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Use of 2-[^{18}F]fluoro-2-deoxy-D-glucose positron emission tomography in patients with Hodgkin lymphoma in daily practice: a population-based study from Northern Italy

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Abstract

We conducted a population-based study to assess how positron emission tomography (PET) is currently used in patients with Hodgkin lymphoma (HL). Four cancer registries from northern Italy were used to identify patients with HL diagnosed from 2006 to 2008. Computed tomography (CT) and PET scans were collected before treatment start (B), at the end (F), and during treatment (I). One hundred and thirty-six patients were identified as the study population. B-PET, I-PET, and F-PET were performed in 82%, 65%, and 85% of patients, respectively. Overall, I-PET was coded as positive in 16% of cases. F-PET was positive in 13% of cases. The I-PET result was a prognostic factor for failure-free survival (FFS) (hazard ratio [HR] 5.33); the F-PET result was the only prognostic factor for overall survival (OS) (HR 14.2). This population-based study confirms the prognostic role of I-PET for FFS also in daily practice; the results of F-PET can be used to predict OS.

Keywords: *Hodgkin lymphoma, FDG-PET, prognostic factor, survival, population-based study, cancer registry*

Introduction

Hodgkin lymphoma (HL) accounts for approximately 10% of malignant lymphomas and is one of the most treatable adult cancers, with long-term cure rates higher than 80% achieved even in patients with advanced disease [1–4].

2-[^{18}F]fluoro-2-deoxy-D-glucose (FDG)-positron emission tomography (PET) was first introduced for the management of lymphomas in the early 1990s. It is now recognized as an important tool for staging and response assessment in Hodgkin and non-Hodgkin lymphomas [5,6]. More recently PET has emerged as a useful prognostic tool in patients with advanced HL, and may predict treatment outcome when performed very early during therapy (early PET) [6–8].

Several investigators suggest that the prognostic role of the early assessment of response with PET may be by far more relevant than any other clinical prognostic score (International prognostic Score; IPS) in patients with advanced disease. For this

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reason, although no data are yet available to support the use of the early assessment of response for adapting and modifying subsequent treatment, it seems that PET is used routinely in patients with HL also outside clinical trials. So far no study has been performed to verify how PET is currently used in daily practice and to assess the prognostic or predictive role of PET results outside clinical trials.

Using a population-based approach we investigated the prescription of PET in patients with HL diagnosed from 2006 to 2008 in four Italian provinces. The main purpose of this study was to investigate how PET is currently used in daily practice and whether results obtained in clinical trials and retrospective series can be generalized to all patients with HL.

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Materials and methods

The study (NCT number 01248000) was conducted in compliance with the Declaration of Helsinki and was accepted by the appropriate research ethics committee. Patients were identified from archives of four population-based Italian cancer registries. The registries cover, respectively, the populations of the contiguous provinces of Modena, Reggio Emilia, Parma, and Ferrara, which are four provinces in the Emilia-Romagna region of northern Italy that contain a total population of about 1 825 000 people. The registries include cancer diagnoses for all persons resident in these provinces via local pathology departments (data of nodal, extranodal [EN], and bone marrow biopsies), from both local and national reports of hospital admissions, and from death certificates. The coverage achieved by the cancer registries can be considered excellent due to the low rate of death certificate only (DCO) reports (0.1%) [9].

Patient selection was based on the following criteria: diagnosis of HL performed between 1 January 2006 and 31 December 2008, age between 18 and 75 years, and human immunodeficiency virus (HIV) negativity. To confirm inclusion, all diagnoses were reviewed, and only patients with confirmed HL based on a local pathology report were considered. Histology was coded according to the third revision of the International Classification of Diseases for Oncology (ICD-O-3), which is based upon the World Health Organization (WHO) classification of lymphoid neoplasms [10,11]. For each case included in the present study, registries provided data on patient demographics, histological type, and primary cancer site. For each confirmed case an active chart review was performed to collect additional data on disease stage and sites of involvement, patient characteristics (performance status, systemic symptoms), and treatment modality, together with response assessment and patient outcome. The stage of disease was defined according to the Ann Arbor system. All cases were included at the time of initial diagnosis. Lymph nodes involved with lymphoma were considered bulky when the maximum transverse diameter was larger than 10 cm or, for thoracic masses, larger than 6 cm on a computed tomography (CT) scan.

