Prognostic value of SUR in patients with trimodality treatment of locally advanced esophageal carcinoma

Note: Except where stated differently, "SUV" denotes "lean body mass SUV".

Correction of SUR values for variable uptake time

According to Eq. 1, correction of SUR for variable uptake time, i.e. normalization of all measured lesion-to-blood ratios SUV/BSUV to a common reference uptake time T_0, is achieved by scaling the measured SUV/BSUV ratio with the ratio of reference and actual uptake time, T_0/T . We provide here a concise derivation of this equation. The interested reader can find a more comprehensive explanation and validation of the approach in (*1*, *2*).

Uptake time dependence of SUR is described by the Patlak equation (*3*, *4*)

$$\mathrm{SUR}(T) = \frac{\mathrm{SUV}(T)}{\mathrm{BSUV}(T)} = K_m \times \frac{\int_0^T \mathrm{BSUV}(s)ds}{\mathrm{BSUV}(T)} + V_r\,. \tag{S1}$$

K_m is the lesion's metabolic rate of FDG accumulation and V_r is the so-called apparent volume of distribution (y-axis intercept of the Patlak plot). Since empirically, starting early after injection, the AIF quite accurately follows an inverse power law (*1*)

$$\mathrm{BSUV}(T) = A \times T^{-b} \quad (T > 1\,\mathrm{min})\,, \tag{S2}$$

with $b \approx 0.3$, the integral in Eq. S1 can be computed and the Patlak equation becomes

$$\mathrm{SUR}(T) = \frac{K_m}{1-b} \times T + V_r\,. \tag{S3}$$

At least for the long uptake times $T \gtrsim 60$ minutes relevant in whole body FDG-PET, it further turns out that it is permissible to neglect the constant V_r (*2*) since $V_r \ll \mathrm{SUR_T}$ so that we finally arrive at

$$\mathrm{SUR}(T) = \frac{K_m}{1-b} \times T\,. \tag{S4}$$

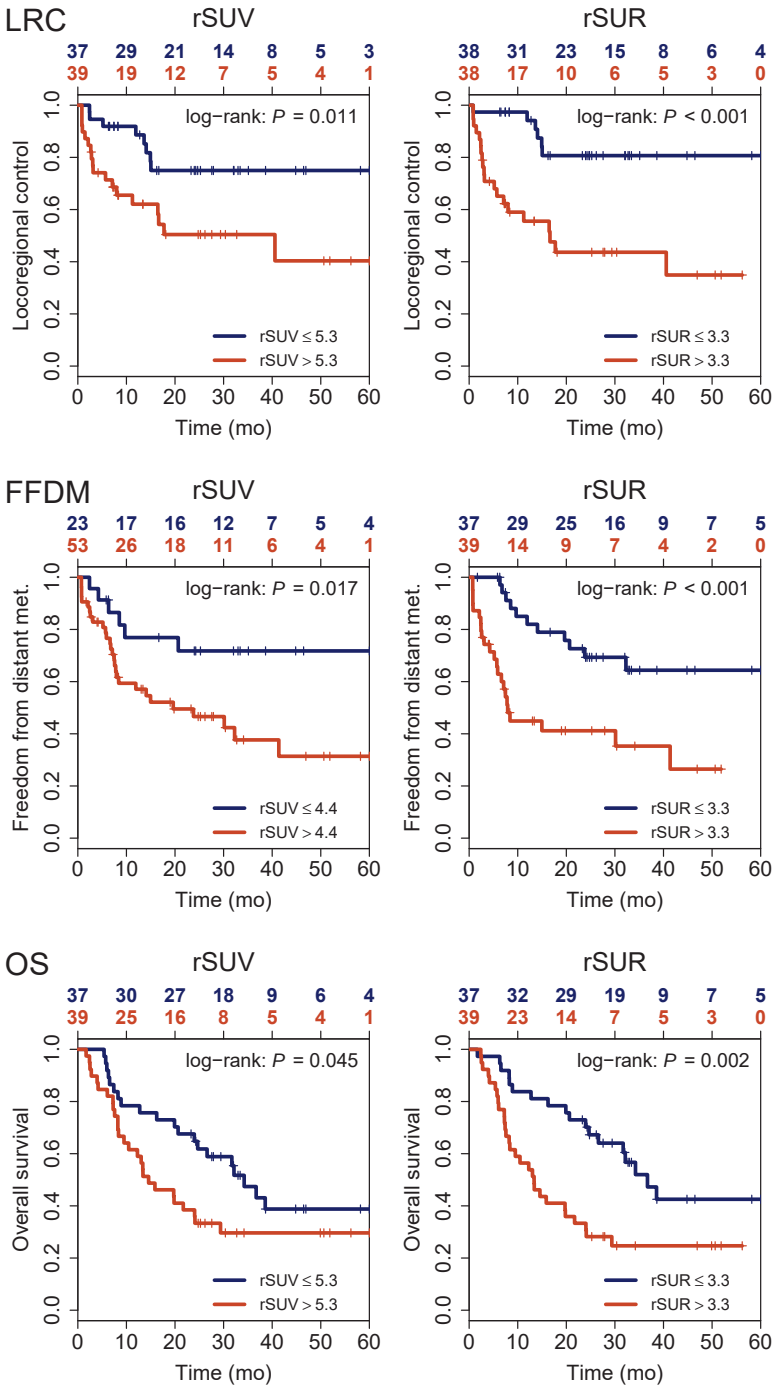
Therefore, it follows that $\mathrm{SUR}(T_0)/\mathrm{SUR}(T) = T_0/T$ and thus

