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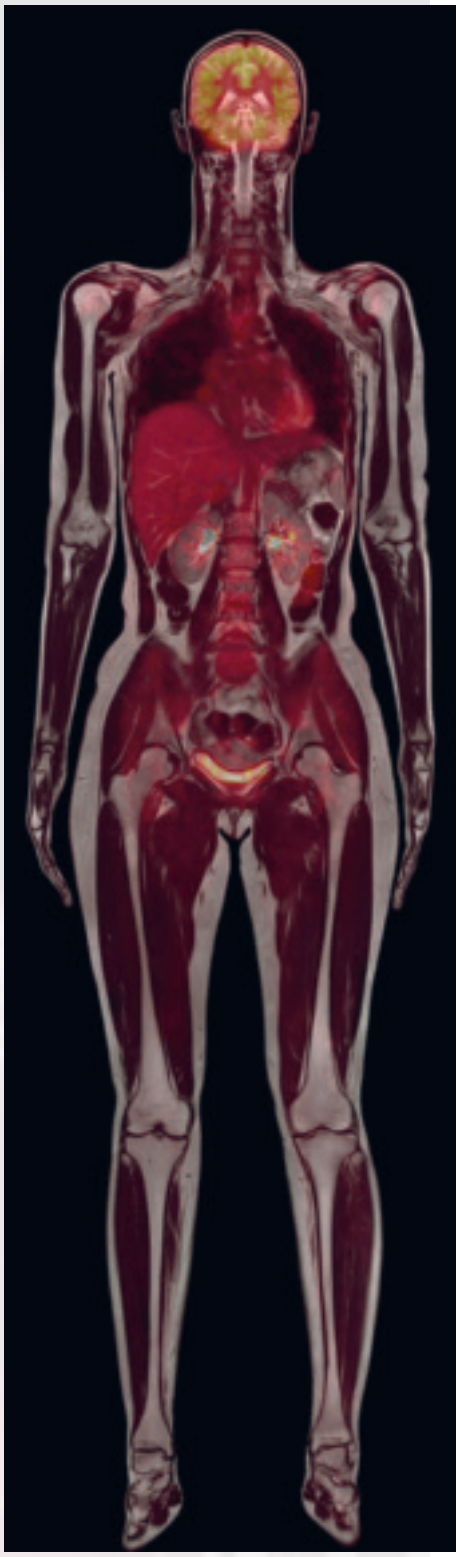

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Spying on Cancer with PET Scans

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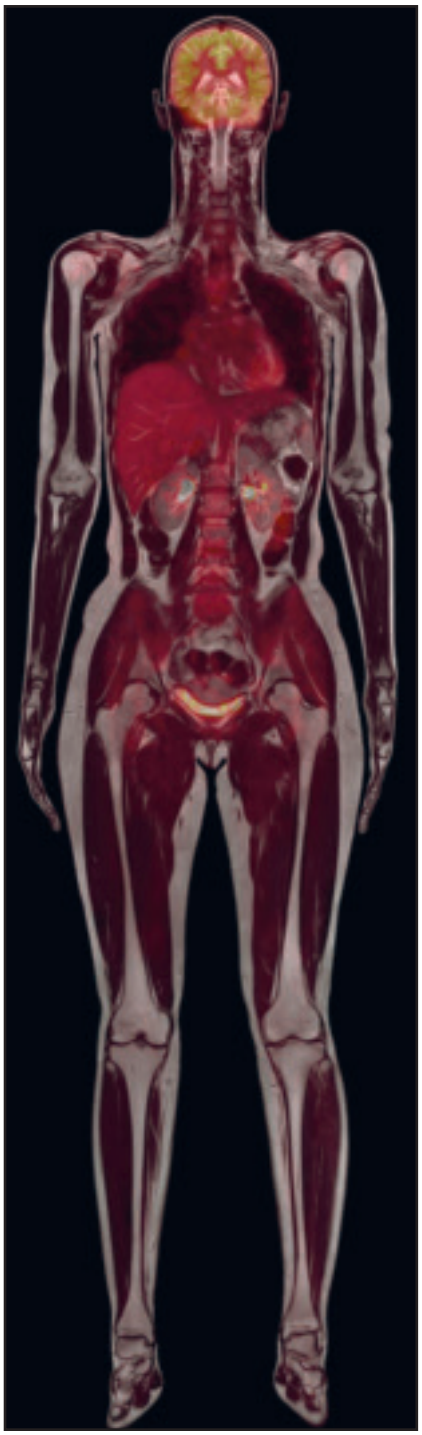


COVER: The ability to peer inside the body non-invasively has revolutionized modern medicine. With positron emission tomography (PET), physicians can not only look at the body's internal structures, but can see the metabolic signs of disease. This is all possible because of basic research in surprisingly diverse areas of science ranging from studies examining the makeup of atoms and the fertilization of sea urchin eggs to those looking at bone replacement in the skeletons of rats. PET, in conjunction with other medical imaging techniques, gives physicians an unprecedented ability to spy on cancer and other diseases. Image credit: Siemens press picture.

PET IMAGING

Spying on Cancer with PET Scans

"The history of the living world can be summarized as the elaboration of ever more perfect eyes within a cosmos in which there is always something more to be seen."

—Henry N. Wagner, Jr., Journal of Nuclear Medicine 27, 1986

"From the very beginning, we wanted to get to the chemical systems of the body that contain the secrets of disease."

