ASTRO Refresher Course 2021:

Modern radiation therapy for lymphoma

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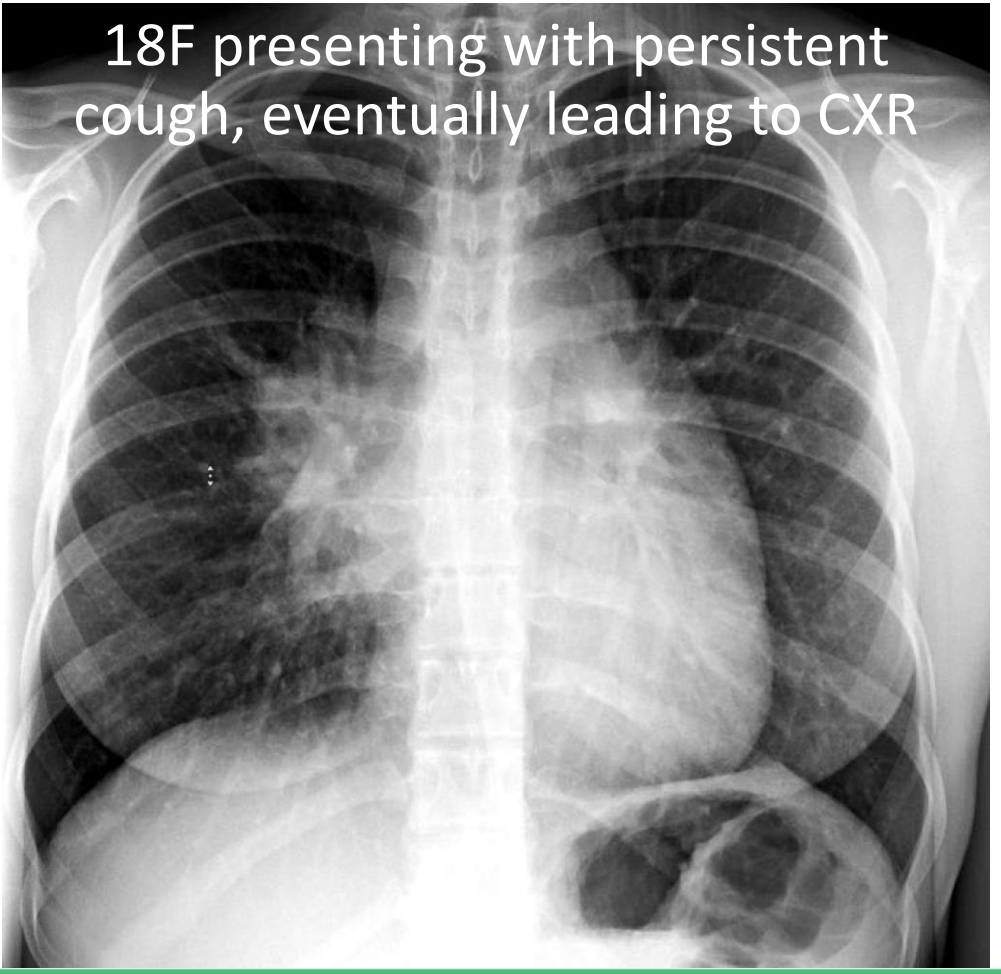
Disclosure

- Employer: University of Washington
- I have no conflicts of interest to disclose

Learning Objectives

- Describe indications for RT in the management of patients with lymphoma
  - Classical Hodgkin lymphoma (HL)
  - Non-Hodgkin lymphoma (NHL): diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), marginal zone lymphoma (MZL)
- 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

Workup for lymphoma (highlights)



H&P	• Systemic symptoms (fatigue, pruritis)
	• B-symptoms
	  • Unexplained fever >100.5 for >=1 mo
	  • Unexplained weight loss >10% body weight in 6 mo
	  • Drenching night sweats
	• LN exam

Labs	• ESR, LDH • Pregnancy test (females of childbearing age)
Path	• Excisional or core biopsy > fine needle

Staging and response assessment

Lugano classification (highlights)

Staging

- PET/CT for routine staging of FDG-avid lymphomas, CT otherwise
- BM biopsy not required for HL and most DLBCL
- Bulky: No X, report longest measurement by CT

Response assessment

- PET/CT is SOC for remission assessment
- Standard reporting through Deauville 5-point scale
- Complete metabolic response even with persistent mass is considered CR

Surveillance

- Routine scanning discouraged for HL and DLBCL

Cheson JCO 2014; Barrington JCO 2014

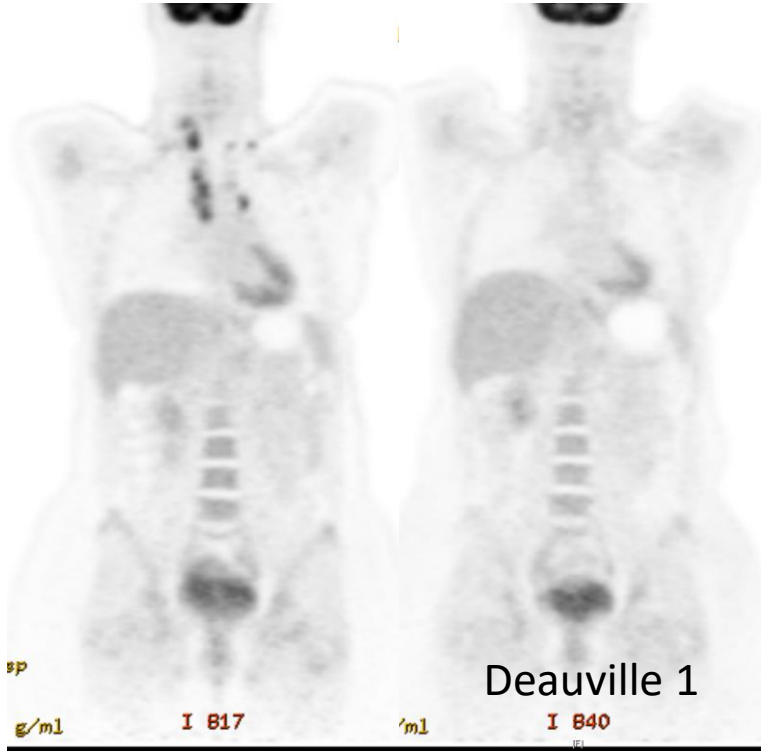
PET/CT Response assessment

Deauville score (Lugano)

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

*for de-escalation studies, Deauville 3-5 considered positive



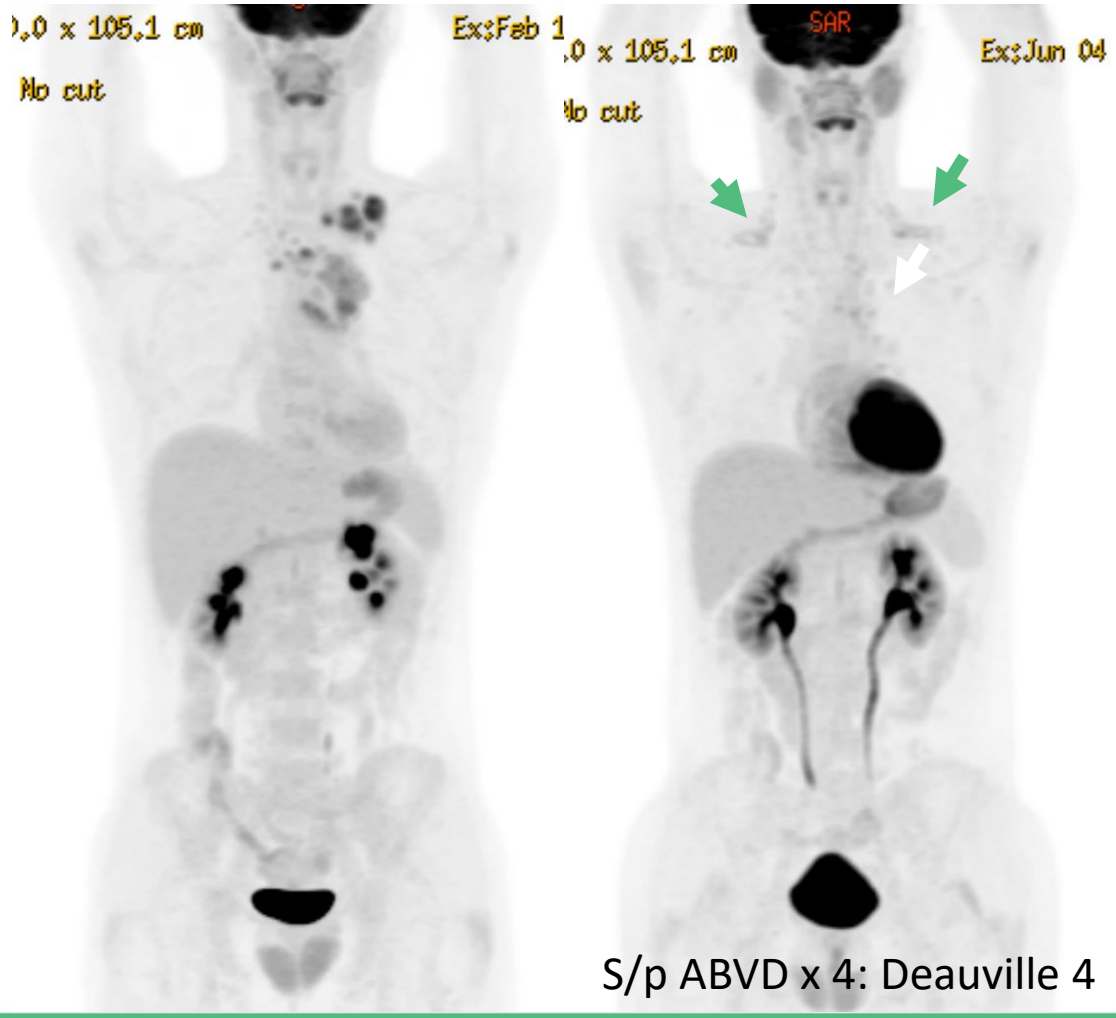
Barrington JCO 2014

PET/CT Response assessment

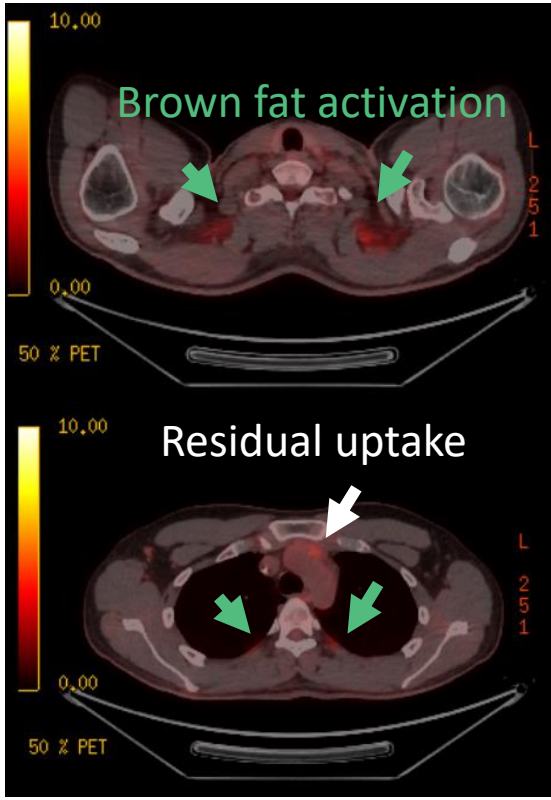
Potential pitfalls

Beware of other FDG uptake on PET

- Brown fat
  - Neck, SCV
  - Mediastinum (peri-aortic)
  - Paravertebral
  - Suprarenal
- Sarcoidosis



S/p ABVD x 4: Deauville 4



Staging: Modified Ann Arbor staging for HL and NHL

Stage	Involvement	Extranodal (E) Status
Limited		
I	One node or a group of adjacent nodes	Single extranodal lesions without nodal involvement
II	Two or more nodal groups on the same side of the diaphragm	Stage I or II by nodal extent with limited contiguous extranodal involvement
II bulky*	II as above with "bulky" disease	Not applicable
Advanced		
III	Nodes on both sides of the diaphragm; nodes above the diaphragm with spleen involvement	Not applicable
IV	Additional noncontiguous extralymphatic involvement	Not applicable

NOTE. Extent of disease is determined by positron emission tomography–computed tomography for avid lymphomas and computed tomography for nonavid histologies. Tonsils, Waldeyer's ring, and spleen are considered nodal tissue.

*Whether stage II bulky disease is treated as limited or advanced disease may be determined by histology and a number of prognostic factors.

- A/B designation only for HL
- Extra-lymphatic involvement: CSF, BM, liver, lungs (not direct extension)

Cheson JCO 2014

Role of RT for Hodgkin lymphoma

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

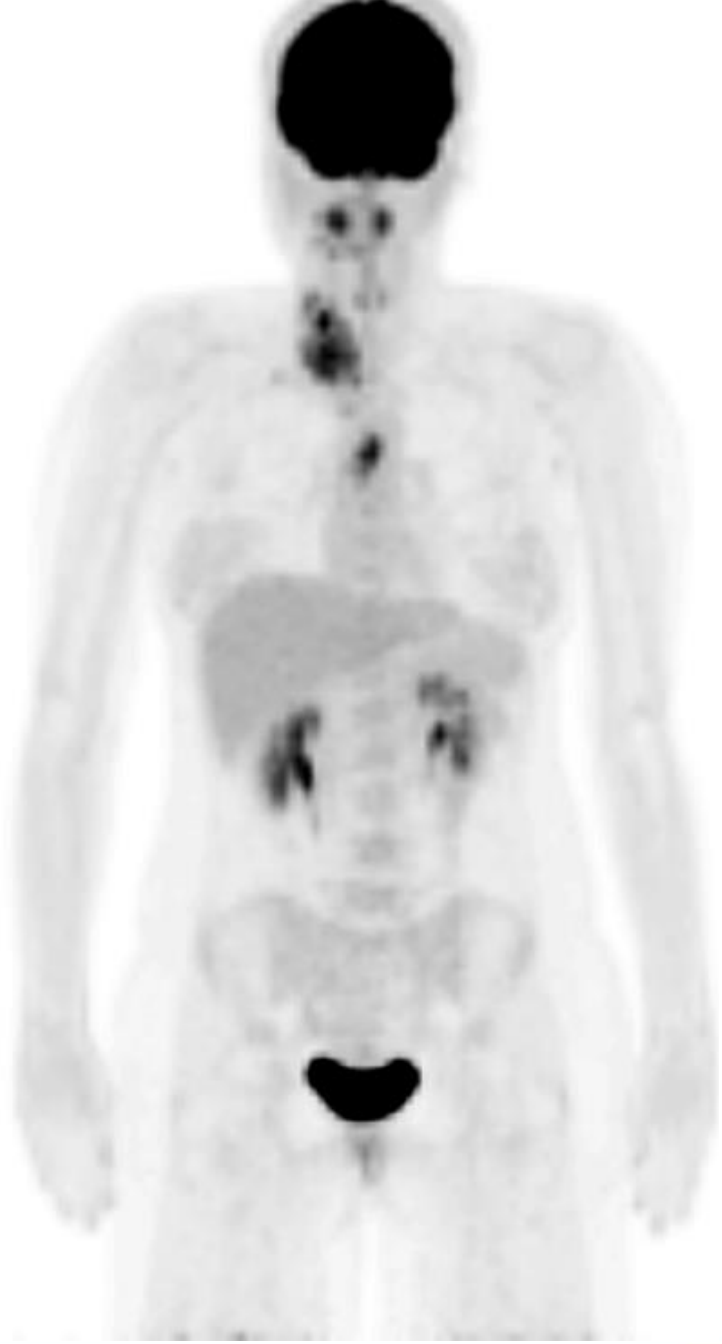
Advanced stage (Stage III/IV, [bulky stage II])
- Incomplete response to chemotherapy
- (Bulky disease)

Relapsed/refractory
- Peri-transplant
- Salvage
- Palliation

Contemporary trials evaluate the role of RT in the era of PET

Case

- 30F with progressive right neck fullness without B-symptoms
- Biopsy demonstrates nodular sclerosing Hodgkin lymphoma
- ESR is 8



Pathology

	Classic Hodgkin lymphoma	Nodular lymphocyte predominant Hodgkin lymphoma (NLPHL)
Immunophenotype	CD15/30+, CD20/45-	CD15/30-, CD20/45+
Neoplastic cell	Reed-Sternberg cells (minority)	"Lymphocytic and histiocytic" cells
Inflammatory background	Composition varies across subtypes	Lymphocytes, histiocytes
	• Nodular sclerosing • Mixed cellularity • Lymphocyte-rich • Lymphocyte-depleted	

Different treatment paradigms for these two pathologic entities

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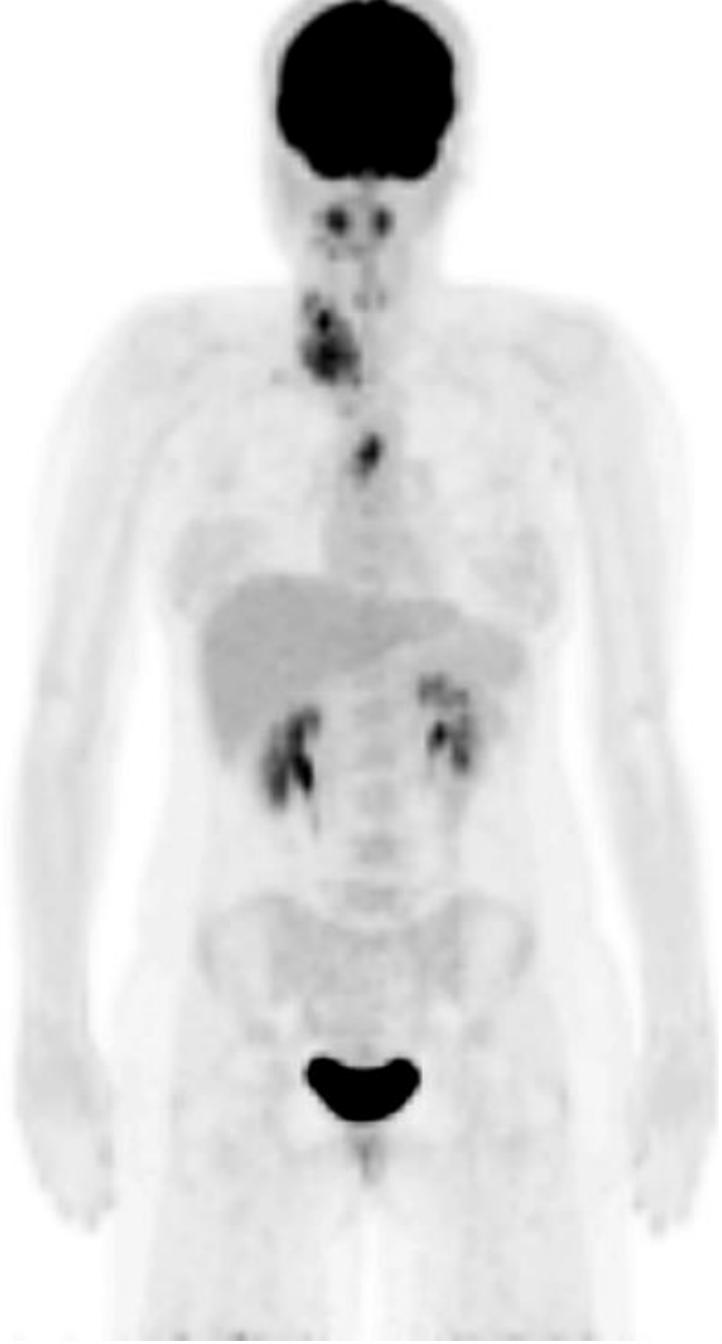


Definition of unfavorable varies across groups

Unfavorable Risk Factors for Stage I–II Classic Hodgkin Lymphoma

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

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

MMR = Mediastinal mass ratio, maximum width of mass/maximum intrathoracic diameter
MTR = Mediastinal thoracic ratio, maximum width of mediastinal mass/intrathoracic diameter at T5-6

From NCCN v2.2021

Evolution of early stage HL strategies

Risk-adapted
- Prognostic features guide Rx

GHSG HD11
- RT dose for unfavorable HL (ABVDx4 + 30 Gy)

GHSG HD10
- De-escalation of treatment for favorable HL (ABVDx2 + 20 Gy)

Evolution of early stage HL strategies

Risk-adapted
- Prognostic features guide Rx

GHSG HD11
- RT dose for unfavorable HL (ABVDx4 + 30 Gy)

EORTC H10
- Favorable HL (ABVDx3+RT vs ABVDx4)
- Unfavorable HL (ABVDx4+RT vs ABVDx6)
- PET2

RATHL
- Stage IIA bulky, IIB-IV HL
- PET2
- ABVDx2 → AVDx4

GHSG HD17
- Unfavorable HL
- PET4
- BEACOPPesc x2 + ABVD x2

2010 2015 2020

GHSG HD10
- De-escalation of treatment for favorable HL (ABVDx2 + 20 Gy)

