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ORIGINAL ARTICLE

# PET-adapted therapy for advanced Hodgkin lymphoma – systematic review

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**ABSTRACT**

**Introduction:** Positron emission tomography-computed tomography (PET-CT) performed after two chemotherapy cycles (PET-2) has become an accepted prognostic tool in Hodgkin lymphoma (HL). We evaluated the effect of PET-adapted strategy on outcome in advanced stage HL.

**Methods:** In August 2017, we searched electronic databases, conference proceedings and ongoing trials. We included all studies in which treatment modification for advanced HL was performed based on the results of the interim PET scan. The primary analysis included randomized controlled trials (RCTs). Outcomes were progression-free survival (PFS) and overall survival (OS).

**Results:** We identified 13 studies (4 RCTs, 7 phase II and 2 retrospective studies), conducted between 1999 and 2014, including 6856 patients. Of the four RCTS: one used therapy escalation, one did de-escalation and two trials performed both. Outcomes were assessed at different time point between 2 and 5 years. Three RCTs for de-escalating therapy, obtained similar outcomes despite reducing therapy, with a 2-year PFS of 88–92% (6 escalated BEACOPP (EB) vs. 4 ABVD cycles), a 5-year PFS of 91–92% (6/8 EB vs. 4 EB cycles) and a 5-year PFS of 80–82% (6 ABVD vs. omitting bleomycin after two successful ABVD cycles). Two RCTs implemented escalation. The randomization was between adding rituximab or not. In both trials, it did not affect outcome, with a 4-year PFS of 68–69% (addition of rituximab to BEACOPP after 2 ABVD cycles) and 5-year PFS of 88–90% (addition of rituximab to EB after 2 EB cycles). Performing true randomization between PET-adapted and a standard ABVD control arm was not feasible, given historical data.

**Conclusions:** This systematic review of PET-adapted therapy, mainly based on RCTs, suggests that a change to the treatment paradigm is appropriate in advanced HL.

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## Introduction

Therapy for advanced stage Hodgkin lymphoma (HL) may be challenging. The standard chemotherapy regimen used for the last two decades in the United States and in most parts of the world has been ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine) with an expected survival rate of approximately 70–80% for patients with advanced disease [1–3]. Studies from the German Hodgkin Study Group suggest that an intensified regimen of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone [escalated BEACOPP (EB)] might improve the results but is more toxic in most patients and might be associated with secondary myeloid neoplasms in a minority of recipients [4,5].

[F-18]-Fluorodeoxy-D-glucose (FDG)-positron emission tomography (PET) combined with computed tomography (CT) has been widely accepted as an imaging tool for tumor staging and response evaluation in lymphoma patients in recent years [6,7]. Establishing the metabolic response to treatment seems to generate more prognostic information than the radiological assessment alone [8,9]. Data from early studies suggest that interim PET-CT assessment during treatment with ABVD better predicts long-term treatment outcome than the baseline international prognostic score (IPS) [10,11]. PET scans showing persistent FDG uptake after two cycles of ABVD (PET-2 positive) seem highly predictive of ABVD treatment failure since only 15–45% of PET-2 positive patients who continue treatment with ABVD achieve long-term progression-free survival (PFS). On the other hand, a negative PET-2 scan is a strong predictor of favorable outcome with standard therapy in patients with advanced HL, with long-term PFS rates reaching 95% [9,12].

The main concept in response-adapted therapy is that the identification of a single early test or biomarker might predict outcome of treatment. By using this marker or test a distinction between those patients in whom treatment is beneficial from those in whom it fails can be done. A failing treatment warrants a modification, while a successful one, may permit a certain decrement, aiming to reduce risks of late toxicities without apparent loss of disease control.

Thus, interim PET can be used as a tool to guide therapy de-escalation or escalation in order to overcome

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overtreatment in good responders or under-treatment in poor responders, respectively.

The purpose of our study was to systematically review all published data, mainly those from randomized controlled trials (RCTs), in order to evaluate the effect of PET-adapted therapy on long-term outcomes including PFS and overall survival (OS) in patients with advanced-stage HL.

