# An overview of imaging techniques and physical aspects of treatment planning in radioimmunotherapy

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Planar and tomographic imaging techniques and methods of treatment planning in clinical radioimmunotherapy are reviewed. In clinical trials, the data needed for dosimetry and treatment planning are, in most cases, obtained from noninvasive imaging procedures. The required data include tumor and normal organ volumes, the activity of radiolabeled antibodies taken up in these volumes, and the pharmacokinetics of the administered activity of radiolabeled antibodies. Therefore, the topics addressed in this review include: (1) Volume determinations of tumors and normal organs from x-ray-computed tomography and magnetic resonance imaging, (2) quantitation of the activity of radiolabeled antibodies in tumors and normal organs from planar gamma camera views, (3) quantitative single-photon emission computed tomography and positron emission tomography, (4) correlative image analysis, and (5) treatment planning in clinical radioimmunotherapy.

## I. INTRODUCTION

Knowledge of the absorbed dose in tumors and normal tissues in clinical and experimental radioimmunotherapy (RIT) is essential for an understanding of the underlying radiobiological principles of tumor dose-response relationships and normal-tissue toxicity. In clinical RIT, the dose is calculated rather than measured, and calculations are usually based on noninvasive imaging procedures. To develop a treatment plan for an individual patient, prospective dose estimates can be made by using a tracer activity of radiolabeled antibody to obtain phamacokinetic information prior to the administration of a larger therapeutic activity. As the pharmacokinetics depend in part on the mass of antibody administered, the mass used for treatment planning purposes should be nearly the same as that used for the therapeutic administration. Additionally, dose calculations often require that tumor and normal organ masses be estimated. This can be done by using one or more of the tomographic methods discussed in this review. Currently, it is impractical to determine the mass of every organ that can be imaged for every patient. However, it is often feasible to compute the mass of those tumors that can be imaged, the mass of the tumor-bearing organ and the masses of those organs that demonstrate a significant uptake of radiolabeled antibody. The dose to other organs can be approximated by making a class dose estimate which can, for example, be based on tabulated values of "$S$" factors.[1] This is particularly important for radionuclides that emit high-energy photons (e.g., $^{131}$I) which irradiate the whole body.

For beta-particle dosimetry, knowledge of tumor and normal organ volumes is not essential as long as the source volumes are large enough so that only a negligible fraction of the energy of the contained activity escapes. For diagnostically detectable tumors this condition is usually met. For calculations of the mean dose only the mean value of the concentration of activity and kinetic information are required. However, for calculations of the variation in local dose, knowledge of the distribution of activity in the source volume is necessary. The quantitation of activity distributions in tumors is an area of considerable current research interest.

Even after all methods of quantitation have been used, the information about the spatial distribution and temporal activity of radiolabeled antibodies in patients is rather limited. It is, therefore, necessary to interpolate and extrapolate the available information and construct a model so that dose calculations can be carried out. In this sense, the dose is calculated for a model rather than the patient.[2] The overall effort in RIT dosimetry and treatment planning is to make the model resemble the patient as much as possible.

In the past decade, much work has been done to develop methodology, computer algorithms and software for quantitative imaging and image analysis to generate the information required for dosimetry in RIT and the development

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of better models. The principal purpose of this review is to summarize these developments so that they will become more readily accessible to those who have an interest in or are entering the field of radioimmunotherapy. The body of this review is organized into five sections: (1) volume determinations from computed tomography (CT) and magnetic resonance (MR) scans, (2) activity quantitation from planar gamma camera views, (3) quantitative single-photon emission computed tomography (SPECT) and positron emission tomography (PET) of radiolabeled antibodies, (4) correlative image analysis, and (5) treatment planning in RIT. The presentation of this material is intended for the nonspecialist and is intentionally nonmathematical. For an in-depth understanding of any of the topics covered, the reader is referred to the literature cited.

### A. Volume determinations from CT and MR scans

In the context of RIT, tumor and normal organ volume computations are used for two purposes: dosimetry and followup studies of patients to assess tumor response to therapy. Although normal-organ volume computations had been carried out by several investigators,[3–5] hepatic tumor volume determinations from CT scans were developed independently by Moss *et al.*[6] and Leichner *et al.*[7] Similar volume determinations for pheochromocytoma tumors were later made by Koral *et al.*[8] These methods were labor intensive and slow because regions of interest (ROIs) corresponding to tumor and normal tissues were generated manually.

