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MACRODOSIMETRY AND MICRODOSIMETRY IN RADIOIMMUNOTHERAPY

PROGRESS REPORT

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MACRODOSIMETRY AND MICRODOSIMETRY IN RADIOIMMUNOTHERAPY

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ABSTRACT

This progress report summarizes the research accomplished and its clinical implementation since July 15, 1989. To improve beta-particle dosimetry, a point-source function was developed that is valid for a wide range of beta-particle emitters. An analytical solution for beta-particle dose rates within and outside of slabs of finite thickness was validated in an experimental tumor system and is now being used in clinical radioimmunotherapy (RIT). Quantitative SPECT was validated in phantom studies, beagle dogs, and patients with Kaposi's sarcoma. It is currently being used in clinical RIT for patients with Hodgkin's disease or hepatoma. Additionally, methodologies and computer software are being developed for quantitative autoradiography to achieve absorbed-dose calculation on the cellular level.

1. Beta-Particle Dosimetry

A generalized, empirical point-source function for beta-particle dosimetry was developed and analytical solutions derived for two source geometries, a thin source of infinite extent and a source of infinite width and infinite extent (1). Absorbed-dose distributions for eight radionuclides (H-3, C-14, S-35, I-131, Ag-111, P-32, Y-90, and Rh-106) with average energies ranging from 0.0057 to 1.43 MeV were calculated from this point-source. The results demonstrated agreement with absorbed-dose distributions tabulated by Berger (2) for point sources in water over the entire energy range and over a wide range of distances from point sources.

The analytical solution for beta-particle dose rates for a thin source was compared with numerical calculations by Cross et al. (3) and determined to be in satisfactory agreement. However, our analytical solution also provided a better understanding of the behavior of the dose rate as a function of the distance z from the source plane. It showed explicitly that in the limit as z approaches zero, the dose rate diverges logarithmically, whereas at larger distances it decreases exponentially. This is the mathematical origin of methods in interpolation that have been suggested, based on numerical calculations (3).

The analytical solution for dose rates within and outside of slabs of finite thickness has a number of applications in experimental and clinical beta-particle dosimetry. In experimental radioimmunotherapy (RIT), the human hepatoblastoma model HepG2, grown subcutaneously in athymic nude mice, was treated with I-131 or Y-90 labeled polyclonal and monoclonal antibodies (4). There were no tumor cures with radiolabeled polyclonal antibody therapy. Additionally, animals treated with 200 or 300 μCi of I-131 labeled monoclonal antiferritin did not show increased survival compared to controls. However, monoclonal antiferritin labeled with Y-90 significantly prolonged survival of animals ($p<0.001$). Fifty % of the animals treated with 200 μCi and 75% of the animals treated with 300 μCi showed no evidence of

disease at 140 days following treatment. Increased survival was accompanied by a decrease in tumor mitotic rate and an increase in cellular polymorphism as determined by pathological examination. In these experiments, absorbed-dose calculations for I-131 and Y-90 beta particles based on the empirical point-source function were compared with direct measurements using thermolumincescent devices (TLD's). Calculations were determined to be accurate, thereby obviating the need for further costly TLD measurements in subsequent experiments.

A further important result, demonstrated by these experiments, was that the radiation-absorbed dose in tumors correlated directly with tumor response following treatment. Specifically, the absorbed dose in tumors for complete decay of the isotopes ranged from 165 and 330 cGy at the periphery and center of small tumors for an administered activity of 200 μCi of I-131 labeled polyclonal antiferritin to 7,573 and 12,400 cGy for 300 μCi of Y-90 labeled monoclonal antiferritin.

Additionally, the dose-rate formulas for plane sources can be applied to curved slabs, provided that the radius of curvature is large compared to the range of the beta particles. Absorbed-dose estimates for the peritoneal surfaces and the diaphragm for intraperitoneally administered colloidal P-32 in ovarian cancer patients were based on this fact (5).

Applications of point-source function based beta-particle dosimetry and computer software, developed in-house, to clinical RIT are summarized in the "Clinical Implementation" Section of this report.

2. Quantitative SPECT

Currently, the conjugate-view method of planar gamma camera imaging is the most widely used approach to the in-vivo quantitation of radiolabeled antibodies in clinical RIT. This method, if applied correctly, can yield reliable results for the total activity in tumors and normal organs if both are sufficiently large and the tumor-to-normal tissue ratio is sufficiently high. The disadvantages of the

conjugate-view method are that it is often difficult to distinguish between activity in the target tumor and surrounding normal tissues, and no information is provided about uptake volumes of radiolabeled antibodies or the distribution of activities within a tumor or normal organ. Dosimetry based on the conjugate-view method, therefore, requires volume determinations from CT or MRI studies of cancer patients and the assumption of a uniform distribution of activity. However, CT/MRI volumes are not necessarily the same as those in which radiolabeled antibodies localize, and the assumption of uniform activity distributions yields mean values of absorbed doses but provides no information about the variation of absorbed dose within target tumors and normal organs.

