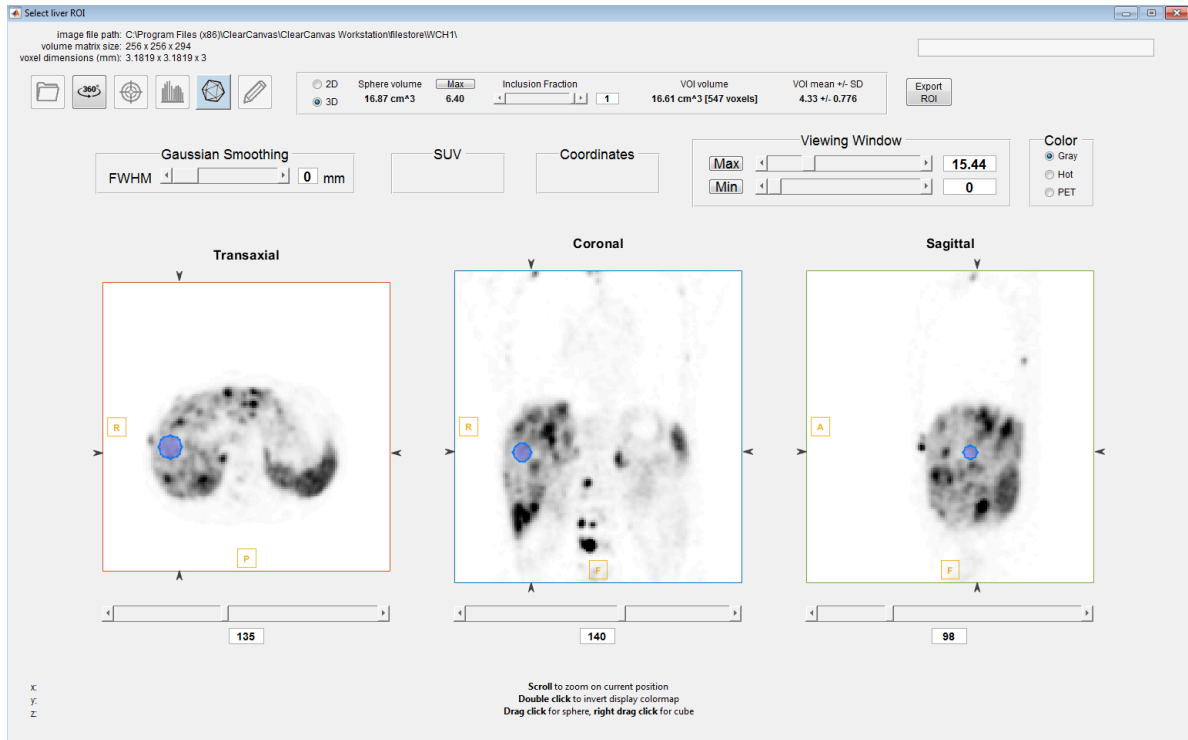
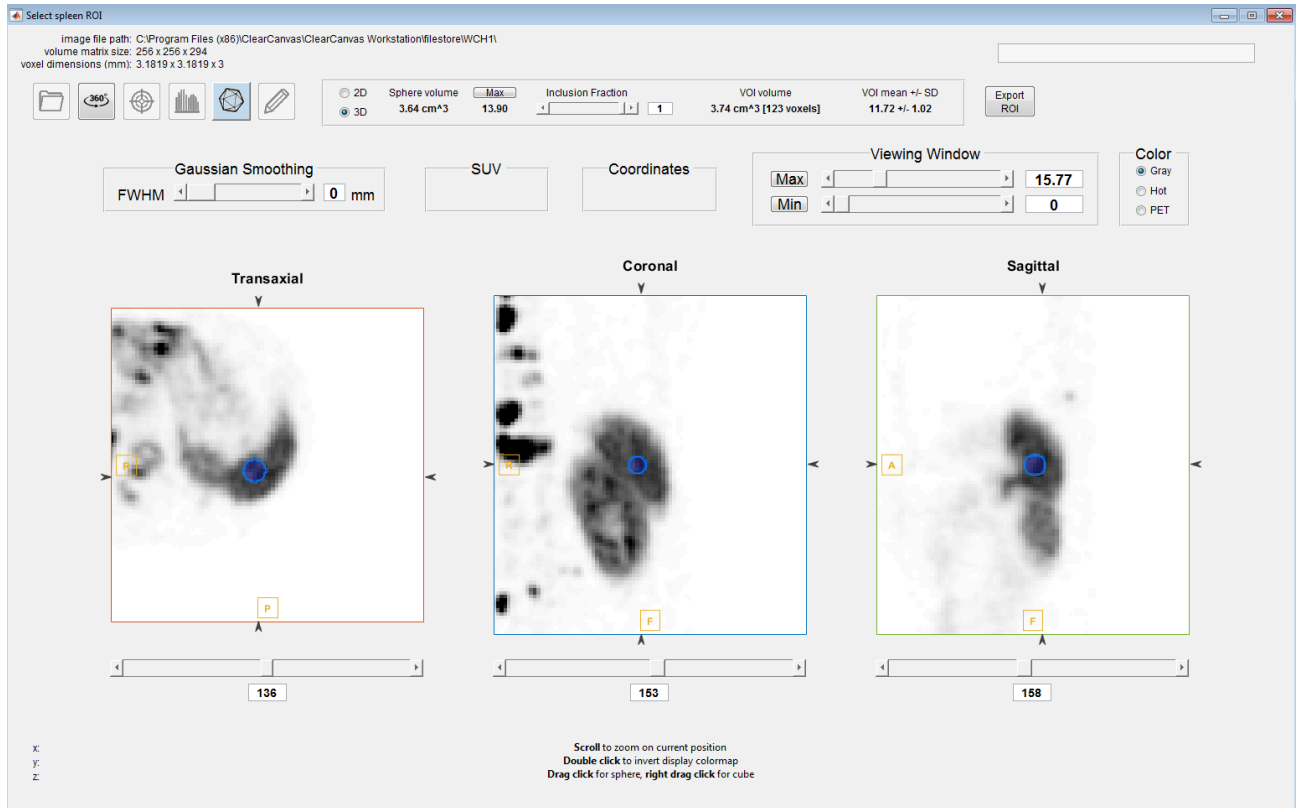


