Role of Positron Emission Tomography (PET) in the Management of Lymphoma

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Introduction

Proper Management of Cancer requires evaluation of tumor extent, monitoring of therapy and evaluation of treatment induced side effects. Imaging modalities are crucial in achieving this all the three main pre-requisites for this proper management. Structural modalities such as computerized tomography (CT) and functional modalities such as gamma camera imaging are complementary rather than competitive for cancer management. Each modality has advantages and limitations. Positron emission tomography (PET) as a recent functional modality is now the most powerful modality in advancing cancer management.

Functional Nuclear Medicine studies including PET provide useful information that cannot be obtained by morphologic modalities (Fig.1). Being a metabolic imaging modality

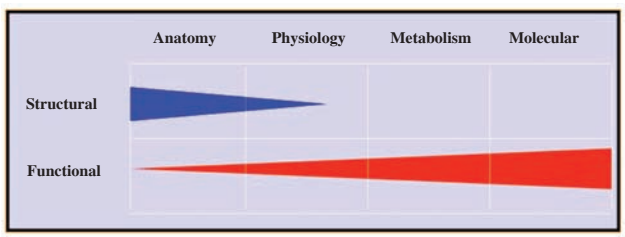

Fig. 1: A diagram illustrating the information provided by different imaging modalities.

using biologically important compounds with Carbon-11 (C-11) Fluorine-18 (F-18), it has the advantage of revealing biochemical parameters of lesions as glucose, oxygen or amino acid metabolism. It has also an outstanding spatial, contrast and temporal resolutions, and it provides accurate quantification and is cost effective as it helps avoid unnecessary diagnostic and therapeutic procedures. The PET-CT combines anatomical and functional imaging and is considered the state-of-the-art imaging technique for the assessment of lymphoma and other malignancies [1].

Lymphoma is a common malignancy that is increasing over the last few decades [2]. PET has an important role in the diagnosis, staging, early assessment of response to therapy, assessment of residual tumor after completion of therapy, detecting recurrence and providing prognostic information. Its role varies however based on the histological type of the tumor [3] [Table 1].

Reliable role (> 90% positive)
• Diffuse large B cell NHL • Follicular NHL • Mantle Cell NHL • Classical HL
Less reliable role (50%-90% positive)
• Marginal zone/mucosa associated lymphoma tissue (MALT) NHL • Small lymphocytic NHL
Undefined role
• T cell NHL • Burkitt-type NHL • Lymphoplasmcytic NHL • Lymphocyte predominance HL
Modified from Friedberg [3]

Table 1: Relation of Lymphoma Histologic Subtypes and Utilization and Value of FDG

Role of PET in Staging

Since traditionally stage I/II can be managed by radiation therapy alone or in combination with chemotherapy while stage III/IV is managed mainly by chemotherapy, changing stage can have a crucial impact on management. Additionally

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this has a prognostic importance as early stage I/II has nearly double the cure rate of stage III/IV. Accurate staging therefore allows proper choice of therapy strategy, avoids unnecessary toxic therapies, such as extended-field radiation therapy or overly aggressive chemotherapy, decreasing the risk of secondary malignancies (which exceeds 10%) and improving the quality of life during and after therapy with tailored defined therapy. PET imaging with Fluoro-deoxy glucose (FDG) provides reliable initial staging of lymphoma (Fig. 2) since it detects metabolically active disease by its increased glycolysis that is proportional to mitotic activity [4]. Like other imaging modalities, it has its own drawbacks including inability to detect very small lesions (<5 mm) and reduced specificity due to increased uptake in metabolically active inflammatory and infective tissues. Dual acquisition including 60 and 120 minute imaging after FDG injection can improve the specificity since FDG would be retained by malignant tissue on delayed imaging. This concept needs to be studied further and could have an important impact on the accuracy of PET in detecting lymphoma lesions and further enhance PET staging and restaging.

