3D inpatient dose reconstruction from the PET-CT imaging of $^{90}$Y microspheres for metastatic cancer to the liver: Feasibility study

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Purpose: The introduction of radioembolization with microspheres represents a significant step forward in the treatment of patients with metastatic disease to the liver. This technique uses semiempirical formulae based on body surface area or liver and target volumes to calculate the required total activity for a given patient. However, this treatment modality lacks extremely important information, which is the three-dimensional (3D) dose delivered by microspheres to different organs after their administration. The absence of this information dramatically limits the clinical efficacy of this modality, specifically the predictive power of the treatment. Therefore, the aim of this study is to develop a 3D dose calculation technique that is based on the PET imaging of the infused microspheres.

Methods: The Fluka Monte Carlo code was used to calculate the voxel dose kernel for $^{90}$Y source with voxel size equal to that of the PET scan. The measured PET activity distribution was converted to total activity distribution for the subsequent convolution with the voxel dose kernel to obtain the 3D dose distribution. In addition, dose-volume histograms were generated to analyze the dose to the tumor and critical structures.

Results: The 3D inpatient dose distribution can be reconstructed from the PET data of a patient scanned after the infusion of microspheres. A total of seven patients have been analyzed so far using the proposed reconstruction method. Four patients underwent treatment with SIR-Spheres for liver metastases from colorectal cancer and three patients were treated with Therasphere for hepatocellular cancer. A total of 14 target tumors were contoured on post-treatment PET-CT scans for dosimetric evaluation. Mean prescription activity was 1.7 GBq (range: 0.58–3.8 GBq). The resulting mean maximum measured dose to targets was 167 Gy (range: 71–311 Gy). Mean minimum dose to 70% of target (D70) was 68 Gy (range: 25–155 Gy). Mean minimum dose to 90% of target (D90) was 53 Gy (range: 13–125 Gy).

Conclusions: A three-dimensional inpatient dose reconstruction method has been developed that is based on the PET/CT data of a patient treated with $^{90}$Y microspheres. It allows for a complete description of the absorbed dose by the tumor and critical structures. It represents the first step in building predictive models for treatment outcomes for patients receiving this therapeutic modality as well as it allows for better analysis of patients’ dose response and will ultimately improve future treatment administration. © 2013 American Association of Physicists in Medicine. [http://dx.doi.org/10.1118/1.4810939]

Key words: Monte Carlo, absolute dose reconstruction, Y-90 microspheres

1. INTRODUCTION

The liver is a principal site of metastasis for a wide variety of cancers. Sixty to eighty percent of patients with a history of colorectal carcinoma, pancreatic carcinoma, breast cancer, and other tumor types will develop liver metastasis. In addition, the liver can also develop primary liver cancer in a form of hepatocellular and cholangiocellular carcinoma.

Surgical resection of primary or metastatic liver cancer is the most effective method of treatment. However, in the majority of patients the tumors will be unresectable. Therefore, a number of pioneering liver-directed treatments have been developed recently that include conformal radiation therapy, hepatic arterial infusion chemotherapy (HAC), radiofrequency ablation (RFA), and radioembolization (RE) with Yttrium-90 ($^{90}$Y) microspheres. RE is a promising catheter-based modality in which the $^{90}$Y microspheres are infused into the hepatic artery with the expectation that the spheres will lodge in the tumor sites and deliver tumoricial doses. The method provides several advantages over more
traditional treatment techniques because of its low toxicity profile, which arises from the anatomic aspects of hepatic malignancies, specifically observations that hepatic tumors derive 80%–90% of their blood supply from the arterial hepatic circulation. This is in contrast to the normal liver, 60%–70% of which is fed by the portal vein. The current methodology for determining the amount of 90Y microspheres activity to be administered to patients is rather rudimentary and does not take into account significant variations in tumor size, shape, or location. There are two radiolabeled microsphere products currently available for treating patients with liver metastasis, SIR-Spheres® (Sirtex SIR-Spheres Pty Ltd., Sydney, Australia) and TheraSphere® (Nordion, Ottawa, Canada). The most commonly used empirical formula (provided by Sirtex Medical) for SIR-Spheres is based on the body surface area (BSA) method

