PET-CT Beyond FDG
A Quick Guide to Image Interpretation
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Luigi Mansi dedicates his contribution to Nagia, his wife, and to his son David, to further stimulate the realization of his dream: become one of us, a molecular imager searching for the keys opening the mind and the eyes to the knowledge.
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Chapter 1  Importance of Radiotracers Other than FDG in Oncology

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Diagnostic imaging is based on two different approaches acting as two separate “monocular visions”: (a) morpho-structural imaging, analyzing anatomy (structure and morphology) and using pathology as the golden standard; (b) functional imaging, analyzing physiology (function) and using pathophysiology as a reference to define the disease.

Traditionally, when multiple diagnostic contributions are available, the final diagnosis is achieved through a visual comparison of the different studies. The computer revolution, permitting work on digital matrixes, has created the option to “fuse” images together. In this way, it is possible to overlap two different images, separately acquired, in a new “fused” image, including both morphostructural and functional information, for a patient.

A major improvement in fusion imaging is the advent of the so-called “hybrid machines”, i.e., of scanners having the capacity to produce two studies simultaneously. Today, while Positron Emission Tomography-Magnetic Resonance (PET-MR) is still in the prototype phase, the Single Photon Emission Tomography – Computed Tomography (SPET-CT) is already in clinical practice. But among hybrid machines, the leading position is certainly occupied by PET-CT, by now a primary tool in the whole diagnostic scenario.

It has to be pointed out that when a PET-CT is used, while the CT information remains the same, the PET component can give various diagnostic contributions, depending on the radiotracer used.

At present, more than 95% of PET studies worldwide are performed in oncologic patients, using F-18 Fluorodeoxyglucose (FDG). But, despite its high diagnostic accuracy in determining the pivotal role in the restaging (and staging) of the neoplasm, FDG is handicapped by false negative and positive results, creating limitations in the differential diagnosis of cancer. Moreover, PET-FDG shares with all the other diagnostic techniques the inability to answer all the questions of the oncologist, the surgeon, and the radiotherapist. It cannot function alone, either in the diagnostic field, or in giving all the information connected with prognosis and pursue a “tailored strategy” for each patient. Therefore, despite its primary role, there is a wide range of indications in oncologic patients that other radiotracers may be useful, and in this chapter we shall try to understand them.

How to Improve Diagnostic Accuracy with PET–FDG

False Negative and False Positive Results of PET-FDG

In oncology, the results concerning neoplastic lesions not detected by the procedure are called false negative results of FDG. Conversely, false positive results are those connected with benign lesions, showing FDG uptake.

It has to be pointed out that false negative and false positive results can also be the consequence of pitfalls and artifacts. For a deeper understanding of these problems we suggest a reading of the Atlas of PET-CT: A Quick Guide to Image Interpretation (Springer, 2009).

A hybrid PET-CT scanner permits higher accuracy with respect to PET alone, because of the added morphostructural information and the anatomical location of the FDG activity allowed by CT. This advantage is particularly significant in evaluating areas with a complex anatomy, e.g. the head and neck, or partially “covered” by the emunctory system, e.g. along the ureteral course; a major diagnostic improvement is obtained in the case of small lesions, such as the evaluation of a lymph node neoplastic involvement. Despite using PET-CT, false negative and false positive results are, however, present. An improvement in sensitivity and specificity with the use of PET radiotracers other than FDG, can therefore significantly increase overall diagnostic accuracy.

With respect to methodology, many causes can affect glucose kinetics, creating difficulties in FDG utilization. The major problem is high glucose serum levels, as observed, in particular, in diabetes; but many other conditions can determine an unfavorable physiological and/or para – physiological distribution, creating pitfalls and artifacts decreasing PET-FDG accuracy. For example, it is well known that determining a nonspecific FDG uptake requires correct timing for a reliable evaluation of patients who have undergone surgery, radiotherapy, or chemotherapy. Therefore, the availability of radiotracers not affected by conditions such as high glucose levels, inflammation, altered permeability or vascularity, can help in finding a rationale to choose an alternative to FDG. Thus, a more effective clinical value can be reached, for example, in diabetic patients, or when the clinical history of
the patient suggests that the analysis obtained by using FDG is not reliable.

**How to Increase Sensitivity with Respect to FDG**

False negative results of PET-FDG are mainly due to lesions that are too small to be PET’s spatial resolution, which is usually above 5 mm. It has to be pointed out that the positive indicators as FDG, i.e., radiotracers with a higher uptake in lesions than in the surrounding normal tissue, can also occasionally detect lesions that are less than the spatial resolution value. As the image is the result of differences in concentration, the detectability of the lesion depends mainly on the lesion/background (L/B) ratio. To use a simile, it is easier to see an ant on white marble on a sunny day than a black cat on a dark night.

