Review

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Unparalleled and revolutionary impact of PET imaging on research and day to day practice of medicine

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Abstract: Positron emission tomography (PET) imaging is the most quantitative modality for assessing disease activity at the molecular and cellular levels, and therefore, it allows monitoring its course and determining the efficacy of various therapeutic interventions. In this scientific communication, we describe the unparalleled and revolutionary impact of PET imaging on research and day to day practice of medicine. We emphasize the critical importance of the development and synthesis of novel radiotracers (starting from the enormous impact of F-Fluorodeouxyglucose (FDG) introduced by investigators at the University of Pennsylvania (PENN)) and PET instrumentation. These innovations have led to the total-body PET systems enabling dynamic and parametric molecular imaging of all organs in the body simultaneously. We also present our perspectives for future development of molecular imaging by multiphoton PET systems that will enable users to extract substantial information (owing to the evolving role of positronium imaging) about the related molecular and biological bases of various disorders, which are unachievable by the current PET imaging techniques.

Keywords: FDG; molecular imaging; PET; positronium imaging; theranostics; total body imaging.

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The introduction of X-ray by Roentgen in 1895 led to a major change in the day-to-day practice of medicine which is still ongoing but has significantly accelerated over the past 5 decades. However, the planar nature of this modality has adversely affected its impact on certain disciplines in medicine such as surgical intervention and radiation therapy. Half a century later in the 1950s, the use of radiolabeled compounds to image organ function was initiated by Casen through the introduction of focused collimation which allowed detection of single gamma emitting radionuclides by rectilinear scanners. A decade later, Anger introduced an instrument called “scintillation camera” which significantly impacted the role of radionuclide-based imaging techniques in medicine [1]. This approach allowed imaging large segments of the body with one data acquisition. Co-incident with this invention, the concept of tomographic imaging was introduced by David Kuhl at the University of Pennsylvania (PENN) and this led to designing prototype tomographic imaging instruments the 1960s and 70s [2]. This imaging technique was based on detecting single gamma rays from multiple projections and reconstructing tomographic scans by the back projection approach. In 1971, Hounsfield designed and built the first X-ray-based tomographic instrument which significantly enhanced the role of imaging over the years [3]. This technology (X-ray computed tomography: XCT) was initially designed for brain imaging but later was modified to perform whole body scans. The design of XCT imaging has significantly improved over the past 4 decades and currently this powerful modality allows acquisition of images within a short period of time of all organs in the body.

Overall, X-ray-based imaging provides low contrast between the disease sites and the background structures. In order to enhance the contrast resolution with XCT, it is necessary to administer iodinated contrast agents which are routinely employed to improve the sensitivity and specificity of this technique. Unfortunately, these agents have significant side effects, particularly in organs such as kidneys. Also, CT is associated with high radiation dose, particularly those performed with spiral XCT machines.

The concept of performing tomographic imaging by Anger camera by investigators at University of Michigan and Berkeley allowed adoption of emission tomography in the day-to-day practice of medicine [4, 5]. Currently, single photon emission computed tomography (SPECT) is the workforce of the specialty of nuclear medicine worldwide. Unfortunately, this tomographic approach suffers from lack of progress in synthesizing novel tracers for research and clinical applications. This is primarily due to the nature of single gamma emitting radioactive elements such as Technetium and Iodine to be labeled to biologically important compounds.

The concept of molecular imaging by positron emission tomography (PET) was introduced by investigators at PENN in the early 70s and this eventually led to synthesizing ^{18}F-Fluorodeouxyglucose (FDG) which was successfully administered on August 1976 to human beings [6]. Parallel with these developments, PET instrumentation was substantially improved by investigators at Washington University led by Ter-Pogossian et al. [7]. The introduction of FDG and other tracers along with significant improvements in PET instrumentation have powered the field of molecular imaging enormously. Simultaneous with such advances made elsewhere around the world, Polish scientists led by Prof. Wiesław Graban and Dr. Zbigniew Pawłowicz, the former director of the Oncology Center in Bydgoszcz, initiated major efforts to introduce PET imaging to the country [8].

