What Is Positron Emission Tomography?

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Introduction: What Is Positron Emission Tomography?

While other modalities such as computed tomography (CT) and magnetic resonance imaging (MRI or MR) have excellent spatial resolution and soft tissue contrast, they may still fail to detect smaller metastases. In addition, response to treatment is usually assessed by observing a decrease in tumor size, which can take weeks to months to manifest.

Nuclear medicine is the only clinical discipline to use intracellular contrast agents in imaging and therefore can detect certain disease processes where other anatomic modalities may not. The best-known is radioiodine for diagnosis (and treatment) of thyroid cancer. However, problems persist with low specificity (since a variety of biological processes can produce any given change in tracer distribution) and spatial resolution of many nuclear imaging systems.

Nuclear medicine involves the use of a radiotracer, where a radioactive atom (the radionuclide) is bound to a pharmaceutical (the tracer) to produce a radiotracer. The pharmaceutical determines the biological activity, and the radionuclide allows for visualization. Two radiopharmaceuticals with the same radionuclide but different radiopharmaceuticals will behave completely differently, whereas two radiopharmaceuticals with the same pharmaceutical but different radionuclides will differ primarily in imaging and physical parameters such as tracer half-life, the number of photons emitted per second, and the energy of the photon, which can have a significant effect on the what is seen on the images. Examples are 123-MIBG and 131-MIBG [1].

Positron emission tomography (PET) is a particular modality of nuclear medicine (the others being single-photon emission tomography, or SPECT, and planar gamma imaging) where the radionuclide is a positron emitter, most commonly fluorine-18 [1]. Other commonly used radionuclides are gallium-68, nitrogen-13, and rubidium-82. PET became clinically useful in the past few decades with the advent of 18F-fluorodeoxyglucose (FDG), an analog of glucose, which has greatly improved diagnosis, staging, and restaging in oncology. Non-oncologic applications exist as well; it can also be used in neurology to find seizure foci and infectious diseases to find foci of occult infection. Rubidium-82 and nitrogen-13 ammonia have applications in myocardial perfusion imaging, and there are a variety of tracers for evaluating

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amyloid plaques (and one recently approved tracer for tau protein) in dementia.

Recently, other tracers such as 18F-FES for estrogen-receptor positive cancers (including breast and endometrial), 18F-FACBC for prostate cancer (with other prostate cancer tracers in the pipeline), Ga68-DOTATATE and DOTATOC for neuroendocrine tumors, and 18F-sodium fluoride for bone metastases have been approved [2]. However, as of yet, there are no dedicated melanoma or sarcoma tracers, and generally FDG is the only tracer that is used for melanoma or sarcoma.

PET has four main applications in oncology: diagnosing cancer, such assessing solitary pulmonary nodule for malignancy; staging, or determining where in the body a cancer has spread; response assessment, or determining whether a tumor has responded to therapy and, if so, how much; and surveillance and restaging, or determining if a cancer has returned and, if so, and how widespread is the recurrence. Additionally, in particular in sarcoma, it may be used to assess the most malignant portion of a lesion in order to guide biopsy.

Physics of PET

When a radionuclide used in PET decays, it does so by emitting a positron, or positively charged antimatter electron (Fig. 1.1). After travelling a few millimeters in tissue, it collides with a normal electron and, being antimatter, annihilates the entire mass of both itself and the electron, which is changed into two photons with energy of 511 keV each travelling 180 degrees apart. The PET scanner is a ring or ring of detectors positioned around the patient which can detect these photons and verify that they reached the detector at the same time (or times within a specified timing window in the case of time-of-flight scanners); this is known as coincidence detection (Fig. 1.2), which allows the placement of the originating photon along a line of response (Fig. 1.3). Coincidence detection allows a higher

