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Prognostic value of baseline total metabolic tumor volume (TMTV0) measured on FDG-PET/CT in patients with peripheral T-cell lymphoma (PTCL)†

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Background: Most peripheral T-cell lymphoma (PTCL) patients have a poor outcome and the identification of prognostic factors at diagnosis is needed.

Patients and methods: The prognostic impact of total metabolic tumor volume (TMTV0), measured on baseline [^{18}F] 2-fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography, was evaluated in a retrospective study including 108 PTCL patients (27 PTCL not otherwise specified, 43 angioimmunoblastic T-cell lymphomas and 38 anaplastic large-cell lymphomas). All received anthracycline-based chemotherapy. TMTV0 was computed with the 41% maximum standardized uptake value threshold method and an optimal cut-off point for binary outcomes was determined and compared with others prognostic factors.

Results: With a median follow-up of 23 months, 2-year progression-free survival (PFS) was 49% and 2-year overall survival (OS) was 67%. High TMTV0 was significantly associated with a worse prognosis. At 2 years, PFS was 26% in patients with a high TMTV0 (>230 cm^3, $n = 53$) versus 71% for those with a low TMTV0, [$P < 0.0001$, hazard ratio (HR) = 4], whereas OS was 50% versus 80%, respectively, ($P = 0.0005$, HR = 3.1). In multivariate analysis, TMTV0 was the only significant independent parameter for both PFS and OS. TMTV0, combined with PIT, discriminated even better than TMTV0 alone, patients with an adverse outcome (TMTV0 >230 cm^3 and PIT >1, $n = 33$,) from those with good prognosis (TMTV0 ≤230 cm^3 and PIT ≤1, $n = 40$): 19% versus 73% 2-year PFS ($P < 0.0001$) and 43% versus 81% 2-year OS, respectively ($P = 0.0002$). Thirty-one patients (other TMTV0–PIT combinations) had an intermediate outcome, 50% 2-year PFS and 68% 2-year OS.

Conclusion: TMTV0 appears as an independent predictor of PTCL outcome. Combined with PIT, it could identify different risk categories at diagnosis and warrants further validation as a prognostic marker.

Key words: FDG–PET/CT, metabolic volume, PTCL

introduction

Peripheral T-cell lymphomas (PTCLs) are a heterogeneous group of rare diseases. The current World Health Organization (WHO) classification system groups them into different categories, based on their clinical features, histological and phenotypic and molecular aspects [1, 2]. The nodal lymphoma group, defined by mature T-cell lymphoma with predominantly nodal presentation, contains the most common subtypes [3, 4]: peripheral T-cell lymphoma (PTCL) not otherwise specified (PTCL-NOS), angioimmunoblastic T-cell lymphoma (AITL) and anaplastic large-cell lymphoma (ALCL) and accounts for more than 55% of T-cell lymphomas [5]. Most PTCLs are associated with a poor prognosis [5, 6], aggressive clinical behavior

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and relatively poor response to chemotherapy. In the literature, the 5-year OS of PTCL patients treated with doxorubicin-based chemotherapy ranges between 25% and 45% [7], and the median time from diagnosis to relapse or progression following first-line therapy is only 6.7 months [8]. Therefore, an early identification at diagnosis of patients who will relapse is needed to guide therapeutic strategy. The International Prognostic index (IPI) [5] and the prognostic index for T-cell lymphoma (PIT) [9] are not sufficient for early risk stratification. Therefore, new prognostic markers are warranted to better identify high-risk patient categories. [^{18}F]2-fluoro-2-deoxy-D-glucose positron emission tomography (FDG–PET)/computed tomography (CT) is now recommended by the International Conference on Malignant Lymphoma group for PTCL staging since most of them are FDG avid [10, 11]. Its value for prognosis prediction at interim and end treatment has been recently investigated [12–14]. Some studies have also suggested that quantitative parameters derived from baseline FDG–PET/CT such as total metabolic tumor volume (TMTV0) could predict outcome in Hodgkin lymphoma (HL) [15] in diffuse large B-cell lymphoma (DLBCL) [16], in primary mediastinal large B-cell lymphoma [17] and in extranodal natural killer/T-cell lymphoma (ENKTCL) [18, 19]. In disseminated disease, TMTV0, which allows the measurement of the viable fraction of all tumor sites, is particularly relevant and seems to be a better predictor than the bulk. Thus, it can be proposed for a general evaluation of the total tumor burden in diffuse diseases such as PTCL.

