Radiotherapy for Non-Hodgkins Lymphoma

(Diffuse Large B Cell Lymphoma & Follicular Lymphomas)

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LEARNING OBJECTIVES

- Radiosensitivity of lymphomas to radiation therapy

  -preclinical evidence and dose response relationship

- Radiation therapy volumes in the modern PET & rituximab era

  - from EFRT to IFRT to ISRT

- Optimizing Radiation doses in the modern PET & rituximab era

  - from 55Gy to 45Gy to 30-36Gy to 20Gy

- Clinical scenarios

  - role of RT for decision making processes

Radiosensitivity of lymphoma cells -The biology behind it

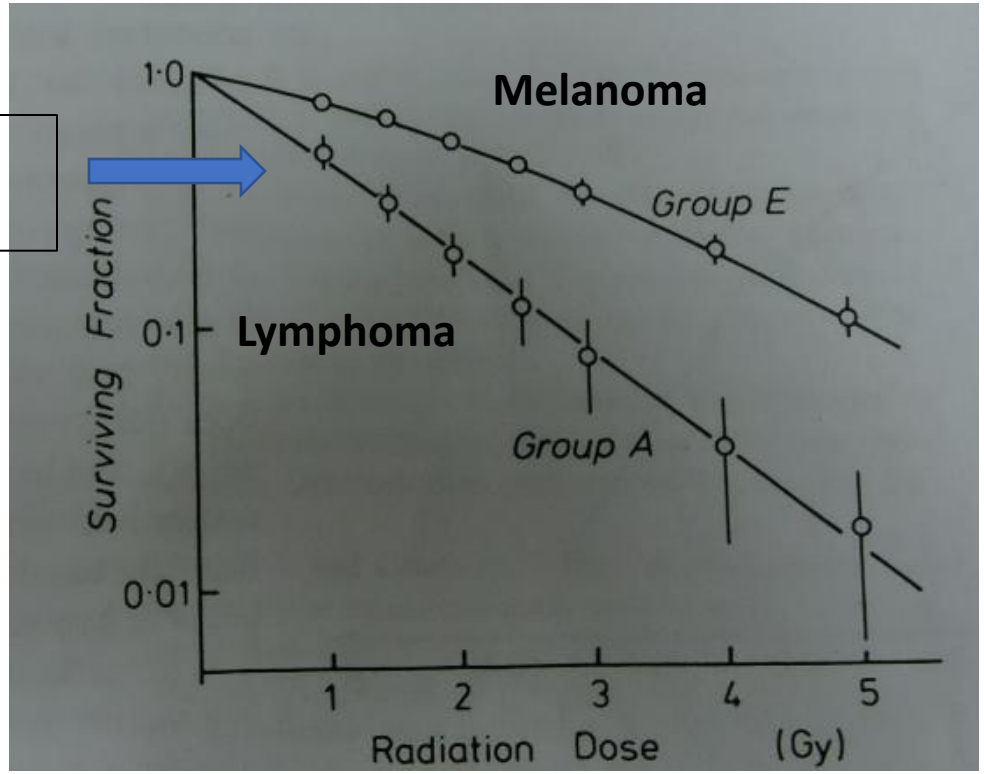
Radiosensitivity of human B-lymphocytic lymphomas in vitro

- 4 lymphoma cell lines studied
- D_0 1.3 to 1.8 Gy.
- No shoulder
- low capacity to accumulate sublethal damage.
- Show high degree of apoptosis
- Absence of hypoxia

Johansson L, et al - Int. J. Radiat. Biol. Relat. Stud. Phys. Chem. Med.1982

In-vitro evidence of radiosensitivity of lymphoreticular tumours

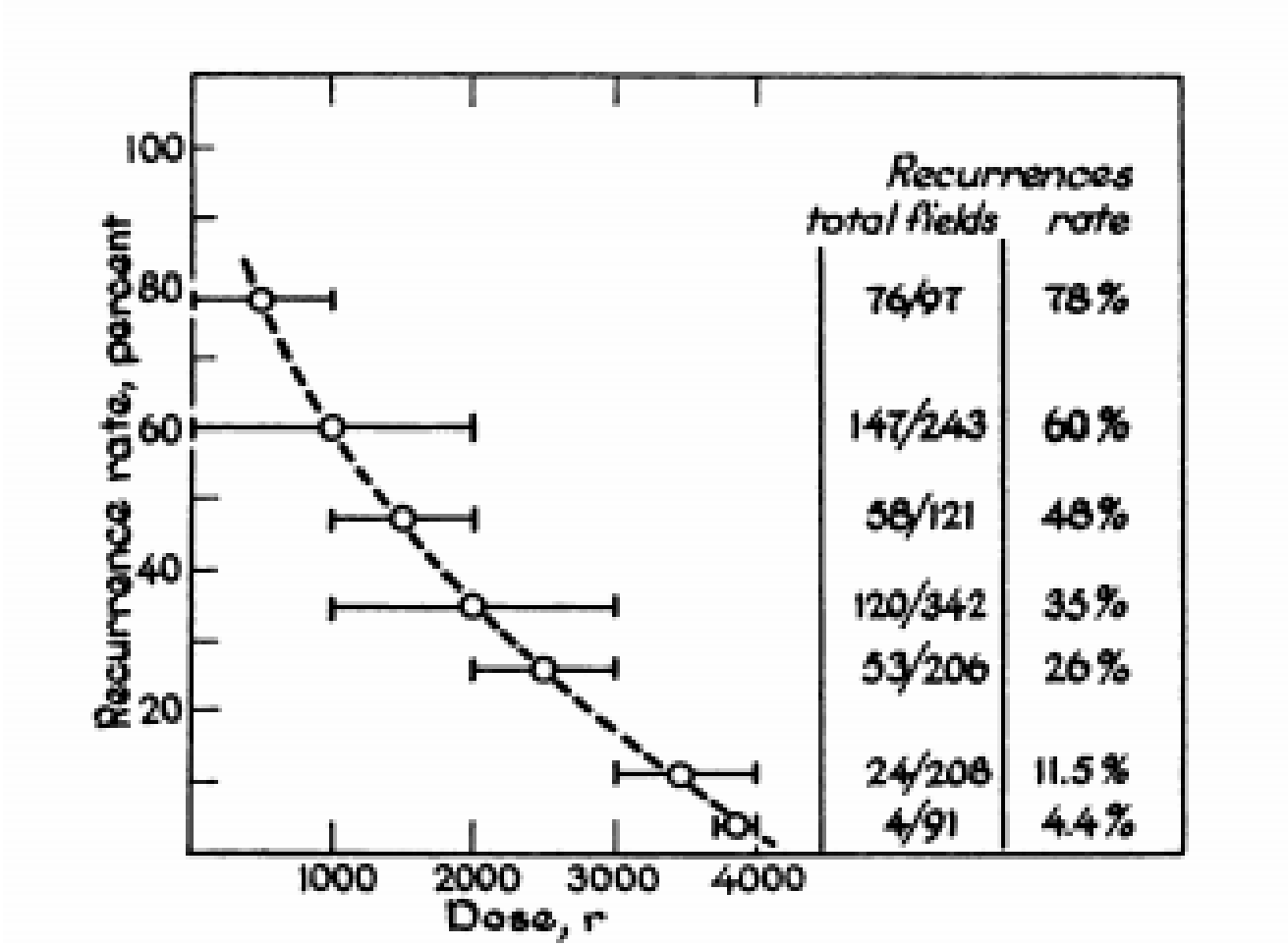
Little or No shoulder



- No SLD repair
- Effect of fraction size is minimal

Deacon J et al, Radiother Oncol 1984
Steel GG, Br J radiol 1988

Evolution dose- response relationship in lymphoma



Lymphomas tends to recur in a treated field with a frequency which is inversely related to dose and approaches zero at a dose of approximately 4000 rads

Kaplan H et al Cancer Res 1966

Radiation therapy dose de-escalation in the modern PET & rituximab era

from 55Gy to 20Gy

The Radiotherapy Era where radiation alone was used

Radiation Doses pioneered by **The Stanford** Group and the **Princess Margaret** Group

Radiation Therapy Era

Evolution of radiation therapy in lymphoma
Dose response relationship

Group/Year	No of pts	Relapse rates	Dose	Remarks
Stanford Group (1960-70)	198	12-15%	44Gy	No dose response relationship across a range of 20-50 Gy
BNLI (1974-81)	82	0%	45Gy	100% response at 45Gy
EORTC group 1970-1980	94 81	30% 13%	<45Gy >45Gy	Dose response at 45 Gy
Toronto group 1967-1978	496		25Gy to 40Gy	No dose response seen above 30Gy