—Michael Phelps, Journal of Nuclear Medicine 32, 1991

Forty-eight-year old Tony R. should have been relieved. Computed tomography (CT) scans taken eight months after he had a cancerous section of his colon removed showed no further evidence of the cancer in his body. But he still had persistent pain in his abdomen. CT scans allow for a look at the internal structures of the body, but may not detect some cancerous growths until they are large enough to be easily seen. Knowing this, his doctor ordered a new procedure. The new procedure, known as a positron emission tomography (PET) scan, looks at the biochemical signs of disease instead of anatomic changes and can reveal cancer much earlier than imaging techniques that focus on structure alone. In Tony's case, a PET scan showed that a multitude of small tumors speckled his bowel and liver. Based on this new information, Tony underwent aggressive chemotherapy, and a five-month follow-up PET scan revealed remission in all known tumor sites.

PET and other medical imaging techniques are noninvasive procedures that allow doctors to look inside the body without surgery. Standard techniques, such as CT and magnetic resonance imaging (MRI) scans, depend on X-rays and the magnetic properties of the body's hydrogen atoms, respectively, and can only reveal the location and size of the tumors. It is often difficult, however, to discriminate cancer from the normal tissue of the surrounding areas. In contrast, PET imaging uses specialized radioactive probes that can detect the biochemical processes that distinguish cancer cells from normal cells to reveal even miniscule tumors within normal tissues.

By spying on tumor activity, PET scans aid the diagnosis, removal, and staging of cancers, as well as let physicians more quickly see if their patients are responding to treatment. PET scans also prevent unnecessary surgeries and help suggest which cancer therapies are likely to be most effective for specific tumor types.

PET is speeding the detection of new drug weapons in the war on cancer. By tagging a potential cancer drug with PET probes, researchers can determine if and to what extent the compound is hitting its target. This can be done in both humans and in animal models and provides early insight into the likely effectiveness of the experimental drug, as well as valuable information on the appropriate dose to test in clinical trials. Such PET imaging has the potential to substantially reduce the cost and time needed to develop cancer drugs and hopefully will improve their success rate. (See box insert "Personalized Medicine—Brought to You by PET Scans")

You would suspect that PET

Personalized Medicine—
Brought to You by PET Scans

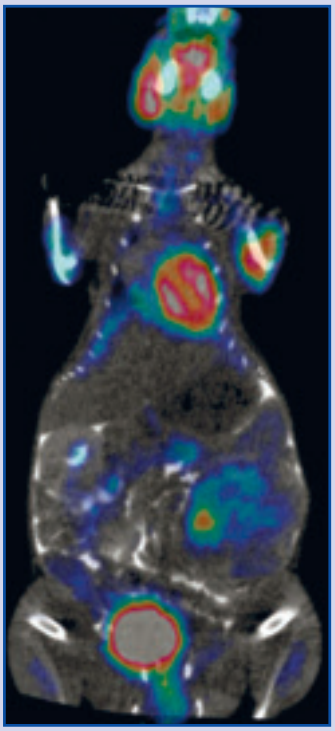
As researchers use genetics and PET imaging to provide a deeper understanding of cancer, they are discovering multiple molecular variations on the same theme. For example, traditionally, breast cancers were classified based on their size, the specific breast tissue of origin (milk ducts versus tissue where milk is produced), and how organized the tumor's growth was when viewed microscopically. More recently, researchers have uncovered that there are different subtypes of breast cancers, depending on what factors fuel their growth. Each subtype may respond differently to the same treatment. Breast cancers that depend on estrogen for their growth will usually respond to hormonal therapy that blocks the effects of estrogen in the body. Other breast cancers are fueled more by a different growth factor and are more likely to respond to the drug Herceptin, which blocks that growth factor.

The effort to tailor therapy to the specific defect that is driving a patient's particular version of a disease is called personalized medicine. PET scans are expected to be extremely valuable in this emerging field. PET probes targeting the tumor cell receptors that enable it to respond to estrogen, for example, can reveal which women's metastatic breast tumors are likely to respond to hormonal therapy without the need for an invasive biopsy.

Based on the fine molecular distinctions that PET probes reveal, drug companies are developing and testing new compounds aimed at targeting the specific molecular defects driving some disorders.

Aiding such drug development are mini-PET scanning devices that can be used on mice and rats. These "preclinical" studies are used to determine compounds worthy of being tested in people and what the safe doses of those compounds should be. Clinical studies of the experimental agent can also benefit from PET imaging. In these studies, PET scans can reveal whether the drug is hitting its target in specific subtypes of patients, whether tumors are no longer actively growing, and other potential treatment benefits. PET imaging can also eliminate the need to do time-consuming and labor-intensive dissections and pathologic analyses of diseased tissues in both animal and clinical studies.

Mini-PET scans done over time on animal models of human diseases, such as cancer or arthritis, can also reveal molecular changes that might be useful drug targets, "providing data that could bridge the gap between basic science and clinical application," noted Paul Workman of the UK Centre for Cancer Therapeutics, in the May 2006 issue of the *Journal of the National Cancer Institute*.



Mini PET/CT scan of mouse
Animal studies play an essential role in the development of new medicines. Not only do they aid in the understanding of fundamental biological principles underlying health and disease, they also help researchers to determine the efficacy of experimental drugs. Shown is a mini PET/CT scan image of a mouse. Using mini PET/CT on mice, rats, and other animal models, researchers can tell if a drug is targeting the appropriate tissues and might be a potential candidate for testing in humans. Photo credit: Dr. Juri Gelovani, The University of Texas MD Anderson Cancer Center. *Special thanks to the Society for Molecular Imaging.*

imaging got its start from decades of biomedical research targeted towards cancer imaging. But rather, it has its roots in many far flung disciplines, from neuroscience and oncology to chemistry, physics, and astronomy, in laboratories across the world. By pursuing the basic building blocks of atoms, what fuels cell growth, and other basic research, the investigators in these different disciplines collectively fostered the development of PET scans and their successful use in the clinic.

