Current status of clinical dosimetry and personalized radionuclide therapy

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Abstract

The number of patients treated with radionuclide therapy (RNT) has made a giant leap with the approval of targeted Lutetium-labelled radiopharmaceuticals by the European Medicines Agency (EMA). Though treatments with radioiodine still make up for over 85% of the RNTs in Europe, the scientific breakthroughs are nowadays achieved with new radiolabelled small-molecules and microspheres in various oncological settings. With these advances, the discussions are again raised regarding the need for standard post-therapy imaging followed by absorbed dose verification. On the one hand, clinical dosimetry has always been considered too complicated, providing results with high uncertainties, and requiring an increased burden on the patient and the department, without scientific evidence to establish a clear clinical benefit yet. On the other hand, important steps are made to standardize various aspects of the dosimetry workflow to improve patient's safety, treatment effectiveness and accuracy. Furthermore, there are numerous small clinical studies that do show distinct dose-effect relationships for both normal organ toxicity and tumor control in RNT, thus suggesting there is room to optimize treatment outcome by performing either personalized dose prescription or better patient selection (1,2).
This overview will define current clinical status of dosimetry to guide Lutetium-labelled targeted therapy and radioembolization treatment in the oncological setting. The fundamental elements for any clinical dosimetry calculation will be discussed, as well as the uncertainties and limitations of such a workflow. To conclude, key research areas in active development are mentioned, and we will glance at the future of personalized radionuclide treatment planning.

Implementation of the EU-directive

The general debate surrounding clinical dosimetry in radionuclide therapy (RNT) has been given additional momentum by the European Union (EU) Council Directive 2013/59/Euratom stating in article 56 that *'For all medical exposure of patients for radiotherapeutic purposes, exposures of target volumes shall be individually planned, and their delivery appropriately verified…'*, suggesting treatment modification based on dosimetry outcomes for radiotherapy, including nuclear medicine for therapeutic purposes. However, in the same EU-Directive the concept of standardized versus non-standardized RNT was introduced. Where standardized refers to prescription of EMA-approved pharmaceuticals, non-standardized therapies are those still in developmental phases or used in an off-label setting. This conflict of EMA-approved dosing versus EU-imposed exposure optimization has led to a confusing situation, which was described in a recent EANM position paper (3). Three compliance levels to the EU-Directive were proposed for the nuclear community:
Level 1. Activity-based prescription and cohort-averaged dosimetry for standardized RNT,
Level 2. Activity-based prescription and patient-specific absorbed dose verification for non-standardized therapies,
Level 3. Dosimetry-guided patient-specific prescription and dose verification.
The majority of RNTs applied in the current clinical setting can be classified as Level 1, except for the transarterial radioembolization (TARE) of liver malignancies currently classified as Level 2-3 depending on the method of activity prescription used. At present, TARE is the only nuclear therapy for which dosimetry-driven treatment planning is advised in recent guidelines (more details in the next paragraph), though technically the radiolabeled microspheres are classified as medical device rather than a radiopharmaceutical. When for radiopharmaceuticals deviations are made from an EMA-approved therapeutic dose or indication, even in a standard clinical setting, it is considered off-label use and Level 2-3 dosimetry is advised. With this proposed EANM-classification, minimal compliance to the imposed EU-Directive can be implemented for

Lutetium-therapies and TARE in many hospitals without much effort. But what will be needed to take RNT one step further, and is personalized dosimetry-based planning the way to improve patient outcome?

Tumor control: a radiobiological perspective

From a radiobiological perspective it makes sense to prescribe high activity dosages of nuclides with high dose rates and long half-lives to achieve maximal tumor control. However, for personalized treatment planning to be clinically relevant and safe, it should include dose thresholds for specific organs-at-risk to reduce the chance of radiation-induced (early) toxicities, and secondly, it should offer data on the tumor-control probability.
Although the relationship between absorbed dose and the induction of a biological effect in tissue is generally acknowledged, there are still fundamental knowledge gaps in this interaction especially for RNT (4). In external beam radiation therapy (EBRT), the abundance of scientific data has led to the development of statistical models to describe the tumor control probability (TCP) and normal tissue complication probability (NTCP) at certain absorbed doses in various tissues. The most complex model can take factors like planned dose, radiosensitivity, repopulation, repair, dose rate, linear energy transfer (LET) and dose heterogeneity into consideration. Nevertheless, the survival chance of a single cell after irradiation, described with the well-established Linear-Quadratic (LQ) model, often forms the basis of these probability models. The cell survival equation consists of a linear component determined by a cell's radiosensitivity ('single hit' response) and a quadratic part which describes a cell's ability to repair sub-lethal damage before a second irradiation event ('multiple hit' response). In EBRT, these models are used to compare different radiotherapeutic fractionation schemes and predict biological effects to optimize treatments (5,6).
Our current understanding of dose-effects relationships in RNT is heavily based on the acquired knowledge from EBRT, but it is also recognized that this cannot reliably be extrapolated as aspects such as dose rate, exposure time, fractionation schemes and type of radiation all differ. For example, an absorbed dose of 40 Gy delivered over three weeks