$$\mathrm{SUR}(T_0) = \frac{T_0}{T} \times \mathrm{SUR}(T) \tag{S5}$$

which is identical to Eq. 1.

Comparison of rSUV and rSUR

Kaplan-Meier analysis for a direct comparison of restaging SUV and SUR was performed. Results are shown in Supplemental Figure 1.

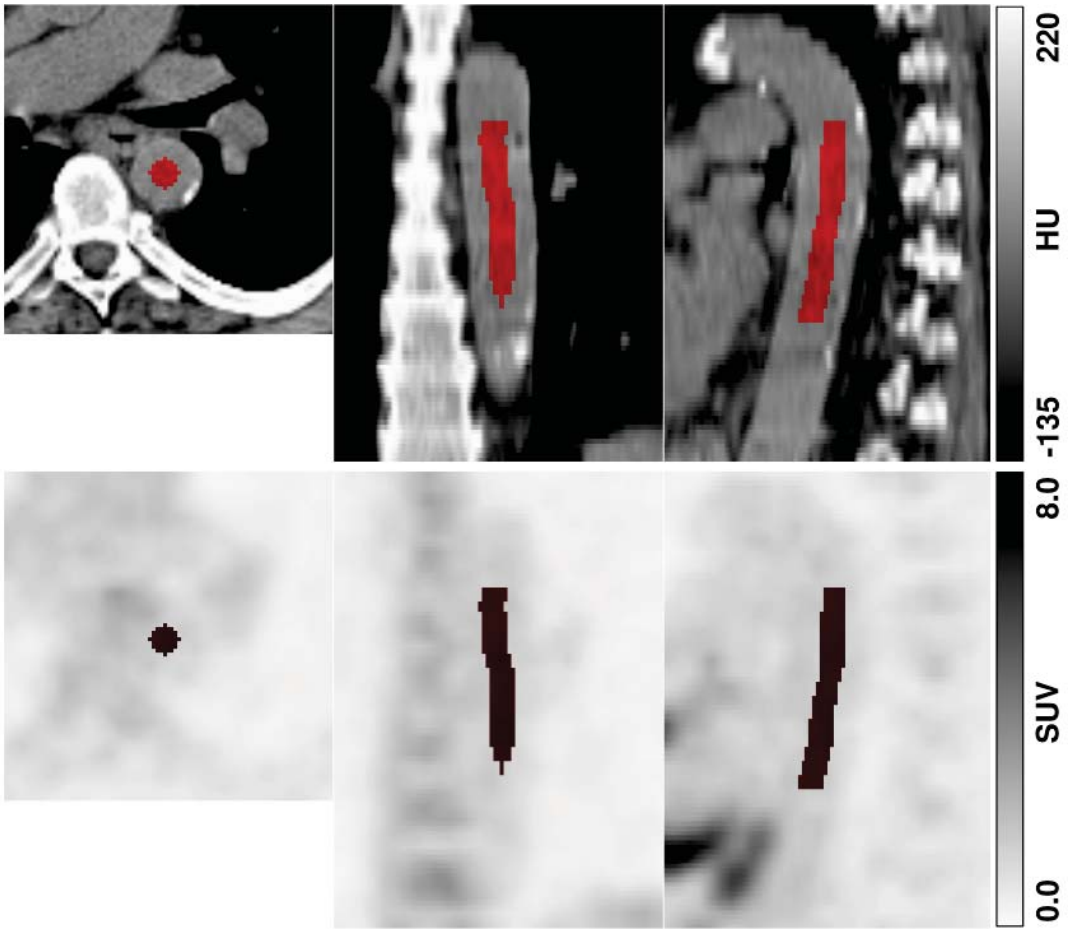


SUPPLEMENTAL FIGURE 1 Kaplan-Meier curves with respect to LRC, FFDM and OS.

Aorta ROI definition for blood SUV determination

SUR computation requires knowledge of the arterial blood SUV (BSUV) which is determined in the aorta. For this purpose, a 3D ROI is defined as follows in the attenuation CT starting below the aortic arch in the lumen of the descending aorta using a dedicated software.

