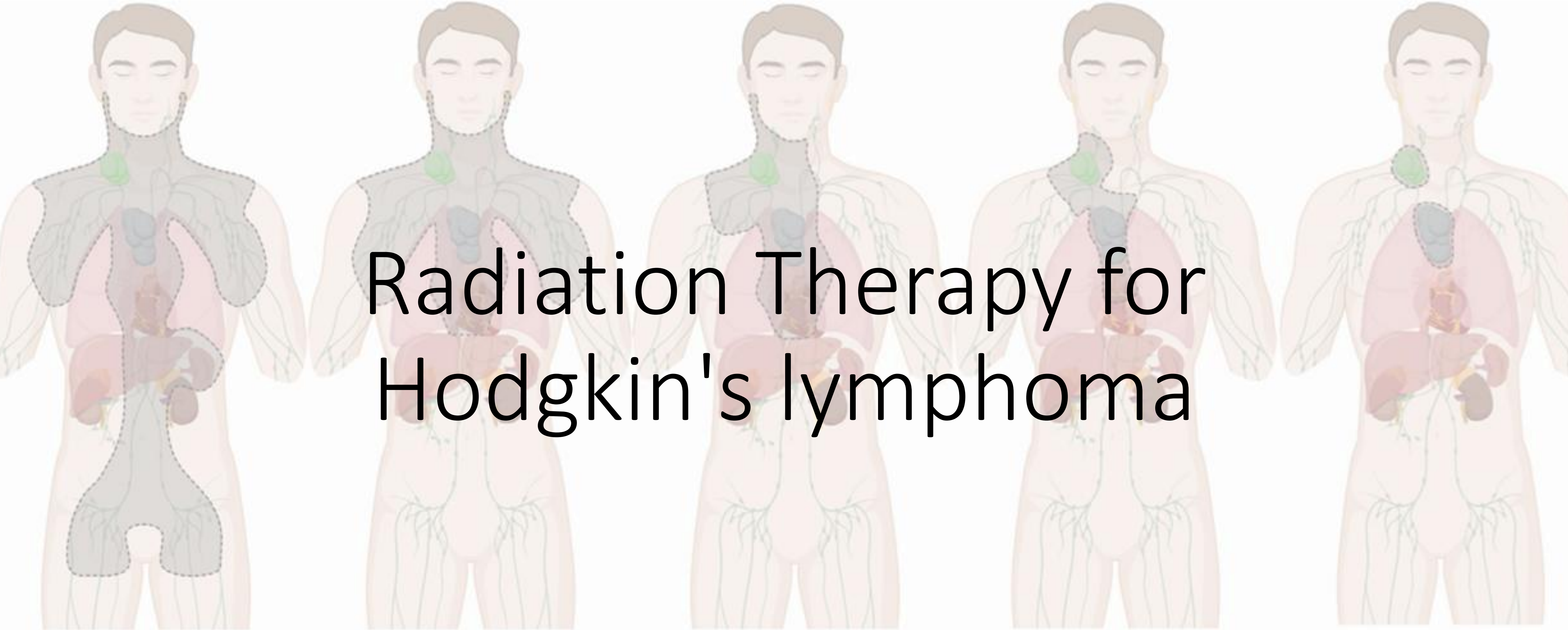
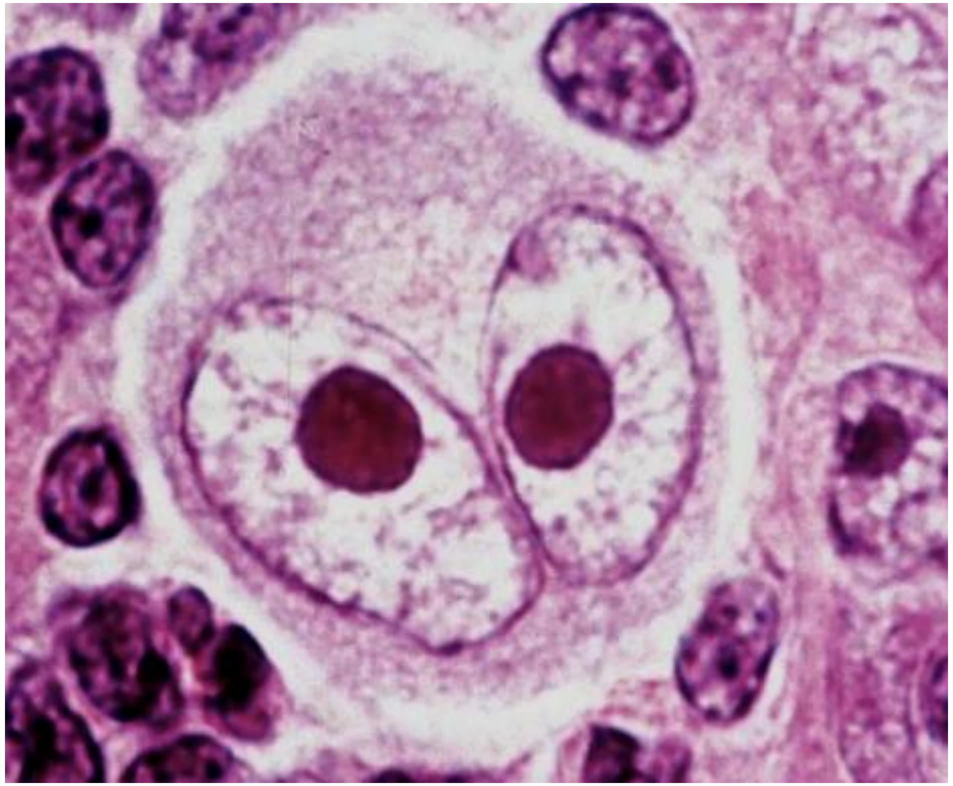


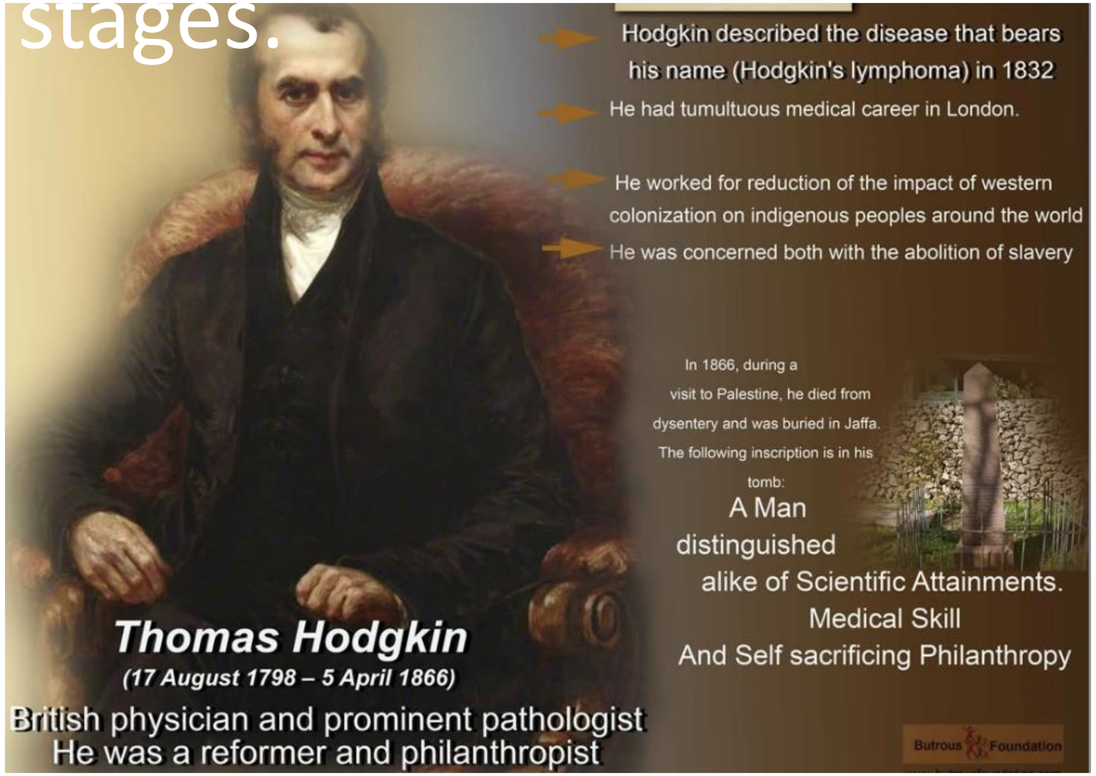
# Radiation Therapy for Hodgkin's lymphoma

Dr Kanika Sood Sharma
Director and Clinical Lead Radiation Oncology
Dharamshila Narayana Superspeciality Hospital
Delhi

# Hodgkin Lymphoma Overview

- a malignant lymphoid neoplasm characterized by
- Represents approximately 10% of all lymphomas.
- Curable with modern therapy, even in advanced stages.

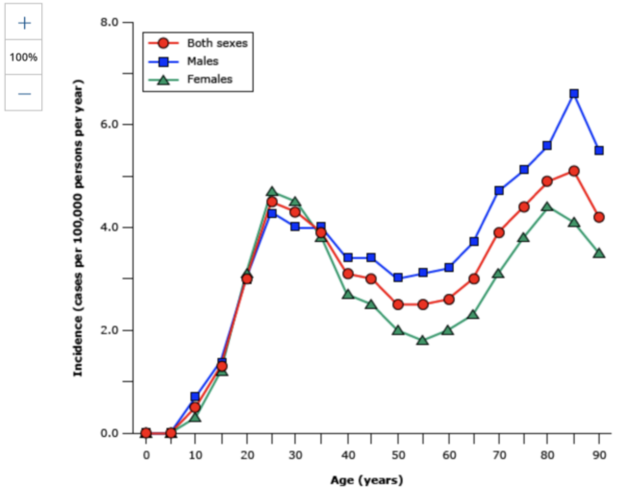




# Epidemiology

- Approx 2.5 cases/ 100,000 people annually in US; ~8,700 new cases estimated in 2025
- Represents about 0.4% of new cancer cases.
- **India: HL = 22.5% of lymphomas; median age ~38 years**
- Male: Female ratio now ~2:1 especially in pediatric population (85% in boys)
- Bimodal age distribution with peaks in young adults & older adults.

**Bimodal age distribution of Hodgkin lymphoma**




Age-specific average annual incidence rates of Hodgkin lymphoma for all races by sex per 100,000 population, 2004 to 2008, in the SEER program. Two peaks are noted: a larger peak in young adults, and a second peak in older adults.

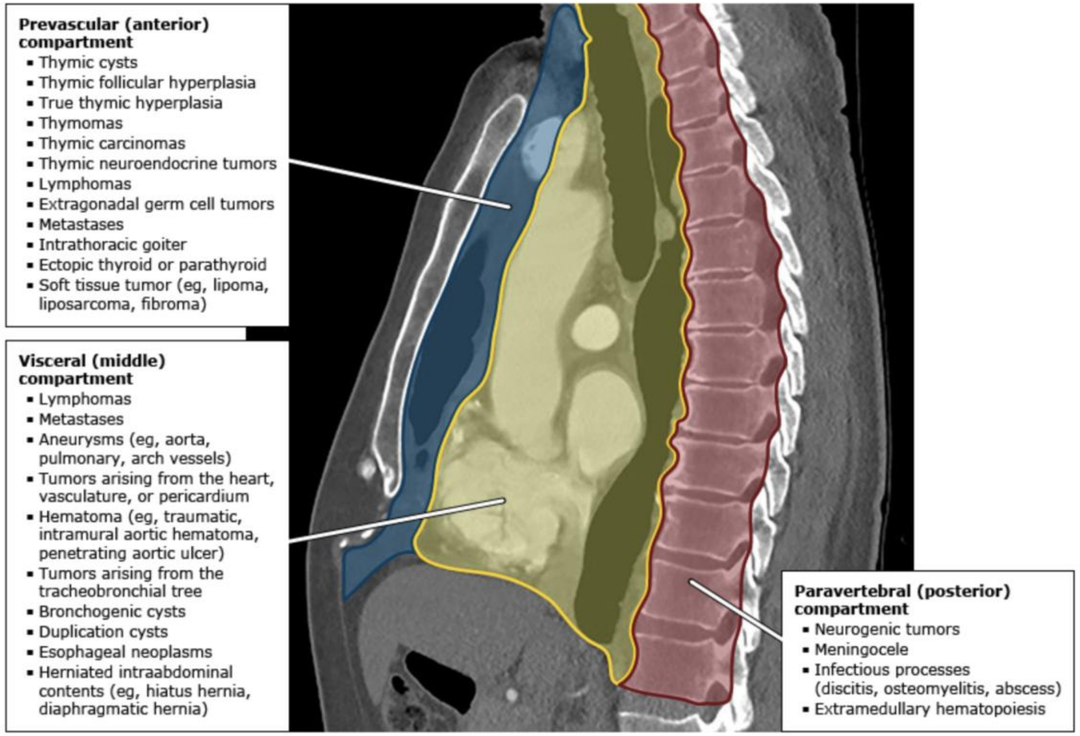
**The most common malignancies in infants, children, and adolescents**

| Cancer type | Age <1 year | Age 1 to 4 years | Age 5 to 9 years | Age 10 to 14 years | Age 15 to 19 years | All pediatric ages |
|---|---|---|---|---|---|---|
| | Percentage of all cancers | | | | | |
| Leukemias | 18 | 40 | 33 | 23 | 35 | 26 |
| Central nervous system tumors | 12 | 19 | 26 | 18 | 22 | 16 |
| Lymphoma | 7 | 8 | 14 | 19 | 22 | 16 |
| Germ cell tumors | 7 | 1 | 2 | 5 | 11 | 6 |
| Soft tissue sarcomas | 7 | 5 | 7 | 8 | 7 | 7 |
| Bone tumors | 0.2 | 0.7 | 5 | 9 | 6 | 5 |
| Neuroblastoma | 23 | 10 | 4 | 1 | 0.5 | 5 |
| Wilms and other kidney cancers | 5 | 8 | 5 | 1 | 0.8 | 4 |
| Melanoma and skin cancers | 2 | 0.7 | 3 | 14 | 27 | 12 |
| Retinoblastoma | 11 | 4 | 0.3 | <0.1 | 0 | 2 |
| Liver tumors | 6 | 3 | 1 | 0.7 | 0.6 | 2 |
| Other tumors | 1 | 0.4 | 0.4 | 0.3 | 0.5 | 0.5 |

The most common causes of pediatric cancer in the United States (2017 to 2021). The percentages for each age group correspond to the age at diagnosis. Data obtained by Data from Cancer in North America (CiNA) and the Surveillance, Epidemiology and End Results (SEER) Registries of the National Cancer Institute, submitted December 2023.

# Clinical Presentation

- (80%), often
- Mediastinal mass (up to 75% in pediatrics, bulky disease >1/3
- Systemic "B" symptoms: fever, night sweats, weight loss
- Other: hepatosplenomegaly, autoimmune cytopenias,Fatigue, pruritus,
- Extranodal involvement: possible in liver, spleen, bone
- CNS (rare)

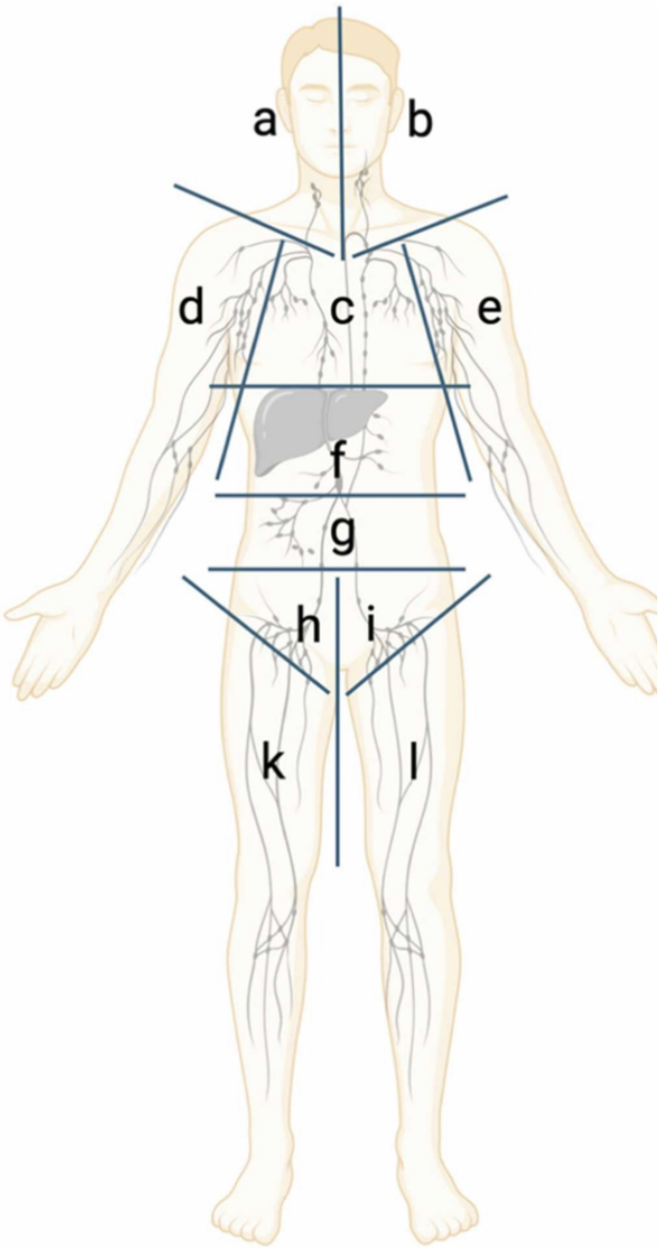



The differential diagnosis of a mediastinal mass depends upon the anatomic compartment in which it arises.

