^{18}F-FDG PET After 2 Cycles of ABVD Predicts Event-Free Survival in Early and Advanced Hodgkin Lymphoma

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Our objective was to assess the prognostic value of ^{18}F-FDG PET after 2 cycles of chemotherapy using doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) in Hodgkin lymphoma (HL) patients overall and in subgroups of patients with early and advanced stages and with low and high risks according to the International Prognostic Score (IPS). **Methods:** One hundred fifteen patients with newly diagnosed HL were prospectively included in the study. All underwent standard ABVD therapy followed by consolidation radiotherapy in cases of bulky disease. After 2 cycles of ABVD, the patients were evaluated with PET (PET2). Prognostic analysis compared the 3-y event-free survival (EFS) rate to the PET2 results, clinical data, and IPS. **Results:** Of the 104 evaluated patients, 93 achieved complete remission after first-line therapy. During a median follow-up of 36 mo, relapse or disease progression was seen in 22 patients. Treatment failure was seen in 16 of the 30 PET2-positive patients and in only 6 of the 74 PET2-negative patients. PET2 was the only significant prognostic factor. The 3-y EFS was 53.4% for PET2-positive patients and 90.5% for PET2-negative ones ($P < 0.001$). When patients were categorized according to low or high IPS risk and according to early or advanced stage of disease, PET2 was also significantly associated with treatment outcome. **Conclusion:** PET2 is an accurate and independent predictor of EFS in HL. A negative interim ^{18}F-FDG PET result is highly predictive of treatment success in overall HL patients, as well as in subgroups with early or advanced-stage disease and with low or high IPS risk.

Key Words: Hodgkin lymphoma; FDG PET; prognostic factor; early response

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Hodgkin lymphoma (HL) is highly sensitive to standard chemotherapy, radiation therapy, or combined-modality therapy, with long-term cure rates expected to be more than 80% in patients receiving the standard treatment (*1–4*). However, the use of cytotoxic therapy causes toxic effects including myelosuppression, neuropathy, pulmonary fibrosis, and cardiac damage; later effects also include risks of myelodysplasia and leukemia, particularly in patients treated with alkylating agents (*5*). Additionally, radiation therapy can cause mucositis and xerostomia and significantly increases the secondary cancer risk (*5*). In several series, mortality resulting from secondary cancers and heart disease has exceeded lymphoma-related deaths after 15–20 y of follow-up (*6,7*). The ultimate goal is to minimize these side effects without losing treatment efficacy. Accordingly, the number of chemotherapy cycles should be limited to the optimum for each individual patient, and the use of radiation therapy should be restricted to those most likely to benefit from it. For patients with resistant disease, it is important to identify early nonresponders since they will ultimately need high-dose chemotherapy and stem cell transplantation. Therefore, the intensity of the treatment needs to be tailored to an individual patient.

The current prognostic models are unable to support a risk-adapted therapeutic strategy. The most widely accepted prognostic model is the International Prognostic Score (IPS) for advanced HL; however, it shows low efficacy and a poor predictive power (*8*). Anatomic conventional imaging for treatment response monitoring is based on reduction in tumor size on CT (*8*). However, this is not an accurate early predictor of outcome, possibly because the malignant cells in HL make up only a small fraction of the tumor volume (1%–2%) and shrinkage of the tumor takes time (*9,10*).

PET might allow assessment of an early response in the course of treatment and has been demonstrated to predict therapy outcome at an earlier stage of treatment, usually after a few initial cycles of chemotherapy (*11–14*). PET

might also be used as an early predictor of response allowing a risk-adapted treatment strategy (*15*). The properties of PET for monitoring early response to therapy are indeed promising, but data are still limited. This prospective study aimed to assess the prognostic value of ^{18}F-FDG PET performed after 2 cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) standard-dose therapy in HL.

MATERIALS AND METHODS

Patients

The study, approved by the Ethical Board of the São Paulo University Clinics Hospital, included 115 consecutive Brazilian patients presenting at the Hematology Division of that hospital with newly diagnosed, biopsy proven, classic HL. Written informed consent was obtained from all patients who were eligible for this prospective study between August 2005 and December 2007. The exclusion criterion was pregnancy.

