The predictive value of PET-scan in diffuse large B-cell in optimizing the treatment decision

Sherif El Refaei MD[1], Mahasen Abougabal MD[1], Rasha Salama MD[2], Hussam Zawam MD[2], Maha Salama MSc[1]

[1]Nuclear medicine unit, Kasr Al-Ainy center of clinical oncology and nuclear medicine, Faculty of Medicine, Cairo University, Egypt.
[2] Clinical oncology unit, Kasr Al-Ainy center of clinical oncology and nuclear medicine, Faculty of Medicine, Cairo University, Egypt
E-mail: roshy.salama@yahoo.com

Abstract: Introduction Diffuse large B cell lymphoma (DLBCL) is the main subtype of histologically destructive non-Hodgkin lymphomas. The role of 18F-FDG PET/CT scan is well established at the baseline and at the end of DLBCL patients therapy. Many studies reported that patients with a negative scan after initial 2-3 cycles of chemotherapy demonstrated both a an improvement in overall survival (OS) and an improvement in progression-free (PFS). Therefore it is important to determine an accurate predictive tool to stratify patients who are more likely to relapse, to allow clinicians to modify their treatment accordingly. **Aim of the work** In our study we are concentrating on the prognosticrate of interim 18F-FDG PET/CT in patients with recently diagnosed pathologically proven DLBCL treated with chemotherapy as first line. **Patients and Methods** This prospective study was performed in Kasralainy Center of Clinical Oncology and nuclear medicine after being approved by the ethical committee. The study included thirty-nine patients, with newly diagnosed pathologically proven DLBCL. Patients were subjected to whole body 18F-FDG PET/CT as a baseline and after 3 cycles of their 1st line chemotherapy (interim PET). **Results** Between June 2015 and July 2017, the study included 39 patients. Thirty-one patients received R-CHOP-21 and 8 patients received R-EPOCH-21). All patients were subjected for a complete assessment with interim PET-I scan (PET-I), a baseline scan and an end-of`-treatment scan (PET-E). According to PET-I (interim PET) results, patients were subdivided into metabolic responders (PET-negative patients) including patients with complete and partial response and metabolic non-responders (PET-positive patients) with progressive and stable disease using Deauville criteria. PET-negative patients 92.3% (36 patients) received three additional courses, whereas in PET-positive patients (3 patients) 2nd line chemotherapy was prescribed (two patients received GEMOX and the other one received ESHAP). Two of them were still non-responder at the end-of-treatment study while the other one became responder. PET/CT scan post therapy was, 89.7% of patients (n=35) were metabolic responders and 10.3% (n = 4) were metabolic non-responders. Two patients of the end treatment non-responders were also non-responder at the interim study while the other two patients were responders at the interim study. Conclusion In DLBCL, optimization of the management of patients has been considered of great importance as conventional chemotherapy has been shown to be effective only in 60% of patients. Using PET-CT is of value in treatment decision and early shift for non-responding patients.

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1. Introduction

Managing of lymphomas must be according to well-documented guidelines depending on the initial staging evaluation. As a result correct staging is the beginning for assortment of suitable treatment approach for the purpose of preventing exceed or sub doses of treatments, also to decrease morbidity associated to the regimens of administered radio-chemotherapy.[1] Some authors defined the diffuse large B cell lymphoma (DLBCL) histologically as the main subtype of destructive non-Hodgkin lymphomas (NHL) and includes mainly about 30% of cases. Many studies reported that patients with a negative scan after initial 2-3 cycles of chemotherapy demonstrated both a improvement in progression-free (PFS) and an improvement in the overall survival (OS)**.**[2]Therefore it is important to determine an accurate predictive tool to stratify patients who are more likely to relapse, to allow clinicians to modify their treatment accordingly.[3] The role of 18F-FDG PET/CT scan is well established at the baseline and at the end of therapy for patients with DLBCL**.**[4] However, the role of interim PET/CT in therapeutic decision making in those patients is yet to be confirmed**.**[5]

Metabolic tumor load can convey both the volumetric and intensity of FDG accretion. Other researchers have found that the metabolic tumor level or total lesion glycolys is very useful for estimation of the response, for the reason that these volumetric parameters pointed to the burdens of metabolic

tumor.[6] In our study we are concentrating on the prognostic importance of interim 18F-FDG PET/CT in subjects with recently diagnosed pathologically proven DLBCL treated with chemotherapy as first line.

