MALIGNANT LYMPHOMAS

By

Assistant Professor Dr. Ali M Alahmedy

- The malignant lymphomas are hematologic cancers that consist of a cluster of diseases of the lymphoid tissue.

- The primary malignant cells for lymphomas are lymphocytes of B-cell, T-cell, and NK-cell origin.

- Lymphoma is categorized into two general headings:
- Hodgkin’s lymphoma (HL) and non-Hodgkin’s lymphoma (NHL).

ETIOLOGY:

- Viruses, such as the Epstein- Barr virus (EBV), have been implicated in HL by epidemiologic, serologic, and molecular studies.

- Kaposi's sarcoma–associated herpes virus, or human herpes virus 8 (HHV-8), and hepatitis C have been implicated in inducing NHL.

- Lymphomas of the gastrointestinal tract are more prevalent in patients with celiac sprue, inflammatory bowel disease, or *Helicobacter pylori* infection.

- Industrial chemicals such as pesticides, herbicides, organic chemicals (e.g., benzene), solvents, and wood preservatives are also associated with NHL.

PATHOPHYSIOLOGY:

- The pathophysiology of HL is defined by the presence of the Reed - Sternberg (RS) cell in a grouping of lymph nodes.

- The RS cell is a large cell morphologically with a multinucleated structure with pronounced eosinophilic nucleoli.

- RS cells express cell-surface antigens CD30 and CD15 while lacking other common B-cell antigens such as CD20.

- The pathophysiology of NHL is governed by numerous environmental and genetic events culminating with a monoclonal population of malignant lymphocytes.

- B cells represent the cells of origin in excess of 90% of cases of NHL.

- Characterization of the **morphology** of the lymphocytes, the reactivity of the other cells in the lymph node, and the lymph node architecture is essential in obtaining a diagnosis and predicting disease course.

Clinical grae and frequency of lymphomas in the REAL classification

Diagnosis	% of all cases
Indolent lymphomas	
Follicular lymphoma	22
Marginal zone B-cell, mucosa-associated lymphoid tissue	8
Chronic lymphocytic leukaemia/small lymphocytic lymphoma	7
Marginal zone B-cell nodal	2
Lymphoplasmacytic lymphoma	1
Aggressive lymphoma	
Diffuse large B-cell lymphoma	31
Mature (peripheral) T-cell lymphomas	8
Mantle cell lymphoma	7
Mediastinal large B-cell lymphoma	2
Anaplastic large cell lymphoma	2
Very aggressive lymphomas	
Burkitt's lymphoma	2
Precursor T-lymphoblastic	2
Other lymphomas	7

