Dosimetry in Radionuclide therapy it's challenges and innovation

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***Abstract*—Systemically administered radiopharmaceuticals are used in radionuclide therapy (RNT), a rapidly expanding cancer treatment technique, to target and kill cancer cells. Although the amount of absorbed radiation supplied to target tissues directly affects the effectiveness and toxicity of RNT, clinical practice has traditionally relied on fixed or empirical dosing regimens. Optimising the therapeutic dose while minimising harm to healthy organs at risk (OAR) is one way that moving towards personalised, dosimetry-guided treatment promises to improve patient outcomes. This review addresses the development of RNT dosimetry, emphasising significant obstacles as well as new developments in imaging, computer techniques, and radiobiological modelling that are opening the door for its broader clinical application.**

***Index Terms*—Dosimetry Radionuclide Therapy Absorbed Dose SPECT /CT Maximum targeted activity (MTA)**

I. INTRODUCTION

illnesses, such as pneumonia and cardiovascular and cerebrovascular disorders.[1]Globally, cancer has a significant impact, contributing to 20.3% of all fatalities, with Medicine has been revolutionized by radioisotopes, which are unstable atoms with nuclei that emit radiation. These radioactive elements, which were first recognized for their propensity for destruction, have proven essential in research, diagnosis, and treatment, improving patient outcomes and advancing our knowledge of human health. Iodine-131 was used to diagnose thyroid function in 1938, marking the first time radioisotopes were used in medicine. (1) The science behind radiotherapy is that our understanding of radiobiology and cancer biology has greatly expanded. Today's radiotherapists are oncologists and cancer specialists. Significant technological progress has been made. Radiation oncology appears to have a promising future because local cancer treatment is the most effective. (2)

Dosimetry can be used on targeted tissues (like cancers), non-targeted tissues (such as bone marrow, kidneys, or healthy liver), or both. Despite being the gold standard for conventional radiation treatment (RT) for many years, dosimetry is still not widely used in RNT. (3) Radionuclides are administered to tumours at the cellular level in radionuclide therapy (RNT), a fast-developing oncologic therapeutic method that aims to selectively harm tumour cells throughout the body while limiting damage to non-targeted cells. Since the initial I-131 treatment for thyroid cancer was carried out in the 1940s, RNT has played a role in the field of cancer treatment. (4)

RNT is usually given systemically, and its ability to reach cells depends on physiologically diverse elements like cell density, receptor density (which is influenced by growth factor regulation and local gene expression), vascularity (which is frequently decreased in the core of tumours), and receptor-ligand binding. Because of the unclear relationship between the bio distribution of the pre-therapy imaging agent and the actual delivered RNT, pre-therapy radiation dose prediction may be less accurate than in RT. Furthermore, it's possible that the radiation biology models used to forecast dose response in RT won't translate well to RNT. The longer residence period in tissues (lower dose rate), the radiation's particle nature, the radiopharmaceutical's more varied dispersion, and potentially several cytotoxic pathways are the causes of this. (5)

II. DOSIMETRY BASICS

Dosimetry is the study of values (dose) that characterize the energy received by a substance and, to a lesser extent, its rate of deposition (dose rate).

Dosimetry measurements, which are carried out by subjecting a dosimeter to a radiation source, aid in assessing the physical, chemical, and/or biological effects that radiation has on a material that has been exposed to it (6).

Process control and validation procedures are employed to guarantee that the irradiation process is conducted safely and that the desired radiation effects (physical, chemical, and/or biological) are realised. The basis of process controls is the connection between the absorbed dosage in an irradiated object and the source parameters. For IR-radiators of isotropic radioactive sources, this connection comprises dwell time, position inside the source rack, and conveyance speed; for accelerator sources, it comprises beam voltage, beam current, scanning width, scanned uniformity, and conveyance speed. Calculations utilising suitable dosimetry equipment with a particular level of precision and accuracy are used to determine the absorbed dosage and dose distribution (7). The main characteristic that makes it possible to evaluate how radiation processing affects an irradiated substance is "radiation interaction with condensed matter," which receives dosage. To account for any mass energy, the absorbed dosage is defined as the stochastic quantity of energy imparted by a source, which is equal to the sum of all energies entering the volume of interest, less all energies exiting this volume. Where dm is the mass of a finite volume, $D = d\varepsilon / dm$

