Who Benefits the Most from Radiation In Hodgkin Lymphoma?

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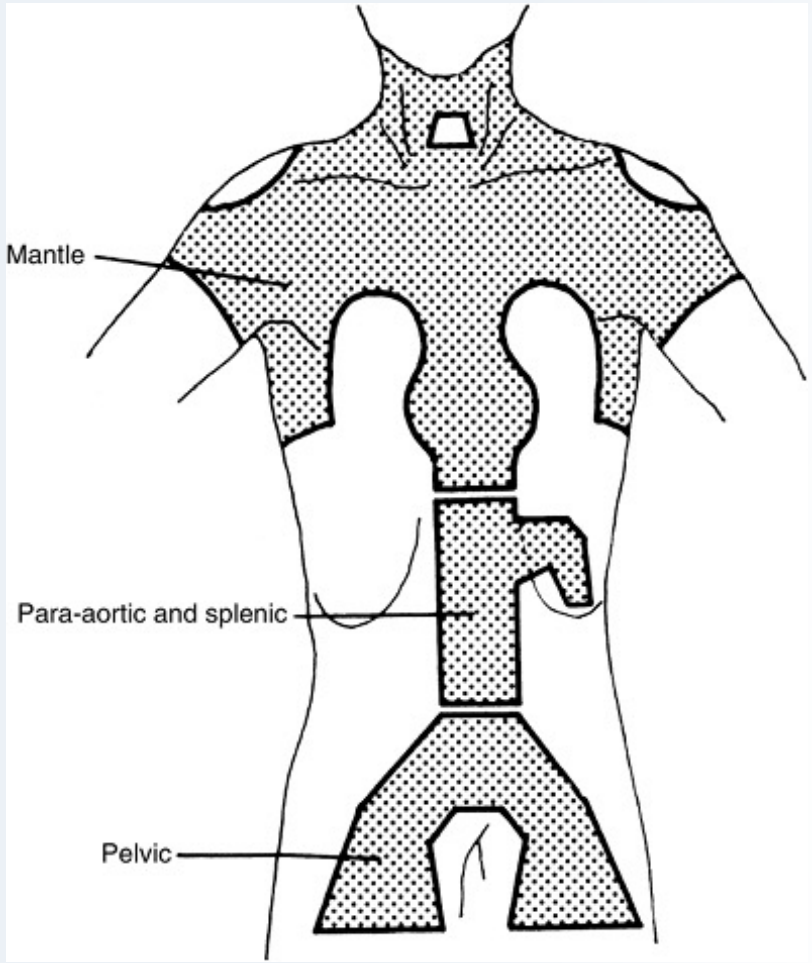
Disclosures

Employer: MD Anderson Cancer Center

Board Member: ASTRO (American Society of Radiation Oncology)

Research Support: Merck Inc.

Early Cures: Total Nodal RT



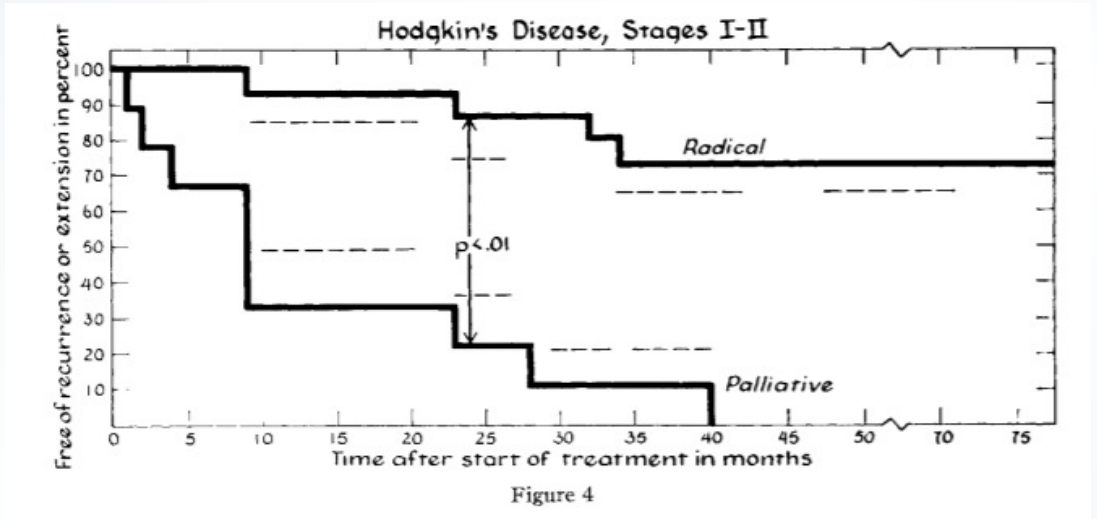


Figure 4

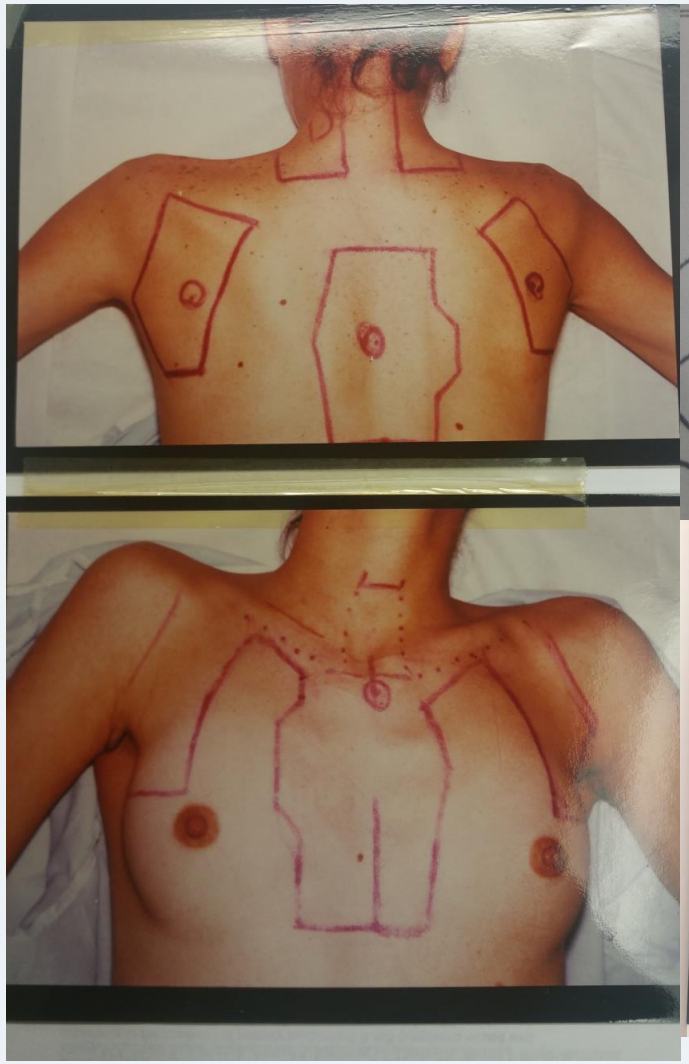
For disease presenting above the diaphragm, the mantle plus para-aortic and splenic ports would be regarded as **extended-field radiation therapy**

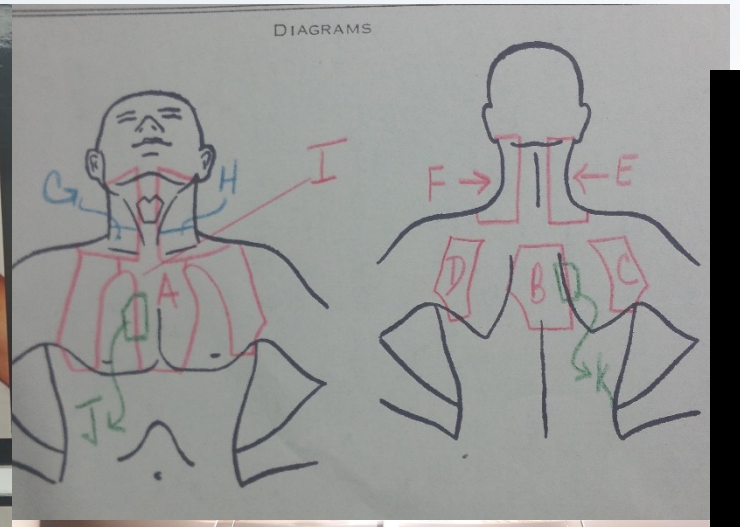
The use of all three ports would be considered **total nodal irradiation**

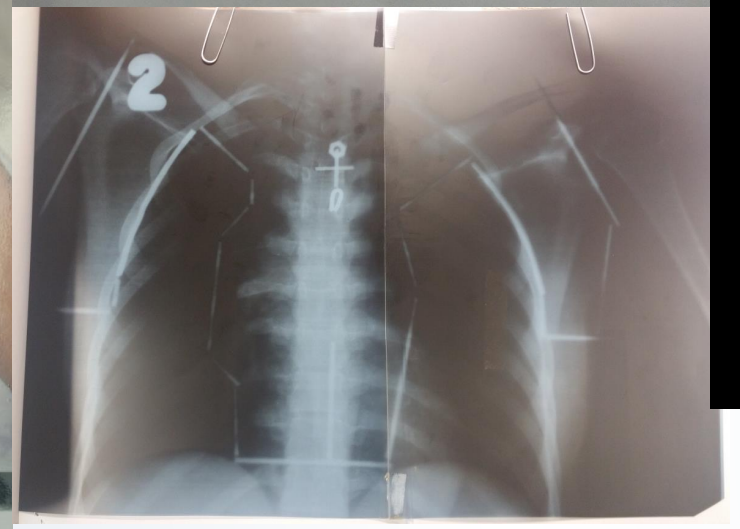
Salzman JR, Kaplan HS. Effect of prior splenectomy on hematologic tolerance during total lymphoid radiotherapy of patients with Hodgkin's disease. Cancer 1972;27:472.

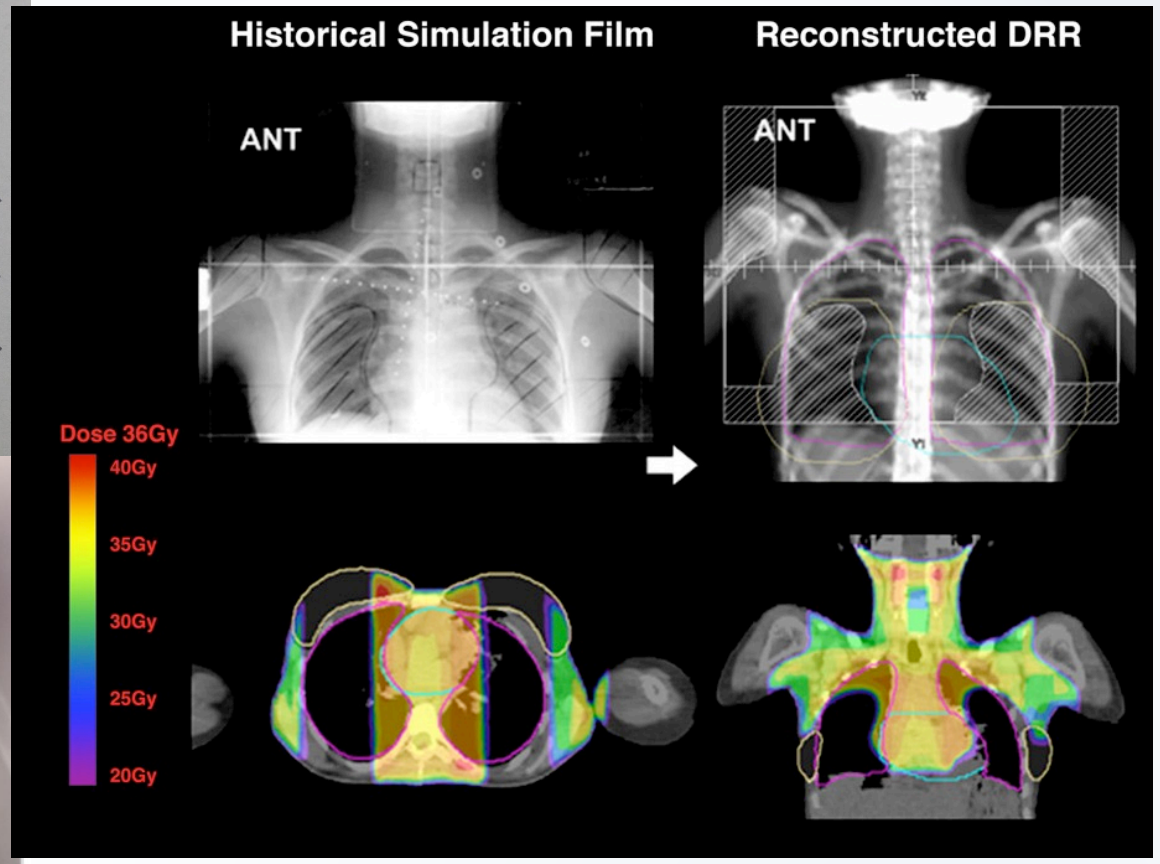
Kaplan, HS. The radical radiotherapy of regionally localized Hodgkin's disease. *Radiology*. 1962;78:553-561.

Mediastinal XRT in 1983









- Cobalt -60 radiation with 2D (xray) planning
- Heart and breasts in field for all patients

The consequences of outdated fields and techniques

Toxicity

hypothyroidism

pneumonitis

secondary malignancy

poor dentition

myocardial infarct

dry mouth

OVARIAN FAILURE

leukemia

HYPOGONADISM

valvular insufficiency

hypothyroidism

renal insufficiency

breast cancer

carotid plaques

pancytopenia

The NEW ENGLAND JOURNAL of MEDICINE

Second Cancer Risk Up to 40 Years after Treatment for Hodgkin's Lymphoma

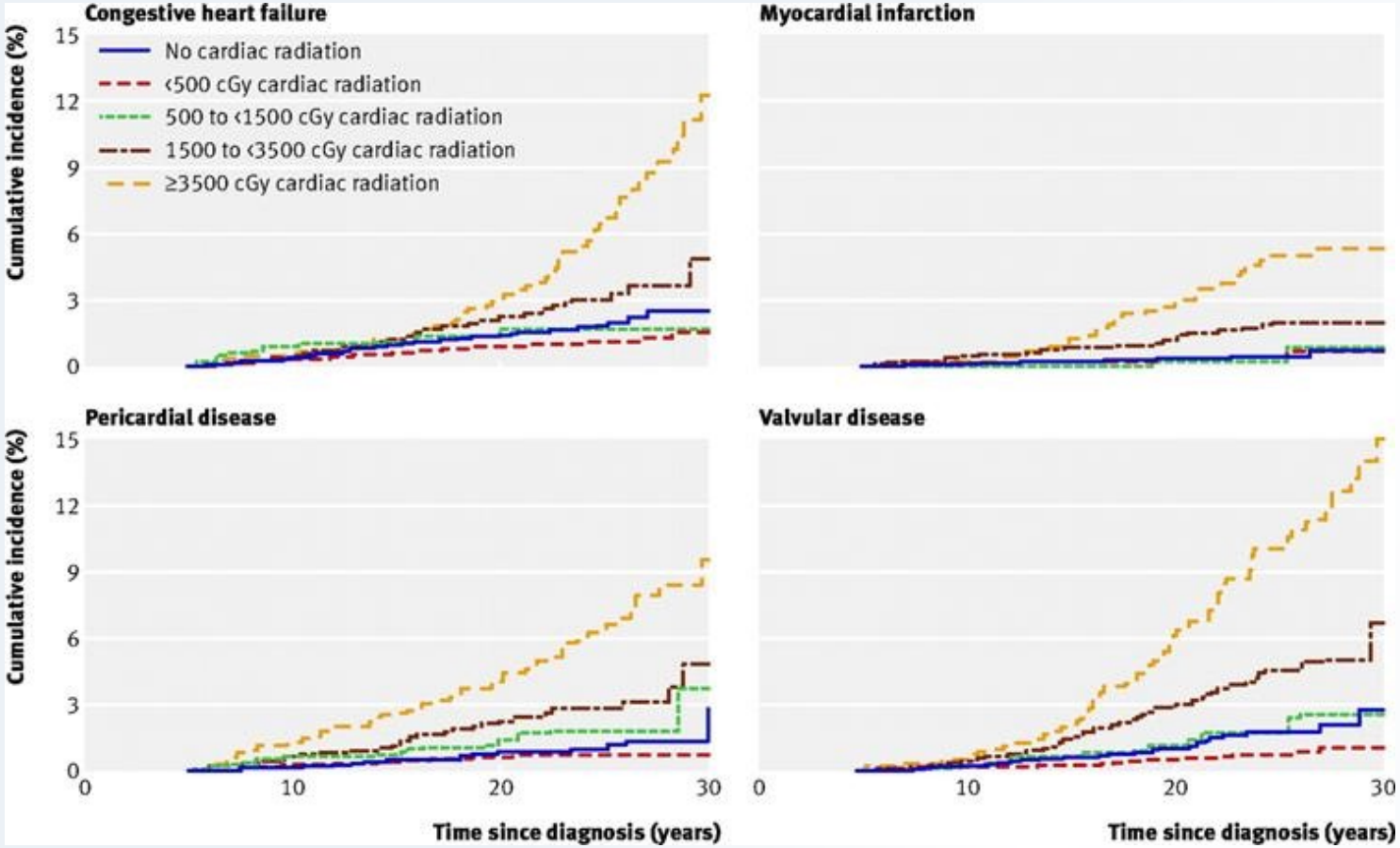
DECEMBER 24, 2015 VOL. 373 NO. 26

- 3,905 5+ yr HL survivors treated between 1965 -2000 in the Netherlands (at age 15-50)
- Median f/u of 19 years
- Cancer risk of survivors compared to cancer incidence in the general population
- 1055 2nd cancers diagnosed in 908 pts
- **Cumulative incidence of 2nd cancer in the study cohort at 40 years was 48.5% (compared with 19% in general population)**
  - Did not differ according to study period (1965-1976, 1977-1988, 1989-2000)

