^{18}FDG PET in lymphoma

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SUMMARY

^{18}F-FDG PET/CT has become essential in the management of patients with Hodgkin's and non-Hodgkin's lymphoma. The utility of ^{18}F-FDG PET/CT imaging is based upon increased anaerobic metabolism of neoplastic tissue. The degree of hypermetabolism is somewhat proportional to lymphoma grade. Based on the ability of ^{18}F-FDG PET/CT to identify hypermetabolic tissue, it has greater sensitivity and specificity for the detection of tumors in general and lymphoma in particular compared to CT or MRI. ^{18}F-FDG PET/CT has made a significant impact in lymphoma management in the following instances: 1. Extent of disease in patients already diagnosed with lymphoma; 2. Identification of hypermetabolic disease in lymphadenopathy identified by other means; 3. Evaluation of response to therapy – with greater specificity than CT alone; 4. Early detection of recurrent disease; 5. Identification of transformation from low grade to high-grade lymphoma; 6. Prediction of response to therapy and prognosis. In many clinical trials, ^{18}F-FDG PET/CT has replaced CT as the standard for assessment of residual disease. It has become a standard procedure at the time of initial diagnosis and following completion of therapy as well at 6-24 month intervals during the follow-up or upon the recurrence of symptoms suggestive of relapse. On an investigational basis, we have demonstrated that resolution of lymph node hypermetabolism, as early as following a single cycle of chemotherapy, is predictive of a prolonged disease-free interval whereas failure to respond after a single cycle indicates that even if there is resolution of disease after completion of a full course of treatment, relapse occurs earlier. If confirmed by additional studies, early ^{18}F-FDG PET/CT evaluation of response may provide a basis to select patients for a change to more aggressive or alternate therapy. In fact, it may also identify a sub-population of patients who do not require an extended course of chemotherapy.

Key words: *Positron-Emission Tomography and Computed Tomography; Lymphoma; Fluorodeoxyglucose F18; Hodgkin Disease; Lymphoma, Non-Hodgkin*

^{18}F-fluoro deoxyglucose [FDG] is a glucose analogue that has had the radioactive positron emitting atom, ^{18}F inserted in place of one of the hydroxyl groups on the glucose molecule. This molecular alteration does not interfere with FDG entry into the cell. Consequently, FDG serves as a marker of energy utilization and provides an assessment of biochemistry and cell physiology as opposed to simply identifying anatomy. Hence FDG PET and FDG PET/CT serve to identify viable tumor even within normal-sized lymph nodes, differentiates viable tumor from fibrotic tissue and also provides an indication as to whether cell metabolism has been disrupted by chemo-, immuno- or radiation therapy. This feature of FDG PET has become essential to the practice of oncology and has made a major contribution to the diagnosis and management of the patient with Lymphoma, both non-Hodgkin's [NHL] and Hodgkin's lymphoma [HL]. This brief review will provide only highlights of the current status of FDG PET in lymphoma as many in-depth reviews are available (1-3).

There are 5 distinct areas in which FDG PET and PET/CT have had a significant clinical impact on oncology practice in general:

- Staging [Extent of Disease]
- Detection of Histopathologic Transformation
- Response to Therapy
- Predict Response and Prognosis
- Detection of Relapse

STAGING [EXTENT OF DISEASE]

The impact of FDG PET/CT imaging on staging is illustrated in Figure 1. The extent of disease based on tumor hypermetabolism is readily identified. All current PET imaging systems are capable of providing a quantitative assessment of the degree of hypermetabolism by determining the FDG activity per unit volume, known as the Standardized Uptake Value [SUV]. Procedures such as splenectomy are no longer necessary to exclude splenic involvement which cannot be excluded by CT imaging alone. Increased FDG localization is readily identified and serves as a marker of lymphoma activity even at sites that are otherwise normal on CT examination. A report published in 2004 documented that FDG PET/CT was more sensitive and specific than contrast-enhanced CT for evaluation of lymph node and organ involvement in NHL. For lymph node involvement, FDG PET had a sensitivity of 94% vs. 88% for CT and a specificity of 100% vs. 86%. For organ involvement, FDG PET had a sensitivity of 88% vs. 50% for CT and a specificity of 100% vs. 90% (4) (Figure 2).

