VOLUME 25 · NUMBER 24 · AUGUST 20 2007

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Early Interim 2-[^{18}F]Fluoro-2-Deoxy-D-Glucose Positron Emission Tomography Is Prognostically Superior to International Prognostic Score in Advanced-Stage Hodgkin's Lymphoma: A Report From a Joint Italian-Danish Study

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Submitted March 14, 2007; accepted June 1, 2007; published online ahead of print at www.jco.org on July 23, 2007.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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0732-183X/07/2524-3746/$20.00

DOI: 10.1200/JCO.2007.11.6525

ABSTRACT

Purpose
Starting from November 2001, 260 newly diagnosed patients with Hodgkin's lymphoma (HL) were consecutively enrolled in parallel Italian and Danish prospective trials to evaluate the prognostic role of an early interim 2-[^{18}F]fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) scan and the International Prognostic Score (IPS) in advanced HL, treated with conventional ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) therapy.

Patients and Methods
Most patients (n = 190) presented with advanced disease (stages IIB through IVB), whereas 70 presented in stage IIA with adverse prognostic factors. All but 11 patients were treated with standard ABVD therapy followed by consolidation radiotherapy in case of bulky presentation or residual tumor mass. Conventional radiologic staging was performed at baseline. FDG-PET scan was performed at baseline and after two courses of ABVD (PET-2). No treatment change was allowed on the basis of the PET-2 results.

Results
After a median follow-up of 2.19 years (range, 0.32 to 5.18 years), 205 patients were in continued complete remission and two patients were in partial remission. Forty-three patients progressed during therapy or immediately after, whereas 10 patients relapsed. The 2-year progression-free survival for patients with positive PET-2 results was 12.8% and for patients with negative PET-2 results was 95.0% ($P < .0001$). In univariate analysis, the treatment outcome was significantly associated with PET-2 ($P < .0001$), stage IV ($P < .0001$), WBC more than 15,000 ($P < .0001$), lymphopenia ($P < .001$), IPS as a continuous variable ($P < .0001$), extranodal involvement ($P < .0001$), and bulky disease ($P = .012$). In multivariate analyses, only PET-2 turned out to be significant ($P < .0001$).

Conclusion
PET-2 overshadows the prognostic value of IPS and emerges as the single most important tool for planning of risk-adapted treatment in advanced HL.

J Clin Oncol 25:3746-3752. © 2007 by American Society of Clinical Oncology

INTRODUCTION

Standard combination chemotherapy with ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) is still considered the gold standard treatment for advanced Hodgkin's lymphoma (HL). However, a substantial proportion of patients fail to achieve long-term disease control because of either therapy-resistant or relapsing disease.[1-4] The use of more intensive regimens such as BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone) has yielded superior disease control, with a 7-year failure-free survival (FFS) of 85%.[5] However, these excellent results have been partially hampered by an increased risk of severe acute toxicity and of secondary malignancies, and, hence, an unfavorable risk-benefit ratio for a considerable subset of the patients.[6] For this

reason, many efforts are underway to tailor a risk-adapted treatment strategy to the individual patient. So far, the most important prognostic tool in advanced HL has been the International Prognostic Score (IPS).[7] This prognostic model is well validated. However, nearly one half of the patients in the most adverse IPS group achieve lasting CR with the ABVD regimen. Therefore, many clinicians do not regard the IPS as the ideal tool to select patients for treatment intensification.

Gallium-67 (^{67}Ga) scintigraphy or positron emission tomography with 2-[^{18}F]fluoro-2-deoxy-D-glucose (FDG-PET) performed early during treatment accurately predicts the treatment outcome in patients treated with standard ABVD chemotherapy.[8,9] Recently, two studies, one from the Italian Intergruppo Linfomi and one from the Danish Lymphoma Group, showed a strong prognostic value of an early interim FDG-PET scan in advanced HL.[10,11] The studies were almost identical with regard to the following aspects: (a) they were prospective, (b) they were multicentric, (c) they included a large cohort of patients treated with first-line standard ABVD chemotherapy, (d) no treatment change was allowed depending on FDG-PET results, (e) the FDG-PET scan evaluations criteria were qualitative, (f) and the results in terms 2-year progression-free survival (PFS) depending on early FDG-PET results were virtually superimposable. However, a major point of criticism and an open question has been: is the prognostic value of FDG-PET merely a crude reflection of the prognostic stratification according to the IPS?