Furthermore, the foundation for imaging with radiolabeled tracers became a reality by the discovery in 1934 of artificial radioactivity in laboratories headed by Maria Skłodowska-Curie in Paris (Institut du Radium) [9], and in Warsaw (Radiological Laboratory) [10]. For this discovery Irene and Frederic Joliot-Curie were awarded the Nobel Prize in Chemistry in 1935. Also, the basis for synthesizing FDG was laid down by the discovery of radioactive Fluorine by Marian Danysz and Michał Żyw who were trainees under the supervision of professor Ludwik Wertenstein in the Radiological Laboratory of the Warsaw Learned Society [10]. The first Fluorine isotope ^{17}F was produced by the reaction $\alpha + {}^{14}N \rightarrow {}^{17}F + n$ [11]. Moreover, the same year, Michał Żyw discovered radioactive Scandium by bombarding potassium with α particles [12]. Currently, Scandium appears to be the most promising radionuclide for labeling various compounds [13] for the *positronium imaging*, a newly developed PET imaging technique invented and developed at the Jagiellonian University in Cracow [14, 15].

Magnetic resonance imaging (MRI) was introduced in the early 1970s which further enhanced the role of imaging in medicine [16]. In spite of initial claims about the ability of this new approach in detecting the disease at the molecular level, MRI remains mostly as a powerful structural imaging technique. Furthermore, the use of contrast agents for molecular disease assessment has proven to be unachievable, and therefore, currently MRI plays a limited role in detecting and characterizing disease processes at the molecular level [17, 18].

Combined PET and CT was introduced by investigators at University of Pittsburgh in the late 1990s which provided a paradigm shift by allowing the co-registration of images generated by CT with those of molecular scans generated by PET [19, 20]. This approach has truly revolutionized applications of PET for both research and clinical purposes. This technology was introduced commercially in 2001 and has become the workhorse of modern nuclear medicine. The main PET tracer employed for PET/CT imaging throughout the world has been FDG which has been extensively used for managing patients with a variety of malignancies and several benign diseases and disorders. The combined PET and MRI instrument was introduced over the past decade and has further enhanced the role of molecular imaging in certain domains [21]. PET/MRI will likely play a major role in assessing brain, cardiovascular, and musculoskeletal disorders. The main challenge for PET/MRI is suboptimal attenuation correction of the gamma rays emitted, particularly in deep structures of the body. This limitation prevents optimal quantification of tracer concentration by this modality.

Based on the experience that the medical community has gained during the last century, it has become quite clear that structural imaging is very insensitive in detecting early disease and assessing response following therapeutic interventions. Measurement of blood flow to various organs such as the brain and the heart as markers of dysfunction has proven to be of some value for assessing function in these organs [22]. However, it is increasingly clear that detection of blood flow alone is limited in many settings and therefore disease assessment at the molecular level will become the main disease activity source in many settings (Figure 1) [23]. Realizing this fact has further enhanced the role of PET as the imaging modality of choice for examining molecular alterations in normal and disease states. The role of SPECT in medicine is substantially minimized by rapid adoption of PET as the modality of choice for detecting and characterizing disease processes, particularly over the past 20 years [24].

One of the major factors in the success of PET was the concept of synthesizing FDG for the first time in the 1970s by investigators at PENN [6, 25, 26]. These investigators had realized the potential of this novel radiolabeled compound for both research and clinical practice based on autoradiographic studies by C14-deoxyglucose in animals. These research studies showed high concentration of this

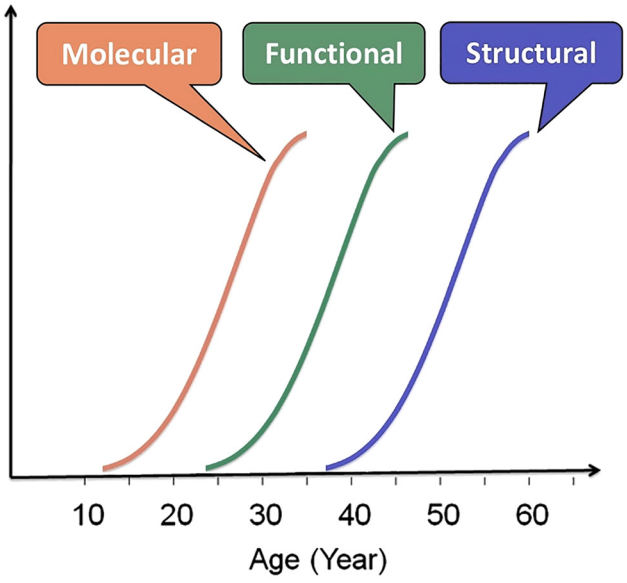


Figure 1: This figure graphically portrays the probable sequence of biological events as they relate to many disorders. Functional changes refer to physiological alterations such as blood flow and organ motility. This pattern is particularly relevant to the assessment of atherosclerosis in the coronary arteries as well as other organ arteries. As such, molecular imaging with PET may provide early evidence of the disease process (Reproduced with permission from Alavi A et al. [23]).

compound in the grey matter of the brains of small animals. This early observation eventually led to synthesizing 18F-FDG by investigators at Brookhaven National Laboratory. The compound was made and tested in animals by the mid-1976 and the first two doses of FDG were administered to human beings by Abass Alavi at PENN in August 1976. These two early images were acquired by using existing planar and SPECT instruments at the institution which resulted in relatively poor quality of the scans generated.

