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EQPlanar: A Maximum-Likelihood Method for Accurate Organ Activity Estimation from Whole Body Planar Projections

N. Song¹, B. He², R. L. Wahl³, and E. C. Frey¹

¹Division of Medical Imaging Physics, Department of Radiology, Johns Hopkins Medical Institutions, Baltimore, MD 21287, USA

²Department of Radiology, Weill Cornell Medical Center, New York, NY 10021, USA

³Division of Nuclear Medicine, Department of Radiology, Johns Hopkins Medical Institutions, Baltimore, MD 21287, USA

Abstract

Optimizing targeted radionuclide therapy (TRT) requires patient-specific estimation of organ doses. The organ doses are estimated from quantitative nuclear medicine imaging studies, many of which involve planar wholebody scans. We have previously developed the Quantitative Planar (QPlanar) processing method and demonstrated its ability to provide more accurate activity estimates than conventional geometric-mean based planar (CPlanar) processing methods using physical phantom and simulation studies. The QPlanar method uses the maximum likelihood-expectation maximization (ML-EM) algorithm, 3D organ VOIs, and rigorous models of physical image degrading factors to estimate organ activities. However, the QPlanar method requires alignment between the 3D organ VOIs and the 2D planar projections and assumes uniform activity distribution in each VOI. This makes application to patients challenging. As a result, in this paper we propose an extended QPlanar (EQPlanar) method that provides independent-organ rigid registration and includes multiple background regions. We have validated this method using both Monte Carlo simulation and patient data. In the simulation study, we evaluated the precision and accuracy of the method in comparison to the original QPlanar method. For the patient studies, we compared organ activity estimates at 24 hours after injection with those from conventional geometric mean based planar quantification using a 24 hour post-injection quantitative SPECT reconstruction as the gold standard. We also compared the goodness of fit of the measured and estimated projections obtained from EQPlanar method to those from the original method at 4 other time points where gold standard data was not available. In the simulation study, more accurate activity estimates were provided by the EQPlanar method for all the organs at all the time points compared with the QPlanar method. Based on the patient data, we concluded that the EQPlanar method provided a substantial increase in accuracy of organ activity estimates from 24 hr planar images compared to the CPlanar using 24 hr SPECT as the golden standard. For other time points, where no golden standard is available, better agreement between estimated and measured projections was observed by using EQPlanar method compared to the QPlanar method. This phenomenon is consistent with the improvement in goodness of fit seen in both simulation data and 24 hr patient data. Therefore, this indicates the improved reliability of organ activity estimates obtained though EQPlanar method.

Index Terms

targeted radionuclide therapy (TRT); organ activity estimate; quantitative nuclear imaging; conjugate-view planar images; SPECT

I. INTRODUCTION

In targeted radionuclide therapy (TRT), it is desirable to deliver lethal doses of radiation to cancerous cells while avoiding adverse effects to normal tissues. Ideally, TRT treatment planning uses estimates of normal organ and tumor doses to avoid adverse effects and predict the likelihood of successful therapy (Eary *et al.*, 1997). However, due to their small size, it may be difficult to locate and estimate dose to all tumors. As a result, high dose strategies often administer a maximum tolerated dose (MTD), i.e. the dose not expected to cause adverse effects to the critical organs. In this strategy, reliable estimates of normal organ dose are essential both in dose escalation studies used to find the MTD and for therapy at the MTD.

Ibritumomab tiuxetan (Zevalin) radioimmunotherapy (RIT) has approved by the U.S. Food and Drug Administration (FDA) for the treatment of patients with refractory or relapsed low- or intermediate-grade non-Hodgkin lymphoma (NHL) (Knox *et al.*, 1996; Wiseman *et al.*, 2000; Wiseman *et al.*, 1997) and was recently approved as consolidation therapy following successful chemotherapy in previously untreated follicular NHL. There are several completed and ongoing clinical trials (Witzig *et al.*, 1999; Wiseman *et al.*, 2000; Molina *et al.*, 2007) searching for the MTD for high dose Zevalin therapy with stem-cell support. During high dose Zevalin therapy, patient specific treatment planning is necessary since the uptake, anatomy and biokinetics vary between patients. The organ's time activity curve (TAC), i.e., the activity in the organ as a function of time, is required as the input to calculate the organ dose for treatment planning. The TAC is obtained from measurements of the activity acquired at multiple times post-administration. The organ activity at a specific time point is currently estimated from quantitative images, e.g., 3D SPECT or 2D planar images, acquired at the corresponding time points.

Quantitative SPECT (QSPECT), using state of the art reconstruction and compensation methods, can provide accurate measurements of the *in vivo* radioactivity distribution (Dewaraja *et al.*, 1998; Dewaraja *et al.*, 2004; Sjogreen *et al.*, 2002; He *et al.*, 2005). However, for a variety of reasons including past experience, the (perhaps incorrect) perception that long acquisition times are required (He and Frey, 2010a), and the need to image at multiple bed positions to cover the entire body, planar imaging is still widely used for organ activity estimation in TRT treatment planning. Thus, methods for quantifying planar images are clinically relevant.

However, quantifying the organ activities in conjugate-view whole body planar scans requires careful compensation for a number of factors. These factors include overlap of an organ's projection with those of other organs and the background, scatter and attenuation in the patient, the limited and spatially varying resolution of the collimator-detector system, and partial volume effects. Conventional quantification methods are typically based on the use of geometric-mean based attenuation compensation combined with energy-based scatter subtraction methods (Ogawa *et al.*, 1991). Various compensation methods have been developed that can improve the quantitative accuracy of the conventional geometric mean based method (Buijs *et al.*, 1998; Liu *et al.*, 1996; Ogawa *et al.*, 1991; Sjogreen *et al.*, 2002). However, its quantitative accuracy can be somewhat limited and variations in accuracy over patient populations can be substantial (He and Frey, 2006; He *et al.*, 2008; He *et al.*, 2009b).

