Chapter 2  Considerations About PET Isotopes

Luigi Mansi, Vincenzo Cuccurullo, and Pier Francesco Rambaldi
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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 radiocompound, 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
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emunctories) and other radiochemical forms such as metabolites, complexes, and free radionuclides.

The goal of this chapter is to discuss the main issues regarding PET radiotracers from the radiochemical and pharmacological points of view.

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 radiopharmacology 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 in vivo pharmacokinetic of the corresponding radiotracers. In this sense, to use C-11, N-13, and O-15 radio-compounds, the following are necessary: the availability of high amounts of radioactivity and, preferably, of a PET scanner allowing a high count rate, and also a very fast or a very slow achievement of a satisfactory tumor/background ratio. As a consequence, radiotracers labeled with C-11, N-13, or O-15 are almost exclusively used today by institutions which own a cyclotron. In these secondary PET centers, the utilization of these radiotracers, but for N-13 ammonia, which is very easily produced, is mainly limited to groups including professional radio-chemists, who also stimulate research of/with new radiotracers.

As a consequence, the diffusion of radio-compounds labeled with C-11, N-13, or O-15 is not too wide at present. In particular, the interest evinced by industries for the distribution of the easiest and cheapest radio-compound strongly stimulated the development of a radiochemistry based on F-18, generators products, and other radio-nuclides with a slower decay. In fact, these radioisotopes permit to produce, distribute, and reliably use a large number of radiotracers other than FDG in PET centers without cyclotrons which are the majority. A routine use of C-11, N-13, and O-15 radiotracers, on the other hand, is feasible only for well organized, complex PET centers. The use of the radiotracers is therefore mainly of interest for research purposes.

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 radioiodine 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 radionuclides 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 nonspecific 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.
PET-CT Beyond FDG
A Quick Guide to Image Interpretation
Fanti, S.; Farsad, M.; Mansi, L.
2010, X, 243 p., Softcover