Modern Techniques for Mediastinal RT

Chelsea Pinnix MD, PhD
Associate Professor, Residency Program Director
Department of Radiation Oncology
MD Anderson Cancer Center
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Radiotherapy in Modern Management of Haematological Malignancies

THE UNIVERSITY OF TEXAS MD Anderson ~~Cancer~~ Center®

ILROG INTERNATIONAL LYMPHOMA RADIATION ONCOLOGY GROUP

Modern Radiation Therapy for Mediastinal Lymphoma

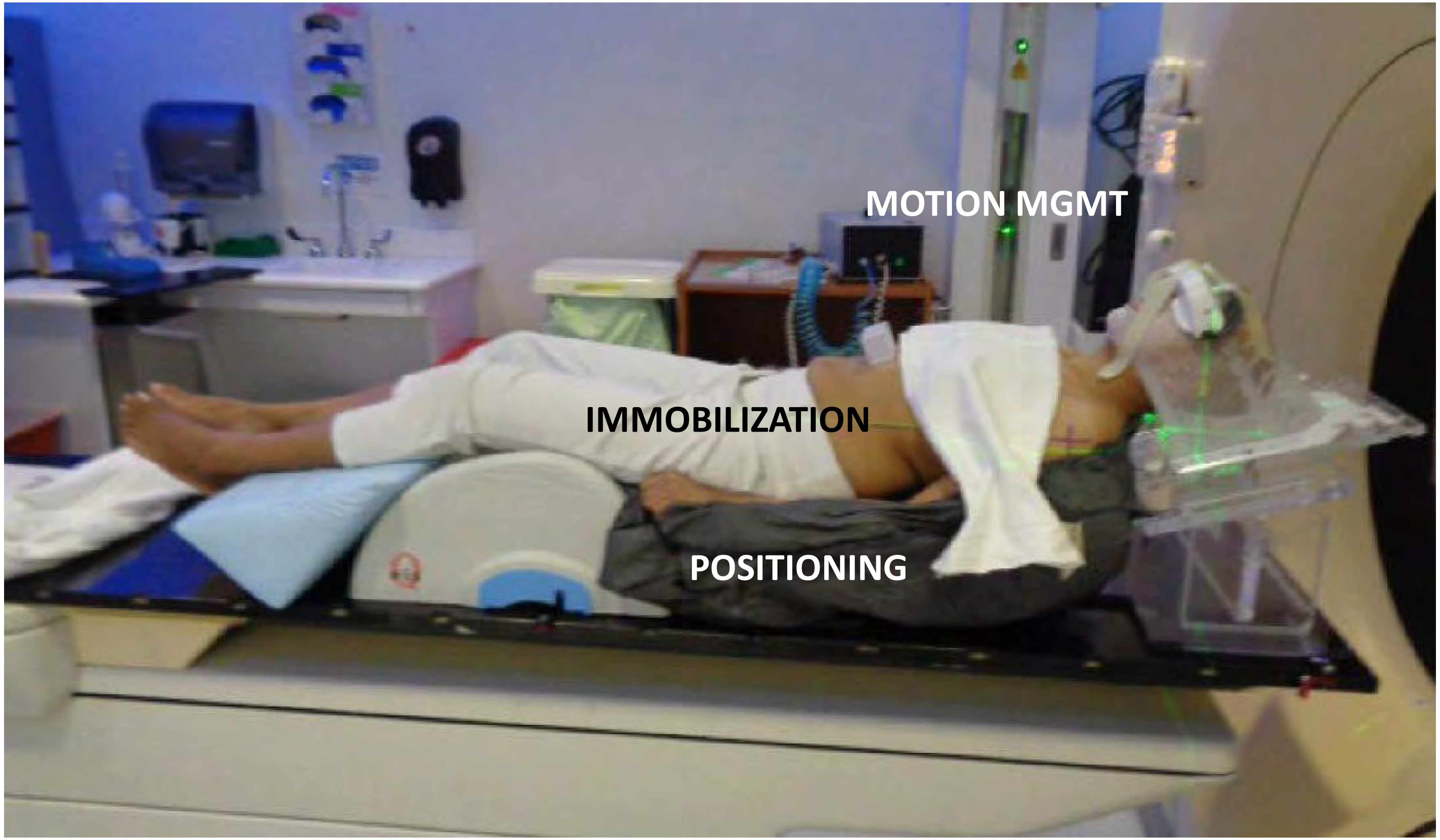
- **Goal: Accurate target coverage with reduced normal tissue exposure**
- Involved Site (ISRT) targeting
- Conformal dose delivery (IMRT, VMAT, Protons)
  - Butterfly beam arrangement
  - PAY ATTENTION to 5 Gy Line
- Incline board
- Deep Inspiration Breathhold
- Image Guidance (Daily low dose CT imaging)
- Organ at Risk Avoidance (Heart and substructures, lung, breasts, salivary glands, thyroid gland, spinal cord)
  - TAKE THE TIME TO CONTOUR NORMAL STRUCTURES OR REVIEW AUTO-CONTOURS

Getting from A to Z

- 1) **Simulation**
  - Motion Management and Immobilization for accurate targeting and optimized normal tissue avoidance
- 2) **Treatment Planning**
  - ISRT contouring approach
  - OAR contouring
- 3) **Plan Assessment**
  - Evaluate doses to OAR and target coverage
  - Always ask for more
- 4) **Treatment Delivery**
  - Daily IGRT (often low dose CT imaging)

Simulation

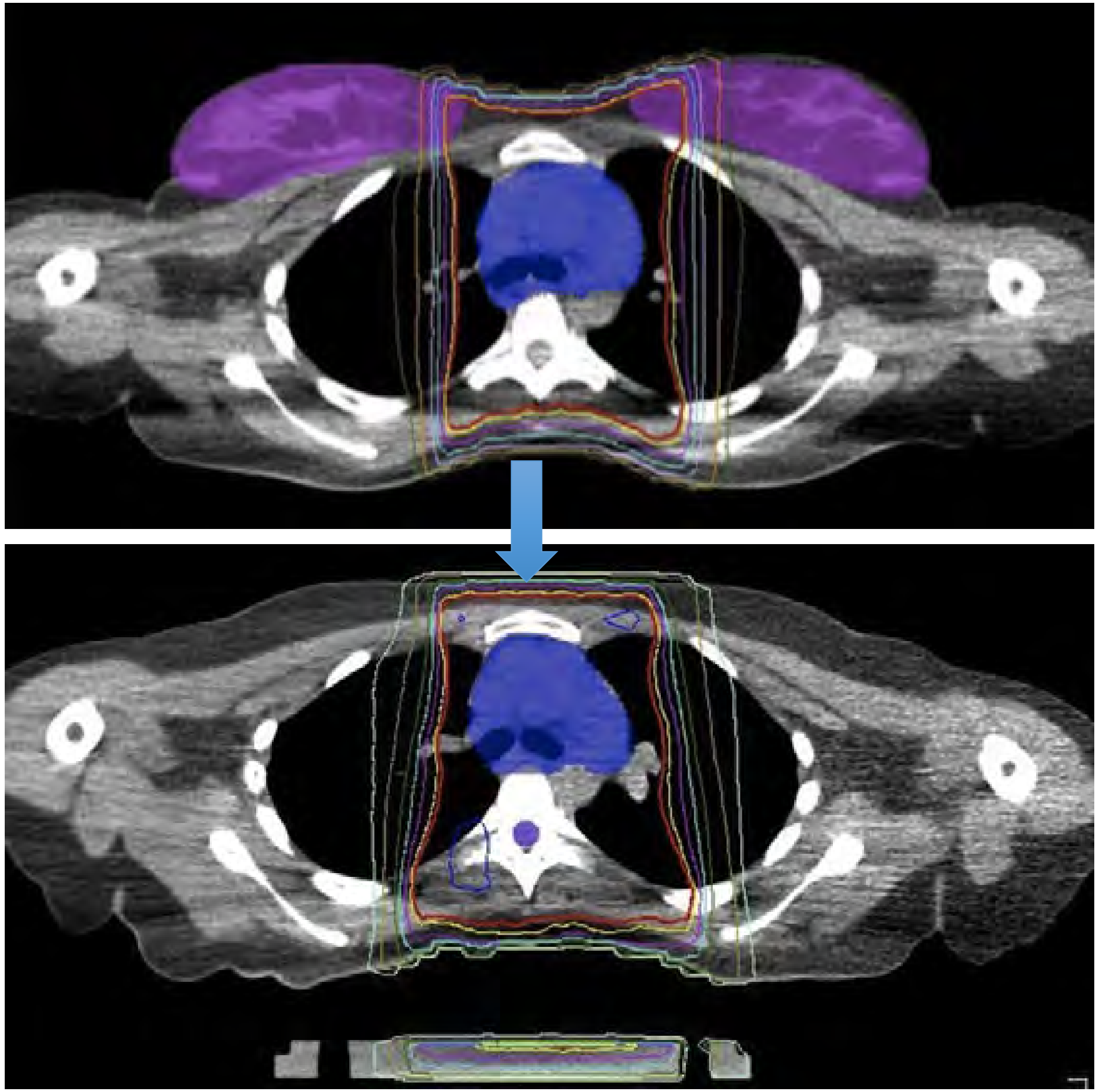
Simulation



Decreasing Breast Dose – Time, **DISTANCE** and Shielding

“Dabaja” Board
15 deg. angle board

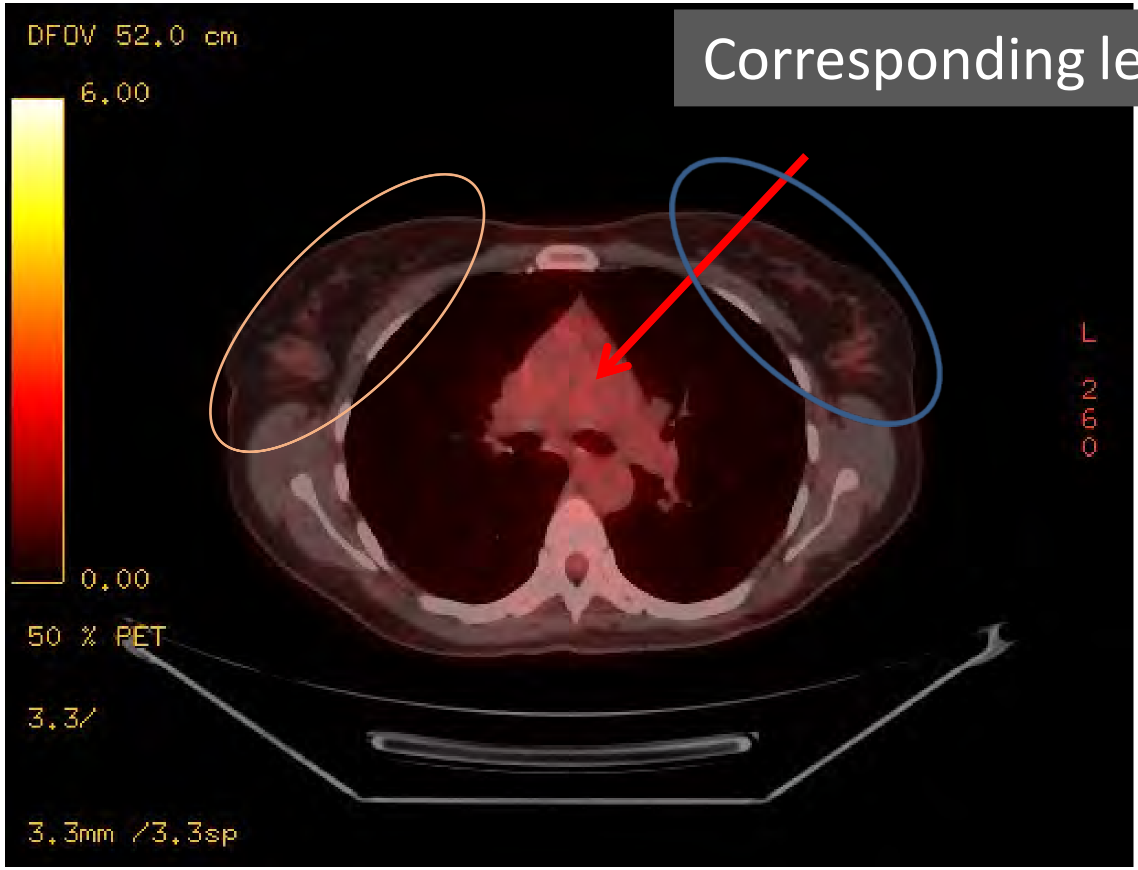
Breast tissue falls inferior



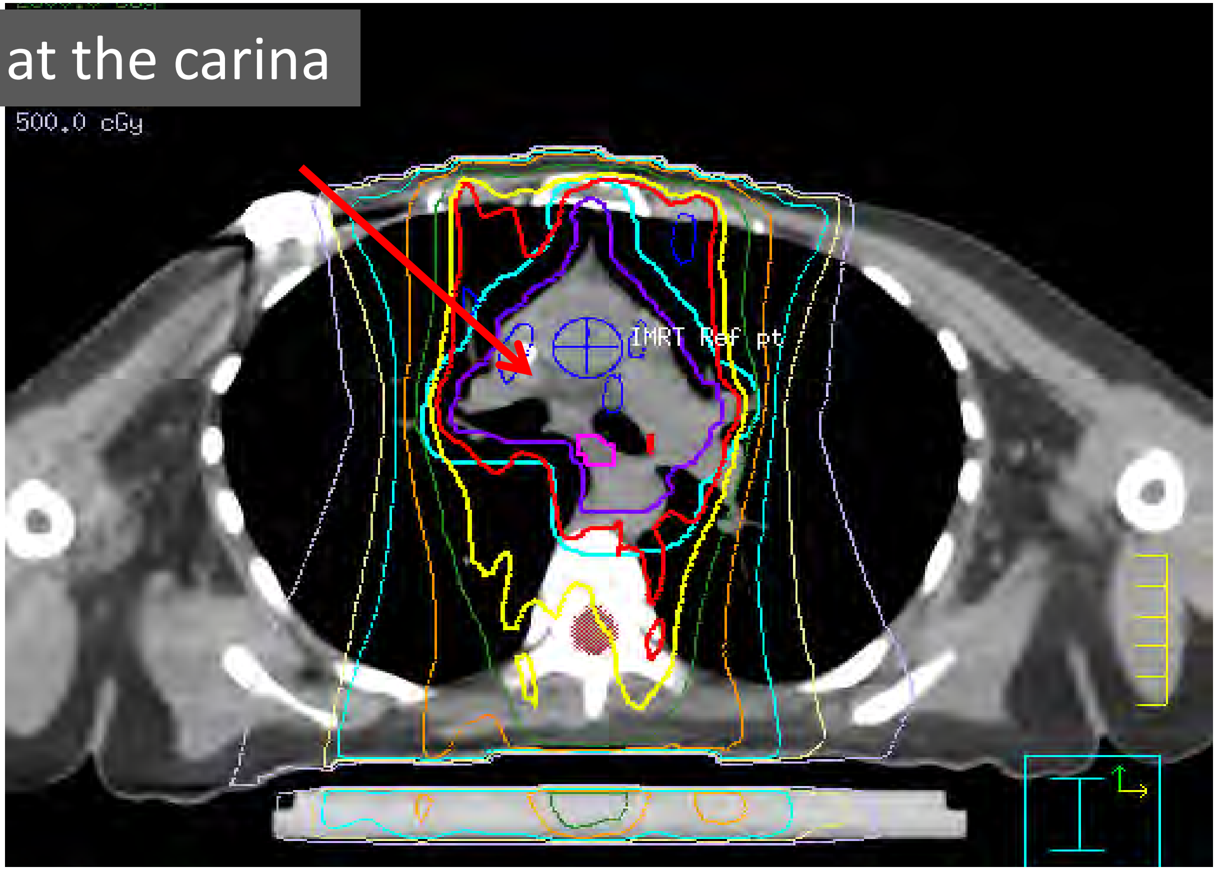
Simulation

Dabaja B et al, Involved field radiation for Hodgkin’s lymphoma: the actual dose to breasts in close proximity, Med Dosim 2012

Decreasing Breast Dose



Corresponding level at the carina

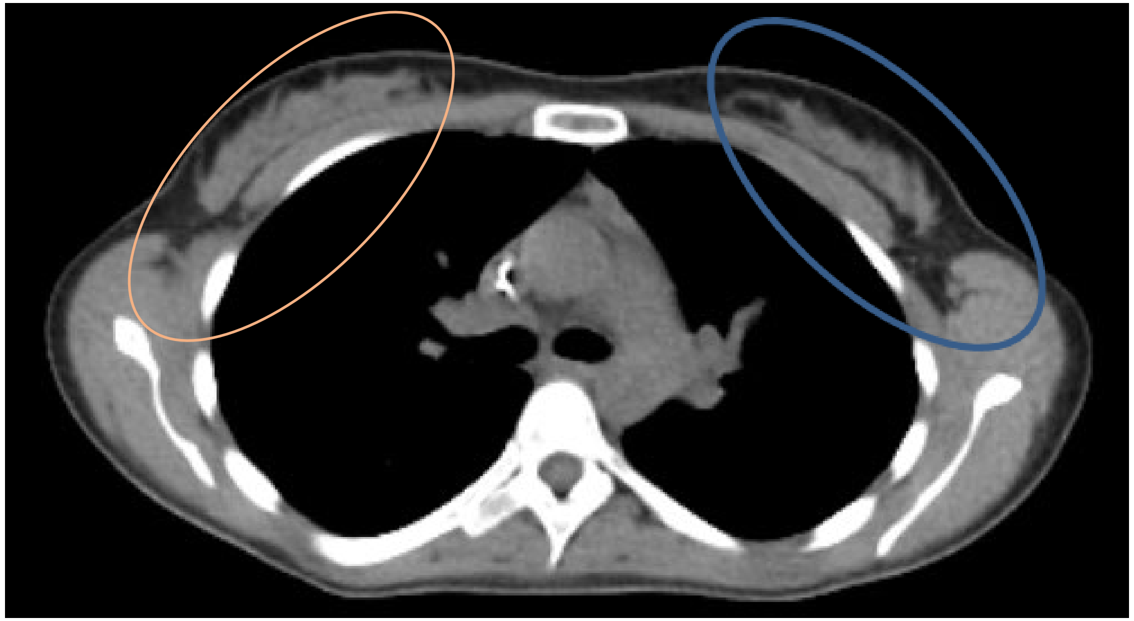


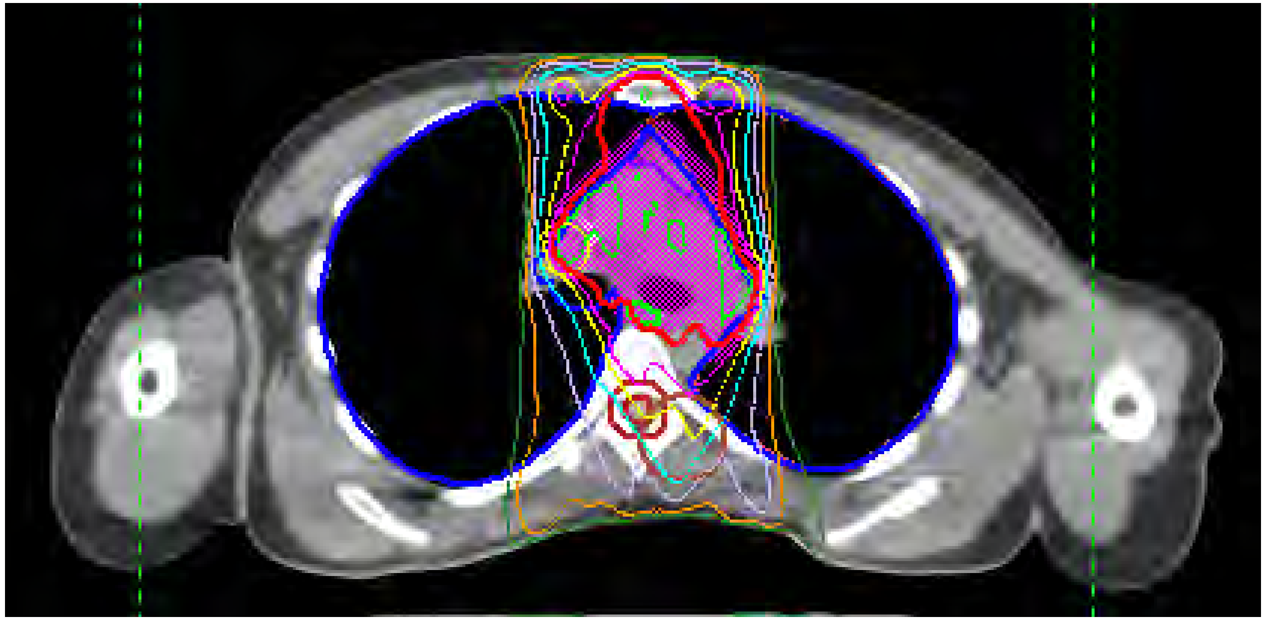
Breast tissue falls inferiorly, laterally, and out of field

Simulation

Dabaja B et al, Involved field radiation for Hodgkin's lymphoma: the actual dose to breasts in close proximity, Med Dosim 2012

Decreasing Breast Dose – Dense Breast Tissue





Breast tissue falls inferiorly, laterally, and out of field

Simulation

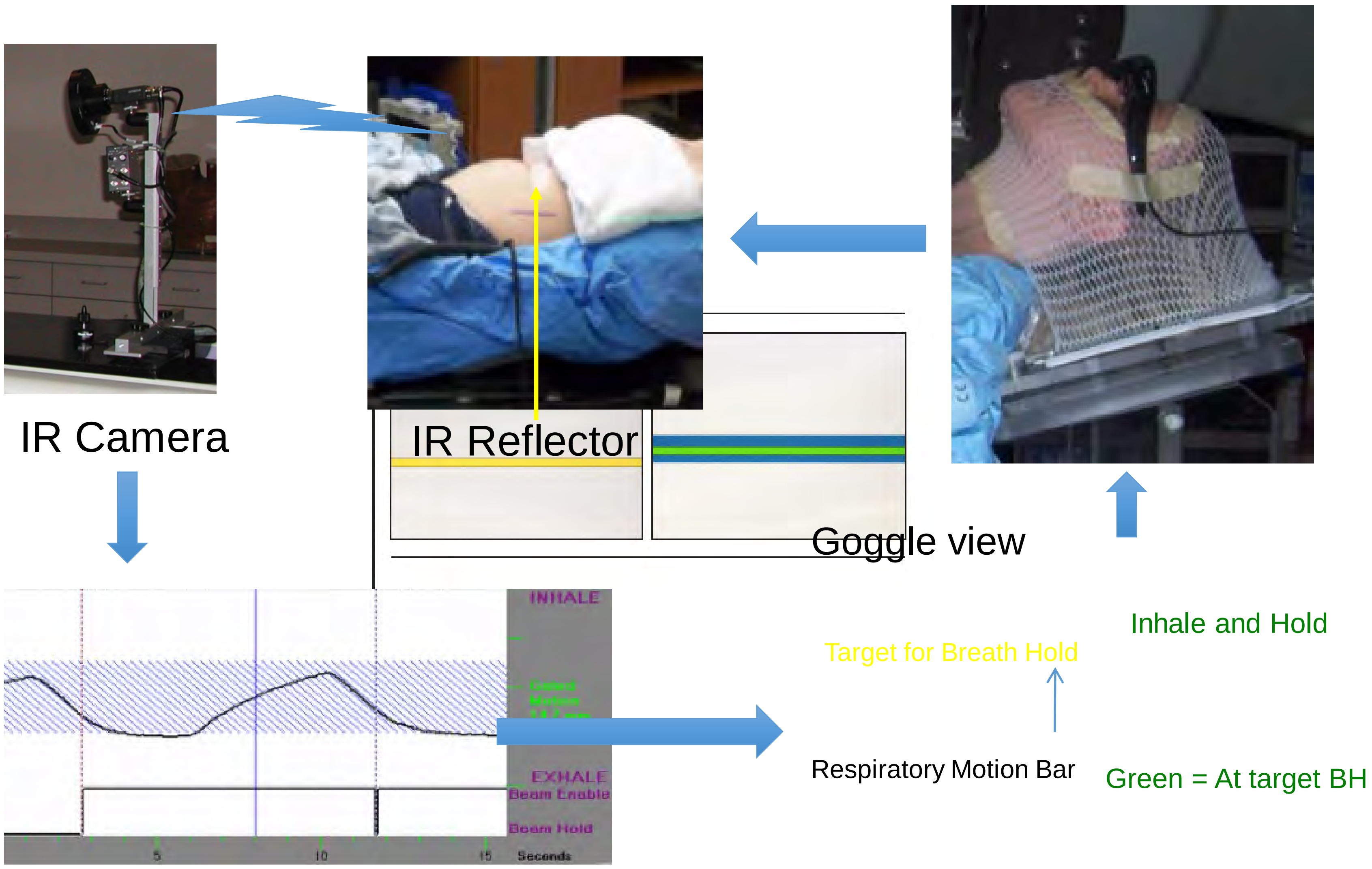
Deep Inspiration Breath-Hold (DIBH)

