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2016 年 12 月修訂

2 參考資料：

Hodgkin’ s Lymphomas NCCN Guidelines V3.2016

全民健康保險藥品給付規定 行政院衛生署一百零四年版

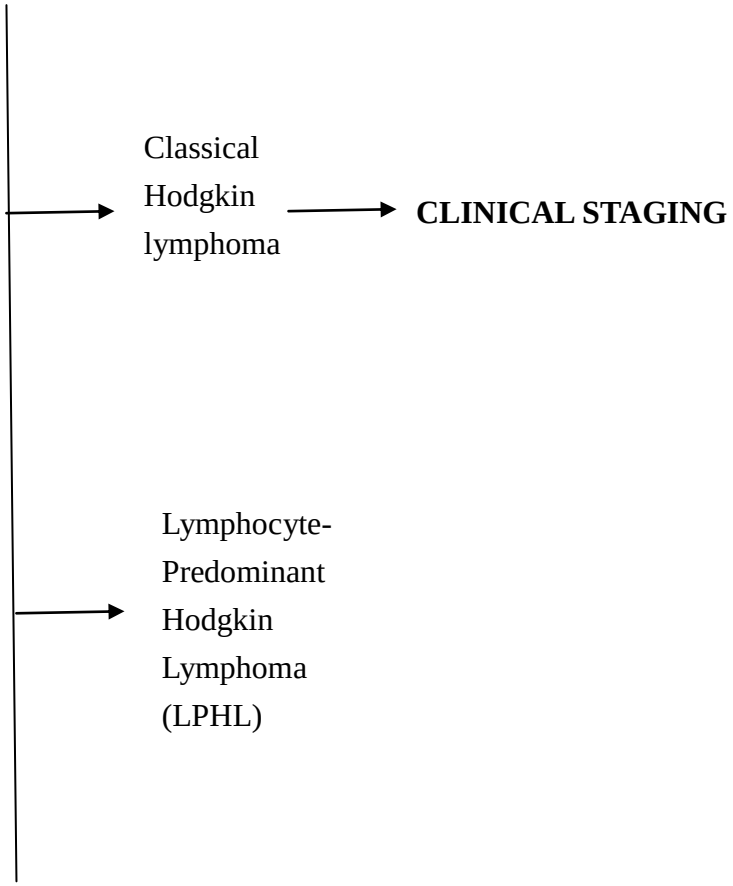
WORKUP

Essential;

- H&P insuluding:B symptoms, alcohol intolerance, pruritus, fatigue, performance status, exam lymphoid regions, spleen, liver
- CBC, differential, platelets
- Erythrocyte sedimentation rate(ESR)
- LDH, LFT, albumin
- BUN, creatinine
- Pregnancy test : women of childbearing age
- Chest x-ray
- Diagnostic chest/abdominal/pelvic CT
- Adequate bone marrow biopsy in stage IB, IIB and stage III-IV (Or select the whole body PET-CT)
- Evaluation of ejection fraction for doxorubicin-containing regimens
- Counseling : Fertility, smoking cessation, psychosocial

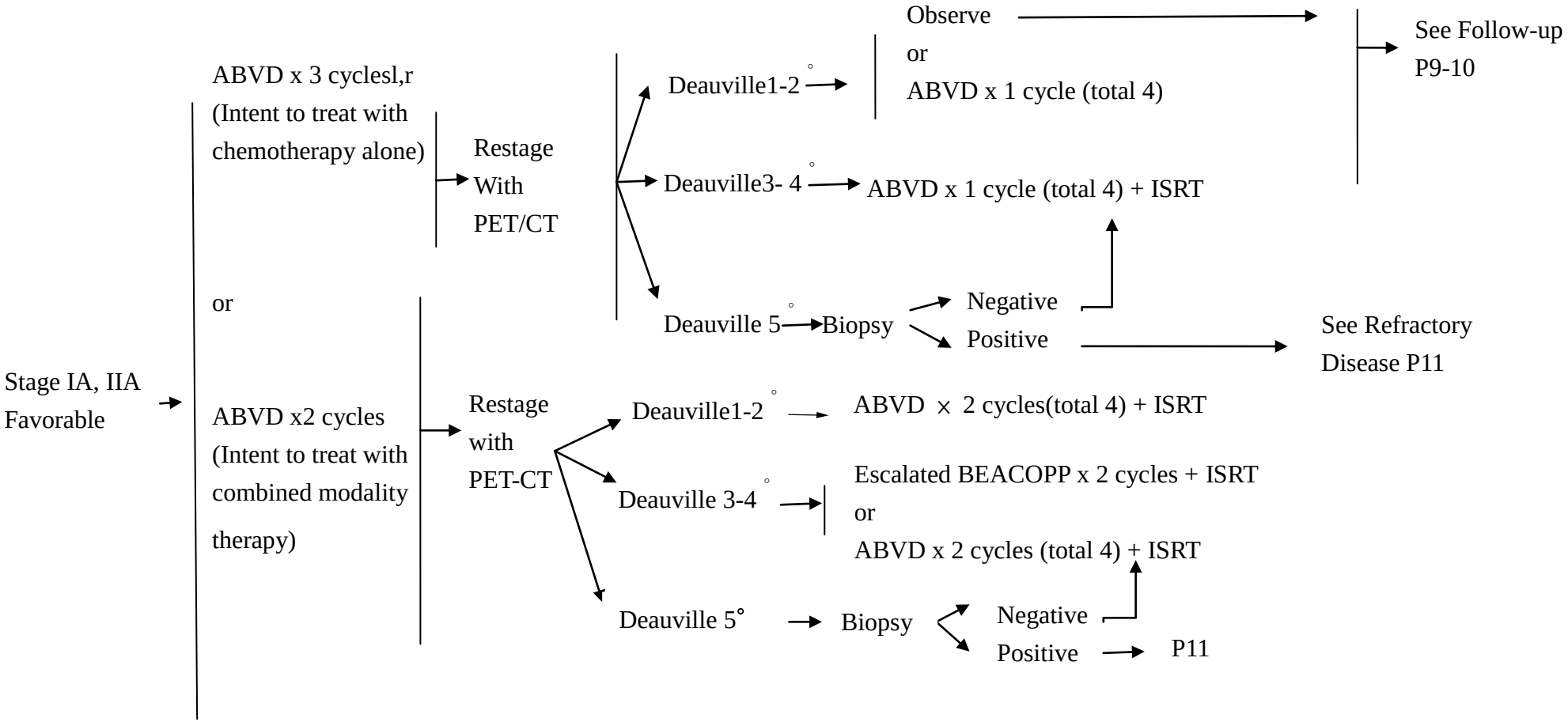
Useful in selected cases:

