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Real-life study on the use of response adapted therapy in patients with Hodgkin Lymphoma: Results from a multicenter experience

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Abstract

Few data are known regarding the use of interim positron emission tomography (iPET) after the first two cycles (iPET2) of chemotherapy in treatment-naïve classical Hodgkin lymphoma (cHL) in routine clinical practice, and about the real-life adoption of intensification strategies for iPET positive patients. We conducted a multicenter retrospective study on cHL to investigate the use of iPET in the real-life setting, its prognostic role and outcomes of patients early shifted to intensification. Six hundreds and forty-one patients were enrolled (62% had advanced stage). iPET2 was positive in 89 patients (14%) including 8.7% and 17% early and advanced stage patients, respectively ($p = 0.003$). Among iPET 2 positive cases treatment was immediately modified in 19 cases; in 14 cases treatment was modified after an additional positive iPET4. Overall 56 iPET2 positive patients never received intensified therapies. Most frequently used intensified therapy was autologous stem cell transplantation followed by BEACOPP. After a median follow-up of 72 months, the 5-year progression-free survival (PFS) was 82% with iPET2 positive patients showing a worse PFS compared with iPET2 negative cases: 31% versus 85%. Focusing on advanced stage patients with a positive iPET2, the 5-year PFS was 59% for patients shifted to intensified therapy at any time point versus 61% for patients who never received intensified therapy. Our study confirmed the higher curability of naïve cHL patients in a real-world setting, and the prognostic role of iPET2 in this setting. A poor adherence to response-adapted strategy which however did not translate into a difference in patient outcomes.

KEYWORDS
Hodgkin Lymphoma, PET, real-world experience, response adapted therapy

1 | INTRODUCTION

Classical Hodgkin Lymphoma (cHL) is a rare disease, which mainly affects adolescents and young adults.[1] ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) and escalated BEACOPP (escBEACOPP: bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone) have been the most widely used first-line chemotherapy regimens.[2] For decades, many attempts have been made to identify patients at high-risk of progression after ABVD and to reduce long-term treatment-related toxicities among treated patients.[3] The concept of interim positron emission tomography (iPET) emerged in the last 15 years for analyzing the evolution of metabolic response during treatment.[4] When performed after two cycles (iPET2), PET allows for evaluating the response identifying early responding chemosensitive patients. When performed after four cycles (iPET4), it identifies late responding patients as well as tumor regrowth (patients with iPET2 negative after two cycles but iPET4 positive). iPET2 thus provides the opportunity to adapt the treatment to the intermediate response: on the one hand to de-escalate the treatment of chemosensitive patients (negative iPET2) in order to limit long-term toxicity with satisfactory tumor control, and on the other hand to escalate the treatment of slow responder patients (positive iPET2) and reverse their poor prognosis. To note, the predictive role of iPET2 in cHL treatment outcome was confirmed using the interpretation criteria of the Deauville five-point scale, in particular for advanced stage patients.[5–7]

De-escalation approaches are supported by well-designed and well-sized randomized clinical trials which were able to confirm the non-inferiority of such alternative approaches if compared to standard therapy.[6,8–13]

Different from de-intensification programs, the evidence supporting escalation program is only based on non-randomized prospective studies and the better efficacy versus conventional approaches has not been clearly demonstrated so far. Nevertheless, most of the available guidelines support the adoption of more intensive therapies for patients without an early complete metabolic response after ABVD.[14–20]

However, few data are known regarding the use of iPET2 in routine clinical practice, and in particular about the real-life adoption of intensification strategies for iPET positive patients, including frequency and type of intensification therapies and related outcomes and, thus, making considerations in this regard difficult.[21–25] In addition, most studies (both clinical trials and real-life observational research) have been referred to advanced stage patients and, thus, possible improvements from additional research need to be investigated.

With the aim to investigate the use of iPET in the real-life setting, its prognostic role and outcomes of cHL patients early shifted to intensification, we conducted a multicenter retrospective study collecting consecutive cHL patients initially treated with ABVD for whom iPET2 was available with a detailed focus on advanced stage cases.

