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Hot Topic

The role of PET/CT in the modern treatment of Hodgkin lymphoma

Jan Maciej Zaucha[a,*], Stephane Chauvie[b], Renata Zaucha[c], Alberto Biggii[d], Andrea Gallamini[e]

[a] Department of Hematology and Transplantology, Medical University of Gdańsk, Poland
[b] Department of Medical Physics, Santa Croce e Carle Hospital, Cuneo, Italy
[c] Department of Oncology and Radiotherapy, Medical University of Gdańsk, Poland
[d] Department of Nuclear Medicine, Santa Croce e Carle Hospital, Cuneo, Italy
[e] Department of Research and Clinical Innovation, A. Lacassagne Cancer Center, Nice, France

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ABSTRACT

Classical Hodgkin Lymphoma is distinguished from other lymphomas by its peculiar biology and heterogeneous chemosensitivity. Most of the patients respond to the standard first-line treatment and are cured, however, in selected cases, the disease relapses or remains primarily refractory. Among predictive/prognostic factors ^{18}FDG positron emission tomography (PET), fully integrated with computed tomography (PET/CT) proved to be extremely useful in identifying patients with poor prognosis at the time of diagnosis, during and at the end of treatment. The aim of this review is to present the current role of PET/CT in cHL at staging, interim and end of therapy assessment and its ability to guide treatment with a response- and risk-adapted strategy in clinical practice. Finally, quantitative PET measurement and the concurrent use of PET with selected biomarkers are discussed.

Introduction

Hodgkin lymphoma (HL) has been the archetype for tumor staging and restaging in oncology [1] with extensive evidence of the high diagnostic accuracy of [^{18}F]-Fluoro-Deoxy-Glucose Positron Emission Tomography (FDG-PET) combined with computed tomography (PET/CT) [2–4]. The exceptional performance of PET/CT in HL results most likely from the peculiar architecture of HL composed of a minority (5%) of neoplastic cells, the Hodgkin and Reed-Sternberg (HRS) cells, embedded in a microenvironment (ME) of non-neoplastic inflammatory/immune cells. The constant cross-talk between malignant and ME cells, mediated by cytokine production, is vital for the HRS cells development and survival [5,6]. It also reprograms metabolism of ME cells, shown in *in vitro* cultures [7], leading to their high FDG uptake. During treatment both chemokine production and glycolytic activity of the HRS cells are abruptly shut down [8–10] making the tumor rapidly PET negative. In this "on-off" phenomenon, ME cell work as a signal amplifier: they maintain a high metabolic activity in chemo-resistant disease or *vice versa*, they are inactivated in the case of HRS cells death, thus dramatically increasing the accuracy of FDG-PET as a prognostic and predictive tool.

PET/CT in HL is recommended for staging, interim (i) and end of therapy (eot) assessment but not during follow-up [11]. The protocol for the PET/CT scanning, is well defined [12]. A single dose of propranolol of 40 mg given orally 60 min prior to the FDG injection reduces its uptake in brown adipose tissue (BAT) improving the accuracy of successive scans if BAT is identified at baseline [13]. The Lugano criteria for Lymphoma treatment response [11] for "i" and "eot" restaging uses the discrete Deauville 5-point scale (DS) that defines the areas of residual FDG uptake in the disease compared to physiological districts [14]. One of the great advantages of DS in quantifying the residual FDG uptake in sites involved by disease is the use of an internal reference organ with a relatively stable metabolic activity and hence not depending on factors affecting standardized uptake value (SUV). However, semi-quantitative PET scan image assessment, specifically SUV-based derived functional metrics has been proposed to improve the accuracy of PET/CT by the measurements of metabolic tumor volume (MTV) and total lesion glycolysis (TLG).

The role of PET/CT in staging by the assessment of the tumor burden.

Staging

PET/CT proved to be more accurate than contrast enhanced computed tomography (ceCT) for HL staging. Although most of the initially published studies comparing ceCT to PET in HL staging used FDG-PET stand-alone [3,15–21], and only two studies fully integrated PET with

* Corresponding author at: Department of Hematology and Transplantology, Medical University of Gdańsk, 17 Smoluchowskiego street, 80-214 Gdańsk, Poland.
E-mail address: jzaucha@gumed.edu.pl (J.M. Zaucha).

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Table 1
Comparison of conventional contrast enhanced CT to ^{18}FDG- PET or ^{18}FDG-PET/CT for staging of Hodgkin lymphoma.

Author/year	No of patients	PET or PET/CT	Upstaging (%)	Downstaging (%)	Change of treatment (%)
Bangerter et al. 1998[15]	44	PET	12	2	14
Partridge et al. 2000[16]	44	PET	41	7	25
Jerusalem et al. 2001[17]	33	PET	9	12	3
Weihrauch et al. 2002[18]	22	PET	18	0	5
Munker et al. 2004[19]	73	PET	29	3	na
Naumann et al. 2004[20]	88	PET	13	8	18
Hutchings et al.2006[3]	99	62% PET/CT	19	5	9
Rigacci et al. 2007[21]	186	PET	14	1	6
Bednaruk-Młyński et al. 2015[4]	96	PET/CT	28	6	21
Barrington et al. 2016* [22]	1171	PET/CT	14	6	na

* All patients with advanced stages HL; na - not applicable.

CT scanners [4,22] (Table 1) the results showed an equal specificity and an higher sensitivity of PET/CT over ceCT scan. Overall, patient upstaging was much more frequent (about 18%) than down-staging (5–6%) (Table 1). Down-staging resulted mainly from the detection of slightly enlarged non-FDG avid lymph nodes, usually in the abdomen or some abnormalities in extra-nodal sites, such as small non-FDG avid lungs nodules [4,22]. Upward stage migration from stage II or III to stage IV in nearly 75% was due to the bone or bone marrow involvement (BMI) [22]. The accepted criterion for BMI by PET/CT in HL, confirmed in some cases by imaging-guided biopsies [23], is a focal FDG uptake with or without bone CT abnormalities, visible in two or more slices at bone or BM level in the co-registered PET/CT images with an intensity > liver [22,24,25]. The diffuse FDG uptake may occur with or without increased focal uptake in 30% of the HL patients [4,24]. However, this is considered an epiphenomenon of cytokine-mediated activation of BM cells, not a harbinger of BM infiltration by HL. Patients with a diffuse FDG uptake in the BM also show a diffuse FDG uptake in the spleen, but have the same treatment outcome as patients with negative PET/CT in the BM [4,24,25]. In contrast, patients showing focal FDG uptake had significantly lower 3-year progression free survival (3-y PFS) compared to the patients with a diffuse uptake (66.7% vs. 82.5%, p = 0.03) [24]. The need of a routine bone marrow biopsy (BMB)[26] to detect BM involvement (BMI) if PET/CT was used at staging has been questioned by several studies [27]. The largest study including 454 HL patients reported that only 6% had positive BMB against 18% patients with focal skeletal PET/CT lesions. None of the patients with a positive BMB had stage I or II and had its treatment changed by BMB. The positive (PPV) and negative (NPV) predictive values of focal skeletal PET/CT lesions for BMB results were 28% and 99%, respectively, which means that only 1% of patients with positive BMB had a negative BM in PET/CT [28]. A systematic review including 955 patients from nine studies showed that the sensitivity and specificity of PET/CT for BMI ranged from 87.5% to 100% and from 86.7% to 100% respectively, with the conclusion that PET/CT should substitute BMB at diagnosis [27]; this statement was included among the expert recommendations for baseline, interim and end-of-treatment PET scan use in Hodgkin and non-Hodgkin lymphoma [11]. The second and third most frequent extra-nodal sites detected by PET/CT at staging were the lungs and spleen [4,22,29]. PET/CT-induced stage migration is clinically relevant. In one study by Bednaruk-Mlyński et al. PET/CT led to a treatment modification in 21% of the patients, in 80% to a more and in 20% to less intense treatment [4]. Picardi at al. reported a better PFS in patients staged with PET/CT compared to patients staged with ceCT and attributed it to the better detection of occult subdiaphragmatic HL involvement [29].