RAPID
- Stage I/IIA HL
- PET3
- ABVDx3 +/- RT

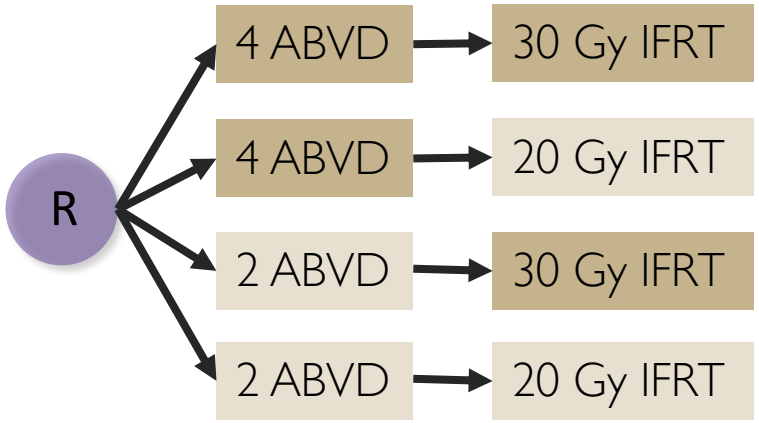
Response-adapted
- PET-guides therapy

GHSG HD16
- Favorable HL
- PET2
- ABVDx2 + 20 Gy

Treatment de-escalation for early stage favorable HL

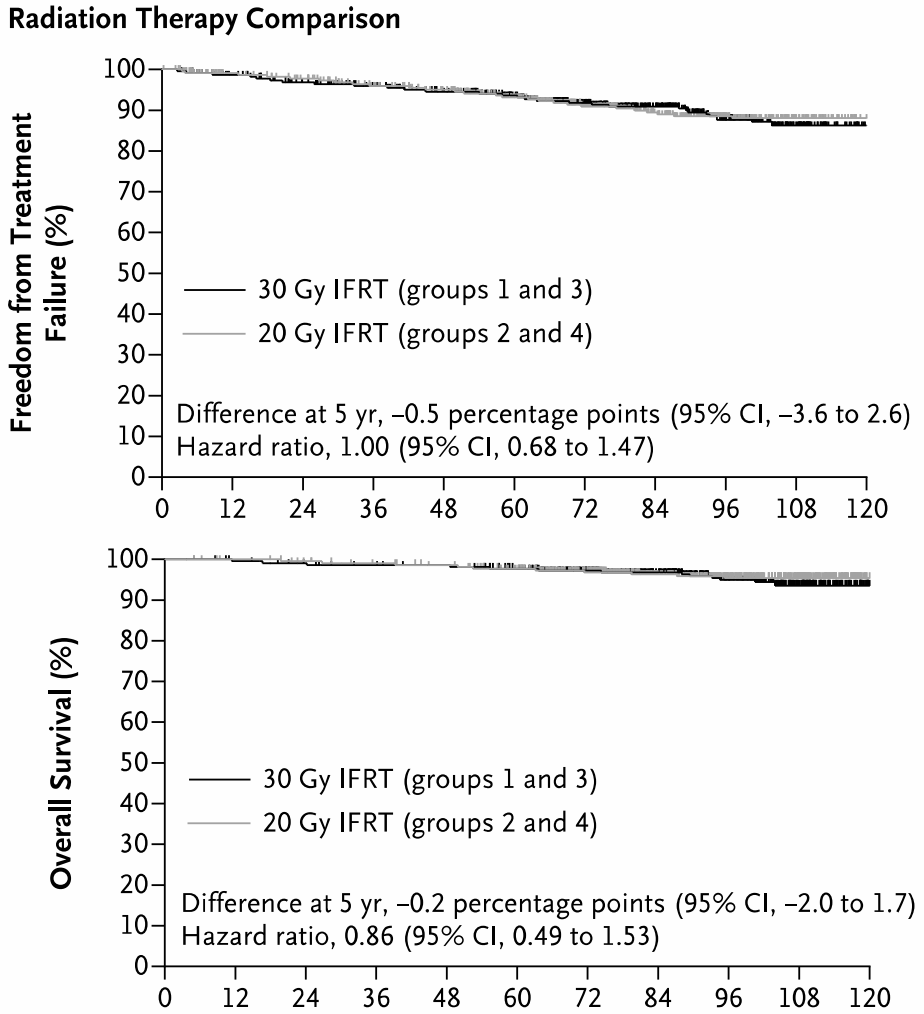
GHSG HD10

Stage I/II without clinical risk factors



ABVD: *Adriamycin, bleomycin, vinblastine, dacarbazine*

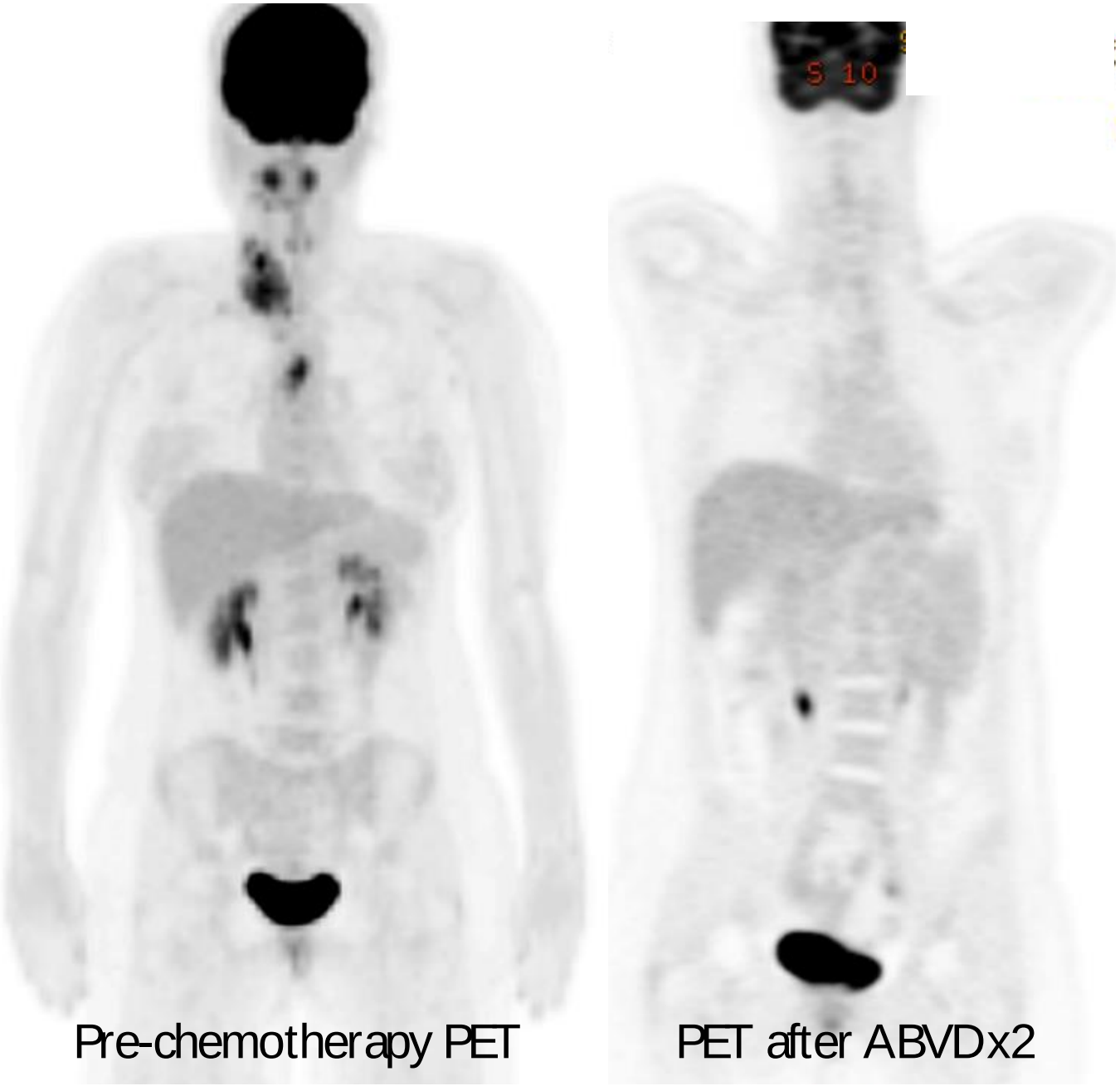
Established ABVDx2 + 20 Gy as standard



Engert NEJM 2010

Case

Undergoes PET/CT after ABVDx2:



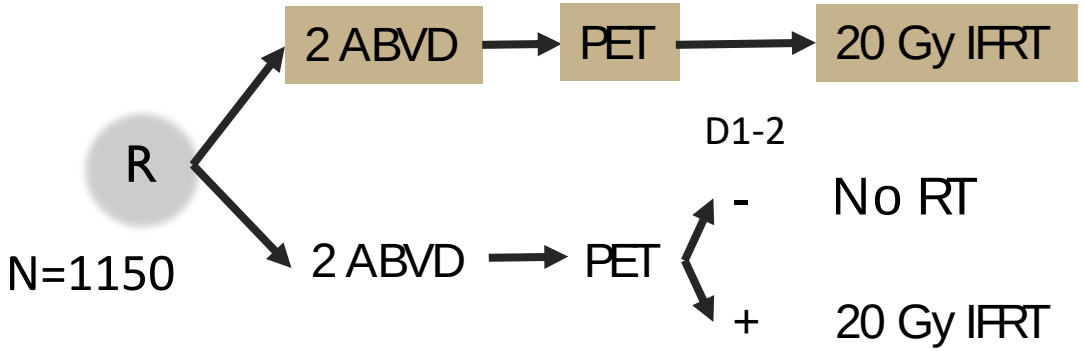
Pre-chemotherapy PET

PET after ABVDx2

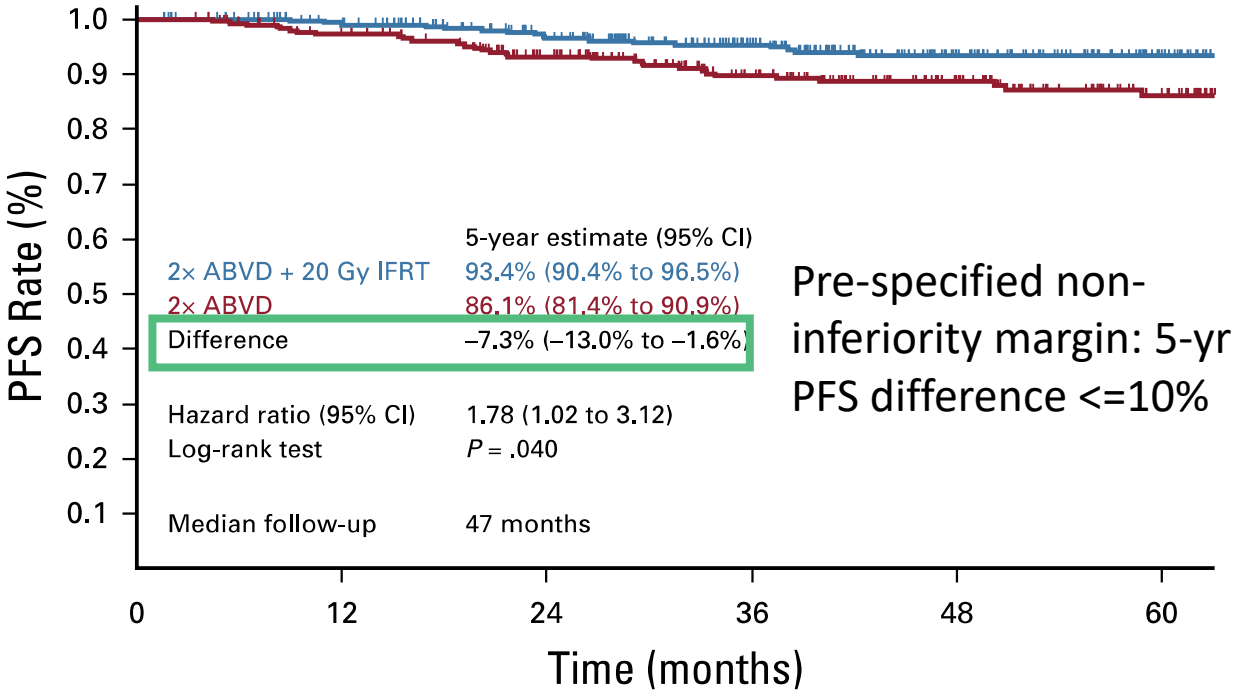
Response-adapted treatment

Can therapy be further de-escalated for favorable HL?

GHSG HD16



PET-2 neg (D1-2) patients



Pre-specified non-inferiority margin: 5-yr PFS difference <=10%

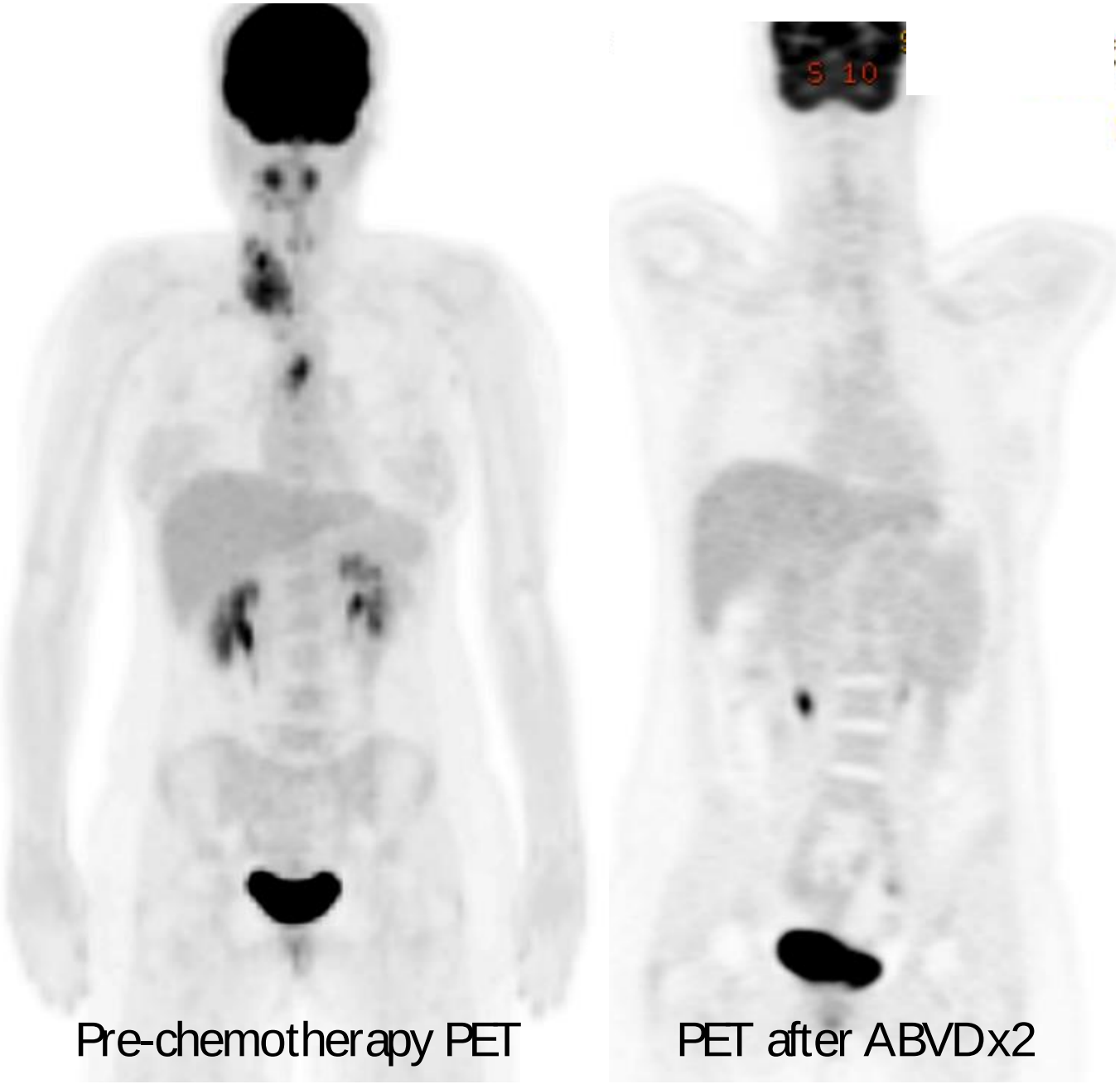
RT cannot be safely omitted after a complete metabolic response to ABVDx2

Fuchs JCO 2019

Case

Undergoes PET/CT after ABVDx2:

Recommended consolidation involved site RT (20 Gy)

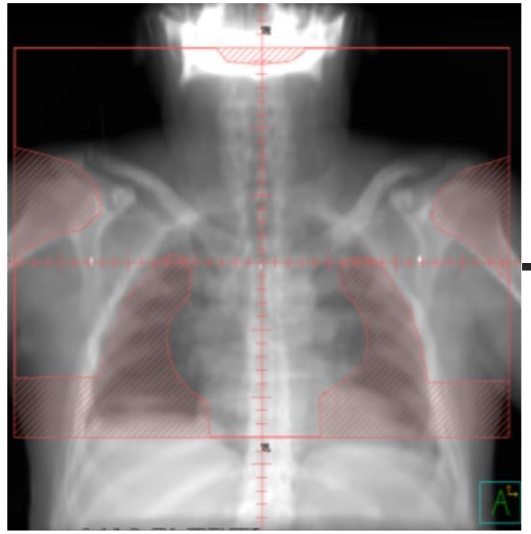


Pre-chemotherapy PET

PET after ABVDx2

Evolution of radiation fields

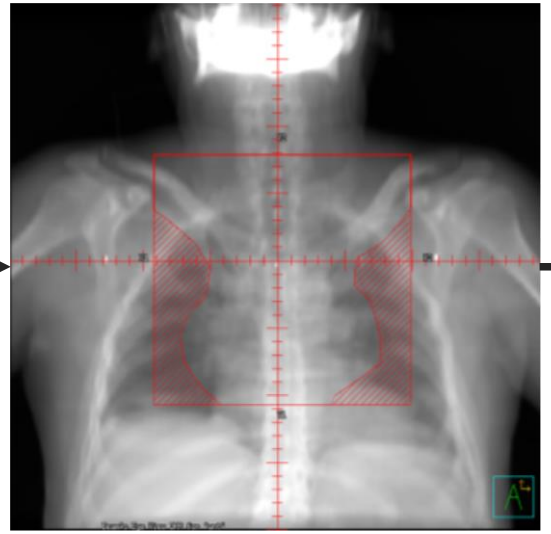
EFRT



Late 1960s

Mantle, inverted Y = TLI
MOPP

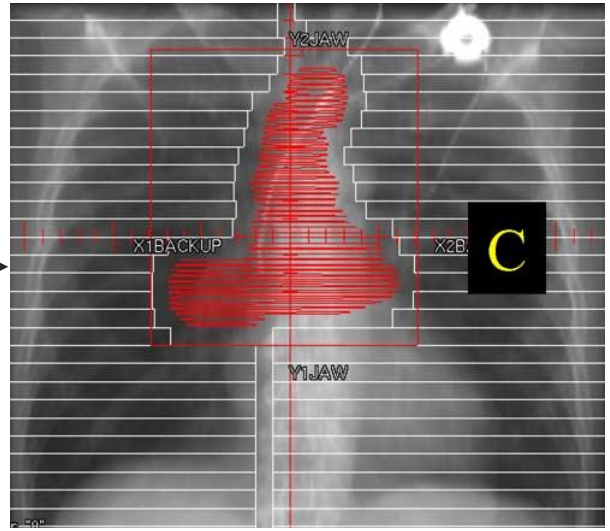
IFRT



Late 1980s-1990s

MOPP → ABVD

INRT/ISRT



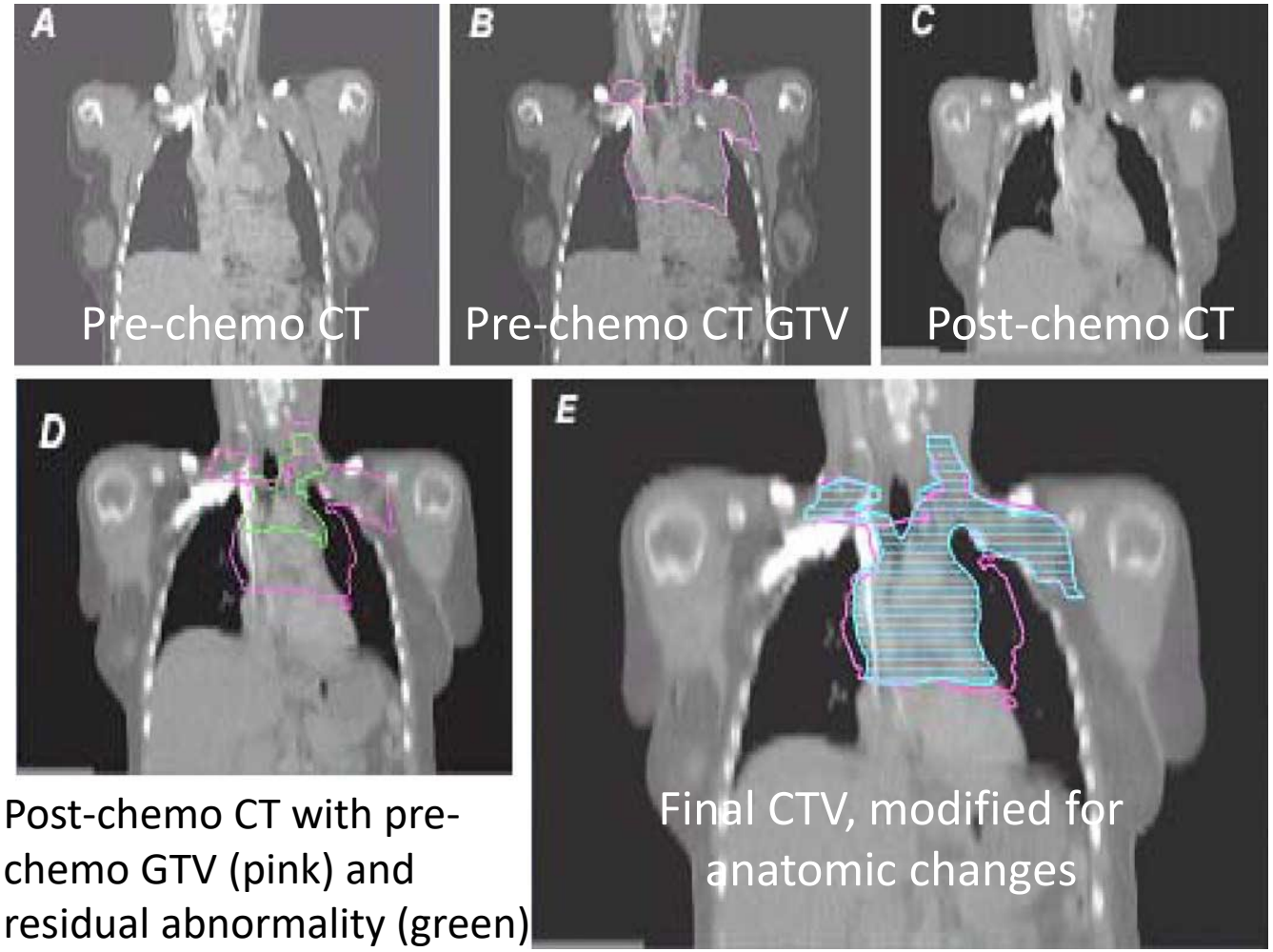
Late 2000s

ABVD

Radiation

Chemotherapy

Involved-node/site radiotherapy technique



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

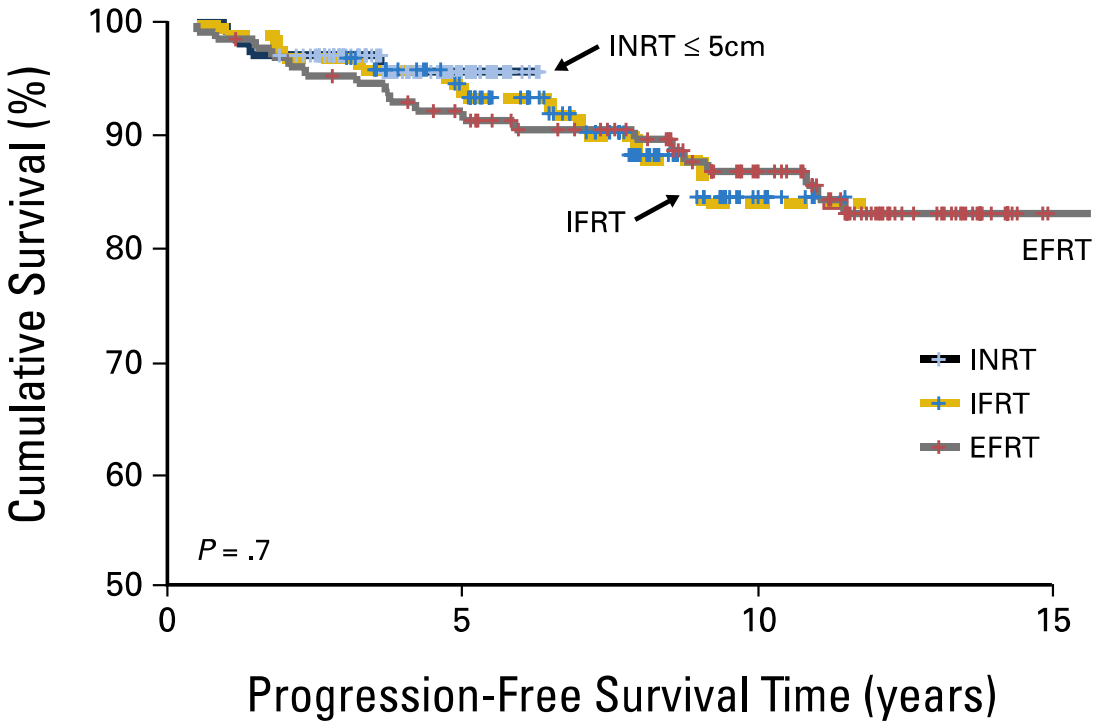
- Pre-chemotherapy GTV determines CTV
- INRT is a special case of ISRT in which optimal imaging is available
- ISRT CTV may be larger to accommodate uncertainties in defining pre-chemo GTV
- Modern RT techniques (3D-planning versus 2D bony anatomy)

