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CASE REPORT

Radiopharmaceutical Therapy: Strategy for Management to Optimize Patient Care – A Case Report

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ABSTRACT
Radiopharmaceutical therapy directly targets radioactive drugs to cancer cells. Incorporating radiopharmaceutical therapy requires quantitative assessment of the radiation dose delivered to the cancer cells and surrounding normal tissue(s). This paper discusses the necessity of tumor and normal tissue dosimetry processes in radiopharmaceutical therapy and strategies to align this therapy within a patient's care plan. We discuss a process to manage radiopharmaceutical therapy within institutions to ensure dose metrics can be incorporated into the care plan for review by participants in patient care.

Introduction

Radiopharmaceutical therapy care for patients with cancer has a rich history and has been an important component for care for patients in many oncology disease areas for decades. With the development of multiple radiolabeled compounds, there is an increasing number of additional therapeutic options currently available for patients with many more radiolabeled treatment options in development for several disease sites. Radiopharmaceutical therapy is poised to potentially make a strong contribution to patient care moving forward. However, to ensure the role of radiopharmaceutical therapy as part of the portfolio of patient care, it will be 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. The transition of radiopharmaceutical management from 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. Additionally, radiation dose with radiopharmaceutical therapy to tumor and normal tissue volumes including dose uniformity remains less well defined. In this paper, we discuss the need to provide tumor and normal tissue dosimetry for radiopharmaceutical therapy applications and define a strategy to include strengths of multiple stakeholders as a therapeutic program to ensure patient safety and the success of radiopharmaceutical management.

Treating Patients with Radiation

External radiation therapy and brachytherapy are used 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 high and uniform radiation dose can be delivered to tumor targets with sharp dose gradients applied 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 can be controlled by careful planning and selective treatment daily fractionation. Image guidance can ensure the treatment is accurately applied with known dose to both tumor and normal tissue. Careful and strategic treatment planning and therapy execution limits normal tissue injury and provides metrics for radiation dose volume standards. This is because each patient is planned, and 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 targets. Although external therapy can exclude a per cent volume of normal tissue from dose, normal tissue dose with radiopharmaceutical therapy can deliver dose to a whole organ over a period of time potentially requiring multiple image sets acquired over the uptake and clearance of activity of the compound 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, systemic radiation therapy was historically delivered as the activity of the isotope rather than a specific absorbed dose to a tumor target with dose volume objectives assigned to a normal tissue. Therefore, 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 quality. With the lack 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 appropriately imbedded in departments of radiology and nuclear medicine. It became a natural next step to apply a similar treatment delivery strategy to radiopharmaceutical therapy 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 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, and specific basic science laboratory initiatives who 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. There has historically been a natural separation between diagnostic applications and therapy applications despite recognizing the increasingly important role of imaging in radiation oncology. 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 radiopharmaceutical therapies are not delivered in isolation but as a continuum of care coupled with chemotherapy in addition to teletherapy and implant radiation therapy. Because downstream consequences associated with radiopharmaceutical therapy are possible, radiation dose to both tumor and normal tissue with radiopharmaceutical therapy can affect the delivery of additional chemotherapy and radiation therapy care possibly in both a positive and negative manner.[1-13]

Radiopharmaceutical therapies today are increasing in utilization and the use of systemic radiation therapy with specific target ligands is now gaining momentum as clinical trials begin to demonstrate a positive outcome. Yttrium-90 (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. 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 onsite quality assurance procedures imbedded in situ. Endocrinologists often 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. The Yttrium-90 therapy is often primarily housed with interventional radiology as the application often requires an intra-arterial approach with a procedure mimicking a cardiac catheterization with delivery of activity once catheter placement is assured and validated. 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 was limited available pathway 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, therapy was considered a step removed from diagnostic applications and radiation safety committee members did not possess a quantitative platform to address otherwise. A modest number of institutions in North America housed radiopharmaceutical therapy applications in radiation oncology as treatment was viewed through the prism of radiation therapy and patients were followed in collaboration with colleagues and stakeholders from multiple departments to support the needs of a program in systemic radiotherapy. The paradigm has begun to change as platforms have emerged to apply voxel related imaging to dose computation for radiopharmaceutical therapy.

