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Clinical Utility of 18F-FDG PET/CT in Lymphoma

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Abstract: Background: The strategy of the initial treatment in patients with lymphoma is based on the determination of the histological subtype, pretreatment identification of risk factors and precise disease staging. Staging of the lymphoproliferative process has classically been carried out based on bone marrow biopsy and CT with intravenous contrast. However, in the last decade, 18F-FDG-PET/CT has demonstrated a better diagnostic yield to detect lymph node and extra lymph node involvement prior to treatment, allowing more correct staging of lymphomas according to the Ann Arbor classification with the Cotswolds modification. PET/CT has greater sensitivity for sites of extranodal involvement a correspondingly has been found to improve baseline staging compared with conventional staging with CT alone. PET/CT findings also can indicate the overall level of metabolic activity of lymphoma, which correlates with level of aggressiveness and with LDH level (a prognostic predictor). In general, indolent follicular lymphoma is associated with low-grade FDG uptake and a low LDH level, whereas higher intensities of FDG uptake are seen in more aggressive lymphoma with higher LDH levels. On comparing PET/CT with conventional CT in the staging of the subtypes of lymphomas mentioned, a sensitivity of 94% vs. 88% and a specificity of 100% vs. 86% have been reported, respectively, thereby demonstrating greater precision of the functional study due to the presence of lesions with metabolic alterations which do not yet present radiological manifestations. Systematic staging of lymphoma should include the following: description of nodal stations involved; representative uni-linear measurements of enlarged lymph nodes in the long axis; identification of sites of extranodal involvement; and detection of coexisting abnormalities that can affect management, such as infection in the lungs and facial sinuses and incidental pathologic and malignant changes.

Keywords: Clinical Utility, 18F-FDG PET/CT, Lymphoma

Introduction: The strategy of the initial treatment in patients with lymphoma is based on the determination of the histological subtype, pretreatment identification of risk factors and precise disease staging. Staging of the lymphoproliferative process has classically been carried out based on bone marrow biopsy and CT with intravenous contrast ***(1).***

However, in the last decade, 18F-FDG-PET/CT has demonstrated a better diagnostic yield to detect lymph node and extra lymph node involvement prior to treatment, allowing more

correct staging of lymphomas according to the Ann Arbor classification with the Cotswolds modification ***(2).***

PET/CT has greater sensitivity for sites of extranodal involvement a correspondingly has been found to improve baseline staging compared with conventional staging with CT alone **(*1).***

PET/CT findings also can indicate the overall level of metabolic activity of lymphoma, which correlates with level of aggressiveness and with LDH level (a prognostic predictor). In general, indolent follicular lymphoma is associated with low-grade FDG uptake and a low LDH level, whereas higher intensities of FDG uptake are seen in more aggressive lymphoma with higher LDH levels ***(2).***

On comparing PET/CT with conventional CT in the staging of the subtypes of lymphomas mentioned, a sensitivity of 94% vs. 88% and a specificity of 100% vs. 86% have been reported, respectively, thereby demonstrating greater precision of the functional study due to the presence of lesions with metabolic alterations which do not yet present radiological manifestations. **(*1).***

Role of PET/CT in Staging of Lymphoma:

Systematic staging of lymphoma should include the following: description of nodal stations involved; representative uni-linear measurements of enlarged lymph nodes in the long axis; identification of sites of extranodal involvement; and detection of coexisting abnormalities that can affect management, such as infection in the lungs and facial sinuses and incidental pathologic and malignant changes. ***(3).***

Ann Arbor classification (Cotswolds modification) for the staging of lymphomas.	
Stage I:	involvement of a single lymph node region or lymphoid structure (i.e. spleen, thymus, Waldeyer ring).
Stage II:	Involvement of 2 or more lymph node regions on the same side of the diaphragm (the mediastinum is a single site: the helium include one on each side); the number of sites is indicated with a subset (i.e. II3).
Stage III:	Involvement of lymphatic regions or lymphatic structures on both sides of the diaphragm.
	III1: Upper abdomen (splenic, celiac, portal).
	III2: Lower abdomen (paraaortic, mesenteric).
Stage IV:	Involvement of extranodal sites beyond those indicated as E. Visceral involvement.
Applicable to any stage:	
-A:	No B symptoms.

-B:	Fever, nocturnal sweats, loss of more than 10% of body weight in previous 6 months.
-X:	Bulky disease: mediastinal widening >1/3 measured at the T5–6 level, or mass >10 cm.
-E:	Involvement of a single extranodal site contiguous or next to the known lymph node localization.
-S:	Splenic involvement.

PET/CT image analysis

PET/CT images were evaluated **visually** and **quantitatively***.* Lymphoma can be diagnosed at PET when there is focal or diffuse increased 18F-FDG uptake that exceeds the background activity. Usually, visual comparison of the described 18F-FDG focus with the blood pool and liver is sufficient to correctly characterize the uptake as low (isointense relative to the blood pool), moderate (nearly isointense relative to the normal hepatic parenchyma), or high (hyperintense relative to the hepatic parenchyma and blood pool. PET scans after completion of therapy generally have changes that are evident on visual interpretation. **(4).** Quantitative measurements such as SUV for interpreting FDG PET scans are limited because of the considerable overlap between SUV measurements in malignant and benign lesions**. (4).** The SUVmax, SUVmean, and MTV were measured from each site (tumor or group of tumors). For each PET/CT dataset, the tumor with the most intense 18F-FDG uptake among all foci was carefully identified, and the SUVmax was measured on the fused PET/CT images using the AW Volume Share™ workstation (GE Healthcare). For each tumor or group of tumors, the MTV was estimated in a 3D manner by selecting volume of interest (VOI) on the axial image, and the size of VOI was manually regulated on the corresponding coronal and sagittal images to include the entire active tumor in the VOI, and an isocontour threshold of 42% of the SUV-max was determined between the background and the maximal pixel value. The SUVmax, SUVmean, and MTV in the VOI were computed automatically by the program **(5)**.

A slight variability in SUV measurements does not affect the clinical interpretation in PET performed for initial staging or follow-up after completion of therapy**..** When evaluating PET for early response to therapy, changes may be subtle and not visually evident. Quantification such as SUV plays a more important role in this scenario; clinical studies to date indicate that most tumors responding to therapy show a 20–40% decrease in SUV early in the treatment course*. **(6)***.The factors affecting SUV are either **biological** such as Body Size weight, blood glucose level & glucose-6-phosphatase as well patient breathing or **technical** such as inter-scanner variability, image reconstruction parameters, calibration error between scanner and dose calibrator, timing mismatch between scanner and dose calibrator, use of contrast material for PET/CT and inter-observer variability.