Girinsky Radiother Oncol 2006; Specht IJROBP 2013

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

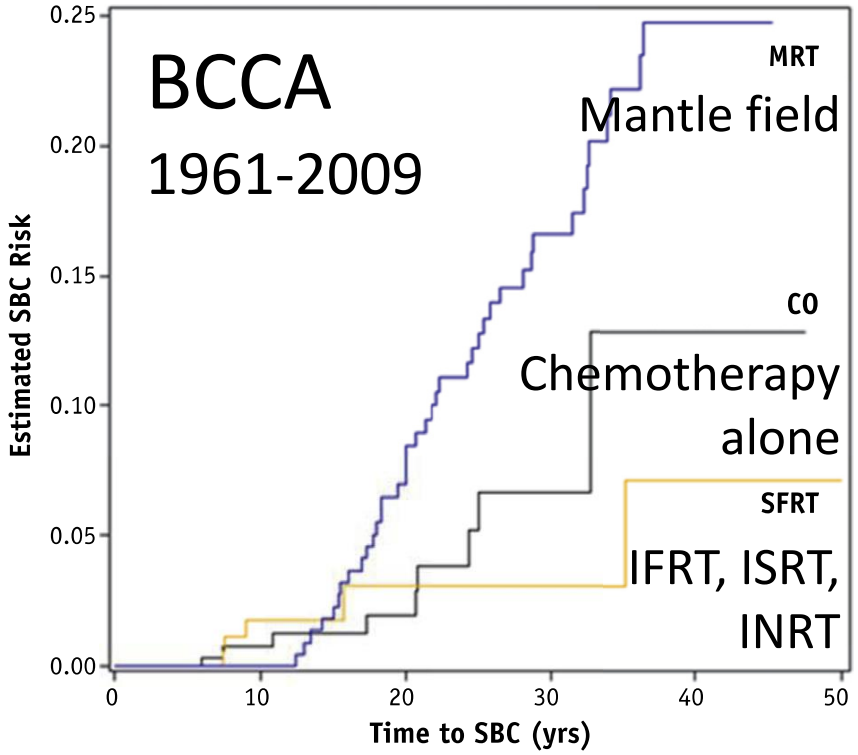


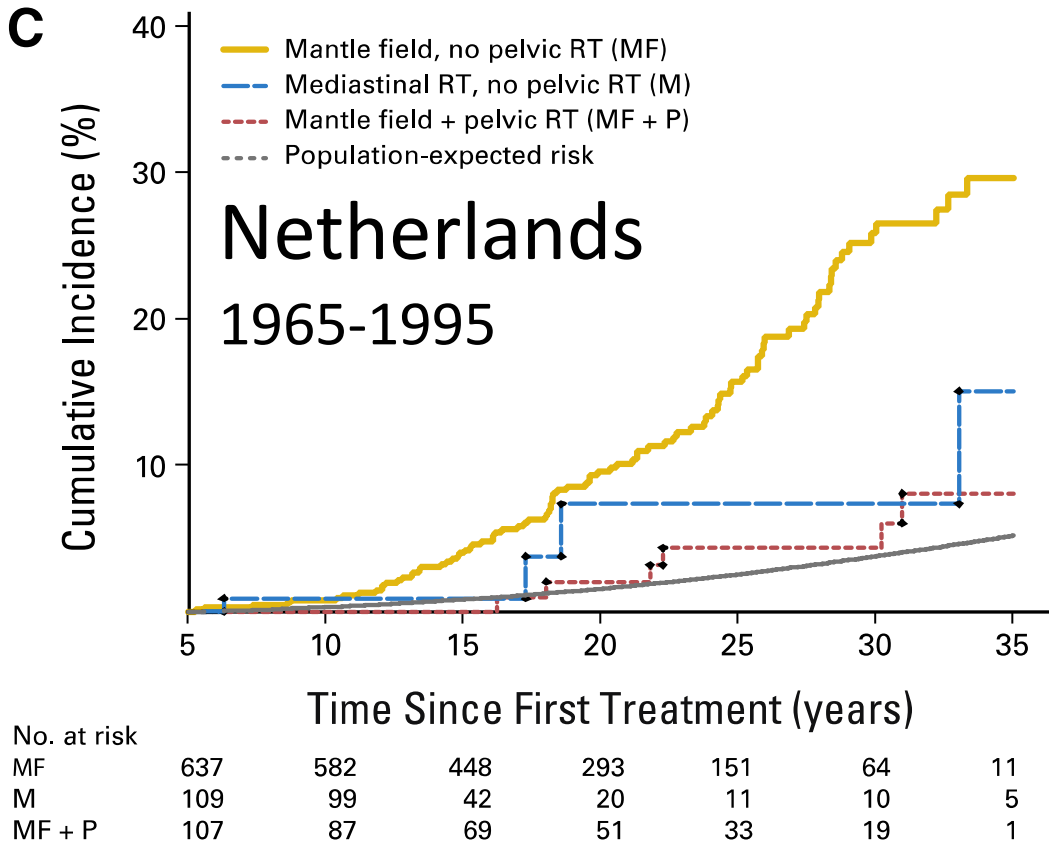
Smaller fields are not associated with increased rates of relapse

Campbell JCO 2008; Nielsen Radiother Oncol 2020

Size does matter

Reduction in breast cancer risk with smaller fields





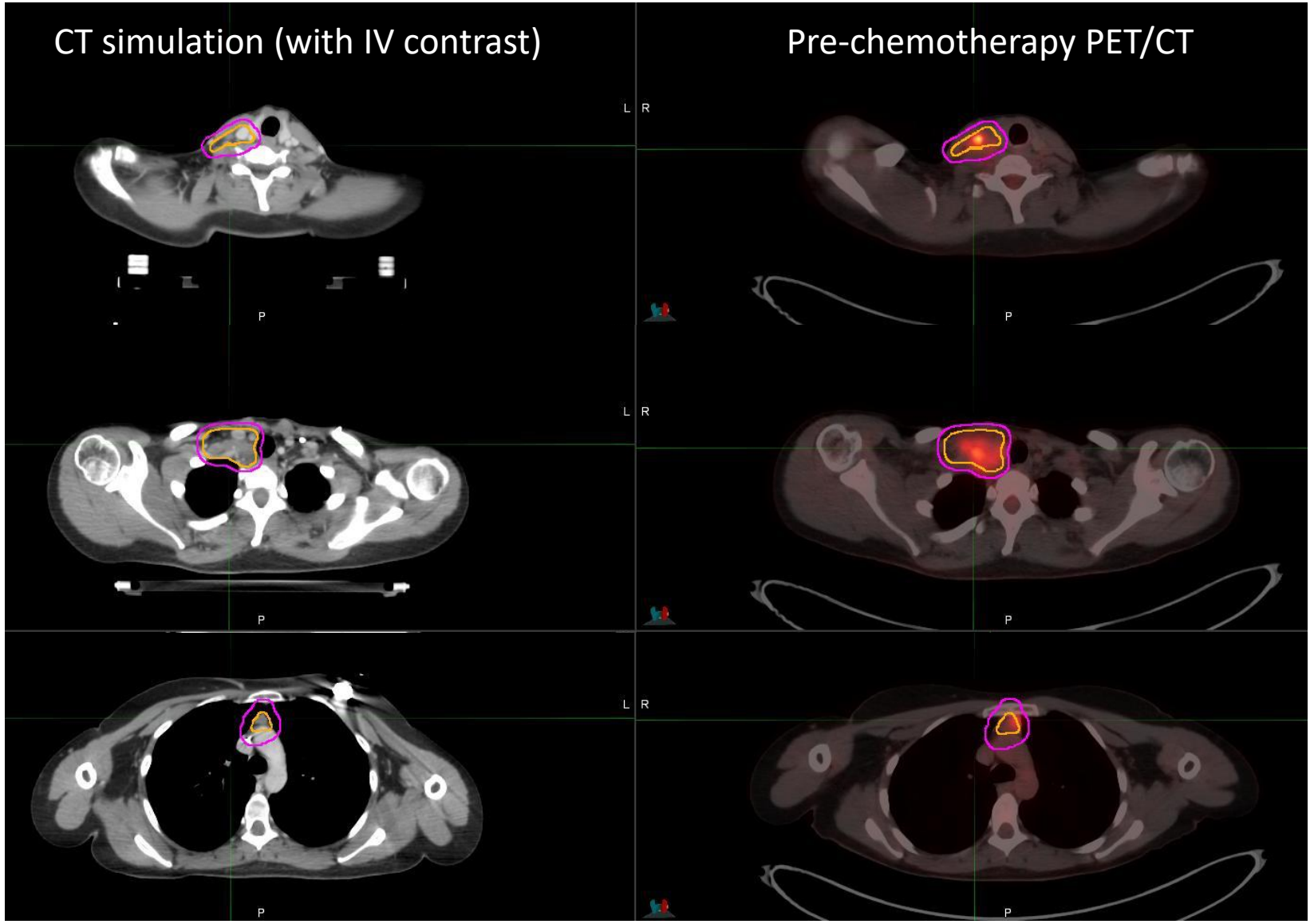
Conway IJROBP 2017; De Bruin JCO 2009

Case

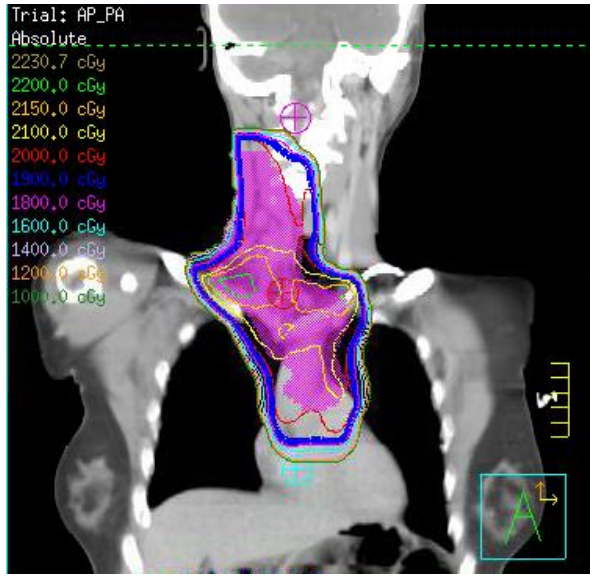
Simulated with arms down → less breast tissue brought in medially *(Denniston Front Oncol 2016)*

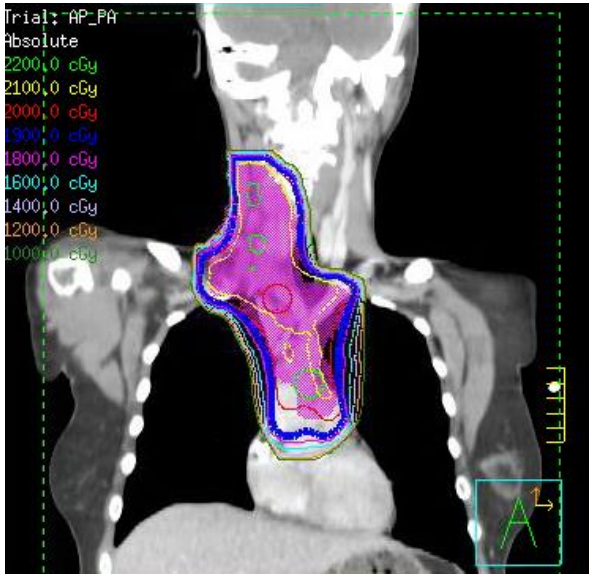
"Toolkit" of RT techniques

- DIBH
- 4D CT
- 3D conformal
- IMRT/VMAT
- Proton therapy
- IGRT



Treatment techniques for mediastinal lymphoma





	Free breathing	Deep inspiration breath hold (DIBH)
Heart (mean)	7.2 Gy	2.8 Gy
Breast (mean)	0.2 Gy	0.2 Gy
Lungs (mean)	4.5 Gy	3.9 Gy
Lungs V20	4%	3%
Lungs V5	25%	22%

Deep inspiration breath hold (DIBH)

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

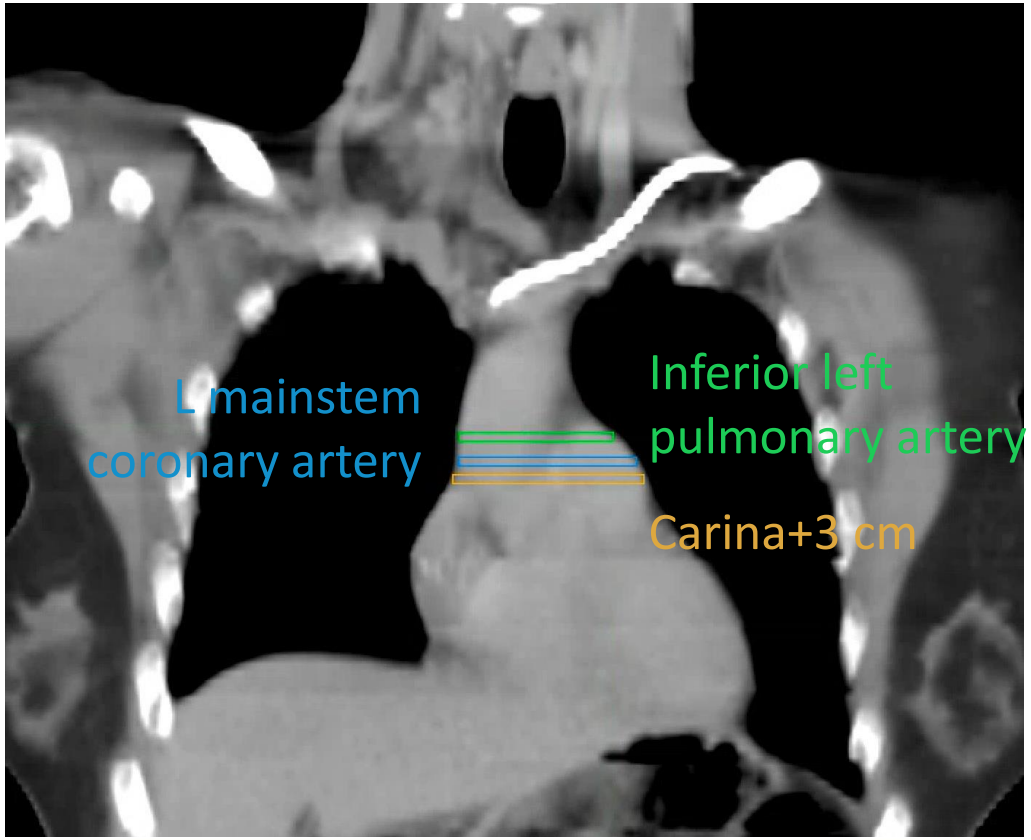
Dosimetric parameter	Patient group	Free-breathing IMRT	Deep-inspiration breath-hold IMRT	Difference	*p* value
Mean coronary dose	All patients (n = 28)	18.2 (15.9–20.6)	15.2 (12.6–17.9)	16%	0.0002
	Upper mediastinum (n = 11)	13.9 (10.1–17.6)	8.8 (5.6–12.1)	37%	0.001
	Whole mediastinum (n = 17)	21.1 (18.7–23.4)	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

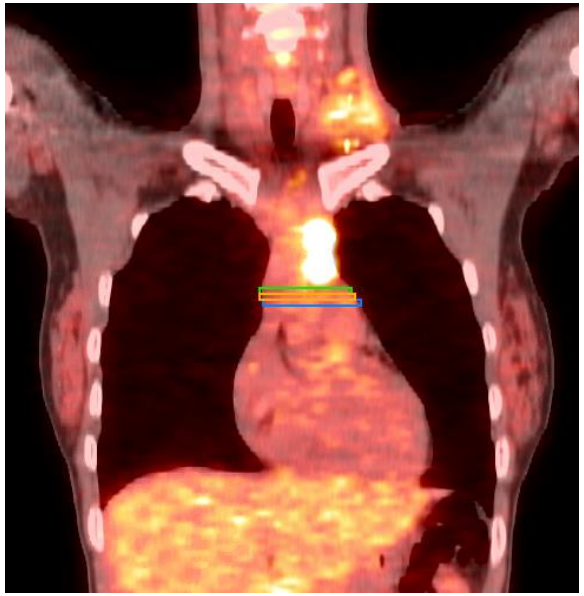
Greatest benefit of DIBH for tumors with only upper mediastinal involvement

Paumier IJROBP 2012

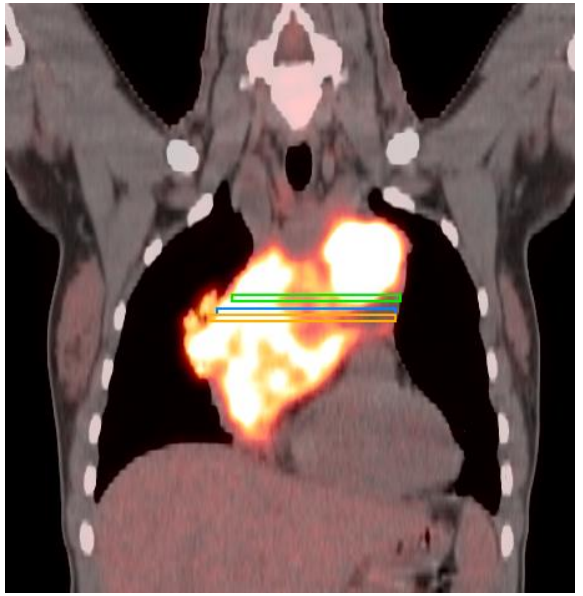
Approaches for lower mediastinal lymphoma

Various landmarks used to define lower mediastinal involvement:





Upper mediastinum

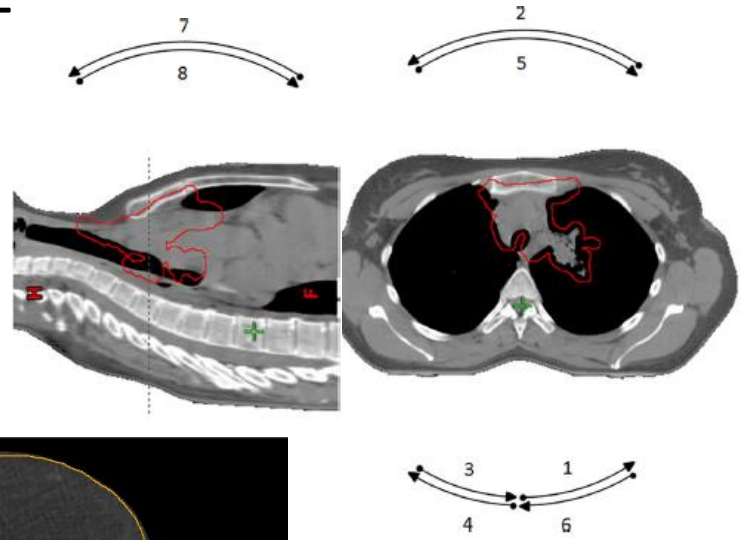


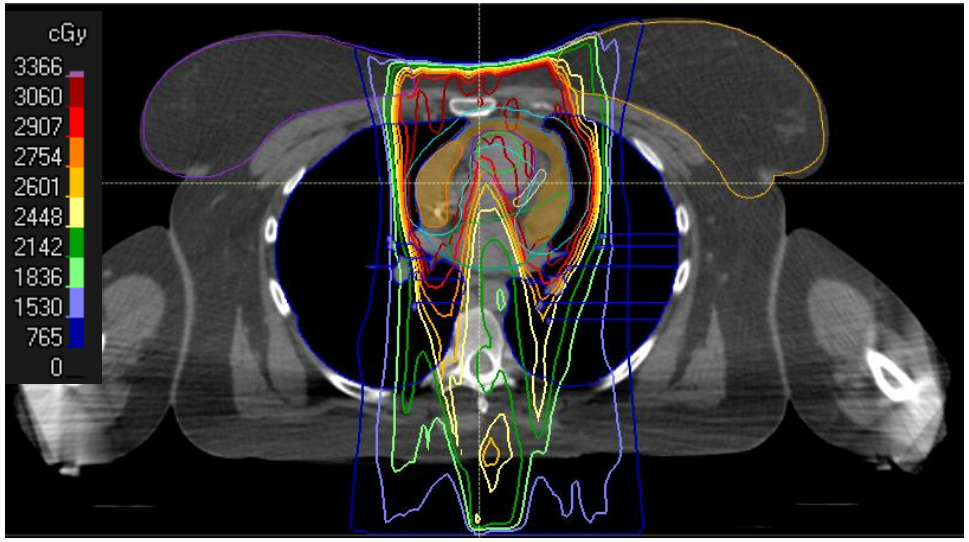
Lower mediastinum

Approaches for lower mediastinal lymphoma

"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

Approaches for lower mediastinal lymphoma

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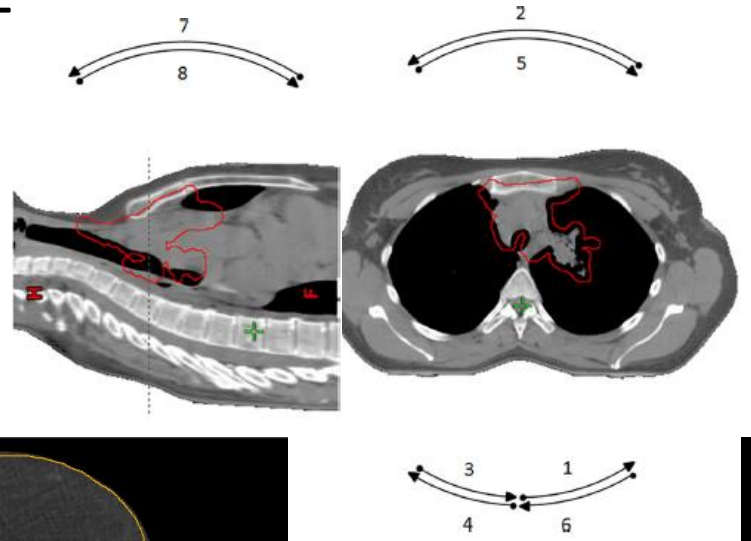
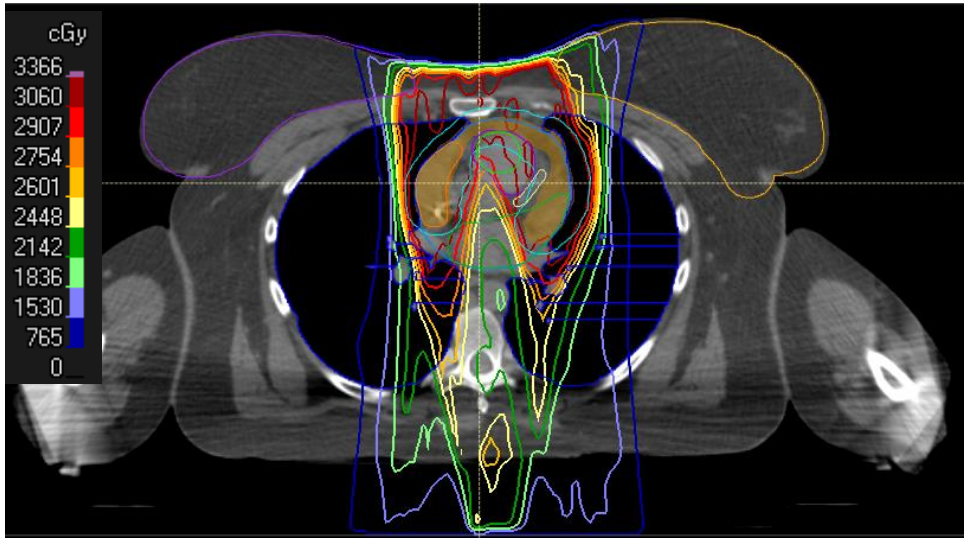
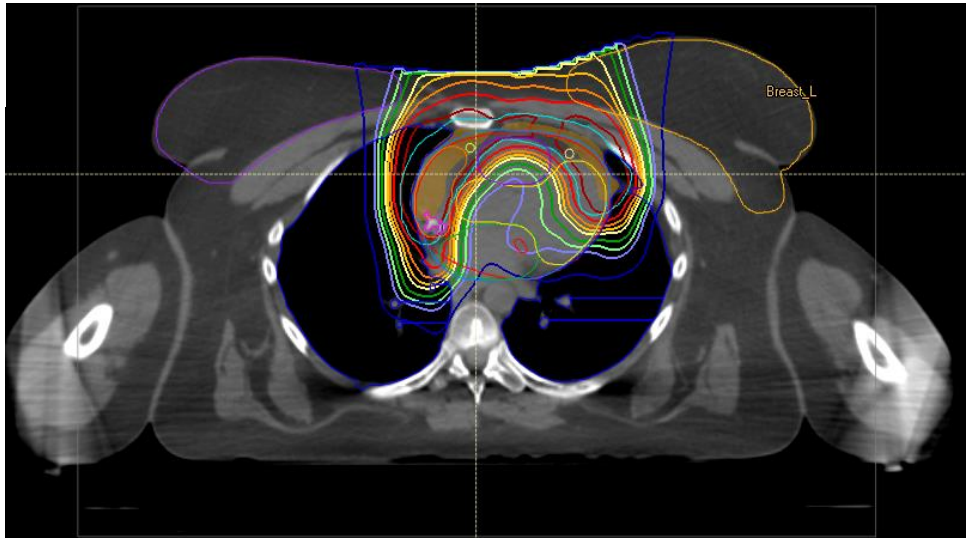


