Primary Mediastinal Large B-Cell Lymphoma

Note: Consider Clinical Trials as treatment options for eligible patients.

PATHOLOGIC DIAGNOSIS

ESSENTIAL:

- Hematopathology review of all slides with at least one paraffin block or 15 unstained slides representative of the tumor. Rebiopsy if consult material is nondiagnostic.
- Adequate morphology and immunophenotyping to establish diagnosis[1]
  - Paraffin Panel: CD3, CD20 and/or another pan-B-cell marker (CD19, PAX-5, CD79a) **or**
  - Flow cytometry immunophenotypic studies: CD54 (LCA), CD3, CD5, CD10, CD19, CD20, CD22, kappa and lambda light chains
- Additional immunohistochemical studies to determine subgroup: PD-L1/L2, CD5, CD10, CD15, CD23, CD54, CD79a, BCL-2, BCL-6, MUM-1/IRF4, and MIB1 (Ki67),

OF USE IN CERTAIN CIRCUMSTANCES:

- EBER *in situ* hybridization, LMP-1, HHV-8, CD138, CD30, TdT and ALK1
- FISH studies to detect gene rearrangements; involving: MYC, BCL-2 and/or BCL-6
- Molecular studies to detect clonality of the IgH gene

STRONGLY RECOMMENDED:

- FNA or core biopsy for tissue array/banking by protocol

INITIAL EVALUATION

ESSENTIAL:

- Physical exam: attention to node-bearing areas, including Waldeyer's ring, and to size of liver and spleen
- ECOG performance status
- B symptoms (Unexplained fever >38°C during the previous month; Recurrent drenching night sweats during the previous month; Weight loss >10 percent of body weight ≤ 6 months of diagnosis)
- CBC with differential, LDH, BUN, creatinine, albumin, AST, ALT, total bilirubin, alkaline phosphatase, serum calcium, uric acid
- Beta 2 microglobulin
- Screening for HIV 1 and 2, hepatitis B and C (HBcAb, HBsAg, HCV Ab)
- Chest x-ray, PA and LAT
- CT with contrast of neck, chest, abdomen and pelvis
- Unilateral or bilateral bone marrow biopsy with or without aspirate
- Calculation of IPI[2]
- Muga scan[3] or echocardiogram
- PET/CT
- Discuss fertility issues and sperm banking for patients of child bearing potential
- Lifestyle risk assessment[4]

OF USE IN SELECTED CASES:

- CT or MRI of head
- Pregnancy test
- Consider lumbar puncture and intrathecal chemotherapy if paranasal sinus, testicular, epidural, ≥ 2 extranodal sites, or if IPI[2] score ≥ 3
- Consider thoracentesis if clinically indicated

See Page 2, Induction Therapy

[1] Typical immunophenotype: diffuse positivity for CD20 or another pan B-cell marker
[2] See Appendix A: International Prognostic Index (IPI)
[3] Muga scan may be omitted for young patients receiving limited anthracycline
[4] See Physical Activity, Nutrition, and Tobacco Cessation algorithms; ongoing reassessment of lifestyle risks should be a part of routine clinical practice

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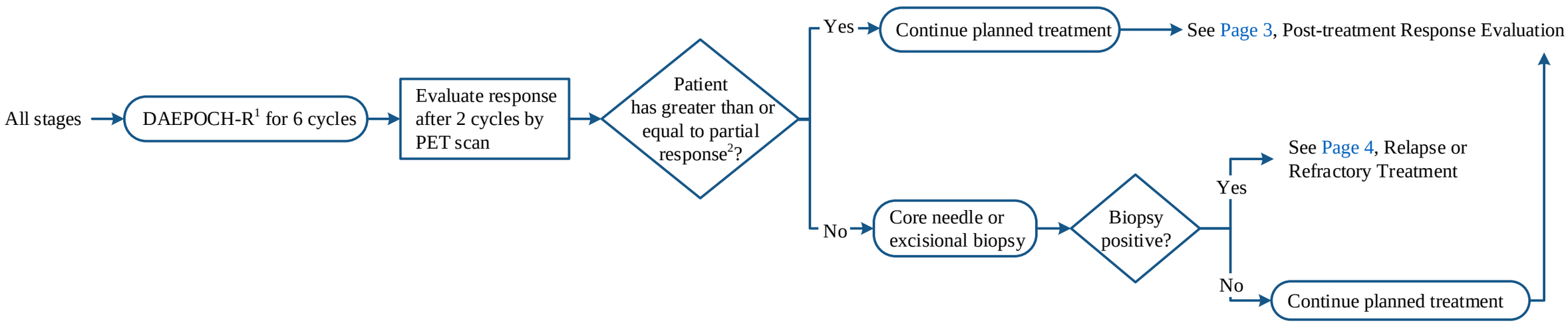
Primary Mediastinal Large B-Cell Lymphoma

Note: Consider Clinical Trials as treatment options for eligible patients.

