- 前言:
- 惡性淋巴瘤(或簡稱淋巴癌)乃由體內淋巴系統包括淋巴細胞、淋巴管、淋巴腺及一些淋巴器官或組織如脾臟、胸腺及扁桃腺等所長出的惡性腫瘤。依腫瘤病理組織型態的不同可分為何杰金氏淋巴瘤(Hodgkin ‘s lymphoma)與非何杰金氏淋巴瘤(Non-Hodgkin’s lymphoma)兩大類，兩者的臨床症狀很相似但其預後卻有所不同。
- 台灣地區及本院的非何杰金氏淋巴瘤發生率皆遠高於何杰金氏淋巴瘤，另依據衛生署民國九十五年癌症統計提料顯示，非何杰金氏淋巴瘤在癌症死因中名列第十一名。
- 因此，血液、肉瘤、腦瘤暨其他癌團隊，特別先針對何杰金氏淋巴瘤擬定臨床指引。為此我們除了參考美國NCCN (National Comprehensive Cancer Network)治療準則外，另依據本院多科團隊之討論修訂，來完成本院第一版何杰金氏淋巴瘤之治療共識。

- 本共識依下列參考資料修改版本:
- NCCN Clinical Practice Guidelines in Oncology- Hodgkin Lymphoma V.2.2015

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# 亞東紀念醫院 Hodgkin Lymphoma 臨床指引

Hodgkin Lymphoma
Clinical Guidelines
in Oncology, FEMH – v.1.2015

## DIAGNOSIS

- **Excisional biopsy (recommended)**
- **Core needle biopsy may be adequate if diagnostic** [a]
- **Immunohisto-chemistry**

## WORKUP

**Essential:**

- **H&P including: 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、HBsAg、Anti-HCV**
- **Pregnancy test: women of childbearing age**
- **Chest x-ray**
- **Diagnostic neck/chest/abdominal/pelvic CT**
- **PET-CT scan(CT or MRI** 不足以診斷時)
- **Adequate bone marrow biopsy in stage IB, IIB and stage III-IV**
- **Evaluation of ejection fraction for doxorubicin-containing regimens**
- **Counseling: Fertility, smoking cessation, psychosocial**

**Useful in selected cases:**

- **Semen cryopreservation, if chemotherapy or pelvic RT contemplated**
- **IVF or ovarian tissue or oocyte cryopreservation**
- **Pulmonary functions tests (PFTs incl. DLCO) if ABVD or BEACOPP are being used**
- **Pneumococcal, H-flu, meningococcal vaccines, if splenic RT contemplated**
- **HIV (encouraged)**

## CLINICAL STAGING

**Classical Hodgkin lymphoma**

- Stage IA, IIA Favorable[b]
- Stage I-II Unfavorable(Non-bulky disease**)**
- Stage I-II Unfavorable[c]**(**Bulky disease)
- Stage III-IV

