Positron emission tomography in lymphoma – fine tuning of International Harmonization Project

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SUMMARY

Lymphoproliferative diseases include a wide range of malignant diseases with various histological characteristics, clinical presentation and therapeutic possibilities. Reliable assessment of the spread of the disease and the knowledge of the biological characteristics of the tumor are the prerequisites of a successful patient treatment. In most patients with lymphoma, positron emission tomography (PET) with fluorodeoxyglucose (^{18}F-FDG) proved to be a useful imaging method which contributes to the assessment of the spread of the disease by identifying increased glycolysis in tumor cells. In the initial phases of the clinical implementation of FDG PET, the method was mostly used to determine the stage of the disease. At present, FDG PET is being increasingly used to assess the effects of therapy and to determine prognostic factor. Today, the treatment of lymphoma patients implies an individualized approach aiming at maximum disease control with the smallest possible risk of late side effects. Numerous prospective studies in patients with lymphoma have contributed to a better understanding of the metabolic changes. FDG PET performed after only 1 or 2 cycles of chemotherapy can assess tumor sensitivity to the therapy. Thus, the long-term response to therapy can be predicted at the very early stage of treatment. Many studies are being conducted in order to assess the potential usefulness of this prognostic information so that the therapy protocols can be altered and the long term administration of drugs that will not result in a sustained response be stopped. It is expected that this approach might result in avoiding late side effects and toxicity. The degree of metabolic activity assessed by interim FDG PET at the very beginning of chemotherapy administration serves as a biomarker of tumor responsiveness to chemotherapy. Because of that, more precise criteria are needed to answer the question "what is a positive interim FDG PET finding". Our understanding of lymphoproliferative diseases and the effects which some therapeutic procedures have on the metabolism of tissue contribute significantly to the accurate interpretation of FDG-PET/CT findings. For successful utilization of FDG PET/CT, a multidisciplinary team which includes hematology, radiation oncology, diagnostic radiology and nuclear medicine specialists is necessary..

Key words: *Lymphoma; Diagnostic Imaging; Positron-Emission Tomography; Positron-Emission Tomography and Computed Tomography; Fluorodeoxyglucose F18*

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INTRODUCTION

Although lymphoproliferative diseases include a wide range of malignant diseases with various histological characteristics, for the majority of patients with lymphoma positron emission tomography (PET) with fluorodeoxyglucose (^{18}F-FDG) proved to be very useful in determining the stage of the disease and in the assessment of the benefit of the administered treatment. During the last ten years, due to the new scientific medical discoveries and the technological progress of the imaging methods, the criteria for the examination and interpretation of FDG-PET findings changed. At the beginning of 2007, the need for unification of these criteria led to the creation of the first international consensus on PET implementation in lymphoma patients ("Use of PET for Response Assessment of Lymphoma: Consensus of the Imaging Subcommittee of International Harmonization Project in Lymphoma"). The purpose of this consensus was to recommend clear guidelines to enable the comparison of the results of the clinical studies of different institutions and thus optimize the use of this method in patients who were included in clinical trials or in everyday clinical practice (1).

In 2007, the FDG-PET was defined as the official criterion for the response assessment in lymphoma patients since it can differentiate active tumor tissue from necrosis or fibrosis in residual tumor mass (2). Introduction of PET as a criterion for treatment assessment in patients with B-large cell non-Hodgkin lymphoma (DLBCL) and Hodgkin lymphoma (HL) resulted in the exclusion of the category "unconfirmed complete remission" (Cru). This, in fact, made FDG-PET an obligatory diagnostic procedure in monitoring of potentially curable types of lymphoma, because without biopsy or the insight into the metabolism, it was not possible to assess the residual tumor mass, which was a relatively frequent finding in these patients. It is well known that these types of lymphoma metabolize FDG and that they belong to the group of "FDG avid" lymphoma so the recommendation has it that the baseline, pre-therapeutic PET study is not required for the reliable interpretation of end of treatment PET finding (2). Various specific problems as well as some practical circumstances were the subject of the analysis of the first "lymphoma consensus". The recommendations agreed on by the consensus somewhat differed in cases of patients who were included in clinical trials and for those in everyday clinical practice implementation. These different recommendations were the result of the necessity to have precisely defined clinical study protocols for research so that the benefit of FDG-PET in different disease treatment phases could be assessed, since it was not entirely known what it was, especially in the group of patients with indolent lymphoma forms. Recommendations are in part the consequence of the limited availability

of the examination in everyday clinical practice. Additionally, the first international consensus coordinated the standardization of the imaging technique, storage and transfer of the digital data, lymphoma types for which PET is recommended, the time at which it is desirable or mandatory to perform the examination and the criteria for PET findings' interpretation regarding the different tissues which may be affected by the disease, such as lymph nodes, liver, spleen, bone system, lungs or skin.

