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ORIGINAL ARTICLE

FDG PET in response evaluation of bulky masses in paediatric Hodgkin's lymphoma (HL) patients enrolled in the Italian AIEOP-LH2004 trial

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Abstract

Purpose We present the results of an investigation of the role of FDG PET in response evaluation of bulky masses in paediatric patients with Hodgkin's lymphoma (HL) enrolled in the Italian AIEOP-LH2004 trial.

Methods We analysed data derived from 703 patients (388 male, 315 female; mean age 13 years) with HL and enrolled in 41 different Italian centres from March 2004 to September 2012, all treated with the AIEOP-LH2004 protocol. The cohort comprised 309 patients with a bulky mass, of whom 263 were evaluated with FDG PET at baseline and after four cycles of chemotherapy. Responses were determined according to combined functional and morphological criteria. Patients were followed up for a mean period of 43 months and for each child we calculated time-to-progression (TTP) and relapse rates considering clinical monitoring, and instrumental and histological data as the reference standard. Statistical analyses were performed for FDG PET and morphological responses with respect to TTP. Multivariate analysis was used to define independent predictive factors.

Results Overall, response evaluation revealed 238 PET-negative patients (90.5%) and 25 PET-positive patients (9.5%), with a significant difference in TTP between these groups (mean TTP: 32.67 months for negative scans, 23.8 months for positive scans; $p < 0.0001$, log-rank test). In the same cohort, computed tomography showed a complete response (CR) in 85 patients (32.3%), progressive disease (PD) in 6 patients (2.3%), and a partial response (PR) in 165 patients (62.7%), with a significant difference in TTP between patients with CR and patients with PD (31.1 months and 7.9 months, respectively; $p < 0.001$, log-rank test). Similarly, there was a significant difference in relapse rates between PET-positive and PET-negative patients ($p = 0000$). In patients with PR, there was also a significant difference in TTP between PET-positive and PET-negative patients (24.6 months and 34.9 months, respectively; $p < 0.0001$). In the multivariate analysis with correction for multiple testing, only the PET result

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was an independent predictive factor in both the entire cohort of patients and the subgroup showing PR on CT ($p < 0.01$).
Conclusion After four cycles of chemotherapy, FDG PET response assessment in paediatric HL patients with a bulky mass is a good predictor of TTP and disease outcome. Moreover, in patients with a PR on CT, PET was able to differentiate those with a longer TTP. In paediatric HL patients with a bulky mass and in patients with a PR on CT, response on FDG PET was an independent predictive factor.

Keywords Hodgkin's lymphoma · FDG PET · Paediatric · Bulky masses · Interim evaluation · Response assessment

Introduction

In the paediatric population, 10–15% of all malignancies are lymphomas, and of these 40% are Hodgkin's lymphoma (HL) [1–8]. The overall survival of paediatric patients with HL has greatly improved over the years [9]. The 5-year survival rate is almost 95% thanks to the introduction of treatments mainly based on the use of risk-adapted regimens that use intensive polychemotherapeutic drugs in combination with involved-field radiotherapy. The excellent results produced so far have created the need for new paediatric studies with the aim of reducing treatment-related morbidity while maintaining high survival rates. Multicentre trials have been conducted or are currently ongoing, mainly focusing on this aim [10–12].

Positron emission tomography (PET) is a useful imaging modality for tumour staging and for evaluating response to therapy. The uptake of ^{18}F-fluorodeoxyglucose (FDG) in PET studies is closely related to tumour growth rate and cellular proliferation, and can help predict response and survival after chemotherapy [1–5]. This imaging modality allows earlier identification of primary tumours as well as their metastatic spread, thus significantly improving therapeutic planning and overall survival. Several recent studies have shown the value of FDG PET for monitoring response to treatment in patients with lymphoma [13–21]. The modality combines functional and anatomical imaging and provides unique information on tissue characteristics after completion of therapy. It can accurately identify patients with residual disease, who might benefit from additional treatment, with particular relevance in patients with residual masses that are often present in children with HL [22, 23]. In these patients, there are commonly no specific morphological criteria able to differentiate viable tumour from fibrotic tissue [24]. Among lymphoma patients showing a residual mass on computed tomography (CT), FDG PET has been able to discriminate between those with a low risk of progression (<20%) from those with a high risk of recurrence (>80%) [25]. However, similar assessment is lacking in the paediatric population, in particular when considering the subgroup of HL patients with a bulky mass, who are known to be at higher risk of recurrence [26, 27].

Based on the above considerations, the Hodgkin Lymphoma Study Group of the AIEOP (*Associazione Italiana di Ematologia e Oncologia Pediatrica*) conducted a dedicated evaluation of the predictive value of FDG PET in response evaluation of paediatric HL patients with a bulky mass in the prospective AIEOP LH2004 therapeutic protocol.