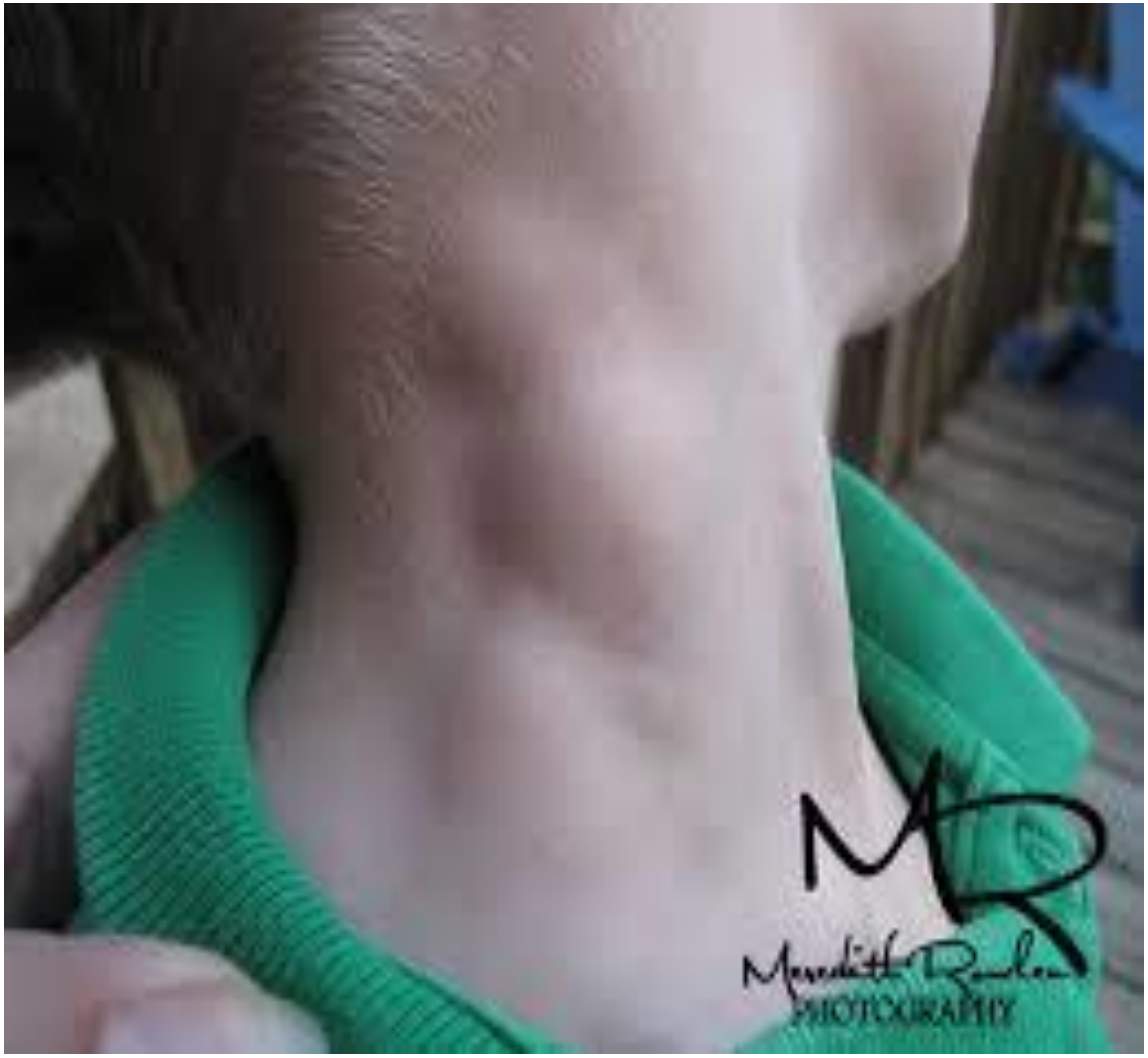
Clinical Presentation and Diagnosis:

Symptoms:

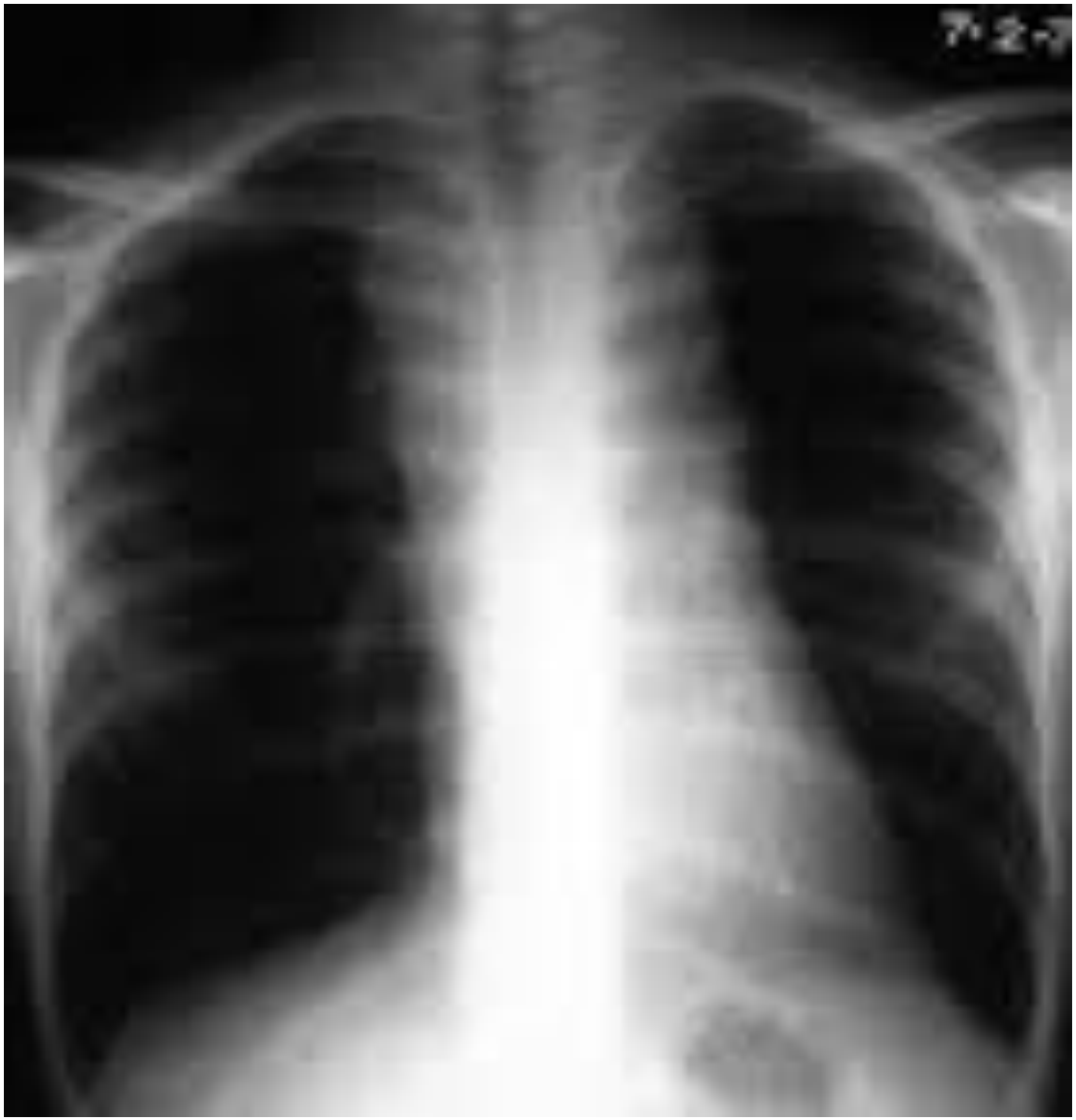
- Lymphadenopathy, generally in the cervical, axillary, supraclavicular, or inguinal lymph nodes
- Splenomegaly
- Shortness of breath, dry cough, chest pressure (patients with mediastinal mass).
- Gastrointestinal complications (e.g., nausea, vomiting, early satiety, constipation, and diarrhea).
- Back, chest, or abdominal pain.

