Mediastinal Lymphoma: Navigating Complexities and Optimizing Outcomes

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Learning Objectives

- Describe indications for RT in the management of patients with mediastinal lymphoma
- Recognize how systemic therapy and diagnostic imaging influence RT recommendations and dose
- Identify strategies to minimize radiation toxicity, including involved site/node RT, and scenarios that may benefit from advanced RT techniques

The Landscape of Mediastinal Masses

What are the clinical differentials for mediastinal mass?

1. Thymoma or Thymic Carcinoma
2. Teratoma (Mediastinal GCT)
3. Lymphomas
4. SCLC

Mediastinal Lymphomas - Overview

- Major subtypes - Hodgkin Lymphoma with mediastinal involvement and Primary Mediastinal B-cell Lymphoma (PMBCL).
- Radiotherapy remains an important treatment modality.
- Current practice emphasizes individualized RT use to maintain excellent disease control while minimizing long-term toxicities.
- Key late effects of concern include cardiac, pulmonary, breast, and thyroid toxicity, particularly in young survivors.

Lymphomas with mediastinal presentation

- Primary Mediastinal Large B-Cell Lymphoma (PMBCL): 7% of DLBCLs; median age 30s; female predominance.
- Nodular Sclerosing Classic Hodgkin Lymphoma (NScHL): Most common HL variant in the mediastinum.
- Mediastinal Grey Zone Lymphoma (MGZL): Aggressive; features intermediate between PMBCL and cHL.
- T-Lymphoblastic Lymphoma (T-LBL): Often in adolescent/young adult males.
- DLBCL

Disease context to Decide for RT

Radiotherapy decisions are based on:

- Histology
- Disease stage
- Bulky disease
- Response to systemic therapy
- End-of-treatment PET-CT findings

Current treatment strategy:

- Individualize RT based on metabolic response and risk factors
- Aim to maximize disease control while minimizing long-term toxicity

PET CT Response assessment- Deauville score

	5-PS scores most intense uptake in a site of initial disease
D1-3: PET -	1 No uptake above background
	2 Uptake <= mediastinum
	3* Uptake >mediastinum but <= liver
D4-5: PET +	4 Uptake moderately higher than liver
	5 Uptake markedly higher than liver and/or new lesions
	X New areas of uptake unlikely to be related to lymphoma

Common clinical scenarios for Radiotherapy

- **Early-stage Hodgkin Lymphoma**
  - Favorable
  - Unfavorable
- **Advanced Hodgkin Lymphoma**
  - Residual PET-positive mediastinal disease after completion of systemic therapy
- **Primary Mediastinal B-cell Lymphoma (PMBCL)**
  - Residual mediastinal mass after chemoimmunotherapy
  - Need for consolidation RT guided by end-of-treatment PET-CT findings
  - Relapse/ Refractory setting

PMBCL

Epidemiology

- Rare and Aggressive subtype of Large B Cell Lymphoma
- Cell of Origin – Thymic B lymphocytes
- Shares clinical and biological features with ns-cHL
- 2-4% of all NHLs
- 10% of all large B Cell Lymphomas
- Strong female predominance (2:1)
- Median age - 37 years

Clinical Presentation

- Stage at presentation: Stage I/II in ~75% patients
- Usual presentation- Large mediastinal mass with Bulky disease (>10cm) ~50% patients
- B symptoms: ~ < 20% patients
- Elevated LDH: ~75% patients
- Owing to local invasion of anterior mediastinum- Pleural or pericardial effusions: ~40% patients
- Quite unusual for PMBL to involve the bone marrow or distant lymph nodes at the time of initial presentation
- Relapses tend to be extra-nodal; Common sites of relapse include the liver, gastrointestinal tract, kidneys, ovaries, and CNS

Management

- Owing to its rarity, prospective randomized studies in PMBCL are scarce, leading to variability in management practices.
- Choice of first-line treatment is guided by the goal of achieving a high cure rate in a typically young patient population while minimizing long-term toxicities like secondary malignancies and cardiovascular issues.
- **Dose-dense immunochemotherapy** has emerged as a preferred strategy based on evidence suggesting it provides superior outcomes compared to standard-interval treatments

Regimen	Advantages	Considerations
DA-EPOCH-R	Excellent EFS/OS; avoids routine radiotherapy.	Complex 24-hour continuous delivery; requires dose adjustments based on nadir counts; higher costs.
R-ACVBP	High efficacy in young patients.	Associated with **greater hematological and mucosal toxicity** compared to R-CHOP14.
R-CHOP14	Improved OS trend over R-CHOP21; easier to deliver than DA-EPOC	Often still paired with radiotherapy in some practices, though PET-guided

LYSA recommendations

- We recommend the use of dose-dense immunochemotherapy regimens: R-CHOP14, DA-EPOCH-R, or R-ACVBP (III, B). The induction phase should comprise four cycles of one of these regimens.

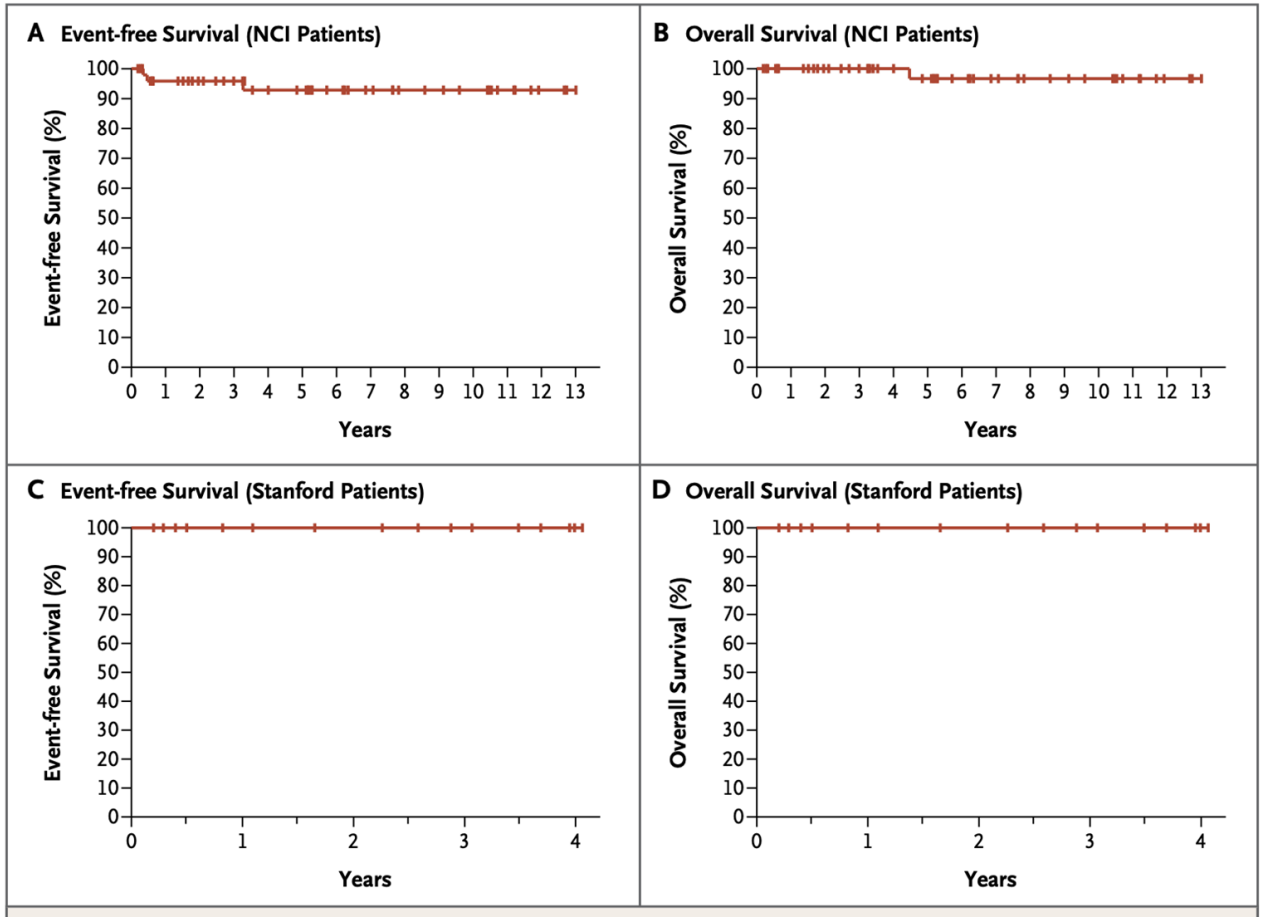
Renaud et al, EJC, 2025

ORIGINAL ARTICLE

Dose-Adjusted EPOCH-Rituximab Therapy in Primary Mediastinal B-Cell Lymphoma

Kieron Dunleavy, M.D., Stefania Pittaluga, M.D., Ph.D., Lauren S. Maeda, M.D., Ranjana Advani, M.D., Clara C. Chen, M.D., Julie Hessler, R.N., Seth M. Steinberg, Ph.D., Cliona Grant, M.D., George Wright, Ph.D., Gaurav Varma, M.S.P.H., Louis M. Staudt, M.D., Ph.D., Elaine S. Jaffe, M.D., and Wyndham H. Wilson, M.D., Ph.D.