Patients were coded as having advanced disease if they had stage II B or bulky III or IV. All other patients were considered at a limited stage. For both CT and PET results, positivity and negativity was referred to nodal sites or extranodal organs. Nodal sites were coded according to previous guidleines [12]. Positivity of nodal sites upon CT scan was defined, according to Cheson *et al.*, in cases of nodes with a maximum transverse diameter greater than 1.5 cm [13].

With respect to therapies, treatment data were collected with details on administered regimen, number of cycles, treatment changes, and administration of radiation treatment. Inclusion in a clinical trial was also retained as a study detail, with the exclusion of those clinical trials that were not aimed at investigating the role of PET and that did not include PET among the required procedures.

All reports of PET scans performed at baseline (B-PET), during treatment (I-PET), and at the end of treatment (F-PET) were collected and results retrospectively coded as positive, negative, or 'inconclusive' according to local interpretation of the study report. All PET scans were performed in one of the nuclear medicine services of the region and originally read by one nuclear physician participating in the study (A.V., L.R., B.B.); scan reports were finally recoded for study purposes by one of the authors (S.L.). Scans were coded as positive or negative if presence or absence of disease was clearly indicated in the report. Indefinite wording such as 'almost complete disappearance' or 'significant reduction of metabolic activity' or 'minimal residual uptake' were considered as inconclusive, and counted as a distinct category. All study analyses were performed only in patients with clearly negative or positive results. Of note, the use of PET for managing patients with lymphoma in Italy is not regulated by law, and reimbursement is not restricted to 'approved' use only.

Results of I-PET were considered for early assessment of response if the examination was performed after 2–3 cycles of therapy. We defined F-PET as a scan performed after chemotherapy if the patient received only chemotherapy or PET performed after radiotherapy if the patient received also radiotherapy.

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All reports of CT scans performed at baseline, during treatment, and at the end of treatment were collected and results retrospectively coded using published criteria for defining disease extent and response. In particular, a cut-off of 1.5 cm was used to identify pathological or residual nodes. Response assessment at the end of therapy was defined according to published criteria [6,13]. In particular, achievement of a negative PET was used to define complete remission (CR) regardless of CT results [6].

Statistical analysis

Statistical analysis was performed using the STATA 8.2/SE software package. All study comparisons were performed using the Fisher exact test and all statistical tests were two-sided with a 5% level of significance. For studying the prognostic value of I-PET, failure-free survival (FFS) and overall survival (OS) were chosen as end-points. FFS for I-PET was calculated only for patients who did not change their treatment according to the scan results. FFS was defined as the time from diagnosis to treatment failure, which included response less than CR, treatment interruption, disease recurrence, and death from any cause. OS was defined as the time from diagnosis to death from any cause. Survival curves were plotted using the Kaplan–Meier method and compared using the log-rank test. Survival functions were also analyzed by means of Cox proportional hazards regression and the effects of covariates expressed in terms of hazard ratios (HRs) and 95% confidence intervals (CIs).

Binary outcomes were analyzed using logistic regression, both in uni- and multivariate analysis, and the effects of covariates expressed in terms of odds ratios (ORs) and 95% CIs. Moreover, we used logistic regression with Firth's penalized likelihood to solve the problem of separation in logistic regression [14].

Kappa statistics [15] was used to measure the inter-rater agreement between stagings derived from CT and PET at diagnosis.

Results

From 2006 to 2008, 185 cases of HL were identified from the cancer registries (CReg) of the provinces of Modena, Parma, Reggio Emilia, and Ferrara. The World Age-Standardized Rate (WASR) was calculated as 3.0 per 100 000 people (range 1.8–4.3). According to inclusion criteria, two patients were excluded because of positivity to HIV, one because the initial diagnosis was performed before 2006, and 29 patients because they were younger than 18 or older than 75 years. Seventeen additional cases were excluded because of missing data. One hundred and thirty-six patients were then identified as the study population (Figure 1).

