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Prognostic value of FDG-PET in patients with mantle cell lymphoma: results from the LyMa-PET Project.

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Keywords:

Mantle Cell Lymphoma; FDG-PET; SUV; LyMa trial

Running Title :

Prognostic value of FDG-PET in patients with MCL

Mantle cell lymphoma (MCL) is an incurable aggressive non-Hodgkin lymphoma (NHL), which accounts for approximately 5% of all NHLs. Novel agents and rituximab maintenance therapy (RM) have greatly improved patient outcomes, [1,2] but most patients still experience recurrent relapses. This highlights the need for risk-adapted therapies[1]. The prognostic value of [(18)F]Fluoro-Deoxyglucose Positron-Emission-Tomography (FDG-PET) has already been demonstrated in various lymphoma entities,[3] but its utility in MCL remains unclear[4–12]. In the LyMa-PET project, we centrally reviewed PET results from patients enrolled in the LyMa trial, a prospective, multicenter, international, randomized phase III trial (NCT00921414) that investigated RM after autologous stem-cell transplantion (ASCT) in young previously untreated MCL patients[2] . Our aim was to investigate the prognostic value of the image-derived FDG-PET quantitative indices.

In the LyMa trial, FDG-PET was optional at diagnosis, before ASCT (iPET) and after-ASCT (eotPET), and not used in the decision-making strategy. FDG-PET images were acquired in voluntary centers participating in the LyMa trial, according to the local protocol and following the rules of good practice[13]. FDG-PET data were centrally collected and analyzed on a dedicated workstation (PLANET®Onco-Solution, Dosisoft, France) and evaluated by two experienced readers (CBM and CB), who were blinded to clinical information, treatment arm and follow-up.

For the initial staging, a positive FDG-PET signal was defined as an area of increased uptake thought to be lymphoma-related. Different quantitative metrics were extracted from the FDG-PET data set, measured as volume of interest (VOI) covering the entire nodal and extra-nodal lesions as visualized by increased FDG uptake: SUVmax, defined as the Standard-Uptake-Value (SUV) of the maximum intensity voxel within the VOI; Metabolic Tumor Volume (MTV), defined as the functional volume of the area with the highest uptake, using a 40% thresholding for the segmentation-step; Total Lesion Glycolysis (TLG), defined as the product of SUVmean (average measure of SUV within the calculated boundaries of a lesion) and MTV of the area with the highest uptake. A SUVmax gradient was calculated at baseline for each patient as the difference between SUVmax and the pathological focus with minimal activity. For each metric, the baseline value (i.e. for SUVmax: SUVmax), the values before-ASCT (i.e. for SUVmax: $SUVmax_{iPET}$) and after-ASCT (i.e. for SUVmax: $SUVmax_{eotPET}$) were considered. The reduction between metrics at iPET, eotPET and PET at baseline were calculated (i.e. for SUVmax: $\Delta SUVmax_{iPET}$ and $\Delta SUVmax_{eotPET}$). iPET and eotPET were also interpreted visually using the five-point Deauville scale (DS), as recommended[3]. Details regarding statistical methods are described in the Supplemental data.

Among the 299 patients enrolled in the LyMa study, FDG-PET data from 104 patients were retrieved from 28 different centers (out of 81 centers). This included 104 examinations performed at diagnosis, 64 prior to ASCT and 44 after ASCT. The LyMa-PET population did not differ statistically from the entire LyMa population regarding baseline characteristics, randomization arm, follow up and outcome (Table S1). The four year-PFS calculated from the time of inclusion for the 104 patients was 71.1 %, 95%CI [61.4%;78.8%]; 4y-OS was 79.6%,

95%CI [70.5%;86.2%] and the estimated median follow-up was 56.5 months, 95%CI [52.6;64.1].