- Single-group, phase 2, prospective study of infusional dose-adjusted DA-EPOCH-R and filgrastim without radiotherapy in 51 patients with untreated primary mediastinal B-cell lymphoma
- 5-year EFS 93%, OS 97% (NCI phase II)
- Avoids need for consolidative RT

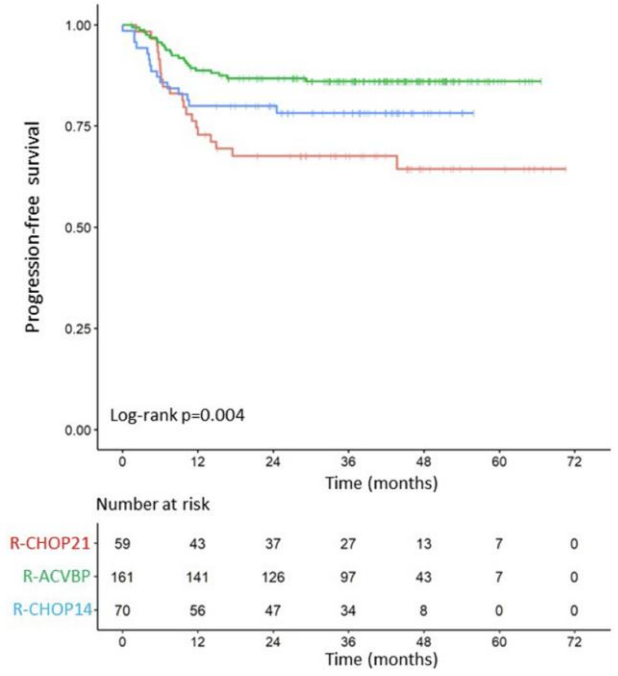


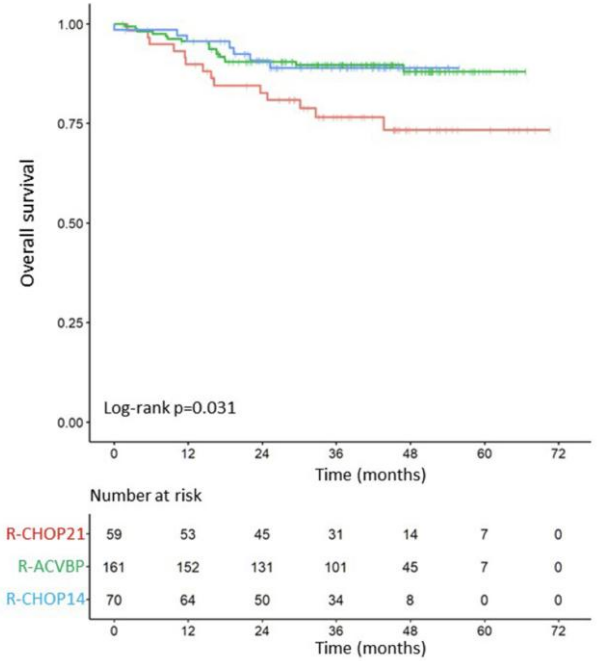
Dunleavy et al, NEJM, 2013

Outcome of Patients with Primary Mediastinal Large B-Cell Lymphoma after R-CHOP21, R-CHOP14 and R-ACVBP: A Pooled Analysis of Clinical Trials from Lysa

David Sibon, MDPhD[1,2,], Christian Gisselbrecht, MD[3], Thierry Jo Molina, MDPhD[4,*], Vincent Camus, MD[5,*], Olivier Casasnovas, MD[6,*], Christian Recher, MD PhD[7,*], Nicolas Ketterer, MD[8], Olivier Fitoussi, MD[9,*], Karim Belhadj, MD[1,*], Julie Bruneau, MD PhD[4,*], Marie Parrens, MD PhD[10,*], Jean-François Emile, MD PhD[11,*], Josette Briere, MD[12,*], Bettina Fabiani, MD[13,*], Thierry Fest, MD PhD[14,*], Herve Ghesquieres, MD PhD[15,*], Franck Morschhauser, MD PhD[16,*], Corinne Haioun, MD PhD[17], Thierry Lamy, MD PhD[18], Olivier Hermine, MD PhD[19], Steven Le Gouill, MD PhD[20], Jean-Philippe Jais, MDPhD[21,*]*

- LYSA pooled analysis: R-CHOP14 & R-ACVBP improved PFS and OS vs R-CHOP21
- Retrospective study (n=313): better outcomes with dose-dense regimens
- 3-year PFS: 89.4% (dose-dense) vs 74.4% (R-CHOP21)





Sibon et al, Blood, 2022

Improved survival for dose-intensive chemotherapy in primary mediastinal B-cell lymphoma: a systematic review and meta-analysis of 4,068 patients

Michael R. Cook,[1] Lacey S. Williams,[2] Charles Scott Dorris,[3] Yutong Luo,[4] Kepher Makambi[4] and Kieron Dunleavy[2]

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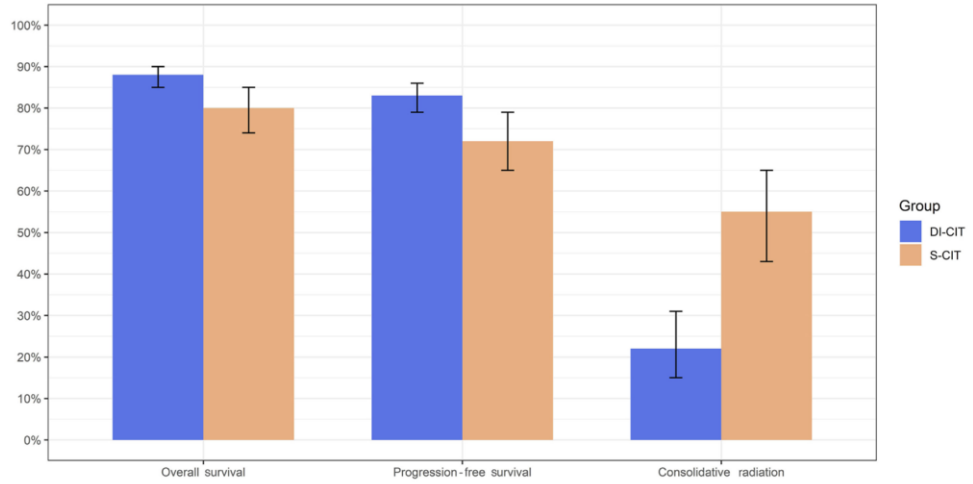
- Standard approach (S-CIT) was defined as R-CHOP-21/CHOP-21, with or without RT. DI-CIT were defined as regimens with increased frequency, dose, and/or number of systemic agents.
- Meta-analysis (n=4,068): DI-CIT improved OS vs standard CIT (88% vs 80%; +8%)
- Benefit sustained with rituximab regimens (91% vs 86%)
- DI-CIT used less RT (22% vs 55%), reducing radiation exposure



Cook et al, Haematologica, 2024

Frontline Consolidation RT

- Historical management often included CRT for all
- Currently, RT is primarily used for patients who do not achieve a complete metabolic response (CMR) after induction chemotherapy
- **IELSG-37 trial** -
  - CRT can be safely omitted in patients who achieve a CMR (DS1–3) after standard anthracycline-based immunochemotherapy.
  - **30-mo PFS:** 96.2% (observe) vs 98.5% (CRT)

Frontline Consolidation RT

LYSA recommendation

- We do not recommend CRT for patients who are good responders at EoT PET (CMR or PMR with DS 4) following dose-dense immunochemotherapy. For patients with DS 4, we recommend considering a watch-and-wait strategy with serial PET imaging or DW-MRI to monitor metabolic evolution and avoid unnecessary overtreatment (IV, B).