- Video based, non-invasive system with patient feedback delivered via goggles
- Lung volume is verified with daily volumetric imaging (CT)

Simulation

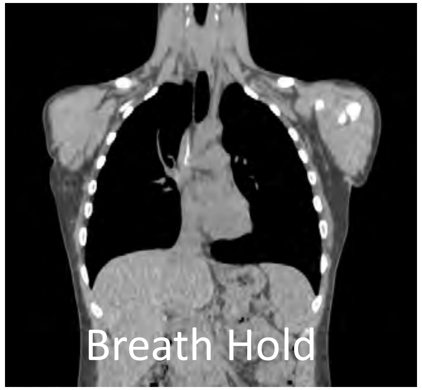
Decreasing Heart and Lung Dose

Breath Hold Technique



Simulation

Impact of Deep Inspiration Breath-hold



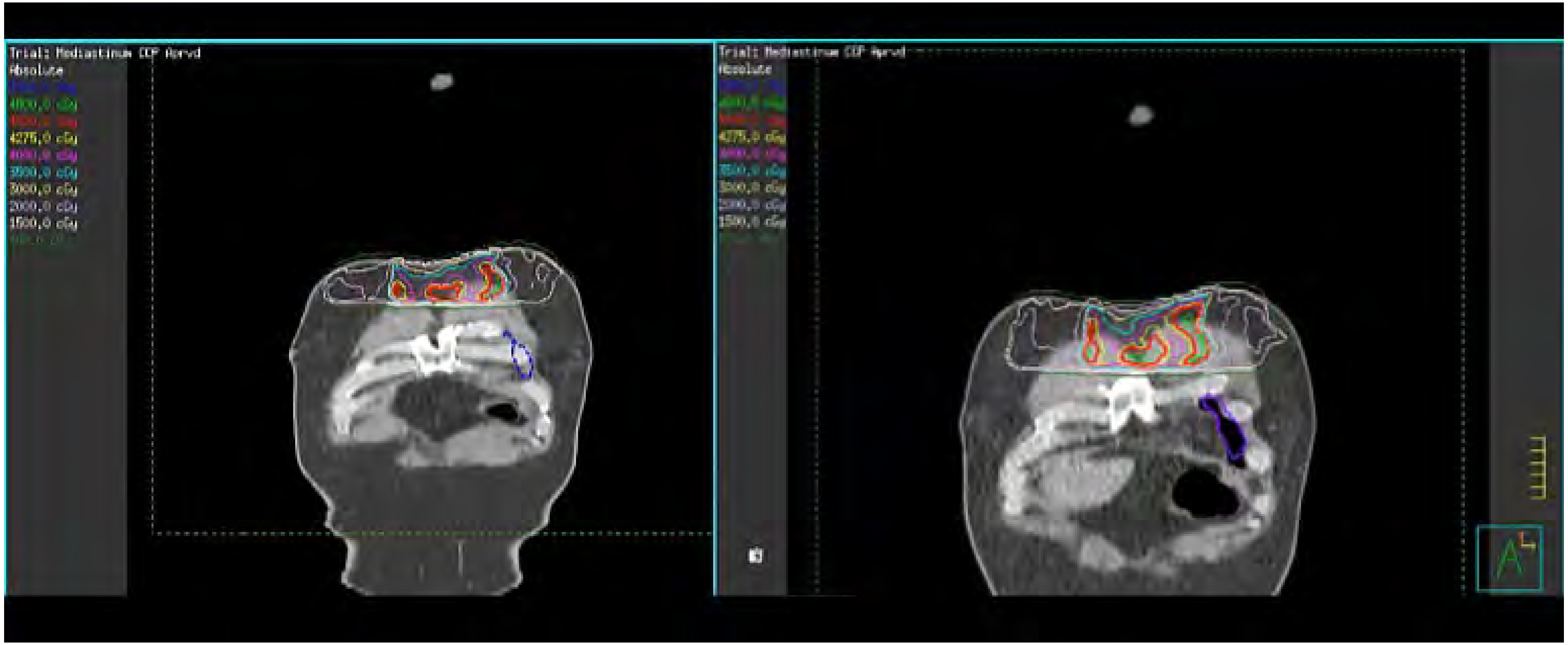
- For 15 lymphoma pts median age 32 years (range 24- 44 yrs) [1]
  - Free breathing → median lung volume 2372.2 ml^3 (range 2076 – 3437)
  - DIBH → median lung volume 4102 ml^3 (range 3003 – 7605)
- Median percentage increase in lung volume 48%, mean percentage increase 64% (range 38-133%)
- In a study among NSCLC pts the mean increase in lung volume was 38%[2]

[1]Moreno, A. C., Gunther, J. R., Milgrom, S., Fuller, C. D., Williamson, T., Liu, A., Wu, R., Zhu, X. R., Dabaja, B. S., & Pinnix, C. C. (2020). Effect of Deep Inspiration Breath Hold on Normal Tissue Sparing With Intensity Modulated Radiation Therapy Versus Proton Therapy for Mediastinal Lymphoma. Advances in radiation oncology, 5(6), 1255–1266.

[2]Barnes EA, Murray BR, Robinson DM, Underwood LJ, Hanson J, Roa WH. Dosimetric evaluation of lung tumor immobilization using breath hold at deep inspiration. Int J Radiat Oncol Biol Phys. 2001 Jul 15;50(4):1091-8. doi: 10.1016/s0360-3016(01)01592-9. PMID: 11429237.

Deep Inspiration Breath-hold

Free Breathing **DIBH**



45 yo male with primary refractory PMBCL treated to 45 Gy post Autologous SCT

Simulation

Treatment Planning

Target Delineation: Involved Site Radiation Therapy

- CTV encompasses initially involved pre-chemo site while considering changes in anatomy post-chemo and differences between diagnostic and sim scans
- PTV expansion dependent on site, immobilization, image guidance
- RT has no role in targeting microscopic disease after complete metabolic PET response after systemic therapy

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2014

Clinical Investigation

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

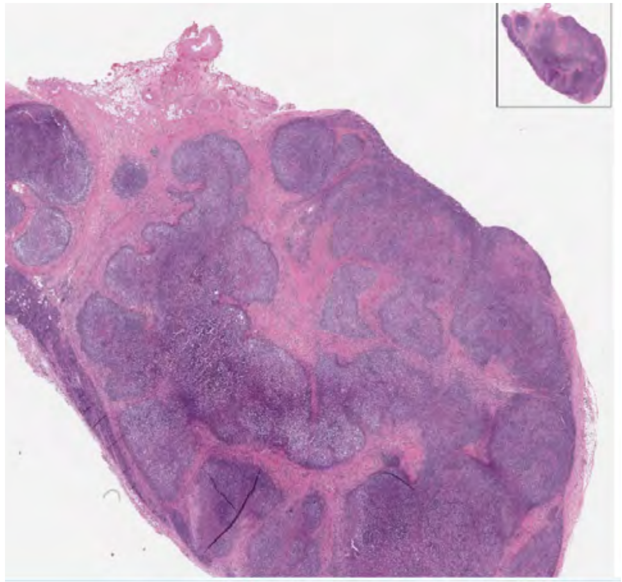
CrossMark

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

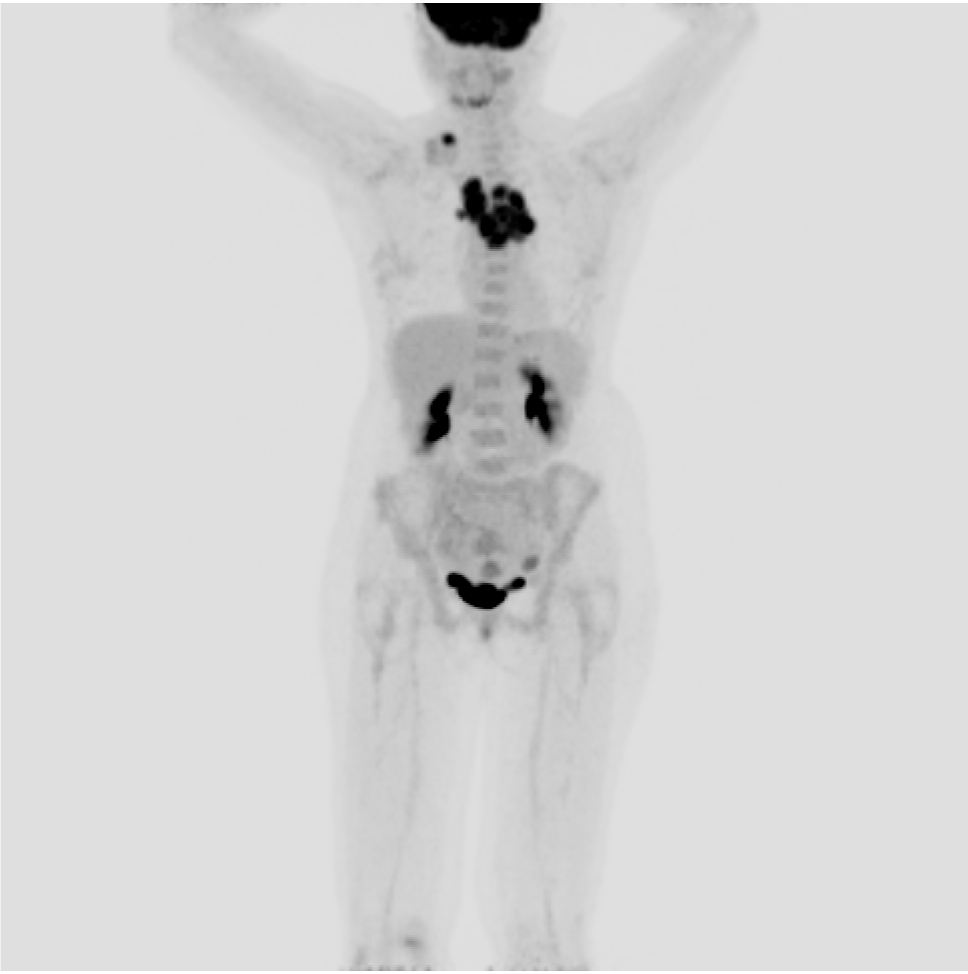
**Department of Oncology and Hematology, Rigshospitalet, University of Copenhagen, Denmark; †Department of Radiation Oncology, Memorial Sloan-Kettering Cancer Center, New York, New York; ‡Institute of Cancer Sciences, University of Manchester, Manchester Academic Health Sciences Centre, Christie Hospital 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*

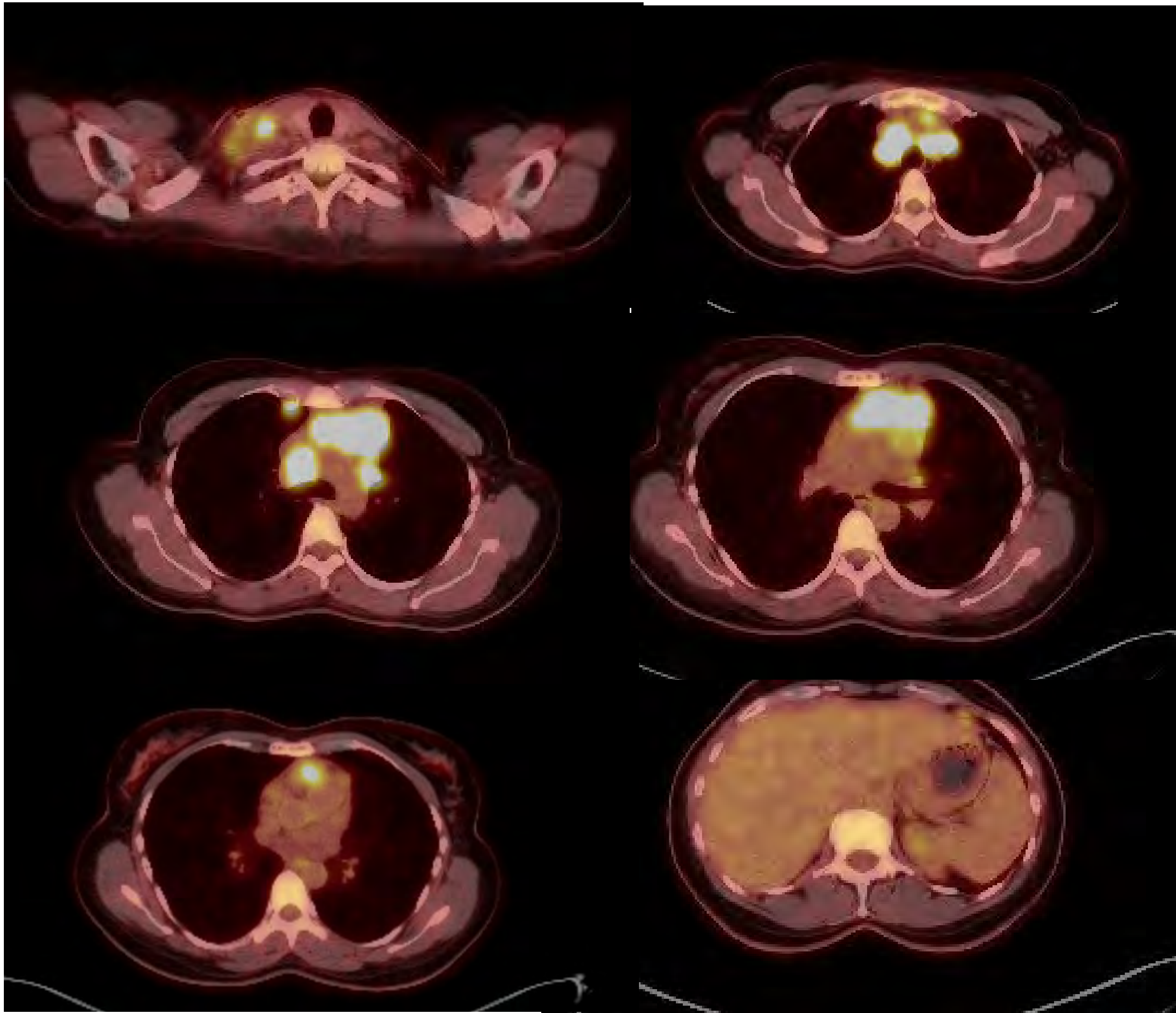
Case

- 39 yo woman self palpated a right SCV mass
- US revealed a 3.3 cm right supraclavicular mass
- Biopsy → Classical HL, Nodular Sclerosis



Case

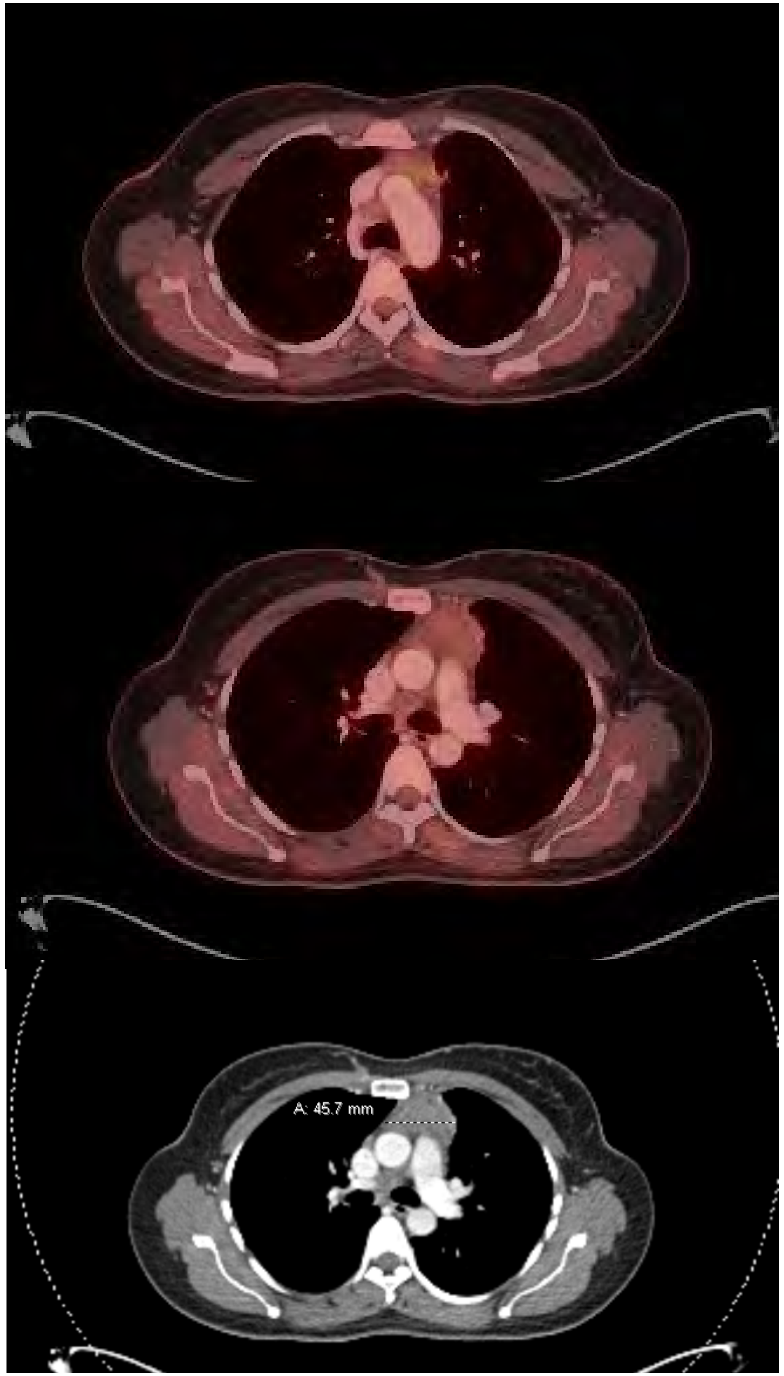




Treatment Planning

Case

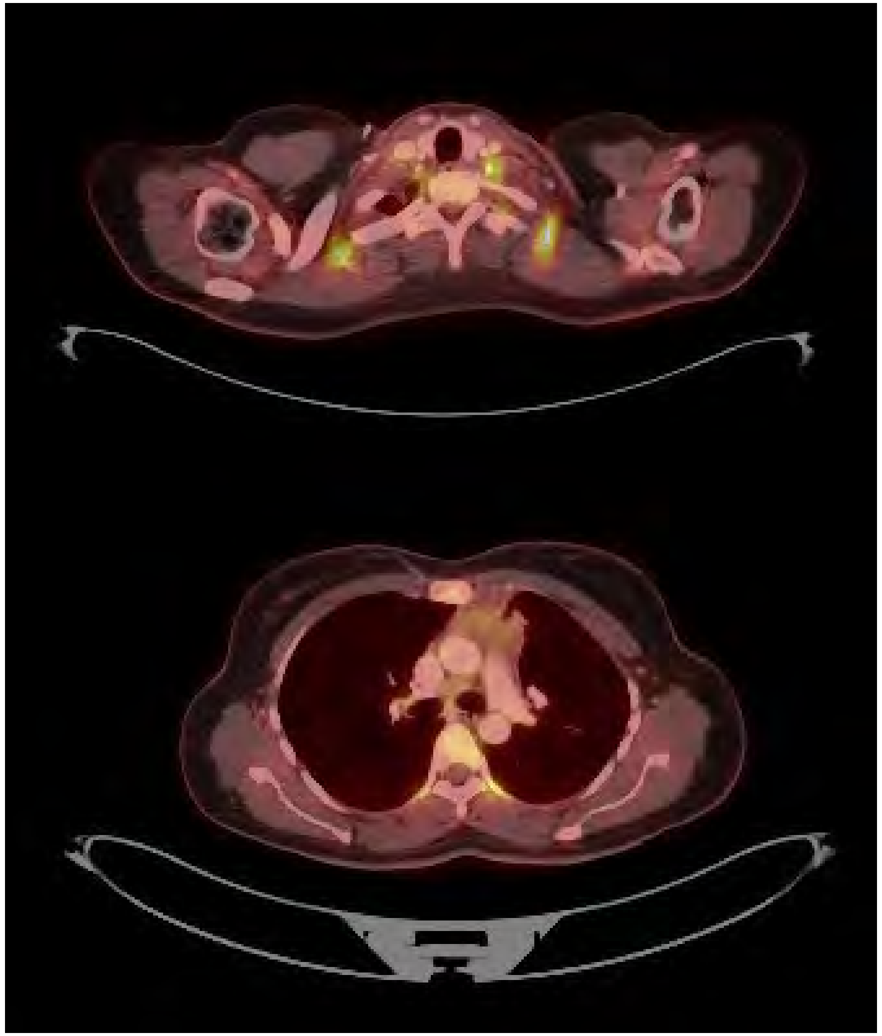
- ABVD x 2 cycles



Treatment Planning

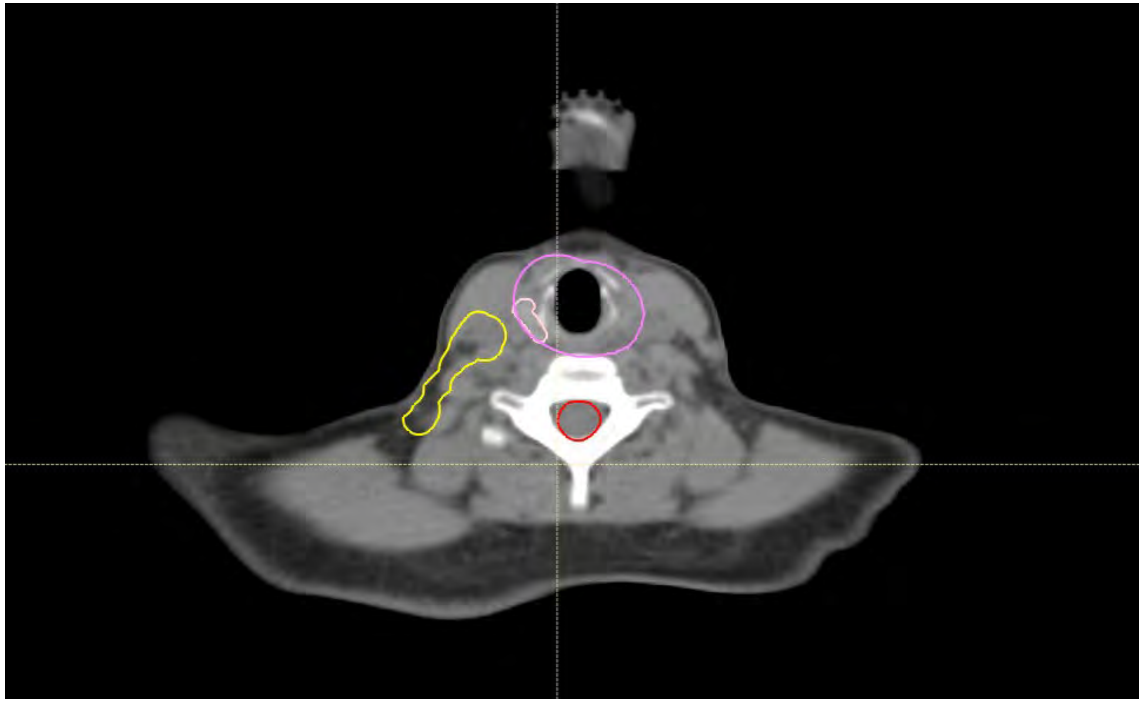
Case

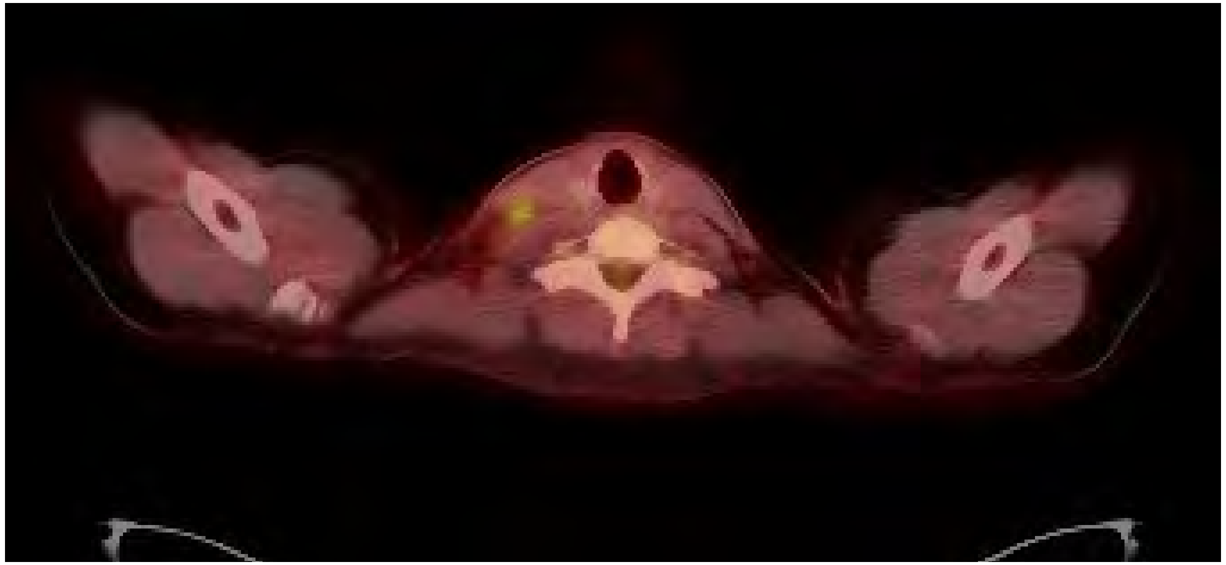
- ABVD x 4 cycles (bleo held C4)
- 5PS = 2