We first analyzed FDG-PET parameters at diagnosis and investigated their prognostic value. As shown in previous reports[11], FDG-PET was pathologic in all patients. The sensitivity of FDG-PET for the detection of splenic lesions was 100% (50/50). According to conventional assessment, 80.8% of patients (84/104) had extranodal locations at diagnosis (including bone marrow, digestive tract or ear/nose/throat sites). The sensitivity of FDG-PET was only 42 % for these extranodal lesions (40/104). Quantitative metrics were extracted in all patients but one, due to deviations on quality controls (n=103) (Table S2). FDG avidity was heterogeneous and varied greatly from one patient to another, with SUVmax ranging from 1.8 to 33.8 (median=7.39, Table S2), in line with reported data[4,5]. A broad intra-individual heterogeneity was also observed with a SUVmax gradient >5 in 53 cases (51%) and >10 in 24 cases (23%). With the oncogenesis of MCL being a multistep process, progressing from a less to a more aggressive form[14], a low SUVmax value might be related to less aggressive MCL cells, while high SUVmax values might reflect a more aggressive tumor with a high proliferative index (as observed in Richter's syndrome). Indeed, an elevated SUVmax (>10.3) was found to be associated with aggressive variants (Fisher-Exact p=0.004 and p=0.003, respectively) and Ki67>30% (n=70; Fisher Exact p<0.001 and p<0.001). In contrast, SUVmax was not associated with the MIPI score (classified as Low/Intermediate/High) (Fisher-Exact p=0.529 and p=0.680). These results support the existence of a close relationship between tumor cell biology and SUV in MCL. In addition, they suggest that SUVmax calculation at diagnosis could be used as a prognostic parameter to assess tumor cell aggressiveness and in particular tumor cell proliferation. Unlike the measurement of Ki67 positivity in a tumor biopsy, FDG-PET has the advantage of being a whole-body non-invasive technique.

In terms of prognostic value, all FDG-PET metrics determined on the area with the highest uptake significantly impacted both OS and PFS in the univariate analyses. Patients with a high SUVmax (>10.3) or SUVmax gradient>10 or a high MTV (>41.47) had a shorter PFS (p=0.0003, p=0.0061 and p=0.0043, respectively) and OS (p=0.0003, p= 0.0275 and p=0.0085, respectively) (Figure 1). In the multivariate analysis, only SUVmax>10.3(Table S3) was associated with shorter PFS (p<0.001, HR=5.41; 95% CI: 2.49–11.78) and OS (p<0.001, HR=6.32; 95% CI: 2.58–15.45). We then investigated the predictive value of a scoring system that combines MIPI (Low-Int vs High) and SUVmax (<=10.3 vs >10.3), as previously described[4]. Patients could be classified into three distinct survival groups (Figure 2). The difference in survival was consistent after adjusting for treatment arm (PFS: Group 1 HR=2.9, Group 2 HR=7.7; OS: Group 1 HR=3.5, Group 2 HR=18.8). Due to the small number of cases in the 2 risk-factors group, these results should be interpreted with caution. When MIPI and SUV max > 10.3 were combined only for intermediate risk patients, a better segregation of two risk groups with significantly different PFS and OS profiles could be achieved (Figure 2). Therefore, patients presenting with a high MIPI or intermediate MIPI plus an SUV max >10.3 at diagnosis might be candidates for alternative therapy.

In contrast to previous reported findings in other lymphoma entities[3], no prognostic value of MTV measured on the whole-body was found for PFS or OS (data not shown). These results were calculated in only 33 patients as part of a preliminary study. A large inter-individual variability was observed, with values ranging from 26.7cm3 to 3931cm3. This large difference and the lack of a predictive value on survival might be explained by the frequent splenic involvement in MCL, which increased the MTV while not generally being associated with a poor prognosis[15]. However, the volumetric analyses performed on the lesion with the highest uptake showed a negative prognostic impact on both PFS and OS. This observation reinforces the hypothesis that the prognosis of MCL is linked to the most aggressive contingent within the lesion with the highest uptake.

We then investigated response according to iPET and eotPET. It is interesting to note that the most recent update for the management of malignant lymphomas[3] does not mandate FDG-PET-based response assessment in MCL outside the context of a clinical trial due to heterogeneous published data[5,7,12]. Indeed, the present work is the first to explore the value of FDG-PET in a large group of homogeneously treated patients enrolled in a multicenter prospective study. Results are presented in Tables S4 and S5. We found that visual analysis of iPET and eotPET were not associated with better survival regardless of the chosen positivity cut-off (DS=5, DS≥4 or DS≥3), while $SUVmax_{iPET}$ and $\Delta SUVmax_{eotPET}$ were associated with improved OS and PFS, respectively. These analyses should be interpreted with caution. Nevertheless, they suggest that the magnitude of residual metabolic activity at an interim timepoint may hold a predictive value and that the tumor's chemosensitivity at the end of the treatment with an objective of complete normalization as measured by $\Delta SUVmax_{eotPET}$ seems to be relevant.