Clinical data

The clinical characteristics of the study population are summarized in Table I. Details on initial treatment were available for all patients; the majority of them received ABVD chemotherapy (adriamycin, bleomycin, vinblastine, and dacarbazine; 116 patients, 85%), 11 patients (8%) received intensified regimens including BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone) or COPP (cyclophosphamide, vincristine, procarbazine, and prednisone)/EBV (epirubicin, bleomycin, and vinblastine)/CAD (lomustine, doxorubicin, and vindesine), six

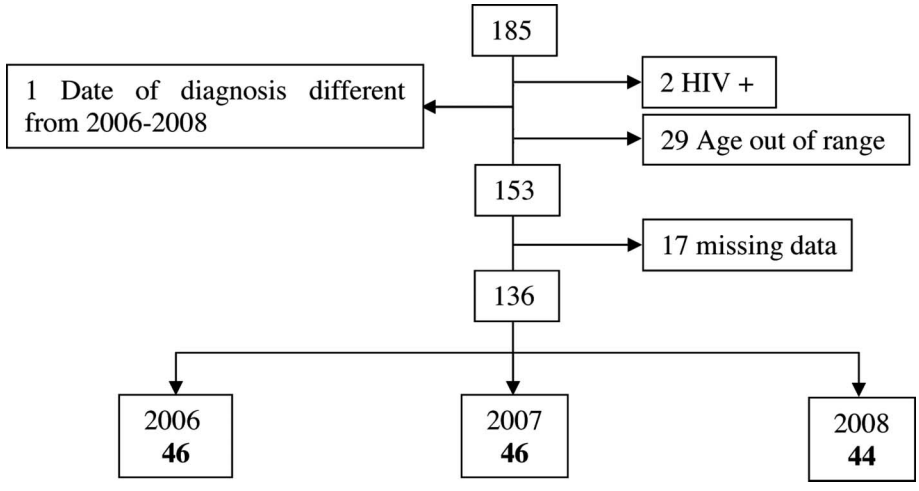

Figure 1. Study flow chart.

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patients (4%) received chemotherapy without anthracycline (VBM: vinblastine, bleomycin, and methotrexate; or MOPP: chlormethine, vincristine, procarbazine, and prednisone), and three patients (3%) received other therapies (two radiotherapy alone, one carboplatinum for concomitant lung cancer). Radiation therapy (RT) was used as the only treatment in two patients; 72 patients received RT at the end of chemotherapy. Overall, 10 (7.3%) patients were enrolled in a clinical trial that required the execution of PET among study procedures (European Organisation for the Research and Treatment of Cancer/Groupe d'Etude Des Lymphomes De l'Adulte/Intergruppo Italiano Linfomi [EORTC/GELA/IIL] H10, NCT number 00433433).

Table I. Clinical characteristics of Hodgkin lymphoma.

Factors	Evaluable cases	*n*	%
Median age, years (range)	136	38 (18–75)	
Age ≥60 years	136	26	19
Age ≥45 years	136	49	36
Male gender	136	70	52
Ann Arbor stage	135		
I		3	2
II		72	53
III		34	26
IV		26	19
BM positive	135	7	5
B-symptoms	135	51	38
Bulky disease	136	41	30
Mediastinal bulk	39	31	79
Enrollment in a clinical trial*	135	10	7
Early disease (I–IIA)	135	58	43
Advanced disease (IIB–IV)	135	77	57
Treatment	136		
ABVD/ABVD-like		116	85
Intensified CT†		11	8
CT without ADM‡		6	4
RT/palliative		3	3

*Inclusion in a clinical trial was limited to studies investigating the role of positron emission tomography (PET).
†BEACOPP, COPP/EBV/CAD.
‡MOPP, VBM.
BM, bone marrow; CT, chemotherapy; ADM, adriamycin; RT, radiotherapy.

At the end of treatment, 113 (83%) patients achieved a CR, nine (7%) patients a partial remission (PR), and 14 (10%) patients had stable/progressive disease.

