PET-3

PET-CT: A NEW ERA OF HYBRID IMAGING TECHNOLOGY- TODAY & TOMORROW

HISTORY

The origins of nuclear medicine stem from many scientific discoveries, most notably the discovery of x-rays in 1895 and the discovery of "artificial radioactivity" in the mid-1930s. A landmark event for nuclear medicine occurred in 1946 when a thyroid cancer patient's treatment with radioactive iodine led to complete disappearance of the patient's cancer. Wide-spread clinical use of nuclear medicine, started in the early 1950s as its use increased to measure the function of the thyroid and to diagnose thyroid disease and for the treatment of patients with hyperthyroidism.

During the mid 1960s, the use of nuclear medicine as a specialty discipline began to see exciting growth with significant advances in nuclear medicine technology. The 1970s brought the visualization of additional organs (besides the thyroid) with nuclear medicine, including liver and spleen scanning, brain tumor localization, and studies of the gastrointestinal track. The 1980s saw the use of nuclear medicine for diagnosing heart disease as well as the integration of digital computers to add additional power to the technique. Today, there are approximately 100 different nuclear medicine imaging procedures which provide information about nearly every organ system. Nuclear medicine is now an integral part of patient care and is extremely valuable in the early diagnosis, treatment and prevention of numerous medical conditions.

Dr. Marshall Brucer, also a "founding father" of nuclear medicine, had tremendous influence on the development of this rapidly expanding discipline. He was the first president of the Society of Nuclear Medicine, the world's largest organization of nuclear medicine professionals.

Hal Anger revolutionized the field of nuclear medicine with his development of the gamma camera in the late 1950s.

The concept of emission and transmission tomography was introduced by David Kuhl and Roy Edwards in the late 1950s. Their work later led to the design and construction of several tomographic instruments at the University of Pennsylvania.

In the 1970s, Tatsuo 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.

Conventional imaging technology compress the 3-dimensional (3D) distributions of radiotracers into a 2-dimensional image. As a result, the contrast between areas of interest and the surrounding territory is often significantly reduced. This reduction limits the diagnostic information that is available in the study. In addition, the exact location of an abnormality can be difficult to determine. Tomographic images remove these difficulties but at the price of longer acquisition times, poorer spatial resolution, and the susceptibility to artifacts. Recent advances in SPECT instrumentation and processing have made marked improvements in each of these areas.

Diagnosing, staging, and re-staging of cancer, as well as the planning and monitoring of cancer treatment, have traditionally relied heavily on anatomic imaging with computed tomography (CT) or magnetic resonance imaging (MRI). These anatomic imaging modalities provide exquisite anatomic detail and are invaluable, especially for guiding surgical intervention and radiotherapy. However, they do have limitations in their ability to characterize tissue reliably as malignant or benign. Anatomic imaging generally has a high sensitivity for the detection of obvious structural alterations (e.g. enlarged structures, abnormal imaging characteristics) but a low specificity for further characterizing these abnormalities as malignant or benign. Necrotic tissue, scar tissue, and inflammatory changes often cannot be differentiated from malignancy based on anatomic imaging alone. In addition, lymph nodes which are not pathologically enlarged by size criteria alone but are harboring malignant cells pose a special diagnostic problem when using traditional cross-sectional imaging.

Therefore, much effort has been forth in the research and development of molecular imaging techniques to detect abnormal behavior of tissues. The nuclear medicine community has developed positron emission tomography (PET) for imaging the activity of an injected radionuclide labeled glucose analogue, Fluorine-18-deoxyglucose (FDG), as a means to discriminate benign from malignant tissues accurately in many clinical settings. This technique is based on the fact that malignant tissue typically exhibits markedly increased rates of glucose metabolism.

In the past decade, functional imaging with ^{18}F-FDG PET has been the fastest growing diagnostic modality in oncology. The high sensitivity for depicting increased metabolism in a wide variety of malignancies adds significant accuracy to many diagnostic regimens compared

with anatomic imaging only (CT, MRI, ultrasound). For several reasons, anatomic and functional imaging has been integrated into one diagnostic modality that is known as image fusion.(5)

DEVELOPMENTS

TYPES OF SCANNERS

Single Photon Detection. Positron-emitting radiopharmaceuticals can be imaged with a single photon system. One of the photons from the positron annihilation can be detected using a standard Anger gamma camera equipped with a collimator. Either planar or single photon emission computed tomography (SPECT) may be used. Single photon detection has the advantage that it is possible simultaneously to collect data from more than one radioisotope, by using multiple pulse height analyzers. For example, fluorine-18 labeled FDG data, and Tc-99mlabeled sestamibi could be used simultaneously to collect myocardial metabolism and perfusion. Simultaneous data acquisition means that the distribution of the two pharmaceuticals is sampled at exactly the same time with the organ of interest in exactly the same position.
Although simultaneous measurement of two radiopharmaceuticals is a major advantage, both planar and SPECT imaging at 511 keV have considerably poorer resolution than PET imaging.

Dual-Use Cameras: Anger cameras with dual heads can be used to collect PET data if they are equipped with coincidence circuitry so that they can identify the two simultaneous annihilation photons. The major difference in configuration between this type of data collection and single photon data collection is that there is no need for a standard collimator. These types of scanners can be used for both SPECT and PET data collection, so they have often been called dual-use cameras. Since coincidence circuits must be added to the SPECT system, this method has also been referred to as coincidence detection; however, this property does not distinguish them from the other PET systems. Many other names have also been used to describe this type of PET camera, e.g., dual-head coincidence detection. One of the major advantages of the dual-use cameras is that the addition of coincidence circuitry to a SPECT camera is relatively inexpensive. Thus, it is possible to add a PET capability to a nuclear medicine department at a much lower cost than is necessary when purchasing a dedicated PET scanner. When starting up PET service, the volume may not be sufficient to purchase a dedicated camera, and a dual-use camera provides a method for introducing the PET technology. The disadvantage of dual-use systems is that the resolution is lower; and even more importantly, the count rate is much lower. As a rule of thumb, dedicated PET scanners can detect many lesions of about 7 mm with

good sensitivity; dual-use cameras require lesions to be about 15 mm for the same detection sensitivity. In many instances, that difference is very important clinically. Although start-up of PET service was a very important niche for dual-use cameras as PET was becoming more wide spread, currently PET volume is such that reasonably sized nuclear medicine practices can move directly to dedicated PET systems.

Major technologic milestones in the development of PET include the discovery of faster and brighter scintillators such as lutetium oxyorthosilicate (LSO), gadolinium oxyorthosilicate, and lutetium yttrium oxyorthosilicate. Furthermore, the continuing development of the detectors, progressing from one-to-one scintillator–to–photomultiplier-tube (PMT) coupling (8,9) to advanced block and Anger readout schemes, helps to limit the costs of a PET scanner by providing a multiplexed readout and reduced electronic channels (10–13).

The use of faster scintillators enabled the transition from 2-dimensional data acquisitions for whole-body PET, using lead or body PET, using lead or tungsten collimators as septa (14–16), to 3-dimensional (3D) acquisitions (17). However, approximately an 8-fold increase in detection sensitivity is accompanied by an increased fraction of random and scattered photon events leading to degradation of image quality if not corrected during image reconstruction (18). This degradation effectively reduces the increase in sensitivity from a factor of 8 to approximately 5-fold. To achieve high-quality and quantitative PET data, various image reconstruction techniques have evolved (19). One simple approach is filtered back projection, which is computationally fast but results in poor image quality if the count statistics of the available PET data are inadequate. Better image quality and improved spatial resolution are achieved by iterative methods such as ordered-subset expectation maximization or maximum-likelihood expectation maximization algorithms (20) together with a posteriori information. Iterative algorithms use the underlying physical model of the scanner to implement geometric factors and corrections for photon scatter and detector penetration (21–23). However, iterative reconstruction approaches are much more computationally intense than filtered backprojection and do not necessarily converge. Appropriate corrections for dead time, detector normalization, photon scatter, random events, and in particular photon attenuation have been developed to obtain quantitative image data. Through the integration of these software and hardware advances, PET has matured as a technology, providing whole-body patient scans within 10–20 min with a spatial resolution of 4–7 mm in the reconstructed image. Because of its high sensitivity, the large variety of available probes, and the potential for development of new

biomarkers, PET is a powerful tool for clinical diagnosis and biomedical research. An important milestone in PET has been the introduction of multimodality imaging—in particular, combined PET/CT—to provide functional and morphologic information in a single patient scan (24,25).