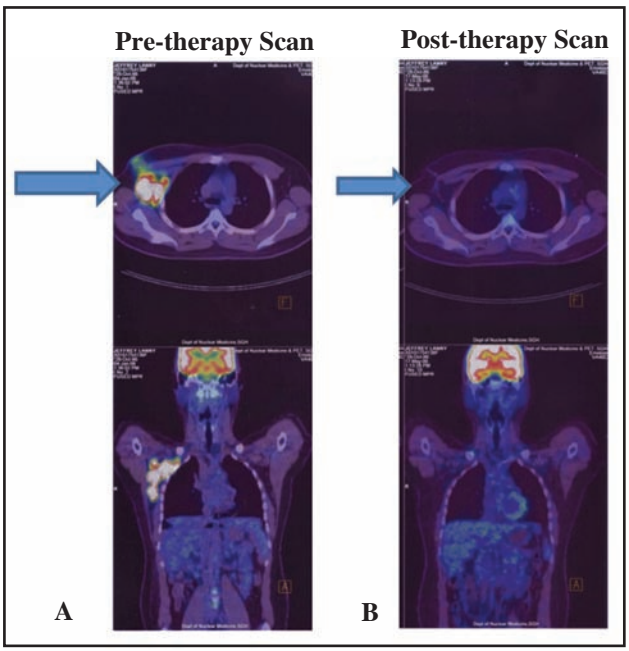

Fig. 2: A representative image of FDG-PET/CT scan performed for staging of a patient with non Hodgkin's lymphoma (a) showing increased uptake in the active disease in the right axilla. The activity clearly disappeared after the patient received chemotherapy as shown on the post therapy scan (b). Courtesy of Professor Ajit Padhy

PET versus CT in staging

CT scan, as the case with other morphologic modalities, has limitations for nodal staging since its criteria are based on size only. PET is superior to CT scan and changes both nodal and extra nodal staging and is particularly useful in detecting isolated splenic disease [5,17] [Table 2].

PET versus Ga-67 in staging

Ga-67 has been used for many years in staging and follow up of several tumors particularly lymphoma. FDG-PET has been found superior to Ga-67 in staging [18]. FDG-PET enhances staging at diagnosis as it detects occult disease above and below the diaphragm (particular value in spleen) more than Ga-67 [19]. In a recent study of 62 patients, sensitivity of PET for patients and lesions was 100% while it was 81% (patients) and 69% (lesions) for Ga-67 [20]. In another similar study of 84 patients these sensitivities were 83% and 87% for PET and 63% and 33% for Ga-67 [21]. Recently Ga-67 SPECT/CT was

Study	Year	n	Histology	Major Findings
Hueltenschmidt [11]	2001	81	HD	PET superior to conventional imaging
Buchmann [12]	2001	52	NHL/HD	PET superior to CT; 4 patients upstaged due to PET
Wirth [13]	2002	50	NHL/HD	PET superior to Ga-67 scans
Kostakoglu [14]	2002	51	NHL/HD	PET superior to gallium.
Weihrauch [15]	2002	22	HD	Four patients upstaged due to PET
Friedberg [9]	2003	36	HD	PET superior to gallium; Spleen better imaged on PET.
Naumann R [16]	2004	88	HD	PET superior to conventional modalities
Rigacci L [17]	2007	156	HD	PET superior to CT

Modified from Friedberg [3]

Table 2: PET versus Other Modalities in Lymphoma Staging

found to provide information not obtained by Ga-67 SPECT alone and facilitates the diagnosis of lesions located in the abdomen (sub diaphragmatic lesions) and provides information that may cause a change in therapeutic strategy [22].