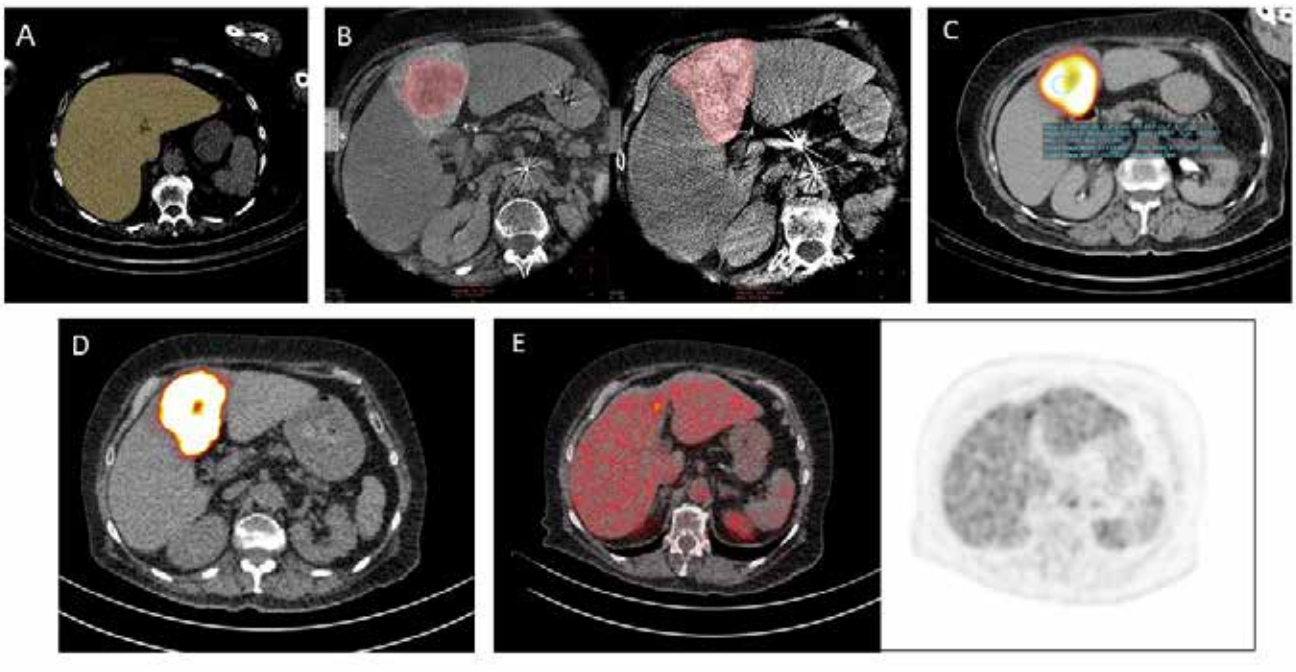

Figure 1. Segmentectomy in a patient with oligometastatic colorectal cancer. Total liver volume determined on CE-CT is 2300ml (A), with one FDG-avid hypervascular tumor lesion located in segment 4. During angiographic work-up a Conebeam-CT is made at the injection position, and treatment volume is segmented (350ml) (B). Tumor-to-normal ratio is estimated at 2.4 on [^{99m}Tc]Tc-MAA SPECT/CT (C). The planned dose on the tumor was 200Gy, resulting in a prescribed activity of 850MBq to the treatment volume. The distribution of ^{90}Y-microspheres (D) nicely matches the [^{99m}Tc]Tc-MAA accumulation. Follow-up FDG-PET one year after radiation segmentectomy shows a marked response and no new lesions (E).