Current treatment strategies for lymphoma

HD, Localized disease (stages 1A and 11A): early stage non-bulky disease: combination chemotherapy ‣ radiotherapy to involved nodes is an option. Radiotherapy is avoided in young patients where possible ‣ although HD is highly radiosensitive there is risk of secondary cancers (e.g. thyroid and breast) within the area of the mantle radiotherapy field. **(5)**. Advanced disease (stages 11B, IIIA/B and IVA/B): extensive combination chemotherapy is used in the first instance (± subsequent consolidatory radiotherapy to any sites of 'bulky' disease to reduce risk of local recurrence) **(5)**. A large mediastinal mass (i.e. > 13 of the intrathoracic diameter at the level of T5) is generally treated with a moderate amount of initial chemotherapy in order to shrink the mass prior to any subsequent radiotherapy – this aims to avoid any excessive irradiation of the lung parenchyma and subsequent radiation fibrosis**. (5)**.

NHL, *Unlike* HD the histological subtype is the major determination of treatment**. (5)**. Common Chemotherapeutic Regimens R-CHOP therapy (rituximab, cyclophosphamide, hydroxydoxorubicin, oncovin, and prednisone) is typically used for therapy is used for NHL—especially CD20-positive lymphoma, since it is indicated for the treatment of patients with relapsed or refractory, low-grade or follicular, CD20-positive B-cell NHL. ***(6)*****.**

Many patients with aggressive types of NHL can now be cured with appropriate intensive therapy. **Recent advances**, including the use of monoclonal antibody based therapies for B cell lymphomas and the more widespread use of early high dose chemotherapy and haematopoietic stem-cell transplantation for patients who have failed initial therapy, have significantly improved the results of treatment for patients with lymphoma. Curative therapy in aggressive NHL involves the use of intensive cytotoxic chemotherapy in the great majority of patients. The overall treatment strategy, the type of chemotherapy to be used and the need for RT is usually determined prior to starting therapy using a range of **prognostic factors specific for the type of lymphoma** in question. In aggressive NHL the International Prognostic Index (IPI) helps to determine treatment choice.

In aggressive lymphomas, intensive chemotherapy, often combined with immunotherapy using a monoclonal antibody is the most important component of therapy. Consolidative RT is often used in early stage diffuse large B cell lymphomas (DLBCL) and in cases with initially bulky tumours (variously defined as masses greater than 5-10 cm in diameter) or residual masses after completion of chemotherapy. RT is now used infrequently as the sole potentially curative therapy in aggressive NHL but remains the standard treatment in early stage follicular lymphoma. ***(6)*****.**

Because patients with aggressive NHL are commonly cured, there is an increasing emphasis on attaining long-term survival with the least acute and late toxicity from chemotherapy and RT. Acute and subacute toxicities of chemotherapy include myelosuppression, neuropathy, pulmonary fibrosis and cardiac damage. Later effects include risks of myelodysplasia and leukaemia, especially in patients treated with alkylating agents. RT can cause mucositis and xerostomia and can significantly increase the risks of second cancers, especially solid

tumours including thyroid and breast carcinoma. For these reasons, when cure is the aim, it is desirable to treat patients with the least-toxic therapy that will achieve a durable complete remission of disease. That could mean limiting the number of cycles of chemotherapy to the optimum number for each individual patient and restricting the use of RT to those most likely to benefit from it. On the other hand, for those patients with more resistant disease it is important that ineffective therapy should be identified promptly and changed and that those patients who will ultimately need high-dose chemotherapy and stem-cell transplantation are identified as early as possible. ***(6)*.**

Potential role of early response assessment in lymphoma

Many individual patients are over-treated and receive more chemotherapy and RT than the minimum needed to attain cure. Similarly, many patients, especially those with advanced disease, receive initial treatment that is insufficient to induce a durable remission. The introduction of response-adapted therapy has been frustrated by the fairly crude methods previously available for assessment of early treatment response. However, it is favorable to identify patient's response at an early stage in therapy, so that less intensive treatment than used in standard therapy would be sufficient to attain cure. Alternatively, if patients with a poor early response were identified, then steps could be taken to institute more intensive therapy at an early stage, before many more cycles of ineffective therapy were delivered. The earlier a reliable response assessment could be made, the better. A precise early prediction of the response to therapy might be able to separate patients who could be cured with conventional therapy or even less intensive and less toxic regimens from patients for whom an early switch to alternative, more aggressive treatment strategies could improve the likelihood and duration of remission. This concept of risk-adapted therapy is being increasingly recognized as a way to achieve a higher cure rate with a lower or equal risk of treatment-related morbidity and mortality. In aggressive NHL, progression free survival ranges from 10% to 50% at one year for patients with early 18F-FDG PET–positive results and from 79% to 100% at one year for patients with early 18F-FDG PET–negative results. The high relapse rate seen in patients with early 18F-FDG PET–positive results is consistent in both early and advanced stages ***(7).***

18F-FDG PET has a high prognostic value after one cycle of chemotherapy. 18F-FDG PET may help predict response as early as after one cycle of treatment.

18F-FDG PET/CT is extremely useful for therapy response assessment due to its capacity to help distinguish between residual metabolically active tumor and areas of necrosis and fibrosis ***(7).***

