Illustrative Cases of Early-Stage Hodgkin Lymphoma

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Potential Conflicts of Interest

- Unpaid consultant: Bristol Meyers Squibb

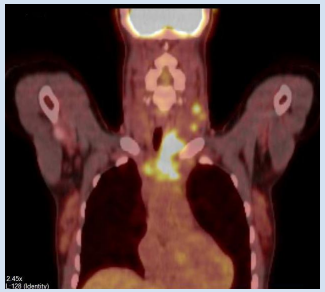
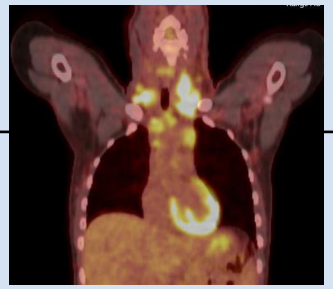
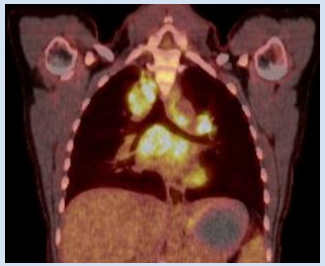
Illustrative Cases of Localized cHL

- Early-stage favorable (GHSG)
- Early-stage favorable (EORTC)
- Early-stage unfavorable
- Localized relapse

1L Early-Stage Hodgkin Lymphoma

Combined Modality Therapy or Chemotherapy Alone?

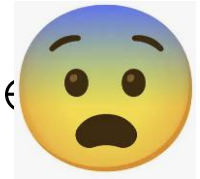
CMT vs. Chemo Alone

		CMT	RT Omission
Early Favorable GHSG (1-2 sites) PET2 negative	 	ABVD x 2 + 20Gy	ABVD x 3-4 if <5cm and PET2 1-2
Early Favorable EORTC (3 sites) PET2 negative		ABVD x 3 + 30Gy	ABVD x 4 if <5cm and PET2 1-2
Early Unfavorable PET2		ABVD x 4 + 30Gy	• A(B)VD x 6 • BEACOPP-

Adapted from slide courtesy of Dr. Da

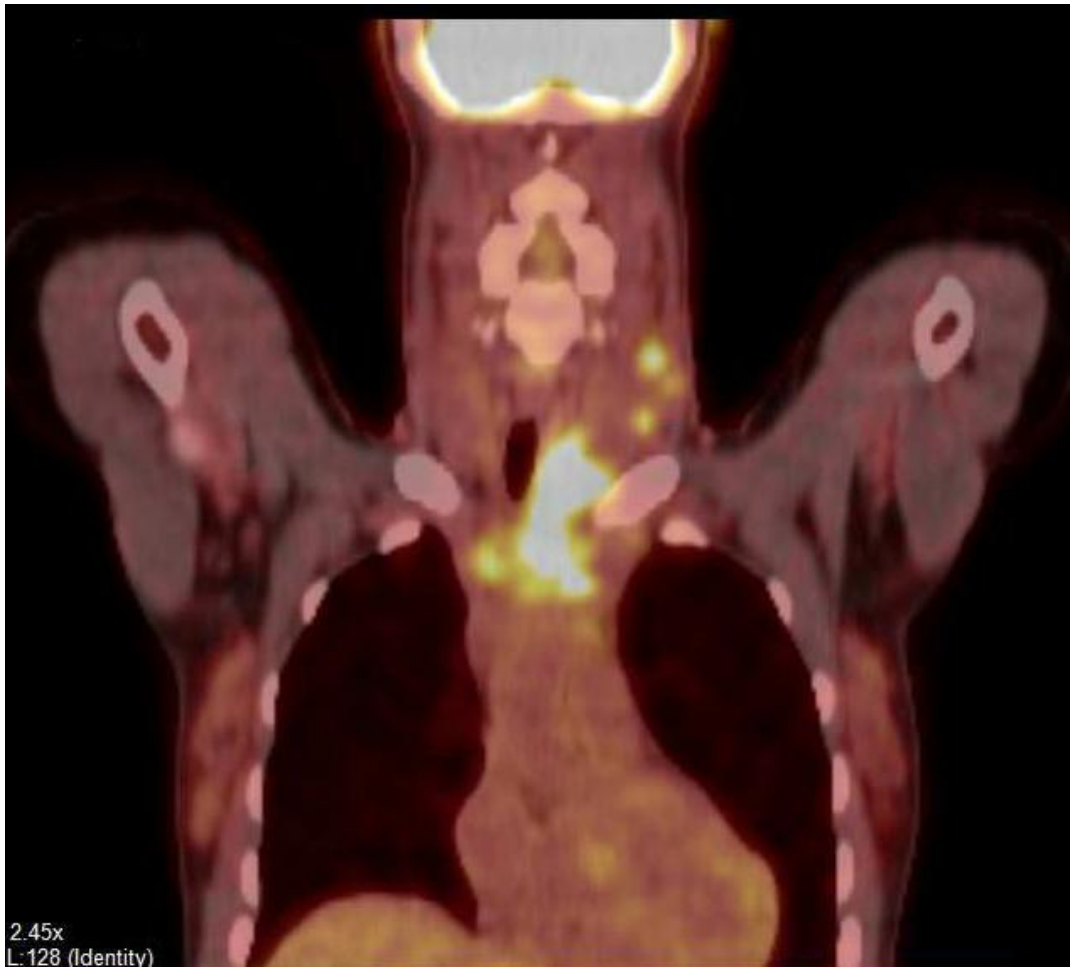
CMT vs. Chemo Alone

- How to decide?
  - Patient characteristics
    - Age
    - Sex

    → Young female 
  - Disease characteristics
    - Bulk
    - Distribution with respect to organs-at-risk
    - Chemotherapy response (interim and end-of-treatment)

Case 1

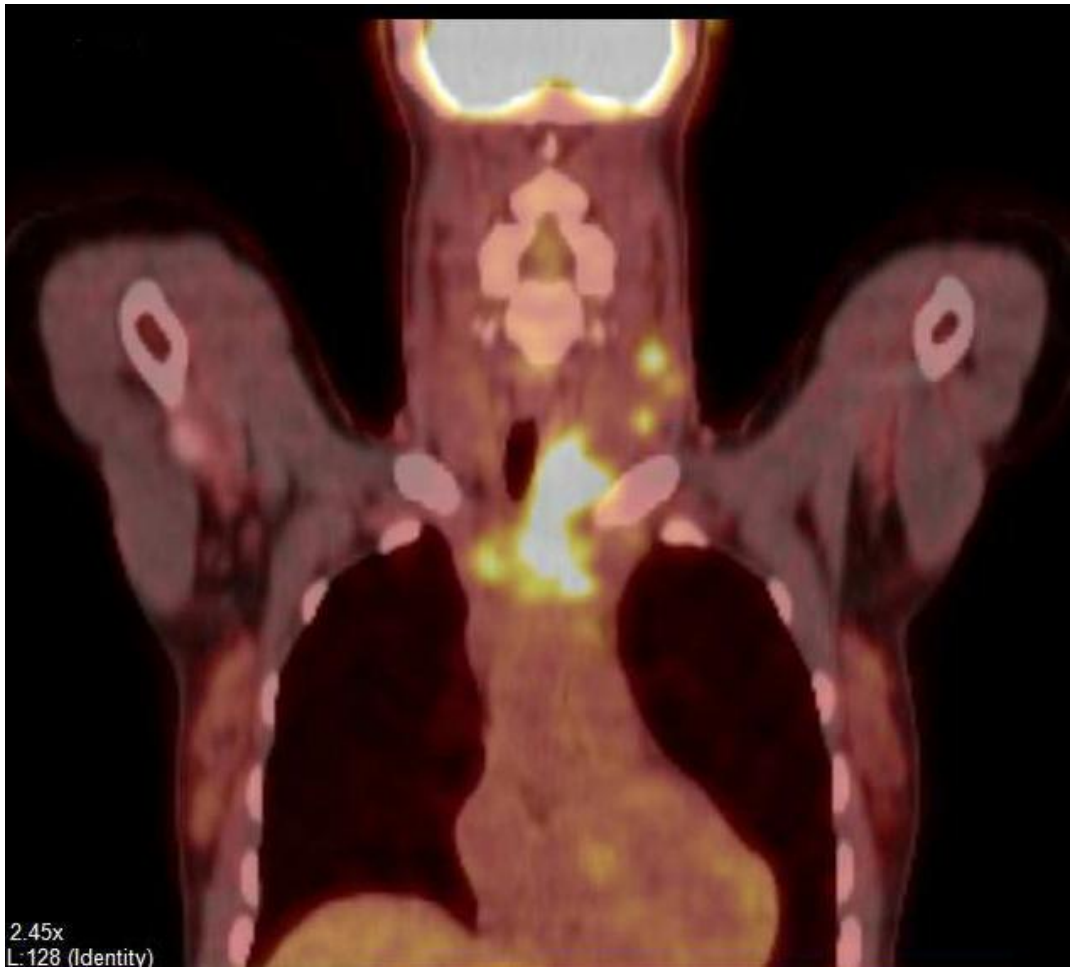
- 25 yo female
- Left neck LAD
- Biopsy: NS cHL
- PET/CT: involvement of left neck and mediastinum, no bulk
- ESR: 10mm/hr



Slide courtesy of Dr. Davic

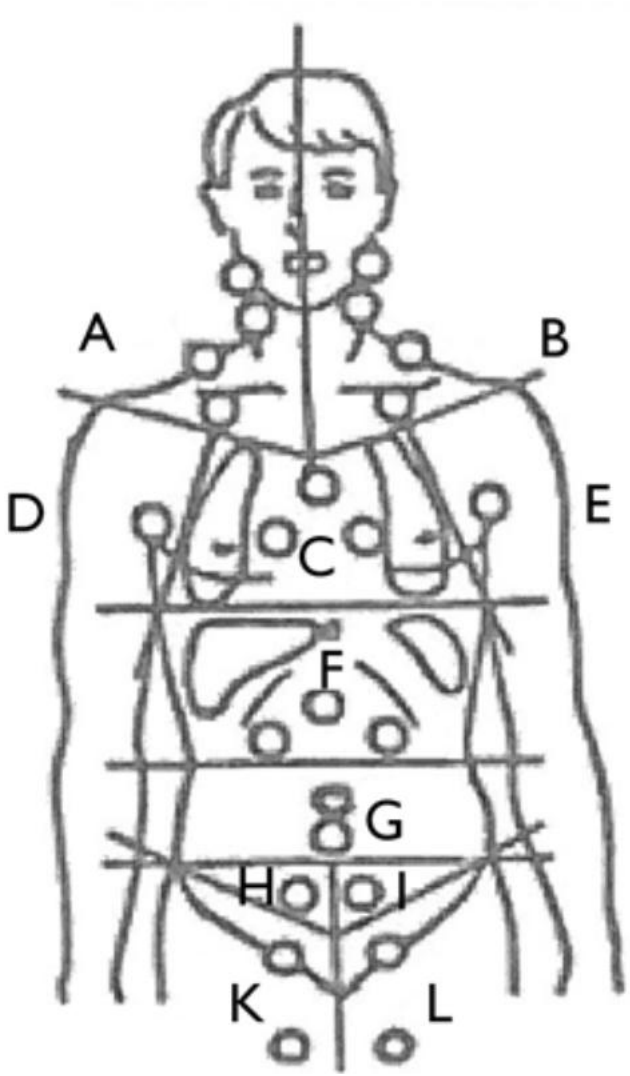
Management Recommendation

1. ABVD x 2 → 20 Gy ISRT
2. ABVD x 3
3. ABVD x 3 → 30 Gy ISRT
4. ABVD x 4



Early-Stage Favorable HL (GHSG)

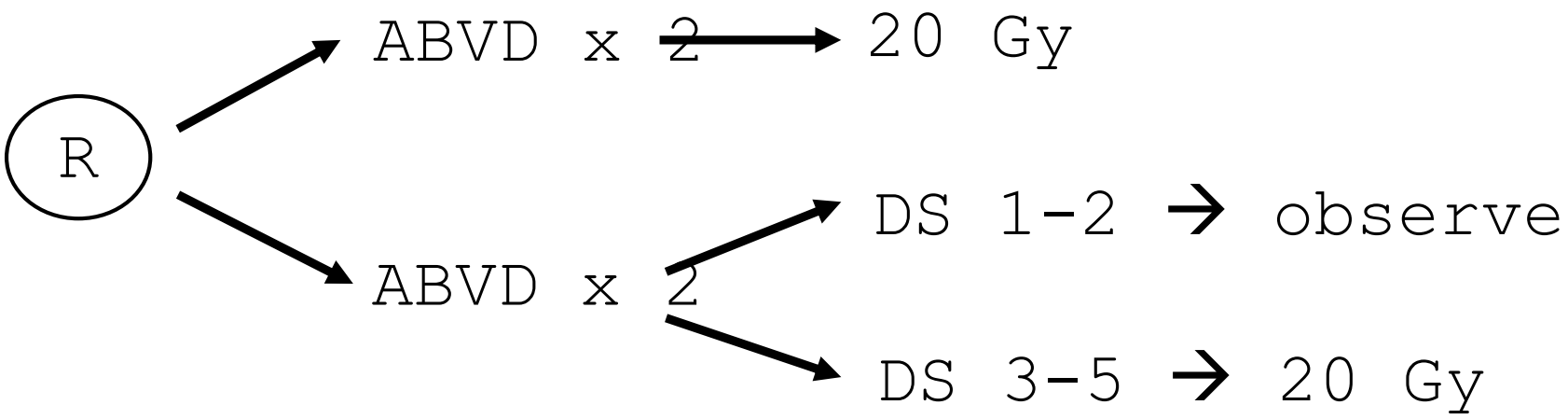
- ≤2 sites of involvement
- No large mediastinal adenopathy
  - <1/3 max intrathoracic diameter on CXR
- No extranodal involvement
- Favorable ESR/B-symptom profile
  - <50, without "B" symptoms
  - <30, with "B" symptoms