Second Cancer or Cancer Site	ICD Code	No. of Patients	Standardized Incidence Ratio (95% CI)	Absolute Excess Risk no./10,000 person-yr (95% CI)	30-Yr Cumulative Incidence (95% CI)
Any cancer, excluding MDS†	—	884	4.6 (4.3 to 4.9)	121.8 (111.8 to 132.4)	32.5 (30.4 to 34.6)
Any solid cancer	C00–C80	757	4.2 (3.9 to 4.5)	100.5 (91.3 to 110.2)	28.5 (26.4 to 30.5)
Lip, oral cavity, or pharynx	C00–C14	20	3.2 (2.0 to 4.9)	2.3 (1.0 to 4.1)	0.5 (0.3 to 0.9)
Gastrointestinal tract	C15–C26	184	4.6 (3.9 to 5.3)	24.0 (19.7 to 28.7)	7.0 (5.9 to 8.3)
Esophagus	C15	38	9.5 (6.7 to 13.1)	5.6 (3.8 to 8.0)	1.5 (1.0 to 2.1)
Stomach	C16	39	7.4 (5.3 to 10.1)	5.6 (3.7 to 8.0)	1.6 (1.1 to 2.3)
Colon	C18	42	2.9 (2.1 to 3.9)	4.6 (2.6 to 7.0)	1.5 (1.0 to 2.1)
Rectum or rectosigmoid junction	C19–C20	25	2.6 (1.7 to 3.9)	2.6 (1.1 to 4.5)	1.0 (0.6 to 1.5)
Pancreas	C25	23	5.7 (3.6 to 8.5)	3.1 (1.7 to 5.0)	1.0 (0.6 to 1.6)
Lower respiratory system	C33, C34, and C45	193	6.7 (5.8 to 7.8)	27.3 (22.9 to 32.1)	7.1 (6.0 to 8.3)
Lung or bronchus	C34	176	6.4 (5.5 to 7.4)	24.6 (20.5 to 29.3)	6.4 (5.4 to 7.6)
Mesothelioma	C45	17	15.1 (8.8 to 24.2)	2.6 (1.5 to 4.3)	0.6 (0.3 to 1.1)
Skin					
Melanoma	C43	34	2.8 (1.9 to 3.9)	3.6 (1.9 to 5.9)	1.1 (0.7 to 1.5)
Nonmelanoma	C44	26	3.4 (2.2 to 5.0)	3.1 (1.6 to 5.1)	0.7 (0.4 to 1.2)
Soft-tissue sarcoma	C47–C49	22	12.0 (7.5 to 18.2)	3.3 (2.0 to 5.2)	0.7 (0.4 to 1.1)
Female breast‡	C50	183	4.7 (4.0 to 5.4)	54.3 (44.7 to 65.0)	16.6 (14.1 to 19.2)
Female genital organ					
Any	C51–C58	34	2.8 (1.9 to 3.9)	3.6 (1.9 to 5.9)	2.9 (2.0 to 4.2)
Corpus uteri	C54	16	3.6 (2.1 to 5.8)	1.9 (0.8 to 3.6)	1.6 (0.9 to 2.6)
Male genital organ					
Any	C60–C63	22	1.1 (0.7 to 1.7)	0.3 (−1.0 to 2.2)	1.8 (1.1 to 2.8)
Prostate	C61	18	1.0 (0.6 to 1.7)	0.1 (−1.1 to 1.9)	1.4 (0.8 to 2.4)
Urinary tract	C64–C68	39	3.5 (2.5 to 4.7)	4.6 (2.7 to 7.0)	1.3 (0.9 to 2.0)
Kidney	C64	12	2.3 (1.2 to 4.1)	1.1 (0.2 to 2.6)	0.4 (0.2 to 0.8)
Urinary bladder	C67	22	4.1 (2.6 to 6.2)	2.8 (1.4 to 4.6)	0.6 (0.3 to 1.1)
Thyroid gland	C73	23	14.0 (8.9 to 21.0)	3.5 (2.1 to 5.5)	0.8 (0.5 to 1.2)
Primary site unknown or ill defined	C76–C80	29	4.9 (3.3 to 7.0)	3.8 (2.2 to 5.9)	1.3 (0.8 to 1.9)
Blood, bone marrow, or lymphatic system	C82–C96	147	10.4 (8.8 to 12.2)	22.2 (18.4 to 26.5)	5.0 (4.1 to 6.0)
Non-Hodgkin's lymphoma	C82–88	104	13.4 (10.9 to 16.2)	16.0 (12.9 to 19.7)	3.7 (3.0 to 4.6)
Leukemia	C91–96	41	9.5 (6.8 to 12.9)	6.1 (4.2 to 8.5)	1.3 (0.9 to 1.7)

Schaapveld M, Aleman BM et al, Second Cancer Risk Up to 40 Years after Treatment for Hodgkin's Lymphoma. NEJM. 2015 Dec 24;373(26):2499-511. PMID: 26699166.

Cardiac Toxicity



<u>30-year incidence of cardiac toxicity for entire cohort</u>

Congestive heart failure 4%
Myocardial infarction 1.3%
Pericardial disease 3%
Valvular disease 4 %

- Childhood Cancer Survivor Cohort of 14,358 5-yr survivors and 3899 siblings
- Cardiac radiation exposure of ≥ 15 Gy increased relative hazard of CHF, MI, pericardial disease and valvular abnormalities by 2-6 fold

Mulrooney Da et al, Cardiac outcomes in a cohort of adult survivors of childhood and adolescent cancer: Retrospective analysis of the Childhood Cancer Survivor Study cohort. BMJ 2009

Cardiac Risks in Childhood Cancer Survivors

- 24,215 5-year childhood cancer survivors (1970 -1999; 115 HL)
- Cardiac Disease: G3-G5 CAD, HF, valvular disease, pericardial disease, and arrhythmias
- 30-year cumulative incidence of cardiac disease: 4.8%
- **Factors associated with increased cardiac disease:**
  - Low to moderate RT doses (5.0 to 19.9 Gy) to large cardiac volumes (≥ 50% of heart) → RR 1.6
  - High RT doses (≥ 20 Gy) to small cardiac volumes (0.1% to 29.9%) → RR 2.4
  - Anthracycline ≥ 250 mg/m2 → RR 4.0 for 0-4 yrs; 2.4 for 4-13 yrs

Bates JE, Howell RM, Liu Q, Yasui Y, Mulrooney DA, Dhakal S, Smith SA, Leisenring WM, Indelicato DJ, Gibson TM, Armstrong GT, Oeffinger KC, Constine LS. Therapy-Related Cardiac Risk in Childhood Cancer Survivors: An Analysis of the Childhood Cancer Survivor Study. J Clin Oncol. 2019 May 1;37(13):1090-1101. PMID: 30860946; PMCID: PMC6494356.

Cumulative Incidence of Cardiac Disease based on Cardiac Constraints

Mean Heart Dose

Heart V20

$V5_{V20=0\%}$

Anthracycline Dose

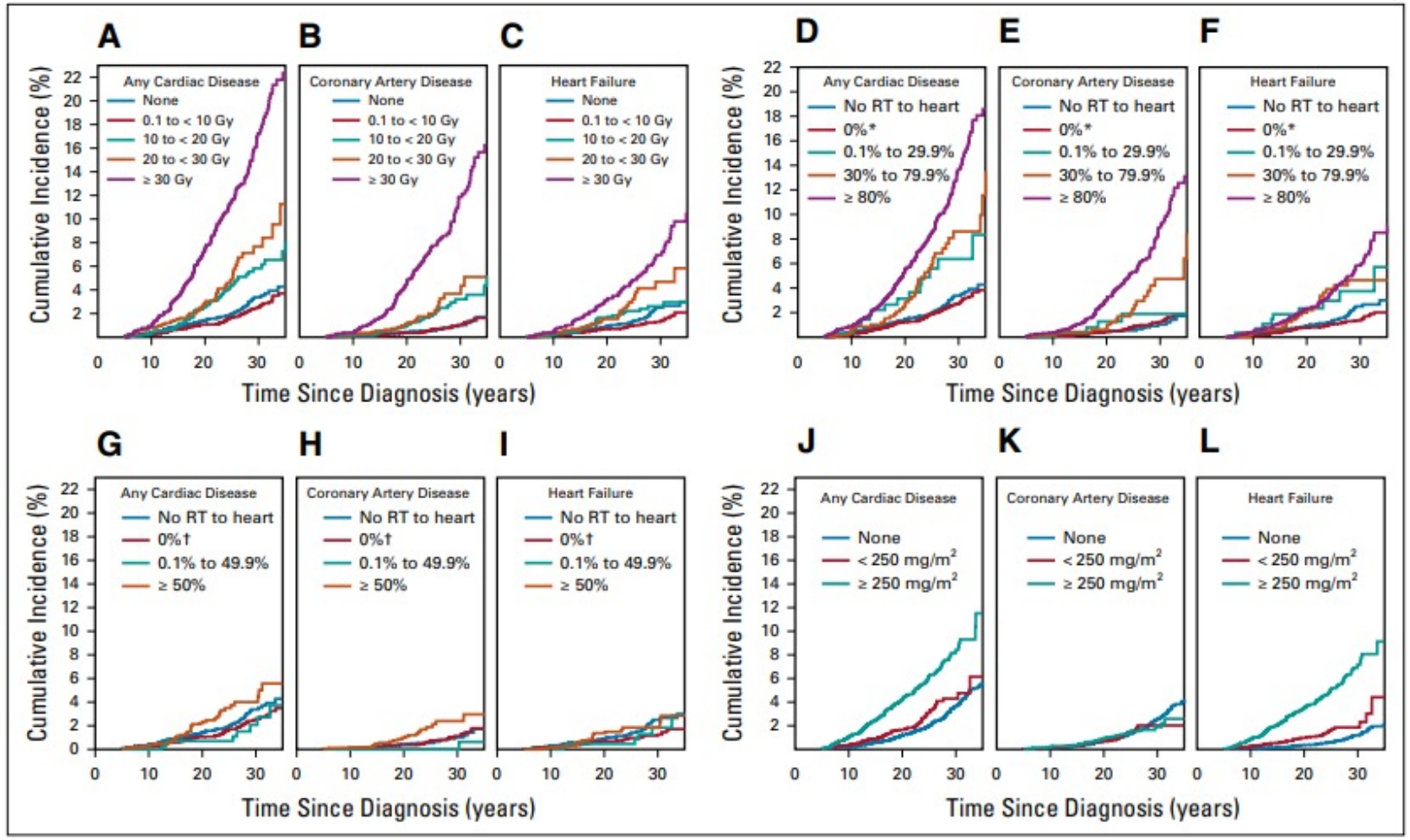
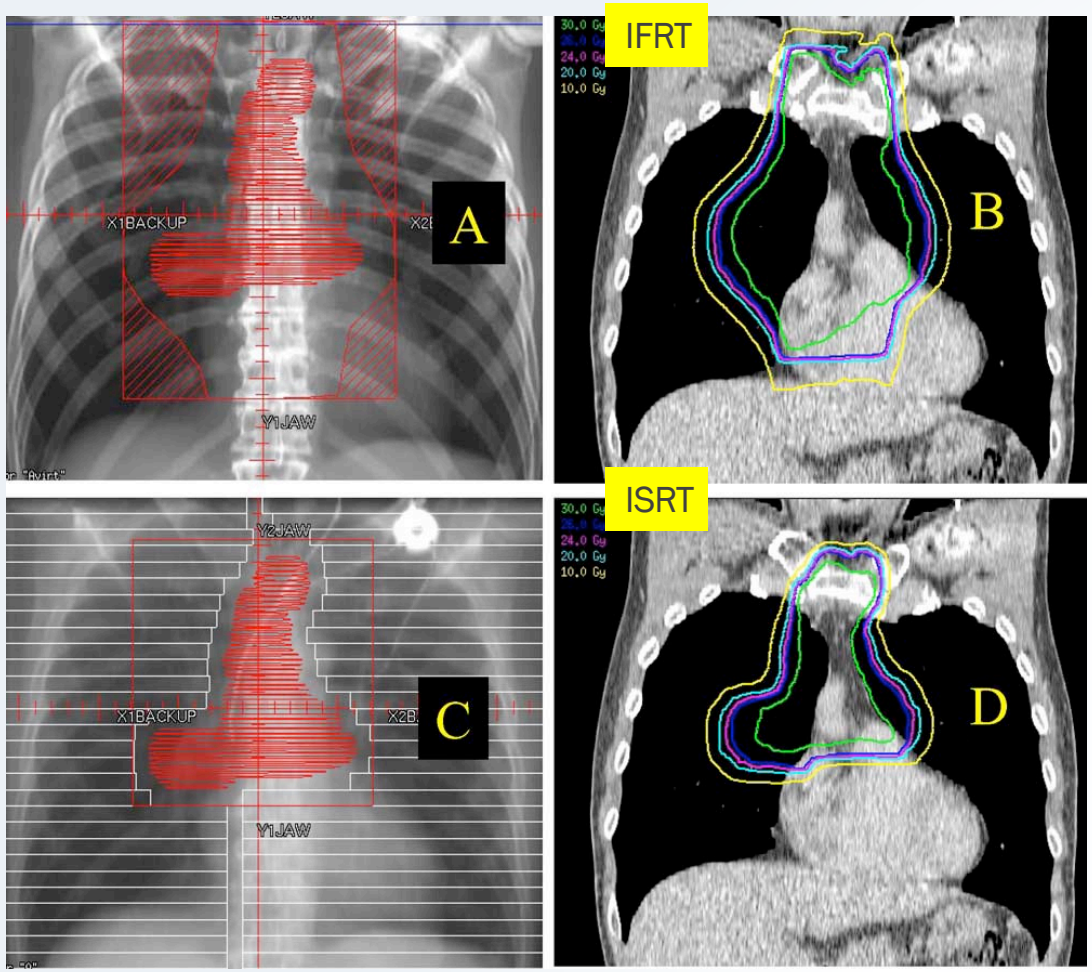


FIG 1. Cumulative incidence, based on (A-C) mean heart dose, (D-F) volume of heart (%) receiving radiotherapy (RT) greater than or equal to 20 Gy, and (G-I) voulme of heart (%) receiving RT greater than or equal to 5 Gy when maximum heart dose is less than 20 Gy. (J-L) Cumulative anthracycline dose. (*) 0% maximum radiation dose to the heart = 0.1 to 19.9 Gy. (†) 0% maximum radiation dose to the heart = 0.1 to 4.9 Gy.

Bates JE, Howell RM, Liu Q, Yasui Y, Mulrooney DA, Dhakal S, Smith SA, Leisenring WM, Indelicato DJ, Gibson TM, Armstrong GT, Oeffinger KC, Constine LS. Therapy-Related Cardiac Risk in Childhood Cancer Survivors: An Analysis of the Childhood Cancer Survivor Study. J Clin Oncol. 2019 May 1;37(13):1090-1101. PMID: 30860946; PMCID: PMC6494356.

