Late Effects of Modern Therapy for Classical Hodgkin Lymphoma

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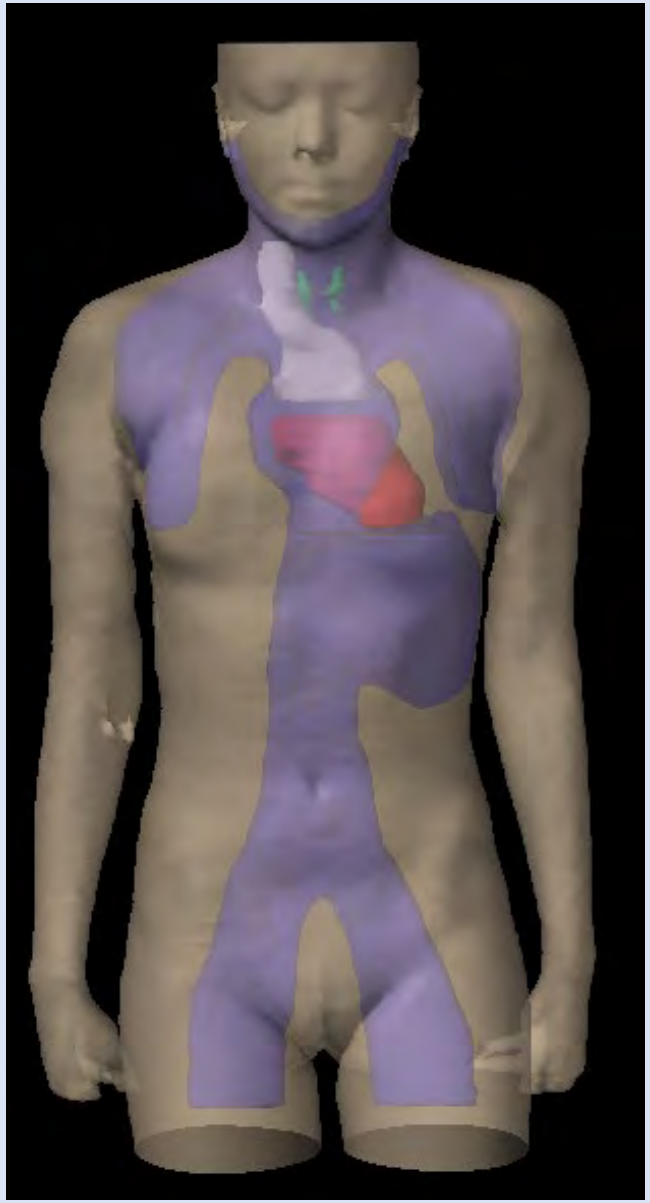
Disclosure

- Consultant, Bristol Myers Squibb, not compensated

Educational Goals

1. Understand how radiation therapy for Hodgkin lymphoma has evolved to reduce normal tissue exposure
2. Recognize that toxicity risks have declined with lower radiation doses and smaller fields
3. Estimate toxicity risks with today's modern techniques
4. Discuss future areas of research to characterize radiation dose-volume-toxicity relationships

Historic RT: Total Lymphoid Irradiation Cured HL



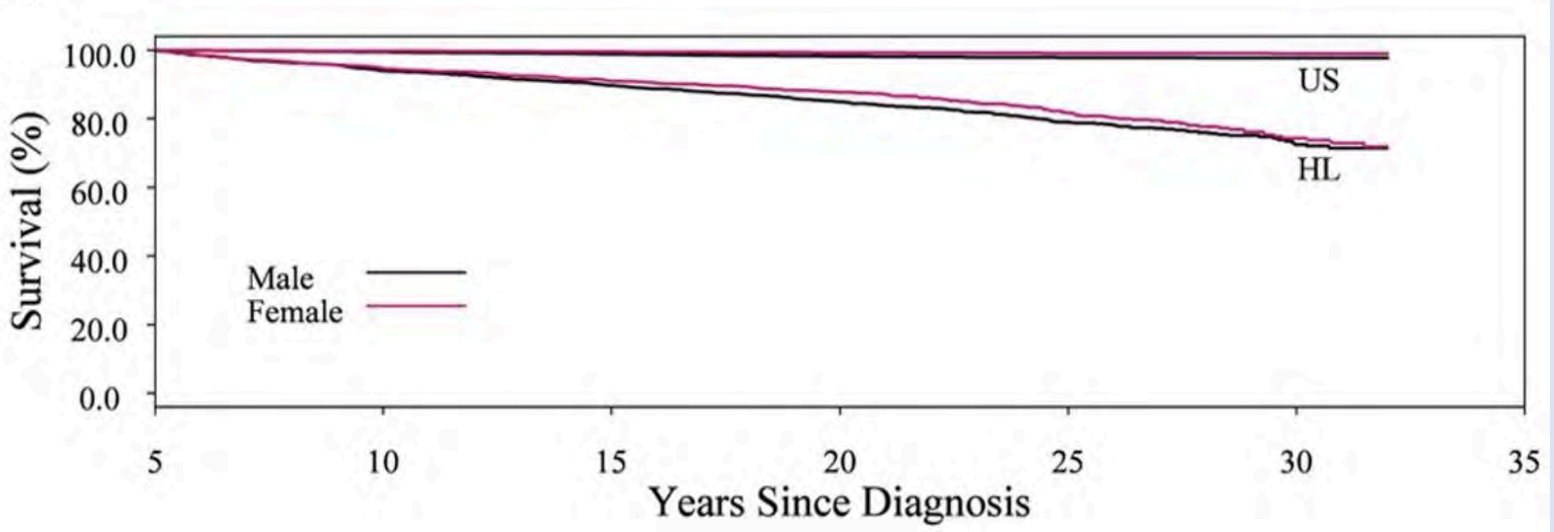
Site of Hodgkin lymphoma

Radiation dose distribution: 36-45 Gy

Heart

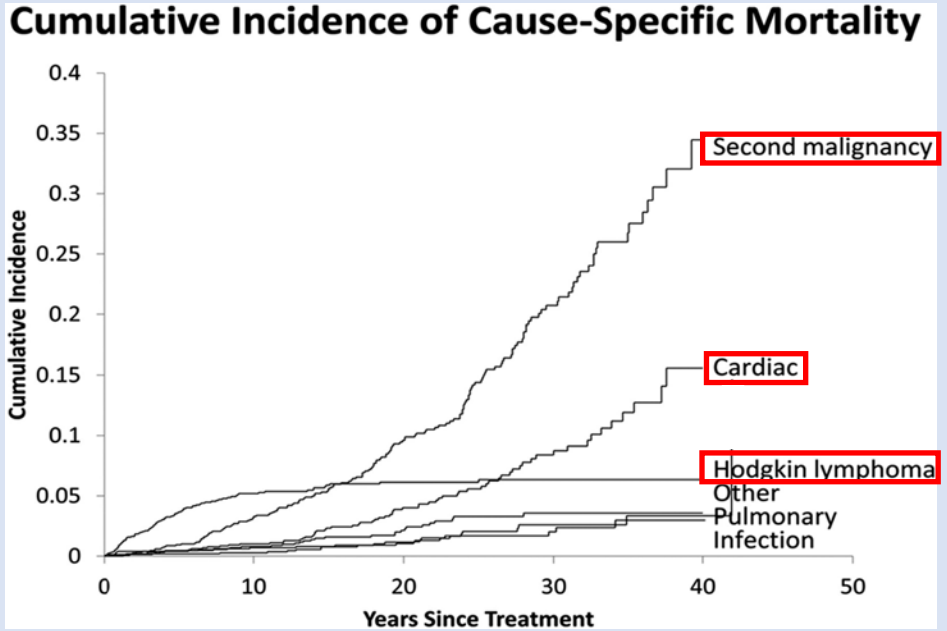
Thyroid

Excess Mortality in 5-Year Survivors of HL in the CCSS, Treated 1970-1986 (n=2,742)



Castellino Blood 2011

Cause-Specific Mortality in Survivors of Stage I-II HL, Treated at a Single Institution 1967-2007 (n=1,542)



Ng Blood 2014

RT Dose & Field are Associated with Mortality

- In a MVA, higher RT doses & larger fields were associated with a greater risk of all-cause mortality & death from a SMN:

Radiation field + dose	HR for death from any cause	95% CI	P
No radiation (reference)	1.0		
Supradiaphragm, < 30 Gy†	0.9	0.2-4.6	.92
Supradiaphragm, ≥ 30 Gy†	3.8	1.1-12.6	.03
Infradiaphragm or Infra diaphragm + supradiaphragm, < 30 Gy†	3.9	1.1-13.9	.04
Infradiaphragm or Infradiaphragm + supradiaphragm, ≥ 30 Gy	7.8	2.4-25.1	< .01

Radiation dose	HR for death from a SMN	95% CI	P
No radiation (reference)	1.0		
< 30 Gy*	1.9	0.4-8.7	.43
≥ 30 Gy	7.4	1.8-30.3	< .01

Castellino Blood 2011

Evolution in RT Approach

- Desire to reduce late effects → new treatment strategies that limit normal tissue radiation exposure
- Evolution in
  - Radiation target volumes
  - Radiation doses
  - Radiation techniques
  - Selection of patients & disease sites for RT