Current Software for Computational Analytics

Colleagues in multiple disciplines recognized the need for quantitative assessment of absorbed radiation dose. Therapeutic radiopharmaceutical applications are generally single photon emitters and time dependent. Time specific activity can be measured by several imaging methodologies including multi-time-point single photon emission computed tomography and computed tomography (SPECT-CT) using voxel dosimetry. An alternative time-sparing approach is to use a hybrid SPECT/planar imaging where the SPECT component is acquired at a single time point and serial planar images are acquired at the remaining time points to measure over time. This is a less cumbersome approach and thought to be reasonably accurate in evaluating dose over time of activity. Positron emission tomography (PET) holds promise to further promote quantitative assessment of absorbed radiation dose to both tumor targets and normal tissues. Multiple computational tools are available for measuring absorbed radiation dose including commercial systems. These include Velocity (Varian) and MIM software. The systems are based on

integration of SPECT images with CT in order to assess activity on SPECT with the anatomical configuration obtained from an aligned CT. As the technology evolves and system methodologies continue to improve, the precision of SPECT estimation will continue to improve. The methodological improvements will increase confidence that dose to targets and normal tissue can be measured with reliability. Harmonization of calibration processes coupled with standards in acquisition protocols and reconstruction will permit investigators to build more comprehensive and reliable radiation dose response and toxicity databases. This will be important and secure positioning of radiopharmaceutical care with dosimetry processes more aligned with radiation therapy.

Reason for Dosimetry

From a historical perspective, radiopharmaceutical therapy has been applied through the prism of "radiochemotherapy". When patients received chemotherapy, treatments are calibrated and aligned with body mass index and infused similar to radiopharmaceutical therapy without a quantitative mechanism to validate how much drug reached the target nor the impact, both acute and chronic, on normal tissue. Acute radiation therapy injuries generally affect tissues of rapid self-renewal potential (nausea, neutropenia, etc.). Acute sequalae can be anticipated and treated on an ongoing continuous method. Prior to the ability to quantify radiation dose to target at an enterprise level, metrics to assess success or failure of the administration were limited to follow up diagnostic imaging and laboratory tests. If there was an injury to normal tissue, the injury would be identified at a delayed time point when there would be limited opportunity to mitigate the injury by titrating further treatment applications. A recent patient treated at our institution represents the reason dosimetry needs to be performed on each patient application treated with radiopharmaceutical therapy with the same rigor applied to radiation oncology.

The patient is an 80-year-old male undergoing staging for a new diagnosis of Gleason grade 8 (4+4) adenocarcinoma of the prostate. A CT identified pelvic and common iliac adenopathy worrisome for metastatic prostate disease meriting treatment, however the study revealed an asymptomatic 12 cm mass situated in hepatic segments 5, 6, and 7 (Figure 1).