The introduction of FDG and significant improvements in instrumentation that followed during the ensuing years substantially improved the prospects for PET imaging for research purposes at major institutions in the United States and Europe. In spite of complexity and technical challenges that were faced by this demanding technology, over the past decades, the critical role of this modality has been validated and very well established for assessing many diseases and disorders [27]. The initial research mainly was focused on brain disorders such as Alzheimer's disease. Other applications that followed included some other brain maladies such as seizure activity in the temporal lobe, cerebrovascular disease and a variety of neuropsychiatric entities such as schizophrenia and depression.

Based on observations that were made initially in animals and later in human beings, the critical role of FDG in detecting and characterizing malignant disorders was soon realized by several groups. While the initial research was focused on brain tumors, since the 1990s, FDG has been extensively employed to assess a variety of malignancies. By now, it is well established that malignant cells are highly glycolytic compared to normal tissues as has been heavily demonstrated by FDG-PET imaging. The use of FDG-PET has significantly contributed to the management of patients with a variety of cancers throughout the world.

FDG-PET has proven to be very effective in detection of infection and inflammation due to a variety of diseases and disorders [27, 28]. It has been employed to detect atherosclerotic plaques in the aorta and major arteries [29, 30]. Furthermore, it has been shown that clots have significant glycolytic activity and can be visualized by this technique [31, 32]. Currently, FDG is frequently used for detecting and characterizing causes of fever of unknown origin [33], inflammatory bowel disease [34], tuberculosis [35]and other common infectious disorders [36].

Over the past decade, the major advances that have been made in designing and building PET instruments have further enhanced the impact of this modality. The introduction of total body PET imaging during the several few years by investigators at University of California, Davis; PENN; United Imaging (in Shanghai); and Siemens has further enhanced the role of this powerful modality in medicine (Figure 2) [37, 38]. This instrument allows imaging the entire body within a few minutes and also requires administering significantly low doses of FDG and other radiotracers for generating optimal results with this very powerful technique. Furthermore, this imaging modality allows screening the entire body for diseases that are diffuse in nature such as atherosclerosis, osteoporosis, vascular complications of many cancers and hematologic malignancies, and systemic manifestation of inflammation including rheumatoid arthritis and psoriasis (Figure 3) [39, 40].

While the synthesis of FDG was somewhat cumbersome and therefore limited to a few centers with sophisticated skills in radiochemistry, due to rapid adoption of PET around the world, this compound is now commercially available to most institutions in the developed countries. Currently, there are nine cyclotrons in Poland that are dedicated to synthesizing PET radiopharmaceuticals with emphasis on supplying FDG to the medical community [41, 42].

PET imaging is the most quantitative modality for assessing disease activity in medicine, and therefore, it contributes to monitoring the course of the disease and determining the efficacy of various therapeutic interventions. Particularly, its ability to provide a single value as evidence for global disease activity is essential for management of multiple malignant and benign diseases

