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Radiopharmaceutical Therapy (RPT): Strategy for Clinical Trial Management to Optimize RPT Patient Care

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ABSTRACT

Radiopharmaceutical therapy (RPT) directs radioactive compounds to malignant cells. Incorporating RPT into clinical trials will require practical treatment guidelines for therapy applications which can be applied by institutions in a uniform manner. Quality assurance (QA) centers support clinical trials by providing site qualification, clinical trial design support, clinical trial credentialing, data acquisition/management, and case review. Successful execution of cancer clinical trials requires participating sites to have tools and personnel to successfully deliver therapy in a consistent manner including the ability to generate composite dosimetry with previous sites of radiation therapy for outcome analysis. Assuring RPT is administered uniformly will require implementing a QA program. Quantitative assessment of the radiation dose delivered to the cancer target volumes and surrounding normal tissue(s) will be essential for the QA process to secure the position of RPT in patient care. This paper reviews the status of clinical trials for RPT therapy and defines what a QA process may require for future clinical trials. For RPT to move forward in clinical trials at an enterprise level, a QA program is necessary to optimize how RPT can integrate with established therapy and align with current cancer management. In this manuscript, we define and propose a practical QA program for modern clinical trials in RPT.

Introduction

RPT care for patients with cancer has a rich history and has been an important component for care for patients in multiple oncology disease areas for decades. With the development of multiple modern radiolabeled compounds, there are increasing additional therapeutic choices available for patients with radiolabeled treatment options. RPT is poised to make a meaningful contribution to patient care moving forward. However, to ensure the role of RPT matures as part of the portfolio of therapy in cancer clinical trials, it is important to optimize our understanding of the dose absorbed by both the tumor and normal tissue as we work to define safety limits and radiation tolerance, especially in patients with multiple previous therapies including teletherapy. Until recently, we had limited understanding about radiation dose absorbed with RPT by both tumor and normal tissue as the quality of therapy delivery was measured by the activity of the compound at the time of delivery. Today modern tools in imaging and quantitative dosimetry are available to support our understanding of radiation dose absorbed by tissues for RPT, therefore it is increasingly important to transition the definition of treatment from the pre-therapy activity of the compound to the radiation dose absorbed by both tumor and normal tissue, similar to quantitative dose calculations performed in radiation oncology teletherapy and brachytherapy applications. RPT has an inherent disadvantage as the absorbed dose can only be measured after therapy is delivered, however the promise of RPT is significant and quantitative dosimetry will improve our understanding of how RPT will align with current patient management. The transition of radiopharmaceutical management from the perception of radiochemotherapy to radiation therapy is essential to understand both the benefits and risks of radiation dose to tumor and normal tissue with radiation therapy applied as a systemic agent. To date, there is limited quantitative information with unknown and unintentional activity in normal tissues with RPT. Additionally, the limits and extremes of radiation dose uniformity with RPT to tumor and normal tissue volumes remain less well defined. In this paper, we discuss the need to provide tumor and normal tissue dosimetry for RPT applications in clinical trials and define strategies to include strengths of multiple involved stakeholders as a therapeutic program to ensure patient safety and the success of radiopharmaceutical management.

Background

External radiation therapy and brachytherapy are used in clinical trials and broadly applied to treat gross tumor and regions of interest which can harbor disease less well defined by current imaging tools. Because external radiation therapy application is planned, disease and volume-specific radiation dose can be delivered to tumor with sharp dose gradients applied at the perimeter of disease to spare normal tissue. Strategic application of radiation dose to select targets can optimize radiation dose to tumor targets and provide improved conformal avoidance to normal tissue. The dose and uniformity of the dose to target can be controlled by careful planning with injury avoided by selective treatment fractionation and normal tissue conformal avoidance. Image guidance can ensure treatment is accurately applied to targets with known dose to both tumor and normal tissue. Careful and strategic treatment planning and therapy execution limits normal tissue injury with established metrics and radiation dose volume standards. The dosimetry care plan is personalized to the clinical situation and the individual. In contrast, radiopharmaceutical applications are applied in a systemic fashion. Radiation dose, therefore, is continuous in nature with potentially non-uniform dose to tumor and normal tissue. Although external therapy can intentionally exclude normal tissue from dose, RPT often delivers dose to the whole organ by default (kidney, liver, etc.) over a period of time requiring multiple data sets for accurate calculation of dose to target.

