REVIEW ARTICLE

# PET-CT: What physicians need to know. Review

**Adolfo E. Lizardo,* Juan Carlos García-Reyna,** Jaime García-Gómez,*** Luis Felipe Alva-López*****

RESUMEN

El cáncer es una de las principales causas de morbimortalidad en el mundo. La tomografía por emisión de positrones (PET) - tomografía computarizada (CT) es una combinación única de la información anatómica en sección transversal proporcionada por la TC y la información metabólica proporcionada por PET, que se adquiere durante un único examen donde se fusionan. El PET-CT es solicitado en oncología, neurología y cardiología. A los radiólogos y médicos nucleares a menudo se les pide llevar a cabo un panel de exámenes de imágenes como parte de la estadificación inicial o de seguimiento de pacientes con cáncer. El uso de radiofármacos específicos para obtener imágenes de la función de los órganos y el estado de la enfermedad es una capacidad única de la medicina nuclear. La mayoría de los radiofármacos utilizados en PET se producen en un ciclotrón. Por lo tanto, la imagen médica debe integrar habilidades polivalentes que permitan a los imagenólogos entender e interpretar todo tipo de imágenes. Decisiones clínicas complejas sobre el tratamiento de los pacientes oncológicos son guiadas en gran parte por los hallazgos de imagen, entre otros factores. La producción de radiofármacos requiere módulos de síntesis automatizados o remotos, que se caracterizan por su eficiencia para incorporar el radiotrazador en un radiofármaco, la longitud de tiempo y la cantidad de la interacción humana necesaria. La comprensión de las técnicas de exploración del PET-TC, así como los potenciales peligros y limitaciones son importantes para el uso ventajoso de esta modalidad de imagen.

**Palabras clave.** PET scan. Radiofármacos. CT scan. Radionúclidos. Cáncer.

*ABSTRACT*

*Cancer is one of the leading causes of morbidity and mortality in the world. Positron emission tomography (PET) - computed tomography (CT) is a unique combination of the cross-sectional anatomic information provided by CT and the metabolic information provided by PET, which are acquired during a single examination and fused. PET-CT imaging is frequently requested in oncology, neurology and cardiology. Radiologists and nuclear medicine physicians are often asked to perform a panel of imaging examinations as part of the initial staging or follow-up of cancer patients. The use of specific radiopharmaceuticals for imaging organ function and disease states is a unique capability of nuclear medicine. The vast majority of PET radiopharmaceuticals today are produced in a cyclotron. Medical imaging must, therefore, integrate polyvalent skills enabling imaging specialists to understand and interpret all types of images. Complex clinical decisions about treatment of oncologic patients are largely guided by imaging findings, among other factors. Radiopharmaceutical production requires automated or remote synthesis modules that are characterized by their efficiency for incorporating the radiotracer into a radiopharmaceutical and the length of time and the amount of human interaction required. Understanding the principles of PET-CT and the optimal scanning techniques and recognizing the potential pitfalls and limitations are important for advantageous use of this imaging modality.*

***Key words.*** *PET scan. Radiopharmaceuticals. CT scan. Radionuclide. Cancer.*

## INTRODUCTION

PET-CT machines constitute major progress in the global management of cancer patients for the initial diagnosis, evaluation of treatment and prognosis, and for surveillance throughout the course of the disease and possible relapse.[1,2] CT and magnetic resonance (MR) imaging rely on anatomic changes for diagnosis, staging, and follow-up of cancer. However, PET has the ability to demonstrate abnormal metabolic activity (at the molecular level) in organs that has yet not show an abnormal appearance based on morphologic criteria. It aids in

* Radiology Resident, Medica Sur Clinic And Foundation, Mexico City, Mexico.
** PET-CT unit, Medica Sur Clinic And Foundation, Mexico City, Mexico.
*** Radiology and Molecular Image Departament, Medica Sur Clinic and Foundation, Mexico City, Mexico.