These difficulties can be overcome to a large extent with quantitative SPECT, limited only by the spatial resolution of gamma cameras and count rates from administered radiolabeled antibodies. We have developed a new SPECT reconstruction algorithm, the Circular Harmonic Transform (CHT) Algorithm that is noniterative and strikes the right balance between complexity, computational requirements, quantitative accuracy, and clinical relevance (6). The CHT algorithm for SPECT is based on the analytic solution of the exponential Radon transform within a convex boundary and the Circular Harmonic Transform - Fourier Transform (CHT-FT) of the centered, or premultiplied, projection data. For SPECT with parallel-hole collimation, a generalized Hankel transform of the image was matched to the CHT-FT of the sinogram. This property allowed for efficient and accurate calculation of the Hankel transform of the image without interpolation of the projection data. The generalized Hankel transform is directly inverted by use of the FFT to obtain image points evenly spaced on a polar grid. For display on a rectangular grid; that is, CRT monitors, a final transformation from polar to Cartesian coordinates is required.

We have demonstrated that this approach to quantitative SPECT requires only one-ninth as many counts/sinogram to achieve the same rms error as conventional reconstruction algorithms (7). This is an important result because radionuclide imaging, in general, suffers from poor photon statistics. The fact that our CHT Reconstruction Algorithm performs nine times better than conventional ones has resulted in accurate quantitation of nonuniform activity distributions in phantom studies (7).

To further test the CHT reconstruction algorithm for quantitative SPECT beagle dogs were imaged using In-111 labeled antibodies as imaging agent. In contrast to phantom studies which represent a static situation, beagle dogs represent a dynamic imaging problem that closely resembles patient imaging with regard to systemic distribution and organ uptake of chelated antibodies. To date, quantitative SPECT studies have been carried out for 8 beagle dogs which were administered 1 to 2 mCi of In-111 labeled antibodies. Planar gamma camera imaging commenced within 35 min post injection and was continued daily for up to 6 days. These data served to determine the effective half-life of In-111 antibody activity in the blood circulation and the liver. SPECT studies were acquired 1 day post injection, using a General Electric rotating gamma camera system with elliptical orbits in a 360-degree rotation (128 views, 15 sec/view, 64x64 matrices). The planar projection data were uniformity-corrected and reconstructed by use of the CHT Reconstruction Algorithm with computer software developed in-house. Liver volumes and In-111 activities in the liver were computed from transverse slices, 1 pixel (6.25 mm) in thickness. Autopsy values of liver volumes and activities were established 8 days post injection. The In-111 liver activities measured at autopsy were back-calculated to the time of SPECT computation, using the effective half-life

determined for each beagle dog from serial gamma camera images. A comparison of SPECT and autopsy measurements of liver volumes and In-111 antibody activities in the livers of the 8 beagle dogs studied is presented in Table 1.

TABLE 1

Comparison of SPECT and Autopsy Measurements of Liver Volumes and In-111 Labeled Antibody Activities in the Livers of Beagle Dogs.

Dog No.	A_o (mCi)	T_e (days)	Liver Volume (ml) SPECT	AUTOPSY	% diff.	Liver Activity (mCi) SPECT	Autopsy	% diff.
1	2.00	2.42	375	393	-4.6	0.303	0.312	-2.9
2	1.67	2.54	412	421	-2.1	0.283	0.277	+2.2
3	1.00	2.84	457	442	+3.0	0.636	0.665	-4.4
4	1.00	2.68	497	492	+1.0	0.641	0.605	+6.0
5	1.35	2.80	357	333	+7.2	0.426	0.461	-7.5
6	1.35	2.91	402	398	+1.0	0.389	0.416	-6.5
7	1.00	3.30	450	460	-2.2	0.524	0.541	+3.1
8	1.00	3.30	435	447	-2.7	0.586	0.573	+2.3

A_o = Administered activity
T_e = Effective half-life

The results in Table 1 demonstrate that SPECT studies can be used to accurately determine the uptake volumes of radiolabeled antibodies and the activities deposited in these volumes. Early results obtained for patients with Kaposi's sarcoma and Hodgkin's disease indicate that SPECT is equally accurate in clinical studies. In view of these results, the dosimetry in clinical RIT is now based on SPECT studies and serial gamma camera imaging, as summarized in the Clinical Implementation Section.