The Evolving Field Size: Involved Site RT



Involved Site Radiation Therapy:

Only treat pre-chemotherapy sites of disease involvement with appropriate set up margin

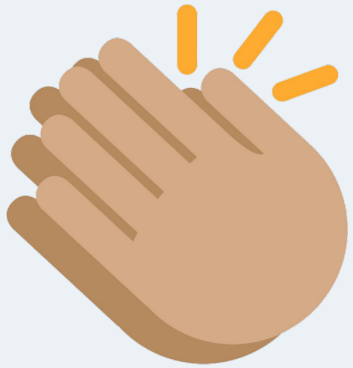
Post-chemotherapy delineation take into account disease response

Specht L, Yahalom J, Illidge T, Berthelsen AK, Constine LS, Eich HT, Girinsky T, Hoppe RT, Mauch P, Mikhaeel NG, Ng A; ILROG. Modern radiation therapy for Hodgkin lymphoma: field and dose guidelines from the international lymphoma radiation oncology group (ILROG). *Int J Radiat Oncol Biol Phys*. 2014

Yahalom J & Mauch P, The involved field is back: issues in delineating the radiation field in Hodgkin's Disease, *Annals Oncol* 2002

Hematologic Malignancy RT Dose Constraints: NCCN

Thank You!!
Richard Hoppe
Bouthaina Dabaja
Christopher Kelsey
Rachel Rabinovitch
Randa Tao
Joachim Yahalom
Joanna Yang



OAR		Dose Recommendation (1.5–2 Gy/fraction)	Toxicity
Head and Neck	Parotid glands	Ipsilateral: Mean <11 Gy (recommended); <24 Gy (acceptable) Contralateral: as low as reasonably achievable (ALARA)	Xerostomia[15,16]
	Submandibular glands	Ipsilateral: Mean <11 Gy (recommended); <24 Gy (acceptable) Contralateral: ALARA	Xerostomia[17]
	Oral cavity (surrogate for minor salivary glands)	Mean <11 Gy	Xerostomia, dysgeusia, oral mucositis[17]
	Thyroid	V25 Gy <63.5% Minimize V30 Gy	Hypothyroidism[18]
	Lacrimal glands	V20 Gy <80%	Dry eye syndrome[19]
	Larynx/Pharyngeal constrictors	Mean <25 Gy	Laryngeal edema, dysphagia[20]
	Carotids	Ipsilateral: Avoid hotspots Contralateral: ALARA	Carotid artery atherosclerosis
Thorax	Heart[c]	Mean <8 Gy (recommended) Mean <15 Gy (acceptable); ALARA given increased risk with even lower doses	Major adverse cardiac events[21-24]
	Aortic and mitral valves	Dmax <25 Gy	Valvular heart disease[22,25,26]
	Tricuspid and pulmonic valves	Dmax <30 Gy	
	Left ventricle	Mean <8 Gy (recommended) Mean <15 Gy (acceptable)	Heart failure[22,27]
	Coronary vessels including the left main, left anterior descending (LAD), left circumflex (LCx), and right coronary artery (RCA)[c]	LAD V15 Gy <10%[c] LCx V15 Gy <14% Coronary vessels (total)- Mean <7 Gy Minimize the maximum dose to individual coronary arteries	Major adverse cardiac events[28]
	Lungs	Mean dose <13.5 Gy V20 <20% (recommended); <30 Gy (acceptable) V5 <55%	Pneumonitis[29-31]

*NCCN Guidelines Version 3.2024 Hodgkin Lymphoma (Age ≥ 18 years

Hematologic Malignancy RT Dose Constraints: NCCN

PRINCIPLES OF RADIATION THERAPY

RT DOSE CONSTRAINT GUIDELINES FOR LYMPHOMA[b]

SECONDARY MALIGNANCIES[e]

OAR	Dose Recommendation (1.8–2 Gy/fraction)	Secondary Malignancy
Breast	Minimize volume >4 Gy (ideally <10%)	Breast cancer (adenocarcinoma)[51]
Colon	Minimize volume >10 Gy	Colon cancer[52]
Lung	Minimize volume >9 Gy	Lung cancer[53]
Esophagus	Minimize volume >30 Gy	Esophageal cancer[54]
Stomach	Minimize volume >25 Gy	Gastric cancer[55]
Pancreas	Minimize volume >5–10 Gy	Pancreatic cancer[56]

Matched case control study 3817 female 1 yr HL survivors diagnosed ≤ 30 years between 1965 – 1994 matched to population based cancer registries

Breast cancer occurred in 105 pts with HL matched to 266 HL pts without breast cancer

RT dose of ≥ 4 Gy → 3.2 fold increased risk

RT dose ≥ 40 Gy → 8 fold increased risk

Travis LB, Hill DA, Dores GM, et al. Breast Cancer Following Radiotherapy and Chemotherapy Among Young Women With Hodgkin Disease. JAMA. 2003;290(4):465–475.

*NCCN Guidelines Version 3.2024 Hodgkin Lymphoma (Age ≥ 18 years

Who Benefits from Radiation Therapy?

	Yes	No	In Select Cases
Early Stage Favorable			
Early Stage Unfavorable			
Relapsed and Refractory			

Early Stage HL: Defining "Favorable" Disease

UNFAVORABLE RISK FACTORS

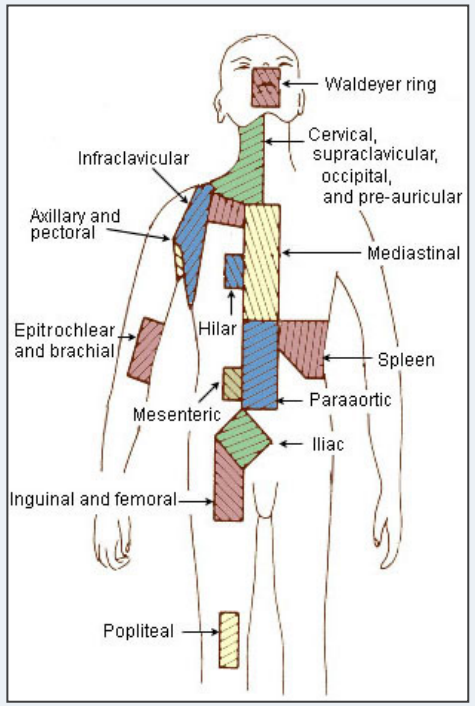
Unfavorable Risk Factors for Stage I–II Hodgkin Lymphoma

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 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

Ann Arbor Staging Regions



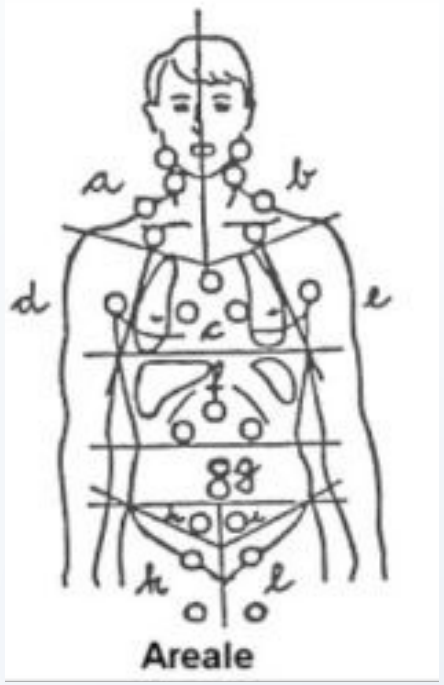
UNFAVORABLE RISK FACTORS

Definitions of Lymph Node Regions*

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

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

GHSG Areas



From NCCN Guidelines, Hodgkin Lymphoma, Version 3.2024 – 3/18/2024

General treatment of limited stage classical HL

Early Stage Favorable (GHSG, UK RAPID, EORTC H10F) with complete response to ABVD (Deauville 1-3)

ABVD x 2 cycles followed by ISRT to 20 Gy (GHSG HD16)

ABVD x 3 cycles followed by ISRT to 30 Gy (UK RAPID, EORTC H10F)

ABVD x 4 cycles alone (CALGB 50604)

Early Stage Unfavorable with complete response (including those with bulky disease)

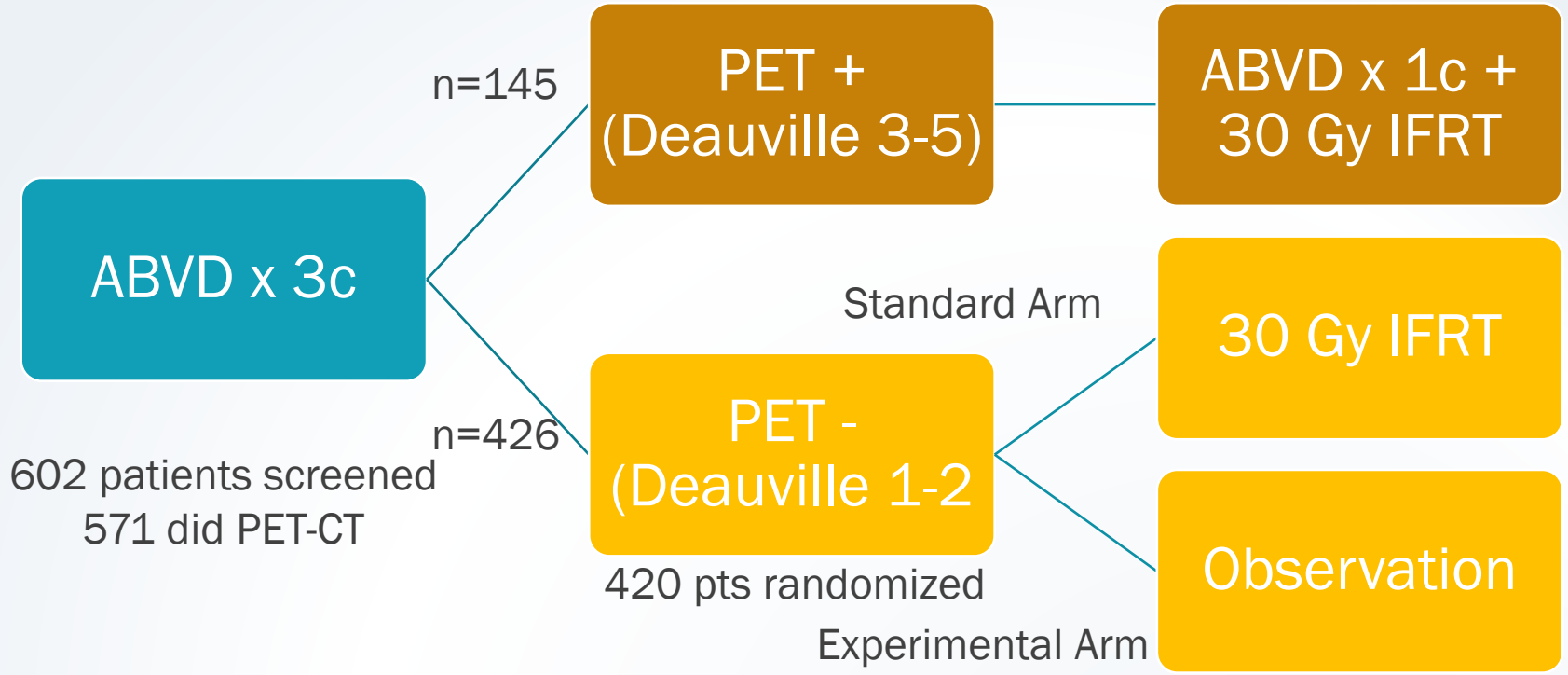
ABVD x 4 cycles + 30 Gy (EORTC H10U)

ABVD x 2 cycles followed by AVD + 4 cycles (RATHL)

*NCCN includes B symptoms with unfavorable

UK RAPID: ABVD x 3 vs ABVD x 3 + 30 Gy

- Randomized non-inferiority Trial
- 602 pts (age 16-75)
- Stage IA or IIA (not PET staged in most cases)
- Non-bulky (<33% max mediastinal diameter)
- Not limited by # nodal sites
- PET Neg: Deauville 1-2
- 30 Gy IFRT
- **Δ PFS: 3-6%**

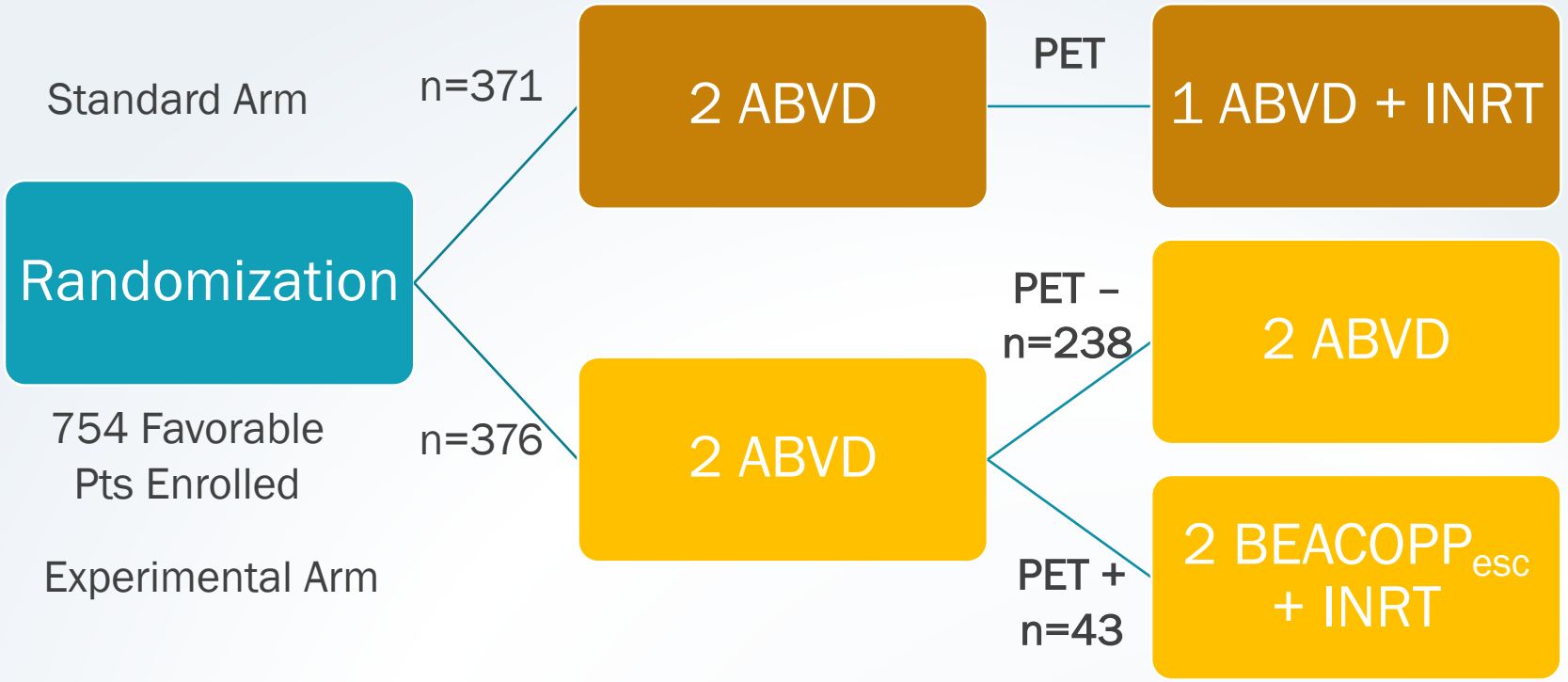


	Intent –to-treat Analysis			Per Protocol Analysis		
	PET-, RT	PET-, no RT	P value	Pet-, RT	PET-, no RT	P value
3-year PFS	93.8%	90.7%	0.16	97%	90.7%	0.02

Radford J, Illidge T, et al, Results of a trial of PET-directed therapy for early-stage Hodgkin's lymphoma. N Engl J Med. 2015 Apr 23;372(17):1598-607. PMID: 25901426.

EORTC H10F: ABVD x 4 vs ABVD x 3 + 30 Gy RT

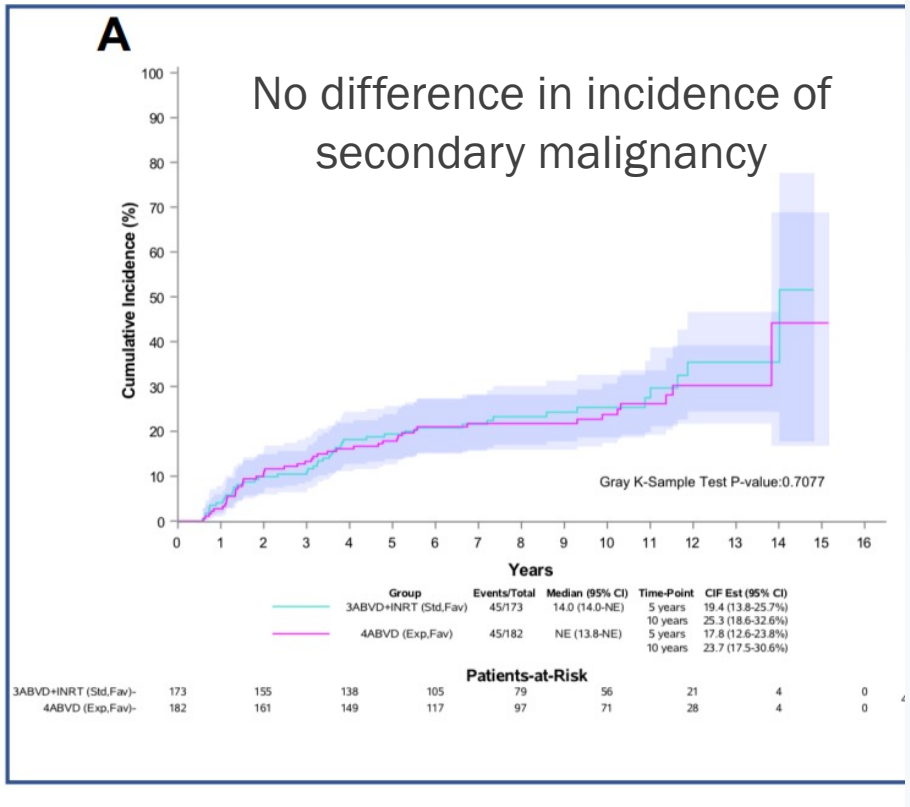
- Randomized non-inferiority Trial
- 754 pts (age 15-70)
- Clinical stage I-II EORTC Fav Non-bulky (MTR <35%)
- 1-3 nodal areas
- PET Neg by IHP: i.e. Deauville 1-2
- 30 Gy INRT
- Median f/u of 5 & 9.5 yrs
- **Δ PFS = 12-14%**



	Intent –to-treat Analysis			Per Protocol Analysis		
	PET-, RT	PET-, no RT	P value	Pet-, RT	PET-, no RT	P value
5-year PFS	99.0%	87.1%	NR (HR 15.8)	NR	NR	
10-year PFS				98.8%	85.4%	<0.0001

André MPE, Girinsky T et al, Early Positron Emission Tomography Response-Adapted Treatment in Stage I and II Hodgkin Lymphoma: Final Results of the Randomized EORTC/LYSA/FIL H10 Trial. J Clin Oncol. 2017 Jun 1;35(16):1786-1794. PMID: 28291393.
Federico M, Fortpied C et al Long-Term Follow-Up of the Response-Adapted Intergroup EORTC/LYSA/FIL H10 Trial for Localized Hodgkin Lymphoma. J Clin Oncol. 2024 Jan 1;42(1):19-25 PMID: 37967311.

