Nuclear Medicine and Biology xxx (xxxx) 1–3

Contents lists available at ScienceDirect

Nuclear Medicine and Biology

journal homepage: http://ees.elsevier.com

Applying radiobiology to clinical molecular radiotherapy

Iain Murray *, Glenn Flux

Joint Department of Physics, The Royal Marsden NHS Foundation Trust and Institute of Cancer Research, Sutton, Surrey SM2 5PT, United Kingdom

ARTICLE INFO

Article history:
Received 22 January 2021
Received in revised form 12 May 2021
Accepted 16 May 2021
Available online xxx

The aim of radiation therapy, including molecular radiotherapy (MRT), is to maximise the biological damage to a target tissue, most commonly malignant cancer cells, whilst minimising the damage to healthy organs. Physics, chemistry and biology all have a role to play in achieving this aim. Appropriate selection and development of the radiopharmaceutical will result in preferential uptake of radioactivity within a specific biological target, but little retention in healthy organs. Imaging enables *in-vivo* verification that this has been achieved at the pre-clinical development stage or for individual patients in the clinic. Quantification of those images is the first step in calculating radiation absorbed doses delivered to both target cells and normal organs. The second step is to model the deposition of energy from distributions of radioactivity, either by bespoke Monte Carlo simulation, convolution of a dose point kernel or application of reference dose-factors which describe radiation transport within a reference geometry [1–4].

Estimates of radiation absorbed doses are key to understanding the likely impact of treatments for which radiation is the primary driver of biological response. The biological response to radiation can be modulated by physical and biological factors. Pre-clinical investigations are critical to the understanding of various factors that impact clinical efficacy of a new radiotherapeutic and can inform initial treatment protocols, saving unnecessary and costly clinical studies.

It has long been understood that the rate at which radiation is delivered has a differential effect on cancer tissues and normal tissues [5]. As a result, a total prescribed dose of external beam radiotherapy (EBRT) is usually delivered in a series of daily fractions over a period of weeks. Development of the linear quadratic (LQ) model of cell death alongside the frameworks of the biologically effective dose (BED) and equivalent 2 Gy fraction dose (EQD2) has allowed the comparison of different fractionation schemes [6,7]. It is worth noting that the LQ model does not describe all aspects of EBRT radiobiology, for example the FLASH phenomenon where delivery of EBRT doses over milliseconds rather than minutes appears to lead to normal tissue sparing [8]. Nonetheless as MRT results in the continuous delivery of exponentially decreasing levels of radiation, it can be considered within the LQ framework as the delivery of infinitely small fractions of radiation and infinitely small intervals. Consequently, extensions of the LQ model have been developed specifically for MRT in order to allow comparison of doses delivered at differing dose-rates [9,10]. This is particularly useful in for MRT since inter-patient pharmacokinetics will lead to inter-patient differences in both absorbed doses and dose-rate within the same normal organs. For example, in the case of 18 patients treated with [^{90}Y]Y-DOTA-TOC, the kidney BED was shown to have a higher correlation with renal toxicity than the absorbed dose alone [11]. These data were further analysed within MIRD pamphlet 20 alongside data from an additional 25 patients who also received [^{90}Y]Y-DOTA-TOC [12]. The authors compared normal tissue complication probabilities (NTCP) in these cohorts as a function of BED and found them to match those derived from patients undergoing EBRT. Hence it could be concluded that the same radiobiological model predicted the effect of both EBRT and MRT in relation to renal toxicity. However, the same analysis applied to patients treated with [^{177}Lu]Lu-DOTA-TATE has demonstrated an increased renal tolerance to radiation [13]. An explanation for this was provided by *ex-vivo* autoradiography studies which demonstrated significant heterogeneity of [^{111}In]In-DTPA-octreotide within kidney tissue [14]. Simulated absorbed dose distributions of ^{90}Y from these data were relatively uniform due to the longer length of ^{90}Y beta particles. Simulated ^{177}Lu absorbed dose distributions matched the underlying heterogeneity of the radiopharmaceutical distribution due to much smaller beta particle path lengths. However, SPECT imaging cannot measure such heterogeneities due to their limited spatial resolution. Therefore it could be concluded that the effect of absorbed dose heterogeneity was to modulate the apparent response to radiation doses that were measured on a macroscopic scale. Equally, analysis of hepatocarcinoma and metastatic colorectal cancer patients treated with ^{90}Y microspheres have demonstrated apparent tumour radiosensitivities lower than those observed in response to EBRT [15–17]. Again, heterogeneity at a microscopic level has been proposed as an explanation