Survival data

After a median follow-up of 30 months (range 3–55), 11 patients had died. The most frequent cause of death was lymphoma (seven patients; 63.6% of deaths), while four (36.4%) deaths occurred in patients with no signs of lymphoma recurrence.

Other events for the definition of time-related endpoints included 23 patients with treatment failure (less than CR) and 10 relapses. The 3-year OS and 3-year FFS were 92% and 73%, respectively. Survival curves are shown in Figure 2.

PET use and results

Overall, 324 PET scans were carried out, i.e. 2.38 examinations per patient (2.51 if only patients with at least one PET are considered). All PET scans were performed using the PET-CT technique. A baseline PET scan was performed in 112 patients (82%); a mid-treatment PET scan was done in 89 (65%)

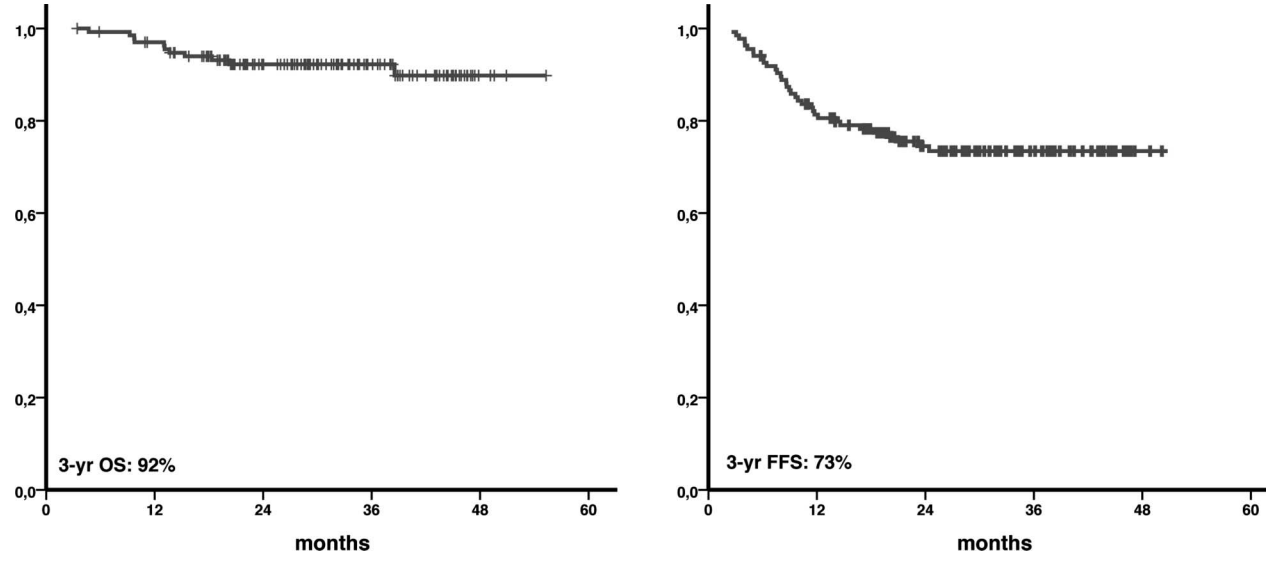

Figure 2. Three-year OS and FFS.

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patients; and I-PET was done after cycle 2 or 3 in 80 and nine cases, respectively. At the end of chemotherapy, a PET scan was performed in 100 (73%) patients; among 72 patients who underwent radiotherapy, 41 had a PET scan at the end of treatment. The overall final assessment of response was performed with PET in 116 patients (85%). Three PET scans (B, I, and F) were performed in 72 (53%) patients, two PET scans (B + I or B + F or I + F) in 43 (32%), and only one PET scan in 13 (10%); in eight patients no PET scan was performed. The use of I-PET was quite homogeneous among CReg, with the exception of Ferrara where no I-PET was done due to the local policy. The use of I-PET was more frequent in patients who were enrolled in a clinical trial ($p = 0.014$) and showed a significant inverse correlation with age (p for trend = 0.002; data not shown).

