Improving the predictive value of end-of-treatment PET/CT in diffuse large B-cell lymphoma

Anne L. Bes,[1,2*] Gerben J.C. Zwezerijnen,[2,3*] Martijn W. Heymans,[4] Ulrich Dührsen,[5] Jakoba J. Eertink,[1,2] Sanne E. Wiegers,[2,3] Pieternella J. Lugtenburg,[6] Andreas Hüttmann,[5] Lars Kurch,[7] Christine Hanoun,[5] N. George Mikhaeel,[8] Luca Ceriani,[9,10] Emanuele Zucca,[10-12] Sándor Czibor,[13] Tamás Györke,[13] Martine E.D. Chamuleau,[1,2] Stefano Fanti,[14] Sze Ting Lee,[15] Otto S. Hoekstra,[2,3] Josée M. Zijlstra,[1,2] Sally F. Barrington[16] and Ronald Boellaard;[2,3] on behalf of the PETRA consortium

[1]Department of Hematology, Amsterdam UMC, Vrije Universiteit Amsterdam, Amsterdam, the Netherlands; [2]Imaging and Biomarkers, Cancer Center Amsterdam, Amsterdam, the Netherlands; [3]Department of Radiology and Nuclear Medicine, Amsterdam UMC, Vrije Universiteit Amsterdam, Amsterdam, the Netherlands; [4]Department of Epidemiology and Data Science, Amsterdam Public Health Research Institute, Amsterdam UMC, Vrije Universiteit Amsterdam, Amsterdam, the Netherlands; [5]Department of Hematology, West German Cancer Center, University Hospital Essen, University of Duisburg–Essen, Essen, Germany; [6]Department of Hematology, Erasmus MC Cancer Institute, University Medical Center Rotterdam, Rotterdam, the Netherlands; [7]Clinic and Polyclinic for Nuclear Medicine, Department of Nuclear Medicine, University of Leipzig, Leipzig, Germany; [8]Department of Clinical Oncology, Guy's Cancer Centre and School of Cancer and Pharmaceutical Sciences, King's College London, London, UK; [9]Department of Nuclear Medicine and PET/CT Centre, Imaging Institute of Southern Switzerland-EOC, Faculty of Biomedical Sciences, Università della Svizzera Italiana, Lugano, Switzerland; [10]SAKK Swiss Group for Clinical Cancer Research, Bern, Switzerland; [11]Department of Oncology, Oncology Institute of Southern Switzerland–EOC, Faculty of Biomedical Sciences, Università della Svizzera Italiana, Bellinzona, Switzerland; [12]Faculty of Biomedical Sciences, Università della Svizzera Italiana, Lugano, Switzerland; [13]Department of Nuclear Medicine, Medical Imaging Centre, Semmelweis University, Budapest, Hungary; [14]Nuclear Medicine Department, Sant'Orsola-Malpighi Hospital, Bologna, Italy; [15]Department of Molecular Imaging and Therapy, Austin Health, Melbourne, Australia and [16]School of Biomedical Engineering and Imaging Sciences, King's College London and Guy's and St Thomas' PET Centre, King's Health Partners, King's College London, London, UK

**ALB and GJCZ contributed equally as first authors.*

Correspondence: A.L. Bes
a.l.bes@amsterdamumc.nl

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Methods S1: Quality control and image analysis

The quality control followed EANM guidelines,[1] requiring a liver SUVmean between 1.3 and 3.0 and a plasma glucose lower than 11 mmol/L. If the liver SUVmean was outside the acceptable range, but the total image activity was 50-80% of the total injected FDG activity (in MBq), scans were still included. Scans were required to be complete and contain all essential DICOM data. All scans were centrally reviewed using standard visual Deauville score criteria applied by each site.