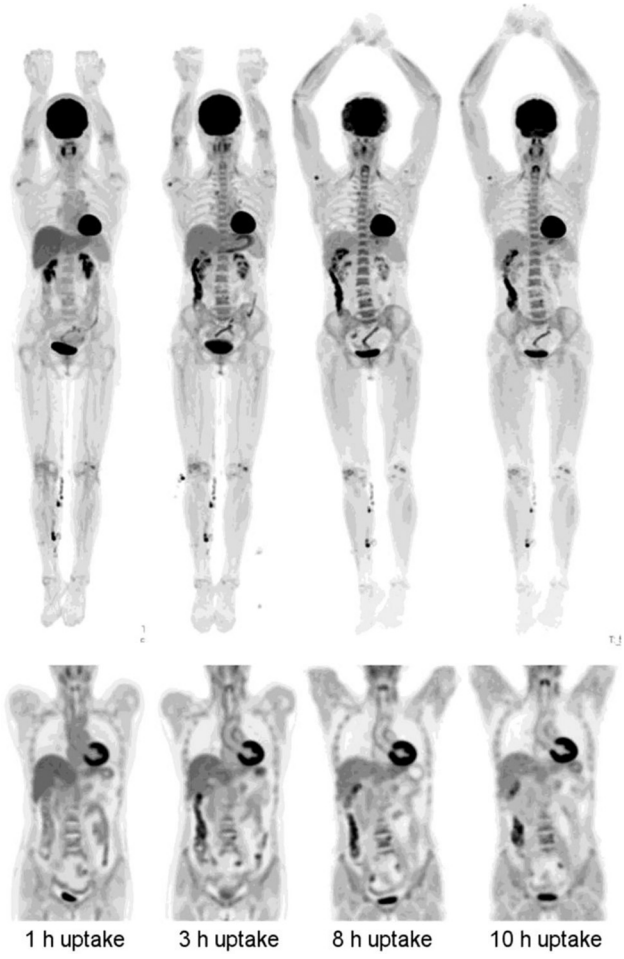


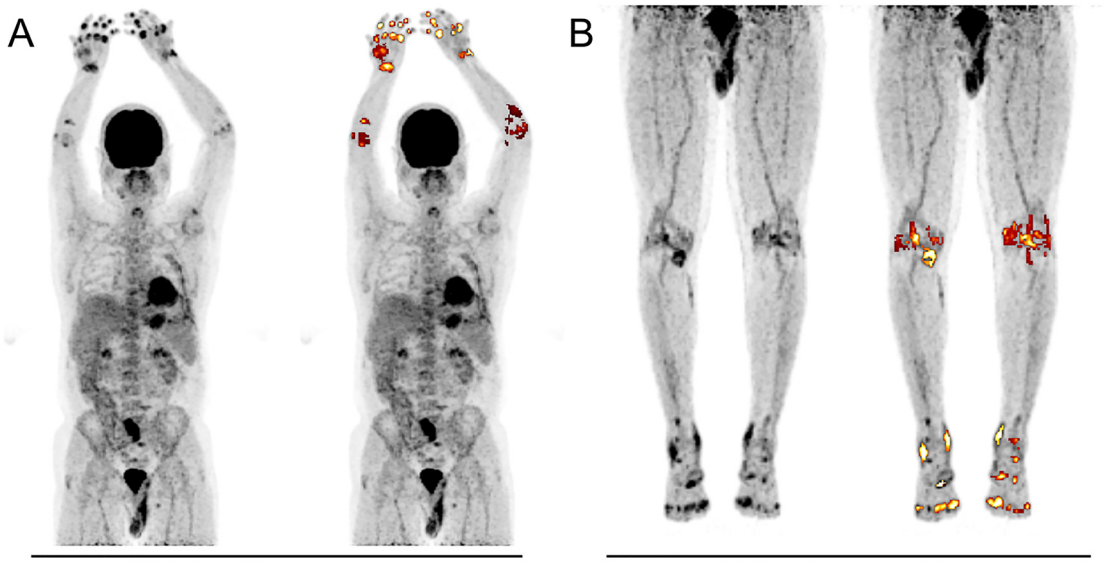
Figure 2: Delayed imaging for subject 2 (256 MBq injected, 14 min scan duration). (Left-to-right) images from scans performed at 1, 3, 8, and 10 h after injection. (Top row) MIP images. (Bottom row) Coronal views of thorax and abdomen. Head motion artifacts are visible in 8-h scan. (This research was originally published in *JNM*. Badawi RD, Shi H, Hu P, Chen S, Xu T, Price PM, Ding Y, Spencer BA, Nardo L, Liu W, Bao J, Jones T, Li H, Cherry SR. First human imaging studies with the EXPLORER total-body PET scanner. J Nucl Med. 2019 Mar;60(3):299–303. © SNMMI [37]).

(Figure 4) [43]. The introduction of total body PET (TBP) instruments [37, 38, 44, 45] has further enhanced the critical role of global assessment by this technique. Therefore, significant advances that have been made for imaging the entire body will result in optimal quantification of various diseases and disorders and monitoring their course by employing these novel instruments.

