EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 7
Issue: 5
240-253
Year: 2020

# LYMPHOMA: A BRIEF REVIEW OF ROLE OF IMAGING IN STAGING AND FOLLOW UP

**[1]Dr. Zohaib Hussain* and [2]Prof. Dr. Parul Dutta**

[1]MBBS, PGT (MD Radiodiagnosis), Department of Radiology, Gauhati Medical College and Hospital, Bhangagarh, Guwahati-781032 Assam, India.
[2]Professor and HOD, Department of Radiology Gauhati Medical College and Hospital, Bhangagarh, Guwahati-781032 Assam, India.

***Corresponding Author: Dr. Zohaib Hussain**
MBBS, PGT (MD Radiodiagnosis), Department of Radiology, Gauhati Medical College and Hospital, Bhangagarh, Guwahati-781032 Assam, India.

**Article Received on 04/03/2020** **Article Revised on 25/03/2020** **Article Accepted on 15/04/2020**

## ABSTRACT
Lymphoproliferative diseases are a group of cancers arising from B cells, T cells and natural killer cells (NK), which differ greatly in their nature, clinical path and therapeutic responses. Non-Hodgkin's lymphoma (NHL) and Hodgkin's lymphoma (HL) constitute the 5th most common malignancy in the west. However incidence in India is one-fourth of that in the western world. The Ann Arbor staging system was first developed in 1971 and updated by "Cotswolds modification" in 1989 and refers to both HL and NHL. Additionally, the Lugano classification (2014) and more recently the RECIL 2017 criteria, have been introduced to simplify and standardize staging and treatment outcome evaluations with primary emphasis on Computed Tomography (CT) and Positron emission tomography-computed tomography (PET-CT) evaluation. CT and PET-CT are being utilized as primary techniques for staging, and MRI being a complementary tool. 18-F- Fluorodeoxyglucose positron emission tomography-computed tomography (18-FDG PET-CT) for functional imaging has now replaced Gallium scans. Lymphoma management depends on its subtype and clinical stage. An attempt is made to provide a better understanding of the Lugano classification and RECIL 2017 criteria that would benefit the radiologist to correctly plan management and achieve desired results illustrated by multiple cases evaluated at the authors' institute. Cure is the goal of managing Hodgkin's lymphoma and aggressive NHLs, such as diffuse large B cell lymphoma or peripheral T-cell lymphoma. Imaging plays an indispensable role in achieving this goal.

**KEYWORDS:** 1. Lymphoma, 2. Imaging, 3. Staging, 4. Response-Assessment, 5. Follow-up, 6. PET-CT

## INTRODUCTION & CLINICAL BACKGROUND
Lymphoproliferative diseases are a group of cancers arising from B cells, T cells and natural killer cells (NK), which differ greatly in their nature, clinical path and therapeutic responses. Lymphoid neoplasms presenting with tumors are commonly called lymphomas, while those with the predominantly circulating cells of the malignant population are referred to as leukaemia. The incidence of non-Hodgkin's lymphoma (NHL) in recent decades has risen steadily but now seems to be plateaued, with a fairly constant incidence of Hodgkin lymphoma (HL) over the same era.[1,2]

NHL and HL make up about 5–6% of all cancers and the lymphoma is the 5th most common malignancy in most western countries. However incidence in India is one-fourth of that in the western world.[3]

HL typically occurs in one or two adjacent locations as lymphadenopathy. It progresses without intervention through the involvement of contiguous nodal sites and spleen until bone marrow, liver, or extranodal invasion. The treatment response rates are excellent, with younger patients showing more than 90 percent cure rates.[4]

The NHL is typically classified as high- and low-grade, but the current World Health Organization (WHO) categorization has drifted away from this to classify individual lymphomas as discrete clinico-pathological entities, which also have unique molecular abnormalities.[5]

The clinical activity of the non-Hodgkin's lymphomas cannot be generalized, but high-grade groups appear to be aggressive, frequently exhibiting lymphadenopathy and B symptoms. They also respond favourably to

heavy-dose chemotherapy; in about 60 percent of cases, full cure is achieved.[6]

Low-grade lymphomas are indolent and can be managed by low-dose therapy, but not healed completely.

As our knowledge of the pathophysiology of lymphoma widens, the difference between low and high-grade NHL has been largely accepted as an over-generalization that does not fit groups like mantle cell lymphoma that includes characteristics of both groups. Extranodal involvement in all types of NHL is usually more common than in HL. This refers to non-contiguous nodes as well.

**STAGING OF LYMPHOMAS**

The Ann Arbor staging system was first developed in 1971 and updated by "Cotswolds modification" in 1989 and refers to both HL and NHL.[7,8] The staging in the system is dependent on the degree to which nodal groups are involved: "stage I, single lymph node group; stage II, multiple lymph node groups, ipsilaterally, to the diaphragm; stage III, lymph nodes groups both above and also below the diaphragm and stage IV, extranodal and non-contiguous disease involvement(e.g., liver, lung, or bone marrow)".**(Table 1).**

The use of the Ann Arbor classification has several exceptions: PCNS and primary cutaneous lymphomas (for example mycosis fungoides and Sezary syndrome) are studied using TNMB classification,[9,10] while Burkitt lymphoma is handled with St Jude criteria or a risk stratification model. Additionally, the Lugano classification, which has recently been introduced to simplify and standardize stage and treatment outcome evaluations, proposes changes to the Ann Arbor staging method. **(Table 2 and 3).**

**Table 1: Staging of lymphoma (Cotswolds-modified Ann Arbor Classification).[11]**

| Stage | Area of involvement |
|---|---|
| **I** | One lymph node region or extra-lymphatic site |
| **II** | Two or more lymph node regions on the same side of the diaphragm |
| **III** | Involvement of lymph node region or structures on both sides of diaphragm, subdivided as follows:<br>III(1*) – with involvement of spleen and/or splenic hilar, coeliac, and portal nodes<br>III(2*) – with paraaortic, iliac, or mesenteric nodes |
| **IV** | Extranodal sites beyond those designated E |
| **Additional Qualifiers** | |
| **A** | No symptoms |
| **B** | Fever, sweats, weight loss (more than 10% body weight) |
| **E** | Involvement of a single extranodal site, contiguous in proximity to a known nodal site |
| **X*** | Bulky disease<br>Mass >1/3 transthoracic diameter at T5 on CXR or any mass >10 cm maximum dimension |
| **CE*** | Clinical stage |
| **PS*** | PS stands for pathological stage and refers to when staging laparotomy existed but is usually taken to refer to involvement of a given site on imaging denoted by a subscript (e.g., M=marrow, H=liver, L=lung, O=bone, P=pleura, D= skin) |

**modifications of Ann Arbor system*

**Table 2: Lugano Classification criteria for involvement of site.[12]**

| Tissue Site | Clinical | FDG Avidity | Test | Positive Finding |
|---|---|---|---|---|
| **Lymph nodes** | Palpable | FDG Avid histologies | PET CT | Increased FDG uptake |
| | | Non-avid disease | CT | Unexplained node enlargement |
| **Spleen** | Palpable | FDG-avid histologies | PET-CT | Diffuse uptake, solitary mass, miliary lesions, nodules |
| | | Nonavid disease | CT | 13 cm or more in vertical length, mass, nodules |
| **Liver** | Palpable | FDG-avid histologies | PET-CT | Diffuse uptake, mass |
| | | Nonavid disease | CT | Nodules |
| **CNS** | Signs, symptoms | | CT | Mass lesion(s) |
| | | | MRI | Leptomeningeal infiltration, mass lesions |
| | | | CSF assessment | Cytology, flow cytometry |
| **Other (e.g., skin, lung, GI tract, bone, bone marrow)** | Site dependent | | PET-CT, biopsy | Lymphoma involvement |