B-PET was positive in all 112 patients. I-PET was evaluated in 89 patients; 67 patients were clearly negative (75%) and 14 patients clearly positive (16%); in eight patients PET provided an indefinite result (9%). F-PET was evaluated in 116 patients; 100 patients had a clearly negative (87%) and 15 patients a clearly positive (13%) result; in one patient the F-PET was inconclusive. Patients with an indefinite result of I-PET and F-PET were excluded from subsequent analysis. At univariate analysis no factors were found for predicting positive mid-PET; advanced disease (OR = 14.2, 95% CI 1.81–112) and the presence of systemic symptoms (OR = 4.12, 95% CI 1.33–12.8) were predictive of a final positive PET. Interestingly, the final PET results were used to define CR in 37 cases that showed residual masses at CT scan according to recently updated response criteria [6].

B-, I-, and F-CT scan was performed in 130 (98.5%), 67 (51.9%), and 111 (86.7%) patients, respectively. B-PET and B-CT scans were available for comparison in 106 patients. PET and CT scans for mid- and final response assessment were available in 43 and 93 patients, respectively. At baseline, the agreement in staging between CT and PET analysis was 78%, with a kappa statistic of 0.572 (standard error 0.068, $p < 0.001$), which was a moderate agreement on the basis of the Landis and Koch interpretation. Overall, the PET scan allowed identification of a higher median number of nodal sites compared with CT (2.83 vs. 2.38; Wilcoxon matched pairs rank test $p < 0.001$). Discordance in the definition of spleen involvement was found in 11% of cases. In 23 cases the PET results would have caused a modification in disease stage, and in 20 patients stage modification would have caused a change in treatment approach. In particular, 50%, 12%, and 23% of stages I, II, and III disease were upstaged by PET, respectively, while 14% and 25% of patients with stages III and IV were downstaged, respectively (Table II). At the end of therapy (chemotherapy ± RT) the agreement between F-CT and F-PET was 58%, with a kappa statistic of 0.196 (standard error 0.083, $p = 0.009$), corresponding to slight agreement.

Treatment and survival data

Overall, in four patients, the actual treatment was modified compared to the planned initial treatment after interim response assessment. Only one patient with positive I-PET and initially treated with ABVD was shifted to BEACOPP, while two patients changed from BEACOPP to ABVD apparently due to toxicity; both were I-PET negative. One patient was treated with four cycles of BEACOPP and then changed to ABVD after two consecutive negative PET scans (after cycles 2 and 4). None of these patients were enrolled in a clinical trial. None of these patients was considered for assessment of the prognostic role of I-PET.

Univariate survival analyses were performed to search for prognostic factors for OS and FFS. The results are shown in Table III. Interestingly, I-PET was predictive of FFS (Figure 3) and F-PET was predictive of OS (Figure 4).

Discussion

In the present article we report the results of a population-based study in a large series of recently diagnosed patients with HL. The aims of the study were to describe how PET is currently used in daily practice and outside clinical trials and to understand whether the prognostic role of PET is confirmed also in this setting.

Our results show that since 2006 CT-PET has been widely adopted in patients with HL. Approximately 74% of patients underwent baseline and final PET and in a lower proportion of 65% of patients

Table II. Comparison of stage definition according to CT or PET scan.

	Stage at CT				
Stage at PET	I	II	III	IV	Total
I	2	0	1	0	3
II	1	49	2	5	57
III	1	3	14	1	19
IV	0	4	5	18*	27
Total	4	56	22	24	106

*Ten patients with bone marrow involvement are included among stage IV patients.
CT, computed tomography; PET, positron emission tomography.

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Table III. Univariate analysis for FFS and OS.