- Fertility preservation
- Neck CT,if neck RT contemplated
- Pulmonary functions tests (PFTs incl. DLCO) if ABVD are being used
- Pneumococcal, H-flu, meningococcal vaccines, if splenic RT contemplated



CLINICAL PRESENTATION:Classical Hodgkin lymphoma

Stage IA,IIA Favorable

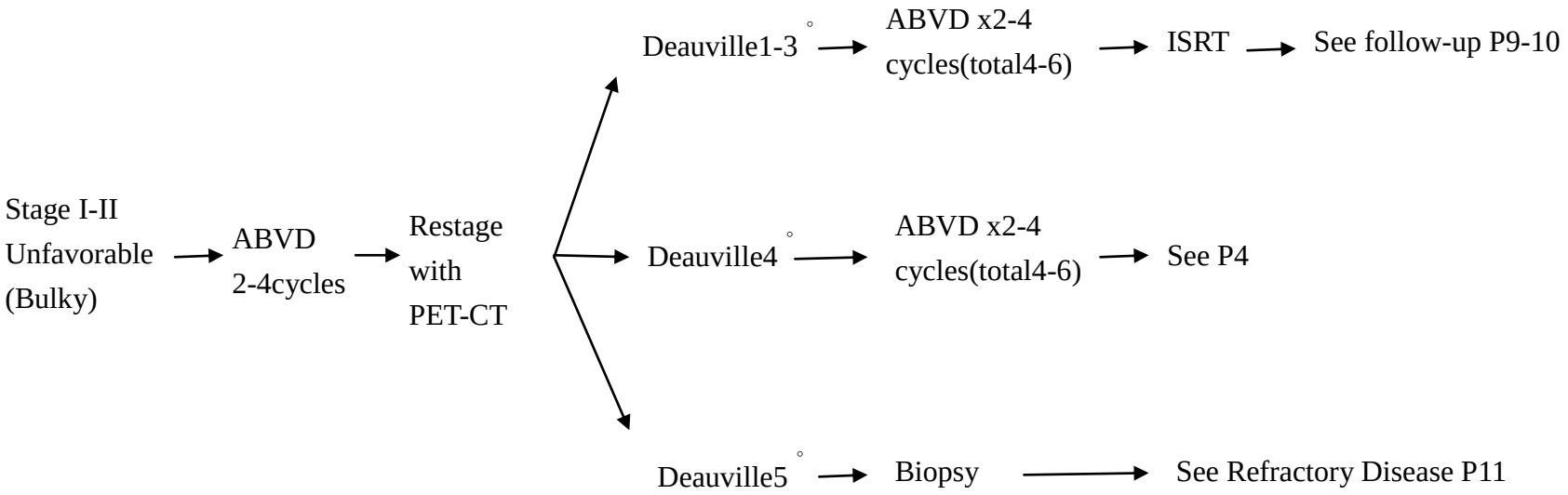


→See Follow-up P9-10