Contouring: ISRT

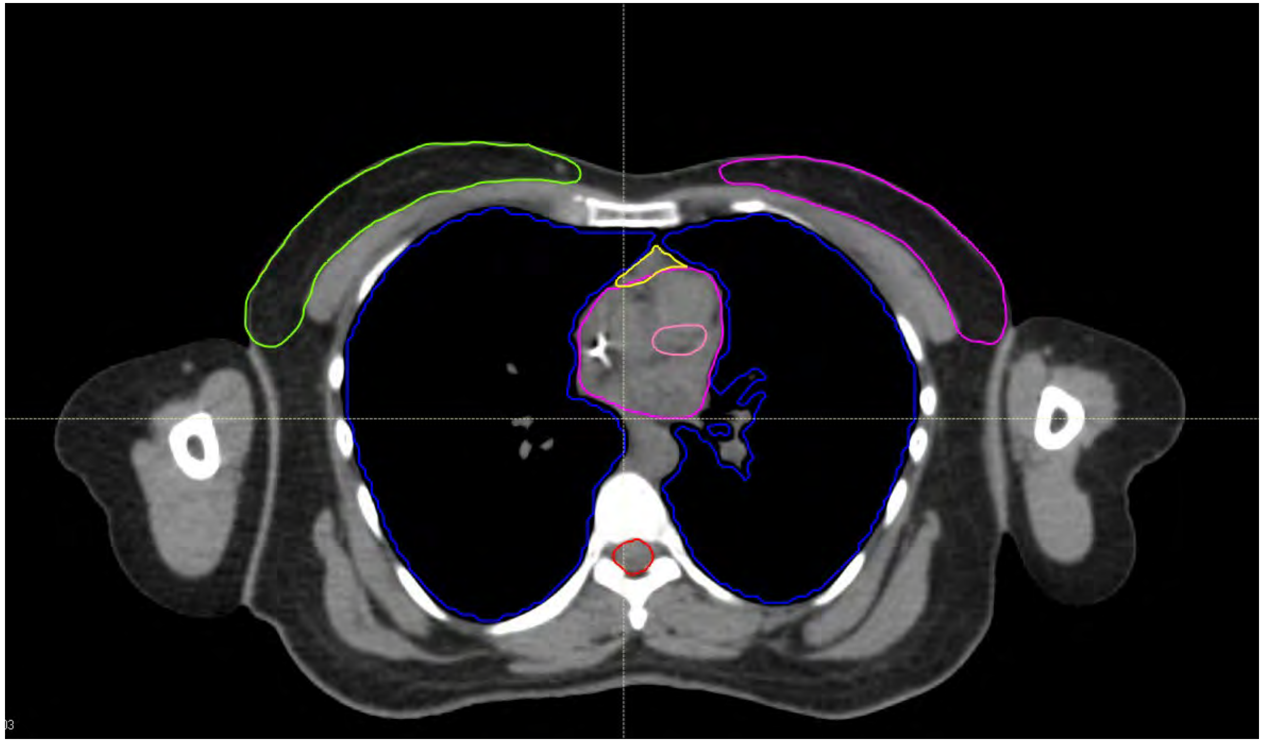
- Identify the most superior slice and inferior slice to start and end contours





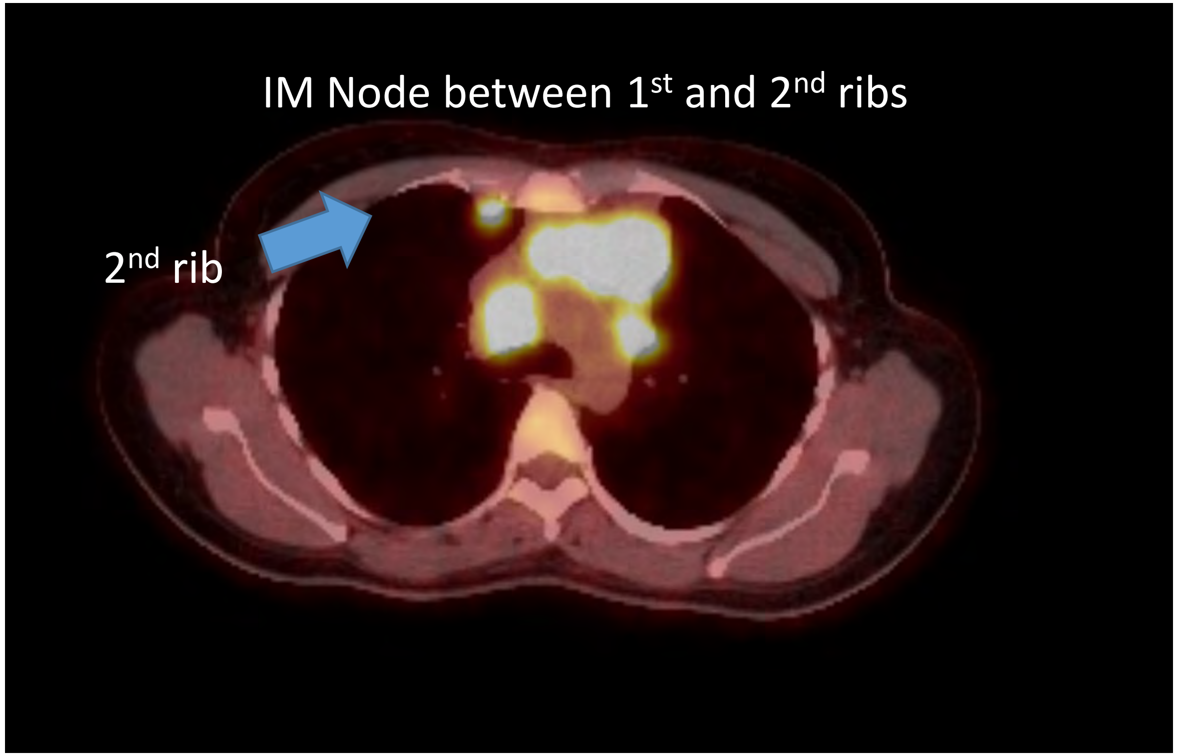
Contouring: ISRT

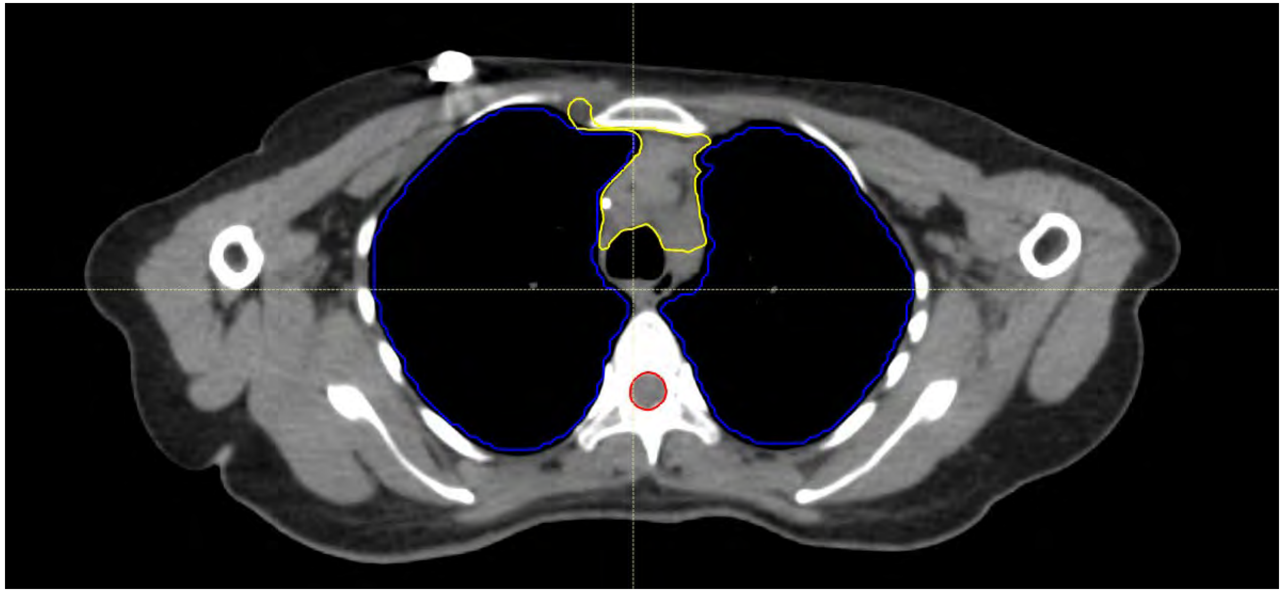
- Identify the most superior slice and inferior slice to start and end contours



Contouring: ISRT

- Identify areas that require unique attention
  - IM node? Between which ribs?
  - Paraesophageal node? At what level?
  - Hilar node? When to start and stop coverage?
  - Precise contouring when abutting the heart





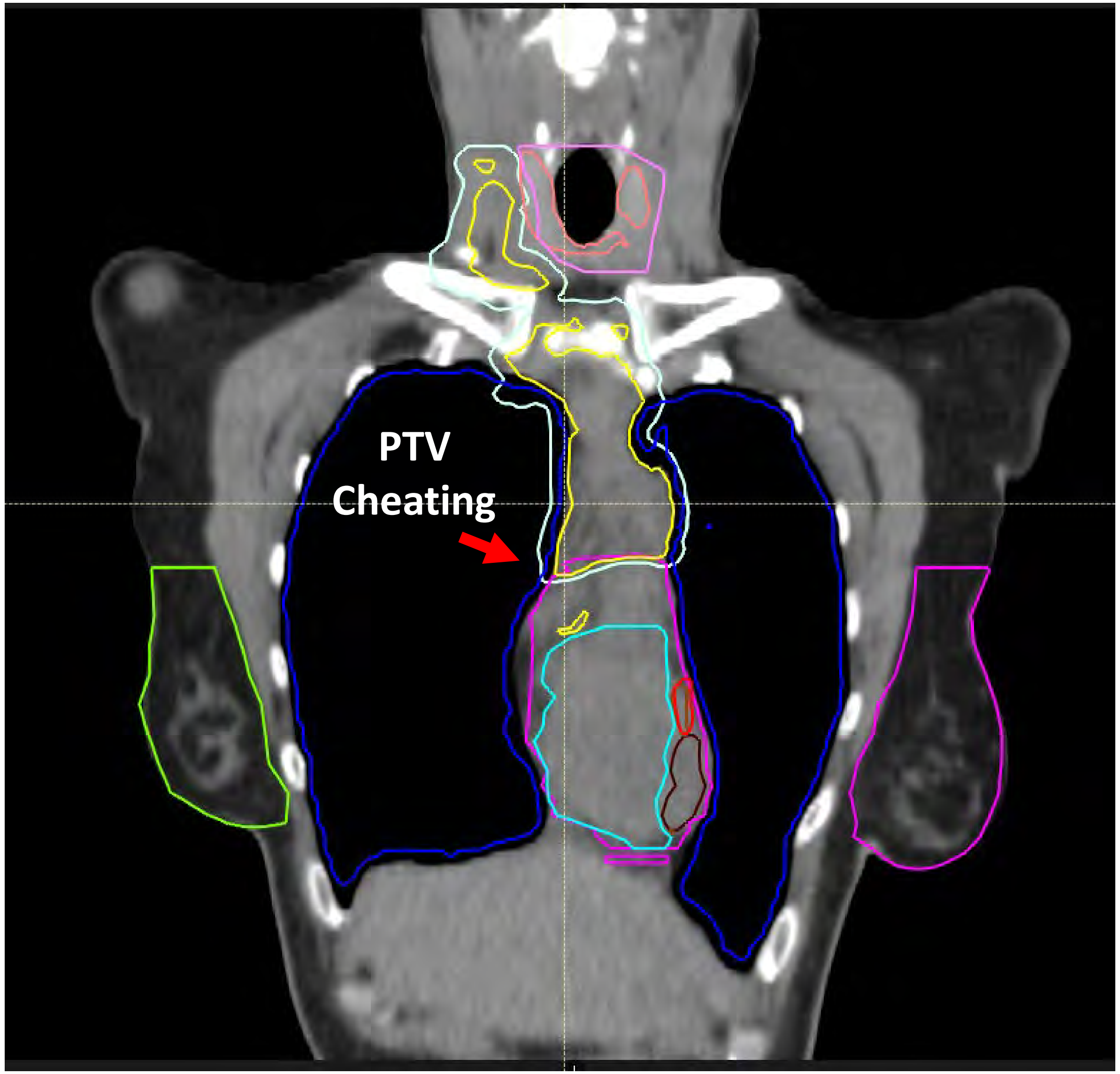
Treatment Planning

Quality of Assurance of CTV Contours

- Ideal: Review with a colleague prior to initiation of treatment planning by dosimetry

What Margin?

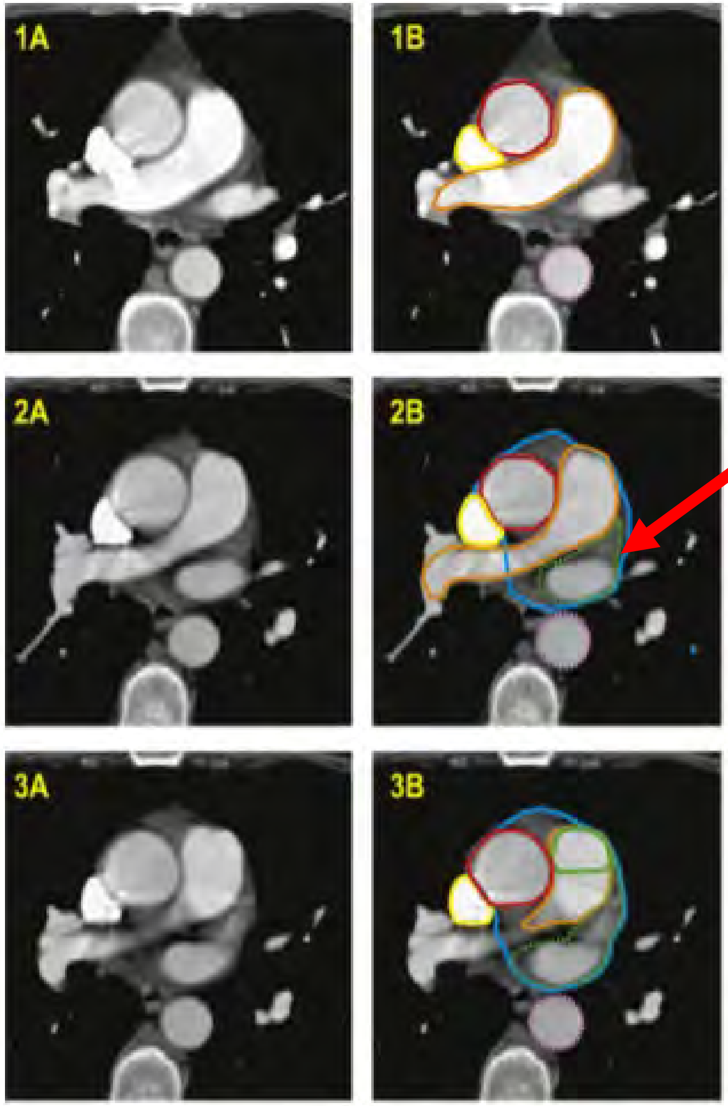
- Depends on your image guidance and motion management
- We typically use 5 mm with DIBH and daily CT



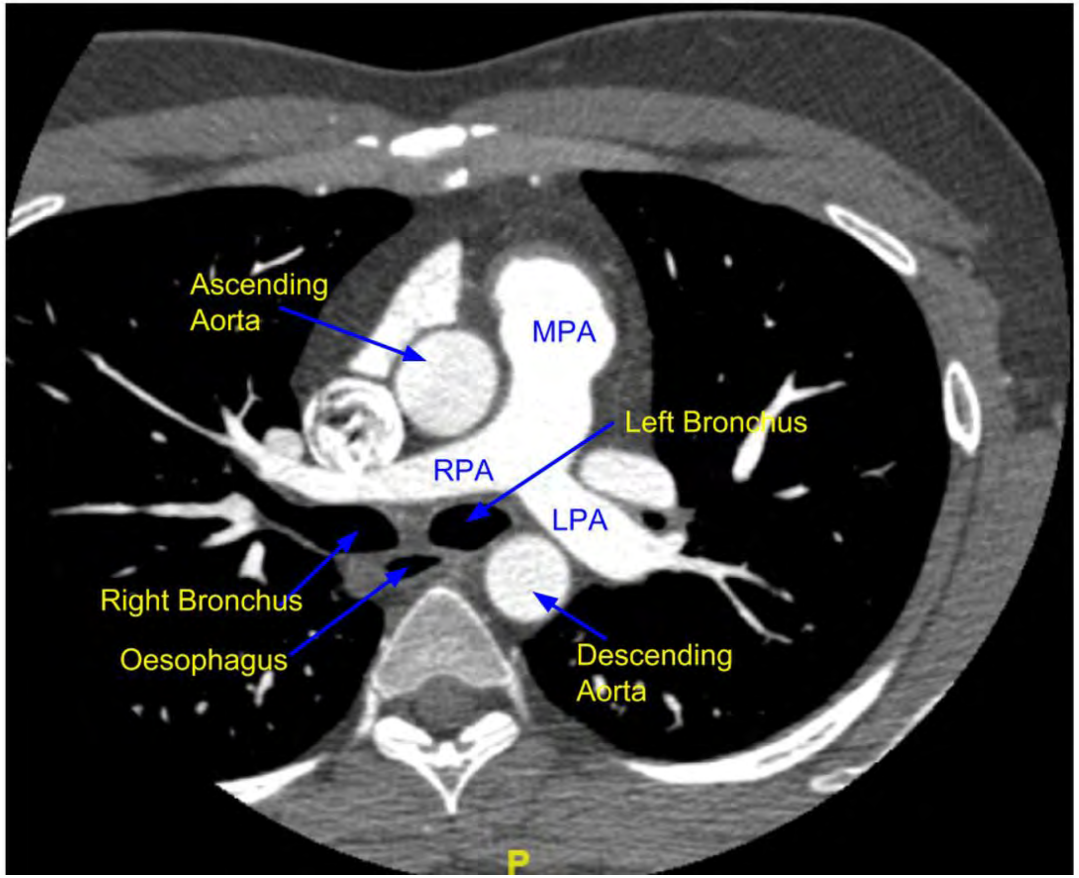
Normal Structure Delineation

- Heart
  - Total heart
  - Left ventricle
  - Left main/LAD
  - Lt circumflex
  - Rt coronary
- Lungs (b/l and individual)
- Thyroid gland
- Breasts
- Salivary Glands
- Spinal Cord
- Esophagus

Heart

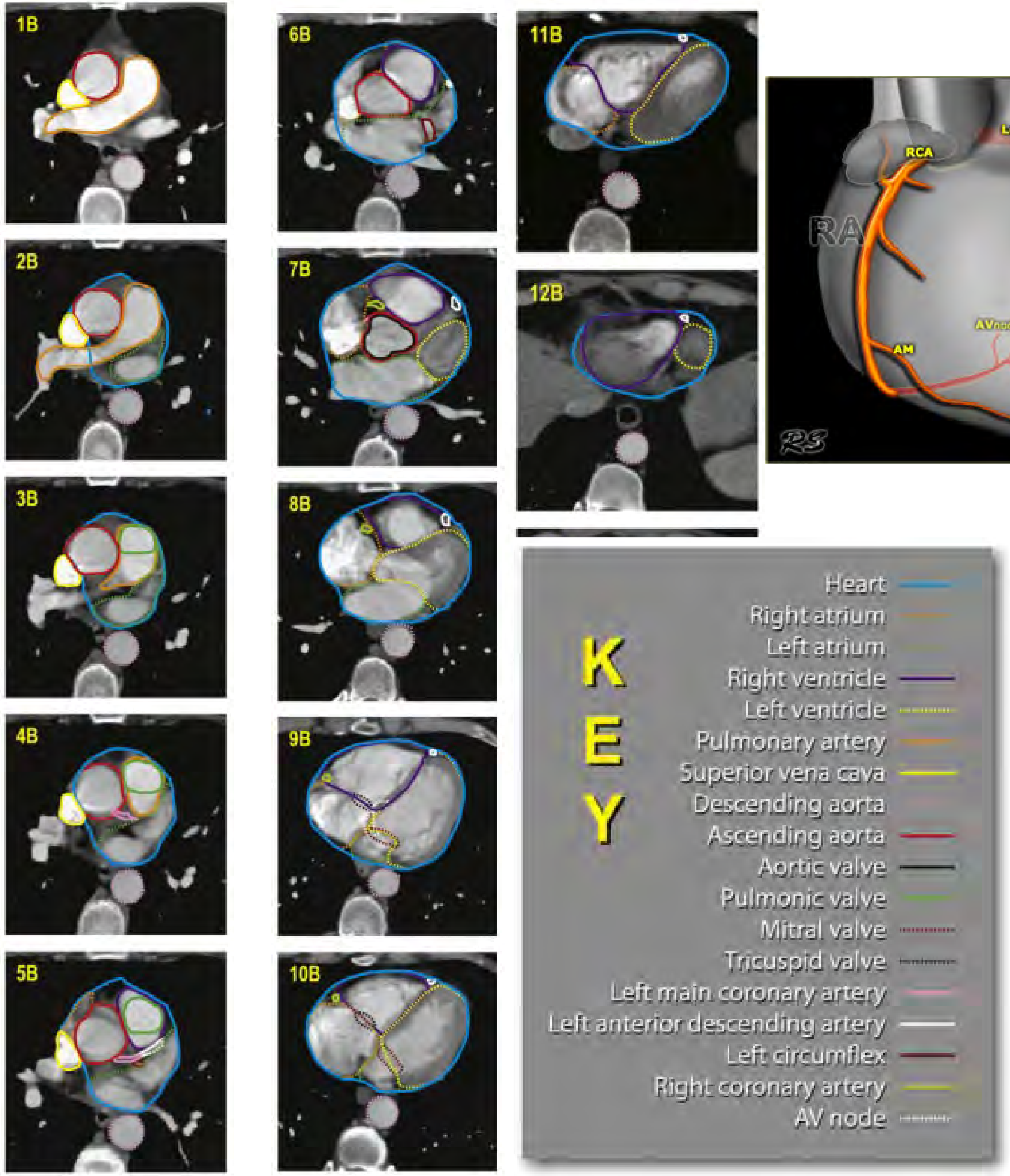


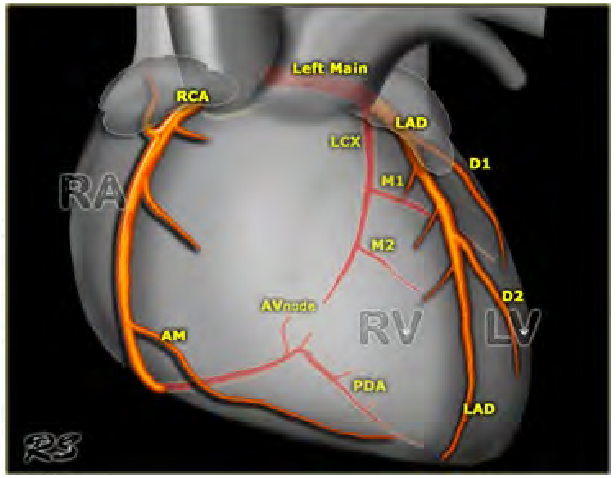
Atlas states start of whole heart contour should be at the level below left pulmonary artery



