Review

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History of positron emission tomography (PET) in Poland

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Abstract: In this short chronological review, we showed the development of positron emission tomography (PET) starting from research on first isotopes through the concepts and prototype of PET machine to the current clinical practice and technological and clinical research. Particular emphasis was placed on a clear description of the milestones of PET development in Poland.

Keywords: J-PET; PET/CT; PET/MRI; positron emission tomography.

Discipline background

The beginning of nuclear medicine dates back to the 18th century when uranium was discovered. In 1858, Abel Niepce de Saint-Victor noticed the blackening of a photographic plate by exposure to uranium, and in 1896 Antoni Henry Becquerel discovered the presence of natural radioactivity of uranium compounds, for which in 1903, he was awarded the Noble Prize. In the same year, Maria Skłodowska–Curie and Pierre Curie were awarded Noble Prize for research on radioactivity. At the end of the 19th century, Paul Villard was the first who observed emission termed later gamma rays, which was confirmed in 1914 by Ernest Rutherford. As a result of the collaboration of A.H. Becquerel, E. Rutherford and Curie, three types of radiation were discovered: alpha, beta and gamma. In 1911 Fryderyk Soddy and Kazimierz Fajns introduced the term: “isotope”. In 1934 George de Havesy, “Father of the nuclear medicine”, applied his radioactive tracers to biological and medical research. This research contributed to the rapid development of nuclear medicine. In 1936 John Lawrence used the isotope in an organism for the first time, and one year later, Emilio Gino Serge and Glen Theodor Seaborg received technetium in a laboratory. In 1938 researchers from Berkley used Iodine 128 (^{128}I) for thyroid tests. A year later, the first results of Phosphorus 32 (^{32}P) treatment for leukaemia were announced, in 1940 Otto Hahn labelled red blood cells with radioactive iron, and in 1941 the first patients with hyperthyroidism received the ^{131}I treatment. In Poland, this took place in 1957 after the first radioisotope centre was established at the Department of Internal Diseases at Poznań University of Medical Sciences in early 1955–1956 [1]. In the meantime, in 1942 in Chicago, the first reactor was launched, and in 1948 Robert Hofstadter developed a scintillation counter for gamma radiation detection. Hal Oscar Anger developed and introduced the first gamma camera almost 10 years later which was installed in the Ohio State University Hospital in the USA in 1962. The first single-photon emission computed tomography (SPECT) camera was introduced in 1963 and 3 years later, it was first applied in a clinical setting [2].

Positron emission tomography on a timeline?

Sometimes it is incorrectly assumed that positron emission tomography (PET) is an invention of recent years. Its history goes back to years as distant as other nuclear medicine techniques (for example, the ^{13}N isotope obtained for the first time by Joliot–Curie in 1934 [3]). In early 1970, the “father of PET” Michel Ter-Pogossian developed the first PET. Tomographic imaging became available when David Chesler developed filtered back projection (FBP) tomographic reconstruction principles in 1971. Soon after, Gordon Brownell and Charles Burnham obtained their first PET scans [4, 5]. The breakthrough in the development of PET was the introduction of multi-row gamma cameras and then hybrid scanners. The idea to connect a PET scanner with other imaging modalities was first conceived by David

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Townsend in 1991. Just 10 years later, in May 2001, the first hybrid PET/computed tomography (CT) scanner (Discovery LS) was launched by General Electric (GE) Healthcare. The second milestone was the introduction of the most widely used radiotracer: glucose analogue labelled with Fluorine 18 (2-[^{18}F]fluoro-2-deoxy-D-glucose, 2-[^{18}F]FDG) mainly in oncology, but also cardiology and neurology [6]. The third milestone was the introduction of the term “time of flight” (TOF) which, used in PET/CT scanners, contributed to an increase in the quality of the images obtained [2].

