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Dosimetry from organ to cellular dimensions

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Abstract

While the conventional Medical Internal Radiation Dose (MIRD) approach is useful for estimating approximate organ absorbed doses in diagnostic applications of isotopes, this strategy is suited neither to the exacting requirements of targeted radionuclide therapy nor to radiopharmaceuticals with a non-uniform activity distribution. For the individual treatment planning of patients treated with common radionuclides emitting high energy betas, the individual activity distribution has to be obtained from CT-SPECT images and the doses to the target organs and critical tissues have to be calculated by point-kernel methods. Due to the stochastic nature, alpha-radioimmunotherapy (alpha-RIT) requires microdosimetric calculations with Monte Carlo on a realistic model of the source and target tissue at the micrometer level. For a prediction of the biological effects of intracellular labelling with Auger electron emitters an accurate subcellular modelling including the DNA structure at the nanometre level with knowledge of the target for the considered biological effect is necessary. © 2001 Elsevier Science Ltd. All rights reserved.

Keywords: Internal dosimetry; Medical internal radiation dose; Point–kernel methods; Alpha-radioimmunotherapy; Auger electrons

1. Introduction

As in other medical applications of ionising radiation, the purpose of dosimetry in nuclear medicine consists primarily in the evaluation of the risk for late effects, e.g. cancer and leukaemia in patients after a nuclear medical examination or therapy. Secondary but not less important (and becoming increasingly important), dosimetry aims to predict the outcome of radionuclide therapy in the individual patient. In oncological therapy applications, this means determination of tumour dose distributions and doses to critical organs and tissues, for e.g. bone marrow.

2. Medical internal radiation dose method

The Medical Internal Radiation Dose (MIRD) schema elaborated by Loevinger and Berman [1] in the early 1970s has proven to be a robust basis for calculating absorbed doses to organs from internal radionuclides for radioprotection purposes. The dose to a target organ r_k from a source organ r_h, containing part of the administered activity, is given by the product of the cumulative activity in the considered source organ and the S value

$$D(r_k \leftarrow r_h) = A_h S(r_k \leftarrow r_h)$$

The cumulative activity A_h is the total number of disintegrations in the source organ. The specific energy $S(r_k \leftarrow r_h)$ is the mean energy deposited in the target organ per disintegration in the source organ divided by the target organ mass.

The S values are the base of the MIRD formalism [2]. They depend on the isotope and the source–target geometry. The MIRD committee has calculated the S-values for all isotopes used in nuclear medicine and for antropomorphic phantoms representing the standard man, woman and children of different ages. In the MIRD formalism the source and target organs can coincide, e.g. the thyroid after administration of radioactive iodine but in most cases doses will be determined in radiosensitive organs or tissues, which are not the source organs, e.g. the liver in a xenon scan of the lungs.

While the organ S-values are extremely useful for absorbed dose estimation in a nuclear medicine examination, a number of assumptions are made in the MIRD model that limit the applicability especially for radionuclide therapy [3]. These limitations are:

- The source–target geometries are standardised: the standard man, woman and children. There are no possibilities to take into account the individual anatomy of the patient.
- The activity is assumed to be uniformly distributed within the source organs which is not always the case,

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e.g. cold spots in the treatment of the thyroid with radioiodine.
- The absorbed dose in target organs is calculated as an average dose.
- The intracellular distribution of radionuclides emitting short-range particles is ignored, which results in large errors in the prediction of the biological effects.

3. Patient dosimetry in radionuclide therapy

Although the MIRD schema is useful for radioprotection purposes in the determination of the radiation burden of the average man and woman due to a nuclear medicine investigation, it can not be applied for patient dosimetry in radionuclide therapy owing to the limitations just mentioned. For an accurate determination of the dose to the target and the critical organs in an individual patient in radionuclide therapy the patient anatomical data have to be acquired via CT and the activity distribution derived from a SPECT scan. The doses to the organs or tissues of interest are then calculated from the three-dimensional activity distribution by point–kernel methods [4,5].