* Corresponding author.
E-mail address: iain.murray@icr.ac.uk (I. Murray)

https://doi.org/10.1016/j.nucmedbio.2021.05.005
0969-8051/© 2021.

for this observation. Although models have been proposed to incorporate the effect of dose non-uniformity, [18,19] quantitative measurements may be beyond the spatial resolution of gamma camera imaging.

Therefore, the development of both alpha particle [20] and Auger electron [21] emitting radiotherapeutics provides new challenges with respect to establishing and understanding a dose-response relationship. Both alpha particles and Auger electrons have a high linear energy transfer (LET) and consequently deposit their energy over micrometre and nanometre ranges respectively, compared to the millimetre range associated with beta particles. Hence, heterogeneity of uptake will result in heterogeneous radiation dose distributions. For Auger electron emitters in particular, knowledge of their localisation within the cell is critical to prediction of the absorbed dose delivered to the cell nucleus. Models describing the deposition of energy to particular cell compartments have been published [22,23].

Heterogeneity is not always taken into account in clinical dosimetry. For example, in the case of the alpha emitter [^{223}Ra]$RaCl_2$ the distribution of activity within bone tissue is assumed to be concentrated within the endosteal layer rather than uniformly throughout the entire bone volume [24]. However, recent publications describing the clinical dosimetry of ^{223}Ra have assumed a uniform distribution of activity within prostate cancer bone metastases and have reported the mean absorbed dose to the entire lesion volume [25,26]. Such an approach also potentially overlooks the stochastic nature of energy deposition at the microscopic scale for high LET particles emitted by highly localised radionuclides. In such scenarios, energy deposition in target cells is better described by probability density functions rather than a single discrete value [27,28]. However, application of these stochastic models demonstrate that as the number of emitted particles increases, the relative deviation around the average specific energy will decrease, such that a macroscopic description using absorbed dose will suffice [27]. This has been demonstrated at the *in-vitro* level [29] and thus may indicate why the ^{223}Ra macroscopic absorbed doses to bone metastases correlate with reported lesion response [25].

Classical microdosimetry models only describe the deposition of energy to a biological target. The radiobiology of short range radiation such as alpha particles or Auger electrons is further complicated by the knowledge that cellular response to radiation is not limited to direct effects [30]. The bystander effect is an umbrella term for the phenomenon whereby irradiation of a single cell can induce cell death in neighbouring cells, either *via* direct cell to cell communication or *via* the release of soluble factors [31] and is not exclusive to alpha particles and Auger electrons. The effect is distinct from the crossfire effect which describes the irradiation from targeted cells to non-targeted cells. Bystander effects have been demonstrated in response to EBRT as well as alpha, beta an Auger electron therapy [31,32]. However, for high LET radiation it is possible that this biological effect will extend beyond the range of radiation with a path length of the order of a cell diameter (or less) and may therefore compensate for heterogeneity of uptake in the absence of a crossfire effect. A number of mathematical models of the bystander effect have been developed [33–35] but overall the clinical relevance is not well understood. Furthermore the immune response is thought to be the biological mechanism behind the abscopal effect whereby EBRT is observed to elicit a response beyond the irradiated volume [36,37]. Whilst mathematical models describing the synergy between immunotherapy and radiotherapy have been developed [38] the relevance of this phenomenon to systemically administered MRT is also unclear.