Proton therapy

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





Voong Radiat Oncol 2014; Starke Radiother Oncol 2018

Suggested acceptable doses to OARs

Mediastinal target

Structures	Ideal	Optimize technique	Optimize field (consider field reduction)	Unacceptable	Avoid maximum dose landing in
Heart: left ventricle, coronary arteries, valves[39-41]	Mean < 5 Gy	Mean, 5-15 Gy	Mean > 15 Gy	Mean > 30 Gy	Coronary vessels
Breast (age dependent)*	Mean < 4 Gy	Mean, 4-15 Gy	Mean > 15 Gy	Mean > 30 Gy	Glandular tissue
Lung[38]	V_5 < 55%	V_5, 55-60%	—	V_5 > 60%	
	V_{20} < 30%	Mean, 10-13.5 Gy		Mean > 13.5 Gy	
	Mean < 10 Gy				
Thyroid[62]	V_{25} < 62.5%	V_{25} < 62.5%			Whole thyroid

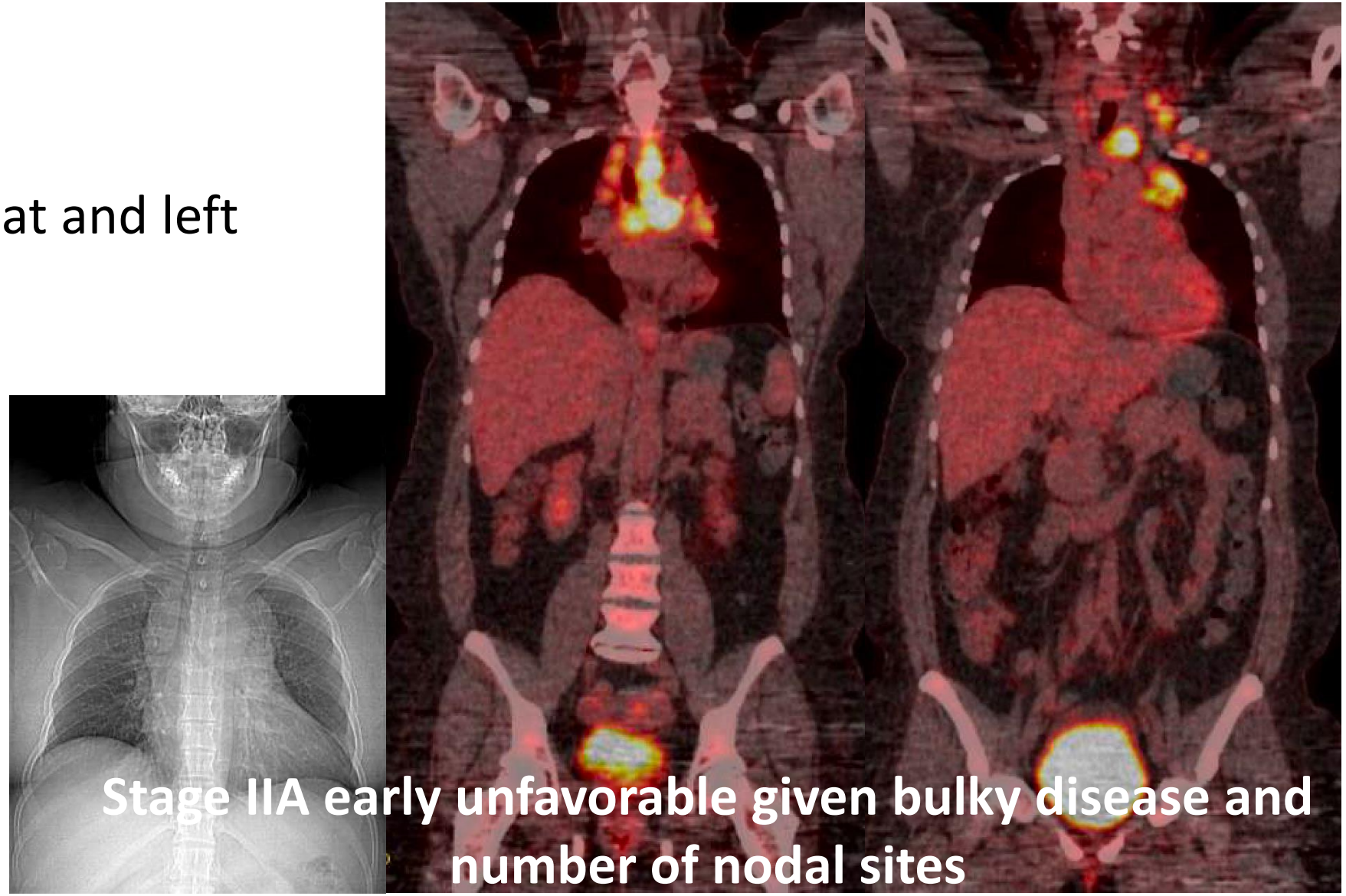
May help guide consideration of advanced RT technique (IMRT/VMAT, proton therapy), or omission of RT if unable to achieve a safe plan

Dabaja Blood 2018

Case

33F with lump in throat and left neck swelling

- Nodular sclerosing HL of both SCV, mediastinum, L hilar, R IMN
- No B-symptoms
- ESR 11



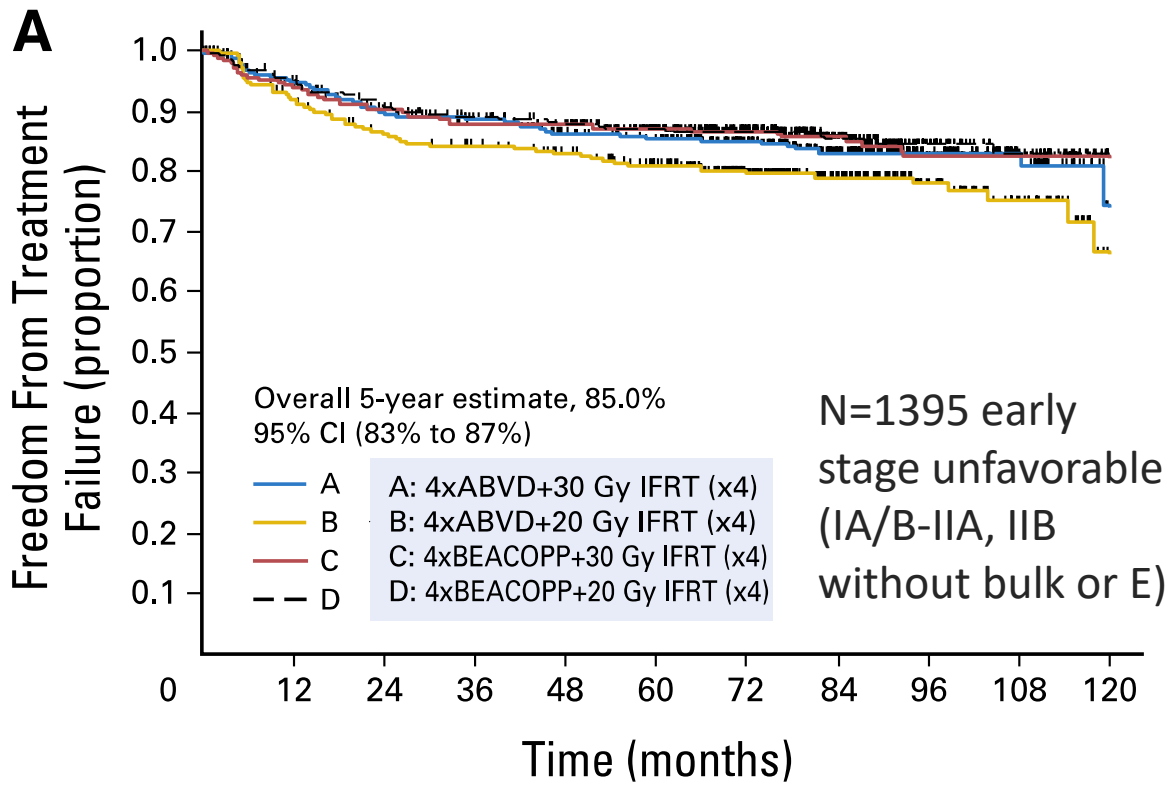
Stage IIA early unfavorable given bulky disease and number of nodal sites

Early stage unfavorable HL

Can dose be de-escalated?

GHSG HD11 (pre-PET era)

- 2 randomizations:
  - ABVD vs BEACOPP (*bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone*)
  - 20 versus 30 Gy IFRT
- Worse FFTF with ABVD+20 Gy
- *Established ABVDx4+30 Gy as standard*
- *RT de-escalation depends on chemo backbone*

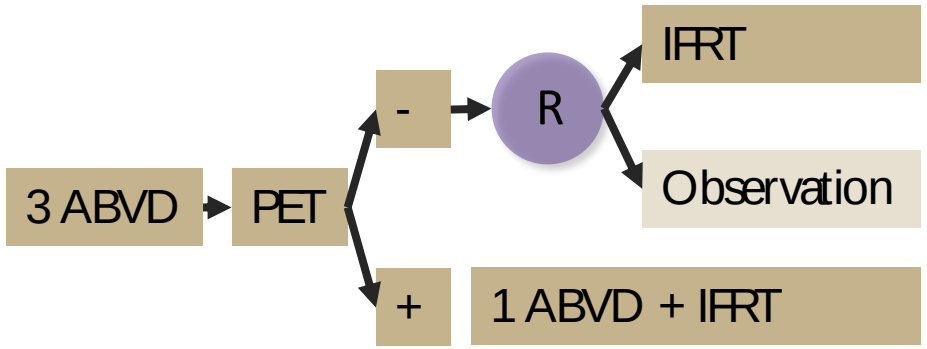


Eich JCO 2010

Response-adapted therapy for early stage HL

Omission of RT in setting of negative PET

UK RAPID



IFRT 30 Gy

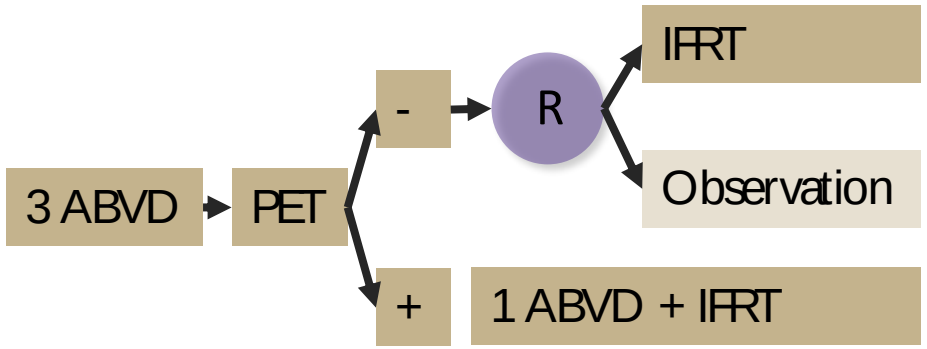
Standard	
Experimental	Deauville 1-2 considered negative PET

Raemaekers JCO 2014; Andrew JCO 2017; Radford NEJM 2015

Response-adapted therapy for early stage HL

Omission of RT in setting of negative PET

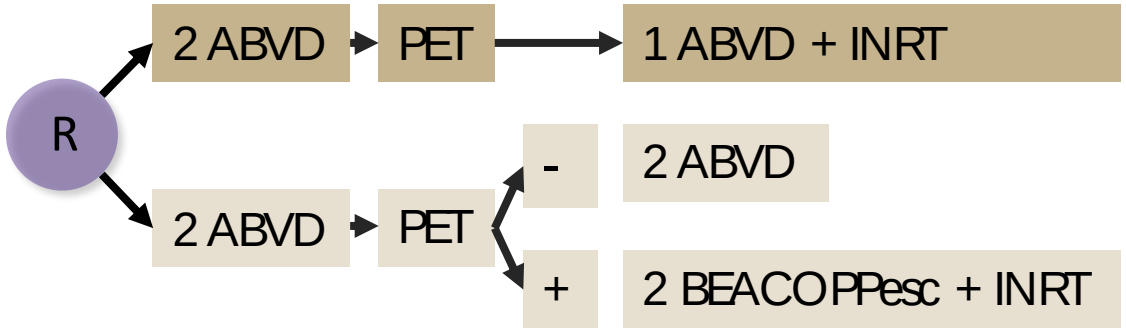
UK RAPID



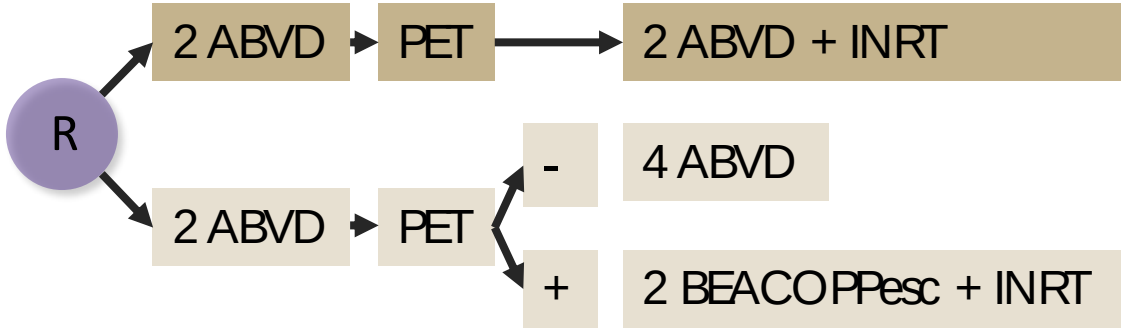
IFRT 30 Gy

Standard	
Experimental	Deauville 1-2 considered negative PET

EORTC H10F



EORTC H10U



INRT 30 Gy

Raemaekers JCO 2014; Andrew JCO 2017; Radford NEJM 2015

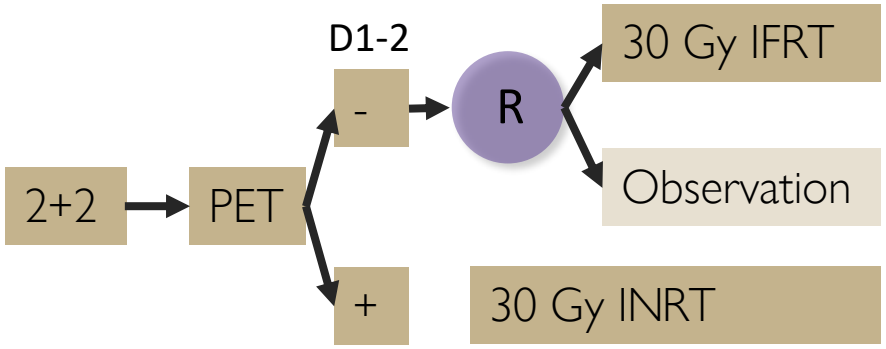
Response-adapted therapy for early stage HL

Omission of RT in setting of negative PET

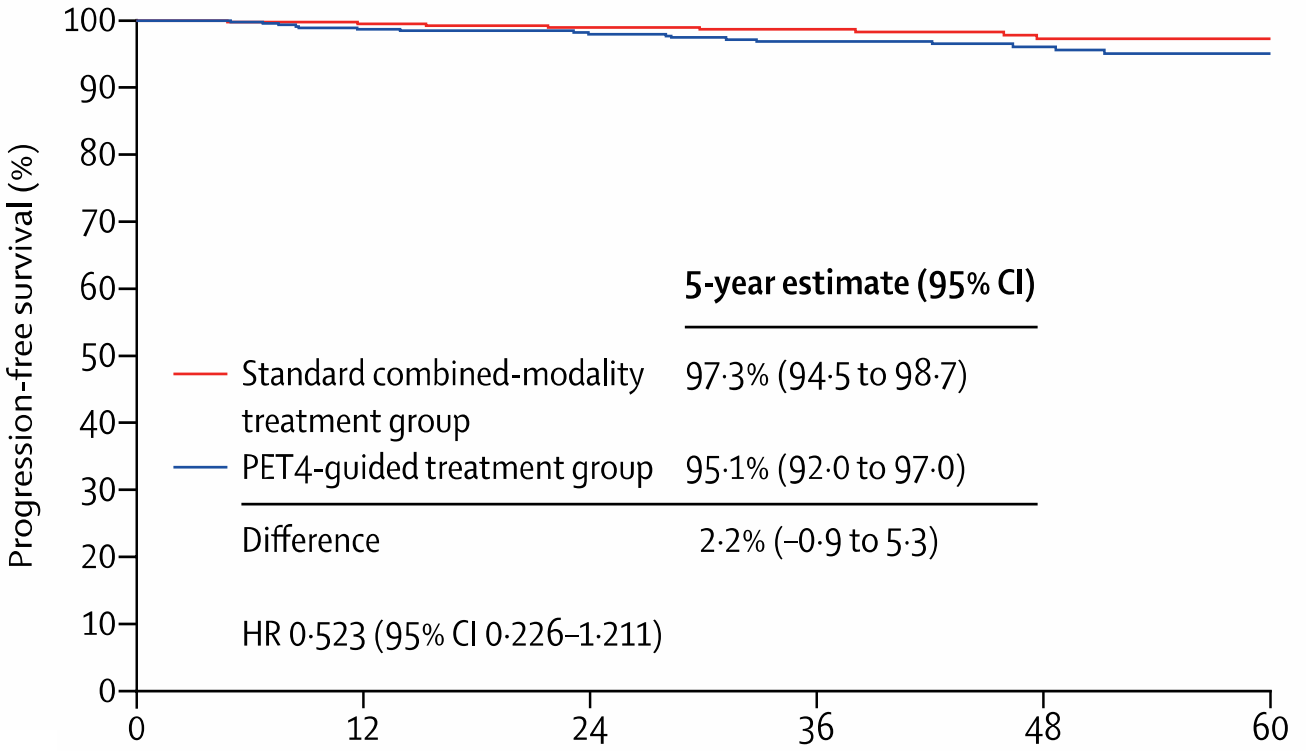
	UK RAPID N=602 (426 PET negative), 64% fav by EORTC	**EORTC H10** N=444/693 favorable/unfavorable
Cohort	Clinical stage IA, IIA • Excluded mediastinal bulk • 2003-2010	Stage I/II • 40% unfavorable patients with bulk • 2006-2010
Design	Non-inferiority • <=7% difference in 3-yr PFS	Non-inferiority • <=10% difference in 5-yr PFS
Results	• PFS_3 94.6% vs 90.8% • △: -3.8% (95% CI -8.8-1.3%)	• Interim analysis declared futility • F PFS_5: 99% vs 87%, HR 15.8 (95% CI 3.8-66.1) • U PFS_5: 92% vs 90%, HR 1.45 (0.8-2.5)

RT cannot be safely omitted after ABVD chemotherapy, even with negative PET/CT

Safe omission of RT depends on chemo backbone



2+2: BEACOPPesc x2 + ABVD x2



GHSG HD17

- Early unfavorable HL
- Non-inferiority margin PFS_5 <=8%
- RT can be safely omitted after negative PET with more intensive chemotherapy backbone (2+2)

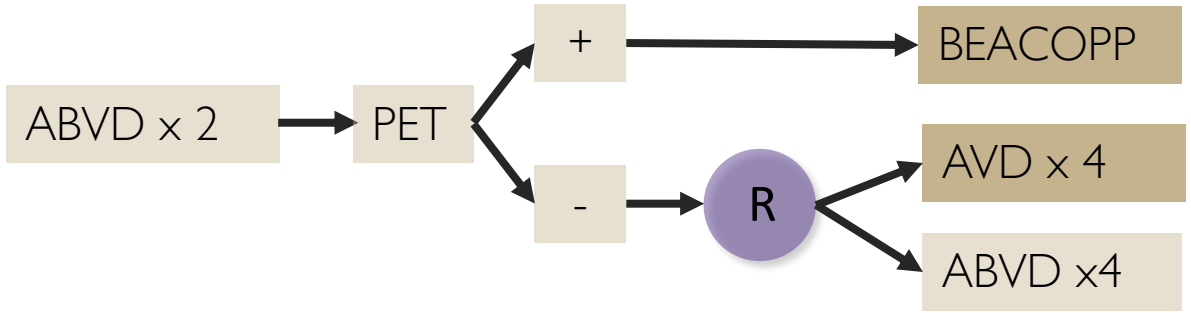
Borchmann Lancet 2021

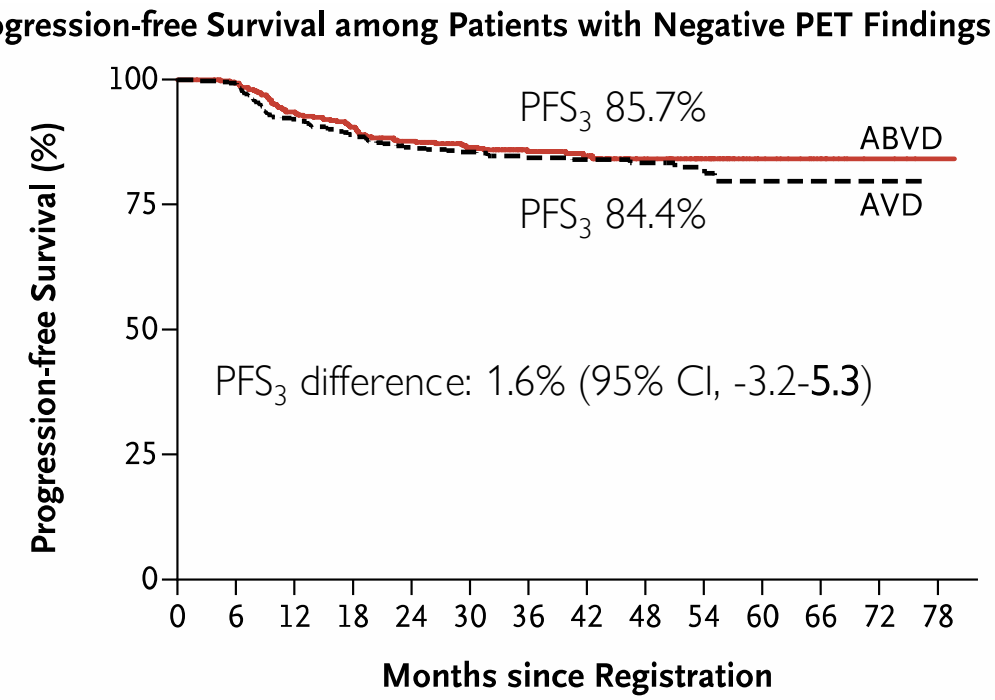
Response-adapted therapy for (early stage) HL

De-escalation of chemotherapy

RATHL

- IIB-IV HL, or IIA with bulky disease or >=3 nodal sites
- Stage II (42%), bulky (32%)
- No RT recommended for patients with negative PET2 (D1-3)
  - RT given 2.6% ABVD, 4.3% AVD
- Technically, did not meet non-inferiority margin (<=5% difference in PFS_3)





Johnson NEJM 2016

My clinical practice for early stage HL

Fulfills criteria for GHSG favorable?

Yes → ABVDx2 → PET/CT (D1-3) → ISRT (20 Gy) [GHSG HD10/HD16]

No

Plan to use PET to guide subsequent management?

