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Overcoming Barriers to Radiopharmaceutical Therapy (RPT): An Overview From the NRG-NCI Working Group on Dosimetry of Radiopharmaceutical Therapy

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Abstract

Radiopharmaceutical therapy (RPT) continues to demonstrate tremendous potential in improving the therapeutic gains in radiation therapy by specifically delivering radiation to tumors that can be well assessed in terms of dosimetry and imaging. Dosimetry in external beam radiation therapy is standard practice. This is not the case, however, in RPT. This NRG (acronym formed from the first letter of the 3 original groups: National Surgical Adjuvant Breast and Bowel Project, the Radiation Therapy Oncology Group, and the Gynecologic Oncology Group)-National Cancer Institute Working Group review describes some of the challenges to improving RPT. The main priorities for advancing the field include (1) developing and adopting best practice guidelines for incorporating patient-specific dosimetry for RPT that can be used at both large clinics with substantial resources and more modest clinics that have limited resources, (2) establishing and improving strategies for introducing new radiopharmaceuticals for clinical investigation, (3) developing approaches to address the radiophobia that is associated with the administration of radioactivity for cancer therapy, and (4) solving the financial and logistical issues of expertise and training in the developing field of RPT.

Introduction

This article was created by members of the National Surgical Adjuvant Breast and Bowel Project, the Radiation Therapy Oncology Group, and the Gynecologic Oncology Group-National Cancer Institute (NRG-NCI) Working Group on dosimetry of selective internal radionuclide therapy (SIRT) and radiopharmaceutical therapy (RPT). The SIRT-RPT Working Group was formed in January 2017, held its first meeting in February 2017, and held a workshop on the topics of (1) current approaches in SIRT-RPT management for enrollment in clinical trials and (2) overcoming barriers to RPT (April 2018).[1,2] Both of these topics will be published with intent to bring awareness to these challenges and to start a conversation on how to address and overcome these issues.

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Adopting New Radiopharmaceuticals for Clinical Investigation: The Need for Standardized Approaches in Patient Dosimetry

Radiation dosimetry is the calculation of absorbed dose in tissue resulting from internal or external exposure to ionizing radiation.[3,4] Dosimetry in external beam radiation therapy has been well established in clinical guidelines for decades, and it has provided a uniform approach for accurately assessing patient outcomes and toxicities in NRG clinical trials with participants from around the world. In RPT, this best practice of providing individualized and standardized approaches for patient specific dosimetry has been more elusive, but technology and strategies are available as the role of RPT continues to expand both in clinical trials and research settings.[4–14]

Dosimetry calculations for therapeutic radiopharmaceuticals have historically[3] used methods developed for dosimetry of diagnostic radiopharmaceuticals. The end-point for dosimetry of diagnostic agents is long-term risk assessment, and the calculation is intended to help compare agents in terms of their stochastic risks. For this end-point, the average absorbed dose to organs is sufficient to evaluate risk. Accordingly, starting with the MIRD phantom in the late 1960s to mid-1970s, organ dosimetry in nuclear medicine in the late 1980s to present day has heavily relied on a series of age-dependent hermaphroditic stylized phantoms developed by the Oak Ridge National Laboratory.[15,16] Monte Carlo radiation transport computations of photon transport within the Oak Ridge National Laboratory phantoms have been used to assess organ cross-dose, whereas more simplified approximations are used for beta and alpha particle dosimetry (organ self-dose with full energy deposition assumed within the source organ). These early methods were inappropriately used to calculate absorbed dose to individual patients undergoing therapy wherein the individual patient anatomy and spatial dose distribution with normal tissues could affect the absorbed dose versus response relationship. Furthermore, the importance of standards and traceability of dosimetry calculations had not been appreciated. Accurate activity measurements are an essential foundation for safe and reliable RPT regimens. During drug development, the ability to compare patient responses across multiple centers requires the measurements made at each site to be made relative to the same standard; that is, there is confidence that the number of becquerels administered to a patient is the same regardless of where the patient is treated. Accuracy and traceability of the administered activity also affects the imaging input for dosimetry calculations. Early absorbed dose calculations were primarily based on planar imaging, which may be considered acceptable for diagnostic agent dosimetry, but accurate 3-dimensional imaging techniques, such as single-photon emission CT (SPECT) and positron emission to-mography (PET), are preferred for dosimetry of RPT. Finally, the absorbed dose value should be related to likelihood of tumor response or tissue toxicity. There is a well-organized body of knowledge regarding the cellular response to targeted effects, DNA damage and repair pathways, cell death pathways, and survival that has emerged from >50 years of radiation research in external beam radiation therapy.[17] However, there are many potential emergent effects associated with RPT that are a consequence of the agent uptake profile, organ distribution and microdistribution, the pharmacologic effect of the carrier itself, immunogenicity of the carrier, the radiation dose rate, dose uniformity, and microdosimetric stochastics. These are

