Value of qPET in Pediatric Patients with Hodgkin Lymphoma

Mehesen M[1,6], Moussa E[2,6], Elsayed W[3,6], Zaghloul MS[4,6], Elwakeel M[5,6], Ali N[3,6]

[1] Department of Nuclear Medicine, National Cancer Institute (NCI), Cairo University, Egypt
[2] Department of Clinical Oncology, Elmenofya University, Egypt
[3] Department of Pediatric Oncology and Hematology, National Cancer Institute (NCI), Cairo University, Egypt
[4] Department of Radiation Therapy, National Cancer Institute (NCI), Cairo University, Egypt
[5] Department of Radiodiagnosis, National Cancer Institute (NCI), Cairo University, Egypt
[6] Children Cancer Hospital Egypt (57357), Cairo, Egypt

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Abstract:

Introduction: qPET is a semi-automatic quantitative measurement used to assess the positron emission tomography (PET) response in lymphoma. The aim of this study was to compare qPET and the Deauville score (DS) and find their concordance in childhood Hodgkin lymphoma (HL) patients treated with the Euronet protocol at the Children Cancer Hospital Egypt (CCHE).

Materials and Methods: qPET is computed by dividing the peak standardized uptake value (SUV) of the hottest residual uptake by the mean SUV of the liver. Interim PET (iPET) will be evaluated in accordance with qPET and Deauville score (DS).

Results: We retrospectively analyzed 424 pediatric patients with HL, with a mean age of 10.1 (2-18) years. Based on iPET measurements, DS1was identified in 24 patients, DS2 in 106 patients, DS3 in 187 patients, DS4 in 77 patients, and DS5 in 30 patients. 317 patients were negative (DS 1-3), while 107 were positive (DS 4-5). qPET revealed that 341 patients were negative (<1.3), and 83 were positive (≥1.3).

We found that 25 patients had a DS 4 (positive) and a qPET 3 (negative), out of these patients, two experienced a relapse, while the remaining twenty-three patients were in complete remission.

The overall survival (OS) and Event free survival (EFS) for negative DS were 99.1% and 90.4%, respectively. Similarly, for negative qPET, the OS and EFS were 99.2% and 88.3%, respectively. In contrast, the OS and EFS for positive DS were 95.3% and 80.1%, respectively, and for positive qPET, they were 94.4% and 83.9%.

Conclusion: Our qPET results indicate that it is a suitable semi-automatic quantitative method for evaluating response in pediatric HL patients treated with the Euronet protocol.

Keywords: qPET, pediatric, Hodgkin Lymphoma, response, interim PET

Authors Information:

Maha Mehesen
Department of Nuclear Medicine, National Cancer Institute (NCI), Cairo University, Egypt and Children Cancer Hospital Egypt (57357).
email: dr.maha_mehesen@yahoo.com

Emad Moussa
Department of Clinical Oncology, Elmenofya University, Egypt and Children Cancer Hospital Egypt (57357).
email: emad.moussa@57357.org

Walaa Elsayed
Department of Pediatric Oncology and Hematology, National Cancer Institute (NCI), Cairo University, Egypt and Children Cancer Hospital Egypt (57357).
email: walaaelsayed2013@gmail.com

Mohamed S Zaghloul
Department of Radiation Therapy, National Cancer Institute (NCI), Cairo University, Egypt and Children Cancer Hospital Egypt (57357).
email: mohamed.zaghloul@57357.org

Madiha Elwakeel
Department of Radiodiagnosis, National Cancer Institute (NCI), Cairo University, Egypt and Children Cancer Hospital Egypt (57357).
email: Madeeha.Elwakeel@57357.org

Nesreen Ali
Department of Pediatric Oncology and Hematology, National Cancer Institute (NCI), Cairo University, Egypt and Children Cancer Hospital Egypt (57357).
email: nesreenalinci@hotmail.com

Corresponding Author:
Nesreen Ali
Department of Pediatric Oncology and Hematology, National Cancer Institute (NCI), Cairo University, Egypt and Children Cancer Hospital Egypt (57357).
email: nesreenalinci@hotmail.com

Introduction:

HL comprises about 10% of malignancies that occur in the pediatric age group. Due to its notable sensitivity to both chemotherapy and radiotherapy, survival rates now exceed 90% with modern protocols [1].

