Role of nuclear medicine in detection and management of Hodgkin's disease and non-Hodgkin's Lymphoma

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Among the improvements in cancer management in recent years are impressive advances in the treatment of Hodgkin's disease (HD) and non-Hodgkin's lymphomas (NHL). Most patients with lymphomas can be treated curatively. Accurate diagnosis and proper selection of treatment and early assessment of response to therapy are to obtain the best outcome. So determination of stage of the disease is one of the major prognostic factors, which has important implications on therapeutic strategy and on prognosis. CT scan is considered the standard technique for anatomic localization of nodal disease sites. Unfortunately, the diagnosis of lymph node abnormalities with CT largely depends of lymph node size. Lymph nodes smaller than 10 mm are usually regarded as disease free. However normally sized lymph nodes may be diseased and in contrast, enlarged ones may be free of disease. In addition, sensitivity of CT for extranodal lymphoma is not optimal, it may miss peripheral sites and the problem of differntiating residual tumor from a residual fibrotic mass is well documented.

The Gallium –67 scan has traditionally had a well documented role in lymphoma, for disease staging, assessing treatment response, early detection of recurrent disease and providing prognostic information early during treatment. Ga-67 scan limitations are its low resolution and physiological biodistribution. The overall gallium scan positivity rate for Hodgkin's lymphoma is 85%-95% and for non-Hodgkin's lymphoma is 75%-90%.

FDG(fluorodeoxyglucose) has high avidity for most types of lymphoma. Intensity of uptake on pretherapy staging has been reported to correlate with prognosis with higher uptake having poorer prognosis. The advantages of FDG-PET scan are its higher resolution and excellent capability of detecting multiple sites of primary and recurrent disease and differentiating viable lymphoma from a residual fibrotic mass post-treatment.

The term lymphoma comprises two clinically and biologically distinct groups of neoplasms, Hodgkin's disease and non-Hodgkin's lymphoma.

Hodgkin's disease

Hodgkin's disease is a B-cell lymphoid neoplasm described as a clinical entity in 1832 by Thomas Hodgkin and define microscopically by pathologists Carl Sternberg and Dorothy Reed at the turn of the twentieth century. The diagnosis is base on the recongnition of Reed – Sternberg cells interspersed among a reactive mixed-cell population of lymphocytes, eosinophils, histiocytes, Plasma cells, and neutrophils. Four histologic types (lymphocyte predominance, nodular sclerosis, mixed- cellularity and lymphocytes depletion) are distinguished on the basis of the morphology and immunohistochemistry. The anatomical extent

of disease, associated symptoms, and to a lesser degree, the histologic subtype are the primary factors determining the presenting features, Prognosis and optimal therapy of Hodghin's disease. As one of the highly curable malignancies,Therapy for Hodgkin's disease is approached with optimism.

Incidence and Epidemiology:

The annual incidence of HD, about 7600 case or 3.2 per 100.000 has been stabl over the past decade in the United States. The incidence is higher in men than women. A biomodal age-incidence curve has been described in which rates rise through early life, peak in the third decade, decline until age 45, and thereafter rise steadily. The nodular sclerosis is more common in young adults, whereas the mixed-cellularity subtype predominates in children and elderly. In the young adult population, high socioeconomic status, high intelligence, small family size, and high educational levels all have been associated with increased risk of HD. In less developed countries, childhood and mixed-cellularity histology predominate. In developed countries, young adults with more favorable histologic subtypes are typical .A large population study has demonstrated abnormally high titers of anti-EBV (Epstein – Barr virus) antibodies in serum of patients.

Pathology:

Nodular sclerosis accounts for 40%-70% of all case of HD. Mixed-cellularity histology is found in 30%-50% of patients at diagnosis. Lymphocyte predominance is uncommon, representing about 10% of cases. Lymphocyte-depleted is a rate from of HD.

Clinical findings:

Constitutional symptoms, referred to as "B" symptoms, may accompany the diagnosis of HD and influence prognosis. These include temperature higher than 38'C, excessive night sweats, and weight loss exceeding 10% of baseline. Detection of an unexplained mass or swelling in the superficial lymph nodes, especially the neck, is the most common presentation of patients with HD. The lymph nodes are nontender and have a rubbery consistency.

Laboratory features:

The laboratory features are nonspecific. A routine complete blood count may reveal granulocytosis, eosinophilia, lymphocytopenia, thrombocytosis or anemia of chronic disease. Cytopenia may occur as a result of marrow involvement, hypersplenism or an autoimmune mechanism.The degree of elevation of ESR has prognostic significance correlating with advanced disease.

