Am J Nucl Med Mol Imaging 2019;9(3):176-184
www.ajnmmi.us /ISSN:2160-8407/ajnmmi0094917

Original Article

Dual-point FDG-PET/CT for treatment response assessment in Hodgkin lymphoma, when an FDG-avid lesion persists after treatment

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Received April 5, 2019; Accepted June 10, 2019; Epub June 15, 2019; Published June 30, 2019

Abstract: FDG-PET/CT (PET) is now considered the standard imaging tool for Hodgkin Lymphoma (HL) staging and restaging. However a CT-detected residual mass at the end of therapy (EoT) is still a challenge for PET interpretation. The aim of our study was to improve the overall accuracy of EoT PET/CT by using a dynamic dual-point scanning at 60 and 120 after FDG injection (2P-PET/CT). Fifty-one HL patients showing a single residual FDG-avid mass (SFAM) at EoT PET/CT were included in the study in Italy and Poland. Treatment was ABVD, ABVD followed by BEACOPP or ABVD plus radiotherapy. Only patients with a SFAM and a Deauville score (DS) > 2 in EoT PET/CT were included in the study. Two independent nuclear medicine reviewed images with a semi-quantitative analysis (SUVMax and retention index, RI) and a visual scoring according to DS. Compared to standard PET, 2P-PET/CT showed only a modest increase in NPV and PPV, from 0.87 to 0.89 and of the PPV from 0.67 to 0.71, respectively. Increase of the overall accuracy became substantial upon including in the analysis only patients whose images were acquired in strict adhesion to original protocol of 2P-PET/CT scanning: (t 120'-6040 min): the sensitivity increased from 0.60 to 1.00, PPV from 0.75 to 0.83 and NPV from 0.89 to 1. This study, with caution for the small number of patients included, seems to suggest that 2P-PET/CT could increase the overall accuracy of EoT PET/CT in correctly classifying treatment response in HL with a persisting SFAM at EoT.

Keywords: Hodgkin lymphoma, dual point PET, retention index, deauville score

Introduction

Hodgkin's lymphoma (HL) has been for long considered the archetype for tumor staging and restaging in oncology [1]. Thanks to its ability to image both anatomical and metabolic characteristics of the tumor, [^{18}F]-Fluoro-Deoxy-Glucose Positron Emission Tomography [FDG-PET] combined with computed tomography (CT), is able to provide a more accurate readout of treatment response compared to the pure radiological diagnostic tools such as contrast-enhanced CT (CeCT). This is especially evident in lymphoma, where a residual mass detected by CeCT at the end of treatment (EoT) is not necessarily considered a harbinger of residual disease. This phenomenon, which occurs in one third of diffuse large B cell lymphoma and in more than two thirds of HL patients, is the main reason of the low accuracy of a CeCT-assessed treatment response in HL patients with bulky mass [2, 3].

In CeCT-restaged HL patients, the persistence of a residual mass in a patient otherwise in clinical complete remission underpinned the defini-

tion of "complete response undefined" (CRU) [2-4]. As a matter of fact, HL patients in CRU showed only an identical or slightly inferior treatment outcome compared to those in CR [5, 6].

On the other hand, a FDG-avid residual mass at End of Therapy (EoT), both in HL and in aggressive B-cell lymphoma is considered a potential risk factor for relapse [6].

Kinetics of FDG cell fixation clearly depends on the nature of tissue imaged. Dual-point FDG-PET/CT (2P-PET/CT) is a PET technique that consists of acquiring the same district/portion of the patient at two different time points to capture the increase/decrease of FDG uptake within a lesion.

Preliminary work showed that 2P-PET/CT images acquired at +45 and 90' after FDG injection showed a significant increase in tracer retention by tumour cells (59% to +198%), whereas the opposite phenomenon was recorded in inflammatory tissue (mononuclear cells) in which the SUV dropped overtime in most cases [7]. Moving from these preliminary observations of FDG kinetics, 2P-PET/CT was proposed as a possible tool to differentiate the inflammatory tissue from the lesions of neoplastic nature. In a limited number of proof-of-concept studies 2P-PET/CT was able to distinguish with a good accuracy inflammatory/benign disorders from malignant lesions [8-13].

The purpose of the present study was to assess the overall accuracy and predictive value on treatment response of EoT 2P-PET/CT compared to standard FDG-PET/CT in HL presenting at baseline with a large nodal mass (LNM), which resulted in a single residual FDG-avid mass (SFAM) after treatment.