at a dose rate that is exponentially reducing has a quite different biological effect on tissues compared to the same dose of 40 Gy delivered at high dose rates in fractions of 2 Gy (e.g., radiotherapy). The different biological effect of RNT compared to EBRT is further complicated due to its heterogeneous localization of the deposited energy, both at a tissue, cellular and subcellular level, which is directly related to the biodistribution of a specific radiopharmaceutical.
To complicate matters even more, therapeutic efficacy and cell survival are also influenced by complex processes within cells that are not directly targeted, so-called 'bystander effect', and activation of the immune system (7).
More preclinical studies should be undertaken that combine (sub)cellular absorbed dose measurements with biological data on for instance DNA damage-repair, cell-survival pathways, immune-activation, radiosensitizers, and so on, to better understand these complicated interactions. While these types of experiments will eventually lead to more suitable dose limits and tumor target doses of RNT, they are often hampered by incomplete physics and dosimetry reporting. Through recognizing these common shortcomings, efforts are now made to 1) standardize dosimetric measures and reporting, 2) define preclinical models for radiobiology, and 3) identify suitable biomarkers of response (8-10). As this research operates on the crossroad between physics, biochemistry, radiobiology, pharmacology, and medicine, collaboration and integration will also be needed to optimize these experiments and clinical trials.

Dosimetry: calculations and uncertainties

A prerequisite for clinical implementation of personalized treatment verification, and eventually treatment planning, are accurate absorbed dose measurements.
As computational and camera technologies progress, internal dosimetry is becoming more widely implemented in clinical studies that assess safety and effectiveness of RNT, thus providing us with the necessary basic data to evaluate dose-response relations. In this respect, it must be recognized that standardization and harmonization of both imaging input data and applied dosimetry models are highly relevant. Proper dosimetry reporting and evaluating the degree of uncertainties in absorbed dose estimates for specific protocols, both in clinical and preclinical setting, will increase the validity of dosimetry and will help to separate true from false dose-effect findings. Recent efforts of the EANM community have resulted in several recommendations that cover the entire dosimetry workflow for specific indications (11-16).

Traditionally, absorbed dose estimates are performed to determine risk profiles of (new) radiopharmaceuticals at a population level, so this MIRD-methodology focusses on absorbed doses (*D* in Gray) in entire organs.
The dose is calculated using the time-integrated activity (A_T in MBq) and an S-factor, which describes the absorbed energy in a specific organ per radionuclide disintegration. The type of decay (alpha, beta, auger electrons, gamma) will determine whether the activity in a certain tissue volume will also contribute to the deposition of energy in nearby tissues (so-called crossfire effect). A spatial S-value distribution is generally referred to as a 'Dose Point Kernel'. To calculate the dose deposited in solid tissues of 2-300 grams by certain alpha, beta, and auger electron emitters, it can be assumed that all energy is deposited in a small area referred to as 'Local Energy Deposition (LED)'. When three-dimensional imaging data is used as input for dose biodistributions either a Dose Point Kernel or Local Energy Deposition model can be used to convert counts into radiation doses. The time-integrated activity is estimated for each treatment by fitting a curve through the uptake data from quantitative imaging acquired at multiple time points after administration.
Quantification of activity in tissue is influenced by multiple factors, for instance type of acquisition (SPECT vs. conjugated view vs. planar), image corrections (scatter, attenuation, partial volume effect, smoothing), camera cross-calibration, count rate, segmentation, and volume of the target. In SPECT-based dosimetry, uncertainties in absorbed dose estimates are dominated by the ability to define its volume and accurately quantify uptake for small lesions or tissues (e.g., salivary glands), while in larger lesions or organs (e.g., kidney, spleen liver), accurate curve fitting of the time-integrated activity has the largest impact.

Dose limits and target doses in TARE

TARE is a special form of RNT as it is performed by arterial administration of radiolabeled microspheres.
They lodge in tumor-associated microvasculature and irradiate the lesions. Currently, this treatment is approved in the third line setting for liver-dominant non-resectable metastatic colorectal cancer or hepatocellular carcinoma. There are three different commercial products available, labelled with either Holmium-166 (^{166}Ho) or Yttrium-90 (^{90}Y); SIR-Spheres (Sirtex), TheraSpheres (Boston Scientific) and QuiremSpheres (Terumo), each product has its characteristics with respect to material, activity per sphere and specific gravity. To simulate the hepatic distribution of microspheres, either [^{99m}Tc]Tc-MAA or ^{166}Ho-Scout is infused at selected tumor-supplying hepatic arteries followed by abdominal SPECT/CT imaging.

