MRT and dosimetry: The EANM perspective
Rationale for dosimetry

Patient protection

Treatment optimisation

Standardisation

Regulatory requirements
Rationale for dosimetry

Patient protection

Treatment optimisation

Standardisation

Regulatory requirements
Secondary childhood acute myeloid leukemia with complex karyotypic anomalies including monosomy 7, monosomy 5 and translocation (1;10) after $^{131}$I- metaiodobenzylguanidine therapy for relapsed neuroblastoma

Sonay İncesoy-Özdemir¹, Ceyhun Bozkurt¹, Nazmiye Yüksel¹, Ayşe Ceyda Ören¹, Gürses Şahin¹, Süreyya Bozkurt², Ulya Ertem¹

¹Department of Pediatric Oncology, Dr. Sami Ulus Children’s Hospital, and ²Department of Basic Oncology, Hacettepe University Institute of Oncology, Ankara, Turkey


The prognosis for relapsing or refractory neuroblastoma (NB) remains dismal, with a five-year disease-free survival of <20%, and no effective salvage treatment has been identified so far. $^{131}$I-metaiodobenzylguanidine ($^{131}$I-MIBG) has come to play an essential role in the imaging and therapy of NB over the past 30 years. The role of $^{131}$I-MIBG in the treatment of NB is continually expanding. $^{131}$I-MIBG treatment together with cumulative doses of other alkylating agents has potential serious late side effects such as myelodysplasia and leukemia, although rare. We describe a secondary acute myeloid leukemia case with complex karyotypic anomalies that included monosomy 5, monosomy 7 and translocation (1;10) in a child with relapsed NB who received therapeutic $^{131}$I-MIBG.

Key words: $^{131}$I-metaiodobenzylguanidine, monosomy 5 and 7, neuroblastoma, secondary myeloid leukemia, translocation (1;10).
Secondary childhood acute myeloid leukemia with complex karyotypic anomalies including monosomy 7, monosomy 5 and translocation (1;10) after $^{131}$I-metaiodobenzylguanidine therapy for relapsed neuroblastoma

Sonay İnce, MD, Güres S. Yılmaz, MD, PhD
1Department of Oncology
2Department of Pediatrics
1University of Health Sciences
2Hacettepe University

Original Article

Secondary Myelodysplastic Syndrome and Leukemia Following $^{131}$I-Metaiodobenzylguanidine Therapy for Relapsed Neuroblastoma

Brian Weiss, MD, Amish Vora, MD, John Huberty, MSc, Randall A. Hawkins, MD, PhD, and Katherine K. Matthay, MD

**Purpose:** To describe three patients with secondary leukemia after treatment with $^{131}$I-metaiodobenzylguanidine (MIBG) for neuroblastoma.

**Methods:** Of 95 children with refractory neuroblastoma treated with $^{131}$I-MIBG at UCSF, 3 have been identified with secondary myelodysplasia leukemia. The case records and bone marrow results were reviewed, along with a review of the literature.

**Results:** Three patients developed secondary myelodysplasia leukemia, at 7, 11, and 12 months following $^{131}$I-MIBG therapy. Cytogenetic abnormalities included $-7q/-7$, $-7q+2q37$, $-11$ and $+12$. Three additional cases were found in literature review of 509 reported patients treated with $^{131}$I-MIBG for neuroblastoma.

**Conclusions:** Therapy with $^{131}$I-MIBG may contribute to the risk of secondary leukemia in patients who have received intensive chemotherapy, thought the risk of this complication is far lower than the risk of disease progression. Further monitoring for this complication is indicated.

**Key Words:** acute myelogenous leukemia, $^{131}$I-MIBG, myelodysplasia, neuroblastoma, secondary leukemia

shown to concentrate in neuroblastoma and therefore holds promise for cell-specific radiation treatment of this tumor. Multiple trials of $^{131}$I-MIBG have shown significant response rates of 30% to 40% and apparent prolongation of survival in children treated after relapse. More recently, some centers have begun testing the use of this agent in newly diagnosed patients and have shown good response rates and minimal toxicity. The intensity of therapy required to successfully treat neuroblastoma necessitates careful consideration of the possible severe late sequelae. Others have reported that increased dose intensity of alkylating agents and etoposide results in a significant percentage of children treated for neuroblastoma developing second malignant neoplasm (SMN), particularly myelodysplasia (MDS) and leukemia. Alkylating agents, topoisomerase inhibitors, and irradiation are all currently important components of induction and myeloablative protocols for neuroblastoma, and all may increase the risk of SMN in long-term survivors. In the ex-
3 patients of 95 developed secondary malignancies

