RESEARCH ARTICLE

WILEY Pediatric Blood & Cancer

Only strongly enhanced residual FDG uptake in early response PET (Deauville 5 or qPET ≥ 2) is prognostic in pediatric Hodgkin lymphoma: Results of the GPOH-HD2002 trial

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Abstract

Purpose: In 2014, we published the qPET method to quantify fluorodeoxyglucose positron emission tomography (FDG-PET) responses. Analysis of the distribution of the quantified signals suggested that a clearly abnormal FDG-PET response corresponds to a visual Deauville score (vDS) of 5 and high qPET values ≥ 2. Evaluation in long-term outcome data is still pending. Therefore, we analyzed progression-free survival (PFS) by early FDG-PET response in a subset of the GPOH-HD2002 trial for pediatric Hodgkin lymphoma (PHL).

Patients/Methods: Pairwise FDG-PET scans for initial staging and early response assessment after two cycles of chemotherapy were available in 93 PHL patients. vDS and qPET measurement were performed and related to PFS.

Results: Patients with a qPET value ≥ 2.0 or vDS of 5 had 5-year PFS rates of 44%, respectively 50%. Those with qPET values < 2.0 or vDS 1 to 4 had 5-year PFS rates of 90%, respectively 80%. The positive predictive value of FDG-PET response assessment increased from 18% (9%; 33%) using a qPET threshold of 0.95 (vDS ≤ 3) to 30% (13%; 54%) for a qPET threshold of 1.3 (vDS ≤ 4) and to 56% (23%; 85%) when the qPET threshold was ≥ 2.0 (vDS 5). The negative predictive values remained stable at $\geq 92\%$ (CI: 82%; 98%).

Conclusion: Only strongly enhanced residual FDG uptake in early response PET (vDS 5 or qPET $\geq$ 2, respectively) seems to be markedly prognostic in PHL when treatment according to the GPOH-HD-2002 protocol is given.

1 | INTRODUCTION

The prognostic value of interim [F18] fluoro-deoxy-glucose–positron emission tomography (FDG-PET) in pediatric and adult Hodgkin lymphoma (HL) has been investigated extensively during the last 15 years.[1–6] The threshold definition to distinguish between normal and abnormal metabolic response has shifted a few times during this period.[7,8] Since 2009, the Deauville scale has become the international standard.[9] It comprises a five-point scoring system that is based on visual comparison of residual glucose metabolism in lymphoma lesions to particular reference regions, i.e., the mediastinal blood pool and the liver.[9] Visual Deauville scores (vDS) 4 and 5 are currently considered as inadequate response during and at the end of chemotherapy.[10] However, visual comparison is subject to considerable interobserver variability.[11] Moreover, numeric measurements instead of assigning residual glucose metabolism to one of the five Deauville categories allow new types of mathematical analyses. Therefore, the qPET method has been developed to easily quantify the degree of glucose metabolism in lymphoma residuals.

Correspondences between qPET values and vDS were proven based on a large group consisting of 898 patients or qPET values, respectively[12]: The statistical distribution of 898 numeric qPET values represented a unimodal peak (mode: qPET = 0.95) with a long tail of outliers, similar to the distribution of a one-sited laboratory parameter.[12] Such a distribution suggested that qPET values within the peak match with adequate metabolic response while the outliers (sensitive approach: qPET $\geq$ 1.3; specific approach: qPET $\geq$ 2.0) correspond to clearly abnormal response. In addition, the pure visually based numerical Deauville scale (or vDS) could be translated into a continuous scale (= quantitative Deauville score [qDS]): The cutoff between the vDS 2 and 3 was at a qPET value of 0.95, between a vDS of 3 and 4 at a qPET value of 1.3 and between a vDS score 4 and 5 at a qPET value of 2.0.[12] The translation of the numeric qPET scale into the five-point visual Deauville scale is shown in Table 1 for reference. However, no correlation of the qPET cutoff values with long-term survival data has been performed so far. So in the present study, we have investigated which of the qPET cutoff values (≥ 0.95, ≥ 1.3, or ≥ 2.0) had highest prognostic impact in the GPOH-HD2002 trial.[13]

In particular, we have tried to confirm the hypothesis from ref. 12 that a clearly abnormal FDG-PET response corresponds to a vDS of 5 and high qPET values $\geq$ 2 in PHL, which might be an indicator of treatment resistance.