In summary, SUVmax of the lesion with the highest uptake determined at diagnosis, has a strong prognostic value for both PFS and OS. A new scoring system combining MIPI and SUVmax might also help to predict patient outcomes. Further prospective investigations are warranted to explore the potential interest of these metrics for therapeutic evaluation. The prospective multicentric LyMa101 study (NCT02896582) will provide an opportunity to confirm these results.

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- Disclosures of conflicts of Interest

- Pr. Le Gouill reports personal fees and non-financial support from Roche, grant support and personal fees from JanssenCilag, personal fees from Celgene, Servier and Gilead outside the submitted work.

- No disclosure for all other authors.

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Figure Legends and Footnotes:

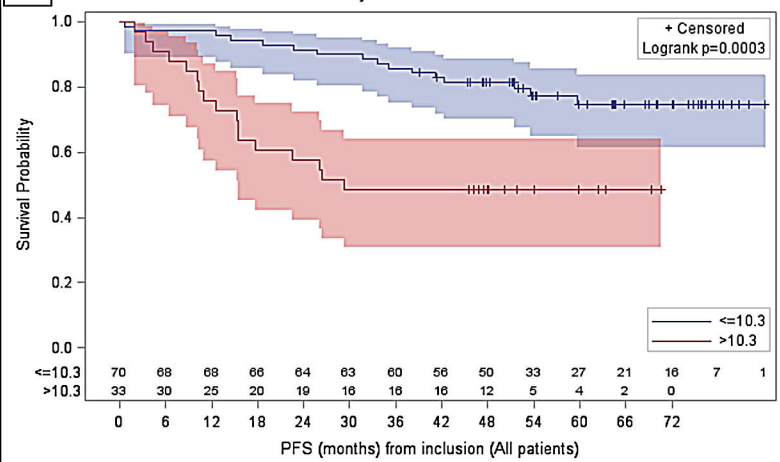
Figure 1-Univariate survival analyses according to metrics threshold

PFS (A) and OS (B) according to SUVmax. PFS (C) and OS (D) according to Metabolic tumor Volume (MTV)-40 %. PFS (E) and OS (F) according to SUVmax gradient.

Figure 2 – Prognostic Index combining MIPI and SUVmax

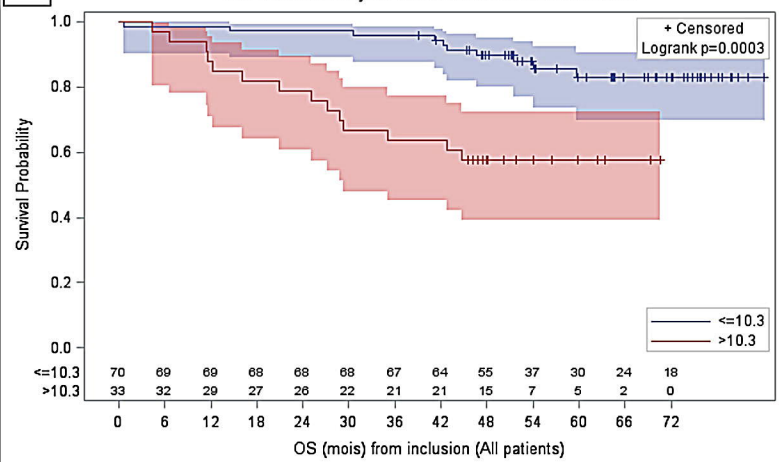
PFS (A) and OS (B) according to MIP and SUVmax. Combining MIPI and SUV max > 10.3 for intermediate patients defines two risk groups with significantly different PFS (C) and OS (D) survival profiles.

