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TITLE: The quest for an accurate functional tumor volume with ^{68}Ga-DOTATATE PET/CT

SHORT RUNNING TITLE: Ga-DOTATATE PET Functional Tumor Volume

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ABSTRACT

Rationale: ^{68}Ga-labelled somatostatin analog PET/CT (SSA PET/CT) is now standard of care component in management of neuroendocrine tumors (NETs). However, treatment response for NETs is still performed with morphologic size measurements from other modalities, which can result in inaccurate disease burden. Functional tumor volume (FTV) acquired from SSA PET/CT has been suggested as a possible metric, but no validated measurement tool to measure FTV exists. We tested the precision of multiple FTV computational approaches compared to morphologic volume measurements to identify a candidate for incorporation into future FTV studies to assess tumor burden more completely and accurately. **Methods:** The clinical and imaging data of 327 NET patients was collected at MSKCC between December 2016 and April 2018. Patients were required to have SSA PET/CT and dedicated CT scans within 6 weeks. and were excluded if they had intervention between scans. When paired studies were evaluated, 150 correlating lesions demonstrated somatostatin analog. Lesions were excluded if they contained necrotic components or demonstrated a lobulated shape. This resulted in 94 lesions in twenty patients. The FTV for each lesion was evaluated with a hand-drawn assessment and three automated techniques – a 50% threshold from SUVmax, 42% threshold from SUVmax, and background-subtracted lesion histogram-based (BSL) method. These measurements were compared to volume calculated from morphologic volume measurements. **Results:** The FTV calculation methods demonstrated varying amount of correlation to morphologic volume measurements. FTV using threshold of 42% of SUVmax with 0.706 correlation, hand-drawn volume from PET imaging with 0.657 correlation, FTV using threshold

of 50% of SUVmax with 0.645 correlation, and BSL method with 0.596 correlation. The Bland-Altman plots indicates that all FTV methods have positive mean difference compared to morphological volume, with FTV from threshold of 50% relative to SUVmax demonstrating the smallest mean difference. **Conclusion**: FTV determined with thresholding of SUVmax demonstrated the strongest correlation with traditional morphologic lesion volume assessment and the least bias. This method outperformed FTV calculated from hand drawn volume assessments with regards to accuracy. Automated FTV assessment based on a threshold shows promise to better determine extent of disease and make better prognostic assessments for patients with NETs.

Keywords: Functional tumor volume, Neuroendocrine tumors, somatostatin analogues PET/CT.

INTRODUCTION

Neuroendocrine tumors (NETs) encompass a group of diverse neoplasms that typically originate from the gastrointestinal tract, the pancreas, and the bronchopulmonary tract. While they can have varying presentations, they have similar histopathological features and may secrete biologically active compounds (*1*). Given a general lack of awareness of the NETs and their slow growing nature, diagnosis is missed 20-40% of the time or is only made at a later stage due to detectable findings such as tumor mass effects or biomarker secretions. At this stage, metastatic disease is typically present, and curative options are no longer feasible (*2*). Common treatments include loco-regional treatments and conventional chemotherapy. Recently, peptide receptor radionuclide therapy with radiolabeled somatostatin analogues has been approved as an additional treatment option for inoperable or metastatic gastroenteropancreatic NETs (*2,3*).

Imaging plays a pivotal role in diagnosis, staging, treatment selection, and follow-up of NETs (*4*). A combination of somatostatin receptor imaging and morphologic cross-sectional CT or MR imaging is now performed to acquire all clinically relevant information. Somatostatin receptor imaging targets the high density of somatostatin receptors that predominate on the cell membranes of low grade NETs. In recent years, the use of PET/CT with ^{68}Ga-labelled somatostatin analogues, such as ^{68}Ga-DOTATATE PET/CT (SSA PET/CT), has demonstrated superior sensitivity and resolution compared to conventional OctreoScan and is now FDA approved and an accepted standard of care imaging modality (*5-7*). It has substantially improved the identification and management of NETs.

Despite the introduction of SSA PET/CT, clinical and research treatment response for NETs is still performed with morphologic size measurements, such as RECIST 1.1, that are obtained solely with CT and MR imaging. This can exclude many sites of disease only identifiable on SSA PET/CT. Additionally, morphologic size measurements have limited applicability for slow growing lesions such as NET's. This can result in underestimation of therapeutic effects and inaccurately bias management decisions (*8-10*). Some lesion assessments, such Choi criteria, attempt to correct for these variables, but the dependance on CT or MR imaging still limits disease assessment for many patients with low grade NETs (*11-13*).