CLINICAL PRESENTATION:Classical Hodgkin lymphoma

Stage I-II Unfavorable

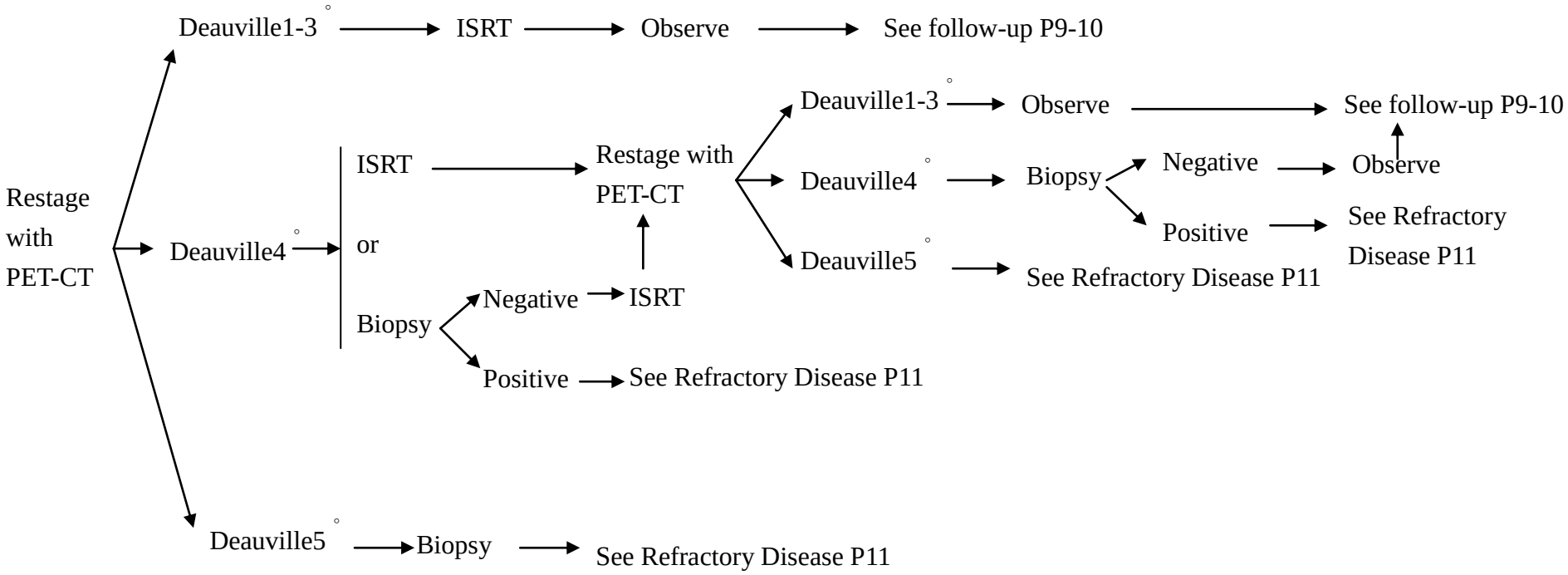
See Refractory Disease P11



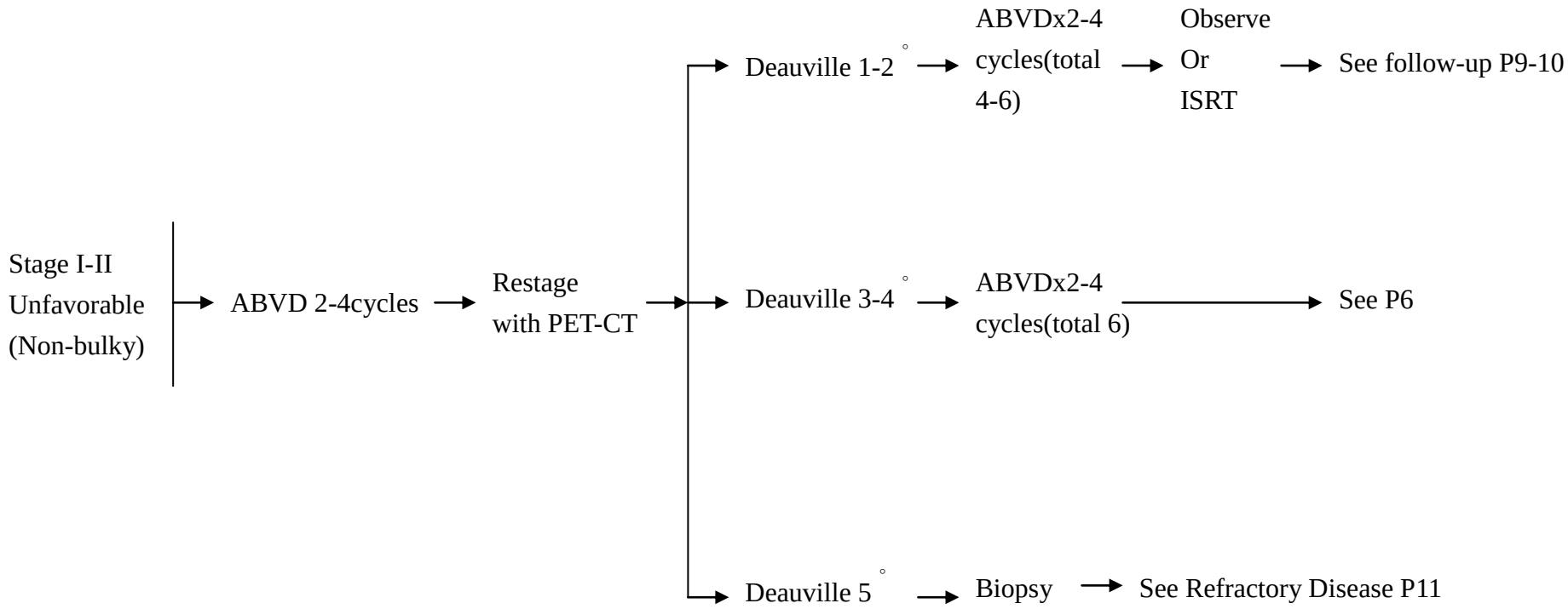
CLINICAL PRESENTATION:Classical Hodgkin lymphoma

Stage I-II Unfavorable(Bulky or Nonbulky)

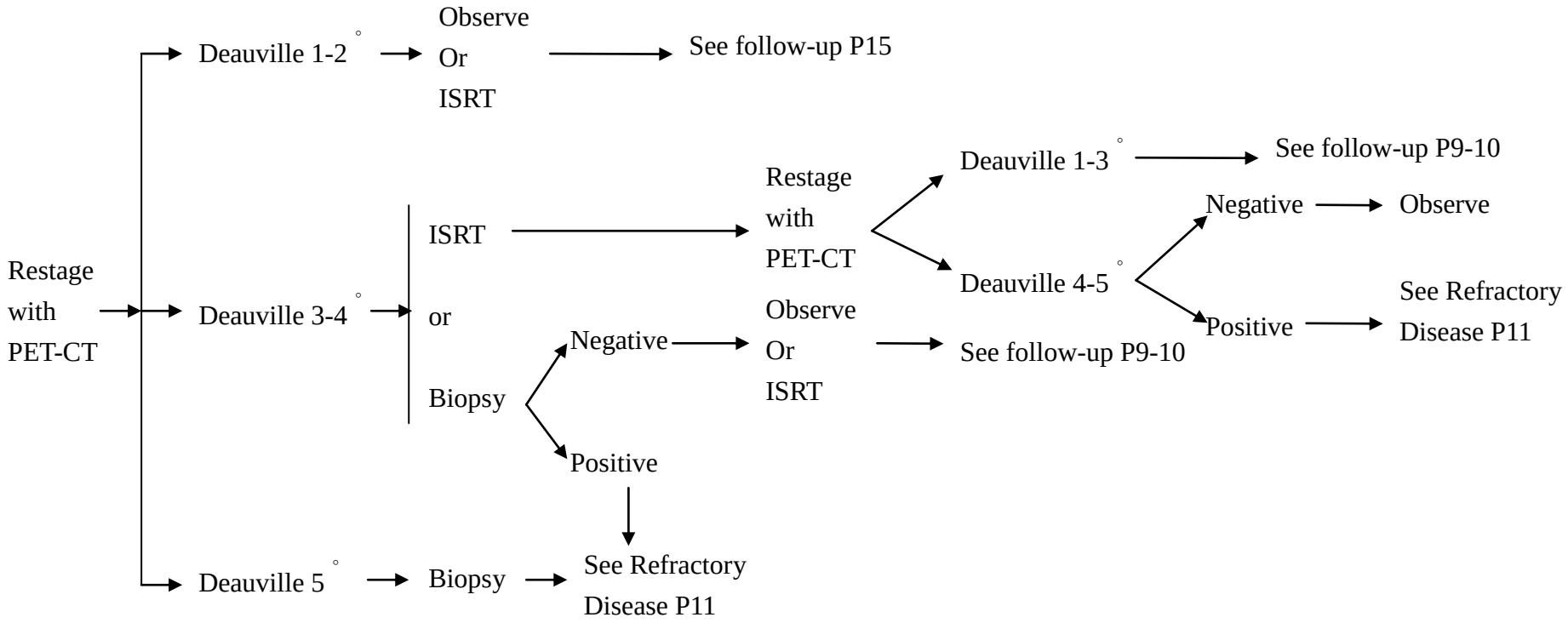
(continued from HODG-4)



