Risk stratification in diffuse large B cell lymphoma using lesion dissemination and metabolic tumor burden calculated from baseline PET/CT.

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Title page

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Running head:

Baseline lesion dissemination and metabolic volume measured by PET in DLBCL

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Highlights

1. Large lesion dissemination measured by high SDmax was a strong prognosticator of shorter PFS and OS in DLBCL patients
2. SDmax results in an accurate risk stratification at baseline, even in advanced Ann Arbor stage patients.
3. SDmax and MTV are independent prognosticators and identified a high risk group among DLBCL patients responding to R-CHOP.
4. SDmax combined with MTV seems superior to IPI or NCCN-IPI stratifications and promising to guide the therapeutic strategy.

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Title

Risk stratification in diffuse large B cell lymphoma using lesion dissemination and metabolic tumor burden calculated from baseline PET/CT.

Abstract

Background: We analysed the prognostic value of a new baseline PET parameter reflecting the spread of the disease: the largest distance between two lesions (Dmax). We tested its complementarity to metabolic tumor volume (MTV) in a large cohort of DLBCL patients from the REMARC trial (NCT01122472).

Patients and methods: MTVs were defined using the 41% SUVmax threshold. From the three dimensional coordinates, the centroid of each lesion was automatically obtained and considered as the lesion location. The distances between all pairs of were calculated. Dmax was obtained for each patient and normalized with the body surface area (SDmax).

Results: 291 patients were included, 91% had an advanced stage and 71% IPI≥3. High vs low SDmax significantly impacted PFS (P<0.0001) and OS (P=0.0027). Patients with SDmax>0.32 m^{-1} (n=82) had a 4y-PFS and OS of 46% and 71% respectively against 77% and 87% respectively for patients with low SDmax. High SDmax and high MTV were independent prognostic factors of PFS (P=0.0001 and P=0.0010 respectively) and OS (P=0.0028 and P=0.0004 respectively). Combining MTV and SDmax yielded three risk groups with no (n=109), one (n=122) or two (n=59) factors (P<0.0001 for both PFS and OS). The 4-year PFS were 90%, 63%, 41% respectively, the 4-year OS 95%, 79%, 66% respectively. In addition, patients with at least 2 of the 3 factors including high SDmax, high MTV, ECOG ≥2 had a higher number of CNS relapse (P=0.017).

Conclusions: SDmax is a simple feature that captures lymphoma dissemination, independent from MTV. These two PET metrics, SDmax and MTV, are complementary to characterise the disease, reflecting the tumor burden and its spread. This score appeared promising for DLBCL baseline risk stratification.

Introduction

Diffuse large B cell lymphoma (DLBCL) is the largest subtype of malignant lymphoma all over the world. It is a very heterogeneous disease entity, with multiple histologic subtypes, morphologic variants (eg primary mediastinal B-cell lymphoma), specific virus (EBV, HV8), specific genetic abnormalities (such as MYC and BCL2, and/or BCL6 rearrangements), and derived from different cells of origin (either germinal center B-cell-like (GCB) or activated B-cell-like (ABC)) (1). Further molecular categorizations based on recurrent somatic mutations have been recently proposed (2,3). Despite the complex heterogeneity of DLBCLs, the R-CHOP regimen (rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone) is regarded as a standard for first line DLBCL therapy, offering a complete remission rate of around 80% (4). Nonetheless, the prognosis of the patients who experience disease recurrence or refractory disease is poor. In clinical practice, a number of features are of value to predict overall survival and disease free survival, including age, LDH, performance status, disease stage, number of involved extranodal sites and are incorporated in prognostic models such as the International Prognostic Index (IPI) and more recently the National Comprehensive Cancer Network (NCCN)-IPI (5)·(6). Unfortunately, all failed identifying the high-risk patients.

In the past few years, an imaging biomarker calculated from FDG PET has been proven useful to improve the risk classification of patients: the total metabolic tumor volume (MTV). This

biomarker estimates the total tumor burden more accurately than the simple dimension of the bulk or even the Ann Arbor Stage. High baseline MTV results in significantly shorter progression-free survival (PFS) and overall survival (OS) in many lymphoma subtypes (7-11). In DLBCL, the prognostic value of MTV overcoming usual prognostic indices(12) is now well established, with data from large prospective series (10,13,14). Even in patients responding to first line R-CHOP therapy, MTV remains a best prognostic factor, as has been recently published from the REMARC study(15) involving patients aged from 60 to 80 years (16). In this cohort, a high MTV identified a subset of approximately half of the patients with a 20-point reduction in 4-year progression free survival (PFS) and overall survival (OS).