In this approximation the source organ is divided into a large number of pixels and the activity in each pixel is considered as a point source. In the next step the dose distribution over the organ from each pixel is calculated using the radial dose behaviour from a point source of the considered isotope: the kernel. In Fig. 1 normalised beta dose point kernels of ^{131}I, ^{186}Re and ^{90}Y are presented. The radial distance is scaled by the range of the isotope. This figure shows that in the case of inhomogeneities in the activity over the source organ the dose over the organ will be more homogeneous for ^{90}Y than for ^{186}Re and for ^{131}I. This is of course due to the higher beta-energy of ^{90}Y.

For the dosimetry of radionuclide therapy, Humm [6] has classified the particulate radionuclide emissions into five groups depending upon their range.

- Long-range betas with range exceeding 1 mm. Typical examples are ^{90}Y, ^{32}P and ^{186}Re.
- Medium-range betas with range exceeding 200 μm and below 1 mm. Typical example is ^{131}I.
- Low-energy betas with range lower than 200 μm such as ^{45}Ca, ^{14}C are of low practical importance for therapy.
- Auger electrons with range in the micron and nanometre level. A lot of isotopes widely used in diagnostic nuclear medicine emit Auger electrons of low energy: ^{51}Cr, ^{67}Ga, ^{99m}Tc, ^{111}In, ^{123}I, ^{125}I, ^{201}Tl.
- The last class consists of alpha particles high LET radiation with range below 100 μm. Isotopes which can be used in practice are ^{211}At, ^{212}Bi and ^{213}Bi.

For radionuclide therapy with long- and medium-range betas, the point–kernel method can be used for the individual patient dosimetry based on the activity distribution derived from SPECT-CT. In this case the range of the ionising particles is much larger than the intercellular distance and the cellular dimensions. In a therapy with labelled cells the dose is uniform over the local tissue and over the cells. The point–kernel method will allow to calculate the dose distribution over the target organ and the critical tissues individually for each patient. Applying this method with diagnostic scans, individual treatment planning as for external beam radiotherapy is feasible.

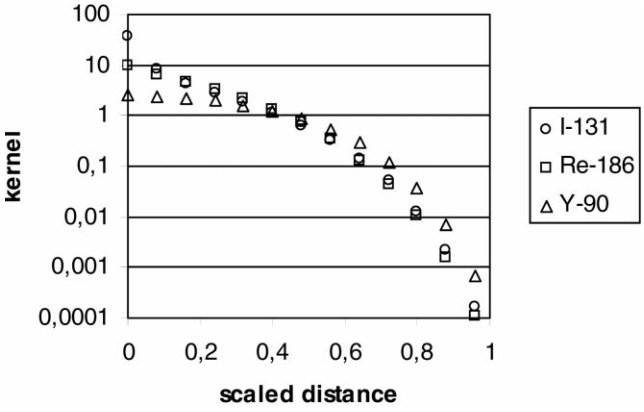

Fig. 1. Beta dose point kernels of ^{131}I, ^{186}Re and ^{90}Y. The radial distance is scaled by the range of the isotope.

In the Nuclear Medicine Department of the University Hospital, Ghent individual patient tumour dosimetry with the point–kernel method is applied for the follow-up of the paediatric patients treated with ^{131}I-MIBG for neuroblastoma. Usually an activity of 3.7–7.4 GBq (100–200 mCi) ^{131}I-MIBG is administered. The anatomical data of the patients are acquired by CT. The patient activity distribution is determined from SPECT images at 2, 7 and 10 days post-administration. The dose-rate distribution over the tumour is calculated at the different time-points of data acquisition applying the point–kernel method. Finally the dose distribution over the tumour is obtained by integration of the functional fit to the dose-rate behaviour.

In Fig. 2 different CT-SPECT combined slices over the tumour region in the case of a neuroblastoma patient are represented. These images were obtained by image fusion worked out by the ELIS-MEDISIP group in collaboration with the Nuclear Medicine Department of the University Hospital, Ghent. The CT data are in grey, the SPECT data obtained after an administration of ^{131}I-MIBG are coloured.