Slide courtesy of Dr. Davic

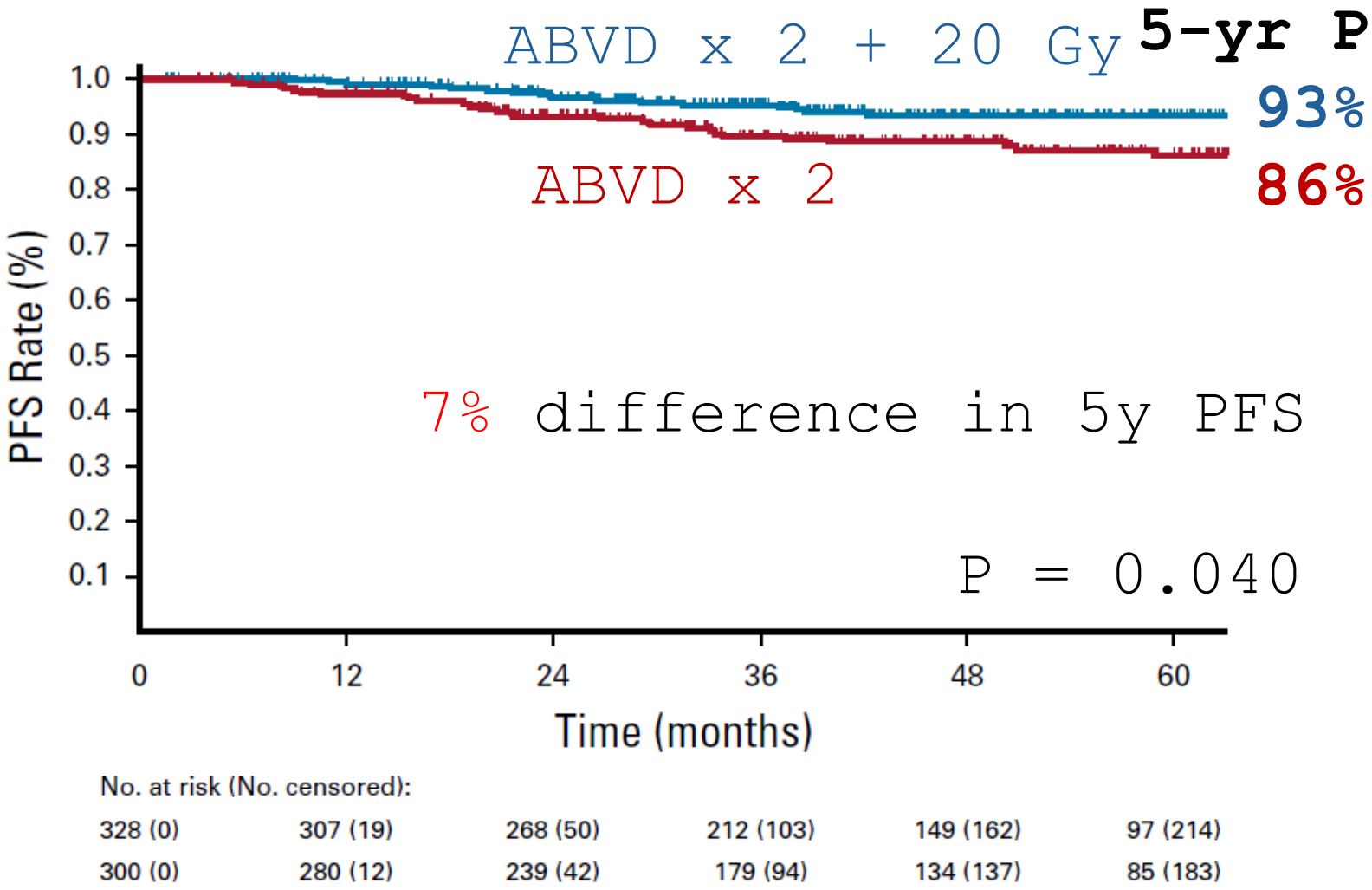
GHSG HD16

- 1150 patients, 18-75 y/o, stage I-II HL w/out GHSG risk factors



Fuchs et al. JCO

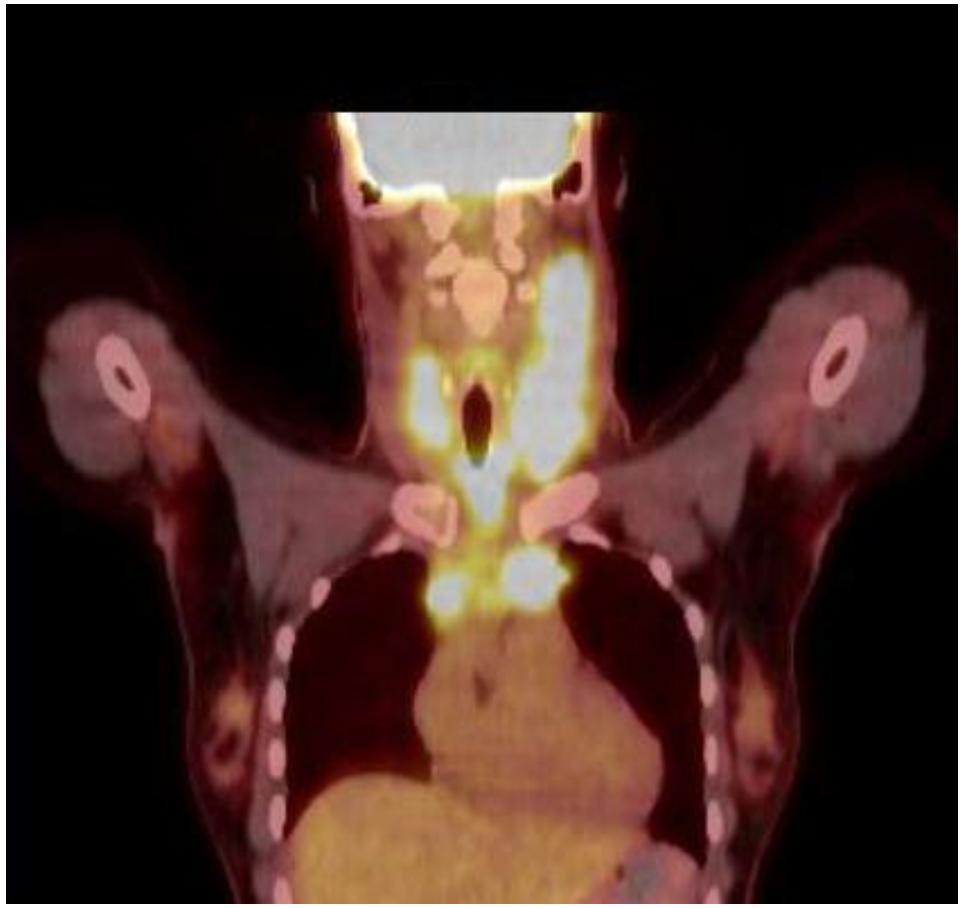
GHSG HD16: Negative PET2 (DS1-2)



Fuchs et al. JCO

Case 2

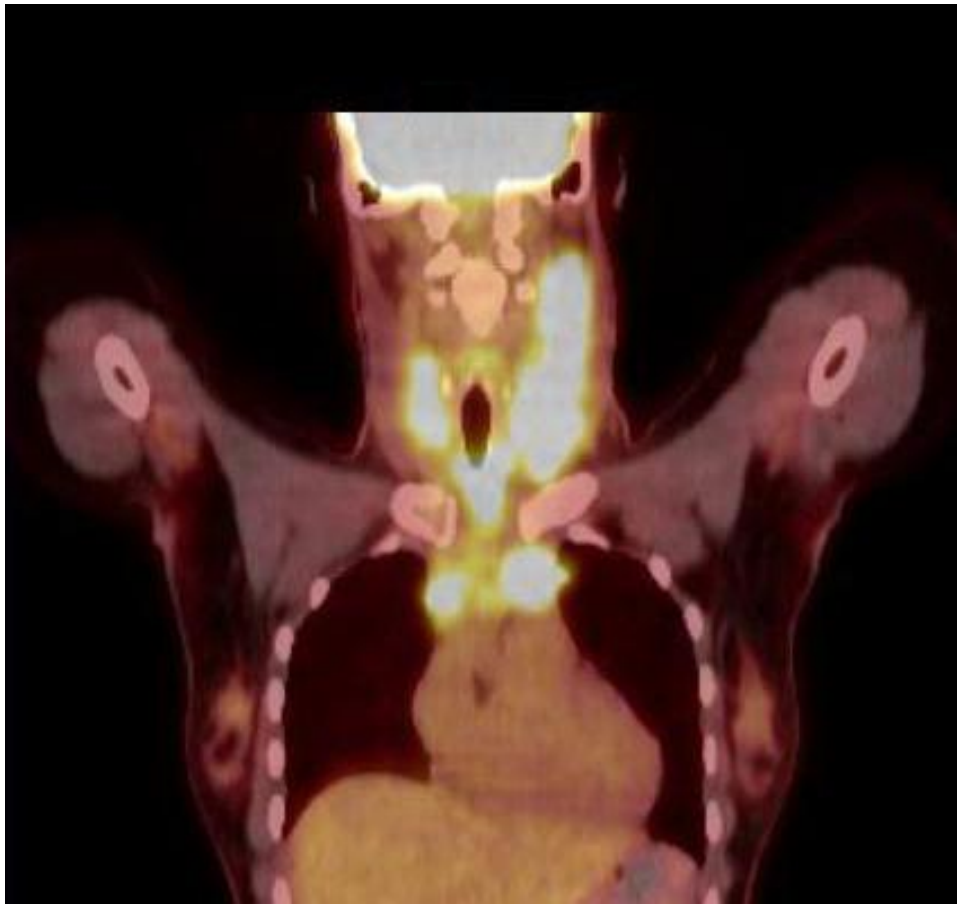
- 25 yo female
- Left neck LAD
- Biopsy: NS cHL
- PET/CT: involvement of left neck, right neck, and mediastinum, no bulk
- ESR: 10mm/hr



Slide courtesy of Dr. Davic

Management Recommendation

1. ABVD x 2 → 20 Gy ISRT
2. ABVD x 3
3. ABVD x 3 → 30 Gy ISRT
4. ABVD x 4
5. ABVD x 4 → 30 Gy ISRT
6. escBEACOPP x 2 → ABVD x 2



Risk Stratification

Stage	Bulky Mediastinal Disease[m] or >10 cm Adenopathy	# of Nodal Regions	ESR ≥50 mm/hr	E-lesion(s)	Type
IA/IIA	No	≤2	No	No	Favorable Disease by GHSG Criteria
	No	≤3	No	Yes/No	Favorable Disease by EORTC Criteria
	Yes	Any	Yes/No	Yes/No	Unfavorable Disease
IB/IIB	Yes/No	Any	Yes/No	Yes/No	Unfavorable Disease
III–IV	Yes/No	Any	N/A	Yes/No	Advanced Disease

NCCN Guidelines

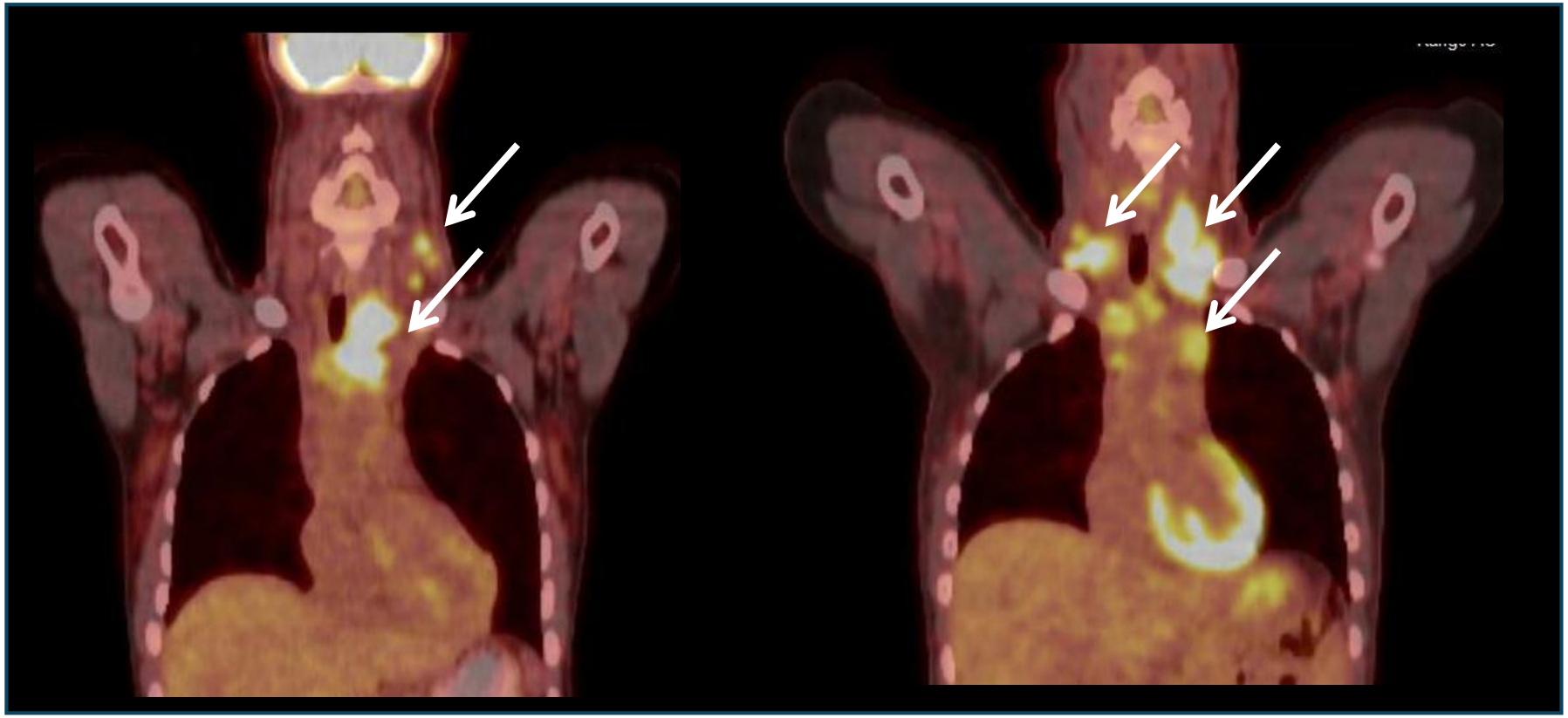
ABVD x 2 + 20 Gy Eligibility

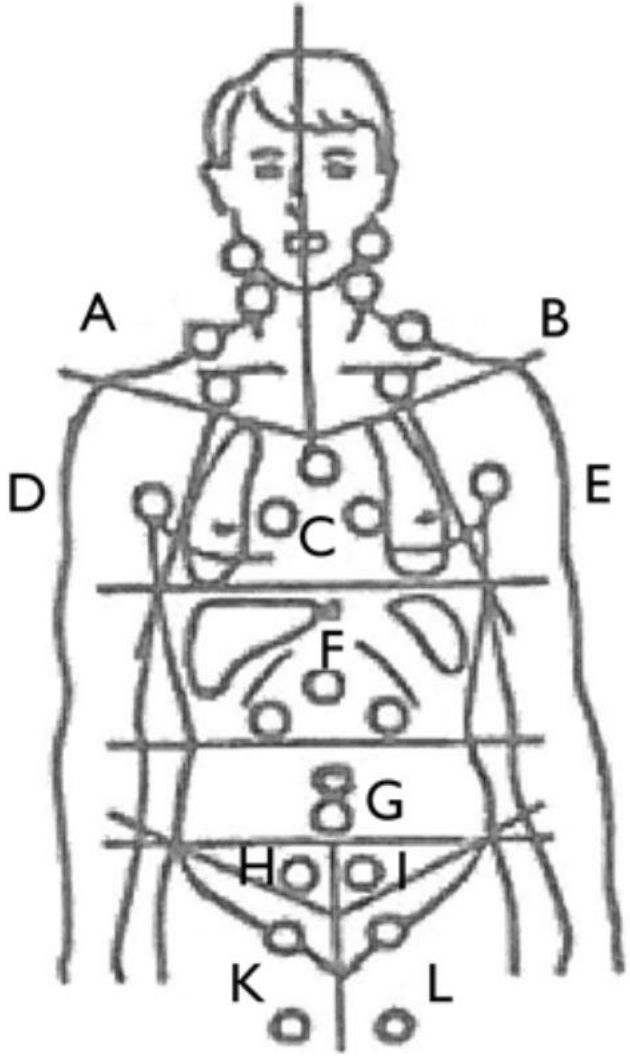
Case 1:

2 sites = eligible

Case 2:

3 sites = ineligible

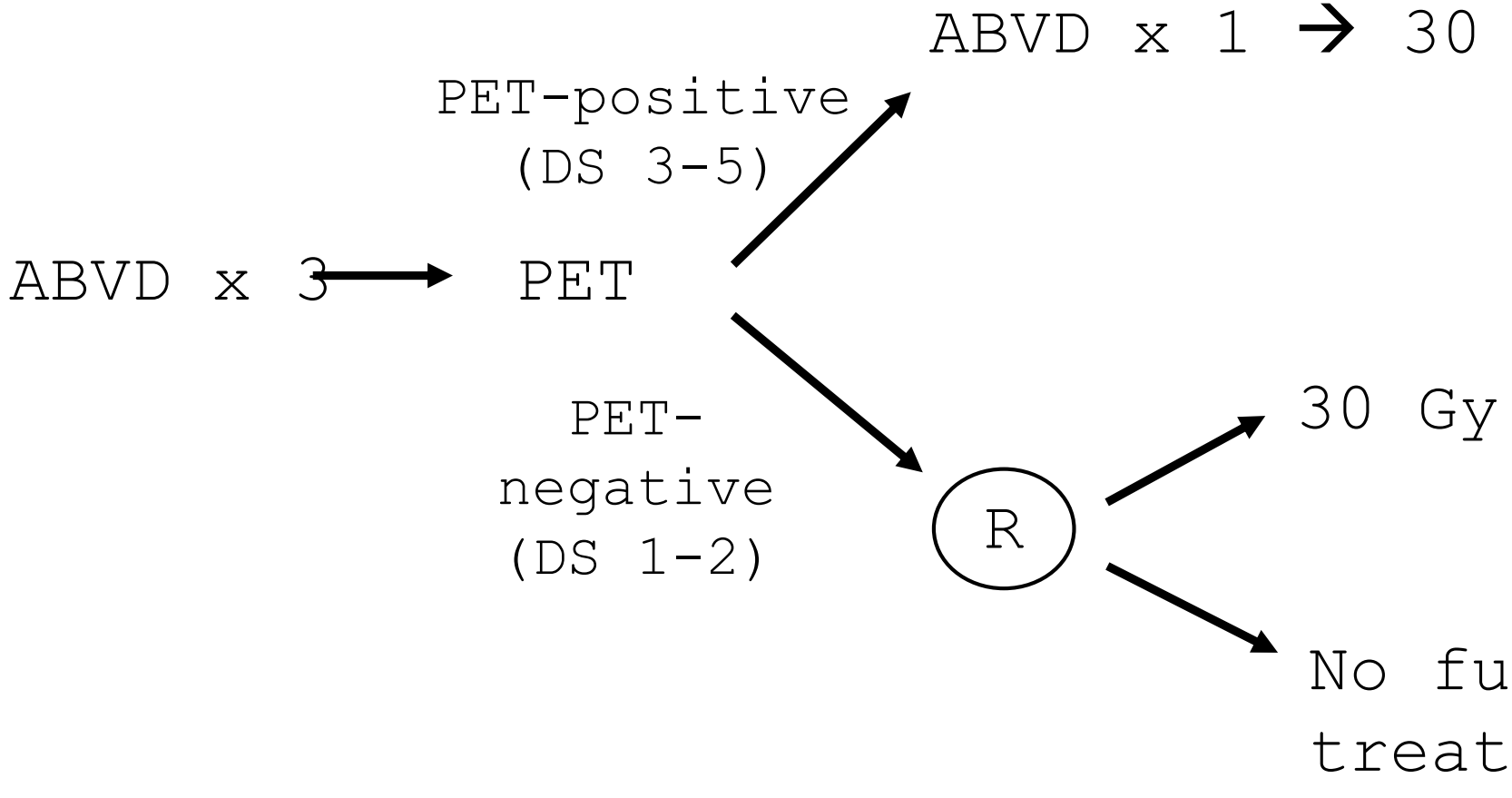




Slide courtesy of Dr. Davic

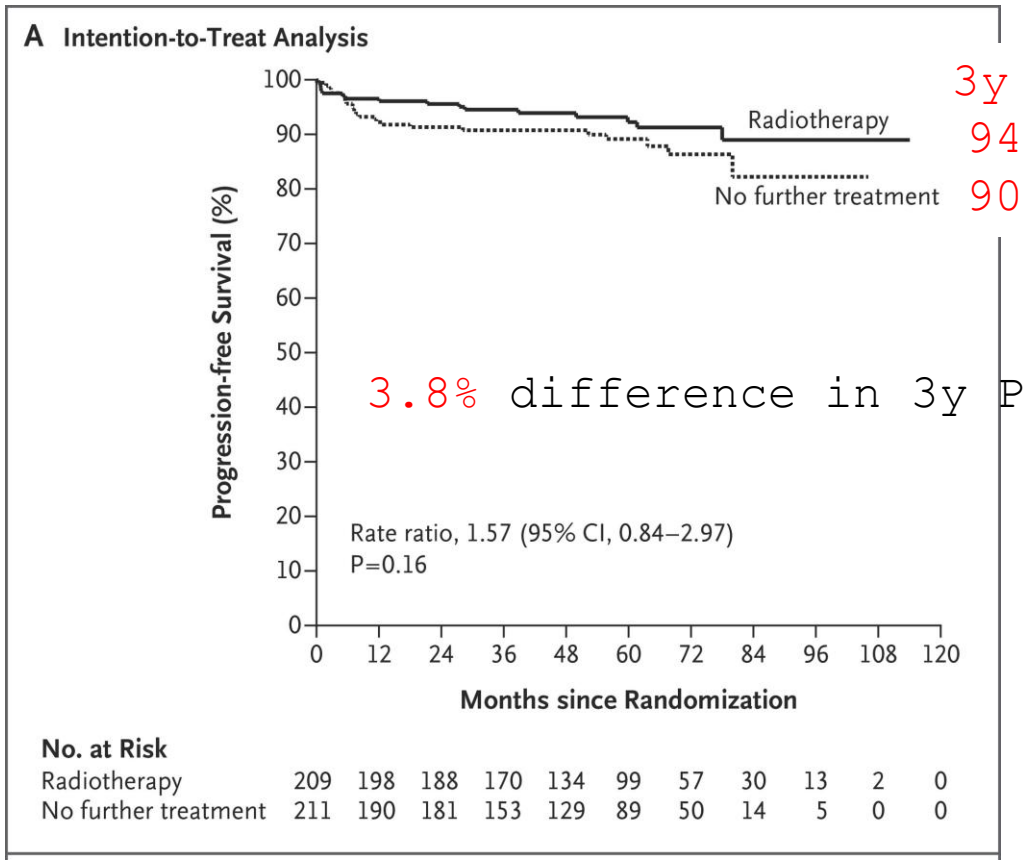
RAPID

- 602 patients, 16-75 y/o, stage IA-IIA cHL, no mediastinal bulk, no B sx



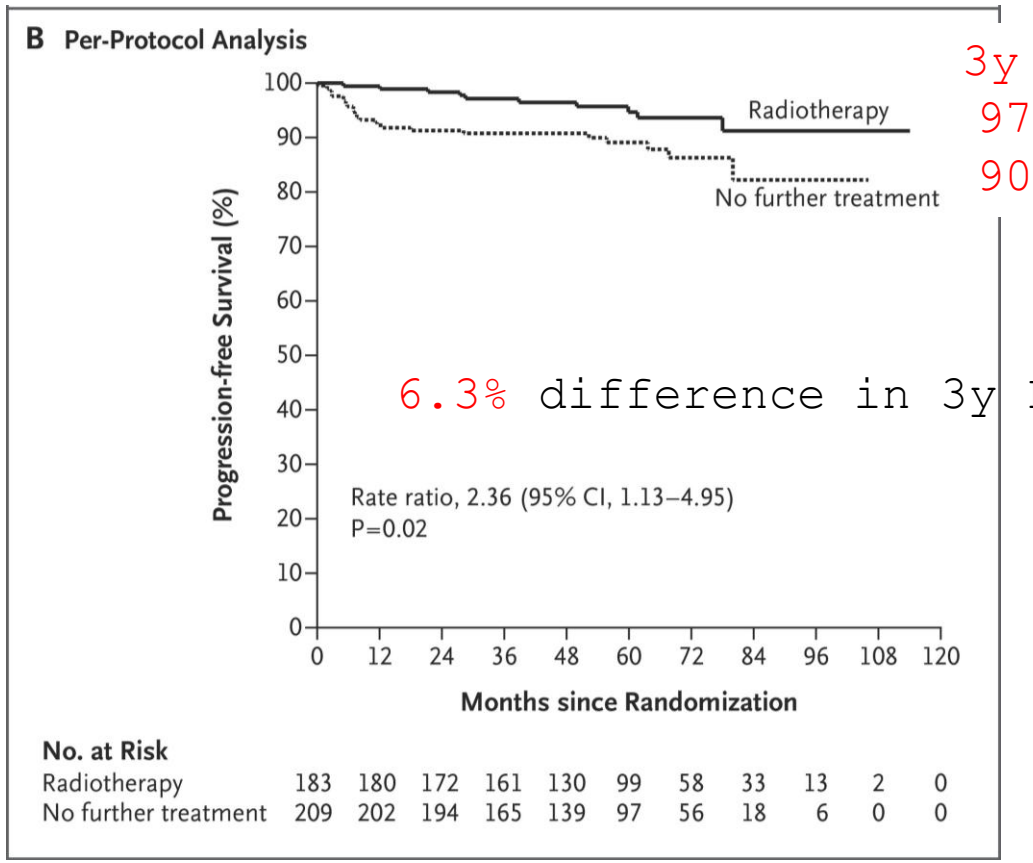
Radford et al. NEJM

RAPID: Negative PET3 (DS 1-2)



3y PFS
94.6%
90.8%

3.8% difference in 3y PFS

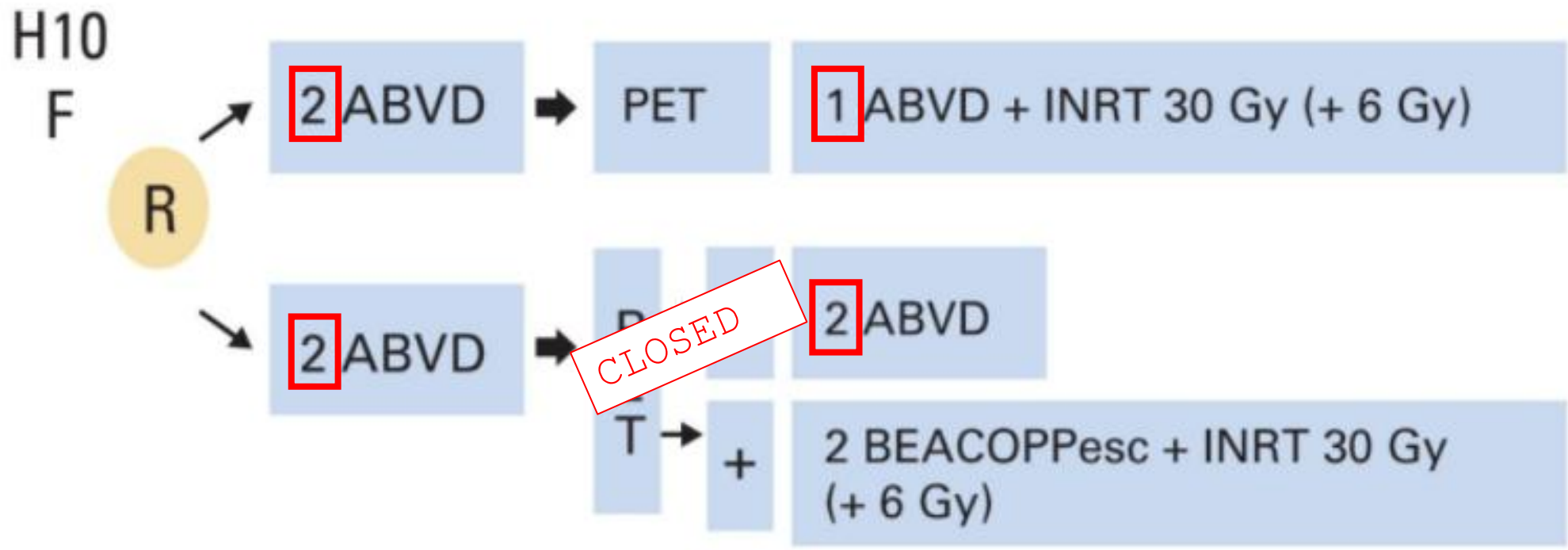


3y PFS
97.1%
90.8%

6.3% difference in 3y PFS

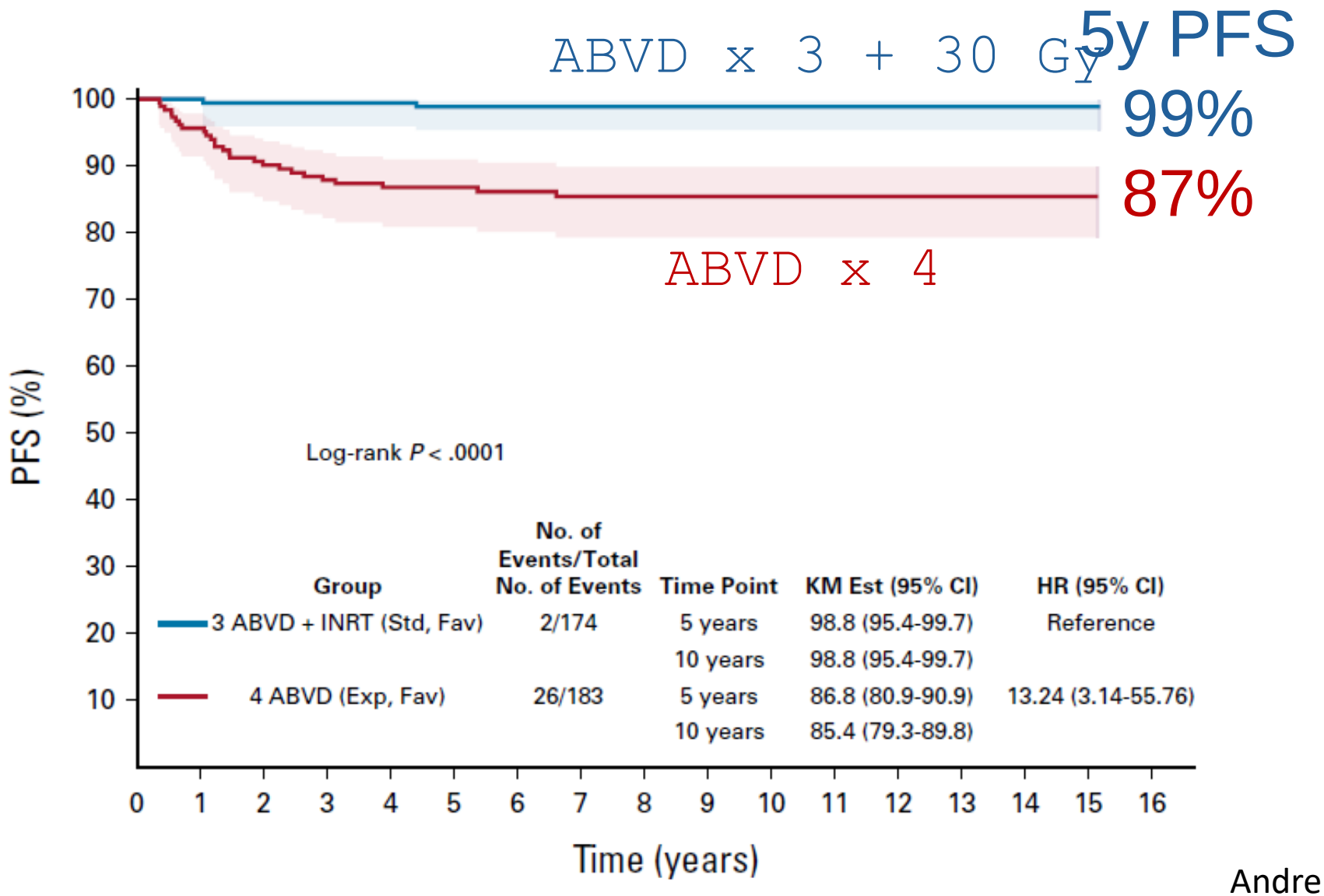
Radford et al. NEJM

EORTC H10F



Andre et al. JCO

EORTC H10F: PET2-Negative

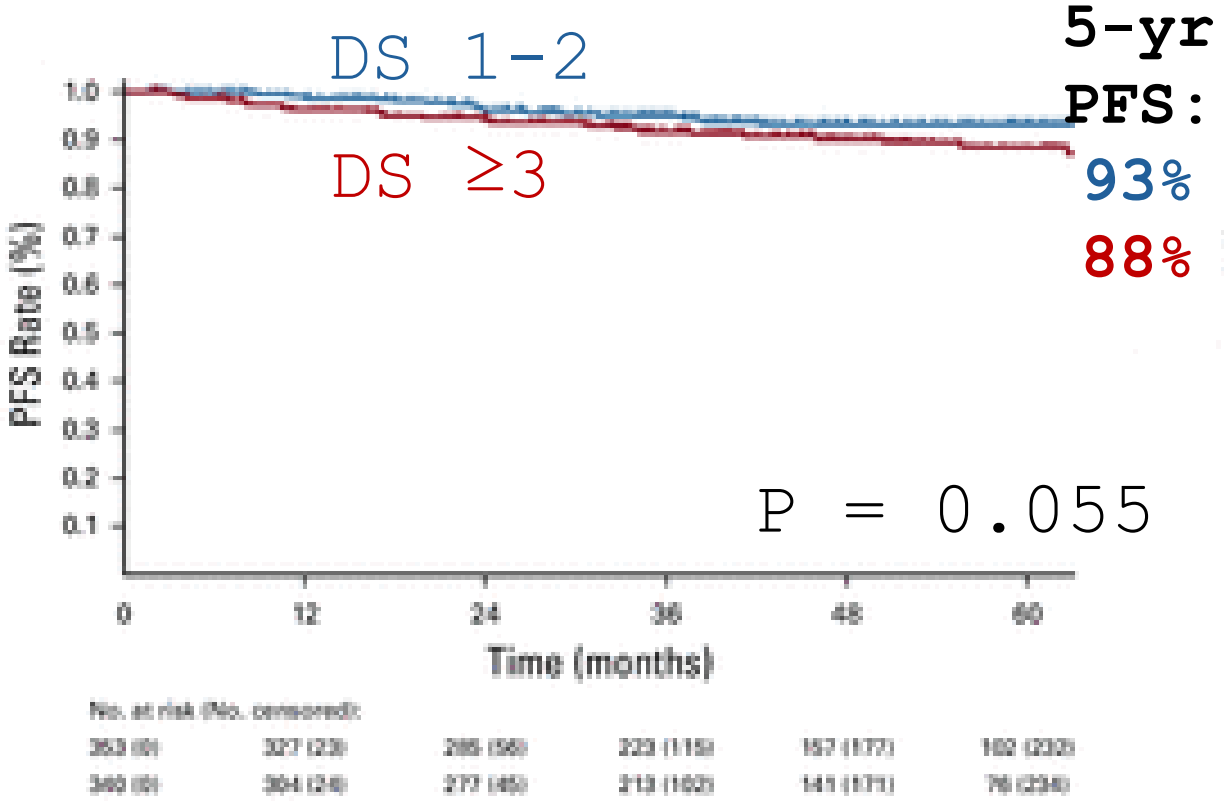


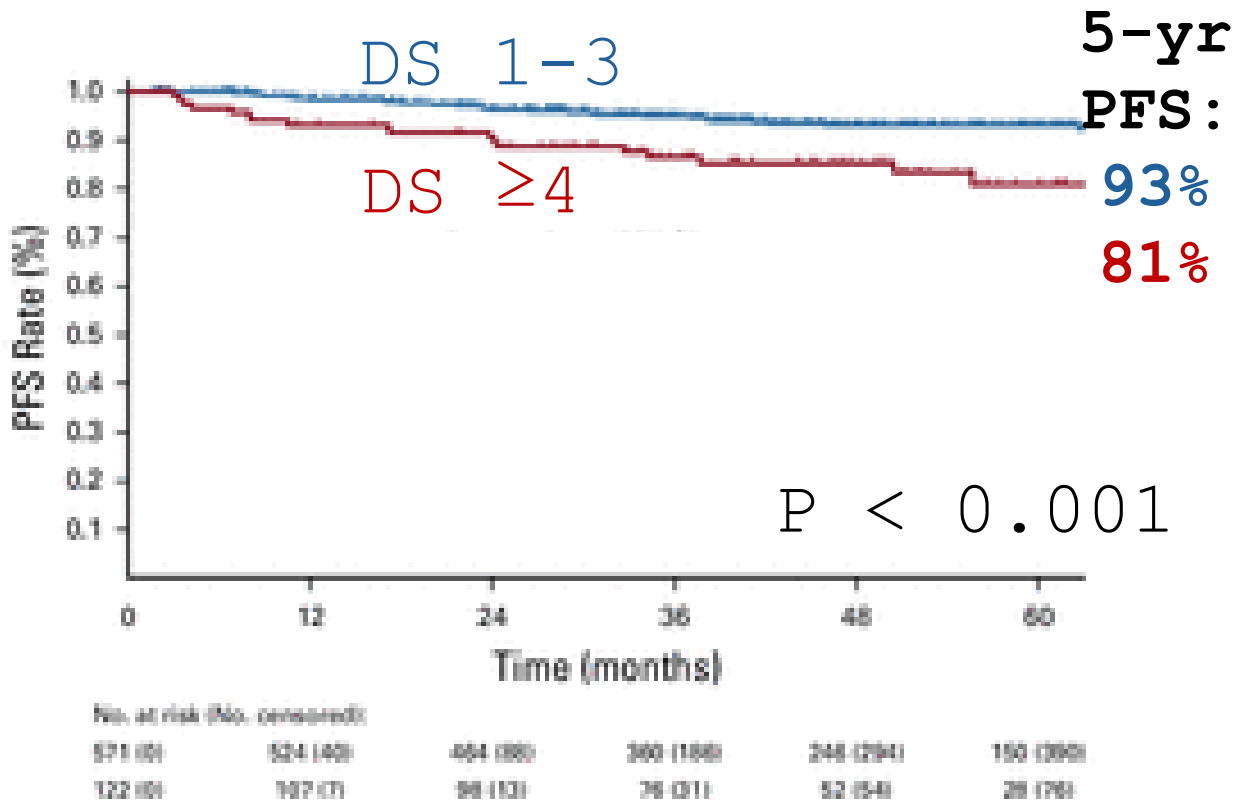
Andre et al. *JCO*. 2017

Conclusion

- In the setting of a CMR after 2-3 cycles of ABVD, RT cannot be omitted without loss of tumor control