The challenge is maintaining a balance between high survival rates and minimizing long-term side effects, especially in the pediatric population. [2]

The most commonly used strategy in the treatment of HL is response-adapted therapy based on response measurement by fluoro-deoxy-glucose-positron emission tomography (FDG-PET) after the first two cycles of chemotherapy. Based on their early response assessment, this strategy can identify patients who can safely reduce their treatment intensity. This is of extreme importance to avoid late effects and secondary malignancies that can occur in pediatric patients due to the high likelihood of cancer survivorship [3].

The prognostic value of interim FDG-PET in patients with HL has been extensively studied over the past years. The DS has been used for PET response assessment. It is a five-point scaling system that depends on a visual comparison of glucose metabolism in lymphoma cells to physiological reference uptake, such as the liver or mediastinum. [4]

Patients with a DS of 1 or 2 in the interim PET are considered to be in complete metabolic remission. The interpretation of score 3 depends on the time of evaluation. Patients with scores 4 and 5 at the interim PET and end of treatment are considered to have an inadequate response and treatment failure, respectively. [5]

However, the main problem is that visual comparison may lead to significant inter-reader variability and need to be more accurate, especially in small residuals. [4]

The quantitative positron emission tomography (qPET) is a semi-automatic method that can measure uptake in small lymphoma residuals and the relevant physiological uptake. So, the DS can be extended to a continuous scale [3]. It is calculated by dividing the peak SUV of the warmest residual uptake over the mean SUV in the liver. It was derived from assessing PET scans of 898 pediatric patients with HL enrolled in the EuroNet-PHL-C1 study [2], in which the correlation between qPET values and visual Deauville scale (vDS) was determined. The qPET statistical distribution is shown as a unimodal-peaked distribution with a mode at qPET = 0.95 and a lengthy tail of outliers. The peak corresponds to a satisfactory metabolic response, whereas the outliers (using a sensitive approach: qPET $\geq$ 1.3; using a specific approach: qPET $\geq$ 2.0) indicate an inadequate response. In addition, the vDS may be converted into a continuous scale known as quantitative DS (qDS). The threshold values for differentiating between vDS 2 and 3, vDS 3 and 4, and vDS 4 and 5 are 0.95, 1.3, and 2.0 at qPET value, respectively [3].

In our study, we tried to detect the degree of concordance between vDS and qPET and their correlation with the outcomes.

Patients and Methods:

This retrospective study analyzed 424 pediatric patients with newly diagnosed HL at the CCHE, from February 2019 to June 2021. Before starting treatment, positron emission tomography-computed tomography (PET-CT) scan was performed for each patient. Interim PET was performed after two cycles of chemotherapy with at least a 10-day interval after the last chemotherapy administration.

In our study, we reanalyzed interim PET using DS and qPET and then detected the degree of concordance between them. Our study received approval from the Institutional Review Board.

An interim PET assessment was conducted by a radiodiagnosis and a nuclear medicine physician, blinded to the results of the patient's outcome. Using the vDS, the lesion uptake was compared based on mediastinal and liver references. The mediastinal reference was a cuboid volume of interest (VOI) with a volume of 13.5 ml (edge length proportion length: width: height = 1:1:2) placed carefully within the blood pool. The hepatic reference was a cuboid VOI with a volume of 30 ml (edge length proportion length: width: height = 2:2:1) placed on the right liver lobe [3].

qPET is the ratio of peak SUV, which is the average SUV of the four hottest connected voxels inside the tumor at the target lesion, to the mean SUV in the right lobe of the liver measured using a 30 ml VOI with length, width, and height proportions of 2:2:1. (mean SUV) [3].

Results:

We retrospectively included 424 patients diagnosed and treated at CCHE. 122 females and 302 males, with a mean age of 10.1 (2-18) years.

Regarding pathologic subtypes, lymphocyte depletion (LD) was observed in 9 patients, mixed cellularity (MC) in 143 patients, Nodular lymphocyte predominant HL (NLPHL) in 2 patients, lymphocytic rich (LR) in 15 patients, and nodular sclerosis (NS) in 255 patients.

In 51 patients, stage IA was identified, stage IB in 12 patients, stage IIA in 104 patients, stage IIB in 40 patients, stage IIIA in 61 patients, stage IIIB in 59 patients, stage IV A in 35 patients, and stage IVB in 62 patients. All patients' characteristics are shown in Table 1.

Regarding negative findings, 317 individuals exhibited negativity in the vDS and qPET CT scans, whereas 83 patients showed positivity in both procedures.