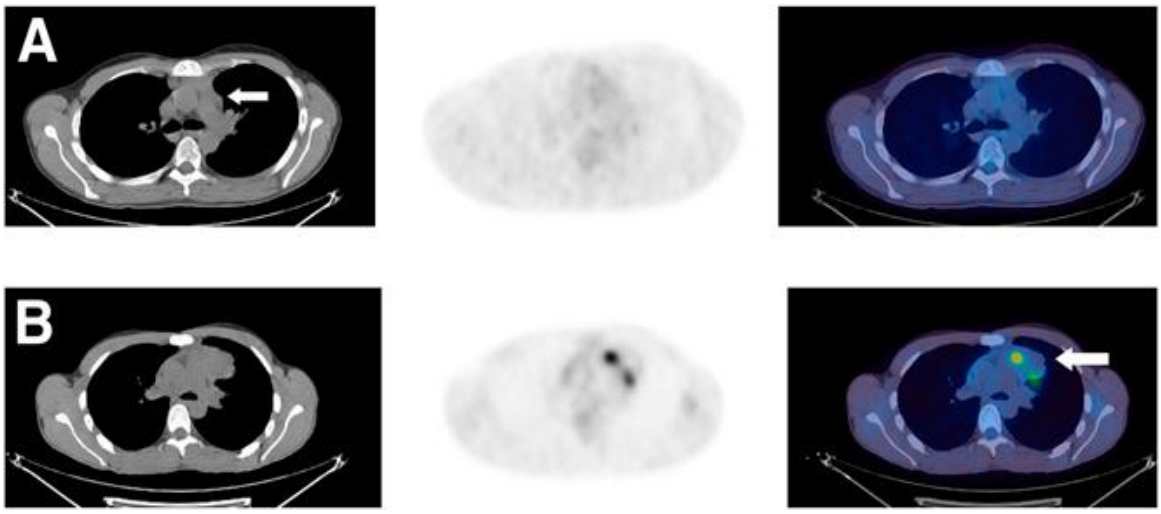

Figure 1: Differences between 2 patients with residual mediastinal masses after treatment. (A) No significant uptake in left anterior mediastinal mass in one patient. (B) Focal uptake in mediastinal mass, suggesting residual tumor, in another patient. Viable lymphoma cells may be contained in large areas of fibrosis, leading to sampling errors at biopsy. (7)

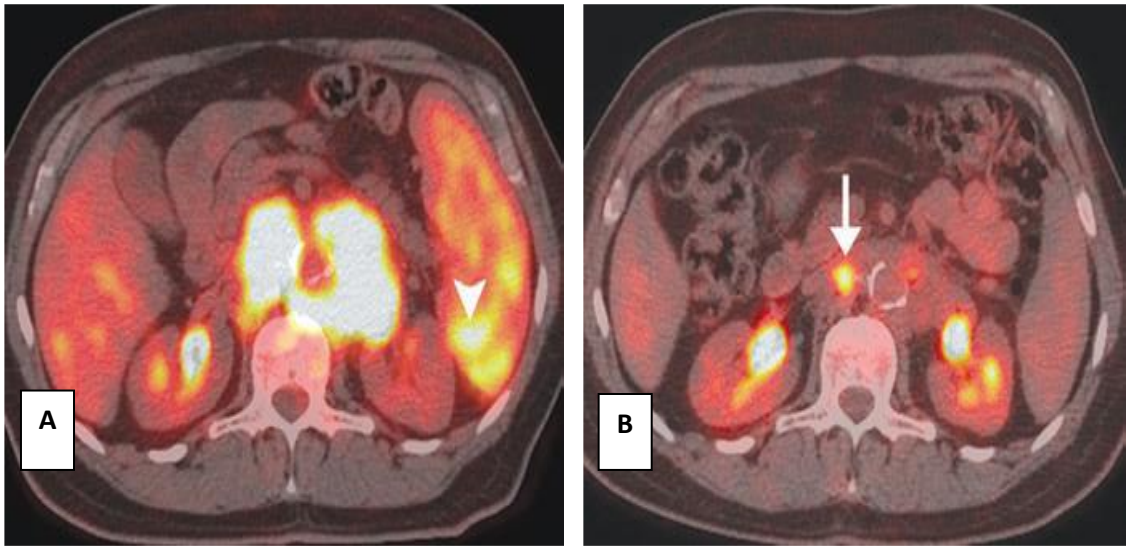

Figure 2: 66-year-old man with stage IV diffuse large B-cell lymphoma. A, Axial fused PET/CT image from baseline PET/CT examination shows 18F-FDG-avid lymphadenopathy in paraaortic regions in addition to splenic involvement (arrowhead). B, three cycles of systemic chemotherapy resulted in marked anatomic response with almost complete interval resolution of lymphadenopathy on CT images. Fused PET/CT image, however, shows persistent abnormal 18F-FDG uptake within small residual lymph node in retroperitoneum (arrow). Finding is consistent with residual viable lymphoma. (7)

PET/CT is an accurate method for evaluating tumor viability in the post-therapy setting. However, appropriate timing of the procedure is fundamental in preventing false-positive or false-negative results. Recent therapeutic intervention may lead to inaccurate results due to nonspecific changes caused by accumulation of inflammatory cells removing the debris of dead tumor cells, "flare phenomena," or "stunning" of the residual tumor cells***. (7).***

The recommended timing for performing end-of therapy PET varies with the treatment modality. Post-therapy PET should be performed at least 4–6 weeks after surgery or chemotherapy and 8–12 weeks after external beam radiation therapy or radioimmunotherapy. These waiting times represent a trade-off between a reliable clinical response and the chances of false-positive and false-negative findings. ***(7).***

As for patients with NHL, there is yet no evidence that patients with HD will benefit from having treatment adapted according to the results of early 18F-FDG PET. The vast majority of patients with early-stage HD (90%) are cured with standard therapy. ***(7).***

Patients who have aggressive NHL and who respond poorly to first-line treatment or relapse soon afterward, generally have a very poor prognosis, even with high-dose salvage regimens. Such patients could benefit from the recognition of treatment failure early during first-line therapy so that a more intensive regimen can be initiated as soon as possible. ***(7).***

In advanced-stage HD, patients who fail to reach remission or relapse early after first-line therapy have a much poorer prognosis and need to be identified as early as possible to lower the risk of treatment failure, avoid unnecessary toxicity, and increase the chance of long-term survival. ***(7).***

It has been clearly established that changes in 18F-FDG uptake reflect a response to chemotherapy and that residual abnormal 18F-FDG uptake after completion of chemotherapy helps identify patients with a poor prognosis. It is less clear what degree of change in 18F-FDG uptake should be expected during chemotherapy: In addition to varying with the number of treatment cycles after which imaging is performed, this parameter is likely to vary (qualitatively or quantitatively) with tumor histological features (generally more rapid response in Hodgkin disease than in aggressive NHL), histological subtype (large B-cell lymphoma versus other aggressive NHLs), and treatment regimen. ***(7).***