To overcome some of the limitations of conventional geometric mean based planar processing, we have previously proposed a new quantitative planar (QPlanar) processing method that uses statistically-based estimation methods, 3D organ VOIs, and rigorous models of image degrading factors (He and Frey, 2006). This method models the physical factors including attenuation (A), scatter (S) and the full (D) collimator-detector response

and uses the maximum likelihood-expectation maximization (ML-EM) (Carson, 1986) algorithm to estimate the set of organ activities that result in the best fit between estimated and measured planar images. The QPlanar method rigorously treats the problem of overlap by the use of non-overlapping 3D organ VOIs. We have previously demonstrated, using Monte Carlo simulation and physical phantom studies, that it is more accurate and reliable than conventional geometric mean based (CPlanar) methods (He and Frey, 2006; He *et al.*, 2005).

However, the QPlanar method makes several assumptions that make application to patient data difficult. First, it requires definition of 3D organ VOIs that are aligned with the organs that gave rise to the 2D planar projections. In practice, the 3D organ VOIs would be obtained with a volume imaging method, for example, SPECT/CT. This is particularly appropriate since hybrid planar/SPECT imaging has been shown to substantially improve the reliability of organ activity estimates with the addition of a single SPECT scan (Assie *et al.*, 2008; Koral *et al.*, 2002; He *et al.*, 2009b; He *et al.*, 2009a; He *et al.*, 2008). Since these images would, in general, be obtained at different times than the planar scans, the VOIs would not be registered with the positions of the organs during the planar scans. We have previously shown that misregistration is a significant source of error (He and Frey, 2010b; Song *et al.*, 2010). Thus, registration between the VOIs and the planar scans is essential. Second, the QPlanar method assumes that the activity distribution in each organ VOI is uniform. As will be shown below, this assumption is especially problematic in the body background where blood vessels, tumors, and other small organs contribute to significant activity distribution nonuniformities.

In this paper, we have proposed extensions to the QPlanar method, referred to hereafter as the EQPlanar method, that address these assumptions. In the new method, we perform both initial whole body rigid registration using a mutual information based registration method (see Section A.2.1) and independent rigid registration of the individual organs during the estimation procedure (see Section A.2.2) to address the misregistration between organ VOIs and planar projections. We also use multiple background VOIs defined from SPECT images to model the nonuniform activity distribution in the background (see Section A.3). The entire EQPlanar method is described in Section A.4.

To validate the method we used a combination of simulations and patient data. In particular, we performed Monte Carlo simulations of In-111 imaging protocols modeling those in the patient studies using anatomically realistic phantoms (Section B.1). Because of limitations in the NCAT phantom and our knowledge of organ activities for small organs, these studies primarily validated the independent organ registration portion of the method. To provide more complete validation, we also used 10 sets of patient data (Section B.2) from a high-dose Zevalin trial. In this trial, planar images were acquired at 1, 5, 24, 72 and 144 hr after administration and thoracic and abdominal SPECT/CT images were acquired at 24 hr after administration. At the 24 hr time point we used the organ activities from the SPECT/CT images as a gold standard. However, at the other time points a gold standard was not available. Thus we evaluated EQPlanar in comparison with QPlanar in terms of the goodness of fit. These studies do not demonstrate the accuracy of EQPlanar, but the improved fits demonstrate that the addition of multiple backgrounds and registration parameters to the estimation procedure did improve the ability to fit the measured projections. The results of the validation study are presented in Section III.

II. MATERIALS AND METHOD

A. Image Processing and Quantification Methods

A.1 QPlanar Method—The QPlanar method assumes that the measured whole body projection can be expressed as a linear combination of the projections of a set of non-overlapping 3D organ and background VOIs. In practice, the organ VOIs would often be derived from SPECT/CT images acquired at a single time point. This SPECT/CT image is useful not only for determining the 3D VOIs, but to enable hybrid SPECT/Planar residence time estimation methods (He *et al.*, 2008; Koral *et al.*, 1994). These hybrid methods have been shown to be more reliable than methods based on simple planar processing, especially when combined with the QPlanar method (He and Frey, 2006).

Similar to iterative reconstruction-based compensation in SPECT, physical factors including attenuation, scatter, and the detector response are compensated for by modeling them in the process of computing the projection of the organ VOIs. In practice, this is accomplished using the same analytical projection algorithms that have previously been developed for SPECT reconstruction. An ML-EM algorithm is then used to estimate the organ activities that result in the best fit between the estimated projections, obtained from the weighted sum of the VOI projections, and measured

$$p_i = \sum_{r=0}^N a_r C_{ir}. \quad (1)$$

In equation (1), p_i represents the measured counts in the projection bin i , a_r is the total activity in the r th VOI times the acquisition time (i.e., the number of disintegrations), C_{ir} is an element of projection matrix C describing the probability that a disintegration in the r th VOI results in a photon detected in projection bin i , and N is the number of VOIs (He and Frey, 2006). The values for $\{a_r\}$ are then estimated using the same iterative ML-EM algorithm used for image reconstruction (Carson, 1986), but where the quantities estimated represent disintegrations in the VOIs rather than in the voxels. Because the number of unknowns is small, the size of the projection matrix is small. It can thus be precomputed and stored, and the activity estimation is performed very rapidly. Note that in the remainder of the paper, for convenience, we refer to the values of $\{a_r\}$ estimated using the above procedure as the total VOI activity. While this is not strictly true, the activities can be simply obtained by dividing the estimated quantities by the acquisition time.

It is clear from the above that the QPlanar method assumes perfect alignment of the 3D organ VOIs and 2D planar images. However, in practice, the planar images are acquired at different time points than the SPECT/CT images used to obtain the 3D organ VOIs. Thus, there usually exists misregistration between 3D organ VOIs and 2D planar images.

The QPlanar method also assumes that the activity distribution in each organ's VOI is uniform, which may not be true, especially for the portion of the patient that is outside the specifically defined organs (i.e., the body background). In practice, only VOIs from large organs (e.g., the heart, lungs, liver, kidneys and spleen) can be defined based on SPECT/CT images, partly because the CT systems for some SPECT/CT scanners are not of diagnostic quality, and partly because contrast agents are not used. As a result, all the tissues outside the 5 major organs shown above would often be lumped together and treated as a single body background. In practice, the activity distribution in this body background is very non-uniform. For example, the blood vessels often have very high activity concentration, particularly at early time points, while other organs and tissues often have much lower activity concentrations.

