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RADIOIMMUNOTHERAPY DOSIMETRY—A REVIEW

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Results from therapeutic trials in systemic radiation therapy with radiolabelled monoclonal antibodies are difficult to compare, because of lack of accurate dosimetry. This applies macroscopically as well as microscopically for both tumours and normal tissues. For treatment planning in radioimmunotherapy both the macroscopic and the microscopic absorbed dose distribution must be known. The former is based on a proper knowledge of parameters, such as activity quantitation techniques in both planar and SPECT imaging, different correction techniques, and high activity measurements. Absorbed dose calculations and treatment planning techniques are based on analytical or Monte Carlo calculations. The PET technique with higher resolution is also suggested for radioimmunotherapy planning. Accurate in vivo absorbed dose measurement techniques to verify the calculated absorbed doses are needed in treatment planning. Monitoring the absorbed rate is desirable to assess radiobiological effect. Several ways of enhancing the therapeutic ratio are suggested, especially novel technique with extracorporeal immunoadsorption. An important topic is small scale dosimetry, which is based on techniques for detailed imaging of activity distributions to calculate the absorbed dose distribution.

Contemporary radiological treatment of cancer can be divided into three categories: external radiation therapy, interstitial and brachy therapy, and systemic radiation therapy (SRT). There are no generally accepted guidelines for the dosimetry of systemic radiation therapy as there are for external radiation therapy. Reports and manuals for external radiation therapy explain how to deliver, measure and quantify the absorbed dose in the patient (1). The radiation quality, beam properties, dose rate and targets are well defined, and the absorbed dose can be delivered in the target region with an accuracy of a few percentage. For systemic radiation therapy, however, this is not true, probably because the modality is new and is more complex than older approaches.

In reporting the results of therapeutic trials in SRT, the total activity administered to the patient in GBq or the activity per mass GBq/kg or per body surface GBq/m^2 is usually reported. The latter two quantities are probably used because of the similarity with systemic chemotherapy. These measures, however, make it impossible to relate therapeutic and toxic effects to absorbed doses in tumours and in critical organs. Even though obtaining absorbed dose information may seem cumbersome, it is important to emphasize that for the successful development of SRT, determination of the absorbed dose distribution in the patient is a prerequisite.

The use of radiolabelled monoclonal antibodies, MAb, has been in clinical practice for more than a decade, and radioimmunotherapy (RIT) has been evaluated in several clinical trials. By radiolabelling, in contrast to labelling with cytotoxic drugs, tumour heterogeneity can to some extent be circumvented, as neighbouring cells without uptake of the radionuclide may also be irradiated. Promising clinical responses with complete or partial remissions of the tumour have been observed in malignant lymphomas

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Table 1

Comparison of factors determining the absorbed dose to the target region in radioimmunotherapy and external radiotherapy

Item	Radioimmunotherapy	External radiation therapy
Radiation source	Not well defined Nonhomogeneous distributed Changing with time	Well defined
Radiation transport & energy imparted	Similar equations for photon and electron transport	
Treatment		
Local	Yes	Yes
Systemic	Yes	No
Optimization of dose distribution	Possible	Yes
Target mass	Macroscopical uncertain to define Microscopical undefined Subcellular distribution unknown	Well defined

(2) and in solid tumours, such as breast carcinoma (3) and neuroblastoma (4). The results are encouraging when it is considered that these studies are based mostly on patients with very advanced tumours.

In systemic radiotherapy the absorbed dose in a tumour or an organ, is dependent on multiple factors. Table 1 briefly compares systemic and external radiotherapy and shows the complexity of the geometry and kinetics of activity distribution and the related energy deposition in systemic radiotherapy. This makes it impossible to develop a general absorbed dose/activity conversion factor for particular therapeutic radiopharmaceutical, and stresses the necessity of individual treatment planning.

