

Review Article, PET/CT.

Diagnostic Accuracy of Surveillance of FDG-PET/CT in Detection of Early Relapse in Malignant Lymphoma.

Serry, O and Moustafa, H.

Nuclear Medicine Unit, Faculty of Medicine, Cairo University, Cairo, Egypt.

ABSTRACT:

Introduction: Integrated PET/CT has been shown to be more accurate for lesion localization and characterization in lymphoma than PET and CT alone. Addition of CECT to PET/CT changed management of lymphoma in only about 10% of patients, while FDG/PET resulted in a management change in almost 50 % of HL patients compared with CECT alone. The majority of patients with high-grade non-Hodgkin's lymphomas (NHL) are cured with combination treatments. However, acute and long-term toxicities impair survival. Patients with poor-risk, progressive, or relapsed disease; the goal is to improve survival with a strategy using more intensive therapy. Hence, the focus of management has now shifted towards reducing the treatment toxicity and long-term side effects while maintaining favorable outcomes especially in low-risk patients. The successful application of this tailored approach is dependent on an

accurate and non-invasive diagnostic test that would reflect the true extent of disease as well as its viability early during the course of treatment. **Metabolic parameters in malignant lymphoma:** An imaging task force was created to update the relevance of existing imaging for staging, assessing bulk, and bone marrow involvement (BMI); the role of interim PET; standardization of PET reporting; and role for quantitative evaluation using PET and CT. A clinical task force assessed the current relevance of Ann Arbor and how best to incorporate PET/CT into staging lymphoma, the relevance of B symptoms and bone marrow biopsy (BMB), as well as to create recommendations relevant to both FDG-avid and non-avid lymphomas. The revised IWG response criteria (rIWG) incorporated FDG PET to accurately assess end-therapy persistent masses in both NHL and HL.

PET/CT in surveillance assessment:

Surveillance CT or PET-CT scans are widely used because of the impression that treatment at relapse is more likely to be effective when the disease is in a preclinical stage with a small tumor burden: the earlier the detection of disease the higher the treatment efficacy. The authors concluded that the routine use of surveillance PET in HL patients entering complete remission after first-line treatment should be reserved for high-risk patients. Current guidelines warrant that, once the first clinical remission is obtained, surveillance should be grounded on frequent physical examination and routine blood tests. By contrast, a

significant proportion of these patients undergo follow-up CT radiological studies and fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT, especially in the first 2 years after therapy. FDG-PET/CT follow up exams may be associated with false positive results. These confounding findings add up to the already significant FDG-PET/CT expense, which in turn is significantly more resource-consuming when compared to clinical and biochemical evaluation. **CONCLUSION:** PET/CT imaging for surveillance in malignant lymphoma may be useful in special subtypes of both Hodgkin and non-Hodgkin lymphoma.

Keywords: Non Hodgkin lymphoma, FDG PET/CT, Surveillance, Relapse.

Corresponding Author: Serry, O.

E-mail: o.serry@hotmail.com.

INTRODUCTION:

Integrated PET/CT combines PET and CT in a single imaging device and allows morphological and functional imaging to be carried out in a single imaging procedure. Integrated PET/CT has been shown to be more accurate for lesion localization and characterization than PET and CT alone. FDG PET is a sensitive imaging modality for initial staging, re-staging as well as for assessment of

therapy response in lymphoma⁽¹⁻³⁾. *Raanani et al.* reported that the addition of CECT to PET/CT changed management of lymphoma in only about 10% of patients, while FDG/PET resulted in a management change in almost 50 % of HL patients compared with CECT alone⁽⁴⁾. However, this study didn't describe what type of treatment changes occurred or whether outcome was altered.

In another group of 47 NHL or HL patients. PET/CE-guided treatment resulted in a 95 % event-free survival (EFS), while separately acquired FDG PET and CECT-guided treatment resulted in a lower EFS of 81 % ($p=0.002$)⁽⁵⁾.

The majority of patients with high-grade non-Hodgkin's lymphomas (NHL) are cured with combination treatments. Nevertheless, these therapies carry acute and long-term toxicities which may impair survival. Thus, the focus of management has now shifted towards reducing the treatment toxicity and long-term adverse effects while maintaining favorable outcomes in low-risk patients⁽⁶⁾.