However, the heterogeneity of the distribution of the lesions is not considered with MTV measurement. Indeed DLBCL often involves multiple disseminated nodal sites possibly associated with extra nodal sites, sometimes with mutational heterogeneity impacting outcome (17). Recently, a simple imaging feature measured from FDG PET scans and reflecting lesions dissemination has been introduced in DLBCL patients: the distance between the two lesions that were the furthest apart (Dmax) (18). A high Dmax was associated with an adverse outcome, independently of MTV, in a cohort of 95 patients with an advanced stage DLBCL. A straightforward model combining MTV and Dmax was demonstrated to be effective at stratifying patients with higher accuracy than Ann Arbor classification. In that context, the objectives of the present study were to confirm the prognostic value of this new PET feature reflecting tumor dissemination, in a different and larger cohort of DLBCL patients, and to test whether combining it with MTV could improve risk stratification at baseline.

Methods

From the REMARC trial (NCT01122472), 301 patients with a baseline PET/CT (before any treatment) were available for retrospective review. All were part of a previous study already

published regarding MTV (16). The REMARC study design details have been reported elsewhere (15). Briefly, patients, 60-80 years old, ECOG PS 0-2, Ann Arbor stage II-IV at diagnosis, aaIPI ≥ 1 at diagnosis, with histologically-proven CD20+ DLBCL according to 2008 WHO criteria , and a complete response or partial response as defined by Cheson 2007 criteria (19) after 6 or 8 cycles of standard R-CHOP were included and randomized 1:1 to lenalidomide maintenance 25 mg/day or placebo for 21 of every 28-day cycle for 2 years. Baseline PET was not mandatory in the trial.

PET/CT analysis

Using the Beth Israel PET/CT viewer plugin for FIJI (20), MTVs were defined by two nuclear medicine physicians (ASC, LV) using 41% SUVmax threshold, blinded to patient outcome. Regional volumes automatically identified by the software were checked visually to confirm inclusion of only pathological lesions and labelled to distinguish between the different nodal sites, using 10 labels (cervical left/right; axillary L/R; mediastinal; abdominal; iliac L/R; inguinal L/R) and extranodal sites. Bone marrow involvement was included in the volume measurement only if there was focal uptake as previously described (21). From the three dimensional coordinates of the metabolic volume of each lymphoma lesion, the center of mass (centroid) of each lesion was automatically obtained and was considered as the lesion location. The distances between all pairs of lesions (including both nodal and extra nodal lesions) were calculated by using the Euclidian formula $AB = \sqrt{(xb - xa)^2 + (yb - ya)^2 + (zb - za)^2}$ (18) with LIFEx software (22). The largest distance Dmax was deduced in each patient and normalized by the patient body surface area (BSA), given by $\sqrt{(\text{weight x height})/3600}$ yielding the standardized Dmax called SDmax thereafter.

Statistical analysis

For the current study, only patients with BSA data available and with at least 2 detectable lesions allowing distance measurement were included. The optimal MTV and SDmax cut-off values for PFS and OS were determined using Receiver Operating Curve analysis and X-tile analysis and confirmed by a training validation method. A random sample of two-thirds of the patients was the training cohort; the remaining one-third was the validation cohort. The cut-off values were chosen as the values maximizing the Youden index defined as the sum of sensitivity and specificity minus one. PFS was measured from the date of randomization to the date of death from any cause, disease relapse or progression, or the date of last contact. CNS relapse was analysed as a specific event and prediction of CNS relapse was separately analysed. OS was calculated from the date of randomization until the date of death from any cause or the date of last contact. Survival functions were calculated using Kaplan-Meier estimates, and comparisons between categories were made with the log-rank test. Characteristics of populations were compared using Fischer's exact test for discrete variables and Mann Whitney test for continuous variables. Variables considered for model design included MTV, Dmax, SDmax, extranodal sites, ECOG PS, LDH, Ann Arbor stage, IPI. Univariate and multivariate analyses were performed using Cox proportional hazard models. Spearman correlation coefficient rho was calculated between SDmax and the number of nodal involved sites. Test results were interpreted as significant if the 2-sided P-value was less than 0.05. Statistical analyses were conducted using MedCalc software (MedCalc Software, Ostend, Belgium) and X-tile 3.6.1 software (Yale University, New Haven, CT).

Results

Among the 301 patients, 11 patients were excluded (2 with BSA data not available, 9 without at least two distinct lesions). The 290 patients' baseline clinical characteristics are shown in

Table 1. After a median follow-up of 5 years, 88 patients (30%) had a PFS event and 54 patients (19%) had an OS event. The 4-y PFS was 69% and 4-y OS was 83%.

PET features

Median baseline MTV was 253 cm^3 (IQR: 86 to 556). Using a cut-off value of 220 cm^3 previously found to be optimal for that patient cohort (16), the sensitivity and specificity were 72% and 54% for PFS and 80% and 52% for OS. Half of the patients (n=158 patients, 55%) had a MTV greater than 220 cm3. Median Dmax was 42 cm (interquartile range [IQR]: 23 to 63), median SDmax was 0.23 m^{-1} ([IQR]: 0.13 to 0.33).