‘The risk is lower than that of disease progression’
Secondary childhood acute myeloid leukemia with complex karyotypic anomalies including monosomy 7, monosomy 5 and translocation (1;10) after $^{131}$I-metaiodobenzylguanidine therapy for relapsed neuroblastoma

Brian Weiss, MD, Amish Vora, MD, John Huberty, MSc, Randall A. Hawkins, MD, PhD, and Katherine K. Matthey, MD

Purpose: To describe three patients with secondary leukemia following therapeutic $^{131}$I-metaiodobenzylguanidine (MIBG) therapy. Cytogenetic abnormalities included $-7q/-5$, $-11$, and $+12$. Three additional cases were found in the review of 509 reported patients treated with $^{131}$I-MIBG for neuroblastoma.

Results: Three patients developed secondary myelodysplasia/leukemia, at 7, 11, and 12 months following MIBG therapy. The case records and bone marrow results were reviewed, along with a review of the literature.

Conclusions: Therapy with $^{131}$I-MIBG may contribute to the development of secondary leukemia in patients who have received prior chemotherapy. The risk of this complication is greater than the risk of disease progression. Further monitoring and prompt treatment of this complication is indicated.

Key Words: acute myelogenous leukemia, $^{131}$I-MIBG, myelodysplasia, neuroblastoma, secondary leukemia
Secondary malignancies – mIBG therapy

5 patients of 119 developed secondary malignancies

An international registry is needed...
1 in 227 children treated with radioiodine will develop a secondary primary malignancy
The evidence base for the use of internal dosimetry in the clinical practice of molecular radiotherapy

Lidia Strigari · Mark Konijnenberg · Carlo Chiesa ·
Manuel Bardies · Yong Du · Katarina Sjögren Gleisner ·
Michael Lassmann · Glenn Flux

Received: 15 May 2014 / Accepted: 19 May 2014 / Published online: 11 June 2014
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Abstract Molecular radiotherapy (MRT) has demonstrated unique therapeutic advantages in the treatment of an increasing number of cancers. As with other treatment modalities, there is related toxicity to a number of organs at risk. Despite the large number of clinical trials over the past several decades investigating dosimetry, an absorbed dose–effect correlation was found in 48. The application of radiobiological modelling to clinical data is of increasing importance and the limited published data on absorbed dose–effect relationships based on these models are also reviewed. Based on
Benua *et al* – 1-2 Gy blood absorbed dose gave severe radiation complication in 1 of 24 cases, 2-3 Gy gave severe complications in 5 of 33 cases, 1 fatal.

Buckley *et al*, Matthay *et al* found correlations of dose with neutropenia and thrombocytopenia

Barone *et al* found ADER in renal failure with Y-90 DOTATOC

Mones *et al*, Ferrer *et al* found ADER (haematological toxicity) for Bexxar & Zevalin

Sangro *et al* found 20% toxicity in patients treated with 37 Gy with microspheres, compared to 26 Gy for no toxicity

Buffa *et al* - correlation between dose and WBC and platelet toxicity
Patient protection

Potential for further radiation therapy. Is previous MRT dose important?

Complications determined by clinical factors as well as AD, including previous treatments

Need to determine ‘acceptable toxicity’?