## Definitions of Lymph Node Regions*

| | | Ann Arbor | EORTC | GHSG |
|---|---|---|---|---|
| Supradiaphragmatic Nodal Regions | R Cervical/Supraclavicular | | | |
| | R ICL/Subpectoral | | | |
| | R Axilla | | | |
| | L Cervical/Supraclavicular | | | |
| | L Infraclavicular/Subpectoral | | | |
| | L Axilla | | | |
| | Mediastinum | | | |
| | R Hilum | | | |
| | L Hilum | | | |
| Infradiaphragmatic Nodal Regions | Celiac/Spleen hilar | | | |
| | Para-aortic | | | |
| | Mesenteric | | | |
| | R Iliac | | | |
| | L Iliac | | | |
| | R Inguinal/Femoral | | | |
| | L Inguinal/Femoral | | | |

*Note that the EORTC includes the infraclavicular/subpectoral area with the axilla while the GHSG includes it with the cervical. Both EORTC and GHSG combine the mediastinum and bilateral hila as a single region.




Area a: right cervical + right infra-/supra-clavicular/nuchal lymph nodes
Area b: left cervical + right infra-/supra-clavicular/nuchal lymph nodes
Area c: right/left hilar + mediastinal lymph nodes
Area d: right axillary lymph nodes
Area e: left axillary lymph nodes
Area f: lymph nodes of the upper abdomen
Area g: lymph nodes of the lower abdomen
Area h: right iliac lymph nodes
Area i: left iliac lymph nodes
Area k: right inguinal + femoral lymph nodes
Area l: left inguinal + femoral lymph nodes

# Pre-treatment Evaluation

- History: Detailed symptomology including adenopathy, B symptoms (fever, night sweats,
- Physical exam: Evaluate lymph node regions, Waldeyer's ring, hepatosplen
- Laboratory: CBC with differential, ESR, liver and renal function tests, viral serologies
- Imaging: CXR, CT, PET-CT (preferred)

Biopsy:

- Diagnosis by biopsy demonstrating HRS cells amid reactive infiltrate.
- Immunophenotyping: CD30+, CD15+ in classical HL; CD20 positive in NLPHL.
- Pathology essential for subtype classification and treatment planning.
- Excisional lymph node biopsy preferred over fine needle aspiration.

Cardiac and pulmonary function

onary

Fertility preservation counselling in reproductive-age patients

# Imaging Modalities

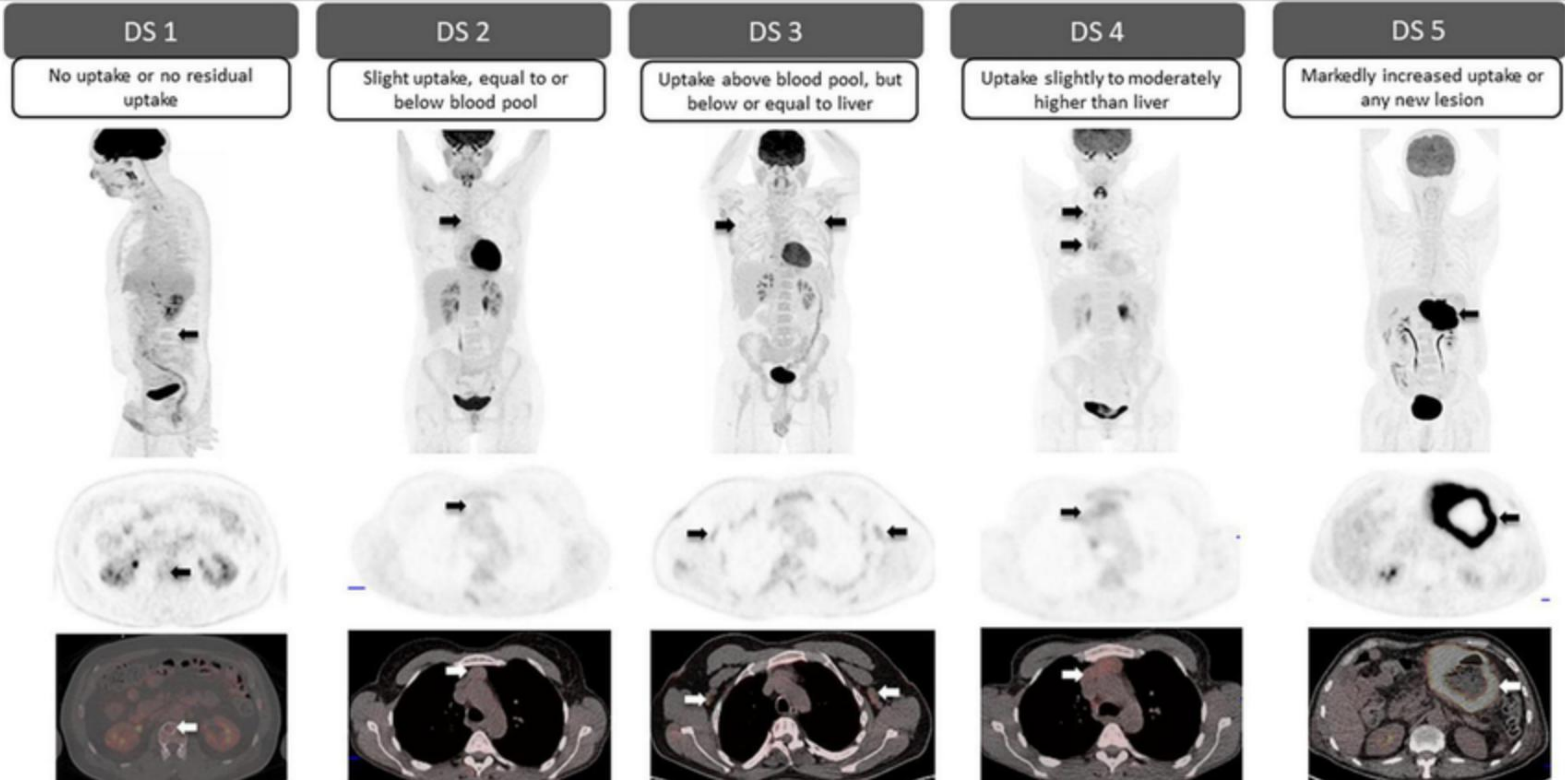
PET/CT - gold standard for staging, response assessment ,scanning from skull base to

Diagnostic CT or MRI - characterize sites especially CNS, liver, or ambiguous PET

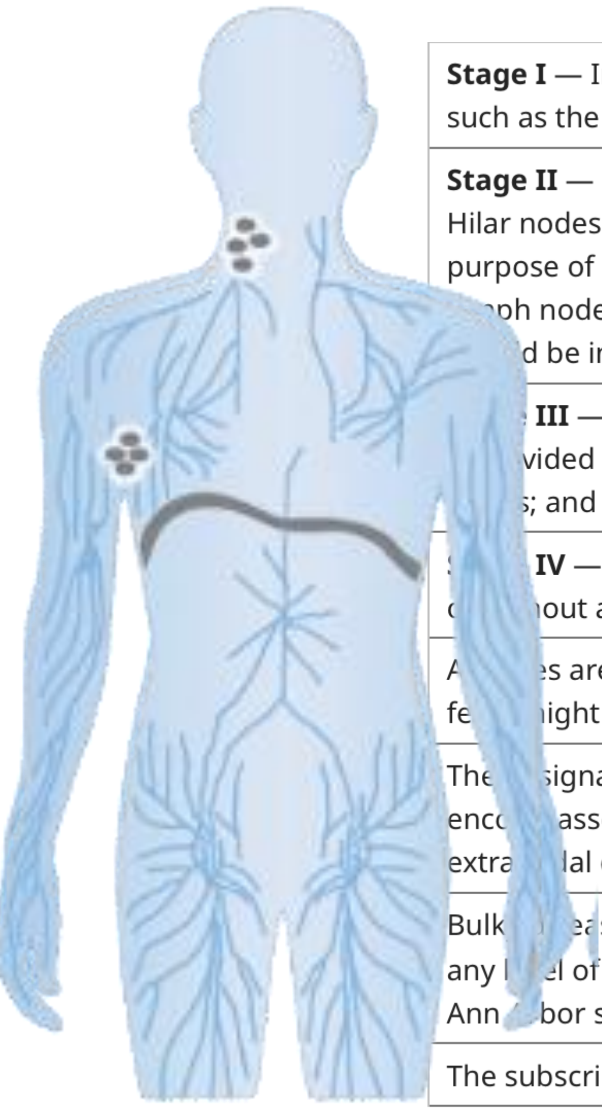
Chest radiography as adjunct for bulky mediastinal masses.

Bone marrow biopsy generally not required if PET/CT negative.

# Deauville Score for FDG PET Interpretation



# Lugano  Staging Classification(derived from Ann Arbor with Cotswolds Modifications)



**Stage I** — Involvement of a single lymph node region (eg, cervical, axillary, inguinal, mediastinal) or lymphoid structure such as the spleen, thymus, or Waldeyer's ring.

**Stage II** — Involvement of 2 or more lymph node regions or lymph node structures on the same side of the diaphragm. Hilar nodes should be considered to be "lateralized" and when involved on both sides, constitute stage II disease. For the purpose of defining the number of anatomic regions, all nodal disease within the mediastinum is considered to be a sin… …ph node region, and hilar involvement constitutes an additional site of involvement. The number of anatomic regi… …d be indicated by a subscript (eg, II-3).

…e **III** — Involvement of lymph node regions or lymphoid structures on both sides of the diaphragm. This may b… …vided stage III-1 or III-2: stage III-1 is used for patients with involvement of the spleen or splenic hilar, celiac, o… …s; and stage III-2 is used for patients with involvement of the paraaortic, iliac, inguinal, or mesenteric nodes.

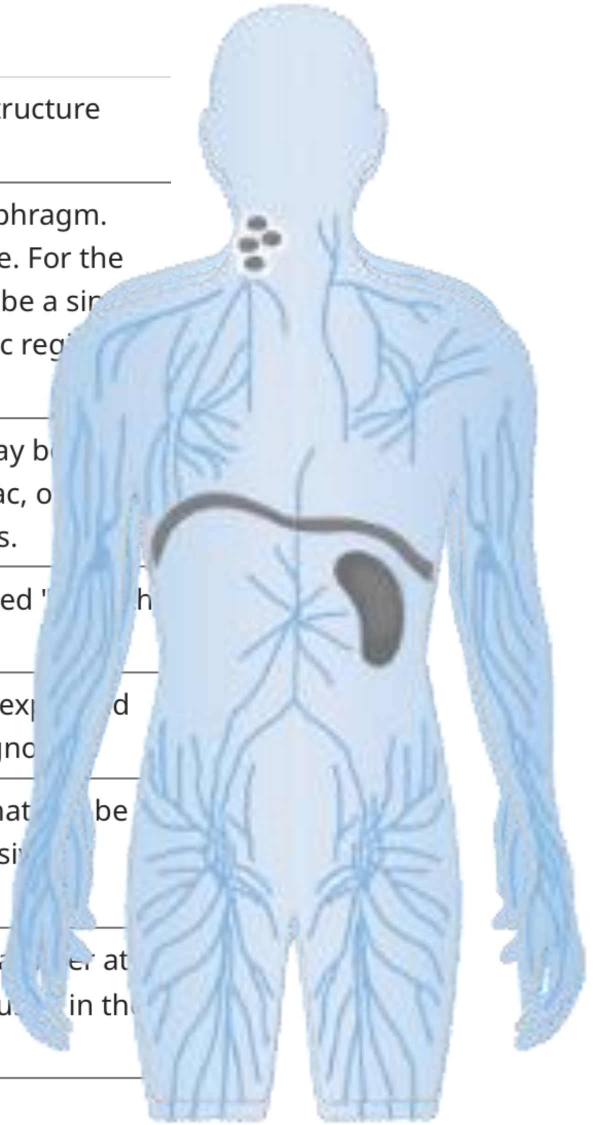
S… **IV** — Diffuse or disseminated involvement of 1 or more extranodal organs or tissue beyond that designated "… …h c… …hout associated lymph node involvement.

A… …es are subclassified to indicate the absence (A) or presence (B) of the systemic symptoms of significant unexp… …d fe… night sweats, or unexplained weight loss exceeding 10% of body weight during the 6 months prior to diagno…

The …signation "E" refers to extranodal contiguous extension (ie, proximal or contiguous extranodal disease) that … be enco…assed within an irradiation field appropriate for nodal disease of the same anatomic extent. More extensi… extra…dal disease is designated stage IV.

Bulk… …se: A single nodal mass, in contrast to multiple smaller nodes, of 10 cm or ≥⅓ of the transthoracic dia… at any l…el of thoracic vertebrae as determined by CT; record the longest measurement by CT scan. The term "X" (u… in th… Ann …bor staging system) is no longer necessary.

The subscript "RS" is used to designate the stage at the time of relapse.



# Treatment Stratification





## UNFAVORABLE RISK FACTORS

**Unfavorable Risk Factors for Stage I–II Hodgkin Lymphoma**

| Risk Factor | GHSG | EORTC | NCCN |
|---|---|---|---|
| Age | | ≥50 | |
| ESR and B symptoms | >50 if A; >30 if B | >50 if A; >30 if B | ≥50 or any B symptoms |
| Mediastinal mass[o] | MMR >0.33 | MTR >0.35 | MMR >0.33 |
| # Nodal sites | >2* | >3* | >3 |
| E lesion | any | | |
| Bulky[o] | | | >10 cm |

GHSG = German Hodgkin Study Group
EORTC = European Organization for Research and Treatment of Cancer

MMR = Mediastinal mass ratio, maximum width of mass/maximum intrathoracic diameter as measured on chest radiograph (CXR)
MTR = Mediastinal thoracic ratio, maximum width of mediastinal mass/intrathoracic diameter at T5–6 as measured on CXR

- **IPS (International Prognostic Score)**5-yr OS: 98% (score 0) → 67% (≥5 factors)
- Advanced Hodgkin lymphoma International Prognostic Index (A-HIPI) incorporates similar factors

model validated in >4000 patients (Other poor prognostic markers: EBV+, macrophage infiltration)

# Role of Radiation Therapy

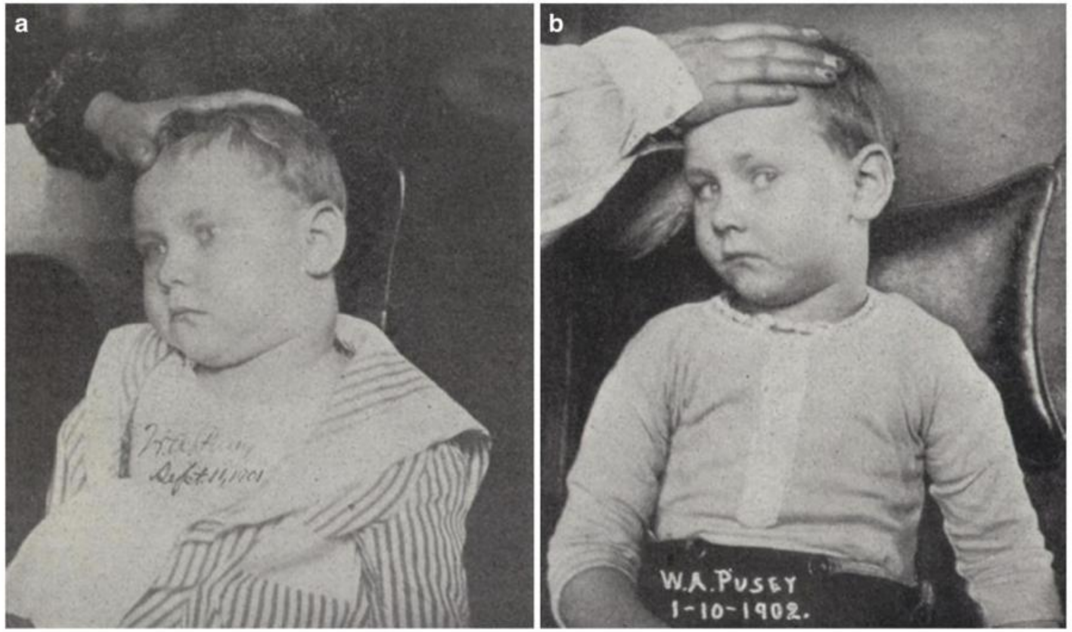



Fig. 1.1 A case of Hodgkin's disease that was treated in 1901 by W. A. Pusey, Professor of Dermatology in the Medical Department of the University of Illinois. (**a**) The patient on September 11, before the start of radiotherapy. (**b**) The condition on January 8, 1902, after the patient was treated intermittently from November 1901. This seems to be the first documented case of radiotherapy for Hodgkin's disease (from Pusey 1902)

