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ORIGINAL ARTICLE

Prognostic impact of metabolic tumor volume using the SUV4.0 segmentation threshold in 1,960 lymphoma patients from prospective LYSA trials

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Abstract

Purpose This study compared the prognostic value of total metabolic tumor volume (TMTV) in lymphoma measured with the recently proposed SUV4.0 segmentation threshold versus the 41% SUVmax across LYSA trials and its impact on intensity and dissemination PET features.

Methods A total of 1960 baseline PET/CT scans of Diffuse Large B cell lymphoma (DLBCL), follicular lymphoma (FL) and Hodgkin lymphoma (HL) patients were collected. After a semi-automatic preselection of region of interest, two different segmentation threshold were applied: 41% SUVmax ($TMTV_{41\%}$) and SUV > 4.0 ($TMTV_{4.0}$).

Results The correlation between $TMTV_{4.0}$ and $TMTV_{41\%}$ was $\rho = 0.90$ for DLBCL, $\rho = 0.65$ for FL and $\rho = 0.60$ for HL. For SUVmax, SUVpeak, Dmax and Dbulk features, a strong correlation was observed with $\rho > 0.95$ whatever the lymphoma subtypes. The predictability of TMTV was high and comparable for the two methods with superimposable confidence intervals for the three subtypes. At the 90th percentile TMTV value, the predicted 7-year PFS was 51.13% with $TMTV_{4.0}$ vs. 49.7% with $TMTV_{41\%}$ for DLBCL patients, 45.5% vs. 39.8% for FL patients, and 82.6% vs. 80.5% for HL patients. A minority of patients showed a predicted PFS deviation > 10% between the two methods: 2.33% in DLBCL, 6.51% in FL and 1% in HL.

Conclusion TMTV measured with the SUV4.0 threshold provides a comparable PFS prediction than the 41%SUVmax method supporting its routine adoption particularly in the diffuse large B cell lymphoma subtype.

Keywords TMTV · Lymphoma · DLBCL · HL · FL · prognostic factor

Introduction

Several studies have highlighted the role of metabolic tumor volume (MTV) as a prognostic and predictive factor across many lymphoma subtypes [1–7]. Indeed, the total MTV (TMTV), measured on 18 F-fluorodeoxyglucose positron emission tomography (18 F-FDG PET) imaging, allows a much better estimate of the whole tumor burden than the current surrogates used in the current prognostic indices [8]. In addition, it is the first step for radiomics analysis and thus directly impacts all the other derived tumor metrics. To determine the boundaries of the metabolically active tumor and because a manual delineation would be too dependent on the contrast scale, semi-automatic delineations have been proposed. Simple thresholding methods, that select regions with high 18 F-FDG uptake above the threshold of a certain SUV, have been favored because widely available in different software contrary to more complex algorithms. In lymphoma, different thresholds have been used, based on absolute threshold such as SUV > 2.5 [5, 9–11] and more

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recently SUV>4 [6, 12], on a liver ratio [7] or on a percentage of the maximum uptake within the lesion such as 25%SUVmax [4, 13] or 41%SUVmax [2, 3, 6, 14–23] as recommended by the European Association of Nuclear Medicine for solid tumors [24]. However, these various methods have led to different TMTV values, and thus different thresholds for categorizing patients hindering progress in the field. Efforts are now directed towards establishing standardized techniques for measuring TMTV in lymphoma [25]. The SUV4.0 segmentation threshold, more recently proposed, automatically segments areas with SUV≥4.0, has gained recognition among researchers, as a quick and easy method [26, 27] implemented in multiple software platforms. An international consortium has constructed a benchmark dataset [28] utilizing this segmentation method across three different imaging software platforms in patients with Hodgkin lymphoma (HL), Diffuse large B cell lymphoma (DLBCL) and follicular lymphoma (FL), aiming at harmonizing TMTV measurements in clinical practice and trials. However, only few published data are available on the $TMTV_{4.0}$ prognostic impact [12, 29–31] and a confirmation on a large data set of lymphoma patients is warranted. This study aimed to evaluate the prognostic impact of TMTV generated with the SUV4.0 segmentation threshold in a large cohort of lymphoma patients, including the three most frequent lymphoma subtypes, HL, DLBCL and FL. We also assessed the impact of the TMTV methods on intensity and dissemination PET features.

