

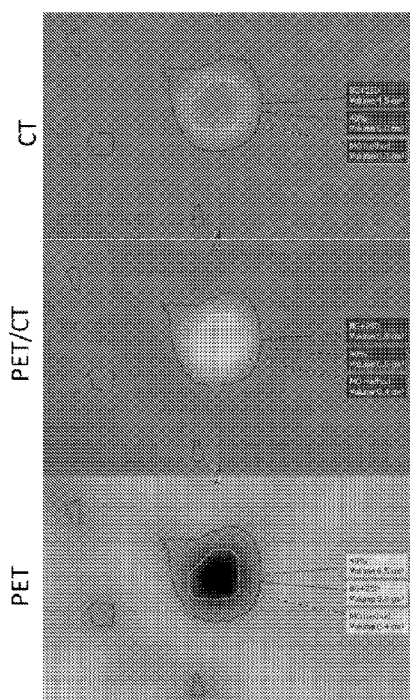


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- (54)
- Title:**
- MULTI-LEVEL OTSU FOR POSITRON EMISSION TOMOGRAPHY (MO-PET)

(57) **Abstract:** The present invention provides a method for accurate characterization of tumor burden and response to therapy. Such a method is highly desirable, because it may help improve the prognosis and survival of cancer patients. The method of the present invention can provide a reliable PET tumor boundary definition and metabolic tumor volumetric quantification that is robust with tumors of various sizes, ^{18}F -FDG and other PET radiotracer uptake levels, and shapes. This method is a valuable user-friendly tool that is clinically applicable in aiding clinicians in diagnosing, staging, planning of radiotherapy and surgery, and determining treatment response of cancer. It can also be a valuable research tool to be used in cancer therapy development.

**FIG. 8**



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MULTI-LEVEL OTSU FOR POSITRON EMISSION TOMOGRAPHY (MO-PET)

CROSS REFERENCE TO RELATED APPLICATIONS

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[0001] This application claims the benefit of U.S. Provisional Patent Application No. 62/139,319 filed March 27, 2015, which is incorporated by reference herein, in its entirety.

FIELD OF THE INVENTION

[0002] The present invention relates generally to medical imaging. More particularly the present invention relates to an automated image segmentation system for characterization and volumetric quantification of target tissue.

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BACKGROUND OF THE INVENTION

[0003] Positron emission tomography (PET) is a functional imaging modality that is used as a routine diagnostic tool in cancer staging and management. In particular, metabolic tumor volume (MTV) of PET scans, most notably with ^{18}F -fluorodeoxyglucose (^{18}F -FDG) PET scans has shown promise as a useful biomarker for assessing treatment response, disease progression, and also plays an important role in planning of radiation therapy treatment and surgery. In fact, the accuracy of the contour or segmentation of tumor affects the precision of radiotherapy, because the prescribed radiation dosage threshold for the tumor in radiation therapy planning is determined based on the contour delineating the tumor. Hence, method for accurate quantification of tumor volume and delineation of its boundary is highly desirable, since it can lead to early assessment of changes in tumor sizes and optimization of an individual patient's therapy, which may ultimately help improve the prognosis and survival of cancer patients.

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[0004] Various methods are currently being utilized for assessing and quantifying metabolic tumor response on ^{18}F -FDG PET scans. One method that is widely used is the visual interpretation of tumor contour in PET images by experienced radiologist. However, the subjective manual contouring is tedious and its reproducibility would be relatively low, resulting in inter-observer variability and intra-observer variability of tumor volumes. A number of automated segmentation methods for metabolic tumor volume have been proposed for reducing inter-observer variability and intra-observer variability, and increasing segmentation accuracy of tumor volumes. One of the most commonly used automated segmentation technique is thresholding. In this technique, one or more thresholds are selected, and the image pixels are classified according to the thresholds as background or tumor. There are several thresholding methods that are commonly used for tumor contouring: fixed threshold method, percentage of maximum standardized uptake value (SUV_{max}) method, and PET Response Criteria in Solid Tumors (PERCIST) criteria method. In fixed threshold method, a SUV_{max} of 2.5 is defined as a threshold for the distinction between malignant and benign lesions. However, the SUV_{max} 2.5 isocontour often fails to accurately characterize small nodules or tumors with low FDG uptake. An alternative thresholding approach that has traditionally been used to delineate tumor is by percentage of the SUV_{max} within a volume of interest (VOI). Some of the commonly used percentage thresholds are ranging from 15% to 50% of SUV_{max} . Another thresholding approach is the PERCIST criteria method, which takes into account of the image background in finding the threshold, proposing a threshold formula of the mean of the background taken over the center of the liver plus two standard deviations (S.D.). All of these commonly used thresholding methods rely upon tumor SUV_{max} or physiologic organ values (e.g. liver, blood pool), which can vary from tumor type and treatment responses. These current methods are problematic because of

their inability to be applied accurately and reproducibly across a range of tumor sizes and tumor ^{18}F -FDG uptake levels, limiting current methods to only specific tumor types and treatment settings (pre-treatment or post-treatment with tumor response). To our knowledge, there has not been a designated, default method of segmentation that can be consistently used across a wide range of tumor sizes and PET SUVs.

[0005] It would therefore be advantageous to provide an accurate and reproducible tumor volumetric quantification and boundary definition across a wide range of tumor sizes and ^{18}F -FDG PET uptake levels.

BRIEF DESCRIPTION OF THE FIGURES

[0006] FIGS. 1A-1H illustrate a comparison of isocontours of the metabolic tumor volumes (MTVs) of a small-sized and low SUV_{max} tumor ($\text{SUV}_{\text{max}} = 4.65$; volume = 0.77 cm^3) using multi-Otsu segmentation method (Level 2 Otsu, displayed as red contours in FIGS 1, 2 and 3) and various other segmentation approaches, according to an embodiment of the present invention.

[0007] FIGS. 2A-2H illustrate a comparison of isocontours of the metabolic tumor volumes (MTVs) of a medium-sized and medium SUV_{max} tumor ($\text{SUV}_{\text{max}} = 10.74$; volume = 2.27 cm^3) using multi-Otsu segmentation method (Level 2 Otsu) and various other segmentation approaches, according to an embodiment of the present invention.

[0008] FIGS. 3A-H illustrate a comparison of isocontours of the metabolic tumor volumes (MTV) of a large-sized and high SUV_{max} tumor ($\text{SUV}_{\text{max}} = 16.19$; volume = 21.01 cm^3) using multi-Otsu segmentation method (Level 2 Otsu) and various other segmentation approaches, according to an embodiment of the present invention.

[0009] FIGS. 4A-4D illustrate Box Plots for metabolic tumor volumes delineated with all 11 segmentation approaches and CT reference gross tumor volume, according to an embodiment of the present invention.

5 [0010] FIGS. 5A-5D illustrate Box Plots for metabolic tumor volumes delineated with all 11 segmentation approaches and CT reference gross tumor volume, according to an embodiment of the present invention.

[0011] FIGS. 6A-6D illustrate Mean Volume Ratio for all 11 segmentation approaches, according to an embodiment of the present invention.

10 [0012] FIGS. 7A-7D illustrate Mean Volume Ratio for all 11 segmentation approaches, according to an embodiment of the present invention.

[0013] FIG. 8 illustrates images that show that the MO method provides the most accurate contour of a small lesion with volume of 0.52 cm^3 in 4:1 LBR.

[0014] FIGS. 9-13 illustrate graphical views of the comparison of the PET segmentation volumes measured using 3 main different PET segmentation methods (percent of max voxel
15 in the lesion, background reference with various standard deviations and various multi-otsu algorithms. PET segmentation methods are compared as a volume ratio to the true volume of the lesion which is a known reference volume using a standard PET phantom (NEMA phantom) with various sizes and filled with various ^{18}F -FDG lesion to background ratios.

[0015] FIG. 14 illustrates images of ^{18}F -FDG PET avid osteosarcoma of the lower
20 extremity involving the proximal tibia in coronal and transaxial PET, CT and fused PET/CT images.

[0016] FIG. 15 illustrates image views of ^{18}F -FDG avid osteosarcoma of the lower extremity involving the left distal femur in coronal and transaxial PET, CT and fused PET/CT images.

[0017] FIGS. 16A and 16B illustrate image views of ^{18}F -FDG avid osteosarcoma of the upper extremity involving the humerus in coronal and transaxial PET, CT and fused PET/CT images.

[0018] FIG. 17 illustrates an image view of ^{18}F -FDG avid melanoma lung metastasis in whole body PET MIP, and in coronal and transaxial PET, CT and fused PET/CT images.

[0019] FIG. 18 illustrates an image view of ^{18}F -FDG avid melanoma lung metastasis in whole body PET MIP, and in coronal PET and CT, and transaxial PET, CT and fused PET/CT images.

[0020] FIG. 19 illustrates an image view of ^{18}F -Sodium Fluoride prostate cancer bone metastasis of the spine in whole body PET MIP, and in sagittal and transaxial PET, CT and fused PET/CT images.

[0021] FIG. 20 illustrates an image view of ^{18}F -DCFPyL PSMA PET avid prostate cancer bone metastases of the spine in whole body MIP, and in sagittal and transaxial PET, CT and fused PET/CT images.

SUMMARY

[0022] The foregoing needs are met, to a great extent, by the present invention, wherein in one aspect a method for automatic tumor delineation includes obtaining a positron emission tomography image of the tumor. The method also includes classifying image pixels based on

their standardized uptake value (SUV). Additionally, the method includes creating multiple classes of image pixels by seeking to minimize each class' average SUV variation from a mean SUV value for the class and maximizing each class' SUV deviation from a mean SUV of other classes. The method includes generating multiple thresholds to define multiple classes of pixels, and selecting an optimal threshold from the multiple thresholds that delineates and quantifies tumor volume.

[0023] In accordance with an aspect of the present invention, ^{18}F -FDG and other non- ^{18}F -FDG PET imaging is used. A non-transitory computer readable medium programmed with the method. Automatic tumor delineation is used for patient monitoring and treatment planning, and contouring the tumor. The method further includes displaying a visual representation of the tumor volume and displaying a visual representation of the PET image after partitioning.

[0024] In accordance with another aspect of the present invention, a system for automatic delineation of tumors and other normal and pathologic anatomic structures and physiological processes includes a Positron Emission Tomography (PET) imaging device configured for obtaining an image of structures or processes of interest. The system includes a non-transitory computer readable medium programmed for receiving the image and processing the image. The non-transitory computer readable medium is programmed for specifying an approximate boundary to indicate the Region Of Interest (ROI) within which automatic delineation is performed. The non-transitory computer readable medium is also programmed for partitioning the distribution of the image data in to multiple classes using threshold levels that minimize intra(within)-class variance (*which is same as maximizing the inter-class variance*) as determined by weighted sum of variances of all the classes, where, variance of a class is the average of squared deviations from the mean of the class. Additionally, the non-transitory

computer readable medium is programmed for selecting an optimal threshold from the multi-level thresholds that effectively delineates and quantifies tumor volume.

[0025] In accordance with yet another aspect of the present invention, the system further comprises a PET radiotracer. The image data or the threshold values are converted to a
5 conventionally prescribed unit representation in PET imaging such as any of the Standardized Uptake Value (SUV) units. An additional benefit of multi-level thresholds is to characterize the heterogeneity of the tumors and other normal and pathologic anatomic structures and physiological processes. The non-transitory computer readable medium is in direct communication with the PET imaging device. The system can use automatic delineation of
10 structures and processes for patient response monitoring and treatment planning. The system can include contouring of structures and processes efficiently based on automatic delineation. The PET radiotracer can take the form of ^{18}F -FDG, for PET imaging of structures or process. The system is configured to display a visual representation of the tumor volume and a visual representation of the PET image after partitioning.

15 DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0026] The presently disclosed subject matter now will be described more fully hereinafter with reference to the accompanying Drawings, in which some, but not all embodiments of the inventions are shown. Like numbers refer to like elements throughout. The presently disclosed subject matter may be embodied in many different forms and should not be
20 construed as limited to the embodiments set forth herein; rather, these embodiments are provided so that this disclosure will satisfy applicable legal requirements. Indeed, many modifications and other embodiments of the presently disclosed subject matter set forth herein will come to mind to one skilled in the art to which the presently disclosed subject

matter pertains having the benefit of the teachings presented in the foregoing descriptions and the associated drawings. Therefore, it is to be understood that the presently disclosed subject matter is not to be limited to the specific embodiments disclosed and that modifications and other embodiments are intended to be included within the scope of the appended claims.

5 **[0027]** The present invention provides a method for accurate characterization of tumor burden and response to therapy, which is highly desirable, because it may help improve the prognosis and survival of cancer patients. Oncology positron-emission tomography (PET) methods have been used to quantify metabolic tumor response on PET scans and have progressed to newer methods which now are able to calculate a PET-derived metabolic tumor
10 volume to determine a patient's tumor burden. However, an accurate and automatic delineation of tumor boundaries based on fluorodeoxyglucose (^{18}F -FDG) PET uptake across a range of tumor sizes and PET standardized-uptake value (SUV) maximum (percent of tumor SUV maximum) or normal physiologic organ values (liver, blood pool), which can vary from tumor type and with different treatment response, is not provided by previous
15 oncology PET methods. The method of the present invention provides a reliable PET tumor boundary definition and metabolic tumor volumetric quantification that is robust with tumors of various sizes, ^{18}F -FDG uptake levels, and shapes. This can be a valuable user-friendly tool that is clinically applicable in aiding clinicians in diagnosing, staging, planning of radiotherapy and surgery, and determining treatment response of cancer. It can also be a
20 valuable research tool to be used in cancer therapy development.

[0028] The segmentation method of the present invention is based on multi-level Otsu's method, which is an extension of the traditional Otsu's method. Multi-level Otsu's method has been utilized in bone or brain segmentation in computed tomography (CT) scans. In the

field of PET imaging, a variation of basic Otsu method has been introduced as a solution to the segmentation problem. However, there is not any prior work related to multi-level Otsu threshold technique. It should also be noted that the protocol for multi-level Otsu CT scanning does not readily apply to PET scanning. For instance, the methods currently

5 available do not provide consistent or objective results when applied to PET. The method of the present invention cures this inconsistency and provides results that are both consistent and objective. Thus, the new diagnostic application of the present invention, which automatically quantifies and contours ^{18}F -FDG PET tumors based on multi-level Otsu method, is a novel image processing approach for PET tumor imaging. To demonstrate the accuracy and

10 robustness of multi-level Otsu method, multi-level Otsu method is compared with other commonly used threshold-based segmentation methods (e.g. percentage of SUV_{max} method and PERCIST criteria method) in delineating tumors across a range of SUVs and tumor sizes.

[0029] Multi-level threshold, as used herein, refers to threshold values that separate out different classes of information present in the image data. For instance, if there are only two

15 classes of information in the image data (such as foreground and background), then the threshold value that separates those two classes would be referred to as Level 1 threshold. Likewise, if there are 3 classes of information present in the image data, such as background, normal foreground part and abnormal foreground part then Level 2 threshold would refer to the threshold that separates normal and abnormal foreground parts.

20 **[0030]** The method of the present invention classifies image pixels based on their standardized uptake values (SUVs). It is designed to create multiple classes of image pixels by seeking to minimize each class's average SUV deviation from the class mean SUV value, while maximizing each class's SUV deviation from the SUV means of the other groups. For a

single image, multiple thresholds are generated to define multiple classes of pixels. Among multiple thresholds that are generated, the threshold that can best delineate and quantify tumor volume is selected to be the optimal threshold. This novel application can help in objective patient monitoring and treatment planning. Accuracy and robustness of this method have been validated with pre- and post-therapy PET-CT scans of patients.

[0031] In an exemplary implementation of the present invention, which is not to be considered limiting, as any implementation known to or conceivable by one of skill in the art is possible, four oncology patients (mean age = 48.3 y; range, 18y to 67y, SD = 21.2; 3 male and 1 female) referred to an academic medical center for ^{18}F -FDG PET/CT scans between September 2009 and April 2012 were retrospectively reviewed. All patients had baseline ^{18}F -FDG PET/CT scans performed as part of the initial staging workup before treatment. A second ^{18}F -FDG PET/CT scan was acquired one to three months after the first scan. Clinical diagnoses were made on the basis of clinical interviews and results of radiological testing by licensed radiologists. Twenty-five tumors (13 from pre-therapy ^{18}F -FDG PET/CT images and 12 from post-therapy ^{18}F -FDG PET/CT images) were selected for this study.

[0032] All patients were scanned with a whole-body GE Discovery RX PET/CT scanner (GE Healthcare Technologies, Waukesha, WI) from skull to mid-thigh, after being injected intravenously with ^{18}F -FDG. Resting glucose values were measured and determined to be acceptable ranges (<150 mg/dL) before ^{18}F -FDG administrations. All patients had their height and weight determined at the time of the scan. ^{18}F -FDG quantities were based on weight and injected intravenously; isotope was distributed for at least 60 minutes in a resting state. Images were reconstructed using an iterative three-dimensional algorithm and stored using a Digital Imaging and Communications in Medicine (DICOM) format. PET image dimensions

were 128 x 128 x 407, 371, 263, or 335 (with voxel sizes of 1.37 mm x 1.37 mm x 3.27 mm for all images). For the purpose of this study, the DICOM data were transferred to a Java-based image analysis program (ImageJ v1.43; NIH, Bethesda, MD). PET-DICOM data were fused to CT with automated coregistration using image processing software in ImageJ.

5 [0033] To ultimately compare the metabolic tumor volumes and CT-based tumor volume, we defined a reference CT-based gross tumor volume, GTV_{CT}. GTV_{CT} was first derived by traditional Otsu's method using single threshold, then the segmented tumor contours was visually reviewed by a license radiologist and received confirmation with regard to the correctness of the tumor boundary.

10 [0034] Pixels in the given PET image represent a distribution of numerical data such as Standardized Uptake Values (SUV) or other quantitative PET values that range from a minimum to a maximum. The entire range of these continuous values can be divided in to series of intervals (L intervals) to count how many pixel values in the image data fall within each interval. Let n_i represent number of pixels in the i^{th} interval. Let $N = \sum_{i=1}^L n_i$ represent
15 total number of pixels in the image. The probability of occurrence (P_i) of each interval i is given by $P_i = n_i/N$.