**Correspondence:**

Adolfo E. Lizardo, M.D.
Radiology and Molecular Image Department. Medica Sur Clinic And Foundation.
Puente de Piedra, Núm. 150, Col. Toriello Guerra, C.P. 14050. Mexico City, Mexico.
Tel.: (+5255) 5424-7200, Ext. 4222.
E-mail: alizardor@gmail.com

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differentiation of malignant from benign lesions and in staging of malignancies.[2] PET is also useful in the follow-up of patients following chemotherapy or surgical resection of tumor, most of who have a complicating appearance at CT or MR imaging due to postoperative changes or scar tissue. The use of specific radiotracers called radiopharmaceuticals for imaging organ function and disease states, is a unique capability of nuclear medicine.[3]

Managed healthcare professionals have recognized the role of PET in the care of oncology patients. What the physicians need to know about PET requires some effort in comprehension, as the basic principles of nuclear medicine are applied to radioactive elements, associated with new concepts combining standard nuclear medicine in terms of whole body scintigraphy and the distribution of the radiotracer in the body. These nuclear medicine issues are then matched with computed tomography with or without contrast administration, thus linking the two imaging procedures, nuclear medicine and radiology.

## MATERIAL AND METHODS

Authors searched Medline, PubMed, Ovid, Google Scholar and Hinari for publications that included review articles and original articles.

## SYNTHESIS

### Basic principles

PET is based on the detection of annihilation photons released when radionuclides emit positrons that undergo annihilation with electrons. The photons released have energies of 511 keV and are detected by coincidence imaging as they strike scintillation crystals made of bismuth germinate, lutetium oxyorthosilicate, or gadolinium silicate. The value 511 keV represents the energy equivalent of the mass of an electron according to the law of conservation of energy. Bombarding target material with protons that have been accelerated in a cyclotron produces positron-emitting radionuclides, which are then used to synthesize radiopharmaceuticals that are part of biochemical pathways in the human body.[4]

### PET-CT technique and protocol

PET is a lengthy examination performed in a patient who has been fasting for at least 4-6 h, to enhance radiotracer uptake as well as to minimize cardiac uptake. They are instructed to avoid physical activity, caffeinated or alcoholic beverages (but can have water, to take their medications, during this period); they are also asked to eat a high protein, low carbohydrate diet. Patients have to sign a consent form and they should also bring renal function tests for the possible use of intravenous contrast.

For a typical whole-body PET-CT study (head, neck, chest, abdomen, and pelvis), scanning begins at the level of the skull base and extends caudally to the level of the symphysis pubis. The brain may be scanned separately. Typical scanning parameters would be a collimator width of 5.0 mm, pitch of 1.5, gantry rotation time of 0.8 second, and field of view of 50 cm. The helical data are retrospectively reconstructed at 2.4-mm intervals. In the conventional PET/CT imaging procedure, a non-enhanced CT scan is performed at the beginning of the examination, on free breathing and at low amperage dose. This CT scan is designed to provide an attenuation map in order to correct PET images and precise anatomical localization.[3,4]

After the study, patients are aware to stay away from children and pregnant women for about 6 h. They can do normal activities after the scan and are advised to drink several glasses of water to help the radioactive substance to dye out of the body.

### Radioprotection

The International Commission on Radiological Protection (ICRP) recommends that the occupational exposure limit for workers should not exceed an effective dose of 20 mSv per year (50 mSmv in Mexico). The practical rule applied in radioprotection is the law of the inverse squares of the distance, which means that the irradiation dose is lower, the greater the distance from the patient.[5]

The radiotracer injection must be performed by highly qualified and well-trained personnel, able to work as rapidly as possible to avoid irradiation of paramedical personnel during the injection. The patient is then kept at a distance, under video surveillance, as it is recommended to avoid contact with an irradiating patient except when absolutely necessary. When optimal radioprotection conditions are observed, the combination of CT scan with intravenous and oral iodinated contrast agent constitutes a valuable aid to interpretation of PET-CT based on a single examination.[6]

### Interpretation of PET-CT fusion

PET provides images of quantitative uptake of the radionuclide injected that can give the concentration

of radiotracer activity. In contrast to PET, which used an external radioactive transmission scan, PET-CT uses CT transmission data to correct for attenuation differences.[7]

There are different methods for assessment of radiotracer uptake by normal and pathologic tissues, such as visual inspection or the standardized uptake value (SUV). This parameter may have a possible role in helping to discriminate a malignant lesion (high SUV) versus a benign inflammatory uptake (low SUV). However, some low-grade tumors or distinct histological tissues have low SUV values, therefore it does not rule out malignancy.[8] Nevertheless, this index is semi-quantitative, as it depends on numerous parameters that influence its reckon.

