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Role of Positron Emission Tomography with 2-Deoxy-2-[fluorine-18] fluoro-D-glucose Integrated with Computed Tomography in the Evaluation of Hepatic Metabolic Activity due to Steatosis in Lymphoma Patients and its Impact on Deauville Score

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Abstract

BACKGROUND: Liver uptake of 2-Deoxy-2-[fluorine-18]fluoro-D-glucose integrated (18F-FDG) is taken as the reference tissue in interpretation of Deauville score (DS), which is considered a response assessment.

AIM: This study was conducted to evaluate the prevalence of hepatic steatosis in patients with lymphoma and the impact of hepatic metabolic activity due to steatosis on 18F-FDG liver uptake and its effect on DS.

MATERIAL AND METHODS: This prospective study was conducted on 77 cases. Seventy-seven patients had baseline positron emission tomography/computed tomography (PET/CT), 69 patients had interim PET/CT, 31 patients had end of treatment (EOT) PET/CT, and 3 patients had follow-up (FU) PET/CT after EOT. The study included 49 female patients (63.6%) and 28 male patients (36.4%). The mean age = 39.5 + 13. Forty-one patients (53.2%) diagnosed as non-Hodgkin lymphoma [HL] while 36 patients (46.8%) diagnosed as HL. Steatosis was diagnosed on the unenhanced CT part of PET/CT examinations using a cutoff value of 42 Hounsfield units. Both maximum standardized uptake value (SUVmax) and SULmax were recorded on the liver and the tumor target lesion. DS was then computed.

RESULTS: Among 77 cases, prevalence of steatosis in baseline (10/77, 12.9%), interim (13/69, 18.8%), and EOT/FU (4/31, 12.9%), there was no significant difference in hepatic steatosis during their time course of their treatment. There was correlation between Liver SUVmax with body mass index (BMI) in each of interim and EOT PET/CT. Regarding SULmax, there was no correlation with BMI. There was no change in interpretation of DS using either SUVmax or SULmax.

CONCLUSION: Steatosis has no practical issue regarding liver metabolic activity (either SUVmax or SULmax) in interpretation of DS. Liver SUVmax is affected by body weight. Unlike, SULmax is not affected by body weight.

Background

Lymphomas are the most common primary hematopoietic malignancy [1]. They are heterogeneous group of lymphoid malignancies, which can be broadly divided into non-Hodgkin lymphomas (NHLs) and Hodgkin lymphomas (HLs) that display different patterns of biological behavior and response to treatment [2]. Positron emission tomography (PET)-computed tomography (CT) with 18F-FDG is a standard staging procedure for most lymphoma subtypes. Performed before and after therapy for HL and aggressive NHL, 18F-FDG PET results have a high prognostic value and correlate with survival [3]. Fatty liver is the leading cause of liver enzyme abnormalities in the developed countries [4]. Patients with fatty liver are at risk of metabolic comorbidities. This disease must not be ignored specially in our country; Egypt is considered a highest endemic area for the prevalence of hepatitis C virus (HCV) infection. Liver steatosis or steatohepatitis represents a comorbid condition that accelerates progression of chronicity; morbidity and mortality among patients with chronic HCV infection. Fatty liver can also be a feature of drug-induced liver injury and was described in patients treated with methotrexate, amiodarone, antiretrovirals, and estrogen receptor modulators, such as tamoxifen [4]. Fatty liver development was also reported as a consequence of cancer chemotherapy, especially for colorectal cancer with treatments containing 5-fluorouracil or irinotecan [4]. The diagnosis of non-alcoholic fatty liver disease (NAFLD) is evaluated by several methods, including liver biopsy, as well as non-invasive radiological modalities, such as CT (discussed later), magnetic resonance imaging, magnetic resonance spectroscopy, and ultrasonography [5].

Standardized uptake value (SUV) is increasingly used in clinical studies in addition to visual assessments. SUV is a measurement of the uptake

in a tumor normalized on the basis of a distribution volume. Most of the published literature relates to SUV (normalized to body weight) measurements. SUV normalized to lean body mass (LBM) is referred to as SUL and is a recommended quantitative measure of FDG uptake. The use of SUL is preferred for response assessment studies when large changes in body weight may occur during the course of the treatment [6].