A.2 Registration Methods—In this work we used registration methods to allow for registration of the VOIs with planar projections. Registration methods can be roughly classified into rigid, affine and non-rigid methods depending on the transformation used to map positions in one image to positions in another. In practice, the motion positions in a patient between different time points are non-rigid. Thus, a single rigid or affine transformation of the entire object cannot fully model relative motions of organs between scans. However, for the case of registering 3D to 2D VOIs, as required in this application, there is likely not enough information to perform general 3D non-rigid registration. In this paper, we performed both initial whole body rigid registration combined with organ independent rigid registration to register the 3D SPECT/CT to the 2D planar scans. This provides a type of non-rigid registration, but uses a much smaller number of registration parameters than required for general non-rigid registration.

A.2.1 Mutual Information Based Registration: A mutual information based rigid registration method was used to provide an initial registration of the whole body with the planar image. Mutual information is a concept from information theory that has found wide application in image registration. It is a measure of the statistical dependence between two random variables, or the amount of information that one variable contains about the other. Mutual information has been used as a measure of image registration since the early 1990's (Viola and Wells, 1997; Studholme *et al.*, 1995; Maes *et al.*, 1996).

The mutual information value is maximal if the two images are geometrically aligned. Because there is no assumption regarding the nature of the relation between the image intensities, it has been found to be a useful and powerful measure for registration in multimodality imaging (Viola and Wells, 1997; W. M. Wells, 1996). In this work, we used a mutual information based whole body rigid registration method to register 2D planar images and 3D SPECT images because of the difference in underlying activity distributions between them resulting from their different times of acquisition.

The rigid registration parameters (x , and z for translation, and xy , yz and xz for rotation) are shown in Figure 1. The translation parameters x and z were defined along the x - and z -axes, respectively; the rotation parameters yz , xz and zx represented rotations around x -, y - and z -axes, respectively. In the 3D-to-2D registration process, a simple projection of the image was taken along the axis of the transformed 3D image that is perpendicular to the anterior and posterior projection image plane to match the 2D image. As a result, it was not necessary to consider the translation along the y -axis. Note that for the EQPlanar method this mutual information based registration was only used for initial registration of the 3D SPECT and planar images.

A.2.2 Independent Organ Registration: Since whole body rigid registration is not able to realistically model the misregistration between 3D VOIs and 2D planar images, an organ independent transformation model was used to perform independent organ registration. In this model, the organs, including the heart, liver, left kidney, right kidney and spleen, were treated as individual units. Each unit was transformed rigidly and independently. Although the rigid transformation did not model nonrigid organ distortion, as might happen when the patient is repositioned on the imaging table, the organ's relative position change was modeled by applying different transformation parameters to each organ. Therefore, it is more realistic than the whole body rigid model and uses substantially fewer parameters to describe the transformation than a more general non-rigid model. Since an effort is usually made to position patients similarly for the different scans, the change in patient position between the two imaging sessions is relatively modest. We thus assume that non-rigid organ distortions can be neglected and that the independent organ rigid transformation model is a reasonable way to model the motion. In the model there is a set of rigid registration

parameters (x , and z for translation, and xy , yz and xz for rotation) for each organ, as shown in figure 2.

Figure 3 shows a flow chart of the organ independent registration method. The inputs include the 3D SPECT/CT image, which, for this work, was acquired at 24 hr post injection, the estimated organ activities at the time point, and the set of 3D organ VOIs defined from the SPECT/CT image. Estimation of the organ activities is discussed below. The first step in this procedure was to define the 3D VOIs from the 3D SPECT/CT image. Then, the estimated rigid transformation parameters were applied to the organ VOIs. The projections of the transformed organ VOIs were calculated with the same analytical projector used in the QPlanar method. The calculated projections were summed to generate the estimated projections. Both the transformation parameters and organ activities, $\{A_i\}$ ($i = 1, \dots, n$, where n is the number of VOIs) were updated by maximizing the statistical likelihood of the estimated and measured planar images using Powell's algorithm (Esteban and Morales, 1995).

During the transformation of individual organs, overlap between organs may occur. When overlap occurred, we used a priority rule where the organ with higher priority filled the overlapping region. The order of the organs' priorities was, from highest to lowest, the heart, liver, spleen, left kidney and right kidney. Also, since we did not independently move the background regions, gaps between the new organ position and the position of the untransformed background were sometimes formed. We treated these gaps as part of the surrounding background VOI and filled them using the local average of the background VOI values.

A.3 Multiple Background VOI Method—As mentioned, the QPlanar method assumes that the activity concentration in each VOI is uniform. However, in patients the background region does not satisfy this assumption. To investigate the effects of non-uniform activity distribution on the organ activity estimates, we estimated the organ activity from the projection of the SPECT image for one patient (patient #3) using the QPlanar method. The projections of the SPECT images were generated using the analytical projector used in the QPlanar method. As a result, the VOIs were exactly aligned with these projections and the image formation model in the QPlanar method was identical with that used to form the projections. Thus, the residual errors were not due to misregistration of the VOIs and the projection data or inaccuracies in the projection model, but were due either to the definitions of the organ boundaries or the assumption of uniform activity concentration inside the VOIs.

Figure 4(a) shows the anterior and posterior views of the estimated projections from the QPlanar method obtained assuming uniform activity distributions in the body background and organs, the analytic projections of the SPECT images and the difference between them. Profiles through the images at the locations noted are shown. Notice that there exist substantial differences between the SPECT and QPlanar estimated projections. This indicates that the non-uniform activity distribution in the VOIs caused significant errors in the estimated projections, and would likely result in errors in activity estimates. Since the body background had a very nonuniform activity distribution, as discussed in A.1, we hypothesized that background nonuniformities were largely responsible for the discrepancies noted.

To test this hypothesis, we segmented the body background VOI into 7 VOIs by intensity thresholding. We still assumed that the voxel values in each of these VOIs were uniform. We used the following voxel value thresholds: 50, 100, 150, 200, 400, and 600. The seventh image included all voxels above the highest threshold. Note that the maximum voxel value in the SPECT background image was about 1,223. We used a larger distance between the

thresholds for higher threshold values to approximately equalize the number of voxels in each background image.