As a result, as demonstrated by bone scans, it is possible to detect lesions “many months before” they attain the theoretically minimum detectable size. This favorable condition, creating a premise for an early diagnosis, happens when a high L/B ratio is achieved. It depends more on the uptake mechanism of the radiotracer than on the PET scanner. With respect to FDG, a higher L/B can be achieved by different radiotracers allowing a higher tumor uptake and/or a lower background activity.

**Radiotracers Allowing a Higher Tumors Uptake with Respect to FDG**

Independent of the size, not all tumors present a higher FDG uptake with respect to normal tissues. Therefore, false negative results can be observed even in patients with tumors of 1 cm or more, characterized by a normal or reduced glucose metabolism. It can happen under many conditions, in differentiated types of tumors, in the presence of slow tumor growth, and in cystic and/or mucinous lesions. For example, many false negative results are observed in patients with prostate cancer or well-differentiated neuroendocrine tumors. In the following chapters of this Atlas, the ability of radiotracers such as choline, somatostatin analogues, acetate, DOPA and tryptophan to significantly improve sensitivity in these patients is demonstrated. However, it is interesting to note that, despite the low sensitivity in patients with well-differentiated tumors, FDG plays an important prognostic role in the follow up of these subjects. For example, in the follow up of patients affected with neuroendocrine tumors and thyroid carcinomas, the presence of FDG uptake, which is an expression of de-differentiation, is a negative prognostic factor.

Another possibility of increasing overall sensitivity with respect to FDG is the use of radiotracers allowing a higher L/B ratio on the basis of a more favorable uptake mechanism. An example (see Chap. 5) is the detection of bone metastases, where a mismatch can be observed between FDG, concentrating on the pathological skeletal content, and F-18 fluoride, becoming part of the mineral bone matrix. As a consequence, radio-fluoride can detect a higher number of skeletal metastases in patients affected by tumors, metastasizing through a neoplastic involvement determining early osteoblastic response (as it frequently happens in prostate, breast and lung cancer). Conversely, FDG can detect a higher number of malignant lesions in patients with myeloma because of the late involvement of a periosteal reaction in the subjects. Therefore, radio-fluoride can find a clinical indication during follow up (and/or staging) of patients with cancer with a high prevalence of bone metastases, when there is an early osteoblastic reaction. Moreover, in some cases, the complementary information provided by fluoride about FDG can be utilized to better evaluate the skeletal involvement to adjacent malignant lesions.

**Radiotracers Allowing a Lower Background with Respect to FDG**

Analysis of the normal FDG distribution in humans shows that the highest uptake is at the level of the brain, the only organ to use glucose exclusively as carburant. Therefore, although PET-FDG is born evaluate brain diseases, the high activity in the normal gray matter creates difficulties in tumor detection. Therefore, although an important role in dementia and in prognostic evaluation of primary cancer, PET-FDG cannot be considered a reliable procedure in detecting brain metastases. Moreover, despite the added value of CT (or MRI) in precisely localizing FDG uptake and anatomical structures, diagnosis of recurrence can be difficult both because of the possible presence of faint nonspecific uptakes and the confusion caused by normal tissue, due to the partial volume effect. To avoid these limitations, the use of radiotracers with a minimal uptake in the normal brain has been proposed. The best results achievable for a clinical use are provided
by radio-amino-acids such as methyonine (see Chap. 4) and thyrosine (Chap. 6). An alternative to better evaluate brain tumors may be the use of radio-choline (Chap. 3) and acetate (Chap. 8).

In the case of whole body analysis, difficulties in evaluating lesions at the level of the head and neck have been significantly reduced by the primary complementary role of CT in improving overall accuracy. Thoracic analysis is characterized by a quite unpredictable myocardial uptake while there is no pulmonary activity. Therefore, this is an area typically characterized by low background FDG, in general easily analyzable with the help of CT. This favorable condition proves more advantageous when a respiratory gating is available. While lesion detection is in general easy for FDG at the level of the limbs, as demonstrated by the high sensitivity in the diagnosis of melanomas, the analysis at the level of the abdomen and pelvis is more complex. Difficulties in liver tumor detection are caused mainly by pathophysiology, being high the sensitivity in detecting hepatic metastases and low accuracy in the diagnosis of liver cancer. As previously described, one of the most critical problems for FDG is detecting tumors localized in areas partially occupied by a nonspecific uptake, as those adjacent and/or interlaced with the emunctory systems. Therefore, a major diagnostic problem can be, for example, diagnosing prostate cancer, where the low accuracy depends both on a high background and on a low FDG tumor uptake, resulting in an unfavorable T/B ratio. In this scenario, a significant improvement can be obtained by radiotracers such as radio-choline or acetate, characterized by an uptake mechanism dependent on an aerobic metabolism less related to malignancy or growth rate with respect to FDG. This ability is an advantage in detecting recurrence or lymphnode metastases. Conversely, the possible uptake by benign lesions limits the diagnosis of primary cancer. To demonstrate the effect of radiochemistry and pharmacokinetics, it is interesting to compare different choline radiotracer pharmacokinetics, as reported in Chap. 3. While no C-11 choline is present in the urine, activity in the bladder can be observed after F-18 choline administration, because of a different excretion or as consequence of an in vivo de-fluorination. It means that a lower background can be observed using the former rather than the latter. Less significant is the role of radiotracers other than FDG in intestinal tumors. CT plays a major role in improving FDG accuracy in the differential diagnosis of recurrent bowel cancer.

