Childhood Hodgkin's Lymphoma

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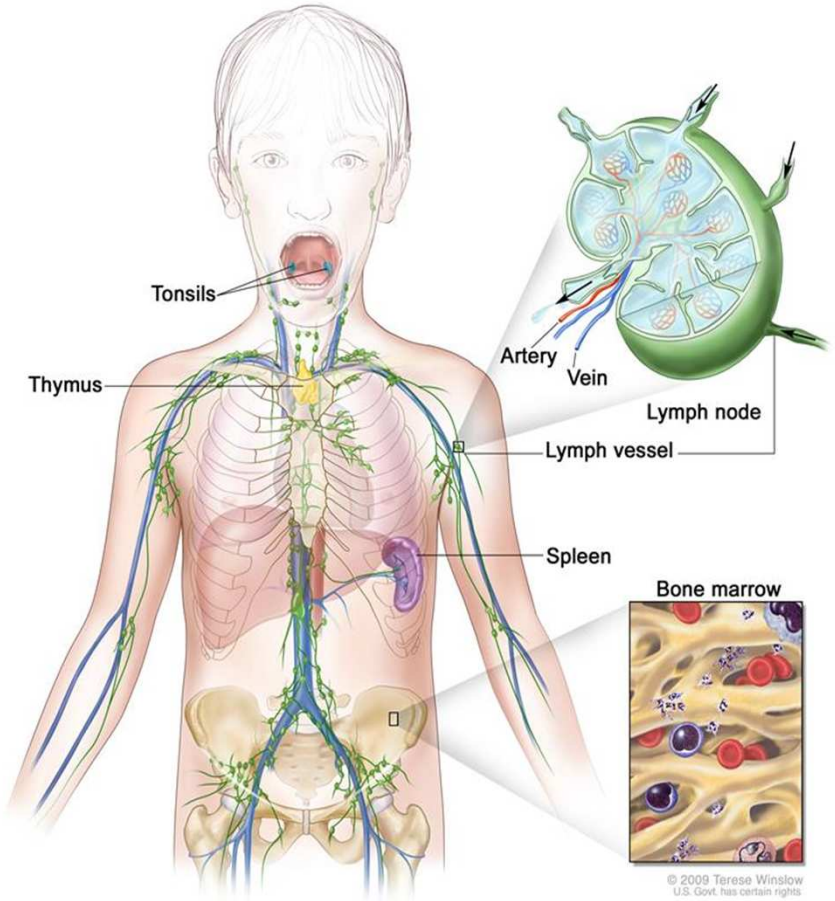
Background

- Highly curable malignancy
- First cancer to be cured with RT alone or with combination chemotherapy
- Therapeutic success has come with long term side effects
- 30-year survivor of HL is more likely to die of therapy-related complications
- New paradigm - risk-adapted, response-based approach to treatment

Lymphatic System



- Lymph
- Lymph vessels
- Lymph nodes
- Spleen
- Thymus
- Tonsils
- Bone marrow

Pathophysiology

- Malignancy of the germinal-center B cells affecting reticuloendothelial and lymphatic systems.
- Reeds Sternberg cell carry clonal immunoglobulin gene rearrangements
- Risk Factors
  - Environmental – Epstein-Barr virus (EBV) infection
  - Genetic – Identical twins have a higher risk than other first degree relatives
  - Immunologic – acquired or congenital immunodeficiency disorders

Epidemiology

- Bimodal distribution - incidence rate increases among teenagers, peaks at about age 20 and another peak occurs in approx 50–60 years
- Uncommon before age 5 years
- Male-to-female ratio of 3:1 in children younger than 10 years. In older children and adults, the male-to-female ratio is about 1:1.

Prognosis

- Overall survival – Stage I and II 90% and
  Stage III and IV 70%
- CHIPS score has 4 factors - predictive of worse event-free survival:
  - ***stage IV disease***
  - ***large mediastinal adenopathy***
  - ***albumin level of less than 3.5 g/dL and***
  - ***fever***

History

- Persistent painless adenopathy, usually cervical and/or mediastinal, unresponsive to antibiotic therapy
- Respiratory symptoms: breathlessness, chest pain or cough - mediastinal adenopathy
- B symptoms
  - unexplained fe**v**er with temperatures above 38°C for 3 consecutive days
  - unexplained **w**eight loss of 10% or more in the previous 6 months and
  - drenching night s**w**eats
- pruritus, urticaria, and fatigue – cytokines
- Immune mediated para neoplastic syndromes

Physical Examination

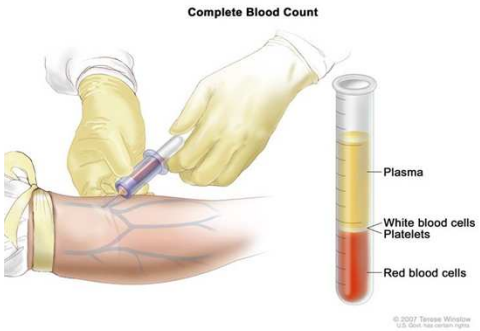
- Evaluation of all lymph node stations, Waldeyer or tonsillar tissues (firm, nontender lymphadenopathy)

  Cervical in 70-80% and axillary in 25%

  Rest supraclavicular, inguinal rarely epitrochlear or popliteal
- Superior vena cava obstruction, respiratory symptoms, or both.
- Splenomegaly, hepatomegaly, or both may be present. Disease extension is predictable, is contigious, and can affect other organs and systems.

Differential Diagnosis

- Acute Lymphoblastic Leukemia
- LCH – Langerhans cell histiocytosis
- ALPS – autoimmune Lymphoproliferative
- Non-Hodgkin Lymphoma
- Brucellosis
- Catscratch Disease
- Cytomegalovirus Infection
- Histoplasmosis
- Lymph Node Disorders
- Mononucleosis and Epstein-Barr Virus Infection
- Toxoplasmosis
- Tuberculosis
- Pediatric Histoplasmosis

