Review Article, PET/CT.

Does Metabolic Liver Steatosis have Impact on Deauville Criteria in Lymphoma Patients in ^{18}F-PET/CT?

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ABSTRACT:

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. They are heterogeneous group of lymphoid malignancies. PET-CT with ^{18}F-FDG is a standard staging procedure for most lymphoma subtypes. Liver uptake of ^{18}F-FDG is taken as the reference tissue in interpretation of Deauville score (DS), which is considered a response assessment.

^{18}F-FDG PET/CT has a role in evaluating prevalence of hepatic steatosis in patients with lymphoma and the effect of hepatic metabolic activity due to steatosis using SUV max, SUL max on Deauville score. 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 SUL max were recorded on the liver and the tumor target lesion. DS was then computed. There was no significant difference in hepatic steatosis during their time course of their treatment in ^{18}F-PET/CT. Liver SUVmax was increasing with high body mass index (BMI) in follow-up PET/CT studies. Regarding SUL max, there was no correlation with BMI. There was no change in interpretation of DS using either SUVmax or SUL max. Steatosis has no practical issue regarding liver metabolic activity (either SUVmax or SUL max) in interpretation of DS. Liver SUVmax is affected by body weight. Unlike, SUL max is not affected by body weight.

Keywords: Steatosis, lymphoma, Deauville score, liver uptake, FDG PET/CT.

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INTRODUCTION:

Lymphomas are the most common primary hematopoietic malignancy [(1)]. They are broadly divided into non-Hodgkin Lymphomas (NHL) and Hodgkin lymphoma (HL) that display different patterns of biological behavior and response to treatment [(2)]. PET-CT with 18F-FDG is a standard staging procedure for most lymphoma subtypes. Performed before and after therapy for Hodgkin lymphoma (HL) and aggressive non-Hodgkin lymphoma (NHL), ^{18}F-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 prevalence of HCV infection. Liver steatosis or steatohepatitis represents a co-morbid 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 (DILI) 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. However, due to heterogeneity in treatment regimens, the true incidence and prevalence of chemotherapy-associated fatty liver is difficult to ascertain [(4)].

The diagnosis of NAFLD: is evaluated by several methods, including liver biopsy, as well as non-invasive radiological modalities, such as CT, magnetic resonance imaging (MRI), magnetic resonance spectroscopy (MRS), and ultrasonography [(5)].

Liver uptake of 18F-FDG is taken as the reference tissue in interpretation of Deauville score (DS), which is considered a response assessment for interim PET and at the end of the treatment (EoT) PET. It depends on visual and semi-quantitative analysis. 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 [(6)]. 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 [(7)].

Role of PET/CT in assessment of treatment response using Deauville score:

^{18}F-FDG PET/CT is being successfully used for both staging and follow-up of HL and NHL [(8)]. PET scanning is now considered essential to the evaluation and initial staging of HL and NHL because of its ability to distinguish between viable tumor and necrosis or fibrosis in residual masses that are often present after treatment in patients who have no other clinical or biochemical evidence of disease [(9)].

Accurate assessment with ^{18}F-FDG PET of the extent and metabolic activity of disease requires proper patient preparation [(10)].

In the framework of treatment evaluation of diffuse large B cell lymphoma (DLBCL), follicular lymphoma (FL) and Hodgkin lymphoma (HL), liver uptake of 18F-FDG is taken as the reference tissue in Deauville score (DS), which underpins current criteria for interim PET and at the end of the treatment (EOT). This score has been shown to have a prognostic value early in the course of treatment and/or at the end of the treatment [(11)]. Importantly, visual assessment has to be confirmed by quantification, which is less user-dependent due to optical misinterpretation due to the influence of background activity [(12)].

The use of liver background is based on previous studies that have determined that ^{18}F-FDG uptake in the liver is relatively constant within the acquisition time specified by the EANM and SNMMI guidelines [(13)].

