Hodgkin Lymphoma

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Hodgkin Lymphoma

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

PATHOLOGIC DIAGNOSIS

ESSENTIAL:

- FNA alone is insufficient
- Hematopathology review of all slides with at least one tumor paraffin block. Rebiopsy if consult material is non-diagnostic. Core needle biopsy may be adequate if diagnostic, but an excisional nodal biopsy is recommended.
- Flow cytometry often not helpful
- Adequate immunophenotype to confirm diagnosis
  - Immunohistochemistry on paraffin panel for Hodgkin lymphoma (HL) including nodular lymphocyte predominant HL:
    - CD20, PAX-5, CD30, CD3, CD15, CD21, and CD45 (LCA)
    - EBER

OF USE IN CERTAIN CIRCUMSTANCES:

- Immunohistochemical studies:
  - LMP1
  - BOB1, OCT2, and CD79a (differential diagnosis with B-cell lymphoma, unclassifiable with features intermediate between classical HL and DLBCL and primary mediastinal large B-cell lymphoma).
  - CD23, or CD35 (follicular dendritic cell markers), BCL6 in cases of nodular lymphocyte predominant HL (may help with T-cell/histiocyte rich large B-cell lymphoma)
  - CD2, CD43, ALK (differential diagnosis with anaplastic large cell lymphoma)

STRONGLY RECOMMEND:

- Core biopsy for tissue banking by protocol

INITIAL EVALUATION

ESSENTIAL:

- History and physical including:
  - Alcohol intolerance
  - Pruritus
  - Exam of nodes
  - B symptoms (Unexplained fever > 38°C during the previous month; Recurrent drenching night sweats during the previous month; Weight loss > 10% of body weight ≤ 6 months of diagnosis)
  - Performance Status
  - Fatigue
  - Size of spleen, liver
- CBC with differential, LDH, BUN, creatinine, albumin, AST, ALT, total bilirubin, alkaline phosphatase, serum calcium, uric acid
- Erythrocyte sedimentation rate (ESR)
- Screening for HIV 1, HIV 2, hepatitis B and C (HBcAb, HBsAg, HCVAb)
- PET/CT with contrast
- Pulmonary Function Tests
- Consider bone marrow biopsy if there are cytopenias and/or inconclusive PET
- MUGA scan or echocardiogram
- Counseling: psychosocial if clinically indicated
- Lifestyle risk assessment[1]
- Discuss fertility preservation

OF USE IN SELECTED CASES:

- Chest x-ray, PA and LAT
- Pregnancy test
- Cardiology consultation at baseline if risk factors for cardiac toxicity [*i.e.*, obesity, abnormal echocardiogram, hypertension (HTN), hyperlipidemia (HLD)]

