Individualization of Radionuclide Therapies

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Nuclear medicine uses radiopharmaceuticals, which are various molecules labeled with radioactive isotopes, for diagnosis and therapy. Evidence shows that better and more predictable outcomes can be achieved with patient-individualized dose assessment. Therefore, the incorporation of individual planning into radionuclide therapies is a high priority for nuclear medicine physicians and medical physicists alike. Internal dosimetry is used in tumor therapy to optimize the absorbed dose to the target tissue. For a nuclear medicine therapy to be considered personalized, treatment planning is essential, including the activity chosen individually for a given patient. The first step in individual planning of radioisotope therapy is to perform a series of diagnostic images, which allows visualizing the distribution and measuring how the activity decreased in time in different organs. The next step is to perform dosimetric measurements. It provides information on the degree of uptake of an administered radiopharmaceutical in pathological tissues and critical organs. The obtained dosimetric report is the foundation for planning the maximum activity on tumors, with a safe level of irradiation of critical organs in a given patient. The last step is to obtain a series of images of the patient recorded after the administration of the therapeutic radiopharmaceutical.

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1. Introduction

Radiopharmaceuticals are sources of radiation, and when introduced into the patient's body (by injection, oral administration, or inhalation), they target specific organs, tissues, or cells. Subsequently, the activity of radiopharmaceuticals in tissues decreases due to their elimination from the body and radioactive decay. Administration of the same activity of a given radiopharmaceutical to different patients can distribute in their bodies differently, and therefore it is important to consider each patient individually. The determination of the total number of nuclear disintegrations that occur in a particular organ allows calculating the mean energy absorbed per kilogram of tissue. This parameter is known as the mean absorbed dose.

The knowledge of the absorbed ionizing radiation dose after administration of a radioactive preparation is of great importance both for the patient's safety and for the proper course of diagnostics or radioisotope therapy. The activity of radioisotopes, administered to patients for diagnostic imaging studies, must ensure the correct image quality while minimizing the dose that will be absorbed. Due to the increase in sensitivity of modern gamma cameras, the reported diagnostic activities are low. However, in the case of radioisotope therapy, the activity of the therapeutic radioisotope should be as high as possible to effectively destroy tumor cells, and at the same time, low enough not to damage critical organs. Therapy using radioactive isotopes is an extremely important and rapidly

developing part of nuclear medicine. Modern radioisotope treatments are based on the idea of theranostics [1][2], according to which a diagnostic examination should be performed with the use of a radiopharmaceutical with the same distribution as the therapeutic radiopharmaceutical. Only when the result of the primary examination shows a sufficiently high accumulation of diagnostic radiopharmaceutical is the patient eligible for the treatment procedure.

In every clinical situation that requires the administration of a radioactive substance to the patient, it is important to know the absorbed dose. Moreover, it is of special importance when the activity is very high, as is the case with radioisotope therapies. Individualized therapy plans, created based on images of a given patient, allow for the optimization of therapy and the minimization of toxic effects [3][4][5][6][7].

Both nuclear medicine and external beam radiotherapy (EBRT) use ionizing radiation to treat malignant tissue. EBRT requires advanced equipment that shapes the external beam to conform to the tumor, and nuclear medicine uses radiopharmaceuticals that are introduced directly into the body. Both treatment techniques should follow the guidelines contained in COUNCIL DIRECTIVE 2013/5/EURATOM from 5 December 2013, concerning the safety of patients diagnosed and treated with ionizing radiation [8]. In Article 56 of the Directive, the following is written: “For all medical exposure of patients for radiotherapeutic purposes, exposures of target volumes shall be individually planned, and their delivery appropriately verified taking into account that doses to non-target volumes and tissues shall be as low as reasonably achievable and consistent with the intended radiotherapeutic purpose of the exposure.” This implies the necessity to personalize the treatment, i.e., the selection of the suitable pharmaceutical, in the right dosage and time. Individual EBRT planning is a common practice that has been developed and used for many years. Teams of physicists involved in treatment planning and clinical dosimetry for each and every patient are the standard in radiotherapy centers. Radiation treatment planning is performed with the use of advanced computer programs using computed tomography (CT), magnetic resonance (MR), or positron emission tomography (PET) images. Modern planning methods include the three-dimensional (3D) technique, which allows for the spatial shaping of radiation beams and the protection of critical organs [9][10].

The situation in nuclear medicine is completely different. Few physicists work in nuclear medicine departments, and radioisotope therapies are usually performed according to standard clinical procedures. Individual calculations of radiopharmaceutical doses for patients are not routinely performed in most nuclear medicine facilities across the world. Nuclear medicine specialists most often use standard activities of radiopharmaceuticals during therapy, considering the patient’s weight or body surface area.

