Journal of Nuclear Medicine, published on October 21, 2021 as doi:10.2967/jnumed.121.262205

18F-FDG PET improves baseline clinical predictors of response in diffuse large B-cell lymphoma: The HOVON-84 study

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Funding: Alpe d'HuZes/KWF fund (VU2012-5848).

Word count: 5000

Running title: PET improves DLBCL response predictors

ABSTRACT

We aimed to determine the added value of baseline metabolic tumor volume (MTV) and interim positron emission tomography (I-PET) to age-adjusted international prognostic index (aaIPI) to predict 2-year progression-free survival (PFS) in diffuse large B-cell lymphoma (DLBCL). Secondary objectives were to investigate optimal I-PET response criteria (using Deauville score (DS) - or quantitative change in maximum Standardized Uptake Value (ΔSUVmax) between baseline and I-PET). **Methods:** Observational I-PET scans were performed after four cycles R(R)-CHOP14 (I-PET4) in the HOVON-84 randomized clinical trial (EudraCT 2006-005174-42), and centrally reviewed using DS (cut-off 4-5). Additionally, ΔSUVmax (prespecified cut-off 70%) and baseline MTV were measured. Multivariable hazard ratios (HR), positive (PPV), and negative predictive values (NPV) were obtained for 2-year PFS. **Results:** 513 I-PET4 scans were reviewed according to DS, and ΔSUVmax and baseline MTV were available for 367 and 296 patients. NPV of I-PET ranged between 82% and 86% for all PET response criteria. Univariate HR and PPV were optimal for ΔSUVmax (4·8 and 53%, respectively) compared to DS (3·1 and 38%, respectively). AaIPI and ΔSUVmax independently predicted 2-year PFS (HRs 3·2 and 5·0, respectively); adding MTV slightly improved this. Low/low-intermediate aaIPI combined with ΔSUVmax>70% (37% of patients) yielded a NPV of 93%, and the combination of high-intermediate/high aaIPI and ΔSUVmax≤70% a PPV of 65%. **Conclusion:** In this DLBCL study, I-PET after four cycles R(R)-CHOP14 added predictive value to aaIPI for 2-year PFS, and both were independent response biomarkers in a multivariable Cox model. We externally validated that ΔSUVmax outperformed Deauville score in 2-year PFS prediction.

Keywords: DLBCL; positron emission tomography; Deauville score; ΔSUVmax; metabolic tumor volume

INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin's lymphoma, characterized by an aggressive clinical course. Standard first-line treatment consists of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) generally administered in two (R-CHOP14) or three weeks intervals (R-CHOP21).

No significant benefits were shown for R-CHOP14 vs R-CHOP21 in two large randomized clinical trials (RCT) (*1,2*). Approximately 25-40% of DLBCL patients experience relapse or progression in the first years after diagnosis. This underlines the need for early stratification between good and poor responders (*3,4*). An early switch to second-line treatment in poor responders might improve patient outcomes.

The international prognostic index (IPI) and age-adjusted IPI (aaIPI), both consisting of baseline clinical characteristics, have retained prognostic value after the introduction of rituximab (*5*). However, these prognostic indices are not widely used for individual treatment adaptation except for research purposes (*6*), do not inform about chemosensitivity, and are unable to identify a subgroup with survival clearly below 50%. Therefore, a powerful biomarker (e.g. imaging characteristics during treatment reflecting chemosensitivity) of early response is needed. Recently, measurement of baseline metabolic tumor volume (MTV) was reported to have prognostic value in DLBCL and was suggested as an alternative for IPI (*7,8*). Combining MTV with early response assessment at 18F-fluoro-2-deoxy-D-glucose (18F-FDG) interim positron emission tomography (I-PET) further improved prediction of progression-free survival (PFS) (*7,8*). Several operationalisations of I-PET response criteria have been proposed, e.g. the visual Deauville 5-point score (DS, with various possible cut-offs) (*9*) and quantitative changes of 18F-FDG uptake between baseline and I-PET (*10,11*).

In the HOVON-84 study, DLBCL patients were randomized between R-CHOP14 and R-CHOP14 with intensified rituximab in the first four cycles (RR-CHOP14, *12*). In both arms an observational I-PET

was performed after four cycles (I-PET4). To our knowledge, this was the first DLBCL RCT in which I-PET4 results did not lead to treatment modification, which enables to examine its predictive value.

Our primary objective was to use prespecified cut-off values and methodologies from previous DLBCL studies in order to validate the potential added predictive value of baseline MTV and I-PET4 response to baseline clinical characteristics (aaIPI) for 2-year PFS in DLBCL in an independent study. Secondary objectives were to determine optimal I-PET4 response criteria.

MATERIALS AND METHODS

Study population

Newly diagnosed DLBCL patients included in the HOVON-84 NHL study (EudraCT2006-005174-42, NTR1014) with an I-PET4 were eligible. For this analysis, we combined the R-CHOP14 and RR-CHOP14 study arms, as there were no statistically significant outcome-differences between the arms (*12*). Randomization was stratified for aaIPI score. Main eligibility criteria of the clinical study are described elsewhere (*12,13*). The HOVON-84 study has been approved by the institutional review board of all centers and participants signed an informed consent form.

Study design

Patients aged ≥66 years received six cycles of R-CHOP14 followed by two additional doses of rituximab; patients ≤65 years received eight cycles R-CHOP14. Baseline PET was highly recommended, but not mandatory. I-PET scans were performed after four cycles R-CHOP14 or RR-CHOP14 (without treatment modifications, I-PET4).

Qualitative and quantitative image analysis

Baseline PET scans were analysed with the semi-automatic ACCURATE-tool (*14*) (Figure 1) to obtain MTV using fixed SUV≥4·0 (*15,16*). Continuous MTV values had a non-normal distribution and were log-transformed (logMTV) using the natural logarithm. We used both the continuous and dichotomized MTV with a prespecified cut-off adopted from the PETAL study to identify a high MTV (>345ml) and a low MTV group (MTV ≤345ml) (*8*).

I-PET4 scans were centrally reviewed by two independent reviewers from a pool of ten reviewers (*13*) according to DS criteria (*9,17*). Discrepancies were resolved by adjudication (OSH). DS4-5 was categorized as no complete metabolic response (PET-positive) and DS1-3 as complete metabolic response (PET-negative) (*9,17*). DS4 was assigned when tumor maximum standardized uptake value (SUVmax) exceeded hepatic SUVmax<3 times, and DS5 in case of new lymphoma lesions or when tumor SUVmax was ≥3 times hepatic SUVmax (*9*). The accuracy of other DS cut-off values (i.e. 1 vs 2-5, 1-2 vs 3-5, and 1-4 vs 5) for I-PET4 were evaluated in sensitivity analyses.

In patients with a baseline PET and an I-PET4 with DS2-5 scores, we measured the SUVmax-change between the baseline and I-PET4 (ΔSUVmax). For DS1, ΔSUVmax was set at 100% reduction (*9*). We applied a prespecified ΔSUVmax cut-off of 70% reduction between baseline and I-PET4 to define a positive (≤70%) or negative (>70%) I-PET (*10*).

Statistical analysis

The primary outcome measure was 2-year PFS, defined as time from randomisation to disease progression, relapse, or death from any cause within 2 years (*18*). Survival curves were obtained with Kaplan-Meier analyses for PFS stratified by dichotomized PET response criteria, and compared with log-rank tests. We used univariate and multivariable Cox proportional hazard regression models to assess effects of baseline clinical factors (aaIPI, age, B-symptoms, MTV, gender, treatment arm) and I-PET4

response criteria (DS, ΔSUVmax) on 2-year PFS. A backward Wald elimination procedure was used to test which prognostic factors were independently associated with 2-year PFS. In addition, 2x2 contingency tables were constructed to calculate diagnostic measures (i.e. sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV)) to predict 2-year PFS. Sensitivity, specificity, predictive values, univariate hazard ratio (HR) and receiver operating curve were used to define optimal I-PET4 response criteria to predict 2-year PFS. We examined whether addition of baseline MTV to the multivariable Cox model improved prediction. Statistical analyses were performed using SPSS Statistics (IBM, version 22) and R (version 3.6.3). A *p*-value <0·05 was considered statistically significant.