Baseline scans were segmented semi-automatically using the ACCURATE tool[2] following the current benchmark method for DLBCL: a fixed SUV4.0 threshold[3] (https://petralymphoma.org/accurate-tool/). However, lesions at end-of-treatment (EOT) often have a low SUV uptake, which cannot be delineated using SUV4.0. Therefore, we used the lesional based L2A method, which was previously tested in interim-PET to successfully delineate low-uptake tumors.[4] This lesion-based approach segments each lesion depending on their uptake values, applying either the SUV4.0 (if SUVmax ≥ 10) or MV3 method (if SUVmax < 10). MV3 is a majority vote method that includes voxels detected by at least 3 of the following delineation thresholds: SUV4.0, SUV2.5, 41% of SUVmax or 50% of SUVpeak.[5] This way it resembles the baseline method for DS5 lesions and, at the same time, is more optimal for lesions with lower uptakes (DS4). A fixed threshold SUV2.5 was used in the few cases the L2A method failed. If necessary, non-lymphoma FDG uptake was manually removed. Segmentations were performed by a trained researcher (ALB) and reviewed by a nuclear medicine physician (GJCZ), including confirmation of lesion uptake classification (DS4-5).

Methods S2: Clinical features

Clinical predictors including age (continuous), sex, Ann Arbor stage (I-IV), IPI score (International Prognostic Index, 4 risk groups) and the five IPI components as binary variables: age (≤60 versus >60), stage (I-II versus III-IV), EN (involvement of extra-nodal sites, 0-1 versus >1), ECOG (performance status according to the Eastern Cooperative Oncology Group <2 versus ≥2) and LDH (lactase dehydrogenase ≤ upper limit of normal (ULN) versus LDH > ULN) were collected. Follow-up and outcome data were extracted from the clinical databases.

Table S1. Patients characteristics of PET-positive patient stratified by study (n=138)

