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## Dosimetry in Radiopharmaceutical Therapy: Clinical Examples

### Thyroid Cancer

Benua *et al.* were the first to adopt a MTD-based approach for radioiodine therapy of metastatic thyroid cancer (1). This involves administering a tracer amount of  $^{131}\text{I}$ -iodide and determining its pharmacokinetics by serial time-activity measurements for blood (based on ex vivo counting of blood samples) and total body (using a whole-body counter or gamma camera). The measured data are then integrated. The radiation dose to blood is assumed to be a surrogate for the dose-limiting bone marrow, receiving contributions from beta-particle (from  $^{131}\text{I}$  in blood) and gamma-ray contributions (from the whole-body activity). The beta particles from  $^{131}\text{I}$  activity in blood are assumed to be non-penetrating and locally deposited. The gamma-ray dose is determined from modeling the patient as a unit-density right circular cylinder and estimating the mean whole-body gamma-ray dose contribution (based on the corresponding mean geometric factor). The  $^{131}\text{I}$  absorbed dose (in MBq/Gy) to blood is calculated. The actual maximum tolerated activity (MTA) is that activity of  $^{131}\text{I}$ -iodide which is projected to deliver an absorbed dose of 2 Gy to blood. Using this MTD-based approach, personalized dosimetry has been conducted for thyroid cancer without significant toxicity to the hematopoietic marrow for 60 years.

Lesion dosimetry for thyroid cancer was originally based upon neck probe uptake counts and the application of the Marinelli or other related dose formulas (2), but lesion dosimetry for patients with metastatic thyroid cancer has been rare, largely because of the difficulty of performing quantitative SPECT with  $^{131}\text{I}$ . Whereas gamma cameras with nonstandard thicker crystals exist, most gamma cameras still have 3/8-inch sodium iodide crystals (ideal for  $^{99\text{m}}\text{Tc}$ ) and therefore low sensitivity for the 364-keV principal gamma-ray emission of  $^{131}\text{I}$ . As quantitative SPECT tools become more widely available, dosimetry based upon serial SPECT/CT images can now be performed. The availability of  $^{124}\text{I}$ , a positron emitter with a 4.2 d half-life provides an opportunity to perform improved dosimetry for radioiodine. A paradigm shift is ongoing in the management of metastatic thyroid cancer, a consequence of recent findings suggesting that uptake and retention of radioiodine in thyroid cancer are mediated by distinct differentiation genes and regulated by different targetable signaling pathways. New drugs that target these pathways have shown potential to re-differentiate thyroid tumors to increase their radioiodine uptake. Quantitative  $^{124}\text{I}$  PET imaging provides a method to determine whether patients formerly unsuitable for radioiodine therapy can become eligible if the uptake and retention of  $^{124}\text{I}$  by serial PET imaging indicates therapeutically efficacious  $^{131}\text{I}$  doses can be delivered to metastatic lesions.

### Peptide Receptor Radionuclide Therapy

Peptide receptor radionuclide therapy (PRRT) utilizes radiolabeled peptides to target with high affinity and specificity receptors which are over-expressed in tumors. The somatostatin receptor agonists DOTATOC and/or DOTATATE labelled with therapeutic isotopes  $^{90}\text{Y}$  or  $^{177}\text{Lu}$  have been successfully employed globally for many years. The  $^{177}\text{Lu}$ -DOTATATE product Lutathera® gained EMA (European Medicines Agency) and FDA approvals in 2017 and 2018, respectively, for the treatment of somatostatin

receptor-positive gastroenteropancreatic neuroendocrine tumors (NETs). Approval was largely influenced by the NETTER-1 trial, a multicenter, randomized, phase-III study with 229 patients. The study demonstrated an improved progression-free survival in the treatment cohort compared to the control arm (3).