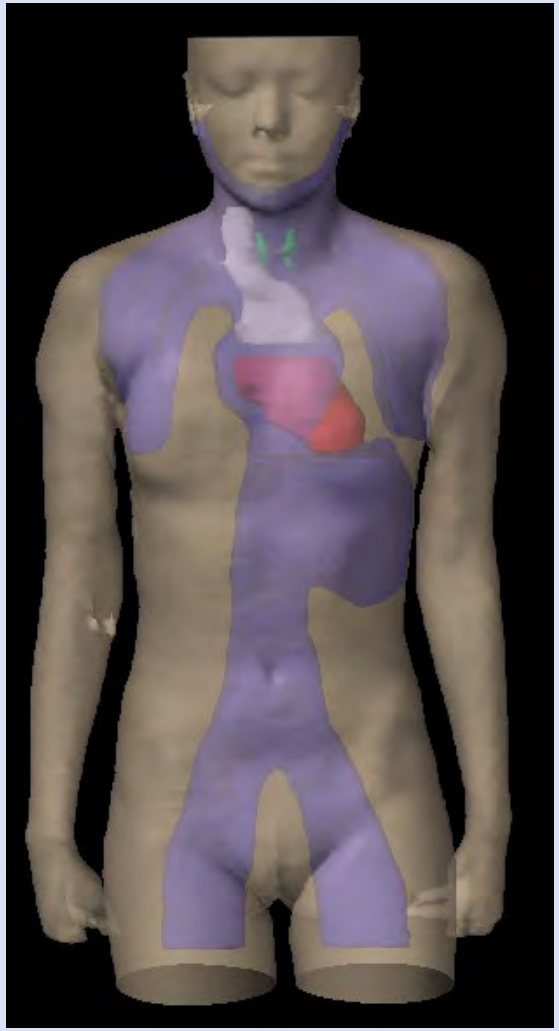
Evolution in RT Approach

- Desire to reduce late effects → new treatment strategies that limit normal tissue radiation exposure
- Evolution in
  - Radiation target volumes
  - Radiation doses
  - Radiation techniques
  - Selection of patients & disease sites for RT