Treatment Planning

Feng et al. IJORBP 2011





Coronary Arteries

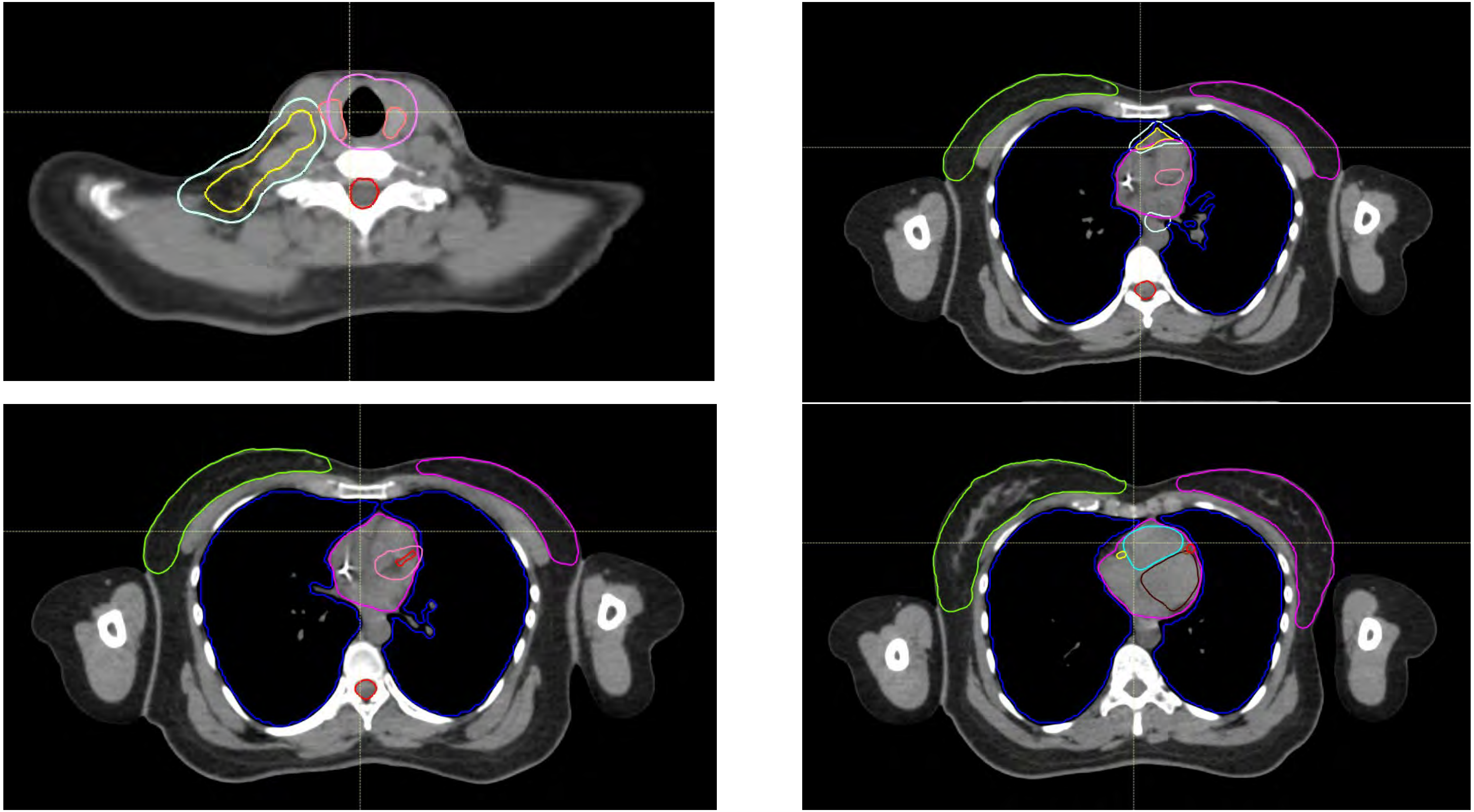
The Left Main Coronary originates from the left side of the AA, inferior to the right pulmonary artery

The LAD originates from the L coronary; runs in the interventricular groove

The left circumflex artery originates from the L coronary; runs between the LA and LV

The RCA originates from the right side of the AA; starts inferior to the L coronary

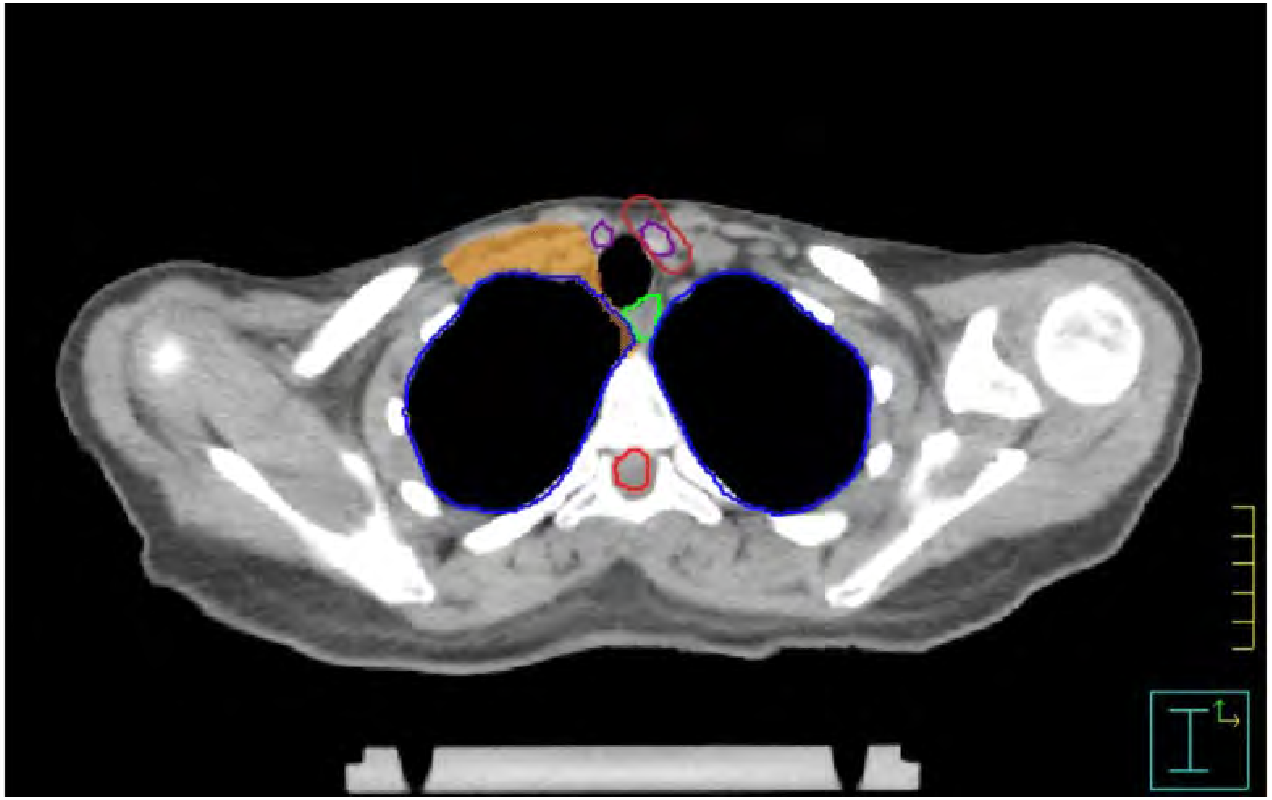
Planning: CONTOUR NORMALS



Treatment Planning

Create your own Avoidance Structures

- To enhance normal tissue sparing create a "realistic" avoidance structure



RESEARCH Open Access

Dosimetric advantages of a "butterfly" technique for intensity-modulated radiation therapy for young female patients with mediastinal Hodgkin's lymphoma

Khinh Ranh Voong[1], Kelli McSpadden[1], Chelsea C Pinnix[1], Ferial Shihadeh[1], Valerie Reed[1], Mohammad R Salehpour[2], Isidora Arzu[1], He Wang[2], David Hodgson[3], John Garcia[1], Michalis Aristophanous[2] and Bouthaina S Dabaja[1*]

Generally:
- 3 anterior beams: restricted 300°–30°
- 2 posterior beams 160°–210°

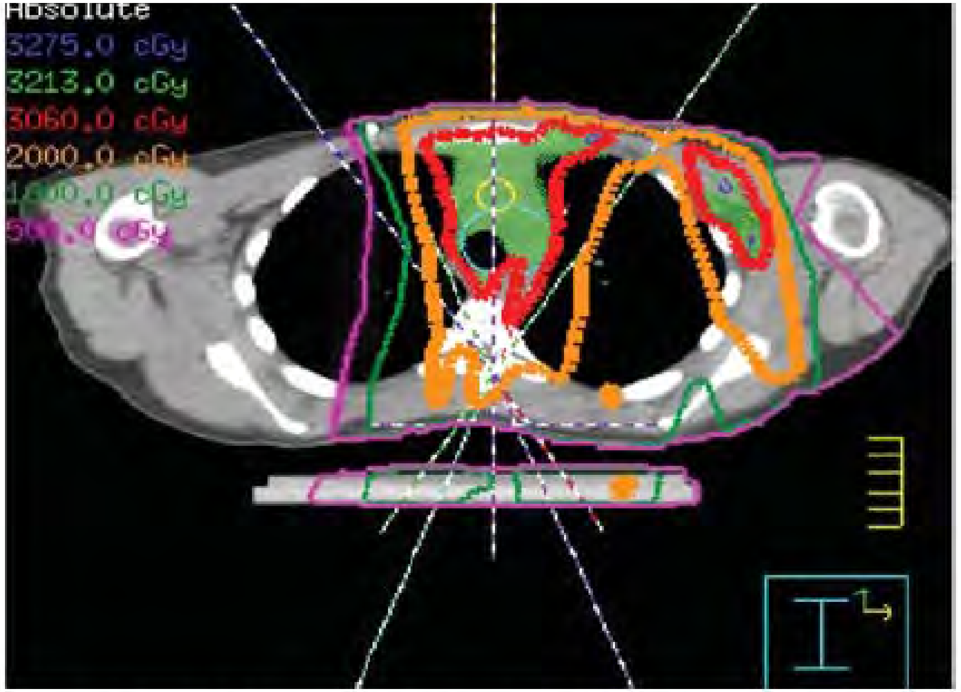


Figure 2 **Axial CT treatment-planning scan shows beam angles for the butterfly technique.**

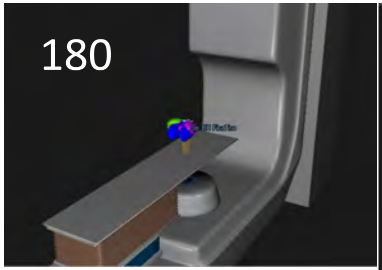
Treatment Planning

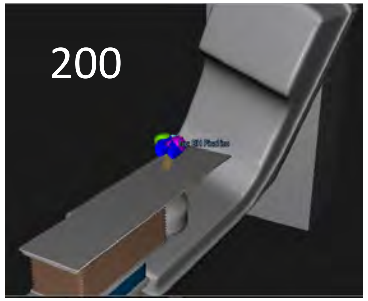
Beam Arrangement: AP/PA Weighted

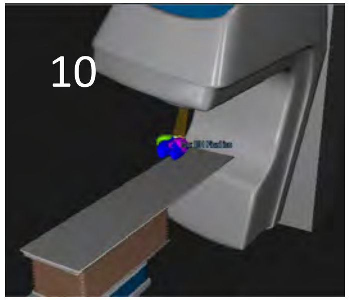
Plan | Beams | Control points | Jaw assignment | Setup beams | Beam dose specification points | Prescriptions

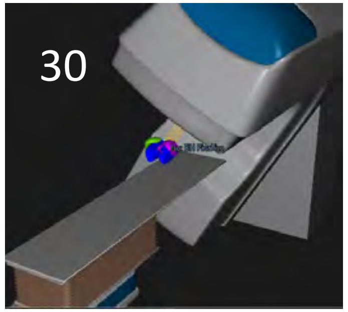
Copy from... | Patient setup... | Create bolus... | Renumber beams... | Load template... | Save as template...

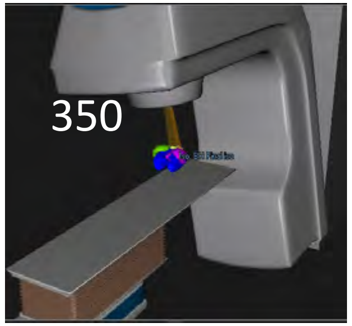
No.		Name	Description	Isocenter [cm] Name	R-L	I-S	P-A	SSD [cm] To surface	To skin	Energy [MV]	Gantry [deg]	Coll. [deg]	Couch [deg Non-IEC] Rotation	No. of segm	MU/fx	Bolus	Jaw max aperture [cm Non-IEC] X1	X2	Y1	Y2
1		A	000-200 B...	BH Final iso	-0.82	43.57	-2.96	72.26	78.59	6	200.0	0.0	0.0	6	73.00	*(None)*	2.60	11.00	5.50	9.00
2		B	000-330 B...	BH Final iso	-0.82	43.57	-2.96	83.93	83.93	6	330.0	0.0	0.0	7	68.00	*(None)*	5.60	9.70	7.50	10.50
3		C	000-350 B...	BH Final iso	-0.82	43.57	-2.96	85.88	85.88	6	350.0	0.0	0.0	11	84.00	*(None)*	9.00	7.20	7.50	10.50
4		D	000-010 B...	BH Final iso	-0.82	43.57	-2.96	86.16	86.16	6	10.0	0.0	0.0	8	76.00	*(None)*	11.10	4.90	7.00	10.00
5		E	000-030 B...	BH Final iso	-0.82	43.57	-2.96	84.87	84.87	6	30.0	90.0	0.0	15	111.00	*(None)*	7.60	9.80	3.00	12.50
6		F	000-160 B...	BH Final iso	-0.82	43.57	-2.96	72.26	78.59	6	160.0	90.0	0.0	9	70.00	*(None)*	6.00	8.10	6.50	7.50
7		G	000-180 B...	BH Final iso	-0.82	43.57	-2.96	73.92	79.88	6	180.0	90.0	0.0	13	126.00	*(None)*	6.00	8.10	9.00	6.00

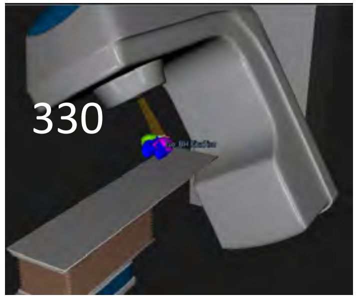












Treatment Planning

What About Protons?

Proton therapy in Hodgkin lymphoma

Life years lost attributable to late effects after radiotherapy for early stage Hodgkin lymphoma: The impact of proton therapy and/or deep inspiration breath hold

Radiotherapy and Oncology 125 (2017) 41–47

Laura Ann Rechner[a,b,*], Maja Vestmø Maraldo[a], Ivan Richter Vogelius[a], Xiaorong Ronald Zhu[c], Bouthaina Shbib Dabaja[d], Nils Patrik Brodin[e], Peter Meidahl Petersen[a], Lena Specht[a], Marianne Camille Aznar[b,f]

[a] Department of Oncology, Rigshospitalet, University of Copenhagen; [b] Niels Bohr Insitute, University of Copenhagen; [c] Department of Radiation Physics, The University of Texas MD Anderson Cancer Center; [d] Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center; [e] Institute for Onco-Physics, Albert Einstein College of Medicine and Montefiore Medical Center, Bronx, USA; [f] Nuffield Department of Population Health, University of Oxford, Oxford, United Kingdom

- Purpose: Compare the life years lost (LYL) attributable to late effects after mediastinal RT using IMRT in free breathing (FB) and DIBH, and proton therapy in FB and DIBH
- Plans for each technique were created for 22 patients with HL
- The use of DIBH, proton therapy, and the combination significantly reduced the LYL compared to IMRT in Free-breathing
- The **lowest LYL was found for proton therapy in DIBH**
- However, **when IMRT in DIBH was compared to proton therapy in FB, no significant difference was found**
- Conclusions: Patient-specific plan comparisons should be used to select the optimal technique when comparing IMRT in DIBH and proton therapy in FB

Proton therapy in Hodgkin lymphoma

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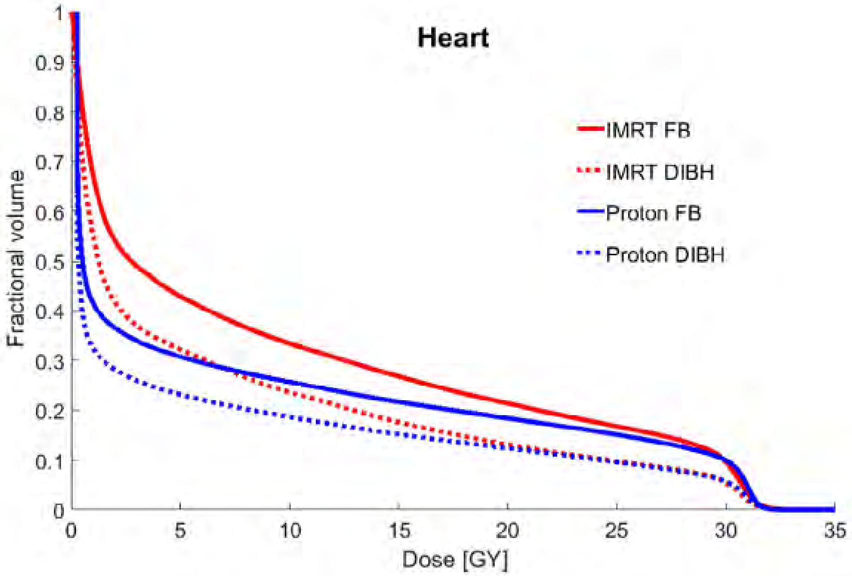


Fig. 2. Mean cumulative dose-volume histograms (DVHs) for the heart for intensity modulated radiation therapy (IMRT) in free breathing (FB), IMRT in deep inspiration breath hold (DIBH), proton therapy in FB, and proton therapy in DIBH for the 22 patients studied.

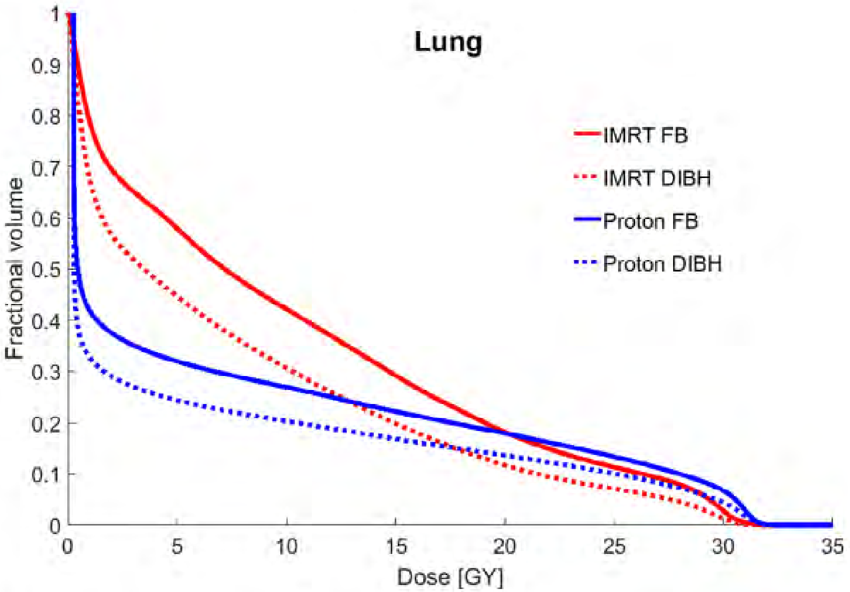


Fig. 3. Mean cumulative dose-volume histograms (DVHs) for the lungs for intensity modulated radiation therapy (IMRT) in free breathing (FB), IMRT in deep inspiration breath hold (DIBH), proton therapy in FB, and proton therapy in DIBH for the 22 patients studied.

IMRT DIBH vs Proton FB: IMRT with increased low doses (5 Gy), Proton with increased higher doses (15-30 Gy)

Treatment Planning

The Impact of DIBH: MDACC

Characteristic	Patients (n=15) No.	%
Age, years, median (range)	32 (24–44)	
Sex		
Male	6	*40*
Female	9	*60*
Lymphoma subtype		
Hodgkin	12	*80*
Marginal zone	1	*7*
PMBCL	1	*7*
T cell	1	*7*
Disease stage		
IB	1	*7*
IIA	6	*40*
IIB	5	*33*
IIIB	1	*7*
Other	2	*13*
Bulky disease		
Yes	6	*40*
No	9	*60*
Pericardial disease		
Yes	12	*80*
No	3	*20*
Right heart disease		
Yes	9	*60*
No	6	*40*
Left heart disease		
Yes	3	*20*
No	12	*80*
Superior disease extent		
Hyoid/larynx	6	*40*
Thyroid	9	*60*
Inferior disease extent		
Middle third sternum	10	*67*
Lower third sternum	5	*33*
Type of mediastinal involvement		
Upper mediastinum only	2	*13*
Whole mediastinum	13	*87*
Chemotherapy		
ABVD	12	*80*
R-CHOP	1	*7*
Other	2	*13*
Chemotherapy cycles		
2	1	*7*
4	4	*27*
6	8	*53*
>6	2	*13*

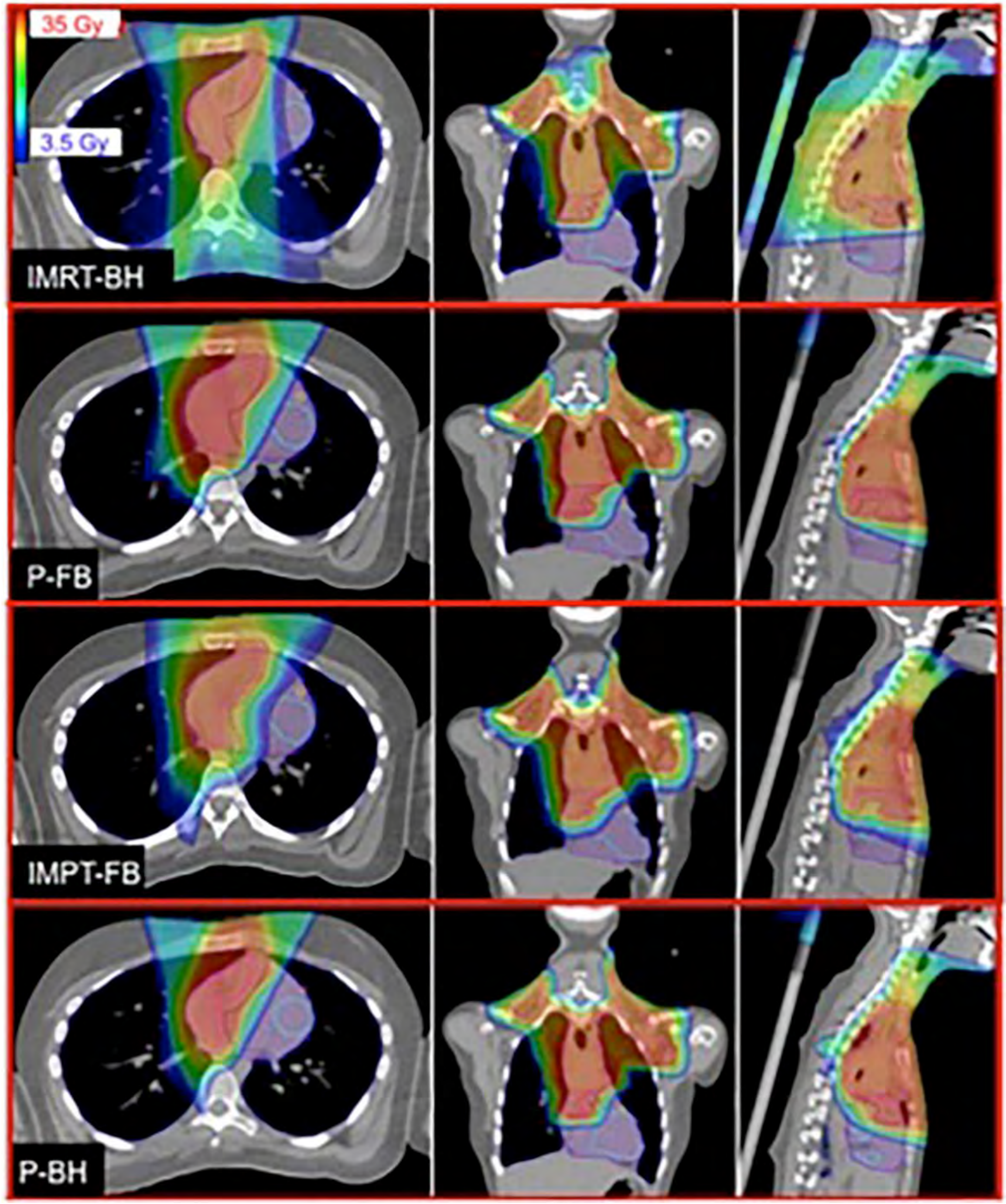
- 15 patients treated with involved-site RT with “butterfly” IMRT-DIBH to 30.6 Gy
- 3 proton comparison plans were generated:
  - Passive Free Breathing (P-FB)
  - Intensity Modulated Proton Therapy Free Breathing (IMPT-FB)
  - Passive Scatter Breathhold (P-BH)
- Dosimetric variables (mean dose, V30, V25, V15 and V5) for OARs were calculated and compared with non-parametric Wilcoxon signed-rank tests

- Median patient age was 32 years
- Most (80%) had Hodgkin lymphoma and involvement of the whole mediastinum (87%)
- **DIBH increased lung volume by a median 47.7% (mean 64.4%, range 38.0–133.5%)**

AC Moreno, JR Gunther, SA Milgrom, T Andraos, CD Fuller, M oyervides, T Williamson, A Lie, R Wu, R Zhu, BS Dabaja and CC Pinnix. A Dosimetric Comparison of Intensity-Modulated Radiotherapy via Breath Hold Technique and Proton Therapy With or Without Breath Hold for Mediastinal Lymphoma, ASTRO 2017 and Submitted

The Impact of DIBH: MDACC

- Of 57 studied OAR parameters, IMRT-BH plans were comparable in:
  - 37 (65%) parameters with P-FB plans
  - 32 (56%) of IMPT-FB parameters
  - 30 (53%) of P-BH
- Doses to coronaries, breasts, and thyroid were generally equivalent among plans
- Mean doses and V5 of the total lung and heart were the highest with IMRT-BH
- IMRT-BH resulted in comparable heart and superior lung V30 parameters relative to proton plans
- Conclusion:
  - **Among patients with mediastinal lymphoma, normal tissue sparing can be reasonably achieved using either IMRT-BH or proton FB techniques**
  - **Proton therapy via BH provides additional benefits in lung sparing.**