CLINICAL PRESENTATION:Classical Hodgkin lymphoma
Stage I-II Unfavorable(Non-bulky)

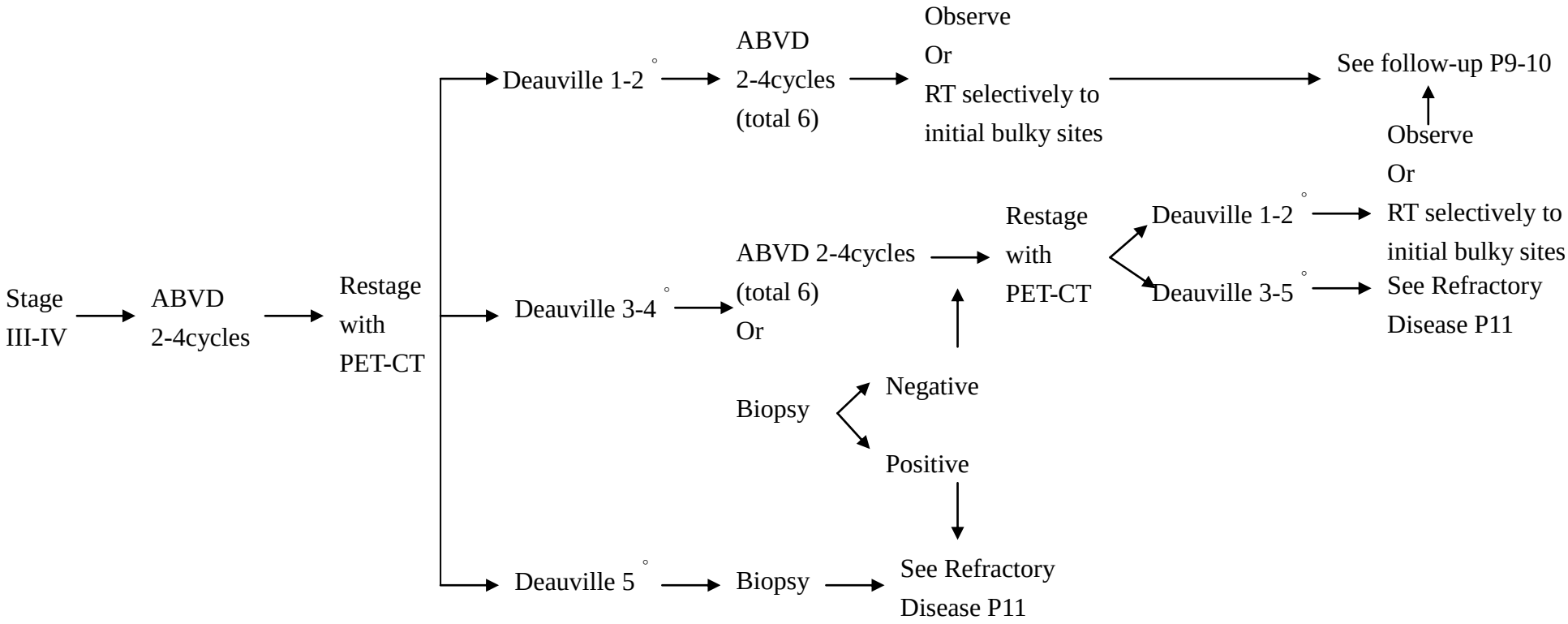


CLINICAL PRESENTATION:Classical Hodgkin lymphoma
Stage I-II Unfavorable(Non-bulky)
PRIMARY TREATMENT(continued from P9)