In teletherapy and brachytherapy, radiation dose to target can be accurately calculated through treatment planning and executed with image guidance. Conversely, because tools for calculation of absorbed dose to targets were not available for enterprise use, RPT was historically delivered as the activity of the isotope rather than a specific absorbed dose to a tumor target with dose volume objectives/constraints assigned to a normal tissue. Therefore, RPT (systemic radiation therapy) was delivered in a manner similar to chemotherapy with the administered activity of the compound as the sole metric for the quantitative measure of treatment quality. Despite the paucity of computational tools, radiopharmaceutical care matured under the umbrella of endocrinology (I-131 thyroid management) and nuclear medicine/ interventional radiology within healthcare institutions as these providers were familiar with radionucleotide delivery platforms and assigned by institutional authorities as authorized users. Historically programs for diagnostic radionuclide administration have been imbedded in departments of radiology and nuclear medicine. It was a natural next step to apply a similar treatment delivery strategy to RPT at the time when radiation dose to volume could not be successfully measured as an absorbed dose since the safety processes of infusion and delivery of isotopes for therapeutic applications mimicked the well-defined processes applied for diagnostic applications. The division of labor and assignments for authorized users within institutions are often driven by the strengths of personnel and expertise of staff within each institution. If radiology/nuclear medicine colleagues had an established process and equipment in situ for infusional radiation applications, it was thought reasonable to apply the same process for therapy. Radiation safety committees housed in academic medical institutions manage safety issues through multiple stakeholder members including but not limited to radiation therapy, diagnostic radiology, nuclear medicine, interventional radiology, and specific basic science laboratory initiatives that use radiolabeled compounds as part of their research programs. Decisions are made collectively by committee members for the safety of patients and workflow within institutions to achieve the goals of patient care by those most expert in diagnostic and therapy applications. This has led to a natural separation between diagnostic applications and therapy applications despite recognizing the increasingly important role of imaging in radiation oncology and radiation dosimetry in radiology/nuclear medicine. However as radiopharmaceutical applications support

both diagnostic and therapeutic objectives, the need for supporting patient care with multiple stakeholders with strength in diagnosis and therapy becomes a more visible need as RPT is not delivered in isolation but as a continuum of care coupled with chemotherapy in addition to teletherapy and brachytherapy. Because downstream consequences associated with RPT are possible including the need for additional treatment including external radiation therapy, radiation dose to both tumor and normal tissue with RPT can influence the delivery of additional chemotherapy and radiation therapy.[1-13]