4. Microdosimetry

In recent years the clinical application of radiolabelled antibodies with an alpha emitter has become possible: alpha-labelled radioimmunotherapy (RIT) [7]. On the other hand, MABG with the alpha emitter ^{211}At replacing the beta-emitter ^{131}I for radionuclide therapy of neuroblastoma has been worked out [8]. Alphas are high LET

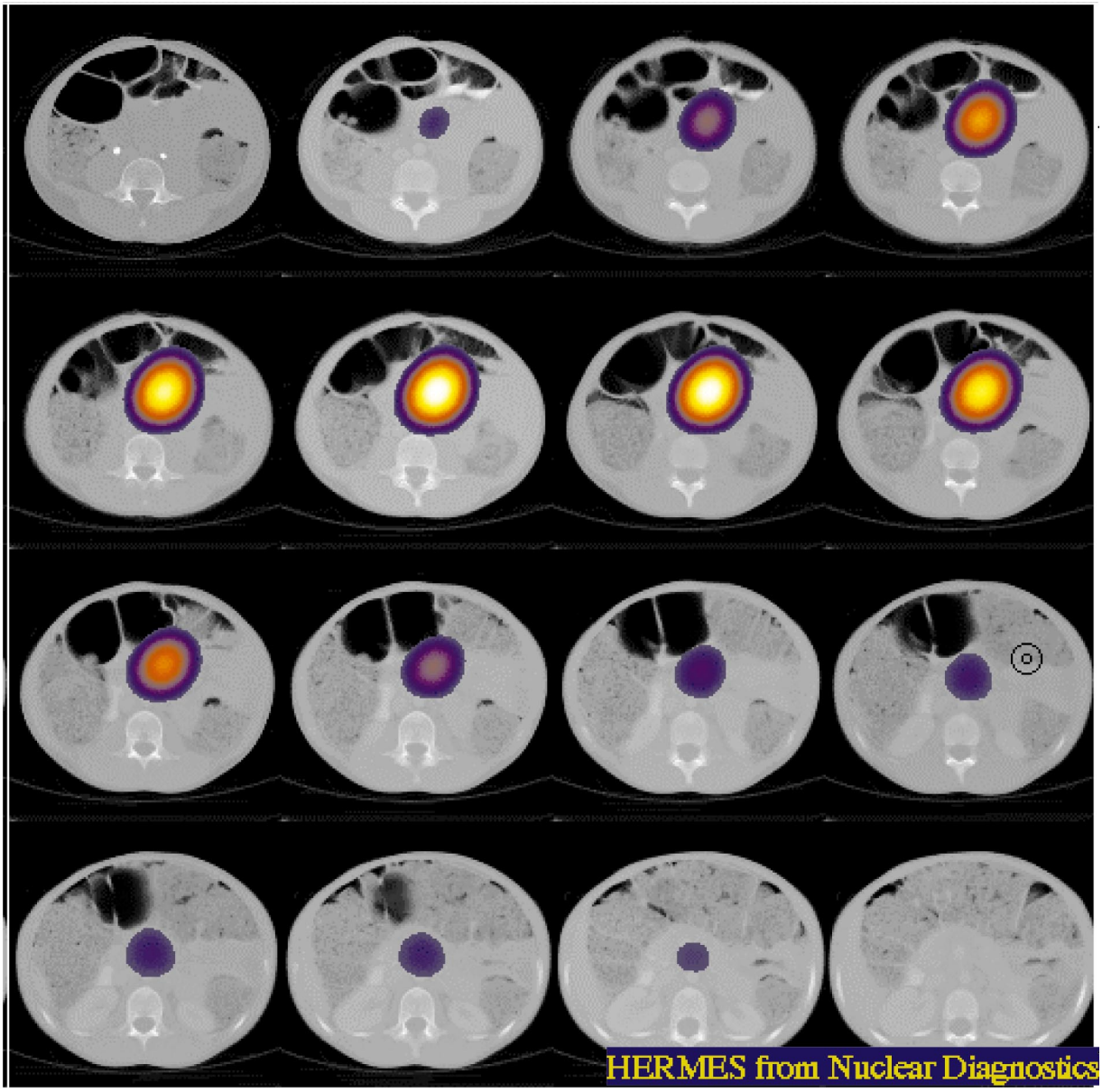

Fig. 2. Abdominal CT-SPECT combined slices over the tumour region in the case of a neuroblastoma patient. These images were obtained by image fusion worked out by the ELIS-MEDISIP group. The CT data are in grey and the SPECT data obtained after an administration of ^{131}I-MIBG are coloured.