Yes → ABVDx2 → PET/CT

- Chemo alone (worse outcomes)
  - D1-2: ABVDx1-2 [H10F, RAPID, no bulk], ABVDx4 [H10U]
  - D1-3: AVDx4 [RATHL]
- Chemo+RT
  - D1-3: ABVDx1-2 + ISRT (30 Gy) [H10, RAPID]
- D4-5: ABVD or intensification of therapy → PET/CT (versus biopsy)

No

ABVDx4 → PET/CT → ISRT [adapted GHSG HD11]

- D1-3: 30 Gy
- D4: 36 Gy

Combined modality approach with best outcomes

- RT improves PFS ~7-10% (bulky), otherwise ~5-7%

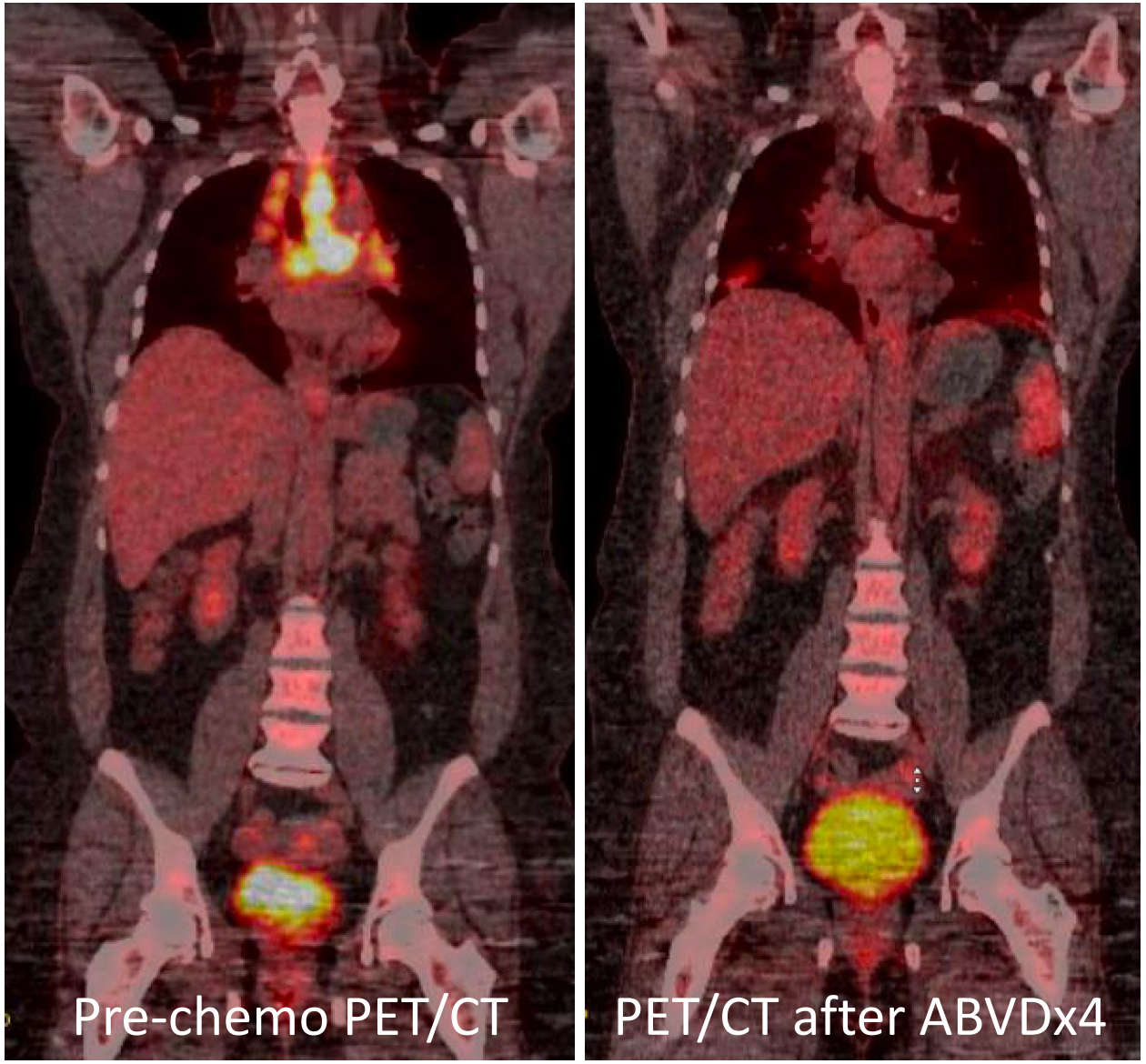
Case

33F with stage IIA unfavorable HL

- Treated with ABVDx4
- Complicated by bleomycin toxicity
- PET/CT Deauville 2

Consolidated with ISRT (30 Gy) with PBS proton therapy

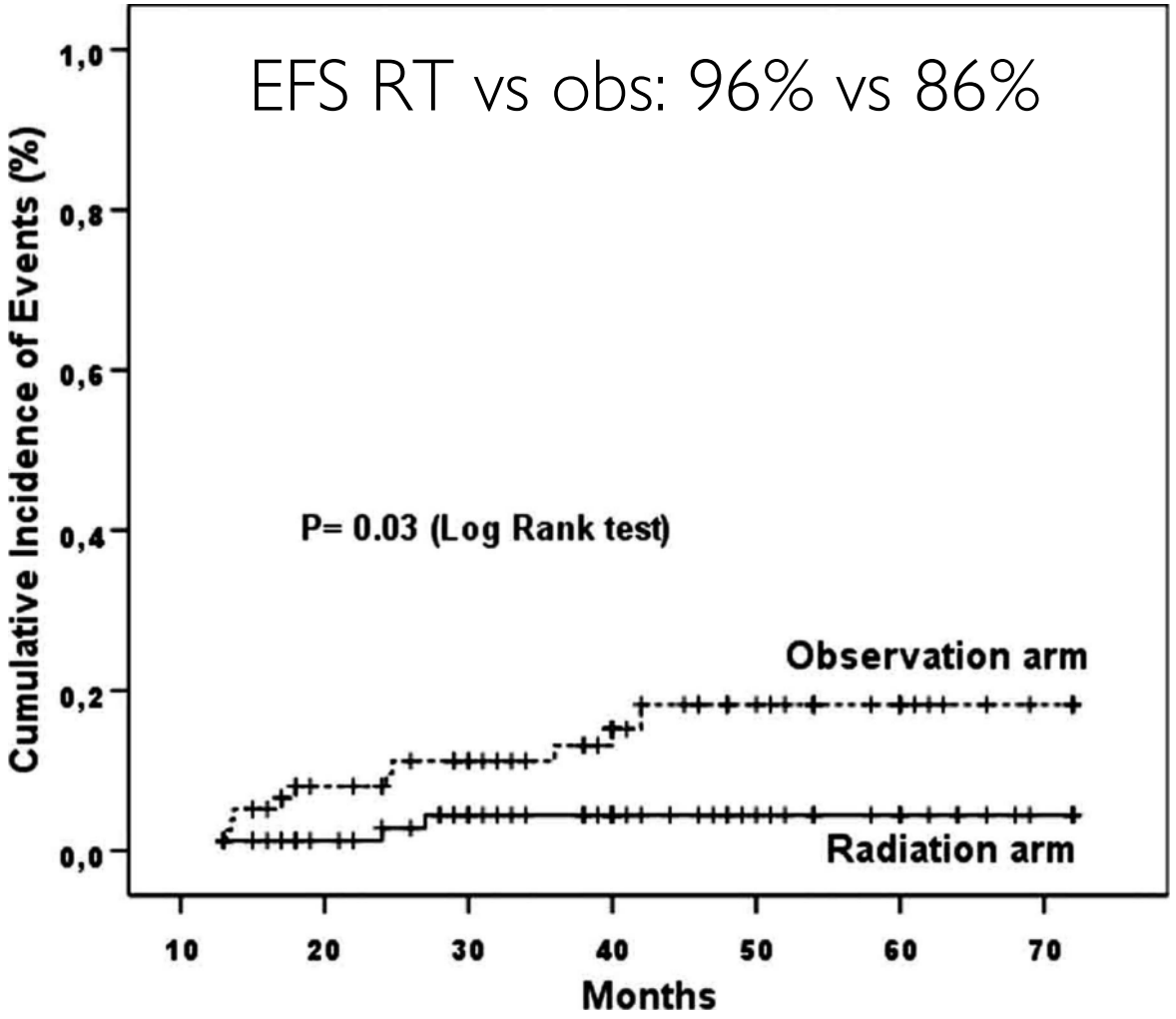
Organ	Photon (DIBH)	Proton (Free breathing)
Total lung	V20 27%	V20 20%
	V5 41%	V5 37%
	Mean 10.5 Gy	Mean 5.9 Gy
Heart	Mean 15.1 Gy	Mean 9 Gy
Breast_Left	Mean 5.78 Gy	Mean 2.4 Gy
Breast_Right	Mean 4.23 Gy	Mean 2.5 Gy
Cord	Max 33 Gy	Max 28 Gy
Esophagus	Mean 20 Gy	Mean 19.4 Gy



Role of RT for bulk

Italian RCT

- N=260 with >=5 cm disease
  - 66% stage I/II
  - **34% stage III/IV**
- VEBEP x6 *(Vinblastine, etoposide, bleomycin, epirubicin, prednisone)*
- Randomized after negative PET to IFRT (32 Gy) versus observation
- RT improves PFS ~10%
- All relapses in obs arm within bulky site and contiguous nodal areas



Picardi Leuk Lymph 2007

Advanced stage Hodgkin lymphoma

Role of RT for initial bulk (>=5 cm) after ABVDx6

Stage IIB-IV HL with negative PET2 and PET6, randomized to 30 Gy versus observation

	Patients	Outcome	
GITIL HD 0607 *Gallamini JCO 2020*	N=296 • 33% >10 cm • 47% stage II • **53% stage III/IV**	• PFS_6: 92% (RT) vs 90% (NS) • PFS_6 (>10 cm): 89% vs 86% (NS)	Trial not powered by a defined statistical design
FIL HD 0801 *Ricardi ESTRO 2019*	N=116 • Median, 8 cm • 29% stage II • **71% stage III/IV**	• ITT: PFS_5 83.7% (RT) vs 85.8% • PP: PFS_5 88.9% (RT) vs 81.5%; p=.24	Trial underpowered

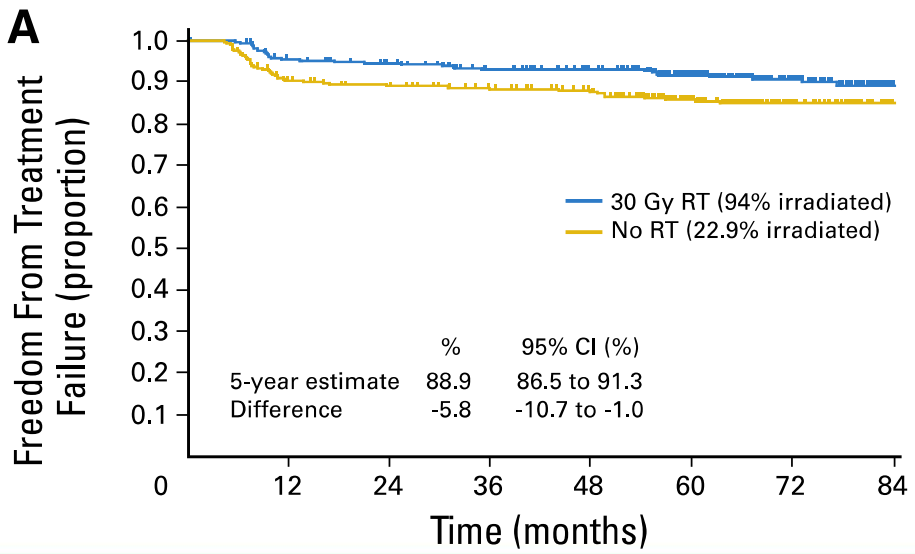
Data may suggest omission of RT after CMR for bulk among advanced HL

Advanced stage Hodgkin lymphoma

RT for residual disease improves PFS

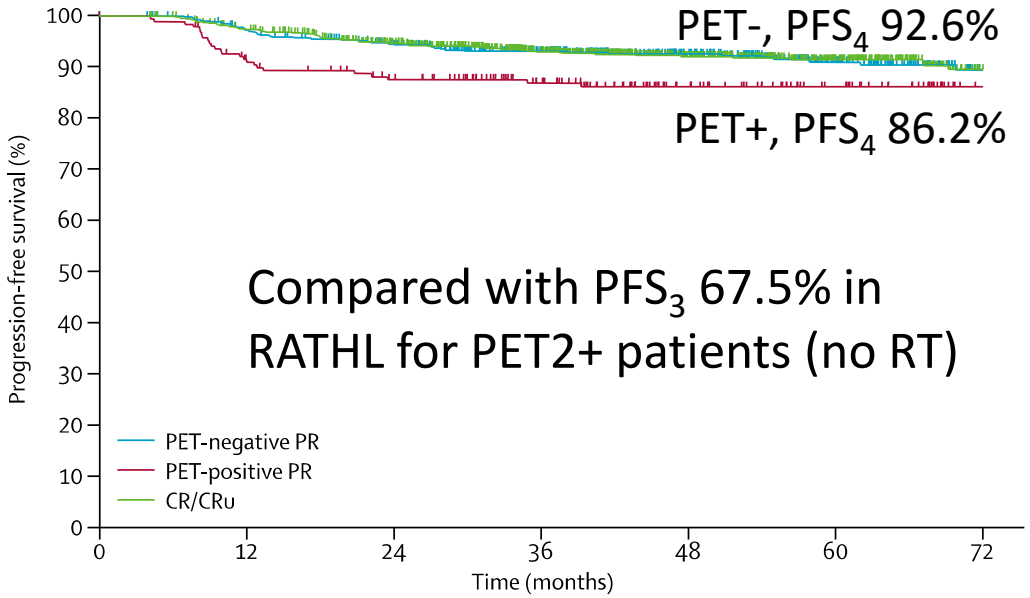
GHSG HD12 (*Borchmann JCO 2011; von Tresckow Lancet Hematol 2018*)

- Randomized 30 Gy vs obs
- >=1.5 cm residual after BEACOPP (no PET)



GHSG HD15 (*Engert Lancet Oncol 2012*)

- Single arm, no randomization
- RT (30 Gy) for PET+ and >=2.5 cm residual after BEACOPP



Compared with PFS_3 67.5% in RATHL for PET2+ patients (no RT)

My clinical practice for advanced stage HL

- ISRT if partial response (36-40 Gy)
- No consolidation for initial bulk after complete metabolic response
  - Exception for stage II (i.e. may be feasible to consolidate all disease)

Relapsed/refractory Hodgkin lymphoma

Indications for RT

First relapse

- Cytoreduction after salvage chemo or ASCT (36-45 Gy)
- Consolidation after ASCT or salvage chemo (30-36 Gy)
  - Primary chemo-refractory
  - FDG+ disease prior to ASCT

Relapsed/refractory after ASCT

- Primary therapy (PMH series, 61% RT alone)
  - CR 30%, PR 50%
  - PFS_2 16%, local PFS_2 65%, systemic PFS_2 17%
  - OS_5 ~30%
- Palliation

Table 2 General indications for radiation therapy as part of salvage in patients with relapsed or refractory Hodgkin lymphoma

1. Localized relapse
2. Disseminated relapse but with sites including the following:
   - A. Bulky disease (≥5 cm)
   - B. Persistent FDG-avid disease after salvage chemotherapy or after SCT
   - C. Critical for local control, such as the following:
     - i. Spinal cord compression (vertebral involvement)
     - ii. Nerve root compression
     - iii. Superior vena cava compression
     - iv. Airway compression
     - v. Lymphedema
     - vi. Hydronephrosis

Goda IJROBP 2012; Milgrom Cancer 2017; Constine IJROBP 2018

Non-Hodgkin lymphomas (NHL)

B-cell lymphomas*

Aggressive
- **DLBCL**
- PMBCL
- High-grade B-cell lymphoma
- Burkitt lymphoma

Indolent
- **Follicular lymphoma**
- **MALT**
- CLL/SLL

T-cell lymphomas*

Aggressive
- NK/T-cell lymphoma
- Peripheral T-cell lymphoma

Indolent
- Mycosis fungoides

*More commonly encountered (not a comprehensive list)

Role of RT for DLBCL

Early stage (Stage I/II)
- Bulky
- Non-bulky
- Partial response
- Skeletal involvement

Advanced stage (Stage III/IV)
- Bulky
- Skeletal involvement
- Partial response

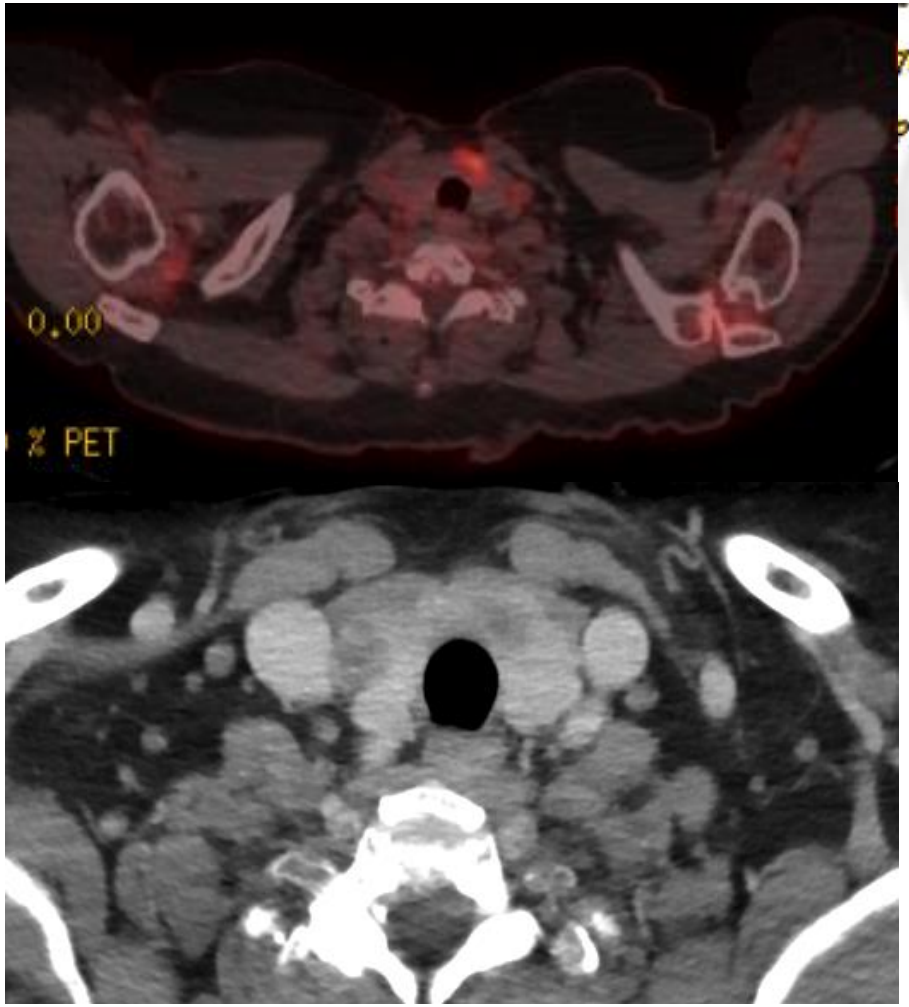
Relapsed/refractory
- Peri-transplant
- Bridge to systemic therapy
- Salvage
- Palliation

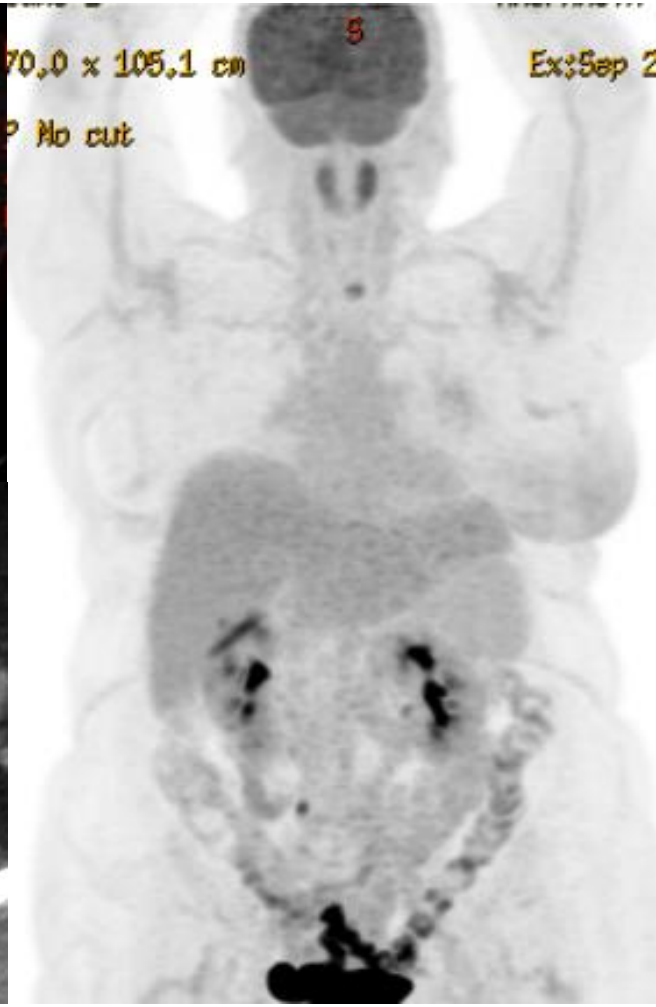
Contemporary trials evaluate RT role in the PET and rituximab era

Case

64F from Ukraine with history of thyroid nodules

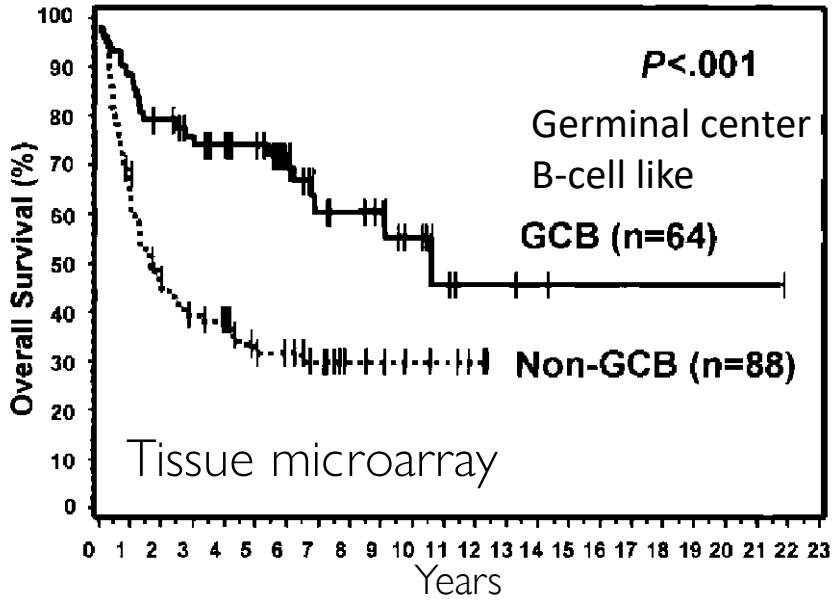
- Change in L thyroid nodule, biopsy non-diagnostic
- PET/CT
- L thyroid lobectomy
  - Small focus of DLBCL, CD10+, CD20+
  - Other pathologic features?





