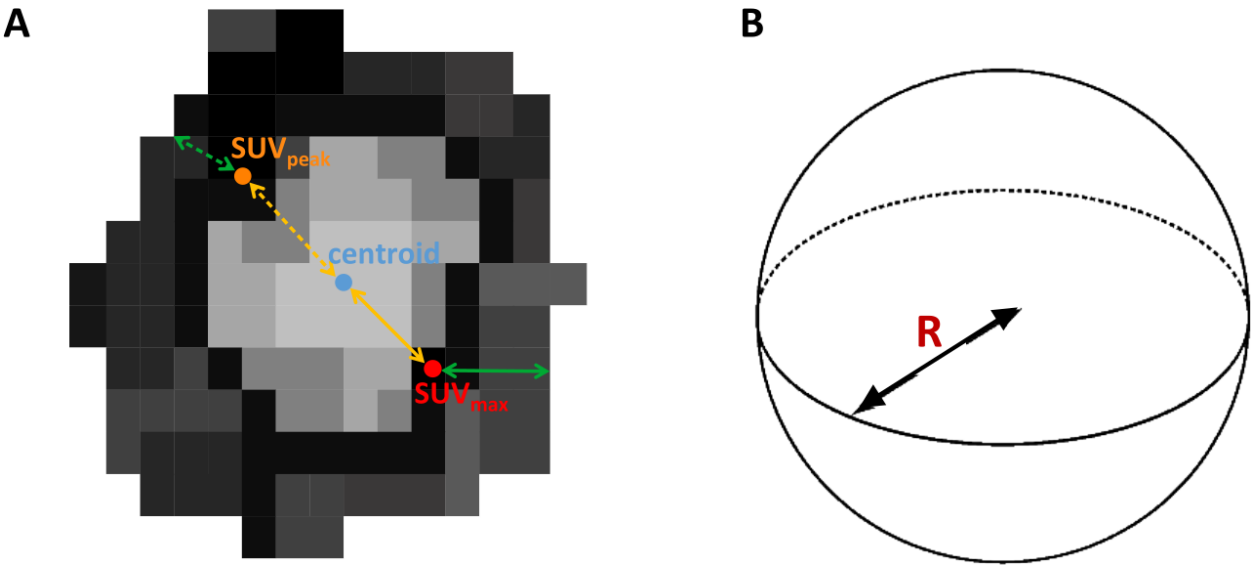
Supplemental Data



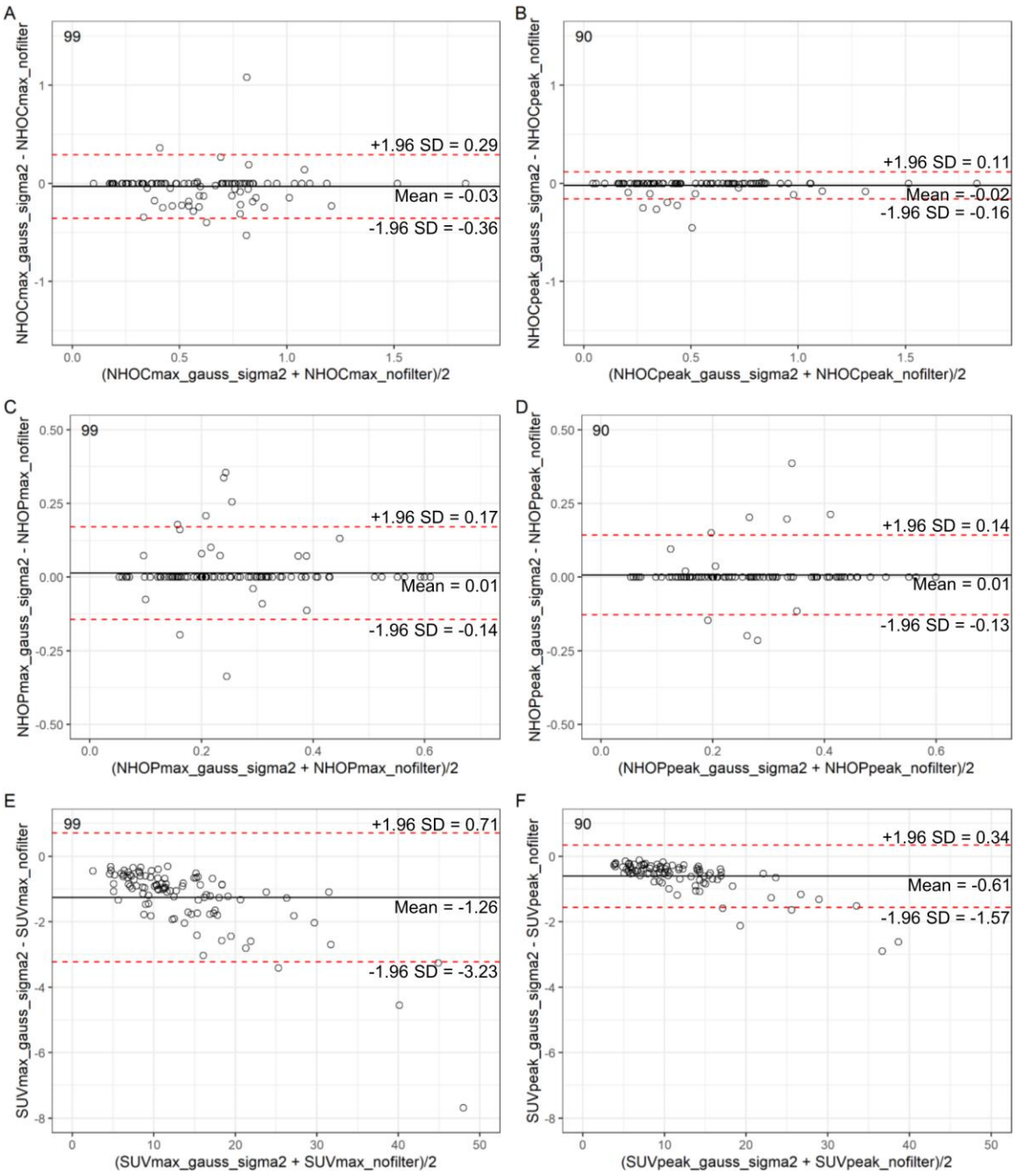
Supplemental Figure 1: NHOC and NHOP definitions. Illustration of A. tumor (black is high SUV, white is low SUV) and B. hypothetical sphere of radius R having the same volume as the tumor.