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additional dose modifying factors that are not considered in classical radiation biology of external beam. Traditional radiobiology determines and defines the effectiveness of a particular radiation based on a standard external source irradiation geometry. In RPT, the source to target geometric configuration can be much more complex. One important emergent property that arises in RPT is the geometric enhancement of the cellular dose that results from tumor cell specific targeting. This phenomenon was observed in the study by Kozak et al,[18] who showed when using an α-emitting ^{212}Bi labeled anti-Tac antibody that 98% cell kill was achieved at an absorbed dose of 12 cGy, whereas when receptor binding was blocked by an excess of cold anti-Tac antibody the cell kill was reduced by more than an order of magnitude to a dosimetric value more consistent with that expected from an external α-beam radioresponse. The average absorbed dose for an in vitro experiment in which tumor cells are incubated with the same activity of a tumor-specific and a nonspecific antibody is identical, yet it is the microdosimetric energy deposition that determines the survival curve responses in these 2 instances. The difference in the radiobiological effect of RPT versus the same activity of a nontumor targeting agent depends on (1) the range and type of the radionuclide emissions and (2) the cell density (the distance between adjacent cells). To clarify this point, consider a radiopharmaceutical that is internalized into target cells via a specific cell surface receptor labeled with a long range β(^{90}Y) or an Auger electron emitter (^{125}I). When the same number of radioactive atoms of this tumor specific radiopharmaceutical vis-à-vis a nonspecific agent is administered then the benefit of targeting is very small for the long-range emitter but potentially infinite for the ultrashort-range Auger emitter.[19–24] The targeted component of the dose is referred to as *self-dose* and the contribution from nonbound radioactivity is referred to as the *cross-dose* (a consequence of nonspecific cross-fire). This highlights the importance of estimating the fraction of on-target versus off-target source in interpreting the radiobiological response from internal emitters. Quantitative estimation of the relative contribution from self-dose to cross-dose from single cells to multicellular clusters has been published for a number of radionuclides by Goddu et al,[25,26] and a tool to calculate cellular doses for different subcellular compartments for multicellular clusters was published by the MIRD committee.[8]

For the last 4 decades, the efficacy of many RPT compounds has been based on cytotoxicity studies that were designed using single tumor cell lines to assess single radiolabeled compounds, alone or in combination with chemotherapeutics, inhibitors, and monoclonal antibodies. The microenvironment of solid tumors consists of multiple cell types, including many immune cell populations that participate and regulate tumorigenesis. Tumor hypoxia and inflammation associated with aberrant vascularization also greatly influence tumor progression and response to therapy and should be considered where possible when using tumor in vitro models. A common component of the preclinical development and characterization of radiopharmaceuticals, including RPTs, is a study of their time-dependent biodistribution in small-animal models (ie, mice or rats). Such studies are used primarily to derive preliminary estimates of the normal-organ dosimetry for first-in-human trials of new radiopharmaceuticals. A critical component of translating the results of rodent biodistribution studies to humans is appropriate allometric scaling, that is, scaling of activities or activity concentrations measured in animal models to the corresponding values in humans. A simple allometric scaling approach is based on the equivalence of the standard

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uptake value (SUV) and the implicit assumption that the SUV, at least in first order, is independent of body mass.[27] The tissue activity concentration (eg, in mCi/g) in humans can therefore be estimated as the SUV measured in the animal model multiplied by the ratio of animal-to-human body-mass ratio.