$$A \ (\text{GBq}) = \text{BSA} - 0.2 + (\text{TV}/\text{TLV}),$$

(1)

where A is the total activity expressed in GBq, BSA is the body surface area (calculated using patient’s height and weight) expressed in the units of m², TV is the tumor volume, and TLV is the total liver volume. For patients treated with Therasphere, the calculation formula has the following form:

$$A \ (\text{GBq}) = \frac{D \ (\text{Gy}) \times M \ (\text{kg})}{49.8 \times (1 - F)},$$

(2)

where D is the desired target dose, M is the liver mass, and F is the ratio of lung to liver uptake (lung shunt) and 49.8 is the empirical dose constant for 90Y expressed in Gy kg GBq⁻¹. Both calculation methods assume homogeneous dose distribution throughout the liver and the target. It should also be noted that neither of activity calculation techniques provides any information about the actual dose which will be delivered by microspheres to different organs in a patient after their administration. The absence of this information tremendously limits the efficacy of this modality, specifically the treatment outcome predictions, which would include the probabilities for tumor control as well as normal tissue complications.

In an earlier attempt to quantify the absorbed dose in a patient, the authors used SPECT images of a patient obtained after hepatic infusion of Tc-99m labeled macroaggregated albumin (MAA) to ascertain the isotope’s spatial distribution and subsequently calculate the absorbed dose. The γ-emitting 99m-Tc-MAA particles have an average size 20–40 μm and were used in the procedure as an imaging surrogate for the beta emitting 90Y microspheres. However, it takes a leap of faith to assume that the spatial distribution of 99m-Tc-MAA is identical to that of 90Y microspheres. The calculated three-dimensional (3D) dose distribution has an associated intrinsic uncertainty in it due to the assumption that 90Y microspheres and Tc-MAA surrogates have identical spatial distributions in a patient. In addition, Tc-99 labeled MAA is infused at a separate visit with a different catheter in place, in hopes that it will approximate the position during the treatment. Therefore, it would be extremely desirable to develop a method for dose reconstruction that is based on the actual distribution of 90Y microspheres.

Yttrium-90 is traditionally thought of in the medical community as a pure electron emitter, originating from 90Y conversion into 90Zr through beta decay process. However, there is a small probability of internal pair production, following beta decay process attributed to a transition in 90Zr. In fact, the first theoretical investigation of this transition was done by Arley and Moller, with the first experimental measurement of the branching ratio (the ratio between the number of emitted positrons to that of electrons) for 90Y reported by Greenberg to be $(3.6 \pm 0.9) \times 10^{-5}$. The most recent measurement of the branching ratio determined by Selwyn is $(3.187 \pm 0.47) \times 10^{-5}$. This decay mode opens up the possibility for coincidence imaging with a PET scanner to directly obtain the spatial distribution of yttrium spheres shortly after their administration.

In the past few years, there has been an explosion of feasibility studies concerning the use of PET imaging for localization of 90Y microspheres in patients that underwent the hepatic radioembolization procedure. These studies qualitatively examined the 90Y microsphere distribution within the liver and adjacent organs. However, to the best of our knowledge, no inpatient dose information has been quantitatively reconstructed from the measured distribution of microspheres. Therefore, it would be extremely desirable to develop a method of 3D dose reconstruction directly utilizing the 90Y PET information.

The method is based on the convolution of the PET-measured inpatient activity distribution with a precalculated dose kernel. Subsequently, the reconstructed 3D dose distribution is superimposed on the CT data for isodose and dose volume histogram analysis.