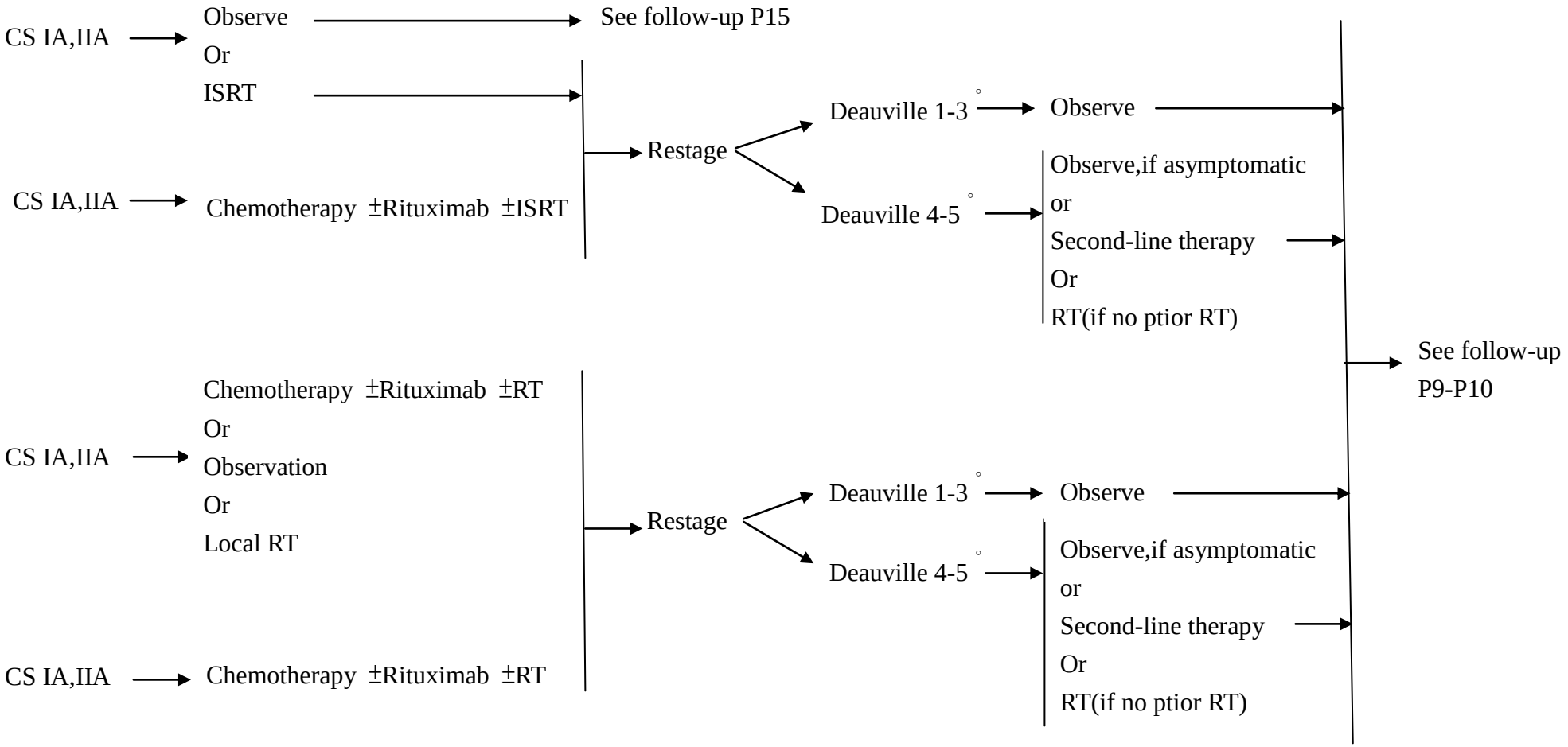


CLINICAL PRESENTATION:Classical Hodgkin lymphoma

Stage III-IV Unfavorable(Non-bulky)



CLINICAL PRESENTATION:Lymphocyte-predominant
Hodgkin lymphoma



FOLLOW-UP AFTER COMPLETION OF TREATMENT AND MONITORING FOR LATE EFFECTS(1 of 2)

- It is recommended that the patient be provided with a treatment summary at the completion of his/her therapy.
- Follow-up with an oncologist is recommended especially during the first 5 y interval to detect recurrence, then annually due to the risk of late complications including Second cancers and cardiovascular disease. Late relapse or transformation to large cell lymphoma may occur in LPHL.
- The frequency and types of tests may vary depending on clinical circumstances; age and stage sat diagnosis, social habits, treatment modality, etc. There are few data to support specific recommendations, these represent the range of practice at NCCN institutions.

Follow-up after completion of treatment	
• Interim H&P:	Every 2-4 mo for 1-2y, then every 3-6 mo for next 3-5 y
• Laboratory studies:	CBC, platelets, ESR (if eveated at time of initial diagnosis),chemistry profile every 2-4 mo for 1-2 y, then every 3-6 mo for next 3-5 y
	TSH at least annually if RT to neck
• Chest imaging:	Chest x-ray or CT every 6-12 mo during first 2-5y
• Abdominal/pelvic CT :	Every 6-12 mo for first 2-3y
• Counseling:	Reproduction, health habits, psychosocial, cardiovascular, breast self-exam, skin cancer risk, end-of-treatment discussion.
• Surveillance PET should not be done routinely due to risk for false positive. Management decisions should not be based on PET scan alone, clinical or pathological correlation is needed.	

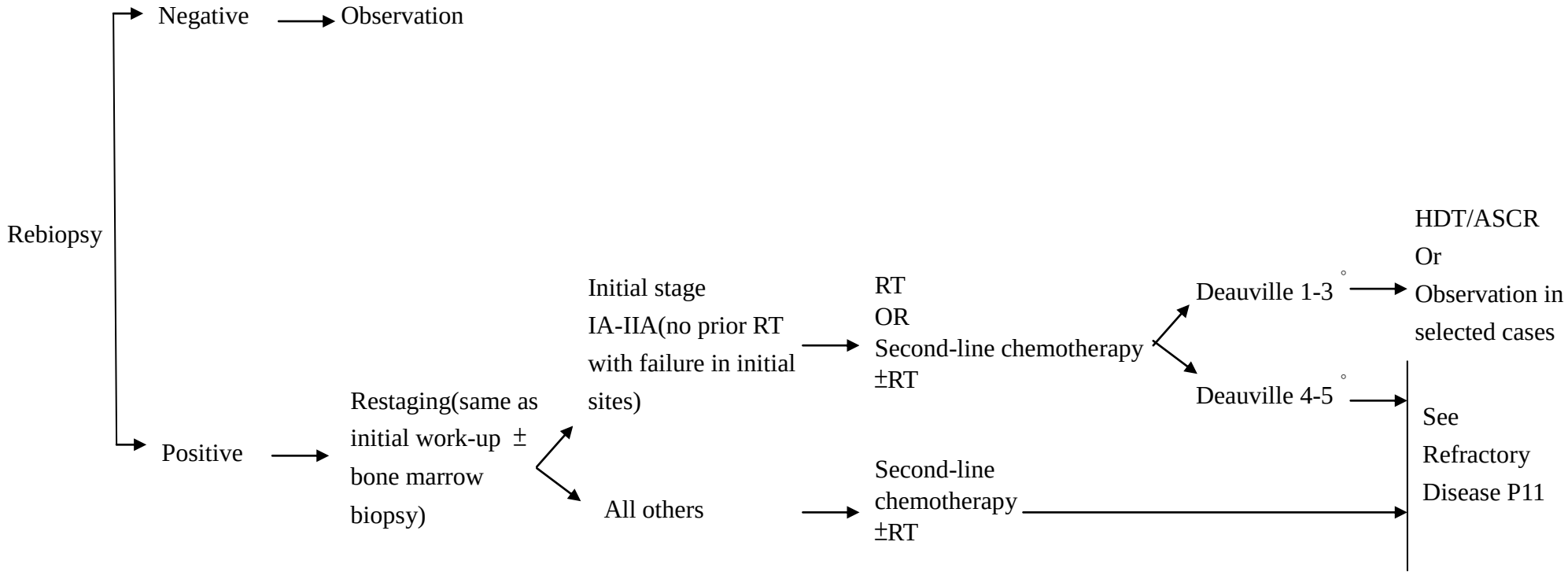
FOLLOW-UP AFTER COMPLETION OF TREATMENT AND MONITORING FOR LATE EFFECTS(2of 2)

Monitoring for Late Effects after 5Years	
• Interim H&P:Annually	Annual blood pressure, aggressive management of cardiovascular risk factors
	Baseline stress test/echocardiogram at 10 y
	Pneumococcal, meningococcal, and H-flu revaccination after 5y, if patient treated with splenic RT or previous splenectomy
	Annual influenza vaccine
• Laboratory studies:	CBC, platelets, chemistry profile annually
	TSH at least annually if RT to neck
	Annual lipids
• Annual chest imaging(chest x-ray or chest CT)for patient at increased risk for lung cancer	
• Annual breast screening:	Initiate 8-10 y post-therapy, or at age 40, whichever comes first,if chest or axillary radiation. The American Cancer Society recommends irradiation to the chest between ages 10 and 30 y.
• Counseling:	Reproduction, health habits, psychosocial, cardiovascular, breast self-exam, skin cancer risk.
• Cardiovascular symptoms may emerge at young age.	
• Treatment summary and consideration of transfer to PCP.	