PET imaging had its beginnings in the early part of the 20th century when the German chemist and physician Otto Warburg was curious about what cells do chemically to generate the energy they need to grow. While working at the Marine Biological Station in Naples, Italy, he explored this in sea urchin eggs and discovered that after the eggs were fertilized and started to grow rapidly, their metabolic rates increased dramatically (Figure 1). Additional experiments led Warburg to discover the biochemical pathways that plant and animal cells follow to produce energy. All of these pathways caused the breakdown of sugar molecules.

Like sea urchin embryos, cancer cells grow rapidly. Did they also use sugar (glucose) to fuel their growth? When Warburg tried to answer that question in the 1920s, he discovered that cancer cells break down sugar at a much faster rate than normal cells. With his quest to understand what fuels cell growth,

which earned him the Nobel Prize in Medicine and Physiology in 1931, Warburg had defined a hallmark of cancer cells that 50 years later would enable scientists and physicians to distinguish the first glimmers of tumors in living organisms. However, turning Warburg's findings into a medical imaging technology wouldn't have been possible if Parisian chemists hadn't been exploring the instability of atoms, and if, across the ocean, an American physicist hadn't begun a quest to uncover the smallest particles in the universe.

Figure 1 – Sea Urchins: Animal models have been and continue to be critical in the development of molecular imaging diagnostic technologies. Dating back to the 19th century, the sea urchin was among the early animal models that helped to demystify the basic biology underlying growth and development. By studying the eggs and embryos of the sea urchin, scientists discovered that after fertilization the rapid growth of the embryo is fueled by dramatic increases in the consumption of oxygen and the breakdown of sugar molecules. This led to the discovery that the rapid growth of cancer cells was similarly characterized by heightened metabolism of sugar and earned Otto Warburg the 1931 Nobel Prize in Medicine and Physiology. More importantly, the study of the lowly sea urchin yielded a distinguishing marker of tumor cells that would allow later clinicians to spy on cancer with PET scans. *Photo credit: Raphaël Rigo.*

Smashing success

Ernest Lawrence was known as an atom smasher because he used the force of high-energy beams to pry apart the particles that comprise the atom (Figure 2). To create those high-energy beams, Lawrence invented, in 1931, what he called a "proton merry-go-round" that later would become known as the cyclotron. This device used a combination of magnetic fields and electricity to speed up charged particles (protons) until they have enough force to split atoms. Lawrence's creation of the cyclotron earned him the Nobel Prize in Physics in 1939, but affected far more scientific fields than just nuclear physics.

Figure 2 – Ernest O. Lawrence: Ernest Lawrence was a Nobel Prize-winning 20th century physicist. Although it was his 1931 invention of what he called a "proton merry-go-round," now known as a cyclotron, that won him the Nobel Prize in Physics, it was the basic research he conducted to understand the composition of atoms that would eventually lead to the development of important medical compounds. These compounds, some of which will be discussed later, would become standard tools in the diagnosis and treatment of cancer and other diseases and would change the course of medical history. *Photo courtesy of the Lawrence Berkeley National Laboratory.*

The basic research Lawrence conducted with his cyclotron was aimed at exploring the depths of the atom. What he soon discovered, with the prompting of Parisian researchers, were the byproducts of his high-energy bombardments—radioactive compounds—that others then used to explore the inner workings of the body.

Those French researchers were Frederic Joliot and Irene Curie, the daughter of Pierre and Marie Curie (Figure 3). Carrying on her family's work, Irene Curie and her husband Joliot conducted a number of experiments aimed at uncovering what exactly happens when a basic element, such as aluminum, is transformed into another basic element (silicon). In 1934, while bombarding aluminum atoms with the radiation emitted by radium, which Curie's parents had discovered, the Parisian couple found that the aluminum didn't get transformed into silicon, as expected, but rather into another unknown atom

that was radioactive (radioactive phosphorus).

This discovery of artificially created radioactive elements led the Curie-Joliots to win the Nobel Prize in Chemistry in 1935 and prompted Lawrence to begin searching for similar artificial radioactive elements in his cyclotron. Within a few years time, Lawrence detected and isolated several such atoms, including radioactive uranium (used in the atomic bomb), fluorine, and phosphorus.

Figure 3 – Frederic Joliot and Irene Curie: Frederic Joliot and Irene Curie, the daughter of Pierre and Marie Curie, were credited with the discovery that radioactive elements could be artificially created. In 1935, the pair was awarded the Nobel Prize in Chemistry for their work. Unlike normal atoms, radioactive atoms release what is known as ionizing radiation, which is easily detectable. Because radioactive atoms give off easily detectable signals, their movement and localization can be tracked, even inside the body. The ability to generate and incorporate radioactive atoms into molecules such as sugar made PET and other medical procedures possible. *Source: Wikimedia Commons.*

Unlike normal atoms, radioactive atoms give off signals that can be detected with Geiger counters and other devices. Such radioactive signaling offered researchers the revolutionary opportunity to trace molecules in action in the body.