Together with a recent diagnostic contrast-enhanced CT or MRI, these images form the basic input for dose planning. The presence of a dose-response relationship for TARE was demonstrated in various clinical trials, and consequently, a shift was made for all types of microspheres from single compartment or body surface area activity prescription towards personalized dose planning (17,18). The dosimetry for TARE is relatively simple, as the therapeutic microspheres do not degrade after administration, the time-integrated activity is only determined by the known physical half-life of the isotope and the distribution remains constant over time. There are three relevant compartments over which the microspheres can distribute: lungs, liver parenchyma and tumor. The standard MIRD formalism states that the activity to be administered (A) could be calculated given a planned tumor-absorbed dose (D_T) by

$$A[GBq] = \frac{D_T\,[Gy] \times (M_N\,[kg] + M_T \times r)}{CF \times r \times (1 - L)}$$

with *M* being the mass of the tumor or parenchyma, r is the ratio of accumulated counts between tumor and parenchyma, *CF* is an isotope dose conversion factor (^{90}Y = 49.67 J/GBq; ^{166}Ho = 15.85 J/GBq) and *L* is the lung shunt fraction. For treatment planning, the volumes and average accumulation should be determined for the lesions and normal parenchyma in each administration positions.
To aid definition of perfusion areas within the liver, it is advised to perform a Cone Beam CT at each planned infusion position. More methodological