Factor	Status	*n*	3-year FFS (%)	HR	95% CI	3-year OS (%)	HR	95% CI
Age	<45	87	71	1.0		95	1.0	
	≥45	49	75	0.88	0.44–1.75	87	2.2	0.67–7.20
Gender	M	70	69	1.0		92	1.0	
	F	66	76	0.74	0.38–1.43	92	1.26	0.38–4.13
Bulky	–	95	75	1.0		92	1.0	
	+	41	67	1.34	0.68–2.64	92	1.3	0.38–4.43
Advanced stage	I–IIA	58	87	1.0		98	1.0	
	IIB–IV	77	61	3.52	1.54–8.02	88	7.55	0.96–58.9
Clinical trial	No	125	73	1.0		92	1.0	
	Yes	10	69	1.11	0.43–2.85	94	0.66	0.08–5.19
BM biopsy	–	128	74	1.0		94	1.0	
	+	7	57	2.36	0.72–7.72	57	9.23	2.43–35.1
Symptoms	A	84	80	1.0		95	1.0	
	B	51	59	2.27	1.17–4.38	88	2.94	0.86–10.0
I-PET*	–	87	81	1.0		98	1.0	
	+	14	29	5.33	2.23–12.8	85	4.43	0.61–31.9
I-CT	–	15	71	1.0		93	1.0	
	+	50	62	1.38	0.46–4.11	87	2.04	0.25–16.6
F-PET*	–	100	86	–	–	98	1.0	
	+	15	–	–	–	68	14.2	3.25–61.8
F-CT	–	54	83	1.0		96	1.0	
	+	56	56	3.68	1.65–8.21	87	4.6	0.96–22.0

*Only patients with clearly positive or negative scan were considered.
FFS, failure free survival; HR, hazard ratio; CI, confidence interval; OS, overall survival; BM, bone marrow; PET, positron emission tomography; CT, computed tomography; F, at treatment end; I, interim.

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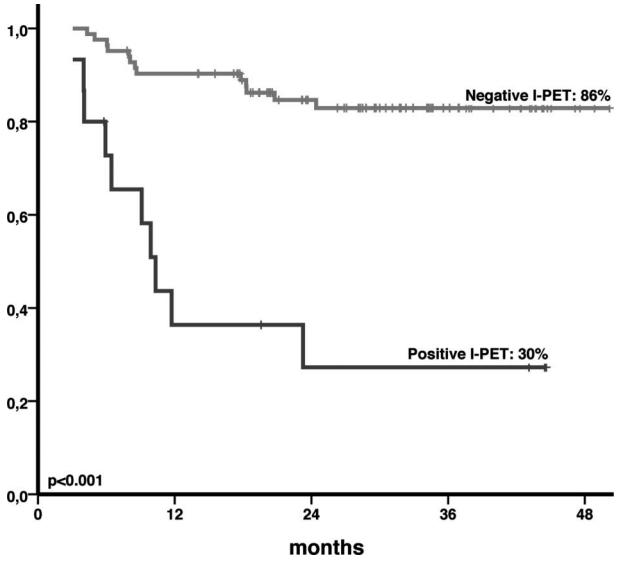

Figure 3. Three-year FFS by I-PET.

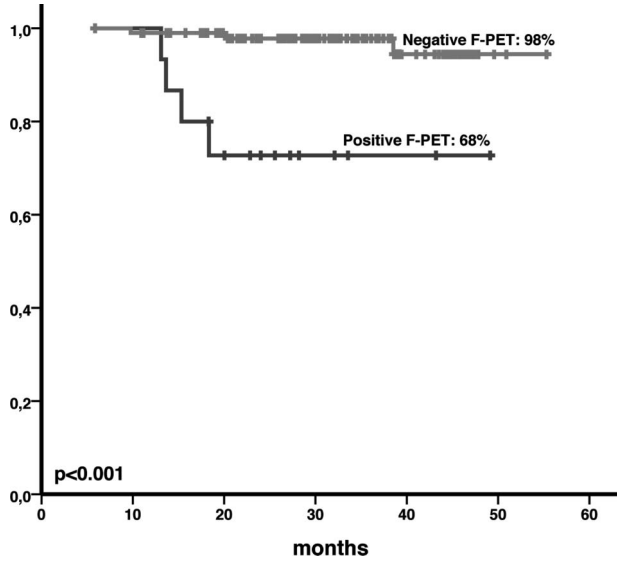

Figure 4. Three-year OS by F-PET.

