高 雄 榮 民 總 醫 院
淋巴癌診療原則

2021年04月20日 第一版

血液暨淋巴癌醫療團隊擬訂

注意事項：這個診療原則主要作為醫師和其他保健專家診療癌症病人參考之用。假如你是一個癌症病人，直接引用這個診療原則並不恰當，只有你的醫師才能決定給你最恰當的治療。

會議討論

上次會議：2020/04/21

本共識與上一版的差異

上一版	新版
1. Extranodal NK/T cell lymphoma , nasal type(p12)	→修正流程圖(p12、13)
2. 附註中CEOP字眼修改(p16)	→修改為CHOP(p16)
3. DLBCL 診斷部分常見IHC panel、Karyotype(p18)	→詳見表格內容(p18)
4. DLBCL之risk of CNS disease內容(p20)	→更新risk of CNS disease內容(p20)
5. DLBCL流程圖更新(p21)	→更新流程圖(p21)
6. DLBCL regimen(R-CHOP、R-CEOP…)(p23-25)中的Rituximab因IV與SC劑量是不同的，所以分開寫出，Doxor改為學名Doxorubicin	→Rituximab 375MG/M2 IVA or Rituximab 1400mg SC、Doxor改為學名Doxorubicin(p23-25)
7. DLBCL regimen(DHAP)(p26)中的Carboplatin AUC x 1.25MG 劑量修正	→修改為Carboplatin AUC x 5MG (p26)
8. DLBCL regimen(DICE)(p27)中註明Ifosfamide可使用最大劑量	→註明Ifosfamide可使用最大劑量為1750mg(p27) →並新增ICE regimen
9. DLBCL regimen(R+B、GemoX)(p28)修正使用藥物、劑量及名稱	→R+B中R的部分修正:Rituximab 375MG/M2 IVA or Rituximab 1400mg SC GemoX註明各項藥物及劑量、途徑:gemcitabine 1000mg/m2 IVA Q12H、oxaliplatin 100mg/m2 IVA 、rituximab 375MG/M2 IVA or Rituximab 1400mg SC(p28) →新增lenalidomide
10. DLBCL文獻參考(p30)	→更新文獻參考資料3~6(p30)

會議討論

上一版	新版
11. HL regimen 之 ABVD(p43)修改Doxorubicin目前應為Epirubicin	→修改Doxorubicin 25mg/m2為Epirubicin 37.5mg/m2
12. HL regimen 之 AVD+BV(p43)修正BV藥名	→Brentuximab修正為Brentuximab vedotin
13. HL regimen(DHAP)(p44)中的Carboplatin AUC x 1.25MG 劑量修正	→修改為Carboplatin AUC x 5MG (p44)
14. Brentuximab、Pembrolizumab(kytruda)的藥名錯誤，重新修改(p45)	→Brentuximab修正為Brentuximab vedotin、kytruda修改為keytruda(p45)
15. FL診斷部分常見IHC panel、Karyotype(p48)	→詳見表格內容(p48)
16. FL regimen(R-CHOP、R-CEOP…)(p52-53)中的Rituximab因IV與SC劑量是不同的，所以分開寫出，Doxor改為學名Doxorubicin	→Rituximab 375MG/M2 IVA or Rituximab 1400mg SC、Doxor改為學名Doxorubicin(p52-53)
17. FL regimen (R+F / RFN)部分補上藥名、劑量	→RF:Fludarabine 25mg/m^2 + Rituximab 375mg/m^2. RFN:Rituximab 375mg/m^2,Fludarabine 25mg/m^2 D1-3,Mitoxantrone 10mg/m^2 D1 , Dexamethasone 20mg/m^2

PROTOCOLS FOR TREATMENT OF MALIGNANT LYMPHOMA

Version 1. 2021

MALIGNANT LYMPHOMA

Kaohsiung Veterans General Hospital
Clinical Practice Guideline Version 1.2021

General Guide

Diagnosis	Staging Work-up
1.Adequate sampling and proper handling of the tissue 2. Effective communication between the clinician and the pathologist 3. Surgical biopsy of the largest lymph nodes or mass lesion* 4. Needle biopsy in certain conditions 5. Flow cytometry or cytogenetic studies: optional * Lymph node	1. Complete history and physical examination including Waldeyer's rings, B symptoms, risk of HIV infection, infection, autoimmune diseases, immunosuppressive therapies 2. Complete blood cell count with a differential, erythrocyte sedimentation rate (ESR) 3. Chemistry profiles: LDH, AST, ALT, Alk-p, bilirubin, uric acid, Cr, Ca, albumin, total protein, sugar 4. EKG, CXR-PA, whole body CT, HBsAg, and anti-HCV 5. Other evaluation: beta2-microglobulin, Urinalysis and stool analysis, cytologic study of third space fluids 6. Bone marrow aspiration and biopsy 7. Lumbar puncture with cytology in selected patients a. All patients with Burkitt lymphoma b. Patients with NHL in certain sites e.g. CNS, epidural space, testes, ethmoid sinus, and large cell lymphoma with bone marrow involvement c. HIV positive patients 8. Gastrointestinal studies a. Esophagogastroduodenoscopy, upper gastrointestinal plus small bowel and lower gastrointestinal series for patients with gastrointestinal tract lymphoma; Endoscopic ultrasonography for gastric MALT lymphoma b. Considered in patients with positive stool occult blood 9. Selected radiologic images as clinically needed, e.g. positron emission tomograph, magnetic resonance imaging, and bone scan 10. Cytogenetic and molecular tests in selected patients (optional); cardiac ejection fraction for age > 60 if anthracycline will be used. Anthracyline is contraindicated if ejection fraction is less than 50%.

MALIGNANT LYMPHOMA

NON-HODGKINS'S LYMPHOMA

Low grade Lymphoma	Intermediate grade lymphoma	High grade lymphoma
Small lymphocytic lymphoma	Follicular lymphoma, grade 3	Diffuse large B cell lymphoma (DLBCL)
Follicular lymphoma, grade 1	Mantle cell lymphoma	High grade B cell lymphoma
Follicular lymphoma, grade 2		NK/T cell lymphoma
Marginal zone lymphoma		Peripheral T cell lymphoma
		Burkitt's lymphoma

MALIGNANT LYMPHOMA

Kaohsiung Veterans General Hospital
Clinical Practice Guideline Version 1.2021

Staging

Lugano Modification of Ann Arbor Staging System*
(for primary nodal lymphomas)

Stage	Involvement	Extranodal (E) status
Limited		
Stage I	One node or a group of adjacent nodes	Single extranodal lesions without nodal involvement
Stage II	Two or more nodal groups on the same side of the diaphragm	Stage I or II by nodal extent with limited contiguous extranodal involvement
Stage II bulky**	II as above with "bulky" disease	Not applicable
Advanced		
Stage III	Nodes on both sides of the diaphragm	Not applicable
	Nodes above the diaphragm with spleen involvement	
Stage IV	Additional non-contiguous extralymphatic involvement	Not applicable

MALIGNANT LYMPHOMA

Kaohsiung Veterans General Hospital
Clinical Practice Guideline Version 1.2021

Staging of gastric MALT LYMPHOMA：comparison of different systems

Lugano Staging System for Gastrointestinal Lymphomas		Lugano Modification of Ann Arbor Staging System	TNM Staging System Adapted for Gastric Lymphoma	Tumor Extension
Stage I	Confined to GI tract[a]			
	I_1 = mucosa, submucosa	I_E	T1 N0 M0	Mucosa, submucosa
	I_2 = muscularis propria, serosa	I_E	T2 N0 M0	Muscularis propria
		I_E	T3 N0 M0	Serosa
Stage II	Extending into abdomen			
	II_1 = local nodal involvement	II_E	T1-3 N1 M0	Perigastric lymph nodes
	II_2 = distant nodal involvement	II_E	T1-3 N2 M0	More distant regional lymph nodes
Stage IIE	Penetration of serosa to involve adjacent organs or tissues	II_E	T4 N0 M0	Invasion of adjacent structures
Stage IV[b]	Disseminated extranodal involvement or concomitant supradiaphragmatic nodal involvement		T1-4 N3 M0	Lymph nodes on both sides of the diaphragm/ distant metastases (eg, bone marrow or additional extranodal sites)
		IV	T1-4 N0-3 M1	

MALIGNANT LYMPHOMA

Kaohsiung Veterans General Hospital
Clinical Practice Guideline Version 1.2021

NON-HODGKINS'S LYMPHOMA

LOW GRADE LYMPHOMA

1)Early Stage (Stage I –II) →
1. Watch & wait
2. Surgical resection
3. Radiation therapy

2)Advanced Stage (Stage III–IV)

- **a) For elderly symptomatic patients in advanced stage:** →
  1) Adopt "watch and wait" policy, deferring treatment until symptoms dictate.
  2) 1st line chemotherapy: Single oral alkylating agents (Single Rituximab or R+B)
  3) R-COP regimen for follicular lymphoma
- **b) For young patients:** → Tailor the treatment to individual condition. Autologous PBSCT post complete remission.

3) Relapsed low grade lymphoma → **Autologous PBSCT for chemo-sensitive disease**

HODGKIN'S Lymphoma

1)Chemotherapy with ABVD regimen + radiation for bulky mass
2)Chemotherapy with AVD + BV regimen for advanced stage III~IV

3)Autologous PBSCT → a)Stage IVb disease post complete remission
b)Failure to achieve 1st complete remission
c)Relapsed disease

MALIGNANT LYMPHOMA

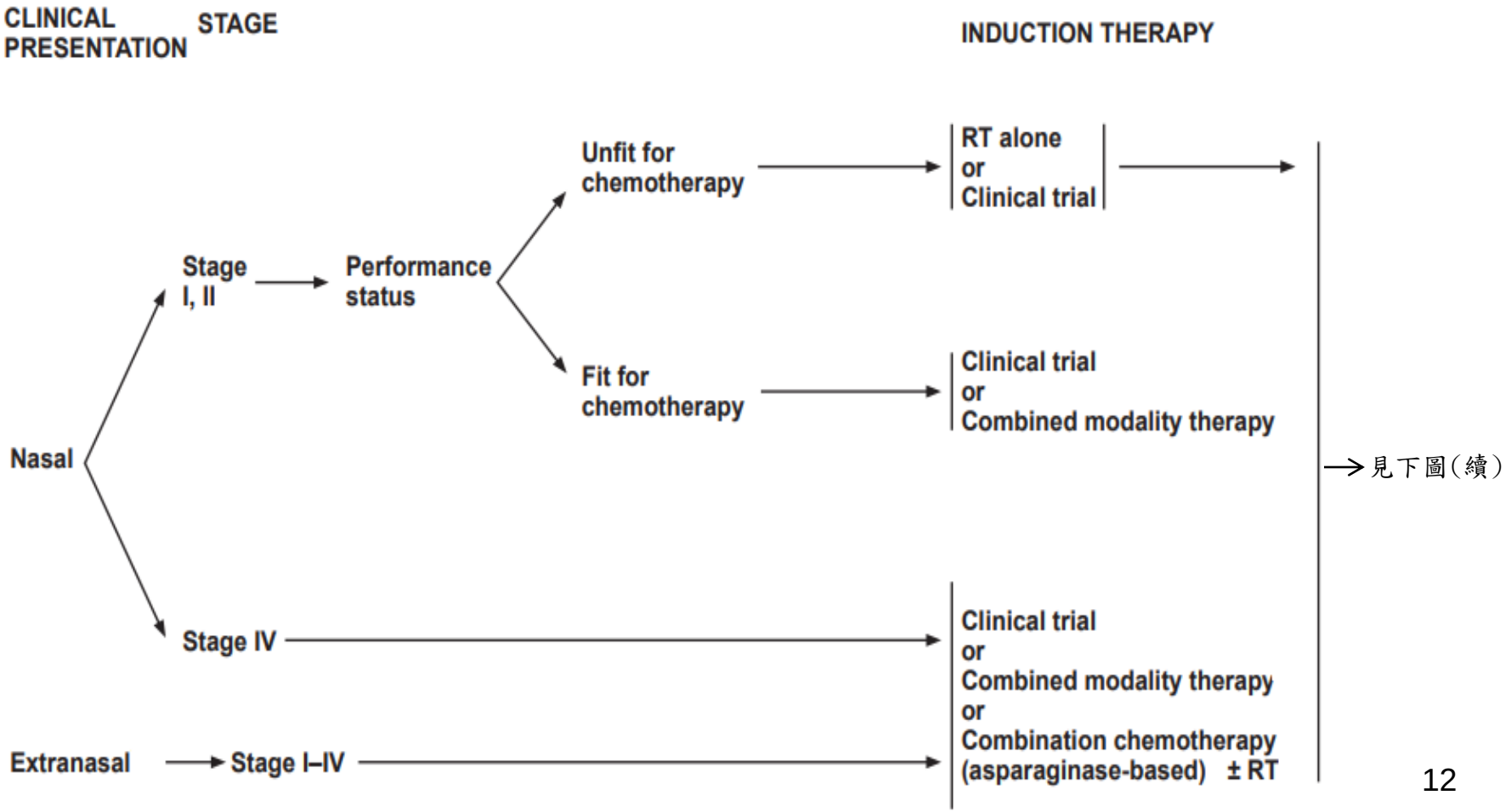
- Lumbar puncture for cerebrospinal fluid (CSF)examination should be performed in patients with the following conditions:

  Diffuse aggressive NHL with
  - bone marrow
  - epidural
  - testicular
  - paranasal sinus
  - nasopharyngeal involvement
  - or patient with two or more extranodal sites of disease.
  - High-grade lymphoblastic lymphoma
  - High-grade small noncleaved cell lymphomas (eg, Burkitt)
  - HIV-related lymphoma
  - Primary CNS lymphoma
  - Patients with neurologic signs and symptoms
  - breast lymphoma

MALIGNANT LYMPHOMA

Kaohsiung Veterans General Hospital
Clinical Practice Guideline Version 1.2021

Extranodal NK/T cell lymphoma , nasal type

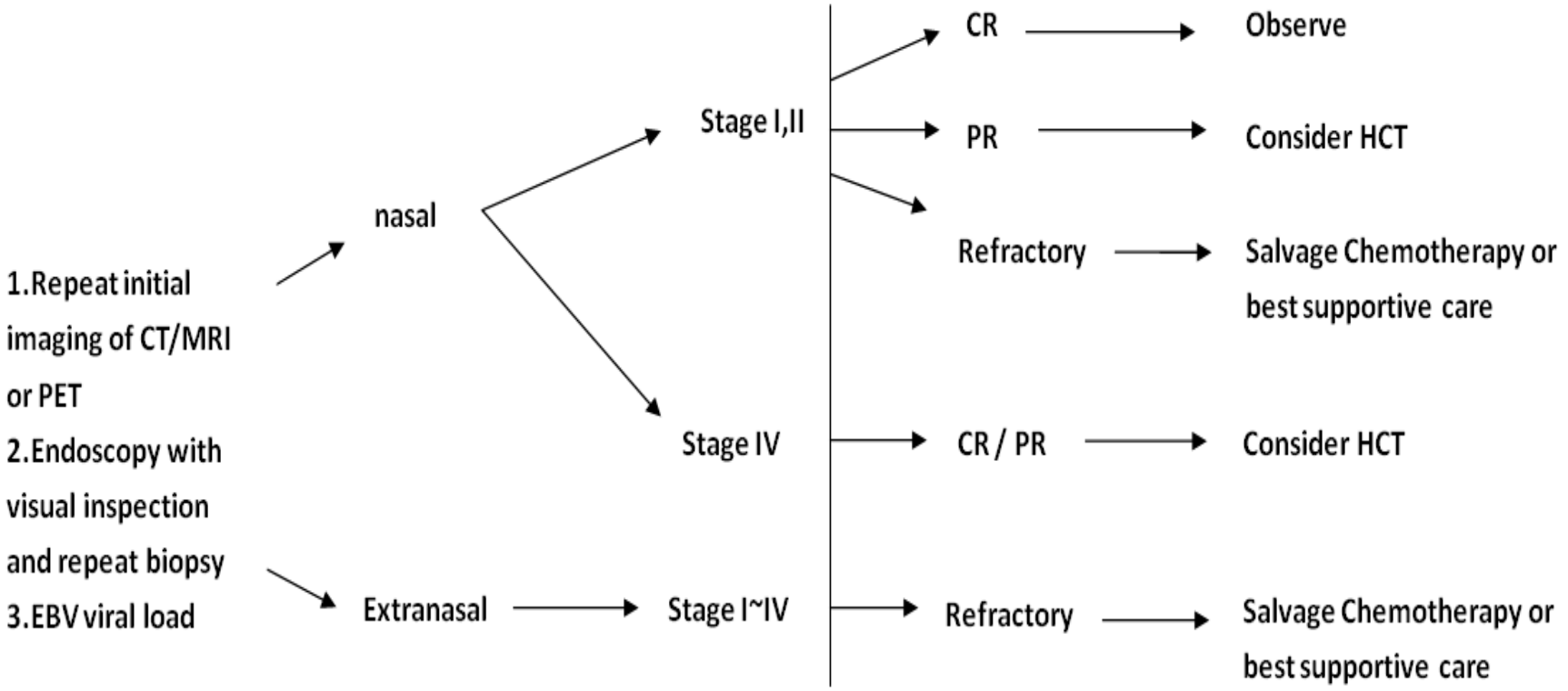


MALIGNANT LYMPHOMA

Kaohsiung Veterans General Hospital
Clinical Practice Guideline Version 1.2021

Extranodal NK/T cell lymphoma , nasal type

End-OF-Treament evaluation



NK/T CELL LYMPHOMA PROGNOSTIC INDEX

PROGNOSTIC INDEX OF NATURAL KILLER LYMPHOMA (PINK)[a]

RISK FACTORS	
Age >60 y	
Stage III or IV disease	
Distant lymph-node involvement	
Non-nasal type disease	
	Number of risk factors
Low	0
Intermediate	1
High	≥2

PROGNOSTIC INDEX OF NATURAL KILLER CELL LYMPHOMA WITH EPSTEIN-BARR VIRUS DNA (PINK-E)[a]

RISK FACTORS	
Age >60 y	
Stage III or IV disease	
Distant lymph-node involvement	
Non-nasal type disease	
Epstein-Barr virus DNA	
	Number of risk factors
Low	0–1
Intermediate	2
High	≥3

References:

1. NCCN guidelines of Non-Hodgkin' s lymphomas, V.1 2020

2.NCCN guidelines of Hodgkin's disease/lymphoma, V.3 2018

3.NCCN guidelines of Non-Hodgkin' s lymphomas, V.4 2018

4.http://www.uptodateonline.com/online/content/search.do

5.http://chemoregimen.com/Lymphoma-c-44-55.html

6.http://chemoregimen.com/Dosage-for-Renal-Dysfunction-c-59-68.html

7.Baxter Oncology - Selected Schedules of Therapy for Malignant Tumors, 11th edition.

8.A cooperative study on ProMACE-CytaBOM in aggressive non-Hodgkin's lymphomas. Leuk Lymphoma 1994; 13:111-8.

9. NCCN guidelines of Non-Hodgkin' s lymphomas, V.1 2021

10. https://www.uptodate.com/contents/treatment-of-extranodal-nk-t-cell-lymphoma-nasal-type 7.Baxter Oncology - Selected Schedules of Therapy for Malignant Tumors, 11th edition.

11. Chan TSY, Li J, Loong F, et al. PD1 blockade with low-dose nivolumab in NK/T cell lymphoma failing L-asparaginase: efficacy and safety. Ann Hematol 2018; 97:193.

12. Kim SJ, Hyeon J, Cho I, et al. Comparison of Efficacy of Pembrolizumab between Epstein-Barr Virus–Positive and –Negative Relapsed or Refractory Non-Hodgkin Lymphomas. Cancer Res Treat 2019; 51:611

13. Li X, Cheng Y, Zhang M, et al. Activity of pembrolizumab in relapsed/refractory NK/T-cell lymphoma. J Hematol Oncol 2018; 11:15

附註

依據本院2009年淋巴瘤年報，罹患瀰漫性大B型淋巴瘤及濾泡型淋巴瘤病患，使用標靶治療Rituximab併用化療CHOP較單用化療處方CHOP顯著增加整體存活率（p值為0.0001）。此統計結論與西方國家的研究報告相同，因此2010年7月本院淋巴瘤治療指引修正為：瀰漫性大B型淋巴瘤及濾泡型淋巴瘤使用Rituximab併用化療CHOP處方，台灣病患治療成績證實與西方國家同樣優秀，因而在療效更好的處方問世前，淋巴瘤團隊建議持續使用Rituximab併用化療處方CHOP。

Diffuse large B cell lymphoma

Kaohsiung Veterans General Hospital
Clinical Practice Guideline Version 1.2021

注意事項：

此治療準則主要作為本院醫療團隊診療病人參考之用途，並非適合所有病人，需由主治醫師視個別性選擇治療方式。

2021/04/20 第一版

Diffuse large B cell lymphoma

Kaohsiung Veterans General Hospital
Clinical Practice Guideline Version 1. 2021

Diagnosis	Staging Work-up
requirement： ＊Hematopathology review of all slides with at least one paraffin block representative of tumor. Rebiopsy if consult material is nondiagnostic. ＊An FNA or core needle biopsy alone is not generally suitable for the initial diagnosis of lymphoma. In certain circumstances, when a lymph nodes is not easily accessible for excisional or incisional biopsy, a combination of core biopsy of FNA biopsies in conjunction with appropriate ancillary techniques for the differential diagnosis may be sufficient for diagnosis. ※IHC panel：CD30,CD5,CD10,CD45,BCL2,BCL6,Ki-67, IRF4/MUM1,MYC ※Cell surface marker analysis by flow cytomerty：kapp/lambda, CD45,CD3,CD5,CD19,CD10,CD20 Useful under certain circumstances： ＊Additional immunohistochemical studies to establish lymphoma subtype ※IHC panel：Cyclin D1, kapp/lambda,CD30,CD138,EBV-ISH ,ALK,HHV8,SOX-11 ＊Karyotype or FISH for BCL2,BCL6 rearrangements if MYC positive	requirement： ＊Physical exam：attention to node-bearing areas,including Waldeyer's rings, B- symptoms and to size of liver and spleen ＊Performance status ＊CBC differential, platelets, LDH, Uric acid ＊Comprehensive metabolic panel ★CT：face / chest / abdominal / pelvic or PET ＊bone marrow biopsy ± aspirate ＊IPI SCORE ＊Hepatitis B、C testing ＊echocardiogram or ejection fraction 選擇性： ＊HIV ＊Discussion of fertility issues and sperm banking ＊Lumbar puncture ＊ Beta2- microglobulin

Diffuse large B cell lymphoma

Kaohsiung Veterans General Hospital
Clinical Practice Guideline Version 1. 2021

INTERNATIONAL PROGNOSTIC INDEX[a]

ALL PATIENTS:	INTERNATIONAL INDEX, ALL PATIENTS:	
• Age >60 years	• Low	0 or 1
• Serum LDH > normal	• Low-intermediate	2
• Performance status 2–4	• High-intermediate	3
• Stage III or IV	• High	4 or 5
• Extranodal involvement >1 site		

AGE-ADJUSTED INTERNATIONAL PROGNOSTIC INDEX[a]

PATIENTS ≤60 YEARS:	INTERNATIONAL INDEX, PATIENTS ≤60 YEARS:	
• Stage III or IV	• Low	0
• Serum LDH > normal	• Low-intermediate	1
• Performance status 2–4	• High-intermediate	2
	• High	3

STAGE-MODIFIED INTERNATIONAL PROGNOSTIC INDEX[b]

STAGE I OR II PATIENTS:	INTERNATIONAL INDEX, STAGE I OR II PATIENTS:	
• Age >60 years	• Low	0 or 1
• Serum LDH > normal	• High	2–4
• Performance status 2–4		
• Stage II or IIE		

NCCN-IPI[c]

		Risk Group	
Age, years		• Low	0–1
>40 to ≤60	1	• Low-intermediate	2–3
>60 to <75	2	• High-intermediate	4–5
≥75	3	• High	≥6
LDH, normalized			
>1 to ≤3	1		
>3	2		
Ann Arbor stage III-IV	1		
Extranodal disease*	1		
Performance status >2	1		

*Disease in bone marrow, CNS, liver/GI tract, or lung.