Macroscopic dosimetry—Treatment planning

The main objective in systemic therapy is to determine the absorbed dose in the target per unit administered activity (Gy/MBq). If this factor can be accurately estimated before therapy, it is possible to determine the activity of the 'therapeutic' radiopharmaceutical necessary to produce the required absorbed dose. This therapeutic dose-activity ratio can be calculated after a 'diagnostic activity' of the radiopharmaceutical or an analogue agent has been administered, provided that the biokinetics are the same as for the 'therapeutic activity'. Both activity in and the mass of the target must be measured to calculate specific activity (MBq/g). In addition, in the follow-up one must be able to determine the actual absorbed dose and the absorbed dose rate in the tumour and 'critical organs'.

Several approaches for RIT planning systems have been suggested (5–9). Most of them rely on activity quantitation by different scintillation camera methods. All absorbed dose calculations include estimation of volume and/or mass of the target region. In planar imaging the superposition of underlying tissues makes volume calculations almost impossible, in contrast to single-photon emission computed tomography (SPECT) and positron emission tomography (PET) both of which are three-dimensional (3D) modalities. In planar imaging, activity quantitation is possible only for simple source geometries, i.e., with no high background or significant overlying/underlying activity source distributions. The mass of the target, however, has to be determined with other imaging modalities, such as CT, MRI and perhaps ultrasound.

Activity within the target can be determined most precisely by SPECT. The images, however, have to be corrected for photon attenuation and scatter. Multiple tomographic SPECT images enable the target volume to be calculated if the boundary of the activity distribution can be determined: the target volume can be estimated by counting the pixels inside that boundary. Because SPECT provides physiological imaging, the macroscopic 'true' target volume is obtained, as pixel sizes and slice thickness are generally known. A limiting factor here is the spatial resolution of the SPECT system.

Volume calculations by SPECT also take into account situations when the source is non-uniformly distributed within the target. This is especially important when calculating absorbed doses. The mass can be estimated with corresponding density maps when the volumes are calculated. The absorbed dose per unit administered activity (Gy/MBq) can then be estimated from the specific activity uptake (MBq/g) within the calculated volume, using the decay-properties for the radionuclide and either Monte Carlo calculations or point dose kernels to estimate radia-

tion transport and energy imparted. For absorbed dose calculations, knowledge of biological and kinetic data of the radiopharmaceutical is essential.

Scatter correction. Scatter in the image is caused by photons that have been scattered within the object, with a change in direction and usually loss of energy. Ideally, these photons should not be detected, but due to the limited energy resolution of NaI(Tl), a relatively wide energy discriminator must be used to get good counting statistics. This means that some scattered photons of lower energy will be detected. Scatter events thus carry erroneous spatial information of the decay sites, which reduces the image contrast and makes quantification difficult. Several correction methods have been suggested and some will be briefly mentioned here. Most correction methods are based either on convolution-subtraction with a scatter line-spread function (spatial domain methods), or based on information from additional energy window acquisitions (energy domain methods). Axelsson et al. (10) investigated a 1D convolution-subtraction method in which mono-exponential functions were used as scatter line-spread functions. This method was then extended to 2D by Msaki et al. (11). A limitation was that the scatter was assumed to be stationary (12). Ljungberg & Strand (13, 14) have developed a method that uses Monte Carlo calculated non-stationary scatter functions.

Modern SPECT cameras allow multiple acquisition into separate data files, which makes the energy window methods attractive. The most commonly used method was published by Jaszczak et al. (15), who used a secondary energy window in the lower Compton region. The scatter in the main photo-peak window was estimated by scaling the secondary acquisition data with a constant k. However, a problem with this method is the difference in spatial distribution of events; the assumed constant k therefore varies with source distribution (12). New multiple energy window methods have been developed by King et al. (16) and Ogawa et al. (17). King's method (16) divides the photo-peak into two separate abutted energy windows, symmetrically located around the photo-peak. It is assumed that the ratio between these two windows is correlated with the scatter fraction by an analytical function. Ogawa's method (17) uses three energy windows—the ordinary photo-peak window and two very narrow windows on each side of the photo-peak. The scatter estimate is obtained by averaging the two narrow windows, taking into account the differences in window size.

