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Review paper

# The contest between internal and external-beam dosimetry: The Zeno's paradox of Achilles and the tortoise

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ABSTRACT

Radionuclide therapy, also called molecular radiotherapy (MRT), has come of age, with several novel radiopharmaceuticals being approved for clinical use or under development in the last decade. External beam radiotherapy (EBRT) is a well-established treatment modality, with about half of all oncologic patients expected to receive at least one external radiation treatment over their disease course. The efficacy and the toxicity of both types of treatment rely on the interaction of radiation with biological tissues. Dosimetry played a fundamental role in the scientific and technological evolution of EBRT, and absorbed doses to the target and to the organs at risk are calculated on a routine basis. In contrast, in MRT the usefulness of internal dosimetry has long been questioned, and a structured path to include absorbed dose calculation is missing. However, following a similar route of development as EBRT, MRT treatments could probably be optimized in a significant proportion of patients, likely based on dosimetry and radiobiology. In the present paper we describe the differences and the similarities between internal and external-beam dosimetry in the context of radiation treatments, and we retrace the main stages of their development over the last decades.

## 1. Introduction

External beam radiotherapy (EBRT) and radionuclide therapy, also named radiopharmaceutical therapy (RPT) or molecular radiotherapy (MRT), make use of ionizing radiation to treat malignant neoplasms and some benign conditions causing pain or discomfort. The role of EBRT in modern medicine is well acknowledged [1]. Based on current indications, it is estimated that about 50 % of patients with cancer should receive at least one treatment with EBRT [2]. The last decade has witnessed an expansion of commercially available radiopharmaceuticals for MRT, whose number is likely to further increase in the future [3,4]. Meanwhile, internal dosimetry, i.e. the set of procedures required for the evaluation of the radiation absorbed doses deriving from internally administered unsealed radioactive sources, has gained momentum. Procedural recommendations and guidelines on how to perform internal dosimetry for specific treatments have been issued by international scientific societies [5–9]. However, internal dosimetry has a heterogeneous acceptance within the clinical community, and still suffers from limited resources and some cultural resistance [10–12]. It is remarkable that some of the most recently approved radiopharmaceuticals, namely

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[$^{177}$Lu]-DOTA-0-Tyr3-Octreotate (Lutathera®, Novartis, Basel, Switzerland) and [$^{177}$Lu]-vipivotide tetraxetan (formerly known as [$^{177}$Lu]Lu-PSMA-617, Pluvicto®, Novartis, Basel, Switzerland) were registered based on fixed posology without considering dosimetry, despite the 2013/59/EURATOM Council Directive mandated planning and verification of the absorbed dose delivered [13–15].

In contrast, calculation of the absorbed dose to the target and to the organs at risk is routinely accomplished in EBRT, where the role of the medical physics expert (MPE) and of dosimetry for treatment optimization and personalization are well established [16,17]. Following a similar route of development, MRT treatments could probably be optimized in a significant proportion of patients, likely based on dosimetry.

The purpose of the present paper is to describe the differences and similarities between internal and external-beam dosimetry in the context of radiation treatments, and to retrace the main stages of their development over the last decades. In comparing the trajectory of these two branches of medical physics, we were inspired by the Zeno's paradox of Achille and the tortoise. In this famous footrace, whenever Achilles reaches the point where the tortoise has stood, he would still have more distance to go in order to get where the tortoise has further advanced. We will let the reader decide who, in our story, is Achilles and who is the tortoise.

## 2. Evolution of dosimetry in MRT and EBRT

### 2.1. MRT

The first use of radionuclides for therapeutic purpose dates to the late 30ies, when patients suffering from chronic leukemia were treated with oral administrations of $^{32}$P sodium phosphate, which accumulates in cells with increased turnover [18]. In these early days of MRT, the natural tropism of $^{32}$P sodium phosphate, as well as of other radionuclides in salt forms, such as [$^{89}$Sr]$SrCl_2$ or [$^{224}$Ra]$RaCl_2$, was also exploited for the treatment of bone metastases, typically from breast or prostate cancer [19], or for the treatment of non-neoplastic bone diseases [20]. At the beginning of the 40ies, radionuclide therapy of hyperthyroidism and differentiated thyroid cancer with [$^{131}$I]NaI were initiated, and stand as the most successful and long lasting MRT [21,22]. These examples indicate that MRT originated within the fields of clinical endocrinology and hemato-oncology, with major focus on physiology and metabolism, rather than on the degree of radiation exposure [23]. Consequently, these radioactive substances were essentially regarded as "pharmaceuticals" for systemic treatments, and therapeutic activities were assessed empirically, either given in standard amounts ($^{131}$I) or normalised to patient weight (e.g. for $^{32}$P and $^{89}$Sr), with an oncological one-fits-all approach. Absorbed doses were regarded, in general, as a collateral aspect, not as the guiding factor. The efficacy of these treatments was high, with acceptable toxicities, at a time when other systemic therapies were lacking. In many cases MRT was adopted for compassionate use, it is therefore not surprising that for many decades the challenges of internal dosimetry and its associated radiobiology remained the passion of a very small scientific community. Marinelli, Quimbi, Benua, and Leeper deserve to be mentioned as pioneers in advocating the relevance of dosimetry [24–26]. They provided absorbed dose formulae to treat hyperthyroidism, and to reduce complications in metastatic thyroid cancer settings, for instance indicating 2 Gy to the blood as a safety threshold to limit possible hematotoxicity. In parallel to initiatives by the International Commission on Radiation Protection (ICRP), the creation of the Medical Internal Radiation Dose (MIRD) Committee in 1964 laid the foundation for the reference formalism for internal dosimetry [27,28]. In this frame, in 1996 Stabin et al. developed MIRDOSE3 [29], a software for internal dosimetry calculation, followed in 2004 by OLINDA/EXM 1.1 which obtained FDA approval [30]. In 1999, to overcome the limitations of the uniform activity distributions in organs applied in this software, a relevant step further was the proposal of a rescaling to account for non-uniform distributions and to allow for 3D voxel dosimetry [31]. Many studies followed to provide voxel dose factors for the most used radionuclides [32]. A completely new era for MRT begun at the end of the last century, driven by the evolution of medical research towards selective anticancer therapies, such as monoclonal antibodies or other peptidic cellular ligands. More complex radiopharmaceuticals were developed based on vector molecules exploiting specific receptor binding, targeted towards a variety of tumours including, among others, non-Hodgkin lymphomas [33], neuroendocrine tumors [34], breast [35], and prostate cancer [36]. Furthermore, medical devices combining radionuclides with microspheres [37] represented breakthrough locoregional strategies for primary or metastatic liver tumors.

