INTERNATIONAL ATOMIC ENERGY AGENCY

Report of a Consultancy Meeting held

26-28 September 2011 at the IAEA Headquarters in Vienna

FOREWORD

The Dosimetry and Medical Radiation Physics (DMRP) section's efforts in Nuclear Medicine Physics follow the section's overall focus on Quality Assurance in radiation medicine, with special emphasis on educating and training medical physicists. For nuclear medicine physics, extra effort has previously been placed on proper radioactivity measurements. Currently the section is involved in providing guidelines for proper quantification of nuclear medicine images. These efforts set the stage for patient-specific dosimetry, a requirement for therapeutic nuclear medicine but also useful for diagnostic procedures.

A consultants' meeting was arranged to provide advice to the Agency on the current status of the field, as well as identifying any gaps that should be addressed. The specific purpose of the meeting was to review current guidelines for internal dosimetry in nuclear medicine, and to provide recommendations for international harmonization of this field.

The consultants were Dr. Manuel Bardies, Centre de Recherche en Cancérologie de Toulouse, France; Dr. Michael Lassmann, University of Würzburg, Germany; Dr. Wesley Bolch, University of Florida, USA; and Dr. George Sgouros, Johns Hopkins University, USA. Scientific secretary for the meeting was Stig Palm, DMRP/NAHU.

CONTENTS

1. ROLE OF INTERNAL DOSIMETRY IN NUCLEAR MEDICINE

1.1. Diagnostic Nuclear Medicine

Clinical applications of nuclear medicine allow functional imaging of normal and diseased tissue. Although they may cover almost all clinical specialities, the localization of malignant tissue and its potential metastatic spread, as well as assessment of myocardial perfusion, are amongst the most common procedures. In these applications, the amount of administered activity is such that the absorbed dose to both imaged and non-imaged tissues are typically very low and thus stochastic risks of cancer induction are greatly outweighed by the diagnostic benefit of the imaging procedure. Nevertheless, these tissues doses and their stochastic risks should be quantified for each patient, and placed in context of both their cumulative values received over multiple imaging sessions, and of doses and risks received by other diagnostic imaging procedures they may have (fluoroscopy and computed tomography, for example). The role of internal dosimetry in diagnostic nuclear medicine is thus to provide the basis for stochastic risk quantification. Once this risk is quantified, it may be used to optimize the amount of administered activity in order to maximize image quality while minimizing patient risk. This optimization process is of particular importance for pediatric patients owing to their enhanced organ radiosensitivities and years over which any stochastic effects may become manifest. This optimization should consider, as much as possible, patient age, gender, and body morphometry, and pharmacokinetics, along with all available image acquisition and processing techniques.

The procedure by which tissues doses are assessed is summarized in MIRD Pamphlet No. 21, and includes (1) quantification of the time-integrated activity Ã for each tissue that localizes the radiopharmaceutical (source tissues), and (2) assignment of S values – the absorbed dose to target tissues per decay in each source tissue. Radionuclide S values for all combinations of the source and target tissue, as needed for internal dosimetry in diagnostic nuclear medicine, should be based upon internationally accepted reference anatomic phantoms as defined by the International Commission on Radiological Protection. In this way, organ dose estimates may be harmonized across all imaging modalities for the purpose of quantifying stochastic risk.

Two options exist for quantification of Ã. The most patient-specific method entails serial imaging of the patient (2D planar, 3D SPECT, or 3D PET), data processing of these images to yield time-activity curves, and then integration of these time-activity curves. In the development of new diagnostic imaging agents, this approach is required for regulatory approval, and should be conducted under standardized protocols to yield the greatest amount of information on agent pharmacokinetics and patient dosimetry. For existing diagnostic imaging agents, one may rely on reference biokinetic models, which when coupled to phantom-based radionuclide S values via the MIRD schema, yield organ dose coefficients – organ dose per unit administered activity. These reference models, however, should be based upon extensive human data sets, should include, where possible variations accounting for patient disease states, and age and gender dependencies.

The most commonly utilized dosimetry quantity for stochastic risk assessment is the effective dose, as defined in ICRP Publication 60 and more recently in ICRP Publication 103. However, the role of the effective dose is reserved for prospective dosimetry in the context of worker and general public radiation protection, and not in retrospective dosimetry for individual patient risk. Stochastic risks in medical imaging are more properly assessed through calculations of individual organ dose and the application of organ-specific risk

coefficients – cancer induction risk per unit organ equivalent dose, for example, as given in the National Academy of Sciences BEIR VII report. Even through this approach, however, one must appreciate the limitations of these risk coefficients and acknowledge that they do not lead to individual estimates of patient stochastic risk. The advantage of this approach, however, is that they preserve our best estimates of the age and gender dependency of stochastic cancer risk. The tissue weighting factors used in the ICRP effective dose purposely average these risks across both genders and over all age groups. In diagnostic nuclear medicine dosimetry, assessment of the mean value of organ absorbed dose is acceptable in that organ risk coefficients, derived from radiation epidemiological data of exposed populations, are based upon an analysis using mean organ doses.