The quantitative response of tumors in animal models to RPT is more complex than that resulting from external beam, where the tumor dose is usually uniform and well defined. Because targeting makes such an important contribution to the response and toxicity of a radiopharmaceutical, translation of dose-response data from animal tumor models to patients is fraught with limitations, first associated with the gross biological differences related to perfusion, immunity, microenvironment, and so forth, and second due to the ranges of the radionuclide emissions relative to the organ sizes between mouse and human. These factors highlight the importance of assessing efficacy and toxicity in human trials wherein quantitative imaging for dosimetry should be collected and the absorbed dose calculation should include an estimate of the uncertainty of the calculation. Providing some estimate of the accuracy of the calculation is essential in recognizing that every absorbed dose calculation reflects a compromise between what would maximize the accuracy and what is clinically and technically possible. If, for example, a simplification scheme is implemented regarding the number of time points collected or if planar instead of SPECT imaging is used or if the calculation does not account for substructure localization of the agent (eg, as in the kidneys or marrow), then the corresponding reduction in accuracy of the calculation should be reflected in the uncertainty associated with the absorbed dose value.

It is also incumbent upon the radiation dosimetry community to identify those instances where dosimetry is *not* essential to determination of the therapy in every patient. Dosimetry is critical to our understanding of radiobiologic effects as well as general radiation safety issues; it will therefore remain critical for therapeutic radiopharmaceutical development. We need to, however, commit to set guidelines to discern whether individual patient dosimetry is a prerequisite for a particular therapy—the simpler the therapy, the greater its utilization (and perhaps the lower its costs).

Recent regulatory approvals in the United States and Europe of therapeutic radiopharmaceuticals, such as $^{223}RaCl_2$ (Xofigo; Bayer)[28–33] and ^{177}Lu-DOTATATE (Lutathera; Advanced Accelerator Applications [AAA], SA/Novartis),[34–38] are significant advances in this field. A high specific activity form of ^{131}I-meta-iodobenzylguanidine (Azedra; Progenics Pharmaceuticals, Inc) has also been recently Food and Drug Administration (FDA)-approved for adult neuroendocrine tumors.[39] These therapeutic radiopharmaceuticals are important additions to the list of existing FDA-approved therapeutic radiopharmaceuticals, including ^{131}I-NaI, ^{153}Sm-lexidronam (^{153}Smethylene diamine tetramethylene phosphonate; Quadramet), $^{89}SrCl_2$ (Metastron), ^{90}Y-ibritumomab tiuxetan (Zevalin), and ^{131}I-tositumomab (Bexxar).

Although some centers continue to use various strategies for dosimetry—particularly radiation absorbed dose to critical organs—to determine the appropriate dose of ^{131}I-NaI in thyroid cancer therapy, there has been decreasing use of dosimetry to guide treatment decisions. The lack of commercial success of Bexxar (which relied on dosimetry to

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individualize treatment), was considered to have failed due to a confluence of timing, a poor roll-out strategy, and competition with drugs that did not require referral to a nuclear medicine or radiation oncology specialist and that were deemed less complicated.[40,41]

Dosimetry requires time and expertise, and it increases demands on instrumentation and human resources in the clinic. Both pre- and post-therapy dosimetry can be complex and need development and validation of simple and practical methods. It is important to acquire dosimetric images (SPECT and PET) as quantitatively as possible to enable accurate measurement of emitted radiation.[9] Although PET is generally acquired and analyzed quantitatively, it is frequently hampered in instances where imaging needs to be carried out over several days. The availability of quantitative SPECT imaging is still limited, though it is becoming more widely available; the limited resolution of SPECT systems is also a drawback. This drawback has been facilitated by simplification of data collection (eg, limited data are now required for RPT participation) that allows use in nonacademic clinics. This simplification process has been based on analytics of more extensive data from clinical trials, with the benefit being that more clinics can adopt this new technology with, however, less patient-specific dosimetry made available.

Although a number of commercial software packages that perform dosimetry for RPT agents are currently available, most implement a simplified phantom-based scheme, and no single package accounts for all of the subtleties highlighted previously. Additionally, in the research realm, there are numerous dosimetry platforms and approaches currently being used that vary drastically in their implementation of temporal multimodality image registration, pharmacokinetic fitting, contouring, dose calculation algorithm (Monte Carlo, point kernel, etc), and so on. Each of these steps in the process are things that will need to be standardized to ensure accurate and reliable dose calculations.