2. METHODS AND MATERIALS

2.1. Calculation of the absorbed dose

The 3D dose absorbed in a patient can be calculated by convolving the total activity density distribution $A(x, y, z)$ with the dose kernel for 90Y source, according to the following expression:

$$D \ (x, y, z) = \frac{1}{\lambda} \int \int K(x - x', y - y', z - z') \times A(x', y', z') \, dx' \, dy' \, dz',$$

(3)

where $\lambda = \frac{\ln 2}{T_{1/2}}$ is the decay constant of 90Y [half-life $T_{1/2} = 64.24$ h (Ref. 11)], $A(x', y', z')$ is the 90Y total source activity (the absorbed dose is overwhelmingly deposited by the electron component, whereas the PET signal is due to photons created through the electron-positron annihilation), and K is the dose kernel, which in general has the contribution in it from all particle species (electrons, positrons, and photons). Since the PET scanner’s resolution is not sufficient to resolve individual spheres, the dose kernel has to be calculated for a volume element of the size equal to that of the PET scan’s voxel size, which was chosen to be $0.4 \times 0.4 \times 0.3$ cm³ during the reconstruction process. Since the branching ratio for 90Y source is only $\sim 32$ ppm, the contribution of the positron component to the dose kernel is neglected.
Therefore, the whole volume of the voxel is assumed to be filled with tissue, with uniformly distributed electron sources in it that emit electrons with energy spectrum corresponding to that of beta electrons of $^{90}\text{Y}$.\textsuperscript{12} The Fluka Monte Carlo code\textsuperscript{13, 14} was used to calculate the voxel dose kernel (VDK) in tissue. The voxel size for dose calculation is equal to the PET scan’s voxel size chosen during the PET reconstruction process. All pertinent interactions including the electron, photon photoelectric, coherent and Compton interactions were turned on during the simulations and up to $10^9$ histories were simulated. 10 keV cutoff for electron, positron, and photon production and transport was also chosen during the simulations. The voxel dose kernel has the units of absorbed dose in Gy per beta decay. Its spatial convolution with the total activity density integrated over time yields the total absorbed dose, given by Eq. (3).

One can rewrite Eq. (3) to express it through the positron activity as

$$D(x, y, z) = \frac{1}{\gamma_{^{86}\text{Y}}\lambda} \iiint K(x - x', y - y', z - z') \times A^p(x', y', z')dx'dy'dz',$$

(4)

where $A^p$ is the activity due to positrons and $\gamma_{^{86}\text{Y}}$ is the branching ratio for $^{86}\text{Y}$. During the reconstruction procedure, however, the reported activity is not $A^p$ but rather the total activity $A^m$ for the radioisotope chosen in the imaging template of the reconstruction process. Thus, care has to be taken in order to properly process the measured activity $A^m$. Current Siemens PET/CT scanners do not provide an option for specifying imaging-related parameters for $^{90}\text{Y}$ isotope. Therefore, $^{86}\text{Y}$ template was used in our image acquisition procedure, which has its own tracer parameters that are different from those of $^{90}\text{Y}$. However, the $^{86}\text{Y}$ template can be used during image acquisition as long as one experimentally determines the calibration factor for $^{90}\text{Y}$ microspheres using the same PET scanner that is used for the subsequent inpatient dose reconstruction (one must use the same imaging template for determining the calibration factor as well as for patient scanning). Equation (4) can be finally recast in the following form:

$$D(x, y, z) = \frac{\gamma_{^{86}\text{Y}}}{\gamma_{^{90}\text{Y}}\lambda} \iiint K(x - x', y - y', z - z') \times A^m(x', y', z')dx'dy'dz',$$

(5)

where $\gamma_{^{86}\text{Y}}$ is the branching ratio of $^{86}\text{Y}$. As can be seen from the equation above, one is not restricted to using only $^{86}\text{Y}$ imaging template. Any other available template provided by the manufacturer can be used as long as the scanning time is much shorter than the half-life of the chosen isotope and the calibration factor $\gamma = \frac{2\lambda}{T_{1/2}}$ is determined for the chosen imaging template $X$.

The calibration factor $\gamma$ for the Siemens Biograph 16 slice PET/CT scanner available at our center was determined by injecting 740 MBq $\pm 11\%$ of $^{90}\text{Y}$-chloride (PerkinElmer) into a vial to within 11% of the total calibrated activity into a 1 l water bag. Subsequently, the "hot" water bag was scanned together with a "cold" identical size water bag using the PET scanner. Due to the fact that the scintillation crystal (lutetium oxyorthosilicate) used in the Siemens PET scanners has intrinsic radioactivity due to the presence of $^{176}\text{Lu}$, which decays by emitting electron with average energy 420 keV, followed by emission of one or more $\gamma$-ray photons, true counts are possible even when there are no injected radioactive tracers.\textsuperscript{15, 16} They represent imager’s background and depend on the scanned object due to the attenuation corrections as well as the reconstruction algorithms.