*Abbreviations: CSF, cerebrospinal fluid; CT, computed tomography; FDG, fluorodeoxyglucose; MRI, magnetic resonance imaging; PET, positron emission tomography.*

*PET-CT is adequate for determination of bone marrow involvement and can be considered highly suggestive for involvement of other extra lymphatic sites. Biopsy confirmation of those sites can be considered if necessary.*

**Table 3: Revised Staging system: Primary nodal lymphomas as per Lugano Classification.[12]**

| Stage | Involvement | Extranodal (E) Status |
|---|---|---|
| **Limited I** | One node or a group of adjacent nodes | Single extranodal lesions without nodal involvement |
| **II** | Two or more nodal groups on the same side of the diaphragm | Stage I or II by nodal extent with limited contiguous extranodal involvement |
| **II bulky*** | II as above with "bulky" disease | Not applicable |
| **Advanced III** | Nodes on both sides of the diaphragm; nodes above the diaphragm with spleen involvement | Not applicable |
| **IV** | Additional non contiguous Extra lymphatic involvement | Not applicable |

*NOTE. Extent of disease is determined by positron emission tomography–computed tomography for avid lymphomas and computed tomography for nonavid histologies. Tonsils, Waldeyer's ring, and spleen are considered nodal tissue.*
**Whether stage II bulky disease is treated as limited or advanced disease may be determined by histology and a number of prognostic factors.*

**Who should be imaged?**
For diagnosis and evaluation, all patients with lymphoma, except for those with primary cutaneous lymphoma, typically skin-limited, subtypes such as mycosis fungoides, should be scanned.

**Staging objectives**
- To stage nodal and extranodal disease.
- To stage primary CNS, orbital and head and neck lymphomas
- To diagnose possible spinal cord compression.
- To investigate marrow invasion.
- To diagnose and assess musculoskeletal involvement.

**Staging recommendations**
- Staging of patients with Hodgkin and aggressive non-Hodgkin's lymphoma and to serve as a baseline for comparison with treatment response scan.
- Staging of cases of early-stage follicular lymphoma (FL) to be assessed for radiation therapy.
- Staging of possible post-transplant lymphoproliferative disorder (PTLD).[13]

**IMAGING MODALITIES**
CT is being utilized as the main technique for staging, and MRI is also useful in some clinical conditions and in paediatric group predominantly. 18-F-Fluorodeoxyglucose positron emission tomography-computed tomography (18-FDG PET-CT) for functional imaging has now replaced Gallium scans.

**Computed Tomography (CT)**
Chest, abdominal and pelvic parts should be imaged in CT routine staging. CT of the head and neck may also be done.
The following are recommended.
• 100–150 ml of iv contrast can be injected at 3–4 ml / sec.
• Post contrast scans must be obtained through the neck, chest, abdomen and pelvic parts (portal vein phase).
• The slice thickness depends on the capacity of the scanner using MDCT. Sections are usually obtained at 1.25-2.5 mm and formatted for display at less than 5 mm.
• For better analysis of mesenteric and retroperitoneal enlarged lymph nodes and for bowel involvement, oral contrast media may be used.[14]

**Magnetic Resonance Imaging (MRI)**
MR imaging has a performance equivalent to CT when detecting the lymph nodes involved, but is usually considered an alternative and problem-solving method to CE-CT in lymphoma evaluation and grading.

MRI is the modality of choice for evaluation of lymphomatous involvement of the central nervous system (CNS). Enhanced imaging with Gadolinium is essential and diffusion-weighted sequences are necessary in brain lesions, since CNS lymphoma typically shows diffusion restriction.

For imaging extra-nodal soft tissue and intraosseous (marrow space) lesions, the superior spatial resolution and the tissue contrast of MRI are indeed superior to CT.[14]

**Positron Emission Tomography (PET)-CT:**
The general availability of 18-FDG PET-CT changed the landscape of lymphoma imaging due to its potential for the acquisition of integrated anatomical and functional data in one study. 18-FDG PET-CT could be effective for physiologically active cancer evaluation, where the FDG's avidity in comparison to healthy tissue is increased due to higher use of glucose by malignant cells. There is significant evidence that the introduction of 18-FDG PET-CT improves staging precision and results in clinical management changes. **(Figure 1).** Nevertheless, the degree of FDG accumulation does not

correspond to the stage or grade of lymphoma.[15] The bulk (over 95%) of NHL and HL cases are FDG-avid.[16]

The proposed utility of 18FDG PET-CT in NHL of lower grades is still being studied. For early stage follicular lymphoma, FDG PET CT is indicated, where radiation therapy is suggested. Research suggests that FDG-avidity with small lymphocytic lymphoma and marginal zone lymphoma display the lowest positive levels in the largest reported series with FDG avidity seen in most of the other lower-grade lymphomas.[17] **(Table 4).**

**Table 4: PET-CT recommended indications in lymphoma.[13]**

| |
|---|
| Staging of patients with HL and aggressive NHL and as a reference for treatment response scan evaluation. |
| Staging of patients of early stage follicular lymphoma (FL) recommended for management with radiation therapy. |
| Interim response review in HL and aggressive NHL patients after 2 cycles in chemotherapy. |
| End of HL and aggressive NHL treatment response evaluations in patients with positive interim imaging. |
| Assessment of possible relapse in symptomatic patients with previously avid FDG lymphomas. |
| Evaluation of second line therapy patient response and subsequent therapies in FDG-avid lymphomas. |
| Diagnosis and staging of possible lymphoproliferative disorder (PTLD) in post-transplant recipients. |
| To determine disease extent and suitability for transplantation before bone marrow transplantation. |
| Assessing the degree and location of an acceptable biopsy site in patients of low-grade lymphomas suspected of high-grade transformation. |

Some practical points to be considered for PET-CT

• Patient's serial PET-CT evaluation must preferably be conducted with the same PET-CT machine as the reference scan in the same centre.

• Four to six hours prior to the beginning of the PET-CT test, non-diabetic patients should fast.

• Diabetics should be given a late-morning appointment and take their regular hypoglycaemic medicine that morning followed by fasting for four hours.

•When the level of blood glucose is > 200 mg / dl, consider a subsequent appointment for the exam.

• Administer 5.4 MBq / kg 18FDG for 2D and 3.5 MBq / kg for 3D acquisition.

• The collection of the PET emissions takes place 60-90 minutes after administration of the FDG.

• The response evaluation scan must be performed after infusion of contrast at the same time and + 10 minutes post-contrast of the original baseline study.[14,18,19]