The latest advances in molecular imaging technology, including PET, MRI, and optical imaging. In PET, significant improvements in tumor detection and image resolution have been achieved by introducing new scintillation materials, iterative image reconstruction, and correction methods. These advances enabled the first clinical scanners capable of time-of-flight detection and incorporating point-spread-function reconstruction to compensate for depth-of-interaction effects. In the field of MRI, the most important developments in recent years have mainly been MRI systems with higher field strengths and improved radiofrequency coil technology. Hyperpolarized imaging, functional MRI, and MR spectroscopy provide molecular information in vivo. A special focus of this review article is multimodality imaging and, in particular, the emerging field of combined PET/MRI. (4)

Although PET has invigorated nuclear medicine by initiating the field of clinical molecular imaging, MRI has also had a profound effect on the practice of radiology. The wide variety of imaging sequences, along with better soft-tissue contrast than that of CT, makes MRI an important diagnostic tool in the areas of cardiology, neurology, and oncology. In addition to the anatomic information delivered by MRI, MR spectroscopy provides spectral and therefore molecular information about tissue composition in vivo. More recently, 7- or even 9.4-T human scanners have been introduced that exhibit superb spatial resolution and a high signal-to-noise ratio (SNR).

These tomographs are especially of interest for studying the physiology of the human brain using functional MRI (fMRI) to visualize and quantify blood-oxygenation-level dependency (BOLD). Another important step was the improvement in radiofrequency coil technology; in this regard, at least for the preclinical field, cryo-coils have entered the market. A current focus of MRI research concentrates on functional imaging using hyperpolarized substances such as 13C or 19F.

In vivo molecular imaging tools include PET, MRI, SPECT, and optical imaging. MRI, PET, and SPECT have demonstrated great clinical value and utility, whereas clinical applications of optical imaging are still in their infancy. All modalities play an important role in preclinical

research, but there are some fundamental technical differences between clinical and preclinical imaging. Light does not propagate deeply in tissues, and therefore although whole-body imaging with optical technologies is possible for mice, it is not possible for humans. Therefore, throughout this review we will discuss each modality in the context of both preclinical and clinical applications. However, optical imaging in general, and PET and MRI in particular, have undergone the most significant technical advancements over the last few years, and we have therefore elected to focus primarily on these 2 modalities. In addition, we briefly describe the principles and advances in optical imaging and CT.

Taking the molecular imaging concept of PET one step further is the combined imaging modality positron emission tomography/computed tomography (PET/CT). PET/CT fuses functional information in the form of PET data and anatomic information in the form of CT data acquired almost simultaneously so that these information sets can be viewed and interpreted together. In PET/CT, both the multidetector CT apparatus and the PET detectors are mounted in the same gantry, one immediately behind the other. Both PET and CT scanning are performed with the patient lying in the same position on the imaging table resulting in optimal correlation of anatomic and metabolic information. For interpretation, the PET data is actually superimposed upon the CT data (co-registration) resulting in improved anatomic localization of normal and abnormal FDG activity.

This fusion process has proven beneficial in more exactly localizing tissues involved by tumor. Better co-registration is especially significant in regions of complex anatomy, such as in the abdomen and in the head and neck.

Diagnostic Effect

Improved lesion characterization and localization will result in increased diagnostic accuracy, which is recognized as a beneficial diagnostic effect. However, better accuracy in staging and restaging of disease is only relevant when it leads to changes in patient management (e.g., by decreasing the indication for invasive procedures). Also, improved lesion localization may lead to better results in other successive diagnostic procedures (e.g., easier CT-guided biopsy).

Effect on Therapy

PET images can be implemented in radiotherapy treatment planning and may be of particular value for high-precision techniques, such as intensity-modulated radiotherapy (IMRT). With IMRT, different dose prescriptions can be delivered to multiple target sites with extremely high dose gradients between tumor and normal tissues. This places demands on the ability of

conventional imaging techniques to localize and delineate tumors. PET scanning can detect additional lesions or may provide complementary information to facilitate the interpretation of equivocal CT findings (e.g., marginally enlarged lymph nodes). Consequent adjustments of the radiotherapy target volume will have a direct effect on the chances of cure, and on the risk and level of side effects and on complications.

In addition, functional PET imaging may identify tumors or regions within tumors with increased radio resistance. Examples are tumor hypoxia and areas of very active tumor cell proliferation that can be detected by specific tracers. A next step in the development of IMRT will be the integration of anatomic and functional information into a biologic target volume. Using the ability of IMRT to deliver nonuniform dose patterns, biologic dose conformality can be pursued, creating higher doses to areas of increased radio resistance, and lower doses in areas of high radio sensitivity.

Although hybrid PET/CT scanners are advertised extensively as the latest achievement in modern imaging technology and as "state-of-the-art" and "must-haves," independent research on real benefits has just begun.

Fig1:- PET-CT Scanner

IMAGE FUSION

Image fusion can be performed at 3 different levels: visual fusion, software fusion, and hardware fusion. In traditional visual image fusion, the physician compares 2 separate imaging modalities viewed next to each other. The fusion takes place in his or her mind. In soft- and hardware image fusion, the results of both procedures are overlaid in an integrated set of images. It is suggested that hybrid PET/CT scanner software fusion is far more superior.

Software for image fusion has been developed by various vendors and is universally applicable to all sorts of image sets. True hardware fusion of PET and CT does not exist at present. It would require the use of a single detector system that registers 2 image sets at the same time (e.g., 511-keV-rays from ^{18}F-FDG and x-rays from CT). An alternative solution is a combined device with separate CT and PET scanners positioned in line. Several companies adopted this principle, and so-called hybrid PET/CT scanners are now widely available commercially.

The limitations in separate CT and PET imaging may be compensated for when the 2 modalities are used in a complementary way. High-resolution anatomic information produced by CT adds significant information to tissue characterization delivered by PET.

WORKING AND DESCRIPTION OF VARIOUS COMPONENTS

Positron-emitting radionuclide are typically produced in cyclotrons by the bombardment of stable elements with protons, deuterons, or helium nuclei. The radionuclide produced have an excess of protons and thus decay by the emission of positrons. The positron-emitting radionuclide used for clinical whole-body PET/CT imaging is Fluorine-18-deoxyglucose (FDG).

In the FDG decay process, positrons are emitted. When a positron is emitted it travels for a short distance from the site of origin (on the order of 1-3 millimeters) gradually losing energy to the tissue through which it passes. When most of the positron's kinetic energy has been lost, it undergoes a process called annihilation. In annihilation, the positron reacts with an electron in the immediate area and the result is the emission of two very high energy (511 keV each) photons. The two 511 keV photons are emitted in opposite directions at approximately 180 degrees from each other. These two photons interact with the PET detector ring at near opposite sites which define a line within the body along which the annihilation occurred. With computer processing, this line between the two emitted photons permits fairly precise localization of the annihilation reaction and thus defines a tissue site in the body where the positron emission occurred (i.e. an area of FDG activity).

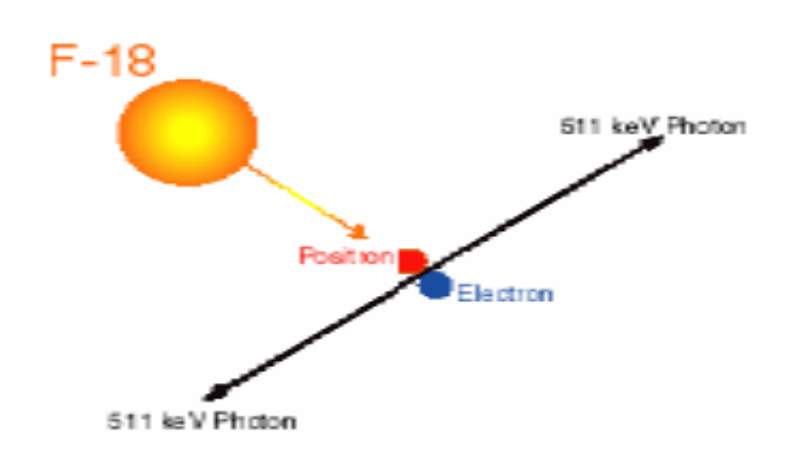

Fig 2: In order to decay by positron decay, an isotope must have at least 1.02 million electron volts (MeV) more energy than the isotope to which it decays. Isotopes that transition with less than this energy cannot undergo positron decay and will decay only by electron capture. Isotopes with enough 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.