For each PET-CT exam, liver maximum standardized uptake values (SUVmax), lean body SUV max (SUL max) and liver mean 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 cut-off 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 [(6)].

SUV max and SUL max 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 /follow-up examinations, the most intense target lesion was located by up-scaling the base of the look up table on the 3D MIP view. SUVmax and SUL max were computed as follows [(6)]:

SUV max=measured activity x body weight (kg) /injected dose (MBq)

SUL max=measured activity x lean body mass (kg) /injected dose (MBq).

The Deauville 5-point-scale (DS) was used to evaluate response for each interim and post-treatment PET/CT exam [(6)].

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.

Prevalence of hepatic steatosis in lymphoma patients:

Steatosis or non-alcoholic fatty liver disease (NAFLD) affects 10–24% of the general population in different countries [(7)].

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.

In our study, Prevalence of steatosis in baseline (10/77, 12.9%), interim (13/69, 18.8%), EOT/FU (4/31, 12.9%); This is more than prevalence of steatosis in general population which is in contrary to ***Salomon et al,***.

In our study, development of hepatic steatosis was documented in 8 patients during their course of treatment (7 patients in interim PET/CT and 1 patient in EOT PET/CT).

In comparison to ***Salomon et al,.*** one patient developed steatosis during his course of treatment, he had BMI > 30 [(6)].

However, in our study there was no statistically significant difference in development of hepatic steatosis throughout different time of PET/CT examinations.

6 patients out of 7 patients had BMI > 30 kg /m2 in interim PET/CT, however other 2 patients had BMI < 30 kg/m2. Unfortunately, other factors influencing fatty liver was limited in our study as certain drug intake, lipid profile, history of dyslipidemia or metabolic risk factors. Similar to ***Salomon et al,.*** we found that hepatic steatosis was not apparently to the time-course of treatment and therefore does not explain the variability of liver ^{18}F–FDG uptake previously observed in patients **(6)**.

Factors affecting hepatic metabolic activity using SUV max, SUL max:

According to liver metabolic activity in our study, there was no significant relation regarding hepatic steatosis , hepatitis B virus, hepatitis C virus, blood glucose level and different lines of chemotherapy with liver metabolic activity either using Liver SUVmax or SUL max in interim or EOT PET/CT studies. This is in concordance with ***Salomon et al,, BenYakov et al,. and Lin et al,.***but we disagreed with ***Salomon et al,. and Keramida et al,.*** Regarding correlation between Liver SUVmax in EOT PET/CT, Liver SUL max in interim and EOT PET/CT with steatosis, they found that liver SUL max and SUVmax were significantly lower in steatotic patients **(6, 14, 15 and 16)**.

Impact of liver SUVmax, SUL max on Deauville score:

Using five point scales of Deauville score 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. Standardized uptake value (SUV) normalized by body weight is affected by amount of body fat. SUV calculated/normalized by lean body mass (LBM, fat free body mass) (SUVLBM or SUL) instead of total weight is recommended to provide more accurate SUV results **(17)**.

In light of above mentioned reasons, We are in accordance with ***Salomon et al., and Sarikaya et al,.*** That higher BMI are associated with high Liver SUVmax. However, no statistical correlation was found between BMI and liver SUL max. We used liver SUL max values instead of the recommended SUVmax values for the determination of Deauville Scores **(6, 17)**.

CONCLUSIONS:

Irrespective to hepatic steatosis, virology, blood glucose level, body mass index (BMI) was significantly correlated with liver SUVmax. In contrary; liver SUL max had no significant correlation with BMI. This confirm fact that Standardized uptake value (SUV) normalized by body weight is affected by amount of body fat. SUV calculated/normalized by lean body mass (LBM, fat free body mass) (SUVLBM or SUL) instead of total weight is recommended to provide more accurate SUV results. Using SUL max 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 SUL max values gave the same DS as SUVmax values. These results suggest that either SUVmax or SUL max 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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