate, this information cannot be reliably acquired only using FDG in routine studies, requiring the simultaneous correction of measured uptake for the number of cells and for their growing rate (as it could be evaluated, for example, with F-18 thymidine). Furthermore, a rigorous comparison should be based on absolute quantitative methods, but at the present there are not yet noninvasive, easy, and repeatable procedures applicable in the clinical practice.

Therefore, waiting for more rigorous techniques, to increase information acquired through visual analysis semiquantitative methods have been developed and proposed in the clinical practice. The presentation and critical evaluation of the most important procedures are out of the goal of our publication. Although more precise and rigorous quantitative procedures have been proposed, the only one today consolidated in the clinical routine is still the so-called SUV, for which we will spend few words.
Standardized Uptake Value (SUV)

SUV is a semiquantitative 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 issues, as serum glucose level, body weight, and compartmental glucose distribution. Furthermore, it is strongly affected by many factors as the machine, detector, used procedure, and including possible improvement achievable, as example, by respiratory gating. Furthermore, it is not possible to compare a SUV measured with a TOF scanner with respect to the one calculated with a standard machine or a PET/MRI, being in general nonidentical values calculated in the same patient when studied in different Institutions.

For these reasons SUV cannot be considered an absolutely reliable information and a warning has to be declared in using this value in the clinical report, for the possible confusion determined in the practitioner when reading values obtained in various centers. Nevertheless, when critically analyzed by nuclear physicians in a homogeneous context (as example, using the same machine) SUV can show a useful clinical role, complementary with visual analysis, increasing (or decreasing) a diagnostic probability of malignancy, better defining a prognostic value in a single histotype population, and more precisely determining temporal variations in follow-up of the same patient or in the evaluation of a tumor response.

Therefore, SUV is widely used for acquiring information described above. Furthermore, SUV has also been proposed to increase a diagnostic accuracy in differential diagnosis of primary tumors, such as pulmonary solitary nodules through the definition of an uptake's threshold: for lesions greater than 1 cm, cancer is more probable in the presence of a SUV higher than 2.5.

At present the usefulness of SUV may also be suggested in all the cases in which a semiquantitative evaluation may be important for a prognostic evaluation and/or when PET-FDG is provided to be used in the evaluation of a therapeutic response.

In all the cases, SUV (and/or other semiquantitative methods) has to be evaluated very carefully, and its role has to be considered more useful in evaluating a tumor response and/or a prognostic evolution than in differential diagnosis of a primary cancer.

It has to clearly be pointed out that a higher diagnostic accuracy in differential diagnosis may be more reliably reached when PET interpretation is complemented by the important contribution of CT, mainly when performed as CECT.