Signs:

- Fever
- Night sweats
- Weight loss greater than 10% within last 6 months (These three are known collectively as *B-symptoms.*)
- Pruritus


MR
PHOTOGRAPHY

Imaging in Thoracic Non-Hodgkin Lymphoma



Laboratory Tests:

- LDH
- ESR
- Serum chemistries
- CBC with differential

Other Diagnostic Tests:

- Physical examination with careful attention to lymph node inspection
- Imaging: Chest x-ray, chest CT scan, abdominal/pelvic CT scan; PET scan may be used to confirm presence of active disease after treatment.
- Bone marrow biopsy
- Biopsy of suspected lymph node(s)—either open lymph node biopsy or core biopsy preferred over fine-needle aspiration.
- Hematopathology evaluation of biopsy specimen— morphologic inspection, immunohistochemistry for cell-surface antigens to characterize lymphoma cells.

Classification system for Hodgkin's lymphoma

Clinical stage	Defining features
I	Involvement of a single lymph node region or lymphoid structure
II	Involvement of two or more lymph node regions on the same side of the diaphragm
III	Involvement of lymph node regions or structures on both sides of the diaphragm: III_1 – with or without involvement of splenic, hilar, coeliac or portal nodes III_2 – with involvement of para-aortic, iliac or mesenteric nodes
IV	Involvement of extranodal site(s) beyond that designated E
Modifying characteristics	A: no symptoms B: fever, drenching sweats, weight loss X: bulky disease >one-third width of the mediastinum >10 cm maximal dimension of nodal mass E: involvement of a single extranodal site, contiguous or proximal to known nodal site CS: clinical stage PS: pathological stage

Disease staging for Hodgkin's lymphoma

Early stage

European Organisation for Research and Treatment of Cancer (EORTC) risk factors in localised disease

A. Favourable (patients must have all features)

1. Clinical stage 1 or 2
2. Maximum of three nodal areas involved
3. Age less than 50 years of age
4. ESR< 50 mm/h
5. Mediastinal/thoracic mass ratio < 0.33 at D5/6

B. Unfavourable

1. Clinical stage 2 with 4 or more nodal areas involved
2. Age >50 years of age
3. ESR >50 mm/h without B symptoms or >30 mm/h with B symptoms (fever, night sweats, weight loss)
4. Mediastinal/thoracic ratio >0.33 at D5/6[a]