Small circular 2D ROIs are positioned at the center of the aorta in consecutive transaxial planes, choosing a ROI diameter such that a distance of 8 mm to the aortic wall is maintained everywhere to avoid partial volume effects (signal spill out). Planes exhibiting high tracer uptake (pathological or otherwise) close to



SUPPLEMENTAL FIGURE 2 Example of aorta ROI definition.

the aorta are excluded to ensure absence of any signal spill in from the vicinity.

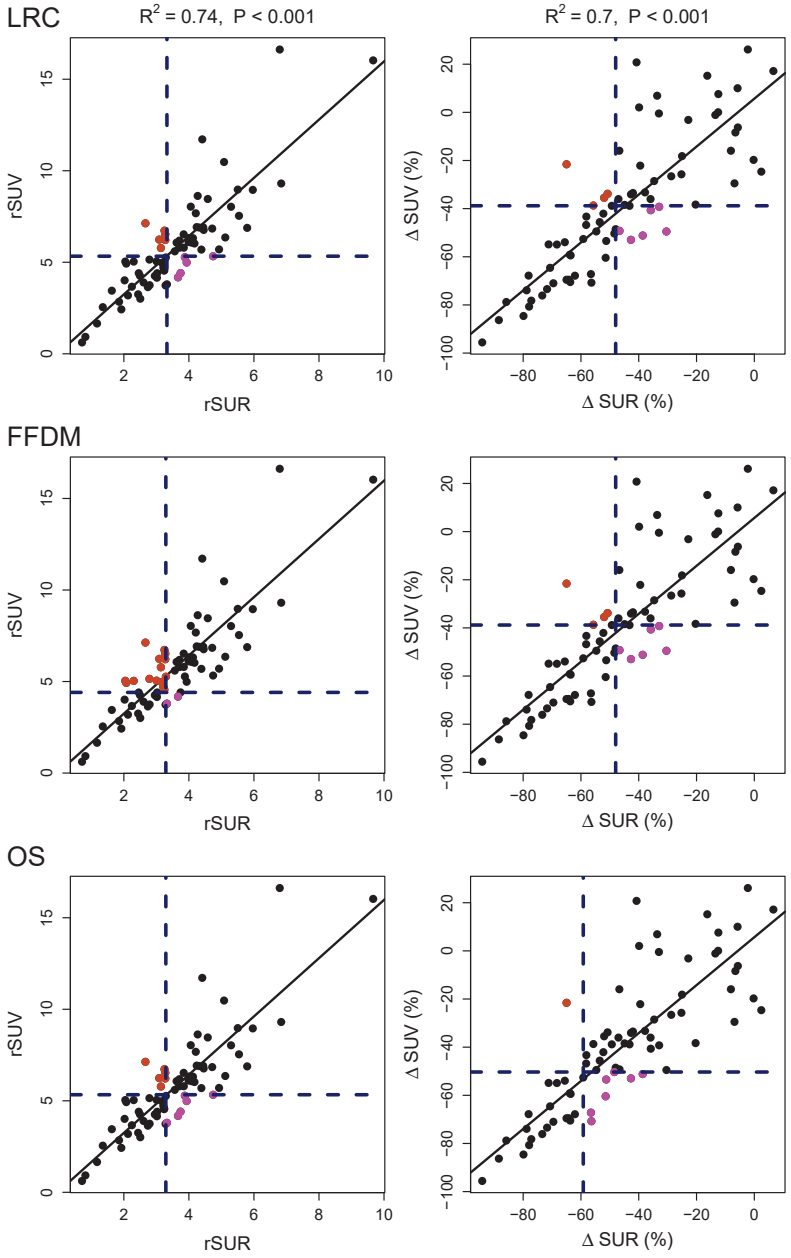
The resulting stack of circular 2D ROIs defines the complete 3D ROI which is then transferred to the PET image for evaluation. Supplemental Figure 2 shows one example of such an aorta ROI. BSUV is computed as mean value of the aorta ROI (for which a minimum volume of 5 ml is observed to ensure high statistical accuracy).