RESULTS

Study population

Five-hundred seventy-four eligible DLBCL patients were included in the HOVON-84 study; 534 (93%) underwent I-PET4. Twenty-one I-PET4 scans were not evaluable (Figure 1). The distribution of baseline characteristics and 2-year PFS were similar for patients with or without baseline MTV, I-PET4, and ΔSUVmax evaluations (Table 1).

Prognostic value of baseline aaIPI and MTV

After a median follow-up of 91 (IQR 84-101) months the estimated 2-year PFS was 79% (95% confidence interval (CI) 76%-83%). Most patients belonged to the low-intermediate or high-intermediate aaIPI groups (35% and 50%, respectively, Table 1). In the Kaplan-Meier analysis both low and low-intermediate aaIPI survival curves and high-intermediate and high aaIPI survival curves crossed each other without statistically significant differences (Supplemental Figure 1a). Dichotomization into low/low-intermediate and high-intermediate/high yielded a 2-year PFS of 91% (95%CI 87%-95%) and

71% (95%CI 66%-76%), respectively with a corresponding univariate HR of 3·6 (95%CI 2·2-5·9, Supplemental Figure 1b, Table 2).

Out of 384 patients who underwent baseline PET, baseline MTV was measurable in 296 (52%, Figure 1). The continuous logMTV had a univariate HR of 1·4 (95%CI 1·2-1·8, Supplemental Table 1). Patients in the low MTV group (MTV≤345ml, *n*=137; 46%) had a 2-year PFS of 86% (95%CI 80%-92%) vs 75% (95%CI 68%-81%) in the high MTV group (MTV>345 ml, *n*=159; 54%), with a corresponding univariate HR of 2·0 (95%CI 1·1-3·4 Table 2). I-PET and end-of-treatment PET scans were both available in 474 patients (Supplemental Table 2), with an overall agreement of 87% (95%CI 84%-90%).

I-PET4 analyses

Out of 513 I-PET4 scans, 113 (22%) were rated as PET-positive (no complete metabolic response). Dichotomization of I-PET4 results in DS4-5 (positive) vs DS1-3 (negative) yielded a 2-year PFS of 61% (95%CI 52%-70%) for I-PET4 positive and 84% (95%CI 81%-88%) for I-PET4 negative patients (P<0·001) with a corresponding univariate HR of 3·1 (95%CI 2·1-4·5, Table 2, Figure 2a). Within the patients who experienced a relapse, the median time to relapse for I-PET4 positives was 8·1 months (IQR 4·4-23·2) vs. 18·1 months (IQR 8·3-46·3) for I-PET negatives, respectively. Corresponding PPV and NPV for 2-year PFS were 38% (95%CI 30%-47%) and 85% (95%CI 81%-88%), respectively.

Optimal I-PET4 response criterion

For various DS cut-off values, NPVs ranged between 82% and 85% for I-PET4 (Table 2). PPVs varied widely for different cut-offs (22%-68%), the highest PPV was seen for the DS5 cut-off in I-PET4 (68%). Also, univariate HR of 7·4 was highest for the cut-off DS1-4 vs DS5, yielding the best separation between good and poor outcome (Supplemental Figure 2). However, only 25/513 patients (5%) had a DS5.

ΔSUVmax analysis was feasible in 367 of 574 patients (64%, Figure 1). In patients with ≤70% ΔSUVmax reduction between baseline and I-PET4 (*n*=38, 10%) the 2-year PFS was 47% (95%CI 31%-63%), vs 83% (95%CI 78%-87%) for patients with >70% reduction (Figure 2b, P<0·001) with a univariate HR of 4·8 (95%CI 2·9-8·0). Corresponding PPV and NPV values for 2-year PFS were 53% (95%CI 37%-68%) and 83% (95%CI 78%-86%), respectively (Table 2). Repeating these comparisons in the 296 patients with complete metrics on baseline MTV yielded similar results (Supplemental Table 3).

PPV and HRs were better for ΔSUVmax compared to the most commonly used DS4-5 cut-off (53% vs 38% and 4·8 vs 3·1, respectively). NPV was above 80% for all applied criteria. When comparing ΔSUVmax to the most commonly used DS4-5 cut-off, ΔSUVmax was preferred for prediction of 2-year PFS, but the highest PPV and HR were found for the DS5 cut-off.

Combined baseline and I-PET4 analysis

Statistically significant prognostic factors for 2-year PFS in univariate Cox regression analyses were ΔSUVmax ≤70%, high-intermediate/high aaIPI, and B-symptoms. In multivariable analysis, high-intermediate/high aaIPI and ≤70% reduction of ΔSUVmax were independently associated with 2-year PFS (Supplemental Table 4). Low/low-intermediate aaIPI and ΔSUVmax>70% (37% of patients) resulted in a NPV of 93% (95%CI 87%-96%), while high-intermediate/high aaIPI and ΔSUVmax≤70% (6% of patients) resulted in a PPV of 65% (95%CI 45%-81%, Supplemental Figure 3).

Dichotomized baseline MTV did not add prognostic value to ΔSUVmax and aaIPI for prediction of 2-year PFS. When adding continuous logMTV to the multivariable Cox model, aaIPI was eliminated by Backward elimination, yielding logMTV, age>60, B symptoms, and ΔSUVmax as independently associated factors with 2-year PFS (Supplemental Table 1).

Overall survival (OS) analyses

Results of the response criteria and uni- and multivariable analyses for 2-year OS are presented in Supplemental Tables 5-7 and Supplemental Figure 4.

DISCUSSION

In this multicenter study in DLBCL I-PET after four cycles of R(R)-CHOP14 added predictive value to baseline clinical characteristics (aaIPI) for 2-year PFS, with high NPVs (82-86%) independent of all I-PET response criteria. However, the PPV was still relatively low. Combining clinical and PET data showed that aaIPI and ΔSUVmax were independently associated with 2-year PFS with HRs of 3·2 and 5·0, respectively. Adding log-transformed baseline MTV only slightly improved the predictive value combined with the ΔSUVmax response criteria. As a secondary objective, we compared the most commonly used visual and semi-quantitative criteria, and externally validated that ΔSUVmax criteria were the optimal I-PET4 criteria to predict 2-year PFS with a HR of 4·8 and PPV of 53%.

Based on the PPV and univariate HR in I-PET, the DS5 cut-off performed best with a PFS clearly below 50% for the DS5 group. However, the percentage of DS5-positive patients is low (5%), but this group could be of interest for future new therapy strategies. The univariate HR for 2-year PFS with DS4-5 cut-off in I-PET4 was 3·1 (95%CI 2·1-4·5), which is similar to the pooled HR of 3·1 (95%CI 2·5-3·9) in a systematic review, even though in that review I-PET was performed after one to four cycles of treatment and less strict I-PET response criteria were applied (*19*). The NPV for 2-year PFS in our study was 85%, which is in line with these previous studies generally reporting NPVs above 80% (range 64%–95%, *19*).

Two recent retrospective DLBCL studies analysed the value of I-PET after four cycles (*20,21*), and both concluded that ΔSUVmax had a higher accuracy and PPV to predict PFS than DS. The retrospective study from Itti et al. (*n*=114, I-PET after two cycles), who analysed different cut-offs for DS after two cycles, reported PPVs for DS4-5 and ΔSUVmax that were remarkably identical to our study (PPV 39% vs

38% and PPV 52% vs 53%, respectively) (*22*). A DLBCL subgroup analysis of the PETAL study also reports a more favourable PPV for ΔSUVmax I-PET assessment compared to the Deauville assessment (*23*).

Baseline clinical characteristics and chemo-immunotherapy sensitivity are both relevant factors for outcome prediction. This was demonstrated in our multivariable analysis, where aaIPI and ΔSUVmax (reflecting chemosensitivity) were both independent predictors of 2-year PFS. Again, the subgroup with both high-intermediate/high aaIPI and ΔSUVmax≤70% had a PFS clearly below 50%, but is relatively small (6% of all patients). Selection of a poor risk group of "only" 6% is justified both from a cost awareness perspective as well as selecting the group most likely not be cured by standard treatment. These patients can be treated within clinical trials investigating the efficacy of new drugs.