2 | PATIENTS AND METHODS

2.1 | Patients

Between 2002 and 2005, a total of 573 children and adolescents with newly diagnosed classical HL have been enrolled onto the Gesellschaft für Pädiatrische Onkologie und Hämatologie Hodgkin Disease 2002 (GPOH-HD2002) treatment optimization study.[13] The trial was approved by the Ethics Committee of the University of Leipzig and the institutional review boards of the participating centers.[13] All patients and/or guardians of patients gave written informed consent to participate in the trial. Risk stratification for treatment in one of three treatment groups (TG) was performed on the basis of the Ann Arbor stage (Supporting Information Table S1). According to the study protocol, the initial staging and response assessment imaging after 2, 4, or 6 cycles of chemotherapy (depending on the TG assignment) included chest CT scans, MRI, or CT scans of the neck, abdomen, and pelvis. FDG-PET did not influence treatment and was therefore not mandatory in the GPOH-HD2002 trial. However, optional FDG-PET images were evaluated to gain experience preparing the subsequent EuroNet-PHL-C1 trial, in which FDG-PET became mandatory for staging and response assessment in order to decide on treatment intensity. During the GPOH-HD2002 trial, FDG-PET was already routinely performed at several participating study centers for staging and response assessment.

Inclusion criteria for this retrospective analysis were (a) enrollment onto the GPOH-HD2002 trial and (b) availability of attenuation corrected FDG-PET scans from skull base to proximal thighs performed

TABLE 1 Translation of quantitative qPET measurements into quantitative Deauville scores (qDS) and relationship between visually assessed Deauville score (vDS) and qPET value

qDS	vDS
qPET under detection limit	1 = No residual uptake
$0 < qPET < 0.95$	2 = Residual uptake < mediastinal bloodpool
$0.95 \leq qPET < 1.30$	3 = Residual uptake >/= mediastinal bloodpool
$1.30 \leq qPET < 2.00$	4 = Residual uptake > liver
$qPET \geq 2.00$	5 = Residual uptake > > > liver

with a dedicated PET scanner for metabolic response assessment following two courses of induction chemotherapy with at least 10 days interval after last chemotherapy administration.[13] Exclusion criteria were (c) diagnosis of lymphocyte-predominant HL, (d) early response FDG-PET not evaluable (e.g., due to bold brown fat activation and/or inflammatory reactions causing unspecific FDG avidity) and (e) qPET calculation not applicable (e.g., inappropriate scanner data/data format or image data were incompatible with qPET-computing software).

2.2 | FDG-PET data, qPET calculation, and qDeauville definition

Original FDG-PET data sets were sent by the participating sites to the central review board of the GPOH-HD2002 trial for second medical opinion. The results have been discussed within the interdisciplinary central review board. Per GPOH-HD2002 protocol, FDG-PET results had no impact on the individual treatment.

For the current analysis, the early interim FDG-PET scans after two courses of induction chemotherapy (for males: OEPA = vincristine, etoposide, prednisone, doxorubicin; for females: OPPA = vincristine, procarbazine, prednisone, doxorubicine[13]) were in direct comparison with the initial PET scan reevaluated by one experienced nuclear medicine physician (>4.000 FDG-PET response evaluation scans in HL). The visually based Deauville score (vDS) and the qPET value of the hottest residual were documented.

The qPET value was determined semiautomatically as previously described.[12] To do this, the mean standard uptake value (SUV) of the four hottest connected voxels within the residual were divided by the mean SUV of a 30 ml volume of interest (VOI) placed in the liver. A software tool has been applied which released the qPET value just after performing two mouse clicks.

