中山醫學大學附設醫院

淋巴癌診療指引

(Diffuse Large B-cell Lymphoma)

2023/12/07　Version13.0
2022/12/22　Version13.0
2021/11/18　Version12.0
2020/12/17　Version11.0
2019/11/21　Version 10.0
2018/11/15　Version 9.0
2017/12/21　Version 8.0
2016/11/17　Version 7.0

本臨床指引參考台灣國家衛生研究院、與美國NCCN版本

淋巴癌多專科醫療團隊編修

癌症委員會主任委員	癌症委員會執行長	癌症中心主任	團隊負責人

修訂內容

頁數	原文	新增
第 15 頁	年度檢閱無修改	

目 錄

一、前言

淋巴瘤，是指由淋巴組織所衍生出的惡性腫瘤。淋巴瘤的臨床表現，常常是不正常的淋巴結腫大，有時還會合併發燒，體重減輕，夜間盜汗等症狀，也就是所謂的B症狀 (B Symptom)。這樣的腫瘤，因其具有不正常增生與分化的特性，所以淋巴瘤基本上都是惡性的。為了在名稱上不會混淆，惡性淋巴瘤反而能更精準的讓病人了解其罹患疾病的特性。

淋巴瘤大致上可分為兩大類，一是何杰金氏淋巴瘤 (Hodgkin lymphoma)，一是非何杰金氏淋巴瘤 (Non-Hodgkin lymphoma)。約莫80%的淋巴瘤屬於非何杰氏金淋巴瘤，而何杰金氏淋巴瘤佔約20%。何杰金氏淋巴瘤與非何杰金氏淋巴瘤的區別在於組織型態的差異。何杰金氏淋巴瘤的癌細胞常常會出現如貓頭鷹眼狀的細胞型態，這類的細胞，我們稱之為 Reed-Sternberg Cell (RS cell)。其癌細胞的免疫組織染色，會呈現陽性的 CD15以及CD30。何杰金氏淋巴瘤的組織分類，根據世界衛生組織 (WHO) 的分類，可區分為兩大類，Lymphocyte predominant，nodular以及典型 (classic) 何杰金氏淋巴瘤。而典型何杰金氏淋巴瘤又細分為五大類，分別是 Lymphocyte-rich classic HL, Nodular sclerosis, Mixed Cellularity, Lymphocyte depleted, 以及無法分類的典型何杰金氏淋巴瘤

非何杰金氏淋巴瘤分類上則相對較複雜。依照其細胞來源，我們簡單的將非何杰金氏淋巴瘤區分為B細胞與T細胞兩大類。非何杰金氏淋巴瘤臨床的分類可以將淋巴瘤分為低惡性度 (Indolent)，高惡性度 (Aggressive)，簡單的說，如果低惡性度的淋巴瘤不治療，病人尚可存活數月甚至數年， 如果高惡性度的淋巴瘤不治療，病人恐怕只可存活數月。 最近世界衛生組織重新將非何杰金氏淋巴瘤做了分類，

二、組織病理分類與分化

2017年WHO淋巴瘤分類 (Classification of lymphoma)

Mature B-cell neoplasms

Chronic lymphocytic leukemia/small lymphocytic lymphoma
Monoclonal B-cell lymphocytosis*
B-cell prolymphocytic leukemia
Splenic marginal zone lymphoma
Hairy cell leukemia
˙Splenic B-cell lymphoma/leukemia, unclassifiable
▲Splenic diffuse red pulp small B-cell lymphoma
▲Hairy cell leukemia-variant
Lymphoplasmacytic lymphoma
▲Waldenstr ¨ om macroglobulinemia
Monoclonal gammopathy of undetermined significance (MGUS), IgM*
Mu heavy-chain disease
Gamma heavy-chain disease
Alpha heavy-chain disease
Monoclonal gammopathy of undetermined significance (MGUS), IgG/A*
Plasma cell myeloma
Solitary plasmacytoma of bone
Extraosseous plasmacytoma

