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# Prospective Study of 3'-Deoxy-3'-<sup>18</sup>F-Fluorothymidine PET for Early Interim Response Assessment in Advanced-Stage B-Cell Lymphoma

Heiko Schöder<sup>1</sup>, Andrew D. Zelenetz<sup>2</sup>, Paul Hamlin<sup>2</sup>, Somali Gavane<sup>1</sup>, Steven Horwitz<sup>2</sup>, Matthew Matasar<sup>2</sup>, Alison Moskowitz<sup>2</sup>, Ariela Noy<sup>2</sup>, Lia Palomba<sup>2</sup>, Carol Portlock<sup>2</sup>, David Straus<sup>2</sup>, Ravinder Grewal<sup>1</sup>, Jocelyn C. Migliacci<sup>3</sup>, Steven M. Larson<sup>1</sup>, and Craig H. Moskowitz<sup>2</sup>

<sup>1</sup>Molecular Imaging and Therapy Service, Department of Radiology, Memorial Sloan Kettering Cancer Center, New York, New York; <sup>2</sup>Lymphoma Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, New York; and <sup>3</sup>Department of Surgery, Memorial Sloan Kettering Cancer Center, New York

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Current clinical and imaging tools remain suboptimal for early assessment of prognosis and treatment response in aggressive lymphomas. PET with 3'-deoxy-3'-<sup>18</sup>F-fluorothymidine (<sup>18</sup>F-FLT) can be used to measure tumor cell proliferation and treatment response. In a prospective study in patients with advanced-stage B-cell lymphoma, we investigated the prognostic and predictive value of <sup>18</sup>F-FLT PET in comparison to standard imaging with <sup>18</sup>F-FDG PET and clinical outcome. **Methods:** Sixty-five patients were treated with an induction/consolidation regimen consisting of 4 cycles of R-CHOP-14 (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) followed by 3 cycles of ICE (ifosfamide, carboplatin, etoposide). <sup>18</sup>F-FLT PET was performed at baseline and at interim (iPET) after 1–2 cycles of therapy. <sup>18</sup>F-FDG PET was performed at baseline, after cycle 4, and at the end of therapy. The relationship between PET findings, progression-free survival (PFS) and overall survival (OS) was investigated. **Results:** With a median follow-up of 51 mo, PFS and OS were 71% and 86%, respectively. <sup>18</sup>F-FLT iPET, analyzed visually (using a 5-point score) or semiquantitatively (using SUV and ΔSUV) predicted both PFS and OS ( $P < 0.01$  for all parameters). Residual <sup>18</sup>F-FLT SUV<sub>max</sub> on iPET was associated with an inferior PFS (hazard ratio, 1.26,  $P = 0.001$ ) and OS (hazard ratio, 1.27,  $P = 0.002$ ). When <sup>18</sup>F-FDG PET was used, findings in the end of treatment scan were better predictors of PFS and OS than findings on the interim scan. Baseline PET imaging parameters, including SUV, proliferative volume, or metabolic tumor volume, did not correlate with outcome. **Conclusion:** <sup>18</sup>F-FLT PET after 1–2 cycles of chemotherapy predicts PFS and OS, and a negative <sup>18</sup>F-FLT iPET result may potentially help design risk-adapted therapies in patients with aggressive lymphomas. In contrast, the positive predictive value of <sup>18</sup>F-FLT iPET remains too low to justify changes in patient management.

**Key Words:** FLT PET; B-cell lymphoma; FDG PET; outcome

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Over the past decade, several changes in the management of diffuse large B-cell lymphoma (DLBCL) have occurred. For instance, the addition of the chimeric monoclonal antibody rituximab (R) to the standard CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) chemotherapy backbone has improved 5-y overall survival (OS) by approximately 15% (1,2). However, DLBCL shows substantial heterogeneity in its clinical behavior, and new management strategies, including the early identification of poor responders, are needed to improve patient outcome.

The role of interim PET (iPET) with <sup>18</sup>F-FDG after a few cycles of chemotherapy in identifying patients with poor outcome has been investigated (3–9). Our group studied the utility of <sup>18</sup>F-FDG iPET as part of a chemotherapy program consisting of induction with R-CHOP-14 followed by consolidation with ICE (ifosfamide, carboplatin, etoposide) (4). In that study, we biopsied sites with residual <sup>18</sup>F-FDG uptake on iPET after 4 cycles of chemotherapy. All patients with a negative biopsy (or a negative iPET) received consolidation with 3 cycles of ICE, whereas patients with positive biopsy received RICE (rituximab, ifosfamide, carboplatin, etoposide) for 3 cycles followed by high-dose therapy and autologous stem cell rescue. Notably, this study demonstrated a high rate of false-positive <sup>18</sup>F-FDG iPET, which was also described by other groups (10). In the current study we, therefore, investigated whether PET imaging with the proliferation marker 3'-deoxy-3'-<sup>18</sup>F-fluorothymidine (<sup>18</sup>F-FLT) (11) after 1 or 2 cycles of therapy could provide better prognostic and predictive information than <sup>18</sup>F-FDG PET does in patients with advanced-stage large cell lymphoma.