The fact that the positron travels a short distance in tissue before the annihilation reaction occurs results in some degree of uncertainty about the exact location of its origin. In addition, the annihilation photons may actually be emitted at angles slightly different than the theoretical 180 degrees (up to 0.25 degree variation greater or less than 180).These limitations contribute to the inherent degradation of spatial resolution in all PET detector systems. However, even given these limitations, the spatial resolution in PET imaging is still superior to that seen in imaging with a gamma camera for other nuclear medicine examinations. Spatial resolution with PET imaging is on the order of millimeters compared to centimeters with standard gamma camera imaging.

POSITRON RANGE.

A positron does not undergo annihilation with tissue electron immediately after emission. First the positron follows a jagged path through the tissue as it interacts by producing ionization. The position of the positron-electron annihilation will be at some distance from the position of the decay. The average distance will depend on the initial energy of the positron and the composition of the tissue, particularly the tissue density. For example, the distance in lung tissue will be about three times the distance in soft tissue, since the density of lung tissue is

about one-third of soft tissue. The initial energy of the positron will vary depending on the distribution of energy between the positron and the neutrino. The path of the positron through the tissue will be governed by the statistical interaction probabilities. Thus, there will be a range of distances from the initial site. For low-energy positron emitters, such as fluorine-18, this distance in soft tissue is small. For high-energy positron emitters, such as rubidium-82, this distance will cause a noticeable loss of resolution.(1)

Table 1: Positron Range

Positron Emitter	*Max _+ Energy*	*Average Range*	Extrapolated range(mm)
F-18	0.64	0.64	2.3
C-11	0.96	1.03	3.9
N-13	1.19	1.32	5.1
O-15	1.72	2.01	8.0
Rb-82	3.35	4.29	16.5

COINCIDENCE DETECTION

The two nearly back-to-back gamma rays are key to positron emission tomography. If two detectors on opposite sides of the patient record an event at nearly the same time, then the annihilation event must have happened somewhere on a straight line between the two detectors. Two detectors are said to be "**in coincidence**" when the camera detects events in both detectors at nearly the same time. The collimator only allows rays that are traveling perpendicular to the detector to pass. Coincidence detection is different from single photon imaging; it does not need a collimator to make an image. Two points, the locations of the detectors, define the line-of-response along which the annihilation must have occurred. This straight line between the detectors is called the **line-of-response**.

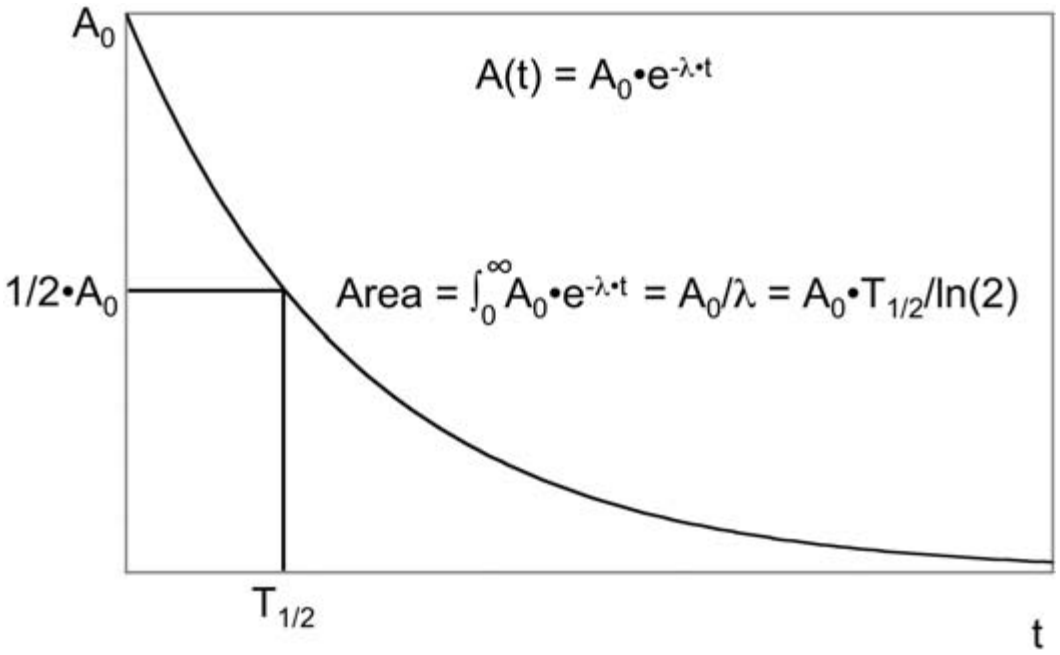

Fig3**:** Exponential Decay. The activity, A(t), during radioactive decay is an exponential function of time, t. At time equal to zero, the activity is equal to A0. The half-life, T1/2, is the time when the activity has decayed to one-half of the initial activity. The decay constant, λ, is equal to the natural logarithm of two, ln(2), divided by the half-life, T1/2. The area of the decay cure is A0/λ.

TYPES OF COINCIDENCE EVENTS

True Coincidence. Most of the description so far has dealt with true coincidence events. When the photons from an annihilation event reach crystals on either side of the ring and are detected as photo peak events, that event is called a true coincidence. However, there are other processes that will be recorded by the scanner as coincidence events that are not true coincidences.

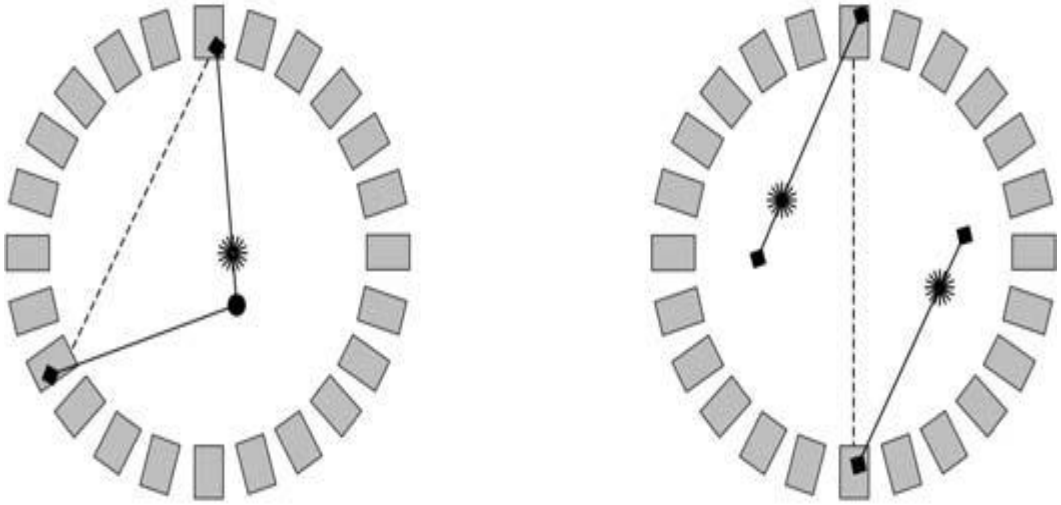

Fig4: Scatter and Random Coincidence. The diagram on the left shows an annihilation event where one of the photons is scattered in the patient. The recorded line-of-response (dashed line) is far from the location of the annihilation in this scenario. On the right, two annihilation events occur at approximately the same time. One of the photons from each annihilation event is absorbed in the patient. The other photons
produce a random coincidence. The line-of-response (dashed line) for this even does not pass near either of the true annihilations.

Scattered Coincidence. One or both of the 511-keV annihilation photons can undergo Compton scattering in the patient's body. As described above, the scattered photon has decreased energy and leaves in a direction that is different from the incoming photon. The energy of the scattered photon may be below the lower-level discriminator of the detector. In that case, Compton scatter affects attenuation. However, frequently the scattered photon has enough energy that the detector will record it as a photo peak event. If the other photon is also detected, then a coincidence event will be recorded; however, the line-of response will be miss-positioned. Compton scatter events will result in a loss of resolution (see Fig)

Random Coincidence. Because of geometry, attenuation, detector efficiency, limitations of the field-of-view, etc., the vast majority of the time only one photon reaches a detector. Thus, it is much more common to have a single event than a coincidence event. If two of these single events occur within the coincidence time of the camera, they will be recorded as a coincidence event even though these two photons have nothing to do with each other. Such an event is called a random coincidence. The diagram on the left of Fig shows a random coincidence.(2)

NON-COLINEARITY OF THE GAMMA RAYS.