Monoclonal immunoglobulin deposition diseases*
Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)
Nodal marginal zone lymphoma
▲Pediatric nodal marginal zone lymphoma
Follicular lymphoma
▲In situ follicular neoplasia*
▲Duodenal-type follicular lymphoma*
Pediatric-type follicular lymphoma*
Large B-cell lymphoma with IRF4 rearrangement*
Primary cutaneous follicle center lymphoma
Mantle cell lymphoma
▲In situ mantle cell neoplasia*
Diffuse large B-cell lymphoma (DLBCL), NOS
▲Germinal center B-cell type*
▲Activated B-cell type*
T-cell/histiocyte-rich large B-cell lymphoma
Primary DLBCL of the central nervous system (CNS)
Primary cutaneous DLBCL, leg type
EBV1 DLBCL, NOS*
EBV1 mucocutaneous ulcer*
DLBCL associated with chronic inflammation
Lymphomatoid granulomatosis

Primary mediastinal (thymic) large B-cell lymphoma
Intravascular large B-cell lymphoma
ALK-large B-cell lymphoma
Plasmablastic lymphoma
Primary effusion lymphoma
HHV8-positive DLBCL, NOS*
Burkitt lymphoma
Burkitt-like lymphoma with 11q aberration*
High-grade B-cell lymphoma, with MYC and BCL2 and/or BCL6 rearrangements*
High-grade B-cell lymphoma, NOS
B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical Hodgkin lymphoma

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Mature T and NK neoplasms

T-cell prolymphocytic leukemia
T-cell large granular lymphocytic leukemia
Chronic lymphoproliferative disorder of NK cells
Aggressive NK-cell leukemia
Systemic EBV1 T-cell lymphoma of childhood*
Hydroa vacciniforme–like lymphoproliferative disorder*
Adult T-cell leukemia/lymphoma
Extranodal NK-/T-cell lymphoma, nasal type
Enteropathy-associated T-cell lymphoma

Monomorphic epitheliotropic intestinal T-cell lymphoma*
Indolent T-cell lymphoproliferative disorder of the GI tract*
Hepatosplenic T-cell lymphoma
Subcutaneous panniculitis-like T-cell lymphoma
Mycosis fungoides
S ´ ezary syndrome
Primary cutaneous CD301 T-cell lymphoproliferative disorders
Lymphomatoid papulosis
Primary cutaneous anaplastic large cell lymphoma
Primary cutaneous gd T-cell lymphoma
Primary cutaneous CD81 aggressive epidermotropic cytotoxic T-cell lymphoma
Primary cutaneous acral CD81 T-cell lymphoma*
Primary cutaneous CD41 small/medium T-cell lymphoproliferative disorder*
Peripheral T-cell lymphoma, NOS
Angioimmunoblastic T-cell lymphoma
Follicular T-cell lymphoma*
Nodal peripheral T-cell lymphoma with TFH phenotype*
Anaplastic large-cell lymphoma, ALK1
Anaplastic large-cell lymphoma, ALK2*
Breast implant–associated anaplastic large-cell lymphoma*

Hodgkin lymphoma

Nodular lymphocyte predominant Hodgkin lymphoma
Classical Hodgkin lymphoma
Nodular sclerosis classical Hodgkin lymphoma
Lymphocyte-rich classical Hodgkin lymphoma
Mixed cellularity classical Hodgkin lymphoma
Lymphocyte-depleted classical Hodgkin lymphoma

Posttransplant lymphoproliferative disorders (PTLD)

Plasmacytic hyperplasia PTLD
Infectious mononucleosis PTLD
Florid follicular hyperplasia PTLD*
Polymorphic PTLD
Monomorphic PTLD (B- and T-/NK-cell types)
Classical Hodgkin lymphoma PTLD

