PET -5

IMPACT OF PET-CT IN NEW ERA OF MEDICINE

Imaging plays an increasing role in the care of cancer patients. Anatomic imaging modalities, such as plain radiographs, CT scan and MRI are commonly used to detect and localize cancer, where tumours are recognized and followed based on their density, shape, size and location. More recently, a new method called “Positron Emission Tomography” (PET) has been established. It is a functional, biochemical and molecular imaging method, which is complementary to anatomic imaging and is proving effective in guiding the care of cancer patients.

Positron emission tomography - computed tomography (better know by its acronym PET-CT) is a medical imaging device which combines in a single gantry system both a Positron Emission Tomography (PET) and an x-ray Computed Tomography, so that images acquired from both devices can be taken sequentially, in the same session from the patient and combined into a single superposed (co-registered) image. Thus, functional imaging obtained by PET, which depicts the spatial distribution of metabolic or biochemical activity in the body can be more precisely aligned or correlated with anatomic imaging obtained by CT scanning. Two- and three-dimensional image reconstruction may be rendered as a function of a common software and control system.

PET-CT has revolutionized many fields of medical diagnosis, by adding precision of anatomic localization to functional imaging, which was previously lacking from pure PET imaging. For example, in oncology, surgical planning, radiation therapy and cancer staging have been changing rapidly under the influence of PET-CT availability, to the extent that many diagnostic imaging procedures and centres have been gradually abandoning conventional PET devices and substituting them by PET-CTs. Although the combined device is considerably more expensive, it has the advantage of providing both functions as stand-alone examinations, being, in fact, two devices in one.

History:

The birth of PET is somewhat controversial. One of the first suggestions to use positron-emitting tracers for medical applications was made in 1951 by W H Sweet and G Brownell at Massachusetts General Hospital, and some attempts were made to explore the use of positron-emitting tracers for medical applications in the 1950s. During the late 1950s and 1960s, attempts were made to build a positron scanner, although these attempts were not very successful. After the invention of the CT scanner in 1972, tomography in nuclear medicine received more attention, and during the 1970s a number of different groups attempted to design and construct a positron scanner.

S Rankowitz and J S Robertson of Brookhaven National Laboratory built the first ring tomograph in 1962. In 1975, M Ter-Pogossian, M E Phelps and E Hoffman at Washington University in St Louis presented their first PET tomograph, known as Positron Emission Transaxial Tomograph I (PETT I). Later the name was changed to PET, because the transaxial plane was not the only plane in which images could be reconstructed. In 1979, G N Hounsfield and A M Cormack were awarded the Nobel Prize for Physiology and Medicine in recognition of their development of X-ray CT.

Since the very early development of nuclear-medicine instrumentation, scintillators such as sodium iodide (NaI) have formed the basis for the detector systems. The detector material used in PET is the determining factor in the sensitivity, the image resolution and the count-rate capability.

The only detector of choice in the mid-1970s was thallium-activated NaI - NaI(Tl) - which requires care when manufactured because of its hygroscopic nature. More importantly, it also has a low density and a low effective atomic number that limits the stopping power and efficiency to detect the 511 keV gamma rays from positron annihilation. Thanks to its characteristics, bismuth germanate, or BGO, is the crystal that has served the PET community well since the late 1970s, and it has been used in the fabrication of most PET tomographs for the past two decades. The first actual tomograph constructed that employed BGO was designed and built by Chris Thompson and co-workers at the Neurological Institute in Montreal in 1978.

Although the characteristics of BGO are good, a new scintillator, lutetium oxyorthosilicate (LSO) (discovered by C Melcher, now at CTI Molecular Imaging in Knoxville, TN), is a significant advance for PET imaging. BGO is very dense but has

only 15% of the light output of NaI(Tl). LSO has a slightly greater density and a slightly lower effective atomic number, but has five times more light output and is seven times faster than BGO. The first LSO PET tomograph, the MicroPET for small animal imaging, was designed at the University of California in Los Angeles (UCLA) by Simon Cherry and co-workers. The first human LSO tomograph, designed for high-resolution brain imaging, was built by CPS Innovations in Knoxville, TN, and delivered to the Max Planck Institute in February 1999.

In the 1970s, Tatsuo Ido at the Brookhaven National Laboratory was the first to describe the synthesis of 18F-FDG, the most commonly used PET scanning isotope carrier. The compound was first administered to two normal human volunteers by Abass Alavi in August 1976 at the University of Pennsylvania. Brain images obtained with an ordinary (non-PET) nuclear scanner demonstrated the concentration of FDG in that organ. Later, the substance was used in dedicated positron tomographic scanners, to yield the modern procedure.

