HODGKINS LYMPHOMA

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HODGKINS	NON HODGKIN
Localised Single grp of LN	Extranodal involvement common Multiple LN Non contiguous spread
REED STERNBERG CELLS	Majority- B cells, few- Tcells
BIMODAL AGE: 25 TO 30 75 TO 80	Median age: 65 years.
EBV	HIV & autoimmune diseases
B symptoms	May be present

HODGKIN'S EPIDEMIOLOGY:

- **RARE** CANCER: 0.56% Of all cancers diagnosed in US.
- **Males** > Females (except for nodular-sclerosing subtype).
- One in eight Lymphoma is Hodgkins type.
- Peak age incidence was found to be between **10 to 30** years.
- Median age of patients at the time of diagnosis is 26 years.
- It is rare in children younger than 10 years.

RISK FACTORS:

PREVIOUSLY TREATED FOR NHL:

- People treated for a previous non Hodgkin lymphoma (NHL) have an increased risk of HL.

LOWERED IMMUNITY:

- HIV or AIDS : General Population - 11 :1
- Organ transplant patient : General population - 4 :1
- Auto immune conditions : rheumatoid arthritis or systemic lupus erythematosus (SLE).

EBV VIRUS:

- Infectious mononucleosis(glandular fever) : increases risk.

SYMPTOMS

- Painless lymphadenopathy (rubbery consisteny)
  cervical: most common
  mediastinal: chest pain, cough, dyspnea.
- B symptoms: unexplained **fever (waxing & waning- Pel Ebstein fever), drenching night sweats, weight loss**, generalized pruritis, fatigue, alcohol induced pain in tissues involved by hodgkins.
- Organ involvement

direct extention

eg-enlarged mediastinal/bronchopulmonary LAP leading to pulmonary parenchyma

hematogenous

nodular disease in liver

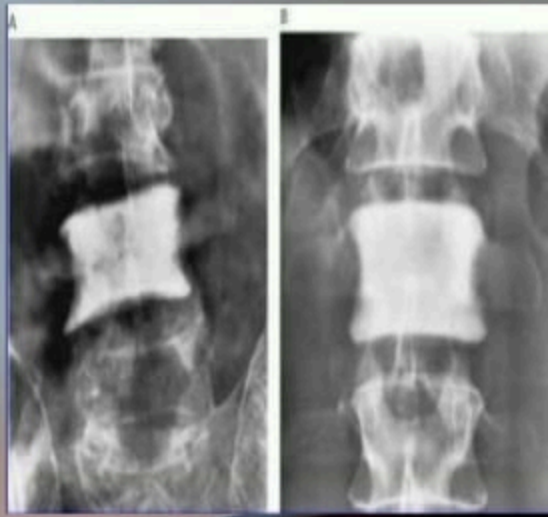
bone mets

EXTRALYMPHATIC DISEASE WITHOUT NODAL INVOLVEMENT IS RARE.

BONE LESIONS:

Blastic changes– IVORY VERTEBRAE

Pelvis, sternum, ribs



DIAGNOSTIC WORK UP

HISTORY:

- B SYMPTOMS- fever, night sweats(drenching), weight loss>10% of body weight in the last 6 months
- Other symptoms : alcohol intolerance, pruritis, respiratory problems, fatigue

PHYSICAL EXAMINATION:

- Palpable nodes(number,size,location,shape,consistency, mobility)
- Palpable viscera

Lab studies:

- CBC with differential
- ESR,Sr Albumin, LDH, LFT
- Blood urea nitrogen, creatinine
- Pregnancy test in women of child bearing age

Radiographic studies:

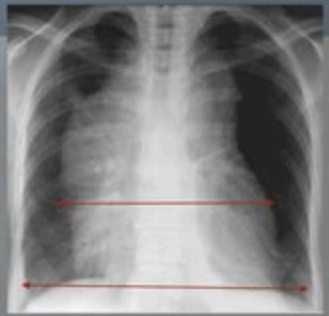
- CXR(PA)
- CT thorax, abdomen ,pelvis
- CECT neck (if indicated)
- PET CT

Additional biopsies:

- Bone marrow, Needle Biopsy(if subdiaphragmatic disease or B symptoms)
- Cytologic examination of effusion
- Percutaneous liver biopsy (if abnormal LFT but normal CT)

CHEST XRAY:

- **Mediastinal mass ratio (MMR)** - This ratio is defined as the maximum single horizontal mediastinal mass measurement divided by the maximum intrathoracic diameter, which is usually near the diaphragm
- **BULKY DISEASE**: MMR **exceeds 1:3 OR mass> 10 cm.**
- Radiographic evaluation should include postero-anterior (PA) and lateral chest radiographs.



CT SCAN:

- CT scans of the chest, abdomen, and pelvis may **reveal adenopathy or organ involvement.**
- Lymph nodes are usually considered to be enlarged on CT if their **short axis measurement exceeds 1 cm.**

BONE MARROW BIOPSY:

Less commonly

Overall involvement of bone marrow in Hodgkins lymphoma is ~ 5%.

- Indicated in pts with- B symptoms
- Clinical evidence of sub diaphragmatic disease
- Stage III-IV
- Recurrent disease

ROLE OF PET CT

- initial, interim, and posttreatment staging.

Interim PET –

- stratify patients that may be treated with chemo alone vs. the benefit from additional chemotherapy and/or involved site radiotherapy.
- prognostic significance - well established for advanced disease, less so for early-stage disease.
- .**End-of-treatment PET positivity** is a negative prognostic factor for both early- and advanced-stage disease.
- .Biopsy is recommended for Deauville 5 classification (below), and if positive, treat as refractory disease.

