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EDITORIAL

Matched pairs for radionuclide-based imaging and therapy

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Introduction

Radionuclide therapies have been used for a century. In the early years of the last century, radioisotopes such as radium were used for internal and superficial applications. However, this type of radiation treatment was not established and was abandoned after a few decades. The reasons were probably the difficulty in preparing reproducible activities and the inability to measure doses at that time.

In the early 1940s radioiodine therapy [1] for thyroid diseases was introduced, and in the following years efforts were made to estimate doses. Nevertheless, for a long time radionuclide therapies including radioiodine therapy were performed using standard activities, and therefore the target doses varied considerably. This approach could be accepted because of the high therapeutic index of the performed therapies and had to be accepted because of the lack of adequate instrumentation at that time both to reliably measure activity concentrations in lesions deep in the body or to determine the target volume.

In order to predict the dose, it is necessary to know the volume of the lesion, and more precisely the tracer accumulating volume of the lesion. It is also necessary to know the activity distribution in the lesion, as inhomogeneities result in inhomogeneous irradiation of the target structures. Finally, the kinetics of the therapeutic radiopharmaceutical need to be measured. The relevant information needed is the time integral over the activity concentration in the target corresponding to the residence time. It may be represented by maximal uptake and half-life time as long as the change in activity accumulation in the lesion is smooth over time. Either the residence time or the maximum uptake plus half-life time needs to be determined individually in each patient. The kinetics depend on the biology both of the lesion and of the rest of the body including, for example, kidney and liver function. One has to consider that the kinetics of the radiopharmaceutical might change between the diagnostic investigation and the actual therapy. For this reason, and for the sake of simplifying the procedure, radionuclide therapies are quite frequently performed simply using standard activities or adopted standard activities, e.g. normalized to body weight.

However, at least for radioiodine therapy of benign thyroid diseases, it is nowadays widely accepted that there is a dose–response relationship and pretherapeutic dosimetry is feasible and should be performed [2–4]. Dosimetry in the treatment of benign thyroid diseases is relatively easy, as the organ is close to the surface and there is little and calculable absorption or scatter, the target volume may be reliably measured by ultrasonography, and the activity distribution is quite homogeneous. Thus, why should these standards not be applied to the much more severe malignant diseases and to radiopharmaceuticals with a much less favourable target to background ratio?

The present supplement deals with this topic for radionuclide therapies employing either radioactive iodine or yttrium. It is intended that the supplement depicts all aspects that are essential for dosimetry prior to therapy using one of the matched pairs for diagnostics/therapy (^{124}I/^{131}I, ^{86}Y/^{90}Y). ^{131}I and ^{90}Y are the most frequently used radionuclides for radionuclide therapy of malignant diseases. Schmitz summarizes in his contribution the relevant aspects of the production of the both positron emitters – ^{124}I and ^{86}Y [5] – that are suitable for PET

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imaging. Both can be produced using "standard" cyclotrons used in PET centres.

Much experience has been gathered during at least the last 50 years of iodine labelling for diagnostic purposes. All the general and specialist knowledge may be transferred to ^{124}I labelling; see, for example, Reubi and Maecke [6] and Decristoforo et al. [7]. Also the experience of labelling with ^{90}Y can be transferred to ^{86}Y labelling. However, as ^{90}Y is for therapeutic use only, there is much less information available; for overviews, see Stöcklin [8] and Sgouros et al. [9].

PET, that is well-known for its high sensitivity, high special resolution and accuracy in quantitative measurement compared to the gamma camera, can be employed, and the combined modality PET/CT, or in the future PET/MRI, give precise volume information. Therefore, these isotopes are promising for pretherapeutic dosimetry yielding an individualized therapy for each patient.

Both isotopes have a complex decay schema that results in true coincidences between gamma rays among themselves or gamma rays and positrons emitted during the same decay. This is a challenge for quantitative measurements with ^{86}Y even more than with ^{124}I [10–12]. The paper from Lubberink and Herzog is dedicated to this aspect [13]. Other important aspects of quantification, which is essential for dosimetry, are discussed by Sgouros et al. [9].