## Methods

### Data sources

Studies were identified by searching the Cochrane Central Register of Controlled trials register (CENTRAL; issue 05.2017) and PUBMED database (1990–2017). Full texts, abstract publications and unpublished data were considered, if sufficient information was available. Furthermore, abstracts from the annual conference proceedings of the following societies from 2012 to 2017 were searched: American Society of Hematology, American Society of Clinical Oncology, European Hematology Association, The International Conference on Malignant Lymphoma (ICML), and databases of ongoing and unpublished trials: http://www.controlled-trials.com/; http://www.clinicaltrials.gov/ct. We checked references of all identified trials, relevant review articles and current treatment guidelines for further literature.

We used the following search term: PET adapted or PET tailored or PET monitored or PET driven or therapy adapted or response adapted therapy or PET2 or interim PET and Hodgkin or Hodgkin's.

### Study selection

We included all studies in patients with advanced HL in which interim PET results served during induction treatment as a decision-making tool regarding treatment protocol. We included trials in which the interim PET was used for escalation (switching to a more aggressive protocol) or for de-escalation (switching to a less aggressive protocol).

For the main analysis, we included RCTs only, since this is the optimal design to assess the value of treatment modification on outcomes. For a secondary analysis, we included all other comparative and non-comparative trials, prospective trials with single arm compared with historical control, prospective cohort studies and retrospective studies.

Language restriction was not applied in order to reduce potential language bias.

### Data extraction and quality assessment

Two authors (IA and AG) independently screened the results of the search for eligibility criteria. Selected studies were independently screened by both authors to determine whether they meet the inclusion criteria.

For randomized trials we used the Cochrane Collaboration's tool to assess the following domains: random sequence generation, allocation concealment, blinding of participants and personnel (only for blinded studies included), incomplete outcome data, selective outcome reporting. Each domain and grade it as low risk of bias, unclear risk or high risk of bias according to the Cochrane collaboration [13].

For non-randomized trials, we assessed risk of bias according to ROBINS-I: a tool for assessing risk of bias in non-randomized studies of interventions [14].

The authors of published trials were contacted in order to get more information, if required.

### Outcomes

We used two primary outcomes: PFS and OS at the end of follow-up.

### Data synthesis and analysis

Due to paucity of studies and heterogeneous designs of studies, we could not perform a meta-analysis, hence studies were systematically reviewed.

## Results

### Description of studies

The literature search identified 559 studies. Of these, 38 were retrieved for further evaluation, and 28 were excluded for various reasons (Figure 1). Ten published studies met inclusion criteria in addition to three suitable abstracts from conference proceedings (with four updates). Thus, in total, we included 13 studies (in 17 publications), conducted between the years 1999 and 2014, and including 6856 patients (data presented in Supplement Table 1(a,b)). Four trials were RCTs (Supplement Table 1(a)). These included patients with stage IIb, III and IV disease, and one study included also stage IIa disease with adverse features [20]. One trial performed escalation of therapy if PET-2 was positive, one performed de-escalation if PET-2 was negative and two performed both escalation and de-escalation. In three trials, PET-2 was interpreted by Deauville's criteria, and in one by the International Harmonization Project (IHP). The primary outcome of all four was PFS (see Table 1). Outcomes were assessed between 16 and 55 months post treatment. Baseline regimens included ABVD [16,20] or EB [15,17–19]. Escalation schemes included various regimens of EB; two of them included randomization with or without rituximab [16–20]. De-escalation consisted of switching from EB to ABVD [15,20].

The other nine studies included: seven phase II trials and two retrospective studies (results presented in Table 2).

Quality assessment of included studies is presented in Supplement Table 2.

### Primary analysis: results of RCTs

#### Studies performing de-escalation therapy when PET-2 was negative

One RCT, the LYSA AHL 2011 study by Casasnovas et al., included 823 patients, and conducted a full randomization between standard therapy (regardless of PET-2 results) and