Before the positron can combine with a tissue electron to form positronium, it must lose almost all of its energy. At that point it is said to be thermal, i.e., have about the same kinetic energy as

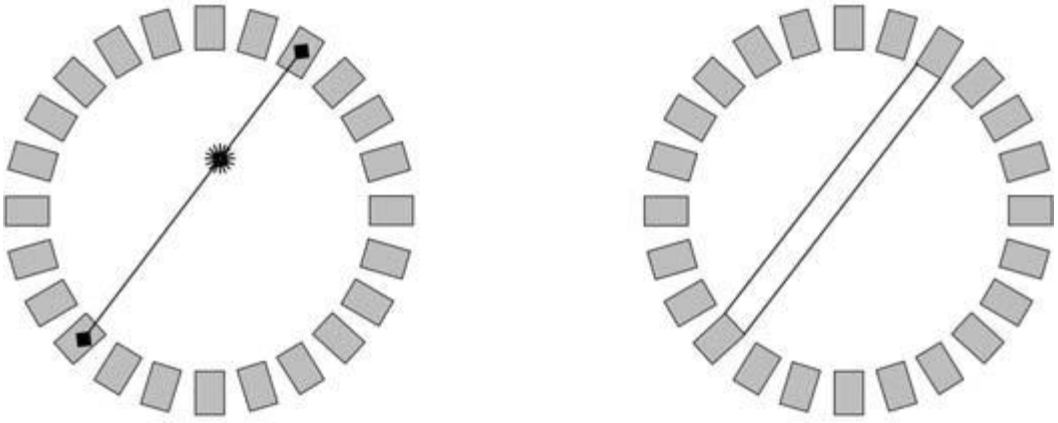

Fig5:- Coincidence Detection. The diagram on the left shows a positron annihilation resulting in two back-to-back photons, which strike crystals on opposite sides of the ring of detectors. The diagram on the right shows the area defined by two crystals. An annihilation from anywhere in this area could result in the two crystals' recording an event at nearly the same time. Outside of this area, it is not geometrically possible for the back-to-back photons to strike both crystals.

that due to the temperature of the tissue. Although the positronium is moving at thermal energies, the momentum of the positronium is not negligible. When it decays, the sum of the momentum of two photons must be the same as the positronium, and since photons have relatively little momentum compared to energy, this small momentum has an effect.

If the positronium was moving in the direction of one of the emitted photons, then that photon will have slightly higher energy than the other photon. The spread in the energy of the 511-keV photons can be detected with high resolution physics instruments but does not affect PET scanners (see Fig)

Mathematically, annihilation photons that are exactly back-to-back are called collinear. If the positronium was moving perpendicular to the annihilation photons, then the two photons would not be exactly 180 degrees apart. Due to conservation of momentum, the photons are slightly non-collinear. The average non-colinearity is typically on the order of less than one degree. For a ring the size of a normal whole body PET scanner, this results in a loss of resolution of 1–2 mm. In small animal, micro-PET scanners, a smaller ring diameter is important for achieving the highest resolution, but for clinical scanning, ring diameter is relatively unimportant in terms of resolution. The major effect of ring diameter in clinical PET is its effect on cost; a larger ring requires more components.(3)

INTERACTION OF THE ANNIHILATION PHOTONS WITH TISSUE

In a 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 and some of the photons will interact with the tissue. This attenuation of photons by the tissue is what is measured in CT scanning. In PET scanning, attenuation is a problem that must be corrected. There are three interactions between the 511-keV annihilation photons and tissue—Rayleigh scattering, the photoelectric effect, and Compton scatter

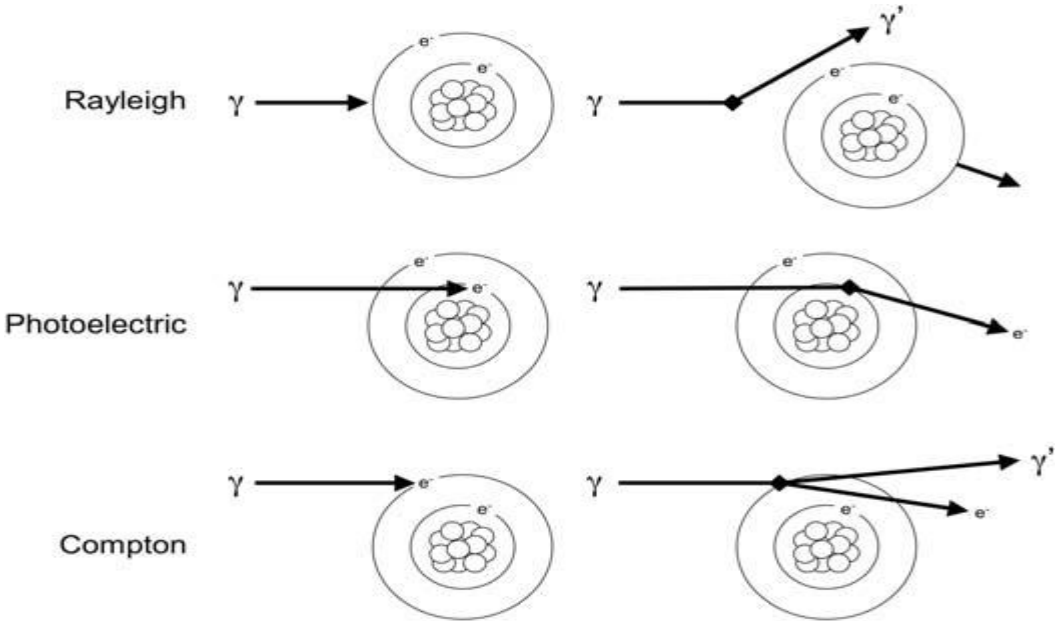

Fig6**:** Interaction of Radiation with Matter. There are three processes by which 511-keV photons can interact with matter. During Rayleigh, or coherent, scattering, the photon, γ, bounces off atoms in the matrix, changing direction with a tiny change in energy. During the photoelectric interaction, the photon is completely absorbed. An inner shell electron, e–, is ejected from an atom. During Compton, or incoherent, scattering, the energy of the incoming photon is partially absorbed. A scattered photon leaves with lower energy. An outer shell electron, e–, is ejected from the atom.

ATTENUATION CORRECTION

Attenuation is the loss of detection of true coincidence events because of their absorption in the body or due to their scattering out of the detector field of view. Attenuation problems are greater with PET imaging compared to traditional nuclear medicine SPECT imaging. Even though the photons are of greater energy than those used in SPECT imaging, in PET imaging two photons must escape the patient simultaneously to be detected as a true event and the mean photon path distance from emission to detection is greater with a PET camera than with a SPECT

camera. The loss of true coincidence event detection due to attenuation in PET imaging can range between 50 to 95%, especially great in a larger person.

Attenuation Equation. The number of photons attenuated in a length of tissue is proportional to the number of photons impinging on the tissue. This relation is analogous to radioactive decay, and the attenuation equation is analogous to the radioactive decay equation:

$I(x) = I_0 \cdot e^{-\mu \cdot x}$

where I(x) is the intensity of photons as a function of the distance, x, into the tissue; I_0 is the intensity at position x equal to zero; and μ is the **linear attenuation coefficient**. The linear attenuation coefficient is given by $\mu = \ln(2)/hvl$

where ln(2) is the natural logarithm of 2 (approximately 0.693), and hvl is the half-value-layer. The **half-value-layer** is the length of tissue over which the intensity of the photons drops to one-half.(1)

Loss of counts due to attenuation increases image noise, image artifacts, and image distortion. Without attenuation correction, significant artifacts which may occur on whole-body PET scans include: (a) prominent activity at body surface edges due to relative lack of attenuation at the surfaces compared to deeper structures, (b) distorted appearance of areas of intense activity (e.g. urinary bladder) due to variable degrees of attenuation in different directions of activity originating from these areas, and (c) diffuse, relatively increased activity in tissues of relatively low attenuation (e.g. lungs).Therefore, attenuation correction of data is necessary for accurate qualitative (i.e. visually normal, increased, or decreased) and quantitative (i.e. standardized uptake values or SUVs) measurements of FDG activity.