Diffuse large B cell lymphoma

Kaohsiung Veterans General Hospital Clinical Practice Guideline Version 1. 2021

Prognostic Model to Assess the Risk of CNS Disease[d]

- Age >60 years
- Serum LDH > normal
- Performance status >1
- Stage III or IV
- Extranodal involvement >1 site
- Kidney or adrenal gland involvement

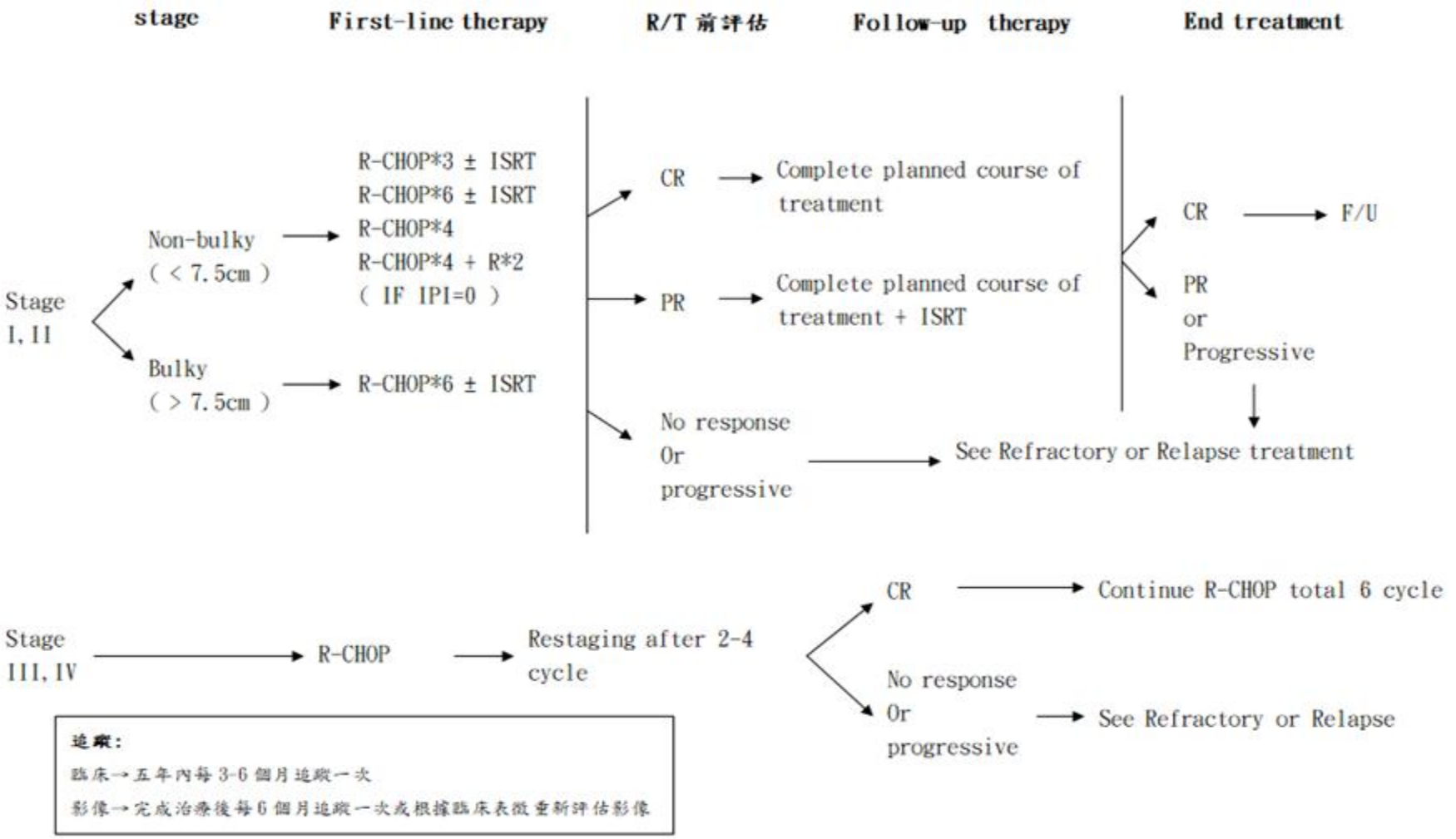
Low risk	0–1	
Intermediate-risk	2–3	
High-risk	4–6	or kidney or adrenal gland involvement

- Additional indications for CNS prophylaxis independent of CNS risk score
  - HIV-associated lymphoma
  - Testicular lymphoma
  - High-grade B-cell lymphomas (HGBLs) with translocations of *MYC* and BCL2 and/or BCL6 HGBL, NOS
  - Primary cutaneous DLBCL, leg type
  - Stage IE DLBCL of the breast

- Suggested CNS prophylactic therapy (Optimal management is uncertain)
  - Systemic high-dose methotrexate (3–3.5 g/m^2 for 2–4 cycles) during or after the course of treatment and/or
  - Intrathecal methotrexate and/or cytarabine (4–8 doses) during or after the course of treatment

Diffuse large B cell lymphoma

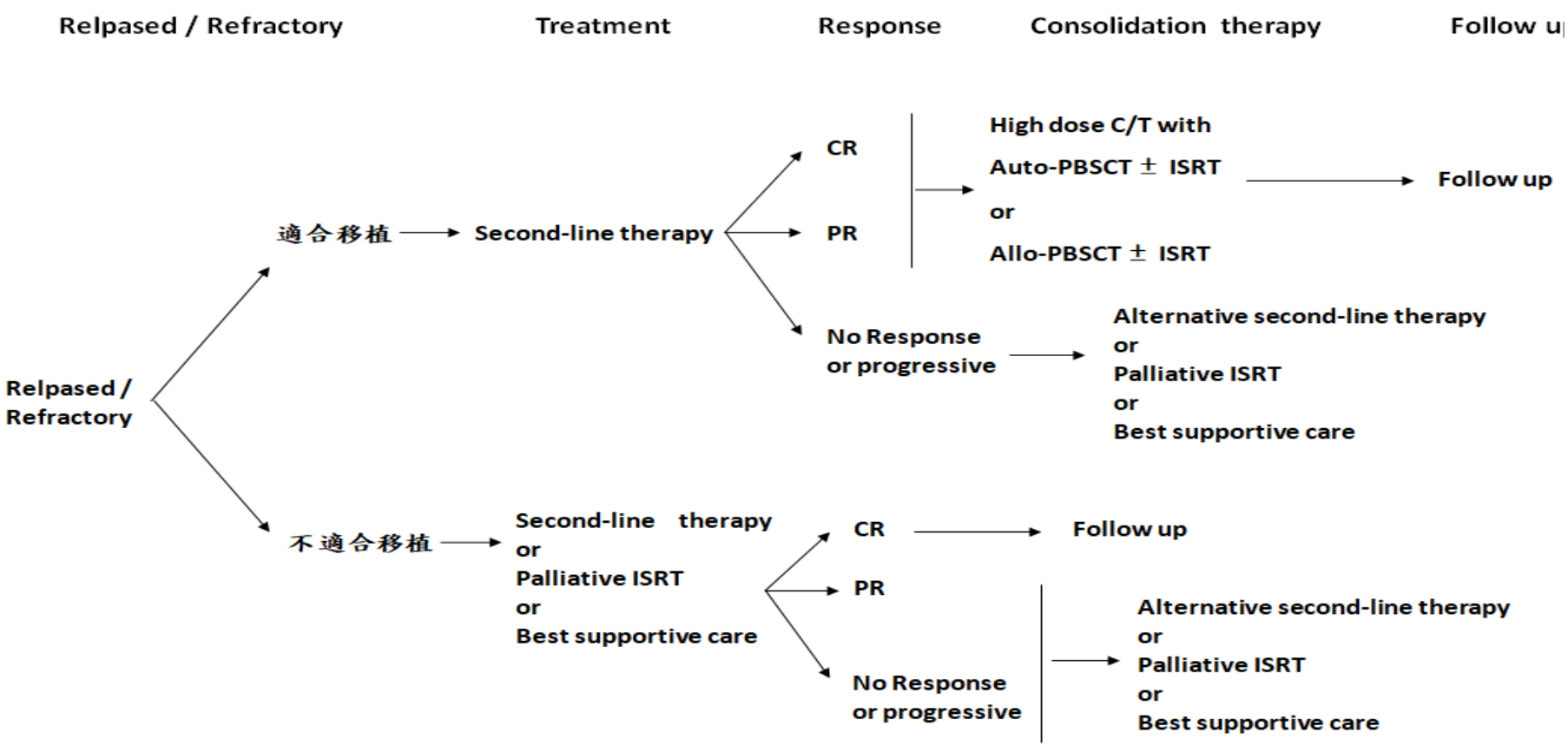
Kaohsiung Veterans General Hospital
Clinical Practice Guideline Version 1. 2021



Diffuse large B cell lymphoma

Kaohsiung Veterans General Hospital
Clinical Practice Guideline Version 1.2021

➢Relapsed / Refractory disease treatment



追蹤：
臨床→五年內每 3-6 個月追蹤一次 H&P 和 labs，然後每年追蹤或根據臨床表徵
影像→完成治療後 2 年每 6 個月追蹤一次或根據臨床表徵重新評估影像

Diffuse large B cell lymphoma

Kaohsiung Veterans General Hospital
Clinical Practice Guideline Version 1.2021

建議治療療程

一線化療	
R-CHOP	± Rituximab 375MG/M2 IVA or Rituximab 1400mg SC on D1
	Cyclophosphamide 750MG/M2 IVA on D1 or D2
	Doxorubicin 50MG/M2 IVA on D1 or D2
	Vincristine 2MG IVA on D1 or D2
	Prednisone 5MG 10TAB BID po for 5days
	References:NO 2.4
R-CEOP	± Rituximab 375MG/M2 IVA or Rituximab 1400mg SC on D1
	Cyclophosphamide 750MG/M2 IVA on D1 or D2
	Epirubicin 75MG/M2 IVA on D1 or D2
	Vincristine 2MG IVA on D1 or D2
	Prednisone 5MG 10TAB BID po for 5days
	References:NO 3

Diffuse large B cell lymphoma

Kaohsiung Veterans General Hospital
Clinical Practice Guideline Version 1.2021

一線化療	
EPOCH-R (DA)EPOCH-R	Etoposide 50MG/M2 IVA D1-4
	Prednisone 10TAB PO BID for 5days
	Vincristine 0.4MG/M2 IVA D1-4
	Epicin 15MG/M2 IVA D1-4
	Cyclophosphamide 750MG/M2 IVA D5
	± Rituximab 375MG/M2 IVA or Rituximab 1400mg SC D1 References: NO 5

Diffuse large B cell lymphoma

Kaohsiung Veterans General Hospital
Clinical Practice Guideline Version 1.2021

一線化療(適用於年紀大或心臟功能不好病人)	
R-CNOP	± Rituximab 375MG/M2 IVA or Rituximab 1400mg SC on D1
	Cyclophosphamide 750MG/M2 IVA on D1 or D2
	Mitoxantrone 10MG/M2 IVA on D1 or D2
	Vincristine 2MG IVA on D1 or D2
	Prednisone 5MG 10TAB BID po for 5days
	References : NO 6
R-COP	± Rituximab 375MG/M2 IVA or Rituximab 1400mg SC on D1
	Cyclophosphamide 800MG/M2 IVA on D1 or D2
	Vincristine 2MG IVA on D1 or D2
	Prednisone 5MG 10TAB BID po for 5days
	References : NO 6