For these reasons, we decided to combine the data from our prospective studies in a joint study with the aim of (a) identifying a clinical prognostic model for treatment planning in advanced-stage HL and (b) defining practical guidelines for standardizing the interim FDG-PET evaluation.

PATIENTS AND METHODS

Study Design

Starting from November 2001 in Denmark and January 2002 in Italy, 163 consecutive, newly diagnosed, advanced-stage HL patients were prospectively enrolled in the trials in 13 Italian (108 patients) and three Danish (55 patients) hematologic centers. The two studies were unified at the beginning of 2006, 97 new patients were enrolled, and finally the data of the 260 patients were pooled and analyzed together. Inclusion criteria were (a) clinical stage IIB to IVB or (b) clinical stage IIA with at least one of the following adverse prognostic factors: at least three nodal sites involved, subdiaphragmatic presentation, bulky disease, and erythrocyte sedimentation rate more than 40, and (c) having signed a written informed consent. A bulky lesion was defined, according to Cotswold criteria, as a mass with a maximum diameter of 10 cm or greater. Baseline staging was done with the procedures recommended by the Cotswold conference[12] and FDG-PET scan. An FDG-PET appraisal of the treatment response after two courses of chemotherapy (PET-2) was performed. The clinicians were blinded to the results of PET. The patients received standard treatment with six courses of ABVD (or ABVD-like regimens) with or without radiotherapy. No therapy change was made on the basis of the PET-2 scan, unless overt progression was documented on clinical or radiologic grounds. All patients were followed at regular intervals for at least 6 months after completion of the entire therapeutic program (Fig 1). The patient characteristics are provided in Table 1.

Treatment

Most patients (249) were treated with six courses of ABVD, eight patients received the COPP (cyclophosphamide, vincristine, procarbazine, and prednisone)/EBV(epirubicin, bleomycin, and vinblastine)/CAD (lomustine, doxorubicin, and vindesine) regimen for six courses, and three with an ABVD-like regimen for six courses. After completion of chemotherapy, 104 patients (40%) received consolidation radiotherapy, either as involved-field radiotherapy to bulky mediastinal disease or extramediastinal bulky nodal mass to a total dose of 30 or 36 Gy, or as irradiation of a residual mass to a total dose of 36 Gy. Assessment of response to therapy was made according to Cotswold publication criteria.[12] However, patients with a computed tomography (CT) scan showing a residual mass at the end of treatment but with a FDG-PET scan showing negative results were considered in CR, according to the revised response criteria for malignant lymphoma.[13]

FDG-PET Imaging

The patients enrolled onto the study were staged and treated in 13 Italian and three Danish hematologic centers, whereas the FDG-PET scans were performed in 11 PET centers. In each patient, the different scans were performed at the same PET center and with the same instrument. Slightly more than half of the patients (137 of 260) were scanned using PET/CT scanners; 50 with dedicated multiring PET, and 73 with full-ring coincidence PET. All patients fasted for at least 6 hours before [^{18}F]FDG tracer injection. Serum