A



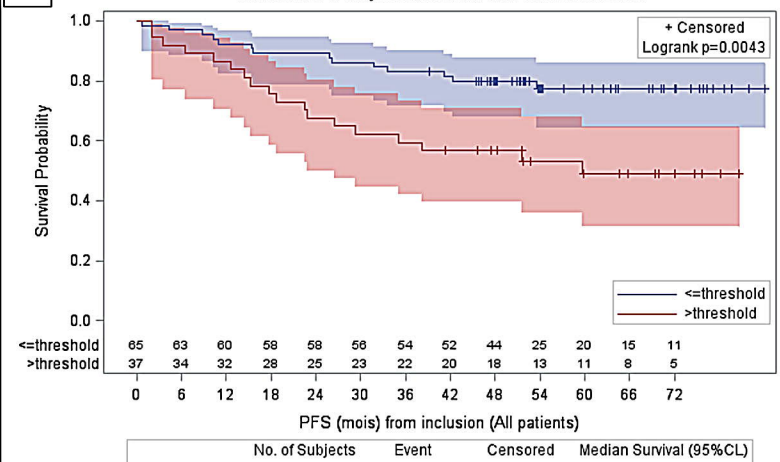
	No. of Subjects	Event	Censored	Median Survival (95%CL)
<=10.3	70	22.9 % (16)	77.1 % (54)	NA (NA ; NA)
>10.3	33	51.5 % (17)	48.5 % (16)	29.3 (15.4 ; NA)

B



	No. of Subjects	Event	Censored	Median Survival (95%CL)
<=10.3	70	14.3 % (10)	85.7 % (60)	NA (NA ; NA)
>10.3	33	42.4 % (14)	57.6 % (19)	NA (29.3 ; NA)

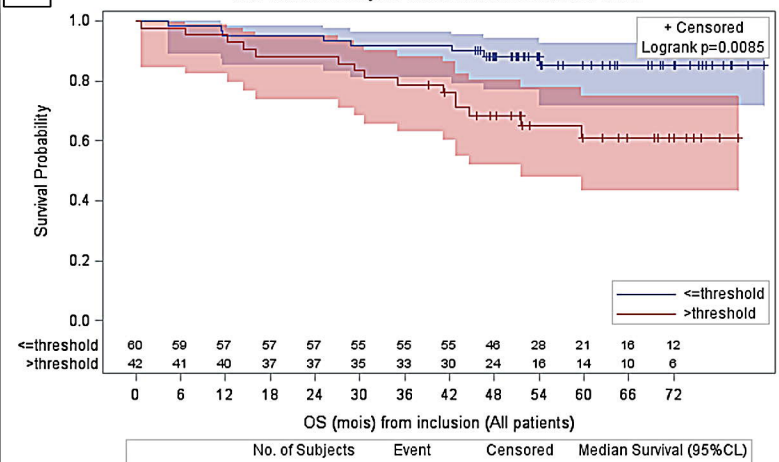
C



	No. of Subjects	Event	Censored	Median Survival (95%CL)
<=threshold	65	21.5 % (14)	78.5 % (51)	NA (NA ; NA)
>threshold	37	48.6 % (18)	51.4 % (19)	59.7 (26.4 ; NA)

Threshold is at 41.47

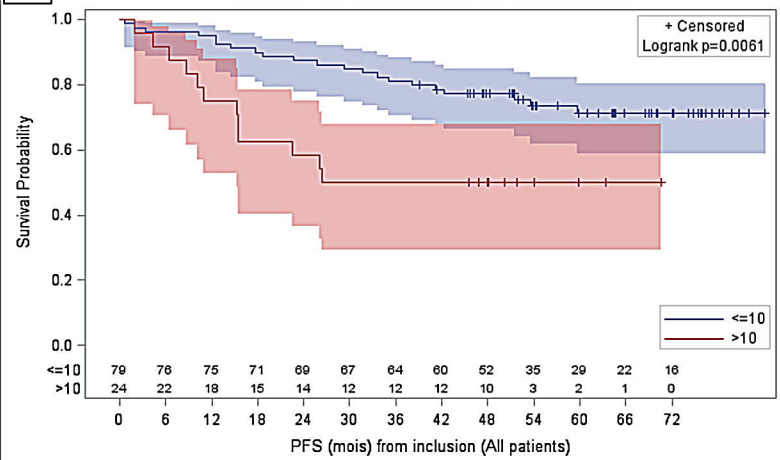
D



	No. of Subjects	Event	Censored	Median Survival (95%CL)
<=threshold	60	13.3 % (8)	86.7 % (52)	NA (NA ; NA)
>threshold	42	35.7 % (15)	64.3 % (27)	NA (51.5 ; NA)