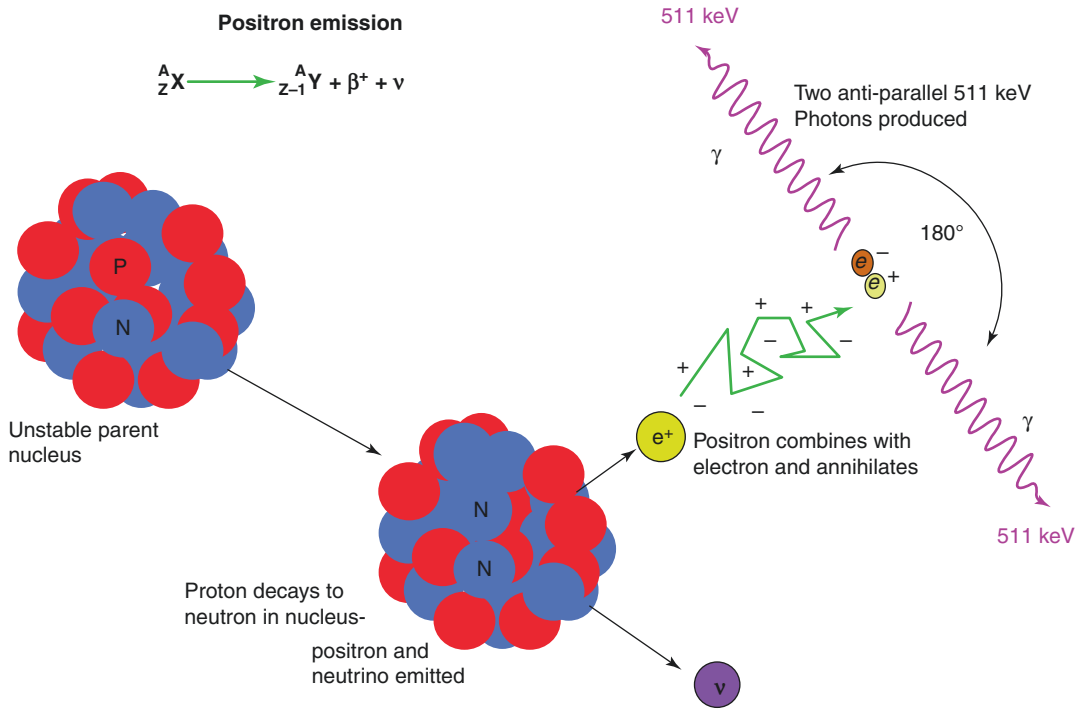

Fig. 1.1 Positron emission and annihilation

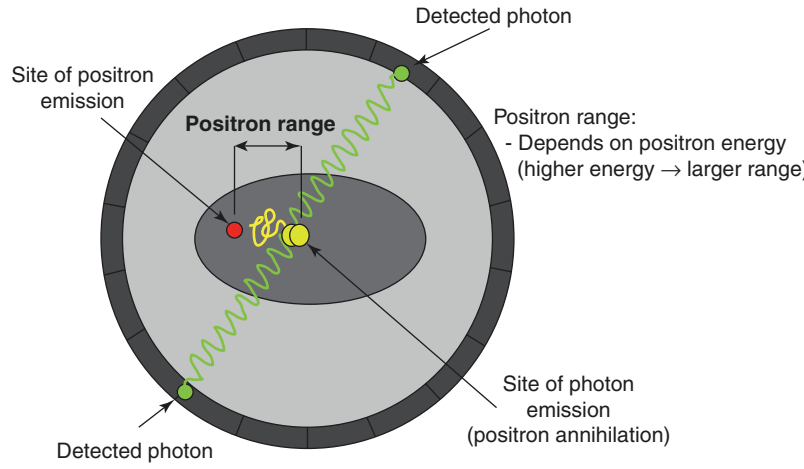

Fig. 1.2 Photon emission and detection

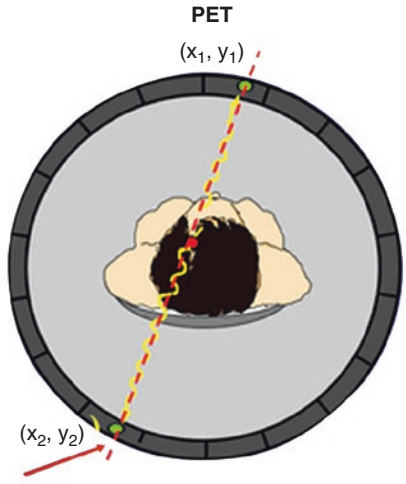

Fig. 1.3 Line of response reconstruction

resolution relative to SPECT and planar gamma imaging and, with attenuation correction as described below, allows for quantitative measurement of uptake in a given volume [3]. Some scanners (those with rapid scintillation crystals and the appropriate software) allow for time-of-flight (TOF) imaging, which uses very precise (picosecond-level) timing of the arrival of the photons to help further localize the origin of the arriving photons.

As the photons move through the body, they are absorbed, or attenuated. This causes underestimation of radioactivity in the center of the body. There is also apparent overestimation of radioactivity at the surface of the body (as well as in low-attenuation structures like the lungs). This is corrected for in the modern era using a CT scan; CT data provide the information on the tissue type and density which is needed for PET attenuation correction. In addition, of course, a CT is a diagnostic imaging scan that can also be useful, both for localizing areas of radioactivity within the body and as a diagnostic scan in its own right [3]. While the CT was initially done without contrast and used solely for anatomic localization and attenuation correction, the CT is now sometimes done as a full diagnostic scan with oral and intravenous contrast. The CT can usually be done within a few seconds, whereas PET acquisition time will usually be a few minutes per bed position for a total time of 20–25 minutes for a whole-body melanoma scan. Fused PET/CT images can be produced that show both anatomic and physiologic information, with the PET displayed as a colored "ghost" over the CT (Fig. 1.4).