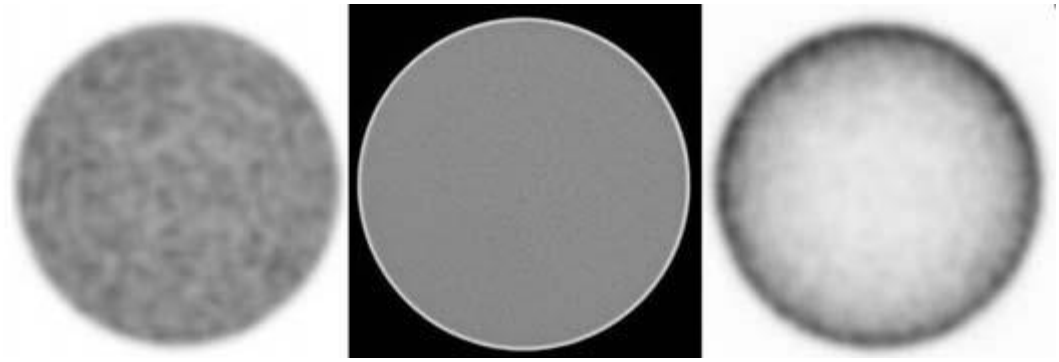

Fig7**:** Uniform Phantom. The image on the left is an attenuation-corrected image of a uniform phantom. The image in the center is a CT scan of the phantom. The bright edge is the wall of the phantom. The image on the right is a non-attenuation-corrected image of the same phantom.

Independence of Attenuation and Depth. Although the attenuation in PET imaging is high, there is a very important property of the attenuation—it is independent of the depth! Since both annihilation photons need to be recorded in order to detect an event, both photons need to escape the body without being attenuated.

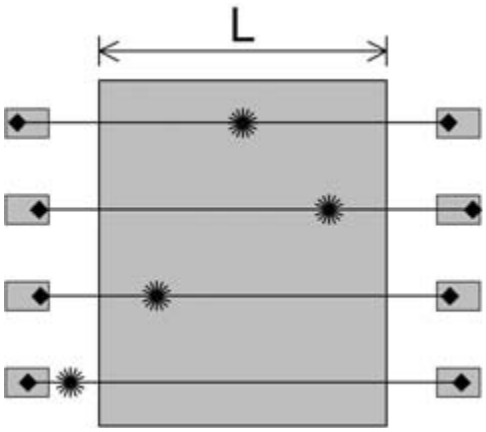

Fig8**:** Independence of Attenuation with Depth. The gray box represents a patient with a thickness of L. Irrespective of the depth of the positron annihilation; the sum of the paths of the two photons is equal to L. Even if a positron source is placed outside the body, as shown on the last row, the path is L.

As described above, the probability that both photons will escape the body is equal to the probability that a single photon will traverse the whole body. If an annihilation event occurs close to one side of the body, the photon on that side has little attenuation. The photon going the other way is highly attenuated. For an annihilation event on the same line-of-response close to the other side of the body, the attenuation of the photons will be reversed. No matter what, the total attenuation will be equal to one photon traversing the whole path. This relation is shown in Fig If an annihilation event occurs outside the body, then the single photon that goes through the body will also have the same attenuation as an annihilation event anywhere along the same line-of-response. Thus, a positron source placed outside the body can be used to measure the attenuation. The difference in measurements made before and after the patient is placed in the scanner is due to the attenuation of the patient.

Since the lines-of-response are determined geometrically, the lines-of response are not dependent on the separation between the detectors. To the extent that the gamma rays are back-to-back, the distance of the detectors from the patient does not affect the resolution. This lack of dependence on being close to the patient is another difference between single photon and PET cameras. In single photon scanning, **patient–detector distance** is an essential factor in good scan quality. Placing the collimator as close as possible to the patient is a key principle that cannot be over emphasized. However, in coincidence scanning, the patient–detector distance is relatively unimportant.

TYPES OF ATTENUATION CORRECTION CALCULATED ATTENUATION CORRECTION:

The attenuation can be calculated given the contour of the body. The length of the path through the body can be determined from the contour and the attenuation calculated. The contour can be obtained from a preliminary uncorrected reconstruction of the PET data. The outer limits can be drawn or determined from a threshold, and then the data can be reconstructed again using this contour. If the tissues within the body are relatively constant in attenuation, this method can work well. It is particularly applicable to the brain. It works least well in the chest where there are major differences in density between the lungs and the other tissues. The major advantage of using calculated attenuation is that the time and expense of measuring attenuation correction can be avoided.

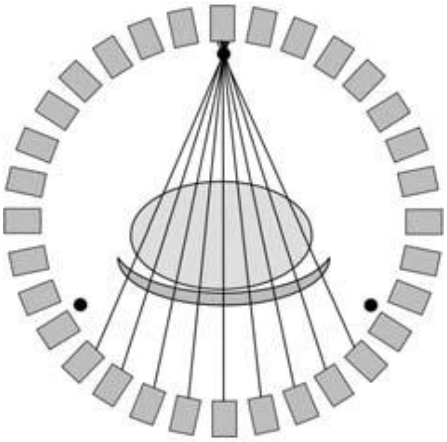

Fig9**:** Rod Sources. Three rod sources of germanium-68 are shown as black dots. (The rods are points in the plane of the crystal rings.) The lines of response that are measured by the top source are shown diagrammatically.

Pairs Transmission Scan: A point source of positrons outside the body can be used to measure the attenuation along each line-of response. This type of measurement is often called a **transmission scan**. By comparison, scanning of the radiopharmaceutical from within the patient is called an **emission scan**. For each line-of-response, a source outside the body has exactly the same total attenuation as the activity from any point in the body along that line-of response. The sources for pairs attenuation correction are made of germanium- 68. Germanium-68 has a 280-day half-life and decays by electron capture to gallium-68 without emitting a gamma ray. Gallium-68 has a 9.5-hour half-life and decays by positron emission. The annihilation radiation from the gallium- 68 is used to measure the attenuation. The germanium-68 is called a **rod source**. It is arranged as a rod in the axial direction; within each imaging

plane the germanium-68 is a point source. Fig shows three line sources as dots within the ring of the crystals. The lines-of-response for the line source at the top are shown.

CT: A PET/CT scanner combines a CT scanner with a PET scanner. The CT can provide anatomical information near the time of the PET imaging. In addition the CT scanner can be used to measure the attenuation information. Some of the cost of the CT scanner can be offset if the attenuation subsystem is not included in the PET scanner. The CT scan time is shorter than the singles transmission scan and much shorter than a pairs transmission scan. Thus throughput can be increased. A much higher photon flux is used during CT scanning than during single or pairs transmission scanning. Thus, very little statistical noise is added by attenuation correction with CT, especially when compared to the statistical noise added by singles or pairs attenuation correction.

In PET/CT x-rays from a CT scan are used to construct an attenuation map of density differences throughout the body that can then be used to correct for the absorption of the photons emitted from FDG decay. Attenuation is much more likely in the center of the body and therefore non-attenuation-corrected images will show diffusely lower level activity deep in the body compared to the skin surface. The attenuation correction process essentially “adds counts back” into areas that are more attenuated due to their being deeper or being surrounded by relatively dense structures. Similarly, it essentially “subtracts counts” from areas that are attenuated much less than all other tissues (e.g. lungs and body surfaces). Both attenuation-corrected and non-attenuation-corrected data sets are provided for review and both should be examined by the interpreter. Reviewing both data sets sometimes allows confirmation of an abnormality or confirmation of the benignity of a process which might have been incorrectly assessed based on review of one set alone.

Activity within tissue closely approximated to very high density material in the body may appear falsely high in intensity on attenuation-corrected data. For example, in correcting for attenuation by metallic density orthopedic hardware the computer may essentially “add” counts into tissues immediately adjacent to the hardware which could at times result in the false appearance of increased activity within tissue (e.g. a lymph node) closely approximated to the hardware. Close inspection of the CT data and the non-attenuation-corrected PET data should confirm that the apparent increase in activity within the lymph node in that example was art factual, related to the attenuation correction process. However, artifacts of activity related to the attenuation correction process can result in equivocal findings even after close inspection of all of the data.

Some lesions located near the surface of the body, such as skin lesions, are more obvious on non-attenuation-corrected data because of the generalized “subtraction” of counts from the surface related to absence of attenuation there compared to deeper structures. On close review, uptake in these lesions will usually be visible on the attenuation corrected data as well.

A disadvantage of CT-measured attenuation correction is that it is more difficult to translate the attenuation of polychromatic x-rays used in CT to the attenuation of 511-keV photons as described in the next section. Many PET/CT protocols collect a whole CT scan followed by a whole PET scan. The last images of the PET scan may be collected considerably later than the attenuation data. This delay can result in patient or physiologic motion between the two scans, which can also lead to errors in attenuation correction.

The ability to measure attenuation exactly in PET can be contrasted with SPECT. The attenuation in SPECT is directly related to the thickness of tissue along a ray from the source to the camera. There is no way directly to measure the attenuation from inside the patient. Instead it must be calculated. Furthermore, the primary SPECT data are the sum of sources at all different depths. Thus, the activity and the attenuation are mixed together. Correcting for attenuation is much more complicated in SPECT than in PET. The ability directly measure and correct for the attenuation for each line-of-response is the reason PET data has been known for its ability to produce quantitative measurements.

