Experts' opinion

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Current state and prospects for the development of nuclear medicine in Poland

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Abstract

The aim of the report is to present the current state of equipment, radiopharmacy, dosimetry, and selected clinical applications, together with proposed new solutions and expected directions of development of classic nuclear medicine and positron emission tomography (PET). The statement presents the individual points of view of the members of the Commission for Nuclear Medicine of the Committee of Medical Physics, Radiobiology and Diagnostic Imaging of the Polish Academy of Sciences in the 2020–2023 term.

KEYwords: single photon emission tomography/computed tomography; positron emission tomography/computed tomography; scintigraphy; radioisotope therapy; radiopharmacy; therapeutic dosimetry

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Introduction

Today, imaging plays an integral role in many aspects of almost all human diseases. Non-invasive nuclear imaging is of great importance in terms of diagnosis, risk assessment, therapeutic decision-making, prognosis, short- and long-term monitoring for oncology, endocrinology, cardiology, neurology, or infections/inflammations. Apart from diagnostics, we treat hyperthyroidism or thyroid cancer, prostate cancer, neuroendocrine tumors, or joint inflammation using radioisotope therapy. The aim of the report is to present the current state of equipment, radiopharmacy, dosimetry, and selected clinical applications, together with proposed new solutions and expected directions of development of classic nuclear medicine and PET. The statement presents the individual points of view of the members of the Commission for Nuclear Medicine of the Committee of Medical Physics, Radiobiology and Diagnostic Imaging of the Polish Academy of Sciences in the 2020–2023 term.

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Equipment

Nuclear medicine plays a crucial role in the diagnosis and treatment of various diseases, and its significance has been on the rise over the past decade. Advanced technologies and devices are employed in nuclear medicine centers to provide real-time information, essential for making binding decisions regarding further therapeutic interventions. The current state of equipment in national and private nuclear medicine centers in Poland is presented below, relying on published data [1], available online information, and the National Consultant's report on the state of nuclear medicine in the years 2021 and 2022.

According to available information, there are currently 64 nuclear medicine centers in Poland, a surprisingly low number compared

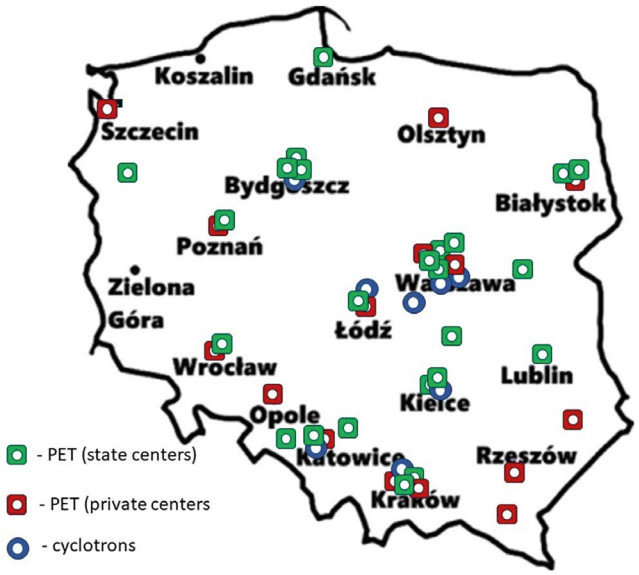

Figure 1. PET infrastructure in Poland in 2023

to other European countries. Most of these centers are in large multi-specialty hospitals. Nuclear medicine departments in smaller facilities, such as county hospitals, are almost nonexistent. Small private clinics, prevalent in other clinical branches of medicine in Poland, are exceedingly rare in nuclear medicine, presenting a limiting factor in its development.

Another significant limiting factor in the development of nuclear medicine appears to be a shortage of medical personnel. According to the April 2023 report [1], there were 195 specialized doctors employed in nuclear medicine centers in Poland in 2022. A crucial question here is how many of these doctors divide their activities between two or more centers. The lack of medical personnel is one of the factors limiting the implementation of nuclear medicine procedures.

Diagnostic studies in the field of scintigraphic procedures are conducted using 30 planar gamma cameras, 34 single photon emission computed tomography (SPECT) scanners, and 50 hybrid single photon emission computed tomography/computed tomography (SPECT/CT) scanners [1]. With the help of this equipment, a wide range of diagnostic and post-therapeutic procedures are performed.

Diagnostic studies involving PET scanners are conducted in 36 centers across the country (Fig. 1). Currently, there are 42 hybrid scanners in Poland, including 39 positron emission tomography/computed tomography (PET/CT) scanners and 3 positron emission tomography/magnetic resonance imaging (PET/MRI) scanners (one of which is dedicated exclusively for scientific research). For PET purposes, there are currently 8 radioisotope production centers, but practically only 5 private centers ensure commercial distribution, while 3 state centers produce radioisotopes for their own needs.

In 2023, the Ministry of Health announced and implemented the "Enhancement of nuclear medicine facilities — PET scanner replacement" initiative. Its aim was to improve access to the latest technical and technological advancements in the diagnosis and treatment of cancer by replacing outdated PET scanners. Their age counted from their first recorded use at least 10 years before January 1, 2023. As part of this initiative, 8 outdated PET/CT scanners were replaced with next-generation scanners, offering innovative features such as continuous table movement during examinations (flow-motion), reduction of metal artifacts in the reconstruction process, and a reduction in absorbed dose.

The project conducted by the Ministry of Health has led to a certain standardization of equipment and implemented procedures. Currently, in Poland, 17 PET/CT scanners belong to the "new generation", manufactured after 2018.