All patients underwent conventional staging procedures including physical examination, complete blood cell counts and blood chemistry, CT scans (cervical, thoracic, abdominal, and pelvic), bilateral bone marrow biopsy, and ^{18}F-FDG PET (PET0).

Risk groups were defined as low risk, with IPS between 0 and 2, and high risk, scoring 3–7 (*7,16*).

Standard Follow-up After First-Line Treatment

Stage I and II patients were treated with 4–6 cycles of chemotherapy using ABVD. Stage III patients were treated with 6–8 cycles of ABVD. Stage IV patients were treated with 8 cycles of ABVD. Radiation therapy was included in stage I or II patients who had no adverse risk factors and were being treated with 4 cycles of chemotherapy and in patients with bulky disease regardless of stage.

After first-line treatment, all patients were restaged according to the Revised Response Criteria for Malignant Lymphoma by the International Harmonization Project (*17*). Patients in partial remission and PET-positive at the end of first-line treatment underwent biopsy to confirm the presence of HL. All patients with confirmed active HL after first-line therapy were treated with high-dose chemotherapy followed by autologous stem cell transplantation according to local protocols.

^{18}F-FDG PET

Whole-body PET was performed after a 60-min uptake period following the intravenous administration of 296–444 MBq (8–12 mCi) of ^{18}F-FDG. Imaging was performed using 2-dimensional acquisition on an Advance PET scanner (GE Healthcare). Attenuation correction was performed using ^{68}Ge sources.

After 2 cycles of chemotherapy, patients underwent PET (PET2). All PET2 scans were performed within the week before (as late as possible) administration of the third ABVD cycle. Two experienced board-certified nuclear medicine physicians interpreted the PET2 scans with side-by-side PET0 correlation and staging CT.

PET2-negative was defined as no pathologic ^{18}F-FDG uptake at any site, including all sites of previously increased pathologic uptake. A study was considered PET2-positive in the presence of focal ^{18}F-FDG uptake that could not be attributed to physiologic biodistribution. PET2 minimal residual uptake (MRU) was defined as low-grade ^{18}F-FDG uptake with avidity less than, equal to, or only slightly higher than the uptake in mediastinal blood pool structures, according to the definition of Gallamini et al. (*14*).

Semiquantitative analyses were calculated in PET2-positive and PET-MRU patients, and the highest maximal standardized uptake value (SUV) measured in any region or organ showing increased uptake on the staging scan (PET0) was used for prognostic stratification. PET0 was reviewed before imaging to ensure PET2 target images of the same locations. An SUV of 2.0–3.5 was regarded as consistent with MRU.

Patients with a PET scan showing MRU were considered PET-negative for the analysis. Differences between the PET reviewers occurred in 7 (6.7%) MRU/PET-positive patients and were solved by consensus (Cohen κ-test, $\kappa = 0.8$).

Statistical Analysis

Three-year event-free survival (EFS) was chosen as the endpoint and defined as the time from diagnosis to treatment failure or last follow-up. Treatment failure was defined as an incomplete response after first-line treatment, progression during therapy, relapse, or death. Data were censored if the patients were alive and free of HL progression or relapse at the last follow-up.