See Pages 3-4: Classical Hodgkin Lymphoma Stage I-II

See Page 5-6: Classical Hodgkin Lymphoma Advanced Stages III, IV

See Page 7: Lymphocyte Predominant Hodgkin Lymphoma

[1] 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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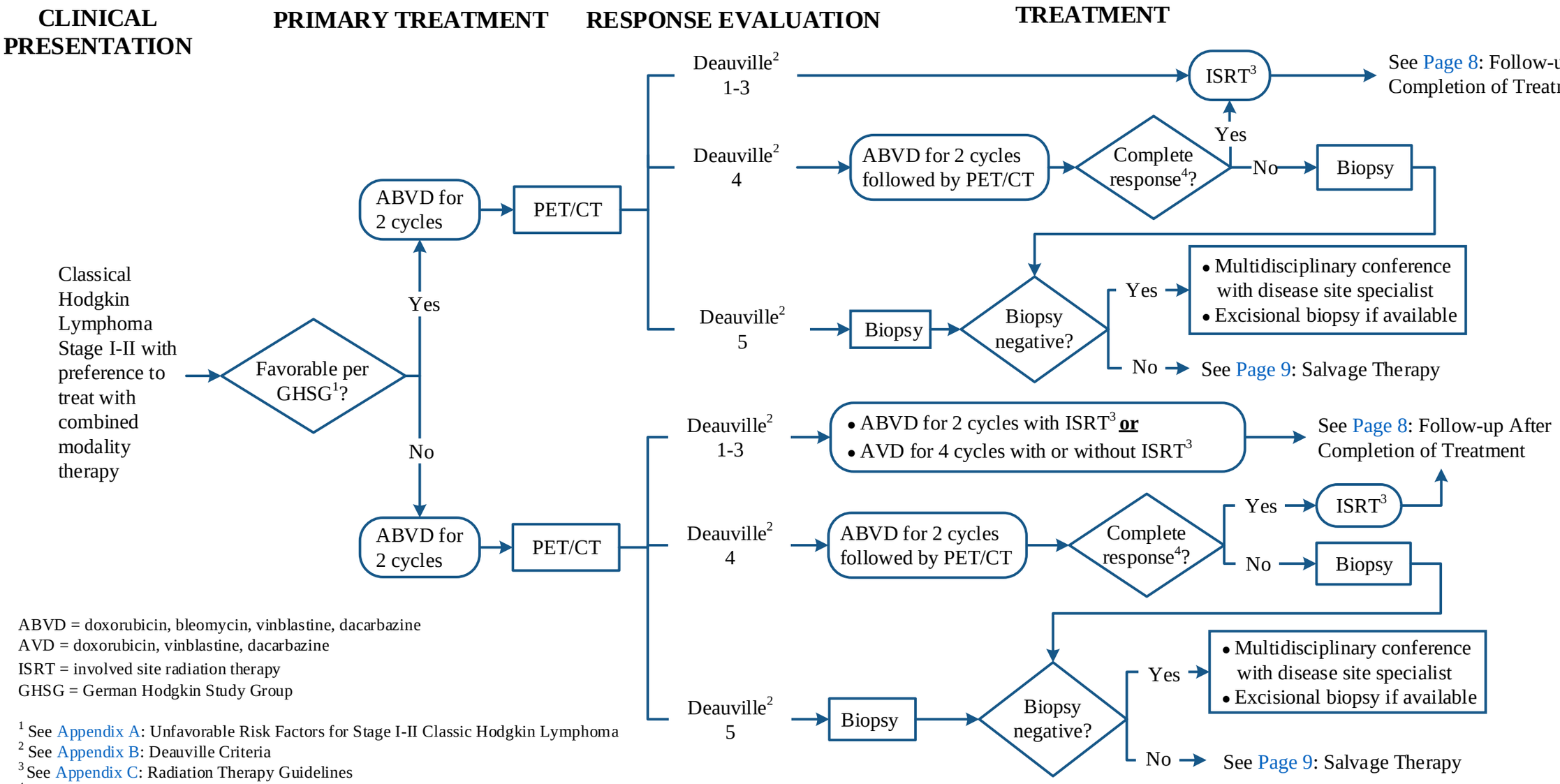

ABVD = doxorubicin, bleomycin, vinblastine, dacarbazine
AVD = doxorubicin, vinblastine, dacarbazine
ISRT = involved site radiation therapy
GHSG = German Hodgkin Study Group

[1] See Appendix A: Unfavorable Risk Factors for Stage I-II Classic Hodgkin Lymphoma
[2] See Appendix B: Deauville Criteria
[3] See Appendix C: Radiation Therapy Guidelines
[4] See Appendix D: Response Criteria for Malignant Lymphoma