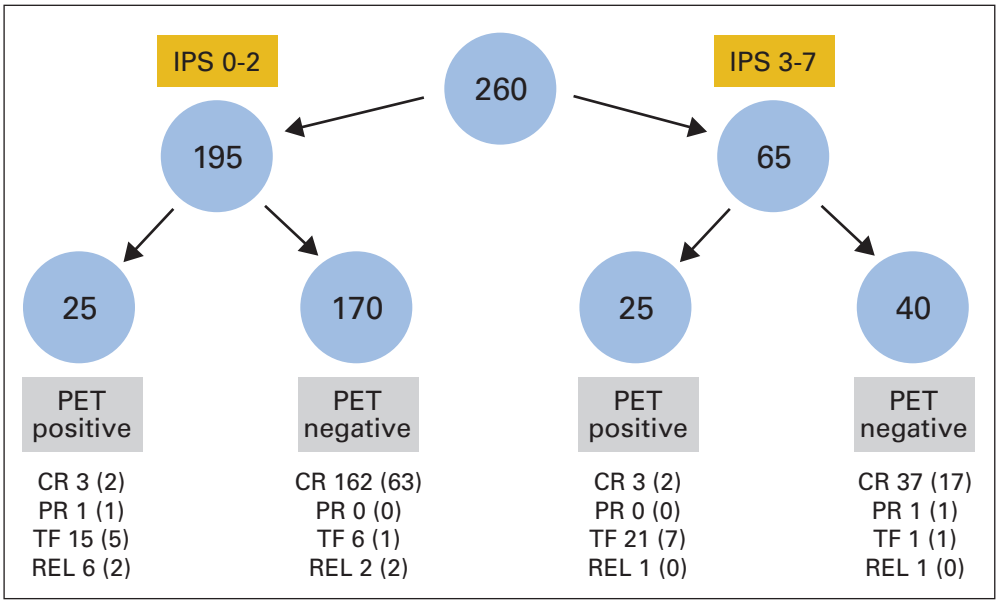

Fig 1. Flow chart showing the clinical outcome for patients according to International Prognostic Score (IPS) group and positron emission tomography (PET) results after two cycles of ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine). Numbers in parentheses represent patients who received radiotherapy to residual masses. CR, continued complete remission; PR, partial remission at last follow-up; TF, primary refractory to chemotherapy/progression within 6 monthts after completion of therapy; REL, late relapses after initial remission.

Table 1. Patient Characteristics

Characteristic	Stage IIA Patients (n = 67)		Stage IIB Patients (n = 70)		Stage III Patients (n = 79)		Stage IV Patients (n = 44)		All Patients (N = 260)	
	No.	%	No.	%	No.	%	No.	%	No.	%
Age, years										
Mean	32.6		35.2		36.5		36.9		35.2	
Median	32.0		32.5		32.0		35.1		32.0	
Range	14-72		16-64		16-79		14-77		14-79	
Sex										
Male	26	39	32	46	44	56	31	71	133	51
Female	41	61	38	54	35	44	13	30	127	49
Follow-up, years										
Mean	2.14		2.35		2.60		2.14		2.34	
Median	1.87		2.17		2.59		2.11		2.19	
Range	0.32-4.97		0.56-5.18		0.47-5.13		0.59-4.95		0.32-5.18	
2-year FFS		86.0		74.8		87.6		55.3		78.4
Clinical outcome										
TF	8	12	16	23	10	13	19	43	53	20
Death	0	0	3	4.3	0	0	5	11	8	3
Histologic type										
NS	58	61	61	87	49	62	32	73	200	77
MC	5	7.5	6	8.6	17	22	11	25	39	15
LD	0	0	0	0	4	5.1	0	0	6	2.3
CHLu	1	1.5	1	1.4	4	5.1	1	2.3	7	2.7
LP	3	4.5	2	2.9	5	6.3	0	0	8	3.1
"B" symptoms	0	0	70	100	43	54	29	66	142	55
Extranodal disease	4	6	7	10	19	24	44	100	74	28
Bulky disease	24	36	30	43	24	30	14	32	92	35
WBC, μL^{-1}										
Mean	9,726		10,335		10,863		11,721		10,573	
Median	9,380		9,645		10,200		9,445		9,645	
Lymphocytes, μL^{-1}										
Mean	1,597		1,566		1,708		1,536		1,612	
Median	1,481		1,444		1,610		1,500		1,535	
Hemoglobin, g/dL										
Mean	13.0		12.5		12.8		12.1		12.6	
Median	13.1		12.4		13.0		12.1		12.8	
Serum albumin, g/dL										
Mean	4.08		3.77		3.88		3.80		3.89	
Median	4.01		3.79		3.94		3.90		3.90	
PET after 2 cycles										
Positive	7		14		11		18		50	
Negative	60		56		68		26		210	
IPS										
0	17		11		10		0		38	
No.	1		1		0		0		2	
1	27		17		24		2		70	
No.	1		3		4		0		8	
2	19		28		26		14		87	
No.	3		5		3		4		15	
Patients PET-positive after 2 cycles										
3	4		12		14		12		42	
No.	2		5		1		6		14	
4	0		1		4		8		13	
No.	0		0		3		3		6	
≥ 5	0		1		1		8		10	
No.	0		0		0		5		5	
First-line treatment										
ABVD	67	100	69	99	76	96	37	84.5	249	96
CEC	0	0	1	1.4	1	1.3	6	14	8	3
Other	0	0	0	0	2	2.5	1	2.3	3	1
Radiotherapy	27	40	46	66	23	29	8	18	104	40

