Quantitative SPECT for Indium-111-Labeled Antibodies in the Livers of Beagle Dogs

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Results are presented for SPECT computations of liver volumes and ^{111}In-labeled antibody activities in the livers of eight normal beagle dogs. Administered activities ranged from 1 to 2 mCi. SPECT studies were acquired 1 day postinjection using a rotating gamma camera system with elliptical orbits in a 360-degree rotation (128 views, 15 sec/view, 64 × 64 matrices). Uniformity-corrected images were reconstructed by use of the circular harmonic transform algorithm with computer software developed in-house. Liver volumes and activities were computed from transverse slices, 1 pixel (6.25 mm) in thickness. Comparison of SPECT and autopsy data demonstrated that absolute values of percent differences between measured and computed liver volumes ranged from 1.0% to 7.2%. Absolute values of percent differences between autopsy data and computed ^{111}In activities in the liver ranged from 2.3% to 7.5%. These results suggest that quantitative SPECT has the potential of becoming an important tool in clinical trials for determining activities and localization volumes of radiolabeled antibodies directly from radionuclide images.

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Dosimetry in clinical radioimmunotherapy (RIT) requires quantitative radionuclide imaging to determine cumulated activities for target tumors and normal tissues. The conjugate-view method of planar gamma camera imaging is currently the most widely used approach to the in-vivo quantitation of radiopharmaceuticals, including radiolabeled antibodies (*1–8*). However, the conjugate-view method provides no information about the volumes in which radiolabeled antibodies localized (localization volumes) and the distribution of activity within these volumes.

In addition to activity measurements, radiation absorbed-dose calculations also require tumor and normal organ masses as input parameters, and volume determinations based on CT or MRI examinations of cancer patients have been used for dosimetric purposes (*4,5,7*). However, localization volumes of radiolabeled antibodies need not necessarily be the same as CT- or MRI-derived volumes because the physiologic uptake of antibodies may not correspond exactly to the anatomical configuration of an organ or tumor. Additionally, dosimetry based on total activity and total volume yields a mean absorbed dose, but provides no information about the range of absorbed doses within a tumor or normal organ. These difficulties can potentially be overcome with quantitative SPECT, limited only by the spatial resolution of gamma cameras and count rates from administered radiopharmaceuticals.

The determination of localization volumes and the activity within these volumes has been the subject of several investigations (*9–14*), which have demonstrated, in principle, that SPECT can be used for quantitative purposes. We have developed a new SPECT reconstruction algorithm, the circular harmonic transform (CHT) algorithm (*15*) that is noniterative and computationally efficient. The validation of this algorithm for quantitative SPECT in phantom studies with ^{111}In and ^{99m}Tc as imaging agents has been presented in a previous publication (*16*). In the current report, it is shown that with the CHT algorithm for quantitative SPECT, liver volumes and ^{111}In activities in the liver of beagle dogs can be obtained with sufficient accuracy to make CHT-based SPECT an important tool for quantitative purposes. Since quantitative SPECT provides more detailed information (activities *and* volumes) about the biodistributions of administered radiopharmaceuticals than can be obtained with the conjugate-view method (activities only), it is reasonable to expect that quantitative SPECT will result in improved dosimetry.

MATERIALS AND METHODS

Normal beagle dogs (average weight 10 kg) received several different antibodies conjugated to ^{111}In by different methods. Administered activities ranged from 1 to 2 mCi. This range of activities was required to maintain reasonable count rates for imaging the beagle dogs for up to 6 days. For the imaging procedures, dogs were immobilized with ketamine HCl (100 mg/ml) and diazepam (5 mg/ml) administered in an intravenous mixture every 15 min or as needed to maintain immobilization. Each administration consisted of 20 mg of ketamine HCl and 0.5 mg of diazepam per kilogram of body weight. Six to nine days following ^{111}In-labeled antibody administration, the dogs were euthanized with ketamine HCl (1 g in 10 ml) and 10 ml of