From the few traditional applications or palliative treatments, MRT evolved into the offer of effective therapies for a much wider patient population suffering from many types of diseases, in some cases associated with a relatively long life-expectancy. Although rare, severe toxicities were observed following MRT, either acute, such as bone marrow suppression following radioimmunotherapy of non-Hodgkin lymphoma [38,39], or chronic, such as toxicity of kidneys following $^{90}$Y-somatostatine analogues [40] or of liver following selective radioembolization [41]. Dosimetry was initially not, or poorly demanded, yet the first dose–effect curves (Normal-Tissue Complication Probability - NTCP) were derived for kidney [42] and liver [43], as well as preliminary Tumor Control Probability (TCP) relationships for SIRT in primary liver cancer [44]. Owing to the limited availability of dosimetry data, and to the requirement of long follow-up, these results represented a huge effort, but marked a turning point. Given the large interpatient variability, it became evident that dosimetry was necessary to quantify the radiation exposure, and to distinguish the effects of various radiopharmaceuticals. It was also pointed out that the radiobiological knowledge from EBRT could not be *tout court* applied to such a different modality as MRT [45,46]. Absorbed dose limits and criteria developed for EBRT could only be regarded as a methodological guide, to start developing an MRT-specific base of radiobiological knowledge. Further evidence of dose–effect relationships and identification of goals to improve the radiobiological understanding have been highlighted [47–52].

The last ten years have witnessed a revolution in MRT, as a result of exchange and complementary contributions from different fields. Significant advances have also occurred in the field of internal dosimetry. During the first decade of this century, the technological development enabled the introduction of hybrid scanners such as SPECT/CT and PET/CT. The shift from planar to 3D imaging also allowed for 3D dosimetry. Furthermore, specific official nomenclature and refined anthropomorphic phantoms were provided [9,53,54]. Scientific societies have been working intensively for dosimetry development, education, and exchange [55–57]. Several studies have contributed to a deepened understanding of the methods and personnel required for dosimetry [58], the sources of errors and uncertainties [59,60], procedures for calibration, activity quantification, and improved standardization [61–63]. Less resource-intensive, simplified protocols have also been proposed to increase the accessibility of dosimetry. In particular, population-based methods using nonlinear mixed models provided interesting results in peptide receptor MRT, even with single point data [64–69]. However, this technique is still under development, and the associated uncertainties may vary depending on the type of radiopharmaceutical and on the organs or tissues considered. Dosimetry systems have been developed based on patient-specific imaging, both commercially and by local experts, open to improvements [70–78]. Today, the introduction of semi- or fully automatic image segmentation methods is in progress for all image modalities and is expected to enable easier and more accurate volume estimation, which is an essential step for accurate absorbed dose calculation [79].

Emerging data demonstrate the clinical advantage of MRT guided by internal dosimetry [80–83]. An increasing number of clinical protocols are designed to include dosimetry [39,84–88]. The interest in MRT from

pharma industry is increasing as is their investments in the exploration of innovative marketable molecules and radionuclides (e.g. alpha emitters) [3,4]. Dosimetry is gradually becoming recognized as a necessary tool, to explore the potential of MRT, to improve patient outcomes and to reduce side effects. Dosimetry-guided MRT is a step towards personalized medicine, to be combined with biological approaches based on tumor genomics, proteomics or metabolomics, and with methods for the enhancement of drug delivery [89,90].