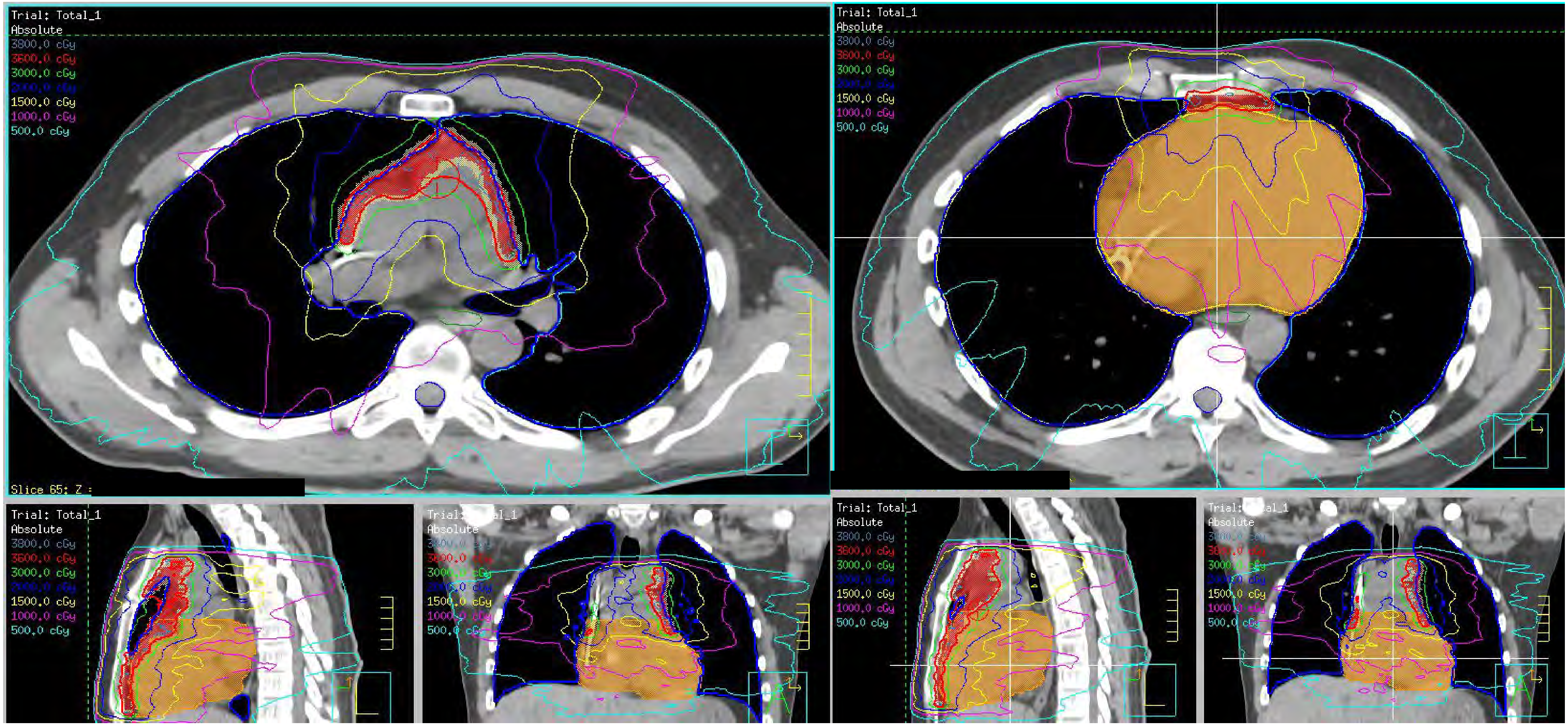


Plan Assessment

Obsession with the 5 Gy Line

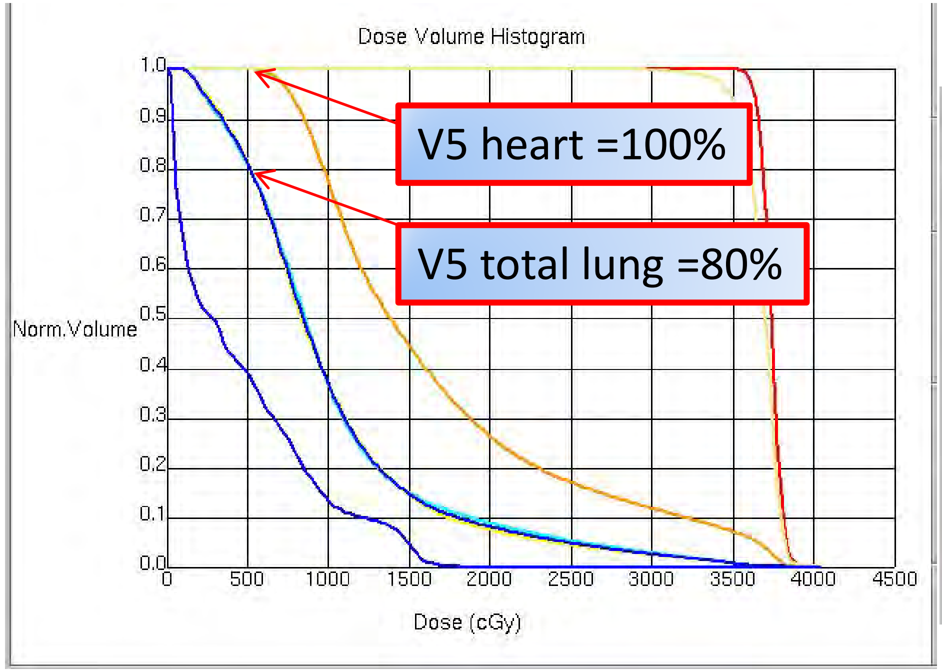
- RT related side effects after moderate dosed radiation therapy (20-30 Gy) have a prolonged latency period
  - This makes it difficult to course correct based on data driven dose constraints
- We optimize plans for the 5 Gy line in an effort to reduce the overall radiation therapy footprint

IMRT for mediastinal lymphoma – Planning Pitfalls



Plan Assessment

IMRT- HIGH CONFORMALITY IS NOT THE PRIORITY



ROI Statistics

Line Type	ROI	Trial or Record	Min.	Max.	Mean	Std. Dev.
	RT LUNG	Total_1	89.5	3788.0	982.4	642.7
	LT LUNG	Total_1	55.2	3818.1	998.0	671.8
	HEART	Total_1	482.6	3998.8	1666.4	858.6
	SPINAL CORD	Total_1	9.6	1813.2	455.2	464.3
	GTV	Total_1	2916.0	4022.6	3735.1	62.5
	CTV	Total_1	1786.9	4022.6	3677.7	122.0
	Total Lung	Total_1	55.2	3818.1	989.6	656.5

High conformality of prescription dose at expense of low doses

Plan Assessment

Cardiac Constraints

- QU
  - “Hist … onably well tolerated
  - “Seems prud … <15 Gy”
  - For r

Cardiac Constraints

- 4122 5-year childhood cancer survivors diagnosed before 1986 (UK and France)
- Higher risk of cardiac death for:
  - Cumulative anthracycline > 360 mg/m^2
  - Mean heart dose > 5Gy
    - RR 12.5 for 5-15 Gy
    - RR 25 for >15 Gy

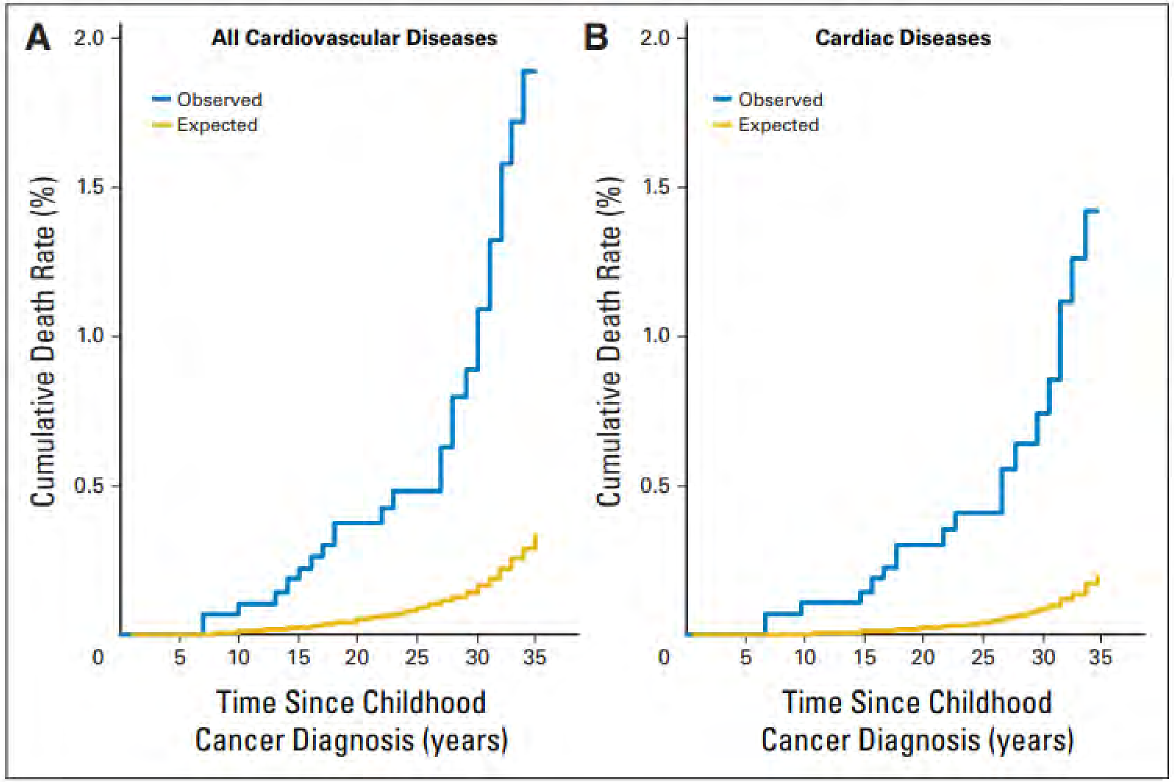


Fig 3. Estimates of (A) cumulative cardiovascular and (B) cardiac mortality in the French-British cohort and expected in the general population in France and Great Britain.

Tukenova M, Guibout C, Oberlin O, Doyon F, Mousannif A, Haddy N, Guérin S, Pacquement H, Aouba A, Hawkins M, Winter D, Bourhis J, Lefkopoulos D, Diallo I, de Vathaire F. Role of cancer treatment in long-term overall and cardiovascular mortality after childhood cancer. J Clin Oncol. 2010 Mar 10;28(8):1308-15. PMID: 20142603.

Cardiac Constraints

- 24,215 5-year childhood cancer survivors (1970 -1999)
- Cardiac Disease: G3-G5 CAD, HF, valvular disease, pericardial disease, and arrhythmias
- Cumulative incidence of cardiac disease 30 yrs from diagnosis: 4.8%
- **Low to moderate radiotherapy doses (5.0 to 19.9 Gy) to large cardiac volumes (≥ 50% of heart)** were associated with an increased rate of cardiac disease (RR, 1.6) compared with survivors without cardiac radiotherapy exposure
- **High doses (≥ 20 Gy) to small cardiac volumes** (0.1% to 29.9%) were associated with an elevated rate (RR 2.4)

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

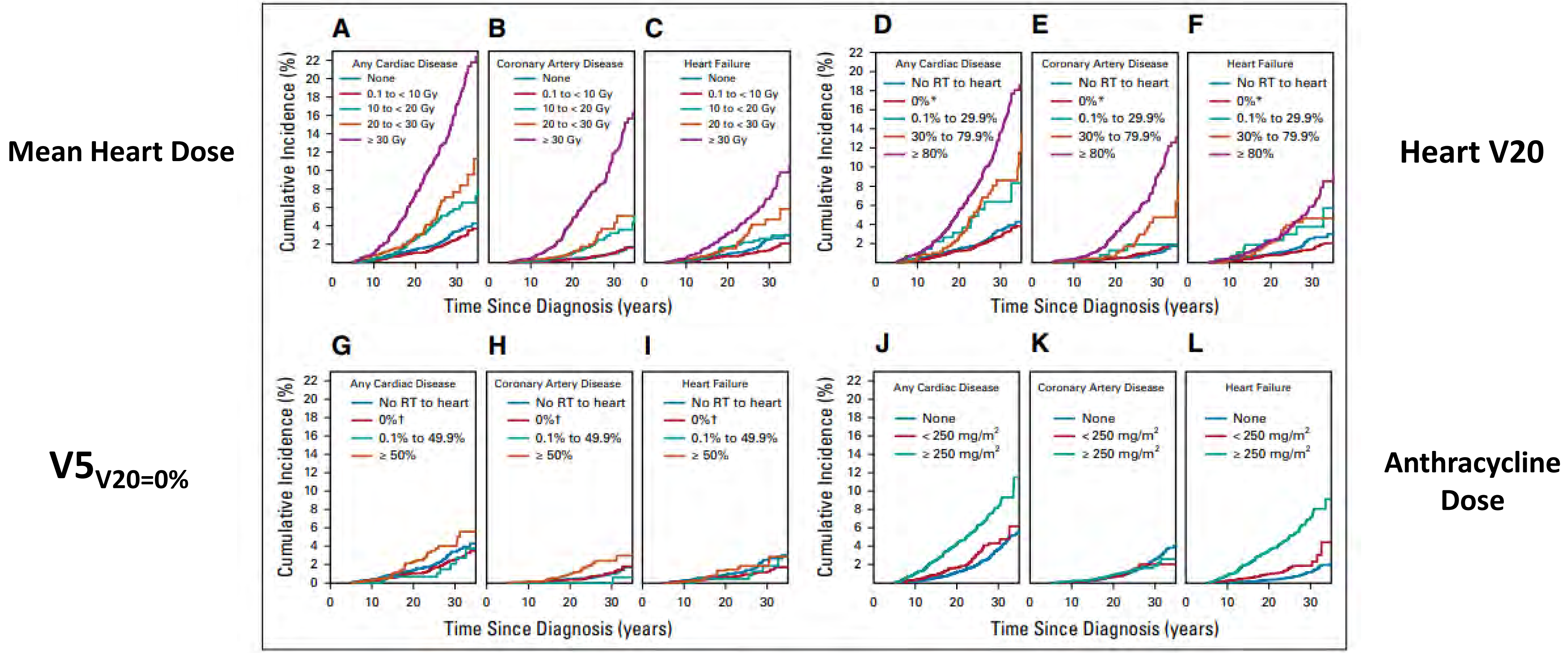


FIG 1. Cumulative incidence, based on (A-C) mean heart dose, (D-F) volume of heart (%) receiving radiotherapy (RT) greater than or equal to 20 Gy, and (G-I) voulme of heart (%) receiving RT greater than or equal to 5 Gy when maximum heart dose is less than 20 Gy. (J-L) Cumulative anthracycline dose.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

RT and Anthracyclines

- Anthracyclines increase heart failure rate by 3 fold independently of RT
- We must work to keep the RT cardiac dose to as low as possible

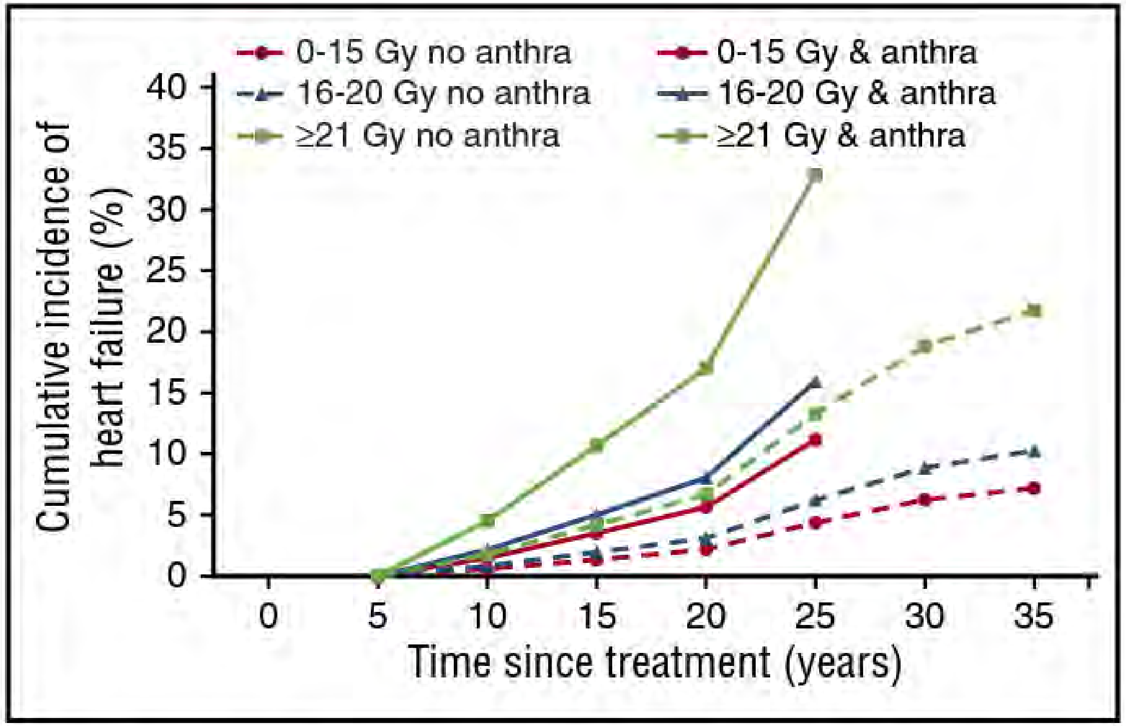


Figure 2. Approximate cumulative risks of HF by MLVD and whether treatment with anthracyclines was given. Modeled cumulative risk of HF as first cardiac event among 5-year survivors of HL by time since initial HL treatment of categories of MLVD (Gy). Lines indicate estimated cumulative incidences for dose categories (0-15 Gy, 16-20 Gy, and ≥21 Gy) with and without anthracycline exposure. Cumulative risks were calculated with other heart disease or death as a competing risk. Further details are given in supplemental Text 3.

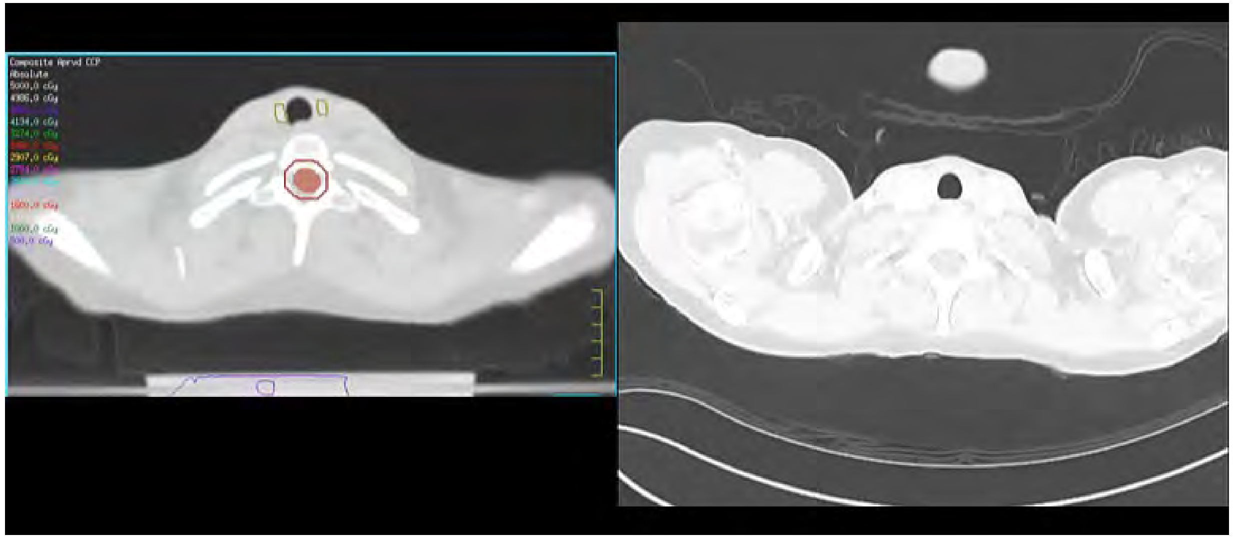
van Nimwegen FA, Ntentas G, Darby SC, Schaapveld M, Hauptmann M, Lugtenburg PJ, Janus CPM, Daniels L, van Leeuwen FE, Cutter DJ, Aleman BMP. Risk of heart failure in survivors of Hodgkin lymphoma: effects of cardiac exposure to radiation and anthracyclines. Blood. 2017 Apr 20;129(16):2257-2265. PMID: 28143884

Radiation Pneumonitis

- Classic presentation: dry cough, dyspnea, low grade fever, pleuritic chest pain

* **Table 1** Radiation Therapy Oncology Group acute radiation morbidity scoring criteria for pneumonitis

Grade	Description
1	Mild symptoms of dry cough or dyspnea on exertion
2	Persistent cough requiring narcotic antitussive agents or dyspnea with minimal effort but not at rest
3	Severe cough unresponsive to narcotic antitussive agents or dyspnea at rest or clinical or radiologic evidence of acute pneumonitis for which intermittent oxygen or steroids may be required
4	Severe respiratory insufficiency requiring continuous oxygen or assisted ventilation



* From Fox AM ,Dosoretz AP, Mauch PM, Yu-Hui C, Fisher DC, LaCasce AS, Freedman AS, Silver BA and Ng AK, Predictive Factors for Radiation Pneumonitis in HL Patients Receiving Combined-Modality Therapy, Red J, Vol 83, 2012

Plan Assessment

Radiation Pneumonitis Among Patients treated with 3D Conformal RT

Study	# RP cases	% RP	Dosimetric Predictors	Risk factors	Type of RT
PMH (Koh *et al*)	2/64	3%	V20>36%, MLD> 14 Gy	HDT and Autologous SCT	3D conformal, IFRT
Harvard (Fox *et al*)	13/92	14% (10% consolidation, 35% RR)	MLD>13.5 Gy, V20>33.5%	Peri-transplant RT for RR disease (esp. pre-SCT)	3D conformal, modified IFRT

- Patients treated for RR (relapsed/refractory) disease at greatest risk
- Mean lung dose and V20 predominate as predictors of RP

Predictors of RP among Lymphoma Patients treated with IMRT to the Mediastinum

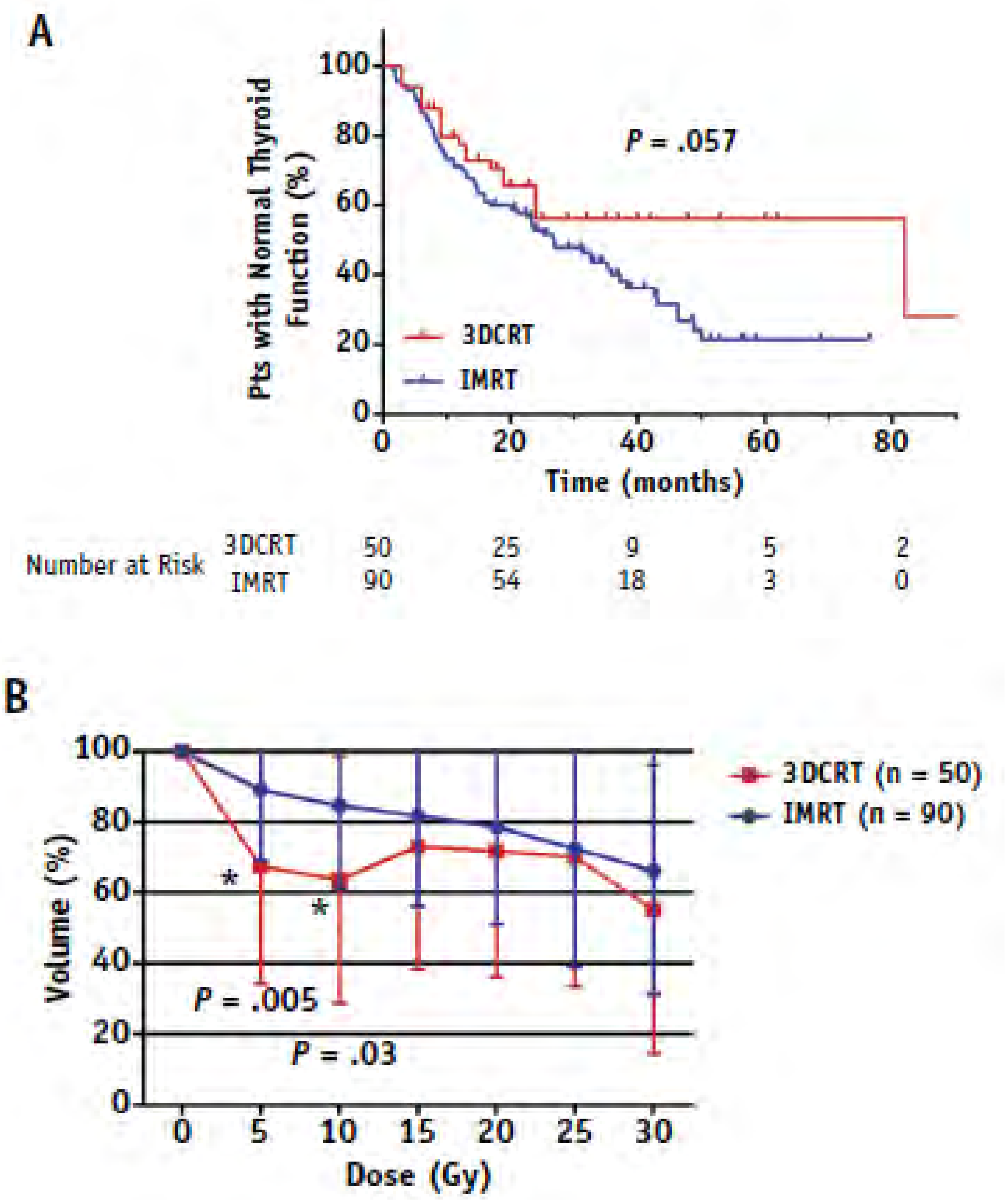
- 150 pts HL or NHL
  - 110 Newly Diagnosed; 40 Relapsed/Refractory
- Overall incidence of RP=14%
  - 10% for patients treated for consolidation
  - 25% for relapsed/refractory disease
- Several dosimetric factors were associated with RP:
  - **Mean Lung Dose (MLD) >13.5 Gy and V5>55%** were most significant
- For patients who received IMRT after frontline chemotherapy, RP incidence was significantly lower after implementation of the DLCs (0/49) compared to those treated before (16/146) (0 vs 11%, p=0.02). (Noticewala S et al, ASTRO 2019)