Abbreviations: FFS, failure-free survival; TF, treatment failure; NS, nodular sclerosis; MC, mixed cellularity; LD, lymphocyte depletion; CHLu, classical Hodgkin lymphoma, not subclassified; LP, nodular lymphocyte predominance; IPS, international prognostic score; ABVD, 6-8 cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine; CEC, COPP (cyclophosphamide, vincristine, procarbazine, and prednisone)/EBV (epirubicin, bleomycin, and vinblastine)/CAD (lomustine, doxorubicin, and vindesine).

glucose level measured at the time of injection was below 160 mg/dL in all patients. Whole-body emission scans were performed approximately 60 minutes after injection. The injected dose was 370 MBq/70 kg at the centers that used a GE scanner (GE Healthcare, Waukesha, WI), 259 MBq/70 kg at the center that used a Philips scanner (Philips Medical Systems, Eindhoven, the Netherlands), and 2 MBq/kg body weight at the centers that used a C-PET scanner. Transmission scans for segmented attenuation correction were acquired with a Germanium-68 or Cesium-137 external ring source or CT. To minimize the accumulation of FDG activity in the urinary bladder, patients were asked to void just before the start of the emission scan. Transaxial, coronal, and sagittal images were reconstructed by means of the ordered subsets expectation maximation iterative reconstruction or row-action maximum likelihood algorithm methods.

PET Image Analysis

PET images were interpreted visually using available clinical information and analyzed using available clinical information. All scans were read by at least two independent nuclear medicine physicians. One expert reviewed all Italian cases and another expert reviewed all Danish cases. Only PET-2–positive and minimal residual uptake (MRU) positive scan were reviewed. Differences between the central PET reviewers and the readers from the individual PET centers were discussed and decided at consensus conferences. Semiquantitative analyses were not routinely applied. Before and after therapy, disease was evaluated site by site for the involved lymph nodes and organs. A negative result was defined as no pathologic FDG uptake at any site, including all sites of previously increased pathologic uptake. A study was considered positive for lymphoma lesions in the presence of a focal FDG concentration outside the physiological uptake areas, with clearly increased activity relative to the background. Hutching's MRU definition[13] was discussed between the two PET reviewers with the effort of standardize the criteria of scan interpretation and redefined as low-grade FDG uptake with avidity smaller than, equal to or only slightly higher than the uptake in mediastinal blood pool structures. A standardized uptake value of 2.0 to 3.5 was regarded as consistent with MRU. Patients with a PET scan showing MRU were considered PET negative for the analysis.

Statistical Analysis

PFS and overall survival (OS) were chosen as end points. PFS was defined as the time from diagnosis to either disease progression or relapse, or to death as a result of any cause. Data were censored if the patients were alive and free of progression/relapse at last follow-up. OS was defined as the time from diagnosis to death from any cause. Data were censored if the patients were alive at last follow-up. Survival curves were calculated by the method of Kaplan and Meier.[15] The association between clinical prognostic factors and the probability of treatment failure was assessed by the log-rank tests as well as univariate regression analyses.[16] To investigate the contribution of individual prognostic factors, a multivariate analysis based on the Cox proportional hazards regression model was performed.[17] The exponentiation of the coefficients estimated from the regression model can be assumed as the hazard ratio of disease progression in the exposed category of each variable, compared with the reference category, after allowing for the other factors entered in the model. Schoenfeld and Martingale residuals plots were employed to check for assumptions of proportional hazards and linearity. The plots were evaluated visually with the help of locally weighted regression fits (LOWESS curves).[18] All data analyses were performed using SPSS version 13.0 (SPSS Inc, Chicago, IL).[18,19]

