

Initial and Iterative Thresholding Segmentation Algorithms

The main difference between the max-ITM and avg-ITM is that the maximum AC and the average AC, respectively, are used to calculate the boundary-reproducing thresholds. Most importantly, the maximum AC remains constant in the max-ITM, whereas the average AC in the avg-ITM is changed in each iteration step. Before application, both ITMs require appropriate initial values that are determined in the initial segmentation algorithm and are further used in the subsequent iterative thresholding segmentation algorithm.

Initial Segmentation Algorithm

The initial segmentation algorithm is shown in Supplemental Figure 1 using a representative tumor image located in the head-neck region. The tumor of interest is selected (white box in Supplemental Fig. 1A). The lower window level (in kBq/mL) is set to zero, whereas the upper window level (in kBq/mL) is sufficiently low for the tumor background to be clearly visible (Supplemental Fig. 1B). To estimate the (average) background AC (B), a background volume of interest (VOI) as a 3D shell (with a thickness of approximately the voxel size) around the object is defined with sufficient distance from the prospective object (Supplemental Fig. 1C). As demonstrated in Supplemental Material, a sufficient distance means that the contour of the 3D background shell should be close to the object boundary (to obtain a reasonable background) while maintaining a distance of approximately the PET spatial resolution (to avoid contribution from the tumor signal caused by spill-out effect). After setting the lower window level to B and the upper window level to an appropriate value, depending on the activity distribution within the tumor, the resulting contours are used to guide the VOI drawing to obtain the initial tumor VOI (red line in Supplemental Fig. 1D). The initial tumor VOI is stored as a template for further use. Thus, the initial segmentation algorithm procedure yields the initial average AC ($I_{\text{init,avg}}$), initial tumor volume (V_{init}), and the background (B) that are further used in the subsequent iterative segmentation algorithm.

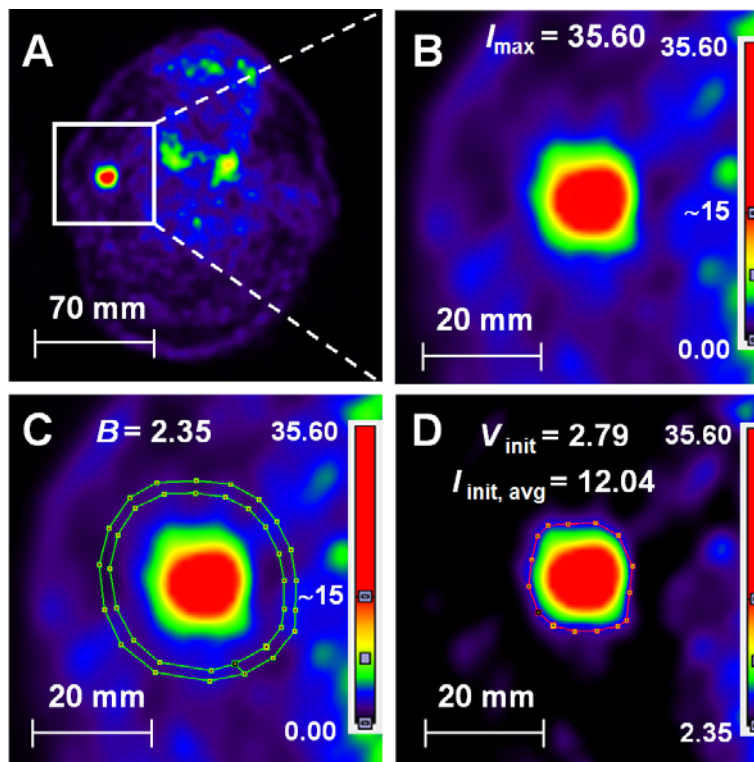
Iterative Thresholding Segmentation Algorithm

