Risk prediction in diffuse large B-cell lymphoma improves when combining baseline PET features with interim PET response

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Short title: Combining PET metrics for risk prediction in DLBCL

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Supplemental Material

Detailed statistical approach

Step 1 - Transformation of $Dmax_{bulk}$, ΔSUV_{max} and SUV_{peak}

Cox regression models were used to investigate the relationship between proression-free survival (PFS) and the delta maximum standardized uptake value (ΔSUV_{max}), the peak standardized uptake value (SUVpeak) and the maximum distance between the largest lesion and the lesion furthest away ($Dmax_{bulk}$), respectively. Transformed values for ΔSUV_{max}, SUV_{peak} and $Dmax_{bulk}$ were plotted against PFS using linear spline (LSP) transformations for each variable, with either 1 knot placed at the 50^{th} percentile, 2 knots placed at the 33^{th} and 66^{th} percentiles or 3 knots placed at the 10^{th}, 50^{th}, 90^{th} percentiles. The LSP model with the best fit was then compared with models including other transformations namely restricted cubic spline, natural logarithmic, linear, linear plus squared, dichotomous and a cubic variant. The best model fit was obtained by choosing the model with the highest R^2 and lowest Akaike information criterion (AIC). The c-index for discrimination was also obtained. To test for robustness of the model, a 'leave-one study' out cross-validation was performed, meaning that models were trained in four studies and tested in the remaining study cohort.

Step 2- Combining clinical characteristics and PET metrics at baseline

Cox regression models were performed to analyze the predictive value of various baseline models incorporating clinical factors and metabolic tumor volume (MTV). SUV_{peak}, SUV_{max} and $Dmax_{bulk}$ were also added as baseline radiomic features to test for further improvements in PFS and overall survival (OS) outcome prediction at baseline [13]. Again, the best model fit was obtained by choosing the model with the highest R^2 and lowest AIC and the c-index for discrimination was obtained.

Step 3 - Adding iPET response to the best baseline model

The best baseline model from step 2 was then combined with addition of chemosensitivity using interim positron emission tomography (iPET) response to test for further improvements in prediction of PFS and OS. For response assessment using iPET, two different methods were applied, the Deauville Score (DS) and the quantitative ΔSUV_{max} method. The DS is a visual 5-point scale, which we used as an ordinal scale (1-5) as well as a dichotomous scale of complete metabolic response (CMR) vs. non-CMR (1-3 vs 4-5). For the ΔSUV_{max} we used the reduction in SUV_{max} continuously. The majority of patients had iPET after 2 cycles of treatment (iPET-2) and a minority after 4 cycles (iPET-4) of treatment. Therefore we tested for differences in outcome prediction according to the timing of iPET using interaction-terms. We used both the continuous ΔSUV_{max}, and the dichotomous cut-offs reported in the literature (ΔSUV_{max} of ≥66% at iPET-2 and ≥70% at iPET-4)

Step 4 - Comparison of the new model to the IMPI and the ClinicalPET model

The best derived predictive model was then compared to the International Metabolic Prognostic Index (1) and the ClinicalPET (2) model using comparisons of model fit and Kaplan-Meier curves displaying PFS and OS dividing the population into risk groups as previously described: low (patients with the lowest 60% score) intermediate (middle 30% score) and high (highest 10% score) (1). The log-rank test was used to test for differences in survival curves with a p-value <0.05 considered statistically significant. Statistical analyses were performed using R (version 4.1.0). Moreover, risk re-classification rates were determined, where we calculated how many patients switched between low, intermediate and high risk groups,

thereby comparing accuracy to detect patients correctly among different risk prediction models (3).

Step 5 - Cross-validation of models

All results from step 1-4 as well as the final model were cross-validated using the leave-one-study-out approach, as described before (1).

Supplemental table 1: Survival rates of the study cohort compared to the original IMPI cohort.

	Study cohort	Original IMPI cohort	p-value
3-year PFS (95% CI)	75.6 (72.9-78.3%)	74.5% (72.1-77.0%)	0.56
3-year OS (95% CI)	83.0 (80.7-85.3%)	81.8 (79.7-84.0%)	0.46

PFS: progression-free survival, OS: overall survival; IMPI: International Metabolic Prognostic Index; 95% CI: 95% confidence interval n.s. not significant

Supplemental table 2.1: Performance of different transformation models for ΔSUV_{max}.