Volume computations were automated to some extent by Yang *et al.*[9] who have described interactive computer software for generating ROIs in transverse CT slices of patients with primary hepatic cancers. This method required an operator to specify lower and upper CT numbers for boundary pixels of the liver and define a "seed pixel" within the liver for a computer search of the first boundary pixel. After the first boundary pixel was located, nearest neighboring pixels were analyzed by the computer software for the same boundary condition. In this manner, a connecting vector was specified for the first and second pixels. This process was repeated until a complete ROI was traced and displayed on a computer graphics work station. If the computer went astray, the operator eliminated the incorrect portion of the ROI interactively. Discrimination between normal liver and tumor was achieved using a histogram method. Histograms of CT number distributions within each ROI were obtained. However, individual histograms did not contain sufficient statistical information to distinguish between tumor and normal liver. Global histograms were, therefore, generated by summing over individual histograms. The global histograms were analyzed by fitting them to the sum of three Gaussian distribution functions. Threshold CT numbers for assigning volume elements (voxels) to either tumor or normal tissues were determined in this manner. Tumor and normal liver volumes were computed by summing over the corresponding voxels. Although the computer software was initially developed for volume computations from CT examinations of patients with primary hepatic cancers, it has been generalized to include MR scans and applied to volumetric analyses of diverse cancers and benign lesions.[10,11] Comparison of CT-based volume computations of liver tumors and normal liver with autopsy data for four patients demonstrated that computations were accurate to within 2.0%–6.4%.[12]

As discussed by Udupa,[13] volume determinations from transverse CT and MR slices represent only one aspect of image segmentation in the field of three-dimensional (3D) imaging in medicine. It is anticipated that 3D imaging will play an important future role in improving dosimetry and treatment planning in clinical RIT.

### B. Activity quantitation from planar gamma camera views

The most widely used methods for quantitating tumor and normal organ uptake of radiolabeled antibodies are based on conjugate (180-deg opposed) gamma camera views. Two methods have been and are used in clinical RIT. One of these was introduced by Sorenson[14] and further developed by Thomas *et al.*[15,16] It requires the acquisition of a transmission scan and conjugate-view count rates for the quantitation of activity. This approach was adopted by Leichner *et al.*[7] to estimate the activity of $^{131}$I-labeled antiferritin in the tumor and liver of patients with hepatoma. In view of the large tumor and liver volumes and the variation of body thickness over these volumes, a pixel-by-pixel attenuation correction was included in a computer program for activity calculations. For smaller tumors in locations where body thickness does not vary greatly, regional attenuation correction should be satisfactory. The same method was used by Hammond *et al.*[17] to quantitate the distribution of $^{131}$I-labeled F $(ab')_2$ fragments of monoclonal antibody in humans. These authors evaluated the validity of this method in phantom studies using a fillable, tissue-equivalent organ-scanning phantom with tumors and organs of various sizes. Less than 10% error was found in quantitating $^{131}$I activities in a 4-cm-diam lesion. However, in a 2-cm tumor the error was greater than 21%. Similar results were obtained by Eary *et al.*[18] in a study using phantoms and dogs.

A variation of the conjugate-view method was developed by Wu and Siegel.[19] This technique also requires count rates for opposing gamma camera views, but the need for a transmission scan is obviated by measuring the buildup factor. The buildup factor results from the increase in transmission under broad-beam conditions in clinical nuclear medicine. It depends on photon energy, source geometry, collimator, and other measurable parameters. By making careful measurements of the buildup factor, these authors demonstrated improved accuracy in quantitating $^{99m}$Tc activities, as compared to the transmission method. More recently, Siegel *et al.*[20] have used the buildup factor method to quantitate the pharmacokinetics of $^{131}$I-labeled monoclonal antibodies in patients with B-cell lymphomas.