radiation in contrast to the low LET nature of betas: the ionisation density along the path of the particle is about 1000 times larger for alphas than for betas. This means that after traverse of the cell nucleus by an alpha particle complex DNA damage occurs which turns out to be irreparable or misrepaired if repaired. As a consequence of this, single cells are sterilised by only two or three traverses of the cell nucleus. Due to this low number, the stochastic nature of the energy deposition has to be taken into account. Therefore prediction of the biological effects of alpha therapy by average quantities of energy deposition as the absorbed dose need to be replaced by simulations of alpha tracks by Monte Carlo techniques, which is the domain of microdosimetry [9].

In alpha therapy the radiobiological effectiveness of the therapy is not determined by the average dose over the cells but by the hit- and energy deposition distribution over the target cell nuclei, e.g. the number of zero hits will determine the number of surviving tumour cells. It is clear that point–kernel dosimetry cannot be applied to alpha therapy dosimetry. To highlight the necessary stochastic character of alpha dosimetry the number of alpha and beta tracks through a lymphocyte, giving an average cell dose of 1 cGy, are considered. An average dose of 1 cGy of betas results in an average number of electron track traverses of 50 per cell with a standard deviation of 7 hits. An average dose of 1 cGy alphas results in a spectrum of individual cell doses ranging from zero to 30 cGy with a mean number of alpha

particle hits per cell of only 0.1 and 90% of the cells experiencing zero hits.

5. Dosimetry of alpha-RIT

Microdosimetry for alpha-RIT is based on Monte Carlo simulation of the alpha tracks in a realistic tissue model with source and target cells. The source compartment consists in this case of monoclonal antibodies at the source cell membranes. The target compartment consists of the nuclei of the target cells. Result of the simulation is not the average dose over the nuclei of the target cells but instead the hit distribution, the specific energy deposition spectrum, the LET distribution.

Microdosimetry with Monte Carlo simulation is schematically represented in Fig. 3. The dark cells represent the source cells. The lighter cells represent the target cells with their nuclei as target compartment. At the membrane of each source cell two radiolabelled antibodies are located. The alpha tracks are represented by the straight lines. From this figure it is clear that the source cells receive a dose from the particles emitted from their own membrane: a self dose. The dose received by the target cells is the result of cross-fire: in the case of Fig. 3 there are two target cells receiving one hit and one cell receiving no hits.

Although alpha particles can be considered as magic bullets killing, e.g. tumour cells by two traverses due to their high LET nature, they are not always the first choice in RIT because of their short range: less than 100 μm. Heterogeneity of antigen expression in the tumour tissue will result in cold spots and tumour cell survival at these locations. Therefore for treatment of bulk disease beta RIT with, e.g. ^{90}Y or ^{131}I as radionuclide, is the first choice and the dose due to cross fire will be dominant. On the other hand, beta-RIT cannot treat micrometastases as the very high number of radionuclide atoms required per cell to sterilise the cell in such small tumour cannot be reached in practice. For the treatment of micrometastases alpha-RIT is necessary with high LET and in those cases where the self-dose is dominant.

In the framework of the European programme of treatment of relapse non-Hodgkin's lymphoma using alpha-immunotherapy, ^{213}Bi-antiCD20 therapy is planned in the University Hospital, Ghent. This innovative treatment will be possible by a close collaboration between the Departments of Nuclear Medicine, Biomedical Physics and Haematology. ^{213}Bi is an alpha emitter with a high energy alpha of 8.4 MeV for 98% and an alpha of 5.9 MeV for 2%. The half-life of 47 min renders this isotope practical for medical applications. It can be obtained by elution from a actinium generator with a half-life of 10 days. In a preliminary study the bone marrow toxicity of ^{213}Bi-antiCD20 therapy was investigated with Monte Carlo microdosimetry [10].