SUPPLEMENTAL FIGURE 1. Step-by-step demonstration of tumor segmentation method using a semi-automated whole-body tumor volume contouring software

Whole body DTTV was generated using the in house developed automated segmentation tool using reference tissues as threshold. For each patient, PET masks were defined by all somatic voxels having values above a defined threshold, and then regions of normal uptake were manually removed leaving only those corresponding to the tumors.



Supplemental Figure 1A: Step 1. A VOI is placed in normal liver parenchyma (avoiding metastases if present) to define the lower threshold used for segmentation

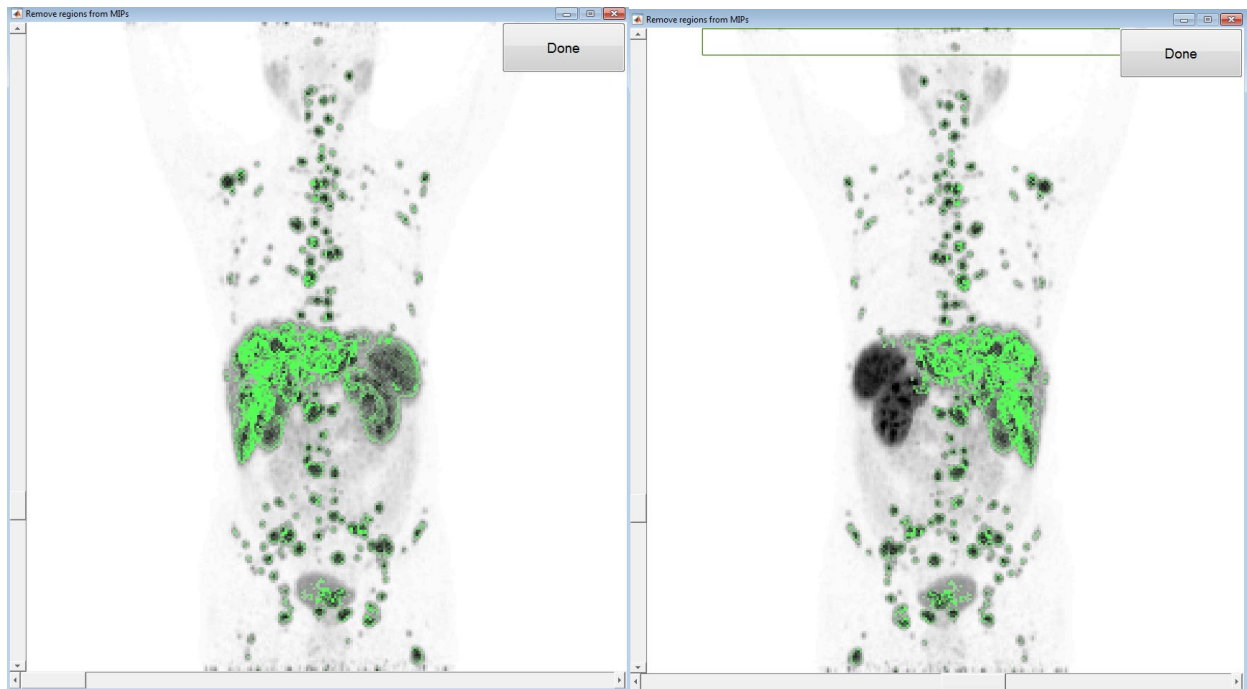