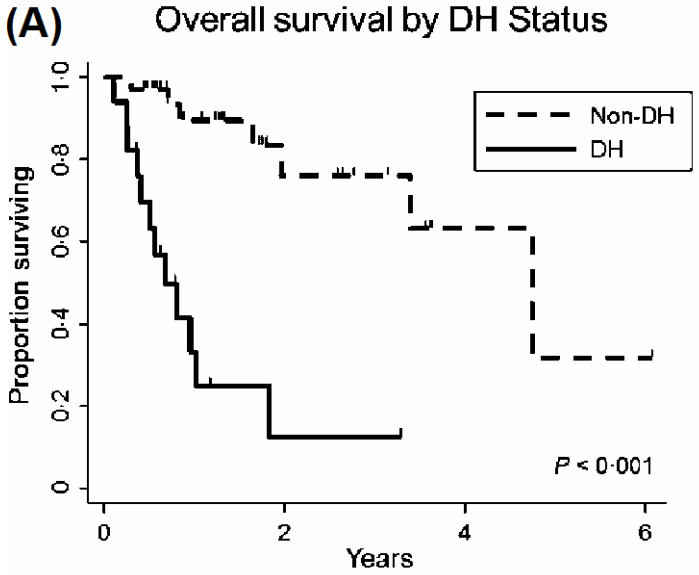
Pathologic prognostic features

Cell of origin



- Gene expression profile is gold standard (fresh tissue)
- IHC used in clinical practice

High-grade B cell lymphoma with *MYC* and *BCL2* and/or *BCL6* translocations



- New category in WHO 2016 classification of lymphoid neoplasms
- Double-/triple-hit lymphoma (DHL/THL)

Hans Blood 2004; Landsburg Br J Haematol 2014

Case

64F with resected DLBCL, GCB-subtype without *MYC* translocation

- Normal LDH
- Excellent performance status
- Risk stratification with international prognostic index (IPI)
  - Performance status >=2
  - **Age >60 years**
  - LDH >normal
  - Stage III/IV
  - Extranodal sites >=2

Table 2. Outcome according to International Prognostic Index (IPI) factors in 365 patients treated with R-CHOP in British Columbia

Risk group	No. of IPI factors	% Patients	4-year PFS, %	4-year OS, %
Standard IPI				
Low	0, 1	28	85	82
Low-intermediate	2	27	80	81
High-intermediate	3	21	57	49
High	4, 5	24	51	59
Revised IPI				
Very good	0	10	94	94
Good	1, 2	45	80	79
Poor	3, 4, 5	45	53	55

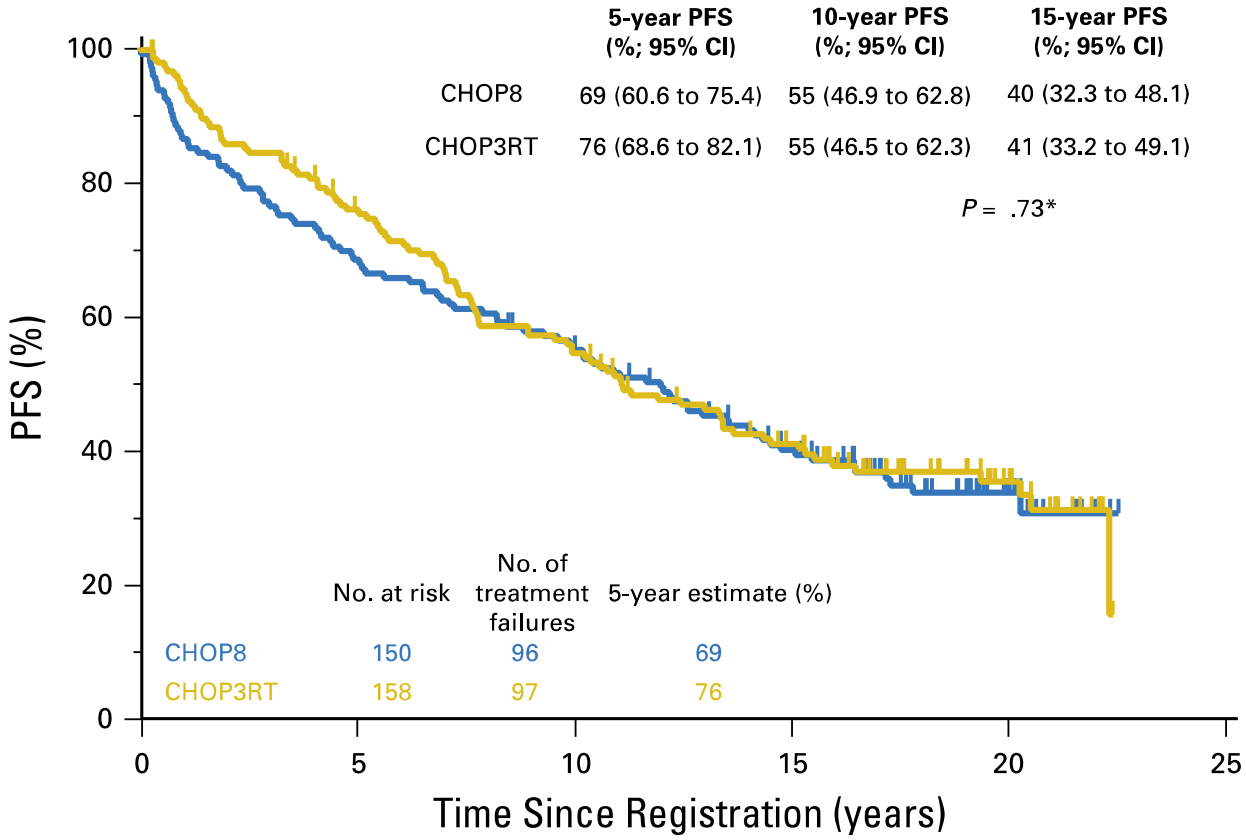
Sehn Blood 2007

Early stage DLBCL

RT role in pre-rituximab, pre-PET era

SWOG 8736, 1988-1995

- Stage I-IIE (bulk allowed for stage I)
- Median FU 17.7 years
- 75% DLBCL, 72% IPI 0-1
- *CHOPx3+RT is equivalent to CHOPx8*



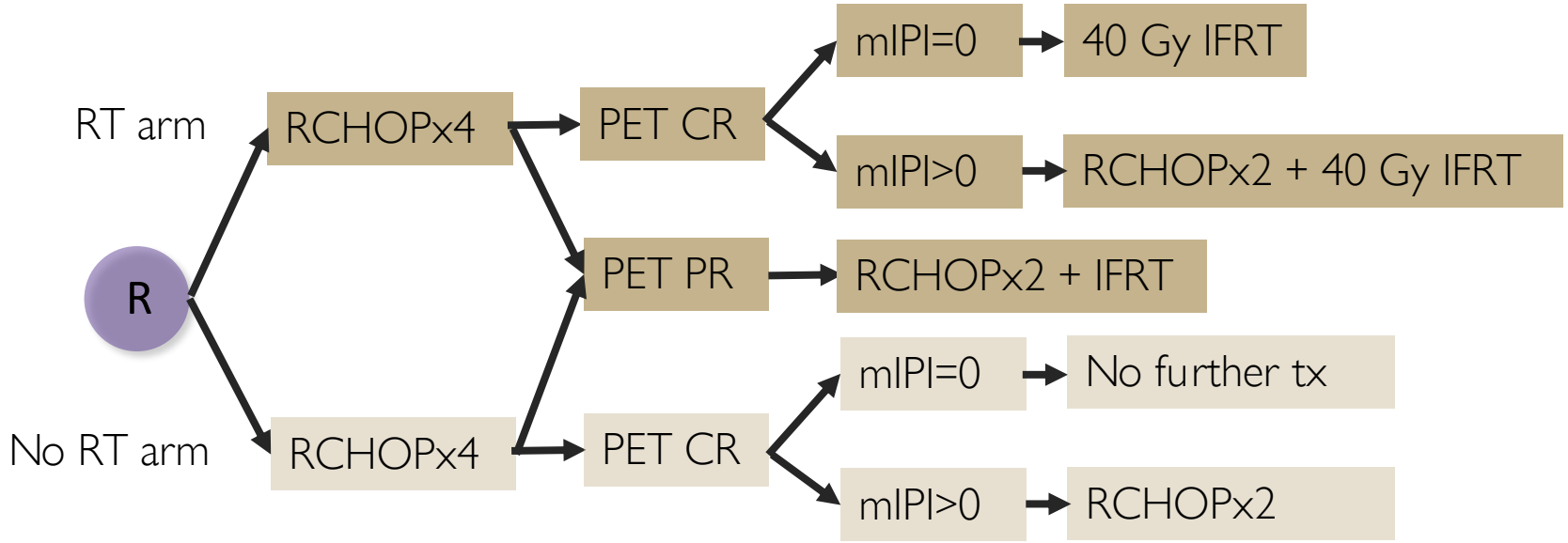
Miller NEJM 1998; Stephens JCO 2016

Early stage, non-bulky DLBCL

RT role in rituximab and PET-era

LYSA 02-03

<7 cm stage I/II DLBCL



- Very favorable cohort
  - 56% smIPI 0 (>60 yo, LDH, stage II, PS>=1)
  - 19% without gross disease before chemo
  - 64% <60 yo
- 43% received >4 cycles RCHOP

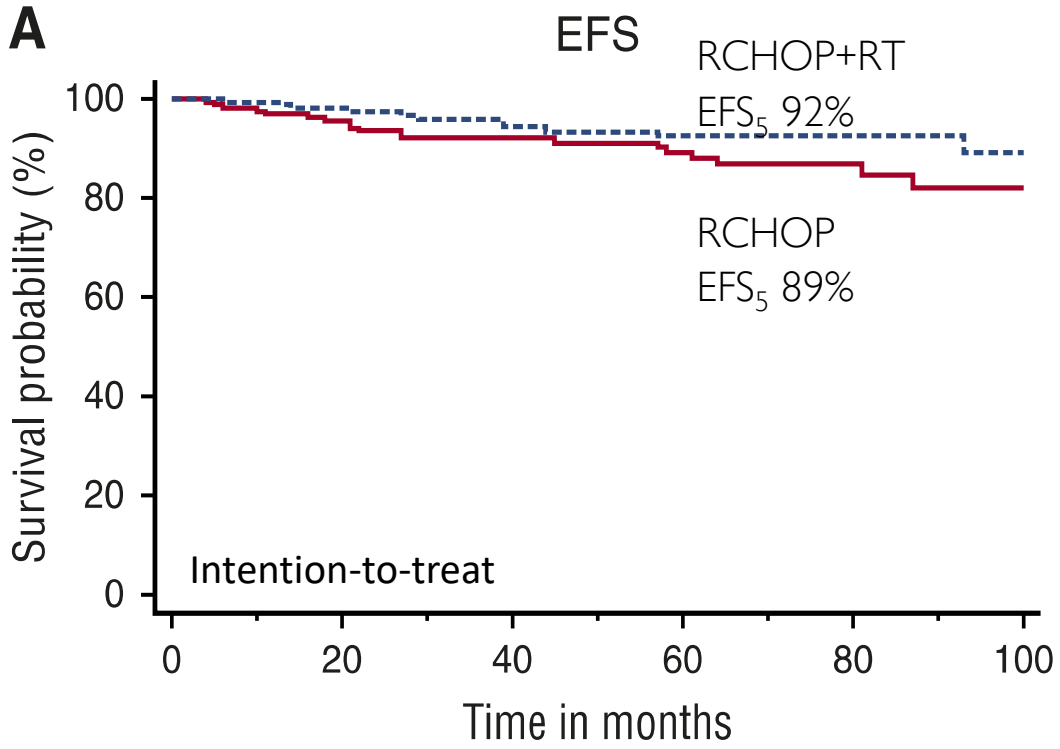
Lamy Blood 2018

Early stage, non-bulky DLBCL

RT role in rituximab and PET-era

LYSA 02-03

- No difference in EFS with addition of RT
- No difference in EFS with CR versus PR → role of RT for PR
- RT improves local control
  - 13 relapses RCHOP (5 initial site)
  - 10 relapses RCHOP+RT (none in RT site)
- Caveats: short FU (64 mo), IFRT, RCHOP14



RT may be omitted in patients with favorable, low volume disease with metabolic complete response after RCHOPx4

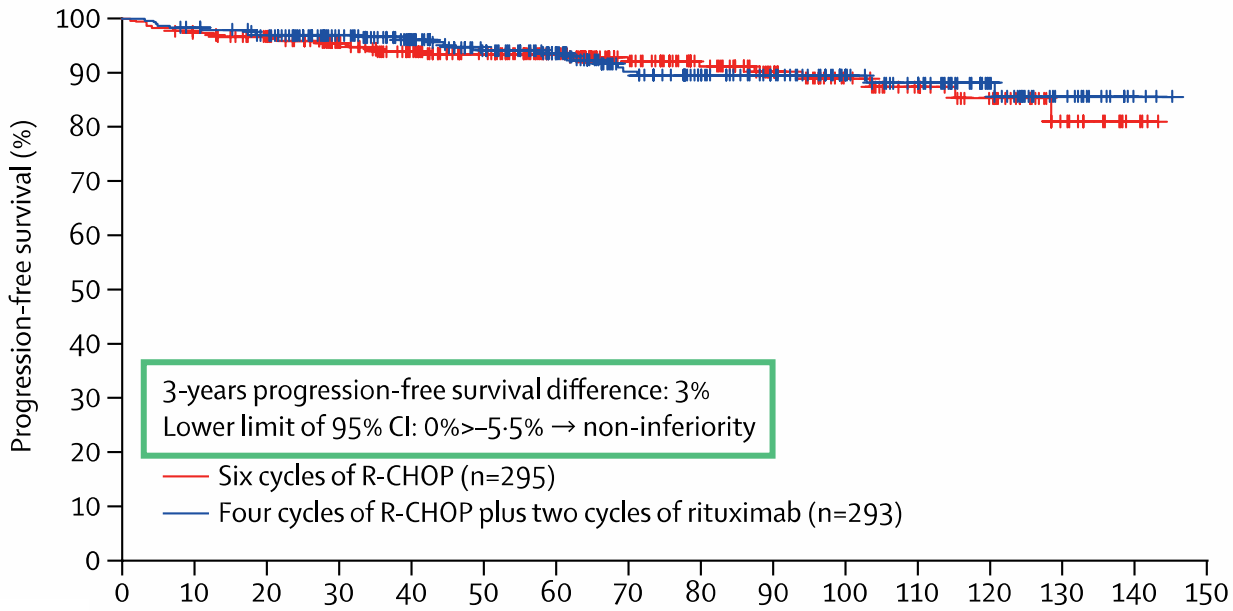
Lamy Blood 2018

Early stage, non-bulky DLBCL

Chemotherapy de-intensification

FLYER

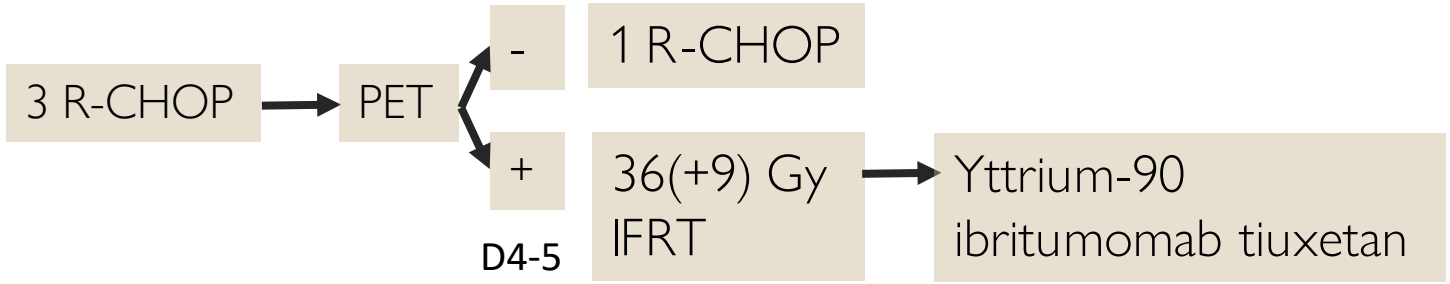
- Very favorable patients
  - No risk factors on aaIPI (normal LDH, ECOG PS 0-1, stage I/II)
  - 18-60 yo (median 48)
- Randomized, non-inferiority trial
- RT not allowed (5% received)
- *Can reduce chemo to RCHOPx4 + Rx2 for young, favorable patients*

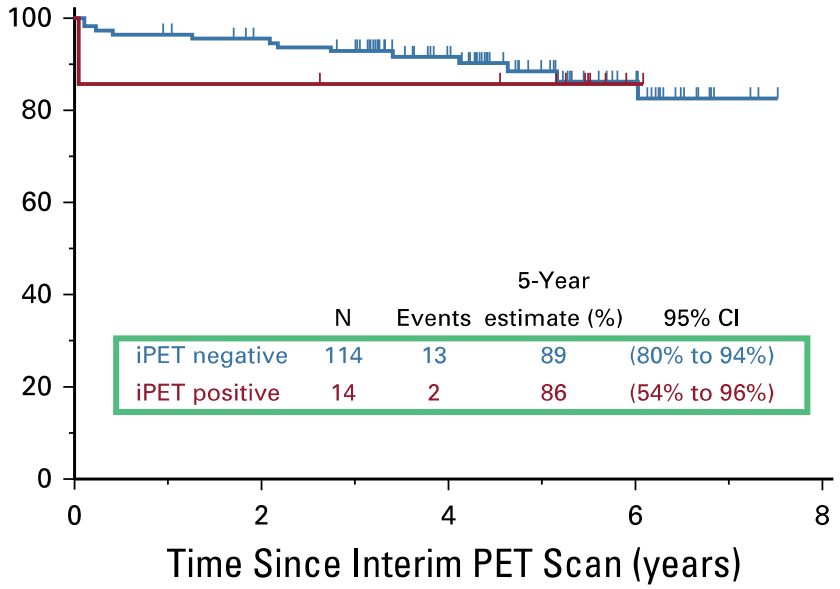


Poeschel Lancet 2020

Early stage, non-bulky DLBCL

RT role in rituximab and PET-era





SWOG 1001 (n=132)

- Ph II, PET-adapted treatment for <10 cm, stage I/II
- Less favorable cohort to LYSA 02-03
  - 27% smIPI 0, 10% without gross disease, median 62 yo (46% <60 yo)
- 11% with PET3-pos: 67% converted from PR to CR after IFRT-Zevalin
- *Highlights role of RT for PR, confirms similar PFS_5 ~90% seen in LYSA, FLYER*

Persky JCO 2020

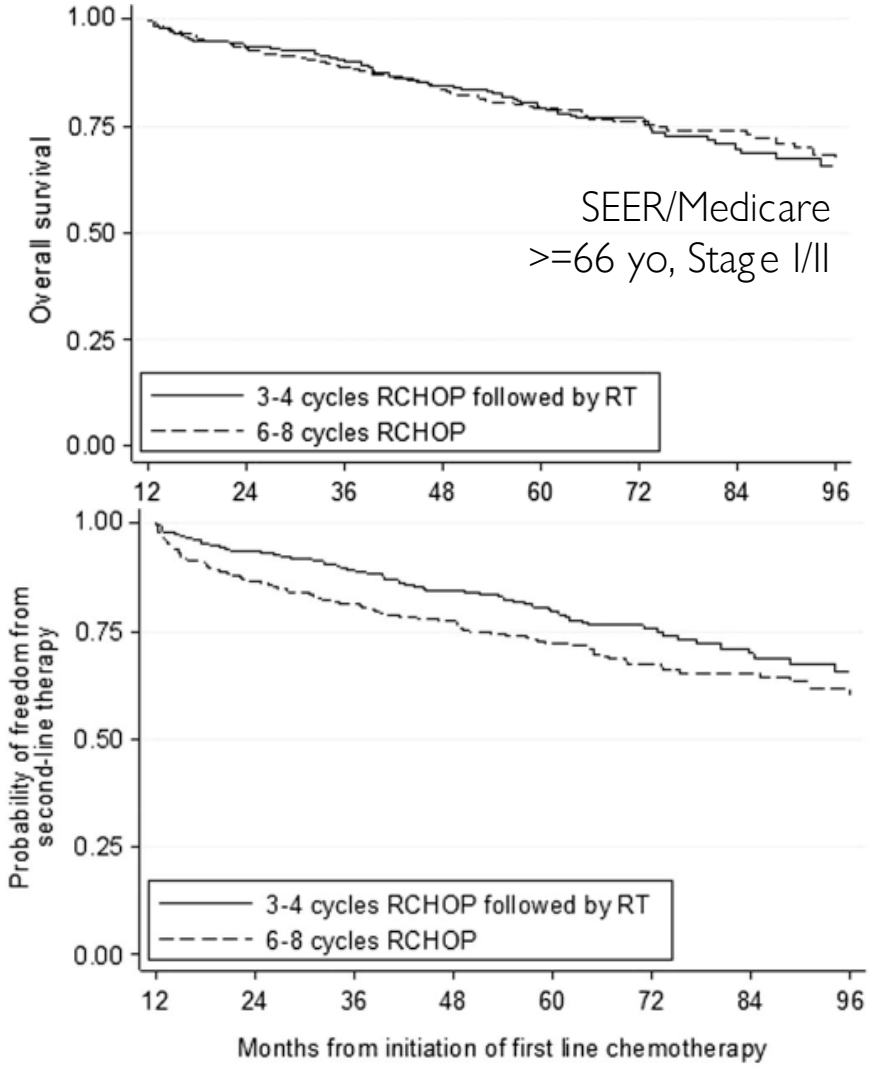
Case: 64F with stage I resected DLBCL of thyroid

Recommended RCHOPx3 → ISRT (30 Gy)

- Would otherwise require RCHOPx6 on LYSA study
- Need more data on RCHOPx4 for >60 yo

Consideration of older patients

- Equivalent outcomes between combined-modality treatment (CMT) and full course chemo
- Lower toxicity rates (heme, neuropathy) with CMT
- Lower anthracycline exposure



Odejide Leuk Lymph 2015

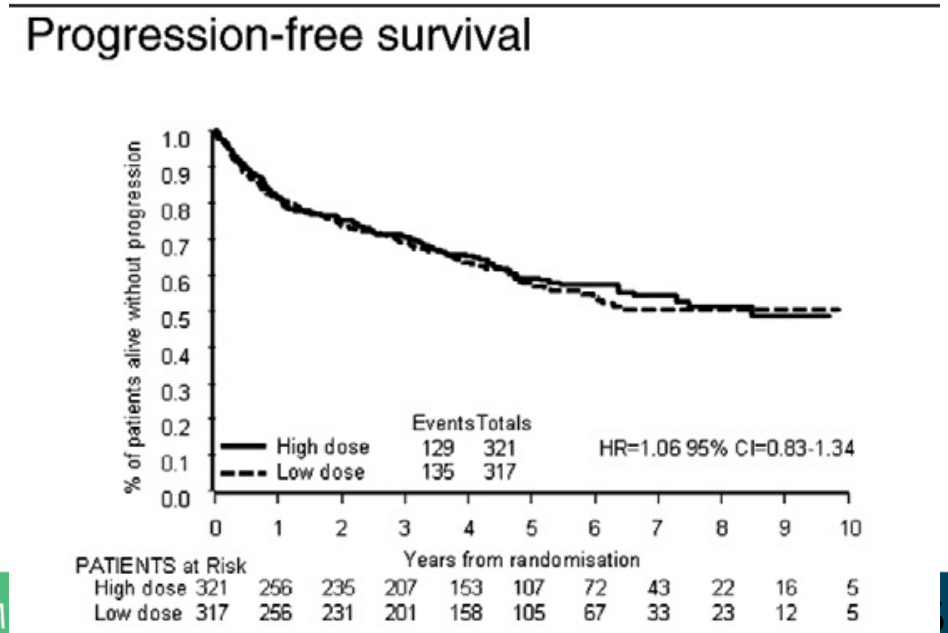
Dose for aggressive NHL

BNLI/NCRI randomized trial

- Aggressive NHL randomized to 1) 40-45 Gy vs 2) 30 Gy
- 13% r/r, 8% palliative, 82% DLBCL
- Primary: ORR, secondary: FFLP
- Dose can be safely de-escalated to 30 Gy for aggressive NHL
- Caveats: Included patients treated with RT alone, no chemo data, no functional imaging

Lowry Radiother Oncol 2011

Response	Indolent		Aggressive	
	24 Gy	40–45 Gy	30 Gy	40–45 Gy
CR	145 (82%)	138 (79%)	249 (82%	251 (83%)
PR	18 (10%)	24 (14%)	29 (9%)	24 (8%)
SD/ progression	14 (8%)	12 (7%)	25 (8%)	24 (8%
Death	0 (0%)	0 (0%)	1 (<1%)	3 (1%)
Not assessable	2	2	0	3
No RT received	1	1	5	3
Missing	0	4	10	13
Total	180	181	319	321