[0035] Let the image be divided into K classes (each class representing certain range of pixel data) $C_1, C_2, C_3, \dots, C_K$ by $(K-1)$ thresholds $T_1, T_2, T_3, \dots, T_{(K-1)}$. C_1 consists of pixel values with the range $[0, \dots, T_1]$, C_2 consists of pixel values with the range $[T_1+1, \dots, T_2]$, C_3
20 consists of pixel values with the range $[T_2+1, \dots, T_3]$, and C_K consists of pixel values with the range $[T_{(K-1)}+1, \dots, L]$. $\mu_1(T_1), \mu_2(T_2), \mu_3(T_3), \dots$, and $\mu_K(T_{(K-1)})$ define the mean levels for each class of pixels. $\sigma_1^2(T_1), \sigma_2^2(T_2), \sigma_3^2(T_3), \dots$, and $\sigma_K^2(T_{(K-1)})$ define the variances of class C_1 ,

$C_2, C_3, \dots, C_K$, respectively. The values of class probabilities, mean values and variances are given by the formula:

Class Probabilities:

$$P_1(T_1) = \sum_{i=0}^{T_1} P_i$$

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$$P_2(T_2) = \sum_{i=T_1+1}^{T_2} P_i$$

$$P_K(T_{K-1}) = \sum_{i=T_{K-1}+1}^L P_i$$

Mean level

$$\mu_1(T_1) = \sum_{i=0}^{T_1} i \frac{P_i}{P_1(T_1)}$$

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$$\mu_2(T_2) = \sum_{i=T_1+1}^{T_2} i \frac{P_i}{P_2(T_2)}$$

$$\mu_K(T_{K-1}) = \sum_{i=T_{K-1}+1}^L i \frac{P_i}{P_K(T_{K-1})}$$

Variance

$$\sigma_1^2(T_1) = \sum_{i=0}^{T_1} (i - \mu_1(T_1))^2 \frac{P_i}{P_1(T_1)}$$

$$\sigma_2^2(T_2) = \sum_{i=T_1+1}^{T_2} (i - \mu_2(T_2))^2 \frac{P_i}{P_2(T_2)}$$

$$\sigma_K^2(T_{K-1}) = \sum_{i=T_{K-1}+1}^L (i - \mu_K(T_{K-1}))^2 \frac{P_i}{P_K(T_{K-1})}$$

The probability-weighted within-class variance is given by:

$$\sigma_w^2(T_1, T_2, \dots, T_{K-1}) = P_1(T_1)\sigma_1^2(T_1) + P_2(T_2)\sigma_2^2(T_2) + \dots + P_K(T_{K-1})\sigma_K^2(T_{K-1})$$

- 5 To find the multi-Otsu threshold value, the within-class variance as given by the equation above is repeatedly computed for all possible set of threshold values $T_1, T_2, \dots, T_{K-1}$ to find the set of threshold values that yield minimum within-class variance (minimization of within-class variance σ_w^2). The corresponding set of threshold values represents multi-Otsu threshold values. If the first threshold in the set is zero, corresponding to air or background, it
- 10 is referred as Level 0 Threshold and the following list of thresholds in the set are referred as Level 1, Level 2 Threshold and so on.

- [0036] To evaluate the segmentation accuracy of multi-Otsu segmentation method and other segmentation methods, we compare the volume ratio (VR), which is the ratio of metabolic tumor volume on PET (MTV_{PET}) to the anatomical gross tumor volumes defined
- 15 on CT (GTV_{CT}).

$$VR = \frac{MTV_{PET}}{GTV_{CT}}$$

VR values range from 0 to 1; VR closest to 1 points toward the better segmentation strategy.

[0037] The significance of differences between the MTVs measured with 11 different segmentation methods and reference CT volumes were evaluated using a two-tailed paired *t*-test; $p < 0.01$ is considered significantly different.

[0038] The range of SUV_{max} of the 25 tumors selected for this study was 3.17 to 25.80 (mean $\pm$ SD, 11.24 ± 6.12). A total of 6 tumors were measured with SUV_{max} between 0.00 to 5.00, 6 tumors were measured with SUV_{max} between 5.01 to 10.00, 7 tumors were measured with SUV_{max} between 10.01 to 15.00, and 6 tumors with SUV_{max} greater than 15.00.

[0039] The mean GTV_{CT} of the 25 tumors was $3.57 \pm 4.27 \text{ cm}^3$ (mean $\pm$ SD), and the range of the tumor volume was $0.59 - 21.01 \text{ cm}^3$. A total of 9 tumors were measured greater than 3.00 cm^3 , 6 tumors measured between 2.00 to 3.00 cm^3 , 3 tumors measured between 1.00 to 2.00 cm^3 , and 7 tumors were measured less than 1.00 cm^3 . Table 1 and Table 2 list the mean metabolic tumor volumes calculated using the respective segmentation methods.

[0040] FIGS. 1A-1H show PET/CT fusion images of a relatively small-sized (volume = 0.77 cm^3) and low SUV_{max} ($SUV_{max} = 4.65$) tumor comparing the metabolic tumor contour obtained with multi-Otsu based segmentation method with other different segmentation methods using the PET/CT fusion image as a reference. For small and low SUV_{max} tumor, multi-Otsu based segmentation method and a fixed threshold method at 40% SUV_{max} performed well and more accurately reproduced the reference contour defined on PET/CT fusion image, whereas large discrepancies were observed with segmentation methods such as PERCIST criteria method (e.g., $Liver_{ref} + 1SD$, $Liver_{ref} + 2SD$, and $Liver_{ref} + 3SD$) and threshold method at fixed percentage of 20%, 60%, and 80% SUV_{max} . FIGS. 1A-1H illustrate a comparison of isocontours of the metabolic tumor volumes (MTVs) of a small-sized and low

SUV_{max} tumor (SUV_{max} = 4.65; volume = 0.77 cm³) using multi-Otsu segmentation method (Level 2 Otsu) and various other segmentation approaches. FIG. 1A is the PET-CT fusion image, which serves as the reference. FIGS. 1B, 1C, 1D, 1E, 1F, 1G, and 1H demonstrate MTVs delineated with thresholds of SUV $\geq$ Level 2 Otsu segmentation method (red) and
 5 with thresholds of SUV $\geq$ Liver_{ref}+1SD (blue), Liver_{ref}+2SD (blue), Liver_{ref}+3SD (blue), 20% SUV_{max} (green), 40% SUV_{max} (green), 60% SUV_{max} (green), and 80% SUV_{max} (green) respectively. All images are from the same patient and same tumor. Depending on the thresholds used by the corresponding segmentation methods, different MTVs were delineated.

10 [0041] FIGS. 2A-2H and 3A-3H show PET/CT fusion images of a medium-sized (volume = 2.27 cm³) and medium SUV_{max} (SUV_{max} = 10.74) tumor and a large-sized (volume = 21.01 cm³) and high SUV_{max} (SUV_{max} = 16.19) tumor respectively. For both cases, Multi-Otsu based segmentation method and PERCIST criteria method produced accurate tumor boundary definition and separation of the tumors from surrounding tissues while the fixed threshold
 15 method at 40% SUV_{max}, 60% SUV_{max} and 80% SUV_{max}, underestimated the tumors size and the fixed threshold method of 20% SUV_{max} overestimated the size of the tumors.

[0042] FIGS. 2A-2H illustrate a comparison of isocontours of the metabolic tumor volumes (MTVs) of a medium-sized and medium SUV_{max} tumor (SUV_{max} = 10.74; volume = 2.27 cm³) using multi-Otsu segmentation method (Level 2 Otsu) and various other
 20 segmentation approaches. FIG. 2A is the PET-CT fusion image, which serves as the reference. FIGS. 2B, 2C, 2D, 2E, 2F, 2G, and 2H demonstrate MTVs delineated with thresholds of SUV $\geq$ Level 2 Otsu segmentation method (red) and with thresholds of SUV $\geq$ Liver_{ref}+1SD (blue), Liver_{ref}+2SD (blue), Liver_{ref}+1SD (blue), 20% SUV_{max} (green), 40%

SUV_{max} (green), 60% SUV_{max} (green), and 80% SUV_{max} (green) respectively. All images are from the same patient and same tumor.

[0043] FIGS. 3A-H illustrate a comparison of isocontours of the metabolic tumor volumes (MTV) of a large-sized and high SUV_{max} tumor (SUV_{max} = 16.19; volume = 21.01 cm³)

5 using multi-Otsu segmentation method (Level 2 Otsu) and various other segmentation approaches. FIG. 3A is the PET-CT fusion image, which serves as the reference. FIGS. 3B, 3C, 3D, 3E, 3F, 3G, and 3H demonstrate MTVs delineated with thresholds of SUV $\geq$ Level 2 Otsu segmentation method (red) and with thresholds of SUV $\geq$ Liver_{ref}+1SD (blue), Liver_{ref}+2SD (blue), Liver_{ref}+1SD (blue), 20% SUV_{max} (green), 40% SUV_{max} (green), 60% SUV_{max} (green), and 80% SUV_{max} (green) respectively. All images are from the same patient and same tumor.

[0044] FIGS. 1A-1H, 2A-2H, and 3A-3H show that multi-Otsu based segmentation method consistently and accurately reproduced the reference tumor contour defined on PET/CT fusion image across tumors of different sizes and different SUVs or intensities of tracer uptake. In the case of the PERCIST criteria method and the fixed threshold method at percentages of SUV_{max}, large discrepancy between reference tumor contour and metabolic tumor definition produced by the segmentation method were observed. For instance, the PERCIST criteria method produced good boundary definition for medium to large-sized tumors and tumors with medium to high SUVs, but showed poor tumor boundary estimation for small-sized tumor or tumor with low SUV. The fixed threshold methods at 60% SUV_{max} and 80% SUV_{max} both underestimated tumor boundary for small-sized/ low SUV, medium-sized/ medium SUV, and large-sized/ high SUV tumors while the fixed threshold methods at 20% SUV_{max} overestimated tumor boundaries. The fixed threshold methods at 40% SUV_{max}

produced good tumor boundary definition for small-sized and low SUV tumor as well as tumor of medium-sized and medium SUV, but underestimated tumor boundary for large-sized and high SUV tumors. In summary, based on the comparison of the isocontours of metabolic tumor volumes delineated with the tested segmentation methods, the multi-Otsu based segmentation method outperformed both PERCIST criteria method and the fixed threshold method at percent SUV_{max} in tumor boundary delineation.

[0045] As shown in Table 1, tumors were grouped into 4 categories depending on their SUV_{max} : (1) SUV_{max} between 0.00 and 5.00; (2) SUV_{max} between 5.01 and 10.00; (3) SUV_{max} between 10.01 and 15.00; and (4) $SUV_{max} > 15.00$. When all 11 segmentation methods were compared against CT-based gross tumor volume, only metabolic tumor volumes delineated with level 2 Otsu ($SUV_{max} = 0.00-5.00$, $p = 0.04$; $SUV_{max} = 5.01-10.00$, $p = 0.70$; $SUV_{max} = 10.01-15.00$, $p = 0.88$; $SUV_{max} > 15.00$, $p = 0.15$), a multi-Otsu based segmentation method, were not significantly different from the CT-based reference tumor volumes for all twenty-five tumors, with SUV_{max} ranging between 3.17 to 25.80. Table 1 shows mean metabolic tumor volumes corresponding to each of the PET image segmentation methods relative to the reference gross tumor volume defined on the CT scan. The levels of statistical significance for paired samples are also shown. Depending on their SUV_{max} value, tumors are classified into 4 different categories: SUV_{max} range 0.00 to 5.00, SUV_{max} range 5.01 to 10.00, SUV_{max} range 10.01 to 15.00, and SUV_{max} range > 15.00 .

[0046] Moreover, according to FIGS. 4A-4D, CT-based gross tumor volumes were well within the range of metabolic tumor volumes determined with level 2 Otsu. Metabolic tumor volumes defined by the threshold method of fixed percentage of 20% SUV_{max} ($SUV_{max} = 5.01-10.00$, $p = 0.007$; $SUV_{max} = 10.01-15.00$, $p = 0.008$) were significantly different from

CT-based gross tumor volume for tumors with SUV_{max} ranging between 5.01 and 15.00.

Also, as shown in FIG. 4, the threshold method of fixed percentage of 20% SUV_{max}

overestimated tumor volume. Significant discrepancies between and metabolic tumor

volumes were also observed when the metabolic tumor volumes were delineated with the

5 threshold method of fixed percentage of 40% SUV_{max} ($SUV_{max} = 10.01-15.00$, $p = 0.009$),

60% SUV_{max} ($SUV_{max} = 10.01-15.00$, $p = 0.001$), 80% SUV_{max} ($SUV_{max} = 0.00-5.00$, $p =$

0.006; $SUV_{max} = 10.01-15.00$, $p = 0.001$), and PERCIST criteria method of $Liver_{ref}+1SD$

($SUV_{max} = 0.00-5.00$, $p = 0.003$), $Liver_{ref}+2SD$ ($SUV_{max} = 0.00-5.00$, $p = 0.002$), and

$Liver_{ref}+3SD$ ($SUV_{max} = 0.00-5.00$, $p = 0.008$). FIGS. 4A-4D illustrate Box Plots for

10 metabolic tumor volumes delineated with all 11 segmentation approaches and CT reference

gross tumor volume. The error bars represent the standardized deviation. FIG. 4A illustrates

tumors with SUV_{max} ranges from 0.00 to 5.00, FIG. 4B illustrates tumors with SUV_{max}

ranges from 5.01 to 10.00, FIG. 4C illustrates tumors with SUV_{max} range 10.01 to 15.00,

FIG. 4D illustrates tumors with SUV_{max} range > 15.00 .

15 TABLE 1

Segmentation Method	Mean Volume $\pm$ SD			
	SUV_{max} Range 0.00-5.00	SUV_{max} Range 5.01-10.00	SUV_{max} Range 10.01-15.00	SUV_{max} Range >15.00
CT	0.79 ± 0.39	2.26 ± 1.67	2.96 ± 1.33	0.79 ± 0.39
Level 1 Otsu	1.83 ± 0.94 ($p = 0.009$)	5.05 ± 3.10 ($p = 0.007$)	5.46 ± 2.84 ($p = 0.010$)	1.83 ± 0.94 ($p = 0.040$)
Level 2 Otsu	1.03 ± 0.53 ($p = 0.040$)	2.37 ± 1.41 ($p = 0.700$)	3.00 ± 1.60 ($p = 0.879$)	1.03 ± 0.53 ($p = 0.152$)
Level 3 Otsu	0.53 ± 0.30 ($p = 0.006$)	1.14 ± 0.65 ($p = 0.067$)	1.53 ± 0.77 ($p = 0.001$)	0.53 ± 0.30 ($p = 0.015$)
Level 4 Otsu	0.21 ± 0.12	0.44 ± 0.27	0.64 ± 0.37	0.21 ± 0.12

	(p = 0.004)	(p = 0.027)	(p = 0.001)	(p = 0.024)
20% SUV _{max}	2.16 ± 1.33 (p = 0.022)	3.90 ± 2.19 (p = 0.007)	4.76 ± 2.32 (p = 0.008)	2.16 ± 1.33 (p = 0.021)
40% SUV _{max}	0.95 ± 0.34 (p = 0.218)	1.43 ± 0.83 (p = 0.132)	2.09 ± 1.10 (p = 0.009)	0.95 ± 0.34 (p = 0.090)
60% SUV _{max}	0.37 ± 0.18 (p = 0.012)	0.60 ± 0.39 (p = 0.033)	1.03 ± 0.58 (p = 0.001)	0.37 ± 0.18 (p = 0.036)
80% SUV _{max}	0.13 ± 0.06 (p = 0.006)	0.20 ± 0.17 (p = 0.024)	0.33 ± 0.21 (p = 0.001)	0.13 ± 0.06 (p = 0.034)
Liver _{ref} +1SD	0.28 ± 0.17 (p = 0.003)	1.96 ± 1.25 (p = 0.277)	3.70 ± 2.07 (p = 0.087)	0.28 ± 0.17 (p = 0.015)
Liver _{ref} +2SD	0.21 ± 0.15 (p = 0.002)	1.76 ± 1.15 (p = 0.132)	3.33 ± 1.94 (p = 0.335)	0.21 ± 0.15 (p = 0.013)
Liver _{ref} +3SD	0.20 ± 0.07 (p = 0.008)	1.58 ± 1.03 (p = 0.088)	3.02 ± 1.84 (p = 0.860)	0.20 ± 0.07 (p = 0.014)

Table 2 and FIGS. 5A-5D demonstrate the degrees of accuracy of 11 different segmentation methods for delineating tumors with sizes between 0.59 – 21.01 cm³. Table 2 shows mean metabolic tumor volumes corresponding to each of the PET image segmentation method relative to the reference gross tumor volume defined on the CT scan. The levels of statistical significance for paired samples are also shown. Depending on their tumor volume, tumors are classified into 4 different categories: tumor size between 0.00 and 1.00 cm³, tumor size between 1.00 and 2.00 cm³, tumor size between 2.00 and 3.00 cm³, and tumor size > 3.00 cm³. Tumors are grouped into 4 categories depending on their CT-based reference volumes: (1) tumor size between 0.00 and 1.00 cm³; (2) tumor size between 1.00 and 2.00 cm³; (3) tumor size between 2.00 and 3.00 cm³; and (4) tumor size > 3.00 cm³. When all 11 segmentation methods were compared against CT-based gross tumor volume, metabolic tumor volume delineated with the fixed threshold method of 20% SUV_{max} (Tumor Size 0-1cm³, p = 0.009; Tumor Size 2-3cm³,

$p = 0.008$; Tumor Size $> 3 \text{ cm}^3$, $p = 0.002$), 60% SUV_{max} (Tumor Size $0-1 \text{ cm}^3$, $p = 0.009$; Tumor Size $2-3 \text{ cm}^3$, $p = 0.00004$; Tumor Size $> 3 \text{ cm}^3$, $p = 0.006$), 80% SUV_{max} (Tumor Size $0-1 \text{ cm}^3$, $p = 0.003$; Tumor Size $2-3 \text{ cm}^3$, $p = 0.000006$; Tumor Size $> 3 \text{ cm}^3$, $p = 0.006$), and PERCIST criteria method of $\text{Liver}_{\text{ref}} + 1\text{SD}$ (Tumor Size $0-1 \text{ cm}^3$, $p = 0.006$), $\text{Liver}_{\text{ref}} + 2\text{SD}$ (Tumor Size $0-1 \text{ cm}^3$, $p = 0.002$) were noted to be significantly different from the CT-based reference tumor volume. Among all 11 segmentation methods, multi-Otsu based segmentation method (level 2 Otsu), 40% SUV_{max} , and PERCIST criteria method ($\text{Liver}_{\text{ref}} + 3\text{SD}$) were the segmentation methods that produced metabolic tumor volumes that were not significantly different from the reference tumor volume across all twenty-five tumors, with sizes between 0.59 and 21.01 cm^3 .

Nonetheless, when comparing the 3 segmentation strategies, both 40% SUV_{max} (Tumor Size $2-3 \text{ cm}^3$, $p = 0.010$) and PERCIST criteria method ($\text{Liver}_{\text{ref}} + 3\text{SD}$) (Tumor Size $0-1 \text{ cm}^3$, $p = 0.016$) are close to being significantly different from the CT-based reference volumes for tumors with sizes between 2 and 3 cm^3 and sizes between 0 and 1 cm^3 , respectively. Metabolic tumor volumes delineated with multi-Otsu based segmentation method (level 2 Otsu) were the least different from the CT-based reference tumor volumes. Also, according to FIGS. 5A-5D, CT-based reference tumor volumes were only well within the range of metabolic tumor volumes determined with level 2 Otsu for tumors of varying sizes; the threshold method at fixed 40% SUV_{max} underestimated the tumor volumes for tumor with sizes between 1 and 3 cm^3 while PERCIST criteria method ($\text{Liver}_{\text{ref}} + 3\text{SD}$) underestimated tumor volumes for tumor with sizes between 0 and 3 cm^3 . Thus, the overall performance of multi-Otsu based segmentation method was still better than all tested segmentation strategies. FIGS. 5A-5D illustrate Box Plots for metabolic tumor volumes delineated with all 11 segmentation approaches and CT reference gross tumor volume. FIG. 5A illustrates tumor size between 0.00

and 1.00 cm³, FIG. 5B illustrates tumor size between 1.00 and 2.00 cm³, FIG. 5C illustrates tumor size between 2.00 and 3.00 cm³, and FIG. 5D illustrates tumor size > 3.00 cm³.