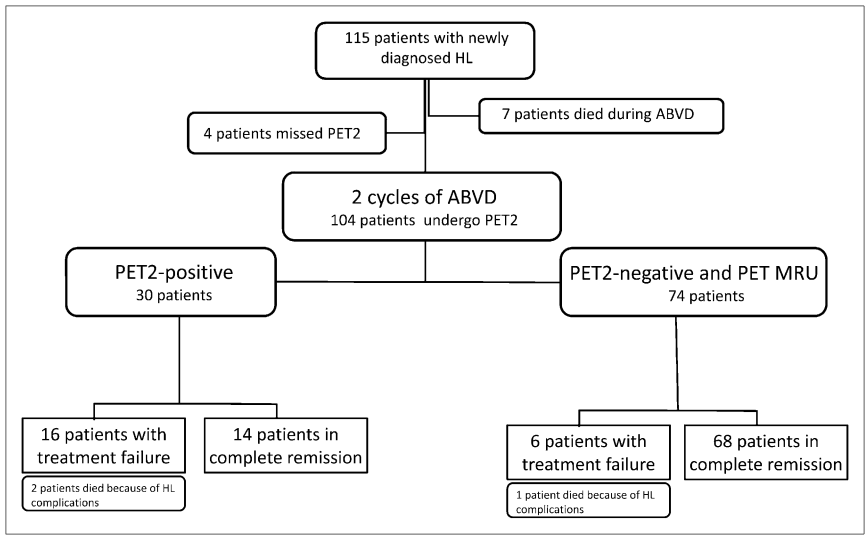

FIGURE 1. Flowchart for clinical study.

TABLE 1. Clinical Characteristics of the 104 Evaluable HL Patients

Characteristic	*n*
Age	
Median (y)	28
Range (y)	13–82
≤45 y	86 (82.7%)
>45 y	18 (17.3%)
Sex	
Male	55 (52.9%)
Female	49 (47.1%)
Type	
Lymphocyte-rich	11 (10.6%)
Nodular sclerosis	59 (56.7%)
Mixed cellularity	10 (9.6%)
Lymphocyte-depleted	3 (2.9%)
Classic HL, not otherwise specified	21 (20.2%)
Stage	
I	2 (1.9%)
II	41 (39.4%)
III	25 (24.0%)
IV	36 (34.6%)
B symptoms	
No	38 (36.5%)
Yes	66 (63.5%)
Bulky disease	
Yes	60 (57.7%)
No	44 (42.3%)
Erythrocyte sedimentation rate (mm/h)	
≤50	49 (47.1%)
>50	55 (52.9%)
Albumin (g/dL)	
≥4.0	36 (34.6%)
<4.0	68 (65.4%)
Hemoglobin (g/dL)	
≥10.5	75 (72.1%)
<10.5	29 (27.9%)
Leukocytes (μ/L)	
<15,000	91 (87.5%)
≥15,000	13 (12.5%)
Lymphocytes (μ/L)	
≥600	93 (89.4%)
<600	11 (10.6%)
IPS	
Low (0–2)	62 (59.6%)
High (3–7)	42 (40.4%)

The association between clinical prognostic factors (age, sex, initial stage, presence of B symptoms, bulky disease, erythrocyte sedimentation rate, albumin, hemoglobin, lymphocytes, and IPS), treatment and PET2, and the probability of treatment failure was assessed by the log rank. Survival curves were calculated by the actuarial method of Kaplan and Meier. The limit of statistical significance for all analyses was defined as a *P* value of less than or equal to 0.05.

The maximal SUV of the PET2-positive patients was compared with the maximal SUV of PET0. The significance of the median maximal SUV reduction relative to PET0 (1 − [SUV of PET2/SUV of PET0]) in patients with or without events was tested using the Mann–Whitney method.

All data analyses were performed using SPSS, version 13.0 (SPSS Inc.). α-error was defined as 0.05, and all tests were 2-sided.

TABLE 2. PET2 Results by Patient Subgroups

Group	PET2		
	Negative	Positive	Total
Overall			
Continued CR	68	14	82
Treatment failure	6	16	22
Total	74	30	104
Early stage (I–II)			
Continued CR	32	5	37
Treatment failure	2	4	6
Total	34	9	43
Advanced stage (III–IV)			
Continued CR	36	9	45
Treatment failure	4	12	16
Total	40	21	61
Low-risk IPS (0–2)			
Continued CR	41	8	49
Treatment failure	3	10	13
Total	44	18	62
High-risk IPS (3–7)			
Continued CR	27	6	33
Treatment failure	3	6	9
Total	30	12	42
Chemotherapy alone			
Continued CR	22	7	29
Treatment failure	2	12	14
Total	24	19	43
Combined therapy			
Continued CR	46	7	53
Treatment failure	4	4	8
Total	50	11	61

RESULTS

After initial staging, all 115 patients were treated with ABVD. After 2 cycles of chemotherapy, the patients underwent PET2 scanning. Eleven patients were excluded from the study, for several reasons, which are listed in Figure 1. The clinical characteristics of the remaining 104 patients are given in Table 1.