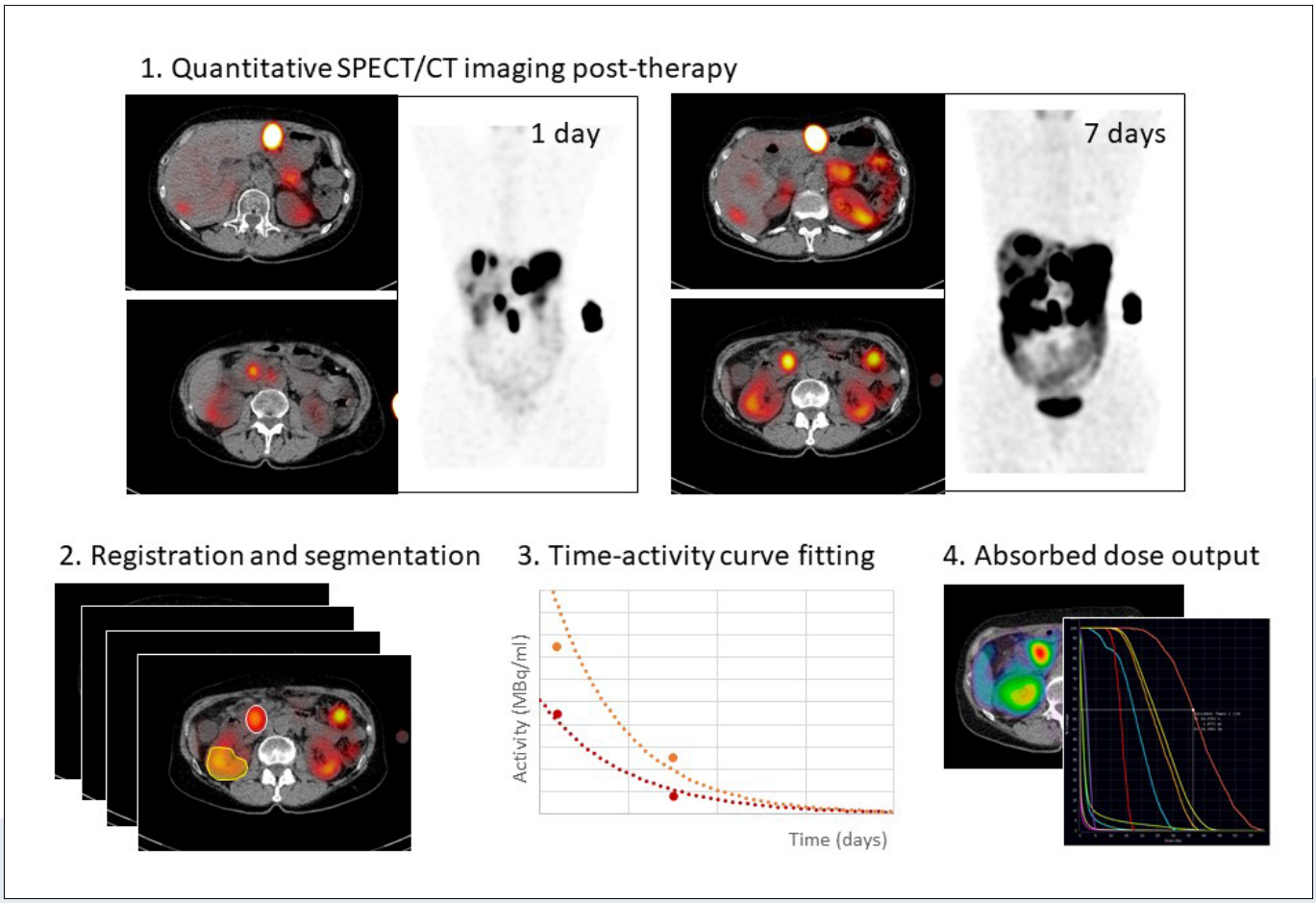

Figure 2. Dosimetric verification of ^{177}Lu-therapies involves nuclear imaging of the biodistribution at 1 and 5-7 days after administration. Post-treatment images are registrated to eachother, and if needed also to diagnostics scans, to delineate organs-at-risk and target lesions. Accumulated activity in each delineated volume is estimated by determining the area under the time-activity curves. Imaging data is converted into an absorbed dose output using predefined Dose Point Kernels.

details regarding the various technical aspects of the dosimetry workflow were recently described by scientific committees (12,19,20). Personalized dose planning can also be performed through voxel-based dosimetry, in which the pre-therapeutic [^{99m}Tc]Tc-MAA or ^{166}Ho-Scout are used to generate 3D-dosemaps like in modern EBRT-planning. Voxel-based dosimetry for TARE is clinically available in various commercial software systems, but its usefulness is still under debate. Both compartment- and voxel-based dosimetry relay on the assumption that the microsphere distribution is accurately simulated with pre-therapeutic SPECT/CT. In specific cases when the distribution is not representative or could not be quantified, for instance in small or infiltrative lesions, one-compartment dosimetry could still be applied.
In personalized treatment planning for TARE a holistic view of the patient is essential, so factors like disease stage, tumor morphology, previous treatments, liver function and arterial liver anatomy need to be considered when defining treatment intent (what do we want to achieve) and therapeutic strategy (how do we want to achieve this). There are roughly three types of treatments defined: bi-lobar (whole liver), lobar, and ablative selective TARE. Though patient work-up for these treatments is quite similar, the dose planning has some specific considerations. In patients with bi-lobar manifestations care must be taken to limit the absorbed dose to the parenchyma. Table 1 provides an overview of the recommended dose limits per commercial product. In patients with limited tumor load in 1-3 liver segments who are not suitable for surgery, a more aggressive and localized form of TARE can be considered, which is also referred to as radiation segmentectomy. Though this approach is relatively new, and most data is acquired for ^{90}Y-microspheres, these high tumor-absorbed doses of over 200 Gy lead to high response rates and long tumor control in both HCC and mCRC. However, radiation segmentectomies can only be performed if arterial liver anatomy is suitable and the remaining liver function is sufficient (18,21,22).

Evidence for organ dose limits in ^{177}Lu-therapies

Over the past years, two important radiopharmaceuticals have been introduced in clinical practice.
The first one is the EMA approved [^{177}Lu]Lu-DOTATATE (Lutathera®, Novartis Europharm Limited).
It is indicated for the treatment of unresectable or metastatic, progressive, well-differentiated, grade I/II somatostatin receptor positive-gastroenteropancreatic neuroendocrine tumours (GEP-NETs) using a regime of 7.4 GBq every eight weeks for four cycles (23). The second one is [^{177}Lu]Lu-vipivotide-tetraxetan (Pluvicto®, Novartis Europharm Limited) for treatment of progressive PSMA-positive metastatic castration-resistant prostate cancer (mCRPC). This radiopharmaceutical is approved by the EMA at a dosing of 7.4 GBq every six weeks for up to a total of six doses (24). In both registrations, dose modifications are allowed to manage severe (≥ Grade 3) or intolerable toxicities, with the most common being hematological toxicity, renal toxicity, and in the case of [^{177}Lu]Lu-vipivotide-tetraxetan, xerostomia. In the EMA registration dossier, there is no mentioning of dose modification to optimize the therapeutic efficacy, but data on absorbed doses in critical organs and tumors from various small prospective studies is available.
Red bone marrow is one of the critical organs in most RNTs, though data covering its dose-effect relation is limited and contradicting. Radiation induced acute **hematological toxicities** is recognized as the most common adverse event in ^{177}Lu-RNT (~10-15% of patients develop grade 3-4 toxicity within weeks), and yet it might not solely be induced by exposure to marrow, but also to some extent to accumulation in the spleen and lymphocytes. Results from the VISION dosimetry sub-study indicate