Optimal management:

Upon establishment of histologic diagnosis of Hodgkin's disease by pathologist, a diagnostic evaluation is undertaken. In addition to a complete history and physical examination, all patients should have CT scans of the chest, abdomen and pelvis. Intrathoracic disease is present in two-thirds of patients at diagnosis. Chest CT may reveal hilar adenophthy, pulmonary parenchymal involvement, pleural effusions and chest wall masses. CT of the abdomen and pelvis may detect celiac, portal, retroperitoneal and pelvic lymph nodes. Exploratory laparatomy has been phased out of study today as a part of routine staging. Bone marrow biopsy is indicated in patients who are symptomatic or have extensive disease or cytopenias. Patients with bone pain should have bone scans and directed skeletal x-rays. As will be pointed out later in detail gallium scan and FDG-PET play

important roles in initial staging and in serial evaluation of patients before and after treatment.

The diagnostic evaluation of the patient with HD will ultimately leads to the assignment of stage and directs the patient's therapy. HD spreads in an orderly fashion from one lymph node group to contiguous lymph node group and extra-nodal disease is not common.

Ann Arbor staging classification has been used to define the extent of HD.

TABLE 1
Hodgkin's Lymphoma Staging:
Ann Arbor Classification

Stage	Criteria
Stage I	Single lymph node region or extra-lymphatic site
Stage II	≥2 lymph node regions on same side of diaphragm
Stage III	Lymph node regions on both sides of diaphragm
Stage IV	Disseminated disease
	>1 extra-lymphatic organ ± lymph node involvement
Substages:	A Asymptomatic
	B Fever, night sweats, ≥10% weight loss

In practice, patients with asymptomatic stage 1 or 2 with no bulky disease, the plan of therapy will be brief chemotherapy in addition to involved–field radiotherapy. In symptomatic or bulky/extranodal disease of stage 1 or 2, the treatment of
choice would be full course chemotherapy plus radiotherapy. In sage 3 and 4 the treatment will be full course chemotherapy with or without radiotherapy (1).

Non-Hodgkin's Lymphoma

NHLs are a heterogeneous group of malignancies that begin as a clonal malignant expansion of B or T lymphocytes. NHL is multifocal disseminated disease rather that a spreading nodal disease. Extranodal involvement is much more demostrated that in patients with HD. The clinical presentation is variable, patients may give a history of chronic asymptomatic lymphadenopathy, which may have been present for months to years, or may present acutely with rapidly progressive lymphadenopathy, constitutional symptoms and organ failure secondary to extranodal involvement from lymphoma.

Incidence and epidemiology:

NHLs remain the fifth most common cause of cancer and cancer- related death in the United States. The incidence appears to be increasing for unknown reasons. The presence of HIV infection appears to be associated with an increased risk of developing NHL. Mortality rates appear to be higher for urban areas and for higher socioeconomic groups. NHL occurs throughout the world at rates that range from a threefold to fourfold increase in recent years. The maximun rates are seen in western developed countries (1).

Classification:

According to Working Formulation, the classification scheme divides NHLs into three distinct groups based on biology and prognosis: low-grade. intermediate-grade and high- grade lymphomas.

Diagnostic and staging investigations:

Lymph node biopsy, complete blood and platelet counts, serum chemistry panel, lactate dehydrogenase level, CT scan of chest, abdomen and pelvis, bone marrow biopsy, MRI of head and other locations, bone scan. Lumbar puncture, SPECT gallium scan and FDG-PET.

Therapeutic options:

In low- grade NHL, therapeutic options include watching and waiting or single agent chemotherapy. In intermediate-grade NHL, standard treatment consists of combination Chemotherapy. In bulky disease in addition to combination chemotherapy,

involved – field radiotherapy is also used. In high – grade NHL, all patients receive aggressive combination chemotherapy. Radiotherapy is not a routine part of treatment (2).

Limitations of CT and MRI in detection of lymphoma

CT and MRI use morphologic criterai to detect disease. The diagnosis of lymph node size. Lymph nodes that are smaller than 10 mm are usually regarded as disease free. However, normally sized lymph nodes may be involved with disese and in contrast, enlarged lymph nodes may show and inflammatory response and be free of disease(3).

Sensitivity of anatomic imaging modalities for extra-nodal disease is suboptimal and peripheral sited will be missed (2). They are also unable to differentiate reliably residual functioning tumoral mass or recurrence from residual necrotic and fibrotic mass post – therapy.

Role of gallium–67 scan in the management of Lymphomas

Gallium –67 is widely used in nuclear medicine as a tumor – imaging agent. Nearly 30 years ago, Edwards and Hayes first described the accumulation of Ga-67 in the lymph nodes of a patient with Hodgkin's disease.

Recent literature shows that gallium-67 scan provide important information for the management of patients with lymphoma after treatment. Before treatment the conventional imaging procedures for staging have been chest-X-ray and CT scan. The effectiveness of Ga –67 scintigraphy in restaging lymphoma depends on proper performance of the test and experience in interpreting the images.