Histiocytic and dendritic cell neoplasms

Histiocytic sarcoma
Langerhans cell histiocytosis
Langerhans cell sarcoma
Indeterminate dendritic cell tumor
Interdigitating dendritic cell sarcoma
Follicular dendritic cell sarcoma
Fibroblastic reticular cell tumor
Disseminated juvenile xanthogranuloma
Erdheim-Chester disease*

三、分期

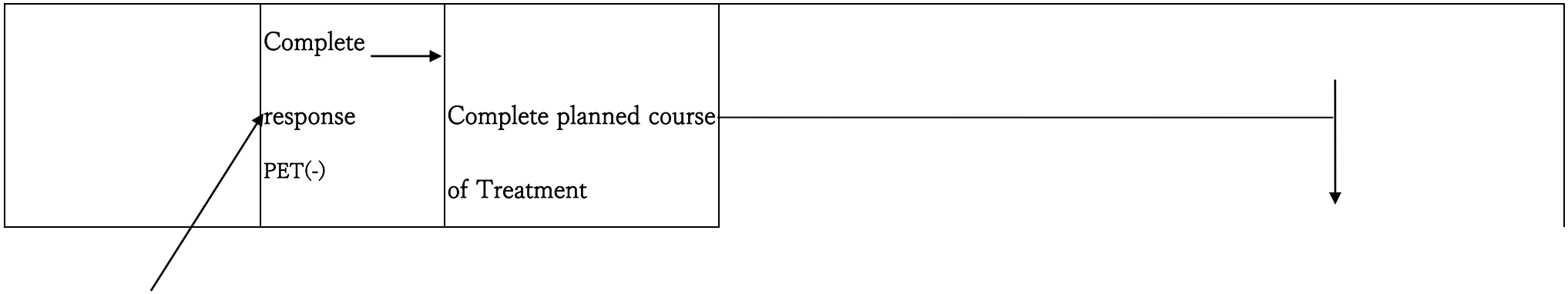
淋巴瘤的分期，是依照 Ann Arbor Staging System 來分期。淋巴瘤一般分為四期，簡單的說，當淋巴瘤只侵犯單一區域淋巴結時，稱為第一期。當淋巴瘤侵犯兩個區域以上淋巴結，且在橫膈膜同側時，稱為第二期。當淋巴瘤侵犯兩個區域以上淋巴結，且在橫膈膜異側時，稱為第三期。當淋巴瘤侵犯淋巴組織以外的地方，或是侵犯肝臟或骨髓時，則稱為第四期。這樣分期的目的，是為了決定治療方式與評估預後。簡單的說，三，四期病患的預後一般來說比一、二期的病患差。