2 | MATERIALS AND METHODS

We have conducted an observational, retrospective, multicenter Italian study on newly diagnosed cHL patients treated between January 2010 and December 2018. Patients aged 18–80 years could be enrolled if treated with ABVD/ABVD-like schemes and if both baseline and iPET2 scans were available.

The study was approved by the institutional board of the Coordinator (Ethical Committee [EC] Milano Area 3, approval id 167-08032022) and by the EC of all participating Centers. All patients gave written informed consent (when applicable) in accordance with the Declaration of Helsinki to retrospectively collect their data. As for the retrospective design of the study, we received an authorization to analyze data also of patients who were deceased or lost to follow-up at the time of data collection.

The primary endpoint of the study was the calculation of the frequency of early intensification based on the iPET2 outcome, expressed as a percentage frequency with a 95% binomial confidence interval (CI).

Secondary endpoints of the study were the evaluation of the clinical outcomes of iPET2 positive patients in terms of response to induction and intensification therapy, progression-free survival (PFS) and overall survival (OS) and the evaluation of the different types of early intensification in a real-life setting with a focused analysis on advanced stage patients. Patients were divided in early and advanced stage based on their stage and symptoms at diagnosis: patients with stage I-IIA were defined as early-stage while were considered in advance stage patients with stage from IIB to IV.

PET was defined as positive or negative based on assessment by the local investigator. Deauville score (DS) was also collected and PET scan with DS 1–3 were considered negative, whereas PET scan with DS 4 or 5 were considered as positive. No formal central review was done, however the imaging procedures were standardized and harmonized in all the study sites as a part of the qualification procedures requested by Fondazione Italiana Linfomi, of which all the participating Centers are members.

PFS was defined as the time between the date of iPET2 to the date of progression or death for any cause or last clinic control for censored cases. OS was calculated from the date of iPET2 to the date of death for any cause or last clinic control.

We identified four sub-groups: iPET2 negative patients, iPET2 positive patients for whom therapy was not changed, iPET2 positive patients for whom therapy was changed immediately and iPET2 positive patients for whom therapy was changed after a further positive PET (iPET4). For further analysis, iPET2 positive patients for whom therapy was changed after a positive iPET4 and iPET2 positive patients for whom therapy was never changed were considered as one single cohort comparing it with the cohort of iPET2 positive patients for whom therapy was changed immediately.

To minimize bias, a shared data dictionary for each variable was provided to all the participating Centers.

Continuous covariates were summarized as median, interquartile distance (IQR) and range, categorical variables were summarized as absolute and percentage frequencies.

The distribution of continuous covariates was compared between two patients' sub-groups (iPET2 positive and iPET2 negative) using the Mann-Whitney test or by Kruskal-Wallis test for more of two groups of comparison.

Comparison by groups for categorical variable was performed using the Fisher's exact probability or chi-squared test, when appropriate.

Measure of associations as odds ratio (OR) were also estimated between clinical characteristics and iPET2 results. The survival functions were computed by means of Kaplan–Meier method, with its 95% CI. Comparisons between groups were done using the log-rank test or Gehan–Breslow–Wilcoxon test as applicable; the effect of covariates was estimated using the Cox proportional hazard regression model and was expressed as hazard ratio (HR), with a 95% CI.

All tests were two-sided and a p value of less than 0.05 was considered statistically significant. Statistical analyses were performed with Stata 17 (StataCorp LP, TX).

3 | RESULTS

3.1 | Whole study population characteristics and treatment modification after iPET2

Six hundreds and forty-one patients were enrolled, with a median age of 37 years (range 18–86). Fifty-two percent were males (n = 336) and 62% (n = 399) had an advanced stage disease (IIB-IV). Patients' characteristics are detailed in Table 1.

Overall, iPET2 was reported as positive in 89 patients (14%) including 21 out of 242 (8.7%) and 68 out of 399 (17%) early and advanced stage patients, respectively (p = 0.003).