Prior to receiving PRRT, patients are screened for receptor overexpression, a requisite for treatment efficacy, by single-photon or PET imaging ( $^{111}\text{In}$ -DTPA-Octreotide (OctreoScan®) or  $^{68}\text{Ga}$ -DOTATOC (SomaKit TOC®), respectively). The vendor recommended treatment schedule consists of four infusions of 7.4 GBq Lutathera® at intervals of eight weeks.

$^{177}\text{Lu}$  has a 6.73 d physical half-life and is a theranostic isotope that emits a beta-particle and also imageable gamma rays (113 and 208 keV) for biodistribution and dosimetry characterization.  $^{177}\text{Lu}$ -DOTATE has shown uptake in the kidneys, tumoral lesions, liver, and spleen, and, in some patients, the pituitary gland and thyroid. Protocols incorporate co-infusing patients with a solution of basic amino acids (lysine/arginine) as a means of reducing renal uptake/absorbed dose. Dosimetry for  $^{177}\text{Lu}$  has been estimated, with kidneys and bone marrow identified as the organs at risk (4). In the approved protocols, the total activity administration will likely not cause significant adverse effects. Several groups have demonstrated variability in dosimetry across populations, and also demonstrated the possibility of tailoring treatments through personalized dosimetry, using MTD regimens - ensuring that no organs exceed their respective dose limits of 27 Gy to kidneys and 2 Gy to marrow. Several authors have found that treatments tailored to individual patients can vary, potentially ranging from 2 to 10 cycles, each of 7.4 GBq(4). Most dosimetry research is performed using multi-time point imaging-based biodistribution characterization, with and without marrow dose calculation. In recent years dosimetry based on single time point imaging has attracted interest, due to its improved practicality (5).

## Pediatric Cancer

### $^{131}\text{I}$ -meta-iodobenzylguanidine (MIBG) Therapy of Neuroblastoma

Dosimetry has been used to guide “high dose”  $^{131}\text{I}$ -MIBG (Azedra™) therapy of neuroblastoma. For patients with cryopreserved marrow, this is generally delivered at an administered activity of 666 MBq/kg (6). In an ongoing clinical trial at Memorial Sloan Kettering Cancer Center (7), patients may receive a second therapeutic administration of  $^{131}\text{I}$ -MIBG at the same administered activity (666 MBq/kg), subject to estimation of the projected cumulative absorbed doses to at-risk normal organs and confirmation that these will not exceed limits of 30, 20, and 15 Gy, respectively, to liver, kidneys, and lungs. Five to seven weeks after the first treatment, dosimetry is estimated using  $^{123}\text{I}$ -MIBG as an imaging surrogate. Patients are injected with  $^{123}\text{I}$ -MIBG (370 MBq/m<sup>2</sup>) and undergo serial whole-body conjugate-view scanning on the day of injection (2–4 h post-injection) and at approximately 24 and 48 h post-injection. Regions of interest (ROIs) are manually drawn on the  $^{123}\text{I}$  images, around the whole body, heart, liver, lung, and a simultaneously imaged  $^{123}\text{I}$  reference standard. For the whole-body and normal-organ ROIs, geometric mean net (i.e., background-subtracted) count rates are converted to activities (kBq) using the standard-derived system calibration factor (cpm/kBq). Exponential functions are then fit to the resulting whole-

body and normal-organ time-activity curves and integrated to yield the  $^{123}\text{I}$  time-integrated activity coefficients. The projected  $^{131}\text{I}$  coefficients are then derived from the  $^{123}\text{I}$ -MIBG time-activity data by adjusting for the difference in physical half-life between  $^{131}\text{I}$  and  $^{123}\text{I}$ . Mean liver, kidney, and lung  $^{131}\text{I}$ -MIBG absorbed doses are then calculated using OLINDA/EXM, selecting the reference anatomic model with a total-body mass closest to that of the patient. If the sum of the  $^{131}\text{I}$ -MIBG absorbed doses to the liver, kidneys, and lungs from the first therapy administration and those projected from the  $^{123}\text{I}$ -MIBG study do not exceed the respective organ limits, the patient receives the second  $^{131}\text{I}$ -MIBG therapy administration at 666 MBq/kg. Otherwise, the activity administered for the second cycle is reduced to not exceed the organ limits. This approach has proven feasible and suitable for planning and limiting organ toxicity for repeat high-activity  $^{131}\text{I}$ -MIBG therapies.