RPT today is increasing in utilization and the use of systemic radiation therapy with specific target ligands is now gaining momentum as clinical trials begin to demonstrate positive outcomes. Y-90 DOTATE has recently demonstrated promise in gastrointestinal neuroendocrine disease. Current therapies commonly used include 100 mCi I-131 radioiodine dose for thyroid ablation, 200 mCi I-131 radioiodine dose for thyroid therapy, 200 mCi I-131 mIBG dose for neuroendocrine tumors, 200 mCi x 4 Y-90 DOTATE dose for neuroendocrine tumors, 200 mCi x 4 for Lu-177 prostate-specific membrane antigen (PSMA) dose for castrate-resistant prostate carcinoma and 50 kBq/kg x 6 Ra-223 dose to treat bone metastasis in multiple disease sites. The administered activity has been developed over time and perceived safe based on available historical data and the clinical experience of the authorized user assigned to deliver the therapy within an institution. Authorized users are designated, in part, by clinical interest, training, expertise, and equipment access with various onsite quality assurance procedures. Endocrinologists became authorized users for I-131 applications as they would take responsibility for following the treated patient for disease control and thyroid function. Radium 223 and PSMA-directed therapies often are housed in nuclear medicine as the application is delivered as an intravenous application in a manner similar to diagnostic radionuclides. Yttrium-90 therapy is often primarily housed with interventional radiology as the application often requires an intra-vascular approach with a procedure mimicking cardiac catheterization with delivery of activity once catheter placement is assured. Procedural consent forms, by default, often place emphasis on procedural risks with less emphasis on risks and acute/chronic sequelae of radiation therapy. This is a natural extension of the workflow as until recently there were limited pathways to measure absorbed radiation dose to both tumor and normal tissue volumes, therefore risk of radiation injury could not be assessed in a quantitative manner. Accordingly, systemic radiation therapy was considered a step removed from diagnostic applications and radiation safety committee members did not possess a quantitative platform to address this process from a different perspective. The paradigm has begun to change as platforms have emerged to apply voxel related imaging to support dose computation for RPT. This has opened the door to evaluate RPT therapy from the perspective of radiation therapy with quantitative metrics to define dose to targets. RPT protocols can now mature. To do so, structure for data management, image acquisition, and dosimetry will need to be imbedded into each cancer clinical trial.[14-20]

Current Software for Computational Analysis

To find common ground to analyze patient care for RPT on clinical trials, quantitative assessment of absorbed radiation dose by both tumor and normal tissue is now recognized as an important vehicle to assess both efficacy and injury. This is important in clinical trials as the development of quantitative metrics remains essential to intercompare therapy on individual cases and assess how RPT therapy can be integrated with more traditional forms of radiation therapy including teletherapy and brachytherapy. Normal tissue tolerance to radiation therapy is significantly influenced by patient pre-existing co-morbidities, surgery, and chemotherapy; therefore, protocol eligibility criteria need to be established including data management strategies with the complete pretherapy portfolio including medical/oncology treatment history. Imaging should be available and stored in a single integrated format to support the assessment of dose absorbed to targets for RPT and define risks and benefits of therapy relative to radiation dose and volume including previous sites of radiation therapy. Therapeutic RPT applications are generally single photon emitters and total dose is dependent on activity and time of exposure to the isotope. Time specific activity can be measured by multiple imaging methodologies including multi-time point single photon emission computer tomography and computer tomography (SPECT-CT) using voxel dosimetry. An alternative time sparing approach is to use hybrid SPECT/planar imaging where SPECT is acquired as a single time point and planar images are acquired at sequential time points over the duration of the activity. The alternative is considered reasonably accurate in evaluating dose over time which is important to understand as dose is delivered as a continuum over time. Positron emission tomography holds promise to further promote quantitative assessment of absorbed dose. Commercial computational tools are available for measuring dose from computational imaging. These include Velocity (Varian) and MIM software as well as additional vendors capable of composite dosimetry with previous teletherapy and brachytherapy. The systems integrate SPECT images with CT including radiation oncology planning computer tomography for anatomical alignment and configuration of dose to target. As tools evolve, the precision of calculation will also improve and increase confidence that dose to target and normal tissue can be accurately assessed. Further harmonization and uniformity of calibration processes coupled with the development of national standards will further secure the positioning of RPT care in clinical medicine. Housing components for treatment delivery, imaging, and dosimetry will be important components for institutions for the credentialing and protocol participation/data management aspects of participation in clinical trials.