Advanced stage

Hasenclever score

1. Age >45 years of age
2. Male gender
3. Serum albumin <40 g/L
4. Hb <10.5 g/dL
5. Stage 4 disease
6. Leucocytosis, that is, WCC >15 × 10^9 L^{-1}
7. Lymphopenia, that is, <0.6 × 10^9 L^{-1} or <8% of total WCC

TREATMENT OF HODGKIN'S LYMPHOMA:

- The number of involved sites, disease involvement on one or both sides of the diaphragm, localized or disseminated extranodal disease, and B-symptoms are factors in assignment of stage.

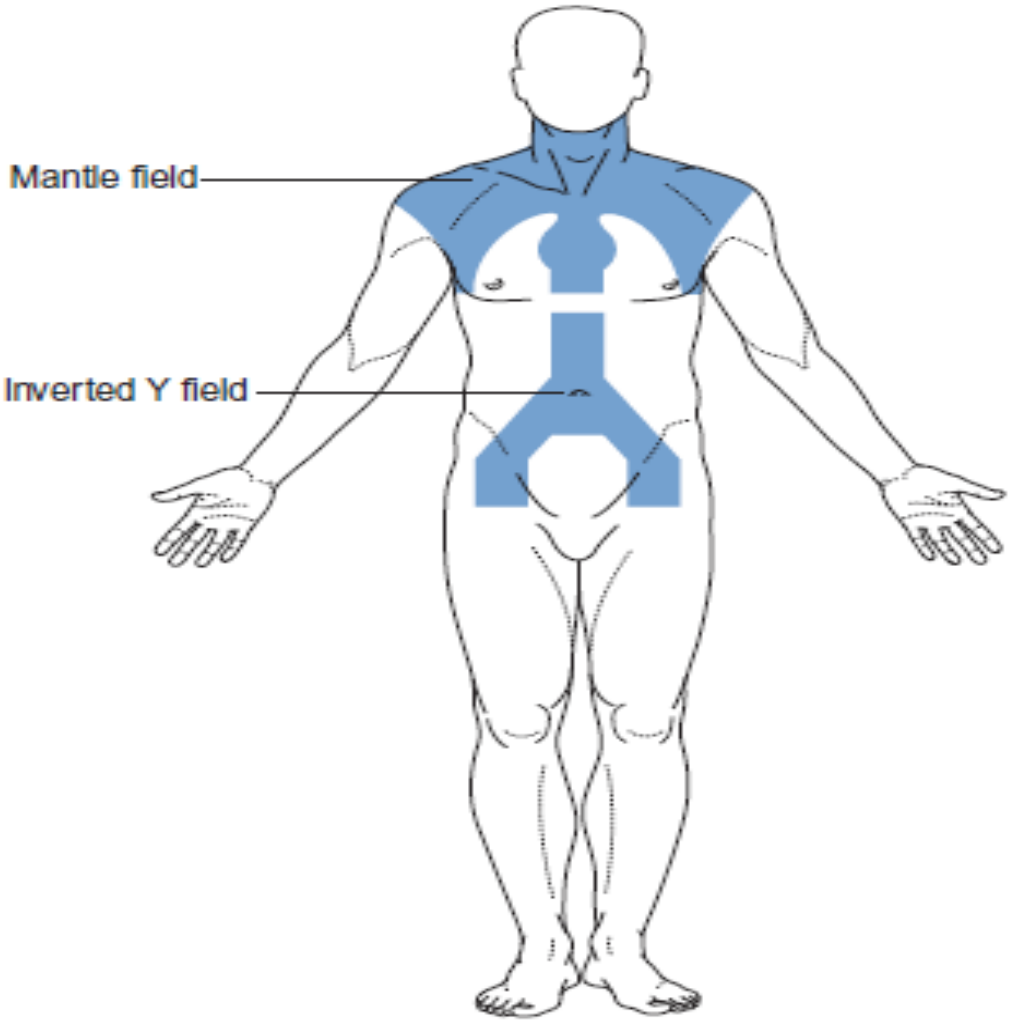
- The principal goal in treating HL is to cure the patient of the primary malignancy.

- HL is a disease sensitive to both radiation and chemotherapy, resulting in an 80% rate of cure with modern therapy.