Odds Ratio Estimates and Wald Confidence Intervals			
Parameter	**OR**	**95% Confidence Limits**	**P-value**
MLD> 13.5 Gy	8.235	3.054 - 22.210	<.0001
V5> 55%	7.117	2.986 - 16.964	<.0001
V10> 40%	4.546	1.950 - 10.595	0.0005
V15> 35%	4.965	2.094 - 11.771	0.0003
V20> 30%	4.353	1.693 - 11.195	0.0023

CC Pinnix, GL Smith, S Milgrom, EM Osborne, JP Reddy, M Akhtari, V Reed, I. Arzu, PK Allen, CF. Wogan, MA Fanale, Y Oki, F Turturro, J Romaguera, L Fayad, N Fowler, J Westin, L Nastoupil, MD, FB. Hagemeister, MA Rodriguez, S Ahmed, Y Nieto, BS Dabaja, MD, **Predictors of Radiation Pneumonitis in Patients Receiving Intensity Modulated Radiation Therapy for Hodgkin and Non-Hodgkin Lymphoma**, Red J, Vol 92, 2015

Hypothyroidism

- Among 50 HL pts treated in Italy with 3D conformal RT, the total thyroid V30 predicted risk of developing hypothyroidism[1]
  - V30≤ 62.5% the risk of HT was 11.5%, vs 70.8% if V30>62.5%
- Among 90 HL pts treated with IMRT at MDACC, the V25 and the volume spared 25 Gy both predicted risk of developing HT[2]
  - V25≤63.5% the risk of HT was 37% vs 80% V25>63.5%
  - Incidence of HT higher among IMRT cohort than Italian cohort
  - Utilization of **thyroid avoidance** structure decreased the risk



Plan Assessment

[1]Cella L et al, Thyroid V30 predicts radiation-induced hypothyroidism in patients treated with sequential chemo-radiotherapy for HL, Red J 2012
[2]Pinnix CC, Cella L et al, Predictors of hypothyroidism in HL survivors after IMRT versus 3D radiation therapy Accepted, Red J 2018

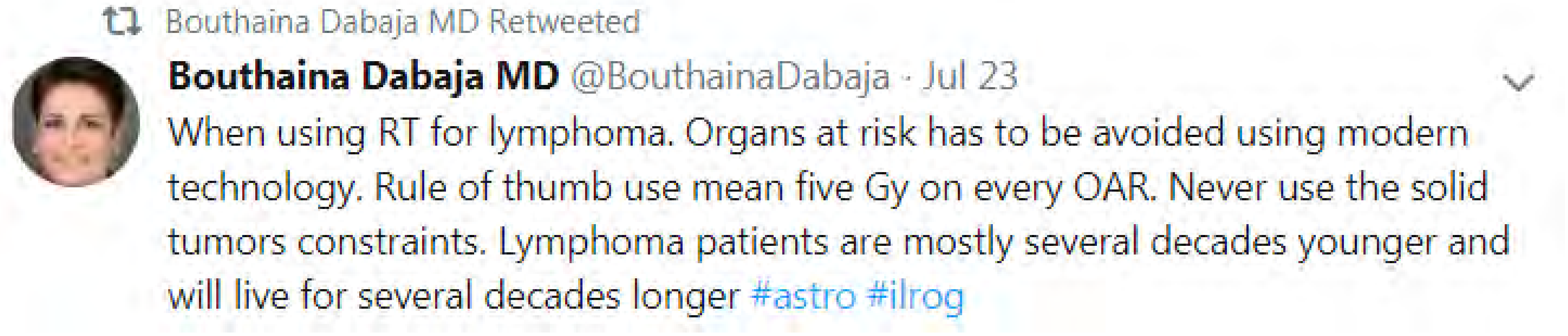
Secondary Breast Cancer

- 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.

Dose constraints for HL Patients

- Submandibular glands: mean < 11 Gy (Ng et al, Red J, 2009), ALARA
- Thyroid: V25<63.5% (IMRT cohort, Pinnix et al Red J 2018; risk 80% vs 37%)
- Lung: Mean ≤ 13.5 Gy, V20 < 30%, V5 < 55% (Pinnix et al, Red J, 2015)
- Heart: Ideally mean < 5 Gy, (Tukenova M et al JCO 2010); Limit V20 dose and V5 dose (Bates et al JCO 2019), If MHD is >15 Gy consider omitting RT (van Nimwegen et al, JCO 2016)
  - Avoid hot spots in coronaries, LV
- Breasts: ALARA/Mean < 4 Gy (Travis JAMA 2003), Keep 5 Gy line off if possible



Plan Assessment

***Richard T. Hoppe, MD/Chair §**
Stanford Cancer Institute

***Ranjana H. Advani, MD/Vice Chair †**
Stanford Cancer Institute

Richard F. Ambinder, MD, PhD †
The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins

Philippe Armand, MD, PhD ‡
Dana-Farber/Brigham and Women's Cancer Center

Celeste M. Bello, MD, MSPH †
Moffitt Cancer Center

Cecil M. Benitez, MD, PhD ¥ §
UCLA Jonsson Comprehensive Cancer Center

Weina Chen, MD, PhD ≠
UT Southwestern Simmons Comprehensive Cancer Center

Sheen Cherian, MD §
Case Comprehensive Cancer Center/ University Hospitals Seidman Cancer Center and Cleveland Clinic Taussig Cancer Institute

Bouthaina Dabaja, MD §
The University of Texas MD Anderson Cancer Center

Megan E. Daly, MD §
UC Davis Comprehensive Cancer Center

Jamie Flerlage, MD, MS €
St. Jude Children's Research Hospital/ The University of Tennessee Health Science Center

Leo I. Gordon, MD ‡
Robert H. Lurie Comprehensive Cancer Center of Northwestern University

Neil Hansen, MD ф
Fred & Pamela Buffett Cancer Center

Alex F. Herrera, MD ‡ ξ
City of Hope National Medical Center

Ephraim P. Hochberg, MD †
Massachusetts General Hospital Cancer Center

Patrick B. Johnston, MD, PhD ‡ † Þ
Mayo Clinic Cancer Center

Mark S. Kaminski, MD †
University of Michigan Rogel Cancer Center

Christopher R. Kelsey, MD §
Duke Cancer Institute

Vaishalee P. Kenkre, MD ‡
University of Wisconsin Carbone Cancer Center

Ryan C. Lynch, MD † ‡
Fred Hutchinson Cancer Center

Kami Maddocks, MD ‡
The Ohio State University Comprehensive Cancer Center- James Cancer Hospital and Solove Research Institute

Jonathan McConathy, MD, PhD ф
O'Neal Comprehensive Cancer Center at UAB

David Morgan, MD † ‡ ξ
Vanderbilt-Ingram Cancer Center

Carolyn Mulroney, MD † ‡ ξ
UC San Diego Moores Cancer Center

Sheeja T. Pullarkat, MD ≠
UCLA Jonsson Comprehensive Cancer Center

Rachel Rabinovitch, MD §
University of Colorado Cancer Center

Karen C. Rosenspire, MD, PhD ф
Abramson Cancer Center at the University of Pennsylvania

Stuart Seropian, MD ‡ † Þ
Yale Cancer Center/ Smilow Cancer Hospital

Michael Spinner, MD ‡
UCSF Helen Diller Family Comprehensive Cancer Center

Randa Tao, MD §
Huntsman Cancer Institute at the University of Utah

Pallawi Torka, MD ‡
Roswell Park Comprehensive Cancer Center

Jane N. Winter, MD ‡ †
Robert H. Lurie Comprehensive Cancer Center of Northwestern University

Joachim Yahalom, MD §
Memorial Sloan Kettering Cancer Center

Joanna C. Yang, MD, MPH §
Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine

NCCN
Megan Lyons, MS
Katie Stehman, PA-C, MMS
Hema Sundar, PhD

- ξ Bone marrow transplantation
- ф Diagnostic radiology
- ‡ Hematology/ Hematology oncology
- Þ Internal medicine
- † Medical oncology
- ф Nuclear medicine
- ≠ Pathology
- ¥ Patient advocacy
- € Pediatric oncology
- § Radiation oncology
- * Discussion writing committee member

Continue

NCCN Guidelines Panel Disclosures

NCCN Guidelines

OAR		Dose Recommendation (1.5–2 Gy/fraction)	Toxicity
Head and Neck	Parotid glands	Ipsilateral: Mean <11 Gy (recommended); <24 Gy (acceptable) Contralateral: ALARA[c]	Xerostomia[15,16]
	Submandibular glands	Ipsilateral: Mean <11 Gy (recommended); <24 Gy (acceptable) Contralateral: ALARA[c]	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[c]	Carotid artery atherosclerosis

OAR		Dose Recommendation (1.5–2 Gy/fraction)	Toxicity
Thorax	Heart[d]	Mean <8 Gy (recommended) Mean <15 Gy (acceptable)	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]
	Pericardium	D100 (heart) <5 Gy	Pericarditis[28]
	Coronary vessels including the left main, left anterior descending (LAD), left circumflex (LCx), and right coronary artery (RCA)[d]	LAD V15 Gy <10%[d] LCx V15 Gy <14% Coronary vessels (total)- Mean <7 Gy Minimize the maximum dose to individual coronary arteries	Major adverse cardiac events[29]
	Lungs	Mean dose <13.5 Gy V20 <30% V5 <55%	Pneumonitis[30,31]

NCCN Guidelines

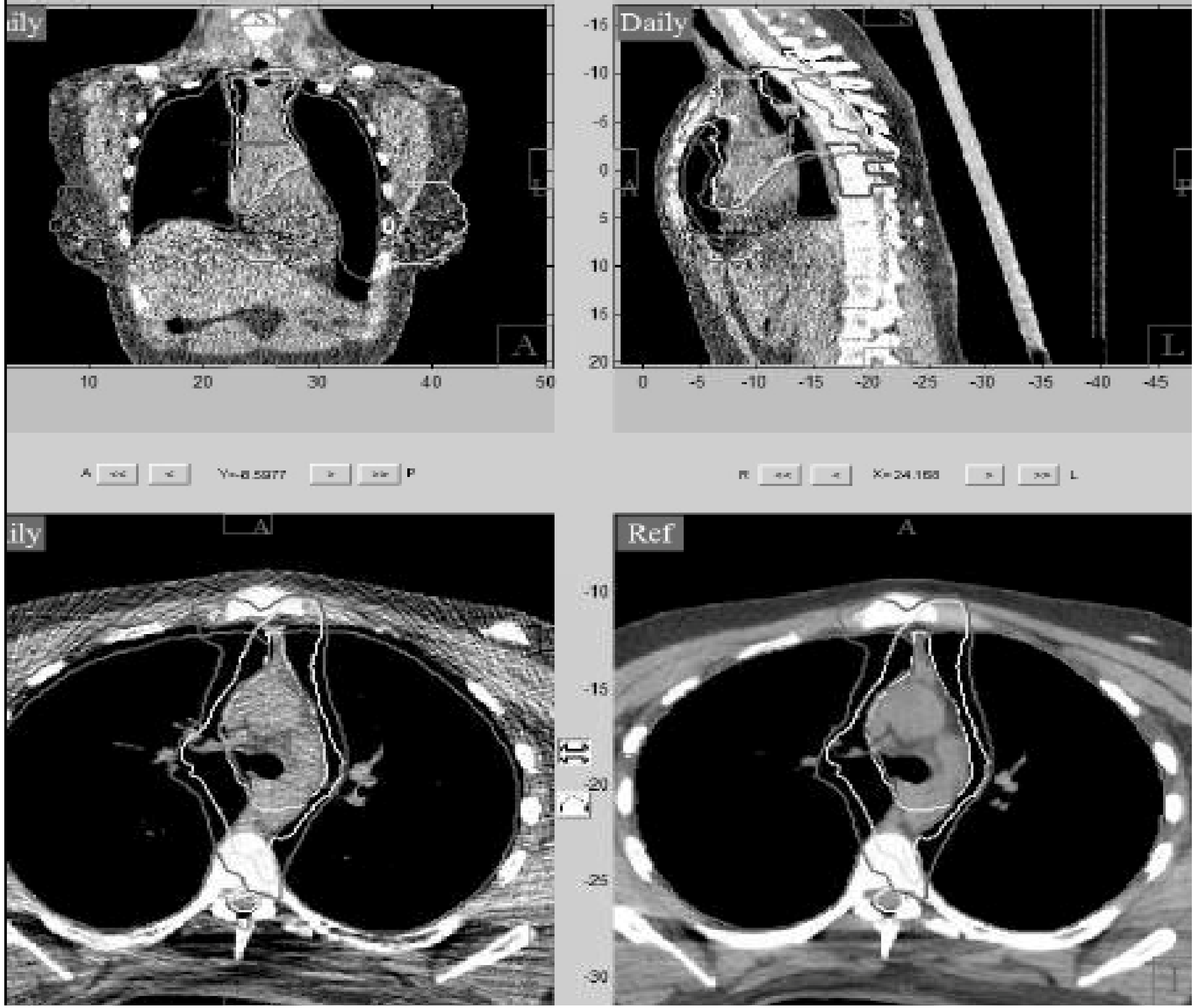
SECONDARY MALIGNANCIES[f]

OAR	Dose Recommendation (1.8–2 Gy/fraction)	Secondary Malignancy
Breast	Minimize volume >4 Gy (ideally <10%)	Breast cancer (adenocarcinoma)[46]
Esophagus	Minimize volume >30 Gy	Esophageal cancer[47]
Stomach	Minimize volume >25 Gy	Gastric cancer[48]
Pancreas	Minimize volume >5–10 Gy	Pancreatic cancer[49]

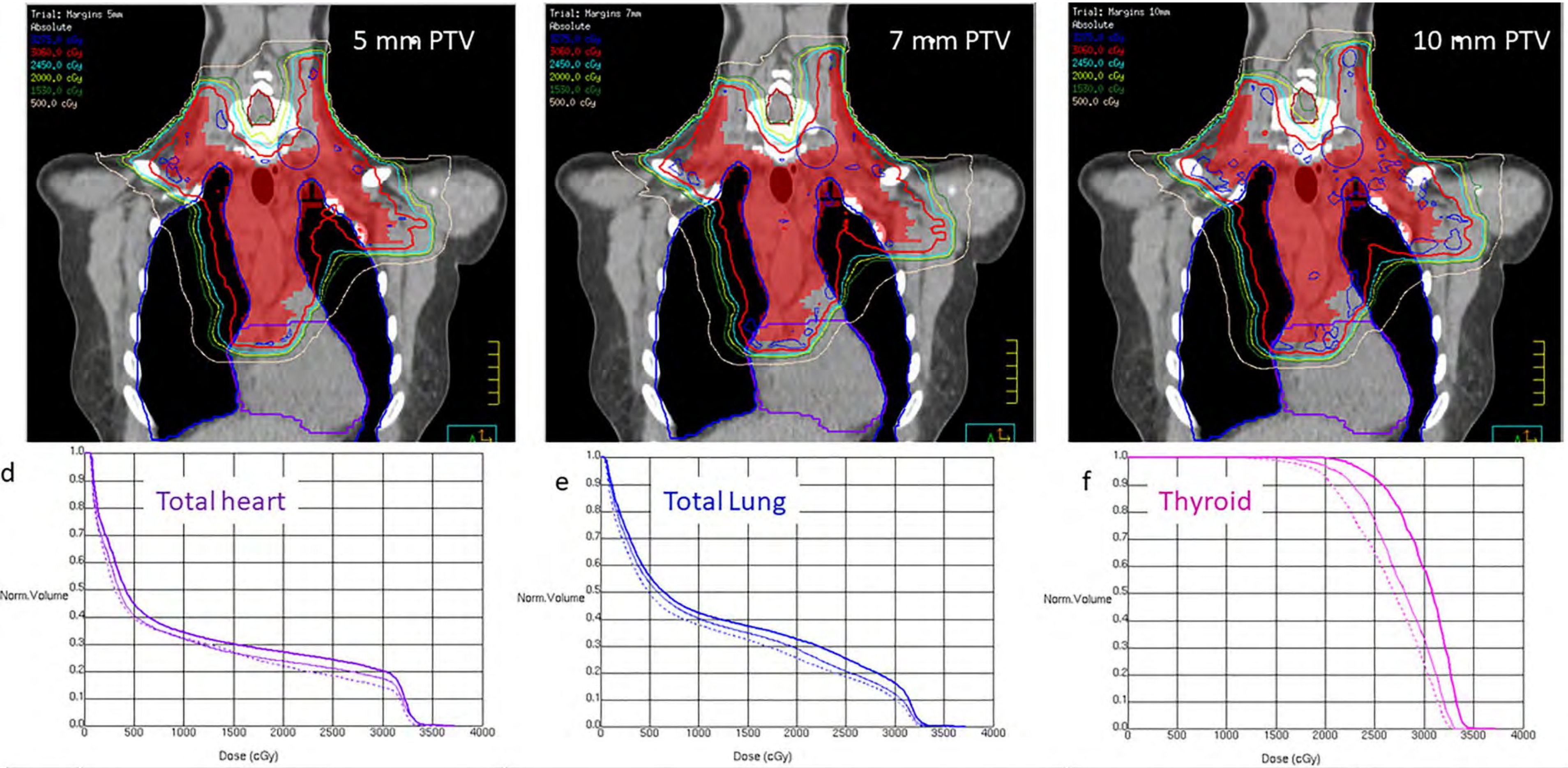
Treatment Delivery

Daily CT Imaging

- Low dose CT protocol of 120 kV/90 mA
- 0.25-0.5 cGy per scan (at patient surface)
- 30 Gy/15 fx will translate to:
  - 0.5 cGy x15 = 7.5 cGy added exposure
- 0.25% of dose



Daily CT Imaging



	Mean Heart	Mean Lung	Mean Thyroid
5 mm	10.18 Gy	9.95 Gy	26.35 Gy
7 mm	10.70 Gy	10.78 Gy	27.61 Gy
10 mm	11.60 Gy	11.70 Gy	30.01 Gy

- Single CTOR 0.34 cGy → add 5.78 cGy over 17 fractions
- Single CBCT 0.43 cGy → add 7.31 cGy over 17 fractions
- Plans regenerated with 1 cm PTV
    - **Increased heart, lung and thyroid doses 28 – 36 fold higher than the total CTOR dose**
    - **Increased heart, lung and thyroid dose 22-29 fold higher than the total CBCT dose**

Treatment Delivery

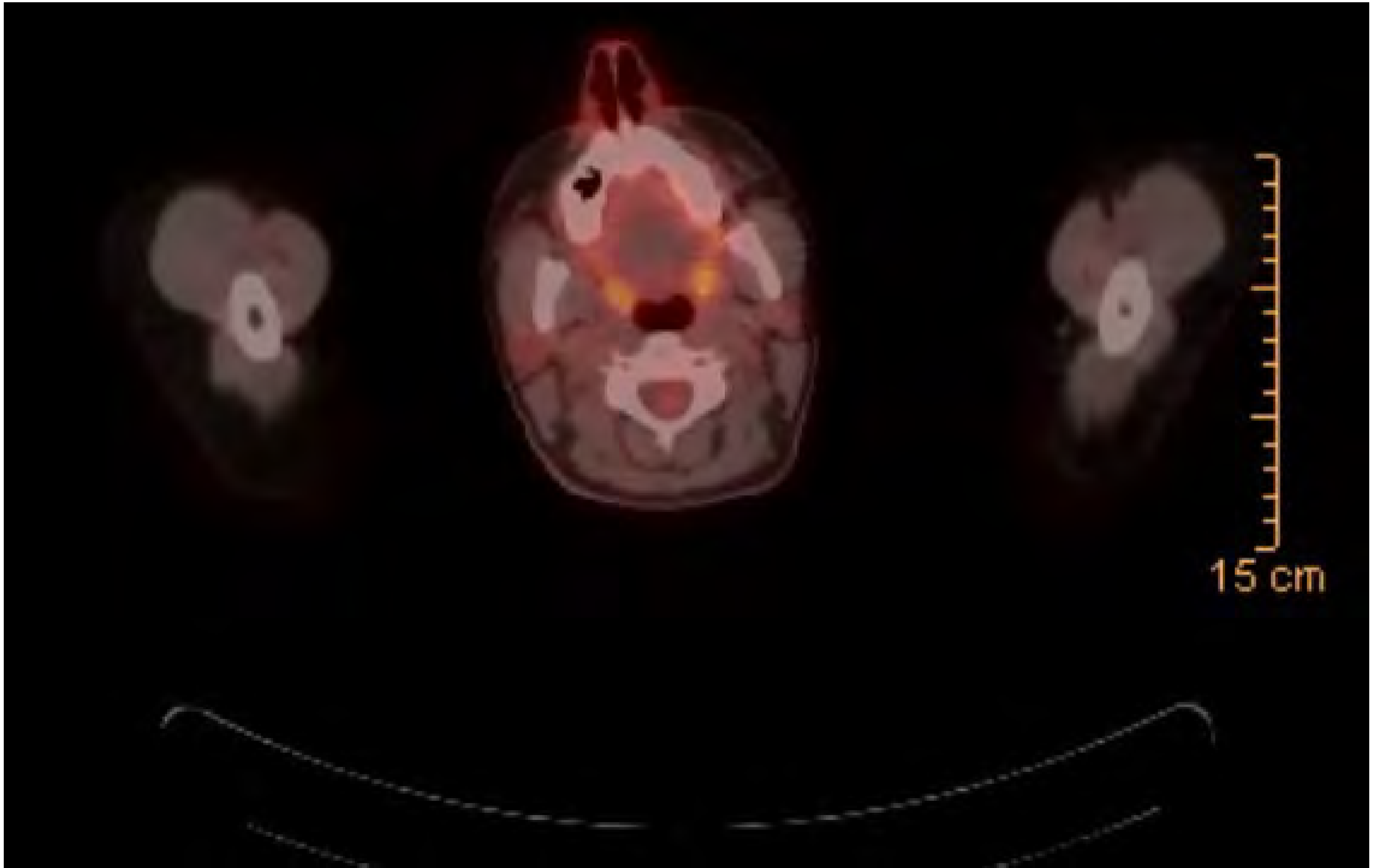
Zhu LL, Martin RM, Gunther JR, Wong PF, Hancock D, Moreno AC, Dabaja BS, Pinnix CC. Daily computed tomography image guidance: Dosimetric advantages outweigh low-dose radiation exposure for treatment of mediastinal lymphoma. Radiother Oncol. 2020 Nov;152:14-18. doi: 10.1016/j.radonc.2020.06.028. Epub 2020 Jun 25. PMID: 32593645.