Several relatively small retrospective studies reported inconsistent results of associations of clinical characteristics and I-PET results (DS and/or ΔSUVmax) with survival in multivariable Cox models (*7,22,24*). Two prospective studies concluded that only I-PET and not IPI was independently associated with event-free survival (*25,26*). The randomized phase III trials PETAL (I-PET after 2 cycles of R-CHOP21) and CALGB-50303 (I-PET after two cycles R-CHOP21 or DA-EPOCH-R) also concluded that I-PET with ΔSUVmax (cut-off 66%) and IPI were independent predictors for EFS and PFS (*11,27*), respectively.

Baseline MTV assessment was not a strong predictor of 2-year PFS in our study (Table 2, Supplemental Table 1,3,5,7). We used a fixed SUV≥4·0 segmentation method, based on a recent study showing that this method performed best and had a similar discriminative power compared to other segmentation methods (*16*). Addition of dichotomized baseline MTV (345ml cut-off) to ΔSUVmax did not improve the predictive value, but log-transformed continuous MTV added some independent predictive value when combined with ΔSUVmax. In a secondary analysis of the PETAL RCT (DLBCL subset, I-PET after two cycles, same MTV-software and -methodology as in our study), baseline MTV and ΔSUVmax were the only independent outcome predictors (*8,28*). We could not confirm these findings; possible explanations are the different PET-timing (HOVON-84: I-PET4) and/or patient characteristics (HOVON-84:

median age 3 years higher, advanced stage 82% vs 58% in PETAL). We chose a higher ΔSUVmax, because the PET timing was different (I-PET4 vs I-PET2) and to validate a formerly presented cut-off (*10,20*). This does not explain the difference in added value of MTV since positivity percentages were the same (10·4% vs 9·6% in PETAL), as well as 2-year PFS for the positive (46·9 and 46·7%) and negative groups (80·2 and 82·5%) according to ΔSUVmax criteria for HOVON-84 and PETAL, respectively. Recently, Vercellino et al. showed that a combination of high baseline MTV and high performance status (≥2) identifies an ultra-risk DLBCL population (*29)*. We could not confirm this extra risk in our study (data not shown).

There were several strengths of our study. First, there are no other large randomized trials with a homogeneous first-line treatment regimen and an observational I-PET after four R-CHOP14 cycles. Another strength was the central review procedure for Deauville scoring with two independent reviewers and a strict DS5 definition, which allowed for an analysis to determine the optimal I-PET4 response criteria (*13*).

Based on the relatively low values for PPV, escalation of treatment for the I-PET4 positive group is not recommend yet for clinical practice, but evidence for I-PET adapted treatment is clearly growing (*11,30-32*). The GAINED RCT (*30*) enrolled 670 DLBCL patients (aged 18-60 years, aaIPI ≥1); I-PET2+/I-PET4- patients (*n*=87) were scheduled to receive high-dose chemotherapy with autologous stem cell transplantation and had no statistically different PFS compared to the I-PET2-/I-PET4- patients (*n*=401) who continued standard treatment. However, no firm conclusions can be made, because there was no randomization within these I-PET adapted groups.

As the NPV is acceptable (>80% for all criteria), reduction of treatment based on I-PET4 could be of interest, especially for low-risk and elderly patients. The randomized FLYER trial showed that in a group of 592 DLBCL patients (aged 18-60 years, no aaIPI risk factors, no bulky disease) that four cycles of R-CHOP21+2R was non-inferior compared to six cycles of R-CHOP21 (*6*), and in an exploratory analysis

the international GOYA RCT found no PFS benefit with eight cycles R-CHOP21 compared with six cycles R-CHOP21+2R (*31*). The S1001 study presented 4 cycles R-CHOP as the new standard for the majority of patients with limited stage disease(*32*).

CONCLUSIONS

In this large DLBCL study, I-PET after four cycles R(R)-CHOP14 added predictive value to aaIPI for 2-year PFS, and both were independent response biomarkers in a multivariable Cox model yielding a high NPV for 2-year PFS of 93%. Comparing the most commonly used DS and ΔSUVmax cut-offs, the optimal response criterion for I-PET4 to predict 2-year PFS was ΔSUVmax.

FINANCIAL DISCLOSURES

Alpe d'HuZes/KWF fund, provided by the Dutch Cancer Society (VU2012-5848).

DISCLOSURES

PJL reports research funding from Roche, Takeda, and Servier, and honoraria for advisory boards from Roche, Takeda, Servier, Genmab, Celgene and Genentech. JMZ reports research funding and advisory boards from Roche.

KEY POINTS

QUESTION: Evaluation of the optimal baseline and early response assessment criteria in a RCT

PERTINENT FINDINGS: AaIPI and ΔSUVmax were independent predictors for 2-year PFS in DLBCL. 6% of patients had a high PPV of 65% resulting in poor survival outcome

IMPLICATIONS FOR PATIENT CARE: this subgroup is of interest for testing new therapy strategies in DLBCL

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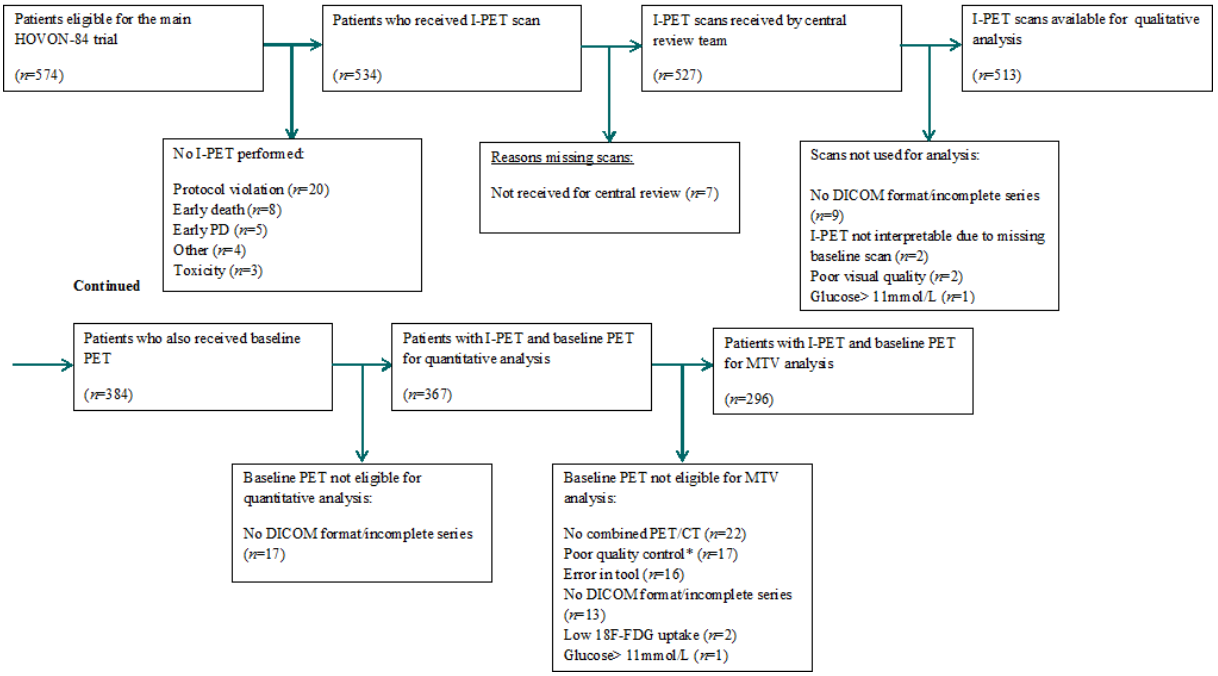
32 Persky DO, Li H, Stephens DM. et al. Positron emission tomography–directed therapy for patients with limited-stage diffuse large B-cell lymphoma: results of intergroup national clinical trials Network Study S1001. *J Clin Oncol.* 2020;38:3003-3011.