ROC optimal cut-off value maximizing the Youden index for SDmax was 0.32 m^{-1} with a sensitivity and specificity of 43% and 80% respectively for PFS. Using this cut-off, sensitivity and specificity were 43% and 77% respectively for OS. Areas under the ROC curves (AUC) were 0.64 (P=0.0002) for PFS and 0.62 (*P* =0.005) for OS. X-tile procedure yielded a cut-off value of 0.38 m^{-1} for PFS (*P*<0.0001) and 0.37 m^{-1} for OS (*P* =0.0099), with a sensitivity of 23% for PFS and 28% for OS, and a specificity of 92% and 88% respectively.

Patient characteristics stratified according to high or low SDmax values are given in Table 1. A high SDmax was associated with advanced Ann Arbor stage (100% vs 88%, *P* <0.001),), a high MTV (72% vs 48%, p<0.001), more than one extra nodal sites involved (68% vs 44%, p<0.001), IPI score 3-5 (85% vs 65%, p<0.001) and high NCCN-IPI score (82% vs 64%, *P* =0.006). SDmax was correlated with the number of nodal involved sites (rho=0.732, *P* <0.0001; Figure 1). There was no significant difference between molecular characteristics of patients (cell of origin determined with Hans algorithm and with Nanostring, and BCL2 or MYC protein overexpression) with high and low SDmax.

Univariate analysis (Table 2, Figure 2 AB)

The presence of more than one extranodal site was a significant adverse factor for both PFS and OS. The number of more than 4 nodal areas involved was prognostic only on PFS. Among the features characterizing lymphoma lesions, Dmax, SDmax and MTV were the most significant to predict both PFS and OS (table 2). A high SDmax (>0.32 m^{-1}) was significantly associated with a shorter PFS (*P* <0.0001, HR=2.7) and OS (*P* =0.0027, HR=2.3) (table 2). The 4-year PFS and OS was 46% and 71% respectively for patients with high SDmax (>0.32 m^{-1}) versus 77% and 87% for patients with a low SDmax (Figure 2 AB).

Although 59 patients (20%) had both a high SDmax (> 0.32 m^{-1}) and a high MTV (>220 cm^3) and 109 patients (38%) had both a low SDmax and a low MTV, 122 patients (42%) had discordant MTV and SDmax: 23 patients (8%) had a high SDmax with a low MTV, while 99 patients (34%) had a low SDmax with a high MTV.

In a sub-analysis of Ann Arbor advanced III-IV stage patients (n=264), SDmax remained a significant prognosticator for both PFS (HR=2.5; *P* <0.0001) and OS (HR=2.1, *P*=0.0059). SDmax also remained a significant prognosticator for PFS in both Lenalidomide arm (HR=2.2, p=0.012) and placebo arm (HR=3.5, p<0.0001). In addition, patients with high SDmax had a higher risk of early relapse than patients with low SDmax, with 2-year PFS of 71% vs 87% in Lenalidomide arm and 2y-year PFS of 53% vs 84% in the placebo arm.

Multivariable analysis (Table 3)

Combining the 2 PET parameters (Model 1 in Table 3) showed that SDmax and MTV were independent prognostic factors of both PFS (HR=2.4, *P*=0.0001 and HR=2.2, *P*=0.001, respectively) and OS (HR=1.8, P=0.028 and HR=3.3, *P*=0.0004 respectively). Three risk categories could be distinguished based on SDmax and MTV (Figure 2 CD and Figure 3) : group 1 (n=109) with low SDmax (≤ 0.32 m^{-1}) and low MTV (≤220 cm^3); group 2 with either high SDmax or high MTV (n=121), and group 3 with both high SDmax and high MTV (n=59).

These three groups had significantly different 4-year PFS rates of 90% (group 1), 63% (group 2), and 41% (group 3), respectively (group 1 vs group 2: HR = 2.1 and p =0.0042; group 1 vs group 3: HR = 4.9 and P < 0.0001 ; group 2 vs group 3: HR = 2.3 and P = 0.0004; Figure 2C). They also had significantly different 4-year OS rates of 95% (group 1), 79% (group 2), and 66% (group 3) respectively (group 1 vs group 2: HR=3.0 and P=0.0024; group 1 vs group 3: HR=6.5 and P<0.0001 ; group 2 vs group 3 : HR=1.8 and P=0.044; Figure 2 D). Finally, patients with a high MTV but a low SDmax (n=99) had similar PFS (P=0.64) and OS (P=0.39) to those of patients with a high SDmax and a small MTV (n=26) (Figure 3).

Model 2 in Table 3 included all individual factors which were significant in univariate analysis. SDmax, MTV and ECOG remained independent prognosticators for PFS (*P*=0.0001, *P*=0.037, *P*=0.0010 respectively). Interestingly, these 3 factors combined were associated with CNS relapse. Patients with 2 or 3 adverse factors among high SDmax, high MTV, ECOG 2-3 (n=79) had a higher risk of CNS relapse (*P*=0.017), namely 6% contrasting with 1% in the group without or with a single adverse factor (n=211). By contrast, MTV combined with ECOG alone failed to identify CNS relapse (data not shown).