We used this new set of VOIs, combined with the organ VOIs, to estimate the VOI activities. In figure 5, the left column shows one transaxial slice of the single body background VOI in the SPECT/CT and its anterior projection. The right side shows one transaxial slice of each of the seven body background VOIs generated from thresholded SPECT and the corresponding 2D anterior projections. A comparison of the estimated projections obtained using the QPlanar activities and multiple body background VOIs with the projections of the SPECT image is shown in figure 4 (b). The mismatch between the projections was substantially reduced.

Table 2 shows the error in the organ activity estimates obtained using the single background VOI and 7 background VOIs. Note that the accuracy was improved for all the organs, and especially for the heart. This confirms the hypothesis that background nonuniformity plays a large role in the inaccuracies seen for the single background VOI and suggests that the use of multiple background VOIs defined as described could be used to help overcome this problem.

A.4 EQPlanar Method—The combination of the above-described registration and multiple-background VOI methods with QPlanar activity estimation forms the EQPlanar method. The entire EQPlanar estimation process is illustrated in Figure 6. Mutual information-based whole body rigid registration is first applied to the 3D SPECT and 2D measured planar images to provide the initial whole body registration parameters. The individual organ VOIs and multiple background VOIs are then transformed by the initial registration parameters. After that, the independent organ registration method is used to estimate both registration parameters and activities for organs by maximizing the likelihood of the estimated and measured planar images.

In this case, there are two types of registration parameter sets defined: one consisting of the whole body transformation parameters, $w = \{x, z, yz, xz, xy\}$, and the other is the individual organ transformation parameters $a_i = \{x_i, z_i, yz_i, xz_i, xy_i\}$, where i is the organ index ($i=1$: heart, 2: liver, 3: spleen, 4: left kidney, 5: right kidney). The whole body parameters were used to transform the whole phantom body, including the body background and all the individual organs. The organ parameters were then used to transform each individual organ and thus to model the organ's relative position change. In the EQPlanar method, we seek the combination of the registration parameters and organ activity estimates that provide the best agreement between the estimated and the measured projections in the maximum likelihood sense. The optimal parameters were found by alternating optimization of the organ registration parameters using Powell's algorithm and linear estimation of the organ activity parameters using the ML-EM algorithm. In both cases the parameters were adjusted to maximize the statistical likelihood between the measured projections given the projection of the object using the current set of registration parameters and organ activities. The organ registration parameters were optimized one organ at a time in the same organ priority order used in the case of organ overlap. We repeated the alternation between organ registration parameter and activity estimation for multiple passes through the list of organs until the overall likelihood converged.

B. Validation experiments

We evaluated the proposed method using both simulation data and real patient data as described in detail below. In the simulation study, because the truth was known, we were able to calculate the accuracy and precision of the organ activity estimates. In the patient study, we compared the organ activity estimates obtained with the EQPlanar method to

those from an implementation of a conventional geometric-mean based planar quantification method (CPlanar) using organ activities estimated using QSPECT as the gold standard.

B.1 Monte Carlo Simulation Studies—We generated 3 phantoms using the realistic 3D NCAT phantom (Segars *et al.*, 2001) to model realistic variations in human anatomy. We rescaled the overall body and organ sizes to approximately model those seen in 3 Zevalin patient studies, as described in (He *et al.*, 2005). The activity distribution at each time point in each phantom was based on the corresponding ^{111}In -Zevalin patient scan. Therefore, different time activity curves including both physical and biological decay were used for different organs. We modeled the case where the 3D VOIs were defined using a SPECT/CT scan obtained 24 hr post administration and planar scans taken at 1, 5, 24, 72, and 144 hr post administration. In the simulation study, the 3D organ VOIs were known exactly from the NCAT phantom. The SimSET Monte Carlo code (Harrison *et al.*, 1993) combined with an angular response function (ARF) to model interactions in the collimator-detector system (Song *et al.*, 2005) was used to generate low noise projection images. This combination has previously been validated for In-111 simulations (He *et al.*, 2005). A GE Discovery VH SPECT/CT system was simulated. We modeled a medium-energy general-purpose (MEGP) collimator and the 2.54 cm thick crystal in this system. Low noise projections were generated in 128×170 matrices using a 0.442 cm projection bin size. After scaling the low noise projections to count levels appropriate for clinical ^{111}In -Zevalin patient scans with 185 MBq injected activity, 10 statistically independent Poisson noise realizations were generated for each phantom. The count level in the low noise SPECT projections corresponded to the clinical scans (20 s per view for 120 views over 360°); the average total counts in a sinogram corresponding to a single reconstructed slice were 1.04×10^5 , 1.21×10^5 , and 0.99×10^5 for phantoms #1, #2 and #3, respectively. The count levels in the planar images corresponded to a 20 min scan time. The total counts in the anterior planar images at the 1hr time point were 3.06×10^6 , 3.58×10^6 and 3.00×10^6 for phantoms #1, #2 and #3, respectively. Anterior planar images of the three NCAT phantoms at the 5 time points are shown in figure 7.

In figure 8, the left two images are the same coronal slice from the attenuation and activity distribution images from phantom #2. The right two images are the noisy planar images for the activity distribution at 24 hr after administration.

For each phantom, after generating the 5 planar images, a new transformed 3D NCAT phantom was generated to simulate the misregistration between 3D organ VOIs and 2D planar images. We first sampled a random set of whole body transformation parameters, w , and used it to move the phantom body. The whole body transformation parameters were sampled from uniform distributions spanning ± 5 pixels for translation parameters (x and z) and $\pm 5^\circ$ for rotation parameters (xy , yz and xz). We then sampled a set of organ transformation parameters $\{x_i, z_i, yz_i, xz_i, xy_i\}$ ($i=1, 2 \dots 5$) with the subscript corresponding to each value of i representing the motion of one particular organ relative to the body. These were sampled from uniform distributions spanning ± 3 pixel for translation parameters (x and z) and $\pm 5^\circ$ for rotation parameters (xy , yz and xz). In order to prevent overlap of organs, we performed the transformations in the following order: liver, heart, spleen and left kidney and right kidney. If the transformation for an organ resulted in overlap with one of the already transformed organs, the set of parameters causing the overlap was discarded and a new randomly-sampled set of parameters was obtained. To study both the accuracy and precision, we sampled 10 combined sets of whole body and organ motion parameters. As a result, for each phantom we generated 5 planar images with activity distributions corresponding to 1, 5, 24, 72 and 144 hr post administration and with the same misregistration parameters relative to the 24hr SPECT images or 3D organ VOIs. In figure 8, the ROIs on the third image from the left are the outlines of the 2D projections

of 3D VOIs generated from the NCAT phantom. The ROIs on the fourth image are the 2D projections of 3D transformed VOIs. The misregistration between the ROIs and the corresponding organ projections in the planar image can be seen clearly in the rightmost image.