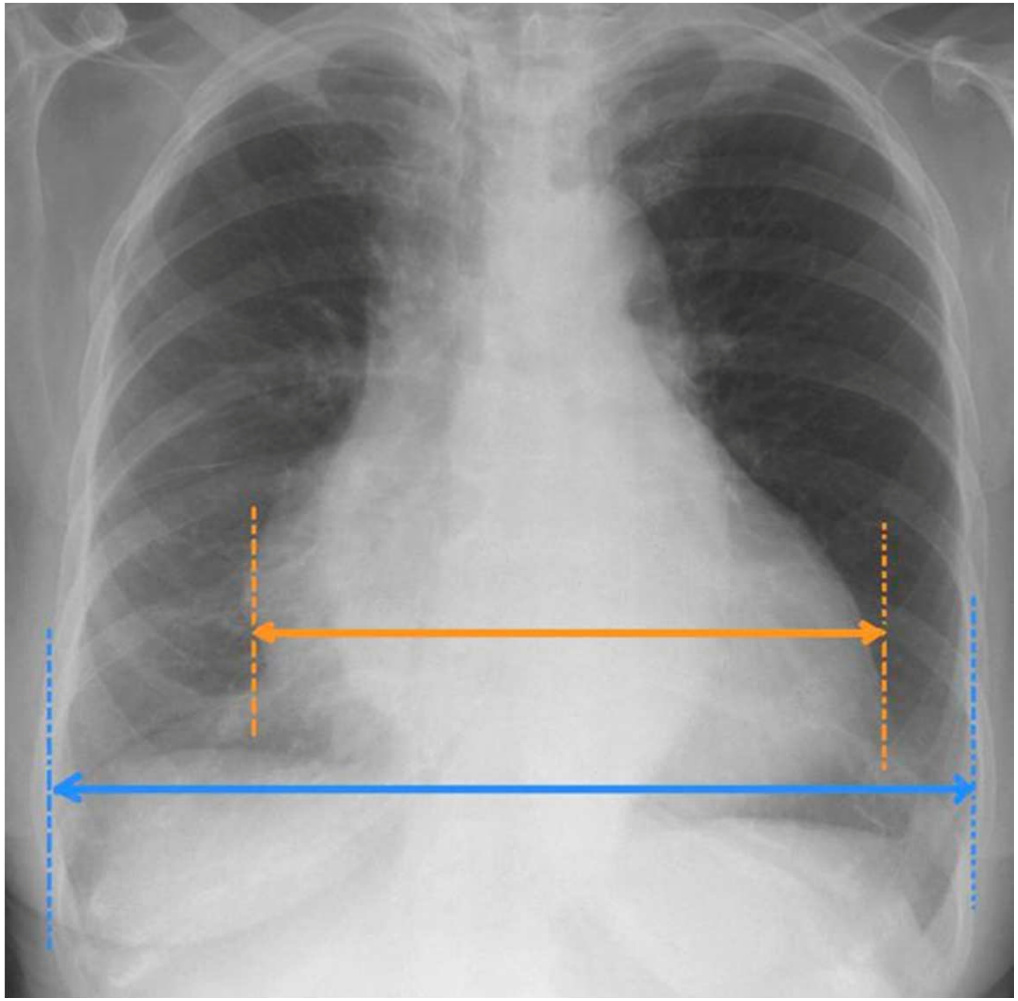


Blood investigations

- Hemolytic anemia, anemia of chronic disease, or anemia secondary to involvement of the bone marrow
- Leukocytosis, lymphopenia, eosinophilia, monocytosis
- Thrombocytopenia due to marrow infiltration or idiopathic thrombocytopenia purpura
- Elevated levels of acute-phase reactants - ESR, CRP, serum Copper and Ferritin levels.
- Elevated levels of serum electrolytes; lactate dehydrogenase (LDH) levels reflects bulk of disease;
- Raised alkaline phosphatase - bony metastasis.
- Urinalysis may reveal proteinuria. Nephrotic syndrome may be associated with Hodgkin lymphoma.

Imaging

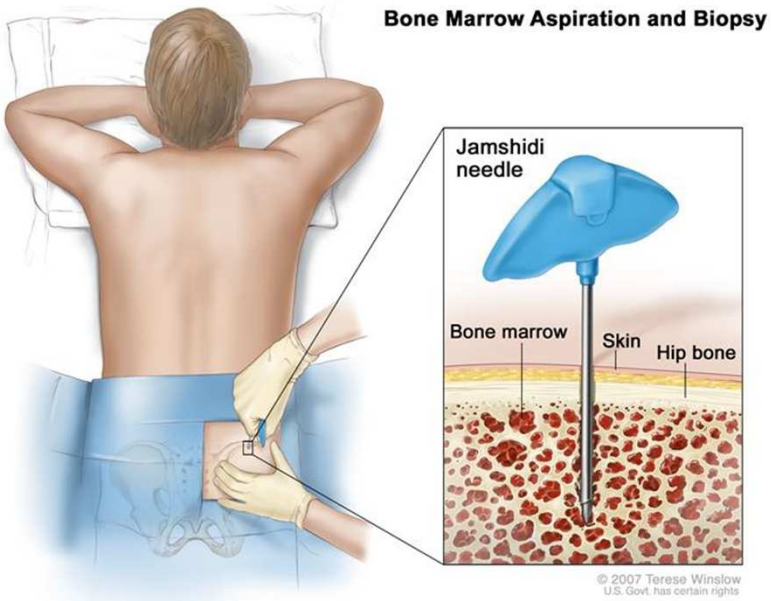
- Chest x-ray - Mediastinal mass with a thoracic ratio of ≥33% is of prognostic importance.



Imaging

- CT or MRI of the Neck, Chest, Abdomen and Pelvis to assess sites of disease (nodal and extranodal), liver and spleen involvement.
- PET CT
  - to identify the extent of disease at diagnosis
  - positive PET after 2 cycles may be predictive of poor outcome
  - for follow-up

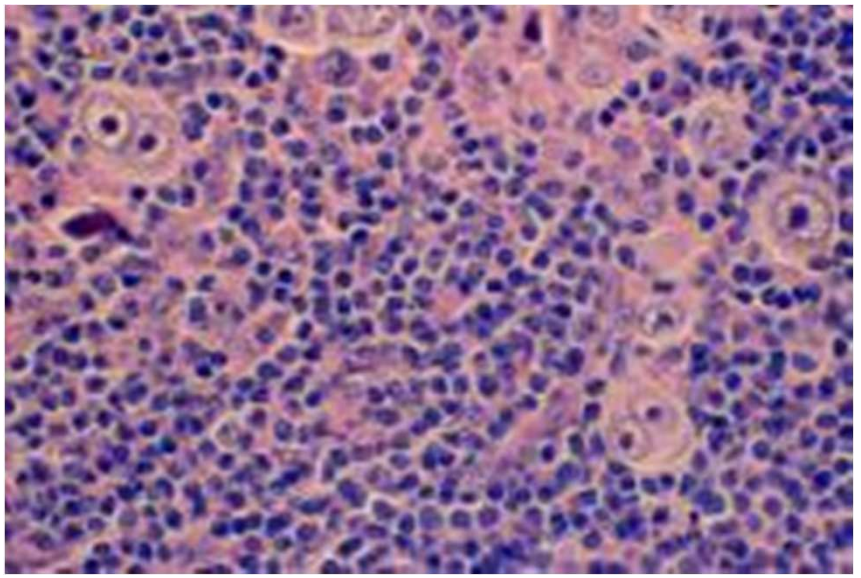
Biopsy



- Biopsy - largest abnormal lymph node should be excised intact
- Bilateral bone marrow biopsy is restricted to advanced disease and or B symptoms
- Staging laparotomy no longer advocated

Histopathology

- Malignant cell represents only a small proportion of the cells
- Majority of cells are small lymphocytes, histiocytes, neutrophils, plasma cells, and fibroblasts – subtypes
- The RSCs - binucleated or multinucleated giant cells "owl's eye" appearance.