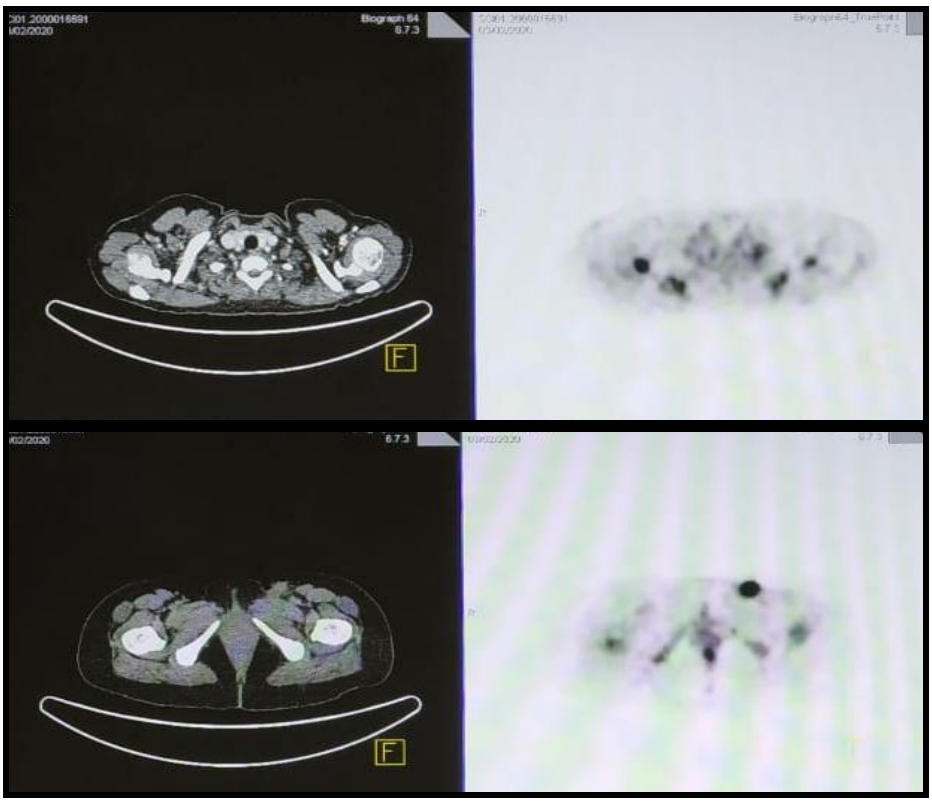


**Figure 1: 37-year-old woman with histologically proven DLBCL. After clinical examination and initial CT, patient was believed to have stage II disease (only inguinal lymphadenopathy). Additional staging with PET/CT was performed. Axial PET images shows enlarged and normal sized FDG-avid lymph nodes in the neck and left inguinal region. Disease severity was increased to stage III (involvement of lymph nodes above and below diaphragm).**

**Low Grade Lymphoma**

Low-grade lymphoproliferative disorders include both B-cell disorders (e.g. chronic lymphocytic leukaemia, follicular lymphoma, marginal lymphoma and small lymphocytic lymphoma) and T-cell disorders (peripheral T-cell lymphoma). Such diseases usually develop gradually, and have been deemed incurable. Management is targeted at symptom control (fatigue, lymphadenopathy) as they become clinically relevant. Such lesions are usually poor in metabolic activity and only have low to no FDG accumulation.[20,21]

As per the less significant stage of the disease than the clinical presentations, PET / CT isn't used for regular staging. Patients of low-grade, aggressive, or highly aggressive early stage lymphoma or those without bulky cancer may be managed with curative purpose with or without an abbreviated course of chemotherapy requiring involved field radiation therapy.[22,23] PET / CT is critical for the treatment of these patients to rule out possible nodal or extranodal lymphoma sites.[24] Radiation therapy should be limited for bulky cancer. Transformation of indolent lymphoma to a higher grade of lymphoma will occur in a small percentage of patients, most typically in DLBCL (known as Richter's transformation). PET / CT was observed to be of benefit in the treatment of these patients when detecting transformation by depicting abnormally high FDG uptake at transformation sites (indolent lymphoma typically has low FDG uptake).[25,26]

**Aggressive and Highly Aggressive Lymphoma**

In general, aggressive and highly aggressive NHLs, the most prominent of which is diffuse large B-cell lymphoma, display marked increase in FDG uptake at PET / CT. **(Figure 2)**. Staging with PET / CT will lead to a rise in stage relative to traditional staging with CT alone, as active disease can be demonstrated in sub-centimeter lymph nodes; uncommon extranodal disease sites and liver and spleen involvement can also be displayed. However, FDG avid foci on PET CT needs to be correlated with clinical history and symptoms of the patient as certain benign inflammatory conditions will also display increased FDG uptake. **(Figure 3).** While a baseline PET / CT test is highly recommended in the treatment of all patients with non-Hodgkin's aggressive or highly aggressive lymphoma for optimizing initial staging and prognostic evaluation, it's not always explicitly essential.[27-29]

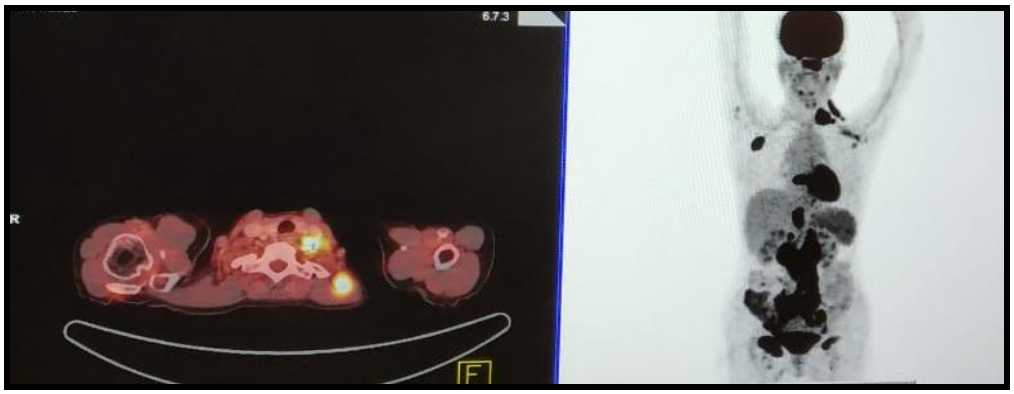
**Hodgkin's Lymphoma**

While Hodgkin's lymphoma is staged in the similar manner as NHL (modified classification of Ann-Arbor), it differs from the NHLs in its tendency to propagate by contiguous nodal invasion as opposed to multifocal nodal involvement. Nodular sclerosing Hodgkin's lymphoma, the most common form, typically presents above the diaphragm as lymphadenopathy; separate involvement of infra-diaphragmatic lymph nodes is uncommon. Hodgkin's lymphoma is avid FDG, and PET / CT is a more precise preliminary staging test than traditional diagnostic CT, especially for the identification of unknown extranodal disease sites.[27]

**TREATMENT OF LYMPHOMA**

Lymphoma management depends on its subtype and clinical stage. Cure is the goal of managing Hodgkin's lymphoma and aggressive NHLs, such as diffuse large B cell lymphoma or peripheral T-cell lymphoma.[30]

**Hodgkin Lymphoma:** For those with early-stage HL, chemotherapy is the focus of the treatment, typically the ABVD protocol (consisting of doxorubicin, vinblastine, bleomycin, and dacarbazine) with or without integrated radiation. Combination chemotherapy is the standard treatment for advanced-stage HL, typically in the United States with the ABVD protocol. The BEACOPP regimen (consisting of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisolone) can be used in certain higher-risk situations. Consolidative radiation for originally bulky cancer can be allowed.[30,31]