No clarity in the dose-response relationship at the clinical level

Radiation therapy era

Limitations of the studies

- The studies were all retrospective
- Radiation volumes were varied

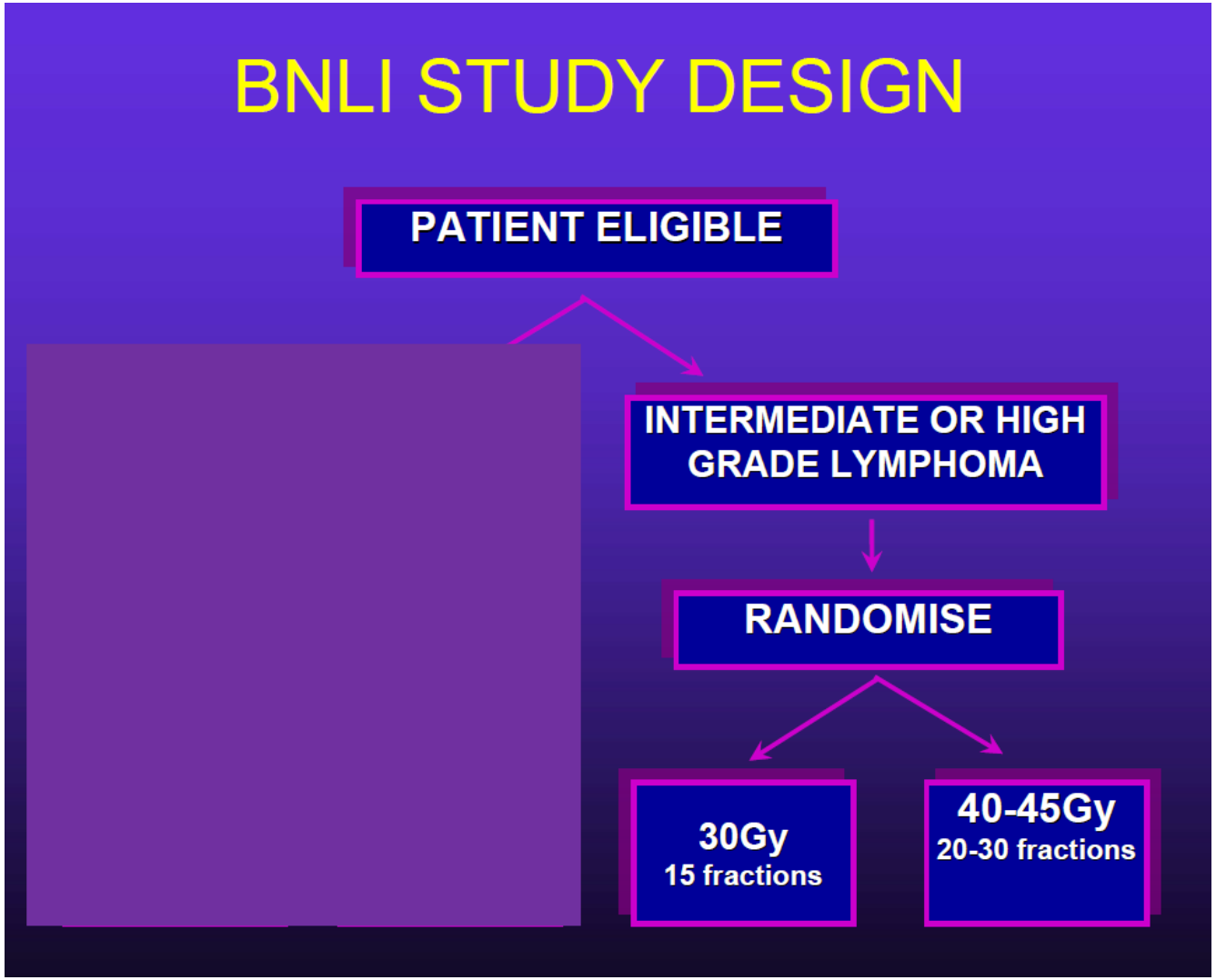
  - extended field to involved field
- Techniques were variable
- Various histologies were included

Their present day applicability is limited by

- changes in treatment practices
- changes in the NHL classification systems over 5 decades
- evolution in radiotherapy technology

Radiotherapy dose de-escalation: for NHL (DLCBL)

Only published Randomized radiotherapy study looking at RT dose de-escalation in DLBCL



30 Gy vs 40-45 Gy

Median f/u 5.6 yrs:

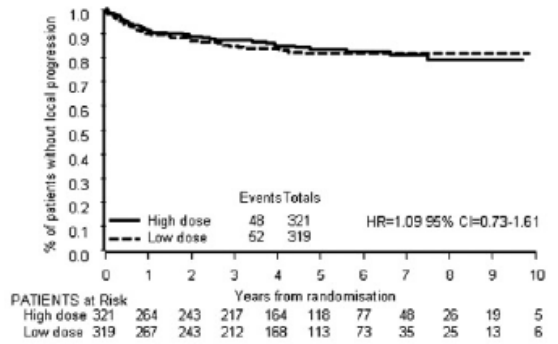
	30 Gy (n=319)	40-45 Gy (n=321)	p-value
CR	82%	83%	-
5y FFLP	82%	84%	0.66
5y OS	64%	68%	0.29

- **Caveats:**
  - Included pts treated with RT alone or receiving salvage/palliative RT
  - No chemo data, mostly without rituximab
  - Lack of functional imaging to determine response to chemo

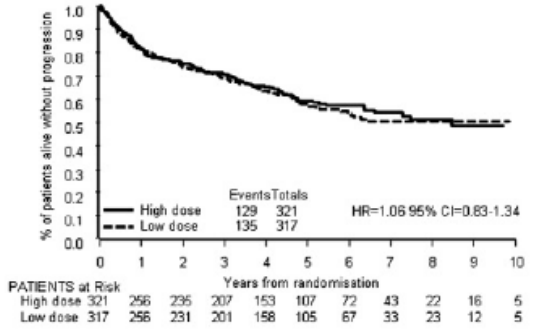
Lowry et al Radiother Oncol 2011

Aggressive group

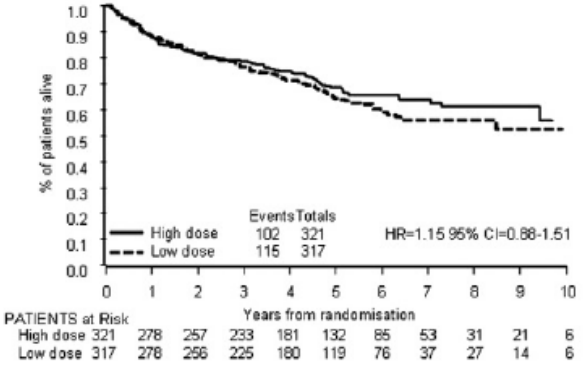
Freedom from local progression



Progression-free survival



Overall survival



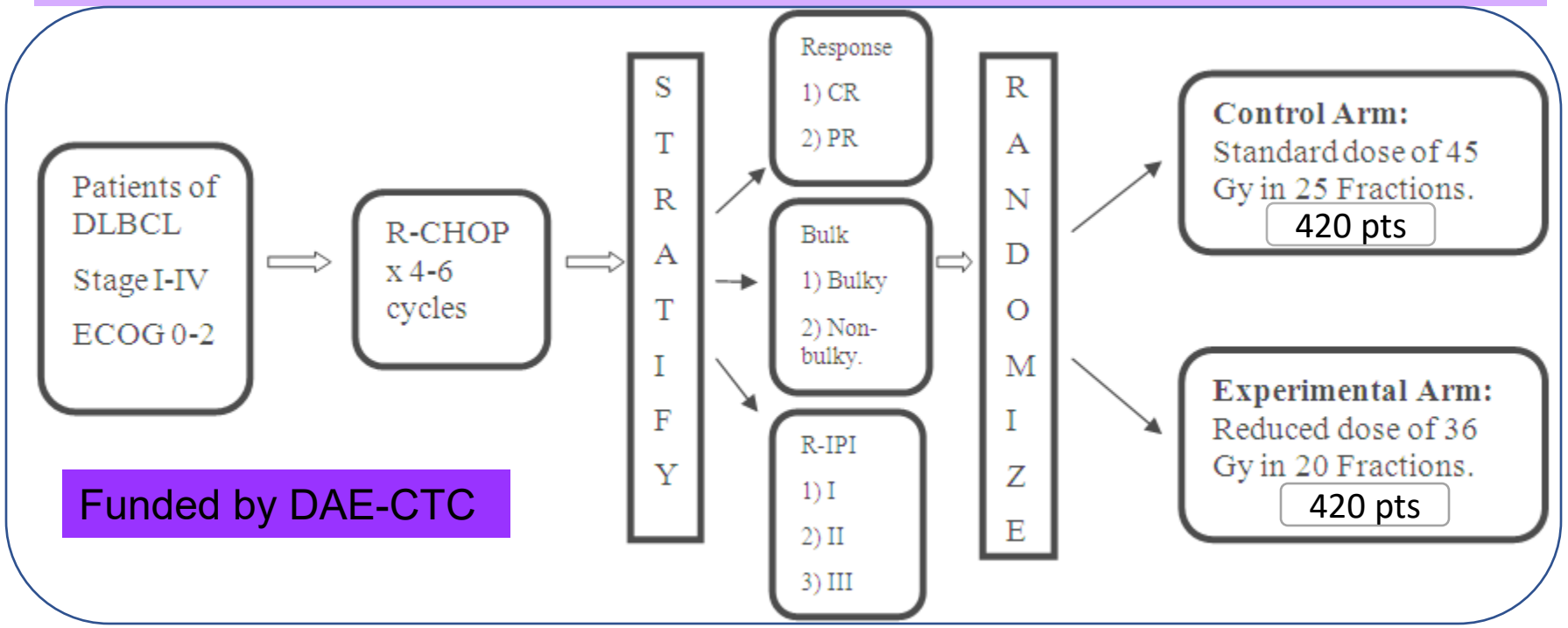
TMH Randomized study

Radiation Dose Optimization in Diffuse large B- cell Lymphoma - A Randomised Phase III non- inferiority trial. (DOBL study)

ClinicalTrials.gov Identifier: NCT02964858
Started active recruitment

Principal Investigator Jayant S. Goda

Co – Principal Investigators: Siddarth Laskar, Nehal Khanna



Funded by DAE-CTC

TMH Randomized study (DOBL) study in the PET era

End Points

- **Primary Endpoint**: 2 year event free Survival (EFS).
- **Secondary Endpoint**:

  2 year local control rates.

  2 year Overall Survival (OS)

  Overall response rate.

  Acute and Late Toxicity.