Challenges and Barriers to Developing New Radiopharmaceuticals for RPT

An understanding of the process whereby existing therapeutic radiopharmaceuticals were approved, and the availability of these therapies, is key to an appreciation of the challenges facing appropriate therapeutic radiopharmaceutical utilization. Strong intellectual property can generate financial investment for for-profit entities to move forward to phased clinical trials and eventual FDA approval when the endpoints are met. This may be somewhat offset by clear market demand (as with fluorine-18 labeled fluorodeoxyglucose (^{18}F-FDG), an imaging agent that lacks intellectual property but is still financially viable due to considerable demand). Commercial interests also identify and obtain a clear path of reimbursement by government-backed insurers like the US Center for Medicare and Medicaid Services and private insurance companies.

Leadership from commercial entities, in collaboration with clinical and scientific communities, to develop the therapeutic radiopharmaceutical is probably the most important factor in radiopharmaceutical development leading to regulatory approval and clinical utilization. This leadership must perforce include help on logistics, training, and a clear reimbursement path. Such leadership is hearteningly growing, as witnessed by Bayer's championship of $^{223}RaCl_2$ and by the recent acquisition of AAA and Endocyte by Novartis,

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and one may look forward to continuing championship of therapeutic radiopharmaceuticals by these and similar large pharmaceutical companies.

Another big challenge in developing a new therapeutic radiopharmaceutical is how to effectively and efficiently screen candidate molecules for further development leading to regulatory approval. Finding the lead candidate depends on important properties of drug development, that is, safety and efficacy. Safety and efficacy can be deduced from preclinical investigations and early phase clinical trials. They also can benefit greatly from corresponding imaging agents for target verification and dosimetric evaluations. Tumor and normal tissue dosimetry can provide insight into the likelihood that there will be normal tissue toxicity and also potential efficacy.

For example, numerous therapeutic radiopharmaceuticals are being developed for treating advanced prostate cancer, targeting prostate-specific membrane antigen (PSMA) using beta- or alpha-emitting radionuclides. ^{177}Lu-PSMA-617 has been studied extensively in Europe and now in the US (by Endocyte/Novartis); other ^{177}Lu-labeled molecules that target PSMA are under commercial development (eg, ^{177}Lu-PSMA-R2 by AAA, ^{177}Lu-CTT1403 by Cancer Targeted Technology, LLC), and several alpha-emitting radionuclides labeled with PSMA-targeting molecules are under development (^{225}Ac-PSMA-617, ^{227}Th-PSMA targeted thorium conjugate from Bayer). All of these developments are strongly backed by the considerable success of PSMA imaging using PET and SPECT.[42]

Radiophobia: In-patient versus outpatient safety

Although these numerous therapeutic radiopharmaceuticals are approved and in use, their availability is often hampered by numerous factors. The peer-reviewed literature is limited in identifying these factors, although some surveys of stakeholders have been reported. Each therapeutic radiopharmaceutical (eg, targeted small molecules, radioembolization, peptide receptor radionuclide therapy, radioimmunotherapy) has unique production, scale-up, and manufacturing/distribution challenges. Furthermore, different regulatory environments impose different barriers across countries and jurisdictions.

A crucial challenge common to all these is the uninformed perception of radioactivity as a “danger,” that is, radiophobia. This aversion to unsealed radioactivity appears to affect professional and layperson alike. Radiation dangers are generally related to nuclear fallout from atomic weapons (exemplified by the Allied bombing of Japanese cities in World War II) and accidental radiation exposure (exemplified by the reactor catastrophe at Chernobyl). The prevalent belief, that there is no “safe” radiation exposure level, furthers this radiophobia. A concerted effort to provide perspective on risk-benefit and educate (regulatory and health care) professionals and lay public about the effects of radiation, particularly in comparison to the deleterious effects of toxic therapies, is critical.