Although the results obtained in phantom studies have demonstrated the validity of the conjugate-view approach, the errors in patient measurements are likely to be significantly greater than phantom results indicate. In part, this is due to the fact that intravenous administrations of cur-

rently available radiolabeled antibodies result in a systemic distribution, with blood pool and liver activities that can persist for days post injection. Consequently, there is a superposition of activities that is difficult to resolve in planar images. On the other hand, if the tumor-to-blood and tumor-to-normal tissue ratios are sufficiently high, measurement errors will be reduced. There are, however, two additional problems associated with planar imaging that can best be resolved with emission tomographic methods. As stated previously, planar gamma camera images do not provide the volumetric information needed for dosimetry. Volumes obtained from CT and MR scans are in most cases used in radiation absorbed-dose calculations. However, CT- and MR-derived volumes need not necessarily be the same as the volumes in which radiolabeled antibodies localize (localization volumes) because the physiological uptake of antibodies may not correspond exactly to the anatomical configuration of an organ or tumor. The second problem is that planar images do not provide sufficient information about the distribution of activity within an organ or tumor. Therefore, only the mean value of the absorbed dose can be calculated. This may be an overestimate in hypoxic or necrotic regions at the core of a tumor and an underestimate at the periphery where the dose may be significantly higher than the mean. To improve dosimetry in clinical RIT, it is important that improvements in quantitative emission tomography continue to be pursued.

### C. Quantitative SPECT and PET imaging of radiolabeled antibodies

The long-term goals of quantitative emission-computed tomography (ECT) include: (1) the determination of localization volumes corresponding to tumors and normal organs, (2) measurements of the distribution and range of radiolabeled antibody activities within large tumors, and (3) the measurement of activity concentration within as small an anatomic ROI as possible. The achievement of these goals is to a large extent governed by the physical characteristics of the imaging system, the emission characteristics of radionuclides, the reconstruction algorithm employed, and the method of data analysis (e.g., definition of ROIs).

Physical factors that affect quantitative SPECT have been discussed by Jaszczak *et al.*[21] and perhaps the most important of these are: (1) scatter and attenuation corrections, (2) limited spatial and energy resolutions of gamma cameras, (3) septral penetration within conventional collimators by high-energy photons (e.g., $^{131}$I), and (4) statistical noise resulting from low count densities.

For SPECT, the spatial resolution is primarily determined by the collimator selected and the radius of rotation used. The collimator also determines the geometric sensitivity or the number of gamma photons that will be detected and, hence, the statistical fluctuations ("noise") that will result in the reconstructed image. The intrinsic resolution of a NaI scintillation crystal is about 3.5 mm; however, at a distance of 15 cm from the camera surface, the geometric resolution of a high-resolution collimator is approximately 8 mm. Therefore, the resulting system resolution is about 9 mm. In general, the full-width-at-half-maximum (FWHM) of SPECT devices ranges from about 7–18 mm. For PET systems, the spatial resolution ranges from about 6–13 mm. As a result, activity quantitation of small tumors, such as metastatic lesions, by ECT methods may be subject to large errors.

One approach to correct for Compton scattering in SPECT is based on the method proposed by Jaszczak *et al.*[22] This approach requires the acquisition of two planar projection data sets, one in the photopeak of the radionuclide and the other suitably windowed to image Compton scattered photons. A fraction ($f$) of the scatter image is then subtracted from the photopeak image to compensate for Compton scatter and improve quantitation. In their original work, Jaszczak *et al.*[22] imaged a $^{99m}$Tc line source in air and water, and from the reconstructed photopeak and scatter images determined a value of $f=0.5$. Subsequently, Koral *et al.*[23,24] demonstrated in phantom studies with $^{99m}$Tc and $^{131}$I as imaging agents that the value of $f$ depends on a number of parameters. Using $^{99m}$Tc and a particular algorithm and ROI, $f$ was independent of source location and background activity.