The ideal situation would be a simultaneous collaborative reading by two imaging specialists (radiology/nuclear medicine). Multidisciplinary staff meetings may be organized to discuss and decide on imaging interpretations.

## Radiopharmaceuticals

The use of specific radiotracers called radiopharmaceuticals for imaging organ function and disease states is a unique capability of nuclear medicine. It gives quantitative information on the distribution of positron emitter labeled radiopharmaceuticals in the body.

Positrons are positively charged beta particles. After losing all of its kinetic energy, it interacts with an electron and is annihilated.[9,10] Both the mass of positron and electron are converted to energy during annihilation and two 511 KeV photons are emitted at a 180° angle to each other. The PET is based on the coincidence detection of the two aforementioned photons.[10,11]

The majority of the radioactive nuclides are artificially produced in cyclotrons or reactors. Of these radioactive nuclides, nine are major positron emitters (Table 1).[12]

Fluorine-18 can often be substituted for a hydroxyl group as in the case of deoxyglucose or can be substituted for a hydrogen atom in a molecule or placed in a position where its presence does not significantly alter the biological behavior of the molecule. This is, currently, the radioisotope most widely used in clinical oncology.[9]

The advantages of PET over traditional radionuclide imaging techniques include higher spatial resolution and sensitivity, quantification of activity, and synthesizing physiologically useful tracers (Table 2).

**Table 1.** Half-life of some radionuclides.

| Radionuclide | Half-life (min) |
|---|---|
| Carbon-11 | 20.4 |
| Nitrogen-13 | 9.98 |
| Oxygen-15 | 2.03 |
| Fluorine-18 | 109.8 |
| Copper-62 | 9.74 |
| Gallium-68 | 68.3 |
| Rubidium-82 | 1.25 |
| Iodine-122 | 3.62 |
| Iodine-124 | 6019.2 |

## PET applications

### *$^{18}$F-Fluorodeoxyglucose (FDG)*

It is the radiotracer most commonly used for PET imaging. The FDG molecule acts like glucose during initial enzymatic reactions within cells, but the altered structure prevents further metabolism. This essentially traps FDG within cells and it accumulates in most tissues at a rate proportional to glycolysis. Physiological uptake includes cerebral cortex, tonsils, myocardium, kidneys, collecting system, liver, soft tissue, gastrointestinal tract, and bone marrow.[13] Malignant cells have increased glucose transporter proteins on their cell surface as well as enhanced rates of glycolysis. The enhanced glycolytic rate of malignant cells facilitates their detection utilizing PET FDG imaging[12] (Figure 1).

It is a useful analogue of glucose in the initial staging of entities such as breast cancer, lung cancer, melanoma, colon, lymphoma, head and neck cancer, lung nodule and others. Inquest for primary tumor as well as in the re-staging and evaluation the response to treatment in cancer of ovaries, uterus, lymphoma, melanoma, colon testis and others.[4,12]

In non-cancer patients it can be used in assessing Alzheimer's disease, other dementias and psychiatric disease, search for epileptic focus, and fever of unknown origin.[12]

### *$^{11}$C-Acetate*

$^{11}$C-Acetate it can be metabolized as a substrate for beta-oxidation through the tricarboxylic acid cycle (Krebs cycle) or it can be used as a substrate for fatty acid synthesis and the production of phospholipids in cellular membranes.[14] It normally accumulates in the pancreas (high), there is variable uptake in the liver and bowel, heart, kidneys, spleen, stomach, and bone marrow.[14,15] Malignancy induced up-regulation of fatty acid synthase (FAS) may play a role in $^{11}$C-acetate uptake in prostate cancers (Figure 2). FAS is a multifunctional enzymatic protein that catalyzes fatty acid biosynthesis; it is overexpressed in prostate cancers, as well as other tumors like renal cell carcinomas, hepatocellular carcinomas and low grade glyomas.[15]