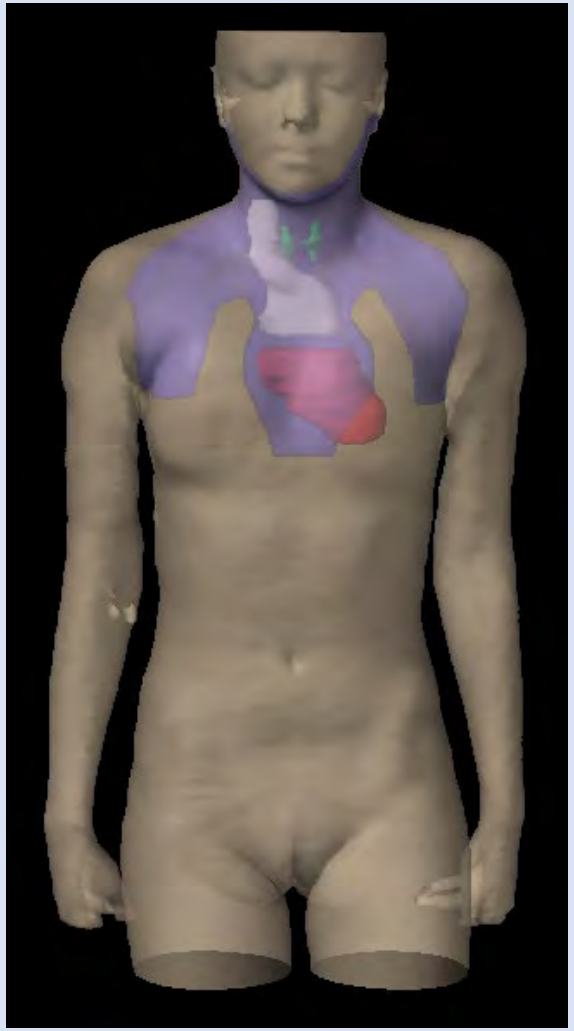
1960's

2000's

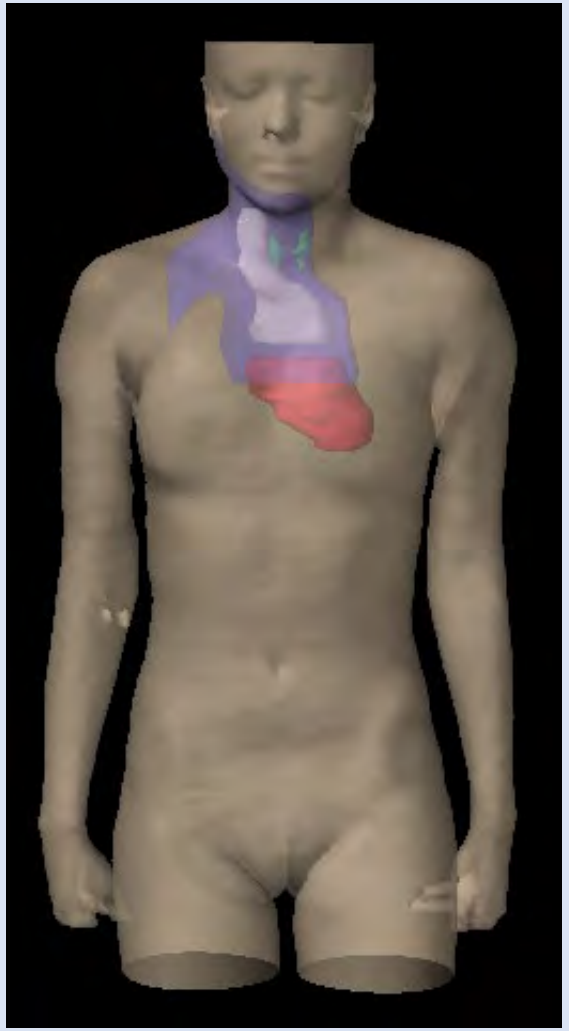
TLI



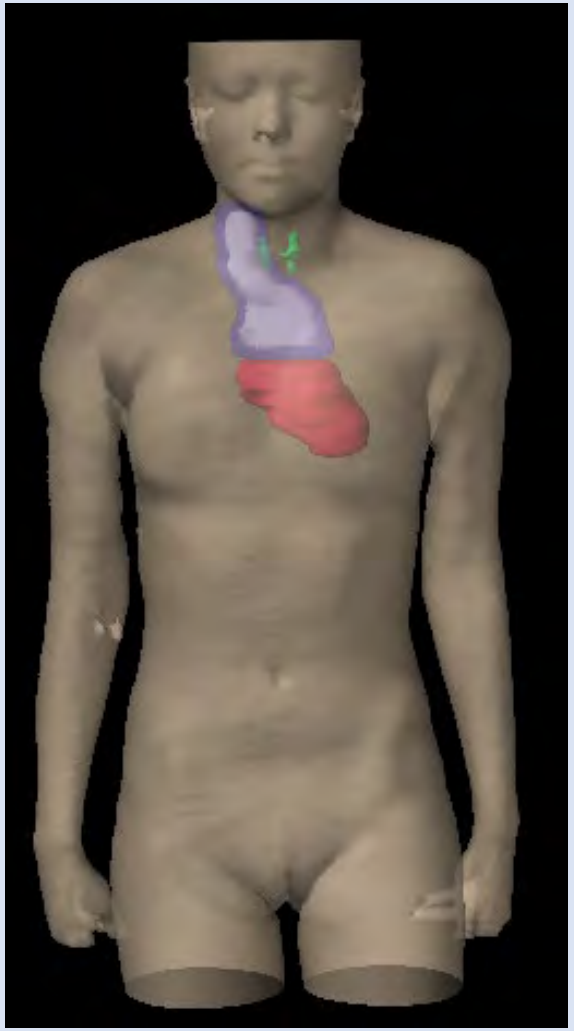
Mantle



IFRT



ISRT/INRT



36-45 Gy

20-36 Gy

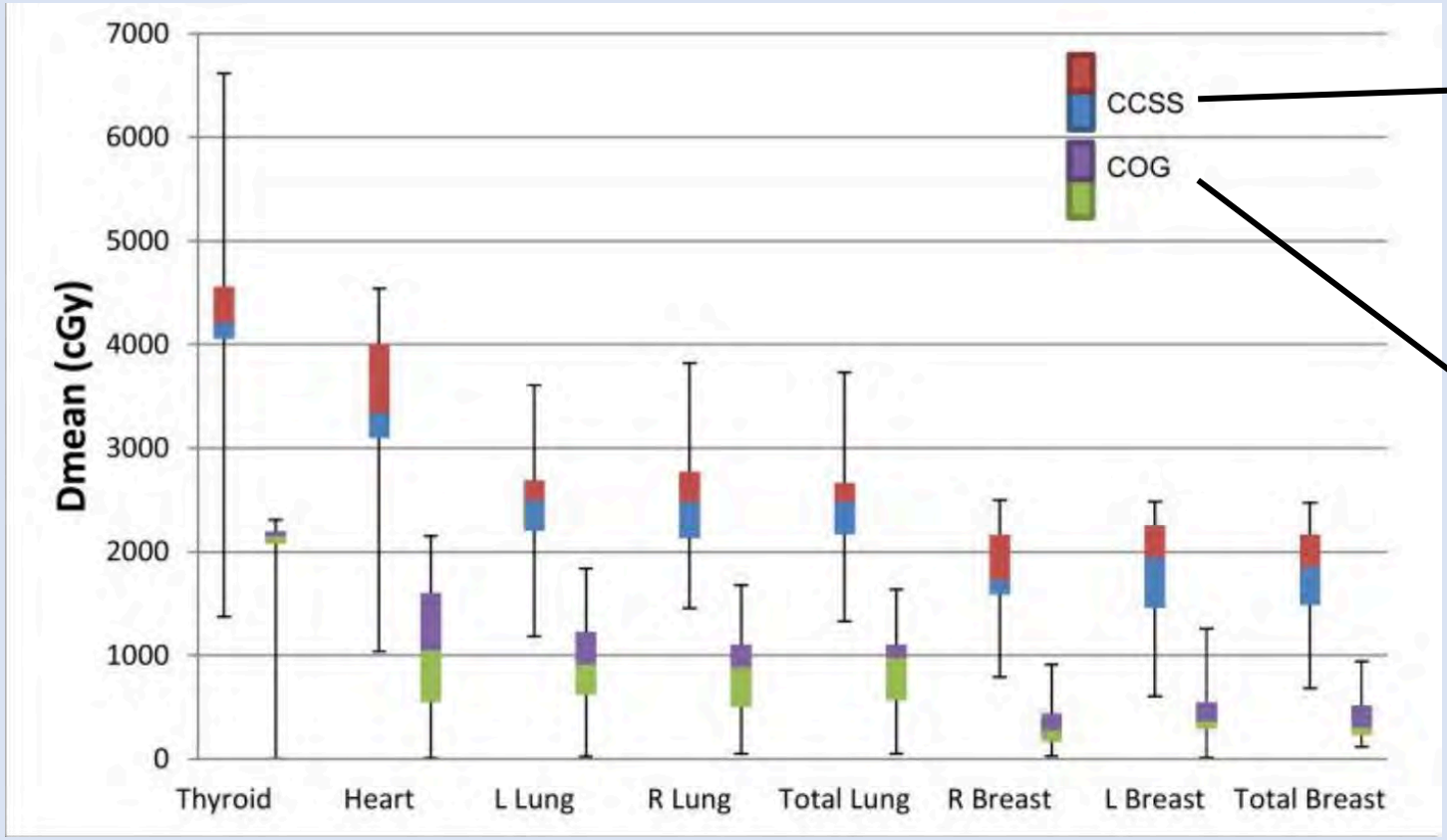
2D

3D

IMRT, Protons,
PET fusion, DIBH, IGRT

Evolution of RT for Lymphoma

Mean dose to normal tissue in matched patients with early-stage HL:



↓ 49%; ↓ 21 Gy

↓ 67%; ↓ 23 Gy

↓ 61%; ↓ 15 Gy

↓ 83%; ↓ 16 Gy

CCSS (1970-1986)
- 44 Gy
- Extended fields
- 2D planning

COG (2002-2009)
- 21 Gy
- IFRT
- 3D planning

Zhou IJROBP 2016

Evolution in RT Approach

- Desire to reduce late effects → new treatment strategies that limit normal tissue radiation exposure
- Evolution in
  - Radiation target volumes
  - Radiation doses
  - Radiation techniques
  - Selection of patients & disease sites for RT

Selection of Patients and Sites for RT

- Historically, RT was used for all sites of disease, in all patients
- Recent trials have explored if radiation exposure can be further reduced through careful selection of patients & sites for RT
  - Early-stage disease
  - Sites at highest risk of relapse
    - Initial bulk
    - SER
    - PR at the end of systemic therapy

↓ field size +

↓ dose +

technological advances +

careful patient/site selection →

Reduction in Normal Tissue Exposure in the Population

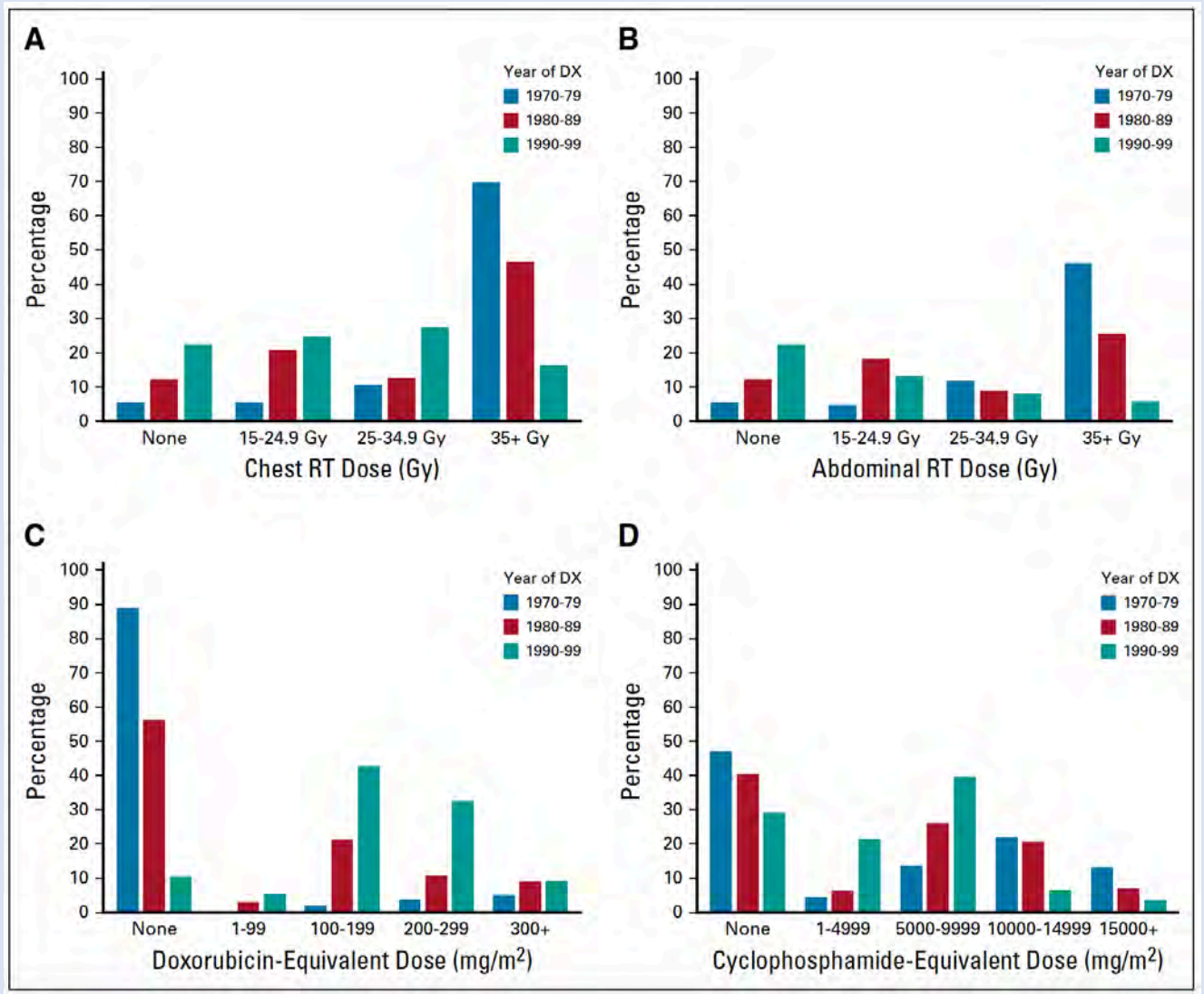
original reports

Impact of Risk-Adapted Therapy for Pediatric Hodgkin Lymphoma on Risk of Long-Term Morbidity: A Report From the Childhood Cancer Survivor Study

Kevin C. Oeffinger, MD[1]; Kayla L. Stratton, MS[2]; Melissa M. Hudson, MD[3]; Wendy M. Leisenring, ScD[2]; Tara O. Henderson, MD, MPH[4]; Rebecca M. Howell, PhD[5]; Suzanne L. Wolden, MD[6]; Louis S. Constine, MD[7]; Lisa R. Diller, MD[8]; Charles A. Sklar, MD[6]; Paul C. Nathan, MD, MSc[9]; Sharon M. Castellino, MD, MSc[10]; Dana Barnea, MD[11]; Susan A. Smith, MPH[5]; Raymond J. Hutchinson, MD, MS[12]; Gregory T. Armstrong, MD, MSCE[3]; and Leslie L. Robison, PhD[3]