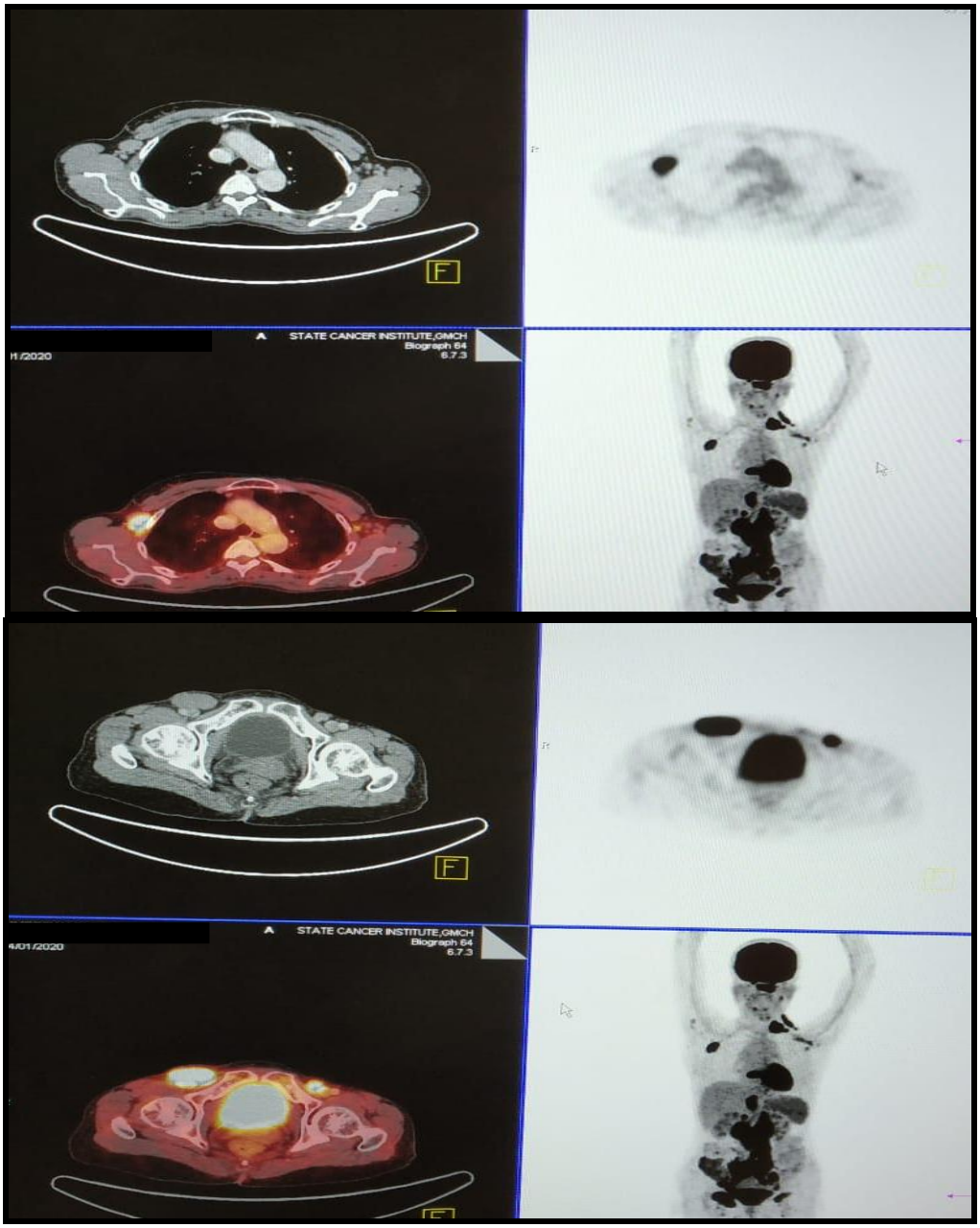



**Figure 2: A case of DLBCL with FDG avid cervical, axillary, abdominal and inguinal lymph nodes not taken any treatment: evaluated for initial staging (stage III).**

**Non-Hodgkin Lymphoma:** In most patients with the most common form of non-Hodgkin lymphoma (diffuse large B-cell lymphoma), with combined chemotherapy-immunotherapy or combined-modality therapy, cure may be obtained. Six cycles of R-CHOP (the anti-CD20 antibody rituximab in combination with cyclophosphamide, vincristine, doxorubicin, and prednisone) is routine therapy in patients with advanced stage illness. Cases with limited-stage cancer may be managed with a shortened regimen of R-CHOP (three or four cycles) followed by radiation therapy with equivalent results to full-stage chemotherapy.[31]

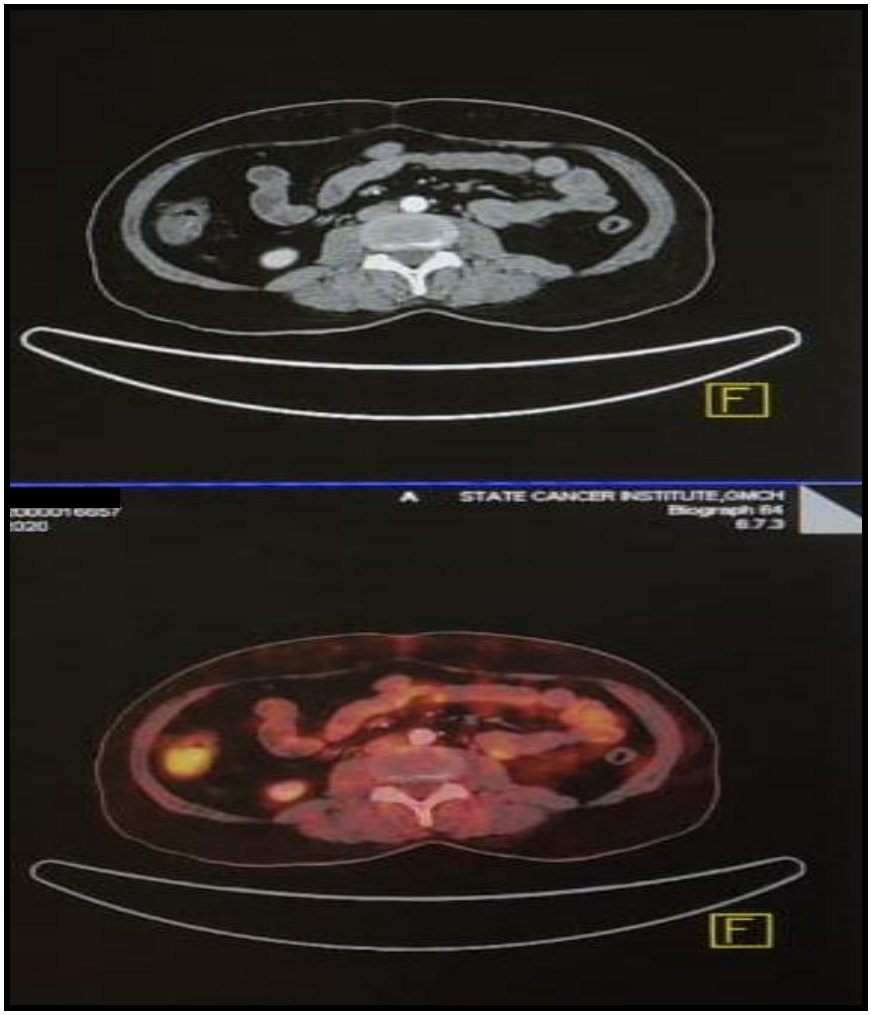



**Figure 3: A 53 years old female with known DLBCL was evaluated for staging. PET CT revealed suspicious FDG avid thickening of bowel loop (ascending colon). Patient had given symptoms of right iliac fossa pain. FDG uptake was secondary to inflammation (appendicitis) and not extranodal lymphoma spread as confirmed upon surgery.**

## ASSESSMENT OF THERAPEUTIC RESPONSE

The advent of radiotherapy and the medical application of CT and subsequent FDG PET / CT scans greatly contributed to the development of lymphoma staging and treatment assessment frameworks.