Impact of PET staging on Management

A survey-based study of referring physicians (52 responses) demonstrated that FDG-PET contributed to changes in clinical stage and major management decisions. Clinical stage was changed for 44% of patients: upstage in 21% and downstage in 23%. Regarding impact on management, there was a change in 68% of patients (inter-modality change in 42% of patients, intra-modality change in 10%, combination in 10% and other changes in 6% of patients) [23]. A multicentric study investigated the contribution of PET to the staging of Hodgkin's disease (HD) by CT scan and attempted to determine whether it has any impact on therapeutic approach. One hundred eighty six consecutive patients with HD from six Italian centers were enrolled in this study. Staging utilizing PET was prospectively compared to that with CT scan. CT scan and FDG-PET stages were concordant in 156 patients (84%) and discordant in 30 patients (16%). PET stage in comparison to CT scan stage was higher in 27 patients (14%) and lower in 3 patients (1%). The programmed treatment strategy was modified in 11 out of 30 patients (37%) after the definition of final stage. Out of the 123 CT staged patients with localized stage, ten patients (8%) with a change of stage from localized to advanced after PET evaluation were treated with different strategy. Accordingly FDG-PET was shown to enhance HD staging, particularly in early stage patients, where a change in stage may modify disease management significantly [17].

Role in Tumor Follow up and Evaluating Response to Therapy

Morphologic image abnormality is not a reliable indicator of active disease. Residual abnormalities occur in 30%-60% after therapy and are usually considered persistent lymphoma as CT scan cannot differentiate between benign fibrous tissue, inflammation or persistent malignant disease. Only 10%-20% of these residual masses at completion of therapy are positive for lymphoma on biopsy and 18% of these will eventually relapse. Additionally distinct subgroups of Non Hodgkin's Lymphoma (NHL) respond differently to various therapeutic approaches [24,25]. Another retrospective review of the chest X- rays of 65 patients treated for mediastinal HD demonstrated residual abnormalities in 88%, mediastinal widening of greater than 6 cm in 42% (19% of these patients relapsed) and mediastinal widening of less than or equal to 6 cm in 58% (24% of these patients relapsed) [26].

PET has an important role in evaluating the response to therapy (Fig. 2). It is usually performed after the completion of therapy. However earlier assessment is becoming popular as a routine part of management in patients with HD and histologically aggressive NHL. Changes in FDG uptake can occur soon after the initiation of therapy and they precede changes in tumor volume seen on morphologic modalities. Recent trials in uniform populations of aggressive NHL (predominantly diffuse large B cell lymphomas) and HD have clarified the value of early response assessment with PET. These studies showed that PET imaging after 2-3 chemotherapy cycles is far superior to CT scan based imaging in predicting progression-free survival and can be at least as reliable as definitive response assessment at the end of therapy [27]. Timing in evaluating the response to therapy is still debatable. Some studies showed that progression free survival correlated better with PET after the first cycle of chemotherapy [14] while others showed that PET after 3 cycles of chemotherapy had higher predictive value for disease recurrence than PET scanning after completion of therapy [3].

In a study comparing the impact of FDG-PET during and after therapy in 40 patients with HD

and 30 patient with NHL, interim PET (after 2-4 cycles of chemotherapy) of 31 (82%) with HD patients demonstrated complete remission which was still present on end of therapy PET. The remaining seven patients with HD (18%) had partial remission on interim PET. For NHL 22 (73%) patients had complete remission on interim PET analysis which was still present on end PET. In the remaining eight patients with NHL, interim PET revealed partial remission in seven and stable disease in one patient. None of all interim PET complete responders progressed until the end of therapy. Thus, of the 196 PET/CT's carried out in our study population, 53 end PET's (27.0%) were carried out in interim complete responders. End-treatment PET/CT is unnecessary if interim PET shows complete remission and the clinical course is uncomplicated. An imaging cost reduction of 27% in our study population could have been achieved by omitting end of treatment FDG-PET/CT in interim complete responders[28].