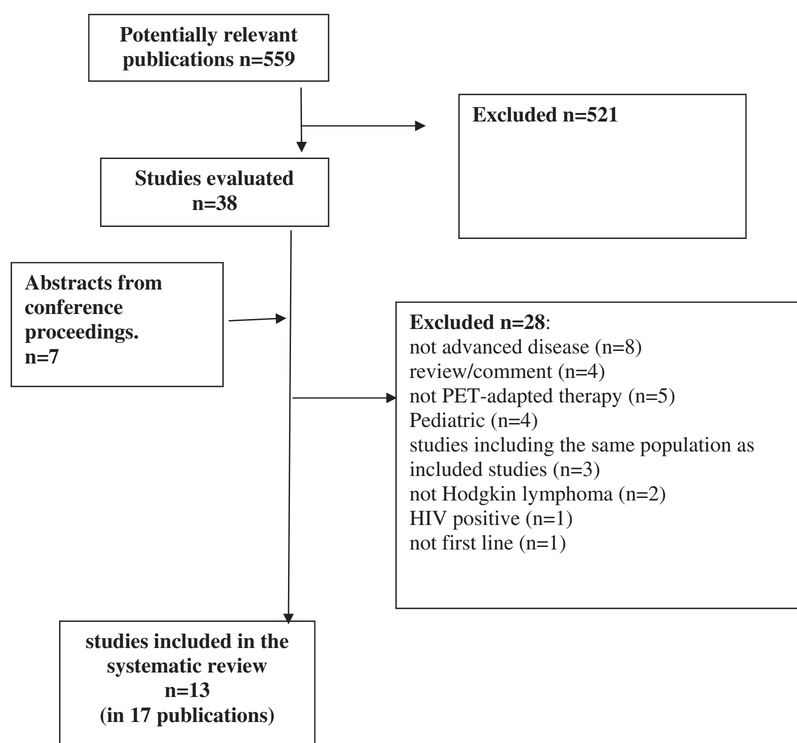


**Figure 1.** Flowchart of included studies according to PRISMA

PET-2 adapted therapy [15]. This trial is still ongoing and the interim analysis only was presented as an abstract. In the PET-adapted arm, after receiving two cycles of EB patients with a negative PET-2 received four ABVD cycles whereas in the standard arm, six cycles of EB were completed. Both arms had a similar (about 12–13%) frequency of PET-2 positive patients. With a median follow up of 16.3 months, the 2-year PFS was similar in the standard and experimental arms, regardless of the results of PET-2 (92% vs. 88%; $p = .79$). Overall, in both arms, patients with PET-2 positive disease had a lower 2-year PFS than patients with PET-2 negative disease (73% vs. 93%; $p < .0001$).

## *Studies performing therapy escalation when PET-2 was positive*

In the Italian GITIL/FIL HL 0607 trial [16], 782 patients were randomized and 500 were evaluated. Treatment was started with two cycles of ABVD in all patients. If PET-2 was positive, patients received four cycles of EB plus four cycles of baseline BEACOPP (BB) and were randomly assigned to the addition of rituximab or not. PET-2 negative patients received additional four cycles of ABVD. PET-2 was positive in 19.5% of patients. In this cohort, PET-2 positive patients were more frequently male, had higher IPS score and bulky disease. PFS at four years was 69% in the PET-2 positive arm compared to 87% in the PET-2 negative cohort [16]. The addition of rituximab did not affect outcome.

## *Studies performing both therapy escalation and de-escalation according to PET-2 results*

Two large RCTs, the HD18 trials and the RATHL trial, performed both escalation and de-escalation of therapy according to PET-2 results. In the HD18 study, 2101 patients were recruited in total. The first 1100 patients were recruited between 2008 and 2011 [17–19].

Of the 40% had a positive PET-2 ($n = 440$), which is substantially higher compared with the other studies, since a Deauville 5-point score of three was considered positive. All patients received initially two cycles of EB. PET positive residues after end of treatment were irradiated in all groups. PET-2 positive patients were randomized to completion of six more EB cycles, either alone or combined with rituximab. The addition of rituximab did not improve outcome, with a 5-year PFS of 90% in the eight cycles of EB arm (standard arm) vs. 88% in the experimental arm (8 cycles of EB with rituximab). In both PET-2 positive allocated groups, 5-year PFS was remarkably better compared to other studies. Recently, the authors presented the outcome of the 1005 PET-2 negative patients, who were randomly assigned to complete a full EB course or de-escalated to complete only four cycles of EB in total. Estimated 5-year PFS was 91% in the standard arm (6–8 EB cycles) and 92% in the experimental arm (4 EB cycles). The abbreviated treatment with four cycles of EB was associated with improved tolerability and led to a significant OS benefit over standard therapy (5-year OS of 98 vs. 95%, $p = .004$). The most frequent causes of death were second malignancies (11 patients in the standard arm and one patient in the experimental arm).