DEAUVILLE CRITERIA:

PET Five Point Scale (5-PS)

1	No uptake above background
2	Uptake ≤ mediastinum
3	Uptake > mediastinum but ≤ liver
4	Uptake moderately > liver
5	Uptake markedly higher than liver and/or new lesions
X	New areas of uptake unlikely to be related to lymphoma

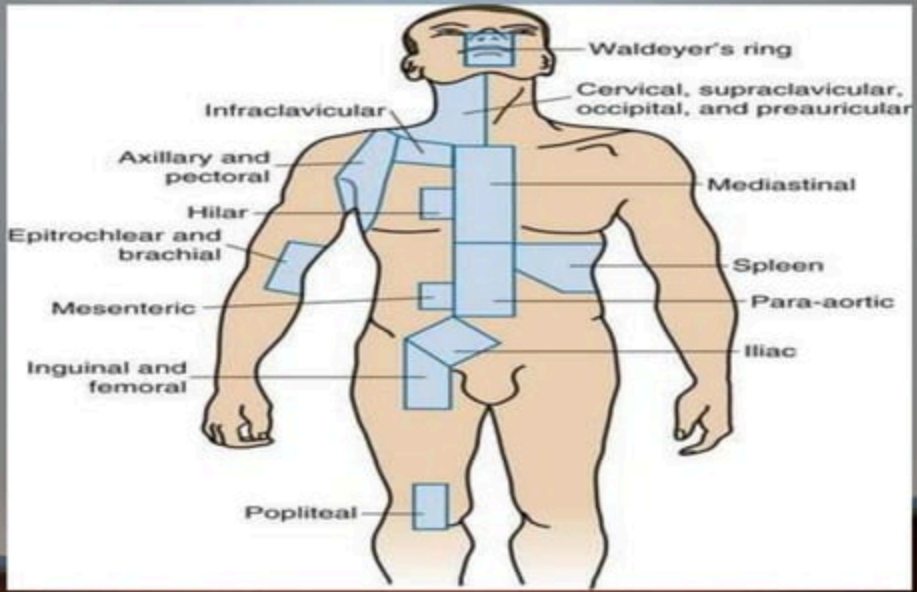
ANN ARBOR STAGING

I	**SINGLE** LYMPH NODE REGION	
II	**>/= 2 LN** REGIONS ON THE **SAME** SIDE OF THE DIAPHRAGM	LOCALISED INV OF **EXTRALYMPHATIC** SITE(IIE) + **>/= 1 LN** ON THE SAME SIDE OF DIAPHRAGM
III	LN REGIONS ON **BOTH** SIDE OF THE DIAPHRAGM + INV OF **SPLEEN** (IIS) OR LOCALISED INV OF **EXTRALYMPHATIC** ORGAN OR SITE (IIE) OR **BOTH**(IISE)	
IV	DISSEMINATED INV OF **>/= 1 EXTRALYMPHATIC** ORGANS OR TISSUES WITH/WITHOUT **LN** INV	

A – absence of B symptoms

B – fever, night sweats, unexplained loss of 10% of body weight in 6 months.

LYMPH NODE REGIONS



DEFICIENCES OF ANN ARBOR STAGING

- FAILURE TO CONSIDER BULKY DISEASE.
- LACK OF A MORE PRECISE DEFINITION OF THE E LESION.

COTSWOLD MODIFICATION

LUGANO MODIFICATION

I	I - SINGLE LYMPHATIC SITE (NODAL REGION + WALDEYER'S RING + SPLEEN + THYMUS)	IE-SINGLE EXTRALYMPHATIC SITE in the absence of lymph node involvement(rare in Hodgkin's)
II	II- >/= 2 LN REGIONS ON THE **SAME** SIDE OF THE DIAPHRAGM	IIE-Contiguous extra lymphatic extension from a nodal site with or without involvement of other nodal site II BULKY- stage II with disease bulk
III	LN REGIONS ON **BOTH** SIDE OF THE DIAPHRAGM + INV OF **SPLEEN** (IIS) OR LOCALISED INV OF **EXTRALYMPHATIC** ORGAN OR SITE (IIE) OR **BOTH**(IISE)	Nodes above the diaphragm with spleen involvement.
IV	DISSEMINATED INV OF >/= 1 **EXTRALYMPHATIC** ORGANS OR TISSUES WITH/WITHOUT **LN** INV	Non-contiguous extralymphatic organ inv + nodal stage II or Any extralymphatic organ inv + nodal stage III or Any inv of CSF, bone marrow, liver or lungs.(other than direct extention)

CLASSIFICATION :-

(WHO 2008)

HODGKINS LYMPHOMA

NODULAR LYMPHOCYTE PREDOMINANT

L & H or Popcorn cells.

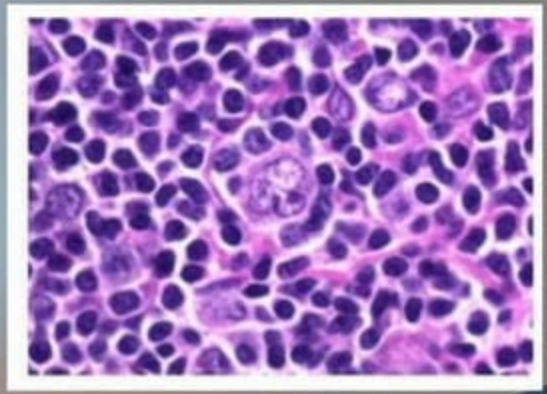
CLASSIC LYMPHOMA

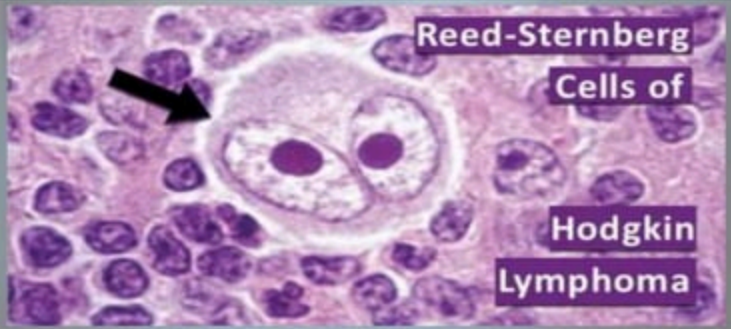
- NODULAR SCLEROSIS
- MIXED CELLULARITY
- LYMPHOCYTE RICH
- LYMPHOCYTE DEPLETED

REEDSTERNBERG CELLS

L&H OR POPCORN CELLS

- LARGE, MULTILOBED, FOLDED NUCLEUS AND IS SURROUNDED BY SMALL LYMPHOCYTES.
- ABNORMAL CELLS OF B CELL LINEAGE.