There must be harmonization of guidelines that are evidence-based and that help promote the safety of these procedures. When they are feasible in the outpatient setting, the psychological benefits to the patient, the limitation of “therapy beds,” and the expense of in-patient therapy can be overcome. For example, according to an assessment carried out in

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European radiopharmaceutical therapy facilities in 20 countries, there were 630 centers that performed therapy with a total of 1520 dedicated radionuclide therapy beds for a population of 434 million. Most of the facilities had 1 to 3 beds, but only a few had 8 to 12 beds available. This report pointed out that 18 of those European countries treated a total of 82,892 patients (191/million inhabitants). These financial and infrastructure requirements impose additional burdens that compete with other necessary hospital resources.

Financial and logistical issues: Expertise and training

Financial and logistical issues may constrain therapeutic radiopharmaceutical utilization. Peptide receptor radionuclide therapy, radioimmunotherapy, and radioembolization all require a significant amount of time for clinical staff and radiation safety staff. When imaging is necessary before therapy, there is an associated temporal delay as well. Reimbursement codes for physics and dosimetry support of RPT are also lacking, and this provides a further financial incentive to avoid dosimetry and treatment-planning-based RPT.

Costs associated with in-patient therapies may limit their utilization, especially in the US. The requirement to perform therapy in the in-patient setting is based on administered activity and radiation exposure to the general public and caregivers. Additionally, the nature of the radionuclide may necessitate special hospital room layouts and structures with added costs. Exposure-based techniques (whereby patient release criteria are satisfied by survey meter measurements) that allow outpatient administration of therapeutic radiopharmaceuticals are thus generally preferred from a radiation safety perspective—and of course patients would rather not be admitted for therapy.

However, instead of basing the requirement of in-patient or outpatient setting on a radiation safety perspective, sometimes this decision is based on the perception of the general radiophobia. Of course, in certain cases such as pediatric procedures, issues related to incontinence, or extremely high doses, in-patient therapy is most appropriate. Nevertheless, the associated significant restrictions related to cost or possibly limited availability of facilities often result in decreased implementation/utilization and delay of treatment.

For therapies that mandate an in-patient setting, the financial burden is generally more significant than outpatient therapy. In-patient costs are also higher than otherwise, given the more extensive room preparation, waste disposal, and monitoring requirements for systemic radiation therapy. In addition, there is a tendency to highlight treatment-related side effects such as myelosuppression, renal toxicity, myelodysplastic syndrome, and other long-term side effects when a radiopharmaceutical is involved even though other nonradiopharmaceutical treatments (eg, chemotherapy) can yield more severe and long-lasting side effects.

Dedicated facilities for RPT, including dedicated in-patient facilities at major centers, would accelerate development and utilization. This would be facilitated by an appropriate presence of key RPT stakeholders on institutional logistic (budget and/or infrastructure) committees.

Collaboration within and between clinical and pharmaceutical communities will also help address logistic, educational, and economic concerns voiced by community physicians. The

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formalization of evidence-based guidelines and guidance by professional organizations and their incorporation into widely used therapeutic guidelines by groups like the National Comprehensive Cancer Network would drive usage and formalize best practices (as evidenced by the growth in $^{223}RaCl_2$ usage after its inclusion in the National Comprehensive Cancer Network guidelines for prostate cancer).

It is important to streamline logistics for practicing RPT. Good lines of communication between the physicians involved is crucial; that would include an established process for ease of scheduling and establishing shared responsibility for patient follow-up and management.

Greater training and increasing the opportunities for licensed physicians to gain experience is also important to the field. The level of knowledge and physician experience with this treatment modality is currently inadequate. Hence, it is important to incorporate these practices into residency and fellowship training programs. It is also important for vendors and developers to provide radiopharmaceutical-specific training needs to trainees and new users.

Development of a structured method for dealing with therapies is highly desirable, even if it entails establishment of a few “magnet” centers of excellence where patients would go to be treated. No therapy is successful unless it is shepherded by a well-trained, experienced professional. A cadre of physicians who are well trained in managing patients throughout the process, from screening and eligibility through therapy and management of any sequelae, is crucially necessary. Development of dedicated RPT training will be accelerated when validated procedures are established; this will be further realized by interdisciplinary groups of physicians and related health care professionals involved, as a team, in the optimal care of the patient receiving RPT.