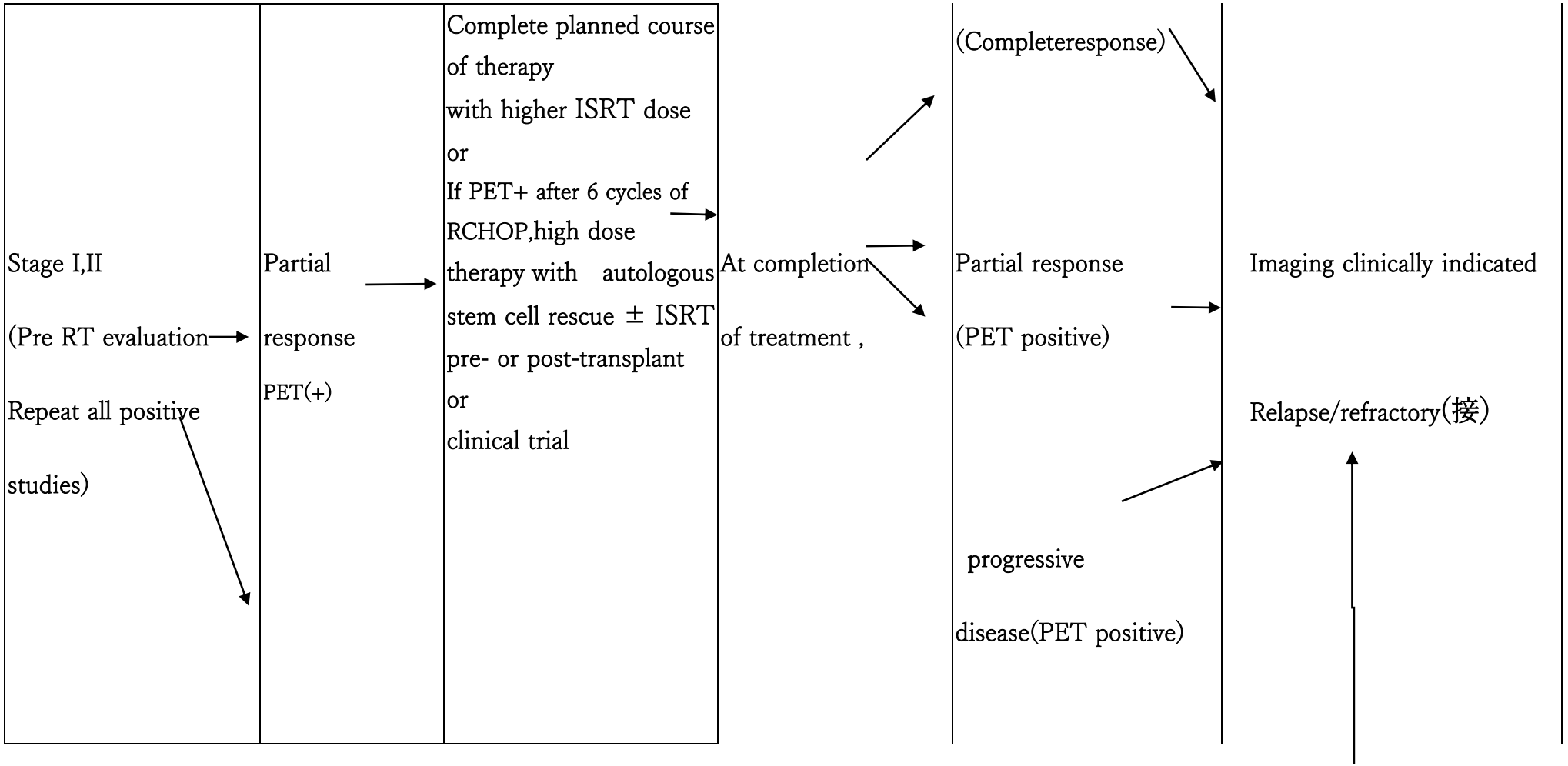
四、淋巴癌臨床指引

Workup	Stage		Fist-line therapy
·Physical Exam ·Performance status ·B symptoms ·CBC/DC ·LDH ·Uric acid	Stage I,II →	Nonbulky →	RCHOP x3cycles+ ISRT Or RCHOP x6cycles± ISRT RCHOP(RCEOP) x 4cycles Or RCHOP(RCEOP) x 4cycles followed by rituximab x 2cycles(if IPI=0)
		Bulky →	RCHOP(RCEOP) x 6 cycles± ISRT
		<7.5cm	
		≥7.5cm	

·Comprehensive metabolic panel ·CT scan with contrast or PET-CT ·Bone marrow biopsy± aspiration ·Calculation of international prognostic index (IPI) ·Hepatitis B、C testing ·echocardiogram ·Beta-2-microglobulin <optional> ·Discussion of fertility issues and sperm banking(optional)	Stage III, IV	Clinical trial or RCHOP	Interim restaging after 2-4cycles

Pre-R/T Evaluation (End of first-line chemoimmunotherapy)	F/U therapy	End-of-treatment restaging	FOLLOW-UP

