




## CLINICAL PRACTICE GUIDELINE

# Imaging recommendations in pediatric lymphoma: A COG Diagnostic Imaging Committee/SPR Oncology Committee White Paper

Joyce Mhlanga<sup>1</sup>  | Adina Alazraki<sup>2</sup>  | Steve Y Cho<sup>3</sup>  | Hollie Lai<sup>4</sup>  |  
Helen Nadel<sup>5</sup>  | Neeta Pandit-Taskar<sup>6,7</sup>  | Jing Qi<sup>8</sup>  | Dhanashree Rajderkar<sup>9</sup>  |  
Stephan Voss<sup>10</sup>  | Pankaj Watal<sup>11</sup>  | Kathleen McCarten<sup>12</sup>

<sup>1</sup>Mallinckrodt Institute of Radiology, Washington University in St. Louis School of Medicine, Saint Louis, Missouri, USA

<sup>2</sup>Departments of Pediatrics and Radiology, Emory University School of Medicine, Children's Healthcare of Atlanta, Atlanta, Georgia, USA

<sup>3</sup>Department of Radiology, Nuclear Medicine and Molecular Imaging Section, University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin, USA

<sup>4</sup>Department of Radiology, Children's Health of Orange County, Orange, California, USA

<sup>5</sup>Department of Pediatric Radiology, Lucile Packard Children's Hospital at Stanford, Stanford University School of Medicine, Stanford, California, USA

<sup>6</sup>Department of Radiology, Molecular imaging and Therapy Service, Memorial Sloan Kettering Cancer Center, New York City, New York, USA

<sup>7</sup>Department of Radiology, Weill Cornell Medical College, New York City, New York, USA

<sup>8</sup>Department of Radiology, Medical College of Wisconsin and Children's Wisconsin, Milwaukee, Wisconsin, USA

<sup>9</sup>Department of Radiology, Division of Pediatric Radiology, College of Medicine, University of Florida, Gainesville, Florida, USA

<sup>10</sup>Harvard Medical School, Department of Radiology, Boston Children's Hospital, Boston, Massachusetts, USA

<sup>11</sup>University of Central Florida College of Medicine, Nemours Children's Hospital, Orlando, Florida, USA

<sup>12</sup>Diagnostic Imaging and Pediatrics, Imaging and Radiation Oncology Core, Lincoln, Warren Alpert Medical School, Brown University, Providence, Rhode Island, USA

## Correspondence

Joyce Mhlanga, Washington University in St. Louis School of Medicine, Mallinckrodt Institute of Radiology, 510 S. Kingshighway Blvd, Campus Box 8223, Saint Louis, MO 63110, USA.  
Email: [jmhlanga@wustl.edu](mailto:jmhlanga@wustl.edu)

## Funding information

National Clinical Trials Network Operations Center, Grant/Award Number: U10CA180886

## Abstract

Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL) are both malignancies originating in the lymphatic system and both affect children, but many features differ considerably, impacting workup and management. This paper provides consensus-based imaging recommendations for evaluation of patients with HL and NHL at diagnosis and response assessment for both interim and end of therapy (follow-up).

## KEYWORDS

diagnosis, Hodgkin's disease, Non-Hodgkin lymphoma, radiology, response evaluation

## 1 | INTRODUCTION

Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL) are both malignancies originating in the lymphatic system and both affect children, but many features differ considerably impacting workup and management. Reports of incidence vary slightly considering source, but these lymphomas are the third most common malignant neoplasm in the pediatric age after central nervous system (CNS) tumors and leukemia.<sup>1</sup> As far as age of presentation, HL is predominantly a disease of adolescents and young adults (AYA), making it the most commonly diagnosed malignancy in adolescents, whereas NHL presents more commonly at a younger age.<sup>2</sup> Overall NHL comprises 60% and HL 40% of pediatric lymphomas.<sup>3</sup>

**Abbreviations:** ALARA, as low as reasonably achievable; AYA, adolescents and young adults; CHL, classic Hodgkin lymphoma; COG, Children's Oncology Group; EFS, event-free survival; F18-FDG PET, F18-fluorodeoxyglucose positron emission tomography; HL, Hodgkin lymphoma; IPNHLSS, International Pediatric Non-Hodgkin Lymphoma Staging System; PA, posterior anterior; SOR, standard of recommendation.

dren, but many features differ considerably impacting workup and management. Reports of incidence vary slightly considering source, but these lymphomas are the third most common malignant neoplasm in the pediatric age after central nervous system (CNS) tumors and leukemia.<sup>1</sup> As far as age of presentation, HL is predominantly a disease of adolescents and young adults (AYA), making it the most commonly diagnosed malignancy in adolescents, whereas NHL presents more commonly at a younger age.<sup>2</sup> Overall NHL comprises 60% and HL 40% of pediatric lymphomas.<sup>3</sup>

Concerning foci of involvement, HL is a nodal disease with spleen also being considered nodal but it can affect lung, bone, bone marrow, and rarely liver. Involvement may be on one or both sides of the diaphragm. NHL on the other hand, is a more disseminated disease, which can involve nodes but more commonly involves organs and can be seen in CNS and gastrointestinal (GI) tract. Mediastinal masses can be large in both HL and NHL. CNS and bone involvement are much more common in NHL and because of this, F18-fluorodeoxyglucose (F18-FDG)-positron emission tomography (PET)/computed tomography (CT) or PET/magnetic resonance imaging (MRI) should include head-to-toe assessment.<sup>3</sup>

Cellular histologies differ in the two types of lymphoma. The characteristic cell of HL is the Reed Sternberg cell, a binucleated or multinucleated neoplastic cell. It is classified into two main types: classic HL (CHL) and nodular lymphocyte predominant HL. CHL is subdivided into four subtypes: nodular sclerosing (more common in adolescents), mixed cellularity (more common in younger children), lymphocyte depleted and lymphocyte rich. There are multiple histologies included in NHL, many of which are seen in adults only. Almost all NHL that occurs in children is high grade, with the most common types being: aggressive B cell or Burkitt's, lymphoblastic, and anaplastic large cell.<sup>2,4</sup>