Materials and methods

Consecutive HL patients, with both early and advanced stage, presenting at baseline with a LNM (see below) and showing an EoT SFAM, were retrospectively enrolled in the study between September 2010 to January 2014, from six Italian and three Polish centers (Cuneo, Rome, Monza, Padua, Venice, Palermo and Bydgoszcz, Olsztyn, Gdansk).

A bulky mass was defined as a nodal mass (or conglomerated multiple nodes) with the largest diameter equal or longer than 10 cm, according to international standard definition [14].

A LNM at baseline was defined as a single nodal mass or multiple conglomerated nodes with the largest diameter equal or longer than 5 cm.

SFAM was defined as a residual mass on the co-registered CT (maximum diameter > 15 mm) characterized by one or more internal hot spots of FDG uptake.

Inclusion criteria

Patients enrolled in the study had to fulfill all the following criteria: (1) age > 18, (2) diagnosis of LH classic; (3) minimum follow-up ≥ 12 months, (4) presence at diagnosis of bulky or LNM, as defined above, (5) presence of SFAM in EoT FDG-PET/CT. The exclusion criteria were: pregnancy, lactation, active infection, sarcoidosis, and a positive serology for HIV. All the enrolled patients signed an informed consent before 2P-PET/CT scanning. The ethic committee of the coordinating center in Cuneo, Italy, approved the study.

Patient scanning protocol

All the following criteria, had to be fulfilled for patients candidate to 2P-PET/CT scanning: (1) Date of EoT FDG-PET/CT acquisition not less than 28 days from the end of the last chemotherapy; (2) In case of radiotherapy (RT) administered at the end of treatment, the patients had to be scanned at least three months after the end of RT. (3) Patients had to keep fasting for at least 6 hours before injection of FDG and between early and late scan. (4) Fasting glucose blood level had to be ≤ 120 mg/dl and (5) a standard intravenous injection of FDG between 3 and 5,3 MBq/kg, based on acquisition technology. (6) The early image acquisition in 2P-PET/CT scanning was set at +60 ± 10' after FDG injection, in agreement to European Association of Nuclear Medicine guidelines for standard FDG-PET/CT scanning [15], while patients were lying in supine position in a quiet room and instructed not to move or talk. (7) Early whole-body scan had to be comprised from base of skull to proximal femur, while late scan was limited to the site of SFAM. (8) Timing of late image acquisition was set at +120' ± 10' according to the previously published studies

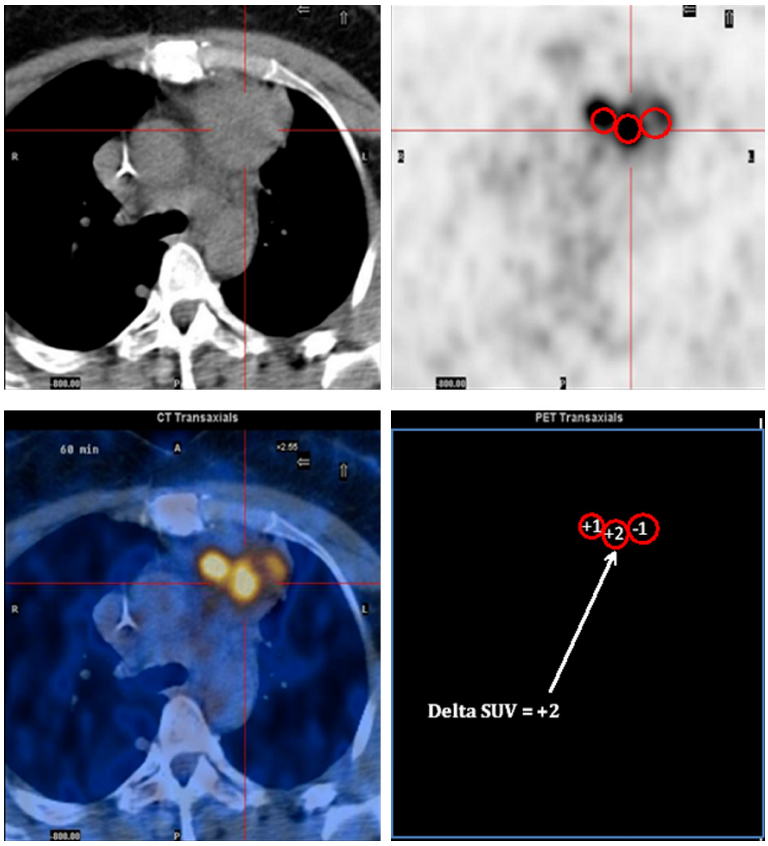

Figure 1. Example of PET interpretation in case of multiple foci (VOI drawn in a large antero-mediastinal mass): if there were several foci with an increase in uptake between 60 and 120 minutes, only the focus with the highest increase was considered.