2.3 | Statistics

The distribution of the qPET values was characterized with histogram, density estimate, and empirical cumulative distribution function; qDS scores were derived as described in ref. 12 (see also Table 1). The primary endpoint was progression-free survival (PFS) defined as time interval from registration to the first of the following events such as death, progression, or relapse. Time-to-event data were analyzed with standard methods (Kaplan–Meier curves and log-rank test).

Sensitivity, specificity, as well as positive and negative predictive values (PPV and NPV), were calculated by qDS categories. In addition, a receiver operating curve (ROC) of the quantitative qPET measurements predicting relapse was plotted, with a confidence band based on parametric bootstrap. The AUC, the Youden index, and prevalence-weighted Youden indices were calculated with bootstrap-derived 95% confidence intervals (CI).

3 | RESULTS

3.1 | Data provenance

One hundred sixteen of the 573 patients who have been enrolled into the GPOH-HD2002 trial (286 females and 287 males) received a FDG-PET for staging and interim response evaluation following two courses of OEPA (males) or OPPA (females) chemotherapy. Twenty-three of the 116 patients with available FDG-PET scans had to be excluded from the analysis, because the qPET value could not be calculated for technical reasons or due to artifacts: In nine patients, the FDG-PET images were acquired with a single-photon emission computed tomography coincidence camera system and not by a dedicated PET scanner, in one patient no attenuation-corrected image data were available, in nine patients bold brown fat tissue activation in initially involved areas was present, in two patients severe inflammatory reactions after chemotherapy occurred with increased glucose metabolism extending also in initially involved regions (no discrimination between increased glucose metabolism due to inflammation and active residual lymphoma possible) and in two patients the PET data format was not compatible with the qPET software. Overall, 93 patients (46 males and 47 females) fulfilled the inclusion criteria and presented no exclusion criteria.

In the GPOH-HD2002 trial, treatment was stratified (Supporting Information Table S1); PFS did not differ by TG.[13] The relative proportions of patients in the three TGs differed significantly between the patients with and without available qPET as shown in Table 2. FDG-PET after two courses of chemotherapy was performed more often in TG1 patients (44 of 93 = approximately 47%) because some treating sites performed PET scans routinely after the end of chemotherapy. Omission of radiotherapy was allowed only in TG1 patients achieving complete morphologic remission (CR, defined as ≥95% volume reduction and ≤2 mL residual volume) at the end of their chemotherapy ([13], Supporting Information Table S1). Of the 44 patients in TG1 included in this analysis, 15 (approximately 34%) achieved a complete morphologic response and were therefore not irradiated. However, radiotherapy omission rates within TG1 did not differ significantly between those with available qPET (n = 44, approximately 34%) and those without available qPET (n = 151, approximately 32%). The 5-year PFS was 89% (95% CI, 83%–96%) in the cohort with qPET and 91% (95% CI, 89%–94%) in the cohort without qPET (Supporting Information Figure S1). Thus, both groups were also comparable regarding outcome (P = 0.89).
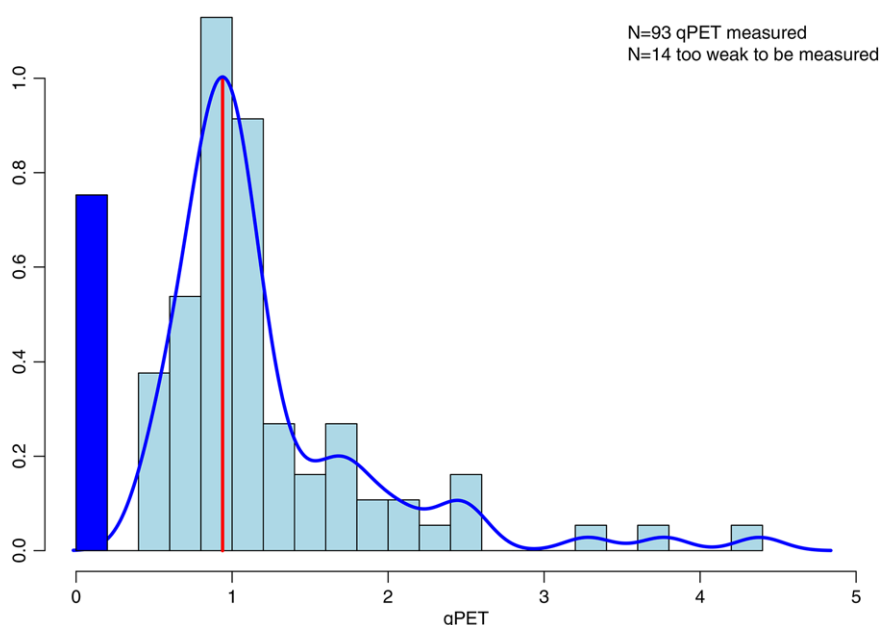
3.2 | qPET distribution curve