In the RATHL trial [20], randomization was carried out for de-escalation only. All patients ($n = 1214$) received two ABVD cycles, after which, those with negative PET-2 scans were randomized to either four cycles of ABVD or AVD (omission of bleomycin), while those with a positive scan, received BEACOPP (either four cycles of EB or six cycles of BEACOPP-14). Overall 84% had negative PET-2

Table 1. PET-2 results and outcomes of RCTs.

| Type, study name | Positive interim scan, % | PET interpretation method | Results | |
|---|---|---|---|---|
| | | | PFS/EFS/FFS | OS |
| **Therapy de-escalation if PET2 negative** | | | | |
| Casasnovas et al., AHL 2011, LYSA study NCT01358747 interim analysis 2015 phase III (abstract) [15] | 12% standard arm 13% experimental arm | DS DS >3 considered positive | 2-year PFS all PET-2 pos: 72.9% all PET-2 neg: 92.8% $p < .0001$ standard arm: 91.6% PET-2 pos: 75.1% PET-2 neg: 94% experimental arm: 88.3% ($p$=.79) PET-2 pos: 70.8% PET-2 neg: 91.6% $p < .0001$ for both | Reported similar in all groups |
| **Therapy escalation if PET2 positive** | | | | |
| Gallamini et al., GITIL/FIL HD 2017 Phase III (abstract) [16] | 19.5% | DS DS >3 considered positive | 4-year PFS PET-2 pos: 69% Standard arm: 69% Experimental arm: 68% ($p = .973$) PET-2 neg: 87% (patients with initial large nodal mass, $n = 296$: 93% in ABVD only arm vs. 96% in ABVD + RxT arm, $p = .288$) | 4-year OS PET-2 pos: 89% PET-2 neg: 97% |
| **Therapy escalation or de-escalation according to PET2 results** | | | | |
| Borchmann et al., HD 18, 2017 Phase III [17–19] | 52% (entire cohort, $n = 2101$) 44% (May 2008–June 2011, $n = 1100$) | IHP/DS DS >2 considered positive | 5-year PFS PET-2 pos (May 2008–June 2011) $n = 434$: standard arm: 89.7% experimental arm: 88.1% PET-2 neg: standard arm: 90.8% experimental arm: 92.2% 3-year PFS PET-2 pos (from June 2011, all completed 6 escBEACOPP) $n = 506$: 92% | 5-year OS PET-2 pos (May 2008–June 2011) $n = 434$: standard arm: 96.4% experimental arm: R-8 esc BEACOPP group 93.9% PET-2 neg: standard arm: 95.4% experimental arm: 97.7% 3-year OS PET-2 pos (from June 2011, all completed 6 esc BEACOPP) $n = 506$: 98% |
| Johnson et al., RATHL, 2016 Phase III [20,21] | 16.3% | DS DS >3 considered positive | 3-year PFS PET-2 pos: 67.5% PET-2 neg: standard arm: 85.4% experimental arm: 84% 5-year PFS PET-2 pos: 65.7% PET-2 neg: standard arm: 82.7% experimental arm: 80.6% | 3-year OS PET-2 pos: 87.8% PET-2 neg: standard arm: 97.2% experimental arm: 97.6% 5-year OS PET-2 pos: 85.1% PET-2 neg: standard arm: 95.3% experimental arm: 95% |

ABVD: adriamycin, bleomycin, vinblastine and dacarbazine; CT: computed tomography; ecsBEACOPP: escalated bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine and prednisonel; DS: Deauville score; IHP: International Harmonization Project; IPS: international prognostic score; neg: negative; OS: overall survival; PET: positron emission tomography; PFS: progression free survival; pos: positive; R: rituximab; RCT: randomized controlled trial; RxT: radiation therapy.

findings. The 3-year PFS and OS rates in both arms were similar (Table 1). In the escalation part of the study, the non-randomized comparison of BEACOPP-14 and EB did not show a significant difference between regimens, and the 3-year PFS rate was 67% with an OS rate of 88%. Recently, the extended follow-up outcomes have been presented [21] ABVD and AVD exhibited a similar 5-year PFS and OS.