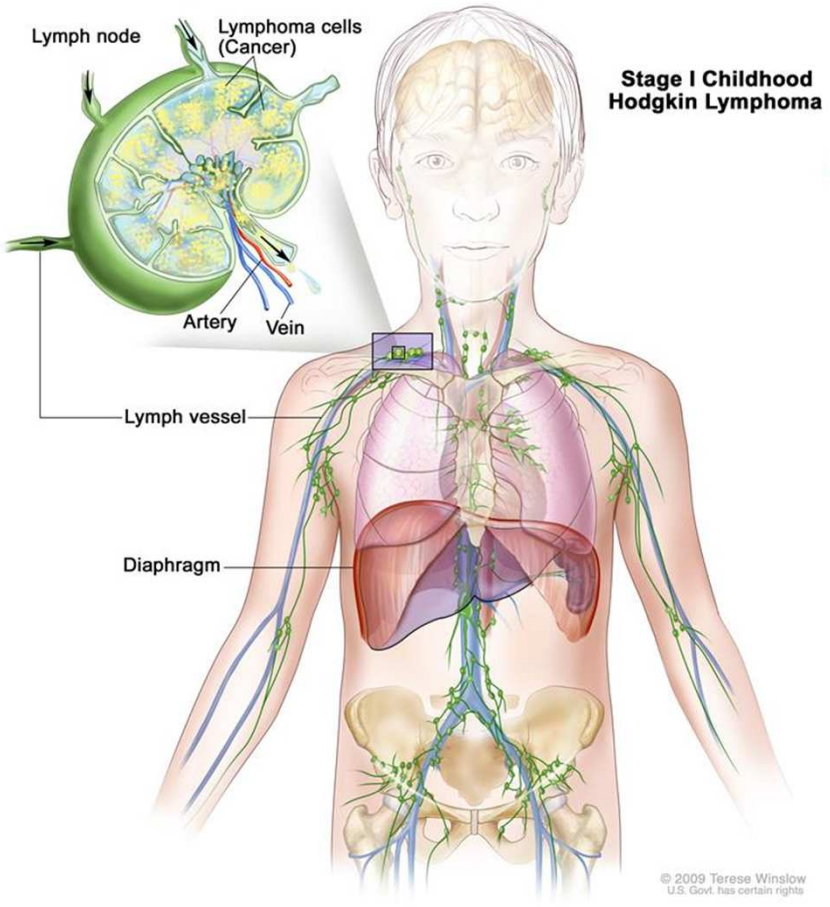
Immunohistochemistry

- **Classic Hodgkin's Lymphoma – T cell**
  - Typical RSC characterized by CD30 positivity
  - Absence of CD 45 and J chains
  - Frequent expression of CD15

1. Nodular sclerosis – fibrous bands
2. Mixed cellularity – Interstitial fibrosis, background of inflammatory cells
3. Lymphoctye rich – RSC rare, cellular background
4. Lymphocyte depletion – sarcomatous variant, hypocellular, fibrosis and necrosis

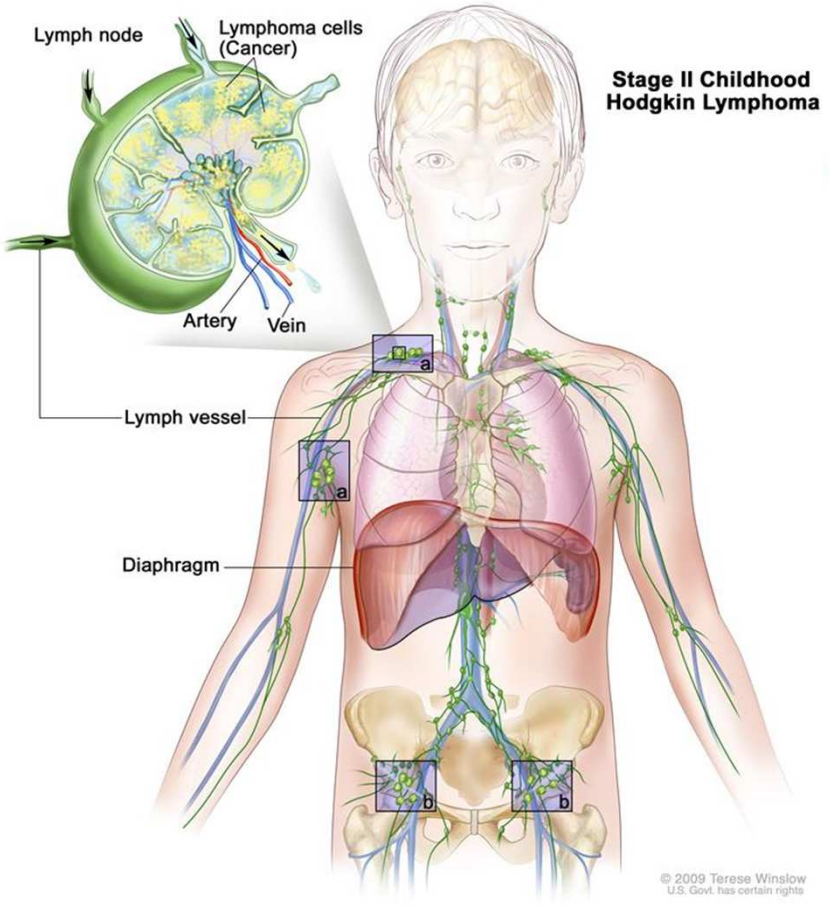
- **Nodular Lymphocy predominant – B cell**
  - A variant of the RSC called "popcorn cell"
  - formally known as the lymphocyte and histiocytic (L&H) cell
  - L&H cells are small with a very lobulated nucleolus and small nucleoli.
  - characterized by CD20, CD 45 positivity and B cell markers.
  - J-chain rearrangements and
  - CD30 and CD15 negativity.

Stage I



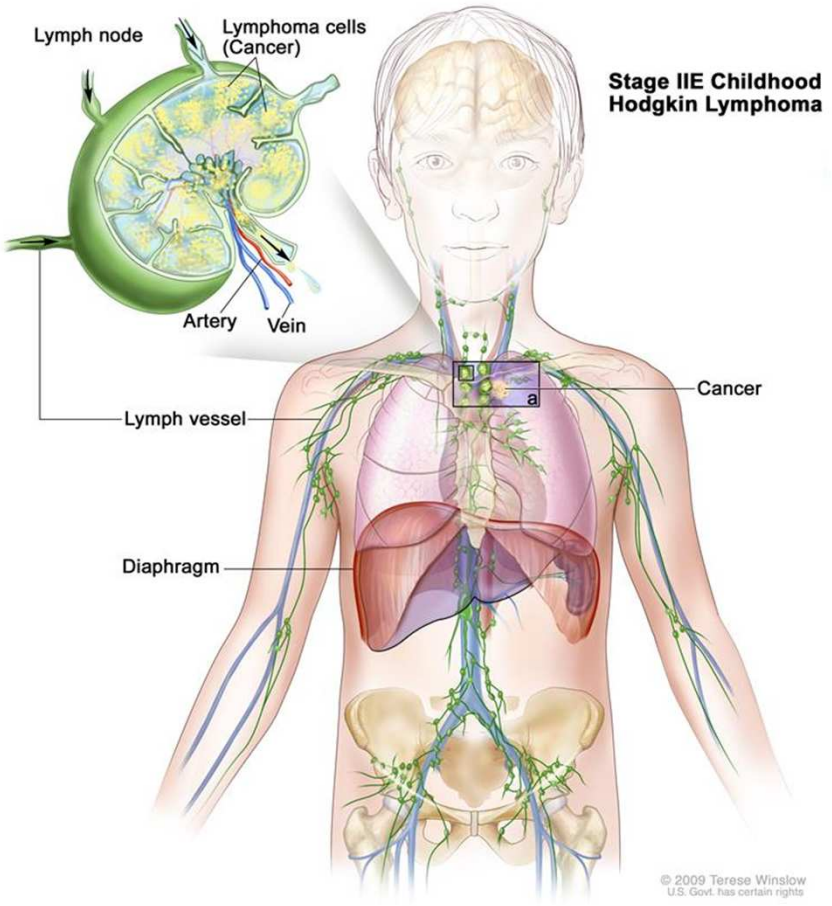
- One or more lymph nodes in one lymph node group.
- Waldeyer's ring.
- Thymus
- Spleen
- Stage IE: Cancer is found outside the lymph system in one organ or area.