The histogram in Figure 1 represents the distribution of the 93 qPET values (qPET cohort). Fourteen of 93 patients (15%) had a complete

TABLE 2 Patients with and without valid qPET according to the three TGs and in comparison to the entire GPOH-HD2002 trial cohort

	qPET cohort (n)	Proportion of TG in qPET cohort	No-qPET cohort (n)	Proportion of TG in no-qPET cohort	GPOH-HD-2002 cohort (qPET + no-qPET = n)	Proportion of TG in the total study cohort
TG 1	44	0.47	151	0.31	195	0.34
TG 2	15	0.16	124	0.26	139	0.24
TG 3	34	0.37	205	0.43	239	0.42
Sum	93	1.00	480	1.00	573	1.00

Pearson χ^2 test: $P = 0.009$.

FIGURE 1 Distribution of qPET signals (n = 93). In 14 patients, qPET was 0 or nearly 0 due to missing residual lymphoma uptake (dark-blue bar). The qPET values of the other 79 patients form the density curve which is characterized by a unimodal distribution with a pronounced mode at qPET = 0.95 (red line), followed by a long tail of outliers.

metabolic remission resulting in a qPET value of zero or nearly zero (dark-blue bar). The density curve (n = 79 qPET values) is characterized by a unimodal distribution with a pronounced mode at qPET = 0.95, followed by a long tail of outliers suggesting a mixture distribution. The unimodal peak of the density curve indicates that these qPET values are consistent with an adequate metabolic response, whereas the tail with the outliers corresponds to clearly abnormal qPET values representing inadequate metabolic responses.

3.3 | vDS and quantitatively derived Deauville scores (qDS) with their prognostic impact

Based on their qPET value, 31 of 44 patients (70%) in the TG 1 were allocated to qDS categories 1 or 2. Thus, the majority of TG1 patients showed qPET values < 0.95 and a clearly adequate response. In TG 2, only 7 of 15 (47%) patients, and in TG 3, 10 of 34 (29%) patients had qDS 1 and 2. TG 3 patients (14 of 34 = 41%) more often showed partial metabolic responses, corresponding to qDS 4 ($2.0 \geq$ qPET ≥ 1.3) or qDS 5 (qPET ≥ 2.0) compared with TG 1 (2 of 44 = 9%) and TG 2 (0 of 15 = 0%) patients (Table 3).

Figure 2 displays the 5-year PFS Kaplan–Meier curves by qDS categories. Among the 93 patients, 11 events occurred (overall 5-year PFS 88.2%). The 5-year PFS did not differ significantly in the qDS categories 1 to 4: qDS 1: 92.9% (CI, 80.3%–100%), qDS 2: 93.6% (95% CI, 85.1%–100%), qDS 3: 95.7% (95% CI, 87.7%–100%), and qDS 4: 90.9%

(95% CI, 75.4%–100%). However, there is a significant difference when comparing categories qDS 1–4 with qDS 5 ($P \leq 0.001$, log-rank test): The 5-year PFS estimate in qDS5 patients was only 44.4% (95% CI, 21.4%–92.3%). Seven of the nine qDS 5 patients had an advanced stage (TG 3) and the remaining two qDS5 patients came from TG1 (early stage). Both TG1 patients with qDS5 were not in complete morphologic response and therefore received radiotherapy. Regarding the five relapses within the qDS5 cohort, four were in TG3 and one in TG1. Two of nine qDS 5 patients died, whereas all 84 patients with qDS 1–4 are alive. A similar result is obtained when the residual metabolism is evaluated purely visually (vDS) (Figure 3). However, prognostic discrimination with vDS was slightly weaker: 5-year PFS rates with vDS 4 and vDS 5 were 80% (95% CI, 58.7%–100%), respectively 50% (95% CI, 25%–100%) (Figure 3).