Diffuse large B cell lymphoma

建議治療療程

二線化療（適用於執行高劑量化療+自體幹細胞移植者）	
DHAP	Dexamethasone 40MG for 4 days
	Cisplatin 100MG/M2/ Carboplatin AUCx 5MG IVA on D1
	Cytarabine 2000MG/M2 IVA Q12H on D2
	註：CCr ＜60 使用Carboplatin References : NO7
ESHAP	Solu-Medrol 500MG IVA for 5days on D1-5
	Etoposide 40MG/M2 IVA for 4days on D1-4
	Cisplatin 25MG/M2 / Carboplatin AUCx1.25MG IVA for 4days on D1-4
	Cytarabine 2000MG/M2 IVA on D5
	註：CCr ＜60 使用Carboplatin References : NO8

Diffuse large B cell lymphoma

Kaohsiung Veterans General Hospital
Clinical Practice Guideline Version 1.2021

建議治療療程

二線化療（適用於執行高劑量化療+自體幹細胞移植者）		
DICE	Ifosfamide 1GM/M2 IVA for 4day on D1-4	註:maximum dose 1750mg
	Cisplatin 25MG/M2 / Carboplatin AUCx1.25MG IVA for 4day on D1-4	
	Etoposide 100MG/M2 IVD for 4day on D1-4	
	Dexamethasone 40MG IVA for 4day on D1-4	
	註：CCr ＜60 使用Carboplatin	References : NO9
MINE	Mesna 1.33GM/M2 IVA for 3days on D1-3	
	Ifosfamide 1.33GM/M2 IVA for 3days on D1-3	
	Mitoxantrone 8MG/M2 IVA on D1	
	Etoposide 65MG/M2 IVA for 3days on D1-3	References : NO9
ICE	Etoposide 100MG/M2 IVD on D1-3	
	Carboplatin AUCx5MG IVA on D2	
	Ifosfamide 1GM/M2 IVA on D2	References : NO9

Diffuse large B cell lymphoma

Kaohsiung Veterans General Hospital
Clinical Practice Guideline Version 1.2021

建議治療療程

二線化療（適用於無法執行高劑量化療者）	
R+B	± Rituximab 375mg/M2 IVA or Rituximab 1400mg SC on Day1
	Bendamustine 50~150MG/M2 IVA References : NO10.11
GemOx (2weeks/cycle)	Gemcitabine 1000MG/M2 IVA on Day1
	Oxaliplatin 100mg/M2 IVA on Day1
	± Rituximab 375mg/M2 IVA or Rituximab 1400mg SC on Day1 References : NO12
Lenalidomide	Revlimid Cap 25mg 1cap po QD x 21days References : NO10.11

Diffuse large B cell lymphoma

Lumbar puncture for cerebrospinal fluid (CSF)examination should be performed in patients with the following conditions:

Diffuse aggressive NHL with

- -bone marrow
- -epidural
- -testicular
- -paranasal sinus
- -nasopharyngeal involvement or patient with two or more extranodal sites
- -High-grade lymphoblastic lymphoma
- -High-grade small noncleaved cell lymphomas (eg, Burkitt)
- -HIV-related lymphoma
- -Primary CNS lymphoma
- -Patients with neurologic signs and symptoms
- -breast lymphoma
- -CNS IPI $\geqq$ 4

Diffuse large B cell lymphoma

Kaohsiung Veterans General Hospital
Clinical Practice Guideline Version 1.2021

References:

1.NCCN guidelines of Non-Hodgkin' s lymphomas, V.2 2021

2.Feugier P ,Van Hoof A, Sebban C,et al. Long-term results of the R-CHOP study in the treatment of elderly patients with diffuse large B-cell lymphoma:a study by the Groupe d′Etude des lymphomes de I′Adulte. J Clin Oncol 2005;23:4117-4126.

3. Moccia A.,Schaff K.,Hoskins P. ,et al. R-CHOP with Etoposide Substituted for Doxorubicin (R-CEOP): Excellent Outcome in Diffuse Large B Cell Lymphoma for Patients with a Contraindication to Anthracyclines. Blood 2009; 114 (22): 408.

4. Peyrade F. ,Jardin F., Thieblemont C.,et al.Attenuated immunochemotherapy regimen (R-miniCHOP) in elderly patients older than 80 years with diffuse large B-cell lymphoma: a multicentre, single-arm, phase 2 trial. Lancet Oncol 2011 May;12(5):460-8. doi: 10.1016/S1470-2045(11)70069-9.

5.Gutierrez M , Chabner B A, Pearson D, Steinberg S M, Jaffe E S, Cheson B D, Fojo A, Wilson W H. Role of a doxorubicin-containing regimen in relapsed and resistant lymphomas: an 8-year follow-up study of EPOCH. J Clin Oncol 2000 Nov 1;18(21):3633-42.doi: 10.1200/JCO.2000.18.21.3633.

6.Fields PA ,Townsend W , Webb A, Counsell N ,Pocock C, Smith P. De Novo Treatment of Diffuse Large B-Cell Lymphoma With Rituximab, Cyclophosphamide, Vincristine, Gemcitabine, and Prednisolone in Patients With Cardiac Comorbidity: A United Kingdom National Cancer Research Institute Trial. J Clin Oncol 2014,32(4):282-287.

7.Velasquez WS. Cabanillas F, Salvador P, et al. Effective salvage therpy for lymphoma with cisplatin in combination with high-dose Ara-C and dexamethasone(DHAP). Blood 1988;71:177-122.

8.Velasquez WS, McLaughin P,Tucker S, ET AL. ESHAP-an effective chemotherpy regimen in refractory and relapsing lymphoma:a 4-year follow-up study.J Clin Oncol 1994;12:1169-1176.

9.Gisselbrecht C, Glass B, Mounier N, et al. Salvage regimens with autologous transplantation for relapsed large B-cell lymphoma in the rituximab era. J Clin Oncol 2010;28:4184-4190.

10.Weidmann E, Kim SZ, Rost A,et al.Bendamustine is effective in relapsed or refractory aggressive non-Hodgkin's lymphoma.Ann Oncol 2002;13:1285-1289.

11.Vacirca JL, Acs PI, Tabbara IA, et al. Bendamustine combined with rituximab for patients with relapsed or refractory diffuse large B cell lymphoma. Ann Hematol 2014;93:403-409.

12.Lopez A, Gutierrez A, Palacios A, et al. GEMOX-R regimen is a highly effective salvage regimen in patients with refractory/relapsing diffuse large-cell lymphoma:a phase II study. Eur J Haematol 2008;80:127-132.

Hodgkin Lymphoma

Kaohsiung Veterans General Hospital
Clinical Practice Guideline Version 1.2021

注意事項：

此治療準則主要作為本院醫療團隊診療病人參考之用途，

並非適合所有病人，需由主治醫師視個別性選擇治療方式

2021/04/20 第一版

Hodgkin Lymphoma

Kaohsiung Veterans General Hospital
Clinical Practice Guideline Version 1.2021

Definitions of Stages in Hodgkin Lymphoma[2]

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 (eg, 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°C; drenching night sweats; or weight loss >10% of body weight (within 6 months prior to diagnosis)

Hodgkin Lymphoma

Kaohsiung Veterans General Hospital
Clinical Practice Guideline Version 1.2021

Unfavorable Risk Factors for Stage I-II Classic Hodgkin Lymphoma

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

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

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

- **Albumin <4 g/dL**
- **Hemoglobin <10.5 g/dL**
- **Male**
- **Age ≥45 years**
- **Stage IV disease**
- **Leukocytosis (white blood cell count at least 15,000/mm³)**
- **Lymphocytopenia (lymphocyte count less than 8% of white blood cell count, and/or lymphocyte count less than 600/mm³)**

†From: Hasenclever D, Diehl V. A prognostic score for advanced Hodgkin's disease: International Prognostic Factors Project on Advanced Hodgkin's Disease. N Engl J Med 1998;339:1506-1514. Copyright © 1998 Massachusetts Medical Society. Adapted with permission.

Hodgkin Lymphoma

Kaohsiung Veterans General Hospital
Clinical Practice Guideline Version 1.2021

DIAGNOSIS/WORKUP

- Excisional biopsy (recommended)
- Core needle biopsy may be adequate if diagnostic
- Immunohisto-chemistry evaluation

→

Essential:

- H&P including: B symptoms (unexplained fever >38°C; drenching night sweats; or weight loss >10% of body weight within 6 mo of diagnosis), alcohol intolerance, pruritus, fatigue, performance status, examination of lymphoid regions, spleen, liver
- CBC, differential, platelets
- Erythrocyte sedimentation rate (ESR)
- Comprehensive metabolic panel, lactate dehydrogenase (LDH), and liver function test (LFT)
- Pregnancy test for women of childbearing age
- ★ PET/CT scan (skull base to mid-thigh or vertex to feet in selected cases)
- Counseling: Fertility, smoking cessation, psychosocial

Useful in selected cases:

- Fertility preservation
- ★ Pulmonary function tests (PFTs incl. diffusing capacity [DLCO]) if ABVD or escalated BEACOPP are being used
- Pneumococcal, H-flu, meningococcal vaccines, if splenic RT contemplated
- HIV and hepatitis B/C testing (encouraged)
- Diagnostic CT (contrast-enhanced)
- Chest x-ray (encouraged, especially if large mediastinal mass)
- ★ Adequate bone marrow biopsy if there are unexplained cytopenias other than anemia (eg, thrombocytopenia or neutropenia) and negative PET
- Evaluation of ejection fraction if anthracycline-based chemotherapy is indicated
- MRI to select sites, with contrast unless contraindicated
- PET/MRI (skull base to mid-thigh) without contrast

Hodgkin Lymphoma

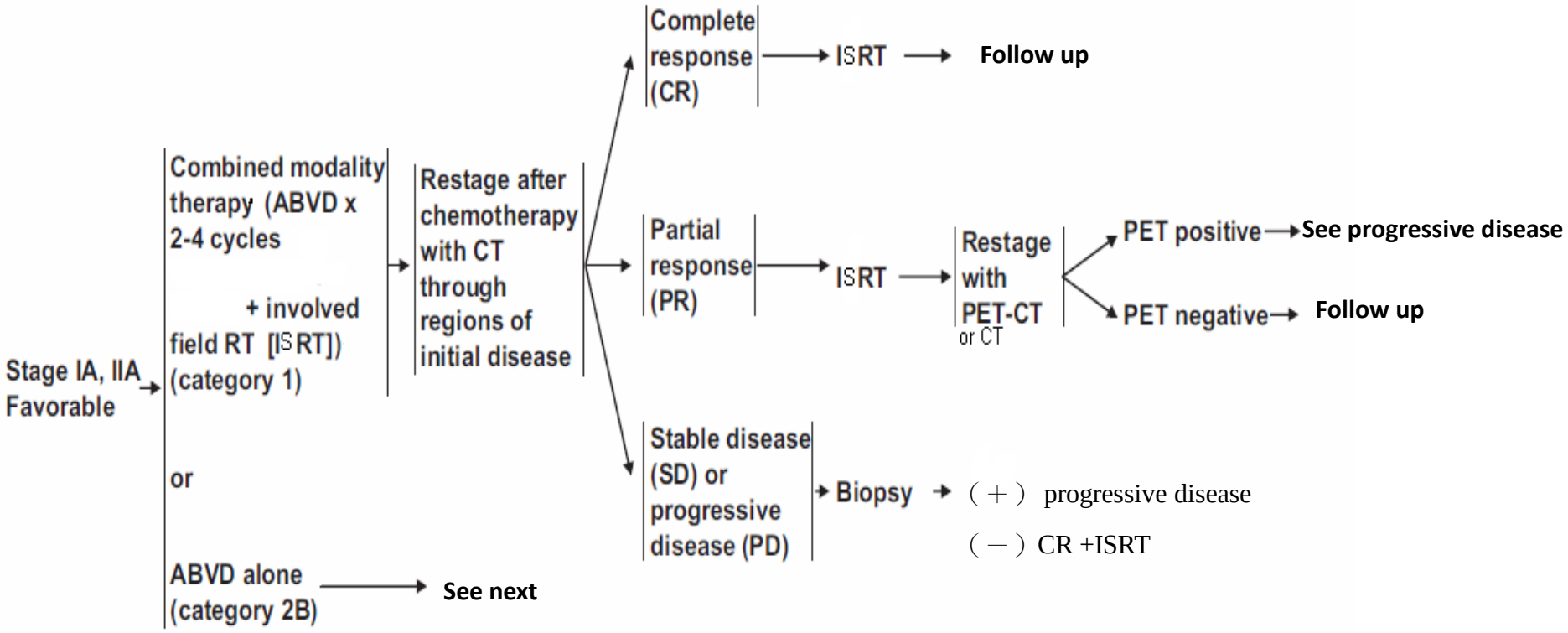
Summary

- Stage IA/IIA (favorable)
  Standard: combined modality with ABVD x 2-4 cycles + ISRT
  ABVD x 6 cycles (or 4 cycles) in selected case
- Stage I/II (unfavorable, non-bulky)
  ABVD x 6 cycles +/- ISRT
- Stage I/II (unfavorable, bulky)
  ABVD x 6 cycles + ISRT
- Stage III/IV
  ABVD x 6 cycles +/- ISRT