Patients undergoing radionuclide therapy are the only population that do not have radiation doses calculated

Potential for centres to be sued

No toxicity seen in some patients – more aggressive treatment is warranted
Rationale for dosimetry

Patient protection

Treatment optimisation

Standardisation

Regulatory requirements
Correlation tumor response vs dose (measured with PET and CT-scan) at end of treatment $^{90}$Y-SMT-487 trial (n = 32)

Stephan Walrand - UCL Brussels
## Radioiodine for thyroid cancer

**Table 4** Studies showing dose–effect relationships for $^{131}$I (NaI) therapy against DTC

<table>
<thead>
<tr>
<th>Reference</th>
<th>No. of patients</th>
<th>Endpoint</th>
<th>Threshold dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>[13]</td>
<td>50</td>
<td>Ablation</td>
<td>300 Gy (remnant)</td>
</tr>
<tr>
<td>[13]</td>
<td>26</td>
<td>Response</td>
<td>80 Gy (metastases)</td>
</tr>
<tr>
<td>[14]</td>
<td>23</td>
<td>Ablation</td>
<td>49 Gy (remnant)</td>
</tr>
<tr>
<td>[15]</td>
<td>449</td>
<td>Ablation</td>
<td>0.35 Gy (blood)</td>
</tr>
<tr>
<td>[16]</td>
<td>122</td>
<td>Complications</td>
<td>2 Gy (blood)</td>
</tr>
<tr>
<td>[17]</td>
<td>198</td>
<td>Toxicity grade 3 or more</td>
<td>2 Gy (blood)</td>
</tr>
<tr>
<td>[18]</td>
<td>17</td>
<td>Toxicity grade 3 or more</td>
<td>1.7 Gy (blood)</td>
</tr>
</tbody>
</table>
# Radioiodine for thyroid cancer

## Table 4

<table>
<thead>
<tr>
<th>Reference</th>
<th>No. of patients</th>
<th>Endpoint</th>
<th>Threshold dose</th>
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<tbody>
<tr>
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<td>50</td>
<td>Ablation</td>
<td>300 Gy (remnant)</td>
</tr>
<tr>
<td>[13]</td>
<td>26</td>
<td>Remission</td>
<td></td>
</tr>
<tr>
<td>[14]</td>
<td>23</td>
<td>Ablation</td>
<td></td>
</tr>
<tr>
<td>[15]</td>
<td>449</td>
<td>Ablation</td>
<td></td>
</tr>
<tr>
<td>[16]</td>
<td>122</td>
<td>Normal Tg</td>
<td></td>
</tr>
<tr>
<td>[17]</td>
<td>198</td>
<td>Tg cure</td>
<td></td>
</tr>
<tr>
<td>[18]</td>
<td>17</td>
<td>Tg control</td>
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## Table 5

<table>
<thead>
<tr>
<th>Reference</th>
<th>No. of patients</th>
<th>Endpoint</th>
<th>Efficacy threshold (thyroid)</th>
</tr>
</thead>
<tbody>
<tr>
<td>[19]</td>
<td>92</td>
<td>&gt;60 % size reduction</td>
<td>200 Gy</td>
</tr>
<tr>
<td>[20]</td>
<td>205</td>
<td>80 % cure hyperthyroidism</td>
<td>200 Gy</td>
</tr>
<tr>
<td>[23]</td>
<td>79</td>
<td>50 % hypothyroidism</td>
<td>60 Gy (96 Gy multinodular disease)</td>
</tr>
<tr>
<td>[26]</td>
<td>147</td>
<td>Hypothyroidism</td>
<td>400 Gy</td>
</tr>
</tbody>
</table>
### Dose – effect for NHL and microsphere treatments

<table>
<thead>
<tr>
<th>Reference</th>
<th>No. of patients</th>
<th>Endpoint</th>
<th>Threshold dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>[37]</td>
<td>76</td>
<td>OS</td>
<td>0.75 Gy (WB)</td>
</tr>
<tr>
<td>[39]</td>
<td>20</td>
<td>PR (&gt;50 % shrinkage)</td>
<td>2 Gy effective uniform dose (tumour)</td>
</tr>
<tr>
<td>[40]</td>
<td>10</td>
<td>PR (&gt;80 % shrinkage)</td>
<td>4.5 Gy (tumour), $p=0.06$</td>
</tr>
<tr>
<td>[42]</td>
<td>37</td>
<td>PFS</td>
<td>20 Gy (WB)</td>
</tr>
<tr>
<td>[43]</td>
<td>19</td>
<td>Cardiopulmonary toxicity</td>
<td>25 Gy (WB)</td>
</tr>
<tr>
<td>[44]</td>
<td>14</td>
<td>Reversible BM toxicity</td>
<td>0.45 Gy (WB)</td>
</tr>
</tbody>
</table>
Dose – effect for NHL and microsphere treatments