Day 1 of treatment

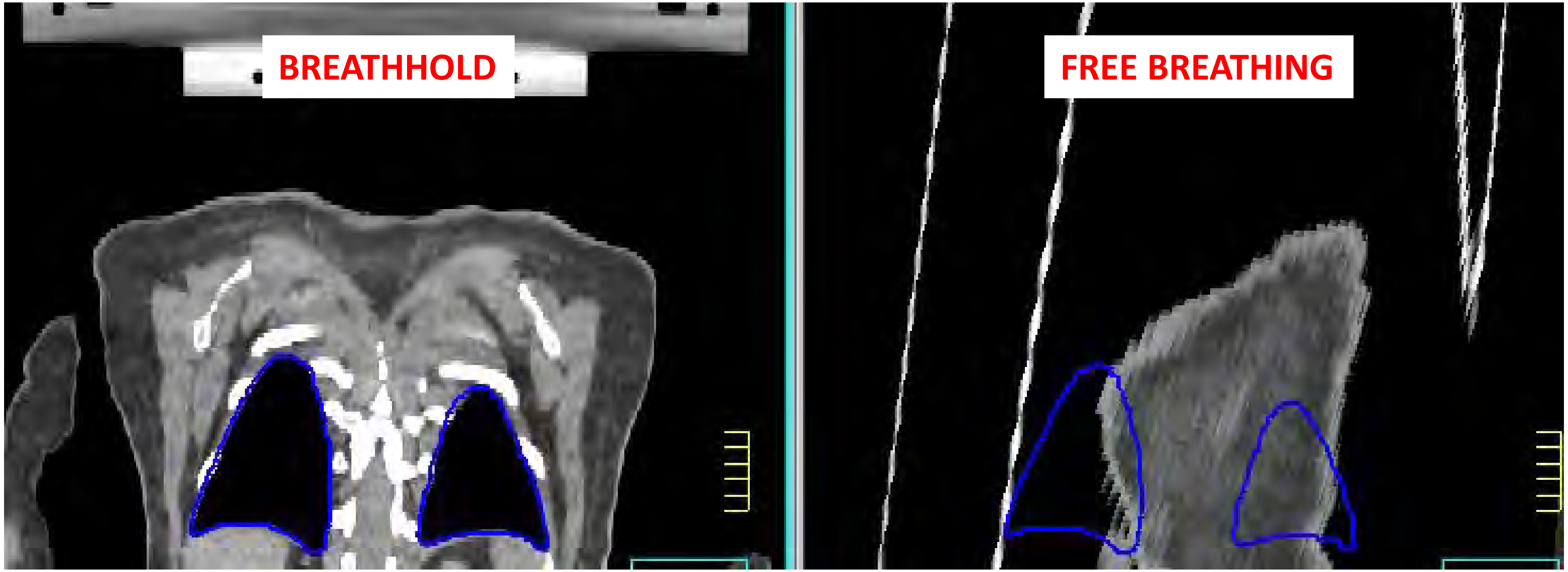
- Upload CTV/PTV and relevant normal structures
- Evaluate lung expansion
- Align to CTV/PTV

Final Case

- 32 yo woman with stage IIB unfavorable non-bulky HL (Unfavorable based on B symptoms and ES of 138)



Benefit of Deep Inspiration Breathhold (DIBH)

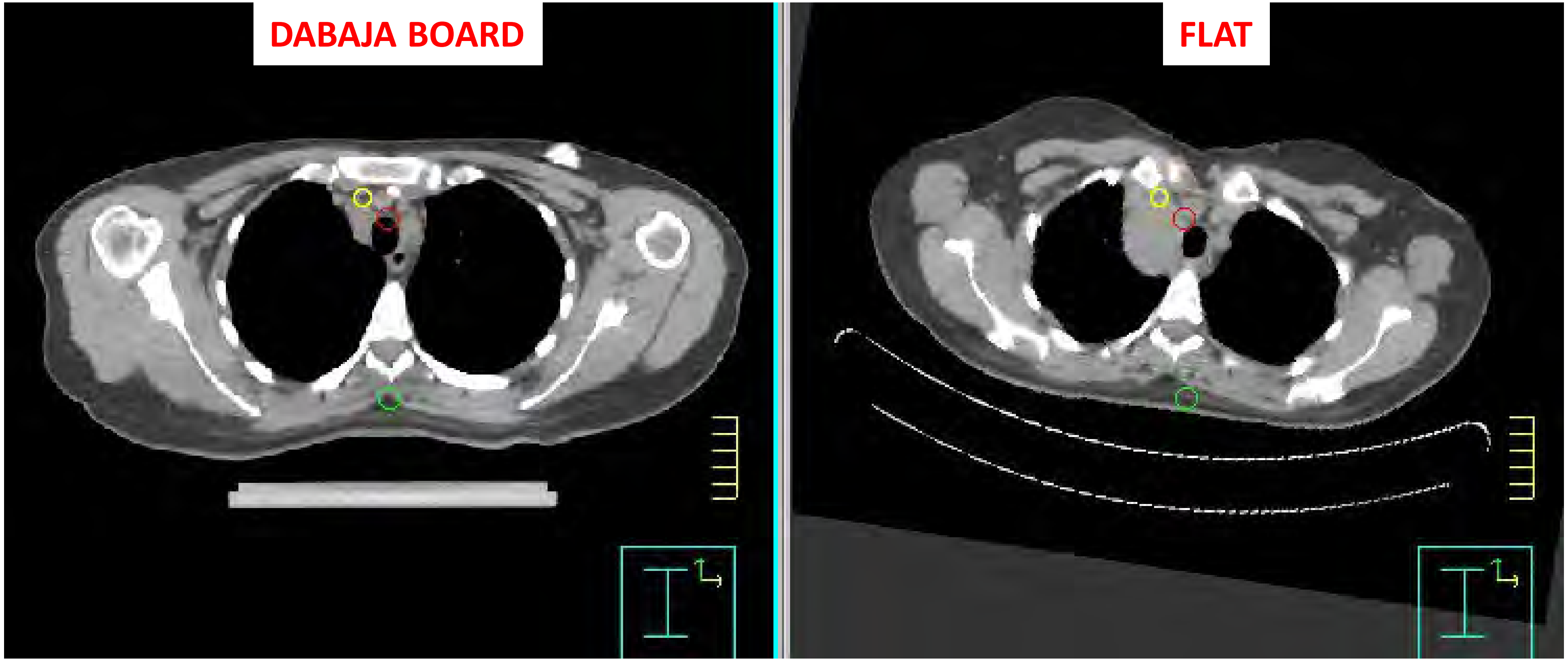


Simulation CT scan with DIBH

Pre-treatment CT scan (Freebreathing)

LARGER LUNG VOLUME AND INFERIOR CARDIAC DISPLACEMENT

Benefit of Incline Board

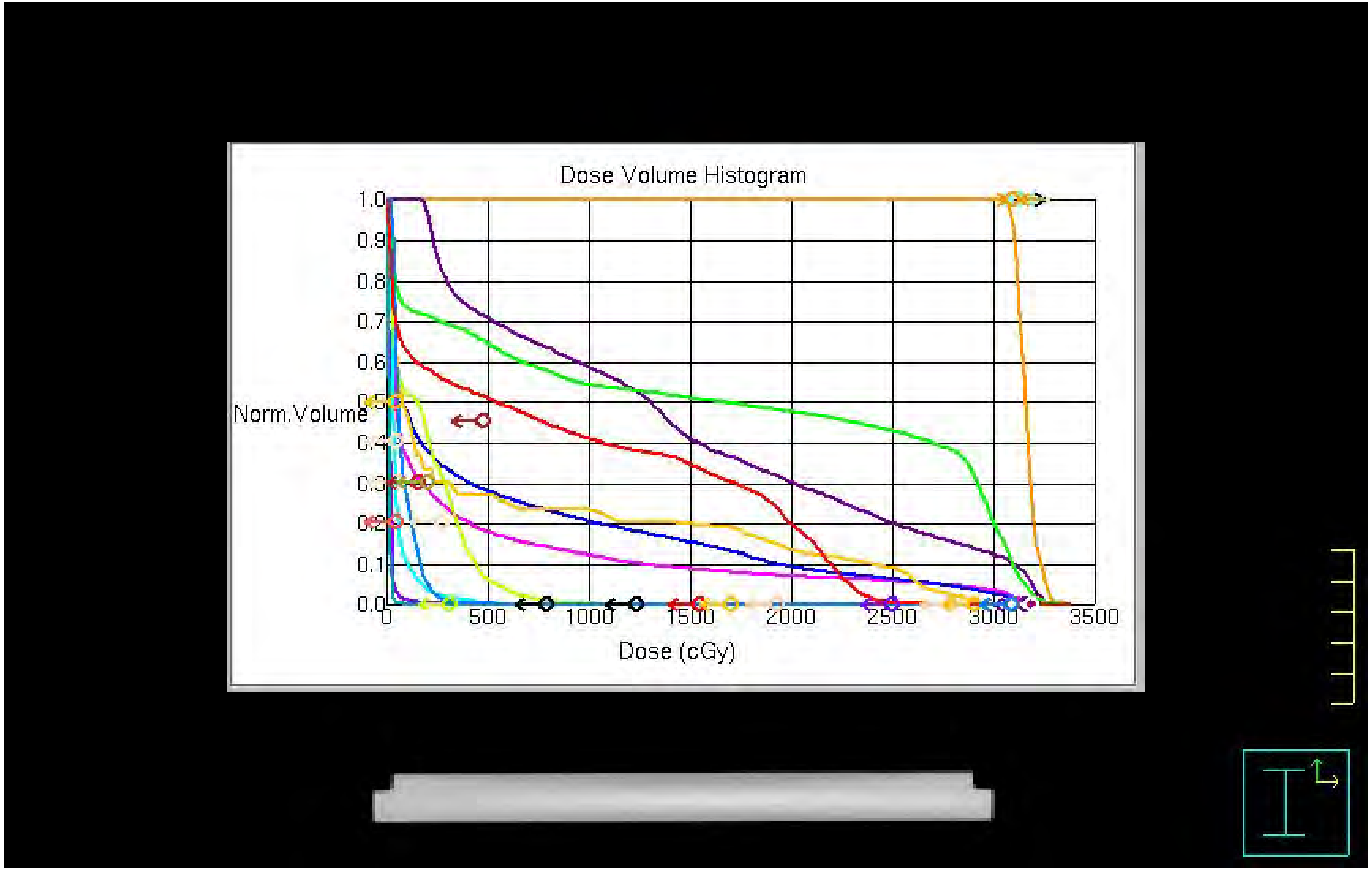


Simulation CT scan with Dabaja Board

Pre-treatment CT scan (Flat)

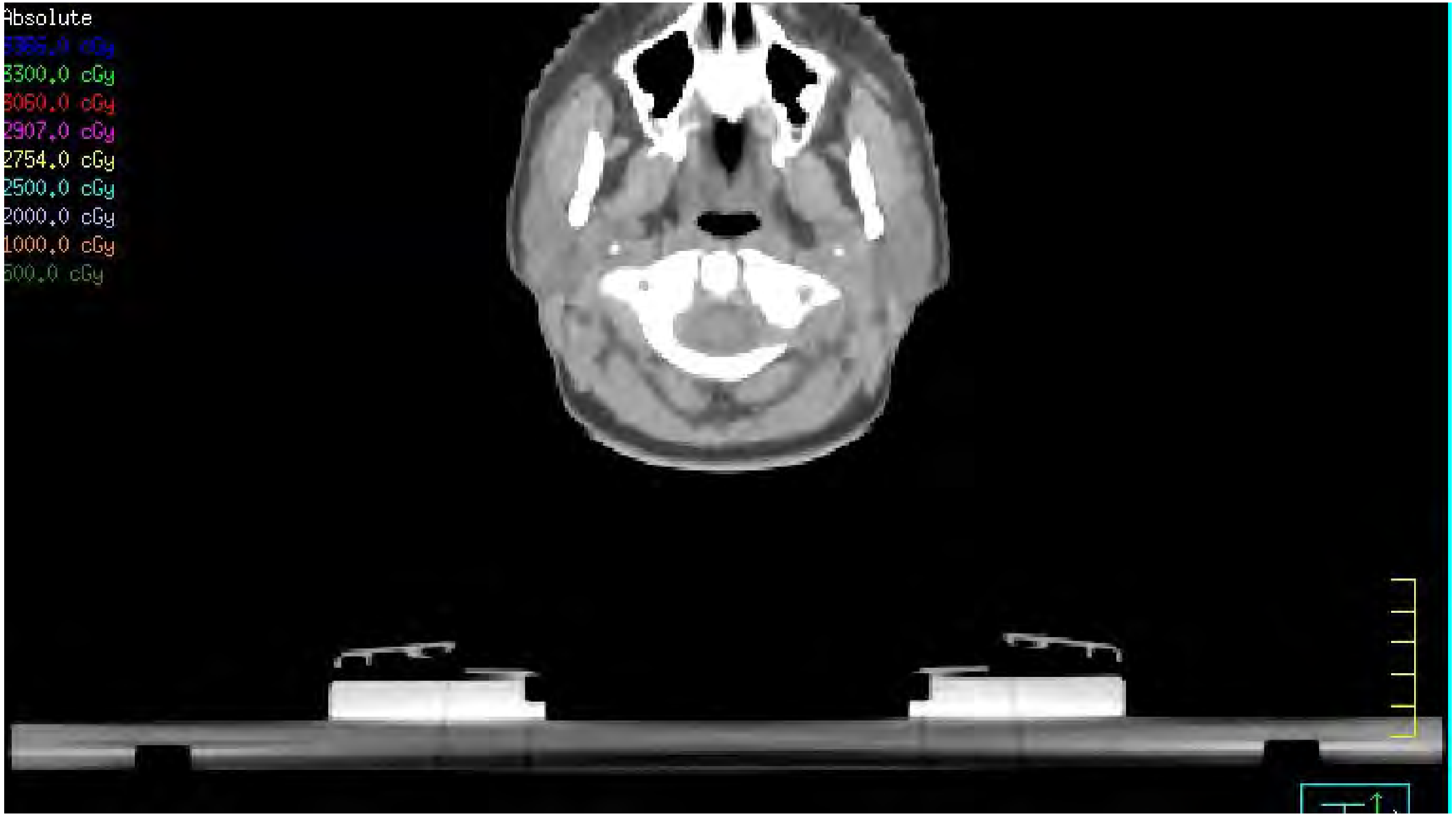
Inferior Breast Displacement

Contouring Organs at Risk (OARs)



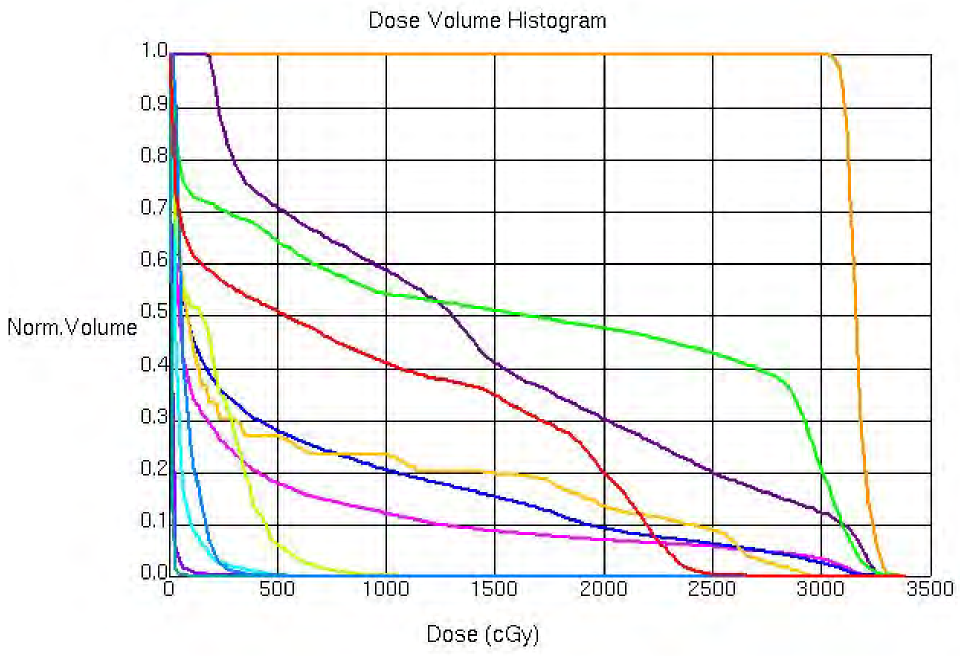
Structures must be identified to avoid them

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	3235.4	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

Scrutinize Doses to OAR based on established Dose Constraints

Conclusions

- Use all tools available to you to minimize normal tissue exposure
- Contour OARS
- Scrutinize RT plans
- Follow patients post therapy

THANK YOU!

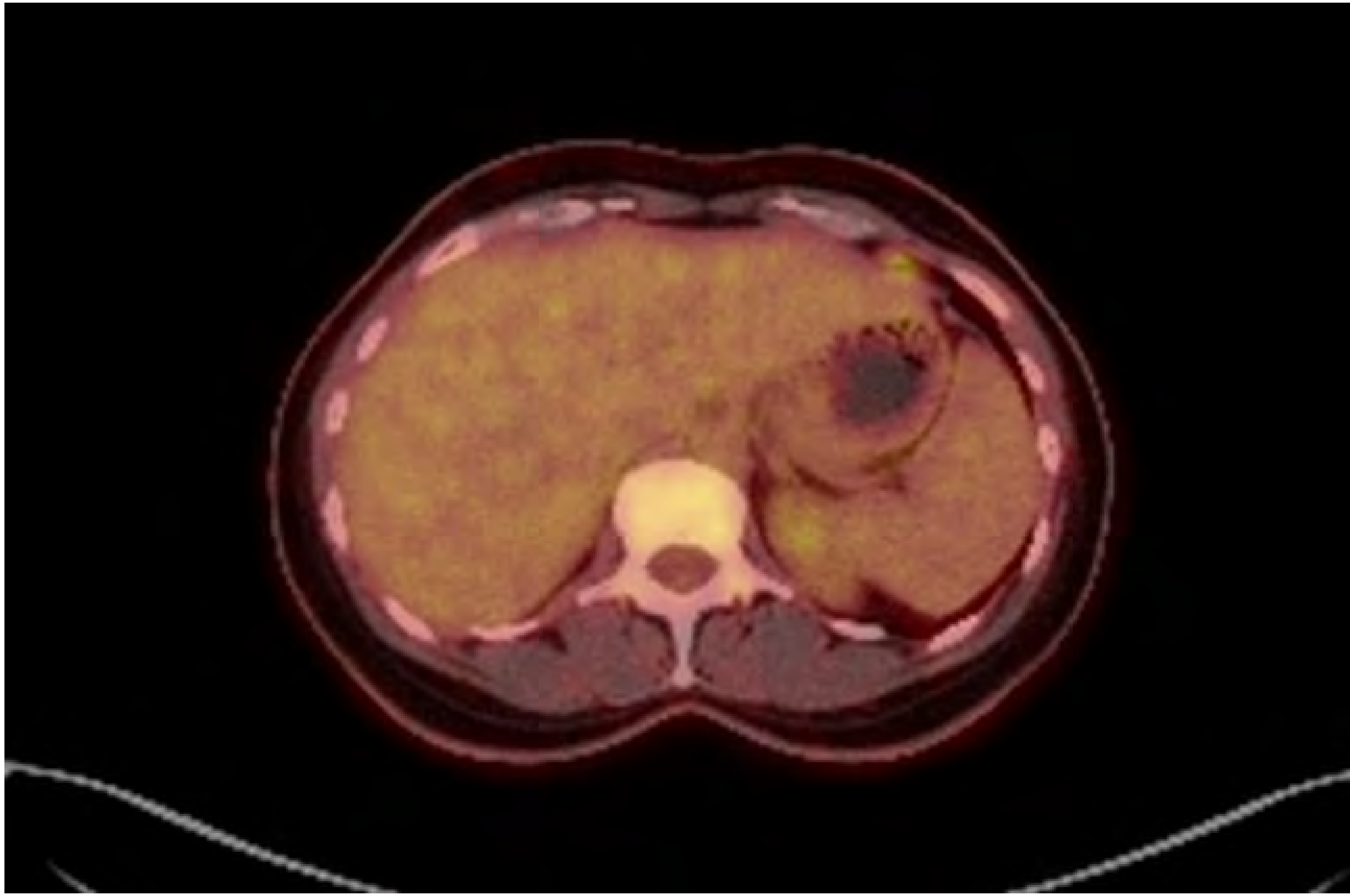
ILROG
INTERNATIONAL LYMPHOMA RADIATION ONCOLOGY GROUP

Conclusions

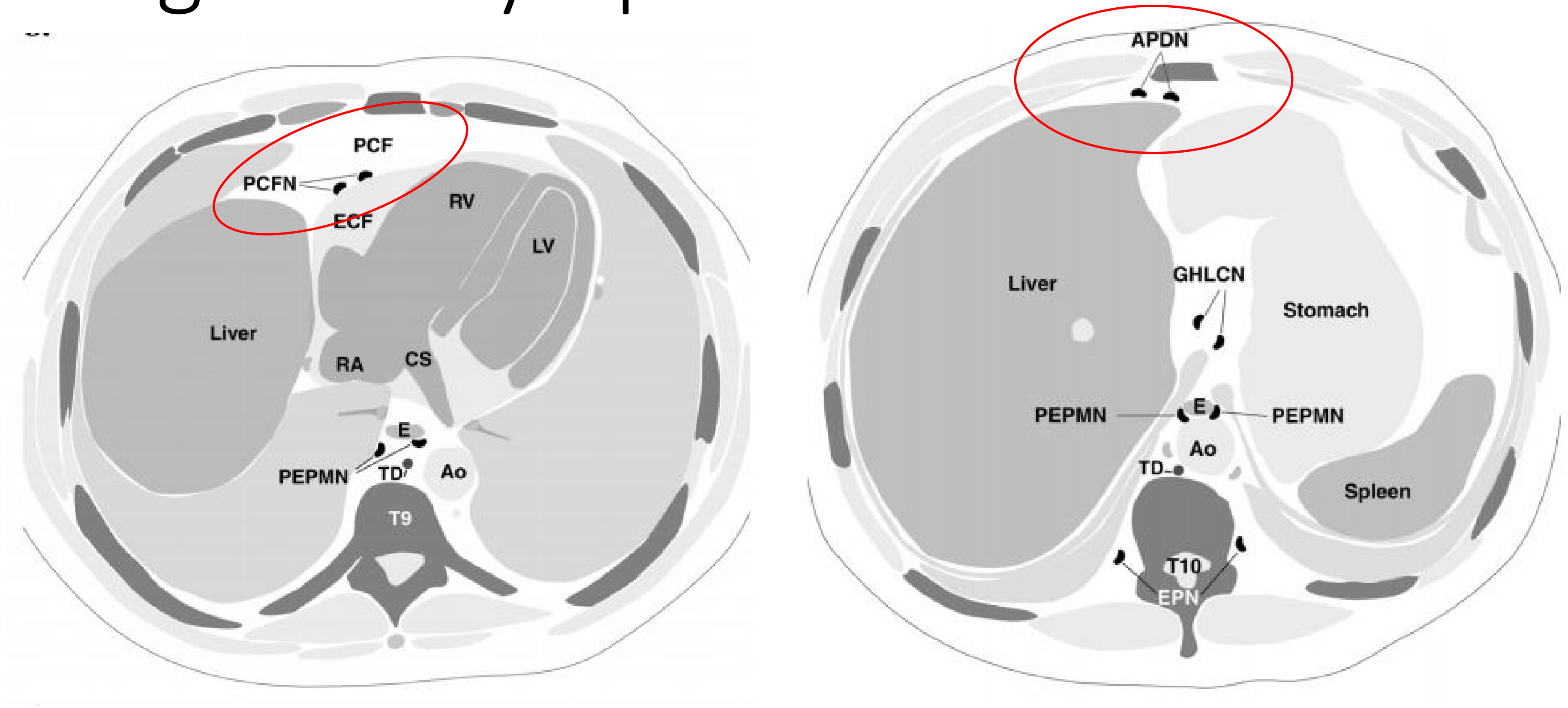
- RT is a valuable tool in the treatment for HL, however the role for RT continues to evolve
- With modern RT approaches and ISRT normal tissue exposure has decreased over the decades
- Radiation oncologists should take the time to minimize doses to OARs

What about the cardiophrenic node?

- Would you cover it?



The Dreaded Pericardial and Anterior Diaphragmatic Lymph Nodes



- Located at inferior aspect of the thoracic diaphragm or abutting the heart along pericardial fat
- Targeting these nodes can result in dramatic increases in cardiac dose as well as increase in pulmonary RT exposure

Figure from Sharma A. et al, Patterns of Lymphadenopathy in Thoracic Malignancies, Radiographics 2004; 24:419-434.

Anterior Diaphragmatic Nodes

Table 1. Patient characteristics.

	All patients [$n = 169$]	Patients with CPLN involvement [$n = 29$]	Patients without CPLN involvement [$n = 140$]
Age, median(range) years	30 (18.5–77.5)	27.1 (18.5–45.4)	30.8 (18.5–77.5)
Women, no. (%)	104 (62)	20 (69)	84 (60)
Ann Arbor disease stage, no. (%)			
I	11 (7)	0 (0)	11 (8)
II	141 (83)	26 (90)	115 (82)
III	12 (7)	2 (7)	10 (7)
IV	5 (3)	1 (3)	4 (3)
B symptoms, no. (%)	74 (44)	16 (55)	58 (41)
Bulky mediastinal disease (>10 cm), no. (%)	70 (41)	16 (55)	54 (39)
Number of chemo cycles, median (range)	6 (1–8.5)	6 (4–6)	6 (1–8.5)
RT for refractory disease, no. (%)	33 (20)	9 (31)	24 (17)
Number of CPLN, median (range)		1 (1–8)	
Size of largest CPLN, cm (range)		2.2 (0.9–10.1)	

CPLN: cardiophrenic lymph node; RT: radiation therapy.