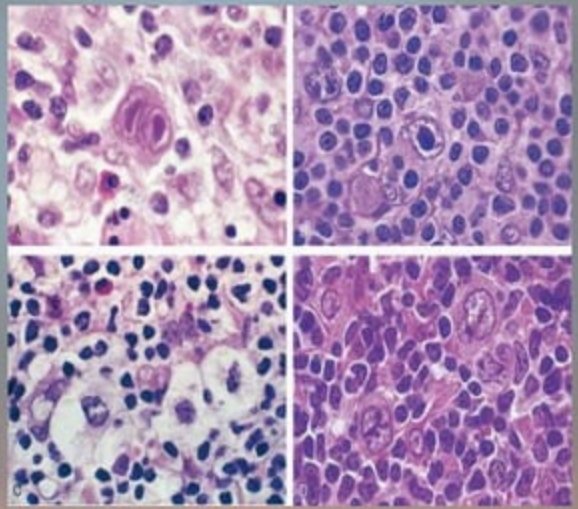




- Neoplastic cell of classic hodgkins lymphoma
- Binucleate …OWL EYE APPEARANCE.
- Prominent centrally looking nucleolus in each nucleus.
- Well demarcated nuclear membrane, and eoisinophilic cytoplasm with a perinuclear halo.
- <1% of cells in the lymph node involved by hodgkins lymphoma,
- Majority are lymphoid cells, eoisinophils, plasma cells and other normal cells.
- Originate from B lineage at various stages of development.
- Positive for CD30, PAX5, CD15 & CD20.
- Negative for CD45, ALK and J chain.

VARIANTS OF RS CELLS

DIAGNOSTIC Reed Sternberg cell-



MONONUCLEAR VARIANT

LACUNAR VARIANT

the cytoplasm shrinks during formalin fixation and processing of tissue, leaving **an empty space around the nucleus.** Such R-S variants are known as "lacunar cells"

LYMPHOHISTIOCYTIC VARIANT (L & H VARIETY OR POPCORN CELLS)

Table 35.1 Characteristics of Hodgkin's lymphoma subtypes

WHO classification	Nodular lymphocyte predominant (NLPHL)	Classic HL (CHL) Nodular sclerosis (NSCHL)	Mixed cellularity (MCCHL)	Lymphocyte rich (LRCHL)	Lymphocyte depleted (LDCHL)
CD15	–	+	+	+	+
CD30	–	+	+	+	+
CD20	+	+/–	+/–	+/–	+/–
CD45	+	–	–	–	–
Incidence/epidemiology	5% all HL More common age > 40	70% CHL More common in adolescents and young adults	20% CHL More common in young children	15% CHL	≤ 5% CHL
Presentation	Often stage I–II, B symptoms <10%	Mediastinum often involved. One-third have B symptoms	Often advanced disease, often subclinical subdiaphragmatic disease in patients with clinically staged I–II above diaphragm	Usually early stage	Rare, mostly advanced with B symptoms in older patients, associated with HIV
Prognosis	Best, occasional late relapse	Intermediate between LRCHL and LDCHL	Intermediate between LRCHL and LDCHL	Good, infrequent relapses	Worst
30 month EFS	94%	89%	86%	97%	55%
30 month OS	97%	97%	94%	97%	87%

RISK CLASSIFICATION:

Early stage HL (stage I-II):

- Favourable(no risk factors)
- Unfavourable(>/= 1 risk factors)

Table 35.5 Unfavorable risk factors for stage I–II HL

Risk factor	GHSB	EORTC	NCIC	NCCN
Age	–	≥50	≥40	–
Histology	–	MC or LD	–	–
ESR or B sx	>50 if A or >30 if B	>50 if A or >30 if B	>50 or any B sx	>50 or any B sx
Large mediastinal adenopathy	MMR > 0.33	MMR > 0.35	MMR > 0.33 or > 10 cm	MMR > 0.33
# nodal sites	>2	>3	>3	>3
Extranodal lesions	Any	–	–	–
Bulky	–	–	–	>10 cm

Mediastinal mass measured on CXR by the mediastinal mass ratio (MMR) maximum width of mass/maximum intrathoracic diameter
Early stage treated with chemo-RT, 5-year FFF 95% and OS >95%

GHSB-GERMAN HODGKIN STUDY GROUP: NCIC-NATIONAL CANCER INSTITUTE CANADA :EORTC: EUROPEAN ORGANISATION OF RESEARCH AND TREATMENT OF CANCER.

- Advanced stage HL (Stage IIB, III, and IV)

Table 35.6 International prognostic score (IPS-7) 1 point per factor for advanced stage HL

Gender	Male	**Albumin**	<4 g/dL
Age	≥45	**Hgb**	<10.5 g/dL
Stage	IV	**WBC**	>15,000/uL
–	–	**Lymphocyte**	<8% or <600 uL

Table 35.7 IPS-7 risk group for advanced stage HL (Hasenclever et al. 1998)

	IPS score	5-year PFS (%)	5-year OS (%)
Good	0	84	89
	1	77	90
Fair	2	67	81
	3	60	78
Poor	4	51	61
	>5	42	56

Table 35.8 IPS-3 risk group for advanced stage HL (Aleman IJROBP 2007)

	IPS score	5-year PFS (%)	5-year OS (%)
1 point per factor	0	83	95
Age ≥ 45	1	74	85
Stage IV	2	68	75
Hgb < 10.5 g/dL	3	63	52

TREATMENT

COMBINED MODALITY TREATMENT :-

- BECOME THE MOST COMMON FORM OF GENERAL MANAGEMENT :-

CHEMOTHERAPY (INITIALLY TO REDUCE THE BULK OF THE DISEASE ESP IN STAGE III & IV)