Tracing the path of molecules

One of the first researchers to use radioactive tracers to try to uncover hidden molecular activity in the body was Hungarian-born chemist and physicist George de Hevesy whose work yielded several surprises. Lawrence sent de Hevesy, radioactive versions of phosphorus, a building block of bone. De Hevesy then explored how this radioactive chemical is taken up or lost by the skeleton of rats over time.

Much to most people's disbelief, this basic research revealed that the bones are not stable entities, but rather are continually being broken down and rebuilt, with about one third of the phosphorus atoms deposited in the rat skeleton being removed in just 20 days. In de Hevesy's experiments, research animals were euthanized after being given the radioactive tracers and then dissected. The dissected animals were then placed on photographic films to capture the images of the distribution of the radioactive tracers. This pioneering work in the development of radioactive tracers to study metabolism led to de Hevesy being awarded the Nobel Prize in Chemistry in 1943 and opened up the possibility of tracing dynamic, physiological processes in the body.

To make that possibility a reality, researchers still had to develop safe tracers whose radioactivity would diminish rapidly so as not to pose undue risk or harm to those injected with it. These tracers then needed sensitive, non-invasive imaging devices that could detect signals that the tracers gave off when they accumulated deep within the body.

The first step on the road to developing tracers to study biological pathways was to create radioactive versions of biologically-important, naturally occurring molecules that could be readily taken up by various tissues from the bloodstream. De Hevesy's research prompted many scientists to design such tracers by substituting radioac-

tive atoms into biochemical compounds normally used by the body or into molecules that bind to specific tissues or proteins. One PET tracer eventually achieved the most prominence. Labeled the "molecule of the 20th century" by neuroimaging pioneer Henry Wagner, this tracer proved remarkably effective at imaging many different tumors.

Molecule of the century

Chemists Tatsuo Ido and Alfred Wolf of Brookhaven National Laboratory made this celebrated molecule in the 1970s by inserting radioactive fluorine into a sugar (glucose) molecule. The radioactive tracer they created, called FDG (fluorodeoxyglucose), is closely related to glucose and is readily taken up from the blood stream by cells, but can't be fully broken down by them. Therefore FDG remains trapped inside the cells that suck it up and its accumulation there provides an indication of glucose metabolism, causing the emission of signals that can easily be detected. (Within hours, this radioactivity rapidly diminishes so it does not pose undue harm to those injected with it.)

Radioactive fluorine, the radioisotope that is incorporated in FDG, is made by adding a positively charged proton to a heavier variant of oxygen. As FDG loses its radioactivity, through a process known as radioactive decay, it converts one of its positively charged protons to a neutrally charged neutron. This results in the release of a positively charged sub-atomic particle, a positron, that then collides with a nearby, negatively charged electron. This collision annihilates both sub-atomic particles, producing gamma rays, which can be detected by a scanning device.

The next step was to make a scanner that could detect the signals resulting from radioactive FDG within the body and turn them into an image. The first scanners were rather crude instruments that gave unfocused images of the radioactive uptake. Investigators from several different scientific disciplines, including physicists, physiologists, neuroscientists, engineers, physicians, and chemists, worked together to refine these early imaging devices.

Biomathematicians and computer scientists also got in the act, creating the complex mathematical formulas and computer programs needed to convert the signals resulting from radioactive tracers into a three-dimensional image of where the tracers were concentrating in the body. The far flung nature of this work can be seen by the fact that some of the mathematics that underlie it were borrowed from those developed by astronomers to image galaxies and other distant celestial bodies, as well as those created by electron microscopists to three-dimensionally reconstruct some of the smallest particles in the cell. The ultimate end product of this disparate research was PET, which was later combined with other types of medical imaging, CT for example, to provide both anatomic and metabolic information. This is described in more detail in the box insert "How Does the PET/CT Scanner Work?"

"The development of PET was entirely dependent on the separate development of scientific concepts that in their early stages were pursued without any thought of their combined use," noted physicist Michel Ter-Pogossian in the July 1992 issue of *Seminars in Nuclear Medicine*. But in the later stages of PET development, those key concepts, developed within divergent scientific disciplines, converged with radical results. Referring to those scientists that helped bring PET to fruition, neuroscientist Marcus Raichle noted in the October 1998 issue of *Seminars in Nuclear Medicine*, "They were a mixture of chemists, engineers, computer scientists, biologists and physicians truly working side by side, exploring new frontiers that fortuitously lay at their very feet. It was indeed an exciting experience for all who were privileged to participate."

Peering into the mind and body

Throughout the 1970s, researchers used FDG in PET scanning not to detect tumors, but rather to image the intense uptake of sugar that was needed to fuel brain cells in action. For the first time, this tracer non-invasively revealed the previously hidden workings of the mind—what parts of the brain are active when individuals carry out various

tasks, such as speaking, hearing, remembering, and the perception of painful events. PET also opened up a whole new physical window into the previously hidden human psyche, tying abnormally low or high activity in specific brain regions to various mental disorders, such as severe depression, substance abuse, and schizophrenia.

Inspired by FDG's success in imaging brain activity in PET scans, several researchers started exploring other clinical applications. Aware of the increased use of sugar by tumors that Warburg had shown decades ago, in 1980, researchers in the Brookhaven group showed that a variety of tumors in animals had greater uptake of FDG than normal tissues. A few years later, radiologist Giovanni Di Chiro, who founded and headed the National Institutes of Health Neuroimaging Branch, showed that brain tumors could be seen as heightened FDG uptake "hot spots" on the PET scans of patients (Figure 4).