Importance of Attenuation. Attenuation of photons decreases with an increase in the energy of the photon. The linear attenuation coefficient for the 140-keV photon of Tc-99m is about 0.15 cm–1, and the coefficient for 511-keV annihilation photons is 0.096 cm–1. The first impression is that the effect of attenuation is less for PET imaging than for single photon imaging with Tc-99m. However, a PET scanner must detect both of the back-to-back photons, whereas with single photon imaging one needs only to detect one photon. Furthermore, when imaging an anterior organ using single photon imaging, an anterior image is used, and when imaging a posterior organ, a posterior image is used. In many instances the depth of the organ is only a few centimeters.

However, in PET imaging most of the photons need to traverse the entire thickness of the patient. The attenuation factor for Tc-99m’s 140-keV photon when imaging an organ that is 4 cm deep is about 0.5. The attenuation factor for a 511-keV photon across a body that is 30 cm thick is about 0.06.

“2D” and “3D” Imaging.

A single pair of small detectors detects annihilation reactions from an area defined by a small tube connecting the detectors. It only detects the coincidence pairs that are traveling nearly parallel to the axis of tube. In order to increase sensitivity, a large number of detectors from one side of the patient need to be put in coincidence with a large number of detectors on the opposite side. The detectors are often arranged in a series of rings. Each crystal in the ring is put in coincidence with an arc of crystals on the other side of the patient. The size of the arc determines the active area of the camera. Fig shows the lines-of-response within a plane of crystals. Often PET scanners are made from a stack of crystal rings. In that case, a crystal in one plane may be placed in coincidence with crystals from a few or many planes of rings.

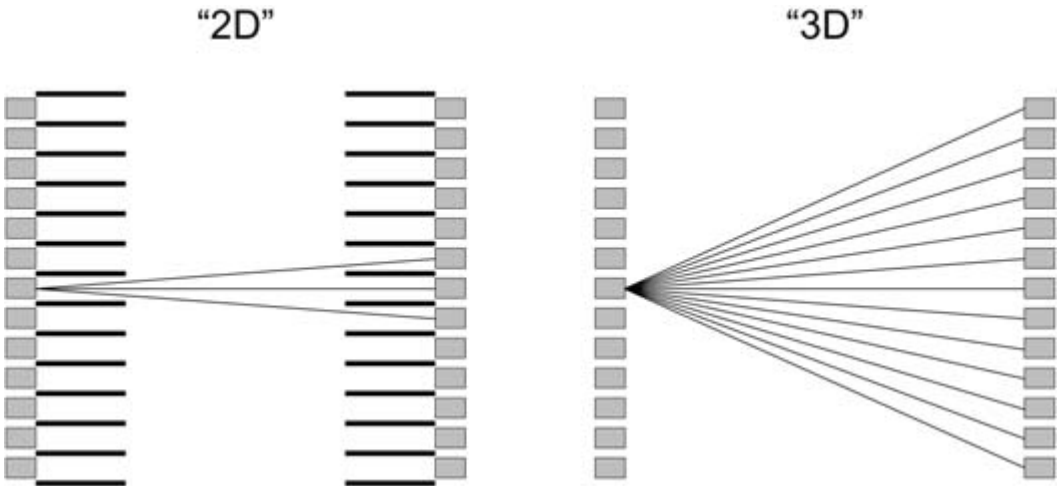

Fig10**:** Cross-Plane Coincidence. This diagram shows the cross-plane coincidence for “2D” and “3D” imaging modes. In “2D” mode, axial collimation is provided by septa shown as heavy dark lines. The septa limit the coincidence to a single plane or the next adjacent plane. In “3D” mode, with no axial collimation, a crystal can be placed “in coincidence” with all of the planes.

When a crystal is in coincidence with only crystals on the same or adjacent rings, the term “2D” imaging is used. When a crystal is in coincidence with crystals from all of the rings, the term 3D” imaging is used. Figure 20 shows the cross plane coincidences for a crystal in “2D” or “3D” mode. The terms “2D” and “3D” are misleading since modern multi-slice PET cameras always produce three-dimensional images of three-dimensional objects. Unfortunately, the terminology has become imbedded in common usage. With “2D” imaging, it is possible to use axial collimation between the slices. Annular tungsten plates centered between the detector rings extend toward the center of the scanner (see Figure 5). These plates stop photons that are not traveling in the plane of the detector ring. With “3D” imaging, these septa need to be removed. “3D” imaging is more sensitive than “2D” imaging, since many more lines-of-response are sampled.(7)

PET Detector. PET imaging utilizes a dedicated PET camera system which includes multiple rings of detectors. Similar to gamma cameras, the PET detectors consist of scintillation crystals coupled with photomultiplier tubes. The scintillation crystals used in clinical PET imaging are either bismuth germanium oxide (BGO), gadolinium oxyorthosilicate (GSO), or lutetium oxyorthosilicate (LSO).

The ring design utilizes the concept that two photons detected in close temporal proximity (on the order of 6 to 12 nanoseconds) by two opposed detectors in the ring are likely to have originated from a single annihilation event in the body, somewhere along a line between the two detectors. Such a simultaneous detection is termed a “coincidence”. All of the coincidence events detected during an imaging period are recorded by the PET computer system as a raw data set. As in single photon emission computed tomography (SPECT) examinations in nuclear medicine, the coincidence data in PET is reconstructed by a computer to produce cross-sectional images in the axial, sagittal, and coronal planes.

Because of photon attenuation and absorption in tissue, many annihilation events result in only one of the two photons reaching the detector, a so called “single event”. These single events are discarded by the PET processing computer. Even though a very large number of the overall photons incident upon the detectors (single events) must be discarded, the principle of coincidence detection provides a so-called “electronic collimation”. Because of this electronic collimation PET scanners are inherently much more efficient than gamma cameras with markedly improved count statistics (better signal to noise ratios) and thus have much better spatial resolution compared to gamma cameras.

State of the art PET scanners are full-ring systems that completely surround the patient. The cameras have multiple adjacent detector rings that allow for a relatively large field of view at each table position. For a fixed total scan time and standardized radiopharmaceutical dose, the large filed of view provided by multiple detector rings allows more time at each table position compared to smaller field of view systems and thus allows more total counts to be detected during an examination with resultant improved sensitivity and resolution.

Reconstruction Methods. The two main categories of reconstruction are Fourier reconstruction and iterative reconstruction. Filtered back-projection is a method that is often used to implement Fourier reconstruction. Fourier reconstruction assumes that the PET scan process has two mathematical properties, linearity and shift invariance. Iterative reconstruction

is more general; it only assumes that the PET scan process is linear. Thus, iterative reconstruction can model many more effects than Fourier reconstruction. The major advantage of Fourier reconstruction is much faster than a full iterative reconstruction. However, a relatively new iterative algorithm **ordered subset estimation maximization** (**OSEM**) ameliorates much of the time penalty of iterative versus Fourier reconstruction. The results produced by the ordered subset method produce results similar to the full estimation maximization algorithm in the domain of medical image reconstruction.

SCINTILLATION CRYSTAL EXAMPLES. Some of the key properties of a few scintillation crystals that can be used for PET scanners are:-

Sodium Iodide Doped with Thallium, NaI(Tl): NaI(Tl) is the workhorse for single photon imaging. The key property of NaI(Tl) is its high light output, yielding good energy and spatial resolution. The limitation of NaI(Tl) for PET scanning is its relatively poor stopping power.

Bismuth Germinate, BGO: For a long time BGO was used widely for PET scanning. The key property of BGO is its high stopping power. Its low light output is a disadvantage for single-photon imaging, and its relatively slow decay time is its major limitation for PET imaging.

Lutetium Oxyorthosilicate Doped with Cerium, LSO(Ce): LSO(Ce) is used in some PET scanners. It has good stopping power, although less than BGO. It has high light output, but the light output is variable. The key advantage of LSO(Ce) is a fast decay time. In addition to LSO(Ce), several other lutetium compounds have been investigated. For example, lutetium orthoaluminate, LuAlO3(Ce) or LuAp, is notable for its high stopping power.

Germanium Oxyorthosilicate Doped with Cerium, GSO(Ce): GSO(Ce) is also used in some PET scanners. It is similar to LSO(Ce). It has lower light output, but the light output is not variable. Again, the key advantage of GSO(Ce) is the fast decay time.

Cesium Fluoride, CsF, and Barium Fluoride, BaF2: These crystals with very fast decay times made possible the construction of time-of-flight PET scanners in the past. However, low light output and poor stopping power have kept them from being used recently.