Materials and methods

Patients

The study population included baseline PET/CT scans of the three most frequent lymphoma subtypes collected from anonymized multicenter imaging trial datasets of the Lymphoma Study Association (LYSA): DLBCL patients from REMARC trial (NCT01122472) [32] and GAINED (NCT01659099) [33], FL patients from RELEVANCE (NCT01650701) [34] and HL patients from AHL 2011 (NCT01358747) [35]. All the PET scans included in these trials underwent quality control by a research engineer. Each of these studies was approved by an ethics committee (see related publications) and ancillary images studies were planned from the initials study protocols. A PET ad hoc analysis was carried out.

TMTV measurement

For each baseline PET, in an open-source viewer for Fiji software [36], the first step was the manual or automatic delineation of uptakes. Automatic delineations were generated using a component tree shaping algorithm and checked by expert physicians trained in TMTV calculations from the LYSA group. The algorithm recognizes the hot spots in the PET images (by detecting high FDG uptake areas based on compacity) and then uses a region-growing method to segment the tumor lesions. Manual delineation could be drawn if necessary and physiologic uptake could be removed. Two different thresholds were then applied to obtain the final TMTV values: 41% SUVmax ($TMTV_{41\%}$) and SUV>4.0 ($TMTV_4$). For the 41%SUVmax method, the SUVmax of each individual VOI was used for the delineation of the MTV. SUVmax, SUVpeak (the 1 mL with the highest SUV within the VOI), Dmax (the maximum distance between two lesions) and Dmaxbulk (the maximum distance between the largest lesion and any other lesion) were also collected.

Statistics

TMTV, intensity and dissemination features distributions were summarized by the median, quartiles and range. Correlations among the 2 different segmentation methods were assessed using Spearman rank coefficients correlation. The association between PFS and (i) the TMTV variable alone or (ii) adjusted on other covariates used to define prognostics scores, were assessed using Cox proportional hazards models. From these models, we estimated HRs and associated 95% CIs. For each segmentation method, the TMTV were considered both in linear and as a binary variable using published thresholds determined on 41%SUVmax TMTV values, according to the type of lymphoma (>220 cm^3 for DLCL [17] and HL and >510 cm^3 for FL [3, 22]). Different TMTV transformations were studied (log2, cubic root, square, polynomial) without significant better performance than linear TMTV (data not shown). In addition, to measure the impact of segmentation methods on outcomes when the TMTV is considered in a prognostic score, previously published scores were modeled for each segmentation method: the MTV/ECOG [20] and IMPI scores [12] for DLBCL and the MTV/FLIPI score for FL.

The Akaike Information Criterion (AIC), Area Under the receiver operating characteristic Curve (AUC) and Brier score were calculated from each model in order to identify the one with the best performances. The AIC is commonly used to determine which model best fits the data, with smaller values being better (provided the difference is greater than 2). The AUC measures a model's ability to separate those individuals who will or will not experience the event of interest [37]. The Brier score is a weighted average of the squared distances between the observed survival status and the predicted survival probability of a model. It measures how close are the estimated risk to the observe

event indicator [37]. As with AIC, smaller values are better. The AUC and Brier score are provided using riskRegression R package [38].

All analyses were performed using R version 4.3.1 statistical software.

Results

A total of 1960 PET/CT scans of lymphoma patients were included in the analysis: 900 DLBCL patients from REMARC trial ($n=255$) [32] and GAINED ($n=645$) [33], 430 FL patients from RELEVANCE [34] and 630 HL patients from AHL 2011 [35]. No significant difference in terms of PFS/OS was observed between these PET cohorts and the whole cohorts (Supplemental S1).

Comparison of features

Median tumor SUVmax was 23.8 (Q1-Q3: 17.1–31) for DLBCL patients, similar in the two cohorts with 24.42 (18.07–31.51) in GAINED cohort and 22.3 (14.615–29.295) in REMARC cohort (Table 1). Median tumor SUVmax was much lower for FL and HL, with a median SUVmax of 11.3 and 14.8 respectively. Median $TMTV_{41\%}$ obtained for DLBCL, FL and HL patients were 252, 333 and 207 cm^3 versus 338, 337, 172 cm^3 for $TMTV_{4.0}$.

The correlation between $TMTV_{4.0}$ and $TMTV_{41\%}$ was very high for DLBCL ($\rho=0.90$) but only moderate for FL and HL ($\rho=0.65$ and 0.60 respectively). For SUVmax, SUVpeak, Dmax and Dbulk features, a strong correlation between the two segmentations was observed with $\rho>0.95$ whatever the lymphoma subtypes.