For each phantom, the organ activities were estimated from the noisy planar images at the 5 time points by the proposed EQPlanar method for each of the 10 sets of misregistered 3D VOIs. The mean and standard deviation of errors in the organ activity estimates were calculated over all the phantoms, noise realizations, and sets of misregistered VOIs. We compared the results with those from the standard QPlanar method to study the effects of misregistration and nonuniform activity distribution in the body background. The standard QPlanar estimation was performed using 3D VOIs obtained after whole body rigid registration only in order to study the effects of misregistration caused by the change in the organs' relative positions. In the NCAT phantom, different activity concentrations were used in the blood vessels, pelvic marrow and background to model non-uniform activity in body remainder. Therefore, the separately simulated VOIs for blood vessels, pelvic marrow and background were used as multiple background VOIs in the EQPlanar method. However, in the simulation study the nonuniformities were not modeled as realistically as in the patient scans. As a result, no obvious difference in organ activity estimates (less than 0.5% for all organs) was observed between using single background VOI and multiple background VOIs. Therefore, the effects of nonuniform background were investigated in patient studies instead of simulation studies.

B.2 Patient Studies—In this work, we used 10 sets of ^{111}In -Zevalin patient data (5 male and 5 female). The injected activity for each patient was 185 MBq. One SPECT/CT (24 hr after administration) and 5 conjugate-view whole body planar images (1, 5, 24, 72 and 144 hr after administration) were acquired using a GE Millenium VG SPECT/CT system (1.59 cm thick crystal) using an MEGP collimator. At the 24 hour time point the patient was allowed to move between the planar and SPECT scans. The scanning speeds for planar images at 1, 5, 24, 72 and 144 hr time points were 10, 10, 7, 5, and 5 cm min^{-1} , respectively. The SPECT projections were acquired at 120 views over 360° with 20 s acquisition time per view. The SPECT images were reconstructed using the ordered-subsets expectation maximization (OS-EM) reconstruction algorithm (Hudson and Larkin, 1994) (5 iterations, 24 subsets per iteration) with A, S and D compensations (He *et al.*, 2005). We manually defined the VOIs for the heart, liver, spleen, left kidney and right kidney from the fused SPECT/CT images for each patient. The region outside these VOIs was defined as the VOI for the body background. For each patient the same set of background VOIs generated from the SPECT at the 24 hr time point was used at the other time points.

Figure 9 shows several slices from the SPECT/CT images with manually-drawn organ ROIs and the geometric mean planar projections acquired at the 5 time points.

To compare the proposed method with the an implementation of a widely used CPlanar method, we estimated organ activities from the 24 hr planar images using both the QPlanar and CPlanar methods and calculated the mean and standard deviation of errors using the activities estimated from the 24 hr SPECT images as a gold standard. The accuracy of organ activity estimates from SPECT images reconstructed using OS-EM with A, S and D compensations, which was used in this work, has been demonstrated by both Monte Carlo simulation and physical phantom studies (He *et al.*, 2005). The CPlanar method used was a rigorous implementation that included scatter, attenuation (including object thickness), overlap, and background corrections. Scatter correction was performed using the triple energy window method prior to computing the geometric mean. Object thickness correction was performed by registering the CT image to the planar image and computing pixel-by-

pixel attenuation factors for the geometric mean method. Organ ROIs were intentionally drawn smaller to avoid organ overlap (figure 9 (b)). The organ counts were then scaled up to reflect the real organ volume estimated from the SPECT/CT images. Background regions and organ thickness factors were defined from the CT images for each organ and used in background correction. The mean background counts times the organ thickness factor was subtracted to perform background correction (Buijs *et al.*, 1998).

Since we did not have an independent assessment of the truth at time points other than 24 hours, we compared the measured projections with those estimated using the QPlanar and EQPlanar methods to assess goodness of fit. Of course this does not directly demonstrate that the method having the best fit had the more accurate activity estimate, but combined with the evidence from 24 hr time point and the simulation study it does provide additional information about whether the EQPlanar method is operating as expected.

III. RESULTS

A. Monte Carlo Simulation Study

Figure 10 shows the difference between measured planar images and estimated planar images using the standard QPlanar method without registration, standard QPlanar method with mutual information based whole body rigid registration, and EQPlanar method. It can be seen that there was a substantial difference without any registration. After whole body rigid registration, the difference was reduced but was still substantial. The EQPlanar method provided the best fit between measured and estimated projections.

Table 3 compares the mean and standard deviation of errors in activity estimates at the 1, 5, 24, 72 and 144 hr time points using the three methods mentioned above. It can be seen that the proposed method improved the accuracy and precision for all the organs at all the time points. In general, the accuracy at 1, 5 and 24 hours was better than at 72 and 144 hours, especially for organs with low activities at those time points. This is likely due to the fact that small errors in activity estimates for larger high-activity organs could result in larger relative errors for low activity organs.

When whole body rigid registration was applied with the standard QPlanar method, the accuracy for small organs was improved but errors were still relatively large. The mean errors were about 8-10% for the spleen, 10-13% for the left kidney, 18-30% for the right kidney and 6-22% for the lungs. This demonstrates that the misregistration caused by the changes of organ's relative position changes generated substantial effects on the activity estimates for small organs.

For the liver, the accuracy was better than $-6 \pm 4\%$ for all the time points using the standard QPlanar method. This demonstrates that large and high uptake organs were affected less by misregistration than small organs, similar to our observations in previous work (Song *et al.*, 2010). The standard QPlanar method provided relatively good accuracy for the heart, except at the 144 hr time point. This is in agreement with the above conclusion because the activity in heart was high at early time points and almost completely washed out at 144 hours (see figure 7).