- CRT or serial PET or DW-MRI surveillance may be considered for patients who achieve a PMR with DS5 on EoT PET if findings from the rebiopsy sample analysis are negative or inconclusive or if rebiopsy is not feasible (V, B).

Renaud et al, EJC, 2025

PET guided Role of RT in residual disease

- Post-chemo PET positivity ≠ always true progression
  - PPV only ~17% in DA-EPOCH-R study
- Deauville 4 is a key gray zone
- IELSG-26 study:
  - DS 4 patients receiving RT → ~90% long-term CR
  - PET-positive (DS4) → RT can convert to cure
- Avoid overtreatment in false positives, but don’t miss salvage window

Relapse scenario – prognostic implication

- Relapsed/refractory PMBCL → poor prognosis
  - ORR to salvage chemo ~25%
  - 2-year OS ~15%
- HDT-ASCT improves outcomes:
  - 2-year PFS ~57%
  - 2-year OS ~67%
- MD Anderson data:
  - ~10% relapse/progression
  - RT + ASCT → durable remissions

RT approach in Relapsed/Refractory- from ILROG guideline

Scenario	Timing	Dose	Volume
1. CMR after salvage (Deauville 1–3)	• **Post-ASCT (preferred):** 4–12 weeks post-transplant • **Pre-ASCT:** ≤4 weeks after salvage chemo	• 30–36 Gy (1.5–2 Gy/fx) • Pre-ASCT option: 30 Gy (1.5 Gy BID)	• Site of relapse ± adjacent initially involved nodes (if safe)
2. Residual FDG avidity (Deauville 4–5)	• **Pre-ASCT (favored):** ≤4 weeks post salvage (stem cell harvest before RT) • **Post-ASCT:** 4–12 weeks	• Pre-ASCT: 36 Gy + boost to 40–45 Gy • Post-ASCT: DS 1–3 → 36 Gy; DS 4–5 → 36 Gy + boost to 40–45 Gy	• Same as Scenario 1
3. Localized refractory disease	• **Pre-ASCT:** ≤4 weeks post salvage (after stem cell harvest)	• 40–50 Gy (1.8–2 Gy/fx) • Option: 35–40 Gy (1.3–1.5 Gy BID) if aggressive disease	• Same as Scenario 1
4.Transplant-ineligible patients	—	• **Palliative:** 8–30 Gy (hypofractionated) • **Curative:** 45–55 Gy • Bulky disease: ~40 Gy ± concurrent chemo	• Palliative: symptomatic sites only • Curative: locoregional disease

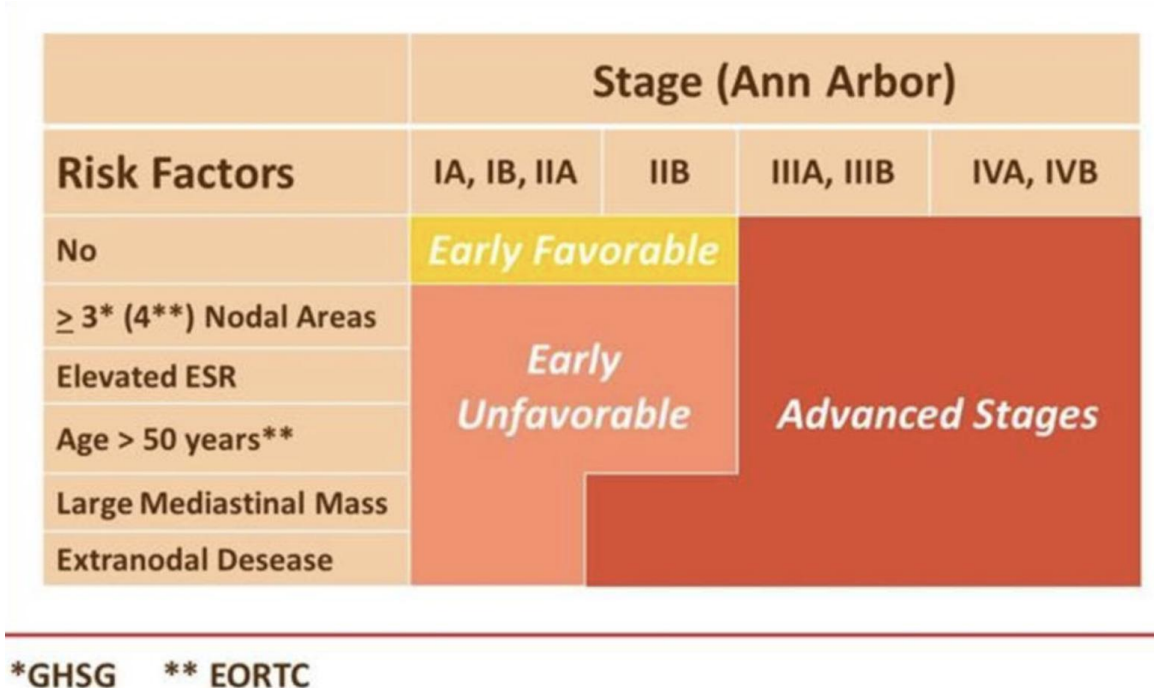
Hodgkin’s lymphoma

Epidemiology

- Bimodal age distribution; initial peak in young adults at around age 25 years and a second peak occurring at age 60 to 70 years
- > 50 % present at early stage
- majority of the cases seen in young adulthood are of a (NS) in developed countries
- mixed cellularity (MC) subtype is the predominant histologic subtype in developing countries
- typically in the cervical, axillary, or mediastinal areas,
- 10% of the time as nodal disease below the diaphragm.
- 25% of patients with Hodgkin's lymphoma have B symptoms.

Risk Stratification

- Goal of treatment for patients with Hodgkin lymphoma is to cure the disease with control of short and long-term complications.
- Treatment is based on the stage of the disease and risk stratification
- Risk stratification categorizes patients as low risk or high risk for recurrence



Role of RT for Hodgkins lymphoma

Early stage (Stage I/II)
- Favorable
- Unfavorable

Advanced stage (Stage III/IV, [bulky stage II])
- Incomplete response to chemotherapy
- (Bulky disease)

Relapsed/refractory
- Peri-transplant
- Salvage
- Palliation

Early stage Favorable HL

Non-PET adapted

- **GHSG HD10:** Treatment De-escalation for Early stage HL
  - ABVD × 2 + 20 Gy ISRT → excellent outcomes

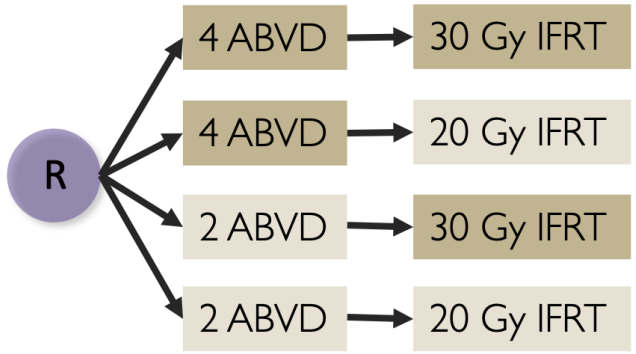
Response adapted therapy for early stage HL

- **GHSG HD16:** Can treatment be further de-escalated in early stage HL
  - RT cannot be safely omitted after a complete metabolic response to ABVDx2
  - ABVD × 2 + 20 Gy ISRT better
- **UK RAPID, EORTC H10F**
  - Chemo alone inferior in PFS; CMT better local control

Reduced Intensity Standard (Non-PET Adapted)