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saturated KCl solution injected intravenously. At autopsy, liver volumes were measured using an immersion technique. The activity of ^{111}In-labeled antibodies in the liver was determined from six 1-ml samples of liver parenchyma. Two of these were taken near the dome of the liver and two each from the left and right lobes. All tissues samples were counted in a well-type NaI (Tl) scintillation counter and the mean value of the activity was determined. The variation of activity in these macroscopic samples was less than one standard deviation from the mean. The mean value of the concentration (μCi/ml) was, therefore, multiplied by the measured liver volume (ml) to obtain the ^{111}In activity for the whole liver.

The experimental imaging protocol for beagle dogs was designed to be consistent with clinical protocols for cancer patients (*7*) in order to validate not only quantitative SPECT but also methods of imaging and image analysis that were used to determine the effective half-life of radiolabeled antibodies in the liver. Therefore, planar camera imaging of beagle dogs commenced within 0.5–3.5 hr postinjection and was continued daily for up to 6 days. Liver uptake of ^{111}In-labeled antibodies was rapid, and a large fraction of the administered activity localized in the liver (see Table 1). Computerized thresholding was therefore used to generate regions of interest (ROIs) corresponding to the liver in planar images. The effective half-life of radiolabeled antibodies in the liver was determined from the number of counts within the ROI in serial images of each dog.

The SPECT acquisition protocol for beagle dogs was the same as that used for patients. SPECT data were acquired on Day 1 following the administration of radiolabeled antibodies using a rotating gamma camera system with elliptical orbits (400 AT STAR, General Electric Corp., Milwaukee, WI). The planar projection data were acquired in a full 360-degree rotation in 128 views, at 15 sec/view and stored in 64 × 64 matrices. Quality control for SPECT studies include a 30-million count uniformity correction, center-of-rotation acquisition, and a measurement of the gamma camera system's sensitivity. Energy windows were ±10%, centered on each photopeak at 173 and 247 keV of ^{111}In. A zoom factor of 1 was used in all image acquisitions. Transverse slices were reconstructed from the planar projections by use of the CHT algorithm for SPECT, as previously described (*15,16*). This algorithm is based on an analytical solution of the exponential radon transform within a convex boundary and includes a correction for uniform attenuation. Two-dimensional Wiener filtering of the planar projections was carried out to compensate for scatter, collimator blur, and to improve quantitation. All reconstructions and image processing tasks were performed on a Microvax II Computer (Digital Equipment Corp., Maynard, MA) interfaced with a SKY array processor (SKY Computers, Inc., Chelmsford, MA). The computer software for reconstructions, image display and analysis was developed in-house. The time required for reconstructions was 30 sec per transverse slice. Liver volumes and activities of ^{111}In-labeled antibodies were computed from transverse SPECT slices, 1 pixel (6.25 mm) in thickness, by using a thresholding method. First, the global maximum for all SPECT slices that bracketed the liver was computed. A voxel (0.244 ml) was then determined to be a liver voxel if it was above a certain percentage of the global maximum. Pixel dimensions were measured using standard techniques (*17*), and the voxel size was the same as that used in a previous study (*16*). We have previously shown in phantom studies that a 33% threshold was optimal to minimize the error in volume determinations over the range and shapes of volumes studied (*16*). In the current study, autopsy results for the first two dogs were used to optimize the threshold for the computation of liver volumes and ^{111}In-labeled antibody activities in the liver. This threshold was determined to be at 35% of the global maximum and was subsequently used for all dogs to generate ROIs for volume and activity computations. For purposes of comparison, the activity in the liver measured at autopsy and computed at the time of SPECT imaging was extrapolated to t = 0, using the effective half-life determined for each dog.