FIGURE 1 Flowchart of PET scans available for the I-PET4, ΔSUVmax and baseline MTV analyses



**PET quality was acceptable when liver SUVmean was 1·3-3·0 and the total image activity between 50-80% of the total injected dose.*

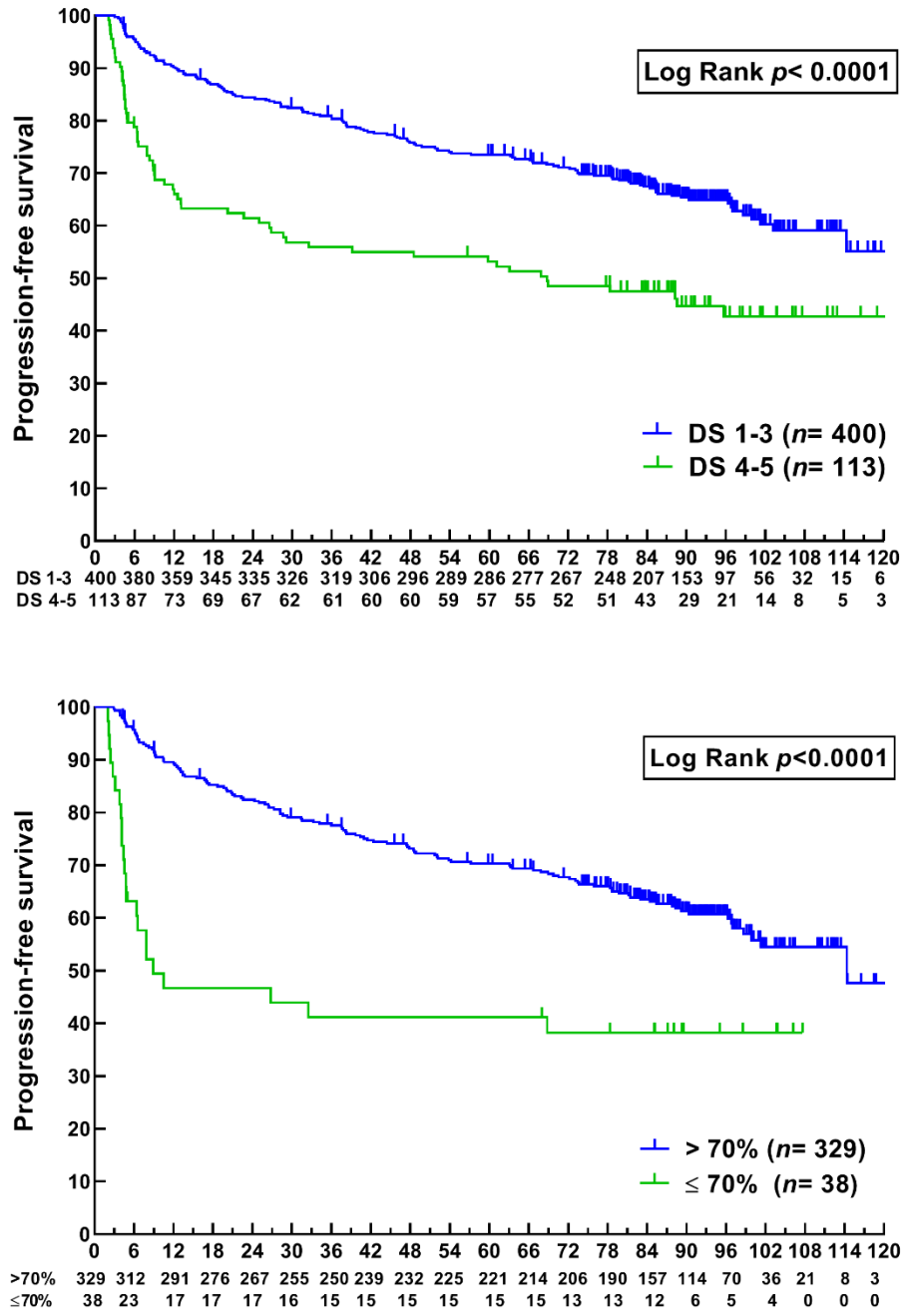


FIGURE 2 Kaplan-Meier curves with numbers at risk for progression-free survival in months stratified by I-PET4 result according to DS (2a) and according to ΔSUVmax result (2b).

Abbreviations: DS=Deauville 5-point scale; I-PET4=interim 18F-FDG PET(/CT) after four treatment cycles; ΔSUVmax=reduction of maximum standardized uptake value between baseline and I-PET4.

TABLES

TABLE 1 Baseline Patient Characteristics

	I-PET4	**ΔSUVmax**	**Baseline MTV**
	N (%)	**N (%)**	**N (%)**
	513 (100)	367 (100)	296 (100)
Age at diagnosis (years)			
median (range)	65 (23-80)	65 (23-80)	65 (23-80)
≤60	172 (33·5)	123 (33·5)	96 (32·4)
>60	341 (66·5)	244 (66·5)	200 (67·6)
Gender			
male	267 (52·0)	192 (52·3)	150 (50·7)
female	246 (48·0)	175 (47·7)	146 (49·3)
WHO performance status			
0	266 (51·9)	201 (54·8)	165 (55·7)
1	183 (35·7)	118 (32·2)	92 (31·1)
2	61 (11·9)	46 (12·5)	37 (12·5)
unknown	3 (0·6)	2 (0·5)	2 (0·7)
Ann Arbor Stage			
II	97 (18·9)	61 (16·6)	52 (17·6)
III	163 (31·8)	113 (30·8)	90 (30·4)
IV	253 (49·3)	193 (52·6)	154 (52·0)
LDH			
normal	171 (33·3)	124 (33·8)	98 (33·1)
>normal	342 (66·7)	243 (66·2)	198 (66·9)
aaIPI			
low	36 (7·0)	23 (6·3)	21 (7·1)
low-intermediate	177 (34·5)	127 (34·6)	97 (32·8)
high-intermediate	255 (49·7)	181 (49·3)	150 (50·7)
high	45 (8·8)	36 (9·8)	28 (9·5)
B symptoms			
no	297 (57·9)	211 (57·5)	169 (57·1)
yes	216 (42·1)	156 (42·5)	127 (42·9)
Treatment Arm			
R-CHOP14	252 (49·1)	186 (50·7)	150 (50·7)
RR-CHOP14	261 (50·9)	181 (49·3)	146 (49·3)
Diagnosis-treatment interval (days)	20 (13-28)	20 (13-28)	20 (14-28)
Median(IQR)	1-112	1-81	1-81
range			
Baseline PET	384 (74·9)	367 (100)	296 (100)