Attenuation correction. Several attenuation correction methods have been developed, and can be categorized into pre-processing methods, post-processing methods and intrinsic methods. Pre-processing methods involve the multiplication of the projection data by an attenuation factor (18). A limitation is that neither source distribution nor non-homogeneous attenuation is easy to implement. A post-processing correction method now used mostly in commercial SPECT systems was developed by Chang (19), in which a correction matrix is calculated from re-projections of a reconstructed SPECT study, but taking attenuation into account. The reconstructed SPECT image is then multiplied by the correction matrix. The method is iterative in that the new corrected SPECT image can serve as a better estimate for calculating the correction matrix. The Chang method has also been used for non-uniform attenuation correction (20). Ljungberg and Strand have developed a similar re-projection method (21) which makes the correction of non-homogeneous attenuation possible by using density maps.

Object outline. An accurate outline of the object is crucial for attenuation correction. A simple approach has been to approximate the object outline with an ellipse. However, human anatomy varies significantly from this geometry. Furthermore, this outline is generally used for all tomographic slices, which may introduce errors for different transaxial slices. The outline can be measured by acquisition in a secondary lower Compton energy window. Since these photons are large-angle scattered, it is assumed that the corresponding reconstructed image will be so blurred that it shows only events, uniformly distributed within the patient. The outline can then be defined by finding the maximum gradient between object and air. However, the uniformity of scatter can be affected by the source distribution, especially if hot lesions are imaged. The outline can be more accurately defined by using density maps obtained either by CT or by an external flood source mounted on the scintillation camera (21). A CT study may have already been done for a RIT-patient, and could then be used for attenuation correction if the file is accessible. Problems may arise in delineation (22). Also, differences between actual photon energy used in the SPECT study and x-ray energies used to generate the CT images must be considered. Transmission studies with SPECT can be used for the proper photon energy.

Absorbed dose calculation. Activity can often be accurately calculated from a SPECT study. One major problem, however, is the limited spatial resolution of the system. A good SPECT system can generally resolve lesions down to about 6–7 mm with a high-resolution collimator and low photon energies. For high photon energies the resolution decreases significantly. For dosimetry applications, the spatial resolution sets a limit on the minimum target mass that can be calculated, although activity can be determined with great precision.

The basic problem in volume calculation is to define the target outline. The surface can be defined by analytical edge-detection, or with count thresholding techniques, for which all pixels with values above the threshold are counted as part of the volume. These methods have been compared before (23–25). To calculate the target mass, density must be known. A simplistic approach when the target location is known is to use known predefined den-

sity values. Generally, however, it is necessary to use density maps of the target region. These can be obtained from CT or transmission studies in which a flood source is mounted directly on the scintillation camera head (21). To obtain the absorbed dose, the imparted energy must be calculated from the SPECT-determined activity contents. One approach is to assume that the energy from the estimated electrons is locally absorbed. In this case, data from the decay scheme of the radionuclide can be used to calculate the imparted energy. For high-energy electrons, these assumptions may not hold and it may be necessary to trace the actual electrons' path to determine the energy fraction that escapes the volume. This may be of importance for the activity boundaries and for radiosensitive organs close to the activity. A simple approach would be to generate electron tracks using the contiguous slowing-down approximation (CSDA). A more detailed implementation involves Monte Carlo calculations, but will require extensive computing time. In addition, one must add the contribution from photons emitted from the activity in the whole body.