The assessment of the tumor burden

The assessment of functional active volume of the tumor made PET/CT very attractive for tumor burden (TB) measurement, which for long has been considered one of the most powerful prognostic parameter in HL [30]. It recapitulates not only the tumor spread *per se*, but also reflects tumor aggressiveness and, related to it, the host's reactivity against the tumor [31]. In fact, the prognostic factors used for the risk stratification of HL patients are indirect surrogates for TB. The first evidence of the strong prognostic value of TB in HL came from Specht et al. [30] and its superiority over any single prognostic factor was confirmed 10 years later by Gobbi et al. [32]through the evaluation of the TB on ceCT scans. In PET/CT the delineation of an active tumor is easier and is the first step toward a semi-quantitative metrics to calculate the total volume of the metabolically active tumor in an area of uptake and express it in cm^3 [33–35]. Initial [33,35] and most current retrospective studies in HL indicate an important prognostic or predictive role of MTV both in early [36,37] advanced [38,39] and relapsed [40,41] HL. MTV is especially useful in early stage HL. It identifies patients with a higher risk for progression who may require more intensive treatment [35]. Recently, in early stage HL patients treated in the standard arm of H10 study Cottereau at al. showed that MTV was a strong predictor of PFS ($p < 0.0001$) and OS ($p = 0.0001$) with a specificity of 86% and 84%, respectively. In multivariable analysis, iPET2 and MTV were independently prognostic, but MTV was a superior prognosticator compared to the current prognostic stratification proposed by EORTC/GELA, GHSG, or NCCN groups. Patients with a high MTV (> 147 cm^3), despite a negative iPET2 had, respectively, a 5- and 7- fold higher risk of treatment failure or to die than patients with a low MTV [37]. On the other hand, patients with high MTV and positive iPET2- had dismal prognosis and did not benefit from second-line standard treatment, thus being good candidates to innovative therapeutic approaches. In conclusion, MTV improved baseline risk stratification and the predictive value of iPET in eHL. In aHL patients treated with upfront ABVD in prospective PET response-adapted trials, the analysis of the prognostic role of MTV is in progress, but the results are not available yet. In patients treated with eBEACOPP the results are conflicting. Preliminary findings (16 months median follow-up) in the AHL2011 trial suggested a highly prognostic value of MTV: 2y-PFS was 81% vs 93% in pts with high (> 350 ml) and low MTV respectively in the whole population ($p = 0.0015$; HR = 3) [38]. In contrast in the HD18 trial, the baseline MTV failed to prognose PFS and OS, however was predictive of iPET2 response which might be explained by the high efficiency of eBEACOPP treatment [39]. Finally, MTV measured before brentuximab in relapsed/refractory (r/r) HL combined with interim PET result immediately before autologous stem cell transplantation proved also to be the most powerful predictor of final treatment outcome PET [40]. The biggest obstacle in the prospective usage of MTV is the lack of standardization of the MTV methodology negatively affecting its reproducibility. One of the major methodologic hurdles in the standardization of tumor delineation and MTV computing procedure is the dissection between pathological FDG uptake by the tumor and physiological uptake by adjacent structures, which normally show high FDG uptake, such as such as ureters, bladder, vertebral bodies, myocardium and cardiac chambers. Several methods have been developed to contour and to segment single MTV focal areas, but none of

Table 2
The prognostic value of metabolic tumour volume (MTV) before treatment in patients with Hodgkin lymphoma.

Author/year	No. of pts	Clinical stage	Treatment	MTV assessment	Median baseline MTV (ml) (range)	Prognostic of PFS (p)	Cut off MTV value (ml)	PFS low MTV	PFS high MTV
Song et al. 2013[35]	127	Early	ABVD +/- RT	MTV2.5*	142.6 (6.1–587.2)	Yes (0.012)	198	0.96 @3-y	0.67 @3-y
Kanoun et al. 2014 [33]	59	Mixed 37% early	Anthracycline based 4-6-8 cycles	MTV41%**	117 (4–1611)	Yes (0.001)	225	0.85 @4-y	0.42 @4-y
Akhtari et al.2018[36]	178	Early unfavourable	ABVD +/- RT	MTV2.5	118.7 (0–1822.5)	Yes (0.0075)	268	0.91 @5-y	0.78 @ 5-y
Cottereau et al. 2018[37]	258	Early	ABVD + RT	MTV41%	67 (32–114)	Yes ($p < 0.0001$)	147	0.92 @5-y	0.71 @5-y
Casasnovas et al. 2016[38]	392	Advanced	eBEACOPP/ABVD	MTV2.5	200 (23–2149)	Yes (0.0015)	350	0.81 @2-y	0.93 @2-y
Mettler et al. 2019[39]	310	Advanced	eBEACOPP (4 or 6 cycles)	MTV41% MTV2.5	142 (6–1590) 355 (4–3563)	No No	—	—	—
Moskowitz et al. 2017[40]	65	Relapsed/ refractory before AHCT	Brentuximab + ICEaug	MTV41%	50 (6.55–782)	Yes (< 0.001)	109.5	0.92 @2-y	0.28 @2-y
Prochazka et al.2018[41]	96	Relapsed/ refractory before AHCT	na	MTV41%	7,97 (1,3–102,1)	Yes (0.05)	7.97	0.53 @2-y	0.12 @2-y

* MTV2.5- contouring method for MTV assessment by the area ≥ Standard Uptake Value $(SUV)_{max}$ 2.5.
** MTV41% - contouring method for MTV assessment using 41% of the SUVmax within the respective lymphoma site; na - not available; AHCT - autologous hematopoietic cell transplantation.

them proved to be both accurate and precise [42]. Segmenting a volume in a three-dimension direction by counting all the voxels with an activity above a fixed (e.g. SUV = 2.5) or relative (41% of SUV_{max}) threshold is the most used method to avoid partial volume effect, since it is simple and easy to apply. In ^{18}F-FDG filled tumor-simulating phantom, MTV measurement adopting a 41% SUVmax relative threshold gave the best concordance between measured and actual volumes [43]. Given the variety of algorithms used and the degree of operator dependence, the variability in MTV measurement can range between 40% and 400%, depending on the method [44]. Thus different medians of baseline MTV and different prognostic cut-off values are being reported (Table 2). Nevertheless, all the above data call for prospective MTV based risk adaptation trials especially in patients with early stage HL providing the consensus on the standardization of the methodology is reached.