PET Physics:

Positron Decay:

Radioisotopes that have excess of proton may decay by electron capture or positron decay. During electron capture, one of the orbital electrons- usually a k-shell electron- is captured by the nucleus and a proton is converted into a k-shell neutron. Electron capture can be written with the equation:

$P^+ + e^- \rightarrow N + v + E$

where p^+ is a proton, e^- is an electron, N is a neutron, v is a neutrino, and E represents the excess energy released during decay. Isotopes undergoing electron capture cannot be imaged with a PET scanner.

In order to decay by positron decay, an isotope must have at least 1.02 MeV more energy than the isotope to which it decays. Isotopes that transition with less than this energy cannot undergo positron decay and will decay only by electron capture. Isotopes with enough energy to undergo positron decay can decay by either positron decay or electron capture. For most commonly used positron emitters the probability of undergoing electron capture is small enough that it can be ignored. In a few cases, however, an important fraction of the isotope decays by electron capture.

Positron decay can be written with the equation:

$P^+ \rightarrow N + \beta^+ + v + E$

Where P^+ is a proton, N is a neutron, β^+ is a positron, v is a neutrino, and E represents excess energy. A positron is antiparticle that corresponds to electron. A neutrino has very little interaction with matter, and can be ignored for PET. The excess energy is shared between the positron and the neutrino with different amounts of energy going to each particle during decay.

Coincidence Detection:

The two nearly back to back gamma rays are key to the positron emission tomography. If two detectors on opposite sides of the patient record an event at nearly same time, then the annhilation event must have happened somewhere on a straight line between the two detectors. The two detectors are said to be "**in coincidence**" when the camera detects events in both detectors at nearly the same time. Key to PET camera is this ability to identify these coincident events.

Many current positron cameras are constructed as annular arrays of small crystals. Crystals on either side of the patient stop the gamma rays from the annhilation reaction.

PET/CT:

Figure1: Showing PET/CT machine

A PET scanner can be combined with a CT scanner into a single machine. Metabolic information is obtained from the PET scanner and anatomic information is obtained

from the CT scan. In addition, CT scan can be used to provide information needed for attenuation correction. The current generation of PET/CT scanners all have a commen bed, which travels from the PET gantry to the CT gantry. It may also be possible to design a scanner with both PET and CT on a single gantry.
In PET scanner, the goal is to detect the two nearly back-to-back photons from the annihilation of the positron with a tissue electron. However, before the photons get to the detector they must pass through the patient, some of the photons will interact with the tissue. This attenuation of photons by the tissue is what measured in CT scanning. In PET scanning, attenuation is a problem that must be corrected. There are three interaction between the 511 KeV annihilation photons and the tissue-Rayleigh scattering, the photoelectric effect, and Compton scatter.

Operation

To conduct the scan, **a short-lived** radioactive tracer isotope, which decays by emitting a positron, which also has been chemically incorporated into a biologically active molecule, is injected into the living subject (usually into blood circulation). There is a waiting period while the active molecule becomes concentrated in tissues of interest; then the research subject or patient is placed in the imaging scanner. The molecule most commonly used for this purpose is fluorodeoxyglucose (FDG), a sugar, for which the waiting period is typically an hour.

As the radioisotope undergoes positron emission decay (also known as positive beta decay), it emits a positron, the antimatter counterpart of an electron. After travelling up to a few millimeters the positron encounters and annihilates with an electron, producing a pair of annihilation (gamma) photons moving in opposite directions. These are detected when they reach a scintillator material in the scanning device, creating a burst of light which is detected by photomultiplier tubes or silicon avalanche photodiodes (Si APD). The technique depends on simultaneous or coincident detection of the pair of photons; photons which do not arrive in pairs (i.e., within a few nanoseconds) are ignored.

Localization of the positron annihilation event

The most significant fraction of electron-positron decays result in two 511 keV gamma photons being emitted at almost 180 degrees to each other; hence it is possible to localize their source along a straight line of coincidence (also called formally the **line of response** or **LOR**). In practice the LOR has a finite width as the

emitted photons are not exactly 180 degrees apart. If the recovery time of detectors is in the picosecond range rather than the 10's of nanosecond range, it is possible to calculate the single point on the LOR at which an annihilation event originated, by measuring the "time of flight" of the two photons. This technology is not yet common, but it is available on some new systems.

Image reconstruction using coincidence statistics

More commonly, a technique much like the reconstruction of computed tomography (CT) and single photon emission computed tomography (SPECT) data is used, although the data set collected in PET is much poorer than CT, so reconstruction techniques are more difficult.

Using statistics collected from tens-of-thousands of coincidence events, a set of simultaneous equations for the total activity of each parcel of tissue along many LORs can be solved by a number of techniques, and thus a map of radioactivities as a function of location for parcels or bits of tissue (also called voxels), may be constructed and plotted. The resulting map shows the tissues in which the molecular probe has become concentrated, and can be interpreted by a nuclear medicine physician or radiologist in the context of the patient's diagnosis and treatment plan.