CLASSICAL HODGKIN LYMPHOMA	SECOND-LINE THERAPY	ADDITIONAL THERAPY		
Refractory disease	Second-line Chemotherapy ±RT	Deauville 1-3。	HDT/ASCR Or Observe(if HDT/ASCR Contraindicated)	
		Deauville 4。	HDT/ASCR or RT or Savage chemotherapy ±RT or Brentuximab vedotin	Deauville 1-4。 HDT/ASCR or Observe(only if CR and HDT/ASCR Contraindicated)
				Deauville 5。 HDT/ASCR or RT or Savage chemotherapy ±RT or Brentuximab vedotin
		Deauville5。	RT OR Savage chemotherapy ±RT or Brentuximab vedotin	Deauville 1-4。 HDT/ASCR or Observe(only if CR and HDT/ASCR Contraindicated)
				Deauville 5。 RT OR Savage chemotherapy ±RT or Brentuximab vedotin

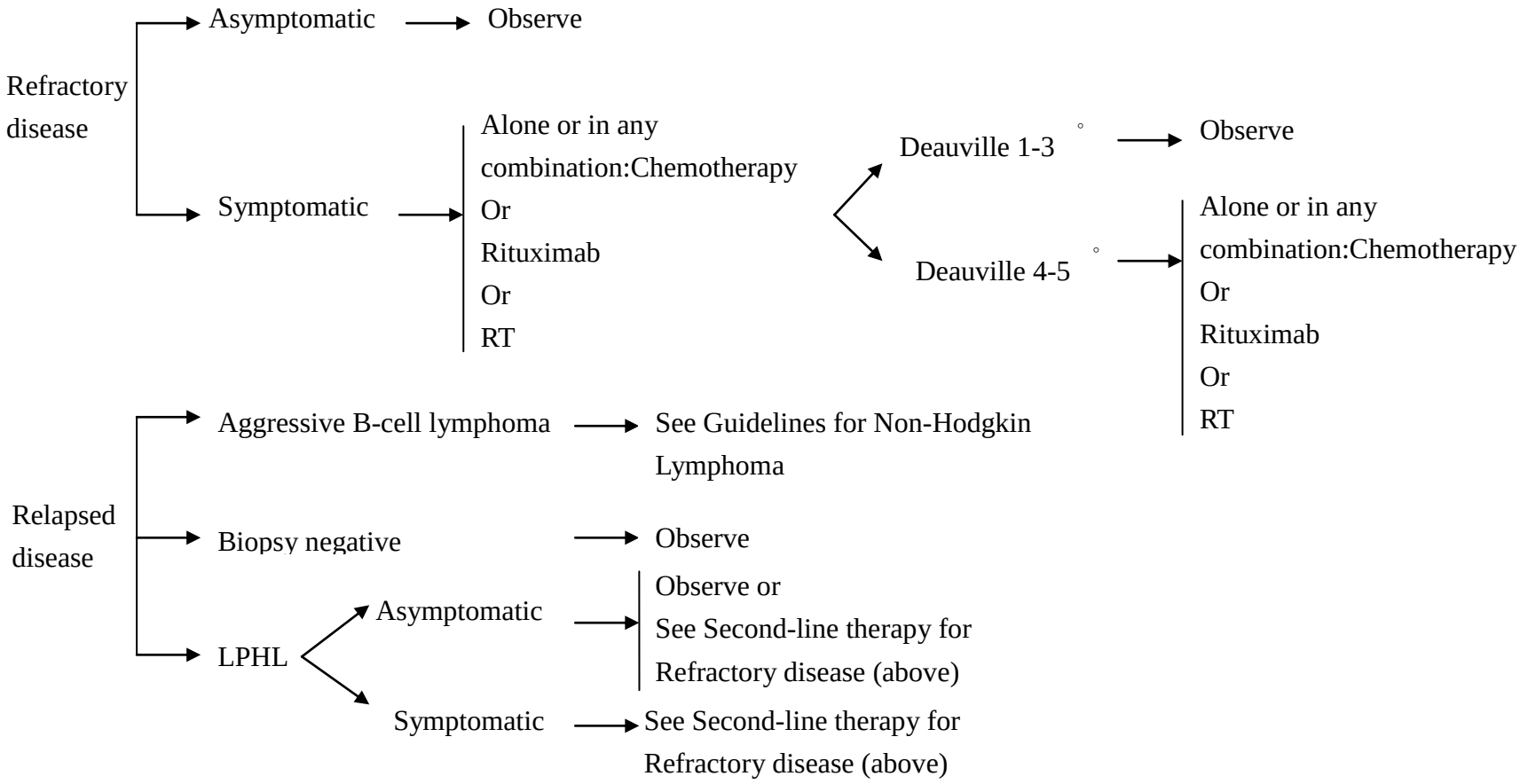
CLASSICAL HODGKIN LYMPHOMA
SUSPECTED RELAPSE

SECOND-LINE THERAPY



LYMPHOCYTE-PREDOMINANT HODGKIN LYMPHOMA REGRACTORY OR RELAPSE

SECOND-LINE THERAPY



Examples of Unfavorable Risk Factor for Stage I-II Hodgkin Disease

Risk Factor	GHSG	EORTC	NCIC	NCCN
Age		≧ 50	≧ 40	
Histology			MC or LD	
ESR and B symptoms	>50 if A; >30 if B	> 50 if A; >30 if B	>50 or any B sx	>50 or any B sx
Mediastinal mass	MMR> .33	MTR > .35	MMR > .33 or >10cm	MMR > .33
# Nodal sites	> 2	>3	>3	>3
E lesion	any			
Bulky				>10 cm

GHSG = German Hodgkin Study Group
EORTC = European Organization for the Research And Treatment of Cancer
NCIC = National Cancer Institute, Canada
MC = Mixed cellularity
LD = Lymphocyte depleted
MMR = Mediastinal mass ratio, maximum width of mass/maximum intrathoracic diameter
MTR = Mediastinal thoracic ratio, maximum width of mediastinal mass/intrathoracic