Supplemental Figure 1B: Step 2. A VOI is placed in normal spleen parenchyma to defined upper threshold for volume segmentation.

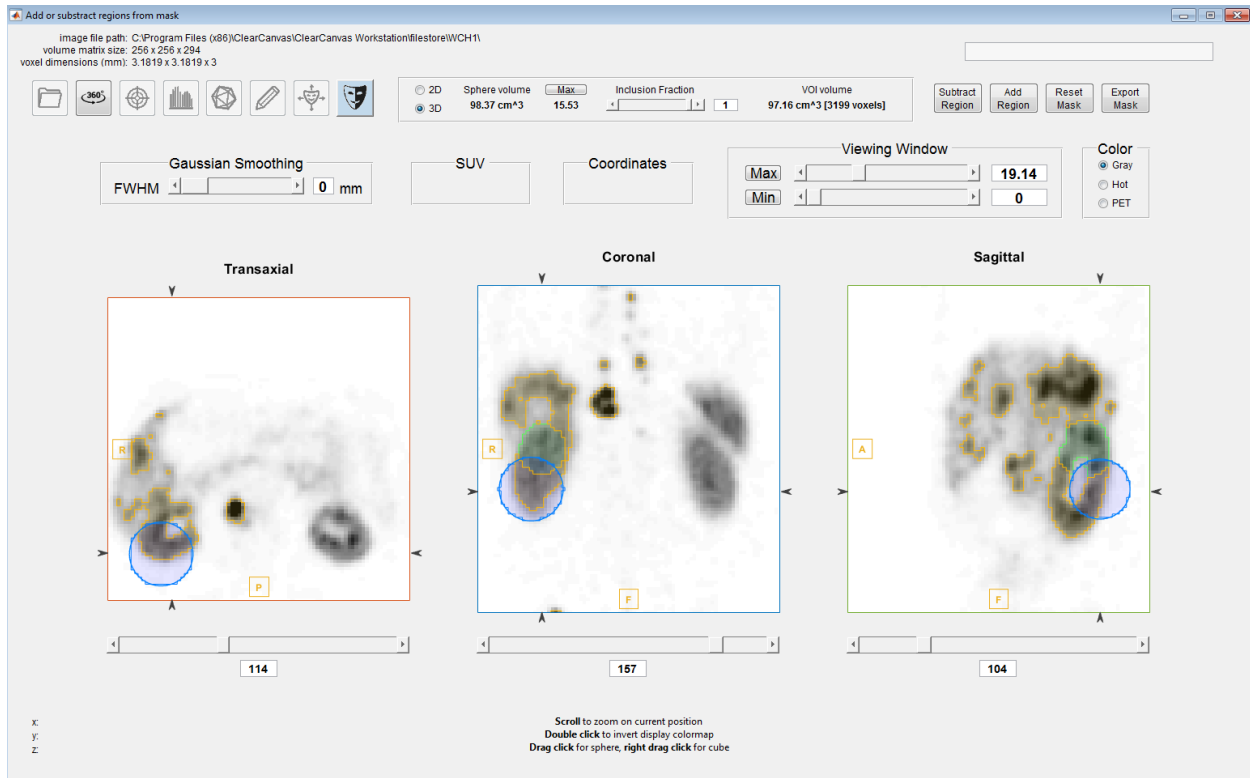
Use?	Method	Threshold						
		Max	Mean+X*SD	Mean	X	Std. Dev		
<input checked="" type="checkbox"/>	Liver	6.4	6.6 =	4.3	+	3	*	0.78
<input checked="" type="checkbox"/>	Spleen	13.9	14.8 =	11.7	+	3	*	1.02
<input type="checkbox"/>	Parotid				+		*	
<input type="checkbox"/>	Blood				+		*	
<input type="checkbox"/>	Manual							

GO

Supplemental Figure 1C: Step 3. After the thresholds are defined, the software will automatically generate a mask with all the somatic voxels containing values above the defined threshold.