  Quality of life scores.(FACT –GEN & FACT –Lym)

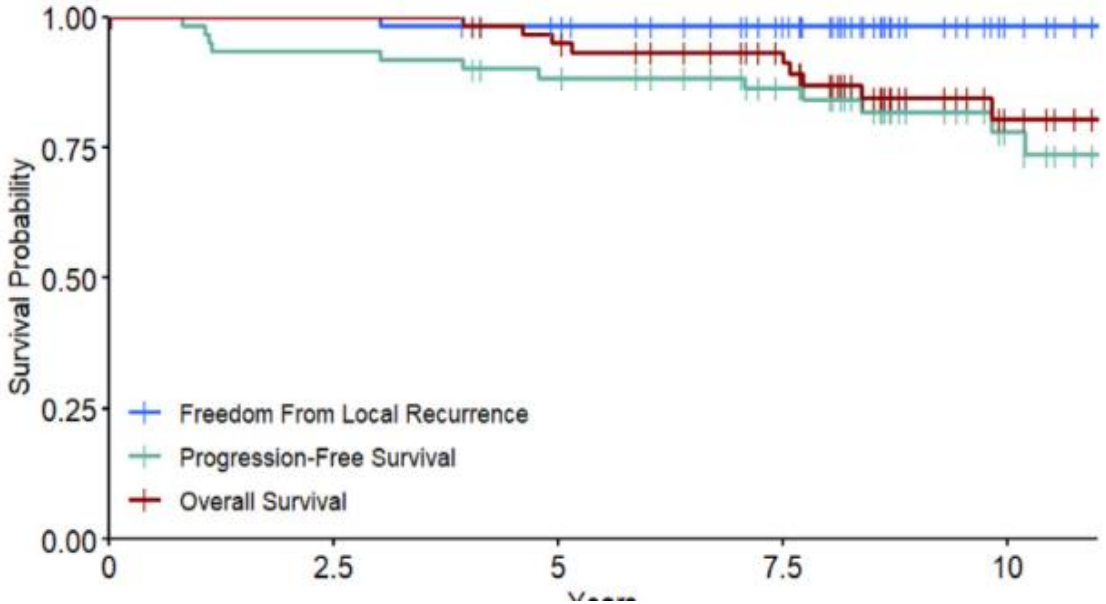
Accrued :425 pts

Interim Analysis will be done by December 2025

Phase 2 Study of Dose-Reduced Radiation in Diffuse Large B-Cell Lymphoma achieving CMR

First study in the PET era

- Single arm Phase-II study
- No of pts:62
- Median followup: 9 years
- Pts should achieve CMR after 3 cycles
- The primary endpoint of the original study was 5-year freedom from local recurrence.
- RT doses :19.5-20Gy
- **On going Randomised study of 240pts(ILROG)**



- Freedom from local recurrence of 98% at 10 years (95% CI, 88%-99%)
- 10 year Progression-free survival: 77% (95% CI, 62%-87%)
- 10 year OS: 80% (95% CI, 64%-89%)

Radiotherapy Dose Deescalation for NHL (Follicular Lymphoma)

- Role of radiotherapy in follicular lymphomas is limited to early stage ds (stage I&II)
- Radiotherapy role is definitive
- Radiotherapy doses for definitive RT have reduced considerably

- Results of two randomized studies have established the doses of radiotherapy

BNLI study (45Gy vs 24Gy) Hoskin et al Radiotherapy oncology

FORT study (24Gy vs 4GY) Hoskin et al Lancet oncology

British National Lymphoma Investigation study : RT dose de-escalation in Low grade Lymphomas :24Gy vs. 45Gy

BNLI STUDY DESIGN

PATIENT ELIGIBLE

LOW GRADE LYMPHOMA

RANDOMISE

24Gy
12 fractions

40-45Gy
20-30 fractions

24Gy vs 40-45Gy

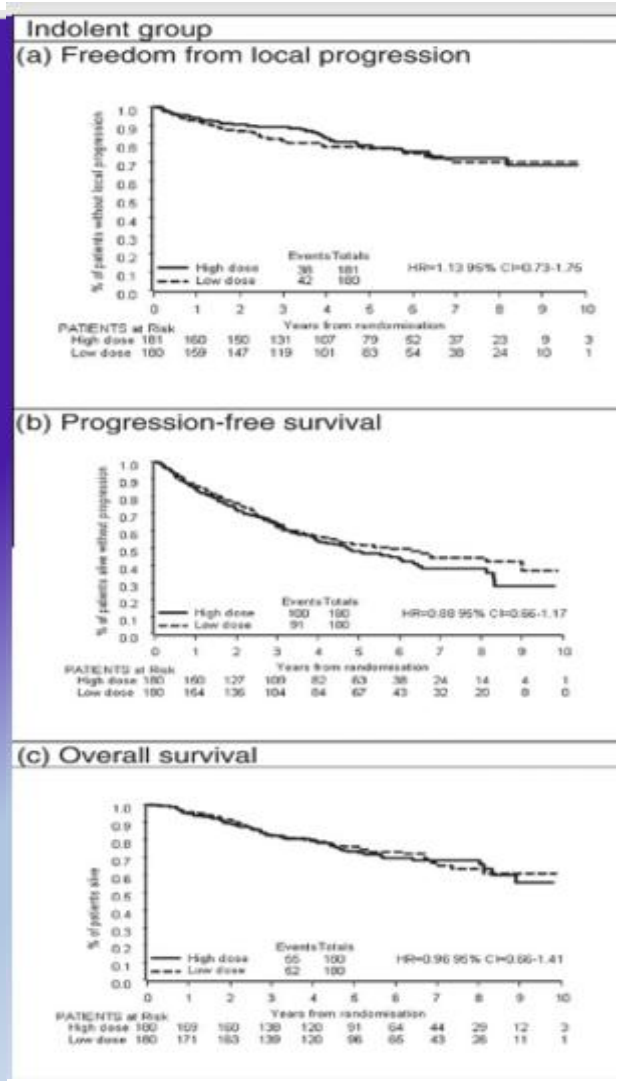
Median Fu of 5.6 yrs

	24 Gy	40-45Gy	P VALUE
CR	82%	79%	
5Yr FFLP	76%	79%	0.68
OS	74%	73%	0.84

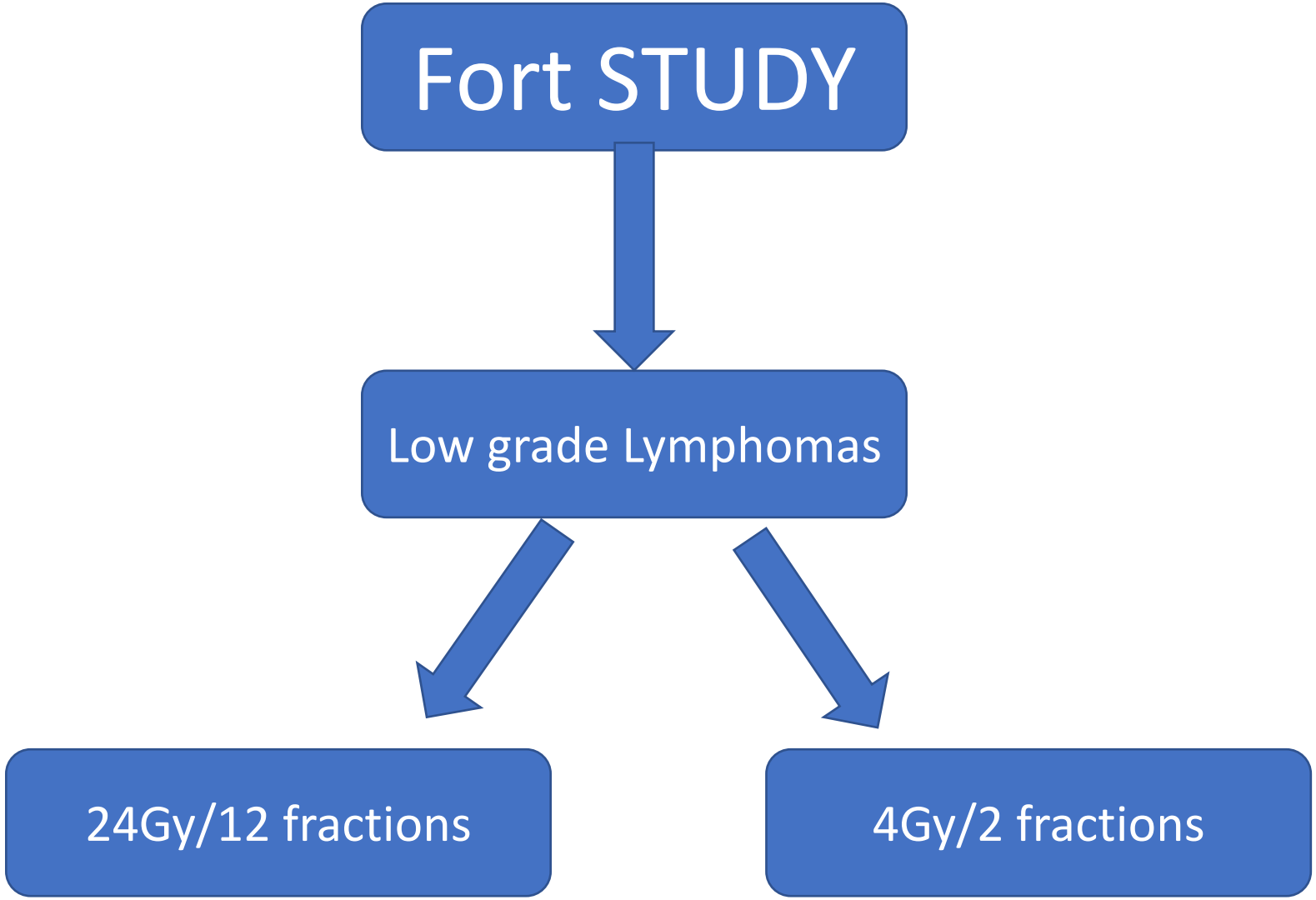
Caveats

-Multiple histologies: follicular(64%), MALT lymphomas(19%)
-Designed in the pre-WHO classification era
-- designed in the pre PET era