GHSG HD16: PET2 Deauville Score with CMT



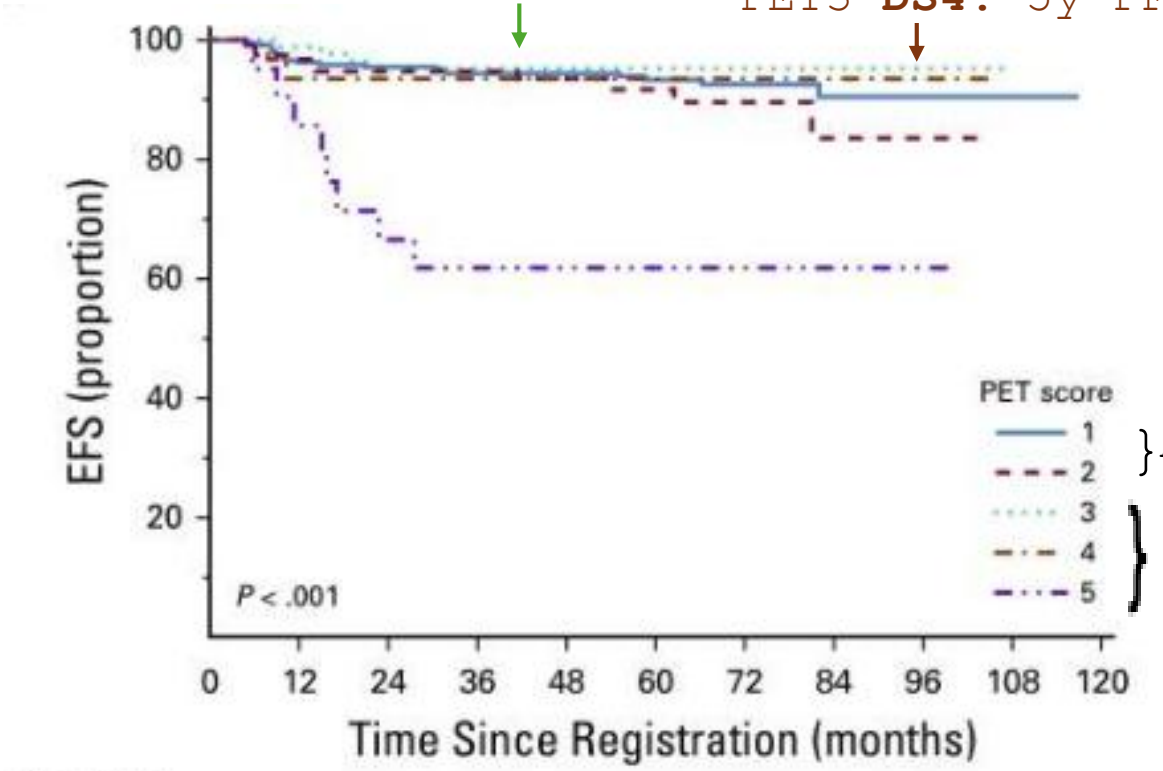


Fuchs et al. JCO

RAPID: PET3 Deauville Score with ABVD +/- RT

PET3 **DS3:** 5y PFS 95%

PET3 **DS4:** 5y PFS 88%



No. at risk:

1:	298	282	273	251	217	166	100	40	14	4	0
2:	121	110	101	85	64	48	24	13	7	0	0
3:	90	86	79	63	48	34	15	6	1	1	0
4:	32	29	27	25	21	13	10	4	1	0	0
5:	21	18	14	11	9	5	5	3	1	0	0

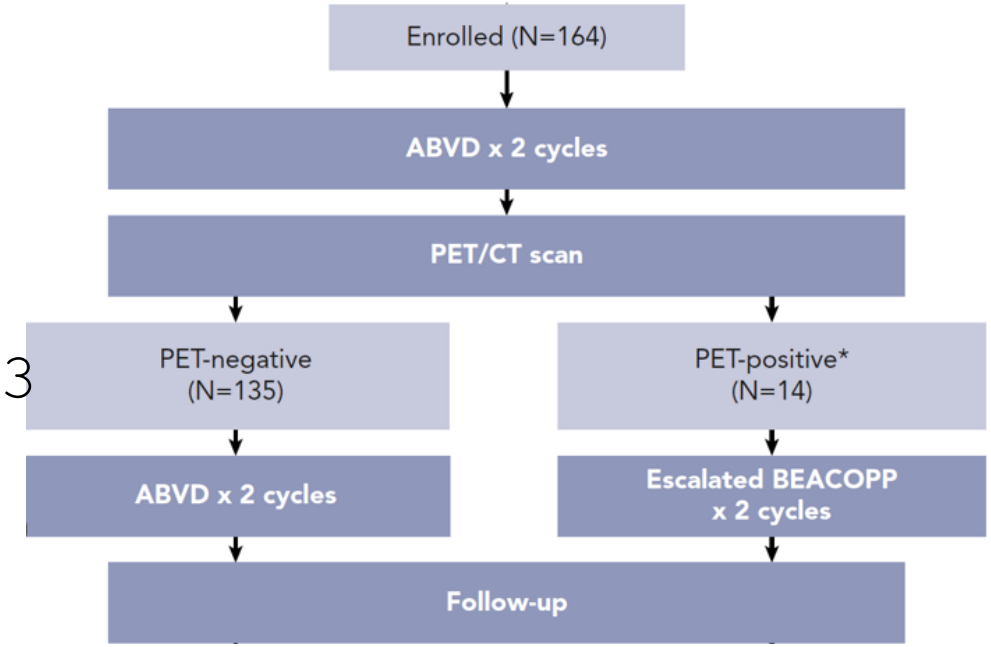
} ABVD x 3 +/- 30 Gy

} ABVD x 4 + 30 Gy

Barrington et al. J

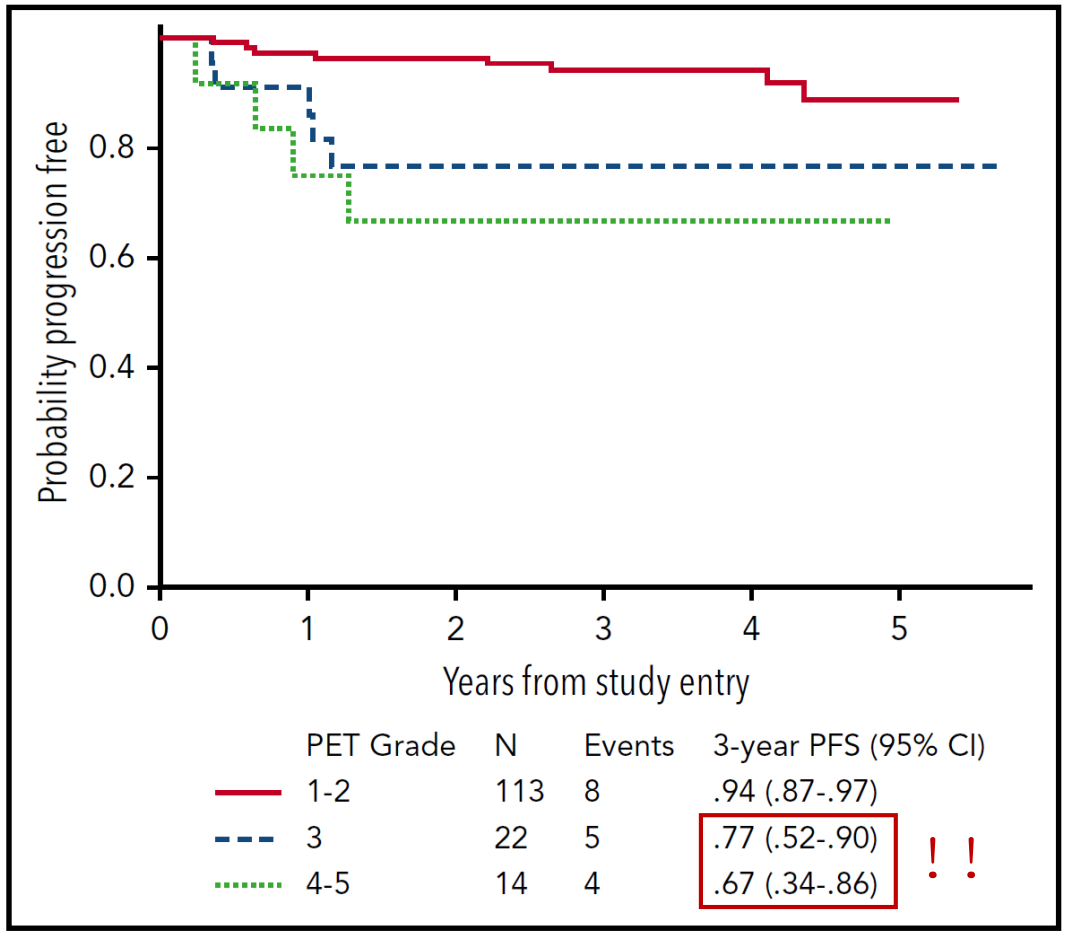
CALGB 50604: PET2 Deauville with Chemo

- Stage I-II, non-bulky



DS1-3

DS≥4

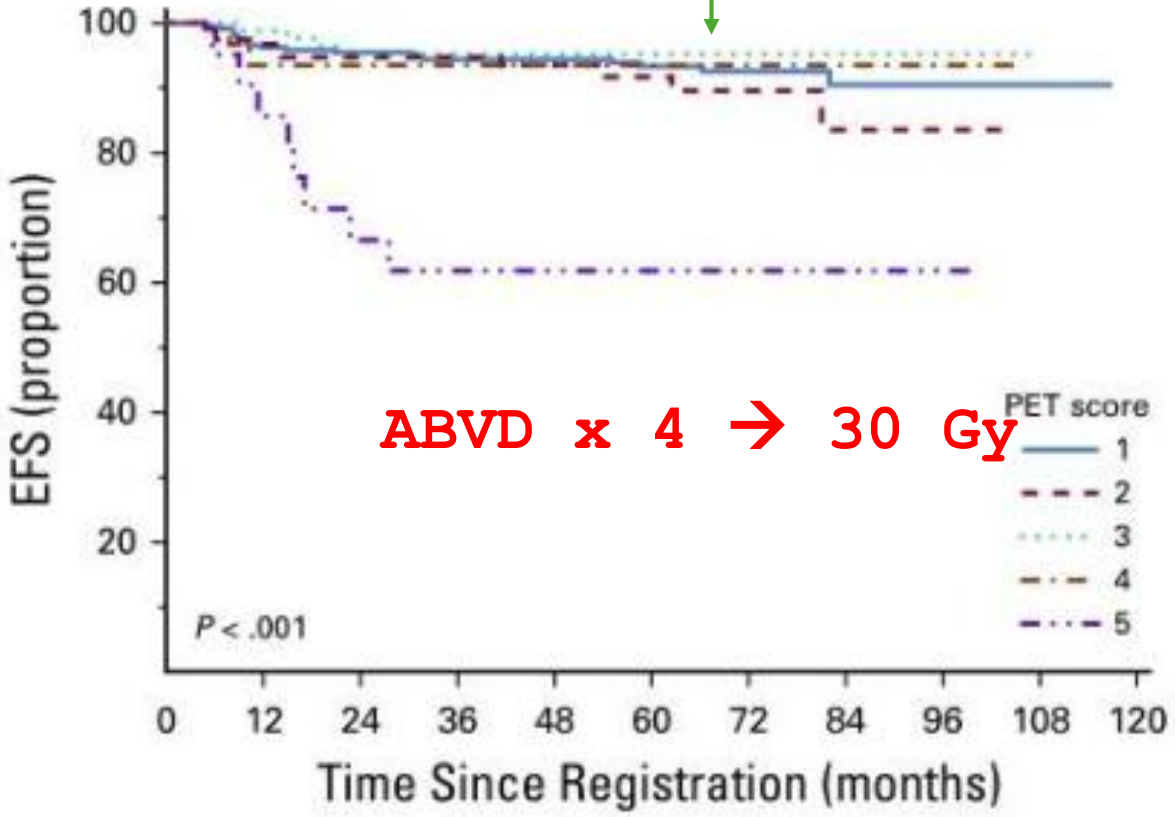


Strauss et al. Bloo

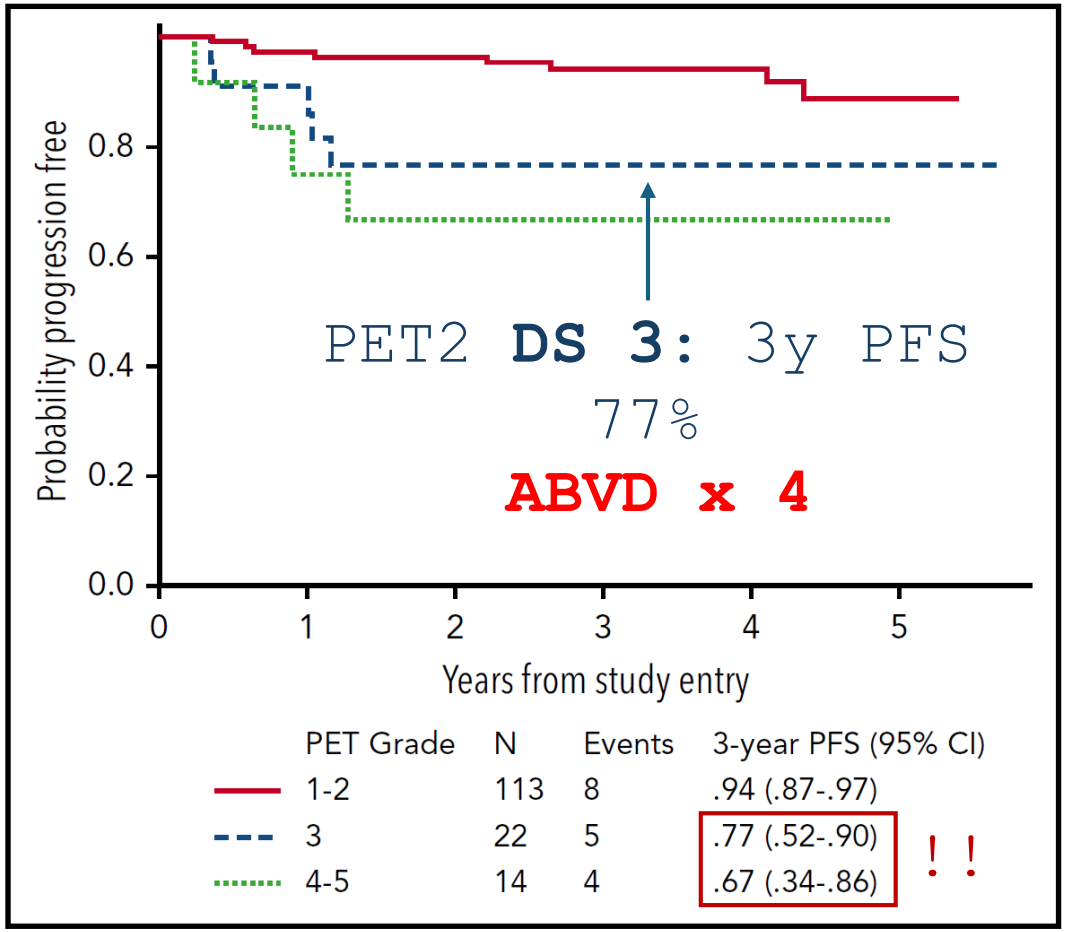
RAPID vs CALGB: DS 3

PET3 **DS 3:** 5y PFS

95%



ABVD x 4 → 30 Gy



PET2 **DS 3:** 3y PFS

77%

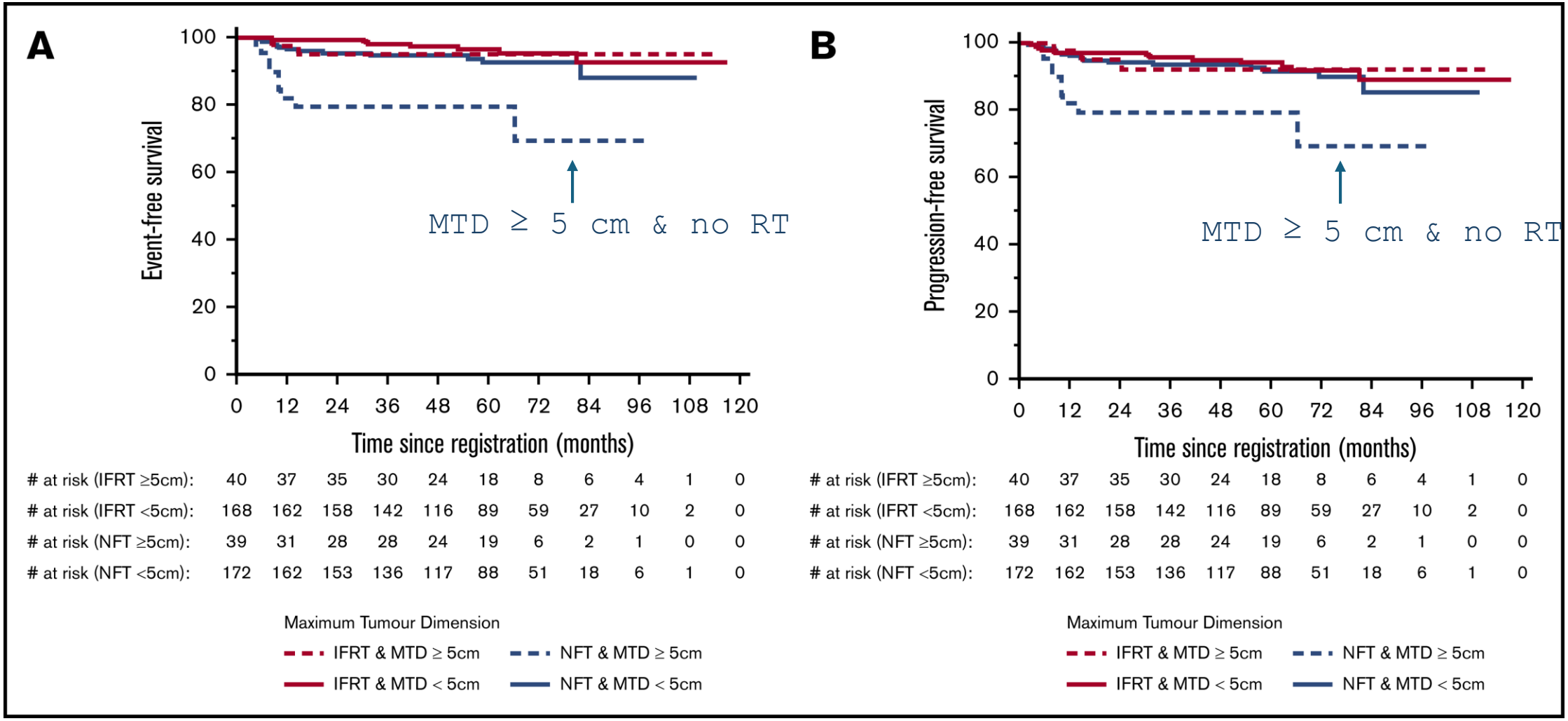
ABVD x 4

!!