Advanced stage at diagnosis was significantly associated with a higher probability of iPET2 positivity (OR 2.16, p = 0.004), while age, International Prognostic Score, B symptoms and sex were not.

After a positive iPET2, treatment was immediately modified in 19/89 cases: nine patients were intensified to escBEACOPP, eight to chemotherapy followed by autologous stem cell transplantation (ASCT) and two to other (unspecified) salvage regimens. Intensified therapy was administered in two out 21 (9.5%) iPET2 positive early-stage patient and in 17 out 68 (24.6%) iPET2 positive advanced stage patients. Among the 70 iPET2 positive patients who did not receive intensified treatment (19 early stage and 51 advanced stage patients) ABVD was administered for two additional courses in all cases and an additional iPET4 was done in 39 patients, resulting positive in 23 and negative in 16 of the cases. Among the 19 early stage iPET2+ cases iPET4 was done in 10 patients and was still positive in eight ones; however none of these iPET2+ early-stage patients received an intensified therapy after iPET4 regardless of metabolic response. Conversely among the 51 advanced stage patients iPET4 was done in 29 cases and was still positive in 15. Intensified regimen was administered to 14 of these advanced stage iPET4+ cases. Intensification after iPET4 was done with chemotherapy followed by ASCT in eight cases and with esc BEACOPP in 2 cases: additional four patients underwent brentuximab vedotin (two BV), DHAP (one, without ASCT consolidation) and radiation therapy (RT) (one). Overall, 56 iPET2 positive patients never received intensified therapies.

After a median follow-up of 72 months (95% CI 68–76) the 5-year PFS in the 641 patients was 82% (95% CI 79%–85%). iPET2 positive patients showed a worse 5-year PFS compared with iPET2 negative cases: 31% versus 85% (HR 3.16, 95% CI 2.15–4.64, $p < 0.001$). The 5-year OS was 95% (95% CI 93%–97%), with worse survival in iPET2 positive patients: 85% versus 97% (HR 3.37, 95% CI 1.74–6.54, $p < 0.001$) (Figure S1 and S2).

3.2 | Advanced stage patients

3.2.1 | Patients characteristics

Considering the cohort of advanced stage cHL (n = 399), the median age was 38 years (range 18–86). Fifty-six percent were males and 72% had B symptoms. Full patients' characteristics are detailed in Table 1.

iPET2 was positive in 68 cases (17%). DS was available in 35 out of the 68 iPET2 positive cases: it resulted as 4 in 25 and 5 in 10 patients respectively.

After a median follow-up of 6.0 years (IQR 4.4–8.2 years), 103 events were registered for PFS including 68 relapses/progressions and 35 deaths; the resulting 5-year PFS was 76% (95% CI 72–80), while the 5-year OS was 94% (95% CI 91–96).

3.2.2 | Univariate analysis of survival

In univariate analysis of PFS, early metabolic response at iPET2 was associated with a significant different risk of progression: the 5-year PFS for iPET2 negative and iPET2 positive patients were 80% (95% CI 75–84) and 60% (95% CI 47–71), respectively (HR 2.26 [1.46–3.50], $p < 0.001$) (Table 2, Figure 1A). Other covariates with a significant association with PFS are shown in Table 2. The prognostic role of iPET2 was retained also after adjusting for age, stage and RT ($p < 0.001$).

In univariate analysis of OS, early metabolic response at iPET2 was associated with a different probability of survival: the 5-year OS for iPET2 negative and iPET2 positive patients were 96% (95% CI 93–98) and 82% (95% CI 70–90), respectively (HR 2.90 [1.44–5.83], p = 0.003, Table 2, Figure 2A). The HR after adjusting by age, stage and RT was 3.54 (95% CI 1.69–7.41, p = 0.001), thus maintaining also for this survival the prognostic role of iPET2. Other covariates with a significant association with OS are shown in Table 2.

TABLE 1 Patients' characteristics.