Lowry et al Radiother Oncol 2011



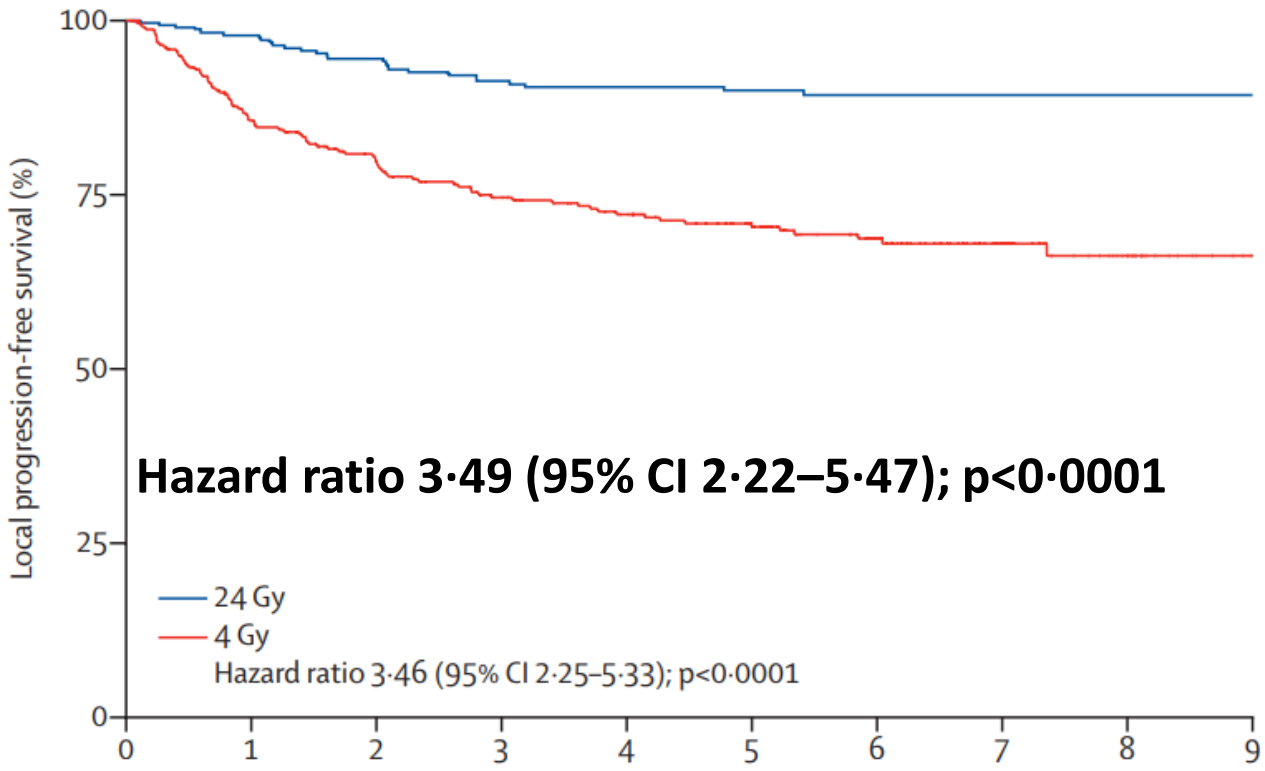
FoRTstudy : RT dose de-escalation in Low grade Lymphomas :24Gy vs. 4Gy



FoRTstudy : RT dose de-escalation in Low grade Lymphomas :24Gy vs. 4Gy

- provides level 1 evidence for use of 24 Gy in 12 fractions in patients
- durable local control with 24Gy/12 fr

- 4Gy in 2fraction (boom – boom) provides local control in two-thirds of pts
- 4Gy in 2 fr can give durable control in palliation



Take home message for Radiotherapy doses

- **For low Grade Follicular Lymphoma**

  -RT doses of 24Gy/12fraction or equivalent (25.2Gy/14fractions)

- **For high grade lymphomas (DLBCL)**

  - RT doses between 30/15fr or equivalent 36Gy/20fr in 2Gy or 1.8Gy /fr.

  - Patients in **CMR** possibility of RT dose reduction to 20Gy/10 fr

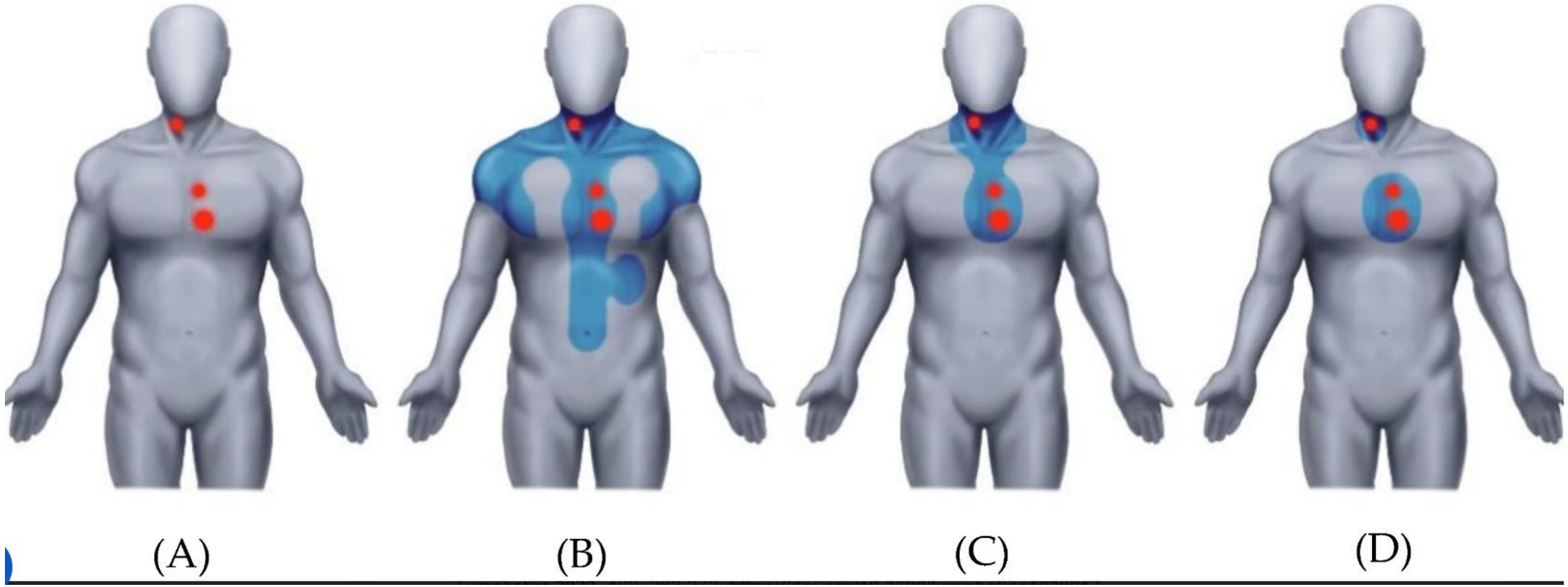
    (pending the final results of the ongoing ILROG study)

Optimizing Radiotherapy volumes in NHL (DLBCL & Follicular Lymphomas)

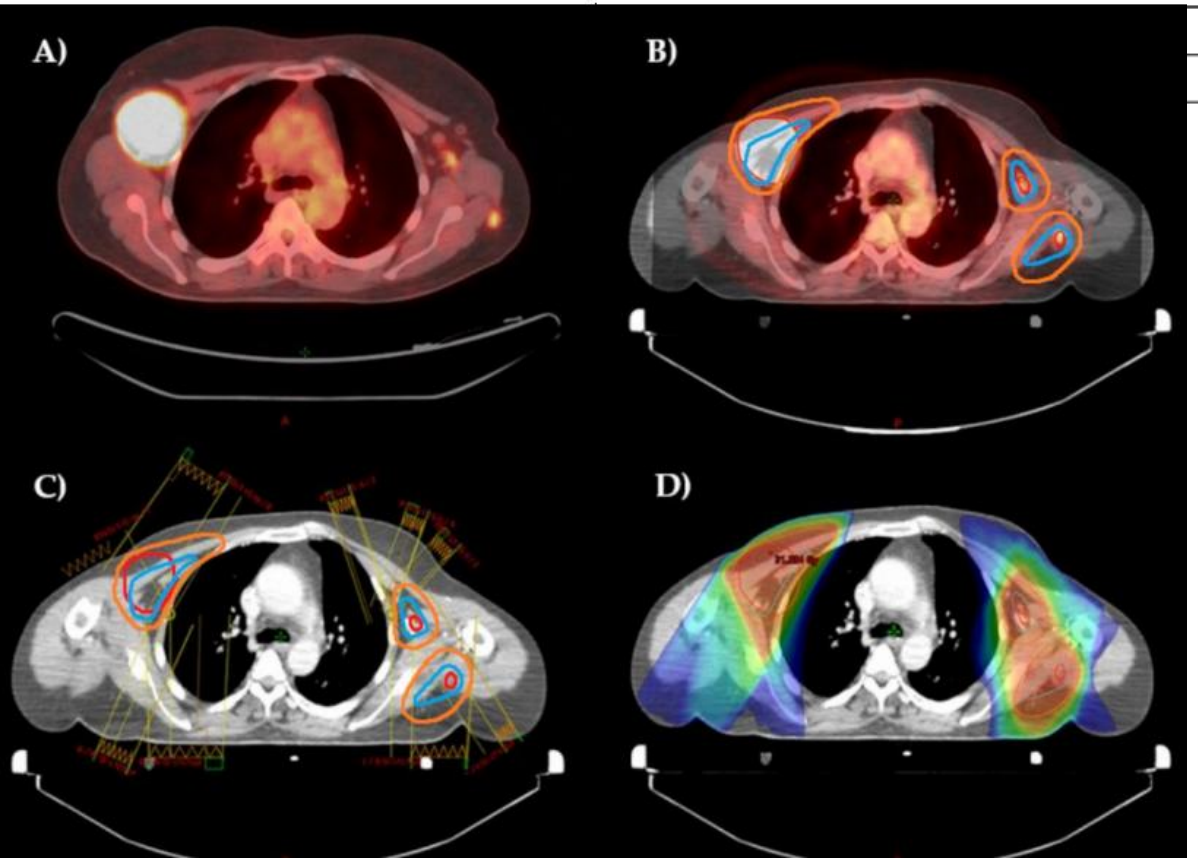
From EFRT to IFRT to ISRT/INRT

Radiation Volumes were pioneered by **The Stanford** Group and the **Princess Margaret** Group

Paradigm shift in the Radiotherapy volumes in the modern PET & rituximab era



Target volume definition and field setup for Involved Site RT(ISRT) : The ILROG guidelines.