, $d\varepsilon$ is the average energy transferred. The absorbed dosage is either joules per kilogram (J/kg) or grey (Gy). (8)

III. APPROACHES TO DOSIMETRY IN RNT

Two axes can be used to arrange the dosimetry approaches in RNT: before and after therapy, and tumour as opposed to non-tumour. First, dosimetry can be done before treatment (preRx) or following each cycle of therapy (postRx). Imaging is carried out in preRx dosimetry, which is typically utilized to forecast the bio distribution of the final treatment and for treatment planning. Therapeutic quantity. This could lead to more or less activity than anticipated (if beginning with a set of empirical tasks). Imaging is utilized in post-Rx dosimetry to determine the actual absorbed dosage of the medication being given. (9)

When planning a subsequent treatment cycle for fractionated RNTs, this information can be utilized to either administer another fixed-activity cycle, modify the activity to be given, or halt therapy because the intended dose threshold has been reached.

Additionally, PostRx dosimetry can be used to monitor cumulative radiation exposure and establish a correlation with reactions as well as toxicities. In clinical practice, dosimetry is not frequently used to adjust the number of cycles or activity per cycle, although preliminary data on this strategy are encouraging. (10)

In general, RNT's aspirational objective for cancer treatment is to optimize radiation dosage to tumours while reducing the amount administered to potentially toxic healthy tissues. In light of this, another significant issue in RNT dosimetry is the question of whether to adjust activity according to absorbed dose to tumours or to tissues that are not tumours (risky organs). When performing lesion dosimetry, the objective is to give a tumour a fixed radiation dose (similar to RT). The justification for lesion according to dosimetry, the tumour-absorbed dose may be related to response, as indicated by numerous studies. (11)

Nowadays, loco regional studies are the most common application for lesion dosimetry. Treatments like Y-90 selective internal radiation therapy (SIRT), which is liver-directed and involves a direct approach, show evidence of a significant tumour dose-response relationship. (12) The goal of the maximum targeted activity (MTA) dosimetry technique is to administer the greatest activity while avoiding dose levels that are known to be harmful. Imaging uptake can be used to determine how much of the initially provided activity is retained throughout the body at a given time point or to evaluate radiation doses to organs most at risk of harm, such as the kidneys. It is much simpler to calculate the absorbed dose to a distinct solid organ like the kidney than it is to estimate the absorbed dose to the red bone marrow, which is distributed throughout the body and may have little defined uptake. Measurements of radiation in successive blood samples have commonly been used in these circumstances as a bone marrow replacement. (13)

Yet, even though patients hardly ever achieve the generally acknowledged 2 Gy (37) or 3 Gy (38) marrow dose (mean bone marrow dose 1.0 Gy over 4 cycles), bone marrow toxicity often occurs following

the typical 4 cycles of 7.4 GBq (200 mCi) Lu-177 Dotatate (14)

3.1 Prescription Algorithms for Dose

(15) Three prescription algorithms are available for RPT: maximum tolerated absorbed dose (MTAD), recommended tumour-absorbed dose (PTAD), and fixed administered activity (e.g., MBq, MBq/kg of body mass, and MBq/m² of body surface area). Patient measurements are not required for the approach that uses a fixed supplied activity, with the possible exception of height and mass. Treatment activities are based on phase 1 and phase 2 clinical studies that resemble chemotherapy in terms of dose escalation. For example, 177Lu-DOTATATE (Lutathera; Advanced Accelerator Applications) is commonly used to treat neuroendocrine tumours that express the somatostatin receptor. It is usually given in 4 cycles of 7.4 GBq separated by 8 weeks. (15).

The simplest, most practical, and least costly method is a fixed administered activity. However, some patients were inevitably under dosed when they might have safely gotten higher (and likely more therapeutically effective) activity. On the other hand, other patients who received the same fixed activity might have overdosed due to overwhelming normal-tissue side effects. (16) tumours that express the somatostatin receptor. It is usually given in 4 cycles of 7.4 GBq separated by 8 weeks. (15).