RESULTS

The results of this study are summarized in Table 1. Liver uptake of chelated antibodies was rapid and maximum activity was attained in less than 3 hr. The clearance curves for the activity of ^{111}In-labeled antibodies in the liver were monoexponential. Effective half-life measurements and correlation coefficients for monoexponential clearance are given in Table 1. In all cases, the correlation coefficients were greater than 0.99. The accuracy of liver volume computations from SPECT slices was in the same range as that achieved with x-ray CT in an experimental study with dogs (*18*). The comparison of SPECT and autopsy measurements of the activity in the liver demonstrates that liver uptake was accurately determined with the CHT algorithm. Additionally, these results show that extrapolation from the time of autopsy to the time of SPECT data acquisition, using half-life measurements, is a valid procedure for calculating liver activity as a function of time post injection. This is of clinical relevance because radiation absorbed dose estimates for patients' normal organs, in particular the liver, are made on the basis of in-vivo quantitation and serial gamma camera imaging (*3–7*). One of the objectives of the current study was to validate this methodology for the liver.

TABLE 1
Comparison of SPECT and Autopsy Measurements of Liver Volumes and ^{111}In-Antibody Activities in the Livers of Beagle Dogs

Dog no.	A_0* (mCi)	Te† (days)	Corr. Coeff.	Liver volume (ml) SPECT	Liver volume (ml) Autopsy	% diff.	Liver activity (mCi) SPECT	Liver activity (mCi) Autopsy	% diff.
1	2.00	2.42	0.999	385	393	−2.0	0.303	0.312	−2.9
2	1.67	2.54	0.998	412	421	−2.1	0.283	0.277	+2.2
3	1.00	2.84	0.999	457	442	+3.0	0.636	0.665	−4.4
4	1.00	2.68	0.992	497	492	+1.0	0.641	0.605	+6.0
5	1.35	2.80	0.998	357	333	+7.2	0.426	0.461	−7.5
6	1.35	2.91	0.991	402	398	+1.0	0.389	0.416	−6.5
7	1.00	3.30	0.999	450	460	−2.2	0.524	0.541	−3.1
8	1.00	3.30	0.997	435	447	−2.7	0.586	0.573	+2.3

* Administered activity.
† Effective half-life of the activity in the liver.
Note: Dogs 1 and 2 were used to establish the 35% threshold (see text).

DISCUSSION

The results presented in this report demonstrate that the CHT algorithm and associated computer software for quantitative SPECT, developed in-house, have provided the capability of accurately determining liver volumes and ^{111}In activities in the livers of normal beagle dogs. In the imaging studies, care was taken to duplicate imaging protocols for cancer patients in radioimmunotherapy trials as much as possible (*7*) in order to validate not only quantitative SPECT but also effective half-life measurements from serial gamma camera images. In particular, consistent with imaging protocols for cancer patients, only one SPECT study was carried out for each dog on Day 1 postinjection for the computation of liver volumes and activities. The agreement with autopsy data demonstrated that this was sufficient due to rapid and high liver uptake and a macroscopically uniform distribution of ^{111}In-labeled antibodies in the liver. We are cognizant of the fact that the CHT algorithm is new and that in addition to phantom and experimental studies, clinical validation is required to make CHT-based SPECT an accepted tool for the in-vivo quantitation of radiopharmaceuticals. In a previous publication, we demonstrated that the CHT algorithm was useful in the reconstruction of patient data (*16*). Further clinical evaluation of this algorithm for quantitative SPECT is in progress for superficial and deep-seated tumors, and we will report the results of these studies upon their completion.

We have shown that the CHT algorithm incorporates the energy-distance relationship, which minimizes the effects of attenuation, scatter, collimator blur, and poor photon statistics. As a result, the CHT algorithm was superior to filtered backprojection in the quantitation of hot and cold lesions in a phantom study using ^{99m}Tc and ^{111}In as imaging agents (*16*). An important practical consideration is that CHT-based reconstructions require the same number of floating-point operations as filtered backprojection. Array-processor equipped nuclear medicine computers that use filtered backprojection for reconstruction are therefore capable of executing CHT computer software with approximately the same efficiency as filtered backprojection.

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