NHOCmax: distance (yellow arrow) from the voxel with maximum SUV (SUVmax, red cercle) to the tumor centroid (blue cercle) divided (normalized) by the radius (R). Called *MORPHOLOGICAL_RadiusSphereNorm-MaxIntensityCoor-RoiCentroidCoor-Dist* in LIFEx.

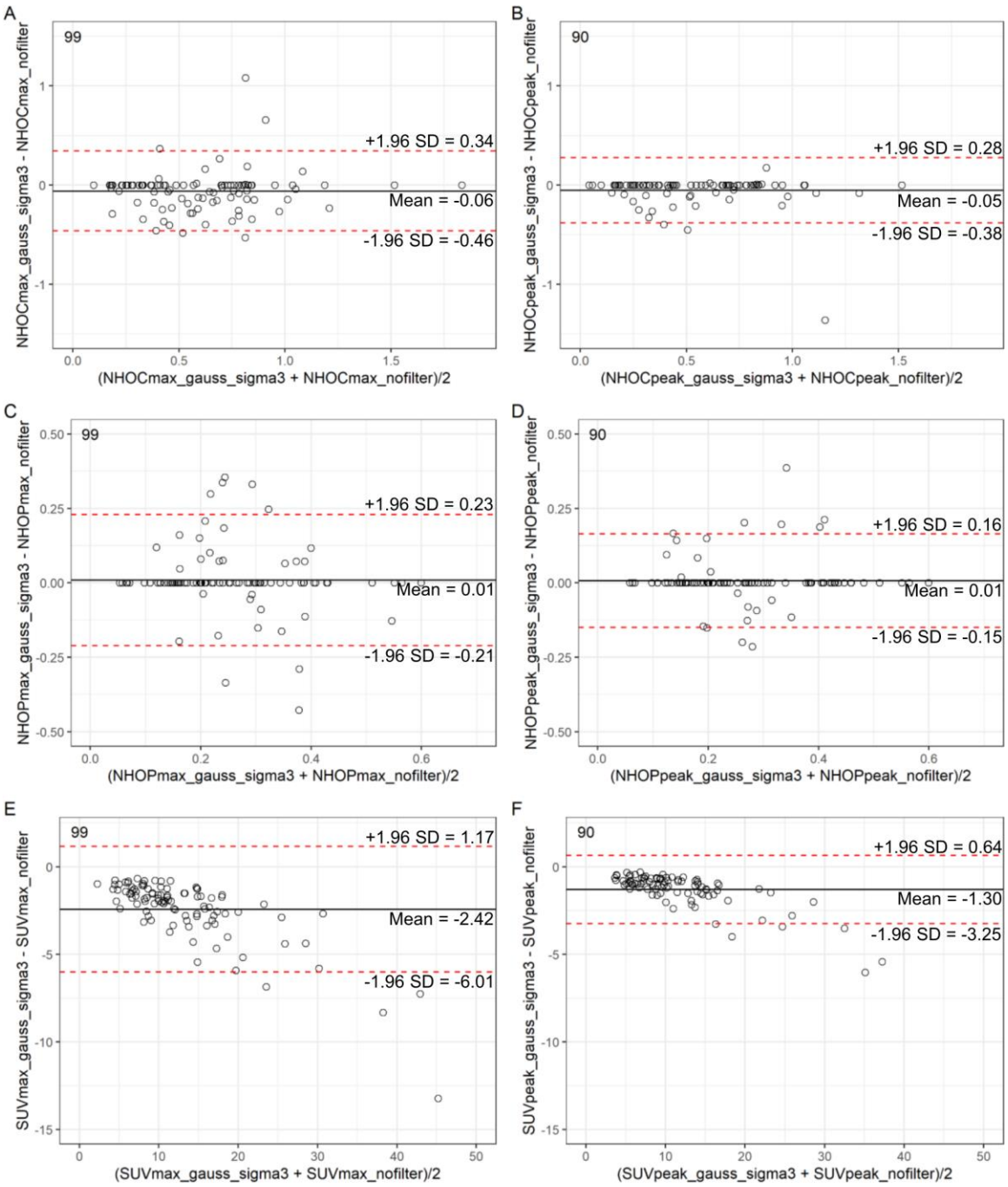
NHOCpeak: normalized distance (yellow dashed arrow) from the hotspot with maximum average SUV (within a 1cm^3 spherical volume, SUVpeak, orange cercle) to the tumor centroid. Called *MORPHOLOGICAL_RadiusSphereNorm-PeakIntensityCoor-RoiCentroidCoor-Dist* in LIFEx.

