非何杰金氏淋巴瘤診療指引

淋巴癌多專科團隊

2010 年 01 月制訂
2011 年 10 月修訂
2012 年 09 月修訂
2013 年 01 月修訂
2013 年 09 月修訂
2014 年 12 月修訂

參考資料：

Non-Hodgkin’ s Lymphomas NCCN Guidelines V1.2014

全民健康保險藥品給付規定 行政院衛生署一百零三年版

WORKUP

Essential:

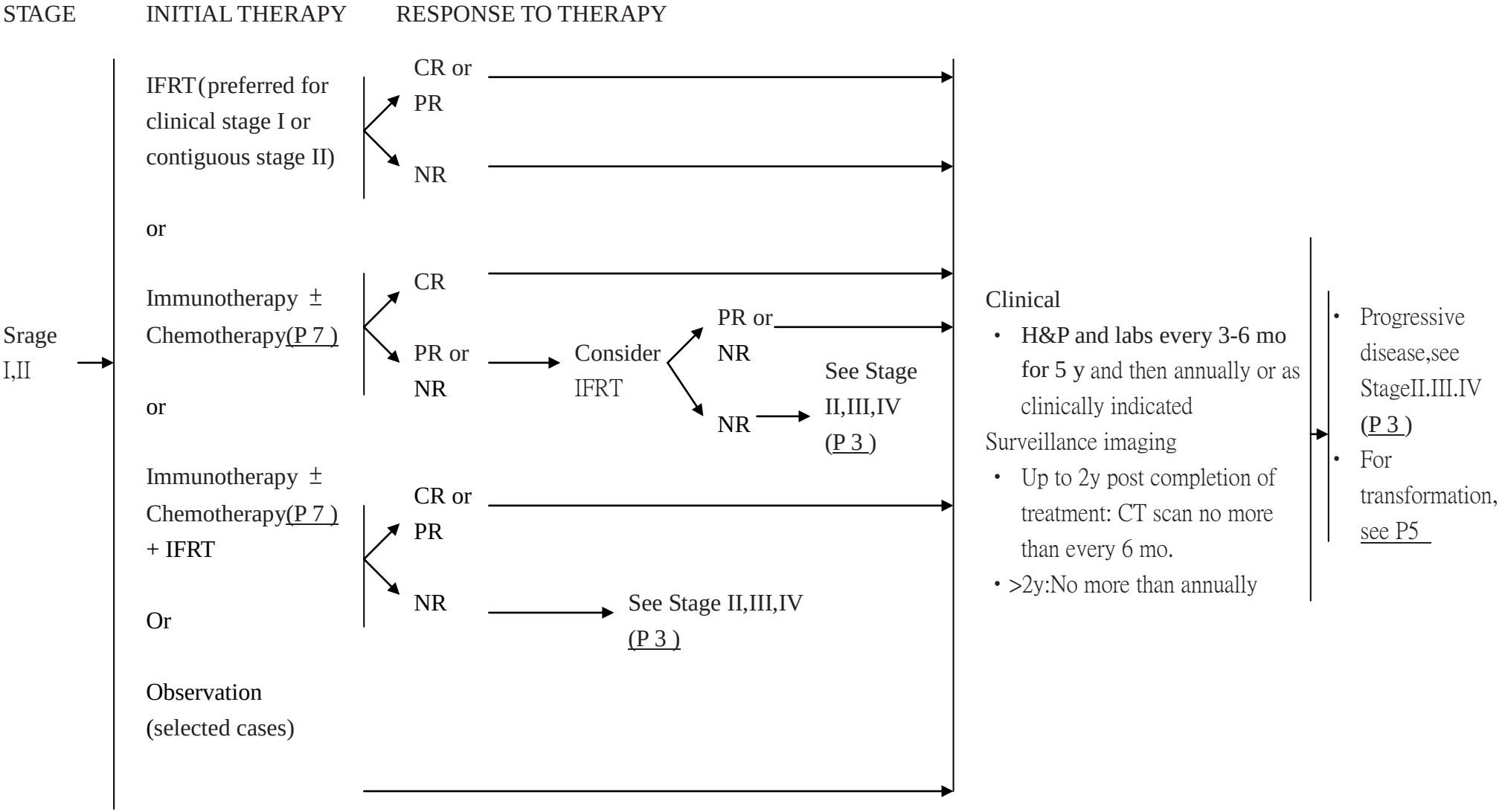
- **Physical exam**:attention to node-bearing areas, including Waldeyer's ring,and to size of liver and spleen
- Performace status
- B symptoms
- CBC,differential,platelets
- LDH
- Beta-2-microglobulin(Optional)
- Comprehensive metabolic panel
- Hepatitis B testing
- Imaging:chest/abdominal/pelvic CT
- Bone marrow biopsy+aspirate
  (Or select the whole body PET-CT)
- Pregnancy testing in women of child-bearing age(if C/T planned)