International Prognostic Score (IPS) 1 point per factor(advanced disease)

- Albumin < 4g/Dl
- Hemoglobin <10.5 g/dL
- Male
- Age ≧ 45 years
- Stage IV disease
- Leukocytosis (white blood cell count at least 15,000/mm^3)
- Lymphocytopenia (lymphocyte count less than 8% of white blood cell count, and/or lymphocyte count less than 600/mm^3)

DEAUVILLE PET CRITERIA

Score	PET/CT scan result
1	No uptake above background
2	Uptake ≦mediastium
3	Uptake >mediastium but ≦ liver
4	Uptake moderately increased compared to the liver at any site
5	Uptake markedly increased compared to liver at any site
X	New areas of uptake unlikely to be related to lymphoma

PRINCIPLES OF SYSTEMIC THERAPY

Classical Hodgkin Lymphoma

ABVD

Doxorubicin 25 mg/m2 IV on day 1 and 15

Bleomycin 10 U/m2 IV on day 1 and 15

Vinblastine 6 mg/m2 IV on day 1 and 15

Dacarbazine 375 mg/m2 IV on day 1 and 15

PRINCIPLES OF RADIATION THERAPY

COMBINED MODALITY-RT DOSES:

- Nonbulky disease (stage I-II):20*-30 Gy(if treated with ABVD), 30Gy (if treated with Stanford V)
- Nonbulky disease (stage IB-IIB) and Bulky and nonbulky disease (stage III-IV):30-36Gy (if treated with BEACOPP)
- Bulky disease sites (all stages):30-36Gy (if treated with ABVD)
- PET scan Deauville 3-4 following chemotherapy : 30-45Gy

RT-ALONE DOSES (uncommon, except for LPHL):

- Involved regions: 30-36 Gy (the dose of 30 Gy is mainly used for LPHL)
- Uninvolved regions: 25-30 Gy

＊ A dose of 20 Gy following ABVD × 2 is sufficient if the patient has nonbulky stage I-IIA disease with an ESR <50, no extralymphatic lesions, and only one or two lymph node regions involved.

REVISED RESPONSE CRITERIA FOR HODGKIN LYMPHOMA

(including PET)

Response	Definition	Nodal Masses	Spleen, Liver	Bone Marrow
CR	Disappearance of all evidence of disease	FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative.	Not palpable, nodules disappeared	Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohistochemistry should be negative
PR	Regression of measurable Disease and no new sites	≧ 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 sites remain positive.	≧ 50% decrease 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	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.		

Relapsed Disease or PD	Any new lesion or increase by ≧ 50% of previously involved sites from nadir	Appearance of a new lesion(s) > 1.5cm in any axis, ≧ 50% increase in SOD of more than one node, or ≧ 50% increase in longest diameter od a preciously identified node >1 cm in shor axis Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy.	>50% increase from nadir in the SPD of any previous lesions	New or recurrent involvement

PET 5-POINT SCALE (DEAUVILLE CRITERIA)

Score	PET/CT scan result
1	No uptake
2	Uptake ≤ mediastinum
3	Uptake > mediastinum but ≤ liver
4	Uptake moderately higher than liver
5	Uptake markedly higher than liver and/or new lesions
X	New areas of uptake unlikely to be related to lymphoma

PRINCIPLES OF SECOND-LINE CHEMOTHERAPY (1 of 2)

- The selection of second-line chemotherapy regimens depends on the pattern of relapse and the agents previously used.
  Examples of second-line chemotherapy prior to transplant include:
  > ICE (ifosfamide, carboplatin, etoposide)
  > DHAP (dexamethasone, cisplatin, high-dose cytarabine)
  > ESHAP (etoposide, methylprednisolone, high-dose cytarabine and cisplatin)
  > MINE (etoposide, ifosfamide, mesna, mitoxantrone)

- Some studies have suggested that patients with minimal disease burden at relapse (not refractory) may not need additional treatmemt perior to high-dose chemotherapy with stem-cell rescue. However, patients tend to have an improved outcome when transplanted in a minimal disease state.Thus, cytoreduction with chemotherapy (see above) before high-dose chemotherapy with stem-cell rescues may be beneficial. In addition, second-line chemotherapy serves as a test for drug sensitivity and to facilitate the harvest of stem cells.

➢ Nitrogen mustard, procarbazine, carmustine, and melphalan may adversely affect both quality and quantity of stem-cell collection.

PRINCIPLES OF SECOND-LINE CHEMOTHERAPY (2 of 2)