The aim of this study was to measure baseline TMTV0 and other FDG–PET-derived quantitative metrics in PTCL and to investigate their potential role as predictive factors at staging which has never been explored. We focused our study on PTCL patients with the most common histological subtypes, i.e. PTCL NOS, AITL and ALCL.

Table 1. Patient clinical characteristics for the whole population and stratified according to pretreatment total metabolic tumor volume (TMTV0) with the 230 cm^3 cutoff

Characteristics	Total population ($N = 108$) No. of patients (%)	Low tumor burden ($N = 55$) No. of patients (%)	High tumor burden ($N = 53$) No. of patients (%)	P
Age median (range)	58 (19–82)	58 (19–78)	56 (19–82)	
>60 years	44 (41)	23 (42)	21 (38)	NS
Female sex, *n*	40 (37)	23 (42)	17 (32)	NS
Histological type				
NOS	27 (25)	12 (22)	15 (28)	NS
AITL	43 (40)	18 (33)	25 (47)	NS
ALK-positive ALCL	14 (13)	11 (20)	3 (6)	NS
ALK-negative ALCL	24 (22)	14 (25)	10 (19)	NS
Ann Arbor stage III–IV	98 (91)	46 (84)	52 (98)	0.03
ECOG 2–3	36 (34)	9 (16)	27 (51)	0.0003
IPI >2	54 (50)	15 (27)	39 (73)	<0.0001
PIT >1	47 (45)	14 (25)	33 (62)	0.0002
BMB+[a]	24 (22)	5 (9)	19 (36)	0.002
Bulk >10 cm	14 (13)	1 (2)	13 (24)	0.002
Increased LDH	57 (53)	15 (27)	42 (79)	<0.0001
Chemotherapy				
CHOP/CHOP-like[b]	87 (80)	45 (82)	42 (79)	NS
ACVBP	21 (20)	10 (18)	11 (21)	NS
Consolidative transplant[c]	23 (21)	10 (18)	13 (24)	NS

[a]BMB+ (positive bone marrow biopsy) were 7 in PTCL NOS, 13 in AITL, 4 in ALCL.
[b]2 miniCHOP, 11 CHOEP (among 4 included on AAT trial), 1 COEP and 1 COPADEM.
[c]82% of transplants were in the CHOP/CHOP-like arm.
IPI, International Prognostic index; PIT, peripheral T-cell index; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; ACVBP, cyclophosphamide, doxorubicin, vindesine, bleomycin.

materials and methods

study population

One hundred eight consecutive patients with confirmed PTCL NOS, AITL or ALCL diagnosed between April 2006 and September 2014 in five LYSA centers (Créteil, Dijon, Marseille, Rouen, all in France and Liège, Belgium) were retrospectively included. Inclusion criteria were: baseline PET/CT and first-line treatment by anthracycline-based chemotherapy (Table 1). Twenty-one patients were included in prospective clinical trials, 10 in ROCHOP (NCT01280526), 6 in REVAIL (NCT01553786), 4 in autologous or allogenic transplantation in T-cell lymphoma, 1 in LNH 05-1T (NCT00136565). Twenty-three patients under 60 years old who achieved complete remission had a consolidative transplant. The study was conducted in accordance with the precepts of the Helsinki declaration and received approval by the Ethical Committee with a waiver of informed consent due to its retrospective nature.

