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Imaging Recommendations for Diagnosis, Staging, and Management of Hematological Malignancies

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Abstract

The NIC defines hematological cancers as those that begin in blood forming tissues such as bone marrow or cells of the immune system and these broadly include three groups: leukemias, lymphomas, and myelomas. The role of imaging is also fundamentally different between the three main groups of hematological malignancies. While imaging is the main tool for staging as well as treatment response assessment in lymphoma, it represents one of several key criteria for the diagnosis and follow-up of myeloma; whereas in leukemia, imaging has a role to play in the detection and management of treatment-related complications which is a crucial part of post-transplant treatment.

Keywords

- hematology
- medical oncology
- radiology

Introduction

The NIC defines hematological cancers as those that begin in blood forming tissue such as bone marrow or cells of the immune system and these broadly include three groups leukemias, lymphomas, and myelomas.[1] The role of imaging is also fundamentally different between the three main groups of hematological malignancies. While imaging is the main tool for staging as well as treatment response assessment in lymphoma,[2,3] it represents one of several key criteria for the diagnosis and follow-up of myeloma[4]; whereas in leukemia, imaging has a role to play in the detection and management of treatment-related complications which is a crucial part of post-transplant treatment.

In myeloma, whole-body magnetic resonance imaging (WB-MRI) is recognized as a highly sensitive test for the assessment of myeloma, and is also endorsed by clinical guidelines, especially for detection and staging. In lymphoma, WB-MRI is presently not recommended, and merely serves as an alternative technique to the current standard imaging, Flourine-**18** fluorodeoxyglucose positron emission tomography/computed tomography ([18F]FDG-PET/CT), especially in pediatric patients.[5]

Even for lymphomas with variable FDG avidity, such as extranodal mucosa-associated lymphoid tissue lymphoma (MALT), contrast-enhanced CT, but not WB-MRI, is presently recommended, despite the high sensitivity of diffusion-weighted MRI and its ability to capture treatment response that has been reported in the literature.[5] In leukemia, neither MRI nor any other cross-sectional imaging test (including PET) is currently recommended outside of clinical trials.[5]

Epidemiology, Clinical Presentation in India and Global

Almost all of these cancers occur almost a decade earlier in India compared with the West. Possible reasons proposed have included the demographics of the Indian population (largely younger), increased incidence of chronic infections and antigenic stimulation, genetics, and socioeconomic status. The average ASR for multiple myeloma (MM) is 0.1 to 1.9 in India, and around 2.8 to 3.9 in the US, with similar figures for Hodgkin's lymphoma (HL).[6] Incidence of leukemias is between 2.4 and 4.6 per 100,000 when compared with 9.6 to 11 in Canada.[6]

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Imaging Guidelines

Lymphomas

PET-CT is recommended for the routine staging of FDG-avid, nodal lymphomas (essentially all histologies except chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), lymphoplasmacytic lymphoma/Waldenström's macroglobulinemia, mycosis fungoides, and marginal zone non-Hodgkin's lymphomas (NHLs), unless there is a suspicion of aggressive transformation) as the gold standard.[7]

CT scan is preferred in the other lymphomas. A chest X-ray is no longer required in lymphoma staging because it less accurate than CT.[8] Moreover, CT identifies more hilar nodes and may better discriminate between a single large nodal mass and an aggregate of individual nodes.[3]

Definition of bulky disease: A single nodal mass, in contrast to multiple smaller nodes, of 10 cm or greater than a third of the transthoracic diameter at any level of thoracic vertebrae as determined by CT is retained as the definition of bulky disease for HL.[9] A chest X-ray is not required to determine bulk because of its high concordance with CT.[8] However, a variety of sizes have been suggested for NHL[10] with limited evidence suggesting 6 cm as best for follicular lymphoma15 and 6 to 10 cm in the rituximab era for diffuse large-B-cell lymphoma (DLBCL).[11] However, none of the proposed sizes have been validated in the current therapeutic era. Therefore, the recommendation for HL and NHL is to record the longest measurement by CT scan, with the term X no longer necessary.[3]