1.2. Therapeutic Nuclear Medicine

In many forms of radiation cancer therapy, to include external beam radiotherapy and brachytherapy, radiation dosimetry is an integral component to treatment planning, where the objective is to maximize the tumor absorbed dose while avoiding or minimizing normal tissue toxicities. In therapeutic nuclear medicine, tumor dosimetry may be problematic owing to (1) lack of imaging data to define the tumor, especially for disseminated and diffuse disease, (2) the dynamic nature of radiopharmaceutical uptake, retention, and washout, (3) non-uniformities in the spatial distribution of the agent at the cellular level, and (4) time-dependent dose rates. Consequently, there is a paucity of data on tumor dose-response relationships, upon which values of prescribed tumor dose may be assessed. Exceptions do occur, such as in treatment of solid tumors and malignant and benign thyroid disease, but even here, there are no standardized clinically accepted protocols for radionuclide treatment planning based upon delivery of a dose prescription to the tumor.

Resultantly, current dosimetry practice in therapeutic nuclear medicine (i.e., molecular radiotherapy) is to assess the absorbed dose to radiosensitive tissues, and based upon a general understanding of toxicity thresholds (taken primarily from previous experience in external beam radiotherapy), adjust administered activities to the cancer patient to maximize uptake and dose to the tumor while avoiding normal organ toxicities. The dose to the tumor is neither quantified nor prescribed.

In contrast to diagnostic nuclear medicine dosimetry, more sophisticated methods of dosimetry are generally required in therapeutic nuclear medicine in order to provide predictive indices of tissue toxicities. In the context of therapy, patient variability in terms of both agent pharmacokinetics and body morphometry must be explicitly considered on an individual patient basis to assure optimized treatment.

Factors that have been shown to be relevant, if not essential, to predicting biological response include (1) the spatial distribution of the radiopharmaceutical at a resolution commensurate with the scale of the radiosensitive structures , (2) dose rate, (3) radiation quality, and (4) prior treatment history. These considerations require the application of radiobiological concepts to translate absorbed dose distributions to biological effects. This is an area of ongoing research involving pre-clinical and in-vitro studies.

In current clinical practice in nuclear medicine therapy, treatment is delivered based upon an administered activity prescription. This prescribed activity is typically established in a Phase I clinical trial from the toxicity response of only three to six patients, and is then applied to all subsequent patients. The failure to account for patient variability will lead, in the majority of cases, to patient under-treatment. The relevant quantity for assuring therapeutic efficacy and

avoiding organ toxicities is the radiation absorbed dose, and thus patient-specific dosimetry is essential for optimal efficacy and patient safety. Recent studies using patient-specific dosimetry have demonstrated the ability to establish dose-response relationships for toxicity avoidance. It is thus now clear that the application of patient-specific dosimetry is an essential element to optimizing molecular radiotherapy. Such optimization in patient nuclear medicine therapy is presently hindered by the lack of qualified personnel trained in the techniques required to perform patient-specific dosimetry.

Improvements in both diagnostic and therapeutic nuclear medicine dosimetry require that the following deficits in data, methods, education, awareness, and human resources be addressed.

1.3. Method Gaps

1.3.1. Diagnostic Imaging – Biokinetic Data

- Lack of standardized image acquisition and dosimetry protocols for new agents

1.3.2. Therapy – Standardization of Methods

- Lack of standardized set of physical phantoms for activity quantification
- Lack of reference approach for determining value of time-integrated activity Ã
- Lack of a standardized calculational approach to patient-specific dosimetry (MC, point kernel, voxel S values, etc.)
- Lack of widely available and standardized software for patient-specific absorbed dose calculation.