Stage II



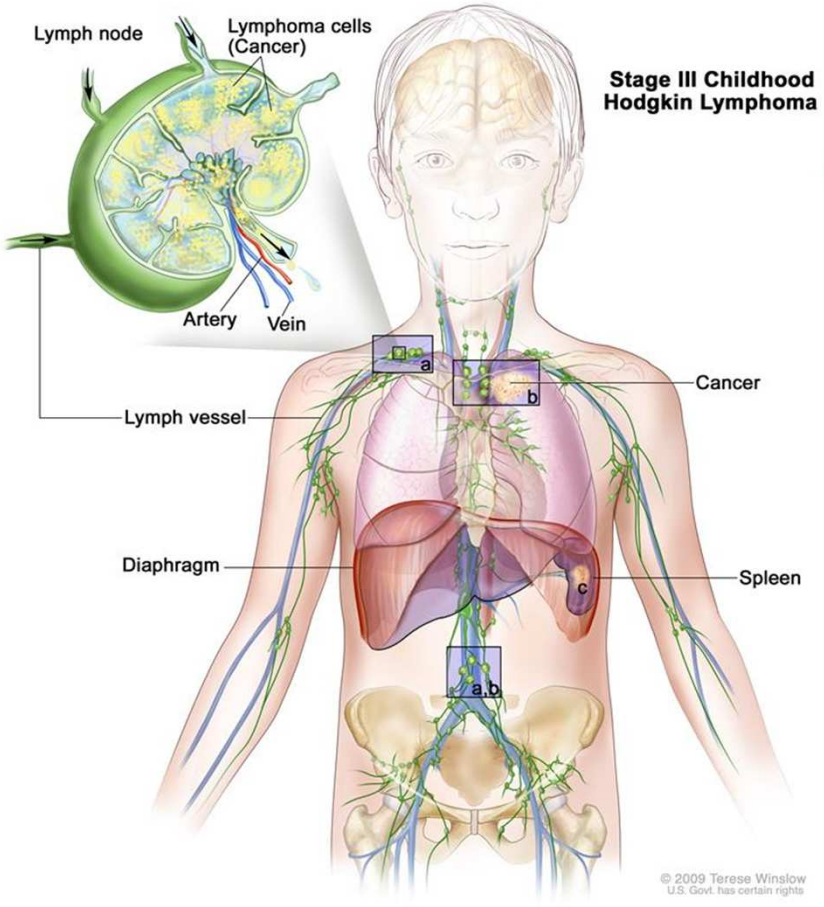
Cancer is found in two or more lymph node groups either above or below the diaphragm

Stage II E



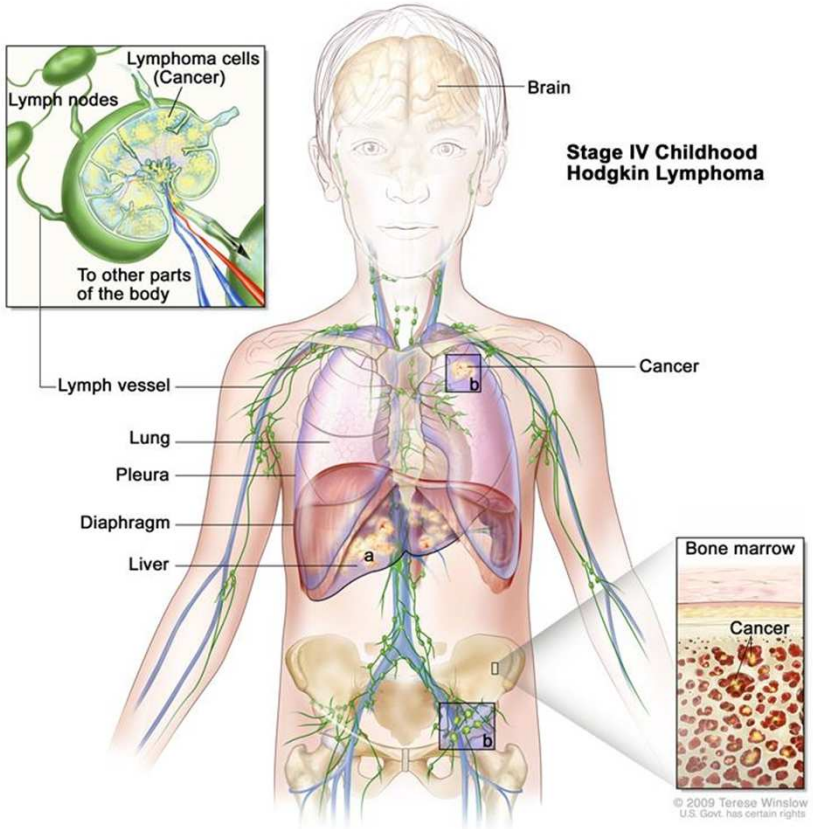
Cancer is found in one or more lymph node groups either above or below the diaphragm and outside the lymph nodes in a nearby organ or area.

Stage III



- Stage III: Cancer is found in lymph node groups above and below the diaphragm
- Stage IIIE: Cancer is found in lymph node groups above and below the diaphragm and outside the lymph nodes in a nearby organ or area.
- Stage IIIS: Cancer is found in lymph node groups above and below the diaphragm, and in the spleen.
- Stage IIIE,S: Cancer is found in lymph node groups above and below the diaphragm, outside the lymph nodes in a nearby organ or area, and in the spleen.

Stage IV



- Diffuse or disseminated involvement of one or more extralymphatic organs (liver, bone marrow, lung) or tissues with or without associated lymph node involvement

B symptoms & Bulky disease

- B Symptoms
  - Drenching night s**w**eats
  - Unexplained fe**v**ers with temperature more than 38°C for 3 consecutive days
  - More than 10% loss of body **w**eight in the past 6 months
- Bulky disease - 10cm or larger mass (=6-cm mass for many paediatric trials) or large mediastinal adenopathy (mass greater than one third maximum thoracic diameter by chest radiography) is an adverse outcome factor.

Risk Groups

Risk Group	Children's Oncology Group	German Multicenter Studies	Stanford/Dana Farber/St. Jude
Low Risk	I A no bulk or E, II A no bulk or E	I A /**B** II A	I A/II A no bulk
Intermediate Risk	I A with bulk or E, I B II A with bulk or E II B III A IV A E	II B III A – E III B	I A bulk I B II A with bulk II B III IV
High Risk	III B IV B	II B – E III A / B - E **IV A** / B	

Significance of Risk Grouping

- Risk assignment allows intensification of treatment according to the risk for relapse
  - low stages required less therapy than those with advanced stages.
- Risk assignment varies among the paediatric cancer cooperative groups, and, therefore, assignment of treatment varies.
- The risk stratification in one cooperative should not be mixed with therapy regimen of another cooperative group.

Goals of Therapy

- Reducing late effects of therapy while maintaining excellent cure rates
- with risk-adapted chemotherapy alone or response-adjusted combined-modality regimens.