Of the 104 evaluable patients, radiotherapy was administered in 61 (58.7%). Of the 43 patients with early-stage disease, 34 (79.1%) underwent combined therapy. Of the 61 patients with advanced disease, 27 (44.3%) underwent combined therapy.

At the end of treatment, 93 patients (89.4%) were in complete remission (CR). Twenty-two (21.1%) patients experienced treatment failure after a median follow-up of 36 mo (range, 32–40 mo): 3 patients progressed before completion of first-line chemotherapy, 8 patients failed to achieve CR, and 11 patients relapsed after CR with first-line therapy. All treatment failures were confirmed by biopsy. Three patients with treatment failure died during follow-up because of HL complications.

^{18}F-FDG PET Results

After 2 cycles of ABVD, 62 of 104 patients were considered PET2-negative; 5 of them showed progression or relapse during follow-up. At the time of progression or

TABLE 3. PET2 Indices and 95% Confidence Intervals by Patient Subgroups

Group	Sensitivity	Specificity	PPV	NPV
Overall	72.2% (0.49–0.88)	82.9% (0.72–0.90)	53.3% (0.34–0.71)	91.8% (0.82–0.96)
Early stage (I–II)	66.7% (0.24–0.94)	86.5% (0.70–0.94)	44.4% (0.15–0.77)	94.1% (0.78–0.98)
Advanced stage (III–IV)	75.0% (0.47–0.91)	80.0% (0.64–0.89)	57.1% (0.34–0.77)	90.0% (0.75–0.96)
Low-risk IPS (0–2)	76.9% (0.45–0.93)	83.7% (0.69–0.92)	55.6% (0.31–0.77)	93.2% (0.80–0.98)
High-risk IPS (3–7)	66.7% (0.30–0.90)	81.8% (0.63–0.92)	50.0% (0.22–0.77)	90.0% (0.72–0.97)

relapse, all patients had a positive PET scan, and one of them died 30 mo after completion of chemotherapy because of complications of HL relapse (Fig. 1).

Twelve PET2 scans were considered to show MRU, with low-grade uptake less than, equal to, or only slightly higher than the uptake in mediastinal blood pool structures, in an area of previous disease. Only 1 patient presented with relapse during follow-up. MRU patients were considered PET2-negative for the analysis.

Thirty of the 104 patients had a PET2-positive scan. Of them, 16 patients progressed or relapsed within 3 y and underwent salvage therapy with high-dose chemotherapy and stem-cell support. In all PET2-positive patients who progressed, the biopsied site of progression showed abnormal uptake on PET2. Two patients died of HL complications. Fourteen PET2-positive patients were in continued CR until the last follow-up.

PET2 results according to clinical stage and IPS are listed in Table 2. The sensitivity, specificity, and positive and negative predictive values of PET2 for treatment failure in patients overall and according to clinical stage and IPS are listed in Table 3.

SUV Analyses

On semiquantitative analysis, among all 30 PET2-positive patients, PET2 showed a 55.6% median maximal SUV reduction relative to PET0 (1 − [SUV of PET2/SUV of PET0]). The median maximal SUV reduction proportion was 60.3% for the 16 patients who had treatment failure and 51.4% for the 14 PET2-positive patients who remained in continued CR ($P = 0.2$). Figure 2 shows the medians and variability of SUV reduction at PET2 relative to PET0 among PET2-positive patients who presented with treatment failure and those who remained in CR.

EFS Analyses

After a median follow-up of 36 mo, the 3-y EFS of all 104 patients was 74.2% and the 3-y overall survival was 94.2%. The univariate analyses (Table 4) showed PET2 as the only factor significantly associated with treatment failure, with 3-y EFS rates of 53.4% for patients with PET2-positive scans and 90.5% for patients with PET2-negative scans ($P < 0.001$). The other clinical characteristics (age, sex, stage, bulky disease, B symptoms, sedimentation rate, albumin, hemoglobin, leukocyte count, lymphocyte count, and IPS) failed to show a significant association.

The 3-y EFS according to the results of PET2 in the patients overall is displayed in Figure 3, and the 3-y EFS according to the results of PET2 in IPS and clinical stage subgroups is displayed in Figure 4.