Supplemental Figure 1D: Step 4. From the generated mask, all areas of physiologic tracer uptake are manually removed (in 3D mode).



Supplemental Figure 1E: Step 5. Further correction of the segmentation using 2D images.

	A	B	C	D	E	F	G	H	I
1	Subject	Ref SUVmax (LIVER)	Ref SUVmax (SPLEEN)	TV volume (LIVER)	TV volume (SPLEEN)	TV SUV max	TV SUV mean (LIVER)	TV SUV mean (SPLEEN)	
2	WCH1	6.4	13.9	726.8369751	147.4935455	61.25040817	11.55508232	21.76831436	
3									

Supplemental Figure 1F: Step 6. The obtained results from the generated volumes are presented in a spreadsheet. These includes: The references values of the defined thresholds, the volume of the tumor (in cc), and the SUVmax and SUVmean within the tumor volume using liver and spleen as thresholds.

Supplemental Table 1. iPET / bPET ratios

iPET / bPET ratios					
		All (n=36)	R (n=30)	NR (n=6)	p-value
Reference	SUVmaxLiver	1.1 ± 0.2 (0.7, 1.8)	0.9 ± 0.2 (0.8,1.2)	1.1 ± 0.4 (0.6, 2.2)	0.046
Tissue					
Median±SD (min max)	SUVmaxSpleen*	1.2 ± 0.4 (0.6, 2.2)	1.2 ± 0.4 (0.6, 2.2)	1.1 ± 0.3 (0.8, 1.5)	0.28
Lesion-based	MeanSUVmax	0.9±0.3 (0.3,1.9)	0.9±0.3 (0.3,1.9)	0.8±0.1 (0.6,1)	0.24
Median±SD (min,max)	MeanSUVmaxT/L	0.8±0.3 (0.2,1.4)	0.8±0.3 (0.2,1.4)	0.8±0.2 (0.6,1.1)	0.85
	MeanSUVmaxT/S*	0.8±0.2 (0.2,1.4)	0.8±0.3 (0.2,1.4)	0.7±0.2 (0.5,1)	0.82
DTTV	DTTV_{liver(cc)}	0.8 ± 0.6 (0.2,3.3)	0.8 ± 0.7 (0.2,3.3)	0.8 ± 0.5 (0.5,1.7)	0.45
Median±SD (min,max)	DTTV_{spleen(cc)}	0.7 ± 0.8 (0,4.1)	0.8 ± 0.8 (0,4.1)	0.8 ± 0.3 (0,4.1.1)	0.81
	DTTVSUV_{max}	0±0.3 (-0.9,1)	0±0.4 (-0.9,1)	0.2±0.2 (-0.1,0.3)	0.22
	DTTV SUV_{mean}Liver	0.7±0.3 (0,1.9)	0.6±0.1 (0,1.9)	0.7±0.3 (0.6,0.8)	0.45

	DTTV SUV_{mean}Spleen	1.1±0.4 (0,1.9)	1.1±0.5 (0,1.9)	1.1±0.2 (0.8,1.3)	0.56
Heterogeneity Median±SD (min,max)	CoV	0.9±0.5 (0.3,1.9)	0.9±0.5 (0.3,1.9)	0.9±0.3 (0.6,1.2)	0.6
	Skewness	0.9±1.5 (0.1,8.8)	1±1.6 (0.1,8.8)	0.7±0.8 (0.2,2.5)	0.29
	Kurtosis	0.9±1.3 (0.1,4.9)	0.7±1.3 (0.1,4.9)	0.9±1.4 (0.2,3.8)	0.31

Supplemental Table 1. Interim PET (iPET)/bPET ratios for reference tissues, lesion-based tumor parameters, DTTV parameters and first order heterogeneity measures.

P-values are shown. R=responders; NR=non-responders; DTTV=DOTATATE tumor volume;

SUV_{max}T/L = meanSUV_{max}/ SUV_{max} liver; SUV_{max}T/S= meanSUV_{max}/ SUV_{max} spleen.