In addition, sensitivity (sens), specificity (spec), negative and positive predictive values (NPV, PPV) using qDS 3+, qDS 4+, and qDS 5 as thresholds for PET positivity were calculated for the entire patient group as well as separately for the groups of TG1 and TG2/3 patients (Supporting Information Table S2). It is of particular clinical interest that the negative predictive values did not differ relevantly within the thresholds: qDS 3+: 94% (95% CI, 82%–98%), qDS 4+: 93% (95% CI, 84%–98%), qDS 5: 93% (95% CI, 85%–97%). But in contrast, the positive predictive value of interim FDG-PET increased markedly from qDS 3+ with 18% (95% CI, 9%–33%) to qDS 4+ with 30.0% (95% CI, 13%–54%) to qDS 5 with 56% (95% CI, 23%–85%).

TABLE 3 Translation of numeric qPET measurements into qDeauville scores (qDS) among the three TGs with their respective 5-year PFS

qDeauville (qDS) categories and qPET ranges	Number (n)	Proportion	TG1 (n)	TG2 (n)	TG3 (n)	PFS
qDS1: qPET under detection limit	14	0.15	10	3	1	92.9%
qDS2: $0 < qPET < 0.95$	34	0.37	21	4	9	93.6%
qDS3: $0.95 \leq qPET < 1.30$	25	0.27	9	6	10	95.7%
qDS4: $1.30 \leq qPET < 2.00$	11	0.12	2	2	7	90.9%
qDS5: $qPET \geq 2.00$	9	0.10	2	0	7	44.4%
Sum	93	1.00	44	15	34	
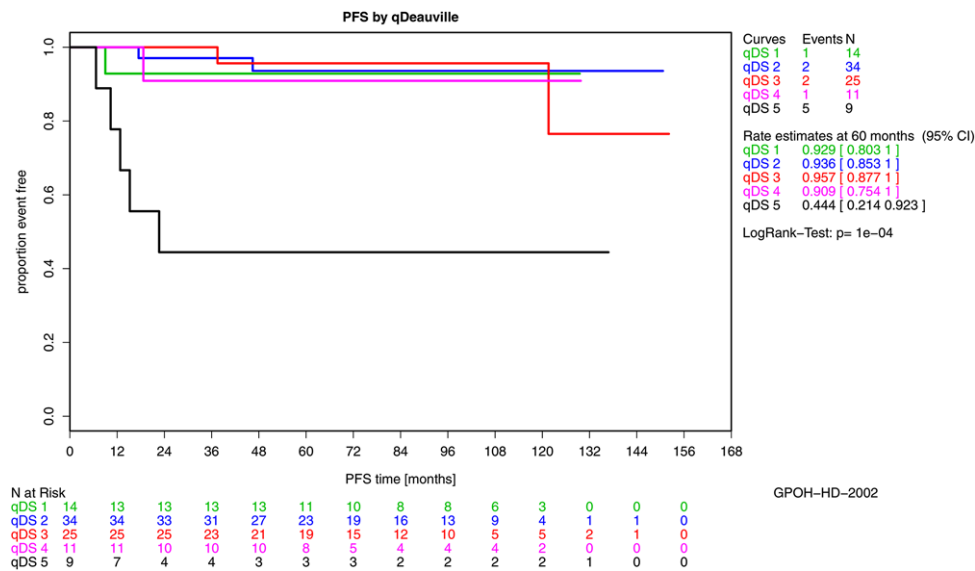
FIGURE 2 Five-year progression-free survival curves according to the five quantitative Deauville (qDS) categories
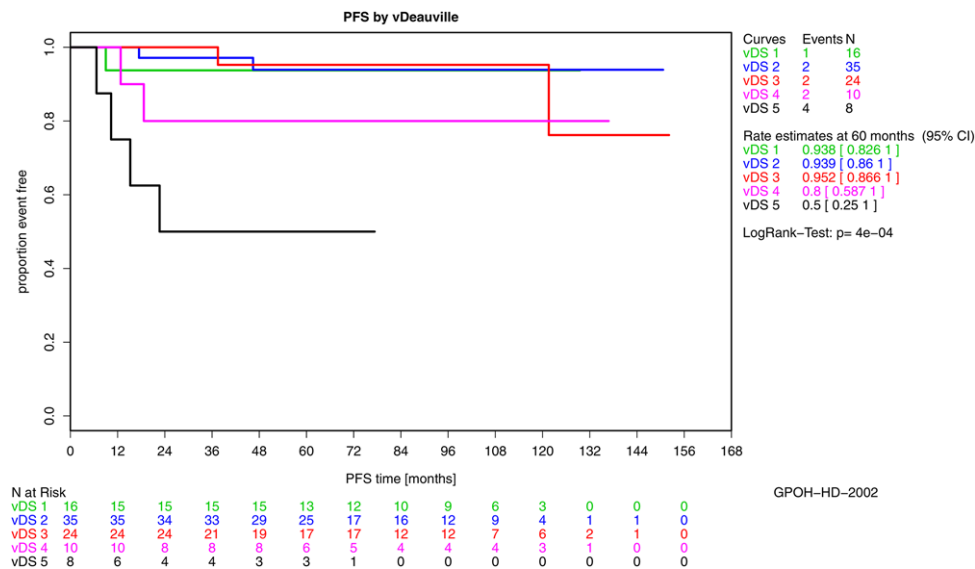
FIGURE 3 Five-year progression-free survival curves according to visual Deauville (vDS) scoring