End of treatment PET/CT

Pre-Deauville PET/CT interpretation

EotPET assessment is intuitively very appealing, due to the possibility of assessing not only the size but also the metabolic activity of the residual tumor. To eliminate or minimize the influence of unspecific ^{18}FDG uptake, eotPET should be performed optimally 4–6 weeks after completion of chemotherapy and at least 12 weeks after radiotherapy (RT) [45]. The revolution in eotPET assessment compared to ceCT was the assumption that not size but, the metabolic activity of the tumor, defines the depth of response. In HL this assumption is particularly important since up to 60% of the responding patients complete treatment with a residual tumor having either unconfirmed complete (CRu) or partial response (PR) [46]. The definition of negative eotPET has evolved gradually overtime. Before 2007, the definition of negative or positive PET scan was simply dichotomized, relying only on the detection of residual “abnormal“ tracer uptake outside the physiological areas of FDG uptake. This imprecise definition led to a wide range of sensitivities from 0.50 to 1.00 and specificities from 0.67 to 1.00, as summarized by two systematic reviews [47,48]. The reported PPV ranged between 60–100% [47] to 13–100% [48,49]. although a consistently high and less variable NPV was shown (71–100%). The reported large intra-studies heterogeneity resulted from differences in PET hardware, in the timing of PET scanning and inconsistent criteria for a positive/negative scan. Therefore, in 2007, the Imaging Subcommittee of the International Harmonization Project in Lymphoma proposed first criteria (IHPC) defining “the boundaries” of a negative eotPET [45]: the intensity of the residual uptake by visual assessment should not be higher than the surrounding background or, in case of larger residual masses (≥2 cm), not higher than the mediastinal blood pool (MBP) (Fig. 1). In 2007, FDG-PET was also incorporated into the revised response criteria for malignant lymphoma [50]. A pivotal validation study of IHPC in 56 patients [51] confirmed the usefulness of integrating functional assessment into traditional radiological imaging, despite a few false-positive results [52,53].

Deauville five-point scale for eotPET assessment

In 2009, the Deauville 5-point scale (DS) was proposed to address the growing need for defining simple, reproducible criteria for the interpretation of the PET/CT images performed early during treatment for which the dichotomous visual assessment was not adequate [14,54]. The intensity of FDG uptake was graded according to a five point-scale with two reference organs: mediastinum and liver (Fig. 1). Introduction of the liver uptake in addition to the MBP as a reference organ was originally proposed by Barrington et al in 2008 [54]. The use of internal reference organs with a relatively stable metabolic activity not depending on factors affecting SUV reduces inter-reader and inter-device inconsistencies resulting in a good reproducibility of results [22]. The graded assessment allowed making the interpretation more flexible and the cut-off thresholds for positive and negative scans could be changed according to the clinical context [55]. DS was recommended for eotPET reporting by the new Lugano criteria for response assessment in Lymphoma [11]. Accordingly, a score of 1 to 3 reliably represents complete metabolic remission (CMR) regardless of the size of the residual mass. A score of 4 to 5, with reduction of uptake intensity from baseline defines partial metabolic response (PMR); and without reduction no metabolic response (NMR). In the presence of an increased FDG uptake or new foci compatible with lymphoma a DS score of 4 to 5 is consistent with progressive metabolic disease (PMD). DS broadened the definition of eotPET negativity since score 3 representing a residual FDG uptake lower than or equal to that of the liver was proposed to be also classified as CMR. In fact score 3 defined clearly a minimal residual uptake (MRU), which was originally proposed [56] as a “low-grade” uptake of FDG in an area of previously existing disease [57,58]. Interpretation of

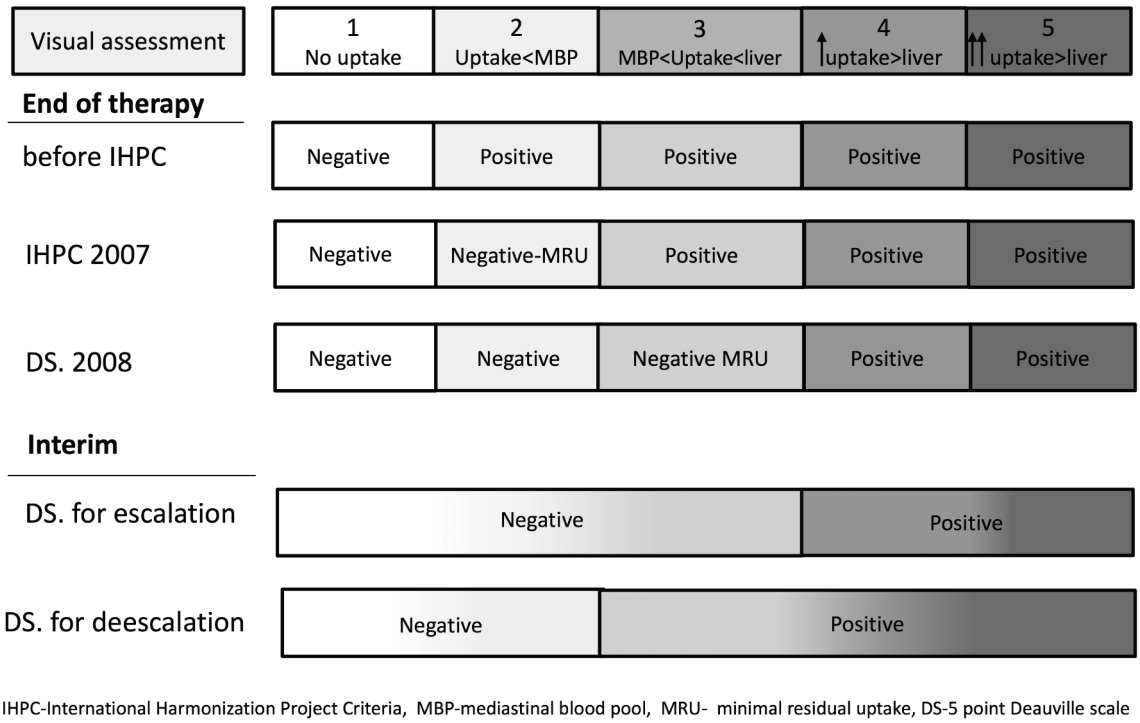

Fig. 1. Overtime evolution of criteria for PET/CT interpretation at interim and at the end of treatment. Initially any FDG uptake above the background, whatever its intensity, was considered positive. International Harmonization Project (IHP) criteria rised the barr for PET positivity from background to the mediastinal blood pool (MBP) uptake, and finally 5-point Deauville scale further rised the positivity threshold to the liver uptake. Unspecific, Minimal residual uptake (MRU) is now defined as the uptake with an intensity equal or lower than liver.

DS3 as negative iPET scan was validated both by retrospective [55,57,59] and in prospective ABVD [22,60,61] and recently BEACOPP escalated (eBEACOPP) based trials [62]. However the data validating this recommendation for eotPET were very limited. Nevertheless, the recently published papers clearly confirmed the higher diagnostic accuracy of the more liberal criteria of PET negativity with DS1-3 compared to the more strict IHPC criteria both for HL and NHL [53,63].

Interim PET (iPET): General concepts and rationale

Early assessment of response to chemotherapy was always intuitively believed to be predictive of final outcome [64]. Traditional radiology imaging with ceCT - especially in HL- lacked specificity for an early response assessment since tumor shrinkage takes time [65]. In contrast, FDG-PET became very successful from the first attempts [66–69], because of the aforementioned "on-off" mechanism leading to metabolic silencing immediately after chemotherapy. In fact, the response assessment with FDG-PET could be performed as early as after a few hours of treatment [70]. The requirements for the optimal time point for iPET assessment are shown in Fig. 2 and can be summarized by the optimal constellation of sensitivity and PPV and specificity and NPV. Based on the experience gained with gallium-67 scintigraphy [69], iPET scans were performed in initial studies after three, two or even one cycle of chemotherapy mainly in patients with aHL [58,69,71].