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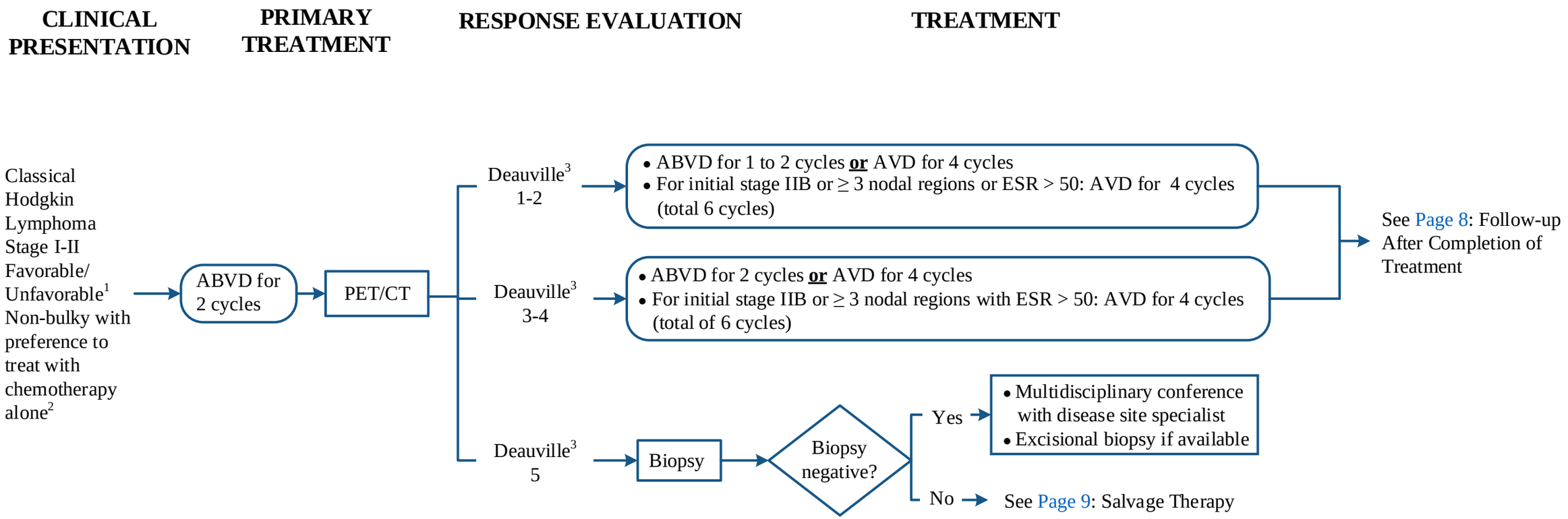
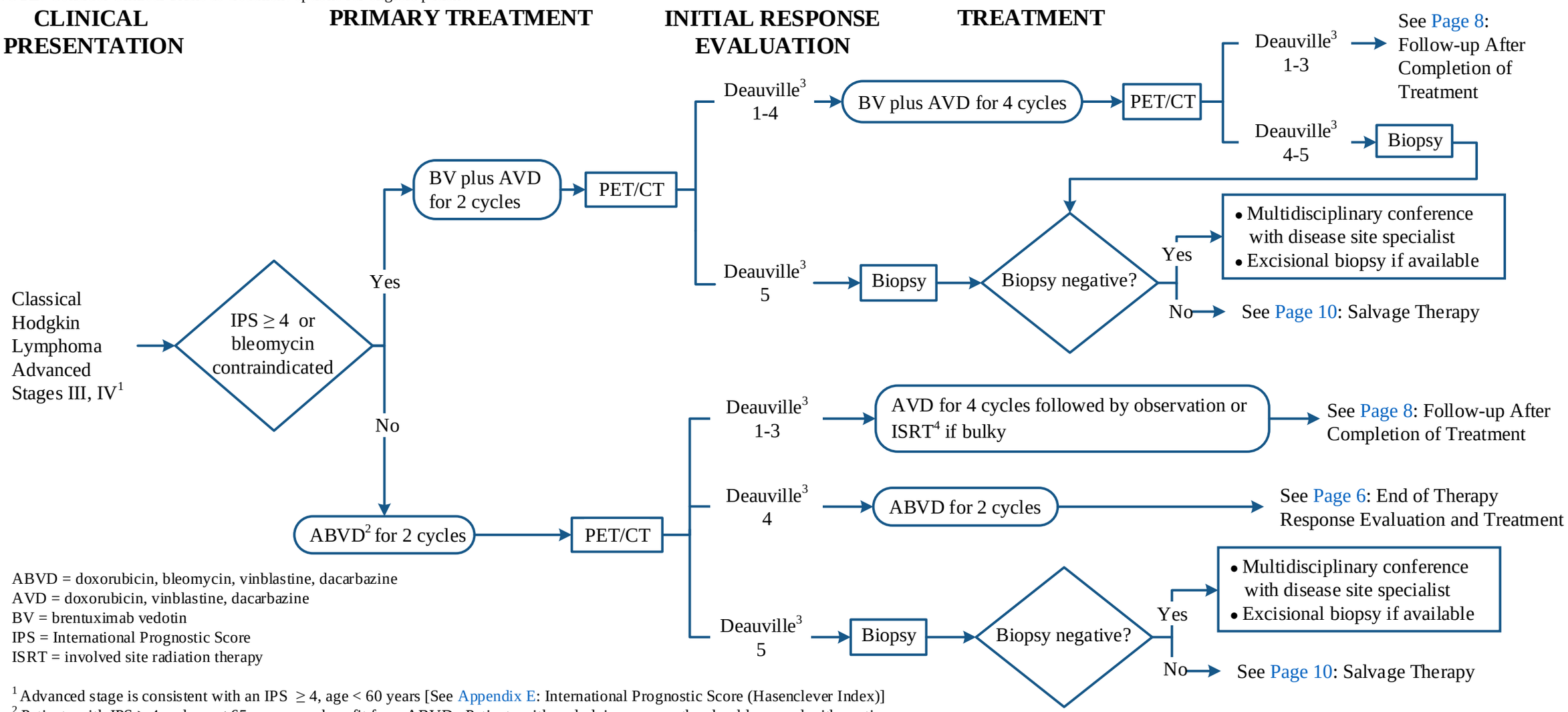