Combination of PET with CT and MRI

PET scans are increasingly read alongside CT or magnetic resonance imaging (MRI) scans, the combination ("co-registration") giving both anatomic and metabolic information (i.e., what the structure is, and what it is doing biochemically). Because PET imaging is most useful in combination with anatomical imaging, such as CT, modern PET scanners are now available with integrated high-end multi-detector-row CT scanners. Because the two scans can be performed in immediate sequence during the same session, with the patient not changing position between the two types of scans, the two sets of images are more-precisely registered, so that areas of abnormality on the PET imaging can be more perfectly correlated with anatomy on the CT images. This is very useful in showing detailed views of moving organs or structures with higher amounts of anatomical variation, such as are more likely to occur outside the brain.

Design Concept

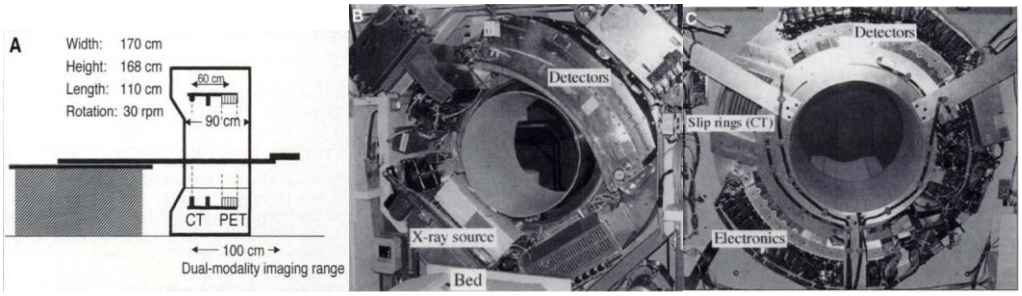

FIGURE 2. (A) Schematic of design concept of combined PET/CT scanner. PET components are mounted on aluminium disk attached to back of rotating CT scanner assembly. Centers of fields-of-view of PET and CT (vertical lines) are 60 cm apart. Combined PET/CT gantry is 110 cm deep, 170cm high, and 168 cm wide. PET and CT data can be acquired over 100 cm axial range of patient. (B) Front view of Somatom AR.SP CT scanner (and front of combined PET/CT scanner) showing x-ray tube housing and x-ray detector assembly. Part of patient bed pallet also is seen. Note that space between x-ray tube and x-ray detectors is insufficient to accommodate 2 opposing ECAT ART detector arrays. (C) View from rear of PET/CT gantry showing
PET detector arrays and electronics; ART detector electronics were rotated sideways 90Â°to fit within CT gantry dimensions. Mechanical slip rings of CT also are labelled.

The PET/CT scanner is based on the combination of a spiral CT scanner, (e.g. a Somatom AR.SP, Siemens, Iselin, NJ), with the PET components from a rotating partial-ring tomograph, (e.g. an ECAT ART scanner, Siemens). Both the PET and CT components are mounted on the same assembly, with the PET components on the reverse side of the rotating support of the CT scanner, as shown schematically in Figure 2A. The entire assembly is housed inside a single gantry, with the centres of the 2 tomographs offset axially by 60 cm. The bed is installed at the front of the combined gantry and is used for both the PET and CT imaging. Bed travel allows dual-modality PET and CT images to be acquired for an axial extent of 100 cm, sufficient to cover the range from chin to lower thigh in most patients. The CT is a third generation helical scanner, a Somatom AR.SP (Fig. 2B). Compared with single-slice CT, helical CT acquires multiple axial slices by a continuous motion of the patient bed. This results in shorter scan times and lower overall dose to the patient. The scanner has a metal ring M-CT 141 tube that produces x-ray spectra of 110 kVp or 130 kVp with a 6.5 mm Al-equivalent filter. The tube is operated with a flying spot, and, thus, 1024 detectors can be read from 512 xenon gas-filled Quantillarc chambers. The x-ray tube, cooling system, detectors, and readout electronics are all mounted on the rotating support of the CT scanner. The packing density of these components precludes the possibility to mount the PET detectors on the same side of the rotating support as the CT. Instead, the PET components are mounted to the rear of the CT support ring, on a separate aluminium annulus attached to the CT support. The PET components include the detectors and electronics, coincidence processor and the optically coupled data transmitters. An asynchronous motor rotates the entire assembly of PET and CT components at 30 rpm. The PET

