# The predictive value of positron emission tomography scanning performed after two courses of standard therapy on treatment outcome in advanced stage Hodgkin's disease

Andrea Gallamini
Luigi Rigacci
Francesco Merli
Luca Nassi
Alberto Bosi
Isabella Capodanno
Stefano Luminari
Umberto Vitolo
Rosaria Sancetta
Emilio Iannitto
Livio Trentin
Caterina Stelitano
Silvia Tavera
Alberto Biggi
Antonio Castagnoli
Annibale Versari
Michele Gregianin
Ettore Pelosi
Pierfederico Torchio
Alessandro Levis

Background and Objectives. We explored the predictive value on therapy outcome of an early evaluation of treatment response by $^{18}$F-fluorodeoxyglucose position emission tomography ($^{18}$F-FDG-PET) scan performed after two courses of conventional standard-dose chemotherapy in advanced-stage Hodgkin's disease.

Design and Methods. One hundred and eight patients with newly-diagnosed Hodgkin's disease in stage IIA with adverse prognostic factors, or in stage IIB through IVB, were re-staged with FDG-PET after two cycles of ABVD (PET-2). The end-point of the study was the predictive value of PET-2 on 2-year progression-free survival and 2-year failure-free survival. No treatment variation based only on PET-2 results was allowed.

Results. Eighty-eight patients attained complete remission (CR) while 20 showed disease progression during therapy or within 6 months after having reached CR; one patient relapsed. PET-2 was positive in 20 patients: 17 progressed during therapy, one relapsed and two remained in CR. By contrast, 85/88 (97%) patients with a negative PET-2 remained in CR; three progressed or relapsed early after the end of the chemotherapy. Thus, the positive predictive value of a PET-2 was 90% and the negative predictive value was 97%. The sensitivity, specificity and overall accuracy of PET-2 were 86%, 98% and 95%, respectively. The 2-year probability of failure-free survival for PET-2 negative and for PET-2 positive patients was 96% and 6%, respectively (log rank test = 116.7, $p<0.01$).

Interpretation and Conclusions. $^{18}$F-FDG-PET scan performed after two courses of conventional standard-dose chemotherapy in advanced-stage Hodgkin's disease was able to predict treatment outcome in 103/108 (95%) of the patients.

Key words: early response, FDG-PET, Hodgkin's disease.

*From the S.C. Ematologia Azienda Ospedaliera S. Croce e Carle, Cuneo (AG, ST); Cattedra di Ematologia Azienda Ospedaliera Universitaria di Careggi, Firenze (LR, LN, AB); S.C. Ematologia Arcispedale S. Maria Nuova, Reggio Emilia (FM, IC); Dipartimento di Oncologia, Università di Modena e Reggio Emilia, Modena (SL); S.C. Ematologia Azienda Ospedaliera S. Giovanni Battista, Torino (UV); U.O. Ematologia, Ospedale SS Giovanni e Paolo, Azienda ULSS 12, Venezia (RS); Divisione di Ematologia e TMO, Policlinico P Giaccone, Palermo (EI); Dipartimento di Medicina Sperimentale Università di Padova, Padova (LT); Divisione di Ematologia, Azienda Ospedaliera Melacrino e Morelli, Reggio Calabria (CS); S.C. Servizio di Medicina Nucleare Azienda Ospedaliera S Croce e Carle, Cuneo (AB); S.O.D. Medicina Nucleare Clinica, Azienda Ospedaliera Universitaria di Careggi, Firenze (AC); S.C. Medicina Nucleare, Arcispedale S Maria Nuova, Reggio Emilia (AV); U.O. Medicina Nucleare Ospedale SS Giovanni e Paolo, Azienda ULSS 12, Venezia (MG); Cattedra di Medicina Nucleare Azienda Ospedaliera S Giovanni Battista, Torino (EP); Cattedra di Statistica Medica Università di Torino, Torino (PT); S.C. Ematologia Azienda Ospedaliera SS Antonio e Biagio, Alessandria (AL).*

*Correspondence:
Andrea Gallamini, SC Ematologia Azienda Ospedaliera S Croce e Carle, via M. Coppino 26, 12100 Cuneo, Italy.
E-mail: gallamini.a@ospedale.cuneo.it*