Presentations differ. Children with HL usually present with painless adenopathy. Staging is based on the Ann Arbor staging system.<sup>3,5,6</sup> As part of the Cotswold amendment to the Ann Arbor staging system, E-lesions or extralymphatic structures contiguous with sites of lymph node involvement were included in the classification system.<sup>7</sup> Prognosis is based on stage plus other factors such as symptoms where a designation of "A" indicates no symptoms and "B" indicates the presence of unexplained fever of the past month, >10% weight loss over 6 months, or drenching night sweats over the past month. Other factors include bulk disease, albumin <3.4, +EBV (Epstein-Barr virus) titer, elevated sedimentation rate, or pleural<sup>8</sup> and/or pericardial effusion.<sup>9</sup> Bulk disease is defined as a mediastinal mass where its maximum transverse diameter on a posterior anterior (PA) chest radiograph is more than one-third of the maximum diameter of the thorax at the level of the diaphragm or a continuous nodal aggregate outside the mediastinum >6 cm in diameter in children (some studies including AYA may utilize >10 cm diameter). One study from the Children's Oncology Group (COG) developed a prognostic scoring system based on findings from earlier protocols indicating that stage 4 disease, large mediastinal mass, albumin <3.5, and fever were independent predictors of event-free survival (EFS).<sup>10</sup> In addition for HL, various collaborative groups have established a SEARCH (Staging, Evaluation and Response Criteria Harmonization) committee for Childhood, Adolescent, and Young Adult Hodgkin Lymphoma (CAYAHL) in order to establish improved international harmonization in this disease with respect to diagnosis and treatment.<sup>6</sup>

Symptoms of NHL vary by subtype, but overall in children there is a predominance of high-grade disease with more extranodal involvement at the time of presentation. Thus, it is often more aggressive and more diffuse than HL when detected.<sup>11</sup> Staging is according to the revised 2015 International Pediatric Non-Hodgkin Lymphoma Staging

**TABLE 1** Ann Arbor staging with Cotswold modification for Hodgkin lymphoma<sup>6</sup>

<b>Stage I</b>	Involvement of a single lymph node region (I) or a single extralymphatic organ or site (IE)
<b>Stage II</b>	Involvement of $\geq 2$ lymph node regions on the same side of the diaphragm (II) or localized extension to extralymphatic organ or site and $\geq 1$ lymph node regions on the same side of the diaphragm (IIE)
<b>Stage III</b>	Involvement of lymph node regions on both sides of the diaphragm (III), which may be accompanied by localized extension to extralymphatic organ or site (IIIE) or by involvement of spleen (IIIS), or both (IIISE)
<b>Stage IV</b>	Diffuse or disseminated involvement of $\geq 1$ extralymphatic organs or tissues (e.g., bone, bone marrow, liver, lungs) with or without associated lymph node enlargement

System (IPNHLSS),<sup>12</sup> which replaced the former St. Jude classification by Murphy.<sup>13</sup> More than in HL, patients with NHL have a greater likelihood of being baseline immunocompromised or have had a prior different malignancy.<sup>14</sup> A complication occasionally seen in NHL is the tumor lysis syndrome caused by a large burden of disease, resulting in the breakdown of malignant cells and producing kidney injury, cardiac arrhythmias, seizures, and even death. Imaging in this circumstance is based on the clinical picture and areas involved.

Treatment with chemotherapy for both HL and NHL are now "response based," that is, further chemotherapy is tailored based on degree of early response to chemotherapy. Long-term survival in HL is currently >90%<sup>5</sup> in most reports, whereas NHL overall is >80%, but this varies considerably depending on the specific histology.<sup>2</sup> Radiation is utilized in HL "on a more targeted basis/approach" as more focally than previously in order to minimize late effects.<sup>15</sup>

F18-FDG PET imaging with CT or MR has become a mainstay of metabolic imaging in HL, both for diagnosis and response assessment with good reliability.<sup>16-18</sup> F18-FDG PET with either CT or MR are interchangeable in the remainder of this paper (F18-FDG PET/CT or F18-FDG PET/MR). The 5-point scale (5-PS), formerly Deauville scale, for evaluating PET response had been validated in adults and subsequently extended to the pediatric age range.<sup>19</sup> The 2014 Lugano adult lymphoma criteria are a combination of both anatomic and metabolic FDG PET 5-PS for lymphoma.<sup>17,18</sup> For those with NHL that are FDG PET avid at presentation, F18-FDG PET is reliable, although some early studies suggested high incidence of a false-positive or false-negative rate in follow-up.<sup>2,3,20</sup>

## 2 | STAGING SYSTEMS

Table 1 shows detail of the Ann Arbor staging system for HL.<sup>6</sup> The staging is largely based on extent of disease and nodal stations involved, highlighting that the more widespread nodal and subsequently extranodal involvement (extra-nodal or "E" disease in HL has no impact

**TABLE 2** International Pediatric Non-Hodgkin Lymphoma Staging System (IPNHLSS) for non-Hodgkin lymphoma<sup>11,12</sup>

<b>Stage I</b>	Single nodal or extranodal site (exclude thorax and abdomen)
<b>Stage II</b>	Single extranodal site with regional node involvement; $\geq 2$ nodal sites on the same side of diaphragm  A primary localized gastrointestinal tumor ( $\pm$ mesenteric nodes)
<b>Stage III</b>	$\geq 2$ Extranodal sites irrespective of anatomical relation to diaphragm  $\geq 2$ Nodal sites on both sides of the diaphragm; primary intrathoracic tumors (mediastinum, pleura, thymus, hilar, pulmonary); primary extensive intra-abdominal disease (malignant ascites and extension to adjacent organs such as liver, spleen, kidney, ovary) or Para-spinal or epidural tumors (irrespective of other sites of disease)
<b>Stage IV</b>	Any of the above sites with central nervous system and/or bone marrow disease

on stage; involvement of solid organs does), the higher the stage of disease. Of note, splenic involvement is not classified as extra-nodal. Similarly, the revised IPNHLSS<sup>11,12</sup> for NHL emphasizes extent of nodal/extra-nodal involvement with advanced stage in the case of CNS or bone marrow disease (see Table 2).