A realistic bone marrow model is of crucial importance in Monte Carlo microdosimetry of bone marrow. Morphometry of histological preparations leads to a trimodal cell distribution: 73% of the cells are small with a diameter of about 6 μm, 17% of the cells are rather large with diameter of about 12 μm and the remaining 10% of the cells are very large with diameter 16 μm. The source compartment consists of 2% of the small cells: CD20 positive B-cells. The target compartment consists of 3% of the cells with 12 μm diameter: CD34 stem cells. Monte Carlo calculations were performed for total cell densities of bone marrow of 10 000, 30 000 and 50 000 cells per microlitre. Realistic labelling efficiencies of 100 and 1000 alpha particles per cell were considered. Fig. 4 represents a 10 μm thick slice of the bone marrow model with a cell density of 30000 cells/μl. Possible target cells are indicated by the light circles. The range of the alpha emitted from the source B-cell in the middle is indicated by a circle.

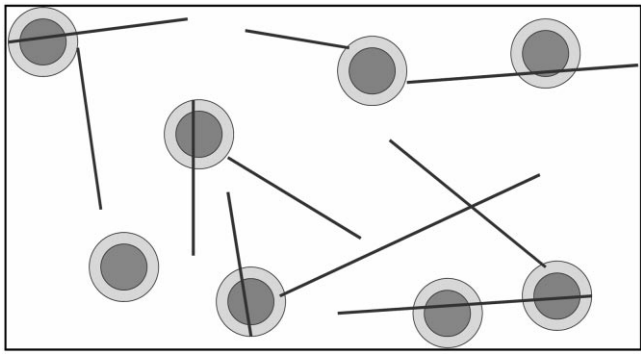

Fig. 3. Schematic representation of microdosimetry with Monte Carlo simulation for alpha-RIT. The dark cells represent the source cells. At the membrane of each source cell two radiolabelled antibodies are located. The lighter cells represent the target cells with their nuclei as target compartment. The alpha tracks are represented by the straight lines.

In Fig. 5, the hit distribution for a labelling efficiency of 1000 alphas per cell in the bone marrow model presented in Fig. 4 is given. About 20% of the target cells receive no hits and about 10% receive only one hit. Assuming that two or more hits are lethal to the cell only 30% of the stem cells will survive the therapy. Verification of the results of the calculations by in vitro experiments with stem cell survival measurements is necessary.

6. Auger electron dosimetry

Auger electron emitters are a real challenge for dosimetrists. The range of low-energy Auger electrons is in general a few nanometres. This means that Auger electrons produce small tracks with high ionisation density and that Auger electrons have a high LET character [11]. The energy of Auger electrons is deposited over subcellular dimensions in the vicinity of the decay site. As an example the Auger electron groups in the decay of ^{99m}Tc, the isotope used in 90% of the nuclear medicine examinations, are shown in Fig. 6 [12]. There is a very high intensity group, two emissions per decay, with only a range of 2 nm, the distance