Several prognostic models have been proposed over the last fifteen years for patients affected by advanced-stage Hodgkin's disease (HD), with the aim of defining risk-adapted therapeutic strategies. In particular, various models based on a retrospective reappraisal of the prognostic role of different sets of clinical variables have been proposed,[1-4] but their predictive powers have been questioned.[5-7] Since 20-30% of patients with advanced-stage HD treated with conventional, standard-dose chemotherapy ultimately die of recurrent of refractory disease,[8] the predictive value of an early assessment of treatment response seems to be very relevant. We report here, on behalf of the Intergruppo Italiano Linfomi (IIL), the results of a prospective clinical trial aimed at exploring the prognostic role of FDG-PET scanning performed very early during therapy in hitherto untreated patients with advanced stage HD undergoing conventional, standard-dose chemotherapy.

## Design and Methods

### Patients

Starting in January 2002, 108 newly-diagnosed patients with advanced-stage HD, consecutively admitted to 11 Italian hematology institutions were enrolled in the trial and gave their written informed consent to partecipation in this study. Their clinical details are summarized in Table 1. Their mean age was 32.6 years (range: 14-79) and the male to female ratio was 51:57. Seventy-four had advanced disease (stages IIB-IVB) and 34 had stage IIA disease with adverse prognostic factors (one of the following: more than three nodal sites involved, sub-diaphragmatic presentation, bulky disease and erythrocyte sedimentation rate > 40 mm/h). Bulky and extra-nodal disease were recorded in 41 and 30 patients, respectively. Histopathology was lymphocyte predominant in four, nodular sclerosis in 88, mixed cellularity in 13 and lymphocyte-depleted in three. All patients were staged at baseline with biochemistry, bone marrow trephine biopsy, computed tomography (CT) scans, and FDG-PET scans (PET-0). They were re-staged after two chemotherapy courses and at the end of the treatment, including radiotherapy (when administered), by CT scans and FDG-PET scans (CT-2, PET-2 and CT-6, PET-6, respectively: Figure 1). Standardized uptake values (SUV) were calculated in all PET scans (*see below*). The end-point of the study was the predictive value of PET-2 for progression-free survival. The mean interval between the end of the second chemothera-

**Table 1.** Patients' clinical details.

| Parameter | N. of patients | Percentage (%) |
|---|---|---|
| Male/female | 51/57 | 47/53 |
| Stage | | |
| Stage IIA unfavorable | 34 | 31 |
| Stage IIB | 24 | 22 |
| Stage IIIA | 15 | 14 |
| Stage IIIB | 13 | 12 |
| Stage IVA | 8 | 7 |
| Stage IV B | 14 | 13 |
| Histology | | |
| Lymphocyte predominant | 4 | 4 |
| Nodular sclerosing | 88 | 81 |
| Mixed cellularity | 13 | 12 |
| Lymphocyte-depleted | 3 | 3 |
| Elevated ESR (> 40 mm/h) | 65 | 60 |
| Abnormal LDH (> 1× normal) | 21 | 19 |
| Anemia (Hb < 10.5 g/dL) | 13 | 12 |
| Leukocytosis (WBC > 15,000 μL) | 19 | 18 |
| Bulky disease (yes/no) | 41/67 | 38/62 |
| Extranodal site (yes/no) | 30/78 | 28/72 |
| International Prognostic Score | | |
| 0 | 28 | 26 |
| 1 | 34 | 31 |
| 2 | 29 | 27 |
| 3 | 10 | 9 |
| 4 | 3 | 3 |
| 5 | 4 | 4 |
| Chemotherapy regimen | | |
| ABVD×6 | 104 | 96 |
| COPP/EBV/CAD | 4 | 4 |



**Figure 1.** Trial overview.

**Table 2.** Characteristics of PET centers.

| Equipment | N. of PET centers | N. of Hematology centers | N. of patients |
|---|---|---|---|
| CT-PET | 3 | 5 | 44 |
| Multiring PET | 1 | 1 | 30 |
| C-PET | 2 | 5 | 34 |

py course and PET-2 was 11.6 days (5-32); the interval between the end of the therapy (either chemotherapy or radiotherapy) and PET-6 was never less than 50 days.