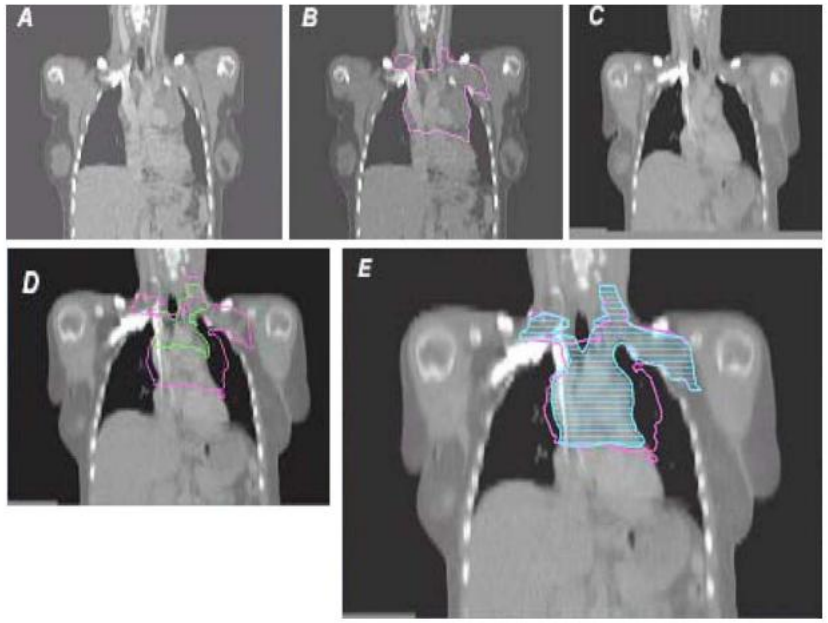
Key Aspects for ISRT Volume Definition in the ILROG Guidelines

Guideline	Key Aspects
Treatment volumes for Hodgkin's lymphoma [5] and nodal non-Hodgkin's lymphoma [4]	**GTV Definition** • Primary treatment (e.g., LPHL): GTV is visualized in simulation. • Combined-modality treatment: GTV is affected due to upfront chemotherapy. The pre-chemo and post-chemotherapy/residual GTV extension should be defined in the simulation study. **CTV Definition** • The CTV comprises the pre-chemo GTV, but excludes OAR tissue with consideration of fusion accuracy, anatomical changes, and potential subclinical disease. • More generous margins and inclusion of directly adjacent lymph nodes (even if uninvolved) is advisable in cases of sole RT. • Nodes more than 5 cm apart can be treated in separate fields. • For irradiation of residual mass after chemotherapy in advanced disease, the CTV consists of the residual GTV (post-chemotherapy) with a margin of 10 mm (larger margins in areas of increased motion, see ITV). **ITV Definition** • ITV is defined on 4D simulation for chest and upper abdomen treatment with margins of 1.5–2 cm craniocaudal extension. **PTV Definition** • PTV definitions vary across institutions based on estimated setup errors. Typical margins around the CTV (or ITV) are 5–10 mm, but should be as small as clinically appropriate, based on individual treatment circumstances.

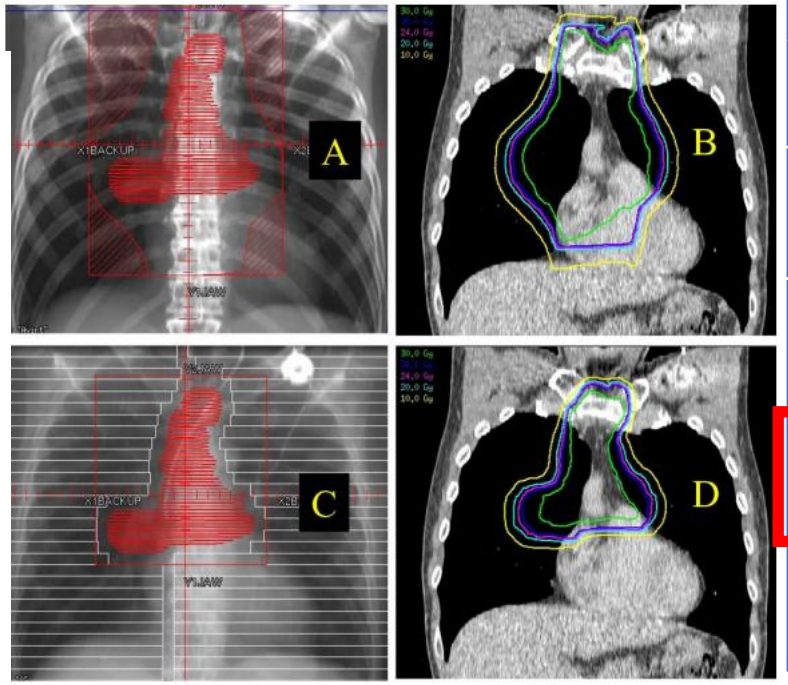
Illidge & Specht IJROBP 2014

Involved-node radiotherapy (INRT) in patients with early stage Lymphoma:Concepts & Guidelines

CTV of a mediastinal lymphoma in an unconfirmed complete remission (CRu) showing CTV volumes (blue color) taking into account the initial tumor volume on a postchemotherapy CT scan.



Comparison RT field sizes and volume of heart irradiation using either IFRT or INRT



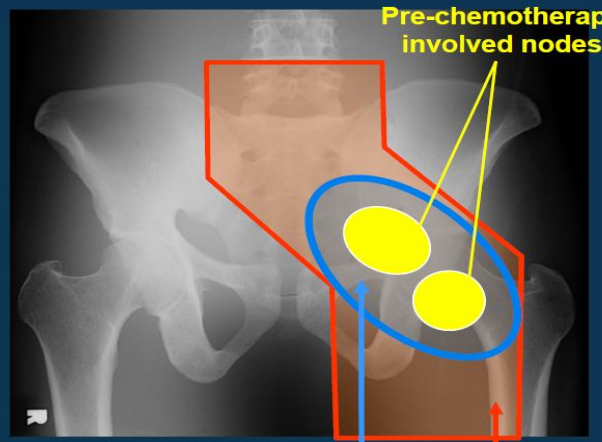
Parameter	Guideline/Description
Definition	INRT = Involved Node Radiation Therapy; targets only initially involved lymph nodes.
Pre-Treatment Imaging	Mandatory PET-CT or CT before chemotherapy for accurate target delineation.
Planning Imaging	CT simulation in treatment position with immobilization devices.
Target Volume Definition	Based on pre-chemo imaging fused with planning CT (GTV → CTV → PTV).
Margins	Margins should be minimal (often 5-10 mm) depending on setup accuracy and imaging.
Dose Guidelines	Depends on disease & protocol (e.g., 20–36 Gy in 1.8–2 Gy fractions).
Image Guidance	Daily IGRT (CBCT, KV imaging) recommended for accurate patient positioning.
Field Size	Smaller than traditional IFRT; includes only pre-chemo involved nodes.

Girinsky et al, Radiotherapy & Oncology 2006

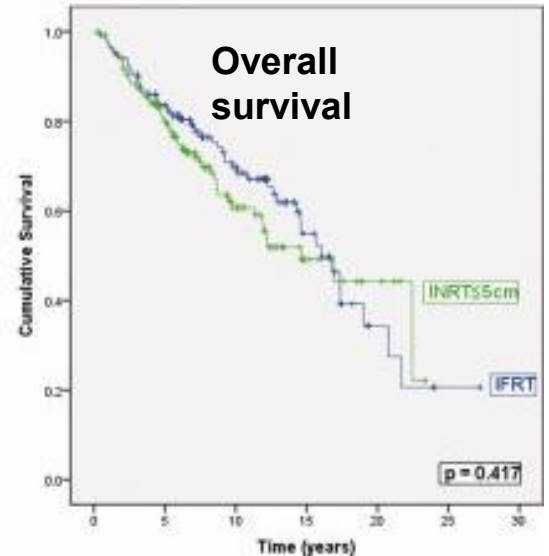
Reducion of RT Volume in DLCBL

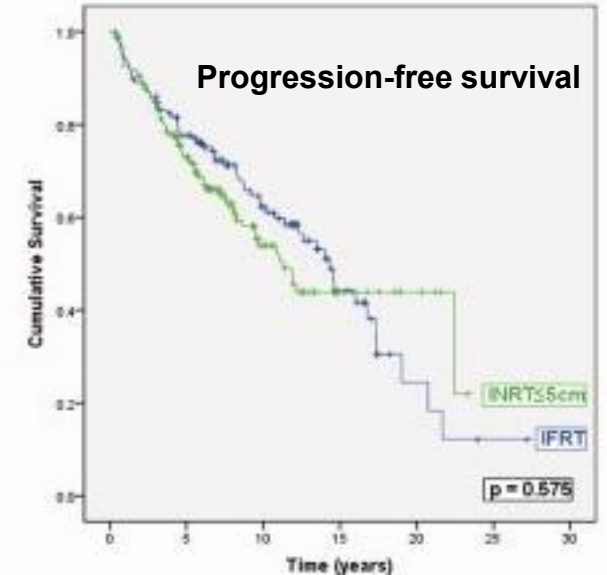
Reducing RT field in limited stage DLBCL

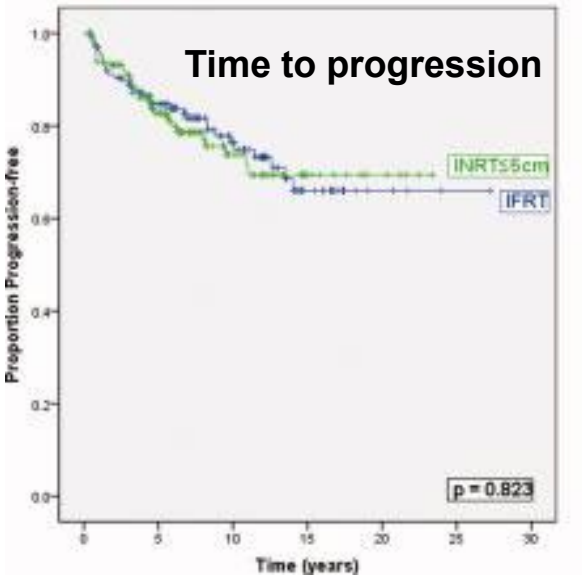
- Reducing the field from involved or regional field to involved site field was effective and safe.
- No increase in in-field or marginal failures.