→ See Primary Treatment

**Lymphocyte-predominant Hodgkin lymphoma (LPHL)** →

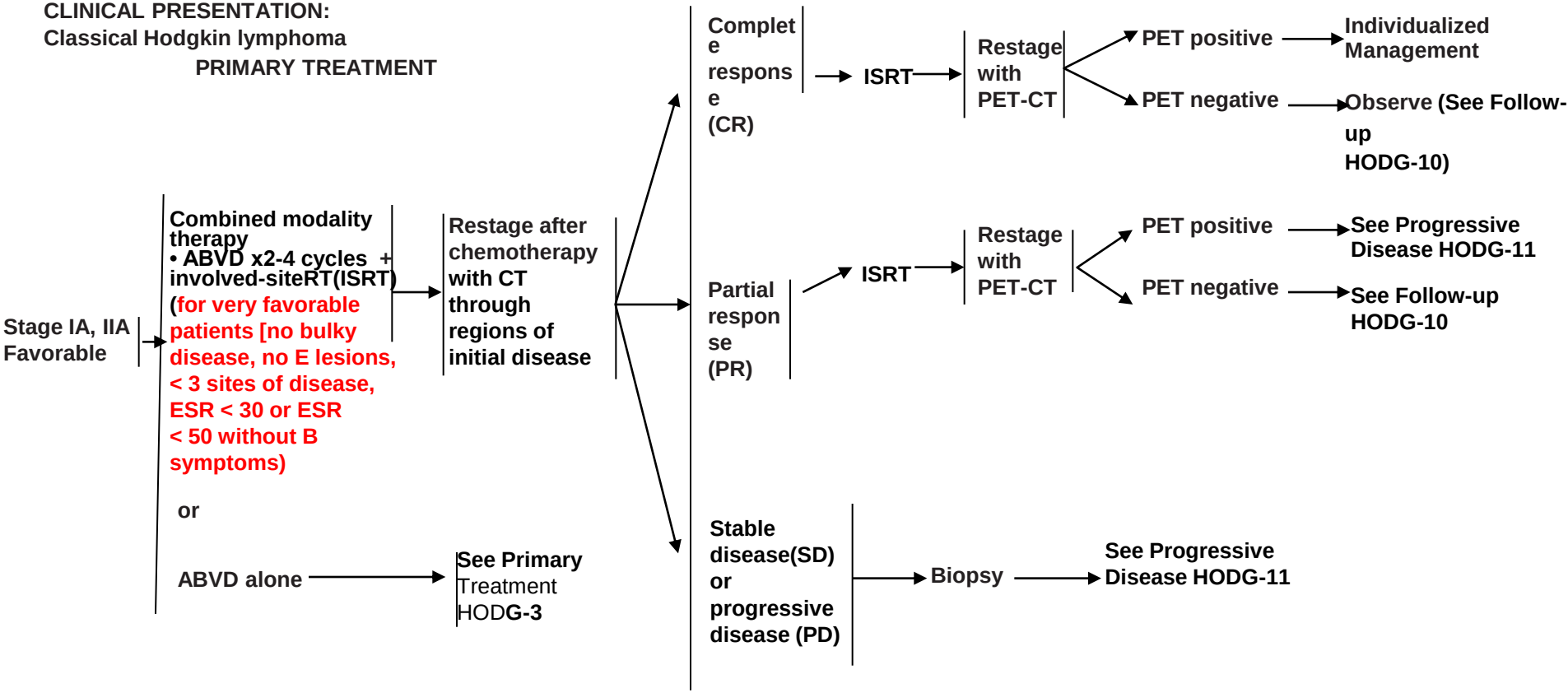
[a] a FNAB alone is to be avoided and only considered to be adequate if called diagnostic of HL by a hematopathologist or cytopathologist

[b] Typical immunophenotype for Classical Hodgkin lymphoma: CD30+, CD15+ **(optional)**; CD3-, CD45-; CD20–(**majority)**. Lymphocyte-predominant Hodgkin lymphoma: CD20+, CD45+; CD3-, CD15-, CD30-. An expanded panel of markers may be required especially if equivocal diagnosis.

[c] NCCN Unfavorable factors for stage I-II disease include bulky mediastinal or > 10 cm disease, B symptoms, ESR >50, >3 sites of disease

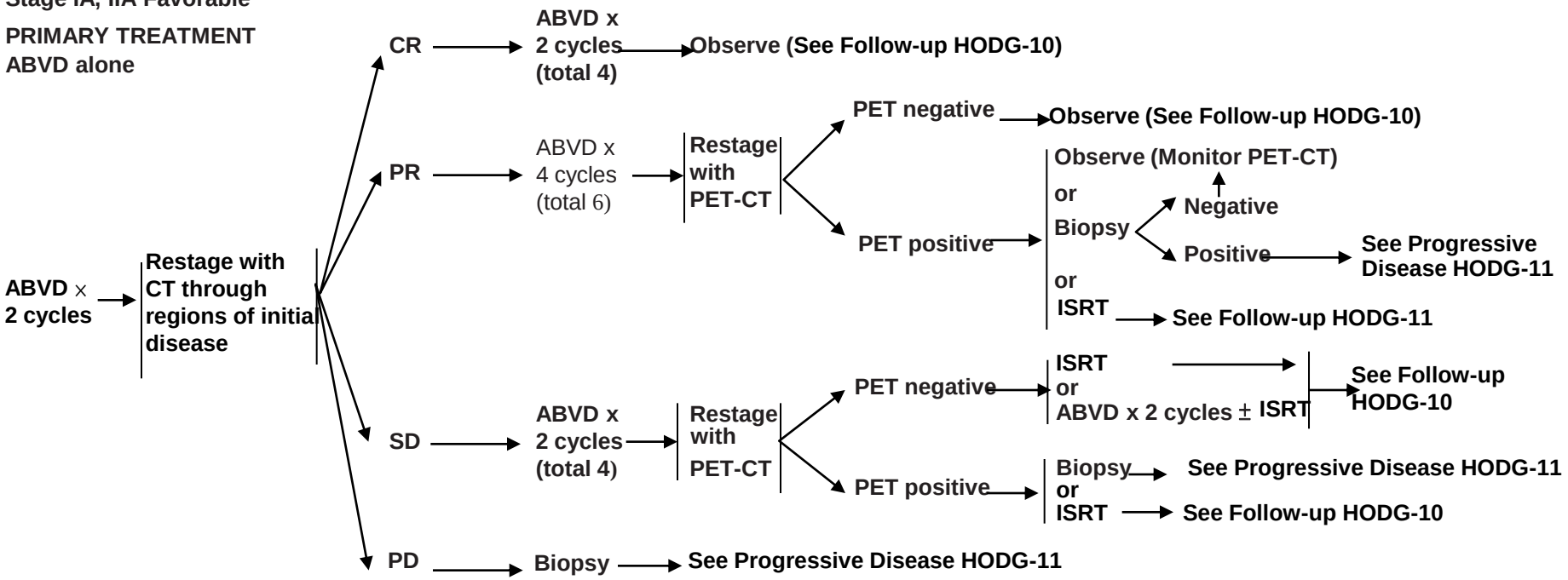
**CLINICAL PRESENTATION:**
**Classical Hodgkin lymphoma**