Methods

This prospective study was performed in Kasr-Alainy Center of Clinical Oncology and Nuclear Medicine (NEMROCK) after being approved by the ethical committee. A total of 77 cases pathologically proven to have lymphoma (Hodgkin and NHL) presented to the NEMROCK between April 2019 and December 2020. The patients were subjected to whole body PET with 2-deoxy-2-[fluorine-18]fluoro-D-glucose integrated with CT (18F-FDG PET/CT) as a baseline staging before therapy, in the middle of their 1st line of chemotherapy interim 18F-FDG PET/CT and end of treatment and/or follow-up (EOT/FU) were performed for the assessment of response.

The medical history of these patients was checked and only patients meeting inclusion criteria and for whom international guidelines for PET tumor imaging had been fulfilled which were included in the study. For each patient, age, sex, initial Ann Arbor staging, history of diabetes, virology (hepatitis B virus [HBV] and HCV), and liver dysfunction were recorded. We excluded pregnant ladies and patients who had active second malignancy.

Patients were instructed for preparation according to the EANM procedure guidelines for 18F-FDG PET/CT tumor imaging: Version 2.0 [6]. Briefly, patients were required to fast for 6 h and asked to void before the examination. The patients were instructed to stay calm and avoid walking or any exercise before and after injection of 18F-FDG to prevent physiologic muscle FDG uptake. Blood glucose level measured before injection, and fasting levels were <200 mg/dL (70–170 mg/dL in our cohort). Warm environment was available before injection to avoid brown fat uptake.

A dose of 3.7–5.2 MBq/Kg of 18F-FDG was injected through a hand or antecubital vein. The injection was performed 45–90 min before the start of PET/CT acquisition. For opacification of bowel loops, 400–600 ml of contrast material diluted with water and swallowed 1 h before PET/CT imaging.

The scanner used in NEMROCK was Ingenuity TF 64 (Philips Healthcare, Cleveland, OH, USA) a PET/CT scanner combining a modular, LYSO-based PET component with a 64-channel CT component. The CT was based on the Ingenuity CT (Philips Healthcare).

Acquisition and reconstruction protocol were previously described [6]. Briefly, a low-dose non-contrast CT scan was performed first, followed by a whole-body PET acquisition then a whole-body contrast-enhanced CT scan. Low-dose CT was acquired in a helical mode, using 120 kV, 60 mAs, and a 512 × 512 matrix size, acquiring a field of view (FOV) of 700 mm. This CT scan was used for attenuation correction.

PET scan was acquired in a three-dimensional mode over the same anatomical regions starting from the skull vertex to the level of the mid-thigh. The acquisition time was 2 min per bed position, in nine bed positions. Reconstructed slice thickness was 5 mm.

Immediately after completing PET acquisition, a diagnostic CT with contrast was acquired using 120 kV, 300 mAs, and a 512 × 512 matrix size. The acquired FOV was 500 mm using dose automatic modulation in the Z direction. Non-ionic contrast media was IV injected using automatic injector at a rate of 4 ml/s, in a dose of 1–2 ml/kg (maximum <150 ml). Slice thickness was 1.0 mm.

The whole study took about 20–30 min. Raw data were reconstructed using a standard manufacturer's iterative algorithm. Axial PET and CT images obtained and then reformatted into sagittal and coronal images to allow easier image interpretation.