TABLE 2

Segmentation Method	Mean Volume $\pm$ SD			
	Tumor Size 0-1cm ³	Tumor Size 1-2cm ³	Tumor Size 2-3cm ³	Tumor Size >3cm ³
CT	0.65 $\pm$ 0.23	1.44 $\pm$ 0.47	2.35 $\pm$ 0.25	7.29 $\pm$ 5.38
Level 1 Otsu	1.62 $\pm$ 0.68 (p = 0.072)	3.23 $\pm$ 0.35 (p = 0.040)	5.20 $\pm$ 1.16 (p = 0.002)	13.54 $\pm$ 10.81 (p = 0.009)
Level 2 Otsu	0.86 $\pm$ 0.35 (p = 0.052)	1.47 $\pm$ 0.22 (p = 0.952)	2.53 $\pm$ 0.39 (p = 0.427)	7.87 $\pm$ 6.31 (p = 0.207)
Level 3 Otsu	0.42 $\pm$ 0.18 (p = 0.004)	0.71 $\pm$ 0.09 (p = 0.140)	1.25 $\pm$ 0.22 (p = 0.001)	4.27 $\pm$ 3.70 (p = 0.001)
Level 4 Otsu	0.16 $\pm$ 0.05 (p = 0.018)	0.25 $\pm$ 0.06 (p = 0.044)	0.47 $\pm$ 0.08 (p = 0.00002)	1.80 $\pm$ 1.49 (p = 0.003)
20% SUV _{max}	1.70 $\pm$ 0.71 (p = 0.009)	2.56 $\pm$ 0.63 (p = 0.147)	3.78 $\pm$ 0.78 (p = 0.008)	11.46 $\pm$ 7.74 (p = 0.002)
40% SUV _{max}	0.77 $\pm$ 0.21 (p = 0.362)	0.89 $\pm$ 0.22 (p = 0.255)	1.51 $\pm$ 0.42 (p = 0.010)	5.62 $\pm$ 4.07 (p = 0.021)
60% SUV _{max}	0.29 $\pm$ 0.06 (p = 0.009)	0.35 $\pm$ 0.08 (p = 0.064)	0.66 $\pm$ 0.21 (p = 0.00004)	2.60 $\pm$ 1.70 (p = 0.006)
80% SUV _{max}	0.10 $\pm$ 0.02 (p = 0.003)	0.12 $\pm$ 0.03 (p = 0.042)	0.21 $\pm$ 0.13 (p = 0.000006)	0.70 $\pm$ 0.31 (p = 0.006)
Liver _{ref} +1SD	0.28 $\pm$ 0.17 (p = 0.006)	1.24 $\pm$ 0.76 (p = 0.701)	2.41 $\pm$ 0.63 (p = 0.843)	10.71 $\pm$ 8.23 (p = 0.013)
Liver _{ref} +2SD	0.21 $\pm$ 0.16 (p = 0.002)	1.10 $\pm$ 0.73 (p = 0.519)	2.11 $\pm$ 0.55 (p = 0.314)	9.95 $\pm$ 7.59 (p = 0.020)
Liver _{ref} +3SD	0.23 $\pm$ 0.11 (p = 0.016)	1.00 $\pm$ 0.72 (p = 0.410)	1.86 $\pm$ 0.50 (p = 0.065)	9.29 $\pm$ 7.04 (p = 0.037)

As shown in Table 3 and FIGS. 6A-6D, multi-Otsu segmentation method, specifically level 2 Otsu, consistently produced mean VR that is close to 1 for tumors with SUV_{max} ranging between 0.00 and 15.00. Table 3. Mean volume ratio corresponding to each of the segmentation method. Depending on their SUV_{max} value, tumors are classified into 4
5 different categories: SUV_{max} range 0.00 to 5.00, SUV_{max} range 5.01 to 10.00, SUV_{max} range 10.01 to 15.00, and SUV_{max} range > 15.00 . FIGS. 6A-6D illustrate Mean Volume Ratio for all 11 segmentation approaches. The error bars represent the standardized deviation. Volume ratio closest to 1 suggests that the segmentation approach results in more similar volumes when compared with CT-based reference volume. FIG. 6A illustrates tumors with SUV_{max}
10 ranges from 0.00 to 5.00, FIG. 6B illustrates tumors with SUV_{max} ranges from 5.01 to 10.00, FIG. 6C illustrates tumors with SUV_{max} range 10.01 to 15.00, FIG. 6D illustrates tumors with SUV_{max} range > 15.00 .

[0047] In fact, level 2 Otsu resulted in the most desirable (closest to 1) mean VR for tumors with SUV_{max} ranging from 0.00 to 5.00 ($VR = 1.32 \pm 0.32$, mean $\pm$ SD), SUV_{max}
15 ranging from 10.01 to 15.00 ($VR = 1.00 \pm 0.19$, mean $\pm$ SD), and SUV_{max} greater than 15.00 ($VR = 1.09 \pm 0.10$, mean $\pm$ SD). This indicates that multi-Otsu segmentation method is able to result in target volumes most similar to our reference CT-based volumes when compared against each of the other segmentation approaches.

[0048] For tumors with SUV_{max} ranging from 5.01 to 10.00, multi-Otsu segmentation
20 method, specifically level 2 Otsu, produced VR that is second closest to the ideal value of one (mean $\pm$ SD, 1.16 ± 0.30), not far behind from the mean VR (mean $\pm$ SD, 0.94 ± 0.30) resulted from PERCIST method (e.g., $Liver_{ref} + 1SD$). Nonetheless, since it is preferable to

slightly overestimate tumor volume rather than underestimating it, level 2 Otsu is still consider as the more desirable segmentation method, which produces greater than one VR that is closest to the ideal value of one.

[0049] As shown in Table 4 and FIGS. 7A-7D, multi-Otsu segmentation method (level 2

5 Otsu) produced the most desirable mean VR (closest to 1) for tumors of various sizes, ranging from small-sized tumor with CT reference volume between 0.00 to 1.00 cm³ (VR = 1.33 ± 0.32, mean ± SD), medium-sized tumor with CT reference volume between 1.00 to 2.00 cm³ (VR = 1.10 ± 0.41, mean ± SD) and 2.00 to 3.00 cm³ (VR = 1.09 ± 0.22, mean ± SD), and large-sized tumor with CT reference volume greater than 3.00 cm³ (VR = 1.06 ±
10 0.17, mean ± SD). In Table 4, mean volume ratio corresponding to each of the segmentation method. Depending on their tumor volume, tumors are classified into 4 different categories: tumor size between 0.00 and 1.00 cm³, tumor size between 1.00 and 2.00 cm³, tumor size between 2.00 and 3.00 cm³, and tumor size > 3.00 cm³. FIGS. 7A-7D illustrate Mean Volume Ratio for all 11 segmentation approaches. The error bars represent the standardized deviation.
15 Volume ratio closest to 1 suggests that the segmentation approach results in more similar volumes when compared with CT-based reference volume. FIG. 7A illustrates tumor size between 0.00 and 1.00 cm³, FIG. 7B illustrates tumor size between 1.00 and 2.00 cm³, FIG. 7C illustrates tumor size between 2.00 and 3.00 cm³, FIG. 7D illustrates tumor size > 3.00 cm³.

20 [0050] In summary, based on the VR analysis, multi-Otsu segmentation method produces the most accurate quantification result of target tumor volume across tumors of various sizes and SUVs when compared against PERCIST criteria method or threshold method of fixed percentage of SUV_{max}.

TABLE 3

Segmentation Method	Volume Ratio $\pm$ SD			
	SUV _{max} Range 0.00-5.00	SUV _{max} Range 5.01-10.00	SUV _{max} Range 10.01-15.00	SUV _{max} Range >15.00
Level 1 Otsu	2.35 $\pm$ 0.61	2.49 $\pm$ 0.61	1.79 $\pm$ 0.43	1.94 $\pm$ 0.49
Level 2 Otsu	1.32 $\pm$ 0.32	1.10 $\pm$ 0.41	1.00 $\pm$ 0.19	1.09 $\pm$ 0.10
Level 3 Otsu	0.67 $\pm$ 0.15	0.56 $\pm$ 0.15	0.52 $\pm$ 0.08	0.59 $\pm$ 0.08
Level 4 Otsu	0.27 $\pm$ 0.08	0.21 $\pm$ 0.05	0.21 $\pm$ 0.04	0.25 $\pm$ 0.05
20% SUV _{max}	2.76 $\pm$ 0.84	2.01 $\pm$ 0.65	1.60 $\pm$ 0.26	1.57 $\pm$ 0.29
40% SUV _{max}	1.41 $\pm$ 0.79	0.72 $\pm$ 0.24	0.72 $\pm$ 0.19	0.80 $\pm$ 0.23
60% SUV _{max}	0.52 $\pm$ 0.24	0.30 $\pm$ 0.11	0.36 $\pm$ 0.12	0.38 $\pm$ 0.15
80% SUV _{max}	0.20 $\pm$ 0.12	0.10 $\pm$ 0.06	0.12 $\pm$ 0.05	0.11 $\pm$ 0.09
Liver _{ref} +1SD	0.33 $\pm$ 0.09	0.94 $\pm$ 0.30	1.22 $\pm$ 0.25	1.58 $\pm$ 0.21
Liver _{ref} +2SD	0.22 $\pm$ 0.13	0.84 $\pm$ 0.28	1.10 $\pm$ 0.26	1.48 $\pm$ 0.24
Liver _{ref} +3SD	0.21 $\pm$ 0.05	0.75 $\pm$ 0.27	1.00 $\pm$ 0.27	1.39 $\pm$ 0.27

TABLE 4

Segmentation Method	Volume Ratio $\pm$ SD			
	SUV _{max} Range 0.00-5.00	SUV _{max} Range 5.01-10.00	SUV _{max} Range 10.01-15.00	SUV _{max} Range >15.00
Level 1 Otsu	2.35 $\pm$ 0.61	2.49 $\pm$ 0.61	1.79 $\pm$ 0.43	1.94 $\pm$ 0.49
Level 2 Otsu	1.32 $\pm$ 0.32	1.10 $\pm$ 0.41	1.00 $\pm$ 0.19	1.09 $\pm$ 0.10
Level 3 Otsu	0.67 $\pm$ 0.15	0.56 $\pm$ 0.15	0.52 $\pm$ 0.08	0.59 $\pm$ 0.08
Level 4 Otsu	0.27 $\pm$ 0.08	0.21 $\pm$ 0.05	0.21 $\pm$ 0.04	0.25 $\pm$ 0.05
20% SUV _{max}	2.76 $\pm$ 0.84	2.01 $\pm$ 0.65	1.60 $\pm$ 0.26	1.57 $\pm$ 0.29
40% SUV _{max}	1.41 $\pm$ 0.79	0.72 $\pm$ 0.24	0.72 $\pm$ 0.19	0.80 $\pm$ 0.23
60% SUV _{max}	0.52 $\pm$ 0.24	0.30 $\pm$ 0.11	0.36 $\pm$ 0.12	0.38 $\pm$ 0.15
80% SUV _{max}	0.20 $\pm$ 0.12	0.10 $\pm$ 0.06	0.12 $\pm$ 0.05	0.11 $\pm$ 0.09
Liver _{ref} +1SD	0.33 $\pm$ 0.09	0.94 $\pm$ 0.30	1.22 $\pm$ 0.25	1.58 $\pm$ 0.21
Liver _{ref} +2SD	0.22 $\pm$ 0.13	0.84 $\pm$ 0.28	1.10 $\pm$ 0.26	1.48 $\pm$ 0.24
Liver _{ref} +3SD	0.21 $\pm$ 0.05	0.75 $\pm$ 0.27	1.00 $\pm$ 0.27	1.39 $\pm$ 0.27

- 5 [0051] The selection of the most appropriate ¹⁸F-FDG PET based segmentation algorithm is crucial, since tumor volumetric quantification with ¹⁸F-FDG PET may impact target radiation cancer treatment. A segmentation method based on multi-level Otsu algorithm is

optimal for various ranges of tumors sizes and FDG uptake levels compared to standard methods. It obtains a better delineation result than that produced via fixed percentage of the maximum SUV (SUV_{max}) or PERCIST criteria method. Multi-Otsu segmentation method can be a valuable user-friendly tool that is clinically applicable in aiding clinicians in diagnosing, staging, planning of radiotherapy and surgery, and determining treatment response of cancer.

[0052] In another exemplary implementation of the present invention, the present invention was tested and validated with the following:

- 1) phantom data, that would allow us to more accurately validate the results using the known boundaries in the phantom
- 2) different representative tumor types compared to the tumor types included in the provisional filing
- 3) different types of radioactive PET tracers used in imaging the tumor

[0053] For validation using phantom data, an extensive validation of the method was performed using the phantom data to address two possible conditions that may frequently arise in a real patient image data. The first condition is the relative signal to noise ratio (S/N ratio) between the tumor-like features and its background in the phantom and the second condition is various possible sizes comparable to small-to-large tumor sizes that can arise in various patient data.

[0054] The PET tumor segmentation method using multi-level Otsu (MO) was validated for accuracy, using standard NEMA image quality (IQ) phantom compared to current

methods. In this exemplary implementation, the NEMA IQ phantom was filled with an ^{18}F solution to have a uniform background activity. The six spherical lesions in the phantom (volume: 0.52, 1.15, 2.57, 5.57, 11.5, and 26.5 cm^3) were filled with ^{18}F activity to have a lesion-to-background ratio (LBR) of either 8:1, 4:1, or 1.5:1. The phantom was imaged using a GE Discovery 710 PET/CT scanner. The lesions in the phantom were segmented using the MO method, to derive a spherical lesion metabolic tumor volume (MTV). Results were compared with MTVs from 8 different PET threshold methods: 20%, 40%, 60%, or 80% of the maximum activity (Bq/ml), and mean background + 1 or +2 standard deviations (SD), and mean background $\times 2$ or $\times 2.5$. Three small lesions were not evaluated in LBR of 1.5:1, because they were not distinguishable from background at this low LBR. To evaluate PET segmentation accuracy, we compared volume ratio (VR) of MTV to the actual volume of the phantom lesions. VR closer to 1 indicated a better segmentation strategy. MO method and 40% threshold showed more consistent mean VRs (closest to 1) for each combination of different lesion sizes and LBR ratios than the other methods. The MO method of the present invention showed stable and relatively accurate estimation of the true volume in all lesions and LBRs. However, 40% threshold substantially overestimated MTV in small lesions or in the setting of low LBR, in contrast to our MO method, as illustrated in FIG. 8. Table 5 shows representative VR data for the MO method, 40%, and mean background +2 standard deviations. FIG. 8 illustrates images that show that the MO method provides the most accurate contour of a small lesion with volume of 0.52 cm^3 in 4:1 LBR.

Table 5. Volume ratio of each lesion using different segmentation methods and LBRs

LBR	Segmentation methods	True volume (cm^3)					
		26.5	11.5	5.57	2.57	1.15	0.52
8:1	MO method	0.83	0.74	0.68	0.71	1.04	1.32
8:1	40%	1.06	1.05	1.14	1.21	0.94	2.16

8:1	BG + 2SD	2.16	3.21	4.50	5.56	8.23	14.34
4:1	MO method	0.81	0.87	0.79	1.07	1.00	0.80
4:1	40%	1.11	1.05	1.04	1.17	1.06	12.46
4:1	BG + 2SD	1.66	2.26	3.02	3.28	5.68	11.14
1.5:1	MO method	0.70	0.90	2.52	N/A	N/A	N/A
1.5:1	40%	3.08	7.08	14.52	N/A	N/A	N/A
1.5:1	BG + 2SD	0.83	1.05	1.14	N/A	N/A	N/A

[0055] It should be noted that herein, three methods (including the MO) are compared:

[0056] 1. The Multi-Otsu method presented in the disclosure denoted by the prefix **MO** (Multi-Otsu), with various options that user can choose to find which of the options work best for given situation.

[0057] 2. The percent tumor maximum standardized uptake value (SUV) method, indicated by various percentage numbers as **20%, 40%, 60%, 80%**, with respect to the maximum value within the region of interest (ROI).

[0058] 3. The reference standard deviation method that uses a threshold value based on the mean value corresponding to a reference region (in this case background, denoted by BG) shifted by a constant multiple of the standard deviation (SD) in the reference region, thus in the figures **BG_SD** and **BG_2SD** represent Background + 1*Standard Deviation and Background + 2* Standard Deviation. Optionally, multiples reference mean can also be used such as, 2*Background and 2.5*Background, denoted by, **2BG**, **2pt5_BG**.

[0059] The ratio numbers **1:1.5**, **1:4**, **1:8** represent the relative S/N ratio or strengths of the mean values of the background and feature of interest, to account for different tumor types that can be imaged with weak or strong distinction using PET. Small lesions sizes require

strong background distinction ratio (1:4, 1:8) compared to large sessions that can be imaged at weak background distinction (1:1.5).

[0060] The bar graphs depicted in FIGS. 9-13 illustrate the comparison of the volumes measured using the 3 different PET segmentation methods described above as a ratio of the true volume of the regions measured using other means (in this case CT) that can work provide reliable distinction the phantom case. (However CT cannot be guaranteed to work with same accuracy in real patient data.) Thus this phantom experiment helps to validate our methods in a setup where other imaging methods can provide reliable reference values. Thus, the method that yields results closest to unity (=1) can be regarded as works better compared to other method.

[0061] It may be readily evident in all the different conditions simulated in the phantom data, MO method (in one of its option – MO3_largest method) consistently yields results close to unity. While one of the other methods may seem to yield a better result in certain situations, that same method may fail in other situations. Most notably, the 40% SUVmax methods (noted as 40% in the graphs) performs well and yields results close to unity in high S/N ratio lesions (1:8 and 1:4 large lesions and 1:8 small lesion) but was inaccurate for low S/N ratio lesions (1:1.5 large lesion and 1:4 small lesion). Another method, BG_2D was accurate for low S/N ratio lesion (1:1.5 large lesion), but not other lesion sizes and S/N ratios. Thus users may have to pick and choose which method might work under different clinical scenarios with varying tumor sizes and S/N ratios by making a subjective guess. Whereas, MO-PET method consistently produces fairly close to unity results across all different conditions chosen here to reasonably reflect real patient data, making MO-PET more reliable compared to other methods.

[0062] For validation on Different Tumor Types, MO-PET, PET tumor segmentation is compared to two standard representative standard PET segmentation thresholds, absolute SUV of 2.0 and relative SUV of 40% of tumor maximum SUV (40% tumor SUV_{max}). This is shown in FIG.14 as follows: light grey contour – MO-PET, dark grey contour- 40% tumor SUV_{max}, and medium grey – SUV 2.0). The MO-PET segmentation methods works most consistently across these broad range of tumor segmentation representative clinical cases.