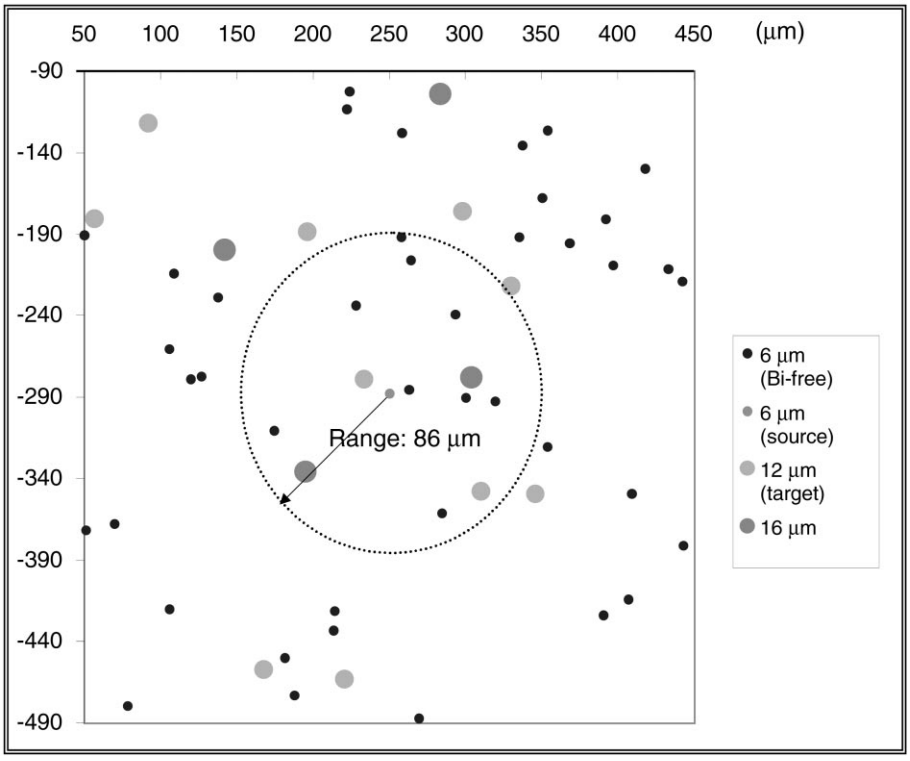

Fig. 4. Model of a 10 μm thick slice of bone marrow with cell density of 30 000 cells/μl. Target cells are indicated by the light circles.

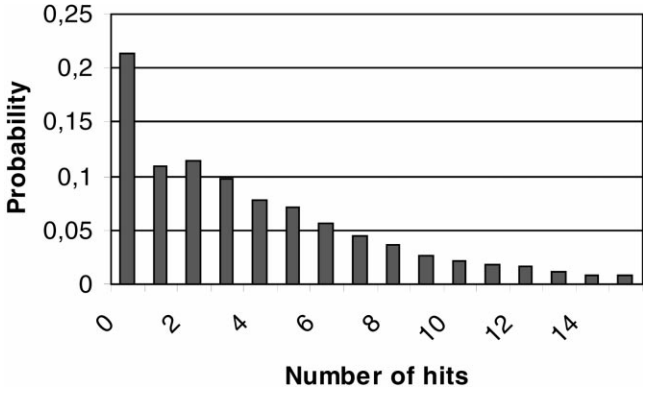

Fig. 5. Hit distribution for a labelling efficiency of 1000 alphas per cell in the bone marrow model presented in Fig. 4.

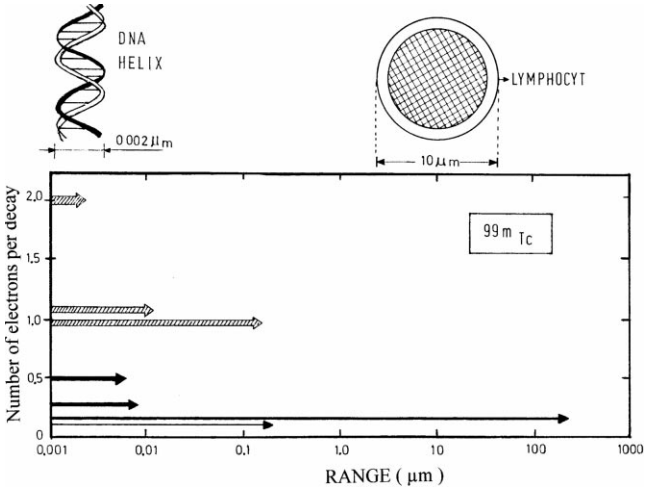

Fig. 6. Comparison of the range in tissue for the important low-energy Auger electron groups in the decay of ^{99m}Tc with the dimensions of a lymphocyte and the DNA double helix structure.

between the two strands of the DNA helix. A second high intensity group with one emission per decay has a range of only 10 nm. It is clear that by taking into account the range of Auger electrons, the biological effect is completely determined by the subcellular distribution of the isotope. The dose over cell concept is meaningless and the radiation biological effect will be determined by the energy deposition in the cellular target for the considered effect. The question that arises is: what is the subcellular structure responsible for the radiation effect? It is already known for a long time that mutagenic effects and reproductive cell death are caused by radiation damage of the DNA helix in the cell nucleus. Intracellular labelling including the nucleus with Auger emitters is highly radiotoxic. ^{99m}Tc-HMPAO used for labelling leucocytes is a well-known example [11].

