RADIOTHERAPY IN PEDIATRIC HODGKIN LYMPHOMA

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EPIDEMIOLOGY AND PATHOGENESIS

- Bimodal incidence curve- 15-35 years & >55 years (subjected to geographic variation)
- EBV positivity - Younger age and low socioeconomic status

  (supports infectious etiology)
- Pediatric HD – M > F & Adolescent – M=F
- Mixed cellularity subtype commonest in India whereas the nodular sclerosing is more common in western world.
- Historic therapies, used in adults, caused substantial morbidities in children.
- As long term survivors pediatric HL patients have served as models for understanding the long-term toxicity of RT and chemotherapy
- Outcomes in India are comparable to western centers.

- Medindia,org .*Cancer* 1999;5(6):325
- *J Pediatr Surg* 1983;18(5):652 Eur J Cancer 2007; 43: 161 – 8

CLINICAL FEATURE

- Most commonly- painless cervical or supraclavicular lymphadenopathy.(upto 90%)
- Lymph nodes are often fixed, firm, rubbery, and Painless
- Mediastinal lymphadenopathy - 66% of patients - dry cough or airway pressure symptoms
- B symptoms (1/3rd f patients) at diagnosis.
  - Recurrent unexplained fevers >38°C during the previous month,
  - drenching night sweats
  - weight loss of more than 10% in the 6 months preceding diagnosis

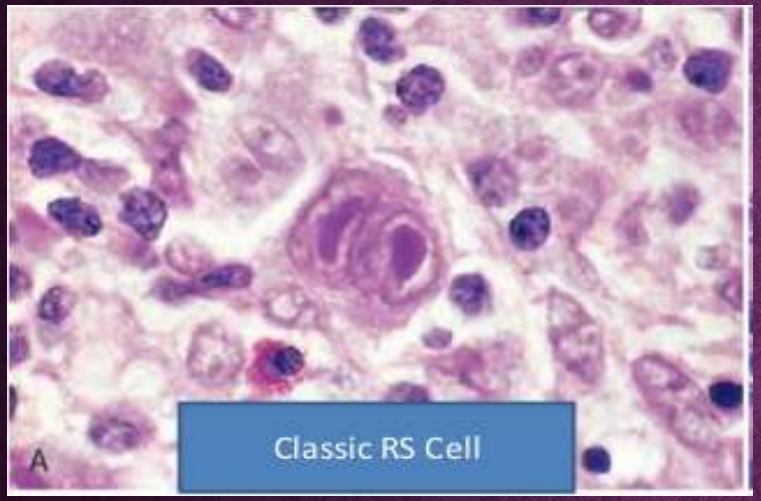
DIAGNOSTIC WORK UP

- Clinical examination (Never forget Waldeyer ring, Liver and spleen)
- Lymph node biopsy
- Fine needle aspiration (FNA) – Not advised (not cost-effective and misguiding)
- CBC, LFT, KFT
- ESR, Sr. Albumin, Sr. LDH, Sr. Uric Acid
- CXR to define mediastinal bulk of disease
- FDG WB CE PETCT
- Bone marrow biopsy – (low rate of involvement at initial presentation if PET negative, restricted to patients with B symptoms or stage III or IV disease)

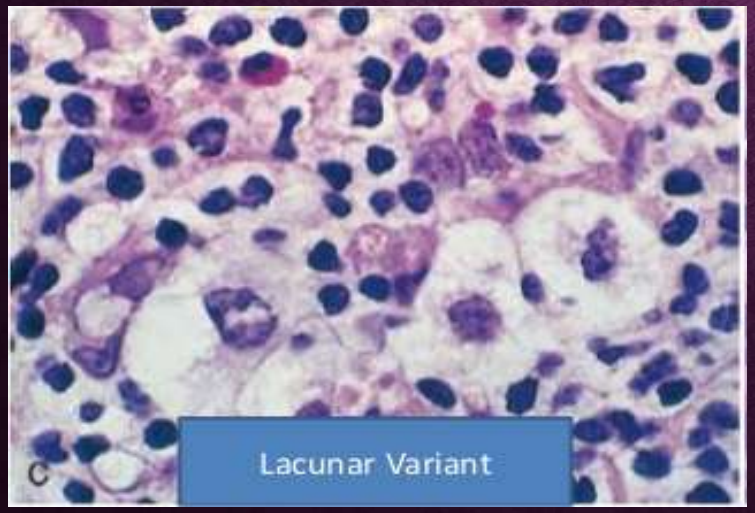
HL Vs NHL

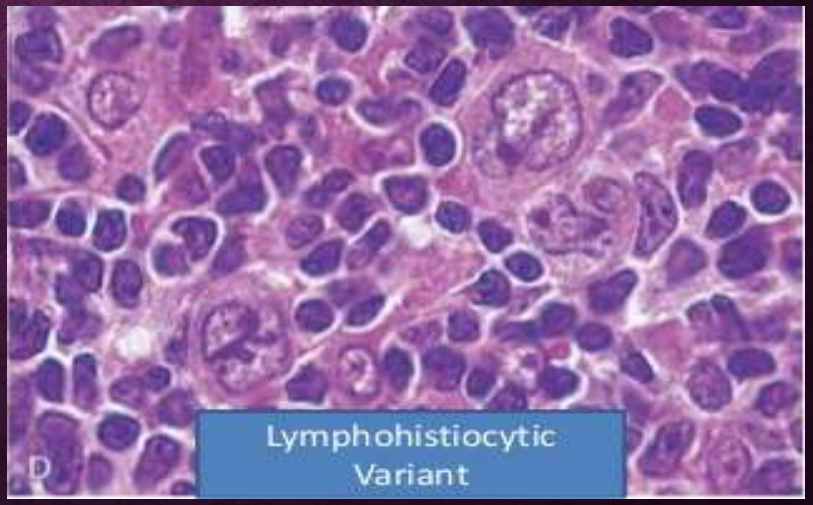
Lymphoma	Hodgkin Lymphoma	Non-Hodgkin Lymphoma
Location	Axial / Central (Cervical, mediastinal, para-aortic)	Multiple peripheral nodes
Presentation	Early age & stage	Late age & stage
contiguity	Contiguous	Noncontiguous spread
Mesenteric nodes and Waldeyer ring	Rarely involved	Commonly involved
Extranodal presentation	Rare	Common
B symptoms	More common	Less common
Malignant cells	R-S cells	Lymphocytes