Materials and methods

Patient population

We analysed data derived from 703 paediatric patients followed by the AIEOP Hodgkin Lymphoma Study Group and enrolled in 41 different Italian Centres between March 2004 and September 2012 (Fig. 1). All patients had histologically proven HL, staged according the Ann Arbor staging classification [27], and all had followed the same therapeutic protocol for paediatric HL (AIEOP-LH 2004). Patients were investigated at baseline (n = 621), after four cycles of therapy (n = 263), after the end of chemotherapy (n = 354) and after radiation treatment (n = 222). For the current analysis, we selected only patients aged <18 years with a mediastinal bulky mass (Fig. 2), defined as a mediastinum/thorax ratio of ≥0.33, who had been investigated with FDG PET at baseline and after four cycles of chemotherapy, considered as an interim evaluation in this specific subgroup of patients. All patient data were retrieved from the official AIEOP storage system of the Cineca consortium (https://www.cineca.it/en/progetti/aieop). The principal characteristics of the study cohort are shown in Table 1.

Therapeutic protocol

The protocol administered to the patients enrolled in the AIEOP-LH 2004 trial was divided into three different risk-adapted regimens, as previously described [28, 29]. The cohort of patients with a bulky mass, regardless of HL stage, followed the group 3 regimen:

(a) *Standard treatment*: six cycles of COPP/ABV (cyclophosphamide, vincristine, procarbazine, prednisolone, Adriamycin, bleomycin, vinblastine) + local field radiation therapy (14.4 Gy)
(b) *Response-based treatment*: Patients with a complete response (CR) after chemotherapy received a subsequent treatment based on local field radiotherapy (14.4 Gy). In

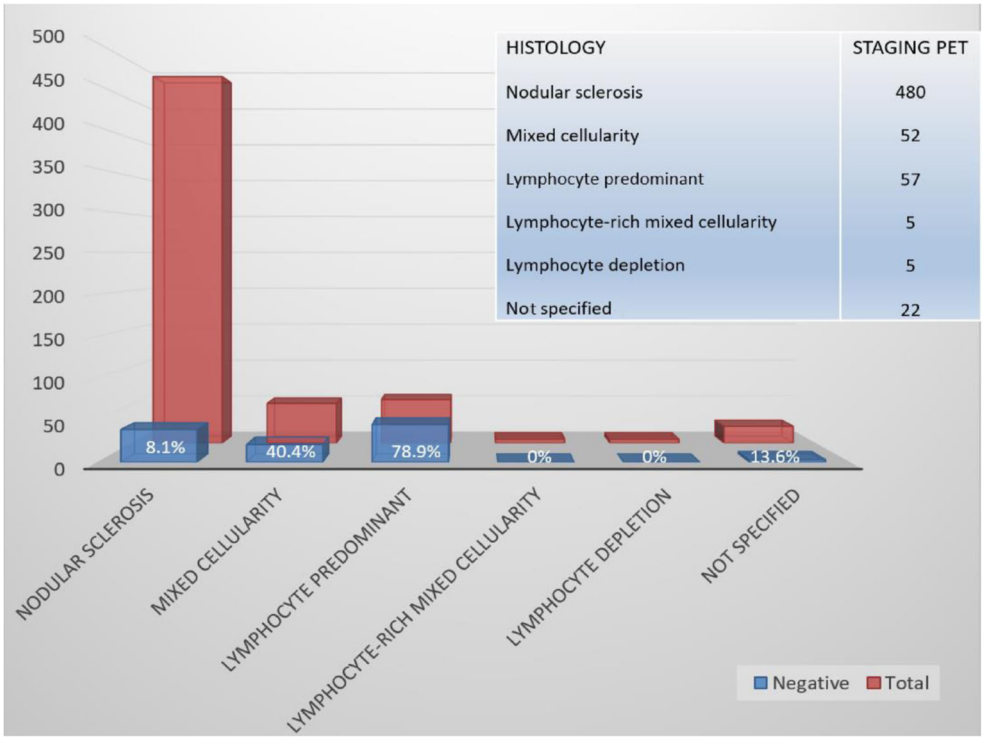


Fig. 1 Distribution of patients in the entire cohort on staging PET in relation to histology

patients with a partial response (PR) after the first four cycles of COPP/ABV, two additional cycles of IEP (ifosfamide, etoposide, prednisolone) with or without two cycles of COPP/ABV were planned, followed by radiation therapy (14.4Gy/25.2Gy, dose depending on CR or PR at the end of chemotherapy)