Work Effort to Date to Support Quantitative Dosimetry for Cancer Clinical Trials

Investigators are assessing the consistency of voxel-level dose calculation from the perspective of the quantitative imaging, image acquisition, and reconstruction as they relate to dose calculation. Consensus suggests

quantitative SPECT Reconstruction is important and will be the infrastructure for the foreseeable future for RPT quantitative dosimetry. Additional RPT dosimetry calculation platform vendors will mature over time as our collective knowledge improves with outcome analysis. Reconstruction algorithm, noise correction, scatter corrections, attenuation correction, and collimator-detector corrections will be integrated with computational process improvements in dose calculation. This will include mechanisms to convert reconstructed quantitative SPECT images from counts to activity. Calibration factors (CF: counts per second per becquerel, cps/Bq) are required for successful computation. These can be determined can be using a phantom image containing a known amount of activity, scanned under the same conditions with the same SPECT scanner.

To apply quantitative SPECT activity for final dose calculations, tumor(s) and organs at risk will be contoured on the CT and SPECT fusion. 3D time-integrated activity curves is obtained for each region of interest by aligning quantitative SPECT images from multiple time points with the SPECT/CT from the user-defined reference timepoint using rigid or deformable registrations. The spatially aligned images can then be used to calculate time-activity curves and absorbed dose. These processes will continue to mature as we acquire more knowledge and experience comparing algorithms with patient outcome.

Site Qualification, Credentialing, and Other Collaborative Efforts

It will be important to work closely with multiple stakeholders and professional organizations to establish standardized processes for RPT dosimetry. A key focus has been developing National Institute of Standards and Technology (NIST)-traceable calibration standards similar to the established model used for external beam radiation therapy. Through secondary standards calibration laboratories (SSCLs), efforts are underway to achieve ±2-3% accuracy in radioactivity measurements when following standardized procedures.

Current initiatives involve collaborations with NIST, academic institutions, and other stakeholders to create a network of SSCLs operating under standardized protocols. Early results from inter-laboratory comparisons show promising consistency, with variations of 2% or less in calibration measurements. This infrastructure is crucial for ensuring accurate activity measurements across clinical trial sites. Efforts have focused on quantitative SPECT reconstruction accuracy, which is crucial for RPT dosimetry. Studies comparing different vendor platforms demonstrated variations in reconstruction algorithms, correction methods, and calibration approaches. This will improve as our knowledge and strategy for standardization of tools mature including efforts to define standards for quantitative SPECT/CT scanner calibration

Multiple collaborative efforts from stakeholders have helped identify key areas requiring standardization:
- NIST-traceable activity measurements
- SPECT quantitative imaging protocols
- Image reconstruction parameters
- Time-activity curve fitting methods
- Absorbed dose calculation algorithms
- Segmentation guidelines

The collaborative work continues through multiple initiatives, including the Society of Nuclear Medicine and Molecular Imaging (SNMMI) Therapy Clinical Trials Network (TCTN) and the American Society for Radiation Oncology (ASTRO), developing standardized practices for clinical trials with the Foundation for the National Institutes of Health (FNIH) Phase 1 projects working toward improved dosimetry methodologies. These efforts aim to create a robust framework for accurate, traceable, and reproducible RPT dosimetry.

Vision for a Program

For all cancer clinical trials, a QA program is important for its success with QA staff supporting the conduct of each trial from protocol development to data analysis including real time review of imaging and radiation oncology planned treatment objects to ensure 1) each patient is enrolled in the correct study 2) all appropriate data including imaging and radiation therapy objects have been submitted at correct study time points 3) response assessment if needed for trial management is complete and 4) planned treatment is consistent with objectives and guidelines established for the trial. QA staff support preparation of both the primary study endpoint for publication as well as secondary study endpoints not always anticipated at the time of design of the study. QA programs provide five fundamental services including site qualification, clinical trial design support, investigator and site credentialing, data acquisition/management, and case review.

QA Processes for RPT Clinical Trials

For RPT cancer clinical trials a similar QA program can be implemented with the same five services. When studies are asking new questions, especially for advanced technology including theranostics, a QA program ensures a uniform approach to study conduct.