#### Intrathecal Radioimmunotherapy of Neuroblastoma Metastatic to the Central Nervous System

Recurrent metastatic neuroblastoma is difficult to cure, particularly in patients with central nervous system (CNS) disease. Intrathecal  $^{131}\text{I}$ -3F8 and  $^{131}\text{I}$ -8H9 (omburtatmab) antibody therapy, administered via an Ommaya reservoir to target leptomeningeal CNS disease as part of a multi-modality treatment strategy, has proven safe and remarkably effective in inducing durable remissions and apparent cures in this otherwise difficult disease setting (8,9). For dosimetry, 74 MBq of  $^{131}\text{I}$ - or  $^{124}\text{I}$ -3F8 or -8H9 are injected intrathecally. Serial cerebrospinal fluid (CSF) (via the Ommaya reservoir) and peripheral blood samples are obtained and weighed aliquots assayed in a scintillation well counter calibrated for  $^{131}\text{I}$  or  $^{124}\text{I}$  to derive the respective time-dependent activity concentrations. The activity concentrations in the CSF in the craniospinal axis and the leptomeningeal disease plaques are measured by serial conjugate-view planar imaging plus SPECT for  $^{131}\text{I}$  and by PET for  $^{124}\text{I}$  at 4, 24- and 48-h post-infusion. Exponential functions are fit to these time-activity data and integrated to yield the  $^{131}\text{I}$  time-integrated activity coefficients (in terms of concentration) in blood, CSF (both by sampling and by imaging), and meningeal disease; the  $^{124}\text{I}$  time-activity data are adjusted for the difference in physical half-life between  $^{131}\text{I}$  and  $^{124}\text{I}$ . The  $^{131}\text{I}$ -3F8 or -8H9 absorbed doses to CSF, ventricles, spinal cord, normal brain, and blood are calculated based on the assumption of complete local absorption of the  $^{131}\text{I}$  beta particles. In the case of 8H9 (omburtamab),  $^{124}\text{I}$  PET-based dosimetry estimations yielded mean  $\pm$  standard deviation  $^{131}\text{I}$  absorbed doses to the CSF of  $0.62 \pm 0.40$  cGy/MBq compared with  $2.2 \pm 2.2$  cGy/MBq and  $1.5 \pm 1.4$  cGy/MBq based on  $^{124}\text{I}$  and  $^{131}\text{I}$  CSF sampling, respectively. The corresponding doses to brain, spinal cord, and leptomeningeal plaques are obtained by applying a multiplicative factor of  $\frac{1}{2}$  to account for  $^{131}\text{I}$  beta particles emitted from *within* the CSF traveling away from these respective tissues. The mean absorbed doses to the blood were  $0.051 \pm 0.11$  cGy/MBq and  $0.07 \pm 0.04$  cGy/MBq for  $^{124}\text{I}$  and  $^{131}\text{I}$  blood samples, respectively. Dosimetric assessment is followed within a week by therapy infusions (up to 4 in total) of 370 - 2,220 MBq of the  $^{131}\text{I}$ -labeled antibody.

PET imaging with  $^{124}\text{I}$ -omburtamab administered intraventricularly allows for non-invasive estimation of dose to CSF and normal organs. High CSF-to-blood absorbed-dose ratios (i.e., therapeutic indices) were demonstrated, with PET-based dose estimates being less variable than CSF sample-based estimates (9).