R-S CELLS


A
Classic RS Cell


B
Mononuclear Variant

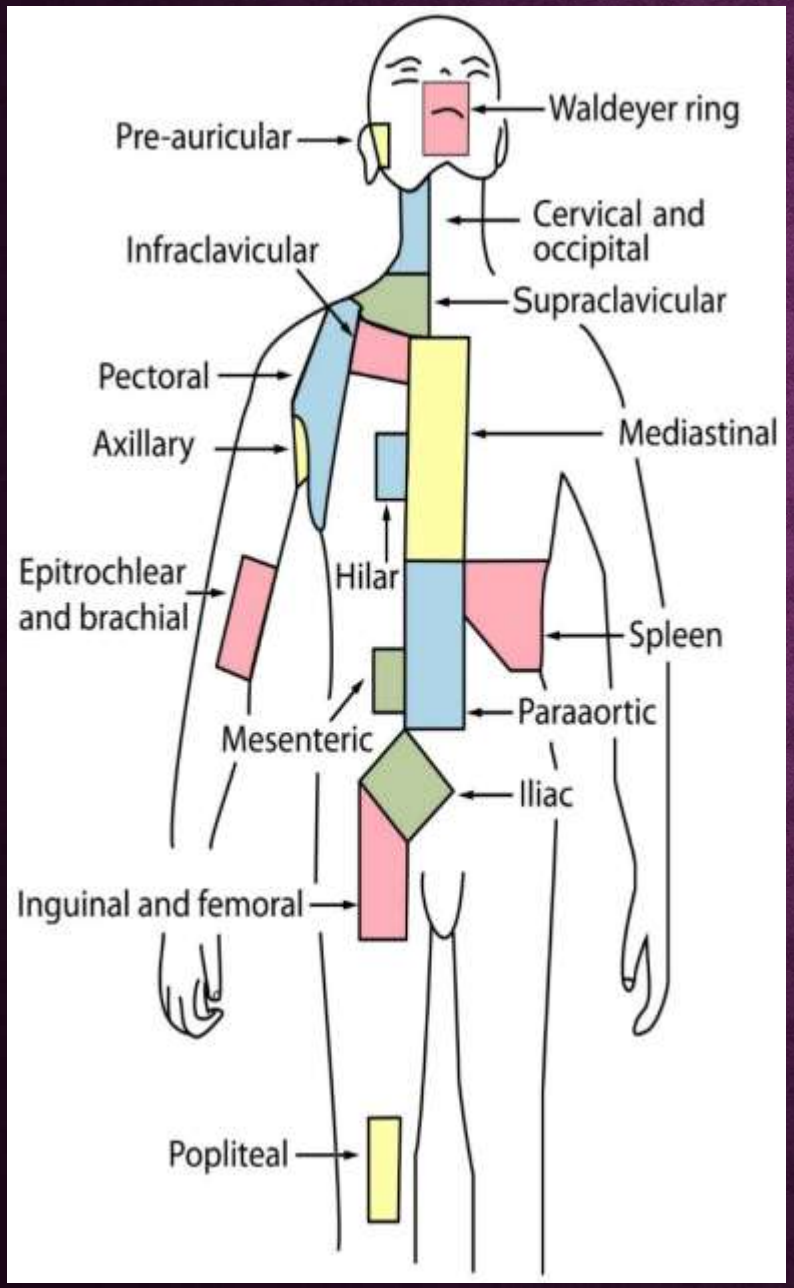

C
Lacunar Variant


D
Lymphohistiocytic
Variant

CLASSIFICATION OF HD

Type	R-S Cell	IHC	EBV
NLPHD	L&H (popcorn cell)	CD15, CD30(-ve) CD 20 (+ve)	-ve
Mixed cellularity	mononuclear & diagnostic	CD15, CD30 (+ve)	+ve
Nodular sclerosis	lacunar cells & diagnostic	CD15, CD30 (+ve)	-ve
Lymphocyte Rich	mononuclear & diagnostic	CD15, CD30 (+ve)	40%-ve
Lymphocyte depleted	diagnostic	CD15, CD30 (+ve)	+ve

STAGING



Ann Arbor Grouping (Not IFRT)

- Lymph nodes -Waldeyer's ring, thymus, and spleen are considered *nodal* sites.
- Extra nodal sites –
  - Adrenal glands,
  - Blood,
  - Bone. bone marrow,
  - Central nervous system
  - Gastrointestinal (GI) tract, gonads,
  - Kidneys, liver, lungs, skin, occular adnexae (conjunctiva, lacrimal glands, and orbital soft tissue),
  - Skin, uterus, and others

ANN ARBOR STAGE (1971)

- Stage I: Single nodal group; or single extranodal organ in the absence of lymph node involvement (IE)
- Stage II: Multiple nodal groups on same side of the diaphragm; involvement of single extranodal organ with regional lymph node involvement (IIE)
- Stage III: On both sides of the diaphragm; accompanied by extralymphatic extension (IIIE)
- Stage IV: Diffuse involvement of 1 or more extralymphatic organs; isolated extralymphatic organ involvement in the absence of adjacent regional LN involvement, but in conjunction with disease in distant sites. Stage IV includes any involvement of liver, bone marrow, lungs (other than direct extension from another site), or cerebrospinal fluid.
- Staging suffixes
  - B: presence of constitutional "B" symptoms (A if no B symptoms)
  - E: Extralymphatic involvement
  - S: splenic involvement
  - X: bulky mediastinal disease

SUBSEQUENT MODIFICATION IN STAGING

COTSWOLD MODIFICATION(1989)

- X - bulky disease
- Subscript to denote no. of regions involved, e.g. II_3
- Stage III may be subdivided into III_1 and III_2:
  - III_1 (splenic, hilar, celiac, or portal nodes)
  - III_2 (para-aortic, iliac, or mesenteric nodes);
- Staging segregated into clinical or pathologic
- Added categories of response to therapy (such as Unconfirmed CR, CRu)
  - CRu - presence of an uncertain radiographic abnormality at the site of treated disease.