Campbell B et al from Vancouver- Cancer 2012







Take home message for Radiotherapy Volumes in Lymphomas

- No role of extended field radiation or magnafield radiation in modern era

  - except when in palliation when no salvage chemotherapy is contemplated then Total Lymphoid Irradiation(TLI) is used

- In centers where Initial Imaging is available (PET/CT or CT)

  - Plan for Involved Site RT (ISRT)

- In centers where Initial Imaging is available (PET/CT) in treatment position

  - Plan for Involved Node RT(INRT)

Evolution in the Role of Radiotherapy in DLBCL

- from past to the present

Why has this evolution happened?

from definitive to adjunct role

Paradigm shift in therapy practices

- from RT alone to chemotherapy(advent of CHOP regimen)
- Advent of better staging and response functional imaging modality(FDG PET/CT)
- Development in more robust therapy response criteria(Deuvelle scoring system)
- Evolution in immunotherapy and cellular therapy

In 1980’s CHOP chemotherapy became the standard of care in NHL

Radiotherapy for NHL: In CHOP &Pre-rituximab era

Study	Patient Population	No.	Med F/u	Treatment Arms	Results	*P* Value
SWOG 8736*[41,42] Stage II – 32% Bulky – 3%	Stage I or IE (bulky and nonbulky) Stage II or IIE (nonbulky only)	401	4.4 y	CHOPx3 → 40-55 Gy IFRT CHOPx8 alone	5-y PFS: 77% 5-y OS: 92% 5-y PFS: 64% 5-y OS: 72%	(*P* = .03) (*P* = .02)
ECOG[44] Stage II-68% Bulky- 31% Ex nodal-47%	Stage I (bulky or EN only); Stage II (bulky and nonbulky)	215	12 y	CHOPx8: → 30 Gy IFRT If CR → No RT If PR → 40 Gy IFRT	6-y DFS: 69% 6-y FFS: 70% 6-y OS: 79% 6-y DFS: 53% 6-y FFS: 53% 6-y OS: 67% 6-y FFS: 63% 6-y OS: 69%	(*P* = .05) (*P* = .05) (*P* = .23)
LNH-93-1[45] Stage II-32% Bulky-11%	Age <60 (10% bulky, 50% EN, 0 aaIPI)	647	7.7 y	ACVBP → MTX, Ifosfamide, VP16, ara-C CHOPx3 → IF RT 30-40Gy	5-y EFS: 82% 5-y OS: 90% 5-y EFS: 74% 5-y OS: 81%	(*P* = .004) (*P* = .001)
LNH-93-4[46] Stage II-32% Bulky - 8%	Age >60 (8% bulky; 56% EN)	576	6.8 y	CHOPx4 → IF RT 40Gy CHOPx4	EFS: 66% OS: 72% EFS: 68% OS: 68%	(*P* = .7) (*P* = .6)

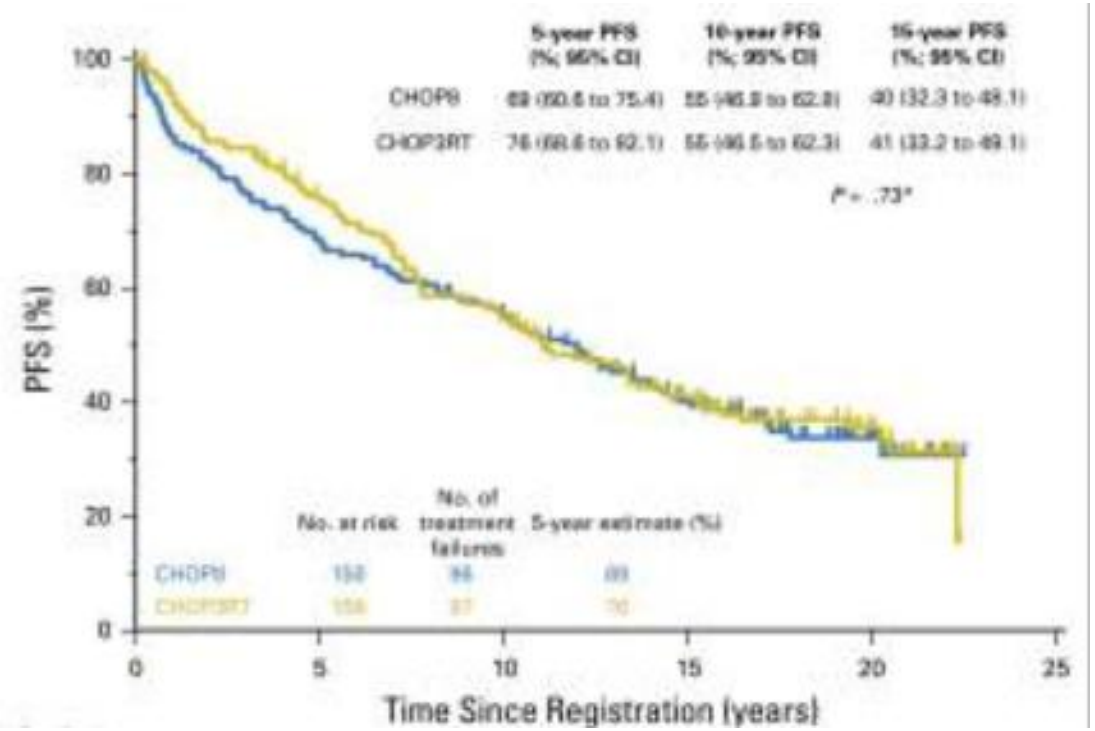
*Updated in abstract form: at median follow-up of 8.4 years, FFS curves overlap at 7 years, and OS curves overlap at 9 years.

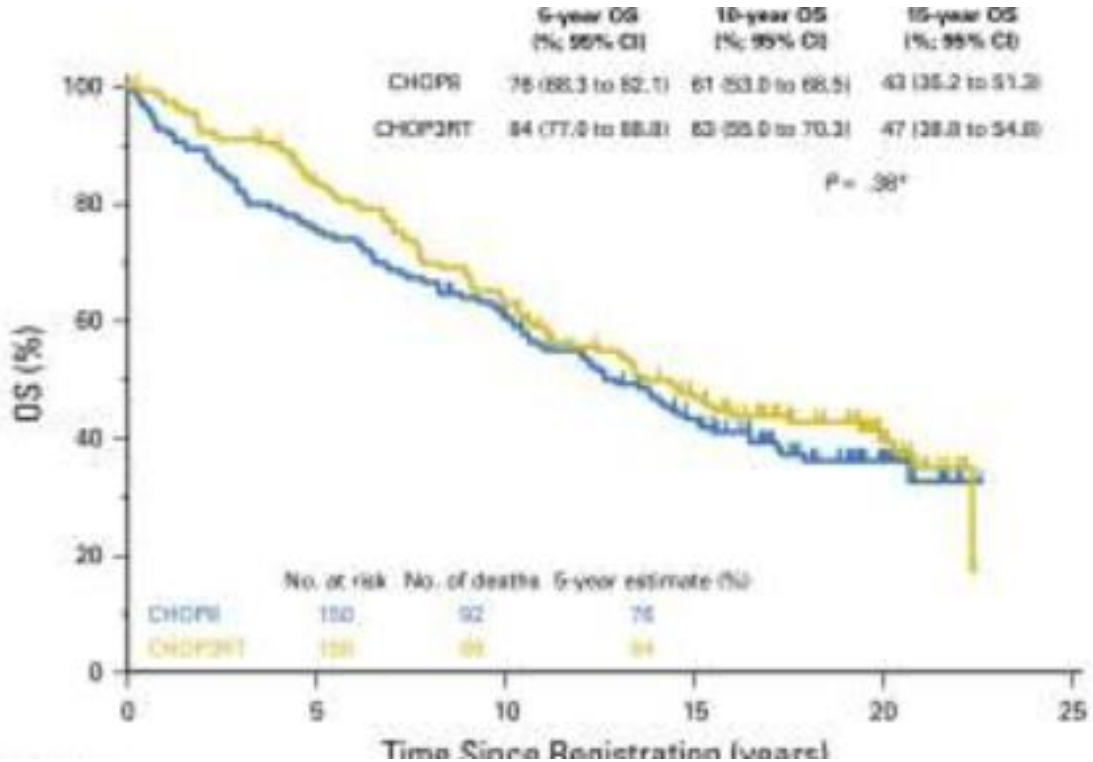
Take home messages from these trials

SWOG 8736	ECOG 1484	LNH93-1	LNH93-4
RT can substitute for 8 cycles of CHOP and provide significantly better outcome	50% of registered were not randomized	No difference in non-bulky (<10 cm) pts	Long delay between chemo to RT (median 7 weeks)
Increased cardiac toxicity with prolonged chemo	Not powered to detect < 20% increase in OS with RT	ACVBP: survival advantage over 8 # of CHOP in advanced-stage	12% pts did not receive RT as assigned, 23% under- dosed. No quality assurance reported.
Excellent outcome in pts with SA IPI of 0 treated with CHOPx3 +RT	20% of CR pts did not receive assigned treatment	High rate of short and long-term toxicity of ACVBP	23% failure in RT field (34% with local component)
Is CHOPX3 adequate for all?	More bulky pts in RT arm vs observation arm: 26% vs 17%	Difficult to justify ACVBP in low-risk pts	More deaths from lymphoma progression in the RT arm (70 vs 65) difficult to explain

Continued Risk of Relapse :Long-term results of the SWOG 8736

- Median FU of 18 years





Stephens et al JCO2016

Radiotherapy for NHL: Post-rituximab & Post PET era

ADVENT OF ANTICD20 RITUXIMAB & PET HAS CHANGED THE LANDSCAPE OF NHL THERAPY

While most cases in the present era will be treated with systemic therapy alone, combined modality therapy (CMT) of systemic chemoimmunotherapy followed by consolidation RT (CRT) remains a well-validated treatment program for aggressive lymphomas (DLBCL).

- I have chosen to focus on 3 commonly encountered clinical scenarios
  - limited stage aggressive NHL (DLBCL)
  - advanced stage aggressive NHL
  - Relapsed/refractory aggressive NHL

Scenario 1: limited stage aggressive NHL (DLBCL)

- RT has evolved in a background of two persistent concerns.