The consensus reached at the time was important, not only to clinicians who refer patients to PET in order to better understand the benefit and limitations of the method, but also to the diagnosticians who analyze PET, because, for the first time, a clear basis for decision making in various ambiguous clinical situations was established. PET positive finding interpretation become more cohesive, which enabled more successful follow up of patients and established fundamentals for bringing together results of numerous clinical trials as well as for planning of new ones. New knowledge enabled more holistic insight into metabolic variability of lymphoma. The significance of baseline PET findings, the prognostic significance of interim PET examinations and the importance of the reference criteria for monitoring of treatment benefit in different treatment phases were partly redesigned compared to the first lymphoma consensus.

STANDARDIZATION OF PET IMAGING PARAMETERS AND TRANSFER OF PET IMAGES

Except for the fact that technological improvement in PET/CT scanners led to the shortening of total imaging time (up to 10 minutes), recommended protocols for performance of the diagnostic procedure were not significantly changed. Recommended minimal dose of FDG radiopharmaceutical in adult patients is 185 MBq (5 mCi) while in children it is 18.5 MBq (0.5 mCi). Prior to FDG administration patient should be fasting for at least 4 hours. Level of glucose in blood must not exceed 10 mmol/L. Whole body imaging is performed after the period of accumulation which lasts for about 60 $\pm$ 10 minutes. Digital data are acquired and analyzed in three planes (axial, sagittal and coronal tomograms) and attenuation correction of the registered gamma rays is obligatory. Independent PET devices have not been manufactured for ten years now, so together with the PET study, a "low-dose" CT is scanned, and it serves for attenuation correction as well as for morphological orientation. In all patients undergoing PET/CT, use of oral contrast media is recommended. In addition and as clinically indicated, classical contrast enhanced diagnostic CT with the intravenous contrast (CECT) may be conducted. CECT is usually recommended for follow up of patients with liver or spleen involvement, since it must be kept in mind that "low-dose" CT is not sensitive to small lesions. Therefore the interpretation of PET metabolic finding is not reliable for such patients. Use of CECT along with PET is avoided whenever possible, in order to reduce the exposure to irradiation, to which the patient is exposed more in CECT than with "low-dose" CT only. It is recommended to measure the size of the lymph nodes or the lesions in all patients whenever possible, regardless of whether it was a "low-dose" CT or CECT scan. The use of the so-called "coincidental scanning" without the possibility of attenuation correction is completely unacceptable since such scanning does not enable the assessment of the SUV values, which is mandatory in the report and it is not possible to visually compare the metabolism ratio in the residual tumor tissue with the metabolism of the surrounding mediastinal vascular structures or liver. PET scans should be available in DICOM format ("Digital Imaging and Communications in Medicine") (1, 2).

FDG AVIDITY IN DIFFERENT TYPES OF LYMPHOMA AND SIGNIFICANCE OF BASELINE PET

Lymphomas are a very heterogeneous group of diseases which have significantly different molecular characteristics and biological behavior (3-5). Although it is not necessary for a diagnostician who deals with a metabolic imaging scan of lymphoma to know in detail each and every subtype of numerous various histological types, it is important that he/she is familiar with the general clinical-pathological division into indolent and aggressive types, because this reflects FDG accumulation, i.e. glucose metabolism in the tumor cells.

According to the published studies, PET/CT registers about 25%-30% more lesions than the conventional imaging methods (6-9). Thus, if possible, it is generally recommended in all patients with Hodgkin (HL) and non-Hodgkin lymphoma (NHL) to evaluate baseline FDG-PET findings prior to the beginning of treatment. Baseline scan is important for the assessment of the extent of the disease and the determination of the tumor metabolic activity. Except in cases of a B-large cell non-Hodgkin lymphoma and Hodgkin lymphoma, in most other lymphoma subtypes PET is not mandatory (1, 2, 8, 9). Not all lymphoma have increased glycolysis in tumor cells, which means that tumors do not metabolize FDG with the same intensity, therefore PET is considered not to be enough reliable diagnostic procedure. It was proved that in histologically indolent types, such as small cell lymphomas (SLL), nodal (NMZL), splenic (SMZL) and extranodal lymphoma of the marginal zone (MALT), FDG accumulation may be variable, very weak or even absent (10-12). Thus, in these patients baseline PET study is a precondition for further metabolic monitoring of treatment benefit. Particularly, if tumor weakly metabolizes glucose, end of treatment PET negative finding in these patients does not mean that there are no active malignant cells and that the patient is cured. Baseline PET scan recommendation in these histological subtypes of lymphoma is mandatory only for clinical trials. Outside of trials, in clinical praxis FDG-PET was generally recommended as a very useful method which is desirable if possible („useful"), but not as a mandatory procedure („essential"). In patients with indolent lymphoma with doubtful initial staging and remaining suspicion of more extended disease, it is necessary to perform baseline PET examination prior to the beginning of the treatment. In patients with aggressive histological types of lymphoma, which evidently metabolize FDG ("FDG-avid"), but the prognosis for which are worse, such as follicular lymphoma and mantle cell lymphoma, PET was not strictly mandatory as a basic examination for everyday clinical practice, but was just recommended at the end of treatment, if possible (1,2,13,14). The probability for a certain histological type of lymphoma to be "avid" was analyzed in the group of 766 patients whose initial "staging" was done by FDG-PET. Positive PET findings were determined in 97% of the histologic type in which tumor was classified as an aggressive type of lymphoma. There was also a relatively high level of 83% positive findings in indolent types of NHL (15).