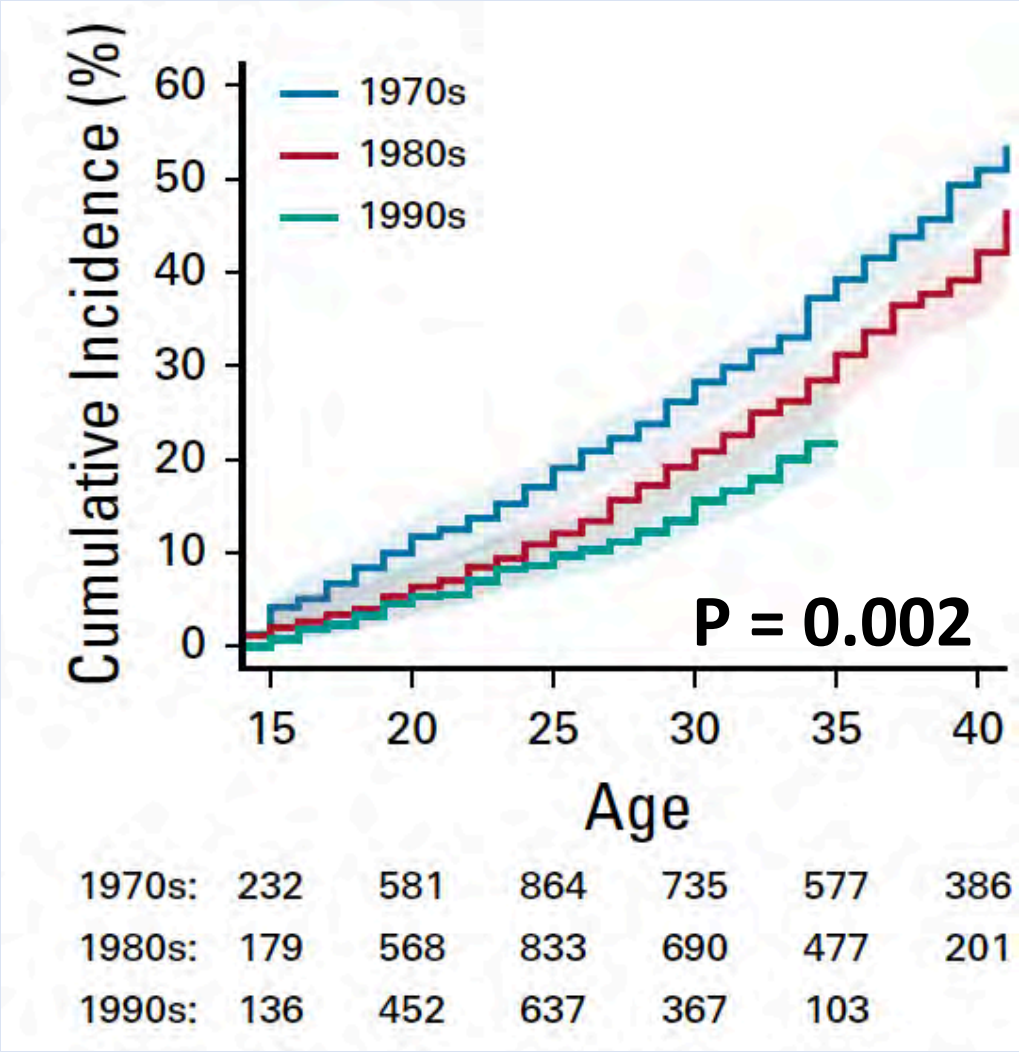
JCO 2021; 39(20)

Decade-Specific Trends in Therapeutic Exposures



Oeffinger JCO 2021

Risk of a Grade 3-5 Health Condition in Survivors



Oeffinger JCO 2021

Risk of a Chronic Condition by Treatment Era & RT Exposure

- In MVA including sex, age, anthracycline dose, & alkylator dose:

Group	Any HR (95% CI)
Era	
1970-1979	1.0 (reference)
1980-1989	0.8 (0.7, 1.0)
1990-1999	0.6 (0.5, 0.8)
Abdominal radiotherapy	
None or < 35 Gy	1.0 (reference)
≥ 35 Gy	1.3 (1.0, 1.6)
Chest radiotherapy	
None	1.0 (reference)
Mantle < 35 Gy	2.3 (1.5, 3.5)
Mantle ≥ 35 Gy	3.0 (2.0, 4.6)
Mediastinal < 35 Gy	2.0 (1.3, 3.6)
Mediastinal ≥ 35 Gy	2.0 (1.2, 3.6)

Oeffinger JCO 2021

Conclusions

- In survivors of HL, the risk of any grade 3-5 chronic health condition decreased by era of treatment
- Lower radiation doses and smaller fields were associated with a lower risk of any grade 3-5 toxicity

Major cardiac events for adult survivors of childhood cancer diagnosed between 1970 and 1999: report from the Childhood Cancer Survivor Study cohort

Daniel A Mulrooney,[1,2] Geehong Hyun,[2] Kirsten K Ness,[2] Matthew J Ehrhardt,[1,2] Yutaka Yasui,[2] Daniel Duprez,[3] Rebecca M Howell,[4] Wendy M Leisenring,[5] Louis S Constine,[6] Emily Tonorezos,[7] Todd M Gibson,[2] Leslie L Robison,[2] Kevin C Oeffinger,[8] Melissa M Hudson,[1,2] Gregory T Armstrong[2]

BMJ 2020; 368

Survivors of HL: Treatment Exposures by Decade

	1970-1979	**1980-1989**	**1990-1999**
Mean Heart RT Dose (Gy):			
None	52 **(5.6%)**	159 **(17.4%)**	410 **(52.0%)**
<15	119 (12.8%)	163 (17.8%)	217 (27.5%)
15 to <35	202 (21.7%)	264 (28.8%)	140 (17.8%)
≥35	558 **(59.9%)**	330 **(36.0%)**	21 **(2.7%)**
Anthracycline Dose (mg/m^2):			
None	824 (89.0%)	507 (56.3%)	82 (10.3%)
<250	31 (3.2%)	263 (29.2%)	597 (75.2%)
≥250	72 (7.8%)	131 (14.5%)	115 (14.5%)

Mulrooney BMJ 2020

Survivors of HL: CAD Risk by Decade

- Incidence of CAD declined significantly with treatment era
  - HR 0.44 for the ‘90s compared with the ‘70s (P = 0.01)
- Attenuated by adjustment for exposure to RT/anthracyclines → reduction in MHD contributed significantly to the decline in CAD incidence

Mulrooney BMJ 2020

Conclusions

- In survivors of HL, MHD declined dramatically over the study period
- The 20-year cumulative incidence of CAD in survivors treated in the ‘90s was <1/2 that of survivors treated in the ‘70s
- Reduction in MHD contributed significantly to the decline in CAD incidence over successive treatment periods

Mulrooney BMJ 2020

Secondary Breast Cancer Risk by Radiation Volume in Women With Hodgkin Lymphoma

Jessica L. Conway, MD,[*,†] Joseph M. Connors, MD,[*] Scott Tyldesley, MD,[*,†] Kerry J. Savage, MD,[*] Belinda A. Campbell, MD,[‡] Yvonne Y. Zheng, MEng, MSc,[§] Jeremy Hamm, MSc,[§] and Tom Pickles, MD[*,†]

**Centre for Lymphoid Cancer, British Columbia Cancer Agency; [†]Department of Surgery, University of British Columbia; [§]Department of Cancer Surveillance and Outcomes, British Columbia Cancer Agency, Vancouver, British Columbia, Canada; and [‡]Division of Radiation Oncology and Cancer Imaging, Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia*

IJROBP 2016; 97(1)

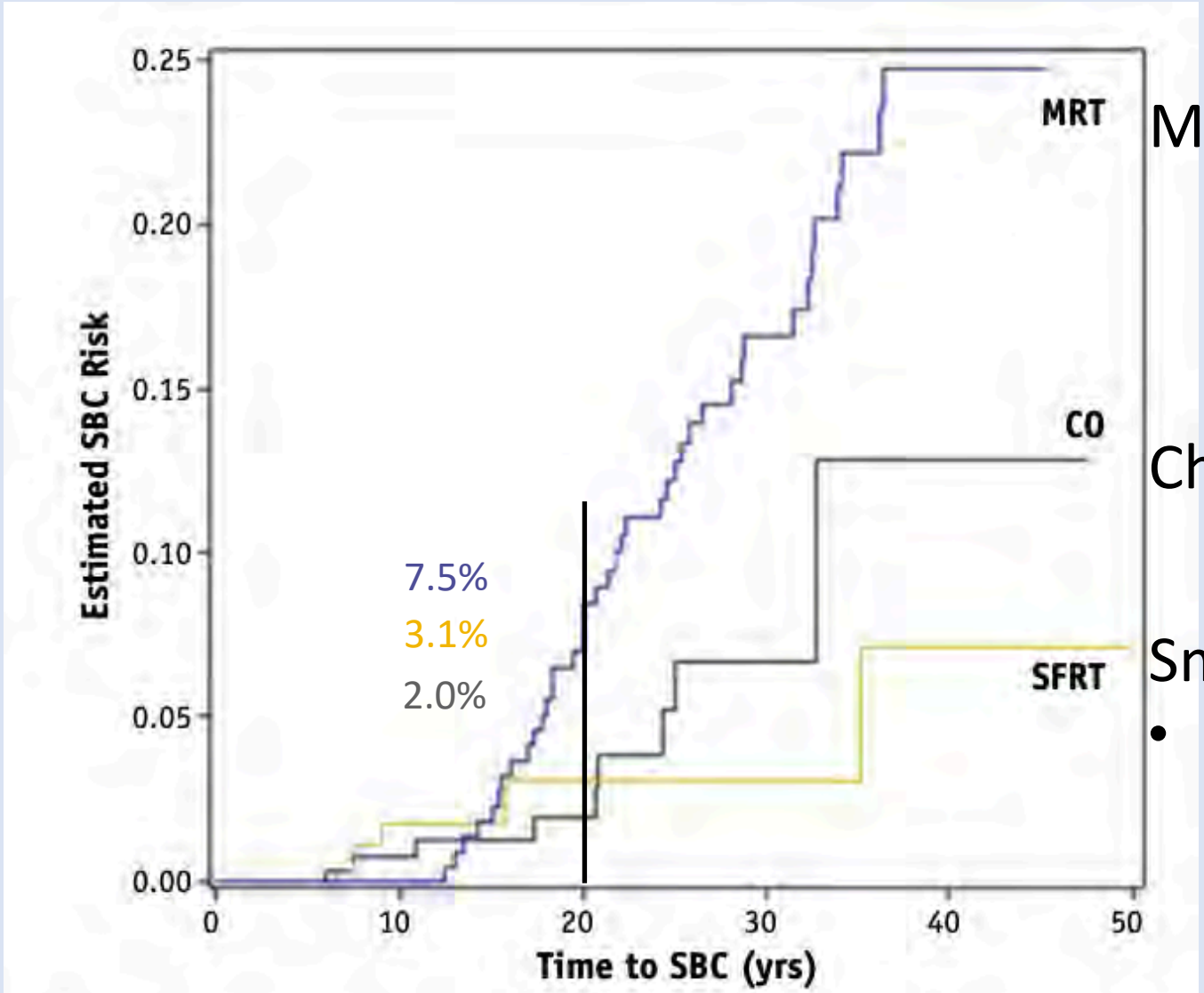


Fig. 2. Cumulative incidence: death and loss to follow-up as competing risks. *Abbreviations:* CO = chemotherapy only; MRT = mantle field radiation; SBC = secondary breast cancer; SFRT = small field radiation.