[0063] FIG. 14 illustrates images of ¹⁸F-FDG PET avid osteosarcoma of the lower extremity involving the proximal tibia in coronal and transaxial PET, CT and fused PET/CT images. MO-PET segments the most appropriate FDG avid tumor contour, with 40% SUV_{max} heterogeneously contouring the most intense FDG avid tumor only and SUV 2.0 segmenting a wider tumor contour.

[0064] FIG. 15 illustrates image views of ¹⁸F-FDG avid osteosarcoma of the lower extremity involving the left distal femur in coronal and transaxial PET, CT and fused PET/CT images. MO-PET and 40% SUV_{max} segments the most appropriate tumor contour with MO-PET more inclusive of moderate and intense uptake, with 40% SUV_{max} contouring the most intense regions only. SUV 2.0 again segments a wider tumor contour as seen on coronal images.

[0065] FIGS. 16A and 16B illustrate image views of ¹⁸F-FDG avid osteosarcoma of the upper extremity involving the humerus in coronal and transaxial PET, CT and fused PET/CT images. In this example with low FDG tumor signal to background ratio, MO-PET segments the most appropriate tumor contour and 40% SUV_{max} segments a larger than appropriate tumor contour extending heterogeneously into background tissue, best seen coronally. SUV

2.0 does not segment any of the low FDG avid tumor with this low tumor to background ratio example.

[0066] FIG. 17 illustrates an image view of ^{18}F -FDG avid melanoma lung metastasis in whole body PET MIP, and in coronal and transaxial PET, CT and fused PET/CT images.

5 MO-PET and 40% SUV_{max} segments the most appropriate tumor contour with MO-PET more inclusive of moderate and intense tumor FDG uptake, with 40% SUV_{max} contouring the most intense regions only. SUV 2.0 again segments a wider than appropriate tumor contour.

[0067] FIG. 18 illustrates an image view of ^{18}F -FDG avid melanoma lung metastasis in
10 whole body PET MIP, and in coronal PET and CT, and transaxial PET, CT and fused PET/CT images. In this example of a small lesion with low S/N ratio, typically seen in early metastases or responding lesions during treatment, MO-PET segments the most appropriate tumor contour, with SUV 2.0 measuring a slightly larger than appropriate contour. In this particular scenario, 40% SUV_{max} segments a much larger than appropriate tumor contour.

15 [0068] For validation on Different Radioactive PET Tracers, FIG. 19 illustrates an image view of ^{18}F -Sodium Fluoride prostate cancer bone metastasis of the spine in whole body PET MIP, and in sagittal and transaxial PET, CT and fused PET/CT images. MO-PET and 40% SUV_{max} segments approximately the same tumor contour, with SUV 2.0 segmenting a wider than appropriate tumor contour.

20 [0069] FIG. 20 illustrates an image view of ^{18}F -DCFPyL PSMA PET avid prostate cancer bone metastases of the spine in whole body MIP, and in sagittal and transaxial PET, CT and

fused PET/CT images. MO-PET and 40% SUV_{max} segments approximately the same tumor contour, with SUV 2.0 segmenting a wider than appropriate tumor contour.

[0070] It should be noted that the imaging protocols, described herein can be executed with a program(s) fixed on one or more non-transitory computer readable medium. The non-
5 transitory computer readable medium can be loaded onto a computing device, server, imaging device processor, smartphone, tablet, phablet, or any other suitable device known to or conceivable by one of skill in the art.

[0071] It should also be noted that herein the steps of the method described can be carried out using a computer, non-transitory computer readable medium, or alternately a computing
10 device, microprocessor, or other computer type device independent of or incorporated with an imaging or signal collection device. An independent computing device can be networked together with the imaging device either with wires or wirelessly. Indeed, any suitable method of analysis known to or conceivable by one of skill in the art could be used. It should also be noted that while specific equations are detailed herein, variations on these equations can also
15 be derived, and this application includes any such equation known to or conceivable by one of skill in the art. The computing device can be specific to the present invention and designed solely for the implementation and to address the issues of the present invention.

[0072] A non-transitory computer readable medium is understood to mean any article of manufacture that can be read by a computer. Such non-transitory computer readable media
20 includes, but is not limited to, magnetic media, such as a floppy disk, flexible disk, hard disk, reel-to-reel tape, cartridge tape, cassette tape or cards, optical media such as CD-ROM,

writable compact disc, magneto-optical media in disc, tape or card form, and paper media, such as punched cards and paper tape.

[0073] Although the present invention has been described in connection with preferred embodiments thereof, it will be appreciated by those skilled in the art that additions, deletions, modifications, and substitutions not specifically described may be made without departing from the spirit and scope of the invention as defined in the appended claims.

CLAIMS

1. A method for automatic delineation of tumors and other normal and pathologic anatomic structures and physiological processes comprising:

5 obtaining a Positron Emission Tomography (PET) image of structures or processes of interest;

specifying an approximate boundary to indicate the Region Of Interest (ROI) within which automatic delineation is performed;

partitioning the distribution of the image data in to multiple classes using threshold
10 levels that minimize intra(within)-class variance (*which is same as maximizing the inter-class variance*) as determined by the class-probability weighted sum of variances of all the classes, where, variance of a class is the average of squared deviations from the mean of the class; and

selecting an optimal threshold from the multi-level thresholds that effectively
15 delineates and quantifies tumor volume.

2. The method of claim 1 further comprising using a PET radiotracer.

3. The method of claim 1 further comprising converting the image data or the threshold values to a conventionally prescribed unit representation in PET imaging such as any of the Standardized Uptake Value (SUV) units or other PET quantitative method.

20 4. The method of claim 1 further comprising an additional benefit of multi-level thresholds to characterize the heterogeneity of tumors and other normal physiological and

pathologic anatomic structures and physiological processes including but not limited to oncological, neurological, cardiology, infection, inflammatory or other processes used for PET imaging.

- 5 5. The method of claim 1 further comprising using a non-transitory computer readable medium programmed with the method.
6. The method of claim 1 further comprising using automatic delineation of structures and processes for patient response monitoring and treatment planning.
7. The method of claim 1 further comprising contouring of structures and processes efficiently based on automatic delineation.
- 10 8. The method of claim 2 further comprising the PET radiotracer taking the form of ^{18}F -FDG and other PET radiotracers, for PET imaging of structures or process.
9. The method of claim 1 further comprising displaying a visual representation of the tumor volume.
10. The method of claim 1 further comprising displaying a visual representation of the
15 PET image after partitioning.
11. A system for automatic delineation of tumors and other normal and pathologic anatomic structures and physiological processes comprising:

a Positron Emission Tomography (PET) imaging device configured for obtaining an image of structures or processes of interest;

a non-transitory computer readable medium programmed for receiving the image and processing the image by,

specifying an approximate boundary to indicate the Region Of Interest (ROI) within which automatic delineation is performed;

5 partitioning the distribution of the image data in to multiple classes using threshold levels that minimize intra(within)-class variance (*which is same as maximizing the inter-class variance*) as determined by weighted sum of variances of all the classes, where, variance of a class is the average of squared deviations from the mean of the class; and

10 selecting an optimal threshold from the multi-level thresholds that effectively delineates and quantifies tumor volume.

12. The system of claim 11 further comprising a PET radiotracer.

13. The system of claim 11 further comprising converting the image data or the threshold values to a conventionally prescribed unit representation in PET imaging such as any of the Standardized Uptake Value (SUV) units or other quantitative PET method.

15 14. The system of claim 11 further comprising an additional benefit of multi-level thresholds to characterize the heterogeneity of the tumors and other normal and pathologic anatomic structures and physiological and pathological processes.

15. The system of claim 11 further comprising the non-transitory computer readable medium being in direct communication with the PET imaging device.

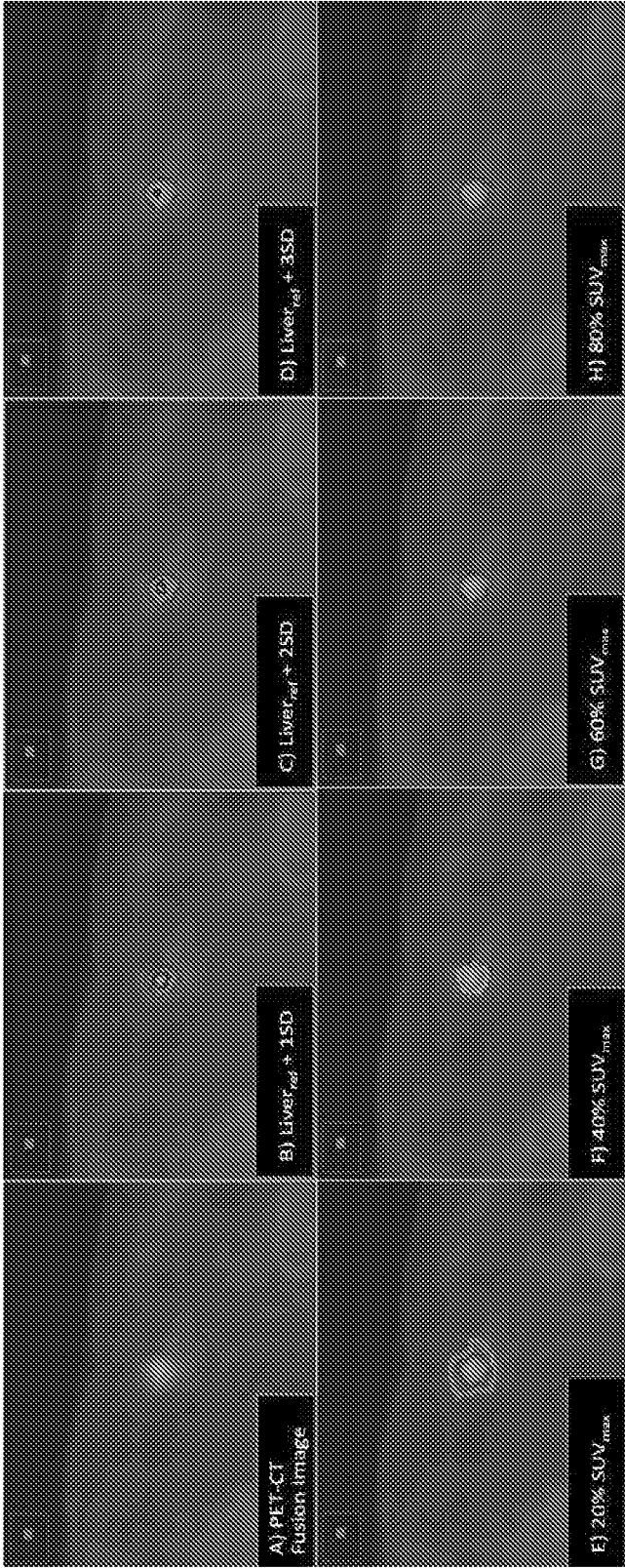
16. The system of claim 11 further comprising using automatic delineation of structures and processes for patient response monitoring and treatment planning.

17. The system of claim 11 further comprising contouring of structures and processes efficiently based on automatic delineation.

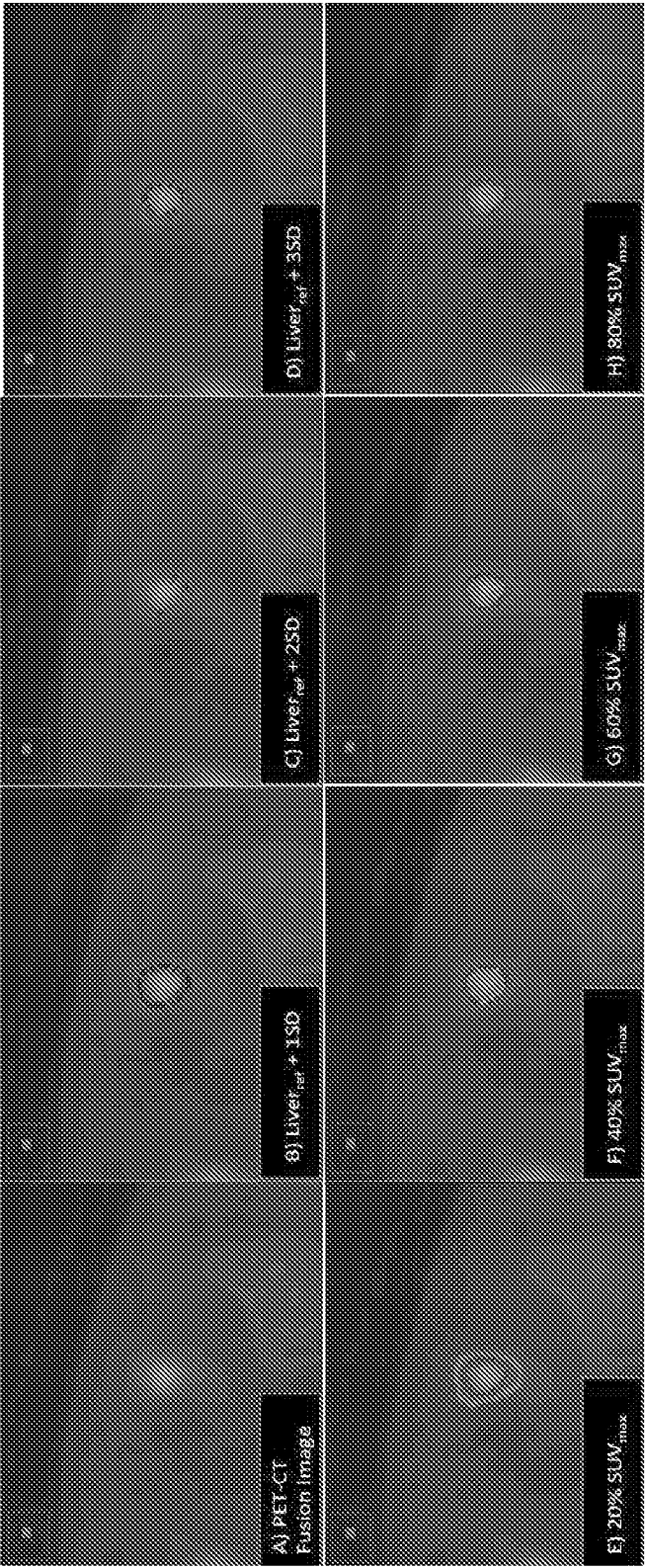
5 18. The system of claim 12 further comprising the PET radiotracer taking the form of ^{18}F -FDG or other PET radiotracers, for PET imaging of structures or process.

19. The system of claim 11 further comprising displaying a visual representation of the tumor volume.

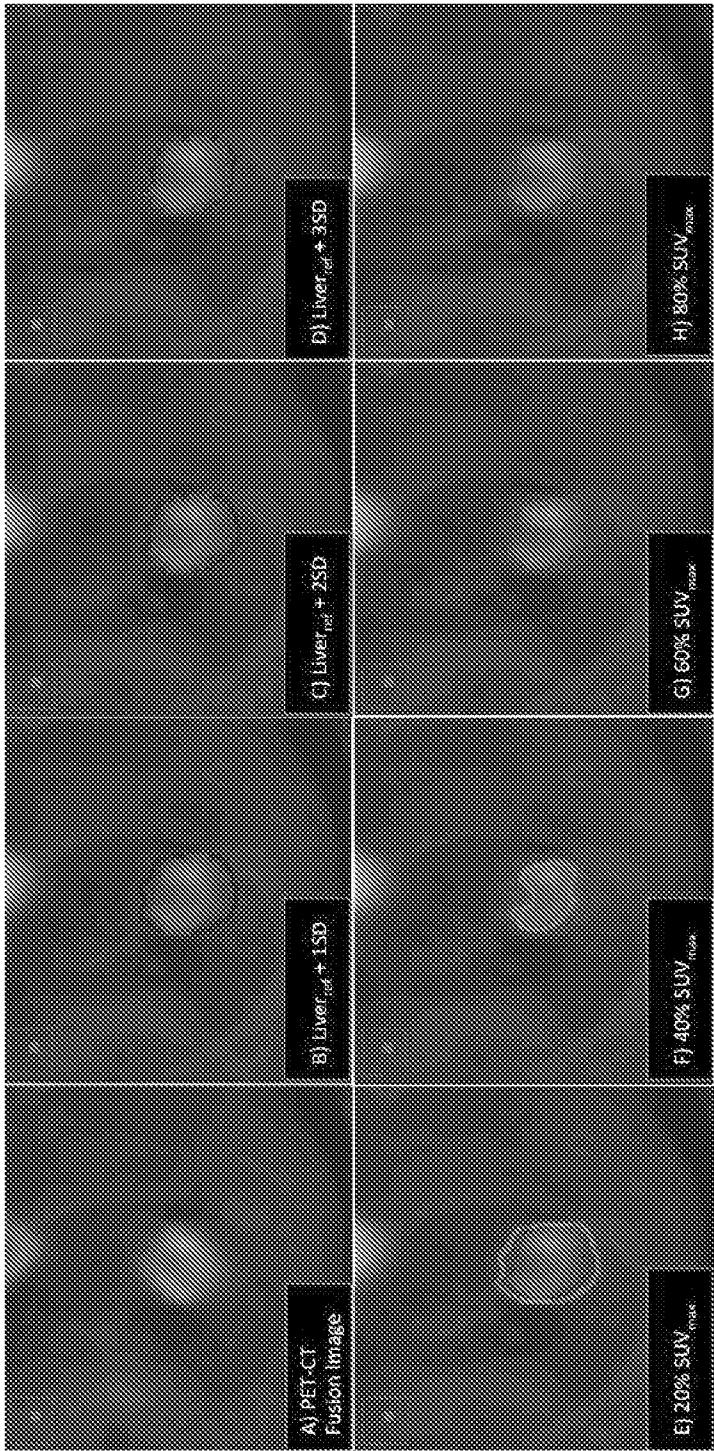
20. The system of claim 11 further comprising displaying a visual representation of the
10 PET image after partitioning.