→ Clinical StageI,II,III,IV

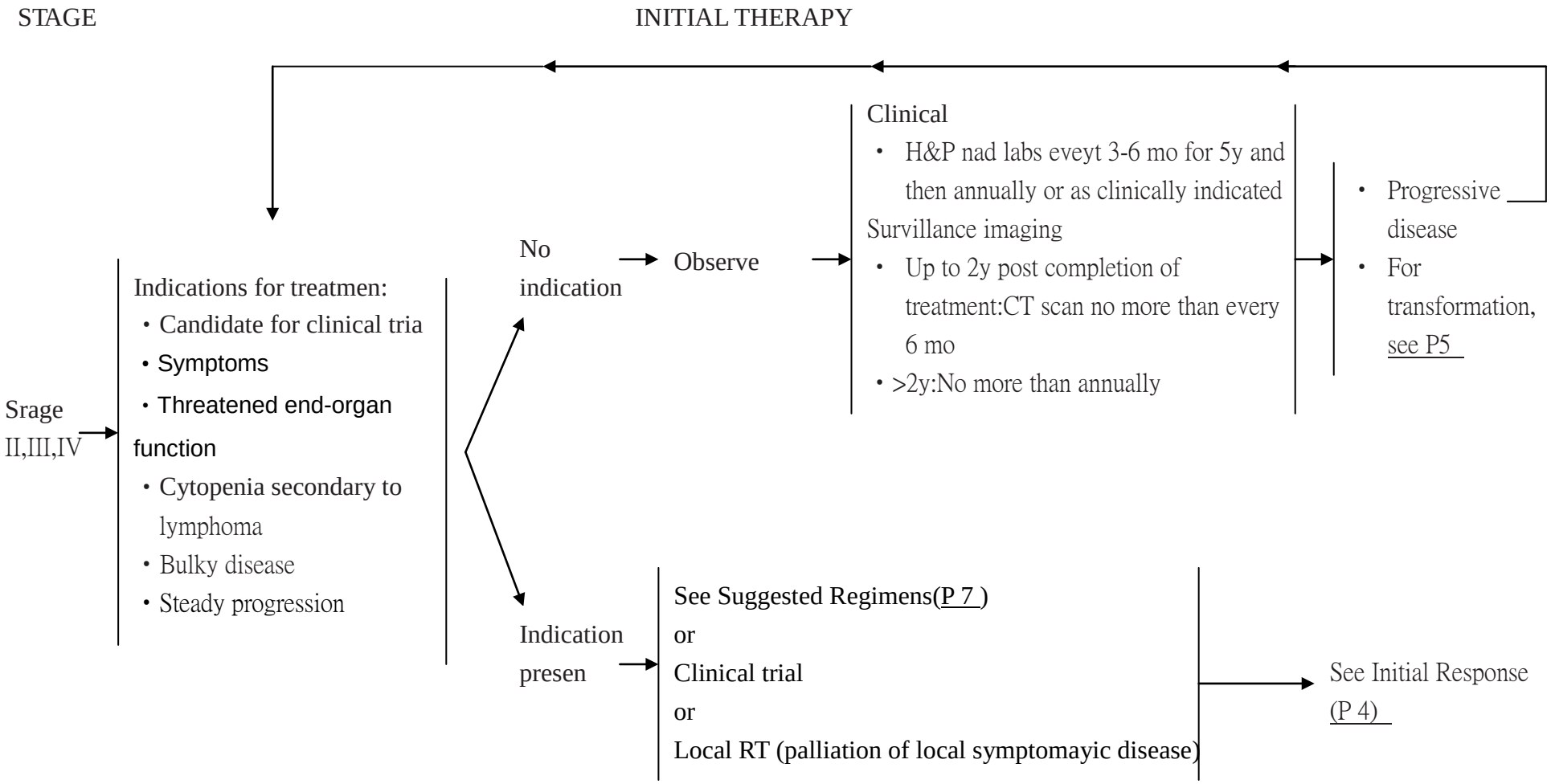
USEFUL IN SELECTED CASES:

- MUGA scan/echo if anthracycle or anthracenedion-based regimen is indicated
- Neck CT
- PET-CT scan(Optional)
- Uric acid
- Discussion of fertility issues and sperm banking
- SPEP and/or quantitative immunoglobulin levels
- Hepatitis C testing

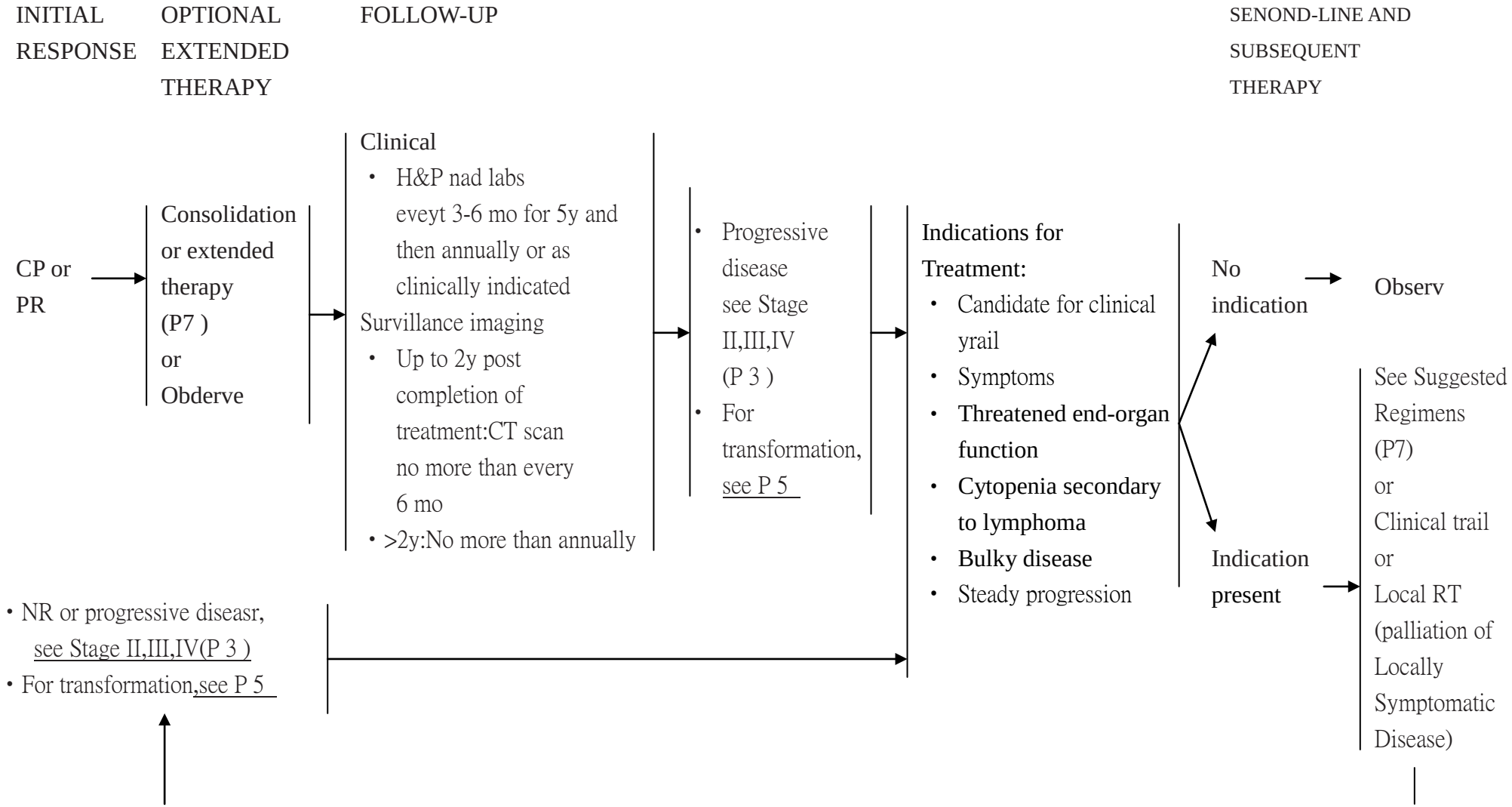
Follicular Lymphoma (grade 1-2)



Follicular Lymphoma (grade 1-2)