Interim PET in advanced HL

Interim PET was first tested in less intense ABVD treated patients. The best constellation of iPET predictive values (NPV 95% and PPV 86%) was achieved after two ABVD cycles at 1–3 days before the start of the third cycle (iPET2) by Gallamini et al. in 2007 [72]. Two years later, in a meta-analysis of 360 aHL patients from 7 studies Terasawa et al. reported an iPET sensitivity of 0.81 with NPV between 86 and 95%, and specificity of 0.97 with PPV 80–100% [73]. Two other later-published studies still reported high NPV of iPET2 (92% [74] and 94%[75]) but the predictive power of positive iPET2 was much lower (3-y-PFS 25% [74] and 55%[75]). The wide range of results in iPET2 positive patients was clearly due to the lack of shared criteria for scan interpretation (Table 3). DS was not existing yet, and the criteria of interim PET/CT interpretation were very subjective (modified IHPC) leading to the high rate of false positive results. This was corroborated by the International Validation Study (IVS) of the DS in which the rate of false positive results was seven times higher in iPET2 positive (12/33: 36%) compared to iPET2 negative results (12/203: 5%) [59]. High NPV (94%) of the retrospective IVS study was not confirmed in a prospective observational study aimed at assessing the PV of iPET performed after 1 and after 2 ABVD cycles. It reported lower NPV for iPET2 of 82% [61].The shift of interim PET after 1 ABVD cycle improves NPV by few percentage points but decreases PPV from 57% to about 40% [61]. Three prospective intervention trials reported a similar NPV of iPET2 (82–87%) (The UK RATHL, the US Intergroup S0816, and the Italian GITIL/FIL HD0607), in which patients with positive iPET2 underwent treatment escalation, whereas those with negative iPET continued standard ABVD treatment [76–79]. The most likely explanation of the difference is the retrospective nature of the first pioneer studies with probable bias due to the patient selection.

Intensity of therapy clearly impacts the PV of FDG-PET as in the case of the more effective, but also more toxic, eBEACOPP program. NPV of iPET (after 2 or 4 cycles) has been reported always high (89–92%) but PPV has been lower [80,81]. The first report of very low PPV (14%) of iPET during eBEACOPP therapy came from a small subgroup of 50 patients from the HD15 trial who underwent iPET after 4 cycles of eBEACOPP which was most likely due to not very specific IHPC criteria used for PET interpretation and lack of baseline PET for iPET reference [82]. The second report referred to the much larger group of 440 patients from HD18 GHSG treated altogether with 8 cycles of eBEACOPP (with or without rituximab). 3-y PFS in patients with FDG uptake above

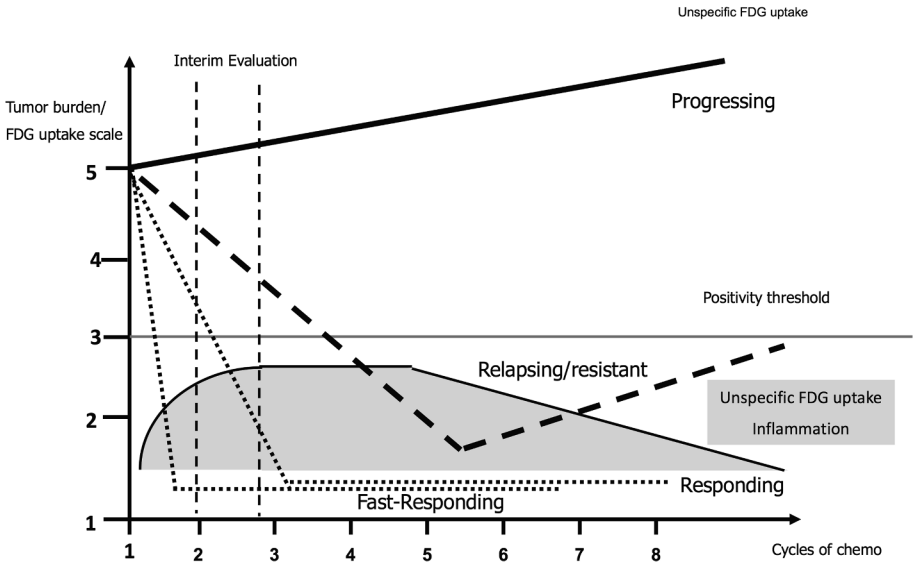

Fig. 2. Optimal timing and criteria for interim PET evaluation. The percentage of iPET negative patients depends on the cut-off for iPET positivity and iPET timing. Very early evaluation after 1 chemotherapy cycle identifies fast responders but about 50% of patients with positive iPET-1 becomes iPET-2 negative, still, with good prognosis [47]. Late interim interpretation may increase the number of false negative results.

liver (DS4 and 5) in iPET2 was 90.7% translating to low PPV [83]. In the AHL 2011 study in the standard arm (6 × eBEACOPP) patients with negative iPET after 2 eBEACOPP cycles had 5-y PFS 88.4% whereas with positive iPET2 73.5% and positive iPET after 4 cycle (iPET4) only 51.9% resulting in better PPV and making this later time point during eBEACOPP treatment even better to identify patients with progressive disease, and who need salvage therapy [80].

Interim PET in early HL

Data on the PV of iPET in eHL gathered slower, and initially were published together with the results in aHL. In the first retrospective analysis, the PV of PET/CT was much less robust for eHL vs. aHL patients- only 2/7 iPET positive eHL relapsed [58]. Conflicting results have been reported on PV of iPET in eHL: In a prospective study on the prognostic role of iPET after 2 cycles of chemotherapy NPV was 100%, whereas PPV only 20% [65]. On the contrary, other investigators reported a lack of significant differences ($p = 0.57$) in PFS between iPET positive and negative eHL patients [84,85]. In contrast, Sher et al. reported different 2-y FFS for PET-negative vs. PET-positive patients after ABVD: 95% and 69%, respectively ($p < 0.01$) [86]. The reported discrepancies in PV of iPET for eHL most likely resulted from the lack of modern criteria of iPET interpretation, but in fact, its PPV was clearly lower than in aHL. Two multicenter retrospective Italian studies adopting modern DS criteria for iPET interpretation confirmed high NPV 96–98% of negative iPET2 (DS:1–3) and only moderate PPV (73–83.7%) of positive iPET2 (DS:4,5) [87,88]. Slightly lower NPV (93%) and PPV (48%) was reported by Cottereau et al. for the patients from the standard arm of *H*10 trial that included IIB patients [37]. Higher NPV (95%) of iPET1 was reported recently in prospectively assessed eHL patients [61]. In a mixed population of eHL and aHL patients an even higher NPV (98.4%) of iPET1 was documented suggesting that negative iPET1 identifies patients with the best outcome ideal for de-escalation studies [89]. Taking this together, all reports of iPET for eHL (Table 3) showed consistently high NPV, and a lower predictive performance for PPV [90], most likely due to the high rescue activity of RT resulting in the very good outcome of eHL treated with combined modality treatment (CMT). The results of the large prospective HD16 trial aimed at assessing the predictive ability of iPET2 corroborated this notion: patients with eHL with favorable prognosis and positive (DS: 4, 5) iPET2 treated with conventional CMT (2 ABVD + IVRT 20 Gy) had significantly worse, but still good 5-y PFS of 80.1% compared to 93.1% of patients with negative iPET2 [91].

Interim FDG PET/CT in PET response-adapted trials

Advanced HL

The excellent PV of iPET seen in non-interventional ABVD based studies paved the way to phase III PET-response adapted trials (Table 4), with the expectation that an early treatment intensification would improve the outcome of iPET positive patients. The obvious candidate for treatment intensification was eBEACOPP used in two retrospective studies including a total of 34 patients with efficacies of 62% [92] and 60% [93]. All three largest trials (RATHL-UK [76], US Intergroup Trial [78], GITIL/FIL HD 0607-Italy [79]), despite differences in patients selection (IIIA- IVB in the US intergroup trial; IIA-IVB in the RATHL study) reported similar percentages of iPET positive scans (DS3-5): 16.3%, 18% and 19%, respectively, and a remarkably similar efficacy of BEACOPP escalation: 65.7%, 64% and 60%, respectively, corroborating the results of retrospective studies. Altogether, PFS of all patients treated with ABVD and PET adapted response increased to: 85.7% @3-y, 79% @2-y, 82% @3-y, respectively. However, the results of these studies also indicated an unsatisfactory low NPV for iPET and relatively low efficacy of a treatment rescue for iPET positive patients not going beyond a 3-y PFS of 65%. In contrast, in the Italian HD0801 study, an alternative intensification with salvage treatment and autologous stem cell transplantation (AHCT) allowed achieving not significantly different 2-y PFS in patients with positive (74%) and negative (81%) iPET2 [77]. However, in this study two or more lines of treatment were given to rescue iPET2 positive patients, with a risk of patient overtreatment as iPET was interpreted with the IHPC criteria, which are known to generate a high proportion of false positive results.