### Treatment

Most patients (104/108) were treated with six courses of ABVD; the other four patients were treated with six courses of the COPP/EBV/CAD regimen. At the end of chemotherapy 57 of the 108 patients had bulky mediastinal disease or an initial lesion with a diameter equal to or greater than 5 cm; these patients were given *consolidation* involved-field (IF) radiotherapy with 36 or 30 Gy, respectively. All patients were given the therapy programmed at baseline, and in no case did the result of the early PET scan (PET-2) influence treatment. Only in the case of clinical evidence of overt resistance to chemotherapy or disease progression was salvage therapy given; this consisted of high-dose chemotherapy followed by autologous stem cell transplantation.

### Response criteria

Response to therapy was assessed according to the criteria defined at the Cotswolds meeting:[9] complete remission (CR) was defined as the disappearance of all clinical evidence of the disease and the normalization of all laboratory values and radiological findings that had been considered abnormal before therapy onset. An unconfirmed CR (CRu) was defined as CR but with the persistence of a residual lymph node mass greater than
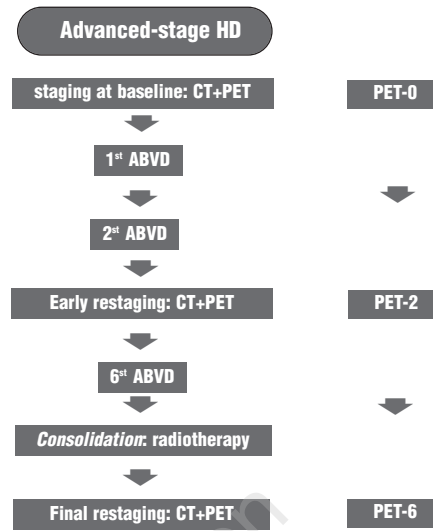
1.5 cm that had regressed by more than 75% of the largest dimension of each measurable anatomical site of disease localization. Partial remission (PR) was defined as a greater than 50% reduction of the largest dimension of each measurable anatomical site of disease localization, for at least 1 month. Stable disease (SD) or non-response (NR) was defined as less than PR but not progressive disease. Progressive disease (PD) was present when there was a more than 50% increase from the smallest size achieved in the largest anatomical diameter of any previously identified abnormal node, or when any new lesion appeared during therapy. Relapse was defined as the appearance of any new lesion or an increase in the size of the previously involved sites by ≥50%. Early and late relapse were defined as a relapse occurring within or later than 6 months after having achieved CR, respectively.

### PET scan imaging

The patients enrolled in the study were staged and treated in 11 Italian hematology institutions, while the FDG-PET scans were performed in six PET centers. For each patient three PET scans were performed at the same PET center and with the same instrument. Scans

were performed with a GE Advance Nxi (multiring PET) in one center, a Discovery LS CT-PET scanner (GE Medical Systems, Milwaukee, WI, USA) operating in a two-dimensional high sensitivity mode in two centers, a Gemini CT-PET scanner operating in a three-dimensional mode (Philips Electronics N.V., Eindhoven, Netherlands) in one center and a *full ring NaI(Tl)PET scanner* (C-PET ADAC, Philadelphia, PA,USA) in two centers (Table 2). All patients fasted for at least 6 h before injection of the ^{18}F-FDG tracer. The serum glucose level measured at the time of injection was below 160 mg/dL in all patients. Whole-body emission scans were performed 60 min after injection. The injected dose was 370 MBq/70 kg at the centers which used a GE scanner, 259 MBq/70 kg at the center which used a Philips scanner and 2 MBq/kg body weight at the centers which 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 in the 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 method (OSEM) or the RAMLA method.

### PET scan analysis

PET images were visually interpreted and analyzed using all available clinical data and results of other imaging modalities. All the positive or equivocal scans were reviewed in each center by two experienced observers, well trained with the equipment used in the same PET center. For *qualitative analysis*, according to conventional criteria, a study was considered positive for lymphoma lesions in the presence of a focal concentration of FDG outside the areas of physiological uptake, with a value increased relative to the background. Before and after therapy, disease was evaluated site by site for the involved lymph nodes and organs. A negative result was defined as no pathological FDG uptake at any site, including all sites of previously increased pathological uptake. For quantitative analysis of regional FDG uptake in tumor, we calculated the SUV. Small, round, (approximately 1 cm diameter) regions of interest (ROI) were defined in the slice displaying the highest tumor activity concentration, site by site. The $SUV_{Max}$ represents the maximum count density concentration recorded for each ROI normalized for the injected dose and body weight. In the baseline PET scan the $SUV_{Max}$ was measured in the lesion with the highest FDG uptake among all the positive lesions. In the PET scan after two cycles of chemotherapy (PET-2) and that at the end of therapy (PET-6), in the case of persisting pathological uptake of FDG in one or more lesions the $SUV_{Max}$ was calculated in the lesion with the highest FDG uptake and its value was correlated with the $SUV_{Max}$ of the same lesion in the baseline study. When the *hot* lesions had disappeared so that they were indistinguishable from the surrounding normal tissue, no activity was measured and the patient was considered to have had a complete metabolic response.