The Ann Arbor staging system with Cotswold modification is recommended for staging pediatric HL (Grade A; standard of recommendation [SOR] 1.09).

The IPNHLSS is recommended for staging pediatric NHL (Grade A; SOR 1.18).

a. Role of imaging in staging and validation of survival outcomes.

**Hodgkin lymphoma:** Imaging is the major component of staging in determining whether disease is present on one or both sides of the diaphragm, whether organs in addition to nodes are involved, and contributes to risk assessment and thus therapy regimen.

**Non-Hodgkin lymphoma:** Imaging is crucial from head to toe because of the common occurrence of disease throughout the body including CNS and bones in addition to nodes.

b. Validation of imaging in survival outcome: Once the diagnosis of lymphoma is made by biopsy, imaging plays a crucial role in the initial staging, assessment of treatment response, and surveillance for relapse.<sup>3,8,17,18,21,22</sup>

**Hodgkin lymphoma:** Therapy is governed by stage, but other confounding factors such as bulk, the presence or absence of clinical symptoms, and inflammatory markers may impact management. Over the past decade, 5-year survival rates after chemotherapy or combined with RT have achieved response  $>98\%$ .<sup>22</sup>

**Non-Hodgkin lymphoma:** The staging system was revised in 2015 to account for new findings of organ involvement and advances in imaging

techniques.<sup>11,12</sup> Survival depends on cell type as well as staging, with cure rates ranging from 65% to  $>90\%$ .<sup>2</sup>

### 3 | ADVANTAGES/DISADVANTAGES OF EACH MODALITY

a. Chest radiograph PA and lateral upright: For both HL and NHL, this is primarily a screening modality to evaluate for the presence of large mediastinal adenopathy and possible airway compromise as a result. *It is recommended to perform a PA and lateral upright chest radiograph as a baseline screening procedure in all patients at diagnosis to assess for mediastinal adenopathy, assess the airway, and evaluate for lung involvement* (Grade: A; SOR 1.82) (Table 3).

Advantages: easily accessible, can detect airway compromise.

Disadvantages: involves some radiation; may not be able to ascertain small lung nodules; less accurate than CT for determining bulk disease.<sup>23</sup>

b. CT scan: This is often the initial exam performed at the primary institution for both HL and NHL. This should include neck, chest, abdomen, and pelvis and should be performed with intravenous (IV) contrast. Oral contrast should be included at least on the initial study; this is more important in NHL where there may be GI involvement. CT of the chest with lung windows must be included to evaluate for lung metastases. The ALARA (as low as reasonably achievable) principle to minimize radiation exposure should be followed. Capability of performing coronal and sagittal reformatted images must be available.

Splenomegaly alone is not indicative of disease; there must be CT, MRI, or ultrasound focal abnormalities with correlation on FDG PET.<sup>3,22</sup>

Advantages: easily accessible, short scan time, more accurately demonstrates mediastinal bulk and its effects on airway.

Disadvantages: involves radiation, limited evaluation of bone marrow involvement, CNS involvement may not be optimally evaluated in NHL.

*A diagnostic dose-optimized CT is recommended as a primary imaging modality for initial staging to detect pulmonary metastases and evaluate lymphadenopathy (with iodinated IV contrast) in accordance with institutional practice and ALARA/Image Gently guidelines* (Grade: A; SOR: 1.18).

c. F18-FDG PET (CT or MR): It is essential in the imaging evaluation of both HL and NHL.

*The current recommendation is for all patients with lymphoma to undergo an F18-FDG PET as the primary imaging modality for diagnosis and initial staging, and follow-up for interim and end-of-therapy assessment of treatment response* (Grade A; SOR 1.10).

**TABLE 3** Modalities for lymphoma advantages and disadvantages

Procedure name	Time point(s)	Advantages(s)	Disadvantage(s)
Ultrasound	Diagnosis	No radiation	Cannot stage disease
Chest radiographs	Diagnosis	Determining bulky mediastinal disease	Cannot stage disease
Computed tomography (CT)	Diagnosis End-of-therapy surveillance	Rapid and detailed exam	Radiation
Magnetic resonance imaging (MRI)	Diagnosis Follow-up	No radiation High-quality anatomic information	May need sedation Whole-body imaging is limited due to lengthy examination times Limited detectability of small lung lesions Tendency to underestimate disease response
F18-fluorodeoxyglucose (F18-FDG)-positron emission tomography (PET)	Diagnosis Follow-up End of therapy	Superior lesion detection over conventional imaging Helps predict lesion response and identify those who would benefit from therapy intensification, and improve cure rate of HL patients who need radiation therapy	Radiation Management of pediatric non-Hodgkin lymphoma is less affected by additional F18-FDG PET findings as most cases are advanced stage at presentation and typically treated with intensive chemotherapy without radiotherapy
FDG PET/MRI	Diagnosis Follow-up End of therapy	Equivalent diagnostic performance as PET/CT	Prolonged scan time and limited availability of PET/MRI

Note: References for procedure guidelines from the various societies.<sup>58</sup>

However, F18-FDG PET should not be routinely utilized for follow-up surveillance imaging for relapse in case of NHL given the high false-positive rate of F18-FDG PET, unless prompted by clinical indications, especially where the tumor was not FDG-avid on the initial baseline exam (Grade B; SOR 1.64).