		Australian	GSTT15	HOVON130	HOVON84	PETAL	IAEA	SAKK
Inclusion	n	15	11	21	43	27	3	18
Sex	Male	10 (66.7%)	5 (45.5%)	3 (14.3%)	17 (39.5%)	15 (55.6%)	0 (0.0%)	8 (44.4%)
	Female	5 (33.3%)	6 (54.5%)	18 (85.7%)	26 (60.5)	12 (44.4%)	3 (100.0%)	10 (55.6%)
Age at diagnosis (years)	Median (range)	70 (55-88)	53 (31-72)	58 (28-76)	64 (23-79)	53 (24-78)	21 (18-83)	57 (26-77)
Follow-up (months)	Median	53	75	32	58	43	-	65
DS	4	2 (13.3%)	8 (72.7%)	5 (23.8%)	26 (60.5%)	11 (40.7%)	0 (0.0%)	10 (55.6%)
	5	13 (86.7%)	3 (27.3%)	16 (76.2%)	17 (39.5%)	16 (59.3%)	3 (100.0%)	8 (44.4%)
PFS (years)	≥ 2	7 (46.7%)	4 (36.4%)	3 (14.3%)	21 (48.8%)	12 (44.4%)	0 (0.0%)	7 (38.9%)
	< 2	8 (53.3%)	7 (63.6%)	18 (85.7%)	22 (51.2%)	15 (55.6%)	3 (100.0%)	11 (61.1%)
Chemo therapy	R-CHOP	15	8	21	43	20	10	18
	5 cycles	0 (0.0%)	0 (0.0%)	1 (4.8)	1 (2.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	6 cycles	6 (40.0%)	8 (100.0%)	1 (4.8)	19 (44.2%)	17 (85.0%)	0 (0.0%)	18
	7 cycles	0 (0.0%)	0 (0.0%)	3 (14.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	8 cycles	9 (60.0%)	0 (0.0%)	16 (76.2%)	23 (53.5%)	3 (15%)	10 (100.0%)	0 (0.0%)
	R-CEOP *(6 cycles)*	0	3	0	0	0	0	0
Ann Arbor Stage	I	0 (0.0%)	1 (9.1%)	0 (0.0%)	0 (0.0%)	4 (14.8%)	0 (0.0%)	3 (16.7%)
	II	0 (0.0%)	0 (0.0%)	3 (14.3%)	2 (4.7%)	4 (14.8%)	1 (33.3%)	4 (22.2%)
	III	6 (40.0%)	1 (9.1%)	6 (28.6%)	8 (18.6%)	7 (25.9%)	0 (0.0%)	4 (22.2%)
	IV	9 (60.0%)	9 (81.8%)	12 (57.1%)	33 (76.7%)	12 (44.4%)	2 (66.7%)	7 (38.9%)
IPI	Low-risk (IPI 0-1)	0 (0.0%)	1 (9.1%)	3 (14.3%)	3 (7.0%)	8 (29.6%)	1 (33.3%)	6 (33.3%)
	Low-intermediate (IPI 2)	2 (13.3%)	2 (18.2%)	4 (19.0%)	9 (20.9%)	7 (25.9%)	0 (0.0%)	5 (27.8%)
	High-intermediate (IPI 3)	7 (46.7%)	4 (36.4%)	12 (57.1%)	12 (27.9%)	4 (14.8%)	0 (0.0%)	4 (22.2%)
	High-risk (IPI 4-5)	6 (40.0%)	4 (36.4%)	2 (9.5%)	19 (44.2%)	8 (29.6%)	2 (66.7%)	3 (16.7%)
IPI-Age (years)	≤ 60	1 (6.7%)	7 (63.6%)	13 (61.9%)	15 (34.9%)	17 (63.0%)	2 (66.7%)	11 (61.1%)
	> 60	14 (93.3%)	4 (36.4%)	8 (38.1%)	28 (65.1%)	10 (37.0%)	1 (33.3%)	7 (38.9%)
IPI-Stage	I/II	0 (0.0%)	1 (9.1%)	3 (14.3%)	2 (4.7%)	8 (29.6%)	1 (33.3%)	7 (38.9%)
	III/VI	15 (100.0%)	10 (91.0%)	18 (85.7%)	41 (95.3%)	19 (70.4%)	2 (66.7%)	11 (61.1%)
IPI-EN (sites involved)	0-1	8 (53.3%)	3 (27.3%)	11 (52.4%)	16 (37.2%)	16 (59.3%)	1 (33.3%)	12 (66.7%)
	> 1	7 (46.7%)	8 (72.7%)	10 (47.6%)	27 (62.8%)	11 (40.7%)	2 (66.7%)	6 (33.3%)
IPI-ECOG	< 2	12 (80.0%)	7 (63.6%)	19 (90.5%)	35 (81.4%)	21 (77.8%)	2 (66.7%)	16 (88.9%)
	≥ 2	3 (20.0%)	4 (36.4%)	2 (9.5%)	8 (18.6%)	6 (22.2%)	1 (33.3%)	2 (11.1%)
IPI-LDH	LDH ≤ ULN	5 (33.3%)	3 (27.3%)	3 (14.3%)	8 (18.6%)	7 (25.9%)	1 (33.3%)	5 (27.8%)
	LDH > ULN	10 (66.7%)	8 (72.7%)	18 (85.7%)	35 (81.4%)	20 (74.1%)	2 (66.7%)	13 (72.2%)

DS=Deauville Score; PFS=Progression free survival; IPI=International Prognostic Index; EN=involvement of extra-nodal sites; ECOG=performance status according to the Eastern Cooperative Oncology Group; LDH=lactase dehydrogenase

Table S2. Patient characteristics of patients with complete metabolic response

		n=622 (100%)
Deauville score	1	303 (48.7%)
	2	167 (26.9%)
	3	152 (24.4%)
Chemotherapy	R-CHOP	622 (100%)
PFS	≥ 2 years	538 (86.5%)
	< 2 years	84 (13.5%)

R-CHOP=standard immunochemotherapy based on rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone

Table S3. Distribution of quantitative PET descriptives

Variable	Median	Q1	Q3
TMTV-BL (ml)	635.42	293.90	1351.92
TMTV-EOT (ml)	11.73	3.61	43.16
ΔTMTV (ml)	559.18	246.87	1317.19
Δ%TMTV	97.58	90.93	99.30
TLG-BL	6120.68	2472.96	12033.09
TLG-EOT	59.36	13.80	378.83
ΔTLG	5214	1820	11521
Δ%TLG	93.32	98.44	99.67
SUVpeak-BL	18.13	12.99	24.91
SUVpeak-EOT	5.76	3.65	12.44
ΔSUVpeak	9.94	3.69	15.75
Δ%SUVpeak	62.85	27.47	79.36
SUVmean-BL	8.90	6.93	10.64
SUVmean-EOT	5.13	3.30	7.41
ΔSUVmean	3.17	0.83	5.71
Δ%SUVmean	39.84	12.03	61.52
SUVmax-BL	21.57	15.92	30.51
SUVmax-EOT	8.82	4.91	17.62
ΔSUVmax	10.71	2.71	18.54
Δ%SUVmax	55.11	13.65	74.20
TLRpeakpeak-BL	8.26	5.83	12.02
TLRpeakpeak-EOT	2.30	1.47	4.94
ΔTLRpeakpeak	5.11	2.15	8.09
Δ%TLRpeakpeak	64.44	38.93	82.65
TLRpeakmean-BL	9.70	6.72	13.87
TLRpeakmean-EOT	2.64	0.98	5.69
ΔTLRpeakmean	6.38	2.70	9.99
Δ%TLRpeakmean	67.20	37.69	82.49
TLRmaxmax-BL	8.26	5.84	11.46
TLRmaxmax-EOT	2.88	1.71	6.09
ΔTLRmaxmax	4.53	1.91	7.49
Δ%TLRmaxmax	58.71	24.29	77.66
NOL-BL (n)	9.50	3.00	19.00
NOL-EOT (n)	2.00	1.00	4.00
ΔNOL (n)	4.50	1.00	13.75
Δ%NOL	66.67	34.62	87.50
DmaxBulk-BL (mm)	308.90	188.10	432.60
DmaxBulk-EOT (mm)	19.60	0.00	156.00
ΔDmaxBulk (mm)	233.20	66.30	352.60
Δ%DmaxBulk	86.01	86.01	100.00

Δ%=percent reduction; -BL=feature at baseline; -EOT=feature at end-of-treatment; TMTV=total metabolic tumor volume; TLG=total lesion glycolysis; TLRpeakpeak=tumorSUVpeak/liverSUVpeak ratio TLRpeakmean=tumorSUVpeak/liverSUVmean ratio; TLRmaxmax=tumorSUVmax/liverSUVmax ratio, NOL=number of lesions; DmaxBulk= distance between the largest lesion and the most distant lesion

Results S1: Univariate Cox and spline transformations

Spline transformations were relevant for TMTV-EOT, Δ%TMTV, TLG-EOT, Δ%TLG, SUV-EOT, Δ%SUV, TLR-EOT, Δ%TLR, NOL-BL and NOL-EOT, ΔNOL and ΔDmaxBulk, see *Table Results S1*. The transformed variables were further used in the models.

The univariate analysis showed statistical significance for the following linear or transformed variables: TMTV-BL, TMTV-EOT and Δ%TMTV, TLG-EOT and Δ%TLG, SUV-EOT, Δ(%)SUV, TLR-EOT and Δ(%)TLR, NOL-BL, NOL-EOT and Δ(%)NOL, DmaxBulk-BL, DmaxBulk-EOT and Δ(%)DmaxBulk. None of the clinical features, except for the DS, were significant.

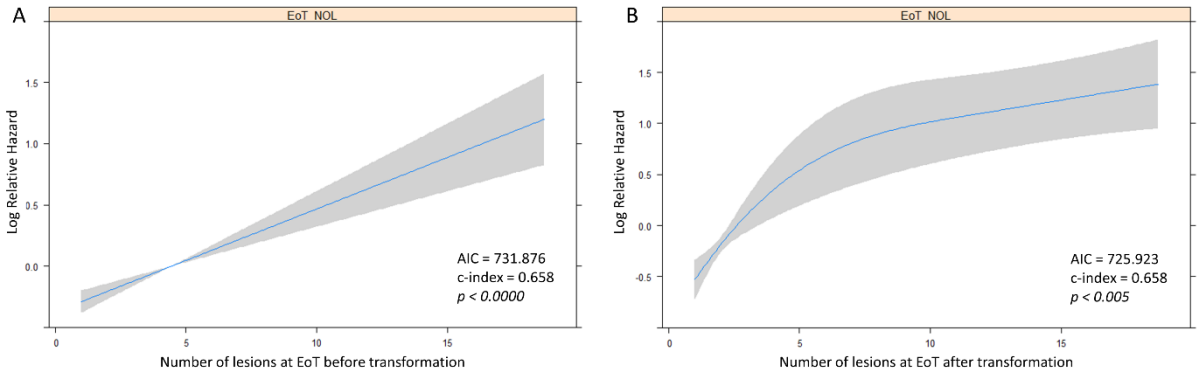

Figure Results S1. Relative log hazard for the number of lesions at end-of-treatment before (A) and after (B) cubic spline transformation.