In the subset of patients with poor-risk, progressive, or relapsed disease, the goal is to improve survival with a strategy using more intensive therapy. Individualized approaches can be devised either prior to therapy using well-defined risk categories based on staging and prognostic factors or early during therapy with the use of predictive factors.

The successful application of this tailored approach is dependent on an accurate and non-invasive diagnostic test that would reflect the true extent of disease as well as its viability early during the course of treatment⁽⁷⁾.

Metabolic parameters in malignant lymphoma:

In 1999, *Cheson et al.* published recommendations from the International Working Group (IWG), initially designed for NHL but adopted for HL as well. These codified definitions for complete and partial response and stable, relapsed, and progressive disease. Although universally adopted, they were not problem-free: the definition of remission was misinterpreted, and the recommendations were dependent on inadequate methods such as physical examination, chest X-ray, CT scans, and gallium scans⁽⁸⁾.

Revised recommendations were published in 2007 that incorporated PET into response assessment and subsequently validated. In 2011, a workshop was held at the 11th International Conference on Malignant Lymphoma (ICML) to reevaluate the staging and response criteria after years of experience with the 2007 version.

An imaging task force was created to update the relevance of existing imaging for staging, assessing bulk, and bone marrow involvement (BMI); the role of interim PET; standardization of PET reporting; and role for quantitative evaluation using PET and CT⁽⁹⁾.

A clinical task force assessed the current relevance of Ann Arbor and how best to incorporate PET/CT into staging lymphoma, the relevance of B symptoms and bone marrow biopsy (BMB), as well as to create recommendations relevant to both FDG-avid and non-avid lymphomas. At the 12th ICML, a follow-up workshop was held to further discuss possible modifications of current staging and restaging criteria in lymphoma ⁽¹⁰⁾.

Consistent data from multiple studies have established the role of post-therapy FDG PET imaging for the prediction DLBCL. A NPV and a PPV of 80% and 100% were reported, respectively, for FDG PET in the identification of residual aggressive NHL after completion of first-line chemotherapy ⁽¹¹⁾.

The revised IWG response criteria (rIWG) incorporated FDG PET to accurately assess end-therapy persistent masses in both NHL and HL ⁽⁷⁾.

PET/CT in surveillance assessment:

Complete response to first-line therapy is frequently observed in patients with Hodgkin's lymphoma (HL) and diffuse large B cell lymphoma (DLBCL).

On the other hand, the rates of subsequent relapses can show considerable variations. Relapses after first-line therapy can occur in 20-50 % of patients with advanced-stage HL or aggressive B-cell lymphoma ^(12, 13).

Treatment failures are usually observed within 3 years of completion of treatment, with the majority of relapses occurring in the first 12 months for HL and 18 months for DLBCL ⁽¹⁴⁾.

Surveillance CT or PET-CT scans are widely used because of the impression that treatment at relapse is more likely to be effective when the disease is in a preclinical stage with a small tumor burden: the earlier the detection of disease the higher the treatment efficacy.

The probability of detecting an impending relapse during patient monitoring for disease recurrence with a given test depend on the intrinsic probability of relapse of the disease in the population being tested, as well as the sensitivity, specificity, and the frequency of the test.

The prevalence of relapse in both HL and DLBCL is rare, reportedly with only one relapse per 68 visits in HL and per 40–45 visits for patients with aggressive NHL based on routine CT scans.

Moreover, several factors could influence the prevalence of relapse and progression in a definite lymphoma subtype including the presence of clinical symptoms, the pre-therapy risk of recurrence, early lymphoma chemo sensitivity assessment, the preferred anatomical regions of recurrence of a given lymphoma subtype and persistence of a residual mass at the end of treatment ⁽¹⁵⁾.

El-Galaly et al., report the value of surveillance PET/CT in a retrospective cohort of 161 HL patients who achieved a complete or partial remission after first-line treatment. During a median follow-up of 34 months, 14 % of patients experienced a relapse.

With an average of 1.9 PET/CT per patient, the positive predictive value (PPV) of routine PET/CT and clinically indicated PET/CT was 22 % and 37 %, respectively (p=0.02).