Barrington et al. JCO 2019

Strauss et al. Blood 2018

RAPID: Bulk



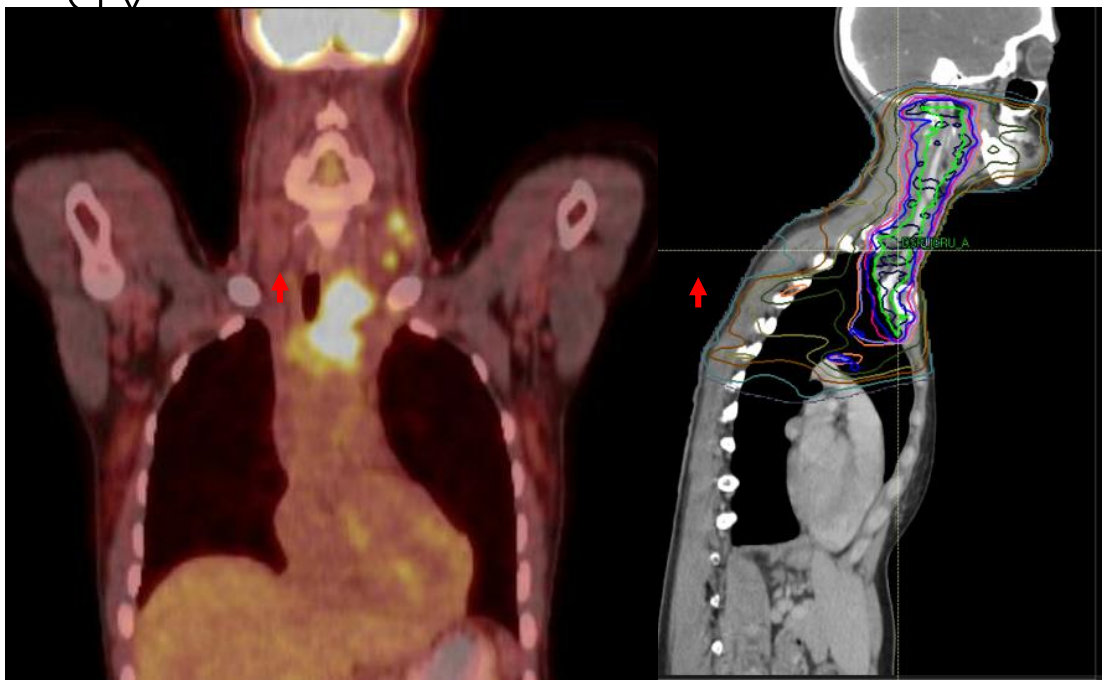
Illidge et al. Blood

Cases

Case 1:

ABVD x 2 → 20 Gy (GHSG HD16)

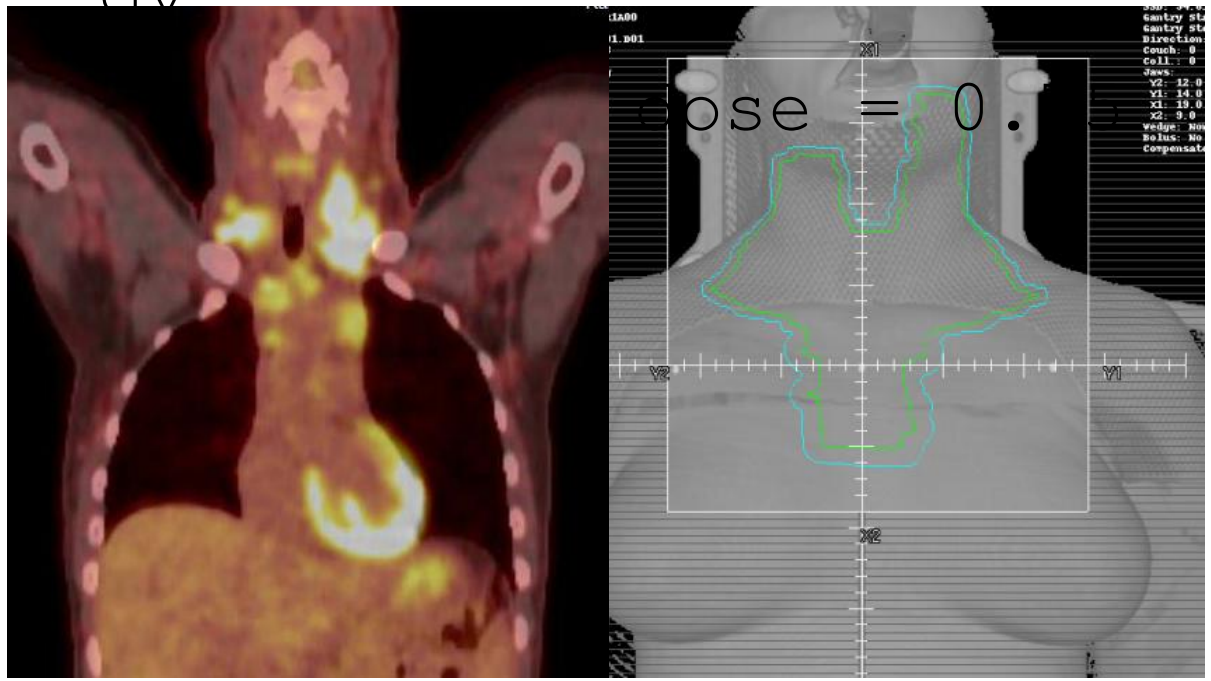
Mean heart dose = 0.60 Gy



Case 2:

ABVD x 3 → 30 Gy (RAPID, H10)

Mean heart dose = 5.0 Gy



Slide courtesy of Dr. Davic

Tumor Board

- *"How could you give radiation therapy to these young women?! You are going to give them breast cancer and cardiac disease!!"*

ILROG Guidelines

International Journal of Radiation Oncology biology • physics

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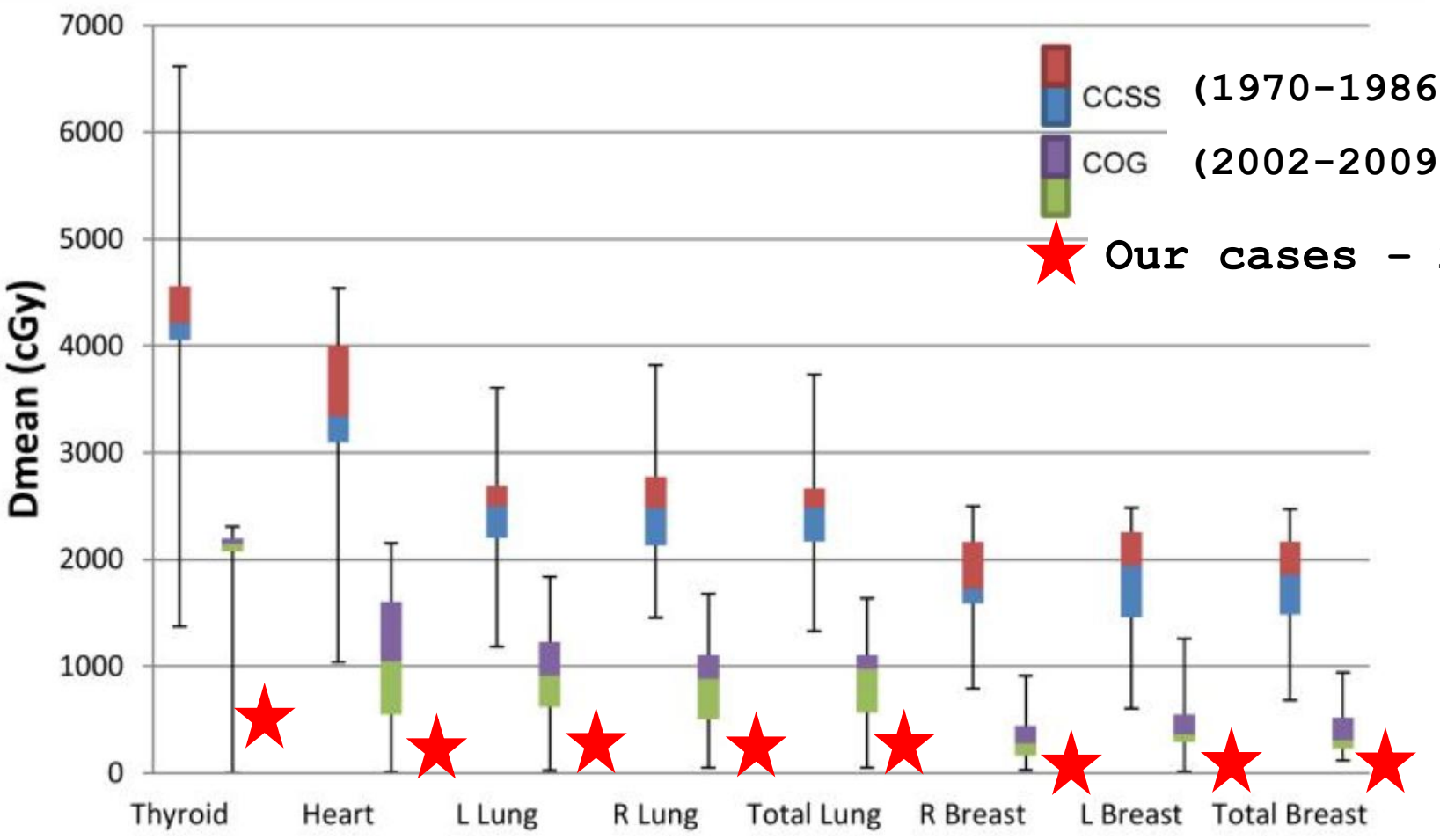
Clinical Investigation

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

Lena Specht, MD, PhD,* Joachim Yahalom, MD,† Tim Illidge, MD, PhD,‡ Anne Kiil Berthelsen, MD,§ Louis S. Constine, MD,|| Hans Theodor Eich, MD, PhD,¶ Theodore Girinsky, MD,# Richard T. Hoppe, MD,** Peter Mauch, MD,†† N. George Mikhaeel, MD,‡‡ and Andrea Ng, MD, MPH††, on behalf of ILROG

*Department of Oncology and Hematology, Rigshospitalet, University of Copenhagen, Denmark; †Department of Radiation Oncology, Memorial Sloan-Kettering Cancer Center, New York, New York; ‡Institute of Cancer Sciences, University of Manchester, Manchester Academic Health Sciences Centre, Christie Hospital NHS Trust, Manchester, United Kingdom; §Department of Radiation Oncology and PET Centre, Rigshospitalet, University of Copenhagen, Denmark; ||Department of Radiation Oncology and Pediatrics, James P. Wilmot Cancer Center, University of Rochester Medical Center, Rochester, New York; ¶Department of Radiation Oncology, University of Münster, Germany; #Department of Radiation Oncology, Institut Gustave-Roussy, Villejuif, France; **Department of Radiation Oncology, Stanford University, Stanford, California; ††Department of Radiation Oncology, Brigham and Women's Hospital and Dana-Farber Cancer Institute, Harvard University, Boston, Massachusetts; and ‡‡Department of Clinical Oncology and Radiotherapy, Guy's & St Thomas' NHS Foundation Trust, London, United Kingdom