Table Results S1. Univariate cox regression before and after spline transformation in DS4 and 5 patients (n=138)

Variable	Before spline transformation				After spline transformation			
	HR (95% CI)	c-index	AIC	p-value	HR (95% CI)	c-index	AIC	p-value
DS-EOT	3.433 (2.113-5.576)	0.640	734.372	6.24e-07*	-	-	-	-
Age	0.994 (0.979-1.010)	0.514	762.061	0.448	-	-	-	-
Stage	1.249 (0.957-1.630)	0.552	759.691	0.102	-	-	-	-
Sex	0.707 (0.452-1.106)	0.531	760.259	0.129	-	-	-	-
IPI	1.146 (0.934-1.406)	0.543	760.895	0.193	-	-	-	-
IPI-Age	0.979 (0.638-1.503)	0.506	762.617	0.922	-	-	-	-
IPI-Stage	1.405 (0.745-2.650)	0.520	761.425	0.293	-	-	-	-
IPI-EN	1.160 (0.755-1.781)	0.524	762.166	0.498	-	-	-	-
IPI-ECOG	0.964 (0.551-1.685)	0.495	762.609	0.896	-	-	-	-
IPI-LDH	1.700 (0.971-2.975)	0.546	758.784	0.063	-	-	-	-
TMTV-BL (ml)	1.000 (1.000-1.000)	0.565	757.361	0.014*	1.000 (0.998-1.001)	0.565	759.040	0.574
TMTV-EOT (ml)	1.003 (1.002-1.004)	0.695	743.728	4.46e-08*	0.849 (0.796-0.906)	0.695	722.794	7.69e-07*
ΔTMTV (ml)	1.000 (1.000-1.000)	0.535	759.597	0.065	1.000 (1.000-1.000)	0.535	761.504	0.760
Δ%TMTV (%)	0.991 (0.984-0.997)	0.639	756.017	0.003*	0.956 (0.932-0.981)	0.638	746.840	0.001*
TLG-BL	1.000 (1.000-1.000)	0.542	760.171	0.103	1.000 (1.000-1.000)	0.542	762.037	0.716
TLG-EOT	1.000 (1.000-1.000)	0.705	748.546	2.01e-06*	0.966 (0.956-0.978)	0.705	719.025	3.72e-09*
ΔTLG	1.000 (1.000-1.000)	0.513	761.644	0.309	1.000 (1.000-1.000)	0.533	763.545	0.752
Δ%TLG	0.992 (0.986-0.998)	0.671	757.141	0.006*	0.941 (0.917-0.965)	0.670	738.481	2.94e-06*
SUVpeak-BL	0.994 (0.970-1.020)	0.532	762.433	0.661	1.013 (0.932-1.100)	0.527	764.348	0.769
SUVpeak-EOT	1.109 (1.077-1.142)	0.710	721.111	3.57e-12*	0.554 (0.384-0.800)	0.710	712.791	0.002*
ΔSUVpeak	0.936 (0.911-0.962)	0.665	737.660	2.20e-06*	1.019 (0.936-1.109)	0.665	739.483	0.670
Δ%SUVpeak	0.983 (0.978-0.988)	0.714	727.082	1.71e-10*	0.975 (0.961-0.990)	0.714	716.866	0.001*
SUVmean-BL	0.948 (0.881-1.019)	0.554	760.445	0.148	1.008 (0.803-1.265)	0.554	762.440	0.945
SUVmean-EOT	1.255 (1.168-1.349)	0.692	728.729	5.79e-10*	0.593 (0.393-0.896)	0.692	724.355	0.013*
ΔSUVmean	0.827 (0.773-0.884)	0.681	729.729	3.27e-08*	0.913 (0.729-1.144)	0.681	731.066	0.428
Δ%SUVmean	0.983 (0.978-0.988)	0.703	729.848	2.95e-10*	0.973 (0.957-0.990)	0.703	720.293	0.002*