LUGANO CLASSIFICATION(2014)

- X - Not necessary (record the tumor diameter).
- A and B suffixes: Only for HL & Not in NHL.
- BM biopsy – Not Mandatory for routine staging of HL
- E - Used only for limited extranodal disease in the absence of nodal involvement (IE) or in patients with Stage II disease and direct extension to a non-nodal site (IIE). (Liver is an exception – directly stage IV)
- E - Irrelevant in advanced stage

DEFINITION OF BULKY DISEASE

- Mediastinum – (X ray or CT scan (Lugano))
  - Mass of more than one-third of the maximum intrathoracic diameter (MMR)
  - Greater than 1/3 of the mediastinal mass to the intrathoracic width at T5-6 (MTR)

- Other site - Absolute mass of >6 cm (some trials ≥5 cm or ≥10 cm)

- Volume definition of bulk- 200 mL estimated using an ellipsoid volume formula where $V = (xyz)/2$ where x, y, and z are the diameters of the mass in three dimensions (Euro-Net-PHL-C1)

RISK STRATIFICATION

Study Group	Risk	IA	IB	IIA	IIB	IIIA	IIIB	IVA	IVB
COG	AHOD0431 – Low								
	AHOD0031 – Intermediate	E X		E X					
	AHOD0831 – High								
EuroNet-PHL-C1*	TG1– Low								
	TG2 – Intermediate	E RF	E RF	E RF					
	TG3 – High				E	E			
EuroNet-PHL-C2	TL1 – Low								
	TL2 – Intermediate	E RF	E RF	E RF					
	TL3 – High				E	E			
Pediatric Hodgkin Consortium	HOD99/HOD08 – Low			< 3 ns					
	HOD05 – Intermediate	E mX		E mX					
	HOD99/HLHR13 – High								

J Clin Oncol 33:2975-2985

RISK STRATIFICATION

- Considerable variation in risk stratification among trials and treatment groups
- Therefore, it is difficult to compare trials
  - In general

RISK GROUP	FEATURES
Favorable	Stage I or II without adverse prognostic factors
Intermediate	Stage I or II with adverse prognostic factors (B symptoms, bulky disease, extranodal extension to contiguous structures, ≥ 3 more nodal areas) & IIIA
Advanced	Stage II BE, II BX, IIIAE, IIIAX IIIB-IV

Kelly KM: Management of children with high-risk Hodgkin lymphoma. Br J Haematol. 2012;157:3-13

TREATMENT PHILOSOPHY FOR PEDIATRIC HD

- Treatment is risk-adapted and response based
- Age and Gender are important factors when deciding treatment
- Due to the concern of long term toxicity the Focus is on combination Chemotherapy with low cumulative doses of individual drugs.
  - **Anthracylines (e.g. - Doxorubicin)- cardiac dysfunction (Dose max- 250 mg/m2)**
  - **Etoposide (VP-16) - secondary leukemia mostly AML (Dose Max - 5gm/m2)**
  - **Bleomycin - pulmonary toxicity (Dose Max – 400 U/m2) Stopped if 20% decrease in pulm. function**
  - **Alkylating agents (e.g. procarbazine & cyclophosphamide) - Sterility in males (Gender based Approach in Europe (OEPA in male and OPPA in female)(GPOH))**
- There has been a constant effort to optimize RT field and doses.

Principles and Practice of Pediatric Oncology. 6th ed. Philadelphia: Wulters Klower/Lippincott, Williams & Wilkins; 2011:639–662

RISK-ADAPTED COMBINED MODALITY THERAPY FOR CLASSIC HODGKIN LYMPHOMA

LOW RISK

TRIAL FOR LOW RISK HD

Trial	N	CT	RT	EFS	OS
GPOH-HD-95	328	OPPA (female); OEPA (male) x 2.	CR : no RT PR: 19.8-30/35 Gy IFRT	CR-97%(10 yr) PR – 92%	CR- 99%(10yr) PR – 99%
GPOH-HD-2002	195	OPPA (female); OEPA (male) x 2.	CR : no RT PR : 19.8-30/35 Gy IFRT	92.0%, (5 years) RT Vs No RT-93% Vs 91%	100% Both
CCG 5942	207	COPP/ABV x 4	CR : randomized to 21 Gy IFRT vs. no RT PR: 21 Gy IFRT	IFRT: 100% no RT:82.9% (P = 0.004) (10Yrs)	IFRT:97.1% no RT:95.9% (P = 0.05) (10Yrs)
COG AHOD0431	287	AV-PC x 3	CR : no RT PR : 21 Gy IFRT	79.8% (4 years)	99.6% (4 years)
P9426 (POG)	294	DBVE x 2–4 (based on response after 2#)	25.5 Gy IFRT	86.3% (8 years)	96.5% (8 years)
Metzger et al. (St. Jude consortium)	88	VAMP x 4	CR (2# CT): no RT PR (2# CT): 25.5 Gy IFRT	RT-89% (5 years) NO RT- 88%	100% (5 years)

British Journal of Haematology, 2015, 169, 647–660

INTERMEDIATE RISK

TRIAL FOR INTERMEDIATE RISK HD

Trial	N	CT	RT	EFS	OS
RT OPTIMISATION					
GPOH-HD-95	256	2 OPPA/OEPA + 2 COPP	CR – NO RT PR – 20-35GY	PR- 91 CR – 69 (10 yr)	PR – 98 CR - 98(10 yr)
GPOH-HD-2002	139	2 OPPA/OEPA + 2 COPP/COPDAC	19.8 GY IFRT BOOST 30-35 GY	88% (5 YRS)	99%(5 YRS)
CCG 5942	225	COPP/ABV x 6	CR : IFRT vs. no RT (21Gy) PR: 21 Gy IFRT	IFRT: 84%(NS) no RT:78% (10Yr)	100% (3Yrs)
CT OPTIMISATION					
POG9425	53	RER- 3ABVE-PC SER – 5ABVE-PC	21GY IFRT	82 88	95 95
BOTH CT AND RT OPTIMISATION					
COG AHOD0031	361	RER- 4 ABVE-PC SER – 4ABVE - PC	CR- NO RT SER/PR – 21GY IFRT	RER - 86.9% SER- 77.4% (4yrs)	RER - 98.5% SER- 95.3%
SER + DECA - 79.3% SER – DECA - 75.2% (P=0.11)			RESULTS OF AHOD0031	RER+CR+IFRT-87.9% RER+CR- IFRT - 84.3% (*P=0*.11)	