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3.2 Activity and Time Activity Data Measurement

It is common practice to measure radiopharmaceutical activity using a dosage calibrator with uncertainties of 65% or less. However, dosage calibrator uncertainties can be significant for isotopes with complex decay schemes with nonequilibrium progeny like some a-particle emitters, pure b-particle emitters (like 90Y), and non-standard source geometries. (17)

To ensure accuracy, reference standard sources that can be traced back to a national agency should be utilized for such isotopes. The overall dosimetry study will be affected by any uncertainties related to activity measures. (18)

Serial planar g-camera imaging can be used to measure the time-dependent activities or activity concentrations of therapeutic radiopharmaceuticals, which are frequently single-photon emitters. (19)

SPECT/CT or a hybrid method that blends planar imaging and SPECT/CT. After accounting for partial-volume effects, scatter, attenuation, and collimator-detector response, the count rate per voxel in reconstructed tomographic images is proportional to the local activity concentration. The corrected count rate (cps) per voxel is divided by a measured system calibration factor [(cps/voxel)/(kBq/mL)] to determine the activity concentrations: The SPECT activity concentration is given by Equation 1, which is kBq ð Þ = mL 5 cps=voxel calibration factor. SPECT/CT imaging takes fifteen to thirty minutes for each bed position. A good alternative is hybrid SPECT/planar imaging, in which only the quicker planar scans are acquired at the other time points, and planar and SPECT/CT scans are collected at a single time point. (20)

The single SPECT/CT examination offers a (more precise) point estimate of activity, whereas the many planar scans give the forms of the source-region time–activity curves (i.e., the kinetics). A scaling factor from SPECT/CT to planar is obtained by comparing the contemporaneous planar and SPECT/CT scans. With very few exceptions, quantitative PET is still more developed than quantitative SPECT. (21)

RPT does not employ positron-emitting radionuclides. However, therapeutic radiopharmaceuticals may use positron emitter-labeled surrogates to provide time-activity data (22). PET/therapeutic radionuclide combination 124I/131I in thyroid cancer that has spread. The therapeutic radionuclides and PET must have a physical half-life that is well matched for serial PET scans to be carried out over an adequate amount of time in order to provide accurate time-activity data estimates for the therapeutic radioactive element. 124I, which has a physical half-life of 4.18 days, and 131I, which life, 8.04 d) meet this requirement.

However, 68Ga-DOTATATE (67.7-minute physical half-life) is too brief to predict subsequent tissue 177Lu-DOTATATE activities (physical half-life: 6.65 d). For radiopharmaceuticals whose kinetics have been thoroughly studied, they show minimal patient variation, population-averaged normal. It is possible to

scale organ time-activity curves using image-derived, patient-particular organ activity assessed at a carefully chosen single point in time (23).

3.3 Patient Specific Dosimetry Paradigm:

The following is the paradigm for RPT patient-specific dosimetry administration of a test activity of either the therapeutic or a surrogate radiopharmaceutical; measurement by serial imaging and possibly blood and whole-body counting of its time- dependent bio distribution; definition of the pertinent anatomy by high-resolution structural imaging computation of the therapeutic radiopharmaceutical's absorbed dose coefficients for the (CT, MRI); derivation of time dependent activity concentration or absorbed dose rate, with approx. adjustment for differences in half-life between the therapeutic and surrogate radionuclides; integration of time–activity data to yield region- or voxel-specific time-integrated activity coefficients (alternatively, time–dose-rate data can be integrated directly to yield absorbed dose);organ at risk or tumour (optional radiobiological modelling adjustments can be included at this stage); and prescription of the activity to deliver the targeted absorbed dose to the organ at risk or tumour. This paradigm assumes that the absorbed dose coefficients for the entire RPT will match those estimated from the test study. This is more likely to occur when the therapeutic radiopharmaceutical and the test have the same chemical makeup. If the target tissue uptake is nonlinearly dependent on administered mass or activity, or if the test and treatment radiopharmaceuticals are dissimilar (24)

The dosimetry paradigm may involve a significant amount of time and work. The radiopharmaceutical's preparation and assay might take 10–20 minutes, while its administration could take as long as 1-2 hours for a steady infusion or less than a minute for a bolus injection. A single static image takes 2–5 minutes to image, a whole-body scan or single-bed-position SPECT/CT study takes 20–40 minutes, and a multiple-bed-position SPECT/CT study takes 1-2 hours. For sufficiently precise dosimetry, a single imaging time point might be enough, significantly cutting down on the amount of time required.