B. Patient Study

For the 24 hour time point we compared the organ activity estimates from the EQPlanar and CPlanar methods using the activity estimated from the 24hr SPECT images as the gold standard. Table 4 shows the mean and standard deviation of the percent errors in organ activity estimates obtained from 24 hr planar projections. The positive and negative values indicate over- and under-estimation, respectively. Since we are also interested in how far the

estimates were from the truth, regardless of direction, we also computed the mean of absolute value of the percent errors. It was found that the accuracy and precision of activity estimates was improved substantially for the heart, liver, spleen and lungs using the EQPlanar method. For the kidneys, the standard deviation was higher for the CPlanar method, but the mean error was smaller. This is because there was approximately an equal amount of over- and under-estimation of kidney activity for this set of phantoms. The means of the absolute errors were, however, reduced from 45.35% to 19.50% for the left kidney and from 44.06% to 25.92% for the right kidney with the EQPlanar method. Therefore, despite having a somewhat larger average error, overall the EQPlanar results provided more reliable estimates due to the lower variability.

The mean errors for the kidneys were higher than for other organs. We believe this is because the kidneys were relatively small, had low uptake, and were in close proximity to high uptake organs: The lower uptake will result in generally poorer precision of activity estimates; the smaller size means that there is a larger effect of residual misregistration on the accuracy of organ activity estimates; and the fact that they are near higher uptake organs means that registration errors would be less obvious, resulting in larger errors on average. This phenomenon was observed and discussed in a previous study of the effects of misregistration on the QPlanar method (Song *et al.*, 2010). As observed in the simulation study, better accuracy was obtained for the left kidney ($-15 \pm 15\%$) than for the right kidney ($-23 \pm 17\%$), likely due to the right kidney's proximity to the liver.

To further illustrate the improvement in the accuracy of the organ activity estimates, we evaluated the correlation and agreement between activity estimates from the EQPlanar and CPlanar methods with those from quantitative SPECT. Figure 11 shows scatter and Bland-Altman plots illustrating the correlation and agreement, respectively. In both cases, we treated the SPECT activity estimate as the truth.

In figure 11 (a) we show the results of a linear regression analysis between the two pairs of data. Note that the regression line for the EQPlanar method was closer to line of identity than for the CPlanar method. The two-tailed p-values for differences between the slopes and intercepts for these two methods were 0.024 and 0.032, respectively. Further, there was less scatter of the data around the fit for QPlanar. The squared correlation coefficient (R^2) was 0.99 for the EQPlanar method versus 0.95 for the CPlanar method.

Perhaps a better way to evaluate two measurement techniques is to assess agreement using Bland-Altman analysis. Figure 11 (b) shows Bland-Altman plots for the EQPlanar and CPlanar methods in comparison to QSPECT. From these plots we see that there was much more variation in agreement between the CPlanar and QSPECT activity estimates than there was for EQPlanar and QSPECT. The 95% confidence intervals for agreement between EQPlanar and QSPECT were $(-0.04 \text{ mCi}, 0.04 \text{ mCi})$ compared with $(-0.1 \text{ mCi}, 0.1 \text{ mCi})$ for CPlanar and QSPECT. All these facts illustrate that the EQPlanar method improved the reliability of the organ activity estimates compared to the CPlanar method.

For other time points (1, 5h, 72 and 144 hr), since the truth was not known, we compared the difference between the estimated and measured projections to assess the goodness of fit. The assumption is that a better fit of the estimated and measured projections indicates that the organ activities were estimated more accurately. Figure 12 shows the projections for patient #3 at 1, 5, 72 and 144 hr in both anterior and posterior views. The measured projections, estimated projections from the EQPlanar method, and the difference between them are shown, from top to bottom. We can see that, in general, there was good agreement between the estimated and measured projections. Similar levels of agreement were observed at other time points.

To quantitatively assess the goodness of fit, we calculated the mean and standard deviation of the percent absolute error for these 4 time points. The percent absolute difference, A_k , was calculated as

$$A_k = \left[\frac{1}{N} \sum_i |e_i - m_i| / m_i \right] \cdot 100\% \quad (3)$$

where k is the patient index, i is the pixel index, N is the total number pixels in the projections, e_i is the value of the i th pixel in the estimated projections, and m_i is the value of the i th pixel in the measured projections.

A comparison of mean and standard deviation of percent absolute difference calculated over 10 patients using EQPlanar and standard QPlanar methods is shown in figure 13. For all the 4 time points, the mean of the absolute difference was improved by about 15%, and the standard deviation was reduced by about 5%. This demonstrates that the EQPlanar method provided a substantial improvement in goodness of fit compared to the original QPlanar method, indicating that the addition of organ registration parameters and the use of multiple background VOIs did allow better fits to the data. This is not direct evidence that the organ activity estimates were better, but is consistent with the improvement in goodness of fit seen in the simulation study and thus provides indirect evidence of the improved reliability of organ activity estimates obtained using the EQPlanar method.

IV. DISCUSSION

In this work, 7 body background VOIs were generated from thresholded 24 hr SPECT images in the patient study. There is a tradeoff between the number of VOIs and the estimability of VOI activity. More VOIs are preferred to model the nonuniform activity concentration, but, on the other hand, too many VOIs could make the estimation problem ill posed. In our experience, 5 to 7 VOIs was a reasonable and sufficient number. We used 7 body background VOIs for patient data in this work. However, for other agents a different number may be appropriate.

In the CPlanar method, the mean counts in a small adjacent background region times the organ thickness factor was subtracted to perform the background correction. The background correction is thus highly dependent on the location and the size of this small region. As a result, the performance of the background correction is very sensitive to the experience of the operator, and high variability can be expected. The QPlanar method also depends on the accuracy of organ VOI definition. However, in our experience, drawing VOIs in 3D, especially when using fused anatomic and SPECT images, is less subjective than drawing them on planar projections. In previous work we have also shown that the QPlanar method is somewhat less sensitive to VOI misdefinition and misregistration than SPECT. As a result, it is expected that the operator variations, which were not explicitly evaluated in this work, would be smaller for the EQPlanar method than for CPlanar methods.