Figure 1 showed the difference of TMTV values between the two techniques. $TMTV_{4.0}$ was higher than $TMTV_{41\%}$ in 77.3% of DLCBL patients, 50.7% of FL patients and 44.2% of HL patients. In DLCBL cohort, we observed that 76.2% (13.9% with $TMTV_{4.0} < TMTV_{41\%}$ and 52.3% with $TMTV_{4.0} > TMTV_{41\%}$) of the patients had a small ratio (between 0 and 50%, i.e. the difference is more than twice less than the mean value) and only 8.7% of patients (4.6% with $TMTV_{4.0} < TMTV_{41\%}$ and 4.1% with $TMTV_{4.0} > TMTV_{41\%}$) had a high ratio (> 100%, i.e. the difference is higher than the mean value). In FL and HL, approximately half of the patients had a small ratio (45.4% and 48.8%, respectively), while 23.9% of FL patients and 22% of HL patients had a high ratio.

Comparison of prognostic performance

The predicted PFS curves for the 10e, 50e and 90e percentile values of linear $TMTV_{41\%}$ and $TMTV_{4.0}$ Cox models are presented in Fig. 2 AB. A very good risk stratification for the two methods was observed although the P90 curve appeared a little more distinct from the P50 curve using $TMTV_{41\%}$. For the 90e percentile value, predicted curve had a 7-year PFS of 49.7% with $TMTV_{41\%}$ vs. 51.3% with $TMTV_{4.0}$ for DLCBL patients, 39.8% with $TMTV_{41\%}$ vs. 45.5% with $TMTV_{4.0}$ for FL patients, and 80.5% with $TMTV_{41\%}$ vs. 82.6% with $TMTV_{4.0}$ for HL patients.

Table 1 Summary statistics of PET features, stratified per segmentation method (SUV4.0 and 41%suvmax methods) and according to each lymphoma subtypes. Volumes are in mL, distances are in mm. Spearman's rank correlation coefficients (Cor) for PET features between the two segmentation methods

Radiomics	DLBCL N=900			FL N=430			HL N=703		
	SUV4	41%	Cor	SUV4	41%	Cor	SUV4	41%	Cor
TMTV			0.90			0.65			0.6
Median(Q1-Q3)	337.8 (129.0 - 702.1)	252.5 (103.0 - 559.7)		337.2 (147.7 - 758.8)	332.8 (166.4 - 753.4)		171.8 (83.4 - 354.2)	206.9 (122.2 - 382.5)	
Range	0 - 6978.2	0 - 3828.5		0.8 - 9854.6	14.2 - 4405.5		0.1 - 2726.7	9.3 - 2230.1	
SUV_MAX			1			1			1
Median(Q1-Q3)	23.8 (17.1 - 31.0)	23.8 (17.1 - 31.0)		11.3 (9.0 - 15.3)	11.3 (9.0 - 15.3)		14.8 (11.0 - 18.9)	14.8 (11.0 - 18.9)	
Range	0 - 179.1	0 - 179.1		2.5 - 44.3	2.5 - 44.3		4.1 - 109.1	4.1 - 109.1	
SUV_MEAN			0.93			0.58			0.82
Median(Q1-Q3)	9.46 (6.9 - 12.3)	10.6 (6.9 - 14.4)		5.2 (4.2 - 6.1)	5.0 (3.9 - 6.2)		6.0 (5.4 - 6.7)	5.3 (3.9 - 7.0)	
Range	0 - 28.6	0 - 35.1		0.9 - 11.5	1.4 - 15.0		4.0 - 12.0	1.5 - 18.0	
SUV_MEDIAN			0.89			0.51			0.73
Median(Q1-Q3)	8.6 (6.2 - 11.7)	10.3 (6.0 - 14.6)		5.0 (3.7 - 5.8)	4.7 (3.6 - 6.7)		5.5 (5.0 - 6.1)	4.9 (3.5 - 6.7)	
Range	0 - 31.5	0 - 35.4		0.7 - 11.7	1.4 - 15.6		4.0 - 12.0	1.3 - 18.4	
SUV_PEAK			0.97			0.98			0.98
Median(Q1-Q3)	18.4 (13.4 - 24.2)	19.2 (14.2 - 24.9)		9.2 (7.2 - 11.9)	9.3 (7.3 - 12.4)		11.0 (8.6 - 13.9)	11.5 (8.8 - 14.7)	
Range	0 - 111.3	0 - 137.6		2.1 - 34.0	2.1 - 34.0		4.0 - 90.4	2.9 - 90.4	
DMAX			0.97			0.97			0.95
Median(Q1-Q3)	394.1 (205.8 - 625.1)	407.8 (217.8 - 639.2)		588.1 (378.3 - 706.3)	601.7 (393.1 - 708.1)		377.7 (259.0 - 582.8)	401.1 (292.0 - 609.4)	
Range	0 - 1690.6	0 - 1690.4		33.36 - 929.28	50.87 - 951.79		4.05 - 930.5	79.8 - 957.4	
DBULK			0.96			0.97			0.91
Median(Q1-Q3)	112.6 (82.6 - 147.2)	109.2 (80.2 - 143.2)		84.8 (20.0 - 121.1)	90.1 (20.0 - 127.89)		120.5 (89.2 - 149.4)	119.9 (90.9 - 143.4)	
Range	0 - 453.9	0 - 437.2		1 - 556.5	1.0 - 542.0		4.1 - 427.5	29.9 - 425.5	