The flow-chart of the iterative thresholding segmentation algorithm is illustrated in Supplemental Figure 3. After calculating the sphere-equivalent diameter using $d_0 = (V_{\text{init}} \cdot 6/\pi)^{1/3}$, the $d_0/FWHM$ ratio is calculated and used to determine the corresponding average-based BRT value from Figure 1. Equation 1 is used to calculate the resulting threshold, T_1 , from the initial average AC, $I_{0,\text{avg}} = I_{\text{init,avg}}$, that is, $T_1 = (I_{0,\text{avg}} - B) \cdot S_{\text{avg}}(d_0/FWHM) + B$. Note that the subscript “0” on the symbols indicates the zero iteration step ($m=0$). The initial tumor VOI that was defined in the initial segmentation algorithm (red line in Supplemental Fig. 1D) is loaded, and the 3D automatic threshold procedure at T_1 is applied. This procedure produces a first-iteration tumor VOI with surface voxel values that are larger than or equal to T_1 . Thereafter, the analysis of the first-iteration tumor VOI yields improved estimations of the volume (V_1) and the average AC ($I_{1,\text{avg}}$). In the next iteration, the values are used to calculate a threshold T_2 , that is, $T_2 = (I_{1,\text{avg}} - B) \cdot S_{\text{avg}}(d_1/FWHM) + B$. The symbol d_1 is the diameter of an equivalent sphere with volume V_1 . After reloading the template tumor VOI and applying the 3D automatic threshold procedure at T_2 , a second-iteration tumor VOI is obtained. This analysis produces the volume (V_2) and the average AC ($I_{2,\text{avg}}$). These values are used in a third iteration to calculate the threshold T_3 . Further iterations follow until one of the termination criteria is satisfied. The algorithm terminates either if the current volume (at T_m) equals the previous volume (at T_{m-1}) or if the segmented tumor volume is less than the minimum volume. As shown in the results section, the minimum volume (V_{min}) is an equivalent sphere with a diameter that equals the PET spatial resolution ($V_{\text{min}} = \pi/6 FWHM^3$).

Signal Contribution Outside the Object Boundary to Estimate the Sufficient Distance for Drawing the 3D Background Shell

A reasonable estimate of the background AC (B) surrounding the tumor is required in the application of the avg-ITM. Because the imaging process causes blurring of the true tumor signal, and a part of the signal lies outside the true tumour boundary, and therefore, contributes to the background. Thus, to obtain a reasonable background AC, the spill-out effect must be accounted for when drawing the 3D background shell around the tumor. The signal contribution of the tumor to the background depends on the distance of the 3D

background shell from the tumor boundary and the size of the tumor. In a sphere model, the AC as a function of the distance from the sphere surface can be calculated by convoluting techniques. Supplemental Figure 2 shows the distance from the sphere boundary (in units of spatial resolution) as a function of the sphere diameter (in units of spatial resolution) at which the imaged AC has declined to values of 1%, 2%, and 5% of the maximum AC. It can be inferred that the spill-out effect at a distance (from the sphere boundary) of the spatial resolution is less than 1% for a sphere with a diameter that equals or exceeds the spatial resolution.



SUPPLEMENTAL FIGURE 1. Illustration of the initial segmentation algorithm (A–D). Units are in kBq/mL for imaged ACs (I) and in mL for volumes (V). White box indicates the tumor of interest (A). The lower threshold is set to zero, whereas the upper threshold is sufficiently low for the background to be clearly visible (B). The 3D background shell for determination of the background AC is indicated in green (C). The red line indicates the initial tumor VOI (D). Rainbow-color map is used for visualization.

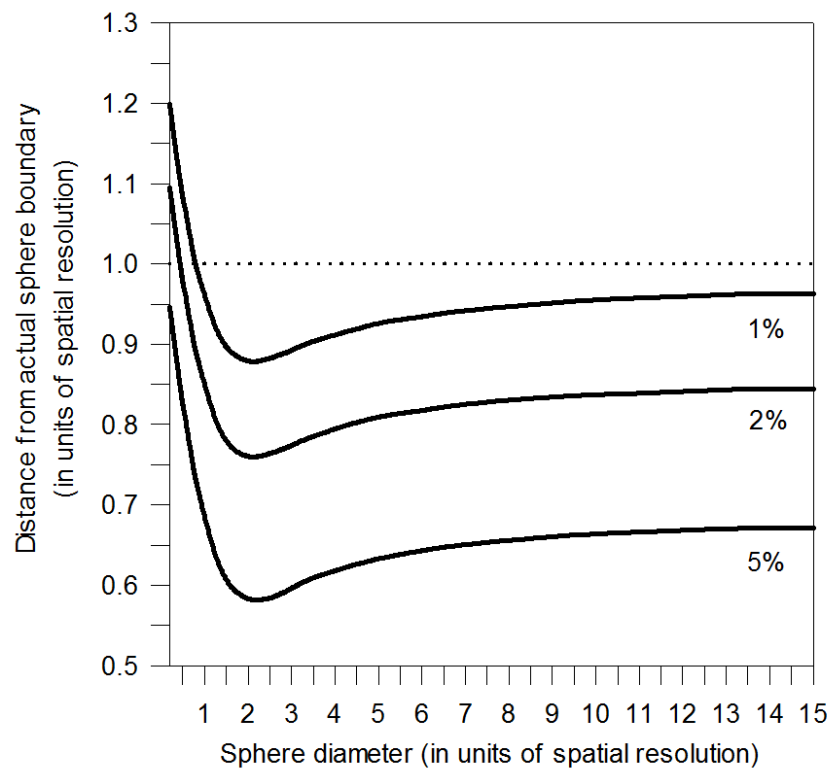


FIGURE 2. Distance (in units of spatial resolution) of the signal from the actual sphere boundary at which the AC is dropped to 1%, 2%, or 5% of the maximum AC as a function of the sphere diameter (also in units of spatial resolution). Dotted line denotes the sufficient distance for estimating the background AC for sphere diameters larger than or equal to spatial resolution.

