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SPECT ASSAY OF RADIOLABELED MONOCLONAL ANTIBODIES

Progress Report

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ABSTRACT

The overall goal of this project is to improve the effectiveness of single photon emission computed tomography (SPECT) to image and quantify radiolabeled monoclonal antibodies (MAbs). During the past year, we have made significant progress toward this goal, and this report summarizes that work. Our efforts have been mainly directed along three fronts. First, we have developed and tested new reconstruction methods including three-dimensional iterative algorithms that model non-uniform attenuation and distance-dependent detector response. Both fan beam and parallel beam collimator geometries have been modeled and novel ways of improving the efficiency of the computationally intensive methods have been introduced. Second, an ultra-high resolution, small field-of-view pinhole collimator has been constructed and evaluated. Reconstructed spatial resolution of 1 to 3 mm (FWHM) has been achieved in phantom scans with a useful field-of-view of 9 to 10 cm. Finally, we have investigated the ability of SPECT to image and quantify astatine-211 distributions. Reconstructed images of phantom data demonstrated quantitative accuracy to within 10% with proper attenuation and scatter compensation.

A. SCOPE AND SPECIFIC AIMS

The long term goal of this project is to improve the effectiveness of single photon emission computed tomography (SPECT) to image and quantify radiolabeled monoclonal antibodies (MAbs). The ability to accurately quantify the biodistribution of the relevant radioisotopes of iodine, indium, and astatine (^{123}I , ^{131}I , ^{111}In , and ^{211}At) will provide an important tool for radioimmunodiagnosis and radioimmunotherapy. This grant was originally funded by the DOE in September 1989. In the competing grant application, funds were requested for five years; however, funds were awarded for the period 1 December 1992 through 30 November 1995. Thus, it has been necessary to reduce the original scope and aims of the project. Specifically, we have eliminated the patient studies that were originally proposed. During this project period, we propose to focus our efforts on developing quantitative reconstruction algorithms and pinhole collimation for SPECT. Evaluations will be performed mainly using phantom studies. Evaluations using animal scans may be performed towards the end of the project period. In order to investigate and improve the quantitative capabilities of SPECT to image MAbs labeled with clinically relevant radionuclides, we proposed the following specific aims:

- 1) To develop and evaluate quantitative reconstruction algorithms for SPECT imaging of radiolabeled MAbs. New filtered backprojection (FBP) and iterative reconstruction algorithms (maximum likelihood-EM and Bayesian) that are computationally fast and compensate for physical factors affecting SPECT data acquisition will be tested for SPECT MAb imaging. The algorithms will be compared to the conventional FBP method in terms of quantitative accuracy.
- 2) To investigate SPECT imaging of radiolabeled therapeutic MAbs using pinhole collimation. The effectiveness of pinhole collimation to minimize quantitative inaccuracies resulting from the septal penetration of the high energy emissions of ^{131}I and ^{211}At will be investigated. Pinhole collimators will be designed and constructed using Monte Carlo simulation and evaluated with experimentally acquired phantom scans.
- 3) To determine the accuracy of SPECT to quantify iodine-123 and PET to quantify iodine-124 activities and biodistributions. Experimentally acquired SPECT scans of ^{123}I in phantoms and ^{123}I -labeled MAbs in dogs with spontaneous tumors will be quantitatively compared with corresponding PET acquisitions with ^{124}I . New methods to register the SPECT and PET scans will be developed using transmission CT and the acquisition of scatter data. This specific aim will require the development of cyclotron targets that can generate ^{124}I . The development of these targets is not part of this grant.

In addition to the research topics outlined above, during the past year we have initiated work in an area that we feel will greatly enhance SPECT MAb imaging—image registration. The correlation of 3D SPECT image data with MR or CT image data can combine high resolution anatomical information with radioisotope distribution information. Also, the 3D Bayesian reconstruction methods can use the anatomical boundary information provided by MR or CT as prior information in the SPECT reconstruction. Finally, registration of the SPECT and gamma transmission data, acquired for attenuation compensation purposes, can correct for patient movement between the SPECT and transmission scans.