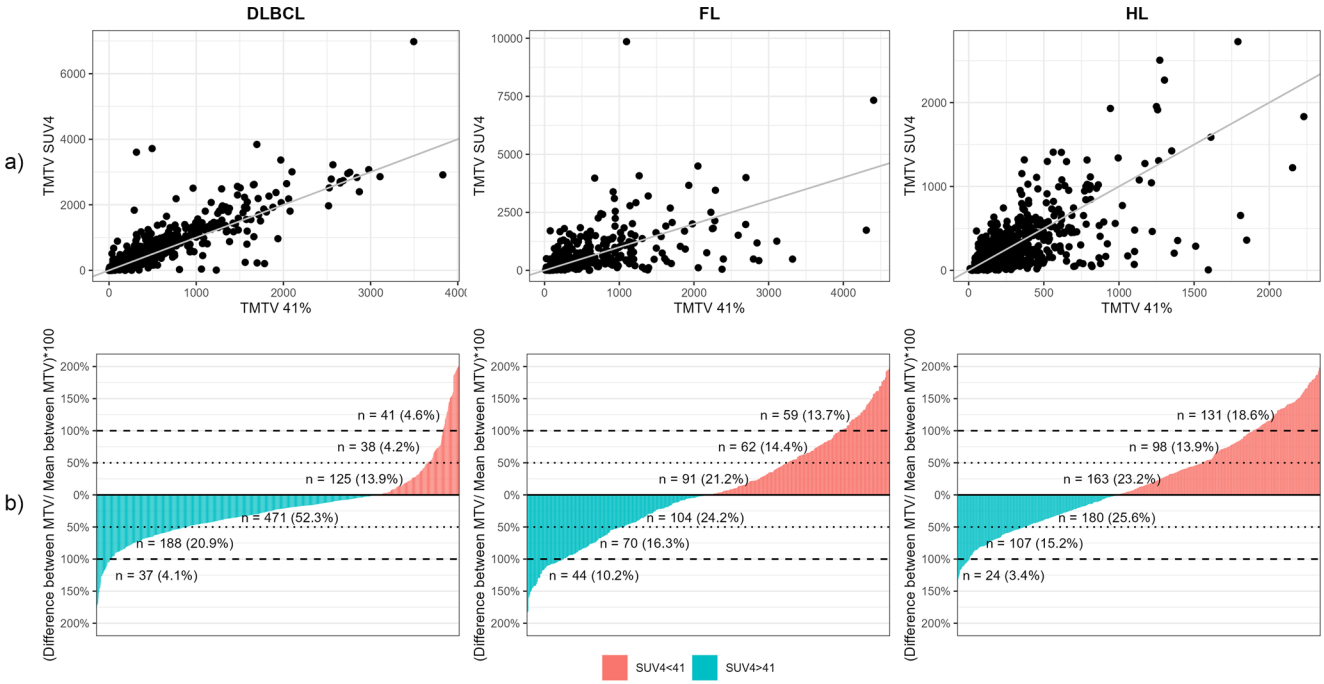

Fig. 1 Comparison of the $TMTV_{4.0}$ and $TMTV_{41}$ values for DLBCL, FL and HL patients. At the top, scatter plot are presented with the diagonal line in grey. Below, for each patient the ratio between the TMTVs difference and the mean TMTV value is reported on the percent scale. Thus, a ratio of 1 (100%) means that the difference between TMTVs is equal to the mean value of TMTVs. Patients are ordered according to the value of the ratio, and different groups of patients are identified: (i) patients with a small ratio (between 0 and 50%, i.e. the difference is more than twice less than the mean value), (ii) patients with an intermediate ratio (between 50% and 100%) and (iii) patients with high ratio (>100%, i.e. the difference is higher than the mean value)

To assess the effect of TMTV segmentation on individual PFS prediction, the predicted values of PFS for each patient were plotted in Fig. 2C using model with linear TMTV alone. A very small fraction of patients, marked in red, exhibited a large deviation (>10%) in predicted PFS between the two segmentation models: 21/900 (2.33%) in DLBCL, 28/430 (6.51%) in FL and 7/703 (1%) in HL.