After the scan, the activity in the "cold" water bag was subtracted from the activity value of the bag containing $^{90}\text{Y}$-chloride. The corrected measured activity was divided by the known total activity at the time of scanning to determine the calibration factor for the given measurement. The average value out of these measurements is used in all subsequent dose calculations.

In addition, Fig. 1 shows the results of the total activity measurements in a "hot" water bag (with no background subtraction applied) versus time (the filled dots) together with the calculated fit (the solid line) to the experimental points. The best exponential decay fit to the experimental points (the correlation coefficient between the fit and the experimental points is 0.998) has an offset $B$ equal to 16 384 Bq (the dashed line). The actual measurements of the background using a "cold" water bag shows average total background activity (from 13 measurements) of 16 896 Bq, which is within 3% of the offset value $B$ obtained from the fitting procedure. This signifies the appropriateness and applicability of the background subtraction method proposed in this work and used in patients dose reconstruction calculations.

2.B. PET image acquisition and processing

Approximately 2 h following the infusion of $^{90}\text{Y}$ microspheres into the patient, either a single PET/CT scan or three back-to-back (if a patient can tolerate longer scanning times) PET scans (with a single CT scan) covering two bed positions...
centered on the liver were performed on a Siemens Biograph 16 Truepoint PET/CT Scanner (Siemens Healthcare). Multiple PET scans would allow one to obtain the voxel dependent average activity density as well as its standard deviation after the infusion of microspheres. The CT scan used automatic dose modulation using 130 kVp, CareDose reference of 100 mAs, 0.6 s rotation, and pitch of 1. The PET scans were acquired in Net-TrueS 3-D acquisition mode with scan time of 10 min per bed position. Since the preset isotopes defined in the scanner did not include $^{90}$Y, we chose to use the $^{86}$Y isotope setting for the PET acquisition as described earlier. The PET scans were reconstructed to 62 cm display field of view using TrueX algorithm with 21 subsets and 2 iterations and voxel size $0.4 \times 0.4 \times 0.3$ cm. This particular choice for the voxel size stems from the initial commissioning performed on the PET/CT scanner available at our institution that provided the optimal balance between signal strength on one side and the scanner’s resolution on the other. In order to limit the amount of data manipulation which eventually leads to a loss of the original information, no postprocessing smoothing filter was applied during the reconstruction procedure. The reconstruction included corrections for random coincidences, scatter, and attenuation.

An additional PET/CT scan was done for each patient under study prior to administration of $^{90}$Y microspheres to account for the presence of the imager’s intrinsic background signal. Moreover, the background signal may also depend on the total activity of the microspheres after their infusion. The inpatient measured background signal after microsphere administration may be different from that before the infusion, depending on the total administered activity. As the total infused activity increases, the background signal increases as well. Figure 2 shows the axial slices of the PET/CT images of a cylindrical water phantom (phantom diameter 81.3 cm) measurements when a vial containing 3 GBq of $^{90}$Y was placed on the top of the phantom (images on the left). The images on the right show PET/CT scans of the same water phantom scanned without any $^{90}$Y activity present. The PET acquisitions have been performed using $^{86}$Y parameters. The integrated measured activity in the whole phantom volume was 828 kBq with the $^{90}$Y source positioned on top of the phantom and 391 kBq without the $^{90}$Y source correspondingly.