Introduction of TBP has initiated an unprecedented, diagnostic paradigm shift for dynamic and parametric imaging of all organs in the body simultaneously. However, the high cost of the current crystal-based PET technology limits rapid dissemination of this very powerful technology in hospitals around the world. Therefore, present development of PET technology focuses on the reduction of costs which may be achievable by reducing the scintillator [46], sparse detector configurations [47, 48] or application of BGO crystals [49–52]. There is also an utterly new solution under development at the Jagiellonian University that can lead to multifold reduction of costs of TBP by application of cost-effective plastic scintillators [13, 53–56]. The first laboratory PET prototypes based on plastics scintillators were built and successfully tested by the Jagiellonian PET (J-PET) research group [57–59]. Figure 5 shows an exemplary design of the total-body J-PET based on plastic scintillators [13] (Figure 5). The J-PET solution would enable economic construction of TBP instruments with even 2.5 m long axial field-of-view. It is estimated that the costs of total-body J-PET will be about five times lower than the cost of commercial TBP crystal systems [13]. Such long axial field-of-view would provide high and uniform sensitivity over the whole patient from the brain to the feet, opening new perspective for diagnosis of diseases affecting the body and brain simultaneously.

The significant impact of PET imaging on many disciplines of medicine has allowed its successful competition with other imaging modalities over the past decades. The widespread use of FDG for managing patients in many disciplines in medicine has revolutionized the practice of modern medicine. In recent years, it has become quite evident that contrast agents administered to enhance the performance of both CT and MRI are associated with significant side effects and toxicity. Therefore, it is conceivable that FDG and other tracers will replace radiologic contrast agents in future applications of medical imaging. It is quite evident that the potential for many novel PET tracers to assess numerous human diseases and disorders is enormous. As such, it is appropriate to portray the introduction of FDG-PET comparable in importance to that of the discovery of X-ray by Roentgen in 1895 and radioactivity by Curie (Figures 6 and 7) [23, 60].

In contrast to CT and MRI which were accepted without any hesitation, there was significant resistance to accepting PET as a viable modality for an extended period of time. In fact, most of the early applications of PET were supported by grants from funding agencies in the US and elsewhere around the world. Clinical applications of this modality were not approved in the US until 1998 when FDG-PET was approved for assessing patients with lung cancer. Fortunately, over the past decade, Medicare (the US government health insurance agency) has expanded its coverage for PET imaging of most malignancies, and this has allowed routine use of this technology in the US on a routine basis. Recently, FDG-PET was approved for routine assessment of inflammatory and infectious disorders, and



	MAV	SUVmax	SUVmean	pvcSUVmean	TLG	pvcTLG
Right Elbow	7.2	4.3	2.0	5.2	14.7	37.5
Left Elbow	20.0	3.4	1.5	3.7	29.9	74.1
Hands	41.8	8.8	3.3	7.0	136.3	292.4
TOTAL	69.0	16.5	6.8	15.9	180.9	404.0

	MAV	SUVmax	SUVmean	pvcSUVmean	TLG	pvcTLG
Right Knee	17.1	6.8	2.6	6.0	44.4	101.5
Left Knee	27.3	5.5	2.2	4.6	60.4	125.9
Right Foot	12.9	11.3	3.7	7.3	47.6	94.0
Left Foot	16.1	7.6	2.9	5.9	47.0	94.6
TOTAL	73.4	31.2	11.4	23.8	199.4	416.0

Figure 3: FDG-PET maximum intensity projection (MIP) of the upper body (A) and lower body (B) of a patient with rheumatoid arthritis. Synovial inflammation was assessed by segmenting FDG-avid joints using an adaptive thresholding algorithm (ROVER software, ABX GmbH, Radeberg, Germany). Metabolically active volume (MAV), max standardized uptake value (SUVmax), mean SUV (SUVmean), partial volume-corrected SUVmean (pvcSUVmean), total lesion glycolysis (TLG), and partial volume-corrected TLG (pvcTLG) were calculated and summed for each segmented region. The overall pvcTLG for this patient was 820.0 (Reproduced with permission from Saboury B et al. [40]).