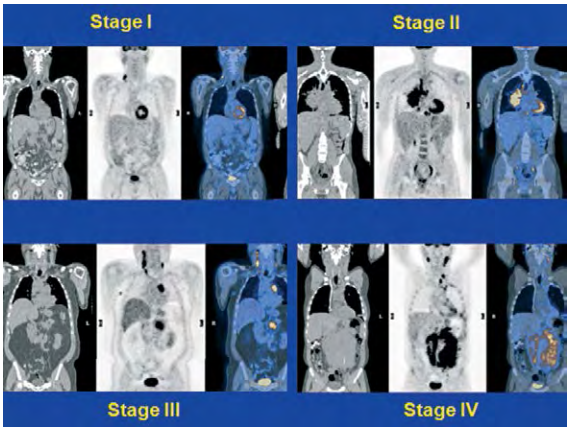

Figure 1. FDG PET/CT in the staging of extent of disease in lymphoma. Coronal images: left to right: CT, FDG PET, PET/CT fusion images illustrating Stage I, Stage II, Stage III and Stage IV involvement prior to treatment. While the larger masses are detectable on the CT images alone, the metabolic assessment demonstrating increased anerobic metabolism is useful to identify small lymph nodes with lymphoma involvement as well as to document the degree of lymphoma involvement in CT detectable masses which may not resolve despite adequate therapy.

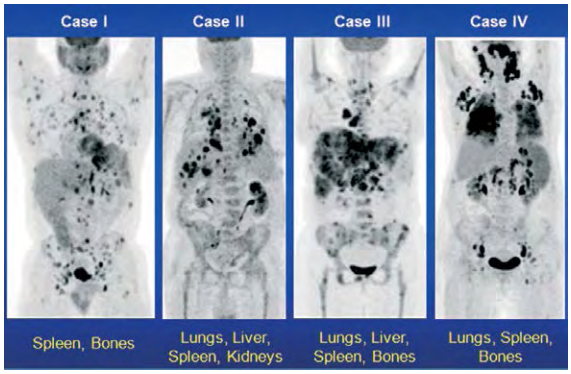

Figure 2. Extra-nodal organ involvement in lymphoma. FDG PET Maximal Intensity Projection [MIP] images [display of all acquired transaxial slices reconstructed in computer memory and displayed so as to appear as a volume display]. 4 different patients illustrating varied and extensive extranodal involvement –usually an ominous clinical finding.

DETECTION OF HISTOPATHOLOGIC TRANSFORMATION

As stated above. the degree of FDG uptake can be quantified and expressed as the Standardized Uptake Value [SUV], an estimate of the fractional FDG uptake per unit volume of tumor or tissue and hence an indicator of anaerobic metabolism. In general, the greater the SUV, the more aggressive the tumor. Non-Hodgkin's lymphoma is classified as Low or High Grade depending upon several clinical features (such as the rapidity of onset of symptoms including tumor appearance). This classification correlates with the histopathologic and various other classifications and serves as a guide to therapy. Amongst the Low grade lymphomas, the most common histopathologic type is the follicular or small cell lymphoma. The most common high grade NHL is large B-cell lymphoma. Typically, patients presenting with high grade lymphomas are acutely ill and require immediate treatment, often with excellent results. By contrast, patients with low grade lymphomas may be diagnosed based upon a medical workup for non-specific symptoms such as fatigue. In many cases, lymph nodes are not grossly enlarged and the patient is otherwise asymptomatic. Consequently, treatment may be deferred. Nevertheless, as the disease progresses, enlargement of the tumor masses produces generalized and local symptoms and treatment is necessary. The disease course, however, may be complicated by Richter's transformation; the transformation of a low grade lymphoma to a high grade lymphoma. This may present a confusing clinical picture but it is important that the correct diagnosis be made so as to select appropriate therapy for the high grade tumor. In Figure 3, transaxial sections demonstrating a low grade lymphoma involving maxillary lymph nodes which are clearly enlarged but confirmed on biopsy as low grade lymphoma with a SUV value in the range of 1.8 to 2.0. The MIP and coronal sections, however, reveal peri-aortic abdominal lymph nodes with an SUV of 16.0-19.5. Biopsy of the abdominal nodes, although inconvenient, revealed transformed Diffuse Large B-cell lymphoma. Treatment was modified in response to this change in the diagnosis.