The model adequation considering the TMTV was high for the two segmentation methods (Fig. 3). However, the AIC, AUC and Brier Score indicators are consistently superior for models with $TMTV_{41\%}$ than to models with $TMTV_{4.0}$ with a combination of lower AICs (with difference>4), higher AUCs at 2 years and lower or equivalent Brier Scores at 2 years for each model, regardless of lymphoma subtype (DLBCL, FL and HL). Nevertheless, the estimated effects remain comparable between $TMTV_{41\%}$ and $TMTV_{4.0}$ with superimposable CIs. Expressing TMTV as a categorical or continuous variable or included in prognostic models, the PFS HRs were significant for both methods in DLBCL and FL patients. In HL, unlike $TMTV_{41\%,}$ $TMTV_{4.0}$ did not reach significance whether using categorical or continuous variable. In comparison to a categorical TMTV variable, linear TMTV had the best or equivalent performance to predict PFS whatever the subtypes and the segmentation methods. Considering TMTV alone, AICs were equal to 2829/2822 with categorical $TMTV_{4.0}$/$TMTV_{41\%}$ vs. 2819/2807 with linear $TMTV_{4.0}$/$TMTV_{41\%}$ for DLBCL, 1992/1984 with categorical $TMTV_{4.0}$/$TMTV_{41\%}$ vs. 1992/1976 with linear $TMTV_{4.0}$/$TMTV_{41\%}$ for FL and 1187/1182 with categorical $TMTV_{4.0}$/$TMTV_{41\%}$ vs. 1189/1184 with linear $TMTV_{4.0}$/$TMTV_{41\%}$ for HL. Focusing on DLBCL patients, both segmentations showed excellent performance to predict PFS: for the linear TMTV (for a standard deviation increase), the HR estimates was 1.28 [1.15;1.43] for $TMTV_{4.0}$ and 1.33 [1.21;1.47] for $TMTV_{41\%,}$ for the IMPI score, 2.03 [1.53; 2.69] vs. 2.42 [1.83; 3.22] respectively.

Similarly, the predictive performances were closed between the two types of segmentation but in favor of $TMTV_{41\%}$. The AUC at 2 years for models with linear TMTV were 61% vs. 64.1% for $TMTV_4$ vs. $TMTV_{41\%}$ respectively in DLBCL, 61.4% vs. 64.8% in FL and 57% vs. 61% in HL. When TMTV was adjusted on other covariates in prognostic scores, the AUC was better with 63.6% and 66% (considering $TMTV_4$ and $TMTV_{41\%}$ respectively) for IMPI score in DLBCL and 63.1% vs. 64.1% for TMTV/ECOG score in FL.

Finally, regarding Brier score at 2 years, the models performances considering $TMTV_4$ vs. $TMTV_{41\%}$ were very close. For models with linear TMTV, the Brier scores were 14.2 vs. 14 for $TMTV_4$ vs. $TMTV_{41\%}$ respectively in