Other goals during treatment include:

- Complete resolution of symptoms of disease
- Minimization of acute treatment-related toxicity
- Minimization of long-term treatment-related toxicity

The mantle and inverted Y fields



Nonpharmacologic Therapy:

1- Subtotal lymphoid irradiation.

2- Prophylaxis with antiemetics such as dexamethasone or prochlorperazine.

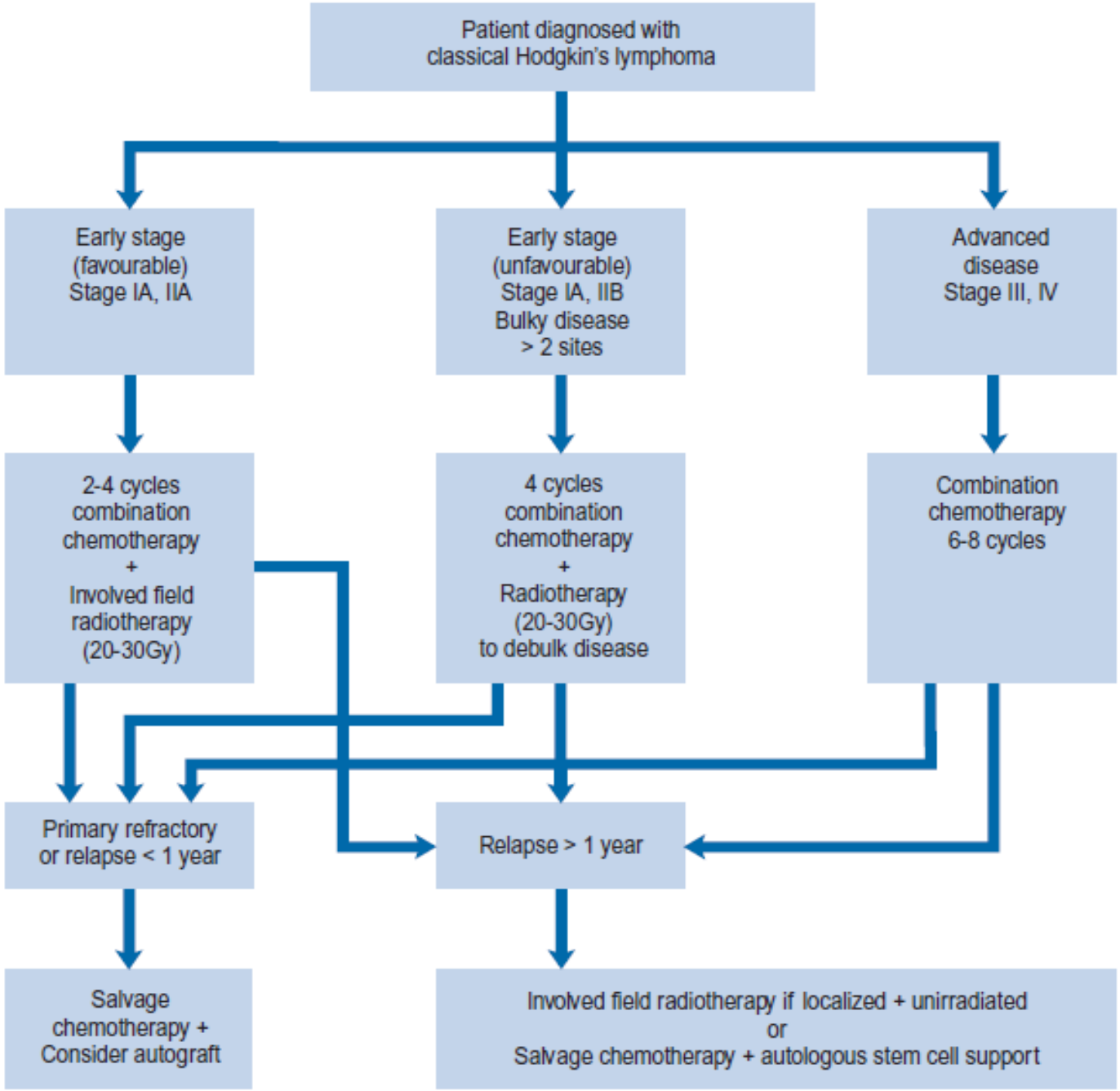
Pharmacologic Therapy :

- At present, combined-modality therapy is considered to be a standard of care for stage I/II HL.