The weakest avidity was registered in primary skin anaplastic T-large cell lymphoma (40%) and lymphomatoid papulosis (50%). According to this study, FDG avidity was very weak in extranodal MALT lymphomas (54%); it was even lower (55% - 82%) than in previously published studies (9, 16, 17). It was also confirmed that avidity was worse in splenic lymphoma of the marginal zone (67%) and in small cell lymphoma (83%), while in all other types of lymphoma, avidity was over 90%. In Hodgkin disease, Burkitt's lymphoma, mantle cell and nodal lymphoma of the marginal zone avidity was 100% (15). It was interesting that as many as one third of patients with skin manifestation of the disease were PET negative, regardless of the histological type and avidity of lymphoma. This confirms the necessity of a clinical skin examination regardless of the potential FDG-avidity of lymphoma and points to the additional caution with PET findings' interpretation in the skin region (15).

Recently, usefulness of baseline PET findings was analyzed, considering positive or negative status of PET findings. It was determined that the baseline PET finding was not important only as the means of initial staging of the patient, but also as additional help in the later interpretations of post therapeutic PET findings. Taking into consideration the high sensitivity of FDG-PET, the possibility of false positive findings due to the numerous benign changes which can increase metabolism, as well as great variability in lymphoma avidity, knowing the regions which were previously affected by the disease contributes to the enhanced accuracy of the end of treatment PET report. In the study which analyzed post therapeutic PET interpretations, performed without baseline PET scan knowledge, and then the same post therapeutic PET was reinterpreted with baseline PET scan knowledge, the result was the report change in as many as one third of patients. With the comparative analysis of a baseline and post therapeutic PET, number of false positive, false negative and also inconclusive PET findings was reduced. In as many as 14% of patients, end of treatment PET findings were opposite to the first diagnostic interpretation, performed without basic PET information (18).

Thus, the studies published during the last couple of years defined the role of baseline PET more clearly, particularly concerning the histological type and lymphoma avidity. Apart from the assessment of the initial disease staging, baseline PET is used for the comparison in treatment monitoring, in the cases of disease relapse, disease transformation into another histological type and as a prognostic factor.

TIMING OF PET PERFORMED FOR TREATMENT RESPONSE ASSESSMENT

Complete remission of the disease is an optimal treatment goal for all Hodgkin and non-Hodgkin lymphoma patients and it may be achieved despite the existence of morphologically visible residual tumor mass. If residual tumor exists and if it is not available for biopsy, it is not possible to be certain of the outcome of the treatment. Therefore, post-treatment evaluation or „end of treatment PET" is of crucial importance for those patients. After the planned treatment has ended, PET is recommended at least 2 weeks after the last administered chemotherapy, i.e. 3 months after radiotherapy (1, 2). It is necessary to follow these instructions due to the possible inflammatory changes which can occur in the residual tumor as a consequence of post therapeutic necrosis. These changes may cause mildly increased glucose metabolism („minimal residual uptake") after many weeks and lead to a false positive findings. Negative and positive predictive value of end of treatment FDG-PET differs depending on the type of HL or NHL. PET has better negative predictive value in HL (around 95%) than in NHL (around 85%), but significantly better positive predictive value in NHL (100%) than in HL (around 75%). This means that positive PET findings quite reliably point to the residual disease in NHL, but not in HL, where after the therapy, inflammatory reactions occur and cause false positive PET findings. Opposite to this, negative PET finding is not such a good guarantee of the successful treatment in NHL, as is the case with HL. This is probably in line with a generally worse prognosis and a greater rate of relapse incidence in NHL patients (19-21). Apart from benefits of end of treatment PET evaluation, two preliminary studies by Hutchings et al. showed usefulness of early PET performed after 2 administered chemotherapy cycles, that is, at the very beginning of the patient's treatment (22, 23). In interim PET positive patients 2-year progression free survival period (PFS) was 0%-6%, as opposed to 94% in interim PET negative patients. Prognostic value of interim PET "overshadowed" all other risk factors. In the same year, a study published by Kostakoglu et al. analyzed PET performed after only one cycle of chemotherapy and confirmed significant difference in PFS between PET positive (12%) and PET negative (100%) patients (24).

After that, a series of prospective studies analyzing significance of interim PET followed. It was observed that the results of a positive (PPV) and a negative predictive value (NPV) of PFS are different in different types of lymphoma and in different chemotherapy protocols (25, 26). Also, it was evident that in significant number of PET positive patients no disease relapse followed and PPV in interim PET was significantly worse than NPV. Additionally, in those prospective interim PET studies different criteria were taken for a positive interim PET finding. So, a need for new unified criteria was recognized again, where these criteria would be more appropriate for early phase of treatment. In 2010, an international workshop on interim positron emission tomography in lymphoma was held in Menton, France and it resulted in so-called "Deauville criteria" recommendation (27). It is a 5-level visual scale which, for the basis of the positive finding takes the comparison of tumor remnant in accordance with liver metabolism (positive PET, if end of treatment PET) or in accordance with lower mediastinal vascular structure metabolism (positive PET, if interim PET). Prognostic reliability of interim FDG-PET studies showed excellent specificity but low sensitivity. So, interim PET is still the subject of debates and without complete consensus on its implementation (28). In clinical practice, interim PET is recommended in early stages of HL for decision making regarding radiotherapy administration, which is not indicated in PET negative patients (e.g. Figure 1a and 1b).