NHOPmax: normalized distance (green arrow) from the SUVmax to the tumor perimeter (closest border). Called *MORPHOLOGICAL_RadiusSphereNorm-MaxIntensityCoor-PerimeterCoor-3DSmallestDist* in LIFEx.

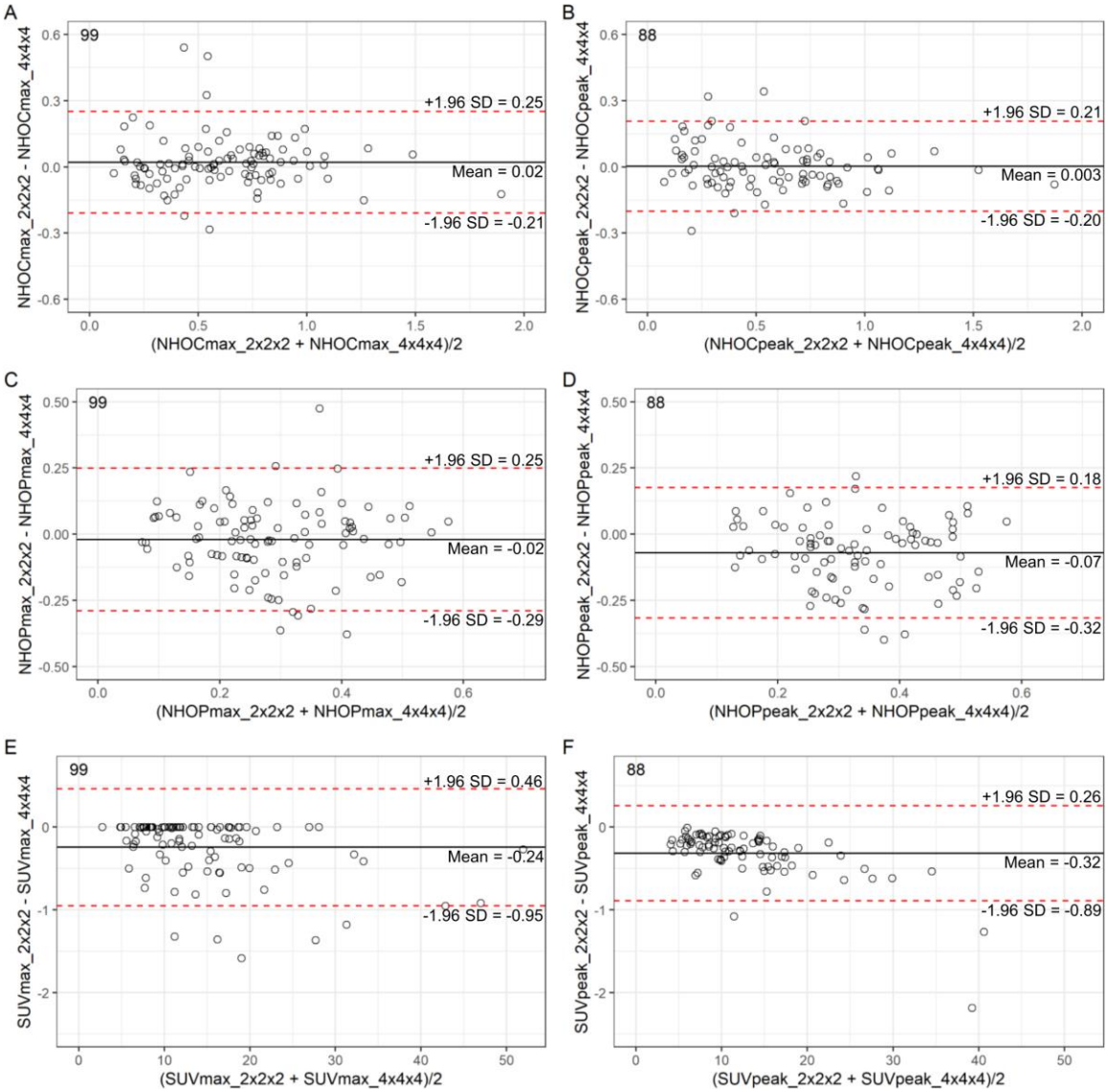
NHOPpeak: normalized distance (green dashed arrow) from the SUVpeak to the tumor perimeter. Called *MORPHOLOGICAL_RadiusSphereNorm-PeakIntensityCoor-PerimeterCoor-3DSmallestDist* in LIFEx.



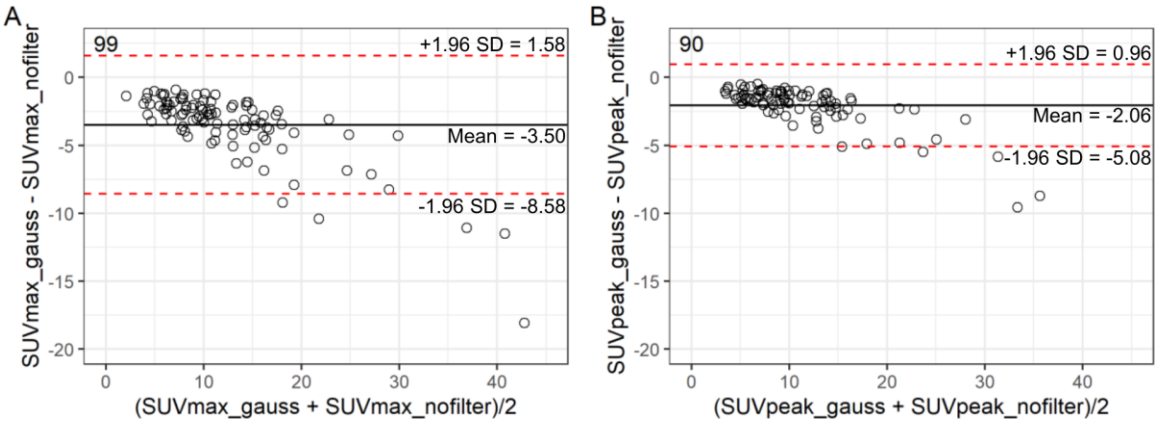
Supplemental Figure 2: Bland–Altman plots for cohort 1. Concordance between feature values extracted from [^{18}F]FDG-PET images (4 mm voxel size) before and after Gaussian post-filtering (sigma of 2 mm), for A) NHOCmax, B) NHOCpeak, C) NHOPmax, D) NHOPpeak, E) SUVmax and F) SUVpeak. Limits of agreement (95%) shown as dotted red lines and bias as solid black line. The figures in the top-left corner of each graph correspond to the number of measurements available.