We observed in both the simulation and patient studies that the accuracy for the left kidney was better than for the right kidney. One explanation for this is that the right kidney is located adjacent to the liver, which usually has high uptake for ^{111}In -Zevalin. Both residual misregistration and partial volume effects from the liver could thus increase errors in activity estimates for the right kidney. This suggests that it may, in general, be difficult to estimate low-activity features that are partially shadowed by high activity organs.

The data in this work indicated that EQPlanar provides a major improvement over the CPlanar method. Previous work has shown that the accuracy of the closely-related QPlanar method approaches the accuracy and precision of QSPECT (He and Frey, 2006). Thus, one conclusion that one might draw is that these methods obviate the need for SPECT imaging in dosimetry applications. However, upon closer examination this is not a valid conclusion. First, although the EQPlanar method estimates organ activities from the wholebody planar projections, it uses SPECT images to generate the multiple background VOIs required to model accurately the nonuniform activity distribution in background regions. Second, in the context of residence time estimation, the acquisition of a SPECT image at one time point enables the use of hybrid SPECT/Planar residence time estimation methods (Koral *et al.*, 1994; He *et al.*, 2009a). Hybrid residence time estimation methods use the planar images to estimate the time activity curve and renormalize the curve so that it passes through the activity estimate from the QSPECT image. These methods have been shown, in both simulation (He *et al.*, 2009a) and patient studies (Assie *et al.*, 2008) to provide improved residence time estimates compared to purely planar residence time estimation. Combined with EQPlanar planar activity quantification, hybrid methods should produce organ residence time methods with reliability approaching that obtained with methods requiring a SPECT image at every time point.

Even if hybrid EQPlanar/QSPECT organ residence time estimates have reliability approaching those from purely QSPECT based approaches, there are situations where acquiring SPECT at every time point may be desirable. First, it is likely that QSPECT is superior for quantification of small objects, e.g., tumors. Second, having a QSPECT image at every time point is important for allowing implementation of voxel-based dosimetry. Advanced voxel-based dosimetry methods allow taking into account the radiobiological effects of the nonuniformity of the dose distribution in tumors and organs as well as dose-rate effects. In situations where these effects are important, for example in radio-peptide therapy where the kidney is dose limiting and the dose-distribution is highly nonuniform, performing SPECT at every time point is likely the method of choice.

In this work, the accuracy of organ activity estimates from EQPlanar method was validated using data at 24 hr time point because of the availability of 24 hr SPECT images, which was considered a golden standard. For 1, 5, 72 and 144 hr time points, the goodness of fit between estimated and measured projections was investigated. It should be noted that although the improvement of goodness of fit cannot serve as direct evidence of improved accuracy for organ activity estimates, it does indicate the improved reliability of organ activity estimates since improved goodness of fit and improved organ activity estimates were observed in the simulation studies.

Note that in the EQPlanar method we used background VOIs obtained from the 24 hr SPECT images for other time points. This would not work in cases where the tracer redistribution was such that the shapes of the background VOIs regions changed at the other time points. However, since the activity in the background VOIs was not fixed, but was fit to the data, and since the 3D background regions did not overlap the organs, the use of the multiple backgrounds should not, in general, degrade the performance of the method and would also be a problem for conventional planar processing. In cases where the shape of background regions changes at every time point the use of SPECT at every time point would be preferred.

V. CONCLUSION

In this work, we have proposed the EQPlanar method, which addresses limitations of the standard QPlanar method resulting from misregistration of organ VOIs and nonuniform

background activity distribution. In particular, we included rigid independent organ registration and multiple background VOIs in the estimation process. The result is a method that uses 3D organ VOIs combined with maximum likelihood estimation and rigorous models of physical image degrading factors to estimate organ activities from planar projections. The method provides rigorous compensation for both the physical factors and organ overlap and background activity.

We evaluated the method using simulations and patient data. The simulation study showed that the EQPlanar method improved the accuracy of organ activity estimates for all the organs at all the 5 time points compared with the standard QPlanar method when organ misregistration was present. For the patient data, we compared the accuracy at the 24 hr time point of the EQPlanar method at to conventional geometric mean based processing including compensation for scatter, object thickness, background, and organ overlap. The gold standard for comparison was 24 hour quantitative SPECT reconstruction with compensation for attenuation, scatter, and the collimator-detector response. The results showed improved reliability of the organ activity estimates in terms of improved accuracy and precision. For other time points, where truth was not known, the method provided a better fit to the measured projections than the original QPlanar method with a single background VOI and only rigid whole body registration. This provides indirect evidence that improved reliability of organ activity estimates were obtained using the EQPlanar method.

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Figure 1.
The rigid registration transformation parameters defined for whole body.

Figure 2.
The rigid registration transformation parameters defined for organs (in this case, the heart).

Figure 3.
Flow chart of the organ independent registration process.
(A: attenuation, S: scatter, CDR: full collimator-detector response).

Figure 4.

Comparison of the estimated projections from QPlanar method using (a) single body background VOI with the projections of the SPECT images and (b) multiple body background VOIs with the projections of SPECT (patient #3).

- Left top : the anterior and posterior projections of the SPECT images.
- Left middle : the anterior and posterior projections resulting from QPlanar estimation of organ activities.
- Left bottom : difference images of the estimated and SPECT projections.
- Right top : comparison profiles through the SPECT and QPlanar estimated anterior projections.
- Right bottom : comparison of profiles through the SPECT and QPlanar estimated posterior projections.

Figure 5.

- (a) Transaxial slice through single body background VOI (top row) and anterior 2D projection of the entire background VOI (bottom row). The position of the transaxial slice in the 2D projection is indicated.
- (b) Transaxial slice through multiple body background VOIs (top row) and the corresponding anterior projections of the VOIs (bottom row). The position of the transaxial slice in the 2D projection is indicated.

Figure 6.
Flow chart of the EQPlanar method using patient data as illustration.

Figure 7.
The anterior planar images of the 3 NCAT phantoms with activity distribution simulated at 1hr, 5hr, 24hr, 72hr and 144hr after administration.

Figure 8.