In some cases, administration of standard radiopharmaceutical activities does not provide a sufficiently high dose per tumor to destroy it. On the other hand, giving too much activity could have harmful effects on critical organs. A small fraction of patients receives optimal activity, while the vast majority receive lower doses. This conservative approach provides “radiation safety” to healthy tissues, but also delivers a lower dose than indicated to the neoplastic tissue, resulting in a low response rate and a higher rate of disease relapse. Individualized treatment planning would provide higher absorbed doses to most patients without risking toxicity. “Personalized dosimetry is a must for appropriate molecular radiotherapy”—this is the title of the article by Stabin (one of the pioneers of internal dosimetry) et al. published in 2019 in the *Medical Physics* journal [11].

2. Radionuclides for Therapies

Due to the intensive development of pharmacology, the number of new radiopharmaceuticals that can be used in therapy is increasing every year. A particular advantage of radioisotope therapies is that they can be used in situations where all other forms of treatment have failed. Most radionuclides used in therapy emit β− particles, and rarely α particles, which are highly potent. **Table 1** contains information on the radionuclides used in radioisotope therapies. **Table 2**, on the contrary, presents the radionuclides currently being tested, which provides the evidence of the intensive development of this method of treatment.

Table 1. Radionuclides used in particular types of radioisotope therapies.

Radionuclide	Basic Radiation Type for Therapy	Chemical and Dosage Form	Indications	Administration Route	References
Iodine ^{131}I	β^-	Sodium iodide	Thyroid carcinoma Hyperthyroidism	Oral	[12][13]
Iodine ^{131}I	β^-	Iobenguane	Pheochromocytoma Paraganglioma Neuroblastoma Carcinoid	Intravenous	[14][15][16][17]
Iodine ^{131}I	β^-	Apamistamab	Leukemia	Intravenous	[18]
Iodine ^{131}I	β^-	Tositumomab	non-Hodgkin's lymphoma	Intravenous	[19][20]
Iodine ^{131}I	β^-	Lipiodol	HCC, liver metastasis	Intra-arterial infusion	[21][22]
Samarium ^{153}Sm	β^-	Lexidronam	Painful skeletal metastases	Intravenous	[23]
Strontium ^{89}Sr	β^-	Strontium chloride	Painful skeletal metastases	Intravenous	[24]
Yttrium ^{90}Y	β^-	Ibritumomabtiuxetan	non-Hodgkin's lymphoma	Intravenous	[25]
Yttrium ^{90}Y Therasphere	β^-	^{90}Y glass spheres	Unresectable HCC Liver metastasis	Intra-arterial infusion	[26]
Yttrium ^{90}Y	β^-	^{90}Y resin spheres	Unresectable HCC Liver metastasis	Intra-arterial infusion	[27]

Radionuclide	Basic Radiation Type for Therapy	Chemical and Dosage Form	Indications	Administration Route	References
SIR-Spheres					
Lutetium ^{177}Lu or Yttrium ^{90}Y	β^-	[^{177}Lu]Lu-DOTATATE [^{90}Y]Y or [^{177}Lu]Lu-DOTATOC	Unresectable or metastasized NETs	Intravenous	[28][29]
Lutetium ^{177}Lu or Actinium^{225}Ac	β^- α	[^{177}Lu]Lu-PSMA	Prostate cancer	Intravenous	[30][31]
		[^{225}Ac]Ac-PSMA	(mCRPC)		
Phosphorus ^{32}P Yttrium ^{90}Y Rhenium ^{186}Re	β^-	Colloids	Radiosynovectomy	Intra-articular injection	[32]

Radionuclide	Basic Radiation Type for Therapy	Indications	References
Yttrium ^{90}Y	β^-	Breast cancer	[35]
Lutetium ^{177}Lu	β^-	Pancreatic cancer	[36][37]
Iodine ^{131}I	β^-	Neuroblastoma Central Nervous System/Leptomeningeal Metastases	[38]
Phosphorus ^{32}P	β^-	Pancreatic cancer	[39]
Copper ^{67}Cu	β^-	Radioimmunotherapy	[40]
Holmium ^{166}Ho	β^-	HCC, liver metastasis	[29]
Indium ^{111}In	Auger e^-	GEP-NETs, lung and bladder cancer	[41][42][43]
Tin ^{117m}Sn	Internal conversion e^-	Painful skeletal metastases	[44]
Bismuth ^{213}Bi	α	Glioblastoma, prostate and bladder cancer	[45][46][47]
Astatine ^{211}At	A	Lung cancer, glioblastoma, radioimmunotherapy	[48][49][50] [51]

GEP-NET: gastroenteropancreatic neuroendocrine tumor; EC: electron capture.

