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MACRODOSIMETRY AND MICRODOSIMETRY IN RADIOIMMUNOTHERAPY

FINAL REPORT

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ABSTRACT

This report summarizes research in beta-particle dosimetry, quantitative single-photon emission computed tomography (SPECT), the clinical implementation of these two areas of research in radioimmunotherapy (RIT), and postgraduate training provided since the inception of this grant or July 15, 1989. To improve beta-particle dosimetry, a point source function was developed that is valid for a wide range of beta emitters. Analytical solutions for beta-particle dose rates within and outside slabs of finite thickness were validated in experimental tumors and are now being used in clinical RIT. Quantitative SPECT based on the circular harmonic transform (CHT) algorithm was validated in phantom, experimental, and clinical studies. This has led to improved macrodosimetry in clinical RIT. In dosimetry at the multi-cellular level studies were made of the HepG2 human hepatoblastoma grown subcutaneously in nude mice. Histologic sections and autoradiographs were prepared to quantitate activity distributions of radiolabeled antibodies. Absorbed-dose calculations are being carried out for ^{131}I and ^{90}Y beta particles for these antibody distributions.

SUMMARY OF OVERALL PROGRESS

There has been excellent progress in all areas of research supported by the agreement and this has resulted in 34 publications in the period 1989 to 1991. A list of these publications is included as an integral part of this report. The remainder of this report is organized into three sections: Beta-particle dosimetry, quantitative SPECT, clinical studies, and postgraduate training.

1. Beta-Particle Dosimetry

In clinical trials of radioimmunotherapy, absorbed-dose estimates are usually based on in-vivo quantitation of the activity of radiolabeled antibodies in tumors and normal organs from gamma camera images. Because of the limited spatial resolution of gamma cameras, clinical dosimetry is necessarily limited to the macroscopic level (macrodosimetry). Macrodosimetry is non-stochastic so that the formalism developed by the Medical Internal Radiation Dose (MIRD) Committee of the Society of Nuclear medicine is appropriate for absorbed-dose calculations. In experimental RIT, tumor dimensions are often comparable to or smaller than the range of beta particles of commonly used radionuclides (e.g. ^{131}I, ^{90}Y). Under this circumstance, deviations from the equilibrium dose must be taken into account in absorbed-dose calculations.

To take tumor dimensions into account in absorbed-dose calculations, a point-source function was developed and analytical solutions derived for several source geometries (1). Initially, these included a thin source of infinite extent and a source of finite width and infinite extent. Since then solutions for spherical geometry have also been derived. Absorbed-dose distributions for eight radionuclides (^{3}H, ^{14}C, ^{35}S, ^{131}I, ^{111}Ag, ^{32}P, ^{90}Y, ^{106}Rh) that emit beta particles with average energies from 0.0057 to 1.43 MeV were calculated from this point-source function. These radionuclides are of general interest in radiobiology and experimental and clinical RIT. Advantages of analytical solutions are that calculations based on them can be made very rapidly and they can be used to test the accuracy of numerical calculations.

Analytical solutions for beta-particle dose rates have a number of applications in experimental and clinical studies. In experimental RIT, the HepG2 human hepatoblastoma model, grown subcutaneously in nude mice, was treated with ^{131}I- or ^{90}Y-labeled polyclonal and monoclonal antibodies (2). In these experiments, absorbed-dose calculations were compared with measurements using thermoluminescent devices (TLD's) that were implanted in tumors. Calculations

were determined to be accurate, thereby obviating the need for further costly TLD measurements in subsequent experiments(2,22). An additional important result of these experiments was that the radiation absorbed dose correlated well with tumor response following treatment. There were no cures of experimental tumors following therapy with radiolabeled polyclonal antiferritin. However, following an administration of 300 μCi of ^{90}Y-labeled monoclonal antiferritin the absorbed dose in tumors was in excess of 100 Gy, and 75% of the animals in this group showed no evidence of disease at 140 days following treatment.

In dosimetry at the multi-cellular level, we have studied the same HepG2 tumor following ^{131}I-labeled antiferritin administrations. Tumors were removed from serially sacrificed nude mice and sectioned in 10-μm sections on a cryostat. Autoradiographs were prepared using emulsion dipping and film techniques. For the quantitation of grain distributions in tissues, autoradiographs and histologic sections were digitized using bright-field and dark-field microscopy. A computer algorithm and software were developed for automated grain counting. The computer software was validated by simulating clusters of grains using a Monte Carlo approach. Absorbed-dose calculations on the multicellular level have been initiated for ^{131}I and ^{90}Y beta particles using a three-dimensional cubic lattice model and random distributions of grains in a Monte Carlo approach. We are currently employing automatic grain counting, point-source functions, and Monte Carlo techniques in the analysis of autoradiographs and the calculation of three-dimensional absorbed-dose distributions.

2. Quantitative SPECT

We have developed a new reconstruction algorithm for quantitative SPECT, based on the CHT algorithm, that incorporates the energy-distance relation (EDR). Incorporation of the EDR in the CHT reconstruction algorithm has resulted in a three-to-one improvement in the-signal-to-ratio (SNR) as compared to earlier reconstruction algorithms (9,23,25,27,33). This is significant because an improvement in the SNR by a factor of three is beyond what could be obtained by

improvements in instrumentation of commercially available scintillation cameras. Improvements in the SNR was accompanied by improved quantitation in phantom studies (27) beagle dogs (30),and clinical studies. A reprint of Paper No. 30 in the publications list is provided in the Appendix, and clinical results are given in the Clinical Studies Section.