**How to Increase Specificity with Respect to FDG**

As in the case of sensitivity, the morphostructural contribution of CT plays a major role in decreasing the false positive results of FDG. Similarly, the achievement of a higher L/B ratio can improve specificity with respect to FDG, because of an easier and more reliable analysis. False positive results of FDG are mainly due to the presence of active inflammation, but they can also be dependent on many physiological, para-physiological and pathological conditions such as active scar, fractures, benign thyroid diseases, active brown fat, muscular stress, posttherapeutic response and others (See Atlas of PET-CT: A quick guide to Image Interpretation (Springer, 2009)).

The following chapters describe a major improvement in specificity with respect to FDG, which can be achieved using radiotracers with an uptake mechanism that does not determine an increased concentration in inflammation. It happens, for example, with the use of amino-acids or DNA precursors, such as F-18 thymidine (FLT). It has to be pointed out, however, that even with alternative PET radiotracers, false negative and positive results are present. For example, many false positives can be detected in the diagnosis of primary prostate cancer with the use of acetate or choline. Similarly, F-18 fluoride permits a higher sensitivity in detecting bone metastases in patients with prostate, lung and breast cancer, but in the presence of a low specificity, due to the large number of benign pathological conditions characterized by increased osteoblastic activity.

Therefore, the choice of an alternative radiotracer should be based on a deep and strong knowledge of the pathophysiological premises of their uptake mechanism. The following chapters describe why, when and how to use these radio-compounds to further improve the pivotal role of FDG in oncology. As a deeper analysis is to be found in the respective chapters, only the major ideas are given here.

**Why and When to Use Different Radiotracers with Respect to FDG in Oncology: To Improve its Diagnostic Accuracy**

As mentioned earlier, the first justification for choosing radiotracers other than FDG is improving accuracy. This result can be achieved in different ways, depending on the clinical situation.
Brain cancer. To improve diagnostic accuracy in brain cancer, the main strategy is to use radiocompounds not concentrated in the normal brain. The ideal radiotracer could also have a specific uptake mechanism, permitting a differential diagnosis between benign and malignant lesions. At present, the main category of tracers already in clinical practice is that of amino-acids, having as clinical prototype methionine and thyrosine. Amino-acids present an increased uptake in tumors, but not in the normal brain and in inflammatory lesions. Therefore they can improve accuracy with respect to FDG (and CT and MRI) in the diagnosis of tumor recurrence, acting both on sensitivity and specificity. Conversely, because of their presence in both benign and malignant tumors, they are not reliable for a prognostic evaluation. A less significant clinical interest is seen with the use of radio-choline and acetate.

Whole body cancer. To improve the diagnostic accuracy of FDG in patients with whole body cancer, one of the main strategies is to choose radiocompounds concentrating through an uptake mechanism present in the differentiated tumors.

a. A favorable result can be obtained using radiotracers concentrating through an oxygen dependent mechanism. This is typical of the differentiated tumors with a substantially conserved regular vascular support and a not significant neo-angiogenesis. This rationale has been used for proposing radiotracers such as acetate and choline, both defining an increased metabolic activity not depending on anaerobiosis. Because of the lack of vesical concentration, the use of these radiocompounds has found clinical value in tumors such as prostate cancer, finding a possible clinical role also in hepatomas, renal cancer and brain tumors.

b. A more specific approach is utilizing the peculiar characteristics of some tumors. A very effective clinical application is the use of somatostatin analogues in neuroendocrine tumors, or the use of catecholamine analogues in phaeochromocytoma and other tumors showing increased metabolism. Similarly, a higher accuracy in restaging differentiated thyroid cancer is obtained with I-124 iodide, which has the advantage of also permitting a more rigorous quantitative evaluation of the corresponding gamma emitters.

c. As previously described, an increased sensitivity in detecting bone metastases can be obtained with F-18 fluoride. It has to be pointed out that this radiotracer presents a nonspecific, although sensitive, uptake mechanism, i.e., increased osteoblastic activity. A better accuracy is permitted by the simultaneous CT acquisition, acting mainly through a significant reduction of false positive results.