ABVD = doxorubicin, bleomycin, vinblastine, dacarbazine
AVD = doxorubicin, vinblastine, dacarbazine

[1] See Appendix A: Unfavorable Risk Factors for Stage I-II Classic Hodgkin Lymphoma
[2] A subset of patients who meet criteria as per the UK Rapid study with stage IA and stage IIA Hodgkin Lymphoma with no mediastinal bulk and negative PET findings after treatment may receive 3 cycles of chemotherapy with or without additional involved site radiation therapy (ISRT)
[3] See Appendix B: Deauville Criteria

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

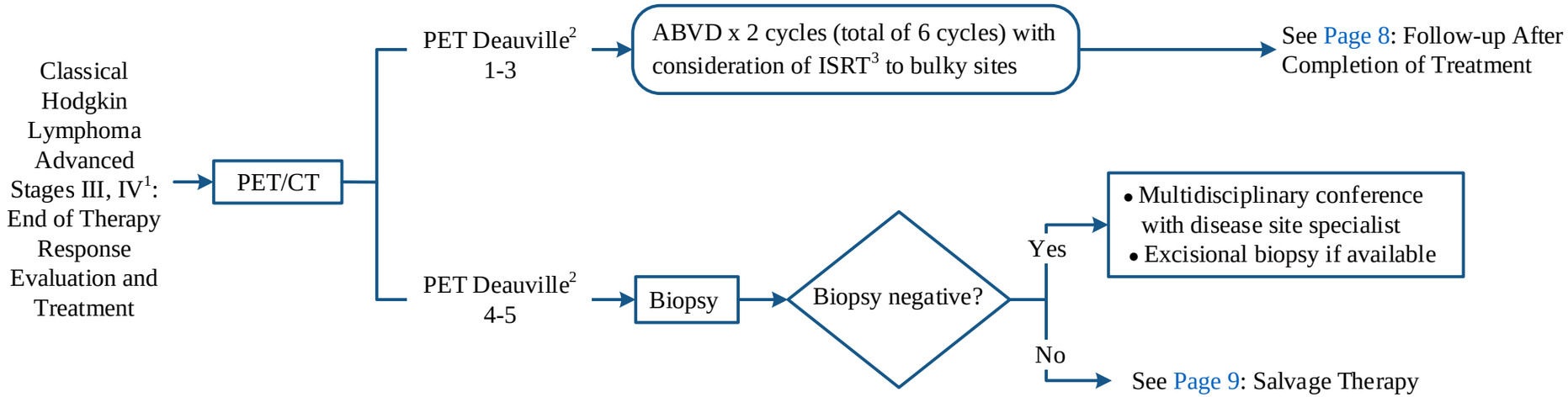


ABVD = doxorubicin, bleomycin, vinblastine, dacarbazine
AVD = doxorubicin, vinblastine, dacarbazine
BV = brentuximab vedotin
IPS = International Prognostic Score
ISRT = involved site radiation therapy

[1] Advanced stage is consistent with an IPS ≥ 4, age < 60 years [See Appendix E: International Prognostic Score (Hasenclever Index)]
[2] Patients with IPS ≥ 4 and age < 65 years may benefit from ABVD. Patients with underlying neuropathy should proceed with caution. Patients who are at higher risk for bleomycin lung toxicity should be considered for BV-AVD.
[3] See Appendix B: Deauville Criteria
[4] See Appendix C: Radiation Therapy Guideline