Mantle RT (n=231)

Chemo only (n=318)

Small field RT (n=185)

- IFRT, ISRT, or INRT

Conway IJROBP 2016

Table 3 Fine and Gray multivariable regression for the risk of SBC: competing risk model (stratified by age)

Factor	HR	95% CI	*P* value
Radiation field			
CO		1.00 (reference)	
MRT	2.90	1.41-5.97	.004
SFRT	0.87	0.28-2.66	.803
Radiation field			
SFRT		1.00 (reference)	
MRT	3.34	1.33-8.40	.01
Premature menopause risk			
Not at risk		1.00 (reference)	
At risk	1.18	0.61-2.27	.63

Abbreviations: CO = chemotherapy only; HR = hazard ratio; MRT = mantle field radiation; SBC = secondary breast cancer; SFRT = small field radiation.

Conway IJROBP 2016

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 24, 2015 VOL. 373 NO. 26

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

Michael Schaapveld, Ph.D., Berthe M.P. Aleman, M.D., Ph.D., Anna M. van Eggermond, M.Sc., Cécile P.M. Janus, M.D., Augustinus D.G. Krol, M.D., Ph.D., Richard W.M. van der Maazen, M.D., Ph.D., Judith Roesink, M.D., Ph.D., John M.M. Raemaekers, M.D., Ph.D., Jan Paul de Boer, M.D., Ph.D., Josée M. Zijlstra, M.D., Ph.D., Gustaaf W. van Imhoff, M.D., Ph.D., Eefke J. Petersen, M.D., Ph.D., Philip M.P. Poortmans, M.D., Ph.D., Max Beijert, M.D., Marnix L. Lybeert, M.D., Ina Mulder, Ph.D., Otto Visser, Ph.D., Marieke W.J. Louwman, Ph.D., Inge M. Krul, M.Sc., Pieternella J. Lugtenburg, M.D., Ph.D., and Flora E. van Leeuwen, Ph.D.

The New England Journal of Medicine

Volume 334 MARCH 21, 1996 Number 12

BREAST CANCER AND OTHER SECOND NEOPLASMS AFTER CHILDHOOD HODGKIN'S DISEASE

SMITA BHATIA, M.D., M.P.H., LESLIE L. ROBISON, PH.D., ODILE OBERLIN, M.D., MARK GREENBERG, M.B., CH.B., GRETA BUNIN, PH.D., FRANCA FOSSATI-BELLANI, M.D., AND ANNA T. MEADOWS, M.D.

VOLUME 27 · NUMBER 26 · SEPTEMBER 10 2009

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Breast Cancer Risk in Female Survivors of Hodgkin's Lymphoma: Lower Risk After Smaller Radiation Volumes

Marie L. De Bruin, Judith Sparidans, Mars B. van't Veer, Evert M. Noordijk, Marieke W.J. Louwman, Josée M. Zijlstra, Hendrik van den Berg, Nicola S. Russell, Annegien Broeks, Margreet H.A. Baaijens, Berthe M.P. Aleman, and Flora E. van Leeuwen

Breast Cancer Following Radiotherapy and Chemotherapy Among Young Women With Hodgkin Disease

Lois B. Travis, MD; Deirdre A. Hill, PhD; Graça M. Dores, MD; Mary Gospodarowicz, MD; Flora E. van Leeuwen, PhD; Eric Holowaty, MD; Bengt Glimelius, MD; Michael Andersson, MD; Tom Wiklund, MD; Charles F. Lynch, MD; Mars B. Van't Veer, MD; Ingrid Glimelius, MD; Hans Storm, MD; Eero Pukkala, PhD; Marilyn Stovall, PhD; Rochelle Curtis, MA; John D. Boice Jr, ScD; Ethel Gilbert, PhD

» Author Affiliations | Article Information

JAMA. 2003;290(4):465-475. doi:10.1001/jama.290.4.465

Conclusion

- These studies have demonstrated a lower risk of SBC in survivors of HL who were treated with smaller field sizes and lower radiation doses

Temporal Change in Secondary Breast Cancer

- However, not all studies have shown a decreased risk of SBC according to era of treatment. Why??
  - Smaller RT fields may not have been adopted widely enough during the most recent periods to translate into a decreased risk of SBC
  - Increased breast cancer screening during the more recent periods may have resulted in the earlier detection of more SBC cases
  - Anthracyclines are used more commonly in the modern era and are associated with a greater risk of SBC
  - Ovarian preservation, due to avoidance of high-dose procarbazine and pelvic RT, may increase the incidence of SBC

Reduced Late Effects with Lower Doses/Smaller Fields

- Clinical data confirm that lower doses/smaller fields are associated with a decreased risk of:
  - Any grade 3-5 chronic health condition
  - CAD
  - Breast cancer
- Importantly, since the survivors reported in these studies were treated for HL, the treatment approach has continued to evolve to reduce dose to organs at risk

JAMA Network | Open

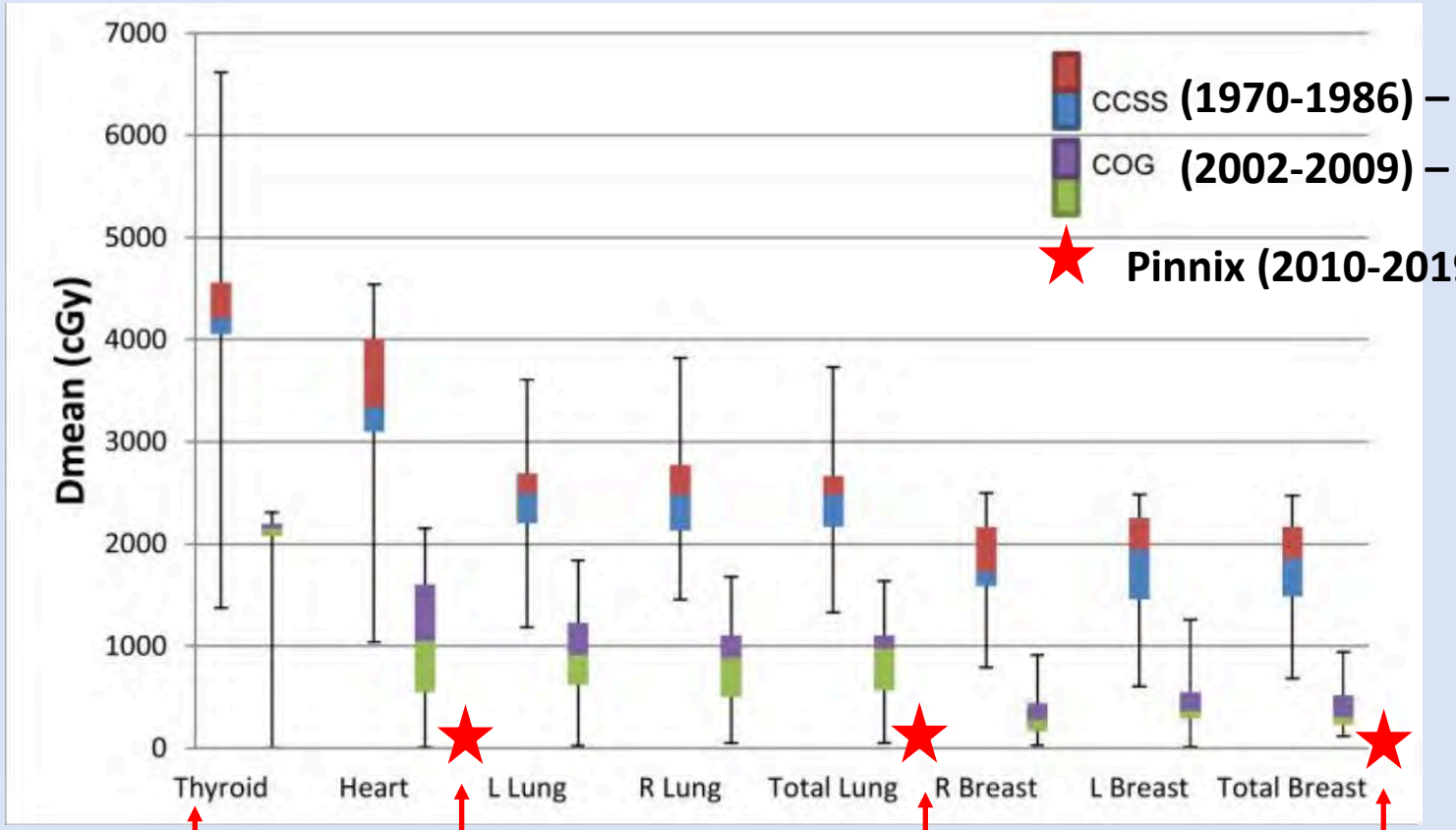
Original Investigation | Oncology

Assessment of Radiation Doses Delivered to Organs at Risk Among Patients With Early-Stage Favorable Hodgkin Lymphoma Treated With Contemporary Radiation Therapy