## MATERIALS AND METHODS

### Study Design and Patient Population

After providing written informed consent, 65 patients with advanced-stage, CD20-positive DLBCL, primary mediastinal large B-cell lymphoma, or follicular lymphoma grade 3B were enrolled in a prospective study (<http://clinicaltrials.gov/show/NCT00712582>). The Institutional Review Board approved the study. All patients were eligible for autologous transplantation and met inclusion criteria as reported previously (4). Patients underwent staging with contrast-enhanced CT (covering chest, abdomen, and pelvis) and <sup>18</sup>F-FDG PET/CT ( $444 \pm 44$  MBq). Additional <sup>18</sup>F-FDG scans were obtained after 4 cycles and 6 wk after completion of chemotherapy. Plasma glucose before <sup>18</sup>F-FDG injections was  $92 \pm 15$  mg/dL. <sup>18</sup>F-FLT PET/CT ( $296 \pm 30$  MBq) was performed

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For correspondence or reprints contact: Heiko Schöder, MD, Molecular Imaging and Therapy Service, Memorial Sloan Kettering Cancer Center, 1275 York Ave., New York, NY 10065.

E-mail: schoderh@mskcc.org

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at baseline and at interim (cohort 1 postcycle 1, planned  $n = 30$ ; cohort 2 postcycle 2, planned  $n = 30$ ). Initial therapy for all patients consisted of dose-dense R-CHOP-14 for 3 cycles (rituximab, 375 mg/m<sup>2</sup> days 1 and 3; cyclophosphamide, 1,000 mg/m<sup>2</sup>; doxorubicin, 50 mg/m<sup>2</sup>; vincristine, 1.4 mg/m<sup>2</sup> [uncapped]; and prednisone, 100 mg oral daily days 2–6). Cycle 4 consisted of CHOP alone (same doses) and was followed by <sup>18</sup>F-FDG iPET. Consolidation consisted of ICE chemotherapy (3) for patients with an initial proliferation index of less than 80%, whereas patients with proliferation index of 80% or more received augmented RICE (rituximab, 375 mg/m<sup>2</sup> day1; etoposide, 200 mg/m<sup>2</sup> every 12 h × 3 doses; ifosfamide, 5 g/m<sup>2</sup>/d by continuous infusion × 2; carboplatin area under the curve 5 d 3 [maximum, 800 mg]) for 3 cycles.

### PET/CT Imaging and Analysis

Patients fasted for 6 h before radiotracer injection. PET/CTs from mid skull to upper thighs were obtained 60 min after injection on Discovery scanners (GE Healthcare) and were analyzed using the PET VCAR program (GE Healthcare). Volumetric regions of interest were placed in reference regions (mediastinal blood pool and normal liver) and over all sites of abnormal uptake in lymph nodes, soft-tissue organs, or bones. All scans were interpreted by 2 nuclear medicine physicians. For visual analysis of <sup>18</sup>F-FDG iPET, we used a 5-point scale (12); grades 1–3 were considered normal. Grades 4 and 5 were considered abnormal, defining grade 4 as uptake considerably (~20%) higher than liver and grade 5 as increase in number or intensity of <sup>18</sup>F-FDG-avid lesions. Abnormal <sup>18</sup>F-FLT uptake was defined as intensity higher than that in surrounding local background. <sup>18</sup>F-FLT response was classified as grade 1, no residual uptake; grade 2, uptake less than or equal to local background; grade 3, uptake slightly greater than local background; grade 4, improvement from baseline with at least 1 lesion showing uptake clearly higher than local background; and grade 5, increase in lesion size, number, or intensity. Grades 1–3 were considered complete response, grade 4 partial response, and grade 5 progression. <sup>18</sup>F-FLT analysis was restricted to lymph nodes and soft-tissue organs other than liver (high physiologic uptake in liver and bone marrow precludes reliable assessment of these organs). The metabolic tumor volume (volume of <sup>18</sup>F-FDG-avid lymphoma, MTV) and total proliferative volume (volume of <sup>18</sup>F-FLT-avid lymphoma, TPV) were defined using PET VCAR and applying a 42% threshold (13).  $\Delta\text{SUV}_{\text{max}}$  ( $[\text{SUV}_{\text{baseline}} - \text{SUV}_{\text{interim}}]/\text{SUV}_{\text{baseline}}$ ) was calculated by comparing a single disease site with the highest uptake in each scan (9) and comparing the summed SUV of the 5 most avid disease sites in each scan. Bone lesions were excluded from SUV-based analysis to enable head-to-head comparison of <sup>18</sup>F-FDG and <sup>18</sup>F-FLT findings.