Quantitative PET, used as a diagnostic, prognostic, or therapy-monitoring tool, employs standardized parameters such as standardized uptake value (SUV), metabolically active tumor volume (MATV), or total lesion glycolysis (TLG). In conducted studies, it is essential for these parameters to be comparable across patients and centers, irrespective of the PET/CT system used. While most causes of quantitative PET measurement discrepancies can be overcome by adhering to existing guidelines starting with patient preparation through image acquisition to final image reconstruction, a specific problem is related to reconstruction-dependent differences encountered in recently introduced advanced image reconstruction algorithms, such as point spread function (PSF) or Bayesian penalty likelihood (BPL) correcting codes. It has been demonstrated [2, 3] that these new image reconstruction schemes yield significantly higher SUV values than conventional reconstruction algorithms, such as ordered subset expectation maximization (OSEM). Therefore, to harmonize the obtained data, an additional filtering stage must be applied. Hence, both in Poland and other European countries, the European Association of Nuclear Medicine (EANM) Research Ltd. (EARL) accreditation program is being implemented, utilizing a specific set of quality control (QC) procedures. An accredited EARL facility commits to standardize all oncological fluorine-18-deoxyglucose positron emission tomography/computed tomography ([^{18}F]FDG PET/CT) quantitative studies, strictly following EANM guidelines to ensure a minimum standard in the acquisition, reconstruction, and interpretation of PET/CT scans, using parameters approved by EARL.

Currently in Poland, the National Center for Radiological Protection (KCOR) is implementing accreditation for 10 nuclear medicine centers, which expressed the need for such accreditation, as part of the POL9027 program. Together with the 5 centers that have already obtained the EARL PET/CT certificate, this will lay the foundation for standardizing quantitative positron emission tomography results and ensuring radionuclide imaging procedures that meet the highest quality standards.

Recent studies [2, 3] conducted in 51 EARL-accredited centers emphasize the need for the legal implementation of quantitative PET harmonization in nuclear medicine centers in Poland through the European EARL PET/CT accreditation program. This task should be crucial for utilizing PET as a quantitative biomarker.

Radiopharmaceuticals

Radiopharmaceuticals are a special group of medicinal products because they contain a radioactive isotope in their structure. The high sensitivity of imaging devices allows them to be administered in very small chemical quantities, most often for

diagnostic imaging (SPECT or PET). Depending on the physical characteristics of the radioisotope emitted radiation, they are used in diagnostics and therapy. Radiopharmaceuticals comprise an essential tool of nuclear medicine.

In Poland, the classical scintigraphy of the lung, thyroid, heart, kidneys, and skeletal system are among the most often performed patient studies. PET examination is performed in the diagnostic imaging of cancer metastases to bone or soft tissue, detection of necrotic foci, primary and secondary tumors, pre-surgery localization and determination of tumor volume, evaluation of disease spread and efficacy of treatment, as well as in the differentiation of benign and malignant neoplasms. The list of standard procedures and guidelines in nuclear medicine was announced by the Minister of Health on 22 December 2014 [4]. The updated version of this list is currently being prepared.

Molecular imaging has found its broad application in oncology, because of the physiologic features of the primary and metastatic lesions, which have been known to researchers since the beginning of the 20th century. The phenomenon of increased demand for glucose by cancer lesions (known as Warburg's effect) is the most frequently utilized imaging mechanism. To achieve that the radiopharmaceutical [^{18}F]FDG (fluorodeoxyglucose) is used, a combination of fluorine-18 and glucose analogue. [^{18}F]FDG belongs to the most often used radiotracers for PET/CT of various body regions.

According to the information available in the medical register maintained by the Ministry of Health [5], in February 2024 in Poland, there were 62 medicinal products that were granted marketing authorization for diagnostics (ATC group V09), which were provided to the market by more than 20 responsible entities both from Poland and from abroad. In this number, when the classic radiopharmaceuticals (*i.e.* radiolabeled with technetium-99m or iodine-131) are concerned, the strongest position is held by the National Centre for Nuclear Research (POLATOM). Among the suppliers of radiopharmaceuticals radiolabeled with fluorine-18, one should mention Voxel SA and Synektik Pharma Ltd. It's worth mentioning, that marketing authorization for commonly used radiopharmaceutical for PET imaging, [^{18}F]FDG, has been granted to 9 different responsible entities. Only a few laboratories produce ^{18}F-radiopharmaceuticals for in-house use and are granted marketing authorization for [^{18}F]FDG: the Maria Skłodowska-Curie National Research Institute of Oncology in Gliwice and Prof. Łukaszczyk Oncology Center in Bydgoszcz. In both these institutions the medical cyclotrons and radiopharmaceutical manufacturing facilities were installed aiming at the manufacture of [^{18}F]FDG and other radiopharmaceuticals radiolabeled with short-lived fluorine-18 or carbon-11 for their patients. The regulations related to the in-house production of radiopharmaceuticals in Poland are not clear. This topic is still raising emotions because the requirement of marketing authorization for locally produced radiopharmaceuticals is difficult to fulfill by healthcare establishments and therefore limits the access of patients to modern diagnostic tools. Working out a reasonable regulatory solution would be appreciated. The recommendations of the Radiopharmacy Committee of the EANM could serve as a reference [6]. In 2022, the number of diagnostic procedures with the use of positron-emitting radiopharmaceuticals reached 70,210 and it was 24.1% higher than in 2021, while the number of classic SPECT diagnostic procedures was a the level of 380,000 [1].

There are 14 radiopharmaceuticals for therapy listed in the Polish medical register (ATC group V10). Among them are radiopharmaceutical precursors (such as ^{177}Lu or ^{90}Y solutions for radiolabeling) as well as ready-to-use medicinal products such as radiopharmaceuticals radiolabeled with iodine-131 (^{131}I-sodium iodide, ^{131}I-metaiodobenzylguanidine), radium-223 (^{223}Ra chloride, Xofigo) or lutetium-177 ([^{177}Lu]Lu-DOTA-TATE, Lutathera). To sum up, both the well-established radiopharmaceuticals and the novel ones are widely available for nuclear medicine applications in Poland. In 2022 around 4,600 treatment procedures were performed in patients with oncological diseases and 15,000 procedures in patients with benign thyroid diseases [1].