Aim of work

We aimed at evaluating the prognostic importance of the interim 18F-FDG PET/CT in subjects with pathologically proven DLBCL to be provide basis for treatment.

2. Patients and Methods

This prospective study was a co-operative work between nuclear medicine unit and clinical oncology unit in Kasr El Ainy Center of Clinical Oncology and nuclear medicine after being approved by the ethical committee. This study included thirty-nine patients, with newly diagnosed pathologically proven DLBCL presented to us between June 2015 and July 2017. Patients were subjected to whole body 18F-FDG PET/CT as a baseline and after 3 cycles of their 1st line chemotherapy (interim PET). According to interim PET results the patients were subdivided into 2 categories; the 1st category is metabolic responders (PET-negative patients) including patients with complete and partial response. The 2nd category is metabolic non-responders (PET-positive patients) with progressive and stable disease according to Deauville criteria (5-point scale), and interpretation of the results was done using EORTEC and RECIST scales. PET-negative patients (36 patients) completed their preplanned treatment protocols, whereas PET-positive patients group (3 patients) received 2nd line chemotherapy.

At the end of treatment (6 cycles of chemotherapy), further follow-up was done by PET-CT scan (PET-E). Metabolic response assessment was done by using Deauville criteria and also interpretation was done using EORTEC and RECIST scales.

PET/CT protocol:

Patients were asked to fast for 6 hours before the 18 F FDG PET/CT scan. Each patient was injected with 0.14 mCi/kg body weight (5.5 MBq/Kg) with 18F FDG. During the uptake phase of the FDG, patients were laid in a quiet warm room, in order to minimize non-desired FDG uptake. After IV injection of 18F FDG by 45 – 60 minutes, PET/CT images were acquired using a combined PET/CT scanner (Philips Gemini Time-of-flight PET/CT machine equipped with LYSO (lutetium–yttrium oxyorthosilicate) crystals). and a 512 x 512 matrix size, acquiring a field of view (FOV) of 700 mm in 22.5 seconds. For each patient, maximum and mean SUV (SUVmax and SUVmean) of the lesions were measured. The tumor boundaries were identified using ellipsoid isocontours and drawn large enough to include all the tumor volume but careful enough to exclude any background activity. The selected volumes were based on the automatically fixed threshold method, this method applies a threshold based on a percentage (typically, 41%) of SUV max within the tumor.[7]

Analysis of the interim scan:

Assessment of metabolic response was done using Deauville criteria. 5-PS scores the most intense uptake in the site of initial disease, if present, in relation to normal uptake in mediastinum and liver.

Analysis of the follow up scan:

Assessment of response to the given treatment was done using Deauville criteria as well as EORTEC and RECIST criteria. Determination of true or false positive and/or negative lesions was based on clinical and radiological follow up as well as histo-pathological examination.

Statistical analysis

SPSS version 21 was used for data analysis. Bivariate relationship was displayed in cross tabulations and Comparison of proportions was performed using the chi-square and Fisher's exact tests where appropriate. T-independent and one-way Annova tests were used to compare normally distributed quantitative data.

Pearson correlation was used to compare normally distributed quantitative data. Accuracy was represented using the terms sensitivity, and specificity. Receiver operator characteristic (ROC) analysis was used to determine the optimum cut off value for TLG and Suvmax in diagnosing cases. Kaplan-Meier survival was used to display the survival function for progression-free survival and disease-free survival cases. P-values less than 0.05 were considered statistically significant.