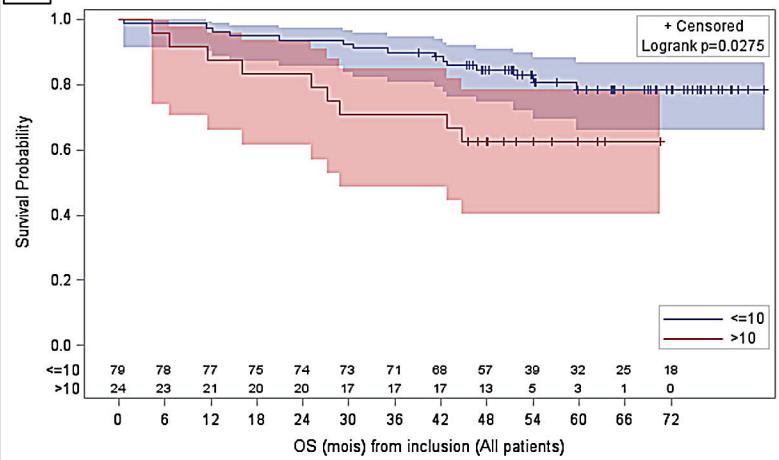
Threshold is at 34.64

E



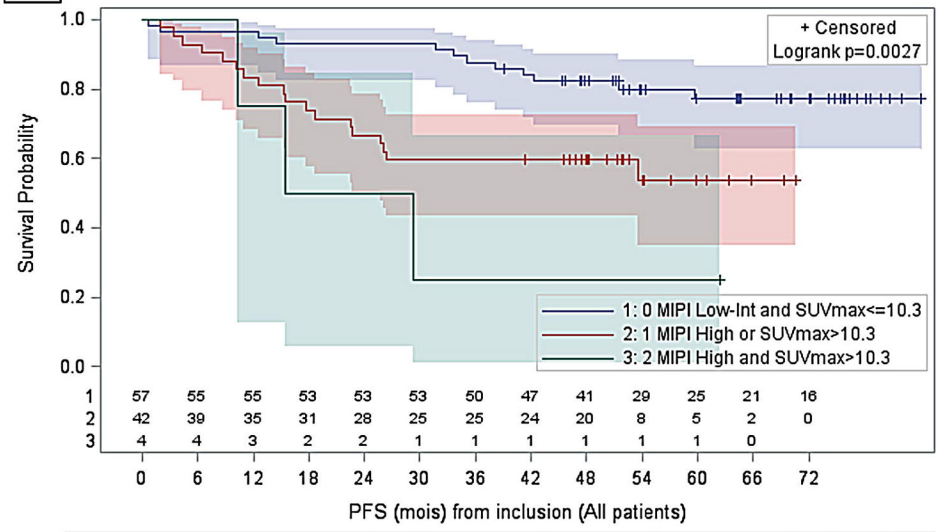
	No. of Subjects	Event	Censored	Median Survival (95%CL)
<=10	79	26.6 % (21)	73.4 % (58)	NA (NA ; NA)
>10	24	50 % (12)	50 % (12)	NA (15.3 ; NA)

F



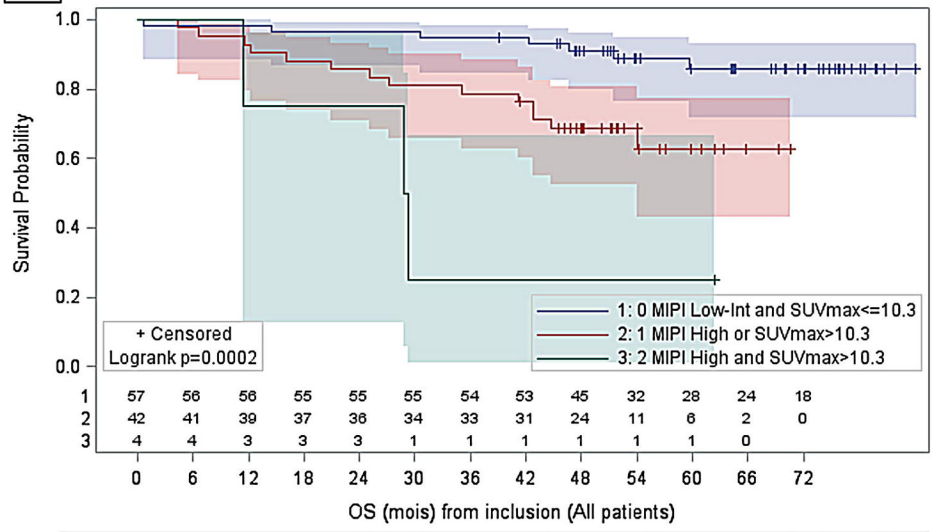
	No. of Subjects	Event	Censored	Median Survival (95%CL)
<=10	79	19 % (15)	81 % (64)	NA (NA ; NA)
>10	24	37.5 % (9)	62.5 % (15)	NA (28.8 ; NA)