If a PET-CT is performed, a bone marrow aspirate/biopsy is no longer required for the routine evaluation of patients with HL. In DLBCL, PET-CT is also more sensitive than bone marrow biopsy (BMB) but has been reported to miss low-volume diffuse involvement of 10 to 20% of the marrow.[12] If the scan is negative, a BMB is indicated to identify involvement by discordant histology if relevant for a clinical trial or patient management.[13]

Response Assessment

Lugano's criteria are used for response assessment as summarized in ►**Table 1**.[18] End-of-treatment assessment is more accurate with PET-CT, especially for patients with radiologic (CT) CRu or partial response (PR) in HL, DLBCL, and follicular lymphoma.[3] PET-CT-based criteria eliminate CRu and improve the prognostic value of PR. In early- and advanced-stage patients with HL, a negative predictive value of 95 to 100% and a positive predictive value of more than 90% have been reported.[14,15] In aggressive NHL, studies have reported a negative predictive value of 80 to 100%, but a lower positive predictive value, ranging from 50 to 100%.[16]

A CT-based response is preferred for histologies with low or variable FDG avidity and in regions of the world where PET-CT is unavailable. However, in the absence of a PET-CT scan, a mass that has decreased in size but persists is considered at best a PR in the absence of a biopsy documenting the absence of lymphoma, and the former term CRu is not to be considered.7

Summary of response and follow-up strategies as per the IWG, NCCN, and ESMO criteria are as follows[3]:

1) PET-CT should be used for response assessment in FDG-avid histologies, using the 5-point scale; CT is preferred for low or variable FDG avidity.
2) A complete metabolic response even with a persistent mass is considered a complete remission.
3) A PR requires a decrease by more than 50% in the sum of the product of the perpendicular diameters of up to six representative nodes or extranodal lesions.
4) Progressive disease by CT criteria only requires an increase in the PPDs of a single node by more than or equal to 50%.
5) Surveillance scans after remission are discouraged, especially for DLBCL and HL, although a repeat study may be considered after an equivocal finding after treatment.
6) Judicious use of follow-up scans may be considered in indolent lymphomas with residual intra-abdominal or retroperitoneal disease.

PET-CT is used for staging and response assessment of lymphomas, during treatment (interim PET) and for remission assessment at the end of treatment.[7] MRI is the modality of choice for suspected central nervous system lymphoma.

Mantle-cell lymphoma is routinely FDG avid; limited data suggest that the sensitivity and specificity of identifying bowel involvement is low and should not replace other investigative measures.

The standard response criteria currently in use for lymphoma are the Lugano criteria which are based on [18F]FDG-PET or bidimensional tumor measurements on computerized tomography scans. These differ from the RECIST criteria used in solid tumors, which use unidimensional measurements.

Imaging Guidelines of Leukemias

PET imaging is considered investigational and experimental for all indications in acute lymphoblastic leukemia, acute myeloid leukemia, and chronic myeloid leukemia. Routine advanced imaging is not indicated in the evaluation and management of chronic myeloid leukemias, myelodysplastic syndromes, or myeloproliferative disorders in the absence of specific localizing clinical symptoms or clearance for hematopoietic stem cell transplantation.[17]

CLL/SLL: PET imaging is not indicated in the evaluation of CLL/SLL except for suspected Richter's transformation.

Suspected transformation (Richter's) from a low-grade lymphoma to a more aggressive type is based on one or more of the following: New B symptoms, rapidly growing lymph nodes, development of extranodal disease, a significant recent rise in LDH above normal range- A PETCT may be advisable in such cases.[18]

Imaging Guidelines for Post-Hematopoietic Stem Cell Transplantation (HSCT)

Selected patients of leukemias/lymphomas are offered HSCT and imaging plays a very important role in surveillance of these patients.