The high NPV of iPET encouraged investigating the de-escalation strategy in iPET2 negative patients in order to limit treatment toxicity. In ABVD treated aHL patients, in the RATHL trial, the omission of bleomycin after negative iPET2 in subsequent ABVD cycles (3–6), did not impair the final outcome [76]. In patients treated much more intensively with eBEACOOP in the HD18 trial, a negative iPET2 allowed shortening the treatment from 8 or 6 to only 4 eBEACOPP cycles, with respective estimates of 5-y PFS 90·8% and 92·2% [81]. An alternative and interesting approach of de-escalating from eBAECOPP to ABVD in patients with high International Prognostic Score (IPS) (> 2) or escalating in patients with low IPS (0–2) from ABVD to eBEACOPP depending on the results of iPET2 was tested by Dann et al. With a median follow-up of 55 months, the long-term disease control was achieved in the majority of patients, with a 5-y PFS of 81% and 68% for iPET2-negative and -positive patients, respectively ($P = 0.08$)[94]. The results

Table 3
Observational (non-response adapted studies in HL).

Author/year	No. of pts	Clinical stage	PET after	RT(%)	Criteria for PET assessment	%of patients PETpos/PETneg	PPV (%)	NPV (%)	2-year (2-y) PFS		Median follow-up (months)
									PET pos	PET neg	
Friedberg et al. 2004[69]	22	IIB-IVB + every stage with bulky disease	3 × ABVD	na	Modified IHPC	23/77	80	95	(-)	(-)	24
Hutchings et al. 2005[58]	85	I-IV (33% in stage III-IV)	2–3 × ABVD	53%	Modified IHPC	15/85	61	94	0.04–6	0.97	39
Hutchings et al. 2006[65]	77	I-IV (37% in stage III-IV)	2 × ABVD (in 91%)	nd	Modified IHPC	21/79	69	95	0.0	0.96	23
Gallamini et al. 2006[8]	108	IIB-IVB, IIA with unfavorable risk factors1	2 × ABVD	53%	Modified IHPC	19/81	90	97	0.6	0.96	20 (mean)
Gallamini et al. 2007[72]	260	IIB-IVB, IIA with Unfavorable risk factors	2 × ABVD	40%	Modified IHPC	19/81	86	95	0.13	0.95	26
Zinzani et al. 2006[126]	40	IIB-IVB	2 × ABVD	na	Modified IHPC	20/80	100	96	(-)	(-)	18
Markova et al. 2009[82]	50	IIB-IV	4 × eBEACOPP	14%	IHPC	14/36	14	97	na	na	25
Cerci et al. 2010[75]	104	I-IV (60% in stage III-IV)	2 × ABVD	59%	Modified IHPC	29/71	53	92	0.53@ 3-y	0.9@ 3-y	36
Zinzani et al. 2012[74]	304	I-IV (52% Iin stages IIB-IVB)	2 × ABVD	30%	IHPC	17/83	73	92	0.27@ 9-y	0.92@ 9-y	31 PET2 neg45 PET2 pos
Barnes et al. 2011[84]	96	IA-IIB, not bulky	2–4 × ABVD	56%	Modified IHPC	18/82	23	91	0.87	0.91	46
Hutchings at al. 2014[89]	126	I-IV (65% in stage III-IV)	1 × ABVD	35%	DS 1–3 vs. 4,5	29/71	59	94	0.41	0.94	29
Gallamini et al. 2014[59]	260	IIA with risk factors-IV (80% aHL)	2 × ABVD	38.5%	DS 1–3 vs. 4,5	17/83	73	94	0.28@ 3-y	0.95@ 3-y	37
Zaucha et al 2017[61]	204	IIB-IV	1 × ABVD	40%	DS 1–3 vs. 4,5	35/65	42	84	0.57@ 3-y	0.84@ 3-y	45
Casasnovas et al.2019 (AHL2011 standard arm)[80]	413	III-IV	2 × eBEACOPP	na	DS 1–3 vs. 4,5	12/88	na	na	0.74 @ 5-y	0.88 @ 5-y	50
Straus et al. 2011[127]	88	I-IIB non-bulky	2 × AVG	na	IHPC	27/73	46	84	0.54	0.88	40
Rossi et al. 2014[120]	59	I-IV	2 × ABVD	32%	DS 1–3 vs. 4,5	22/78	46	85	0.45	0.81	50
Sher et al. 2009[86]	46	I-IV (10% in stages III-IV)	2–4 × ABVD	63%	IHPC	43/57	15	96	0.85	0.95	41
Filippi et al. 2013[85]	80	IA-IIA	2 × ABVD	100%	DS 1–2 vs. 3–5	12/88	0	99	1.00@ 3-y	0.97@ 3-y	36
Zaucha et al. 2017[61]	106	I-IIA	1 × ABVD	91%	DS 1–3 vs. 4,5	18/82	33	95	0.59@ 3-y	0.94@ 3-y	45
Borchmann et al.2017[81]	217	IIB-IV	2 × eBEACOPP	35%	DS 1–2 vs. 3–5	NA	6	NA	0.90	0.91	68
HD18 standard treatment	504			3%			NA	95	@ 5-y	@ 5-y	53
PET positive arm*											
PET negative arm**											
Cottereau et al. 2018[37] (H10 standard arm)	258	I-IIB	2 × ABVD	100%	DS 1–3 vs.4,5	8/92	48	93	0.38@ 5-y	0.93@ 5-y	55

DS – Deauville scale; IHPC- International Harmonization Project Criteria; RT-radiotherapy PFS- progression free survival, neg - negative; pos - positive; na- not available; *8 × eBEACOPP; **8 × eBEACOPP or 6 × eBEACOPP.

Table 4
Response adapted studies in early and advanced Hodgkin Lymphoma.

