RADIOPHARMACEUTICAL CLINICAL TRIALS: THE IMPORTANCE OF DOSIMETRY

Although cancer incidence and mortality rates have declined over the past two decades, it remains a top health concern in the United States and worldwide. The American Cancer Society estimates about 1.8 million Americans will receive a new cancer diagnosis in 2021.

The development of more effective and targeted treatments has helped improve survival rates, giving hope to those facing a diagnosis. The largest single-year drop in death rate ever recorded took place between 2016 and 2017: 2.2%. Cancer deaths declined by 29% from 1991 to 2017.

Radiation therapy has been utilized for over 100 years and is considered the oldest cancer therapy. Radiation interventions have evolved to include a broader range of more targeted, effective therapies. There are exciting recent innovations in how we administer radiation. Radiopharmaceutical therapy (RPT) uses isotopes that are conjugated to tumor-targeting agents (e.g., peptides, antibodies, and novel small molecules). Radioligand conjugates, antibody and peptide conjugates have been studied extensively. Due to the fact that radioactive particles bind to cancer cells during RPT, the theragnostic method allows radiation oncologists to visualize precision medicine approaches to cancer treatments.

Improved dosimetry for RPT will make a profound impact on patient outcomes, both in treatment for disease and in RPT clinical trials. A dosimetry methodology based on toxicity and efficacy will help move this promising new field into the current era of precision medicine.

For decades, there have been well established dosimetric techniques in radiation oncology for external beam treatments and brachytherapy. Currently, there are limited prospective dosimetry studies for RPT. The current focus is on correlative solid tumor dose-response; not prospective RPT planning. Recent emphasis on RPT with beta-emitter and alpha-particle emitters underscores the urgency to adopt consistent dosimetric methods.

WHAT IS DOSIMETRY?

Dosimetry refers to the measurement of radiation. The quantities and units of radiation dose are inherently more complex than those used in toxicology or pharmacology, and additional complexity has resulted from several changes required by evolving concepts in radiation dosimetry.

Radiation oncology has a long history of dosimetry-based treatment planning experience from conventional radiation tools, techniques, as well as personnel and infrastructure readily adaptable to newer radiation modalities. Radiation dosimetry is used to estimate the absorbed dose (Gy/GBq) in normal tissues, organs and/or solid tumors. The process of dosimetry helps define an optimal radiation treatment dose that can effectively kill cancerous cells while avoiding injury to critical organs.

A dosimetry system consists of the following three parts:

- A set of rules to distribute the source inside a defined target to achieve a clinically acceptable dose distribution
- A method to calculate the patient's tumor and organ at risk radiation dose
- A system for dose prescription

Researchers defined these elements long before the era of CT, MRI, and PET scans, not to mention digital technology. A system that uses today's more accurate calculation methods and imaging techniques will lead to more successful RPT clinical trials and more effective therapies for patients.

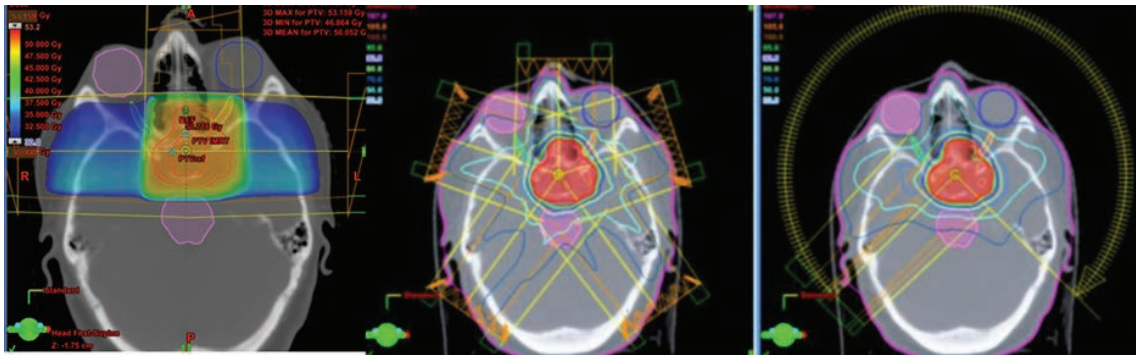
TYPES OF RADIATION THERAPY FOR SOLID TUMORS

Radiation oncology has a long history of dosimetry-based treatment planning that can adapt to newer radiation modalities. While most radiation therapies have stood the test of time, the risks associated with treatment, including radiation exposure to physicians and patients, have prompted researchers to explore alternative methods such as RPT.