The Compton scatter subtraction method was employed by Green *et al.*[25] in phantom and clinical studies with $^{131}$I-labeled monoclonal anti-CEA. Energy windows were set at 364 keV $\pm$ 10% for the photopeak and 277 keV $\pm$ 18% for the scatter window. With these window settings, the count rates for the photopeak and scatter images were the same. The gamma camera employed by Green *et al.* was equipped with a 400-keV high-resolution collimator, and the system was calibrated in a series of phantom studies. The reconstruction algorithm included an attenuation correction using the method of Chang.[26] For their gamma camera system and reconstruction algorithm used, Green *et al.* determined that $f=0.54$, was optimal for $^{131}$I which is quite close to that obtained by Jaszczak *et al.*[22] for $^{99m}$Tc. In clinical studies with $^{131}$I anti-CEA, Green *et al.* validated scatter-corrected SPECT by estimating the activity concentration in the heart obtained from ROIs and comparing it to the activity in blood samples. This yielded a correlation coefficient of 0.96. Additionally, scatter-corrected SPECT was compared with the transmission conjugate-view method by measuring the activity in the liver and spleen. Planar imaging resulted in significantly higher values than SPECT for the spleen but showed no significant difference for the liver. This is consistent with the statements made earlier that the activity in a small tumor or organ is likely to be overestimated if it is surrounded by underlying and overlying activity.

SPECT quantitation of $^{131}$I has also been reported by Israel *et al.*[27] who used filtered backprojection to generate tomographic slices. SPECT studies were validated in a series of phantom measurements and in patients by measuring bladder urine concentrations. A different approach to quantitative SPECT was adopted by Denardo *et al.*[28] who used an empirical method of scatter correction for $^{123}$I and $^{111}$In. These authors generated a post reconstruction matrix using a linear attenuation coefficient that varied with the distance of pixels from the boundary. This removed

scattered photons and image counts in transverse slices were related to the counts from an equivalent source in air.

There is considerable interest in developing special image processing techniques for quantitative imaging of radiolabeled antibodies[29–31] and improved reconstruction algorithms to more accurately compensate for scatter, attenuation, and collimator blur.[32–34] An analysis of four intrinsic attenuation correction methods by Glick *et al.*[35] has shown that of the methods studied, those developed by Bellini *et al.*[33] and Hawkins *et al.*[34] have the least nonstationary 3D modulation transfer functions and 3D point-spread function with minimal noise amplification. For a uniform attenuation medium, these two algorithms are good choices when post-reconstruction filtering is considered. Furthermore, the intrinsic reconstruction algorithm described by Hawkins *et al.*[34] has been validated in phantom studies[36] with nonuniform activity distributions of $^{99m}$Tc and $^{111}$In and for $^{111}$In-labeled antibodies in the livers of beagle dogs.[37] Preliminary data obtained for patients who were administered $^{111}$In- or $^{131}$I-labeled antibodies have shown that this algorithm yields activity concentrations (Bq/ml) that are the same as those in patients' tissue samples.[38] Much interest is also being shown in maximum likelihood-expectation maximization (ML-EM) reconstruction algorithms.[39,40] Recent work has demonstrated that these techniques can result in smaller relative noise magnitude as compared to filtered back projection[30,31] and produce fewer artifacts.[41–43] Additionally, there are ongoing efforts in image reconstruction to use a priori information concerning the source.[44,45] These approaches have the potential of significantly improving quantitative SPECT in clinical studies.

Although the emphasis in this review is on recent developments in imaging related to clinical RIT and radioimmunodiagnosis (RAID), quantitative SPECT has been studied by many investigators,[46–54] and it is, in part, their work that has provided the foundation for the ongoing efforts discussed above.

In addition to the development of improved reconstruction algorithms, progress has been made in developing better imaging systems. The resolution and sensitivity of SPECT devices can be improved simultaneously by using specially designed collimators[55–59] and SPECT systems having larger detector areas.[60–65]

The common denominator of all the quantitative SPECT studies cited is careful validation of the methodology used to extract quantitative information from reconstructed images. Validation is absolutely essential because different SPECT devices and reconstruction algorithms have a profound effect on the quality of reconstructed images.

The use of PET devices in oncologic imaging has been limited in the past but there is growing interest in the application of positron emitters in the diagnosis and treatment of cancer. As is the case for SPECT devices, there is a variety of PET systems. Positron instrumentation has been described in reviews by Brownell *et al.*[66] and Ter-Pogossian.[67] PET reconstruction algorithms have, for example, been reported by Phelps *et al.*[68,69] The advantages of PET over SPECT imaging are increased spatial resolution, as discussed, and attenuation correction with a high degree of precision. The resulting image quality is superior to that achieved with SPECT. The growing interest in oncologic PET imaging is, in part, related to the increasing number of whole-body devices and the fact that PET studies have the potential to provide the physiological information for the diagnosis of cancer based on altered tissue metabolism and to monitor the effects of therapy on metabolism. A detailed description of the applications of PET in oncologic imaging has recently been given by Strauss and Conti.[70] In the field of clinical RIT, Larson *et al.*[71] and Pentlow *et al.*[72] have reported PET scanning of $^{124}$I-labeled 3F8 monoclonal antibody as a method of tumor dosimetry and treatment planning prior to the administration of $^{131}$I-3F8 for the therapy of neuroblastoma. These authors conclude that this technique shows promise for determining the radiation-absorbed dose for $^{131}$I-3F8 RIT.