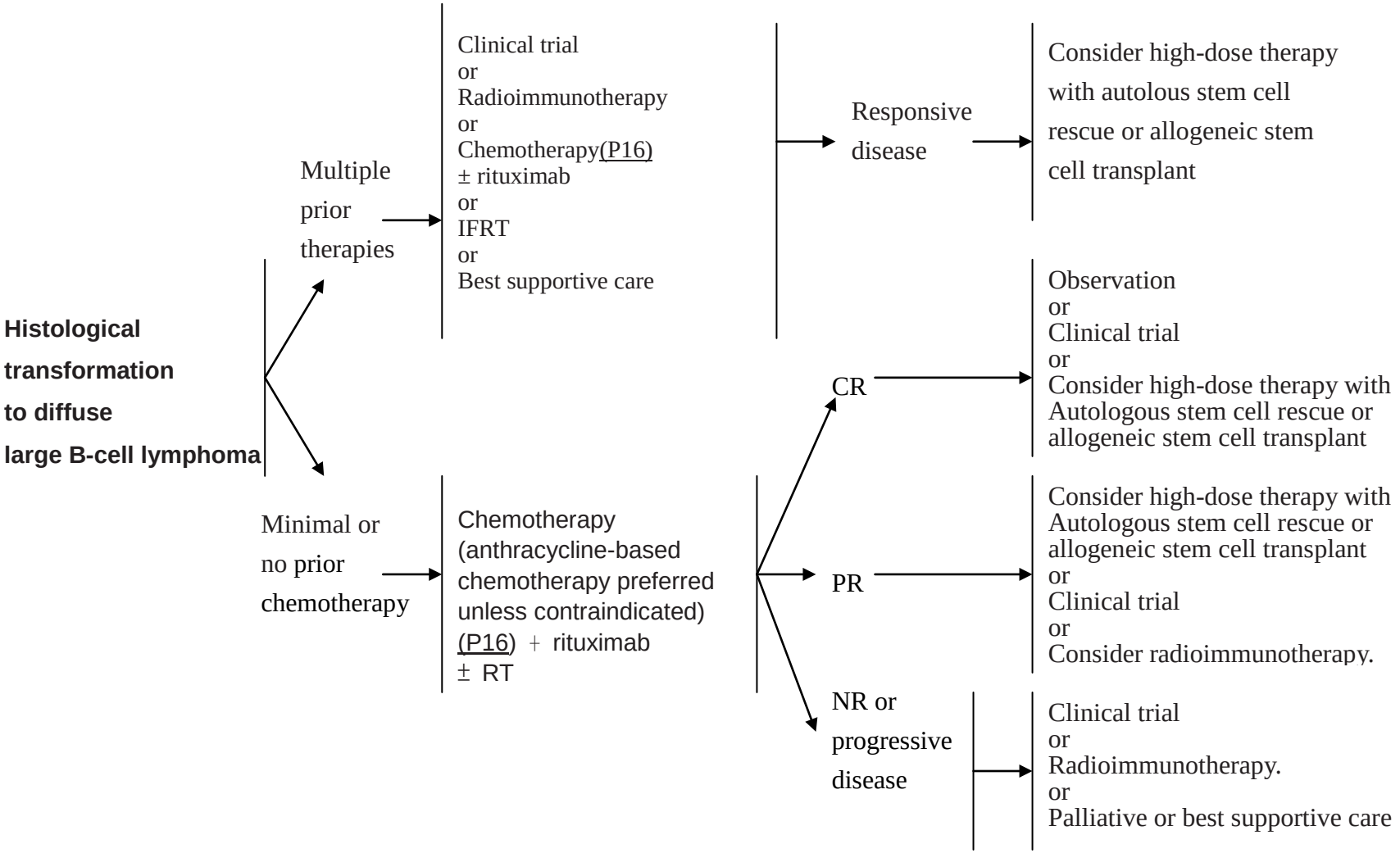


Follicular Lymphoma (grade 1-2)



Follicular Lymphoma (grade 1-2)

HISTOLOGIC TRANSFORMATION TO DIFFUSE LARGE B-CELL LYMPHOMA



Follicular Lymphoma (grade 1-2)

GELF CRITERIA

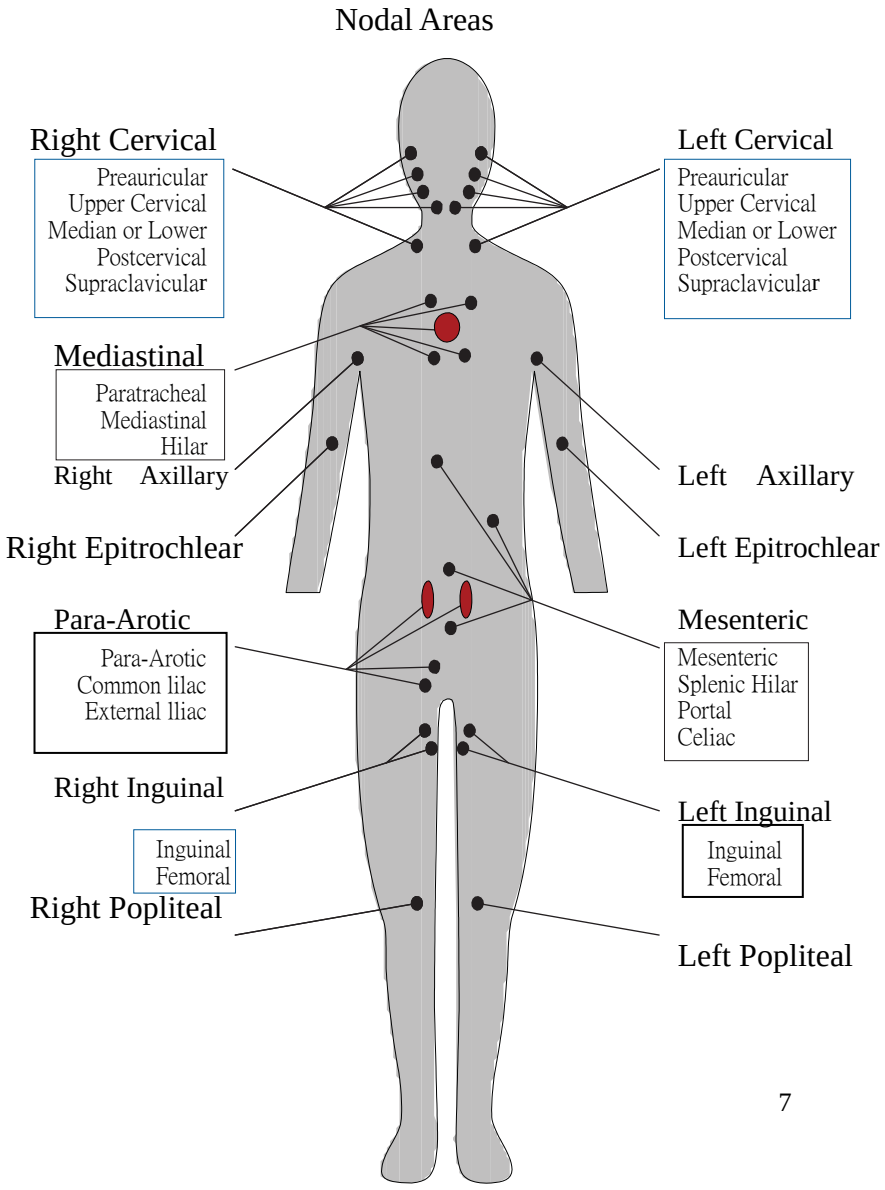
- Involvement of 3 nodal sites, each with a diameter of ≧ 3 cm
- Any nodal or extranodal tumor mass with a diameter of ≧ 7 cm
- B symptoms
- Splenomegaly
- Pleural effusions or peritoneal ascites
- Cytopenias (leukocytes < 1.0 x 10^9/L and/or platelets < 100 x 10^9/L)
- Leukemia (> 5.0 x 10^9/L malignant 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	≧ 5