Classical Hodgkin Disease Rx Protocol

RX Group-1:
Stage IA/B and IIA

OEPA x 2 or
ABVD x 2

Reassess PET

Negative → Stop Rx

Positive → IFRT

Rx Group-2:
Stage IIB, IIE, IIIA ,IE

OEPA x 2 or
ABVD x2

Reassess PET

Negative → COPP x 2

Positive → COPP x 2 → IFRT

Rx Group-3:
Stage IIIB, IIIE, IIB&E, IV A&B

OEPA x 2 or
ABVD x2

Reassess PET

Negative → COPPx4

Positive → COPP x4 → IFRT

Paediatric Chemotherapy Regimens

Europeans Regimens:

- OPPA: Vincristine (Oncovin), procarbazine, prednisone, and doxorubicin (Adriamycin)
- OEPA: Vincristine (Oncovin), etoposide, prednisone, and doxorubicin (Adriamycin)
- COPP: Cyclophosphamide, vincristine, procarbazine, and prednisone
- COPDAC: Cyclophosphamide, vincristine, prednisone and dacarbazine
- VBVP: Vinblastine, bleomycin, etoposide, and prednisone

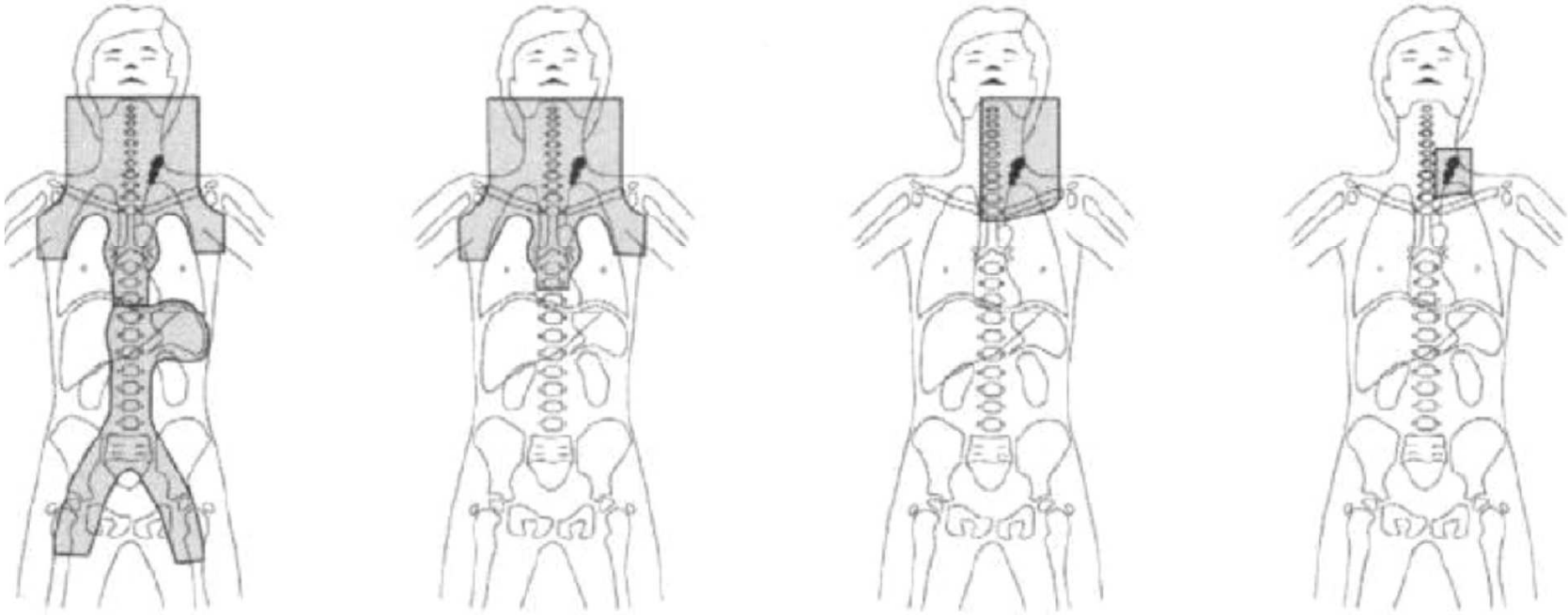
American Regimen (Children's Oncology Group)

- ABVE: Doxorubicin, bleomycin, vincristine, and etoposide
- ABVE-PC: Doxorubicin (Adriamycin), bleomycin, vincristine, etoposide, prednisone, and cyclophosphamide
- BEACOPPesc: Bleomycin, etoposide, doxorubicin (Adriamycin), cyclophosphamide, vincristine, procarbazine, and prednisone
- COPP/ABV: Cyclophosphamide, vincristine, procarbazine, prednisone, doxorubicin (Adriamycin), bleomycin, and vinblastine
- VAMP/COP: Vincristine, doxorubicin (Adriamycin), methotrexate, and prednisone alternating with cyclophosphamide, vincristine, and prednisone
- Stanford V: Doxorubicin (Adriamycin), vinblastine, mechlorethamine, vincristine, bleomycin, etoposide, and prednisone

Assessment of Treatment Response

Response	Definition	Nodal Masses
CR	Disappearance of all evidence of disease	(a) FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative (b) Variably FDG-avid or PET negative; regression to normal size on CT
PR	Regression of measuable disease and no new sites	≥ 50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes (a) FDG-avid or PET positive prior to therapy; one or more PET positive at previously involved site (b) Variably FDG-avid or PET negative; regression on CT
SD	Failure to attain CR/PR or PD	(a) FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease and no new sites on CT or PET (b) Variably FDG-avid or PET negative; no change in size of previous lesions on CT
Relapsed disease or PD	Any new lesion or increase by ≥ 50% of previously involved sites from nadir	Appearance of a new lesion(s) > 1.5 cm in any axis, ≥ 50% increase in SPD of more than one node, or ≥ 50% increase in longest diameter of a previously identifed node > 1 cm in short axis Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy

RT Techniques



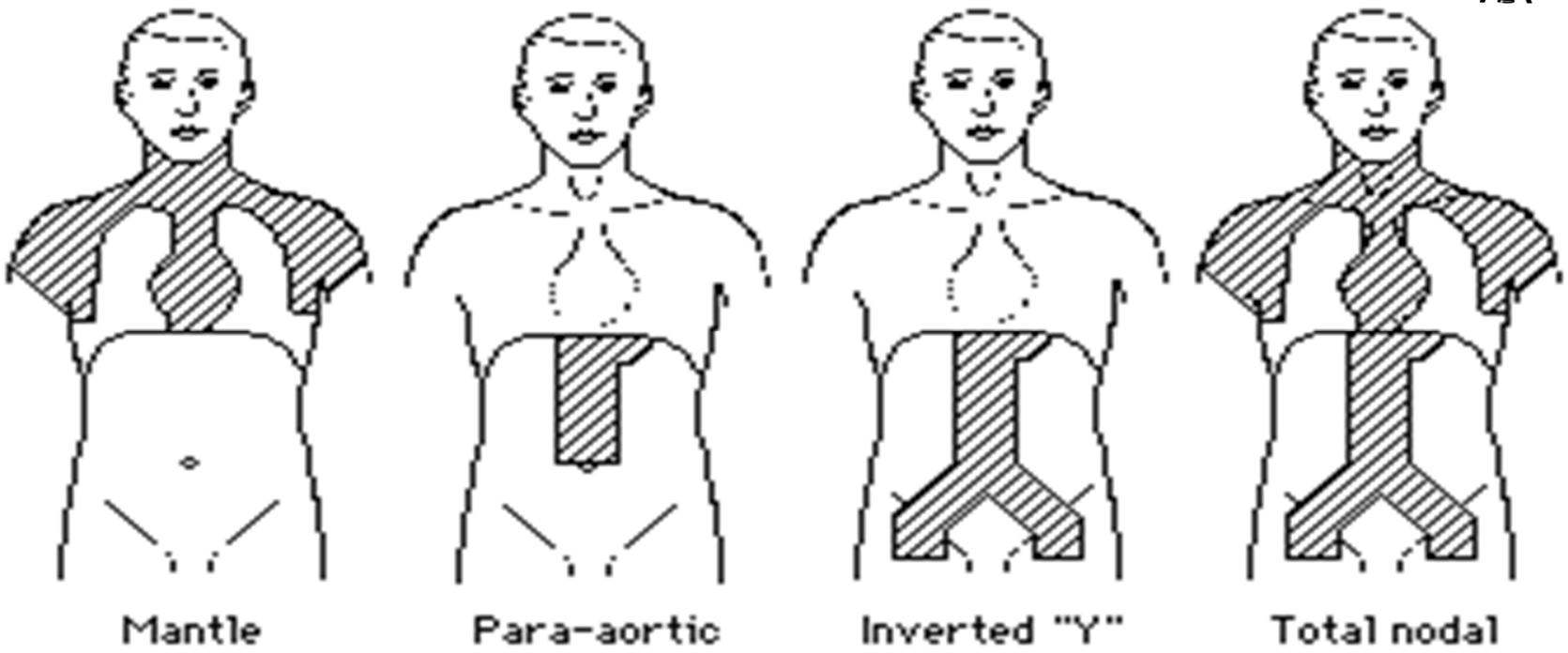
TOTAL NODAL ⟶ EXTENDED FIELD ⟶ INVOLVED FIELD ⟶ INVOLVED SITE

INVOLVED NODAL

Extended field RT Indications

- Role of larger field RT is now limited essentially to salvage treatment in patients in whom chemotherapy is unsuccessful and who are unable to embark on more intensive salvage treatment schedules
- No data to support the use of extended fields that can cause toxicity and compromise the safety of subsequent therapy such as stem cell transplantation

Older RT Techniques



- TLI: Combination of Mantle and inverted Y fields
- STLI: Combination of Mantle and inverted Y fields EXCEPT pelvic fields

Modern Radiation Therapy for Hodgkin Lymphoma: Field and Dose Guidelines From the International Lymphoma Radiation Oncology Group

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Radiation Therapy as Primary Treatment

i. Early-stage lymphocyte-predominant Hodgkin lymphoma (LPHL)
ii. Selected cases of early-stage classic HL in patients who are not candidates for primary chemotherapy

Adjuvant Radiotherapy

i. Early-stage classic HL
   - After adequate systemic chemotherapy in all age groups
   - RT improves freedom from treatment failure even in patients with negative positron emission tomography (PET) scans and allows treatment with fewer chemotherapy cycles

ii. Advanced-stage disease
   - Localized RT may be used for residual lymphoma after full chemotherapy
   - RT may be an integral part of some regimens for advanced-stage disease

- To reduce complications, risk-adapted or response-based and low-dose

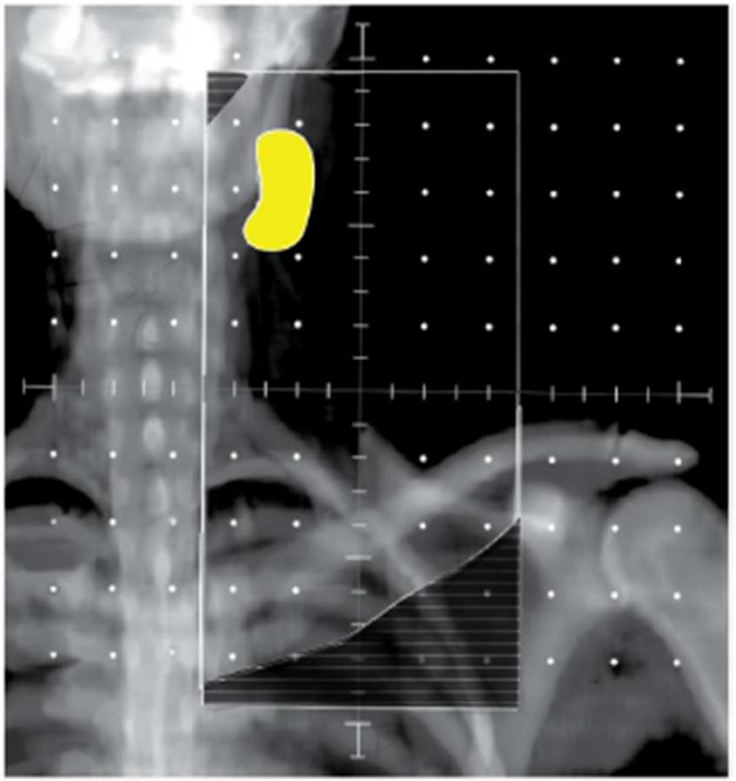
Involved Field Radiotherapy

- Treat a region not a single lymphnode
- Prechemotherapy length and post chemotherapy width (Mediastinum and paraaortic region)

CALGB GUIDELINES ANNALS OF ONCOLOGY 2006

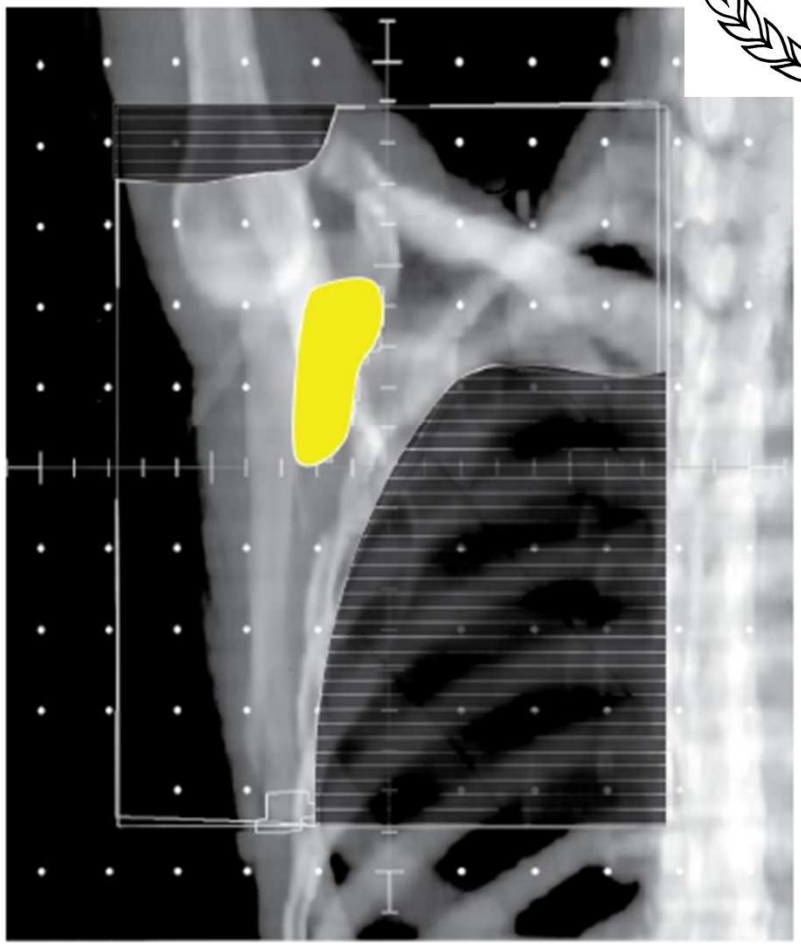
IFRT - Cervical Chain

- Unilateral or bilateral neck nodes including supraclavicular region extending from skull base to clavicle(s)
- Patient positioned supine with Aquaplast mask
- Oral cavity block placed if tumor coverage will not be compromised