At this point, it would be worth mentioning the achievements of Polish researchers in the implementation of radioligand treatment (RLT) and later on the targeted alpha therapy (TAT) and the impact of their investigations on the global trends in therapeutic applications of radiopharmaceuticals. The RTL has more than 20 years long history in Poland [7]. The pioneering roles of Warsaw Medical University and Jagiellonian University Medical College deserve respect in this context. RTL is further developed in Poland, and several studies are ongoing in this area, an example being the multicenter project DuoNen. The protocol of the DuoNEN clinical trial, a phase III, multicenter, non-commercial clinical study (EudraCT No. 2020-006068-99) was designed to develop the optimal algorithm of radioligand treatment for patients with disseminated neuroendocrine tumor (NET) based on personalized dosimetry.

Many projects and investigations on novel radiopharmaceuticals were carried out in cooperation with clinical centers. One of the first research programs was oriented on the usefulness of radiolabeled somatostatin analogs in the localization of primary tumors and for the assessment of the level of disease advancement in patients with neuroendocrine neoplasms (NEN), which were named carcinoids at that time. Initially, these studies were carried out by researchers from POLATOM within the International Atomic Energy Agency coordinated project and continued within the international collaboration in COST Actions, among them COST Action B12 "Radiotracers for In vivo Assessment of Biological Function — New Directions"; COST Action MB0607 "Targeted Radionuclide Therapy"). Further on the collaborative research grant between Jagiellonian University Medical College and POLATOM resulted in the introduction of somatostatin agonist (^{99m}Tc–EDDA/HYNIC-octreotate) into the diagnostic algorithm of patients and the broader use of somatostatin receptor scintigraphy [8]. This novel diagnostic modality not only demonstrated that the incidence of NEN is higher than anticipated but also provided a sensitive tool for localizing diagnostics of NEN, for optimization of staging and therapy follow-up, which revolutionized the clinical management in this group of patients [8]. The first original diagnostic radiopharmaceutical [^{99m}Tc]Tc–EDDA/HYNIC-octreotide (Tektrotyd) was granted marketing authorization in 2004 (National Centre for Nuclear Research, POLATOM). At present, the radiolabeled somatostatin analogs (now more often when radiolabeled with gallium-68 for PET) are used routinely and the results of imaging serve the choice of therapeutic schemes. In addition, these studies gave deeper insight into the biology of NENs, which is still a challenge for clinicians.

The collaboration with Prof. Helmut Macke from the University of Basel, Switzerland/University Hospital in Freiburg, Germany, needs to be emphasized. It prompted the first diagnostic and

therapeutic applications of somatostatin analogs. Based on it several new projects were initialized and completed with the support of international grants. They are briefly characterized here. The technetium-99m radiolabeled GLP-1 receptor ligand was found very effective in detecting insulinoma, the tumor which is very difficult to localize using other techniques [9]. Another example of this multicenter international collaboration was the project "Phase I clinical trial using a novel CCK-2/gastrin receptor-localizing radiolabeled peptide probe for personalized diagnosis and therapy of patients with progressive or metastatic medullary thyroid carcinoma" Grant-T-MTC (Transcan; 2012–2018; FP7) and recently another project "Novel ^{99m}Tc-labeled somatostatin receptor antagonists in the diagnostic algorithm of neuroendocrine neoplasms — a feasibility study" TECANT (ERA PerMed; 2018–2023; Horizon 2020). Both projects were coordinated by the Jagiellonian University Medical College with the contribution of POLATOM and clinical partners from Austria, Slovenia, Germany, Italy, and the Netherlands. The safety of the novel radiolabeled gastrin analog (CP04) and its efficacy in the detection of the primary tumors and their metastases in patients with medullary thyroid carcinoma was demonstrated in the phase 0/1 clinical trial conducted in the first of these projects [10]. In the second project, it was demonstrated that using the radiolabeled somatostatin receptor antagonist it is possible to assess the status of receptor expression in neuroendocrine neoplasm tissue compared to the routinely used agonists [11]. The results of both these projects open the pathway to further studies on the therapeutic application of both biomolecules in modern radionuclide therapy in personalized precision medicine algorithms.

Next to the existing radionuclide production facilities such as the Maria research reactor at NCBJ and several medical cyclotrons located both in public and private hands, there are new infrastructures expected, to mention the unique 30 MeV cyclotron accelerating protons, deuterons, and alpha particles, located in the CERAD facility at NCBJ. It is expected to increase the availability of novel radionuclides for medical applications.

Oncology

Despite significant advancements in nuclear medicine in Poland, the numbers concerning the essential diagnostic procedures in oncology are insufficient. Total number of PET/CT or PET/MRI procedures performed with different tracers accounted for 83,605, including 70,210 procedures with [^{18}F]FDG, 4,743 with [^{18}F]F/[^{11}C]C-choline, 4,175 with [^{68}Ga]Ga-PSMA, 1,546 with [^{18}F]F-PSMA, 2,303 with [^{68}Ga]Ga-DOTA-TATE [1]. It is important to note that nuclear medicine facilities are mainly located in large, multidisciplinary hospitals, which generally act as tertiary referral centers. In smaller hospitals, such as district hospitals, there are typically no nuclear medicine units. This means that for most cancer patients, the nearest SPECT or PET scanners are over 100 km away. Consequently, physicians often do not refer patients for nuclear medicine examinations and instead limit themselves to radiological examinations, which are more readily available. Another main limitation in the development of Polish nuclear oncology stems from a shortage of well-trained medical personnel. Considering the reasons for this situation, it should be emphasized that the salary of specialized medical personnel in our country is unfortunately insufficient. Many specialists leave the country to seek employment abroad. These limitations are likely responsible for the relatively slow pace of catching up on the backlog caused by the COVID-19 pandemic. In 2022, we still had not reached the number of diagnostic procedures in oncology compared to the pre-pandemic state in 2019 [1]. A decrease in the number of procedures was noted in the area of [^{153}Sm]Sm-EDTMP, which is likely related to the gradual phase-out of this radiopharmaceutical, which can be replaced by alternative radiopharmaceuticals. Similar reasons probably underlie the 10.7% decline in [^{131}I]-mIBG. A rather concerning decrease was observed in the area of radiolabeled somatostatin analogs, including DOTA-TATE, which likely has other, commercial causes. Overall, the catching-up process can be considered satisfactory in terms of an average increase of 4.8%, but unsatisfactory in terms of the insufficient number of diagnostic oncology procedures.