3. Quantitative Autoradiography

Radiolabeled antibodies injected into experimental animals distribute heterogeneously in tumors and normal organs. The quantitative characterization of this distribution is essential for the calculation of the radiation-absorbed dose in malignant and normal tissues. It is highly desirable to use stained tissue sections

dipped in emulsion fo the analysis that we wish to perform. Staining is necessary to identify specific tissue structures. Emulsion dipping is necessary to obtain maximum sensitivity, resolution, and dynamic range in the autoradiograph. We are developing an algorithm that will permit us to distinguish between exposed grain density, stained tissue structures, and identify regions of grain saturation (overexposure). This algorithm utilizes darkfield and brightfield microscopy and spectral classification.

We have in progress calibration experiments with I-131 labeled antibodies and are continuing to develop classification schemes in brightfield and darkfield images. Our image analysis system permits the user to specify a class size, and the system sorts all pixels into classes of the specified size. The brightfield/darkfield images are acquired at relatively low magnification, 25x, to maximize the area of the tissue section that can be digitally imaged. At this magnification, blood vessels, lesions, and heterogeneous grain distributions can be observed. Although staining is necessary to identify tissue structures, it obscures the exposed grains. We have circumvented this problem by taking the ratio of digitized darkfield and brightfield images. As staining reduces image pixel intensity by a certain amount for both darkfield and brightfield images, the ratio of brightfield-to-darkfield images results in a new image for which the classes are proportional to grain density. This was ascertained by selecting small regions of interest (ROI's) within each class and magnifying them 1000x. Computer software, developed in-house, was used to automatically count grains within the ROI's and relating the grain density (no. of grains/μm^2) to the image classes. Although the algorithm is currently still in the development stage, the data accumulated suggest that the analysis can be used to quantitatively determine the heterogeneous distribution of radiolabeled antibodies.

The advantage of working with spectral classes of grain densities is that it greatly simplifies absorbed-dose calculations in tissue sections. These calculations can be based on the known grain densities for each class rather than individual grains.

4. Clinical Implementation and Dissemination of Information

Improved methods of beta-particle dose calculations and quantitative SPECT, as summarized above, have been implemented for clinical trials in radioimmunotherapy at the Johns Hopkins Hospital, and computer software developed by our group has been transferred to other major medical institutions.

At the Johns Hopkins Hospital, we are employing quantitative SPECT in clinical trials with I-131 and In-111 labeled antibodies. A pilot study with I-131 labeled antiferritin of three patients with Kaposi's sarcoma has been completed. In this study, the results of quantitative SPECT were compared with the activity in tissue samples obtained from punch biopsies. The activity in tissue samples was counted in well-type scintillation counters, and the results expressed in units of $\mu Ci/g$. Reconstructed transverse SPECT slices were analyzed using ROI software developed in-house. The computer software is written such that the activity (number of counts) within ROI's is also expressed in $\mu Ci/g$. For the three patients studied, the agreement of SPECT results with the measured activity in tissue samples was exact.

We also have ongoing clinical trials in Hodgkin's disease and hepatoma. In these trials, In-111 labeled antiferritin is used as the imaging agent, with administered activities ranging from 3 to 7 mCi. The In-111 imaging studies include serial gamma camera imaging and quantitative SPECT. Serial gamma camera images are analyzed to generate disappearance curves of the activity in tumors and normal organs. SPECT studies are acquired one day post injection, reconstructed by use of the CHT reconstruction algorithm, and transverse slices analyzed with computer software, developed in-house. These data are then used to predict the range of

absorbed doses in malignant and normal tissues for possible treatment with Y-90 labeled antiferritin. If treatment is indicated on the basis of In-111 antiferritin imaging, appropriate activities of Y-90 antiferritin are administered. If there is insufficient tumor uptake, patients proceed to other protocols.

It is important to note that dosimetric evaluation of radiolabeled antibody cancer therapy for each protocol patient is carried out exclusively on the basis of serial gamma camera images and quantitative SPECT. Input from other imaging modalities (e.g. CT or MRI) is <u>not</u> required for dosimetric purposes. Of equal importance is the fact that quantitative SPECT makes it possible to determine the range of absorbed doses in tumors and normal organs. These developments have resulted in greatly improved dosimetry in clinical trials, and it is anticipated that they will provide a better understanding of the dose-response relationships in radioimmunotherapy.

An important function of our group is the training of physicists and physicians from other major medical centers in dosimetry and SPECT, and the transfer of computer software to these institutions. Computer software is made available free of charge, and the training program is funded by the American College of Radiology (ACR) for members of the Radiation Therapy Oncology Group (RTOG). Since July, 1988, we have trained physicists and physicians from he following institutions and made software available to them:

Fox Chase Cancer Center, Philadelphia, PA

NIH/NCI, Bethesda, MD

Mary Hitchcock Hospital, New Hampshire

Loma Linda University Medical Center, Loma Linda, CA

Royal Free Hospital School of Medicine, London, England

Albert Einstein Medical Center, Philadelphia, PA

University of Alabama Medical Center, Birmingham, AL

M.D. Anderson Cancer Center, Houston, TX

Medical College of Wisconsin, Milwaukee, WI

Memorial Sloan-Kettering Cancer Center, New York, N.Y.