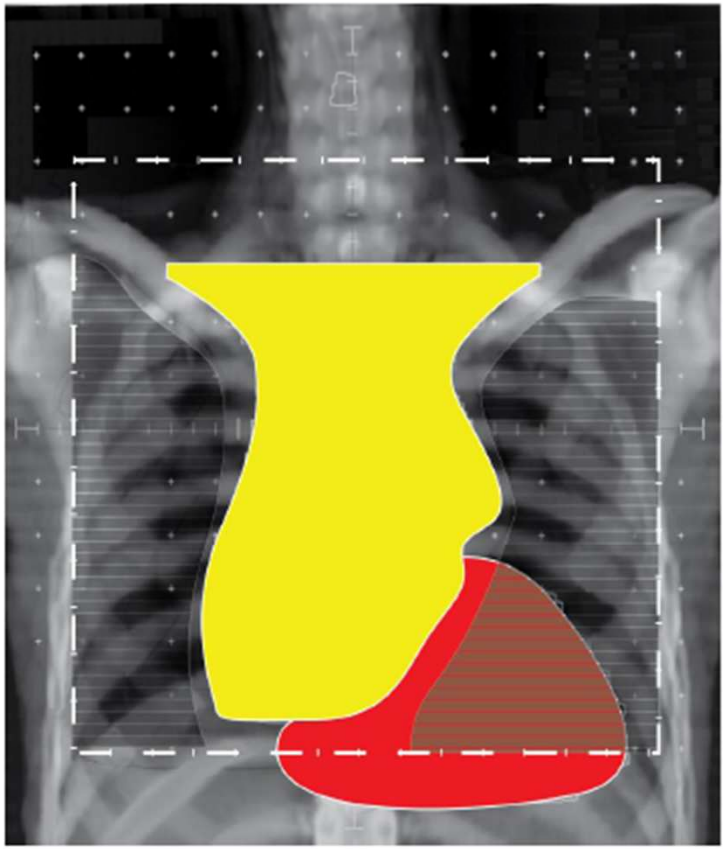
IFRT - Axillary Field

- Treatment of axillary, supraclavicular, and infraclavicular nodes
- Superior border – C5-C6 interspace
- Inferior border – Tip of scapula or 2 cm below most inferior node
- Medial border – Ipsilateral transverse process
- Lateral border – Flash axilla



IFRT - Mediastinum

- Mediastinal nodes, bilateral hila, and bilateral supraclavicular nodes
- Superior border – C5-C6
- Inferior border – 2 cm below pre-chemotherapy extent
- Lateral border – 1.5 cm on post-chemotherapy volume



Involved Nodal Radiotherapy

- Accurate pre-chemo imaging is requied
- The CTV encompasses the original location and extent of the disease (before any intervention)
- Normal structures such as lungs, kidneys, and muscles that were clearly uninvolved should be excluded from the CTV based on clinical judgment

EORTC GELA LYMPHOMA GROUP RADIATION ONCOLOGY 2006

Involved Nodal Radiotherapy

- The PTV is the CTV with a margin taking into account organ movement and set-up variations. In most situations, a 1 cm isotropic margin is considered adequate
- Better sparing of normal tissues (salivary glands, heart, coronary arteries, and breast in female patients) is expected with the use of INRT compared with conventional IFRT

IFRT VS INRT of Neck

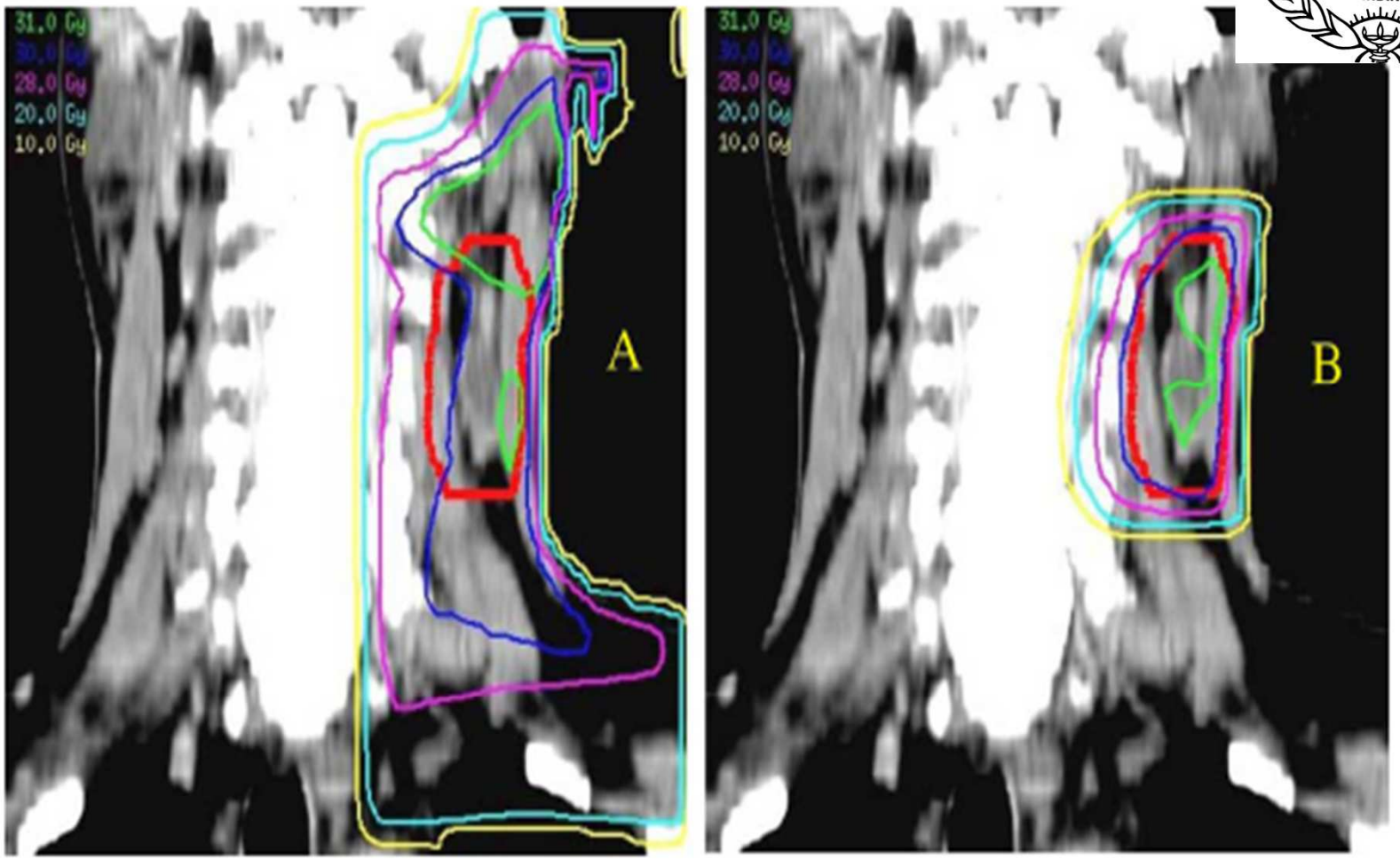


Fig. 7. Comparison between dose distributions using either IFRT (A) or INRT (B) for involved cervical lymph nodes.