### Sample size

The number of patients enrolled in this prospective study was based on the following assumptions: to detect an absolute difference of 65% in progression-free survival (from 15% to 80% at 18 months) between PET-2-positive and PET-2-negative patients, with 90% power and using a significance level $\alpha$=0.05 (two-sided), 17 patients per group would be needed. Because only 15% of HD patients are PET-2-positive and allowing some loss during the follow-up, the first target was to enroll 108 patients into the trial.

### Statistical analysis

All data were analyzed with the SAS System 8.2 statistical package.[10] Progression-free and failure-free survival rates were calculated from the date of diagnosis, according to the method of Kaplan and Meier.[11] Failure was defined as partial remission, progression during therapy, early or late relapse, treatment interruption due to toxicity or toxic death. The association between clinical prognostic factors and the probability of treatment failure was assessed by the log-rank test.[12] To control for potential confounders, a multivariate analysis based on a Cox proportional hazards regression model[13] was performed. The variables analyzed included all the factors that were found to be significant in the univariate analysis. For each variable, the proportional hazards assumption was tested graphically. The exponentiation of the coefficients estimated from the regression model can be assumed as the hazard ratio of disease progression in the category with each variable, compared with the reference category, after allowing for the other factors entered in the model. Several Cox regression models were fitted. The goodness-of-fit of each model was assessed with the D statistic = -2, the likelihood ratio and the comparison between two models, when feasible, was tested calculating the likelihood ratio.[14] The limit of statistical significance for all analyses was defined as a $p$ value of 0.05. All statistical tests were two-sided.

## Results

The mean follow-ups from the diagnosis and from final restaging were 603 days (73-1421) and 359 days (0-1148), respectively. Eighty-eight patients attained CR while 20 were resistant to chemotherapy. Of these 20 patients, 16 had disease progression during therapy and four had early relapses (within 6 months) after having achieved CR: (+28 - +178 days). One out of the 88 patients who achieved CR had a late relapse 18 months after CR. In all these cases a second biopsy confirmed the histological diagnosis of HD. At the time of writing only one out of 88 patients in CR has relapsed. No treatment interruptions where necessary because of toxicity and no toxic deaths occurred.

### PET scan analysis

On qualitative analysis PET-2 was positive in 20 patients. Of these 20 patients, 13 progressed during therapy and four relapsed within 6 months from having
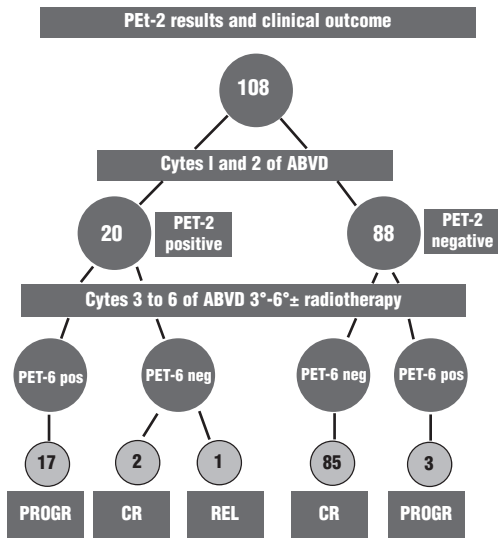
**Figure 2.** PET-2 result and treatment outcome.