- 169 HL pts treated between 2009- 2015 with combined modality therapy
- 29 of 169 pts had radiographic evidence of CPLN involvement (**17%**)
- 3 RT fields utilized: Standard (S)-ISRT, reduced dose (RD)-ISRT or modified (M)-ISRT
- 20 pts received RT after a complete response to chemotherapy

Pinnix CC, Wirth A, Milgrom SA, Andraos TY, Aristophanous M, Pham M, Hancock D, Ludmir EB, Gunther JR, Fanale MA, Oki Y, Nastoupil L, Chuang HH, Mikhaeel NG, Dabaja BS. Omitting cardiophrenic lymph nodes in the treatment of patients with Hodgkin lymphoma via modified involved-site radiation therapy. Leuk Lymphoma. 2018 Apr 4:1-10.

Modified Involved Site Radiation Therapy

Characteristic	Patients with CPLN treated to full dose (S-ISRT, $n = 4$)	Patients with CPLN treated to lower dose (RD-ISRT, $n = 8$)	p value (S-ISRT vs. RD-ISRT)	Patients with CPLNs excluded from field (M-ISRT, $n = 8$)	p value (S-ISRT vs. M-ISRT)
Mean heart dose, Gy	16.6	14.9	.441	11.8	**.043**
Heart V25, %	41.0	29.4	.078	25.8	**.025**
Heart V5, %	67.0	66.8	.979	49.6	.082
Mean left ventricle dose, Gy	6.9	7.2	.836	4.4	.181
Left ventricle V25, %	8.3	5.4	.431	3.3	.179
Left ventricle V5, %	36.8	40.9	.724	22	.217
Mean dose to left main/LAD, Gy	16.7	16.9	.971	12.8	.323
Left main/LAD V25, %	44.3	43	.935	27.3	.276
Left main/LAD V5, %	58.5	64.8	.616	51.1	.555
Mean dose to right coronary, Gy	25.2	20.4	.372	16.9	.127
Right coronary V25, %	73.5	43.3	.140	46.3	.181
Right coronary V5, %	84.5	80.3	.812	60.8	.183
Mean lung dose, Gy	11.7	11.5	.797	10.3	.203
Lung V20, %	27.3	26.5	.824	24.0	.341
Lung V5, %	53.3	55	.714	49.0	.378
Mean dose to right breast, Gy	3.35	4.2	.359*	1.9	.359*
Right breast V25, %	5.5	2.6	.170	1.3	.055
Right breast V5, %	17.5	23.6	.429*	10.3	.429*
Mean dose to left breast, Gy	1.3	5.1	.122*	1.5	.122*
Left breast V25, %	1	5	.363	1.5	.905
Left breast V5, %	5.5	25.8	.064*	6.3	.064*

- Mean heart dose and heart V25 lower among patients with the CP node excluded from the field (compared to S-ISRT)

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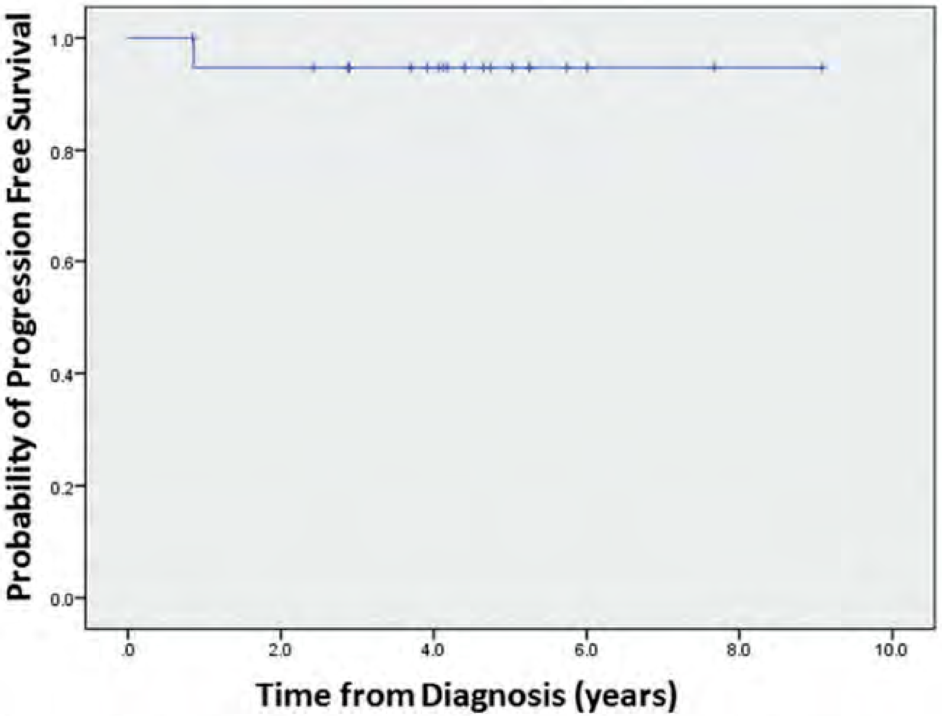
Anterior Diaphragmatic Nodes



Number of Patients at risk 20 18 13 2 1

Figure 1. Progression-free survival for 20 patients with cardiophrenic lymph node involvement treated with ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) chemotherapy followed by consolidative radiation therapy.

- 4 year PFS was 94.7%
- One relapse occurred at a non-CPLN site after RD-ISRT

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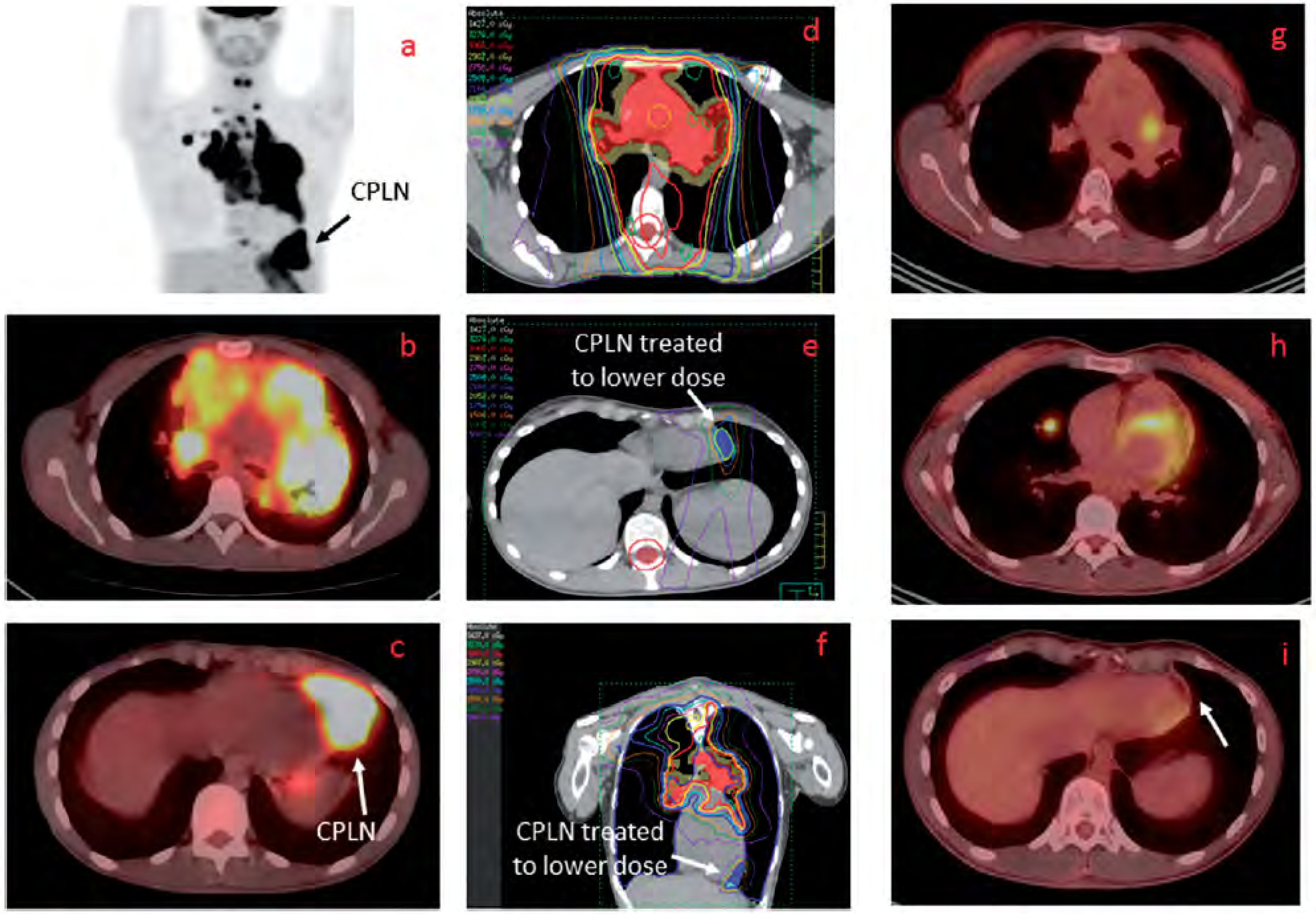

Figure 2. 22-year-old patient with stage IIB bulky Hodgkin lymphoma and cardiophrenic lymph node (CPLN) involvement treated with reduced dose involved site radiation therapy (RD-ISRT). (a–c) Baseline PET–CT scan before chemotherapy with the initial site of CPLN involvement annotated. (d–f) The administered intensity-modulated radiation therapy (IMRT) treatment plan, with deep-inspiration breath hold and the CPLN site treated to a dose of 21.6 Gy and the remaining field to 30.6 Gy. (g, h) Sites of relapsed disease at three months after RT in the right lung and mediastinum. (i) The site of the CPLN that received 21.6 Gy (annotated) was not a site of relapse.

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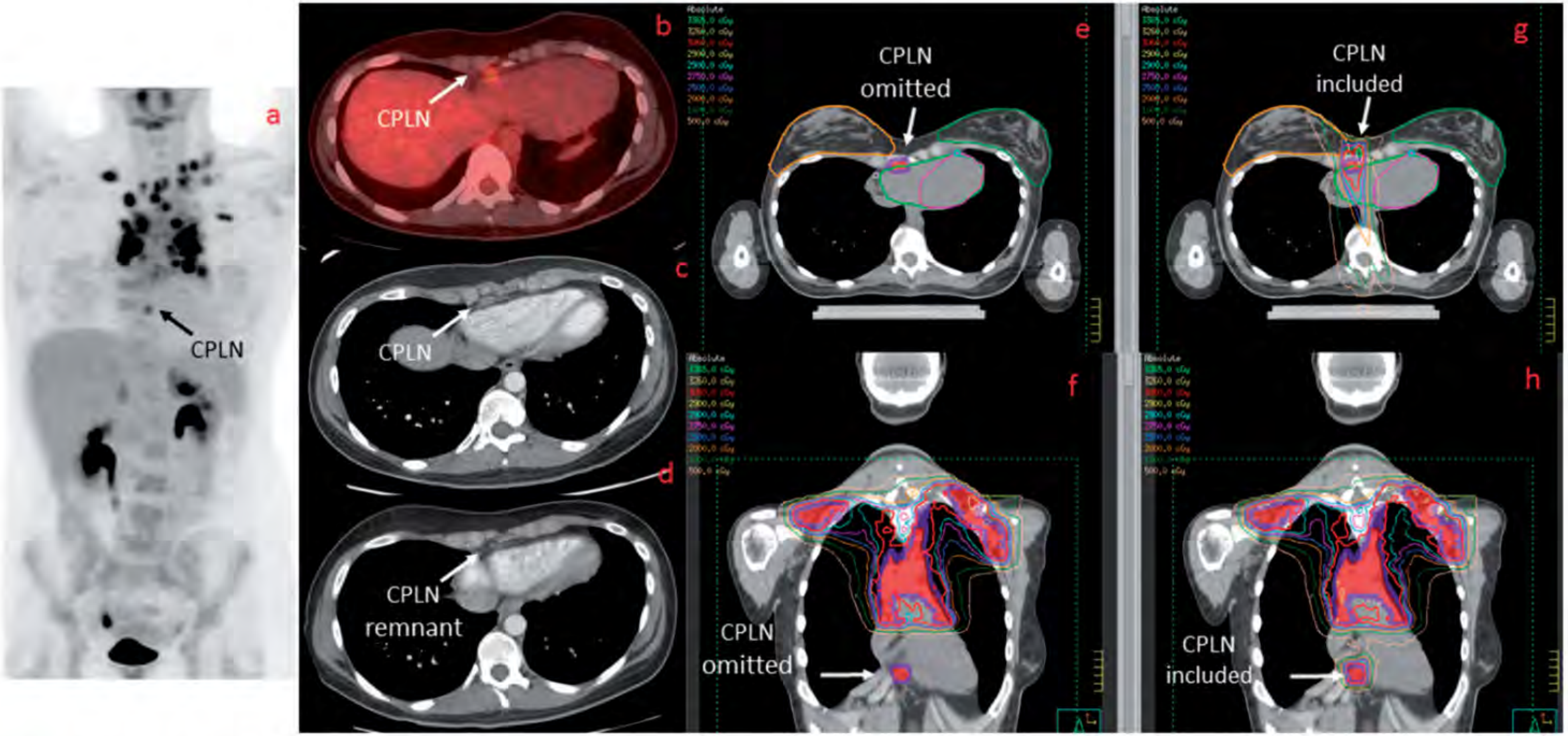

Figure 3. Comparison plans in a patient treated with modified involved-site radiation therapy (M-ISRT). (a, b) Baseline PET-CT scan prior to chemotherapy with the initial site of CPLN involvement marked. (c) Baseline contrast-enhanced CT scan prior to chemotherapy, with cardiophrenic lymph nodes (CPLNs) annotated. (d) Post-chemotherapy contrast CT scan shows residual CPLN remnant. (e, f) The M-ISRT plan administered with the CPLN region omitted. (g, h) Comparison plan with the CPLN region included. The mean heart dose increased from 7.7 to 11.7 Gy with standard ISRT (S-ISRT).

- Pt treated with M-ISRT replanned with S-ISRT: Mean heart dose increased from 7.7 to 11.7 Gy

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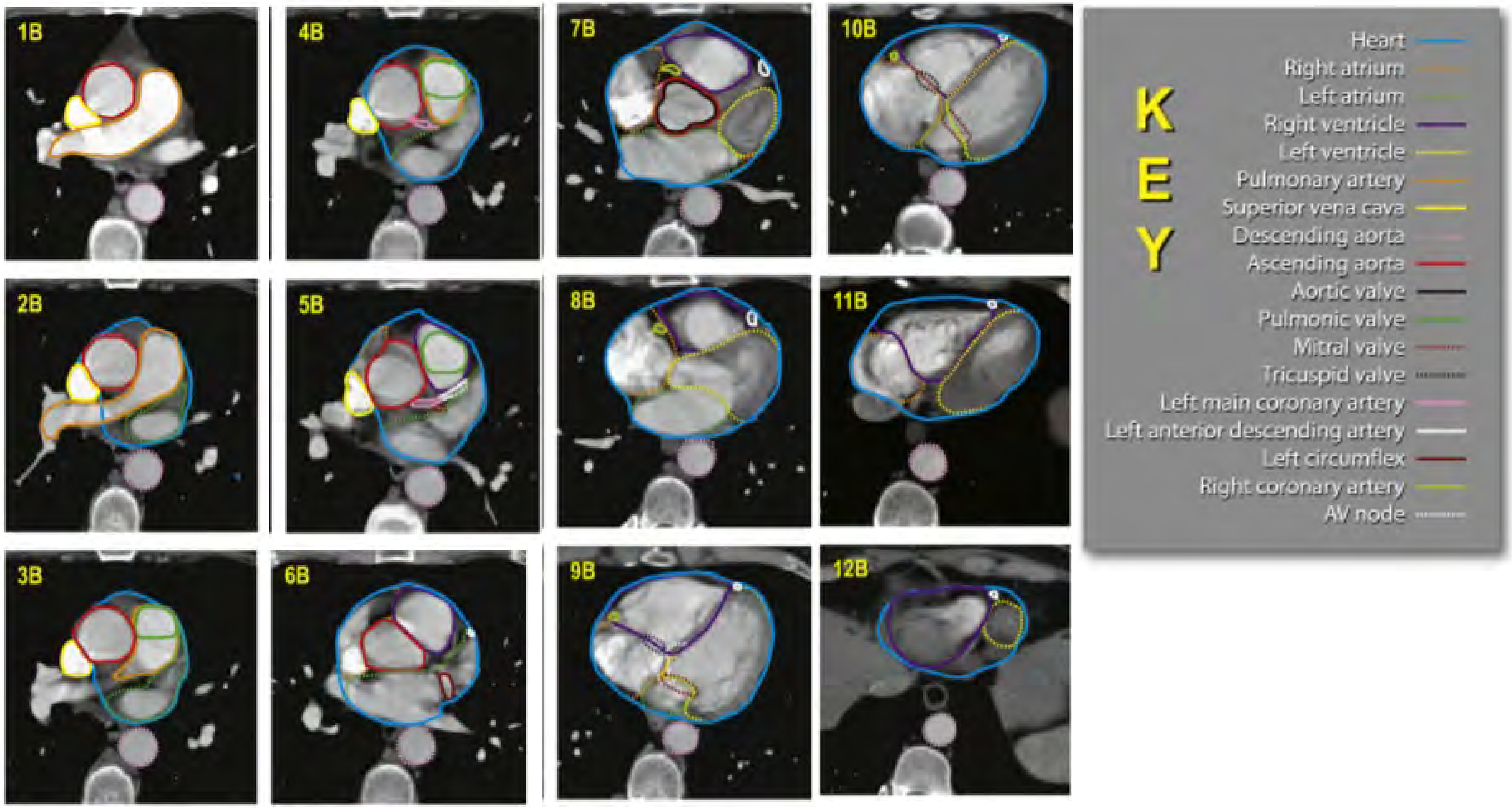
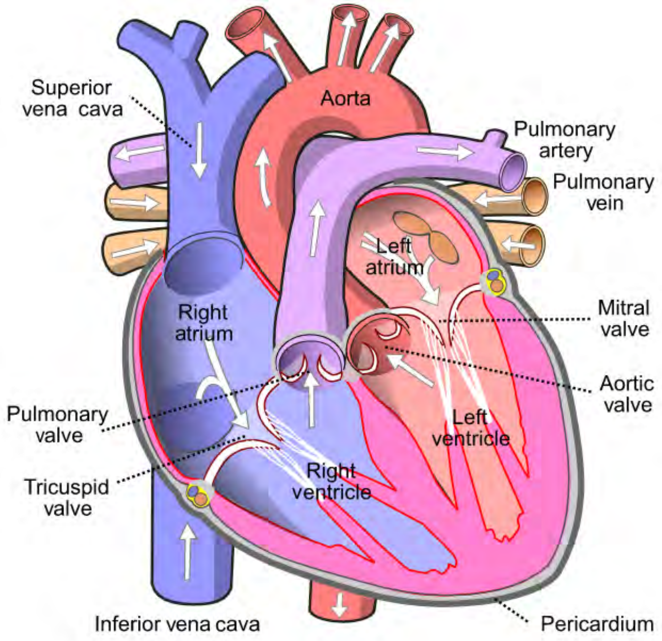
Heart





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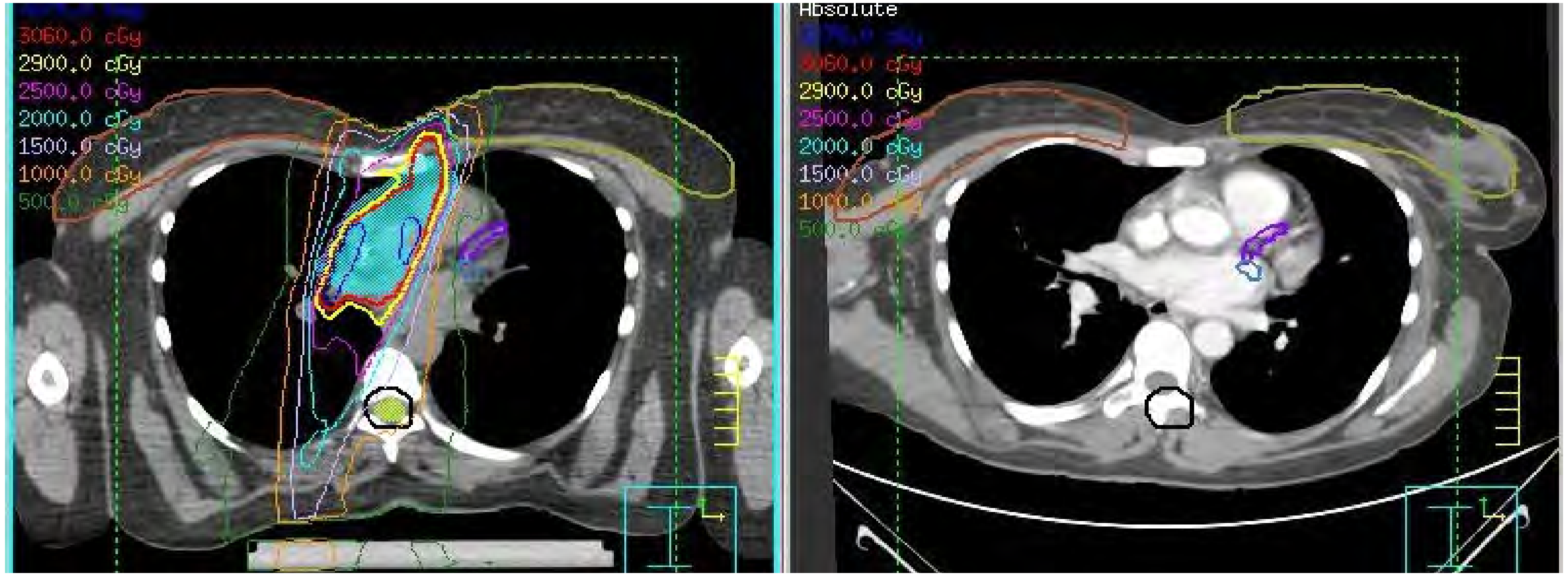
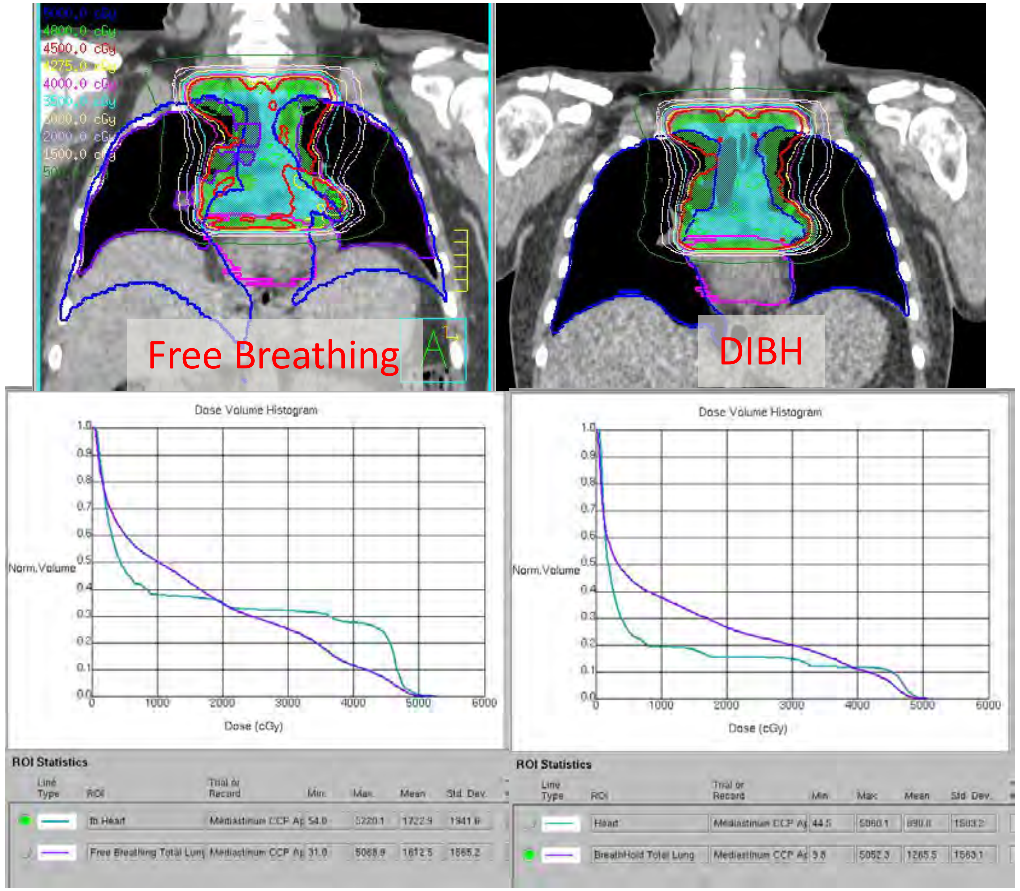
Pushing dose off LAD and LV



Deep Inspiration Breath-hold

Lung V5=60%
MLD 16.1 Gy
Mean Heart: 17.2 Gy



Lung V5=46%
MLD 12.7 Gy
Mean Heart 12.7 Gy

- DIBH improves heart and lung dosimetry