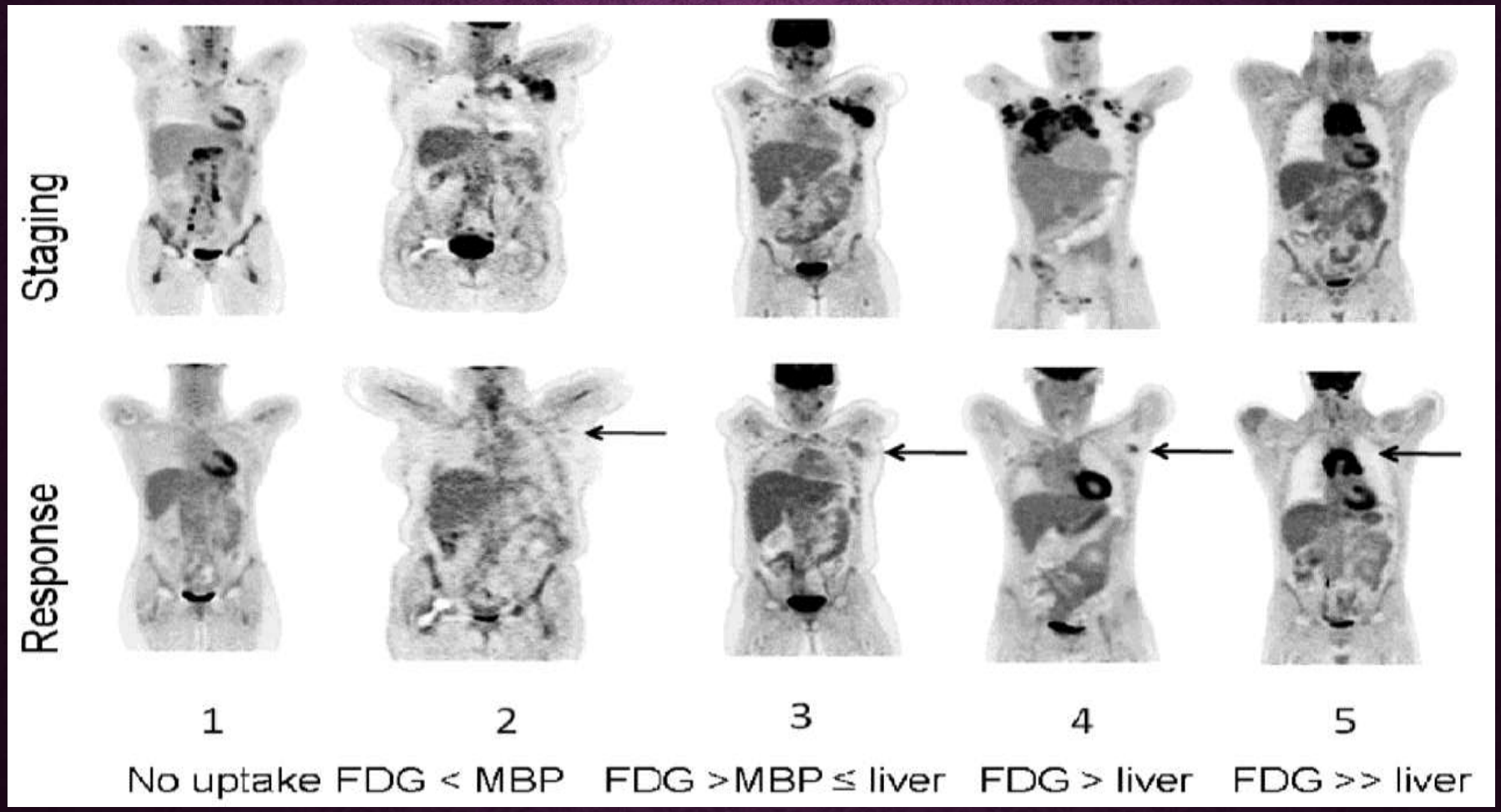
HIGH RISK

TRIAL FOR HIGH RISK HD

Trial	N	CT	RT	EFS/OS	OS
GPOH-HD-95	341	2 OPPA/OEPA + 4 COPP	CR – NO RT PR – 20-35GY	PR- 89 CR – 83 (10 Yrs)	PR – 95 CR – 100 (10Yrs)
GPOH-HD-2002	239	2 OPPA/OEPA + 4 COPP/COPDAC	19.8 GY IFRT BOOST 30-35 GY	87% (5 YRS)	95%(5 YRS)
POG 9425	163	RER- 3ABVEPC SER – 5ABVEPC	21GY IFRT	88 82	95 95
CCG 5942	66	COPP/ABV/High dose ARA - C+ Etoposide 2# each	CR : randomized to 21 Gy IFRT Vs no RT PR: 21 Gy IFRT	IFRT: 88.5% no RT:80 % NS (10Yr)	IFRT:97.1% no RT:95.9% (P = 0.05) (10Yr)
COG AHOD 0831	166	2# ABVEPC→ PETCT RER- 2# ABVEPC SER- 2#IV+2#ABVEPC	RER – 21Gy/14# (X) SER- 21Gy/14# (X+RER)	79.1% (5 yr) RER-83.5% SER – 73.2%	95%(5 yr)