quantitative PET parameters computation

All the centers involved followed the recommended rules for performing FDG–PET/CT in oncology [20]. All PET/CT images were anonymized and collected for central review in DICOM format. Quantitative parameters were computed by a nuclear medicine physician (ASC) blinded to patient outcome, on semiautomatic software (Planet Onco, version 2.0; DOSISoft). Reproducibility was assessed independently by a second nuclear medicine physician (SB) in a subgroup of 50 randomly selected patients. Lesions were identified by visual assessment with PET/CT images scaled to a fixed standardized uptake value (SUV) display and color table. Several parameters were measured: (i) TMVT0 was obtained by summing the metabolic volumes of all nodal and extranodal lesions. This method used the 41% maximum standardized uptake value (SUV_{max}) threshold method, as recommended by European Association of Nuclear Medicine, because of its high interobserver reproducibility already described in lymphoma [21]. A volume of interest was set around each lesion (node or organ involvement) as previously described [15, 16, 21]. Bone marrow involvement was included in volume measurement only if there was focal uptake. Spleen was considered as involved if there was focal uptake or diffuse uptake higher than 150% of the liver background; (ii) the total lesion glycolysis (TLG) was the sum of the product of the metabolic volume of each local tumor times its SUV_{mean} ($TLG = \sum MTV_L \times SUV_{mean_L}$); (iii) The patient SUV_{max} was the highest SUV_{max} measured in the tumor sites.

statistical analysis

The procedure to determine optimal cut-off values of the quantitative parameters for survival prediction followed these steps. We verified, by including cubic smoothing splines in the risk function of the Cox model, that the cut-point model for binary outcome was appropriate for TMTV0 [22]. A confirmatory analysis was carried out using X-tile® analysis [23]. The best cut-off value was checked with receiver operating curve (ROC) analysis. Progression-free survival (PFS) and overall survival (OS) were defined according to the revised NCI criteria [24]. Survival functions were estimated using the Kaplan–Meier (KM) method and compared using the log-rank test. Multivariate analyses were carried out using a Cox proportional hazards model. Characteristics of the population were compared between groups, using Fisher's exact or χ^2 tests, as appropriate. Differences between the results of comparative tests were considered significant if the two-sided P value was <0.05. Statistical analysis was conducted using MedCalc (MedCalc Software, Ostend, Belgium) and S-Plus7 software (Insightful).

results

Patient characteristics are given in Table 1. The median age was 58 years. The majority had stage III/IV disease. On baseline FDG–PET/CT, 31 patients had spleen involvement, 14 had a lesion of >10 cm and 22 patients had focal or heterogenous diffuse bone uptake. Six of them had a positive bone marrow biopsy (BMB+). The median follow-up was 23 months (1–97 months) for the whole population. The 2-year PFS and OS were 49% and 67%, respectively. The 2-year PFS and OS were 40% and 49% for PTCL NOS, 43% and 70% for AITL, 46% and 58% for ALK–ALCL patients. ALK + ALCL patients had much better prognosis with a 2-year PFS and OS of 85% and 92%. The majority of patients were treated with CHOP/CHOP-like regimen with no statistical difference of PFS and OS for those treated by ACVBP ($P = 0.75$, $P = 0.76$). Treatment with new drugs (romidepsin, lenalidomide) or consolidative transplant had no impact on patients' outcome ($P = 0.4$, $P = 0.8$).