### 2.2. EBRT

In the early days of EBRT, following the discovery of X-rays by Roentgen in 1895, the therapeutic approach was closely linked to the concept of surgery. Despite the technical limitations (low energy, poor depth penetration, lack of imaging and planning capabilities), the potential of EBRT was foreseen, and efforts focused on boosting the irradiation of the tumor. The resulting evident toxicities (typically, erythema and epilation) highlighted the need for improving the radiation delivery and the optimization of the therapeutic window. This mindset paved the way to improvements and innovations in many fields, including radiation delivery and measurement technology, predictive dosimetry and radiobiological models, as well as pre- and during-treatment imaging [91,92]. At the beginning, superficial lesions were treated with conventional X-rays generated by potential differences of 20 kV to 250 kV while more deeply located tumors were treated with the gamma rays of Cobalt-60 source (mean photon energy 1.25 MeV). An early technological advancement was the transition to the high-energy megavoltage photons (up to 20 MV) generated by linear accelerators, with a higher penetrating ability [91,93]. This change in beam quality had the advantage of decreasing skin irradiation and reducing side effects. Linear accelerators also provided electron beams with energies of 6–20 MeV that enabled penetration up to 5 cm and were characterized by a sharp dose drop-off beyond the tumor. These characteristics were exploited for treatment of superficial lesions, e.g. skin, nodes, head and neck cancers, chest wall in breast cancer, and for delivering boost doses. The advent of CT in 1967 [94–96] and its introduction into the clinic during the 1970́ties [97] enabled the transition from 2D- to 3D-based treatment planning, as well as the production of digital dose distributions. Computer-based dose distribution calculation algorithms (treatment planning systems, TPSs), both in 2D and 3D, were then introduced. In parallel, the subsequent replacement of the traditional shielding (customized blocks to shape the beams) with the multileaf collimators (MLC) enabled improved strategies in the optimization and delivery of EBRT, termed Intensity Modulated Radiation therapy (IMRT). In the conventional static-fields approach (3D-CRT), the planner defined beam parameters, including beam directions with respect to the patient, beam modifiers and shapes of the beam, and performed optimization by manually iterating these parameters and the monitor units delivered by each beam, until the dose distribution fulfilled the clinical requirements. The advent of IMRT inverse planning techniques was mainly based on two components: i) a mathematical objective function describing the problem to find the optimal dose distribution, also incorporating dose-volume constraints; ii) an iterative algorithm seeking the optimal solution. From this iterative process, the weights of a series of beam segments were obtained and used to calculate the dose distribution. In this way, the distribution of absorbed dose could be shaped to closely follow the shape of the tumor with an increased healthy-tissue sparing. The introduction of MLC and IMRT inverse planning techniques allowed for better precision than typical dose distributions from 3D-CRT calculation. The need for ensuring accurate radiation delivery increased with the complexity of the delivery techniques and with the conformity requirements for the dose distribution, especially in procedures requiring high doses per fraction. In this context, the image-guided radiation therapy (IGRT) played an important role, focusing on the delivery aspect. For instance, cone beam computed tomography (CBCT)/kilovoltage (kV) imaging detectors mounted on the treatment machines enabled detection and correction of potential set-up errors before treatment delivery. Moreover, dedicated software were introduced that integrated with a high-precision motorized bed for correction of small deviations of the planned patient position. This increased precision in daily patient positioning enabled reduction of the margins applied to balance set-up errors, thus avoiding unnecessary doses to healthy tissues. A step further was the introduction of TPSs coupled to CT simulators, overcoming the weaknesses of dose distribution calculation based on poor radiographic images, external patient's contour identification and operator dependency [91]. CT simulators represented a breakthrough that enabled consideration of both the 3D patient anatomy and different tissue densities for heterogeneity-based dose distribution calculations [98]. Accurate segmentation of irregularly shaped tumors and organs at risk [99] became feasible.

In EBRT the concepts of gross tumor volume (GTV), clinical target volume (CTV) and planning target volume (PTV) from the first ICRU (International Commission of Radiation Units and Measurements) Report 50 have been under constant revision for the last 30 years [100,101]. The ICRU Report 83 refined concepts and introduced new ones, such as the dose prescription based on parameters of Dose Volume Histogram (DVH), minimum dose and maximum dose within the PTV [102].

Besides definition of the target, another need was the identification of doses that were tumoricidal or toxic for normal tissues. The first important effort by an expert committee converged into the so-called "Emami paper", providing tolerance doses for a wide range of organs [103]. In spite of its limitations, including an arbitrary contouring of normal tissues, the use of conventional fractionation only, and no information about DVHs, this was used as reference until a panel of experts focusing on Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) was formed and their work published in 2010 [104,105]. The main objectives were to gather patient-specific toxicity data and to provide predictive models describing the relationship between the dose-volume parameters and normal tissue damage. These models led to a variety of biological metrics, with the common concept of the radiobiological effect, that is the surviving fraction (SF) of cells, and the biologically effective dose (BED) used to predict the SF. The BED was later replaced by the concept EQDX: Equi-effective dose [106]. The BED (or EQDX) is used to compare doses required to yield a given radiobiological endpoint for different treatment schedules, and to combine the contributions of sequential treatments, including delivery modalities with continuous decreasing dose rate (brachytherapy and MRT) or the use of high-LET particles. The main radiobiological definitions and parameters, as well as commonly used acronyms used over the years both in EBRT and in MRT are summarized in Table 1.

Additional advances, with regards to both technology and theory, have resulted in more effective EBRT and possible expansion of the therapeutic window. Helical Tomotherapy represents a major innovation regarding treatment geometry, with the possibility of irradiating the patient in continuous motion mimicking a helical CT scanner [112]. This modality allowed for highly conformal dose distribution, reducing the occurrence of toxicities with preserved TCP. Hadrotherapy techniques (proton therapy, carbon-ion therapy etc.) have further increased the therapeutic window and efficacy, particularly in highly radioresistant tumors or in case of pediatric patients [113–115]. Recent developments also include the Ultra-High Dose Rate Radiotherapy, with the aim to produce the FLASH effect. A dose rate far exceeding the conventional ones ($\geq$40 Gy/s) is used, which allows reducing side effects while keeping the same level of tumor response [116,117].

## 3. Radiobiology and models for radiobiological response

Within the field of EBRT extensive knowledge and data have been gathered on the dose-volume response of normal tissue to radiation. However, similar data are missing for exposures from internal radiation, where the dose rate and distribution can vary significantly.