RESPONSE EVALUATION

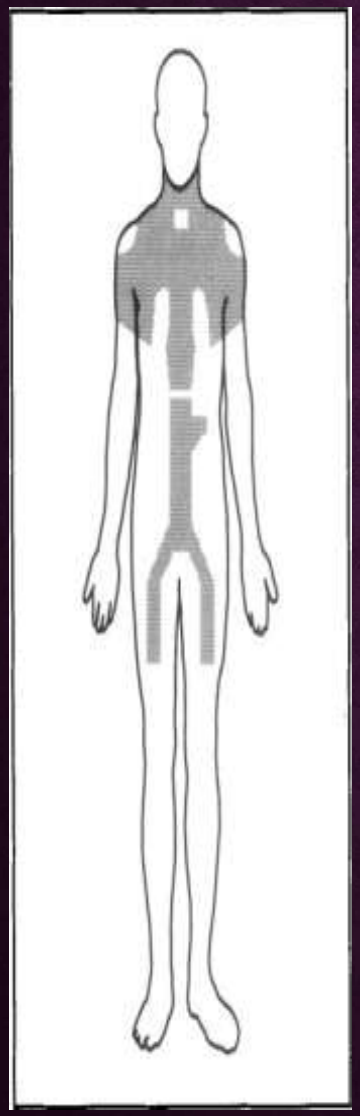
RESPONSE EVALUATION(DEAUVILLE SCORE)



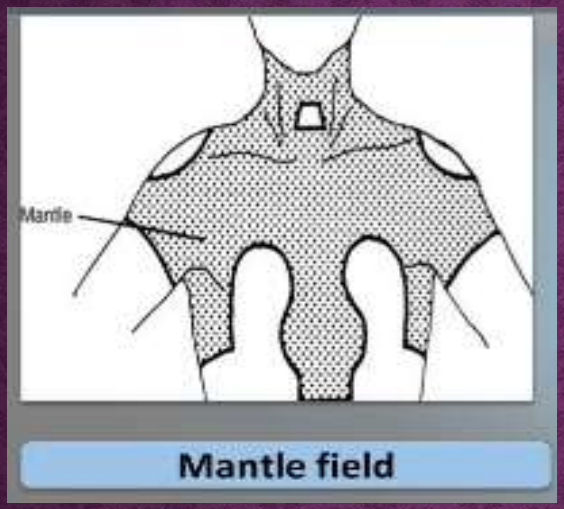
Haematologica November 2016 101: 1279-1283