If done by hand, segmenting (also known as contouring) normal organs and tumours might take many hours. This process can be sped up by automated and semi-automated segmentation techniques, and eventually, AI-based routines could make segmentation completely automated and quick. Calculating absorbed doses or dose distributions and fitting or integrating mathematical functions to collected data are subsequent phases in the workflow that require a lot of computing power but are mostly automated. Those who perform clinical dosimetry calculations need to be properly trained and fully comprehend the procedure. According to recent international guidelines, a medical physicist should devote 1.1 days of their time to each case's computations. (25)

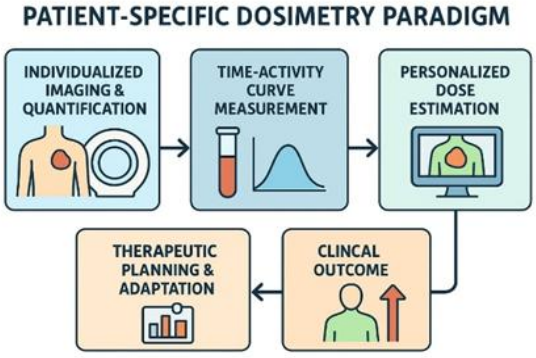

Figure 1 Patient – specific dosimetry paradigm

3.4 Absorption Dose Calculation

Estimating the source region time-integrated activity coefficients which are represented as areas under activity/activity concentration or dose rate curves is necessary to compute absorbed doses. Mathematical functions, usually sums of exponentials, can be used to fit these data, and they can then be analytically integrated to infinity. As an alternative, one might integrate to the final measured point using numerical techniques (such as trapezoidal integration) with an extra contribution to account for terminal behaviour. Operationally, based on the last two observations, the terminal contribution might be interpreted as corresponding to physical deterioration or apparent clearance. (26)

For radionuclides with comparatively lengthy half-lives (such as 131I [8.0 d] and 177Lu [6.7 d]), this is rarely done. Compartmental modelling is another method for determining areas under curves (27)

Three techniques can be used to calculate the absorbed dose from internal radionuclides: dose factor-based computing (such as the MIRD formalism), dose point kernel convolution, and Monte Carlo (MC) radiation transport simulation. (28)

For a target region rT irradiated over a time period TD, the absorbed dose coefficient d or Þ T, TD (mGy/MBq) is defined in the organ-level time-independent formulation of the MIRD schema (56) as the absorbed dose (mGy) normalized to the administered activity (MBq). (29)

This is the absorbed dose (Gy) that, if administered at the mathematically limit of an indefinitely low dose rate, is predicted to have some biologic effect. Like the physiologically effective dose, the Equi effective dose (EQDX, in Gy) depends on the a/b ratio and is typically expressed as EQDXa/b (30).

The reference dosage is usually X 5 2 Gy since it is commonly used in conventionally fractionated XRT, which yields EQD2a/b. This notation, which represents a reference dose per fraction of 0 Gy and denotes radiation treatment given at an infinitely low dose rate or by an infinite number of infinitely small fractions, could be used to indicate the biologically effective dose as EQD0a/b. Because of the geographical irregularity in the dose distribution, mean absorbed doses might not match normal tissue damage or tumour treatment response. The one value of the absorbed dosage is equal to the corresponding uniform dose if distributed uniformly. (31).

The "equivalent uniform biological effective dose" is the formulation for the equivalent uniform dose. Numerous investigations have demonstrated that the equivalent uniform dose has a better response correlation than the tumour mean absorbed dose. (32)