As the inclusion of SSA PET/CT better evaluates the full extent of NET disease, a measurement technique utilizing this PET imaging data can provide a more complete and accurate disease assessment for NETs. Prior literature has suggested that functional tumor volume (FTV) as a possible suitable metric (*14,15*) and has shown the promise of prognostic utility for FTV in NETs (*15-19*). However, no validated approach has yet been developed to calculate FTV in SSA PET/CT imaging. In prior investigations, the method to calculate FTV has varied and was often chosen arbitrarily based on prior approaches and techniques with FDG PET/CT. For example, Abdulrezzak et al. (*16*) and Torihara et al. (*17*) used 50% threshold of SUVmax, Ohnana et al. (*18*) used a 41% threshold of SUVmax, and Tirosh et al. (*15*) used patient-customized method to subtract background uptake.

The development and validation of an algorithm or analytic process that most accurately measures FTV using SSA PET/CT imaging data would help standardize these prognostic assessments and more accurately identify the full extent of low grade NET disease that can be indolent on CT/MR imaging. This could help create a more reproducible and

accurate biomarker to identify patients most at risk for disease-progression and help to manage treatment decisions.

We have selected some of the techniques previously used to compute tumor volume from SSA PET/CT in order to assess which method best approximates and correlates with morphologic size measurements that is the current standard of practice. One of these measurement techniques is computing tumor volume using a threshold related to the respective lesion's SUVmax ranging from 40% to 50% to remove background uptake (*20*). We chose to test thresholds of 42% and 50%, as these have been utilized in prior studies evaluating tumor volume for both FDG PET/CT and SSA PET/CT imaging as noted above. Another method uses customized background-based estimation including background-subtracted lesion activity (BSL) that surrounds each lesion with a single volume of interest (VOI) and then analyzes the resultant histogram of that VOI to remove any background uptake for each individual lesion (*21,22*). In this study, our aim is to evaluate these different functional tumor volume measurement methods with SSA PET/CT and compare these results with lesion volumes calculated from morphologic size measurements.

MATERIAL AND METHODS

Patient and Lesion Selection

The institutional review board approved this retrospective single-center study and waived the informed consent requirement.

The Memorial Sloan Kettering Cancer Center (MSKCC) GE Picture Archiving and Communication System was retrospectively searched for patients who had underwent an ^{68}Ga-

DOTATATE PET/CT between December 2016 and May 2018. This search identified 327 patients with NETs cared for by our service. The clinical, histopathological, and imaging data of these patients was obtained and organized. We then restricted our population to the 211 patients who had undergone both a ^{68}Ga-DOTATATE PET/CT and a contrast-enhanced CT.

Additional clinical data was used to include only patients with both a ^{68}Ga-DOTATATE PET/CT and a triphasic contrast-enhanced CT exam within 6 weeks of each other. Also, only patient with concordance of the SSA PET/CT and CT findings of neoplastic disease in the dictated nuclear medicine and radiology reports were included to ensure all lesions demonstrated somatostatin avidity. In addition, patients were excluded if they had any therapeutic intervention between their SSA PET/CT and CT examinations. These criteria resulted in twenty-five patients with paired SSA PET/CT and CT examinations and concurrent findings.

The paired ^{68}Ga-DOTATATE PET/CT and contrast-enhanced CT exams were evaluated, and 150 lesions demonstrated somatostatin analog uptake and were clearly identifiable in all planes on CT imaging. Lesions were then excluded if they either contained necrotic components or were lobulated, as an accurate morphologic volume would be difficult to calculated for these types of lesions from traditional morphologic size assessments. Additionally, one lesion was excluded because no biopsy results were obtained during that patient's care at MSKCC. This resulted in 94 clearly identifiable lesions from twenty patients. Each of these ellipsoid-shaped lesions demonstrated precise correlation between the PET imaging and the contrast-enhanced CT imaging in all dimensions.

Diagnostic Imaging Acquisition Protocols

All patients were examined with the routine ^{68}Ga-DOTATATE PET/CT clinical protocol acquired on a GE Discovery 690 or 710 PET/CT. Both scanners use the same PET acquisition hardware and software. Each patient received an intravenous injection of ^{68}Ga-DOTATATE with a mean injected activity of 193.51 MBq (range: 166.5 to 203.5 MBq) and were scanned after an average 64-minute time delay (range: 60 to 75 min). The low-dose, non-iodinated-contrast CT sequence and PET sequence were obtained from the mid skull to the upper thighs. The standardized uptake values were normalized to patient's body weight. All PET/CT scanners used at MSKCC are cross calibrated for the standardized uptake values measurement, allowing a valid comparison between SUVmax measurements made on different scanners.

All patients were also examined with separate triple-phase contrast-enhanced Computed Tomography exams performed with the routine MSKCC clinical protocol. After oral and intravenous iodinated contrast administration, multislice helical sections were obtained from the thoracic inlet to the pubic symphysis. Imaging of the abdomen included a pre-contrast phase, a timed arterial phase imaged 35 seconds after contrast injection, and a timed portal phase imaged 80 seconds after contrast injection.