<table>
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<td>76</td>
<td>OS</td>
<td>0.75 Gy (WB)</td>
</tr>
<tr>
<td>[39]</td>
<td>20</td>
<td>PR ≥ 50 % (partial response)</td>
<td>2 Gy effective radiation dose (average)</td>
</tr>
<tr>
<td>[40]</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>[42]</td>
<td>37</td>
<td></td>
<td></td>
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<td>19</td>
<td></td>
<td></td>
</tr>
<tr>
<td>[44]</td>
<td>14</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 9: Studies showing dose–effect relationships for intraarterial therapy of liver cancer using radiolabelled microspheres

<table>
<thead>
<tr>
<th>Reference</th>
<th>No. of patients</th>
<th>Radionuclide</th>
<th>Carrier</th>
<th>Endpoint</th>
<th>Threshold dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>[47]</td>
<td>71</td>
<td>$^{90}$Y</td>
<td>Ivalon microspheres</td>
<td>PR (&gt;50 % reduction), pneumonitis</td>
<td>225 Gy (lesion), 30/50 Gy (lung)</td>
</tr>
<tr>
<td>[48]</td>
<td>36</td>
<td>$^{90}$Y</td>
<td>Glass microspheres</td>
<td>Response (PR+CR)</td>
<td>205 Gy (lesion)</td>
</tr>
<tr>
<td>[49]</td>
<td>185</td>
<td>$^{188}$Re</td>
<td>Lipiodol</td>
<td>OS</td>
<td>30 Gy (tumour)</td>
</tr>
<tr>
<td>[50]</td>
<td>12</td>
<td>$^{90}$Y</td>
<td>Resin microspheres</td>
<td>Metabolic FDG response &gt;50 %</td>
<td>260 Gy (tumour)</td>
</tr>
<tr>
<td>[51]</td>
<td>8</td>
<td>$^{90}$Y</td>
<td>Resin microspheres</td>
<td>Metabolic FDG response &gt;50 %</td>
<td>46 Gy (tumour)</td>
</tr>
<tr>
<td>[52]</td>
<td>52</td>
<td>$^{90}$Y</td>
<td>Glass microspheres</td>
<td>EASL density response (PR+CR)</td>
<td>500 Gy (lesion)</td>
</tr>
<tr>
<td>[53]</td>
<td>73</td>
<td>$^{90}$Y</td>
<td>Resin microspheres</td>
<td>50% TCP (PR+CR) 5 % ≥ G2 liver toxicity</td>
<td>150 Gy (tumour), 50 Gy BED (liver)</td>
</tr>
<tr>
<td>[54]</td>
<td>45</td>
<td>$^{90}$Y</td>
<td>Resin microspheres</td>
<td>REILD</td>
<td>40 Gy (liver)</td>
</tr>
<tr>
<td>[55]</td>
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<td>$^{90}$Y</td>
<td>Glass microspheres</td>
<td>Tumour density reduction, liver decompensation</td>
<td>200 Gy (tumour), &gt;60 Gy to the parenchyma</td>
</tr>
<tr>
<td>[56]</td>
<td>15</td>
<td>$^{166}$Ho</td>
<td>Polylactic acid microspheres</td>
<td>G3 liver and blood toxicity</td>
<td>80 Gy (liver)</td>
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Correlations also found for I-131 mIBG of neuroblastoma (Matthay et al) and lymphoma (Kaminski, Wahl, Ferrer...)

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<td>PP ≥ 40%</td>
<td></td>
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<td>80 Gy (liver)</td>
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</table>
Rationale for dosimetry

Patient protection

Treatment optimisation

Standardisation

Regulatory requirements
Industry led standardisation

Sr-89 for bone metastases: 150 MBq

Sm-153 for bone metastases: 37kBq/kg

Ra-223 for bone metastases: 50 kBq/kg for 6 treatments

Zevalin for NHL: 14.8 MBq/kg for patients with normal platelets, 11.1 MBq/kg if relapsed or refractory, maximum 1184 MBq

Bexxar for NHL: 75 cGy WB dose

Y-90 microspheres for HCC and liver metastases: Various models for glass and resin microspheres
Radioiodine for ca & benign thyroid

EANM Guidelines: ‘The “optimal” activity for radioiodine ablation of post-surgical thyroid residues macroscopic disease is generally a single administration of 1 - 5 GBq.