Transformation model for ΔSUV_{max}	AIC		R2		c-index	
	PFS	OS	PFS	OS	PFS	OS
Linear	3273.53	2266.32	0.06	0.06	0.62	0.61
Logarithmic linear spline	3309.96	2290.38	0.03	0.03	0.62	0.61
Squared	3270.27	2266.18	0.07	0.06	0.62	0.61
Restricted cubic spline	3274.51	2265.11	0.07	0.06	0.62	0.63
Linear spline 1 knot	3273.53	2263.83	0.06	0.06	0.62	0.67
Linear spline 2 knots	3273.79	2259.61	0.07	0.07	0.62	0.67
Linear spline 3 knots	3275.55	2260.15	0.07	0.07	0.62	0.67
Dichotomous	3286.44	2279.38	0.05	0.04	0.58	0.59
Cubic	3292.53	2278.13	0.05	0.05	0.62	0.61

ΔSUVmax: delta maximum standardized uptake value, AIC: Akaike information criterion; PFS: progression-free survival, OS: overall survival

Supplemental table 2.2: Performance of different transformation models for $Dmax_{bulk}$.

Transformation model for $Dmax_{bulk}$	AIC		R2		c-index	
	PFS	OS	PFS	OS	PFS	OS
Linear	3259.64	2263.83	0.08	0.06	0.67	0.67
Logarithmic linear spline	3292.17	2276.38	0.05	0.05	0.67	0.67
Squared	3256.80	2259.34	0.08	0.07	0.67	0.67
Restricted cubic spline	3258.20	2260.61	0.08	0.07	0.67	0.67
Linear spline 1 knot	3259.64	2263.83	0.08	0.06	0.67	0.67
Linear spline 2 knots	3259.70	2259.61	0.08	0.07	0.67	0.67
Linear spline 3 knots	3259.52	2260.15	0.08	0.07	0.67	0.67
Dichotomous	3283.70	2279.65	0.05	0.04	0.62	0.62
Cubic	3260.59	2256.89	0.08	0.07	0.67	0.67

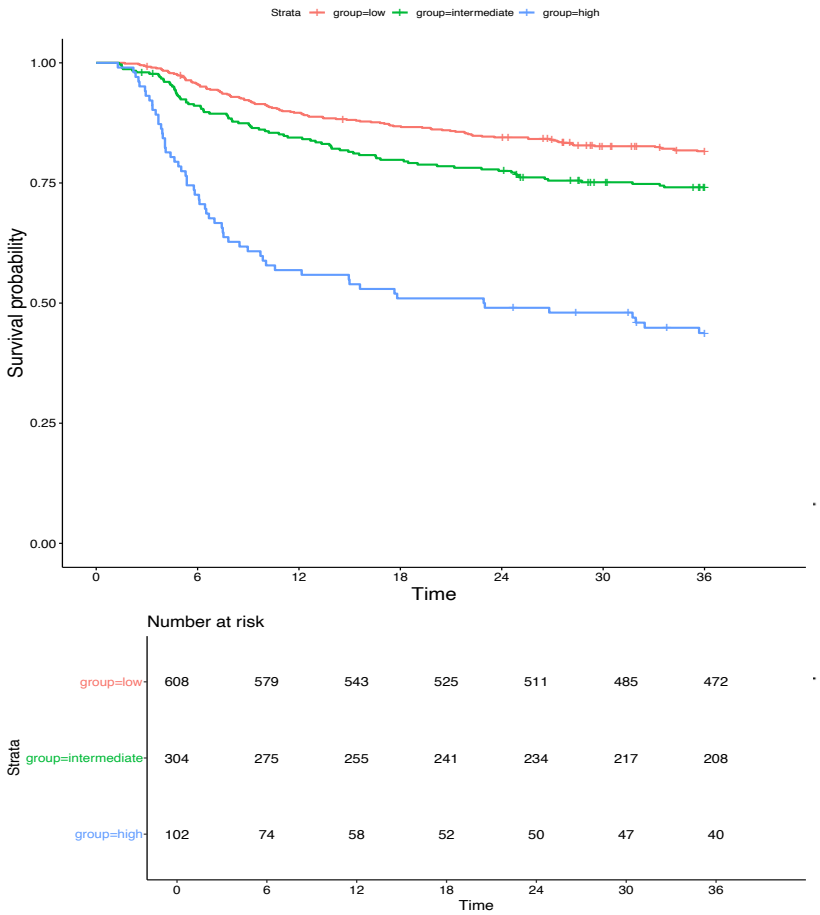
$Dmax_{bulk}$: maximum distance between the largest lesion and the lesion furthest apart (in mm); AIC: Akaike information criterion; PFS: progression-free survival, OS: overall survival