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

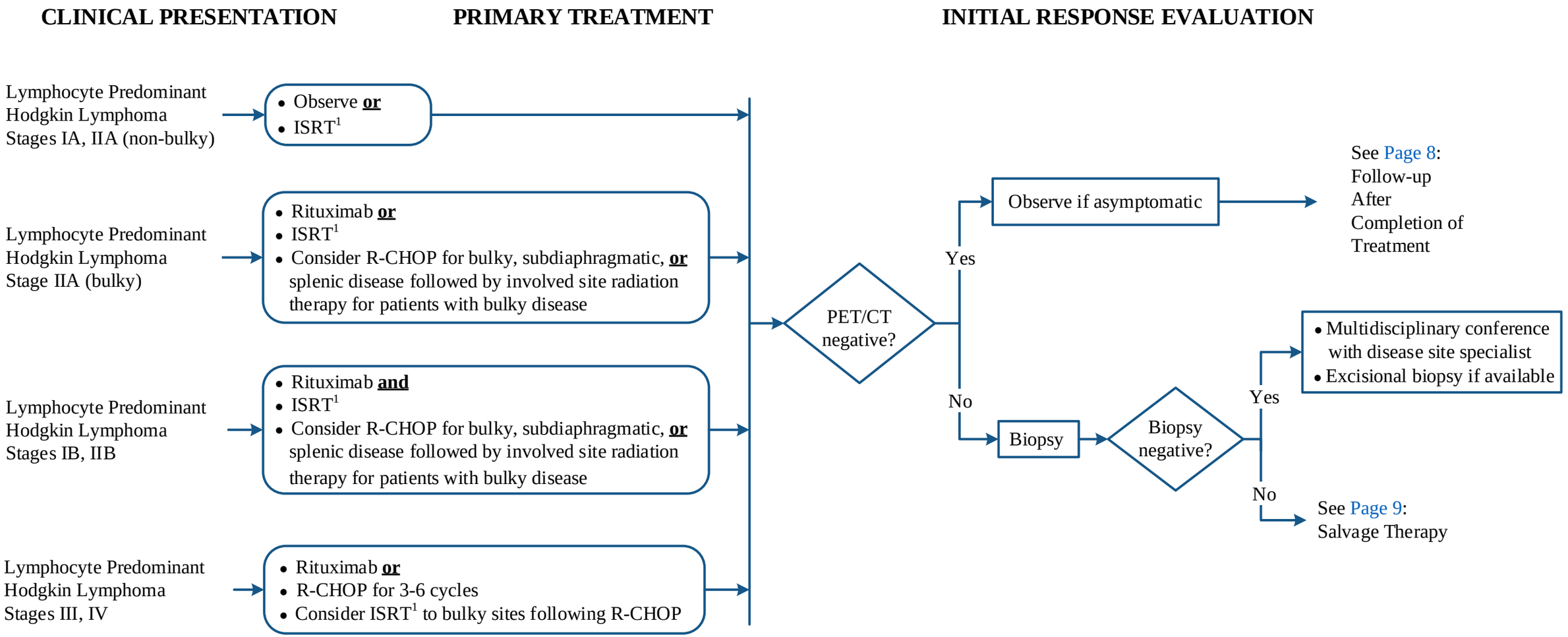
CLINICAL PRESENTATION | **RESPONSE EVALUATION** | **TREATMENT**



ABVD = doxorubicin, bleomycin, vinblastine, dacarbazine
ISRT = involved site radiation therapy

[1] Advanced stage is consistent with an International Prognostic Score ≥ 4, age < 60 [See Appendix E: International Prognostic Score (Hasenclever Index)]
[2] See Appendix B: Deauville Criteria
[3] See Appendix C: Radiation Therapy Guideline

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



ISRT = involved site radiation therapy
R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone

[1] See Appendix C: Radiation Therapy Guideline

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

FOLLOW-UP AFTER COMPLETION OF TREATMENT

- Follow-up with an oncologist is recommended
- Interim history and physical: every 4 months for years 1 and 2, then every 6 months for year 3, then annually
- Pneumococcal and meningococcal revaccination if patient treated with splenic radiation therapy: See Management of Adult Asplenic/Hyposplenic Patients algorithm