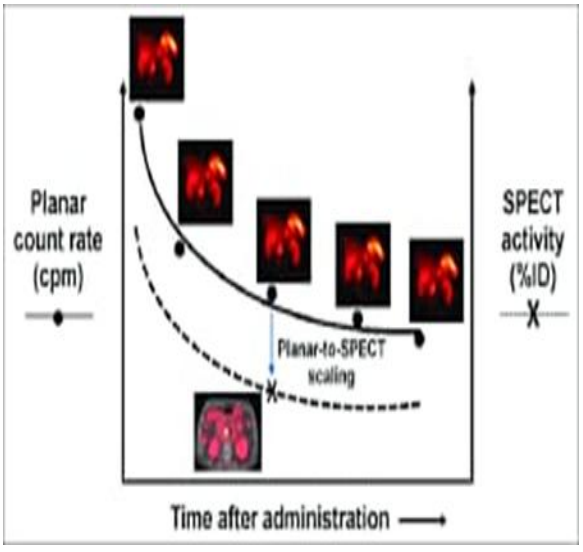

Figure 2: Hybrid SPECT / planar imaging approach to imaging-based measurement time activity data

IV. THERAPEUTIC EFFECTS IMPLEMENTED IN RADIONUCLEAR DOSIMETRY

4.1 Radioiodine therapy for thyroid cancer

Differentiated thyroid tumors, or carcinomas starting from the follicular epithelium, account for the bulk of thyroid malignancies. Radioactive iodine therapy can be used as a curative or palliative approach in individuals with severe metastatic illness or as an adjuvant therapy to remove thyroid remnants after a thyroidectomy. The two dosimetric methods used in radioiodine therapy for thyroid cancer are pre-therapeutic and pre-treatment dosimetry. The former aims to assess activity before treatment, enabling the destruction of any remaining malignant tissue and preventing the reach of a preset threshold for absorbed doses in organs at risk, whereas the latter assesses doses after the treatment, which can help navigate the number of administrations. (33)

While the latter evaluates doses after the treatment, which can aid in navigating the number of administrations, the former seeks to evaluate activity before the treatment, allowing ablation of the remaining malignant tissue and avoiding reaching a predetermined threshold for absorbed doses in organs at risk.

There have been efforts to increase the effectiveness of thyroid cancer treatment since it has been in use for many years. Since its initial application in the 1950s, there has been debate on the ideal radioactivity of iodine 131I while treating differentiated thyroid carcinoma. Clinical advantages of applied dosimetry have been demonstrated. (34)

Dosimetry-guided radioactive iodine 131I treatment enables the highest absorption dose to be administered to maximize therapeutic benefit. For patients who did not respond well to traditional fixed-dose therapy, the maximum safe dose determined by bone marrow irradiation offers an efficient therapeutic option. Estimating the 131I uptake in the tumor or blood is the foundation of dosimetric techniques for assessing 131I activity for the treatment of metastasis or recurrence in differentiated thyroid cancer. According to Jin Lee et al., 40–50 Gy is probably going to work when applied to a metastatic lesion. (35)

4.2 Treatment of liver malignancies with microspheres

One of the best-known uses of dosimetry is in the treatment of liver malignancies with microspheres

(90Y glass or resin microspheres). Clinical success rates for safe and effective therapy are high when dosimetric studies are used to determine the activity to be injected. (36).

A single tomographic scan can provide the estimate since microspheres are permanently implanted in the tumour through the hepatic artery, negating biological clearance. Before the therapy, simulation with 99mTc-macroaggregates of albumin permits maximizing therapeutic effects by predicting the absorbed dose to lesions and non-tumoral liver. It enables the selection of a single, safe, and effective treatment, and typically, no more than one administration is required. In 2017, Garin et al. provided a multivariate study of radio embolization in hepatocellular cancer (37) demonstrating that the only element linked to an increase in overall survival was the dose received by the lesion (more than 205 Gy). Whether patient dosimetry should be determined by toxicity criteria or efficacy thresholds is still up for debate. Dosimetric prediction for non-humoral liver is more accurate than for lesions, according to Chiesa et al. (38)