A



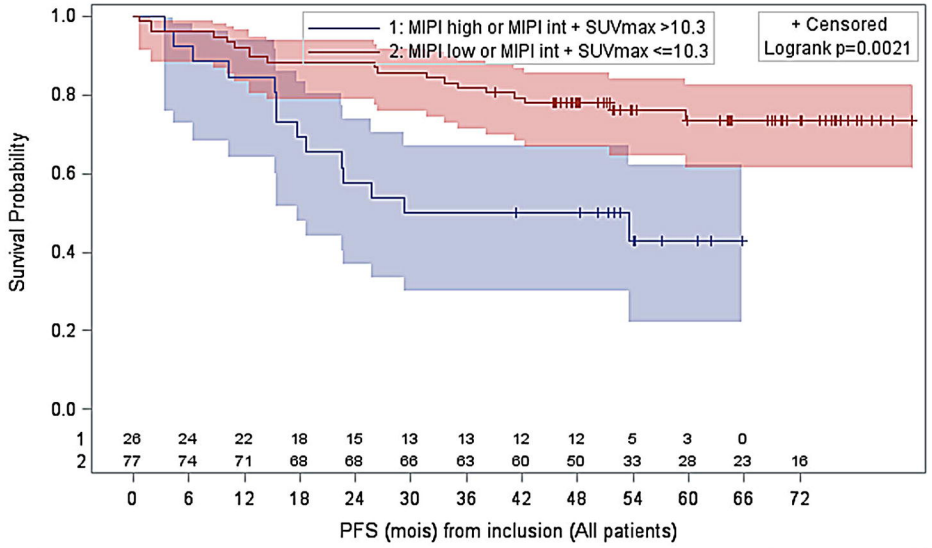
	No. of Subjects	Event	Censored	Median Survival (95%
0 MIPI Low-Int and SUVmax<=10.3	57	21.1 % (12)	78.9 % (45)	NA (NA ; NA)
1 MIPI High or SUVmax>10.3	42	42.9 % (18)	57.1 % (24)	NA (25.8 ; NA)
2 MIPI High and SUVmax>10.3	4	75 % (3)	25 % (1)	22.4 (10.3 ; NA)

B



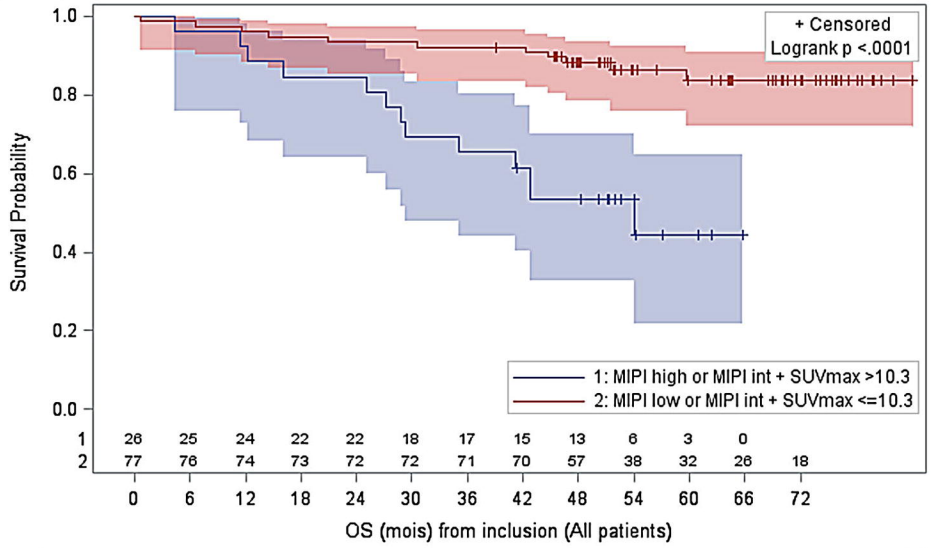
	No. of Subjects	Event	Censored	Median Survival (95%
0 MIPI Low-Int and SUVmax<=10.3	57	12.3 % (7)	87.7 % (50)	NA (NA ; NA)
1 MIPI High or SUVmax>10.3	42	33.3 % (14)	66.7 % (28)	NA (54.1 ; NA)
2 MIPI High and SUVmax>10.3	4	75 % (3)	25 % (1)	29.1 (11.4 ; NA)

