Dosimetry-based Treatment planning for Molecular Radiotherapy; a summary of the 2017 Report from the Internal Dosimetry Task Force

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Abstract

Background: The forthcoming European directive on basic safety standards (Council directive 2013/59 Euratom) mandates dosimetry-based treatment planning for radiopharmaceutical therapies. The aim of a report produced by the Internal Dosimetry Task Force of the European Association of Nuclear Medicine is to address this aspect of the directive. A summary of the report is presented.

Results and conclusions: A brief review of common therapy procedures is included, focused on the potential to perform patient specific dosimetry. Individualised treatment planning with tracer diagnostics and verification of the absorbed doses delivered following therapy is found to be scientifically feasible for almost all procedures investigated, using quantitative imaging and/or external monitoring. Translation of this directive into clinical practice will have significant implications for clinical practice and for resource requirements.

Introduction

Radiopharmaceuticals have been used for the treatment of various forms of cancer and benign diseases since the 1940s [1, 2]. The level of radioactivity administered is primarily fixed, sometimes adjusted by body weight, body surface area, or clinical factors. Prescription levels for different treatments are commonly determined empirically, using similar approaches as for chemotherapy. The term ‘molecular radiotherapy’ (MRT) has gained acceptance recent years to describe the use of radiotherapeutics informed by patient-specific absorbed dose calculations. Uniquely, for MRT the patient-specific biodistribution can be determined by in vivo nuclear medicine imaging of the radiopharmaceutical. Quantitative imaging of a tracer amount of either the radiopharmaceutical or of a companion diagnostic prior to therapy can enable the therapeutic administration to be chosen to achieve prescribed absorbed doses to
different tissues. Post therapy imaging enables the prescribed absorbed dose to be verified.

Recently the panel of mechanisms and targets for radiopharmaceuticals has increased significantly. Together with newly available radiotherapeutics this has raised greater awareness of the field of molecular radiotherapy, and in combination with technical developments has also rekindled the interest for patient specific dosimetry in research settings and in clinical practice.

The forthcoming European Council directive 2013/59/Euratom mandates the use of dosimetry for treatment planning and verification [3]. In Chapter VII, Medical Exposures, Article 56, it is stated 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.”

Furthermore, from Chapter II, Definitions, Article 4, Definition 81, it is stated that:

“‘radiotherapeutic’ means pertaining to radiotherapy, including nuclear medicine for therapeutic purposes”.

The directive is due to come into force February 2018, and has been subject to considerable debate regarding interpretation and how the requirements may be fulfilled. Therefore, in 2015 the multi-disciplinary Internal Dosimetry Task Force (IDTF) was established by the European Association of Nuclear Medicine (EANM) to address aspects of the 2013/59/ Euratom Directive specifically concerned with dosimetry for MRT. The EANM IDTF consists of 17 members from Belgium, Czech Republic, Germany, Greece, Italy, The Netherlands, Norway, Spain, Sweden, Switzerland, Turkey, and the United Kingdom. Treatment specific sections were drafted for 11 different categories of therapy procedures and indications. The report on
the potential and prospects for dosimetry-based treatment planning for MRT will be made available on the EANM website. The aim of this article is to summarise the IDTF report and briefly review examples of treatment specific dosimetric planning procedures.

Summary of report

The radiopharmaceutical procedures covered in the report are listed in Table 1, which also displays selected post-therapy imaging and measurement methods that can form the basis for verification of absorbed doses delivered. Furthermore, the possibility for administration of a tracer amount of the radiopharmaceutical itself or of a ‘companion diagnostic’ to estimate absorbed doses ‘up front’ are indicated. Current clinical therapy regimens vary from single administrations to multiple cycles, and prescriptions range from the delivery of a fixed amount of radioactivity to dosimetric treatment planning. The range of current practice is reported in an IDTF survey on implementation of dosimetry procedures in Europe [Gleisner et al, submitted manuscript].

In the following sections individual therapy procedures and the potential for dosimetric treatment planning are summarised for common therapy procedures. In the full report a brief introduction to the disease and radiopharmaceutical is given for each procedure, followed by a brief review of the reported effectiveness of the treatment, the potential for quantitative imaging that underpins normal tissue and target dosimetry, and existing evidence for absorbed dose-effect correlations. The potential for personalised dosimetry-based treatment planning is then considered. Finally, issues specific to the treatment are considered along with questions that merit further investigation.
Iodine-131 NaI for the treatment of differentiated thyroid cancer (DTC) with ablative intent and in the case of recurrent disease

The amount of Iodine-131 NaI activity to administer for DTC treatment is commonly empirically determined. Typically a fixed activity of Iodine-131 NaI ranging between 1.11 GBq and 7.4 GBq is given [4]. Currently, in the treatment of DTC there are no well-established values for absorbed doses to remnants and metastases which may be used as prescription values. In the case of recurrent disease, the administered activity may be calculated based on the absorbed dose constraints of the normal tissue (usually red marrow) [5].