Characteristics		All study population ($n = 641$)	Advanced-stage patients cohort ($n = 399$)
Age, years, median (range)		37 (18–86)	38 (18–86)[a]
		n (%)	n (%)
Age, years	≤45	412 (64)	247 (62)
	45–60	131 (20)	87 (22)
	>60	98 (15)	65 (16)
Sex	M	336 (52)	222 (56)
	F	305 (48)	177 (44)
IPS[b] $n = 560$	0/2	384 (69)	198 (55)
	3/7	176 (31)	162 (45)
Stage	I	33 (5)	-
	II	305 (48)	96 (34)
	III	149 (23)	149 (37)
	IV	154 (24	154 (39)
Symptoms	A	352 (55)	113 (28)
	B	289 (45)	286 (72)
Advanced (IIB/IV)	No	242 (38)	NA
	Yes	399 (62)	399 (100)

Abbreviation: IPS, International Prognostic Score.

[a]Only 1 86-year-old patient aged, treated with ABVD and iPET2 negative. He did not modify the treatment and it was alive at the last follow-up. All the other patients respected all inclusion criteria.

[b]$n = 560$.

3.2.3 | Survival analysis of iPET2 positive patients

The 5-year PFS was 59% for iPET2 positive patients with immediate intensification versus 61% for patients who didn't undergo an immediate change of treatment ($p = 0.851$) (Figure 1B).

The 5-year OS was 84% for patients with immediate intensification versus 81% for patients who didn't change treatment immediately after the positive iPET2 ($p = 0.520$) (Figure 2B).

From the end of induction, iPET negative showed a better outcome (Figure 3A,B), while no statistical difference was observed for both PFS and OS ($p = 0.424$ and 0.450 for PFS and OS, respectively) (Figure 3C,D) comparing patients who have never received intensified therapy after a positive iPET2 with patients who received an intensified therapy at any timepoint after the first iPET2 positivity (either after iPET2 or iPET4).

4 | DISCUSSION

This multicenter experience in naïve cHL describes the use of iPET, the frequency of iPET positivity and the percentage of intensification in a real-life setting in the era of the PET-response adapted therapy. Our results follow what has recently been reported in other studies regarding the use of iPET and its real use as a method to direct the patient to a path of early intensification.[14–19] Remarkably, in our experience a significant proportion of patients, in the face of a positive iPET, did not change therapy. In fact, overall, only 21.3% of iPET2 positive patients received immediate intensification and in a significant proportion of cases the decision to intensify treatment was postponed after 2 additional ABVD courses. Moreover, looking at intensified regimen, ASCT was more frequently used than BEACOPP. Considering the landmark survival analysis for the date of iPET, the different approach to iPET2 positive cases was not associated with different outcomes. These results should be taken with caution due to the few patients analyzed and to the high CI of survival measures and cannot be used to recommend against the use of treatment intensification in iPET2 positive patients. However, these data require a careful discussion to highlight some possible limitation of currently used approaches.

The observation of frequent deviations from the general rule of treatment intensification for all iPET2 positive cases may have some explanations. Lacking randomized evidence, the early exposure to a toxic regimen such escBEACOPP has to compare with how early metabolic response has been evaluated and interpreted by clinicians in this real-world analysis. In most centers included in this study, case by case multidisciplinary discussion has been adopted likely allowing to include in the assessment additional parameters compared to the

TABLE 2 Univariate analysis with progression-free and overall survival in the cohort of advanced stage patients.