1.3.3. Therapy – Uncertainty Analysis

- Lack of statistically rigorous approaches to the determination of acquisition time points in pharmacokinetic analyses
- Acknowledged lack of culture in providing uncertainties in dose estimates

1.4. Data Gaps

1.4.1. Diagnostic Imaging – Biokinetic Data

- Lack of human biokinetic data for some radiopharmaceuticals
- General lack of biokinetic data for pediatric patients for all radiopharmaceuticals
- Need for updating ICRP reference biokinetic models in terms of both age and gender dependency

1.4.2. Diagnostic Imaging – Balancing image quality and patient risk

- Need for a survey of world-wide use of radiopharmaceuticals in children
- Need for considering patient morphometry beyond weight / age in pediatric dosing guidelines

1.4.3. Therapy – Efficacy and Toxicity Endpoints

- Lack of a data pooling culture for collecting dose-response data. Studies that do exist generally do not implement the latest dosimetry methodologies, nor do they properly report their dosimetry methods in peer-reviewed literature
- Lack of clear definition of biological and/or clinical endpoints relevant to a specific treatment

1.5. Education and Training Gaps

1.5.1. Diagnostic Imaging – Balancing image quality and patient risk

- Need for improved understanding of stochastic risks from ionizing radiation
- Need for better understanding and consideration of CT doses in hybrid imaging
- Need for improved instrumentation and software based dose reduction strategies

1.5.2. Diagnostic Imaging – Application of ICRP models and effective dose

- Need for better understanding the limitations of the effective dose concept in medical dosimetry of the patient. Need to consider alternative means of assessing stochastic risk such as the use of organ doses and BEIR VII risk models

1.5.3. Therapy – Standardization of Methods

- Lack of training of nuclear medicine physicists on proper radioactivity measurements for therapy related radionuclides based upon IAEA TRS-454
- Lack of training of nuclear medicine physicists on methods of patient-specific dosimetry

1.5.4. Therapy – Uncertainty Analysis

- Lack of training in statistical methods needed for error analysis in internal dosimetry

1.5.5. Therapy – Efficacy and Toxicity Endpoints

- Lack of training in fundamental concepts in radiation biology as needed to relate absorbed dose distributions to biological effect and response.

1.6. General gaps

- Lack of specific training and education programs in nuclear medicine dosimetry
- Current training of medical physicists typically excludes concepts related to the design and implementation of clinical trials in both imaging and therapy

1.7. Human Resource Gaps

- Severe shortage of qualified medical physicists to support dosimetry in nuclear medicine

2. RECOMMENDATIONS

2.1. Diagnostic Nuclear Medicine

- Adopt most recent ICRP reference computational phantoms to standardize dose calculations
- Form collaborative efforts to collect biokinetic data for children and adults (potential role for RDCs – see below)
- Initiate a collaboration with UNSCEAR to conduct a world-wide survey to identify the most common radiopharmaceuticals used in pediatric nuclear medicine. This effort could also involve pediatric committees of member state nuclear medicine professional organizations.
- Harmonize current consensus guidelines for pediatric dosing world-wide
- Update ICRP reference biokinetic models in terms of both their age and gender dependency

2.2. Therapy Nuclear Medicine

- Promote the development of disease-based standard protocols for patient-specific dosimetry
- Incorporate uncertainty analyses in dosimetry reporting
- Establish database structures that permit global sharing and quality assessment of dose-response data (potential role of RDCs – see below)

2.3. General Recommendations

- Utilize and disseminate results from ongoing IAEA CRP E2.10.07 on accuracy of quantitative imaging in nuclear medicine. Establish laboratory intercomparisons based upon the experience of the IAEA CRP E2.10.07
- Develop and initiate training courses / educational materials for both diagnostic and therapeutic nuclear medicine dosimetry to address the educational/training gaps listed above
- Promote collaborative efforts between medical physicists and other medical staff to facilitate the incorporation of dosimetry in nuclear medicine to improve patient care

2.4. Recommendations to the IAEA

- Renew existing CRP E2.10.07 on image quantification in nuclear medicine
- Initiate a collaboration with UNSCEAR to conduct a world-wide survey to identify the most common radiopharmaceuticals used in pediatric nuclear medicine. This effort could also involve pediatric committees of member state nuclear medicine professional organizations.
- Establish set of standards for Regional Designated Centers (RDCs) for Radiopharmaceutical Dosimetry
- Set up Regional Designated Centers (RDCs) for Radiopharmaceutical Dosimetry
- Form liaisons with professional organizations to promote existing courses and educational resources in nuclear medicine dosimetry

- Develop Guidance Documents on methods for calculating and reporting uncertainties for patient dose estimates in diagnostic nuclear medicine (risk assessment) and therapeutic nuclear medicine (efficacy and toxicity assessment)
- Increase the web visibility of IAEA documents related to nuclear medicine dosimetry through enhanced website design and outreach efforts as has been established in the RPOP program.