on 2P-PET/CT scanning in lymphoma [13, 16, 17]. (9) In both scanning time points images had to be acquired with the patient lying in the same bed position and finally the acquisition time for single bed had to be normalized to the longer time lag between tracer injection and image acquisition.

Image interpretation and quantification

Two expert nuclear medicine physicians (S.M. and C.Z.), reviewed the 2P-PET/CT scan images as follows: in the early acquisition images (60') the number of sites of residual FDG-avid focal spots in a single or multiple nodal sites visible at FDG-PET/CT fused images were noted. For the purpose of the present study only scans with a Deauville five-point scale (DS) score ≥ 2 in a node previously involved by disease were included in the analysis. SUVmax of all sites of focal spots was measured in a 3D Volume of Interest (VOI) of at least 10 mm diameter. To account for partial volume effect in SUVmax quantification, VOIs were considered separately according to their size, depending on the maximum diameter length (> or ≤ 15 mm).

The same VOIs were copied to the late acquisition images (120' images) and SUVmax was measured. The DSUVmax (SUVmax 120'-SUVMmax 60') and the Retention Index (RI: DSUVmax/SUVmax 60') were then measured in each VOIs.

If the residual foci of FDG uptake had a discordant behavior in the single patient (e.g. coexisting positive and negative DSUVmax in the same or different nodal sites), only the ΔSUVmax positive foci were considered (**Figure 1**). In case of several concordant increasing or decreasing VOIs in the single patient, the highest ΔSUVmax value was chosen for the semi-quantitative analysis.

Beside a semi-quantitative analysis by SUVmax assessment, a visual scoring according to the DS was also performed in early PET scan images. DS was not evaluated in late images because the scans were limited to the site of SFAM, only occasionally including MBPS and liver.

Statistical analysis

To analyze the prognostic relevance of qualitative vs. semi-quantitative readout for 2P-PET/CT interpretation, the parameters were dichotomized by applying the receiver operating characteristic (ROC) analysis, to predict with the best sensitivity (SE) and specificity (SP) the treatment outcome, in term of 2 years Failure-Free Survival (FFS). FFS was defined as the time from diagnosis to either disease progression or relapse, or to death by any cause. The resulting cut-off were used to calculate the number of True Positive (TP), True Negative (TN), False Positive (FP) and False Negative (FN) results and the derived (SE), (SP), Positive

Table 1. Demographics

Parameter	Modality	Results
Gender	M/F	28/23
Age	Median (range)	29.7 (19-61)
Stage	II	19
	III	11
	IV	21
Bulky	Ø ≥ 5 cm	39
	Median Ø (cm)	9.6 (5.2-15.3)
Therapy	ABVD	34
	ABVD/BEACOPP	15
	Other	2
Consolidation RT	Involved field	19
Biopsy	Disease	10
	Other	4
Mean follow up time	Months (range)	48 (2-56)
Number of Residual Lesion (RL)	0	23
	1	12
	2	9
	3	2
	6	1
	Not Applicable	4
Site of RL	Mediastinum/pre-vascular	17
	Axilla	4
	Pulmonary hilum	1
	Lateral cervical	1
	Not Applicable	28

Predictive Value (PPV) and Negative Predictive Value (NPV) to predict treatment outcome.

Results

Demographics and treatment

Sixty patients fitting the inclusion criteria were retrospectively enrolled in the study from September 2010 to January 2014. Nine cases were excluded from the analysis for the following reasons: negative baseline PET (1 patient), non FDG-avid SFAM (6 patients) and further treatment (radiotherapy) after final restaging with 2P-PET/CT (2 patients). Fifty-one patients were suitable for the analysis. The patient demographics are shown in **Table 1**. Female to male ratio was 23/28, the mean age was 29.7 (19-61) years. The mean diameter of the LNM was 9.1 cm (range 5.2-15.3 cm). Stage breakdown was as follows: stage II 19, stage III 11 and stage IV 21. Thirty-four patients were treated with ABVD for six cycles, 15 according to the international HD0607 study combining ABVD and BEACOPP [18] and 2 were treated with other therapy. Nineteen patients received consolidation RT on the residual mass persisting after chemotherapy.