quantitative PET parameters

In the whole population, median pretreatment TMTV0 was 224 cm^3 (range: 5–3824 cm^3). ROC optimal cut-off values (i.e. giving the best sensitivity specificity ratio) were close to those found with spline and X-tile® analysis, 230 cm^3 for PFS with a sensitivity of 70.6% and a specificity of 71.9% and 260 cm^3 for OS with a sensitivity of 62.0% and a specificity of 67.6%. Areas under the ROC curves (AUC) were 0.698 ($P = 0.0002$) and 0.625 ($P = 0.0275$). The population was dichotomized with a cutoff of 230 cm^3 given its best sensitivity and specificity for PFS. Patients with a high metabolic tumor volume (TMVT0 >230 cm^3, $n = 53$) had a significantly worse outcome, with a 2-year PFS and OS of 26% and 50% versus 71% and 80% for patients with a lower metabolic tumor volume ($P < 0.0001$ for PFS and $P = 0.0005$ for OS) (Figure 1A, Table 2). When we analyzed only patients in advanced stage, TMTV0 remained a prognostic factor for both PFS and OS ($P < 0.0001$, $P = 0.002$). Excluding ALK + ALCL patients, known to have a better prognostic, a significant difference of PFS and OS was still observed between the high and low TMTV0 groups ($P = 0.0001$, $P = 0.0055$). In a subgroup analysis grouping together PTCL-NOS and AITL histologies, patients with a high TMTV0 still have a worse PFS and OS ($P = 0.0002$, $P = 0.01$) (Figure S1, available at *Annals of Oncology* online). Similar results were found for ALCL patients ($P = 0.006$ for PFS, $P = 0.02$ for OS) (Figure S1, available at *Annals of Oncology* online). Moreover, TMTV0 maintained its prognostic value on PFS and OS across the chemotherapy regimen groups, CHOP/CHOP-like ($P = 0.001$, $P = 0.02$) or ACVBP ($P = 0.0008$, $P = 0.003$). TMTV0 calculation was highly reproducible (Lin's concordance correlation coefficient: $\rho = 0.995$, 95% CI = 0.992–0.997). The overall agreement using dichotomization was very good ($\kappa = 0.87$). Patient characteristics stratified according to high or low TMTV0 values are presented in Table 1. Patients with a high TMTV0 had a more aggressive disease, with significantly more advanced stage.

The median TLG was 1155 (range: 19–20 800). The ROC curve analysis showed an optimal cut-off value of 1068, for both PFS and OS but the AUC was only significant for PFS. TLG was significantly predictive of PFS ($P = 0.0005$) and OS ($P = 0.01$), but less than TMTV0. In multivariate analysis including TMTV0 and TLG as covariates, only TMTV0 retained statistical significance (for PFS, TMTV0 $P = 0.0013$ and TLG $P = 0.83$; for OS $P = 0.021$ and $P = 0.99$).

The median patient SUV_{max} was 14, with a wide range of values (3.4–39.0). The mean SUV_{max} was 13 (±6.4 standard deviation) in AITL, slightly but significantly lower than the SUV_{max} of the other histological subtypes (3–4 SUV_{max} units) ($P = 0.023$). More than 80% of the patients had a SUV_{max} above 10. Only three patients had an SUV_{max} under 5: two of them had a negligible TMTV0 (~15 cm^3) and one a high TMTV0 due to splenic involvement. In univariate analysis, patient SUV_{max} was not related with outcome, irrespective of the histological subgroup.

clinical and biological parameters

In univariate analysis, age, performance status (ECOG), Ann Arbor stage were not associated with PFS or OS, whereas LDH level, bulk and bone marrow biopsy appeared to be prognosticators (Table 2). PIT was significantly related to progressive disease and death (Table 2, Figure S2, available at *Annals of Oncology* online), as well as the IPI. In a subanalysis of each histological subtype, PIT remained a significant prognostic factor only for AITL patients, which was the largest subgroup ($P = 0.0028$ for PFS, $P = 0.015$ for OS).

combining TMTV0 and clinical parameters

In multivariate analysis testing TLG, TMTV0, Bulk, IPI, PIT, histologies (ALK + versus others) and treatments (CHOP versus others) (Table S3), only TMTV0 was a significant independent predictor for both PFS and OS ($P = 0.0002$, $P = 0.03$). PIT just reached significance for OS ($P = 0.05$). TMTV0 remained the only significant factor in two simplified models including histologies or PIT, treatments and interactions between treatments and these risk factors.