SUPPLEMENTAL TABLE 1 Summary statistics of investigated PET parameters.

Parameter	Mean ± SD	Median	IQR	Range
Baseline PET				
MTV (ml)	21.2±21.9	14.6	7 – 28.8	0.5 – 131.5
TLG (ml)	166.6±206.1	89.9	38.5 – 236	2.4 – 1077.6
SUV	11.2±5.8	9.9	7 – 14	2.4 – 31.1
SUR	7.7±4.1	6.5	5.5 – 8.7	2.2 – 21.5
Re-staging PET				
rMTV(ml)	9.2±11.8	5.9	2.3 – 11.4	0.08 – 76.7
rTLG(ml)	38.5±52	22.4	9.1 – 49.4	0.05 – 300.9
rSUV	5.8±2.7	5.6	4.2 – 6.8	0.6 – 16.6
rSUR	3.6±1.4	3.4	2.7 – 4.3	0.7 – 9.7
Fractional difference				
Δ MTV (%)	-47.3±43.7	-61	-76.9 – -25.2	-99.7 – 88.1
Δ TLG (%)	-60.1±43.6	-72.5	-90.1 – -43.6	-100 – 114.9
Δ SUV (%)	-39.5±28.5	-39.9	-59.7 – -22	-95.6 – 26.1
Δ SUR (%)	-45.3±24	-47.5	-63.7 – -32.3	-94.2 – 6.6

Correlation of SUV and SUR

As is to be expected, SUV and SUR are significantly (P<0.001) correlated (baseline PET: R^2 = 0.86, restaging PET: R^2 = 0.74, fractional difference: R^2 = 0.7). Supplemental Figure 3 shows scatterplots for restaging PET and fractional difference together with the optimal cutoff values for LRC, FFDM, and OS, respectively (dashed lines). As can be seen, a substantial number of patients is reclassified from low to high risk or vice



SUPPLEMENTAL FIGURE 3 Correlation of SUV and SUR in restaging PET (left) and fractional difference of baseline PET and restaging PET(right). Solid lines represent the least squares straight line fits to the data. Dashed lines depict the optimal cutoff values for LRC (top), FFDM (middle), and OS (bottom), respectively.

versa when switching from SUV to SUR (restaging LRC: N= 11, FFDM: N= 18, OS: N= 12; fractional difference LRC: N= 10, FFDM: N= 10, OS: N= 8) and this reclassification ultimately leads to the improved prognostic value of SUR.

Cutoff stability

Stability of optimal cutoff values for all parameters and endpoints was tested using the bootstrap method (random resampling with replacement, 10^5 samples). In each case, the optimal cutoff determined in the original data was used for all bootstrap samples as the common cutoff defining the high and low risk groups. For each parameter/endpoint the procedure was as follows.

For each generated sample, univariate Cox regression was performed. The resulting hazard ratios (HR) and P-values were averaged over all samples. The cutoff determination for the considered parameter/endpoint was judged to be stable if $P_{\text{mean}} < 0.1$ was obtained. Additionally, the percentage of samples yielding P< 0.05 and P< 0.1, respectively, was determined in each case. The latter numbers can be viewed as the probabilities that the cutoffs derived in the present study would lead to significant effects (or trend for significance) in further patients groups of comparable size.