Group		n (events)	5-year PFS (95% CI)	HR (95% CI)	*p*
Overall PFS		399 (103)	76 (72–80)	-	-
PET2	Negative	331 (75)	80 (75–84)	1.00	
	Positive	68 (28)	60 (47–71)	2.26 (1.46–3.50)	<0.001
IPS[a]	0/2	198 (42)	80 (74–85)	1.00	
	3/7	162 (49)	74 (66–80)	1.45 (0.96–2.18)	0.079
Sex	M	222 (62)	74 (68–80)	1.00	
	F	177 (41)	79 (73–85)	0.85 (0.58–1.27)	0.432
Stage	IIb/III	245 (54)	80 (74–85)	1.00	
	IV	154 (49)	71 (63–77)	1.59 (1.08–2.33)	0.020
Age	≤45	247 (61)	76 (71–81)	1.00	
	45–60	87 (18)	80 (70–87)	0.84 (0.50–1.43)	0.530
	>60	65 (24)	70 (56–81)	1.55 (0.96–2.48)	0.071
Age, continuous[a]	(Age-40)/10			1.12 (1.00–1.25)	0.051
Symptoms	A	113 (27)	80 (71–86)	1.00	
	B	286 (76)	75 (70–81)	1.20 (0.77–1.85)	0.426
Radiotherapy[b]	No	280 (81)	74 (69–79)	1.00	
	Yes	115 (19)	84 (76–90)	0.52 (0.32–0.86)	0.010
Overall OS		399 (35)	94 (91–96)	-	-
PET2	Negative	331 (23)	96 (93–98)	1.00	
	Positive	68 (12)	82 (70–90)	2.90 (1.44–5.83)	0.003
IPS[c]	0/2	198 (9)	98 (93–99)	1.00	
	3/7	162 (20)	9 (86–95)	2.79 (1.27–6.12)	0.011
Sex	M	222 (26)	91 (86–94)	1.00	
	F	177 (9)	97 (93–99)	0.44 (0.21–0.94)	0.033
Stage	IIb/III	245 (17)	97 (93–98)	1.00	
	IV	154 (18)	90 (83–94)	1.88 (0.97–3.64)	0.063
Age	≤45	247 (9)	97 (93–98)	1.00	
	45–60	87 (7)	96 (90–99)	2.36 (0.87–6.33)	0.089
	>60	65 (19)	77 (63–87)	10.1 (4.56–22.5)	<0.001
Symptoms	A	113 (10)	95 (89–98)	1.00	
	B	286 (25)	93 (89–96)	1.03 (0.50–2.15)	0.930
Radiotherapy[d]	No	280 (29)	93 (89–95)	1.00	
	Yes	115 (4)	97 (91–99)	0.33 (0.12–0.94)	0.037

Note: Events for PFS included progression of disease or death due to any cause, events for OS included only deaths due to any cause.

Abbreviations: CI, confidence interval; HR, hazard ratio; IPS, International Prognostic Score; OS, overall survival; PET, positron emission tomography; PFS, progression-free survival.

[a]*N* = 360 (91events).

[b]*N* = 395 (100 events).

[c]*N* = 360 (29 events).

[d]*N* = 395 (33 events).

use of metabolic response only. Unfortunately we were not able to define the individual role of additional parameters in the evaluation of single parameters, and the qualitative definition of DS was not available for all cases. Starting from our observation we believe our data suggests that reducing treatment decision to the assessment of one single parameter such DS, even if feasible in the setting of a