RADIATION THERAPY IN ADULT (20 TO 36 GY)

Table 35.9 Chemotherapy Regimens

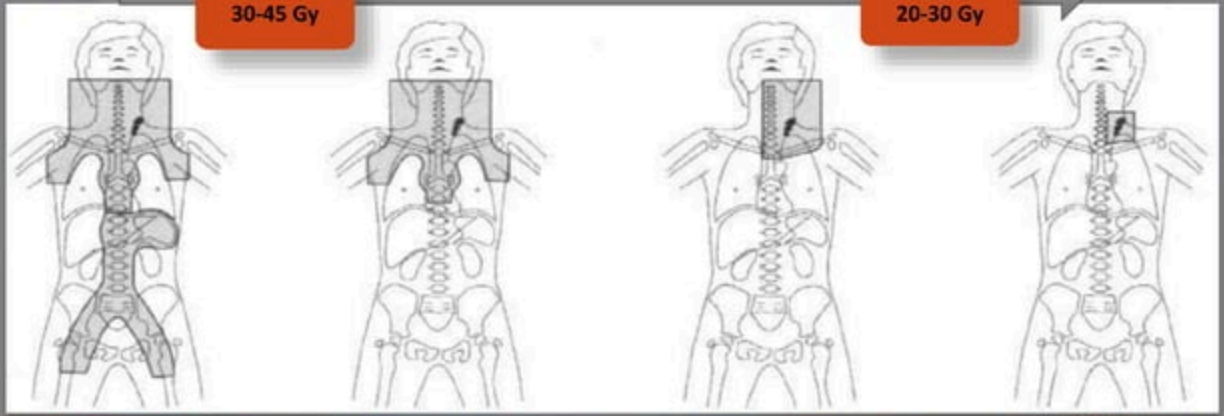
Combination	Drug	Days	Cycle (days)	Comment
ABVD	Adriamycin (doxorubicin)	1, 15	28	Decreased sterility and second malignancies vs. MOPP
	Bleomycin	1, 15		
	Vinblastine	1, 15		
	Dacarbazine	8–14		
Stanford V	Mechlorethamine	1	28	Decreased bleomycin and doxorubicin toxicity vs. ABVD
	Doxorubicin	1, 15		
	Vinblastine	1, 15		
	Vincristine	8, 22		
	Bleomycin	8, 22		
	Etoposide	15, 16		
	Prednisone	Qod		
BEACOPP	Bleomycin	8	21	Eight cycles total. Filgrastim from day 8 of each cycle until leukocyte count normalizes. RT given for disease >5 cm
	Etoposide	1–3		
	Adriamycin (doxorubicin)	1		
	Cyclophosphamide	1		
	Oncovin (vincristine)	8		
	Procarbazine	1–7		
	Prednisone	1–14		
EPOCH	Etoposide [why underlined?]	1–4	21	DA-EPOCH = dose adjustment each cycle based on neutropenia and thrombocytopenia
	Prednisone	1–5		
	Oncovin (vincristine)	1–4		
	Cyclophosphamide	5		
	Hydroxydaunorubicin (doxorubicin)	1–4		
Other	Rituximab (anti-CD20)	NLPHL expresses CD20		
	Brentuximab (anti-CD30)	CHL expresses CD30		
	Nivolumab (anti-PD1)	HL has a high immune cell infiltrate		

Stage	Primary treatment	PFS (%)	OS (%)
I–II favorable CHL	ABVD × 2–4 cycles → restage → ISRT	90	95
I–II favorable NLPHL	RT alone	90	90
I–II unfavorable bulky	ABVD × 4 cycles → restage → ±ABVD × 2 cycles (4–6 total) → ISRT	85	90
I–II unfavorable non-bulky	ABVD × 4 cycles → restage → ABVD × 2 cycles (6 total) → ±ISRT		
III–IV	ABVD × 6–8 cycles	60	70

RADIOTHERAPY TECHNIQUES

30-45 Gy

20-30 Gy



Total nodal radiotherapy

All LN of both sides of diaphragm

Extended field radiotherapy

Multiple involved & uninvolved LN groups of one side of diaphragm

Involved field radiotherapy

Field Limited to site of clinically involved LN

Involved node/site radiotherapy

Most limited RT field , includes only involved LN.

FIELD DESIGN : OLD TECHNIQUES

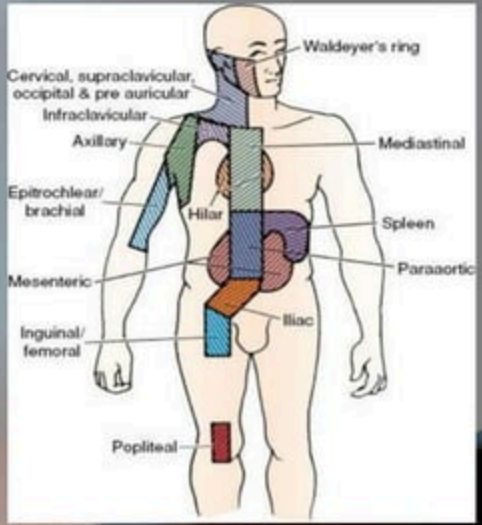
Extended field RT

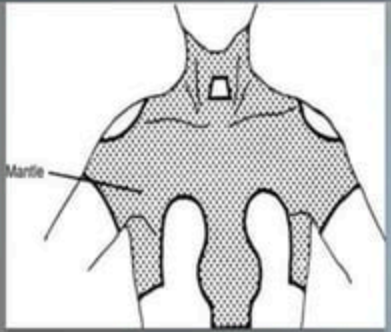
Supradiaphragmatic:

- Mantle
- Mini mantle
- Modified mantle
- Extended mantle

Infradiaphragmatic

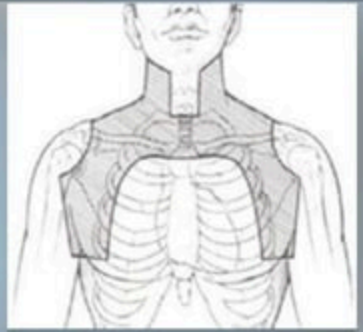
- Paraaortic
- Spleen
- Pelvic
- Inverted Y





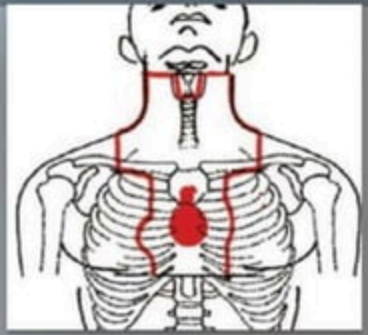
Mantle field

B/L cervical
Supraclavicular
infraclavicular,
axillary
hilar
mediastinal.