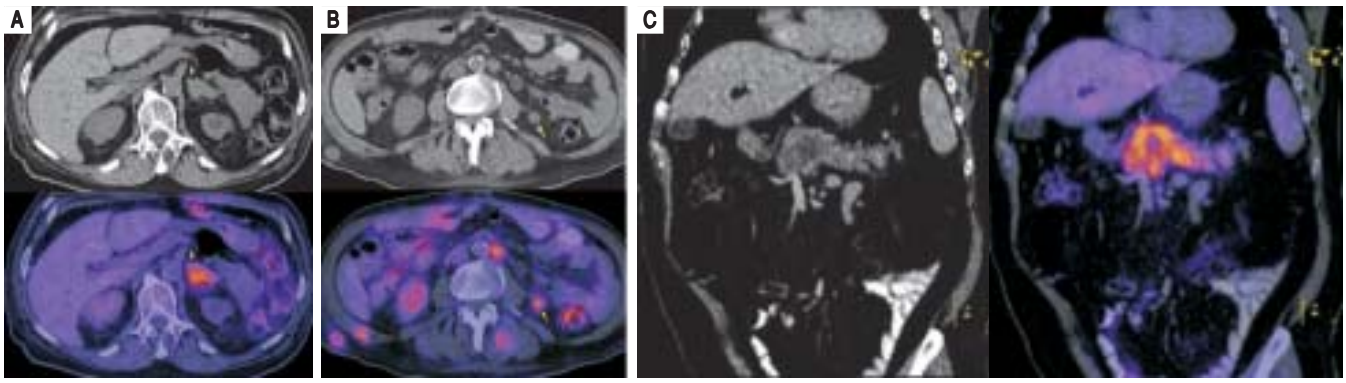


**Figure 1.** $^{18}$F-FDG PET-CT. **A-B.** 70 y.o. male with metastatic urinary bladder cancer: high glycolytic uptake in an increased and nodular left adrenal gland, as well as in some lymphadenopathies in the retroperitoneal space, mesentery, muscular and subcutaneous tissue. **C.** 63 y.o. male with pancreatic adenocarcinoma: Abnormal glycolytic activity in an irregular mass on the head of the pancreas, associated with fat stranding and lymphadenopathy.