EORTC H10: Long Term Follow Up



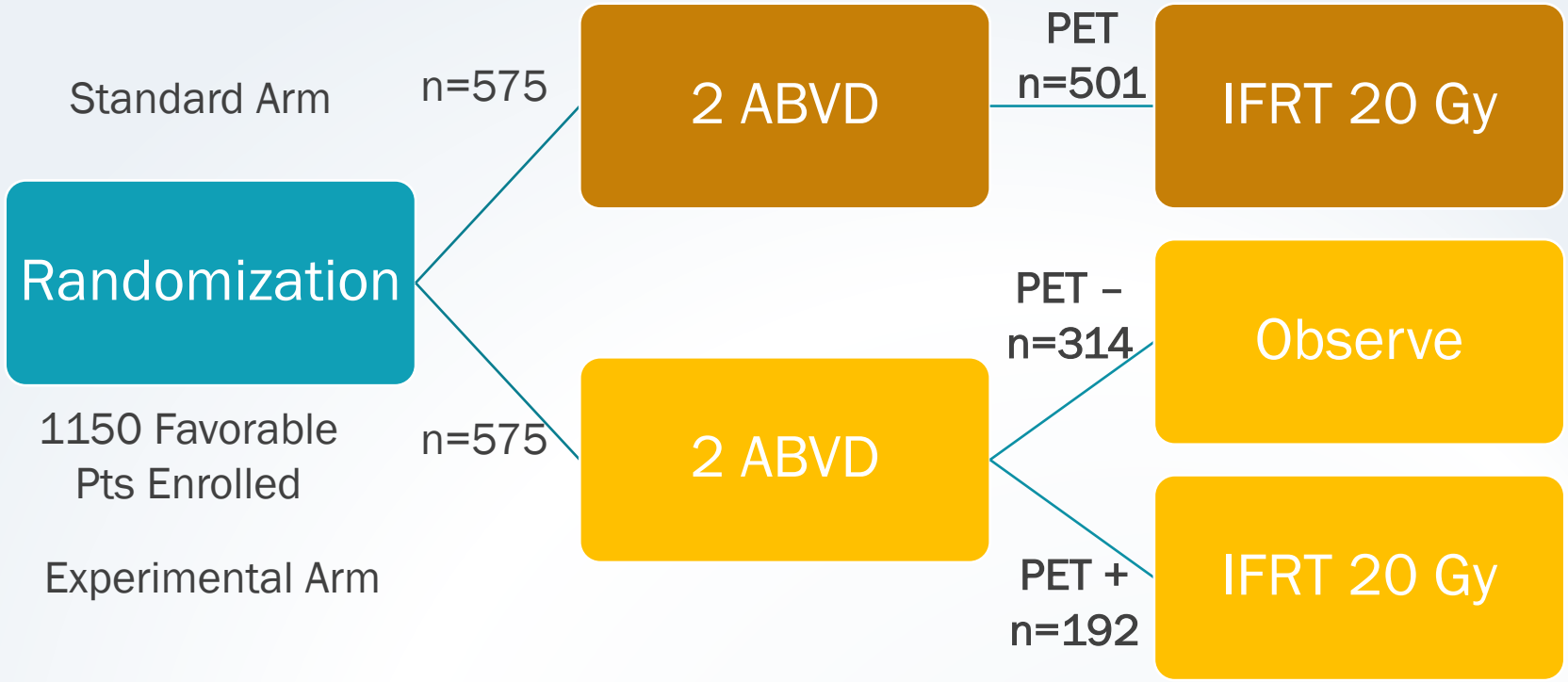
e-PET Negative

	Favorable Standard (3ABVD+INRT) n=173	Favorable Experimental (4ABVD) n=182	Unfavorable Standard (4ABVD+INRT) n=205	Unfavorable Experimental (6ABVD) n=214
Any long-term second malignancy	7 (4.0)	7 (3.8)	14 (6.8)	14 (6.5)
Non-hematologic SM				
Colo-rectal	0 (0.0)	0 (0.0)	0 (0.0)	1 (7.1)
Lung	0 (0.0)	0 (0.0)	1 (7.1)	0 (0.0)
Breast	1 (14.3)	0 (0.0)	4 (28.6)	5 (35.7)
Prostate	1 (14.3)	0 (0.0)	0 (0.0)	0 (0.0)
Stomach	0 (0.0)	0 (0.0)	0 (0.0)	1 (7.1)
Bone sarcoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Kidney	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Thyroid	1 (14.3)	0 (0.0)	0 (0.0)	0 (0.0)
Skin	1 (14.3)	2 (28.6)	3 (21.4)	1 (7.1)
Hematologic SM				
Non-Hodgkin Lymphoma	0 (0.0)	2 (28.6)	3 (21.4)	3 (21.4)
Myeloproliferative disease	0 (0.0)	0 (0.0)	1 (7.1)	1 (7.1)
Leukemia/MDS	1 (14.3)	0 (0.0)	1 (7.1)	1 (7.1)
Other sites	2 (28.6)	3 (42.8)	3 (21.4)	5 (35.7)

Federico M, Fortpied C et al Long-Term Follow-Up of the Response-Adapted Intergroup EORTC/LYSA/FIL H10 Trial for Localized Hodgkin Lymphoma. J Clin Oncol. 2024 Jan 1;42(1):19-25 PMID: 37967311.

GHSG HD16: ABVD x 2 vs ABVD x 2 + 20 Gy

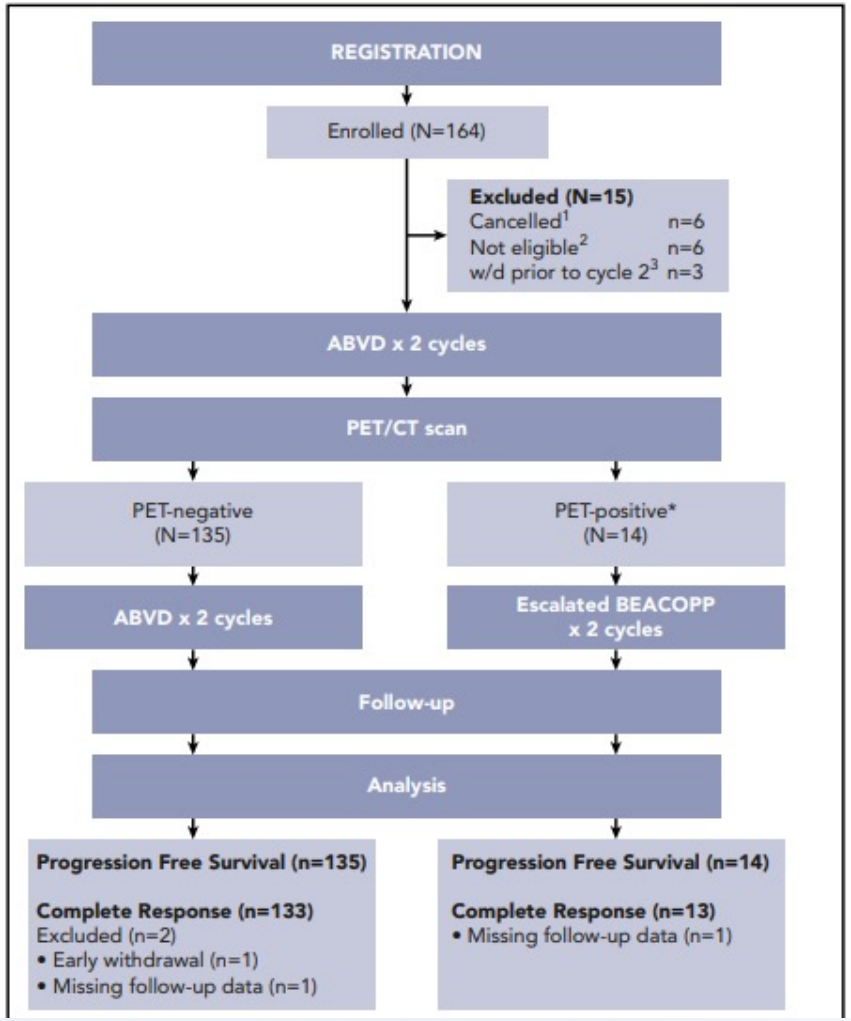
- Randomized, non-inferiority trial
- 1150 pts (age 18-75)
- Clinical stage I-II favorable by GHSG criteria (non-bulky, 1-2 nodal areas)
- PET Negative: Deauville 1-2
- 20 Gy IFRT
- Median f/u 47 months
- **ΔPFS = 7%**



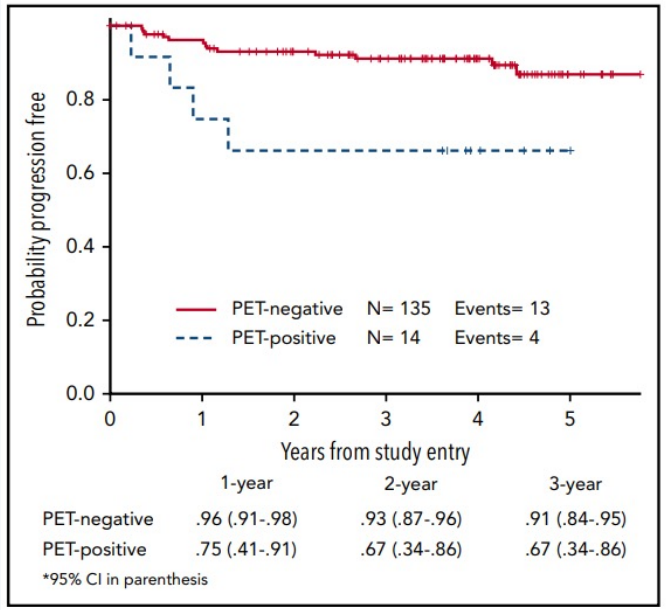
	Intent –to-treat Analysis			Per Protocol Analysis		
	PET-, RT	PET-, no RT	P value	Pet-, RT	PET-, no RT	P value
5-year PFS				93.4%	86.1%	0.040

Fuchs M, Goergen H, et al, Positron Emission Tomography-Guided Treatment in Early-Stage Favorable Hodgkin Lymphoma: Final Results of the International, Randomized Phase III HD16 Trial by the German Hodgkin Study Group. J Clin Oncol. 2019 Nov 1;37(31):2835-2845. PMID: 31498753.
Fuchs M, Jacob AS et al. Follow-up of the GHSG HD16 trial of PET-guided treatment in early-stage favorable Hodgkin lymphoma. Leukemia. 2024 Jan;38(1):160-167. PMID: 37845285;

CALGB 50604:Risk adapted treatment of non-bulky early-stage HL based on interim PET



Characteristic	N (%)
ESR	
<50	108 (66)
50+	41 (25)
Not reported/unknown	15 (9)
GHSG*	
Favorable	60 (40)
Unfavorable	89 (60)
EORTC/LYSA/FIL*	
Favorable	88 (59)
Unfavorable	61 (41)



	1-year	2-year	3-year
PET-negative	.96 (.91-.98)	.93 (.87-.96)	.91 (.84-.95)
PET-positive	.75 (.41-.91)	.67 (.34-.86)	.67 (.34-.86)

*95% CI in parenthesis

- Not randomized
- Negative PET= Deauville 1-3
- Median f/u of 3.8 years
- 3-year PFS interim pet negative = 91%
- 3-year PFS interim PET positive 66%
- "Our interpretation of CALGB 50604 is that the 91% PFS is acceptable for ABVD without RT for interim PET2 patients in view of the potential late risks of IFRT or INRT."

Straus DJ, et al, CALGB 50604: risk-adapted treatment of nonbulky early-stage Hodgkin lymphoma based on interim PET. Blood. 2018 Sep 6;132(10):1013-1021. PMID: 30049811.

Randomized PET Adapted Trials in Early Stage Favorable Hodgkin Lymphoma

Study	Patient no.	Inclusion	PET criteria	Timing of PET	Chemotherapy post interim PET (experimental arm)	RT field and dose	PET negative rate	Primary endpoint	Outcome		
									No RT	RT	PFS difference
UK RAPID	602	Stage I or II without B-symptoms or bulk	Deauville 1-2	ABVD × 3	None	IFRT 30 Gy	75%	3-y PFS	90.8%	97.1%	6.3%
H10	754	Early favorable by EORCT criteria[12]	IHP	ABVD × 2	ABVD x 2	INRT 30 Gy ± 6 Gy	87%	5-y PFS	87.1%	99.0%	11.9%
HD16	1150	Early favorable by GHSG criteria[15]	IHP	ABVD × 2	None	IFRT 20 Gy	66%	5-y PFS	86.1%	93.4%	7.3%

Abbreviations: ABVD = adriamycin, bleomycin, vinblastine and dacarbazine; IFRT = Involved field radiation therapy; IHP = International Harmonization Project criteria; INRT = involved nodal radiation therapy; PET = Positron Emission Tomography; PFS = progression free survival; RAPID = Randomized Phase III Trial to Determine the Role of FDG–PET Imaging in Clinical Stages IA/IIA Hodgkin's Disease; RT = radiation therapy.

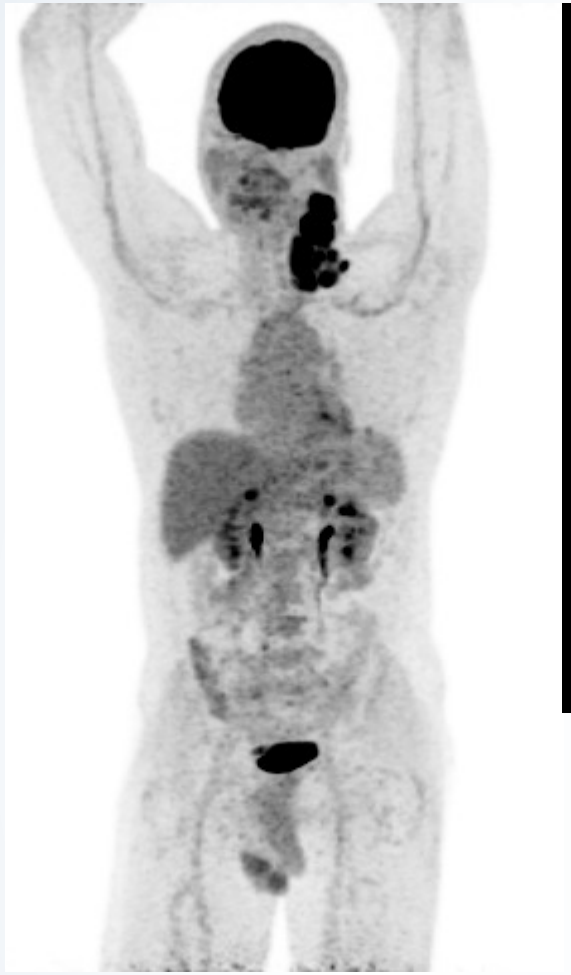
Bakst RL, Campbell BA, Pinnix CC. PET Guided Therapy for Early Stage Hodgkin Lymphoma: Are We Positive About a Negative Interim Scan? Int J Radiat Oncol Biol Phys. 2020 May 1;107(1):12-17. PMID: 32142868.