**Table 3.** Kaplan-Meier cumulative proportion of 2-year failure-free survival (FFS) according to factors associated with a higher probability of progression.

| Variable | Modality | n | Two-year probability of FFS (standard error) | Log –rank (p) |
|---|---|---|---|---|
| PET 2 | Positive | 20 | 0.06 (0.06) | 116.7 (p<0.01) |
| | Negative | 88 | 0.96 (0.02) | |
| Gender | Male | 51 | 0.68 (0.12) | 0.4 (p>0.05) |
| | Female | 57 | 0.82 (0.05) | |
| Stage | II-III | 86 | 0.86 (0.04) | 21.2 (p<0.01) |
| | IV | 22 | – (–)* | |
| Age (years) | ≤≤31 | 56 | 0.82 (0.07) | 2.0 (p>0.05) |
| | >31 | 52 | 0.74 (0.06) | |
| International Prognostic Score | 0-1 | 62 | 0.89 (0.04) | 6.8 (p<0.01) |
| | 2-5 | 46 | 0.59 (0.11) | |
| ESR (mm/h) | ≤ 40 | 43 | 0.87 (0.07) | 4.8 (p<0.05) |
| | > 40 | 65 | 0.72 (0.06) | |
| LDH | normal | 87 | 0.82 (0.04) | 1.2 (p>0.05) |
| | abnormal | 21 | 0.58 (0.16) | |
| WBC (n /μL) | ≤ 15000 | 89 | 0.83 (0.05) | 9.7 (p<0.01) |
| | > 15000 | 19 | 0.56 (0.12) | |
| Hemoglobin (g/dL) | ≥10.5 | 95 | 0.80 (0.05) | 1.2 (p>0.05) |
| | < 10.5 | 13 | 0.64 (0.15) | |
| Bulky disease | No | 67 | 0.81 (0.06) | 1.3 (p>0.05) |
| | Yes | 41 | 0.73 (0.08) | |
| Extranodal sites | No | 78 | 0.87 (0.04) | 8.0 (p<0.01) |
| | Yes | 30 | 0.54 (0.12) | |

*no patient reached 2-year follow-up.

**Table 4.** Factors significant in multivariate analysis from a Cox proportional hazards regression analysis. Values are given as hazard ratios with 95% confidence intervals.

| Variable | Modality | n | Hazard ratio (95% C.I.) |
|---|---|---|---|
| PET 2 | Positive | 20 | 55.5 (16.0-192.8) |
| | Negative | 88 | 1.0 |

reached CR; these 17 patients all underwent salvage therapy with high-dose chemotherapy and autologous stem cell transplantation. Two other patients, showing a progressive reduction of SUV in subsequent PET scans up to complete negativity, remained in CR; one patient had a late relapse 18 months after entering CR. By contrast, 85/88 (97%) patients with a negative PET-2 also had a negative PET-6 and remained in CR. In one of the two patients with a positive PET-2 the focal abnormality was in the same area involved in the baseline study, while in the second patient the uptake was recorded in the medial right pulmonary lobe, close to the focal area involved at baseline (mediastinal nodes), but in a different site. However, because a confirmatory biopsy could not be obtained, the scan was considered a true positive. Three patients showed disease progression in spite of having a negative PET-2. The clinical characteristics of these patients were not dissimilar from those of the overall population: one patient was in stage IIIA and two in stage IVB while the Hasenclever score was 2 in all three. The PET-2 scans were uniformly negative without any focal FDG uptake (Figure 2). In all three patients the PET-6 scan was positive. Two of these patients were studied using a Discovery LS CT-PET scanner and the third patient was studied using a Gemini CT-PET scanner.

On quantitative analysis, in the 20 patients with a PET-2-positive scan, the mean percentage of the reduction of SUV$_{Max}$ in PET-2 with respect to PET-0 was 39%. The mean percentage of the SUV$_{Max}$ reduction in the 12 patients who progressed during therapy and in the five patients who relapsed was 35% while for the two patients with a PET-2-positive scan who remained in CR the SUV$_{Max}$ reduction was 80% (p>0.05). For the 88 patients with PET-2-negative scans the SUV$_{Max}$ reduction was 100%. CT-2 (performed in 97 patients.) showed PR in 92 patients and CR in five. The median International

Prognostic Score value of PET-2-positive patients was higher than that of the PET-2-negative patients: 2.0 vs. 1.0, respectively (p<0.05).