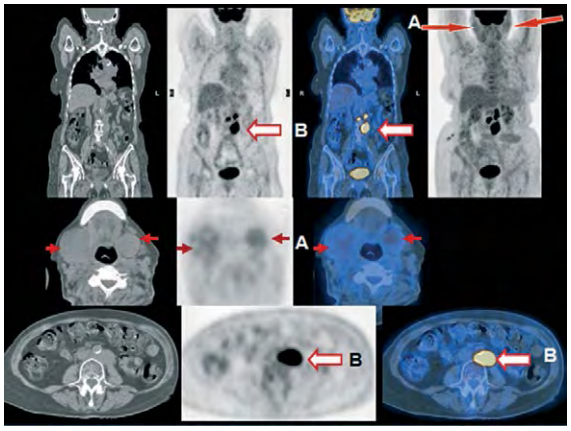

Figure 3. Left to right: CT, FDG PET and PET/CT fusion images. Top row: Coronal sections. Image on far right is an MIP image demonstrating mildly increased FDG activity in bilateral parotid masses [A] and prominent hypermetabolic masses [B] in the abdominal peri-aortic lymph nodes. Middle row: Transaxial sections of mildly hypermetabolic parotid masses, SUV max 1.8-2.9, which were the presenting symptom and finding. FDG PET characterization of these masses is typical of a low grade lymphoma which was confirmed on biopsy. Bottom row: Transaxial images of peri-aortic lymph nodes which are markedly hypermetabolic, SUV max 16.0-19.5. Biopsy demonstrated Large B-cell lymphoma, a high grade variant which would not have been detected or biopsied without the FDG finding.

RESPONSE TO THERAPY

FDG PET and PET/CT document the response to therapy with greater overall accuracy than CT alone by demonstrating the reduction and absence of the increased FDG uptake even though the mass identified on CT may persist. The CT mass represents residual fibrous tissue and may persist throughout the remaining life of the patient. In former times, prior to FDG PET/CT, this would lead to a patient being classified as less than a Complete Response even though all symptoms may have cleared and the patient remains free of clinical symptoms without treatment for many years. Recently, particularly for the assessment of the response to therapy in patients with NHL, it has been proposed that the classical criteria for characterization of a response to therapy, RECIST [Response Evaluation Criteria In Solid Tumors], be modified to include the assessment of tumor SUV using FDG PET (5). The revision is known by the acronym, PRECIST [PET Response Evaluation Criteria In Solid Tumors].

PREDICTING RESPONSE AND PROGNOSIS

Chemotherapy of lymphoma involves many cycles of treatment. Each cycle may involve therapy with drug combinations for 3 of 4 weeks per cycle and each cycle is repeated for 6-9 months.

Given that FDG PET/CT provides an assessment of the tumor metabolism, it is appropriate to speculate as to whether it is possible to predict response or non-response early in the course of treatment rather than delay evaluation until completion of the course of therapy?

The ability to predict response would be valuable in at least two instances:

- In the event that it is possible to predict treatment failure early in the course of therapy, rather than continue an ultimately unsuccessful therapy with it's own inherent toxicity, patient's can move on to second line or alternate therapies without exposure to the full toxicity from the initial course of therapy.

- If therapeutic success can be reliably predicted early in the course of a prolonged treatment, consideration may be given to abbreviating the duration of the therapeutic course. In the past, without a metric on which to predict therapy, there was no alternative other than the full course of therapy which was defined in the past based on trial and error.

