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Theranostics – present and future

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Abstract: Theragnostics in nuclear medicine constitute an essential element of precision medicine. This notion integrates radionuclide diagnostics procedures and radionuclide therapies using appropriate radiopharmaceutics and treatment targeting specific biological pathways or receptors. The term *theragnostics* should also include another aspect of treatment: not only whether a given radioisotopic drug can be used, but also in what dose it ought to be used. Theragnostic procedures also allow predicting the effects of treatment based on the assessment of specific receptor density or the metabolic profile of neoplastic cells. The future of theragnostics depends not only on the use of new radiopharmaceuticals, but also on new gamma cameras. Modern theragnostics already require unambiguous pharmacokinetic and pharmacodynamic measurements based on absolute values. Only dynamic studies provide such a possibility. The introduction of the dynamic total-body PET-CT will enable this type of measurements characterizing metabolic processes and receptor expression on the basis of Patlak plot.

Keywords: future of theragnostics; nuclear medicine; theranostics.

Introduction

Development of medicine is associated with new ideas, new paradigms, and new perspectives. These ideas are constructed according to the more general insights – medical cosmologies.

According to Jewson, three cosmologies were formulated in the modern history of medicine: the first is defined as bedside medicine, the second – hospital medicine and third – laboratory medicine [1].

The first of these notions was based on the doctor's intuition and experience, as well as direct relationship between the doctor and the patient. The patient was considered as the subject of the procedure. The most telling example of this period in the history of medicine is depicted in the painting made by Chandler presenting a famous London physician – Gleason, who, based on the examination of the heart rate only (the patient is hidden behind a curtain) and personal connection, was able (or was he really?) to establish a diagnosis and prescribe appropriate medications. The nineteenth and twentieth centuries brought the development of hospital (clinical) medicine. According to this cosmology, one should learn about the structure and function of each organ separately and analyze clinical symptoms based on observations and knowledge. Thus, the organ became the subject of the proceedings; the patient was divided into systems and organs. This procedure has laid the groundwork for *evidence-based medicine*. This philosophy contributed to the development of nosology and the principle stating that the same disease symptoms indicate the same disease, the treatment of which therefore requires the use of the same drugs. This view assumes that a standard therapy will be effective in most, but not all, patients, and that there will be a group of patients in which such treatment will not be effective, and a group in which it will be even harmful. This type of approach to medicine gradually becomes history. Currently, the idea of precision medicine dominates more and more often. Its beginning may be traced back to 2015, when Barack Obama granted the first funds for its development [2]. The main concept of precision medicine is the individual choice of the treatment procedure for an individual patient. This idea assumes that every patient can benefit from the proposed, individually selected treatment. Precision medicine requires a series of new diagnostic tools necessary to form a diagnosis based on functional disorders defined at the molecular level: genomics, proteomics, metabolomics, as well radiomics.

Thus, modern medical cosmology will be the basis for the development of therapeutic procedures in oncology, in particular. Since precision (or laboratory) medicine relies on the analysis of biochemical disorders, it requires imaging at the molecular level. From the practical point of view, nuclear medicine constitutes a method dedicated to molecular imaging. It should be noted that many premises indicate the increasing importance of nuclear medicine in clinical practice. One of the important aspects of precision medicine is theragnostic (or theranostic) medicine.

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Present theragnostic nuclear medicine

The term *theragnostic medicine* is derived from two words: *therapy* and *diagnostics*. It refers to a procedure consisting of a diagnostic test, the result of which allows a specific treatment to be applied with a very high probability of success. It was formulated in 1998 by John Funkhouser, director of PharmaNetics, who developed a test for monitoring the efficacy of a new anticoagulant drug in a study on the company's development strategy [3]. This strategy assumed the development of diagnostic tests applicable in strictly defined therapeutic procedures. This demand resulted from high costs of innovative medical procedures and the necessity to limit them through precise qualification of patients and control of treatment effectiveness [4, 5]. A frequently cited example of theragnostic concept's application is a simultaneous introduction of Herceptin and the HER-2 receptor expression test in treatment of patients with advanced breast cancer; the treatment should be used only if a significantly increased expression of HER-2 receptors is demonstrated earlier in the histopathological examination. This procedure has been approved by the FDA in 1998. Some authors consider this to be the origin of theragnostics.