Why and When to Use Different Radiotracers with Respect to FDG: To Answer Different Questions

In modern medicine, tumor detection is certainly the major request of the clinician, but it does not provide all the information needed for a diagnostic and therapeutic strategy “tailored” for each single patient. Therefore, a wide field of applications for radiotracers other than FDG is available, to give more information, and answer many questions not answered by FDG, especially those connected with prognosis and therapy.

Some of the most interesting possibilities already available in the clinical field in humans are considered here, with a deeper analysis of the clinical aspects in “specific” chapters.

Prognostic information. A promising approach to add a relevant clinical improvement to FDG in prognostic evaluation and in better defining the tumor response is related to the use of radiocompounds tracing the growth rate. The best proposal, already in clinical practice, is linked to the use of radiolabeled thymidine (see Chap. 9), a marker of the DNA multiplication rate. This information, although nonspecific, is different from that obtained by FDG, because it is not significantly influenced by anaerobiosis and the presence of inflammatory cells. FLT could also be important in the near future for a reliable evaluation of tumor response. In fact, FDG plays a significant role in this field, but with an uptake mechanism not strictly related to the growth rate. Although its contribution will certainly remain important for this application, FLT could occupy a clinical role in better defining an early response.

Hypoxia. The presence or absence of hypoxia is relevant in predicting therapeutic efficacy. These data can create an important diagnostic premise, mainly in the evaluation of patients undergoing radiotherapy.

Receptor state. It is well known that the presence of receptors is crucial, both in defining prognosis and in better deciding a therapeutic strategy. In this sense, clinical improvement can be obtained, for example, using radio-compounds tracing hormone receptors (estradiol and
androgens) or somatostatin receptors in neuroendocrine tumors.

Cathecolamine and serotonin precursors. This is a limited but very important field of clinical interest, not only in oncology. In fact, despite the presence of reliable radiotracers labeled with gamma emitters, the use of PET in patients with pathological conditions such as pheochromocytoma and neuroendocrine tumors, and with non-oncologic cardiac or neurological diseases, could give a significant impulse for a better definition of therapeutic strategies.

Angiogenesis. One of the most important frontiers in oncology is to acquire all information on tumor angiogenesis in the patient. The availability of radiocompounds tracing this target can make a major contribution, more than mere diagnosis, to the prognostic evaluation and the definition and monitoring of the best therapeutic strategies.

Relationship between diagnosis and therapy. Historically, the major success of radionuclide therapy has been (and continues to be) obtained in patients with differentiated thyroid cancer. In these subjects, a whole body diagnosis using a gamma emitter, such as I-131 or I-123, permits the recruitment of pretherapeutic patients who will benefit from an effective radionuclide therapy. In this field, a positron emitter such as I-124 could permit the accurate calculation of dosimetry, and the lowest dose to be administered. Similarly, useful information can be obtained from patients undergoing radionuclide therapy using other radiocompounds such as somatostatin analogues, cathecolamine precursors, and bone seeking indicators.

In conclusion, although FDG will be the workhorse of clinical PET for many years, today nuclear medicine can already offer the oncologist, the surgeon, and the radiotherapist many other weapons effective in destroying the big killer: cancer.

To better define the role of these new acquisitions in clinical practice, the deep involvement of pioneers working in Institutions having a scientific background, based not only on imaging, but also on radiochemistry, physiology, pharmacology, molecular biology and clinics, will be important. But to reach the goal three other protagonists are mandatory: (1) the Industry, that has to invest in the production and distribution of new radiotracers already available for clinical practice; (2) the nuclear physician, who has to optimize the use of these new powerful instruments; and (3) the clinician, who has to understand the real relevance of these procedures in clinical practice.

The objective of the authors of this Atlas is to contribute their best efforts in the stimulating new areas of clinical development of nuclear medicine.
Chapter 2  
Considerations About PET Isotopes

Luigi Mansi, Vincenzo Cuccurullo, and Pier Francesco Rambaldi
Nuclear Medicine and Molecular Imaging

Human beings, like all living organisms, are made of biomolecules. Health can be considered as the expression of homeostasis, i.e., the ability of a system to regulate its internal environment, thereby tending to maintain a stable and “normal” condition. In this sense, the real essence of life is the phenomenon in which multiple dynamic equilibrium and regulation mechanisms are needed to make homeostasis possible. Many diseases result from disturbances in homeostasis and are characterized by a condition known as homeostatic imbalance, where a molecular system goes out of equilibrium.