DISCUSSION

Current therapies fail to cure about one third of patients with HL, and a similar proportion of patients may be overtreated (*18–20*). A precise early-prediction tool of response to therapy should be able to discriminate patients who could be cured with conventional therapy or even less intensive or toxic regimens from patients who need to switch to more aggressive treatment strategies that could improve outcome.

However, current prognostic models, including IPS, have low efficacy and poor predictive power and are unable to support a risk-adapted therapeutic strategy (*7,20–22*). Indeed, in our study patients, IPS did not show a significant prognostic impact on the 3-y EFS rate of the 104 patients evaluated. With a 3-y EFS rate of 53.4% for patients with PET2-positive scans and 90.5% for patients with PET-negative scans ($P < 0.001$), PET2 turned out to be the only significant factor associated with treatment failure, in accordance with the literature (*11–14*).

Hutchings et al. (*11*) retrospectively described the prognostic value of PET after 2 or 3 cycles of chemotherapy, most with ABVD, in 88 HL patients. They found a 5-y progression-free survival of 39% and 92% for PET-positive and PET-negative patients, respectively. Further, Hutchings et al. (*12*) prospectively showed that 58 of 61 PET2-

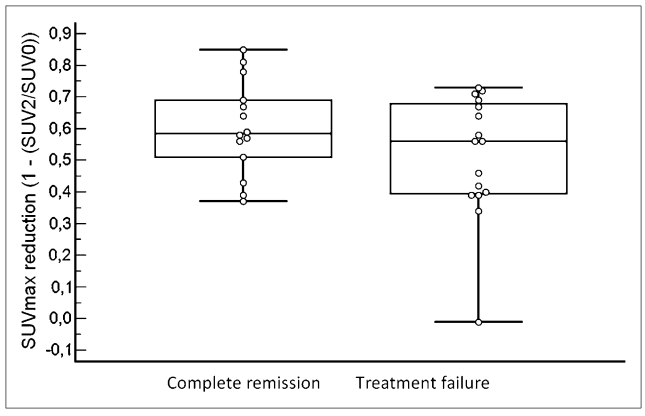

FIGURE 2. Comparison of SUV reduction (SUV of PET2/SUV of PET0) in PET2-positive patients who have treatment failure and PET2-positive patients who are in continued CR. SUVmax = maximal SUV.

TABLE 4. Univariate Prognostic Calculated Using Log-Rank Test Analysis

Characteristic	Overall survival	*P*	EFS (%)	*P*
Age (y)				
≤45	97.7	0.01	77.6	0.82
>45	56.3		78.8	
Sex				
Male	88.3	0.63	73.6	0.47
Female	95.6		84.2	
Stage				
I–II	100.0	0.18	83.1	0.24
III–IV	87.0		76.7	
B symptoms				
No	97.1	0.15	88.3	0.4
Yes	77.8		74.4	
Bulky disease				
Present	85.6	0.76	86.9	0.15
Absent	97.6		73.4	
Erythrocyte sedimentation rate (mm/h)				
≤50	95.9	0.59	82.5	0.22
>50	87.2		76.0	
Albumin (g/dL)				
≥4.0	100.0	0.26	90.3	0.29
<4.0	88.4		74.1	
Hemoglobin (g/dL)				
≥10.5	90.3	0.82	83.8	0.27
<10.5	93.3		67.8	
Leukocytes (μ/L)				
<15,000	100.0	0.45	79.4	0.94
≥15,000	89.8		76.0	
Lymphocytes (μ/L)				
≥600	92.1	0.22	90.4	0.82
<600	90.5		77.7	
IPS				
Low risk (0–2)	100.0	0.04	78.4	0.99
High risk (3–7)	82.1		80.2	
PET2				
Negative	90.1	0.22	90.5	<0.001
Positive	91.3		53.4	

negative HL patients were progression-free after 2 cycles of chemotherapy, whereas 13 of 16 PET2-positive patients relapsed or died. Gallamini et al. (*13*) evaluated 108 patients with advanced HL who were restaged with PET2. At a mean follow-up of 1 y, 18 of 20 PET2-positive patients had progressed or relapsed, whereas 85 of 88 PET2-negative patients remained in CR.