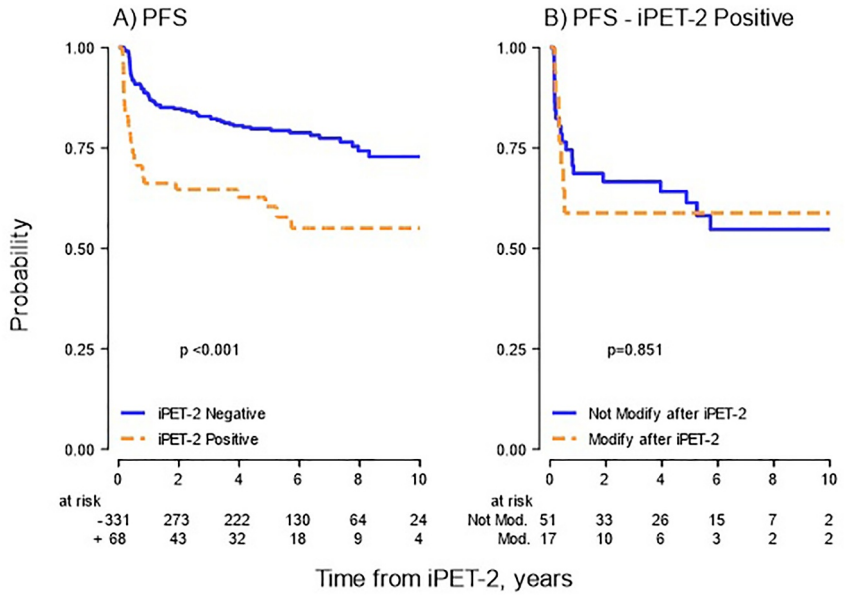

FIGURE 1 Progression-free survival. (A), iPET2 negative versus iPET2 positive advanced stage patients (B) iPET2 positive advanced stage patients: modified treatment versus no modified treatment.

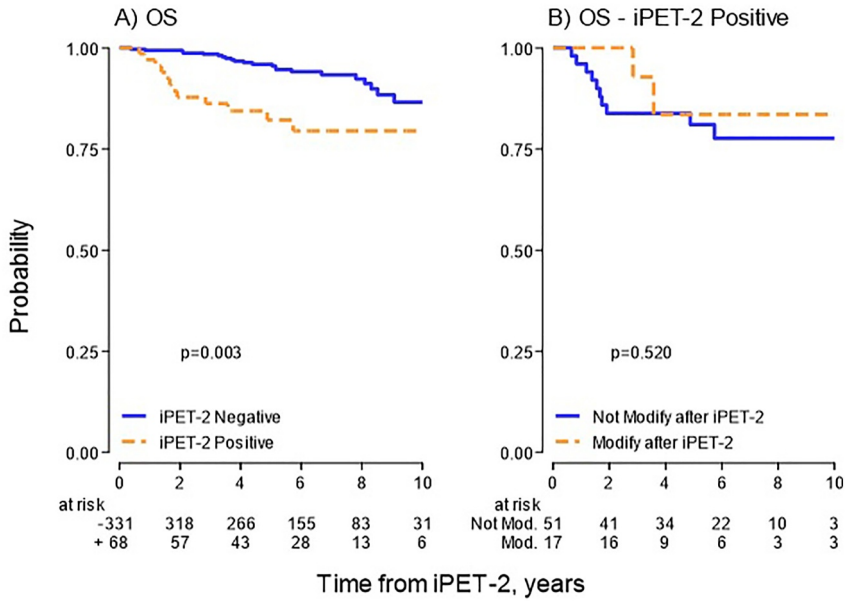

FIGURE 2 Overall survival. (A), iPET2 negative versus iPET2 positive advanced stage patients (B) iPET2 positive advanced stage patients: modified treatment versus no modified treatment.