Functional Target Volume Quantification Analysis

The FTV was determined as the summation of all voxels within the identified VOI that demonstrates a measure of radiotracer uptake that matched a predetermined guideline. All FTV measurements and analysis were performed using the software AW server VolumeShare 7 (Advantage Workstation) by GE (General Electric Healthcare). Initially, a VOI was created to

encircle each identifiable lesion on the ^{68}Ga-DOTATATE PET/CT scan. Each VOI was created to select only a single lesion and to minimize the amount of physiologically elevated background uptake surrounding each lesion within the VOI.

Then, a hand drawn volume was created to circumscribe each lesion, using each lesion's visible tumor activity as demonstrated on the diagnostic PET imaging and excluding any surrounding regions of physiologically increased background activity as could be visibly determined.

The initial VOI of each lesion was then used to calculate FTV using thresholding values. The first method summed the voxels that demonstrated uptake that matched or exceeded a threshold fraction of the lesion's SUVmax uptake. For this method, two different thresholds were evaluated, 42% and 50%.

Lastly, the BSL method was performed (*21,22*). For each lesion, the imaging data from the initial VOI was transposed into a histogram to calculate the BSL activity. The histograms represent the voxels of the VOI as a function of standardized uptake values. Then the background activity surrounding the lesion was removed by subtracting a Gaussian fit over the peak of the VOI's histogram. Any negative values were reset to zero. The remaining positive values in the histogram could be summed to calculate the FTV based on BSL.

To establish a reference standard for lesion volume, the contrast-enhanced CT exams were used to measure the morphologic volume of each lesion using GE Picture Archiving and Communication System. Each lesion was measured manually in three dimensions using the arterial and venous phase sequences. For each lesion, the longest diameter on segmented axial imaging was measured, followed by the longest perpendicular diameter. A third craniocaudal

diameter was then measured using segmented sagittal or coronal imaging sequences. Since only ellipsoid-shaped lesions were included, the morphologic volume could be calculated using the formula $Volume = \frac{4}{3}\pi abc$. Figures 1 and 2 demonstrate example lesions with their calculated FTVs and morphologic volumes.

Statistical Analysis

Pearson's correlation coefficient was used to evaluate the correlation of morphologic lesion volume with the four approaches for FTV assessment. Linear models with a random intercept were used to account for any intra-patient correlation between lesions from the same patient. Additionally, the FTVs measured by the four approaches were statistically compared to morphological volume by the included Bland–Altman plots. A log-transformation for the Bland-Altman plots was used to correct the skewness in the distribution of the volumes.

RESULTS

Of the twenty patients included, 65% were women, and 35% were men. The mean age at PET scan was 56 ± 12 years old. Primary tumor sites included pancreas for eleven patients (55%) and small intestine for five patients (25%). There was one patient with an unknown primary (5%). Additionally, there were two patients with gastric primary and one patient with a renal primary (Table 1).

Metastases were detected in 18 patients (90%). The most common metastatic site was the liver with 18 patients (90%). Other common sites of metastasis were nodal for 8 patients (40%) and bone for 3 patients (15%). A single patient had a local recurrence. Additionally, 2

patients had adrenal metastases, 2 had mesenteric metastases, 1 had cardiac metastasis, and 1 had a splenic metastasis (Table 1).

According to ENETs 2017 and 2019 WHO Classification staging and grading systems, patients with gastroenteropancreatic neuroendocrine tumors could be classified as G1 tumors (Ki67 < 3%) for 5 patients (29%), G2 tumors (Ki67 = 3-20%) for 9 patients (53%), and G3 tumors (Ki67 > 20%) for 3 patients (18%). There were 3 patients with NET carcinoid tumors without Ki67 information (Table 1).

Only eight of the patients had a clinical syndrome at the time of the diagnosis with diarrhea or flushing, and only eight patients were under treatment with cold somatostatin analogs at time of SSA PET/CT imaging. Patients had a variety of prior treatments including primary resection in 9 patients, liver directed therapies in 7, chemotherapy in 4, and radiotherapy in 1 (Table 2).

A total of 94 lesions were analyzed for FTV. The mean SUVmax of the lesions was 36.9 ± 27.0. Most lesions were in the liver (69). Additional sites of lesions include lymph nodes (10), pancreas (5), bones (5), small bowel (2), perihepatic implant (2), and one mesenteric lesion (Table 3).

The different FTV calculation methods demonstrated varying correlation to morphologic volume measurements for the full population of 94 lesions. Calculating FTV using the thresholding of 42% relative to SUVmax provided a 0.706 correlation. The hand-drawn volume from the PET imaging provided a 0.657 correlation. The other methods were thresholding of 50% relative to SUVmax with a 0.645 correlation and BSL method with a 0.596 correlation (Figure 3).