B. WORK IN PROGRESS

During the past year, our efforts have been directed mainly in three areas: developing and testing new 3D iterative reconstruction algorithms, constructing and evaluating an ultra-high resolution pinhole SPECT system, and investigating the ability of SPECT to image and quantify, astatine-211 distributions. We believe that these studies have improved the capability of SPECT to quantify *in vivo* biodistributions of radiolabeled MABs and will enhance the clinical application of MABs for diagnosis and therapy. The following describes in greater detail our accomplishments in these areas.

Three-dimensional iterative reconstruction methods

The major impediments to quantitative accuracy in SPECT imaging include attenuation, detector response, and scatter. The iterative methods can accurately model these effects and improve the overall quality of the SPECT image; however, the computational requirements of these methods can be prohibitive for clinical use. Therefore, we have focused our efforts in this area on developing 3D iterative methods that not only accurately model the physics of SPECT data acquisition but also execute within practical time and memory requirements.

Accurate modeling of attenuation in the thorax region requires information of the non-uniform attenuation distribution in this region, and we have explored a novel method of obtaining this information (Turkington TG *et al* 1993(d)). The method may serve as an alternative to transmission scanning in lung perfusion or ventilation studies, or other thorax imaging wherein a preliminary perfusion or ventilation scan is done to locate the lungs. In this method, we define the lungs and outer contour from preliminary reconstructions and make a non-uniform attenuation map based on these features, assigning $\mu=0.15/\text{cm}$ to pixels inside the lungs and $\mu=0.051/\text{cm}$ to pixels outside the lungs. The method was tested using a filtered backprojection/Chang reconstruction method, although a 3D iterative method could be used instead. Improved quantitation (within 15% accuracy) resulted from the non-uniform method compared with uniform

compensation.

In another study we investigated non-uniform attenuation compensation for brain imaging, studying specifically the effect of skull attenuation (Turkington TG *et al* 1993(b)). The attenuation of 140 keV photons was measured in three empty skulls by placing a ^{99m}Tc line source inside each one and acquiring projection data. These projections were compared to projections of the line source alone to determine the transmission through each point in the skull surrounding the line source. The effective skull thickness was calculated for each point using an assumed dense bone attenuation coefficient. The relative attenuation for this thickness of bone was compared to that of an equivalent amount of soft tissue to evaluate the increased attenuation of photons in brain SPECT relative to a uniform soft tissue approximation. For the skull regions surrounding most of the brain, the effective bone thickness varied considerably, but was generally less than 6 mm, resulting in a relative attenuation increases of less than 6%.

A maximum likelihood-expectation maximization (ML-EM) reconstruction algorithm for SPECT was evaluated in terms of the contrast and noise in the reconstructed image (Gilland DR *et al* 1993(a)). These measures are relevant to the tasks of both lesion detection and quantitation in SPECT. The ML-EM algorithm, which models the three-dimensional collimator response and uniform attenuation, was compared to the conventional filtered backprojection (FBP) method with Chang attenuation compensation and either a Hann or a Metz filter. The test data were generated from Monte Carlo simulations of hot, two cm diameter lesions in a uniform background. The simulation included the effects of attenuation and detector response but not scatter. Several iteration stopping points were considered for ML-EM and several cut-off frequencies (Hann filter and powers (Metz filter)) for FBP. Four different measures of image noise which have been used by other investigators were examined. Plots of image noise versus lesion contrast were figures-of-merit for the evaluation. For noise measures that are primarily sensitive to variation in the estimated background intensity, ML-EM performed better than FBP. However, for noise measures sensitive to variation in the estimated lesion intensity, ML-EM performed worse than FBP with Metz filter. These results illustrate the problem of using such indices as predictors for the task of lesion detection. In terms of SPECT quantitation, the results suggest that for the selected source geometry, ML-EM is better for determining uptake ratio, whereas FBP with a Metz filter is better for determining lesion activity.

A three-dimensional physical model for iterative reconstruction in SPECT has been developed and applied to experimental data (Gilland DR *et al* 1993(b)). The model incorporates non-uniform attenuation using reconstructed transmission CT data and distance-dependent detector response for fan and parallel beam collimators based on response function measurements over a range of distances from the detector. The 3D model has been implemented in a computationally efficient manner with practical memory requirements. Several features of the model provide

efficiency including a new region-dependent reconstruction (RDR) technique. With RDR, filtered backprojection is used to reconstruct areas of the image of minimal clinical importance, and the result is used to supplement the iterative reconstruction of the clinically important areas of the image. The 3D model was incorporated into the ML-EM reconstruction algorithm and tested in three phantom studies—a point source, a uniform cylinder, and an anthropomorphic thorax—and a patient ^{99m}Tc -sestamibi study. Reconstructed images with the 3D method exhibited excellent noise and resolution characteristics. With the sestamibi data, the RDR technique produced essentially the conventional ML-EM estimate in the cardiac region with substantial time savings.