Study/Author/year	No. of pts	Design	Clinical stage	PET after	Criteria of PET positivity	PET-negative therapy	PET-positive therapy	Outcome		Median Follow-up
								PET2 negative	PET positive	
RAPID Radford et al. 2015[99]	571	RCT	EARLY Stage IA-IIA Non-bulky	3 × ABVD	DS: 3–5	IFRT or NFT	1 × ABVD + IFRT	3-y PFS: IFRT: 0.97 vs. NFT: 0.91 3-y OS: IFRT: 0.97 vs. NFT: 0.99	3-y PFS: 0.88	60
*H*10 Andre et al. 2017[101]	1925	RCT	EARLY Stage I-II Favorable (F) and Unfavorable (UF)	2 × ABVD	DS: 3–5	1 × ABVD + INRT or 2 × ABVD (F); 2 × ABVD + INRT or 4 × ABVD (UF)	1 × ABVD + INRT or 2 x eBEACOPP + INRT (F) or 2 × eBEACOPP + INRT (UF)	5-y PFS: F: INRT: 0.99 vs. NFT: 0.87 UF: INRT: 0.92 vs. NFT: 0.90 5-y OS: F: INRT: 0.97 vs. NFT: 0.98 UF: INRT: 0.92 vs. NFT: 0.90	5-y PFS: ABVD + INRT: 0.77 vs. eBEACOPP + INRT: 0.91 5-y OS: ABVD + INRT: 0.89 vs. eBEACOPP + INRT: 0.96	54
Israel study Dann et al. 2017[94]	170	PhII	EARLY	2 × ABVD	DS: 4, 5	F: INRT or 2 × ABVD* UF: 2 × ABVD + INRT or 4 × ABVD*	F: 2 × ABVD + INRT UF: 4 × ABVD + INRT	5-y PFS: 0.91 no RT (58%): 0.94 with RT (42%): 0.89	5-y PFS: 0.69	55
CALGB 50604 Straus et al. 2018 [98]	149	PhII	EARLY Stage IA-IIA Non-bulky	2 × ABVD	DS: 4, 5	4 × ABVD without RT	2 × eBEACOPP + 30.6 Gy IFRT	5-y OS: 1.00 3-y PFS: 0.91	5-y OS: 0.95 3-y PFS: 0.66	45
HD16 Fuchs et al. 2018[91]	628	RCT	EARLY Favorable	2 × ABVD	DS: 3–5	2 × ABVD or 2 × ABVD + IFRT 20 Gy	na	5-y PFS 2 × ABVD: 0.86 vs. 2 × ABVD + IFRT: 0.93 5-y OS 2 × ABVD: 0.98 vs. 2 × ABVD + IFRT: 0.98	na	47
RATHL Johnson et al. 2016[76]	1119	RCT	ADVANCED Stage IIB-IV	2 × ABVD	DS 4, 5	4 × ABVD or 4 × AVD	BEACOPP-14 or eBEACOPP	3-y PFS: ABVD: 0.86 vs. AVD: 0.84 3-y OS: ABVD: 0.97 vs AVD: 0.98	3-y PFS: BEACOPP: 0.68 3-y OS: BEACOPP: 0.88	41
GITIL/FIL HD 0607 Gallamini et al. 2018[79]	782	RCT	ADVANCED Stage IIB-IV	2 × ABVD	DS: 4, 5	4 × ABVD pts with large > =5 cm randomized to RT or NFT	eBEACOPP (4 × esc and 4 × bas) with R vs. non-R	3-y PFS: ABVD 0.87 for pts with large > =5 cm 3-y PFS INRT: 0.97 vs. NFT: 0.93	3-y PFS all patients: 0.60 3-y PFS: R-eBEACOPP: 0.63 vs. eBEACOPP: 0.57	43
SO816 US Intergroup Trial Press et al. 2016[78]	336	Ph II	ADVANCED Stage III-IV	2 × ABVD	DS: 4, 5	4 × ABVD	6 × eBEACOPP	2-y PFS: 0.82	2-y PFS: 0.64	40
HD0801 Study Zinzani et al. 2016[77]	520	Ph II	ADVANCED Stage IIB-IV	2 × ABVD	IHPC	4 × ABVD	4x IGEV + BEAM AHCT or allo-HCT	2-y PFS: 0.81	2-y PFS: 0.74	27
HD15 PET substudy Engert et al. 2012[96]	739	Ph II	ADVANCED Stage IIB-IV PR > 2.5 cm residual mass	6 × or 8 x eBEACOPP or 8 × BEACOPP14	DS: 3–5	NFT	INRT (26%)	4-y PFS: 0.93	4-y PFS: 0.87	48

(*continued on next page*)

Table 4 (*continued*)

Study/Author/year	No. of pts	Design	Clinical stage	PET after	Criteria of PET positivity	PET-negative therapy	PET-positive therapy	Outcome		Median Follow-up
								PET2 negative	PET positive	
Israel study Dann et al. 2017[94]	185	Ph II	ADVANCED	2 × ABVD IPS:0–2 2x eBEACOPP IPS > 2	DS: 4, 5	4 × ABVD	4 × eBEACOPP	5-y PFS: 0.79 IPS 0–2 (ABVD): 0.80 IPS > 2 (eBEACOPP): 0.82	5-y PFS: 0.68 IPS 0–2 (ABVD): 0.59 IPS > 2 (eBEACOPP): 0.79	55
HD18 Borchmann et al.2017[81]	1439	RCT	ADVANCED Age 18-60y; stage IIB -IV	2 × eBEACOPP	DS: 3–5	6 or 4 × eBEACOPP vs. 2 × eBEACOPP	6 × eBEACOPP or 6 × R-eBEACOPP	5-y OS: 0.98 5-y PFS: 8 or 6x eBEACOPP: 0.91 vs. 4x eBEACOPP: 0.92	5-y PFS: 0.91 5-y PFS: eBEACOPP: 0.90 vs. R-eBEACOPP: 0.88	66
AHL2011 Casasnovas et al. 2019[80]	823	RCT	ADVANCED Age 18-60y; stage IIB -IV	2 × eBEACOPP	DS: 4, 5	4 × ABVD cycles	4 × eBEACOPP	5-y PFS: 0.89	5-y PFS: 0.71	50

F - Favorable; UF - Unfavorable; RCT - randomized clinical trial; ph II - prospective phase II study; IFRT - involved-field radiotherapy; NFT - no further treatment; neg - negative; pos - positive; pts-patients; INRT- involved-node radiotherapy; IHPC- International Harmonization Project Criteria, RT- radiotherapy; IGEV - ifosfamide, gemcitabine, and vinorelbine; BEAM-carmustine, etoposide, cytarabine, and melphalan; AHCT-autologous hematopoietic cell transplantation; all-HCT - allogeneic hematopietic cell transplantation; PR-partial response; na- not applicable; * at physician discretion.

were comparable to those reported in PET-response-adapted trials in which ABVD was started in all patients independently from the IPS score. This suggests that IPS is not an effective tool for the selection of a more or less intense treatment. Finally, a similar de-escalating strategy from eBEACOPP to ABVD for patients with negative iPET2 after 2 eBEACOPP cycles was explored in the prospective AHL2011 study. Patients with a negative iPET2 were switched to 4 ABVD cycles (providing negative iPET result after 2 subsequent ABVD cycles), whereas patients with positive iPET2 continued eBEACOPP for 4 cycles (providing negative iPET4). Final results reported a similar 5-y PFS of 86.7% for patients in the standard arm, who received 6 cycles of eBEACOPP and 85.4% for patients in the PET-driven arm, which indicates that de-escalation of treatment to ABVD in patients with negative iPET after 2 eBEACOPP cycles is a safe option and significantly decreases the treatment related toxicities such as anemia, thrombocytopenia, febrile neutropenia and infection [80]. Similarly, a 10-y PFS of 87.2% and significantly reduced toxicity was shown in a smaller Polish retrospective study adopting the same de-escalation strategy after eBEACOPP [95].

Finally, PET response adapted trials in aHL proved that the omission of consolidation RT in iPET2 negative patients does not compromise their outcome. For ABVD treated patients in the RATHL trial only 12 (2.6%) iPET2 negative patients received consolidation RT [76] whereas in HD0607 trial [79], a randomized addition of RT did not improve PFS significantly (97% vs. 93%, respectively; $p = 0.29$). Similarly, for patients treated with eBEACOPP in the HD15 trial, a negative eotPET (DS:1,2) reduced the percentage of patients receiving RT from 71% in an earlier trial to 11% [96]. Four-year PFS was 92.6% for patients with CMR, with no difference between patients with a complete radiologic response and patients with a residual mass [96]. All the above robust data resulting from the large prospective PET response adapted trials both for patients treated with ABVD and eBEACOPP strongly argue for the use of iPET2 guided treatment in the routine every-day practice.