Later, Gallamini et al. (*14*) combined data from the last 2 studies (*12,13*) with 97 new cases including patients with advanced-stage HL, resulting in a cohort of 260 patients, treated mostly with ABVD. Treatment failure was observed in 43 of 50 PET2-positive patients and 10 of 210 PET2-negative patients. In multivariate analyses, PET2 was the only prognostic factor. Regardless of IPS, PET2-positive patients had a poor prognosis and PET2-negative patients had an excellent survival.

Although the prognostic value of PET2 in HL patients is the strongest prognostic factor in all studies, some differences are to be noted (Table 5). In our study, the higher EFS in PET2-positive patients and lower EFS in PET2-negative patients may be related to our longer follow-up and to the fact that the patients had a higher incidence of advanced-stage disease (34.6% stage IV) and a higher incidence of bulky disease (57.7%). Patients with more extended and bulky disease may take more time to present a complete metabolic response than do patients with less disease. In previous studies (*12–14*), only 8%–20% of the population evaluated was composed of patients with stage IV disease, and 34%–38% of patients had bulky disease. The data of the last 2 studies (*13,14*) are not strictly comparable since patients with stage I and stage IIA without adverse factors (with good prognosis) were excluded from analysis, possibly allowing the reduction of a potentially false-positive incidence. However, our results showed that PET2 is a powerful prognostic factor in patients with advanced HL and in patients with initial-stage HL.

PET response is usually defined as a separation into 2 visual response categories: patients with and patients without PET evidence of persistent disease. However, almost 98% of HL masses consist of inflammatory cells, and chemotherapy also can trigger an inflammatory response that may take up ^{18}F-FDG; these may account

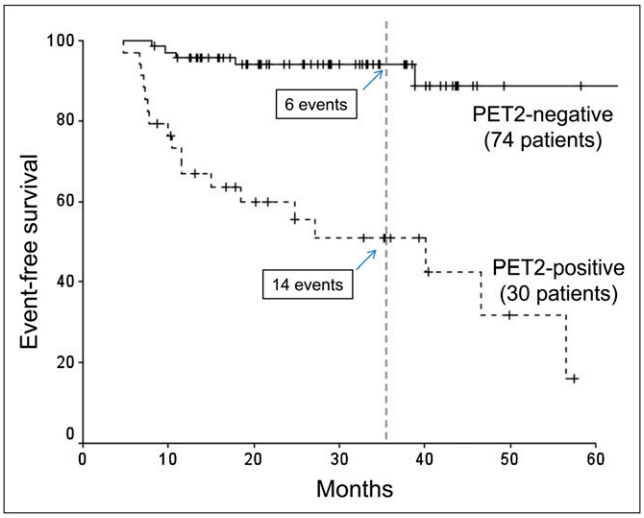

FIGURE 3. Kaplan–Meier plot showing EFS for PET2 results.

for some nonmalignant minimal residual low-grade uptake. Hutchings et al. (*11*) refined these categories by incorporating the category of MRU to denote those difficult cases in which there was low-level residual uptake in a lesion that would otherwise be considered to have responded completely. Further, Gallamini et al. (*14*) considered MRU as low-grade ^{18}F-FDG uptake with avidity even slightly higher than the uptake in mediastinal blood pool structures (the same criterion used in our study). Debate continues about the role and the best definition of MRU. However, the analysis of our data confirms that the highest predictive value is achieved when interim scans with MRU are counted as negative scans.

PET2 evaluates only the effect of ABVD. False-positive results are therefore expected to be more frequent in the combined-treatment patients than in the patients treated with only chemotherapy. However, of the 61 patients who underwent combined therapy in our study, 7 (11.4%) had false-positive PET2 results, whereas of the 43 patients who underwent only ABVD, 7 (16.3%) had false-positive results, with no statistical differences between the 2 groups ($P = 0.344$). In our population, SUV reduction could not discriminate between PET2-positive patients with treatment failure and those without, in accordance with Gallamini et al. (*13*).