Table 1 Lugano response criteria for PET-CT follow-up in lymphomas[28]

Modality	Complete response	Partial response	Stable disease	Progressive disease
CT	Lymph modes $\leq$ 1.5 cm in Ldi Complete disappearance of radiologic evidence of disease	Single lesion: $\downarrow \geq$ 50% in PPD Multiple lesions: $\downarrow \geq$ 50% in SPD of up to six lymph nodes or extranodal sites	$\downarrow \leq$ 50% in SPD of up to six lymph nodes or extranodal sites (no criteria for progressive disease are met)	1) New lymphadenopathy or $\uparrow$; single node must be abnormal with: a) Ldi $>$ 1.5 cm and b) PPD $\geq$ 50% and c) Ldi or Sdi $\uparrow$ 0.5 cm if $\leq$ 2.0 cm and $\uparrow$ 1.0 cm if $>$ 2.0 cm
				2) $\uparrow$ splenic volume: a) with prior splenomegaly: $\uparrow >$ 50% of its prior $\uparrow$ beyond baseline b) without prior splenomegaly: $\uparrow >$ 2.0 cm c) New or recurrent splenomegaly
				3)New or Larger non measured lesions
				4) Recurrent previously resolved lesions
				5) New extranodal lesion $>$ 1.0 cm in any axis (new lesions $<$ 1.0 cm in any axis are included if attributable to lymphoma)
FDG-PET-CT	Scores 1, 2, 3 in nodal or extra nodal sites with or without a residual mass	Scores 4 or 5 with $\downarrow$ uptake compared with baseline and residual mass(es)	Scores 4 or 5 with no obvious change in FDG uptake	Scores 4 or 5 any lesion with $\uparrow$ uptake from baseline and /or new FDG-avid foci

Abbreviations: FDG-PET-CT, fluorodeoxyglucose positron emission tomography/computed tomography; LDi,—; PPD,—; SPD,—.

Pretransplant Imaging in HSCT: This imaging generally takes place within 30 days prior to transplant, and involves a reassessment of the patient's disease status as well as infectious disease clearance. CT of the sinuses, neck, chest, and/or abdomen/pelvis is recommended. Nuclear renal function study to ensure adequate renal function and echocardiogram are routinely indicated to ensure adequate cardiac function to proceed with the transplant.

Post-transplant Imaging in HSCT: There are many common complications from HSCT, including infection, graft versus host disease, hepatic sinusoidal obstruction syndrome, restrictive lung disease, among others. These can be classified into early (less than 30 days) and delayed (more than 100 days) complications.

These patients often require several CT chest scans in the post-transplant period due to their susceptibility to infection (most commonly lung). At the very least, scans for disease response generally takes place at day 30 and day 100 post-transplant. CT chest without contrast is indicated for patients with bronchiolitis obliterans with organizing pneumonia, a delayed post-transplant complication for surveillance and evaluation of acute changes.

Imaging Guidelines of Myelomas

Plasma cell disorders range from the spectrum of the mostly benign monoclonal gammopathy of unknown significance to the intermediate smoldering multiple myeloma to the frankly malignant MM.[19] Imaging of bone lesions forms a major stay in the diagnosis and management of MM. The CRAB criteria: Hyper***c***alcemia, ***R***enal insufficiency, ***A***naemia and ***B***one lesions—at least one or more bone lesions on X-Ray/CT/PET-CT—form the four pillars upon which a diagnosis is made in patients with clonal bone marrow plasma cells more than 10%.[19]

At least one well-defined lytic lesion of diameter greater than 5mm is necessary to satisfy the bony lesion category of CRAB lesions.[4] Advances in cross-sectional imaging have led the IMWG to form newer guidelines with the definition of myeloma-defining events) in which at least two or more focal lesions in the marrow of size greater than 5 mm can be used to make the diagnosis, in the absence of focal lytic lesions on X-ray or CT.[4] Newer advanced sequences like diffusion-weighted imaging with background suppression (DWIBS) have also helped to increase sensitivity and specificity of bony lesion detection; however, their inclusion into a formal role as defining criteria is awaited pending further research.