FIG. 2. PET/CT images of a cylindrical water phantom scanned with a vial containing 3 GBq of $^{90}$Y microspheres placed on the top of the phantom (the images on the left side). The images on the right side show the PET/CT scan of the same cylindrical water phantom without any $^{90}$Y activity present. The PET acquisitions have been performed using $^{86}$Y parameters. The integrated measured activity in the whole phantom volume was 828 kBq with the $^{90}$Y source positioned on top of the phantom and 391 kBq without the $^{90}$Y source correspondingly.

ter the microsphere infusion are measured. In addition, since the measured activity in the spinal cord can only be due to the background signal (there is no known physiological mechanism that would transport spheres from the liver into the spinal cord), the average values of the activity density in a spinal cord before and after the infusion of microspheres are measured as well. The ratio between the two values of the activity density for the water bag as well as the spinal cord provides an average value for the scaling factor $\kappa$. By multiplying the measured average value of the pretreatment activity density in the liver by this scaling factor, one obtains the background activity signal in the liver after the infusion of microspheres. This background signal is subsequently subtracted from the measured inpatient activity distribution after administration of microspheres.

2.C. Error analysis

It is necessary to quantify the uncertainties in the reconstructed dose using the proposed approach. If patients undergoing the RE procedure could be scanned several times before and right after the infusion of microspheres, it would provide all of the required information to estimate the statistical uncertainties in the final absorbed dose. However, due to the physical condition of many of these patients, multiple PET scans before the treatment and shortly after may not be feasible. Under these limiting conditions, one can identify two major sources of uncertainties in the dose measurements...
for the proposed reconstruction method. The first is the already mentioned positive bias due to the intrinsic radioactivity of scanner’s crystals as well as the contribution of bremsstrahlung photons. Since the spatial distribution of this signal is random and has a unique pattern for each scan, no voxel-by-voxel subtraction of the bias is possible. However, the intensity distribution of the background has a certain structure to it. Figure 3 shows the activity density distribution of the pretreatment signal of the patient with the average structure to it. The histogram of the measured background activity density \( \bar{A}_b \) has the standard deviation \( \sigma_b \approx 27 \text{ Bq/ml} \). One could get the voxel dependent average activity \( \bar{A}_b \) from which one could get the voxel dependent average activity density, \( \bar{A}_\text{Meas}(x, y, z) \approx \bar{A}_b \). In addition, if multiple postinfusion scans are tolerable by the patient and can be done, there is a third source of uncertainty coming from the postinfusion measurements of the activity density \( A^\text{m}(x, y, z) \) in each voxel of patient’s reconstructed data. Even though the original photon detection follows the Poisson statistics, the reconstructed data (which also includes the attenuation corrections) are not Poissonian any more and one cannot easily estimate the uncertainty in this measurement. Therefore, the quantification of this uncertainty requires several postinfusion PET scans of a patient from which one could get the voxel dependent average activity \( \bar{A}^\text{m}(x, y, z) \) as well as its standard deviation \( \sigma^\text{m}(x, y, z) \).

Applying the standard error propagation technique \(^\text{17}\) to the equation that relates the measured activity density to the total activity density,

\[
A(x, y, z) = \frac{1}{\gamma} \left( \bar{A}^\text{m}(x, y, z) - \kappa \bar{A}_b^\text{m} \right),
\]

where the calibration factor \( \gamma \) has the standard deviation \( \sigma^\text{cal} \), the average voxel dependent postinfusion activity density \( \bar{A}^\text{m}(x, y, z) \) has the standard deviation \( \sigma^\text{m}(x, y, z) \), and the average postinfusion liver background \( \kappa \bar{A}_b^\text{m} \) has the corresponding standard deviation \( \kappa \sigma_b^\text{m} \), one arrives at the expression for the standard deviation in the calculation of the total activity density,

\[
\sigma(x, y, z) = A(x, y, z) \times \sqrt{\frac{\sigma^2(x, y, z) + \kappa^2 \sigma_b^2}{(\bar{A}^\text{m}(x, y, z) - \kappa \bar{A}_b^\text{m})^2}} + \sqrt{\left(\frac{\sigma^\text{cal}}{\gamma}\right)^2}.
\]

Substituting Eq. (6) into Eq. (3), one obtains the reconstructed inpatient dose distribution with the corresponding dose uncertainties. It should be noted here that if multiple postinfusion PET scans are not possible, then the expression for the absolute uncertainty in the total activity density will only have two terms, those describing the variance in the average background signal as well as the variance in the conversion factor.