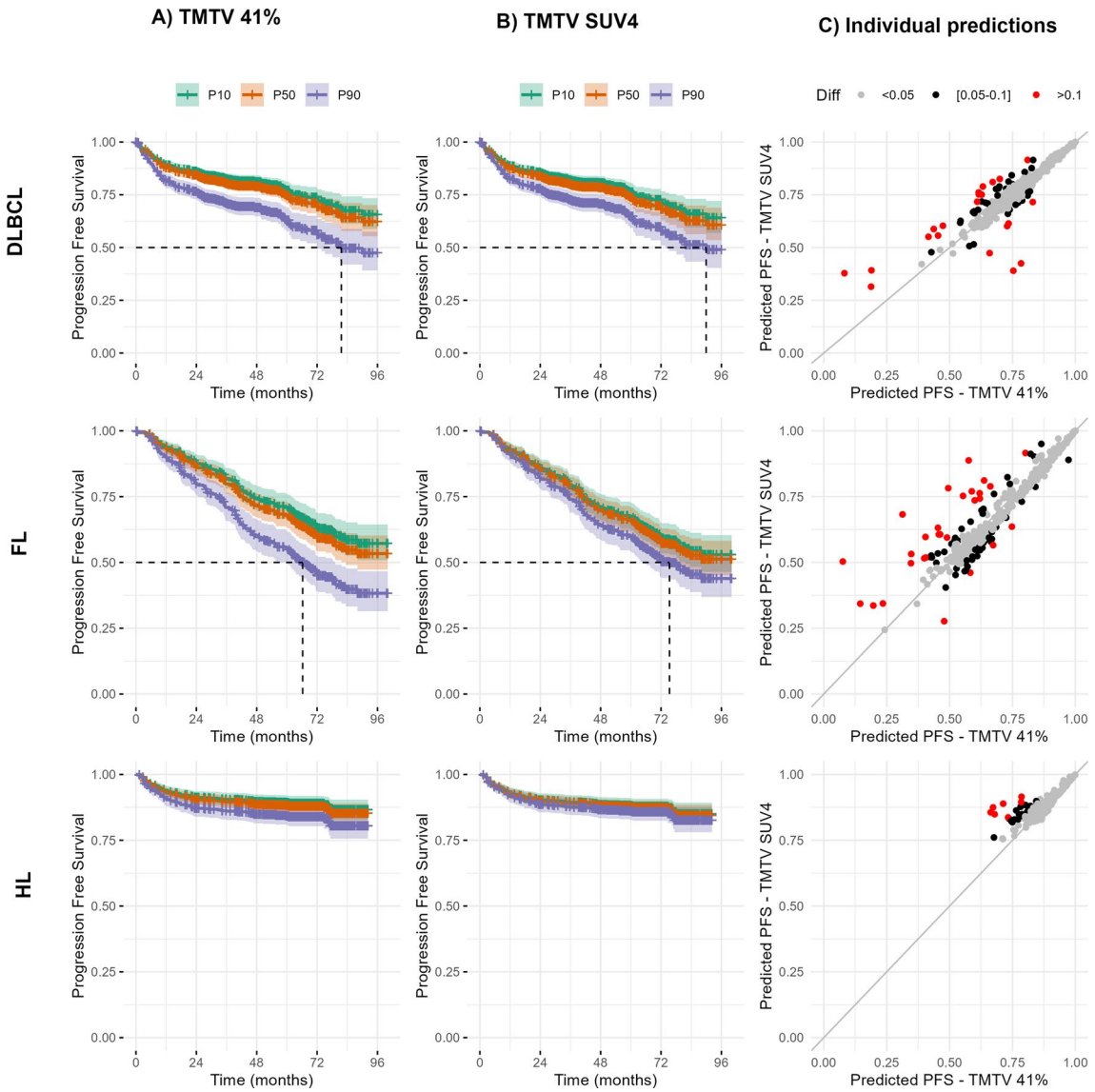

Fig. 2 For each lymphoma subtype are represented for **A** and B columns the predicted PFS curves for the 10e, 50e and 90e percentile values (P10, P50 and P90) of linear TMTV41 and TMTV4 cox models and for **C** the individual predictions of these two models in a scatter plot. In the latter plot, patients with a large difference (> 10%) between the predicted values of PFS by the two models are highlighted in red

DLBCL, 13 vs. 12.9 in FL and 9.4 vs. 9.3 in AHL. As for AUC, the Brier score was better when TMTV was adjusted on other covariates in prognostic scores with 14 and 13.8 (considering $TMTV_4$ and $TMTV_{41\%}$ respectively) for IMPI score in DLBCL and 12.7 vs. 12.7 for TMTV/ECOG score in FL.

Discussion

While TMTV has proven to be prognostically valuable in lymphoma, the use of various segmentation methods hinders direct comparisons across studies and hampers its use as a biomarker in clinical trials and in clinical practice. Recently, the SUV4.0 segmentation threshold has been proposed [28] to promote the widespread adoption of TMTV measurement. However, only few data are available on the $TMTV_{4.0}$ prognostic impact in DLCBL [6, 12] and HL [29, 30] and no data have been published on follicular lymphoma patients.