Imaging Guidelines

For screening and diagnosis:

1) X-ray is not to be used unless it is the only modality available. Similarly, there is no role of technetium scans.[20]
2) Whole-body low-dose CT (WBLDCT) is the ideal screening tool. It is the scan with arms over the head (to reduce beam hardening artifacts on vertebrae if arms are placed on the side of the body).[21] Even one focal lesion of size greater than 5 mm is sufficient for diagnosis.[22]
3) In clinically suspected MM patients who are screening negative on WBLDT, WBMRI is strongly advised.[23] Conventional T1 sequences pick up marrow infiltration and diffusion-weighted imaging has been shown to be the single most sensitive sequence.[22]
4) Imaging of bone marrow is the opposite of imaging findings elsewhere in the body: Normal bone marrow shows restricted diffusion with low apparent diffusion coefficient (ADC) values, whereas disease (metastases/myeloma) leads to a facilitated diffusion with a progressive increase in ADC values. ADCs of normal bone marrow is very low (range, $0.2–0.5 \times 10^{-3}$ mm^2/sec), whereas a value greater than 0.597×10^{-3} mm^2/s showed 96% sensitivity and 100% specificity for MM.[24]
5) DWIBS**:** It is a free-breathing sequence wherein multiple thin slice axial sections of the whole body are acquired. It relies on the relatively unchanged "incoherent" motion within a voxel during respiration where the "coherent" motion is affected. It is the incoherent motion of the water molecules that determines diffusivity. This

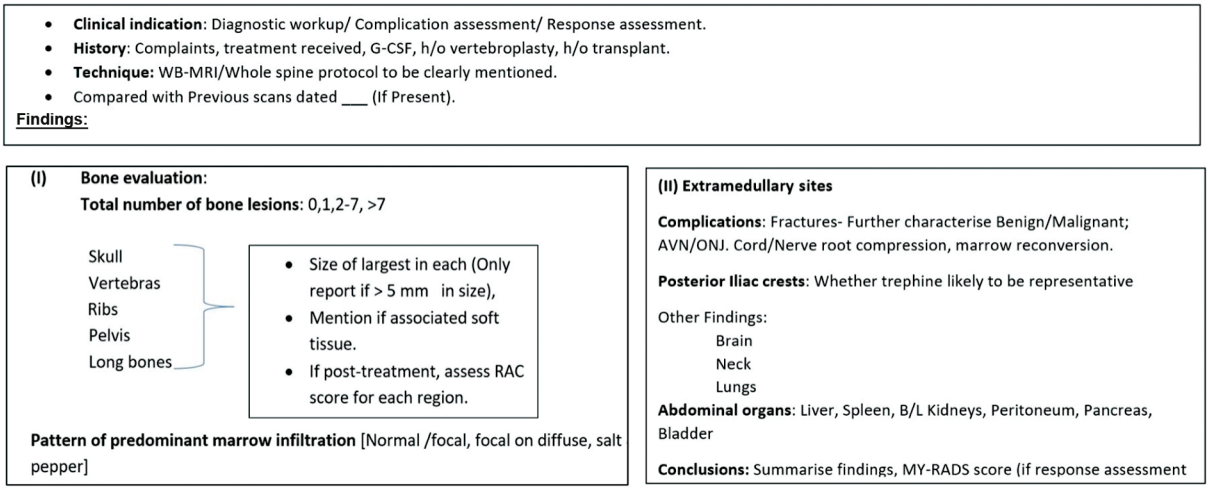

Fig. 1 Structured reporting format of myelomas.[27] AVN,—; G-CSF,—; MY-RADS, Myeloma Response Assessment and Diagnosis System; ONJ,—; RAC,—; WB-MRI, whole body magnetic resonance imaging.

sequence is commonly acquired in the coronal plane and short tau inversion recovery sequence is the commonly employed pre-pulse fat saturating sequence that is combined with DWIBS to achieve uniform fat suppression.[25] B values generally range from 800 to 1000 seconds mm^2.

For post-treatment assessment: 18 FDG-PET-CT is the gold standard for assessing post-treatment response. Complete suppression of FDG avidity on post-therapy scans confers increased overall survival and serves as a good prognostic marker.[26]

Structured Reporting System

In an effort to promote standardization and diminish variations in the acquisition, interpretation, and reporting of whole-body MRI in myeloma and allow response assessment, the IMWG and NICE UK group together developed the Myeloma Response Assessment and Diagnosis System (MY-RADS).[27] A sample of the reporting template is described below (►**Fig. 1**).

Disclaimer

This article is not an original paper and is only a compilation of imaging guidelines from various sources, which have been cited appropriately.

Conflict of Interest

None declared.

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