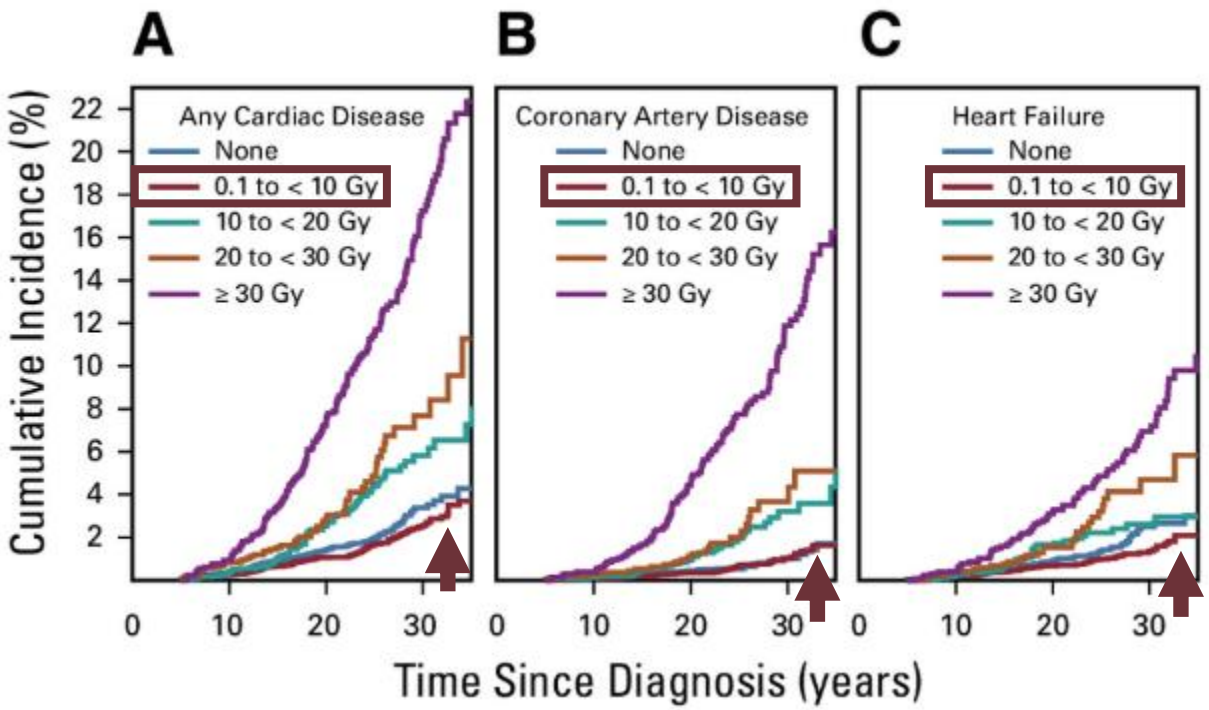
Low OAR Doses with Modern ISRT



Zhou et al. IJROB

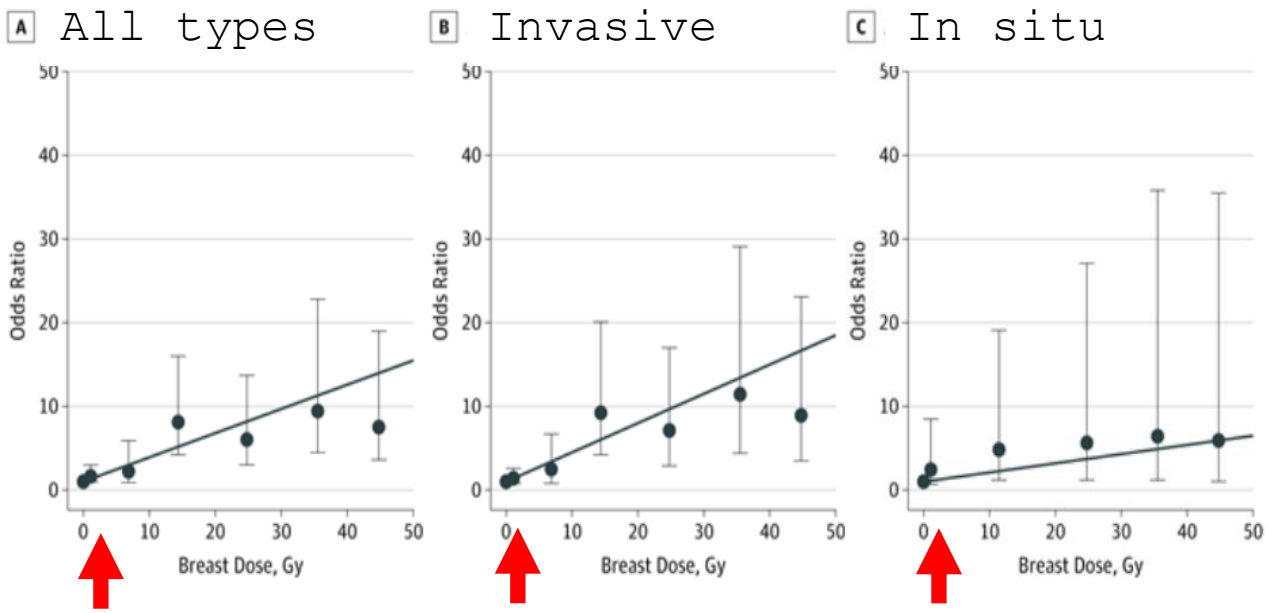
Late Toxicity of Modern RT

CARDIAC DISEASE



Bates et al. JCO 2019

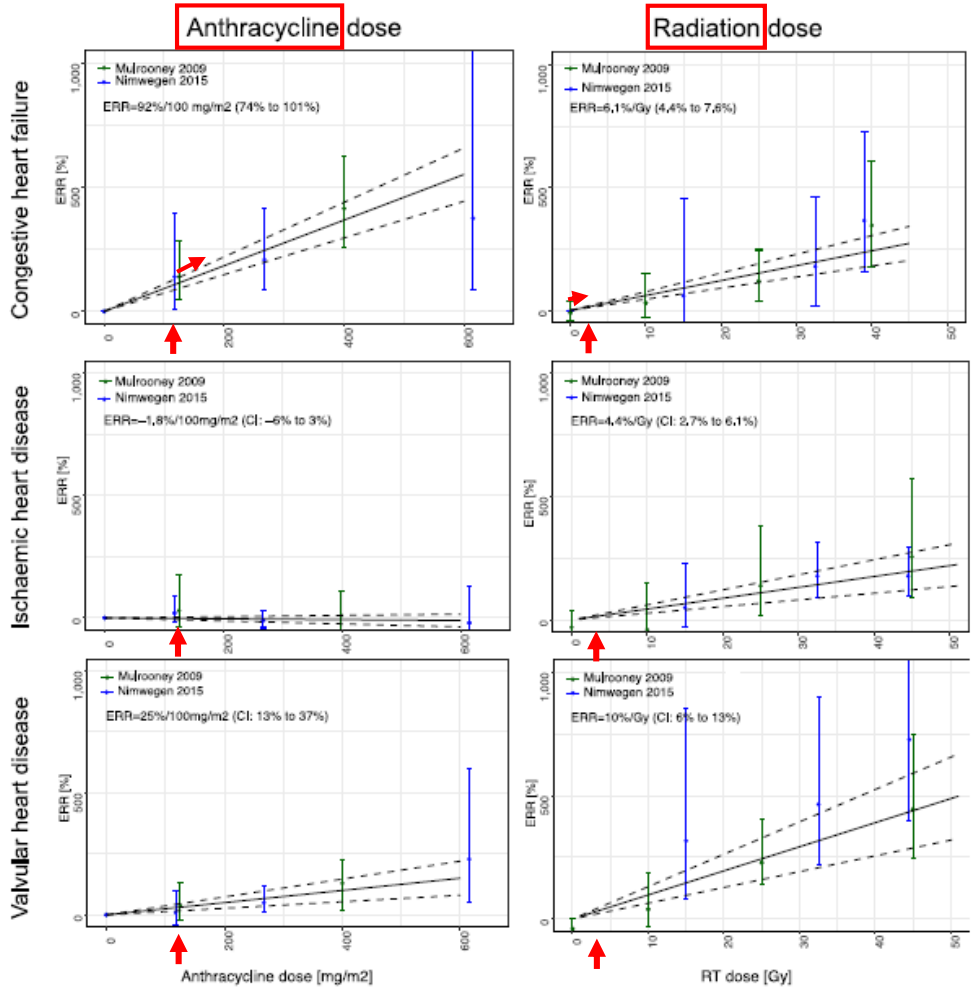
BREAST CANCER



Veiga et al. JAMA Ped 2019

Weighing Risks of CMT vs ABVD

CARDIAC



Nygard et al, Hematol Oncol 2025

BREAST CANCER

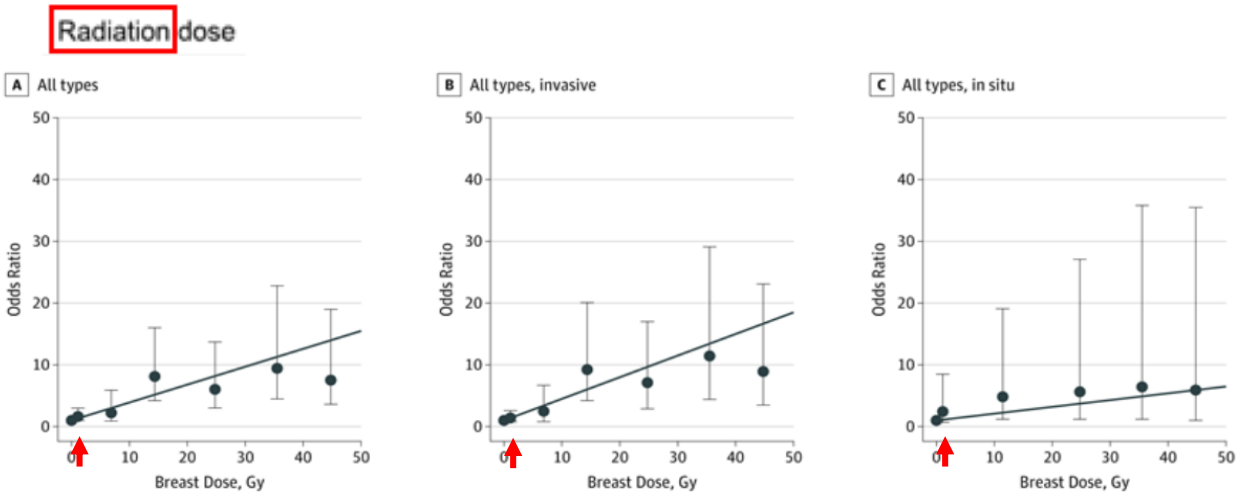


Table 2. Odds Ratio for Breast Cancer According to Receipt of Anthracyclines and Quartile of Cumulative Anthracycline Dose by Breast Cancer Estrogen Receptor Status[a,b]

Variable	Cases	Controls	OR (95% CI)	*P* Value for Trend
Cumulative anthracycline dose, mg/m²				<.01
1-223	28	70	2.3 (1.3-4.2)	
224-343	26	68	2.4 (1.3-4.6)	
344-455	14	72	1.5 (0.7-3.2)	
>455	18	70	3.8 (1.8-8.2)	
Unknown dose	8	37	2.3 (0.9-5.9)	
OR per 100 mg/m² (95% CI)	1.23 (1.09-1.39)			

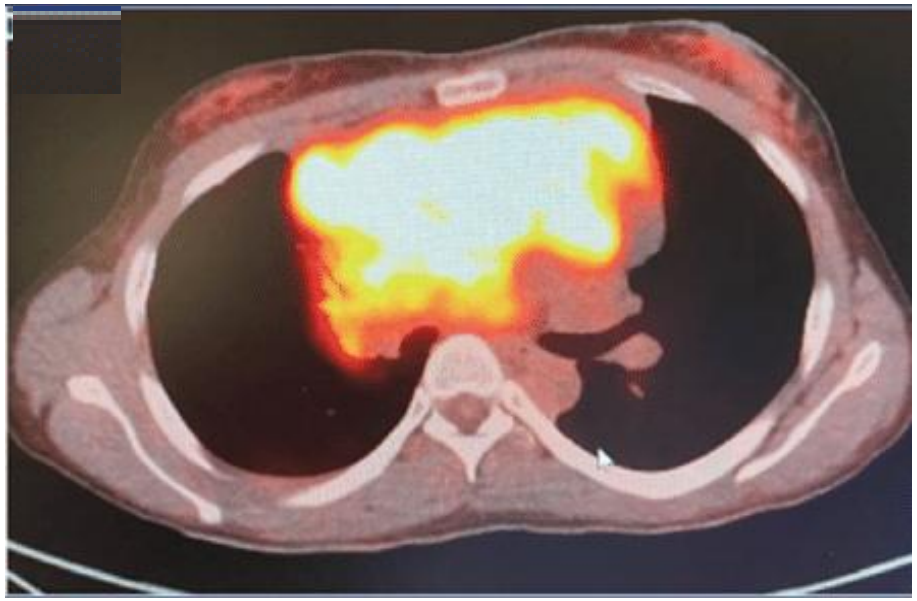
Veiga et al. JAMA Ped 2019

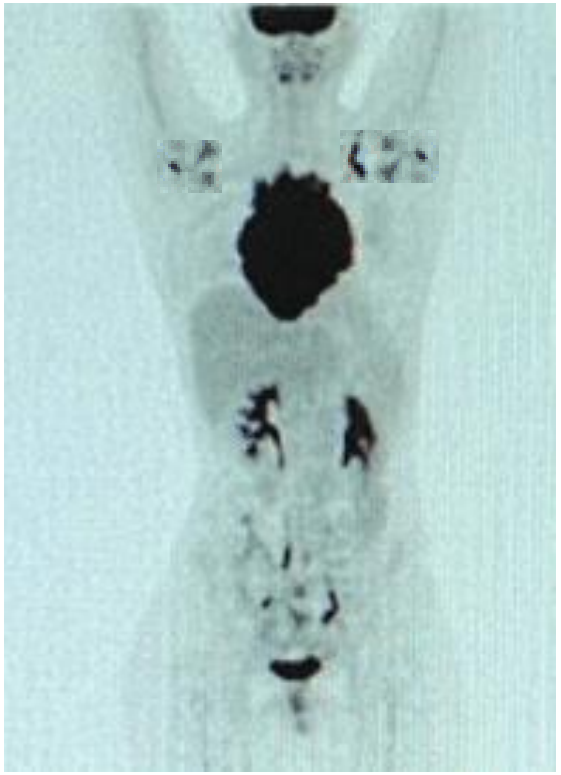
Back to Tumor Board

- *"You are right! In these patients with early-stage favorable HL, there is minimal dose to organs-at-risk! CMT offers outstanding cure rates with low toxicity risks, even in those young women!"*

Case 3

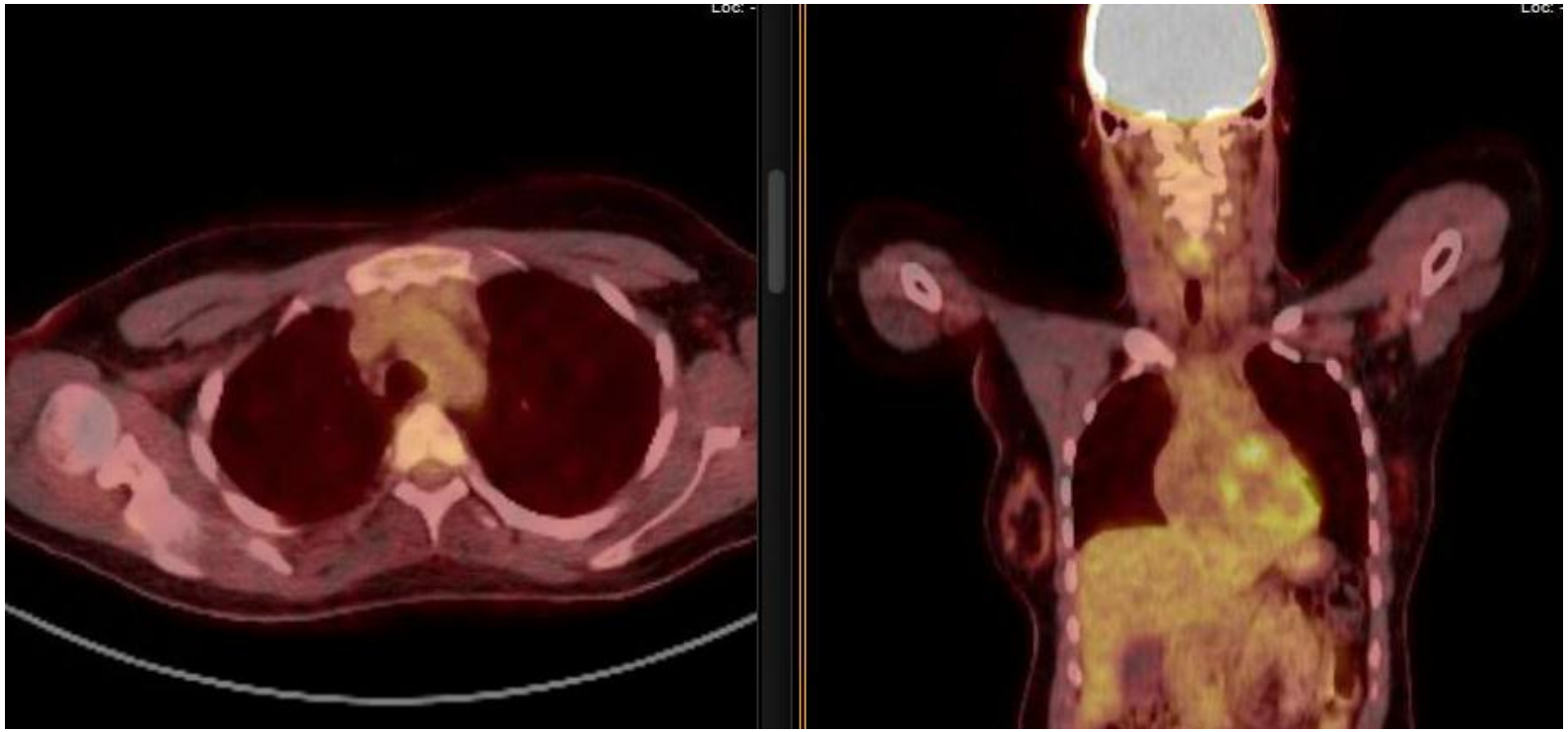
- 19 yo female
- Cough & shortness of breath
- Biopsy: NS cHL
- PET/CT: bulky mediastinal mass, bilateral axillary LAD
- ESR: 70mm/hr





Case 3

- ABVD x 2 → Deauville 2

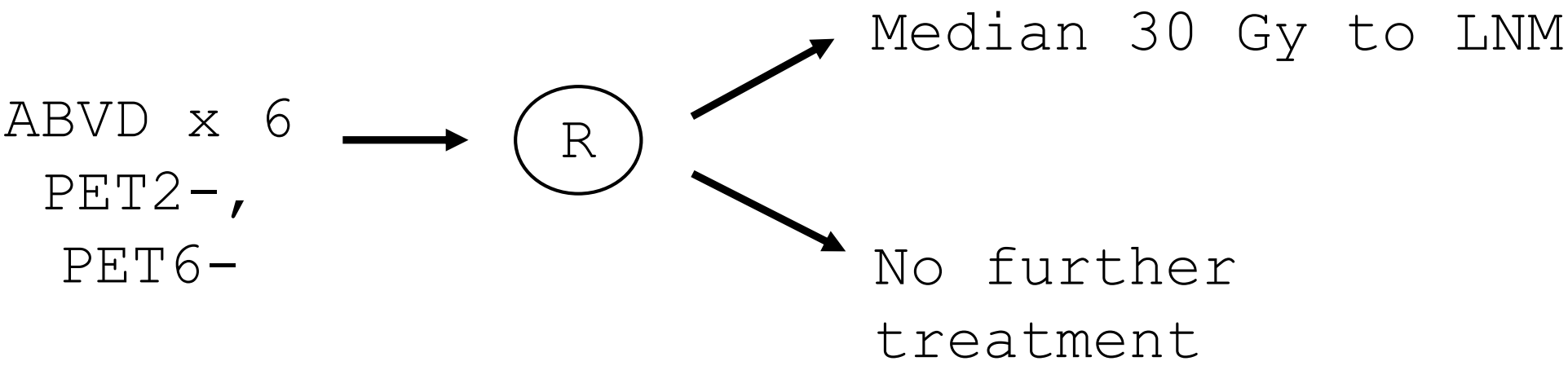


Tumor Board

- Systemic therapy alone
  - Chemo-sensitive disease
  - Radiation dose to heart and breasts would be high given disease distribution
- *"Does she need radiation given the initial bulk?"*

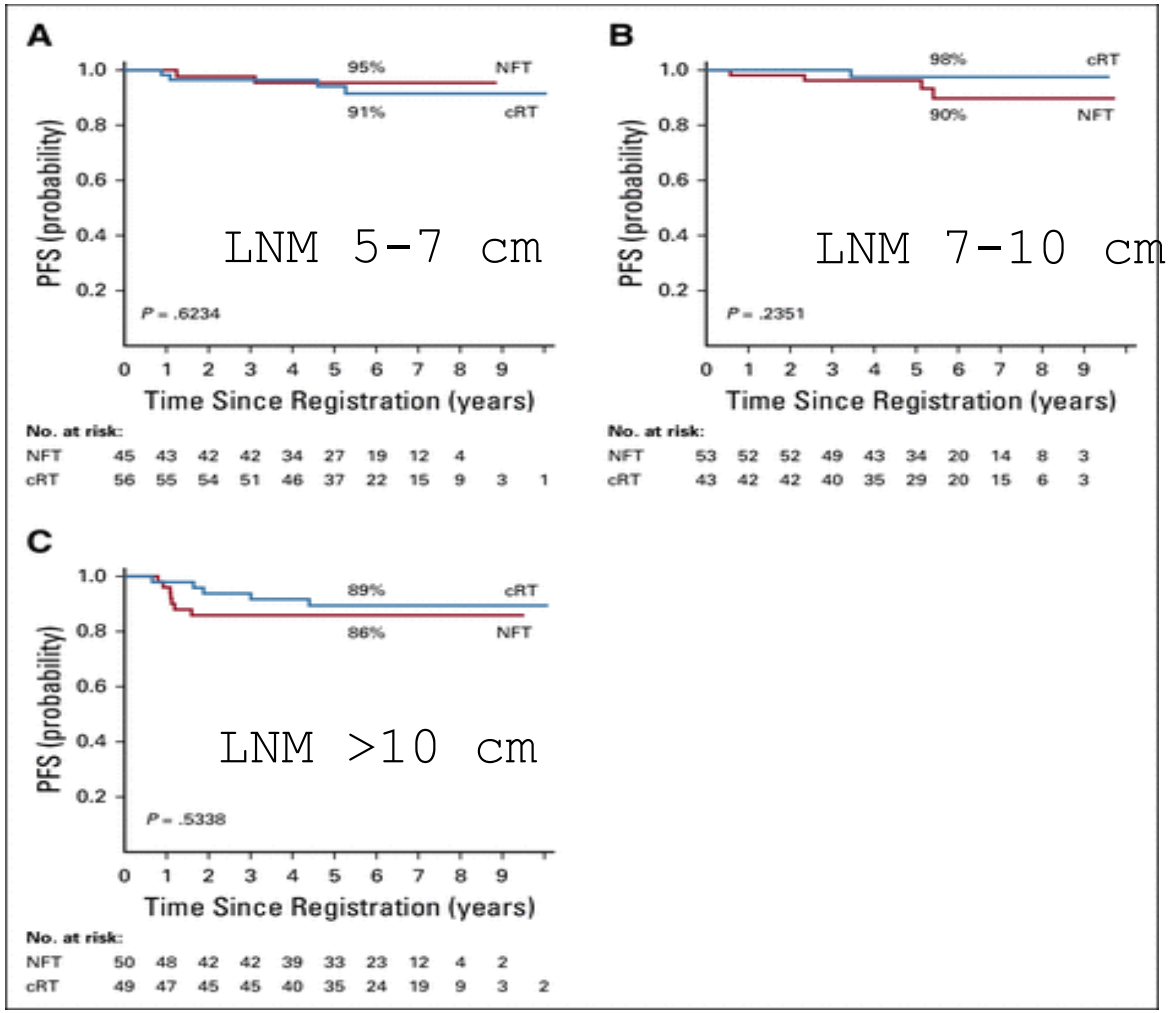
GITIL/FIL HD0607

- 320 patients, 18-60 y/o, stage IIB-IV cHL (42% IIB), large nodal mass (≥5 cm)