**Table 1**
Common abbreviations, main radiobiological parameters, and definitions.

| Acronym | Name | Meaning | Field | References |
|---|---|---|---|---|
| GTV | Gross Tumour Volume | The visible or palpable extent of malignant tumour, grouping the primary tumour (GTV-T), the metastatic lymphadenopathy (GTV-N) and other metastasis (GTV-M) | EBRT | [100,101] |
| CTV | Clinical Target Volume | GTV + subclinical involvement around GTV and microscopic infiltrations not visible on diagnostic images | EBRT | [100,101] |
| PTV | Planning Target Volume | CTV + margins to consider patient motion and breathing | EBRT | [100,101] |
| DVH | Dose Volume Histogram | A plot of a cumulative dose-volume frequency distribution that graphically summarizes the simulated radiation distribution within a volume of interest | EBRT MRT | [102,107] |
| $TD_{50}$ | Tolerance Dose at 50 % | Tolerance absorbed dose that results in 50 % complication rate | EBRT MRT | [108] |
| NTCP | Normal Tissue Complication Probability | The probability that a given absorbed dose of radiation will cause an organ or tissue structure to experience complications considering the specific biological cells of the organ or tissue structure. | EBRT MRT | [9] |
| TCP | Tumour Control Probability | The probability to control or eradicate the tumor giving a certain amount of absorbed dose | EBRT MRT | [9] |
| QUANTEC | Quantitative Analysis of Normal Tissue Effects in the Clinic | The QUANTEC reports provide a summary of knowledge of normal tissue reactions following radiation exposure in terms of clinical outcomes as a function of absorbed dose and organ volume irradiated during EBRT. | EBRT | [104,105] |
| BED or EQDX | Biologically Effective Dose or Equieffective dose | The absorbed dose that is required to cause a given biological effect if the absorbed dose is delivered with infinitely small doses per fraction or, equivalently, at very low absorbed dose rate. | EBRT MRT | [106,109,110] |
| EUD | Equivalent Uniform Dose | The absorbed dose that, when homogeneously delivered to a tumour or organ, yields the same biological effect as the given non-homogeneous irradiation. | EBRT MRT | [111] |
| CTR | Clinical Treatment Region | Analogue of GTV and CTV in EBRT, represents the region (s) to treat, including macroscopic disease and microscopic disease | MRT | [9] |
| DTR | Dosimetric Treatment Region | Analogue of PTV in EBRT | MRT | [9] |

Most of the concepts listed were developed in EBRT, some have been applied for MRT as well, some others have been developed specifically for MRT.

The biological effects of radiation originate principally in damage to DNA. The mechanism underling the higher biological effectiveness of high-LET radiation compared to low-LET radiation is the induction of multiple sites of DNA damage, which are more complex to repair than single-strand breaks. Examples of high LET particles used in radiation treatments include protons in EBRT and alpha emitters in MRT. A summary of the physical characteristics of radiations and particles used in EBRT and MRT is provided in Table 2.

The linear quadradic (LQ) model describes the fraction of surviving cells S after a delivered absorbed dose D:

$$S = e^{-\left(\alpha D+\beta D^2\right)}$$

where the α term reflects lethal damage caused by a single incident particle, while the β term represents cell death resulting from the interaction of damage from different radiation events and therefore scales proportionally to $D^2$.

In EBRT it is conventional to fractionate the absorbed dose D, delivering a small dose d, over n fractions, such that

$$S = e^{-n\left(\alpha d+\beta d^2\right)} = e^{-D(\alpha+\beta d)}$$

Given that $dD$ is less than $D^2$ the magnitude of the quadratic contribution to cell killing is reduced, leading to an increase in cell survival. The radiosensitivity of different tissues is expressed by the $\alpha/\beta$ ratio. In tissues with high $\alpha/\beta$ single-hit killing dominates, while a low $\alpha/\beta$ traduces in an efficient DNA repair with improved cell sparing. Typical $\alpha/\beta$ values are 10 for lesions and 3 for normal tissue, allowing non-target organs

**Table 2**
Physical characteristics of radiations and particles used for EBRT and MRT.

| Particle | Linear Energy Transfer (LET) | Range (in soft tissues) | Biological scale |
|---|---|---|---|
| β− | 0.3 keV/μm | 0.05—12 mm | 4—10 000 cell diam. |
| $\alpha^{2+}$ | 100 keV/μm | 40 – 100 μm | 4—10 cell diam. |
| Auger electrons | 4–26 keV/ μm | 2—500 nm | ~ DNA |
| Linac X-rays (6–15 MeV) yielding secondary electrons from Compton interaction in tissue. | 0.3 keV/μm | Similar to β − particles | Similar to β − particles |
| 50–150 MeV protons | 0.5 keV/ μm | 2–14 cm (Bragg peak depth) / ~ 5–10 mm Bragg peak width | ~ 10 000 cell diam. (Bragg peak width) |

time to repair between fractions without significant detriment to tumour control. For high LET radiations single-hit killing dominates.

Comparisons of different fractionation schemes is possible using the BED as defined by Fowler [109,110]:

$$BED = D\left(1 + \frac{d}{\alpha/\beta}\right)$$

This parameter represents the dose needed to deliver the same level of effect as an unfractionated treatment.

For MRT, dose rates are typically thousands of times less than EBRT and delivered over a protracted period as the radioisotope decays. It therefore follows that DNA repair will occur during the radiation period which can be incorporated into the LQ model using the Lea-Catcheside time factor, G, such that

$$S = e^{-\left(\alpha D + G\beta D^2\right)}.$$

Where $G$ is defined as

$$G = \frac{2}{D^2}\int_0^T \dot{D}(t)dt \int_0^T \dot{D}(w)e^{-\mu(t-w)}dw$$

and $\dot{D}$ is the dose rate and $\mu$ is the repair rate constant $\mu = ln(2)/T_{Rep}$ [118] When integrating to infinite and assuming a single exponentially decaying dose rate,

$$BED = \left(1 + \frac{D}{\alpha/\beta}\frac{\lambda}{\lambda+\mu}\right)$$

It is inevitable that, when irradiating a target, absorbed dose will spatially vary. Absorbed dose heterogeneity is expected to be particularly relevant in MRT, where the delivery of the vector molecule can be affected by variation in vascularity, or receptor density. For EBRT, normal organs are more likely to receive inhomogeneous exposure as the beams have to propagate through healthy tissue to expose the target. It also follows that if a portion of the tissue receives little or zero absorbed dose, tumor control or tissue complications may be significantly reduced. An average absorbed dose, which assumes uniform radiation is therefore not always appropriate. Equivalent uniform dose (EUD) [111] is the absorbed dose that, when homogeneously delivered to a tumor or organ, yields the same response as the given non-homogeneous irradiation. The concept EUD was extended to incorporate the BED, into EUBED [119]. For N sub-regions, the EUBED can be written

$$EUBED = \frac{1}{\alpha}\left(\frac{\sum_{i=1}^{N} e^{-\alpha BED_i}}{N}\right)$$

## 4. Dosimetry in EBRT and MRT – similarities and differences

There are both similarities and differences between EBRT and MRT regarding the means of radiation delivery and how absorbed dose calculations are approached and performed (Table 3).