The qPET CT findings and DS results were consistent across all patients, with DS 1 (24/24) and DS 5 (30/30). However, there was a notable difference in patients with DS4, where 25 patients had a positive DS4 result and a negative qPET 3 result. Across these patients, only 2 had recurrence, while the rest achieved complete remission. Table 2

Our analysis revealed that the two-year overall OS for negative DS was 99.1%, whereas the two-year OS for positive DS was 95.3 (P = 0.30). Similarly, the two-year OS for negative qPET was 99.2%, and the two-year OS for positive qPET was 94.4 (P = 0.18). Figure 1

Regarding EFS, we found that those with a negative DS had a 2-year EFS rate of 90.4%, while those with a positive DS had a 2-year EFS rate of 80.1%. The statistical analysis showed a substantial difference between the two groups, with a P value of 0.004. The 2-year EFS rate for patients with a negative qPET is 88.3%. On the other hand, the 2-year EFS rate for patients with a positive qPET is 83.9%. The difference in survival outcomes between the two groups is statistically significant, as shown by a p-value of 0.03. Figure 2 & Table 3.

Table 1: Baseline disease characteristics and survival outcome of the study participants

Study participants (n =424)	
Age at diagnosis (months)	The mean age of 10.1, Range (2–18) years
Gender	
Male	302 (71%)
Female	122 (29%)
Pathologic subtypes,	
CHL	
NS	255
MC	143
LR	15
LD	9
NLPHL	2
Stage of disease	
stage IA	51
stage IB	12
stage IIA	104
stage IIB	40
stage IIIA	61
stage IIIB	59
stage IV A	35
stage IVB	62
Survival outcome	
2-Year OS	98%
2-Year EFS	85%

CHL: Classic Hodgkin Lymphoma, NS: Nodular Sclerosis, MC: Mixed Cellularity, LR: Lymphocyte Rich, LD: Lymphocyte Depletion, NLPHL: Nodular Lymphocyte Predominant Hodgkin Lymphoma, EFS: Event Free Survival, OS: Overall Survival

Table 2: Comparison of visual DS scores and qPET

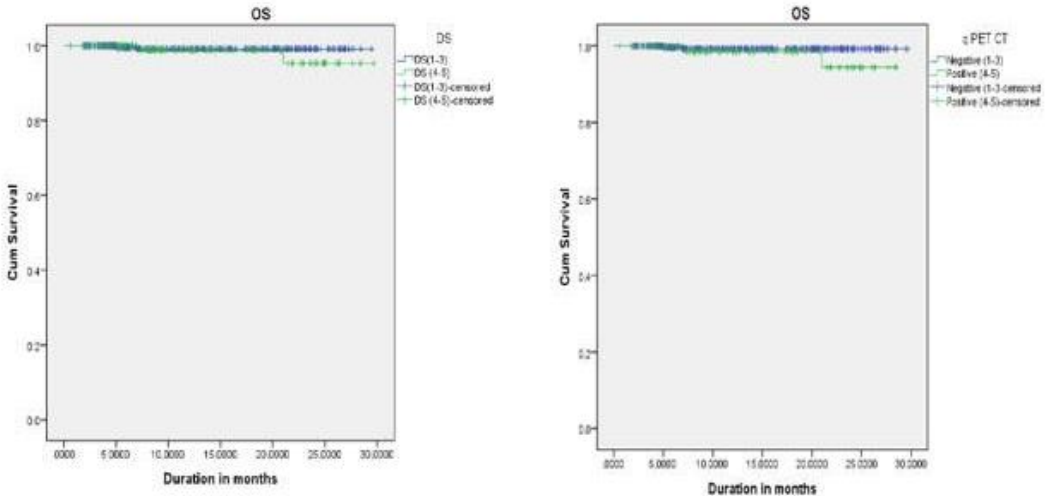
	qPET 1	qPET 2	qPET 3	qPET4	qPET 5	Total
vDS1	**24**	0	0	0	0	24
vDS 2	0	**96**	10	0	0	106
vDS 3	0	63	**123**	1	0	187
vDS 4	0	0	25	**50**	2	77
vDS 5	0	0	0	0	**30**	30
Total	24	159	148	51	32	424

vDS: visual Deauville score, qPET: quantitative positron emission tomography, Bold line for concordance cases