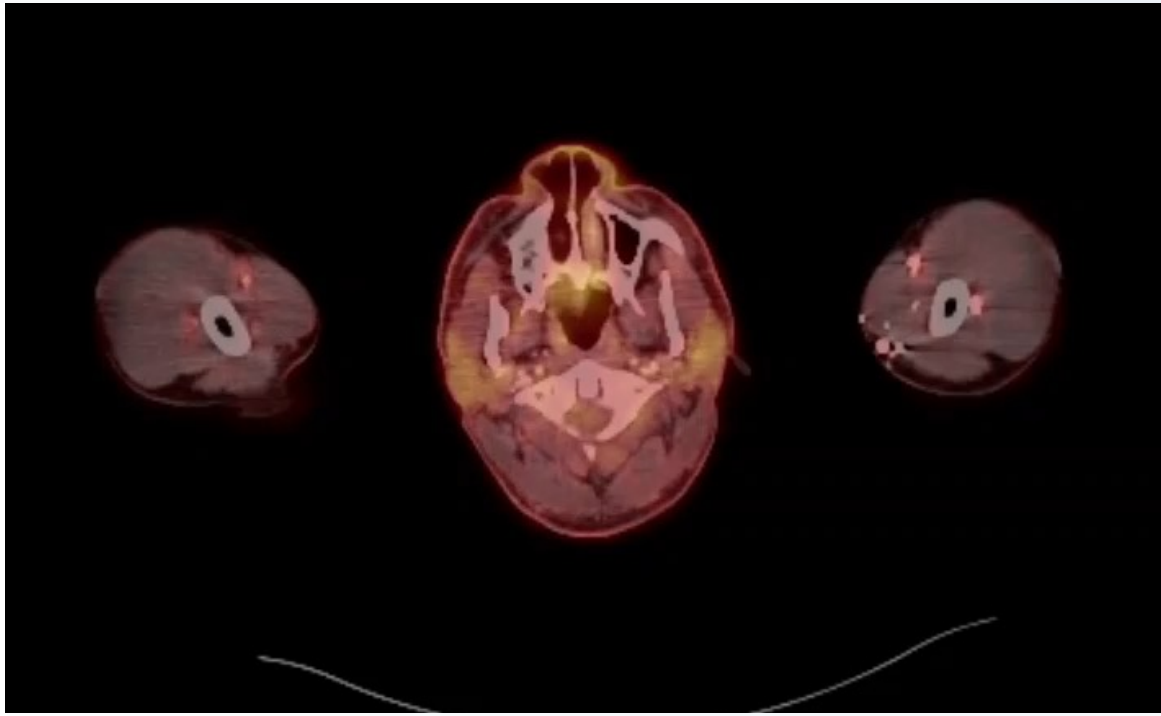
Take Home Message Early Stage Favorable HL

- The RAPID, EORTC H10F and GHSG HD16 trials showed a statistically significant loss in disease control for stage I/II favorable HL patients who received 2-4 cycles of ABVD alone and achieved a negative PET with differences in 3 Yr PFS of 3.8% (ITT 6.3% RAPID), 5 Yr PFS of 11.9% (H10F) and 5 Yr PFS of 7.3% (GHSG HD16)
- If the primary goal of treatment is to achieve the greatest disease control then utilization of a PET-adapted strategy to omit RT is not supported by randomized data
- However outcomes for limited stage favorable patients are generally good and omission of RT could be considered if the potential long term risks of therapy may outweigh benefits in disease control

Case: Early Stage Favorable HL

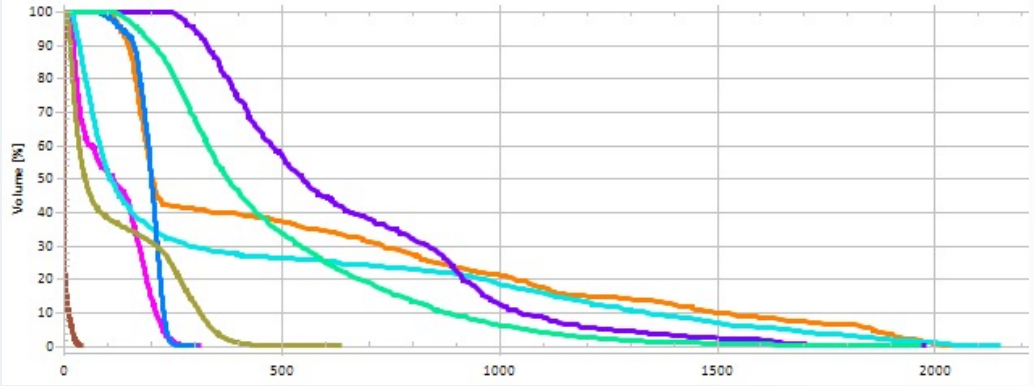
- 38 year old male stage IIA HL (cervical, SCV, ICV neck)
- ESR 42, no B symptoms
- 5PS of 2 after ABVD x 2

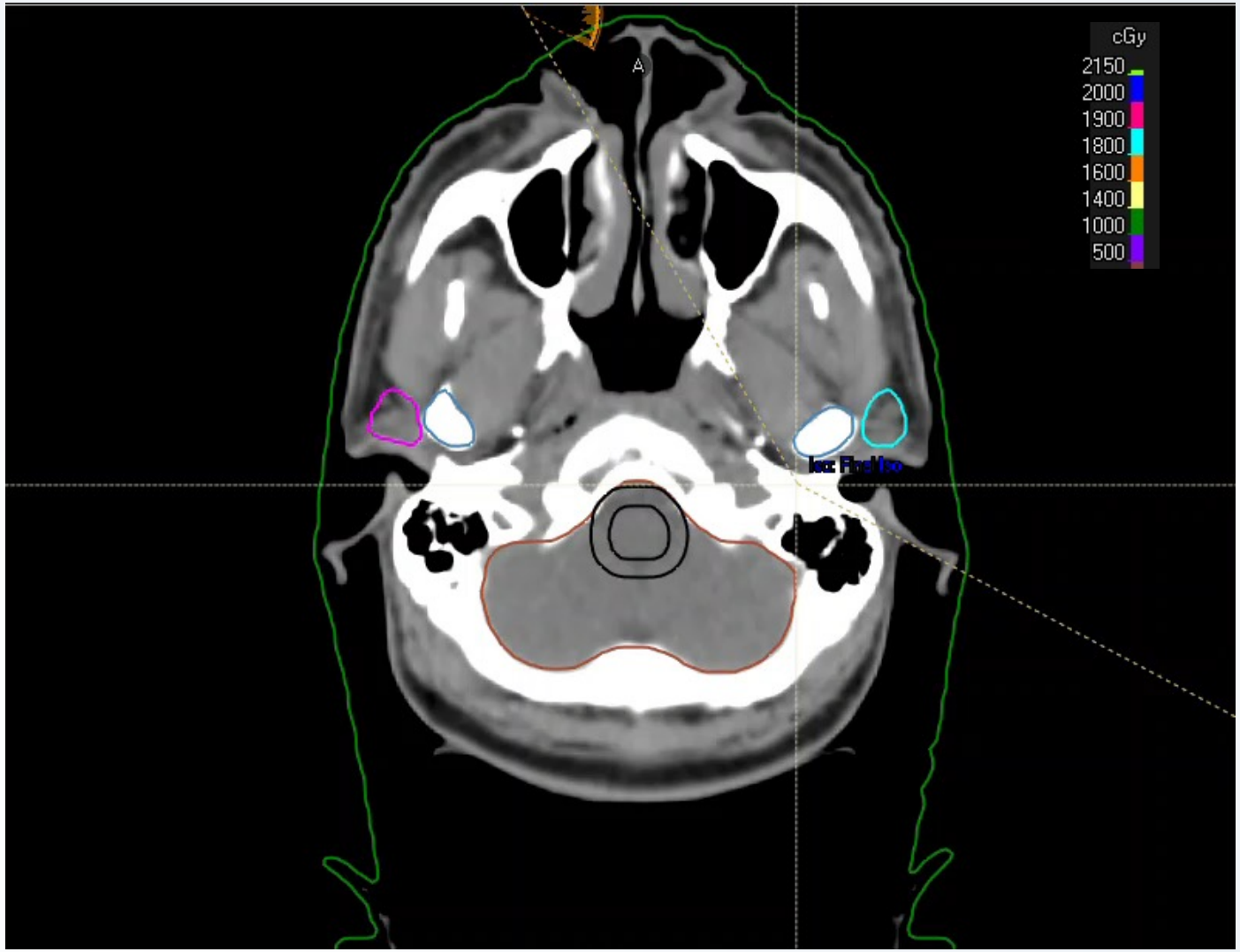




Case: Early Stage Favorable HL

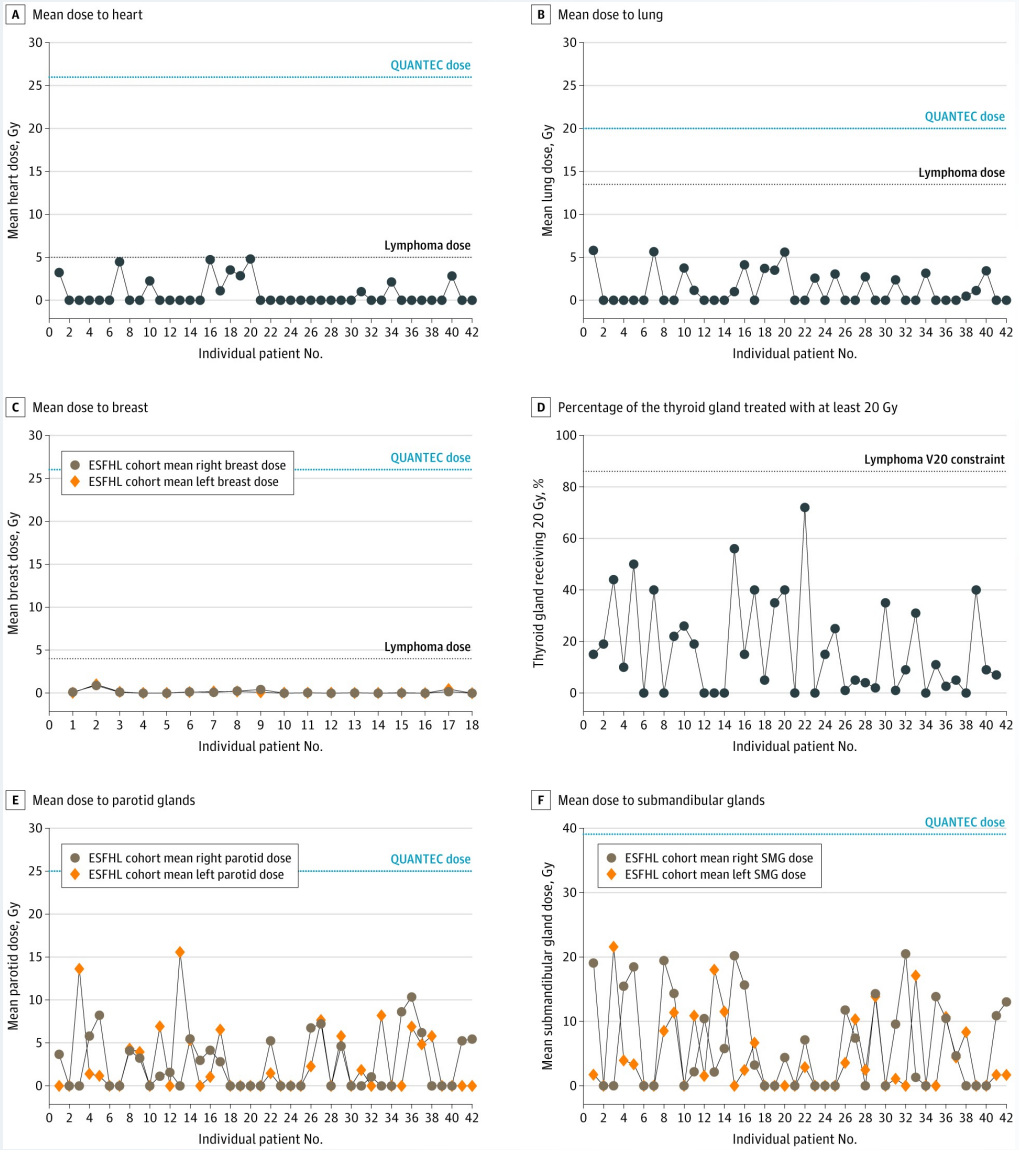
ROI	Dose [cGy] Average
Brain	3
Cavity_Oral	122
Glnd_Submand_L	652
Glnd_Submand_R	197
Larynx	473
Parotid_L	405
Parotid_R	112
Thyroid	555

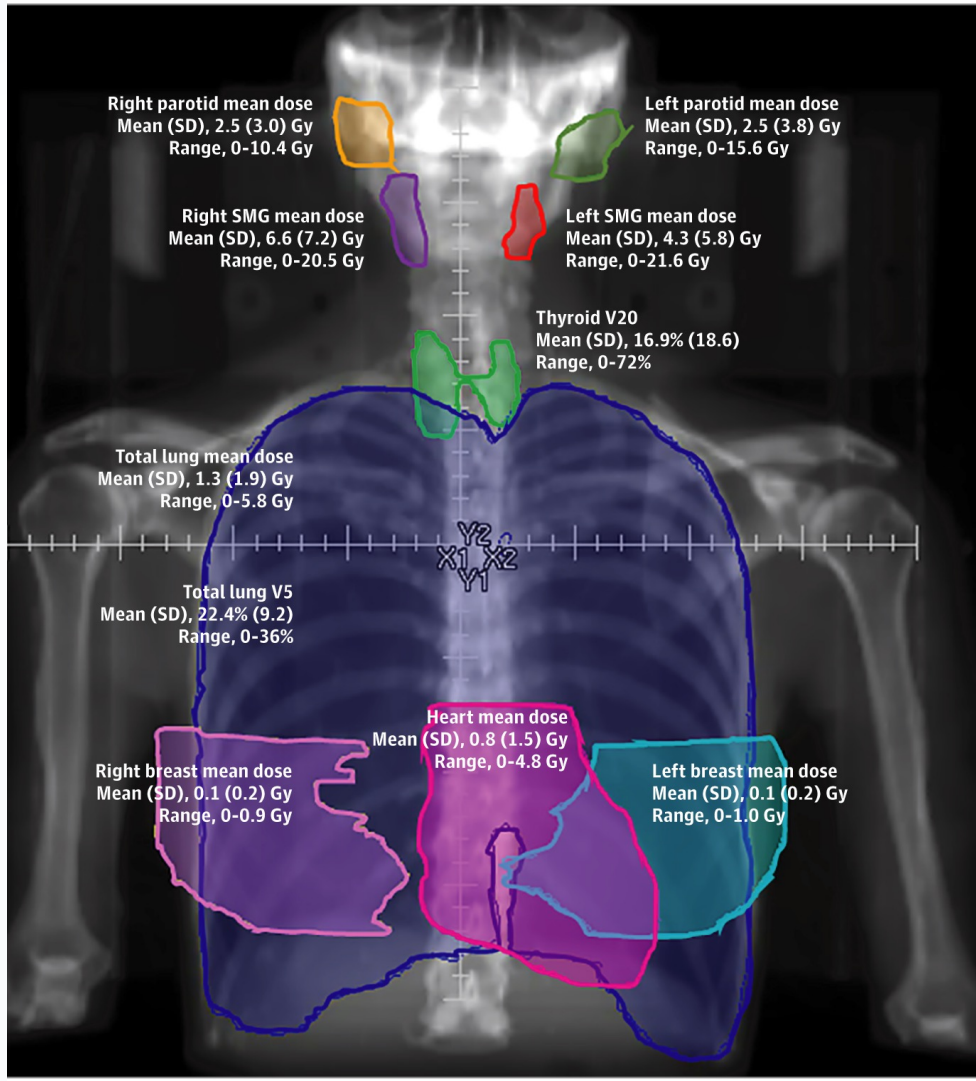




Modern RT for Early Stage Favorable HL

- Case series of 42 patients with ESFHL (GHSG criteria)
- 33% mediastinal involvement
- Mean heart dose < 5 Gy in all patients (mean 0.8 Gy)
- Mean breast dose < 1 Gy in all patients
- 3-year PFS 91.2%





Pinnix CC, Gunther JR, Fang P, Bankston ME, Milgrom SA, Boyce D, Lee HJ, Nair R, Steiner R, Strati P, Ahmed S, Iyer SP, Westin J, Parmar S, Rodriguez MA, Nastoupil L, Neelapu S, Flowers C, Dabaja BS. Assessment of Radiation Doses Delivered to Organs at Risk Among Patients With Early-Stage Favorable Hodgkin Lymphoma Treated With Contemporary Radiation Therapy. JAMA Netw Open. 2020 Sep 1;3(9):PMID: 32990738.