- Annual influenza vaccine (especially if patient treated with bleomycin or chest radiation therapy)
- Laboratory studies:
  - CBC with differential, LDH, BUN, creatinine, albumin, AST, ALT, total bilirubin, alkaline phosphatase, serum calcium, uric acid every 4 months for years 1 and 2, then every 6 months for years 3, then annually
  - TSH every 6 months if radiation therapy to neck and optional for all other cases
- CT neck, chest, abdomen and pelvis with contrast at 6, 12, and 24 months or as clinically indicated. PET/CT only if last PET was Deauville 4-5, to confirm complete response
- Annual breast screening: initiate alternating mammography and MRI 8 years post therapy or at age 40, whichever is sooner, if radiation therapy above diaphragm
- Counseling: reproduction, health habits, psychosocial, cardiovascular, breast self-exam, skin cancer risk, end-of-treatment discussion
- Recommend written follow-up instructions for the patient
- Stress test/echocardiogram at 10-year intervals after treatment is completed
- Consider carotid ultrasound at 10-year intervals if neck irradiation

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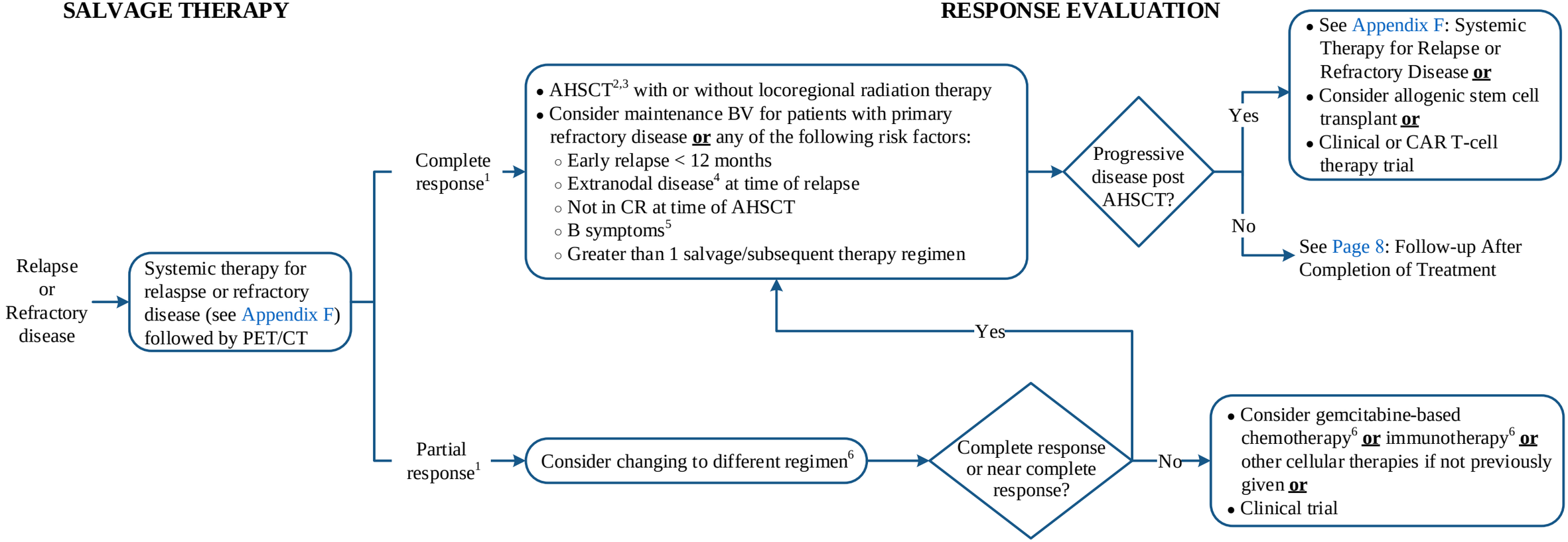
SALVAGE THERAPY