Lanthanum Halides (LaCl3, LaBr3): These crystals have not been used for PET scanners; however, they have very good decay times and high light output. Sub-nanosecond coincidence times have been reported, raising the possibility of a time-of-flight scanner. The major disadvantage of these crystals is their relatively poor stopping power.(6)

PET-CT

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.

Approximately 30 to 60 minutes after intravenous FDG administration the patient is placed on the examination couch. The CT data is acquired first (lasting around 30 seconds) followed by a repeat slower transit of the patient through the bore for PET data acquisition (lasting around 30-45 minutes).

Simultaneous CT and PET imaging provides several distinct advantages over PET scanning alone, in which case PET images would typically be correlated with CT images acquired at a different time. Most importantly, acquiring the CT and PET data in very close temporal proximity with the patient in the same position on the imaging couch minimizes patient motion between the two acquisitions which allows more precise anatomic localization of FGD activity. This results in fewer equivocal findings, such as when activity can be determined as physiologic in nature rather than pathologic (e.g. excreted activity in a ureter rather than in an adjacent retroperitoneal lymph node). Another advantage of the combined modality is that a CT transmission scan provides more accurate and efficient attenuation correction compared to a transmission scan using a radioactive source as is typically used in dedicated PET systems not combined with CT. Also, total imaging times are shorter using CT transmission for attenuation correction rather than a radioactive transmission source.

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 centers 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.

The only other obstacle to a wider dissemination of PET-CT is the difficulty and cost of producing and transporting the radiopharmaceuticals used for PET imaging, which are usually extremely short-lived (for instance, the half life of radioactive fluor18 used to trace glucose metabolism (using fluorodeoxyglucose -- FDG) is two hours only. Its production requires a very expensive synchrotron as well as a production line for the radiopharmaceuticals.

PET RADIONUCLIDES

Radionuclide's 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 radionuclide 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 labeled compounds are known as radiotracers. Some 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 radio labeled 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 is 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.(7)

FUTURE PERSPECTIVE:-PET-CT

PET/CT imaging resolves the limitations of dedicated PET by making use of a rapid low-noise CT scan for attenuation correction, thereby improving image quality while decreasing patient discomfort and increasing patient throughput. PET/CT integrates functional (PET) and structural (CT) information into a single scanning session, improving lesion localization and interpretation accuracy. PET/CT is currently the most advanced technique of metabolic imaging and the most accurate tool for tumor staging in the pretreatment, post-treatment and follow-up phases. Progressive technological development of PET/CT scanners is foreseeable in the near future with an increase in the efficiency of detector crystals, the spatial resolution and a reduction in acquisition times of the emission images. As has already occurred over the past two years,

most PET centers tend to acquire PET/CT scanners and an increase in their availability is definitely foreseeable.

Today, work is concentrating on the use of PET for more specific oncology areas such as response to therapy applications and radiotherapy treatment planning. Although FDG has demonstrated certain success in areas such as these, the advent of new 18F radiopharmaceuticals, developed to probe particular molecular targets, are expected to be in the forefront of these new imaging applications. The requirements for the continuous success of PET in existing oncology applications, as well as its expansion in new specific oncology areas such as those mentioned above, are the development of more specific imaging molecules in combination with improvements in PET hardware and software technology. The goals for current PET technology developments have been an improvement in patient throughput coupled with increased diagnostic accuracy. The recognition of PET as the diagnostic tool of choice in other major cancers as well as the development of new oncology application areas will continue to impose requirements for higher patient throughput without an associated increase in cost. This requirement, coupled with the need for improved image quality and quantization for the accurate and detailed characterization of new radiopharmaceuticals, should dominate any future advancement in the PET technology arena. As such, these advancements will most certainly be concentrating on higher sensitivity devices. The present commentary concentrates on the current status and future developments in PET technology (excluding the area of radiopharmaceuticals) and how these developments may further influence the role of PET in clinical practice, particularly in the area of oncology.

A substantial body of evidence exists today on the accuracy of CT-based attenuation correction (CTAC) in PET. In terms of scaling the CT attenuation coefficients (energies of 70–80 keV) to those corresponding to PET (511 keV), a post-processing step such as scaling, segmentation or a combination of the two are currently implemented in clinical combined systems.(25) Studies carried out to date using such methodologies have demonstrated comparable quantitative accuracy combined with an improved signal to noise ratio in the reconstructed PET images compared with radioactive source-based attenuation corrections (26). Potential issues are associated with the presence of CT contrast agents or metallic implants, which can lead to image artifacts and compromise PET quantitative accuracy in those areas (26). Potential solutions include the use of post-acquisition processing steps, such as segmentation of areas with contrast or metallic objects and subsequent reclassification of the CT numbers in order to minimize such effects (27,28). In addition, artifacts present at the level of the diaphragm as a result of differences in respiration conditions between the two acquisitions, may be reduced by

using a "normal expiration and breath hold" CT acquisition protocol (29). Such a breath hold pattern however, may be difficult to achieve for some patient conditions. Although respiratory artifacts at the level of the diaphragm were more severe in early PET/CT systems utilizing a single slice CT scanner (30), they have been reduced with the introduction of multislice CT scanners (at least 4 slices), allowing whole body CT acquisitions of <30 s.

Future developments in combined PET/CT systems will include the use of state of the art multislice {16 to 32} CT scanners (31), allowing a more efficient dose utilization as well as submillimetre collimation for most imaging protocols. However, faster CT imaging times should not have a significant effect on combined PET/CT oncology investigations, as the present limiting factor is the time required to acquire PET whole body images of sufficient quality.

As already described up to this point, PET technology has in the past been continuously evolving with changes driven predominantly by clinical need and established oncology applications focusing on whole body imaging protocols. This trend should continue over the next few years, with developments concentrating on enhancing patient throughput and establishing new and more focused clinical applications. One such emerging clinical application currently attracting increased interest is the use of PET in radiotherapy treatment planning. Intensity-modulated conformal radiotherapy aims to deliver higher doses in the area of interest whilst simultaneously minimizing the dose to normal tissues. PET/CT systems can be the ideal instruments for radiotherapy treatment planning by providing exact anatomical localization of the area of interest in combination with an accurate delineation of the 3D functional volume to be treated. There are however, certain problems that need to be addressed before PET can become the gold standard in radiotherapy treatment planning. First, if combined PET/CT systems are to fulfill both roles of accurate localization and treatment volume delineation they need to be integrated in the treatment planning process. This involves establishing the CT component of the PET/CT scanner as the treatment simulation system by integrating with such systems a number of additional components. These include re-alignment lasers allowing the unification of the coordinate system of acquired CT datasets with the radiotherapy treatment systems, the incorporation of flat scanning beds as well as potentially larger patient ports. In addition, issues associated with misregistration of PET and CT datasets as well as inaccuracies in the delineation of functional volumes as a result of respiratory motion will have to be addressed. A proposed solution involves the acquisition of respiratory gated PET datasets, resulting in a number of frames corresponding to different points throughout the respiratory

cycle (32,33). The problem associated with this approach is that the resulting PET images are of reduced resolution since only a fraction of the available counts is used in each of the reconstructed frames. Future directions in addressing this problem will involve combining models that describe the movement of internal organs with reconstruction algorithms utilizing the patient specific respiratory motion information recovered from gated PET acquisitions.

Finally, in the area of combined imaging devices one should not forget the potential of combining PET and MRI devices, the principle of which has already been demonstrated few years ago through the development of a small scale system (34). Although a number of challenges will have to be met before such a system is scaled up for human studies, it is certainly possible that it may become a reality within the next few years.

As already mentioned earlier, research is continuing into new scintillator materials for PET. However, the performance of a PET system can be also strongly affected by the photo detector employed or the overall detector design itself. Requirements of an ideal detector design include the correct identification of crystal elements, preservation of crystal intrinsic energy resolution and finally, through the use of appropriate electronics, a fast timing response. Despite the domination over the past two decades of the block detector concept (35) in clinical PET systems, new detector designs are appearing. For example, in the case of the Philips AllegroTM there is a continuous light guide coupling the individual crystal elements with a pack of photomultiplier tubes (PMTs) which minimize the variation in light collection from different crystals, thus improving the energy resolution of the detector. In addition, flat panel detectors using a variant of the block detector known as "quadrant sharing design" are also emerging. This detector design has a better encoding ratio than the traditional block detector designs and can therefore resolve smaller crystals for a given PMT size, allowing an improvement in positional information without an associated loss in energy resolution and a large increase in the overall cost. Such small panel detectors have already been used in the construction of a research brain tomograph. A prototype whole body system based on 5 rotating panel LSO detectors (52 cm x 36 cm) has been also constructed. As a result of the large axial extent of this system in comparison with 15 cm in traditional ring designs, it has been suggested that this system will be able to perform whole body acquisitions in 5 min to 10 min without any compromise in image quality. If such a performance can be realized in routine clinical practice it will most definitely shape the future of PET technology.