### 4.1. Radiation delivery

#### 4.1.1. EBRT

Accomplishing radiation delivery in EBRT can in principle be considered as a geometric problem with regards to radiation transport. In brief, a therapy course starts with the acquisition of a 3D planning CT of the patient. If required for tumor volume delineation, additional imaging modalities (e.g. MRI or PET) may be used. Recently, MRI-only workflows have been implemented and are under constant development for treatment planning, which enable the conversion from MRI signal intensity to a synthetic electron density map [120,121].

Structures of interest, such as the GTV, CTV and OARs are outlined by the radiation oncologist, and additional volumes, such as the PTV and planning organ-at-risk volumes (PRV), are determined to take into account uncertainties due to setup errors and organ motion. A dose planning procedure is then undertaken, mainly consisting in inverse planning, to determine the optimal fluence for each field/arc required to obtain the desired dose distribution, according to pre-defined dose-volume constraints for target volumes and OARs. Current treatment techniques, such as IMRT, volumetric modulated arc therapy (VMAT), and stereotactic radiotherapy, produce highly conformal dose distributions with a good coverage of the target volumes, while respecting dose constraints for OARs. A basic requirement for radiation delivery is that the geometry of the patient, defined at treatment planning, is reproduced at each treatment occasion. To accomplish this, the patient is positioned on the treatment couch, and with the aid of image-guidance (IGRT) the positions of the patient and of the target are verified. IGRT techniques consist of the use of volumetric imaging, such as cone-beam CT to directly visualize the target, the use of stereoscopic X-ray imaging to visualize bone anatomy, or surface imaging to correctly align the surface of the patient. Differences between the planned and actual geometry may occur if the positioning is inaccurate, and in case of anatomical variations due to e.g. weight loss or tumor shrinkage (inter-fraction variations), or tumor motion due to e.g. breathing (intra-fraction variations). In EBRT, verification of the delivered absorbed doses is mainly accomplished indirectly, for example by use of imaging to follow the patient position and geometry at treatment and then re-calculating the dose distribution. Currently, methods are being developed that enable tracking of the dose as it accumulates in tumor and healthy tissues over fractions, for example by MR-guided radiotherapy (MRgRT) with real-time imaging to adjust the radiation delivery [122].

**Table 3**
MRT versus EBRT: similarities and differences of radiation delivery and absorbed dose calculation.

| | MRT | EBRT |
|---|---|---|
| **Radiation delivery** | | |
| Divergence of radiation | Very important | Less important |
| Motion during radiation delivery | Less important | Very important |
| Exact monitoring of patient position at radiation delivery | Less important | Very important |
| **Absorbed dose calculation & analysis** | | |
| Characterization of the source strength | Complex, not standardized procedures. | Standardized procedures |
| Traceability to standard laboratory in source output | Often not established | Always established |
| Radiation transport algorithms, key quantity, or equation | Monte Carlo, absorbed fraction (AF) | Monte Carlo and Deterministic, radiation transport equation (RTE) |
| Patient-specific factors/ distributions that are fed into the absorbed-dose calculation | SPECT/CT images Attenuation coefficients Mass density distribution or target region mass | Mass- and electron-density distributions from CT |
| Spatial resolution of the absorbed dose distribution | Poor, limited by the spatial resolution of the SPECT/CT images. | Good, limited by the spatial grid used for absorbed dose calculation |
| Use of regions of interest (VOIs) drawn on images | Quantify the absorbed doses to organs and tumours, integral in the dosimetry calculation. | For treatment planning and analysis of absorbed dose coverage thought DVH |
| End result of the absorbed dose calculation | Mean absorbed dose in target regions, i.e. regional absorbed-dose estimates. | A 3D description of the absorbed dose distribution. These are analyzed by isodose lines, DVHs and quantities derived thereof. |

#### 4.1.2. MRT

Accomplishing radiation delivery in MRT can in principle be

considered as a pharmacologic problem with regards to the accumulation of the radiopharmaceutical in target regions and normal tissue. The radiopharmaceutical distribution in the patient's body is a dynamic process, governed both by biochemical and physiological mechanisms, i.e., the pharmacokinetics. The absorbed dose results from the pharmacokinetics and the physical decay properties of the particle (and photon) emission characteristic of the radionuclide. The photon emissions resulting from the radionuclide decay (energy range ~ 100–511 keV), allow for imaging of the uptake in the patient during the therapy. By repeated SPECT/CT imaging after administration, the activity distribution can be quantified and followed over time, and the time-integrated activity in different organs and tissues calculated. Owing to recent technical developments, such as a more wide-spread use of quantitative SPECT/CT and the introduction of dosimetry calculation software in the clinical environment, individual-patient dosimetry can now be implemented for a variety of radiopharmaceuticals. Planning of MRT based on dosimetry requires a characterization of the patient-specific pharmacokinetics to derive the predicted absorbed dose distribution in tumor and critical organs. Such prediction can be accomplished by use of a pre-therapy administration of a tracer amount of the same, or biochemically similar, radiopharmaceutical. The knowledge of the patient-specific tracer pharmacokinetics and extrapolated planning dosimetry is key to guide the prescription of the therapeutic administered activity. In case of therapies administered over multiple cycles, such as [$^{177}$Lu]-DOTA-TATE, imaging-based dosimetry after one single cycle can be used to predict the absorbed doses to critical organs for a subsequent cycle. Furthermore, for fractionated MRT, i.e., MRT given in repeated cycles, dosimetry from a preceding cycle can be used to tailor the prescribed number of therapy cycles and/or the total administered activity, and/or the activity per cycle.