INDUCTION THERAPY



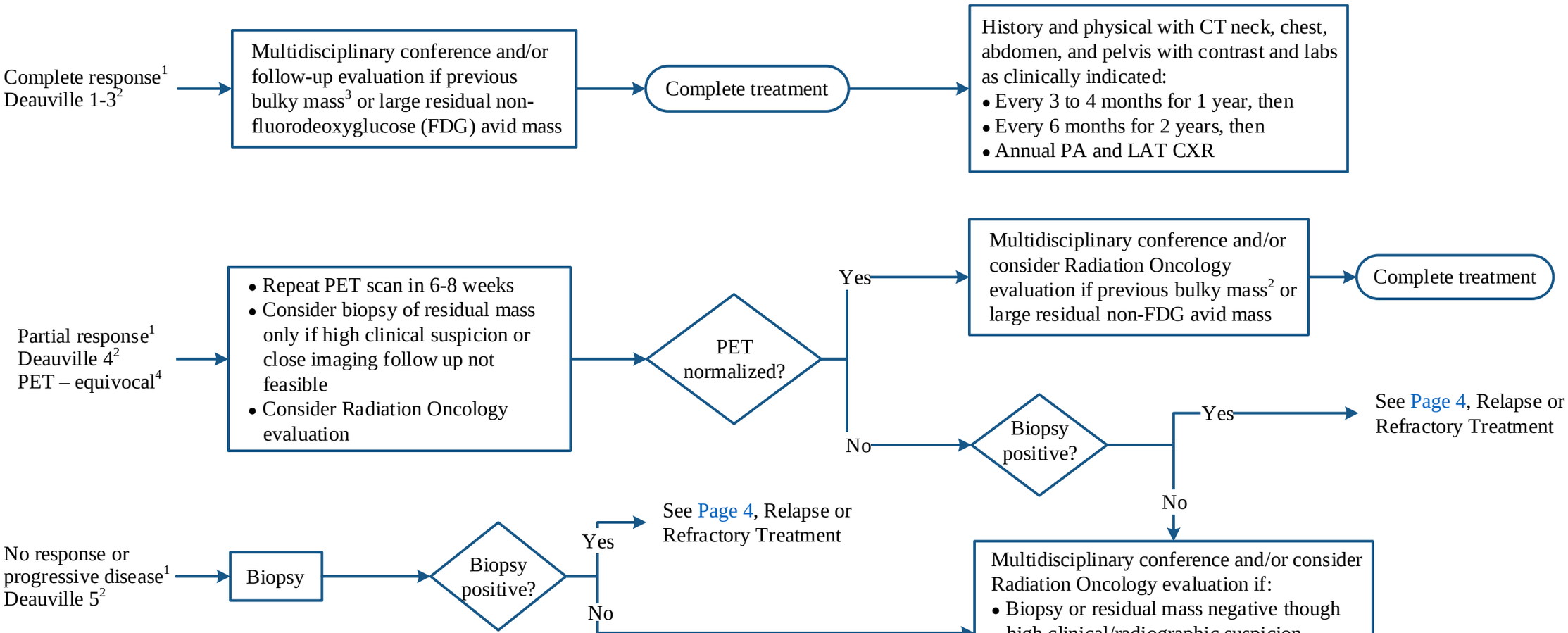
[1] DAEPOCH-R: dose adjusted EPOCH-R: etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin and rituximab (see Appendix B); administration is based on age and performance status of the patient

[2] See Appendix C: Response Criteria for Malignant Lymphoma

Primary Mediastinal Large B-Cell Lymphoma

Note: Consider Clinical Trials as treatment options for eligible patients.