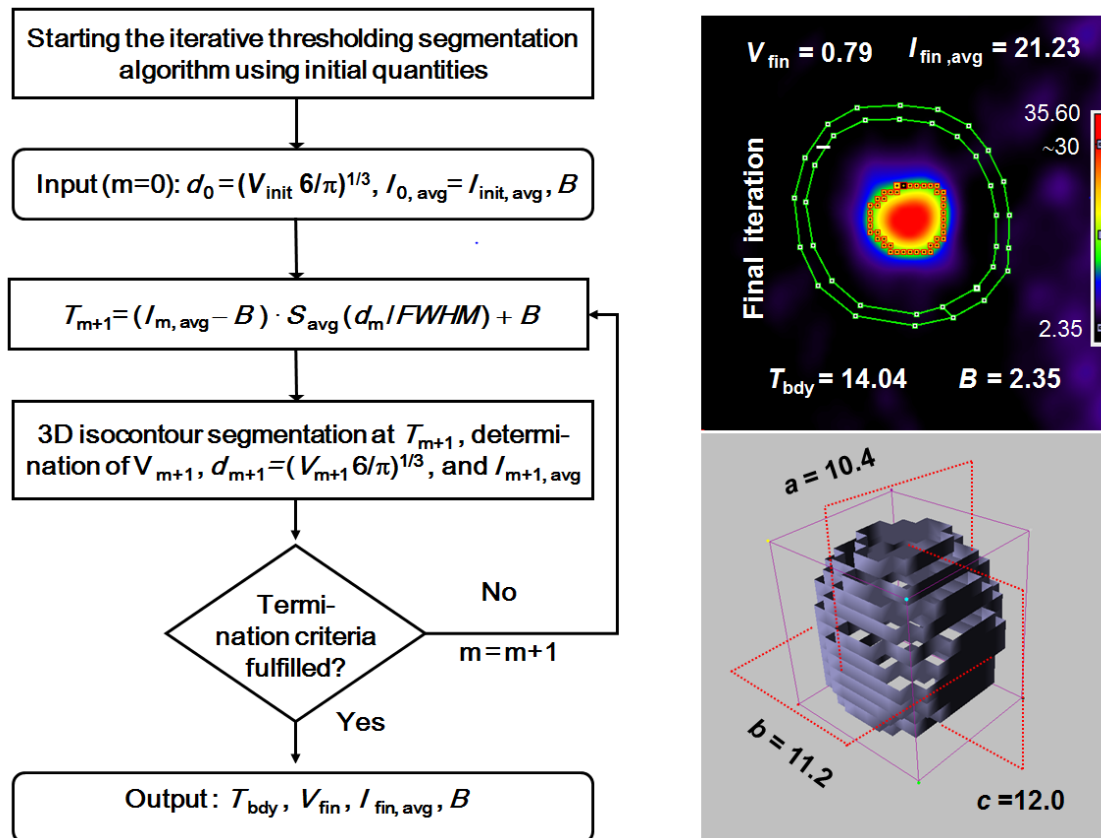


FIGURE 3. Flow-chart of the iterative thresholding segmentation algorithm for the avg-ITM (left). Final results are obtained (T_{bdy} , V_{fin} , $I_{\text{fin, avg}}$). In the image (right, top), final object VOI (red) and the background 3D shell (green) are shown. Rainbow-color map is used in the image. A 3D segmented tumor image is also shown (right, bottom). Imaged ACs and thresholds are shown in units of kBq/mL. The volumes and extensions (a , b , c) are shown in units of mL and mm, respectively.