GHSG HD10

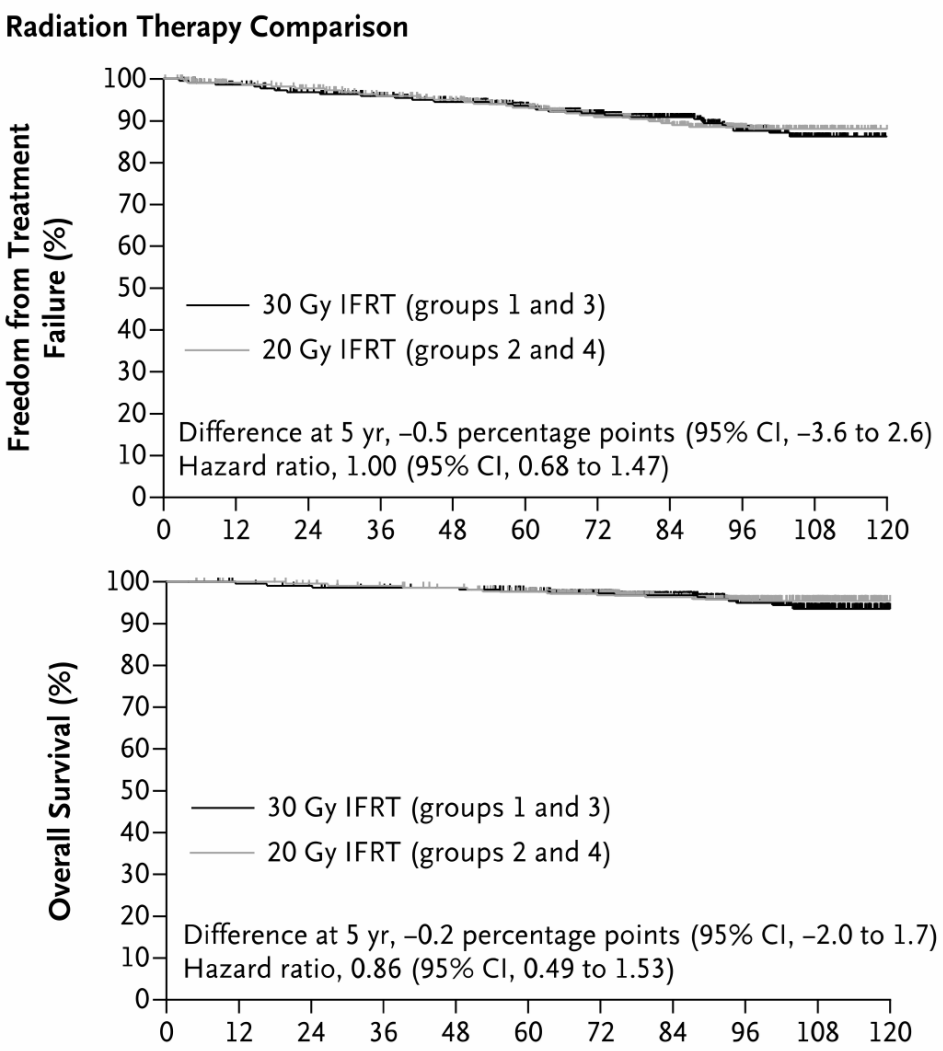
Stage I/II without clinical risk factors



ABVD: *Adriamycin, bleomycin, vinblastine, dacarbazine*

Equivalence in Efficacy

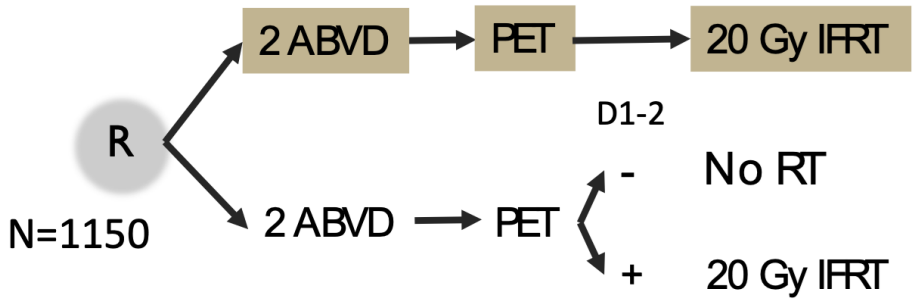
The reduced intensity regimen was effective, yielding an 8-year PFS of 86.5% and an 8-year OS of 95.1%.

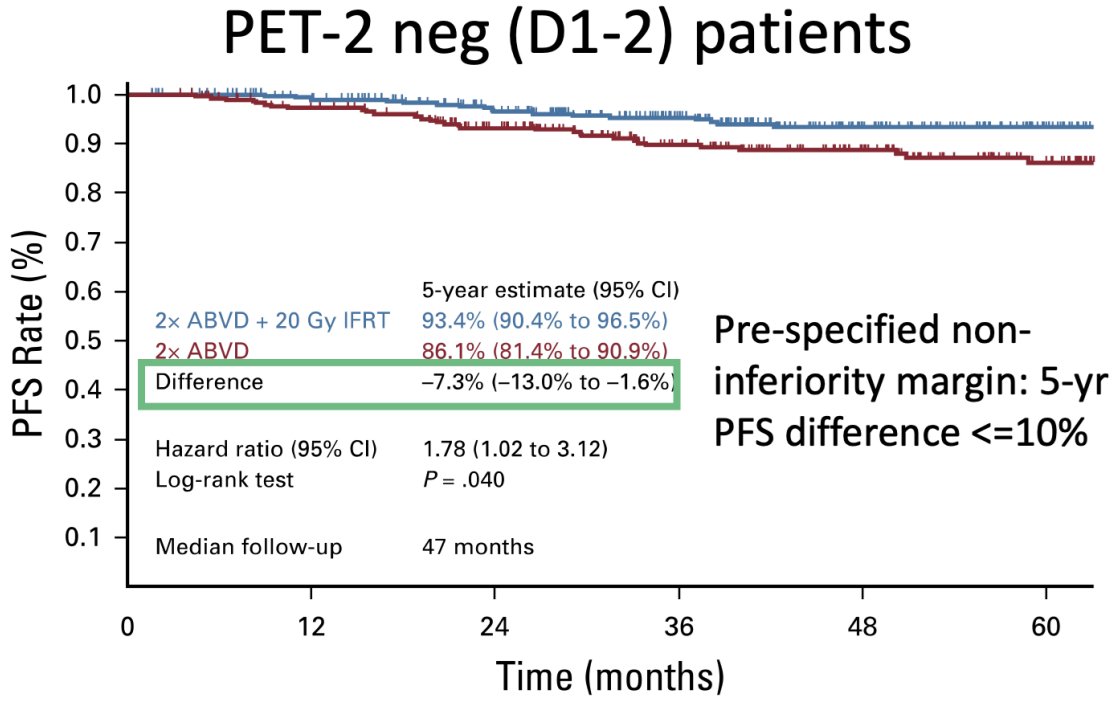


Engert, NEJM, 2010

Can therapy be further de-escalated for favorable HL?

GHSG HD16





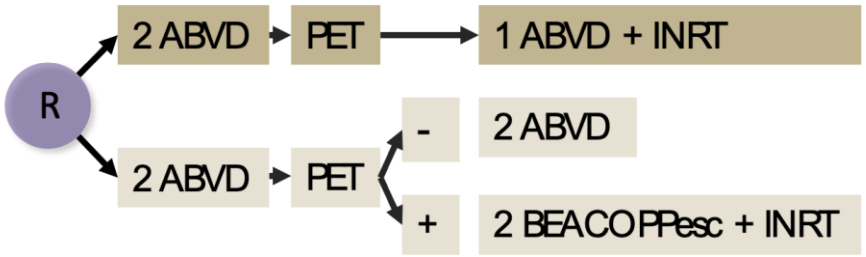
PFS : 5-year PFS was **93.4% (CMT)** vs. **86.1% (Chemo Only)**. OS was comparable (98.1% vs. 98.4%).

Fuchs, JCO, 2019

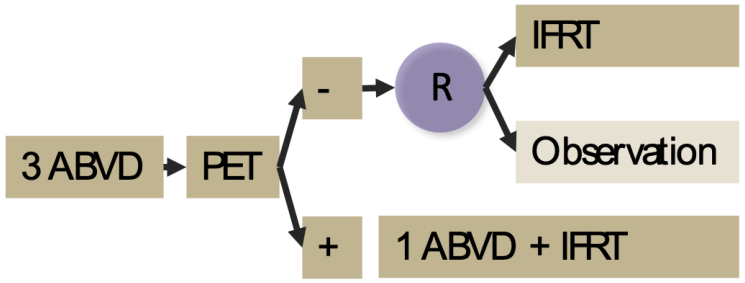
RT cannot be safely omitted after a complete metabolic response to ABVDx2

PET-Adapted RT Omission Trials

EORTC H10F



UK RAPID



RT Omission Showed Inferior PFS

Trial	Risk Group & PET Definition	Key Outcome Comparison
EORTC H10 (Favorable Arm) Raemaekers, JCO 2014	Favorable Early-Stage HL (PET-negative defined as **DS 1-2)**	5-year PFS was **99% (CMT)** vs. **87.1% (Chemo Only)**. Trial was closed prematurely because the non-RT arm exceeded the relapse boundary limit.
UK RAPID Radford, NEJM 2015	Favorable Early-Stage HL, Non-Bulky (PET-negative defined as **DS 1-2**)	3-year PFS was **94.6% (CMT)** vs. **83% (Chemo Only)**. However, the 3-year OS was comparable (97.1% vs. 99.0%). CMT improved PFS