PET/CT with dose-optimized attenuation correction (AC) CT is typically performed. If performed without IV contrast, a separate diagnostic CT with contrast needs to be performed to evaluate lung or other extranodal involvement. A single PET/CT exam with IV contrast can also be performed. The use of IV contrast CT for AC of the PET does not significantly affect SUV quantification.<sup>24</sup> F18-FDG PET can be complementary to bone marrow biopsy in detection of marrow involvement, where three FDG PET positive foci in bone without CT change are usually considered consistent with bone marrow involvement.<sup>21,25–28</sup>

It is recommended to perform F18-FDG PET with a dose-optimized CT scan on an integrated PET/CT scanner for the purpose of attenuation correction and usually performed without IV contrast. Use of IV contrast in follow-up studies may preclude the need for a separate contrast-enhanced CT<sup>29</sup> (Grade A; SOR 1.36).

Advantages: excellent correlation with foci of disease in both HL and NHL if NHL is FDG PET avid, if performed with IV contrast, a separate CT could be avoided.

Disadvantages: involves radiation exposure, low-dose CT may miss small lung metastases, some forms of NHL are not PET avid, and in this circumstance this would not be an adequate modality particularly for follow-up to determine response.<sup>11</sup>

d. F18-FDG PET/MRI: Currently, this modality is available only at a limited number of institutions, although accessibility may increase in the future. F18-FDG PET/MRI is recommended as an alternative imaging modality to PET/CT for tumor diagnosis where PET/MR is currently utilized and has demonstrated similar efficacy to PET/CT<sup>30</sup> (Grade: A; SOR 1.45). With high soft tissue contrast, it may be more valuable in NHL with extranodal involvement; large amounts of data evaluating the role in staging are lacking, but one early study is encouraging.<sup>31</sup>

Advantages: less radiation than PET/CT, excellent soft tissue differentiation.

Disadvantages: not universally available, long exam time, especially in young children who may require sedation, limited evaluation of lung disease if lesions are small and not FDG-avid.<sup>32</sup>

e. MRI: This can be used as an adjunct to other imaging modalities that do not optimally demonstrate the pathology; for example, bone, spleen, or CNS lesion that may be F18-FDG PET avid but not well seen on CT at presentation.<sup>12,17</sup> The thymus is treated like a nodal station, and any focal thymic FDG activity requires CT-MR correlate.<sup>33</sup>

f. Total body MRI: It has been utilized in limited series, but is not widely used.<sup>34–36</sup>

Advantages: no radiation, excellent tissue differentiation.

Disadvantages: long exam time, limited in evaluation of treatment response.

**TABLE 4** Lymphoma PET/CT protocol

Study name	Patient prep (NPO guidelines, warning, etc.)	Radiopharmaceutical	Dose range	Delivery	Time from dose to imaging (uptake time)	Imaging acquisition	Comment
<sup>18</sup> F-FDG PET	Minimum fasting interval of 4–6 hours prior to radiopharmaceutical injection to prevent excessive muscle uptake Measures to limit physiologic brown fat activation can be employed (see guidelines) <sup>a</sup>	<sup>18</sup> F-FDG (fluorodeoxyglucose)	0.10–0.14 mCi/kg Minimum dose: 0.7 mCi	Intravenous	60 minutes	PET/CT: CT for attenuation correction and anatomic localization Emission PET AC and NAC images PET/MRI: MRI – whole-body Dixon 2-point VIBE, axial T2-weighted HASTE for AC and anatomic localization of the PET findings Emission PET AC and NAC images	For diabetic patients, see references for recommended patient preparation If blood glucose >200 mg/dl, reference guidelines

Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging; PET, positron emission tomography.

<sup>a</sup>References for procedure guidelines.<sup>37,38,58</sup>

## 4 | IMAGING AT DIAGNOSIS AND INITIAL STAGING

The imaging for HL and NHL is essentially the same.

1. PA and lateral upright chest radiograph in all patients at diagnosis to assess for mediastinal adenopathy, assess the airway, and evaluate for lung involvement.
2. Contrast-enhanced CT of neck, chest, abdomen, and pelvis. If F18-FDG PET/CT is performed with IV contrast (which varies by institutional practice), a diagnostic chest CT is needed to exclude lung metastases (see below).
3. F18-FDG PET that in NHL needs to include total body to the distal lower legs.
4. MRI as needed to verify CNS involvement or to evaluate indeterminate foci.

### 4.1 | Imaging parameters

CT: Imaging should be performed with iodinated IV and oral contrast using age- and weight-based adjustments to kVp and mA, in accordance with institutional practice and ALARA/Image Gently guidelines. In patients with tumor lysis syndrome, evaluate the risk versus benefit of the IV contrast.

F18-FDG PET: Nearly all PET/CT scanners in use today are integrated/hybrid PET/CT scanners. Generally, a low-dose CT scan is performed on integrated PET/CT scanners for the purpose of attenuation correction and usually performed without IV contrast. Typically, this CT is of nondiagnostic quality and is not acceptable for staging or response assessment or for RT planning.<sup>37,38</sup> PET/CT may be performed with full diagnostic quality CT scan (with IV contrast and

appropriate CT parameters) and allow for single session imaging for FDG PET and CT scan. Such combined dedicated F18-FDG PET and CT imaging is preferred for patient convenience. PET/CT studies are generally always acquired from the vertex to the proximal thighs or can extend to the feet if required. Posttherapy F18-FDG PET scans should be performed with the same parameters as the pretherapy baseline scans, especially keeping the scanning parameters such as uptake time similar to avoid large differences in SUV due to uptake time difference. Liver and blood pool background mean and maximum activities must be noted and included in the report. Table 4 details a proposed lymphoma PET/CT imaging protocol.

MRI: May be used as an alternative modality after completion of treatment during the follow-up phase only, provided the institution is able to acquire images using phased array surface coils, cardiac gating, and respiratory triggering, in order to minimize artifacts from cardiac motion, diaphragmatic motion, and bowel peristalsis. MRI can also be used to evaluate the bone marrow and soft tissue involvement at the time of the initial staging. Table 5 details proposed lymphoma CXR, CT, and MRI imaging protocols, and Table 6 details a suggested whole-body MRI protocol for initial evaluation.