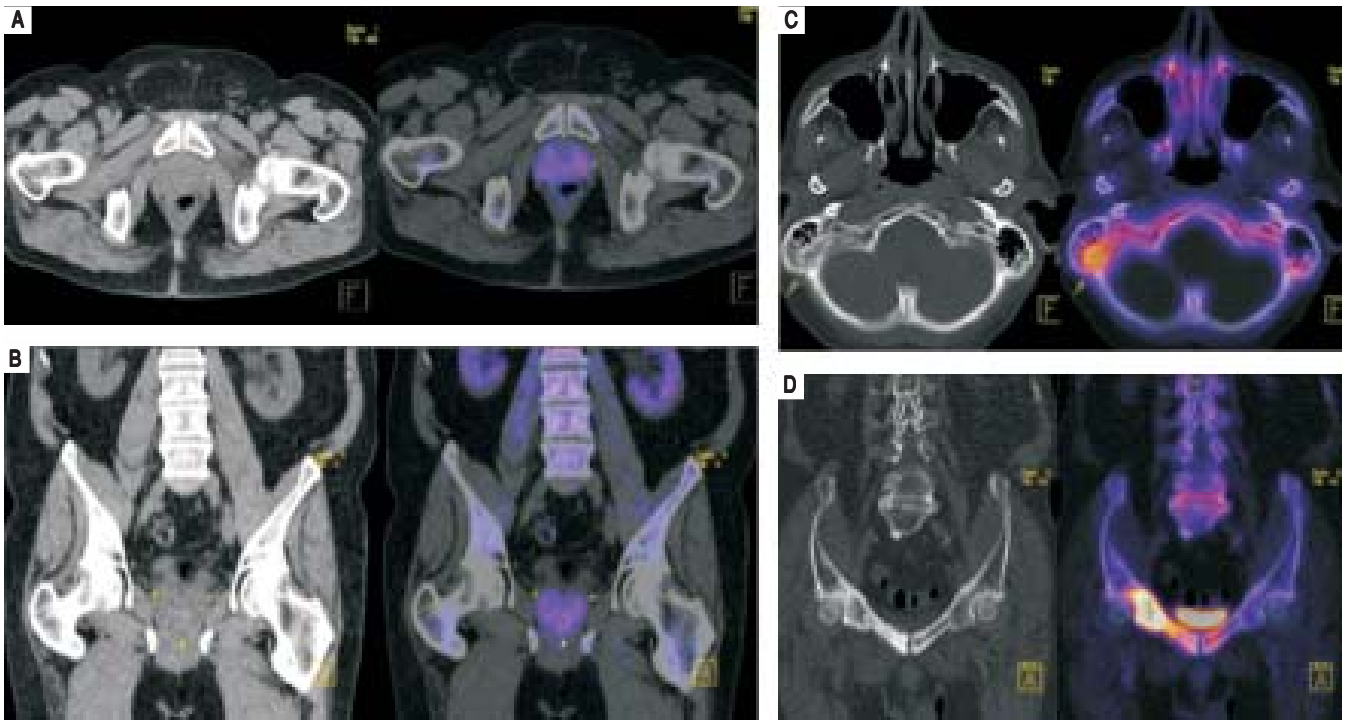


**Figure 2. A-B.** $^{11}$C-Acetate PET-CT. 72 y.o. male with prostate cancer: High oxidative metabolism in a focal area of the prostate's left lobe. **C-D.** $^{18}$F-NaF PET-CT. 77 y.o. male with blastic metastasis of prostate cancer: high NaF concentration in sclerotic lesions of the right mastoid bone and both superior pubic ramus, right predominant.

### *$^{11}$C-Choline*

It is an agent that is incorporated into tumor cells by conversion (a phosphorylation reaction that is catalyzed by choline kinase) into $^{11}$C-phosphorlycholine, which is trap-ped inside the cell. This is followed by synthesis of $^{11}$C-phosphatidylcholine, which constitutes a main component of cell membranes.[15] Prominent tracer uptake is seen in the liver, renal cortex, and salivary glands. Less intense uniform tracer uptake can be seen in then lungs, spleen, skeletal muscles, bone marrow, choroid plexus, and pituitary gland. Variable uptake is seen in the small bowel and urinary bladder.[16]

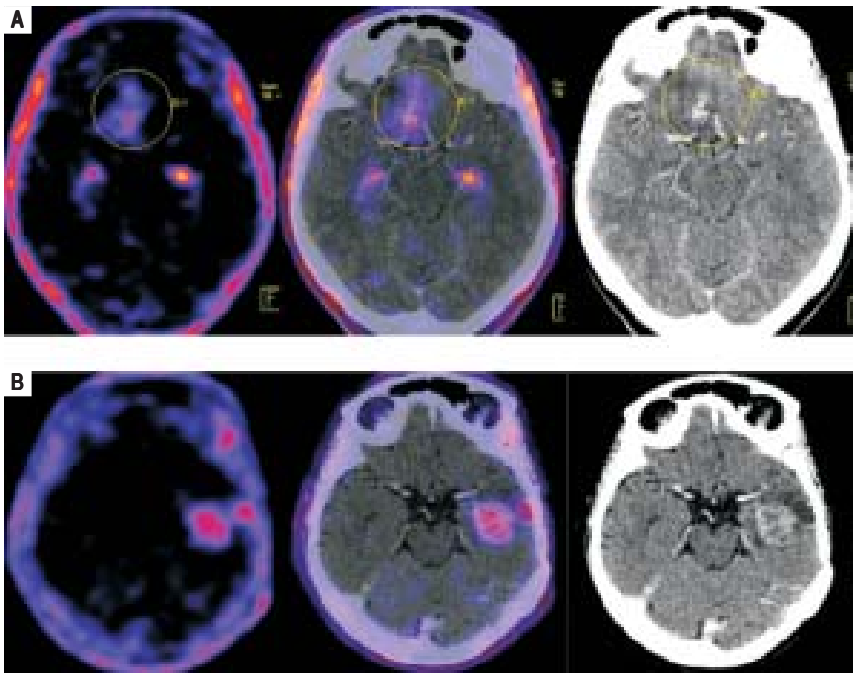


**Figure 3. A.** $^{11}$C-Choline PET-CT. 36 y.o. female with brain glioma: high oxidative activity in right frontal lobe. **B.** $^{18}$F-FLT PET-CT. 52 y.o. female with high-grade astrocytoma: high uptake seen in two lesions of the left temporal lobe associated with post I.V. contrast enhancement and edema.