### 4.2. Characterization of the source strength

#### 4.2.1. EBRT

In EBRT the radiation source is most often a linear accelerator, in which electrons are either used directly to treat superficial tumors or accelerated towards a target of high-Z material to generate bremsstrahlung to treat deeply located tumors. The resulting photon energy spectrum ranges from zero (or very low photon energies) up to the maximum energy corresponding to the acceleration potential of the electron beam. Characterization of the radiation source strength, i.e., the field output intensity from the linear accelerator in a flat field, detected in air or water, is a well-established and well-documented procedure [123–125]. Such reference dosimetry is performed according to standardized protocols and traceability to standard laboratories is maintained by regular, external calibration of a reference ionization chamber.

#### 4.2.2. MRT

In MRT, the radiation source is constituted by the radioactive nuclei distributed internally within the patient's body. The energy and yield of charged particles and photons are governed by the decay characteristics of the radionuclide. For a given radionuclide, the intensity of irradiation of tissues is determined by the activity concentration over time in regions that accumulate the radiopharmaceutical and by the interaction and propagation of radiation from these regions to different tissues. Contrary to EBRT, the source strength cannot be characterized in advance in detail but needs to be determined for each patient. Characterization of the source strength is a less standardized and a comparatively more complex procedure than for EBRT. The reference instrument is the dose calibrator, as this is used to quantify the activity in a reference geometry, such as a vial or syringe, before patient administration and camera calibration. Still today, not all countries have established a calibration service for radionuclides used in MRT, and traceability to standard laboratories cannot always be ascertained. Moreover, quantification of the activity distribution in the patient based on quantitative SPECT/CT is a challenging task, as there are numerous sources of error or uncertainty [63]. For radionuclides that emit gamma radiation for imaging, accurate quantitative tomographic reconstruction requires that the corrections for photon interactions, i.e., attenuation- and scatter corrections, are capable to fully compensate for these phenomena. It also requires that the calibration factor, used to convert from reconstructed count rate to activity, is correctly determined from prior calibration studies and that it adequately represents the true calibration in a patient geometry. In addition, the spatial resolution of reconstructed SPECT images is typically around 1 cm, thus yielding a blurred representation of the real, underlying activity distribution. To mitigate these problems, modern tomographic reconstruction software include collimator modelling and resolution recovery algorithms. However, resolution-induced partial volume effects remain, and spatial variations on a small scale cannot be resolved from SPECT images. In addition, the partial volume effects severely affect the values estimated for small regions and produce falsely low or high activity concentration values due to spill-out or spill-in of counts. Particular attention should be paid when dealing with high count rates, characteristic of early time-points image acquisitions after therapeutic administration in MRT. Under such conditions, camera dead time and detection pile-up can affect the accuracy of quantitative imaging and need therefore to be characterized and corrected for [126].

### 4.3. Absorbed dose calculation

#### 4.3.1. EBRT

The actual energy deposition in tissue (the absorbed dose) is caused by interactions of electrons generated by the primary photon beam interaction in the irradiated tissues. The fluence of both photons and electrons can be described by the *radiation transport equation* (RTE), defined in a six-dimensional phase-space coordinate system. To calculate the absorbed-dose distribution, the RTE needs to be solved for the electron fluence. Analytical solution is generally not feasible, and instead different numeric algorithms are used. These include stochastic methods, i.e., Monte Carlo, and deterministic methods such as the collapsed-cone algorithm, or the grid-based Boltzman equation solver [127] that consider the patient-specific geometry from the planning CT and the Hounsfield unit to tissular electronic density calibration usually obtained from a dedicated CIRS phantom CT acquisition [128].

Patient treatments are generally delivered by a set of radiation fields from different angles with respect to the isocenter or, more recently, by coplanar or non-coplanar modulated arcs. The totally delivered absorbed dose is thus calculated as the sum of the dose contribution from the different fields.

#### 4.3.2. MRT

In MRT, charged particles responsible for the energy deposition in tissues include electrons (beta particles, conversion and Auger electrons) and/or alpha particles. Similarly, as for EBRT, electrons may also be generated by gamma photons interacting with matter, although their contribution to the total absorbed dose is small. For absorbed dose calculation in MRT a fundamental parameter is the *absorbed fraction* (AF), which represents the fraction of the radiation energy absorbed in a target region per emitted energy in a source region [129]. Note that the terminology between EBRT and MRT here diverges, as in MRT a target region can be any region for which the absorbed dose is calculated, including the source region itself, whereas in EBRT the word target usually indicates the region(s) to treat. The AF in MRT depends on patient geometry, tissue composition, source-to-target distance from zero (when source and target coincide) up to ~ two meters (head to feet), and it is specific for the considered radionuclide. Hence, the AF needs to be calculated for each radionuclide and for each relevant source-target combination, depending on the specific pharmacokinetics of the radiopharmaceutical. In a human-like geometry, analytical solution for the energy deposition is generally not feasible, and the Monte Carlo method

is used instead.

For convenience to the community, international organizations involved in internal dosimetry have made Monte Carlo-computed AF available for standard human-like geometries. The earliest were provided for photons by the MIRD committee of the Society of Nuclear Medicine using relatively simple geometrical representations of source and target organs, such as spheres, cylinders, or planes, described in analytic coordinates [130]. More recently, the ICRP developed more refined standardized voxel-based phantoms, tailored to represent the reference male and female geometry [53]. This representation is now also supported by different Monte Carlo codes. If only short-range particles are involved, the assumption of local energy deposition may be adequate, otherwise dose-kernel convolution methods could be applied [31,129]. To further improve absorbed dose estimates in a patient-specific configuration, Monte Carlo radiation transport calculations can also be implemented directly on the geometry defined by the SPECT/CT. In this process, the absorbed dose in tissues can be computed at the voxel level by direct time-integration of the voxel dose-rate during the treatment period. Such patient-specific Monte Carlo calculation is the approach that most closely resembles methods used for absorbed-dose calculation in EBRT.