Treatment planning. One approach to developing an RIT planning system has been published by Sgouros et al. (26). Their system is based on activity distribution maps from which the absorbed dose distribution is calculated, using radionuclide-specific absorbed dose point kernels. The resulting dose distributions are superimposed on CT images on which isocontours of the absorbed dose can be displayed. A simple way of calculating the absorbed dose in a target is to use the medical internal radiation dosimetry (MIRD) formalism, if the target can be assumed to be identical to one of the organs defined in the MIRD scheme (27). Another approach is to use the Monte Carlo technique (28). Three dimensional treatment planning with information from SPECT or PET using Monte Carlo-derived dose kernels has been proposed by Sgouros et al. (26). This approach uses contours drawn around the activity distribution in all tomographic slices. The 3D matrix is then used as source for 3D dose calculations. The program is linked to an ordinary external beam 3D treatment planning system (29). These authors also use CT- and MRI images to overlay the absorbed dose calculation maps. This enables optimization of the tumour to non-target ratio obtained with various radionuclides as sources, and calculation of the absorbed dose distributions assuming similar biokinetics for thee radiolabelled MAbs. This is possible when using radioactive isotopes of the same element which theoretically should not change the in vivo behavior. In one of their findings, the activity distribution and the CT study differed significantly, emphasizing the necessity of incorporating functional imaging in anatomical imaging.

Table 2

Comparison of planar and tomographic imaging

Modality	Spatial resolution	Sensitivity
Planar imaging	10–20 mm	moderate
SPECT	7–15 mm	low
PET	3–10 mm	high

Count rate performance. The count rate performance of a scintillation camera is crucial when monitoring high activities, in patients undergoing radionuclide therapy. At high photon fluence rates, pulse pile-up in the crystal and count losses will occur in the camera. Afterglow of scintillation light at the decay point results in a pile-up pulse, if the following photon interaction occurs before the preceding scintillation light pulse has decayed. If no efficient pile-up rejection is included in the camera electronics, the pile-up results in severe image distortion at high activities (30, 31).

SPECT versus PET. The limited resolution in SPECT makes volume determinations of small objects difficult (32). The use of PET as an alternative for treatment planning has been suggested by Larson et al. (4). PET offers the advantage over SPECT of better spatial resolution and easier quantitation. Table 2 compares resolution versus sensitivity for planar imaging, SPECT, and PET. Attenuation correction in PET is simpler, but problems still exist with scattered events and random coincidences. A spatial resolution of about 4–5 mm is now available in most commercial systems although in research machines, resolutions as good as 2.6 mm have been obtained (33). One drawback of PET continues to be the lack of routine labelling methods. Recently, however, new methods and radionuclides have been suggested. Examples on positron emitters to label proteins, i.e., MAbs, are given in Table 3. Another drawback of modern PET systems, consisting of

Table 3

Examples on positron emitters for MAb-labelling

Radioisotope	Halflife	Note
^{124}I	4.18 d	Standard iodination labelling methods
^{76}Br	6.2 h	Standard iodination labelling methods
^{73}Se	7.2 h	^{73}Se-methionine for internal labelling
^{55}Co	17.53 h	Standard chelating labelling methods
^{64}Cu	12.7 h	Mimicking ^{67}Cu (61.92 h, β^-) for therapy
^{110}In	69 m	Standard indium labelling methods

scanners with ring detector arrays, is the high cost. Alternatives have been presented by Sandell et al. (34).

Optimization of systemic radiation therapy. Optimization means deconvolution of the kernel from the ideal dose distribution to give a desired ideal weighting distribution. This strategy of RIT optimization is straightforward and can easily be performed mathematically. Its practicality has not yet been proven. Extracorporeal immunoadsorption (ECIA, described below), seems to be a useful method for manipulating the antibody biokinetics, to obtain an increased relative antibody uptake in the tumour. Combining ECIA with different antibodies, fragments and radionuclides would provide a tool for the optimization of the absorbed dose distribution. This new technique needs extensive research efforts. A theoretical approach is presented by Sgouros (35), who used ECIA in combination with excess antibodies, to overcome the binding site barrier and obtain more homogeneous dose distributions in smaller tumours. Conformal dose planning is ideally suited to systemic radiotherapy because the scalar values in external radiotherapy, which describe the energy released per unit mass of medium of each volume element (36), are equal to the energy transfer in systemic radiotherapy i.e., the activity distribution. Activity is located at the sites of energy release, where energy is transferred to the medium through radioactive decay, producing photons and/or low or high energy electrons or α-particles. In external radiotherapy energy is transported by photons from the radiation source through the medium, where interaction occurs. The energy transport from that localization is therefore the same for the different transitions. The 3D function describing energy transport into a uniform medium can be generated by Monte Carlo calculations, and describes the fraction of energy absorbed at a point, per unit energy released per unit volume in the medium, by a particle generated at the site of the energy release. For systemic radiation therapy, the integration must be done with regard to the residence time in the medium.