The Bland-Altman plots (Figure 4) are well distributed across 0 for each FTV calculation method, but all four FTV methods have positive mean difference when compared to morphological volume. The FTV calculated using the thresholding of 50% relative to SUVmax shows the smallest mean difference. This difference between each FTV method and the morphological volume is not affected by the size of lesion.

DISCUSSION

In our study, we evaluated different methods to calculate FTV from SSA PET/CT and compared these to morphologic volumes. An FTV calculated using thresholding methods related to SUVmax outperformed other techniques and may more completely and accurately assess tumor burden for NETs than traditional morphologic assessments.

Since the arrival of SSA PET/CT into the clinical sphere, there have been attempts to understand how to best utilize it for patient management. It has been suggested that FTV may represent a better correlation with prognosis than SUVmax by better capturing extent of disease and response to therapy (*14-19*). But there is no consensus or validated FTV method with SSA PET/CT, so we appropriated some of previously utilized FTV methods. These included SUVmax thresholding methods related to SUVmax, hand drawn volumes, and a BSL method described in prior published studies by MSKCC.

Use of the hand drawn volumes for calculation of FTV performed favorably with a strong correlation to the morphologic volume. Unfortunately, this technique also consistently demonstrated the largest overestimation of lesion size compared to morphologic volume. It is

unclear if this bias is due to companion CT images of the PET examination. An additional major limitation of this method is the time required to manually circumscribe each lesion.

While the FTV calculation based on the BSL technique exhibited promise for the FDG PET/CT, this demonstrated poorest correlation of calculated FTV with morphologic volume compared to other methods. Additionally, this technique also greatly overestimated lesion size compared to morphologic volume. This suggests that the distribution of somatostatin analog uptake from the background parenchyma cannot be completely estimated by a classical Gaussian distribution method.

Both FTVs computed based on thresholding values set in reference to SUVmax demonstrated strong correlations with morphologic lesion volume and the smallest overall differences to morphologic lesion volume. The use of the 42% threshold had the highest correlation when compared to the morphologic volume, including the hand drawn volume, and the second smallest mean difference. The 50% threshold demonstrated the smallest mean difference from morphologic volume or the smallest overestimation and the third strongest correlation to morphologic volume. This suggests that using an FTV with thresholding values may be the best candidate for a FTV measurement technique to assess tumor burden for low grade NETs. As the use of the 42% and 50% thresholds were arbitrarily chosen given their prior utilization for tumor volume assessments in the literature, a threshold value set to different percentage could demonstrate a stronger correlation to morphological tumor volume with less bias or overestimation. As the 50% threshold with least bias demonstrated a lower correlation than a 42% threshold, it is possible that second variable is needed to adjust FTV to best

approximate morphologic volume. These results suggest that more inquiry is likely needed to answer these questions.

We would like to note the main limitation of our study, our exclusion of lesions with necrotic components and those with more complex three-dimensional volumes. These were excluded due to the difficulty of calculating an accurate morphological volume for these lesions via CT imaging. Future studies are needed to evaluate if a FTV method based on a thresholding value set in reference to SUVmax can used to accurately measure the somatostatin analog positive portions of these types of NET lesions.

CONCLUSION

As SSA PET/CT can better evaluate the full extent of NET disease than CT or MR imaging, a measurement technique utilizing this PET imaging data can provide a more complete and accurate assessment of total disease. Our study demonstrated a strong correlation between functional tumor volume calculated using a thresholding value set in reference to SUVmax and traditional morphologic lesion volumes. This method also demonstrated the most accurate measurements when compared to morphologic lesion volumes. Additionally, this method outperformed FTV calculated from hand drawn volume assessments with regards to accuracy. Future evaluation of this FTV assessment technique is the best candidate for further evaluation and incorporation of tumor volume algorithms including total body tumor volume to more completely and accurately assess tumor burden and prognosis for patients with NET .

DISCLOSURES

RR is a non-remunerated consultant for AAA-Novartis and Curium. LB is a non-remunerated consultant/speaker for AAA-Novartis, Ipsen, ITM, Curium, Clovis Oncology, Iba, and MTTI; LB received a research grant from AAA-Novartis. No other potential conflicts of interest relevant to this article exist.

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KEY POINTS

QUESTION: What is the best functional tumor volume measurement method for Ga68 SSA PET/CT imaging of neuroendocrine tumors?

PERTINENT FINDINGS: We found a strong correlation and smallest bias between functional tumor volume and traditional morphologic lesion volume when using a threshold relative to SUVmax of SSA PET/CTs. Additionally, this method of computation outperformed FTV calculated from hand drawn volume assessments with regards to accuracy.

IMPLICATIONS FOR PATIENT CARE: Functional tumor volume assessment technique based on a threshold of SUVmax is a promising basis for more accurate assessment of tumor volume and should be further studied to create FTV algorithms to better determine extent of disease and make better prognostic assessments.