detectors are standard ECAT ART components. The ECAT ART is a partial-ring, rotating tomograph comprising dual arrays of BOO block detectors. Each array consists of 11 blocks (transaxially) by 3 blocks (axially), covering an arc of 83Â°.The detector arrays are not symmetrically opposed (Fig. 2C) but are offset by 15Â°to increase the effective diameter of the transaxial field of view to 60 cm without requiring additional detector blocks. The detector blocks are 54 mm X 54 mm X 20 mm in size, cut into 8x8 crystals each of dimension 6.75 mm X 6.75 mm X 20 mm. Thus, the axial field of view is 16.2 cm (24 partial rings of 6.75 mm). Additional shielding of the PET components from out-of field activity is provided by arcs of lead, 2.5 cm thick, mounted on both sides of the detector assembly and projecting 8.5 cm into the field of view beyond the front face of the detectors. The entire rotating assembly is housed within a single gantry 170 cm wide and 168 cm high. As shown in Figure 2A, the overall tunnel length is 110 cm, with a 60 cm axial displacement between the centers of the CT and PET imaging fields of view. As a consequence of the extended length of the gantry, the tilt capability of the CT was disabled. A new, strengthened tunnel cover extending from the CT field of view to the rear gantry support was installed. The lasers for the PET imaging volume and the CT encoder are mounted on the outer surface of the cylindrical tunnel. The encoder operates optically, with a copper ring containing 2048 slots passing through the encoder slit. The position information of the x-ray tube is obtained from the number of angular pulses generated by the slotted ring running through the optical encoder light switch as the assembly rotates. The zero position of the x-ray tube is determined from an index slot on the encoder ring. The CT frequency controller was adjusted to take into account the slower acceleration of the gantry that was due to the additional load of the PET components. The positional information from the CT encoder is shared with the ART communication controller so that the lines of response (LORs) from the PET acquisition are correctly assigned in the sinogram. Power supply and data transfer to and from the PET and CT components follow separate paths. The input voltage for the x-ray tube is transformed from 110 V to 500 V outside the gantry and transmitted over mechanical slip rings. Power and serial communications to the ART components are transmitted over a different set of mechanical slip rings mounted with the ART detector arrays. High-speed digital data transfer from the ART is by optical transmission. As with the standard ART scanner, the combined PET/CT scanner rotates continuously, eliminating the need for additional gantry cooling for the PET components. Fans start automatically if, for any reason, gantry rotation is halted. The CT scanner is cooled by 2 fans in the upper corners of the gantry that operate at all times. The x-ray tube is oil cooled.

Bed Support

The Siemens CT bed and pallet, mounted to the front of the scanner as shown schematically in Figure 2A, is used to support the patient. Subjects up to 200 kg can be supported and positioned in the gantry to an accuracy of Â±0.5mm. To position the patient in both the CT and PET imaging fields, extended bed travel is required in addition to a support mechanism to prevent vertical deflection of the bed. The extended bed travel is required because of the 60 cm axial displacement between the CT and PET imaging fields of view. The use of an extended pallet allows an axial range of 100 cm (Fig. 2A) to be scanned by both CT and PET, sufficient to cover most patients from chin to upper thigh. To ensure accurate alignment between the 2 imaging modalities, the patient bed should be supported throughout the length of the tunnel.

Singles Transmission Sources

To allow the combined scanner to be operated as a PET scanner only, additional transmission sources were incorporated into this prototype design. Dual, 550 MBq 137Cssources are mounted at opposite ends of the 2 PET detector arrays and transmission data are acquired in singles mode. The availability of singles transmission sources also enables a comparison to be made between CT-based attenuation correction factors and standard PET attenuation correction factors.

PET/CT Image Processing

The CT and PET components of the combined scanner are operated independently from separate consoles. The Somatom CT console, a SUN workstation, is used for CT image acquisition and reconstruction, and it also can be used for image display and evaluation, such as measurements of tumor size. The 512 X 512 CT images are transferred over an Ethernet connection to the PET console, where combined PET/CT image processing is performed. The PET console comprises a 300-MHz UltraSparc processor with 1 Gbyte RAM, a 2 Gbyte local disk, and a 9 Gbyte external disk. Before PET image reconstruction, the emission sinogram data are corrected for scatter and attenuation. Attenuation correction is based on a rescaling of the CT image and scatter correction on a single scatter model. PET image reconstruction of the corrected 3-dimensional sinogram data is based on the Fourier rebinning algorithm FORE followed by 2-dimensional iterative reconstruction using the ordered-subset EM approach (OSEM) (/5). The specific implementation of the FORE + OSEM reconstruction procedure has been described elsewhere. The reconstructed PET and CT images are viewed in the pixel resolution (512 X 512) of the CT image on the PET console. A tool has been developed to display transverse, coronal, and sagittal sections of the PET and CT image volumes, either adjacently with linked cross-hairs

or in fused mode with the PET images superimposed on the CT images. For fused image display, an interlaced pixel approach is used with CT images in grayscale and the PET images superimposed in colour (hot metal). The display scale of each image in both separate and fused mode can be adjusted independently. Zooming and region-of-interest capabilities are also provided.