Supplemental table 2.3: Performance of different transformation models for SUV_{peak}.

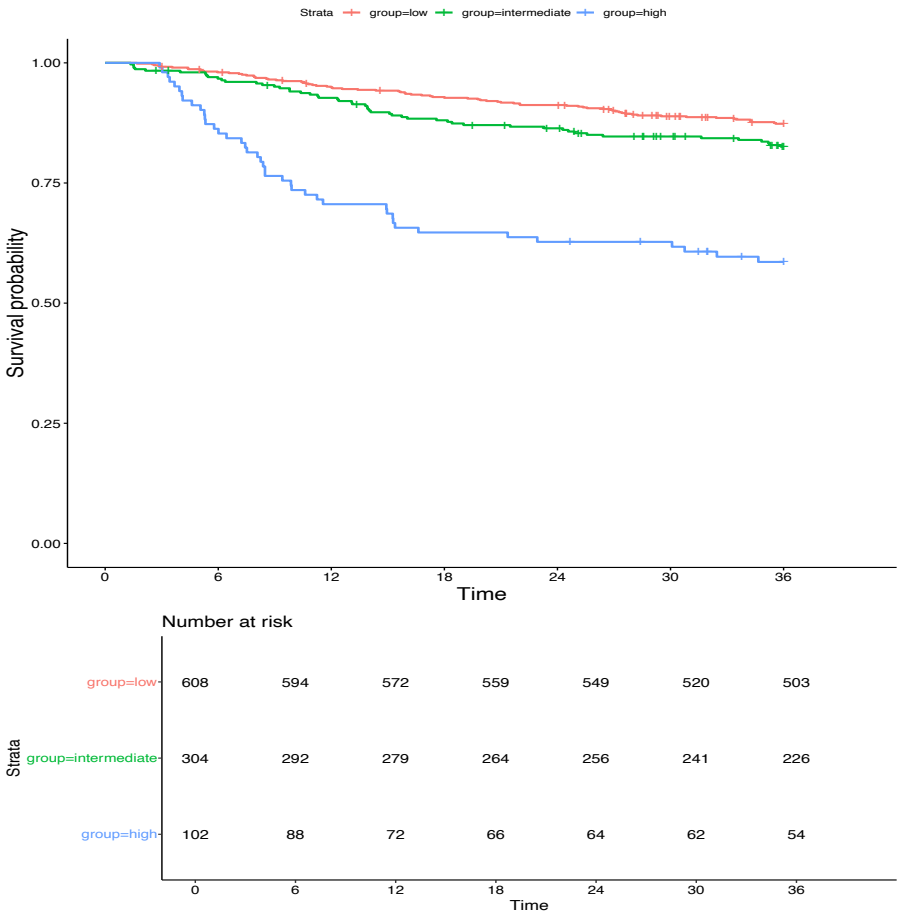
Transformation model for SUV_{peak}	AIC		R2		c-index	
	PFS	OS	PFS	OS	PFS	OS
Linear	3337.74	2319.59	0.00	0.00	0.51	0.51
Logarithmic linear spline	3338.55	2319.99	0.00	0.00	0.51	0.49
Squared	3336.66	2313.80	0.00	0.01	0.53	0.55
Restricted cubic spline	3337.07	2314.71	0.00	0.01	0.53	0.55
Linear spline 1 knot	3337.74	2319.59	0.00	0.00	0.52	0.51
Linear spline 2 knots	3336.61	2316.00	0.00	0.01	0.55	0.56
Linear spline 3 knots	3337.78	2316.59	0.00	0.01	0.52	0.51
Dichotomous	3337.65	2319.85	0.00	0.00	0.52	0.51
Cubic	3338.36	2320.03	0.00	0.00	0.52	0.51