- Two and four cycles of a standard regimen for HL, such as **ABVD** (doxorubicin, bleomycin, vinblastine, and dacarbazine) with involved-field radiation.

- Treatment of advanced-stage (stage III–IV) HL is focused on the use of multiagent chemotherapy for six to eight total cycles.

- Patients who are ***not candidates*** for high dose chemotherapy with autologous SCT may receive multiagent salvage chemotherapy, such as etoposide methylprednisolone cytarabine cisplatin (ESHAP) or Dexamethasine Cytarabine Cisplatin (DHAP).


Patient diagnosed with classical Hodgkin's lymphoma
Early stage (favourable) Stage IA, IIA
Early stage (unfavourable) Stage IA, IIB Bulky disease > 2 sites
Advanced disease Stage III, IV
2-4 cycles combination chemotherapy + Involved field radiotherapy (20-30Gy)
4 cycles combination chemotherapy + Radiotherapy (20-30Gy) to debulk disease
Combination chemotherapy 6-8 cycles
Primary refractory or relapse < 1 year
Relapse > 1 year
Salvage chemotherapy + Consider autograft
Involved field radiotherapy if localized + unirradiated or Salvage chemotherapy + autologous stem cell support

TREATMENT OF NON-HODGKIN'S LYMPHOMA:

- As with HL, the number of involved sites, disease involvement on one or both sides of the diaphragm, localized or disseminated extranodal disease, and ***B-symptoms*** are factors in staging assignment.

- Treatment goals for NHL depend on the presence of ***follicular low-grade*** versus ***diffuse aggressive*** disease.

Nonpharmacologic Therapy:

- Radiation therapy has a limited role in NHL relative to HL.

- Overall survival favored the CHOP/radiation arm for 5 years where combined modality therapy is first-line treatment for early-stage NHL.

Pharmacologic Therapy:

- Chemotherapy such as single-agent oral cyclophosphamide or fludarabine is often offered initially for low-grade lymphomas.
- In patients in whom a more rapid response is desired, **multiagent** chemotherapy such as cyclophosphamide vincristine prednisone (CVP) or cyclophosphamide doxorubicin vincristine prednisone (CHOP) may be used.
- NHL of B-cell origin expresses CD20 in greater than 90% of cases.
- Novel strategies for treatment of low-grade lymphomas include the combination of monoclonal antibodies directed against CD20 with a *radioactive* moiety attached.

- **The mainstay** of therapy for **diffuse**, **aggressive NHL** has been the administration of anthracycline-based combination chemotherapy.