Risk group according to FLIPI chart

		Number of factors
Mediastinal	**Low**	**0-1**
	Intermediate	**2**
	High	≧ 3



SUGGESTED TREATMENT REGIMENS
(in alphabetical order)

◆ R-CVP

Rituximab	375mg/m2 IV on day 1
Cyclophosphamide	400 mg/m2 IV on day 1-5
	(or 800 mg/m2 IV on day 1-)
Vincristine	1.4 mg/m2 IV on day (maximum 2mg)
Prednisone	60 mg/m2 PO on day 1-5

Cycled every 21 days for 6-8 cycles

◆ R-CHOP

Rituximab	375mg/m2 IV on day 1
Cyclophosphamide	750 mg/m2 IV on day 1
Doxorubicin	50 mg/m2 IV on day 1
Vincristine	1.4 mg/m2 IV on day 1 (maximum 2mg)
Prednisone	60 mg/m2 PO on day 1-5

Cycled every 21 days for 6-8 cycles

SUGGESTED TREATMENT REGIMENS

References

First-line therapy

Bendamustine + rituximab

Rummel MJ, Niederle N, Maschmeyer G, et al. Bendamustine plus rituximab is superior in respect of progression free survival and CR rate when compared to CHOP plus rituximab as first-line treatment of patients with advanced follicular, indolent, and mantle cell lymphomas: Final results of a randomized phase III study of the StiL (Study Group Indolent Lymphomas, Germany) [abstract. Blood 2009;114:Abstract 405.

Cyclophosphamide

Peterson BA, Petroni GR, Frizzera G, et al. Prolonged single-agent versus combination chemotherapy in indolent follicular lymphomas: a study of the cancer and leukemia group B. J Clin Oncol 2003;21:5-15.

CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) + rituximab

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.

Hiddemann W, Kneba M, Dreyling M, et al. Frontline therapy with rituximab added to the combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) significantly improves the outcome for patients with advanced-stage follicular lymphoma compared with therapy with CHOP alone: results of a prospective randomized study of the German Low-Grade Lymphoma Study Group. Blood 2005;106:3725-3732

CVP (cyclophosphamide, vincristine, prednisone) + rituximab

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.

FND (fludarabine, mitoxantrone, dexamethasone) + rituximab

McLaughlin P, Hagemeister FB, Rodriguez MA, et al. Safety of fludarabine, mitoxantrone, and dexamethasone combined with rituximab in the treatment of stage IV indolent lymphoma. Semin Oncol 2000;27:37-41.

Rituximab

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.

Colombat P, Salles G, Brousse N, et al. Rituximab (anti-CD20 monoclonal antibody) as single first-line therapy for patients with follicular lymphoma with a low tumor burden: Clinical and molecular evaluation. Blood 2001;97:101-106.

Radioimmunotherapy

Kaminski MS, Tuck M, Estes J, et al. 131I-tositumomab therapy as initial treatment for follicular lymphoma. N Engl J Med 2005;352:441-449. Kaminski MS, Tuck M, Estes J, et al. Tositumomab and iodine I-131 tositumomab for previously untreated, advanced-stage, follicular lymphoma: Median 10 year follow-up results. Blood 2009;114:3759.

First-line consolidation or extended dosing

Chemotherapy followed by radioimmunotherapy

Press OW, Unger JM, Braziel RM, et al. Phase II trial of CHOP chemotherapy followed by tositumomab/iodine I-131 tositumomab for previously untreated follicular non-Hodgkin's lymphoma: Five-year follow-up of Southwest Oncology Group Protocol S9911. J Clin Oncol 2006;24:4143-4149.

Morschhauser F, Radford J, Van Hoof A, et al. Phase III trial of consolidation therapy with Yttrium-90–Ibritumomab Tiuxetan compared with no additional therapy after first remission in advanced follicular lymphoma. J Clin Oncol 2008;26:5156-5164.

Hagenbeek A, Radford J, Van Hoof A, et al. 90Y-Ibritumomab tiuxetan (Zevalin®) consolidation of first remission in advanced-stage follicular non-hodgkin's lymphoma: Updated results after a median follow-up of 66.2 months from the international, randomized, phase III First-Line Indolent Trial (FIT) in 414 Patients [abstract]. Blood 2010;116:Abstract 594.

Chemotherapy followed by rituximab

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

Diffuse Large B-Cell Lymphoma(High grade NHL)

DIAGNOSIS

ESSENTIAL:

- Hematopathology review of all slides with at least one paraffin block representative of the 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 node is not easily accessible for excisional or incisional biopsy, a combination of core biopsy and FNA biopsies in conjunction with appropriate ancillary techniques for the differential diagnosis (immunohistochemistry, flow cytometry, PCR for IgH and TCR gene rearrangements, and FISH for major translocations) may be sufficient for diagnosis.
- Adequate immunophenotyping to establish diagnosis and GCB versus non-GCB orgin
  - IHC panel: CD20, CD3, CD5, CD10, CD45, BCL2, BCL6, Ki-67, IRF4/MUM1
    or
  - Cell surface marker analysis by flow cytometry: kappa/lambda, CD45, CD3, CD5, CD19, CD10, CD20

USEFUL UNDER CERTAIN CIRCUMSTANCES:

- Additional immunohistochemical studies to establish LYMPHOMA SUBTYPE
  - IHC panel: Cyclin D1, kappa/lambda, CD30,CD138, EBER-ISH,ALK,HHV8
- Molecular analysis to detect: antigen receptor gene rearrangements; CCND1, BCL2, BCL6, MYC[e] rearrangements by either FISH or IHC
- Cytogenetics or FISH: t(14;18);[e] t(3;v); t(8;14)