Changing MAb biokinetics. The absorbed dose distribution in RIT, macroscopically and microscopically in tumour and in normal tissues, is governed by the in vivo behavior of the antibodies. If MAb biokinetics could be influenced in vivo, it might be possible to change the Ab-Ag binding profiles in tumours thereby modifying the absorbed dose distributions within tumour cell clusters (35). It should also be possible to enhance the image contrast and therapeutic ratio. This would be a first step to optimize the absorbed dose distributions in tumours and make systemic radiotherapy more comparable to conformal external beam therapy (36). Various methods have been suggested to enhance the tumour-to-normal tissue ratio. Some of them are: removal of the non-targeted radioactive antibodies by a second non-labelled antibody directed against the first one (37); plasmapheresis (38); biotinylated antibodies with a second injection of radiolabelled avidin; more stable protein labelling with minor loss of radionuclide in vivo; pre-treating the tumour with local external irradiation (39, 40) or hyperthemia; use of biological response modifiers for increasing the expression of the antigen, e.g. α-interferon (41) or interleukin 2 (3); intra-arterial injection with obstruction (42). All these methods, however, lack the ability of altering the biokinetics without increasing the absorbed dose in other organs, or in more general terms, to manipulate the biokinetics of single or multiple injected MAbs. A better method may be ECIA.

Extracorporeal immunoadsorption. The idea of applying ECIA in radioimmunodiagnosis and RIT was proposed earlier by our group (43), and has since been investigated in different models with tumour-bearing, and normal animals. The technique has also been used in a number of patients to enhance contrast in diagnosis (44) or to minimize the effect of radiation on bone marrow (45). A new method for ECIA, based on a biotin-avidin system for MAb has been developed, that does not require the development of anti-idiotypic antibodies, and can be used for antibody cocktails (46–48). The use of ECIA to reduce blood activity in radioimmunodiagnostics and RIT has been suggested earlier (43). It was shown that ECIA would reduce the background and whole body absorbed dose, and enhance contrast and therapeutic ratios. Bigler et al. (49) examined the rationale for radioimmunotherapy, postulating the removal of 90% of the excess MAb by ECIA. These authors showed that the absorbed dose to the bone marrow was significantly reduced and that increased therapeutic indices were achievable. After removal of the bulk disease by surgery and/or external irradiation the combination of RIT and ECIA could be used as sequential treatment of distant micrometastases. Wahl et al. (50), working in an animal model, reported systemic vascular perfusion with saline solution, thus simulating ECIA. The total body activity was reduced by almost 50%. The authors suggested it as an alternative method, feasible in some clinical situations. Norrgren et al. (51) used a compartment model to calculate contrast enhancement and absorbed dose reduction in critical organs after ECIA. It was shown that the tumour/whole body and tumour/bone marrow absorbed dose ratios were mostly influenced for short-lived radionuclides, when the initial uptake in bone marrow is the critical factor. The pharmacokinetic modeling of the postulated ECIA procedure was then validated in a rat model using ^{125}I-labelled anti-OV albumin MAb (47). After injection, circulating antibodies were adsorbed on an affinity column. About 90% of circulating antibodies in plasma were eliminated by ECIA. In a recent study with ECIA in nude rats heterotransplanted with human melanoma and injected with ^{125}I-labelled 96.5-antibodies, Norrgren et al. (48) showed that tumour uptake was reduced by 20–25%. The kidney, liver, lung and bone marrow uptake were reduced by 75–80% and the reduc-