Of course, either of these options would have to be evaluated in a clinical trial prior to modifying the current clinical practice.

A number of investigators have explored the potential of assessing FDG SUV in lymphoma patients after 3 or 4 therapy cycles, so-called mid-course assessment. At the Weill Cornell Medical Center in New York, physicians at the Center for Lymphoma & Myeloma and the Division of Nuclear Medicine & Molecular Imaging have evaluated the FDG SUV response from images obtained after a single cycle of chemotherapy and found that it was an even better predictor of the duration of response than assessment after the completion of therapy (6) (Figure 4). In patients who have had complete elimination of metabolic activity in involved lymph nodes after a single cycle of chemotherapy, the Progression Free Survival [PFS] was quite prolonged, greater than 3 years in some patients at the time of analysis of results whereas in patients with residual metabolic activity after the first cycle, the PFS had a median value of less than a year. The Negative Predictive Value of FDG PET after a single cycle of therapy was 100% and the Positive Predictive Value was 87.5% compared to 91% and 92% respectively after completion of therapy. In a study of 34 patients, Kostakoglu, Goldsmith et al found that 90% of the patients with a positive FDG-PET after one cycle relapsed with a median PFS of 5 months (6). There was one false positive which in retrospect should have been interpreted as thymic tissue rebound. 85% of patients with negative FDG-PET after 1 cycle remained in complete remission with a minimum follow-up of 18 months. By contrast, in patients who had negative FDG-PET at completion of therapy, the relapse rate was 35%. The relapse rate was 15% if the FDG-PET was negative after the first cycle (6).

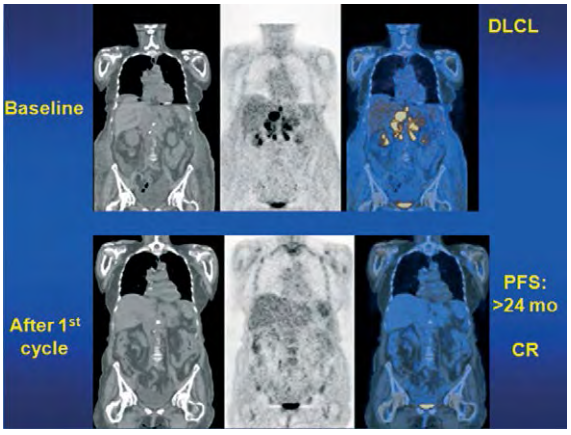

Figure 4. Coronal projections, CT, FDG PET and PET/CT fusion, in a patient with diffuse Large B cell lymphoma at baseline (top row) and after the 1st cycle of CHOP chemotherapy (bottom row). All evidence of tumor hypermetabolism has resolved after a single cycle of therapy. The full course of therapy, 9 cycles, was completed and at the time of review, the patient continued to be free of symptoms or evidence of disease progression after 24 months, confirming that it is possible to assess efficacy early in the course of therapy.

DETECTION OF RELAPSE

Given the well documented sensitivity of FDG PET to detect NHL, it is a reasonable recommendation that FDG PET/CT should be the procedure of choice in the follow-up of NHL patients. In asymptomatic patients, this procedure might be performed as infrequently as 2 year intervals whereas in a patient who is suspected of relapsed disease, FDG PET/CT is the procedure of choice at that time as opposed to CT with contrast. The nuclear medicine physician, of course, must be mindful that so-called Low Grade lymphoma may have relatively low SUVs. In this regard, making full use of the hybrid imaging component of PET/CT images is necessary for optimal results (4, 5, 7).

SUMMARY AND CONCLUSION

FDG PET/CT represents a remarkable advance in imaging lymphoma. The technique provides the most sensitive and the overall most accurate means of

- detecting tumor activity
- evaluating the response to therapy by differentiating viable residual tumor from fibrous tissue
- providing prognostic information early in the course of chemotherapy
- follow-up of patients in remission or suspected of relapse (1-7).

Conflict of interest

We declare no conflicts of interest.

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