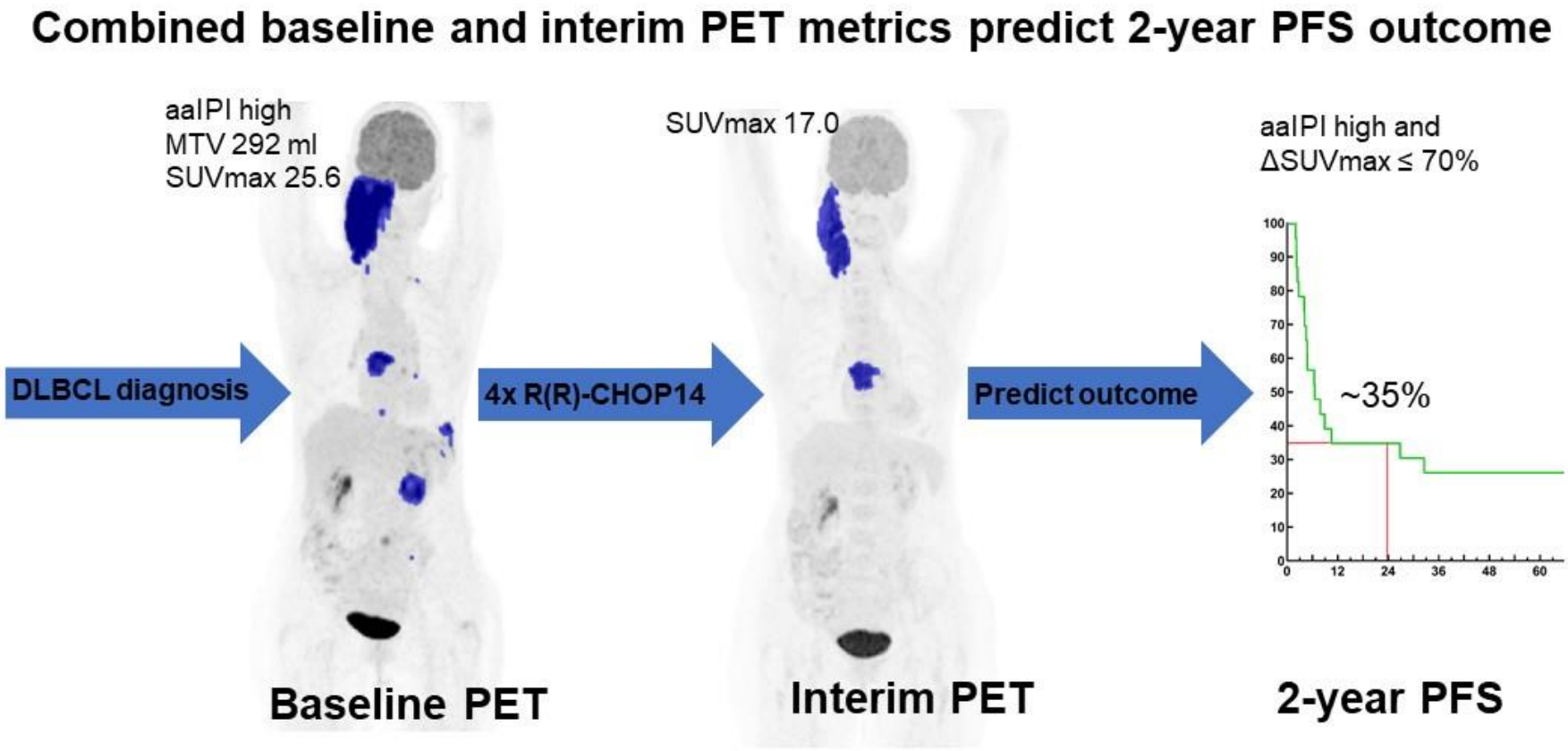
Abbreviations: aaIPI=age-adjusted international prognostic index; ΔSUVmax=reduction of maximum standardized uptake value between baseline and I-PET4; I-PET4=interim 18F-FDG PET(/CT) after four cycles; IQR=interquartile range; LDH=lactate dehydrogenase; MTV=metabolic tumor volume; WHO=world health organization.

TABLE 2 Diagnostic and prognostic measures for aaIPI, baseline MTV, for different cut-off values of the Deauville 5-point scale at I-PET4, and ΔSUVmax for 2-year PFS

			Diagnostic information				Prognostic information		Discrimination
		Number of patients (*n*)	**Negative Predictive Value %(95%CI)**	**Positive Predictive Value %(95%CI)**	**Sensitivity %(95%CI)**	**Specificity %(95%CI)**	**Univariate Hazard Ratio (95%CI)**	***p*-value**	**AUC (95%CI)**
AaIPI	**L/LI vs HI/H**	213 vs 300	91·1 (86·5-94·2)	28·7 (23·9-34·0)	81·9 (73·5-88·1)	47·6 (42·8-52·4)	3·59 (2·18-5·90)	<0·0001	0·63 (0·58-0·68)
Baseline MTV	**≤345ml vs >345ml**	137 vs 159	86·1 (79·4-90·9)	25·2 (19·2-32·4)	67·8 (55·1-78·3)	49·8 (43·5-56·1)	1·96 (1·13-3·38)	0·0161	0·58 (0·52-0·65)
I-PET4	**DS1 vs DS2-5**	178 vs 335	82·0 (75·7-87·0)	21·8 (17·7-26·5)	69·5 (60·2-77·5)	35·8 (31·3-40·5)	1·26 (0·83-1·91)	0·275	0·53 (0·48-0·57)
	DS1-2 vs DS3-5	290 vs 223	84·5 (79·9-88·2)	26·9 (21·5-33·1)	57·1 (47·6-66·2)	60·1 (55·2-64·7)	1·95 (1·32-2·87)	<0·0001	0·59 (0·54-0·64)
	DS1-3 vs DS4-5	400 vs 113	84·5 (80·6-87·7)	38·1 (29·6-47·3)	41·0 (32·0-50·5)	82·8 (78·9-86·2)	3·07 (2·08-4·54)	<0·0001	0·62 (0·58-0·66)
	DS1-4 vs DS5	488 vs 25	82·0 (78·3-85·1)	68·0 (48·4-82·8)	16·2 (10·4-22·4)	98·0 (96·2-99·0)	7·40 (4·39-12·48)	<0·0001	0·57 (0·56-0·59)
ΔSUVmax	**>70% vs ≤70% ≤70%**	329 vs 38	82·7 (78·2-86·4)	52·6 (37·3-67·5)	26·0 (17·5-36·7)	93·8 (90·4-96·0)	4·80 (2·88-8·00)	<0·0001	0·60 (0·57-0·63)

Abbreviations: AaIPI=age-adjusted international prognostic index; AUC=area under the receiver operating curve; DS=Deauville 5-point scale; ΔSUVmax=reduction of maximum standardized uptake value between baseline and I-PET4; H=high risk group; HI=high-intermediate risk group; I-PET4=interim 18F-FDG PET(/CT) after four cycles; MTV=metabolic tumor volume; PFS=progression-free survival

GRAPHICAL ABSTRACT



SUPPLEMENTAL MATERIALS

1. **SUPPLEMENTAL TABLES**
2. **SUPPLEMENTAL FIGURES**
3. **SECONDARY OUTCOME MEASURES**

SUPPLEMENTAL TABLES

SUPPLEMENTAL TABLE 1 Uni- and multivariable Cox Proportional Hazard analyses including baseline MTV for 2-year PFS (*n*=296)

	2-year PFS			
	Univariate HR (95%CI)	***p*-value**	**Multivariable HR (95%CI)**	***p*-value**
Age (≤60 vs >60)	1·44 (0·80-2·59)	0·222	1·83 (1·01-3·32)	0·046
aaIPI (low/low-intermediate vs high-intermediate/high)	2·83 (1·50-5·34)	0·001*		
B symptoms (no vs yes)	1·97 (1·18-3·30)	0·010*	1·75 (1·04-2·98)	0·036
Baseline MTV log-transformed	1·43 (1·16-1·76)	0·001*	1·32 (1·07-1·62)	0·010
ΔSUVmax (>70% vs ≤70%)	7·44 (4·29-12·92)	<0·0001*	7·87 (4·48-13·83)	<0·0001*
Gender (male vs female)	0·73 (0·44-1·23)	0·240		
Treatment arm (R-CHOP14 vs RR-CHOP14	0·85 (0·51-1·42)	0·539		

** Statistically significant difference*

Abbreviations: 95%CI= 95% confidence interval; aaIPI= age-adjusted international prognostic index; HR= Hazard Ratio; LDH= lactate dehydrogenase; MTV=metabolic tumor volume; PFS= progression-free survival; WHO= world health organization

SUPPLEMENTAL TABLE 2 I-PET4 and EoT-PET 2x2 contingency table

	EoT-PET positive (DS 4-5)	**EoT-PET negative (DS 1-3)**	**Total**
I-PET4 positive (DS 4-5)	54	42~	96
I-PET4 negative (DS 1-3)	20^	358	378
Total	74 *	400 †	474

Abbreviations: DS= Deauville 5-point scale; EoT-PET= end-of-treatment ^{18}F-FDG PET(/CT); I-PET4= interim ^{18}F-FDG PET(/CT) after four treatment cycles.

**No I-PET4 was performed in 5 patients with positive EoT-PET (reasons unknown)*

†No I-PET4 was performed in 14 patients with negative EoT-PET(reasons unknown), in 3 patients I-PET4 was not available for qualitative analysis (high glucose, poor visual quality and not interpretable due to missing baseline scan, respectively)

^ Twenty patients (4.2%) switched from a negative I-PET4 to a positive EoT-PET, sixteen of these patients had a high-intermediate or high aaIPI and had a 2-year PFS of 40% (95%CI 18-62%).