References

[1]Moskowitz CH, Nimer SD, Zelenetz AD, et al. A 2-step comprehensive high-dose chemoradiotherapy second-line program for relapsed and refractory Hodgkin disease: analysis by intent to treat and development of a prognostic model. Blood 2001;97(3):616-623.
[2]Takenaka T, Mikuni C, Miura A, et al. Alternating Combination Chemotherapy C-MOPP (Cyclophosphamide, Vincristine, Procarbazine, Prednisone) and ABVD (Adramycin, Bleomycin, Vinblastine, Dacarbazine) in Clinical Stage II-IV Hodgkin's Disease: a Multicenter Phase II Study (JCOG 8905). Jpn. J Clin Oncol. 2000;30(3):146-152.
[3]Montoto S, Camos M, Lopez-Guillermo A, et al. Hybrid chemotherapy consisting of cyclophosphamide, vincristine, procarbazine, prednisone, doxorubicin, bleomycin, and vinblastine(CMOPP/ABV) as first-line treatment Hodgkin disease. Cancer. 2000;88(9):2142-2148.
[4]The International ChIVPP Treatment Group. ChIVPP therapy for Hodgkin's disease: Experience of 960 patients. Ann Oncol. 1995;6(2):167-172.
[5]Josting A, Rudolph C, Reiser M, et al. Time-intensified dexamethasone/cisplatin/cytarabine: an effective salvage therapy with low toxicity in oatients with relapsed and refractory Hodgkin's disease. Ann Oncol 2002;13(10)1628-1635.
Abali H, Urün Y, Oksüzoğlu B, Budakoğlu B, et al. Comparison of ICE (ifosfamide-carboplatin-etoposide) versus DHAP (cytosine arabinoside-cisplatin-dexamethasone) as salvage chemotherapy in patients with relapsed or refractory lymphoma. Cancer Lnvest 2008;26(4):401-406.
[6]Aparicio J, Segura A, Garcera S, et al. ESHAP is an active regimen for relapsing Hodgkin's disease. Ann Oncaol 1999;10(5):593-595.
Akhtar S, Abdelsalam M, El Weshi A, et al. High-dose chemotherapy and autologous stem cell transplantation for Hodgkin's lymphoma in the kingdom of Saudi Arabia: King Faisal specialist hospital and research center experience. Bone Marrow Transplant 2008;42 Suppl 1:S37-S40. Fernández de Larrea C, Martínez C, et al. Salvage chemotherapy with alternating MINE-ESHAP regimen in relapsed or refractory Hodgkin's lymphoma followed by autologous stem cell transplantation. Ann Oncol 2010;21(6):1211-1216.
[7]Bartlett N, Niedzwiecki D, Johnson J, et al. Gemcitabine, vinorelbine, and pegylated liposomal doxorubicin (GVD), a salvage regimen in relapsed Hodgkin's lymphoma: CALGB 59804. Ann Oncol 2007;18(6):1071-1079.
[8]Santoro A, Magagnoli M, Spina M, et al. Ifosfamide, gemcitabine, and vinorelbine: a new induction regimen for refractory and relapsed Hodgkin's lymphoma. Haematologica 2007;92(1):35-41.
[9]Colwill R, Crump M, Couture F, et al. Mini-BEAM as salvage therapy fir relapsed or refractory Hodgkin's disease before inten sive therapy and autologous bone marrow transplantation. J Clin Oncol. 1995;13:396-402.
Martín A, Fernández-Jiménez MC, Caballero MD, et al. Long-term follow-up in patients treated with Mini-BEAM as salvage therapy for relapsed or refractory Hodgkin's disease. Br J Haematol 2001;113(1):161-171.
[10]Rodriguez MA, Cabanillas FC, Hagemeister FB, et al. A phase II trial of mesna/ifosfamide, mitoxantrone and etoposide for etoposide for refractory lymphomas. Ann Oncol 1995;6(6):609-611.
[11]Phillips JK, Spearing RL, Davies JM, et al. VIM-D salvage chemotherapy in Hodgkin's disease. Cancer Chemother Pharmacol 1990;27(2):161-3.
12Gopal AK, Press OW, Shustov AR, et al. Efficacy and safey of gemicitabine, carboplatin, dexamethasone, and rituximab in patients with relapsed/refractory lymphoma: a prospective multui-center phase II study by Puget Sound Oncology Consortium. Leuk Lymphoma. 2010;51:1523-1529.
[13]Sweetenham JW, Taghipour G, Milligan D, et al. High-dose therapy and autologous stem cell rescue for patients with Hodgkin's disease in first relapse in first relapse after chemotherapy; results from the EBMT. Lymphoma Working Party of the European Group for Blood and Marrow Transplantation. 1997;20(9):745-752.
[14]Bierman PJ, Anderson JR, Freeman MB, et al. High-dose chemotherapy followed by autologous hematopoietic rescue for Hodgkin's disease patients following first relapse after chemotherapy. Ann Oncol 1996;7(2):151-156.
[15]Chopra R, McMillan AK, Linch DC, et al. The place of high-dose BEAM therapy and autologous bone marrow transplantation in poor-risk Hodgkin's disease. A single-center eight-year study of 155 patients. Blood 1993;81:1137-1145.
[16]Stewart DA, Guo D, Gluck S, et al. Double high-dose therapy fir Hodgkin's disease with dose-intensive cyclophosphamide, etoposide, and cisplatin (DICEP) prior to high-dose melphalan and autologous stem cell transplantation. Bone Marrow Transplant2000;26(4):383-388.

Table 1

Definitions of Stages in Hodgkin's Disease

Stage I Involvement of a single lymph node region (I) or localized involvement of a single extralymphatic organ or site (I_E).

Stage II Involvement of two or more lymph node regions on the same side of the diaphragm (II) or localized involvement of a single associated extralymphatic organ or site and its regional lymph node(s), with or without involvement of other lymph node regions on the same side of the diaphragm (II_E)

Note: The number of lymph node regions involved may be indicated by a subscript (e.g. II_3).

Stage III Involvement of lymph node regions on both sides of the diaphragm (III), which may also be accompanied by localized involvement of an associated extralymphatic organ or site (IIIE), by involvement of the spleen (III_S), or by both (III_{E+S}).

Stage IV Disseminated (multifocal) involvement of one or more extralymphatic organs, with or without associated lymph node involvement, or isolated extralymphatic organ involvement with distant (nonregional) nodal involvement.

A No systemic symptoms present

B Unexplained fevers >38 ℃; drenching night sweats; or weight loss >10% of body weight

Adapted from **Carbone PP, Kaplan HS, Musshoff K et al. Report of the Committee on Hodgkin's Disease Staging Classification. Cancer Res 1971;31(11):1860-1.**

Ann Arbor Stage

StageI	Involvemet of a single lymphatic site(i.e. nodal region,Waldeyer's ring,thymus or spleen)(I); or localized involvemet of a single extralymphatic organ or site in the absence of any lymph node involvemet(IE)(rare in Hodgkin lymphoma)
StageII	Involvemet of two or more lymph node regions on the same side of the diaphragm(II); or licalized involvemet of a single extralymphatic organ or site in association with or without involvemet of other lymph node regions on the same side of the diaphragm(IIE).The number of regions involved may be indicated by a subscript,as in,for example.II.
StageIII	Involvemet of lymph node regions on both sides of the diaphragm(III),which also may be accompanied by extralymphatic extension in association with adjacent lymph node involvemet (IIIE) or by involvemet of the spleen (IIIS) or both (IIIE,S).Splenic involvemet is designated by the letter S.
StageIV	Diffuse or disseminated involvemet of one or more extralymphatic organs,with or without associated lymph node involvemet;or isolated extralymphatic organs involvemet in the absence of adjacent regional lymph node involvemet,but in conjunction with disease in distant site(s).Stage IV includes any involvemet of the liver or bone marrow,lungs(others than by direct extension from another site),or cerebrospinal fluid.

Modifiers for Group:

- ☐ E Extranodal
- ☐ S Spleen

A & B Classification (Symptoms):

- ☐ A Asymptomatic
- ☐ B Symptoms:fever ,night sweats,weight loss