High LET particles also have a higher relative biological effectiveness (RBE), defined as the ratio of low LET absorbed dose compared to the high LET absorbed dose required to achieve a defined biological endpoint [39]. RBE values for alpha particles have typically been found to have a value between 3 and 5 *in-vitro* [40]. In the absence of human *in-vivo* data a value of 5 is normally assumed [41]. The LQ framework has been extended to alpha particles in order to incorporate RBE into the calculation of both the BED [9,42] and the EQ2D [43]. Thus predictions of efficacy or toxicity can be made using tissue radiosensitivity parameters derived from EBRT data. Such calculations were recently applied in a study by Belli et al. of dose to the salivary glands and the probability of xerostomia in metastatic castrate resistant prostate cancer patients treated with the alpha emitter [^{225}Ac]Ac-PSMA-617 [44]. (Salivary glands express PSMA and are therefore known to be organs at risk in these treatments.) The authors simulated potential [^{225}Ac]Ac-PSMA-617 absorbed doses by converting dosimetry data acquired in a cohort of patients undergoing [^{177}Lu]Lu-PSMA-617 treatment. Absorbed doses were converted to both BED and EQ2D and used to predict NTCP as a function of the administered activity of [^{225}Ac]Ac-PSMA-617. The authors then compared these predictions to recorded observed instances of xerostomia in a separate cohort of patients treated with [^{225}Ac]Ac-PSMA-617 (but lacking dosimetry data). They noted a significant difference between predictions of xerostomia based on the LQ formalism and those observed clinically. As the authors themselves suggested, this discrepancy could be due to a lack of consideration of absorbed dose heterogeneity within the salivary glands as well as uncertainty around the value of the RBE.

Finally it should be noted that the LQ model is a mechanistic model of radiation damage and does not take into account the tumour microenvironment or systemic reactions. Over the past twenty years the field of radiobiology has been revitalised by a succession of new discoveries and observations [45]. The biochemical response of cells exposed to radiation damage is increasingly well understood, resulting in a new generation of radiation sensitizers. For example, Olaparib is an inhibitor of PARP-1, a DNA damage sensor protein associated with DNA repair [46]. Preclinical investigations of radiation sensitizers in combination with molecular radiotherapy have demonstrated encouraging efficacy regarding the treatment of cancer cells [47]. When combined with EBRT the potential for increased radiation sensitivity and toxicity in normal organs has been noted [48]. It would seem prudent to assume the same could be true in MRT. Therefore as clinical trials of radiation sensitizers in combination with molecular radiotherapy are developed, further modulations to existing radiobiological models are likely to be required.

In summary, initial applications of radiobiological modelling to [^{90}Y]Y-DOTA-TOC therapy suggested that models developed for EBRT could be applied to MRT. This is an attractive proposition due to the considerable body of literature describing the response of both normal organs and tumour tissue in EBRT [49,50]. As new therapeutic modalities such as targeted alpha therapies are introduced, a common radiobiological framework would allow fair comparison of alternative strategies. However, it has been demonstrated that even for lower energy beta emitters such as ^{177}Lu, deviations from uniform dose deposition within tissue will result in apparently different radiosensitivities to those predicted. Strategies to model heterogeneity beyond the spatial resolution of gamma camera imaging have been proposed. Digital autoradiography performed on *ex-vivo* samples can be used to relate the mean absorbed dose within an organ to the absorbed dose within a particular sub-volume of interest [41]. A drawback of such an approach is that the same model would need to be applicable to a population and would result in a systematic shift in measured doses. Alternatively, kinetic modelling of radiopharmaceuticals has been proposed as a means of inferring time activity curves within sub volumes of tissue [41,51].

As clinical trials of new MRT strategies are developed, it is important that adequate dosimetry is conducted. In order to understand and inform the modulations to current radiobiological models that are required to address the issues raised in this commentary, dosimetry metrics relating to individual outcomes need to be collected. In the first instance they can be used to test dose-response relationships predicted by pre-clinical radiobiology. When discrepancies between predicted and observed outcomes occur, the same data can be used to refine the models and further the development of clinical protocols that fully realise the potential of this treatment modality.

References

[1] W.E. Bolch The Monte Carlo method in nuclear medicine: current uses and future potential. J Nucl Med 2010;51:337–339.