At EoT, 18 patients had a SFAM with the largest diameter measured in the co-registered CT ranging between 10 and 15 mm, 30 had a larger SFAM (range 16-95 mm), and 3 had a multiple SFAMs with diameter higher or lower than 15 mm. Characteristics of SFAMs are showed in **Tables 2** and **3**.

After a mean follow-up of 48 (range 2-56) months, 38 patients showed continuous complete remission (CCR). Eleven patients failing frontline therapy entered a 2nd CR and three out of them relapsed and achieved a 3rd CR. Two patients have died for disease progression.

Histological confirmation and outcome

Nine out of 51 (17%) cases in which a histologic confirmation was deemed feasible and ethic by their treating physicians underwent a diagnostic biopsy. In 7 patients with pathological evidence of persisting HL, 5 showed both positive ΔSUVmax and RI, (see **Table 2**), while 2 showed negative ΔSUVmax and RI values (-0.30; -0.06 and -0.41; -0.24 respectively). In one patient whose biopsy showed only inflammatory cells, ΔSUVmax and RI values were 1.08 and 0.59, respectively. In the last one, with a histologically proven classic thymic tissue, both negative ΔSUVmax and RI (-0.94 and 0.41, respectively) confirmed the absence of disease. In conclusion, in three out of 9 patients undergoing confirmatory biopsy, results were apparently discordant from functional imaging data.

Image analysis

Dual-point imaging by semi-quantitative analysis was compared to standard qualitative analysis performed in early FDG-PET/CT scan images.

Table 2. Patients showing SFAM with VOI > 15 mm, biopsy and outcome

UPN	VOIs	VOI1 60'	VOI2 60'	VOI3 60'	VOI1 120'	VOI2 120'	VOI3 120'	ΔSUVMax	RI	CONC/ DISC	BIOPSY result	OUTCOME
001001	1	4.0			4.3			+0.3	+0.09	CONC		PROG
001003	1	2.2			1.3			-0.9	-0.41	CONC	Thymus	RCC
001006	1	3.5			4.0			+0.5	+0.14	CONC		Death
001008	2	2.5	2.6		1.7	1.4		-0.8	-0.32	CONC		RCC
001009	1	1.6			1.3			-0.3	-0.19	CONC		RCC
002001	2	9.6	6.7		18.5	9.9		+8.9	+0.93	DISC	Disease	PROG
002002	1	2.0			2.0			+0.0	0	CONC		RCC
003002	1	2.1			2.8			+0.7	+0.33	CONC		RCC
003004	1	1.3			1.3			+0.0	0	CONC		RCC
003006	1	1.5			1.0			-0.5	-0.33	CONC		RCC
006001	2	5.3	3.3		5.0	3.9		-0.3	-0.06	DISC	Disease	PROG
007001	1	1.7			1.1			-0.6	-0.35	CONC		RCC
007002	1	3.2			3.0			-0.2	-0.06	CONC		RCC
007007	2	2.4	2.4		1.8	2.3		-0.1	-0.04	CONC		RCC
007009	1	1.5			1.2			-0.3	-0.20	CONC		RCC
007010	3	2.7	2.5	1.5	3.0	1.7	1.7	+0.2	+0.13	DISC		RCC
007013	4	2.2	9.9	8.2	12.1	12.1	9.6	+9.9	+4.50	CONC	Disease	PROG
007014	1	2.2			2.3			+0.1	+0.05	CONC	Disease	PROG
007015	1	1.9			1.3			-0.6	-0.32	CONC		RCC
007016	1	1.7			1.3			-0.4	-0.24	CONC	Disease	PROG
007017	1	2.6			2.6			+0.0	0	CONC		RCC
008002	4	9.0	7.1	3.4	9.6	10.3	5.8	+2.4	+0.71	CONC		PROG
009003	3	4.2	2.8		4.0	3.8	2.8	+1.0	+0.36	DISC	Disease	PROG
009005	1	1.3			0.8			-0.5	-0.38	CONC		RCC
009006	1	2.5			4.0			+1.5	+0.60	CONC		PROG
009007	1	1.1			0.9			-0.2	-0.18	CONC		RCC
009008	2	2.5	2.9		2.5	NA		+0.0	+0.00	CONC		RCC
011001	1	3.0			5.2			+2.2	+0.73	CONC		RCC
pol8	1	1.1			1.0			-0.1	-0.09	CONC		RCC
pol4	1	1.6			1.6			+0.0	+0.00	CONC		Death
pol7	1	1.4			0.9			-0.5	-0.36	CONC		RCC

VOI's number, SFAM > 15 mm. Biopsy: result if possible. Outcome: RCC: Continuous Complete Remission; PROG: disease progression or failure after End of First Line Treatment, N.A.: not applicable.