RADIOTHERAPY

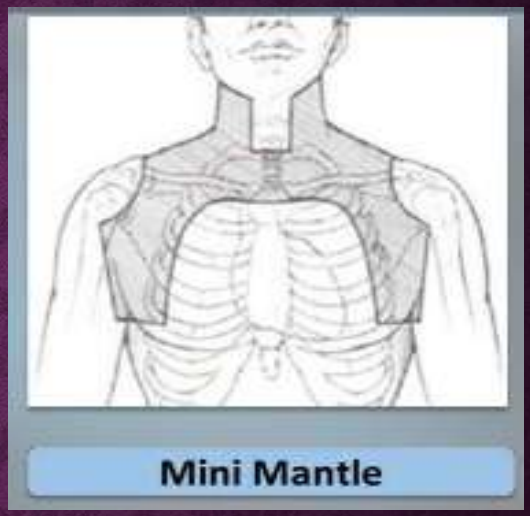
EVOLUTION OF RT FIELDS



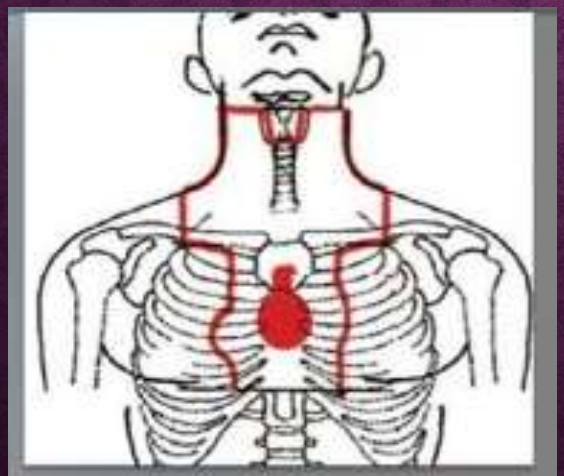
TLI



Mantle field



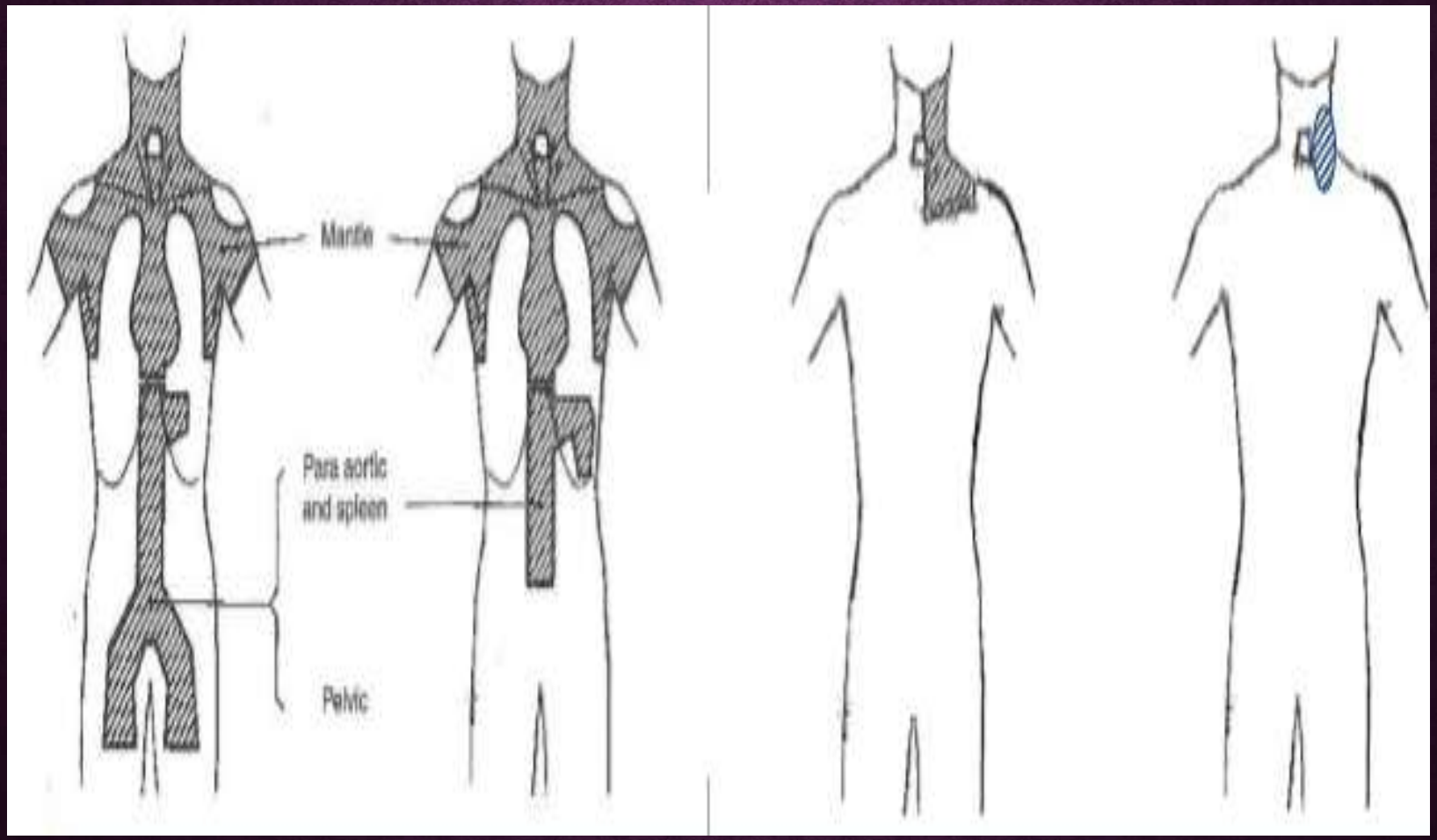
Mini Mantle



Modified Mantle

Inverted 'Y' field

EVOLUTION OF RT FIELDS



TLI STLI IFRT ISRT/INRT

IFRT

SITE	VOLUME
Unilateral neck	Unilateral neck + ipsilateral supraclavicular
Supraclavicular	Supraclavicular + mid/low neck + infraclavicular
Axilla	Axilla ± infraclavicular/supraclavicular
Mediastinum	Mediastinum + hila + infraclavicular/supraclavicular
Hila	Hila ± mediastinum
Spleen	Spleen ± adjacent para-aortics
Para-aortics	Para-aortics ± spleen
Iliac	Iliacs + inguinal/femoral

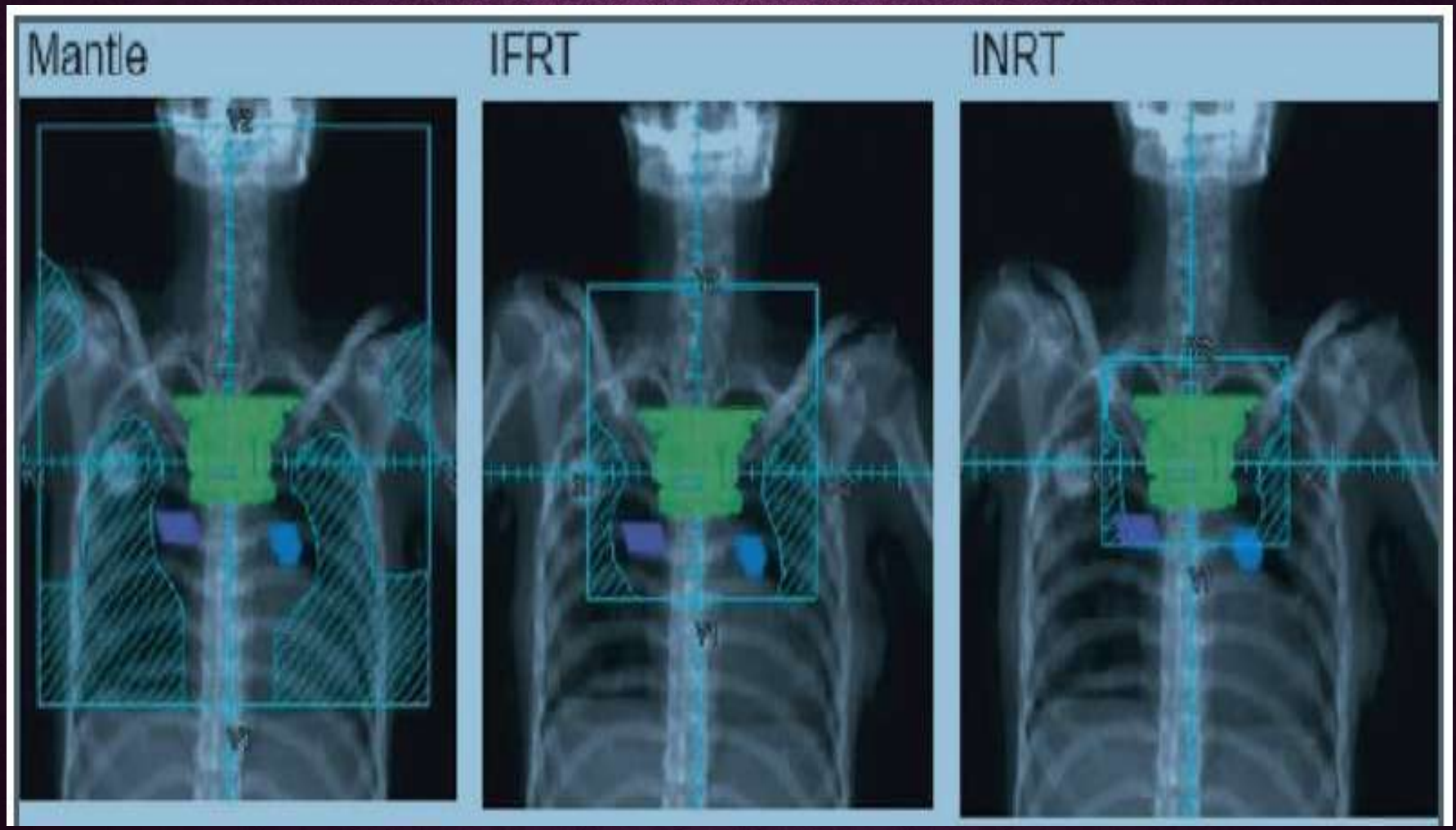
MODIFIED IFRT

- Modified involved field radiation therapy (mIFRT) is the term used in the EuroNet PHL-C1 trial
- Treatment volumes contains the involved lymph node(s) as seen before chemotherapy plus ITV-PTV margins of 1-2 cm depending on the area of involvement.
- These volumes are comparable with ISRT fields, although the development preceded the widespread availability of CT based planning.
- The subsequent EuroNet PHL-C2 trial employs INRT.