SUBTYPES

- Subtypes included:
  - DLBCL, NOS
  - DLBCL coexistent with follicular lymphoma of any grade
  - DLBCL coexistent with gastric MALT lymphoma
  - DLBCL coexistent with nongastric MALT lymphoma
  - Follicular Lymphoma grade 3
  - Intravascular large B-cell lymphoma
  - DLBCL associated with chronic inflammation
  - ALK positive DLBCL
  - EBV positive DLBCL of the elderly
  - T-cell/histiocyte rich large B-cell lymphoma
- Subtypes *not* included:
  - Primary cutaneous B-cell lymphoma
  - Primary DLBCL of the CNS

See Workup (P10)

Diffuse Large B-Cell Lymphoma(High grade NHL)

WORKUP

ESSENTIAL:

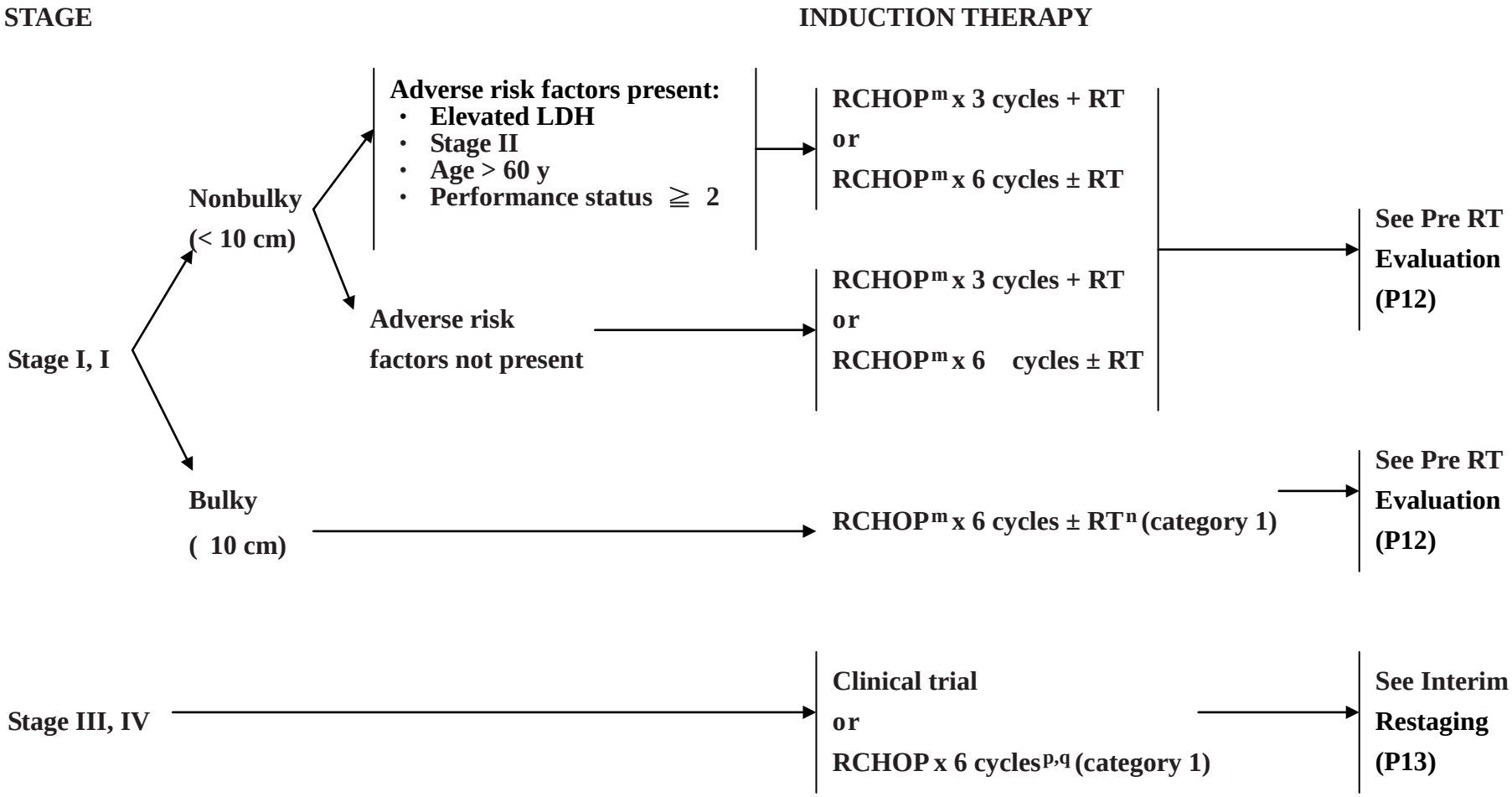
- **Physical exam: attention to node-bearing areas, including Waldeyer's ring, and to size of liver and spleen.**
- **Performance status**
- **B symptoms**
- **CBC, differential, platelets**
- **LDH**
- **Comprehensive metabolic panel**
- **Uric acid**
- **Chest/abdominal/pelvic CT with contrast of diagnostic quality**
- **Adequate bone marrow biopsy (>1.6 cm) ± aspirate**
- **Calculation of International Prognostic Index (IPI)**
- **Hepatitis B testing**
- **MUGA scan/echocardiogram if anthracycline or anthracenedione- based regimen is indicated**
- **PET-CT scan(optional)**
- **Pregnancy testing in women of child-bearing age**
- **Beta-2-microglobulin**

USEFUL IN SELECTED CASES:

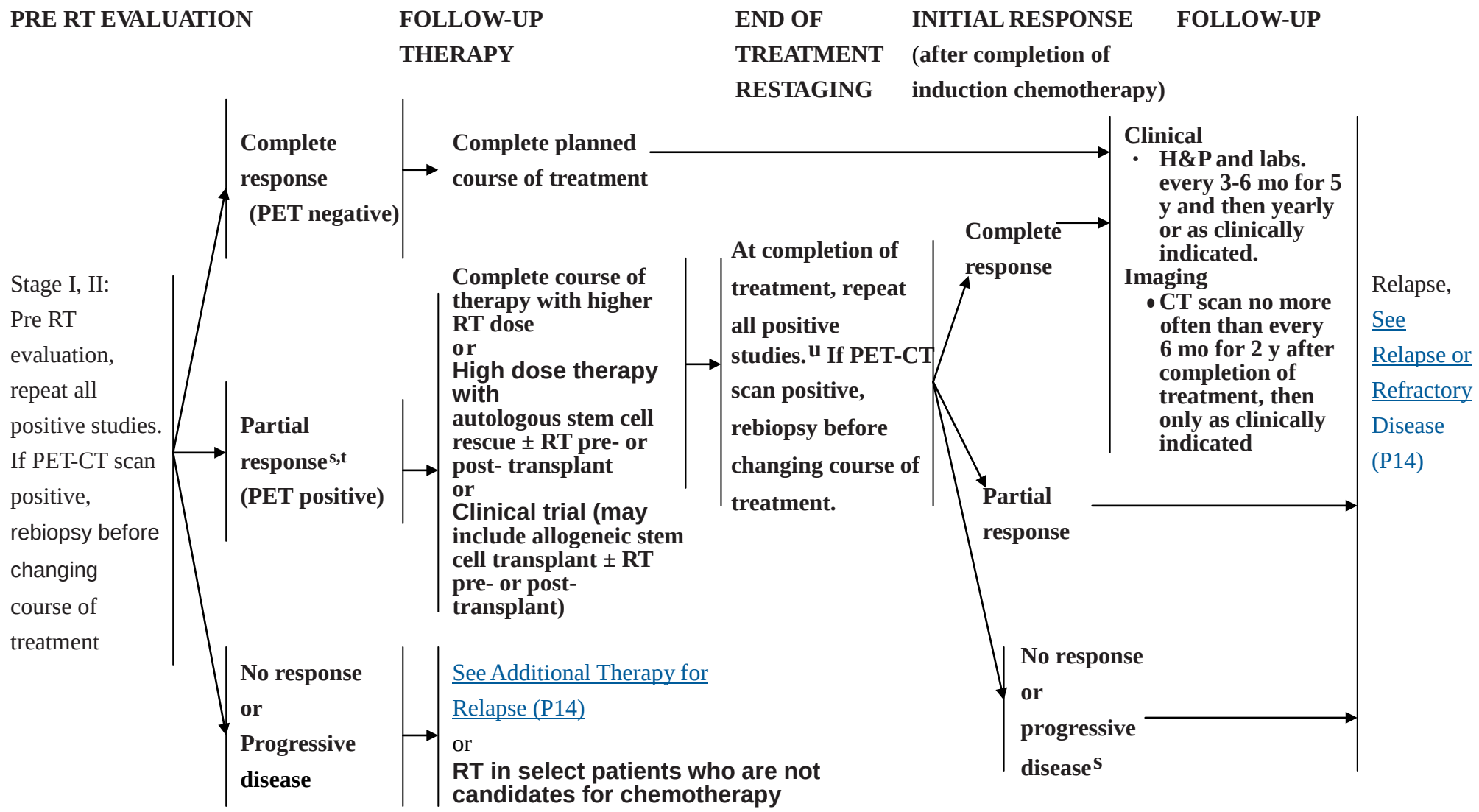
- **Neck CT, Head CT, or MRI**
- **Discussion of fertility issues and sperm banking**
- **HIV**
- **Lumbar puncture, if paranasal sinus, testicular, epidural, bone marrow with large cell lymphoma, HIV lymphoma, or ≧ 2 extranodal sites and elevated LDH**

See InductionTherapy (P11)

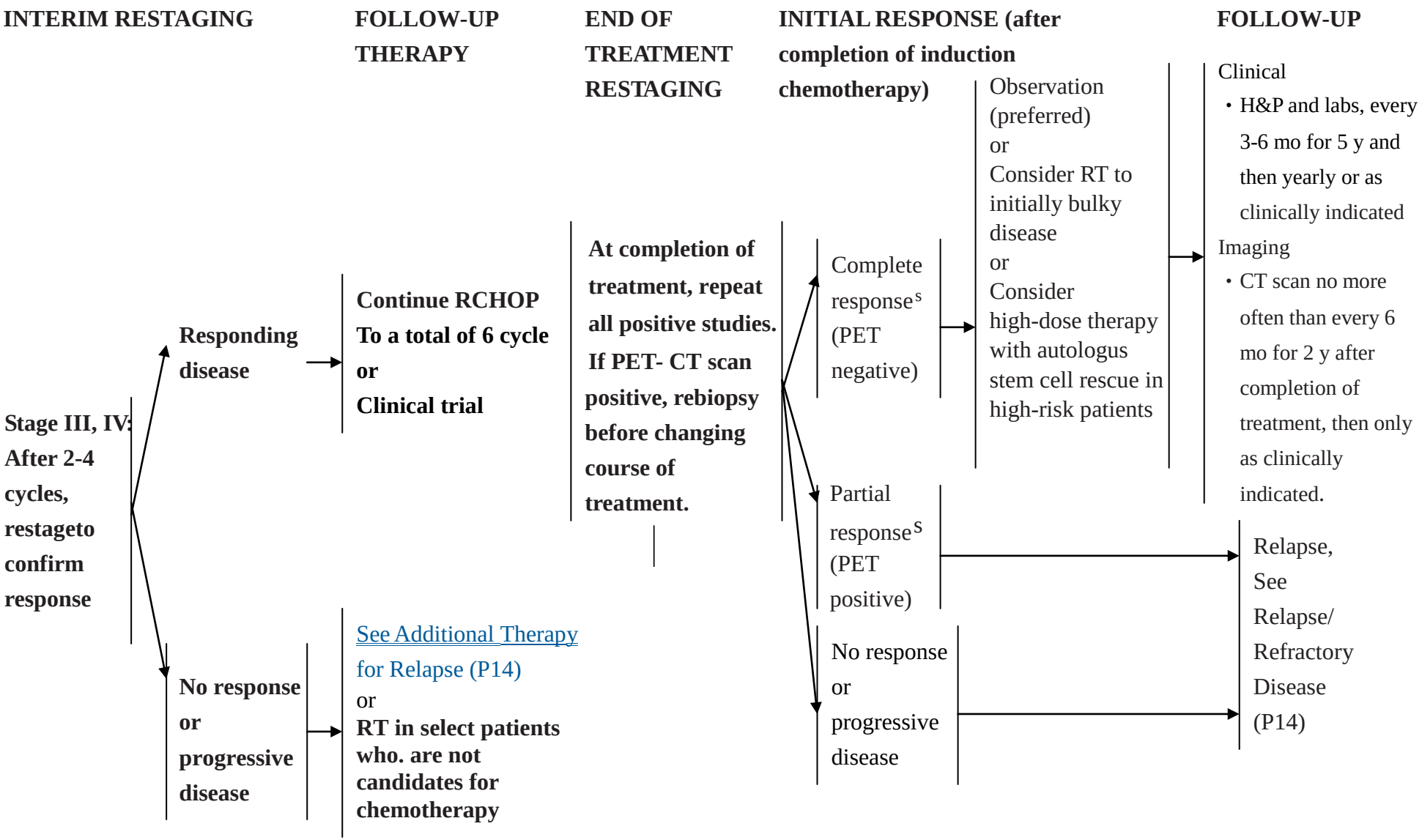
Diffuse Large B-Cell Lymphoma(High grade NHL)