## Results of non-randomized studies

### Studies performing de-escalation therapy when PET-2 was negative

Three studies [22–24] evaluated de-escalation of treatment; in case of a negative PET-2 (one study performed interim PET after three ABVD cycles [22]). These included, two phase II and one retrospective study. Characteristics and results of these studies are shown in Supplement Table 1b and Table 2, respectively.

**Table 2.** Results and outcomes of non-RCTs.

| Type, study name | Positive interim scan, % | PET interpretation method | Results | |
|---|---|---|---|---|
| | | | PFS/EFS/FFS | OS |
| **Therapy de-escalation if PET2 negative** | | | | |
| Pavlovsky et al.,<br>GATLA TRIAL HL-05, 2016<br>Phase II (abstract) [22] | 31%<br>PET3 pos:<br>(all demonstrated partial response) | DS<br>DS >3 considered positive | 3-year EFS<br>advanced disease cohort:<br>PET3 pos: 57.1%<br>PET3 neg: 90% | 3-year OS<br>entire cohort<br>96% |
| Kedmi et al., 2016<br>Avigdor et al., 2010<br>Phase II + retrospective [23,24] | 25%<br>(all defined as partial response) | IHP | 5-year PFS<br>PET2 pos: 60%<br>PET2 neg:80%<br>All patients de-escalated to 4 cycles ABVD | 5-year OS<br>PET2 pos: 79%<br>PET2 neg: 98%<br>All patients de-escalated to 4 cycles ABVD |
| Deau, 2015<br>Retrospective [25] | 14% | DS<br>DS >3 considered positive | 2-year PFS<br>PET2 pos: 47%<br>PET2 neg: 87% | OS for both groups was 100% during all follow-up. |
| **Therapy escalation if PET2 positive** | | | | |
| Press et al.,<br>US intergroup S0816, 2016<br>Phase II [26] | 18% | DS<br>DS >3 considered positive | 2-year PFS<br>PET2 pos: 64%<br>PET2 neg: 82% | 2-year OS<br>(calculated)<br>for<br>entire cohort: 98% |
| Zinzani et al.,<br>HD0801 study, 2016<br>Phase II [27] | 20% | IHP | 2-year PFS<br>PET2 pos: 76%<br>PET2 neg: 81% | 2-year OS<br>(calculated)<br>entire cohort:<br>97% |
| Ganesan et al., 2015<br>Phase II [28] | 16% | DS<br>DS >3 considered positive | 2-year EFS<br>PET2 pos: 50%<br>PET2 neg: 82% | 2-year OS<br>entire cohort:<br>88% |
| Gallamini et al., 2011<br>Retrospective [29] | 17% | DS<br>DS >3 considered positive | 2-year FFS<br>PET2 pos: 65%<br>PET2 neg: 92% | 2-year OS<br>entire cohort:<br>95.1% |
| **Therapy escalation or de-escalation according to PET2 results** | | | | |
| Dann et al.,<br>Israeli H2, 2017<br>Phase II [30] | 12% IPS <3<br>19% IPS ≥3 | DYNAMIC SCORE and retrospectively, DS<br>DS >3 considered positive | 5-year PFS<br>IPS>**3** T2 neg **80**.4%<br>PET2 pos 59%<br>IPS ≥3<br>PET2 neg 81.5%<br>PET2 pos 78.6% | |
| Dann et al., 2012<br>Phase II [30,31] | 28% positive $Ga^{67}$ scan<br>22% positive PET-CT | DYNAMIC SCORE | 10-year PFS<br>positive interim scintigraphy: 83%<br>negative interim scintigraphy: 87%<br>for entire high-risk group: 87%<br>for entire standard risk group: 87% | 10-year OS<br>For entire high-risk group: 87.7% |

ABVD: adriamycin, bleomycin, vinblastine and dacarbazine; CT: computed tomography; ecsBEACOPP: escalated bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine and prednisonel; DS: Deauville score; IHP: International Harmonization Project; IPS: international prognostic score; neg: negative; OS: overall survival; PET: positron emission tomography; PFS: progression free survival; pos: positive; R: rituximab; RCT: randomized controlled trial; RxT: radiation therapy.

Interim PET was positive in 12–31% of patients. PFS in the PET-2 positive arms ranged between 47–73%. PFS in the PET-2 negative arms ranged between 80–93%.