### 3. RESULTS

Figure 4 shows the VDK as a function of a distance from the center of a \(^{90}\text{Y} \) source uniformly distributed within 0.4 \( \times \) 0.4 \( \times \) 0.3 cm\(^3\) voxel size, of the PET scan. As one can see, the kernel can be viewed as a point spread function with FWHM \( \approx 0.35 \text{ cm} \). Its effect on the dose calculation consists in smearing out or averaging the activity distribution over the

![Figure 4](image-url)
FIG. 5. The PET/CT images of the cold (top) and the hot (bottom) bags (the upper-left quadrant of the figure) after the injection of yttrium-chloride. The upper right quadrant shows the cumulative activity volume histograms for both bags. The upper left image is the axial view, the bottom right is the sagittal view, and the bottom left is the coronal view.

Effective size of the kernel. It is calculated only once (for the given value of the PET scan’s voxel size) and stored in a separate file for the convolution calculations for specific patients, which usually take less than 10 s of processing time.

Figure 5 shows the fused PET/CT images of the two 1 l water bags, one containing 740 MBq ± 11% of 90Y-chloride and the other containing water only. A total of 13 PET/CT scans were acquired over the course of 244.1 h. Table I shows the results of the first seven measurements only (the results of the subsequent six measurements at much later times are not included in the table since the total measured activity in a “hot” bag becomes comparable to the background activity at these later measurement times). The positive bias (the “cold” water bag reading obtained during each measurement time) was subtracted from each measured “hot” water bag activity to yield the net measured activity (the third column). Dividing the net PET-measured activity by the total activity at the time of imaging (the fourth column) yields the calibration factor. It should be noted here that the relative uncertainty in the calibration factor measurements is

\[ \frac{\sigma_{\text{cal}}/\gamma}{\gamma} = \sqrt{0.0434^2 + 0.11^2 \times 100\% \approx 12\%}. \]

The calibration factor was calculated from each of the scans and the average value for Siemens Biograph 16 slice PET/CT scanner was found to be \( \gamma = (1.05 \pm 0.13) \times 10^{-4} \). This calibration factor is subsequently used for all inpatient dose reconstruction calculations.

In addition, the accuracy of the total activity calibration procedure was verified by injecting water containing known activities of Y-90 into the cylindrical inserts of an ACR PET phantom, and measuring the cylinder activities by performing PET scan of the phantom a few times over a period of several days. The measured total activities were well correlated (\( R^2 = 0.9992 \)) with the cylinder activities (\( \sim 5 \) to \( \sim 280 \) MBq) at the time of the measurements.

Since the branching ratio for 86Y isotope is 0.319, the Siemens Biograph PET scanner measured branching ratio for 90Y isotope is \( \gamma_{90Y} = \gamma \times 0.319 = (3.34 \pm 0.41) \times 10^{-5} \) (since the scanning time is only 10 min, one can neglect the half-times difference between 90Y and 86Y isotopes), which is well within 1 \( \sigma \) of the most recent experimental value of \( (3.2 \pm 0.5) \times 10^{-5} \) reported in Ref. 6.

<table>
<thead>
<tr>
<th>Time interval (h)</th>
<th>Background activity (Bq)</th>
<th>Net activity from PET of 90Y (Bq)</th>
<th>Activity in bag at time of imaging (MBq)</th>
<th>Calibration factor ( \gamma = \frac{\text{Measured activity in bag}}{\text{activity in bag}} )</th>
</tr>
</thead>
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<td>73 474</td>
<td>696</td>
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</tr>
<tr>
<td>4.90</td>
<td>17 359</td>
<td>75 714</td>
<td>695</td>
<td>( 1.09 \times 10^{-4} )</td>
</tr>
<tr>
<td>5.10</td>
<td>18 089</td>
<td>76 367</td>
<td>693</td>
<td>( 1.10 \times 10^{-4} )</td>
</tr>
<tr>
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<td>73 829</td>
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<tr>
<td>43.78</td>
<td>19 856</td>
<td>46 855</td>
<td>456</td>
<td>( 1.03 \times 10^{-4} )</td>
</tr>
<tr>
<td>44.30</td>
<td>19 264</td>
<td>43 944</td>
<td>453</td>
<td>( 0.97 \times 10^{-4} )</td>
</tr>
<tr>
<td>44.50</td>
<td>21 119</td>
<td>46 190</td>
<td>452</td>
<td>( 1.02 \times 10^{-4} )</td>
</tr>
</tbody>
</table>
FIG. 6. The PET/CT image of a patient prior to injection of $^{90}$Y microspheres. The average value for the measured activity density in a liver for this patient is 29.6 Bq/ml. The window width is set at 111 Bq/ml and the window level is set at 55 Bq/ml. The upper left image is the axial view, the bottom right is the sagittal view, and the bottom left is the coronal view.