My clinical practice for early stage DLBCL

Non-bulky (<7.5 cm)

IPI=0

- RCHOPx3 + ISRT [adapted SWOG 8736]
- RCHOPx4 if PET-neg [LYSA 02-03]*

IPI>0

- RCHOPx3 + ISRT [adapted SWOG 8736]
- RCHOPx6

RT for PET partial response [LYSA 02-03, SWOG 1001]

*Favored if all gross disease resected before treatment

- Role of RT is to allow minimization of systemic therapy
- Abbreviated RCHOP with RT is equivalent to full course RCHOP, and in older patients, may be better tolerated
- In low volume, very favorable patients, chemo alone may be adequate after a metabolic CR

Case

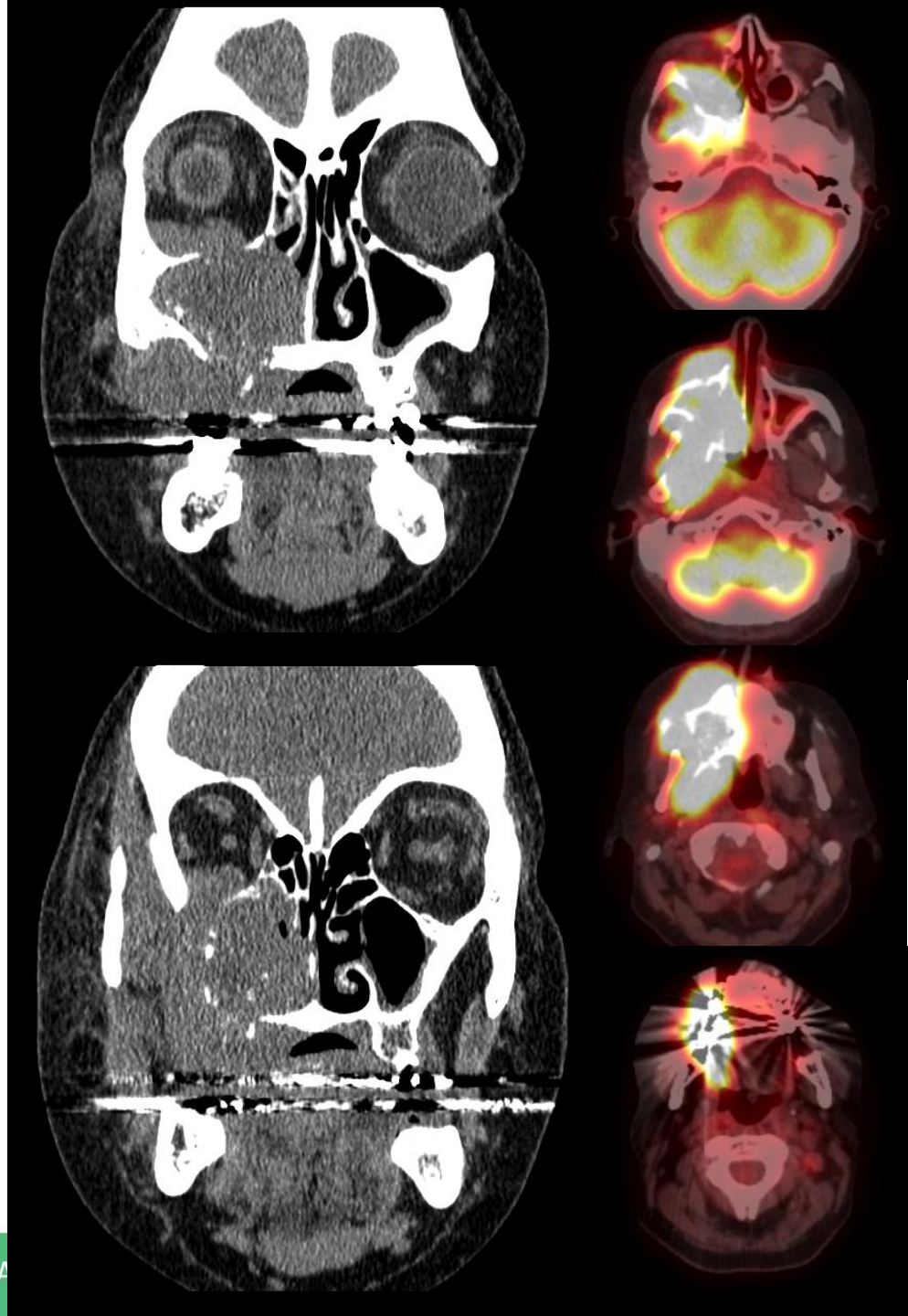
51F with prolonged healing after dental work

- CT: 8.3x6 cm tumor of R masticator space, maxillary sinus, nasal cavity
- Biopsy DLBCL, GCB-subtype, FISH negative for *MYC* re-arrangement
- PET/CT: additional involvement of neck, mediastinum, bowel

Stage IV DLBCL with bulky involvement

Treated with RCHOPx6 → D4 (max sinus)

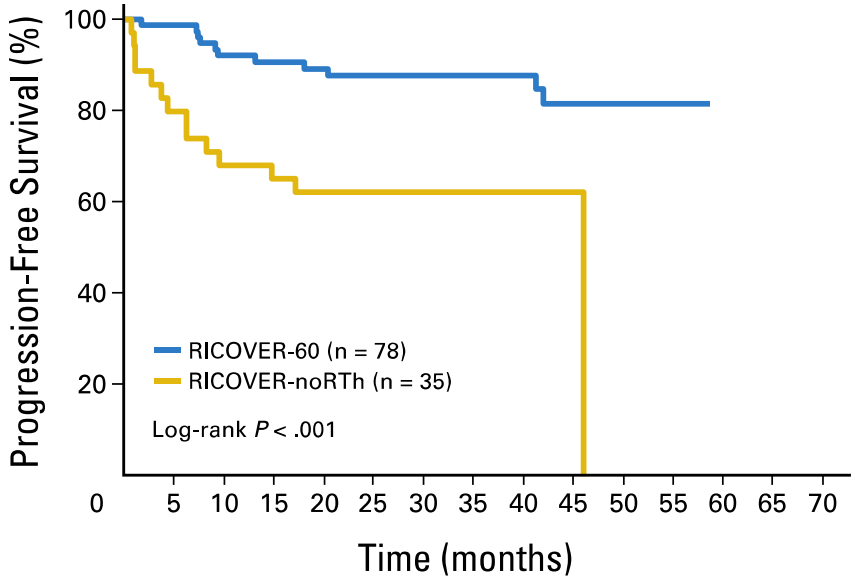
Received ISRT (36 Gy) to initial bulk

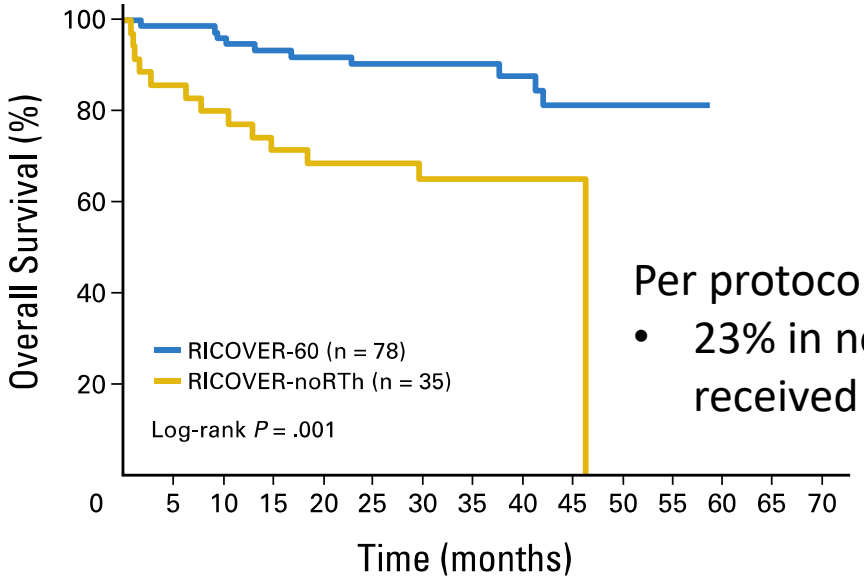


Role of RT for bulky DLBCL

>60 yo patients

Prospective, non-randomized sequential arms from RICOVER-60



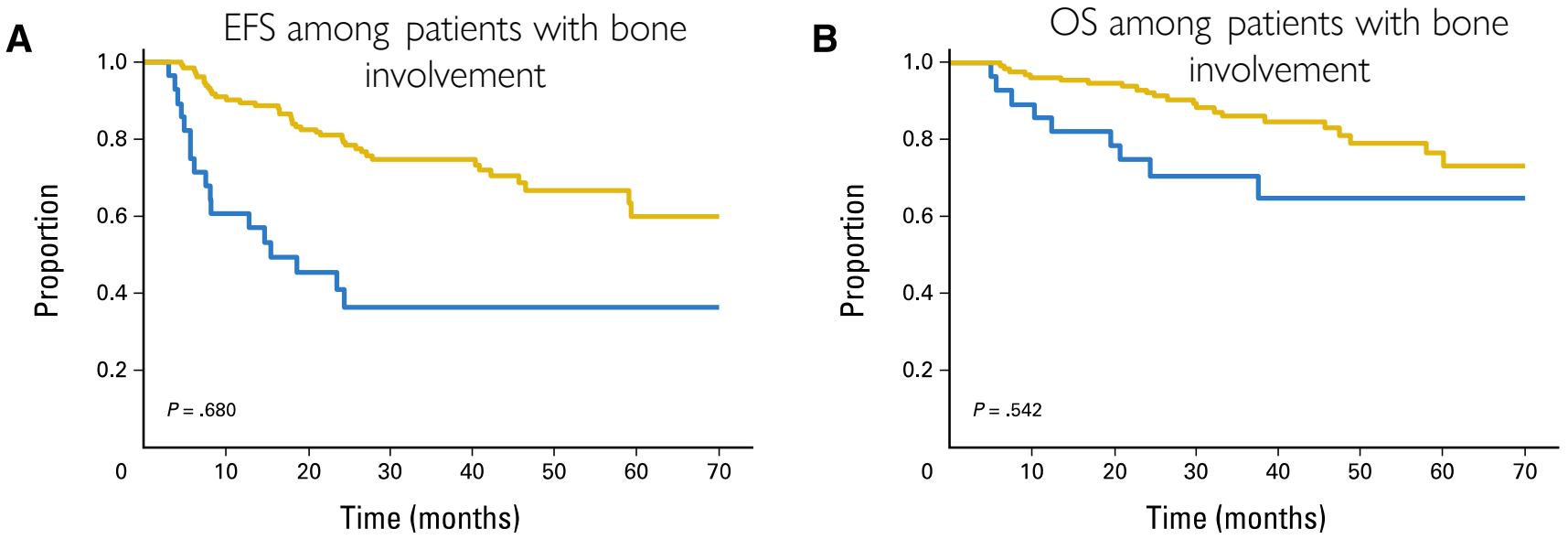


Per protocol analyses
- 23% in no-RT arm received RT

- RICOVER-60 arm: RCHOPx6 + Rx2 → IFRT (36 Gy) to sites of initial bulk (>=7.5 cm)
- *RT for bulk associated with improved PFS, OS*
- Ongoing, prospective studies: OPTIMAL>60 (>60 yo, PET-directed), UNFOLDER (<60 yo)

Held JCO 2014

Role of RT for skeletal involvement



Re-analysis of 9 DSHNHL trials

- 292 (7.6%) with bone involvement
- RT for bone involvement recommended in trials, but not mandated
- Improved EFS with RT: 3-yr 75% vs 36% (p<.001)

Held JCO 2013

My clinical practice for DLBCL with risk factors

RT offered for

- Bulk (>=7.5 cm)
- Skeletal involvement
- Metabolic partial response

Dose

- CR: 30 Gy
- PR: 36-50 Gy

- Role of RT is to supplement full-course chemotherapy (RCHOPx6) given presence of adverse risk factor
- No randomized, prospective data, though studies ongoing for bulk

Relapsed/refractory DLBCL

Indications for RT

Curative intent

- Localized disease
- Incomplete response to salvage chemotherapy or ASCT
- Critical sites where LC is important
- Bulky disease
- Skeletal involvement

Palliative intent

- Symptoms
- Bridging to systemic therapy

Dose

Cytoreduction prior to ASCT

- 40-50 Gy (higher range if chemo-refractory)
- Hyperfractionated (if rapidly growing): 1.3-1.5 Gy BID to 35-40 Gy

Consolidation after ASCT

- CR (D1-3): 30-36 Gy
- Residual FDG-avidity: 40-45 Gy

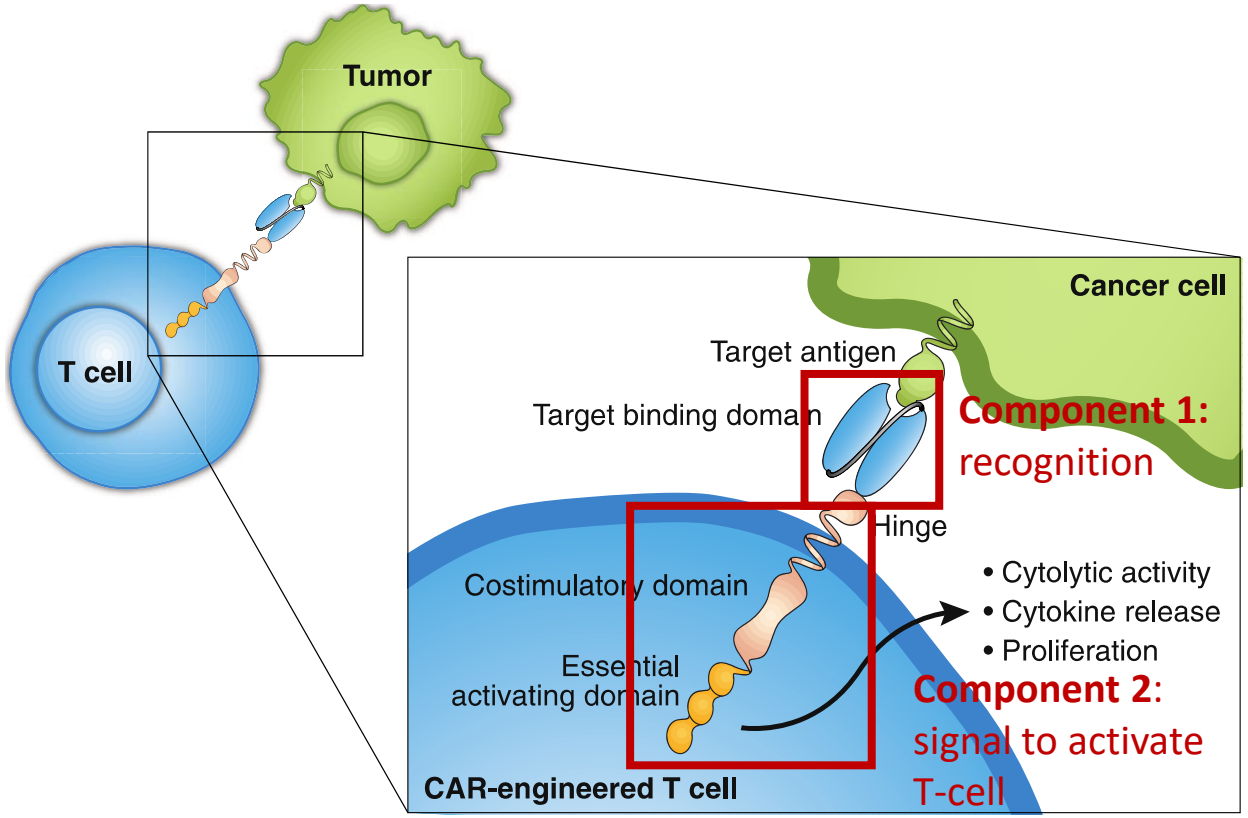
Not transplant candidate

- Limited life expectancy: 8-39 Gy
- Curative-intent: 45-55 Gy

Ng IJROBP 2018

Novel therapies for DLBCL

Chimeric antigen receptor (CAR) T-cells

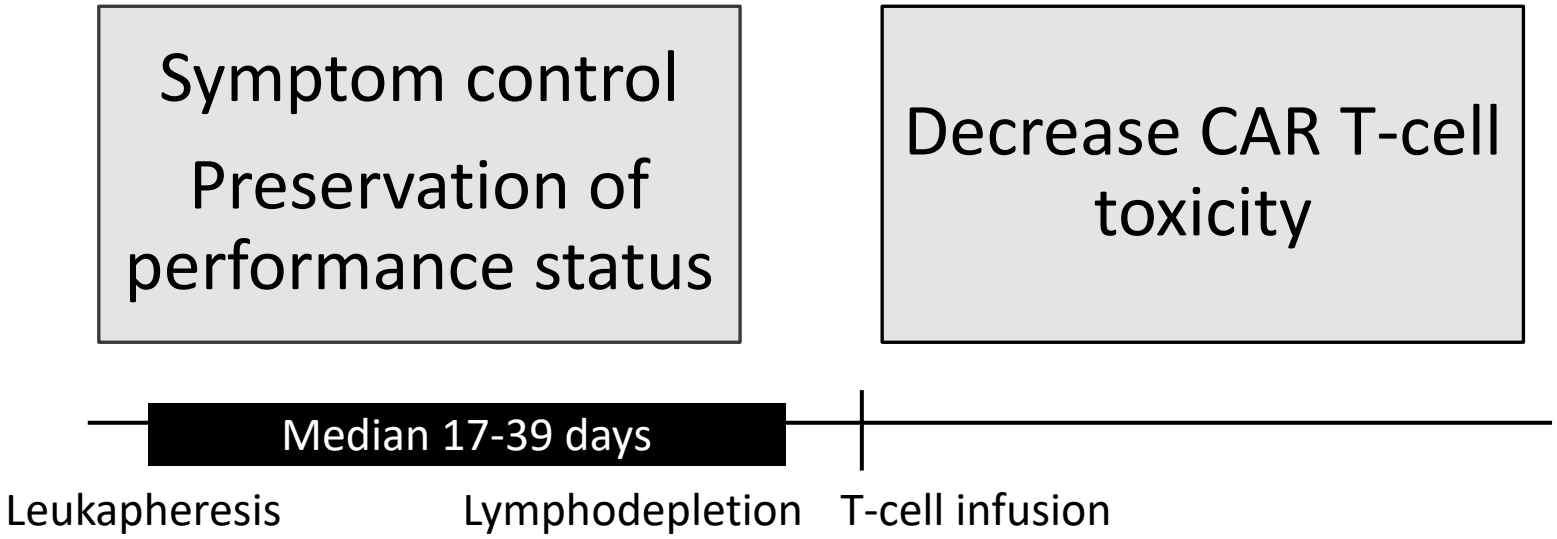


Removing barriers for the immune system to eradicate cancer cells

- Autologous lymphocytes, modified, and reinfused
- Modification of membrane receptor targeting specific antigen
- FDA-approved for r/r NHL
  - Tisagenlecleucel (2017)
  - Axicabtagene ciloleucel (2017)
  - Lisocabtagene maraleucel (2021)

Roberts Leukemia Lymphoma 2017

How RT can interface with CAR T-cells



- Optimal "bridging RT" dose/fx and target unknown
  - Cytoreduce symptomatic and/or bulky disease
  - Limited by time to infusion
- If possible, hold off on starting RT until after leukapheresis
- RT does not appear to decrease CAR-T efficacy

Adapted from Tseng ASTRO 2019

Role of RT for follicular lymphoma (FL)

Localized (15-30%)

Stage I, contiguous stage II

- Curable (DFS_{10} 50-70%)
- ISRT alone (24 Gy, can boost to 30 Gy if bulky)
- Chemoimmunotherapy + ISRT [TROG 99.03]

Non-contiguous stage II

- Chemoimmunotherapy +/- ISRT
- Observation

Advanced stage (70-85%), **relapsed/refractory**

- Considered incurable
- Systemic therapy (GELF criteria)
  - Symptoms
  - Threatened end-organ function, including cytopenias
  - Bulky disease (>=7 cm)
  - Large disease burden
- Observation
- If symptoms, palliative ISRT (2 Gy x 2)

Workup for localized follicular lymphoma

PET/CT

- >95% are FDG-avid
- Addition of PET alters management in ~45% of patients (*Peter MacCallum Cancer Center*)
  - 30% upstaged to stage III/IV
  - 15% treated with larger fields, including stage I→II

Bone marrow biopsy

Pathology

- 90% with t(14;18)
- Grade influences clinical aggressiveness and treatment

Grade 1-2	<=15 centroblasts/HPF	
Grade 3	>15 centroblasts/HPF	
Grade 3A	Centrocytes still present	Treat as G1-2 or G3b
Grade 3B	Sheets of centroblasts	Treat as DLBCL

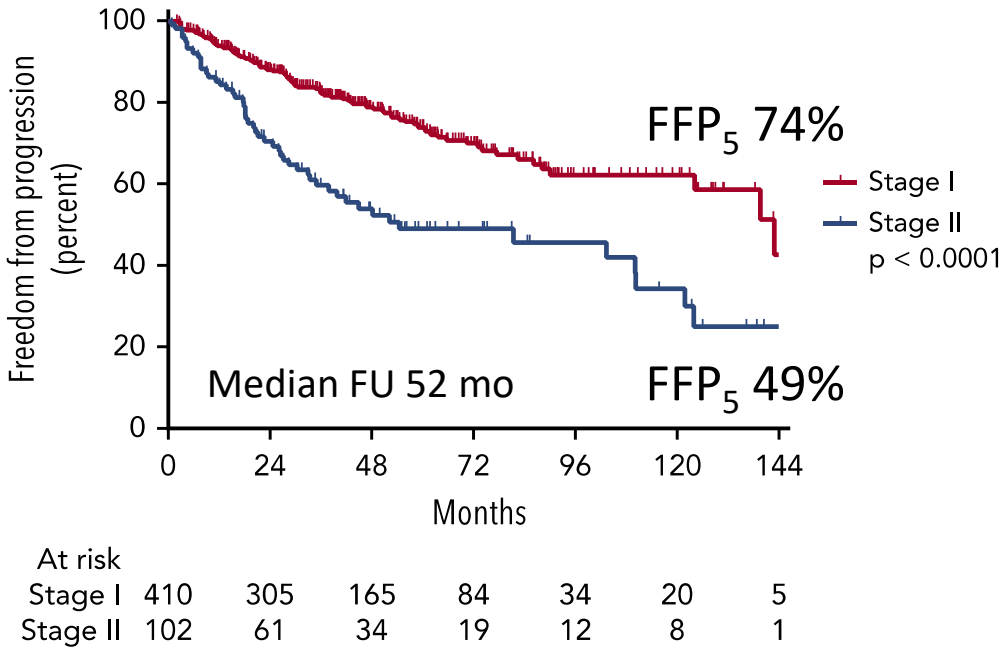
Wirth IJROBP 2008

Outcomes with RT alone for localized FL

Modern staging with PET/CT

ILROG multi-institutional retrospective study

- N=512 patients staged with PET/CT, 94% BM bx
- RT alone for stage I/II FL (G1-3a)
  - Median 30 Gy (IFRT, ISRT, INRT)
  - 80% stage I
- LC 97.6%: 1.6% in-field, 0.8% marginal relapse
  - Patterns of failure is predominantly distant (92%)
- Outcomes in PET-staged patients better than historical controls (40-50%)
  - Impact of modern staging
  - Previously underestimated RT's curative potential for truly localized disease