tion in plasma was 90–95% (ECIA performed 24 h post-injection). Also, ^{99m}Tc-labelled red blood cells have been used to correct for circulating blood activity in different tissues (46). The corrected ^{125}I-96.5 uptake in tumours was 10–20% lower than uncorrected data. Corrected specific tissue uptake showed reduction of approximately 80% in kidney, liver and bone marrow. The same animal and tumour model was used in these two experiments. The results of the RBC method seem to correlate well with the reduction in activity achieved after ECIA in the latter study (48). Henry et al. (52) used plasma exchange to improve tumour-to-background ratios in a nude rat model with human ovarian carcinoma. These authors found decreases of 5% in tumour activity, 79% in blood activity, 85% in liver, 77% in kidneys and 72% in lungs. Lear et al. (44) removed excess antibodies in the blood by ECIA in patients with lung or breast carcinomas injected with ^{111}In-labelled KC-4G3 MAb. In seven patients ECIA was done at different times post injection, with a goat anti-mouse antibody-treated column. About 80% of the circulating MAbs were removed. A 20–40% reduction of whole-body absorbed dose was calculated by Johnson et al. (53). Significantly, there was no alteration in tumour kinetics. DeNardos et al. (45) used ECIA in a clinical situation in B-cell lymphoma patients, treated with ^{131}I-Lym-1. The addition of ECIA to the treatment protocol with the maximum tolerated dose reduced bone marrow irradiation by 50% thanks to the removal of 70–80% of circulating blood activity; thus, myelotoxicity was lessened. To overcome the problem of the need to develop a unique system for each antibody, a new ECIA method has recently been described (48) using biotinylated antibodies and an agarose-avidin column. This system also led to improvement of the tumour-to-tissue ratio. The agarose-avidin column can be used, for any antibody system and an individual anti-antibody coupled to the column is not required. With the production of human or chimeric antibodies it will be possible to repeat RIT several times without inducing an endogeneous antibody production, which impairs the tumour uptake of MAb. The use of cocktails against several antigens might decrease the heterogeneity of antibody tumour uptake. The ECIA method based on agarose-avidin reaction, can be combined with MAb cocktails. By preinfusing large amounts of unlabelled MAb (preload) it may be possible to saturate non-specific sites in critical organs, so that a subsequent dose of radiolabelled MAb is delivered to the tumour. The effect of preload has been described for L6 (54) and also for other MAbs (55–57). Preloading with L6 may also enhance the tumour uptake of a second injection of radiolabelled L6, due to increased vascular permeability mediated through the interleukin 2 receptor and/or activation of complements (3, 58). Thus by combining preload and ECIA, it may be possible to further improve the tumour/critical organ ratio.

Antigen accessibility. One major problem of RIT is that cell surface antigens in macroscopic solid tumours are largely inaccessible to circulating MAbs, especially when short-lived radionuclides and radionuclides with short-range particles are used. Factors responsible for inaccessibility are heterogeneous blood supply, elevated interstitial pressure towards the center of the tumour, and large transport distances through at least two physiological barriers within the tumour, e.g., the vascular endothelium and the interstitial fluid (59, 60). The vascular endothelium in solid tumours is characterized by tight intercellular junctions backed by continuous basement membranes forming an effectively impenetrable barrier to circulating molecules of the size, surface charge and topology of immunoglobulin (61, 62). Because of the characteristic sinusoidal vasculature of tissues in RES (i.e., the liver, spleen, lung and bone marrow), with wide interstitial junctions, numerous fenestrae, and an absent or discontinuous basement membrane, circulating molecules even as large as MAbs instantly equilibrate between plasma and the extracellular space of the RES, which is another severe limitation for RIT (62). On the other hand, tumours of the RES will also be more accessible and vulnerable to radiolabelled antibodies than solid tumours. There are already several reports of successful palliative RIT in patients with lymphomas and leukemia (2). The interstitial transport rate can be increased in solid tumours by using low molecular antibodies with high specificity. Approaches satisfying these requirements are the use of genetically engineered single chain antibodies (63) and the use of low molecular weight pro-drugs with enzyme-conjugated antibodies (64). Local radiotherapy (39, 40) and the use of interleukin might also enhance the antibody penetration (7).