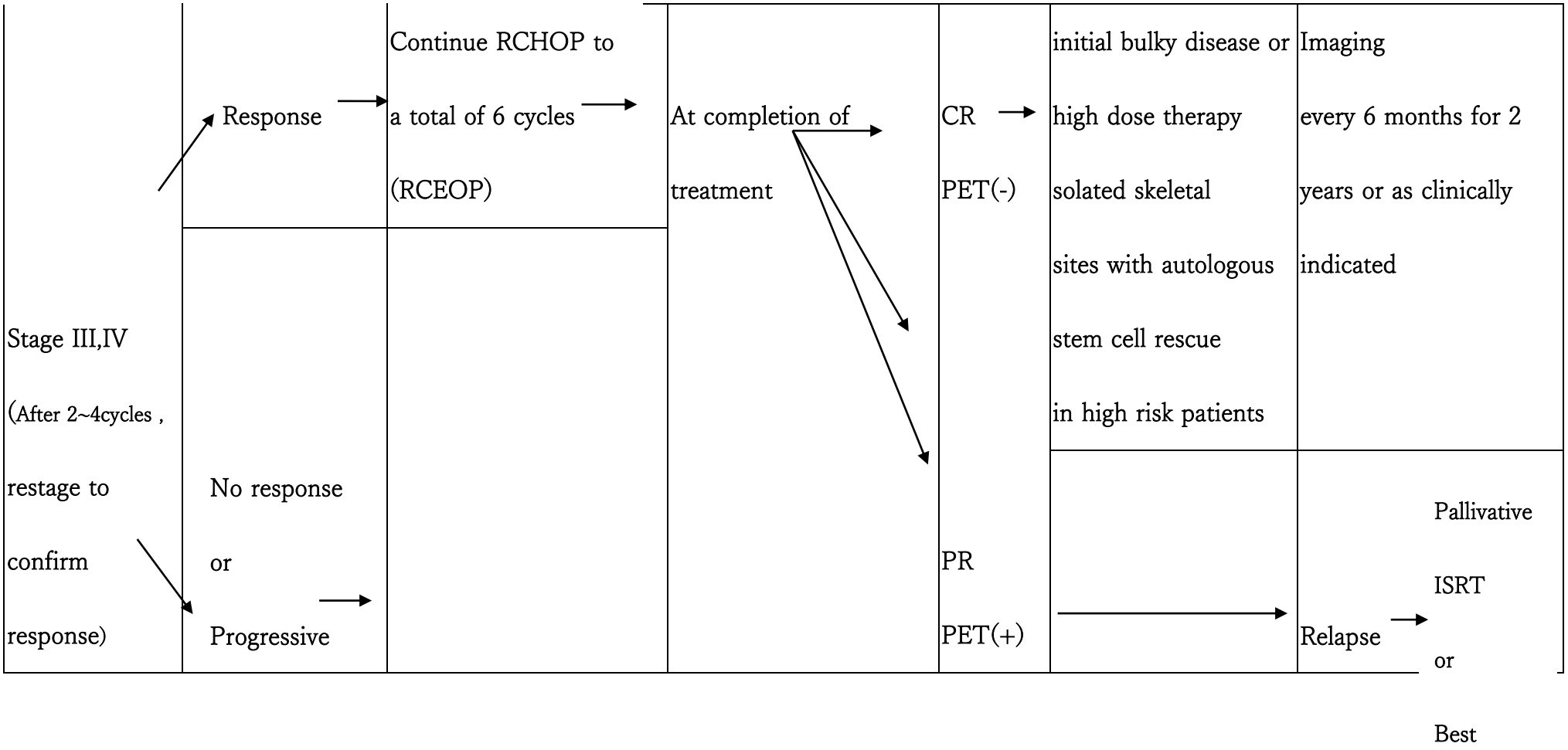



Stage I,II
(Pre RT evaluation
Repeat all positive
studies)
Partial
response
PET(+)
Complete planned course
of therapy
with higher ISRT dose
or
If PET+ after 6 cycles of
RCHOP,high dose
therapy with autologous
stem cell rescue ± ISRT
pre- or post-transplant
or
clinical trial
At completion
of treatment ,
(Completeresponse)
Partial response
(PET positive)
progressive
disease(PET positive)
Imaging clinically indicated
Relapse/refractory(接)