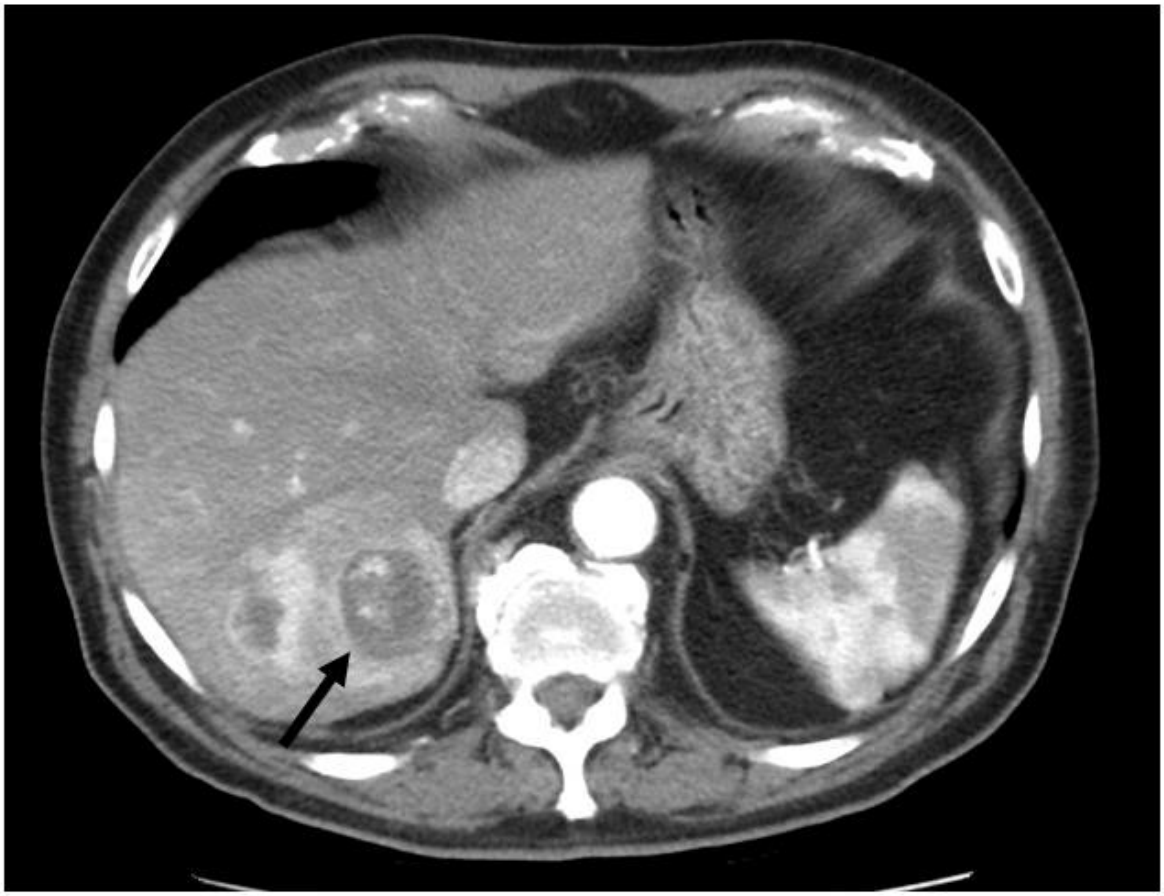

Figure 1. Location of primary hepatocellular carcinoma at presentation.[14]

Biopsy confirmed a well differentiated hepatocellular carcinoma. The patient was carefully evaluated by both the genitourinary and hepato-oncology teams and a decision was made to move forward with hormonal therapy for the prostate cancer and Y-90 therapy for the hepatocellular carcinoma. After appropriate preparatory study, 134 miC was administered to the lesion. Qualitative planar SPECT study done on the same day was completed revealing post therapy uptake in the liver. The report indicated where the visible activity was located however quantitative dosimetry was not performed. Six months after the Y-90 administration, an additional 151 miC was administered due to image guided evidence of persistent disease. Qualitative SPECT performed on the same day was again reported as "dose confined to the liver", again reported without computational metrics. The patient was referred to radiation oncology for definitive treatment for the prostate carcinoma. Because of the need to treat lymph node targets in the retroperitoneal region, as part of radiation therapy treatment preparation, the radiation oncology CT planning images were brought above the diaphragm and both SPECT studies were fused into the planning CT. This was performed in order to generate composite dosimetry for planning of radiation therapy and provide conformal avoidance as necessary to structures at and in close approximation to the region treated with Y-90. The Radiation Oncology department has software RapidSphere in Velocity that work with our Treatment Planning System Eclipse (Varian) which can calculate biological effective dose to volume for radiopharmaceutical applications. Imaging studies were not available to evaluate washout kinetics, however performing the dosimetry on a same day time point helped provide valuable information for the management of treatment planning for the prostate cancer. The composite dosimetry confirmed that the right kidney received significant dose from both Y-90 applications due to the proximity of the right kidney to the target. Sixty-two and four tenths' percent (62.4%) of the right kidney received 20 Gy or greater which is established as tolerance. Performing the composite dosimetry was extremely helpful as we were able to generate a plan with conformal avoidance to the renal volumes. To date, the patient remains well from the prostate cancer perspective with a prostate specific antigen (PSA) of <0.1, however during the past eight months his creatine has increased from 0.8 to 2.75 without a change in medications. Although renal function issues can be multifactorial in origin, the renal injury is influenced, in part, by the unintentional radiation dose to the right kidney by the Y-90 applications. The dose volume histogram reflecting renal dose from Y-90 is seen in Figure 2.