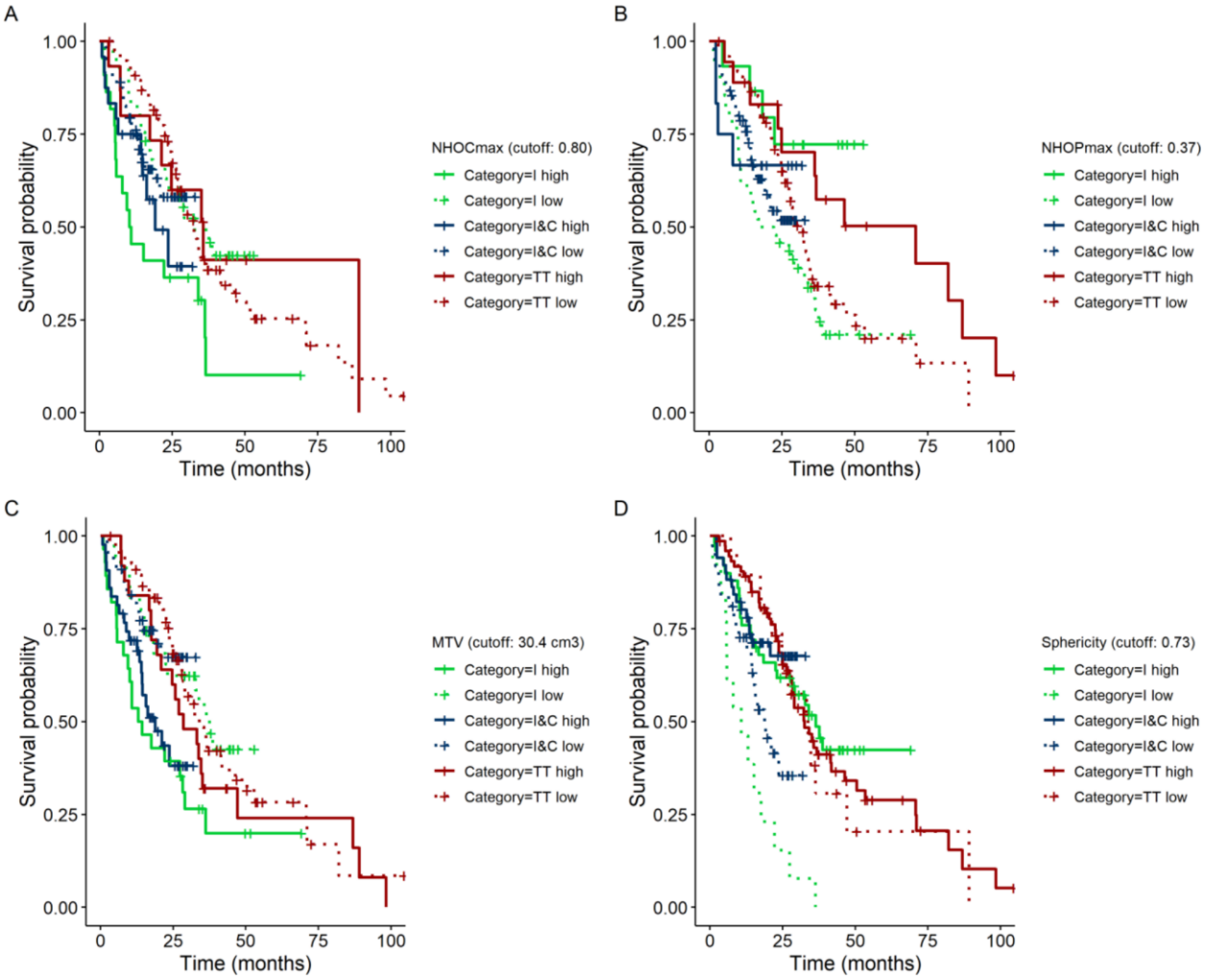
Supplemental Figure 3: Bland–Altman plots for cohort 1. Concordance between feature values extracted from [^{18}F]FDG-PET images (4 mm voxel size) before and after Gaussian post-filtering (sigma of 3 mm), for A) NHOCmax, B) NHOCpeak, C) NHOPmax, D) NHOPpeak, E) SUVmax and F) SUVpeak. Limits of agreement (95%) shown as dotted red lines and bias as solid black line. The figures in the top-left corner of each graph correspond to the number of measurements available.