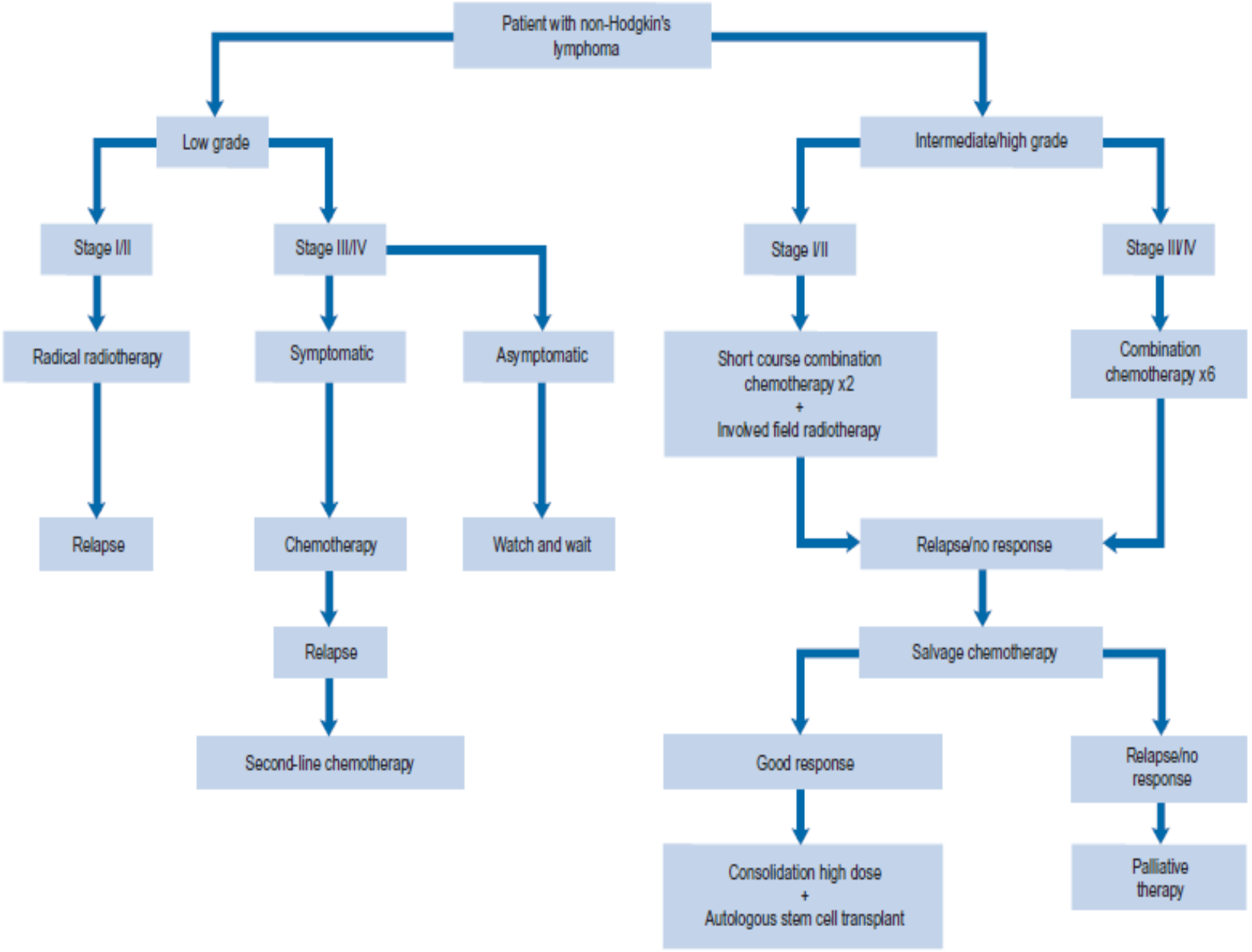
- *Intrathecal* therapy with **methotrexate** is indicated with documented CNS infiltration of tumor or involvement of the sinuses.

- Regimens such as **hyper-CVAD**, which alternate cycles of hyperfractionated *cyclophosphamide*, *doxorubicin*, *vincristine*, and dexamethasone with high-dose cytarabine and methotrexate, often are substituted for CHOP.

- The best-studied indication for SCT is for patients with intermediate- or high-grade disease that fails to respond to conventional therapy.

Chemotherapy in NHL

Drug	Dose and route	Day of administration
R-CHOP (21-day cycle)		
Cyclophosphamide	750 mg/m² i.v.	Day 1
Doxorubicin (hydroxydaunorubicin)	50 mg/m² i.v.	Day 1
Vincristine (Oncovin)	1.4 mg/m² (max 2 mg) i.v.	Day 1
Prednisolone	100 mg orally	Days 1–5
Rituximab	375 mg/m² i.v.	Day 1
R-CVP (21-day cycle)		
Cyclophosphamide	750 mg/m² i.v.	Day 1
Vincristine (Oncovin)	1.4 mg/m² (max 2 mg) i.v.	Day 1
Prednisolone	100 mg orally	Days 1–5
Rituximab	375 mg/m² i.v.	Day 1
FC (28-day cycle)		
Fludarabine	40 mg/m² orally	Days 1–3
Cyclophosphamide	250 mg/m² daily orally	Days 1–3
CHOP (21-day cycle)		
Cyclophosphamide	750 mg/m² i.v.	Day 1
Doxorubicin (hydroxydaunorubicin)	50 mg/m² i.v.	Day 1
Vincristine (Oncovin)	1.4 mg/m² (max 2 mg) i.v.	Day 1
Prednisolone	100 mg orally	Days 1–5


Patient with non-Hodgkin's lymphoma
Low grade
Intermediate/high grade
Stage I/II
Stage III/IV
Stage I/II
Stage III/IV
Radical radiotherapy
Symptomatic
Asymptomatic
Short course combination chemotherapy x2 + Involved field radiotherapy
Combination chemotherapy x6
Relapse
Chemotherapy
Watch and wait
Relapse/no response
Relapse
Salvage chemotherapy
Second-line chemotherapy
Good response
Relapse/no response
Consolidation high dose + Autologous stem cell transplant
Palliative therapy