3. Trends in Personalized Internal Dosimetry

Most of the listed dosimetric problems should be solved within the next few years, and intensive work is currently being undertaken on simplifying the internal dosimetry techniques.

The first simplification concerns the number of necessary scans performed on one patient. The question arises if performing multiple patient acquisitions is necessary and how many of them should be carried out for individual

dosimetric calculations. Freedman et al. [52] propose to decrease the series of four standard acquisitions to two post-treatment scans for PRRT with [^{177}Lu]Lu-DOTATATE. However, the authors emphasize the need for further research, as they are concerned that the methods of estimating absorbed doses based on only two scans would be even more user-dependent and require careful analysis of the volumes of interest (VOIs) in images. In a number of papers, published both many years ago and recently [53][54][55][56][57][58][59][60][61][62][63], the authors propose to limit the number of imaging tests performed for dosimetric purposes to one single SPECT/CT acquisition. It is under debate if such simplified dosimetry, based on one measurement, could work properly at all. From a mathematical point of view, there is a lack of measured data to estimate the dose absorbed in a patient's tissue. However, missing data can be filled with empiric data on the biokinetics of used radiopharmaceuticals. The single time-point dosimetry method requires knowledge about population averages for tracer kinetic parameters. If the biokinetics of the radiopharmaceutical in the analyzed organ and the shape of the TAC have been previously determined based on studies of a given patient population, only one quantitative measurement of the activity at the time corresponding to approximately 1.5 Teff is sufficient (where Teff is the effective elimination half-life of the radiopharmaceutical from the organ) [56][59]. Accuracy analysis of the absorbed dose estimation showed that, for the vast majority of patients, measurement errors were less than 10% [64]. The solution to underestimated or overestimated measurement results could be the creation of databases on the biokinetics of the radiopharmaceutical used in the population. Therefore, in addition to using results of clinical dosimetry measurements to optimize the treatment of individual patients, the obtained data on the biodistribution of used radiopharmaceuticals should also be used to build pharmacokinetic databases on the biokinetics of various radiopharmaceuticals. This population biodistribution should soon become an integral part of programs for simplified, individual internal dosimetry.

The second simplification aims to overcome the difficulties of accurately segmenting organs in SPECT images. Since they have significantly limited resolution, the VOI containing all the accumulated activity is difficult to outline. Moreover, since it is generally larger than the organ itself, the determination of the VOI based on CT images cannot be used because it would not contain all the activity accumulated in the organ. Based on the assumption that the activity in the critical organ is relatively evenly distributed, it has been proposed to evaluate the cumulative dose in the organ based on a "small" VOI placed inside the organ itself [65][66][67]. Since the positioning of this VOI can be difficult and cause differences in dose assessment, an automatic segmentation method has been proposed that eliminates these difficulties [68].

Computer scientists and physicists are developing more and more universal and accessible software for internal dosimetry [69][70][71][72][73].

Due to the rapid development of radiopharmacy, new radiopharmaceutical surrogates can be expected for therapeutic radiopharmaceuticals, which cannot be imaged with the gamma camera [74][75][76]. Radiation dosimetry assessment is often initiated with measuring biodistribution of new radiopharmaceuticals in small animals. To study the biological distribution of radiopharmaceuticals in the human body, it is necessary to find the biological distribution in the rodent body and then the results can be generalized to humans. Preclinical dosimetry studies using small animals are an indispensable step in the pathway from in vitro experiments to clinical implementation of

new radioisotope therapies. A lot of studies have shown the practicality of using animal distribution as a model for estimating the absorbed dose in humans [77][78][79][80][81].

Due to the growing awareness of the importance of dosimetry, the Internal Atomic Energy Agency conducts training in that field for doctors and medical physicists. For several years, The European School of Multimodality Imaging and Therapy (ESMIT) has been operating within EANM, the aim of which is to educate specialists at three educational levels, both online and in-person [82][83]. The Dosimetry Project Group, operating within ESMIT, organizes advanced courses for the practical application of clinical dosimetry in radioisotope therapy. The courses enable direct contact with dosimetry experts, exchange of experiences, and cooperation of clinicians, implementing individual internal dosimetry in nuclear medicine facilities around the world. These activities are also related to the existing need for standardization and harmonization of internal clinical dosimetry tools.

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