[2] W.E. Bolch, L.G. Bouchet, J.S. Robertson, B.W. Wessels, J.A. Siegel, R.W. Howell, et al. MIRD pamphlet no. 17: the dosimetry of nonuniform activity distributions - radionuclide S values at the voxel level. J Nucl Med 1999;40:11S–36S.
[3] L.G. Bouchet, W.E. Bolch, H.P. Blanco, B.W. Wessels, J.A. Siegel, D.A. Rajon, et al. MIRD pamphlet no. 19: absorbed fractions and radionuclide S values for six age-dependent multiregion models of the kidney. J Nucl Med 2003;44:1113–1147.
[4] P.B. Zanzonico Internal radionuclide radiation dosimetry: a review of basic concepts and recent developments. J Nucl Med 2000;41:297–308.
[5] U. Fano, L.D. Marinelli Note on the time-intensity factor in radiobiology. Proc Natl Acad Sci U S A 1943;29:59–66.
[6] Eric J. Hall Radiobiology for the radiologist. Philadelphia: Lippincott; 1994.
[7] Radiobiological considerationsJ ICRU13201389104
[8] J.D. Wilson, E.M. Hammond, G.S. Higgins, K. Petersson Ultra-high dose rate (FLASH) radiotherapy: silver bullet or fool's gold? Front Oncol 2019;9:1563.
[9] R. Dale, A. Carabe-Fernandez The radiobiology of conventional radiotherapy and its application to radionuclide therapy. Cancer Biother Radiopharm 2005;20:47–51.
[10] R.G. Dale The application of the linear-quadratic dose-effect equation to fractionated and protracted radiotherapy. Br J Radiol 1985;58:515–528.
[11] R. Barone, F.O. Borson-Chazot, R. Valkerna, S. Walrand, F. Chauvin, L. Gogou, et al. Patient-specific Dosimetry in predicting renal toxicity with Y-90-DOTATOC: relevance of kidney volume and dose rate in finding a dose-effect relationship. J Nucl Med 2005;46:99S–106S.
[12] B.W. Wessels, M.W. Konijnenberg, R.G. Dale, H.B. Breitz, M. Cremonesis, R.F. Meredith, et al. MIRD pamphlet no. 20: the effect of model assumptions on kidney dosimetry and response-implications for radionuclide therapy. J Nucl Med 2008;49:1884–1899.
[13] M. Cremonesi, M.E. Ferrari, L. Bodei, C. Chiesa, A. Sarnelli, C. Garibaldi, et al. Correlation of dose with toxicity and tumour response to (90)Y- and (177)Lu-PRRT provides the basis for optimization through individualized treatment planning. Eur J Nucl Med Mol Imaging 2018;45:2426–2441.
[14] M. Konijnenberg, M. Melis, R. Valkema, E. Krenning, M. de Jong Radiation dose distribution in human kidneys by octreotides in peptide receptor radionuclide therapy. J Nucl Med 2007;48:134–142.
[15] C. Chiesa, M. Mira, M. Maccauro, C. Spreafico, R. Romito, C. Morosi, et al. Radioembolization of hepatocarcinoma with Y-90 glass microspheres: development of an individualized treatment planning strategy based on dosimetry and radiobiology. Eur J Nucl Med Mol Imaging 2015;42:1718–1738.
[16] Y.K. Dewaraja, T. Devasia, R.K. Kaza, J.K. Mikell, D. Owen, P.L. Roberson, et al. Prediction of tumor control in (90)Y radioembolization by logit models with PET/CT-based dose metrics. J Nucl Med 2020;61:104–111.
[17] E.M. Abbott, N. Falzone, B.Q. Lee, C. Kartsonaki, H. Winter, T.A. Greenhalgh, et al. The impact of radiobiologically informed dose prescription on the clinical benefit of Y-90 SIRT in colorectal cancer patients. J Nucl Med 2020;61:1658–1664.
[18] Y.K. Dewaraja, M.J. Schipper, P.L. Roberson, S.J. Wilderman, H. Amro, D.D. Regan, et al. I-131-Tositumomab radioimmunotherapy: initial tumor dose-response results using 3-dimensional dosimetry including radiobiologic modeling. J Nucl Med 2010;51:1155–1162.