Based on this premise, one of the most effective approaches to diagnose and treat diseases is to follow biomolecular kinetics in the normal state (physiology) and in illness (pathophysiology). This can become a reality when tracers for that specific molecule are available. To follow the bio-molecular kinetics, without interfering with the native molecule, tracers need to be detected by an outside scanner to become a diagnostic tool.

We call this Molecular Imaging, a new term that has to be well understood to avoid confusion. If we want to image a normal or altered molecular system, i.e., an environment where specific molecules are connected through a dynamic interaction, we do not have to modify it. In other words, a molecular process can be studied, without being disturbed, using tracing molecules, the number of which will be relatively low when compared to the total number of native molecules involved in the system. Interference and/or effects on the kinetics that are to be analyzed can be avoided by using tracing molecules. Starting from this premise, it is possible to obtain a true molecular imaging today, in the large majority of the systems (and/or diseases), only by nuclear medicine (NM) and optical imaging (OI). In fact, only NM and OI can produce images with pico/nanomolar amounts of tracers, while CT and MRI need micro/millimoles, too high to permit a rigorous and harmless functional evaluation.

Although it plays a pivotal role in basic research, OI is not yet ready for clinical use because of its incapability to analyze deep structures. Therefore, molecular imaging in humans can be almost identified with NM today.

It is important to note that NM is born and can exist only as Molecular Imaging or therapy. For example, since the 40s, Iodine-131 has been a diagnostic (and therapeutic) tool in patients with thyroid diseases because of its molecular uptake mechanism. Today’s molecular imaging of thyroid can be identified with the old thyroid scintigraphy because radioiodine’s concentration in normal and differentiated malignant cells has become a matter of importance for the molecular biologist; in fact, through the molecular thyroid scintigraphy, it is possible to demonstrate the in vivo presence of the iodine symporter gene both in normal and in neoplastic cells.

Therefore, NM is and has ever been Molecular Imaging; if this term sounds new, born in the third millennium, it is only because we have recently entered the Genome era, with gene and bio-molecules at the center of the diagnostic universe; a further impulse to the diffusion of this term has been given by the incredible technological evolution: it is possible today to study bio-phenomena with a very high spatial and temporal resolution, enabling to detect and characterize lesions sub-millimeters (in animal imaging). The best instrument to image bio-molecules in humans is PET–CT, which gives standard morpho-structural information with CT and a variegated spectrum of functional solutions through the PET scanner.

As described in the previous chapter, although F-18 Fluorodeoxyglucose (FDG) in oncology represents, at present, more than 95% of clinical indications, there is a wide field of new applications, both for FDG in the non-oncologic area and, using other radiotracers, FDG in oncology.

The goal of this Atlas being the presentation of the capabilities of positron emitter radiotracers other than FDG in the oncologic clinical practice, the following chapters provide a wider discussion of each specific radio-compound, analyzing general problems and common issues.

Radiotracers, Radioisotopes, and “in vivo” Distribution of Radioactivity

A radiotracer is a radio-compound, constituted by a radionuclide (radioisotope) labeling a vector molecule (cell), determining the in vivo distribution. In the radio-compound, the radionuclide acts as a label permitting the detection of the tracer by an external scanner. From a theoretical point of view, all imaged radioactivity would correspond only to the radiotracer and its distribution would be dependent only on specific uptake mechanisms.

Practically, after in vivo administration, radioactivity can image both the injected radiotracer (with a distribution determined by specific and nonspecific mechanisms, or by its presence in the vascular pool or in the
Considerations About PET Isotopes

Radioisotopes: Most Diffuse Positron Emitters

The most diffuse positron emitters are those that can be produced with a small cyclotron. In this series are included Carbon-11 (C-11), Nitrogen (N-13), Oxygen (O-15), and Fluorine (F-18). While the first three permit radiolabeling through an isotopic radiochemical substitution of atoms present in the large majority of bio-molecules, F-18 is a halogen, i.e., it can substitute hydrogen by halogenation. Leaving the deeper analysis of radiochemistry and radio-pharmacology to other books and specific papers, this work focuses on the half life (HL) of positron emitters which is the primary physical characteristic to be known before their in vivo use in humans. In fact, to reliably use a radiotracer, we have to first consider the total time needed for the various steps such as radiochemistry, quality control, time of arrival of the dose to the patient, and pharmacokinetics after the administration of the radiotracer. It is clear that too short an HL can create problems in its clinical use.

Positron Emitters with a Short Half-Life: C-11, N-13, O–15

Among the four radio-nuclides presented above, because of its very short HL, tracers labeled with O-15 (HL: 2.03 min) cannot be used in the absence of a cyclotron adjacent to the scanner’s room. To permit a reliable utilization of C-11 (HL: 20.4 m) and N-13 (HL: 9.98 m) radio-compounds, the cyclotron should be positioned preferably in the same place where the PET scanner is located. Moreover, because of their fast decay, C-11, N-13, and O-15 radio-compounds have to be produced very rapidly and in high amounts, therefore requiring the in loco presence of expert radio-chemists and of a well organized complex structure.