3. Results

Between June 2015 and July 2017, the accrual of patients was done. The study included 39 evaluable patients. Patients were evenly divided between males and females (20 females and 19 males). Median age was 45 years with ECOG performance status of 0 in 28.2% of the patients, 1 in 59 % and 2 in 12.8%. Ann Arbor stage I, II, III, or IV was found in 5 (12.8 %), 6 (15.4 %), 7 (17.9 %), and 21 patients (53.8 %), respectively. An IPI score of 0 to 2 was found in 20 patients (51.3 %) and a score of 3 to 5 was found in 19 patients (48.7%). According to the Tally algorithm[8], 5 patients (27.8 %) were classified as non–germinal center DLBCL, and 13 patients (72.2 %) had germinal center DLBCL (of 18 evaluable samples).

Table 1: patient's characteristics.

Characteristics	No	%
Age, years		
Median	45	
Range	22-69	
Sex		
Female	20	51.3%
Male	19	48.7%
Ann Arbor stage		
I	5	12.8%
II	6	15.4%
III	7	17.9%
IV	21	53.8%
Performance status		
0	11	28.2%
1	23	59%
2		
LDH, IU/L		
Normal	15	38.5%
High	24	61.5%
No. of extranodal lymphoma sites		
0	13	33.3%
One site	12	30.8%
More than one site	14	35.9%
5	12.8%	
IPI score		
0,1 (low)	12	30.8%
2 (low intermediate)	8	20.5%
3 (high intermediate)	11	28.2%
4,5 (high)	8	20.5% DLBCL
GC (Tally algorithm)	13	72.2%
Non-GC	5	27.8%
Interim PET-I (Deauville)		
Complete response	15	38.5%
Partial response	21	53.8%
Stable disease	0	0.0%
Progressive disease	3	7.7%
End-of-treatment PET-E (Deauville)		
Complete response	22	56.4%
Partial response	13	33.3%
Stable disease	0	0.0%
Progressive disease	4	10.3%
End-of-treatment PET-E (EORTEC)		
Complete response	15	38.5%
Partial response	15	38.5%
Stable disease	4	10.3%
Progressive disease	5	12.8%
End-of-treatment PET-E (RECIST)		
Complete response	12	30.8%
Partial response	19	48.7%
Stable disease	4	10.3%
Progressive disease	4	10.3%

Abbreviations: DLBCL, diffuse large B-cell lymphoma; GC, germinal center; IPI, International Prognostic Index; LDH, lactate dehydrogenase; PET, positron emission tomography; PET-I, PET scan after two cycles of therapy; PET-E, PET scan after end of therapy (6 cycles). EORTEC, European Organization for Research and treatment of cancer; RECIST, Response Evaluation Criteria in Solid Tumors.

Nearly all patients had nodal disease at time of presentation (except for only one patient only who had purely extra-nodal disease). Thirteen patients (33.3 %) had no extra-nodal disease and 26 patients (66.7 %) had extra-nodal disease (12 patients with one extra-nodal site and 14 patients with more than one extra-nodal site). LDH level was normal in 15 patients (38.5%) and was high in 24 patients (61.5%). Bone marrow biopsy was done in 12 patients and it was found positive in two patients and negative in the other 10 patients. 13 patients (33.3 %) had bulky disease and 26 patients (66.7 %) had no bulky disease. Patient's characteristics **(Table 1).**

PET/CT Results:

A total of 39 subjects undergo primary pretreatment interim PET/CT and PET/CT following three cycles of 1st line chemotherapy. Thirty-one patients received R-CHOP-21 and 8 patients received R-EPOCH-21). All thirty-nine patients were subjected for a complete assessment with using interim PET-I scan, a baseline (PET-I) scan, and an end-of-treatment scan (PET-E). Involved field radiotherapy to bulky disease to 9 patients was delivered regardless of PET/CT results. According to PET-I (interim PET) results, patients were subdivided into metabolic responders (PET-negative patients) including patients with complete and partial response and metabolic non-responders (PET-positive patients) with progressive and stable disease using Deauville criteria. PET-negative patients 92.3% (36 patients) received three additional courses, whereas in PET-positive patients (3 patients) 2nd line chemotherapy was prescribed (two patients received GEMOX and the other one received ESHAP). Two of them were still non-responder at the end-of-treatment study while the other one became responder. Scan with PET/CT post-therapy, an average of 89.7% of subjects (n=35) were metabolic responders and 10.3% (n = 4) were metabolic non-responders. Two patients of the end treatment non-responders were also non-responder at the interim study while the other two patients were responders at the interim study.