When PET is used after completion of therapy it is recommended to be performed at least three weeks but preferably 6-8 weeks after chemotherapy or chemo-immunotherapy and 8-12 weeks after radiation or chemo-radiotherapy [29]. Since HD and diffuse B-cell NHL (DLBCL), follicular lymphoma and mantle cell lymphomas are FDG avid, initial PET scan is not mandatory although it can facilitate better assessment of post therapy scan. In other subtypes such as T-cell lymphomas and all subtypes of indolent NHL other than follicular lymphomas with variable avidity to FDG, pretherapy scans are mandatory [29].

When PET is not available, Ga-67 imaging can also provide information regarding the presence or absence of residual active lymphoma [30]. Using SPECT imaging, the literature quotes sensitivities mostly in the 85% - 95% range, and specificities greater than 98% [31,34]. Most importantly, the positive predictive value for the presence of active disease has consistently been shown to be greater than that for morphologic imaging techniques such as CT scan and MRI. A recent study [35] of 40 patients with newly

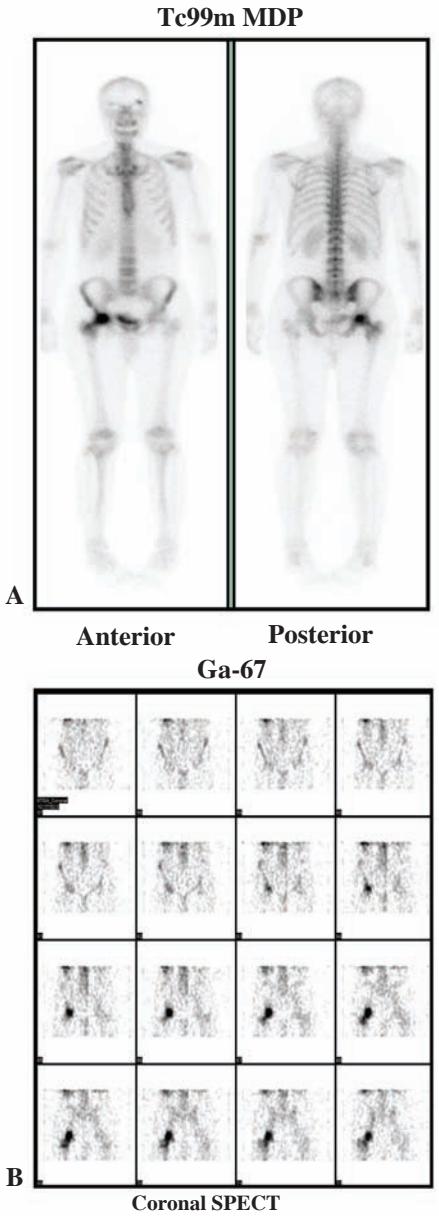

Fig. 3: Bone scan (a) and SPECT gallium-67 scan (b) in a single focus primary NHL illustrating intense ga-67 uptake in the right femoral head.

diagnosed aggressive lymphoma studied with PET and Ga-67 scans before & after 3 cycles of CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) or 2 cycles of ACVBP (doxorubicin, cyclophosphamide, Vincristine, bleomycin, prednisone), with or without rituximab. Thirty five patients had diffuse large B-cell lymphoma (DLBCL), 2 patients had mantle-cell lymphoma and 3 patients had T-cell lymphoma. Four patients relapsed despite early negative FDG-PET & Ga-67 including all 3 patients with T-cell lymphoma. Nine patients stayed in remission despite positive PET and/or