1971: The Ann Arbor staging classification with anatomic stages.[32]

1989: Modifications by Cotswolds applied for staging evaluation following the implementation of CT.[33]

1999: The guidelines of the International Working Group identified five types of clinical response that were focused on lesion CT imaging.[34]

2007: Clinical response based on PET / CT imaging of metabolic activity was described by the International Harmonization Project guidelines for response evaluation.[35] The Deauville criteria for assessing FDG avidity on PET were eventually introduced in 2009.[36]

2014: The Lugano classification was introduced.[37]

### Lugano Classification

Lugano classification reflects a significant shift in response evaluation standards from the Ann Arbor staging system and from the International Working Group system. The purpose of the Lugano classification is to simplify and standardize the evaluation and recording of responses. The new classification also discusses FDG PET / CT's role in the evaluation of the staging and intermediate response to treatment assessment. In brief, FDG PET / CT was thoroughly integrated into FDG-avid lymphoma staging and response assessment.[37]

4 categories for CT have been defined: (a) "complete radiological response", all nodes under or equal to 1.5 cm in the longest diameter, absence of all CT lymphoma findings; (b) "partial response", 50% or greater decrease in disease burden; (c) "stable disease", less than 50% decrease in disease burden; and (d) "progressive disease", new or worsened adenopathy or new extranodal disease.

The FDG PET / CT response assessment is focused on metabolic activity, demonstrated by the FDG uptake. The SUV functions as an indicator of metabolic activity, and the response assessment is now focused on a visual evaluation of FDG uptake and graded according to the "five-point scale" which integrates the Deauville criteria originally proposed for assessment on interim FDG PET / CT imaging.[36,37] The five-point scale includes the following categories:

1. No FDG uptake compared background.
2. FDG uptake less than mediastinum.
3. FDG uptake more than mediastinum but less than liver.
4. FDG uptake moderately more than liver.
5. FDG uptake markedly more than liver and/or new lesions.
X. New areas of FDG uptake unlikely to be related to lymphoma.

Four categories of response have been outlined as follows: (a) "complete metabolic response"—score of 1, 2, or 3; **(Figure 4)** (b) "partial metabolic response"—score of 4 or 5 with reduced FDG uptake; **(Figure 5)** (c) "no metabolic response"—score of 4 or 5 without significant change in FDG uptake; and (d) "progressive metabolic disease"—score of 4 or 5 with increased FDG uptake or with new lesions. **(Figure 6)** The five-point criteria are now applicable to the FDG PET / CT response assessment, both interim and end-of-treatment.[37]

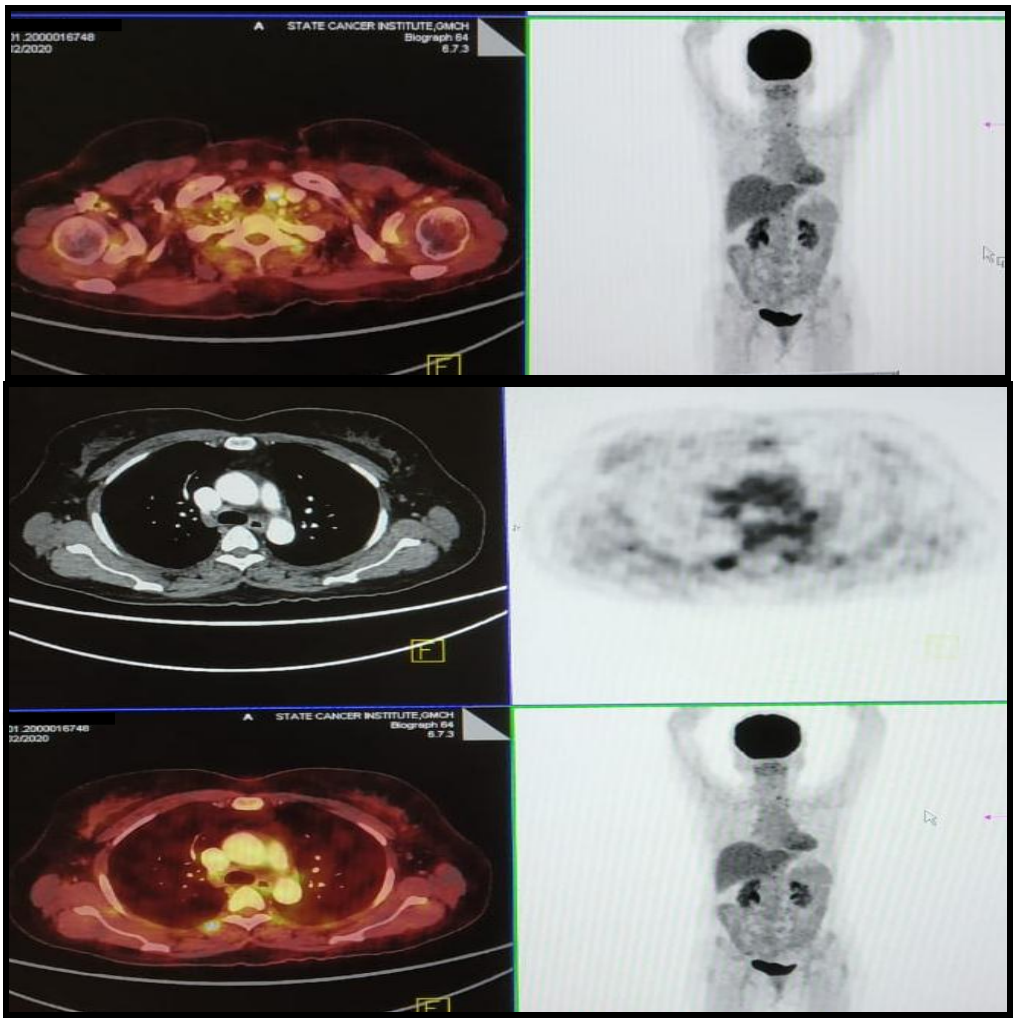
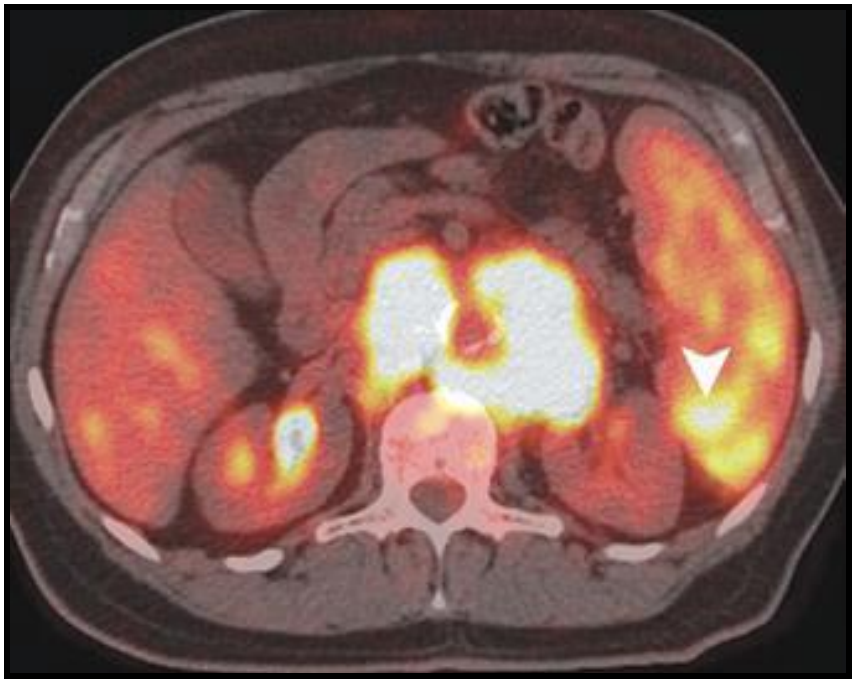
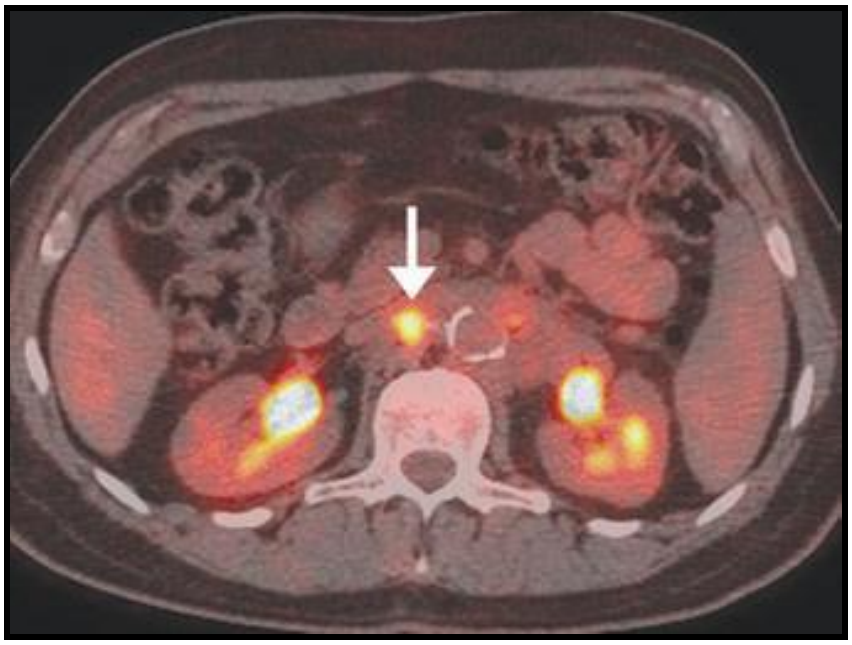