Evaluation of therapeutic response of lymphomas by 18F-FDG-PET/CT

There are generally two ways of evaluating response to therapy: early assessment, after one to three cycles of treatment, and late assessment of the overall response, usually performed approximately one month after cessation of chemotherapy. An early assessment of those who respond to therapy is particularly helpful in patients with a malignancy for which there may be multiple potential chemotherapeutic regimens. Early assessment also helps prevent unnecessary side effects from useless regimens and reduces cost by discontinuing expensive therapy in patients who do not respond to treatment. ***(8)*.**

Interpretation of the PET CT findings were qualitative and semi-quantitative. The qualitative evaluation (visual) included the description of all the hypermetabolic lesions (activity > liver) defined as positive scan that attain focal or diffuse FDG uptake above background in a location incompatible with normal anatomy or physiology, (Other causes of false-positive scans should be ruled out) with regard to the localization and size (maximum diameters) by CT. The semi-quantitative evaluation or SUV bases evaluation was performed using the maximum standardized uptake value (SUVmax) in a region of interest located over the hypermetabolic lesion. The reduction in metabolic activity of the lesions was quantified using the percentage of reduction of SUVmax ***(8)*.**

Most common response evaluation guideline in lymphoma was done according to:

1. International Workshop Criteria IWC (1999) guidelines
2. Revised response criteria by international harmonization project (IHP) ***(8)*.**
3. Modified Deauville Criteria
4. PERCIST — Positron Emission tomography Response Criteria in Solid Tumors.

International Workshop Criteria IWC (1999) guidelines:

These criteria are used to standardize response criteria of NHL and HD. It was based mainly on morphologic changes, with a reduction in tumor size on CT being the most important factor. After the completion of therapy, CT scans often reveal residual masses. By conventional methods, it is very difficult to assess whether these masses represent viable lymphoma cells or fibrotic scar tissue ***(9).***

Table 1: International Workshop Criteria IWC (1999) guidelines to standardize response criteria for NHL and HD (Hutchings & Barrington, 2009).

RESPONSE CRITERIA FOR NON-HODGKIN'S LYMPHOMA
(not including PET)

Response Category	Physical Examination	Lymph Nodes	Lymph Node Masses	Bone Marrow
CR	Normal	Normal	Normal	Normal
CRu (unconfirmed)	Normal	Normal	Normal	Indeterminate
	Normal	Normal	>75% decrease	Normal or indeterminate
PR	Normal	Normal	Normal	Positive
	Normal	≥50% decrease	≥50% decrease	Irrelevant
	Decrease in liver/spleen	≥50% decrease	≥50% decrease	Irrelevant
Relapse/ Progression	Enlarging liver/spleen, new sites	New or increased	New or increased	Reappearance

Source: Table 2 from Cheson BD, Horning SJ, Coiffier B, et al: Report of an International Workshop to Standardize Response Criteria for Non-Hodgkin's Lymphoma. J Clin Oncol 1999; 17:1244. Reprinted with permission from the American Society of Clinical Oncology.

An international harmonization project (IHP) ***(10).***

It was set up to overcome viable lymphoma cells /fibrotic scar situation and increase in the widespread use of 18F-FDG-PET for response assessment has prompted a need to re-evaluate and update the IWG criteria ***(11).***

Complete metabolic response (CR)

The designation of CR requires the following ***(10):***

Complete disappearance of all detectable clinical evidence of disease and disease-related symptoms if present before therapy.

A-Typically FDG-avid lymphoma: **"complete resolution of FDG uptake"** in patients with no pretreatment PET scan or when the PET scan was positive before therapy, a post-treatment residual mass of any size is permitted as long as it is PET negative. This is usually a good prognosis, even though microscopic disease can't be excluded.

B- Variably FDG-avid lymphomas/FDG avidity unknown: in patients without a pretreatment PET scan, or if a pretreatment PET scan was negative, all lymph nodes and nodal masses must have regressed on CT to normal size (≤1.5 cm in their greatest transverse diameter for nodes >1.5 cm before therapy). Previously involved nodes that were 1.1 to 1.5 cm in their long axis and more than 1.0 cm in their short axis before treatment must have decreased to ≤ 1 cm in their short axis after treatment.

The spleen and/or liver, if considered enlarged before therapy on the basis of a physical examination or CT scan, should not be palpable on physical examination and should be considered normal size by imaging studies, and nodules related to lymphoma should disappear. However, determination of splenic involvement is not always reliable because a spleen considered normal in size may still contain lymphoma, whereas an enlarged spleen may reflect variations in anatomy, blood volume, the use of hematopoietic growth factors, or causes other than lymphoma.

If the bone marrow was involved by lymphoma before treatment, the infiltrate must have cleared on repeat bone marrow biopsy. The biopsy sample on which this determination is made must be adequate (with a goal of > 20 mm unilateral core). If the sample is indeterminate by morphology, it should be negative by immunohistochemistry. A sample that is negative by immunohistochemistry but that demonstrates a small population of clonal lymphocytes by flow cytometry will be considered a CR until data become available demonstrating a clear difference in patient outcome.

Partial response (PR)

The designation of PR requires all of the following ***(10):***

At least a 50% decrease in sum of the product of the diameters (SPD) of up to six of the largest dominant nodes or nodal masses. These nodes or masses should be selected according to all of the following: they should be clearly measurable in at least 2 perpendicular dimensions; if possible they should be from disparate regions of the body; and they should include mediastinal and retroperitoneal areas of disease whenever these sites are involved.

50 or 25% decrease after one cycle of chemotherapy or > 25% SUV decrease after more than one cycle treatment.

No increase should be observed in the size of other nodes, liver, or spleen.

Splenic and hepatic nodules must regress by ≥ 50% in their SPD or, for single nodules, in the greatest transverse diameter.

With the exception of splenic and hepatic nodules, involvement of other organs is usually assessable and no measurable disease should be present.

Bone marrow assessment is irrelevant for determination of a PR if the sample was positive before treatment. However, if positive, the cell type should be specified (e.g., large-cell lymphoma or small neoplastic B cells). Patients who achieve a CR by the above criteria, but who have persistent morphologic bone marrow involvement will be considered partial responders. When the bone marrow was involved before therapy and a clinical CR was achieved, but with no bone marrow assessment after treatment, patients should be considered partial responders.

No new sites of disease should be observed.

Typically, FDG-avid lymphoma: for patients with no pretreatment PET scans or if the PET scan was positive before therapy, the post-treatment PET should be positive in at least one previously involved site.