Using the EORTEC criteria; 38.5% of the studied population had complete response, 38.5% had partial response, 10.3% had stable disease and 12.8% had metabolic progression. Morphologic response according to the modified RECIST response criteria showed that 30.8% of the studied population had complete response, 48.7% had partial response, 10.3% had stable disease and 10.3% had morphologic progression. Again, patients with stable and those with progressive disease were grouped together as non-responders and those with complete or partial response were labeled responders.

3- Measurements of the baseline scan:

Mean baseline SUVmax was 31.8 (range=4.3-46.2) while mean baseline TLG was 4099.9(range-=25-87862.7) **(Table 2).**

Table 2: Measurements of the baseline scans.

Parameter	Mean	Median	Range	Minimum	Maximum
Baseline SUVmax	31.8	19.1	41.9	4.3	46.2
Baseline TLG	4099.91	517.30	87837.70	25.00	87862.70

Correlation between baseline measurements and response at the end of treatment:

ROC analysis of SUV max and TLG showed no statistical correlation between baseline measurements and response at the end of treatment. The identified SUVmax value of 19.1 and TLG value of 532.90 gave only modest sensitivity (52% and 48.6% respectively) and specificity of 49% and 50% respectively.

Correlation between interim PET-CT and response of treatment:

Using Deauville criteria, results of the interim PET-CT were directly correlate with treatment outcome *(P value= 0.002)*. ROC analysis of the interim results by the quantitative approach using the ΔSUVmax between baseline and interim PET-CT was also statistically significant *(P value = 0.05)*. The ROC analysis identified ΔSUVmax value of 80.85 % as the best predictive cut-off value for the presence of response with 74.3% sensitivity, 75% specificity and 74.3% accuracy. It had higher negative predictive value of 96.3% with lower positive predictive value of 25%. The relationship between different clinical factors of the studied population, such as age, gender, stage, IPI score, bulky disease as well as nodal and extra-nodal disease were examined for possible associations with the treatment outcome. However, the fore-mentioned studied parameters showed *no statistical significance* in identifying the future metabolic response to treatment except for presence of bulky disease (>7.5) cm that shows strong significant difference (*P value 0.003)* **(Table 3).**

Table 3: Relationship between different studied clinical parameters and metabolic response to treatment.

		PET-E (Deauville)				
		Non-responding		Responding		
		Number	percent	Number	percent	P value
Age category	≤60 years	3	75.0%	27	77.1%	0.923
	>60 years	1	25.0%	8	22.9%	
Gender	Male	3	75.0%	16	45.7%	0.267
	Female	1	25.0%	19	54.3%	
Bulky disease	No	0	0.0%	26	74.3%	*0.003* (*significant*)
	Yes	4	100.0%	9	25.7%	
IPI score	Low	0	0.0%	12	34.3%	0.196
	Intermediate	2	50.0%	17	48.6%	
	High	2	50.0%	6	17.1%	
Stage	Early (I,II)	0	0.0%	11	31.4%	0.186
	Late (III,VI)	4	100.0%	24	68.6%	

5. Further follow-up

atients were subjected to regular follow up after end of treatment with mean period of 14.8 months and median of 14 months.

Correlation of interim PET-CT with PFS and OS showed no significant difference between PET-positive and PET-negative patients (P=0.25 and P=0.596 significantly).