A further problem of the clinical use of short lived positron emitters is connected with the scanner’s room. To permit a reliable utilization of C-11 (HL: 20.4 m) and N-13 (HL: 9.98 m) radio-compounds, the cyclotron should be positioned preferably in the same place where the PET scanner is located. Moreover, because of their fast decay, C-11, N-13, and O-15 radio-compounds have to be produced very rapidly and in high amounts, therefore requiring the in loco presence of expert radio-chemists and of a well organized complex structure.

Radio-Fluorine (F-18)

F-18 is today the most diffuse positron emitter. The main reason being its favorable HL, which is 109.8 min, and this in turn gives the advantages of radioprotection (not being too long), of technical and methodological issues, and of the possibility of a long travel transport. In fact, radio-fluorinated compounds can be produced by cyclotrons located at a distance of 3 hours and more from the PET scanner; therefore they are utilizable by a high number of PET centers spread over a wide territory. This condition, together with the unique possibility of labeling the glucose tracer, deoxy-glucose, gave F-18 a fundamental role in the diffusion of PET. The advantages described above stimulated radio-chemists and industries to develop new syntheses using this radionuclide. The number of F-18 radiotracers available for clinical use in humans is increasing each day, frequently substituting radio-compounds previously labeled with C-11. Some examples are reported in the following chapters of this Atlas. From the radiopharmaceutical point of view, it has to be remembered that the possibility of an in vivo de-fluorination of F-18 radiotracers determining the production of
metabolites and of free fluorine have to be considered in a rigorous pharmacokinetic evaluation.

Radio-Iodine (I-124)

Historically, starting from old experiences based on I-131 and I-125, radio-iodination has a pivotal position in radiochemistry. At present, there is a wide use of the pure gamma emitter I-123 for diagnostic purposes. The positron emitter isotope I-124 is characterized by a very long HL (6019.2 minutes, almost 5 days). This condition is advantageous for the worldwide shipment of high amounts of radioactivity, ready for use. Conversely, as negative consequence, dosimetry (for the patient, the personnel, the relatives and the environment) can reach unjustified values when compared with the I-123 corresponding radiotracers, permitting, however, to achieve satisfactory clinical results. Another major disadvantage is the expense and danger involved in the treatment of radioactive wastes. Moreover, although radiochemistry of radiiodine makes the synthesis of a large series of radiotracers, of targets such as antibodies, peptides, and many other molecules, possible, the in vivo presence of a significant de-iodination can create problems both in dosimetry and in rigorous pharmacokinetic analysis. As consequence, the only diffuse and the one already used in clinical practice, the compound labeled with I-124, is the simplest and that is iodide. Also in competition with I-123 and I-131, on the basis of being most cost/effective, I-124 had better clinical diagnostic value for patients with thyroid cancer; it helps both in permitting a rigorous pretherapeutic individual dosimetry and in the follow up.

Radio-Copper (Cu-64)

Copper by 64 (Cu-64) is a positron emitter produced in a large majority by reactors today, although the development of syntheses by cyclotrons have already been available. From the physical point of view, Cu-64 is characterized by the simultaneous emission of positron and beta minus radiations, with an HL of 12.8 h. Therefore, tracers labeled with this radionuclide can be used, clearly at different dosages, both for diagnostic and therapeutic purposes. This prerogative created significant interest in developing new radio-compounds, with the main focus on those used for radionuclide therapies also. Examples of radiotracers ready for clinical practice in humans are presented in the following chapters of this Atlas.

Radio-Gallium (Ga-68)

The pivotal role in the development of medicine carried out by generators and, in particular, by the Mo-99/Tc-99m system is well known to nuclear physicians. This technology is, since many years, available also for positron emitters, mainly with reference to the Ge-68/Ga-68 generator. Germanium 68 has an HL of 271 days, permitting a relatively cheap routine availability of positron emitters for many days, without needing a cyclotron. Gallium - 68 has a favorable HL of 68.0 min and is very promising and already in clinical use. The main utilization is in labeling peptides and, among them, somatostatin analogues. A strong and stable radiochemical bond is obtained through chelation. It has to be pointed out that a similar radiochemistry is utilized for labeling the same molecules using gamma emitters, as Indium-111, or beta minus emitters, as Yttrium-90 or Lutetium-177. With respect to In-111 radio-compounds, radiotracers labeled with Ga-68 permit a higher diagnostic accuracy mainly because of the use of the PET technique. The similarity with the corresponding radiochemical forms labeled Y-90 and Lu-177, used for radionuclide therapy, stimulated the clinical use of Ga-68 radiotracers for the recruitment of patients to be treated; moreover, it is possible to calculate the dosimetry pretherapeutically, permitting a better definition of the dose to be administered. It has to be pointed out, as a minor limitation, that for a rigorous dosimetry, Ga-68 is characterized by a relatively too short HL to calculate the pharmacokinetic analysis of the in vivo distribution up to 24–48 h and longer.