Gallamini et al. JC

GITIL/FIL HD0607



Gallamini et al. JC

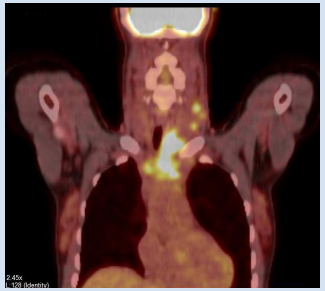
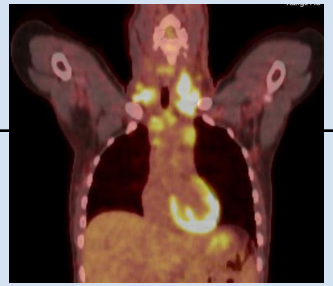
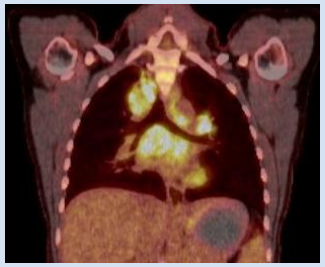
Bulky Early-Stage HL

- After A(B)VD x 6 with a negative PET2 & PET6, RT can be omitted (GITIL/FIL HD0607, RATHL)
- Option if an extensive RT field would result in unacceptable toxicity risk

Conclusions: 1L Early-Stage HL

- RT is
  - Essential after ABVD x 2 (HD16)
  - Important after ABVD x 3 with initial tumor > 5cm or interim PET DS 3-4 (RAPID, CALGB)
  - Unnecessary after A(B)VD x 6 with negative PET2/PET6 (Gallimini, RATHL)
- Individual toxicity risk should be considered when deciding between CMT & chemotherapy alone
  - Abbreviated chemo + low-dose, small-field modern RT → excellent PFS & low toxicity risk in favorable cases
  - Chemotherapy alone should be considered in patients who would have extensive radiation fields and

Summary

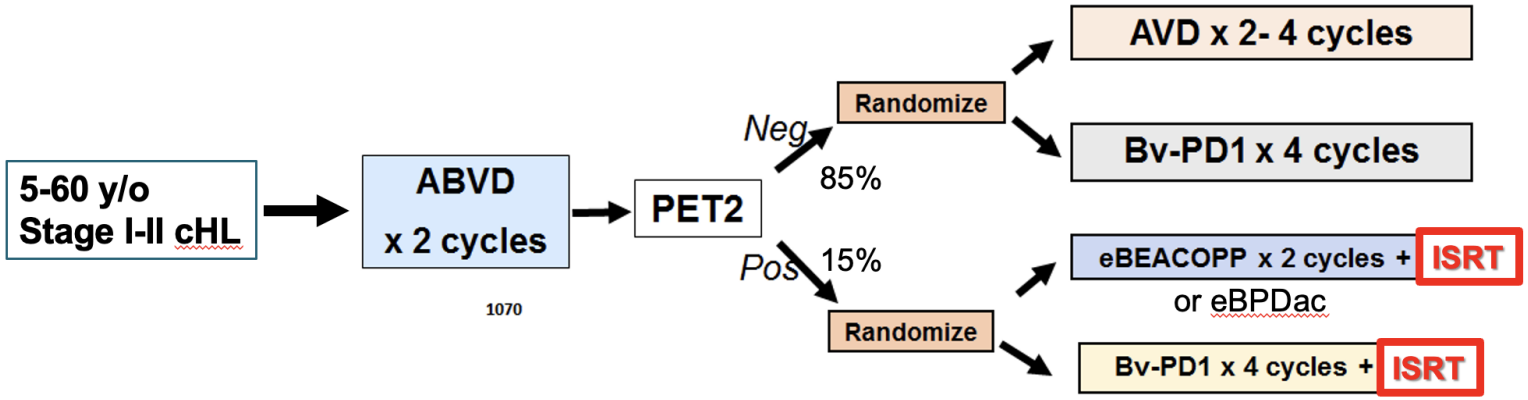
		CMT	RT Omission
Early Favorable GHSG (1-2 sites) PET2 negative		ABVD x 2 + 20Gy	ABVD x 3-4 if <5cm and PET2 1-2
Early Favorable EORTC (3 sites) PET2 negative	 	ABVD x 3 + 30Gy	ABVD x 4 if <5cm and PET2 1-2
Early Unfavorable		ABVD x 4 + 30Gy	• A(B)VD x 6 • BEACOPP-

Adapted from slide courtesy of Dr. Da

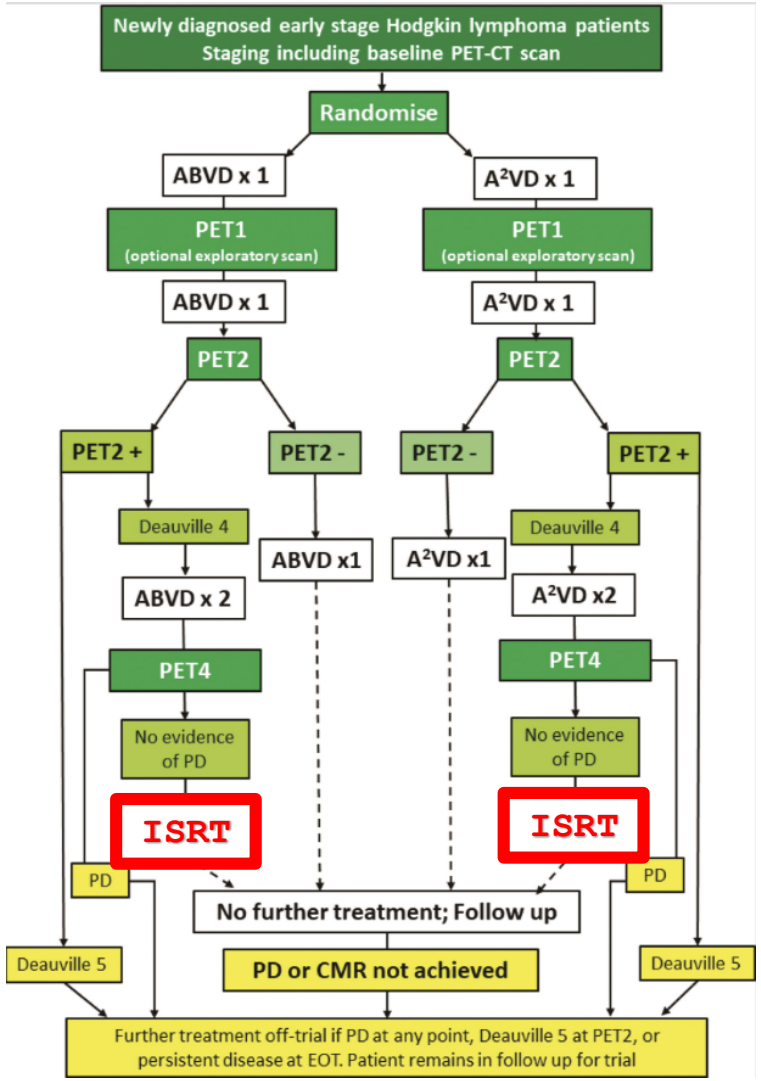
Future Directions

- Current cooperative group studies seek to optimize first-line treatment of early-stage HL using novel agents (BV, nivo)
- Risk & response-based RT used selectively for patients with highest relapse risk

AHOD2131



RADAR

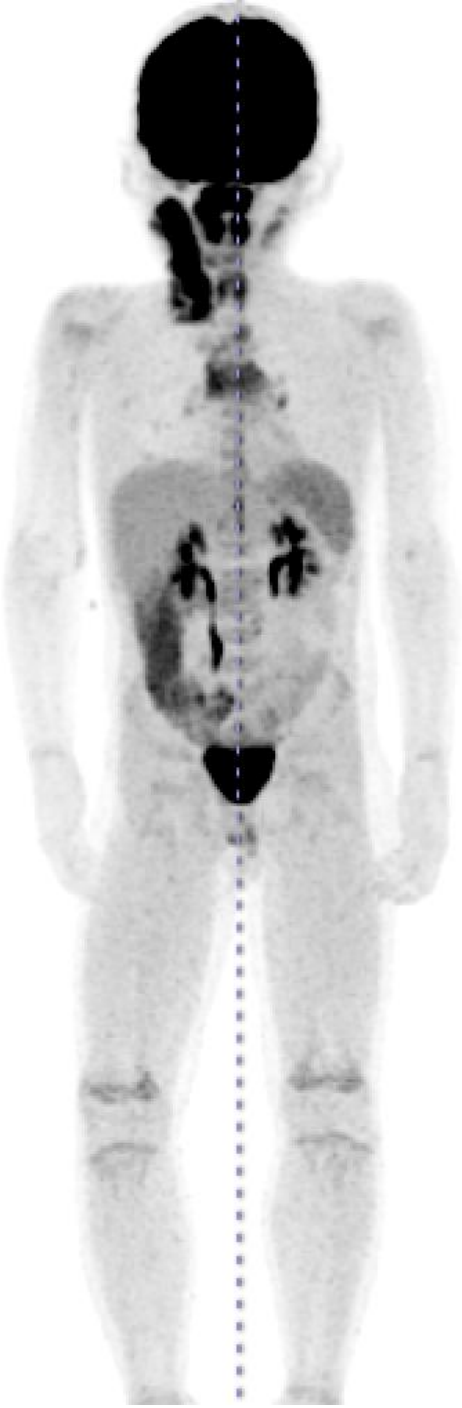


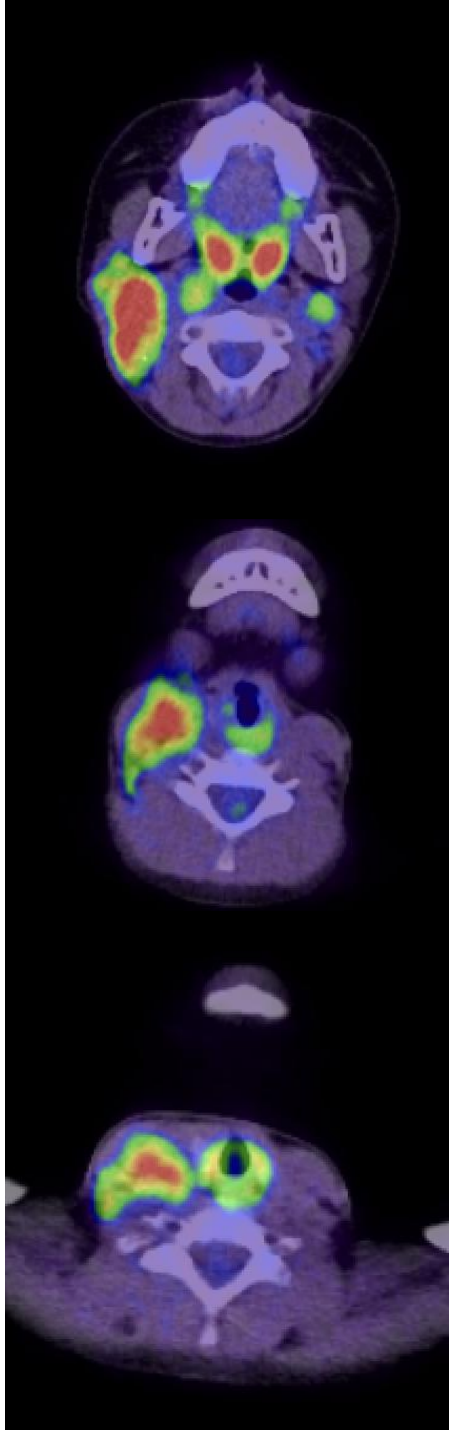
Case 4

- 12M with relapsed cHL
  - 2021: diagnosed with stage IIA cHL, NS subtype (bilateral neck)
  - ABVD x 4 in Nicaragua, completed Jan 2022
  - Feb 2025: right neck adenopathy
  - Biopsy → relapsed cHL
  - Moved to USA

Case 4

- No B symptoms
- CBC & ESR WNL
- Path: cHL, NS subtype, EBER-ISH-negative
- PET/CT: FDG-avid right neck LAD



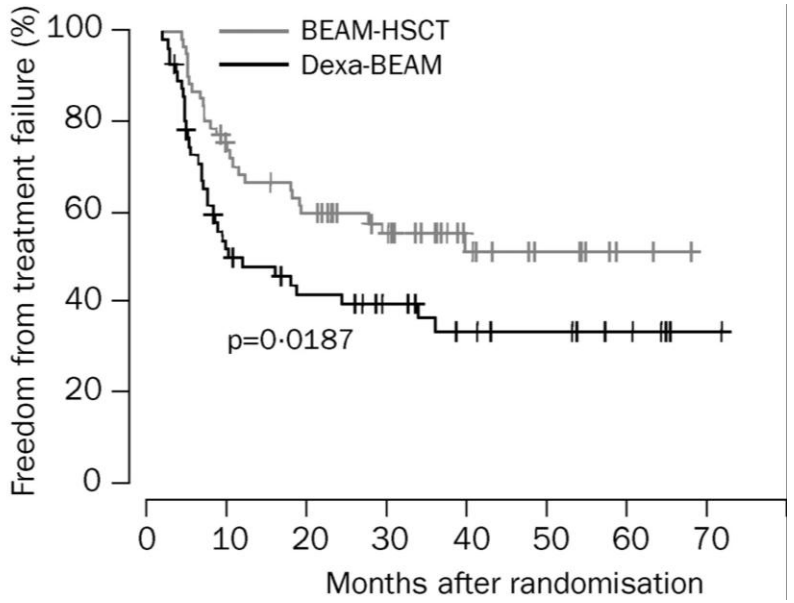


Management Recommendation?

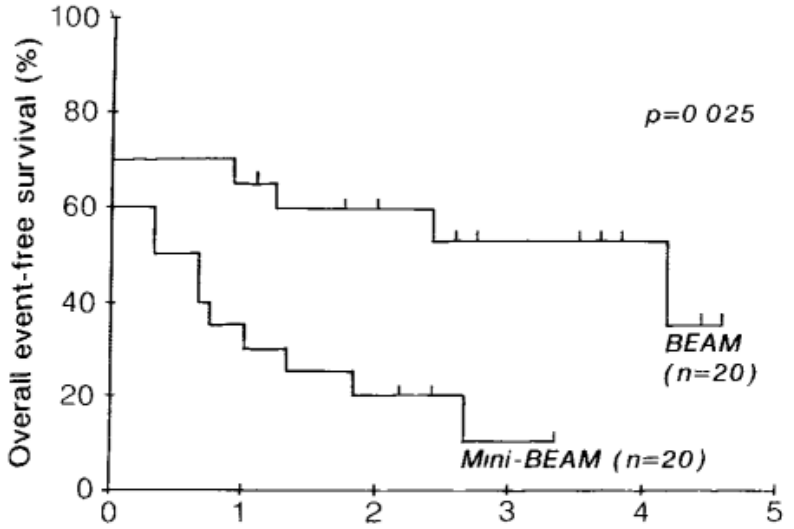
1. Re-induction therapy → HDC/ASCT
2. Re-induction therapy → HDC/ASCT → ISRT
3. Re-induction therapy → ISRT

Salvage of R/R cHL

- Until recently, salvage therapy for R/R cHL has been second-line chemo → HDC/ASCT
- Effective, but associated with toxicity:
  - Acute: cytopenias and mucositis
  - Late: infertility, cardiopulmonary toxicity, SMN



Schmitz et al. Lancet 2002



Linch et al. Lancet 1993

CCSS Pediatric HL Late Effects Study

- Incidence of grade 3-5 late effects
- Reference group: "alkylator + anthracycline w/o che[illegible]

Treatment Group	Any HR (95% CI)	SMN HR (95% CI)	CPD HR (95% CI)	Endo HR (95% CI)
≥35 Gy extended* field RT (n=570)	4.0 (2.4, 6.5)	2.8 (1.3, 5.7)	3.0 (1.2, 7.3)	4.4 (2.0, 9.7)
≥35 Gy chest RT w/o chemo (n=191)	2.5 (1.5, 4.4)	1.3 (0.6, 3.1)	2.8 (1.1, 7.2)	3.8 (1.6, 8.7)
≥35 Gy chest RT + alkylator or anthracycline (n=237)	3.1 (1.8, 5.2)	1.7 (0.7, 3.7)	3.3 (1.3, 8.6)	3.4 (1.5, 7.7)
15-34 Gy chest RT + alkylator + anthracycline (n=383)	2.7 (1.6, 4.5)	1.9 (0.9, 4.3)	2.1 (0.8, 5.5)	3.7 (1.6, 8.2)
Alkylator + anthracycline without chest RT (n=216)	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)
Salvage therapy** (n=296)	4.7 (2.8, 7.8)	1.7 (0.7, 3.7)	6.5 (2.6, 16.2)	4.0 (1.8, 9.1)

Oeffinger et al. J

Salvage of R/R cHL

- Can some patients with R/R cHL be salvaged successfully without HDC/ASCT?
- Can risk-based stratification inform treatment intensity, with ASCT-free salvage used for “low-risk” relapses?