Chelsea C. Pinnix, MD, PhD; Jillian R. Gunther, MD, PhD; Penny Fang, MD; Mikaela E Bankston, BA; Sarah A. Milgrom, MD; David Boyce, MD; Hun Ju Lee, MD; Ranjit Nair, MD; Raphael Steiner, MD; Paolo Strati, MD; Sairah Ahmed, MD; Swaminathan P. Iyer, MBBS; Jason Westin, MD; Simrit Parmar, MD; M. Alma Rodriguez, MD; Loretta Nastoupil, MD; Sattva Neelapu, MD; Christopher Flowers, MD; Bouthaina S. Dabaja, MD

Pinnix JAMA Netw Open 2020

Evolution of RT for Lymphoma



Thyroid V_{20}: 16.9%

Mean heart:
0.8 Gy total cohort
1.8 Gy mediastinal dz above L main
4.8 Gy mediastinal dz below L main

Mean lung: 1.3 Gy

Mean breast: 0.1 Gy

Zhou IJROBP 2016
Pinnix JAMA Netw Open 2020

Risk of Late Effects with Modern Radiation

- Doses to normal tissues are substantially lower in patients treated today, compared to those in survivors with available late effects data
- Do not have long-term clinical data regarding late effects with today's limited RT doses/volumes
- There is a long latency period before late effects are observed
- Can estimate the risk from available dose-toxicity data

Estimated Cardiac Toxicity Risk

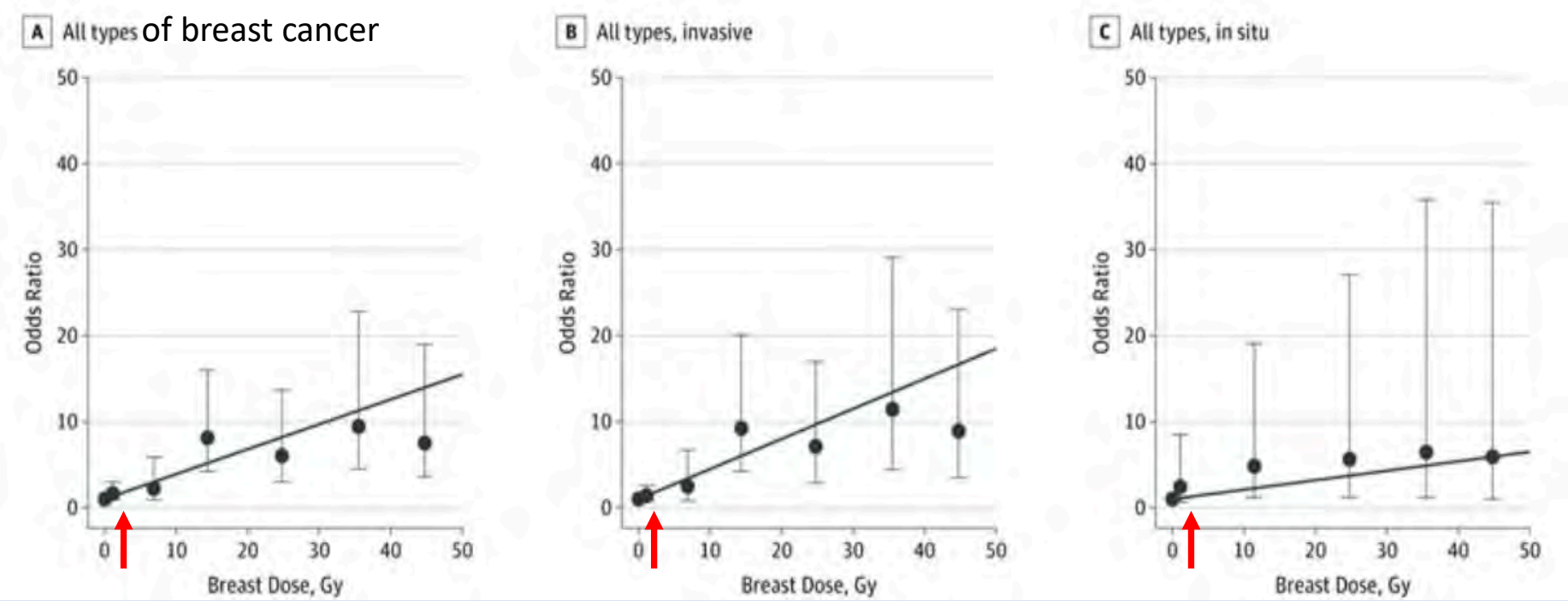
Average	NCCN Constraint	GHSG HD17 (Oertel)	RNRT in HR-HL (Metzger)	ISRT in ES-Fav-HL (Pinnix)
Mean heart dose	< 8Gy (rec) <15 Gy (accept)	13 Gy	5.29 Gy	1.8 Gy med dz above L main 4.8 Gy med dz below L main

Variable	Any Cardiac Disease			CAD			HF		
	30-Year Cumulative Incidence (%) (95% CI)	Adjusted RR (95% CI)	P	30-Year Cumulative Incidence (%) (95% CI)	Adjusted RR (95% CI)	P	30-Year Cumulative Incidence (%) (95% CI)	Adjusted RR (95% CI)	P
Mean cardiac radiotherapy dose, Gy									
None	3.4 (2.6 to 4.2)	Ref	Ref	1.0 (0.6 to 1.5)	Ref	Ref	2.5 (1.8 to 3.2)	Ref	Ref
0.1-9.9	2.6 (2.0 to 3.1)	0.8 (0.6 to 1.1)	.12	1.0 (0.7 to 1.4)	1.0 (0.6 to 1.5)	.88	1.4 (1.0 to 1.7)	0.7 (0.5 to 1.0)	.05
10-19.9	5.8 (4.2 to 7.4)	2.2 (1.6 to 2.9)	< .001	3.2 (1.9 to 4.5)	3.0 (1.9 to 4.8)	< .001	2.6 (1.6 to 3.6)	1.7 (1.1 to 2.7)	.01
20-29.9	7.7 (5.2 to 10.2)	2.8 (2.0 to 3.8)	< .001	3.7 (1.9 to 5.4)	3.2 (1.9 to 5.4)	< .001	4.7 (2.7 to 6.7)	2.9 (1.9 to 4.6)	< .001
≥ 30	17.3 (14.5 to 20.0)	6.4 (4.8 to 8.5)	< .001	11.9 (9.5 to 14.3)	7.5 (4.9 to 11.4)	< .001	6.9 (5.2 to 8.7)	6.7 (4.6 to 9.9)	< .001

Bates et al. JCO 2019

Estimated Breast Cancer Risk

Average dose	NCCN Constraint	GHSG HD17 (Oertel)	RNRT in HR-HL (Metzger)	ISRT in ES-Fav-HL (Pinnix)
Mean breast	Minimize V_{4Gy} (ideally <10%)	3.6 Gy	3.21 Gy	0.1 Gy



OR 1.7 (95% CI 1.0-3.0) for survivors with 1-5 Gy breast dose compared to 0 Gy

Veiga et al. JAMA Ped 2019

Estimated Thyroid Cancer Risk

Average dose	NCCN Constraint	RNRT in HR-HL (Metzger)	ISRT in ES-Fav-HL (Pinnix)
Mean thyroid	V_{25Gy} <63.5% Minimize V_{30Gy}	4.46 Gy	V_{20Gy} 16.9%

Characteristic	Relative risk of thyroid cancer (95% confidence interval)[a]	*P* value[b]
Thyroid radiation dose, Gy (mean)		
0	1.0	<0.001
>0–<5 (0.8)	1.2 (0.6, 2.5)	
5–<10 (7.4)	8.5 (3.2, 22.6)	
10–<15 (12.3)	10.6 (4.5, 24.9)	
15–<20 (17.4)	13.8 (6.3, 30.3)	
20–<25 (22.0)	14.6 (6.8, 31.5)	
25–<30 (27.3)	9.3 (3.9, 21.9)	
30–<35 (32.4)	8.9 (3.6, 21.7)	
35–<40 (37.5)	3.6 (1.3, 10.2)	
≥40 (45.6)	2.8 (1.1, 7.1)	

Bhatti Rad Res 2010

Conclusion

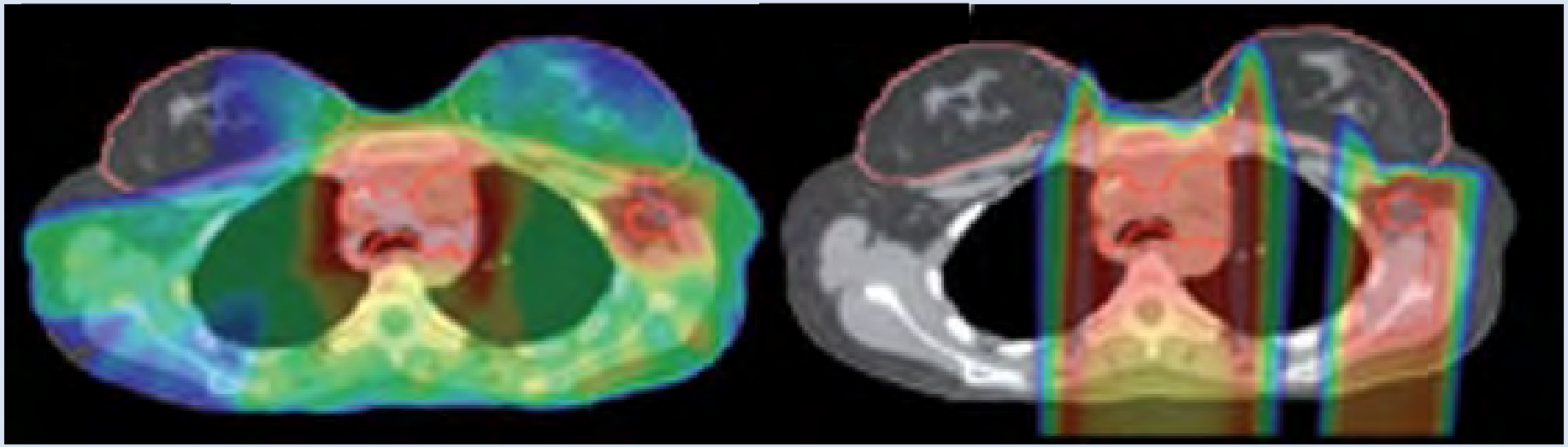
- Long-term follow-up data for patients treated with contemporary RT techniques will not be available for decades
- However, OAR doses are low with the small target volumes/low doses used for modern RT in HL
- Known radiation dose-toxicity relationships suggest a low risk of late effects in patients treated today, compared to survivors treated with older approaches