The left two images are for the same slice from coronal view of attenuation map and activity map from NCAT phantom #2. The right two images are noisy planar images at 24hr time point. The ROIs on the third image are the 2D projections of 3D VOIs. The ROIs on the last image are the 2D projection of 3D transformed VOIs.

Figure 9.

(a) Slices of patient SPECT/CT images with manually drawn organ VOIs. (b) Geometric mean of patient planar images at 1, 5, 24, 72 and 144 hr after administration.

Figure 10.

Comparison of the difference between measured and estimated planar images using the standard QPlanar method without registration, standard QPlanar method with whole body rigid registration and EQPlanar method from the simulation study.

Figure 11. Results of (a) linear regression analysis and (b) Bland-Altman analysis of organ activity estimates from EQPlanar method (black) and CPlanar (red) method compared to the QSPECT activity estimate in patient study.

Figure 12.

Comparison of the estimated projections from the EQPlanar method with the measured planar projections of patient #3 acquired at 1 hr, 5 hr, 72 hr and 144 hr after administration. (difference = estimated – measured).

Figure 13.

The average and standard deviation of absolute difference between the measured projections and the estimated projections using the EQPlanar method and standard QPlanar method in patient study.

Table 1

List of abbreviations used in the text.

QPlanar	Quantitative Planar
EQPlanar	Extended Quantitative Planar
CPlanar	Conventional Planar
QSPECT	Quantitative SPECT
VOI	Volume of interest
MEGP	Medium-energy general-purpose
OS-EM	Ordered-subset estimation-maximization

Comparison of the organ activity estimate from patient #3 planar images using QPlanar method with single background VOI and multiple background VOIs.

Table 2

	Heart (%)	Liver (%)	Spleen (%)	LKidney (%)	RKidney (%)	Lungs (%)
Single VOI	28.88	6.44	8.90	24.48	24.97	-21.95
Multiple VOIs	2.63	-1.18	-8.42	-8.89	-10.95	10.05

Table 3

Comparison of the mean and standard deviations of errors of the activity estimates from planar images in the simulation study.

	Heart (%)	Liver (%)	Spleen (%)	LKidney (%)	RKidney (%)	Lungs (%)
1 hr	*					
	2.9 ± 3.5	-6.0 ± 3.4	10.2 ± 7.1	-15.6 ± 13.0	-29.6 ± 8.8	9.8 ± 10.5
	**					
	1.7 ± 2.6	-4.7 ± 2.4	8.0 ± 5.3	-13.6 ± 10.7	-21.5 ± 6.9	6.5 ± 6.0

	1.4 ± 2.8	-2.0 ± 1.4	3.7 ± 3.6	-6.4 ± 4.5	-7.7 ± 4.9	5.0 ± 6.0
5 hr	*					
	3.0 ± 3.2	-5.5 ± 3.3	10.6 ± 6.4	-14.0 ± 12.5	-29.3 ± 9.2	9.9 ± 10.6
	**					
	2.0 ± 3.1	-4.4 ± 3.0	8.6 ± 5.1	-12.1 ± 10.6	-19.1 ± 7.1	6.0 ± 6.7

	1.7 ± 3.0	-2.9 ± 1.9	2.2 ± 3.3	-6.2 ± 2.4	-8.2 ± 5.4	5.4 ± 6.9
24 hr	*					
	3.7 ± 4.0	-5.1 ± 2.9	12.7 ± 5.1	-12.8 ± 13.6	-32.0 ± 9.6	10.8 ± 11.4
	**					
	3.6 ± 3.9	-2.8 ± 1.8	8.4 ± 4.4	-10.5 ± 9.3	-24.1 ± 8.6	6.0 ± 7.1

	2.3 ± 2.8	-1.5 ± 1.4	1.4 ± 4.4	-6.1 ± 3.7	-7.12 ± 5.2	4.6 ± 6.4
72hr	*					
	7.6 ± 5.8	-4.5 ± 2.3	15.4 ± 7.5	-14.1 ± 14.2	-31.5 ± 10.5	13.6 ± 15.7
	**					
	6.9 ± 4.0	-2.0 ± 1.5	8.6 ± 6.1	-12.5 ± 11.3	-25.3 ± 8.3	9.9 ± 12.3

	5.7 ± 4.2	-1.9 ± 1.8	3.5 ± 3.0	-10.7 ± 5.0	-12.7 ± 5.6	8.2 ± 5.6
144hr	*					
	18.2 ± 13.8	-3.6 ± 2.0	18.1 ± 10.5	-14.0 ± 16.9	-37.8 ± 11.4	35.7 ± 32.5
	**					
	16.3 ± 10.1	-2.7 ± 1.7	9.7 ± 7.16	-13.2 ± 10.5	-29.7 ± 7.2	22.5 ± 21.4

	7.1 ± 5.4	-2.2 ± 1.5	2.7 ± 3.16	-12.2 ± 4.2	-14.6 ± 5.3	17.5 ± 10.4

The activity errors were calculated as (estimated activity – true activity)/true activity.

* : standard QPlanar method without any registration

** : standard QPlanar method + mutual information based whole body rigid registration

*** : EQPlanar method

LKidney : left kidney, RKidney: right kidney.

Table 4

Comparison of the errors in activities estimates for organs from 24 hr planar projections in patient study.

	Heart (%)		Liver (%)		Spleen (%)		LKidney (%)		RKidney (%)		Lungs (%)	
	*	**	*	**	*	**	*	**	*	**	*	**
mean $\pm$ STD (errors)	2.9 $\pm$ 3.2	5.9 $\pm$ 20.7	-5.9 $\pm$ 2.6	-12.5 $\pm$ 12.7	0.2 $\pm$ 7.9	13.8 $\pm$ 13.8	-15.1 $\pm$ 15.3	3.4 $\pm$ 49.9	-21.7 $\pm$ 16.9	-10.5 $\pm$ 47.2	-7.6 $\pm$ 11.8	17.7 $\pm$ 25.8
mean absolute errors	3.88	17.78	5.95	14.34	6.21	17.53	19.50	45.35	25.92	44.06	11.97	28.77

The activity errors were calculated as (estimated activity – true activity) / true activity.

* : the EQPlanar method,

** : the geometric mean based (CPlanar) method

LKidney : left kidney, RKidney: right kidney.