4.3 Treatment of Metastasized Castrate-Resistant Prostate Cancer

Making use of PSMA 177Lu Lu-labelled PSMA ligands is a novel treatment for metastasized castrate-resistant prostate cancer (mCRPC) that has progressed. Before starting treatment, imaging using [68Ga] Ga-PSMA PET/CT is necessary to precisely identify lesions. The absorbed dose for tumours and at-risk organs (liver, kidneys, salivary glands, lacrimal glands, and bone marrow) has been determined by numerous published studies. (39) The majority of the data exhibit significant variability, necessitating dosimetric computations. In the case of organs at risk, calculated radiation-absorbed doses per GBq were 0.72–0.88 Gy/GBq for kidneys, 0.21–1.17 Gy/GBq for parotid glands, and 0.02–0.03 Gy/GBq for bone marrow. (40) Furthermore, there were typically no appreciable differences in the organ-absorbed dosages between cycles. According to Okamoto, the mean absorbed dosage per cycle for tumour lesions was 3.2 ± 2.6 Gy/GBq (range: 0.22–12 Gy/GBq). But with each cycle, the doses absorbed by the tumour lesions progressively dropped. Compared to other organs, malignant tumours have substantially higher accumulated doses. In a study conducted by Fendler and colleagues. (41)

Compared to vital organs, the dose given to the tumour was six to twelve times higher. The dose that the parotid glands absorbed was greater than the dose that the kidneys absorbed in another investigation. Pre-therapeutic dosimetry was assessed by Kabasakal et al., who, like the others, proposed that the parotid glands, not the kidneys and bone marrow, are the dose-limiting organs. (42)

V. CHALLENGES IN RADIOTHERAPY DOSIMETRY

5.1 Limitations of conventional dose comparison methods in IMRT: However, several of these methods miss the spatial details that define, for example, the areas of contention. Comparisons of distributions (such as dosage difference histograms, comparisons between planned and measured dose volume histograms, and others that call for the specification of structures on both distributions under comparison). (43)

5.2 Technical reasons: Technically, dosimetric imaging and analysis are difficult. There are no universal guidelines for the proper calibration and measurement of QSPECT/CT. Absence of commercially available software that is accessible and integrated (works in progress). The requirement for several patient acquisitions. Uncertainty and questionable correctness.

5.3 Other Issues: lack of medical physicists with the necessary training and experience to carry out internal dosimetry. Some therapeutic radionuclides are difficult to scan (surrogates needed). Other issues involving alpha-emitters. Healthcare workers' ignorance of the enhanced efficacy of radioisotope treatment carried out with dosimetric calculations. (44)

5.4 In-vivo dosimetry and dose reconstruction: exposed to radiation. Lastly, dosage validation can be carried out during patient irradiation. In vivo dosimetry is now used for this purpose, and dose reconstruction from exit beam data recorded during treatment delivery will be used in the future as a radiation device for adaptive radiation therapy. (45)

5.5 Evaluation and Analysis of Dose QA Data in IMRT: The evaluation of the dose QA results, especially in the verification of dose distributions, should be covered as the last step in the dosimetry validation process. Large 2D and maybe 3D data sets will result from many of the tests in Table 1 and need to be compared with the intended dose data. As a result, the evaluation could be complicated and require particular software tools for comparison and data registration. If the contours coincide, the method of overlaying dosage contours from ten years ago might be adequate; however, if not, it is difficult to comprehend. It is possible to create dose difference maps that show areas where calculations and measurements diverge. (46)