In model 3 testing IPI with MTV and SDmax (Model 3, Table 3), only MTV and SDmax remained significant for PFS (*P*=0.0001 and *P*=0.0016 respectively). For OS, only MTV was significant (*P*=0.0006) whereas SDmax did not reach significance (*P* =0.061).

Discussion

Early identification of DLBCL patients who are unlikely to be cured with R-CHOP is an important step to enable testing of alternative treatment approaches. This requires a refined risk-scoring approach where metrics extracted from baseline PET could play a significant role. Among them, the high prognostic value of MTV is now established. In the present study, we

showed in a large series of 290 elderly DLBCL patients in response to first line therapy that a new feature SDmax, which is the largest distance between lymphoma sites normalized with the body surface area, had a prognostic impact on DLBCL outcome. This parameter, capturing the spread of the disease, was independent from MTV for outcome prediction. These two biomarkers combined identified an ultra-risk group of DLCBL patients before treatment. These results confirmed our previous data in a series of 95 DLBCL young patients undergoing an interim PET guided therapy (18).

Textural and morphological characterization of tumoral metabolic patterns in 18FDG-PET have been investigated in lymphoma patients, with little evidence so far that they provide additional diagnostic or prognostic information (23-26), except for MTV. Regarding heterogeneity, Ceriani and colleagues showed in Primary Mediastinal B-cell Lymphoma that the metabolic heterogeneity (MH) (25,26) of the mass was a predictor of outcome. However when this parameter was applied to a population of 141 DLBCL patients from the prospective SAKK38/07 study (NCT00544219) (26), in multivariate analysis only MTV retained statistical significance for predicting outcome. In all these studies, textural parameters were computed from one (the largest or with the highest SUV) up to 3 tumor sites which might not adequately reflect the disease heterogeneity. In addition, lymphoma often involves lymph nodes and extranodal sites. The texture analysis of only one to three lesions might thus not be sufficient to characterize lymphoma disease. The need to account for the disease heterogeneity is suggested in a recent report (17) that highlights the spatial heterogeneity based on whole exome sequencing in two tumors from the same DLBCL patient at baseline. Consistent with the importance of taking the spatial heterogeneity of the disease into account, the prognostic value of the largest diameter of a single bulk mass is much lower than that of the MTV, which includes all or most lymphoma lesions (9-11).

Our results are in line with the effort to characterize the heterogeneity of the disease. Here, we have normalized Dmax with the body surface area to take into account the size and height of each patient, yielding the Standardized Dmax (SDmax), with still a strong prognostic value for outcome. SDmax, which intuitively reflects the dissemination of the disease, outperformed Ann Arbor stage for prognostication, and therefore remained relevant even among patients with an advanced disease. It is highly correlated with the number of nodal sites involved, but much

more significant for PFS or OS prediction, suggesting the prognostic importance of lymphoma spread. (27). Even if Lenalidomide globally improves patients PFS in the REMARC trial, its effect seems more pronounced in the high SDmax group than in the low SDmax group: patients with high SDmax have a 4-year PFS of 66.6 % in Lenalidomide arm contrasting with a 4-year PFS of 20.8% in the placebo group. For patients with low SDmax, the difference was much lower, with a 4-year PFS of 81.6% in Lenalidomide arm vs 73.1% in the placebo group. In addition, patients with high SDmax had a higher risk of early relapse than patients with low SDmax, with 2-year PFS of 71% vs 87% in Lenalidomid arm and 2-year PFS of 53% vs 84% in the placebo arm.

SDmax is a very simple feature that captures the disease dissemination. It is a 3D feature that is easy to understand and calculate. Unlike sophisticated radiomic features often difficult to interpret from a biological point of view, SDmax intuitively reflects the spatial migration of the disease to different sites. Being a distance between the centroids of two lesions, it is not expected to be highly impacted by the PET/CT scanner performance and generation, facilitating its widespread use. In addition, it is not substantially impacted by MTV measurements, since the centroid of the VOI does not change much with the size of the VOI.

In the present study, SDmax and MTV had independent predictive value. We suggested a prognostic scoring system based on these two features extracted from the baseline PET/CT scan that are complementary in that sense that they characterise two different aspects of the disease: the tumor burden and its dissemination. This score appeared more beneficial for patient risk stratification in guiding therapy than the current Ann Arbor staging system, which failed to predict outcome in this cohort, or than the current prognostic indices such as IPI. This model combining two PET features significantly separated three different prognostic groups: group 1 with no risk factor, group 2 with one risk factor, group 3 with two. Specifically, this score could identify a group of patients with a poor prognosis, even in response after R-CHOP, for whom clinicians might consider alternative treatment approaches. Indeed, patients with high baseline MTV (>220 cm^3) and high SDmax (>0.32 m^{-1}) had a much worse prognosis than the other patients with 4-year PFS of 41% and 4-year OS of 66%.