Variably FDG-avid lymphomas/FDG-avidity unknown: for patients without a pretreatment PET scan, or if a pretreatment PET scan was negative, CT criteria should be used. In patients with follicular lymphoma or mantle-cell lymphoma, a PET scan is only indicated with one or at most two residual masses that have regressed by more than 50% on CT; those with more than two residual lesions are unlikely to be PET negative and should be considered partial responders.

Stable Disease (SD):

Stable disease (SD) is defined as the following ***(10):***

A patient is considered to have SD when he or she fails to attain the criteria needed for a CR or PR, but does not fulfill those for progressive disease (see Relapsed Disease [after CR]/Progressive Disease [after PR, SD]).

Between < 25% SUV increased & < 15% SUV decrease.

Typically FGD-avid lymphomas: the PET should be positive at prior sites of disease with no new areas of involvement on the post treatment CT or PET.

Variably FDG-avid lymphomas/FDG-avidity unknown: for patients without a pretreatment PET scan or if the pretreatment PET was negative, there must be no change in the size of the previous lesions on the post-treatment CT scan.

Relapsed Disease (after CR)/Progressive Disease after (PR, SD) ***(10).***

Lymph nodes should be considered abnormal if the long axis is more than 1.5 cm regardless of the short axis. If a lymph node has a long axis of 1.1 to 1.5 cm, it should only be considered abnormal if its short axis is more than 1.0. Lymph nodes ≤ 1 cm x ≤ 1 cm will not be considered as abnormal for relapse or progressive disease.

Appearance of any new lesion more than 1.5 cm in any axis during or at the end of therapy, even if other lesions are decreasing in size. Increased FDG uptake in a previously unaffected site should only be considered relapsed or progressive disease after confirmation with other modalities. In patients with no prior history of pulmonary lymphoma, new lung nodules identified by CT are mostly benign. Thus, a therapeutic decision should not be made solely on the basis of the PET without histologic confirmation.

At least a 50% increase from nadir in the SPD of any previously involved nodes, or in a single involved node, or the size of other lesion (e.g. splenic or hepatic nodules). To be considered progressive disease, a lymph node with a diameter of the short axis of less than 1.0 cm must increase by ≥ 50 % and to a size of 1.5 cm x 1.5 cm or more than 1.5 cm in the long axis.

At least a 50% increase in the longest diameter of any single previously identified node more than 1 cm in its short axis.

Greater than 25% increase in SUV or new lesions.

Lesions should be PET positive if observed in a typical FDG avid lymphoma or the lesion was PET positive before therapy unless the lesion is too small to be detected with current PET systems (< 1.5 cm in its long axis by CT).

Measurable extranodal disease should be assessed in a manner similar to that for nodal disease. **For these recommendations, the spleen is considered extra-nodal disease.** Disease that is only assessable (e.g., pleural effusions, bone lesions) will be recorded as present or absent only, unless, while an abnormality is still noted by imaging studies or physical examination, it is found to be histologically negative. ***(10).***

According to the IHP definitions, residual masses of 2 cm or more in greatest transverse diameter (GTD) with 18F-FDG activity visually exceeding that of mediastinal blood pool structures are considered PET positive, whereas residual masses 1.1 to 1.9 cm are considered PET positive only if their activity exceeds surrounding background activity, a smaller residual mass or a normal-sized lymph node (e.g. <1 × 1 cm) should be considered positive for disease if its activity is higher than that of the surrounding background ***(11).***

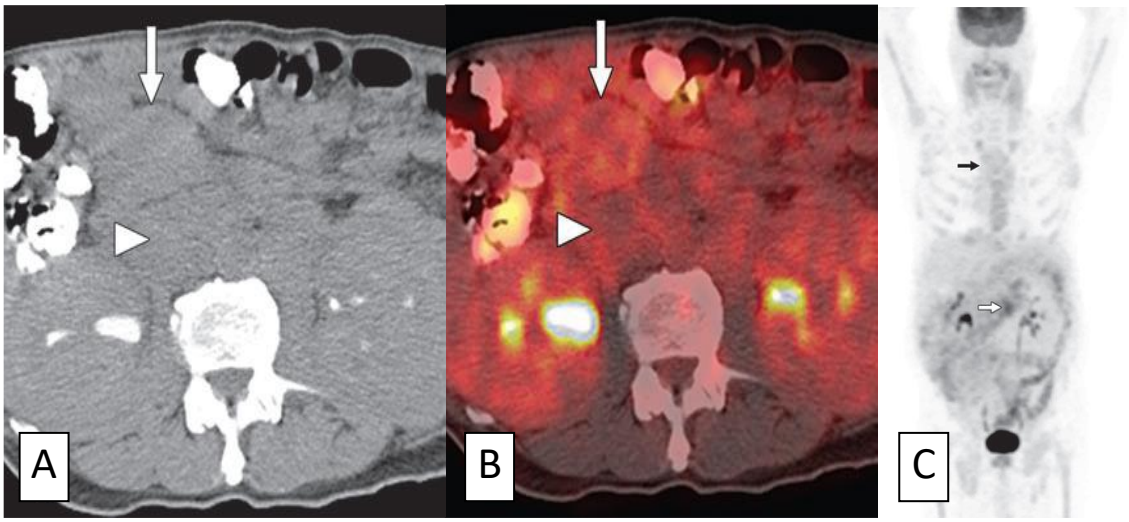

Figure 3: 67-year-old man with mantle cell lymphoma who underwent reevaluation with PET/CT after chemotherapy. A, Axial unenhanced CT image from PET/CT examination shows persistent lymphadenopathy measuring more than 2 cm in diameter in retroperitoneum (arrowhead) and small-bowel mesentery (arrow). B, Axial fused PET/CT image at same level as A shows 18F-FDG uptake in retroperitoneal lymphadenopathy (arrowhead) is no greater than that in surrounding normal tissue, consistent with absence of detectable metabolically active lymphoma. Arrow indicates lymphadenopathy in small-bowel mesentery. C, PET image shows low-grade 18F-FDG uptake within lymphadenopathy in small-bowel mesentery (white arrow), which is greater than that in mediastinum (black arrow), consistent with persistent viable lymphoma. Because of this abnormal 18F-FDG uptake, complete remission was not achieved, and second-line chemotherapy was initiated. (11)

Despite the fact that PET has eliminated many limitations attributed to CT, there are several disadvantages to using PET, including limited resolution, accurate localization of the abnormalities, and physiologic variations in 18F-FDG distribution. Therefore, PET and CT are complementary, so a combined PET/CT analysis should in fact be integrated into practice ***(11)***