Further, no neurologic deficits secondary to radionecrosis have been observed in long-term survivors treated with both external-beam radiation therapy and intrathecal radioimmunotherapy, including patients who underwent repeat external-beam therapy. Such radioimmunotherapy thus may safely proceed in patients treated with conventional radiotherapy without increasing the risk of radionecrosis.

### Intralesional Radioimmunotherapy of Cerebellar Pontine Glioma

Diffuse intrinsic pontine glioma is one of the deadliest CNS tumors of childhood, with a median overall survival of less than 12 months. Convection-enhanced delivery has been proposed as a means to efficiently deliver therapeutic agents directly into the brainstem while minimizing systemic exposure and associated toxic effects.  $^{124}\text{I}$  has a number of the same physical properties which make  $^{131}\text{I}$  suitable for therapy: a suitably long physical half-life (4.02 d), emission of annihilation gamma-rays for PET and thus imaging-based dosimetry, and abundant emission of therapeutically effective beta particles (i.e., positrons), with a range in soft tissue of 0.8 mm. Further, the average energy emitted per decay in the form of particulate radiations is nearly identical for  $^{124}\text{I}$  ( $3.09 \times 10^{-14}$  kg-Gy/Bq-s) and  $^{131}\text{I}$  ( $3.04 \times 10^{-14}$  kg-Gy/Bq-s). Direct intralesional administration of an  $^{124}\text{I}$ -labeled agent can deliver therapeutically effective radiation doses while high-resolution, quantitatively accurate PET imaging makes accurate dosimetry for the actual therapy administration achievable. In a phase-1, single-arm, single-center, dose-escalation study at Memorial Sloan Kettering Cancer Center (10), 7 dose-escalation cohorts were evaluated utilizing a standard 3+3 design, in pediatric patients with diffuse pontine glioma. Patients received a single intralesional administration of 9.25, 18.5, 27.75, 37, 92.5, 120.25, or 148 MBq, with catheter placement performed by intra-operative MRI guidance. Serial whole-body (including brain) PET/CT scans (3-5 scans) were acquired at 1–6 h,  $48 \pm 24$  h,  $96 \pm 24$  h, and  $7 \pm 1$  days after completion of infusion, with up to two optional scans between days 7 and 14. Peripheral blood samples were drawn at each imaging time point and weighed aliquots assayed in a scintillation well counter calibrated for  $^{124}\text{I}$ . Volume-of-interest (VOI) analysis of the serial PET/CT scans were performed to measure the time-dependent activities in the lesion, whole body, and select normal organs. Exponential functions were then fit to the resulting lesion, whole-body, normal-organ, and blood time-activity curves and integrated to yield the respective  $^{124}\text{I}$  time-integrated activity coefficients; for blood, the activity and time-integrated activity were expressed in terms of concentrations. Absorbed doses to blood and lesion were calculated based on the assumption of complete local absorption of the  $^{124}\text{I}$  positrons. The absorbed doses to the total body and normal organs were calculated using OLINDA/EXM, selecting the reference anatomic model with a total-body mass closest to that of the patient. The lesion absorbed dose was calculated using OLINDA/EXM's sphere module, implicitly modeling the lesion as a unit density sphere. The mean lesion absorbed dose across all 7 cohorts was  $0.39 \pm 0.20$  Gy/MBq. The total lesion absorbed doses increased with the total administered activity and ranged from 14.5 Gy for Cohort 1 to 24.4 Gy for Cohort 7. The mean whole-body absorbed was  $0.0336 \pm 0.0324$  Gy, corresponding to a lesion-to-whole-body absorbed dose ratio (i.e., therapeutic index) of  $1285 \pm 1019$ . The Blood absorbed doses were uniformly very low, of the order of 0.01 Gy or less.

PET-based dosimetry of the theranostic antibody [ $^{124}\text{I}$ ]-8H9 validated the principle of using convection-enhanced delivery in the brain to achieve high intra-lesional dosing with negligible systemic exposure.