**PRIMARY TREATMENT**



**CLINICAL PRESENTATION:**
**Classical Hodgkin lymphoma**
**Stage IA, IIA Favorable**

**PRIMARY TREATMENT**
**ABVD alone**

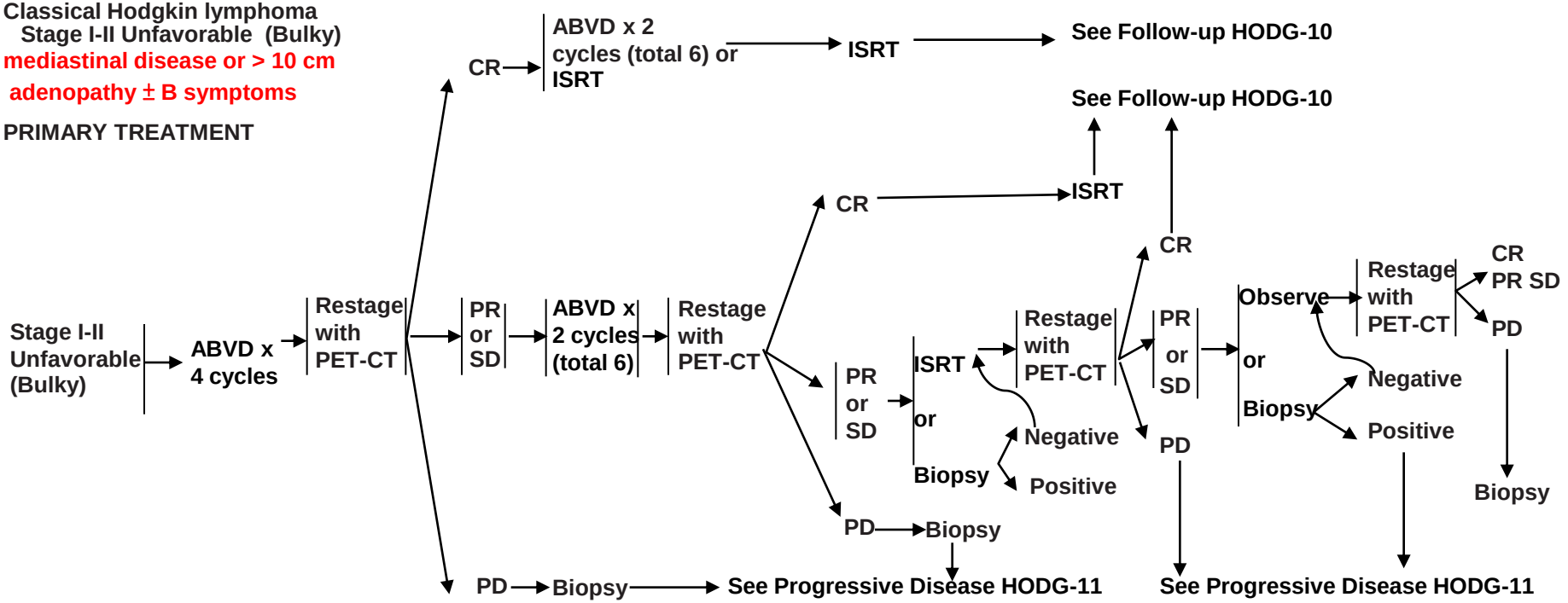


# 亞東紀念醫院 Hodgkin Lymphoma 臨床指引



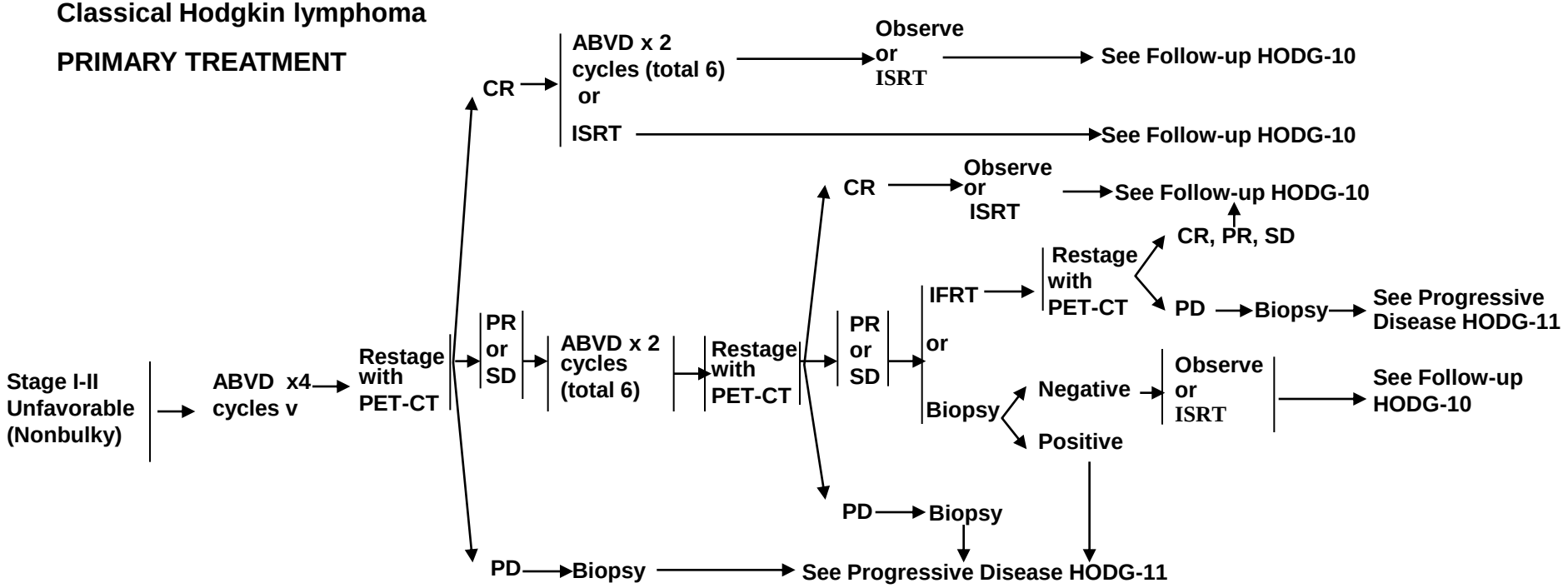