## 5 | IMAGING AT INTERIM AND END-OF-THERAPY FOLLOW-UP

Exams and timing may be regulated by protocol requirements if patient is enrolled in a clinical trial or treated in the same fashion as prior clinical trial.

1. F18-FDG PET is essential after an indicated number of cycles of chemotherapy. Early PET response in HL suggests improved



**TABLE 5** Lymphoma CXR, CT, and MRI protocols

Study name	Contrast	Coverage	Time from dose to imaging (uptake time)	Parameters	Comment
Computed tomography (CT)	IV	Neck, chest, abdomen, and pelvis	55–60 seconds after injection	IV contrast is required but only a single standard portal venous phase is needed, 60 seconds after injection	Evaluate chest on lung windows for nodules/lesions Evaluate lesion(s) on portal-venous phase, and examine abdomen/pelvis Chest, abdomen and pelvis can be performed in one breath hold on newer generation (faster) scanners with high-pitch capability
Magnetic resonance imaging (MRI)	IV gadolinium contrast is preferred, but not necessary for MRI	Neck, chest, abdomen, and pelvis	n/a	Specify sequences for MR (see below)	
Chest radiograph (CXR)	None	Chest	n/a	2 view PA and lateral CXR	Assess for mediastinal bulk

**TABLE 6** Suggested whole-body MRI protocol for initial evaluation

Plane	Sequence	Contrast phase	Coverage	Required/optional	Comment
<i>Pre-contrast imaging</i>					
Axial and coronal	T1	Pre-contrast	<sup>a</sup> H,N,C,A,P	Required	
Axial and coronal	FSE T2	Pre-contrast	<sup>a</sup> H,N,C,A,P	Required	TSE or FSE sequence; usually without fat suppression
Axial	Dixon 2-point VIBE	Pre-contrast	<sup>a</sup> H,N,C,A,P	Required	For AC
<i>Dynamic contrast-enhanced imaging can be performed of a specific region if clinically relevant (e.g., brain, chest, abdomen or pelvis, extremities)</i> <i>If MRI is used for imaging of the thorax, abdomen, and/or pelvis, an unenhanced computed tomography of the chest should still be obtained to evaluate the lungs</i>					3D volumetric GRE sequence Gadobenate dimeglumine contrast agent recommended
Multiplanar	T1 fat suppressed	Post-gadolinium Portal venous	<sup>a</sup> Specify region? Neck, chest, abdomen or pelvis	Optional	45–60 seconds after injection

Abbreviations: FSE, fast spin echo; MRI, magnetic resonance imaging; TSE, turbo spin echo; VIBE, volumetric breath-hold interpolated.

<sup>a</sup>Coverage field of view = skull vertex to proximal thighs or feet.

- prognosis.<sup>3,39</sup> CT or MRI may be needed if a change in size of masses is required (e.g., as part of a clinical trial).
2. F18-FDG PET is indicated at end of therapy unless interval PET is negative, in which case it may not need to be repeated. CT scan is usually required at end of therapy, particularly if radiation is planned.
  3. One complication seen in NHL is tumor lysis syndrome caused by breakdown of malignant cells, which can cause renal injury, cardiac arrhythmias, seizures, and even death. This may require CT or

renal ultrasound to evaluate for tissue damage. Otherwise in NHL, follow-up is often only CT or MRI unless the original masses were FDG-avid. If distal bone lesions were not present at the time of the initial PET scan, imaging can stop at mid-thigh at follow-up. If a patient is being treated with steroids, tumor uptake by FDG PET/CT may be blocked resulting in a false negative.<sup>40</sup>

If disease is localized to one area on pretherapy (baseline) study exams, follow-up could require coverage of only the affected areas

seen at baseline to limit radiation on CT. For NHL, if there are no bone lesions that are PET positive below the hips, follow-up need only go to the mid-thigh region. *F18-FDG PET of the whole body from the vertex to the toes in NHL and in HL is recommended at staging, diagnosis, response assessment, and end-of-therapy time points*<sup>16,20,41</sup> (Grade: B; SOR 1.91).

## 6 | CRITERIA FOR TUMOR RESPONSE ASSESSMENT

- a. *Hodgkin lymphoma*: F18-FDG PET is currently the modality of choice for response. F18-FDG PET imaging has become a mainstay of metabolic imaging in HL, both for diagnosis and response assessment with good reliability, and provides oncologists information regarding extent of disease involvement and can provide prognostic information. The 5-PS, formerly Deauville Score but updated in Lugano,<sup>17</sup> is utilized with the metabolic assessment criteria of complete response varying among protocols as to whether it is 5-PS2, which is less than or equal to mediastinal blood pool, or 5-PS3, which is greater than blood pool but less than or equal to liver. *The 5-PS scoring system is recommended for evaluating metabolic activity at staging and PET response assessment, and has been validated in adults and subsequently extended to the pediatric age range. Imaging response is now based on F18-FDG PET response rather than decrease in size of nodes or mass. 5-PS score at end of therapy may dictate radiation planning in HL*<sup>17,42</sup> (Grade A; SOR 1.09).
- b. *Non-Hodgkin lymphoma*: If the tumor burden was PET-avid at presentation, response can be evaluated by FDG PET/CT. If it was not F18-FDG-avid initially, CT scans would be necessary to follow regression of tumor masses.<sup>11,12</sup>

## 7 | IMAGING OFF THERAPY/SURVEILLANCE FOLLOW-UP<sup>43</sup>

- a. *Hodgkin lymphoma*: Surveillance tends to be clinical at 6 and 12 months, but CT and MRI may be obtained by some at those time points. Most oncologists only perform clinical follow-up in the second year. NCCN guidelines suggest follow-up at 3–4-month intervals for the first 2 years, with subsequent follow-up being clinical and related to long-term effects. FDG PET/CT imaging is usually performed only if there is a change in CT or a new finding by other imaging.
- b. *Non-Hodgkin lymphoma*: Similarly, follow-up by CT or MRI depending on initial sites of involvement at 6-month intervals for 2 years, with subsequent clinical follow-up.