  - The incremental benefits of CMT may be lost with optimization of risk-adapted anti-CD20 anchored chemoimmunotherapy with functional positron emission tomography (PET) imaging

Sehn LH, Blood 2015

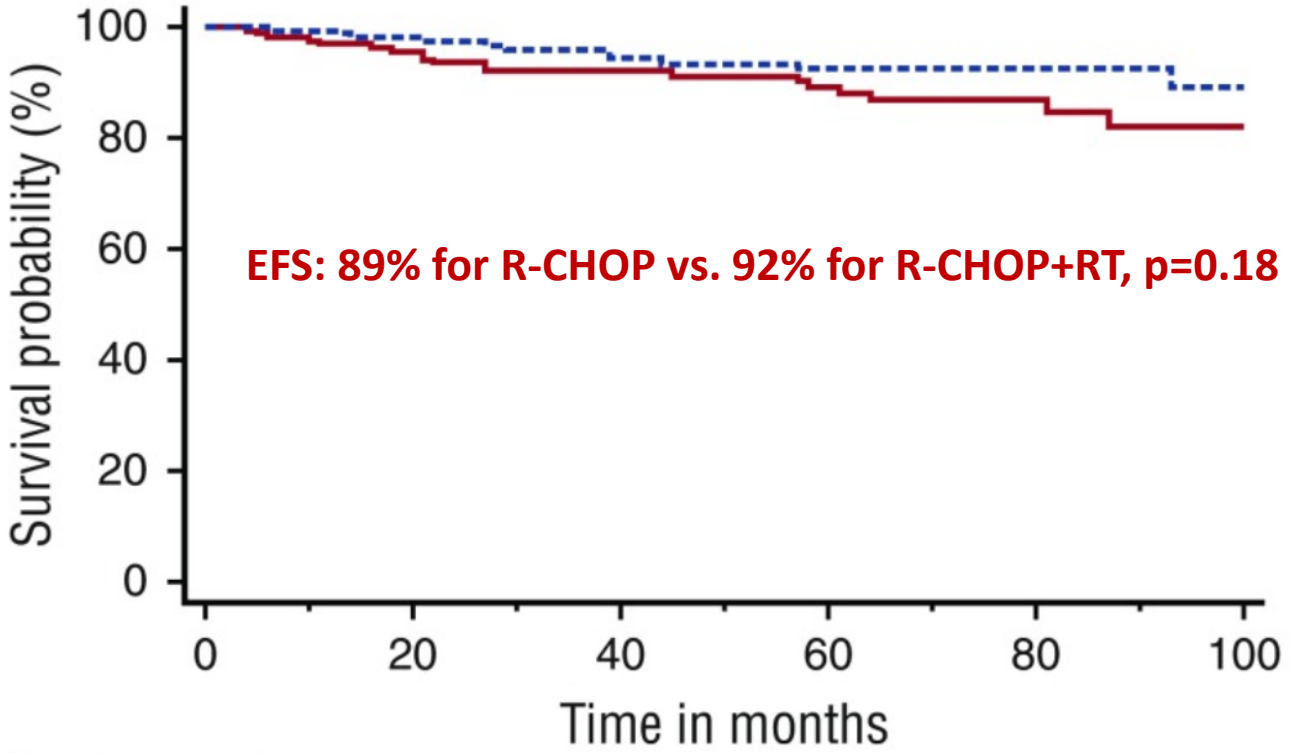
-There remain lingering concerns about the long-term toxicities of RT.

-The consequence has been a clear decline in the utilization of CMT, and a focus on prospective trials which seek to limit indications for RT.

Vargo JA, JCO 2015

Limited role of RT for favorable limited stage disease

- LYSA/GOELAMS 02–03 trial
- 319 evaluable stage I/II
- nonbulky (< 7 cm)
- Modified IPI of 0,1
- 4 cycles of R-CHOP followed by PET imaging
- RCHOP was given every 14 days
- Pts withPET –PR & smIPI ≥ 1 : recd 6 cycles of R-CHOP ⟶ cRT
- PET-CR patients were randomized to cRT vs observation

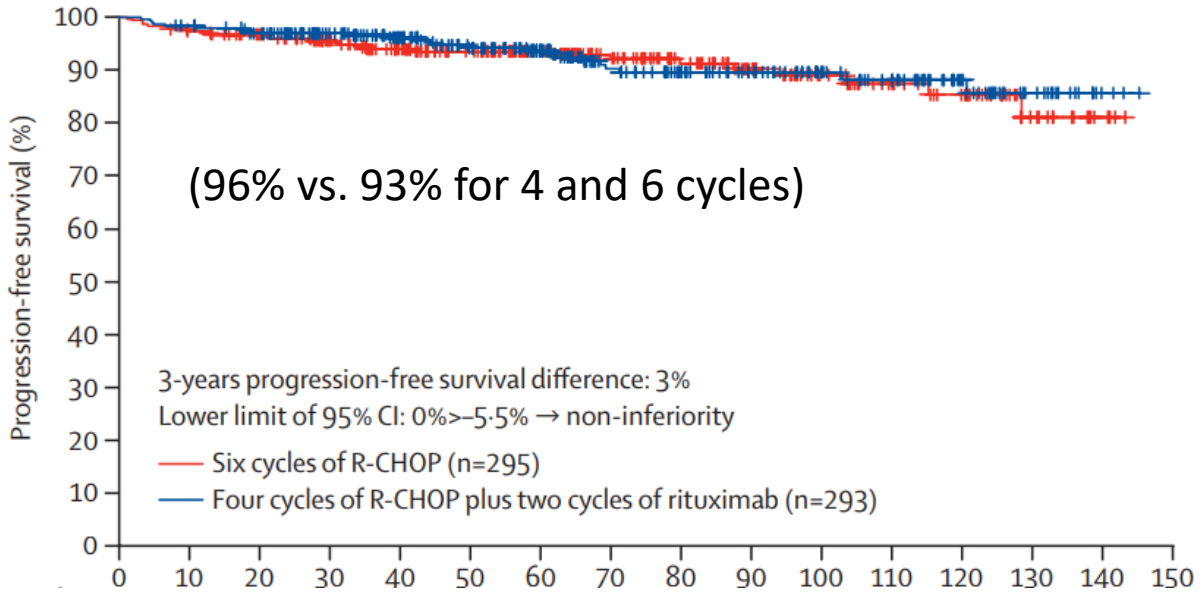


Interpretation of the trial

- It is true that overall outcomes were excellent
- The highest risk patients, the partial responders, by design received RT and thus biased the CMT analytics
- conceivable that RT is the reason why the two arms had similar outcomes
- could be argued for the need for risk-adapted CMT

Limited role of RT for favorable limited stage disease

- **German FLYER study**
- 592 favorable, young patients with non-bulky stage I/II disease
- IPI:0
- median follow-up of 66 months
- No radiotherapy was planned except for testicular lymphoma treatment
- RCHOP + 2 R vs 6 R-CHOP



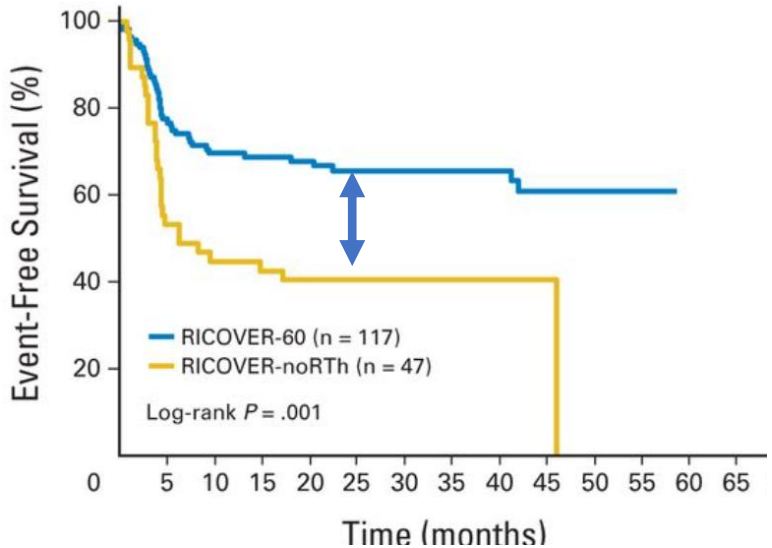
Interpretation of the trial

- It is true that overall outcomes were excellent with 4 vs 6 RCHOP
- Response was based on CT scan
- The study did not have any randomiseation arms of cRT vs no cRT

Specific scenarios to consider CRT in limited stage aggressive NHL:RICOVER 60 & RICOVER noRTh ,JCO 2014

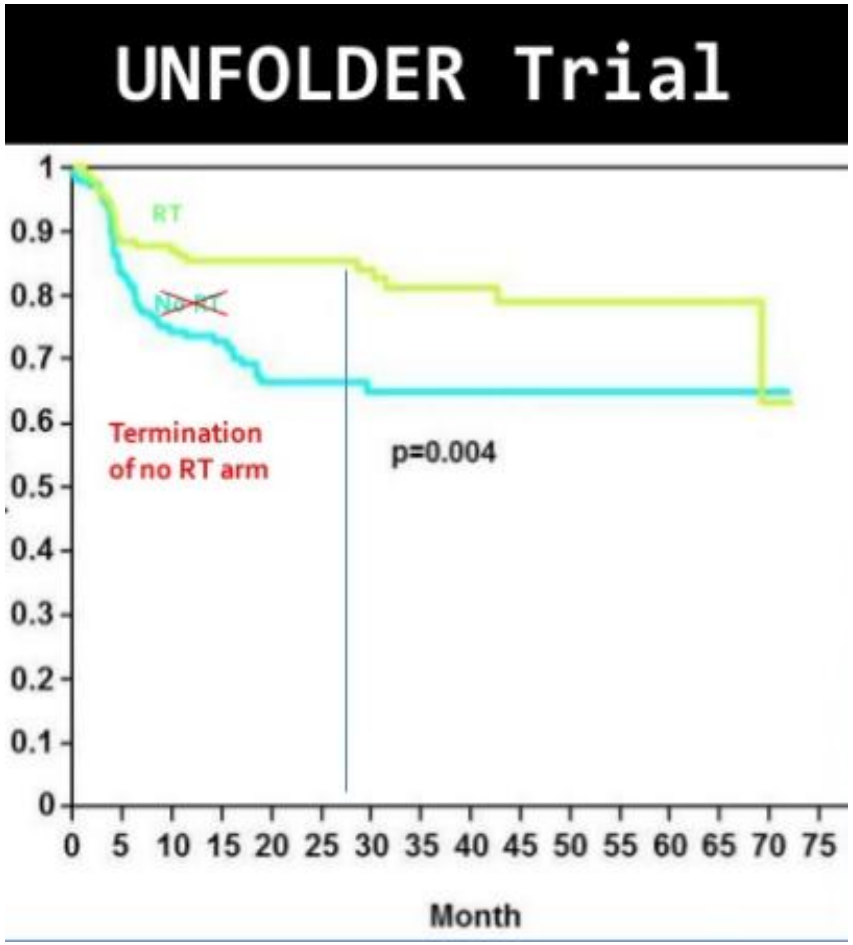
- **Bulky disease**
  - Poor prognosis even after adjustment with the use of rituximab
  - RCHOP was given every 2 weeks
  -RT Dose of 36Gy