### Prognostic factors

In order to assess the risk of disease relapse or progression, for the univariate analysis we took into account the clinical variables considered in the International Prognostic Score (Table 3). Besides the PET-2 result (p<0.01), the clinical factors that were significantly associated with a higher probability of treatment failure were stage (p<0.01), International Prognostic Score (p< 0.01),
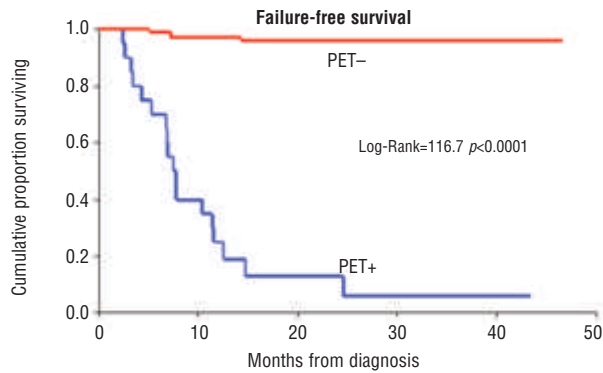
**Figure 3.** Probability of failure-free survival according to PET-2 results.

white cell count ($p<0.01$), erythrocyte sedimentation rate ($p< 0.05$), and involvement of extra-nodal sites ($p<0.01$). Since leukocytosis and stage are two clinical factors included in the International Prognostic Score, only the latter was considered for the multivariate analysis. The only factor that turned out to have an independent prognostic significance for relapse or progression in the multivariate analysis was a positive PET-2 scan, with a very high hazard ratio (55.5; 95 % C.I. 16.0-192.8) (Table 4). In terms of disease progression, the positive predictive value of the PET-2 scan was 90% and the negative predictive value was 97%. The sensitivity of PET-2 was 86%, the specificity was 98% and the overall accuracy 95%. The 2-year probabilities of failure-free and progression-free survival for PET-2-negative and for PET-2-positive patients were 96% and 96% and 6% and 13%, respectively (failure-free survival log rank test = 116.7, $p<0.01$; progression-free survival log rank test=106.4, $p<0.01$: Figure 3).

The positive predictive value of PET-6 was 92% and the negative predictive value was 97%. The sensitivity of PET-6 was 79%, the specificity was 99% and the overall accuracy 96%.

## Discussion

The optimal treatment for patients with advanced-stage HD is still matter of debate. ABVD therapy is able to offer long-term disease cure in about two-thirds of patients and, according to most groups, it remains the gold standard for randomized trials of advanced HD.[15-17] Recently BEACOPP, a new dose-escalated and accelerated regimen, has shown superior disease control with an updated 7-year failure free-survival of 85%,[18] but at the cost of a not trivial incidence of acute and late-onset side effects.[19] The authors claimed that this new intensified regimen was so effective that there was no longer need for prognostic indicators in HD.[7]

The current prognostic models are unable to support a risk-adapted therapeutic strategy: they show low efficacy and a scarce predictive power.[5] The most widely accepted and well-known prognostic model is the International Prognostic Score for advanced HD; in this series, however, only 7% of patients with a score ≥5

(with very poor prognosis), and only 19% patients with scores 4 and 5 had a less than 50% probability of progression-free survival at 7 years. The authors concluded that there was no distinct group of patients that could be identified as being at very high risk of disease progression.[4] For these reasons new prognostic models, based on specific biological characteristics of the tumor, such as chemosensitivity[20,21] or cytokine production,[22,23] have been proposed. The former was evaluated in 207 cases of advanced-stage HD in the EORTC 1981-86 trial: patients attaining the so-called *early complete respons*e after four cycles of chemotherapy showed a 14-year overall survival rate of 80% vs. 65% for patients without an early complete response ($p<0.01$).[24] More recently, response was assessed in HD patients after one, two, three, and four courses of chemotherapy by total body ^{67}Ga-scans[25] or ^{18}F-FDG-PET scans in preliminary reports in HD patients,[26-29] and more extensively, in non-Hodgkin's lymphoma.[30-32] In HD the sensitivity and specificity of PET scanning performed after the first cycle for predicting 18-month outcome were 82% and 92%, respectively, with an overall accuracy of 87%.[26] In the largest study published so far by Hutchings on 77 patients,[29] FDG-PET was the most accurate parameter for predicting progression-free survival; however, since nearly two-thirds (63%) of the patients were in clinical stage I-II, with a probability of cure of about 90%, the prognostic role of PET in this group of patients was overemphasized. The rationale for appraising the response to chemotherapy so early during therapy lies in the high sensitivity of PET scans in detecting the persistence of potentially resistant clones responding to treatment more slowly than chemosensitive tumor cells, which might re-expand at the end of treatment and ultimately cause disease progression.[33] Several clinical trials have indicated that quantification of the change in ^{18}F-FDG uptake may provide an early and sensitive pharmacodynamic marker of antiblastic chemotherapy, and recommendations on ^{18}F-FDG measurements of uptake have been reported.[34] Calculation of SUV has been considered the most suitable approach for measuring therapy-induced changes in tumor FDG uptake. In our population, however, probably due to the high chemosensitivity of Hodgkin's neoplastic cells, most of the patients had PET-2-negative scans, and therefore the evaluation of the response based on a quantitative measure did not offer any advantage over a qualitative evaluation. Only 20 out of our 108 patients had PET-2-positive scans and most of these (18/20) were chemoresistant (mean SUV reduction of 39%); in the two patients in continuous CR the mean reduction of SUV was 80% ($p>0.05$). For this reason we think that a larger study population is necessary to demonstrate the utility of quantitative analysis in the early evaluation of patients with a positive PET scan. The main end-point of the study was the predictive value of PET-2 for 2-year progression-fee survival. All but one of the 20 failures recorded in the present study (16 progressions and 4 early relapses) occurred within 6 months after achieving CR.