PET was also used for early assessment of response. When this study was started, concerns were raised about the possibility that available data on the prognostic role of early PET assessment [7,8] would be inappropriately used, before a formal validation, to drive treatment decisions in patients who were treated also outside clinical trials [6]. Based on our results we can conclude that the risk of using PET results to drive therapeutic decisions was low. Actually, I-PET was prescribed in approximately half of the cases and more frequently in patients who were enrolled in a clinical trial; moreover, in one of the four analyzed CReg, I-PET was never done because this was not allowed due to the local policy.

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Interestingly, then, only four patients modified their planned treatment based on I-PET results, and most of these changes were toward treatment de-intensification (ABVD after BEACOPP in three cases) rather than toward intensification (BEACOPP after ABVD in one case). This finding was quite unexpected and may confirm that, at least in our region, there are still some concerns about the safety of the BEACOPP regimen.

Another finding from our study comes from comparison between the results of PET and of conventional CT scans. This was performed in a smaller group of patients who underwent the two procedures in the same treatment phase. Our results seem to confirm that the correlation between the two procedures varies from moderate to weak when defined at baseline or at the end of treatment, respectively. In particular, PET was more accurate than CT in defining the number of nodal areas and spleen involvement, and may bring about the need for more intensive treatment in a relevant proportion of cases. A lower correlation, as expected, was found comparing PET and CT results at the end of treatment; interestingly, PET results were used to define response in 37 cases that would have been classified as PR if only a CT scan was available. We believe that this feature needs to be further explored to correctly define the role of the CT scan in the era of PET. In our trial we also attempted to define whether the presence of a residual CT mass larger than 1.5 cm among patients with a negative final PET scan could represent a prognostic factor. The low number of patients analyzed did not allow any definitive conclusion; this issue also need further investigation.

Finally, we analyzed the prognostic role of PET results in our series of patients with HL. Before discussing our results we should acknowledge that PET scans in our study were coded according to local interpretation of the study report. This choice was taken to provide a better picture of what happens in daily practice where most clinical decisions are taken on the basis of examination reports and without a retrospective formal centralized review. It is then possible that a clear-cut distinction between clearly positive and clearly negative cases is lacking, and that some cases with minimal residual uptake are incorrectly coded. For these reasons and considering that a consensus on the rules for coding PET results is still lacking, all study analyses were limited to clearly positive and clearly negative scans only. This choice mainly affected interpretation of the I-PET results where eight cases were classified as inconclusive, and had a minimal effect on F-PET (one case). Based on this assumption our findings show that patients with a clearly positive early PET scan have a poorer FFS compared with those with a clearly negative scan. As a new important finding, we can describe a prognostic role of the F-PET result for OS, which to our knowledge has not been described before.

Different from the report by Gallamini *et al.* [16], we were able to study the prognostic role of I-PET in all patients and not only in those with advanced disease: the inclusion of both early and advanced cases may explain the better outcome observed in our study for patients with positive I-PET, compared to the Gallamini report assuming that patients with early disease and a positive I-PET have a better outcome than those with advanced disease [17], or, less likely, that a higher rate of false-positive scans may occur in early stages.

The use of cancer registries for performing clinical studies is the best strategy to assess the real impact of a new finding or procedure and to try to validate with a stronger methodological approach the results of prospective studies or clinical trials. Actually, cancer registries can provide patient series that are not or are minimally affected by biases from patient selection, typical of retrospective studies. Moreover, patients identified from CReg are mostly patients who were not enrolled into a clinical trial and are then a better picture of the 'real world.' Unfortunately, the excellent representation provided by population-based studies can be counterbalanced by a lower complexity of analyses that can be performed, compared with prospective studies. This limit can be partly overcome by providing cancer registries with dedicated teams and research programs for high-resolution studies on specific disease subsets.

In conclusion, PET is widely used for patients with HL in daily practice and provides additional information compared to the CT scan both for staging and for response assessment. Though the use of PET is still an open field for research and its use outside clinical trials cannot be encouraged, our study confirmed that also in the 'real world' patients with a negative I-PET have a better FFS compared with those with a positive scan; in addition, the results of F-PET can be used to predict OS.

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