Interim PET can be recommended when termination or a change of the initiated therapy is considered, due to the side effects or some other unpredicted complications of treatment. So far, there is no data whether in the case of positive interim PET findings change in therapy can produce a more favorable outcome in those patients. Clear recommendations regarding how to act in such cases are still not available.

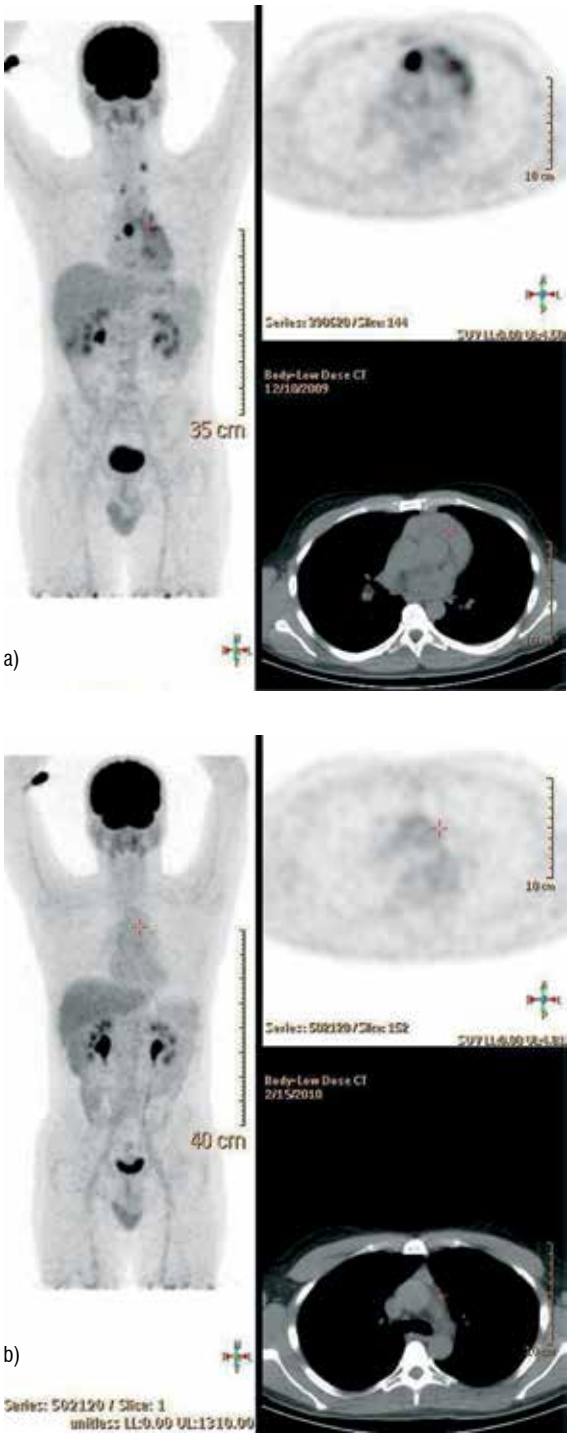

Figure 1a,b. Hodgkin lymphoma: baseline PET (1a) and negative interim PET after 2 cycles of ABVD chemotherapy with residual mediastinal lymph nodes (1b)

INTERPRETATION OF PET SCANS AND POTENTIAL PITFALLS

Interpretation of diagnostic imaging results is a starting point on which the entire patients' treatment strategy is based on. Criterion for a positive finding in this imaging method may be a visual or a quantitative assessment (29). Visual interpretation of metabolism within the tumor compared to the metabolism of the surrounding structures is a principal factor for the assessment of the positive or negative finding. A positive finding is a focal or diffuse activity more intensive than the surrounding region. Metabolism in a certain region or in a tumor can be quantified taking into account the weight, height or surface of the patient's body and the injected FDG activity. Thus SUV index values (Standardized Uptake Values) which show metabolic activity and, indirectly, the aggressiveness of a tumor lesion are obtained for specific regions. Cut-off value of the SUV index of 2.5 was earlier considered to be showing the activity of malignant diseases. It was revealed that median value of SUV index in lymphoma depends on the histological type of lymphoma. SUV index values are in the range from 2.0 (splenic lymphoma of the marginal zone, extranodal MALT, SLL) up to 20.0 and over (DLBCL, HL, follicular lymphoma). Indolent tumors rarely have SUV values over 10.0. High SUV index is bad prognostic factor regarding overall survival and regarding the achievement of the disease remission. Patients with SUV index > 8.0 have significantly worse overall survival and more frequent recurrence of the disease. In patients with SUV index > 15.0 complete disease remission is extremely rare. Bearing in mind that FDG is not a tumor-specific radiopharmaceutical and that FDG activity in some regions may be the consequence of some benign changes, SUV index is useful information but not the crucial for the interpretation of positive findings. It is known that there are numerous benign causes which may lead to an increased metabolism and false positive PET findings, such as various inflammatory lung diseases, obstructive pneumonia, chronic bronchitis, interstitial pneumonitis, bronchiectasis, silicosis, granulomatous inflammations, tuberculosis and sarcoidosis. Those diseases may result in an increased metabolism of mediastinal lymph nodes and other tissues. Figure 2 represents the patient with a disseminated type of sarcoidosis, involving lymph nodes, bone system, lungs, liver and spleen, which was histologically confirmed by a biopsy of the inguinal lymph node.