### Statistical Analysis

OS time was calculated from the start of treatment until the date of death or last follow-up. Progression-free survival (PFS) was calculated from the start of treatment until the date of disease progression, death, or last follow-up. Survival analysis was performed using the Kaplan–Meier method for dichotomous variables and compared using the log-rank test. Cox proportional hazards regression was used to assess continuous variables. For all iPET scans, patients were dichotomized by residual uptake: grade 1–3 versus grade 4 and 5. A sensitivity analysis was performed to identify the thresholds for change in SUV or  $\text{SUV}_{\text{max}}$ . This was performed using maximal  $\chi^2$  test for PFS or OS. We used Kaplan–Meier analysis with the log-rank test to examine the relationship between PFS, OS, and the PET 5-point scale response. Because of limited power, multivariate survival analyses could not be performed. *P* values of less than 0.05 were considered significant. Analyses were performed using SPSS Statistical Software (version 22.0, 2013; IBM Corp.) or R software (version 3.0.1; R-Foundation for Statistical Computing).

## RESULTS

### Patient Characteristics

All 65 patients enrolled to the protocol were analyzed for PFS and OS (Table 1). Two patients progressed before <sup>18</sup>F-FDG iPET, 1 patient progressed between iPET and end of planned therapy, and 1 patient developed drug-related toxicity. The remaining 61 patients completed treatment according to the protocol. Accordingly, 63 patients were analyzable for <sup>18</sup>F-FDG iPET and 61 patients for <sup>18</sup>F-FDG end-of-treatment PET. For logistic reasons (unavailability of radiotracer, scheduling difficulty in patients with rapidly progressive disease, or withdrawn consent), only 52 patients underwent <sup>18</sup>F-FLT scanning at baseline, and 55 underwent interim <sup>18</sup>F-FLT scanning.

### Baseline Imaging Characteristics

All patients had <sup>18</sup>F-FDG-avid disease (Table 2). <sup>18</sup>F-FLT uptake was always lower than <sup>18</sup>F-FDG uptake, regardless of disease site. Discrepant findings (<sup>18</sup>F-FDG-positive/<sup>18</sup>F-FLT-negative) were observed for 90 of 2,860 regions (3%), mainly because disease in bones (69 regions) or liver (6 regions) was not detected on the <sup>18</sup>F-FLT scan. Other regions of <sup>18</sup>F-FDG-positive/<sup>18</sup>F-FLT-negative disease were noted in lymph nodes ( $n = 11$ ), lungs

**TABLE 1**  
Clinical and Demographic Characteristics

Variable	Value
<b>Sex</b>	
Female	36 (55%)
Male	29 (45%)
Median age (y)	54.7 (age range, 20.8–71.7)
<b>Stage</b>	
I/II	9 (14%)
III–IV	56 (86%)
<b>Ki-67</b>	
Median	70%
Range	20%–90%
<80%	43 (68%)
≥80%	22 (32%)
<b>International prognostic index score</b>	
Low	8 (12.3%)
Low-intermediate	16 (24.6%)
Intermediate-high	21 (32.3%)
High	20 (30.8%)
Extranodal sites >1	39 (60%)
Bone marrow biopsy positive	16 (25%)
<b>Histology</b>	
DLBCL	51 (78%)
Primary mediastinal B-cell lymphoma	13 (20%)
Follicular 3B	1 (2%)

Values outside parentheses are medians for continuous variables and counts for categorical variables. X denotes diameter > 10 cm.

**TABLE 2**  
PET Imaging Findings

Parameter	Time point	<i>n</i>	Median	Range
<sup>18</sup> F-FLT single SUV <sub>max</sub> (g/mL)	Baseline	52	13.0	2.7–41.4
	Interim	55	2.5	1.2–17.2
<sup>18</sup> F-FLT sum of hottest 5 SUV <sub>max</sub> (g/mL)	Baseline	52	32.3	2.7–127.2
	Interim	55	7.6	1.2–68.0
<sup>18</sup> F-FLT ΔSUV <sub>max</sub> (%)	Baseline to interim	50	↓77.1%	↑0.6% – ↓92.7%
<sup>18</sup> F-FLT TPV* (cm <sup>3</sup> )	Baseline	52	139.4	1.3–2,080.9
<sup>18</sup> F-FDG single SUV <sub>max</sub> (g/mL)	Baseline	65	23.4	6.1–48.0
	Interim	63	2.3	1.4–29.6
	Final	61	2.0	1.2–25.7
<sup>18</sup> F-FDG sum of hottest 5 SUV <sub>max</sub> (g/mL)	Baseline	65	59.3	8.5–192.4
	Interim	63	7.8	1.4–72.9
	Final	61	6.9	1.8–98.4
<sup>18</sup> F-FDG ΔSUV <sub>max</sub> (%)	Baseline to interim	63	↓88.9%	↑0.3% – ↓96.4%
	Baseline to final	61	↓89.8%	↓74.4 – ↓96.1%
<sup>18</sup> F-FDG MTV (cm <sup>3</sup> )	Baseline	65	225.6	8.4–3,452.6

\*Excluding bone and liver disease, for which volumes cannot be measured accurately because of high physiologic background activity.