Today computational and quantitative tools are available for patient care. Accordingly, modern radiopharmaceutical care requires the skill and expertise of multiple medical disciplines housed in traditional departments within medical centers and academic institutions. Medical oncology, radiation oncology, radiation safety, and multiple divisions within radiology and nuclear medicine are needed to successfully manage the patient in a modern multi-disciplinary environment. Accordingly, radiopharmaceutical care can be viewed as a matrix program within an institution drawing upon expertise housed in multiple departments with the patient at the center of the program. For example, in hepatocellular oncology, experts in medical oncology, interventional radiology, abdominal radiology, radiation oncology, hepatocellular gastrointestinal medicine, and support staff participate in frequent conferences to identify the optimal approach to care and which treatment and sequence of care should be applied. Radiopharmaceutical care will require the same strategic participation and cooperation between disciplines in disease areas influenced by RPT to manage a successful clinical trial program. Each discipline within the program

brings strength in procedural care, computation, and dose analysis. All stakeholders participate in interpretation of radiation dose to volume to assess the success and associated intended and unintended risks associated with the application. These conversations demonstrate how additional therapies could be applied moving forward and as clinically indicated. Through these processes, the whole of the matrix interactions becomes greater than the sum of the parts in the program as experts from each department participate in dialogue and patient care to support clinical excellence and academic development of the program. Each area learns to appreciate the strengths of colleagues by placing the patient in the center of the dialogue. There are multiple well-intended stakeholders in the care of the patient and recognizing the contribution of each discipline will make good programs outstanding and serve to move the field forward in a timely and meaningful manner.[21-26]

While the teletherapy QA services provide a framework, there are differences with RPT that must be considered. From a clinical trial perspective, RPT applications do not allow pre-treatment review of imaging and radiation therapy objects, therefore the QA will need to place emphasis on site qualification and credentialing. The therapy imaging and radiation oncology objects will be collected and reviewed post therapy and may influence the strategy for additional therapy.

Site qualification will require essential elements of equipment, radiation safety, and staff to be certain treatment can be administered in a protocol compliant manner. This will include a plan for imaging treatment and dose/volume computation. Cancer clinical trials will be written in a manner to specify specific imaging and radiation therapy data for transfer and provide a vehicle to transfer information in a secure and safe manner. Credentialing can consist of review of imaging and dose computation of a previous patient to ensure that images are study compliant and dose calculations are performed per study guidelines. In other trials, knowledge tests are used as credentialing tools. Images of treatment can be given to a participating site, and a dose plan can be generated and submitted for review. This would ensure dose to volume was calculated in a study compliant manner and contours of tumor and normal tissue are drawn per study guidelines.[14-26]

The following QA will be the foundation for RPT clinical trials.

QUALIFICATION

For site qualification, participating sites will need to demonstrate possession of onsite personnel and infrastructure for therapy administration, imaging, and computational software to receive, maintain, deliver, and monitor therapy and outcome. It is expected the site will be able to forward information in a digital format including pre-therapy imaging and post process dosimetry which can be re-calculated at QA centers with single source software for clinical trial evaluation. It is anticipated that teams of investigators at each participating sites will be identified for participation generated from multiple disciplines and departments within sites participating in clinical trials.

CLINICAL TRIAL DESIGN SUPPORT

QA Center staff will work with study investigators to develop protocol guidelines which will ensure success of the clinical trial including criteria for patient participation and data necessary for trial participation. The objectives will be to develop the protocol to meet study objectives without barriers to study participation. Data to be forwarded to the QA centers will be well defined and will make every effort to minimize the burden of data acquisition for each participating site. Feedback to investigators will be provided in a timely manner.