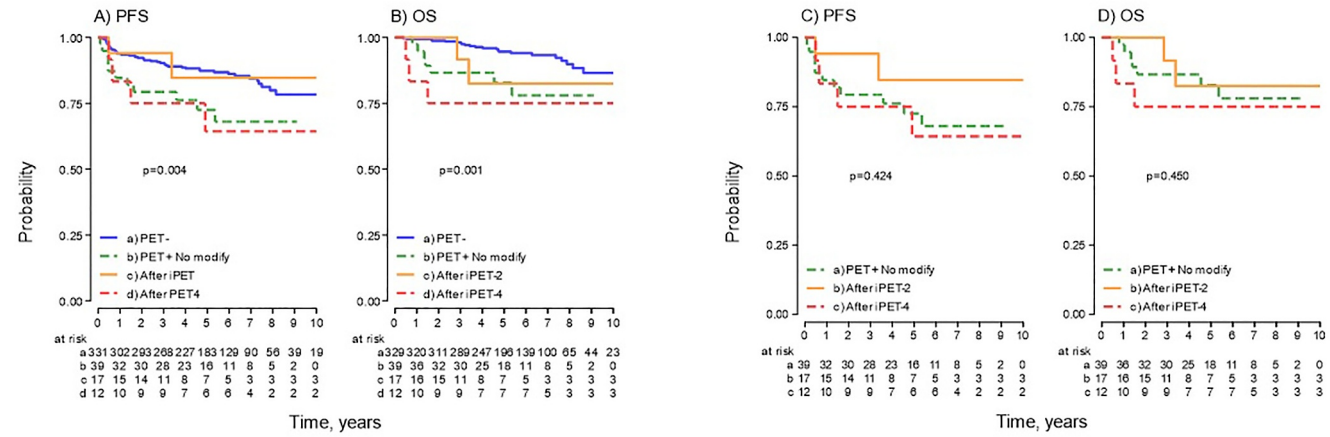

FIGURE 3 Progression-free survival and overall survival according to adopted strategy after iPET2 positive in advanced stage patients.

clinical trial, is likely an oversimplified approach when moved to the real world. In addition, recent data highlighted some limitation of the accuracy of DS as prognostic factor. Mainly due to technology advancements made with FDG-PET, the higher sensitivity of modern scanners is likely moving the definition of metabolic persistence of disease to the DS 5 leaving the cases with a score 4 to an area of uncertainty.[26]

Finally considering the more frequent use of ASCT instead of BEACOPP as intensified regimen for interim PET positive patients, this observation likely mirrored the management of patients as done in the HD0801 study which had been adopted in several centers in Italy.[18] Moreover the use of ASCT to intensify iPET positive cases after cycle 4 suggests that clinician interpreted persistence of disease as failure of induction therapy.

Limitations of our study include its retrospective nature and the lack of central review for iPET. Furthermore, due the low frequency of patients who are iPET2 positive and the wide CIs, makes it is also possible that small differences were not detected.

Based on our results iPET positivity is confirmed as a strong prognostic factor but its predictive role is questioned. Compared to the first data about the prognostic role of early response subsequent validation studies showed lower positive predictive value and better outcomes of iPET positivity.[4,27] Nevertheless comparing available study for patients initially treated with ABVD, response adapted therapies were not able to eliminate the risk of treatment failure associated with lack of early response. Also based on what we were able to observe in our study, we believe that rather only focusing on intensifying iPET2 positive cases a more reasonable strategy should be to reduce the rates of iPET2 cases. This has been achieved using intensified therapies upfront but at the cost of high toxicity (e.g., escBEACOPP).[28,29] More recently the incorporation of novel agents in the front line ABVD backbone as CPIs or BV have showed that it is possible to increase the efficacy of first line HL therapy without a detrimental effect of the patients safety.[17,30–32] Of note none of these recent trials included a response adapted approach in the design of the experimental therapy, leading to a wrong conclusion that treatment personalization could be abandoned. A return to the one size fits all approach in HL, even if resulting in an easier management of therapy, in our opinion represents an oversimplified approach.

In conclusion, in our series iPET has a strong prognostic value that was apparently not influenced by an early intensification strategy.

Our study highlighted some of the obstacles that might have had an impact on the use of the response adapted therapies in the real life. The management of high-risk patients remains an important field for clinical research. In this scenario response adapted therapy has the ability to optimize risk to benefit ratio of treatment and thus still has a useful role. With the recent improvement in the imaging technology with the promising data coming from the analysis of ctDNA and with more effective available therapies novel approaches to response adapted therapies shall be defined.

AUTHOR CONTRIBUTIONS

Vittorio Ruggero Zilioli, and Stefano Luminari conceived the study; Vittorio Ruggero Zilioli, Emanuele Cencini, and Stefano Luminari wrote the manuscript; Vittorio Ruggero Zilioli, Emanuele Cencini, Sonya De Lorenzo, Luca Pezzullo, Michele Merli, Flavia Rivellini, Cristina Muzi, Barbieri Emiliano, and Stefano Luminari provided study data; Luigi Marcheselli conducted all data analyses; all authors read and approved the final version of the manuscript after revising it critically. All authors have access to the final database.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflict of interest.

DATA AVAILABILITY STATEMENT

The data underlying this article are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The study was approved by Ethical Committee Milano Area 3, approval id 167-08032022 and was conducted in accordance with the Declaration of Helsinki.

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PEER REVIEW

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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