(*n* = 3), and spleen (*n* = 1). However, all of these patients presented with multiple other disease sites that were clearly <sup>18</sup>F-FLT-positive. There were no patients with disease recognized only on <sup>18</sup>F-FLT PET/CT.

#### iPET/CT During Chemotherapy

Fifty-five patients underwent <sup>18</sup>F-FLT iPET after 1 cycle (*n* = 27) or after 2 cycles (*n* = 28) of R-CHOP. Time between the end of cycle and <sup>18</sup>F-FLT iPET was 9.8 ± 1.9 d for cohort 1 and 9.4 ± 1.2 d for cohort 2. Complete proliferative response (CPR) was observed in 29 patients (grade 1, *n* = 21; grade 2, *n* = 7; grade 3, *n* = 1), including 3 patients without baseline <sup>18</sup>F-FLT PET: because aggressive lymphoma is follicular lymphoma-avid at baseline (14–16), lack of uptake in residual nodes on iPET was considered CPR. The other 26 patients showed partial response (grade 4, *n* = 22) or progression (grade 5, *n* = 4). CPR tended to be more common after cycle 2 (78% vs. 44% after cycle 1, Supplemental Table 1 [supplemental materials are available at <http://jnm.snmjournals.org>]). However, differences were not significant and therefore data were analyzed jointly. Eighteen patients showed diffusely increased splenic uptake attributable to recent granulocyte colony-stimulating factor administration. The median <sup>18</sup>F-FLT ΔSUV was 77%.

On <sup>18</sup>F-FDG iPET, performed 18 ± 1 d after cycle 4, complete metabolic response was noted in 38 patients (grade 1, *n* = 24; grade 2, *n* = 10; and grade 3, *n* = 4). Grade 4 (partial response) was noted in 24 patients and grade 5 (progression) in 1 patient. The median <sup>18</sup>F-FDG ΔSUV was 89%. Among patients with <sup>18</sup>F-FDG uptake grades 1–3, the median ΔSUV was 89% (range, –74% to –96%) as compared with 80% (range, +7.3% to –95%) in patients with grades 4 or 5. Similar numbers were derived when analyzing the 5 lesions with the most intense uptake at baseline and at interim in each patient (median ΔSUV of 76% and 88% for <sup>18</sup>F-FLT and <sup>18</sup>F-FDG, respectively).

#### Biopsy Findings and Patient Management After Interim <sup>18</sup>F-FDG Scan

Twenty-one patients with persistent <sup>18</sup>F-FDG uptake on iPET (SUV range, 2.1–27.4) underwent biopsy to verify imaging findings. Eleven of these sites were residual mediastinal or mesenteric masses. Residual disease was proven only in 2 patients (SUV, 5.3 and 27.4); the other 19 biopsies (SUV, 2.1–6.6) showed inflammation only. Only the 2 patients with a positive biopsy underwent high-dose therapy and autologous stem cell transplant; all remaining patients received ICE-based consolidation only. Only 6 of the 21 patients had a positive <sup>18</sup>F-FLT iPET result (1 biopsy-positive, 5 biopsy-negative).

#### Survival Analysis and Assessment of Prognostic Factors

At a median follow-up for surviving patients of 51 mo (range, 35–71 mo), the Kaplan–Meier estimates for the proportion of patients alive and progression-free were 87% and 71%, respectively (Fig. 1). None of the clinical parameters were associated with outcome including age, sex, B symptoms, elevated lactate dehydrogenase, poor Karnofsky performance score, stage, extranodal site involvement (>1 site), Ki-67, or international prognostic index score.

Findings on baseline <sup>18</sup>F-FLT or <sup>18</sup>F-FDG PET (in particular SUV<sub>max</sub>, <sup>18</sup>F-FDG MTV, and <sup>18</sup>F-FLT TPV) were not associated with patient outcome. Further analysis was therefore focused on PET response parameters. Tables 3 and 4 show the relationships between response on <sup>18</sup>F-FLT iPET and patient outcome. <sup>18</sup>F-FLT uptake by visual analysis (grades 1–3 vs. grades 4–5) was predictive of PFS and OS (Fig. 2). A χ<sup>2</sup> analysis (Table 4) revealed optimal cut-points for residual SUV (4.6) and ΔSUV (36%). Analysis of PFS according to these cut-points was highly predictive (Fig. 3). Nevertheless, in view of the small sample size these cut-points should be interpreted with caution and require further validation.