Finally, in terms of new photo detectors and overall detector designs, a number of alternative technologies already employed in smaller scale animal PET scanners [36] may find their way in future clinical PET systems. These include the combination of small surface area crystal elements (<2 mm x 2 mm) in combination with new photo detectors such as position sensitive PMTs or Avalanche Photodiodes (APDs). A number of such detector designs may either form the basis of a combined PET/MRI system (as a result of the reduced sensitivity of such photo detectors in the presence of magnetic fields) or lead to improvements in resolution uniformity across a scanner's field of view.

In conclusion, major developments in PET technology have already played a major part in defining and establishing the role of this imaging modality in oncology. The introduction of PET/CT has further revolutionized and is in the process of refining this role. New software developments combined with the introduction of new scintillators and PET detector designs hold the potential to improve the throughput of this technique and open the way to new clinical applications. The present is bright but the future will certainly be exciting.

REFERENCES

1. H.Jadvar and J.A.Parker. Clinical PET and PET/CT October 2004
2. Cherry SR, Sorenson JA, Phelps ME. *Physics in Nuclear Medicine*. third edition ed. Philadelphia: Saunders, 2003.
3. Hill DL, Batchelor PG, Holden M, Hawkes DJ. Medical image registration. *Phys Med Biol* 2001; 46(3):R1–45.
4. Bernd J. Pichler, Hans F. Wehrl and Martin S. Judenhofer. Latest advances in molecular imaging instrumentation. Journal of Nuclear Medicine Vol. 49 No. Suppl_2 5S-23S
5. Nutt R. 1999ICP Distinguished scientist award: the history of Positron Emission Tomography.mol imaging Biol 2002;4:11-26
6. Surti S, Karp, J.S., Muehllehner, G., Raby, P.S. Investigation of Lanthanum Scintillators for 3-D PET. *IEEE Trans Nucl Sci* 2003; 50(3):348–354.
7. Phelps ME. Nuclear medicine, molecular imaging, and molecular medicine. J Nucl Med. 2002;43:13N–14N.[Medline]
8. Ter-Pogossian MM, Phelps ME, Hoffman EJ, Mullani NA. A positron-emission transaxial tomograph for nuclear imaging (PETT). Radiology. 1975;114:89–98.[Abstract]

9. Karp JS, Surti S, Daube-Witherspoon ME, et al. Performance of a brain PET camera based on anger-logic gadolinium oxyorthosilicate detectors. J Nucl Med. 2003;44:1340–1349.[Abstract/Free Full Text]
10. Wienhard K, Dahlbom M, Eriksson L, et al. The ECAT EXACT HR: performance of a new high resolution positron scanner. J Comput Assist Tomogr. 1994;18:110–118.[Medline]
11. Casey ME, Nutt R. A multicrystal two dimensional BGO detector system for positron emission tomography. IEEE Trans Nucl Sci. 1986;33:460–463.
12. Dahlbom M, Hoffman EJ. An evaluation of a two-dimensional array detector for high resolution PET. IEEE Trans Med Imaging. 1988;7:264–272.[CrossRef][Medline]
13. Townsend DW, Geissbuhler A, Defrise M, et al. Fully three-dimensional reconstruction for a PET camera with retractable septa. IEEE Trans Med Imaging. 1991;10:505–512.[CrossRef][Medline]
14. Cherry SR, Dahlbom M, Hoffman EJ. 3D PET using a conventional multislice tomograph without septa. J Comput Assist Tomogr. 1991;15:655–668.[Medline]
15. Spinks TJ, Jones T, Bailey DL, et al. Physical performance of a positron tomograph for brain imaging with retractable septa. Phys Med Biol. 1992;37:1637–1655.[CrossRef][Medline]
16. Lartizien C, Comtat C, Kinahan PE, Ferreira N, Bendriem B, Trebossen R. Optimization of injected dose based on noise equivalent count rates for 2- and 3-dimensional whole-body PET. J Nucl Med. 2002;43:1268–1278.[Abstract/Free Full Text]
17. Lewitt RM, Matej S. Overview of methods for image reconstruction from projections in emission computed tomography [abstract]. Proc IEEE. 2003;91:1588.[CrossRef]
18. Wang CX, Snyder WE, Bilbro G, Santago P. Performance evaluation of filtered backprojection reconstruction and iterative reconstruction methods for PET images. Comput Biol Med. 1998;28:13–24.[CrossRef][Medline]
19. Shepp LA, Vardi Y. Maximum likelihood reconstruction for emission tomography. IEEE Trans Med Imaging. 1982;1:113–122.[Medline]
20. Rafecas M, Boning G, Pichler B, Lorenz E, Schwaiger M, Ziegler SI. A Monte Carlo study of high-resolution PET with granulated dual-layer detectors. IEEE Trans Nucl Sci. 2001;48:1490–1495.[CrossRef]
21. Schmitt D, Karuta B, Carrier C, Lecomte R. Fast point spread function computation from aperture functions in high-resolution positron emission tomography. IEEE Trans Med Imaging. 1988;7:2.[CrossRef][Medline]

22. Karuta B, Lecomte R. Effect of detector weighting functions on the point spread function of high-resolution PET tomographs: a simulation study. IEEE Trans Med Imaging. 1992;11:379–385.[CrossRef][Medline]
23. Beyer T, Antoch G, Blodgett T, Freudenberg LF, Akhurst T, Mueller S. Dual-modality PET/CT imaging: the effect of respiratory motion on combined image quality in clinical oncology. Eur J Nucl Med Mol Imaging. 2003;30:588–596.[Medline]
24. Townsend DW, Carney JP, Yap JT, Hall NC. PET/CT today and tomorrow. J Nucl Med. 2004;45(suppl 1):4S–14S.[Abstract/Free Full Text]
25. Kinahan PE, Townsend DW, Beyer T, Sashin D. Attenuation correction for a combined 3D PET/CT scanner. Med Phys 1998;25:2046–53.
26. Visvikis D, Costa DC, Croasdale I, Lonn AHR, Bomanji J, Gacinovic S, et al. CT based attenuation correction in the calculation of semi-quantitative indices of 18FDG uptake in PET. Eur J Nucl Med 2003;30:344–53.
27. Nehmeh SA, Erdi YE, Kalaigian H, et al. Correction for oral contrast artefacts in CT attenuation corrected PET images obtained by combined PET/CT. J Nucl Med 2003;44:1940–4.
28. Carney JP, Beyer T, Brasse D, et al. Clinical PET/CT scanning using oral CT contrast agents. J Nucl Med 2002;45:57P.
29. Goerres GW, Kamel E, Heidelberg TNH, Schwitter MR, Burger C, von Schulthess GK. PET-CT image coregistration in the thorax: influence of respiration. Eur J Nucl Med 2002;29:351–60.
30. Beyer T, Townsend DW, Blodgett TM. Dual modality PET/CT tomography for clinical oncology. Q J Nucl Med 2002;46:24–34.
31. Flohr T, Stierstorfer K, Bruder H, Simon J, Schaller S. New technical developments in multislice CT – Part 1: Approaching isotropic resolution with sub-millimeter 16-slice scanning. Rofo Fortschr Geb Rontgenstr Neuen Bildgeb Verfahr 2002;174:839–45.
32. Nehmeh SA, Erdi YE, Ling CC, et al. Effect of respiratory gating on quantifying PET images of lung cancer. J Nuc Med 2002;43:878–81.
33. Visvikis D, Barret O, Fryer TD, Turzo A, Lamare F, Cheze Le Rest C, et al. A posteriori respiratory motion gating of dynamic PET images. IEEE Symposium in Nuclear Sci and Med Imag Conference records 2003.
34. Shao Y, Cherry SR, Farahani K, Meadors K, Siegel S, Silverman RW, et al. Simultaneous PET and MR imaging. Phys Med Biol 1997;42:1965–70.
35. Casey ME, Nutt R. A mutlicrystal two dimensional BGO detector system for positron emission tomography. IEEE Trans Nucl Sci 1986;33:460–3.

36. Cherry S. In vivo molecular and genomic imaging: new challenges for imaging physics. Phys Med Biol 2004;49:R13–R48.