**CLINICAL PRESENTATION:**
**Classical Hodgkin lymphoma**
**Stage I-II Unfavorable (Bulky)**
**mediastinal disease or > 10 cm**
**adenopathy ± B symptoms**

**PRIMARY TREATMENT**



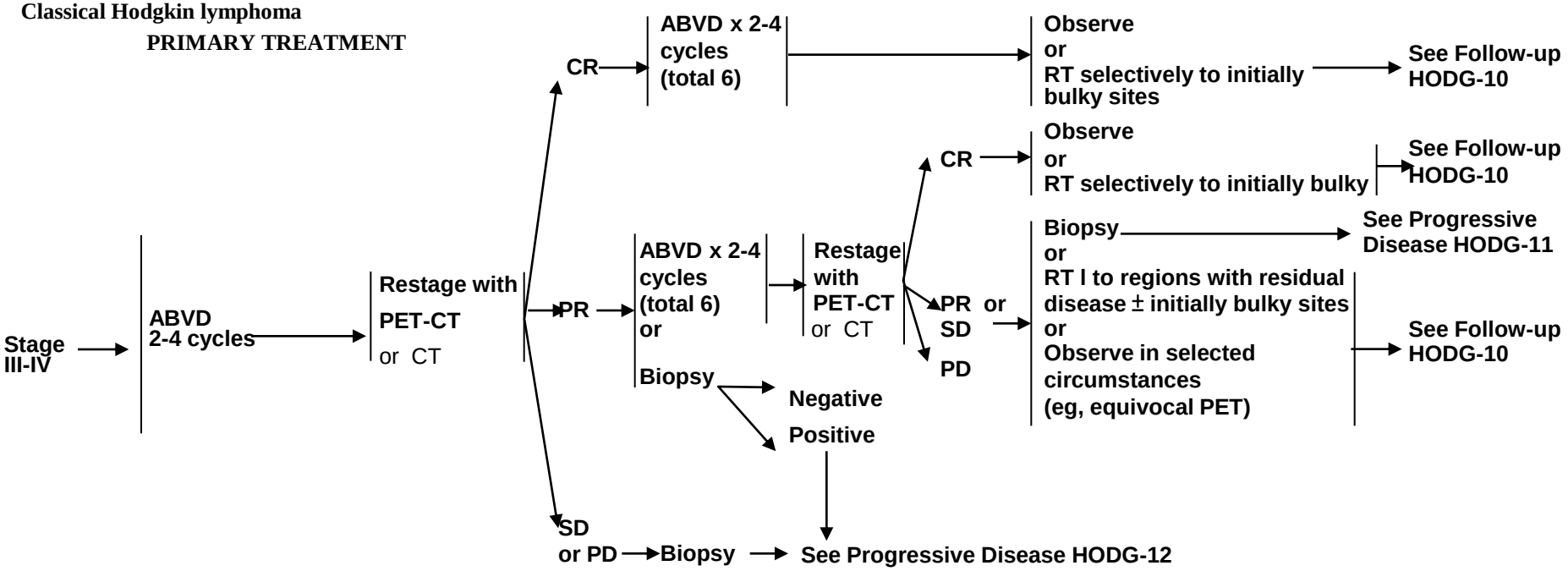
## CLINICAL PRESENTATION:
## Classical Hodgkin lymphoma