Mini Mantle

Mantle field without mediastinal & hilar LNs



Modified Mantle

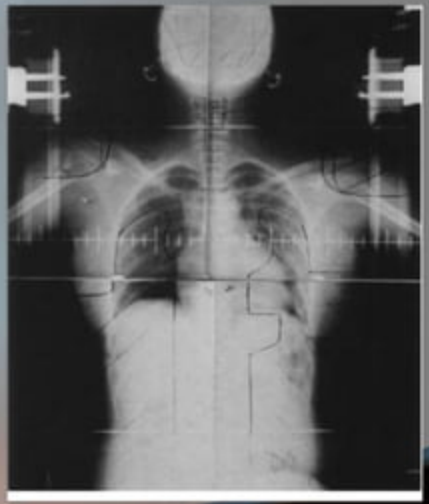
Mantle field without axillary LNs.

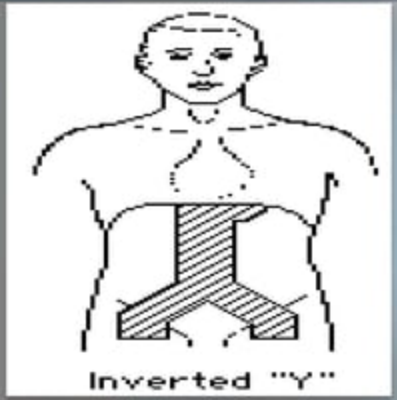
Extended mantle field

To avoid need of matching mantle and paraaortic fields

Includes mantle & paraaortic in a single port

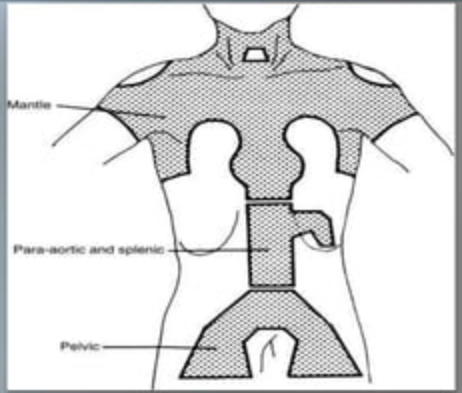
↑ed probability of bone marrow suppression & acute morbidities with larger volume treatment





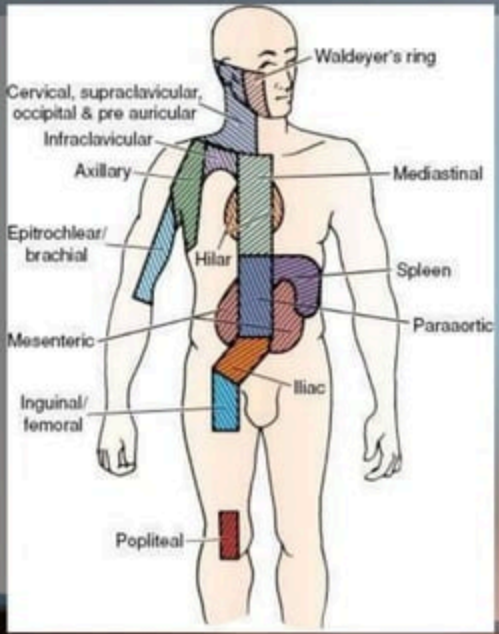
Inverted “Y “field

Para aortic ,
bilateral pelvic,
B/L inguinal-femoral
Splenic ±



Total nodal irradiation

Mantle + Inverted Y + Spleen



Involved field RT

- Waldeyer's ring
- Neck
- Mediastinum
- Axilla
- Paraaortic
- Pelvic
- Inguino-femoral

Involved node RT

Involved site RT

Modern Radiotherapy Fields

Involved-field (IFRT)	Includes involved nodes before chemotherapy and its entire nodal region If extranodal: includes the involved organ alone, if no LN involvement
Involved LN (INRT)	Includes the originally involved nodes before chemotherapy. Requires FDG-PET before and after chemotherapy for RT planning, with reproducible patient positions

Simulation

- **Positioning**: supine ,customized on the basis of site of irradiation & OAR shielding
- Custom Immobilization devices used
  - Cervical RT: neck rest, mask
  - Thoracic RT: wing board
  - Pelvic RT: knee rest
  - Body moulds
- Customized tissue compensators used for neck, mediastinal fields
- Wire grossly involved nodes

- Plain Xray simulation
- Contrast enhanced CT simulation
- PET CT simulation

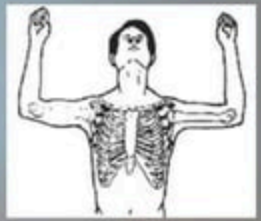
- Field shaping done with: customized block or MLCs

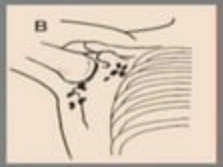
Simulation: For mediastinum, axillary & SCF nodes