Regarding <sup>18</sup>F-FDG iPET, residual uptake (visual grades 1–3 vs. grades 4–5) predicted PFS (Fig. 4) but not OS (not shown). To

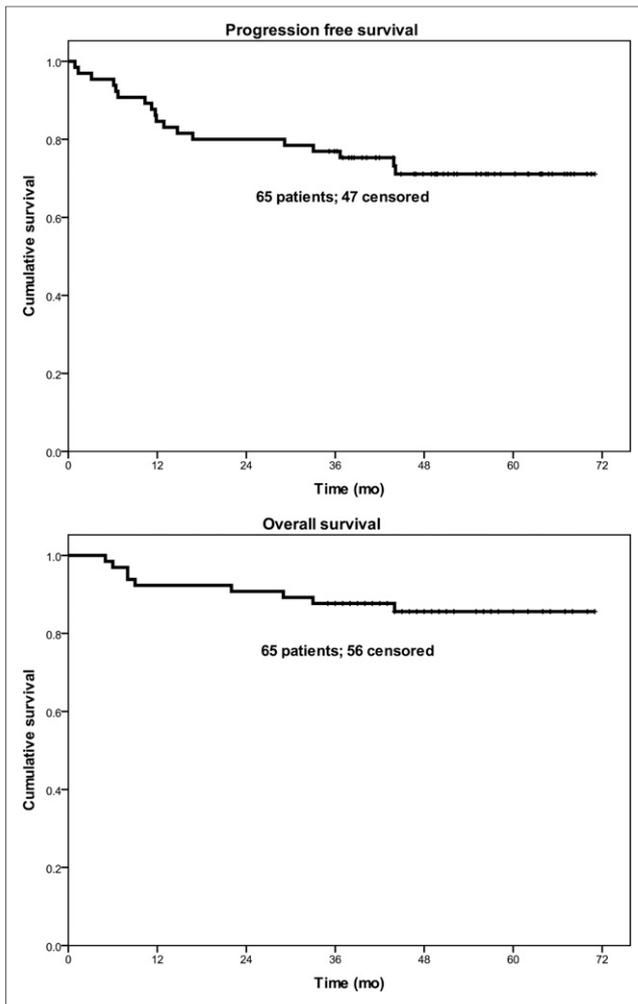


FIGURE 1. PFS and OS for entire patient population.

evaluate the impact of  $\Delta$ SUV, we analyzed both PFS and OS at the median. There was a significant improvement in PFS (Table 3) and a trend to improved OS for patients with  $\Delta$ SUV greater than the median. Similar results were obtained when analyzed by residual  $SUV_{max}$  on iPET: patients with  $SUV_{max}$  below median experienced better PFS and a trend to better OS. We then investigated whether a cutoff could be determined that optimized the prognostic significance of  $\Delta$ SUV  $\delta$  and  $SUV_{max}$  (Table 4). Of note, analyzing a total of 5 lesions in each pair of scans was no more informative or predictive than analysis confined to the single hottest lesion per scan. We also evaluated the prognostic value of the previously proposed postcycle 4  $^{18}F$ -FDG  $\Delta$ SUV 77% (9). In our dataset, only 4 patients showed an  $\Delta$ SUV of less than 77%. Therefore, neither this cutoff nor other proposed cutoffs for  $^{18}F$ -FDG iPET provided meaningful separation of prognostic groups. We then applied the estimated cut-point for  $^{18}F$ -FDG  $\Delta$ SUV (83%) from our maximal  $\chi^2$  analysis ( $M: 1.99, P = 0.34$ ). Thus, whereas  $^{18}F$ -FDG  $\Delta$ SUV predicted PFS in the univariate analysis, we could not identify a clear cutoff to separate prognostic groups because there was considerable overlap:  $\Delta$ SUV was 89% in patients without progression (range,  $-74\%$  to  $-97\%$ ) and 76% in patients who progressed (range,  $+7\%$  to  $-94\%$ ).

Among parameters analyzed for the end of treatment  $^{18}F$ -FDG scan, residual SUV and  $\Delta$ SUV from baseline to final scan were both associated with both PFS (hazard ratio, 1.18 and 0.96, respectively, each  $P < 0.05$ ) and OS (hazard ratio, 1.20 and 0.96, respectively, each  $P < 0.05$ ). The final visual score was predictive of PFS ( $P = 0.03$ ) but not OS.

## DISCUSSION

In the current study, early  $^{18}F$ -FLT iPET had a high negative predictive value, with a negative scan clearly identifying patients with good prognosis. This information might help optimizing risk-adapted therapy for patients with advanced-stage aggressive lymphoma. In contrast, the positive predictive value (PPV) of  $^{18}F$ -FLT iPET, although somewhat better than the PPV for  $^{18}F$ -FDG iPET, remains too low to justify changes in patient management. Contrary to expectation and suggestions in the literature, volumetric parameters ( $^{18}F$ -FLT TPV,  $^{18}F$ -FDG MTV) were not associated with patient outcome when our induction/consolidation treatment regimen was used.