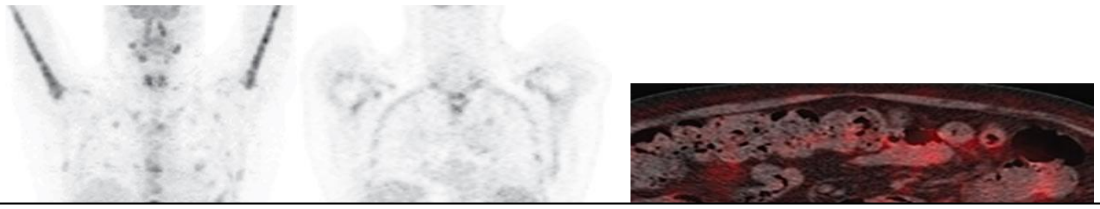

Figure 4: 56-year-old man with stage IV Burkitt's lymphom. A, Coronal MIP PET image from baseline staging PET/CT examination shows marked 18F-FDG uptake within intraabdominal (mesenteric and retroperitoneal) lymphadenopathy. Patchy bone marrow uptake also is evident. B, Coronal PET image from restaging PET/CT examination after completion of systemic chemotherapy shows interval resolution of abnormal 18F-FDG uptake with one isolated focus of residual abnormal activity in right side of retroperitoneum (arrow) anterior to psoas muscle. Finding was suspicious for residual viable lymphoma. C, Axial fused PET/CT image shows abnormal 18F-FDG uptake corresponding to physiologic activity within right ureter (arrow). Appearance represents complete metabolic response to therapy. (11)

Modified Deauville Criteria:

It is important to note that the NCCN (national comprehensive cancer network) modified Deauville scores mostly rely on reassessment of initially avid sites and that the NCCN recommends FDG PET scans for initial staging and for evaluating residual masses at the end of treatment ***(12)***. The Deauville criteria for reporting interim scans have proved useful in evaluating response to treatment. Follow-up of these patients is required to see the positive and negative predictive value of interim scans ***(12)***.

Table 2: NCCN modified Deauville score (12).

Score	PET/CT Scan Result
1	No uptake above background
2	Uptake at an initial site that is less than or equal to mediastinum
3	Uptake at an initial site that is greater than mediastinum but less than or equal to liver
4	Uptake at an initial site that is moderately increased compared to the liver at any site. "Uptake > the maximum SUV in a large region of normal liver (21)"
5a	Uptake at an initial site that is markedly increased compared to the liver
5b	Uptake markedly increased compared to the liver at any new site that is possibly related to lymphoma "uptake is 2 X to 3 X > the maximum SUV in the liver (21)".
X	New areas of uptake unlikely related to lymphoma

Assessment of treatment response

Complete response (CR): scores 1, 2 or 3 together with absence of FDG-avid bone marrow lesion(s) are interpreted as complete metabolic response (CR), irrespective of a persistent mass on CT

Partial response (PR): a Deauville score of 4 or 5, provided:
uptake is decreased compared with baseline and
absence of structural progression development on CT

Stable disease (SD), also called no metabolic response: a Deauville score of 4 or 5 without significant change in FDG uptake from baseline.

Progressive disease (PD): a Deauville score of 4 to 5 with increasing intensity compared to baseline or any interim scan and/or any new FDG-avid focus consistent with malignant lymphoma.

"PERCIST"—Positron Emission tomography Response Criteria in Solid Tumors (based on peak SUL).

The premise of the PERCIST 1.0 criteria is that cancer response as assessed by PET is a continuous and time dependent variable. A tumor may be evaluated at any number of times during treatment, and glucose use may rise or fall from baseline values. SUV will likely vary for the same tumor and the same treatment at different times. For example tracer uptake by a tumor is expected to decline over time with effective treatment. Thus, capturing and reporting the fractional change in SUV from the starting value and when the scan was obtained are important. ***(12).***

Follow -UP

Positive PET findings of residual lesional activity suggest aggressive lymphoma, but negative PET findings do not necessarily indicate that the patient is disease free. A long period of disease-free survival can be expected in HD patients with negative PET findings, whereas early relapse will occur if positive PET findings are seen after standard chemotherapy**.** ***(13)***

There are efficacious therapies for patients with recurrent lymphoma. It is believed that early therapy for recurrent disease is more effective than delayed therapy, especially for HD. Therefore, early detection of disease with frequent follow-up is believed to have an important effect on outcome. ***(13)***

PET for post-therapy surveillance is performed following treatment in the absence of clinical, biochemical, or radiographic evidence of recurrent disease, with the goal of early detection of recurrence. Most studies, however, suggest that more than 80% of the time, it is the patient or the physician who first suspects early recurrence, even with routine screening including CT scans. ***(13)***

Identification of Aggressive Transformation

Aggressive transformation of lymphoma represents a change from low-grade lymphoma to high-grade disease. The development of transformed B-cell NHL is one of the most common features of the aggressive phase of indolent lymphoma. For the diagnosis of transformation, repeat biopsy is required in all patients with indolent lymphoma who have relapsing or progressive disease. Histological transformation of indolent lymphoma is a dramatic event that occurs in 5%–10% of patients and carries a dismal prognosis. Previous studies have shown that indolent lymphoma has lower 18F-FDG uptake than the aggressive lymphoma has. **(*14*).**

In all low-grade lymphomas, the presence of foci of intense uptake should raise suspicion for conversion to high-grade disease **(*14*).**

PET has been evaluated to confirm the clinical suspicion of transformation from an indolent to an aggressive histology. In this setting, PET may support the clinical suspicion and help select the optimal biopsy site for definitive histopathological confirmation (i.e., the one with the highest SUV) **(*14*).**A change in the avidity of 18F-FDG uptake of a lesion may be the first clue of transformation**. (*14*).**

SUVmax of more than 13 was associated with about a 90% probability of aggressive lymphoma, while a SUVmax of less than 6 was associated with a very high probability of indolent lymphoma. Unfortunately, the SUVmax ranges of more than 13 and less than 6 comprise only about half of the patients, the remaining half having equivocal SUVs **(*14*).**