Of course, if the patient moves (voluntarily or involuntarily such as breathing motion) between the PET and CT scans, lesions will be mislocalized and interpreting physicians must be careful interpreting areas of high motion such as the chest and abdomen near the diaphragm, as well as any

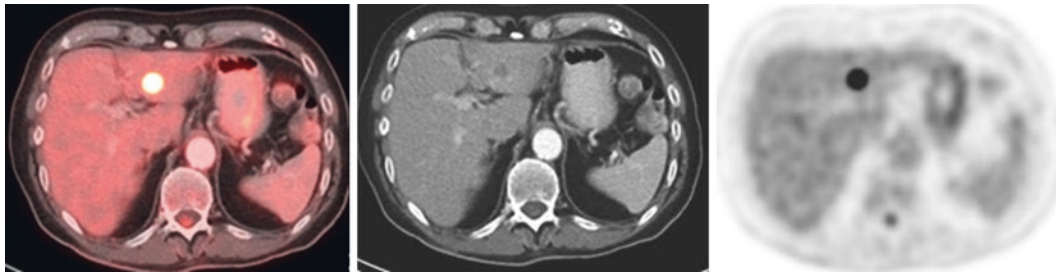

Fig. 1.4 Fused image (left), with component CT (middle) and PET (right) images

location where image fusions suggest the CT and PET do not coincide. In such cases reference to the non-attenuation-corrected images is useful. Additionally, breathing motion causes "smearing" and decrease in registered signal on PET.

Seeing Tumors on PET

As previously discussed, the most commonly used tracer in clinical PET imaging is FDG, or 2-[18f]-fluoro-2-deoxy-D-glucose. FDG is similar enough to glucose to be taken up by glucose transporters and phosphorylated to FDG-6-phosphate. However, both cancer cells and normal cells are unable to further break down FDG-6-phosphate due to the replacement of a hydroxyl group with a fluorine atom, and it is trapped there. In addition, cancers disproportionately consume glucose due to a breakdown in aerobic metabolism (known as the Warburg effect) and tend to have lower expression of an enzyme known as glucose-6-phosphatase which can dephosphorylate the molecule and allow it to leave the cell. Together, these factors increase the accumulation of FDG in cancer cells and allow us to visualize them on PET [1].