Hodgkin Lymphoma

Kaohsiung Veterans General Hospital
Clinical Practice Guideline Version 1.2021

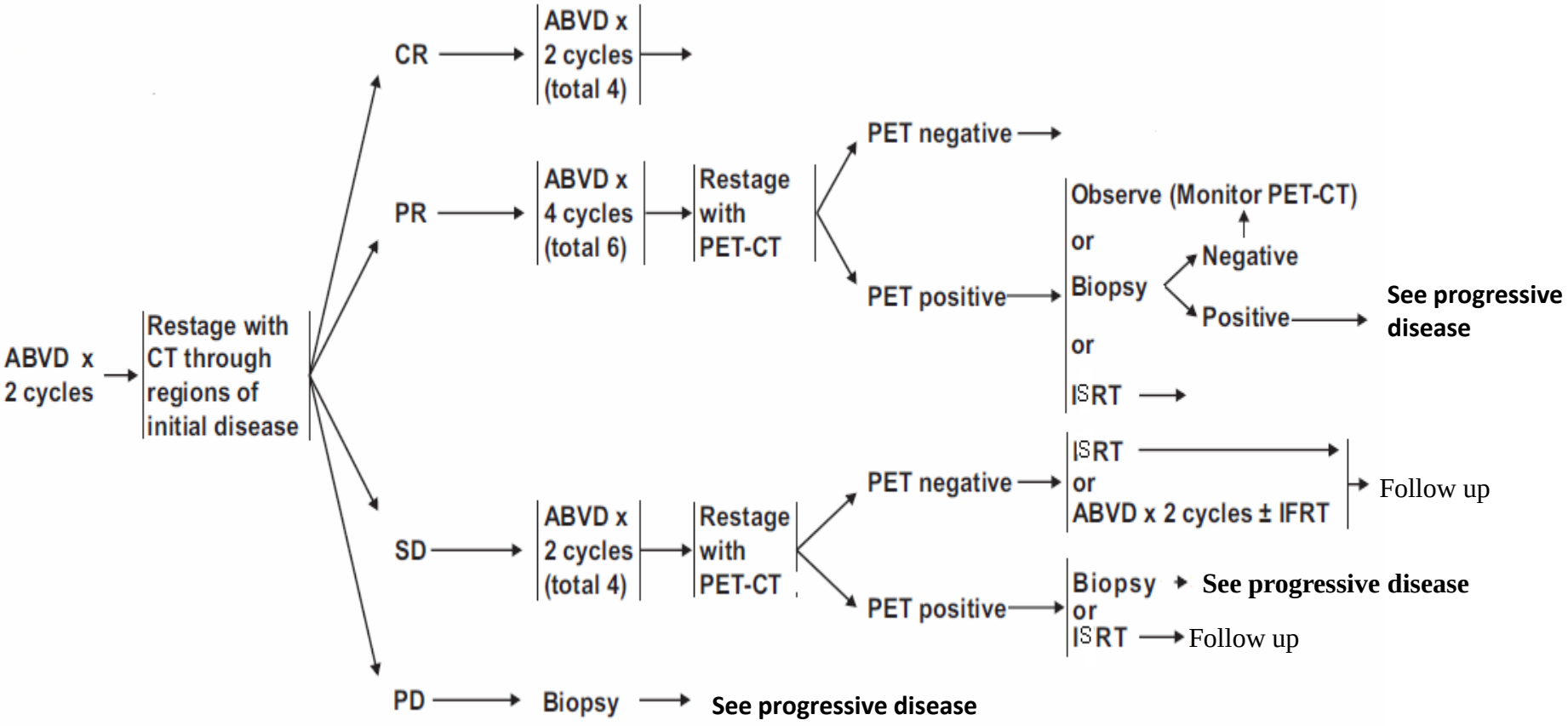
Classical Hodgkin Lymphoma Stage IA-IIA Favorable



Hodgkin Lymphoma

Kaohsiung Veterans General Hospital
Clinical Practice Guideline Version 1.2021

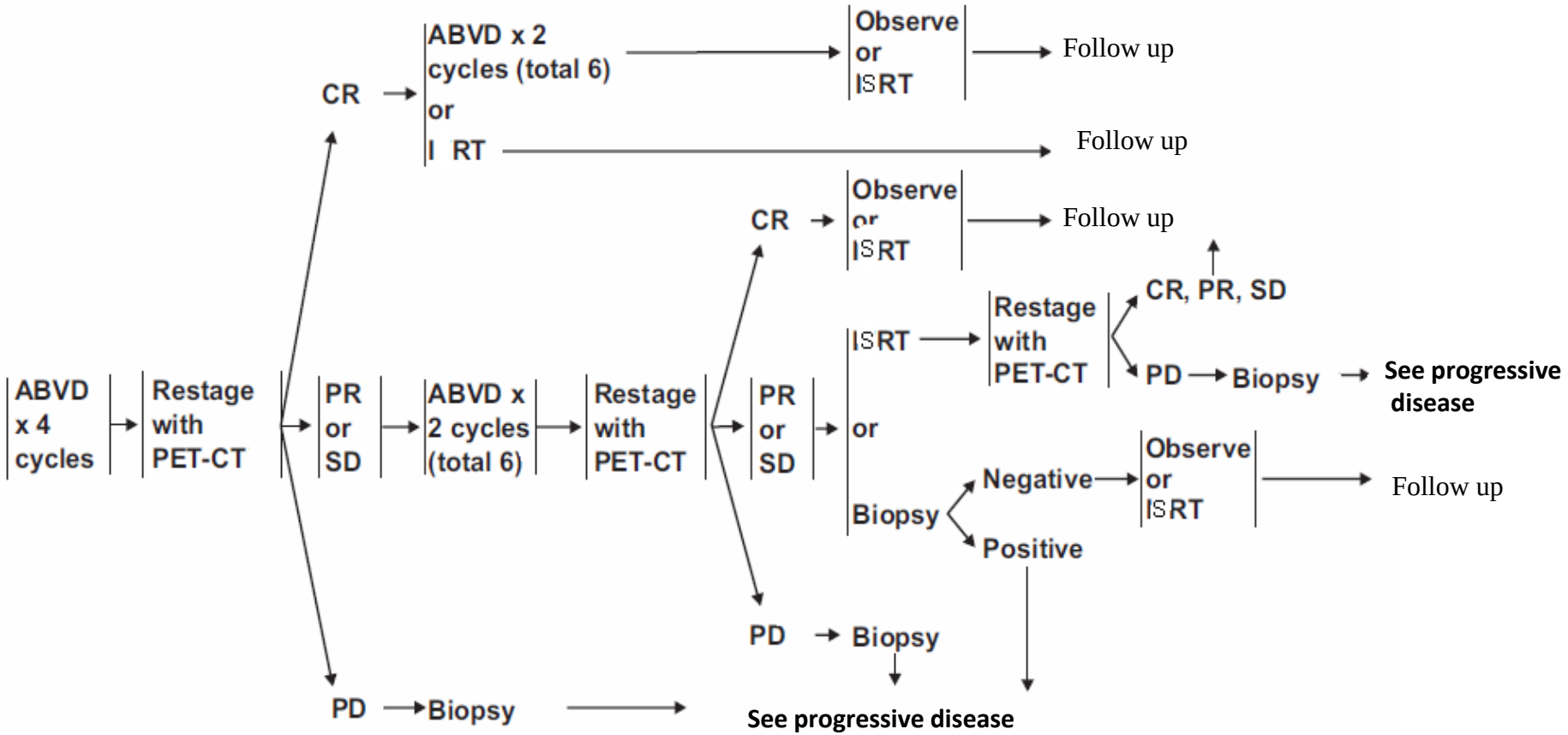
Classical Hodgkin Lymphoma Stage IA-IIA Favorable (C/T alone first)



Hodgkin Lymphoma

Kaohsiung Veterans General Hospital
Clinical Practice Guideline Version 1.2021

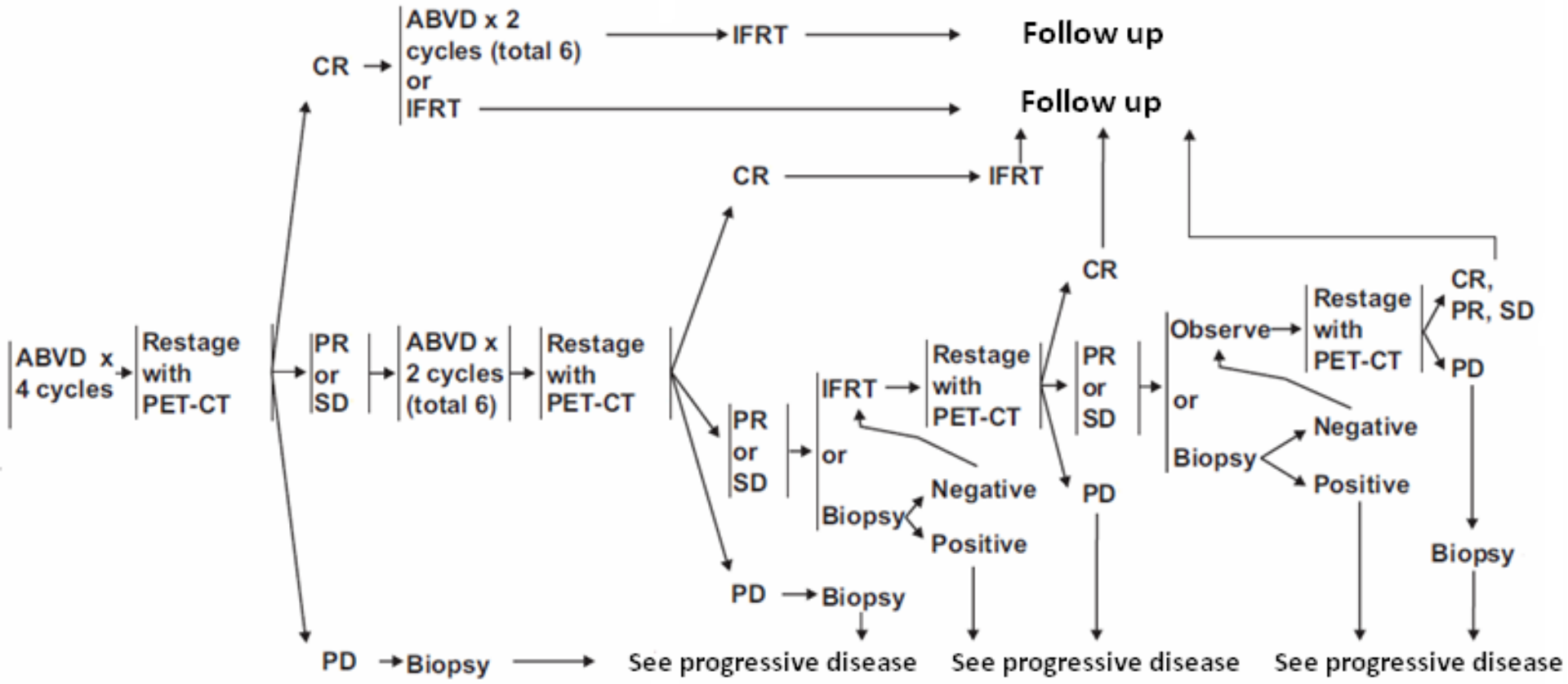
Classical Hodgkin Lymphoma Stage I-II Unfavorable (Non-bulky, C/T alone first)