^{124}I/^{131}I: thyroid and beyond

Iodine is the classic element for nuclear medicine diagnostics and therapy. It combines some favourable characteristics. In the human body iodine is only stored in the thyroid resulting in extreme target to background ratios. That is the ideal situation for both diagnostics and therapy. ^{131}I is the therapeutic nuclide with short-range beta radiation and in addition a gamma ray fraction that allows it to be traced. Using these gamma rays, pre- and intratherapeutic tracing has long been established and dosimetric approaches have been considered frequently. The half-life time of ^{131}I is close to the optimum for some applications including treatment of thyroid diseases. Furthermore, iodination of biomolecules is well established, and therefore a variety of radiopharmaceuticals labelled with iodine are available, and frequently it is the first label in novel developments (MIBG, receptor tracer, antibodies). On the other hand ^{123}I has been established for diagnostics using the gamma camera technique for a long time; the resulting pictures are of quite good quality. However, ^{123}I is hampered by some drawbacks: The half-life time of ^{123}I is too short to measure the biokinetics for a sufficiently long time to determine reliably the radiation dose deposited in a subsequent internal targeted therapy with the corresponding ^{131}I radiopharmaceutical, e.g. in thyroid cancer. Until recently gamma camera applications including single photon emission tomography (SPECT) showed a lack of quantitative ability. However, there has been recent progress in this field for SPECT. The current state of SPECT quantification is described in the paper by Ritt et al. [14].

The positron emitter ^{124}I has been proven to overcome these shortcomings. It has an adequate half-life time of 4.2 days and can be measured using PET. The consequence is high spatial resolution and the potential for precise quantification. The combined modality PET/CT frequently demonstrates the morphological structure correlating with the PET findings, resulting in precise volume information, which is needed for dosimetry. The combination of PET and MRI even more frequently allows volumetry (Nagarajah et al., submitted for publication). ^{124}I has been used for a long time (in our institution for about 20 years), but in the early years it was very rarely applied. The development of faster PET scanners allowing whole-body imaging, the development of spiral CT, and the combination of both in PET/CT were the breakthroughs for ^{124}I pretherapeutic dosimetry, that has been investigated quite systematically mainly in radioiodine therapy of thyroid cancer [9, 15] and MIBG therapy [16] during the last decade.

^{86}Y/^{90}Y: a matched pair to come

Things are somewhat different in the case of ^{90}Y. This nuclide is a virtually pure β-emitter and is therefore hard to image. Traditionally it has been imaged by bremsstrahlung that results in relatively poor image quality and does not allow quantification at all. Recently the very rare E_0-decay of the 1.78-MeV excited state of ^{90}Y (34±4 ppm branching ratio) has been used in PET imaging [17]. Its clinical value cannot yet be judged. A long imaging time is needed and the reliability of quantitative analysis is not yet known. Anyway, ^{90}Y is a "therapeutic" nuclide and is therefore not suited to pretherapeutic imaging and dosimetry. To overcome the absence of an yttrium isotope suitable for gamma camera imaging, ^{111}In-labelled tracer has been used for dosimetry [18]. However, the kinetics may (somewhat) differ for different labelling metals.

There are no yttrium isotopes suitable for gamma camera imaging, but ^{86}Y [5] can be used in PET imaging. ^{86}Y has a somewhat short half-life time of only 14.7 h and is therefore of limited value for predicting the ^{90}Y therapy dose if the therapeutic radiopharmaceutical biodistribution significantly changes during the time of relevant irradiation. This is not the case, however, for the most common ^{90}Y therapies [19], SSRT therapy [20], SIRT [21] or radioimmunotherapy [22].

Pretherapeutic dosimetry using an yttrium label is in a more experimental stage. The quantification of ^{86}Y PET investigations is more of a challenge than that of ^{124}I investigations because of the higher number of disturbing gamma rays per β-decay [13].

The potential of internal targeted radiotherapy has been proven for more than 60 years. Some novel modalities have been introduced and promising developments have taken place over the last years. However, specific and intense accumulations as in radioiodine therapy of benign thyroid diseases are not in sight. Therefore, pretherapeutic dosimetry is an essential prerequisite. It is applied in animal studies [19, 23] and in humans [15, 16]. Dosimetry with the matching nuclide is of high value for gathering knowledge as how to influence the therapeutic dose. Relevant and open questions need to be answered in general and individually, e.g. What is the dose needed for cure? What dose may be tolerated by healthy tissue – depending on the radionuclide and radiopharmaceutical? How can the kinetics be influenced, not only in the target but also in nontarget structures, e.g. the salivary gland in thyroid radiotherapy? The first investigations of this kind are under way. Only pretherapeutic dosimetry allows the repeated simulation of the therapy under various conditions, such as targeted receptor therapy or radioiodine treatment of thyroid cancer under rhTSH or endogenous TSH stimulation [24] or to influence the radiation exposure of nontarget tissue [25].

The idea of using matched pairs in radionuclide treatment will open the door to further developments in nuclear medicine. The present supplement is intended to supply information on this exciting field for both clinicians and scientists.

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