$^{18}F$ -FLT is a proliferation marker for PET imaging (11), with high correlation between Ki-67 and  $^{18}F$ -FLT SUV reported in lymphoma (17). One might therefore expect high baseline  $^{18}F$ -FLT SUV or high  $^{18}F$ -FLT TPV to be markers of poor prognosis, but our findings do not support this hypothesis. However, visual inspection of residual  $^{18}F$ -FLT uptake on iPET predicted both PFS and OS. Quantitative parameters, such as residual  $^{18}F$ -FLT SUV and  $\Delta$ SUV on iPET, also predicted patient outcome, although cut-points identified in  $\chi^2$  analysis require independent validation in a larger dataset. The optimal timing of  $^{18}F$ -FLT iPET remains to be determined. Because no prior prospective study had identified an optimal time point for iPET with  $^{18}F$ -FLT, we investigated 2 early time points and

TABLE 3  
Univariate Analysis for PFS

Parameter	Hazard ratio	P
$^{18}F$ -FLT single $SUV_{max}$		
At baseline	0.99	0.91
At interim	1.26	0.001
$^{18}F$ -FLT sum of hottest 5 $SUV_{max}$		
At baseline	1.003	0.633
At interim	1.063	0.001
$^{18}F$ -FLT $\Delta$ SUV $_{max}$ baseline-interim	0.966	0.001
$^{18}F$ -FLT PTV baseline	1.0	0.84
$^{18}F$ -FDG single $SUV_{max}$		
At baseline	0.98	0.53
At interim	1.14	0.021
In final scan	1.18	0.023
$^{18}F$ -FDG sum of hottest 5 $SUV_{max}$		
At baseline	1.00	0.930
At interim	1.057	0.014
In final scan	1.048	0.010
$^{18}F$ -FDG $\Delta$ SUV $_{max}$ baseline-interim	0.97	0.021
$^{18}F$ -FDG $\Delta$ SUV $_{max}$ baseline-final	0.96	0.015
$^{18}F$ -FDG MTV baseline	1.00	0.91

**TABLE 4**  
Maximal  $\chi^2$  Statistics for PFS

Variable	Estimated cut-point	M	P
<b><math>^{18}\text{F}</math>-FLT single <math>\text{SUV}_{\text{max}}</math></b>			
At baseline	15.5	1.07	0.936
At interim	4.6	3.58	0.003
<b><math>^{18}\text{F}</math>-FLT sum of hottest 5 <math>\text{SUV}_{\text{max}}</math></b>			
At baseline	24.3	2.52	0.119
At interim	6.05	3.65	0.004
<b><math>^{18}\text{F}</math>-FLT <math>\Delta\text{SUV}_{\text{max}}</math></b>			
	35.6	3.57	0.004
<b><math>^{18}\text{F}</math>-FDG single <math>\text{SUV}_{\text{max}}</math>, at baseline</b>			
At baseline	37.9	1.64	0.625
At interim	3.8	1.86	0.327
<b><math>^{18}\text{F}</math>-FDG sum of hottest 5 <math>\text{SUV}_{\text{max}}</math></b>			
At baseline	34.9	1.87	0.44
At interim	7.8	2.52	0.108
<b><math>^{18}\text{F}</math>-FDG <math>\Delta\text{SUV}_{\text{max}}</math></b>			
	83.1	1.99	0.344

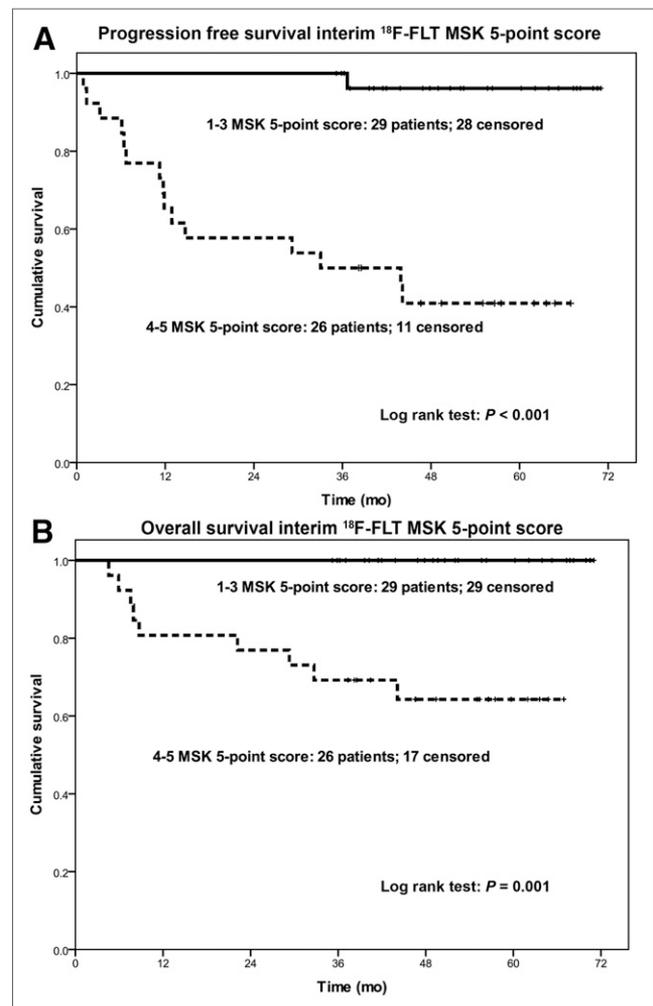
studied 2 cohorts. CPR tended to be more common after cycle 2; thus, whereas complete resolution of uptake can be observed earlier, scanning after cycle 2 may be more meaningful for risk stratification. Regardless, early response assessment with  $^{18}\text{F}$ -FLT iPET may potentially inform patient management. For example, patients with negative  $^{18}\text{F}$ -FLT iPET can likely be cured with standard chemotherapy. In fact, if the high negative predictive value of  $^{18}\text{F}$ -FLT iPET is confirmed in future studies, some patients with high  $\Delta\text{SUV}$  might potentially be cured with an abbreviated chemotherapy regimen, maintaining excellent outcome but reducing treatment-related toxicity. Thus,  $^{18}\text{F}$ -FLT PET may be useful to guide a de-escalation of therapy strategy. An early negative  $^{18}\text{F}$ -FLT iPET result may also be reassuring and help eliminate biopsies of sites with residual  $^{18}\text{F}$ -FDG uptake on iPET as this uptake is likely false-positive. In contrast, the PPV of  $^{18}\text{F}$ -FLT does not appear sufficiently high to justify any escalation of therapy strategy (including therapy with novel agents) without biopsy confirmation. Regardless,  $^{18}\text{F}$ -FLT iPET appears more accurate (in particular postcycle 2) in predicting patient outcome than  $^{18}\text{F}$ -FDG PET is. A recent multicenter study showed that early iPET with  $^{18}\text{F}$ -FDG after 1 cycle of therapy cannot safely discriminate prognostic groups in large cell lymphoma (18).