The GATLA HL-05 phase II trial [22], evaluated 377 patients, who performed interim PET after three cycles of ABVD (PET-3), and patients with a negative scan were given no further treatment. PET-3 was positive in 31% of patients (method of PET-CT interpretation not mentioned). Patients with advanced stage and negative PET-3 had a 3-year event-free survival (EFS) of 90%, compared with 57% PFS for patients with positive PET-3 (exhibiting partial response), who completed a full ABVD course only age and PET-3 result were significant in multivariate analysis for EFS.

Two other studies, a phase II study [23] and a retrospective study [24] performed, in case of negative PET-2, de-escalation of treatment. Baseline therapy included two cycles of EB and de-escalation, was to four ABVD cycles. Both studies showed that negative PET-2- patients had a PFS around 80–87% after switching to ABVD, despite a difference in their design as well as in the PET interpretation method.

### *Studies performing therapy escalation when PET-2 was positive*

Four studies [26–29], evaluating 1562 patients, performed escalation of therapy in patients with a positive PET-2 result.

In three prospective phase II studies, evaluating 897 patients, patients received two ABVD cycles [26–28]. Escalation regimens included 4–6 cycles of EB or four cycles of ifosfamide-based salvage followed by ASCT. In these

studies, PET-2 positivity rate ranged between 16–20%. Two-year PFS or EFS was 81–82% for PET-2 negative patients and 50–76% for PET-2 positive patients.

### *Studies performing both therapy escalation and de-escalation according to PET-2 results*

In two phase II studies, chemotherapy regimen (ABVD or EB) was directed according to patients' IPS, and the regimen was tailored according to PET-2 results [30,31]. In the latest study [30], patients with IPS score less than three-started treatment with two cycles of ABVD, while those with IPS score higher than three began with two EB cycles. Therapy was adapted according to the PET-2 results: patients with a positive scan or a negative scan received four EB cycles and four ABVD, respectively. IPS did not significantly affect outcome. Those with a negative PET-2 and an IPS $<3$ reached a 5-year PFS of 80%, and patients with IPS $\geq 3$ had PFS of 81%. Five-year PFS for those with a positive PET-2 was 59% (IPS $<3$) and 79% (IPS $\geq 3$), respectively. In the earlier study by Dann et al., using tailored therapy with EB and standard BEACOPP (six cycles in total), 10-year PFS was 87% for those with a negative scan (PET or Gallium) and 83% for those with a positive scan [31].

## Discussion

Our systematic review describes all studies that evaluated the concept of modifying therapy in advanced HL according to interim PET results, both for de-escalation and for escalation. Thirteen studies were included, four of which were RCTs.

Taken overall, the results from three available RCTs for de-escalation post negative PET-2, seem to be favorable across the studies to date. Not only that de-escalation is equally efficient, it is better tolerated as well. In the LYSA trial [15], HD18 and the RATHL trial, the PFS in the standard arm vs. the experimental PET-adapted arm were quite similar [17–19,20,21].

In the two randomized controlled escalation trials, GITIL [16] and HD18 [17–19], the addition of rituximab, did not result in superior outcomes.

Of note is the variability between the PFS in these two escalation trials. While the HD18 trial reported a remarkable outcome, with a 5-year PFS exceeding 88% in both PET-2 positive and PET-2 negative patients, an interim scan after two ABVD cycles in the GITIL trial was predictive of patients' outcome.

No RCT of escalation therapy conducted a true randomization between PET-adapted (escalated arm) and a standard control arm using ABVD regimen. Given historical data, continuing ABVD after positive PET-2 can be a matter of debate [10].

It appears that starting ABVD in patients with advanced disease and escalating to BEACOPP in PET-2 positive patients is feasible, with results somewhat comparable to the de-escalation studies.

Interestingly, the PFS in the PET-2 negative groups that completed a full course of ABVD was substantially below the historic 95% [10]. This is a consistent finding across different groups, implying that the interim PET scan has its own intrinsic technical limitations, rather than interpretation method errors. Alternatively, this implies that PET -2 negative patients are a heterogeneous group and a proportion of patients with negative PET-2 might benefit from treatment escalation.

Moreover, classical prognostic factors other than PET might affect prognosis. For instance, the RATHL study found that the negative predictive value of interim PET scans after two cycles of ABVD is lower in patients with a more advanced stage or a higher IPS [20,21]. Similarly, the GITIL study found that patients with a higher IPS score were less likely to be PET-2 negative 16]. Thus, baseline prognostic factors as IPS and stage still affect prognosis [20].