### D. Correlative image analysis

Three-dimensional (3D) representations of 2D tomographic data and correlative analysis of CT, MR, PET, and SPECT scans have become increasingly important in medicine. Work in 3D rendering of bony structures carried out by Hemmy *et al.*[73] and Herman *et al.*[74] was based on CT scans and proved clinically useful in craniofacial surgery and orthopedics. In this early work only bony surfaces were visualized and soft-tissue information was lost or not used in the process of reformatting the CT data. However, subsequent investigations by Goldwasser *et al.*,[75] Jackel,[76] Lenz *et al.*,[77] and Hoehne *et al.*[78] have addressed the software and hardware problems of 3D displays that preserve the gray-scale information of the original data. These efforts have produced display systems that are generally applicable to diagnostic radiology and surgical planning. In the past few years, computer systems for 3D displays of medical images have become commercially available.

Three-dimensional correlative imaging has been employed by several authors in the treatment of brain tumors and neurological disorders. For example, Schad *et al.*[79] have used 3D correlative imaging in radiotherapy treatment planning of brain tumors. Their technique required a stereotactic head holder made of wood to precisely and reproducibly localize the target volume during CT, MR, and PET imaging and radiotherapy. Magnetic resonance scans were obtained in addition to CT because of MRs superior soft tissue contrast. For PET imaging, ($^{18}$F)-2-deoxyglucose (FDG) and $H_2{}^{15}O$ tracers were used to assess the rate of glucose utilization and perfusion of brain tumors. The target volume was defined by manually drawing ROIs in tomographic slices and subsequently generating 3D displays of this volume and the patients' head contour. Others, for example, Vannier and Gayou,[80] have advocated computer solutions for automated registration of multimodality images because these are noninvasive and can be applied retrospectively.

One such approach has been described by Pelizzari *et al.*[81] who generated surface models of the head based on CT, PET, and MR scans to derive the coordinate transfor-

mations required for 3D congruence of these models. After the transformations were determined, volume information could be transferred between scans and displayed three dimensionally or in tomographic slices. As the work of Levin *et al.*[82] has shown, this technique can result in striking 3D and 2D representations of MR and PET images that are of clinical importance in planning brain surgery. Although correlative imaging has not yet been employed in the RIT of malignant brain tumors, it is quite possible that MR and PET imaging would be useful in assessing tumor response to therapy. For example, FDG and $H_2{}^{15}O$ PET studies following RIT could be used to monitor changes in glucose utilization and perfusion and related to possible anatomic changes in MR images.

Correlative CT-SPECT imaging was used by Kramer *et al.*[83] to identify anatomic sites corresponding to uptake of $^{111}$In-labeled monoclonal anti-CEA ($^{111}$In-MAb) in patients with colorectal adenocarcinoma. SPECT and CT studies of the abdomen were acquired for each patient. In the initial studies, $^{57}$Co point sources were placed at anatomic landmarks to provide coordinate information for subsequent matching of CT and SPECT data sets. In later studies, flexible $^{57}$Co line sources were used because these yielded information about the shape and location of the body surface in SPECT scans and permitted matching with the body surface in CT scans. For this reason, separate SPECT acquisitions were made for $^{111}$In-MAb and the $^{57}$Co markers. Transaxial CT and SPECT slices were reformatted into a common matrix size. Initial matching of pairs of CT and SPECT slices was achieved by identifying coordinates belonging to anatomic landmarks (CT) and markers (SPECT). If necessary, CT slices were translated and rotated until superposition of anatomic landmarks and the corresponding $^{57}$Co markers was achieved in a "fused" image. Once the CT and SPECT studies had been matched, ROIs in SPECT slices representing tissue uptake of $^{111}$In-MAb were transferred to CT slices. Correlative CT-SPECT imaging enabled identification of anatomic sites of tumor uptake of $^{111}$In-MAb as well as nonspecific tissue accumulation and confirmed a small lesion detected by CT.

