中山醫學大學附設醫院

淋巴癌診療指引
(Hodgkin Lymphoma)

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本臨床指引參考美國NCCN版本與淋巴癌多專科醫療團隊編修

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修訂內容：

頁數		
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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’s 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，典型 (classic) 何杰金氏淋巴瘤及nodular lmphocyte predominant。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

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*
m heavy-chain disease
g heavy-chain disease
a 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
ALK1 large B-cell lymphoma
Plasmablastic lymphoma
Primary effusion lymphoma
HHV81 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 andclassical Hodgkin lymphoma
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、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(Hodgkin Lymphoma)臨床指引

WORK-UP-主要檢查	STAGE	PRIMARY TREATMENT	Restage and Following Treatment
Physical Exam Performance status B symptoms CBC/DC LDH、ESR、Liver function Uric acid<optional> Comprehensive metabolic panel CT scan with contrast<optional> Bone marrow biopsy± aspiration Calculation of International Prognostic Score (IPS) Hepatitis B、C testing<optional> echocardiogram<optional> PET-CT <optional> Discussion of fertility issues and sperm banking(optional)	Stage IA – IIA **(No bulky disease)**	Chemotherapy (ABVD) * 2 cycles→restage with PET/CT	CR→Observe or CR→ABVD*1cycle (total 3) or AVD*4cycle (total 6) PR→ABVD*2cycle (total 4) or AVD*4cycle (total 6) ABVD x 1cycle + ISRT 30 Gy(per RAPID, H10F) Biopsy- proven refractory disease→Second-line systemic therapy
	Stage I – II Unfavorable[1] (No bulky disease) Or Bulky mediastinal Disease >10cm	Chemotherapy (ABVD)*2 cycles→restage with PET/CT	CR→ABVD*2 cycles (total 4) + ISRT or PR→ABVD*2cycles (total 4) + ISRT Escalated BEACOPP*2 cycle + ISRT NR→Biopsy Negative→AVD x 4 cycles(total 6) + ISRT→F/U Positive→restage with PET/CT
	Stage III - IV	Chemotherapy (ABVD)* 2 cycles →restage with PET/CT	CR→AVD*4 cycle→ ISRT CR→ABVD*2 cycle→Observe or ISRT to initially bulky (total 4)→restage with PET/CT PR→Escalated BEACOPP x 2 cycles→restage with PET/CT→CR or PR→biopsy

五、化學治療原則(Principles of chemotherapy)

Hodgkin lymphoma：

ABVD：(doxorubicin、bleomycin、vinblastine、dacarbazine)

Doxorubicin (Adriamycin) 25 mg/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 Q4w

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

AAVD (Adcetris、Adriamycin、Velban、Dacarbazine)

Brentuximab vedotin (Adcetris) 1.2 mg/kg	IV	D1 and 15	
Doxorubicin (Adriamycin) 25 mg/m2	IV	D1 and 15	
Vinblastine (Velban) 6 mg/m2	IV	D1 and 15	
Dacarbazine (DTIC) 375 mg/m2	IV	D1 and 15	Q4w

1.MSK 13-034: Kumar A, Casulo C, Yahalom J, Schöder H, Barr PM, Caron P, Chiu A, Constine LS, Drullinsky P, Friedberg JW, Gerecitano JF, Hamilton A, Hamlin PA, Horwitz SM, Jacob AG, Matasar MJ, McArthur GN, McCall SJ, Moskowitz AJ, Noy A, Palomba ML, Portlock CS, Straus DJ, VanderEls N, Verwys SL, Yang J, Younes A, Zelenetz AD, Zhang Z, Moskowitz CH. Brentuximab vedotin and AVD followed by involved-site radiotherapy in early stage, unfavorable risk Hodgkin lymphoma. Blood. 2016 Sep 15;128(11):1458-64. Epub 2016 Jul 25. link to original article dosing details in manuscript have been reviewed by our editors free full text available at EuroPMC EuroPMC NCT01868451

六、放射線治療原則 (Second-Line or Subsequent Therapy Options)

1. Brentuximab vedotin (only for CHL)
2. Involved-site Radiation Therapy (ISRT)

Dose:

(1)Combined Modality Therapy

Non-bulky disease (stage I-II): 20–30 Gy (if treated with ABVD)，30 Gy (if treated with Stanford V); 1.5-2.0 Gy per fraction

*Non-bulky disease (stage IB-IIB): 30 Gy; 1.5-2.0 Gy per fraction

*Bulky disease sites (all stages): 30–36 Gy; 1.5-2.0 Gy per fraction

(2)ISRT Alone (uncommon, except for NLPHL):

*Involved regions: 30–36 Gy (the dose of 30 Gy is mainly used for NLPHL); 1.5-2.0 Gy per fraction

*Uninvolved regions: 25–30 Gy; 1.5-2.0 Gy per fraction

★Brentuximab vedotin 1.8mg/kg 以 30 分鐘以上靜脈輸注方式給藥，每 3 週一次，若患者體重超過 100kg，應以 100kg 算所需劑量。持續治療直到疾病惡化(disease progression)或出現無法接受的毒性為止。

達到病況穩定(stable disease)或改善的患者，應接受最少 8 個療程，最多至 16 個療程(約 1 年)的治療。

★健保給付原則:

Brentuximab vedotin (如 Adcetris)，限用於成人患者：

1.治療復發或頑固型 CD30+何杰金氏淋巴瘤(HL)：(1)已接受自體幹細胞移植(ASCT)，或(2)無法使用 ASCT 或多重藥物化療，且先前至少已接受兩種治療。

2.治療復發或頑固型全身性退行分化型大細胞淋巴瘤(systemic anaplastic large cell lymphoma；sALCL)。

3.每次申請療程以 4 個療程為限，再申請應檢附前次治療結果評估資料。若病人病情已達完全緩解，得再給付 4 個療程。健保給付以 16 個療程為上限。

★Additional Therapy Options(only for CHL)

1. Bendamustine
2. Nivolumab (for patients previously treated with brentuximab vedotin)
3. Pembrolizumab(for patients previously treated with brentuximab vedotin)

備註:Canellos GP et al. Chemotherapy of advanced Hodgkin's disease with MOPP, ABVD, or MOPP alternating with ABVD. N Eng J Med 1992; 327:1478.

七、 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)

八、Unfavorable Risk Factors for Stage I-II Classical 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**

九、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、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）。

十一、參考文獻(Reference)

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

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

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

7. Canellos GP et al. Chemotherapy of advanced Hodgkin’s disease with MOPP, ABVD, or MOPP alternating with ABVD. N Eng J Med 1992; 327:1478.

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

9.MSK 13-034: Kumar A, Casulo C, Yahalom J, Schöder H, Barr PM, Caron P, Chiu A, Constine LS, Drullinsky P, Friedberg JW, Gerecitano JF, Hamilton A, Hamlin PA, Horwitz SM,Jacob AG, Matasar MJ, McArthur GN, McCall SJ, Moskowitz AJ, Noy A, Palomba ML, Portlock CS, Straus DJ,VanderEls N, Verwys SL, Yang J, Younes A, Zelenetz AD, Zhang Z, Moskowitz CH. Brentuximab vedotin and AVD followed by involved-site radiotherapy in early stage, unfavorable risk Hodgkin lymphoma. Blood. 2016 Sep 15;128(11):1458-64.