For radioiodine ablation in children, some centres adjust activity by body weight (e.g. to 1.85–7.4 MBq/kg) or surface area or by age.’

ATA: ‘No prospective randomized trial to address the optimal therapeutic approach has been published.’ The RAI activity administered can be given empirically or determined by dosimetry.

FDA: For thyroid carcinoma, the usual sodium iodide I-131 therapeutic dose is 3700 to 5550 MBq. For ablation of post-operative residual thyroid tissue, the usual dose is 1850 MBq.
Dosimetry Committee Publications

GUIDELINES

EANM Dosimetry Committee series on standard operational procedures for pre-therapeutic dosimetry
I: blood and bone marrow dosimetry in differentiated thyroid cancer therapy

Michael Lassmann · Heribert Hänscheid · Carlo Chiesa · Cecilia Hindorf · Glenn Flux · Markus Luster

© EANM 2008

Abstract
Introduction The purpose of the EANM Dosimetry Committee Series on “Standard Operational Procedures for Pre-therapeutic Dosimetry” (SOP) is to provide advice to scientists and clinicians on how to perform pre-therapeutic and/or therapeutic patient-specific absorbed dose assessments. Material and Methods This particular SOP gives advice on how to tailor the therapeutic activity to be administered for systemic treatment of differentiated thyroid cancer (DTC) such that the absorbed dose to the blood does not exceed 2 Gy (a widely accepted limit for bone marrow toxicity). The methodology of blood-based dosimetry has been developed in the 1960s and refined in a series of international multi-centre trials in the framework of the introduction of new diagnostic and therapeutic tools, e.g. recombinant human thyroid-stimulating hormone in the management of DTC.

Conclusion The intention is to guide the user through a series of measurements and calculations which the authors consider to be the best and most reproducible way at present.

Keywords Dosimetry · Thyroid cancer · SOP

Introduction
EANM Standardisation for dosimetry

GUIDELINES

EANM Dosimetry Committee Series on Standard Operational Procedures for Pre-Therapeutic Dosimetry
II. Dosimetry prior to radioiodine therapy of benign thyroid diseases

Heribert Hänscheid · Cristina Canzi · Wolfgang Eschner · Glenn Flux · Markus Luster · Lidia Strigari · Michael Lassmann

Received: 22 February 2013 / Accepted: 26 February 2013
© EANM 2013

Abstract The EANM Dosimetry Committee Series “Standard Operational Procedures for Pre-Therapeutic Dosimetry” (SOP) provides advice to scientists and clinicians on how to perform patient-specific absorbed dose assessments. This particular SOP describes how to tailor the therapeutic activity to be administered for radioiodine therapy of benign thyroid diseases such as Graves’ disease or hyperthyroidism. Pretherapeutic dosimetry is based on the assessment of the individual $^{131}$I kinetics in the target tissue after the administration of a tracer activity. The present SOP makes
EANM Dosimetry Committee guidelines for bone marrow and whole-body dosimetry

Cecilia Hindorf • Gerhard Glatting • Carlo Chiesa • Ola Lindén • Glenn Flux

Published online: 22 April 2010 © EANM 2010

Abstract

Introduction The level of administered activity in radionuclide therapy is often limited by haematological toxicity resulting from the absorbed dose delivered to the bone marrow. The purpose of these EANM guidelines is to provide advice to scientists and clinicians on data acquisition and data analysis related to bone-marrow and whole-body dosimetry.

Materials and methods The guidelines are divided into sections “Data acquisition” and “Data analysis”. The Data acquisition section provides advice on the measurements required for accurate dosimetry including blood samples, quantitative imaging and/or whole-body measurements with a single probe. Issues specific to given radiopharmaceuticals are considered. The Data analysis section provides advice on the calculation of absorbed doses to the whole
Standardisation

Currently no authority to govern standardisation for therapy (cf ICRU for EBRT)

Lack of dosimetry standardisation often given as an excuse to avoid it

However, more standards in preparation, including:

- I-131 mIBG treatment
- Lu-177 for adult NETs
- Error analysis
- Microsphere treatments

Significant boost with input from MetroMRT, and role of European metrology institutes
Rules and regulations

Article 56

Optimisation

1. Member States shall ensure that all doses due to medical exposure for radiodiagnostic, interventional radiology, planning, guiding and verification purposes are kept as low as reasonably achievable consistent with obtaining the required medical information, taking into account economic and societal factors.