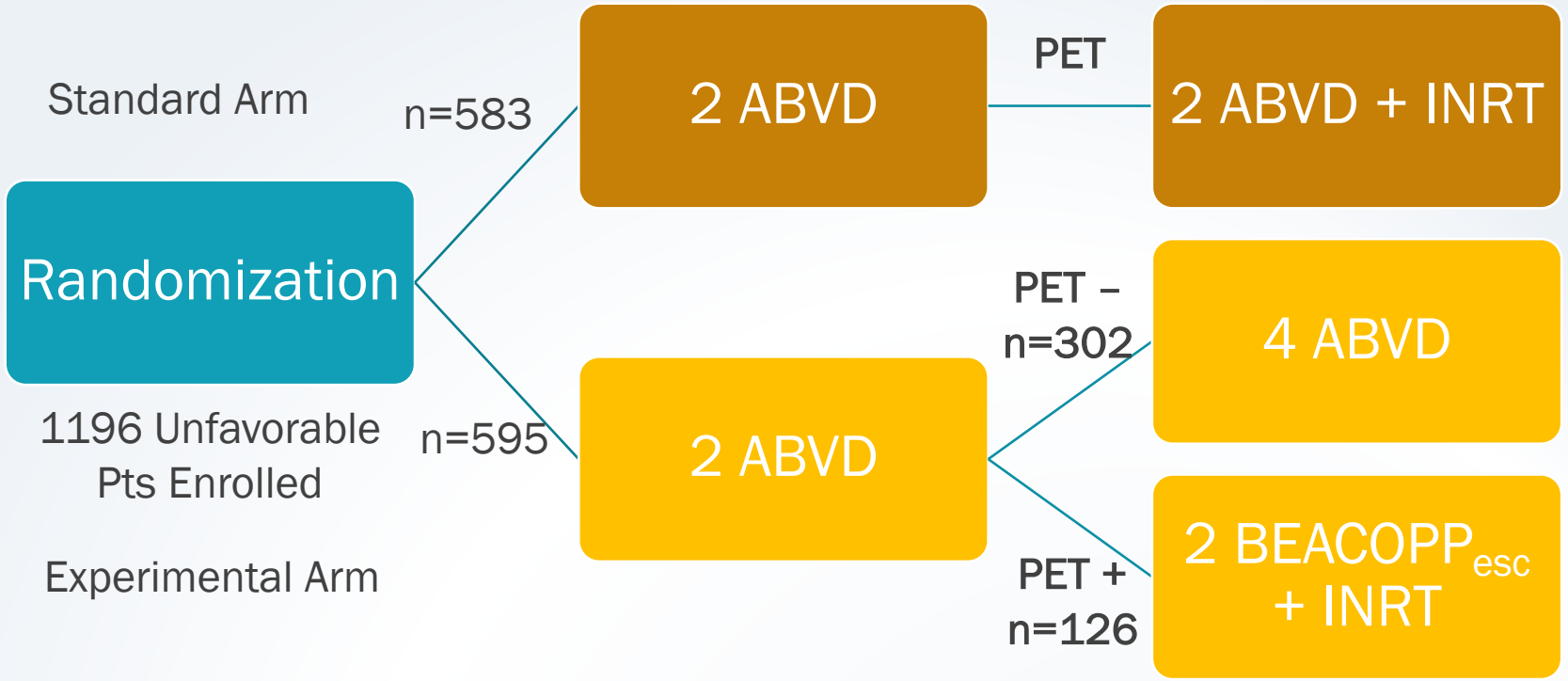
Who Benefits from Radiation Therapy?

	Yes	No	In Select Cases
Early Stage Favorable	X		
Early Stage Unfavorable			
Relapsed and Refractory			

- In the vast majority of patients with ES Favorable HL the disease distribution is optimal for involved site RT
- If substantial dose to the heart, breasts is expected → should avoid RT

EORTC H10U: ABVD x 6 vs ABVD x 4 + 30 Gy RT

- Randomized non-inferiority Trial
- 1196 pts (age 15-70)
- Clinical stage I-II EORTC Unfavorable
- Bulky dz ~40%
- PET Neg by IHP: i.e. Deauville 1-2
- 30 Gy INRT
- Median f/u of 5.1 & 9.5 years
- **Δ PFS = 2-4% (NS)**



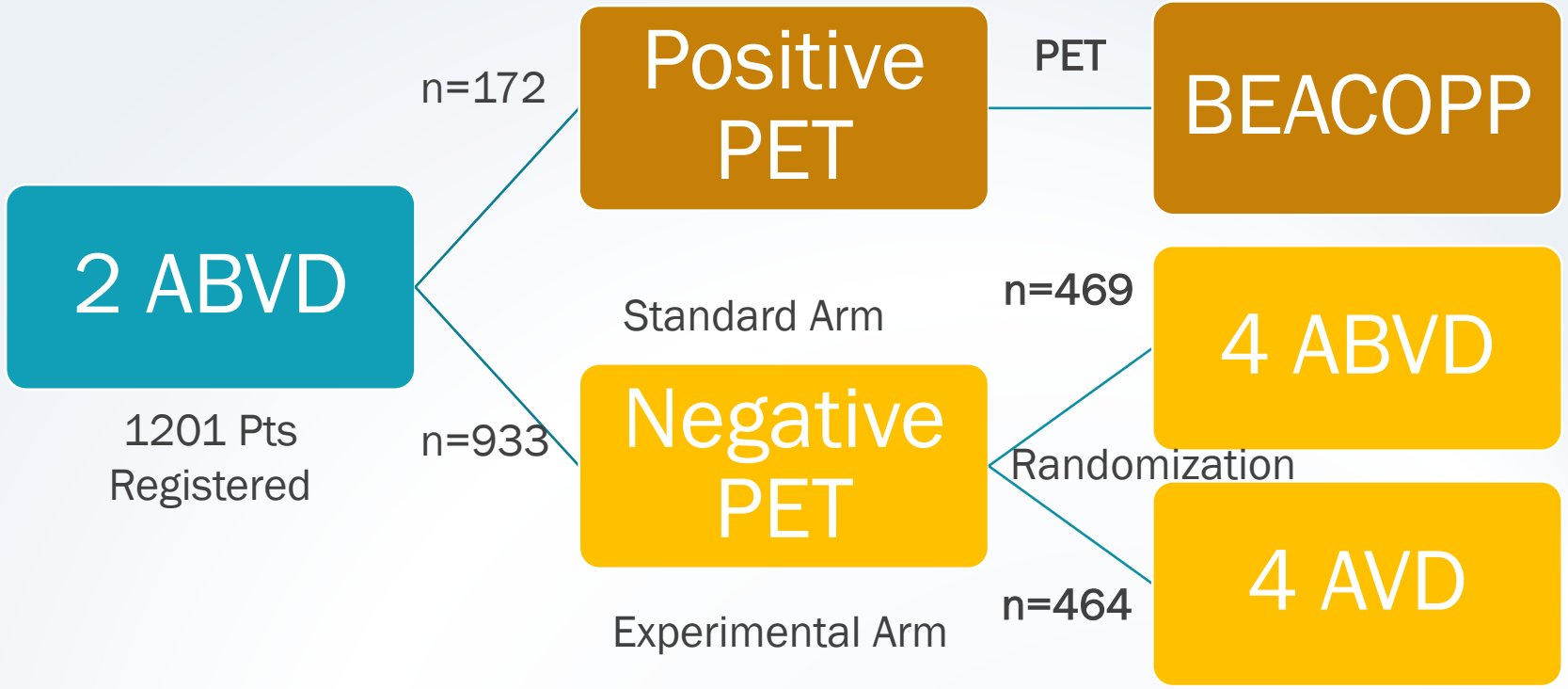
	Intent –to-treat Analysis			Per Protocol Analysis		
	PET-, RT	PET-, no RT	P value	Pet-, RT	PET-, no RT	P value
5-year PFS	92.1%	89.6%	NR (HR 1.45)	NR	NR	
10-year PFS				91.4%	86.5%	0.1628

André MPE, Girinsky T et al, Early Positron Emission Tomography Response-Adapted Treatment in Stage I and II Hodgkin Lymphoma: Final Results of the Randomized EORTC/LYSA/FIL H10 Trial. J Clin Oncol. 2017 Jun 1;35(16):1786-1794. PMID: 28291393.

Federico M, Fortpied C et al Long-Term Follow-Up of the Response-Adapted Intergroup EORTC/LYSA/FIL H10 Trial for Localized Hodgkin Lymphoma. J Clin Oncol. 2024 Jan 1;42(1):19-25 PMID: 37967311.

Response Adjusted Therapy for Advanced HL (RATHL): ABVD x 6 vs ABVD2-AVD4

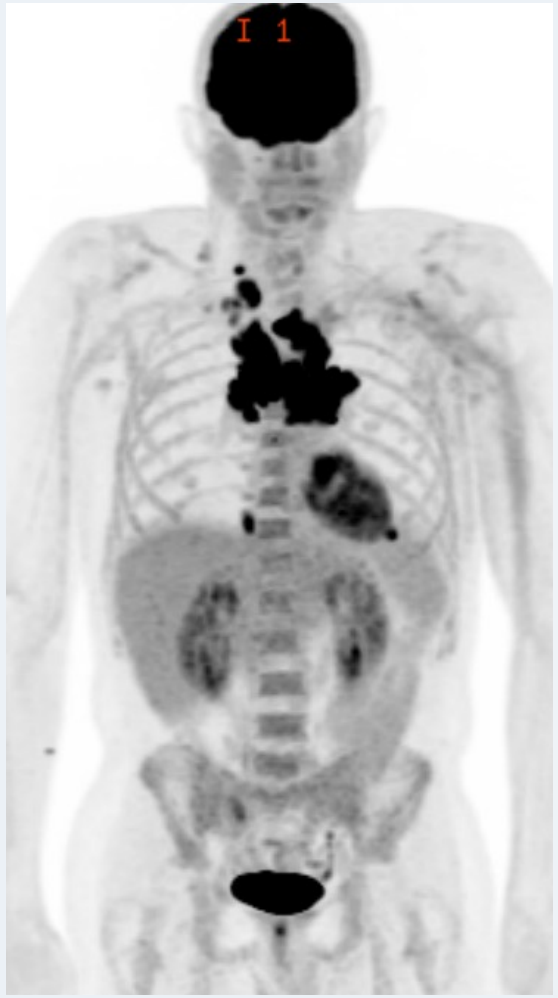
- Randomized non-inferiority Trial
- 1201 adult pts
- **Stage IIB-IV or IIA with bulk or ≥ 3 involved sites**
- PET Negative: Deauville 1-3
- RT discouraged for iPET neg
- ~42% stage II, 32% bulky
- Median f/u of 7.3 years
- **3-year ΔPFS of 1.3% falls in predefined noninferiority margin**

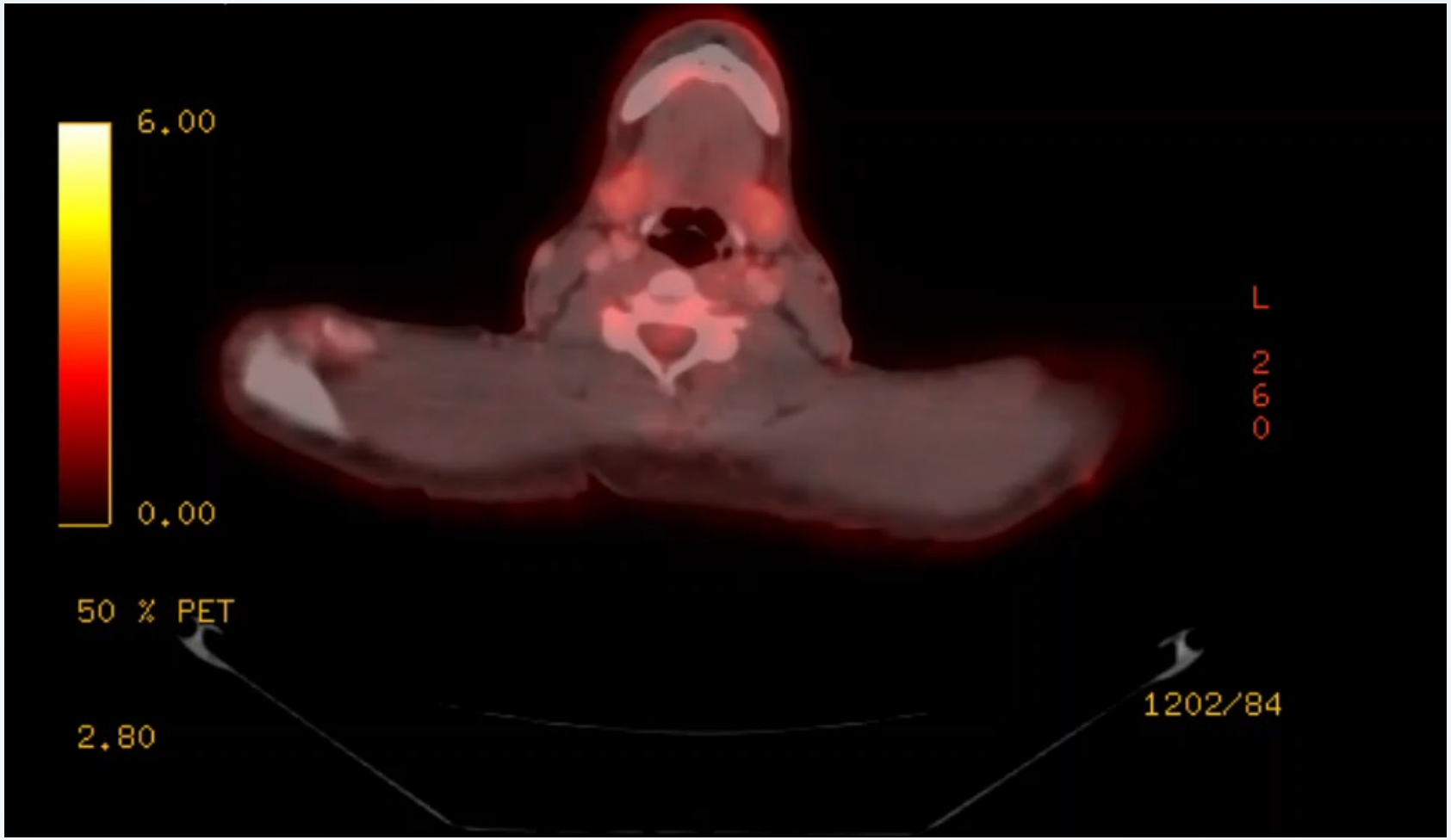


	Intent –to-treat Analysis		
	PET-, ABVD	PET-, AVD	P value
3-year PFS	85.5%	84.3%	NR (HR 1.10)
7-year PFS	81%	79.2%	

Luminari S et al, Long-Term Follow-Up of the Response-Adjusted Therapy for Advanced Hodgkin Lymphoma Trial. JCO Vol 21, Issue 1, 2023