	No response or Progressive disease	RT if not candidate for chemotherapy	

Interim restaging	FOLLOW-UP THERAPY	End of treatment restaging	Initial response

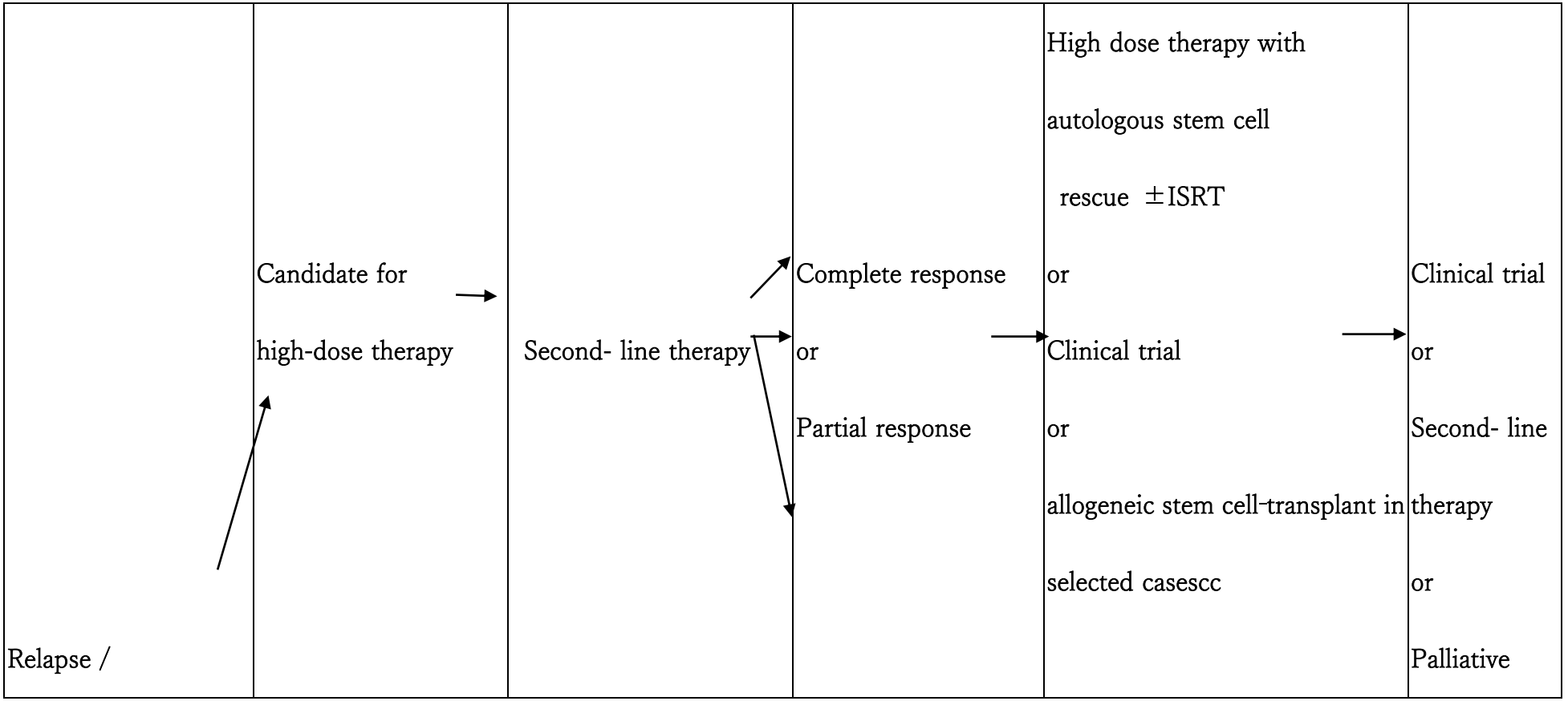
					Observation Consider ISRT to	


Stage III,IV
(After 2~4cycles ,
restage to
confirm
response)
Response
Continue RCHOP to
a total of 6 cycles
(RCEOP)
No response
or
Progressive
At completion of
treatment
CR
PET(-)
PR
PET(+)
initial bulky disease or
high dose therapy
solated skeletal
sites with autologous
stem cell rescue
in high risk patients
Imaging
every 6 months for 2
years or as clinically
indicated
Relapse
Pallivative
ISRT
or
Best

	disease	See relapse or refractory disease ISRT in select patients who are not candidates for chemotherapy		NR or PD	→	