As for the state of scientific research in nuclear oncology, it is more than satisfactory in our country. It mainly concerns systemic radionuclide therapies applied in oncology. These issues are discussed in more detail in the chapter on isotope therapy.

According to the authors, the Polish nuclear medicine community is prepared for the next challenges in the field of oncology. The development of new technologies in nuclear medicine depends not only on the use of modern equipment, but above all, on the introduction of new radiopharmaceuticals that enable the assessment of unknown aspects of neoplastic processes. New radiopharmaceuticals will also play an important role in the development of a new approach to treatment — in the development of precision medicine.

Precision medicine means a new personalized therapeutic approach that takes into account individual biological factors in each patient. This assumption replaced the previous idea of using similar treatment methods in groups of patients with similar disease symptoms. Precision medicine requires a full analysis of the molecular profile in each patient. Obtaining such a profile requires the introduction of some specific biomarkers. A molecular profile is possible to obtain if the following tests are available: genomic, epigenetic, transcriptomic, proteomic, and metabolomics.

One of the elements of precision medicine is theranostics — which stands for the integration of the obtained medical data with the intent to choose the best method of treatment. This approach follows the rule: "first check whether the given treatment will be effective then (and only then!) apply it". Nuclear medicine is a dedicated specialty in the development of this new idea in medical science. In line with this principle, radioisotopic methods of analgesic treatment have been introduced in patients with bone metastases: treatment of pain symptoms with radiopharmaceuticals labeled with beta/alpha emitters is indicated if the examination after administration of a diagnostic radiopharmaceutical (with the same pharmacological profile, but labeled with gamma emitter ^{99m}Tc) shows high accumulation in metastatic foci.

Another example pertains to the isotope treatment of patients with neuroblastoma or phaeochromocytoma. These tumors show a significantly increased expression of norepinephrine transport mechanisms. The same mechanisms can transport the adrenaline analog meta-iodo-benzyl-guanidine (mIBG). In patients with inoperable or advanced distant metastatic tumors, [^{131}I/^{123}I]I-mIBG imaging plays a pivotal role in assessing response to treatment and in assessing potential therapy [^{131}I]I-mIBG. Therapy with [^{131}I]I-mIBG may be considered if scintigraphy after

administration of the diagnostic dose indicates a sufficiently high accumulation of the radiopharmaceutical.

Correspondingly, a similar principle applies to the treatment of neuroendocrine tumors (NETs). These tumors are usually diagnosed in the stage when multiple metastases occur and surgical treatment proves insufficient. A characteristic feature of many of these tumors (but not all) is a very high expression of the somatostatin receptor system. Therefore, radiolabeled somatostatin analogs can be used as a therapeutic radiopharmaceutical. Nevertheless, treatment of neuroendocrine tumors with radioisotope-labeled analogs of somatostatin is proposed if a diagnostic scan with somatostatin analogs is positive. The positive results of this study constituted the basis for the approval of [^{177}Lu]Lu-DOTA-TATE therapy in the United States and Europe.

At present prostate cancer is the most commonly diagnosed cancer among men in the Western world, accounting for approximately 25% of all new male cancer cases. Therefore, imaging studies are recommended in the initial diagnosis, staging, restaging as well as relapse of the disease. Recently, treatment of prostate cancer with beta/alpha emitters — prostate specific membrane antigen (PSMA) is being evaluated, but only in the group of patients with positive results of [^{68}Ga]Ga-PSMA scan. The use of PSMA is the best example of the theragnostic procedures currently being introduced in nuclear medicine. It should be noted that the procedures listed are performed in Polish nuclear medicine facilities.

However, introducing new procedures to the healthcare system is delayed. As a rule, this process takes 3–5 years. We are currently waiting for a decision on financing the theranostic procedure related to the treatment of prostate cancer. Convincing decision-makers about the need to introduce the changes proposed by our community is one of the most difficult tasks.

Radionuclide treatment in oncology is also discussed in the section on therapy.

Endocrinology

The issues of diagnosis and therapy in endocrinology became the earliest tasks of nuclear medicine. However, with the advancement of diagnostic methods, some nuclear medicine procedures performed for the diagnosis of thyroid diseases have been replaced by other, non-isotopic methods. For instance, thyroid scintigraphy has lost its privileged position in the diagnosis of thyroid nodules in favor of ultrasonographic examination. The main indication for thyroid scintigraphy now is the suspicion, based on a finding of a decreased TSH concentration, of an autonomic nodule. Also important is imaging with ^{131}I in suspicion of thyroid retrosternal goiter. Whole body scintigraphy with ^{131}I is performed for diagnosis of metastasis due to well-differentiated thyroid cancer. Nuclear medicine plays also an important role in the treatment of iodine avid metastases.

The thyroid iodine uptake test is no longer a routinely used method for assessing thyroid function and is currently performed when planning thyroid benign disease treatment with radioiodine ^{131}I. It should be mentioned that treatment with ^{131}I is still a very valuable non-invasive widely used procedure performed in patients with euthyroid goiter, toxic goiter, and Graves Basedow disease.

Radioimmunoassays for determining hormones have also been replaced by immunoenzymatic methods. Apart from thyroid diseases diagnostic and treatment procedures in the field of endocrinology most applicable are the following indications:

1. In primary hyperparathyroidism, where [^{99m}Tc]Tc-MIBI scintigraphy allows the localization of a parathyroid adenoma [12].
2. In parathyroid cancer, but also in parathyroid adenoma, choline PET/CT allows often the localization of parathormone-secreting foci. Most often, [^{18}F]Fluorocholine may be used [12]. Alternatively, in case of negative standard imaging, other PET radiopharmaceuticals should be applied.
3. In ACTH-independent Cushing's syndrome, where scintigraphy using radioiodine-labeled cholesterol detects an autonomic adenoma of the adrenal cortex [13].
4. Similarly, adrenal scintigraphy is used to localize the primary hyperaldosteronism foci. However, instead of iodinated cholesterol, it is more useful to perform PET/CT using [^{11}C]-labeled metomidate [14].
5. In neuroendocrine tumors, for detection of somatostatin receptors [15].