Although the work of Kramer *et al.* was qualitative in that quantitation of the activity of $^{111}$In-MAb was not the goal of their investigation, it opens up the possibility of relating quantitative SPECT to anatomical imaging modalities (CT and MRI) for dosimetry and treatment planning in clinical RIT. In preliminary work, Koral *et al.*[84] used five point markers for superimposing SPECT and CT images of a lymphoma RIT patient. Patient dosimetry was based on volumes of interest transferred from CT to SPECT after superposition had been achieved.

### E. Treatment planning

Treatment planning relies on quantitative imaging, radiation absorbed-dose estimates, and biological input parameters for the development of treatment strategies. An example of a biological input parameter is hematopoietic toxicity, often the dose-limiting toxicity in clinical RIT. The development of clinical protocols for the treatment of hepatoma with $^{131}$I- and $^{90}$Y-labeled polyclonal antiferritin IgG is an example of how dosimetric and medical considerations can be used in clinical RIT.[85,86] In a Phase I-II Trial, administered activities of $^{131}$I-labeled antiferritin ranged from 1.18 to 5.81 GBq. It was determined that an administered activity of 1.11 GBq "saturated" most hepatomas and that larger activities did not result in increased tumor uptake. Additionally, an evaluation of the hematopoietic toxicity associated with the intravenous injection of $^{131}$I antiferritin IgG demonstrated that an activity of 1.85 GBq was well tolerated by most patients.[87] These considerations led to a treatment regimen of administering 1.11 GBq on Day 0 and 0.74 GBq on Day 5. The time interval between administrations was approximately equal to the effective half-life of $^{131}$I antiferritin IgG in the hepatoma. The second injection, therefore, "re-saturated" or maximized the activity and dose rate in the tumor and led to an increase in the integrated absorbed dose. Bone marrow toxicity has remained a limiting factor in RIT. In a effort to alleviate marrow suppression, Meredith *et al.*[88] used fractionation in the administration of radiolabeled antibodies in patients with metastatice colon cancer. Up to three weekly fractions were used to administer a total activity of 1.33 GBq of $^{131}$I-labeled antibodies. These authors reported only a minimal reduction in bone marrow toxicity for this fractionation schedule and the antibody and radiolabel used. To date, the most promising responses to RIT have been achieved by Press *et al.*[89] through the use of large administered activities (8.58–22.5 GBq) of $^{131}$I-labeled antibodies and autologous bone marrow transplantation in the treatment of refractory non-Hodgkin's lymphoma.

The development[90] of $^{90}$Y-labeled antiferritin IgG was based on the fact that, due to their higher energy, $^{90}$Y beta particles would produce a higher absorbed-dose rate and a more uniform absorbed-dose distribution than $^{131}$I beta particles. Vriesendorp *et al.*[91] have compared two groups of patients with refractory non-Hodgkin's disease who were treated with $^{131}$I- and $^{90}$Y-labeled antiferritin IgG and shown that the frequency and duration of tumor response was significantly greater in those patients who were administered $^{90}$Y-labeled antiferritin. An obvious disadvantage is that $^{90}$Y cannot be imaged quantitatively and that a second radionuclide, $^{111}$In, has to be conjugated to the same antibody for imaging and dosimetry. A review of imaging, dosimetry, and treatment planning for $^{131}$I-labeled antiferritin and anti-AFP in hepatoma, $^{131}$I-labeled anti-CEA in intrahepatic biliary cancer, and $^{111}$In-labeled antiferritin in hepatoma and Hodgkin's disease has been given by Leichner *et al.*[10]

The general requirements for treatment planning is clinical RIT have been discussed by DeNardo *et al.*[92] A computer program and imaging methodology, specifically developed for this purpose, have been described by Macey *et al.*[93] In this approach, a whole-body transmission image is acquired, using a line source containing $^{131}$I, prior to the administration of $^{131}$I-labeled antibodies. Following intravenous infusion of $^{131}$I-labeled MoAb, serial conjugate images of the whole-body, brain, chest, abdomen, and pelvis

are acquired. The activity in a tumor or normal organ is calculated from these data by the transmission conjugate-view method, previously described. Radiation absorbed-dose calculations are made according to the MIRD schema.