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TABLES

Table 1. Demographic data and Histopathologies

Patients	N = 20
Female, n (%)	13 (65%)
Male, n (%)	7 (35%)
Age in years at ^{68}Ga-DOTATATE PET ±SD (range)	56 ± 12 (28, 78)
NETs Primary tumor subtype (%)	
P-NETs	11 (55%)
SI-NETs	5 (25%)
Others primary tumor sites	3 (15%)
Unknown primary	1 (5%)
GEP-NETs grade	
G1 (Ki67 < 3%)	5 (29%)
G2 (Ki67 between 3-20%)	9 (53%)
G3 (Ki67 > 20%)	3 (18%)
Local recurrence	1 (5%)
Metastases	
No	2 (10%)
Yes	18 (90%)
Metastatic sites	
Liver	18
Nodes	8
Bone	3
Adrenal	2
Mesenteric	2
Cardiac	1
Splenic	1
Clinical syndrome	
Non-functioning tumor	12 (60%)
Functioning tumor	8 (40%)

SI-NETs = small intestine neuroendocrine tumors, P-NETs = pancreatic neuroendocrine tumors
SD: standard deviation

Table 2. Medical and surgical treatments prior to imaging

Resection of the primary tumor	9 (45%)
Additional Treatments	
Liver directed therapy	7 (35%)
Chemotherapy	4 (20%)
Radiotherapy	1 (5%)
Peptide Radionuclide Receptor Therapy	0
Treatment with cold SSA at time of ^{68}Ga-DOTATATE PET/CT scan	8 (40%)

Table 3. DOTATATE-avid lesion locations and measurements

Mean SUVmax ± SD (range)	36.9 ± 27.0 (1.3, 188.3)
Number of lesions analyzed	94
Site of lesions	
Liver	69 (73.4%)
Node	10 (10.6%)
Pancreas	5 (5.3%)
Bone	5 (5.3%)
Bowel	2 (2.1%)
Perihepatic implant	2 (2.1%)
Mesenteric Node	1 (1.1%)

SD: standard deviation

FIGURES

Figure 1. Example Lesion 1. A. CT evaluation of lymph node. (1) Longest diameter, 2.2 cm. (2) Longest perpendicular diameter, 1.3 cm. B. PET evaluation of lymph node. Yellow: 50% threshold segmentation, Green: 42% threshold segmentation, Blue: Manual segmentation, Red: BSL segmentation.