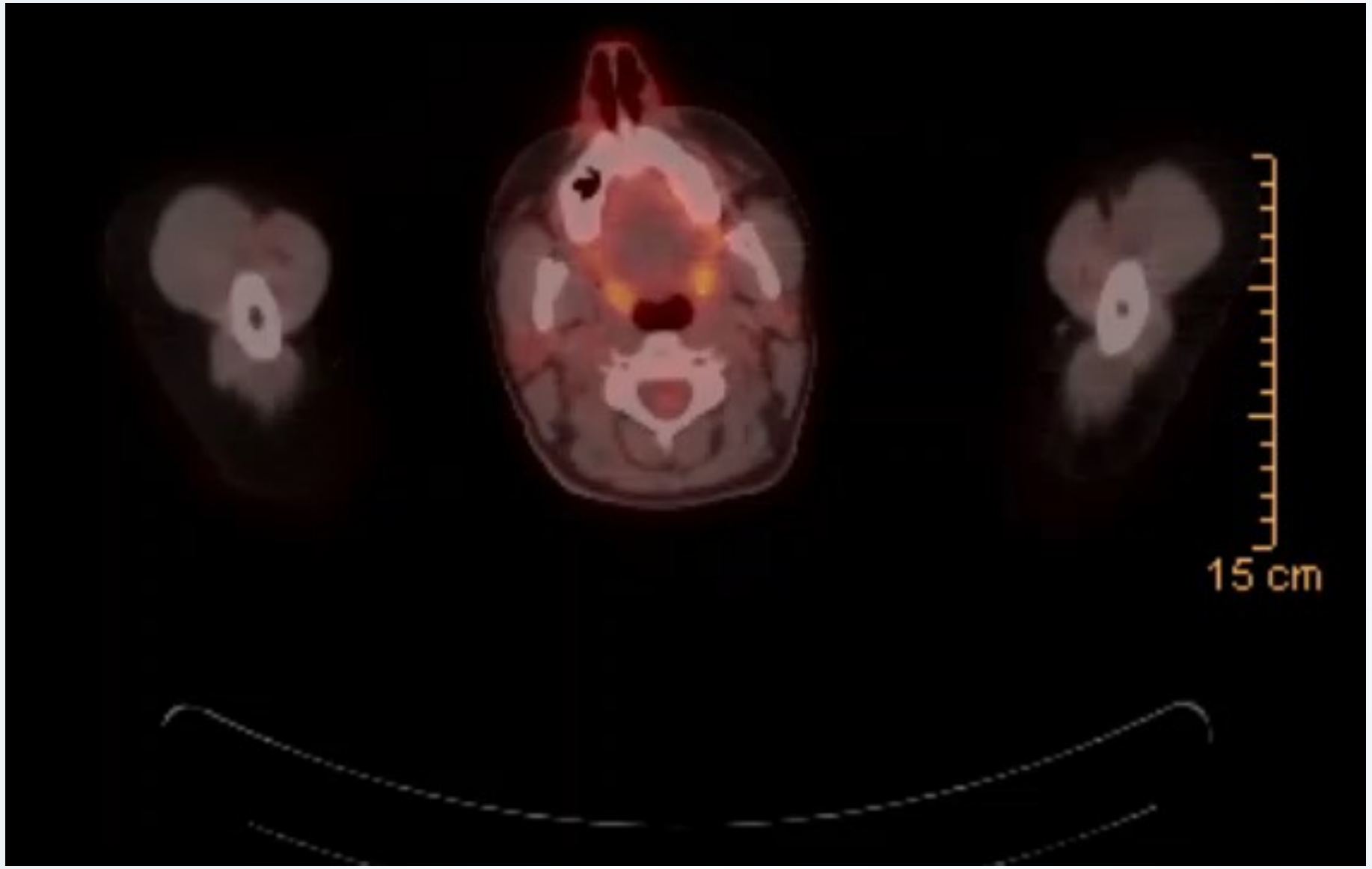
Case #2: Early stage unfavorable HL



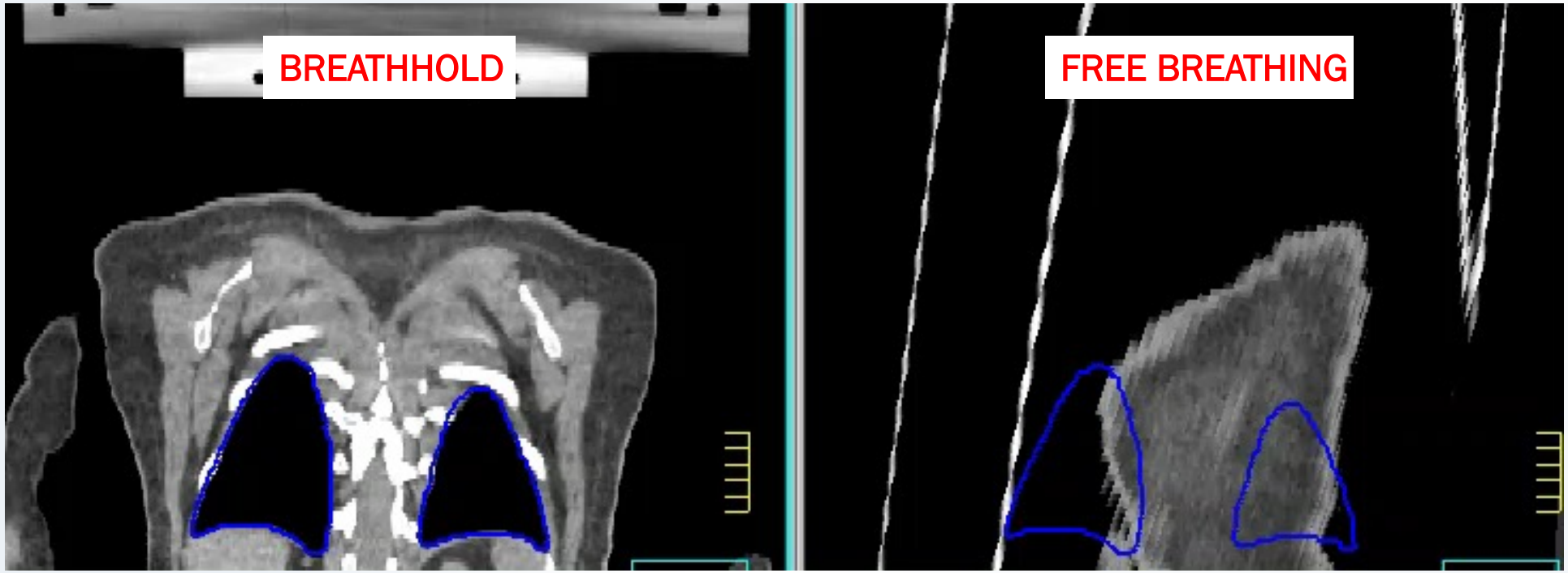


Heart dose would be in excess of 8-10 Gy → monotherapy preferred

Case #3: 32 yo woman with stage IIB unfavorable non-bulky HL (Unfavorable based on B symptoms and ESR of 138)



Benefit of Deep Inspiration Breathhold (DIBH)

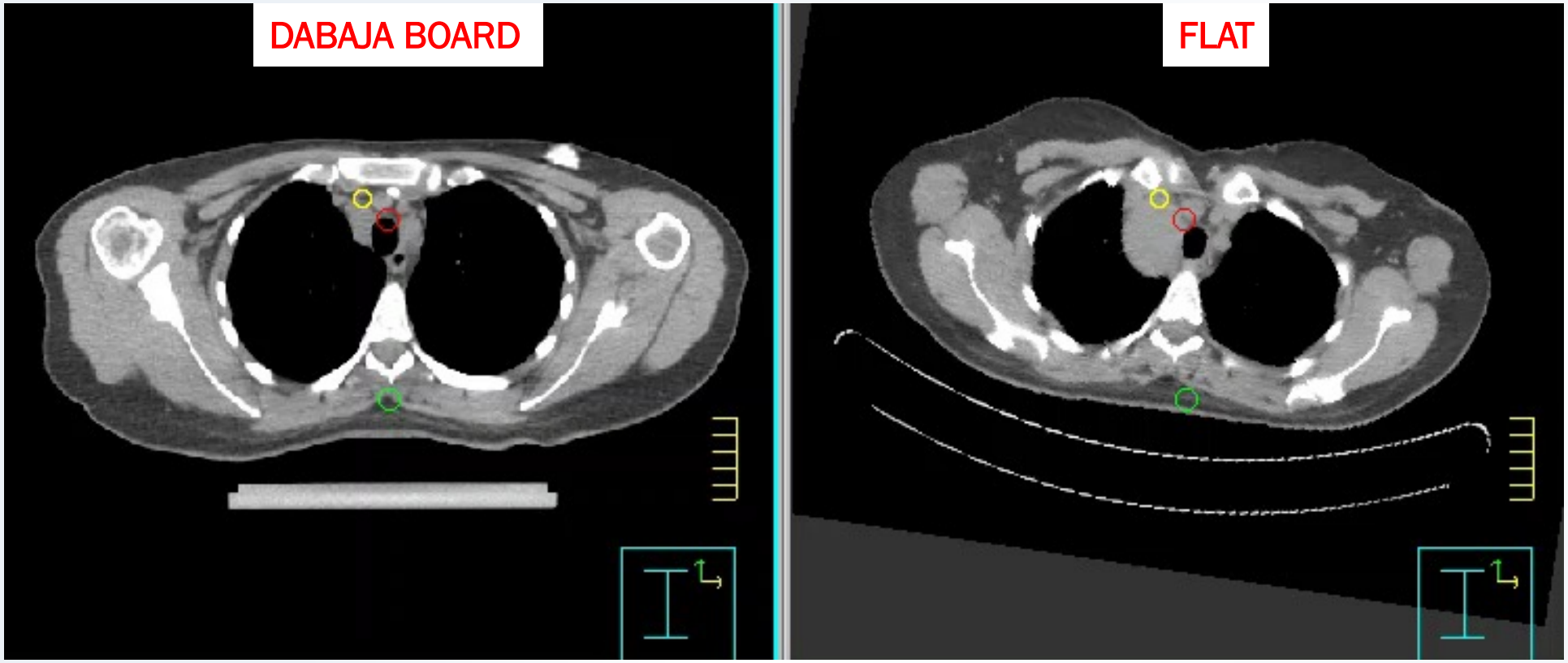


Simulation CT scan with DIBH

Pre-treatment CT scan (Freebreathing)

LARGER LUNG VOLUME AND INFERIOR CARDIAC DISPLACEMENT

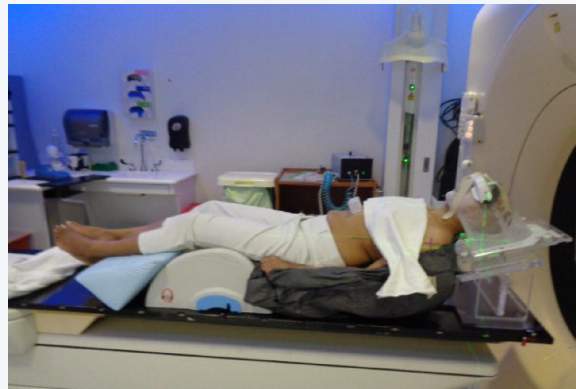
Benefit of Incline Board



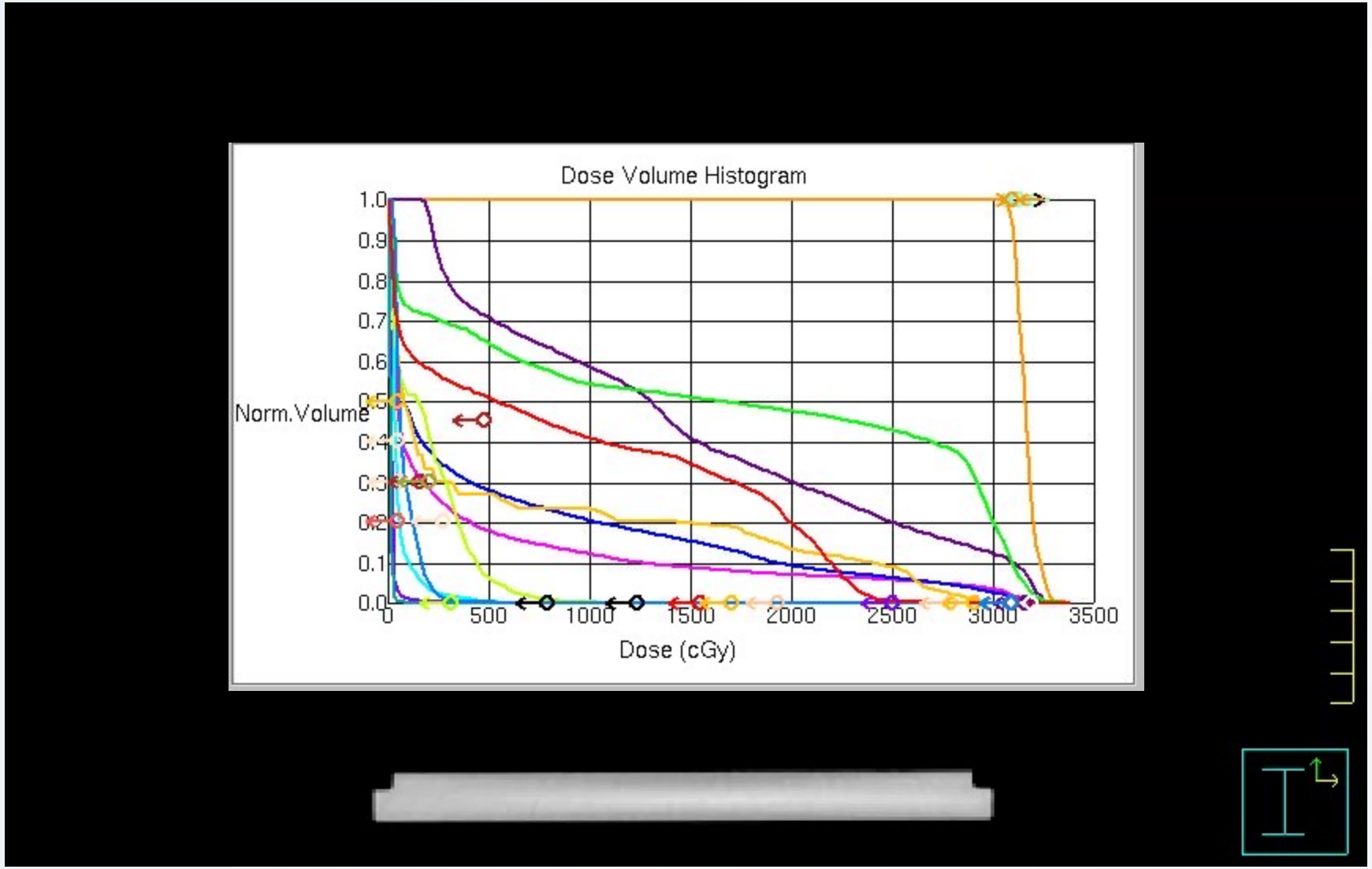
Simulation CT scan with Dabaja Board

Pre-treatment CT scan (Flat)

Inferior Breast Displacement

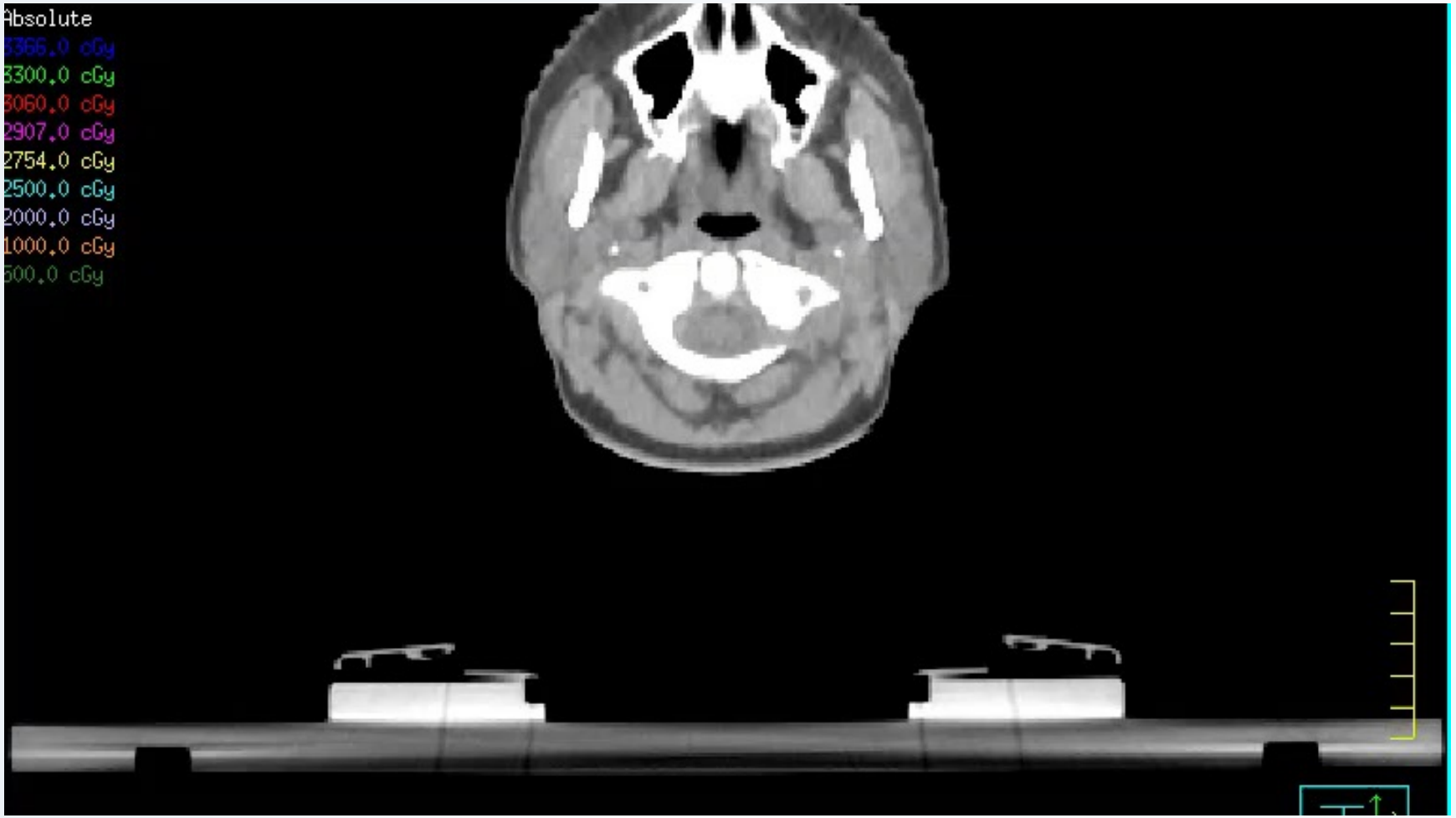


Contouring Organs at Risk (OARs)



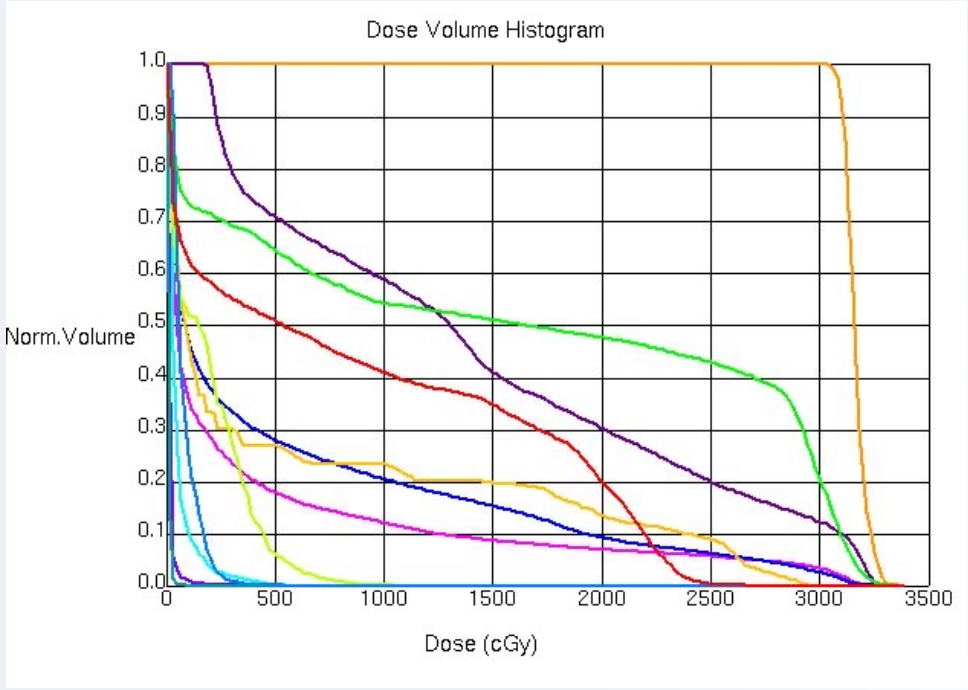
Structures must be identified to avoid them

Plan Evaluation



Pay Attention to Target Dose but also Low Doses (5 Gy)

Plan Evaluation



Line Type	ROI	Trial or Record	Min.	Max.	Mean
	Heart	BH Mediastinum CCF	2.1	3245.7	375.6
	Lungs	BH Mediastinum CCF	0.9	3332.3	534.9
	Thyroid	BH Mediastinum CCF	181.4	3295.4	1412.8
	Left Ventricle	BH Mediastinum CCF	17.7	549.5	53.6
	Right Coronary	BH Mediastinum CCF	12.8	2949.7	573.9
	Left Main LAD	BH Mediastinum CCF	20.3	1049.9	190.5
	Right Breast	BH Mediastinum CCF	--	353.7	17.4
	Left Breast	BH Mediastinum CCF	--	93.3	9.6

Mean Heart Dose = 3.8 Gy
Mean LV dose= 0.6 Gy
Mean Lung Dose= 5.3 Gy
Mean breast doses <1 Gy
Thyroid V25 = 20%

Scrutinize Doses to OAR based on established Dose Constraints

Who Benefits from Radiation Therapy?