Theranostics in nuclear medicine constitute an essential element of precision medicine. This notion integrates radionuclide diagnostics procedures and radionuclide therapies using appropriate radiopharmaceutics and treatment targeting specific biological pathways or receptors [4].

In general, the term in nuclear medicine is being increasingly used specifically for imaging and therapy with the same radiopharmaceutical or two very similar radiopharmaceuticals [5].

The term is widely used today, but its origins can be traced back to the mid-1950s. The first theragnostic procedure was the use of radioiodine in treatment of thyroid diseases: initially, a scintigraphic examination with radioiodine was performed and if lesions (autonomic tumor, thyroid cancer metastases) showed tracer uptake – radioiodine in therapeutic doses was used [6, 7].

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 [8–10].

Another example pertains to the isotope treatment of patients with neuroblastoma or phaeochromocytoma [11–14]. These tumors show a significantly increased expression of norepinephrine transport mechanisms. The same mechanisms can transport the adrenaline analog meta-iodo-benzyl-guanidine (mIBG); thus, norepinephrine and mIBG are taken up into tumor cells by the same norepinephrine transporter (NET, SLC6A2) that is highly expressed in neuroendocrine neoplasms. 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. In patients with neuroblastoma and phaeochromocytoma, a [^{123}I] I – mIBG scan is characterized by a high sensitivity (97% and 94%, respectively) and specificity (up to 96% and 92%, respectively). Therapy with [^{131}I] I-mIBG may be considered if scintigraphy after administration of diagnostic dose indicates a sufficiently high accumulation of the radiopharmaceutical. Targeted therapy with [^{131}I] I-mIBG shows encouraging efficacy with tolerable toxicity in relapsed or refractory neuroblastomas with response rates of 20–40% either alone or in combination with high-dose chemotherapy followed by autologous stem cell transplantation.

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 therapeutic radiopharmaceutical (PRRT). Nevertheless, treatment of NETs with radioisotope labeled analogs of somatostatin is proposed if diagnostic scan with somatostatin analogs is positive [15–18]. PET examination with the use of ^{68}Ga-labeled somatostatin analogs has been approved for NET imaging and the qualification of patients for peptide receptor radionuclide therapy [16, 17]. The efficacy of therapy of NETs with radiolabeled analogs of somatostatin was examined in the NETTER-1 trial [14]. The positive results of this study constituted the basis for the approval of [^{177}Lu]Lu-DOTATATE therapy in the United States and Europe.

Nowadays, 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 initial diagnosis, staging, restaging as well as relapse of the disease. Recently, treatment of prostate cancer with beta/alpha emitters -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.

PSMA is a homolog of the protein N-acetyl-L-aspartyl-L-glutamate peptidase I (NAALADase I or folate hydrolase I) and consists of 750 amino-acids. PSMA has a number of essential regulatory functions present in the cells: PSMA acts as an enzyme that takes part in nutrient uptake (folate) and plays a role in cell migration, survival, and proliferation. Its activity is also associated with the process of angiogenesis that accompanies the development of cancerous tissue. Increased PSMA expression was also found in the stroma adjacent to the newly formed vasculature of solid tumors [19–22]. PSMA occurs in the epithelium of otherwise normal prostate gland, but in the setting of cancer, its expression increases 100–1000-fold.

Recent studies show that it is possible to label PSMA with 99m-technetium or 68-gallium and picture its expression in SPECT and PET scans respectively. Apart from these radiotracers, there is ongoing research that aims to develop PSMA derivatives labelable with ^{18}F.

It seems that the importance of PET radiopharmaceuticals, considering a higher resolution of the PET gamma camera, will be on the increase.