The PET-2 positive patients comprise a heterogeneous group as well. In all escalation trials, a Deauville score (DS) of four or more was considered positive, while in the HD18 a DS of three and above was considered positive. The RATHL and GITIL trials suggest that PET-2 positive patients with a score of five, as opposed to four, are at a particularly higher risk for relapse [16,20,21]. This implies that other approaches, such as early myeloablative therapy or combining novel biologic therapies, such as antibody-drug conjugates, should possibly be examined in this population.

Although a direct comparison between studies is impossible due to variations in design, treatment regimens and time points for assessment of outcomes, it seems that a negative interim PET scan has the highest negative predictive value in patients with less extensive disease at presentation and in those treated with the most intensive chemotherapy.

Previous systematic reviews regarding PET adapted therapy in HL have been published [32–34]. The strength of our systematic review, lies within the fact that it was based on a comprehensive search, according to a defined protocol and search terms. The methodology of the studies included in our review was critically assessed. We report the most recent data that might apply to patients with advanced HL, with an emphasis on RCTs, thus reporting the highest level of evidence available.

Yet, several limitations merit consideration. The main one is that we cannot strictly compare between de-escalation and escalation. The included trials were very heterogeneous in design, thus we could perform only a systematic review and not a meta-analysis of the RCTs. Results of the escalation studies could not be pooled due to the difference in the primary treatment regimen itself (ABVD in the GITIL trial vs. EB in the HD18). Moreover, the time frame for reporting the outcomes of PFS and OS differed and ranged from 2 to 5 years. Furthermore, not all PET scans were centrally assessed and a minority of them was interpreted using scores other than the 5-point DS. This heterogeneity poses difficulty in the interpretation of results and in comparing between the PFS of the escalation and de-escalation studies. There is also no stratified data on OS according to the treatment arm in some of the studies, mainly due to short follow-up periods. Finally, the studies differed in methodology, the major issue with most of these trials is the lack of a true randomization between PET-adapted and standard control arm in which

therapy is continued regardless of interim PET-CT results. In order to overcome this limitation, we based the analysis on RCTs alone. Nevertheless, only four RCTs could be included.

### *Implications for practice*

This systematic review of all available data of PET-adapted therapy, with an emphasis on RCTs, suggests that a change to the treatment paradigm is appropriate. In advanced HL, using an early PET-adapted treatment approach for all patients should become the standard of care. A positive PET-2 after two ABVD cycles might warrant a change in treatment regimen, whereas omitting bleomycin after a negative interim scan will minimize toxicity without affecting clinical response. Escalation with rituximab does not result in better outcomes. IPS and advanced stage lower the negative prognostic value of a negative PET after two ABVD cycles but not after two EB cycles. Completing only four EB cycles in PET-2 negative patients is as effective as six cycles and less toxic. A subclass of patients, with 5-point score lesions, have a particularly higher risk of treatment failure and for them, escalating from ABVD to EB is not sufficient.

### *Implications for research*

Since, RCTs are the only true method to provide insight regarding long-term outcomes of PET-adapted therapy, future trials should be designed as RCTs to evaluate PET adapted therapy and should stratify according to the traditional prognostic factors as stage and IPS, as well as evolving biomarkers.

There have been some attempts to improve both the negative and positive predictive value of the interim PET scan, for example, the use of very early PET-adapted escalation with interim PET-CT after one cycle of ABVD [35], but only retrospective results have been published so far. Another approach might be the use of biological stratification of the disease at diagnosis, by immunohistochemistry or gene expression analysis as an adjunct to PET, methods which have been proposed as predictive of treatment failure in pilot studies [36,37].

The trials discussed in our systematic review have largely used ABVD and EB as front-line therapy, but other novel combinations, incorporating novel agents, such as brentuximab, are currently being evaluated with excellent initial results [38].

And finally, national imaging, as total metabolic tumor volume (TMTV) and tumor proliferation using different radiotracers, such as fluorodeoxy thymidine (FLT) and integrated PET/MRI, is an ongoing evolving field aiming to enhance staging, characterization and prognostication in HL in the era of personalized medicine [39].

## Disclosure statement

No potential conflict of interest was reported by the authors.

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