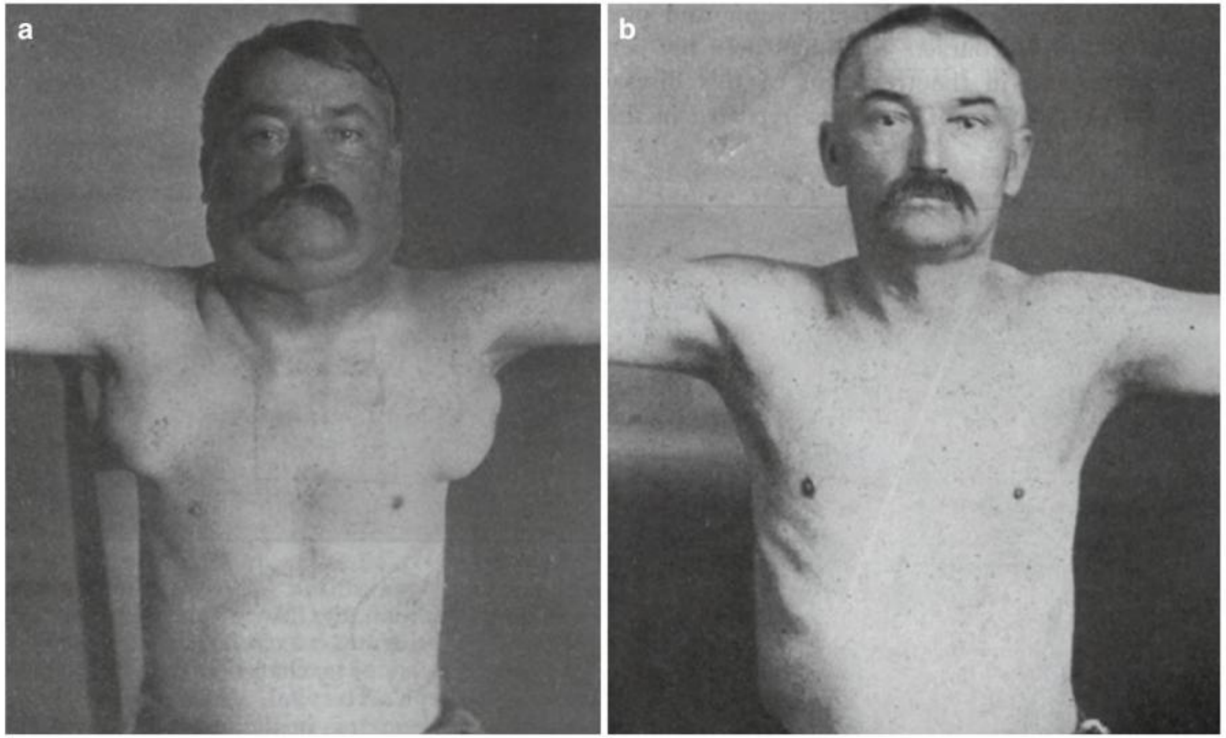



Fig. 1.2 A case of pseudoleucæmia, or Hodgkin's disease, that was treated in 1902 by N. Senn, Professor of Surgery, Rush Medical College, Chicago. (**a**) The patient before radiotherapy. (**b**) April 24, 1902, at the end of radiotherapy (from Senn 1903)

First Documented Cases Of RT(1902)

## RCTs comparing CT alone vs CMT in CS I or II Hodgkin's `lymphoma

| Trial | Patient population | No. patients | Treatment arms | Median follow-up | Results |
|---|---|---|---|---|---|
| Aviles et al. | CS I–II supradiaphragmatic, bulky disease | 99 | 6×ABVD | 11.4 years | DFS (12 years) 48%, OS (12 years) 59% |
| | | 102 | 6×ABVD+MFRT | | DFS (12 years) 76%, OS (12 years) 88% |
| Bloomfield et al. | "Poor prognosis" PS I or II | 18 | 6×CVPP | 1.8 years | Complete remission 61% |
| | | 19 | 6×CVPP+IFRT | | Complete remission 95% |
| Eghbali et al. | CS I–II without risk factors (see Table 2.1, EORTC criteria), in CR after 6×EBVP | 130 | 6×EBVP | 4.3 years | EFS (5 years) 69%, OS (5 years) 97% |
| Noordijk et al. | | 448 | 6×EBVP+IFRT (20 or 36 Gy) | | EFS (5 years) 87%, OS (5 years) 99% |
| Pavlovsky et al. | CS I–II | 142 | 6×CVPP | 4 years | DFS (7 years) 62%, OS (7 years) 82% |
| | | 135 | 3×CVPP+IFRT (30 Gy)+3×CVPP | | DFS (7 years) 71%, OS (7 years) 89% |
| Straus et al. | CS I–II and CS IIIA (13% of pts.), no bulky disease | 76 | 6×ABVD | 5.6 years | FFP (5 years) 81%, OS (5 years) 90% |
| | | 76 | 6×ABVD+IFRT or modified EFRT (36 Gy) | | FFP (5 years) 86%, OS (5 years) 97% |

CS: clinical stage; PS: pathological stage; ABVD: adriamycin, bleomycin, vinblastine, dacarbazine; CVPP: cyclophosphamide, vinblastine, procarbazine, prednisone; EBVP: epirubicine, bleomycin, vinblastine, prednisone; MFRT: mantle field radiotherapy; IFRT: involved-field radiotherapy; EFRT: extended-field radiotherapy; DFS: disease-free survival; EFS: event-free survival; FFP: freedom from disease progression; OS: overall survival

**Table 2.3** Randomized controlled trials comparing chemotherapy alone with chemotherapy combined with radiotherapy in newly diagnosed early-stage Hodgkin lymphoma. Trials with less than 80% of patients in CS I or II, and trials where the number of chemotherapy cycles varied between treatment arms

| Trial | Patient population | No. patients | Treatment arms | Median follow-up | Results |
|---|---|---|---|---|---|
| Laskar et al. | All stages included, in CR after 6×ABVD. Here are only CS-I-II included | 44 | 6×ABVD | 5.3 years | EFS (8 years) 94%, OS (8 years) 98% |
| | | 55 | 6×ABVD+IFRT | | EFS (8 years) 97%, OS (8 years) 100% |
| Nachman et al. | Children with any stage in CR after chemotherapy. Here are only CS I-II included | 173 | 4×COPP/ABV (no adverse factors) | Not reported | EFS (3 years) 91%, OS (3 years) 100% |
| | | | 6×COPP/ABV (adverse factors) | | EFS (3 years) 83%, OS (3 years) 100% |
| | | 189 | 4×COPP/ABV+IFRT (21 Gy) (no adverse factors) | | EFS (3 years) 97%, OS (3 years) 100% |
| | | | 6×COPP/ABV+IFRT (21 Gy) (adverse factors) | | EFS (3 years) 87%, OS (3 years) 95% |
| O'Dwyer et al. | CS IB-IIIA | 17 | 6×MOPP | 6 years | Four relapsed, two died |
| | | 16 | EFRT+6×MOPP | | Three relapsed, three died |
| Picardi et al. | CS I-IV with bulky disease (≥5 cm) with residual PET mass after chemotherapy | 80 | 6×VEBEP | 3.3 years | EFS (5 years) 86%, OS (5 years) 100% |
| | | 80 | 6×VEBEP+IFRT (32 Gy) | | EFS (5 years) 96%, OS (5 years) 100% |
| Kung et al. | PS I–IIIA, children | 78 | 6×MOPP/ABVD | 8.3 years | EFS (8 years) 83%, OS (8 years) 94% |
| | | 81 | 4×MOPP/ABVD+IFRT (25.5 Gy) | | EFS (8 years) 91%, OS (8 years) 97% |
| Meyer et al. | CS I-IIA, without bulk (≤10 cm), unfavorable (see Table 2.1, NCIC criteria) | 137 | 4–6×ABVD | 4.2 years | FFP (5 years) 88%, OS (5 years) 95% |
| | | 139 | 2×ABVD+STNI (35 Gy) | | FFP (5 years) 95%, OS (5 years) 92% |

CR: complete remission; CS: clinical stage; PS: pathological stage; ABVD: adriamycin, bleomycin, vinblastine, dacarbazine; COPP: cyclophosphamide, vincristine, procarbazine, prednisone; MOPP: mechlorethamine, vincristine, procarbazine, prednisone; VEBEP: etoposide, epirubicine, bleomycin, cyclophosphamide, prednisone; IFRT: involved-field radiotherapy; EFRT: extended-field radiotherapy; STNI: subtotal nodal radiotherapy; EFS: event-free survival; FFP: freedom from disease progression; OS: overall survival

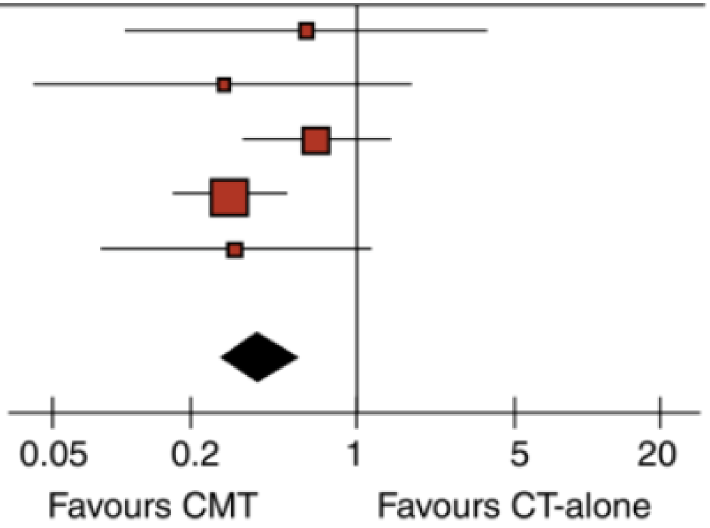
# Rationale of usage of RT in early disease

| Study | Weight | Hazard Ratio Random, 95% CI |
|---|---|---|
| CALGB 7751 | 5.1% | 0.63 [0.11, 3.65] |
| EORTC-GELA H9-F | 4.6% | 0.27 [0.04, 1.74] |
| GATLA 9-H-77 | 30.7% | 0.68 [0.33, 1.40] |
| Mexico B2H031 | 50.4% | 0.29 [0.17, 0.51] |
| MSKCC trial #90-44 | 9.2% | 0.31 [0.08, 1.14] |
| **Total (95% CI)** | **100.0%** | **0.40 [0.27, 0.59]** |

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 3.89$, df = 4 (P = 0.42): $I^2 = 0\%$

Test for overall effect: Z = 4.57 (P < 0.00001)

**Hazard Ratio Random, 95% CI**




CT vs CMT Approach…Metaanalysis

13 randomized clinical trials Multiagent CT+RT Vs Radiation alone
At 10 years RFSR 85% and 67% p=0.00001 10-year OAS 79% and 76% (p=0.07).

Herbst et al

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

# Two Cycles of Doxorubicin, Bleomycin, Vinblastine, and Dacarbazine Plus Extended-Field Radiotherapy Is Superior to Radiotherapy Alone in Early Favorable Hodgkin's Lymphoma: Final Results of the GHSG HD7 Trial

*Andreas Engert, Jeremy Franklin, Hans Theodor Eich, Corinne Brillant, Susanne Sehlen, Claudio Cartoni, Richard Herrmann, Michael Pfreundschuh, Markus Sieber, Hans Tesch, Astrid Franke, Peter Koch, Maike de Wit, Ursula Paulus, Dirk Hasenclever, Markus Loeffler, Rolf-Peter Müller, Hans Konrad Müller-Hermelink, Eckhart Dühmke, and Volker Diehl*

From the First Department of Internal Medicine, Coordination Center for Clinical Trials, and Department of Radiotherapy, University Hospital of Cologne, Cologne; Department of Radiation Oncology, Ludwig-Maximillans Universität München, München; First Department of Internal Medicine, University Hospital of Hamburg; Department of Internal Medicine II, University Hospital Eppendorf, Homburg; Department of Internal Medicine, Kreiskrankenhaus, Gummersbach; Practice for Hematology and Oncology, Diakonie-Hospital, Frankfurt; Department of Hematology, Otto v. Guericke University, Magdeburg; Department of Oncology, University Hospital of Münster, Münster; Institute for Medical Informatics, Statistics and Epidemiology, University of Leipzig, Leipzig; Institute of Pathology, University of Würzburg, Würzburg, Germany; Sezione EMATOLOGIA, Università degli studi "La Sapienza," Roma, Italy; and the Swiss Group for Clinical Cancer Research, Bern, Switzerland.

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## ABSTRACT

**Purpose**
To investigate whether combined-modality treatment (CMT) with two cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) followed by extended-field radiotherapy (EF-RT) is superior to EF-RT alone in patients with early favorable Hodgkin's lymphoma (HL).

**Patients and Methods**
Between 1993 and 1998, 650 patients with newly diagnosed, histology-proven HL in clinical stages IA to IIB without risk factors were enrolled onto this multicenter study and randomly assigned to receive 30 Gy EF-RT plus 10 Gy to the involved field (arm A) or two cycles of ABVD followed by the same radiotherapy (arm B).

**Results**
At a median observation time of 87 months, there was no difference between treatment arms in terms of complete response rate (arm A, 95%; arm B, 94%) and overall survival (at 7 years: arm A, 92%; arm B, 94%; $P = .43$). However, freedom from treatment failure was significantly different, with 7-year rates of 67% in arm A (95% CI, 61% to 73%) and 88% in arm B (95% CI, 84% to 92%; $P \leq .0001$). This was due mainly to significantly more relapses after EF-RT only (arm A, 22%; arm B, 3%). No patient treated with CMT experienced relapse before year 3. Relapses were treated mainly with bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone, or with the combination cyclophosphamide, vincristine, procarbazine, and prednisone/ABVD; treatment of relapse was significantly more successful in arm A than in arm B ($P = .017$). In total, there were 39 second malignancies, with 21 in arm A and 18 in arm B, respectively. The incidence was approximately 0.8% per year during years 2 to 9 and was highest in older patients ($P < .0001$) and those with "B" symptoms ($P = .012$).

**Conclusion**
CMT consisting of two cycles of ABVD plus EF-RT is more effective than EF-RT alone.

- More relapses after EFRT
- CMT- lesser incidence of Second malignancies

# Approach to Early-Stage cHL

Standard: ABVD chemotherapy (2 cycles)

Interim PET after 2 cycles (PET2) = pivotal decision point

CR (Deauville 1–3): Chemo + ISRT (based on GHSG criteria, location, toxicity)

PET2 Response & Management

PR or less: escalation or combined modality treatment

Deauville 4 (single site): Add 2 cycles ABVD → PET4 → RT if remission

Deauville 4–5 (multiple): Biopsy → if positive: treat as refractory HL

*Leukemia & Lymphoma*, September 2007; 48(9): 1721 – 1727



ORIGINAL ARTICLE: CLINICAL

# Randomized comparison of consolidation radiation *versus* observation in bulky Hodgkin's lymphoma with post-chemotherapy negative positron emission tomography scans

MARCO PICARDI[1], AMALIA DE RENZO[1], FABRIZIO PANE[1], EMANUELE NICOLAI[2], ROBERTO PACELLI[3], MARCO SALVATORE[3], & BRUNO ROTOLI[1]

[1]*Department of Biochemistry and Medical Biotechnology, Federico II University Medical School, Naples, Italy,* [2]*SDN, Istituto di Ricerca Diagnostica-Nucleare, Naples, Italy, and* [3]*Department of Biomorphological and Functional Sciences, Federico II University Medical School, Naples, Italy*

*(Received 21 April 2007; revised 27 June 2007; accepted 6 July 2007)*

**Abstract**

This study aimed at evaluating the role of consolidation radiation in a setting of Hodgkin's lymphoma (HL) patients, using event-free survival (EFS) as end point. Among 260 patients treated with induction chemotherapy for bulky HL, 160 patients achieved negative residual masses at 2-[18F]fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) scans. They were randomly divided into two well-matched groups to receive either 32 Gy radiotherapy to bulky area or no further therapy. At a median follow-up of 40 months, histology showed a malignancy in 14% of patients in the chemotherapy-only group (HL, 11 patients) and in 4% of patients in the chemotherapy + radiotherapy group (HL, 2 patients; carcinoma in previously irradiated area, 1 patient) ($P = 0.03$). All the relapses in the chemotherapy-only group involved the bulky site and the contiguous nodal regions. Thus, the overall diagnostic accuracy of FDG-PET to exclude future relapses in the patients nonprotected by radiotherapy was 86% with a false-negative rate of 14%. Our study suggests that the addition of irradiation helps improve EFS in HL patients with post-chemotherapy FDG-PET-negative residual masses.