CREDENTIALING

Unlike teletherapy clinical trials, theranostics does not easily lend itself to real time review of study objects, therefore emphasis in credentialing will be important for trials in this area. Test cases including SPECT imaging and radiation therapy treatment planning CT studies can be forwarded as a package to institutions to 1) contour objects including normal tissues and 2) calculate does to tumor targets and normal tissues. This exercise/knowledge test will help QA centers understand participating sites' equipment and how image fusion/registration, and computation are performed. QA centers can provide support to ensure compliance to study objectives and data acquisition.

DATA ACQUISITION/MANAGEMENT

QA Centers will work with investigators to facilitate data transfer and ensure the data needed to support the study are available. The data needed includes the record(s) of area(s) previously irradiated. This will support protocol outcome analysis and facilitate development of metrics for tumor dose and normal tissue tolerance for future studies.

CASE REVIEW

Case review will be performed by study investigators with timely reports generated to site investigators.

Future Directions

Practical dosimetry for RPT is advancing in clinical care, now moving forward beyond historical challenges which precluded accurate calculation of dose absorbed both by tumor and normal tissue. Important and well-designed imaging hardware and software has recently been introduced which will further support this important area of clinical growth. Gamma cameras and SPECT scanners with solid-state detector technologies that permit optimal energy and spatial resolution and SPECT scanners with full-ring detector geometries will make whole-body SPECT faster and more clinically feasible and reliable. PET scanners allowing whole-body dynamic imaging including reliable imaging of lower administered tracer activities than those currently used will enhance both imaging and interpretation/calibration of dose. Advancements in commercial software and regulatory approval of tools that facilitate clinical implementation will provide new opportunities for standardization of methods across multiple centers thus supporting cancer clinical trials. Artificial intelligence–assisted workflows that may reduce dosimetry time and improve standardization are also being developed. These will all serve to standardize workflow operations and calculation

of dose and these processes can be re-purposed for management of RPT clinical trials. RPT dosimetry remains a work in progress but will continue to improve as we acquire more experience in case management and patient outcome analysis. These processes need to be optimized if RPT is to be used at an enterprise function in clinical care. Experts from multiple disciplines will continue to refine methodology for dose computation, introduce new compounds, investigate integrated combined-modality therapies including immunotherapy, and define mechanisms for radiation injury with mitigation strategies. Work to standardize and validate dosimetry calculations and streamline the dosimetry process will need to evolve and become facile to be successfully applied in a multicenter clinical trial. As the field expands, successfully managed clinical trials will need reproducible structure with dosimetry that is reliable to assure the field will move forward and the trial outcomes trusted. Eliminating doubt and ambiguity concerning RTP dosimetry and reconciling RTP with patient outcomes will prevent non-inferiority evaluation with systemic therapy/chemotherapy.

Given the need for expertise among multiple disciplines and skill required of program leaders to move care forward, radiopharmaceutical programs will need to draw upon expertise currently housed in multiple departments including radiology, medicine, radiation safety, and radiation oncology to successfully manage the program and optimize patient care. When individual program members can recognize the strengths of colleagues, clinical care improves, and good programs become excellent. Excellent programs become outstanding when protocols are developed, outcomes are reviewed, and contributions to the literature are seen as process improvements for patient care. Radiopharmaceutical care will move forward as all disciplines make meaningful contributions to determine how best to optimize radiopharmaceutical care into the portfolio of treatment options. This is how programs mature and generate contributions to patient care and translational science [26-37].

Conclusion

RPT is developing at a rapid pace, and additional compounds are expected to be available for clinical use in the near future. Radiation dose absorbed by tumor and normal tissue can now be measured with computational software often using SPECT to estimate temporally the course of activity localization at sites within the patient which in turn can be applied to absorbed dose calculation to targets and normal tissue. Additional tools including PET will, in many applications, further improve the accuracy of absorbed dose calculations. It will be important moving forward to approach RPT dosimetry with the same rigor for radiation dose calculation as applied in radiation oncology teletherapy and brachytherapy treatments. This will serve to support the position of RPT in the growing portfolio of patient care.

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