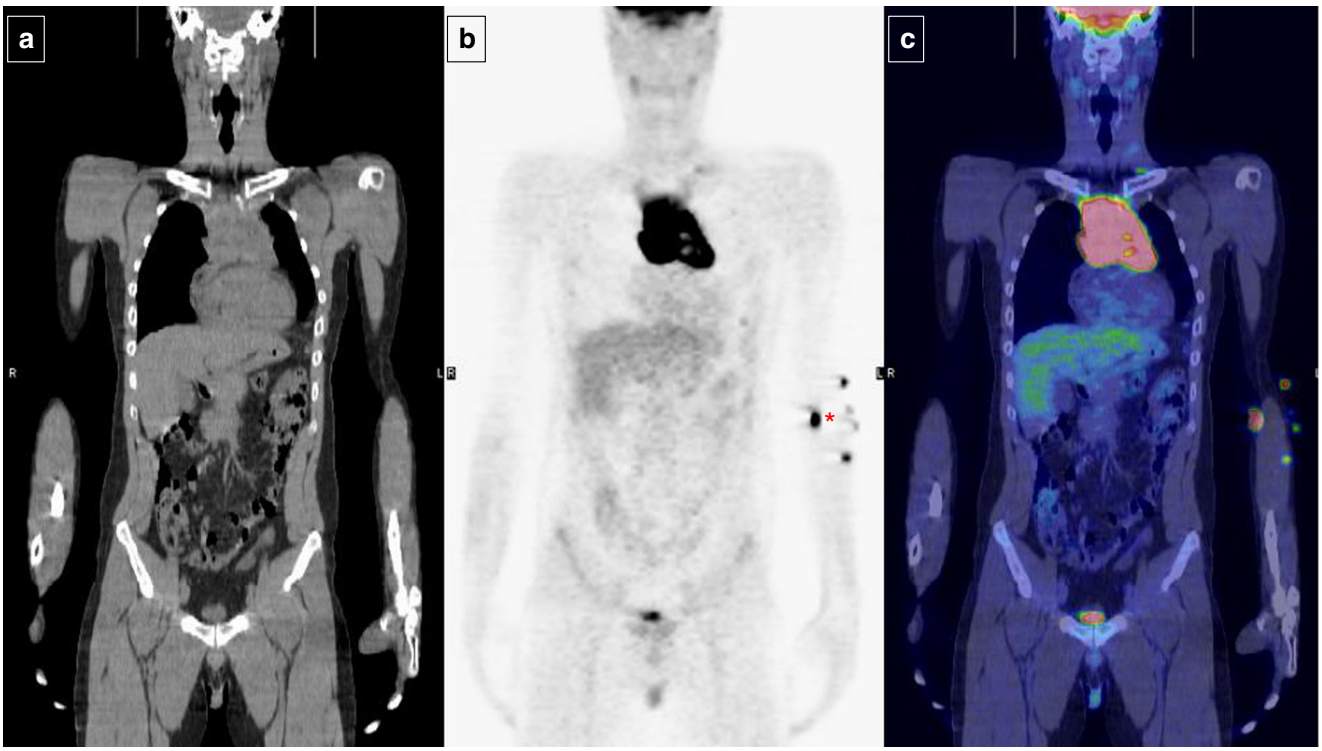


Fig. 2 PET/CT imaging in an example patient with a bulky mass in the mediastinum defined on the basis of a mediastinum/thorax ratio of ≥0.33, calculated on an anterior–posterior plain radiograph of the thorax. (**a**) Low-dose CT image, (**b**) FDG PET image, and (**c**) fused PET/CT image at the level of the mediastinum. *Red asterisk* spot of tracer contamination at the injection site

Table 1 Clinical characteristics and therapeutic approach in the entire population and study cohort

	Total population	Study cohort
Number of patients	703	263
Gender		
Male	388	140p
Female	315	123
Age (years)		
Mean	13.04	13.4
Range	2.74–17.99	2.74–17.99
Histology, *n* (%)		
Nodular sclerosis	520 (74)	225 (85.5)
Mixed cellularity	63 (9)	21 (8)
Lymphocyte-rich mixed cellularity	24 (3)	3 (1)
Lymphocyte-depleted	7 (1)	2 (0.8)
Lymphocyte-predominant	65 (9)	5 (2)
Not classified	24 (3)	7 (2.7)
Stage, *n* (%)		
I	44 (6)	18 (7)
II	361 (51)	103 (39)
III	158 (23)	38 (14)
IV	140 (20)	104 (40)
Bulky mass, *n* (%)	309 (44)	263 (100)
B symptoms, *n* (%)	258 (37)	144 (55)
Therapeutic group, *n* (%)		
1	130 (18.5)	–
2	158 (22.5)	–
3	415 (59)	263 (100)
Radiation therapy, *n*	513	222
Dose (Gy), range	14.4–36	14.4–36
Follow-up period (months)		
Mean	43	32
Range	3–99	3–99

FDG PET and image interpretation

FDG PET scanning was carried out according to standard procedures [29] and based on EANM guidelines with either a dedicated PET system (GE Advance, GE Medical Systems; or ECAT Exact 921/47, Siemens) or a hybrid PET/CT system (GE Discovery LS or STE, GE Medical Systems; Gemini TF64, GXL or TF16, Philips; and BiographTP16, Siemens). If the findings from the dedicated PET scans were uncertain, the study could be completed with a segmental PET/CT acquisition. Each scan was interpreted on-site by experienced nuclear medicine physicians, and the PET findings were reported as positive or negative on the basis of visual analysis by excluding physiological FDG uptake and natural pathways of tracer biodistribution. Centralized review of the images was not planned in the trial, which was started in 2004.