The purpose of the ongoing training program is to standardize dosimetry in radioimmunotherapy so that RTOG-wide clinical protocols can be evaluated consistently. Through dissemination of information, our existing grant from the Department of Energy, therefore, is having an important positive impact on the treatment of cancer with radiolabeled antibodies not only at the Johns Hopkins Hospital but also at major medical institutions throughout the United States.

7. Summary

All of the goals set forth in the grant proposal for the contract period July 15, 1989 to July 14, 1990 are being achieved. The percent efforts of senior personnel devoted to this project were the same as stated in the budget summary (Form ER F 4620.1):

Peter K. Leichner, Ph.D., Associate Professor of Oncology,

Principal Investigator: 30%

Jerry R. Williams, D.Sc., Professor of Oncology: 10%

Jerry L. Klein, Ph.D., Associate Professor of Oncology: 10%

William G. Hawkins, Ph.D., Senior physicist: 25%

These percent efforts will remain the same for the remainder of the contract period. In addition to the technician and half-time secretary funded under this grant, we have also been able to provide part-time employment for 2 computer science students.

6. Literature Cited

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5. Leichner, P.K., Cash, S.A., Backx, C., and Durand, R.E.: Effects of injection volume on the tissue dose, dose rate, and therapeutic potential of intraperitoneal P-32. Radiology 141: 193-199, 1981.
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8. Research plans for the Budget Period 7/15/90 - 7/14/91

The research to be carried out in the upcoming budget period 7/15/90 - 7/14/91 will be as described in the original proposal, entitled "Macrodosimetry and Microdosimetry in Radioimmunotherapy." An approximate timetable, given on p.19 of this proposal, is reproduced here:

Year 2:

Quantitative SPECT. Continue clinical studies of I-131 and In-111 labeled antibodies in patients with Hodgkin's disease and validate SPECT studies using tumor tissue samples. Refine SPECT alforithm and software to include non-uniform attenuation required for thoracic studies. Validate SPECT for thoracic studies using an existing tissue-equivalent anthropomorphic phantom. Concurrently, refine existing computer software for correlative image analysis to include isodose curves.

Macrodosimetry. Refine computer algorithm for absorbed-dose calculations of non-uniform activity distributions and validate in phantom studies.

Microdosimetry. Fully develop quantitative autoradiography and initiate absorbed-dose calculations for microdosimetry, utilizing validated methodology and computer software for macrodosimetry.

9. Bibliography: Publications Resulting from this Project (1989/90)

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2. Klein, J.L., Nguyen, T.H., Laroque, P., Kopher, K.A., Williams, J.R., Wessels, B.W., Dillehay, L.E., Frincke, J., Order, S.E., and Leichner, P.K.: Yttrium-90 and Iodine-131 Radioimmunoglobulin Therapy of an Experimental Hepatoma. Cancer Research 49:6383-6389, 1989.

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Other Publications (1989/90

1. Vriesendorp, H.M., Herpst, J.M., Leichner, P.K., Klein, J.L., and Order, S.E.: Polyclonal Y-90 Labeled Antiferritin for Refractory Hodgkin's Disease. Intl. J. radiat. Oncol. Biol. Phys. 17: 815-821, 1989.

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3. Stillwagon, G.B., Order, S.E., Guse, C., Klein, J.L., Leichner, P.K., Leibel, S.A., and Fishman, E.K.: 194 Hepatocellular Cancers Treated by Radiation and Chemotherapy Combinations: Toxicity and Response: A Radiation Therapy Oncology Group Study. Intl. J. Radiat. Oncol. Biol. Phys. 17:1223-1229, 1989.

APPENDIX

MACRODOSIMETRY AND MICRODOSIMETRY IN RADIOIMMUNOTHERAPY

Reprints of three publications:

1. Leichner, P.K., Hawkins, W.G.,a nd Yang, N-C: A Generalized, Empirical Point-Source Function for Beta-Particle Dosimetry. Antibody, Immunoconjugates, and Radiopharmaceuticals 2:125-144, 1989.

2. Klein, J.L., Nguyen, T.H., Laroque, P., Kopher, K.A., Williams, J.R., Wessels, B.W., Dillehay, L.E., Frincke, J. Order, S.E., and Leichner, P.K. Yttrium-90 and Iodine-131 Radioimmunoglobulin Therapy of an Experimental Hepatoma. Cancer Research 49:6383-6389, 1989.

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