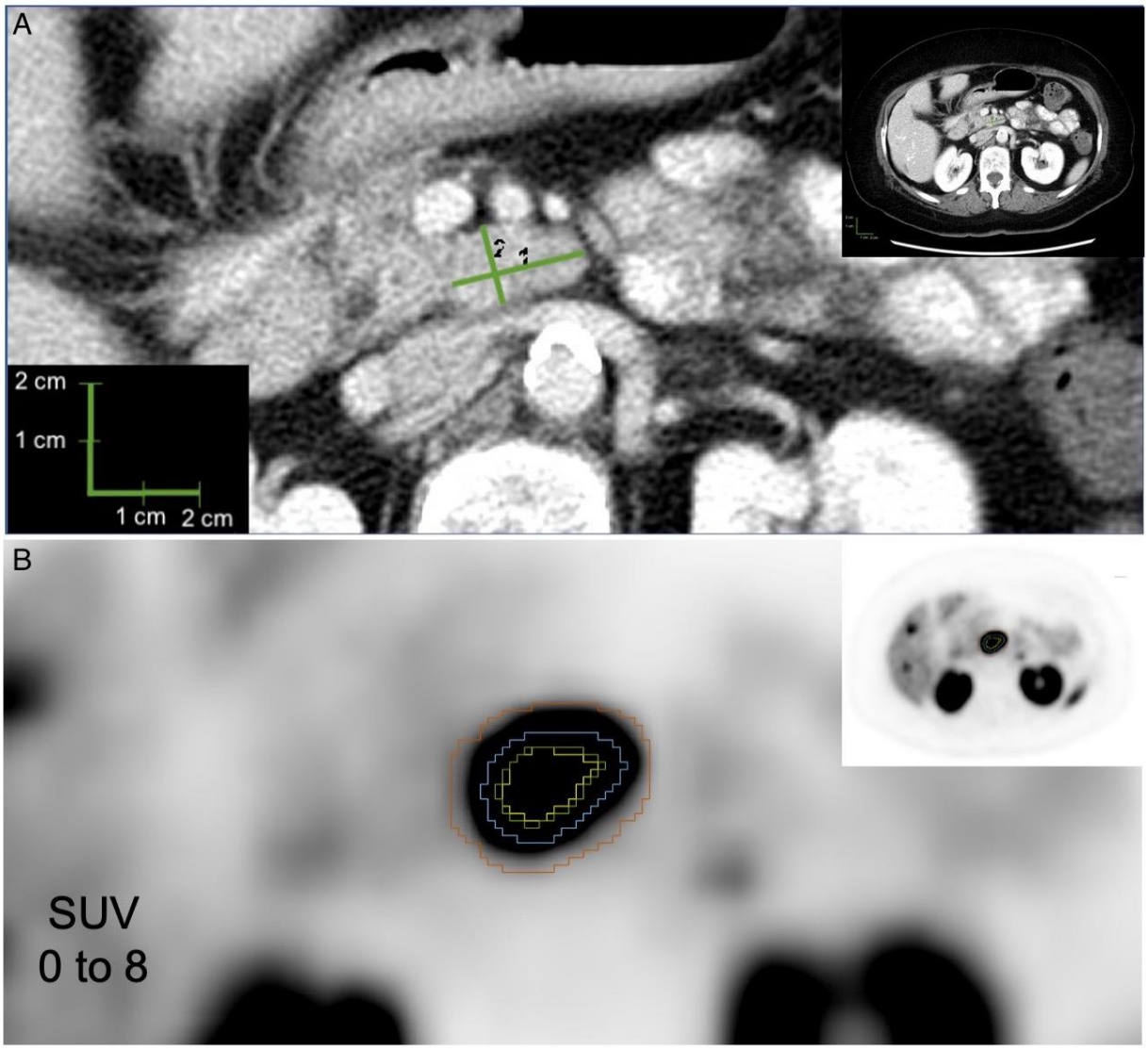


Figure 2. Example Lesion 2. A. CT evaluation of hepatic metastasis. (1) Longest diameter, 2.3 cm. (2) Longest perpendicular diameter, 1.8 cm. B. PET evaluation of hepatic metastasis. Yellow: 50% threshold segmentation, Green: 42% threshold segmentation, Blue: Manual segmentation, Red: BSL segmentation.