Scans were also interpreted using the standardized uptake value (SUVmax). The references for semiquantitative evaluation were based on: (a) vascular blood pool in patients with mediastinal lesions including bulky masses, (b) mean hepatic uptake in those with parenchymal lesions, and (c) background uptake in those with lesions at other locations. PET scans were performed at diagnosis, after four cycles of chemotherapy and before radiotherapy at the end of chemotherapy. When the protocol was initiated (2004) there was insufficient evidence to reduce standard treatment based solely on interim PET/CT, so the prognostic PET value was finalized to intensified treatment in poor responder patients.

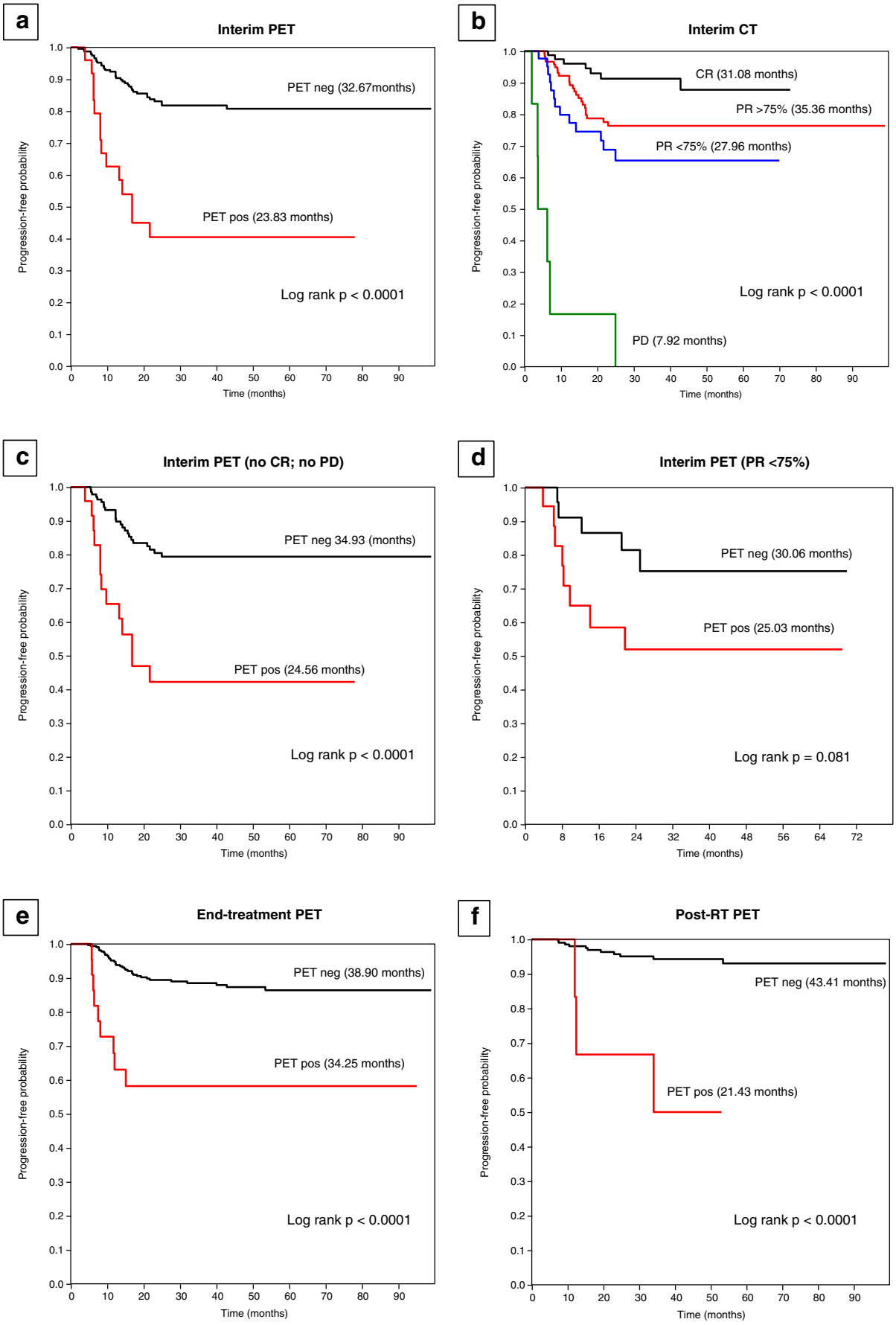
CT scanning and response assessment

A reference CT scan was always available for evaluation of morphological response, as previously described [28, 29], although overall response was determined according to the guidelines presented by Cheson et al. and the International Harmonisation Project (IHP) [30, 31]. CR in patients with a bulky lesion was defined as PET-negative for any lesion size on the CT scan and complete dimensional response on the CT scan or a dimensional reduction of ≥75% of the initial volume. PR was defined as regression of measurable disease of ≥50% and <75% in the sum of the product of the diameters ($a \times b \times c \times 0.52$) on the CT scan or a reduction of ≥75% with a PET-positive result, and no new sites of disease. Stable disease (SD) was defined as no CR/PR or PD. Progressive disease (PD) was defined as new PET-positive lesions and/or an increase of ≥50% in previously involved sites from the nadir or new nodes >1 cm in diameter on the CT scan. The AIEOP-LH 2004 protocol also recorded two subclassifications for morphological PR (<75% and ≥75%) that were separately analysed for the specific aims of the current study.

Statistical analysis

According to the time of enrolment, for each child we calculated time-to-progression (TTP). The aim of this study was to evaluate the predictive value of interim PET with respect to patient outcome and TTP was considered as the time from the beginning of therapy until progression or relapse. Separate analyses were also performed to determine the added value of FDG PET in HL patients with morphological PR (either <75% or ≥75%). In a patient-based analysis, outcomes were remission (no evidence of lymphoma) or active disease, according to combined criteria, which included clinical and