Early stage unfavorable HL

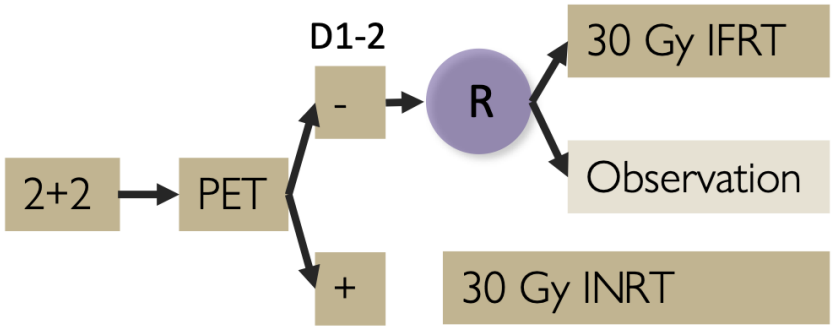
Non-PET adapted

- **GHSG HD11 and GHSG HD14**
  - ABVD × 4 or BEACOPPesc x2 + ABVD x2 + 30 Gy ISRT

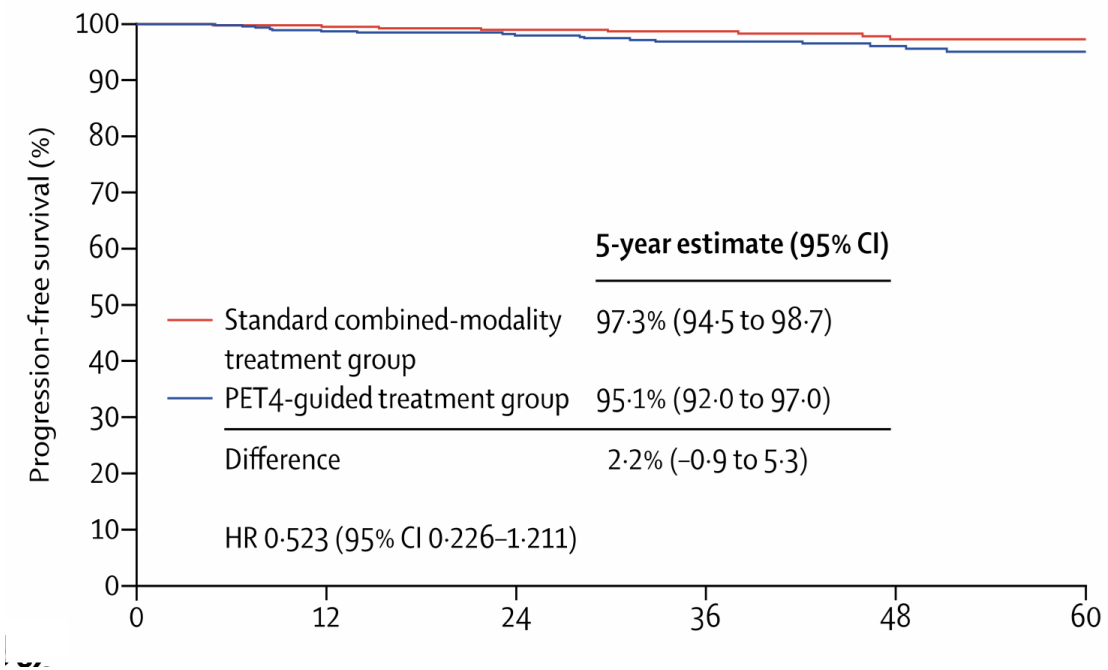
Response adapted therapy for early stage HL

- **GHSG HD17:**
  - Safe omission of RT depends on chemo backbone
  - BEACOPPesc x2 + ABVD x2

Safe omission of RT depends on chemo backbone



2+2: BEACOPPesc x2 + ABVD x2



GHSG HD17

- Early unfavorable HL
- Non-inferiority margin PFS5 <=8%

Borchmann, Lancet, 2021

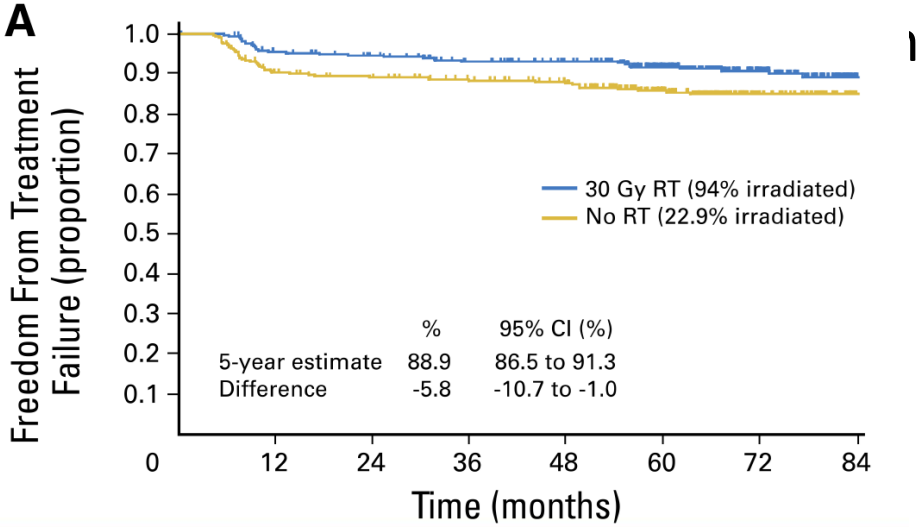
RT can be safely omitted after negative PET with more intensive chemotherapy backbone (2+2)

Advanced stage

RT for residual disease improves PFS

GHSG HD12 (*Borchmann JCO 2011; von Tresckow Lancet Hematol 2018*)

- Randomized 30 Gy vs obs
- A
- P



GHSG HD15 (*Engert Lancet Oncol 2012*)