Di Chiro then went on to show that the degree of aggressiveness of certain brain tumors was linked to how bright those hot spots appeared in the PET scans. Survival rates could even sometimes be predicted better with PET scans than by the traditional prognostic microscopic features seen in the tumors after they were removed.

CT scans and MRIs reveal physical structures within the body that have been changed by

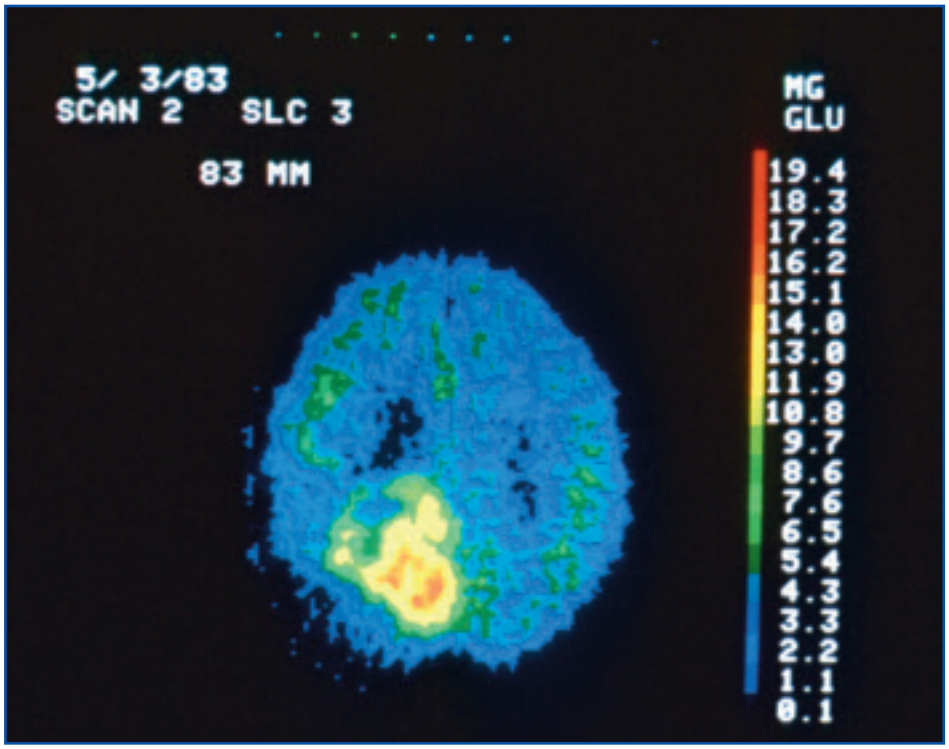


Figure 4 – Brain tumor: Shown is a PET scan image of a patient diagnosed with a brain tumor (astrocytoma). The patient was injected with a radioactive tracer, fluorodeoxyglucose (FDG). FDG is an analog of glucose that is readily taken up by cells, as if it were glucose. Because it has a slightly different chemical structure than glucose, FDG cannot be broken down by the cells of the body and accumulates. The cells that accumulate the radioactive tracer the fastest, such as cancer cells, light up the most on a PET scan image. As a result of its increased uptake of the radioactive tracer, the tumor appears as the bright orange and yellow area on the lower left side of the brain. *Source: Dr. Giovanni De Chiro, National Institute of Neurological Disorders and Stroke.*

cancer or its treatment. However, some changes in structure, which include the development of scar tissue, may not indicate an actively growing tumor. In contrast, PET detects metabolic activity, rather than tissue damage. Thus actively growing tumors can be easily distinguished from scar tissue and will light up in PET images. Di Chiro showed that PET scans could distinguish between the radiation scars of treated tumors and those of tumor recurrences, unlike CT scans and MRIs. As one radiologist pointed out, MRIs and CT scans detect the reaction to an abnormality, such as a tumor, but PET scans reveal the actual abnormality.

Within a few years, the early PET findings exploded into a number of clinical applications, with physicians using PET to image several different tumor types in their patients. The use of PET in oncology became especially common by the early 1990s after researchers showed that whole-body images could reveal metastatic tumors that had spread throughout the body from the primary cancer site, often months before they could be detected on CT scans or MRIs (Figure 5).