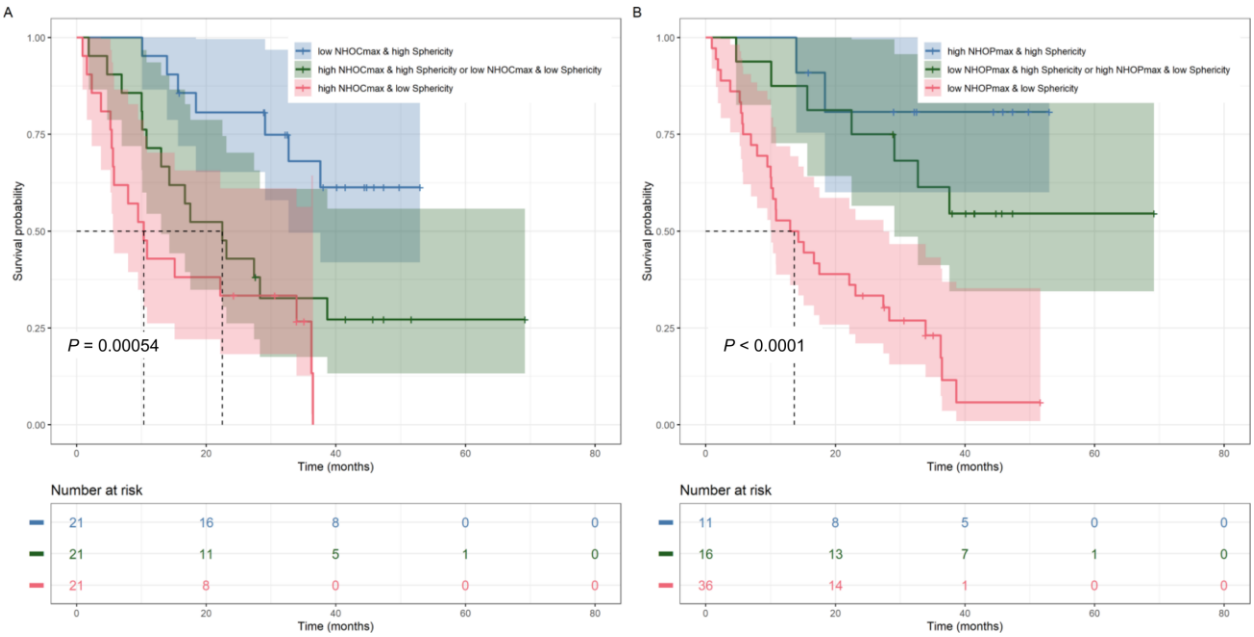
Supplemental Figure 4: Bland–Altman plots for cohort 1. Concordance between features values extracted from [^{18}F]FDG-PET images resampled to 2x2x2 and 4x4x4 mm3, for A) NHOCmax, B) NHOCpeak, C) NHOPmax, D) NHOPpeak, E) SUVmax and F) SUVpeak. Limits of agreement (95%) shown as dotted red lines and bias as solid black line. The figures in the top-left corner of each graph correspond to the number of measurements available.



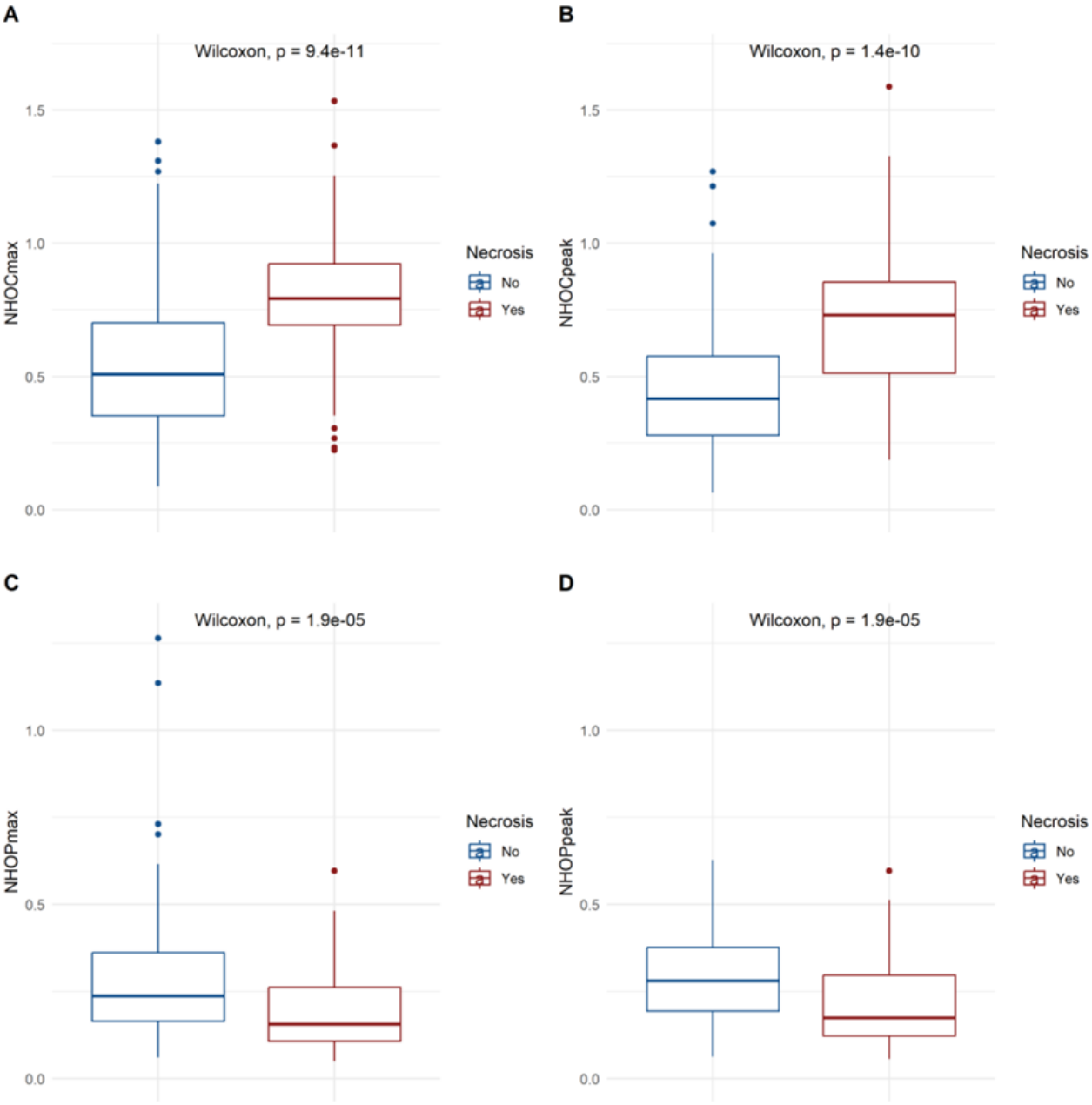
Supplemental Figure 5: Bland–Altman plots for cohort 1. Concordance between feature values extracted from [^{18}F]FDG-PET images (4 mm voxel size) before and after Gaussian post-filtering (sigma of 4 mm), for A) SUVmax, B) SUVpeak. Limits of agreement (95%) shown as dotted red lines and bias as solid black line. The figures in the top-left corner of each graph correspond to the number of measurements available.