Figure 6 shows the PET/CT scan of a patient prior to injection of $^{90}$Y microspheres. Due to the already mentioned presence of a positive bias in Siemens PET/CT scanners, the PET image of the patient has nonzero activity distribution, which depends on patient size due to the attenuation corrections. This activity is randomly distributed in space and its distribution changes with each scan even for the same patient. Thus, one cannot just subtract this 3D activity distribution from the PET/CT scan of the same patient (voxel by voxel subtraction) after the microspheres have been injected. Therefore, we used a patient specific bias, which is calculated as a volume averaged (over the liver’s volume) value of the measured

FIG. 7. The PET/CT image of a patient 2 h after the injection of $^{90}$Y microspheres. The average value for the measured activity density in a liver for this patient after the injection of microspheres is 144 Bq/ml with the global maximum and minimum ranging from 12 to 731 Bq/ml correspondingly.
pretreatment activity density multiplied by the scaling factor \( \kappa \), which for the given patient was \( A^\text{in}_{\text{pretreatment}} \approx 29.6 \times 2.0 = 59.2 \text{ Bq/ml} \). This value was subtracted from the 3D patient measured activity distribution obtained after the microspheres were injected into the hepatic artery.

Figure 7 shows one of the three PET scans of the same patient 2 h after the infusion of microspheres. The mean value of the measured activity density in the liver for this patient was 144 Bq/ml, with the minimum and maximum values ranging between 12 and 733 Bq/ml. The bias adjusted measured inpatient activity density distribution is subsequently used in Eqs. (3) and (6) for dose reconstruction calculations. Figure 8 shows the reconstructed dose distribution superimposed on the CT scan of the patient shown in Fig. 7 calculated using the developed method. The outermost and innermost lines represent 10% and 80% of the maximum dose of 296.2 Gy. Applying the error analysis to the patient’s dose data, one finds that 80% isodose line has 26% uncertainty in it (237 ± 62 Gy), 60% isodose line has 30% uncertainty in it (178 ± 53 Gy), 20% isodose line has 56% dose uncertainty (59 ± 33 Gy), and 10% isodose line has 100% dose uncertainty. Thus, 10% isodose line for this case is not reliable and should be examined with care. Figure 9 shows the dose volume histogram for tumor sites (GTV1, GTV2, GTV3), and critical structures. As one can see from these figures, the dose distribution inside the liver is quite inhomogeneous. Moreover, the three tumors received a good coverage for this particular case with \( D_{90} \) (the minimum dose covering 90% of the tumor volume) ranging from 62 Gy for GTV3 to 121 Gy for GTV1.

A total of seven patients have been analyzed so far using the proposed reconstruction method. Four patients underwent treatment with SIR-Spheres for liver metastases from colorectal cancer and three patients were treated with Therasphere for hepatocellular cancer. A total of 14 target tumors were contoured on post-treatment PET-CT scans for dosimetric evaluation. Mean prescription activity was 1.7 GBq (range: 0.58–3.8 GBq). The resulting mean maximum measured dose to targets was 167 Gy (range: 71–311 Gy). Mean minimum dose to 70% of target \( D_{70} \) was 68 Gy (range: 25–155 Gy). Mean minimum dose to 90% of target \( D_{90} \) was 53 Gy (range: 13–125 Gy). The mean volume of liver receiving at least 30 Gy \( V_{30} \) was 856 cc (range: 257–1199 cc). The mean maximum dose to 1 cc of the right kidney was 29 Gy.