It has to be reported that some researchers, on the basis of some similarities with the Tc-99m radiochemistry, are working on the possible use of Ga-68 for labeling instant kits. At present, this is more a perspective, but it is already evident that there is keen interest in developing the highest number of radiochemical syntheses involving Ga-68.

General Considerations About Radiotracers

Although radio-compounds can trace bio-molecules, following their functional pathways, the pharmacokinetics of these compounds do not completely overlap as they are conditioned by radio-labeling. In other words, the same
molecule can present some differences in the in vivo distribution, if labeled with different radio-nuclides, with different activities of the same radionuclide, with a different specific activity (i.e., with a different amount of the vector molecule). The reason, as already explained above, is that after the in vivo administration, the image is the resultant of a radioactivity’s distribution which is dependent not only on the injected radiotracer (specific and non-specific uptake, presence in the vascular pool or in the emunctories), but also on all the other in vivo produced radiochemical forms such as, metabolites, complexes, and free radionuclide.

This is a major risk in using “new” radiotracers in clinical practice. A reliable use can be obtained only when the “molecular imager” has a deep and wide knowledge of patho-physiological premises; he/she has to learn uptake and distribution mechanisms determined by physiology, para-physiological conditions, pathological events; he/she has to know normal patterns, pitfalls and artifacts; he/she has to predict the behavior in benign and malignant diseases.

Therefore, a thorough but fascinating study is required to become an expert in PET–CT. In particular, it is necessary to learn the functional premises, pathophysiology, radiochemistry, and pharmacology to avoid the major mistake, that is, to think that PET – CT is simply indicating a colored spot on an anatomical structure.

In this Atlas, we want to open your mind to the widening field of the clinical use of PET outside the FDG kingdom. In this Atlas, you will learn that, to detect prostate cancer it is better to choose a radiotracer, which is not eliminated through the urine, to detect brain recurrence an amino-acid is better than FDG because of the lack of uptake by normal cells, and to diagnose differentiated neuroendocrine tumors, radiopeptides have a higher accuracy than FDG. You will also understand that it is possible to acquire important prognostic information, connected to the growing rate, through radiolabeled thymidine, or that you can decide a better therapeutic strategy for women with breast cancer, starting from the knowledge of in vivo distribution of estrogen receptors. In this scenario, you will understand how oncologists, surgeons, radiotherapists, and all the other clinicians can acquire further advantage in addition to the pivotal role already played by FDG. The first area of interest can be found in fields where FDG has limitations because of the presence of false negative or false positive results. But a further relevant indication for the use of PET radiotracers other than FDG is the former’s incapability, shared with all the diagnostic procedures, to answer alone all the possible questions concerning diagnosis, prognosis, and those connected with the therapy.

We conclude this chapter with a final major remark: as far as PET–CT is concerned, while CT always gives the same morpho-structural information, it is PET that permits this hybrid machine to declare its primacy in Molecular Imaging in humans.
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Radiolabeled Choline (labeled to $^{11}$C or $^{18}$F) is one of the most applied and promising PET tracers for cancer imaging. Choline is a substrate for the synthesis of phosphatidylycholine, which is a major phospholipid in the cell membrane. It has been hypothesized that uptake of radiolabeled Choline reflects proliferative activity by estimating membrane lipid synthesis. However, the exact uptake mechanism has to be established.

Choline was first labeled to $^{11}$Carbon for cancer imaging in 1997. $^{11}$C-Choline is cleared very rapidly from the blood, and optimal tumor-to-background contrast is reached within 5–7 min after administration of tracer. This allows for imaging as early as 3–5 min after tracer injection and provides images of good diagnostic quality. Physiologically increased tracer uptake is noted in salivary glands, liver, kidney parenchyma and pancreas and faint uptake in spleen, bone marrow and muscles. Bowel activity is variable and occasionally urinary bladder activity can be observed. $^{11}$Carbon has, however, a short half-life time (20 min) and must be used rapidly after production; it requires a local cyclotron and is therefore not a widely available option.