In **Figure 2** are shown the ROC curves to determine the optimal cut-off in predicting treatment outcome for the different interpretation methods for the total of 51 patients. The most accurate cut-off value for DS was 4 with an area under curve (AUC) of 0.83 (95% CI: 0.68-0.98). For semi-quantitative analysis the best cutoff value was 0.02 for RI (AUC 0.84 95% CI: 0.70-0.97) and 0.05 for ΔSUVmax (AUC 0.82 95% CI: 0.67-0.98). Among patients treated with combined modality (chemotherapy followed by RT), 2P-PET/CT results interpreted by qualitative assessment yielded 2 false positive (FP) out of 5 results and only 1 FP out of 4 when interpreted by semi-quantitative analysis.

Discussion

The present study was aimed to compare the overall accuracy in predicting the long-term treatment outcome of dynamic vs. standard FDG-PET/CT imaging in HL, when a SFAM is recorded at EoT. Moving from the assumption that a second imaging test (either contrast-enhanced CT scan or a "full" FDG-PET/CT scan) would have been repeated in presence of

Table 3. Patients showing SFAM with VOI < 15 mm and mixed VOI < 15 and > 15 mm, Biopsy and Outcome

UPN	VOIs	VOI1 60'	VOI2 60'	VOI3 60'	VOI1 120'	VOI2 120'	VOI3 120'	ΔSUVMax	RI	CONC/ DISC	BIOPSY result	OUTCOME
001002	1	2.4			2			-0.4	-0.17	CONC		RCC
001005	1	1.2			1			-0.2	-0.17	CONC		RCC
001007	2	10	8.4		14.2	8.2		4.2	0.42	DISC	Disease	PROG
001010	1	3.7			2.8			-0.9	-0.24	CONC		RCC
003001	1	1.5			1.2			-0.3	-0.20	CONC		RCC
003003	2	2.2	2.4		3.1	3.4		0.9	0.41	CONC		PROG
003005	1	2.4			2.2			-0.2	-0.08	CONC		RCC
007003	1	1.9			1.7			-0.2	-0.11	CONC		RCC
007006	1	2.1			1.8			-0.3	-0.14	CONC		RCC
007008	1	3.4			3.4			0	0	CONC		RCC
008004	1	1.5			0.8			-0.7	-0.47	CONC		RCC
009001	2	2.6	2.3		2.1	1.4		-0.5	-0.19	CONC		RCC
009004	1	2.4			1.3			-1.1	-0.46	CONC		RCC
009010	1	2			1.5			-0.5	-0.25	CONC		RCC
007022	1	0.6			0.6			0	0	CONC		RCC
007025	1	1.3			1.1			-0.2	-0.15	CONC		RCC
pol9	1	1.6			0.9			-0.7	-0.44	CONC		RCC
pol6	1	2.1			1.5			-0.6	-0.29	CONC		RCC
006001	2	5.3	3.3		5	3.9		-0.3	-0.06	DISC	Disease	PROG
007011	2	1.8	1.7		1.4	2.7		1	0.59	DISC	Normal	RCC
007012	2	1.9	1.8		1.7	1.4		-0.2	-0.11	CONC		RCC

VOI's number, SFAM < 15 mm and SFAM with VOI < 15 and > 15 mm. Biopsy: result if possible. Outcome: RCC: Continuous Complete Remission; PROG: disease progression or failure after End of First Line Treatment, N.A.: not applicable.