A computer simulation for treatment planning, applicable to RIT, has been reported by Sgouros *et al.*[94] In this calculational method, it is assumed that tumor and normal organ uptake of nonuniformly distributed radionuclides is accurately known and that this information can be transferred readily to CT images. Radiation absorbed-dose calculations are based on independently determined cumulated activities, the corresponding CT volumes, and a convolution of the source volume cumulated activity with a point-source kernel. The electron-gamma shower (EGS) Monte Carlo code, discussed elsewhere in this volume, is used to generate point-source kernels in the form of lookup tables. The results of absorbed-dose calculations are stored in a two-dimensional dose matrix which is converted into a set of color-coded isodose contours. The contours are then displayed superimposed on CT images corresponding to the target plane. As the point-source kernels are generated for an infinite medium of uniform composition, tissue inhomogeneities and boundary effects, such as soft-tissue bone interfaces, are not taken into account. However, methods for including these effects in absorbed-dose calculations are presented in another section of this volume.

The commonality in the various approaches to treatment planning is that radiation absorbed-dose calculations for tumors and normal tissues are made as accurately as possible within the limitations of available imaging devices and reconstruction algorithms for quantitative ECT. Accurate dosimetry is essential for gaining a better understanding of tumor dose–response relationships and assessments of the toxicity associated with the administration of radiolabeled antibodies. It is anticipated that with continued progress in biotechnology, immunochemistry, quantitative imaging and dosimetry, treatment planning in clinical RIT will play an increasingly important role. To maximize the radiation absorbed dose in tumors and reduce normal-tissue toxicity, treatment planning may include the route of administration (e.g., intravenous, intra-arterial, intraperitoneal, intrapleural, etc.) a choice of antibodies or fragments of antibodies, and a choice of radionuclides (e.g., low-energy electron or alpha emitters for micrometastases and high-energy beta emitters for large tumors). To optimize the therapy of primary and metastatic lesions it may, in fact, be advantageous to administer combinations of antibodies labeled with different radionuclides. The number of permutations is potentially very large, and it will be the objective of treatment planning to optimize RIT for each individual patient.

## II. SUMMARY AND DISCUSSION

In this overview of imaging techniques and treatment planning in RIT, we have described the physical aspects of these methods based principally on the recent literature. A summary of the steps involved in quantitative imaging and treatment planning for macroscopic tumors that can be imaged using CT, MR, or ECT is given below. We recognize that these methods are not applicable to micrometastases or circulating leukemia cells. However, there are many ongoing clinical trials in RIT for which quantitative imaging and treatment planning provide important information about tumor targeting, radiation-absorbed doses in tumors and normal organs, and an assessment of response to treatment.

### A. Data acquisition and calculations prior to therapy

Radiolabeled antibody imaging using a tracer activity before the administration of a therapeutic activity is essential to determine tumor and normal organ uptake and provide a rationale for therapy. In general, at least one and preferably two or more SPECT or PET studies should be acquired in addition to planar views to reliably determine clearance rates and cumulated activities for tumors and normal organs. The mass of antibody used in the imaging studies should be nearly the same as that for the therapeutic administration to avoid differences in pharmacokinetics due to differences in administered antibody masses. In addition to ECT studies, CT or MR scans in conjunction with correlative image analysis are important for volume determinations and a definitive identification of anatomical structures that show uptake of radiolabeled antibodies.

As hematopoietic toxicity is a limiting factor in RIT, information about the marrow dose is necessary for gaining a better understanding of the relationship between marrow dose and toxicity in patients who may have had prior treatment with chemotherapy, radiotherapy, or a combination of both. Activity in bone marrow can be estimated from serial gamma camera images using a method described by Siegel.[95] This should be compared with the activity in serial blood samples to estimate the fraction of blood in the marrow for use in absorbed-dose calculations.