Some therapeutic procedures, most of all irradiation, but also chemotherapy, can cause increased metabolism by directly affecting the tissue or they can do it indirectly, leading to, e.g. thymus hyperplasia or myocardial ischemia, which may be the cause of false positive findings. Besides, some other benign diseases, like thyroid adenomas, oral cavity or teeth region inflammations, injuries, traumas, must be kept in mind when interpreting PET scan. Even a physiologically increased metabolism in brown fat tissue, intestines or ovaries, can be a source of an inaccurate PET interpretation. All these potential changes must be considered when analyzing PET findings. Particularly, if end of treatment PET scan shows increased metabolism in the region which was not previously affected by the disease and there is no other sign of activity in all other previously affected regions, PET finding is considered as negative. The occurrence of newly formed lung infiltrates after the end of treatment (often after the treatment with cytostatic bleomycin), in patients who previously had normal morphological and metabolic lung findings and have no any other signs of residual disease, is also considered to be negative finding, regardless of the size or the metabolism of the infiltrate in the lungs. These patients should merely be followed up. Because of the numerous possibilities for the false positive findings, FDG-PET is not recommended as a routine method in later follow up of patients who express no signs of the disease (30). Residual liver and spleen lesions larger than 1.5 cm are considered positive for active disease if they have metabolism greater or even equal to the metabolism of the surrounding parenchyma. Lesions

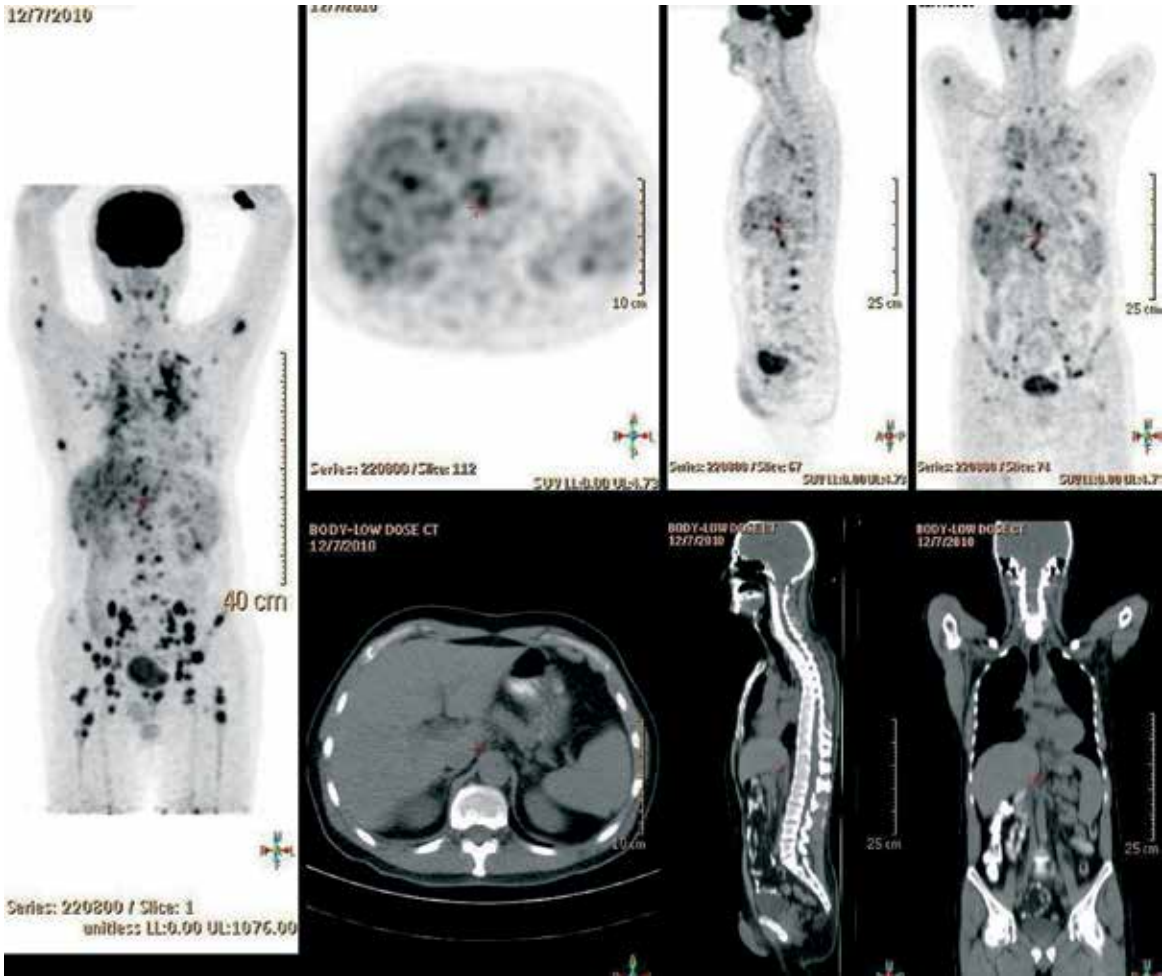

Figure 2. Sarcoidosis disseminated in lymph nodes, bones, lungs, liver and spleen