RESULTS

The clinical characteristics of the patients are shown in Table 1. After a median follow-up of 2.19 years (range, 0.32 to 5.18 years), 205 patients were in continued complete remission (cCR), two patients were in partial remission (PR), 43 patients progressed during therapy or immediately after (during the first 6 months), and 10 relapsed. No unconfirmed CRs (CRUs) were observed. No treatment interruption caused by toxicity or toxic deaths were recorded. Eight patients died, all as a result of HL. All patients were administered the therapy planned at baseline, at a full dose in 100% of the patients, with some delay in drug administration for neutropenia in very few patients ($< 3\%$). No treatment change was made depending on the PET-2 results, and therefore the compliance to the protocol was 100%. Only in case of clinical evidence of overt chemotherapy resistance or disease progression was salvage therapy, consisting of high-dose chemotherapy followed by autologous stem-cell transplantation, administered. Fifty patients were PET-2 positive and 210 patients were PET-2 negative. Of 50 PET-2–positive patients, 43 (86%) showed treatment failure (progression/relapse), whereas six were in cCR and one in PR at the latest follow-up. Of 210 PET-2–negative patients, 199 (95%) were in cCR and one patient in PR at the latest follow-up, whereas 10 patients had experienced treatment failure (Fig 1). Only one of 210 PET-2–negative patients died compared with seven of 50 PET-2–positive patients ($P < .0001$). The results of the Italian cohort and the Danish cohort in the original articles were exactly the same: overall, 108 Italian and 55 Danish patients in the two studies were evaluated, with the same 2-year PFS for negative-PET and similar PFS for positive-PET patients.[10,11] The results were almost unchanged after the subsequent accrual of 97 new patients.

The sensitivity, specificity, and overall accuracy of PET-2 for predicting 2-year PFS were 81%, 97%, and 92%, respectively. The positive predictive value was 93% and the negative predictive value was 92%. The distribution of the patients according to stage, IPS, and PET-2 results is shown in Table 1. The 2-year PFS was 12.8% for PET-2–positive patients and 95.0% for PET-2–negative patients ($P < .0001$). The PFS according to IPS groups is shown in Figure 2. In Figure 3, PFS is shown according to PET-2 results for both patients with a low IPS of 0 to 2 and a high IPS of 3 to 7.

The factors significantly associated with treatment failure in univariate analyses were PET-2 ($P < .0001$), extranodal disease ($P < .0001$), bulky disease ($P < .012$), and three of the seven IPS elements: stage IV disease ($P < .0001$), leukocytosis ($P < .0001$), and lymphopenia ($P < .001$). A multivariate regression analysis was performed including PET-2 and IPS as a continuous variable. This model showed no prognostic value of IPS when the information from PET-2 is added (Table 2). Only PET-2 and stage IV disease had significant

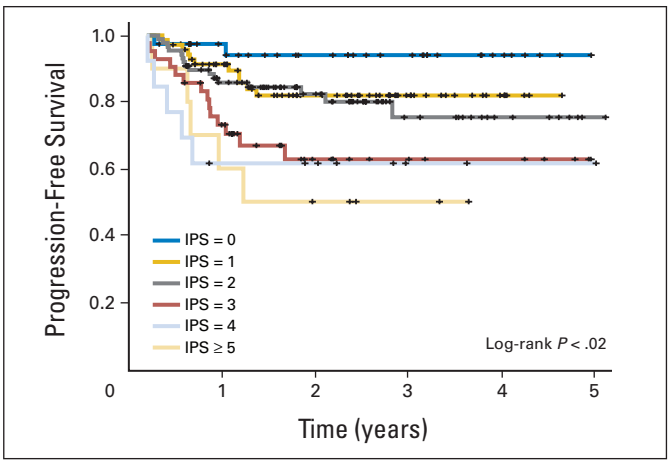

Fig 2. Kaplan-Meier plot showing the progression-free survival according to International Prognostic Score (IPS) group.

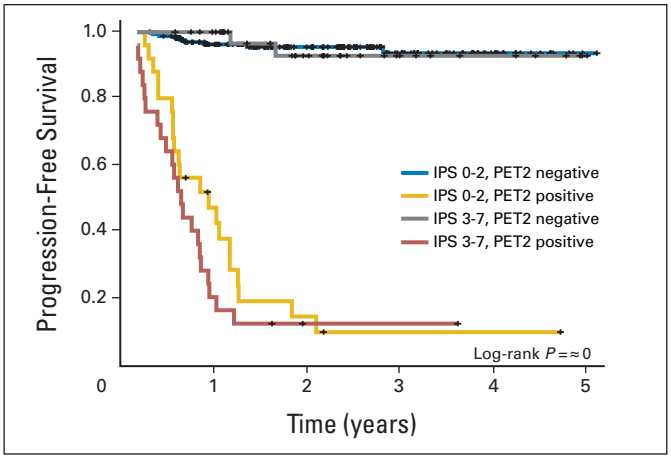

Fig 3. Kaplan-Meier plot showing the progression-free survival according to International Prognostic Score (IPS) group and positron emission tomography results after two cycles of ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine).