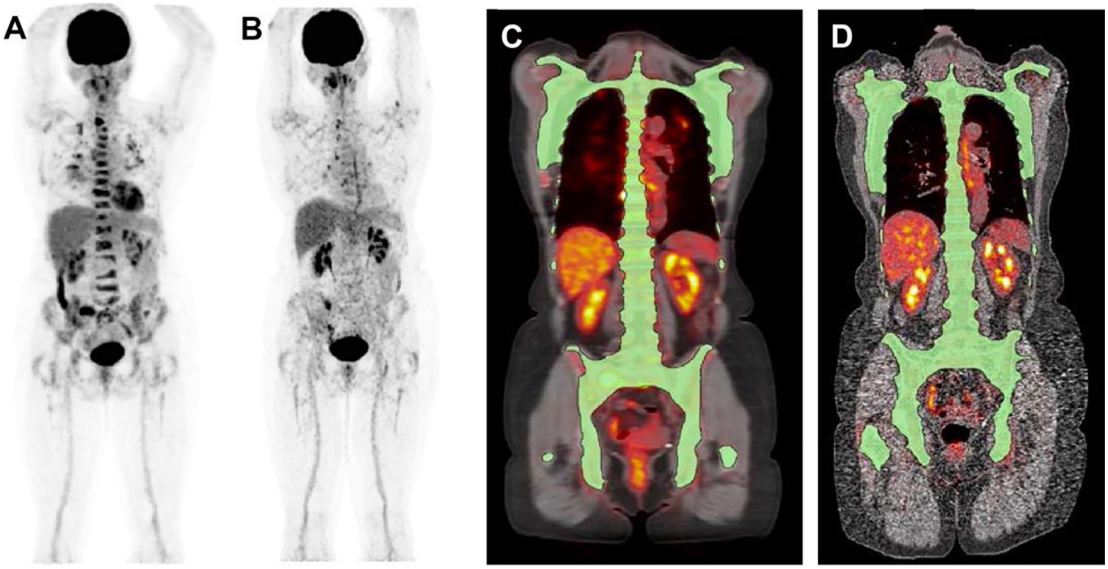


Figure 4: Potential role of global disease assessment by PET in MM. FDG uptake changes of MM lesions before (A) and after the treatment (B). High diffuse FDG uptake is observed in the entire spine before the treatment (A), whereas substantial reduction in FDG uptake is visually noted after the treatment (B). Segmentation of the entire skeleton followed by a closing algorithm allows for one to perform global disease assessment (OsiriX software, Pixmeo SARL, Bernex, Switzerland) (C, D). The pretreatment global average SUVmean (C) was 3.1 and decreased to 1.8 after the completion of the treatment (D) (Reproduced with permission from Zadeh MZ et al. [43]).

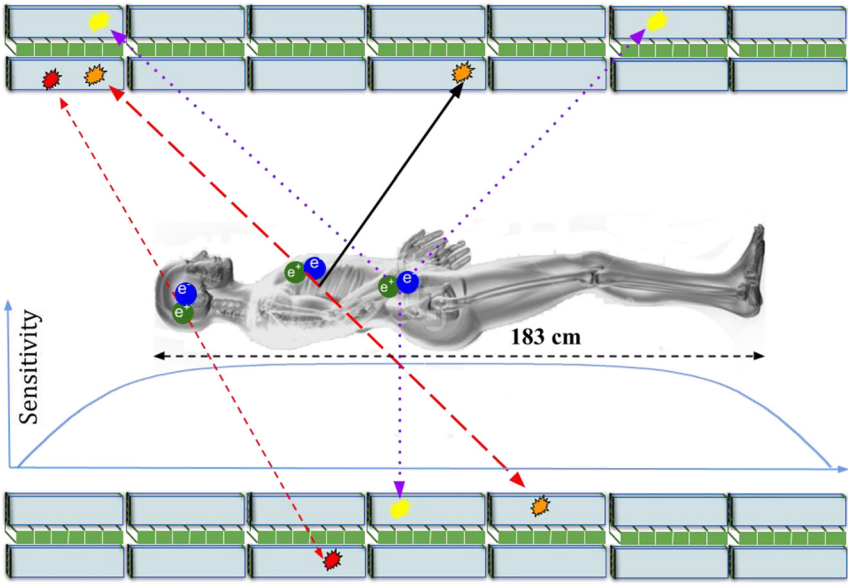


Figure 5: Example design of total-body PET based on plastic scintillators with superimposed view of the 183 cm tall patient [13]. Axial cross section of the tomograph composed of seven rings is presented. Each ring consists of independent detection modules composed of scintillator and WLS strips read out by SiPM matrices [55]. Here elements are not presented to scale. Dashed and long-dashed red arrows indicate example lines of response originating from e + e–annihilation into two photons. Black arrow indicates prompt photon useful for positronium imaging [15]. Blue dotted arrows demonstrate example of e + e–annihilation into three photons which may be also useful for positronium imaging [68]. Superimposed chart indicates the sensitivity (in arbitrary units) along the axial field-of-view. The presented sensitivity was calculated using the formula described in Moskal P et al. [67], and it includes the attenuation of annihilation photons in the patient. The attenuation in the patient flattens the sensitivity inside the long AFOV scanner.