**Keywords:** *Hodgkin's lymphoma, bulky disease, radiotherapy, FDG-PET*

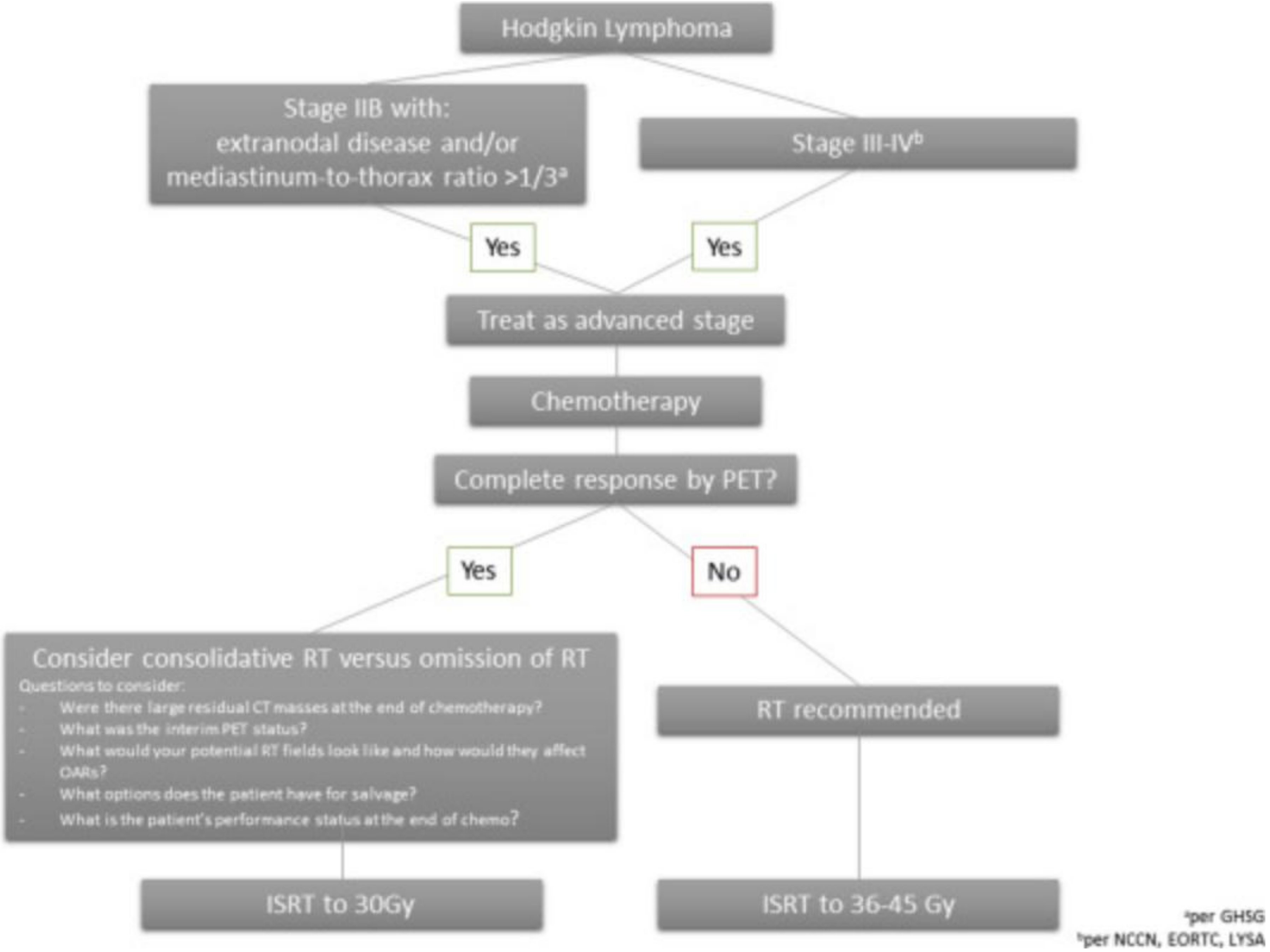
# RT in advanced disease

| | Stage | Treatment | Time[a] years | DFS/EFS/FFS/RFS % | DFS/EFS/FFS/RFS P | OS % | OS P |
|---|---|---|---|---|---|---|---|
| *Chemotherapy only* | | | | | | | |
| CALGB (Canellos et al. 1992) $n=361$ | IIIA2, IIIB and IVA or IVB | A:6–8 MOPP alone, no radiotherapy | 5 | 50 | B versus other 0.02 | 66 | B versus other 0.28 |
| | | B:MOPP alternating with ABVD 12 cycles, no radiotherapy | 5 | 65 | | 75 | |
| | | C:6–8 ABVD alone, no radiotherapy | 5 | 61 | | 73 | |
| CALGB/ECOG/SWOG/NCIC (Duggan et al. 2003) $n=856$ | $III_2A$, IIIB or IV or relapse after definitive radiotherapy | A:8–10 ABVD, no radiotherapy | 5 | 63 | 0.42 | 82 | 0.82 |
| | | B:8–10 MOPP-ABV hybrid, no radiotherapy | 5 | 66 | | 81 | |
| *Chemotherapy with or without radiotherapy (by randomization)* | | | | | | | |
| SWOG 7807 (Fabian et al. 1994) $n=278$ | III or IV HL in CR after chemotherapy | A:6 MOP-BAP, no radiotherapy | 5 | 66 | >0.2 | 79 | 0.14 |
| | | B:6 MOP-BAP + IFRT | 5 | 74 | | 86 | |
| GELA H89 (Ferme et al. 2000; Ferme et al. 2006) $n=533$ | IIIB/IV in CR or good PR after six cycles of chemotherapy | A:8 MOPP-ABV hybrid | 10 | 76 | 0.09[b] | 78 | 0.03[c] |
| | | B:6 MOPP-ABV hybrid + (S)TNI | 10 | 79 | | 82 | |
| | | C:8 ABVPP | 10 | 70 | | 90 | |
| | | D:6 ABVPP + (S)TNI | 10 | 76 | | 77 | |
| EORTC 20884 (Aleman et al. 2003a) $n=739$ | IIIA or IV in CR after chemotherapy | A:6–8 MOPP-ABV, no further treatment | 5 | 84 | 0.35 | 91 | 0.07 |
| | | B:6–8 MOPP-ABV + IFRT | 5 | 79 | | 85 | |
| *Chemotherapy and radiotherapy on indication* | | | | | | | |
| Stanford V (Horning et al. 2000) $n=47$ | III or IV or bulky mediastinal disease | Stanford V + radiotherapy in case of bulky mediastinal disease, nodal masses ≥5 cm, macroscopic nodules in an intact spleen on CT scan | 5 | 83 | – | 96 | – |
| GHSG HD9 (Diehl et al. 2003; Diehl et al. 2004) $n=1,201$ | unfavorable stage IIB or IIIA or stage IIIB or IV | A:COPP-ABVD + radiotherapy on originally bulky disease or residual tumor | 7 | 67 | A versus B versus C: <0.001 | 79 | A versus B versus C: 0.004 |
| | | B:BEACOPP baseline + radiotherapy on originally bulky disease or residual tumor | 7 | 75 | | 84 | |
| | | C:BEACOPP escalated + radiotherapy on originally bulky disease or residual tumor | 7 | 84 | | 90 | |

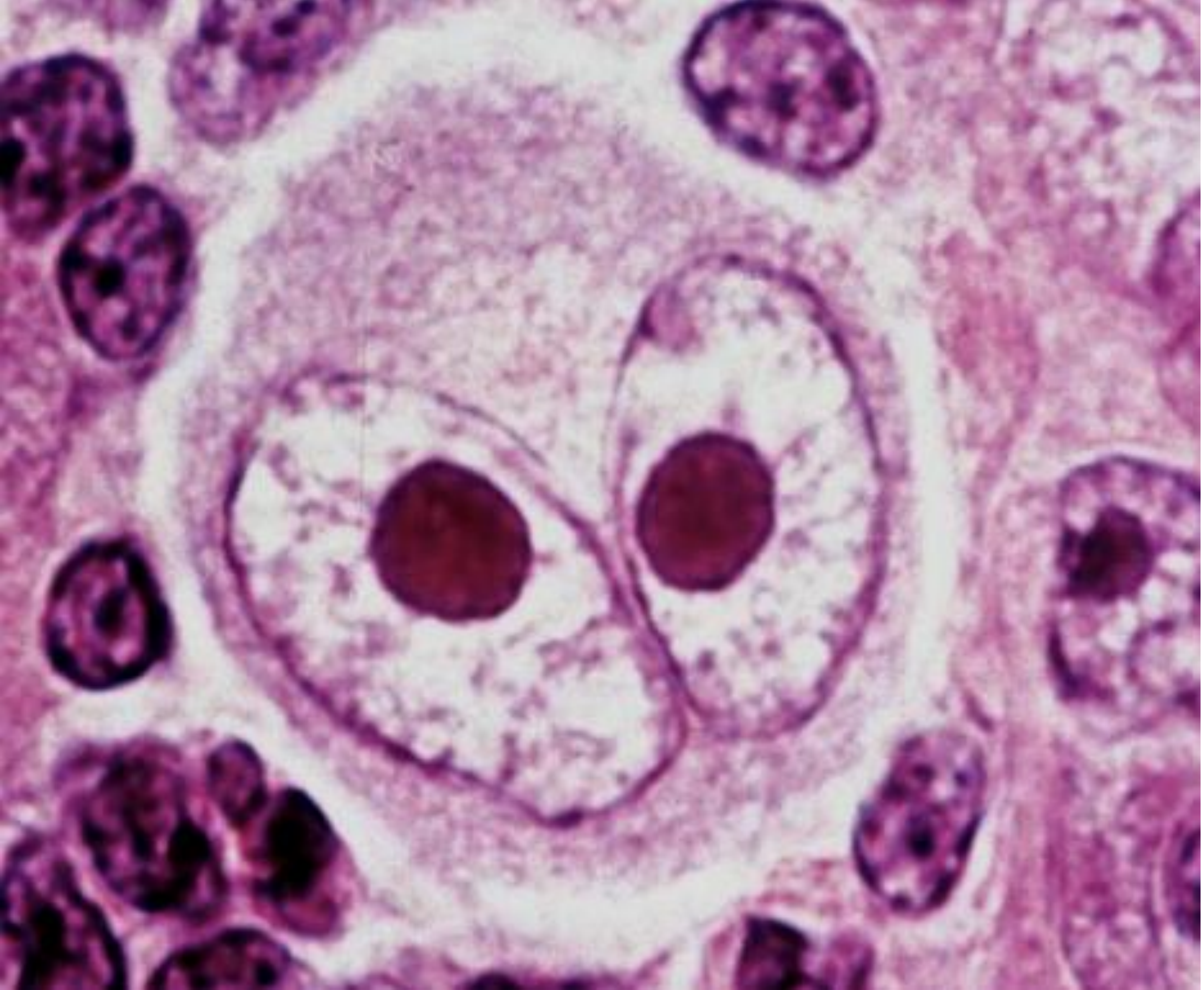
# RT Details of studies incorporating RT in advanced Hodgkin's Lymphoma

| Trial | Radiation fields | PET era | Radiation dose |
|---|---|---|---|
| UK Lymphoma Group LY09[4] | Initial bulky disease (>1/3 transthoracic ratio or >10 cm outside of chest) or residual CT mass | No | Variable (minimum 30 Gy ranging to >39 Gy) |
| EORTC[11] | IFRT to all sites of originally involved nodal areas + extranodal sites with or without a boost | No | 24 Gy to nodal sites if CR; 30 Gy (± 4-10 Gy boost) to nodal sites if PR; 18-24 Gy to extranodal sites |
| GHSG HD12[12] | Sites of initial bulky disease (defined as ≥5 cm) or residual disease ≥1.5 cm on CT; also bone lesions with instability risk; whole anatomic region encompassed in volume | No | 30 Gy |
| GHSG HD15[7] | RT for persistent postchemotherapy PET-avid mass ≥2.5 cm and bone lesions regardless of residual PET activity if instability/fracture risk; 1.5 cm margin used | Yes | 30 Gy |
| ECOG E2496[14] | Bulky disease (defined as mass greater than one-third of the maximum intrathoracic diameter on standing posteroanterior chest x-ray in ABVD arm; any pretreatment sites of disease >5 cm in Stanford V arm) | No | 36 Gy |
| GITIL/FIL trial HD 0607[15] | Bulky disease (defined as ≥5 cm) | Yes | 30 Gy |
| FIL trial HD 0801 (abstract only)[16] | Bulky disease (any initial mass with diameter >5 cm) | Yes | Not yet reported |

*Abbreviations*: CR = complete response, CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; EORTC = European Organization for Research and Treatment; FIL = Fondazione Italiana Linfomi; IFRT = involved-field radiation therapy; GHSG = German Hodgkin Study Group; GITIL/FIL = Gruppo Italiano Terapie Innovative nei Linfomi/Fondazione Italiana Linfomi; PET = positron emission tomography, PR = partial response.




Advances in Radiation Oncology (2020) 5, 809-816



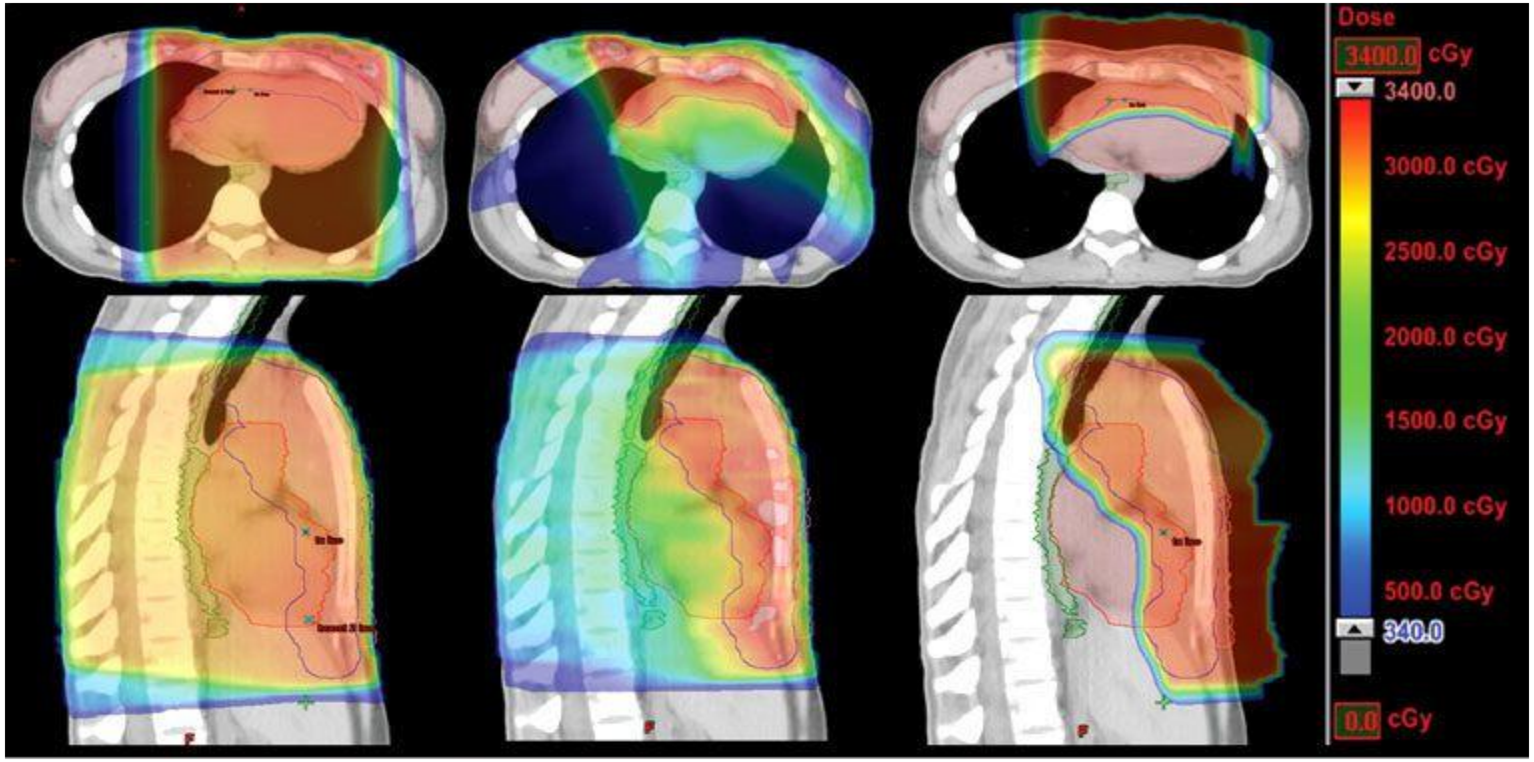
# RT planning Hodgkin's lymphoma

Dr Vera Peters Pioneer of curative RT in Hodgkins Lymphoma

Prof Maurice Tubiana –Founder Lymphoma Group EORTC

# Choosing the right technique

- Most clinical scenarios, 3D conformal trt planning & opposed-field trt is appropriate
- IMRT - better dose conformality, improved DVH criteria for heart, coronary arteries, esophagus & lungs
- IMRT leads to low-dose “bath,” which may put larger volumes of normal tissue at risk for development of secondary cancer
- IMRT may be most useful in situations of re-irradiation




Color-wash dose distributions for 3 different plans for treating mediastinal HL: for conventional photon 3D conformal AP/PA fields (left), IMRT photon (middle), and anterior proton field (right).