Diagnosis and Staging

Given its high sensitivity, 18F-FDG-PET can be used for detecting most types of lymphoma. However, even if the 18F-FDG-PET scan is positive in a pattern that is highly suggestive of lymphoma, diagnosis of lymphoma requires histological confirmation. The major utility of 18F-FDG-PET in diagnosis is often in directing a biopsy. A patient may present with a suspicious mass that is relatively inaccessible for biopsy. ***(11)*** PET can also be used to guide

biopsies to the site of highest 18F-FDG uptake, representing the most aggressive site of lymphoma. ***(15)*** 18F**-**FDG-PET may identify other involved regions, which can be biopsied at much lower morbidity. 18F-FDG-PET imaging used for diagnosis simultaneously provides staging information. ***(11)***

Accurate staging is critical for identifying patients with early-stage (stage I or II) lymphoma, which is treated with involved-field radiation therapy. PET/CT may be of particular value prior to therapy in patients with early-stage lymphoma. Chemotherapy is performed in patients with more advanced-stage disease (stage III or IV). ***(15)***

Pretreatment staging determines the extent of disease and helps direct therapy. Traditionally, the Ann Arbor staging system was based on physical examination and bone marrow evaluation but, more recently, CT scans have been incorporated. PET may provide complementary information to conventional staging as it is highly sensitive in detecting nodal and extra-nodal involvement by most histological subtypes of lymphoma prior to and following treatment ***(15)*** in lymphoma staging, PET/CT tends to upstage rather than downstage tumors ***(11)***

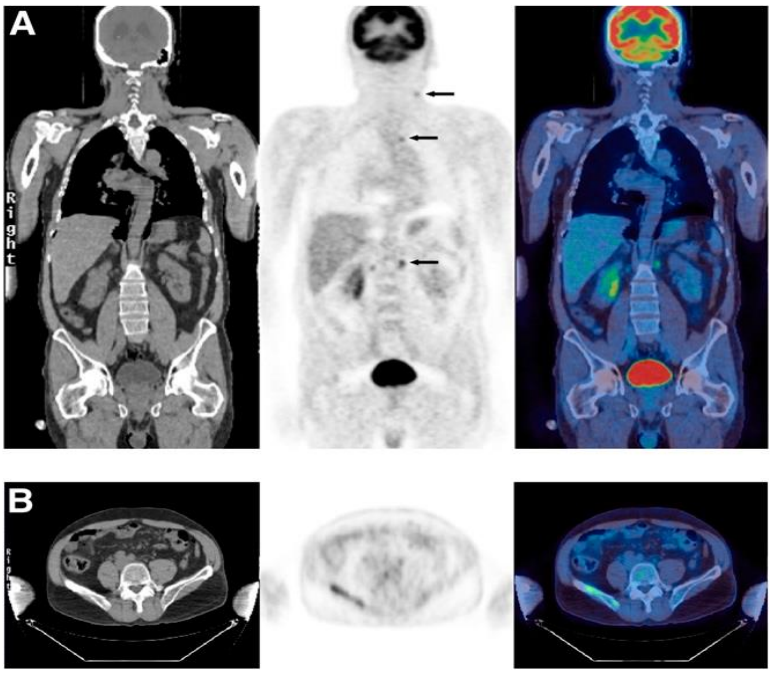

Figure 5: Patient diagnosed with NHL from biopsy of left cervical node. In addition to disease in left neck, 18F-FDG uptake in normally sized lymph nodes in left superior mediastinum and paraaortic nodes below diaphragm (arrows in A) and in right iliac bone (B) was indicative of stage IV rather than stage II disease. (13)

The advantages of 18F-FDG PET/CT for the staging and restaging of both NHL and Hodgkin disease are mostly attributed to the detection of 18F-FDG-avid, normal-sized lymph nodes (usually <1 cm), and of extra-nodal sites that were previously missed at CT (most commonly the liver, spleen, cortical bone, bone marrow, and skin). In a few cases, para-spinal and pulmonary lesions that were interpreted as benign at CT are seen to be malignant at PET/CT ***(11)***

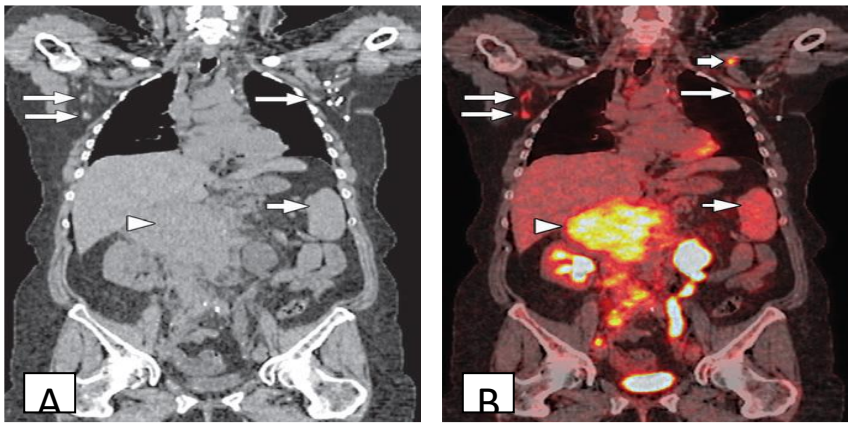

Figure 6: 3-year-old woman with follicular lymphoma newly diagnosed after biopsy of retroperitoneal mass. (Baseline staging with PET/CT). A, Coronal CT image shows large retroperitoneal mass consistent with known site of biopsy proven lymphoma (arrowhead). Also present are indeterminate subcentimeter lymph nodes in axillae (long arrows). Spleen (short arrow) is of normal size. At CT, mass was considered stage II, representing involvement of more than one lymph node station on one side of diaphragm. B, Coronal fused PET/CT image shows intense 18F-FDG uptake by retroperitoneal mass (arrowhead) and abnormal 18F-FDG uptake in small axillary lymph nodes (long arrows). Unexpected G-avid lymph node (thick short arrow) was found in left infraclavicular region. Diffuse intermediate-grade 18F-FDG uptake in spleen (thin short arrow) greater than that in liver is considered to represent diffuse lymphomatous infiltration. Disease severity was increased to stage IIIS. (11).

Evaluation of Autologous Stem Cell Transplantation Patients

Positive PET findings prior to autologous stem cell transplantation may carry a high risk of transplantation failure. Pre-procedure 18F-FDG PET is important for the evaluation of lymphoma patients with a poor prognosis. However, post-transplantation PET does not appear to be essential in patients with negative pre-transplantation PET findings. ***(16).***

Special consideration in 18F-FDG PET lymphoma assessment:

Multiple confounding factors may lead to the erroneous interpretation of a PET/CT study, resulting in a high number of false-positive findings, particularly at post-therapy assessment. Potential imaging pitfalls include brown fat 18F-FDG uptake, bone marrow and splenic activation, and recent therapeutic intervention (e.g. surgery, radiation therapy, or chemotherapy). ***(17)***.