4. Discussion

It is recommended that for assessing PET data from patients it should be select the consistent method before designing an scheduling an intervention research in which we compare between different treatment protocols which evaluate the results of interim 18F-FDG PET/CT. In our study, 39 patients potentially were included to specifically define the prognostic role of scanning with interim PET/CT in subjects with DLBCL taken standardized therapy and under valuation circumstances. In addition, we were looking for evaluating the use of interim 18F-FDG PET/CT for risk-adapted strategy for newly diagnosed patients with DLBCL. The predictive importance of interim 18F-FDG PET/CT done for patients having DLBCL through first-line treatment is remain indistinct. Preceding work indicated that the results of interim 18F-FDG-PET/CT scanning had reduced reproducibility and incompatible precision and sensitivity, this may be attributed to using of variable modalities of therapies and response criteria. In a trial for standardization of interim 18F-FDG PET/CT obtaining data, the "First International Workshop on Interim 18F-FDG PET in Lymphoma," produced in 2009, developed a compromise of response parameters for the interim PET. These criteria were essentially depended on visual and semi-quantitative study. The criteria of visual response according to the Deauville which composed of five-point scale (5-PS): 1, no uptake; 2, uptake ≤ mediastinum; 3, uptake > mediastinum while ≤liver; 4, uptake moderately elevated in comparison with the liver uptake at any place; and 5, obviouslyelevated uptake in contrast with the liver at any place and new places and/or new places of illness. For semi-quantitative analysis and while maximal standardized uptake value (SUVmax) is the frequently applied semi-quantitative tool of PET analysis in oncology, evaluation of the reduce in SUVmax after a small number of cycles of chemotherapy in comparison with basal or pretreatment SUV symbol as a percentage (ΔSUVmax) which can be of valuable in interim PET assessment.[9] Many investigations were carried out to develop the NPV and PPV in subjects with DLBCL by applying additional quantitative advance depending on ΔSUVmax among interim 18F-FDG-PET/CT and baseline. [(10-11)]

Some authors like Spaepen et al. recorded the importance of interim PET in prognosing the outcome of DLBCL individuals who had been subjected for treatment with variable regimens of chemotherapy depending on delta-SUV-based parameters.[12] In this study, our results confirmed that results of the interim 18F-FDG-PET-CT by visual assessment using Deauville criteria were directly correlated with treatment outcome *(P value= 0.002)*. ROC analysis of the interim results by the quantitative approach using the ΔSUVmax between baseline and interim PET-CT was also statistically significant *(P value = 0.05)*. The ROC analysis identified ΔSUVmax value of 80.85 % as the most excellent prognostic cut-off value for the occurrence of reaction with 74.3% sensitivity, 75% specificity and 74.3% accuracy. It had higher negative predictive value of 96.3% with lower positive predictive value of 25%.

In another study, the negative prognostic value (NPV) of a negative interim PET/CT, which

recognized a cluster of individuals with good prediction and a 2-year EFS of 70.9%.[13] On the other hand, the positive prognostic value (PPV) of a positive interim PET/CT recognized a group of individuals with poor prediction, and the risk for an incident was 51.8%in the first 2 years. Certainly, half the PET-2–positive subjects had transformed to PET negative by the end of the therapy. These records were established in their central assessment and in the review that applied Deauville criteria (1 to 3 *v* 4 to 5 points) with 73.1% for the NPV and 58.6% for the PPV, respectively. These values were obviously lower when compared with the predictive role of an interim PET/CT in Hodgkin lymphoma; where, NPV recorded 96% and PPV recorded 19%**.**[14]

The obtained data from this study established the satisfactory predictive importance of an interim PET/CT in DLBCL subjected for treatment along six cycles of R-CHOP-21 or R-EPOCH-21 in a prospective trial. Our results failed to show satisfactory PPV of the interim 18F-FDG PET/CT that could reflect the clinical outcome for patients with DLBCL treated with standard first line chemotherapy with no sufficient data to conduct therapeutic decisions such as treatment intensification/deintensification at the current stage, yet when standardized therapy and assessment measures for PET are being applied in a practically large group of diseased individuals.[15]

Nowadays many enduring trials were conducted for determining the importance of an interim PET/CT in DLBCL diseased persons, and initial data of trials applying an interim 18F-FDG-PET/CT for treatment assist are previously existing. Our data suggested that interim PET assessment is the accurate predictive factor for predicting response at the end of treatment *(P value 0.002)* compared to other clinical prognostic factors which had no significant correlation with response at the end of treatment except for presence of bulky disease (>7.5 cm) that shows strong significant difference (*P value 0.003)*. In contrast to the results, in **Adams et al.** study, the NCCN-IPI (National Comprehensive Cancer Network International Prognostic Index) was revealed to be the merely independent predictive factor of both PFS and OS in R-CHOP-treated DLBCL**.** However, in our trial, correlation between interim PET-CT with progression and disease-free survival showed no significant difference between PET-I positive and PET-I negative patients *(P value* 0.250 and *0.596 respectively*).[16]