As far as we know, this is the biggest single-center sample evaluating ^{18}F-FDG PET after 2 cycles of ABVD, but like all previous studies, the major drawback is the small sample size. However, the approximately 500 patients evaluated with PET2 allow for ongoing trials testing the effects of less toxic treatment for patients with PET2-negative scans, who have a low risk of failure, and the effects of treatment intensification for patients having a high risk of failure on the basis of PET2-positive results (*22,23*). Whether response-

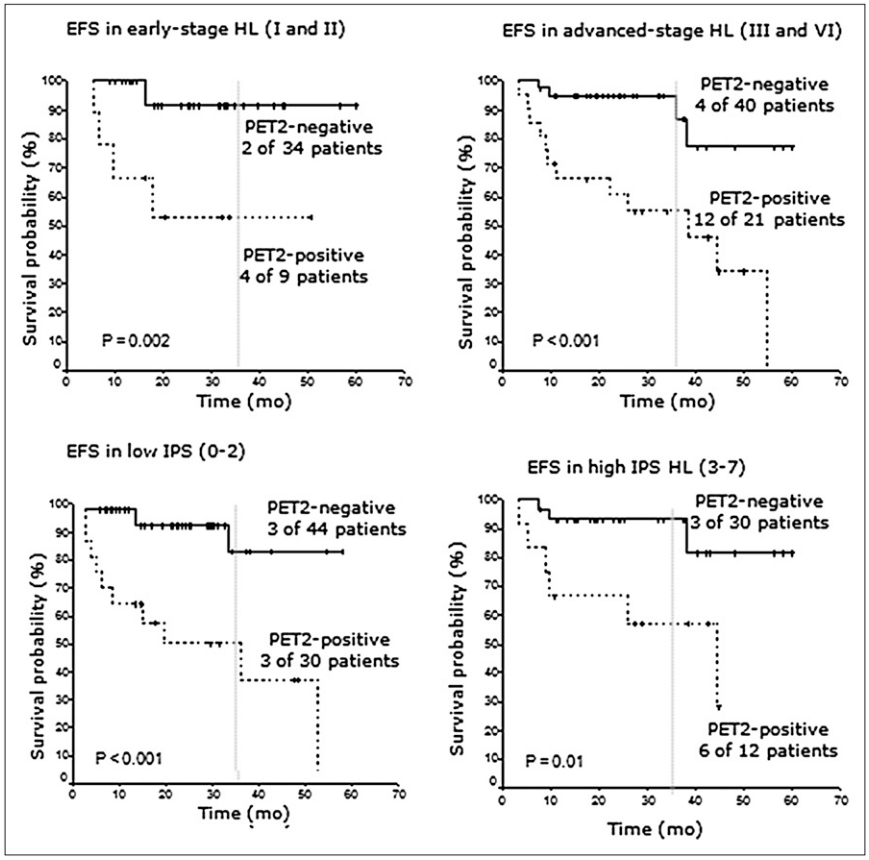

FIGURE 4. Kaplan–Meier plot showing EFS for PET2 results according to IPS and stage.

TABLE 5. Major Studies Evaluating Prognostic Impact of PET2 in HL

Study	Year	Number of cycles	Number of patients	EFS		Follow-up (mo)
				PET-positive	PET-negative	
Hutchings et al. (*12*)	2005	2 or 3	85	46%	96%	6–125
Hutchings et al. (*11*)	2006	2	77	0%	96%	2–41
Gallamini et al. (*13*)	2006	2	108	6%	96%	2–47
Gallamini et al. (*14**)	2007	2	97	13%	95%	4–62
Present study	2009	2	104	24%	90%	28–40
Total			471	18%	95%	

*Included only the 97 new cases.

adapted treatment strategies based on PET2 may improve patient outcome remains to be confirmed.

CONCLUSION

PET2 appears to be the most important prognostic factor in HL and provides valuable prognostic information in patients with HL treated with ABVD, with 3-y EFS rates of 53.4% for patients with a PET2-positive scan and 90.5% for patients with a PET2-negative scan. A negative interim ^{18}F-FDG PET scan is highly predictive of treatment success in HL patients overall and in subgroups with early- or advanced-stage disease, independent of the risk according to IPS. However, clinical trials are needed to define the best way to use this important new prognostic factor in designing response-adapted therapies.

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