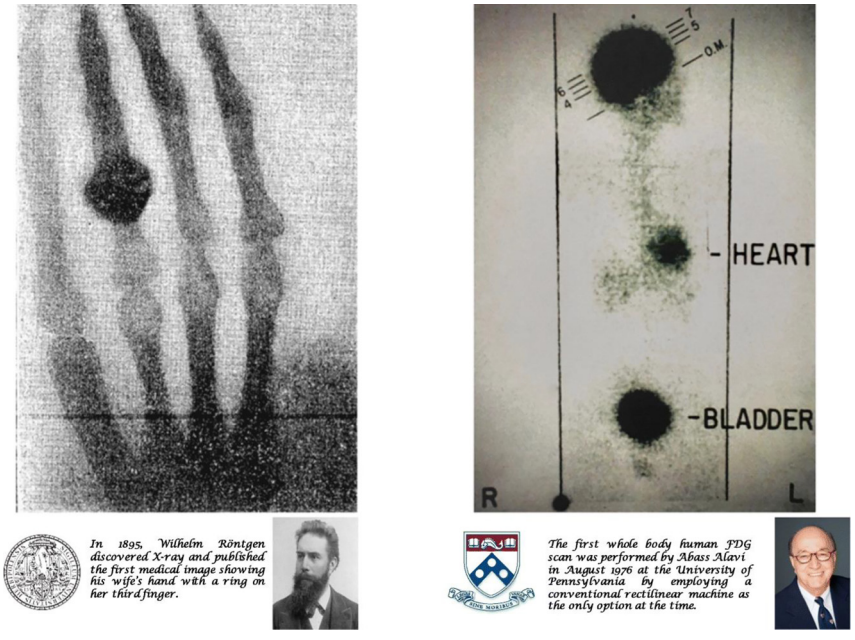


Figure 6: Introduction of X-ray to medicine by Röntgen in 1895 (left) has had a substantial impact on the day-to-day practice of medicine. Similarly, imaging with FDG (right) has been another major step forward by enhancing the role of medical imaging and this has led to an unparalleled impact on both research and patient care (Reproduced with permission from Alavi A et al. [27]).

this further enhances the role of this modality as one of the most effective imaging techniques in medicine.

Since its invention 6 decades ago, the evolution of PET technology has accelerated substantially during the past 20 years. The advent of TBP with significantly higher sensitivity (20–40 fold higher than conventional PET instruments [13, 38]) opened new diagnostic possibilities and led extending PET application to many complicated and important domains [13, 29, 38, 61–63]. The unprecedented increase of sensitivity provided by TBP enables unique

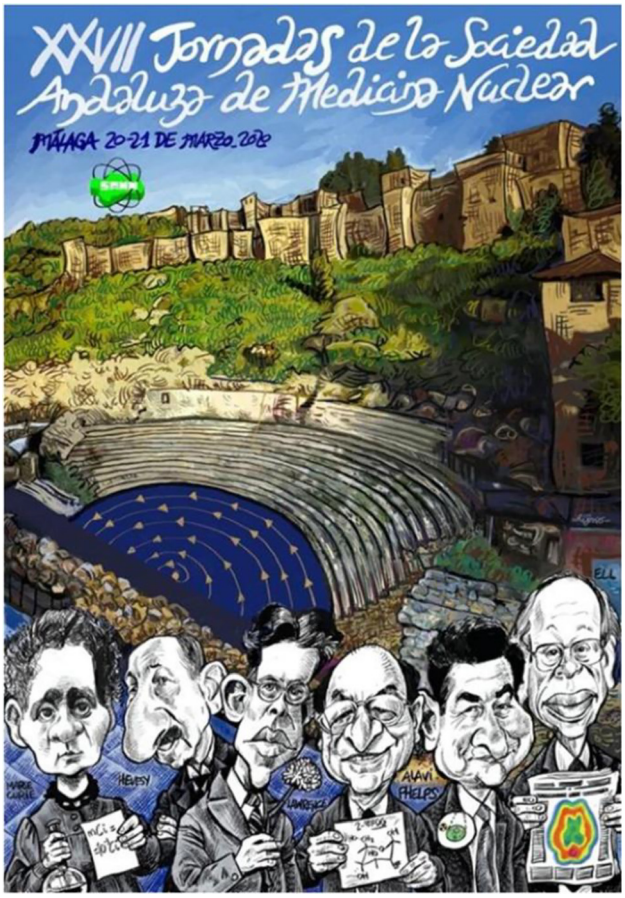


Figure 7: This poster was the symbol of the 27th annual congress of the Andalusian Society of Nuclear Medicine representing pioneers in the field of molecular imaging. These pioneers include (from left to right): Marie Curie (1867–1934), George Hevesy (1885–1966), Ernest Lawrence (1901–1958), Abass Alavi (1938-), Michael Phelps (1939-), and Peter Ell (1944-) (Reproduced with permission from Høilund-Carlsen PF et al. [60]).