### PRIMARY TREATMENT



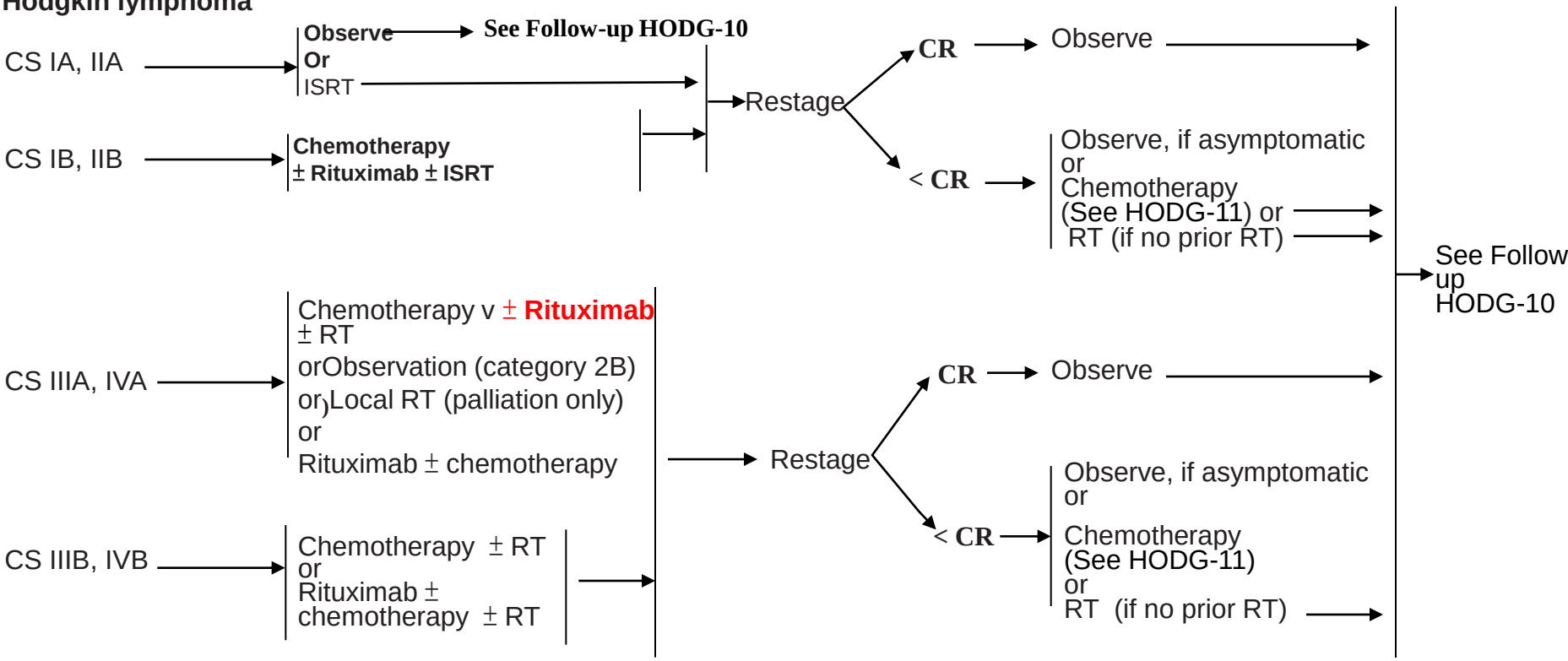
**CLINICAL PRESENTATION:**
**Classical Hodgkin lymphoma**