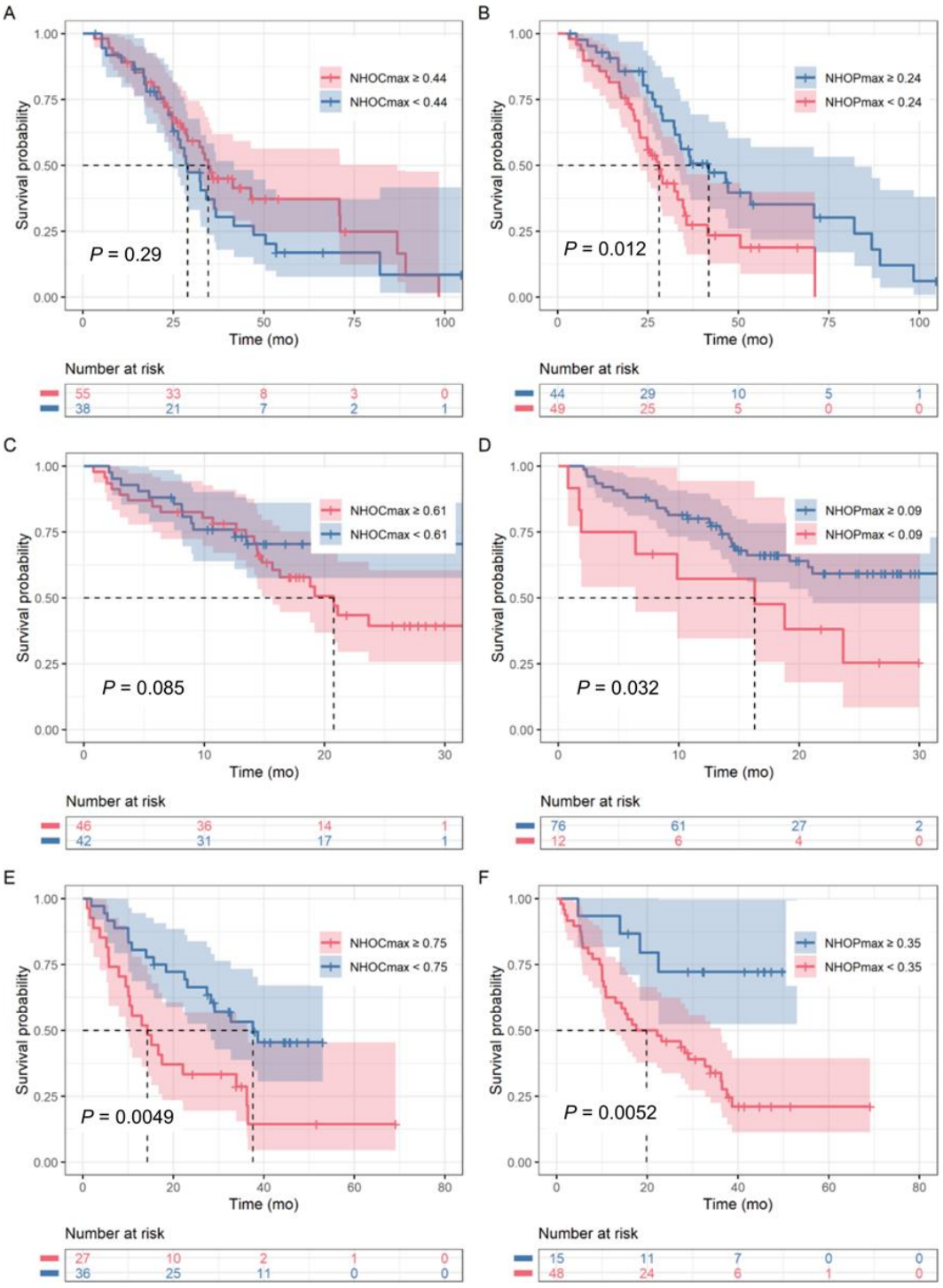
Supplemental Figure 6: Kaplan-Meier curves. For each feature, a common cut-point was determined considering all patients of cohort 2 regardless of their treatment. TT: targeted therapy, I&C: immuno-chemotherapy, I: immunotherapy. High: feature value ≥ cut-off, low: feature value < cut-off.