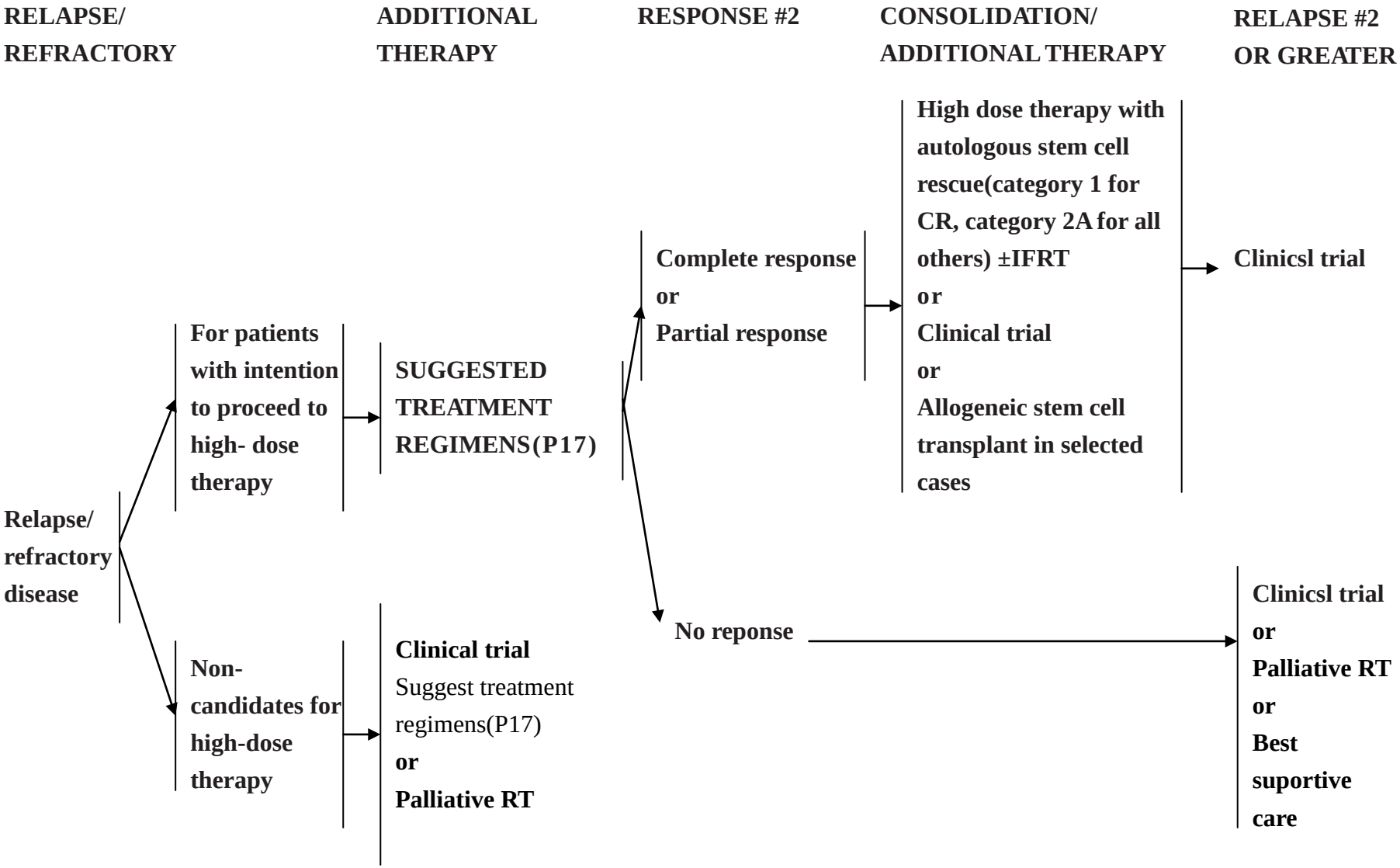
Diffuse Large B-Cell Lymphoma(High grade NHL)



Diffuse Large B-Cell Lymphoma(High grade NHL)



Diffuse Large B-Cell Lymphoma(High grade NHL)



INTERNATIONAL PROGNOSTIC INDEX

ALL PATIENTS:

- **Age > 60 years**
- **Serum LDH > normal**
- **Performance status 2-4**
- **Stage III or IV**
- **Extranodal involvement > 1 site**

INTERNATIONAL INDEX, ALL PATIENTS:

Low	**0 or 1**
Low intermediate	**2**
High intermediate	**3**
High	**4 or 5**

AGE-ADJUSTED INTERNATIONAL PROGNOSTIC INDEX

PATIENTS ≦ 60YEARS

- **Stage III or IV**
- **Serum LDH > normal**
- **Performance status 2-4**

INTERNATIONAL INDEX, PATIENTS ≦ 60 YEARS

- **Low 0**
- **Low/intermediate 1**
- **High/intermediate 2**
- **Hight 3**

SUGGESTED TREATMENT REGIMENS

(in alphabetical order)

◆ **R-CHOP**

Rituximab	375mg/m2 IV on day 1
Cyclophosphamide	750 mg/m2 IV on day 1
Doxorubicin	50 mg/m2 IV on day 1
Vincristine	1.4 mg/m2 IV on day 1 (maximum 2mg)
Prednisone	60 mg/m2 PO on day 1-5

Cycled every 21 days for 6-8 cycles

◆ **CHOP**

Cyclophosphamide	750 mg/m2 IV on day 1
Doxorubicin	50 mg/m2 IV on day 1
Vincristine	1.4 mg/m2 IV on day 1(maximum 2mg)
Prednisone	60 mg/m2 PO on day 1-5

Cycled every 21 days for 6-8 cycles

◆ **CVP**

Cyclophosphamide	400 mg/m2 IV on day 1-5 (or 800 mg/m2 IV on day 1-)
Vincristine	1.4 mg/m2 IV on day (maximum 2mg)
Prednisone	60 mg/m2 PO on day 1-5

Cycled every 21 days for 6-8 cycles

◆ **R-EPOCH**

Rituximab	375mg/m2 IV on day 1
Etoposide	50 mg/m2 IV on day 1-4
Prednisone	60 mg/m2 PO on day 1-5
Vincristine	0.4 mg/m2 IV on day 1-4
Cyclophosphamide	750 mg/m2 IV on day 5,begin after infusion

Cycled every 21 days for 6-8 cycles

◆ **ESHAP**

Etoposide	40 mg/m2 IV on day 1-4
Methylprednisolone	500 mg/m2 IV on day 1-4
Cisplatin	25 mg/m2 IV on day 1-4
Cytarabine	2000 mg/m2 IV on day 5 after completion of Cisplatine and Etoposide