Radioisotopes

Radionuclides used in PET scanning are typically isotopes with short half lives such as carbon-11 (~20 min), nitrogen-13 (~10 min), oxygen-15 (~2 min), and Fluorine-18 (~110 min). These radionuclides are incorporated either into compounds normally used by the body such as glucose (or glucose analogues), water or ammonia, or into molecules that bind to receptors or other sites of drug action. Such labelled compounds are known as radiotracers. Some tracers distribute in tissues by partially following the metabolic pathways of their natural analogues; others bind with specificity in the tissues containing the particular receptor proteins for which they have affinity. It is important to recognize that PET technology can be used to trace the biologic pathway of any compound in living humans (and many other species as well), provided it can be radiolabeled with a PET isotope. Thus the specific processes that can be probed with PET are virtually limitless, and radiotracers for new target molecules and processes are being synthesized all the time; as of this writing there are already dozens in clinical use and hundreds applied in research. Due to the short half lives of most radioisotopes, the radiotracers must be produced using a cyclotron and radiochemistry laboratory that are in close proximity to the PET imaging facility. The half life of Fluorine-18 is long enough such that Fluorine-18 labeled radiotracers can be manufactured commercially at an offsite location.

Acquisition Protocols for Clinical Imaging

For clinical imaging, a typical PET/CT acquisition protocol begins with a 260 MBq injection of FDG and a 60 min uptake period. The patient is positioned in the scanner with the first transaxial section to be imaged aligned with the field of view of the CT. An initial scout scan (topogram) is performed to determine the axial range of the spiral scan. The maximum axial extent of a single spiral scan depends on the defined slice width and pitch. The total axial length to be scanned is subdivided into contiguous, 15 cm long segments. The spiral scan of each segment typically takes about 40 s, and x-ray tube cooling sometimes may be required between segments.

Patients are asked to hold their breath during the CT scan. For patients who cannot hold their breath for 40 s, either shorter axial spiral are selected or the patients are instructed to breathe shallowly. The total time for the complete CT scan is 5-10 min. Once the spiral scans covering the full axial length are completed, the patient bed is moved to the start position of the multibed PET acquisition, and the PET scan is initiated. An emission scan time of 6-10 min per bed position is selected depending on the number of bed positions, resulting in a total PET scan duration of 45-60 min. Typically, an axial overlap of 4 cm is used between contiguous bed positions.

Limitations

The minimization of radiation dose to the subject is an attractive feature of the use of short-lived radionuclides. Besides its established role as a diagnostic technique, PET has an expanding role as a method to assess the response to therapy, in particular, cancer therapy, where the risk to the patient from lack of knowledge about disease progress is much greater than the risk from the test radiation.

Limitations to the widespread use of PET arise from the high costs of cyclotrons needed to produce the short-lived radionuclides for PET scanning and the need for specially adapted on-site chemical synthesis apparatus to produce the radiopharmaceuticals. Few hospitals and universities are capable of maintaining such systems, and most clinical PET is supported by third-party suppliers of radiotracers which can supply many sites simultaneously. This limitation restricts clinical PET primarily to the use of tracers labelled with F-18, which has a half life of 110 minutes and can be transported a reasonable distance before use, or to rubidium-82, which can be created in a portable generator and is used for myocardial perfusion studies. Nevertheless, in recent years a few on-site cyclotrons with integrated shielding and hot labs have begun to accompany PET units to remote hospitals. The presence of the small on-site cyclotron promises to expand in the future as the cyclotrons shrink in response to the high cost of isotope transportation to remote PET machines.

Because the half-life of F-18 is about two hours, the prepared dose of a radiopharmaceutical bearing this radionuclide will undergo multiple half-lives of decay during the working day. This necessitates frequent recalibration of the remaining dose (determination of activity per unit volume) and careful planning with respect to patient scheduling.

Image reconstruction

The raw data collected by a PET scanner are a list of **'coincidence events'** representing near-simultaneous detection of annihilation photons by a pair of detectors. Each coincidence event represents a line in space connecting the two detectors along which the positron emission occurred.

Coincidence events can be grouped into projections images, called sinograms. The sinograms are sorted by the angle of each view and tilt, the latter in 3D case images. The sinogram images are analogous to the projections captured by computed tomography (CT) scanners, and can be reconstructed in a similar way. However, the statistics of the data is much worse than those obtained through transmission tomography. A normal PET data set has millions of counts for the whole acquisition, while the CT can reach a few billion counts. As such, PET data suffer from scatter and random events much more dramatically than CT data does.