**PRIMARY TREATMENT**



**CLINICAL PRESENTATION:** **PRIMARY TREATMENT**

**Nodulur Lymphocyte-predominant Hodgkin lymphoma**



## FOLLOW-UP AFTER COMPLETION OF TREATMENT AND MONITORING FOR LATE EFFECTS

- 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

- The frequency and types of tests may vary depending on clinical circumstances; age and stage at diagnosis, social habits, treatment modality, et
  There are few data to support specific recommendations, these represent the range of practice at NCCN institutions.

(

- Interim H&P:
  Every 2-4 mo for 1-2 y, then every 3-6 mo for next 3-5 y

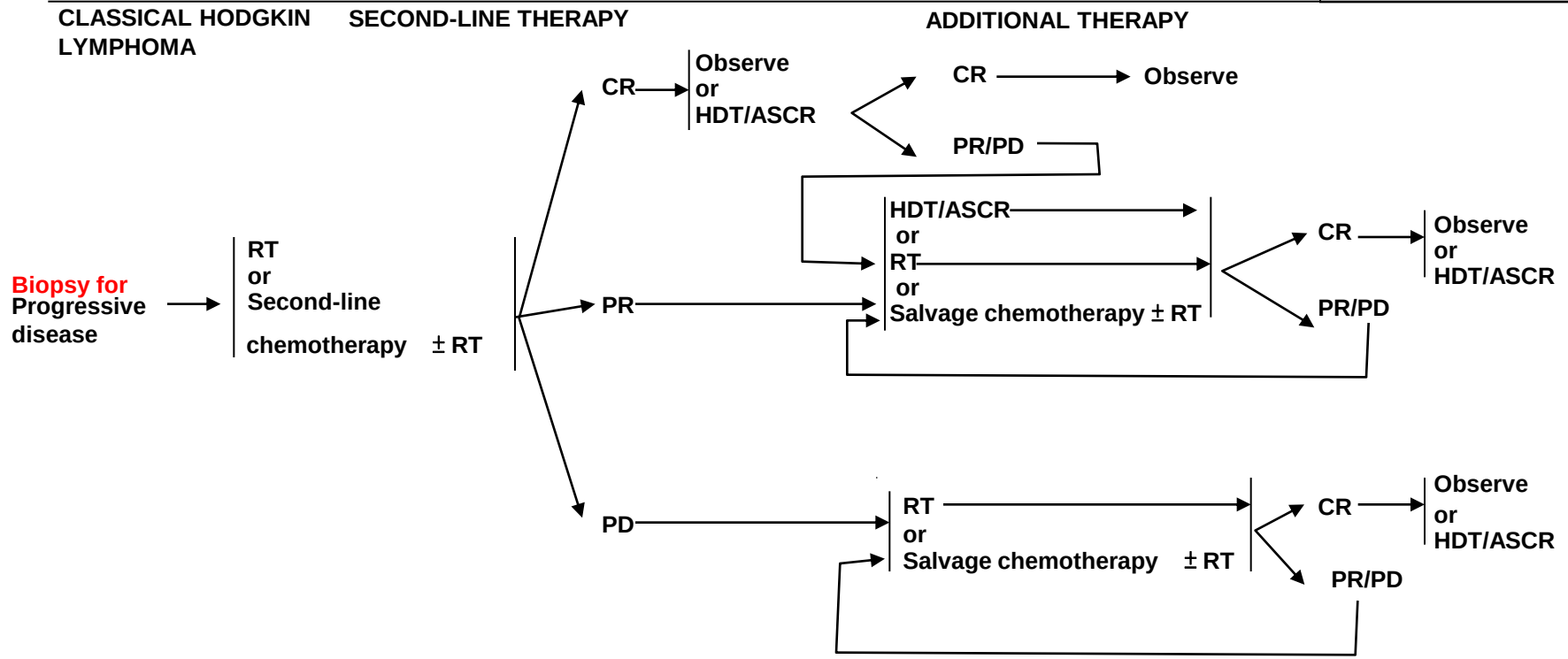
Follow-up after completion of treatment

> Annual influenza vaccine

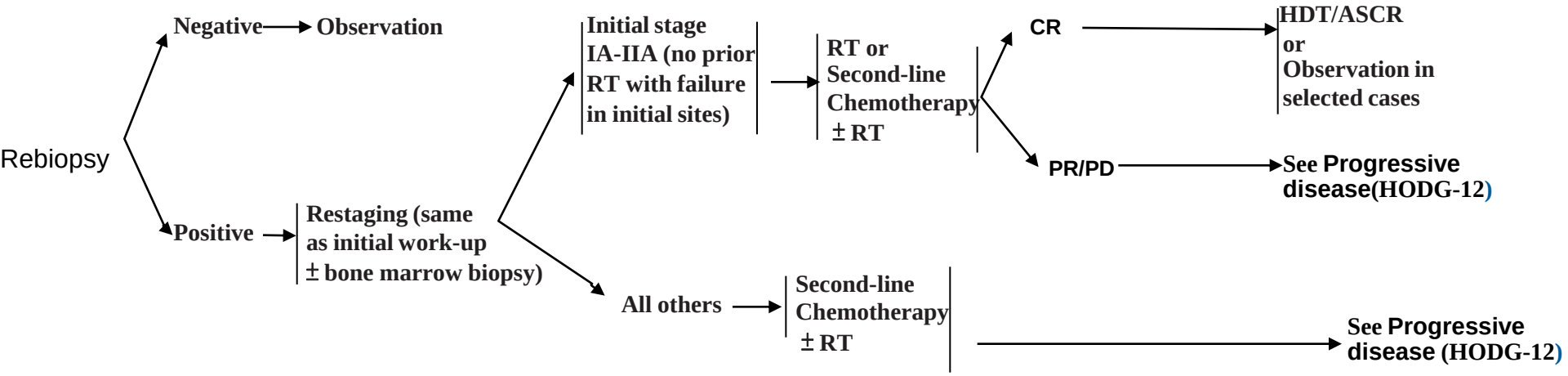
- Laboratory studies:
  - > CBC, platelets, ESR (if elevated at time of initial diagnosis), chemistry profile every 2-4 mo for 1-2 y, then every 3-6 mo for next 3-5 y
  - > TSH at least annually if RT to neck.
- Chest imaging:
  Chest x-ray or CT every 6-12 mo during first 2-5 y
- Abdominal/pelvic CT (category 2B):
  Every 6-12 mo for first 2-3 y)
- 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 positives. Management decisions should not be based on PET scan alone, clinical or pathological correlation is needed.

### Monitoring for Late Effects after 5 Years

- 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 5-7 y, if patient treated with splenic RT or previous splenectomy
  - > Annual influenza vaccine
- Consider baseline stress test/echocardiogram at 10 y, especially if chest irradiation
- 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 patients 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 NCCN Hodgkin Lymphoma Guidelines Panel recommends breast MRI in addition to mammography for women who received irradiation to the chest between ages 10 and 30 y, which is consistent with the American Cancer Society Guidelines.