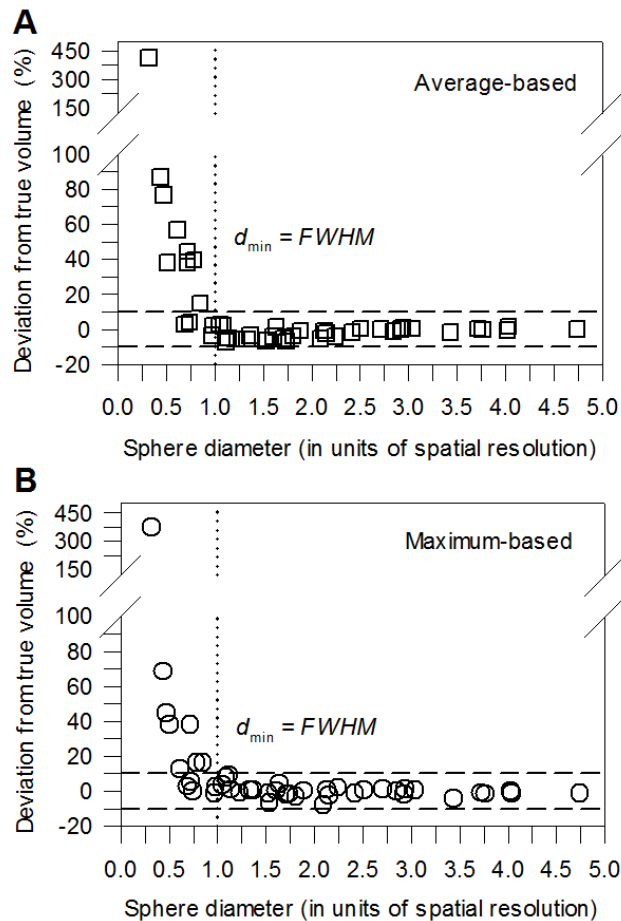


FIGURE 4. Percentage deviations between segmented sphere volumes derived using either the avg-ITM (A) or the max-ITM (B) and true volumes. Acceptable ranges ($\pm 10\%$) are indicated by horizontal dashed lines. Vertical dotted lines represent the minimum diameter.

SUPPLEMENTAL TABLE 1

Average-based and Maximum-based BRT Values as a Function of the Ratio of
Diameter (d) to PET Spatial Resolution ($FWHM$)

$d/FWHM$	S_{avg}	S_{max}	$d/FWHM$	S_{avg}	S_{max}
0.450	94.07	87.58	1.625	67.64	41.68
0.500	93.07	85.08	1.750	65.90	40.11
0.550	92.00	82.49	1.875	64.56	39.00
0.600	90.84	79.82	2.000	63.28	38.26
0.650	89.60	77.12	2.500	59.84	37.73
0.700	88.29	74.41	3.000	57.75	38.94
0.750	86.89	71.72	3.500	56.37	40.35
0.800	85.42	69.09	4.000	55.44	41.53
0.850	84.27	66.53	5.000	54.15	43.22
0.900	82.91	64.06	7.500	52.60	45.48
0.950	81.58	61.68	10.00	51.90	46.61
1.000	80.26	59.43	15.00	51.23	47.74
1.125	77.28	54.33	20.00	50.85	48.31
1.250	74.25	50.04	30.00	50.43	48.87
1.375	71.82	46.56	40.00	50.41	49.15
1.500	69.48	43.80	50.00	50.28	49.32

SUPPLEMENTAL TABLE 2

Inter- and Intra-observer Variability of the Volumes (in mL) Assessed by Calculating the Relative Standard Deviation (*RSD*) Obtained from Five Real Tumors and Analyzed by Five Observers (WJ, AM, AP, DW, VH) Using the Avg-ITM (Avg.) and Max-ITM (Max.)

Observer/ RSD	Tumor 1 (neck)		Tumor 2 (back)		Tumor 3 (axilla)		Tumor 4 (neck)		Tumor 5 (neck)	
	Avg.	Max.	Avg.	Max.	Avg.	Max.	Avg.	Max.	Avg.	Max.
WJ	3.86	3.24	0.48	0.45	0.83	0.73	1.06	0.93	1.38	1.18
AM	3.74	3.19	0.47	0.45	0.82	0.68	0.98	0.90	1.35	1.17
AP	3.96	3.30	0.48	0.47	0.85	0.70	1.06	0.92	1.38	1.19
VR	3.89	3.26	0.47	0.45	0.86	0.71	1.09	0.94	1.37	1.18
DW	3.84	3.23	0.46	0.45	0.86	0.72	1.06	0.92	1.36	1.18
<i>RSD (%)</i>	±2.1	±1.2	±1.8	±2.0	±2.2	±2.7	±3.9	±1.6	±5.0	±0.6
WJ	3.86	3.24	0.48	0.45	0.83	0.73	1.06	0.93	1.38	1.18
WJ	3.82	3.22	0.59	0.48	0.89	0.73	1.03	0.94	1.37	1.18
WJ	3.81	3.22	0.47	0.46	0.86	0.71	1.11	0.95	1.36	1.18
WJ	3.79	3.20	0.53	0.48	0.85	0.71	1.02	0.9	1.37	1.18
WJ	3.73	3.18	0.53	0.48	0.86	0.70	1.10	0.95	1.36	1.17
<i>RSD (%)</i>	±1.3	±0.70	±9.2	±3.0	±2.5	±1.9	±3.8	±2.2	±0.6	±0.4