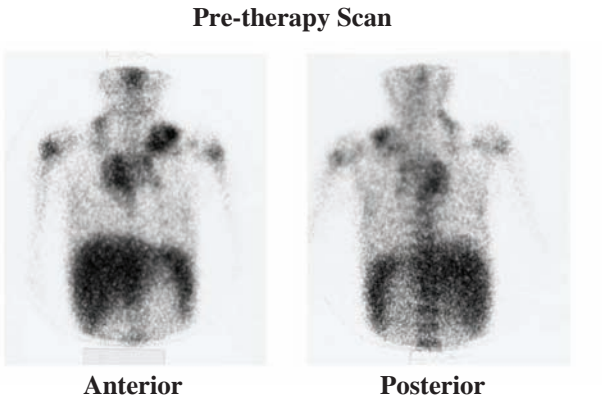

Fig 4a

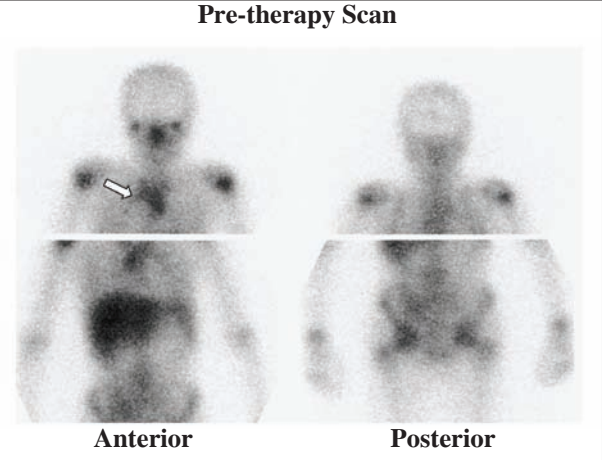

Fig 4b

Fig. 4: Ga-67 scan of a 7 year old boy with HD showing multiple foci of increased accumulation of the radiotracer in the lower neck and chest (a). The post chemotherapy scan (b) shows clearing of activity indicating good response to therapy. Note that there is mediastinal uptake (arrow) seen post therapy secondary to thymic rebound which can be seen after treatment and represents benign hyperplasia.

Ga-67. Five of those patients showed moderate intensity residual bone uptake. Seven of these nine with early positive scans had negative examinations at the end of treatment. Examples of Ga-67 scans (Fig. 3) illustrate gallium avid lymphoma lesions and follow up changes after therapy.

Role in Predicting Prognosis and Outcome

PET can also provide valuable prognostic information [36,37]. A study of 34 patients with untreated lymphoma reported on PET imaging during a follow up of 15-50 months after starting therapy [36]. Patients with recurrence had higher pre-therapy (SUV) Standard Uptake Value than patients in remission. Survival was also longer for patients with SUV of less than 8.0 [35]. The 2-year event-free survival was 85% for negative PET patients and 30% for positive PET patients while it was 78% for negative Ga-67 patients and 33% for positive Ga-67 patients. Sensitivity, specificity and accuracy were 90%, 76% and 80% respectively, while it was 70%, 80% and 77% for Ga-67 with no significant differences. The study indicates that both FDG-PET and Ga-67 are valuable tools to early predict outcome in patients with diffuse large B-cell lymphoma [36].

Summary

PET enhances staging of lymphoma and is superior to CT scan. It consequently provides more accurate basis for treatment regimens. It provides a better assessment of response to therapy and is the most useful non-invasive modality to differentiate residual tumor from fibrosis/necrosis. Persistent uptake during and after chemotherapy appear to have a high sensitivity in predicting subsequent relapse although some patients may remain in prolonged remission. A negative finding after therapy indicates a very favorable prognosis.

We still need better refinement to set off patients who could really benefit from the additional information and better definition of the optimal timing of imaging in clinical practice, The use of early PET response in determining choice of therapy should be utilized with caution until some critical questions are answered. These include: When is the best time to use PET for response assessment? what is the most suitable methodology, visual or quantitative? can early responders be cured with less intensive therapy? will survival be better for patients treated more intensively because they have a poor interim metabolic response?. Further evaluation of alternative PET radiotracers and whether they are superior to FDG and evaluation of the added value of dual FDG-PET acquisition are needed. When PET is not available, Ga-67 imaging of lymphoma can also provide information regarding the presence or absence of active lymphoma particularly in assessing the response to therapy and predicting the outcome.

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