SUVmax-BL	0.992 (0.972-1.012)	0.537	762.017	0.439	1.001 (0.926-1.081)	0.537	764.017	0.985
SUVmax-EOT	1.073 (1.050-1.095)	0.702	727.022	5.63e-11*	0.738 (0.612-0.889)	0.702	718.026	0.001*
ΔSUVmax	0.949 (0.929-0.969)	0.670	735.753	9.39e-07*	0.996 (0.926-1.070)	0.670	737.739	0.906
Δ%SUVmax	0.984 (0.979-0.989)	0.707	727.139	3.45e-10*	0.978 (0.964-0.992)	0.707	719.379	0.003*
TLRpeakpeak-BL	0.998 (0.954-1.045)	0.506	762.621	0.940	0.895 (0.738-1.086)	0.545	763.315	0.262
TLRpeakpeak-EOT	1.249 (1.177-1.326)	0.722	722.002	2.54e-13*	0.229 (0.107-0.490)	0.722	707.862	1.46e-04*
ΔTLRpeakpeak	0.906 (0.860-0.955)	0.625	747.591	2.41e-04*	1.035 (0.872-1.228)	0.625	749.441	0.696
Δ%TLRpeakpeak	0.987 (0.982-0.991)	0.702	736.406	4.24e-09*	0.971 (0.958-0.986)	0.702	720.026	7.65e-05*
TLRpeakmean-BL	1.000 (0.963-1.037)	0.504	762.626	0.984	0.933 (0.803-1.084)	0.536	763.767	0.362
TLRpeakmean-EOT	1.215 (1.153-1.280)	0.722	722.094	3.12e-13*	0.271 (0.139-0.528)	0.722	707.624	1.26e-04*
ΔTLRpeakmean	0.926 (0.886-0.968)	0.614	749.464	6.11e-04*	1.041 (0.908-1.195)	0.614	751.136	0.562
Δ%TLRpeakmean	0.986 (0.981-0.990)	0.701	736.209	1.04e-08*	0.971 (0.957-0.985)	0.701	720.071	6.29e-05*
TLRmaxmax-BL	0.991 (0.945-1.040)	0.514	762.488	0.711	0.902 (0.733-1.111)	0.534	763.517	0.333
TLRmaxmax-EOT	1.214 (1.153-1.280)	0.721	723.322	3.29e-13*	0.409 (0.249-0.673)	0.721	711.100	4.30e-04*
ΔTLRmaxmax	0.885 (0.838-0.935)	0.650	740.985	1.32e-05*	1.059 (0.879-1.275)	0.650	742.636	0.548
Δ%TLRmaxmax	0.986 (0.982-0.991)	0.704	730.927	1.21e-10*	0.977 (0.964-0.990)	0.704	718.900	0.001*
NOL-BL (n)	1.008 (0.998-1.019)	0.586	760.514	0.124	0.920 (0.847-1.000)	0.587	758.568	0.049*
NOL-EOT (n)	1.092 (1.064-1.119)	0.658	731.876	8.56e-12*	0.339 (0.162-0.710)	0.658	725.923	0.004*
ΔNOL	0.998 (0.985-1.011)	0.502	762.549	0.783	1.112 (1.017-1.217)	0.503	759.781	0.020*
Δ%NOL (%)	0.996 (0.993-0.999)	0.571	755.871	0.004*	1.000 (0.992-1.009)	0.571	757.871	0.995
DmaxBulk-BL	1.001 (1.000-1.002)	0.565	757.197	0.018*	0.999 (0.997-1.002)	0.565	759.062	0.715
DmaxBulk-EOT	1.004 (1.002-1.005)	0.651	734.642	1.46e-09*	0.994 (0.988-1.001)	0.651	733.912	0.100
ΔDmaxBulk	0.999 (0.998-1.000)	0.545	760.226	0.126	1.003 (1.000-1.005)	0.531	758.962	0.058*
Δ%DmaxBulk	0.992 (0.988-0.996)	0.611	748.764	5.82e-05*	0.999 (0.990-1.008)	0.611	750.690	0.787