In the current study we observed a very strong correlation between $TMTV_{41\%}$ and $TMTV_{4.0}$ values in a large cohort of 900 DLBCL patients from prospective trials. PFS analysis showed excellent performance for both methods. For the highest 10th percentile TMTV values, half of the patients experienced a PFS event at 7 years, regardless of the method applied. A similar discriminative power has been also reported previously by Barrington et al. in a cohort of 140 DLBCL [27]. This supports the use of this simple

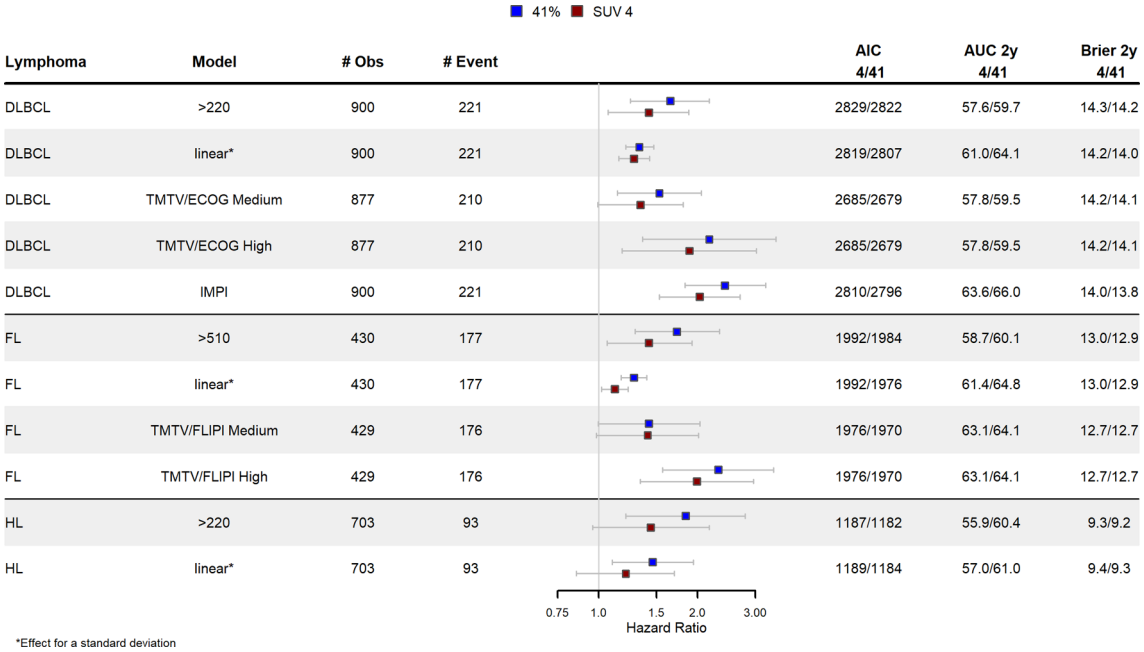

Fig. 3 Forestplot showing for each model the estimated HRs with their 95%CI using cox model for the two segmentation methods (SUV4 and 41%SUVmax). The Akaike information criterion (AIC), Area Under the receiver operating characteristic Curve (AUC) at two years and Brier Score at two years for each model are reported. For each lymphoma subtype, TMTV is considered both as a binary and a continuous (linear) variable in the univariate cox models. For DLBCL, the TMTV/ECOG score in three categories (low, medium, high) and the continuous IMPI score are also estimated. Similarly for FL, the TMTV/FLIPI score in three categories (low, medium, high) is estimated

method, quick to perform using both academic and commercial software to risk stratify DLBCL patients. In addition, Mikhaeel and colleagues recently proposed the use of TMTV as a continuous variable rather than a dichotomized [12]. In our study we also demonstrated that using TMTV as a continuous risk factor provided significant additional value, resulting in higher HR values in both DLBCL and FL patients. This approach enables a more tailored risk assessment and enhances clinical decision-making compared to using a predefined risk group.

For FL patients, the prognostic value has been published only using the 41%SUVmax method [3, 22, 39]. In the current study, we firstly assessed the significant prognostic impact of TMTV measured using the SUV4.0 method in this lymphoma subtype, well known to have a more heterogenous distribution of SUV values, with lower SUVmax value than in DLBCL. Interestingly, half of the patients had higher TMTV values with 41%SUVmax method and half with the SUV4.0 method illustrating the heterogenous distribution of SUV values in FL. However, at the end, only a small number of patients (6%) showed a deviation greater than 10% in predicted PFS between the two segmentations. These results suggested that the SUV4.0 method could be used to stratify FL patients at baseline.