Quantitative SPECT has led to greatly improved dosimetry and treatment planning in clinical RIT (3,7,14,15,17,21,22,34) for the following reasons. In the early work on the dosimetry of radiolabeled antibodies, tumor and normal organ volumes obtained from cancer patients' CT and/or MRI examinations were used in conjunction with activity quantitation from conjugate (180-degree opposed) gamma camera views. However, volumes obtained from CT and MR scans 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 difficulty was that planar images did not provide sufficient information about the distribution of activity within an organ or tumor. Due to this lack of information, the assumption of uniform activity distribution was invoked. This yielded a mean value of absorbed dose which may have been an overestimate in hypoxic or necrotic regions at the core of the tumor and an underestimate at the periphery where the dose may have been significantly higher than the mean. It has been shown (21,30) that these difficulties can be overcome with quantitative SPECT. Quantitative SPECT directly provides the following information from tomographic slices:

- Localization volumes of radiolabeled antibodies,
- Distributions of activity within these volumes.

Consequently, radiation absorbed-dose estimates in clinical RIT can be made of the mean value and range of absorbed doses. Additionally, no other imaging modalities are required for dosimetry.

3. Clinical Studies

Quantitative SPECT was validated in two clinical protocols. In one protocol, patients with refractory Hodgkin's disease were administered ^{111}In-labeled polyclonal antiferritin for imaging and radiation absorbed-dose calculations prior to therapy with ^{90}Y-labeled polyclonal antiferritin. Validation of quantitative SPECT for ^{111}In antiferritin in patients was, therefore, essential. Comparison of the ^{111}In activity in two needle biopsies with the activity computed from transverse SPECT slices demonstrated satisfactory agreement (Table 1).

Table 1

Comparison of ^{111}In antiferritin activities obtained from needle biopsies and transverse SPECT slices

Activity (μCi/g)	
Biopsy (2 samples)	SPECT
0.13 (0.12-0.14)	0.15 (0.12-0.21)

In a second protocol, patients with Kaposi's sarcoma were administered ^{131}I-labeled polyclonal antiferritin to determine its potential for therapy. Quantitative SPECT studies were carried out to measure the biodistribution of ^{131}I antiferritin in these patients. Additionally, computed activities were compared with those obtained from punch biopsies. These results reinforced the validity of the CHT algorithm for quantitative SPECT (Table 2).

Table 2

Comparison of ^{131}I antiferritin activities obtained from punch biopsies and transverse SPECT slices

Patient No.	Activity (μCi/g) Biopsy	SPECT
1	0.18(0.16-0.20)	0.18(0.15-0.19)
2	0.40(0.34-0.45)	0.43(0.36-0.50)
3	0.38(0.36-0.39)	0.39(0.32-0.42)

In view of the validation of quantitative SPECT in phantoms, beagle dogs and patients, the dosimetry for radiolabeled antibodies at this institution is based exclusively on radionuclide imaging. As discussed, dosimetry based on volumes and activities obtained from SPECT studies is currently the most reliable method for absorbed-dose calculations in clinical trials.

4. Postgraduate Training

Dissemination of information and transfer of computer software to other medical institutions is an important function of our group. We have trained physicists and physicians from the following institutions in the use of computer software developed by our group:

1. Fox Chase Cancer Center, Philadelphia, PA
2. National Cancer Institute, Bethesda, MD
3. Mary Hitchcock Hospital, New Hampshire
4. Loma Linda University Medical Center, Loma Linda, CA
5. Royal Free Hospital School of Medicine, London, England
6. Albert Einstein Medical Center, Philadelphia, PA

7. University of Alabama Medical Center, Birmingham, AL
8. M.D. Anderson Cancer Center, Houston, TX
9. Medical College of Wisconsin, Milwaukee, WI
10. Memorial Sloan-Kettering Cancer Center, New York, NY
11. City of Hope National Medical Center, Duarte, CA

Additionally, computer software was made available to these institutions if they so desired. Through dissemination of information, our grant from the Department of Energy is, therefore, having an important impact on dosimetry in radioimmunotherapy at major medical institutions throughout the United States.

5. Conclusions and Evaluation of Progress in Research

The summary of overall progress presented in this report and the list of 34 publications for the period 1989-1991 demonstrate that there has been excellent progress in the areas of research supported under this grant. Specifically, we have achieved the following:

- Improvements in beta-particle dosimetry for experimental tumors, documented by TLD measurements.
- Beta-particle dosimetry in autoradiography.
- Development of quantitative SPECT, its clinical implementation, and clinical dosimetry based on quantitative SPECT.
- Postgraduate training of physicists and physicians from 10 major cancer centers.

In the remaining period of time remaining under this grant (through July 14, 1992) we will generalize the CHT algorithm for quantitative SPECT to include nonuniform attenuation and continue to improve quantitative autoradiography and beta-particle dose calculations for experimental tumors.

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APPENDIX

Reprint of article, entitled "Quantitative SPECT for Indium-111-Labeled Antibodies in the Livers of Beagle Dogs" by Peter K. Leichner, et al.

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