Fig. 3 Kaplan-Meier curves with respect to TTP in the entire cohort of patients with a bulky mass: (**a**) interim PET, (**b**) interim CT, (**e**) end-of-treatment PET, (**f**) after radiotherapy PET. (**c**, **d**) Separate curves for interim PET in patients with SD (**c**, i.e. no CR/no PD) and patients with PR <75% (**d**). The mean survival time for each group of patients is shown


a
Interim PET
PET neg (32.67months)
PET pos (23.83 months)
Log rank p < 0.0001
b
Interim CT
CR (31.08 months)
PR >75% (35.36 months)
PR <75% (27.96 months)
PD (7.92 months)
Log rank p < 0.0001
c
Interim PET (no CR; no PD)
PET neg 34.93 (months)
PET pos (24.56 months)
Log rank p < 0.0001
d
Interim PET (PR <75%)
PET neg (30.06 months)
PET pos (25.03 months)
Log rank p = 0.081
e
End-treatment PET
PET neg (38.90 months)
PET pos (34.25 months)
Log rank p < 0.0001
f
Post-RT PET
PET neg (43.41 months)
PET pos (21.43 months)
Log rank p < 0.0001
Progression-free probability
Time (months)

instrumental monitoring. Positive and negative predictive values (PPV and NPV, respectively) with respect to outcome were computed for all PET times (i.e. interim, after chemotherapy and after radiotherapy). Correlations between FDG PET results and patient outcomes were evaluated using the chi-squared test or Fisher's exact test as appropriate. Associations with TTP were evaluated using the Kaplan-Meier method [32] and differences between groups were evaluated using the log-rank test [33]. Univariate and multivariate analyses were performed using Cox proportional hazards regression. A p value less than 0.05 was considered statistically significant. Correction for multiple testing was done using the Bonferroni method.

Results

Between March 2004 and September 2012, 703 patients were enrolled in the Italian AIEOP-LH2004 trial. In total, 309 patients (43.9%) had a bulky mass and the most frequent site was the mediastinum (85%). Patients with the latest enrolment dates were referred to therapeutic group 3 as discussed above in section "Therapeutic protocol". The mean age of this cohort was 13.4 years (range 3–18 years). The characteristics of the 263 patients analysed are presented in Table 1. The numbers of patients with stages I, II, III and IV were 18, 103, 38 and 104, respectively. Of the 263 patients, 222 received radiation therapy at the end of chemotherapy. The discrepancy with regard to the therapeutic regimen described in the protocol was due to lack of compliance or withdrawal. The mean duration of follow-up was 32 months (range 3–99 months). Overall, nine patients died due to disease progression.