While the methods, based on [^{99m}Tc]Tc-MIBI and on other [^{99m}Tc]Tc-based radiopharmaceuticals are generally accessible in the whole of Poland, the application of PET/CT methods is more limited to the specialized centers. We may stress that, unfortunately, PET/CT diagnostic methods based on [^{11}C]-derivatives are generally not available in our country. Thus, we may conclude that further development of [^{11}C]-based PET radiochemistry is necessary to meet the needs of modern endocrinology.

Nuclear medicine methods play a very important role in the diagnosis and treatment of neuroendocrine tumors, it has become an integral part of endocrinology over the last 30 years. Neuroendocrine tumors account for about 2% of all malignancies, and their incidence steadily rises. They are usually slowly growing tumors diagnosed quite often at an advanced stage. The diagnosis is based on the patient clinical picture, blood biomarker evaluation, and imaging modalities like CT, MRI, and somatostatin receptor scintigraphy. Scintigraphy is done mainly with the radiopharmaceutical [^{99m}Tc]-EDDA/HYNIC-TOC or [^{68}Ga]Ga-DOTA-TATE. The second one requires the ^{68}Ge/^{68}Ga generator and PET/CT modality which makes the procedure less available than somatostatin receptor scintigraphy with technetium-labeled radiopharmaceutical. The radioisotope-labeled somatostatin scintigraphy is helpful in diagnosing, necessary for staging and crucial in deciding on treatment with not labeled so-called "cold" or radio-labeled "hot" somatostatin analogs for metastatic neuroendocrine tumors [16, 17].

Approving of Lutathera® — a somatostatin analog labeled with ^{177}Lutetium by the European Medicines Agency (EMA) in 2017 and by the Food and Drug Administration (FDA) in 2018 as the first radiopharmaceutical for the treatment of inoperable or metastatic neuroendocrine tumors of the pancreas and gastrointestinal tract gives the chance of very effective palliative treatment in patients with disseminated disease [18, 19].

More information about radionuclide treatment is provided in the section on therapy.

Cardiology

Of the 32 current guidelines of the European Society of Cardiology (ESC), 11 refer to clinical situations taking into account radioisotope diagnostics. Nine of them contain indications for

myocardial perfusion scintigraphy (MPS) using the SPECT or PET technique, six of which have class I indications [20–26]. These are guidelines on chronic coronary syndromes (CCS), myocardial revascularization, adult congenital heart disease, cardiovascular assessment and management of patients undergoing non-cardiac surgery, management of patients with ventricular arrhythmias and the prevention of sudden cardiac death, and on cardio-oncology.

Cardiac isotope imaging with the assessment of myocardial perfusion, function, and viability has been known for decades and remains a robust, evidence-based, and widely available modality for assessing clinical status and resulting therapeutic recommendations. In CCS, the superiority of PET over SPECT MPS examinations may be observed in patients with suspected coronary microvascular angina due to the quantitative assessment of myocardial blood flow (MBF) and coronary flow reserve (CFR) [21, 22]. PET MPS allows dynamic imaging with ^{82}Rb, [^{13}N]NH_3, [^{15}O]H_2O to quantify in absolute terms MBF, but because of the complexity of protocols for short-living positron radioisotopes, this technique has been rarely used. In Poland, in 2021, PET share in cardiological heart examinations was only 0.8% (269 examinations) [27]; the classic nuclear medicine share in cardiological patients was over 99% and the most frequently performed cardiological study was SPECT MPS with [^{99m}Tc]Tc-MIBI. The situation may change with the introduction of promising novel fluorine ^{18}F-labeled perfusion tracers, of which [^{18}F]Flurpiridaz is at the most advanced stage. There are several other ^{18}F-tracers for PET MPS under development, including Polish original product [^{18}F]SYN2 — ^{18}F-labelled derivative of N-nonyl acridine orange.

Contemporary applications of nuclear cardiology beyond perfusion assessment improve the assessment and facilitate the treatment of systemic diseases with cardiovascular consequences. The current development of nuclear cardiology, which is gaining clinical acceptance, can be summarized in three terms: infection, infiltration, and inflammation [28, 29].

In suspected transthyretin (ATTR) cardiac amyloidosis (CA), heart scintigraphy with bone markers [^{99m}Tc]Tc-DPD/HMDP/PYP is a class I indication [30]. In patients with known heart failure, especially heart failure with preserved ejection fraction, in whom echocardiography or cardiac MRI shows findings suggestive of CA, in the absence of monoclonal gammopathy, SPECT/CT scintigraphy if negative, excludes ATTR CA, or if positive, is highly specific for ATTR CA [31]. The test result allows for avoiding endomyocardial biopsy and, in the case of a positive test, for introducing targeted therapy. Amyloid-binding PET tracers, developed for imaging beta-amyloid in the brain, are capable of imaging several types of amyloid in the heart ([^{11}C]C-PiB, [^{18}F]Florbetapir, [^{18}F]Florbetaben, [^{18}F]Flutemetamol, [^{124}I]I-Evuzamitide). The tracers are currently under investigation for diagnostic efficiency in ATTR CA, light-chain (AL) CA, and rare forms of CA. As PET is quantitative, work is currently underway to quantify amyloid burden for identification of early CA and response to therapy. However, the binding of the mentioned tracers is independent of precursor protein, and PET imaging cannot differentiate among the various types of amyloidosis. Further research and large-scale studies are necessary to assess the diagnostic role of positron tracers in CA [32].