**Figure 4: 53y/F of DLBCL on biopsy from cervical nodes, follow up after completing 6 cycles of chemotherapy. No evidence of FDG avid nodes in neck or mediastinum: complete response as per Lugano criteria.**



A



B

**Figure 5: 67-year-old man with stage IV DLBCL.**
**A, Axial fused PET/CT image from baseline PET/CT examination shows FDG-avid lymphadenopathy in paraaortic regions in addition to splenic involvement.**
**B, After systemic chemotherapy there is marked anatomic response with almost complete interval resolution of lymphadenopathy on fused PET/CT image, however, there is persistent abnormal FDG uptake within small residual lymph node in retroperitoneum : Partial response as per Lugano criteria.**

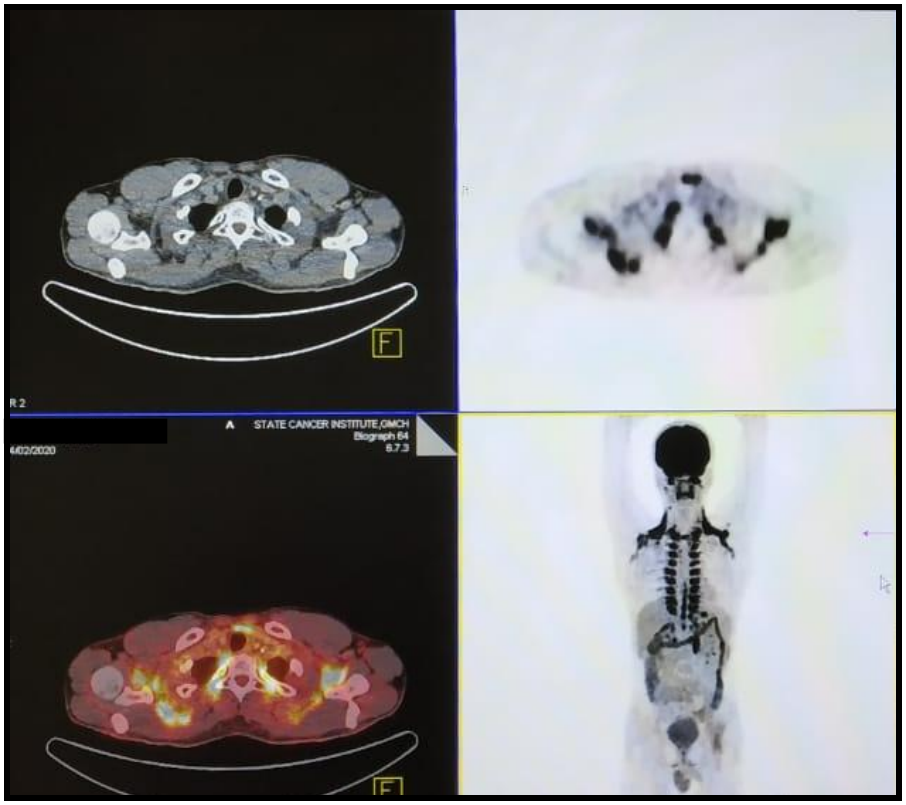



**Figure 6: A case of Hodgkin's Lymphoma follow up after completing 4 cycles of CT and 17 cycles of RT : Progressive disease as per Lugano criteria.**

**Additional Recommendations in the Lugano Classification**

1. All clinical studies need to be integrated for diagnostic evaluation, irrespective of the imaging method.
2. Assessment of bulky disease and B symptoms has historically been misleading; elimination of the related "X" and "B" modifiers can serve to optimize staging.
3. Patients are to be classified more precisely as having either "limited" (previously Ann Arbor stage I or II) or "advanced" disease (previously Ann Arbor stage III or IV).
4. At baseline staging, the tumor burden shall be measured using "sum of the product of the diameter" or SPD.

**Interim Imaging**

Interim FDG PET / CT scans are done after induction, mostly during either the 2nd or 4th cycle of a typical 6 cycle course, before conclusion of treatment.[38] Several large clinical trials in the US and around the world are underway to further research the efficacy of response-adapted therapy based on results from preliminary FDG PET / CT scans.[39] Changing therapy based on results at interim PET-CT alone is generally not recommended, except in the situation of clear progression of illness.[40]

**Imaging after Completing Treatment**

In both Hodgkin's lymphoma and DLBCL, a negative FDG PET / CT scan after treatment ends excludes residual viable tumor with high degree of certainty.[41] In general, in up to 80 per cent of presentations, clinical symptoms and signs provide us the earliest evidence of recurrent cancer.[42] The Lugano classification gives a consensus assertion on follow-up imaging advice against routine monitoring FDG PET / CT scans in asymptomatic cases and recommends CT imaging as suggested by clinical signs or symptoms for follow-up.

**Quantification of Treatment Response with FDG PET/CT**

The Lugano classification proposes a five-point response evaluation scale based on visual examination with FDG PET / CT. A different method is to calculate lymphoma response to therapy. Response can be quantified on FDG PET / CT scans by calculating variations in metabolic activity, expressed as the ΔSUV: ΔSUV (%) = (SUV current – SUV baseline)/ SUV baseline. Nevertheless, ΔSUVs are only an exploratory tool at present and can be used only as part of research methodologies. E.g. : For DLBCL, a Δ SUV more than 66% (after two cycles of chemotherapy) or 77% (after four cycles of chemotherapy) has been suggested as a marker of good treatment response which is related to better survival rates.[43,44]

**International Working Group consensus response evaluation criteria in lymphoma (RECIL 2017)**

The standard lymphoma response evaluation criteria currently in use are the Lugano Criteria that are based on PET or CT bidimensional tumor measurements for non-

FDG-avid lymphomas, or when there is no availability of PET scanning.[45] Those vary from the RECIST guidelines used in solid tumors utilizing single dimensional measurements.[46] A lymphoma-adapted RECIST has been shown to be easier to use in a pilot study than the 2007 lymphoma response criterion, yet delivering comparable levels of response.[47,48] In 2013 some of the authors performed a 2nd pilot analysis using 175 cases from 4 major academic centres, which also validated this theory and contributed to the creation of this new criteria. Against this backdrop, a group of leading global lymphoma specialists from academic centers and drug firms, radiologists and statisticians established a system to harmonize the parameters for lymphoma response evaluation with RECIST and to determine the effect of using two-dimensional or one-dimensional parameters on determining the best response for each subject, the proportion of subjects involved and disease free survival of each group. The new response evaluation criteria in lymphoma (RECIL) **(Table 5 and 6)** was adopted and accepted on the 25th of September 2016 at the International Workshop on Non-Hodgkin's Lymphoma (iwNHL) at San Diego.[49]