In practice, considerable pre-processing of the data is required - correction for random coincidences, estimation and subtraction of scattered photons, detector dead-time correction (after the detection of a photon, the detector must "cool down" again) and detector-sensitivity correction (for both inherent detector sensitivity and changes in sensitivity due to angle of incidence).

Filtered back projection (FBP) has been frequently used to reconstruct images from the projections. This algorithm has the advantage of being simple while having a low requirement for computing resources. However, shot noise in the raw data is prominent in the reconstructed images and areas of high tracer uptake tend to form streaks across the image.

Iterative expectation-maximization algorithms are now the preferred method of reconstruction. The advantage is a better noise profile and resistance to the streak artifacts common with FBP, but the disadvantage is higher computer resource requirements.

Attenuation correction: As different LORs must traverse different thicknesses of tissue, the photons are attenuated differentially. The result is that structures deep in the body are reconstructed as having falsely low tracer uptake. Contemporary scanners can estimate attenuation using integrated x-ray CT equipment, however

earlier equipment offered a crude form of CT using a gamma ray (positron emitting) source and the PET detectors.

While attenuation corrected images are generally more faithful representations, the correction process is itself susceptible to significant artifacts. As a result, both corrected and uncorrected images are always reconstructed and read together.

2D/3D reconstruction: Early PET scanners had only a single ring of detectors, hence the acquisition of data and subsequent reconstruction was restricted to a single transverse plane. More modern scanners now include multiple rings, essentially forming a cylinder of detectors.

There are two approaches to reconstructing data from such a scanner: 1) treat each ring as a separate entity, so that only coincidences within a ring are detected, the image from each ring can then be reconstructed individually (2D reconstruction), or 2) allow coincidences to be detected between rings as well as within rings, then reconstruct the entire volume together (3D).

3D techniques have better sensitivity (because more coincidences are detected and used) and therefore less noise, but are more sensitive to the effects of scatter and random coincidences, as well as requiring correspondingly greater computer resources.

Applications:

PET is both a medical and research tool. It is used heavily in clinical oncology (medical imaging of tumors and the search for metastases), and for clinical diagnosis of certain diffuse brain diseases such as those causing various types of dementias. PET is also an important research tool to map normal human brain and heart function.

PET is also used in pre-clinical studies using animals, where it allows repeated investigations into the same subjects. This is particularly valuable in cancer research, as it results in an increase in the statistical quality of the data (subjects can act as their own control) and substantially reduces the numbers of animals required for a given study.

While some imaging scans such as CT and MRI isolate organic anatomic changes in the body, PET scanners, like SPECT are capable of detecting areas of molecular biology detail (even prior to anatomic change). The PET scanner does this via the

use of radiolabelled molecular probes that have different rates of uptake, depending on the type and function of tissue involved. The changing of regional blood flow in various anatomic structures (as a measure of the injected positron emitter) can be visualized and relatively quantified with a PET scan.

PET is a valuable technique for some diseases and disorders, because it is possible to target the radio-chemicals used for particular bodily functions.

1. **Oncology:** PET scanning with the tracer fluorine-18 (F-18) fluorodeoxyglucose (FDG), called FDG-PET, is widely used in clinical oncology. This tracer is a glucose analog that is taken up by glucose-using cells and phosphorylated by hexokinase (whose mitochondrial form is greatly elevated in rapidly-growing malignant tumours). A typical dose of FDG used in an oncological scan is 200-400 MBq for an adult human. Because the oxygen atom which is replaced by F-18 to generate FDG is required for the next step in glucose metabolism in all cells, no further reactions occur in FDG. Furthermore, most tissues (with the notable exception of liver and kidneys) cannot remove the phosphate added by hexokinase. This means that FDG is trapped in any cell which takes it up, until it decays, since phosphorylated sugars, due to their ionic charge, cannot exit from the cell. This results in intense radiolabeling of tissues with high glucose uptake, such as the brain, the liver, and most cancers. As a result, FDG-PET can be used for diagnosis, staging, and monitoring treatment of cancers, particularly in Hodgkin's disease, non Hodgkin's lymphoma, and lung cancer. Many other types of solid tumors will be found to be very highly labeled on a case-by-case basis--a fact which becomes especially useful in searching for tumor metastasis, or for recurrence after a known highly-active primary tumor is removed. Because individual PET scans are more expensive than "conventional" imaging with computed tomography (CT) and magnetic resonance imaging (MRI), expansion of FDG-PET in cost-constrained health services will depend on proper health technology assessment; this problem is a difficult one because structural and functional imaging often cannot be directly compared, as they provide different information. Oncology scans using FDG make up over 90% of all PET scans in current practice.
2. **Neurology:** PET neuroimaging is based on an assumption that areas of high radioactivity are associated with brain activity. What is actually measured indirectly is the flow of blood to different parts of the brain, which is generally