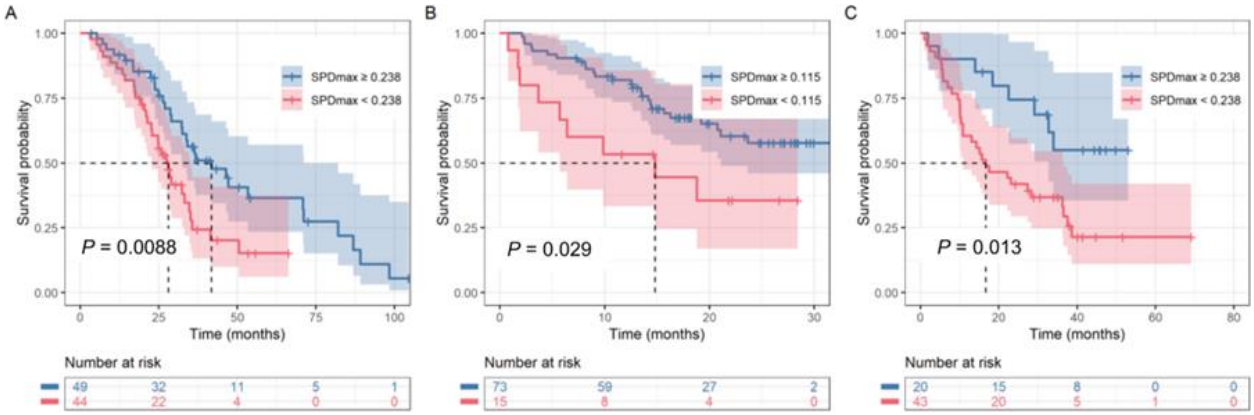
Supplemental Figure 7: Kaplan-Meier curves from multivariate analysis. NHOCmax-Sphericity and NHOPmax-Sphericity combinations for stratifying 3 risk-category groups in Immunotherapy sub-cohort. Log-rank test ($p < 0.05$).



Supplemental Figure 8: Impact of visually assessed necrosis on NHOC and NHOP values. A. NHOCmax, B. NHOCpeak, C. NHOPmax and D. NHOPpeak. Wilcoxon rank test ($p < 0.05$). The horizontal lines in boxes indicate the medians, n = 244 patients.



Supplemental Figure 9: Kaplan-Meier curves without addition of necrotic core in the VOI. Overall survival curves with best cut-off values for NHOCmax and NHOPmax for patients treated by: A-B. targeted therapy, C-D. immuno-chemotherapy and E-F. immunotherapy only, based on baseline [^{18}F]FDG-PET scans.



Supplemental Figure 10: Kaplan-Meier curves. Overall survival curves with best cut-off values for SPDmax for patients treated by A. targeted therapy, B. immuno-chemotherapy and C. immunotherapy only, based on baseline [^{18}F]FDG-PET scans.

Scanner model	Manufacturer name	Slice thickness (mm)	Pixel spacing (mm)	Reconstruction method*
Discovery 710	GE	3.27	[2.73; 2.73]	VPFXS
Discovery 690	GE	3.27	[2.73; 2.73]	VPFXS
Discovery MI	GE	2.80	[2.73; 2.73]	QCFX
Discovery IQ	GE	3.26	[2.73; 2.73]	QCHD
Discovery RX	GE	3.27	[5.47; 5.47]	3D IR
GeminiGXL 16	Philips	4.00	[4.00; 4.00]	LOR-RAMLA
Guardian Body	Philips	4.00	[4.00; 4.00]	LOR-RAMLA
GEMINI TF TOF 16	Philips	4.00	[4.00; 4.00]	BLOB-OS-TF
Ingenuity TF	Philips	2.00	[2.00; 2.00]	BLOB-OS-TF
Biograph 20	SIEMENS	5.00	[4.07; 4.07]	PSF+TOF 3i21s
Biograph 40	SIEMENS	2.03	[4.07; 4.07]	PSF+TOF 2i21s
Biograph 64	SIEMENS	1.65	[1.65; 1.65]	PSF+TOF 3i5s
Biograph Horizon	SIEMENS	2.03	[2.89; 2.89]	PSF+TOF 6i10s

Supplemental Table 1: Imaging protocol parameters. * non-EARL-compliant reconstructions.

Feature	ICC (rater1, rater2)
SUVmin	0.80
SUVmax	1.00
SUVpeak	1.00
SUVmean	0.97
NHOCmax	0.92
NHOCpeak	0.94
NHOPmax	0.90
NHOPpeak	0.80
MTV	0.99
TLG	0.99
Sphericity	0.77
JointEntropyLog10	0.92
InvDiffMoment	0.97
ShortRunEmph	0.96
LongRunEmph	0.98
LowGrayZoneEmph	0.78
HighGrayZoneEmph	0.73

Supplemental Table 2: Intraclass Correlation Coefficient results. Inter-operator reproducibility for feature measurement. n=30 patients. One-way model.