PET/CT and CE-CT interpretation

PET/CT analysis

For each PET-CT exam, liver maximum SUV (SUVmax), lean body SUV max (SULmax), and liver mean Hounsfield units (HU) were measured using an automatic 3 cm diameter volume of interest (VOI) set in the right liver lobe, avoiding liver lesions in the case of focal liver involvement. Spleen mean HU was also recorded using a 2 cm diameter VOI. Several cutoff values were used to define steatosis: Mean liver HU ≤ 42, ratio between liver and spleen mean HU values (CTL/S) ≤0.8, and difference between liver and spleen mean HU values (CTL-S) ≤−9 [7]. SUVmax and SULmax in the mediastinum were measured in an automatically placed 1 cm diameter and 2 cm height cylinder in the descending thoracic aorta. In baseline examinations and in case of remaining lesions in interim and EOT/FU examinations, the most intense target lesion was located by upscaling the base of the look up table on the 3D MIP view. SUVmax and SULmax were computed as follows:

SUVmax=Measured activity x body weight (kg)/injected dose (MBq)

SULmax=measured activity x LBM (kg)/injected dose (MBq).

The Deauville 5-point scale (DS) was used to evaluate response for each interim and post-treatment PET/CT examination

DS1= No uptake
DS2= Uptake ≤Mediastinum
DS3 =Uptake >Mediastinum but ≤Liver
DS4 =Moderately increased uptake compared to the liver
DS5= Markedly increased uptake compared to the liver (defined as 2 times liver) and/or new lesions

Statistical analysis

Data were statistically described in terms of mean ± standard deviation (± SD), median, range, and IQR, or frequencies (number of cases) and percentages when appropriate. Numerical data were tested for the normal assumption using Kolmogorov–Smirnov test. Comparison of numerical variables between the study groups was done using Student's t-test for independent samples in comparing two groups of normally distributed data and Mann–Whitney U-test for independent samples for comparing not normal data. Comparison between more than 2 groups was done using Kruskal–Wallis test. For comparing categorical data, Chi-square (χ^2) test was performed. Exact test was used instead when the expected frequency is <5. Correlation between various variables was done using Pearson moment correlation equation for linear relation of normally distributed variables and Spearman rank correlation equation for non-normal variables/non-linear monotonic relation. Correction of liver SULmax values was done according to the method described by Solomon *et al*., 2017. Two-sided $p < 0.05$ was considered statistically significant. All statistical calculations were done using computer program IBM SPSS (Statistical Package for the Social Sciences; IBM Corp, Armonk, NY, USA) release 22 for Microsoft Windows.

Results

A total of 77 cases were included, the mean age=39.5 + 13, 49 patients were female (63.6%), 28 patients were male (36.4%), 41 patients (53.2%) diagnosed as NHL while 36 patients (46.8%) diagnosed as HL; Ann Arbor Stage I, II, III, or IV was found in 6 (7.8%), 25 (32.5%), 25 (32.5%), and 21 patients (27.3%), respectively, as. All 77 patients received first line of treatment after baseline PET/CT; 36 patients received ABVD (46.8%), 39 patients received R-CHOP (50.7%), and 2 patients received REPOCH (2.5%). Nine patients out of 68 patients (who did interim PET/CT) received second line of treatment after interim PET/CT; DHAP (2/9, 22.2%), ESHAP (6/9, 66.6%), and lenalidomide (1/9, 11.1%) (Table 1).

Table 1: Population characteristics

Characteristics	No	%
Age, years		
Mean ± SD	39.5 ± 13	
Gender		
Female	49	63.6
Male	28	36.4
Ann Arbor stage		
I	6	7.8
II	25	32.5
III	25	32.5
IV	21	27.3
Pathology		
NHL	41	53.2
HL	36	46.8
First line of CTH		
ABVD	36	46.8
R-CHOP	39	50.7
REPOCH	2	2.5
Second line of CTH		
DHAP	2	22.2
ESHAP	6	66.6
Lenalidomide	1	11.1
HCV		
Positive	5	6.5
Negative	72	93.5
HBV		
Positive	3	3.9
Negative	74	96.1
Baseline liver functions		
AST	19 (12–22)	
ALT	24 (21.5–39.5)	
Liver functions in FU		
AST	20 (15–25)	
ALT	30 (24–40)	

ABVD: Adriamycin, bleomycin, vinblastine, dacarbazine, REPOCH: Rituximab, Etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, R-CHOP: Rituximab, cyclophosphamide, hydroxydaunomycin, oncovin, prednisolone, DHAP: (D)examethasone, (H)igh-dose (A)ra-C - cytarabine, (P)latinol (cisplatin), ESHAP: Etoposide, methyl-prednisolone, cytarabine (Ara-C), cisplatin (platinum)

Steatosis in baseline, interim, and EOT PET/CT

There was no significant difference between liver density (steatosis and non-steatosis) in baseline PET/CT versus interim PET/CT with p = 0.3 and in interim PET/CT versus EOT PET/CT with p = 0.6 (Tables 2 and 3).