五、復發的評估

Relapse/Refractory disease	Additional therapy	RESPONSE #2	Consolidation/Additional therapy	Relapse or greater #2


Relapse /
Candidate for
high-dose therapy
Second- line therapy
Complete response
or
Partial response
High dose therapy with
autologous stem cell
rescue ±ISRT
or
Clinical trial
or
allogeneic stem cell-transplant in
selected casescc
Clinical trial
or
Second- line
therapy
or
Palliative

Refractory disease ↘		Clinical trial or	No response →	Clinical trial or	ISRT or
	Not Candidate for high-dose therapy →	Second- line therapy or Palliative ISRT or Best supportive care		Palliative ISRT or Best supportive care	Best supportive care

六、International prognostic Index (IPI)

All patients: Age > 60 years Serum LDH > 1X normal Performance status 2-4 Stage III or IV Extranodal involvement > 1 site	International Index, All patients: Low 0 - 1 Low intermediate 2 High intermediate 3 High 4 - 5

Age-adjusted International prognostic Index (IPI)

Patients≦60 years **Stage III or IV** **Serum LDH > 1X normal** **Performance status 2-4**	International Index, Patients≦60 years: Low Low intermediate 0 High intermediate High 1 2 3

七、化學治療原則(Principles of chemotherapy)

	Regimen	*Dosage	Reference
First- line	RCHOP	Rituximab 375 mg/m² i.v. on day 1 Cyclophosphamide 750 mg/m² i.v. on day 1 Doxorubicin 50 mg/m² i.v. on day 1 Vincristine 1.4 mg/m² i.v. on day 1(maximum dose of 2 mg) Prednisone 100mg p.o. daily on day1-5	McKelvey EM. cancer 1976;38:1484-1493.Lenz G. J clin Oncol 2005;23:1984-1992. Hiddemann W.Blood 2005;106:3725-3732
	RCEOP	Rituximab 375 mg/m² i.v. on day 1 Cyclophosphamide 750 mg/m² i.v. on day 1 Epirubicin 50 mg/m² i.v. on day 1 Vincristine 1.4 mg/m² i.v. on day 1(maximum dose of 2 mg) Prednisone 100mg p.o. daily on day1-5	

	DA-EPOCH + Rituximab	Etoposide Prednisone Vincristine Cyclophosphamide Doxorubicin	
註: patients >80 of age with comorbidities R-mini CHOP			
Second- line	DHAP± Rituximab	Cisplatin 80-100 mg/m² CIVI over 24 h on day 1 Cytarabine 2000 mg/m² i.v. q12h x2 dose on day 2 Dexamethasone 40 mg/m² p.o./i.v. daily on day 1-4 Repeat cycle every21-28 d	Velasquez WS. Blood 1988;71:117-122.

	ESHAP± Rituximab	Etoposide 40 mg/m² i.v. daily on days 1-4 Methylprednisolone 500 mg/m² i.v. daily on days 1-5 Cytarabine 2000 mg/m² CIVI on day 5 Cisplatin 25 mg/m² i.v. daily on days 1-4 Repeat cycle every21-28 d	Velasquez WS. J clin Oncol 1994;12:1169-1176.
	ICE±Rituximab	Ifosfamide 5000 mg/m² CIVI over 24h on day 2 Mesna 5000 mg/m² CIVI over 24h on day 2 Carboplatin AUC 5 i.v. on day 2(maximum dose of 800 mg) Etoposide 100 mg/m² i.v. daily on days 1-3 ±rituximab 375 mg/m² i.v. 48 h before start of cycle 1 and on day 1 of each cycle Repeat cycle every 14-15 d	Moskowitz CH0J clin oncol 1999;17:3776-3785. Kewalramans T. blood 2004;103:3684-3688