- Single arm, no randomization
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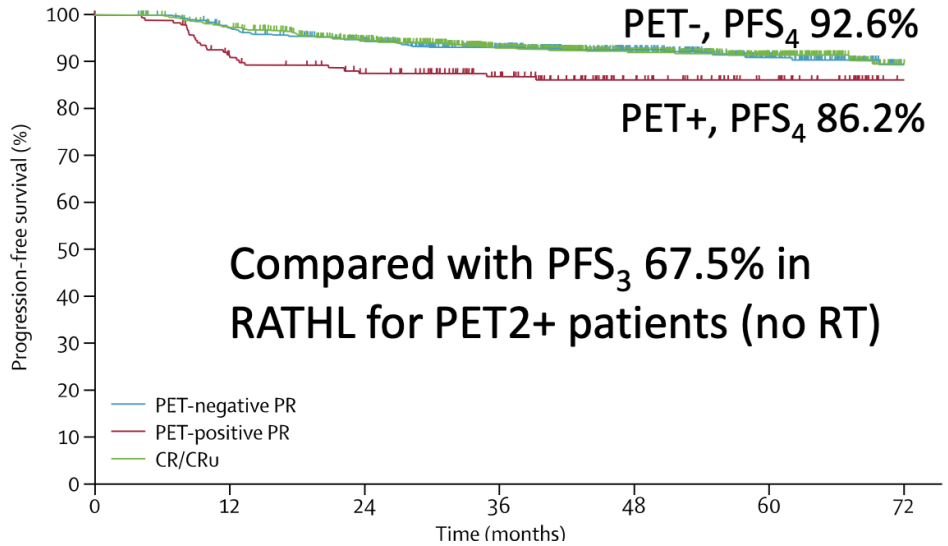
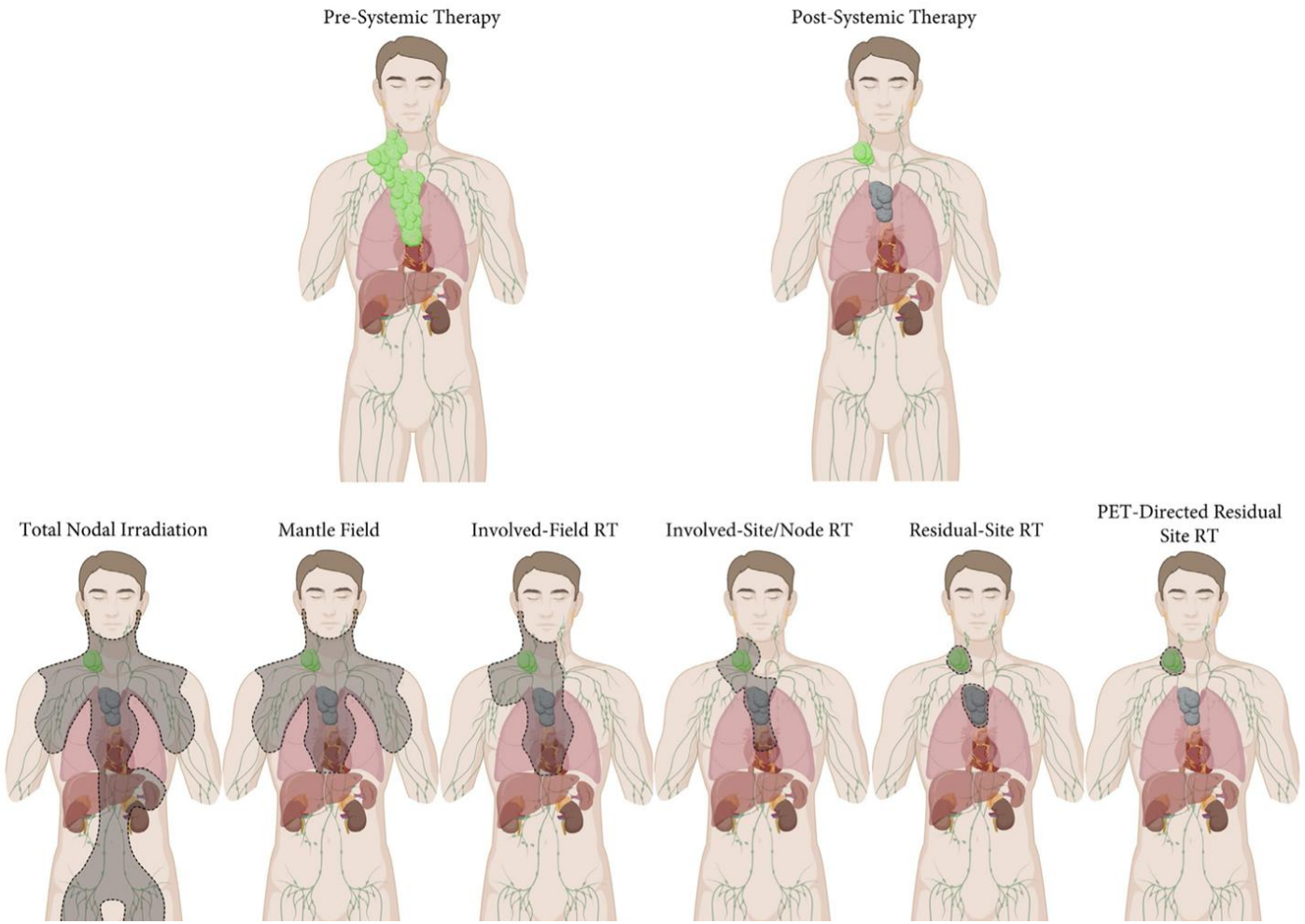


RT Doses

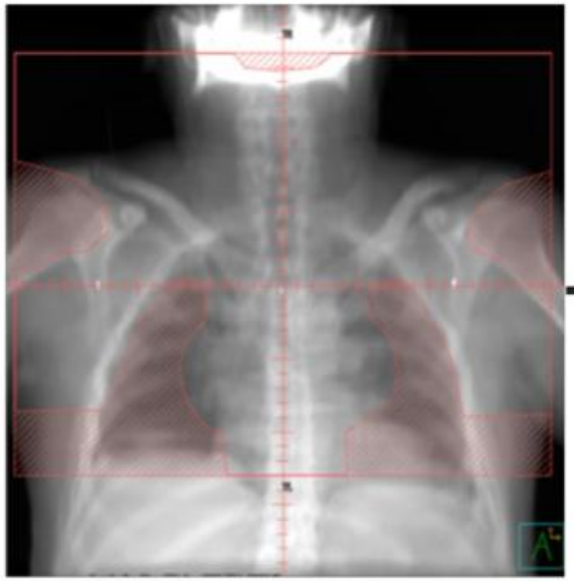
Risk Group	PET	RT Dose
Early Stage Favorable	Negative	20 Gy
Early Stage Unfavorable	Negative	30 Gy
Incomplete Response	Positive	36–45 Gy

Evolution of Radiotherapy fields



- As the understanding of radiation therapy improved, so did the awareness regarding safe radiation doses for organs at risk (OARs).
- This led to a **trend toward smaller radiation fields** over time, facilitated by advances in imaging techniques and the integration of systemic therapy.