Radioiodine uptake in thyroid remnants and metastases can be determined with gamma-camera planar imaging or with SPECT/CT which can provide more accurate quantification [6]. Camera calibrations and radiation protection measures may be demanded due to a high photon flux [6]. PET/CT imaging can also be performed using 124I NaI, which may be advantageous for determination of remnant mass and small metastases [7]. EANM guidelines recommend the calculation of red-marrow absorbed doses from whole-body and blood dosimetry [5], and a constraint of 2 Gy is considered when using this methodology [8].

Additional organs at risk may include lungs and salivary glands [9-11]. Issues regarding the alteration of biodistribution can occur due to the debated ‘stunning effect’ for Iodine-131 NaI [12, 13] or due to prior administration of recombinant human thyroid-stimulating hormone (rhTSH) [14], which may have to be considered if treatment planning is performed.

metaiodobenzylguanidine (mIBG) for the treatment of neuroblastoma in children and young adults

The metaiodobenzylguanidine (mIBG) molecule structurally resembles norepinephrine (also called noradrenaline), and tumours expressing the norepinephrine transporter show mIBG uptake capacity. The prescription of Iodine-131 mIBG for neuroblastoma is often made according to
whole-body absorbed dose, which is related to bone marrow absorbed dose and neutropenia [15].

If stem cell rescue is not scheduled, the main organ at risk is usually the bone marrow, with an absorbed dose constraint of 2 Gy [16]. An increasingly common protocol is to deliver a whole-body absorbed dose of 4 Gy in two administrations of activity separated by 2 weeks, followed by stem cell rescue. The first administration is delivered according to a body mass-based prescription of 444 MBq/kg [17]. The whole-body absorbed dose can be estimated by dose-rate measurements by a probe. However, if there is bone marrow involvement, imaging is necessary to perform dosimetry. Quantitative imaging can be performed essentially as for $^{131}$I NaI, with the same technical considerations [6].

$^{177}$Lu-DOTATATE for the treatment of neuroendocrine tumours

$^{177}$Lu-DOTATATE is a radiolabelled somatostatin analogue developed for the treatment of patients with somatostatin receptor positive neuroendocrine tumours. The most frequent treatment protocol is currently to administer 7.4 GBq for up to four times with a 6 to 10 weeks interval between each administration [18]. However, protocols delivering cycles of 7.4 GBq until a maximum prescribed absorbed dose to the kidneys and the bone marrow is reached are under investigation [19].

Although the photon yield is relatively low, the high level of activity administered makes quantitative gamma camera imaging of $^{177}$Lu possible [20]. Medium energy general purpose collimators with an energy window centred at 208 keV is recommended [21]. Late treatment related kidney toxicity has not been reported for patients receiving a kidney dose over 28 Gy, a commonly used tolerance limit, indicating that this may be a conservative value [22]. A clear correlation between tumour absorbed doses and the response to the treatment was
reported in pancreatic neuroendocrine tumours [23]. Although it has been demonstrated that
patient-specific absorbed doses for $^{177}$Lu can be calculated and have a clinical benefit, the
absorbed dose limits for normal tissue and the desirable absorbed dose to the tumours require
further investigations.

$^{223}$Ra dichloride for the treatment of bone metastases from castration resistant prostate
cancer

$^{223}$Ra dichloride is an alpha emitting radiopharmaceutical approved for the treatment of
patients with castration-resistant prostate cancer, symptomatic bone metastases and no known
visceral metastatic disease. Being an analogue to calcium, cationic radium is taken up by
areas of increased osteoblastic activity. A fractionated approach is routinely used for the
delivery of this treatment with 6 administrations of 55 kBq/kg body weight.

The low yield of photons, combined with the low amount of activity administered, makes
quantitative imaging of $^{223}$Ra challenging. However, it has been demonstrated that prolonged
gamma camera imaging is feasible [24, 25], and that activity can be quantified to within 20% - 50%, depending on the volume imaged. A study showed that absorbed doses delivered to
normal organs vary by an order of magnitude between individual patients [26]. Uptake of
$^{223}$RaCl$_2$ in metastases has been seen to correlate with that of $^{99m}$Tc MDP [27], demonstrating
a potential for treatment planning. There is no evidence as yet of correlations between the
absorbed doses delivered and effect. Besides developing reliable dosimetric methodology for
this treatment, the relative biological effect are yet to be determined, and the short range of
the alpha emissions necessitates an investigation of microdosimetry.