SUV_{peak}: peak standardized uptake value; AIC: Akaike information criterion; PFS: progression-free survival, OS: overall survival

Supplemental figure 1a-b: Survival probabilities for PFS and OS according to ΔSUVmax at iPET



Supplemental figure 1a



Supplemental figure 1b

PFS: progression-free survival; OS: overall survival, ΔSUV_{max}: delta maximum standardized uptake value, iPET: interim positron emission tomography

Supplemental figure 1 a-b shows Kaplan-Meier (KM) curves displaying progression-free survival (PFS) (Figure 1a) and overall survival (OS) (Figure 1b) by dividing the population into risk groups according to interim positron emission tomography (iPET) response using delta maximum standardized uptake value: low (patients with the lowest 60% risk) intermediate (middle 30% risk) and high (highest 10% risk). Patients with a poor iPET response had an unfavorable outcome compared to those with a favorable outcome for both, PFS and OS. However, segregation of KM curves was less sharp compared to the baseline-iPET model (see main manuscript Figure 1 and 2).

Supplemental figure 2a-b: Survival probabilities according ΔSUVmax at iPET after cycle 2 and cycle 4, respectively.

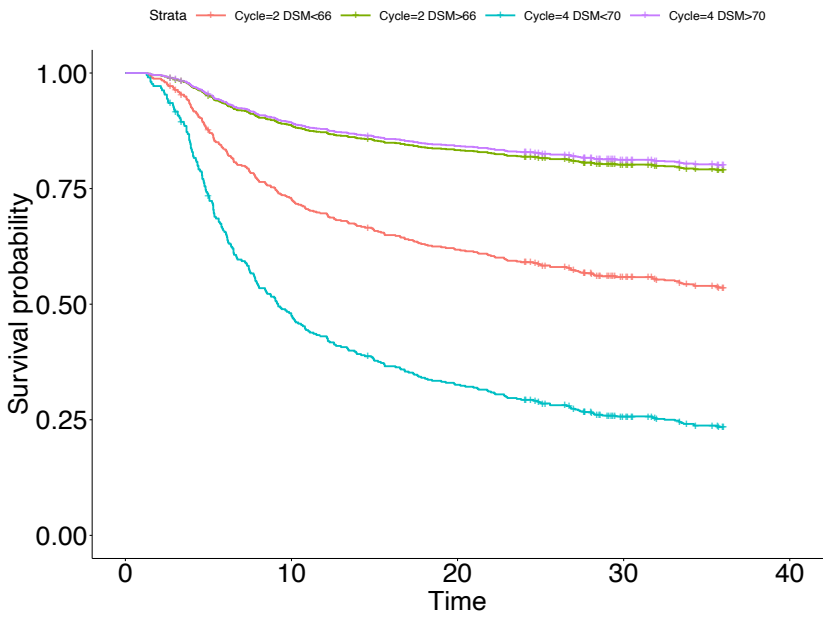


Figure 2a

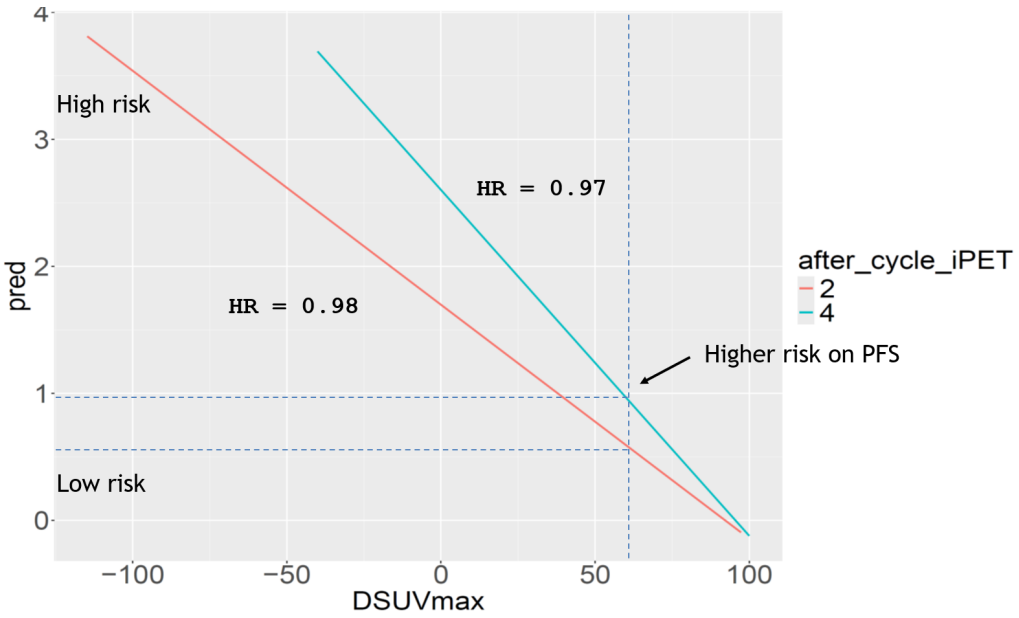


Figure 2b

PFS: progression-free survival; ΔSUV_{max}: delta maximum standardized uptake value, iPET: interim positron emission tomography; HR: hazard ratio

Patients with a delta maximum standardized uptake value (ΔSUVmax) of >66% after cycle 2 or >70% after cycle 4 had a favorable outcome for progression-free survival with superimposable survival curves (Hazard Ratio (HR) 0.79; 95% CI 0.76-0.82 and HR 0.80; 95% CI 0.75 – 0.85, respectively), while patients with an ΔSUVmax <66% after cycle 2 or <70% after cycle 4 had an unfavorable outcome (Figure 1a). In these patients, outcome was better for those patients with an ΔSUVmax <66% after cycle 2 (HR 0.54; 95%CI 0.44 – 0.65) compared to <70% after cycle 4 (0.23;