In vivo absorbed dose measurements

Many efforts have been made to develop treatment planning systems for calculating the absorbed dose in the tumour and other critical organs in systemic radiation therapy (26, 28, 65). However, as in all internal dosimetry, individual patients can, because of the actual biokinetics, receive absorbed doses significantly different from the estimated ones. Thus methods for the direct measurement of the absorbed dose in vivo are highly desirable.

For SRT dosimeters should be small and sensitive to photons and charged particles. They should also be insensitive to the in vivo milieu and allow continuous measurements for long periods (up to weeks). An important feature of the dosimeter could also be its ability to measure dose rate which is of interest for the biological effect (65, 66). Miniaturized thermoluminescent dosimeters (TLD) can be used for direct measurements of the absorbed dose in vivo, as was first suggested by Wessels et al. (67–70). Mini-TLDs are small rods consisting of $CaSO_4$:Dy embedded in Teflon. Wessels' group have implanted such

dosimeters into a variety of animal organs, and have used them in several in vitro systems (71). Mini-TLDs are hygroscopical, and the signal slowly fades with time. A recent publication characterizes the effect on the signal from the mini-TLDs when used in vivo (72). These results showed extensive fading, which increases with time. After nine days in gel or muscle tissue at room temperature the signal had faded to one third of its original value. The dosimeters must be kept in constant darkness and there is a strong pH dependence. Similar results have been reported by Williams et al. (73). A recent study with electron microscopy (EM) and micro-CT has shown the disappearance of crystal material from the Teflon matrix after in vivo incubation (72). This emphasizes the need to carefully calibrate the mini-TLDs before in vivo use. In addition to the absorbed dose in vivo it is also essential to know the dose rate. A system that shows promising characteristics for dose and dose rate measurements is the MOSFET detector (74). These inexpensive dosimeters can be built very small, and make it possible to directly measure absorbed dose, which can be read at any time and used to calculate the dose rate.

Therapy with low energy electrons

Auger electron emitters are at present subject of increasing interest for systemic radiation therapy. Numerous radiobiological experiments in vitro and in vivo, have emphasized the high LET type cell killing that occurs when Auger emitting radionuclides are incorporated into DNA or enter in its vicinity in proliferating cells (75–84). Radionuclides decaying by electron capture (EC) or isomeric transition (IT), with high probability for internal conversion, result in the emission of many low energy electrons from atomic Auger processes (77, 85). A large number of these electrons have very low energies (200 eV to a few keV) and extremely short ranges (nm to a few μm) in biological material (77, 85). Therefore, when the decay occurs inside or very near the DNA double helix, the burst of Auger electron results in a highly localized energy deposition around the decay site, and molecules in the immediate vicinity of the decaying atom may become damaged leading to cell death. Thus, Auger electron emitting radionuclides hold great promises in systemic radiotherapy if appropriate carriers can be found. Attempts have been made to develop chemo-Auger combination therapy with Auger emitters labelled to bleomycin (86, 87) and carboplatin (88, 89). Many cancer cells contain hormone receptors in the cytoplasm or on the cell membrane, to which hormones or anti-hormone drugs labelled with an Auger electron emitting radionuclide may be targeted. Two examples are oestrogens (90, 91) and tamoxifen (92, 93). For Auger electron emitters it is essential that translocation to the nuclei of the cell takes place, as in the case for steroid receptors and internalizing monoclonal antibodies, which are other possible vehicles for Auger emitters in SRT.