As a consequence, microdosimetry with accurate subcellular modelling including the DNA is necessary for dosimetry of Auger electrons. Incorporation of ^{123}I, ^{125}I and ^{77}Br-deoxyuridine, thymidine analogues, in the DNA structure during DNA synthesis results in a tremendous high LET effect on the cell survival [13]. However, although the

intensity of the Auger electron groups in the considered three isotopes is completely different, the effect per decay in the DNA-helix on the survival is the same [14]. This indicates that the energy deposition in the DNA helix is not relevant for the observed biological effect. The explanation can be found in the field of genetics. DNA consists of active and non-active sites, and only the active sites play a role in the transfer of the hereditary material and in the molecular biology of cellular processes. So for microdosimetry of Auger electron emitters the problems lie in the biological model. Concerning radiation-induced apoptosis it remains unclear what has to be considered as subcellular target, where the apoptotic event is launched by the ionisation track. These can be sites at the DNA structure, the membrane and even the mitochondria [15]. This can be investigated by appropriate radionuclide-labelled substances emitting Auger electrons. Hence, Auger electron emitters represent powerful biological probes at the nanometre level for fundamental studies of radiation effects. More insight in this matter will allow the development of cellular models useful in microdosimetry.

7. Conclusions

The increasing importance of radionuclide therapy with new radiopharmaceuticals labelled with beta- and alpha-emitters, targeted to specific cells, has created the need for a thorough dosimetric analysis. This analysis requires that target and source are defined on a micron scale. Depending on the isotope used a macroscopic or microscopic approach is necessary taking into account the accurate distribution of the radiopharmaceutical, which may be non-uniform. A lot of research still has to be done before a real patient specific treatment planning in radionuclide therapy can be performed as in external beam radiotherapy.

8. Summary

In nuclear medical applications of isotopes the purpose of dosimetry consists primarily in the evaluation of the risk for late effects, e.g. cancer and leukaemia in patients. Secondary but not less important (and becoming increasingly important), dosimetry aims to predict the outcome of radionuclide therapy in the individual patient. For radioprotection purposes the Medical Internal Radiation Dose (MIRD) schema elaborated in the early 1970s has proven to be a robust basis for calculating absorbed doses to organs from internal radionuclides. Although the MIRD schema is suited for the determination of the radiation burden of the average man and woman due to a nuclear medicine investigation, it cannot be applied for patient dosimetry in radionuclide therapy owing to a number of limitations. In the first place there are no possibilities to take into account the individual anatomy of the patient. For an accurate determination of the dose to the target and the critical organs in an individual patient in radionuclide therapy the patient anatomical data have to be acquired via CT and the activity distribution derived from a SPECT scan. The doses to the organs or tissues of interest are then calculated from the three-dimensional activity distribution by point–kernel methods. In the Nuclear Medicine Department of the University Hospital, Ghent, individual patient tumour dosimetry with the point–kernel method is applied for the follow-up of the paediatric patients treated with ^{131}I-MIBG for neuroblastoma. For this analysis CT-SPECT combined images obtained by image fusion are used. In alpha therapy single cells are sterilised by only two or three traverses of the cell nucleus due to the high LET nature of alpha particles. Therefore average quantities of energy deposition as the absorbed dose need to be replaced by Monte Carlo simulations of alpha tracks for the prediction of the biological effects of alpha therapy. In this approximation the radiobiological effectiveness of the therapy is determined by the hit- and energy deposition distribution over the target cell nuclei and not by the average dose over the cells. In the framework of the European programme of treatment of relapse non-Hodgkin's lymphoma using alpha-immunotherapy, ^{213}Bi-antiCD20 therapy is planned in the University Hospital, Ghent. In a preliminary study the bone marrow toxicity of ^{213}Bi-antiCD20 therapy was investigated with Monte Carlo microdosimetry. For this study a realistic model of bone marrow was deduced from morphometric data of histological preparations.

Auger electron emitters are a real challenge for dosimetrists as the range of low-energy Auger electrons is in general a few nanometres and Auger electrons have a high LET character. Taking into account the range of Auger electrons, the biological effect is completely determined by the subcellular distribution of the isotope. As a consequence, microdosimetry with accurate subcellular modelling including the DNA and knowledge of the target for the considered radiation effect is necessary for dosimetry of Auger electrons. In this way Auger electron emitters represent powerful biological probes at the nanometer level for fundamental studies of radiation effects. More insight in this matter will allow the development of cellular models useful in microdosimetry. As a general conclusion we can state that a lot of research still has to be done before a real patient specific treatment planning can be performed in radionuclide therapy as in the case of external beam radiotherapy.

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