- Counseling:
  Reproduction, health habits, psychosocial, cardiovascular, breast self-exam, skin cancer risk.
- Cardiovascular symptoms may emerge at a young age.
- Treatment summary and consideration of transfer to PCP.


CLASSICAL HODGKIN LYMPHOMA
SECOND-LINE THERAPY
ADDITIONAL THERAPY
Biopsy for Progressive disease
RT or Second-line chemotherapy ± RT
CR
Observe or HDT/ASCR
CR
Observe
PR/PD
PR
HDT/ASCR or RT or Salvage chemotherapy ± RT
CR
Observe or HDT/ASCR
PR/PD
PD
RT or Salvage chemotherapy ± RT
CR
Observe or HDT/ASCR
PR/PD

## CLASSICAL HODGKIN LYMPHOMA
## SUSPECTED RELAPSE



## Examples of Unfavorable Risk Factors 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 > 10 cm | 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 diameter at T5-6

*The GHSG definition of nodal sites differs from the Ann Arbor system in that the infraclavicular region is included with the ipsilateral cervical/supraclavicular, the
bilateral hila are included with the mediastinum, and the abdomen is divided into 2 regions, upper (spleen hilum, liver hilum, celiac) and lower.

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

- **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/mm $^3$)**
- **Lymphocytopenia (lymphocyte count less than 8% of white blood cell count ,and/or lymphocyte count less than 600/mm $^3$) 3)**

## PRINCIPLES OF SYSTEMIC THERAPY (1 of 2)

### Classical Hodgkin Lymphoma

· **The most common variants of chemotherapy used at NCCN member institutions include ABVD and Stanford V. Routine use of growth factors is not recommended. Leukopenia is not a factor for delay of treatment or reduction of dose intensity (except for escalated BEACOPP).**