[19] J.A. O'Donoghue Implications of nonuniform tumor doses for radioimmunotherapy. J Nucl Med 1999;40:1337–1341.
[20] H. Jadvar Targeted alpha-therapy in cancer management: synopsis of preclinical and clinical studies. Cancer Biother Radiopharm 2020;35:475–484.
[21] A. Ku, V.J. Facca, Z. Cai, R.M. Reilly Auger electrons for cancer therapy - a review. EJNMMI Radiopharm Chem 2019;4:27.
[22] S.M. Goddu MIRD Cellular S-values: Self-abosorbed Dose Per Unit Cumulated Activity for Selected Radionuclides and Monoenergetic Electron and Alpha Particle Emitters Incorporated Into Different Cell Compartments. Society of Nuclear Medicine; 1997.
[23] E.L. Rojas-Calderon, O. Avila, G. Ferro-Flores Monte Carlo calculations of the cellular S-values for alpha-particle-emitting radionuclides incorporated into the nuclei of cancer cells of the MDA-MB231, MCF7 and PC3 lines. Appl Radiat Isot 2018;135:1–6.
[24] R.F. Hobbs, H. Song, C.J. Watchman, W.E. Bolch, A.K. Aksnes, T. Ramdahl, et al. A bone marrow toxicity model for (2)(2)(3)Ra alpha-emitter radiopharmaceutical therapy. Phys Med Biol 2012;57:3207–3222.
[25] I. Murray, S.J. Chittenden, A.M. Denis-Bacelar, C. Hindorf, C.C. Parker, S. Chua, et al. The potential of Ra-223 and F-18-fluoride imaging to predict bone lesion response to treatment with Ra-223-dichloride in castration-resistant prostate cancer. Eur J Nucl Med Mol Imaging 2017;44:1832–1844.
[26] M. Pacilio, G. Ventroni, G. De Vincentis, B. Cassano, R. Pellegrini, E. Di Castro, et al. Dosimetry of bone metastases in targeted radionuclide therapy with alpha-emitting Ra-223-dichloride. Eur J Nucl Med Mol Imaging 2016;43:21–33.
[27] W. Hofmann, W.B. Li, W. Friedland, B.W. Miller, B. Madas, M. Bardies, et al. Internal microdosimetry of alpha-emitting radionuclides. Radiat Environ Biophys 2020;59:29–62.
[28] J. Booz, L. Braby, J. Coyne, P. Kliauga, L. Lindborg, H.-G. Menzel, et al. Report 36. J Int Commission Radiat Units Meas 2016. [os19:NP-NP].
[29] N. Chouin, K. Bernardeau, M. Bardies, A. Faivre-Chauvet, M. Bourgeois, C. Apostolidis, et al. Evidence of extranuclear cell sensitivity to alpha-particle radiation using a microdosimetric model. II. Application of the microdosimetric model to experimental results. Radiat Res 2009;171:664–673.
[30] D. Murray, A.J. McEwan Radiobiology of systemic radiation therapy. Cancer Biother Radiopharm 2007;22:1–23.
[31] K.M. Prise, J.M. O'Sullivan Radiation-induced bystander signalling in cancer therapy. Nat Rev Cancer 2009;9:351–360.
[32] M. Boyd, S.C. Ross, J. Dorrens, N.E. Fullerton, K.W. Tan, M.R. Zalutsky, et al. Radiation-induced biologic bystander effect elicited in vitro by targeted radiopharmaceuticals labeled with alpha-, beta-, and auger electron-emitting radionuclides. J Nucl Med 2006;47:1007–1015.
[33] M.A. Ebert, N. Suchowerska, M.A. Jackson, D.R. McKenzie A mathematical framework for separating the direct and bystander components of cellular radiation response. Acta Oncol 2010;49:1334–1343.
[34] S.J. McMahon, K.T. Butterworth, C.K. McGarry, C. Trainor, J.M. O'Sullivan, A.R. Hounsell, et al. A computational model of cellular response to modulated radiation fields. Int J Radiat Oncol Biol Phys 2012;84:250–256.