Bone marrow involvement is indicative of a worse prognosis in patients with lymphoma. The development of diffuse bone marrow activation in the weeks following chemotherapy and the use of growth factors constitutes a known limitation in making the correct diagnosis. The pattern of FDG uptake in bone marrow activation is typically diffuse, involving the axial

skeleton in a symmetric fashion and, sometimes, the spleen and thymus. It is important to know when the patient received treatment, particularly treatment with colony-stimulating factors, and to understand that diffusely increased FDG uptake in the bone marrow may persist for more than four weeks after treatment. Nevertheless, whenever the distribution of 18F-FDG uptake becomes more multifocal and heterogeneous, the presence of lymphomatous involvement should be suspected. ***(17)***.

Diffusely increased uptake in the spleen—even if more intense than the liver—in association with diffuse bone marrow uptake is usually due to chemotherapy effects. Such uptake should not be misinterpreted as splenic involvement even if focal uptake was present in the spleen at baseline PET ***(18).***

A focal reduction of uptake in sites of marrow involvement at baseline PET occurs because of marrow ablation with successful treatment. Focal increased uptake may occur at sites where there was no disease on baseline PET because of chemotherapy stimulation. The patterns of uptake at baseline PET and interim PET may therefore mirror each other, with sites of initial disease becoming cold and sites of normal marrow becoming hot on the treatment scan. Focal uptake in the marrow with this pattern should not be misinterpreted as disease ***(18).***

Symmetric tonsillar uptake (on baseline and interim PET) is most likely to represent nonspecific inflammatory uptake in Hodgkin lymphoma and should not be misinterpreted as lymphoma. Asymmetric uptake on interim PET should be regarded as disease only in the presence of clear evidence of tonsillar involvement at baseline ***(18).***

The lesions in gastric and cerebral lymphoma are sometimes difficult to characterize on PET/CT images due to physiologic gastric and cortical accumulation of 18F-FDG. ***(18).***

18F-FDG uptake in the mediastinum may lead to false-positive PET findings. 18F-FDG uptake is observed in lymph nodes with sarcoid involvement. Even 18F-FDG PET/CT cannot help differentiate between malignant lymphoma and sarcoidosis. ***(18).***

Physiologic colonic uptake may be mistaken for lymphoma; however, diligent reading of integrated PET/CT images is useful for making an accurate diagnosis ***(19).***

Small-volume lesions may be undetectable on both pre- and post-therapy PET scans when there is moderate or high background activity around the lesions. Correlation with anatomic CT findings is essential for avoiding these pitfalls; thus, integrated PET/CT is especially helpful. ***(18).***

Chemotherapy for lymphoma often results in immunocompromising the patient and an increase in infections. These infections can be seen on 18F-FDG-PET, and it is important to distinguish them from new sites of disease. ***(19).***

Thymic rebound

After chemotherapy, there may be a rebound in the thymus. A histologically normal thymus may increase in size and become FDG-avid. Since the anterior mediastinum is also an important location of recurrent lymphoma, thymic rebound can easily be confused with relapse. In thymic rebound, the thymus usually retains its normal shape, whereas with

lymphomatous involvement, it often will show a mass-like shape. The time course of thymic rebound is usually within months of the end of therapy. On subsequent 18F-FDG-PET imaging, the thymic uptake decreases in intensity. Moderate 18F-FDG uptake in a normally shaped thymus gland in a child or in a young adult after chemotherapy is easily identified as physiologic uptake. Intense FDG uptake in a rounded mass in an older adult is easily identified as disease. In less clear-cut cases, follow-up studies are needed to establish the correct diagnosis. **(20).**

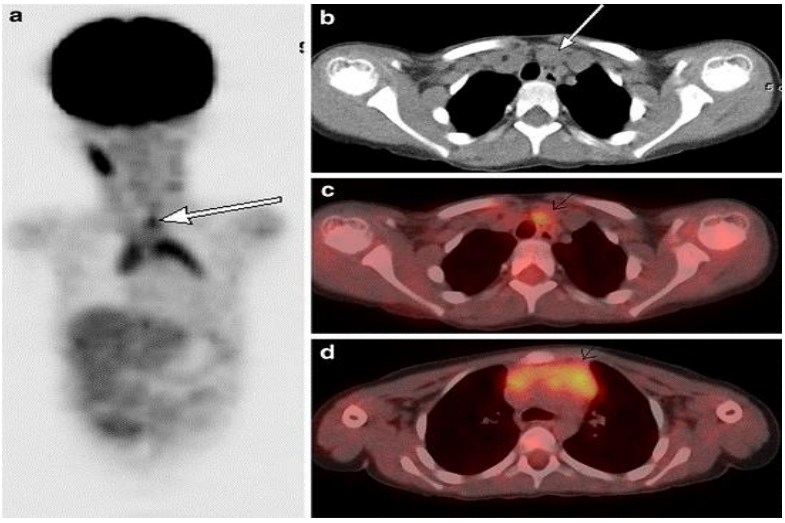

Figure 7: 3.5-year-old boy with abdominal Burkitt's lymphoma. Coronal 18F-FDG PET scan obtained 5 months after completion of treatment shows increased activity in the thymus in an inverted V configuration and in superior thymic extension (white arrow). Note physiologic activity within the right neck in the sternocleidomastoid muscle (a). Axial CT image from the same 18F-FDG PET-CT study performed 5 months after treatment shows a nodule (white arrow) anteromedial to the left brachiocephalic vein (b). Axial fusion image shows that the FDG activity in the superior mediastinum corresponds to this enlarged nodule anteromedial to left brachiocephalic vein (white arrow) (c). Axial fusion image shows increased activity in an enlarged thymus consistent with thymic hyperplasia (white arrow; standardized uptake value 3.0) of similar intensity to activity in superior mediastinum (d) It presents as a soft tissue nodule anteromedial to the left brachiocephalic vein and represents a remnant of thymic tissue along the path of migration in fetal life. In patients with thymic hyperplasia, a superior mediastinal nodule in this location may represent

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