Experience with  $^{18}\text{F}$ -FLT PET in lymphoma is limited. In some studies (14,15),  $^{18}\text{F}$ -FLT  $\Delta\text{SUV}$  on iPET after 1 cycle emerged as a predictor of survival, but baseline  $^{18}\text{F}$ -FLT SUV did not. An optimal cut-point was not reported. In another study including 50 patients with DLBCL (16), residual SUV greater than 1.9 and  $\Delta\text{SUV}$  less than 65% after 1 cycle of R-CHOP identified patients with worse PFS and OS in receiver-operating characteristic analysis. We suggest caution when interpreting these suggested cut-points. Larger studies and standardization of time points and imaging techniques are required before any particular SUV number or  $\Delta\text{SUV}$  can be applied for clinical decision making. It is difficult to compare our study to these prior investigations because of differences in patient population, lack of established criteria for interpretation of  $^{18}\text{F}$ -FLT iPET, and differences in statistical approaches to data interpretation. Nev-

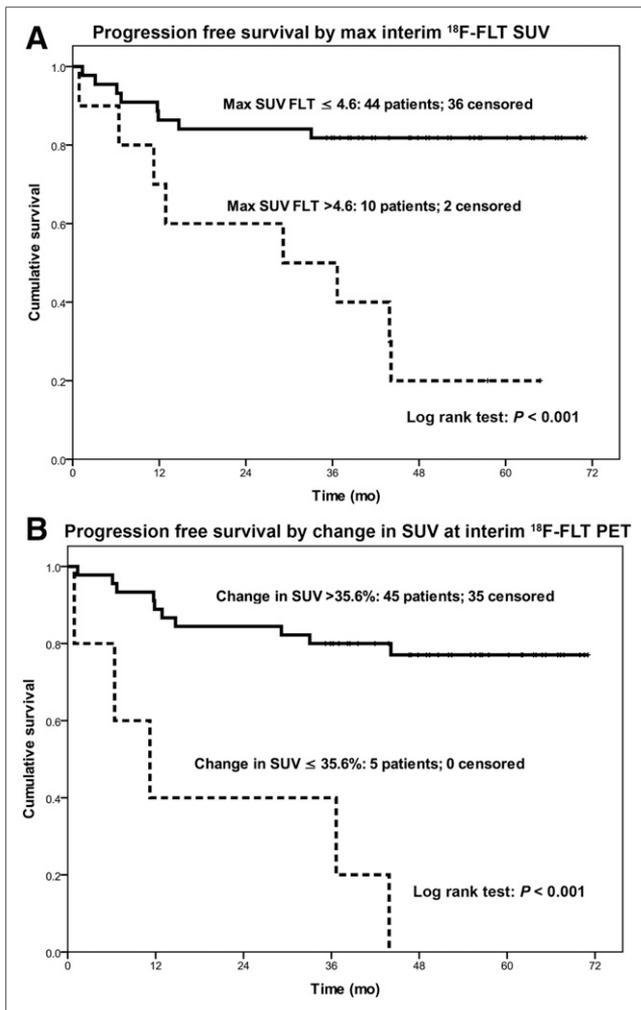
ertheless, the overall (albeit limited) evidence suggests  $^{18}\text{F}$ -FLT iPET as a promising marker for early response assessment in aggressive lymphomas.