Pinhole Collimation for ultra-high resolution SPECT

The objective of this investigation was to evaluate small field-of-view, ultra-high resolution pinhole collimation for a rotating-camera SPECT system that could be used to image small laboratory animals (Jaszczak RJ et al 1993(a)). Pinhole collimation offers distinct advantages over conventional parallel-hole collimation when used to image small objects. Since geometric sensitivity increases markedly for points close to the pinhole, small diameter and high magnification pinhole geometries may be useful for selected imaging tasks when used with large field-of-view scintillation cameras. The use of large magnifications can minimize the loss of system resolution caused by the intrinsic resolution of the scintillation camera. A pinhole collimator has been designed and built that can be mounted on one of the scintillation cameras of a triple-head SPECT system. Three pinhole inserts with approximate aperture diameters of 0.6, 1.2, and 2.0 mm have been built and can be mounted individually on the collimator housing. When a ramp filter is used with a three-dimensional filtered backprojection (FBP) algorithm, the three apertures have in-plane SPECT spatial resolutions (FWHM) at 4 cm of 1.5, 1.9, and 2.8 mm, respectively. In-air point source sensitivities at 4 cm from the apertures are 0.9, 2.6, and 5.7 counts/sec/ μCi (24, 70, 154 counts/sec/MBq) for the 0.6, 1.2, and 2.0 mm apertures, respectively. *In vitro* image quality was evaluated with a micro-cold rod phantom and a micro-Defrise phantom using both the 3D-FBP algorithm and a 3D ML-EM algorithm. *In vivo* image quality was evaluated using two (315 and 325 g) rats. Ultra-high resolution pinhole SPECT is an inexpensive and simple approach for imaging small animals that can be used with existing rotating camera SPECT systems.

Measuring astatine-211 distributions with SPECT

We have investigated standard SPECT techniques (rotating gamma cameras, multi-hole collimators, and filtered backprojection reconstruction) for imaging astatine-211 distributions (Turkington TG et al 1993(c)). Since ^{211}At emits alpha particles, this nuclide has potential for use in radiotherapy. The capability of imaging this nuclide would allow *in vivo* evaluation of the

distribution and stability of potential ^{211}At -labeled radiotherapeutic agents. ^{211}At decay yields x-rays in the 77-92 keV range in addition to 500-900 keV gamma rays. This study evaluated the feasibility of SPECT imaging using the x-ray emissions of ^{211}At . We evaluated several collimators, with the determination that the medium-energy collimators were suitable, with 7% penetration (uncollimated counts versus collimated counts). Several phantoms were imaged and attenuation coefficients were measured (narrow beam $\mu=0.182$ for 77-80 keV x-rays in water). Reconstructed images demonstrate qualitative capabilities and a simple quantitative study demonstrated good correction for attenuation and scatter ($\sim 10\%$ error), at low count densities for the phantom geometries used in this study.

Image registration

The accuracy of a surface fitting algorithm for three-dimensional image registration of SPECT, PET, and MR images was tested using a three-dimensional, water-filled brain phantom (Turkington TG et al 1993(a)). Multi-slice or volume image sets were acquired for each modality. Small fiducial markers were attached to assist the accuracy of the surface fitting and to provide an alternate fitting technique. A maximum gradient technique was found to work well for SPECT and PET edge detection. Transformation parameters for translation, rotation, and scaling were determined by the surface fit to match each SPECT and PET scan with the MR images. Using the markers, overall translation errors were found to be less than 2 mm in each direction and rotational errors less than 2 degrees in every case. Errors for specific internal regions were also determined to be less than 2 mm for most regions, with only a few fits resulting in error greater than 3 mm for some cortical regions. These results indicate surface fitting to be sufficiently accurate for visual comparison of registered images and for enhanced SPECT and PET image reconstruction.

D. PUBLICATIONS SINCE LAST PROGRESS REPORT

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