SUV_{mean}Liver/ spleen=meanSUV in segmented volume using liver/spleen as threshold.

SD=standard deviation; CoV=coefficient of variance.

UVA		HR (95%CI)	p-value
bPET Parameter			
Demographic	Age	0.97 (0.93,1.02)	0.24
	Gender		0.4
	F	Reference	
	M	1.54 (0.57,4.16)	
	Ki 67	0.99 (0.93,1.05)	0.67
Reference tissues	Reference SUVmax	1.13 (0.78,1.63)	0.52
	Liver		
	Reference SUVmax	0.99 (0.92,1.06)	0.72
	Spleen*		
Lesion-based	Mean SUVmax	0.98 (0.97,1)	0.023
	SUVmax T/L	0.92 (0.85,0.99)	0.028
	SUVmax T/S	0.86 (0.75,1)	0.047
Tumor volume	DTTV _{Liver}	1 (1,1)	0.99
	DTTV _{Spleen}	1 (1,1)	0.61
	DTTV SUV max	0.99 (0.99,1)	0.13
	DTTV SUV _{mean} Liver	0.92 (0.87,0.98)	0.0053
	DTTV SUV _{mean} Spleen	0.98 (0.95,1.01)	0.13
Heterogeneity	CoV	0.62 (0.14,2.67)	0.52
	Skewness	1.49 (1.07,2.07)	0.017
	Kurtosis	1.06 (1.01,1.11)	0.022

iPET Parameter			
Reference tissues	Reference SUVmax	0.89 (0.61,1.28)	0.53
	Liver		
	Reference SUVmax	0.98 (0.91,1.05)	0.55
	Spleen*		
Lesion-based	Mean SUVmax	1 (0.97,1.03)	0.96
	SUVmax T/L	0.99 (0.87,1.13)	0.88
	SUVmax T/S	0.9 (0.6,1.33)	0.59
Tumor volume	DTTV _{Liver}	1 (1,1)	0.83
	DTTV _{Spleen}	1 (1,1)	0.5
	DTTV SUVmax	1 (0.99, 1.01)	0.96
	DTTV SUV _{mean} Liver	0.95 (0.86, 1.06)	0.36
	DTTV SUV _{mean} Spleen	0.99 (0.95, 1.03)	0.69
Heterogeneity	CoV	1.57 (0.07, 38.08)	0.78
	Skewness	1.41 (0.72,2.77)	0.32
	Kurtosis	1.07 (0.95,1.2)	0.27
iPET/bPET ratios			
Reference tissues ratio	Reference SUVmax	0.01 (2.1e-04,0.5)	0.021
	Liver		
	Reference SUVmax	0.42 (0.05,3.45)	0.42
	Spleen*		
Lesion-based ratio	Mean SUVmax	0.49 (0.09,2.59)	0.4
	SUVmax T/L	1.31 (0.21,8.04)	0.77

	SUVmax T/S	0.66 (0.09,5.09)	0.69
Tumor volume ratio	DTTV _{Liver}	1.29 (0.62,2.7)	0.49
	DTTV _{Spleen}	0.79 (0.29,2.11)	0.64
	DTTV SUVmax	0.48 (0.07,3.27)	0.46
	DTTV SUV _{mean} Liver	0.97 (0.11,8.24)	0.98
	DTTV SUV _{mean} Spleen	1.24 (0.3,5.15)	0.63
Heterogeneity ratio	CoV	0.75 (0.2,2.77)	0.66
	Skewness	1 (0.57,1.75)	0.99
	Kurtosis	1.15 (0.75,1.76)	0.53

Supplemental Table 2. Complete univariate analysis of lesions-based, TV based and heterogeneity parameters including at baseline (bPET), interim PET (iPET), and iPET/bPET ratios as predictors of PFS.

P-values of Cox proportional hazards model are shown. HR=hazard ratio; 95% CI=95% confidence interval; SUVmax T/L=mean SUVmax/ SUVmax liver; SUVmax T/S=mean SUVmax/SUVmax spleen;

DTTV_{Liver/spleen}= ⁶⁸Ga-DOTATATE tumor volume with liver or spleen as threshold; DTTV SUV_{mean} Liver/Spleen=meanSUV from tumor volume obtained with liver or spleen as threshold. CoV=coefficient of variance. PFS=progression free survival.