~ Forty-two patients (8.9%) had a positive I-PET4 and turned negative at EoT-PET, of these only 4 patients had progressive disease within 2 years after randomization of whom 2 died within this period. These converting patients had a 2-year PFS of 90% (95%CI 81-99%).

SUPPLEMENTAL TABLE 3 Diagnostic and prognostic measures for aaIPI, baseline MTV, for different cut-off values of the Deauville 5-point scale at I-PET4, and ΔSUVmax for 2-year PFS for subset of patients with baseline MTV analysis (*n*=296)

		Diagnostic information					Prognostic information		Discrimination
		Number of patients (*n*)	**Negative Predictive Value %(95%CI)**	**Positive Predictive Value %(95%CI)**	**Sensitivity %(95%CI)**	**Specificity %(95%CI)**	**Univariate Hazard Ratio (95%CI)**	***p*-value**	**AUC (95%CI)**
AaIPI	**L/LI vs HI/H**	118 vs 178	89·8 (83·1-94·1)	26·4 (20·5-33·3)	79·7 (67·7-88·0)	44·7 (38·5-51·2)	2·83 (1·50-5·34)	0·0013	0·61 (0·55-0·67)
Baseline MTV	**≤345ml vs >345ml**	137 vs 159	86·1 (79·4-90·9)	25·2 (19·2-32·4)	67·8 (55·1-78·3)	49·8 (43·5-56·1)	1·96 (1·13-3·38)	0·0161	0·58 (0·52-0·65)
I-PET4	**DS1 vs DS2-5**	88 vs 208	84·1 (75·1-90·7)	21·6 (16·6-27·7)	76·3 (64·0-85·3)	31·2 (25·7-37·4)	1·42 (0·78-2·59)	0·252	0·54 (0·48-0·59)
	DS1-2 vs DS3-5	159 vs 137	86·8 (80·7-91·2)	27·7 (20·9-35·8)	64·4 (51·7-75·4)	58·2 (51·9-64·3)	2·39 (1·40-4·07)	0·0014	0·61 (0·55-0·67)
	DS1-3 vs DS4-5	226 vs 70	86·7 (81·7-90·5)	41·4 (30·6-53·1)	49·2 (36·8-61·6)	82·7 (77·4-87·0)	3·99 (2·39-6·66)	<0·0001	0·65 (0·60-0·70)
	DS1-4 vs DS5	280 vs 16	83·2 (78·4-87·1)	75·0 (50·5-89·8)	20·3 (12·0-32·3)	98·3 (95·7-99·3)	9·49 (5·00-18·01)	<0·0001	0·59 (0·57-0·62)
ΔSUVmax	**>70% vs ≤70%**	266 vs 30	85·0 (80·2-88·8)	63·3 (45·5-78·1)	32·2 (21·7-44·9)	95·4 (91·9-97·4)	7·46 (4·30-12·95)	<0·0001	0·64 (0·61-0·67)

Abbreviations: 95%CI= 95% confidence interval; AaIPI= age-adjusted international prognostic index; AUC= area under the receiver operating curve; DS= Deauville 5-point scale; ΔSUVmax= reduction of maximum standardized uptake value between baseline and interim 18F-FDG PET(/CT); H=high risk group; HI= high-intermediate risk group; I-PET= interim 18F-FDG PET(/CT) after four cycles; MTV= metabolic tumor volume; PFS= progression-free survival

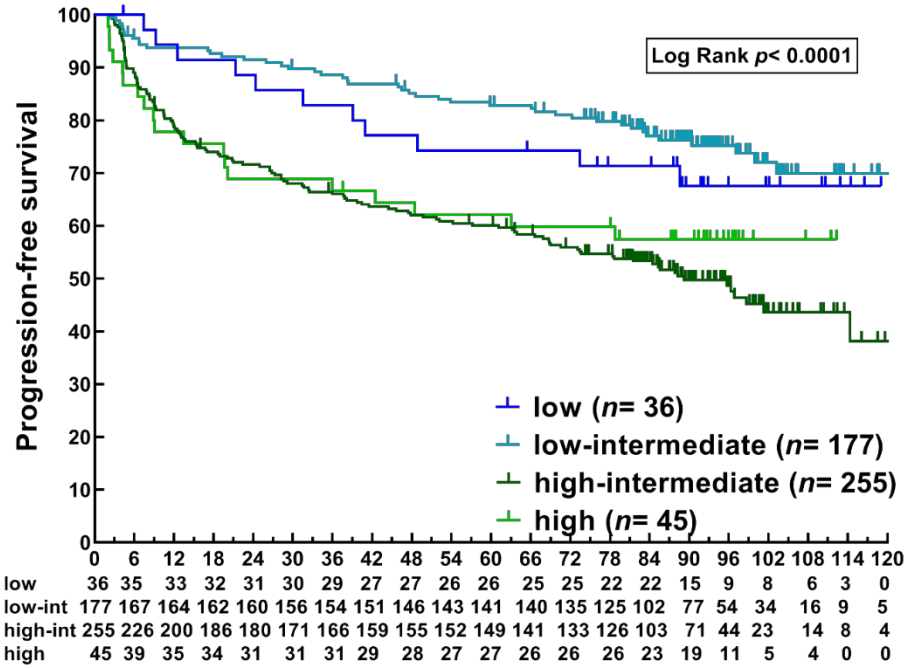
SUPPLEMENTAL TABLE 4 Uni- and multivariable Cox Proportional Hazard analyses of ΔSUVmax analysis-group for 2-year PFS (*n*=367)

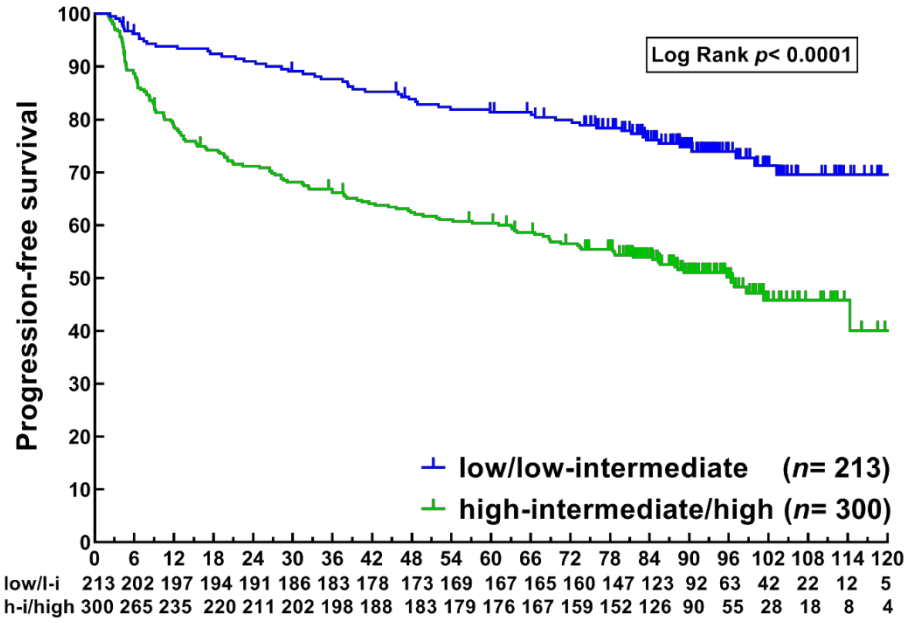
	2-year PFS			
	Univariate HR (95%CI)	***p*-value**	**Multivariable HR (95%CI)**	***p*-value**
Age (≤60 vs >60)	1·60 (0·95-2·69)	0·075		
aaIPI (low/low-intermediate vs high-intermediate/high)	3·16 (1·80-5·55)	<0·0001*	3·27 (1·86-5·75)	<0·0001*
B symptoms (no vs yes)	1·67 (1·07-2·61)	0·025*		
ΔSUVmax (>70% vs ≤70%)	4·80 (2·88-8·00)	<0·0001*	5·01 (3·00-8·36)	<0·0001*
Gender (male vs female)	1·25 (0·80-1·96)	0·335		
Treatment arm (R-CHOP14 vs RR-CHOP14	0·99 (0·63-1·54)	0·957		