[35] S.J. McMahon, K.T. Butterworth, C. Trainor, C.K. McGarry, J.M. O'Sullivan, G. Schettino, et al. A kinetic-based model of radiation-induced intercellular signalling. PLoS One 2013;8:e54526.
[36] S. Demaria, S.C. Formenti Radiation as an immunological adjuvant: current evidence on dose and fractionation. Front Oncol 2012;2:153.
[37] S.J. Gandhi, A.J. Minn, R.H. Vonderheide, E.J. Wherry, S.M. Hahn, A. Maity Awakening the immune system with radiation: optimal dose and fractionation. Cancer Lett 2015;368:185–190.
[38] R. Serre, S. Benzekry, L. Padovani, C. Meille, N. Andre, J. Ciccolini, et al. Mathematical modeling of cancer immunotherapy and its synergy with radiotherapy. Cancer Res 2016;76:4931–4940.
[39] S.J. McMahon, K.M. Prise Mechanistic modelling of radiation responses. Cancers (Basel) 2019;11.
[40] L.E. Feinendegen, J.J. McClure Meeting report - alpha-emitters for medical therapy - Workshop of the United States Department of Energy - Denver, Colorado, May 30-31, 1996. Radiat Res 1997;148:195–201.
[41] G. Sgouros Dosimetry, radiobiology and synthetic lethality: radiopharmaceutical therapy (RPT) with alpha-particle-emitters. Semin Nucl Med 2020;50:124–132.
[42] R.G. Dale, B. Jones The assessment of RBE effects using the concept of biologically effective dose. Int J Radiat Oncol Biol Phys 1999;43:639–645.
[43] R.F. Hobbs, R.W. Howell, H. Song, S. Baechler, G. Sgouros Redefining relative biological effectiveness in the context of the EQDX formalism: implications for alpha-particle emitter therapy. Radiat Res 2014;181:90–98.
[44] M.L. Belli, A. Sarnelli, E. Mezzenga, F. Cesarini, P. Caroli, V. Di Iorio, et al. Targeted alpha therapy in mCRPC (metastatic castration-resistant prostate cancer) patients: predictive dosimetry and toxicity modeling of Ac-225-PSMA (prostate-specific membrane antigen). Front Oncol 2020;10.
[45] J.P. Pouget, C. Lozza, E. Deshayes, V. Boudousq, I. Navarro-Teulon Introduction to radiobiology of targeted radionuclide therapy. Front Med (Lausanne) 2015;2:12.
[46] M.J. O'Connor Targeting the DNA damage response in cancer. Mol Cell 2015;60:547–560.
[47] D.L. Nile, C. Rae, I.J. Hyndman, M.N. Gaze, R.J. Mairs An evaluation in vitro of PARP-1 inhibitors, rucaparib and olaparib, as radiosensitisers for the treatment of neuroblastoma. BMC Cancer 2016;16:13.
[48] L.M. Lourenco, Y.Y. Jiang, N. Drobnitzky, M. Green, F. Cahill, A. Patel, et al. PARP inhibition combined with thoracic irradiation exacerbates esophageal and skin toxicity in C57BL6 mice. Int J Radiat Oncol Biol Phys 2018;100:767–775.
[49] C.M. van Leeuwen, A.L. Oei, J. Crezee, A. Bel, N.A.P. Franken, L.J.A. Stalpers, et al. The alfa and beta of tumours: a review of parameters of the linear-quadratic model, derived from clinical radiotherapy studies. Radiat Oncol 2018;13.
[50] L.B. Marks, R.K. Ten Haken, M.K. Martel Guest editor's introduction to QUANTEC: a users guide. Int J Radiat Oncol Biol Phys 2010;76:S1–S2.
[51] J. Taprogge, I. Murray, J. Gear, S.J. Chittenden, C.C. Parker, G.D. Flux Compartmental model for Ra-223-dichloride in patients with metastatic bone disease from castration-resistant prostate cancer. Int J Radiat Oncol Biol Phys 2019;105:884–892.