Table 2: Cross-tabulation between baseline and interim PET/CT

Characteristics		Interim		p value
		Steatosis	Non-steatosis	
Baseline	Steatosis	6	3	**0.3**
		8.7%	4.3%	
	Non-steatosis	7	53	
		10.1%	76.8%	
Total = 69 (100%)		13	56	
		18.8%	81.2%	

N.B: Only three patients known to have follow-up after end of treatment, these studies are excluded due to their small sample size.

In this comparison, cases that lost interim or EOT PET/CT were excluded, therefore, 68 patients were included in comparison between baseline and interim PET/CT and 23 patients were included in comparison between interim and EOT PET/CT (Tables 2 and 3).

Table 3: Cross-tabulation between interim and EOT/FU3

Characteristics		Interim		p value
		Steatosis	Non-steatosis	
EOT/FU	Steatosis	2	1	0.6
		8.7%	4.3%	
	Non-steatosis	3	17	
		13%	73.9%	
Total = 23 (100%)		5	18	
		21.7%	78.3%	

Development of steatosis in interim PET/CT

Seven patients (10.1%) developed steatosis in interim PET/CT; six out of seven patients who developed hepatic steatosis in interim PET/CT had BMI >30 kg/m^2 (three patients received RCHOP while others received ABVD), however, one patient out of seven patients who developed steatosis in interim PET/CT had BMI <30 kg/m^2 diagnosed as NHL and received 3 cycles of R-CHOP as shown in Table 2.

Disappearance of steatosis in interim PET/CT

Three patients had a disappearance of steatosis interim PET/CT, two patients of them were male with BMI <30 kg/m^2, however, one patient was female with BMI >30 kg/m^2 as shown in Table 2.

Development of steatosis in EOT PET/CT

One female patient developed steatosis in EOT diagnosed as HL received 6 cycles of ABVD and had BMI 23.5 kg/m^2 (Table 3).

Disappearance of steatosis was recorded in three patients (two male patients and one female patient) in EOT with BMI <30 kg/m^2 (Table 3).

Table 4: Correlation between BGL, HBV, HCV, BMI, and steatosis and each of liver SUVmax and SULmax in interim

			Liver SUVmax	Liver SULmax
Spearman's rho n = 69 patients	BMI	Correlation coefficient	0.573	−0.116
		p value	0.001	0.344
	Steatosis	Correlation coefficient	0.087	−0.116
		p value	0.478	0.344
	HBV	Correlation coefficient	−0.079	−0.270
		p value	0.520	0.025
	HCV	Correlation coefficient	−0.231	−0.011
		p value	0.056	0.929
	BGL	Correlation coefficient	−0.007	−0.033
		p value	0.955	0.789

Correlations of liver uptake on interim and EOT PET scan (77 cases)

1-Correlation of steatosis, blood glucose level, BMI, HBV, and HCV with each of SUVmax and SULmax in interim and EOT PET/CT

Median/range of liver SUVmax and SULmax in interim PET/CT was 2.3 (1.9–2.9) and 1.6 (1.3–2), respectively.

Median/range of liver SUVmax and SULmax in EOT PET/CT was 2.6 (2.2–3) and 1.7 (1.3–2.8), respectively.

Median/range of BMI in interim and EOT PET/CT was 28.3 (22.2–32.4) and 27.5 (24.4–32.8), respectively.

There was a positive correlation between liver SUVmax values with BMI in both interim and EoT groups with an r value equal to 0.5 ($p < 0.001$) and 0.67 ($p < 0.001$), respectively.