Table 1. Approximate proposed dose limits and tumor-absorbed doses for TARE.

		SIR-Spheres	TheraSpheres	QuiremSpheres
Dose limit	Liver parenchyma	≤40 Gy	≤120 Gy	≤60 Gy
	Pre-treated liver or compromised function	≤30 Gy	Not mentioned	Not mentioned
	Lung	Single ≤30 Gy	Single ≤30 Gy	Single ≤30 Gy
Target dose	Tumour (HCC/mCRC)	100-120 Gy	200-250 Gy	>100-150 Gy
	Ablative TARE	>150 Gy	>400 Gy	Not mentioned

that the calculated absorbed dose to red marrow was 0.25 ± 0.15 Gy for one cycle and 1.5 ± 0.9 Gy for six cycles of 7.4 GBq (n = 29 patients); for [^{177}Lu]Lu-DOTATATE this was 0.22 Gy for one cycle (n = 20 patients). Previous small-scale studies showed quite similar absorbed dose values for [^{177}Lu]Lu-DOTATATE ranging from 0.02-0.08 Gy/GBq (25,26,27). Late-onset myelodysplastic syndrome (MDS) and acute leukemia have been observed after treatment with [^{177}Lu]Lu-DOTATATE, but disease etiology and its relation to dose parameters are lacking. In hematological non-compromised patients, a dose threshold of 2 Gy has been associated with an increased risk of acute toxicity (based on data from Iodine-131 therapy), but it is being debated whether a dose limit of 2 Gy is safe in patients with impaired hematological function or those who received prior chemotherapy or EBRT.
The physiological excretion of small-molecules and peptides is mainly through the kidneys, so these organs are generally relevant in defining the patient's tolerability to RNT (28). Due to an unspecific reabsorption of [^{177}Lu]Lu-DOTATATE in the proximal tubular cells, the kidneys are the dose-limiting organs for this specific therapy. Sub-acute radiation induced **kidney toxicity** can progressively develop over months to years after treatment, however severe adverse events are rare (< 1.5% for Grade 3-4) in Lutetium-based RNT when proper renal-protection protocols including aminoacid-infusions are applied. Still, early onset kidney impairment is frequently observed (5-25% for Grade 1-2) and may result in a persistent reduction of kidney function that requires dose reduction or permanent discontinuation of therapy. Extrapolations of absorbed doses from EBRT have led to advised renal dose thresholds of 23-28 Gy for patients with compromised kidney function, and up to 40 Gy for non-compromised patients. Data from the VISION and NETTER-1 studies demonstrated average calculated absorbed doses to the kidneys of 0.43 ± 0.16 Gy/GBq (19 ± 7.3 Gy for six cycles) and 0.65 ± 0.29 Gy/GBq (4.8 Gy for one cycle), respectively. In literature, both [^{177}Lu]Lu-DOTATATE (with renal protection) and [^{177}Lu]Lu-PSMA (various ligands) absorbed doses vary per study and per patient, but ranges roughly between 0.6-1.0 Gy/GBq. Patients with mild or moderate preexisting renal impairment may be at greater risk of developing radiation induced toxicities as the residence times (biological half-life) may be prolonged.