lesser than 1.5 cm are positive only if they are more intensive than the surrounding parenchyma. Resulting from all said above, it is clear that the interpretation of the findings in liver and spleen is not reliable if, at the same time, CECT is not performed, because a lesion of about 1.5 cm can not be accurately observed with "low-dose" CT. Obviously, without a morphologically visible lesion, it is not possible to confirm that the metabolism which is "equal to the surrounding parenchyma" is actually a positive PET finding. A diffusely increased metabolism in the entire spleen, which is more pronounced than the liver metabolism, is considered to be an active disease, unless 7 days prior to the PET examination patients received hematopoietic stimulation therapy (G-CSF). A diffusely increased metabolism of the bone marrow may also frequently be found after chemotherapy as a consequence of physiological activation of bone marrow and marrow hyperplasia. Pathological metabolism suggestive of skeletal involvement is usually evident as focally increased metabolism. Negative PET finding in bone marrow does not exclude the existence of a mild or moderate skeletal involvement. If malignant cell representation in the bone marrow is less than 10%, pathologically increased metabolism of the bone marrow does not necessarily have to be visible. Thus, bone marrow biopsy is still an inevitable diagnostic procedure. In spite of technological progress of the PET/CT devices, PET/CT is poorly sensitive for lymphoma of the brain region and the negative finding does not exclude the existence of the disease. FDG-PET is often false negative in lymphoma involving testicles, again because of the physiologically increased metabolism within this region, therefore clinicians and diagnosticians must bear this in mind (20, 21, 29).

LYMPHOMA GUIDELINES

Utility of a certain diagnostic method, including FDG-PET/CT, depends on the information if such examination was used for disease diagnostics, for initial patient workup, for monitoring of the treatment benefit ("response assessment") or for follow-up. Furthermore, significance of some diagnostic procedures is usually categorized in guidelines as basic or essential, useful in selected cases or not useful, but even potentially harmful.

Data on PET/CT efficacy for certain clinical circumstance of different types of lymphoma, derived from many prospective studies conducted over the years were gradually built and made accessible as national and international oncological guidelines for treatment and monitoring of lymphoma patients. There are numerous directives published by various oncological or hematological associations; in some aspects they differ in different countries and are still subject to changes. Usually, they are updated every two years. Having in mind that there is a large number of published guidelines, which, in some countries, depend on the availability of PET/CT examination and other economic factors, the most generally

accepted in clinical practice of majority European countries are the guidelines which are regularly published by the National Comprehensive Cancer Network (NCCN).

In the guidelines, published during 2011, FDG-PET role was presented in various types of lymphoproliferative diseases (31, 32). In NCCN Guidelines for Hodgkin lymphoma published in September 2011, FDG-PET was recommended as a basic and essential procedure for initial workup of patients, for treatment assessment after the end of the planned therapy and as a standard for restaging of patients in the case of unsuccessful treatment or progression, i.e. the relapse of the disease (31). All PET positive findings after restaging are recommended to be histologically verified (biopsied) prior to the commencement of the further treatment, especially in the case of the disease relapse. Rationale for that is the risk of false positive finding, but also the possibility of transformation of HL type nodular lymphocyte predominance into a more aggressive type of lymphoma. PET is also recommended during the treatment, in the early phase of the disease treatment after 2 cycles of ABVD therapy („interim PET") in HL stage I and II with favorable and unfavorable risk factors. In higher disease stages (III and IV) PET is recommended after 4 cycles of therapy with ABVD or BEACOPP. In the follow up of patients with HL, PET is not recommended as a standard diagnostic procedure.

NCCN Guidelines for implementation of PET in NHL are significantly different for different types of lymphoma (32). In diffuse B-lymphoma of large cells (DLBLC), PET is recommended as "essential" for the initial patient workup, for end of treatment restaging and for assessment prior to the decision regarding radiotherapy treatment in all patients with stages I and II after ending 3 to 6 cycles of R-CHOP chemotherapy („pre-RT evaluation"). Radiotherapy is avoided in cases of negative PET. In patients with the higher stages (III and IV) interim PET restaging is recommended after the end of 2 to 4 cycles of R-CHOP-a. Biopsy of PET positive findings is always recommended prior the decision on further treatment. In small cell lymphoma (SLL), PET is generally not recommended as a useful method, except when there is a suspicion of Richter transformation in DLBLC or HL. In follicular lymphoma it is recommended as useful in the initial workup disease evaluation. Also, when there is a suspicion of progressive disease or the disease transformation, it is always recommended with histological biopsy confirmation of the positive metabolic findings. In some rare types of NHL, such as primary skin type of B-lymphoma and the indolent lymphoma, PET is recommended as useful in the initial workup evaluation, as well as when progressive disease is suspected. It is always recommended with the biopsy confirmation of the positive metabolic findings and information gained from PET can be used for directing of biopsy.