External beam radiation: A linear accelerator (LINAC) aims radiation—high-energy protons, photons, or electrons—at the tumor. Examples include 3D conformal radiation therapy, intensity-modulated radiation therapy, image-guided radiation therapy, and stereotactic radiosurgery, among others.

There are two ways to predict, determine, and validate that the aim from the LINAC is accurate to achieve the best-possible therapeutic index:

- Model a digital anatomic map of where the radiation is going to be deposited. These maps are most useful for prediction of absorbed radiation dose in tissue, organs and tumors.
- Phantom devices calculate absorbed radiation dose and show where that radiation was deposited. Imaging phantoms are physical objects that are scanned or imaged, whereas anatomic maps are digital renditions.



Brachytherapy: Brachytherapy is a specific form of radiation therapy used to treat cancer. It consists of placing sealed, radioactive sources directly into or next to the tumor to be treated, either directly or by means of catheters, needles, instruments or balloons. Brachytherapy has been a part of radiation treatments since the early 1900s. A few years after the discovery of radioactivity, Pierre Curie and Alexander Graham Bell independently observed shrinkage of malignant tumors when radioactive sources were implanted directly inside a cancerous mass. Throughout the mid-20th century, the use of brachytherapy increased, and the technique became the standard of care as a single modality or as a boost after external-beam radiotherapy (EBRT) for tumors requiring a high radiation dose to be cured.

Now, brachytherapy remains a tool in the context of radiation dosimetry. There are many applications for this such as in cervical cancer, prostate, endometrial, breast, head and neck, skin, and many other solid tumor indications. There are many dosimetric advantages with brachytherapy as compared to external beam. There are sharp radiation dose gradients compared with conventional external-beam techniques. There is no beam going through the body and thus the integral radiation dose is low.

As the radioisotope is right near or within the tumor, the radioactive source moves with the tumor and thus there is no need for additional “uncertainty margins” around the clinical target volume. Conventional EBRT, requires additional margins for set-up and organ motion uncertainties.

Brachytherapy combines optimal tumor-to-normal tissue gradients while minimizing the integral dose to the rest of the patient. However, brachytherapy is an invasive radiation treatment. The main limitation of interstitial and intracavitary brachytherapy is that it is invasive, often requiring a short procedure in the operating room or outpatient suites to place sources, catheters, or devices.

Another key point of brachytherapy is that the quality of implantation is an important factor for success. Poor positioning of the sources may cause the tumor to be underdosed. Physicians and staff are more likely to receive unnecessary radiation exposure from brachytherapy as compared to traditional EBRT.

Given the logistical, scheduling, and radiation safety issues inherent to brachytherapy and the high level of expertise required for physician implantation, there is an increasing temptation to propose alternative techniques that are easier to implement to broader patient populations with fewer logistical challenges.

Radiopharmaceutical therapy (RPT): An emerging approach where radiation is systemically or locally delivered using a targeting molecule and protein that either bind to the cancer or accumulate. Clinicians image the radionuclides, which allows them to monitor the progress of the agent.

For RPT to work, there must be a unique target on the tumor cell, a ligand to bind it, a linker to attach the isotope or atom. This method allows clinicians to deliver higher radiation doses to concentrated tumor volumes with less damage to normal tissue. A highly complex treatment to develop and administer, RPT brings together radiochemistry, radiobiology, oncology, pharmacology, medical physics and radionuclide imaging and dosimetry.

In terms of RPT therapy- Radioligand therapy consists of 4 key components:

1. Unique target on the tumor cell
2. A ligand to bind it (antibody, small peptide, small molecule)
3. A chelator/linker to attach the isotope
4. The isotope/atom itself

Then there is the theragnostic paradigm whereby administering a small pre-therapeutic activity of the therapeutic itself or a companion diagnostic agent with the same target and imaging over multiple time points, gives you more effective, targeted therapy.

In terms of mechanism of action, the RLT can be injected systemically and concentrated into target tumor sites, or the radiopharmaceutical can bind to receptors on the target cell membranes.

Depending on the radioligand, it might remain on the cell surface or may be integrated and internalized into the cell. The radioligand then delivers radiation to the target cell, induces DNA strand break and cell death. The great advantage of RLT is that it can be used for both imaging and/or therapeutic purposes using different isotopes on the same targeting ligand. This can either be a diagnostic imaging isotope, positron or gamma emitter or a therapeutic radioisotope such as Lu 177 or actinium 225 or Lead 212.