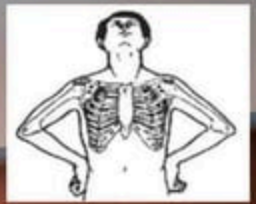
•Positioning: supine

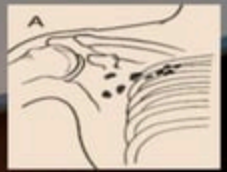
•Arms :4 positions

1. Above head:
   - axillary nodes move away from chest wall, helps in lung shielding.
   - enhanced skin Rxn in SCF
2. At 90* angle towards the side: decreased skin fold at neck
   - Increased dose to breasts & heart
3. Akimbo position, i.e., hands on the waist.
4. Arms down
   - permits shielding of the humeral heads,
   - minimizes skin reaction in the tissue folds



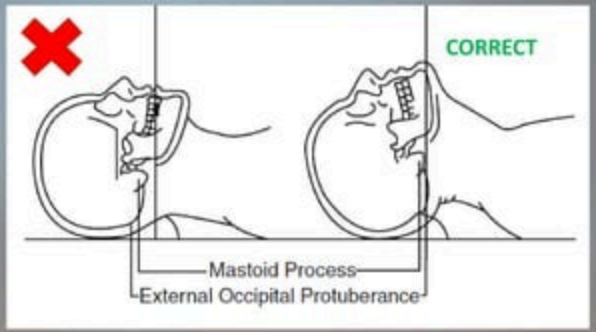






Neck should be in maximum extension

- to exclude the oral cavity and teeth from the RT field
- to decrease the dose to the mandible.

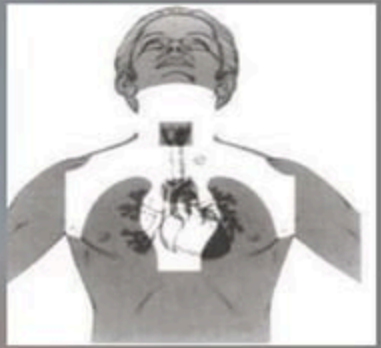


RT techniques

- Conventional
- 3D CRT
- IMRT
- Proton beam therapy

Mantle field

- Target volume:
- cervical, supraclavicular, infraclavicular, axillary, mediastinal, and hilar regions
- Organ at risk:
- Larynx, spinal cord, humeral head, lung, heart,

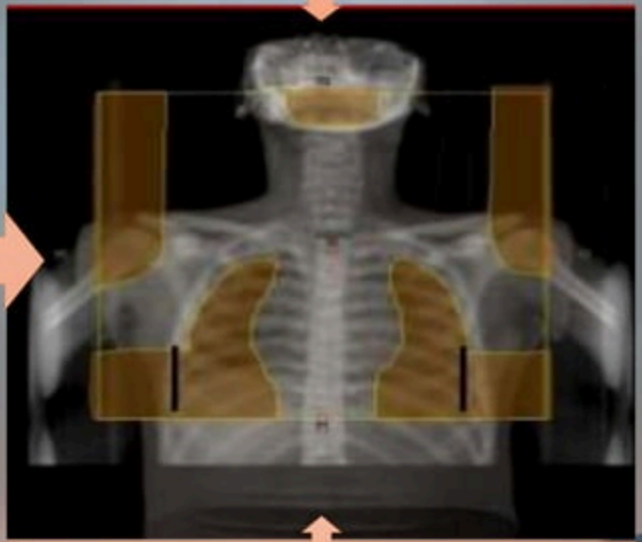


Superior: Passes through mastoid bisecting the mandible

Lateral border:

Superior-flash axilla, beyond humeral head with shield

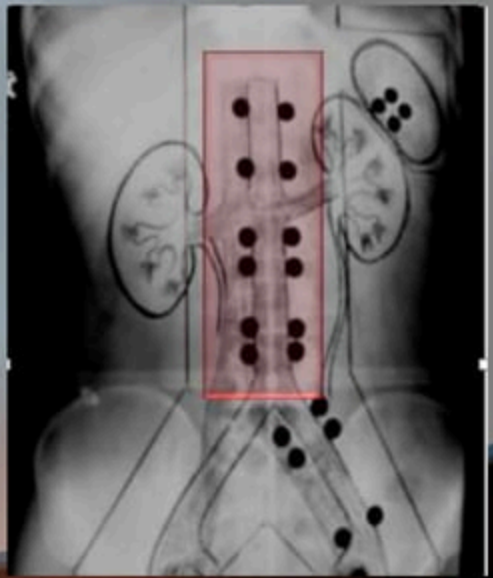
Inferiorly-inferior border of scapula /T7



Inferior: bottom of diaphragm, lower border of T10/11

Para aortic field

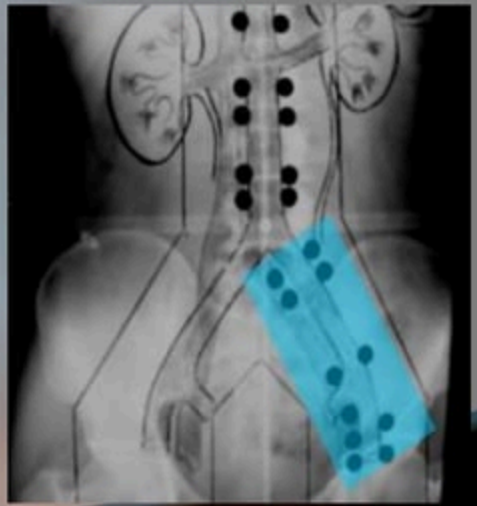
- Upper border – matched with mantle (T10)
- Inferior border - at the L4-L5 interspace
- Lateral border – edges of transverse processes or about 1.5-2cm lat to border of vertebral bodies (width of 8-10cm)



Pelvic field

- **Superior border** – matched with PA Field (upper border of L5)
- **Inferior border** – lower border of ischial tuberosity
- **Laterally** - field shaped with blocks to spare iliac wing bone marrow without compromising coverage of iliac lymph nodal chain

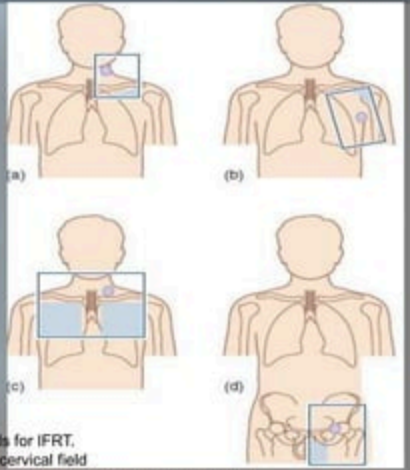
- **Central block** - 4 cm block extending from the inferior edge of field & superiorly to sacroiliac joint to protect bladder and rectum



IFRT: involved field RT

Targets a smaller area rather than a classical extended field.

