

---

## Volume 10 - Issue 3, 2010 - Cover Story

### Multimodality Imaging for Pre-Therapeutic Molecular Radiotherapy Dosimetry

---

The treatment of cancer with radiopharmaceuticals is expanding rapidly, in terms of both the numbers of patients treated and the range of treatments offered (Carlsson et al. 2003). An increasing number of radiopharmaceuticals are now being introduced to the clinic and there is a strong potential for this modality to play a larger role in cancer management alongside surgery, external beam radiotherapy (EBRT) and chemotherapy. The ongoing development of new tumour targeting agents is complemented by recent advances in imaging technology and methodology, which facilitate quantitative assessment of image data and absorbed dose determination. This can provide the basis for a radical change in the manner in which molecular radiotherapy (MRT) is performed.

Whilst MRT is generally administered in a similar fashion to chemotherapy, with fixed or weight-based activities, the use of multimodality quantitative imaging for internal dosimetry offers the possibility for individualised treatment planning as is performed for EBRT. A key element in treatment planning is a pre-therapy assessment of the spatial and temporal distribution of uptake of a tracer administration of the radiopharmaceutical to be used for therapy, or of a surrogate. The advent of hybrid multimodality imaging (SPECT/CT and PET/CT), imparting corresponding functional and anatomical information, now makes accurate dosimetry-based treatment planning achievable.

#### Multimodality Imaging for Dosimetry

Pre- and peri-therapeutic dosimetry studies indicate that a wide range of absorbed doses are delivered to both normal organs and tumours. A high inter-patient variability is observed, thereby justifying a dosimetric approach to individualised patient care (Flux et al. 2009, Matthay et al. 2001). The methods required to implement pre-therapeutic dosimetry are broadly similar to those employed for peri-therapeutic dosimetry. Accurate dosimetry is reliant on multimodality imaging for visualisation, image quantification and absorbed dose calculation.

#### Visualisation and image quantification

Multimodality imaging enables the localisation of functional uptake in the context of corresponding anatomical information. This is a prerequisite for pre-therapeutic assessment of a potential therapy procedure. Initially, it is necessary to identify the sites and extension of disease to direct the therapeutic procedure itself. Volume definition and delineation, required for the calculation of mean absorbed doses, is challenging when applied to functional data owing to the relatively poor spatial resolution of SPECT/PET imaging with respect to CT or MRI. Multimodality imaging is also necessary to identify normal organs/tissues that may be irradiated by uptake in adjacent tumours. This may be the case, for example, if a tumour is located close to a sensitive organ such as the spinal cord (see figure 1). Activity taken up in metastatic lung deposits will irradiate normal lung tissue, to an extent dependent on the size of the deposit and the radiation used.

deposit and the radiation used. Accurate image quantification is essential for the calculation of clinically useful absorbed doses. In the case of gamma-emitting radionuclides, planar scintigraphy or SPECT must be performed. Gamma cameras are not well designed for activity quantification and corrections must be implemented to produce accurate results, particularly in the case of high-energy emitters such as I-131, which is widely used for MRT. Image quantification is limited by several effects, including dead-time (caused by high activity imaging), photon attenuation and scatter and partial volume effect for small structures. It is possible to correct for all these effects, empirically or using specific developments (Ljungberg et al. 1994).

Most recent approaches consider the integration of correction algorithms during the reconstruction process (within the projector), and require anatomical information (most often CT) to be provided. However, the influence of SPECT or PET reconstruction algorithms on image quantification needs to be taken into account, as most modalities are optimised for provision of high contrast images without preserving the count rate (Divoli et al. 2007). Registered image data have commonly been obtained by fusing patient scans acquired separately from CT and from scintigraphy. A large body of literature has been produced to address the issue of image registration, which in the past often entailed the use of fiducial markers attached to the patient (Sjogreen et al. 1997, Papavasileiou et al. 2001). The advent of hybrid imaging, whereby registered anatomical and functional data can be acquired in one scanning session, has introduced a significant advance for quantitative imaging.