Hodgkin Lymphoma

Kaohsiung Veterans General Hospital
Clinical Practice Guideline Version 1.2021

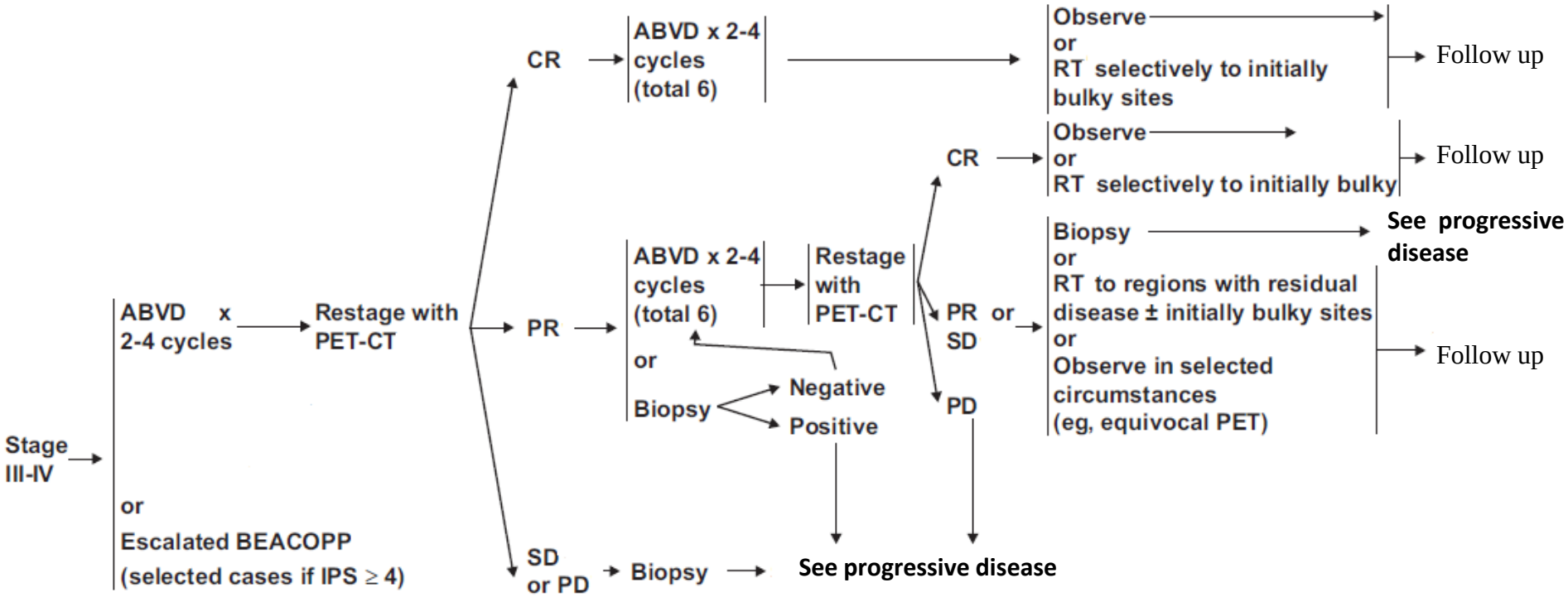
Classical Hodgkin Lymphoma Stage I-II Unfavorable (Bulky, C/T alone first)



Hodgkin Lymphoma

Kaohsiung Veterans General Hospital
Clinical Practice Guideline Version 1.2021

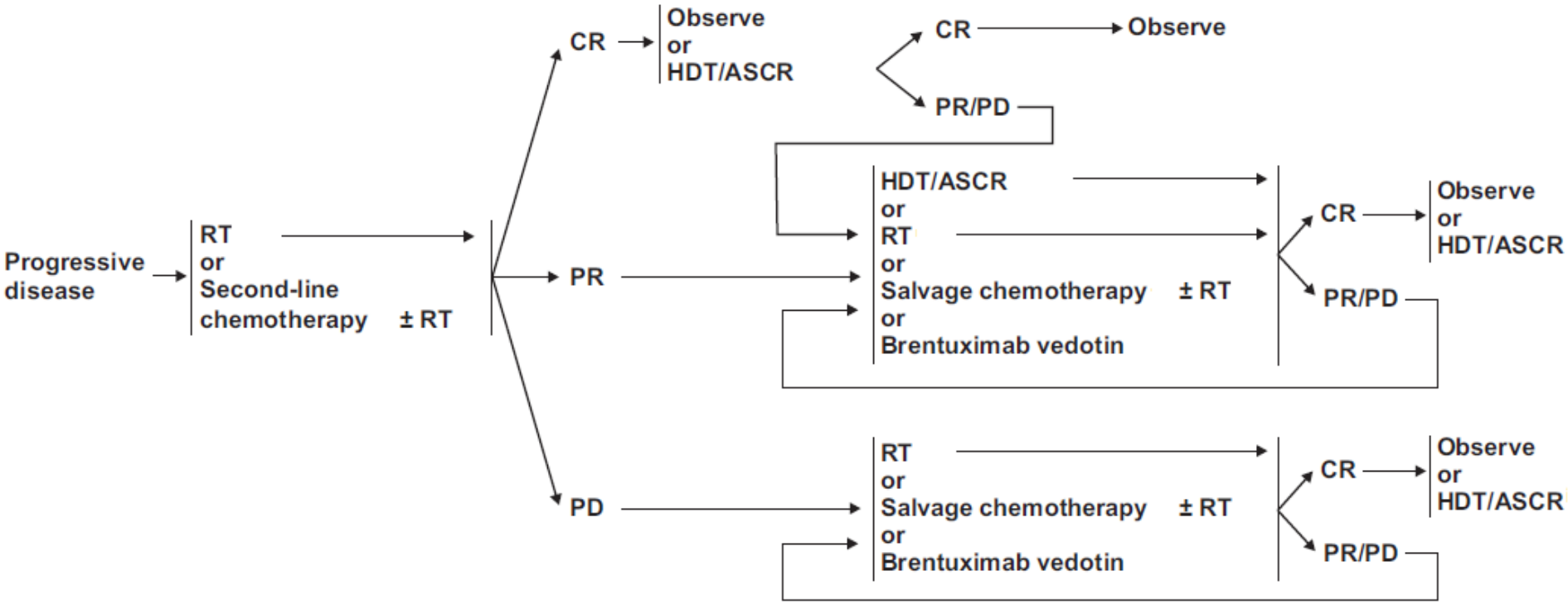
Classical Hodgkin Lymphoma Stage III-IV



Hodgkin Lymphoma

Kaohsiung Veterans General Hospital
Clinical Practice Guideline Version 1.2021

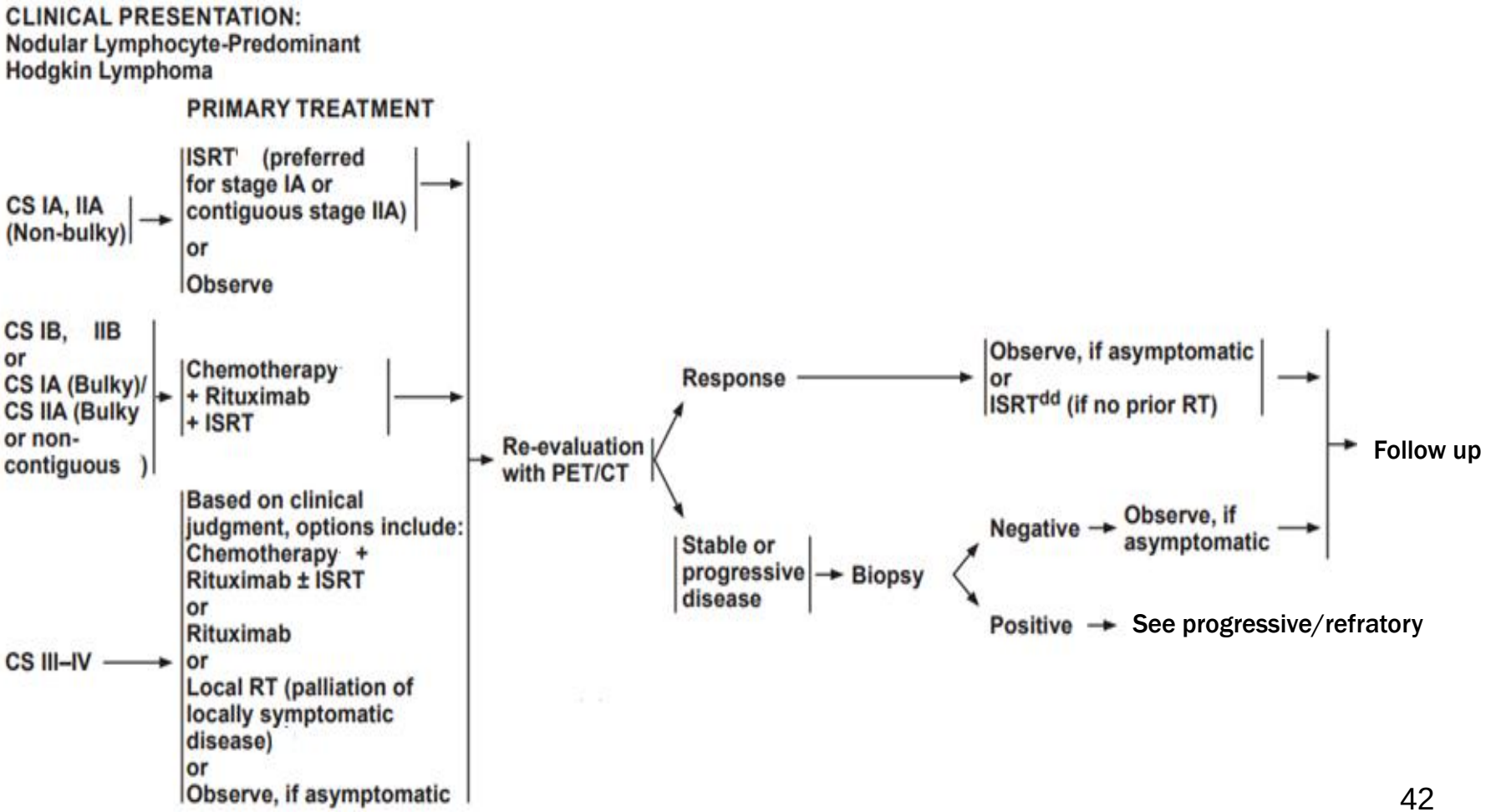
Classical Hodgkin Lymphoma (progressive disease or relapse)



Hodgkin Lymphoma

Kaohsiung Veterans General Hospital
Clinical Practice Guideline Version 1.2021

Lymphocyte-predominant Hodgkin Lymphoma



Hodgkin Lymphoma

Kaohsiung Veterans General Hospital
Clinical Practice Guideline Version 1.2021

Hodgkin lymphoma-Commonly used chemotherapy regimen

ABVD (Q4W)	Epirubicin 37.5mg/m2 iv d1 and 15
	Bleomycin 10 U/m2 iv d1 and 15
	Vinblastine 6 mg/m2 iv d1 and 15
	Dacarbazine (DTIC) 375 mg/m2 iv d1 and 15
	References : NO3、4

HL used chemotherapy regimen for advance stage	
AVD+BV (Q4W)	Epirubicin 37.5mg/m2 iv d1 and 15
	Vinblastine 6 mg/m2 iv d1 and 15
	Dacarbazine (DTIC) 375 mg/m2 iv d1 and 15
	Brentuximab Vedotin(Adcetris) 1.8mg/Kg IV
	References : NO3、4