The mean follow-up in the present study (603 days), although relatively short, was  longer than that needed to define progression and not very different from the

follow-ups in other studies[26,29] with the same end-point.

Secondly, in the present study we demonstrated the high predictive value of PET-2 on overall treatment outcome: the sensitivity, specificity and accuracy of PET-2 were 86%, 98% and 95%, respectively. The positive predictive value was 90% and the negative predictive value 97%; these results are very similar to those reported by Kostakoglu.[26]

Thirdly, we confirmed the high chemosensitivity of HD neoplastic cells. Indeed, only 20 out of 108 patients (18.5%) had PET-2-positive scans: most of these (17/20) showed disease progression or early relapse, with only one showing a *late* relapse more than one year after achieving CR suggesting that the PET-2-positive scan was due to the persistence of chemoresistant clones. However, since only a small fraction of patients had a PET-2-positive scan (18.5%), very large series of PET-2-positive patients must be monitored to confirm the prognostic impact of an early positive scan. In any case, our results appear relevant considering that this was a multicenter trial and that different PET scanners were used. While the results of the PET-2 scan reflect the chemosensitivity of the cells to therapy, the result of the PET-6 scan reflect the global effect of the therapy. The prognostic information obtained at the end of therapy was of the same magnitude as that observed by others.[35]

Finally, our data seem to indicate a strong prognostic role for PET scans performed early during treatment. The cohort of patients studied, although including a small subset with unfavorable stage IIA disease, was characterized by a high tumor burden and sub-optimal treatment response, with a non-trivial risk of relapse of 30-35% at 10 years. For these reasons we explored, besides early PET, other prognostically relevant clinical variables for their value to predict treatment outcome, such as International Prognostic Score, stage, erythrocyte sedimentation rate and white cell count. The fact that the PET-2 scan emerged as the only significant factor in multivariate analysis confirms the relevance of chemosensitivity as a prognostic factor strictly related to the biology of the tumor, and independent of other variables such as tumor burden.

The rationale of our study was to evaluate the predictive value on treatment outcome of PET performed after two courses of ABVD in advanced-stage HD, in order to identify patients primarily refractory to therapy as early as possible. It is well known that these patients have a worse outcome than patients who relapse early or late after having achieved CR,[36-37] and therefore they should be treated with a different therapeutic strategy and very aggressively from the onset of their disease. Our data are in keeping with this concept: the 2-year probability of failure-free survival for PET-2-negative and PET-2-positive patients was 96% and 6%, respectively (log rank test =116.7, $p<0.01$: Figure 3). These results, together with Hutching's data,[29] seem robust enough to unequivocally confirm the prognostic role of PET-2 in the therapeutic strategy of advanced stage HD and to prompt the design of new clinical trials in these patients focused on early evaluation of chemosensitivity through FDG-PET scanning. The place of this prognostic tool in the global therapeutic strategy for advanced HD could be better defined, in PET-2-positive- patients, by randomized trials comparing standard therapy with early chemotherapy intensification followed by autologous stem cell transplantation, with an unmodified therapeutic strategy.

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