Sensitivity and specificity of PET in the assessment of primary tumors, as well as evaluation of lymph nodes metastasis, was estimated. For patients with biochemical recurrence, positive [^{68}Ga]Ga-PSMA PET scans increased with higher pre-PET prostate-specific antigen (PSA) levels. For PSA 0.5–0.99, 1–1.99, and ≥2 ng/mL, the percentages of positive scans were 59%, 75%, and 95%, respectively. No significant differences in positivity were noted between Gleason sums ≤7 and ≥8. Significant differences in positivity after biochemical recurrence in the prostate bed were noted between radical prostatectomy (22%) and radiotherapy (52%) patients. On per-node analysis, high sensitivity (75%) and specificity (99%) were observed [22].

Lately, prostate-specific membrane antigen (PSMA) has been established as a theranostic target in this group of patients. A randomized phase III registration study has now been completed. The study showed that the use of [^{177}Lu]Lu-labeled PSMA-617 in the treatment of castration-resistant metastatic prostate cancer (mCRPC) was superior to the standard of care (VISION study [23]).

The impact of [^{68}Ga]Ga-PSMA PET/CT on management intent in prostate cancer were analyzed and, overall, [^{68}Ga]Ga-PSMA PET/CT scanning led to a change in planned management in 51% of patients. The impact was greater in the group of patients with biochemical recurrence after definitive surgery or radiation treatment (62% change in management intent) than in patients undergoing primary staging (21% change). Imaging with [^{68}Ga]Ga-PSMA PET/CT revealed unsuspected disease in the prostate bed in 27% of patients, in locoregional lymph nodes in 39%, and distant metastatic disease in 16% [24].

Additional aspects of theragnostic nuclear medicine

It must be strongly emphasized that the term *theragnostics* should also include another aspect of treatment: not only whether a given radioisotopic drug can be used, but also in what dose it ought to be used. The radioisotope drug should be administered – like any other drug – in an adequate dose. Nuclear medicine provides the right tool designed to estimate the appropriate dose of the radionuclide drug – dosimetry.

Dosimetry allows determining the relationship between the amount of radioactivity administered and the absorbed dose of radiation in tumors, organs, or the entire body. Dosimetry also allows for a correlation between the radiation dose used and the clinical results. It enables treatment planning with the aim of avoiding excessive toxicity. In general, the doses calculated for radionuclide therapy are less accurate than for external beam radiotherapy, but sufficient in clinical practice. It results from the limitations related to obtaining accurate information about the heterogeneity of radiation distribution in the lesion and information about the pharmacokinetics and pharmacodynamics of the radiopharmaceutical. The absorbed radiation doses can be calculated from the quantification of radioactivity and the specific absorbed fraction for the target. The specified fraction absorbed takes into account the type and energy of the radiation emission, the fraction of the energy from the source absorbed by the target and the mass of the target. The MIRD Committee is an entity responsible for defining the guidelines for methods for calculating the estimated absorbed radiation dose for the whole body and organs. This methodology has been aligned with radionuclide therapy. However, the proposed methodology requires still more research to further improve the available models and methods.

Moreover, theragnostic procedures allow predicting the effects of treatment based on the assessment of specific receptor density or the metabolic profile of neoplastic cells. As an example the role of [^{18}F]-FDG scan in planning of the radioisotope treatments can be used; in 1920, Warburg described that cancer cells metabolize glucose in an anaerobic cycle, whether there is hypoxia or normoxia.

This phenomenon turned out to be the basis for introducing PET examinations with the use of [^{18}F]FDG in the diagnostics of oncological diseases in particular. Additionally, it was found that neoplastic cells showing a much greater potential for aggressiveness are characterized by a much higher consumption of glucose. Thus, the degree of [^{18}F]FDG accumulation – in general – may be the basis for prognosis of the course of the disease and therefore may be a determining factor in selecting a more or less aggressive treatment. The observations to date provide a lot of evidence supporting this general principle.