In May 2012, the latest NCCN Guidelines for HL with amendments regarding the patients with the favorable prognostic factors of I and II stages were published (33). PET scans are not recommended for interim restaging of patients with stage I to II disease. After reevaluating the available evidence on the use of interim PET imaging, panel for this group of patients recommends the use of diagnostic CT scan of involved sites for interim restaging after completion of chemotherapy. So, we witness the change after only 6 months from the last proposed NCCN guidelines for HL in September 2011. Fine tuning of guidelines is a never ending story; a difficult and time-consuming task, but worth the effort.

CONCLUSION

In patients with lymphoma, the initially performed FDG-PET/CT leads to modification of the extent in about 15% to 30% of patients. In about 5% to 15%, this results in change of the treatment plan. FDG-PET provides prognostic information and represents a useful noninvasive imaging method to monitor the treatment benefits in patients with lymphoproliferative diseases. Knowledge of interpretation despite the limitations of this method is highly reliable.

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Conflict of interest

We declare no conflicts of interest.

REFERENCES:

1 Juweid ME, Stroobants S, Hoekstra OS, Mottaghy FM, Dietlein M, Guermazi A, et al; Imaging Subcommittee of International Harmonization Project in Lymphoma. Use of Positron Emission Tomography for Response Assessment of Lymphoma: Consensus of the Imaging Subcommittee of International Harmonization Project in Lymphoma. *J Clin Oncol*. 2007;25:571-8.

2 Cheson BD, Pfistner B, Juweid ME, Gascoyne RD, Specht L, Horning SJ, et al; International Harmonization Project on Lymphoma.Revised response criteria for malignant lymphoma. *J Clin Oncol*. 2007;25:579-86.

3 Matasar MJ, Zelenetz AD. Overview of lymphoma diagnosis and management. *Radiol Clin North Am*. 2008;46:175-98.

4 Mrzljak A, Gasparov S, Kardum-Skelin I, Colic-Cvrlje V, Ostojic-Kolonic S.Febrile cholestatic disease as an initial presentation of nodular lymphocyte-predominant Hodgkin lymphoma. World J Gastroenterol. 2010;16(35):4491-3.

5 Radić-Kristo D, Planinc-Peraica A, Ostojić S, Vrhovac R, Kardum-Skelin I, Jaksić B. Primary gastrointestinal non-Hodgkin lymphoma in adults: clinicopathologic and survival characteristics. *Coll Antropol*. 2010;34(2):413-7.

6 Munker R, Glass J, Griffeth LK, Sattar T, Zamani R, Heldmann M, et al. Contribution of PET imaging to the initial staging and prognosis of patients with Hodgkin's disease. *Ann Oncol*. 2004;15:1699-704.

7 Raanani P, Shasha Y, Perry C, Metser U, Naparstek E, Apter S, et al. Is CT still necessary for staging in Hodgkin and non-Hodgkin lymphoma patients in the PET/CT era? *Ann Oncol*. 2006;17:117-22.

8 Elstrom R, Guan L, Baker G, Nakhoda K, Vergilio JA, Zhuang H, et al. Utility of FDG-PET scanning in lymphoma by WHO classification. *Blood*. 2003;101:3875-6.

9 Podoloff DA, Advani RH, Allred C, Benson AB 3rd, Brown E, Burstein HJ, et al. NCCN task force report: positron emission tomography (PET)/computed tomography (CT) scanning in cancer. *J Natl Compr Canc Netw*. 2007;5:S1-S22.

10 Karam M, Novak L, Cyriac J, Ali A, Nazeer T, Nugent F. Role of FDG-PET scan in the evaluation and follow-up of patients with low-grade lymphomas. *Cancer*. 2006;107:175-83.

11 Perry C, Herishanu Y, Metzer U, Bairey O, Ruchlemer R, Trejo L, et al. Diagnostic accuracy of PET/CT in patients with extranodal marginal zone MALT lymphoma. *Eur J Haematol*. 2007;79:205-9.

12 Rutherford SC, Andemariam B, Philips SM, Elstrom RL, Chadburn A, Furman RR, et al. FDG-PET in prediction of splenectomy findings in patients with known or suspected lymphoma. *Leuk Lymphoma.* 2008;49(4):719-26.

13 Le Dortz L, De Guibert S, Bayat S, Devillers A, Houot R, Rolland Y, et al. Diagnostic and prognostic impact of 18F-FDG PET/CT in follicular lymphoma. Eur J Nucl Med Mol Imaging. 2010;37(12):2307-14.

14 Lopci E, Zanoni L, Chiti A, Fonti C, Santi I, Zinzani PL, et al. FDG PET/CT predictive role in follicular lymphoma. *Eur J Nucl Med Mol Imaging*. 2012;39(5):864-71.