For follow-up F18-FDG PET for both HL and NHL, Cheson et al. in their Lugano Classification Paper<sup>17</sup> stated “published studies fail to support routine surveillance scans, and they are discouraged. The false-positive rate with F18-FDG PET scans is greater than 20%, leading to unnecessary investigations, radiation exposure, biopsies, expense,

and patient anxiety. Follow-up scans should be prompted by clinical indications.”<sup>44–46</sup>

## 8 | ADVANCEMENTS IN IMAGING

Research efforts are focusing on increasing use of F18-FDG PET-based quantitative standardized uptake value (SUV) and tumor burden parameters such as metabolic tumor volume (MTV) and total lesion glycolysis (TLG) for prognosis and risk-adaptation,<sup>47,48</sup> although future prospective studies using homogeneous clinical datasets with standardized and automated methodologies are needed for further validation and wide-scale utilization. Baseline assessment of MTV has been shown to be predictive of EFS for intermediate-risk pediatric HL and an independent predictor of PFS in pediatric HL.<sup>49,50</sup> In pediatric NHL, baseline MTV may be an independent predictor of disease-free survival (DFS) in pediatric anaplastic large cell lymphoma,<sup>51</sup> and baseline MTV and TLG have been shown to be predictive of progression free survival (PFS) overall survival (OS) in pediatric mature B-cell NHL<sup>52</sup> and Burkitt's lymphoma.<sup>53</sup> Quantitative SUV-based PET (qPET) has been developed as a surrogate of the visual 5-PS to improve the reproducibility of F18-FDG PET response assessment,<sup>54</sup> which has been utilized by European collaborative pediatric and adult groups.<sup>55,56</sup> Immunotherapy-based therapies can trigger an immune-mediated inflammatory response to therapy, resulting in a potential tumor flare phenomenon with resultant increased FDG activity and/or pseudo-progression with objective increase in anatomic tumor complicating response assessments. The lymphoma response to immunomodulatory therapy criteria (LYRIC) has been developed as an adaptation of the LUGANO criteria for assessing treatment response in lymphoma incorporating an “indeterminate response” classification requiring confirmation of these lesions by biopsy or follow-up imaging within 12 weeks.<sup>57</sup>

## ACKNOWLEDGMENTS

This study was funded in part by the National Clinical Trials Network Operations Center Grant U10CA180886. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

## CONFLICT OF INTEREST

None of the authors have any relevant financial conflicts of interest to disclose. Helen Ruth Nadel discloses that she is on the Board of Directors at Society of Nuclear Medicine and Molecular Imaging (SNMMI), but has no relevant financial conflict of interest in the subject matter discussed.