RT TECHNIQUES

IFRT	INRT	ISRT
Involved region+ 1 level up and down	Involved LN only	Involved node with adequate margin
Limited use of imaging	Solely Image dependent	Image dependent
Large field	Smallest field	Reasonably small field
Predefined adjacent lymph node groups with possibility of disease spread	Individual lymph nodes with evidence of disease at presentation	Include nodal tissue immediately adjacent to what appear to be involved nodes
Pre chemo Imaging is not required	Pre Chemo PETCT in RT treatment position and image fusion during RT planning	Pre Chemo PETCT not in treatment position or Not available

RT FIELDS



TARGET DELINEATION GUIDELINES ISRT

Practical Radiation Oncology (2014) xx, xxx–xxx

practical radiation oncology
pro
www.practicalradonc.org

Special Article

Implementation of contemporary radiation therapy planning concepts for pediatric Hodgkin lymphoma: Guidelines from the International Lymphoma Radiation Oncology Group

David C. Hodgson MD [a, b,*], Karin Dieckmann MD [c], Stephanie Terezakis MD [d], Louis Constine MD, [e] for the International Lymphoma Radiation Oncology Group

SIMULATION

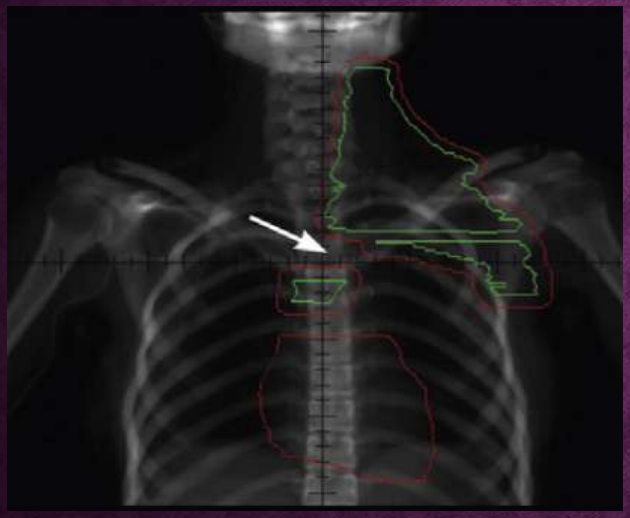
- Same as adult HL
- Occasionally May need Anesthesia
- Proper reproducible positioning with an eye on OAR and skin folds is warranted
- Fusion of staging imaging (CECT or CEPET-CT) with the planning CT dataset
- RT planning scans encompass the full extent of organs at risk (eg, lungs) to evaluate the DVH.

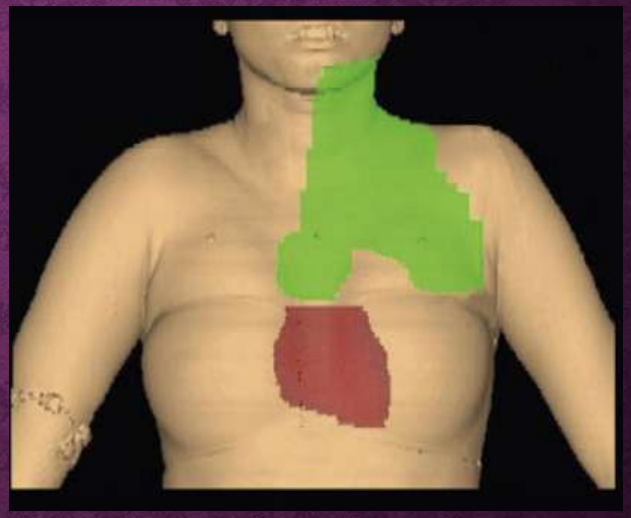
VOLUMES

- **Pre-chemotherapy GTV** - Nodal and non-nodal tissues with lymphoma involvement prior to any treatment
- **Post-chemotherapy GTV** – Residual Imaging abnormalities at initially involved sites post chemotherapy **(GTV pet –ve + GTV pet +ve)**
- **Post-chemotherapy CTV** - The CTV should include the pre-chemotherapy GTV by taking into account the reduction in axial diameter.
- In most cases, the superior and inferior extent of the post-chemotherapy CTV will be the same as the pre-chemotherapy GTV or slightly larger due to imaging uncertainty

VOLUMES

- Normal appearing nodal tissue may be included in the CTV if located between 2 anatomically close (ie, within 5 cm) sites of obvious disease involvement





- ITV - CTV with an added margin to account for variation in shape and motion within the patient.
- PTV - encompass the ITV (or CTV if no ITV expansion has been used) and accounts for geometric variation in daily setup.

OAR

Organ	Dose limit	Incidence	End point
Thyroid	>15 Gy >26 Gy	30% 65-75%	Late thyroid dysfunction
Heart	D mean <15Gy D mean < 35Gy	< 3% < 6-10%	CAD, CHF, Valvular disease, Pericarditis
Lung (Bleomycin)	V24 <30%	5%	Pneumonitis
Breast	5-10Gy ALARA	 Linear relation	Hypoplasia Breast cancer
Skeletal	8Gy	Linear relation	Growth plate effect
RT plans should not include substantial dose gradients (ie, >10-15 Gy) across vertebrae			
Soft tissue	>25-30Gy		Muscle hypoplasia
Ovaries (Alkylating Agents)	4-6 Gy		Premature Ovarian Failure
Secondary Malignancy			

LYMPHOCYTE-PREDOMINANT HODGKIN LYMPHOMA (NLPHD)