For HL patients the correlation was moderate, like those for FL, due to a more heterogenous lesions uptake, with $TMTV_{41\%}$ higher than $TMTV_{4.0}$ in 2/3 of the population. Like our finding, in 105 PET scans from both newly diagnosed and relapsed/refractory HL patients, SUV4.0 resulted in significantly lower TMTV values than the 41% SUVmax method [29]. Although similar PFS predictions were observed between the two methods in our cohort of 630 HL patients, only $TMTV_{41\%}$ reached significance. By contrast, in 107 early stage HL from the HD16 trial, Van Heek et al. [28] found that the SUV4.0 method had a higher predictive value for PET-2 positivity compared to 41% SUVmax. These fluctuating results highlighted that the prognostic significance of TMTV is probably weaker in HL compared to DLBCL and the lower number of PFS events makes the search for biomarkers particularly challenging in HL patients.

Dmax, which reflects lymphoma dissemination, is another promising parameter for lymphoma risk stratification. Originally proposed for DLBCL [40, 41], its prognostic value has since been rapidly established in other lymphoma subtypes [42]. This study is the first to demonstrate that Dmax is not affected by the choice of MTV segmentation method, highlighting its potential as a robust tool. In addition, as a very easily assessed dimensional feature, unlike SUV PET- derived features, Dmax is not impacted by the reconstruction/acquisition parameters, supporting its use as a robust and accessible biomarker.

This study was based on scans conducted between 2008 and 2015, but PET/CT technology is constantly evolving

as evidenced by the development of AI-based algorithms for image post-processing. However, although MTV may vary depending on the types of reconstructions, the SUV4.0 method appears to be the least affected among several PET image reconstruction protocols [43]. The ComBat method [44, 45] could be also used to transfer the current results to new reconstruction techniques.

A common criticism of the 41% threshold is its time-consuming nature, as it requires an initial step of selecting regions of interest one by one before applying the 41% threshold. This can occasionally result in incorrect application of the method, with some users mistakenly employing the patient's SUVmax rather than the SUVmax for each specific lesion. To address this, Kanoun et al. proposed an algorithm that automatically identifies areas with elevated 18 F-FDG uptake based on compacity, independently of the thresholding method [24], allowing to apply different thresholding methods thereafter.

TMTV computation will likely be performed using artificial intelligence (AI) in the coming years to build an automated clinical decision tool which would facilitate objective and standardized assessment regardless of observer experience. Recent research has demonstrated that convolutional neural networks can effectively segment lesions in lymphoma patients, showing impressive results when comparing features derived from PET scans to those extracted from manually segmented lesions [46–49]. Revailler et al. [50] proposed to train the CNN against a probability map of segmentation that reflected the segmentation methodology differences in 1218 baseline 18FDG-PET/CT. Four different thresholds were then applied to the mask created by nuclear medicine physicians to calculate the probability of the voxel being included in the TMTV segmentation: 41% SUVmax, SUV > 2.5 and SUV > 4.0 and Otsu method (histogram-based threshold). This algorithm is now being used for a real-time on-line blinded independent central review of TMTV for CARMOD trial (NCT06271057) to accelerate the segmentation process. An alternative method suggested by Capobianco et al. [51] involves identifying FDG uptake through multi-foci segmentation of the image, followed by classification with CNNs to differentiate between tumor and physiological uptake. Some studies seek to bypass the segmentation step and generates predictions directly from the PET images. For instance, the use of MIPs instead of TMTV for predicting treatment outcomes has been suggested in DLBCL [52, 53]. However, the predicted probabilities made by CNN models are directly influenced by the reconstruction protocol applied and by image resolution and this should be considered in future developments of AI methods for survival prediction [54]. External validation is also crucial to assess the reproducibility and generalizability of AI models. Finally, the challenge of using AI is the need to maintain control over the suggested result, with the final MTV requiring approval by a physician. Recently, a consortium of 117 experts from 50 countries, called FUTURE-AI, have built guideline to standardize and improve the reliability and safety of AI development in healthcare [55].

To conclude, in a large cohort of 1,960 lymphoma patients from the three most common lymphoma subtypes, we demonstrated that TMTV measured with the recently proposed SUV4.0 segmentation threshold yields a PFS prediction comparable to that of 41% SUVmax supporting its potential for widespread adoption. In DLBCL and FL, a continuous approach significantly enhances the predictive value of TMTV and should therefore be considered for more tailored risk assessment. In Hodgkin lymphoma, the role of TMTV is likely more nuanced, requiring additional research to optimize risk assessment.

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Data availability The datasets analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethical approval This study was performed in line with the principles of the Declaration of Helsinki.

Consent to participate Informed consent was obtained from all individual participants included in the study, as part of prospective trials.

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