	Yes	No	In Select Cases
Early Stage Favorable	X		
Early Stage Unfavorable			X
Relapsed and Refractory			

In select cases based on patient factors and disease distribution: combined modality therapy may be preferred

Radiation Therapy for Relapsed and Refractory HL after High Dose Chemotherapy & Autologous SCT

Study	Year	Pt #	Conditioning	Pts receiving RT	RT technique	Timing in relation to HSCT	Median RT dose (range)	Outcome	Subsets of Patients Benefiting from RT
Biswal (East Carolina University, Duke and University of Rochester)	1993-2003	62	BEAC	32	IFRT	After	30.6 Gy (6-44.2)	3 year OS 69.6 vs 40 (p=0.05), DSS 82.1 vs 57.6% (p=.08) LC (p=.03)	
Kahn (Emory)	1995-2008	92	BuCyE	46	IFRT	83% before	30 Gy (21-45)	DFS not significant (p=.204)	Bulky disease for DFS (p=0.032)
Eroglu (Turkey)	1995-2012	45	BEAM or ICE	21	IFRT	76% before	30 Gy (25-44)	5 year OS 81% IFRT vs 48% no RT, p=0.045 for early stage patients	1-2 nodal regions at relapse, early stage patients
Levis (Italy)	2003-2014	73	BEAM or FEAM	21	IFRT	Before or within 3 weeks	30 Gy (25.2 -43.2)	Overall no difference with IFRT but worse prognostic factors in IFRT group	Limited stage disease at relapse and PET positive had trend to improved PFS
Wilke (University of Minnesota Transplant Database)	2005-2014	80	Cyclophosphamide, carmustine, etoposide	32	"localized fields limited to areas of disease involvement before transplant or radiographically suspicious"	After	30.6 Gy (16-44)	Improved PFS with RT (67% vs 42%, p=0.01)	Bulky disease (p=.02), B symptoms (p=.05), primary refractory HL (p=.02), partial response on pre-transplant imaging (p=.02)
Milgrom (University of Penn and MDACC)[	2006-2015	189	BCNU, BEAM or CBV	22	Varied	After in 95%	36 Gy (25.2 -41.4)	No difference in LC, PFS or OS	Local control benefit among primary refractory disease and FDG avid at the time of SCT (p=.02)

Biswas T, et al Involved field radiation therapy following high dose chemotherapy and autologous stem cell transplant benefits local control and survival in refractory or recurrent Hodgkin lymphoma. Radiother Oncol 2012; 103: 367-372.

Kahn S, Flowers C, et al Esiashvili N. Does the addition of involved field radiotherapy to high-dose chemotherapy and stem cell transplantation improve outcomes for patients with relapsed/refractory Hodgkin lymphoma? Int J Radiat Oncol Biol Phys 2011; 81: 175-180.

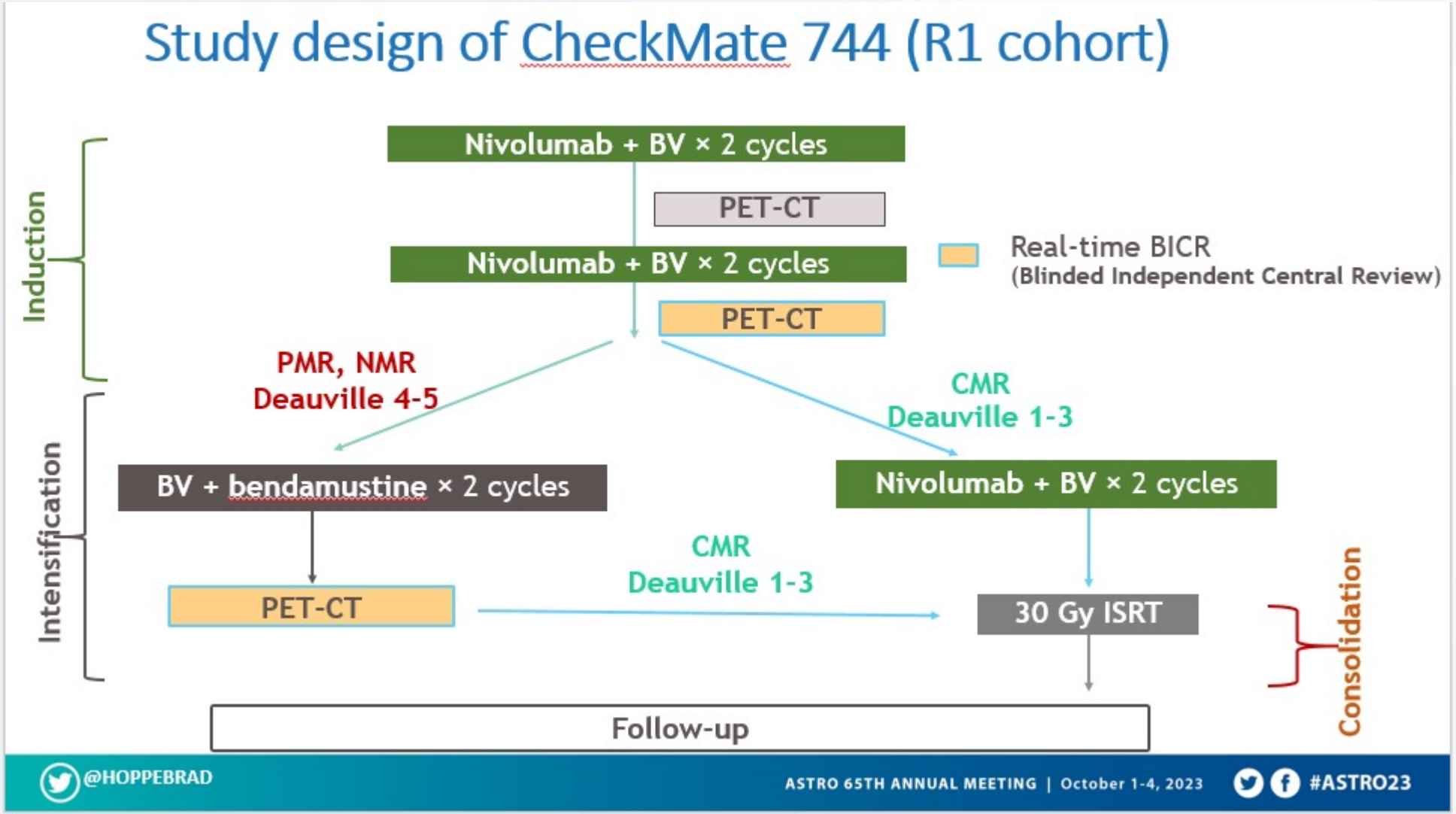
Eroglu C, et al Contribution of involved-field radiotherapy to survival in patients with relapsed or refractory Hodgkin lymphoma undergoing autologous stem cell transplantation. Am J Clin Oncol 2015; 38: 68-73.

Levis M, Piva C, Filippi AR et al. Potential Benefit of Involved-Field Radiotherapy for Patients With Relapsed-Refractory Hodgkin's Lymphoma With Incomplete Response Before Autologous Stem Cell Transplantation. Clin Lymphoma Myeloma Leuk 2017; 17: 14-22
Wilke C, Cao Q, Dusenbery KE et al. Role of Consolidative Radiation Therapy After Autologous Hematopoietic Cell Transplantation for the Treatment of Relapsed or Refractory Hodgkin Lymphoma. Int J Radiat Oncol Biol Phys 2017; 99: 94-102

Milgrom SA, Jauhari S, Plastaras JP et al. A multi-institutional analysis of peritransplantation radiotherapy in patients with relapsed/refractory Hodgkin lymphoma undergoing autologous stem cell transplantation. Cancer 2017; 123: 1363-1371.

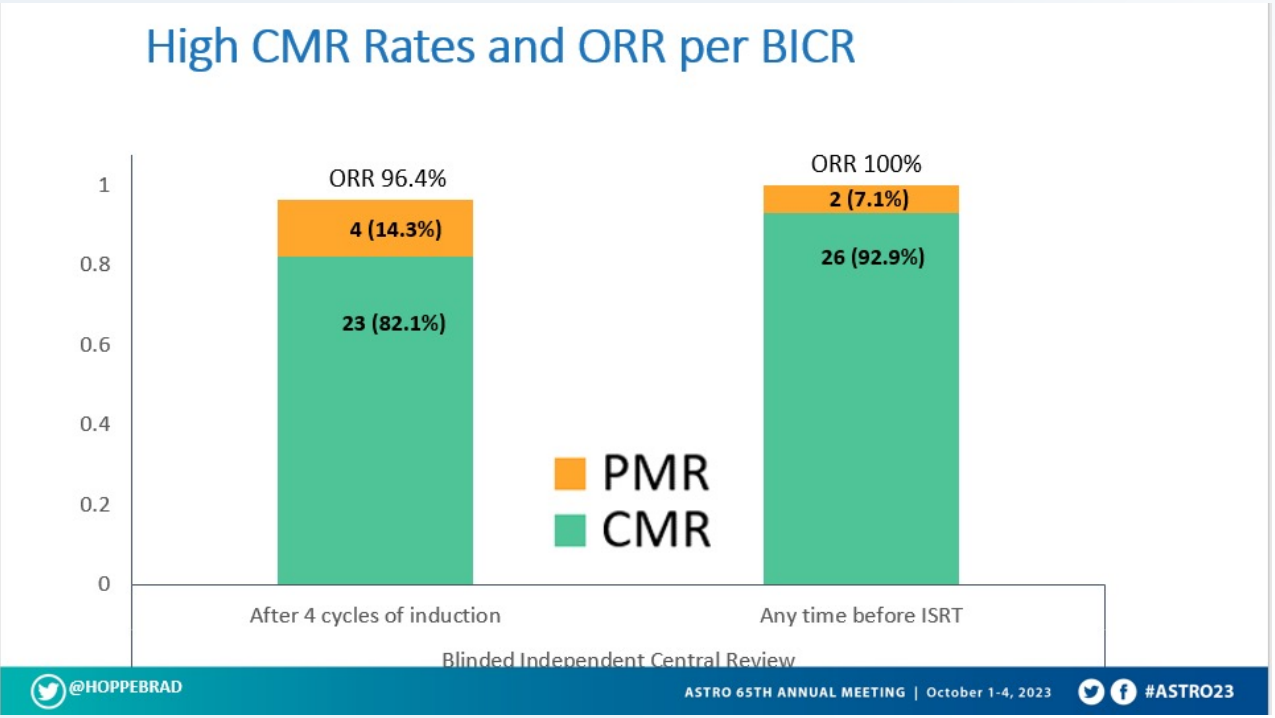
- RT treatment decisions driven by retrospective data
- Patients that may benefit: **Limited stage relapse; bulky disease, PET positivity before transplant**

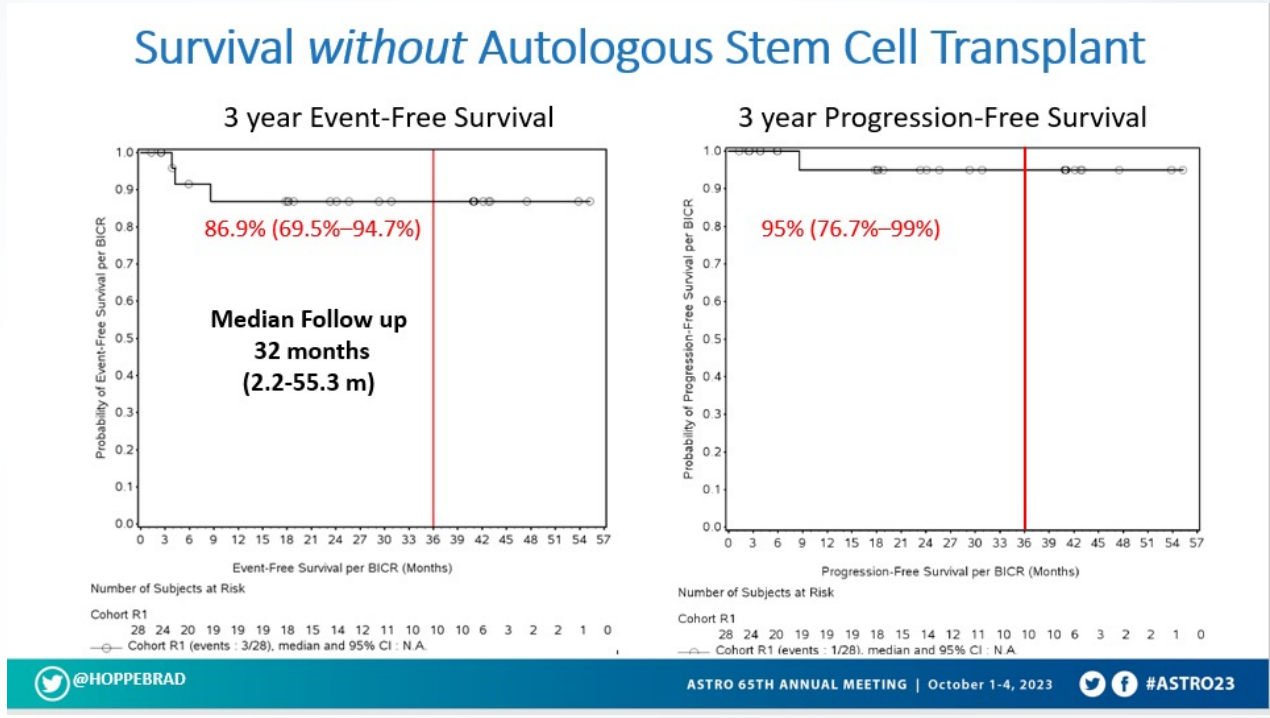
Consolidative RT for R/R HL Treated Without SCT



Consolidative RT in place of ASCT in patients with low-risk relapsed/refractory (R/R) classic Hodgkin lymphoma (cHL) treated with nivolumab plus brentuximab vedotin: CheckMate 744. Hoppe B et al, ASTRO 2023

Consolidative RT for R/R HL Treated Without SCT





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Who Benefits from Radiation Therapy?

	Yes	No	In Select Cases
Early Stage Favorable	X		
Early Stage Unfavorable			X
Relapsed and Refractory			X

In select cases based on patient factors and disease distribution:

Limited stage relapse, bulky disease, PET positivity before transplant; patients with limited sites of disease that are omitting SCT

Conclusions

- Patients with early stage favorable HL benefit from combined modality therapy when maximizing disease control is the treatment priority
- Patients with early stage unfavorable HL may be best treated with systemic therapy alone (especially in cases where involved site RT fields would be extensive)
- Patients with relapsed and refractory HL undergoing autologous SCT may benefit from RT
  - Limited stage disease
  - Bulky disease
- RT may be beneficial for patients with PET positivity at the time of HDC and ASCT and may be especially beneficial for R/R HL patients forgoing autologous SCT

Acknowledgements

Department of Radiation Oncology

Bouthaina Dabaja MD
Jillian Gunther MD, PhD
Penny Fang MD
Susan Wu MD
Joann Shank
Paula Barrenechea
Shryll Turner
Erin Espinosa
Bettina Calalang

Donna White

Albert Koong

Department of Lymphoma/Myeloma

Loretta Nastoupil MD
Sattva Neelapu MD
Paolo Strati MD
Sairah Ahmed MD
Ranjit Nair MD
Jason Westin MD
Luis Fayad MD
Hun Ju Lee MD
Frederick Hagemeister MD
Alma Rodriguez MD
Felipe Samaniego MD
Michael Wang MD
Swami Iyer MD
Dai Chihara MD
Christopher Flowers MD

Misha Hawkins
Sherry Adkins

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Pictured (from left to right): Penny Fang MD, Chelsea Pinnix MD, PhD, Bouthaina Dabaja MD, Jillian Gunther MD, PhD, Susan Wu MD

Thank You!