Based on these principles there are now a wide range of targeted radioligand therapies for oncology across the weaponry board.

There are many dosimetric advantages of radiopharmaceuticals compared with new oncology drug entities. First, dosimetry is advantageous because you can see what you intend to treat and can visualize the likely biodistribution. Second, imaging and early dosimetry may further expedite drug development programs by anticipating potential risks earlier in the game. Dosimetry can be used as a tool and a surrogate for toxicity and tumor response/efficacy.

Radiopharmaceutical dosimetry has suffered from a perceived failure to demonstrate relevance and success in terms of predicting biological outcomes. This may be due to the fact that earlier in the game, there were imaging and dosimetry methods used that were not as accurate (using standard planar as an imaging modality) or were not as complete (two few or poorly chosen time points). Also, previously, there were no calculations for uncertainties associated with absorbed dose in the literature.

The European Association of Nuclear Medicine helped correct this problem when they published a methodology and guide to calculate uncertainties for dose calculations that will benefit the RPT field.

METHODS OF DOSIMETRY

Dosimetrists use several methods to measure dose, absorbed dose, and dose distribution over a specified material volume.

S value MIRD is the most well established and commonly applied method. It is done no matter what for reporting. Dosimetrists use the **absorbed fraction** method (S value, MIRD) primarily for reporting and as a QC guide. Our dosimetrists use direct Monte Carlo (MC) combined or in parallel with the **voxel-based** method.

Direct MC dosimetry methods are the most accurate and versatile approach for performing voxel level calculations.

The **Direct MC** method is a statistical approach to solving the radiation transport equation. MC simulations model each physical process that affects the transport of radiation in a medium. Individual particles are tracked from creation until the particle is absorbed, escapes the region of interest or reaches an energy that is below the threshold value. Direct MC simulations are more computationally demanding than other internal dosimetry approaches.

There is also the **Dose Point Kernel (DPK)** method. DPKs describe the dose deposition from an isotropic point source as a function of distance from the source. They are obtained from MC simulations. DPKs were first limited to monoenergetic electron sources in water but eventually isotope specific DPKs were generated.

Voxel S value method (VSV) was developed as an extension of the MIRD formalism from organ S values to voxel level S values. VSVs are calculated by integrating the DPK over the source and target voxels. VSVs must be tabulated for each radionuclide, voxel size, source to target distance and absorbing medium.

Dosimetry, like drug development itself, is moving toward a personalized approach. Clinical trial success will require qualified radiation oncologists, physicians, physicists, and clinical trial research teams that understand and apply dosimetry methods to collect the appropriate data for each enrolled patient.

DOSIMETRY IN EARLY-PHASE RPT TRIALS

RPT helps identify potential toxicities early in drug development. To determine toxicity, radiation activity is increased until toxicity is reached. The organ responsible for dose-limiting toxicity is identified through histopathology. This data, combined with absorbed doses data, is used to identify the optimal dose for Phase I trials.

In Phase I, dosimetry allows for efficient escalation schemes. Researchers can integrate patient-specific 3D imaging-based dosimetry calculations into Phase I trials. Endpoints include PK analysis and imaging data for dosimetry.

SITE IMAGING QUALIFICATION AND SCANNER COLLABORATION

To qualify sites for RPT dosimetry studies, the imaging CRO must send feasibility questionnaires to the recruiting sites early in the study startup process. The imaging CRO uses the information provided to evaluate whether the site has the necessary equipment, experience, and knowledge to perform the study.

Qualification scans are required before site activation for the following reasons:

- To assess equipment setup and image quality
- To assess sites' capability to transfer images electronically to the imaging CRO (in our case Medpace Imaging Core Labs)
- To calibrate the scanner(s) for future dosimetry calculation