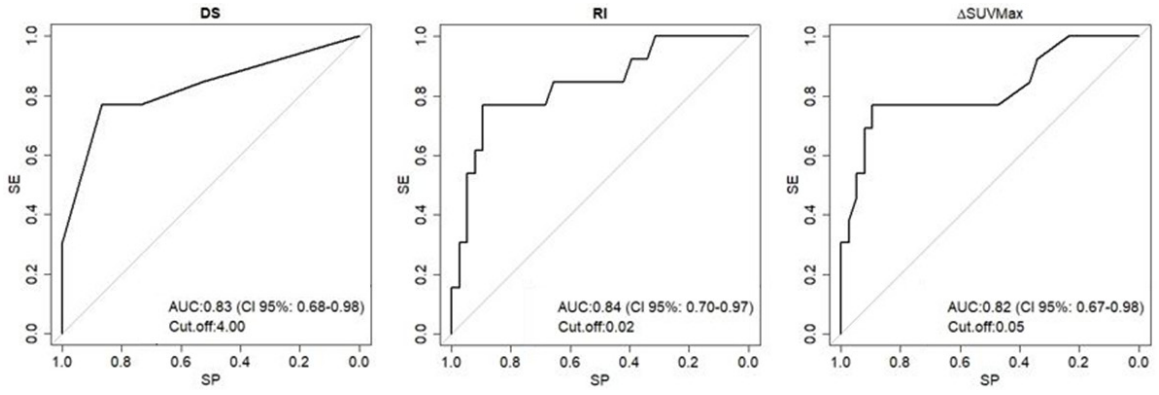

Figure 2. ROC's curves for the total of 51 patients.

equivocal or frankly positive EoT FDG-PET/CT scan, we deemed that 2P-PET/CT scanning with an acquisition field limited to SFAM could be the best tradeoff between cost and benefits for the patient.

When considering the entire cohort of 51 patients, FDG-PET/CT was able to correctly reclassify as responders or non-responders 34 and 10 patients, respectively (overall 44/51: 86%), who, by conventional CT scan, would have been classified as RCU or RP. However, 2P-PET failed to outperform standard static scanning, when the latter was reported with DS. As a matter of fact, comparable results were obtained with both method of analysis. In

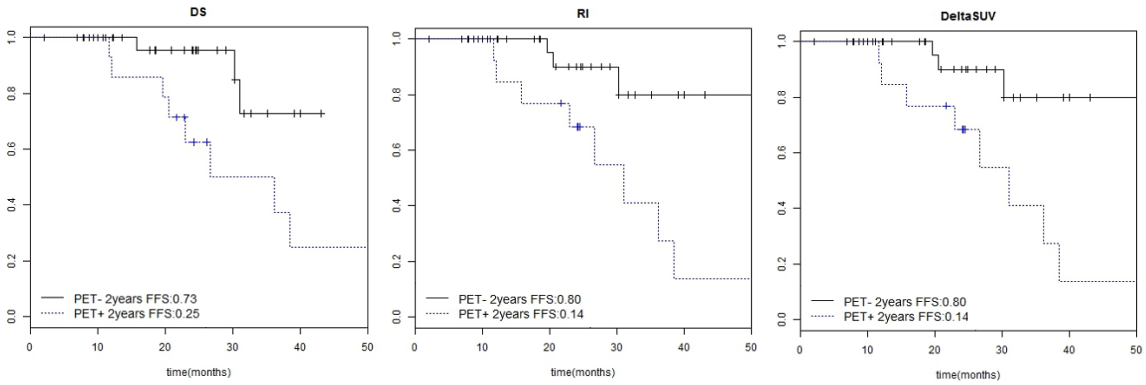

Figure 3. PFS's curves for the total of 51 patients.

Table 4. Sensibility, Specificity, PPV and NPV for the total of 51 patients

Parameters	TP	TN	FP	FN	SE (CI 95%)	SP (CI 95%)	PPV (CI 95%)	NPV (CI 95%)
DS	10	33	5	3	0.77 (0.46-0.95)	0.87 (0.72-0.96)	0.67 (0.38-0.88)	0.92 (0.78-0.98)
RI	10	34	4	3	0.77 (0.46-0.95)	0.89 (0.75-0.97)	0.71 (0.42-0.92)	0.92 (0.78-0.98)
ΔSUVmax	10	34	4	3	0.77 (0.46-0.95)	0.89 (0.75-0.97)	0.71 (0.42-0.92)	0.92 (0.78-0.98)

True Positive (TP), True Negative (TN), False Positive (FP) and False Negative (FN) results and the derived sensibility (SE), specificity (SP), Positive Predictive Value (PPV) and Negative Predictive Value (NPV) to predict treatment outcome for the total of 51 patients.