SUPPLEMENTAL TABLE 2 Evaluation of bootstrap samples and cutoff range. Columns 4 and 5 show the fraction of bootstrap samples for which the same cutoff value leads to P< 0.1 and P< 0.05, respectively.

	bootstrap				**cutoff range P<0.1**			
Parameter	mean HR	mean P	P < 0.05	P < 0.1	$\text{cutoff}_{\text{min}}$	HR	$\text{cutoff}_{\text{max}}$	HR
LRC								
MTV	3.61	**0.04**	83 %	90 %	21.6ml	1.8	32.9ml	2.71
TLG	2.22	0.19	42 %	55 %	–	–	–	–
rMTV	4.18	**0.024**	89 %	94 %	2.9ml	2.2	10.6ml	1.9
rTLG	4.03	**0.025**	89 %	94 %	5.43ml	8.41	60.3ml	3.46
rSUV	3.28	**0.069**	71 %	82 %	3.89	7.18	5.81	1.79
rSUR	5.94	**0.0082**	97 %	98 %	2.49	7.24	4.02	1.83
Δ MTV	2.37	0.16	49 %	62 %	–	–	–	–
Δ TLG	3.2	0.12	54 %	68 %	–	–	–	–
Δ SUR	2.51	0.16	47 %	61 %	–	–	–	–
FFDM								
MTV	2.12	0.16	47 %	60 %	–	–	–	–
rMTV	3.68	**0.018**	91 %	96 %	1.52ml	12.2	10.1ml	1.77
rTLG	3.83	**0.019**	91 %	95 %	5.42ml	12.2	38.3ml	1.71
rSUV	3.48	**0.079**	66 %	79 %	3.88	3.13	5.02	1.73
rSUR	3.78	**0.013**	94 %	97 %	2.47	5.01	3.75	1.61
Δ MTV	2.68	**0.055**	77 %	85 %	-24.8%	1.82	-60.1%	1.75
Δ TLG	2.4	**0.096**	64 %	75 %	-41.9%	1.65	-57.4%	1.63
Δ SUV	2.75	**0.062**	74 %	83 %	-35.7%	1.6	-52.8%	1.8
Δ SUR	2.73	**0.065**	73 %	83 %	-44.6%	1.76	-51.8%	1.78
OS								
MTV	2.24	**0.089**	67 %	77 %	21.6ml	1.64	27.1ml	1.56
TLG	2.2	0.12	60 %	71 %	–	–	–	–
rMTV	2.52	**0.042**	82 %	89 %	5.28ml	1.6	10.3ml	1.57
rTLG	3.25	**0.059**	73 %	84 %	5.5ml	2.86	19.3ml	1.59
rSUV	1.92	0.14	51 %	64 %	–	–	–	–
rSUR	2.64	**0.031**	86 %	92 %	2.93	1.74	3.75	1.55
Δ SUR	2.04	0.18	42 %	55 %	–	–	–	–

Furthermore, the range of cutoff values for which P remains below 0.1 in univariate analysis was determined by successively decreasing/increasing the cutoff (starting at the optimal cutoff) and repeated uni-

variate Cox regression in the original patient group. This procedure was restricted to parameters for which the cutoff determination was considered stable by the above bootstrap procedure. Results of the stability analysis are shown in Supplemental Table 2.

SUPPLEMENTAL TABLE 3 Univariate and multivariate Cox regression with respect to FFDM. In multivariate analysis, each PET parameter was analyzed separately together with histology the only significant clinical parameter in univariate Cox regression. Note that the HRs and the P-values of the clinical parameters were averaged over all analyses. Column "Bootstrap" shows the sample-averaged P value resulting from the corresponding bootstrap analysis. Only PET parameters with P<0.1 were included in multivariate analysis.