believed to be correlated, and has been measured using the tracer oxygen-15. However, because of its 2-minute half-life O-15 must be piped directly from a medical cyclotron for such uses, and this is difficult. In practice, since the brain is normally a rapid user of glucose, and since brain pathologies such as Alzheimer's disease greatly decrease brain metabolism of both glucose and oxygen in tandem, standard FDG-PET of the brain, which measures regional glucose use, may also be successfully used to differentiate Alzheimer's disease from other dementing processes, and also to make early diagnosis of Alzheimer's disease. The advantage of FDG-PET for these uses is its much wider availability. PET imaging with FDG can also be used for localization of seizure focus: A seizure focus will appear as hypometabolic during an interictal scan. Several radiotracers (i.e. radioligands) have been developed for PET that are ligands for specific neuroreceptor subtypes such as [^{11}C] raclopride and [^{18}F] fallypride for dopamine D2/D3 receptors, [^{11}C]McN 5652 and [^{11}C]DASB for serotonin transporters, or enzyme substrates (e.g. 6-FDOPA for the AADC enzyme). These agents permit the visualization of neuroreceptor pools in the context of a plurality of neuropsychiatric and neurologic illnesses. A novel probe developed at the University of Pittsburgh termed PIB (Pittsburgh Compound-B) permits the visualization of amyloid plaques in the brains of Alzheimer's patients. This technology could assist clinicians in making a positive clinical diagnosis of AD pre-mortem and aid in the development of novel anti-amyloid therapies.

3. **Cardiology, atherosclerosis and vascular disease study:** In clinical cardiology, FDG-PET can identify so-called "hibernating myocardium", but its cost-effectiveness in this role versus SPECT is unclear. Recently, a role has been suggested for FDG-PET imaging of atherosclerosis to detect patients at risk of stroke.
4. **Neuropsychology / Cognitive neuroscience:** To examine links between specific psychological processes or disorders and brain activity.
5. **Psychiatry:** Numerous compounds that bind selectively to neuroreceptors of interest in biological psychiatry have been radiolabeled with C-11 or F-18. Radioligands that bind to dopamine receptors (D1,D2, reuptake transporter), serotonin receptors (5HT1A, 5HT2A, reuptake transporter) opioid receptors (mu) and other sites have been used successfully in studies with human subjects. Studies have been performed examining the state of these receptors in patients compared to healthy controls in schizophrenia, substance abuse, mood disorders and other psychiatric conditions.

6. **Pharmacology:** In pre-clinical trials, it is possible to radiolabel a new drug and inject it into animals. The uptake of the drug, the tissues in which it concentrates, and its eventual elimination, can be monitored far more quickly and cost effectively than the older technique of killing and dissecting the animals to discover the same information. PET scanners for rats and non-human primates are marketed for this purpose. The technique is still generally too expensive for the veterinary medicine market, however, so very few pet PET scans are done. Drug occupancy at the purported site of action can also be inferred indirectly by competition studies between unlabeled drug and radiolabeled compounds known apriori to bind with specificity to the site.

Thus we can see that PET/CT offers the duel benefits of PET's metabolic information with the anatomical precision of CT. The two techniques presents different types of information about human body taking the two scans virtually simultaneously ensures that the patient remains in place and therefore, that the two images form a precise computer overlay that the tumour “hot spot” on the PET scan correspondence directly to the physical mass on the CT scan. This fused provided more reliable alternative to the traditional side by side visual comparison of PET and CT images. PET/CT also eliminates the common problem of delay between the two studies during which time the patient's condition may change.

Oncology indications for 18F-FDG-PET/CT includes but are not limited to the following:

A) Differentiating benign from malignant lesion
B) Searching for an unknown primary tumour when metastatic disease is discovered as the first manifestation of cancer or when the patient presents with paraneoplastic syndrome.
C) Staging known malignancies
D) Monitoring the effect of therapy on know malignancies.
E) Determining whether residual abnormalities detected on physical examination or on other imaging studies after treatment, represent tumour or post treatment fibrosis or necrosis.
F) Detecting tumours recurrent, especially in presence of elevated leaves of tumours markers
G) Selecting the region of a tumours most likely to yield diagnostic information for biopsy
H) Guiding radiation therapy planning.

The US FAD has approved the use of PET in the diagnosis, staging and restaging of non-small cell lung cancer head and neck cancer, Oesophagus cancer, colorectal cancer, melanoma, lymphoma; initial staging of cervical cancer; staging and restaging of breast cancer for characterization of solitary pulmonary nodule, in thyroid cancer when iodine scan is negative and serum thymoglobulin leaves are high and for diagnosis in unknown primary cancers. PET is also being used in other cancer like brain tumour, GIST (gastro-intestinal stromal tumour), ovarian cancer, sarcoma, uterine cancer, hepatocelluler cancer, pancreatic cancer cholangiocarcinoma, testicular cancer and small call lung cancer.