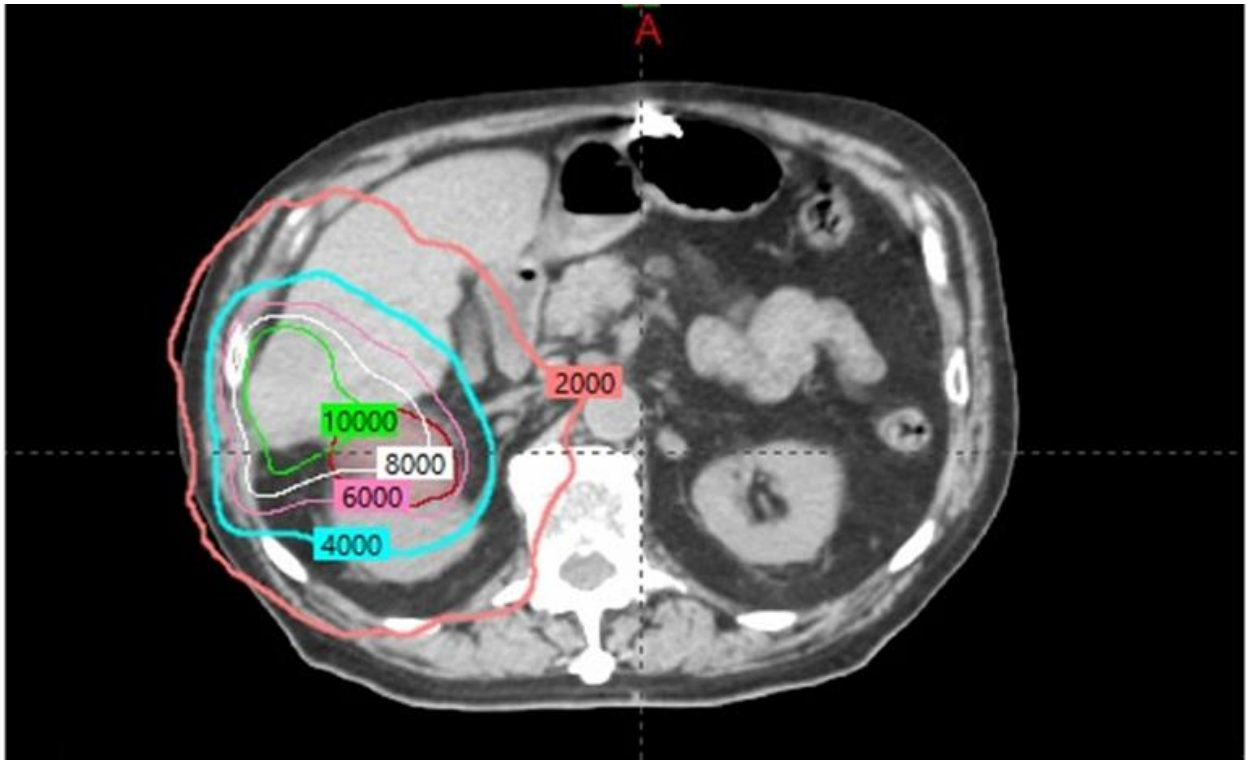

Figure 2. Radiation dose from Y-90 applications to the right kidney.[15]

One can argue that if dosimetry was performed after the initial application, alternative strategies providing conformal avoidance of renal volumes including external radiation therapy and stereotactic body radiotherapy (SBRT) may have been applied to limit dose to the right kidney. This may/may not have mitigated the current status of the injury.[14,15]

Although compound activity is documented pre-therapy, one of the challenges of radiopharmaceutical applications is the absorbed dose can only be measured after the application. Unlike external radiation therapy and brachytherapy, with the exception of fractionation and evaluation for additional therapy, planning cannot be refined and adjusted to normal tissue constraints for radiopharmaceutical therapy. Adjustments in strategy can only be made after the treatment is delivered unless unanticipated shunting is recognized at the time of a preliminary mapping study. This is why dosimetry needs to be performed for each patient and calculated for review in a manner identical to teletherapy/brachytherapy plans in order to optimize care for the patients and quantify risks of injury moving forward. All members of the therapeutic program share this responsibility. Dosimetry will support reviewing radiopharmaceutical management through the prism of radiation therapy and begin to align radiopharmaceutical care and normal tissue risk assessment with radiation oncology in concert with medical oncology/chemotherapy. Unlike chemotherapy, absorbed radiation dose to target can be measured and with comprehensive analysis, adjustments can be made to optimize patient care and dose to target when identified.[11-13, 16-20]

Vision for a Program

Now that computational and quantitative tools are available for patient care, modern radiopharmaceutical care requires the skill and expertise of multiple medical disciplines housed in several 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. In hepatocellular oncology, experts in medical oncology, interventional radiology, abdominal radiology, radiation oncology, hepatocellular gastrointestinal medicine, and support staff all participate in a weekly conference 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 all disease areas influenced by radiopharmaceutical therapy to manage a successful program. Each discipline within the program brings strength in procedural care, computation, and dose analysis. All stakeholders participate in interpretation of dose to volume in order to assess the success/risk of 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]

Future Directions

Practical dosimetry is rapidly advancing in clinical care, now progressing well beyond historical challenges which precluded accurate calculation of dose absorbed both by tumor and normal tissue. Important and well-designed imaging hardware has recently been introduced which will further serve to 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. The PET scanners allowing whole-body dynamic imaging including reliable imaging of much lower administered 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 cooperative group 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.

Radiopharmaceutical dosimetry remains a work in progress but needs to be optimized if

radiopharmaceutical therapy 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 in order 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. Otherwise, the field will succumb to non-inferiority evaluation with systemic therapy/chemotherapy and thought less necessary if doubt and ambiguity concerning dosimetry is not reconciled with patient outcome.

Given the need for expertise between 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, 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. If radiopharmaceutical care is to move forward, all disciplines will need to make meaningful contributions to determine how best to optimize radiopharmaceutical care into the portfolio of treatment options. This is how programs mature and make meaningful contributions to patient care and translational science.[27-40]

Conclusion

Radiopharmaceutical therapy 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 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 some applications further improve the accuracy of absorbed dose calculations. It will be important moving forward to approach radiopharmaceutical dosimetry with the same rigor for radiation dose calculation as applied in radiation oncology teletherapy and brachytherapy treatments. This will serve to support the important position of radiopharmaceutical therapy in the growing portfolio of patient care.

Conflicts of Interest Statement

The authors have no conflicts of interest to declare.

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