RESPONSE EVALUATION



AHSCT = autologous hematopoietic stem cell transplant
BV = brentuximab vedotin
CAR = chimeric antigen receptor

[1] See Appendix D: Response Criteria for Malignant Lymphoma
[2] Conventional-dose chemotherapy may precede high-dose therapy. Sequence of therapy may vary.
[3] Perform biopsy if plan to treat with high-dose chemotherapy
[4] Extranodal disease (*i.e.*, any tumor spread that involves tissues other than those of the lymph nodes, spleen, thymus, Waldeyer's tonsillar ring, appendix, and Peyer's patches)
[5] Unexplained fever > 38°C during the previous month, recurrent drenching night sweats during the previous month, weight loss > 10% of body weight ≤ 6 months of diagnosis
[6] See Appendix F: Systemic Therapy for Relapse or Refractory Disease

APPENDIX A: Unfavorable Risk Factors for Stage I-II Classic Hodgkin Lymphoma

Risk Factor	GHSG	EORTC	NCCN
Age		≥ 50	
Histology			
ESR and B symptoms[1]	ESR > 50 mm/hour if A; ESR > 30 mm/hour if B	ESR > 50 mm/hour if A; ESR > 30 mm/hour if B	ESR ≥ 50 mm/hour **or** any B symptoms[1]
Mediastinal mass	MMR > 0.33	MTR > 0.35	MMR > 0.33
# Nodal sites	Area ≥ 3[2]	Sites > 3[2]	Sites > 3
E lesion	any		
Bulky[3]			Size > 10 cm

A = no B symptoms
GHSG = German Hodgkin Study Group
EORTC = European Organization for the Research and Treatment of Cancer
MMR = Mediastinal mass ratio, maximum width of mass/maximum intrathoracic diameter
MTR = Mediastinal thoracic ratio, maximum width of mediastinal mass/intrathoracic diameter at T5-6
NCCN = National Comprehensive Cancer Network

[1] Unexplained fever > 38°C during the previous month, recurrent drenching night sweats during the previous month, weight loss > 10% of body weight ≤ 6 months of diagnosis
[2] The EORTC includes the infraclavicular/subpectoral area with the axilla area while the GHSG includes this area with the cervical. Both EORTC and GHSG combine the mediastinum and bilateral hila as a single region.
[3] Bulky may be defined as MMR > 0.33 **or** any mass >10 cm in size

APPENDIX B: 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

APPENDIX C: Radiation Therapy Guidelines

Consider intensity-modulated radiation therapy (IMRT) or proton therapy, as appropriate, to minimize toxicity

Dose if radiation therapy is given alone:
30-45 Gy, depending on treatment intent, disease bulk, *etc.*