		univariate				multivariate		
Parameter	Risk	HR	95% CI	P-value	Bootstrap	HR	95% CI	P-value
Clinical parameters								
Age	< 54y	1.56	0.79 – 3.09	0.2	na	–	–	–
T stage	> 2	1.87	0.57 – 6.12	0.3	na	–	–	–
N stage	> 0	1.34	0.47 – 3.82	0.58	na	–	–	–
UICC-stage	> 2	1.63	0.71 – 3.74	0.25	na	–	–	–
Histology	SCC	3.45	1.66 – 7.15	< **0.001**	na	3.5	1.67–7.33	**0.001**
Baseline PET								
MTV	> 13.6ml	1.94	0.97 – 3.87	**0.06**	0.16	–	–	–
TLG	> 52.9ml	1.51	0.73 – 3.1	0.26	–	–	–	–
SUV	> 13.4	0.63	0.28 – 1.46	0.28	–	–	–	–
SUR	> 6.28	0.78	0.4 – 1.54	0.48	–	–	–	–
Re-staging PET								
rMTV	> 5.61ml	3.26	1.57 – 6.8	**0.002**	**0.018**	3.23	1.53–6.81	**0.002**
rTLG	> 18.7ml	3.15	1.46 – 6.79	**0.004**	**0.019**	3.39	1.55–7.43	**0.002**
rSUV	> 4.41	2.82	1.16 – 6.84	**0.022**	**0.079**	2.65	1.09–6.43	**0.031**
rSUR	> 3.29	3.38	1.64 – 6.99	**0.001**	**0.013**	5.39	2.52–11.6	< **0.001**
Fractional difference								
Δ MTV	> -35%	2.5	1.27 – 4.91	**0.0081**	**0.055**	2.27	1.15–4.48	**0.018**
Δ TLG	> -51.7%	2.24	1.13 – 4.44	**0.021**	**0.096**	1.92	0.96–3.84	0.065
Δ SUV	> -38.8%	2.48	1.23 – 5.02	**0.012**	**0.062**	2.23	1.1–4.53	**0.027**
Δ SUR	> -48%	2.47	1.22 – 5.01	**0.012**	**0.065**	2.29	1.12–4.66	**0.023**

SUPPLEMENTAL TABLE 4 Univariate and multivariate Cox regression with respect to OS. In multivariate analysis, each PET parameter was analyzed separately together with the clinical parameters which were significant prognostic factors (or exhibited a trend for significance) in univariate Cox regression. Note that the HRs and the P-values of the clinical parameters were averaged over all analyses. Column "Bootstrap" shows the sample-averaged P value resulting from the corresponding bootstrap analysis. Only PET parameters with P<0.1 were included in multivariate analysis.

		univariate				multivariate		
Parameter	Risk	HR	95% CI	P-value	Bootstrap	HR	95% CI	P-value
Clinical parameters								
Age	< 68y	0.61	0.34 – 1.12	0.11	na	–	–	–
T stage	> 2	1.63	0.64 – 4.12	0.3	na	–	–	–
N stage	> 0	1.87	0.67 – 5.22	0.23	na	–	–	–
UICC-stage	> 2	2.07	0.96 – 4.43	**0.062**	na	1.21	0.534–2.75	0.65
Histology	SCC	2.58	1.42 – 4.68	**0.002**	na	2.6	1.41–4.82	**0.004**
Baseline PET								
MTV	> 23.8ml	2.07	1.14 – 3.78	**0.017**	**0.089**	2.06	1.09–3.91	**0.027**
TLG	> 232ml	2.02	1.08 – 3.8	**0.028**	0.12	–	–	–
SUV	> 10.6	1.45	0.82 – 2.57	0.21	–	–	–	–
SUR	> 5.83	1.58	0.83 – 2.99	0.16	–	–	–	–
Re-staging PET								
rMTV	> 6.6ml	2.34	1.3 – 4.21	**0.005**	**0.042**	2.16	1.17–3.99	**0.014**
rTLG	> 8.74ml	2.75	1.23 – 6.17	**0.014**	**0.059**	2.24	0.935–5.39	0.07
rSUV	> 5.33	1.8	1.01 – 3.23	**0.048**	0.14	–	–	–
rSUR	> 3.29	2.44	1.35 – 4.43	**0.003**	**0.031**	3.19	1.7–6.01	< **0.001**
Fractional difference								
Δ MTV	> -73.8%	1.72	0.87 – 3.39	0.12	–	–	–	–
Δ TLG	> -69.4%	1.54	0.86 – 2.73	0.14	–	–	–	–
Δ SUV	> -50.3%	1.65	0.89 – 3.06	0.11	–	–	–	–
Δ SUR	> -59.2%	1.85	0.94 – 3.66	**0.076**	0.18	–	–	–

Comparison of SUV with and without uptake time correction.

Lesion SUV values were uptake time corrected as described in (*1*):

$$\mathrm{SUV_{utc}} = \mathrm{SUV} \times \left(\frac{T_0}{T}\right)^{1-b}, \tag{S6}$$

where T is the actual scan time p.i. and T_0 is the chosen standard uptake time to which the SUV values are normalized (75min in the present work). The parameter b describes the shape and decrease of the arterial input function over time (we used $b = 0.313$, see (*1*) for details). For both, uncorrected and corrected SUV, univariate Cox regressions were performed. Results are shown in Supplemental Table 5.