## ORCID

Joyce Mhlanga  <https://orcid.org/0000-0002-6136-265X>

Adina Alazraki  <https://orcid.org/0000-0003-1094-282X>

Steve Y Cho  <https://orcid.org/0000-0003-2724-7778>

Hollie Lai  <https://orcid.org/0000-0001-6747-7338>

Helen Nadel  <https://orcid.org/0000-0003-0236-7298>

Neeta Pandit-Taskar  <https://orcid.org/0000-0003-1551-2036>

Jing Qi  <https://orcid.org/0000-0003-1027-6687>

Dhanashree Rajderkar  <https://orcid.org/0000-0002-5962-2854>

Stephan Voss  <https://orcid.org/0000-0002-2092-2219>

Pankaj Watal  <https://orcid.org/0000-0002-2570-2602>

## REFERENCES

1. Cancer stats: major cancer sites overview - NCCR statistical report. NIH, NCI Childhood Cancer Data Initiative (CCDI). Accessed January 17, 2022. <https://seer.cancer.gov/statistics/nccr/major.html>
2. Allen CE, Kelly KM, Bollard CM. Pediatric lymphomas and histiocytic disorders of childhood. *Pediatr Clin North Am*. 2015;62(1):139-165.
3. McCarten KM, Nadel HR, Shulkin BL, Cho SY. Imaging for diagnosis, staging and response assessment of Hodgkin lymphoma and non-Hodgkin lymphoma. *Pediatr Radiol*. 2019;49(11):1545-1564.
4. Sandlund JT, Downing JR, Crist WM. Non-Hodgkin's lymphoma in childhood. *N Engl J Med*. 1996;334(19):1238-1248.
5. Kelly KM, Hodgson D, Appel B, et al. Children's Oncology Group's 2013 blueprint for research: Hodgkin lymphoma. *Pediatr Blood Cancer*. 2013;60(6):972-978.
6. 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.
7. Connors JM, Klimo P. Is it an E lesion or stage IV? An unsettled issue in Hodgkin's disease staging. *J Clin Oncol*. 1984;2(12):1421-1423.
8. McCarten KM, Metzger ML, Drachtman RA, et al. Significance of pleural effusion at diagnosis in pediatric Hodgkin lymphoma: a report from Children's Oncology Group protocol AHOD0031. *Pediatr Radiol*. 2018;48(12):1736-1744.
9. Marks LJ, McCarten KM, Pei Q, Friedman DL, Schwartz CL, Kelly KM. Pericardial effusion in Hodgkin lymphoma: a report from the Children's Oncology Group AHOD0031 protocol. *Blood*. 2018;132(11):1208-1211.
10. Schwartz CL, Chen Lu, McCarten K, et al. Childhood Hodgkin International Prognostic Score (CHIPIS) predicts event-free survival in Hodgkin lymphoma: a report from the Children's Oncology Group. *Pediatr Blood Cancer*. 2017;64(4):e26278.
11. Sandlund JT, Guillerman RP, Perkins SL, et al. International pediatric non-Hodgkin lymphoma response criteria. *J Clin Oncol*. 2015;33(18):2106-2111.
12. Rosolen A, Perkins SL, Pinkerton CR, et al. Revised international pediatric non-Hodgkin lymphoma staging system. *J Clin Oncol*. 2015;33(18):2112-2118.
13. Murphy SB. Classification, staging and end results of treatment of childhood non-Hodgkin's lymphomas: dissimilarities from lymphomas in adults. *Semin Oncol*. 1980;7(3):332-339.
14. Conde L, Bracci PM, Halperin E, Skibola CF. A search for overlapping genetic susceptibility loci between non-Hodgkin lymphoma and autoimmune diseases. *Genomics*. 2011;98(1):9-14.
15. Friedman DL, Chen L, Wolden S, et al. Dose-intensive response-based chemotherapy and radiation therapy for children and adolescents with newly diagnosed intermediate-risk Hodgkin lymphoma: a report from the Children's Oncology Group study AHOD0031. *J Clin Oncol*. 2014;32(32):3651-3658.
16. Cerci JJ, Etchebehere EC, Nadel H, et al. Is true whole-body (18)F-FDG PET/CT required in pediatric lymphoma? An IAEA multicenter prospective study. *J Nucl Med*. 2019;60(8):1087-1093.
17. 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):3059-3067.
18. Barrington SF, Mikhael 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.
19. Hutchings M, Loft A, Hansen M, et al. FDG PET after two cycles of chemotherapy predicts treatment failure and progression-free survival in Hodgkin lymphoma. *Blood*. 2006;107(1):52-59.
20. Ingley KM, Nadel HR, Potts JE, Wilson DC, Eftekhari A, Deyell RJ. The Utility of PET/CT in guiding radiotherapy reduction for children with Hodgkin lymphoma treated with ABVD. *J Pediatr Hematol Oncol*. 2020;42(2):e87-e93.
21. Badr S, Kotb M, Elahmadawy MA, Moustafa H. Predictive value of FDG PET/CT versus bone marrow biopsy in pediatric lymphoma. *Clin Nucl Med*. 2018;43(12):e428-e438.
22. Flerlage JE, Kelly KM, Beishuizen A, et al. Staging Evaluation and Response Criteria Harmonization (SEARCH) for Childhood, Adolescent and Young Adult Hodgkin Lymphoma (CAYAH): methodology statement. *Pediatr Blood Cancer*. 2017;64(7):e26421.
23. Bradley AJ, Carrington BM, Lawrance JAL, Ryder WDJ, Radford JA. Assessment and significance of mediastinal bulk in Hodgkin's disease: comparison between computed tomography and chest radiography. *J Clin Oncol*. 1999;17(8):2493-2498.
24. Yau Y-Y, Chan W-S, Tam Y-M, et al. Application of intravenous contrast in PET/CT: does it really introduce significant attenuation correction error? *J Nucl Med*. 2005;46(2):283-291.
25. Adams HJA, Kwee TC, De Keizer B, et al. Systematic review and meta-analysis on the diagnostic performance of FDG PET/CT in detecting bone marrow involvement in newly diagnosed Hodgkin lymphoma: is bone marrow biopsy still necessary? *Ann Oncol*. 2014;25(5):921-927.
26. Purz S, Mauz-Körholz C, Körholz D, et al. [18F]Fluorodeoxyglucose positron emission tomography for detection of bone marrow involvement in children and adolescents with Hodgkin's lymphoma. *J Clin Oncol*. 2011;29(26):3523-3528.
27. Salaun PY, Gastinne T, Bodet-Milin C, et al. Analysis of 18F-FDG PET diffuse bone marrow uptake and splenic uptake in staging of Hodgkin's lymphoma: a reflection of disease infiltration or just inflammation? *Eur J Nucl Med Mol Imaging*. 2009;36(11):1813-1821.
28. Cheng G, Chen W, Chamroonrat W, Torigian DA, Zhuang H, Alavi A. Biopsy versus FDG PET/CT in the initial evaluation of bone marrow involvement in pediatric lymphoma patients. *Eur J Nucl Med Mol Imaging*. 2011;38(8):1469-1476.
29. Pfannenberger AC, Aschoff P, Brechtel K, et al. Value of contrast-enhanced multiphase CT in combined PET/CT protocols for oncological imaging. *Br J Radiol*. 2007;80(954):437-445.
30. Schäfer JF, Gatidis S, Schmidt H, et al. Simultaneous whole-body PET/MR imaging in comparison to PET/CT in pediatric oncology: initial results. *Radiology*. 2014;273(1):220-231.
31. Kurch L, Kluge R, Sabri O, et al. Whole-body [(18)F]-FDG PET/MRI for staging of pediatric non-Hodgkin lymphoma: first results from a single-center evaluation. *EJNMMI Res*. 2021;11(1):62.
32. Chandarana H, Heacock L, Rakheja R, et al. Pulmonary nodules in patients with primary malignancy: comparison of hybrid PET/MR and PET/CT imaging. *Radiology*. 2013;268(3):874-881.
33. Jerushalmi J, Frenkel A, Bar-Shalom R, Khoury J, Israel O. Physiologic thymic uptake of 18F-FDG in children and young adults: a PET/CT evaluation of incidence, patterns, and relationship to treatment. *J Nucl Med*. 2009;50(6):849-853.
34. Regacini R, Puchnick A, Luisi FAV, Lederman HM. Can diffusion-weighted whole-body MRI replace contrast-enhanced CT for initial staging of Hodgkin lymphoma in children and adolescents? *Pediatr Radiol*. 2018;48(5):638-647.
35. Littooij AS, Kwee TC, Barber I, et al. Whole-body MRI for initial staging of paediatric lymphoma: prospective comparison to an FDG PET/CT-based reference standard. *Eur Radiol*. 2014;24(5):1153-1165.