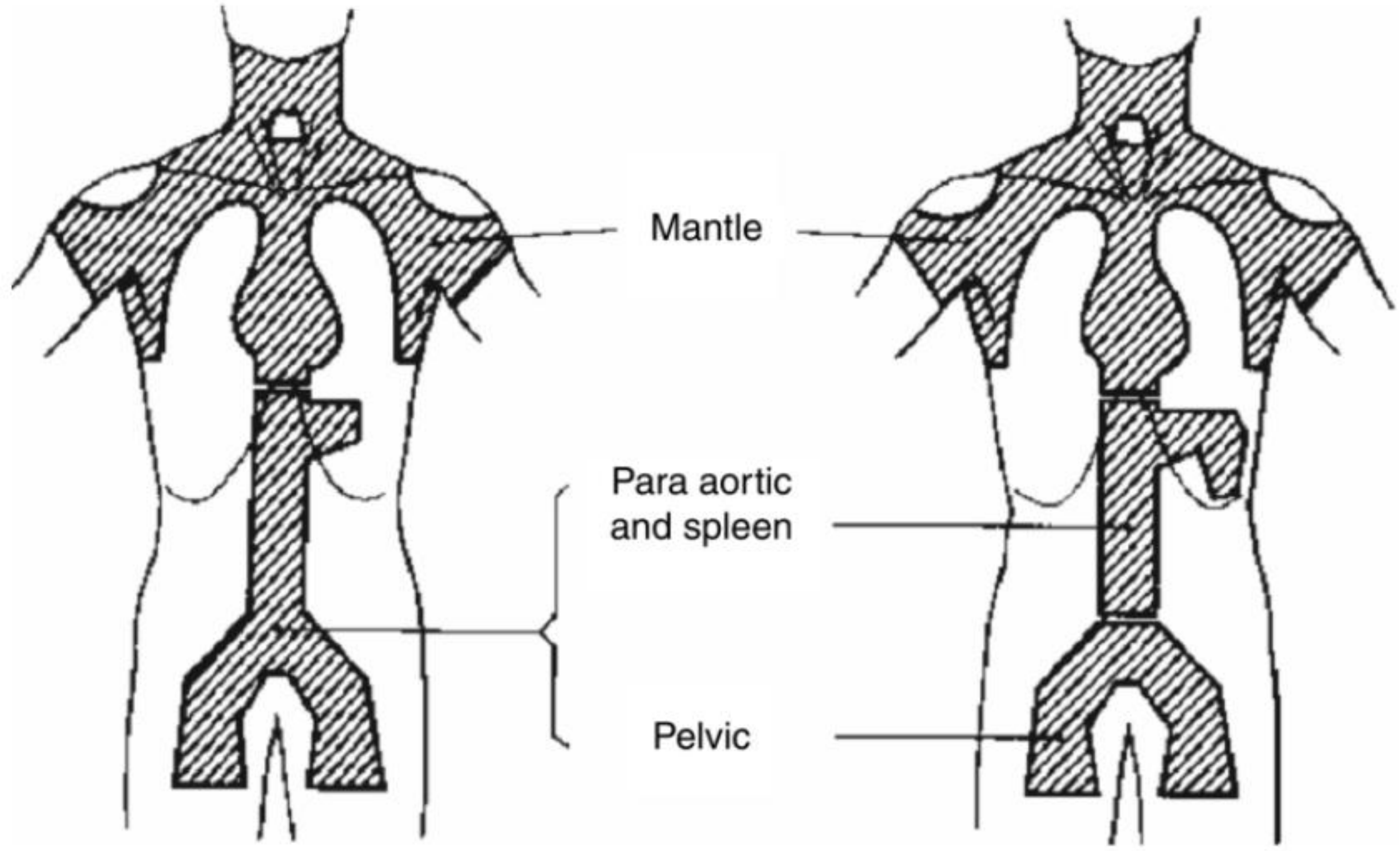
# Prerequisites

- Evaluation of all imaging studies, especially diagnostic CT and integrated PET-CT scans
- Precise simulation with appropriate immobilization
- Consideration of organ motion
- Detailed treatment planning
- Effective treatment delivery
- Including portal imaging
- Appropriate quality assurance measures.

# PET-CT Simulation

- Provides accurate information regarding  initial extent of ds.
- Initial scan is not usually in  trt position or on a flat couch.
- Initial staging PET-CT should be then be merged with planning scan  in order to localize  initial sites of disease.
- Accuracy of registration varies on pt positioning for two studies→ needs to be accounted for in ultimate treatment fields design
- CT simulation with 2.5-5 mm slices  through intended treatment volume
- Ideally IV contrast preferable
- For abdominal & pelvic lesions-oral contrast preferred for bowel delineation
- Target motion should be assessed(especially if lesion is close to diaphragm)

# Classical Fields for Radiation Therapy for Lymphoma

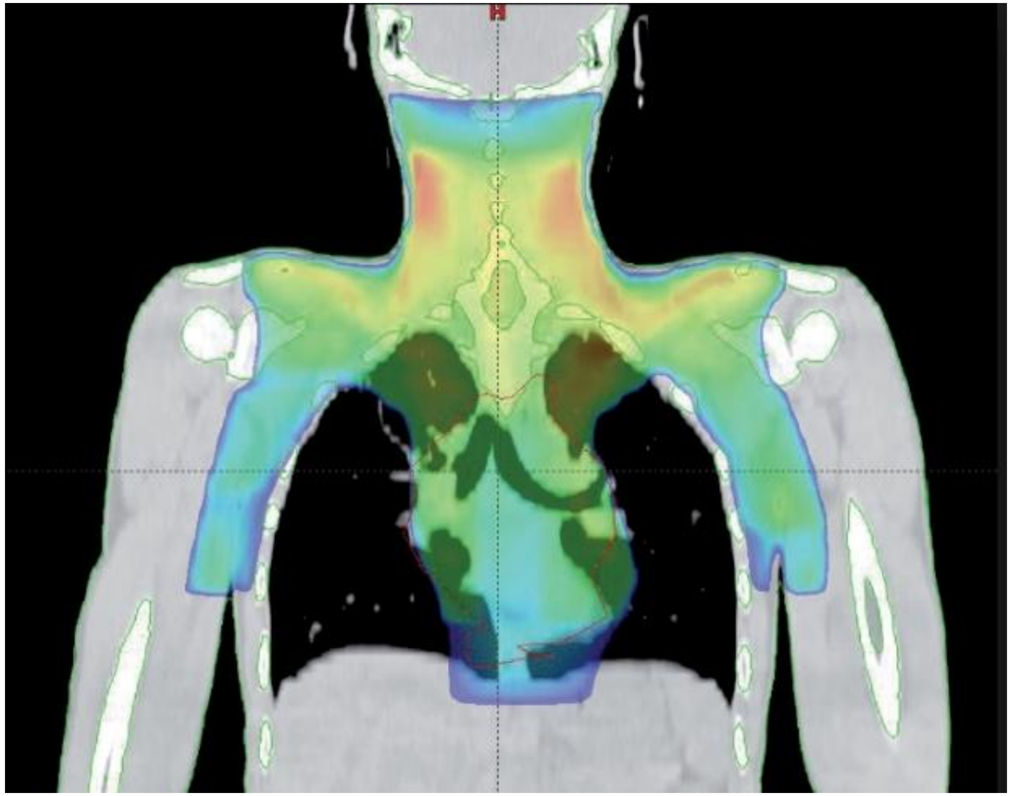



Total Lymphoid Radiotherapy

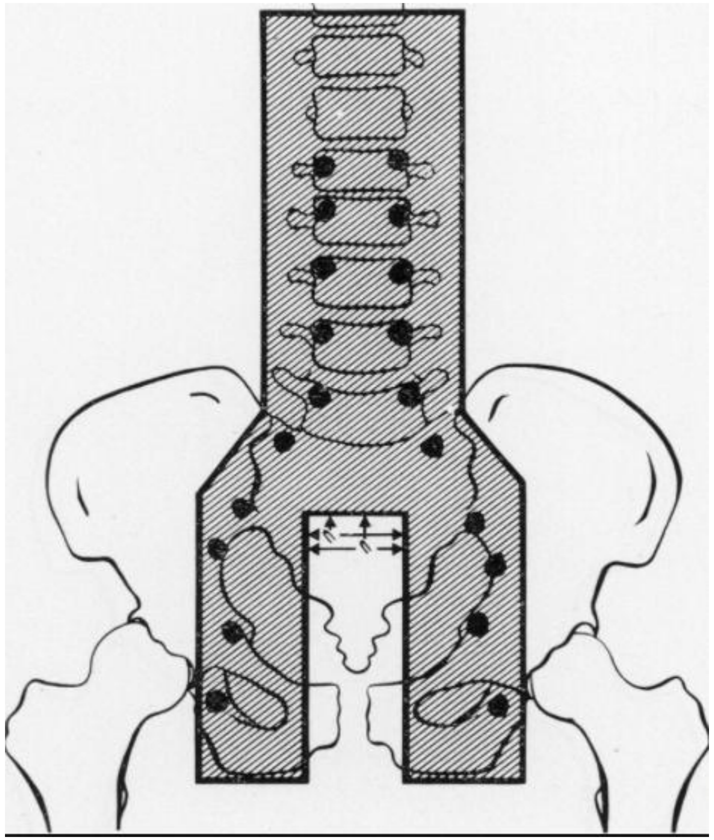
Post Splenectomy

No Splenectomy

# Classic field configurations for the treatment of Hodgkin lymphoma by Radiotherapy alone



Mantle Field



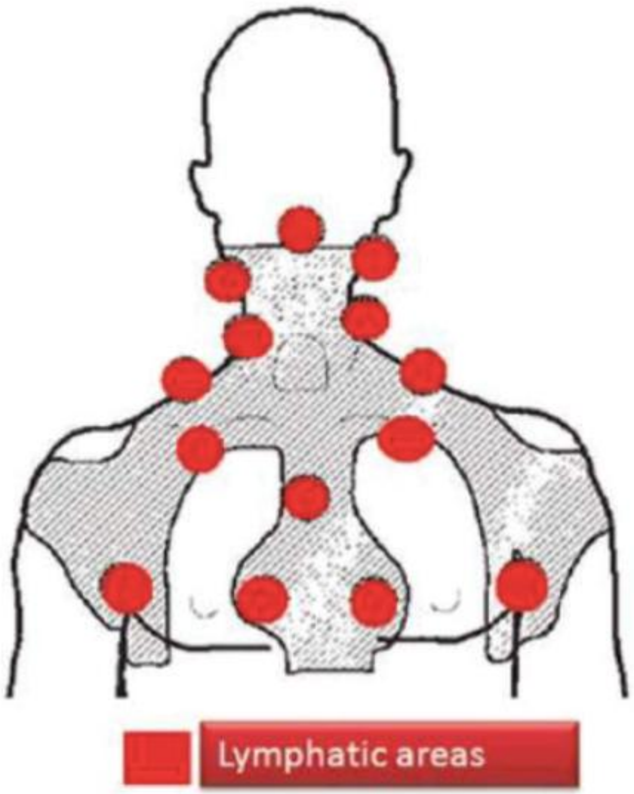
Inverted-Y.

**Extended-field radiation (EFRT):** Includes not only clinically involved nodes but also adjacent, clinically uninvolved nodes; this is called mantle-field or inverted-Y field

# Mantle field

Type of Extended field RT ->includes multiple involved & uninvolved LN groups above diaphragm

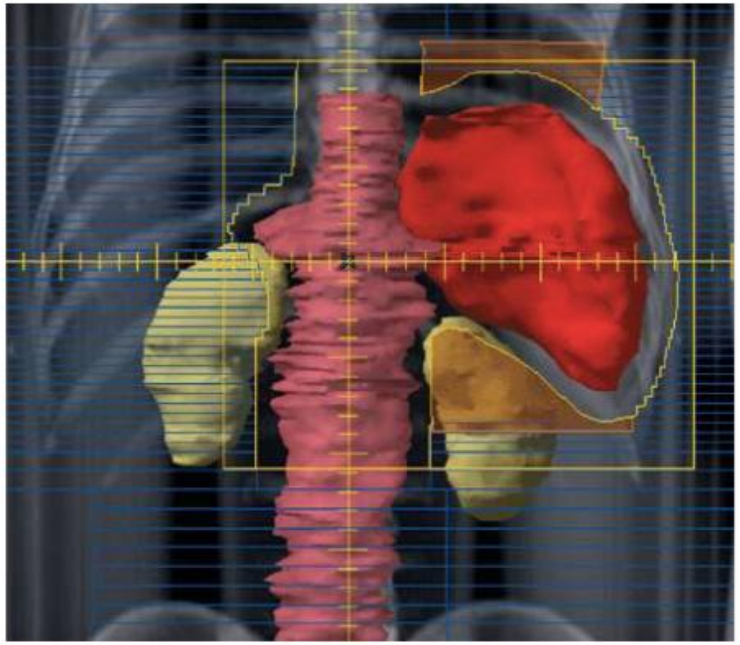
- Bilateral Cervical
- Bilateral Supraclavicular
- Bilateral Infra-clavicular
- Bilateral Axillary
- Bilateral Hilar
- Bilateral Mediastinal



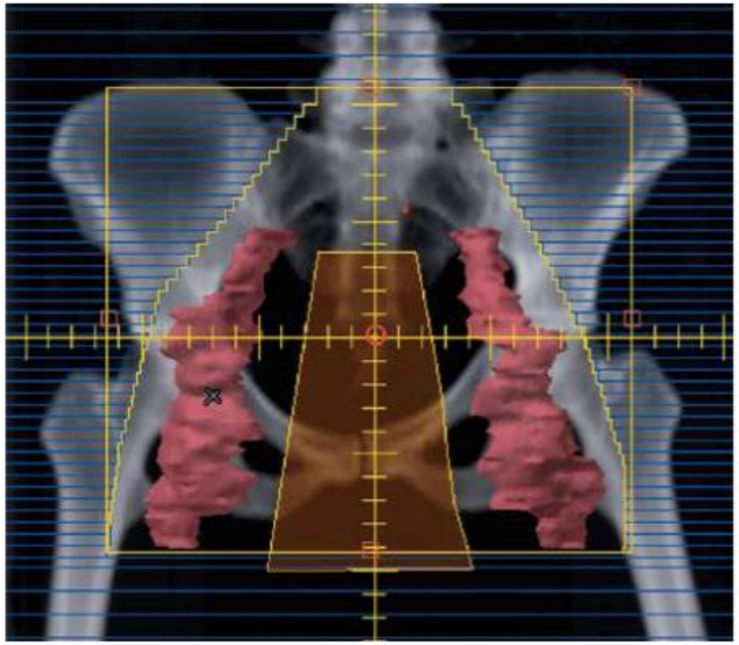
# Inverted Y

- Combination of para- aortic, pelvic & inguino- femoral fields with or without spleen
- Used for pts with infra- diaphragmatic ds or in patients receiving TNI