- IFRT encompasses region and not an individual lymph node.
- For conventional planning: field border are decided on basis of anatomical landmark
- For 3DCT Plan: target are contoured based on pre CT volume & areas at risk of microscopic spread



opposing fields for IFRT.
(a) Unilateral cervical field
(b) (b) Axillary field with shielding of humeral head.
(c) Neck and mediastinum with lung shielding.
(d) Groin with shielding of testes and small bowel

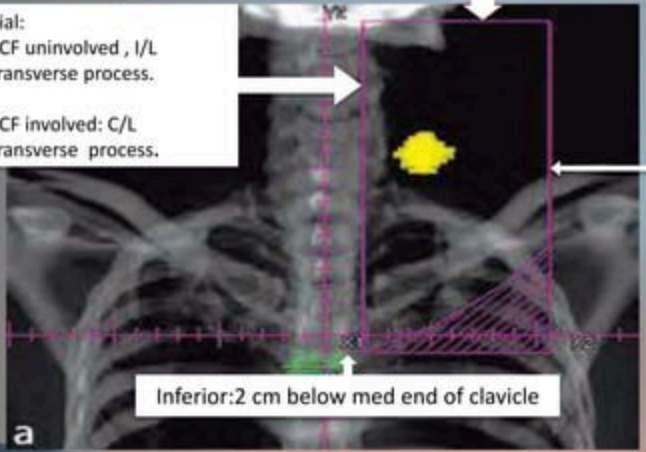
Conventional field border for IFRT

Unilateral Cervical /Supraclavicular Field

Superior:1-2 cm above the tip of mastoid & mid point through the chin

Medial:

- SCF uninvolved , I/L transverse process.
- SCF involved: C/L transverse process.



Lateral: up to med 2/3 rd of clavicle

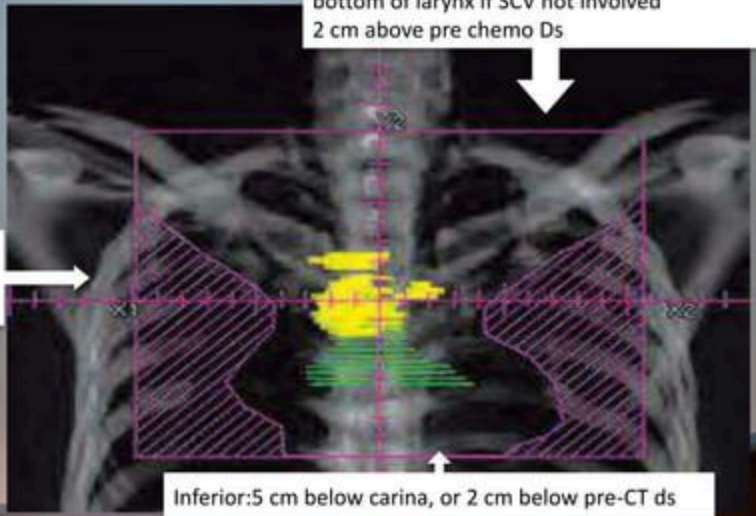
Inferior:2 cm below med end of clavicle

MEDIASTINAL/HILAR LN:-

Block
- Larynx
- Post. Cervical cord
- Lung
- Heart

Superior:
C5-C6 interspace –
top of larynx if SCV involved,
bottom of larynx if SCV not involved
2 cm above pre chemo Ds

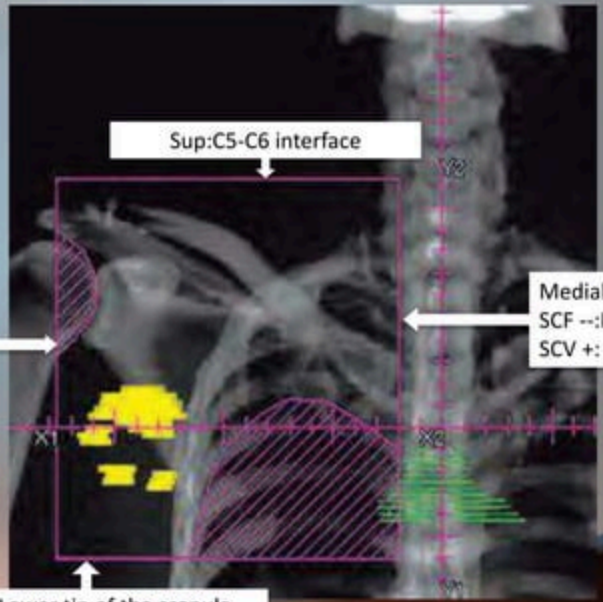
Lateral: Post-CT GTV + 1.5 cm margin



Inferior:5 cm below carina, or 2 cm below pre-CT ds

AXILLARY FIELD

Block
- Humerus
- Lung .