Table 3: Response of the patients according to vDS and qPET and survival outcome

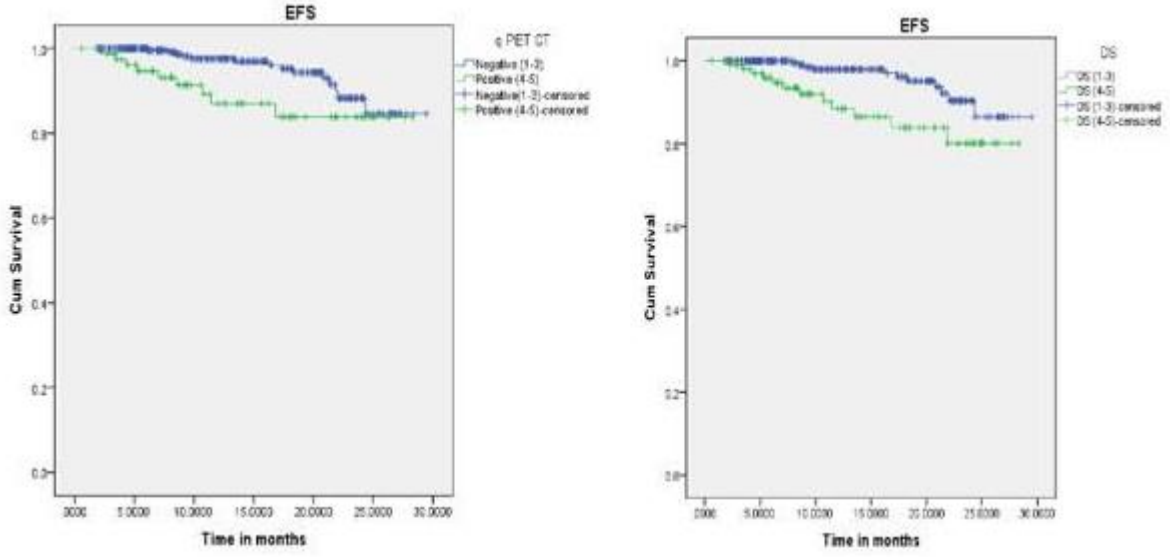
Total number 424	Number (n)	OS	EFS	Concordance
Negative by q PET (<1.3)	341	99.2%	88.3%	93 %
Negative by DS (1-3)	317	99.1%	90.4%	
Positive by qPET (>1.3)	83	94.4	83.9%	
				77.5%
Positive by DS (4-5)	107	95.3%	80.1%	

DS: Deauville score, qPET: quantitative positron emission tomography, EFS: event free survival, OS: overall survival



DS: Deauville score, qPET: quantitative positron emission tomography, OS: Overall survival

Figure 1:
A: 2 years OS for negative DS (99.1%), 2 years OS for positive DS (95.3), p value 0.30
B: 2 years OS for negative qPET (99.2%), 2 years OS for positive qPET (99.4), p value 0.18



DS: Deauville score, qPET: quantitative positron emission tomography, EFS: Event free survival

Figure 2:
A: 2 years EFS for negative DS (90.4%), 2 years DFS for positive DS (80.1), p value 0.004
B: 2 years EFS for negative qPET (88.3%), 2 years DFS for positive qPET (83.9), p value 0.03

Discussion:

The interim FDG PET (iPET) has shown its reliability as an imaging tool for early therapy implementation [5,6]. In general, iPET scans have a substantial negative predictive value, often ranging from 91% to 100% [8-10]. Nevertheless, the literature reveals a broad range of positive predictive values, ranging from 0% to 100% [7-9]. Through extensive investigation, the threshold for distinguishing between positive and negative interim FDG-PET results has been continuously adjusted [10,11].

The Lugano classification is the standard method for evaluating iPET. It uses the DS, a five-point scale, to assess the residual uptake in the sites affected initially by lymphoma [12].

Nevertheless, relying solely on DS for visual evaluation of iPET may be susceptible to inaccuracies, including significant differences in interpretation among readers [5,13]. These discrepancies can arise when attempting to compare the level of FDG uptake in small remaining lymphomatous lesions with uptake in normal reference organs (such as the liver or mediastinum) that are physically distant. Additionally, the perception of uptake intensity is influenced by the surrounding background (known as the simultaneous contrast illusion) [14].

Using qPET to assess iPET originated from a study including 898 children with HL who participated in the EuroNet-PHL-C1 study [6,15]. This method is presently being applied in the EuroNet-PHL-C2 study [16], which has already included over 1700 patients.

The RAPID study, which had 602 adult patients with HL, discovered that the distribution of qPET values closely resembled that of C1 patients. The distribution displayed an unimodal 'normal' pattern, with a long tail towards the right. This suggests that most patients had a favorable response, but a minority had less favorable responses, as shown by the outlying values. The RAPID study employed qPET criteria from C1 and observed an 86% agreement between vDS and qDS [17].