## 5. Analysis of the absorbed dose distribution

In EBRT, analysis of the absorbed dose distribution in a patient is generally performed at dose planning, and possibly at re-calculations at later fractions due to detected deviations from the reference anatomical system. The absorbed dose distribution is well suited for analysis with isodose levels. Dose distributions can be evaluated visually at each single CT slice or on reconstructed sagittal or coronal planes. A quantitative assessment of the dose distribution is obtained with the calculation of DVHs, for the target volumes (GTV and CTV) and for each OAR involved in the treatment plan. DVHs represent the fractional volume receiving a certain absorbed dose, or metrics derived thereof, such as conformity and homogeneity indexes.

The in-vivo dosimetry of patients could be used to verify the delivered doses [131]. In-vivo dosimeters can be divided in real-time (diodes, MOFSET, electronic portal images devices-EPID, plastic scintillators) and passive ones (termoluminescent dosimeters-, optical stimulated luminescent dosimeters-, radiophotoluminescense dosimeters) and both need to be calibrated comparing their response against a calibrated ionizing chamber. With the implementation of new IGRT technologies allowing for daily monitoring of patient's anatomy (MRI, CBCT), Monte Carlo simulation can be a good verification tool of the delivered dose together with EPID's dose map [132]. In this way it could be possible to daily verify the dose delivered to the patient, especially in stereotactic treatments. Summing the dose maps of every single fraction allows to gain an estimation of the real dose delivered to the target and the organs at risk. This makes in-vivo dosimetry non-invasive but is not possible to obtain direct measure of dose at a certain point.

In contrast, MRT has the advantage of allowing for easy verification of the absorbed doses delivered, as often the radioactive therapeutic drug permits for imaging during the therapy. Moreover, in MRT any organ motion or movement only affect the absorbed-dose delivery to a marginal extent, although these factors may affect the accuracy with which the absorbed doses are estimated. However, In MRT, the spatial resolution of current SPECT/CT systems puts a limit to the spatial scale at which the absorbed dose can be accurately quantified, introducing a source of uncertainty. Most commonly, the estimated quantity in internal dosimetry is thus the mean absorbed dose to a target region. For larger organs, such as liver or bone marrow, the absorbed dose may also be estimated for sub-regions.

The radiobiologically sensitive cells and tissues are presumably the same for EBRT and MRT. In EBRT, the spatial distribution of the absorbed dose can, on a microscale, be regarded as uniform, and the estimated absorbed doses thus well represent those delivered to the radiosensitive cells. In contrast, in MRT, the absorbed dose distribution on a microscale is governed by the uptake pattern of the radiopharmaceutical and the range of the emitted particle radiation, and the underlying absorbed dose distribution may thus be highly non-uniform. The mean absorbed dose to a target region, estimated on a macro scale from SPECT/CT imaging, may thus be only partly representative of that delivered to the radiosensitive structures. When absorbed doses to the same target region are compared between patients given the same radiopharmaceutical, this discrepancy between the macro- and microscale is probably of minor importance, as the uptake pattern can be assumed to be similar between patients. However, when attempting extrapolation of absorbed doses or dose–effect relationships between radiopharmaceuticals, the discrepancy might become relevant. Especially for short-range electron radiation or alpha particles, this discrepancy may render extrapolations invalid [133,134].

## 6. Physicists' role in MRT and EBRT

Council Directive 2013/59/EURATOM describes the role and competences of Medical Physics Expert (MPE) in services where ionizing radiation is routinely involved in diagnostic and therapeutic procedures, i.e. in radiology, radiation oncology, and nuclear medicine departments [13]. Explanation and commentaries on the role of MPE (including indications for staffing resources) have been published in the Radiation Protection Report 174, ''European Guidelines of Medical Physics Expert'' of the European Commission [135] and by the European Federation of Organizations for Medical Physics (EFOMP) in the policy statement 16 [136], as well as in the policy statement 19, published in the same issue as this paper [137]. In particular, the MPE takes responsibility for patient dosimetry with focus on optimization of diagnostic and therapeutic procedures.

At present, the extent of the involvement of the MPE in patient-specific dosimetry differs significantly between radiation oncology and nuclear medicine. In the case of EBRT, the MPE is involved in each treatment planning procedure, regardless on whether the treatment has curative or palliative intent. The MPE also has responsibilities all along the quality assurance (QA) process, in close collaboration with the radiation oncologists. This collaboration has historical roots, and the MPE role in EBRT has always been to define a treatment plan for the patient, either with a spreadsheet as in the past, or with advanced TPSs as it is nowadays [138]. Specific tasks performed by the MPE in EBRT include i) commissioning and periodic maintenance of the irradiation devices, with particular focus on the characterization of the radiation beam; ii) characterization of the imaging technologies used for guidance; iii) planning and verification of the absorbed doses delivered to the PTV and other regions. In contrast, the role of the MPE in therapeutic nuclear medicine is less recognized and is not standardized across institutions and countries [10,15]. While the role of MPE is evident in most countries for validation and optimization of quantitative diagnostic imaging procedures, including responsibility for the optimization of image acquisition and reconstruction parameters, the same does not apply to therapeutic procedures. If fact, the majority of MRT treatments are not optimized based on patient-specific characteristics, and the radiation doses delivered are not planned nor verified. This is in contrast with the optimization principle defined by the EURATOM Directive art-56 [14,139]. Recently, the European Association of Nuclear Medicine (EANM) published a position statement inspired by the indication of levels in prescribing, recording and reporting of absorbed doses after radiotherapy defined by the ICRU, indicating the application of three progressive levels of dosimetry for therapeutic nuclear medicine [140]. Such a position statement is a pragmatic attempt to comply with the Euratom Directive art-56, however, does not satisfy it. In particular, level-3 dosimetry, implying planning and verification of absorbed doses to the target, as requested by the Directive, is recommended only for a few ''non-standardized'' therapeutic procedures, where the definition of "standardized" therapies includes all those that received commercial

approval. According to such interpretation of the EURATOM Directive, dosimetry is recommended only for off-label prescriptions and in the preliminary phases of radiopharmaceutical development [140]. Other interpretations of the EURATOM Directive have been issued, one jointly by the Italian associations of nuclear medicine (AIMN) and medical physics (AIFM) which recommended dosimetry-based optimization for a larger number of therapeutic procedures, irrespective of the registered posology [141].