IFRT VS INRT Mediastinum

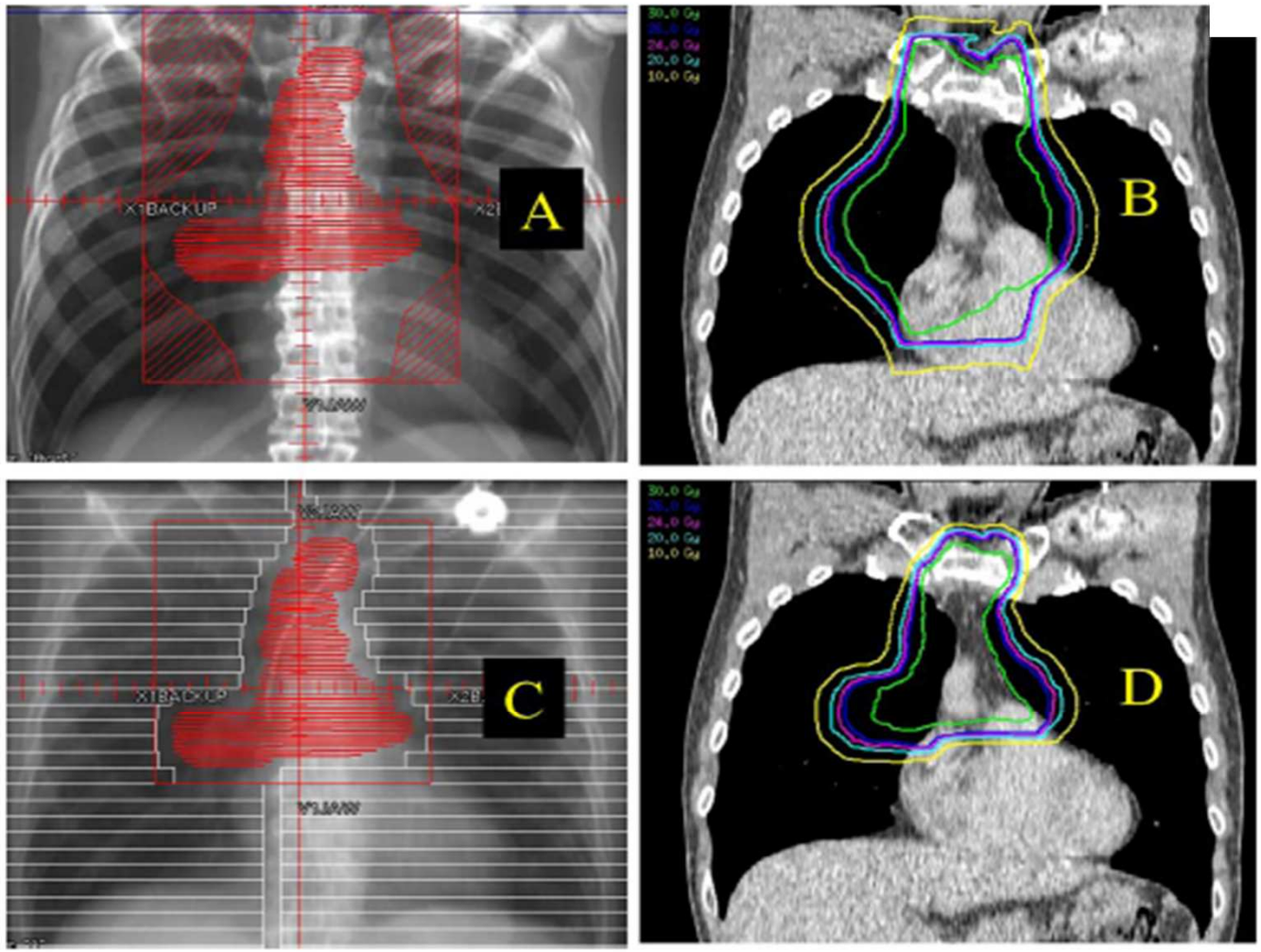


Fig. 8. Comparison between radiation field sizes and the volume of heart irradiation using either IFRT (A and B) or INRT (C and D) for a mediastinal tumor mass (PTV in red color).

Involved Site Radiotherapy

- The concept of ISRT was developed on the basis of the INRT concept

- ISRT accommodates cases in which optimal pre chemotherapy imaging is not available

- In ISRT, clinical judgment in conjunction with the best available imaging is used to contour a larger CTV that will accommodate the uncertainties in defining the pre chemotherapy GTV

Involved Site Radiotherapy

- To gather description of :
  - The pre chemotherapy physical examination of the patient
  - The location of scars and scar tissue on the post chemotherapy planning CT scan
  - The patient's and the family's recollections of the location of the presenting lymph node(s)

- The CTV should be contoured taking into account all of this information, making generous allowance for the many uncertainties in the process

INRT vs ISRT

- INRT mandates use of prechemotherapy planning PET CT imaging
- ISRT accomodates cases where ideal prechemotherapy imaging is not available
- Hence ISRT has generous margins for CTV expansions compared to INRT

Dose of Radiotherapy

- In early stage Hodgkins lymphoma, RT doses ranging from 20 to 30Gy is used
- If RT is used as single modality doses upto 36Gy is used.
- For bulky disease and residual mass dose upto 36Gy is used.

In Conclusion

- Treatment is more effective with Conformal Treatments
- CT and FDG-PET scans before chemotherapy are critical in the delineation of GTV
- Postchemotherapy imaging for extent of residual disease
- Boost radiation might be appropriate in cases of bulky residual disease or when responses are poor.

Long Term Complications

- Long-term survivors (30 years) are more likely to die from treatment-related complications
- Hypothyroidism after neck and chest irradiation affects as many as 50% of patients 10 years after treatment.
- Cardiac and pulmonary - depend on the cumulative doses of anthracyclines, Bleomycin and on the radiation dose.
- High risk for infertility due to high doses of alkylating agents (Male patients must be councelled ablout sperm banking)
- 30% patients may develop a secondary malignancy upto 30 years later. The most common secondary malignancies are thyroid cancer, breast cancer, non melanomatous skin cancer, non-Hodgkin lymphoma, and acute leukemia.

Patient Education

- Before the initiation of treatment, patients should be counselled about the potential complications of Hodgkin lymphoma.
- All patients should be counselled on health habits that may help reduce the risk of cancer and cardiovascular disease, including avoidance of smoking, control of lipids, and the use of sunscreen.
- Patients should understand the risk of psychosocial problems that may affect survivors of Hodgkin lymphoma.
- Consultations with social workers, psychologists, and psychiatrists may be helpful to manage some of these issues.

Retrieval therapies for relapsed Hodgkin lymphoma

- IV – Ifosfamide and Vinorelbine or
  GV – Gemcitabine and Vinorelbine
- Combination of Bortezomib, a proteasome inhibitor, to Ifosfamide/Vinorelbine (IV). Methotrexate, Ifosfamide, Etoposide, and Ddexamethasone has also been studied.
- BEAM (Carmustine, Etoposide, Cytarabine and Melphalan) followed by Autologous stem cell transplantation

Salvage Radiotherapy

  - Important role in local control for patients who have primary refractory disease dominated by a local site
  - Important for patients who experience relapse after achieving a CR with initial therapy
  - RT should also be considered as a salvage option in the setting of ASCT failure, after relapse, or after progression
- Salvage RT yields high response rates and high local control rates in refractory and relapsed HL and in relapses after ASCT

Take Home Messages

- Highly curable malignancy
- New paradigm - risk-adapted, response-based approach to treatment
- IHC- CD 15, CD 20, CD 30 and CD 45
- Role of PET to assess treatment response
- Risk grouping and its significance
- IFRT vs INRT vs ISRT
- Long term complications