Future Directions

- Greater insights into dose-volume-toxicity relationships
  - Impact of a low dose to a large volume of healthy tissue vs. higher dose to a small volume?
  - Critical question given the different dose distributions with newer technologies, such as IMRT/VMAT and proton therapy

IMRT: more low dose

Protons: more high dose



Holzman Acta Oncol 2013

OXFORD

JNCI J Natl Cancer Inst (2022) 114(9): djac125

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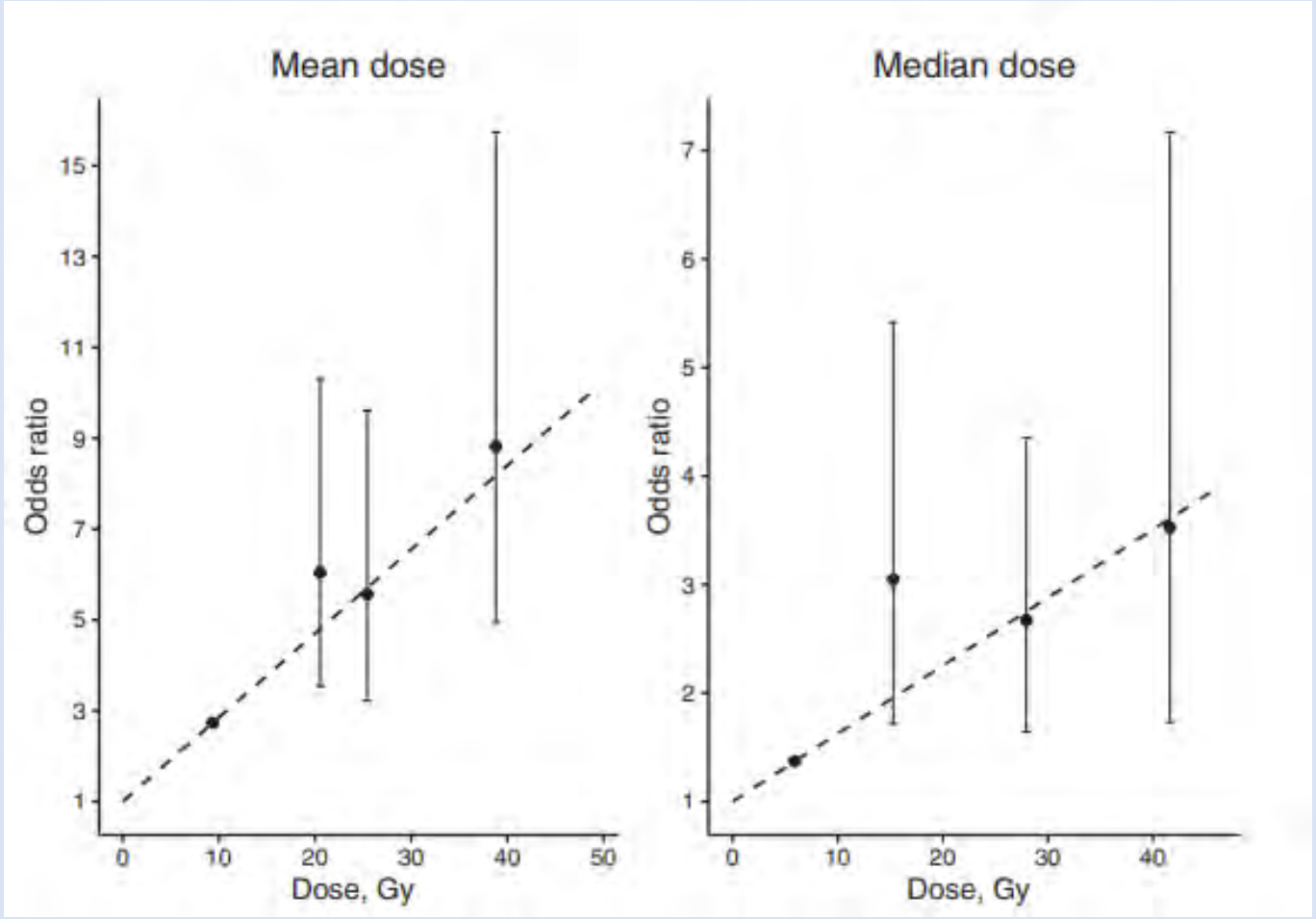
Article

Radiotherapy-Related Dose and Irradiated Volume Effects on Breast Cancer Risk Among Hodgkin Lymphoma Survivors

Sander Roberti, MSc,[1] Flora E. van Leeuwen, PhD,[1] Cécile M. Ronckers, PhD,[2] Inge M. Krul, MSc,[1] Florent de Vathaire, PhD,[3,4,5] Cristina Veres, MSc,[5,6,7] Ibrahima Diallo, PhD,[5,6,7] Cécile P.M. Janus, MD,[8] Berthe M.P. Aleman, MD,[9] Nicola S. Russell, MD,[9] Michael Hauptmann, PhD[2,*]

Dose-Volume Effect on Breast Cancer Risk



Roberti JNCI 2022

Dose metric	OR (95% CI) Tertile of dose metric 1st	2nd	3rd	EOR/unit[a] (95% CI)	P_{trend}[b]	Deviance[c]
Not accounting for mean dose						
Mean dose	1 (Referent)	2.11 (1.29 to 3.43)	2.15 (1.31 to 3.52)	0.19 (0.05 to 1.06)	<.001	398.26
D20	1 (Referent)	2.03 (1.31 to 3.15)	2.49 (1.26 to 4.95)	0.08 (0.02 to 0.27)	<.001	401.35
D50[d]	1 (Referent)	2.28 (1.38 to 3.76)	2.04 (1.25 to 3.33)	0.06 (0.02 to 0.19)	<.001	402.50
D80	1 (Referent)	2.34 (1.42 to 3.83)	2.05 (1.24 to 3.37)	0.41 (0.13 to 1.43)	<.001	396.51
V5	1 (Referent)	2.13 (1.31 to 3.46)	2.16 (1.30 to 3.60)	0.05 (0.01 to 0.30)	<.001	399.20
V20	1 (Referent)	2.27 (1.39 to 3.73)	2.06 (1.25 to 3.39)	0.06 (0.01 to 0.23)	<.001	400.69
V30	1 (Referent)	2.08 (1.30 to 3.33)	2.14 (1.31 to 3.50)	0.06 (0.02 to 0.21)	<.001	398.15
V35	1 (Referent)	2.41 (1.48 to 3.92)	2.16 (1.33 to 3.52)	0.07 (0.02 to 0.22)	<.001	395.94
Gini index	1 (Referent)	0.79 (0.48 to 1.28)	0.53 (0.30 to 0.91)	−0.08 (−0.10 to 0.01)[e]	.06	412.24
MAD	1 (Referent)	1.44 (0.92 to 2.26)	1.97 (1.20 to 3.24)	0.37 (0.06 to 4.93)	<.001	403.17

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Dose metric	OR (95% CI) Tertile of dose metric 1st	2nd	3rd	EOR/unit[a] (95% CI)	P_{trend}[b]	Deviance[c]
Accounting for mean dose[f]						
D20	1 (Referent)	1.38 (0.84 to 2.27)	1.52 (0.72 to 3.18)	−0.01 (−0.30 to 0.17)	.85	398.23
D50[d]	1 (Referent)	1.45 (0.83 to 2.55)	1.09 (0.61 to 1.95)	−0.01 (−0.54 to 0.18)	.91	398.25
D80	1 (Referent)	1.48 (0.84 to 2.60)	1.10 (0.60 to 2.00)	0.37 (−0.23 to 1.42)	.17	396.38
V5	1 (Referent)	1.31 (0.75 to 2.31)	1.10 (0.59 to 2.05)	−0.008 (NA to 0.22)	.90	398.24
V20	1 (Referent)	1.44 (0.83 to 2.51)	1.09 (0.60 to 1.97)	−0.33 (NA to 0.02)	.07	394.89
V30	1 (Referent)	1.35 (0.79 to 2.30)	1.15 (0.64 to 2.07)	0.04 (NA to 0.21)	.66	398.07
V35	1 (Referent)	1.68 (0.98 to 2.88)	1.23 (0.69 to 2.21)	0.08 (−0.04 to 0.22)	.12	395.83
Gini index	1 (Referent)	0.79 (0.48 to 1.31)	0.83 (0.47 to 1.49)	0.17 (−0.09 to 5.94)[e]	.42	397.60
MAD	1 (Referent)	0.99 (0.60 to 1.61)	1.44 (0.84 to 2.46)	−0.01 (−0.28 to 1.08)	.94	398.25