However, combining TMTV0 with PIT gave added predictive value. Three risk categories could be identified depending on the presence or absence of adverse factors: group 1 if TMTV0 ≤230 cm^3 and PIT ≤1 ($n = 40$); group 2 defined as TMTV0 >230 cm^3 and PIT ≤1 or TMTV0 ≤230 cm^3 and PIT >1 ($n = 31$), group 3 with TMTV0 >230 cm^3 and PIT >1 ($n = 33$). These groups had significantly different outcome, with 2-year PFS

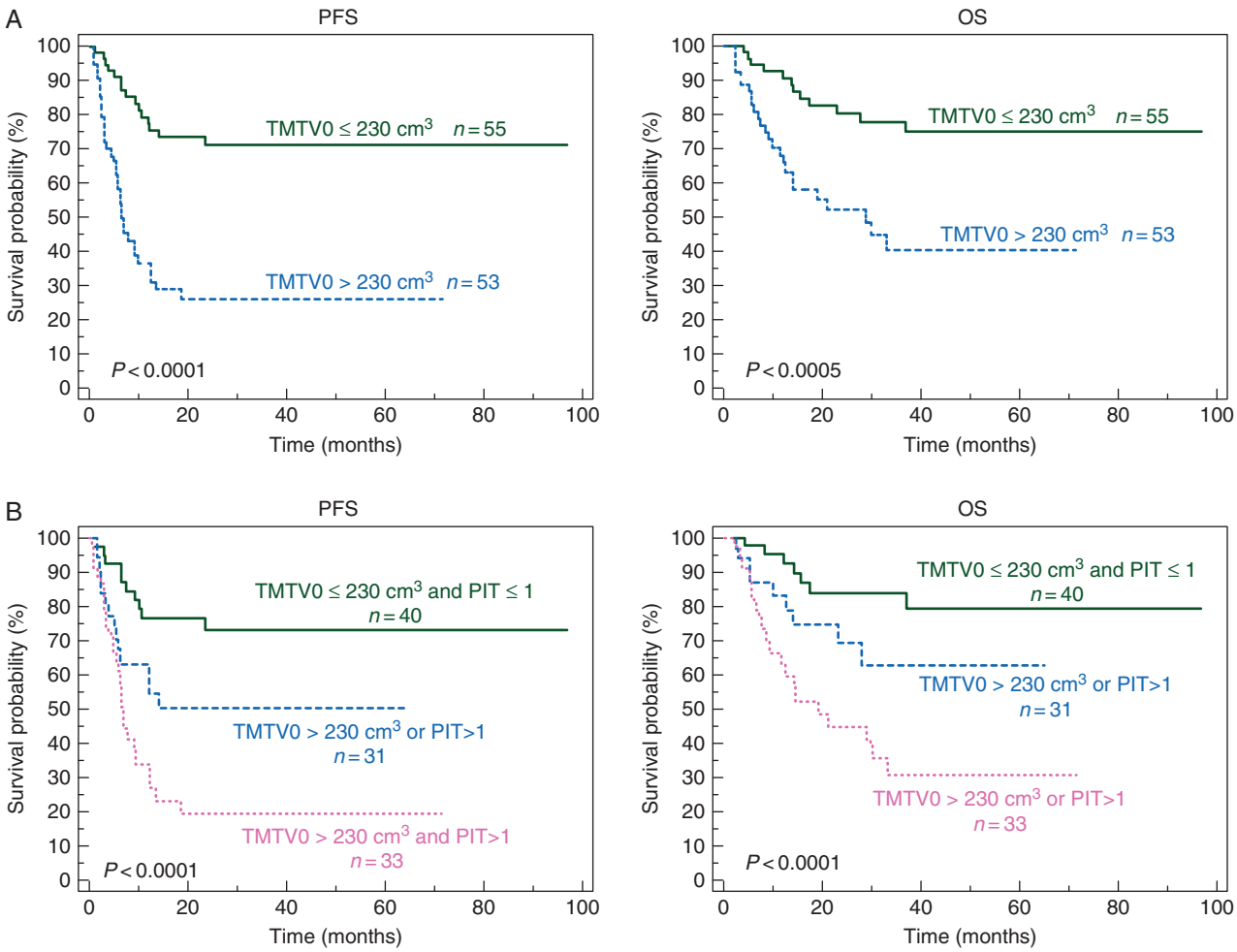

Figure 1. Kaplan–Meier estimates of progression-free and overall survival according to the baseline total metabolic tumor volume (TMTV0) in the whole population (A) and according to the peripheral T-cell index (PIT) combined with TMTV0 (B). PIT was available in 104 patients since 4 had no bone marrow biopsy.

of 73%, 50% and 19% ($P < 0.0001$) and 2-year OS of 81%, 68%, 43% ($P = 0.0002$) (Figure 1B), respectively. Although the median PFS in patients with PIT >1 was 9 months, the median PFS in group 3 was 6.9 months. In a subanalysis, we confirmed that patients from group 3 had a significantly worse PFS and OS than patients from group 2 ($P = 0.036$ and $P = 0.035$), and similarly for patients from group 1 compared with group 2 on PFS ($P = 0.032$) with a trend for OS ($P = 0.13$).

discussion

Our results demonstrate that pretreatment TMTV0 is highly predictive of outcome in PTCL patients irrespective of the Ann Arbor stage or the presence of large (bulky) tumor lesions. Patients with a high metabolic tumor burden had a worse outcome, with a higher number of relapses. TMTV0 obtained from baseline FDG-PET is a measure of the viable fraction of tumors and would probably give a good estimate of the metabolic tumor burden. We have shown that the method used in this study for TMTV0 measurement is reproducible in PTCL, as already reported in HL and DLBCL, where TMTV0 has been proposed