**Para Aortic fields**

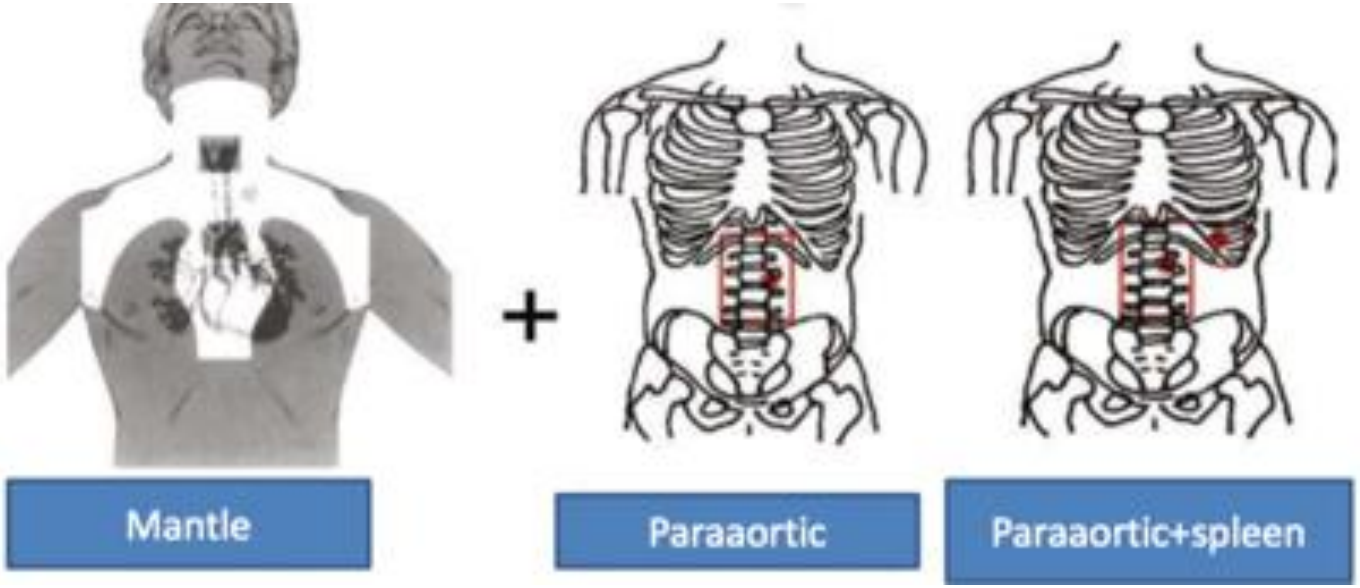


**Pelvic field**



# Subtotal Nodal/Lymphoid RT – Mantle &paraaortic/splenic

- Used infrequently
- No difference in PFS or OS in pt with favourable ds treated with either ABVD/ STNI
- STNI is used when a pt with localized ds is refractory to multiple lines of chemo

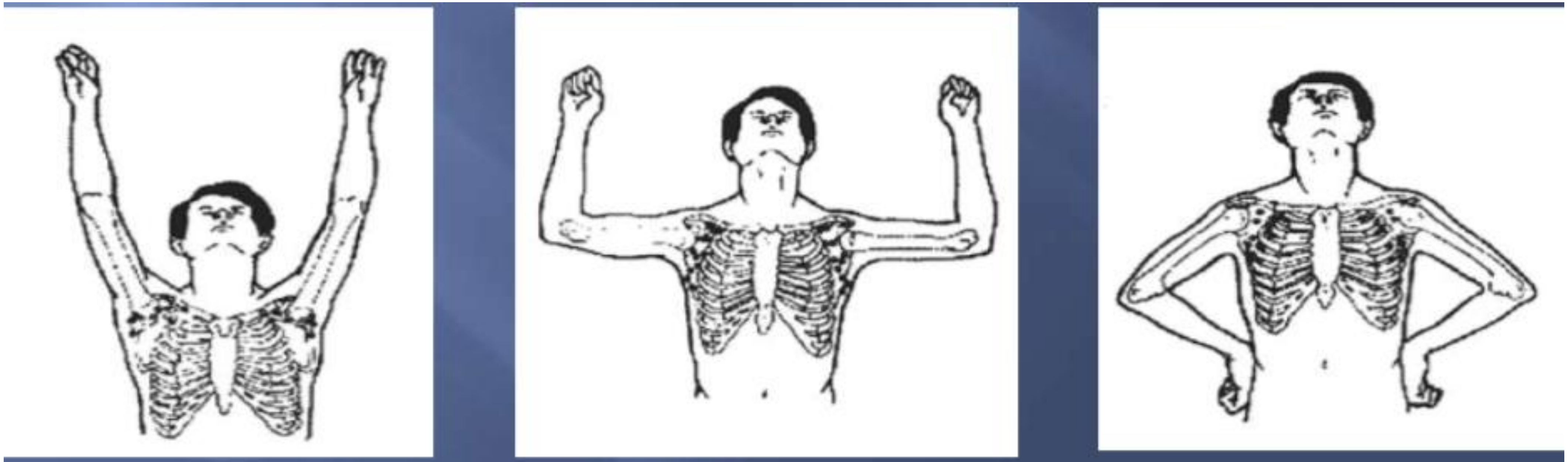


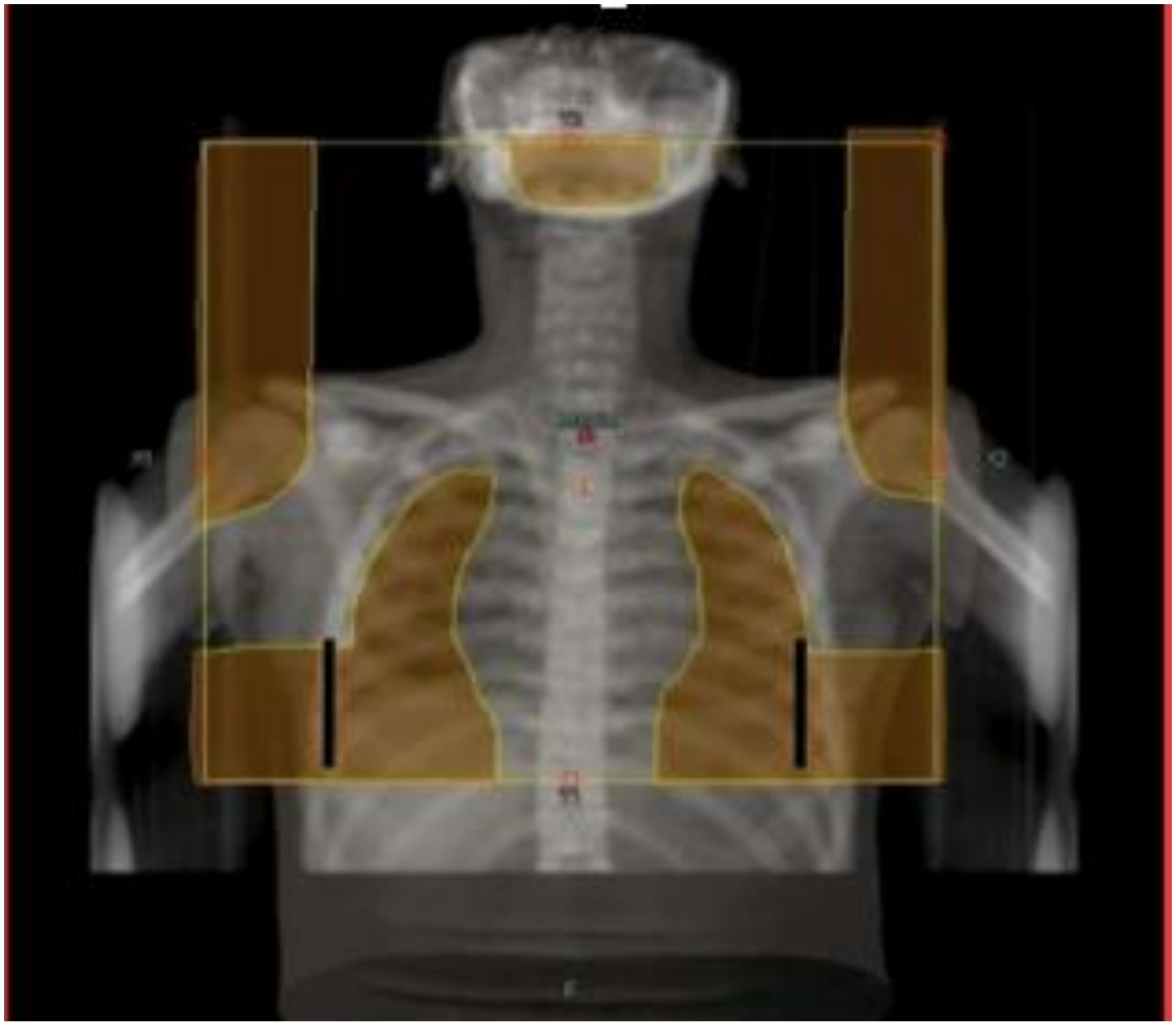

- Initial trt is bilateral cervical, supraclavicular, axillary mediastinal & hilar LN(Mantle field)
- Dose -30Gy followed by a boost 10Gy to sites of gross disease)
- Prophylactic RT to paraaortics and spleen after 2 weeks

Meyer et al 2012

# Treatment position

- Supine with maximum extension of neck & arms above  head, or at 90* angle towards side, or in akimbo‟ position
- Humeral heads can be shielded and also it minimize skin folds in SCF/low neck regions.

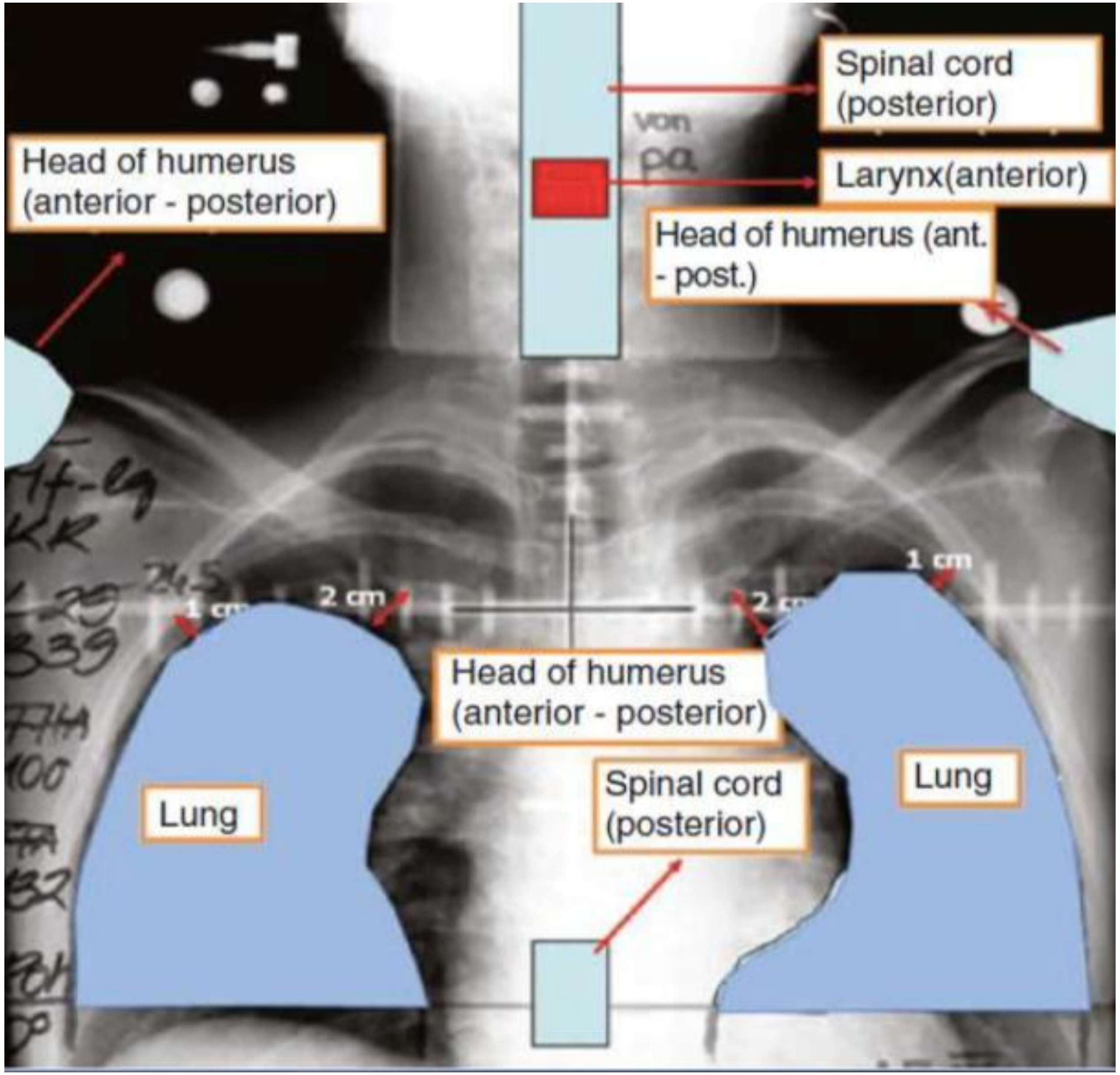




# BORDERS

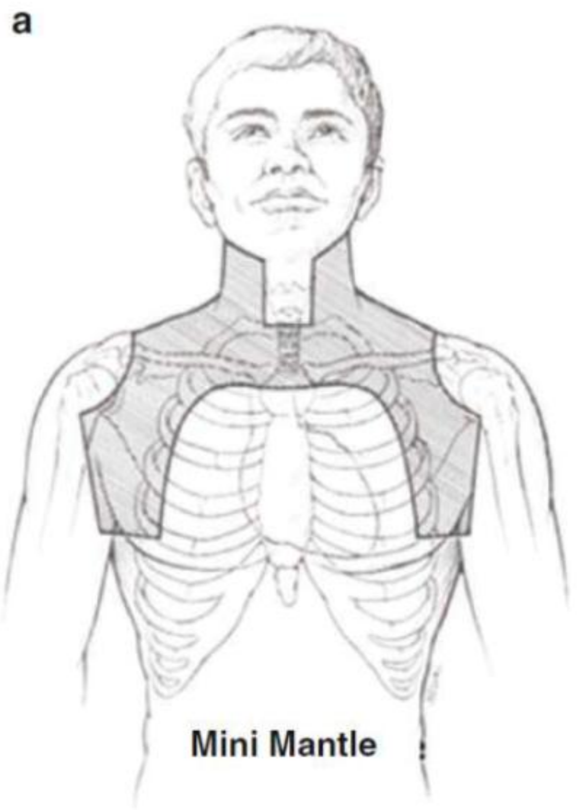
- **Superior** : Through chin, bisecting mandible, to mastoid process.
- **Lateral** : Flashing axillae
- **Inferior**
- **Inferior axillary** at inferior tip of scapula(D7).
- **Inferior mediastinal** at initial mediastinal extent of disease with a ~ 5 cms margin ( T10-T11 interspace ).

# SHIELDING

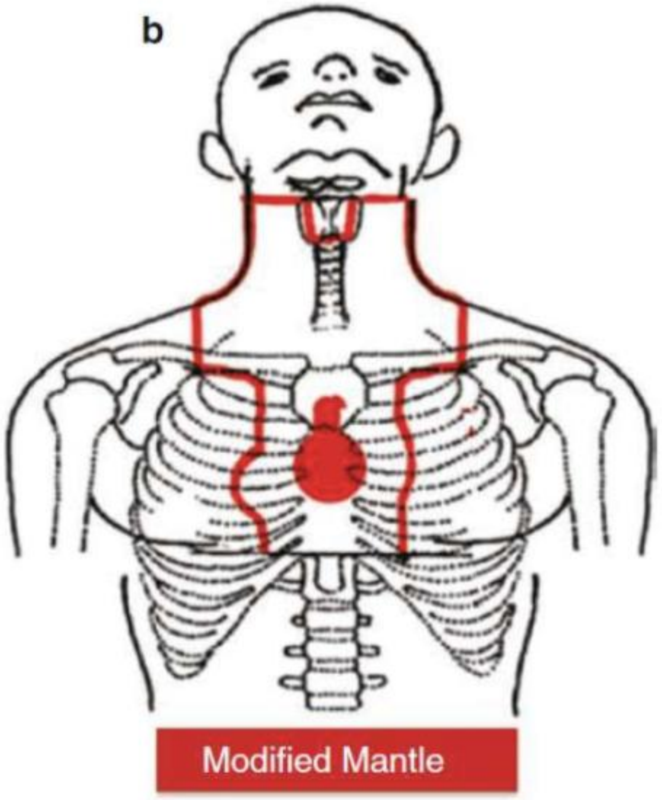



- Head of Humerus is shielded both ant & post
- Larynx is shielded anteriorly- 2cm block from thyroid notch to inferior border cricoid
- Heart is shielded below hilar level without including mediastinal LN"s both anteriorly & posteriorly.
- Spinal cord shielding - in midline for dosages >40 Gy. A 1.5 cm block is put at inferior border of spinal cord posteriorly . And top of the field to C7
- Oral cavity is shielded if sup border includes oral cavity.

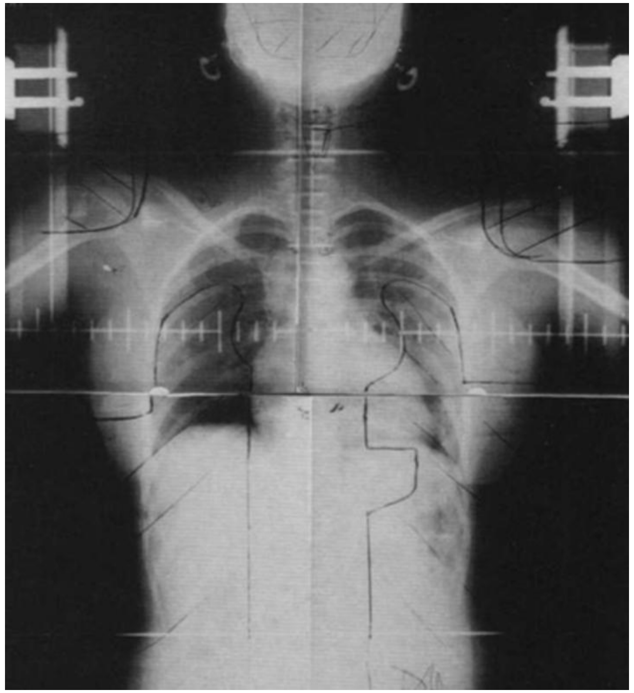
# Modifications of mantle field




Hilar and Mediastinal lymph nodes are not included.