Intensity of a malignant tumor is correlated with a number of factors. The number of malignant cells in the tumor mass is the most important factor; thus sparse tumors such as invasive lobular breast carcinoma or tumors that produce a noncellular substance such as mucinous tumors will be less avid. The overall anaerobic metabolic activity (in terms of glucose consumption) is also relevant, with more aggressive tumors generally being more FDG-avid. In addition, most effective therapies will decrease the number or metabolic activity of malignant cells or both, decreasing the amount of FDG uptake. This allows monitoring of response to therapy by PET much more closely than with CT or MR as the metabolic signal decreases much faster after effective therapy than size. One cannot exclude that microscopic disease, undetectable by PET, might remain in tumor. The likelihood of this to happen depends on the type tumor (e.g., lymphoma vs lung cancer) and its overall prognosis. In such cases, a short-tem (e.g., 6 weeks) follow-up PET would be beneficial to capture any regrowth of cancer cells in an early stage.

It is worth noting that white blood cells and fibroblasts are also highly FDG-avid, causing uptake in benign processes such as infection and inflammation (Fig. 1.5). The best way to avoid false positives is to look at the pattern of uptake (focal mostly indication cancer vs diffuse or linear mostly indicating inflammation) and to obtain the medical history and determine any history of infectious or inflammatory processes. We often tell referring clinicians to defer obtaining PET scans on patients with active infection until such infection has resolved (where possible), unless the indication is to look for infection. Unfortunately, there is no consensus on how long to wait after chemotherapy, surgery, or radiation to significantly decrease the risk of a false positive [4].

A possible cause of false negatives is physiologic FDG uptake by muscle (Fig. 1.6), drawing off glucose from the tumor. The most common causes of physiologic muscle uptake are due to exercise or insulin secretion, either

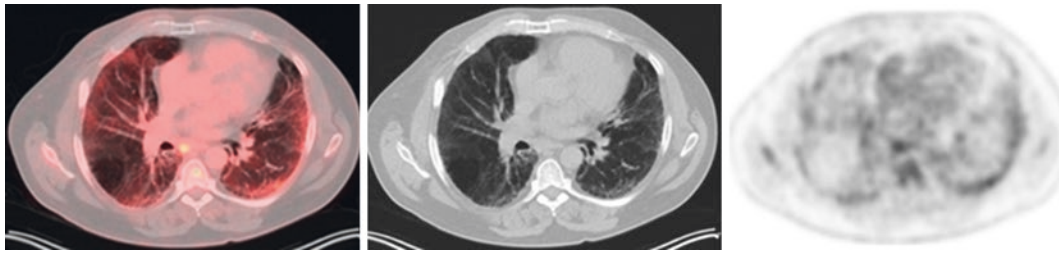

Fig. 1.5 Lung uptake on fused images (left), CT (middle), and PET (right) showing the correspondence of uptake to areas of active inflammation