FIG. 8. Reconstructed inpatient dose distribution superimposed on patient’s CT data (axial slice). The numbers indicate the percent line of the maximum dose of 296 Gy.

FIG. 9. Dose volume histogram for three tumors (GTV1, GTV2, GTV3), liver (without GTVs), right kidney, bowel, and gallbladder.
(range: 13–48 Gy). The mean maximum dose for Therasphere and SIR-spheres was 301 versus 111 Gy. The mean D70 for Therasphere and SIR-Spheres was 85 versus 40 Gy. The mean D90 for Therasphere versus SIR-Spheres was 62 and 33 Gy.

4. DISCUSSION

The available clinical data for incidence of complications after selective internal radiation therapy or SIRT suggest that if patients are selected appropriately and target delivery is performed meticulously, the complication probability is relatively low. However, a number of radiation induced complications have been reported in the literature, such as radiation induced pneumonitis, gastrointestinal and pancreatic complications, radiation-induced liver disease, biliary duct complications, and radiation-induced cholecystitis. All these complications are due to the excessive dose levels delivered to different critical structures. The quantification of risk of these complications was not possible up to this point due to the lack of precise information about inpatient dose distribution. With the development of this reconstruction procedure, the doses to different organs can be finally scored and complication as well as tumor control probabilities can be estimated. In spite of the complications listed above, the toxicity rate appears to be exceptionally low. This implies that tumor control may be improved in a large segment of patients with escalated dose regimen. However, dose escalation may only be performed safely with dosimetry data showing doses to tumors, normal liver, and surrounding organs such as lung, right kidney, bowel, and gallbladder.

An important issue that needs to be addressed in future studies is to find out if any correlations between the pretreatment Tc-MAA SPECT images and 90Y PET scans exists. In general, such correlation for all patients most likely will not be present, since the concentration of particles for MAA and resin microsphere suspensions is significantly different (microspheres are concentrated tenfold). This may result in a difference in the distribution kinetics between the two particle species which may lead to their different accumulation within liver and tumor compartments. However, the correlation studies may answer the question under which clinical conditions MAA and 90Y microspheres distributions are similar or different. For those cases where the ascertained clinical conditions would indicate positive correlation between the two image sets, one could design a treatment plan before the infusion of microspheres. As an example, one could use the information from the Tc-MAA SPECT/CT scan to predict whether the tumor will receive an adequate dose as well as the critical structures are not going to be overdosed after administration of 90Y microspheres and if this is the case, an appropriate activity scaling may be done.

Another important issue that needs to be further investigated is the background quantification of the PET/CT scanner. The reconstructed absolute dose depends on the way the positive bias is taken into account during the data processing. In the current approach, an average value of inpatient activity density in the liver before the administration of microspheres multiplied by the scaling factor $\kappa$ is subtracted from the activity density distribution after the microspheres have been injected into the blood stream, requiring at least two PET/CT scans for the given patient. Additional research needs to be done in order to reduce the image noise, which would ultimately reduce the dose uncertainty. This issue will be explored in our future investigation of the image background management at the sinogram level before the reconstruction is done. Therefore, the 10%–20% isodose lines distribution should be examined with care and caution on a case-to-case basis.

Finally, the proposed dose reconstruction method will eventually need to be benchmarked against an independent dose verification method, such as gel dosimetry. In a future investigation, a preset activity of microspheres will be injected into a gel phantom with a subsequent PET/CT scan and optical tomography reconstruction of the dose.

5. CONCLUSIONS

A three-dimensional inpatient absolute dose reconstruction method has been developed that is based on the PET/CT data of a patient treated with 90Y microspheres. It allows for a complete description of the absorbed dose by the tumor and critical structures. It represents the first step in building predictive models for treatment outcomes for patients receiving this therapeutic modality as well as it allows for better analysis of patients’ dose response and will ultimately improve future treatment administration.

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