- NLPHL is considered indolent with a favorable prognosis with OS rates of close to 100%, typically presenting as a localized, early-stage disease.
- Relapse rates of 4.8% and 8.3% over 10- and 15-year respectively, with similar OS rates in patients with relapsing and non-relapsing patients.
- Increased risk of transformation to NHL in upto 5-12% of cases
- Completely resection stage IA can be observed alone
- Unresected stage IA/IIA can be treated with less intense chemo with RT only for those with poor response
- Higher stages of disease have better outcomes when treated on cHL regimens

REFRACTORY OR RELAPSED HD

- Treatment failures in pediatric HL most commonly develop within the first 3yrs.
- The most common site of relapse following risk-adapted therapy is primary site
- Favorable prognostic factors
  - Site of relapse (nodal better than extra-nodal)
  - Stage at relapse (early better than advanced)
  - Histology
  - Response to first-line salvage chemotherapy
- Chemo like Ifosfamide and Vinorelbine, ICE, MINE, GDP
- Allogeneic hematopoietic stem cell transplantation 5 Yr PFS 30% & OS 45% (Claviez et al.)
- Newer Targeted agents

NEWER AGENTS

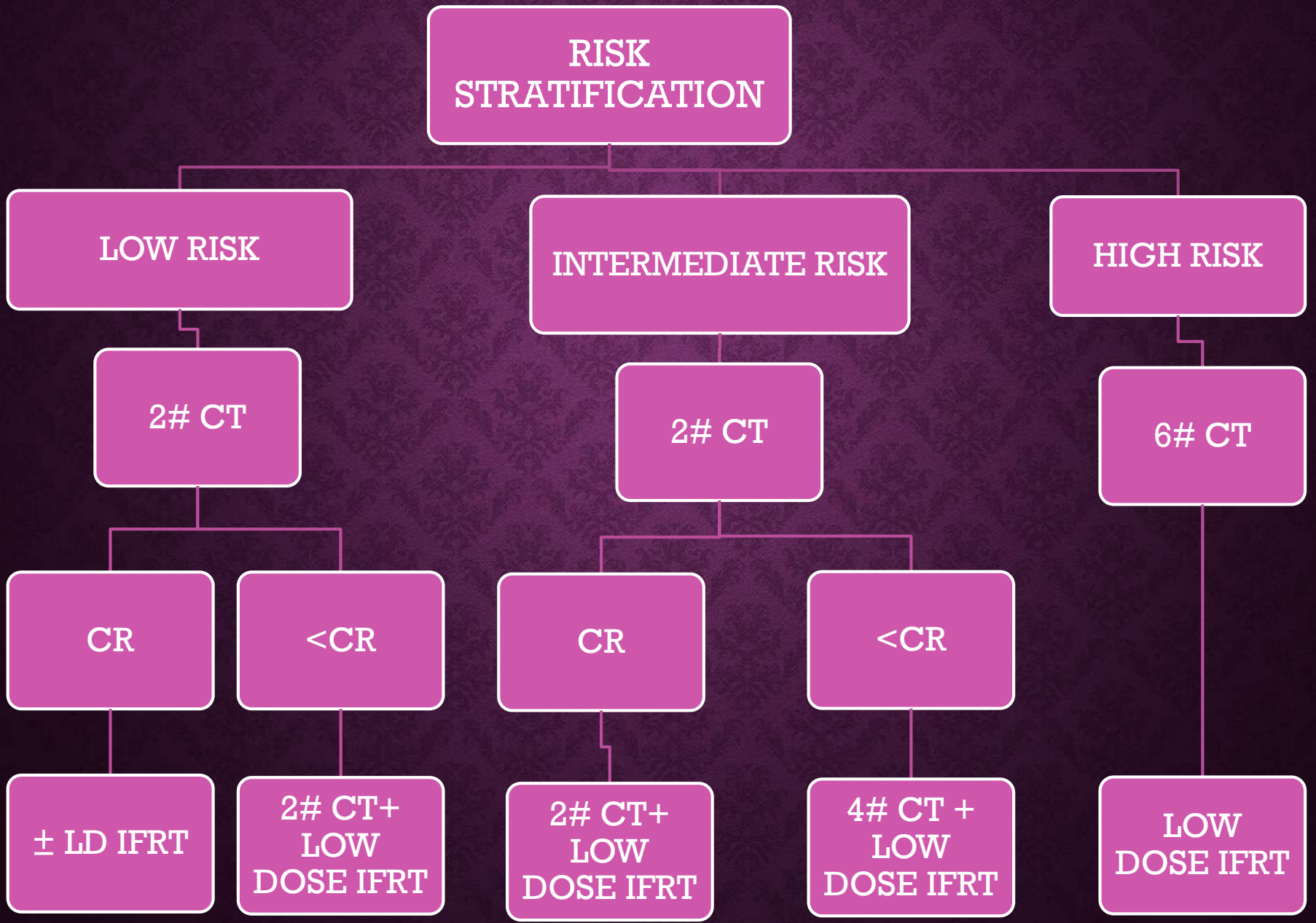
- Anti CD 30 Antibody – Brentuximab vedotin

- mTOR inhibitors – everolimus
- Histone deacetylase inhibitors- panobinostat
- Anti PD -1 Inhibitor - Nivolumab

} Under investigation

TAKE HOME MESSAGE

- The initial evaluation of the patient must be very meticulous with proper documentation of the disease with proper Risk stratification.
- As the Pediatric Hodgkin lymphoma Has very good prognosis the long term toxicity of both Chemotherapy and radiation therapy must be kept in mind while choosing treatment.
- Multi agent chemotherapy with low cumulative dose of individual agents is given along with low dose of Radiation by IFRT or ISRT/INRT.
- Treatment is response adapted.


RISK STRATIFICATION
LOW RISK
INTERMEDIATE RISK
HIGH RISK
2# CT
2# CT
6# CT
CR
<CR
CR
<CR
± LD IFRT
2# CT+ LOW DOSE IFRT
2# CT+ LOW DOSE IFRT
4# CT + LOW DOSE IFRT
LOW DOSE IFRT

RADIATION DOSES

Response	Dose	Fractions	Dose/#
CR	14.4 – 19.8Gy	8 - 11	180 cGy
< CR	25.2 – 30.6 Gy	14 - 17	180 cGy

THANK YOU