If the same paradigm was followed for MRT and EBRT, MRT would always involve the MPE as responsible for measurements, imaging and dosimetry. This would imply the appropriate use of the medical equipment involved in the therapeutic workflow, also including quantitative imaging devices such SPECT/CT and PET/CT, and the development of methods and procedures for dosimetry. The technical implementation of these tasks is beyond the scope of this publication and has been addressed elsewhere [57,58]. In selective internal radiation therapy (SIRT) with Y-90 labelled microspheres, therapeutic nuclear medicine is approaching the EBRT paradigm, and predictive and post-treatment dosimetry are strongly recommended by current guidelines [142,143]. The MPE should also be involved in the multidisciplinary tumor board, including medical oncologists, radiation oncologists, hepatologists, interventional radiologists, nuclear medicine specialists, technologists, and surgeons. Dosimetry software enable to assist dosimetry calculation based on compartmental models or more refined 3D voxel-based methods, providing DVH and isocontour absorbed dose information, as in EBRT. The groundwork for dosimetry-based treatment planning in MRT is already in place to support the personalized treatment, with an expected positive impact on treatment efficacy. However, in contrast to EBRT, the allocated resources are in most cases inadequate [144], and in most countries reimbursement procedures are not in place for internal dosimetry.

## 7. Discussion and future perspectives

In EBRT, within the therapeutic window, the concept that the higher the absorbed dose the higher the probability of cancer response and risk of toxicity is not a matter of discussion. Technical innovations and improvements in dosimetry are introduced into clinical practice based on geometrical considerations (higher conformity of beams aperture to the target) or information derived from other studies. Radiobiology is a fundamental part in the education syllabi for radiation oncologists, relying on solid preclinical and clinical experience, and epidemiological studies. Therefore, radiation oncologists, and, consequently, private companies, facilitate research leading to technological advancements towards the improvement of the therapeutic window of loco-regional treatments.

On the other hand, therapeutic applications of nuclear medicine have long been limited to radioiodine treatments of hyperthyroidism and differentiated thyroid cancer, and the physiology of radioactive salts used for MRT has long been the most important focus. For several reasons, including the selectivity of radionuclide delivery and the remarkable efficacy of radioiodine, the usefulness of absorbed dose calculations to the target and to the organs at risk has been largely neglected, if not questioned [145]. Moreover, the putative systemic nature of MRT, as well as the systemic route of radiopharmaceutical administration, make it in several aspects closer to chemotherapy – where, traditionally, treatments are not tailored on individuals but on cohorts of patients with similar characteristics - than to EBRT. Ionizing radiation is the main driver of the therapeutic effect both for EBRT and MRT, but the lack of a clear path to include radiation dose calculation in MRT represents a gap that needs to be filled [146]. Similarly, as for EBRT, the evolution towards personalized treatments in MRT is, in our opinion, inevitable. Looking at this evolution from the perspective of internal dosimetry it is natural to regard the role of dosimetry in EBRT and its conceptual evolutionary path. In the last years the scientific community has initiated studies on the implementation, standardization, accuracy improvement, and quality controls, also involving treatment planning systems and radiobiological models. The results of such efforts are already emerging and augmenting internal dosimetry approaches, protocols, and software towards a more robust structure [77,78,147–151]. Simplified procedures, such as single time-point protocols, though suboptimal, are easier to implement in clinical practice, and may represent the initial steps towards the adoption of more refined dosimetry methods for some MRTs [64–69]. The unique possibility of MRT to obtain predictive and post-treatment images, enabling a *de facto* in-vivo patient dosimetry represents a huge strength in terms of quantitative information of radiopharmaceutical biodistribution, unbeatable for other systemic anticancer therapies, yet not fully exploited. In parallel with EBRT, MRT dosimetry should support the process of decision making and informed radiopharmaceutical prescriptions for patients, in terms of injected activities and their constraints, as well the number and cycles and time intervals between them. Possibly, internal dosimetry will not be relevant for radionuclide therapies only, but will become a prerequisite for concomitant, adjuvant and radiosensitizer treatments, and/ or for the planning of subsequent external radiation therapies in selected patients. The differences between EBRT and MRT should not be neglected but highlighted to exploit their specific potential. Thus, the gold standards in MRT may not be necessarily the same quantitative references as for EBRT but should have the same methodological rigor. Even with different focuses, the common objective is treatment optimization, and data collection is fundamental to improve the quality of patient's care, possibly within the frame of combined treatments with potential toxicity [87,88,152]. The Zeno's challenge of Achilles and the tortoise well represents the intrinsic differences between MRT and EBRT dosimetry, as well as the direction of their respective evolution paths. The apparent paradox developed into a clear solution once new mathematical theories - based on infinitesimal calculus - were identified. The most exciting value of this challenge was the discussion that it was able to stimulate, leading to research and evolution. It is of upmost importance to merge information, and to inspire optimization by observing the fundamental aspects of both therapies and their developments. Exchanging and improving knowledge open the way to unexplored treatment opportunities, new radiobiological models, and combined therapies with different radiation modalities and drugs.

In conclusion, both radiotherapeutic modalities are continuously evolving towards personalization. In EBRT, this evolution is mainly driven by technology, dosimetry and radiobiology. In MRT, the development towards therapy optimization is currently not matter of a technical evolution but more of a cultural revolution.

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