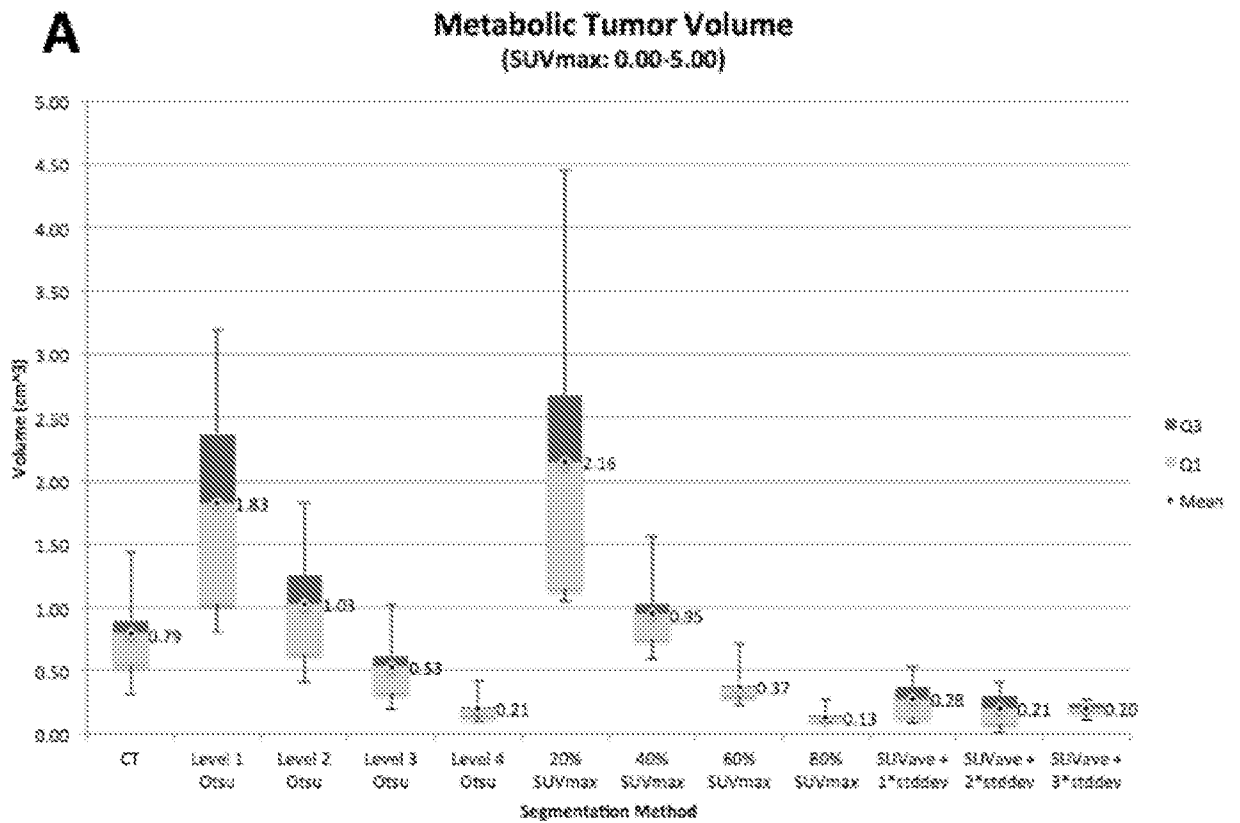
FIGS. 1A-1H



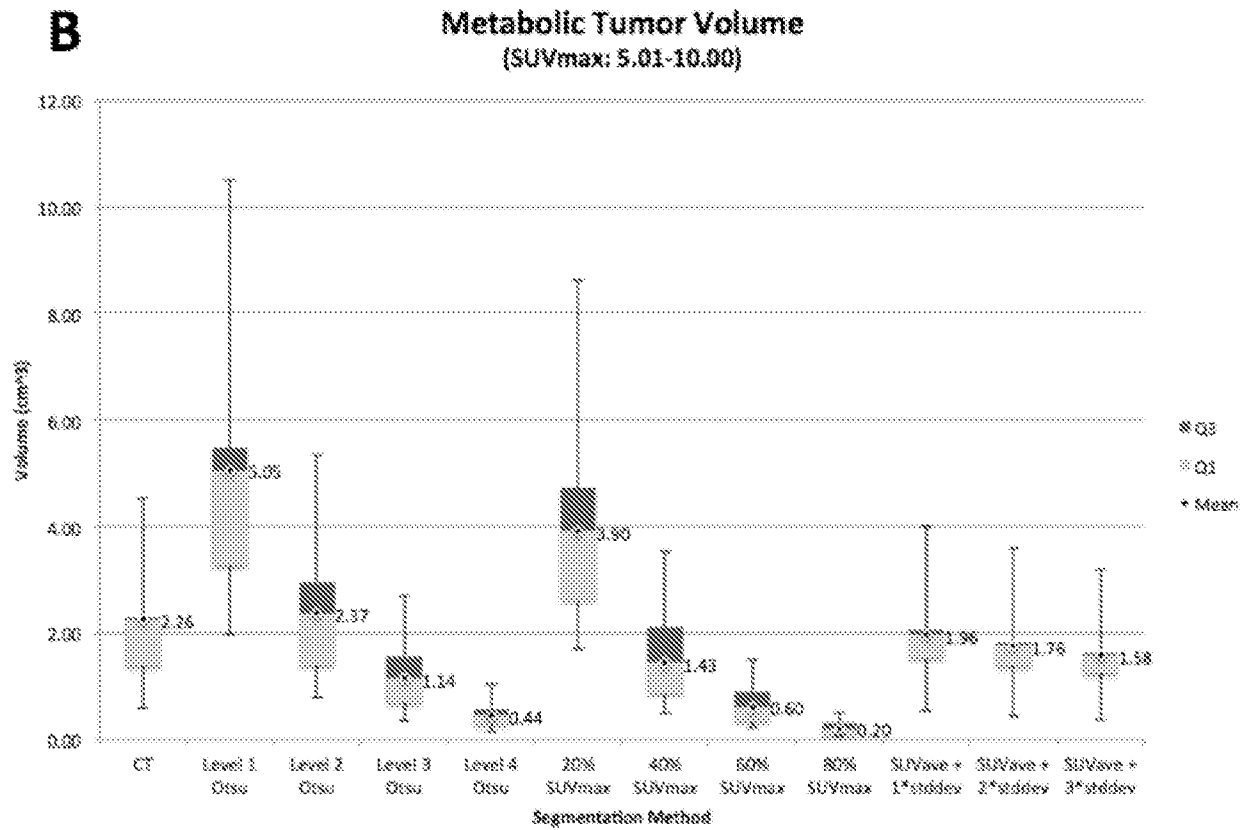
FIGS. 2A-2H



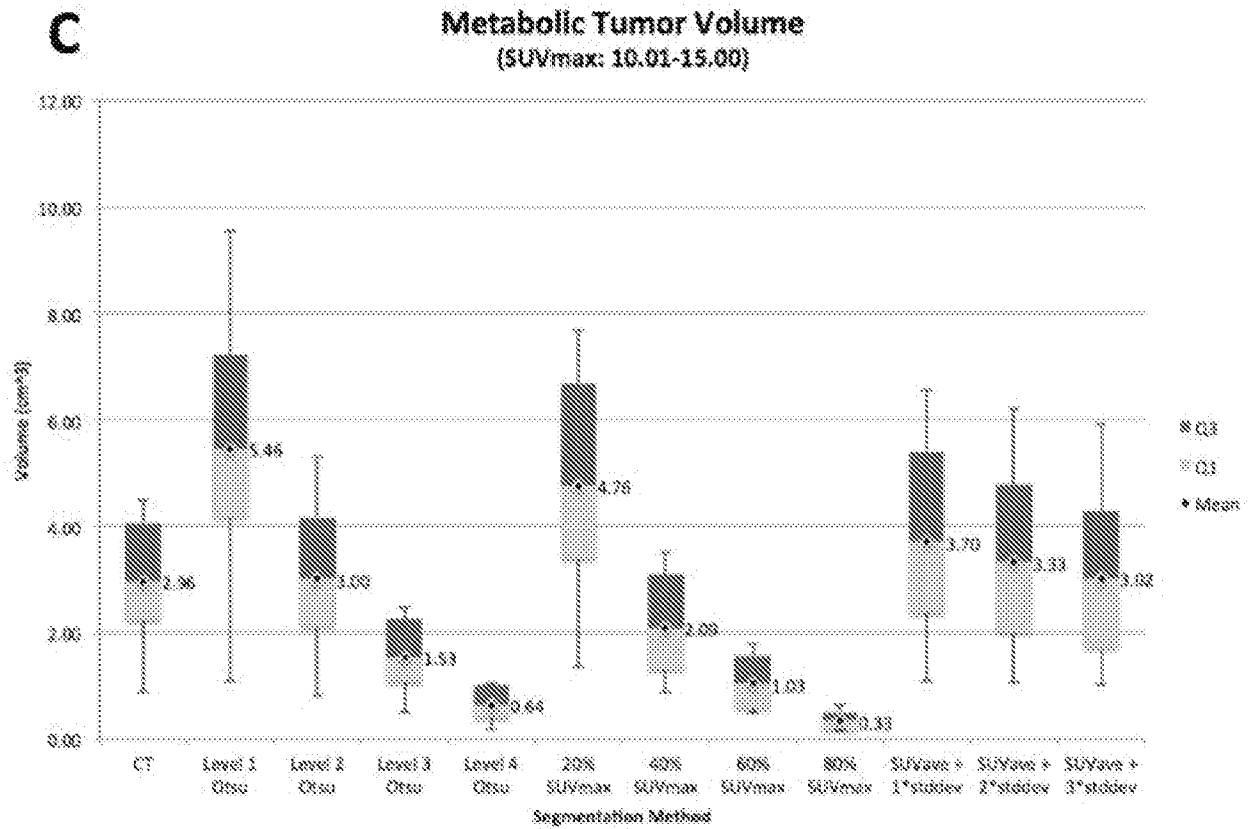
FIGS. 3A-3H

**FIG. 4A**

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**FIG. 4B**

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**FIG. 4C**

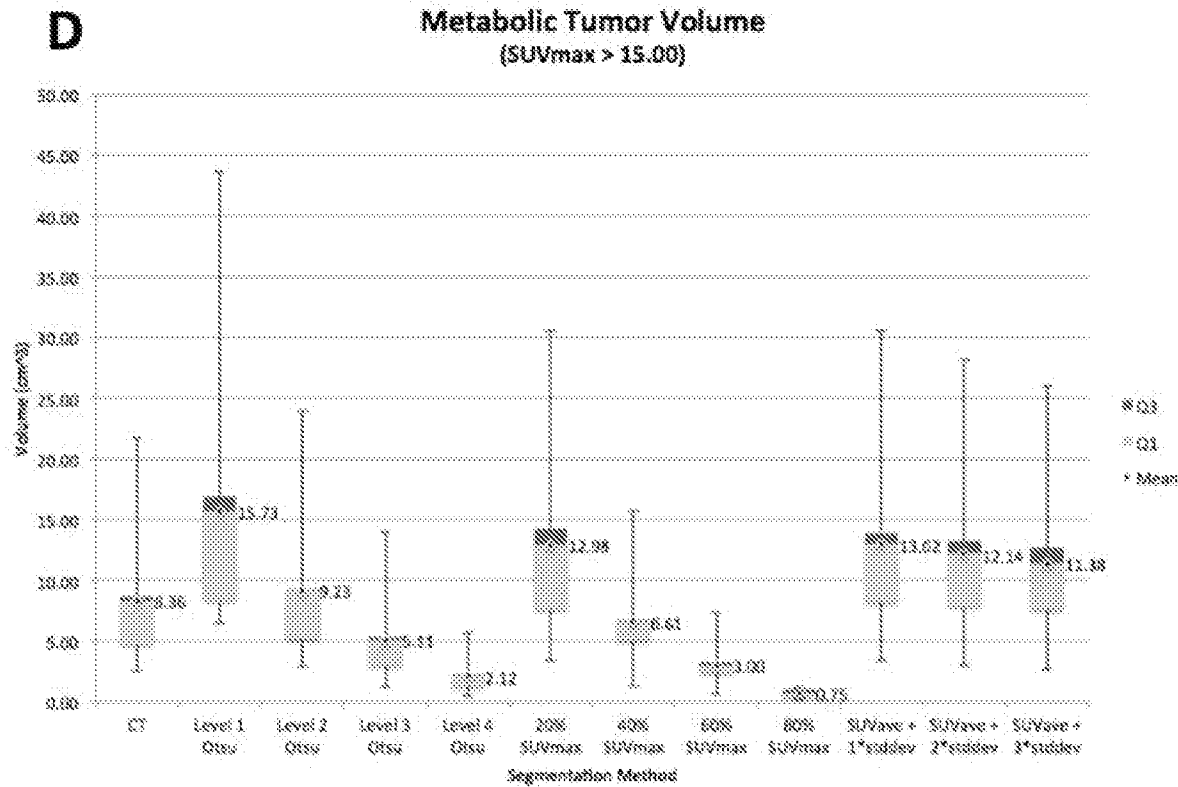
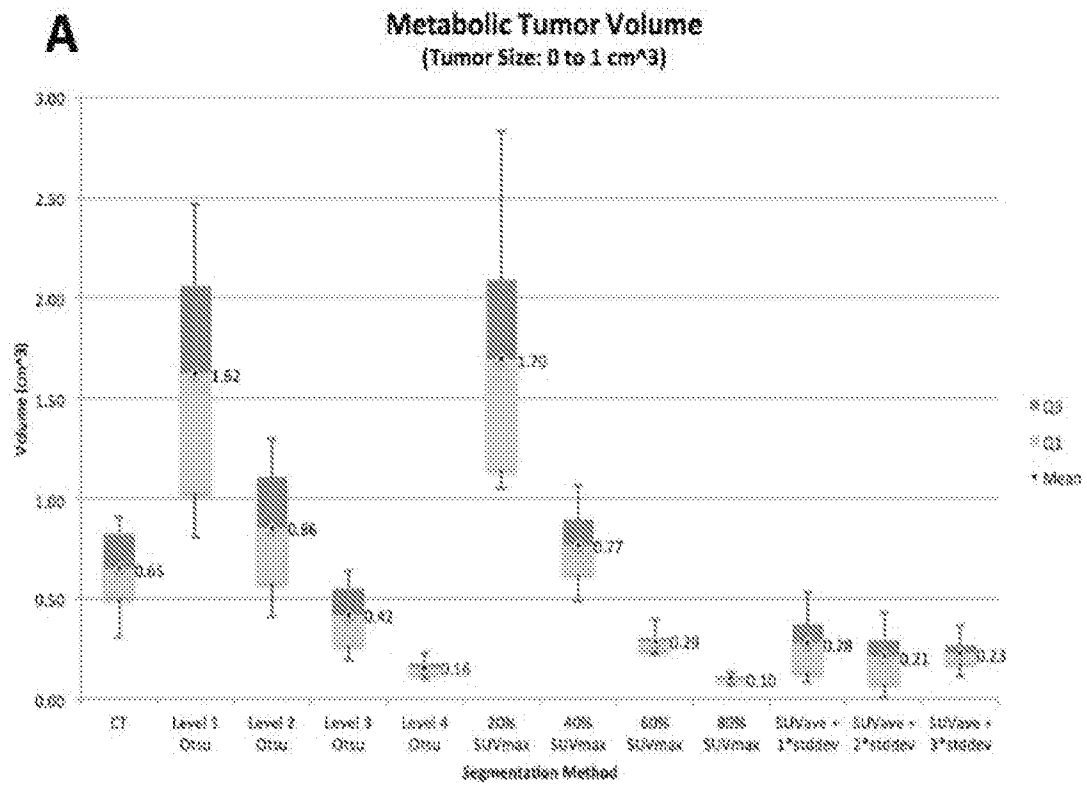
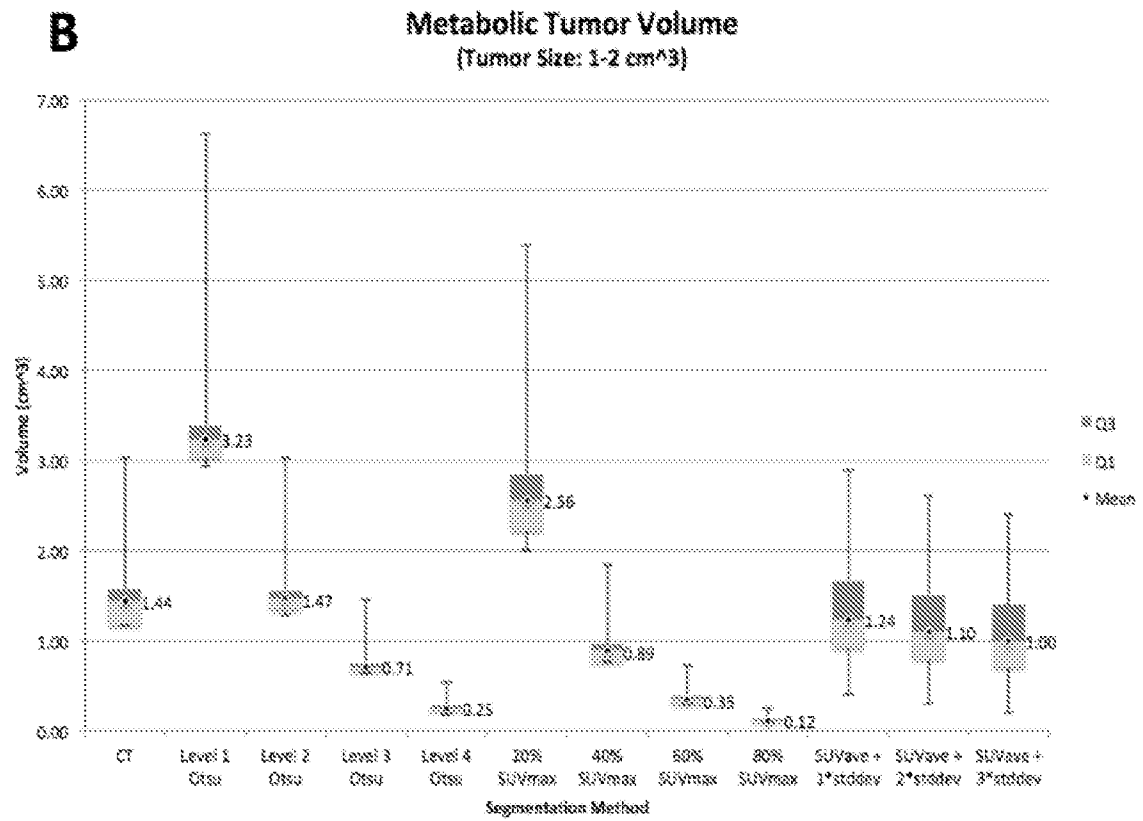