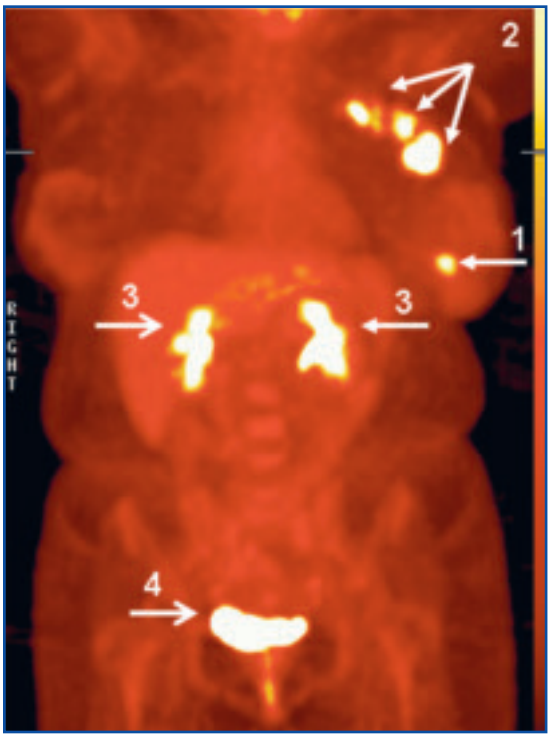


Figure 5 – Whole body PET/CT scan: Not only can PET be used to look at specific areas or organs, it can also be used to look at the entire body. Shown is what is considered to be a standard "whole body" (includes the neck and pelvis and areas in between) fused PET/CT scan image. Because PET looks at the accumulation of the radioactive tracer and uses that to infer the presence of malignant cancers, knowledge of the body's normal variation in tracer uptake is critical to proper interpretation of a PET image. For example, the kidneys and bladder often appear as brighter areas on a PET image because they are actively involved in the removal of FDG that is not absorbed by cells. Similarly, tissues and organs with higher than average metabolic rates, such as bones recovering from breaks or the heart, also show up as bright spots on a PET image. Because PET/CT scans can non-invasively look at the whole body, doctors can tell at a very early stage when cancer has metastasized (spread from one part of the body to another). The patient shown had been diagnosed with cancer of her left breast (1), and PET/CT revealed that the cancer had spread to her lymph nodes (2). As described above, normal excretion of the tracer is seen in both the kidneys (3) and the bladder (4). *Images courtesy of Annick D. Van den Abbeele, MD, Heather Jacene, MD, and Tricia Locascio, CNMT, Department of Imaging, Dana-Farber Cancer Institute.*

Machine of the year

Another development that dramatically expanded the use of PET scans was the debut of combination PET/CT scanning devices. Created by University of Pittsburgh physicist David Townsend and engineer Ronald Nutt, with financial support from the National Cancer Institute, the PET/CT machine was called the "Medical Science Invention of the Year" by *Time* magazine in 2000. The PET/CT scanner enabled physicians to pinpoint more precisely the location of tumors, especially in relation to other organs and tissues. There are now close to 2,000 PET or PET/CT scanners in the United States that are routinely used to diagnose and stage a variety of tumors, as well as to monitor the effectiveness of treatment and to detect tumor recurrence. (See also PET/CT scanner sidebar)

PET imaging of cancer

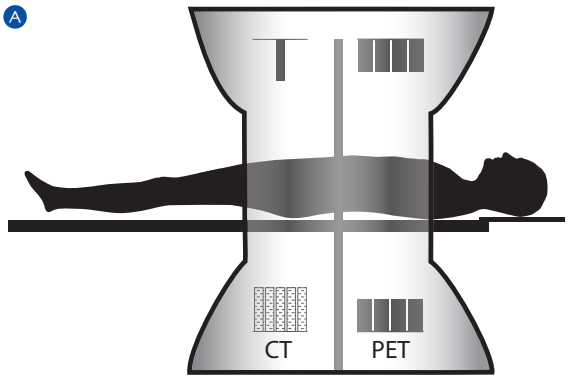
When a person is first diagnosed with cancer, his or her physician uses various imaging techniques to determine how far the cancer has spread, which determines the severity of the disease and the optimal treatment. By detecting metastases to which other imaging modalities are blind, PET can enable more accurate staging of cancers, thus indicating whether surgical removal of the organ initially affected by the cancer is warranted.

For example, lung cancer patients often have surgery to remove all or part of their cancerous lung if CTs or MRIs don't detect the cancer elsewhere in the body. But if the cancer has spread to other sites, surgery usually does not extend life and instead causes much of the last few months of life to be spent recovering from surgery. Studies find that compared to conventional imaging PET scans are twice as likely to detect early metastases, indicating that patients might want to pursue other treatments besides surgery.

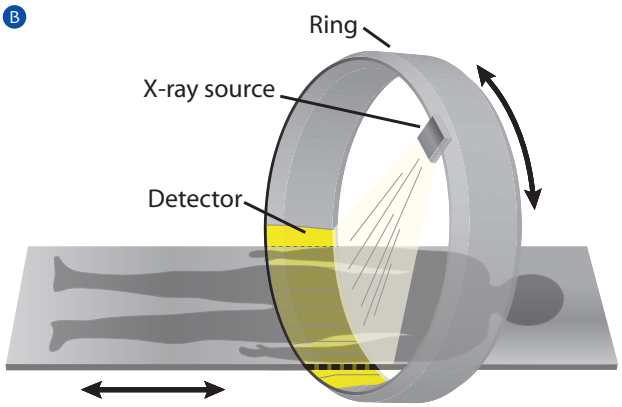
Studies further indicate that more than one-third of the time PET scans change how cancer patients are treated. For some types of cancers, PET scans enhance doctors' ability to detect unsuspected tumors, thus triggering earlier treatment that in some cases leads to cures. For example, one study found that after treatment for colorectal cancer, patients who received PET scans, as opposed to more conventional CT or MRI scans, had their cancer recurrences detected sooner and had a cure rate that was five times that of those who received conventional imaging.

PET is particularly useful in detecting cancer that has spread to the lymph nodes. Cancer cells

How Does the PET/CT Scan Work?