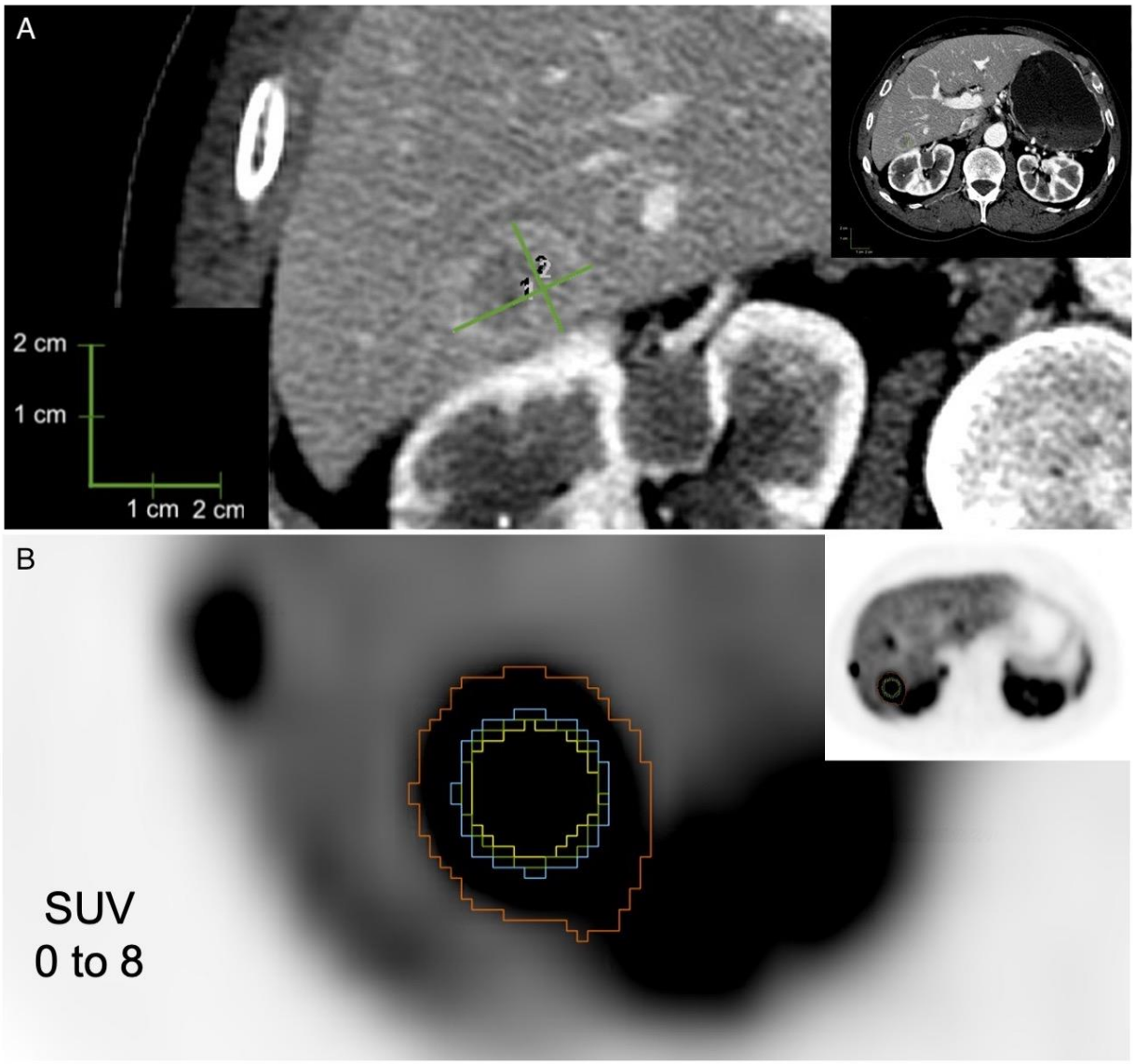


Figure 3. Correlation Charts of FTV Calculations to Morphologic Measurements. A. VOLNM = Manual volume from the PET imaging; B. VOLBSL = Background subtracted lesion method*;* C. VOL50 = Threshold of 50% relative to SUVmax; D. VOL42 = Threshold of 42% relative to SUVmax.