**Table 5: RECIL 2017: Response categories based on assessment of target lesions.[49]**

| % Change in sum of diameters of target lesions from nadir | | | | | |
|---|---|---|---|---|---|
| | **Complete response** | **Partial response** | **Minor response** | **Stable disease** | **Progression of disease** |
| **% change from baseline** | • Complete disappearance of all target lesions and all nodes with long axis <10mm.<br>• >30% decrease in the sum of longest diameters of target lesions (PR) with normalization of FDG-PET | >30% decrease in the sum of longest diameters of target lesions but not a CR | > 10% decrease in the sum of longest diameters of target lesions but not a PR (<30%) | <10% decrease or <20% increase in the sum of longest diameters of target lesions | • >20% increase in the sum of longest diameters of target lesions<br>• For small lymph nodes measuring <15mm post therapy, a minimum absolute increase of 5mm and the long diameter should exceed 15mm<br>•Appearance of a new lesion |
| **FDG-PET** | Normalization of FDG-PET (Deauville score 1-3) | Positive (Deauville score 4-5) | Any | Any | Any |
| **Bone marrow involvement** | Not involved | Any | Any | Any | Any |
| **New lesions** | No | No | No | No | Yes or No |

**Table 6: Comparison between Lugano lymphoma classification and RECIL 2017.[49]**

| | Lugano criteria | RECIL 2017 |
|---|---|---|
| **Number of target lesions** | Up to 6 | Up to 3 |
| **Measurement method** | Bi-dimensional: perpendicular diameters | Uni-dimensional: long diameter of any target lesion |
| **Incorporates PET results to describe complete response** | Yes | Yes |
| **Minor response** | No | Yes, reduction in sum of long diameters between >10% and <30% |
| **Stable disease** | -50% to +50% | decrease <10% to increase <20% |
| **Progression of disease** | Increase in the sum of products of perpendicular diameters by>50%, or any single lesion by>50% | Increase in sum of the longest diameters by 20%. For relapse from complete response, at least one lesion should measure 2 cm in the long axis with or without PET activity |

## FUTURE IMAGING MODALITIES

With the continued advancement of medical science both in terms of technical advancements and the implementation of these developments in lymphoma detection and treatment, many imaging modalities are currently under study and may be used more widely in the future. Some of these are

- **Whole-body MRI/whole-body diffusion- weighted imaging (WBDWI)**-may offer a favourable alternate to CT and 18FDG PET-CT with lack of ionising radiation and iodinated contrast material.[50]
- **Non-FDG novel tracers**-As noted above, 18FDG PET-CT has comparatively poor sensitivity in diagnosing certain low- grade lymphomas. 18F-fluoro-L-thymidine (FLT) , 11C- methionine (MET) and 18F-fluoroethyl-L-tyrosine (FET) reflect the exaggerated proliferation rate transport and protein

synthesis of cancer cells and are hypothesised to be more specific for the tumor cells.[51,52]

- **Integrated PET / MRI** devices are being adopted into regular clinical practice and can provide true multifunctional scanning, including spectroscopy, functional MRI, and arterial spin labelling, bolstered by PET metabolic / molecular results.[53]

## CONCLUSION

The lymphomas are a diverse class of malignancies, all of which derive from a specified point in lymphocytic ontogeny but have extremely variable clinical and imaging presentations. Diagnostic imaging plays a vital role in the clinical examination, evaluation, monitoring and follow-up of patients with lymphoma. A better understanding of the Lugano classification and RECIL 2017 criteria would have additional benefit for the radiologist as a part of the clinical oncology group.

## ACKNOWLEDGEMENT

We, the authors would like to express our gratitude to all the senior and junior faculties, students, colleagues and technical staff of the Department of Radiology at Gauhati Medical College and Hospital, Guwahati, Assam, India. We would especially like to thank the staff of our Nuclear Imaging and PET-CT sub-division.

## REFERENCES

1. Adamson P, Bray F, Costantini AS *et al.* Time trends in the registration of Hodgkin and non-Hodgkin lymphomas in Europe. *Eur J Cancer*, 2007; 43(2): 391–401.
2. Roman E, Smith AG. Epidemiology of lymphomas. *Histopathology*, 2011; 58(1): 4–14.
3. Chiu BC, Weisenburger DD. An update of the epidemiology of non-Hodgkin's lymphoma. *Clin Lymphoma* 2003; 4(3): 161–168.
4. Brenner H, Gondos A, Pulte D. Ongoing improvement in long-term survival of patients with Hodgkin disease at all ages and recent catch-up of older patients. *Blood*, 2008; 111(6): 2977–2983.
5. Campo E, Swerdlow SH, Harris NL *et al*. The 2008 WHO classification of lymphoid neoplasms and beyond: evolving concepts and practical applications. *Blood*, 2011; 117(19): 5019–5032.
6. American Cancer Society. Cancer Facts and Figures 2011. Atlanta: American Cancer Society, 2011.
7. Townsend W, Linch D. Hodgkin's lymphoma in adults. Lancet, 2012; 380(9844): 836–847.
8. Matasar MJ, Zelenetz AD. Overview of lymphoma diagnosis and management. Radiol Clin North Am, 2008; 46(2): 175–198, vii.
9. Olsen E, Vonderheid E, Pimpinelli N, et al. Revisions to the staging and classification of mycosis fungoides and Sezary syndrome: a proposal of the International Society for Cutaneous Lymphomas (ISCL) and the cutaneous lymphoma task force of the European Organization of Research and Treatment of Cancer (EORTC). Blood, 2007; 110(6): 1713–1722.
10. Olsen EA, Whittaker S, Kim YH, et al. Clinical end points and response criteria in mycosis fungoides and Sézary syndrome: a consensus statement of the International Society for Cutaneous Lymphomas, the United States Cutaneous Lymphoma Consortium, and the Cutaneous Lymphoma Task Force of the European Organisation for Research and Treatment of Cancer. J Clin Oncol, 2011; 29(18): 2598–2607.
11. Lister TA, Crowther D, Sutcliffe SB et al. Report of a committee convened to discuss the evaluation and staging of patients with Hodgkin's disease: Cotswolds meeting. J Clin Oncol, 1989; 7(11): 1630–1636.
12. Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol, 2014; 32(27): 3059–3068.
13. The Royal College of Radiologists. Evidence-based indications for the use of PET-CT in the United Kingdom 2013. London: The Royal College of Radiologists, 2013.
14. Chua S, Taylor B, Whitehouse R, Barrington S. Lymphoma. In: Nicholson T (ed). Recommendations for cross-sectional imaging in cancer management, Second edition. London: The Royal College of Radiologists, 2014.
15. Cheson B. Role of functional imaging in the management of lymphoma. J Clin Oncol, 2011; 29: 1844-1854.
16. Elstrom R, Guan L, Baker G et al. Utility of FDG-PET scanning in lymphoma by WHO classification. Blood, 2003; 101(10): 3875–3876.
17. Weiler-Sagie M, Bushelev O, Epelbaum R et al. (18)F-FDG avidity in lymphoma readdressed: a study of 766 patients. J Nucl Med, 2010; 51(1): 25–30.
18. Berthelsen AK, Holm S, Loft A, Klausen TL, Andersen F, Højgaard L. PET/CT with intravenous contrast can be used for PET attenuation correction in cancer patients. Eur J Nucl Med Mol Imaging, 2005; 32: 1167–1175.
19. Rodríguez-Vigil B, Gómez-León N, Pinilla I et al. PET/CT in lymphoma: prospective study of enhanced full-dose PET/CT versus unenhanced low-dose PET/CT. J Nucl Med, 2006; 47: 1643–1648.
20. Juweid ME, Cheson BD. Role of positron emission tomography in lymphoma. J Clin Oncol 2005; 23:4577–4580
21. Okada J, Yoshikawa K, Imazeki K, et al. The use of FDG-PET in the detection and management of malignant lymphoma: correlation of uptake with prognosis. J Nucl Med, 1991; 32:686–691.
22. Tsang RW, Gospodarowicz MK, Pintilie M, et al. Stage I and II MALT lymphoma: results of treatment with radiotherapy. Int J Radiat Oncol Biol Phys, 2001; 50: 1258–1264.
23. MacDermed D, Thurber L, George TI, Hoppe RT, Le QT. Extranodal nonorbital indolent lymphomas of the head and neck: relationship between tumor