	Polatuzumab vedotin-piiq ± bendamustine ± rituximab	Polatuzumab vedotin-piiq (Polivy) 1.8mg/kg i.v. at 90min repeat cycle every 21 d ± Benamustine 90mg/m²/day on day1, day2 ± rituximab 375 mg/m² i.v. on day 1 Total 6 cycle	Morschhauser F, Flinn IW, Advani R, et al. Polatuzumab vedotin or pinatuzumab vedotin plus rituximab in patients with relapsed or refractory non-Hodgkin lymphoma: final results from a phase 2 randomised study (ROMULUS). Lancet Haematol 2019;6:e254-e265. Sehn LH, Herrera AF, Flowers CR, et al. Polatuzumab vedotin in relapsed or refractory diffuse large B-cell lymphoma. J Clin Oncol 2020;38:155-165.
	RB	Rituximab 375 mg/m² i.v. on day 1	

		Bendamustine 90-120mg/m² day 1-2	

*化學治療原則劑量會依病患體能狀況，調整劑量。

八、放射線治療原則（Principles of radiation）

Non-Hodgkin's lymphoma

Disease	Indication	Target area	Dose	Note
Diffuse large B	Stage I~II, CR [a] Non-bulky [b]	Locoregional RT	30-36Gy	1. testicular lymphoma should include contralateral testis to 30-36Gy 2. Refractory -40-55Gy 3. RT as primary treatment：40-55Gy
	Stage I~II, CR [a] Bulky	Locoregional RT	30-36Gy[a]	
	Stage I~II, PR [c]	Locoregional RT	36-50Gy	

a: complete response from previous chemotherapy

b : with adverse effects such as elevated LDH, stage II, age > 60y, performance status ECOG > 2

c: partial response from previous chemotherapy

九、安寧緩和照護原則

若預期疾病難以治癒時，病人存活期小於 6 個月便適合安寧療護(Pomeranz & Brustman, 2005；Waldrop & Rinfrette, 2009)。若藉由症狀、檢驗數據、及確切的腫瘤診斷，證實臨床上該惡性腫瘤已經廣泛侵犯、或進展快速；功能分數（Palliative Performance Scale）低於 70%；拒絕進一步腫瘤治癒性治療，或者在治療之下仍持續惡化者，即可轉介緩和醫療團隊（彭等，2006）。

十、實證醫學

Categories of Evidence and Consensus :
Category 1: There is uniform NCCN consensus, based on high-level evidence, that the recommendation is appropriate.
Category 2A: There is uniform NCCN consensus, based on lower- level evidence including clinical experience, that the recommendationis appropriate.

Category 2B: There is nonuniform NCCN consensus (but no major disagreement), based on lower-level evidence including clinical
experience, that the recommendation is appropriate.
Category 3: There is major NCCN disagreement that the recommendation is appropriate.
All recommendations are category 2A unless otherwise noted.

十一、參考文獻(Reference)

1. NCCN Clinical Practice Guidelines in Oncology. B-Cell Lymphomas V4. 2020

2.McKelvey EM. cancer 1976;38:1484-1493.Lenz G. J clin Oncol 2005;23:1984-1992. Hiddemann W.Blood 2005;106:3725-3732

3.Velasquez WS. Blood 1988;71:117-122.

4.Velasquez WS. J clin Oncol 1994;12:1169-1176.

5.Moskowitz CH0J clin oncol 1999;17:3776-3785.

6.Kewalramans T. blood 2004;103:3684-3688

7. BLOOD, 19 MAY 2016 x VOLUME 127, NUMBER 20:2376