FIG. 4D

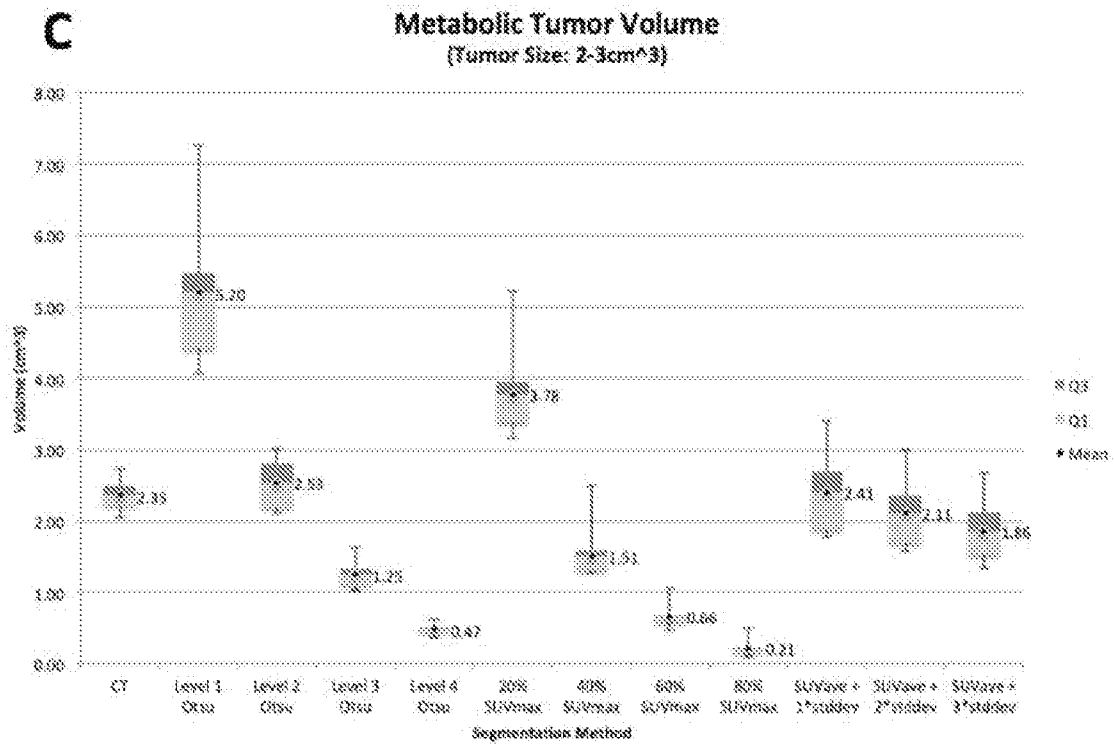
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**FIG. 5A**

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**FIG. 5B**

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**FIG. 5C**

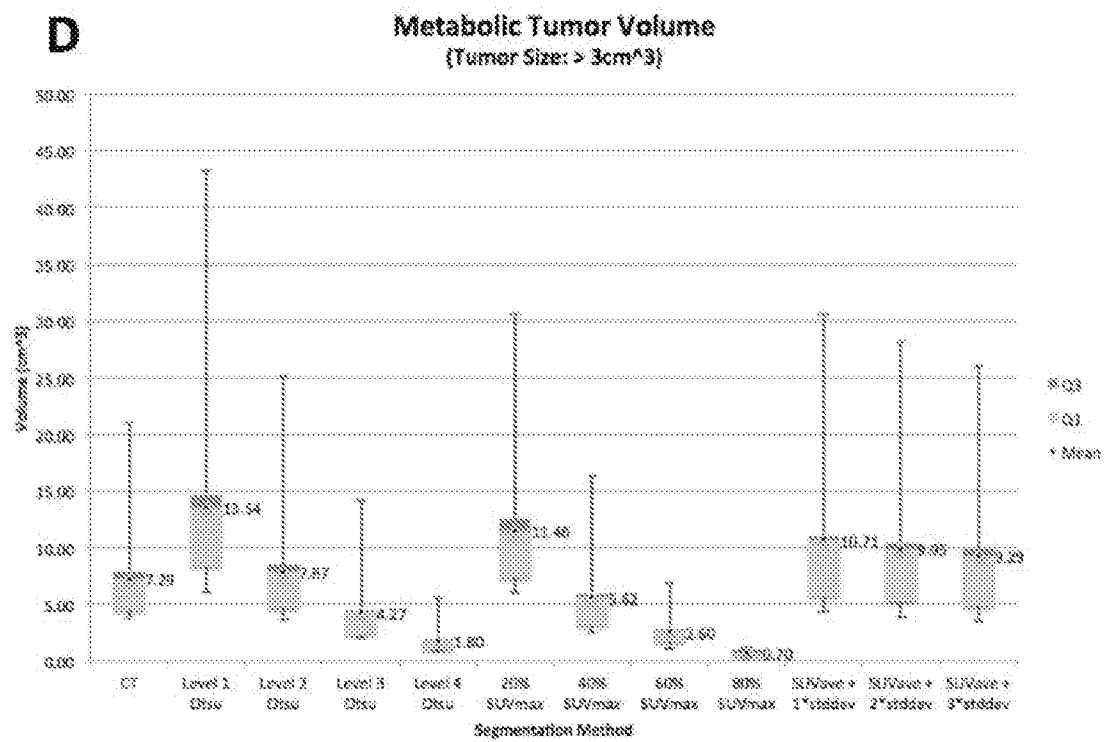


FIG. 5D

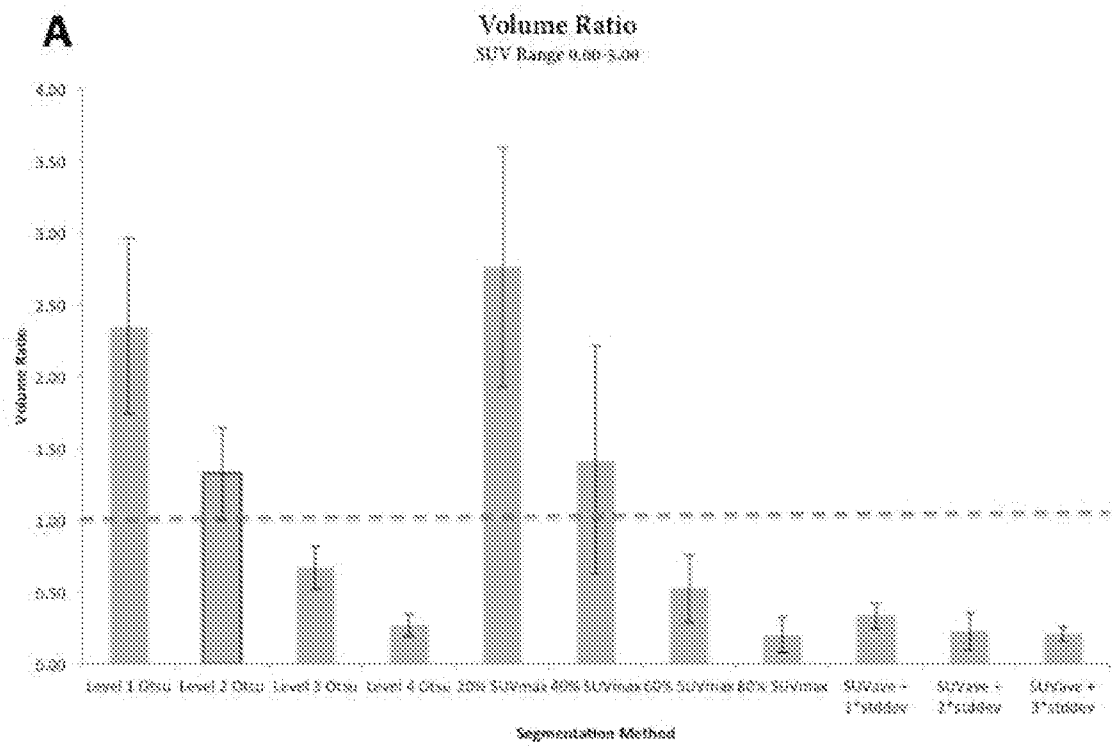
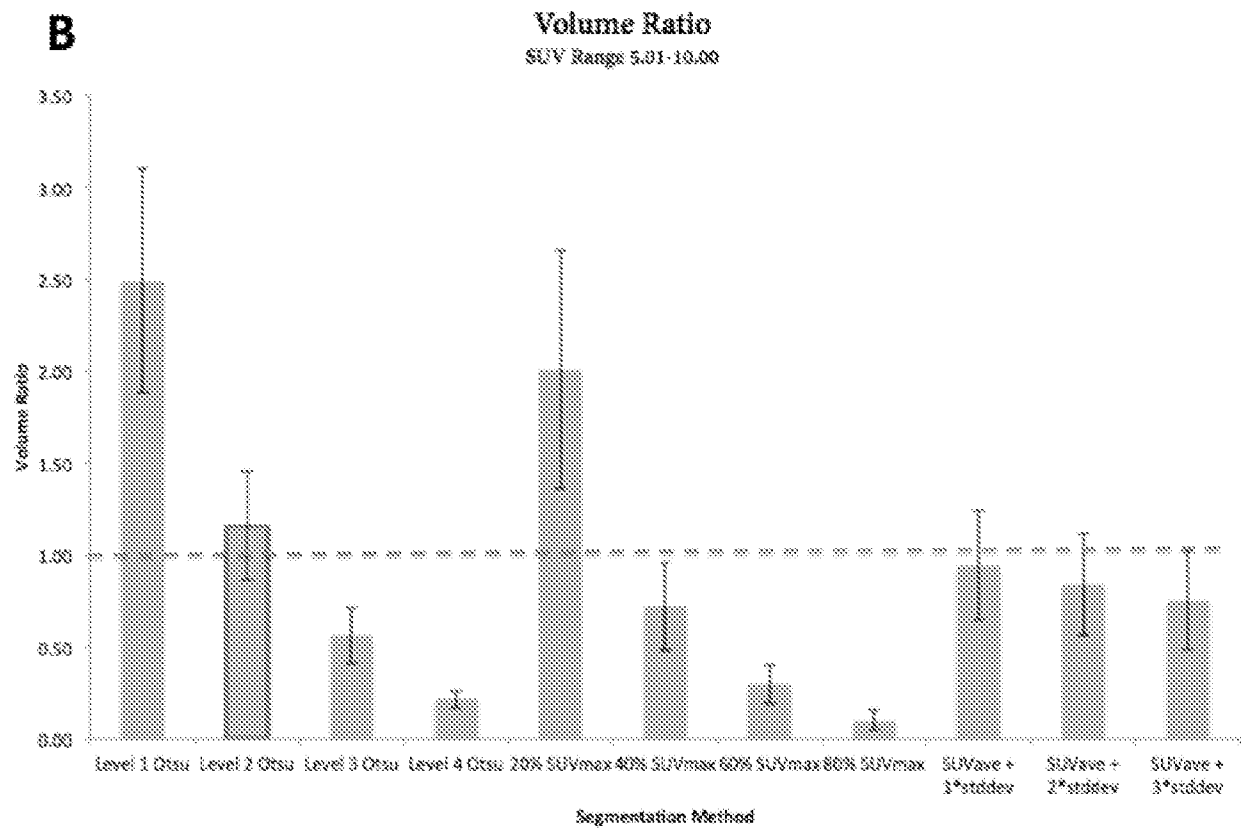
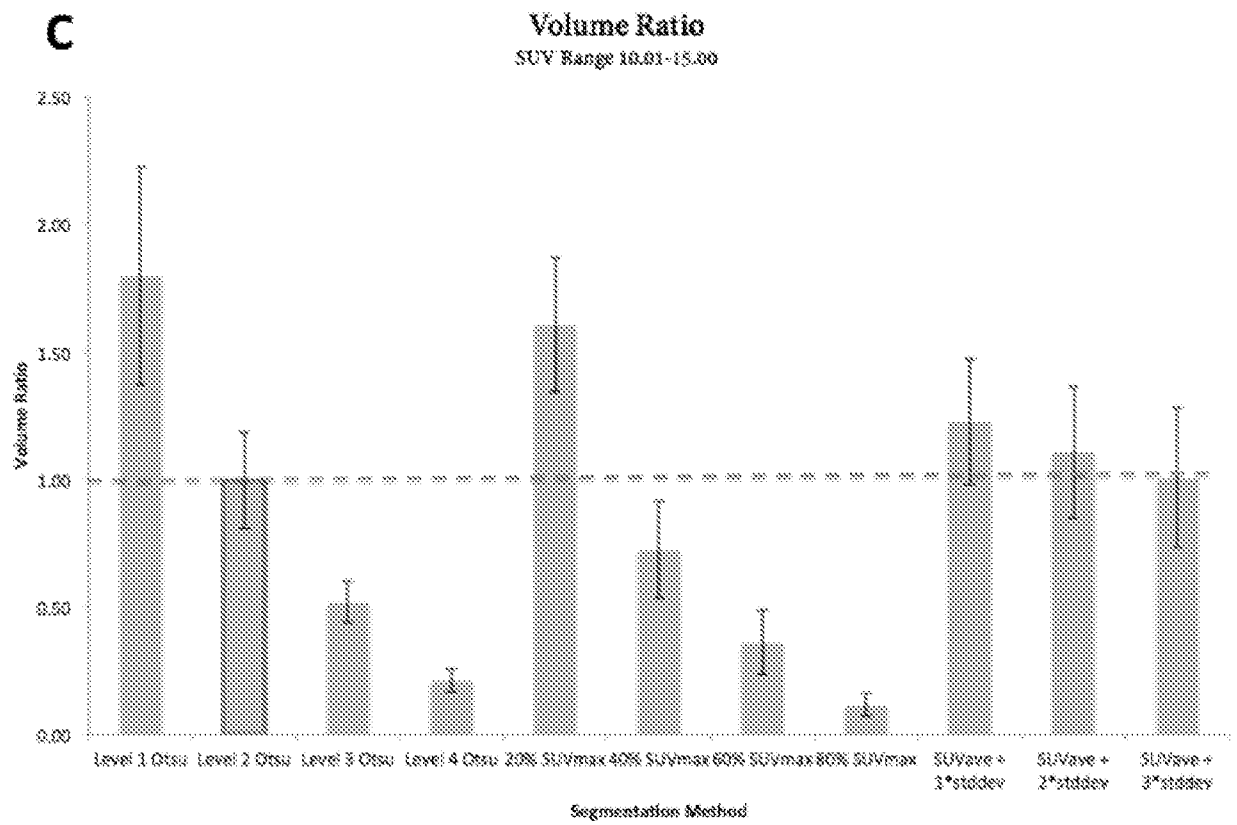


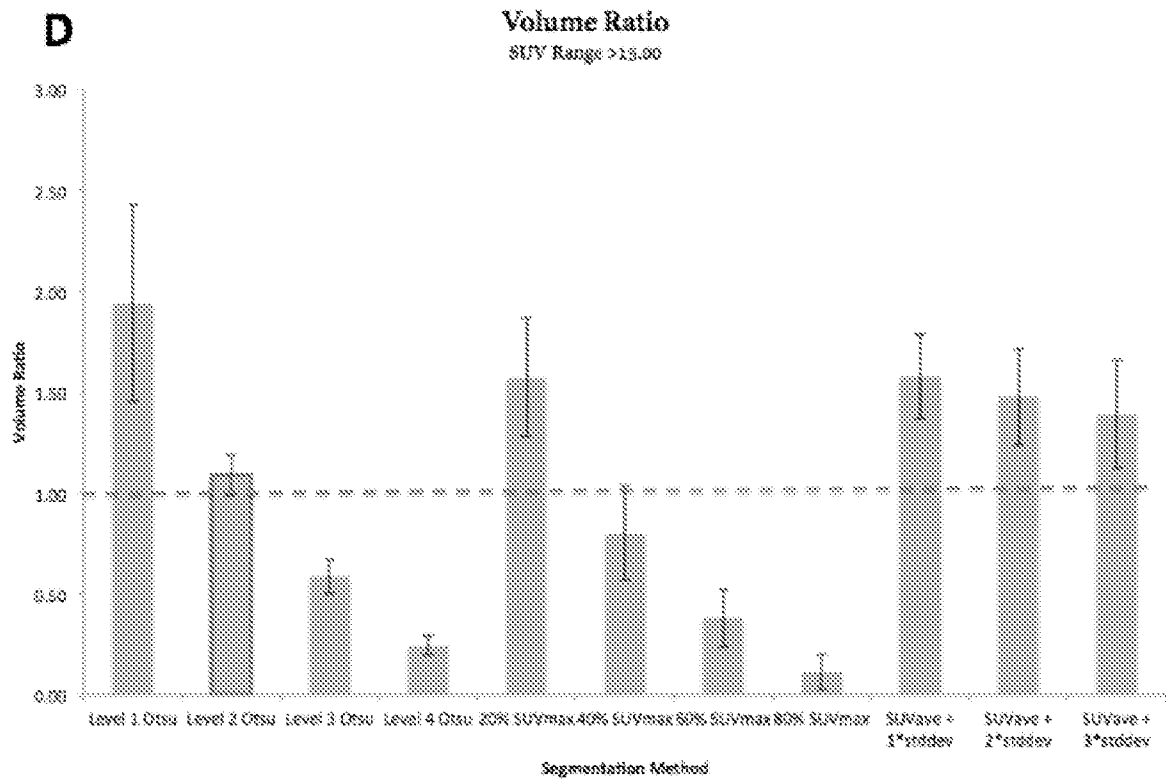
FIG. 6A

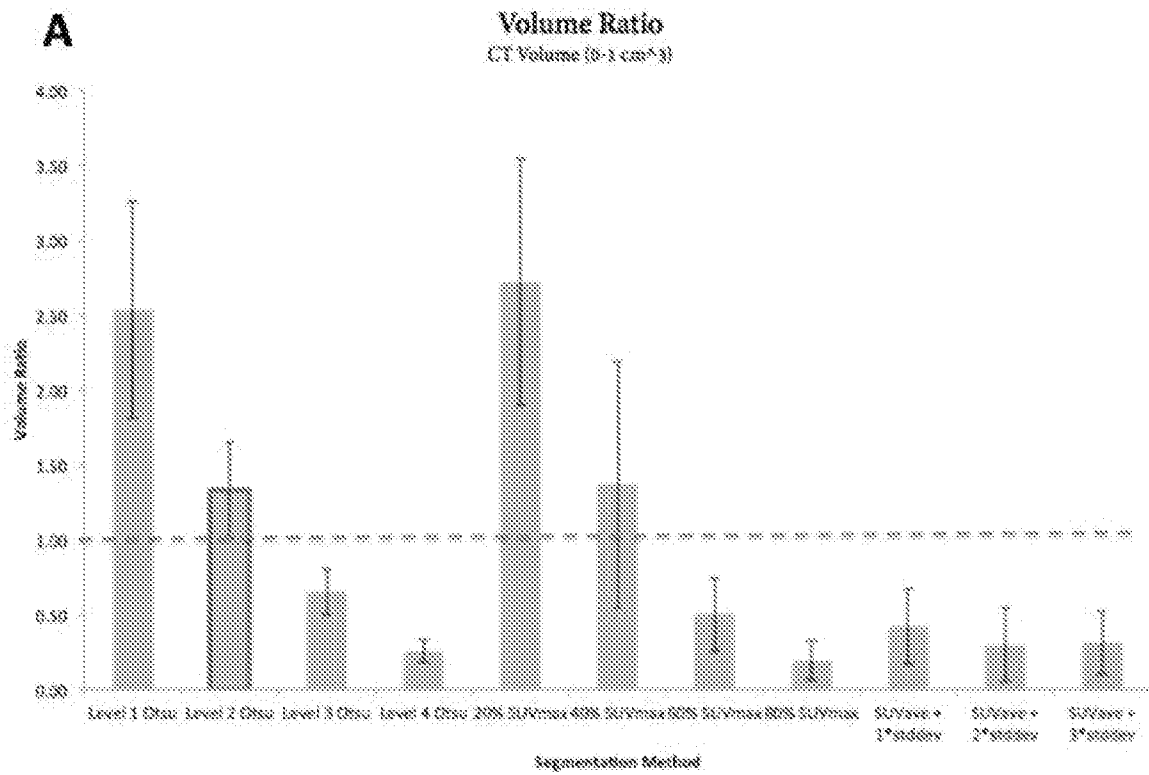
**FIG. 6B**

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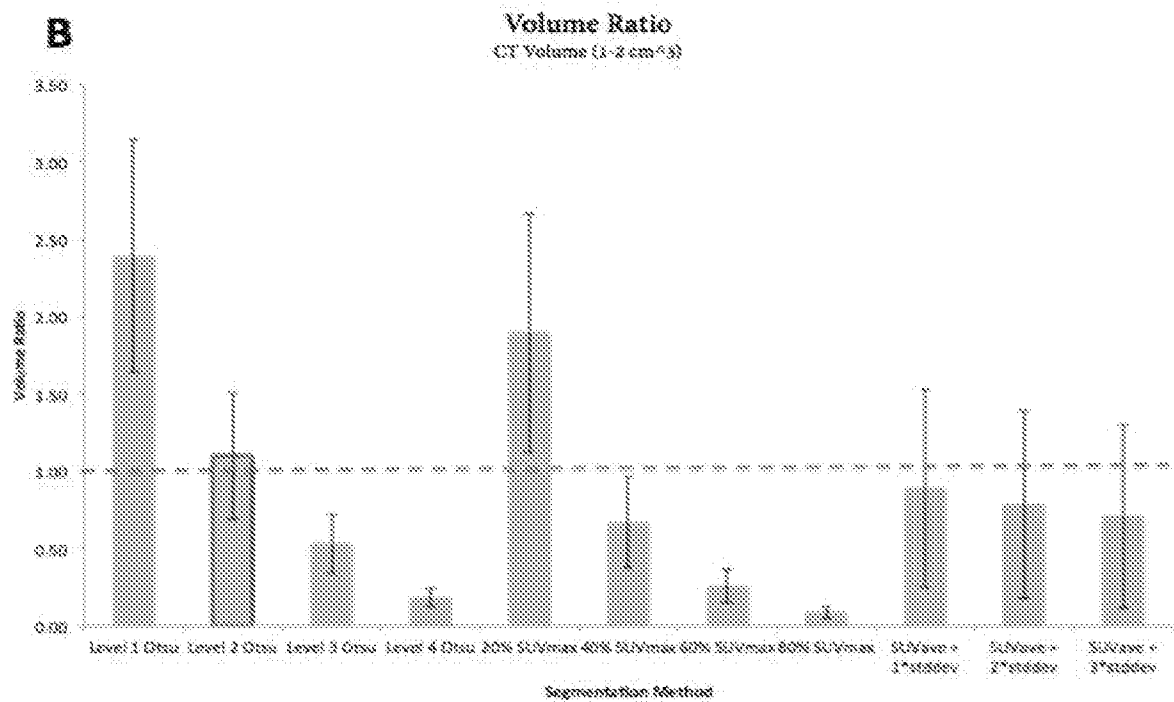
**FIG. 6C**