Axillary lymph nodes are not included.



Extended mantle

Includes mantle & paraaortic in a single port

# Limited field irradiation

(IFRT): Field encompasses all of clinically involved regions (eg, the mediastinum and the

**Involved-site radiation (ISRT):** Field that includes pre- and post-chemo nodal volumes plus a 1.5-cm

**Involved-node radiation (INRT):** Includes pre- and post-chemo nodal volumes plus a 1-cm margin of healthy

# Involved-node radiotherapy (INRT) in patients with early Hodgkin lymphoma: Concepts and guidelines

Theodore Girinsky[a,*], Richard van der Maazen[b], Lena Specht[c], Berthe Aleman[d], Philip Poortmans[e], Yolande Lievens[f], Paul Meijnders[g], Mithra Ghalibafian[a], Jacobus Meerwaldt[h], Evert Noordijk[i], on behalf of the EORTC-GELA Lymphoma Group

[a]*Department of Radiation Oncology, Institut Gustave Roussy, Villejuif, France,* [b]*Department of Radiotherapy, Nijmegen, The Netherlands,* [c]*The Finsen Centre Rigshospitalet, Copenhagen University Hospital, Denmark,* [d]*Department of Radiotherapy, The Netherlands Cancer Institute, Amsterdam, The Netherlands,* [e]*Department of Radiotherapy, Dr Bernard Verbeeten Instituut, LA Tilburg, The Netherlands,* [f]*Radiotherapy Department, Leuven, Belgium,* [g]*Department of Radiotherapy, Antwerpen, Belgium,* [h]*Department of Radiation Oncology, Medisch Spectrum Twente, Enschede, The Netherlands,* [i]*Department of Clinical Oncology, Leiden University Medical Center, The Netherlands*

## Abstract

***Background and purpose*: To describe new concepts for radiation fields in patients with early stage Hodgkin lymphoma treated with a combined modality.**

***Patients and materials*: Patients receiving combined modality therapy with at least 2 or 3 cycles of chemotherapy prior to radiotherapy. Pre- and postchemotherapy cervical and thoracic CT scans are mandatory and should be performed, whenever possible, in the treatment position with the use of image fusion capabilities. A pre-chemotherapy PET scan is strongly recommended to increase the detection of involved lymph nodes.**

***Results*: Radiation fields are designed to irradiate the initially involved lymph nodes exclusively and to encompass their initial volume. In some cases, radiation fields are slightly modified to avoid unnecessary irradiation of muscles or organs at risk.**

***Conclusions*: The concept of involved-node radiotherapy (INRT) described here is the first attempt to reduce the size of radiation fields compared to the classic involved fields used in adult patients. Proper implementation of INRT requires adequate training and an efficient prospective or early retrospective quality assurance program.**

 Radiotherapy and Oncology 79 (2006) 270–277.

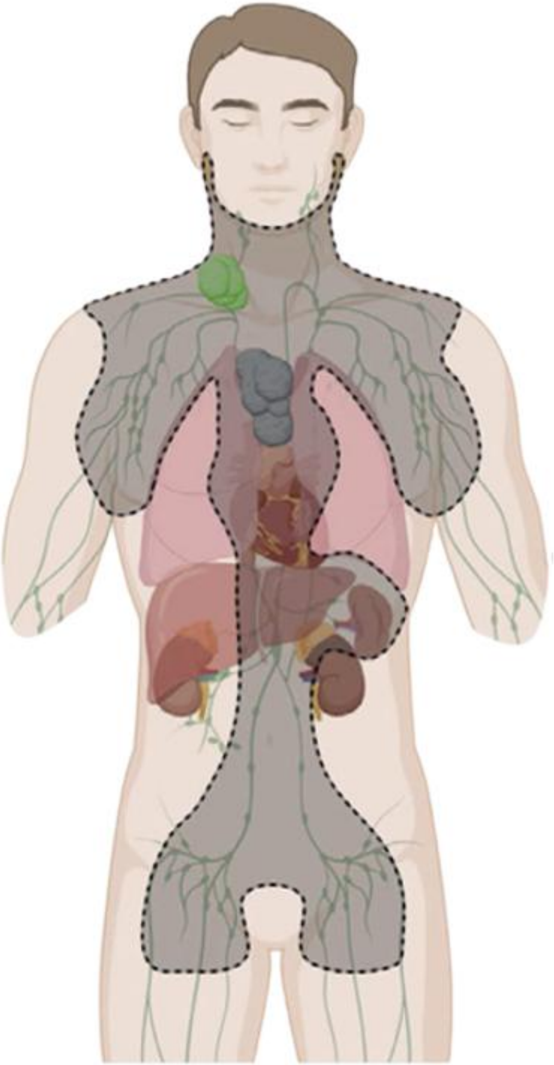
## Involved-node RT in early-stage Hodgkin's lymphoma
## Definition &guidelines of the German Hodgkin Study Group (GHSG)

- Patient must be examined by RO before  start of chemo.
- Complete staging CT scans.
- RT planning CT before & after chemo with pts in the trt position is recommended.
- Usage of PET-CT scans with pts in trt position is recommended
- CTV encompasses initial volume of  LN(s) before chemo &incorporates initial location & extent of  ds taking displacement of normal tissues into account.
- Margin of  PTV -2 cm in axial & 3 cm in CC direction.
- If necessary, it can be reduced to 1-1.5 cm. To minimize lung & cardiac toxicity, target definition in  mediastinum is different.

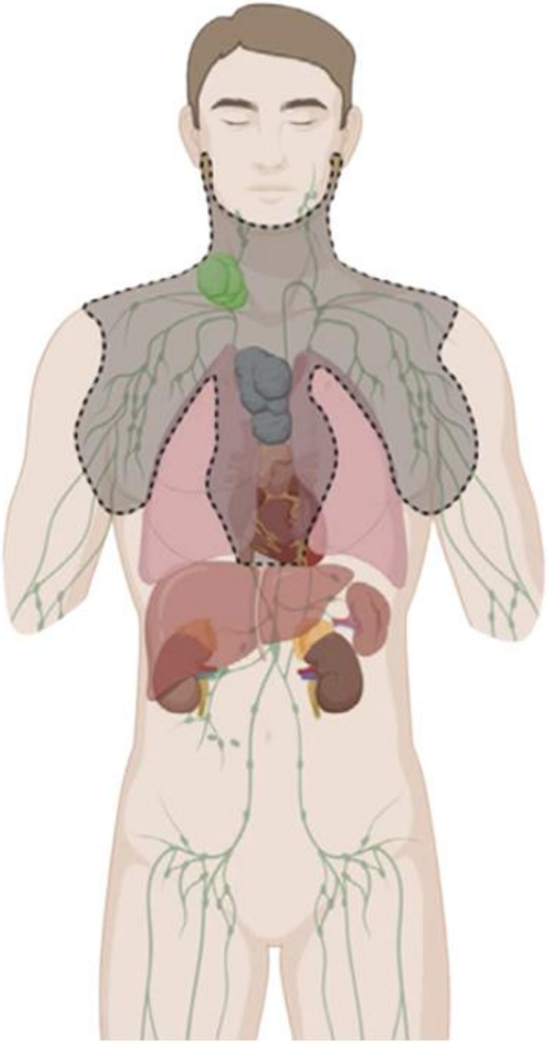
Eich et al

| | superior | inferior | medial | lateral | notes |
|---|---|---|---|---|---|
| cervical | 1-2 cm above mastoid tip and chin | 2 cm below clavicle | Ipsilateral transverse process | Include medial 2/3 rd clavicle | Add laryngeal block after 19.8 Gy |
| mediastinal | C5-6 interspace | Lower of 5 cm below carina and 2 cm below pre chemo disease | n/a | Post chemo volume with 1.5 cm margin | Include hilum with 1 cm margin(1.5 cm if involved) |
| axilla | C5-6 interspace | Lower of tip of scapula or 2 cm below lowest prechemo node | Ipsilateral transverse process | Flash axilla | Include lung block |
| Paraaortic | Higher of T11 or 2cm above pre chemo disease | Lower of L4 and 2 cm below prechemo disease | n/a | Transverse processs or 2 cm margin on post chemo volume | Kidney blocks may be neccessary |
| inguinal | Middle of sacroiliac joint | 5 cm below lesser trochanter | Medial border of obturator foramen with 2 cm margin on pre chemo disease | Greater trochanter or 2 cm lateral to pre chemo disease | |

# Field Definitions

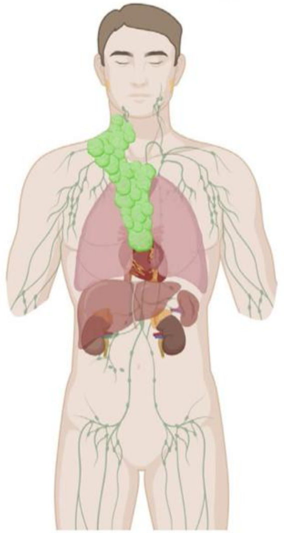


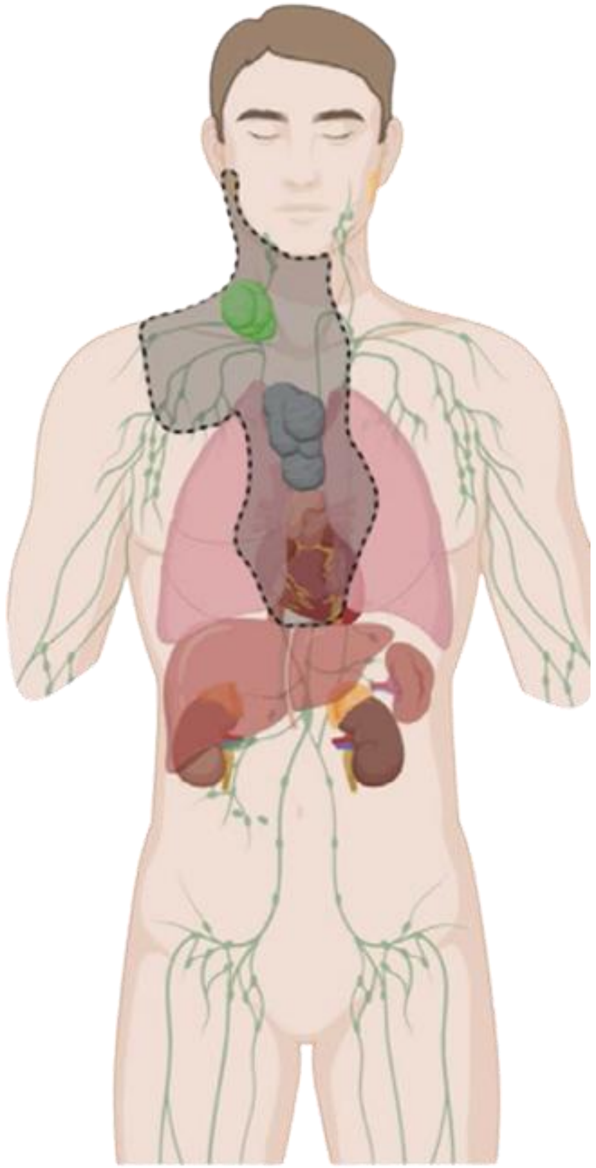
Total Nodal Radiation



Mantle field

Extended field Radiation

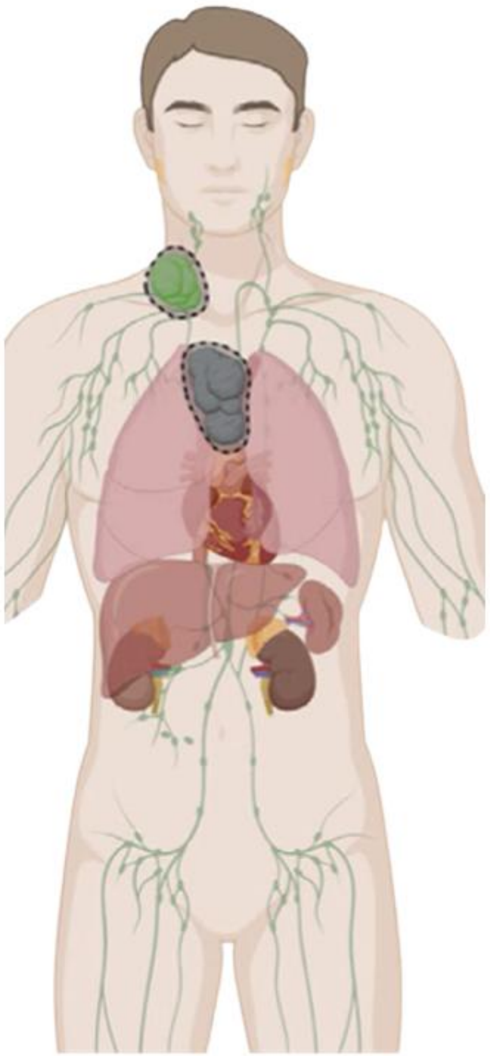


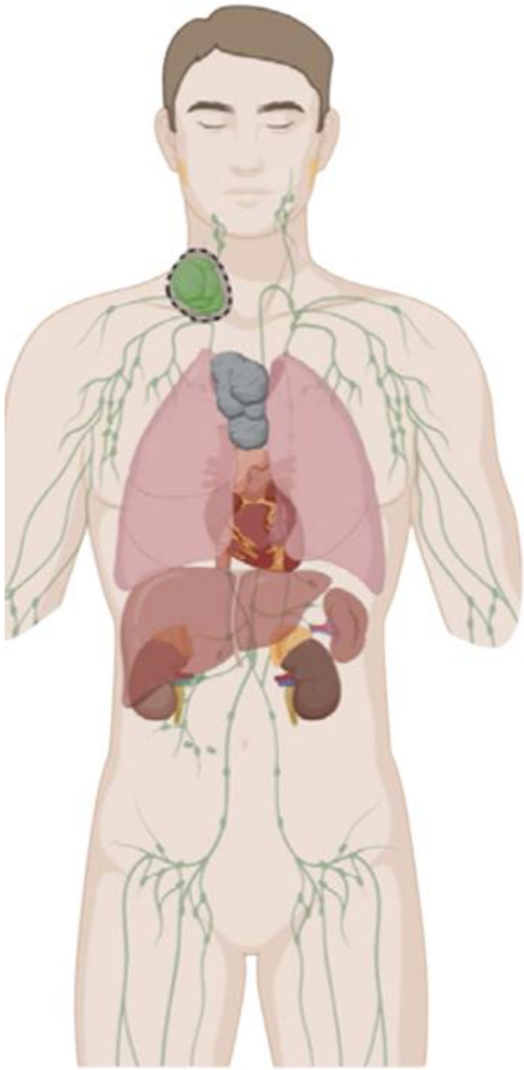
Involved Field RT

# Involved field RT

- Complete involved lymphoid region , when any portion of that region is involved
- **Extra nodal involvement then whole organ only if lymph nodes not involved**
- Include initially involved pre CT sites & volume , except transverse diameter of mediastinal & paraaortic lymph nodes for which post CCT volume
- **SCF region treated when sup mediastinum involved**
- **Iliac lymph nodes treated when inguino-femoral nodes involved**



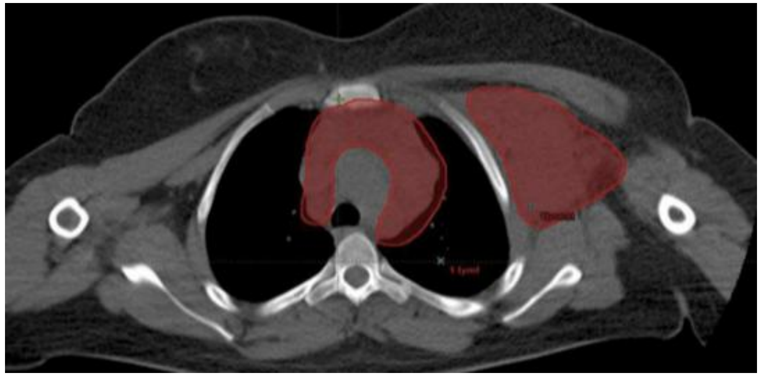
Residual Disease RT

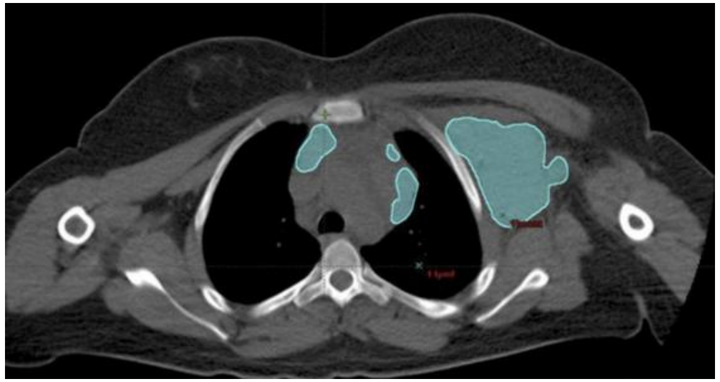


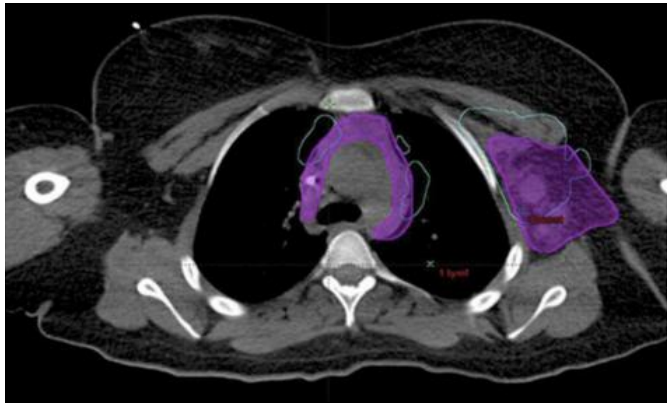
PET Directed RT

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

INTERNATIONAL JOURNAL OF RADIATION ONCOLOGY • BIOLOGY • PHYSICS
VOLUME 89, ISSUE 4, PAGES 854-862, 15 JULY 2014







Volumetric treatment planning instead of 2D osseous anatomy.
Modern imaging have rendered this 2D approach obsolete and favor Volumetrically defined targets
Cross sectional and functional imaging fused and matched manually and electronically  allow such manipulations

# ILROG Mini-Atlas: Head and neck Location

59-year-old male presenting with bilateral cervical adenopathy

Work up and staging revealed Diffuse Large B cell Lymphoma involving the right nasopharynx and bilateral cervical neck (Figure 1)

Treatment Plan: 3 cycles of R-CHOP (Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, Prednisone) followed by consolidative radiation therapy to 30 Gy. The patient achieved a complete response on PET-CT imaging (Five Point Score of 2 of 5) after completion of R-CHOP (not shown).