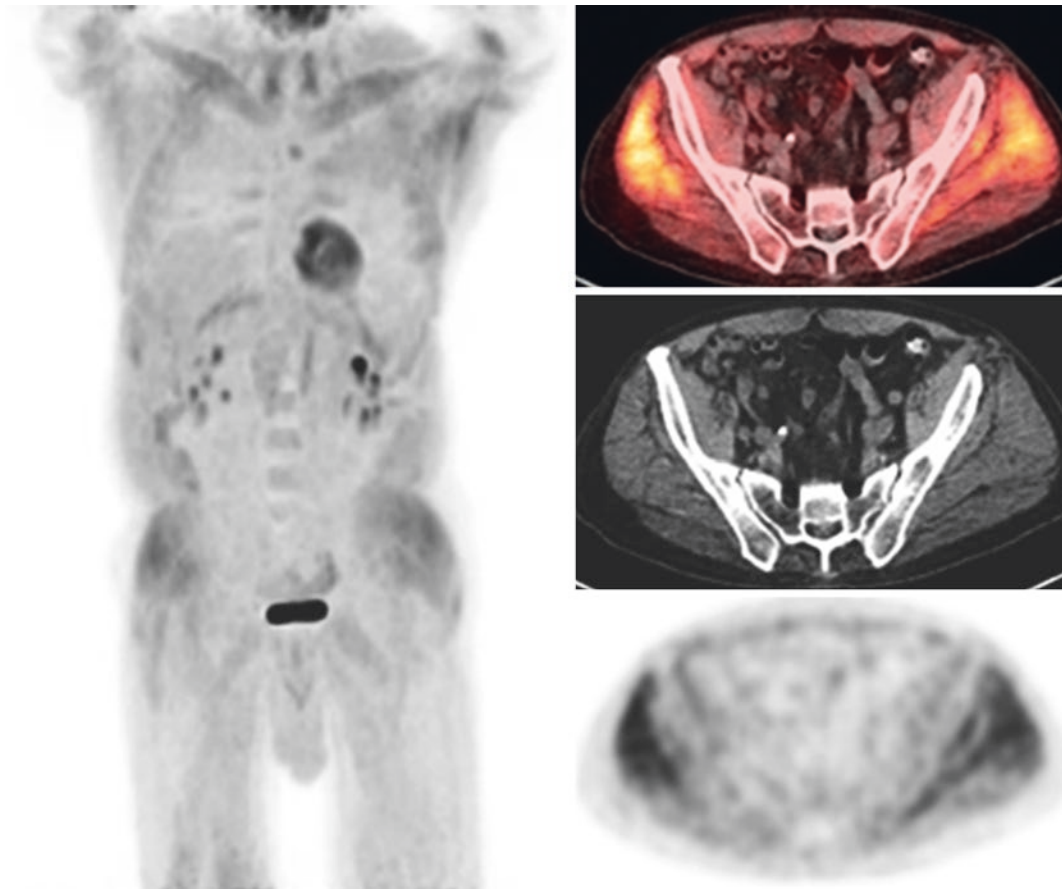

Fig. 1.6 Diffuse muscular uptake, as can be seen with insulin administration

exogenous or physiologic from food consumption. As a result, patients are instructed to avoid excessive physical activity for 24 hours before their appointment and fast (including glucose-containing drinks and intravenous glucose) for at least 4–6 hours beforehand as well. In addition, fasting lowers the serum glucose level to decrease competition for glucose uptake sites in the tumor. For similar reasons, high glucose levels in diabetics (above about 200–250 mg/dL) may decrease sensitivity, and institutions will usually try to wait to perform PET until diabetes is sufficiently controlled. Of course, this may not be possible in all cases, and in such situa-

tions image quality should be assessed and discussed in the report if necessary [2].

Brown fat may be present in the neck and supraclavicular regions (as well as in the posterior mediastinum and upper abdomen less frequently), particularly in younger patients and women and on unusually cold days (Fig. 1.7), and is often intensely avid and can obscure pathology in these areas. Use of benzodiazepines before the examination can reduce uptake, and warm blankets can be used as well. In general, it is preferable to have uptake rooms as warm as possible [2].