36. Kellenberger C, Miller S, Khan M, Gilday D, Weitzman S, Babyn P. Initial experience with FSE STIR whole-body MR imaging for staging lymphoma in children. *Eur Radiol*. 2004;14(10):1829-1841.
37. Parisi MT, Bermo MS, Alessio AM, Sharp SE, Gelfand MJ, Shulkin BL. Optimization of pediatric PET/CT. *Semin Nucl Med*. 2017;47(3):258-274.
38. Nadel HR, Shulkin B. Pediatric positron emission tomography-computed tomography protocol considerations. *Semin Ultrasound CT MR*. 2008;29(4):271-276.
39. Nadel H, et al. Validation of standardized interpretation criteria for early response evaluation with (18F)FDG PET/CT in pediatric lymphoma - a report on an IAEA multicenter prospective study. In: *European Journal of Nuclear Medicine and Molecular Imaging*. 2018. Springer. <https://link.springer.com/content/pdf/10.1007/s00259-018-4148-3.pdf>
40. Sharp SE, Gelfand MJ, Absalon MJ. Altered FDG uptake patterns in pediatric lymphoblastic lymphoma patients receiving induction chemotherapy that includes very high dose corticosteroids. *Pediatr Radiol*. 2012;42(3):331-336.
41. Spijkers S, Littooi AS, Kwee TC, et al. Whole-body MRI versus an [(18)F]FDG PET/CT-based reference standard for early response assessment and restaging of paediatric Hodgkin's lymphoma: a prospective multicentre study. *Eur Radiol*. 2021;31(12):8925-8936.
42. Flerlage JE, Hiniker SM, Armenian S, et al. Pediatric hodgkin lymphoma, version 3.2021. *J Natl Compr Canc Netw*. 2021;19(6):733-754.
43. Voss SD, Cairo MS. Surveillance imaging in pediatric lymphoma. *Pediatr Radiol*. 2019;49(11):1565-1573.
44. Jerusalem G, Beguin Y, Fassotte MF, et al. Early detection of relapse by whole-body positron emission tomography in the follow-up of patients with Hodgkin's disease. *Ann Oncol*. 2003;14(1):123-130.
45. Liedtke M, Hamlin PA, Moskowitz CH, Zelenetz AD. Surveillance imaging during remission identifies a group of patients with more favorable aggressive NHL at time of relapse: a retrospective analysis of a uniformly-treated patient population. *Ann Oncol*. 2006;17(6):909-913.
46. Luigi Zinzani P, Stefoni V, Tani M, et al. Role of [18F]fluorodeoxyglucose positron emission tomography scan in the follow-up of lymphoma. *J Clin Oncol*. 2009;27(11):1781-1787.
47. Barrington SF, Meignan M. Time to prepare for risk adaptation in lymphoma by standardizing measurement of metabolic tumor burden. *J Nucl Med*. 2019;60(8):1096-1102.
48. Frood R, Burton C, Tsoumpas C, et al. Baseline PET/CT imaging parameters for prediction of treatment outcome in Hodgkin and diffuse large B cell lymphoma: a systematic review. *Eur J Nucl Med Mol Imaging*. 2021;48(10):3198-3220.
49. Milgrom SA, Kim J, Chirindel A, et al. Prognostic value of baseline metabolic tumor volume in children and adolescents with intermediate-risk Hodgkin lymphoma treated with chemo-radiation therapy: FDG PET parameter analysis in a subgroup from COG AHOD0031. *Pediatr Blood Cancer*. 2021;68(9):e29212.
50. Kanoun S, Rossi C, Berriolo-Riedinger A, et al. Baseline metabolic tumour volume is an independent prognostic factor in Hodgkin lymphoma. *Eur J Nucl Med Mol Imaging*. 2014;41(9):1735-1743.
51. Mathew B, Vijayasekharan K, Shah S, et al. Prognostic value of 18F-FDG PET/CT-metabolic parameters at baseline and interim assessment in pediatric anaplastic large cell lymphoma. *Clin Nucl Med*. 2020;45(3):182-186.
52. Chen S, He K, Feng F, et al. Metabolic tumor burden on baseline (18)F-FDG PET/CT improves risk stratification in pediatric patients with mature B-cell lymphoma. *Eur J Nucl Med Mol Imaging*. 2019;46(9):1830-1839.
53. Albano D, Bosio G, Pagani C, et al. Prognostic role of baseline 18F-FDG PET/CT metabolic parameters in Burkitt lymphoma. *Eur J Nucl Med Mol Imaging*. 2019;46(1):87-96.
54. 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.
55. Kluge R, Wittig T, Georgi TW, et al. Comparison of interim PET response to second-line versus first-line treatment in classic Hodgkin lymphoma: contribution to the development of response criteria for relapsed or progressive disease. *J Nucl Med*. 2021;62(3):338-341.
56. Georgi TW, Kurch L, Hasenclever D, et al. Quantitative assessment of interim PET in Hodgkin lymphoma: an evaluation of the qPET method in adult patients in the RAPID trial. *PLoS One*. 2020;15(4):e0231027.
57. Cheson BD, Ansell S, Schwartz L, et al. Refinement of the Lugano Classification lymphoma response criteria in the era of immunomodulatory therapy. *Blood*. 2016;128(21):2489-2496.
58. Vali R, Alessio A, Balza R, et al. SNMMI procedure standard/EANM practice guideline on pediatric (18)F-FDG PET/CT for oncology 1.0. *J Nucl Med*. 2021;62(1):99-110.

**How to cite this article:** Mhlanga J, Alazraki A, Cho S, et al. Imaging recommendations in pediatric lymphoma: A COG Diagnostic Imaging Committee/SPR Oncology Committee White Paper. *Pediatr Blood Cancer*. 2022;e29968. <https://doi.org/10.1002/pbc.29968>