After course 4 of chemotherapy (at the interim assessment), ^{18}F-FDG PET/CT demonstrated a response rate of 90.5% (238/263), whereas 9.5% of patients (25/263) had a PET-positive residual mass. Figure 3a shows Kaplan-Meier curves comparing TTP in HL patients with and without a PET-positive bulky mass. TTP was 32.7 months in those with a negative scan and 23.8 months in those with a positive scan ($p < 0.0001$). Likewise, on the interim CT scan, 85 patients (33%) showed CR, 6 (2%) PD, and 165 (65%) PR. Figure 3b shows Kaplan-Meier curves comparing TTP between patients with CR and PD on CT: TTP was 31.1 months and 7.9 months, respectively ($p < 0.0001$). Considering the final outcomes, the relapse rate was 61.9% in PET-positive patients and 13.5% in PET-negative patients at the interim assessment ($p = 0.000$, Fisher's exact test). Figure 4 shows PET/CT imaging in one patient with PR in the mediastinum, who showed early disease progression on the postchemotherapy PET scan.

We then specifically analysed the value of FDG PET in patients showing PR on CT. In these patients, there was a significant difference in TTP between PET-negative and PET-positive patients (34.9 months and 24.6 months, respectively, $p < 0.0001$; Fig. 3c). In particular, dividing patients according to their morphological response (<75% or ≥75% in the sum of the product of the diameters, $a \times b \times c \times 0.52$, on the CT scan), Kaplan Meier analysis showed a longer TTP in PET-negative patients with a PR of <75%, although the difference did not reach statistical significance (log-rank test; Fig. 3d).

We also performed a multivariate analysis of interim PET results together with other clinical factors (Table 2), both in the entire cohort of patients and in the subgroup showing no CT/no PD on CT. After correction for multiple testing, only the interim PET result was an independent predictive factor in both analysed cohorts ($p < 0.01$).

The interim PET results were confirmed at the end of chemotherapy: PET-negative patients had a longer TTP than PET-positive patients (38.9 months and 34.2 months, respectively, $p < 0.0001$; Fig. 3e). As expected, there was a significant difference in relapse/progression among patients with different results on postchemotherapy PET: 40.1% and 10.8% in PET-positive and PET-negative patients, respectively ($p = 0.0005$).

Finally, among 222 of the 263 patients referred for radiotherapy after chemotherapy, TTP was longer in PET-negative patients than in PET-positive patients (38.9 months and 34.2 months, respectively, $p < 0.0001$; Fig. 3f). Similarly, the relapse rates differed significantly: 27.2% of PET-positive patients showed relapse/progression after radiotherapy compared with 5% of PET-negative patients ($p = 0.025$). Considering the final patient outcome, the predictive values of all the different PET scans were calculated (Fig. 5). There were significant differences between interim PET and the postchemotherapy and postradiotherapy PET scans.

Discussion

The discrimination of residual masses after chemotherapy, whether fibrotic or active lymphoma tissue, is a key point in the evaluation of response to treatment and for planning of subsequent therapeutic strategies (i.e. increasing chemotherapy or elimination of radiotherapy). Neither CT nor MRI can easily distinguish the nature of residual tissue [22]. This aspect is of particular importance in the paediatric setting and when the mediastinum is involved, for which access can be guaranteed only by invasive procedures, i.e. open surgery or mediastinoscopy [23, 34].

In this study, we evaluated a very large paediatric population with HL and treated according to the Italian AIEOP-LH2004 protocol. We focused on HL patients presenting with bulky disease. In all children, PR was ascertained on interim CT (after four cycles of chemotherapy) and after the end of chemotherapy. First, we found that patients negative on the interim PET assessment had a longer TTP than patients