SUPPLEMENTAL TABLE 5 Results of univariate Cox regression for SUV with and without uptake time correction (subscript "utc" indicates uptake time corrected values)

Parameter	Risk	HR	95% CI	P value
LRC				
SUV	> 13.4	0.61	0.23 – 1.63	0.33
$\mathrm{SUV_{utc}}$	> 10.3	1.62	0.75 – 3.5	0.22
rSUV	> 5.33	2.81	1.22 – 6.48	**0.015**
$\mathrm{rSUV_{utc}}$	> 4.17	6.43	1.52 – 27.25	**0.012**
Δ SUV	> -38.8	1.59	0.73 – 3.47	0.24
$\Delta\mathrm{SUV_{utc}}$	> -60.2	1.95	0.73 – 5.19	0.18
FFDM				
SUV	> 13.4	0.63	0.28 – 1.46	0.28
$\mathrm{SUV_{utc}}$	> 10.3	1.39	0.71 – 2.74	0.34
rSUV	> 4.41	2.82	1.16 – 6.84	**0.022**
$\mathrm{rSUV_{utc}}$	> 4.16	4.14	1.45 – 11.78	**0.0078**
Δ SUV	> -38.8	2.48	1.23 – 5.02	**0.012**
$\Delta\mathrm{SUV_{utc}}$	> -43.4	2.07	1.02 – 4.19	**0.043**
OS				
SUV	> 10.6	1.45	0.82 – 2.57	0.21
$\mathrm{SUV_{utc}}$	> 10.3	1.47	0.83 – 2.62	0.19
rSUV	> 5.33	1.8	1.01 – 3.23	**0.048**
$\mathrm{rSUV_{utc}}$	> 4.16	2.17	1.05 – 4.5	**0.038**
Δ SUV	> -50.3	1.65	0.89 – 3.06	0.11
$\Delta\mathrm{SUV_{utc}}$	> -52.6	1.76	0.93 – 3.34	**0.084**

Comparison of SUV normalized to body weight and SUV normalized to lean body mass

Univariate Cox regression was performed for SUV normalized to body weight and SUV normalized to lean body mass. Results are shown in Supplemental Table 6.

SUPPLEMENTAL TABLE 6 Results of univariate Cox regression for SUV normalized to body weight (SUV_{bw}) and for SUV normalized to lean body weight (SUV_{lbm}).

Parameter	Risk	HR	95% CI	P value
LRC				
SUV_{bw}	> 16.7	0.56	0.21 – 1.49	0.25
SUV_{lbm}	> 13.4	0.61	0.23 – 1.63	0.33
$rSUV_{bw}$	> 7.17	2.3	1.04 – 5.09	**0.039**
$rSUV_{lbm}$	> 5.33	2.81	1.22 – 6.48	**0.015**
ΔSUV_{bw}	> -39.2	1.65	0.76 – 3.59	0.21
ΔSUV_{lbm}	> -38.8	1.59	0.73 – 3.47	0.24
FFDM				
SUV_{bw}	> 16.7	0.59	0.26 – 1.35	0.21
SUV_{lbm}	> 13.4	0.63	0.28 – 1.46	0.28
$rSUV_{bw}$	> 7.33	1.97	1 – 3.87	**0.05**
$rSUV_{lbm}$	> 4.41	2.82	1.16 – 6.84	**0.022**
ΔSUV_{bw}	> -41.2	2.18	1.08 – 4.42	**0.03**
ΔSUV_{lbm}	> -38.8	2.48	1.23 – 5.02	**0.012**
OS				
SUV_{bw}	> 16	0.76	0.4 – 1.41	0.38
SUV_{lbm}	> 10.6	1.45	0.82 – 2.57	0.21
$rSUV_{bw}$	> 7.17	1.66	0.93 – 2.96	**0.085**
$rSUV_{lbm}$	> 5.33	1.8	1.01 – 3.23	**0.048**
ΔSUV_{bw}	> -53.1	1.76	0.93 – 3.34	**0.084**
ΔSUV_{lbm}	> -50.3	1.65	0.89 – 3.06	0.11

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