C



	No. of Subjects	Event	Censored	Median Survival (95
MIPI high or MIPI int + SUVmax >10.3	26	53.8 % (14)	46.2 % (12)	41.4 (17.7 ; NA
MIPI low or MIPI int + SUVmax <=10.3	77	24.7 % (19)	75.3 % (58)	NA (NA ; NA)

D



	No. of Subjects	Event	Censored	Median Survival (95
MIPI high or MIPI int + SUVmax >10.3	26	50 % (13)	50 % (13)	54.1 (29.3 ; NA
MIPI low or MIPI int + SUVmax <=10.3	77	14.3 % (11)	85.7 % (66)	NA (NA ; NA)

Supplementary Data

Statistics:

At initial staging, FDG-PET results were compared to the status of the disease determined by histology findings (if available), clinical and imaging follow-up. For each of FDG-PET potential metrics, a threshold value was determined using X-tile software (Yale University, New Haven, CT). For visual analysis, three positivity cut-off were studied DS =5, DS ≥4 and DS≥3. End points studied were PFS and OS, determined by clinical and imaging follow-up. Survival functions were calculated using Kaplan-Meier estimates and comparison between categories was made with the log-rank test. Univariate and multivariable analyses were performed using Cox proportional hazards models. Because survival was significantly prolonged in the RM group in the LyMa population, treatment arm was also considered in this analysis along with other baseline factors (aggressive morphological variants, Ki67>30%, MIPI score). The association between SUVmax at diagnosis and these baseline factors was evaluated using the Fisher's exact test. Only p-values< 0.05 were considered as statistically significant.

Multivariate analysis was conducted by first determining the best baseline model for survival using baseline clinical information (including treatment arm and MIPI score) and FDG-PET measures. Because SUVmax and SUVpeak showed similar prognostic values, we chose to assess FDG-uptake only as measured with SUVmax, this metric being the most widely used. For both PFS and OS, the base model was study arm (Non-randomized vs Obs vs RM), MIPI (Low vs Intermediate vs High) and SUV max (<=10.3 vs >10.3). There was no evidence of interaction effects across the three factors. Each metric was added to this model to determine if it provided any additional prognostic value.

Tables:

Table S1-Demographical and baseline characteristics

	LYMA-PET population N=104	LYMA population N=299	Test
Age at inclusion (years)			Wilcoxon
n	104	299	P = 0.523
Missing	0	0	
Median	57.0	57.0	
Min ; Max	41.0 ; 65.0	27.0 ; 65.0	
Sexe			Fisher Exact
Male / Female	78 /26 (75.% / 25%)	236/63 (79%/21%)	P = 0.236
Arm (randomized patients)			Fisher Exact
OBSERVATION	44 (47.8%)	120 (50.0%)	P = 0.691
RITUXIMAB	48 (52.2%)	120 (50.0%)	
LDH			Fisher Exact
N	61 (58.7%)	184 (61.5%)	P = 0.943
> N	40 (38.4%)	108 (36.2%)	
Not done	3 (2.9%)	7 (2.3%)	
Ann Arbor Staging			Fisher Exact
Missing	0	1	P = 0.089
2	4 (3.8%)	18 (6.0%)	
3	16 (15.4%)	31 (10.4%)	
4	84 (80.8%)	249 (83.6%)	
MIPI			Fisher Exact
Low	55 (52.9%)	159 (53.2%)	P = 0.507
Int	32 (30.8%)	82 (27.4%)	
High	17 (16.3%)	58 (19.4%)	