Hodgkin Lymphoma

Kaohsiung Veterans General Hospital
Clinical Practice Guideline Version 1.2021

Second –line chemotherapy regimen

Bendamustine 50~150MG/M2 IVA for 2days	
DHAP	Dexamethasone 40MG for 4 days
	Cisplatin 100MG/M2/ Carboplatin AUCx5MG IVA on D1
	Cytarabine 2000MG/M2 IVA Q12H on D2
	註：CCr ＜60 使用Carboplatin References : NO5
ESHAP	Solu-Medrol 500MG IVA for 5days on D1-5
	Etoposide 40MG/M2 IVA for 4days on D1-4
	Cisplatin 25MG/M2 / Carboplatin AUCx1.25MG IVA for 4days on D1-4
	Cytarabine 2000MG/M2 IVA on D5
	註：CCr ＜60 使用Carboplatin References : NO6、7

Hodgkin Lymphoma

Kaohsiung Veterans General Hospital
Clinical Practice Guideline Version 1.2021

Sceond –line chemotherapy regimen

MINE	Mesna 1.33GM/M2 IVA for 3days on D1-3	
	Ifosfamide 1.33GM/M2 IVA for 3days on D1-3	
	Mitoxantrone 8MG/M2 IVA on D1	
	Etoposide 65MG/M2 IVA for 3days on D1-3	References : NO8
Brentuximab	Brentuximab vetodin(Adcetris) 1.8mg/Kg IV	
Pembrolizumab	Pembrolizumab(Keytruda) 200mg IV	

Hodgkin Lymphoma

Kaohsiung Veterans General Hospital
Clinical Practice Guideline Version 1.2021

Reference

1.NCCN guidelines of Hodgkin' s lymphomas, V.3. 2018

2.Engert A et al. Two cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine plus extended-field radiotherapy is superior to radiotherapy alone in early favorable Hodgkin's lymphoma: Final results of the GHSG HD7 trial. J Clin Oncol 2007; 25:3495

3.Savage KJ, Skinnider B, AI-Mansour M, et al.Treating limited stage nodular lymphocyte predominant Hodgkin lymphoma similarly to classical Hodgkin lymphoma with ABVD may improve outcome.Blood 2011;118:4585-4590.

4.Eich HT, Diehl V, Gorgen H, et al. Intensified chemotherapy and dose-reduced involved-field radiotherpy in patients with early unfavorable Hodgkin′s lymphoma:final analysis of the German Hodgkin Study Group HD 11 trial. J Clin Oncol 2010;28:4199- 4206.

5.Velasquez WS. Cabanillas F, Salvador P, et al. Effective salvage therpy for lymphoma with cisplatin in combination with high-dose Ara-C and dexamethasone(DHAP). Blood 988;71:177-122.

6.Aparicio J, Segura A, Garcera S,et al. ESHAP is an active regimen for relapsing Hodgkin's disease.Ann Oncol 1999;10(5):593-595.

7.Labrador J, Cabrero-Calvo M, Perez-Lopez E,et al.ESHAP as salvage therapy for relapsed or refractory Hodgkin's lymphoma.Ann Hematol 2014;93:1745-1753.

8.Colwill R, Crump M, Couture F, et al. Mini-BEAM as salvage therapy for relapsed or refractory Hodgkin′s disease before intensive therapy and autologous bone marrow transplantation. J Clin Oncol 1995;13:396-402

Follicular Lymphoma

Kaohsiung Veterans General Hospital
Clinical Practice Guideline Version 1.2021

注意事項：

此治療準則主要作為本院醫療團隊診療病人參考之用途，

並非適合所有病人，需由主治醫師視個別性選擇治療方式

2021/04/20 修訂

Follicular lymphoma

Kaohsiung Veterans General Hospital
Clinical Practice Guideline Version 1.2021

Diagnosis Essential：

＊Hematopathology review of all slides with at least one paraffin block representative of tumor. Rebiopsy if consult material is nondiagnostic.

＊ An FNA or core needle biopsy alone is not generally suitable for the initial diagnosis of lymphoma. In certain circumstances, when a lymph nodes is not easily accessible for excisional or incisional biopsy, a combination of core biopsy of FNA biopsies in conjunction with appropriate ancillary techniques for the differential diagnosis may be sufficient for diagnosis.

＊ Additional immunophenotyping to establish diagnosis:

- IHC panel：CD20,CD3,CD5,CD10,BCL2,BCL6,CD21,CD23, with or without
- Cell surface marker analysis by flow cytomertry with perip heral blood and/or biopsy spceimen : kapp/lambda,CD19, CD20,CD5,CD23,CD10

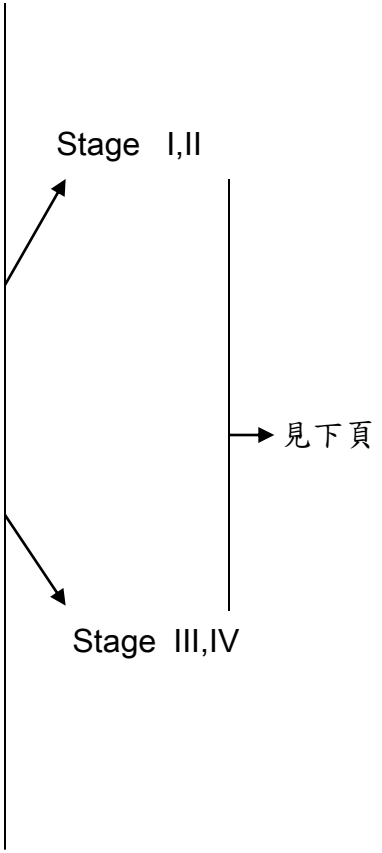
＊ Useful under certain circumstances：

- IHC panel：Ki-67, IRF4/MUM1 for FL,grade3 ,cyclin D1
- Karyotype or FISH : t (14;18) ; BCL6, IRF4/MUM1 rearrangements
- NGS panel

Work-up Essential：

＊ Physical exam：attention to node- bearing areas , including Waldeyer's rings, and to size of liver and spleen
＊ Performance status
＊ B- symptoms
＊ CBC & differential, LDH, Uric acid
＊ Comprehensive metabolic panel
◆ CT：face / chest / abdominal / pelvic or PET
◆ bone marrow biopsy ± aspirate
＊ IPI SCORE
＊ Hepatitis B、C testing
＊ Echo cardiogram or ejection fraction

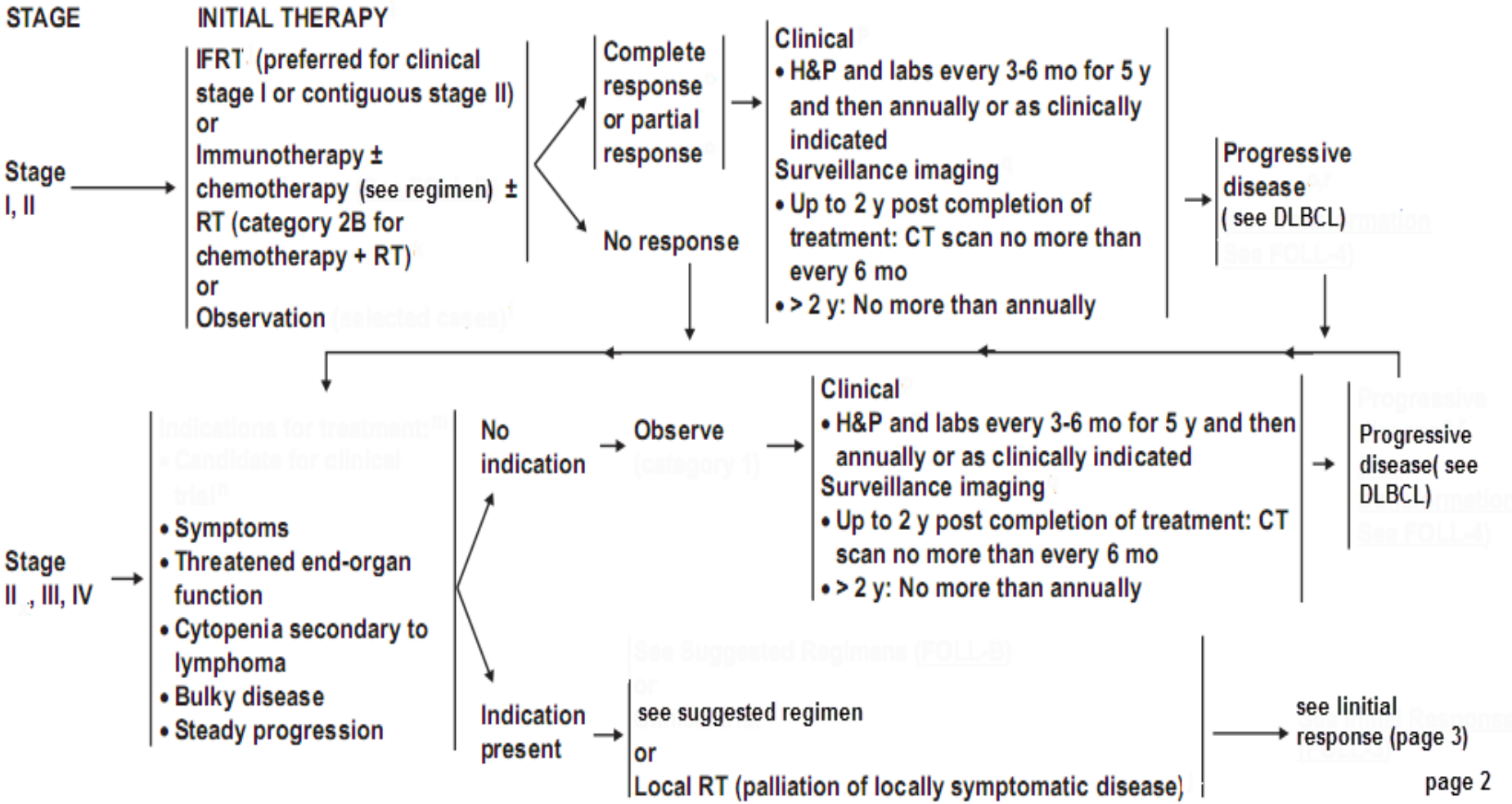
選擇性：
* HIV
* Discussion of fertility issues and sperm banking
* Lumbar puncture
* Beta2 - microglobulin



備註：Follicular lymphoma grade 3 is commonly treated according to the DLBCL

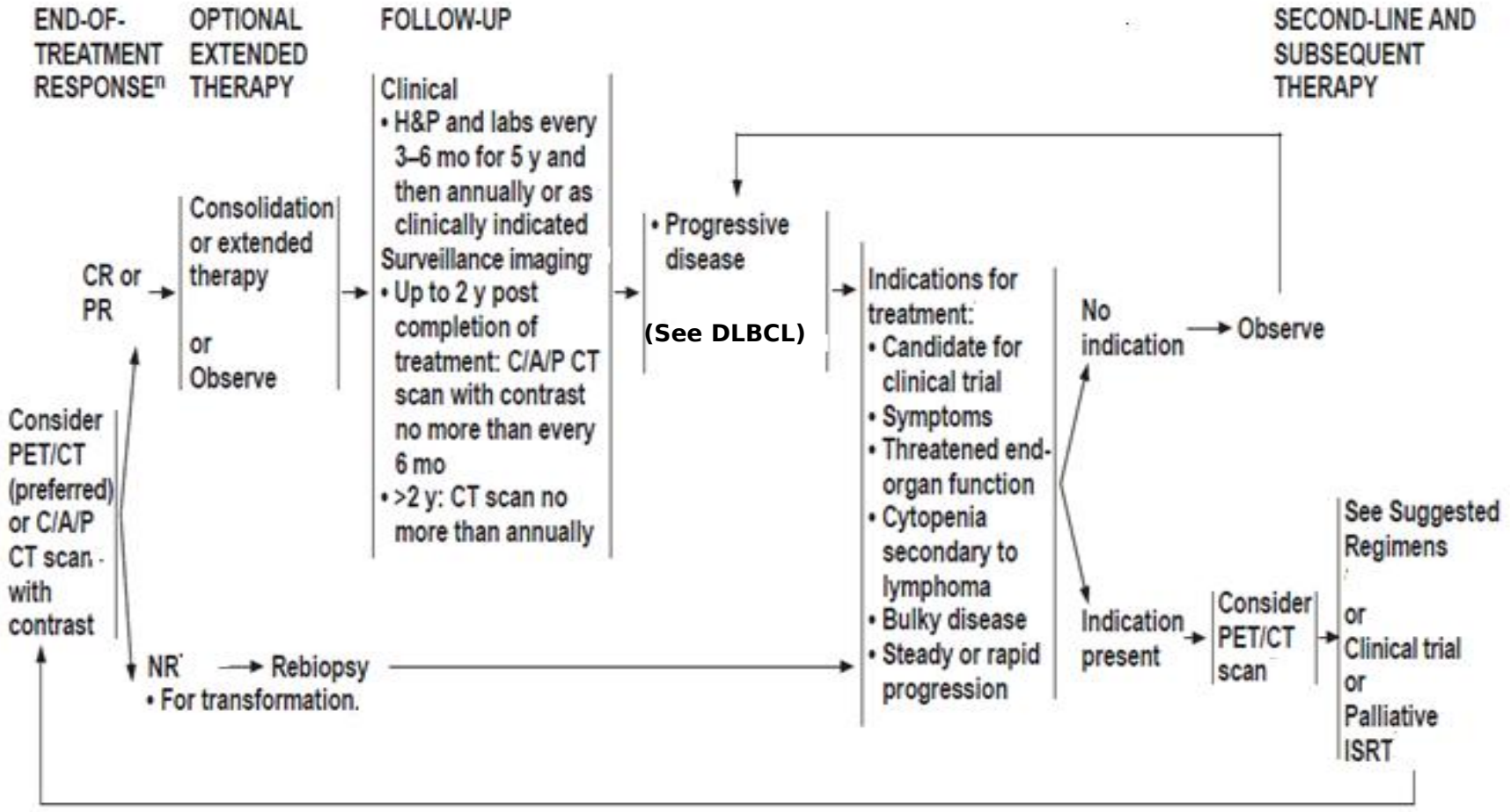
Follicular lymphoma (grade 1-2)