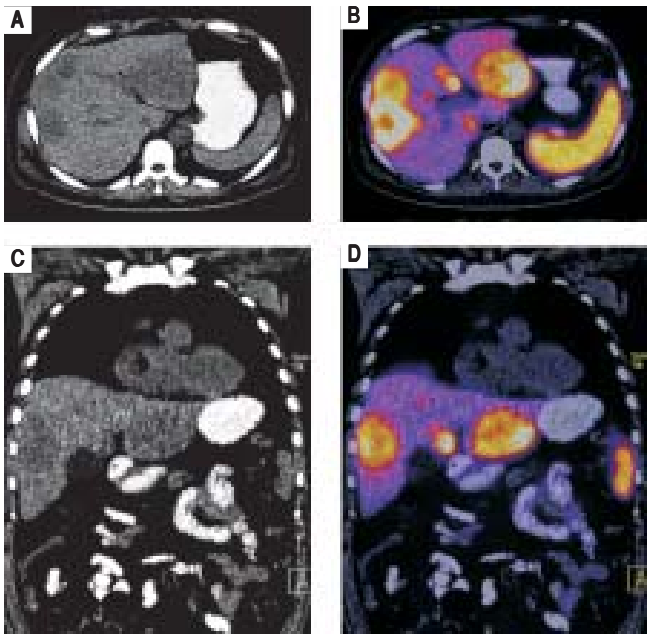


**Figure 4.** $^{68}$Ga-octreotide. 53 y.o. male with liver neuroendocrine carcinoma: abnormal radiotracer activity in multiple hypodense focal lesions in the liver. Normal physiologic uptake is seen in the spleen.

Because tumor cells duplicate very quickly, the biosynthesis of cell membranes is also very fast and there is increased uptake of choline (has short half-life)[15] (Figure 3).

### *$^{68}$Gallium-Octreotide*

The normal biodistribution is seen in the spleen, liver, and genitourinary tract due to excretion; uptake is also seen in the pituitary, adrenal glands and in the pancreatic head.[17] This radiopharmaceutical selectively binds to somatostatin receptors, so its usefulness lies in the detection of neuroendocrine tumors which are frequently not well evaluated on FDG imaging due to a low proliferation rate such as carcinoid, insulinoma, gastrinoma, vipoma, glucagonoma, neuroblastoma, paraganglioma, esthesioneuroblastomas. It offers higher sensitivity and specificity compared to octreotide scintigraphy[18] (Figure 4).

### *$^{18}$F-Sodium Fluoride (NaF)*

It is suitable in the assessment of blastic and lytic bone metastases (prostate, breast, lung, kidney and thyroid). Shows greater sensitivity than scintigraphy, it uses the mechanisms of chemisorption to the hydroxyapatite matrix, which evaluates the metabolism of bone regeneration[19,20] (Figure 2).

### *$^{18}$F-Fluorothymidine (FLT)*

Thymidine is a nucleotide incorporated exclusively into DNA (not RNA). Therefore, it provides a measure of DNA

synthesis and tumor cell proliferation. Useful in the initial assessment and monitoring the response to treatment of brain tumors, especially high-grade tumors.[10] Normal uptake can be seen in proliferating tissue such as the bone marrow; as well as liver, renal, and genitourinary activity also seen.[21] Typically has low CNS uptake, which provides good contrast with tumor uptake (compared to FDG, which has significant CNS activity)[22] (Figure 3).

### *$^{18}$F-Estradiol (FES)*

This agent is an analog of estradiol and regulates gene expression by binding to specific estrogen receptors;[10] has high prognostic value in assessing response to hormone therapy.[19] Normal physiological uptake can be seen in liver, gall bladder, uterus and urinary bladder. Double protocol with FDG can be used in those breast cancers that have heterogeneous molecular background.[23]

### *$^{18}$Fluoro-misonidazole (F-MISO)*

With increasing tumor size, there is a reduced ability of the local vasculature to supply sufficient oxygen to rapidly dividing tumor cells, resulting in hypoxia.[10] This radiopharmaceutical evaluates cellular hypoxia conditions in malignant tumors, which determines decreased lethal DNA damage in chemotherapy and radiotherapy, in other words, radio-resistance. Patients with tumors that have significant hypoxia have a worse prognosis and shorter disease free