Early HL

The outcome of eHL patients with CMT is very good, with PFS rates as high as 90–95%. Increasing concern exists, however, regarding the late and serious treatment related mortality attributed to the RT which is still an essential part of CMT [97]. In a phase II CALGB 5064 trial, non-bulky patients with negative iPET2 (DS1-3) after 2 ABVD cycles (91% of enrolled patients) had excellent 3-y PFS of 91%, with only 2 additional ABVD cycles without RT. [98] Therefore, randomized PET response adapted trials in eHL patients were mainly non-inferiority trials focused on the de-escalating strategy aimed at omitting consolidating RT (Table 4). The RAPID trial enrolled non-bulky stage IA-IIA HL patients with favorable prognostic factor such as absence of B-symptoms and extra-nodal involvement [99]. Patients with negative PET/CT (DS1,2) after 3 ABVD cycles were randomized to involved field RT (IFRT) versus non-IFRT. At a median follow-up of 60 months, the 3-y PFS patients who received IFRT vs. non-IFRT was 94.6% vs. 90.8%, respectively. The difference between PFS had 95% confidence intervals of 1.2 to − 9.9%, with the lower limit exceeding the prespecified (7%) non-inferiority boundary. In the EORTC H10 study randomizing favorable (F) and unfavorable (U) eHL patients to an iPET-adapted versus a standard treatment with 3 or 4 ABVD courses, followed by IFRT, the non-inferiority margin was higher (10%). The iPET-adapted arm assessed the superiority of treatment escalation to 2 BEACOPP cycles in iPET2-positive patients with a DS score of 3–5 and the non-inferiority of de-escalation therapy by omitting RT in iPET2-negative patients with a DS of 1–2. The non-inferiority part of the trial was stopped for futility [100]. Nevertheless, the long term disease control of iPET2 negative patients treated with chemotherapy alone was relatively good, with a 5-y PFS of 87.1% and 89.6% in F and U groups, respectively [101]. Similar findings were recently reported by the non-inferiority part of the large HD16 trial in which eHL F patients with negative iPET2 (DS:1,2)

were randomized either to IFRT (20 Gy) or no further treatment (NFT): estimated 5-y PFS was 93.4% with CMT and 86.1% with NFT (difference 7.3%) with no difference in OS: 98.1% vs. 98.4% with CMT and NFT, respectively [91].

About 50% to 70% of the patients with a negative iPET treated without RT relapsed in the initially involved nodes [91,99,101], and rescue treatment with INRT was able to re-induce CR in some of them [99,101]. However, whether these patients indeed could be effectively rescued by RT only, needs to be verified in a prospective trial. In summary, both studies showed that the majority of HL patients with a negative iPET could be cured using chemotherapy alone, albeit with a significant reduction in an immediate disease control. On the other hand, patients with positive iPET2 in the H10 trial experienced significant improvement in 5-y PFS from 77.4% in the standard ABVD + INRT arm to 90.6% in BEACOPPe + INRT arm ($p = 0.002$), which suggests that RT itself is not sufficient to rescue selected iPET positive patients treated with ABVD. Most likely from this reason PET after end of ABVD chemotherapy (eocPET) and before preplanned RT is performed in daily practice with increasing frequency leading unfortunately to confusion. Since it is not known yet which patient should receive second-line treatment and which the pre-planned RT in case of positive eocPET. As a matter of fact, most eHL patients with positive iPET2 [101] or eocPET [102] subjected to preplanned RT are cured (5-y PFS = 77–78%). This result, together with the recently published trial [103], suggest that the majority (81%) of properly selected patients with positive eocPET/CT who achieved a very good PR to ABVD and had only low volume residual FDG-avidity at the time of completion of chemotherapy could be salvaged with RT alone. Baseline MTV may further improve better selection of patients in the future. However, for now being the available data strongly favors the routine usage of iPET2 to identify high-risk eHL (iPET2 positive) requiring treatment intensification.

The role of PET/CT in long-term follow-up

There is no role of monitoring HL patients with PET/CT after achieving CMR at the end of treatment [104].

The role of PET/CT in relapsed/refractory HL

Before autologous and allogeneic HCT

Several groups confirmed that chemosensitivity to salvage treatment assessed by PET/CT turned out as one of the most important predictive factors for a good final response after autologous hematopoietic cell transplantation (AHCT) in relapsed/refractory (r/r) HL with a NPV for PFS ranging between 55 and 85% [105–108]. In a recent meta-analysis, the pooled sensitivity and specificity of pretransplant FDG-PET in predicting treatment failure were 67.2% (95% CI: 58.2–75.3%) and 70.7% (95% CI 64.2–76.5%), respectively [108]. When performed immediately before AHCT, PET/CT with a DS cut-off score for positivity 2 [40] or recently 3 [41,109] was predictive of transplant outcome. In a large, international study to assess the predictive factors for survival after AHCT on 546 patients with r/r HL from 9 prospective clinical trials (the RisPACT consortium), the only significant factors predictive of PFS were (a) an inadequate PET/CT result before AHCT (b) stage IV, (c) time to relapse ≤ 3 months, (d) ECOG performance status ≥ 1 and (e) a bulk nodal lesion > 5 cm [110]. In contrast, PET/CT performed immediately before allogeneic SCT in patients with nonprogressive r/r HL has a relatively modest impact on survival outcomes [111].

During treatment with novel agents

PET/CT is commonly used for monitoring treatment response to brentuximab vedotin in patients with r/r HL [112] showing a very good NPV (75%) [113]. In contrast, the interpretation of PET/CT results during and after immunotherapy with the immune checkpoint inhibitors (anti–programmed cell death-1 monoclonal antibodies e.g., nivolumab, pembrolizumab) is more challenging. These drugs reactivate endogenous tumoricidal immune activity [114] that might be manifested as an increase in the size of existing lesions, increase in the FDG uptake or even the appearance of new lesions that might be related to granulomatosis, as recently reported [115,116]. Therefore a provisional modification of the Lugano criteria was proposed through the introduction of a new response category termed indeterminate response (IR) [114]. Type 3 of IR is defined as an increase in FDG uptake without a concomitant increase in lesion size fulfilling the criteria for a progressive disease. Therefore, by itself, an increase in FDG uptake should not be taken as granted of a progressive disease with checkpoint inhibitors [114].

Improvements of the predictive role of PET other than MTV

Combining of iPET/CT with tissue biomarkers

Beside MTV, a number of cellular biomarkers assessed by immunohistochemistry (IHC) in HRS or ME cells in the diagnostic tissue samples with the technique of Tissue Macro Array (TMA) were tested to improve the predictive value of iPET. In iPET2 negative patients, the expression of CD68/KP1 (≥25%) and PD1 in ME cells, and STAT1 negativity on HRS cells identified a subset of iPET2 negative patients (33/208: 19%) with a 3-y PFS significantly lower than that of the remaining iPET2 negative population: 66.7% vs. 94.7%, $p < 0.0001$ [117]. These results were confirmed by another retrospective study in which strong and independent predictors for PFS were a negative iPET2 (85% vs. 28%, $P < 0.0001$) and CD68+ cell counts < 5% (89% vs. 67%, $P = 0.006$) [118]. In summary, tissue biomarkers proved useful to improve the NPV of iPET2 by discriminating two patients subsets with a negative iPET2 and different responses to ABVD. A new and very promising way of improving iPET accuracy is related to the change in circulating tumor cell free DNA (cfDNA) from baseline to the time point of iPET2. A drop of 2-fold-log10 in tumor cfDNA was associated with CR and cure. All cured patients that had false positive iPET2 turned out to have a > 2 log10 drop in tumor cfDNA. In contrast, all relapsed patients that had false negative iPET2 had a < 2 log10 drop in tumor cfDNA [119].