Table 5: Correlation between BGL, HBV, HCV, BMI, and steatosis and each of liver SUVmax and SULmax in EOT/FU

			Liver SUVmax	Liver SULmax
Spearman's rho n = 31 patients	BMI	Correlation coefficient	0.672	−0.127
		p value	0.001	0.521
	Steatosis	Correlation coefficient	−0.065	−0.114
		p value	0.729	0.557
	HBV	Correlation coefficient	0.041	−0.204
		p value	0.827	0.289
	HCV	Correlation coefficient	0.098	0.081
		p value	0.600	0.675
	BGL	Correlation coefficient	0.154	0.086
		p value	0.407	0.659

There was no correlation between steatosis, blood glucose level, HCV, HBV, and each of liver SUVmax and SULmax in both interim and EOT PET/CT (Tables 4 and 5).

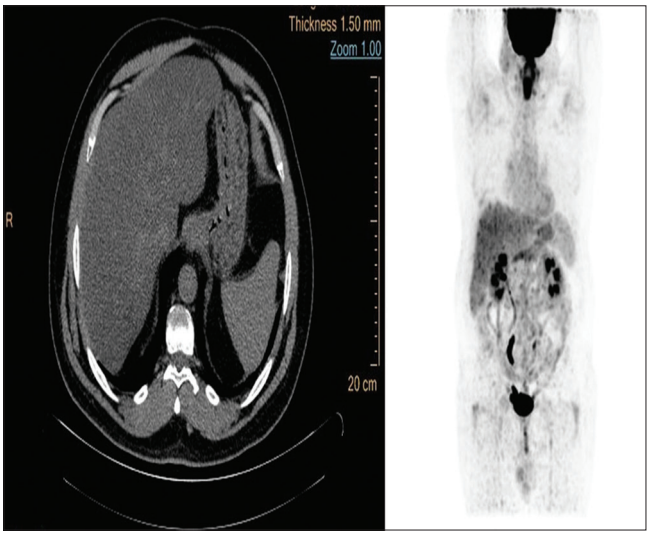

Figure 1: Representative example of steatotic patient. Maximal intensity projection and axial computed tomography (CT) image for a 45-year-old male patient addressed for interim positron emission tomography/CT of Hodgkin lymphoma scored Deauville score 2. Body mass index (BMI) was increasing throughout follow-up. BMI; initially was 29.8 kg/m^2, BMI at interim and EOT was 34.3 and 33.6 kg/m^2, respectively

Representative example of steatotic patient is shown in Figure 2 and representative example of non-steatotic patient is shown in Figure 2.

Discussion

Lymphoma broadly divided into Hodgkin's and non-Hodgkin's lymphoma, and it accounts for one of the most common malignant diseases in the general population [8]. Steatosis or NAFLD affects 10–24% of the general population in different countries [6]. Drug-induced fatty liver was described in patients treated with chemotherapy. It is difficult to determine prevalence of chemotherapy induced fatty liver due to heterogeneity in treatment regimens [4]. Our aim

is to evaluate the prevalence of hepatic steatosis in patients with lymphoma and its impact on Deauville score (DS).

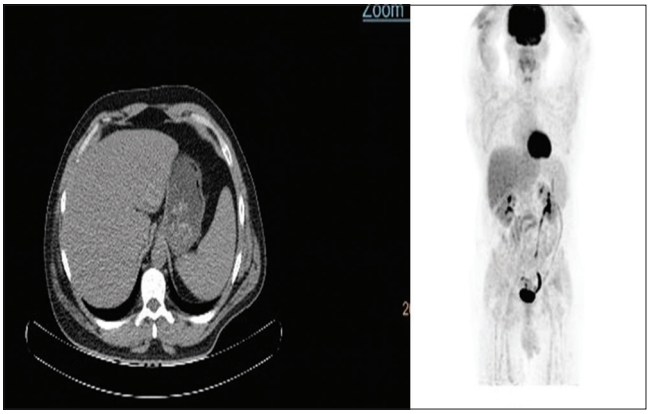

Figure 2: Representative example of non-steatotic patient. Maximal intensity projection and axial computed tomography (CT) image for a 42-year-old male patient addressed for interim positron emission tomography (PET)/CT of HL scored DS 1. Body mass index (BMI) was mildly increasing throughout follow-up. BMI was 36.2 and 37 kg/m^2 during baseline and interim PET/CT examinations, respectively.