In the case of ambiguous cases of infective endocarditis (IE), especially in the case of artificial valves and implantable devices supporting the functioning of the heart, molecular examinations are of high value, with SPECT/CT being a more specific technique and PET/CT being a more sensitive one [33, 34]. In IE, PET scan with [^{18}F]FDG is a class I indication in suspected prosthetic valve IE, and scintigraphy studies with labeled leukocytes — class IIa [33]. PET is also a class I indication to detect pocket infection in suspected CIED (cardiovascular implanted electronic device) — associated IE (and class IIb to detect lead infection). Brain or whole-body imaging with PET or classic scintigraphy is a class IIa indication to detect distant lesions in suspected native or prosthetic valve IE. In Poland in 2021, the most frequently performed PET examination in cardiological patients was the diagnosis of inflammation in the chest.

Molecular imaging enabling the assessment of inflammation of vessel walls and the morphology of atherosclerotic plaque, especially in the aspect of the ongoing atherosclerotic process, remains the domain of PET, PET/CT, and PET/MRI examinations.

In primary systemic vasculitides, a heterogeneous group of autoimmune diseases characterized by inflammation of blood vessels, [^{18}F]FDG PET/CT plays a role in the diagnostic work-up of large- and medium-sized vessels such as giant cell arteritis (GCA) and Takayasu arteritis (TAK) and can provide complementary information to other imaging techniques [35–37]. In primary large vessel vasculitis, USG of temporal and axillary arteries remains a first imaging modality in patients with suspected GCA, but [^{18}F]FDG PET/CT was introduced as a second-line alternative for the assessment of cranial and extracranial arteries. In patients with suspected TAK, MRI is a preferable tool of choice to confirm diagnosis, with [^{18}F]FDG PET/CT being an alternative imaging modality.

In the diagnosis of vascular graft and endograft infections (VGEI) and its extent, routine assessment includes computed tomographic angiography (CTA) as the first imaging diagnostics performed in most cases. EANM guidelines on imaging infection in vascular grafts, published in 2022, state that molecular imaging (SPECT/CT with labeled leukocytes and [^{18}F]FDG PET/CT) is a useful diagnostic tool (with high sensitivity, reaching up to 100%) in suspected VGEI, especially in cases of negative or doubtful CTA results [38]. The main disadvantage of PET/CT is relatively low specificity (59–81%) and SPECT/CT seems to be more beneficial in the early postoperative period due to the lower number of false-positive results [39, 40]. Further clinical studies are necessary to develop the best diagnostic algorithm in patients with VGEI.

A molecular imaging method that is currently undergoing validation, is coronary microcalcifications assessment with [^{18}F]NaF PET/CT. While vascular macrocalcifications identified in CT imaging represent a stable end-stage of coronary plaque development, microcalcifications of the coronary arteries are identified with the formation and progression of early atherosclerotic changes, and at the same time high-risk, unstable plaques. The idea was based on observations of increased uptake of [^{18}F]NaF in atherosclerotic culprit lesions responsible for myocardial infarction (MI) [41]. It is suggested that [^{18}F]NaF uptake is a powerful independent factor of MI in patients with established coronary artery disease (CAD) [42, 43]. Machine learning methods confirm the role of the [^{18}F]NaF PET/CT in risk stratification in patients with CAD [44]. Also, in patients with cardiovascular disease high thoracic aortic [^{18}F]NaF uptake was associated with stroke risk [45].

The progress that has been made in the field of cardiac imaging is characterized by several aspects. First, nuclear cardiology has benefited from the widespread acceptance of hybrid

imaging technology. The combination of isotope imaging with CT enables the assessment of functional and morphological abnormalities in one place, for example by integrating the assessment of perfusion with the assessment of calcium in the coronary vessels, or narrowing of the coronary vessel lumen. However, SPECT MPS examinations, performed using classic Anger gamma cameras, suffer from the lack of quantitative assessment of regional blood flow (MBF, in mL/g/min). Another aspect of progress in nuclear cardiology is a strong trend toward shortening acquisition times and reducing radiation exposure. This can be achieved using semiconductor detectors for dedicated cardiac SPECT systems [46]. Since 2007, an increasing number of nuclear medicine departments are using cardiac-centered gamma cameras, in which the large conventional sodium/iodine (NaI) scintillating crystal has been replaced by many small semiconductor cadmium-zinc-telluride (CZT) detectors. There were 5 CZT systems in Poland in 2021. CZT gamma cameras provide a three- to eight-fold higher system sensitivity compared to conventional Anger cameras. Also, the configuration of multiple detectors provides angular coverage of the object (heart) sufficient for performing tomography and the systems do not rotate to obtain SPECT acquisition. These technological solutions (solid-state stationary SPECT cameras of high sensitivity) enable fast dynamic 3D imaging creating the basis for quantitative assessment of MBF in absolute terms [47] and therefore it has become possible to evaluate ischemia in terms of microcirculatory disorders. Further development of CZT SPECT MBF methodology requires further work on image correction, in particular on attenuation correction, but this technology holds the promise of moving closer to the PET MBF methodology and improving the diagnostic and prognostic accuracy of perfusion imaging with classic nuclear cardiology.

Therapy

The systemic application of various pharmaceuticals in the treatment of disease has begun with the initiation of 131-radioiodine administration for patients with Graves–Basedow disease [48]. The enormous success of this type of therapy led to the application attempts of various radiopharmaceuticals in different diseases, but up to now, the application possibilities in the treatment of cancer are considered most frequently. In Poland, radioiodine therapy in hyperthyroidism has gained many followers in last years. However, the discussion between the choice for prolonged antithyroid drugs therapy and radioiodine therapy is still unsolved.

Systemic radioisotopic therapies are finding broader applications in nuclear oncology. The precursor to this was radioactive iodine therapy in thyroid cancer, introduced in the 1940^s and representing a significant advancement in the treatment of differentiated thyroid cancer [48]. However, progress in medical science has led to more precise and, therefore, more limited, personalized indications for its use [49]. Undoubtedly, the success of this therapy has paved the way for the development of other radioligand therapies in various cancers originating from different organs. Radioiodine therapy is currently being used in seven centers in Poland — in Gliwice, two in Warsaw, Łódź (Zgierz), Poznań, and Białystok. A center in Lublin has recently been established and is thriving. These centers are deemed to fully meet the demand for radioactive iodine treatment of thyroid cancer in our country and are well-prepared for modern treatment [50]. The reimbursement provided by the National Health Fund for this therapy, including support for recombinant human TSH, appears to be sufficient.