		NHOCmax + SUVmax	NHOCmax + MTV	NHOCmax + Sphericity	NHOCmax + SPDmax	NHOPmax + SUVmax	NHOPmax + MTV	NHOPmax + Sphericity
TT	**1y survival rate (%)**							
	0 RF	100.0%	88.6%	85.7%	90.0%	100.0%	92.3%	92.9%
	1 RF	86.5%	93.5%	94.7%	90.2%	88.6%	88.9%	86.7%
	2 RF	84.8%	72.7%	84.6%	87.1%	80.8%	75.0%	89.5%
	p-values (risk factors)							
	0 vs 1	0.390	0.310	0.500	0.163	0.275	0.108	0.650
	0 vs 2	0.390	0.310	0.200	0.464	**<0.001**	**0.002**	0.630
	1 vs 2	0.750	0.130	0.360	**0.048**	**0.015**	**0.023**	0.630
I&C	**1y survival rate (%)**							
	0 RF	72.2%	80.9%	79.1%	75.9%	61.4%	82.7%	81.4%
	1 RF	73.0%	76.2%	78.4%	90.0%	85.2%	79.2%	79.2%
	2 RF	83.2%	74.1%	72.9%	55.6%	53.0%	60.6%	59.3%
	p-values (risk factors)							
	0 vs 1	0.790	0.481	0.966	0.520	0.600	0.025	0.120
	0 vs 2	0.790	**0.034**	**0.032**	0.130	0.890	0.047	0.120
	1 vs 2	0.790	0.206	**0.040**	0.210	0.600	0.922	0.580
I	**1y survival rate (%)**							
	0 RF	87.9%	88.9%	95.2%	93.8%	93.3%	100.0%	100.0%
	1 RF	55.6%	66.7%	71.4%	76.0%	72.4%	71.4%	87.5%
	2 RF	41.7%	44.4%	42.9%	45.5%	47.4%	55.2%	52.8%
	p-values (risk factors)							
	0 vs 1	0.085	**0.006**	**0.015**	**0.014**	**0.019**	**0.012**	0.288
	0 vs 2	**0.041**	**0.004**	**<0.001**	**0.003**	**0.016**	**0.001**	**0.001**
	1 vs 2	0.495	0.791	0.118	0.149	0.272	0.134	**0.001**

Supplemental Table 3: Summary of multivariate analysis with Kaplan-Meier estimate considering 3 risk categories per feature-combination. For each sub-cohort and risk factor (RF: 0 with no risk factor, 1 with one risk factor, 2 with two risk factors) the 1-year survival rate and the p-values of the risk-category stratification (pairwise comparisons) are displayed. TT: targeted therapy, I&C: immuno-chemotherapy, I: immunotherapy. In bold: p-value lower than 5%.

Feature	p-value	Mean ± SD	
		necrotic (n=68)	**non-necrotic** (n=176)
SUVmin	<0.001	1.6 ± 1.8	2.8 ± 2.0
SUVmax	<0.001	16.5 ± 7.3	11.5 ± 5.7
SUVpeak	<0.001	13.2 ± 6.2	10.0 ± 5.0
SUVmean	0.849	7.2 ± 3.9	7.0 ± 3.5
NHOCmax	<0.001	0.80 ± 0.26	0.55 ± 0.26
NHOCpeak	<0.001	0.70 ± 0.27	0.45 ± 0.24
NHOPmax	<0.001	0.20 ± 0.12	0.28 ± 0.17
NHOPpeak	<0.001	0.22 ± 0.12	0.29 ± 0.13
MTV (cm3)	<0.001	133.5 ± 190.2	277.0 ± 50.7
TLG	<0.001	897.3 ± 1507.1	199.4 ± 387.9
Sphericity	0.050	0.76 ± 0.08	0.77 ± 0.11
JointEntropyLog10	<0.001	2.79 ± 0.36	2.48 ± 0.34
InvDiffMoment	0.269	0.21 ± 0.09	0.22 ± 0.09
ShortRunEmph	0.478	0.95 ± 0.03	0.95 ± 0.03
LongRunEmph	0.214	1.27 ± 0.25	1.22 ± 0.2
LowGrayZoneEmph	0.083	0.01 ± 0.01	0.01 ± 0.01
HighGrayZoneEmph	0.177	833.4 ± 971.7	714.1 ± 958.6

Supplemental Table 4: Comparison of feature values in necrotic and non-necrotic tumors. Wilcoxon rank test ($p < 0.05$). Cohort 2, n = 244 patients.

	TT		I&C		I	
Features	cutoff	p-value	cutoff	p-value	cutoff	p-value
NHOCmax_Nincl	0.435	0.290	0.608	0.076	0.793	**0.007**
NHOCmax_Nexcl	0.435	0.290	0.608	0.085	0.746	**0.005**
NHOPmax_Nincl	0.238	**0.024**	0.115	0.180	0.361	**0.002**
NHOPmax_Nexcl	0.238	**0.012**	0.087	**0.032**	0.347	**0.005**

Supplemental Table 5: Summary of survival analyses with Kaplan-Meier estimate of OS. TT: targeted therapy, I&C: immuno-chemotherapy, I: immunotherapy. Suffix Nincl for Necrosis included, Nexcl for Necrosis excluded. Bold: p<0.05.

	TT			I&C			I		
Features	cutoff	p-value	C-index	cutoff	p-value	C-index	cutoff	p-value	C-index
NHOPmax	0.238	0.024	0.572	0.115	0.180	0.510	0.361	0.002	0.541
SPDmax	0.240	0.009	0.582	0.115	0.029	0.528	0.356	0.013	0.540

Supplemental Table 6: Summary of survival analyses with Kaplan-Meier estimate of OS. Results based on SPDmax (2D) and NHOPmax (3D) approaches. TT: targeted therapy, I&C: immuno-chemotherapy, I: immunotherapy.