Finally, attempts have been made to create a quantitative analog to the Hounsfield unit for CT in the form of the SUV, or standardized uptake value. It is a unitless, semiquantitative measure of tracer uptake in a region of interest, normalized to injected dose and body weight. (Technically, it is counts × weight/dose.) As the SUV is a number with a different value at each point in space resolvable by the scan, some summary statistic is necessary. The most commonly used is the SUVmax, the *most intense* pixel in the tumor. SUVmax is less dependent on reader and region of interest (ROI) because the most intense pixel is almost always agreed upon by different observers. On the other hand, SUVmean, the average of SUVs of pixels in a defined volume, is very much dependent on the size and contour of ROI. With other words, SUVmax is much more reproducible than SUVmean, although it tends to underestimate the signal intensity due to small size of a single pixel. Other metrics include the SUVpeak, the average of the SUVs in a sphere with a diameter of 1 cm centered around the most intense area [5].

These parameters generally cannot differentiate malignant from benign tumors and are influenced by additional factors such as uptake time, body weight, blood glucose, and technical factors affecting image quality such as scanner resolution and image reconstruction algorithm. However, they can be useful in research studies to compare subjects and in clinical settings to assess response to therapy [6, 7] (assuming factors such as scanner type and uptake time can be controlled for). An association of SUVmax with prognosis (higher SUVmax has worse prognosis, likely reflecting a more aggressive tumor) has

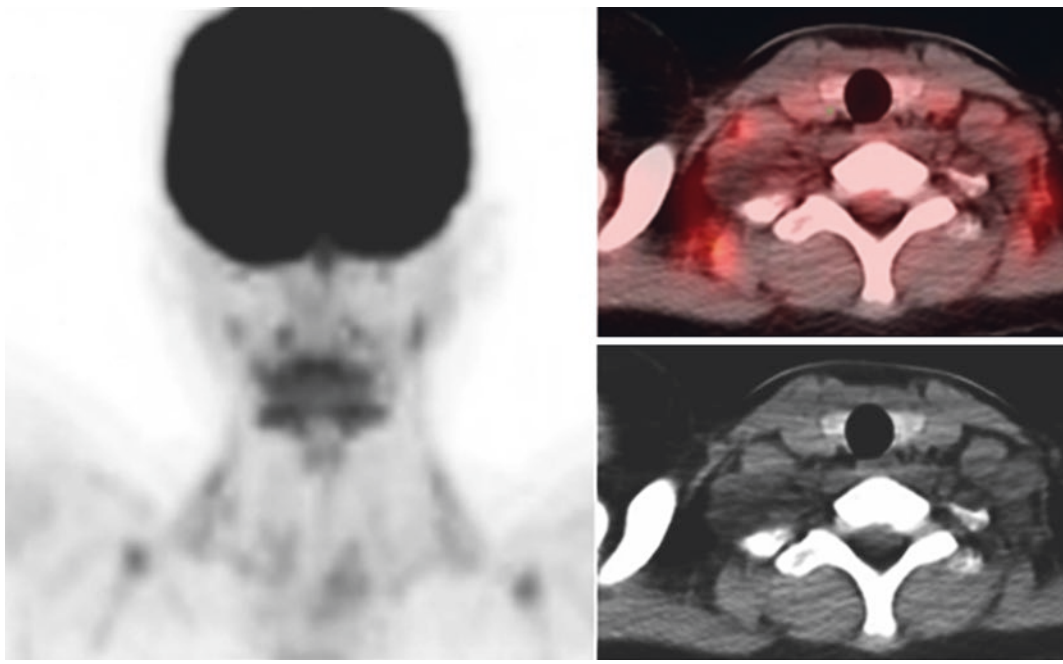

Fig. 1.7 Maximum intensity projection (left), fused (right-top), and CT (right-bottom) images of brown fat

been demonstrated across multiple tumor types and settings. In melanoma, a higher SUVmax correlates with risk of recurrence and poorer survival [8, 9], although other parameters such as MTV (metabolic tumor volume, the total amount of metabolically active tumor) and TLG (total lesion glycolysis, the SUV integrated over the MTV) may be more useful [10]. In sarcoma as well, a higher SUVmax correlates with more dedifferentiated tumors [4] and poorer survival [11, 12], although again MTV and TLG may be more useful [13].

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