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**FIG. 6D**

**FIG. 7A**

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**FIG. 7B**

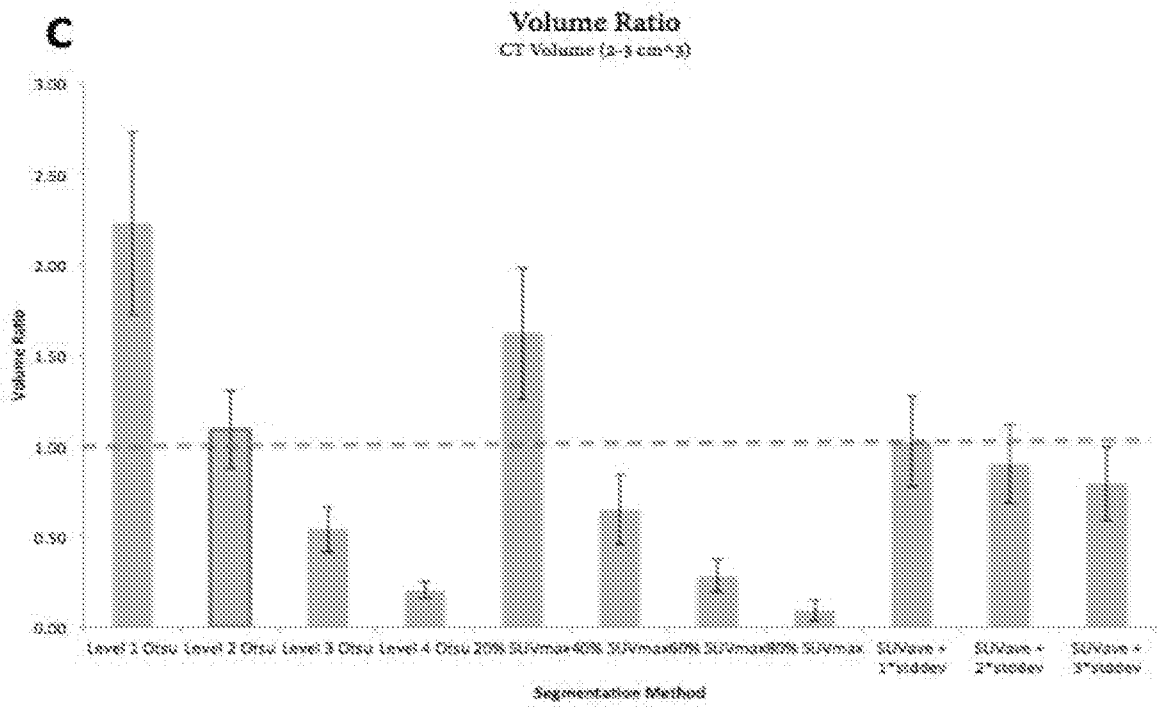


FIG. 7C

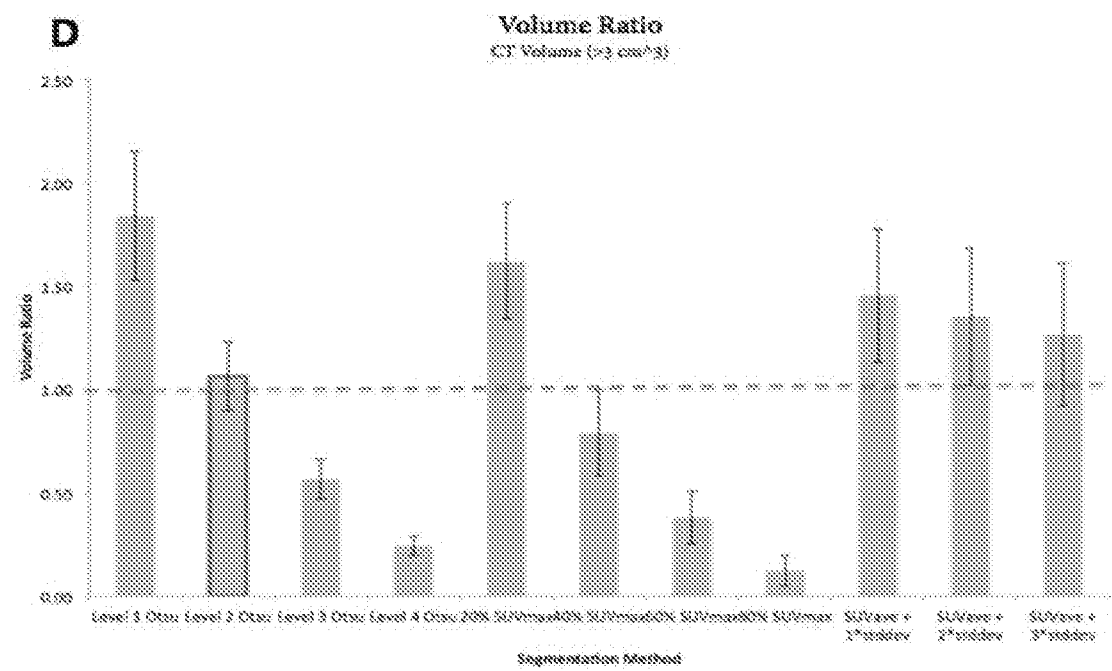


FIG. 7D

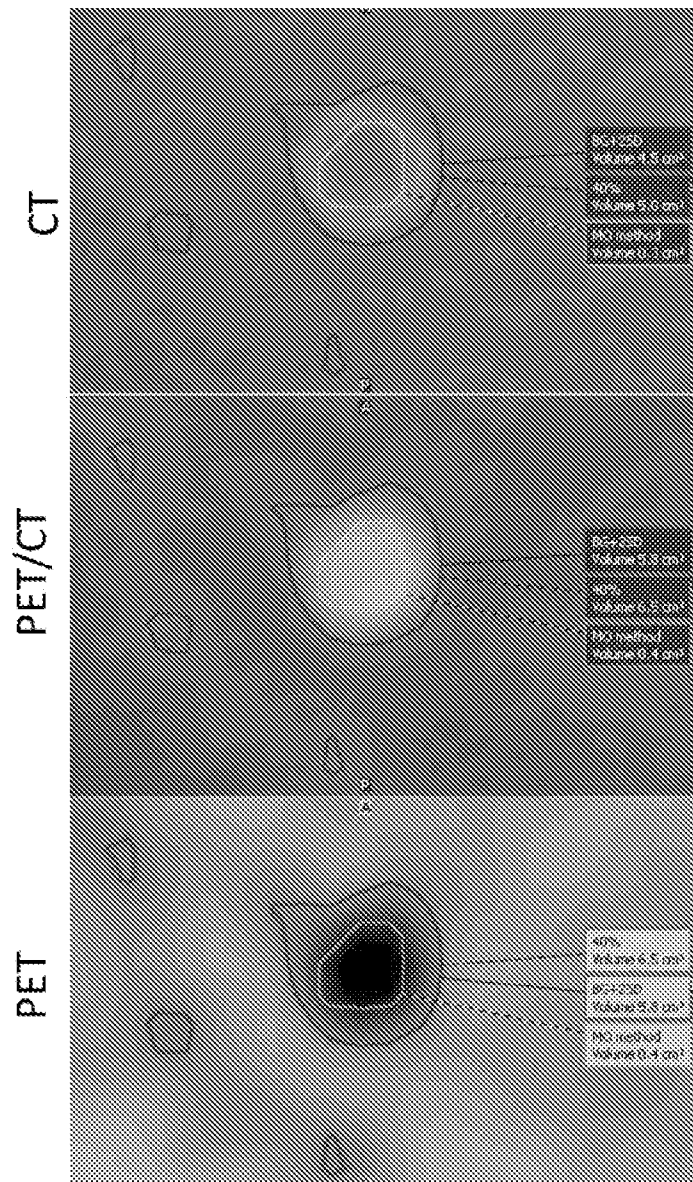


FIG. 8

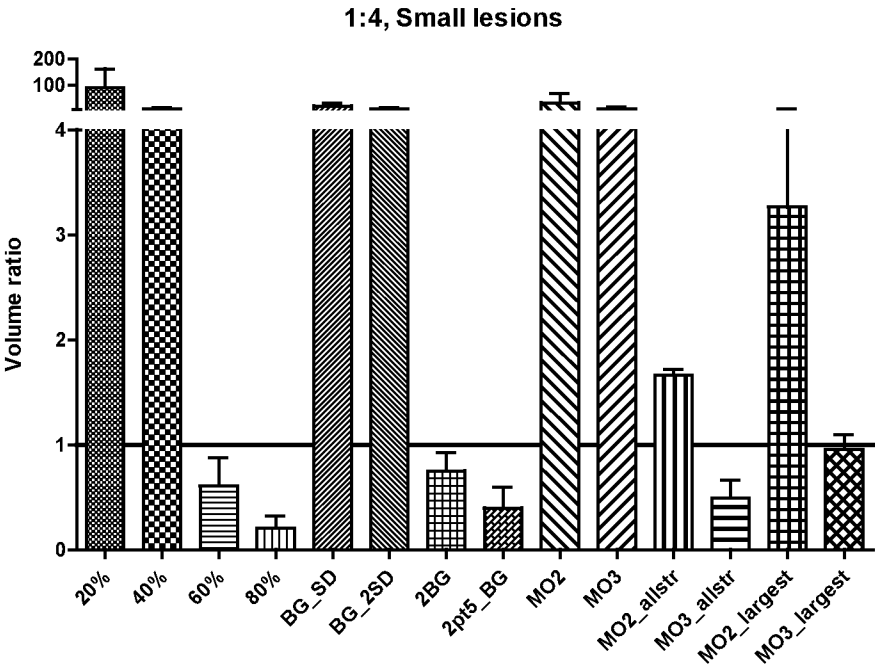


FIG. 9

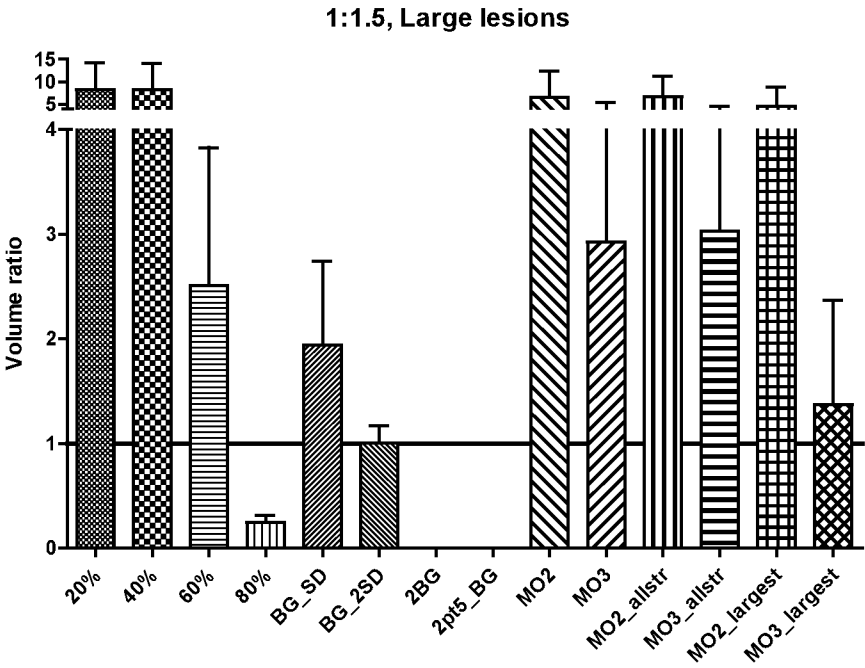
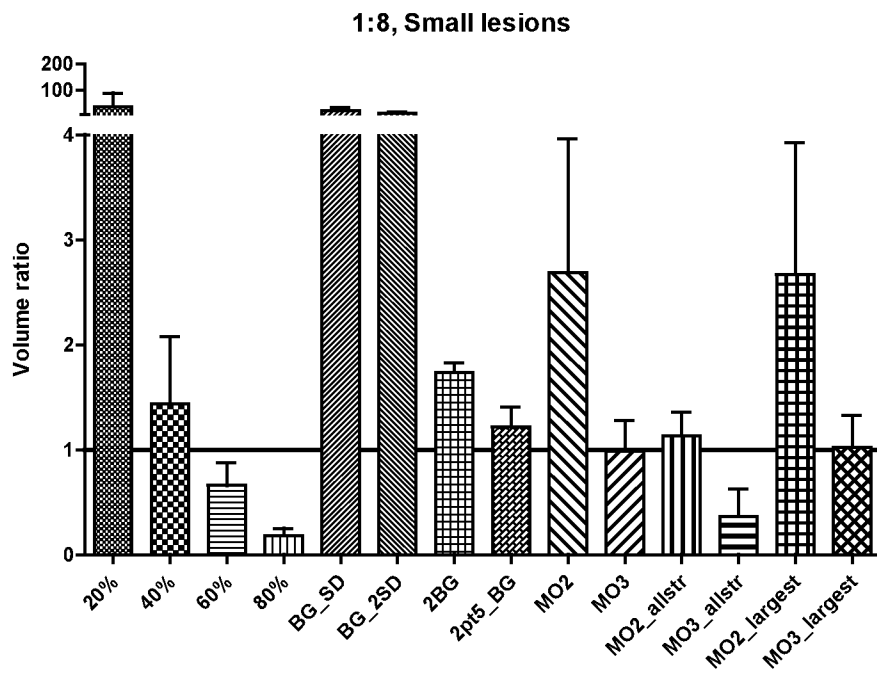
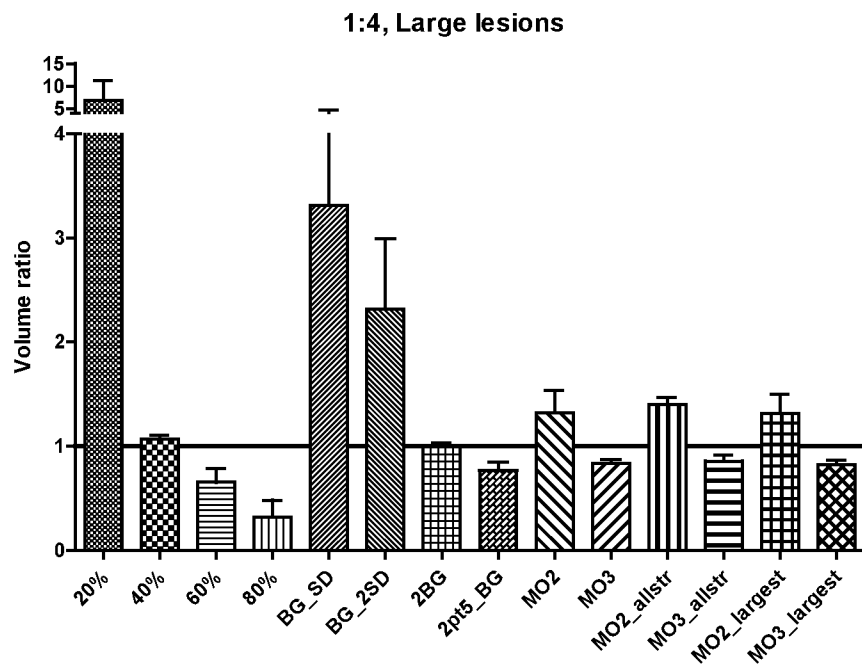