Y microspheres for the treatment of primary and metastatic liver cancer

Intra-arterial locoregional liver therapies have their rationale in the fact that liver lesions are
fed mainly by the arterial stream, while normal parenchyma is supplied by portal vein blood
flow. At present both Y glass microspheres and Y resin microspheres are used, both
licensed as medical devices to treat liver primary hepatocarcinoma (HCC) and liver
metastases [28]. Toxicity is of particular importance, as patient death from radioembolisation-
induced liver disease leading to liver failure can be a consequence of a standard treatment
[29]. With current recommendations dosimetry is sometimes used as a basis for treatment
planning, although methods for dose prescription vary.

Simulation scanning is performed with Tc-albumin macro aggregate (MAA) administered
under angiographic guidance for quantitative imaging and pre-treatment dosimetry [28]. The
permanent trapping into liver capillaries of the Tc MAA and of the therapeutic Y
microspheres allows dosimetry to be performed from only one scan [29]. Post therapy
quantitative imaging can be performed by Y bremsstrahlung SPECT or Y PET with
suitable corrections [30, 31]. Correlations between the absorbed doses delivered and toxicity
and response have been reported both for hepatocellular carcinoma [32-34] and colorectal
metastases [35, 36].

Resource requirements

Implementation of dosimetry for therapy, particularly on a routine basis, has implications for
infrastructure resourcing. The level of resources required will depend on the complexity of the
dosimetry procedure and will vary according to local and national protocols and guidelines.
Each procedure will have resource implications for both an initial set up of a dosimetry
service and for ongoing support.
Resources fall into categories of equipment and staff. Whole-body dosimetry may be performed with a portable or externally mounted compensated Geiger counter which enables multiple measurements to be made by either staff or, if necessary, by comforters and careers. Blood dosimetry may be derived from samples measured in a well counter. Image-based dosimetry requires a gamma camera or PET system that has been set up for the radionuclide under investigation at activity levels relevant to the procedure. In addition to routine quality control procedures, this entails determination of calibration factors for image quantification and characterisation of camera deadtime. Volume estimation may be acquired from radiological images or, in the case of radioiodine treatment of benign thyroid disease, from ultrasound scanning as well as from the SPECT and PET data.

As a multidisciplinary area, a range of trained staff are necessary to provide a comprehensive service. These include medical physicists for image quantification and absorbed dose calculations, nuclear medicine technologists and radiographers with experience in quantitative imaging, nuclear medicine physicians and radiologists for volume outlining, and possibly other specialists to contribute on patient-specific prescriptions and procedures.

**Discussion**

The potential for dosimetry-based treatment planning was demonstrated for all therapy procedures, either using the same radiopharmaceutical or diagnostic analogues. Both planning and verification can be technically demanding due to low activity levels in patients and/or low photon yield. However, extensive work has laid the foundation for individualised dosimetry of MRTs. Absorbed dose-effect relationships have been determined for many therapy procedures in single centre studies, and multicentre clinical trials are necessary to gather further evidence.
and substantiate these findings. However, relevant data can be collected by simply performing
post-therapy imaging and dosimetry routinely in current practice, and by comparison of the
absorbed doses delivered with effectiveness data. For many MRTs, a requirement for post-
therapy verification may therefore represent a rational and feasible manner of initiating a
dosimetry-based treatment planning program.

In conclusion, molecular radiotherapy is undergoing a significant expansion. Many new
radiotherapeutics are being introduced into the clinic and an increasing number of patients are
being treated for common as well as rare cancers. This will have a significant effect on
healthcare funding, patient management, and on the logistical and scientific challenges faced
by nuclear medicine departments and their collaborators. As medicine in general has begun to
focus on personalised treatment, often accompanied by molecular imaging, this growth in
radiotherapeutics offers unprecedented opportunities for recognition, support and significant
development. The EANM IDTF report provides an overview of the potential and prospects
for dosimetry-based treatment planning of MRT, revealing that the groundwork is already in
place. The report focuses on the overall aspects of treatment planning, and further work may
be required to complement the status summary. Topics of interest include the use of
companion diagnostics, resource implications, the study of dose-effect correlations,
refinement of technical aspects including image quantification and voxel-based dosimetry
software, biophysical considerations including BED calculations, education and training.

These investigations are important to ensure the clinical and cost-effectiveness of new
radiotherapeutics, as well as for established therapy procedures.
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