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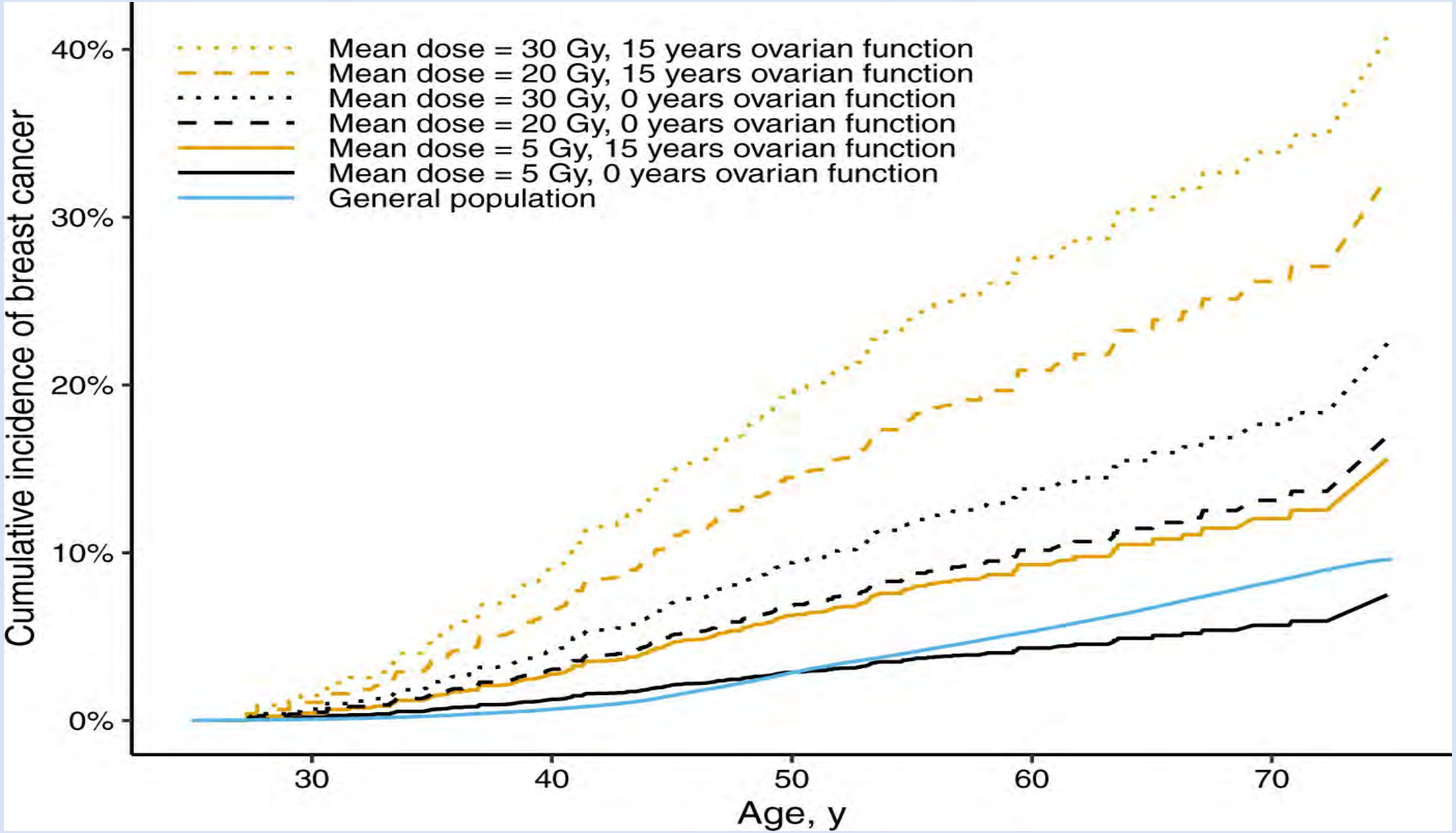

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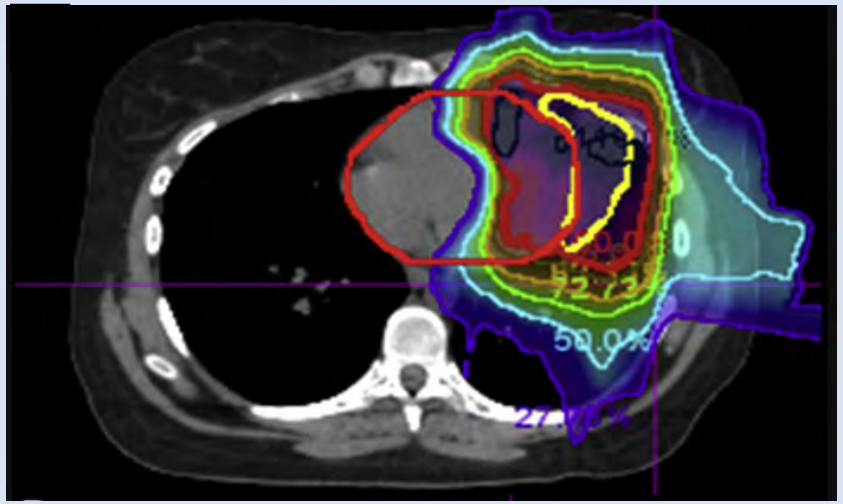
Conclusions

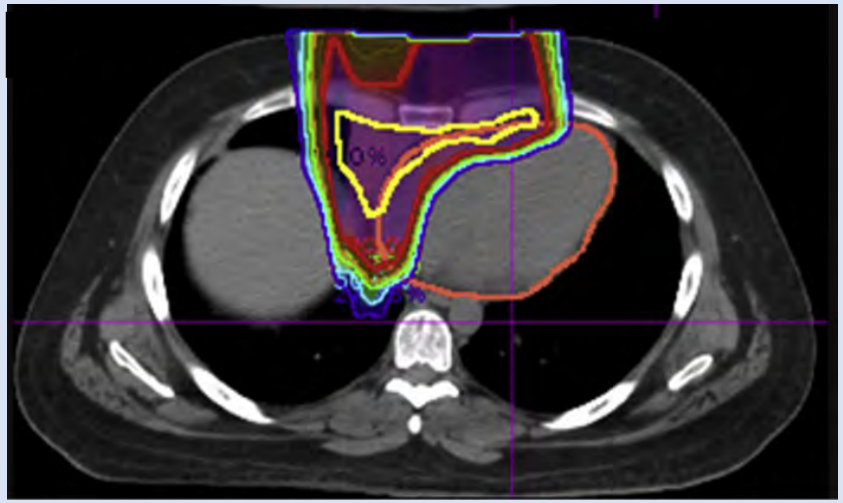
- SBC risk increased with increasing mean and median breast dose
- Numerous other dose-volume metrics were associated with BC risk, but significance was not maintained after adjusting for mean dose
- Limitations:
  - Possible uncertainty in reconstruction of historic 3D dose distributions
  - Limited variability in breast doses because a limited number of RT field types were very common or were variations of similar fields (mantle)
- Future study of patients treated with a larger variety of breast doses & accurate patient-level dosimetry may further elucidate dose-volume-toxicity relationships

Future Directions

- Greater insights into dose-volume-toxicity relationships
  - Particularly radiosensitive substructures of organs at risk?
  - Critical question to guide treatment planning and predict toxicity risk



MHD: 12 Gy
Mean LAD dose: 28 Gy
Mean LV dose: 18 Gy



MHD: 12 Gy
Mean LAD dose: 3 Gy
Mean LV dose: 1 Gy

Hoppe PRO 2020

Original Reports | Pediatric Oncology

Cardiac Substructure Radiation Dose and Risk of Late Cardiac Disease in Survivors of Childhood Cancer: A Report From the Childhood Cancer Survivor Study

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Structure	Percentage Increase per 1 Gy Increase in Mean Dose on Linear ERR Model, %	Goodness of Fit for Linear ERR Model (lower is better)	Goodness of Fit for Quadratic ERR Model (lower is better)	χ^2 for Difference in Goodness of Fit	*P* (likelihood ratio test for comparing quadratic ERR *v* linear ERR)
Coronary artery disease					
Whole heart	21.7	6,111.1	6,107.0	4.13	.042
Left anterior descending artery	22.9	6,100.2	6,100.1	0.12	.73
Left circumflex artery	19.0	6,127.0	6,126.8	0.15	.70
Left main coronary artery	17.1	6,120.7	6,116.8	3.92	.048
Right coronary artery	28.7	6,118.8	6,118.7	0.04	.84
Left atrium	16.9	6,134.7	6,134.5	0.12	.73
Right atrium	23.3	6,122.7	6,119.2	3.48	.062
Aortic valve	18.3	6,133.0	6,132.8	0.15	.69
Mitral valve	17.1	6,135.0	6,135.0	0.06	.81
Pulmonic valve	18.0	6,131.9	6,131.9	0.05	.82
Tricuspid valve	19.4	6,128.6	6,128.5	0.08	.77
Left ventricle	28.4	6,124.2	6,123.2	0.99	.32
Right ventricle	19.4	6,129.4	6,128.0	1.36	.24

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Conclusions

- Cardiac toxicity outcomes were associated with doses to specific substructures
- Future study of patients treated with a large variety of cardiac doses & accurate patient-level dosimetry may further elucidate dose-volume-toxicity relationships

Summary

- High risk of late M&M in survivors of HL after historic RT
- Contemporary RT employs smaller target volumes, lower doses, advanced techniques, careful patient/site selection
- Dose to normal tissues is lower with a modern approach → decreased risk of treatment-related toxicity
- Management of HL continues to evolve
- Future study of dose-volume-toxicity relationships will inform radiation planning
- **Overall goal: reduce the risk of late effects without compromising relapse-free survival**

Thank you!

Questions?

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