AIC=Akaike information criterion; *p<0.05

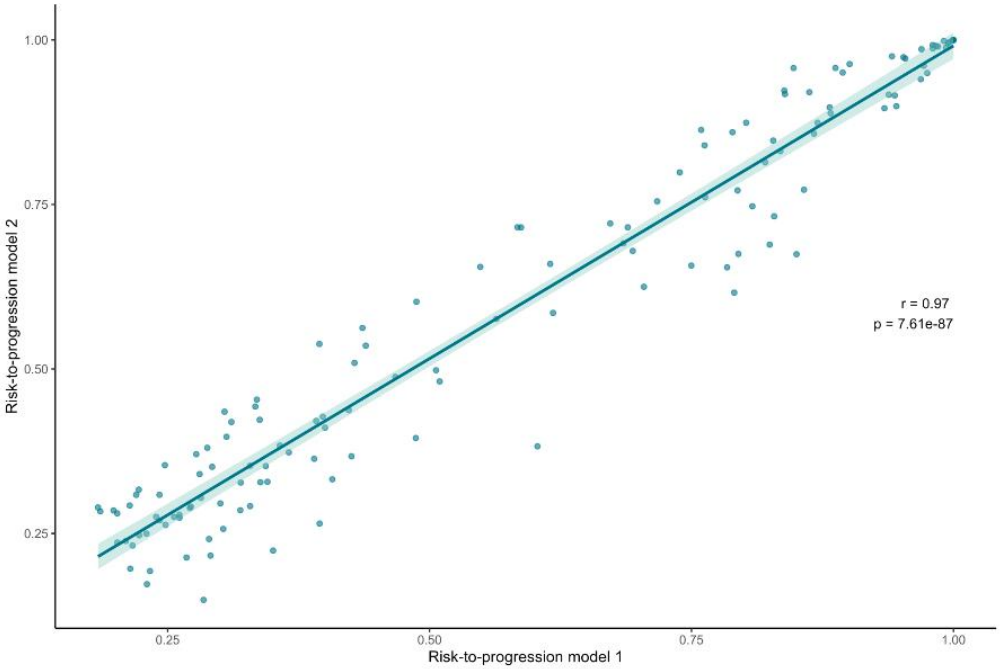

Figure S1. Correlation plot comparing risk-of-progression between model 1 and 2

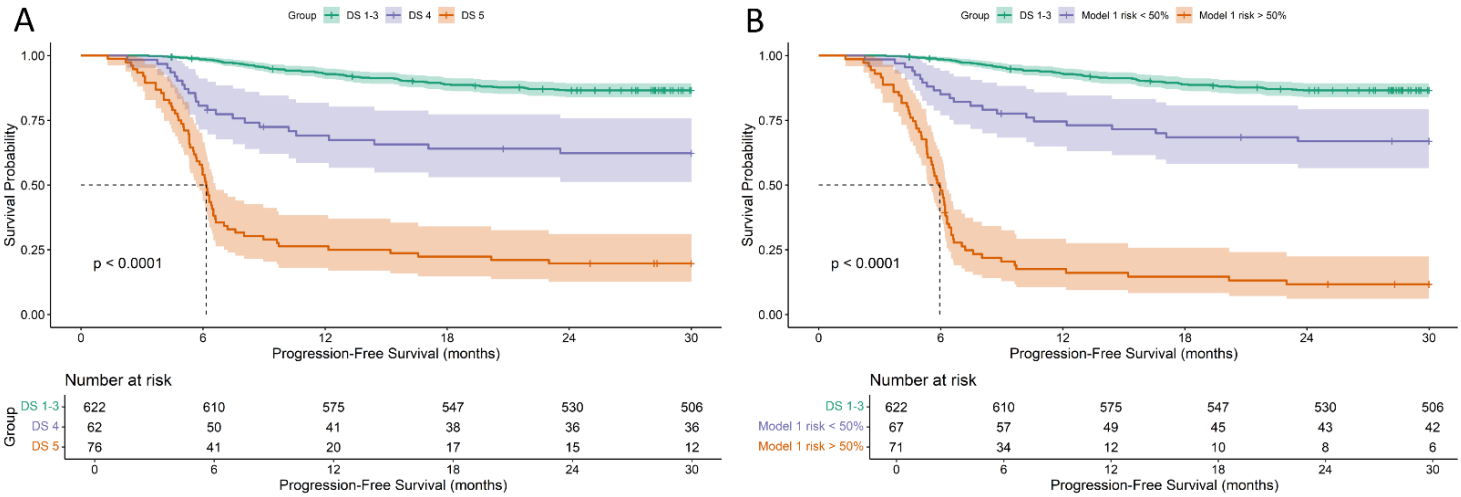

Figure S2. Kaplan-Meier survival curves comparing Deauville score (A) to the model 1 <50% and >50% risk groups for 2 year progression-free survival (B)

Table S4. Sensitivity scores using the clinical PET model

Risk to progression (%)	Correctly classified (n)	False positives (n)	False negatives (n)	Sensitivity	Specificity	Accuracy	PPV	NPV
5	84	37	17	0.798	0.315	0.609	0.644	0.500
10	79	22	37	0.560	0.593	0.573	0.681	0.464
20	73	12	53	0.369	0.778	0.529	0.721	0.442
30	62	6	70	0.167	0.889	0.449	0.700	0.407
40	59	6	78	0.071	0.982	0.428	0.857	0.405

Table S5. Overview of second-line therapy

Type	n = 138	Time in months between EOT PET and start therapy (median, IQR)
No second-line therapy	50	-
Radiotherapy (RT)	18	1.15 (0.46-1.25)
Chemo(immuno)therapy	29	1.08 (0.44-4.90)
Chemo(immuno)therapy + ASCT (+ RT*)	17	1.12 (0.62-6.47)
Chemo(immuno)therapy + RT	4	1.95 (1.28-3.24)
Unknown	20	-

*5 patients in this group had also received radiotherapy (RT); ASCT=Autologous stem cell transplantation

Table S6. Distribution of PFS for patients receiving radiotherapy

	Event	No Event	Total
Radiotherapy	12	15	27 (19.6%)
No Radiotherapy	63	32	95 (68.8%)
Unknown	9	7	16 (11.6%)
Total	84	54	138 (100.0%)