3.4 | ROC analysis and empirical cumulative distribution function

The ROC curve is shown in Supporting Information Figure S2 and characterized by an AUC of 0.71 (95% CI, 0.5–0.9). The bootstrap-based confidence band is wide. The best cutoff value calculated with the unweighted Youden index is 1.8, but again the confidence interval is broad (95% CI, 1.1–3.1). The 15% prevalence-weighted Youden index, which is more relevant in PHL patients with low event rates, yields a best qPET cutoff value at 2.7 (95% CI, 1.8–3.6). The empirical cumulative distribution function of qPET values by relapse status is shown

in Supporting Information Figure S3: The proportion of patients still in remission and with a qPET value ≥ 2.0 during early response assessment is about 5%. By contrast, this proportion is about 45% in patients who suffered from recurrence or progression.

4 | DISCUSSION

HL is characterized by high cure rates, low rates of relapse and fast metabolic response in FDG-PET following only few cycles of initial chemotherapy.[14] Accordingly, the negative predictive value of interim FDG-PET is generally high, ranging from 91% to 100%.[4,15,16] However, for the positive predictive value, wide ranges from 0% to 100% can be found in the literature.[4,15,16] During the last 15 years with intensive research work, the cutoff between positive and negative interim FDG-PET has been gradually adapted.[7–9] For HL in general, in 2012 an international consensus on the definition of adequate metabolic response in FDG-PET was achieved based on the Deauville scoring: A residual glucose metabolism up to a visually based Deauville score of 3 in interim and end-of-treatment FDG-PET is considered as adequate response in patients receiving standard treatment.[17] In contrast, Deauville scores of 4 and 5 are interpreted as PET positive.[17] In ref. 12, we developed the qPET method as a quantitative extension of the visual Deauville scale to improve reproducibility and allow additional analyses. The analysis presented here relies on quantitative qPET measurements.[12] Important properties of the qPET method are confirmed: First, the shape of the qPET density curve calculated based on 93 patients was nearly the same as the respective qPET density curve determined from more than 898 PHL patients.[12] Especially the mode at a qPET value of 0.95 was identical. Second, comparison between the quantitatively derived Deauville score (qDS) and the vDS with respect to 5-year PFS rates suggests that qDS might increase the precision of the vDS system: Using qDS instead of vDS led to a shift of a small proportion of patients originally assigned to Deauville 4 based on visual scoring (vDS 4) to either qDS3 or qDS 5. However, a larger data set would be required to confirm this hypothesis. A recent publication provided by Biggi et al on 82 adult HL patients also demonstrated that the addition of quantitative methods, particularly SUVpeak measurements, led to a more accurate evaluation of the residual metabolic activity, which in turn increased the positive predictive value of interim PET.[18] Third, having quantitative qPET measurements instead of Deauville scores allows additional analyses: We performed a ROC analysis and determined the 15% prevalence-weighted Youden index, suggesting that a qPET cutoff value of ≥2.7 might be optimal to select particularly high-risk cases. However, due to the low rate of only 11 events, the ROC curve is unstable and shows a broad confidence level, what precludes definitive conclusions. From a statistical point of view, stable and reliable results can be expected if more than 50 relapses with a qPET value ≥ 2.0 are available for analyses. For a definite answer, the results of the EuroNet-PHL-C1 (2006-000995-33) trial with more than 2000 PHL patients have to be awaited.