$^{18}\text{F}$ -FDG iPET is used routinely to assess treatment response in DLBCL (9,19). In some studies, iPET provided meaningful prognostic information (3,5,8,9), but in other studies, the end-of-treatment scan proved to be more informative (6,7,20). We previously (4) reported a low PPV of  $^{18}\text{F}$ -FDG iPET, at least in part resulting from rituximab-induced inflammation in the R-CHOP regimen (10) and from the use of iPET interpretation criteria that are now obsolete (12,21). In the current study,  $^{18}\text{F}$ -FDG iPET again showed limited PPV, despite altering the drug regimen and timing of iPET regarding the preceding cycle and despite using updated iPET interpretation criteria. Higher PPVs were reported with standard regimens that are probably less effective (9), but  $^{18}\text{F}$ -FDG iPET remains a suboptimal test in the setting of an induction/consolidation regimen. In contrast,  $^{18}\text{F}$ -FDG PET performed after completion of chemotherapy provided better prognostic information.

Measuring  $\Delta\text{SUV}$  may improve the predictive value and inter-observer agreement in reading  $^{18}\text{F}$ -FDG iPET (5,8,9,22). Cutoffs of 66% for iPET after 2 cycles (5) and 70%–92% after 4 cycles

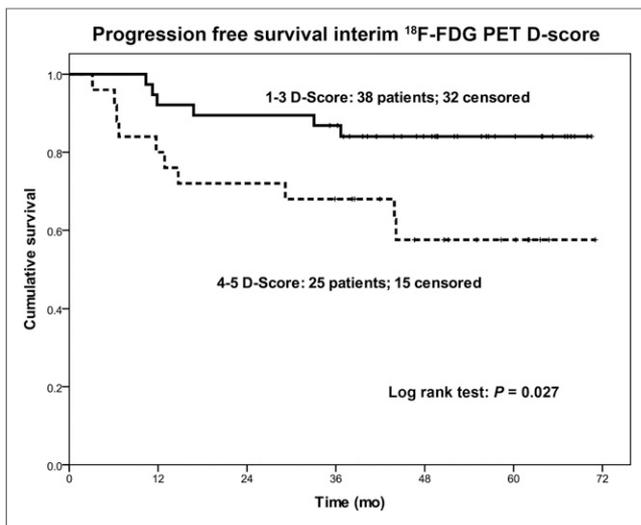


**FIGURE 2.** PFS (A) and OS (B) as stratified by 5-point visual score on  $^{18}\text{F}$ -FLT iPET. MSK = Memorial Sloan Kettering.



**FIGURE 3.** PFS as stratified by  $SUV_{max}$  on  $^{18}F$ -FLT iPET (A) and by  $^{18}F$ -FLT  $\Delta$ SUV (B).

(5,9,23,24) have been proposed. We could not confirm any of these cut-points in the setting of our induction/consolidation regimen. Although  $\Delta$ SUV appears highly reproducible, visual assess-



**FIGURE 4.** PFS as stratified by 5-point score on  $^{18}F$ -FDG iPET.

ment remains the first essential step in scan interpretation;  $\Delta$ SUV should not be used in isolation.

There is growing interest in studying volumes of PET-avid disease (25–28). Direct comparison of published data is hampered by considerable heterogeneity in methodologies and patient populations. For instance, Sasanelli et al. (26) segmented  $^{18}F$ -FDG MTV in 114 patients with large cell lymphoma using a 41% threshold. Their raw data (median, 315 mL; range, 4–2,650 mL) are similar to our findings. However, whereas an MTV of 550 mL, derived from receiver-operating characteristic analysis, proved significant in their analysis, we did not find any association between median MTV and patient outcome. Similarly,  $^{18}F$ -FLT TPV did not prove prognostic in our analysis. It is conceivable that any prognostic value TPV might convey in other settings was overcome by the effectiveness of our induction/consolidation therapy regimen.

Our prospective study has some limitations. For logistic reasons, not all patients underwent  $^{18}F$ -FLT PET as planned, and  $^{18}F$ -FLT and  $^{18}F$ -FDG iPET were performed at different time points. Performing additional  $^{18}F$ -FDG iPET after 1 or 2 cycles was not feasible for logistic and financial reasons and because of dosimetry concerns. The overall sample size was also limited by current cost for  $^{18}F$ -FLT and funding.  $^{18}F$ -FLT was of limited use for disease in bone and liver (because of high physiologic uptake); nevertheless,  $^{18}F$ -FLT predicted for early failure in a setting where  $^{18}F$ -FDG did not (4). Although  $^{18}F$ -FLT is widely available from commercial vendors, it remains an investigational agent.

## CONCLUSION

$^{18}F$ -FLT iPET was a clinically meaningful predictor of treatment response, which may potentially help design risk-adapted therapies in patients with aggressive lymphomas.

## DISCLOSURE

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