** Statistically significant difference*

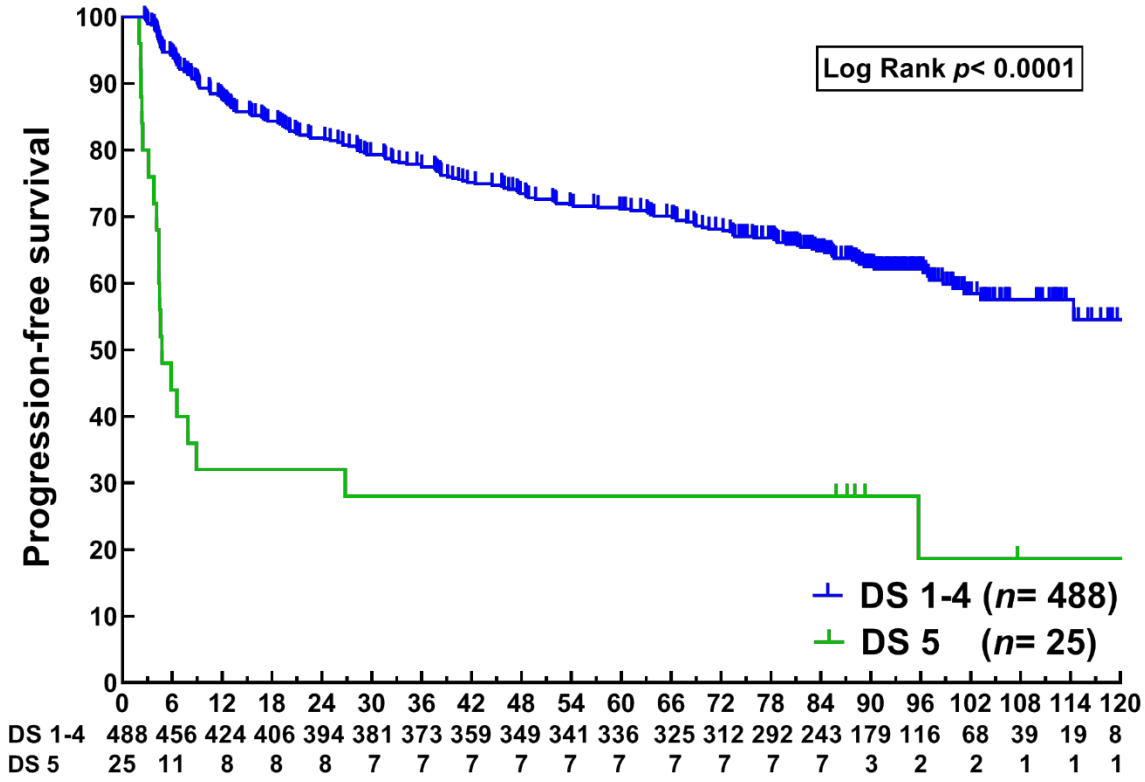
Abbreviations: 95%CI= 95% confidence interval; aaIPI= age-adjusted international prognostic index; ΔSUVmax= reduction of maximum standardized uptake value between baseline and interim 18F-FDG PET(/CT); HR= Hazard Ratio; LDH= lactate dehydrogenase; PFS= progression-free survival; WHO= world health organization

SUPPLEMENTAL FIGURES

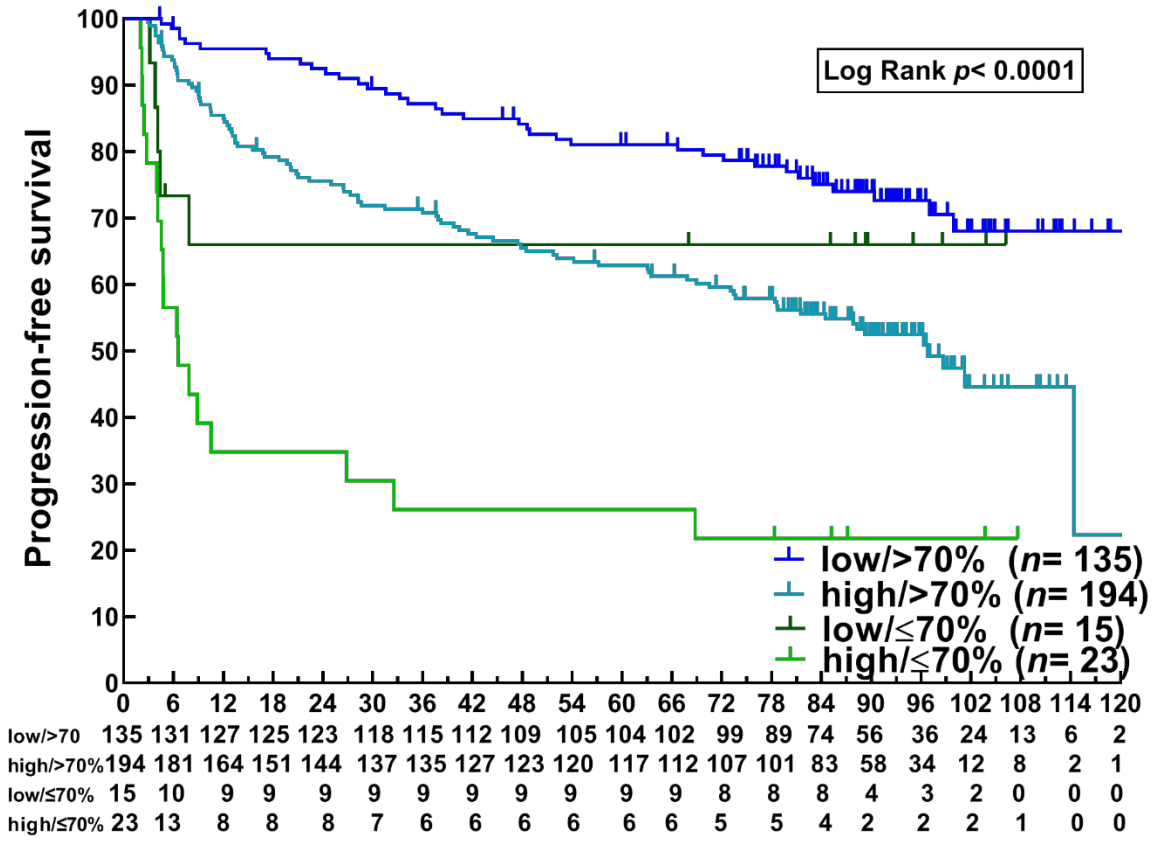




SUPPLEMENTAL FIGURE 1 Kaplan-Meier curves for progression-free survival in months stratified by ordinal aaIPI (1a) and dichotomized aaIPI (1b)



SUPPLEMENTAL FIGURE 2 Kaplan-Meier curves for I-PET4 with numbers at risk for progression-free survival in months stratified by DS1-4 vs DS5 result.