Appropriate patient selection:

Appropriate patient selection is an important first step in maximizing the success of Ga-67 scanning for lymphoma. The use of Ga –67 is appropriate in all cases of HD and for higher grade NHLs. The overal avidity of Ga –67 in these patients in high. The magnitude of Ga-67 uptake is highest in the nodular sclerosis form of HD. Ga–67 can be variable in uptake, even between different individuals with the same histologic type of lymphoma (4). For this reason it is important that a Ga-67 scan be performed before therapy, to established the gallium avidity of the tumor. Because Ga-67 uptake by the tumor can decrease with even a single dose of chemotherapy, it is critical that a baseline gallium scan be performed before beginning therapy.

For low–grade NHL. Ga–67 uptake is variable. Although many advocate the use of Ga-67 for low–grade lymphoma (5,6), many practitioners prefer to use Tl–201 or Tc-99m MIBI for patients with low–grade lymphoma (7,8). In 30% of patients, who initially have low–grade lymphomas, conversion to higher grade occurs and is often associated with the development of strongly gallium avid tumor (4). For NHS of intermediate grade, a Ga–67 scan performed before any therapy should establish whether the tumor is gallium avid. If it is, the Ga-67 likely can be used to assess the response of this specific tumor to future therapy.

Staging of the lymphoma:

For the initial staging of lymphoma, it is well accepted the Ga-67 imaging is considerably inferior to anatomic imaging, such as CT scan (9). An initial Ga-67 scan, in patients with newly diagnosed lymphoma,

should be done, however to establish the gallium avidity of the tumor, not to stage the patient. Radiographic findings are likely to be abnormal as a result of the previously treated tumor, with fibrotic masses, at sites of previous bulky disease, postsurgical and radiation changes and scarring (10). However, even with initial staging, the information gained by the Ga-67 scan occasionally can change the stage of the tumor. For this reason it is important that the nuclear medicine practitioner have a clear understanding of lymphoma staging systems.

Predictions of tumor's response to treatment:

There are several studies that demonstrate the efficacy of Ga-67 scan in predicting the response of the lymphoma to therapy (11-14). This approach is most beneficial in those patients with poor prognosis and aggressive disease who have persistent signs of symptoms despite the recent initiation of therapy. In these patients, it would be useful to know as early as possible if the therapy chosen was a failure, so that changes could be made to maximize the patient's chance of survival.

It is not entirely clear how early in the course of treatment a Ga-67 scan can be performed that will predict a tumor's response. Imaging can be done after 2-4 cycles, or midway in a round of chemotherapy, The mechanism for an early decrease in Ga-67 uptake with appropriate treatment is not clear, because it is likely that the tumor is nonetheless still viable (4).

The most common and best-supported use for Ga-67 imaging is in predicting adequate response of eradication of the tumor after completion of radiation and chemotherapy (15). Because imaging can fail to reveal the presence of tumor after even a single dose of chemotherapy, It is important to wait a reasonable interval after completing therapy to allow any remaining viable tumor to regain metabolic of chemotherapy or proliferative activity. It is recommended that injection of Ga-67 be delayed 3-6 weeks after completion of chemotherapy or radiation (16). However, Many clinicians are reluctant to wait this long, because the initiation of additional chemotherapy should be as timely as possible, if residual tumor is still present. So, many nuclear medicine specialists are willing to reduce the requisite interval to 2 weeks after completion of therapy, which should be considered the absolute minimum. It should be reemphasized that injection of Ga-67 at intervals less than 3 weeks after completion of chemotherapy could lead to a false- negative exam, when the exam is performed to determine whether the tumor has been completely eradicated by the chosen therapy (4).

According to literature, the sensitivity of planar Ga-67 scintigraphy before treatment, is 66%-97% and for SPECT imaging it is 85%-97%. The specificity is 66%-100% for planar imaging, and 94%-100% for SPECT scintigraphy . Ga-67 scan is more sensitive and specific that CT in the evaluation of patients after therapy. For the evaluation of response and the differentiation of residual mass from residual cancer after treatment, Ga-67 scan provides a sensitivity of 64 %-100%; in contrast, the accuracy of CT for evaluation of the chest is 53%-55% and for the abdomen it is only 5%. For the diagnosis of recurrence, the sensitivity of Ga-67 scan is 89%-95%. Versus 45%-55% for CT. Ga-67 scan is a good

predictor of survival after induction treatment. There is statistically significant association between Ga-67 imaging results after treatment and survival, but not between CT results and survival. Ga-67 scan has the potential to indicate the need to change ineffective chemotherapy at an early stage in the treatment protocol (17).