as a prognostic index [15, 16]. In T-cell lymphoma, the prognostic value of metabolic tumor burden has been reported only in ENKTCL [18, 19]. Low cut-off values were found (35 and 14 $cm,^3$ respectively) explained by the specific clinical features of this lymphoma subtype, that is mostly localized cases. In contrast, PTCL NOS, AITL and ALCL are generally disseminated diseases with different proportions of microenvironmental cells, responsible for FDG uptake.

To the best of our knowledge, the current study is the first to evaluate the prognostic significance of TMTV0 in a large series of patients with the commonest PTCL entities. It is the best prognostic factor among the other quantitative parameters derived from staging FDG–PET. A high TLG was also predictive of a lower PFS and OS, but less significant than TMTV0. Unlike ENKTCL [18], SUV_{max} was not associated with outcome in our population, probably because the intensity of FDG uptake was very heterogeneous. TLG and SUV_{max}, obtained from quantitative absolute measurements, are more sensitive to technical parameters than TMTV measured with a fixed threshold method.

Our data confirmed the predictive value of PIT, introduced by Gallamini et al. for PFS and OS. A few studies have shown that combining clinical or biological factors with imaging (so-called integrative PET) allows us to identify different risk categories for patients with lymphoma [15, 25, 26]. In the present study, we

Table 2. Univariate analysis (log-rank test) of the difference between progression-free survival (PFS) and overall survival (OS) according to dichotomized total metabolic tumor volume (TMTV0), total lesion glycolysis (TLG), lactate dehydrogenase (LDH), the presence of a bulk, bone marrow biopsy (BMB), International Prognostic index (IPI), prognostic index for T-cell lymphoma and histologies