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.
Article 56

Optimisation

1. Member States shall ensure that all doses due to medical exposure for radiodiagnostic, interventional radiology, planning, guiding and verification purposes are kept as low as reasonably achievable consistent with obtaining the required medical information, taking into account economic and societal factors.

For all medical purposes, and planned and 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.

(81) "radiotherapeutic" means pertaining to radiotherapy, including nuclear medicine for therapeutic purposes;
Rules and regulations

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(81) "radiotherapeutic" means pertaining to radiotherapy, including nuclear medicine for therapeutic purposes;

CHAPTER X

FINAL PROVISIONS

Article 106

Transposition

1. Member States shall bring into force the laws, regulations and administrative provisions necessary to comply with this Directive by 6 February 2018.
EANM Internal Dosimetry Task Force

To address the EU directive:

**Aim:**
1. To review whether it is possible to implement the directive
2. To consider implications of doing so

Survey underway: Number of therapy procedures and administration protocols

Open call for contributors

Feasibility of dosimetry based treatment planning for all radiotherapeutics?
Existing therapy procedures

I-131 NaI for Thyroid Cancer
I-131 NaI for Benign Thyroid Diseases
Y-90 for Non-Hodgkin Lymphoma
I-131 for Non-Hodgkin Lymphoma
Y-90 for Liver Tumors
I-131 mIBG for Neuroblastoma
I-131 mIBG for Adult Neuroendocrine Disease
Lu-177 Radiopeptides for Adult Neuroendocrine Disease
Y-90 Radiopeptides for Adult Neuroendocrine Disease
Re-188 for Benign Bone Diseases
Y-90 for Benign Bone Diseases
Re-186 for Benign Bone Diseases
Er-186 for Benign Bone Diseases
Re-186 for Bone Metastases
Sm-153 for Bone Metastases
Sr-89 for Bone Metastases
Ra-223 for Bone Metastases
P-32 for Myeloproliferative Neoplasms
Prospective therapy procedures

Lu-177 for Prostate Cancer
Ho-166 Microspheres for Intra-arterial Treatment
Re-188 Microspheres for Intra-arterial Treatment
Y-90 Microspheres for Intra-arterial Treatment
Ac-225 for Leukaemia
Bi-213 for Leukaemia
Bi-212 for Leukaemia
Ra-223 for Leukaemia
At-211 for Leukaemia
Tb-149 for Leukaemia
Pb-212 for Leukaemia
Y-90 for Brain Tumors
Y-90 for Breast Cancer
Y-90/Lu-177 for Colorectal Carcinoma
I-131 for Pancreatic Carcinoma
Y-90 for Pancreatic Carcinoma
I-131 for Renal Carcinoma
Sn-117m DTPA Bone Metastases
Th-227 and Other Alpha Emitters

Therapy/diagnostic pairs:

$^{90}\text{Y}/^{111}\text{In}$
$^{131}\text{I} / ^{124}\text{I}$
$^{44}\text{Sc}/^{47}\text{Sc}$
Conclusion

Dosimetry based treatment planning is mandatory for external beam therapy and for brachytherapy.

It should also be mandatory for therapy with radiopharmaceuticals.

This is a major challenge – scientifically, logistically, politically.

Possibly the most exciting and dangerous time for therapy in nuclear medicine!
The march of time... still smiling...

Michael Lassmann
Manuel Bardies
Myriam Monsieurs
Sven-Erik Strand
Sauli Savolainen
Carlo Chiesa
Mark Konijnenberg
Klaus Bacher
Michael Ljungberg
Katarina Sjogreen-Gleisner
Lidia Strigari
Stig Palm
Gian Luca Poli

EANM congress Hamburg, October 10th – 14th: Do.MoRe 6th International Symposium on DOSimetry and MOlecular Radiotherapy (abstract deadline 27th April)