Another radioligand therapy that sparked broad interest in introducing systemic therapy in oncology is RLT — radioligant therapy — applied in 2008 by Kwekkeboom in treating advanced neuroendocrine tumors of the gastrointestinal system [51]. This therapy is based on somatostatin analogs labeled with radioactive lutetium. The first prospective, randomized clinical trial — NETTER-1 — demonstrated its safety and effectiveness [52]. Our country has made significant contributions to the introduction of RTL based on excellent radiopharmaceuticals prepared at the Świerk Center [7]. Thanks to these, a substantial group of nuclear medicine specialists across nuclear medicine centers in Poland has gained clinical experience in treating advanced neuroendocrine tumors with radioligands, with four centers — in Warsaw, Katowice, Gliwice, and Kraków — being certified as Centers of Excellence by the European Neuroendocrine Tumor Society (ENETS). It is expected that the recent introduction of the drug program B.139 will provide access to this treatment for all patients with advanced neuroendocrine tumors of the gastrointestinal system in our country.

We are currently witnessing significant research development in the application of new radioligand therapies in oncology based on PSMA-lutetium labeled ligands [53]. The safety and efficacy of these therapies are currently being tested in advanced and castration-resistant prostate cancer. Considerations for such therapies in other cancers are undertaken where cancer cells exhibit PSMA expression. It is worth noting that thanks to funding from the Medical Research Agency, Polish researchers have had the opportunity to conduct non-commercial clinical trials on the introduction of new systemic radioligand therapies for malignant tumors into practice.

Radioisotope therapy of cancer bone metastases belongs also to systemic therapies applied in oncology. Initially, this type of therapy was limited to prostate cancer. Bone-seeking radiopharmaceuticals, beta-minus particle emitting, like strontium-89 or rhenium-186, rhenium-188, and samarium-153 derivatives, have been incorporated into the treatment of prostate cancer bone metastases. Despite their strong pain-relieving effect, they failed to extend the overall survival in patients. Recent clinical trials indicated that the radium-223 dichloride, as an alpha-particle emitting radiopharmaceutical, improved the overall survival of prostate cancer patients with cancer bone spread [54]. Therapy with radium-223 dichloride was available in Poland as a drug program and was extensively used by specialized centers with positive experiences. Unfortunately, the implementation of the drug program was broken last year and we hope that it will be restored soon.

Currently, many novel strategies are being explored and novel radiopharmaceutical therapeutic agents including peptide-based ligands as well as antibodies or antibody fragments are being developed preclinically or are in early-phase clinical trials.

An interesting proposal is the use of melatonin-targeting radiopharmaceuticals in patients with metastatic melanoma. BA52 is a benzamide that binds melanin. Labelled with ^{123}I, it shows specific binding of pigmented metastases in planar/SPECT imaging and may assist in selecting patients who are likely to benefit from therapy. The pilot studies performed after administering [^{131}I]I-BA52 proved to be encouraging.

Another candidate is fibroblast activating protein (FAP). FAP is a serine proteinase. In adults, it is mainly found in the foci of healing or fibrosis. FAP is also highly active on the cell surface of activated cancer-associated fibroblasts (CAFs) but not resting fibroblasts. CAFs in the tumor stroma play an important role in promoting tumor growth, invasion, metastasis, and immunosuppression. Studies have shown that these fibroblasts are found in over 90% of epithelial neoplasms. This makes FAP a potential imaging target and treatment of a wide variety of malignancies. The clinical usefulness of ^{18}F-labeled FAP inhibitors (FAPI) was demonstrated. The use of quinoline-based inhibitors allowed the labeling of FAPI with diagnostic and therapeutic radioisotopes. FAPI-04 has proved to be the most advantageous. Clinical studies have confirmed the favorable biodistribution of the radiopharmaceutical. Observations on the therapeutic use of ^{90}Y-labeled FAPI have commenced.

Radionuclide treatment is also discussed in the sections on oncology and endocrinology.

Dosimetry

The purpose of dosimetric measurements in diagnostic nuclear medicine is to assess the radiological exposure of patients. Estimated effective doses of radiopharmaceuticals used in diagnostics, calculated according to updated standards, are available in the publication [55]. These doses are given in relation to the administered radioactivity unit of a radiopharmaceutical, and are considered sufficiently accurate, especially since they generally remain at low values.

However, in the case of therapeutic dosimetry, the matter is much more complicated. The idea of this dosimetry is to ensure the highest possible effectiveness of radionuclide therapy (possibly a high dose absorbed by a target of therapy) while maximizing the protection of so-called critical organs, *i.e.* those that are most exposed to radiation. This goal requires that the doses are measured. Although the very idea of conducting therapy with ionizing radiation based on known doses absorbed by individual organs should not raise doubts, achieving this goal poses numerous difficulties, the most important of which are:

- the need to perform a quantitative study (basically SPECT/CT) several times, at preset time intervals, to assess the distribution and kinetics of a radiotracer;
- in the case of radionuclides that do not emit gamma radiation, such as ^{90}Y, the need to use substitute isotopes;
- access to specialized software enabling dose estimation based on images of the distribution of a radiopharmaceutical;
- lack of financing for dosimetry measurements;
- shortage of equipment and staff in overloaded nuclear medicine centers.