Differentiated thyroid cancer has a strong affinity for ^{131}I and for that reason shows a good response for iodine treatment. On the other hand, dedifferentiated changes in thyroid cancer tend to lose affinity for radioiodine. This process is accompanied by increased glucose metabolism [25–33]. The observations so far indicate that there is a correlation between an increased [^{18}F]FDG uptake and tumor grade, and a worse prognosis. Hence, [^{18}F]FDG PET is considered a valuable tool for the detection of radioiodine-negative metastases in the observation of patients with differentiated thyroid cancer. In addition, [^{18}F]FDG PET seems promising as a valid instrument for predicting the long-term prognosis of thyroid cancer. Therefore, [^{18}F]FDG PET after thyroid remnant ablation should hold a prognostic value for the management of high-risk patients with differentiated thyroid cancer.

What is more, similar relations were described in patients with advanced NETs: scans after injection of the labeled somatostatin analog define the density of the somatostatin receptors and indicate whether radioisotope labeled analogs can be considered a solution for treatment. On the other hand, it is generally accepted that upregulated glycolytic activity is an unfavorable prognostic factor associated with a more aggressive clinical course. On that account, [^{18}F]FDG PET defines the probability of successful treatment. Quantitative meta-analysis presented by Alevroudis et al. [34] demonstrates that the disease control rate in patients with NET receiving PRRT with a negative [^{18}F]FDG PET prior to treatment initiation was 91.9%, vs. 74.2% in patients with a positive [^{18}F]FGD PET. Progression free survival (PFS) analysis revealed that patients with positive [^{18}F]FDG PET prior to PRRT initiation had a 2.9-fold increased risk of progression compared to NEN patients with a negative [^{18}F]FDG PET and overall survival (OS) analysis confirmed an approximately 2.3-fold increased risk of overall mortality in NET patients with a positive [^{18}F]FDG PET prior to PRRT compared to patients with a negative one in this setting. The authors also found that patients with PET positive [^{18}F]FDG tumors had a higher risk of progression and death after initially favorable outcome of PRRT. Therefore, [^{18}F]FDG PET can be used as a predictive tool in NET patients receiving PRRT.

Another prognostic indicator constitutes tumor hypoxia. Hypoxia indicates a more aggressive tumor phenotype [35–37]. Hypoxia is also a factor that reduces the cytotoxic effect of photon radiotherapy due to the lower availability of oxygen radicals. This effect is determined from the oxygen enhancement factor (OER) value [38]. For these reasons, noninvasive determination of the degree of hypoxia should decide on the form of treatment of oncological diseases. One method of noninvasive measurement of hypoxia is positron-emission tomography (PET) with hypoxia-specific radiotracers. The most commonly used radiotracer for hypoxia is ^{18}F-fluoromisonidazole (FMISO). PET measured hypoxia is a useful indicator and has a strong impact on the treatment option of selected tumors. Special importance of PET examination with the use of radiopharmaceuticals imaging hypoxia in head and neck cancers is emphasized [39, 40].

Future of theragnostic nuclear medicine

The future of theragnostic procedures in nuclear medicine certainly depends on two elements: the development of new gamma cameras and new radiopharmaceuticals.

Modern theragnostics already require unambiguous pharmacokinetic and pharmacodynamic measurements based on absolute values. Only dynamic studies provide such a possibility. The introduction of the dynamic total-body PET-CT will enable this type of measurements characterizing metabolic processes and receptor expression on the basis of Patlak plot. While static PET provides a simple snapshot of radiopharmaceutical concentration, dynamic PET with tracer kinetic modeling can provide parametric images that show how tissue is actually behaving. Parametric images have the potential to better detect lesions and assess the response to cancer therapy. Full compartmental modeling for the region containing the pathology provides complementary information which contributes to a more accurate diagnosis than conventional static Standardized Uptake Value (SUV) imaging. Results from the current study to conduct total-body dynamic PET scans in patients with cancer suggested that it can be used to generate high-quality images of metastatic cancer and to obtain quantitative data characterizing neoplastic disease [41, 42]. The recent advent of total-body PET technology opens a new paradigm for personalized medicine by enabling simultaneous, dynamic, and parametric imaging

of all organs of the body [43–46] and the recent development of multiphoton PET imaging [47–49] may open new possibilities in theragnostic by paving a way to positronium and simultaneous multi-isotope imaging.