Statistical tests performed between LYMA-PET and Non LYMA-PET populations

Table S2- Description of FDG-PET metrics studied at baseline

	N=103
SUVmax	
Mean (SD)	8.7 (5.0)
Median	7.39
Q1 ; Q3	5.27 ; 11.64
Min ; Max	1.82 ; 33.85
SUVpeak	
Mean (SD)	4.81 (2.59)
Median	4.18
Q1 ; Q3	2.84 ; 6.74
Min ; Max	0 ; 13.96
Metabolic Tumor Volume (cm3)	
Mean (SD)	192.8655 (435.536)
Median	24.39
Q1 ; Q3	9.712 ; 124.890
Min ; Max	0.870 ; 2482.570
Total Lesion Glycolysis (cm3)	
Mean (SD)	820.5 (1667.83)
Median	105.18
Q1 ; Q3	32.93 ; 535.40
Min ; Max	0 ; 9384.41

Table S3- Multivariate survival analyses

Based on the LYMA-PET patient set the best Cox model for PFS includes study arm (Non-randomized vs Observation vs Rituximab), MIPI (Low vs Intermediate vs High) and SUV max (<=10.3 vs > 10.3). There was no evidence of interaction effects across the three factors.

Table S3.1 - Cox Model (Arm, SUVmax and MIPI) for PFS

Parameter	Modality tested	Hazard Ratio	95% Hazard Ratio Confidence Limits		Pr>ChiSq
			Lower	Upper	
SUVmax	>10.3	5.415	2.489	11.779	<.0001
MIPI SCORE	High	2.137	0.808	5.652	0.1257
	Int	2.562	1.133	5.796	0.0239
D arm	Non-randomized	17.454	6.539	46.588	<.0001
	RITUXIMAB	0.358	0.134	0.952	0.0395

Model is based on 103 patients (33 with events and 70 censoring).

Table S3.2 - Cox Model (Arm SUVmax and MIPI) for OS

Parameter	Modality tested	Hazard Ratio	95% Hazard Ratio Confidence Limits		Pr>ChiSq
			Lower	Upper	
SUVmax	>10.3	6.318	2.584	15.445	<.0001
MIPI SCORE	High	4.966	1.548	15.934	0.0071
	Int	3.134	1.172	8.375	0.0228
D arm	Non-randomized	10.507	3.784	29.178	<.0001
	RITUXIMAB	0.900	0.304	2.669	0.8499

Model is based on 103 patients (24 with events and 79 censoring).

Table S4- Description of FDG-PET metrics studied after induction therapy and at end of treatment

	Before transplantation N=64	End of Treatment N=44
SUVmax		
Median	1.9	1.9
Range	[0.5-16]	[0.5-24.1]
ΔSUVmax		
Median	- 68%	- 76 %
Range	[-100% - +271%]	[-100% - +17%]
SUVpeak		
Median	1.4	1.4
Range	[0.3-20.3]	[0.4-17.2]
ΔSUVpeak		
Median	69%	-78%
Range	[-95% - +278%]	[-96% - + 13%]
Deauville Score		
1	19 (29.6%)	23 (52.3%)
2	23 (35.9%)	12 (27.3%)
3	8 (12.5%)	6 (16.6%)
4	6 (9.3%)	1 (2.3%)
5	8 (12.5%)	2 (4.5%)

Table S5-Prognostic values (p-value and Hazard Ratios when p-value < 0.05) of metrics derived FDG-PET before transplantation and end of treatment.

		Metrics	Modality	P-value	Hazard Ratio	95% Hazard Ratio Confidence	
						Lower	Upper
Before Transplantation (n=64)	*PFS*	$SUVmax_{iPET}$	>6,3	0.0977	3.627	0.789	16.667
	OS	$SUVmax_{iPET}$	>6,3	0.0199	6.927	1.357	35.351
	PFS	$\Delta SUVmax_{iPET}$	>-29.65%	0.2976	-	-	-
	OS	$\Delta SUVmax_{iPET}$	>-29.65%	0.1089	-	-	-
End of Treatment (n=41)	*PFS*	$SUVmax_{eotPET}$	>1,18	0.3879	-	-	-
	OS	$SUVmax_{eotPET}$	>1,18	0.0708	0.228	0.046	1.134
	PFS	$\Delta SUVmax_{eotPET}$	>-90.88%	0.0209	0.196	0.049	0.781
	OS	$\Delta SUVmax_{eotPET}$	>-90.88%	0.1836	-	-	-