independent prognostic value, although age greater than 45 years seemed borderline significant when included in the model. The results are provided in Table 3. Identical models were fitted after removal of stage IIA patients from the analysis. This resulted in no change in the overall picture and only slight adjustments to the hazard ratios of PET-2 and stage IV disease.

No significant difference was found between the prognostic accuracy of the different PET modalities. Among the 187 PET-2 studies performed with dedicated PET, eight were falsely negative and seven were falsely positive; among the 73 PET-2 studies performed with C-PET, two were falsely negative and none were falsely positive.

DISCUSSION

Unlike the International Prognostic Index (IPI) for aggressive B-cell lymphoma, IPS and other prognostic models retrospectively constructed for advanced HL have proved of limited clinical value, and their predictive power has been questioned.[20,21] More recently, to avoid an indiscriminate overtreatment for a substantial fraction of the patients, a risk-adapted therapy tailored to the individual patient has been proposed. This strategy uses the tumor chemosensitivity assessment by FDG-PET early during therapy to predict the probability of achieving disease control.

Table 2. Multivariate Analysis of Progression-Free Survival.

Variable	*P*	HR	95% CI for HR
Step 1			
PET after 2 cycles	< .0001	35.8	17.3 to 74.0
IPS (continuous variable)	.445	1.08	0.88 to 1.32
Step 2			
PET after 2 cycles	< .0001	38.3	18.9 to 77.5

NOTE. Variables in the equation at step 1 are PET after two cycles and IPS (continuous variable).
Abbreviations: HR, hazard ratio; IPS, International Prognostic Score; PET, positron emission tomography.

Table 3. Multivariate Analysis of Progression-Free Survival

Last Step	*P*	HR	95% CI for HR
Equation a*			
PET after 2 cycles	< .0001	43.0	20.2 to 91.3
Age > 45 years	.046	0.49	0.25 to 0.99
Stage IV disease	< .001	2.52	1.35 to 4.68
Equation b†			
PET after 2 cycles	< .0001	35.3	17.3 to 72.1
Stage IV disease	.026	1.93	1.08 to 3.43

Abbreviations: HR, hazard ratio; IPS, International Prognostic Score; PET, positron emission tomography.
*PET after two cycles, the individual factors of the IPS (with or without the presence of B-symptoms, extranodal disease, and bulky disease).
†PET after two cycles, WBC count, lymphocyte count, stage IV disease (with or without extranodal disease and bulky disease).

The best results obtained in terms of long-term disease control in advanced HL have been reported by the German Hodgkin Study Group in a large, multicenter, randomized clinical trial comparing standard chemotherapy with ABVD-COPP with escalated BEACOPP: the 5-year freedom from treatment failure rates were 69% versus 87% ($P < .001$).[5] However, major toxicities reported after eight courses of escalated BEACOPP were febrile neutropenia, increased risk of secondary leukemia and early menopause.[5,6,22]

It is well accepted that an interim FDG-PET scan performed very early during treatment in advanced HL is an important prognostic factor.[9-11,14,23-26] So far, the published literature has shown that (a) the negative predictive value for treatment outcome ranged between 100% and 97%, (b) the positive predictive value ranged between 87% and 90%, (c) qualitative reading is superior or equal to quantitative evaluation, and (e) the patients with a negative early FDG-PET had a 2-year PFS of 96% versus 0% to 6% for PET-positive patients. However, the clinical impact of these results, compared to standard clinical prognostic models such as IPS, is still unknown.