It is also worth mentioning that therapeutic radiopharmaceuticals are granted marketing authorization for administration in standard radioactivity doses. This is due to the perception of radiopharmaceutical therapy as systemic therapy and therefore, following the example of classic oncological drugs, determining the maximum tolerated activity instead of, as is the case with other forms of radiotherapy, determining the maximum tolerated doses absorbed in defined regions of patient's body (*e.g.* [^{177}Lu]Lu-DOTA-TATE, registered under the name Lutathera®, is designed for administration in four cycles each with the standard radioactivity dose of 7.4 GBq). This method of applying therapeutic radiopharmaceuticals results in significant differences (among patients) in doses absorbed by critical organs and in targets of therapy [56]. Currently, research results are available showing the relationship between absorbed radiation doses and the effectiveness of therapy and its radiotoxicity. For example, correlations were found between the absorbed dose and the effectiveness of ablation in radioactive iodine therapy for differentiated thyroid cancer, between the absorbed dose and the reduction in the volume of pancreatic neuroendocrine tumors treated with the radiopharmaceutical [^{177}Lu]Lu-DOTA-TATE, and between the dose absorbed by kidneys in therapy with the radiopharmaceutical [^{90}Y]Y-DOTATOC and the radiotoxicity of this therapy [57]. On this basis, it is emphasized that when applying therapeutic radiopharmaceuticals in standard radioactivity doses, optimal therapy effectiveness is probably not achieved because of tumor absorbed doses are too low, although in some cases doses to critical organs may be too high [58, 59]. This method of therapy does not ensure optimal effects due to the lack of control over the individual response to the administered radiopharmaceutical.

Numerous authors emphasize the need of prospective, multicenter studies aimed at determining maximum doses tolerated by critical organs (*e.g.* kidneys, bone marrow), because the dose values used so far, adopted directly from therapy with external radiation sources, are considered inadequate due to a much lower dose rate in radionuclide therapy and heterogeneity of the absorbed dose [57, 60]. For this reason, the absorbed dose is replaced by the so-called biologically effective dose (BED), which takes into account a low dose rate associated with continuous irradiation by therapeutic radionuclides [58].

Due to requirements for individual dose planning during ionizing radiation treatment imposed by Council Directive 12013/59/EURATOM, the European Association of Nuclear Medicine (EANM) issued in 2021 recommendations on the practical implementation of this requirement in nuclear medicine activities [61]. It features three levels of dose reporting in radionuclide therapy: 1) administering therapeutic radiopharmaceuticals according to standard activities and reporting doses in the form of average values in a cohort of patients, 2) administering according to standard activities when performing and reporting individual dosimetric measurements, 3) applying individually planned activities determined based on dosimetric measurements performed in the patient. The publication also assigns recommended dose reporting levels to individual types of therapy.

In parallel, a report was prepared by the International Committee for Radiological Units (ICRU) on dosimetry procedures for radionuclide therapies [62], the recommendations of which, despite the introduction of also three levels of dose reporting, clearly differ. From the point of view of standardization, it should be emphasized that this report introduces a systematic nomenclature of areas important from the point of view of radionuclide treatment.

The Polish Atomic Law Act, which complies with the requirements of the EURATOM directive, contains a statement that the tasks of a person conducting medical exposure include the optimization of doses in order to reduce them while maintaining conditions for obtaining the expected clinical information or the expected therapeutic effect. This statement requires at least knowledge of the administered radiation doses.

Currently, a project DuoNen, financed by the Agency for Medical Investigations, is being carried out. The protocol of DuoNEN clinical trial, a phase III, multicenter, non-commercial clinical study (EudraCT No. 2020-006068-99) was designed to develop an optimal algorithm of Peptide Receptor Radionuclide Therapy for patients with disseminated NET based on personalized dosimetry and to evaluate the safety and effectiveness of personalized therapy with mixed doses of [^{177}Lu]Lu-DOTA-TATE and [^{90}Y]Y-DOTA-TATE compared to [^{177}Lu]Lu-DOTA-TATE in standard doses. This study is in progress, the first results have been presented.

In turn, the Department of Nuclear Medicine of the Pomeranian Medical University carries out investigations on the implementation of clinical, individual internal dosimetry to therapy of neuroendocrine neoplasms with Lutathera®.

At present, dosimetry and radiation protection during internal radiotherapy are the topic of several European projects, an example being the SINFONIA project (https://www.sinfonia-appraisal.eu/), with the contribution of three Polish research teams.

Summary

The presented opinions of the members of the Commission for Nuclear Medicine of the Committee of Medical Physics, Radiobiology and Diagnostic Imaging of the Polish Academy of Sciences show the important diagnostic and therapeutic role of nuclear medicine in Poland and the world.

There are 64 nuclear medicine centers in Poland, equipped with 114 gamma cameras (including 34 SPECT and 50 hybrid SPECT/CT scanners) and/or with 42 hybrid PET scanners (including 39 PET/CT and 3 PET/MRI scanners, installed in 36 centers). Crucial for utilizing PET as a quantitative biomarker, should be the legal implementation of quantitative PET standardization in Poland, through the available European EARL PET/CT accreditation program.

The development of new technologies in nuclear medicine depends not only on the use of modern equipment, but above all, on the introduction of new radiopharmaceuticals that enable the assessment of unknown aspects of the disease processes and play an important role in the development of precision medicine. Precision medicine means a new personalized therapeutic approach that takes into account individual biological factors in each patient. One of the elements of precision medicine is theranostics — which stands for the integration of the medical data obtained during the diagnostic process with the intent to choose the best method of treatment. Nuclear medicine is a dedicated specialty in the development of this new idea in medical science. In Poland, there is good access to radiopharmaceuticals for diagnostics and therapy, including the latest generation radiopharmaceuticals; this is not a factor that would limit the availability of nuclear medicine services. However, introducing new procedures to the healthcare system is delayed.

The idea of therapeutic dosimetry is to ensure possibly high doses absorbed by a target of therapy while maximizing the protection of critical organs most exposed to radiation. When applying therapeutic radiopharmaceuticals in standard radioactivity doses, optimal therapy effectiveness is probably not achieved. Radiopharmaceutical therapy should rely not on determining the maximum tolerated activity but on determining the maximum tolerated doses absorbed in defined regions of the patient's body. Optimal algorithms of radioisotope therapy based on the implementation of personalized, individual internal dosimetry, are in progress.

Article information and declarations

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Author contributions

Conceptualization — AT; writing: original draft preparation: AT, RM, BJ, LK, AP, JB, MK, MD, BB, BM; writing: review and editing — AT; supervision — AT and LK; figure — JB.

Conflict of interest

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Supplementary material

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