control and radiotherapy. Int J Radiat Oncol Biol Phys 2004; 59:788–795
24. Wirth A, Foo M, Seymour JF, Macmanus MP, Hicks RJ. Impact of [18f] fluorodeoxyglucose positron emission tomography on staging and management of early-stage follicular non-Hodgkin lymphoma. Int J Radiat Oncol Biol Phys, 2008; 71: 213–219.
25. Tsimberidou AM, Wierda WG, Plunkett W, et al. Phase I-II study of oxaliplatin, fludarabine, cytarabine, and rituximab combination therapy in patients with Richter's syndrome or fludarabine-refractory chronic lymphocytic leukemia. J Clin Oncol, 2008; 26: 196–203.
26. Bodet-Milin C, Kraeber-Bodéré F, Moreau P, Campion L, Dupas B, Le Gouill S. Investigation of FDG-PET/CT imaging to guide biopsies in the detection of histological transformation of indolent lymphoma. Haematologica, 2008; 93: 471–472.
27. Naumann R, Beuthien-Baumann B, Reiss A, et al. Substantial impact of FDG PET imaging on the therapy decision in patients with early-stage Hodgkin's lymphoma. Br J Cancer, 2004; 90: 620–625.
28. Buchmann I, Reinhardt M, Elsner K, et al. 2-(fluorine-18) fluoro-2-deoxy-D-glucose positron emission tomography in the detection and staging of malignant lymphoma: a bicenter trial. Cancer, 2001; 91: 889–899.
29. Schoder H, Meta J, Yap C, et al. Effect of wholebody 18F-FDG PET imaging on clinical staging and management of patients with malignant lymphoma. J Nucl Med, 2001; 42:1139–1143.
30. Intlekofer AM, Younes A. Precision therapy for lymphoma—current state and future directions. Nat Rev Clin Oncol, 2014;11(10): 585–596.
31. Moskowitz CH, Schöder H, Teruya-Feldstein J, et al. Risk-adapted dose-dense immunochemotherapy determined by interim FDG PET in Advanced-stage diffuse large B-Cell lymphoma. J Clin Oncol 2010;28(11):1896–1903.
32. Carbone PP, Kaplan HS, Musshoff K, Smithers DW, Tubiana M. Report of the Committee on Hodgkin's Disease Staging Classification. Cancer Res, 1971; 31(11): 1860–1861.
33. Lister TA, Crowther D, Sutcliffe SB, et al. Report of a committee convened to discuss the evaluation and staging of patients with Hodgkin's disease: Cotswolds meeting. J Clin Oncol, 1989; 7(11): 1630–1636.
34. Cheson BD, Horning SJ, Coiffier B, et al. Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas. NCI Sponsored International Working Group. J Clin Oncol, 1999; 17(4): 1244.
35. Cheson BD. The International Harmonization Project for response criteria in lymphoma clinical trials. Hematol Oncol Clin North Am, 2007; 21(5): 841–854.
36. Meignan M, Gallamini A, Meignan M, Gallamini A, Haioun C. Report on the First International Workshop on Interim-PET-Scan in Lymphoma. Leuk Lymphoma, 2009; 50(8): 1257–1260.
37. Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol, 2014; 32(27): 3059–3068.
38. Townsend W, Linch D. Hodgkin's lymphoma in adults. Lancet, 2012; 380(9844): 836–847.
39. Kostakoglu L, Gallamini A. Interim 18F-FDG PET in Hodgkin lymphoma: would PET adapted clinical trials lead to a paradigm shift? J Nucl Med, 2013; 54(7): 1082–1093.
40. Barrington SF, Mikhaeel NG, Kostakoglu L, et al. Role of imaging in the staging and response assessment of lymphoma: consensus of the International Conference on Malignant Lymphomas Imaging Working Group. J Clin Oncol, 2014; 32(27): 3048–3058.
41. Martelli M, Ceriani L, Zucca E, et al. [18F] fluorodeoxyglucose positron emission tomography predicts survival after chemoimmunotherapy for primary mediastinal large B-cell lymphoma: results of the International Extranodal Lymphoma Study Group IELSG-26 Study. J Clin Oncol, 2014; 32(17): 1769–1775.
42. Seam P, Juweid ME, Cheson BD. The role of FDG-PET scans in patients with lymphoma. Blood, 2007; 110(10): 3507–3516.
43. Itti E, Meignan M, Berriolo-Riedinger A, et al. An international confirmatory study of the prognostic value of early PET/CT in diffuse large B-cell lymphoma: comparison between Deauville criteria and DSUVmax. Eur J Nucl Med Mol Imaging, 2013; 40(9): 1312–1320.
44. Hasenclever D, Kurch L, Mauz-Körholz C, et al. qPET - a quantitative extension of the Deauville scale to assess response in interim FDG-PET scans in lymphoma. Eur J Nucl Med Mol Imaging, 2014; 41(7): 1301–1308.
45. Cheson BD, Fisher RI, Barrington SF et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol, 2014; 32(27): 3059–3068.
46. Eisenhauer EA, Therasse P, Bogaerts J et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer, 2009; 45(2): 228–247.
47. Cheson BD, Pfistner B, Juweid ME et al. Revised response criteria for malignant lymphoma. J Clin Oncol, 2007; 25(5): 579–586.
48. Assouline S, Meyer RM, Infante-Rivard C et al. Development of adapted RECIST criteria to assess response in lymphoma and their comparison to the International Workshop Criteria. Leuk Lymphoma, 2007; 48(3): 513–520.
49. Younes A, Hilden P, Coiffier B, Hagenbeek A, Salles G, Wilson W, Seymour JF, Kelly K, Gribben J, Pfreunschuh M, Morschhauser F. International

Working Group consensus response evaluation criteria in lymphoma (RECIL 2017). Annals of Oncology, 2017 Jul 1; 28(7): 1436-47.
50. Kwee TC, Takahara T, Ochiai R, Nievelstein RA, Luijten PR. Diffusion-weighted whole-body imaging with background body signal suppression (DWIBS): features and potential applications in oncology. Eur Radiol, 2008; 18(9): 1937–1952.
51. Nuutinen J, Leskinen S, Lindholm P et al. Use of carbon-11 methionine positron emission tomography to assess malignancy grade and predict survival in patients with lymphomas. Eur J Nucl Med, 1998; 25(7): 729–735.
52. Wheatley DN. On the problem of linear incorporation of amino acids into cell protein. Experientia, 1982; 38(7): 818–820.
53. Boss A, Bisdas S, Kolb A, et al. Hybrid PET/MRI of intracranial masses: initial experiences and comparison to PET/CT. J Nucl Med, 2010; 51(8): 1198–1205.