As the spatial resolution of imaging devices is limited, image-based dosimetry provides macroscopic information about absorbed-dose distributions. Additionally, the errors in quantitating tumor and normal organ uptake of radiolabeled antibodies depend on the radiolabel used, the volume, and the imaging device. In a SPECT study of $^{111}$In-labeled antibodies in the livers of beagle dogs,[37] absolute values of percent differences between autopsy data and computed activities ranged from 2.3% to 7.5%. However, these were relatively large volumes (in the range of 400 ml) and from the discussion of the FWHM of SPECT devices it follows that for smaller volumes the percent differences will be larger. Similarly, from the discussion of PET devices it follows that PET imaging will provide more accurate data than SPECT imaging of radiolabeled antibodies.[71,72] With SPECT or PET, activity distributions can be determined in sufficiently large tumors.[71] Nevertheless, the local absorbed dose on the multicellular level will need to be determined from autoradiographs or histologic measurements of tumor biopsies. As shown by Hui *et al.*[96] in a study of absorbed-dose distributions in follicular lymphoma, the local absorbed dose may vary from the average dose by a factor of two and 70% to 80% of the tissue may receive less than the average dose. These data are indicative

of the variations in absorbed dose to be expected in clinical RIT.

For photon-emitting radionuclides (e.g., $^{131}$I) "*S*" values for tumors and tumor-bearing organs can be estimated by at least two methods. A computer program developed by Johnson[97] accounts for the presence of tumors using Monte Carlo calculations. These calculations were made for spherical tumors only, and organ distortion due to the presence of a tumor was not taken into account. A more general approach to tumor geometry was adopted by Stinchcomb *et al.*[98] who calculated "*S*" values for tumors and host organs on the basis of tabulated values of the specific absorbed fractions calculated by Berger.[99,100] This had the advantage of making calculations faster than those based on the Monte Carlo approach. Additionally, the tumor was modeled as a rectangular solid with three shape parameters which made this method more flexible, and organ distortion was taken into account in the computations. By interfacing their computations with a computer program[101] available for implementing the MIRD system, Stinchcomb *et al.*[98] were thus able to compute the dose to tumors and normal organs, including the tumor-bearing organ.

After all available methods of quantitation have been employed and dose calculations made, medical and radiobiological considerations enter into the treatment decision. For example, in a study of $^{90}$Y-labeled antiferritin in patients with hepatoma,[86] treatment was based on achieving a calculated minimum initial tumor dose rate of 10 cGy/h. If calculations indicated that this minimum dose rate was not achievable at a given level of administered activity, patients were entered into other protocols. In other studies, administered activities were fractionated because of limited tumor uptake[85] or in an effort to reduce marrow toxicity.[88] If marrow toxicity is circumvented by autologous bone marrow transplantation, second-organ toxicity may become the constraint in administered activity.[89]

### B. Data acquisition and calculations following the therapeutic administration

The radionuclide imaging that is feasible after the administration of a therapeutic activity of radiolabeled antibodies depends on the radiolabel used and the administered activity itself. Although it has been suggested by Clarke *et al.*[102] that quantitative bremsstrahlung imaging is feasible for therapeutic activities of $^{90}$Y-labeled antibodies, this is an as yet untried method. A difficulty is that if $^{111}$In-labeled antibodies are used for treatment planning, a large fraction of the bremsstrahlung spectrum will be obscured by the photopeaks and Compton scattered photons of $^{111}$In. For radionuclides that emit beta particles and also have photopeaks (e.g., $^{131}$I, $^{67}$Cu, $^{186}$Re, $^{188}$Re) imaging is constrained only by dead time considerations of gamma cameras. This problem is more severe for $^{131}$I than for the other radionuclides mentioned because of the relatively large abundance of the 364-keV photons (0.82/dis) of $^{131}$I. For most commercially available large-field-of-view gamma cameras, a total-body activity of approximately 1.11–1.85 GBq of $^{131}$I appears to be the upper limit for imaging. The importance of imaging therapeutic activities lies in monitoring therapy and testing whether scaling from the tracer to the therapeutic activity introduced changes in the pharmacokinetics and hence the absorbed dose. In addition to imaging, blood and urine samples are obtained to determine clearance rates and test for immune complexes, anti-antibodies and metabolites.

Followup CT or MR scans to assess tumor response to therapy are currently employed by most investigators as an objective means of determining this important parameter.

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