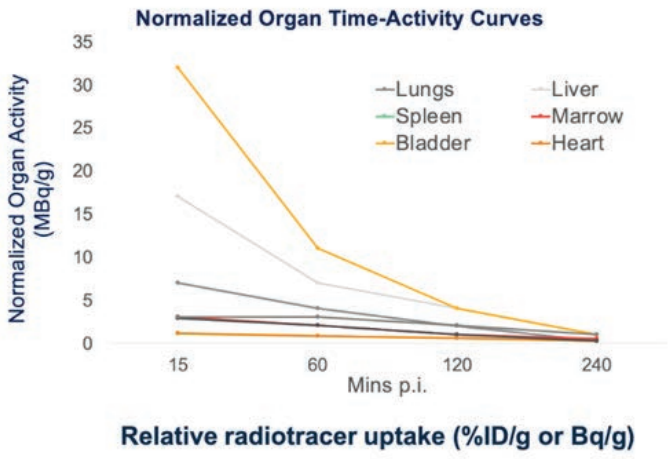
The imaging CRO must collect gamma counter and dose calibration certificates as well as phantoms scans using the studied isotope. The gamma counter determines radioactivity in blood, plasma, and urine samples while the dose calibrator measures radioactivity and injected radioactivity in the reference source. Sites must calibrate both the gamma counter and dose calibrator before use of the studied isotope. Recalibration should not routinely be necessary throughout the trial but maintenance of involved devices is essential throughout a study's duration, and records of periodic recalibration and maintenance may be collected.

The calibration of scanner(s) is absolutely necessary for the quantification of images acquired for RPT. SPECT/CT and Planar imaging is not inherently quantitative and most currently investigated therapy isotopes are gamma-emitters (as opposed to positron-emitters, imaged with PET/CT). Therefore, calibration of Gamma cameras, is a fundamental step to quantify images and derive dosimetry data from patient imaging.

IMAGING PATIENTS FOR DOSIMETRY

Imaging patients for dosimetry studies is far more complex and involves more stringent requirements than routine clinical imaging. In addition, certain challenges can be posed by the high activities that are administered and the technical parameters for image quantification typically lie outside of normal clinical practice. Strict adherence to the protocol is especially important for RPT dosimetry studies. Imaging on the wrong parameters will render the time point unquantifiable. Further, re-administering a dose of a radioactive therapy to obtain a better-quality image is not possible.

To determine the time that the isotope spends in each of the key tissues, clinicians must image across a range of time points. Early time points determine peak uptake in the tissue and late time points observe the washout. Between three to five time points is needed to produce an accurate dosimetry calculation.



For therapy isotopes with longer half-lives, imaging is conducted over a week to produce a full set of dosimetry scans. Images should focus on primary disease as well as possible disease extension. Critical organs, such as the brain and heart, should also be imaged for safety purposes. Considering imaging requires multiple 45-minute scans spread over multiple visits, the patient burden is significant. However, RPT in general involves a shorter duration of treatment compared to external beam radiation and/or chemotherapy.

With images complete, sites must turn around data quickly because safety reviews and dose-adjustment committees must take place immediately due to short dosimetry analysis timelines. To accomplish this, sites must engage closely with their CRO to develop a plan to mitigate potential roadblocks and deliver data as quickly as possible.

DATA MANAGEMENT FOR DOSIMETRY

Data management for dosimetry hinges on meeting tight timelines. The timeline from data acquisition at the site to the time the dosimetrist can use the data for calculation is between two and five weeks. Efficiency is crucial.

Typically the site's nuclear medicine team collects initial dosimetry data and delivers it to the study team, which enters data into the electronic data capture (EDC) system. **Data collected include:**

- Injected activity value
- Data and time of scans
- Biological sample counts

The study team must have a defined procedure to receive data from the nuclear medicine department to ensure a smooth-running handoff. **To prevent delays, CROs must understand the following:**

- **How long does it take to perform image uploads?** Time frame varies from a few days to a few weeks depending on the site. If the sponsor needs data immediately, the CRO can negotiate with the site to speed up the anonymization process.
- **What processes does the site have in place to exchange data between nuclear medicine and the study team?** During site training, determine the site's standard procedure for communicating data. Depending on the site, the study team may work more efficiently with source data or spreadsheets.
- **What is your data verification process?** A CRA must verify all study data to ensure accuracy of all data entered into the EDC. Unverified injected activity data, for example, may lead to incorrect dosimetry calculations or incorrect dose estimations for the next cycle or patient.

CONCLUSION

Radiotherapy innovation parallels other therapies in its precision medicine approach. RPT holds promise as an effective, precise treatment with fewer side effects than other cancer therapies. Conducting successful RPT dosimetry studies requires sites with multiple specialists that can follow a strict, complex protocol. Proper site qualification, efficient data management and extra attention to patient comfort will go a long way toward advancing RPT therapies.

FULL-SERVICE CLINICAL DEVELOPMENT

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