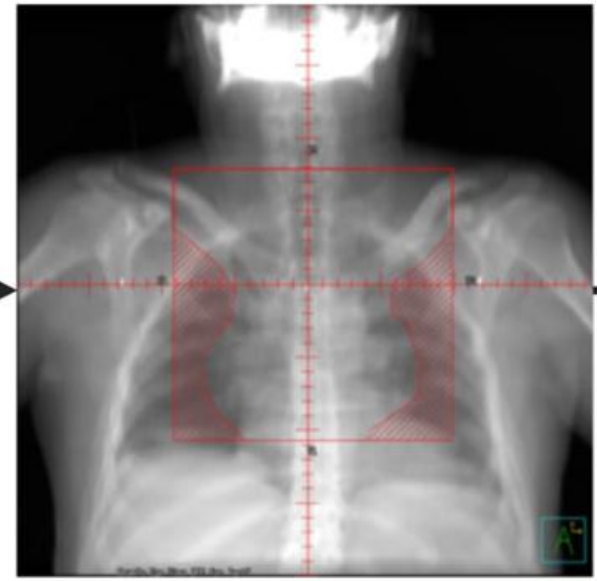
EFRT



Late 1960s

Mantle, inverted Y = TLI
MOPP

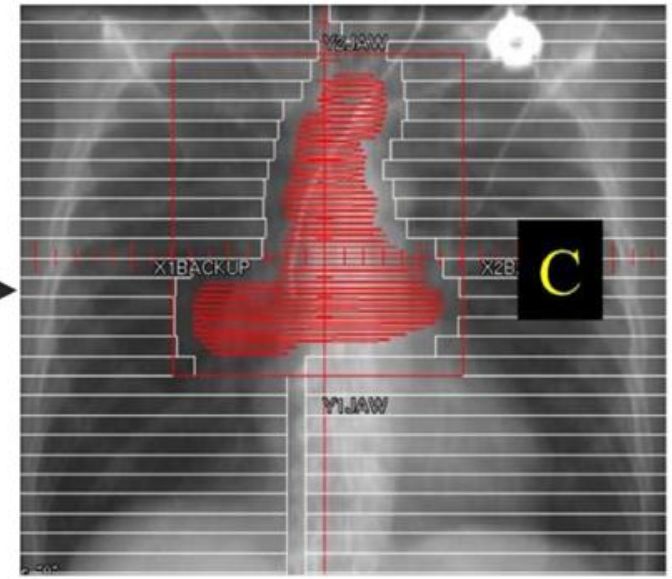
IFRT



Late 1980s-1990s

MOPP → ABVD

INRT/ISRT



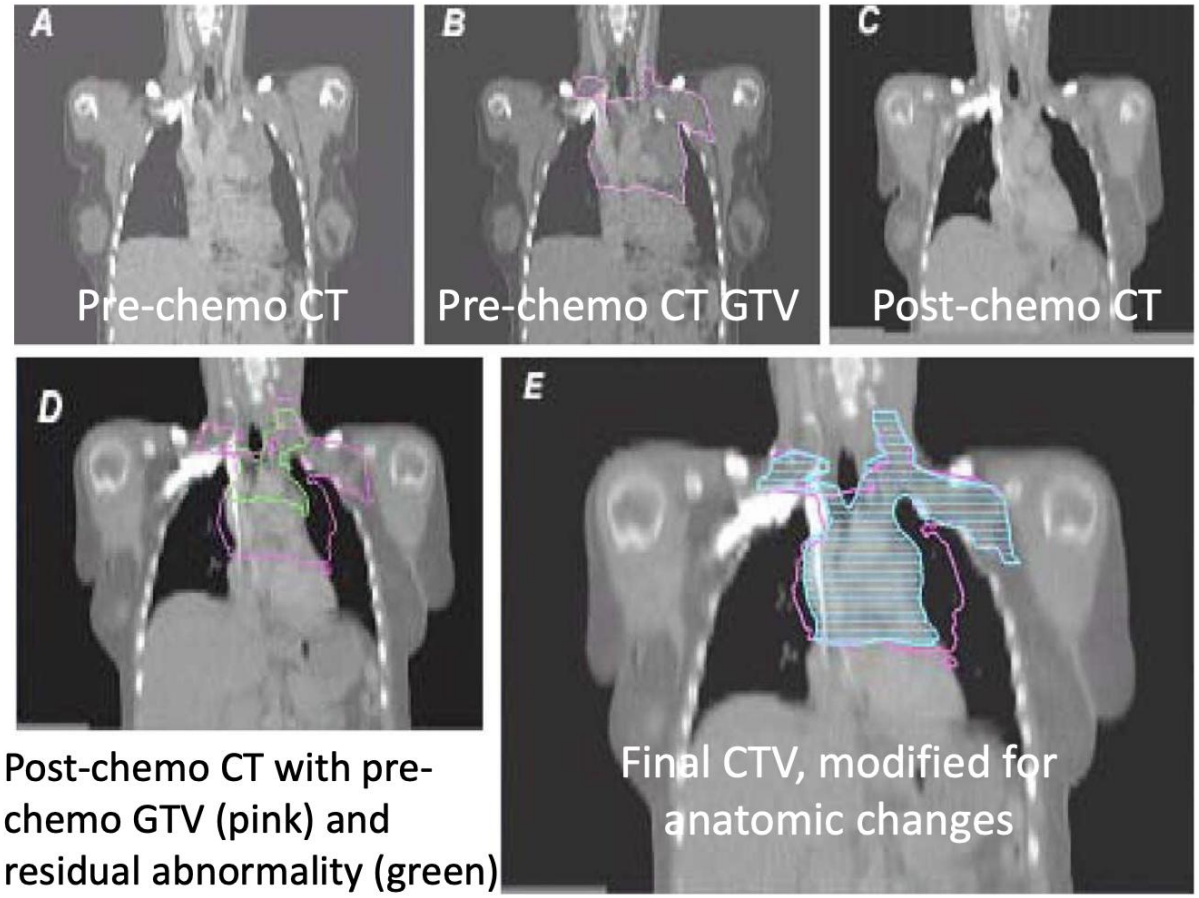
Late 2000s

ABVD

Radiation

Chemotherapy

Involved Node/ Site Radiotherapy technique



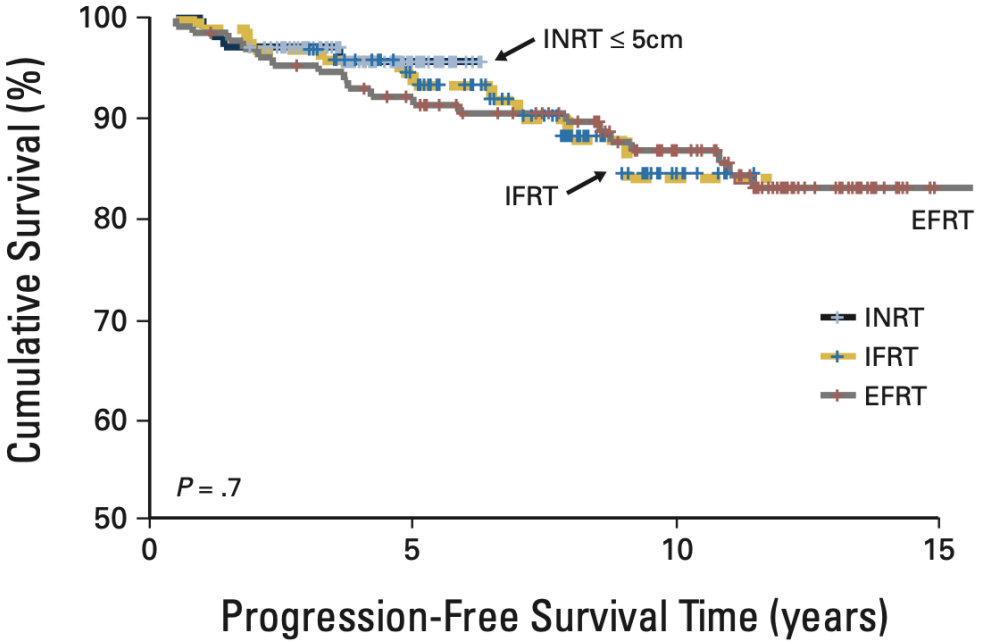
Post-chemo CT with pre-chemo GTV (pink) and residual abnormality (green)

- Pre-chemotherapy GTV determines CTV
- INRT is a special case of ISRT in which optimal imaging is available
- ISRT CTV may be larger to accommodate uncertainties in defining pre-chemo GTV
- Modern RT techniques (3D- planning versus 2D bony anatomy)

Outcomes with smaller fields

No randomized data on IFRT versus ISRT/INRT

- Prospective data (EORTC H10)
- Retrospective data
  - *BCCA:* LRR (2%) in 5 (EBRT 3, IFRT 2)
  - *University of Copenhagen* (INRT): 'in- node' relapse in 2 (1.2%)
  - No marginal relapses



Smaller fields are not associated with increased rates of relapse

Campbell JCO 2008; Nielsen Radiother Oncol 2020

Deep Inspiratory Breath Hold(DIBH)

Dosimetric comparison of DIBH versus free breathing (FB): Institut Gustave Roussy

Dosimetric parameter	Patient group	Free-breathing IMRT	Deep-inspiration breath-hold IMRT	Difference	*p* value
Mean coronary dose	All patients (n = 28)	18.2 (15.9–20.6)	15.2 (12.6–17.9)	16%	0.0002
	Upper mediastinum (n = 11)	13.9 (10.1–17.6)	8.8 (5.6–12.1)	37%	0.001
	Whole mediastinum (n = 17)	21.1 (18.7–23.4)	19.3 (17.2–21.6)	9%	0.002
Mean heart dose	All patients (n = 28)	8.4 (6.1–10.7)	7.1 (4.7–9.6)	15%	0.002
	Upper mediastinum (n = 11)	3.6 (2.5–4.7)	1.8 (1.4–2.2)	50%	0/001
	Whole mediastinum (n = 17)	11.5 (8.6–14.4)	10.6 (7.6–13.6)	8%	NS
Mean lung dose	All patients (n = 28)	11.8 (10.6–12.9)	9.4 (8.3–10.4)	20%	<0.0001
	Upper mediastinum (n = 11)	9.2 (8.4–10.1)	6.8 (6.3–7.3)	26%	0.001
	Whole mediastinum (n = 17)	13.4 (12–14.8)	11 (9.9–12.1)	18%	0.0003
Lung V20	All patients (n = 28)	21 (18–24)	15 (12–16)	28%	<0.0001
	Upper mediastinum (n = 11)	16 (13–19)	10 (8–12)	38%	0.001
	Whole mediastinum (n = 17)	24 (21–28)	17 (15–20)	29%	0.0003

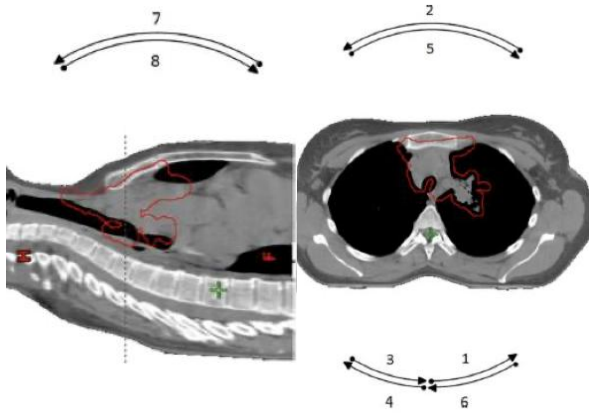
Greatest benefit of DIBH for tumors with only upper mediastinal involvement