95%CI 0.12 – 0.44; Figure 2a) and same degree of ΔSUVmax reduction was associated with worse outcome when corresponding interim positron emission tomography was assessed after cycle 4 compared to cycle 2 (Figure 2b) .

Supplemental table 3: Survival data for 3-year OS according to different risk models based on 60-30-10 risk groups

3-year OS (95% CI)			
	Baseline-iPET model	IMPI	ClinicalPET model
Low risk group	0.93 (0.91-0.95)	0.91 (0.89-0.93)	0.91 (0.89-0.93)
Intermediate risk group	0.77 (0.73-0.82)	0.76 (0.73-0.82)	0.78 (0.73-0.83)
High risk group	0.41 (0.32-0.52)	0.56 (0.47-0.66)	0.51 (0.42-0.62)

CI: confidence interval; OS: overall survival; 96%CI: 95% confidence interbal; iPET: interim positron emission tomography; IMPI: International Metabolic Prognostic index

Supplemental table 4: Survival data for 1-year PFS and 1-year OS according to different risk models based on 60-30-10 risk groups.

1-year PFS (95% CI)			
	Baseline-iPET model	IMPI	ClinicalPET model
Low risk group	0.93 (0.91-0.95)	0.91 (0.89-0.93)	0.90 (0.88-0.93)
Intermediate risk group	0.82 (0.78-0.87)	0.81 (0.77-0.86)	0.84 (0.80-0.88)
High risk group	0.44 (0.35-0.54)	0.59 (0.50-0.70)	0.56 (0.47-0.66)
1-year OS (95% CI)			
Low risk group	0.97 (0.96-0.98)	0.97 (0.95-0.98)	0.96 (0.94-0.97)
Intermediate risk group	0.90 (0.87-0.94)	0.88 (0.84-0.92)	0.90 (0.87-0.93)
High risk group	0.63 (0.55-0.74)	0.74 (0.66-0.83)	0.72 (0.64-0.82)

PFS: progression-free survival; OS: overall survival; 96% CI: 95% confidence interval; iPET: interim positron emission tomography; IMPI: International Metabolic Prognostic index

Supplemental table 5: Internal Validation of risk model performance according to PFS

	Train c-index	Test c-index
Baseline-iPET model	0.74	0.72
IMPI	0.68	0.65
ClinicalPET model	0.70	0.68
IPI	0.64	0.63

PFS: progression-free survival; iPET: interim positron emission tomography; IMPI: International Metabolic Prognostic Index; IPI: International Prognostic Index

Internal validation according to the leave-one-study-out cross-validation approach confirmed best discrimination performance for the baseline-iPET model.