dynamic and parametric imaging data with great success [64]. Such capabilities will enhance the role of PET in assessing patients with infections, cancer, and inflammatory diseases. While the first TBP systems are being introduced and tested in various clinics around the globe [37, 38, 44, 45], its critical role as the most advanced imaging modality is assessed in many settings. This is because, high sensitivity enables effective multiphoton imaging and use in PET tomography of three-photon annihilations and prompt photons emitted by some of the isotopes used for labeling radiopharmaceuticals such as ^{68}Ga or ^{44}Sc [13].

Three-photon annihilations and prompt photons emitted by radionuclides may provide useful diagnostic information about intra- and inter-molecular spaces and the concentration of bio-active molecules such as oxygen in various normal and disease sites [65]. In particular, the newly invented *positronium imaging* [14, 66, 67] which generates images of positronium properties in intramolecular spaces is a promising biomarker for *in vivo* tissue pathology [13]. The first three-photon image [68] and the first positronium image [15] acquired simultaneously along with standard PET metabolic image were recently reported by the J-PET research group. The positronium image of phantom comprised of tissues collected from patients, revealed meaningful differences of positronium lifetime in normal adipose and cancerous cardiac myxoma tissues [69, 70]. Recently, it was shown that positronium lifetime is changing linearly with the concentration of oxygen in organic liquids [71, 72], indicating its potential for detecting and quantifying hypoxia. An example of potential positronium imaging applications is shown in Figure 8. (Figure 8) This figure provides a pictorial explanation of positronium formation in prostate cancer cells. The radiotracer, [44Sc]Sc-PSMA-617, can be used in this domain since it possesses high affinity to prostate specific membrane antigen (PSMA), which is highly overexpressed in prostate epithelial cancer cells. Application of [44Sc]Sc-PSMA-617 and multiphoton TBP is an example of the possible enhancement

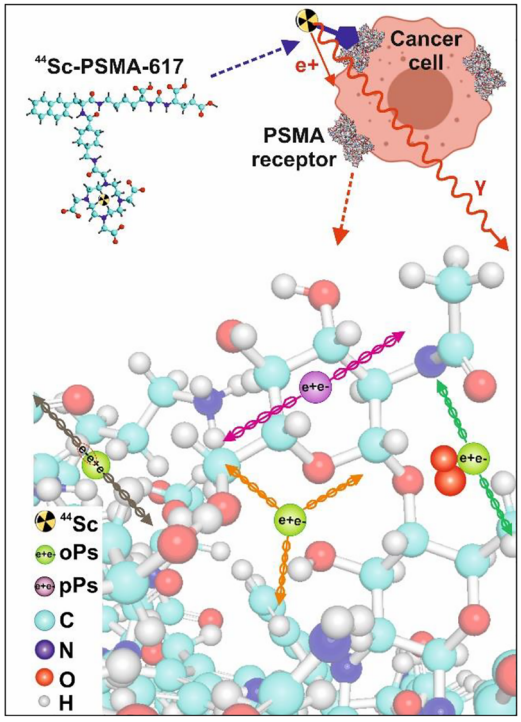


Figure 8: Basic processes involved in the "*positronium imaging*" of the prostate cancer [13]. PSMA-617 ligand is labeled with ^{44}Sc radionuclide emitting positron (e^+) and prompt gamma (γ) positron may form positronium atoms (oPs or pPs) trapped in intermolecular voids in PSMA receptors as indicated in the lower part of the sketch. Subsequently positronium atoms decay inside the molecule into two or three photons depending on the annihilation process. (Reproduced with permission from Moskal P et al. [13]).

of accurate diagnosis by simultaneous receptor overexpression imaging and positronium imaging. Finally, it is worth to stress that the high sensitivity of TBP imaging provided by positronium and multiphoton imaging capabilities will enable simultaneous multi-tracer imaging [13] opening a paradigm shift for introducing PET-based theranostics for personalized medicine in the future.

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