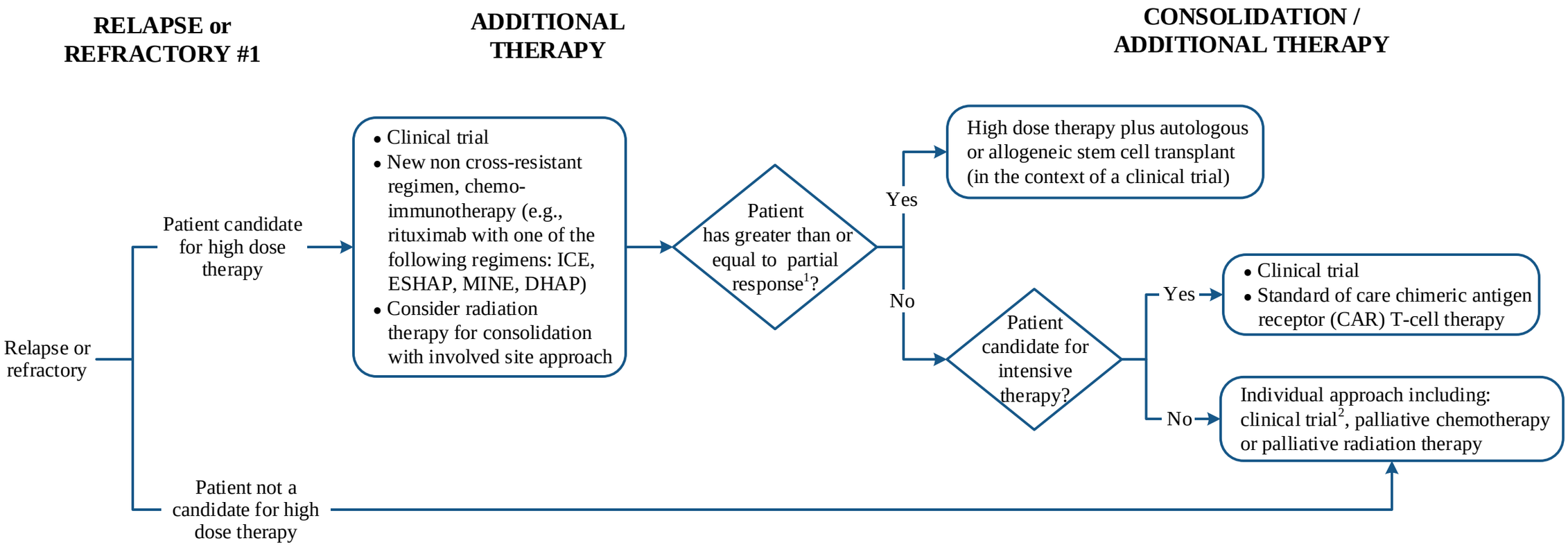
RESPONSE EVALUATION



[1] See Appendix C: Response Criteria for Malignant Lymphoma
[2] See Appendix D: Deauville Criteria
[3] Bulky disease: mass ≥ 7.5 cm on CT imaging
[4] PET equivocal: maximum standardized uptake value (SUV) greater than mediastinal blood pool in the residual mediastinal mass

Primary Mediastinal Large B-Cell Lymphoma

Note: Consider Clinical Trials as treatment options for eligible patients.



ICE = ifosfamide, carboplatin, etoposide
ESHAP = etoposide, methylprednisolone, high-dose cytarabine, cisplatin
MINE = mesna, ifosfamide, mitoxantrone, etoposide
DHAP = dexamethasone, cytarabine, cisplatin

[1] See Appendix B: Response Criteria for Malignant Lymphoma
[2] Clinical trials or individual regimens: except for patients with disease-free interval, those who progress after three successive regimens are unlikely to derive additional benefit from currently utilized combination chemotherapy regimens

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APPENDIX A: International Prognostic Index (IPI)

Pre-Treatment Characteristics, ALL PATIENTS:
- Age > 60 years old
- Serum LDH greater than upper limit of normal
- ECOG performance status 2-4
- Stage III or IV
- Extranodal involvement > 1 site

International Index, ALL PATIENTS:

	Number of characteristics
• Low	0 or 1
• Low intermediate	2
• High intermediate	3
• High	4 or 5

Age-Adjusted IPI

Pre-Treatment Characteristics, ALL PATIENTS ≤ 60 YEARS:
- Serum LDH greater than one times upper limit of normal
- ECOG performance status 2-4
- Extranodal involvement > 1 site

International Index, ALL PATIENTS ≤ 60 YEARS:

	Number of characteristics
• Low	0
• Low intermediate	1
• High intermediate	2
• High	3

APPENDIX B: Dose Adjusted EPOCH-R

Table 1. EPOCH-R starting dose level

Drug	Dose, route, treatment days
Rituximab	375 mg/m^2 IV day 1
Etoposide	50 mg/m^2/day continuous IV days 1-4
Doxorubicin	10 mg/m^2/day continuous IV days 1-4
Vincristine	0.4 mg/m^2/day continuous IV days 1-4
Cyclophosphamide	750 mg/m^2/day IV day 5
Prednisone	60 mg/m^2 PO twice daily days 1-5
Filgrastim product	5 mcg/kg subcutaneously daily starting on day 6 until ANC > 5 K/microliter
Next Cycle[1]	Day 21

[1] Begin on day 21 if the ANC ≥ 1 K/microliter and the platelet count ≥ 100 K/microliter

Table 2. EPOCH dose-adjustment paradigm

Nadir measurements[2]	Dose-adjustment
If nadir ANC ≥ 0.5 K/microliter	20% increase in etoposide, doxorubicin and cyclophosphamide above last cycle
If nadir ANC < 0.5 K/microliter on 1 or 2 measurements	Same doses as last cycle
If nadir ANC < 0.5 K/microliter on at least 3 measurements **or** If nadir platelet count < 25 K/microliter on 1 measurement	20% decrease in etoposide, doxorubicin and cyclophosphamide below last cycle

Note: Dose adjustments above starting dose level apply to etoposide, doxorubicin and cyclophosphamide. Dose adjustments below starting dose level apply to cyclophosphamide only.