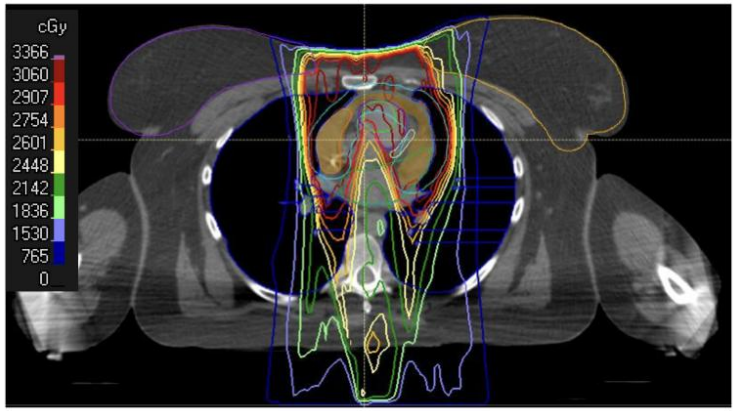
Paumier IJROBP 2012

Approaches for lower mediastinal lymphomas

"Butterfly" IMRT/VMAT

- 5-7 total beams
- 2-3 non-coplanar arcs
- Anterior 300°-30°
- Posterior 160°-210

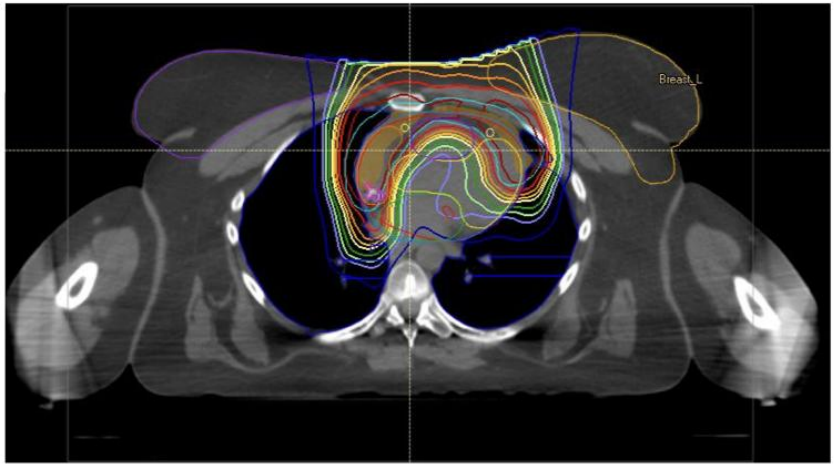




Voong Radiat Oncol 2014; Starke Radiother Oncol 2018

Proton therapy

- Anterior or anterior oblique +/- posterior beams
- Volumetric repainting if using a single beam



Dose constraints for Mediastinal Lymphoma

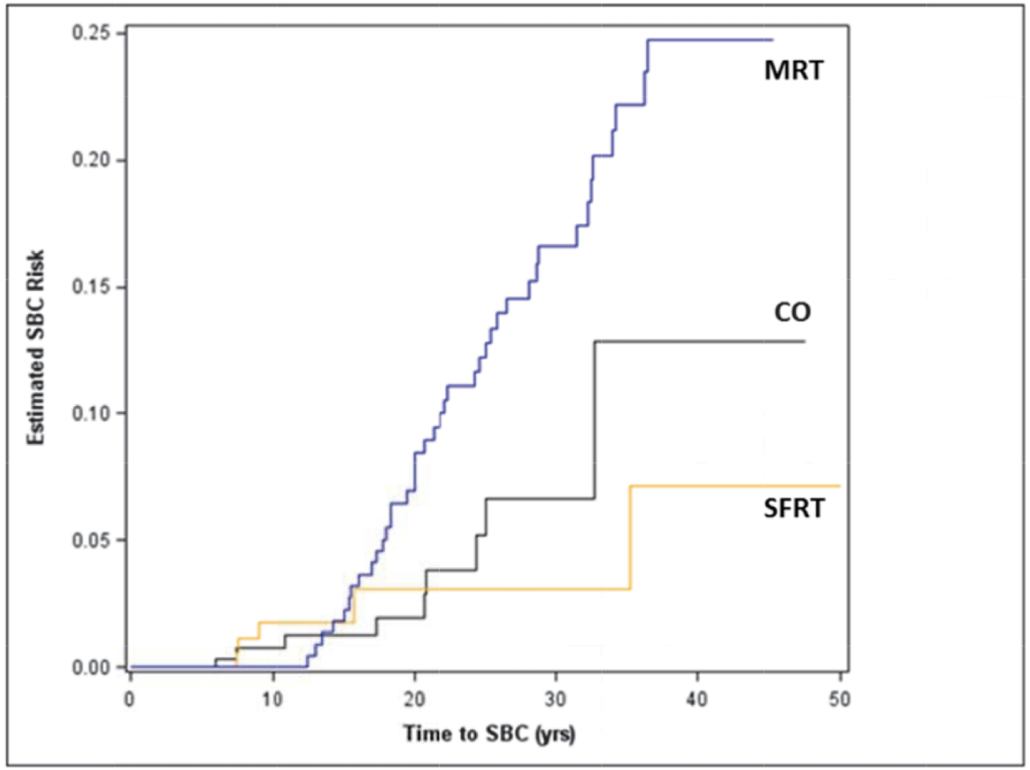
- When treating DLBCL located in the mediastinum, especially in young patients, late toxicity considerations are crucial.
- Small reductions in mediastinal treatment volumes can significantly reduce the exposure of cardiac substructures, such as the coronary arteries.
- Dose constraints should be applied with flexibility.

Organ At Risk	Measure	Optimal	Acceptable	If Necessary
Heart	Mean (Gy)	<5	5–10	10–18
Coronary Arteries & Left Ventricle	V15	<10%	10%–25%	25%–35%
	V30		<15%	15%–20%
Lung	V5	<35%	35%–45%	45%–55%
	V20	<20%	20%–28%	28%–35%
	Mean (Gy)	<8	8–12	12–15
Breast (Glandular tissue)	Mean (Gy)	<4	4–15	>15
	V4	<10%	10%–20%	>20%
	V10		<10%	>10%

Wirth IJROBP 2020

Reduction in Breast Cancer Risk with smaller fields

- Large volume mantle radiotherapy is associated with a markedly increased risk of SBC; however, more modern small volume radiotherapy is not associated with a greater risk of SBC than chemotherapy-alone.



MRT = Mantle field radiation; SFRT = Small field radiation; CO = Chemotherapy only;

SBC = Secondary breast cancer

Conway IJROBP 2017

Long term toxicities and second malignancies

- Historically, long-term toxicities were a major concern, but current radiation techniques employ smaller radiation fields and lower doses, reducing toxicities
- Concerning long-term toxicities- cardiotoxicity and secondary malignancies, such as breast cancer in young female patients undergoing mediastinal RT.
- It is critical to balance the risks, as chemotherapy itself carries significant toxicity; anthracycline strongly associated with cardiac toxicity and breast cancer.
- In the modern era of conformal RT, the mean radiation dose to the heart is commonly kept below 10 Gy in patients with mediastinal disease

Take home message

1. Paradigm Shift: "Less is More"
Volume Reduction: The days of Extended Field (EFRT) and Involved Field (IFRT) are gone. The global standard is now **Involved Site Radiation Therapy (ISRT)** or **Involved Node Radiation Therapy (INRT)**.
Dose De-escalation: Trust the biology of lymphoma. For consolidative treatment in Hodgkin Lymphoma with a complete metabolic response (CMR), **20–30 Gy** is highly effective. Avoid the instinct to treat lymphomas with epithelial-tumor doses.

2. The Golden Rule of Contouring
Treat the **post-chemotherapy residual volume** but completely encompass the **pre-chemotherapy initial extent in the craniocaudal (vertical) direction**.
Always look at the pre-chemotherapy PET/CT side-by-side with your planning scan to avoid missing original nodal stations that have collapsed after systemic therapy.

3. Mitigate Late Toxicities Remorselessly

Mediastinal lymphoma patients are frequently young females with decades of life ahead. Your planning decisions today dictate their risk of **coronary artery disease, valvular dysfunction, and secondary breast/lung cancers** 15 to 30 years down the line.

Keep Mean Heart Dose (MHD) as low as reasonably achievable—ideally **less than 5 Gy**, though every gray decreased counts.

4. Leverage Advanced Technology

Do not routinely use simple 3D-CRT unless necessary. Utilize **VMAT / IMRT** to tightly sculpt doses, but remain vigilant about the "low-dose bath" to the lungs.

Actively incorporate motion management: **Deep Inspiration Breath Hold (DIBH)** is a powerful tool to naturally elongate the thorax, pushing the heart inferiorly and away from the high-dose mediastinal target. Use proton therapy if available and constraints are unmet.

💡 **The Resident's Mantra:** "Cure is highly likely; your primary job is to deliver that cure with the lowest possible biological cost. Tailor the volume, control the motion, and respect the OARs (Organs at Risk)."

Thank you