In our study, the prevalence of steatosis in baseline (10/77, 12.9%), interim (13/69, 18.8%), and EOT/FU (4/31, 12.9%); this is more than prevalence of steatosis in general population which is in contrary to Salomon *et al*. [2]. In our study, development of hepatic steatosis was documented in eight patients during their course of treatment (seven patients in interim PET/CT and one patient in EOT PET/CT). In comparison to Salomon *et al*. [6], one patient developed steatosis during his course of treatment, he had BMI >30. However, in our study, there was no statistically significant difference in development of hepatic steatosis throughout different time of PET/CT examinations. Six patients out of seven patients had BMI >30 kg/m^2 in interim PET/CT, however, other two patients had BMI <30 kg/m^2. Unfortunately, other factors influencing fatty liver were limited in our study as certain drug intake, lipid profile, history of dyslipidemia, or metabolic risk factors. Similar to Salomon *et al*. [6], we found that hepatic steatosis was not apparently to the time-course of treatment and therefore does not explain the variability of liver 18F-FDG uptake previously observed in patients.

According to liver metabolic activity in our study, there was no significant relation regarding hepatic steatosis, HBV, HCV, blood glucose level, and different lines of chemotherapy with liver metabolic activity either using liver SUVmax or SULmax in interim or EOT PET/CT studies. This is in concordance with Salomon *et al*. [6], Ben Yakov *et al*. [3], and Lin *et al*. [9], [10], but we disagreed with Salomon *et al*. [6] and Keramida *et al*. [11], regarding correlation between liver SUVmax in EOT PET/CT and liver SULmax in interim and EOT PET/CT with steatosis, they found that liver SULmax and SUVmax were significantly lower in steatotic patients.

Using 5-point scales of DS as visual and semi-quantitative analysis in response assessment in lymphoma patients, DS1–3 versus D4–5 is used to discriminate between responders and non-responders, respectively. This score has been shown to have a prognostic value early in the course of treatment and/or at the end of the treatment. SUV normalized by body weight is affected by amount of body fat. SUV calculated/normalized by LBM (LBM, fat-free body mass) (SUVLBM or SUL) instead of total weight is recommended to provide more accurate SUV results [12].

In light of above-mentioned reasons, we are in accordance with Salomon *et al*. and Sarikaya *et al*. [6], [12] that higher BMI is associated with high liver SUVmax. However, no statistical correlation was found between BMI and liver SULmax. We used liver SULmax values instead of the recommended SUVmax values for the determination of DS. In our study, SULmax values gave the same DS as SUVmax values. These results suggest that either SUVmax or SULmax can be used to score patients with relatively consistent results.

Conclusion

There are limitations in our study

First, we need larger and more homogeneous studies of patients initially scored DS4. Second, limited number of patients especially steatotic for better assessment of liver uptake in steatotic patients and using of liver correction methods. Third, other factors interfering with fatty liver as certain drug intake, lipid profile, history of dyslipidemia, or metabolic risk factors.

We concluded that irrespective to hepatic steatosis, virology, blood glucose level, and BMI was significantly correlated with liver SUVmax. In contrary, liver SULmax had no significant correlation with BMI. This confirms fact that SUV normalized by body weight is affected by amount of body fat. SUV calculated/normalized by LBM (LBM, fat-free body mass) (SUVLBM or SUL) instead of total weight is recommended to provide more accurate SUV results. Using SULmax has the advantage of giving the opportunity to reveal and potentially take into account parameters other than BMI that could influence the liver uptake. Liver SULmax values gave the same DS as SUVmax values. These results suggest that either SUVmax or SULmax can be used to score patients with relatively consistent results. According to the EANM procedure guidelines for tumor imaging, the use of SUL is preferred for response assessment studies when large changes in body weight may occur during the course of the treatment.

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