A critical organ for RNT with [^{177}Lu]Lu-PSMA-ligands are the salivary glands, due to both specific and a-specific binding that may lead to **salivary gland toxicity.** Mechanisms underlying this radiation-induced salivary gland hypofunction and xerostomia (e.g., feeling of dry mouth) are largely unknown, but various studies do document acute reversible (mild) xerostomia in many patients treated with [^{177}Lu]Lu-PSMA (> 30% of the patients, Grade 1-2) (29). During EBRT in head and neck cancer, reported absorbed doses vary around 20-30 Gy, which results in a dose-dependent loss of secretory cells, so absorbed dose limits of ± 20 Gy have been proposed to reduce the probability of developing salivary gland toxicity (30). For [^{177}Lu]Lu-vipivotide-tetraxetan, data from the VISION trial showed an average calculated absorbed doses to the salivary glands of 0.63 ± 0.36 Gy/GBq (28 ± 16 for six cycles), other studies report mean absorbed doses between 0.5-2.5 Gy/GBq.
As can be concluded from the above, there is basic data on dose thresholds for organs-at-risk that can be used as starting point for dosimetry-based personalized RNT. Treatment planning can also be achieved by optimizing the dose to the tumor, as is the case for TARE. However, dosimetry-based activity prescription of systemic RNT is more complicated as tumor accumulation of targeted radiopharmaceuticals shows large inter- and intra-patient variability, and different tumor phenotypes will react differently to radiation. Furthermore, consolidation of retrospective data to deduce dose-effect relations will be difficult as the approved ^{177}Lu-based therapies are currently applied in a second- or third-line setting resulting in large variabilities regarding patient data. Identification of radiobiological mechanisms that might indicate why certain patients do, and others do not, benefit from RNT is likely to be overshadowed by inherent variations in therapeutic schemes and absorbed dose calculations. So currently, no specific recommendations can be provided to guide treatment using tumor target doses for RNT.

First steps to personalize ^{177}Lu-therapies

Personalization and optimization of RNT can come in many forms as differences in number of given cycles, activity dosing per cycle, time between fractions, peptide and specific activity of the radiopharmaceutical are all factors that will influence the induced biological effects within the body, both for normal tissue and tumor lesions. Recently published data of prospective studies mainly focused on individualized treatment with [^{177}Lu]Lu-DOTATATE based on renal dosimetry.
The PP-PRRT trial (NCT02754297) is a prospective, single-center study, in which the injected activity per cycle was adjusted to reach a prescribed cumulative absorbed kidney dose of 23 Gy over four cycles [^{177}Lu]Lu-octreotate (31). The prescribed activity was determined according

to GFR, body surface area and prior absorbed renal doses, aiming at 5-6 Gy per cycle. Dosimetry was done per cycle, so at approximately 4, 24 and 72 hours after administration quantitative SPECT/CTs were performed covering liver, kidneys, vertebral bodies, and target tumor lesions. This therapeutic regime led to a wide-ranging per-cycle activities (0.7-32.4 GBq; median 8.8 GBq). Not only was the cumulative administered activity 1.24 times higher compared to empiric dosing at four-times 7.4 GBq, also the median absorbed dose in tumor lesions increased 1.26-fold. It must be noted that the incidence of severe toxicities was quite similar to those reported for the empiric dosing. Data to determine the progression-free and overall survival is not yet complete, but first preliminary results are encouraging.

The ILUMINET trial (NCT01456078), a prospective phase-II study, also evaluated the safety and efficacy of individualized [^{177}Lu]Lu-octreotate therapy in 97 patients (32). In this study, cycles of 7.4 GBq [^{177}Lu]Lu-octreotate were given until the kidney dose threshold of 27 Gy was achieved, and patients without risk factors for renal or hematological toxicity could receive up to 40 Gy (both defined as cumulative Biological Effective Dose). For dosimetry, planar scintigraphy at 1, 24, 48, 96 and 168 hour post injection were combined with one SPECT/CT at 24 hours. This prescription methodology resulted in a considerable variation in number of treatment cycles, as absorbed kidney doses show quite some patient variability. The overall toxicity was mild, and the median kidney absorbed dose per cycle was 4.5 Gy (range 2.2-14.3). After a follow-up of 42-months, the PFS and OS were 29 months and 47 months, respectively, and the best overall response rate was 34% (complete plus partial response). Though direct comparison of this study with the results from the NETTER-1 trial is difficult (28 and 48 months, 18%, respectively), dosimetry-based RNT seems to be more effective.