Positron emission tomography infrastructure in Poland

The first ever publication on positron emission tomography in Poland was an interview with Prof. Wiesław Graban in 1983 [7, 8] and the first PET scanner in Poland was placed in the Oncology Centre in Bydgoszcz in 2003 (Figure 1). Moreover, this Centre also bought the first cyclotron and module synthesis, essential to conducting PET

Figure 1: Beginning of the Department of Nuclear Medicine in Oncology Centre in Bydgoszcz: Department of Nuclear Medicine (A), Cyclotron RDS 111 (B), Computer Technology and Imaging, CTI, USA; PET/CT scanner (C), Biograph, Siemens. Thanks to the Doctor of Health Science Violetta Pankowska.

examinations. Access to radiopharmaceuticals in Poland was limited, and they were delivered from abroad (especially from Berlin, Germany). Hence, the decision made by the then head of the Centre in Bydgoszcz turned out to be beneficial for the development of nuclear medicine. Based on the program introduced in 2005 by the Ministry of Health called "PET/CT network in Poland" during the next four years, next PET/CT scanners were placed at the Maria Skłodowska–Curie Institute of Oncology in Gliwice, Holy Cross Cancer Centre in Kielce (Figure 2), Medical University of Gdańsk, Greater Poland Cancer Centre in Poznan, and two in Warsaw: the Maria Skłodowska-Curie Institute of Oncology and Warsaw University of Medical Science [9]. In parallel to PET/CT scanners placed under the Ministry program, private PET/CT centres were established by Euromedic: in Warsaw (2009), Wrocław (2010) and Poznan (2010). Similarly, in 2011 in Olsztyn and then, owing to the European Union (EU) funds granted to VOXEL, PET/CT centres were opened in Łódź and Krakow [9].

The first registration of the [^{18}F]FDG for clinical **applications** in Poland was performed in 2007 by IASON Austria and in 2009 by Zingler/Eckert. While up to 2012, two Polish Centres (Gliwice and Bydgoszcz) had their cyclotrons; the production of radioisotopes was only for personal purposes. In 2012, the first radiopharmaceutical production was launched in Kielce. At the end of 2014, there were six cyclotrons [1], and at the end of 2019, there were nine cyclotrons in Poland for use for PET-radiopharmaceutical production, mainly [^{18}F]FDG, [^{18}F]FLT, [^{18}F]FET and [^{11}C]C-acetate [10]. The Polish radioisotope centre (POLATOM) is currently mainly responsible for producing and delivering radiopharmaceuticals in Poland [1]. In 2004 Bedford M. et al., in their manuscript, reported that in Poland, based on

Figure 2: Beginning of the Department of Nuclear Medicine in the Holy Cross Cancer Centre: beginning of construction works, March 2007 (A); reception of the building, January 2008 (B); Dispenser, Comecer (C); PET/CT scanner (Biograph, Siemens) (D). Thanks to the Professor Janusz Braziewicz.

epidemiology in European countries and indications for PET/CT, there should have been 28 centres with PET/CT scanners [11]. While in 2009 there were only nine centres with PET/CT scanners, till the end of 2012, this number doubled (up to 18 centres), and in 2014 there were 24 centres with PET/CT scanners in Poland [1]. The number of patients examined rose from 14,860 (in 2009) to 26,103 (in 2012). Currently, in Poland, there are 31 centres with PET/CT scanners. Unfortunately, centres that do not have access to their own cyclotron and, thus, cannot produce radiopharmaceuticals have a limited possibility of performing several PET/CT studies because of the high production and delivery costs. This shows the importance of developing and introducing PET/CT scanners into clinical practice, especially oncology.

New imaging modalities provide more precise disease diagnosis, including innovative hybrid imaging: positron emission tomography with magnetic resonance imaging (PET/MRI). Oncology Centre in Bydgoszcz was the first to have a PET/MRI in Poland (in 2013). Currently, two centres (Bydgoszcz and Białystok) provide these examinations for clinical/human purposes. This modality is beneficial not only in prostate cancer (with [^{18}F]F-choline or more recently with [^{68}Ga]Ga-prostate-specific membrane antigen [PSMA]) but also in the detection of other malignancies [12, 13]. As a curiosity, a mention should also be made of PET/MRI at the Warsaw University of Life Sciences (third, but not clinical, unit in Poland), used in animal research [14].