We retrospectively analyzed 424 pediatric patients newly diagnosed with HL and treated at the Children Cancer Hospital in Egypt. The analysis showed DS1 in 24 patients, DS2 in 106 patients, DS3 in 187 patients, DS4 in 77 patients, and DS5 in 30 patients. 317 patients had an adequate response (vDS 1-3), while 107 had an inadequate response (vDS 4-5). Regarding qPET, 341 patients were negative (less than 1.3), and 83 were positive (more than 1.3).

Twenty-five patients of DS 4 (positive) were qPET 3 (negative), while one patient of DS 3 (negative) was a qPET 4 (positive). Two patients out of twenty-five (2/25) who were positive by DS and negative by qPET experienced a relapse, while the remaining twenty-three patients were in complete remission, so qPET CT should be considered a strong negative test.

The qPET threshold gave 93% concordance for vDS and qPET as regards negative value and 73% concordance for positive value. Regarding EFS, our study found that those with a negative DS had a 2-year EFS rate of 90.4%, while those with a positive DS had a 2-year EFS rate of 80.1% with a P value of 0.004. While the 2-year EFS rate for patients with a negative qPET is 88.3% and for those with a positive qPET is 83.9% with a p-value of 0.03.

This was in agreement with a study conducted by Georgi et al. [17], it was reported that patients who had a qPET value of 2.0 or above and a vDS of 5 experienced 5-year progression-free survival (PFS) rates of 44% and 50%, respectively. Patients with qPET values below 2.0 and vDS scores ranging from 1 to 4 had 5-year PFS rates of 90% and 80%, respectively. The iPET had a positive predictive value of 18% (9%; 33%) when using a qPET threshold of 0.95 (vDS $\leq$ 3), 30% (13%; 54%) when using a qPET threshold of 1.3 (vDS $\leq$ 4), and 56% when the qPET threshold was $\geq$ 2.0 (vDS 5). The negative predictive values were consistent at a minimum of $\geq$92% (CI: 82%; 98%).

In addition, S. Pacella et al. conducted a retrospective analysis of 63 newly diagnosed pediatric HL cases, with a median follow-up period of 44 months for disease-free survival (DFS) and 55 months for OS. Two patients had disease progression and subsequently died, while eight patients experienced recurrence. The iPET scan yielded negative results in 56 individuals, accounting for 89% of the total, whereas positive results were seen in 7 patients, making up 11%. A correlation was found between qPET readings and OS with a p-value of 0.01. However, no significant association was seen between qPET and DFS, with a p-value of 0.07. The iPET test demonstrated perfect accuracy in predicting positive results, with a positive predictive value (PPV) of 100%. Additionally, it showed high accuracy in predicting negative results, with a negative predictive value (NPV) of 92%. The researchers determined that individuals who had an iPET scan with a qPET value of 1.3 or higher had a worse prognosis in terms of OS [18].

Conclusion:

qPET can be used as a quantitative expansion of the DS in evaluating the response of interim FDG-PET in pediatric HL patients treated with the Euronet protocol. The qPET data show a concordance rate of 93% for negative results and 77.5% for positive results in relation to vDS. These results also exhibited a substantial correlation with the survival outcome. Therefore, interim qPET should have prognostic significance in pediatric HL patients.

List of abbreviations:

CCHE: Children Cancer Hospital Egypt
CHL: Classic Hodgkin Lymphoma
DS: Deauville score
EFS: Event Free Survival
FDG-PET fluoro-deoxy-glucose-positron emission tomography
HL: Hodgkin Lymphoma
iPET: Interim- fluoro-deoxy-glucose-positron emission tomography
LD: Lymphocyte Depletion

LR: Lymphocyte Rich
MC: Mixed Cellularity
NCI: National Cancer Institute
NLPHL: Nodular Lymphocyte Predominant Hodgkin Lymphoma
NS: Nodular Sclerosis
OS: Overall Survival
PET-CT: Positron emission tomography–computed tomography
PFS: Progression free survival
qDS: quantitative Deauville score
qPET: quantitative positron emission tomography
SUV: Standardized Uptake Value
vDS: visual Deauville scale
VOI: volume of interest

Conflict of interest:

The authors states that they have no conflicts of interest to disclose.

Authors contributions

NA, MM, and WE: concept of the study, data analysis and data interpretation and writing the manuscript. EM, ME and MSZ: assisted in the analysis of the data and drafted the manuscript. All authors approve the manuscript

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