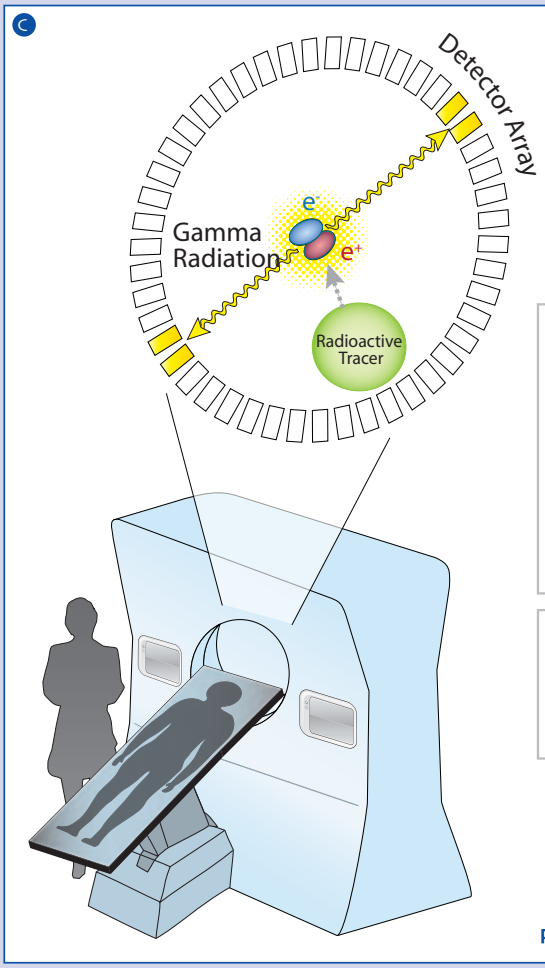


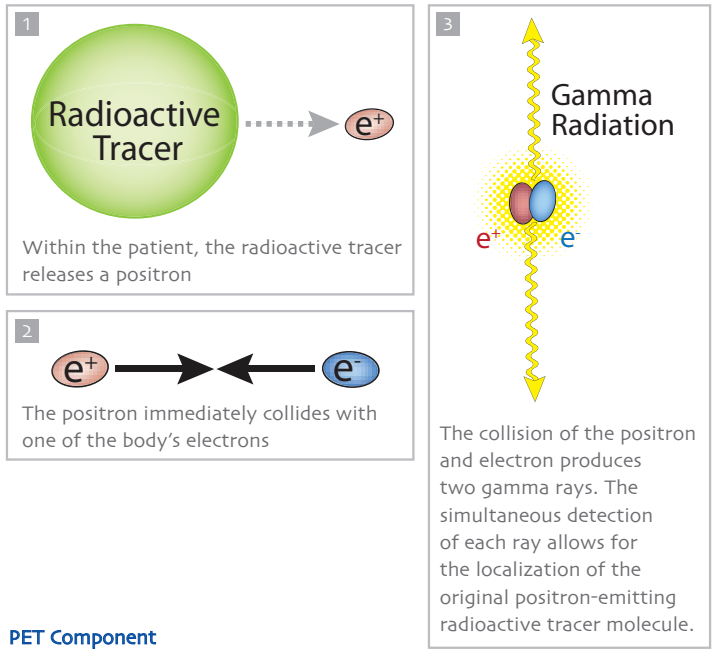
Overview of a Dual PET/CT Scanner



CT Component

X-rays are emitted and travel through the patient to the detector on the opposite side of the ring. As the X-rays travel through the patient, they are differentially absorbed depending on the type of tissue – for example, bone absorbs much more X-ray radiation than muscle. A large number of two-dimensional images taken around the patient are used to reconstruct a three-dimensional (3D), anatomical image of the inside of the body. A 3D PET scan image can then be superimposed onto the 3D CT scan image.





PET Component

When FDG is injected into a patient's vein, it is taken up more readily from the blood stream by actively growing tumor cells than by normal cells. Once these cells suck the compound up, it remains trapped inside them, as the cells cannot break the FDG down. So, after a short period of time, FDG becomes concentrated in tumor sites.

At these uptake sites, each atom of the radioactive fluorine in FDG decays, giving off two positrons in the process. These positively charged particles immediately collide with negatively charged electrons in mini explosions that result in two gamma rays being shot off in opposite directions. (Gamma rays are similar to the X-rays used in CT scans.) Simultaneous detection of these two gamma rays by the PET machine enables the precise location of the original positrons emitted by the FDG molecule.

A computer then compiles the data from all the decaying FDG molecules to provide a three-dimensional image of concentrated pockets of FDG in the body. This molecular image is superimposed on a CT scan that provides an anatomical image of the body in the same position as when the PET scan was done, so physicians can detect what organs and tissues contain active tumors.
Illustration by Corporate Press.

tend to travel first to these pea-sized organs of the immune system, which are scattered throughout the body, before reaching other organs and tissues. Those cancers found to be affecting lymph nodes are often treated more aggressively than those limited to the original organ in which they appeared. Lymph nodes are considered cancerous on a CT or MRI scan if they are greater than about a centimeter in size. But tumors in the lymph nodes can be seen as bright spots on a PET scan before lymph nodes grow to that size.

For some cancers, such as certain forms of cervical cancer, treatment effectiveness depends on aggressively targeting affected lymph nodes with radiation therapy. PET's greater sensitivity in imaging these nodes has made it key to determining where to target high-dose radiation therapy for this cancer.

By more accurately showing the extent of tumors, PET/CT scans can also improve radiation therapy and surgical removal of cancers. Surgery's success in treating many types of cancer depends on its complete removal of the initial tumor. But it can be difficult to locate the edges of a tumor. Researchers are currently testing hand-held PET scanners that can image, during surgery, the hot spots of breast cancers and other tumors that avidly take up FDG. By making these tumors glow during surgery, their margins are likely to be more visually obvious to the surgeon.

PET can also reveal sooner than a CT or MRI whether tumors are responding to treatment—in some cases just a day after treatment is given—because responding tumors often become less active before they shrink in size. The lessened activity can be detected by PET scans, but not by conventional imaging, which just detects tumor shrinkage. Typically, conventional imaging does not reveal an unresponsive tumor until several months following treatment—time that might have been better used receiving an alternative therapy.