Parameter	2-year PFS (95% CI)	*P*-value Hazard ratio	2-year OS (95% CI)	*P*-value Hazard ratio
TMTV0				
Low	71% (64.6% to 77.4%)	$P < 0.0001$	80% (74.4% to 85.6%)	$P = 0.0005$
High	26% (19.4% to 32.6%)	HR = 4	50% (42.4% to 57.6%)	HR = 3.1
TLG				
Low	65% (58% to 72%)	$P = 0.0005$	79% (72.9% to 85.1%)	$P = 0,01$
High	37% (30.4% to 43.6%)	HR = 2.75	56% (49% to 63%)	HR = 2.3
LDH				
Normal	68% (61.1% to 74.9%)	$P = 0.0001$	79% (72.7–85.3)	$P = 0.0016$
Increased	32% (25.5–38.5)	HR = 3.1	56% (49.1% to 62.9%)	HR = 3.02
Bulk >10 cm				
Present	29% (17% to 41%)	$P = 0.0009$	50% (37% to 63%)	$P = 0.027$
Absent	53% (48% to 58%)	HR = 3.0	69% (64% to 74%)	HR = 2.4
BMB				
Negative	58% (52.2% to 63.8%)	$P = 0.026$	68% (63% to 73%)	$P = 0.24$
Positive	21% (12% to 30%)	HR = 1.92	57% (46% to 68%)	HR = 1.5
IPI				
Low (≤2)	63% (56% to 70%)	$P = 0.003$	76% (70% to 82%)	$P = 0.009$
High (>2)	35% (28% to 42%)	HR = 2.3	57% (50% to 64%)	HR = 2.4
PIT				
Low (≤1)	64% (57.3% to 70.7%)	$P = 0.004$	78% (72.3% to 83.7%)	$P = 0.001$
High (>1)	32% (24.9% to 39.1%)	HR = 2.3	53% (45.4% to 60.6%)	HR = 3.1
Histology				
ALK-positive ALCL	85% (76% to 94%)	$P = 0.013$	93% (−87% to 99%)	$P = 0.019$
Others	43% (38% to 48%)	HR = 4.9	63% (58% to 68%)	HR = 7.4

have combined a clinical score, PIT and TMVT0, to stratify patients into three categories, according to the presence of 0, 1 or 2 adverse factors. This has resulted in identifying three groups of patients with a significant different outcome. Especially, patients with a high TMTV0 and PIT >1 had a very poor prognosis (2-year-PFS = 19%), with a median PFS of 6.9 months. With an equal PIT score, patients with a high TMTV0 had a worse prognostic score. Grouping small subsets of patients with different PTCL entities and different treatment regimens is a limitation of the present study but these entities are distributed as observed in France (4). Therefore, a subanalysis of PTCL NOS and AITL patients on the one hand and ALCL patients on the other hand was done and still showed a significant difference of PFS and OS between patients with a high TMTV0 and patients with a low TMTV0, using the same cutoff of 230 cm^3. Similar results were observed excluding ALK + ALCL patients, who have a better prognostic. Moreover, TMTV0 maintained its prognostic value across the different chemotherapy regimen groups, CHOP or ACVBP. Some patients were included in prospective trials (19%) testing new drugs but the small number of patients and heterogeneous treatments make impossible to determine their specific impact on TMTV0 prognostic value. These deserved to be tested since new targeted agents, such as romidepsin [27] or brentuximab vedotin [28] are currently investigated in ongoing trials.

The present study represents the first series of PTCL so far investigated with an analysis of PET–CT quantitative functional parameters. TMTV0 was the most powerful predictive parameter of outcome. Combined with PIT, it could be used for precise prediction of patient prognosis. Particularly, patients with a very high risk of progression or relapse might benefit from more aggressive treatment plans. As it could help guiding therapy in the era of new drugs development, these results encourage to conduct a prospective trial to validate the prognostic role of TMTV0 in the different histologies of PTCL.

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disclosure

The authors have declared no conflicts of interest.

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