In our data, only patients with a visually determined Deauville score of 5, but particularly with a qPET value ≥ 2.0 during early response assessment had a significantly reduced 5-year PFS (to about 50%). This tentatively confirms the model-based hypothesis that qDV5 selects a group of patients with clearly abnormal metabolic response with a high proportion of treatment failures.[12] qDV5 may be an indicator of different tumor biology, making respective patients possible candidates for alternative treatment approaches. The hypothesis that a markedly enhanced FDG-PET signal (Deauville score of 5 or a qPET value ≥ 2.0) indicates treatment resistance is further supported by Johnson et al[19] who investigated advanced adult HL patients. Here, FDG-PET was applied to guide further treatment following two courses of initial ABVD chemotherapy. Patients with a negative interim FDG-PET (vDS 1–3) received either ABVD or AVD, whereas patients with a positive interim PET (vDS 4–5) received a more intensive chemotherapy (either BEACOPP-14 or BEACOPP escalated). Johnson et al[19] noticed that a vDS of 5 was associated with a higher risk of relapse. In their Deauville 5 group (n = 38 patients), 20 treatment failures were observed despite treatment escalation. Conversely, with treatment according to the GPOH-HD-2002 protocol, there are no apparent prognostic differences within qDS1-4 data, suggesting that the applied therapy is sufficient in these patients. The data presented here do not allow determining whether standard treatment may be reduced in selected patients with adequate metabolic response. However, preliminary results of the EuroNet-PHL-C1 study show that radiotherapy can be omitted in about 50% of all PHL patients with vDS < 3 without major loss of efficacy.[20,21] In the ongoing EuroNet-PHL-C2 study (EurdraCT 2012-004053-88), only patients with inadequate response (qPET ≥ 1.3 corresponding to Deauville scores 4 and 5) are candidates for radiotherapy. This will lead to a further reduction of radiation therapy rates, but data on outcome are not yet available. Depending on the results of EuroNet-PHL-C2, further optimization of the qPET threshold toward qDS4 may help reducing radiotherapy rates and avoiding radiation-related late effects.[22–24]

In conclusion, we successfully applied the qPET method and its translation into qPET Deauville scores to data of GPOH-HD2002. We tentatively confirmed the hypothesis that qPET ≥ 2 or qDS = 5 represents a clearly abnormal metabolic response and has a markedly unfavorable prognosis, while qDS1–4 shows a uniformly favorable outcome with standard therapy. This finding needs confirmation in a larger, separate trial with balanced proportions of all TGs. Moreover, we demonstrated that using quantitative qPET measurements allows novel types of analysis and possibly further optimization of response-adapted therapy.

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CONFLICTS OF INTEREST

None of the authors has a conflict of interest in connection with the GPOH-HD2002 study and the data presented here.

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SUPPORTING INFORMATION

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