15 Weiler-Sagie M, Bushelev O, Epelbaum R, Dann EJ, Haim N, et al. (18)F-FDG avidity in lymphoma readdressed: a study of 766 patients. *J Nucl Med*. 2010;51:25-30.

16 Alinari L, Castellucci P, Elstrom R, Ambrosini V, Stefoni V, Nanni C, et al. 18F-FDG-PET in mucosa-associated lymphoid tissue (MALT) lymphoma. *Leuk Lymphoma*. 2006; 47:2096-101.

17 Beal KP, Yeung HW, Yahalom Y. FDG-PET scanning for detection and staging of extranodal marginal zone lymphomas of the MALT type: a report of 42 cases. *Ann Oncol*. 2005;16:437-80.

18 Quarles van Ufford H, Hoekstra O, de Haas M, Fijnheer R, Wittebol S, Tieks B, et al. On the Added Value of Baseline FDG-PET in Malignant Lymphoma. *Mol Imaging Biol*. 2010;12:225-32.

19 Zijlstra JM, Lindauer-van der Werf G, Hoekstra OS, Hooft L, Riphagen II, Huijgens PC. 18F-fluoro-deoxyglucose positron emission tomography for post-treatment evaluation of malignant lymphoma: a systematic review. *Haematologica*. 2006;91:522-9.

20 Cronin CG, Swords R, Truong MT, Viswanathan C, Rohren E, Giles FJ, et al. Clinical Utility of PET/CT in Lymphoma. *AJR*. 2010;194:W91-W103.

21 Connors J. Positron Emission Tomography in the Management of Hodgkin Lymphoma. *Hematology*. 2011:317-22.

22 Hutchings M, Loft A, Hansen M, Pedersen LM, Buhl T, Jurlander J, et al. FDG-PET after two cycles of chemotherapy predicts treatment failure and progression-free survival in Hodgkin lymphoma. *Blood*. 2006;107(1):52-9.

23 Gallamini A, Hutchings M, Rigacci L, Specht L, Merli F, Hansen M, et al. Early interim 2-[18F]fluoro-2-deoxy-D-glucose positron emission tomography is prognostically superior to international prognostic score in advanced-stage Hodgkin's lymphoma: a report from a joint Italian-Danish study. *J Clin Oncol*. 2007;25(24):3746-52.

24 Kostakoglu L, Goldsmith SJ, Leonard JP, Christos P, Furman RR, Atasever T, et al. FDG-PET After 1 Cycle of Therapy Predicts Outcome in Diffuse Large Cell Lymphoma and Classic Hodgkin Disease. *Cancer*. 2006;107:2678-7.

25 Andre M, Vander Borght T, Bosly A. Interim FDG-PET Scan in Hodgkin's Lymphoma: Hopes and Caveats. *Advances in Hematology*. 2011;ID430679:1-6.

26 Itti E, Juweid ME, Haioun C, Yeddes I, Hamza-Maaloul F, El Bez I, et al. Improvement of Early F-FDG PET Interpretation in Diffuse Large B-Cell Lymphoma: Importance of the Reference Background. *J Nucl Med*. 2010;51:1857-62.

27 Meignan M, Gallamini A, Haioun C, Polliack A. Report on the Second International Workshop on interim positron emission tomography in lymphoma held in Menton, France, 8-9 April 2010. *Leuk Lymphoma.* 2010;51(12):2171-80.

28 Meignan M, Gallamini A, Itti E, Barrington S, Haioun C, Polliack A. Report on the Third International Workshop on Interim Positron Emission Tomography in Lymphoma held in Menton, France, 26-27 September 2011 and Menton 2011 consensus. *Leuk Lymphoma*. 2012 Apr 23. [Epub ahead of print]

29 Delbeke D, Stroobants S, de Kerviler E, Gisselbrecht C, Meignan M, et al. Expert opinions on positron emission tomography and computed tomography imaging in lymphoma. *Oncologist*. 2009;2:30-40.

30 El-Galaly TC, Mylam KJ, Brown P, Specht L, Christiansen I, Munksgaard L, et al. PET/CT surveillance in patients with Hodgkin lymphoma in first remission is associated with low positive predictive value and high costs. *Haematologica.* 2012;97(6):931-6.

31 Hoppe RT, Advani RH, Ai WZ, Ambinder RF, Bello CM, Bierman PJ, et al; NCCN Hodgkin Lymphoma. NCCN Clinical Practice Guidelines in Oncology: Hodgkin lymphoma. *J Natl Compr Canc Netw*. 2011;9(9):1020-58.

32 Zelenetz AD, Abramson JS, Advani RH, Andreadis CB, Bartlett N, Bellam N, et al. NCCN Clinical Practice Guidelines in Oncology: non-Hodgkin's lymphomas. *J Natl Compr Canc Netw*. 2011;9(5):484-560.

33 Hoppe RT, Advani RH, Ai WZ, Ambinder RF, Aoun P, Bello CM, et al. Hodgkin Lymphoma, Version 2.2012 Featured Updates to the NCCN Guidelines. *J Natl Compr Canc Netw*. 2012;10(5):589-97.