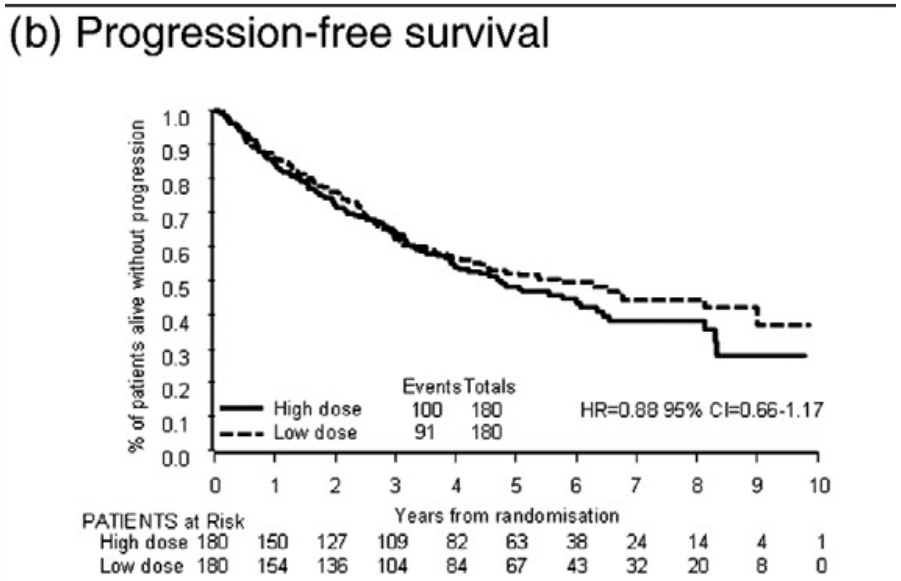
Brady Blood 2018

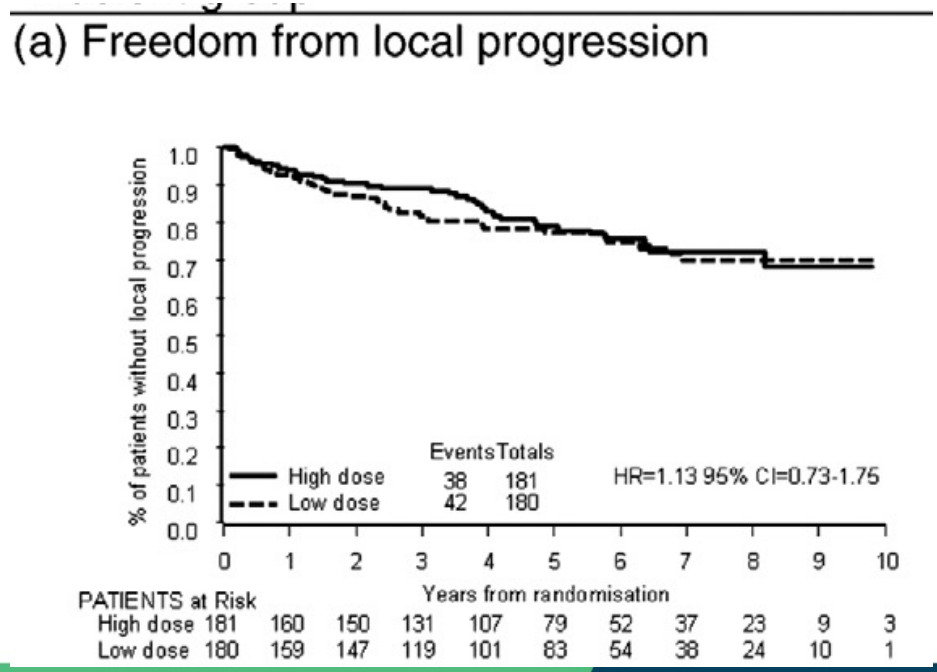
Radiation dose for FL

24 Gy is standard of care

BNLI randomized study

- N=361 indolent NHL (FL 64%, MZL 19%)
- Randomized to
  1) 40-45 Gy/20-23, versus
  2) 24 Gy/12
- 24 Gy is non-inferior to 40-45 Gy with respect to ORR: 92% vs 93%
- No difference in FFLP or PFS



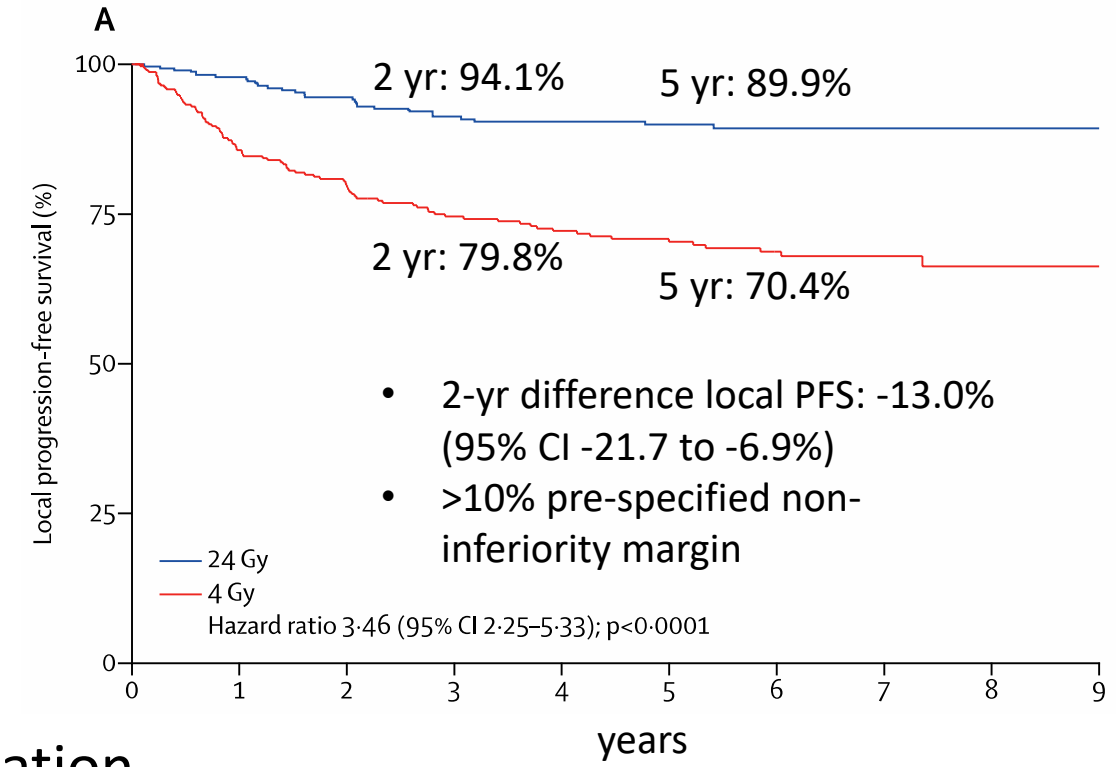


Radiation dose for FL

24 Gy is standard of care

FORT non-inferiority randomized trial

- Median FU 73.8 mo
- 24 Gy is more effective than 4 Gy
  - Time to local progression (primary)
  - ORR
- 4 Gy (2 Gy x 2) useful alternative for palliation



	24 Gy		4 Gy		p value*
	Complete response (%)	Complete response plus partial response (%)	Complete response (%)	Complete response plus partial response (%)	
All patients	176/260 (68%)	236/260 (91%)	137/281 (49%)	227/281 (81%)	0·0095
Follicular lymphoma	152/226 (67%)	205/226 (91%)	116/243 (48%)	194/243 (80%)	0·0096
Marginal zone lymphoma	24/34 (71%)	31/34 (91%)	21/38 (55%)	33/38 (87%)	0·71

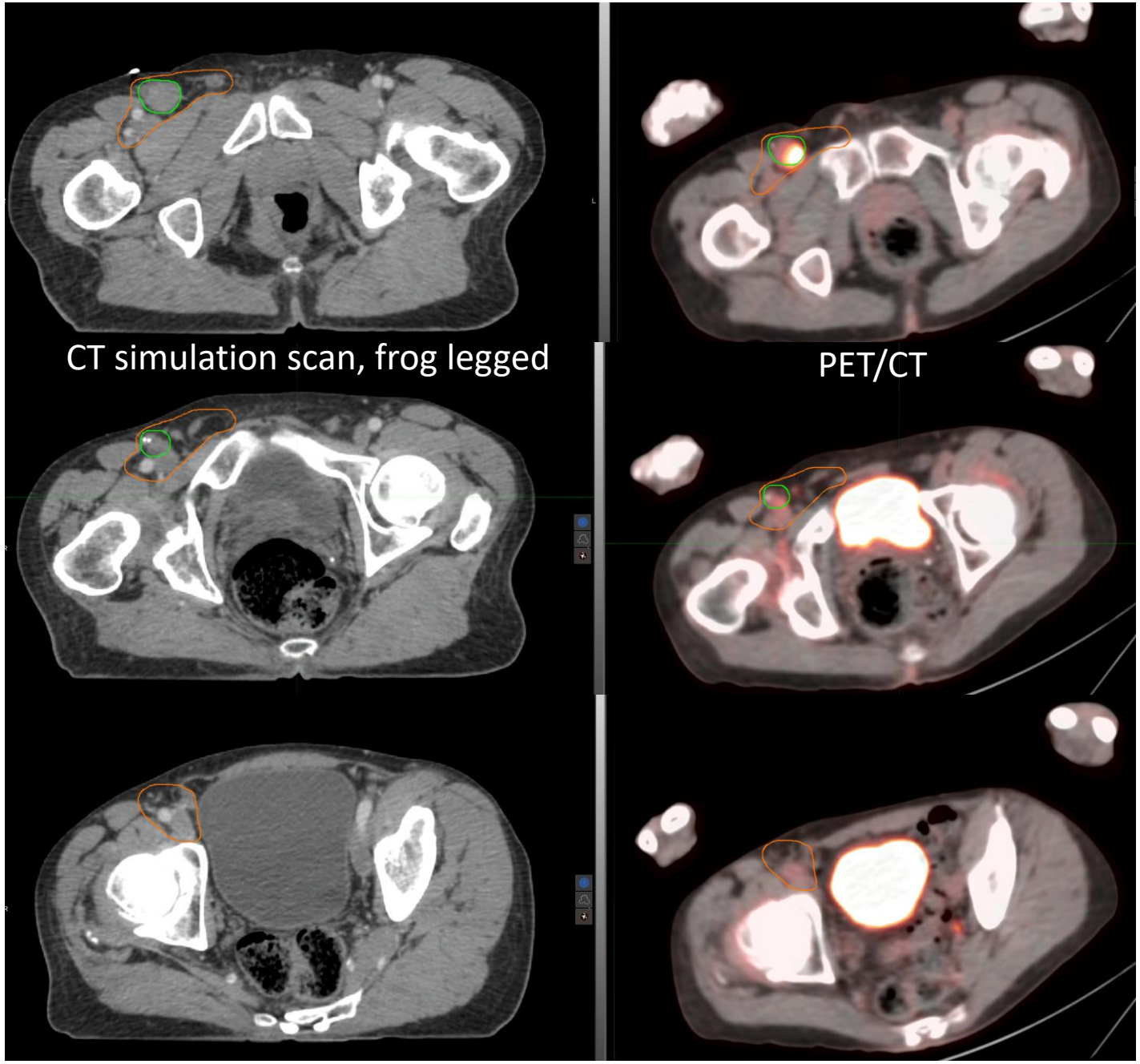
Hoskin Lancet Oncol 2014; Hoskin Lancet 2021

ISRT fields for FL
RT alone

"CTV should incorporate GTV and include as a minimum adjacent lymph nodes in that site and a generous margin dictated by the clinical situation."

70M with stage I G1-2 FL of R groin

- Treated 24 Gy/12
- Achieved complete metabolic response (D2) 3 months post-RT



Illidge IJROBP 2014

Marginal zone lymphoma (MZL) subtypes

Extranodal MZL of mucosa associated lymphoid tissue (MALT lymphoma) (5-10% NHL)

- May comprise ~50% of lymphomas at certain sites:
  - Stomach-65% of MALT
  - Orbit
  - Lung
- Other sites: breast, salivary glands, Waldeyer's ring, thyroid
- 60-70% present with stage I/II

Nodal MZL (1% NHL)

Splenic MZL (<1% NHL)

Gastric MALT

Workup

- Endoscopy with adequate biopsies
- If H. pylori positive, test for t(11;18) by PCR or FISH
  - t(11:18) associated with higher rates of relapse or no response to antibiotics
- Diagnostic CT CAP +/- PET (50% EMZL FDG+)
- Can involve duodenum and/or peri-gastric LN

Treatment for stage I/II

H. pylori-pos

- Antibiotic therapy for H. pylori eradication → 80% with CR of MALT
- Time to CR can be slow
  - 60% CR in 3 mo
  - 25% CR in 12 mo
  - 15% CR >12 mo
- ISRT as salvage treatment

H. pylori-neg or H. pylori-pos with t(11;18)

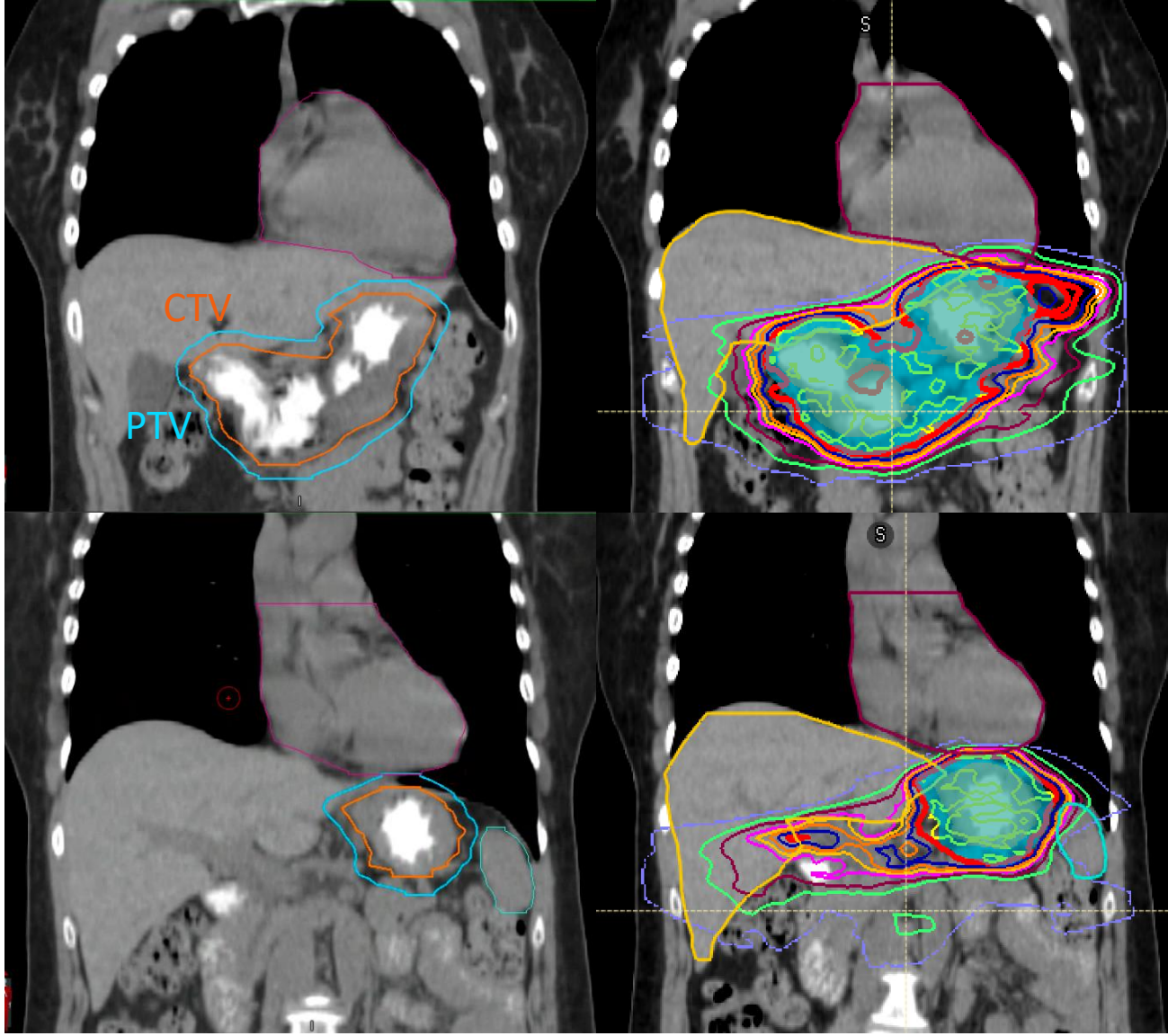
- ISRT (CR 80-100%, FFP 90-100%)
- Rituximab (if RT contraindicated)

Wundisch JCO 2005; Schmelz J Gastroenterol 2019

Case

57F presented with hematemesis, epigastric pain, and early satiety.

- Stage I gastric MALT, H. pylori negative
- Simulation
  - NPO 3 hours prior
  - 3 DIBH scans with small volume barium (30 cc)
  - Arms up
- CTV: entire stomach including gastro-duodenal junction, contour across all 3 scans to create “iCTV”



VMAT (2 coplanar arcs), 25.2 Gy/14 fx

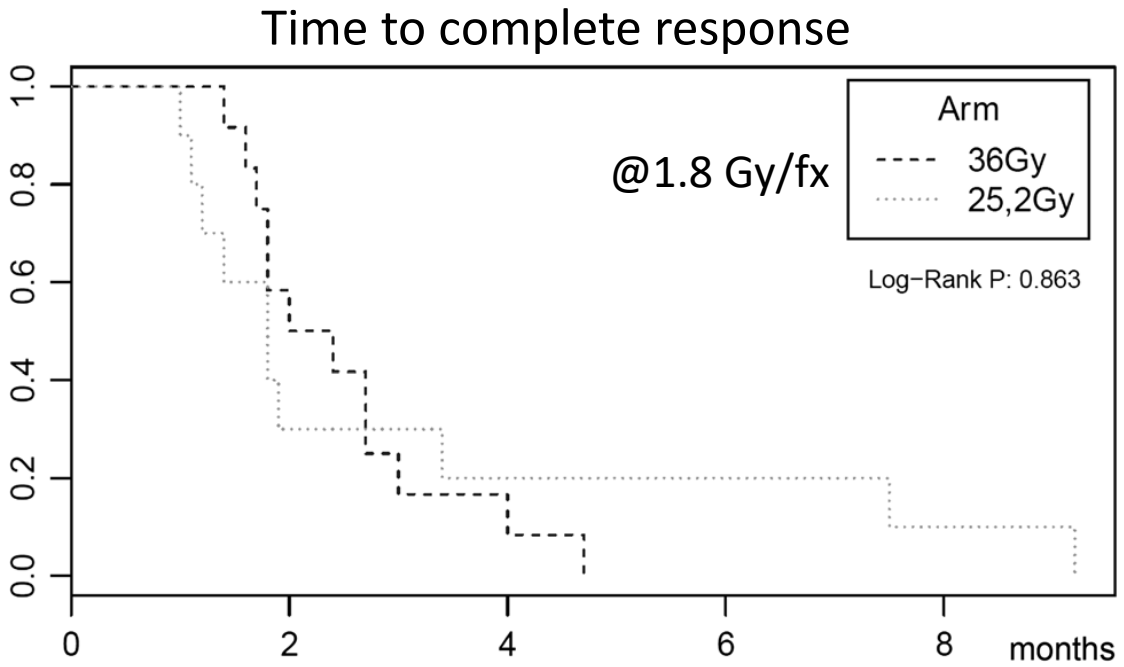
Daily ondansetron pre-tx with PPI

Gastric MALT

Techniques

- 3D-CRT, IMRT/VMAT
- DIBH
  - Lower mean heart, lung, and liver dose compared to free breathing
- Consider daily CBCT to assess reproducibility of stomach

Dose: 24-30 Gy in 1.5-2 Gy/fx



HELYX II phase 2 trial (n=29)

- No difference in CR at 12 months (100%) or risk of recurrence (median FU 79 mo)

Specht IJROBP 2014; Schemlz J Gastroenterol 2019; Choi Radiat Oncol 2019

MALT of non-gastric sites

E.g. Ocular adnexa, salivary glands, lung, skin

- Definitive treatment for early-stage with RT alone
- ISRT: 24 Gy/12 fractions
- Can consider 4 Gy/1-2 fractions in palliative setting

Guidelines

Modern Radiation Therapy for Extranodal Lymphomas: Field and Dose Guidelines From the International Lymphoma Radiation Oncology Group

Joachim Yahalom, MD,* Tim Illidge, MD, PhD,† Lena Specht, MD, PhD,‡ Richard T. Hoppe, MD,§ Ye-Xiong Li, MD,|| Richard Tsang, MD,¶ and Andrew Wirth, MD#, on behalf of the International Lymphoma Radiation Oncology Group

Yahalom IJROBP 2015

Changes in management in era of COVID-19

ILROG emergency guidelines for radiation therapy of hematological malignancies during the COVID-19 pandemic

Joachim Yahalom,[1] Bouthaina Shbib Dabaja,[2] Umberto Ricardi,[3] Andrea Ng,[4] N. George Mikhaeel,[5] Ivan R. Vogelius,[6] Tim Illidge,[7] Shunan Qi,[8] Andrew Wirth,[9] and Lena Specht,[6] on behalf of the International Lymphoma Radiation Oncology Group (ILROG)

care delivery reviews

Considerations for Managing Patients With Hematologic Malignancy During the COVID-19 Pandemic: The Seattle Strategy

Mary-Elizabeth M. Percival, MS, MD[1,2,3]; Ryan C. Lynch, MD[1,3,4]; Anna B. Halpern, MD[1,2,3]; Mazyar Shadman, MPH, MD[1,3,4]; Ryan D. Cassaday, MD[1,2,3]; Chaitra Ujjani, MD[1,3,4]; Andrei Shustov, MD[1,2,4]; Yolanda D. Tseng, MD[1,3,5]; Catherine Liu, MD[1,3,6,7]; Steven Pergam, MD[1,3,6,7]; Edward N. Libby, MD[1,3,4]; Bart L. Scott, MD[1,3,4]; Stephen D. Smith, MD[1,3,4]; Damian J. Green, MD[1,3,4]; Ajay K. Gopal, MD[1,3,4]; and Andrew J. Cowan, MD[1,3,4]

- In vaccine era, no major changes to my clinical practice
  - May delay RT start for patients with localized, low-grade NHL or NLPHL per patient comfort
- Increased use of 2 Gy x 2 for low-grade NHL to defer systemic therapy and risk of immune suppression prior to vaccine

Yahalom Blood 2020; Percival JOP 2020

Summary and key points

Modern radiation therapy for lymphoma

Modern RT aims to maintain excellent disease control while minimizing late toxicity

- Smaller fields and 3D treatment planning (ISRT, INRT)
- Lower doses (20-30 Gy HL, 30 Gy DLBCL, 24 Gy or 4 Gy FL/MZL)

Many de-escalation protocols, including those for RT omission, use a PET-adapted approach

- RT cannot be safely omitted for HL even with a CMR to ABVD
- Ongoing studies for DLBCL

Radiation remains the cornerstone of treatment for localized, indolent NHL

- Improved diagnostic imaging and workup better select those who benefit from local therapy

Resources: ILROG guidelines

Hodgkin lymphoma	Modern RT for HL (ISRT)	*Specht IJROBP 2014* *Wirth IJROBP 2020*
	RT for r/r HL	*Constine IJROBP 2018*
Non-Hodgkin lymphoma	Modern RT for nodal NHL	*Illidge IJROBP 2014*
	Modern RT for extra-nodal NHL	*Yahalom IJROBP 2015*
	RT for r/r DLBCL	*Ng IJROBP 2018*
Other hematologic	Total body irradiation	*Wong IJROBP 2018*
	RT for CNS leukemia	*Pinnix IJROBP 2018*
	RT for lymphoblastic lymphoma	*Dabaja IJROBP 2018*
	Modern RT for primary cutaneous lymphoma	*Specht IJROBP 2015*
	RT for solitary plasmacytoma and multiple myeloma	*Tsang IJROBP 2018*
Proton therapy	Proton therapy for mediastinal lymphoma	*Dabaja Blood 2018*
Mini atlas	ISRT guidelines	*Dabaja IJROBP 2020*
Other	RT for lymphomas during COVID-19	*Yahalom Blood 2020*
	Optimal use of imaging for RT	*Mikhaeel IJROBP 2019*