Heterogeneous activity distribution. A major problem in systemic radiation therapy is the non-homogeneous distribution of activity in tumuroal and normal tissues, which makes relevant radiation dosimetry at the cellular level important. An additional question, especially for low energy electron-emitting radionuclides, is the intracellular activity distribution and the kinetics of cellular uptake. Autoradiography is an important instrument (94, 95) that covers many applications in biomedical research, from studies at the macroscopic level, i.e., biodistribution in whole-body sections from animals, and at the light microscopic level, i.e., distribution studies in tissues and cells, to studies on the electron microscopic level, i.e. subcellular localization. Jönsson et al. (96) selected different techniques of autoradiography to investigate the distribution of ^{111}In at the macroscopic level in the rat (97) and at the microscopic level in the testes and bone marrow. These authors showed that the ^{111}In-compounds accumulated in a strikingly heterogeneous fashion in many organs and tissues, and localized particularly in tissue characterized as rapidly proliferating, such as the bone marrow, testes, lymphatic tissue and intestinal wall. In light and electron microscopic studies, high concentrations of silver grains were found in and around the radiosensitive cells in the testes and bone marrow. Electron microscopic autoradiography confirmed the assumption that indium isotopes are internalized and retained in tissue cells.

Cellular and subcellular activity distribution. Another approach to the study of the kinetics of activity uptake is cellular and subcellular separation using different biochemical techniques. Such methods are well established for the separation of mammalian cells, and for isolation of subcellular organelles and membranes (98). Cellular and subcellular fractionation using differential centrifugation techniques makes it possible to separate different cells and cell organelles for the quantification of activity and the kinetics of uptake. The procedure outlined by MIRD (99, 100) assumes that the radionuclide and the total energy imparted are uniformly distributed within an organ or tissue. Thus, the estimated absorbed dose to all single cells in an organ is the same as the calculated mean absorbed dose to the organ itself (101, 102). The heterogeneous distribution of radionuclides within an organ, tissue or cell is neglected. In the case of radionuclides emitting low energy electrons, special attention should be paid to cellular distribution and subcellular decay sites (77, 79, 82–84, 101, 103–109). Several authors have discussed methods for estimating the 'absorbed dose', or the energy imparted, to parts of tissues, i.e. cell clusters or individual cells (76, 80, 103, 106, 108, 110). It is to be hoped that research in cellular or small scale dosimetry will improve our understanding of localized energy depositions. However, this approach has to be combined with studies of the relative

biological effectiveness of Auger electron emitting radionuclides to give an idea of their potential in future applications of systemic radiotherapy. It is possible that 3D dosimetry (26, 111) will become a reality for cellular and subcellular absorbed dose distributions. Quantitative autoradiography offers techniques that make it possible to study in detail the non-uniform distribution of a radioactive compound in the tumour and tissue of interest, and at the same time estimate its activity concentration (97, 112).

Concluding remarks

The present overview stresses that for the future development and evaluation of systemic radiation therapy, e.g. RIT, dosimetry should be as accurate as possible. Treatment planning and dose measurement are indistinguishable components in these efforts. Below are some suggestions for a future strategy in systemic radiation therapy, e.g. RIT, that might serve as a guideline for treatment planning.

- Selection of MAbs by biopsy and immunohistochemistry using a panel of MAbs to partly overcome non-homogeneous activity distributions.
- Treatment planning based on quantitative SPECT to determine tumour and normal tissue activity, and functional imaging for volume quantitation.
- Treatment planning with 'conformal dose planning' and optimal choice of combinations of MAbs (e.g. fragments or single chains) and radionuclides.
- In vivo dosimetry for verification.
- Small scale dosimetry, to determine localized absorbed doses from non-homogeneous activity distributions and cellular localization.

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