[2] Measurements of ANC and platelet nadir are based on twice weekly CBC only

APPENDIX C: Revised Criteria for Response Assessment

Response and Site	PET-CT-Based Response	CT-Based Response
Complete	Complete metabolic response	Complete radiologic response (all of the following)
Lymph nodes and extralymphatic sites No Uptake Deauville 1-3	Score 1, 2, or 3 with or without a residual on 5PS It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (e.g., with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal in the mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake.	Target nodes/nodal masses must regress to ≤ to 1.5 cm in LDi No extralymphatic sites of disease
Nonmeasured lesion	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesion	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology
Partial	Partial metabolic response	Partial remission (all of the following)
Lymph nodes and extralymphatic sites Deauville 5	Score 4 or 5 with reduced uptake compared with baseline and residual mass(es) of any size At interim, these findings suggest responding disease At end of treatment, these findings indicate residual disease	Decrease of ≥ 50% in sum of product diameter (SPD) of up to 6 target measurable nodes and extranodal sites When a lesion is too small to measure on CT, assign 5 mm x 5 mm as the default value When no longer visible, 0 x 0 mm For a node > 5 mm x 5 mm, but smaller than normal, use actual measurement for calculation
Nonmeasured lesion	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement Deauville 4	Not applicable	Spleen must be regressed by > 50% in length beyond normal
New lesion	None	None

Cheson, B. D., Fisher, R. I., Barrington, S. F., Cavalli, F., Schwartz, L. H., Zucca, E., & Lister, T. A. (2014). Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: The Lugano classification. *Journal of Clinical Oncology*, *32*(27), 3059-3067.

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Primary Mediastinal Large B-Cell Lymphoma

APPENDIX C: Response Criteria for Response Assessment - continued

Response and Site	PET-CT-Based Response	CT-Based Response
Partial	Partial metabolic response	Partial remission (all of the following)
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan.	Not applicable
No response or stable disease	No metabolic response	Stable disease
Target nodes/nodal masses, extranodal lesions	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Nonmeasured lesion	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesion	None	None
Bone marrow	No change from baseline	Not applicable
Progressive disease	Progressive metabolic response	Progressive disease requires at least 1 of the following PPD progression
Individual target nodes/ nodal masses Extranodal lesions	Score 4 or 5 with an increase in intensity of uptake from baseline and/or New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	An individual node/lesion must be abnormal with: • > 1.5 cm **and** • Increase by ≥ 50% from PPD nadir **and** • An increase in LDi **or** SDi from nadir: ◦ 0.5 cm for lesions ≤ 2 cm ◦ 1 cm for lesions > 2 cm • In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (e.g., a 15 cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by ≥ 2 cm from baseline. • New or recurrent splenomegaly

Cheson, B. D., Fisher, R. I., Barrington, S. F., Cavalli, F., Schwartz, L. H., Zucca, E., & Lister, T. A. (2014). Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: The Lugano classification. *Journal of Clinical Oncology*, *32*(27), 3059-3067.

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APPENDIX C: Revised Criteria for Response Assessment - continued

Response and Site	PET/CT-Based Response	CT-Based Response
Progressive disease	Progressive metabolic response	Progressive disease requires at least 1 of the following PPD progression
Nonmeasured lesions	None	New or clear progression of preexisting nonmeasured lesions
New lesion	New FDG-avid foci consistent with lymphoma rather than another etiology (e.g., infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered.	Regrowth of previously resolved lesions A new node > 1.5 cm in any axis A new extranodal site > 1 cm in any axis; if < 1 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

Cheson, B. D., Fisher, R. I., Barrington, S. F., Cavalli, F., Schwartz, L. H., Zucca, E., & Lister, T. A. (2014). Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: The Lugano classification. *Journal of Clinical Oncology*, *32*(27), 3059-3067.

APPENDIX D: Deauville Criteria

- Score 1: no uptake
- Score 2: uptake less than or equal to mediastinum
- Score 3: uptake greater than mediastinum but less than or equal to liver
- Score 4: uptake greater than liver at any site
- Score 5: uptake greater than liver and new sites of disease
- Score X: new areas of uptake unlikely to be related to lymphoma

A score of 1-3 is regarded as negative and 4 or 5 as positive

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