However, in a subset of high-risk patients (with extra nodal disease, a positive PET result at interim or therapy completion), the PPV increased to 36 %, whereas in those without risk factors the PPV was only 5 %.

Consequently, the authors concluded that the routine use of surveillance PET in HL patients entering complete remission after first-line treatment should be reserved for high-risk patients ⁽¹⁶⁾.

Current guidelines warrant that, once the first clinical remission is obtained, surveillance should be grounded on frequent physical examination and routine blood tests.

By contrast, no international agreement has been reached on the use of follow-up imaging in asymptomatic patients. Nevertheless, a significant proportion of these patients undergo follow-up CT radiological studies and fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT, especially in the first 2 years after therapy ⁽¹⁷⁾. However, while FDG-PET/CT has a definite role in staging and response assessment in lymphomas, its routine use for surveillance in patients in remission is highly controversial. FDG-PET/CT offers the advantage of detecting metabolic changes, which usually occur earlier than morphological alteration, most disease relapses are actually heralded by clinical signs or by relapse of B-symptoms ⁽¹⁸⁾.

FDG-PET/CT follow up exams may be associated with false positive results. These confounding findings often imply further evaluation in order to ascertain their precise nature; their cost can then add up to the already significant FDG-PET/CT expense, which in turn is significantly more resource-consuming when compared to clinical and biochemical evaluation. Performing PET scanning for surveillance in patients who achieved a complete remission is still a debated issue. *Jerusalem et al.*, performed PET imaging in 36 HL patients at the completion of therapy and every 4 to 6 months thereafter for 2 to 3 years. One patient with persistent tumor and four relapses were identified a few months before clinical, laboratory or CT evidence of disease. However, there were also six patients with false-positive PET studies requiring additional restaging procedures for further clarification, including subsequent PET scans performed several months later, all of which turned out negative. One of the main concerns over using FDG-PET for surveillance is the high rate of false-positive results, which may lead to unnecessarily treating otherwise non-disease bearing patients (19).

Also, *Rhodes et al* describes the use of FDG-PET in the follow-up of a group of

41 children with either HL or NHL after complete remission. Although the precise PET scanning time points are not reported, the authors described a high rate of false-positive results (41% in NHL and 63% in HL). The overall incidence of false-positive cases in their series is limited (16/1789 scans), although higher for NHL cases. Differences in results are likely related to criteria for PET positivity (20).

On the other hand, *El Galaly et al.*, Suggested that FDG-PET/CT may have a role in the early detection of relapse in the setting of a higher biological recurrence risk. Actually, the clinical relevance of surveillance FDG-PET/ CT in lymphoma is almost entirely founded on the assumption that an early salvage treatment could improve survival on selected patients, even though evidence supporting this concept was relatively scarce. A multicenter study has surprisingly highlighted a lower disease burden and a possible survival advantage in case of imaging-detected relapse in selected subgroups of lymphoma patients. They demonstrated that early treatment of relapsing disease, driven by prompt detection on medical images, granted a 40% risk reduction for death among patients with diffuse large B cell lymphoma (DLBCL) (21).

Zinzani et al., investigated the usefulness of FDG-PET in the follow-up of patients with malignant lymphoma. The major finding was the capability of FDG-PET to identify unsuspected relapse (among favorable and unfavorable risks) in a relevant number of patients (approximately 10% of scans in HL patients at 6 and 12 months and in NHL patients at 6, 12 and 18 months), thus supporting the usefulness of performing a scan at these time points. The number of true-positive PET responses is clearly related to the likelihood of relapse, whereas false-positive findings were almost stable in 6 patients at 6 months, 3 patients at 12 months, 3 patients at 18 months and

4 patients at 24 months ⁽²²⁾.

Torrey et al., Reported how relapse in 157 out of 709 HL patients (22%) was suspected primarily by symptoms in patients, physical examination in 14%, chest x-ray in 23%, and abdominal x-ray in 7%. Nonetheless, it is clearly useful to detect early relapse as early as possible in lymphoma patients, in order to increase the possibility of obtaining a remission by changing time of therapy ⁽²³⁾.

CONCLUSION:

PET/CT imaging for surveillance in malignant lymphoma may be useful in special subtypes of both Hodgkin and non-Hodgkin lymphoma.

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