FDG-PET in Lymphoma

The ability of FDG-PET (Fluorodeoxyglucose Positron Emission Tomography) to localize primary tumoral sites, regional lymph nodes and distant metastatic sites is well documented in the literature. Metabolic imaging with FDG-PET has

TABLE 2. Sensitivity and specificity of ^{67}Ga scintigraphy in patients with lymphoma

First author	No. pts HD	No. pts NHL	No. pts LNHL	Sensitivity		Specificity	
I. Sensitivity and specificity at diagnosis before treatment							
Anderson et al. (48)	21	31		HD	NHL	HD	NHL
				97%	92%	100%	100%
Tumeh et al. (20)	33	7		Chest:		Chest:	
				Planar: 66%		Planar: 66%	
				SPECT: 96%		SPECT: 100%	
				Abdomen:		Abdomen:	
				Planar: 69%		Planar: 87%	
				SPECT: 85%		SPECT: 100%	
Front et al. (7)	38	39		78%		97%	
Ben-Haim et al.(19)			57	79%		94%	
II. Sensitivity and specificity for diagnosis of CR and patients' prognosis after treatment							
Israel et al. (5)	19	6		100%		95%	
Wylie et al. (6)	25			80%		70%	
Front et al. (7)	38	39		Planar: 84%		Planar: 96%	
				SPECT: 92%		SPECT: 99%	
Kaplan et al. (8)		37		76%		75%	
Front et al. (10)	43	56		PPV/HD: 80%		NPV/HD: 84%	
				PPV/NHL: 73%		NPV/NHL: 84%	
Gasparini et al. (43)	34			86%		100%	
Kostakoglu et al. (11)	30			96%		80%	
Cooper et al. (52)	48					80%	
King et al. (13)	33			PPV: 90%		NPV:92%	
Hill et al. (36)	21	13		PPV: 75%		NPV: 31%	
				HD: 67%		HD: 35%	
				NHL: 100%		NHL: 20%	
Ben-Haim et al. (17)	3	11		64%			
Bar-Shalom et al. (16)	8	12		95%			
III. Sensitivity and specificity of diagnosis of relapse							
Weeks et al. (9)		10		90%			
Front et al. (12)	27	8	1	95%		89%	
Ben-Haim et al. (19)			28	89%			

HD, Hodgkin's disease; NHL, non-Hodgkin's lymphoma; LNHL, low-grade non-Hodgkin's lymphoma; SPECT, single-photon emission computed tomography; CR, complete response; PPV, positive predictive value; NPV, negative predictive value.

The literature search for the sensitivity and specificity of Ga-67 imaging in patients with lymphoma is summarizes in table 2:

brilliant impact on the unresolved problems in the management of lymphoma patients in staging and restaging. as well as therapy monitoring.

Ga-67 scan, though has been extensively show to be valuable in assessing response to therapy, early detection of recurrent disease, and in providing prognostic information early during treatment, has limitations such as relatively low resolution, physiological biodistribution complicating abdominal evaluation and requirement of delayed imaging time (2-14days) after injection. Comparisons of PET and Gallium in lymphoma are few in the literature (18).

FDG has high avidity for most types of lymphoma (18,19) There is a correlation between FDG uptake and proliferative activity (20), but correlation of uptake and grade of lymphoma is controversial (20,21).

Intensity of uptake on peritherapy staging has been reported to correlate with prognosis, with higher SUV (standardized uptake value) having poorer prognosis (22). Because lymphoma is not treated surgically and all presumed lesions can not be undergo biopsy, The true sensitivity, specificity and accuracy of the imaging modalities used for staging can not be evaluated. Data found in the literature usually compare two imaging modalities: concordant sites of disease are considered true disease, and discordant sites are discriminated by biopsy, when possible, or by clinical and radiological follow – up (23).

Sensitivity of FDG uptake for initial staging was found to be at least comparable with that of CT (18,19,24) On a retrospective

analysis of 50 patients with either HD or NHL (19), total sensitivity of PET was similar to that of CT (86% for PET versus 81% for CT). Specificity of PET, however was 96% and only 41% for CT. PET was reported to detect additional sited of disease unsuspected by conventional imaging in 17% of patients, missing sited diagnosed by conventional imaging in only 5% of patients (18).

The potential of FDG – PET to predict tumor response as early as after 1 cycle of chemotherapy was suggested in a number of patients(30). Residual mass detected by anatomic imaging, especially in patients with primary bulky disease, is a well – documented problem in the early assessment of response to treatment, and in the long term follow – up for detection of recurrent lymphoma (31). Several studies showed the excellent capability of FDG-PET to detect recurrent disease and differentiate viable lymphoma from a residual fibrotic mass postreatment (19,24). FDG-PET has positive predictive value (PPV) of 94% - 100% for predicting short-term relapses, compared with PPV of 38% - 60% for CT. In the presence of residual mass on CT with negative PET, the risk of relapse is significantly decreased compared with positive PET (4% to 26%). A positive PET scan after treatment indicates lower survival rates than for PET – negative patients (32-33).

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