Formula to calculate the risk of progression, relapse or death from any cause (ie using PFS)

The Cox model (hazard rate) can be written as (1, formula 3.3):

$$h(t) = \exp(lp_{risk} - lp_{centered}) \times h_0(t)$$

where lp_{risk} consists of the Cox regression coefficients for MTV, Age, $Dmax_{bulk}$ and ΔSUV_{max} times the individual patient values (see below) and $lp_{centered}$ is used to mean center the linear predictor of the Cox model and $h_0(t)$ is he baseline hazard rate.

We obtained the $lp_{centered}$ and baseline hazard value at 36 months in our data set and these were 0.4526372 and 0.2271963674, respectively. We used these values in formula 3.3 for the Cox model and adjusted this formula to obtain the outcome risk for specific patients by making use of the relationship between the Cox hazard and survival function as (4, formula 1.5):

$$S(t) = \exp(-H(t)),$$

Where S(t) is the survival function and $H(t)$ the hazard function (which can be estimated from the Cox model, formula 3.3). Implementing formula 3.3 into formula 1.5 and subtracting from 1 we can obtain the outcome risk of progression, relapse or death from any cause (outcome PFS) as:

Risk formula = 1 - (exp(-(exp(lp_risk - 0.439058) * 0.2271963674)))

The individual patient risk, called lp risk, consists of the coefficients for MTV, Age, $Dmax_{bulk}$ and ΔSUV_{max} obtained from the Cox regression model. The coefficients were:

	coef	coef*	se(coef)	z	p
lsp(MTV, 307.9)MTV	0.0027014	0.002620355	0.0007371	3.665	0.000247 ***
lsp(MTV, 307.9)MTV'	-0.0023599	-0.002289109	0.0007690	-3.069	0.002151 **
Age	0.0129575	0.012568802	0.0053846	2.406	0.016111 *
DmaxBulk	0.0021716	0.002106488	0.0003326	6.530	6.59e-11 ***
DSUVmax	-0.0193221	-0.018742449	0.0017188	-11.241	< 2e-16

*coefficients corrected after internal-external cross-validation by applying a shrinkage factor of 0.97.

Now the lp_risk can be calculated as:

0.002620355 x (MTV lower than the median of 307.9ml) -0.002289109 x (MTV higher than the median of 307.9ml) + 0.012568802 x Age + 0.002106488 x DmaxBulk -0.018742449 x DSUVmax

We can calculate the lp risk for every patient and use it as input in the risk formula to calculate the risk of progression, relapse or death from any cause (outcome PFS). For example for high risk patient A and low risk patient B these calculations are as follows:

Patient A (high risk patient) with an MTV value of 3000ml, an age of 65, DmaxBulk of 500 and DSUVmax of 30 the lp risk is:

(0.002620355 x 3000) – (-0.002289109x(3000-307.9) + (0.012568802 x 65) + (0.002106488 x 300) + (-0.018742449 x 30) = 2.5852

The risk of progression, relapse or death from any cause is:

1 - (exp(-(exp(2.5852 - 0.439058) * 0.2271963674))) * 100= 68.51%

Patient B (low risk patient) with an MTV value of 1000ml, an age of 55, DmaxBulk of 30 and DSUVmax of 70 the lp risk is:

(0.002620355 x 1000) – (-0.002289109x(1000-307.9) + (0.012568802 x 55) + (0.002106488 x 30) + (-0.018742449 x 70) = 0.47857

The risk of progression, relapse or death from any cause is:

1 - (exp(-(exp(0.47857 - 0.439058) * 0.2271963674))) * 100= 21%

Supplemental Reference

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