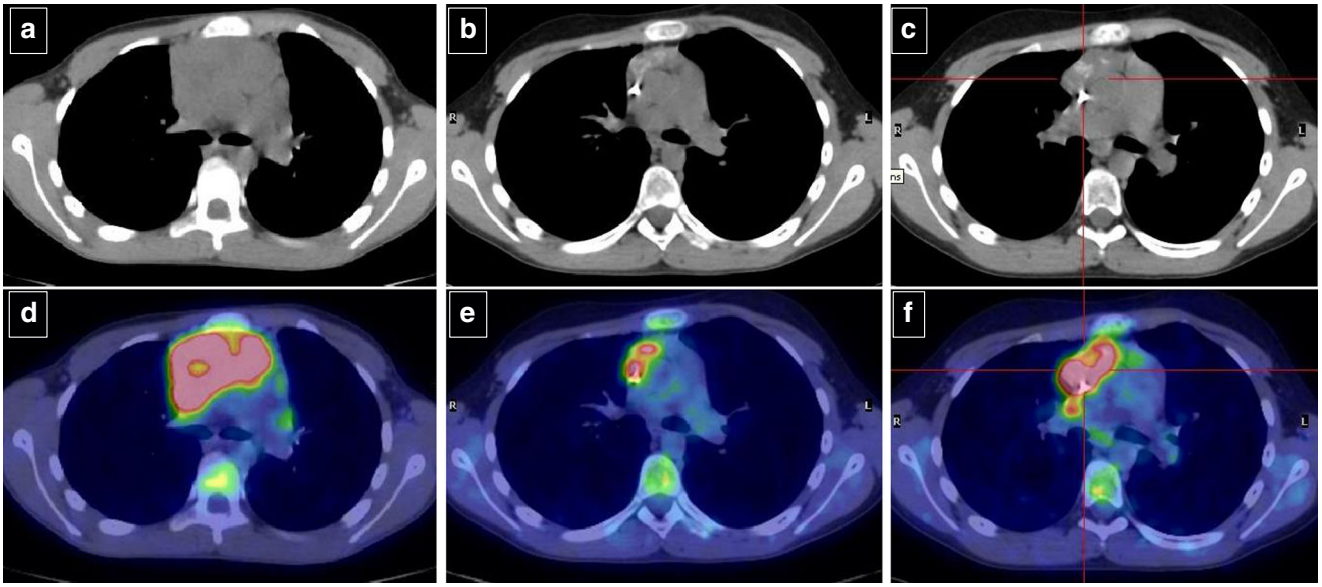


Fig. 4 PET imaging in a patient with a mediastinal bulk at baseline (**a**, **d**), after four cycles of chemotherapy (**b**, **e**) and after the end of treatment (**c**, **f**). Axial low-dose CT images (**a**–**c**) and corresponding axial fused PET/CT images (**d**–**f**) at the level of the pathological area within the mass show residual disease at the interim evaluation

positive on PET (33 months and 24 months, respectively). In addition, they showed a significantly lower relapse rate than PET-positive patients. When pooled with the other clinical factors, the interim PET result was an independent predictive factor in our cohort. To the best of our knowledge, this is the largest/first trial in paediatric HL investigating the impact of interim FDG PET on survival of patients with bulky disease. Comparison with the results of other studies is therefore difficult because of differences in study design and response evaluation criteria and timing.

In adult HL, Oki et al. [35] found that patients negative on interim PET had a 3-year progression-free survival rate higher than patients positive on interim PET, in both nonbulky disease and bulky disease, although interim PET was performed after cycle 2 or 3, and not after cycle 4 as in our study. In the adult setting, Gallamini et al. [36] confirmed the superiority of early interim PET/CT over the International Prognostic Score and its value in treatment planning in patients with advanced HL. Similarly, our results showed a better survival rate in responder patients, regardless of CR, PR or SD, than in patients with PD on CT. These findings are in line with those of the Children's Oncology Group study AHOD0031, a randomized phase III study [10], which identified a group of patients with rapid early response on CT and CR at the end of chemotherapy who could be spared radiation therapy without affecting efficacy. Additionally, in the same trial, patients considered slow responders on CT and negative on interim PET had 4-year event-free survival comparable to those with a rapid response. On the other hand, in patients considered slow early responders and positive on interim PET, event-free survival

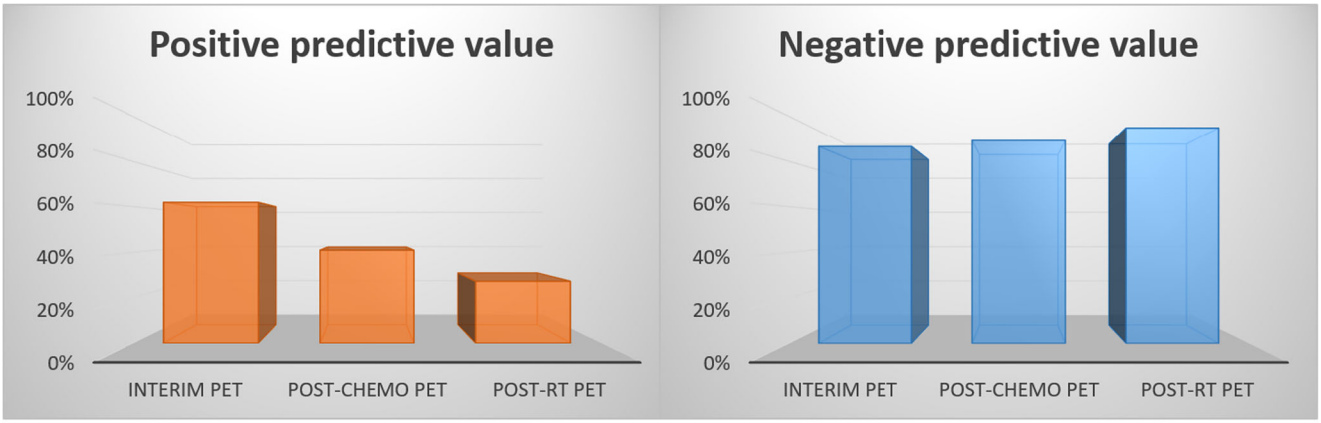
Table 2 Univariate and multivariate analyses of various factors in relation to the interim PET results in the study cohort and in patients showing a no CR/no PD on CT