	EFS			PFS			OS		
Variable	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***
RICOVER-noRTh *v* RICOVER-60	2.1	1.3 to 3.5	.005	1.8	1.0 to 3.3	.058	1.6	0.9 to 3.1	.127



Specific scenarios to consider CRT in limited stage aggressive NHL: UNFOLDER Trial;JCO 2018

- **Bulky disease NHL**
- 2×2 randomization of R-CHOP-14 and R-CHOP-21 followed by 39.6 Gy or observation to **bulky or extranodal sites.**
- Median FU :66months
- significantly better EFS in the patients who received RT.
- 3yrs EFS of 66% (no CRT) Vs 84%(with CRT) p=0.001
- Pre-PET era study



Clinical scenario 2: advanced stage aggressive NHL

- Since RT is a focal therapy, its utility for advanced stage NHL remains a topic of great debate

- Indications of RT in advance stage disease

  Initial bulky disease

  Extranodal sites especially bone disease

  Partial response to induction chemotherapy

- Appropriate patient selection, judicious usage of CMT :maximize upfront therapeutic success and/or limit chemotherapy exposure

Has PET guidance in DLBCL changed the therapeutic Paradigm

- Role of PET guidance to inform the necessity of consolidation RT (CRT) remains controversial and practice patterns are variable.

- In contrast to Hodgkins Lymphoma ,there is no recommendation to use this information for CRT decision making.

- There is less debate that CRT should be considered for patients with residual PET positivity

  -The British Columbia group analyzed 702 newly-diagnosed advanced stage

  -Within the PET+ group, consolidation ISRT was associated with significantly improved outcomes (5-year PFS of 77% vs. 29%).

Freeman CL, Blood 2017

Has PET guidance in DLBCL changed the therapeutic Paradigm

OPTIMAL>60 study of the Dshnhl group(German NHL group)

Elderly patients of all stages are randomized to 4 R-CHOP or R-CHLIP regimens.

Patients with initial bulk (>7.5cm) undergo a PET scan after chemotherapy and receive 39.6 Gy if positive and observation if negative

Interim results showed that PET guidance may reduce the need for cRT by about ~40%

PET positive patients who were not irradiated had significantly poorer outcomes

Pfreundschuh M, JCO 2017

Recommendations of ILROG for RT in advance stage NHL

- **ILROG continues to see a role for CRT in select patients with PET CR after upfront treatment**.
- There are at least 4 reports demonstrating improved outcomes with CRT. following CR after upfront chemoimmunotherapy.

Recommendations of ILROG for RT in limited stage NHL

- early stage non-bulky IPI 1 : cRT is recommended after 3-4 cycles of R-CHOP till proper evidence emerges
- early stage non bulky IPI 0 : cRT is can be avoided after 4 cycles of R-CHOP and pt can be consolidated with 2 cycles of R

Studies demonstrating clinical benefit for CRT after complete response following upfront chemoimmunotherapy

Study	Design	Patient inclusion	Proportion of CR after chemo	Study intervention	Assessment of CR	Patients receiving RT	RT parameters	Outcomes
Phan et al.[33] (2010)	Retrospective	• n=469 • 60% stage III-IV • 37% bulky (>5 cm)	• Overall 72% • 100% of irradiated population	Chemotherapy (84% R-CHOP) with or without IFRT	• CR: N=99 (CR by PET and CT) • CRu: N=43 (CR by PET, PR by CT)	• Overall: n=142 (30%) • AS: 39 (14%)	• 30 Gy if non-bulky • 36–39.6 Gy if bulky or PR by CT	• Matched pair analysis showed significantly improved outcomes with IFRT for all stages • For AS patients, IFRT associated with significantly improved 5-year PFS (76% vs. 55 %; P=0.003) and OS (89% vs. 66 %; P=0.008) • MVA of patients who achieved CR showed improved OS and PFS were significantly associated with CRT
Dorth et al.[64] (2012)	Retrospective	• N=79 • 100% stage III-IV • CR	• 100%	Median of 6 cycles of chemo (65% R-CHOP) with or without ISRT	• PET 73% • Gallium 14% • CT 13%	• Overall / AS: 38 (48%)	• Median of 25 Gy	• CRT was associated with improved LC (92% vs. 69%, p=0.03) and EFS (85% vs. 65%, respectively, p = 0.01) but no difference in OS (85% vs. 78%, p = 0.15) compared to no CRT • On MVA no CRT associated with greater risk of local failure and EFS
Shi et al.[58] (2013)	Retrospective	• n=110 with stage III-IV disease who achieved CR after chemo	• 100%	Median of 6 cycles of R-CHOP with or without RT	• PET 86% • CT 14%	• n=14 (13%)	• Median 30.6 Gy • RT to all initial sites in 50% and only bulky sites in 50%	• RT was associated with significantly improved LC (92% vs 49%), PFS (85% vs 44%), and OS (92% vs 69%; all p<.0001) at 5 years compared to R-CHOP alone
Aviles et al.[59] (2019)	Prospective, randomized	• N=258 with AS and presence of bulky nodal disease (>10 cm) who achieved CR after chemo • 100% stage III-IV	• 100%	6 cycles of R-CHOP with or without RT to bulky sites	• CT 100%	• Overall/ AS: n=127 (49%)	• 30 Gy in 10 fractions	• CRT significantly improved 5-year PFS (87% vs. 45%, p=<0.001) and OS (91% vs. 59%, p<0.001)

Clinical scenario 3: Relapsed/refractory aggressive NHL

- 50% patients will have primary refractory /relapse after upfront therapy
- Therapy is extremely challenging in these pts as outcomes are very poor
- RT retains strong activity even for chemorefractory disease
  - plays an important role – with or without systemic therapy, as a component of curative-intent and palliative-intent programs.
  - Role of salvage RT (SRT) in the r/r setting will continue to expand and evolve

Peri-transplant irradiation

- Role of peri-transplant RT was established in the 1980s, given that nearly 80% of patients who relapsed following AHCT failed in a **pre-transplant site of disease**

Philip T,NEJM 1987

- **PARMA trial**, **pre AHCT IFRT** was recommended for **bulky (>5 cm) or extranodal sites**; **reduction in overall and local relapses** occurred in the patients who received RT.

Gisselbrecht C,J Clin Oncol 2010

- **Benefit of RT**

- **Extends to the primary refractory** setting, where patients with limited stage disease.

- Principal advantages of pre-transplant RT is that it can help to **cytoreduce** patients from **PR to CR to maximize their post-AHCT outcomes**

Wendland MMM, Am J Clin Oncol2007
Vardhana SA, British Journal of Hematology 2017
Hoppe BS, J Clin Oncol 2008

Pre- transplant vs.Post-transplant irradiation

Pre- Transplant	Post Transplant RT
Larger fields are irradiated	Smaller volumes are irradiated
The window of opportunity to cytoreduce the disease is better when RT is given before Transplant	There is a risk that the patient will miss a window if post-transplant recovery is delayed.
Cytopenias will be lower in case of Pre transplant RT as the donor marrow has not been infused	Exposes reinfused stem cells to RT. Therefore increased chance of cytopenias

ILROG treatment guidelines for relapsed refractory NHL: for peri-transplant RT

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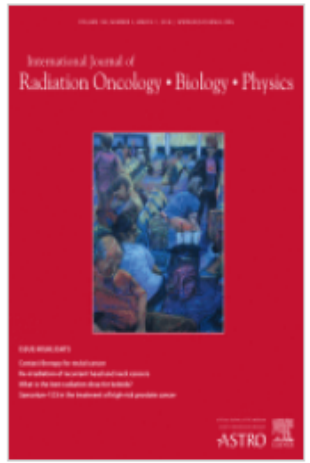

Role of Radiation Therapy in Patients With Relapsed/Refractory Diffuse Large B-Cell Lymphoma: Guidelines from the International Lymphoma Radiation Oncology Group

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Radiation therapy recommendations for specific case scenarios of relapsed/refractory lymphoma

Scenario	Timing	Dose	Volume
Relapsed/refractory after primary chemo, with CMR (Deauville 1-3) to salvage chemotherapy	Post-transplant RT: within 4-12 wk after transplantation Pretransplant RT per: within 4 wk of salvage CT	30-36Gy ;1.5-2Gy/fr 30-36 Gy in 1.5-2 Gy/fr or 30 Gy in 1.5 Gy/fr BID	Follow ILROG ISRT guidelines for Nodal and extranodal disease
Relapsed /refractory after primary chemo with reduction in FDG uptake, focus/foci of residual FDG avidity (Deauville 4-5) after salvage chemo	Post-transplant RT: within 4-12 wk after transplantation Pretransplant RT (favored): within 4 wk (but as soon as practical); perform stem cell harvest before initiation RT	Post-transplant:36 Gy in 1.8-2 Gy/fr with to final dose of 40-45 Gy in 1.8-2.2 Gy/fr Pretransplant: 36 Gy in 1.8-2 Gy/fr, boost to a final dose of 40-45 Gy in 1.8-2.2 Gy/fr to residual FDG-avid focus	Follow ILROG ISRT guidelines for Nodal and extranodal disease
Localized refractory disease to primary or salvage chemotherapy	Pretransplant RT: within 4 wk perform stem cell harvest before initiation RT	50 Gy in 1.8-2 Gy/fr OR consider 35-40 Gy in 1.3-1.5 Gy/fraction BID if evidence of rapidly progressive disease	Follow ILROG ISRT guidelines for Nodal and extranodal disease

Thank you!