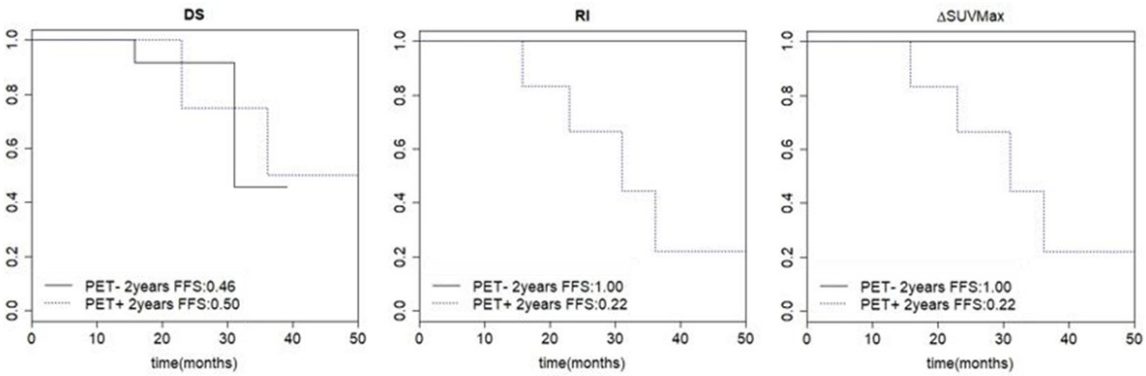

Figure 4. PFS's curves for 23 patients with a pre-defined uptake time.

one case only, in a patient with a DS score of 4, 2P-PET/CT was able to correctly reclassify result as a true negative, showing a ΔSUVmax of -0.40 and a RI of -0.17. As a consequence, a modest increase of NPV was recorded, from 0.87 (DS) to 0.89 (RI) and of the PPV from 0.67 (DS) to 0.71 (RI), see **Figure 3** and **Table 4**.

Upon inclusion in the analysis of the patients acquired with the allowed ranges in uptake time only, the differences in SE and PPV became substantial: RI analysis proved able to reclassify the scanning results in two patients, considered as FP in the visual analysis to TN in the semi-quantitative assessment. Upon quantitative analysis the SE switched from 0.60 to 1.00. The PPV arose from 0.75 to 0.83. Considering the NPV the superiority of semi-quantitative over qualitative analysis was even more evident than in the cohort of 51 patients as NPV rose from 0.89 to 1. However, the low number of patients scanned with a correct uptake time and the low ΔSUVmax values blunt the relevance of this observation. Therefore, the above results need urgent validation with a larger cohort of patients, see **Figure 4** and **Table 5**.

Biopsy at EoT was performed in a limited number of patients (9/51: 17%), and in 6 of them it

Table 5. Sensibility, Specificity, PPV and NPV for patients with a pre-defined uptake time

Parameters	TP	TN	FP	FN	SE (CI 95%)	SP (CI 95%)	PPV (CI 95%)	NPV (CI 95%)
DS	3	17	1	2	0.60 (0.15-0.95)	0.94 (0.73-1)	0.75 (0.19-0.99)	0.89 (0.67-0.99)
RI	3	17	1	30	1 (0.36-1)	0.94 (0.73-1)	0.83 (0.36-1)	1 (0.73-1)
ΔSUVmax	5	17	1	30	0.85 (0.55-0.98)	0.82 (0.66-0.92)	0.61 (0.36-0.83)	0.94 (0.80-0.99)

True Positive (TP), True Negative (TN), False Positive (FP) and False Negative (FN) results and the derived sensibility (SE), specificity (SP), Positive Predictive Value (PPV) and Negative Predictive Value (NPV) to predict treatment outcome for patients with a pre-defined uptake time.

confirmed the treatment response assessed by 2P-PET/CT. Due to these low numbers no definite data on concordance rate between the two diagnostic tools could be drawn; however, sampling problems could have affected also the rate of positive biopsies.

In conclusion, the present study, although retrospective and conducted in a limited patient sample, showed that dual-point PET/CT scan is a tool potentially able to differentiate inflammatory from neoplastic tissue in the context of single residual mass showing persisting FDG uptake at the end of treatment for HL. However, due to the relatively narrow temporal lag between early and late scan, a thorough adhesion of the FDG-PET/CT scanning protocol and in particular, respecting the correct acquisition time, could sensibly improve the overall accuracy of the scanning procedure.

Disclosure of conflict of interest

None.

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