Eur J Nucl Med Mol Imaging (2014) 41:1–3
DOI 10.1007/s00259-013-2589-2

EDITORIAL

Biting the magic bullet: celebrating a decade of the EANM Dosimetry Committee

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Published online: 7 November 2013

In 1946 Seidlin et al. [1] treated metastatic thyroid cancer with a 'cocktail' of 3,774 MBq ^{130}I and 759 MBq ^{131}I in several fractions. Pretherapy tracer studies were performed to identify iodine-avid lesions, and the cumulative absorbed doses delivered to both the tumour and to the blood were determined from measurements with a Geiger counter and specific lesion mass estimates. Extensive scanning was performed with the aim that radioiodine therapy would continue for as long as there was visible uptake. Biomarkers of response were measured to establish that while the leucocyte count from administration from ^{130}I was temporarily depressed, there was no significant effect from ^{131}I. Autoradiography of a biopsy sample showed that the radioiodine localized in tumour cells. The patient was reported to have a good response.

Radioiodine therapy has proven highly successful in the ablation of thyroid remnants. This has helped to perpetuate the illusion that a successful cancer treatment is simply a matter of identifying the 'magic bullet'. Unfortunately this is not the case for other cancers and still remains untrue for high-risk thyroid cancer. The scientific method, as applied in that first study, subsequently became largely lost.

Even by 1953 Rawson et al. [2] remarked that 'Some of our earlier attempts to treat metastatic cancer of the thyroid with radioactive iodine were without therapeutic effect. This was true probably because we were satisfied with minimal, even poor, uptake of the isotope by the metastatic lesions' and that 'Unfortunately, …patients have been treated empirically with frequent comparatively small doses of radioactive iodine by the calendar rather than by considerations of the capacity of such tumors to concentrate radioiodine or of the radiosensitivity of the tumors.'

An increasing number of therapeutic radiopharmaceuticals have been introduced to the clinic to treat a range of diseases, although little has changed in the half century since that publication with regard to the rationale underlying methods of administration. In particular, the single most important factor governing response to any form of radiotherapy—the absorbed doses delivered to tumours and to normal organs—is almost universally ignored.

The Dosimetry Task Group, which subsequently became a committee of the EANM, was formed in 2001 at the behest of the former EANM president, Dr Wolfgang Becker.

In the last decade much has been accomplished:

- Teaching courses have been initiated at the EANM in Vienna on both basic dosimetry and therapy (in close collaboration with the Therapy Committee) and on advanced dosimetry techniques (mainly for physicists). Numerous lectures are given throughout Europe each year for national societies and for the European School of Nuclear Medicine. In addition, a curriculum for education and training of medical physicists in nuclear medicine has been developed in collaboration with European Federation of Organisations in Medical Physics [3], the umbrella organization for medical physics in Europe. Among other subjects this curriculum addresses the necessary training for dosimetry used for image-guided radionuclide therapy, molecular radiotherapy (MRT).
- Guidelines for dosimetry have been generated [4–9] and are regularly updated to match the needs of the community.
- The Paediatric Dosage Card [5, 6], formulated in collaboration with the Paediatric Committee of the EANM, has been widely used and is under revision to

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account for evolution in the field of paediatric imaging. The associated iApp has been downloaded more than 600 times, and an android version is in preparation.

- Four International Symposia of Targeted Radionuclide Therapy and Dosimetry (iSTARD) were organized between 2004 and 2012 in collaboration with the SNM MIRD and RADAR committees; three of them as separate tracks within the annual congress of the EANM [10–12].

The 10th anniversary of the Dosimetry Committee was marked by the 4th iSTARD meeting. The overwhelming success of this meeting was an indication of the rapid and long overdue growth of internal dosimetry in the 21st Century. Almost 300 abstracts were submitted and 81 oral presentations were given. Sessions, held throughout the congress, had a regular attendance of over 300, with only PET/CT receiving greater participation as a category. This is in striking contrast to the earlier days of select meetings of the 'usual suspects'.

After many years of development and lobbying from physicists, nuclear medicine physicians and oncologists, the scene is now set for a paradigm shift in the treatment of cancer with radiopharmaceuticals. The clinical need for this is becoming increasingly evident.

There can be no doubt that response to treatment in any given patient is primarily dependent on the absorbed doses delivered to tumours and to organs at risk. Yet there is now ample evidence that administrations of fixed activities, albeit modified according to patient weight or body surface area, deliver a range of absorbed doses that can vary by orders of magnitude due to differences in patient biokinetics [13–15]. The inevitable implication is that population-based administrations, necessarily governed by the most vulnerable of patients, will severely undertreat the majority. Routine application of patient-specific dosimetry would ensure that patients able to tolerate higher activities would receive higher absorbed tumour doses, whilst those potentially at risk would have administered activities mediated accordingly.

Accurate dosimetry requires more complex methods than have been the standard to date. Absorbed dose calculations based on planar data, under the assumptions that all patients have identical organ geometry and retention, without corrections for attenuation or scatter, will yield poor results that do not correlate with outcome. Significant advances in personalized dosimetry must now translate to routine practice. For example, Monte Carlo simulations, as used for external beam radiotherapy, can now accurately characterize PET and SPECT cameras to enable activity quantification in vivo and can determine the biodistribution of absorbed doses on a patient-specific basis [16, 17]. Three-dimensional dosimetry, developed over 20 years ago, is necessary to evaluate absorbed dose distributions and can now be determined with academic and commercial software packages. Radiobiological modelling, long since accepted for external beam radiotherapy, is now being explored for MRT and offers significant clinical benefit [18].

Inevitably, this brings into question the issue of cost. Although there will be variations in local practice, the time taken to perform internal dosimetry is similar to that for an intensity-modulated radiation therapy (IMRT) plan. Compared with emerging commercial products for the treatment of bone metastases, liver cancer, neuroendocrine tumours and non-Hodgkin's lymphoma, the cost of accurate dosimetry is minimal and would be easily offset by the prevention of one or two unnecessary treatments each year. As remarked by Rawson et al., a radiopharmaceutical 'used for patients whose tumours concentrate so little of the isotope that a therapeutic effect is impossible' constitutes a 'misuse' [2].

A slow revolution has been underway that is now rapidly gaining momentum. In an era of converging disciplines, it is essential that the nuclear medicine community grasps this opportunity to stake its place in the front line of cancer treatment. There is a wealth of clinical opportunities to explore, including 'up-front' treatments, radiopharmaceutical cocktails and concomitant treatments with external beam radiotherapy or with chemotherapy agents, particularly where these may act as radiosensitizers.

There are many challenges ahead, as indicated by the current lack of national databases or guidelines concerning administrations and best practice. Academic led multicentre trials are critical to the development of this treatment, and will require a heightened degree of cooperation in the community, although the stage is surprisingly well set for this. Each year in Europe 100,000 patients are treated with radiopharmaceuticals [19]. In most countries a wide range of activities and radiopharmaceuticals are administered. This effectively constitutes a large-scale, multicentre, simultaneous phase I/II/III trial that would swiftly produce absorbed dose–response correlations that would radically transform clinical practice and would lead to significant clinical benefit. As a community we need only to collect and analyse the data.

With the increasing interest in imaging, dosimetry, and patient-specific treatment, the wheel has come full circle from where it started 70 years ago. Acceptance of MRT as a form of radiotherapy rather than chemotherapy will enable it to realize its full potential.

In the decade since the first and only survey of European practice [19] there have been significant advances in dosimetry-based MRT. The technology, the education, the will, and increasingly the perceived need exist to support a sea change in treatment strategies. There is no bullet with properties so magical that it would not benefit from the application of science.

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