## Prostate Cancer

In terms of potential patient numbers, RPT for prostate cancer is likely to dominate the field for the foreseeable future. Recently reported results of randomized clinical trials (11,12) show that  $^{177}\text{Lu}$ -PSMA-617 can produce significant improvements in outcome (progression-free survival, prostate-specific antigen (PSA) response) for patients with metastatic castrate-resistant prostate cancer who have had significant prior treatment. Ongoing studies will provide guidance on the use of RPT in earlier stages of the disease process and as part of combined modality treatments. Currently, most investigational treatments feature  $^{177}\text{Lu}$ , a beta-particle emitter, but there is intense interest in the use of alpha emitters such as  $^{225}\text{Ac}$  and  $^{212}\text{Pb}$ , based on promising but essentially anecdotal clinical results. Although there are a variety of potential molecular vectors, most are relatively similar small molecules (~1.2 kDa) that target prostate specific membrane antigen (PSMA) via a characteristic glutamate-urea-lysine binding motif. This extended family of PSMA-targeting small molecules are derived from neurobiological inhibitors of glutamate carboxypeptidase II (a molecular synonym of PSMA).

Treatment schedules for  $^{177}\text{Lu}$ -PSMA are typically around 7.4 GBq every 6 weeks for 4-6 cycles. Patient selection, irrespective of stage in disease progression, requires a positive PSMA PET scan (with either a  $^{68}\text{Ga}$ - or  $^{18}\text{F}$ -labeled imaging agent) and potentially an additional non-discordant  $^{18}\text{F}$ -FDG PET scan (as was required for the TheraP study). Treatment schedules for  $^{225}\text{Ac}$ -PSMA have typically been approximately 8 MBq or less at 2-3 monthly intervals.

Radiation dose estimates for  $^{177}\text{Lu}$ -PSMA have been published (13); it has been suggested by the authors that a parameter “total-body tumor dose” may be a predictor of clinical response. The total-body tumor dose is a representation of the average absorbed dose to all sites of disease in the body, derived from serial SPECT/CT scans. Tissues at risk include bone marrow and kidney but also the salivary/lacrimal glands. Clinically, xerostomia can be dose-limiting, especially for  $^{225}\text{Ac}$ -PSMA therapy. It is not clear to what extent the high salivary gland uptake represents specific PSMA targeting, as it is not observed in  $^{89}\text{Zr}$ -huJ591 PET scans (14). Modifying PSMA-targeting agents by the incorporation of a low-affinity albumin-binding motif to improve kinetics and biodistribution is an area of active research (15).

## New Modalities

### Alpha Emitters

The emergence and relevance of alpha producing isotopes are discussed in the main text.

### Auger Electron Emitters

Auger and Coster-Kronig electrons are emitted when radionuclides decay by electron capture or internal conversion resulting in an electron vacancy in an inner-shell orbital. This vacancy is filled by an electron transition from a higher-energy orbital with the emission of either a fluorescent x-ray photon or an Auger

or Coster-Kronig electron producing two inner shell vacancies. This process continues with the emission of a cascade of extremely low-energy, short-range electrons until all vacancies reach the outmost electron shells. The number of electrons emitted and the focal positive electrical charge remaining on the progeny may produce a very high-LET event at the decay site that can be even more locally damaging than an alpha-particle track. The physics explaining the high radiotoxicity of Auger electron emitters was first presented by Charlton (16), who used electron track structure to show the electron emission spectra produced a dense “cloud” of ionization tracks around the decay site.