Doses for combined modality radiation therapy:
- Early stage favorable: 20 Gy to involved site
- Early stage unfavorable: 30 Gy to involved site

Salvage radiation therapy when Deauville ≥ 4[1]:
36-45 Gy, depending on disease bulk and response to chemotherapy

Radiation Fields:
Involved Site Radiation Therapy: Treatment of involved lymph nodes regions only

[1] See Appendix B: Deauville Criteria

APPENDIX D: Response Criteria for Malignant Lymphoma

Response Category	Nodal Masses	Spleen, Liver	Bone Marrow
CR (Complete Response: disappearance of all evidence of disease)	• FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative • Variably FDG-avid or PET negative; regression to normal size on CT	Not palpable, nodules disappeared	Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohistochemistry should be negative
PR (Partial Response)	• Decrease of ≥ 50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes • FDG-avid or PET positive prior to therapy; one or more PET positive at previously involved site • Variably FDG-avid or PET negative; regression on CT	Decrease of ≥ 50% in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen	Irrelevant if positive prior to therapy; cell type should be specified
SD (Stable disease: failure to attain CR/PR or PD)	• FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease and no new sites on CT or PET • Variably FDG-avid or PET negative; no change in size of previous lesions on CT		
Relapse or Progressive disease (Any new lesion or increase by ≥ 50% of previously involved sites from nadir)	• Appearance of a new lesion(s) > 1.5 cm in any axis, ≥ 50% increase in SPD of more than one node, or ≥ 50% increase in longest diameter of a previously identified node > 1 cm in short axis • Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy	Increase of ≥ 50% from nadir in the SPD of any previous lesions	New or recurrent involvement

FDG, [^{18}F] = fluorodeoxyglucose
SPD = sum of the product of the diameters

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APPENDIX E: International Prognostic Score (Hasenclever Index[1])

- Albumin < 4 g/dL
- Hemoglobin < 10.5 g/dL
- Male
- Age ≥ 45 years
- Stage IV disease
- White blood cell count ≥ 15 K/microliter
- Lymphocyte count < 8% of white blood cell count, and/or lymphocyte count < 0.6 K/microliter)

Each factor = 1 point

[1] Hasenclever, D., Diehl, V., Armitage, J. O., Assouline, D., Björkholm, M., Brusamolino, E., … Eghbali, H. (1998). A prognostic score for advanced Hodgkin's disease. *New England Journal of Medicine, 339*(21), 1506-1514. doi:10.1056/NEJM199811193392104

APPENDIX F: Systemic Therapy for Relapsed or Refractory Disease

Disease	Chemotherapy Options	Subsequent Options[1]
Classic Hodgkin Lymphoma	• Brentuximab vedotin • Brentuximab vedotin plus bendamustine • Brentuximab vedotin plus nivolumab • DHAP (dexamethasone, cisplatin, high dose cytarabine) • ESHAP (etoposide, methylprednisolone, high dose cytarabine, cisplatin) • Gemcitabine/bendamustine/vinorelbine • BGVD (gemcitabine, vinorelbine, liposomal doxorubicin) • ICE (ifosfamide, carboplatin, etoposide) • IGEV (ifosfamide, gemcitabine, vinorelbine)	• Bendamustine • Everlolimus • GCD (gemcitabine, carboplatin, dexamethasone) • Lenalidomide • MINE (etoposide, ifosfamide, mesna, mitoxantrone) • Mini-BEAM (carmustine, cytarabine, etoposide, melphalan) • Nivolumab • Prembrolizumab
Lymphocyte Predominant Hodgkin Lymphoma	• Rituximab plus DHAP (dexamethasone, cisplatin, high dose cytarabine) • Rituximab plus ESHAP (etoposide, methylprednisolone, high dose cytarabine, cisplatin) • Rituximab plus ICE (ifosfamide, carboplatin, etoposide) • Rituximab plus IGEV (ifosfamide, gemcitabine, vinorelbine)	

[1] Subsequent options also include chemotherapy options that were not previously given

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DEVELOPMENT CREDITS

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