**Table 2.** Radiotracer mostly used in clinical practice.

| Radiotracer | Target mechanism | Applications |
|---|---|---|
| $^{18}$F-Fluorodeoxyglucose (FDG) | Glucolitic activity | • Cancer: breast, lung, melanoma, colon, ovaries, testis, lymphoma, head and neck cancer, lung nodule, and others.<br>• Staging and response to treatment.<br>• Non-cancer: Alzheimer's disease, other dementias andpsychiatric disease, search for epileptic focus, and fever of un known origin. |
| $^{11}$C-Acetate | Fatty acid synthesis and phospholipids production in cellular membranes | • Prostate cancer, renal and bladder cancer, lung cancer, hepatocellular carcinomas, multiple myeloma and low grade glyomas and others. |
| $^{11}$C-Choline | Membranes synthesis | • Recurrent prostate cancer, renal cell carcinomas and low grade glyomas and others. |
| $^{68}$Gallium-octreotide | Selectively binds to somatostatin receptors (SSTR1-5) | • Carcinoid, insulinoma, gastrinoma, vipoma, glucagonoma, neuroblastoma, paraganglioma, esthesioneuroblastomas and other neuroendocrine tumors. |
| $^{18}$F-Sodium Fluoride (NaF) | Bone activity metabolism | • Blastic and lytic bone metastases (prostate, breast, lung, transitional cell carcinoma, colon, and more). |
| $^{18}$F-Fluorothymidine (FLT) | Cell proliferation | • Lymphoma, breast, head and neck, brain, cervical, pancreatic, esophageal, kidney, lung, colorectal, neuroendocrine cancers and others. |
| $^{18}$F-Estradiol (FES) | Antigen receptors binding | • Breast cancer; has high prognostic value in assessing response to hormone therapy |
| $^{18}$Fluoro-misonidazole (F-MISO) | Cells hypoxia | • Response to treatment in head and neck tumors, central nervous system, lung, myocardial ischemia and others. |
| $^{68}$Ga- Prostate-specific membrane antigen (PSMA) | Enhanced expression levels of PSMA | • Poorly differentiated, aggressive, metastatic and hormone-refractory prostate carcinomas).<br>• Ability to identify and localize recurrence. |

survival when compared to better-oxygenated tumors.[19] Its value is as a prognostic factor of response to treatment in head and neck tumors, as well as in central nervous system.[24]

### *$^{68}$Ga-PSMA*

A novel PET radiotracer, Gallium labeled prostate-specific membrane antigen (PSMA) ligand, also known as glutamate carboxypeptidase II or *N*-acetyl-*L*-aspartyl-*L*-glutamate peptidase; its expression correlates with the malignancy of the disease, being increased in metastatics and hormone-refractory patients, especially in metastatic castrate-resistant prostate cancer.[25]

PSMA is a cell surface target that is normally expressed by lung, spleen, kidneys, neart and muscles, however, nearly all prostate cancers with enhanced expression levels found in poorly differentiated, aggressive tumors, metastatic and hormone-refractory carcinomas. Due to the high PSMA uptake in prostate cancer cells it is an ideal biological target for PET imaging of this cancer, especially for visualizing small lymph node, bone and liver metastases.[26] The ability to identify and localize recurrence in patients with elevated serum (PSA), as low as 1 ng/mL, but with no other symptoms after definitive therapy is the goal of PSMA PET-CT.[26]

## CONCLUSIONS

PET-CT fusion is a complex task requiring a concerted effort of chemists, radio-pharmacists, physicists, and physicians. Its correlation provides the best of both worlds: The exquisite spatial resolution and anatomic detail of multidetector CT images and the metabolic, functional activity of PET imaging. This fusion increases the ability to diagnosis, stage, and re-stage malignancies accurately, as it can demonstrate malignancies even before morphologic changes are evident.

It is useful to know the general principles of radiotracers, along with their preparation and use. Further development and implementation of new PET-tracers in clinical routine will continually increase the number of PET/CT indications.

## HIGHLIGHTS

- PET has the ability to demonstrate abnormal metabolic activity in lesions with normal appearance on CT. It helps in staging of malignancies.
- PET is useful in the follow-up of patients following chemotherapy or surgical resection of tumor.
- Radiotracers gives quantitative information on the distribution of radiopharmaceuticals in the body for imaging organ function and disease states.
- There are different methods for assessment of radiotracer uptake by normal and pathologic tissues, such as visual inspection or the standardized uptake value (SUV).
- $^{18}$F-FDG is the radioisotope most widely used in clinical oncology.

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