Several common radionuclides used in Nuclear Medicine decay by electron capture or internal conversion including  $^{67}\text{Ga}$ ,  $^{99\text{m}}\text{Tc}$ ,  $^{123}\text{I}$  and  $^{201}\text{Tl}$ . However, the emission ranges of Auger electrons are sub-micron, and the high-relative biological effectiveness (RBE) effects are observed only for decays occurring within a nanometer of the DNA. Therefore, the extreme radiotoxicity observed for these radionuclides is not manifest unless the radionuclide is attached to a radiopharmaceutical that transports the radioactive atom within sub-nanometer proximity of the DNA. The site specificity of Auger electron emitters has been studied showing the dependency of radiotoxicity with proximity to the DNA (17). These data support the use of standard MIRD methodology for  $^{99\text{m}}\text{Tc}$ ,  $^{123}\text{I}$  and other Auger electron emitter-labeled pharmaceuticals unless the carrier molecule has a specific sub-cellular localization. When such specific sub-cellular localization does occur, it is recommended that cellular S factors are used to correctly apportion the radiation dose burden to the targeted cell population. If DNA targeting occurs, then average dose estimates do not apply, and it is necessary to supplement standard dosimetry methods with radiotoxicity data derived from in-vitro or in-vivo measurements with the experimental radiopharmaceutical. This is the case for thymidine analogs, alkylating agents, and other DNA-associating pharmaceuticals. Auger electron-emitting radionuclides are the ideal radionuclide probes to perform radiobiology research because the location of the damage is exquisitely focal to a radiopharmaceutical target site. Only a small number of clinical trials have been performed with Auger electron emitters, as the field waits for realization of a suitable targeting vector.

### Combined Modalities Featuring Radiopharmaceutical Therapy

In general, combined modality therapies are more effective than single agents due to the existence of non-overlapping toxicity, differential therapeutic effectiveness, and, potentially, synergistic interactions. For RPT, combinations with cytotoxic chemotherapy, check-point blockade immunotherapies, and DNA repair modulators are under investigation (18). It is possible that these types of combinations could have an impact on RPT absorbed dose limits for normal tissues, but little is known at this time.

Other combinatorial approaches may feature the use of multiple radiopharmaceuticals or combining RPT with XRT. It has previously been suggested that, based on their emission characteristics, different radionuclides have different ranges of action and that the use of multiple radionuclides may expand the size range of maximal effect. This was shown to be a valid concept in preclinical studies (19) and has been investigated clinically (20).

With the increasing availability of alpha-emitting radionuclides and radiopharmaceuticals, it is possible that these could be incorporated into multi-radionuclide combination strategies. From a purely dosimetric perspective, alpha particles have a limited range (a few cell diameters) and the optimal target size would be anticipated to be of sub-millimeter dimensions. It would also be expected that the adverse effects of non-uniform radiopharmaceutical uptake in macroscopic disease would be particularly severe for alpha particle-based agents. Taken together, this suggests RPT using alpha-particle emitters ( $\alpha$ RPT) would be optimally used in the adjuvant or neo-adjuvant role, specifically addressing sub-clinical microscopic disease.

However, there have been remarkable clinical responses observed in a minority of patients with macroscopic disease treated with  $\alpha$ RPT, often after a limited clinical response to RPT with beta particle-emitting radionuclides (21,22). Reasons for this unanticipated clinical effectiveness may include immunological or abscopal factors, possibly in addition to absorbed dose contributions from diffusible alpha particle-emitting progeny.

The potential use of combined modality approaches with RPT is particularly compelling for XRT. RPT toxicities are typically systemic or off-target whereas XRT toxicities are local and determined by nearby tissues at risk. RPT is ideal for disseminated microscopic disease and tumor imageability is not essential for effective targeting. In contrast, XRT is ideal for macroscopic disease and tumor imageability is essential for effective targeting. Moreover, RPT and XRT are similar in that they are both based on ionizing radiation, have comparable tissue dose tolerances, and can be described by the same radiobiological models and parameters. Although many clinical scenarios may be suitable for this combined modality approach, a particularly obvious “low-hanging fruit” is oligometastatic prostate cancer with likely microscopic dissemination. Clinical studies featuring this approach are ongoing (23) .

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