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EDITORIAL COMMENTARY

Defining the role for dosimetry and radiobiology in combination therapies

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The potential of combination therapies has long been recognized, and surgery, external beam radiotherapy (EBRT) and chemotherapy are often associated to maximize the probability of curative treatment. Molecular radiotherapy (MRT) is an attractive option as it combines the tumoricidal effect of EBRT with systemic therapy. The recent article by Ferrari et al. shows that MRT can play a key role in an overall cancer management strategy, particularly if radiopharmaceutical administration is personalized according to the absorbed dose delivered and if radiobiological considerations are taken into account [1].

The combination of surgery with radiotherapy has proven to be highly successful, not only for EBRT treatments but also for the ablation of thyroid remnants with radioiodine. IART® achieves specificity with a combination of targeting via avidin/biotin affinity and locoregional administration in the tumour bed following surgical excision. The multimodality approach is completed with subsequent irradiation with EBRT, which also targets the tumour bed, but for which normal tissues at risk differ.

Ferrari et al. [1] rightly raise the issue of standards, an area that has been overlooked in MRT. Whilst there are a number of guidelines emerging for quantitative imaging and dosimetry, these have yet to be accepted as standards. A brief review of the literature will readily show a large variation in image acquisition and processing procedures, as well as in the levels and frequency with which activity is administered. This indicates the critical need for the community to gather and report evidence from which standards for all aspects of treatment can be formulated [2]. This is a daunting challenge as, in contrast to the situation for EBRT, there are few centres that treat large numbers of patients. To conduct the clinical trials necessary to define these standards and to develop evidence-based protocols, close collaboration between European centres is therefore required along with significant support. This becomes an even greater challenge for combined modality therapies.

Overly sophisticated dosimetry is not always necessary. Although there is a growing tendency to evaluate three-dimensional distributions of absorbed dose as long-awaited software becomes available, this article demonstrates that when uptake is reasonably uniform over the target volume the calculation of a mean absorbed dose is sufficient to give a biologically meaningful result. The range of treatment regimens followed requires dosimetry methods of varying complexity. Correlations between absorbed dose and clinical effect have been demonstrated both for relatively simple and for more refined imaging and dosimetry procedures. Barone et al. [3] demonstrated a correlation between the biologically effective dose and kidney toxicity using sequential ^{86}Y PET imaging, target volumes derived from pretherapy CT scans and linear quadratic modelling to obtain radiobiological parameters. Conversely, Buckley et al. [4] found a correlation between the whole-body absorbed dose and marrow toxicity using only a series of external dose rate measurements. Such results are likely to impact patient management as personalized treatment emerges to replace current population-based approaches.

For the purposes of radiation protection, as well as to optimize treatment, calculation of the absorbed doses delivered from MRT is essential. If the patient subsequently undergoes EBRT, dosimetry should be assessed for both modalities. However, this alone is not sufficient. As dose

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rates and particle energies are significantly different for the two treatments, radiobiological parameters are also of critical importance, for example to enable comparisons between the absorbed dose delivered from a decaying internal source of radiation and that delivered in 2-Gy fractions [5]. This is also extremely relevant in the context of MRT with radionuclide cocktails [6].

Radiobiology has been 'rediscovered' after falling out of fashion for almost 20 years, and concepts initially developed for EBRT are now being applied to MRT [7]. Radiobiology effectively consists of two aspects – that of mathematical modelling, generally based on the linear quadratic model, and biologically orientated experiments to examine the effect of radiation on tissue. The translation of models from one modality to another should come with a strong caveat. Parameters including the biologically effective dose and equivalent uniform dose were developed primarily for EBRT [8, 9], where the distribution of an absorbed dose across a target volume should vary by no more than 95–107 % [10]. Whilst used in this study for small volumes of relatively uniform uptake, further study of the relevance of these models to larger volumes containing 'cold spots', possibly related to hypoxia, is warranted. These parameters are seldom considered in EBRT although they are necessary if radiotherapy treatments are combined. Tumour control probability (TCP) models could also be of importance. These are arguably the endpoint for dosimetry calculations as they directly predict outcome. Nahum [11] performed calculations for various radionuclides and sphere sizes to generate iso-TCP curves, incorporating interpatient variations in radiosensitivity. Normal tissue complication probability models are also used in EBRT, but have yet to be studied for MRT.