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. Labeled 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 [50].

Another candidate is fibroblast activating protein (FAP). FAP is a serine proteinase. It is presents in many cell types during embryonic development. In adults, however, 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 [51]. 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 FAPI was demonstrated [52–55]. The use of quinoline-based inhibitors allowed labeling of FAPI with diagnostic and therapeutic radioisotopes [53]. 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 [53].

Radioisotope labeled neurotensin derivatives are another radiopharmaceuticals that may be considered to be introduced as theranostic drugs in nuclear medicine. Neurotensin is a 13 amino-acid neuropeptide. It occurs physiologically in the central nervous system, gastrointestinal tract, and in the heart muscle [56, 57]. There are three types of membrane receptors for neurotensin (NTSR): NTSR1, NTSR2, and NTSR3. An increased expression of the NTRS1 receptor has been demonstrated on neoplastic cells of small cell and non-small cell lung cancer, colorectal cancer, and breast and pancreatic cancer [57]. Binding of neurotensin to NTSR1 stimulates tumor cell proliferation through various signaling pathways [58]. On this basis, neurotensin antagonist (SR48692) was used in oncological therapy. Based on autoradiographic studies, a very high density of NTSR1 receptors on pancreatic adenocarcinoma cells was found [59]. These observations indicate that radiolabeled NTSR1 ligands could prove to be a new form of treatment for pancreatic cancer. The proposed radiopharmaceutical in the diagnosis and treatment of pancreatic adenocarcinoma is ^{177}Lu-3BP-227. This radiopharmaceutical is an antagonist for NTSR1 and shows a very high affinity for the NTSR1 receptor [60]. The results of preclinical studies showed that the new radiopharmaceutical is characterized by high accumulation in an experimental pancreatic tumor and relatively low accumulation in other organs (kidneys, lungs, and gastrointestinal tract) [61]. The first encouraging treatment results in humans were obtained with ^{177}Lu-3BP-227 [62]. A phase I/II trial is underway in the treatment of advanced NTSR1 positive neoplasms.

Many other radiopharmaceuticals that are candidates for new radioisotope theragnostics are currently under investigation:

- Radiolabeled daratumumab is an anti-CD38 antibody. This antibody is used to treat patients with multiple myeloma [63–65]; [^{89}Zr]Zr-DFO-daratumumab is currently being evaluated in human clinical trials. Preliminary results show a high uptake of radiopharmaceutical in the disease sites. DFO-daratumumab seems to be an attractive candidate for targeted therapy with alpha emitters such as ^{225}Ac;
- Many reports indicate that integrin VLA-4-based radiopharmaceuticals may be an alternative, targeted form of diagnosis and therapy of melanomas. Integrins are transmembrane adhesion receptors [66–69]. A first-in-human imaging trial is ongoing to evaluate human dosimetry and safety of ^{64}Cu-LLP2A;
- A number of papers indicate the possibility of using the therapy based on the receptor for chemokines – CXCR 4 [70–72]. Radiolabeled analogs of CXCR-4 antagonist Pentixafor have been used for imaging and treatment in lymphoma patient populations. The first clinical observations of ^{177}Lu/^{90}Y – Pentixather in the myeloma patient population are very encouraging;
- Antibodies directed against HER2 are other radiopharmaceuticals taken into account for theragnostic procedures in nuclear medicine. Trastuzumab is a humanized monoclonal antibody of the IgG1 isotype that is directed against the extracellular regions of HER2. Radiolabeled with ^{227}Th antibodies against HER2 may be useful in the radiotherapy of HER2-positive breast tumors [73, 74].

Conclusions

The aim of this minireview is to present solely the most important milestones that determine the development of theragnostic procedures in nuclear medicine. It is currently one of the most dynamically growing branches in medicine. The development of these methods will determine the progress of precision medicine in the future.

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