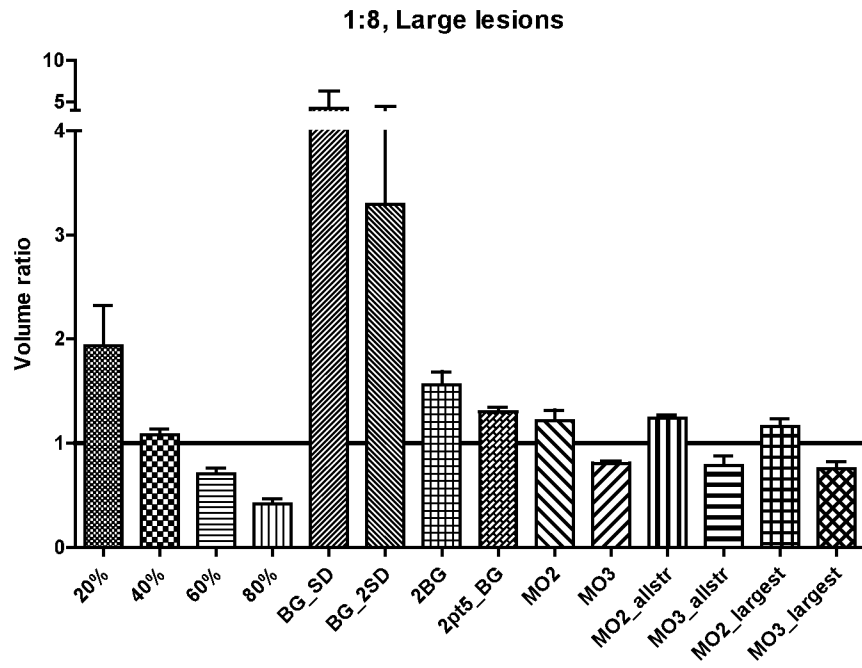
FIG. 10

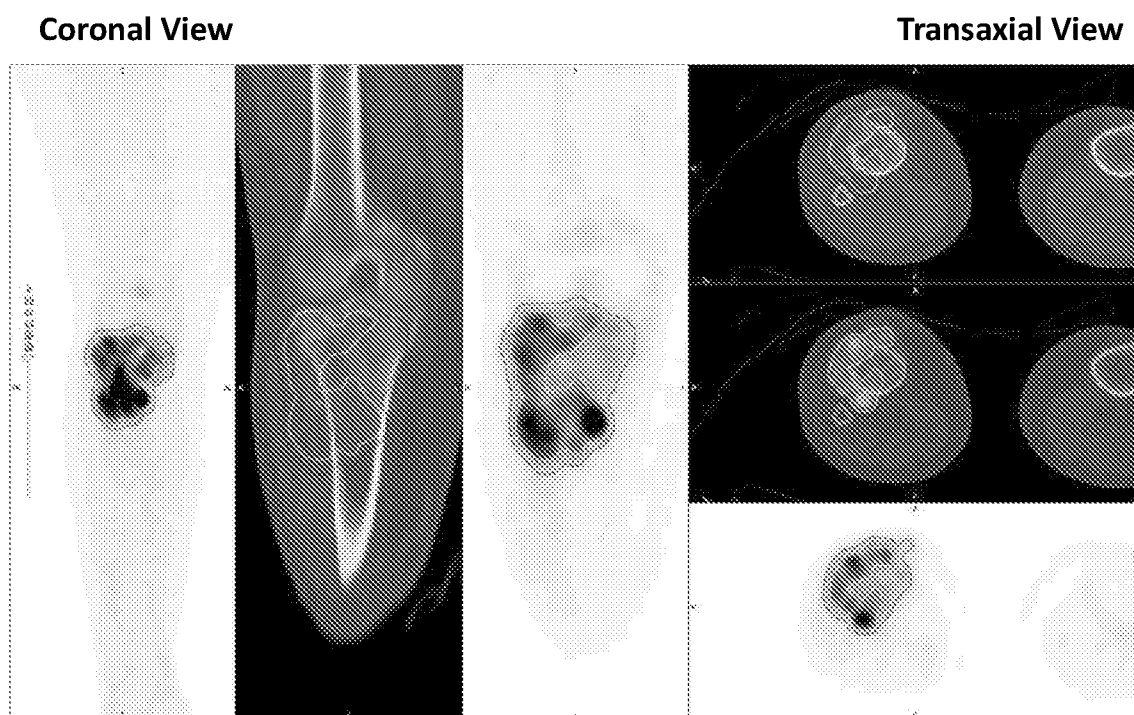
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**FIG. 11**

**FIG. 12**

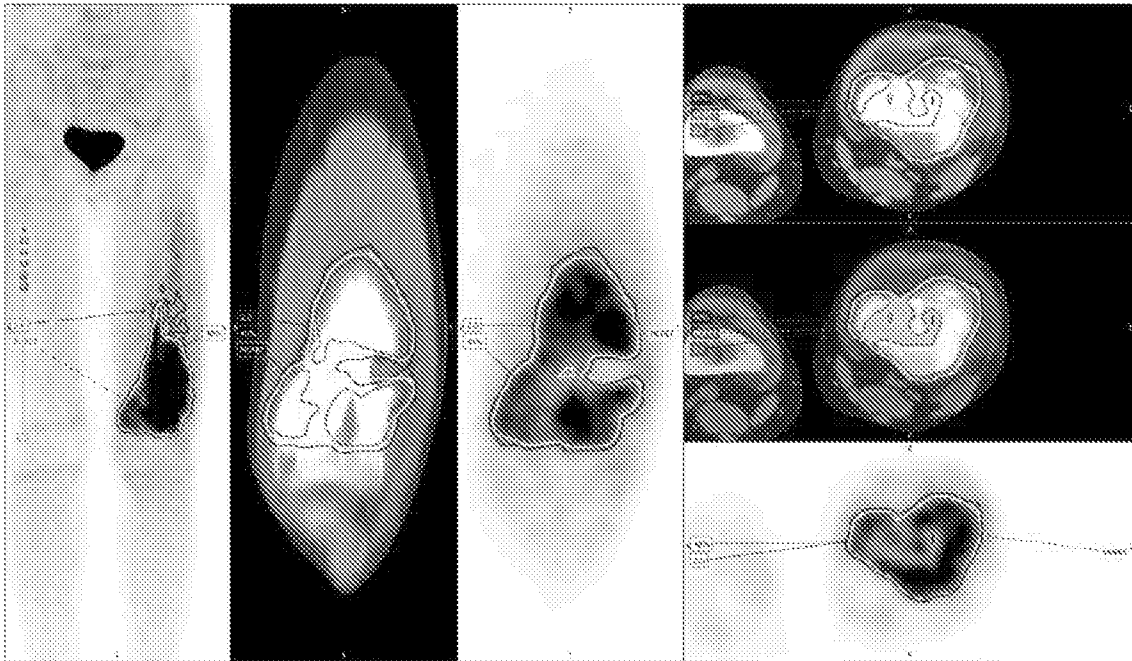
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**FIG. 13**

**FIG. 14**

Coronal View

Transaxial View

**FIG. 15**

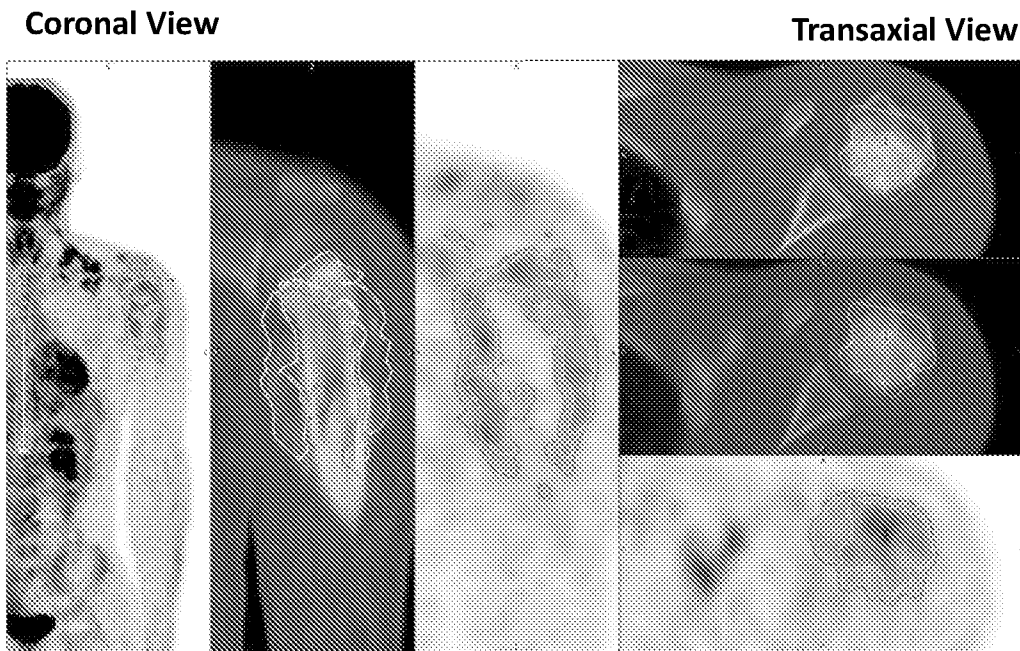


FIG. 16A

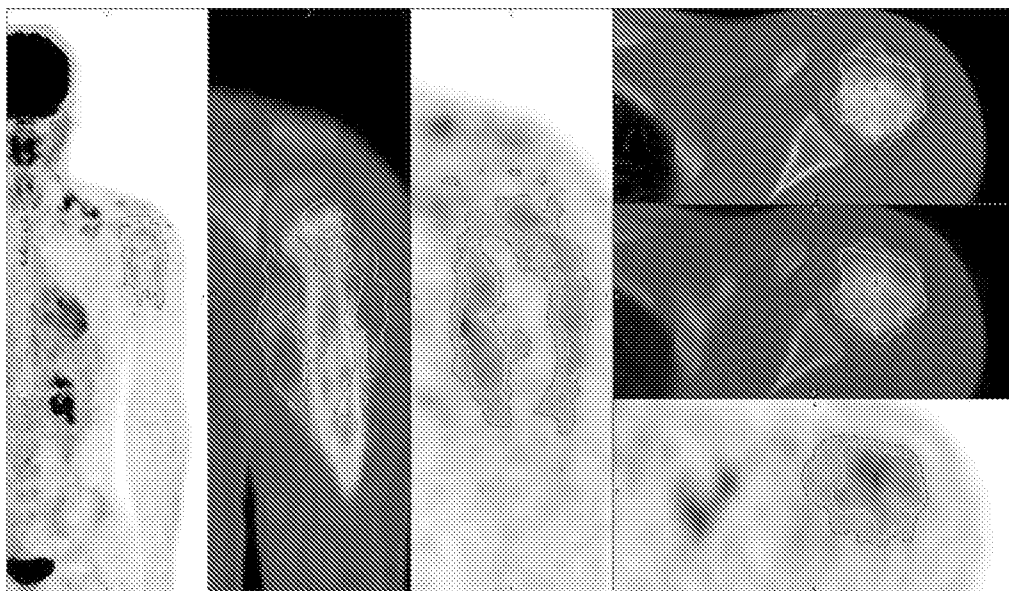


FIG. 16B

MIP

Coronal View

Transaxial View

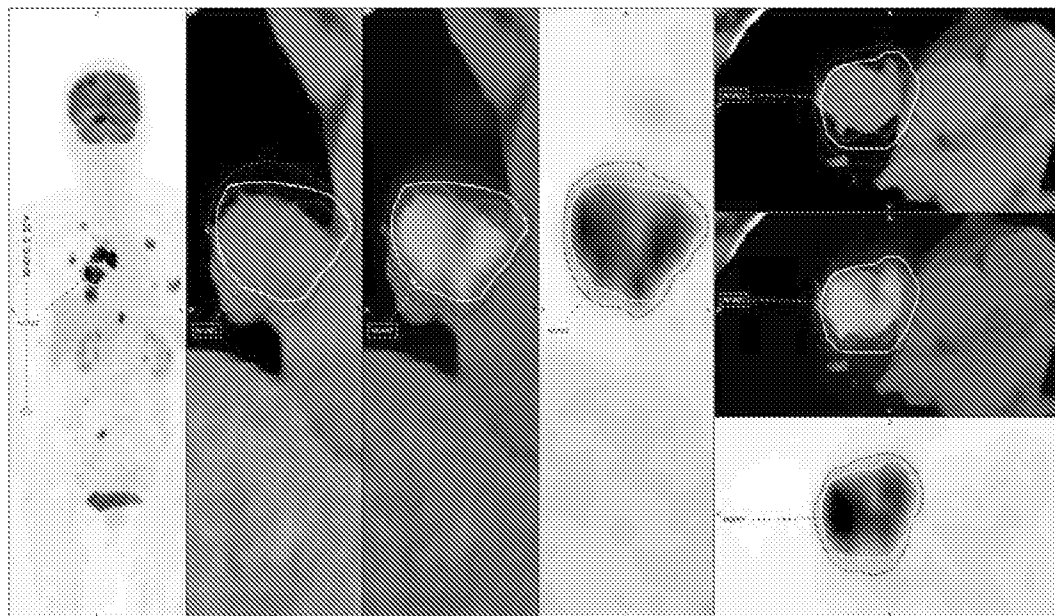
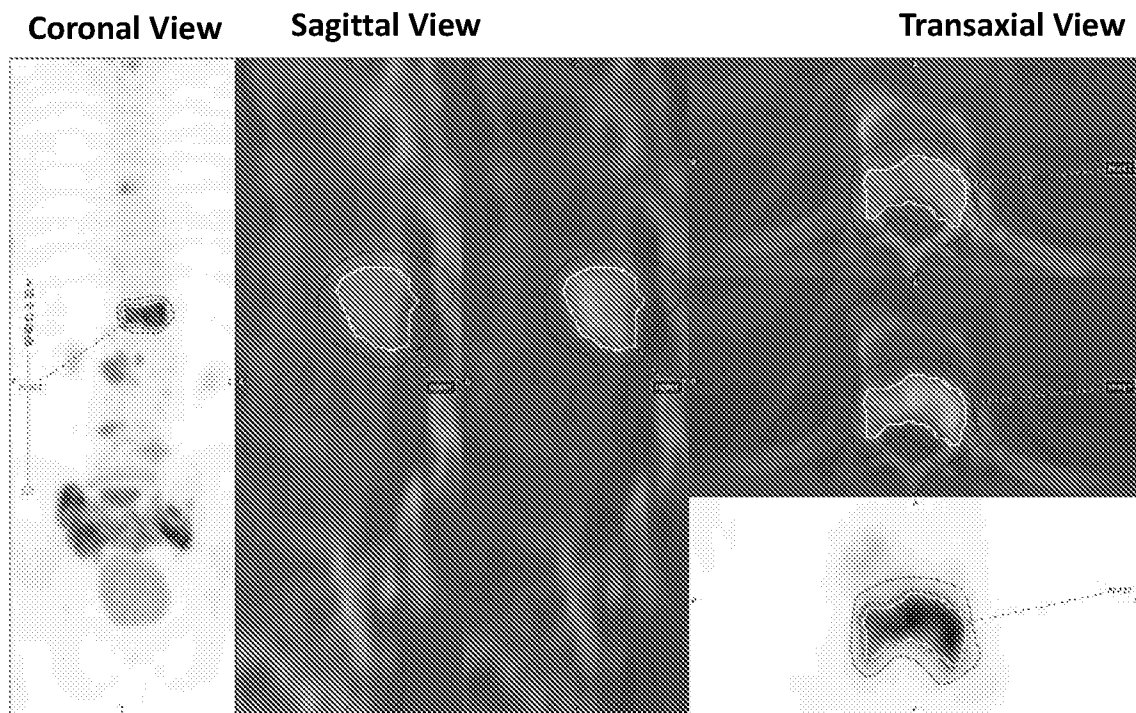
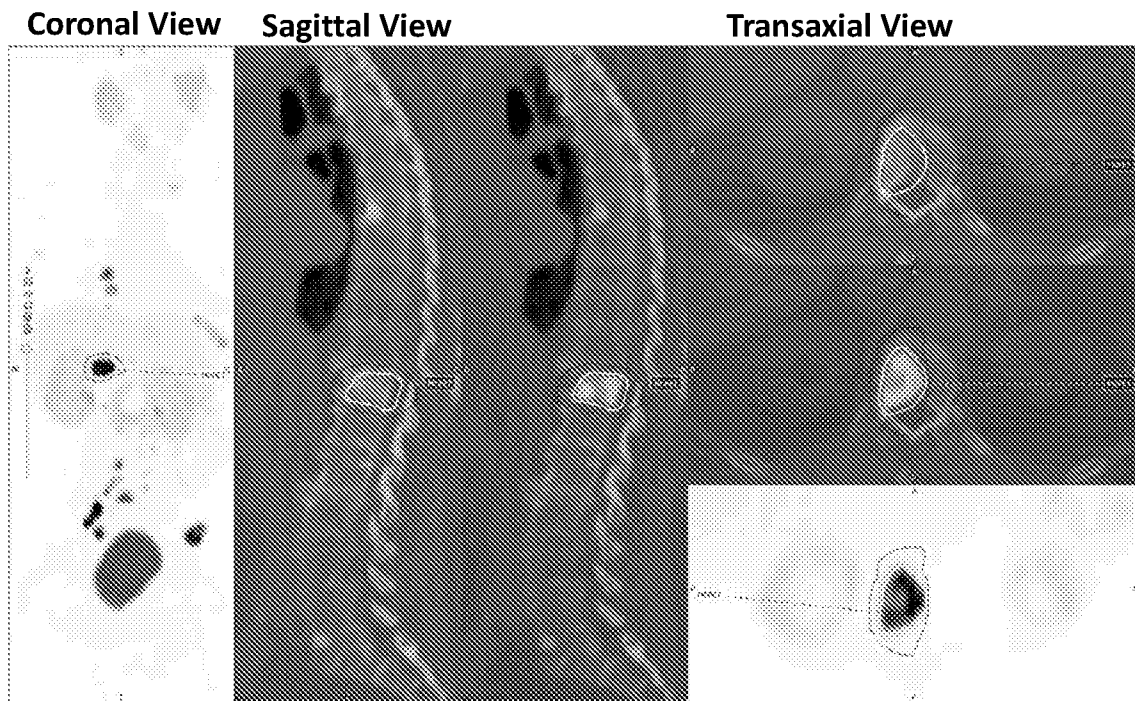
**FIG. 17**



FIG. 18

**FIG. 19**

**FIG. 20**

A. CLASSIFICATION OF SUBJECT MATTER**A61B 5/055(2006.01)i**

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61B 5/055; G06G 7/60; G06K 9/46; G01T 1/161; A61B 6/00; G06K 9/00

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Korean utility models and applications for utility models

Japanese utility models and applications for utility models

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

eKOMPASS(KIPO internal) & Keywords: positron, emission, tomography, standardized, uptake, value, threshold, variance, automatic, delineation

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2009-0234626 A1 (SHIPENG YU et al.) 17 September 2009 See paragraphs [7]-[9],[31]-[39],[43]-[46] and figures 1-7.	1-20
A	US 2007-0081712 A1 (XIAOLEI HUANG et al.) 12 April 2007 See paragraphs [3]-[13],[73]-[75],[83]-[85] and figures 8,13.	1-20
A	US 2009-0234627 A1 (SHIPENG YU et al.) 17 September 2009 See paragraphs [28]-[39],[79]-[83],[118]-[129] and figures 1-3,5.	1-20
A	US 2012-0134557 A1 (MATTHEW DAVID KELLY et al.) 31 May 2012 See paragraphs [16]-[32],[51]-[57] and figures 1-4.	1-20
A	KR 10-2013-0068817 A (INDUSTRIAL COOPERATION FOUNDATION CHONBUK NATIONAL UNIVERSITY) 26 June 2013 See paragraphs [3]-[7],[40]-[45], claims 1-3 and figures 3-6.	1-20



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

21 June 2016 (21.06.2016)

Date of mailing of the international search report

27 June 2016 (27.06.2016)

Name and mailing address of the ISA/KR

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/US2016/024133

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