The article by Ferrari et al. draws attention to issues critical to the current status and future potential of MRT and follows increasing investigation of the combination of radiation potentiators with radiopharmaceutical therapy [12, 13]. Administration protocols must be carefully selected to ensure the delivery of the maximum absorbed dose to the target whilst minimizing the absorbed doses delivered to normal organs, as has been routinely accepted in EBRT for many decades. The absorbed doses delivered to individual patients must be calculated with the most suitable imaging and dosimetry methods and the biological implications of these calculations should be investigated. This will provide the foundation to advance from a current 'one-size-fits-all' approach to highly personalized treatment. The full potential of MRT to treat cancer will then be realized and, as is shown by Ferrari et al. [1], it can take its place within an overall management strategy alongside surgery, EBRT and chemotherapy.

References

1. Ferrari ME, Cremonesi M, Di Dia A, Botta F, De Cicco C, Sarnelli A, et al. 3D dosimetry in patients with early breast cancer undergoing Intraoperative Avidination for Radionuclide Therapy (IART®) combined with external beam radiation therapy. Eur J Nucl Med Mol Imaging. 39(11):1702–11. doi:10.1007/s00259-012-2197-6.
2. Lassmann M, Chiesa C, Flux G, Bardiès M. EANM Dosimetry Committee Guidance Document: good practice of clinical dosimetry reporting. Eur J Nucl Med Mol Imaging. 2011;38(1):192–200.
3. Barone R, Borson-Chazot F, Valkema R, Walrand S, Chauvin F, Gogou L, et al. Patient-specific dosimetry in predicting renal toxicity with (90)Y-DOTATOC: relevance of kidney volume and dose rate in finding a dose-effect relationship. J Nucl Med. 2005;46:99S–106.
4. Buckley SE, Chittenden SJ, Saran FH, Meller ST, Flux GD. Whole-body dosimetry for individualized treatment planning of 131I-MIBG radionuclide therapy for neuroblastoma. J Nucl Med. 2009;50(9):1518–24.
5. Bodey RK, Flux GD, Evans PM. Application of the linear-quadratic model to combined modality radiotherapy. Int J Radiat Oncol Biol Phys. 2004;59:228–41.
6. Savolainen S, Konijnenberg M, Bardiès M, Lassmann M, Strigari L, Chiesa C, et al. Radiation dosimetry is a necessary ingredient for a perfectly mixed molecular radiotherapy cocktail. Eur J Nucl Med Mol Imaging. 2012;39(3):548–9.
7. Pouget JP, Navarro-Teulon I, Bardiès M, Chouin N, Cartron G, Pèlegrin A, et al. Clinical radioimmunotherapy – the role of radiobiology. Nat Rev Clin Oncol. 2011;8(12):720–34.
8. Niemierko A. Reporting and analyzing dose distributions: a concept of equivalent uniform dose. Med Phys. 1997;24(1):103–10.
9. Fowler J. 21 years of biologically effective dose. Br J Radiol. 2010;83:554–68.
10. International Commission on Radiation Units and Measurements. Prescribing, recording and reporting photon beam therapy. Report 50. Washington: ICRU; 1993.
11. Nahum AE. Microdosimetry and radiocurability: modelling targeted therapy with β-emitters. Phys Med Biol. 1996;41:1957–72.
12. Gaze MN, Chang YC, Flux GD, Mairs RJ, Saran FH, Meller ST. Feasibility of dosimetry-based high-dose 131I-meta-iodobenzylguanidine with topotecan as a radiosensitiser in children with metastatic neuroblastoma. Cancer Biother Radiopharm. 2005;20(2):195–9.
13. Morris MJ, Pandit-Taskar N, Carrasquillo J, et al. Phase I study of samarium-153 lexidronam with docetaxel in castration resistant metastatic prostate cancer. J Clin Oncol. 2009;27:2436–42.