Variable	Study cohort				no CR/no PD			
	Univariate		Multivariate		Univariate		Multivariate	
	Hazard ratio	*p* value	Hazard ratio	*p* value	Hazard ratio	*p* value	Hazard ratio	*p* value
Age (years)	0.978	0.692	0.976	0.680	1.005	0.947	1.003	0.974
Histology	0.988	0.929	1.019	0.895	0.848	0.430	0.833	0.445
Stage[a]	0.765	0.501	0.865	0.724	1.192	0.677	1.711	0.214
B symptoms	2.172	0.021*	1.897	0.092	2.805	0.006*[b]	2.614	0.024*
Interim PET	5.560	0.000*[b]	6.557	0.000*[b]	4.607	0.000*[b]	5.327	0.000*[b]

*$p < 0.05$

[a] Reported disease stage III values

[b] Significant after Bonferroni correction for multiple testing



Predictive values	INTERIM PET		POST-CHEMO PET		*p* value	POST-RT PET		*p* value
	%	95% CI	%	95% CI		%	95% CI	
PPV	61.90%	38.44-81.89%	40.91%	20.71-63.65%	**< 0.0001**	27.27%	6.02-60.97%	**< 0.0001**
NPV	86.55%	81.36-90.74%	89.16%	85.31-92.29%	0.3882	94.79%	90.86-97.37%	**0.0037**

Fig. 5 Predictive values of interim PET, postchemotherapy PET and postradiotherapy PET in relation to final patient outcome. The table shows *p* values from the chi-squared analysis for interim PET versus the other two PET scans

was improved with the escalation of chemotherapy, suggesting that interim PET may help in deciding on further therapy.

In a prospective study, Furth et al. [11] found that FDG PET for early response assessment (PET-2) in paediatric HL showed excellent sensitivity and NPV, both about 100%. None of the patients -negative on PET-2 had relapse of lymphoma during the follow-up. Moreover, the specificity of PET-2 was significantly higher than that of conventional imaging, i.e. MRI, CT and ultrasonography (68% versus 3%, respectively). Likewise, in patients with PR on CT, FDG PET-negative patients and PET-positive patients showed different TTP. This difference was also seen between patients with PR in the range 50–75% and those with a response of ≥75%. Furthermore, Bakhshi et al. [12], in a recent study evaluating the role of interim FDG PET after two cycles of chemotherapy in a paediatric HL cohort, found that interim PET/CT had a significantly higher specificity than conventional imaging. However, they did not recommend treatment reduction based on the interim PET/CT assessment by either the Revised International Working Group criteria or the Deauville score, as few patients would have benefited from less intense therapy.

In contrast to our results and those discussed above, Schwartz et al. [26] found that the Childhood Hodgkin International Prognostic score at diagnosis based on four parameters (stage 4 disease, large mediastinal mass, albumin level, and fever) was superior to early response evaluated on CT and PET, though the latter were able to identify patients with a poor response.

Finally, post-treatment assessment by FDG PET confirmed the results of the early assessment. Indeed, at the end of chemotherapy patients with a negative PET scan had longer survival. Similarly, they had a lower relapse rate. Among patients who received radiotherapy, PET-negative patients also showed a longer TTP than PET-positive patients, although they received a higher dose of radiotherapy. These results are similar to those of the studies discussed above [11, 12] in which both early and late therapy response assessment with ^{18}F-FDG PET were able to identify paediatric HL patients with longer survival. Comparing the calculated predictive values for all three PET scans (i.e. interim, postchemotherapy and postradiotherapy), The NPV was high overall, but slightly better for post-radiotherapy PET, although at the expense of a lower PPV.

Despite these interesting results, the present study had some limitations. First, only some of the HL patients had both CT and PET interim evaluations available. Second, we did not consider overall survival in our analysis. Third, the majority of previous studies compared early evaluation after two cycles of therapy, whereas in our study the analysis was performed after four cycles.

Conclusion

This study to the best of our knowledge shows for the first time and in a large series of paediatric HL patients the predictive value of interim PET in patients with a mediastinal bulky mass in the same therapeutic trial (AIEOP LH2004). The results of our study, given the response-adapted treatment management in HL patients in this trial, demonstrate that the risk of relapse/progression in patients with a residual mass and negative PET after four cycles of chemotherapy is

superimposable on that of patients without residual tissue. Given the known risk for secondary malignancies and treatment-related toxicities, the information provided by FDG PET in patients with bulky HL, even in those with radiological residual tissue after the first courses of therapy, may help reduce the aggressiveness of subsequent treatments, especially the dose and volumes of radiation therapy, in patients with metabolic CR. This aspect, that has largely been assessed in the adult population with HL, needs to be investigated in the paediatric context; hence the importance of the results yet to come from the ongoing international trials.

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Compliance with ethical standards

Ethical approval All procedures performed in the AIEOP-LH 2004 protocol involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the principles of the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

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