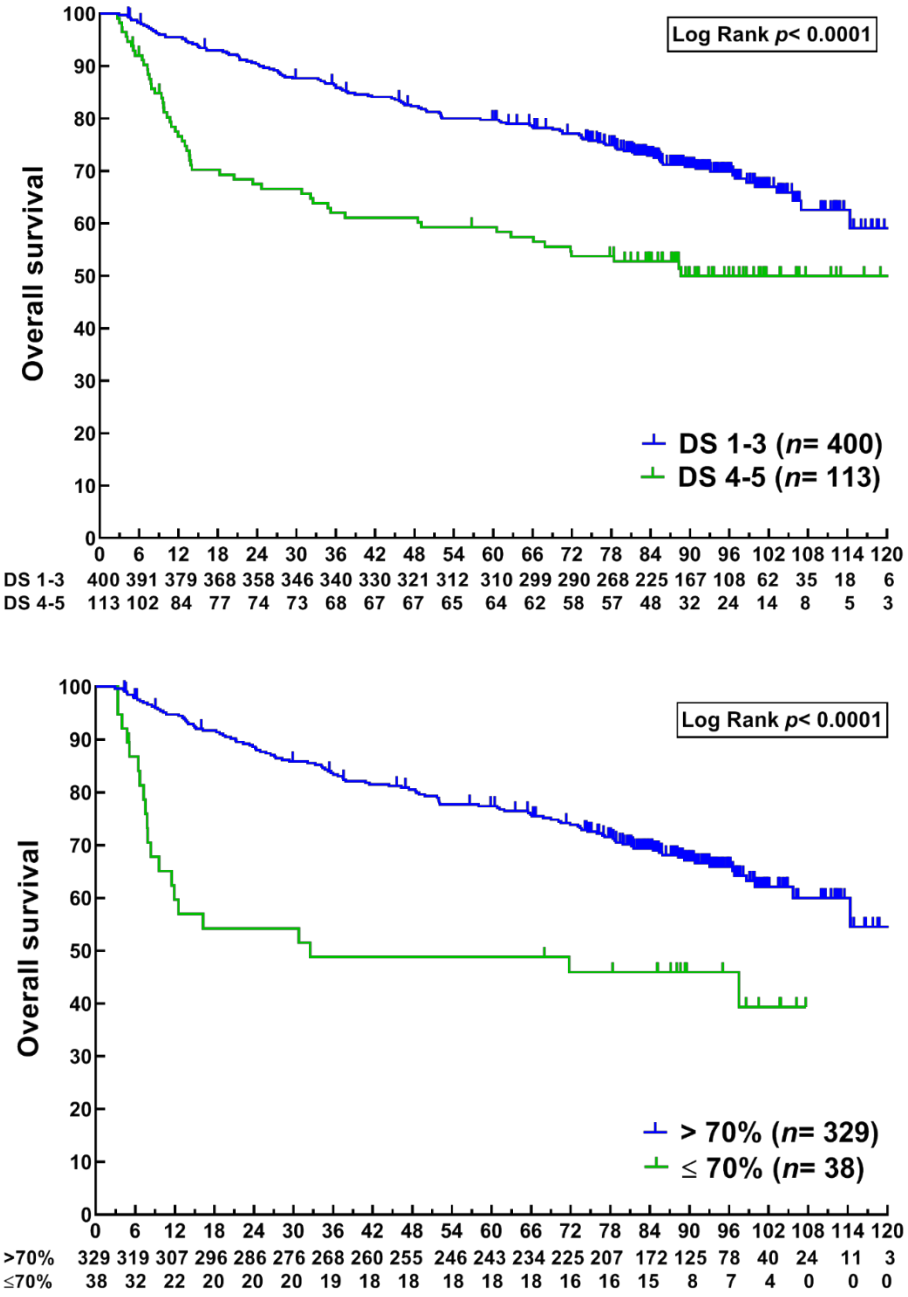
SUPPLEMENTAL FIGURE 3 Kaplan-Meier curves for progression-free survival in months stratified by combined aaIPI and ΔSUVmax subgroups.

3. SECONDARY OUTCOME MEASURES

Definitions:

Overall survival (OS) was defined as time from randomisation to death, patients still alive were censored at date of last contact.

Kaplan-Meier curves for OS



SUPPLEMENTAL FIGURE 4 Kaplan-Meier curves with numbers at risk for overall survival in months stratified by I-PET4 result according to DS (4a) and according to ΔSUVmax result (4b).

SUPPLEMENTAL TABLE 5 Diagnostic and prognostic measures for baseline MTV, for different cut-off values for the Deauville 5-point scale at I-PET4, and ΔSUVmax for 2-year OS

		Diagnostic information				Prognostic information	Discrimination
		Negative Predictive Value %(95%CI)	**Positive Predictive Value %(95%CI)**	**Sensitivity %(95%CI)**	**Specificity %(95%CI)**	**Univariate Hazard Ratio (95%CI)**	**AUC (95%CI)**
Baseline MTV	**≤345ml vs >345ml**	90·5 (84·4-94·4)	20·1 (14·6-27·0)	71·1 (56·6-82·3)	49·9 (43·3-55·6)	2·23 (1·17-4·24)	0·59 (0·52-0·66)
I-PET4	**DS1 vs DS2-5**	87·6 (82·0-91·7)	15·5 (12·0-19·8)	70·3 (59·1-79·5)	35·5 (31·2-40·1)	1·29 (0·79-2·13)	0·53 (0·47-0·64)
	DS1-2 vs DS3-5	90·3 (86·4-93·2)	20·6 (15·8-26·4)	62·2 (50·8-72·4)	59·7 (55·0-64·2)	2·35 (1·47-3·75)	0·61 (0·55-0·66)
	DS1-3 vs DS4-5	90·5 (87·2-93·0)	31·6 (24·0-40·9)	48·7 (37·6-59·8)	82·5 (78·6-85·7)	4·02 (2·55-6·35)	0·65 (0·61-0·70)
	DS1-4 vs DS5	88·3 (85·2-90·9)	68·0 (48·4-82·8)	23·0 (14·9-33·7)	98·2 (96·5-99·1)	9·85 (5·69-17·03)	0·60 (0·58-0·62)
ΔSUVmax	**>70% vs ≤70%**	88·8 (84·9-91·7)	44·7 (30·2-60·3)	31·5 (20·7-44·7)	93·3 (90·0-95·6)	5·52 (3·10-9·83)	0·62 (0·59-0·66)

Abbreviations: 95%CI= 95% confidence interval; AUC= area under the receiver operating curve; DS= Deauville 5-point scale; ΔSUVmax= reduction of maximum standardized uptake value between baseline and interim 18F-FDG PET(/CT); I-PET= interim 18F-FDG PET(/CT) after four cycles; MTV= metabolic tumor volume; OS= overall survival

SUPPLEMENTAL TABLE 6 Uni- and multivariable Cox Proportional Hazard analyses of ΔSUVmax analysis-group for 2-year OS (*n*=367)

	2-year OS			
	Univariate HR (95%CI)	***p*-value**	**Multivariable HR (95%CI)**	***p*-value**
Age (≤60 vs >60)	1·65 (0·88-3·08)	0·116	1·92 (1·01-3·62)	0·046*
aaIPI (low/low-intermediate vs high-intermediate/high)	2·85 (1·47-5·52)	0·0002*	2·42 (1·24-4·76)	0·010*
B symptoms (no vs yes)	2·12 (1·23-3·65)	0·0007*	1·82 (1·01-3·16)	0·036*
ΔSUVmax (>70% vs ≤70%)	5·52 (3·10-9·83)	<0·0001*	6·03 (3·36-10·81)	<0·0001*
Gender (male vs female)	0·68 (0·40-1·18)	0·172	0·55 (0·31-0·95)	0·034*
Treatment arm (R-CHOP14 vs RR-CHOP14	1·01 (0·59-1·72)	0·969		

** Statistically significant difference*

Abbreviations: 95%CI= 95% confidence interval; aaIPI= age-adjusted international prognostic index; ΔSUVmax= reduction of maximum standardized uptake value between baseline and interim 18F-FDG PET(/CT); HR= Hazard Ratio; OS= overall survival

SUPPLEMENTAL TABLE 7 Uni- and multivariable Cox Proportional Hazard analyses including baseline MTV for 2-year OS (*n*=296)

	2-year OS			
	Univariate HR (95%CI)	***p*-value**	**Multivariable HR (95%CI)**	***p*-value**
Age (≤60 vs >60)	1·36 (0·70-2·62)	0·367		
aaIPI (low/low-intermediate vs high-intermediate/high)	2·43 (1·20-4·91)	0·013*		
B symptoms (no vs yes)	2·15 (1·19-3·91)	0·012*		
Baseline MTV log-transformed	1·62 (1·25-2·08)	0·0002*	1·55 (1·20-2·00)	0·001*
ΔSUVmax (>70% vs ≤70%)	7·33 (3·97-13·55)	<0·0001*	6·75 (3·63-12·55)	<0·0001*
Gender (male vs female)	0·67 (0·37-1·21)	0·182		
Treatment arm (R-CHOP14 vs RR-CHOP14	0·97 (0·54-1·74)	0·923		

** Statistically significant difference*

Abbreviations: 95%CI= 95% confidence interval; aaIPI= age-adjusted international prognostic index; HR= Hazard Ratio; MTV=metabolic tumor volume; OS= overall survival