This score based on the SDmax and MTV PET imaging features will have to be correlated with other individual clinical or biological data in larger cohorts. Indeed, using the same REMARC cohort, it has been published recently that among all investigated clinical and biological factors, only ECOG complemented MTV, yielding a new simple score to discriminate high risk patients (16). It has been suggested that the combination of this score with other molecular profiles recently described in DLBCL could help select new therapeutic strategies(3). Investigating the combination of this score with SDmax is challenging in the present cohort because the overall favourable outcome of patients (responders to R-CHOP) resulted in a relatively low number of events, reducing the statistical power of an analysis involving small subgroups of patients characterized by different factors. Despite this limitation, SDmax, MTV and ECOG remained independent significant predictors for PFS. For OS, SDmax did not reach significance possibly due to statistical power limitation. In addition, a higher rate of CNS relapse was observed in the group with 2 or 3 adverse factors (high MTV, high SDmax, ECOG 2-3) whereas MTV and ECOG failed to predict CNS relapse, although these data should be interpreted with caution due to the small number of CNS relapse. Large studies are needed to determine what is the best combination of prognostic factors and what are the easiest factors to use in clinical routine. Standardization of MTV calculation is ongoing and will be soon achieved at an international level (28). Although SDmax is in its early stage, our results strongly suggest that current prognostic index could be refined including such a disease dissemination feature derived from PET imaging. Current tumor burden surrogates and Ann Arbor classification might be reconsidered given that baseline quantitative PET metrics are of value for optimizing personalized management.

Conclusion

By reflecting information regarding the dissemination of the disease, SDmax complements the lymphoma tumor burden measured by MTV. A simple score based on MTV and SDmax therefore enhances the prognostic value of PET staging and appears promising to guide the therapeutic strategy. It should be of interest to understand which categories of patients have a high SDmax, and to correlate the group with both high MTV and large spread with the different groups identified using molecular data (2,3). These results warrant further assessment in other large cohorts and comparison with existing prognostic models to overcome the limitations of current clinical prognostic indices in DLBCL patients.

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Authorship Contributions

Administrative support: LYSA-RC

Conception and design: ASC, IB, MM

Provision of study material or patients: CT, OC.

Collection and assembly of data: ASC, NC, LV.

Data analysis and interpretation: ASC, IB, CT, MM, LC, LV, CN.

Manuscript writing: ASC, IB, CT, MM, OC, JC.

Final approval of manuscript: All authors

Accountable for all aspects of the work: All authors

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Tables

Table 1 Patients characteristics

Characteristics	Total Population n=290	SDmax ≤0.32 m^{-1} n=208	SDmax >0.32 m^{-1} n=82	P value
Female	120 (41%)	91 (44%)	29 (35%)	0.23
Ann Arbor stage				
I-II	26 (9%)	26 (12%)	0 (0%)	<0.001
III-IV	264 (91%)	182 (88%)	82 (100%)	
ECOS PS				
0-1	238 (82%)	175 (84%)	63 (77%)	0.11
≥2	47 (16%)	29 (14%)	18 (22%)	
missing	5 (2%)	4 (2%)	1 (1%)	
Extranodal sites				
<2	143 (49%)	117 (56%)	26 (32%)	<0.000
≥2	147 (51%)	91 (44%)	56 (68%)	1
Elevated LDH > ULN				
No	111 (38%)	84 (40%)	27 (33%)	0.28
Yes	175 (60%)	121 (58%)	54 (66%)	
missing	4 (2%)	3 (2%)	1 (1%)	
MTV				
<220 cm^3	132 (45%)	109 (52%)	23 (28%)	<0.001
≥220 cm^3	158 (55%)	99 (48%)	59 (72%)	
IPI				
<3	81 (28%)	71 (34%)	10 (12%)	<0.001
≥3	205 (71%)	135 (65%)	70 (85%)	
missing	4 (1%)	2 (1%)	2 (2%)	
NCCN-IPI				
Low intermediate	72 (25%)	62 (30%)	11 (13%)	0.006
high intermediate and high	201 (70%)	133 (64%)	67 (82%)	
Missing	17 (5%)	13 (6%)	4 (5%)	
Treatment arm for maintenance				
Placebo arm	140 (48%)	106 (51%)	34 (42%)	0.15
Lenalidomide arm	150 (52%)	102 (49%)	48 (58%)	
CNS relapse				
No	283 (98%)	205 (99%)	78 (95%)	0.10
Yes	7 (2%)	3 (1%)	4 (5%)	
BCL2 expression (%)				
<50%	19 (15%)	16 (19%)	3 (8%)	0.18
≥50%	104 (85%)	69 (81%)	35 (92%)	
missing	167	123	44	
MYC expression (%)				
< 40%	56 (58%)	41 (61%)	15 (50%)	0.38
≥ 40%	41 (42%)	26 (39%)	15 (50%)	
missing	193	141	52	
Double expressor				0.18
No	67 (65%)	50 (69%)	17 (55%)	
yes	36 (35%)	22 (31%)	14 (45%)	
	187	136	51	

missing				
GCB/ABC profile (nanostring)				
ABC	71 (36%)	44 (32%)	27 (46%)	0.073
GCB	96 (49%)	71 (51%)	25 (43%)	
Unclassified	23 (12%)	20 (14%)	3 (5%)	
NA/missing	7/93	4/69	3/24	
GCB/non GCB profile (hans)				
GCB	88 (48%)	63 (48%)	25 (47%)	0.99
Non-GCB	97 (52%)	69 (52%)	28 (53%)	
missing	105	76	29	

LDH=lactate dehydrogenase IPI=International Prognostic Index, aaIPI=age adjusted IPI, NCCN-IPI = National Comprehensive Cancer Network IPI.