The results of this study also showed that neither SUVmax in the most active lesion, nor whole-body TLG were predictive of response of treatment in R-CHOP- or R-EPOCH treated DLBCL. ROC analysis of SUV max and TLG were statistically non-significant *(P value 0.3 and 0.4 respectively)*. The identified SUVmax value of 19.1 and TLG value of 532.90 gave only modest sensitivity (52% and 48.6% respectively) and specificity of 49% and 50% respectively.

In a retrospective work that comprised 140 DLBCL subjects who were subjected for treatment with R-CHOP, **Kim et al. (2013)** found that high whole-body TLG values were separatelyprognostic of reduced PFS and OS, while Ann Arbor stage and IPI score did not forecast survival.

Drawbacks of that study by were disappointment to record whether 18 F-FDG PET/CT readers were blinded to conclusion, anapply of two variant PET/CT tools, and comparison with the old model of IPI as a substitute of the recently upgraded NCCN-IPI**.**[17]

Gallicchio et al. carrieda retrospective investigation on 52 individuals diagnosed as DLBCL. Through applying of univariate Cox regression analysis, the results revealed to a low whole-body SUVmax to be related with decreased PFS, while whole-body TLG and whole body MTV were not prognostic of PFS at univariate analysis. They reported in their investigation that high-risk IPI patients not taken in their consideration, did not reach to a conclusion whether the 18 FDG PET/CT readers were blinded to result, and retrospectively determined optimal cut-off values for 18 F-FDG PET/CT metrics with ROC analysis which undoubtedly has overvalued the predictive importance of SUVmax at univariate analysis.[18]

The current work had many restrictions in this point. First, a inadequate number of quantitative whole-body FDG-PET/CT metrics were inspected. Although whole-body SUVmax and whole-body TLG are nowadays more prevalent in both research and clinical practice, additional, a lot of innovative tools such as quantifying tumor heterogeneity in FDG-PET/CT by texture analysis [19] or quantitative dynamic FDG-PET studies [20] have not been explored yet in this work. It should be observed, yet, that the second are technically more interesting and more problematic to implement in clinical practice than the FDG-PET/CT parameters that were inspected in the current work. Second, observer agreement of whole-body SUVmax, whole body MTV, and whole-body TLG measurements was not assessed.

Conclusion

In DLBCL, optimization of the management of patients has been considered of upmost importance as conventional chemotherapy has been shown to be effective only in 60% of patients. Interim 18F-FDG PET/CT allows for prediction of response and selection of patients who can benefit from second line therapies and therefore early alteration of ineffective therapy regimens.