#### Absorbed dose calculations

Absorbed dose calculation relies on organ/tissue volume and density determination, as for a given cumulated activity (i.e. the total number of radioactive decays) the mean absorbed dose is inversely proportional to the mass of the volume of interest. Dose conversion factors (S values) can be obtained from anthropomorphic reference model tables (Stabin et al. 2005). These can, to a certain extent, be scaled to patient-specific organ masses obtained via multimodality imaging (Divoli et al. 2009). Patient-specific absorbed dose calculations can also be derived using multimodality imaging, where a combination of functional (activity) and anatomic (volume and density) parameters are used to model radiation transport and energy deposition via Monte-Carlo codes (Zaidi and Andreo 2003, Chiavassa et al. 2006) (see figure 2, p. 23).

#### Current Issues

The implementation of treatment planning based on multimodality imaging and dosimetry presents a number of challenges. In practice, many centres are unable to accommodate the additional scans necessary for pre-therapeutic dosimetry and it is likely that the logistics of routine dosimetry based on multimodality imaging must be addressed on a Europe-wide scale. Scientifically, there are two major issues to be

© For personal and private use only. Reproduction must be permitted by the copyright holder. Email to [copyright@mindbyte.eu](mailto:copyright@mindbyte.eu).

addressed. The first is the predictive accuracy with which pre-therapeutic dosimetry can be performed. In many cases it is impractical to use the therapeutic radionuclide for the pre-therapeutic tracer study, and a surrogate is used. A common example is the use of In-111 as a tracer for Y-90, particularly for the treatment of lymphoma with monoclonal antibodies (Chiesa et al. 2007, Cremonesi et al. 2006).

Similarly, there is an increase in the use of positronemitting radioisotopes of the therapeutic radionuclide such as Y-86 (for Y-90) or I-124 (for I-131) as tracers (Pauwels et al. 2005, Sgouros et al. 2004). Bremsstrahlung imaging of Y-90 is feasible using SPECT/CT (Minarik et al. 2009, Fabbri et al. 2009). The predictive accuracy of these procedures depends not only on the reproducibility of patient biokinetics but also on the accuracy with which the image data can be quantified, since errors inherent in both the tracer and the therapy study will be compounded.

Use of the therapeutic radiopharmaceutical as a tracer has the distinct advantage that differences between absorbed doses delivered therapeutically and those predicted are not due to different methods applied to image quantification or to the dose calculations themselves, but to differences in uptake and retention between the tracer and the therapy study, both of which can be calculated accurately (Flux et al. 2003). The second major issue to be studied is the possible extent to which a tracer study can affect the uptake of a radiopharmaceutical given for therapy as there is some evidence that sequential therapies may in some situations affect the biokinetics (lassmann et al. 2004, Sisson et al. 2006).

#### **Conclusion**

An increasing number of radionuclides are available to treat the same disease. Neuroendocrine tumours may be treated with I-131 mIBG or with peptides labelled with Lu-177 or Y-90. Liver tumours and lymphomas may also be treated with either I-131 or with Y-90, and palliation of bone metastases has been achieved with Sr-89, Sm-153, P-32, Re-186, Re-188, Lu-177 and the alpha emitter Ra-223. For any given patient, the ideal radiopharmaceutical will depend on the level and distribution of functional uptake, the retention of the radiopharmaceutical, and the geometric extent and localisation of uptake with respect to normal organs. Pre-therapeutic multimodality imaging can now enable individualised treatment planning to a level of accuracy not previously considered achievable. In comparison with EBRT, only a small number of patients are treated with radiopharmaceuticals in individual cancer centres. Multi-centre, Europe-wide collaboration is necessary for the advancement of MRT using dosimetry based on multimodality imaging to determine dose-effect correlations.

**Acknowledgements:** The authors would like to acknowledge the participation of all EANM Dosimetry Committee members: K. Bacher, M. Bardiès, C. Chiesa, G.D. Flux, M. Konijnenberg, M. Lassmann, S.E. Strand, I. Strigari. G.F. would like to acknowledge NHS funding to the NIHR Biomedical Research Centre.

Published on : Wed, 10 Nov 2010