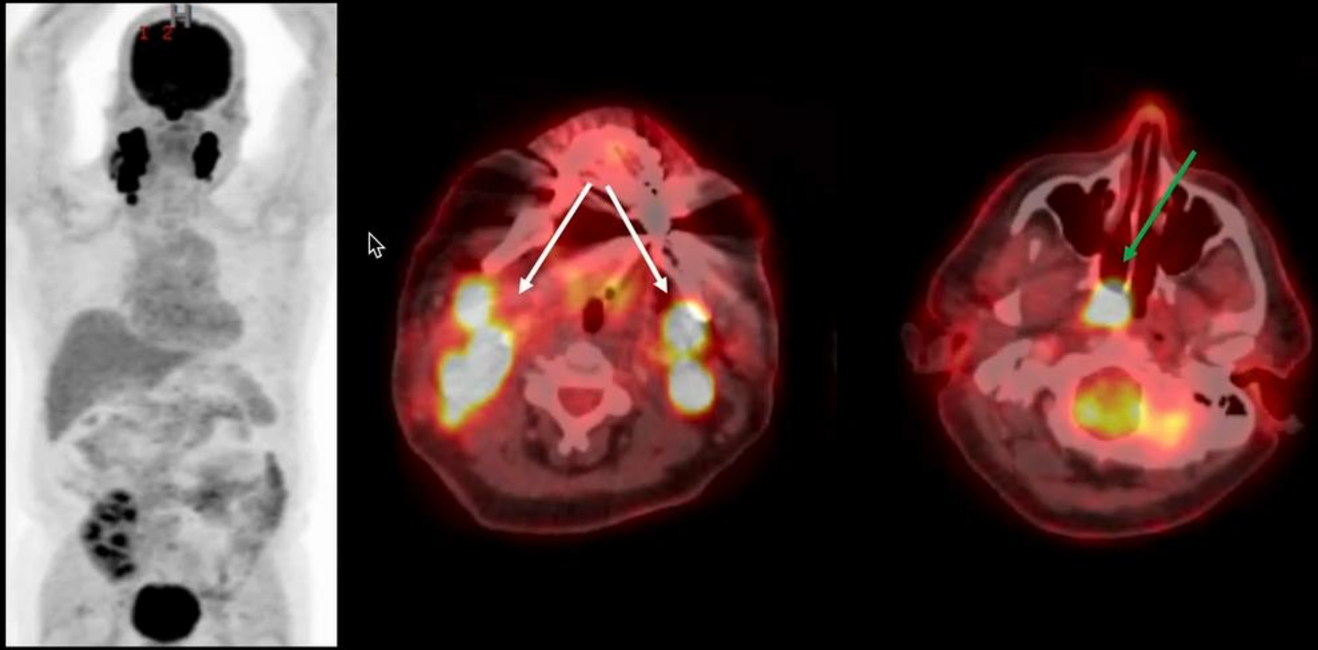


Figure 1. PET-CT demonstrating FDG avid bilateral cervical neck adenopathy (white arrow) and avid nasopharyngeal involvement (green arrow)

# ILROG Mini-Atlas: Mediastinal Location- Planning with Breath Hold

28-year-old female, presenting with a right neck mass and shortness of breath, neck biopsy confirmed the diagnosis of Hodgkin Lymphoma. PET/CT below showing the disease involving the bilateral necks, and mediastinum. The case was best classified as early unfavorable per GHSG 11 [7]. The Patient , as per GHSG received 4 cycles of ABVD, achieving complete remission by PET/CT then presented for consolidation radiation therapy with ISRT[4] to 3060cGy.

Presenting PET/CT showing the disease location

7:Eich et al; JCO vol 28 N 27 sep 20 2010
4:Specht et al. IJROBP. 2014 Jul 15;89(4):854-62

# Evolution of Radiation Doses in Hodgkin's Lymphoma

## Early Era: Extended-Field RT

- 1960s–1980s: Extended-field RT (Mantle + Para-aortic) used as sole modality
- Typical doses: 40–45 Gy
- High local control but significant late toxicities (cardiac, breast, thyroid, second malignancies)

## Combined Modality: EFRT → IFRT

- GHSG HD7 & EORTC H8: Superiority of chemo + RT over RT alone
- IFRT replaced EFRT
- Doses: 30–36 Gy consolidation RT after chemotherapy
- Reduced fields, less late toxicity

## Dose De-escalation Trials

- GHSG HD10 (early fav.): 20 Gy after 2 cycles ABVD non-inferior to 30 Gy
- GHSG HD11 (early unfav.): 30 Gy sufficient after 4 cycles ABVD/BEACOPP
- Demonstrated safety of lowering RT dose while maintaining efficacy

## Early-stage classic HL in CR after chemo

Dose to the CTV :

- Determined on the basis of results of the German Hodgkin Studies HD 10 and 11

- Favourable characteristics : 20 Gy in 10 fractions
- Unfavourable characteristics : 30 Gy in 15 fractions

## Dosages Early-stage LPHL :

- 30 to 35 Gy in 1.8 to 2 Gy per fraction is recommended dose to the CTV
- No advantage has been shown for higher doses
- Residual lymphoma after chemotherapy :
- 36 to 40 Gy in 18 to 20 fractions

# Radiation Dose NCCN Recommendation

- Combined Modality Therapy (CMT)
  - Non-bulky disease (stage I–II): 20[a]–30 Gy (if treated with ABVD); 1.5–2.0 Gy per fraction
  - Non-bulky disease (stage IB & IIB): 30 Gy; 1.5–2.0 Gy per fraction
  - Bulky disease (all stages): 30 Gy; 1.5–2.0 Gy per fraction
  - Partial response/refractory disease (Deauville 4–5): 36–45 Gy
- ISRT Alone (uncommon, except for NLPHL)
  - Involved regions: 30–36 Gy (the dose of 30 Gy is mainly used for NLPHL); 1.5–2.0 Gy per fraction
  - Uninvolved regions: 25–30 Gy; 1.5–2.0 Gy per fraction. ISRT fields for NLPHL generally include adjacent but clinically uninvolved nodes when treated with RT alone.
- Palliative RT: 4–30 Gy

# Studies evaluating the radiation-associated complication risk for OARs in Hodgkin lymphoma.

| Author Year | Question | Endpoints | NTCP Model/ Risk Estimation | Results | Conclusion |
|---|---|---|---|---|---|
| Hodgson et al. 2007 [26] | Estimated risk difference in secondary malignancies for RT mantle 35 Gy, 35 Gy IFRT and 20 Gy IFRT | Lung cancer breast cancer | Radio-biological modeling of carcinogenesis | Compared to mantle RT, 35 Gy IFRT reduced 20-year ERR of breast cancer and lung cancer by 63% and 21%, respectively, 20 Gy IFRT reduced ERR by 77% and 57% | IFRT is predicted to have a decreased risk compared to mantle RT, but considerable interindividual variations exist |
| Pepper et al. 2021 [10] | Impact of RT technique on radiation induced lung disease | Pneumonitis, pulmonary secondary malignancies | LKB QUANTEC EQD-based function | According to QUANTEC parameters, pneumonitis risk is increased by 1% for 5-field IMRT and 2.6% for 7-field IMRT, in comparison to APPA (smaller risk increase with LKB model). Secondary pulmonary malignancy risk is increased by 0.1% and 0.19% for 5-field IMRT and 7-field IMRT, in comparison to APPA | Mediastinal radiation holds a very low risk for lung toxicities with APPA showing the lowest estimated risk out of the examined radiation techniques |
| Cutter et al. 2021 [31] | Prediction of 30-year absolute excess risk of radiation-related cardiovascular disease in a post-hoc analysis of the RAPID trial | Cardiovascular morbidity and mortality (cardiac disease and stroke) | Estimated increase in mortality rate per unit dose | Average excess in cardiovascular mortality was predicted to be 0.56% (range 0.01–6.79%), average predicted excess in incidence was 6.24% (range 0.31–31.09%) due to RT | Low predicted risk for most patients. A minority of patients receiving high doses to cardiovascular structures might profit from advanced radiation techniques or omitting RT |

Cancers 2024, 16, 1168

# OAR Recommendations

**RT DOSE CONSTRAINT GUIDELINES FOR LYMPHOMA[b]**

| **OAR** | | **Dose Recommendation (1.5–2 Gy/fraction)** | | **Toxicity** |
|---|---|---|---|---|
| **Abdomen** | Liver | Mean <15 Gy<br>V20 <30%<br>V30 <20% | | Hepatic toxicity[37,38] |
| | Stomach | Dmax <45 Gy | | Ulceration[39] |
| | Spleen | Mean <10 Gy<br>V5 ≤30%<br>V15 ≤20% | | Late infections[40]<br>Lymphopenia[41] |
| | Pancreas | Mean <21 Gy | | Diabetes[42-45] |
| | Small bowel | V15 <120 cc<br>Dmax <45 Gy | | Diarrhea[35]<br>Obstruction, ulceration, fistula[35] |
| | Kidney | Single organ<br>Mean <5 Gy (recommended); <8 Gy (acceptable)<br>V10 <30%<br>V20 <15% (recommended); <25% (acceptable) | Bilateral<br>V5 <58% | Renal insufficiency[46-48] |
| **Other** | Bone marrow[e] | V5: ALARA<br>V10 <50%<br>V25 <25% | | Acute cytopenias[49-50]<br>Chronic cytopenias[51] |
| | Long bone | V40 <64% | | Fracture[52] |

# Pulmonary toxicity

- Risk for pneumonitis is related to vol of lung irradiated, total dose, and fraction size.
- Higher risk for RTOG grade 2 pneumonitis when MLD > 14 Gy or V20 > 35%.
- May be increased with use of bleomycin
- **Stanford Guideline is not to exceed a mean lung dose of 15 Gy after treatment with ABVD or 17 Gy after treatment with Stanford V, treating with 1.5-Gy fractions.**
- **Lung cancer risk may be increased after doses as low as 5 Gy, → define the lung V5 and try to minimize it**

# Cardiac toxicity

- Acute effects (pericarditis), limited data suggest keeping mean pericardial dose to <26 to 27 Gy and V30 to <46%.
- Threshold effect at 30 Gy was suggested for cardiac mortality.
- Cardiac V25 of <10% is associated with a very low risk of cardiac mortality.
- IMRT may succeed in reducing cardiac dose

# Secondary malignancies

- Excess risk of secondary breast cancer that exists for doses as low as 4 Gy,
- Track the breast V4 and keep that volume as small as possible, especially for women <30 years of age.

**SECONDARY MALIGNANCIES**[f]

| OAR | Dose Recommendation (1.8–2 Gy/fraction) | Secondary Malignancy |
|---|---|---|
| Breast | Minimize volume >4 Gy (ideally <10%) | Breast cancer (adenocarcinoma)[56] |
| Colon | Minimize volume >10 Gy | Colon cancer[57] |
| Lung | Minimize volume >9 Gy | Lung cancer[58] |
| Esophagus | Minimize volume >30 Gy | Esophageal cancer[59] |
| Stomach | Minimize volume >25 Gy | Gastric cancer[60] |
| Pancreas | Minimize volume >5–10 Gy | Pancreatic cancer[61] |

# End of Treatment Assessment

PET/CT: 6–8 weeks post-chemo OR 12 weeks post-RT

CR = Deauville ≤3

Surveillance

Persistent Deauville 4–5

biopsy and manage as refractory

**The International Working Group response criteria for Hodgkin lymphoma**

| Response category | Definition |
|---|---|
| Complete remission | No clinical evidence of disease or disease-related symptoms. |
| | A post-treatment residual mass of any size is permitted as long as it is PET negative. |
| | Spleen and liver must be non-palpable and without nodules. |
| | If a pre-treatment bone marrow biopsy was positive, an adequate bone marrow biopsy (with a core size of at least 20 mm) from the same site must be cleared of infiltrate; if this is indeterminate by morphology, immunohistochemistry should be negative. |
| Partial remission | A decrease by at least 50 percent in the sum of the products of the largest perpendicular diameters (SPD) of up to six of the largest measurable lesions. |
| | The post-treatment PET should be positive in at least one previously involved site. |
| | There should be no increase in the size of other nodes, liver, or spleen and no new areas of disease. |
| | Splenic or hepatic nodules must decrease by at least 50 percent in the SPD (or in the greatest transverse diameter for single nodules). |
| | Bone marrow biopsy results are not useful in determining PR. However, if the patient otherwise fits the CR criteria but has a positive bone marrow biopsy, the patient is labeled as having a PR. |
| Stable disease | Failure to attain a CR or PR with no evidence of progressive disease. The post-treatment PET should be positive at prior sites of disease and no new sites should be present on PET or CT. |
| Progressive disease or relapse after CR | Any new lesion or an increase from nadir by at least 50 percent of previously involved sites. |
| | Development of a new lesion is defined by the appearance of any new lesion more than 1.5 cm in long axis. If the long axis diameter is from 1.1 to 1.5 cm, the lesion should only be considered abnormal if its short axis is more than 1.0 cm. |
| | Progressive disease is also defined as an increase of at least 50 percent in the longest diameter of a previously identified node more than 1 cm in short axis or in the SPD of more than one node. |
| | Lesions should be PET positive unless they are below a detectable size (ie, <1.5 cm in long axis by CT). |

# Follow-up & Monitoring

- Clinical eval: Q3–6m (Y1–2) → Q6–12m (Y3) → annually
- Labs: CBC, chemistry, ESR if relapse suspected
- Imaging: No routine surveillance PET/CT
- Health maintenance: thyroid tests annually (if neck/mediastinal RT), vaccinations, breast/skin/cardiovascular checks, monitor

- Growth impairment, thyroid dysfunction, gonadal toxicity
- Cardiotoxicity, pulmonary fibrosis
- Secondary malignancies (breast, thyroid, AML, sarcoma)
- Increased late mortality: >25% cumulative severe morbidity at 25 yrs

# Summary

- Radiation therapy remains integral to Hodgkin lymphoma management, especially for early-stage disease
- Modern protocols emphasize reduced radiation field size and modest dosing to minimize long-term toxicities, including secondary cancers and organ dysfunction, while maintaining disease control.
- In early stages, CMT  (chemotherapy + radiation) is superior to RT alone for DFS and functional imaging  guides the selective use of RT.
- For advanced or bulky disease, consolidative RT is considered primarily for residual, bulky, or PET-positive sites after chemo, following current NCCN and ILROG guidelines.
- Role of RT in refractory or relapsed settings persists, especially post-novel agents, where efficacy is balanced against late effects.
- Ongoing clinical trials and evolving guidelines continue to optimize RT delivery, balancing benefits in disease control against risks of toxicity and striving for personalized, risk-adapted care

# Thank you


Health talk by Dr Kanika