References

1. Ferrari, C., Minoia, C., Asabella, A. N., et al. "Whole body magnetic resonance with diffusion weighted sequence with body signal suppression compared to 18 F-FDG PET/CT in newly FDG PET/CT in newly diagnosed lymphoma diagnosed lymphoma." Hellenic journal of nuclear medicine (2014): 40.
2. P. Lu, "Staging and classification of lymphoma," Seminars in Nuclear Medicine, vol. 35, no. 3, pp. 160–164 (2005).
3. -Baba S, Abe K, Isoda T. et al. "Impact of FDG-PET/CT in the management of lymphoma. Ann Nucl Med (2011); 25: 701-716.
4. I. N. Micallef, M. J. Maurer, G. A. Wiseman et al., "Epratuzumab with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone chemotherapy in patients with previously untreated diffuse large B-cell lymphom," Blood, vol. 118, no. 15, pp. 4053–4061, (2011).
5. Cheson, B. D., Fisher, R. I., Barrington, S. F., et al. "Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification." *Journal of Clinical Oncology 32.27* (2014): 3059-3067.
6. Kim TM, Paeng JC, Chun IK, et al. Total lesion glycolysis in positron emission tomography is a better predictor of outcome than the International Prognostic Index for patients with diffuse large B cell lymphoma. Cancer (2013); 119.
7. Hyun SH, Choi JY, Shim YM, et al. Prognostic value of metabolic tumor volume measured by 18F-fluorodeoxyglucose positron emission tomography in patients with esophageal carcinoma. Annals of surgical oncology. 2010; 17(1):115-122.
8. Meyer PN, Fu K, Greiner TC, et al: Immunohistochemical methods for predicting cell of origin and survival in patients with diffuse large B-cell lymphoma treated with rituximab. J ClinOncol (2011) 29:200-207.
9. Itti E, Meignan M, Berriolo-Riedinger A, et al: An international confirmatory study of the prognostic value of early PET/CT in diffuse large B-cell lymphoma: Comparison between Deauville criteriaand _SUVmax. Eur J Nucl Med Mol Imaging 40(2013):1312-1320:1195–202.
10. Casasnovas RO, Meignan M, Berriolo-Riedinger A, et al: SUVmax reduction improves early prognosis value of interim positron emission tomography scans in diffuse large B-cell lymphoma. Blood 118(2011):37-43.
11. Meignan M, Itti E, Gallamini A, et al: Interim 18F-fluorodeoxyglucose positron emission tomography in diffuse large B-cell lymphoma: Qualitative or quantitative interpretation—Where do we stand? Leuk Lymphoma 50(2009):1753-1756.
12. Spaepen K., Stroobants S., Dupont P. et al., "Early restaging positron emission tomography with 18F-fluorodeoxyglucose predicts outcome in patients with aggressive non-Hodgkin's lymphoma," *Annals of Oncology*, vol. 13, no. 9, pp. 1356–1363, (2002).
13. Christoph Mamot, Dirk Klingbiel, Felicitas Hitz, et al. Final Results of a Prospective Evaluation of the Predictive Value of Interim Positron Emission Tomography in Patients With Diffuse Large B-Cell Lymphoma Treated With R-CHOP-14. J Clin Oncol (2015); 33:2523-2529.
14. Le Roux PY, Gastinne T, Le Gouill S, et al: Prognostic value of interim FDG PET/CT in Hodgkin's lymphoma patients treated with interim response-adapted strategy: Comparison of International Harmonization Project (IHP), Gallamini and London criteria. Eur J Nucl Med Mol Imaging (2011) 38:1064-1071.
15. Safar V, Dupuis J, Itti E, et al: Interim [18F] fluorodeoxyglucose positron emission tomography scan in diffuse large B-cell lymphoma treated with anthracycline-based chemotherapy plus rituximab. JClin Oncol 30(2012):184-190.
16. Hugo J. A. Adams, John M. H. de Klerk, Rob Fijnheer, et al: Prognostic superiority of the National Comprehensive Cancer Network International Prognostic Index over pretreatment whole-body volumetric–metabolic FDG-PET/CT metrics in diffuse large B-cell lymphoma. European Journal of Haematology 94 (2014):532–539.
17. Zhou Z, Sehn LH, Rademaker AW, et al. An enhanced International Prognostic Index (NCCN-IPI) for patients with diffuse large B-cell lymphoma treated in the rituximab era. Blood (2014); 123:837–42.
18. Gallicchio R, Mansueto G, Simeon V, et al. F-18 FDG PET/CT quantization parameters as predictors of outcome in patients with diffuse large B-cell lymphoma. Eur J Haematol (2014); 92:382–9.
19. Chicklore S, Goh V, Siddique M, Roy A, Marsden PK, Cook GJ. Quantifying tumour heterogeneity in 18F-FDG PET/CT imaging by texture analysis. Eur J Nucl Med Mol Imaging (2013); 40:133–40.
20. Dimitrakopoulou-Strauss A, Pan L, Strauss LG. Quantitative approaches of dynamic FDG-PET

and PET/CT studies (dPET/CT) for the evaluation of oncological patients. Cancer Imaging (2012);12:283–9.

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