Kaohsiung Veterans General Hospital
Clinical Practice Guideline Version 1.2021



Follicular lymphoma (grade 1-2)

Kaohsiung Veterans General Hospital
Clinical Practice Guideline Version 1.2021



Follicular lymphoma

Kaohsiung Veterans General Hospital
Clinical Practice Guideline Version 1.2021

GELF CRITERIA

- Involvement of ≥ 3 nodal sites, each with a diameter of ≥ 3 cm
- Any nodal or extranodal tumor mass with a diameter of ≥ 7 cm
- B symptoms
- Splenomegaly
- Pleural effusions or peritoneal ascites
- Cytopenias (leukocytes < 1.0 x 10^9/L and/or platelets < 100 x 10^9/L)
- Leukemia (> 5.0 x 10^9/L malignant cells)

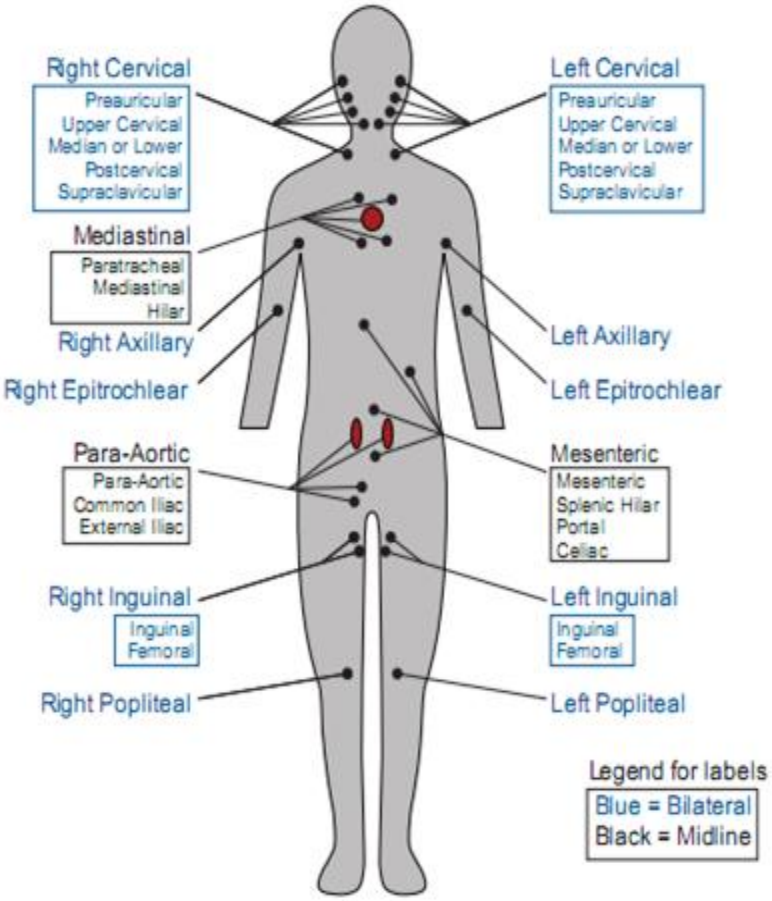
FLIPI - 1 CRITERIA

Age	≥ 60 y
Ann Arbor stage	III-IV
Hemoglobin level	< 12 g/dL
Serum LDH level	> ULN (upper limit of normal)
Number of nodal sites[d]	≥ 5

Risk group according to FLIPI chart

	Number of factors
Low	0-1
Intermediate	2
High	≥ 3

Nodal Areas



Follicular lymphoma（grade 1-2）

Kaohsiung Veterans General Hospital
Clinical Practice Guideline Version 1.2021

First line regimen：

R-CHOP	± Rituximab 375mg/m^2 IVA or Rituximab 1400mg SC on D1
	Cyclophosphamide 750mg/m^2 IVA on D1 or D2
	Doxorubicin 50mg/m^2 IVA on D1 or D2
	Vincristine 2mg IVA on D1 or D2
	Prednisone 5mg 10TAB BID po for 5days Reference:NO2.3
R-CEOP	± Rituximab 375mg/m^2 IVA or Rituximab 1400mg SC on D1
	Cyclophosphamide 750mg/m^2 IVA on D1 or D2
	Epirubicin 75mg/m^2 IVA on D1 or D2
	Vincristine 2mg IVA on D1 or D2
	Prednisone 5mg 10TAB BID po for 5days Reference:NO2.3

Follicular lymphoma（grade 1-2）

Kaohsiung Veterans General Hospital
Clinical Practice Guideline Version 1.2021

First line regimen：

R-COP	±Rituximab 375mg/m^2 IVA or Rituximab 1400mg SC on D1
	Cyclophosphamide 800mg/m^2 IVA on D1 or D2
	Vincristine 2mg IVA on D1 or D2
	Prednisone 5mg 10TAB BID po for 5days Reference:NO4
R+B	±Rituximab 375mg/m^2 IVA or Rituximab 1400mg SC on D1
	Bendamustine 50-150mg/m^2 IVA on D1 Reference:NO6

Rituximab 375mg/m^2 IVA or Rituximab 1400mg SC weekly for 4 doses
Reference:NO5

Follicular lymphoma（grade 1-2）

Kaohsiung Veterans General Hospital
Clinical Practice Guideline Version 1.2021

First line regimen for elderly or infirm：

1.Rituximab 375mg/m^2 IVA or Rituximab 1400mg SC weekly for 4 doses
2.Single-agent alkylators ± Rituximab 375mg/m^2 Reference:NO7

First line consolidation or extended dosing（optional）：

1.Rituximab 375mg/m^2 one dose every 12weeks for 8doses
2.Obinutuzumab (Gazyva) 1000mg every 8weeks for 12 doses
3.If initially treated with single-agent Rituximab,consolidation with Rituximab 375mg/m^2 one dose every 8weeks for 4 doses
Reference:NO8

Follicular lymphoma（grade 1-2）

Kaohsiung Veterans General Hospital
Clinical Practice Guideline Version 1.2021

Second line and subsequent therapy ：

1.Bendamustine 50~150mg/m^2 + Rituximab 375mg/m^2
2.R-FCM（±Rituximab 375mg/m^2,Fludarabine 25mg/m^2 D1-3, Cyclophosphamide 200mg/m^2 D1-3, Mitoxantrone 8mg/m^2 D1）
3.Fludarabine 25mg/m^2 ＋ Rituximab 375mg/m^2
4.Rituximab 375mg/m^2
5.RFN（±Rituximab 375mg/m^2,Fludarabine 25mg/m^2 D1-3,Mitoxantrone 10mg/m^2 D1 , Dexamethasone 20mg/m^2） Reference:NO9.10.11.12

Second line consolidation or extended dosing：

1.High dose therapy with autologous stem cell rescue
2.Allogeneic stem cell transplant for highly selected patients
3.Rituximab maintenance 375mg/m^2 one dose every 3 months up to 2years
Reference: NO11

Follicular lymphoma（grade 1-2）

Kaohsiung Veterans General Hospital
Clinical Practice Guideline Version 1.2021

references

1.NCCN guidelines of Non-Hodgkin’ s lymphomas, V.4 2018

2.Czuczman MS, Weaver R, Alkuzweny B, et al. Prolonged clinical and molecular remission in patients with low-grade or follicular non-Hodgkin′s lymphoma treated with rituximab plus CHOP chemotherapy:9-year follow-up. J Clin Oncol 2004;22:4711-4716.

3.Czuczman MS, Koryzna , Mohr A, et al. Rituximab in combination with fludarabine chemotherpy in low-grade of follicular lymphoma J Clin Oncol 2005;23:694-704.

4.Marcus R ,Imrie K,Solal-Celigny P ,et al.Phase III study of R-CVP compared with cyclophosphamide,vincristine,and prednisone alone in patients with previously untreated advanced follicular lymphoma.J Clin Oncol 2008;26:4579-4586.

5.Hainsworth JD,Litchy S, Burris HA, III, et al. Rituximab as first-line and maintenance therapy for patients with indolent Non- Hodgkin′s lymphoma. J Clin Oncol 2002;20:4261-4267.

6.Rummel MJ,Niederle N, Maschmeyer G, et al. Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas:an open-label, multicentre, randomised, phase 3 non-interiority trial. Lancet 2013;381:1203-1210.

7.Scholz CW, Pinto A, Linkesch W,et al. (90)Yttrium ibritumomab tiuxetan as frist-line treatment for follicular lympoma:30months of follow-up data from an international multicenter phase ll clincal trial.J Clin Oncol 2013;31:308-313.

Follicular lymphoma（grade 1-2）

references

8.Salles GA,Seymour JF,Offner F,et al.Rituximab maintenance for 2 years in patients with high tumour burden follicular lymphoma responding to riyuximab plus chemotherapy(PRIMA):A phase 3,randomised controlled trial.The Lancet 2011;377:42-51

9.Sehn LH,Chua N,Mayer J, et al.Obinutuzumab plus bendamustine versus bendamustine monotherapy in patients with rituximab-refractory indolent non-Hodgkin lymphoma(GADOLIN):a randomised, controlled, open-label, multicentre,phase 3 trial. Lancet Oncol 2016;17:1081-1093.

10.Ghielmini M, Schmitz SH, Cogliatti SB, et al. Prolonged treatment with riyuximab in patients with follicular lymphoma significantly increases event-free survival and response duration compared with the standard weekly × 4 schedule.Blood2004;103:4416-4423.

11.Van Oers MHJ, Van Glabbeke M, Giurgea M, Giurgea L, et al. Rituximab maintenance treatment of relapsed/resistant follicular Non-nodgkin′s lymphoma:Long-term outcome of the EORTC 20981 Phase lll randomized Intergroup Study. J Clin Oncol 2010;28:2853-2858.

12.Forstpointer R, Unterhalt M, Dreyling M,et al.Maintenance therapy with rituximab leads to a significant prolongation of response duration after salvage therapy with a combination of rituximab, fludarsbine,cyclosphamide,and mitoxantrone(R-FCM) in patients with recurring and refractory follicular and mantle cell lymphomas:Results of a prospective randomized study of the German Low Grade Lymphoma Study Group(GLSG).Blood 2006;108:4003-4008.