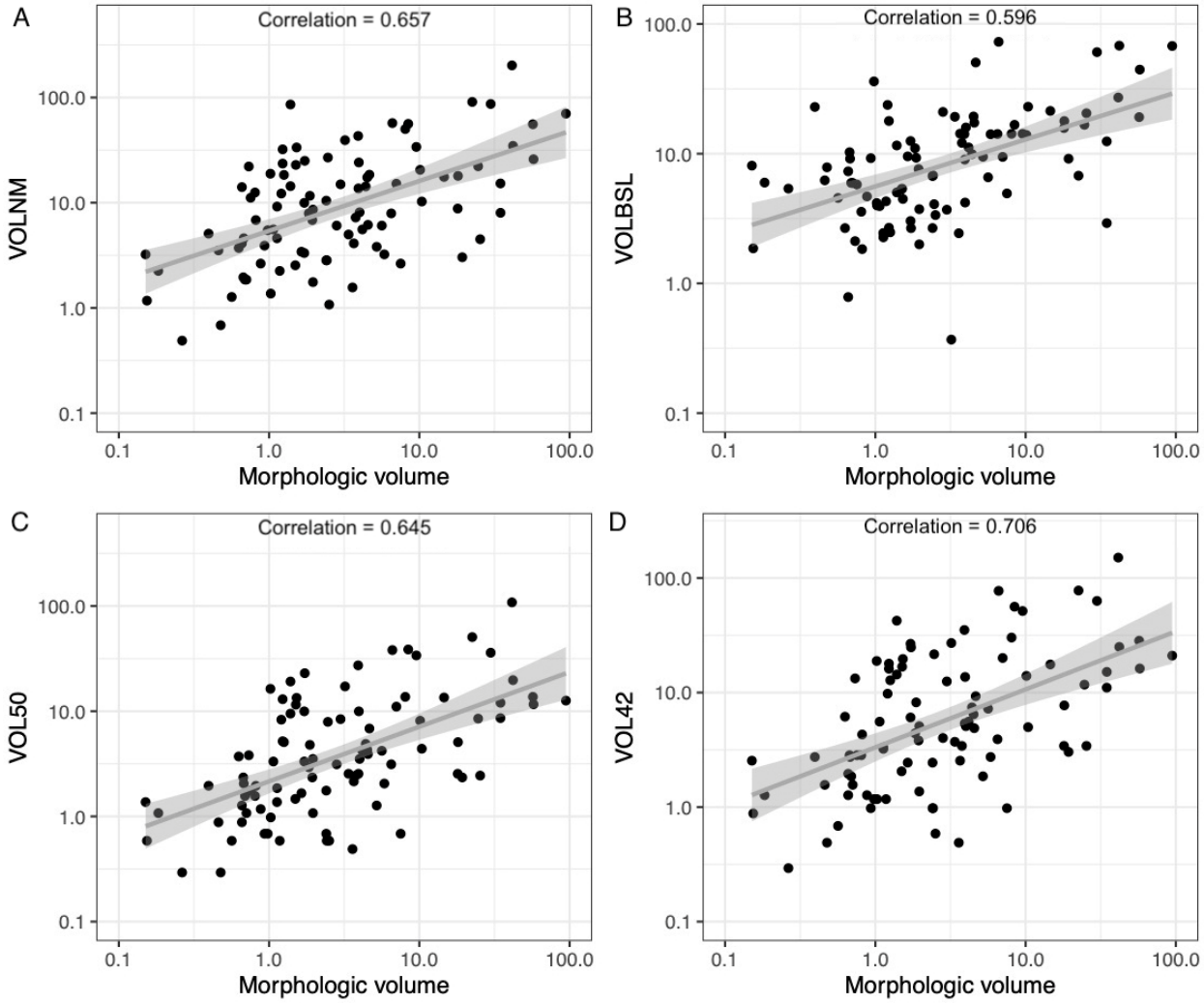
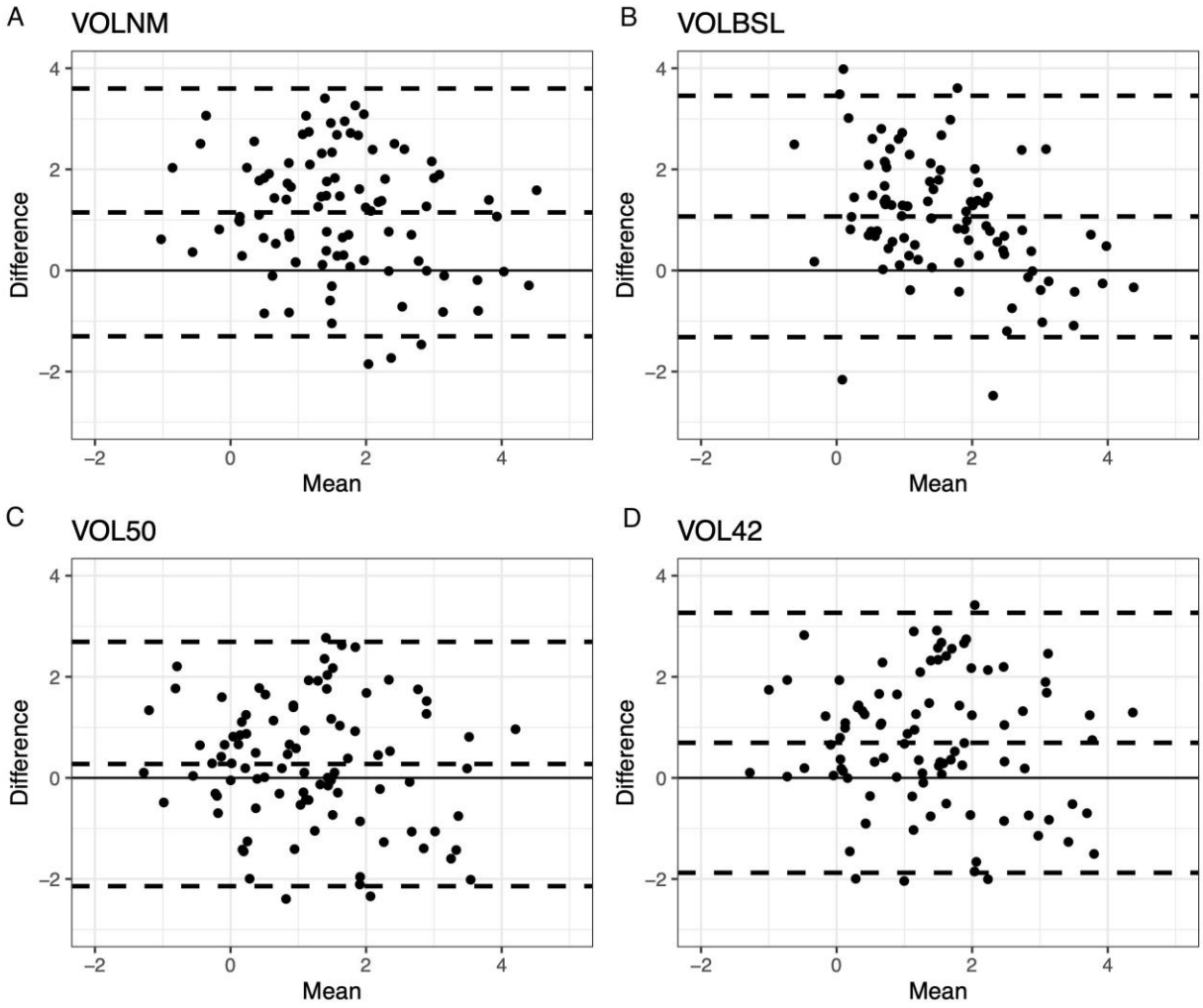


Figure 4. Bland–Altman scatterplots. Plots show the relative difference between FTV method as labeled and the morphologic volume on the y-axis and mean volume of the FTV method as labeled and morphologic volume on the x-axis. The dashed lines represent the upper limits of agreement, lower limits of agreement, and bias (or mean difference). A log-transformation was used to correct the skewness in the distribution of the volumes. A. VOLNM = Manual volume from the PET imaging; B. VOLBSL = Background subtracted lesion method; C. VOL50 = Threshold of 50% relative to SUVmax; D. VOL42 = Threshold of 42% relative to SUVmax.



Graphical Abstract