Table S7. Distribution of PFS for patients receiving second-line therapy (general)

	Event	No Event	Total
Second-line therapy	53	18	71 (51.4%)
No Second-line therapy	21	29	50 (36.2%)
Unknown	10	7	17 (12.3%)
Total	84	54	138 (100.0%)

Results S2: Consolidating radiotherapy

A subgroup of 122 patients in our database had data available on receiving consolidating radiotherapy. In this group 27 (22%) patients received radiotherapy after first-line treatment, of which 14 patients had a single lesion at EOT and 12 patients showed progression within 2 years. The radiotherapy status (binary) did not improve the performance of model 1 (p=0.340) and 2 (p=0.603), suggesting limited additional predictive value (*Table Results S2)*.

Table Results S2. Hazards of models after addition of radiotherapy in a subset of n=122 patients

	Model 1 (AIC=600.163, c-index=0.752)		Model 2 (AIC=597.707, c-index=0.773)	
Variable	HR (95% CI)	p-value	HR (95% CI)	p-value
TLRpeakmean-EOT	2.007 (1.454-2.773)	2.33e-05*	1.906 (1.368-2.656)	1.37e-04*
TLRpeakmean-EOT'	0.254 (0.111-0.582)	0.001*	0.316 (0.132- 0.753)	0.009*
NOL-EOT	1.185 (0.962-1.458)	0.110	1.164 (0.946-1.432)	0.152
NOL-EOT'	0.703 (0.317-1.556)	0.384	0.735 (0.332-1.627)	0.447
SUVmean-BL	-	-	0.912 (0.835-0.996)	0.041
Radiotherapy	0.733 (0.387-1.388)	0.340	0.840 (0.435-1.621)	0.603

'= splined variable; HR=hazard ratio; *p<0.05

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