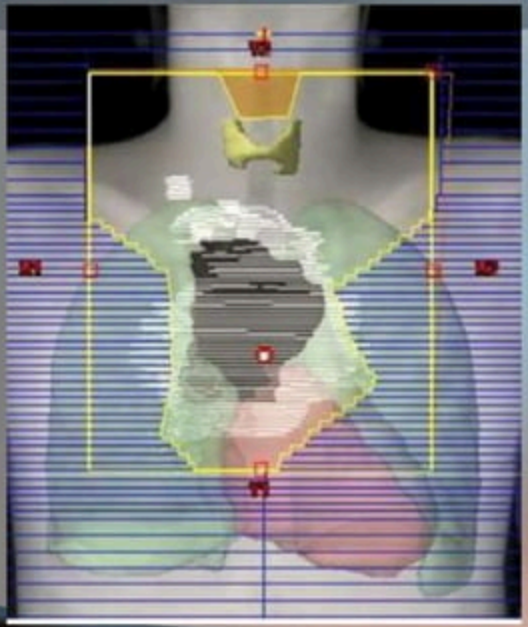


3DCRT Planning

- 3D CT simulation required
- Target volumes are outlined on CT

- TARGET VOLUMES
- GTV: prechemo volume of involved L.N clinically and radiologically, PET
- CTV:GTV +whole nodal regions that contains involved L.N + adjacent “at-risk” L.N
- PTV: Depends on immobilization,reproducibility,organ motion. Usually CTV+ 1cm margin

- treatment planning :field designed for target coverage, MLC used for shielding
- Allows to optimization & analyse DVHs in order to ensure adequate tumor coverage and sparing of organs at risk (OARs)



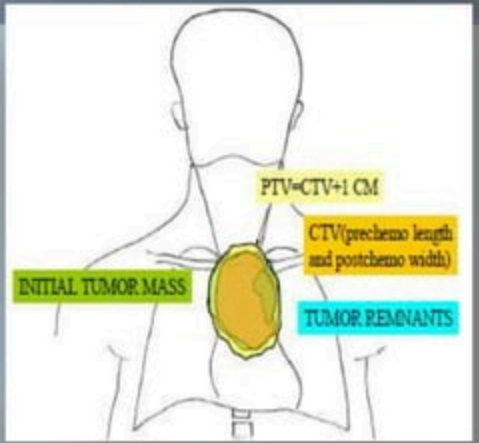
3DCRT PLANNING

- massive mediastinal and right SCF node
- White, pre-chemo PET+ disease;
- black, post chemo residual ds. on CT

- Design of a modified "involved field"
- include the mediastinum, bilateral hila, and SCF areas with an anterior larynx block.

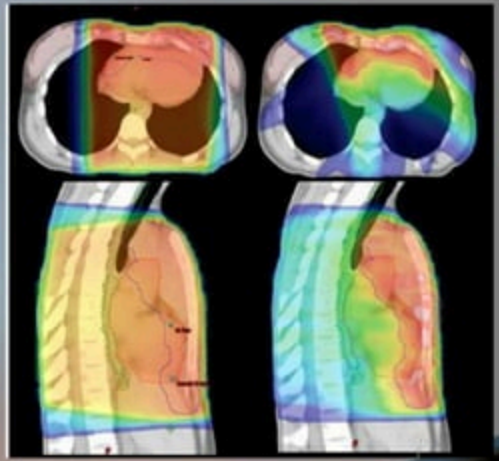
- Note that inferiorly the field includes the prechemo GTV plus 2-cm margin.
- However, laterally the field encompasses only residual disease on CT plus 2-cm margin.

- Pre-requisite:
  - modern imaging & RT planning Techniques
  - pre Chemo diagnostic CT & PET CT in treatment position.
  - post chemo contrast-enhanced CT simulation
  - fusion of the pre and post CT images
  - fields designed to treat only initially involved nodes with modification to avoid OARs.
  - This GTV then becomes the CTV,
  - 1-cm expansion of the CTV defines the PTV
  - In case when target volumes are not well defined: ISRT preferred



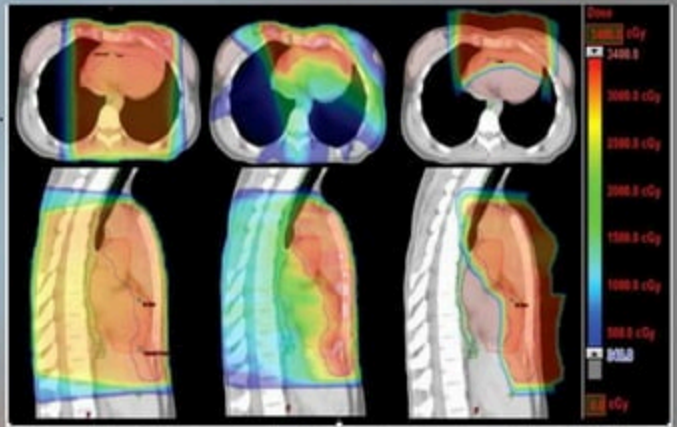
IMRT planning

- IMRT may be most useful in some situations like complex fields & reirradiation
- Advantage: better dose conformity, improved DVH for the heart, coronary arteries, oesophagus, and lungs,
- Disadvantage: low-dose “bath,” put larger volumes of normal tissue at risk for development of secondary cancer



Proton therapy

- dosimetric advantage
- especially advantageous for mediastinal treatment.
- maximal sparing of the oesophagus, lungs, and heart
- avoiding low-dose exposure to the breasts and lungs
- minimizing potential risks of second malignancy
- Experience is limited



colour-wash dose distributions for three different plans for treating mediastinal Hodgkin lymphoma:
axial sections (*top*) and sagittal sections (*bottom*) for 3DCRT AP-PA fields (*left*), IMRT photon (*middle*), and anterior proton field (*right*).

DOSE PRESCRIPTIONS:

Early stage classic HL, CR to chemotherapy.

- 20 Gy if favorable (I–IIA, ESR <50, no extralymphatic disease, <1–2 regions involved) treated with ABVD.
- 30 Gy if unfavorable or treated with Stanford V.

- Early stage NLPHL: 30–35 Gy.
- Residual lymphoma after chemotherapy: 36–40 Gy.

FOLLOW UP:

- Every 3–6 months X 1–2 years,
  every 6–12 months until year 3,
  then annually with H&P, labs as indicated.
- …CT at 6, 12, and 24 months after treatment. Or, PET/CT if last PET was Deauville 4–5.
- …thyroid function if in RT field
- Annual breast screening initiated 8–10 years after therapy or at age 40, whichever first, for women treated with chest or axillary RT.