Summary of the barriers and challenges of RPT

Figure 1 summarizes the different aspects of RPT and their corresponding barriers. RPT continues to demonstrate tremendous potential in improving the therapeutic gains in radiation therapy by delivering selective radiation to tumors that can be well assessed in terms of dosimetry and imaging. In this overview, the NRG-NCI Working Group has reviewed some of the challenges ahead for improving RPT. The main priorities for advancing the field include

- Adopting patient-specific dosimetry for RPT as best-practice guidelines that can be used at both large clinics with substantial resources and the more modest clinics that have limited resources
- Improving strategies for bringing new radiopharmaceuticals for clinical investigation
- Addressing radiophobia for both in- and outpatient care
- Solving the financial and logistical issues of expertise and training in the developing field of RPT

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We hope that this document and future ensuing discussions stimulated by this work will help streamline and reduce the length of this list.

Disclosures:

C.D. reports serving as an adviser/consultant to Janssen Inc, Invicro LLC, ReleXion Inc, and Tomopath Inc. E.C.F. reports other from Radiopharmaceutical Imaging and Dosimetry, LLC (Rapid) during the conduct of the study and other from GE Health Care outside the submitted work. R.F.H. reports personal fees from Radiopharmaceutical Imaging and Dosimetry, LLC (Rapid), outside the submitted work. In addition, R.F.H. has a patent 12/514,853 issued, a patent 12/687,670 issued, a patent 12/690,471 issued, and a patent 61/719,283 issued. R.M. is a member of the Scientific Advisory Committee of OranoMed. Y.S. reports grants from the National Cancer Institute during the conduct of the study. G.S. reports personal fees from Bayer, Inc, personal fees from Orano Med, other from Radiopharmaceutical Imaging and Dosimetry (Rapid) outside the submitted work. In addition, G.S. has a patent US 9,387,344 B2, a patent US 8,693,629 B2, and a patent US 9,757,084 B2, all licensed to Rapid.

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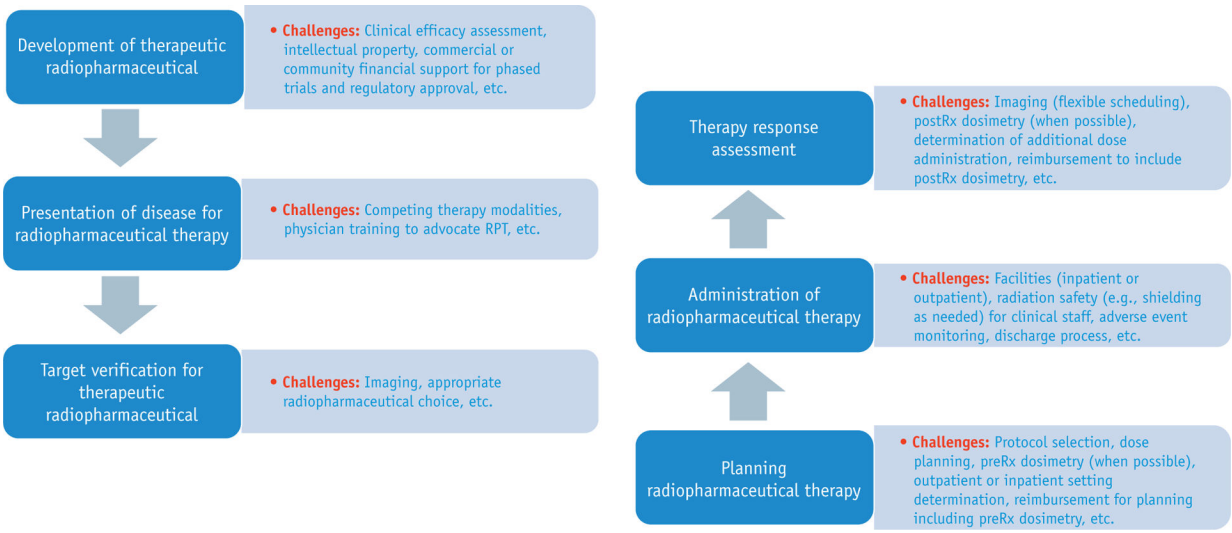

Fig. 1.

Summary of challenges associated with implementation of radiopharmaceutical therapy (RPT) and a treatment-planning approach to its delivery.