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The Translation of Dosimetry into Clinical Practice: What It Takes to Make Dosimetry a Mandatory Part of Clinical Practice

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Nuclear medicine for therapeutic purposes, here termed molecular radiotherapy (MRT), is a rapidly developing field, mostly in the context of metastatic cancer treatment.

Within MRT, there is an ongoing debate on whether patient dosimetry has a role to play, either to optimize and personalize treatments or to meet regulatory requirements on radiation protection (*1*). In the European Union, EURATOM Directive 2013/59 mandates that "For all medical exposure of patients for radiotherapeutic purposes, exposures of target volumes shall be individually planned and their delivery appropriately verified taking into account that doses to non-target volumes and tissues shall be as low as reasonably achievable and consistent with the intended radiotherapeutic purpose of the exposure" (*1*). However, dosimetry is seldom implemented in clinical practice. The most recent and successful therapeutic radiopharmaceuticals introduced to the market have been approved with fixed activity posology and without a demand for posttherapeutic imaging, thereby effectively precluding the possibility to plan or verify the irradiation delivered. Dosimetry has generally been confined to early-phase trials and considered for only a small subset of patients. Furthermore, a recent survey (*2*) performed by the Special Interest Group for Radionuclide Internal Dosimetry of the European Federation of Organisations for Medical Physics highlighted that clinical dosimetry has tended to decrease when radiopharmaceuticals move from research to clinical routine. Nevertheless, there is increasing evidence for absorbed dose–effect relationships (*3*) that support the benefit of dosimetry for patients.

For example, [^{177}Lu]Lu-DOTATATE was granted marketing authorization for the treatment of patients with metastatic, progressive, well-differentiated somatostatin-receptor–positive gastroenteropancreatic neuroendocrine tumors. The basis for approval was the NETTER-1 trial, in which 116 patients received [^{177}Lu]Lu-DOTATATE (*4*). Only 20 patients underwent dosimetry. For normal tissues, the reported relative SDs were approximately 50%–100% of the mean. For tumors, the absorbed doses ranged from less than 10 Gy to more than 1,500 Gy (*5*), although there was no attempt to correlate these data with outcomes. Several articles have recently reported results on absorbed dose–effect relationships regarding both toxicity (*6*) and efficacy (*7*). Had such results been obtained from the NETTER-1 trial, there would now be a significant amount of data to inform the development of personalized treatment protocols.

It is self-evident that outcomes from cancer treatments based on the delivery of radiation are dependent on the level of radiation delivered. The continuing development of MRT stubbornly refuses to take individual patient dosimetry into account. There are several possible explanations for what, effectively, constitutes a willful blindness. First, with the exception of the treatment of thyroid pathologies with radioactive iodine, nuclear medicine has developed mainly as a diagnostic specialty in which fixed levels of radioactivity are administered, possibly adjusted by patient weight. Application of similar concepts to therapy has led to the common perception that MRT is a form of radioactive chemotherapy, for which imaging and dosimetry are not necessary. Second, regulatory agencies do not enforce patient-specific, dosimetry-based MRT development. Third, dosimetry is seldom reimbursed, and there is a lack of resources, both of trained staff and of infrastructure. Fourth, although dosimetry software solutions are now available, procedures for standardization of the clinical dosimetry workflow to ensure metrologic traceability are not yet in place. Finally, the pharmaceutical industry appears persistently reluctant to include investigations of dosimetry within clinical trials.

Although industry has not openly stated objections to dosimetry, it is probable that several issues may present a perceived impediment. Foremost is a lack of infrastructure and physics support within nuclear medicine departments, mirrored by a lack of radiation physics expertise within pharmaceutical companies. In stark contrast to external-beam radiotherapy, this precludes attempts at providing a comprehensive service or integrating dosimetry into product development. An additional impediment is the acknowledged lack of experience with the clinical impact of dosimetry in a therapeutic setting. This has understandably left a knowledge gap in how to implement dosimetry to maximize clinical benefit, such that dosimetry in clinical trials at present is reduced to an exercise in recordkeeping.