### Regimens and References

**ABVD (Doxorubicin, Bleomycin, Vinblastine and Dacarbazine) ± RT**

Eich HT, Diehl V, Gorgen H, et al. Intensified chemotherapy and dose-reduced involved-field radiotherapy in patients with early unfavorable Hodgkin's lymphoma: final
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Engert A, Plutschow A, Eich HT, et al. Reduced treatment intensity in patients with early-stage Hodgkin's lymphoma. N Engl J Med 2010;363:640-652.
Meyer RM, Gospodarowicz MK, Connors JM, et al. Randomized comparison of ABVD chemotherapy with a strategy that includes radiation therapy in patients with
limited-stage Hodgkin's lymphoma: National Cancer Institute of Canada Clinical Trials Group and the Eastern Cooperative Oncology Group. J Clin Oncol. 2005;23(21):4634-4642.
Bonadonna G, Bonfante V, Viviani S, Di Russo A, Villani F, Valagussa P. ABVD plus subtotal nodal versus involved-field radiotherapy in early-stage Hodgkin's disease:
Long-Term Results. J Clin Oncol. 2004;22(14):2835-2841.
Duggan DB, Petroni GR, Johnson JL, et al. Randomized comparison of ABVD and MOPP/ABV hybrid for the treatment of advanced Hodgkin's disease: Report of an
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## PRINCIPLES OF SYSTEMIC THERAPY (2 of 2)

**Lymphocyte-predominant Hodgkin Lymphoma 1**

- **The most common chemotherapies used at NCCN member institutions for LPHL include:**
  - **ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) ± rituximab 2,3**
  - **CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) ± rituximab**
  - **CVP (cyclophosphamide, vincristine, prednisone) ± rituximab**
  - **EPOCH (cyclophosphamide, doxorubicin, etoposide, vincristine, prednisone) ± rituximab**
  - **Single agent rituximab 4-6**

## PRINCIPLES OF RADIATION THERAPY

COMBINED MODALITY-RT DOSES:
· Nonbulky disease (stage I-II): 20*-30 Gy (if treated with ABVD), 30 Gy (if treated with Stanford V)
· Nonbulky disease (stage IB-IIB) and Bulky and nonbulky disease (stage III-IV): 30-36 Gy (if treated with BEACOPP)
· Bulky disease sites (all stages): 30-36 Gy (if treated with ABVD), 36 Gy (if treated with Stanford V)

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

## RADIATION FIELDS

· When possible, the high cervical regions (all patients) and axillae (women) should be excluded from the radiation fields.
· Consider oophoropexy to preserve ovarian function in pre-menopausal women.
Involved-field: involved lymphoid region(s) only, modified as above

*A dose of 20 Gy following ABVD x 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 | ³ 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. | ³ 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 ³ 50% of previously involved sites from nadir | Appearance of a new lesion(s) > 1.5 cm in any axis, ³ 50% increase in SPD of more than one node, or ³ 50% increase in longest diameter of a previously identified node > 1 cm in short 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 |

## 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)

>C-MOPP(cyclophosphamine,vincristine,procarbazine,prednisone)

> ChlVPP (Chlorambucil, vinblastine, procarbazine, prednisone)

>DHAP(dexamethasone,cisplatin,high-dose cytarbine)

>ESHPA(etoposide,methylprednisolone,high-dose cytarabine and cisplatin)

>GVD (gemcitabine, vinorelbine, liposomal doxorubicin)

>IGEV((ifosfamide,gemcitabine,vinorelbine)

>Mini-BEAM(carmustine, cytarabine, etoposide,melphalan)

> MINE (etoposide, ifosfamide, mesna, mitoxantrone)

> VIM-D (etoposide, ifosfamide, mitoxantrone and dexamethasone)

>GCD(gemcitabine,carboplatin,dexamethasone)

· Some studies have suggested that patients with minimal disease burden at relapse (not refractory) may not need additional treatment prior 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 with stem-cell rescue 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

Mpskowitz 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.

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 Invest 2008;26(4):401-406.

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4 The International ChlVPP Treatment Group. ChlVPP therapy for Hodgkin's disease: Experience of 960 patients. Ann Oncol. 1995;6(2):167-172.

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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 Invest 2008;26(4):401-406.

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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.

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9 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.

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.

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16 Stewart DA, Guo D, Gluck S, et al. Double high-dose therapy for Hodgkin's disease with dose-intensive cyclophosphamide, etoposide, and cisplatin (DICEP) prior to high-dose melphalan and autologous stem cell transplantation. Bone Marrow Transplant 2000;26(4):383-8.

*Table 1*

Definitions of Stages in Hodgkin's Disease 1

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

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 (IIE).

Note: The number of lymph node regions involved may be indicated by a subscript (e.g. II3 ).

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 (IIIS ), or by both (IIIE+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)

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.