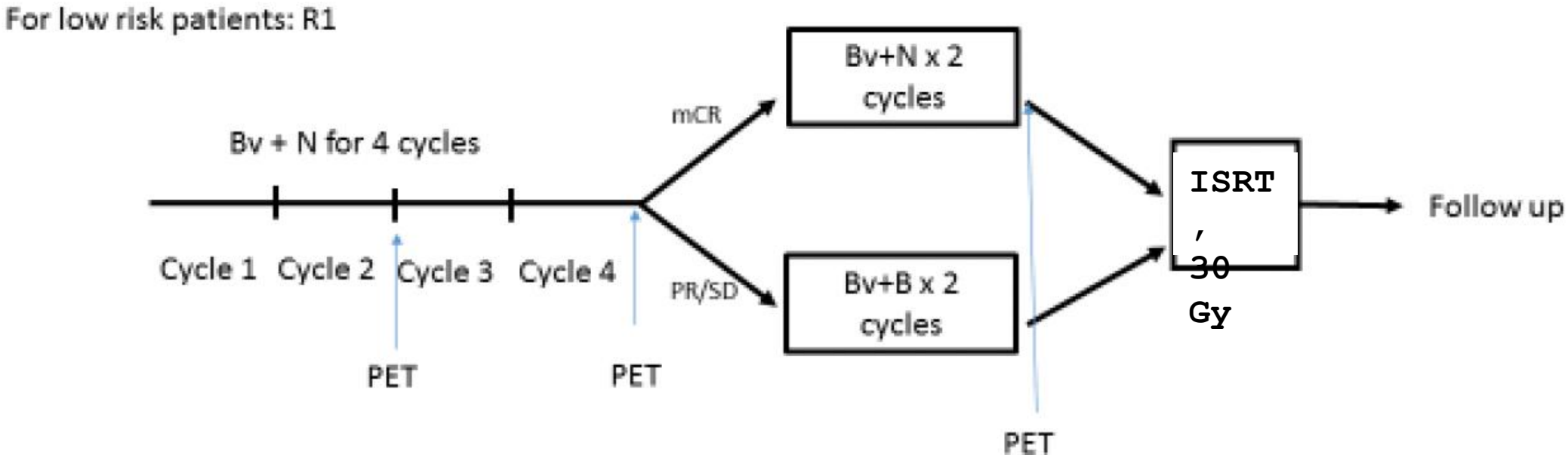
CheckMate 744 R1 cohort

- 28 patients, 5-30 y/o, "low-risk" relapsed cHL

Stage at Initial Diagnosis	Time to Relapse (From End of Therapy)	B Symptoms[a] or Extranodal Disease at Relapse, Extensive Disease Where RT Was Contraindicated at Relapse, or Relapse in Prior Radiation Field	Relapse Risk Category
IA, IIA	≥12 months	No	R1 cohort: low risk
	3–12 months (≤3 cycles and no RT)		
IB, IIB, IIIA	>12 months	No	
All others			R2 cohort: standard risk[b]

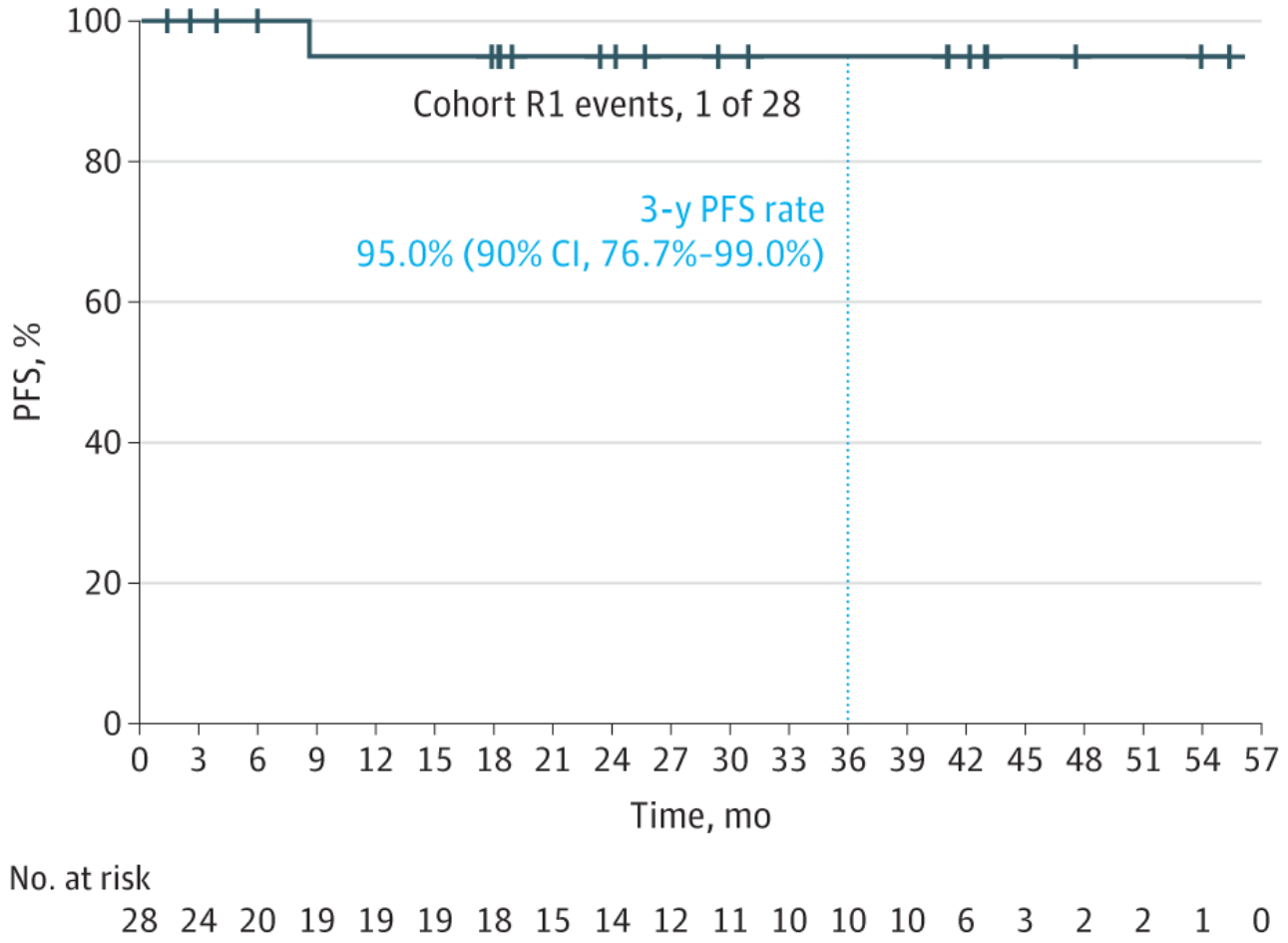
Daw et al. JAMA Onco

R1 Treatment Schema



Daw et al. JAMA Onco

R1 Progression-Free Survival



Daw et al. JAMA Onco

EuroNet-PHL-R1

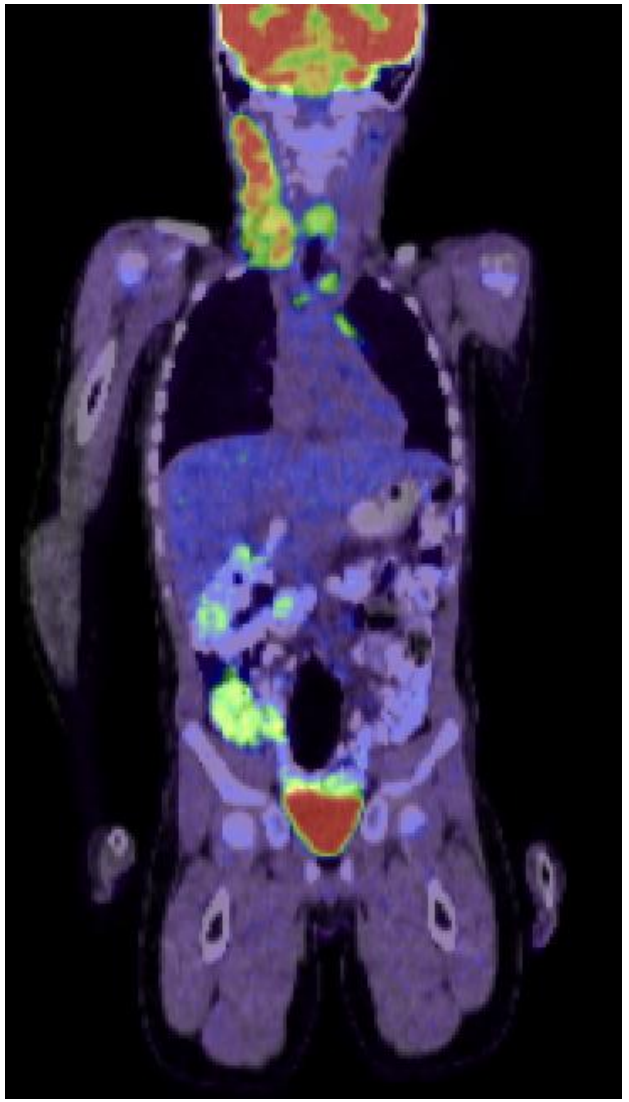
- Multicenter, non-randomized trial of patients <18 yo with first R/R cHL
  - "Low-risk"
    - Relapse >12 months after 1L with 2 cycles of chemotherapy for early-stage disease
    - Relapse >3 months after 1L AND DS 1-2 at ERA after C1 of salvage chemotherapy
  - IEP/ABVD → RT
  - 5-year PFS 90% & OS 97%

Daw et al. JAMA Onco

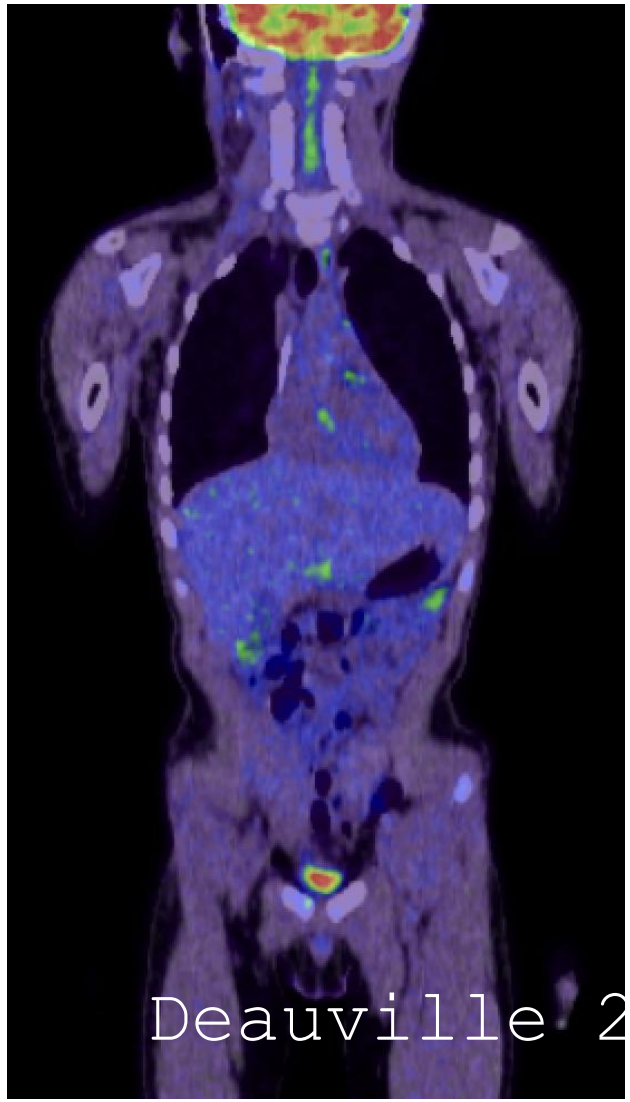
Conclusions: Low-Risk Relapses

- Low-risk relapses are effectively salvaged without HDC/ASCT
- Risk-stratified, response-based algorithms should be used for second line therapy, like for first line
- Incorporation of RT into salvage is attractive:
  - RT is a highly effective for cHL, even R/R cHL
  - Risk of toxicity associated with RT has decreased substantially with modern approaches
  - RT is used less frequently upfront → more relapses in RT-naïve patients

Our Case

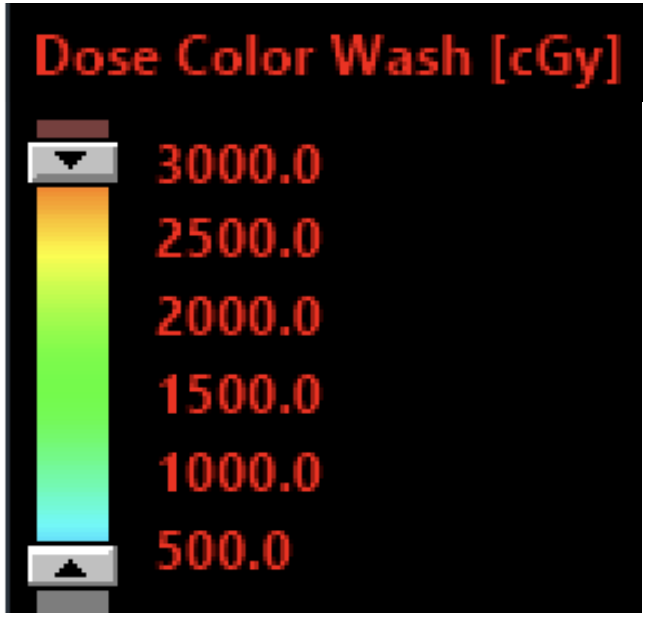


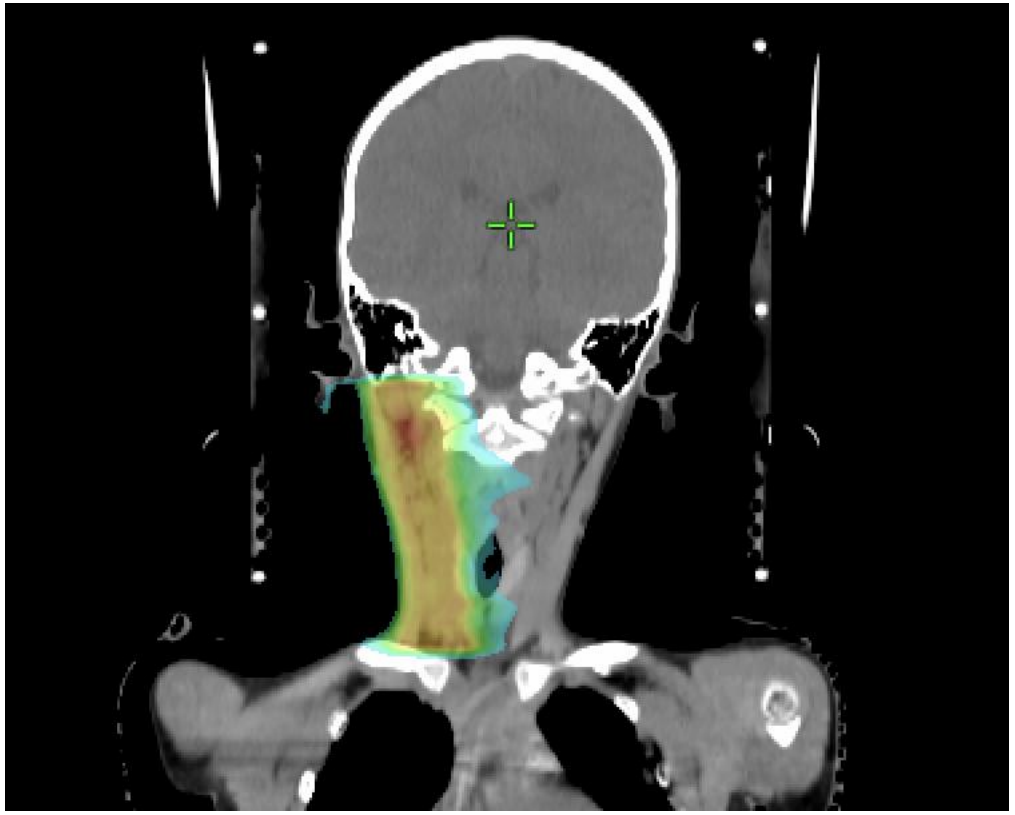
BV+N x 4

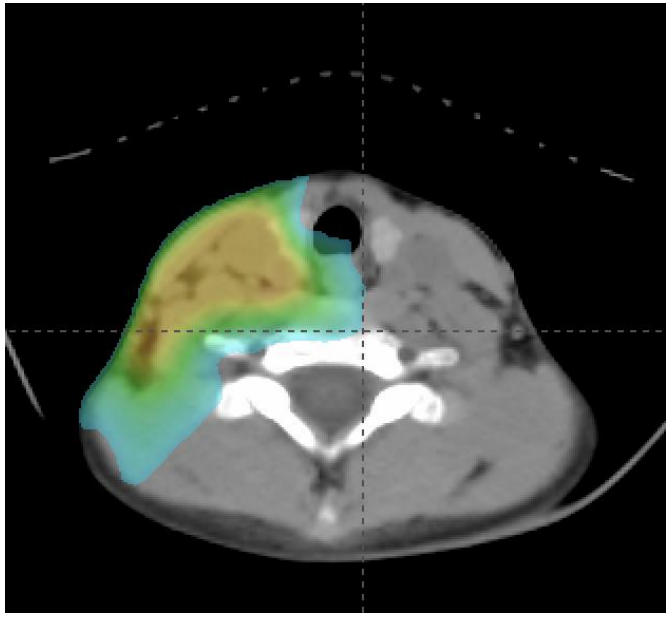


BV+N x 2

Our Case







Acute Tolerability

- BV+N: grade 1 transaminitis, grade 1 fatigue
- ISRT: grade 1 esophagitis, grade 1 dermatitis
- Continued to attend school & play soccer

Risk of Late Effects?

- Late toxicity associated with novel agents?
  - AHOD2131 incorporates N+BV into frontline management of early-stage cHL for patients 5-60 yo
    - Patients followed for 12 years, with physician- and patient-reported AEs
  - Alliance A151804 will establish a biorepository to explore immune-related adverse events in children & adults

Future Direction

- Intergroup trial in development to compare consolidation with ISRT vs. HDC/ASCT for low-risk relapses
  - PFS
  - Patient reported QoL

Conclusions

- Overall goal in HL: excellent disease control with minimal toxicity
- Integration of modern RT into management is often consistent with this goal
- To maximize the therapeutic ratio, we must continue to study late effects associated with
  - Modern RT
  - Various treatment regimens, including novel therapies