Semiquantitative approaches

In the DS the score attribution is made by visual comparison of nodal and extranodal residual uptake to standard physiological reference uptake in mediastinal blood pool structures and in liver, with all the limitations related to the quality of images and the distance between the residual and the reference organ. Another source of confusion is the optical distortions due to the influence of surrounding backgrounds with differing activity (simultaneous contrast illusion). Therefore, a semi-quantitative readout has been proposed by SUVmax assessment and/or its increase or decrease compared to SUVmax at baseline in the same region (ΔSUVmax) [120] or the ratio of SUV uptake [121], but this failed to give a superior performance in HL. New SUV-based derived functional metrics have also been studied such as MTV and total lesion glycolysis (TLG), that reflect TB and tumor biology. MTV was described earlier. TLG is calculated by multiplying the SUVmean in the area of uptake and the MTV. It is expressed in grams, representing an index that includes the tumor volume and the uptake within the entire tumor. TLG was assessed in 100 aHL patients enrolled in the RATHL study. A threshold of 3318 gr was used to divide patients into low and high TLG. The HL event rate was 12.8% and 23.9%, respectively: $p < 0.002$, HR 2 [122]. It is unknown if TLG can

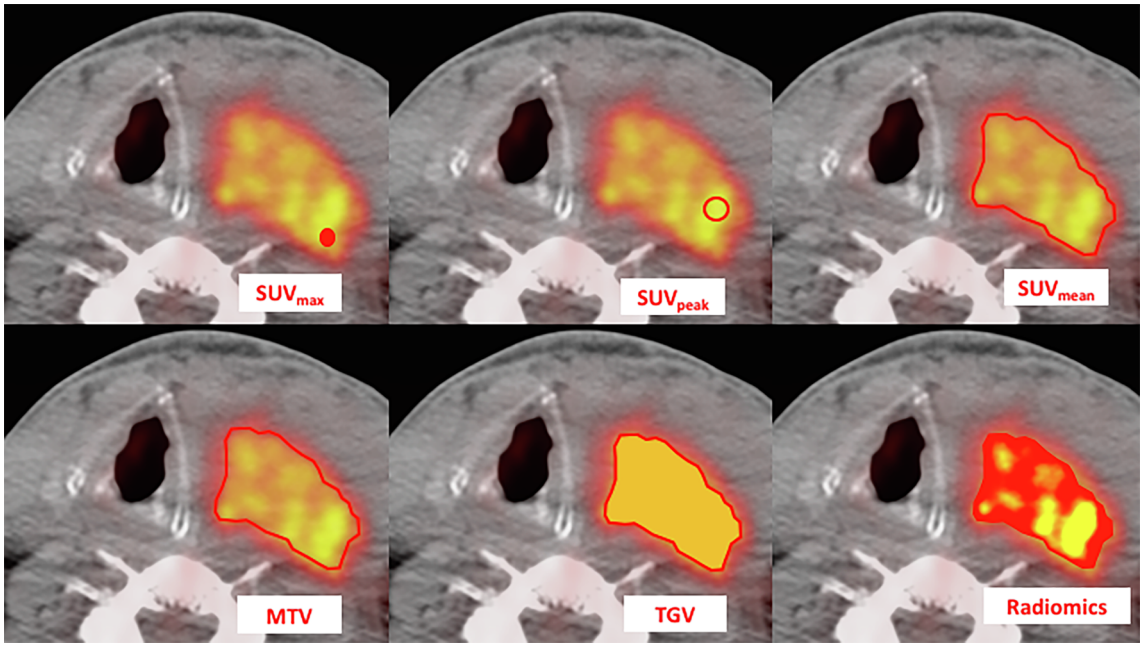

Fig. 3. Different SUV metrics used for the definition of a large latero-cervical lesion: SUV_{max} is defined as the maximum value for SUV in the lesion, SUV_{peak} represents the maximum tumor activity within a 1 cm^3 volume in the hottest part of the tumor, SUV_{mean} is the average value of SUVs in a volume encircling the tumor, MTV determines the Metabolically active Tumor Volume, TGV is the Tumor Glycolytic Volume, that is the product of SUV_{mean} and MTV, and, the last Radiomics, indicating the ensemble of metrics describing the heterogeneity of the tumor.

improve prognostic and predictive values of PET/CT better than MTV. However, before TLG can be tested prospectively, standardization of the MTV and TLG methodology has to be completed and approved.

Radiomics and perspective nuclear medicine specialist for future

Since SUV-based methods are limited by several factors related to the standardization of imaging procedures including patient preparation, harmonization of image acquisition, reconstruction and analysis [123], other features derived from PET/CT images are currently being explored (Fig. 3). Specifically, radiomics has been proposed to identify in a large data set of patients morphologic features that can be clustered by a quantitative and unsupervised analysis into a well-defined homogeneous subgroup of patients sharing specific morphologic characteristics and a possible similar disease outcome [124]. The underlying hypothesis of radiomics is that these quantitative features related to the shape, morphology and heterogeneity of the lesion reflects the physiopathological properties of the tumor: vascularization, cellularity, hypoxia, metabolism, cell density, and necrosis. The process of radiomics comprises the extraction of these quantitative features from the images and their correlation to the clinical variables and patient outcome. The first experience in radiomics has been reported by Ben Bouallegue et al. in 57 patients with lymphoma [125] Quantitative SUV-related metrics, heterogeneity indexes and shape parameters were computed and compared to the results of iPET. The features associated with CMR were low MTV ($p = 0.01$), low TLG ($p = 0.003$), high power spectral density ($p = 0.007$), high surface extension ($p = 0.006$), low 2D fractal dimension ($p = 0.007$), and low 3D fractal dimension ($p = 0.003$). Based on this initial experience it is recommended to include radiomics in well-designed prospective clinical trials in order to explore its possible utility in clinical practice.

Summary - is PET/CT a trump card in the management of HL?

In summary, PET/CT became an integral part of the modern management of HL. It is essential for clinical staging at diagnosis since it is much more accurate that ceCT and allows to skip a blind bone marrow biopsy. It is also essential for response assessment at the end of the therapy since a clearly positive eotPET represent most likely treatment failure; although in case of any doubts histological confirmation of active disease should be undertaken. In contrast, the prognosis of a patient with negative eotPET is good enough that no additional treatment, specifically adjuvant radiotherapy in aHL is required, provided that first line treatment has been planned with an effective chemotherapy regimen like ABVD or eBEACOPP. There is also substantial data based on several large randomized trials supporting the PET/CT response adapted strategy using interim PET/CT assessment after 2 cycles of chemotherapy could be safely undertaken in aHL in every day practice. Specifically, ABVD treated patients with positive iPET2 both in early and advanced stages benefit from treatment intensification to eBEACOPP. Whereas patients with aHL and negative iPET2 could have treatment safely de-escalated: either by omission of Bleomycin in ABVD treated patients or either shortening treatment to 4 cycles of eBEACOPP or shifting to ABVD in the eBEACOPP program. De-escalation does not impair the final results, but also significantly decreases the short, and hopefully long-term, toxicity especially in eBEACOPP treated patients. On the other hand, patients with eHL treated with a PET-response adapted strategy need an individualized approach: omission of RT increases the risk of progression, but the overall survival is the same or even better. MTV and TLG proved very strong prognostic parameters which can substantially improve the predictive values of iPET2. However, not uniformly established methodology still precludes the use of these parameters for risk stratification in clinical practice. Other methods of improving the accuracy of iPET and eotPET such as biomarkers and radiomics is still in the field of clinical research.

Declaration of Competing Interest

None of the authors have any conflicts of interest or financial ties to disclose.

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