PET/CT imaging has rapidly emerged as an important imaging tool in oncology. The success of PET CT imaging is based on several features. First patient benefit from a comprehensive diagnostic anatomical and functional (molecular) whole body survey in a single session. Second, PET/CT provides more-accurate diagnostic information that PET or CT alone. Third PET/CT allows radiation oncologist to use the functional information provided by PET scans for radiation treatment planning.

Numerous studies have evaluated the use of FDG-PET for monitoring tumour response to chemotherapy and radiotherapy. These studies have shown that residual FDG uptake after completion for therapy is strong predictor of patient survival in malignant lymphomas and several solid tumours. Studies have also indicated that in responding tumours FDG uptake decreases markedly with in the first chemotherapy cycle (i.e. 34 weeks after the start of therapy). Conversely, the absence of a measurable decrease in tumour FDG uptake after the first chemotherapy cycle has been found to predict lack of tumour shrinkage and poor patient survival. This result suggests that FDG-PET could be used to identify nonresponsive tumours early in the course of therapy, and do adjust treatment regimens according to the individual chemosensitivity of the tumour tissue.

Traditionally, treatment planning in radiation oncology has been based on the result of CT and MRI. PET has the potential to delineate gross tumour volume (GTV) with a higher accuracy with reduced inter-observer variability.

PET/CT provides multiple exciting new opportunities to integrate functional and morphological information for tumour staging, radiation treatment planning and monitoring of tumour response to therapy. Most importantly, however PET/CT

imaging greatly facilitates the integration of PET in clinical practice and medical research.

Future developments

The current PET/CT designs from the major manufacturers comprise a commercial CT scanner in tandem with a commercial PET scanner. The level of physical integration is actually less than that of the original prototype where the CT and PET components were mounted on the same rotating support. Based on the positive clinical experience with PET/CT at UPMC and other institutions, there is going to be a demand for a reduction in cost of these devices and for a greater level of integration. This may obviously be achieved through the design of a scanner specifically for combined anatomical and functional imaging, rather than combining separate CT and PET scanners, as in the current approaches. By avoiding the duplication of data acquisition and image reconstruction functions, for example, a more integrated design should also allow cost savings over current commercial PET/CT scanners. The goal is then to design and build a device specifically for imaging the function and anatomy of cancer in the most informative and effective way, without conceptualizing it as combined PET and CT. The development of devices specifically for imaging a particular disease (e.g. cancer) differs from the conventional approach of, for example, an all-purpose anatomical imaging device such as a CT scanner. This new concept relates more to a disease management approach than the usual subdivision into medical specialties such as radiology and nuclear medicine. For such an approach to succeed, the new designs must be cost-effective and reliable [9]. The rapidly increasing use of functional imaging such as PET in areas that have traditionally been dominated by anatomical imaging modalities will demand reliable and easy-to-use PET/CT scanners that can achieve high throughput. The recent introduction of fast scintillators such as LSO and GSO for PET detectors is occurring at just the right moment for PET/CT where a reduction in the lengthy PET imaging time is required, more closely matching that of the CT. While it is unlikely that the PET imaging time will be reduced to the 30–60 s or so required for CT scanning, an order of magnitude reduction is to be expected with new high-performance LSO detectors. For example, it is anticipated that an LSO scanner with integrated CT could achieve an overall whole-body scan time of less than 10 min. Such a scanner would represent a breakthrough in cancer imaging, eliminating problems of patient movement and substantially reducing artefacts due to respiration. Throughput would increase, as would patient comfort and convenience. New applications, such as dynamic whole-body scans and the use of short-lived radioisotopes (e.g. 11C) would then be within reach. Future developments in

combined PET/CT scanners will be exciting, attaining a higher level of integration and anatomical and functional imaging performance than ever before. By playing an important role, not only in diagnosis and staging of cancer, but in designing and monitoring appropriate therapies, the combined PET/CT scanner will have a significant impact on patient care, survival and quality of life.

Further reading

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2. D W Townsend 2004 From 3-D Positron Emission Tomography to 3-D Positron Emission Tomography/Computed Tomography: What Did We Learn? *Molecular Imaging and Biology* **6.**

3. PET and PET-CT in Oncology by P. Oehr, H. J. Biersack R. Edward Coleman (Publisher Springer).

4. *Clinical PET and PET/CT by H. Jadvar, J. Anthony Parker* (Publisher-Springer).

5. *PET-CT in Radiotherapy Treatment Planning by Arnold C Paulino.* (Publisher-Elsevier Health Sciences)