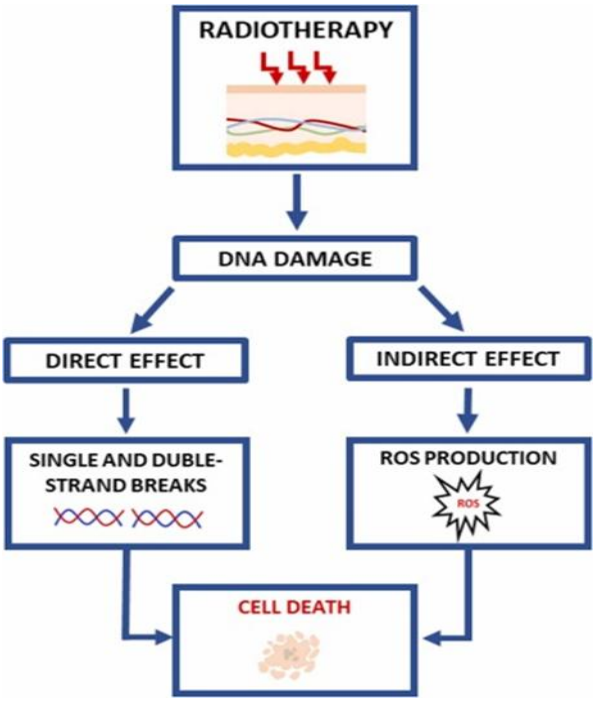

Figure 3: Process of radiotherapy during cell death

VI. INNOVATION OF RADIOTHERAPY DOSIMETRY

In our introduction, we discussed the repercussions of implementing poorly evaluated innovations or failing to implement previously demonstrated innovations (the so-called research implementation gap), which sparked our interest in this study. According to earlier studies that examined the extent of innovations used in Dutch radiation centres, these facilities are highly dynamic and inventive and swiftly absorb new developments in their field. Between 2011 and 2013, 525 innovations were adopted by radiation centres, 168 of which were treatment advancements. (47)

When comparing the implemented treatment innovations with this literature review study, we found no documented significant impact on patient outcome (survival/toxicity) for the breath-hold technique in breast cancer, SBRT for pancreatic cancer, IMRT for lung cancer, and IMRT for gynecological cancers. But it turned out that the breath-hold method was a significant technological breakthrough. The ALARA principle (as low as reasonably practicable) should guide the implementation of this breakthrough, which dramatically reduces the radiation exposure to the heart. Since the reproducibility of this technique is comparable to that of radiation during free breathing, there is no possibility that tumour cells will be missed. (48

The amount of evidence in publications about organizational innovation was lower than that of medical papers about radiation. Comprehensive Phase I, II, and III studies can be used to test new medical treatments and (sometimes) new technologies. These trials have a greater level of proof than the type of study often carried out in managerial practice. Randomized controlled clinical trials are typically impractical in management practice; instead, observational studies or research designs with lower evidential value are employed. Research is frequently conducted multiple times under various conditions to build an evidence base. (49)

Even though a lot of research has been done over the last 20 years to give management practice a strong evidence base, the majority of management ideas are still derived from professionals' individual experiences. Additionally, researchers and practitioners in management practice typically work in separate domains, which leads to the practitioners frequently not completely understanding and supporting study findings. (50) The implementation of IMRT for lung cancer and SBRT for pancreatic cancer most likely took place in a multicenter trial, and the outcomes of the two- or five-year follow-up are yet unclear. We couldn't find any such studies for IMRT for gynecological cancers or in the Netherlands during that time period on http://www.trialregister.nl or http://clinicaltrials.gov. We think it is essential to

incorporate as many potentials but untested technologies as feasible in a study environment, unless the ALARA principle is applicable and the innovation is cost-effective (ALARP principle). This is particularly true in cases when the technology is expensive, like particle treatment, for example. (51) Standard techniques from evidence-based medicine are helpfully supplemented by approaches from health economics and health technology assessment. 6. A model-based method, which is already employed for the introduction of proton treatment (ideally in already-existing centres) in the Netherlands, provides an additional choice to assess efficacy. (52)

Since treatment approaches may alter significantly over time and the benefits and drawbacks take time to materialize, it is difficult to evaluate the reduction in secondary cancers and other late-toxicities in particle therapy through randomized clinical trials. We do think that the association between dose and complications is known for many toxicities and can therefore be utilized to estimate the value of particle therapy, despite the fact that these models have some uncertainty. Thus, under the Netherlands' model-based approach, criteria will be used to establish clinical benefit based on the grade of toxicity, including late toxicities and subsequent cancers. (53)

VII. CONCLUSION

RNT is an oncologic therapeutic method that is interesting and growing quickly. Dosimetry holds considerable promise for RNT customisation, despite a number of lingering issues. However, considerably more dosimetry integration into clinical trials, as well as more standardized dosimetry calculation techniques and clinical practice standards, are required to ascertain the genuine additional value of dosimetry-based activity regulation in RNT. Thus, dosimetry-based personalized treatment schedules, rather than only fixed administrations, must be permitted by radiopharmaceutical businesses and regulatory bodies. Optimizing information and dosimetry could help with PRRT optimization, even though we are still far from reaching high response rates because the majority of patients treated with PRRT are thought to be palliative patients. For example, three phase II studies reported response rates ranging from 7 to 54%, but failed to reach the maximum tolerated given activity

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