The aforementioned studies of early interim FDG-PET in HL were based on patient cohorts too small to reliably answer these questions. Hence, we decided to gather data from the Italian and Danish groups in a joint study, and 260 patients were enrolled. This cohort of patients is noteworthy because (a) the patients were enrolled in a prospective manner, (b) the treatment was standard and homogeneous for all the patients, (c) no treatment change was made depending on the PET-2 results, and (d) the median follow-up was longer than 2 years. It is well known that up to 90% of the treatment failures are recorded within the first 2 years after diagnosis.[27] The goal of the joint study was to define a simple, reproducible model to prospectively identify a small subset of advanced HL patients requiring more intensive treatment and, conversely, a larger fraction of patients for which a conventional ABVD treatment was preferable. Stage IIA patients with adverse prognostic were included as in the original IPS study. In the final analyses, the inclusion of stage IIA patients did not influence the results.

In the present study, apart from PET-2, the only prognostic factors contained in the IPS that proved to influence treatment outcome was the presence of stage IV disease. As demonstrated in Figure

2, the known prognostic properties of the IPS are present in our cohort, and as shown in Table 1, the higher the IPS value, the higher the risk of being PET-2 positive. However, in multivariate analysis, the IPS loses its value with the addition of PET-2. Indeed, the PET-2–positive patient from a low-risk IPS group has equally high risk of treatment failure as the PET-2 positive from a high-risk IPS group. Similarly, the PET-2 negative patient from a high-risk IPS group has an equally low risk of treatment failure compared with the PET-2 negative patient from a low-risk IPS group (Fig 3).

Recently, a prognostic model combining PET-2 results with IPI or IPS has been proposed for relapsed lymphoma patients; the authors were able to identify four different classes with a FFS ranging between 100% and 5%.[26] Again, in the case of HL, the contribution of clinical factors seemed to be modest. IPS, however, could still have some role in deciding the intensity of treatment for the first two courses of chemotherapy. In this perspective, Dann et al[23] reported encouraging overall event-free survival an OS for advanced HL patients treated at the disease onset with 2 courses of standard or escalated BEACOPP depending on an IPS risk class of 0 to 2 or 3 to 7, respectively, and with a subsequent therapy modification based on PET-2 or ^{67}Ga scintigraphy results. However, the percentage of interim negative studies with either FDG-PET scan or ^{67}Ga scan was approximately the same in the two risk groups, 84% versus 79%, indicating a limited benefit in the treatment modification depending on baseline IPS score in patients treated initially with BEACOPP. In contrast, at least in our hands, after two courses of ABVD, some difference exists between the proportion of PET-2 negative patients (87% for IPS 0 to 2 *v* 61% for IPS 3 to 7).

Although the criteria for a so-called normal FDG-PET scan are well agreed on, some uncertainty still exists in the criteria for interim FDG-PET evaluation in HL. First of all, qualitative rather than quantitative criteria seem to be preferred by most authors.[9-11] Secondly, some problems arise with scans showing faint residual uptake, MRU. Hutchings et al[10,14] showed that the prognosis for patients with MRU was almost the same as for PET-2–negative patients, and thus considered MRU as PET-2 negative. We propose to define as PET-2 positive a study showing a residual focal uptake within a lesion that was positive in the baseline study with an FDG uptake that is clearly higher than in the mediastinal blood pool structures and, conversely, a study as MRU positive in presence of a nonfocal uptake with a standard uptake value lower than, equal to, or slightly higher than mediastinum. A qualitative approach with MRU regarded as PET negative, especially in a large mediastinal mass, is in keeping with the new uniform guidelines for performing and interpreting post-therapy FDG-PET scans in lymphoma patients, recently published by the International Harmonization Project subcommittee.[28] These guidelines have been adopted in the newly revised response criteria for malignant lymphomas.[13]

In conclusion, an early interim FDG-PET scan seems to be the most useful prognostic factor in advanced HL. This prognostic tool is a surrogate test for the chemosensitivity of the tumor, and it identifies two different categories of patients for which different therapeutic strategies are appropriate.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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Acknowledgment

We thank Ettore Pelosi, Antonio Castagnoli, Annibale Versari, Michele Gregianin, Umberto Ficola, Massimo Ippolito, Susanne Keiding, and Liselotte Højgaard for positron emission tomography interpretation; and Silvia Tavera, Roberta Calvi, Patrizia Pregno, Isabella Capodanno, Fiorella Ilariucci, Luca Nassi, Valerio Zoli, Vincenzo Callea, Alessandro Mistretta, Peter Kamper, Lars Møller, and Lena Herlev for data collection.