Table 2: Univariate Analyses for Progression-Free Survival (PFS) and Overall Survival (OS)

Characteristics	Univariate analysis of PFS HR (95% CI)	*P*	Univariate analysis of OS HR (95% CI)	*P*
Female	0.9 (0.6-1.3)	0.49	0.8 (0.5-1.4)	0.40
Ann Arbor stage III-IV	1.9 (0.8-4.6)	0.16	2.8 (0.7-11.5)	0.15
Elevated LDH (> ULN)	1.2 (0.8-1.9)	0.38	1.3 (0.7-2.3)	0.36
Extranodal sites > 1	1.9 (1.2-2.9)	0.0031	2.2 (1.2-3.8)	0.0068
ECOG 2-3	2.5 (1.5-4.0)	0.0002	2.7 (1.5-4.8)	0.0007
IPI 3-5	1.8 (1.1-3.0)	0.03	2.8 (1.3-6.3)	0.0099
NCCN-IPI High	1.5 (1.0-2.0)	0.024	1.9 (1.2-2.9)	0.0049
MTV >220 cm^3	2.5 (1.6-3.9)	0.0001	3.7 (1.9-7.2)	0.0001
Dmax > 0.47 m	2.3 (1.5-3.5)	0.0001	2.3 (1.3-3.8)	0.0024
SDmax > 0.32 m^{-1}	2.7 (1.8-4.2)	<0.0001	2.3 (1.3-3.9)	0.0027

Table 3 : Multivariate Analyses for Progression-Free Survival (PFS) and Overall Survival (OS)

Characteristics	Multivariate analysis of PFS HR (95% CI)	*P*	Multivariate analysis of OS HR (95% CI)	*P*
Model 1				
High SDmax > 0.32 m^{-1}	2.4 (1.6-3.7)	0.0001	1.8 (1.1-3.2)	0.028
MTV>220cm^3	2.2 (1.4-3.5)	0.0010	3.3 (1.7-6.5)	0.0004
Model 2 : individual factors				
High SDmax > 0.32 m^{-1}				
MTV>220cm^3	2.3 (1.5-3.6)	0.0001	-	-

Characteristics	Multivariate analysis of PFS		Multivariate analysis of OS	
	HR (95% CI)	***P***	**HR (95% CI)**	***P***
Model 1				
High SDmax > 0.32 m^{-1}	2.4 (1.6-3.7)	0.0001	1.8 (1.1-3.2)	0.028
MTV>220cm^3	2.2 (1.4-3.5)	0.0010	3.3 (1.7-6.5)	0.0004
ECOG 2-3	2.0 (1.2-3.2)	0.037	2.9 (1.5-5.8)	0.0021
Extranodal sites > 1	2.3 (1.4-3.7)	0.0010	2.2 (1.3-4.0)	0.0063
	-	-	-	-
Model 3				
High SDmax > 0.32 m^{-1}	2.4 (1.6-3.7)	0.0001	1.7 (1.0-3.0)	0.061
MTV>220cm^3	2.1 (1.3-3.4)	0.0016	3.3 (1.7-6.4)	0.0006
IPI 3-5	-	-	-	-

Figures legends

Figure 1: Scatter diagram showing the correlation between SDmax and the number of nodal areas involved.

Figure 2 Kaplan–Meier estimates of progression-free survival (PFS) and overall survival (OS) according to SDmax (A,B) and according to SDmax and baseline metabolic tumour volume (C,D).

Figure 3: Maximal intensity projection of patients with low risk (low MTV and low SDmax), intermediate risk (high MTV with low SDMmax or low MTV with high SDmax), and high risk (high MTV and high SDmax)