Although the national average cost of a PET/CT scan can be close to $5,000, most experts consider the scan cost effective because of the savings provided in the prevention of unnecessary treatment or by improving the choice of initial treatment. According to a *Journal of Nuclear Medicine* article by Andreas Buck, studies suggest that, for some cancers, PET/CT scans offer a net savings of around $2,000 per patient.

PET imaging on the horizon

Researchers continue to develop new ways of using PET. One recent development has been the combination of PET and MRI into a single apparatus. Compared to CT, MRI generally provides more detailed images, which can aid in the more precise localization of cancerous growths (Figure 6). This also has the advantage of reducing the radiation exposure for patients during imaging procedures. Similarly, researchers continue to develop innovative cancer tracers that can be used in PET. Instead of detecting heightened sugar uptake or blood flow, these tracers detect other traits common to tumors, such as leaky blood vessels, excessive growth factor receptors, or heightened cell division that, along with, or instead of FDG, might better image tumors and even suggest which treat-

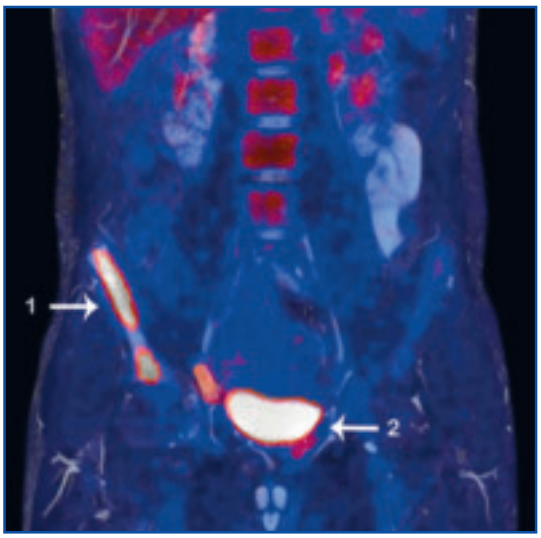


Figure 6 – Abdominal PET/MRI scan: Increasingly, researchers are providing physicians with better and better tools to aid in the diagnosis and treatment of disease. One such upgrade is the combined use of PET and MRI. MRI provides much better resolution, and therefore a more detailed anatomical map, than CT. When used with PET, this increases the capacity of doctors to pin point the exact location of cancerous tissues. Shown is an image of the abdominal region of a patient with bone cancer, seen as the white rod-like area on the lower left (1). (As previously described in Figure 5, the bladder appears as the white kidney-shaped object in the lower center area (2).) *Image credit: Siemens press picture.*

ments are more likely to work. (See box insert on personalized medicine)

Experimentally, PET is also extending its reach into other medical specialties besides oncology. PET imaging is starting to help detect atherosclerosis and inflammation in blood vessels that are some of the first steps along the road to a heart attack. Researchers have also begun to explore the potential of this imaging to detect the onset of arthritis before there has been much damage to the joints, allowing early treatment. Most recently PET probes that detect amyloid, one of the features of Alzheimer's disease neurodegeneration, have shown that accumulation occurs long before much memory loss. The hope is to make PET probes that accurately detect abnormal molecular activity early in the progression of these diseases, prior to the occurrence of tissue damage, and then to develop treatments that prevent disease progression before the body is significantly harmed. Basic research has revealed key molecular players that underlie the development of these disorders and has provided researchers with a palette of potential PET probes for detecting the early signs of disease before symptoms appear.

PET imaging for early heart disease, bone or joint disorders, or Alzheimer's disease has yet to become routine in the practice of medicine, but initial studies in animals and people have generated some promising findings that suggest eventually we may be able to detect and then beat a disease before it firmly takes root in the body.

Practical implications of PET scans continue to unfold and could not have been predicted by the initial pursuits of researchers, who were pursuing answers to basic questions about diverse topics, from the smallest components of the atom to distant celestial objects. This cadre of curious and determined researchers from a range of disciplines contributed to the development of PET imaging as a way to detect diseases during their earliest stages, when they are most likely to be amenable to treatment. By so effectively spying on disease, PET has helped to pave the way for a revolution in the practice of medicine.

Additional suggested reading:

Wagner, H.N. 1998. *A Brief History of Positron Emission Tomography, Seminars in Nuclear Medicine.* 28(3):213-220.

Podoloff, D.A., Ball, D. W., Ben-Josef, E. et al. 2009. *NCCN Task Force: Clinical Utility of PET in a Variety of Tumor Types, Journal of the National Comprehensive Cancer Network. 7, Supplement 2*.

Morrison, A.R., and Sinusas, A.J. 2010. *Advances in Radionuclide Molecular Imaging in Myocardial Biology, Journal of Nuclear Cardiology*. 17(1):116-134.

Cohen, R.M. 2007. *The Application of Positron-Emitting Molecular Imaging Tracers in Alzheimer's Disease, Molecular Imaging Biology*. 9:204-216.

Biographies:

Margie Patlak writes about biomedical research and health from the Philadelphia region. She has written for Discover, Glamour, Physician's Weekly, Consumer Reports on Health, The Washington Post, Los Angeles Times, Dallas Morning News and numerous other publications. She has written frequently for the National Institutes of Health and the National Academy of Sciences, and currently works with a number of trade journals, such as Endocrine News and the Journal of the National Cancer Institute. This is her eighth article in the Breakthroughs in Bioscience series.

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