For these reasons, F-labeled Choline tracers like Fluoro-ethyl-choline (FEC) and Fluoromethyl-dimethylhydroxyethylammonium (FCH) were proposed. Both compounds show similar properties (rapid blood clearance and uptake in prostate tissue) with minor differences (later peak uptake for FEC). The main contrast with $^{11}$C-Choline is the early urinary appearance of $^{18}$F-Choline, probably caused by incomplete tubular reabsorption.

Although Choline PET has been used for identification of various tumor tissues, the main application field of Choline PET is prostate Imaging. PET imaging has been proposed for early detection of primary prostate cancer, for staging of tumor and identification of nodal involvement, and finally for detection of tumor recurrence.

Choline uptake seems to be similar in patients with benign prostatic diseases (prostatitis, prostatic hypertrophy) and proven prostate cancer. This finding, in addition to the limited spatial resolution of PET-CT devices, clearly represents the major limits for the use of this tracer for identification of primary tumor. Despite a tendency towards a higher uptake of Choline in prostate cancer foci, taking all preliminary results into account, Choline PET cannot be recommended for diagnosing primary prostate cancer.

With regard to prostate staging, Choline PET imaging seems not to be accurate enough to be proposed for evaluation of extracapsular extension, seminal vesicle involvement, and detection of lymph node micrometastases. This is mainly due to the limited spatial resolution of PET-CT devices. However, Choline PET may have a role in selected cases: in patients with high-risk prostate cancer, it may assist the clinicians in the decision of aborting surgical treatment in presence of lymph node or distant metastasis. In addition, Choline PET imaging could be helpful by showing lymph node metastasis outside the generally recommended surgery regions, which could have an impact on extent of lymphadenectomy and on survival after radical prostatectomy. However, at present, the use of Choline PET imaging in predicting stage at presentation cannot be recommended for a routine clinical use.

Choline PET imaging plays a more relevant role in the detection of prostate cancer relapse. Choline PET shows higher specificity and consequently higher accuracy compared to all conventional imaging methods together for detection of prostate cancer recurrence. Choline PET imaging, supplying a whole body tomography exam, has the major advantage of detecting local and distant metastasis within a single session with a good accuracy.

However, patient referral criteria still have to be defined. At present, no definite data exist with regard to the thresholds of serum PSA level under which radiolabeled Choline should not be used. Moreover, the influence of medication (e.g., testosterone deprivation) and PSA kinetics on PET-CT detection rate has to be clarified. Despite these limitations, the use of PET-CT with Choline in patients with biochemical failure has shown a significantly better detection rate, when compared to CT or bone scan.

Therefore, in absence of general patient referral criteria for Choline PET Imaging in detection of prostate cancer recurrence, it seems reasonable to use PET imaging in individual cases, where a satisfactory sensitivity is to be expected and imaging findings will have a therapeutic relevance. In particular, patients with high risk of distant metastases or those susceptible to surgery and/or radiation therapy could benefit the most from early identification of the site of recurrence.

Besides prostate cancer imaging, Choline PET has also been used for other minor aims. The minimal background activity of $^{11}$C-Choline in the pelvis, due to the low level of excretion via the urinary tract has permitted the use of this tracer in various tumors of urogenital tract other than prostate cancer (bladder and uterine cancer). Diagnostic accuracy of Choline PET for detection of residual bladder cancer after TURB seems to be comparable to CT, but Choline PET appears to be superior to CT for the evaluation of potential additional lymph node.
metastases. However, only few studies are present in literature on this issue and there is, therefore, a weak rationale for Choline PET imaging in these cancers.

Radiolabeled Choline also seems to be a suitable PET tracer for brain tumor imaging. Choline PET shows a low accumulation in normal brain tissue and allows for the detection of brain tumors with a high tumor/background ratio. Choline PET has been applied successfully for characterization of brain lesions and seems to be in conjunction to MR imaging as an accurate diagnostic tool for identification and detection of high-grade gliomas and meningiomas. On the other hand, Choline PET does not allow one to differentiate low-grade gliomas from nonneoplastic lesions. Despite these good preliminary results, in the absence of data from large series of patients, the clinical role of Choline PET for the evaluation of brain tumors is not fully established, and MET PET remains the metabolic tracer of choice for brain tumor imaging.

Choline PET was also used for identification of myelomatous lesions. Choline PET appeared to be more sensitive than FDG PET for the detection of bony myelomatous lesions, and surprisingly, the SUVmax turned out higher with Choline compared to FDG. However, these data have to be confirmed in a larger series of patients.
Case 1  Biodistribution

11C-Choline

16
Physiologic \(^{11}\text{C}\)-choline uptake.
Case 3  Bladder Excretion

**Teaching point**

Urinary excretion of $^{11}$C-choline may increase over time, and has to be taken into account especially if the scan is acquired more than 5 min after injection.
**11C-choline finding**

Pathologic increased $^{11}$C-choline uptake in iliac lymph node.