Clinical practice and research

Based on the European Association of Nuclear Medicine (EANM) rapport of 2005, in West Europe, there were 259 centres where PET or PET/CT scanners were placed. Still, only 10% of the examinations were performed for research purposes only. While PET/CT modality is mainly used in oncology (staging, restaging and detecting distant metastases of various cancer diseases), it plays a vital role in cardiology, neurology and other non-oncological conditions:

- Cardiology: Diagnosis and management of coronary artery disease, assessment of atherosclerosis plaque, myocardial viability, myocardial perfusion, etc. [15, 16].
- Neurology: Evaluation of various epileptic syndromes, in differentiating Alzheimer disease from other degenerative dementias, such as frontotemporal dementia (FTD) and Lewy bodies dementia (LBD) [17].
- Others: Diagnosis and treatment monitoring of inflammatory and infectious diseases [18–21], in HIV positive patients [22], in patients with fever of unknown origin (FUO) [23].

In Poland, the National Health Fund (NFZ) covers the cost of PET in:

- Oncology: Lymphomas (Hodgkin and non-Hodgkin), lung tumours, head and neck cancers (including Cancer of unknown primary (CUP) syndrome patients), melanoma, oesophagal cancer, colorectal cancer, breast cancer, thyroid cancer, recurrence of ovarian cancer, bone metastases (preferably with [^{18}F]fluoride), prostate and kidney cancer, neuroendocrine tumours and in patients planning for radiotherapy.
- Neurology: Epilepsy and brain tumours.
- Cardiology: Myocardial viability and perfusion.

Majority of the above mentioned indications are performed with most widely used radiotracer – [^{18}F]FDG, however, several PET centres also provide examinations with: [^{18}F]fluoride, [^{18}F]Choline, [^{18}F]FDOPA, [^{18}F]FET, [^{18}F]FLT, [^{68}Ga]Ga-DOTATE.

At present, it is crucial to introduce new radiopharmaceuticals and newer machines to personalize treatment. Research and innovations related to PET in Poland are visible both from a clinical and technological perspective. Lately, Królicki et al. used labelled DOTA-Substance P with the alpha emitter ^{213}Bi to treat recurrence in glioblastoma multiforme (GBM) [24]. Kunikowska et al. used radiotracer for prostate imaging – [^{68}Ga]Ga-PSMA-11 in imaging of hepatocellular carcinoma [25]. Both authors showed a pioneer use of radiopharmaceuticals in terms of better diagnosis and personalized treatment.

In December 2019, Poland's first ever digital PET/CT scanner (a United Imaging Healthcare uMI550 scanner) was installed in Warsaw (NUCLEOMED), and the first scans were performed at the beginning of 2020 [26]. It is the first system to shorten scan time to four bed positions (usually around 10–14 bed positions). Thus, it increases patient's comfort and reduces the possibility of movement artefacts during patient's examination.

The first PET tomography, which operates based on plastic scintillators, was designed and built at the Institute of Physics of the Jagiellonian University. Jagiellonian PET (J-PET) is a unique research device worldwide that allows not only imaging the metabolism of selected substances in living organisms but also imaging tissue pathology *in vivo* by measuring the properties of positronium (an atom composed of an electron and a positron) [27, 28]. **Moreover, the J-PET team recently reported another significant achievement: the first multi-photon PET [29] obtained by their machine. Another achievement**

worth noting in development of PET in Poland refer to radiopharmaceutical research group of Prof. Aleksander Bilewicz and group from the Heavy Ion Laboratory in Warsaw [30, 31]. The first group is working on the targeted Auger therapy using ^{193m}Pt and ^{195m}Pt radionuclides in breast and hepatocellular carcinoma [30] while the second one in the PET-SCAND grant aims to obtain radiopharmaceuticals based on scandium radionuclides, especially ^{43}Sc, ^{44}Sc and ^{47}Sc for PET imaging [31]. The first and only J-PET developed in Poland **together with progress in radiopharmaceutical production** opens way to new diagnostic approaches in terms of personalized treatment.

Conclusions

Polish science has played an essential role in establishing nuclear medicine as a medical discipline. Polish scientists and clinicians are currently conducting intensive research on innovative methods of using PET and new technological developments in this area.

The infrastructure of the PET centres in Poland has rapidly increased since the 1990s. Nevertheless, staying tuned to the latest PET developments needs continuous replacement of old machines by new ones that allow delivering the latest medical procedures with the required precision and patient's comfort improvement.

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