Cycled every 21 days for 6-8 cycles

◆ **DHAP**

Cisplatin	100 mg/m2 IV over 24 hours on day 1
Cytarabine	2000 mg/m2 IV over 3 hours every 12 hours for 2 doses on day 2 after completion of Cisplatine influsion
Dexamethasone	40 mg/m2 PO or IV on day 1-4

Cycled every 21 days for 6-8 cycles

◆ **Hyper-CVAD/MTX-Ara-C**

Cyclophosphamide	300 mg/m2 IV every 12 hours for 6 doses on day 1-3
Mesna	600 mg/m2 on day 1-3 to start 1 hour before Cyclophosphamide until 12 hours after completion of Cyclophosphamide
Vincristine	2 mg/m2 IV on day 4 and 11
Doxorubicin	50 mg/m2 IV over 24 hours on day 4
Dexamethasone	40 mg/m2 PO or IV on day 1-4 and day11-14

Admonister every 3-4 weeks on cycles 1,3,5,and 7

Methotrexate	200 mg/m2 IV over 2 hours followed by 800 mg/m2 over 22hours on day 1

SUGGESTED TREATMENT REGIMENS

References

First-line Therapy

CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone)+ rituximab with RT

Miller TP, Dahlberg S, Cassady JR, et al. Chemotherapy alone compared with chemotherapy plus radiotherapy for localized intermediate- and high-grade non-hodgkin's lymphoma. N Engl J Med 1998;339:21-26

Horning SJ, Weller E, Kim K, et al. Chemotherapy with or without radiotherapy in limited-stage diffuse aggressive non-hodgkin's lymphoma: Eastern Cooperative Oncology Group Study 1484. J Clin Oncol 2004;22:3032-3038

Persky DO, Unger JM, Spier CM, et al. Phase II study of rituximab plus three cycles of CHOP and involved-field radiotherapy for patients with limited-stage aggressive B-cell lymphoma: Southwest Oncology Group Study 0014. J Clin Oncol 2008;26:2258-2263

CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) + rituximab

Coiffier B, Thieblemont C, Van Den Neste E, et al. Long-term outcome of patients in the LNH-98.5 trial, the first randomized study comparing rituximab-CHOP to standard CHOP chemotherapy in DLBCL patients: a study by the Groupe d'Etudes des Lymphomes de l'Adulte. Blood 2010;116:2040-2045

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 l'Adulte. J Clin Oncol 2005;23:4117-4126

Pfreundschuh M, Trumper L, Osterborg A, et al. CHOP-like chemotherapy plus rituximab versus CHOP-like chemotherapy alone in young patients with good-prognosis diffuse large-B-cell lymphoma: a randomised controlled trial by the MabThera International Trial (MInT) Group. Lancet Oncol 2006;7:379-391

Pfreundschuh M, Schubert J, Ziepert M, et al. Six versus eight cycles of bi-weekly CHOP-14 with or without rituximab in elderly patients with aggressive CD20+ B-cell lymphomas: a randomised controlled trial (RICOVER-60). Lancet Oncol 2008;9:105-116

Dose-dense CHOP 14 + rituximab

Blayney DW, LeBlanc ML, Grogan T, et al. Dose-intense chemotherapy every 2 weeks with dose-intense cyclophosphamide, doxorubicin, vincristine, and prednisone may improve survival in intermediate- and high-grade lymphoma: a phase II study of the Southwest Oncology Group (SWOG 9349). J Clin Oncol 2003;21:2466-2473

randomized phase III trial for the treatment of patients with newly diagnosed diffuse large B-cell non-Hodgkin lymphoma [abstract]. J Clin Oncol 2011;29: Abstract 8000

Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide doxorubicin) + rituximab

Purroy N, Lopez A, Vallespi T, Gironella M, Bergua J, Sancho JM. Dose-adjusted EPOCH plus rituximab (DA-EPOCH-R) in untreated patients with poor risk large B-cell lymphoma. A phase 2 study conducted by the Spanish PETHEMA Group [Abstract]. Blood 2009;114:Abstract 2701

Wilson WH, Dunleavy K, Pittaluga S, et al. Phase II study of dose-adjusted EPOCH and rituximab in untreated diffuse large B-cell lymphoma with analysis of germinal center and post-germinal center biomarkers. J Clin Oncol 2008;26:2717-2724

First-line Therapy for patients with poor ventricular left function

CDOP (cyclophosphamide, liposomal doxorubicin, vincristine and prednisone) + Rituximab

Martino R, Perea G, Caballero MD, et al. Cyclophosphamide, pegylated liposomal doxorubicin (Caelyx), vincristine and prednisone (CCOP) in elderly patients with diffuse large B-cell lymphoma: Results from a prospective phase II study. Haematologica 2002;87:822-827.

Zaja F, Tomadini V, Zaccaria A, et al. CHOP-rituximab with pegylated liposomal doxorubicin
for the treatment of elderly patients with diffuse large B-cell lymphoma. Leuk Lymphoma 2006;47:2174-2180

CNOP (cyclophosphamide, mitoxantrone, vincristine, prednisone) + rituximab

Bessell EM, Burton A, Haynes AP, et al. A randomised multicentre trial of modified CHOP versus MCOP in patients aged 65 years and over with aggressive non-Hodgkin's lymphoma.
Ann Oncol 2003;14:258-267.

Bezwoda W, Rastogi RB, Erazo Valla A, et al. Long-term results of a multicentre randomised, comparative phase III trial of CHOP versus CNOP regimens in patients with intermediate- and high-grade non-Hodgkin's lymphomas. Novantrone International Study Group. Eur J Cancer 1995;31A:903-911.

Sonneveld P, de Ridder M, van der Lelie H, et al. Comparison of doxorubicin and mitoxantrone in the treatment of elderly patients with advanced diffuse non-Hodgkin's lymphoma using CHOP versus CNOP chemotherapy. J Clin Oncol 1995;13:2530-2539.

RCEOP (ritximab, cyclophosphamide, etoposide, vincristine, prednisone)

Moccia A, Schaff K, Hoskins P, et al. R-CHOP with etoposide substituted for doxorubicin(RCEOP): Excellent outcome in diffuse large B cell lymphoma for patients with a contraindication to anthracyclines [abstract]. Blood 2009;114:Abstract 408

First-line consolidation

Stiff PJ, Unger JM, Cook J, et al. Randomized phase III U.S./Canadian intergroup trial (SWOG S9704) comparing CHOP {+/-} R for eight cycles to CHOP {+/-} R for six cycles followed by autotransplant for patients with high-intermediate (H-Int) or high IPI grade diffuse aggressive non-Hodgkin lymphoma (NHL) [abstract]. J Clin Oncol 2011;29: Abstract 8001

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 bss