Figure 1

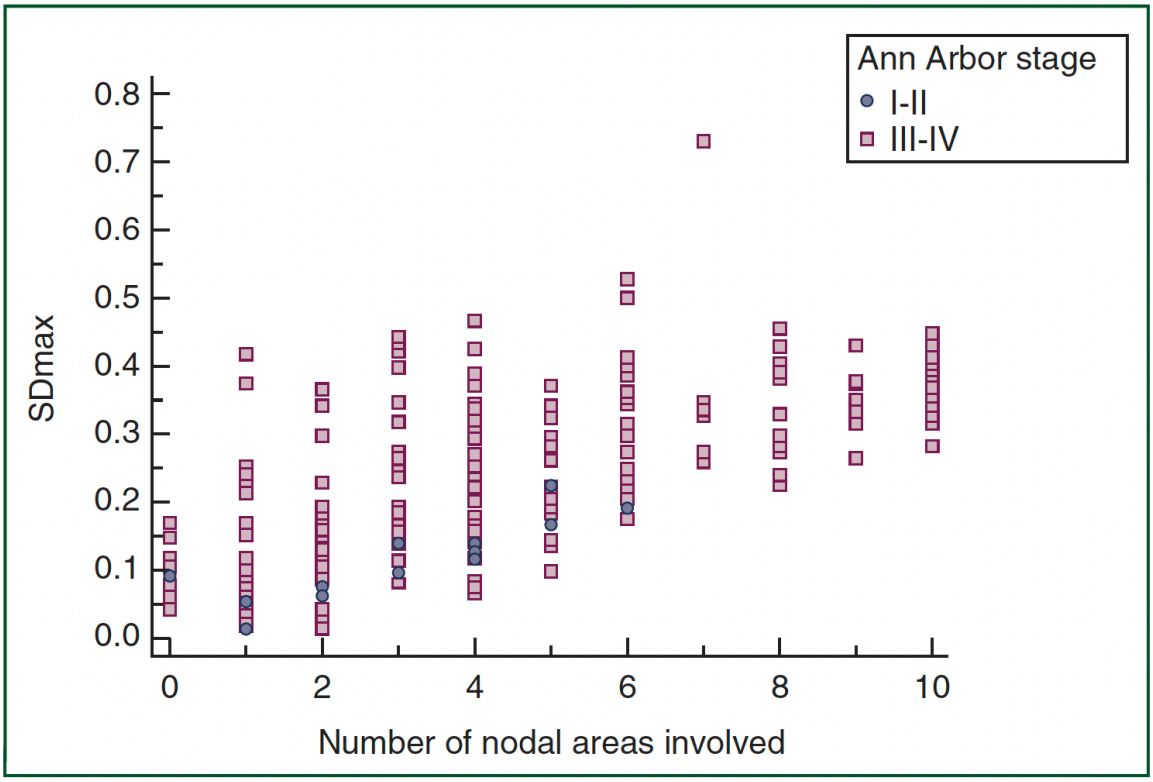

Ann Arbor stage
I-II
III-IV
SDmax
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0
2
4
6
8
10
Number of nodal areas involved