Future of dosimetry in RNT

In the Netherlands, efforts are ongoing to harmonize post-therapy imaging for ^{166}Ho and ^{177}Lu SPECT/CT, with respect to imaging time-points and acquisition protocols. These efforts started to limit variations in data acquired in prospective clinical trials, including the CAIRO-7 (NCT05092880, ^{166}Ho-TARE in elderly and frail) and the Bullseye (NCT04443062, [^{177}Lu]Lu-PSMA in oligometastatic PCa), but they are gaining increasing support from other centers. It is hopeful that in a well-equipped country such as the Netherlands the ambition exists to at least harmonize post-treatment imaging and dosimetry data collection. Additionally, there are a few recent developments that, when combined, can take RNT one step further towards personalized dosimetry-based planning.

Image processing and voxel-based dosimetry

The conversion of imaging data into dose maps is often seen as a complex undertaking that needs extensive support from skilled personnel, however proper implementation of a dosimetry workflow is becoming less complicated with the advances in quantitative camera technologies and image processing software. The main camera suppliers have nowadays implemented quantitative SPECT/CT workflows with protocolized quality assurance suitable for the clinical practice. The biggest progress is made in the post-processing software. Vendors such as Hermes, MiM, Dosisoft and ABX-CRO are introducing CE-marked solutions for TARE and ^{177}Lu-therapies that can be used for clinical decision making, thus making in-house developed software redundant. To generalize, these applications convert count-data using predefined calibration factors into voxel-based dose maps that can be displayed as 3D dose-isocontours or dose volume histograms to visualize the spatial distribution of the administered dose or predict absorbed doses based on previous treatments. These vendors are now pointing their arrows on the approval of AI-based algorithms for segmentation of both normal organs and tumor lesions.

Single-timepoint curve fitting

As the goodness-of-fit for the time-activity curve determines the accuracy of absorbed dose estimates, so ideally SPECT/CT would be made at multiple time-points after administration of systemic RNT. This sequential imaging and (manual) segmentations are a highly time- and resource-intensive process that hamper broader clinical implementation of dosimetry. So, studies have focused on methods to limit the number of scans, while balancing accuracy and uncertainty of absorbed dose estimates (33,34,35). To estimate individual organ absorbed doses in [^{177}Lu]Lu-PSMA therapy, a single-timepoint SPECT/CT at 24-48 hours after administration could be used in combination with predefined population-based organ-specific kinetics. Evaluation of tumor lesions is more complex as it shows a larger inter- and intra-patient variability, so in addition to one early time-point a second 'late' time-point (168 hours) might be needed. A similar approach may be adopted for other receptor-targeted Lutetium-based RNTs.

Pharmacometric modelling

Understanding and interpreting the dose-concentration-effect relationship is an eminent part of

drug-development. Pharmacokinetic (dose-concentration) and pharmacodynamic (concentration-effect) models are widely applied for instance to translate preclinical results to humans, select a safe dose for first-in-man studies, or start phase I/II studies. In later phases of research, models can be used to assess for instance population variability or predict an individual's biodistribution in a certain physiological status. The physiologically based pharmacokinetic (PBPK) models help to understand and predict kinetics, by combining predefined drug-specific information with physiological or biological data in a complex multi-compartment model to predict tissue accumulation profiles. The population PK models, on the other hand, are based on lumbed compartments to describe concentration-time profiles and its variability within a population of interest. Combination of these pharmacokinetic models with pharmacodynamic and tumor-growth data for therapeutic radiopharmaceuticals is very new but could provide important insights into the various factors that impact biodistribution (36). Recent studies have used pharmacometrics modeling to for example estimate time-integrated activities with limited imaging time-points, predict treatment response for [^{177}Lu]Lu-PSMA and related pretreatment Gallium-68 imaging with [^{177}Lu]Lu-PSMA accumulation (37,38,39).

Conclusion

With the proposed EANM-classification for RNT prescription and dosimetry, minimal compliance to the EU-Directive 2013/59/Euratom can be implemented for the EMA-approved [^{177}Lu]Lu-therapies and TARE in most Dutch hospitals. Still the field is moving on, and despite important knowledge gaps with respect to radiobiology, evidence for more individualized RNT prescription is mounting. For TARE personalized treatment planning is now recommended for all types of microspheres and indications. The clinical implementation of dosimetry for treatment planning and verification in systemic ^{177}Lu-based RNT is not widely applied and adopted in guidelines. Still, important leaps are made to reduce imaging time-points, userfriendly CE-marked dosimetry software, harmonization of quantitative imaging and clinical RNT protocols.

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