As MRT develops, a visionary reorganization of practice is required in which personalized dosimetry–guided drug delivery

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TABLE 1
Absorbed Dose–Guided Trials

Phase	Main aims of trial
1	Determination of side effects and maximum absorbed doses to regions at risk (absorbed-dose ranging)
2	Refinement of optimal absorbed doses to target regions and regions at risk, to balance treatment efficacy with risks of side effects
3	Comparison of treatment effectiveness and safety against standard of care, at therapeutic absorbed doses defined in previous trials
4	Postmarketing surveillance in public, to monitor long-term effects after administration of therapeutic absorbed doses

would be an important component. We would propose that dosimetry is incorporated into clinical trials to promote treatment optimization: this may be easily achieved by replacing the term *dose* by *absorbed dose,* according to its Système International d'Unités–derived definition (Table 1).

Trial outcomes would then indicate the levels of absorbed dose required to treat disease effectively and provide understanding of radiation-induced side effects (*8*). This would allow intensification of treatment for many patients or, conversely, reduction or interruption of treatment when there are safety concerns, thus facilitating risk–benefit balancing and justifying treatment exposure. Furthermore, the possibility to combine radiotherapeutic modalities, such as external-beam radiotherapy with α- and β-emitting radionuclides, could then be guided by the objective appraisal of the delivered radiation exposure. The inclusion of dosimetry during development of a new product would be a low-cost yet highly effective means to introduce informed treatments into clinical practice.

Widespread and routine implementation of dosimetry in MRT would have significant but uncertain financial implications. Although it is not the role of the pharmaceutical industry to support the missing infrastructure, this would nevertheless be needed at present with the lack of reimbursement. Further, it is likely that routine dosimetry, including pretherapy planning, would lead to seeking alternative treatment options earlier for patients who would not be expected to receive a clinically meaningful irradiation. Although this would impact short-term profits, the more clinically effective and cost-effective treatments could present stronger competition to established treatments.

So, will dosimetry be introduced on a large scale in MRT? Is it really happening?

In a recent meeting (*9*) organized by the Special Interest Group for Radionuclide Internal Dosimetry of the European Federation of Organisations for Medical Physics, more than 180 professionals gathered to discuss advances in the field, indicating that medical physicists are eager and ready to take on the challenge. Considerable efforts are being made to ensure the accuracy, metrologic traceability, and reproducibility of patient-specific dosimetry (*10*). Incorporation of artificial intelligence tools will enable further automation, standardization, and consistency (*11*).

Whilst awaiting the results of future dosimetry-guided clinical trials, the introduction of dosimetry into the routine clinical practice of existing procedures will continue to build the experience of effectiveness, enable follow-up of any treatment-related adverse events, and facilitate informed decision-making for repeated cycles. In addition to adhering to radiation-protection principles and regulations, this can yield only patient benefit in the longer term.

There are, no doubt, many challenges ahead, but as dosimetry becomes accepted into routine clinical practice, the increased infrastructure required will only benefit the field of nuclear medicine.

MRT presents the unique capability to follow the fate of the drug that is administered to the patient. This allows the calculation of an objective index, the absorbed dose, that provides a deeper understanding of the effects of the therapeutic procedure. This is too good an opportunity to miss. Our field is currently caught in a vicious circle. Insufficient evidence for clinical benefit of dosimetry has supported arguments against its implementation, which in turn have prevented the accumulation of evidence. It is time to change this vicious circle to a virtuous one: dosimetry implemented from the start of radiopharmaceutical development will accumulate results that can in turn be used to optimize patient management.

DISCLOSURE

Manuel Bardiès is currently supervising a PhD student sponsored by DOSIsoft and is a consultant advisor for Bain Capital and ITM. Katarina Sjögreen Gleisner is a consultant advisor for Immedica Pharma. No other potential conflict of interest relevant to this article was reported.

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