Figure 2

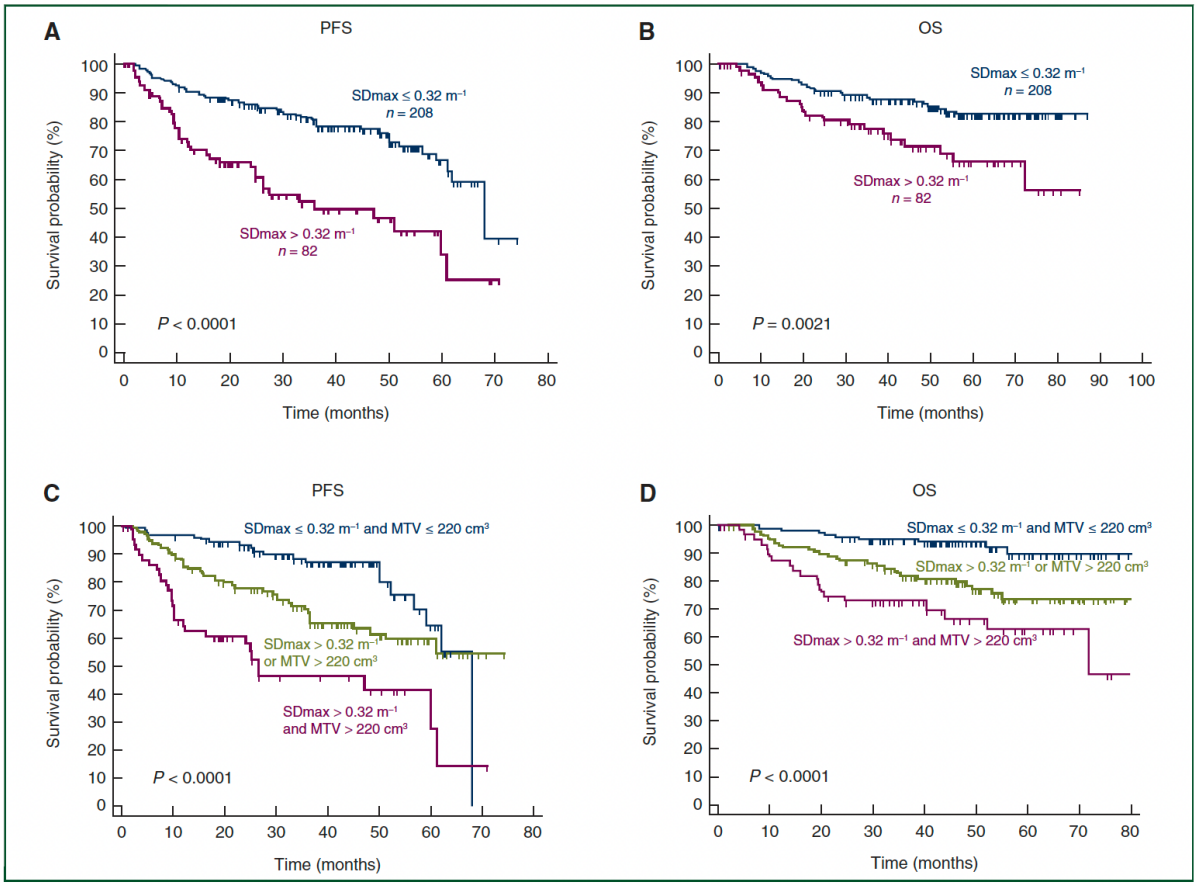
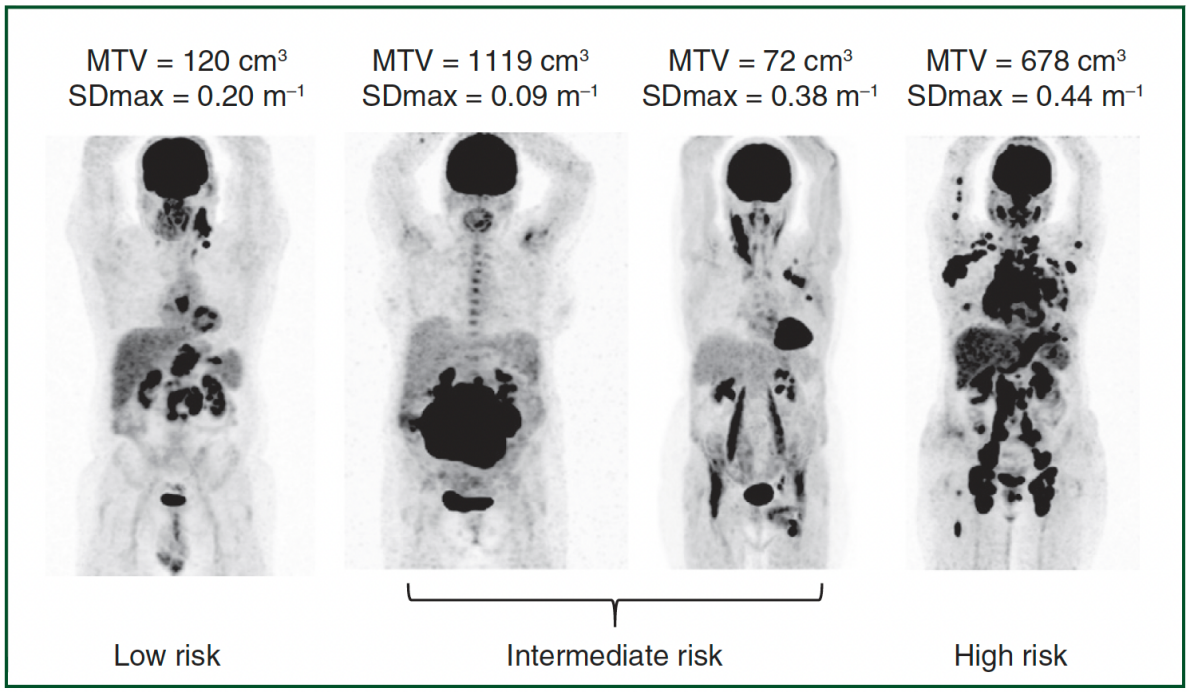

A
PFS
Survival probability (%)
SDmax ≤ 0.32 m⁻¹
n = 208
SDmax > 0.32 m⁻¹
n = 82
P < 0.0001
Time (months)
B
OS
SDmax ≤ 0.32 m⁻¹
n = 208
SDmax > 0.32 m⁻¹
n = 82
P = 0.0021
Time (months)
C
PFS
SDmax ≤ 0.32 m⁻¹ and MTV ≤ 220 cm³
SDmax > 0.32 m⁻¹ or MTV > 220 cm³
SDmax > 0.32 m⁻¹ and MTV > 220 cm³
P < 0.0001
Time (months)
D
OS
SDmax ≤ 0.32 m⁻¹ and MTV ≤ 220 cm³
SDmax > 0.32 m⁻¹ or MTV > 220 cm³
SDmax > 0.32 m⁻¹ and MTV > 220 cm³
P < 0.0001
Time (months)

Figure 3


MTV = 120 cm³
SDmax = 0.20 m⁻¹
MTV = 1119 cm³
SDmax = 0.09 m⁻¹
MTV = 72 cm³
SDmax = 0.38 m⁻¹
MTV = 678 cm³
SDmax = 0.44 m⁻¹
Low risk
Intermediate risk
High risk