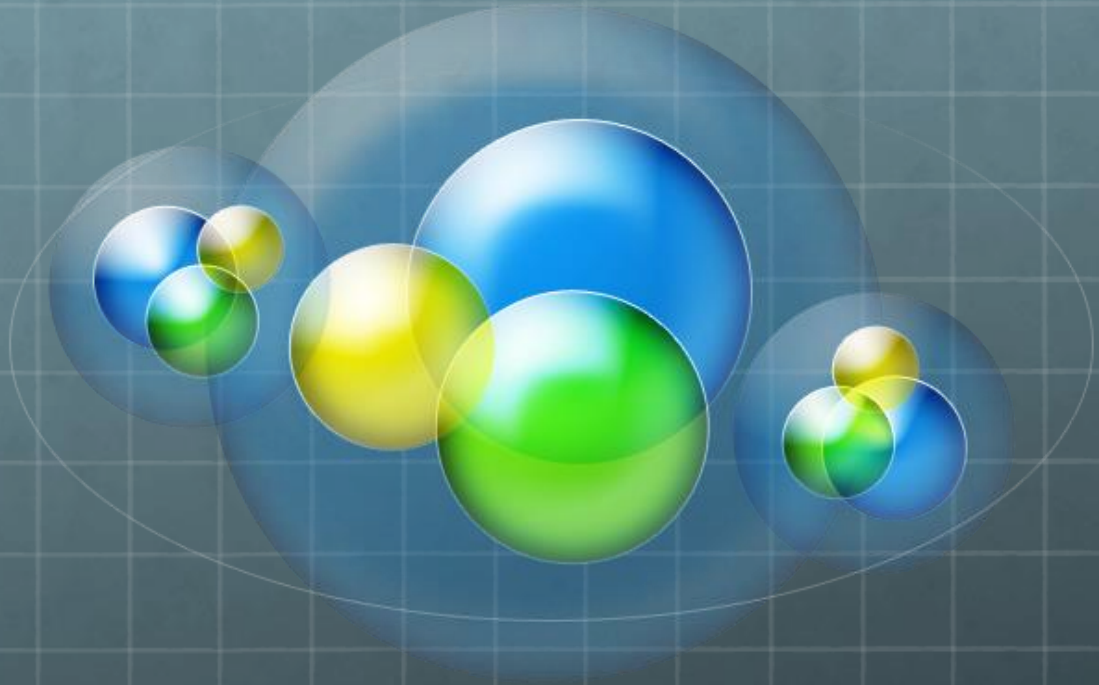


Modern Radiotherapy for Lymphomas

Christopher Platta, MD
Radiation Oncologist
Aspirus Regional Cancer Center

Disclosure

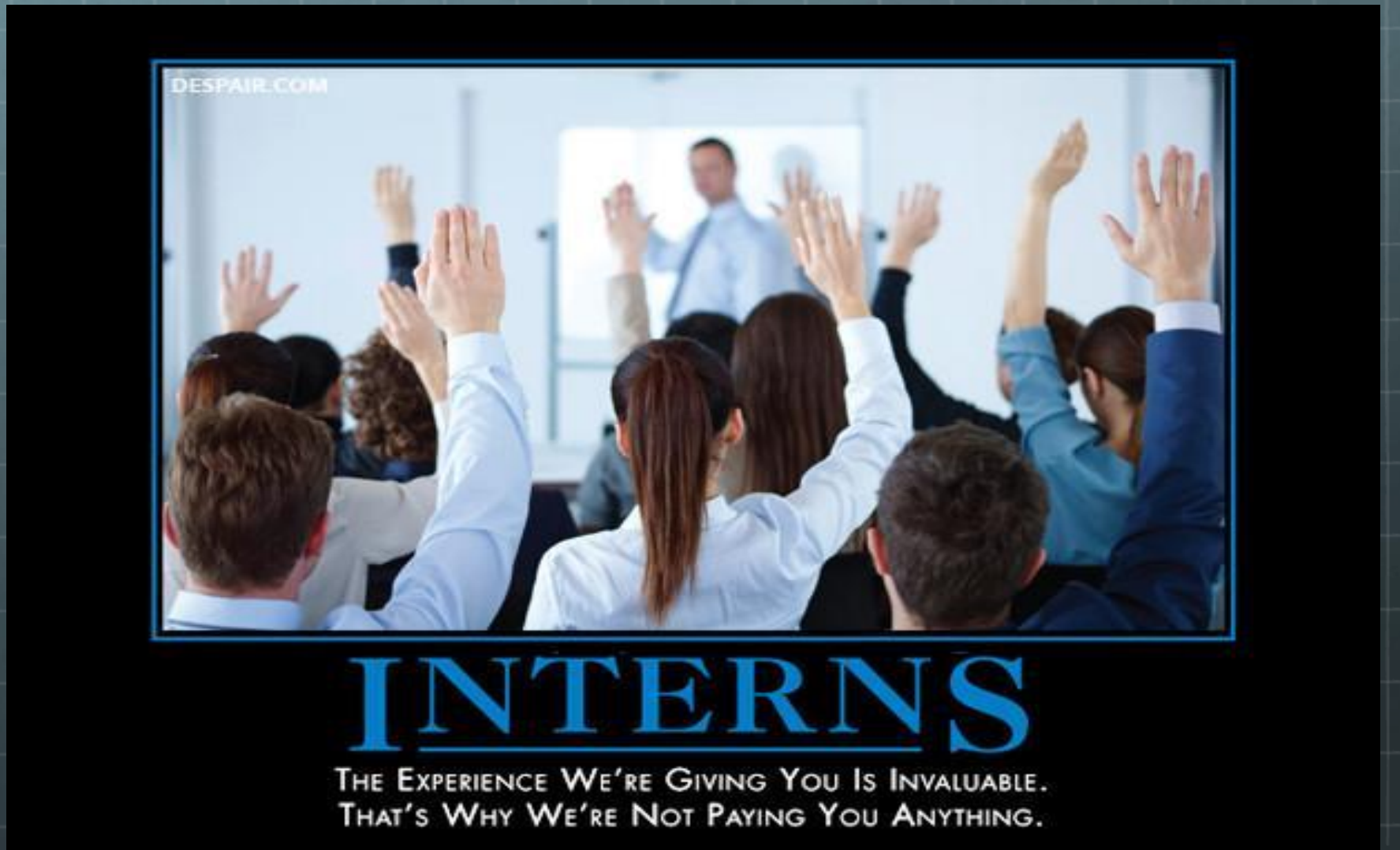
- I have no conflicts of interest.

Objectives

- Review the evolution of the use of radiation therapy in Hodgkin and non-Hodgkin lymphoma and discuss the current role of radiation therapy in early and advanced stages of lymphoma.
- Describe the rationale for the use of smaller radiation fields (Involved Site RT) in the treatment of both Hodgkin and non-Hodgkin lymphoma.
- Compare the short and long term toxicity of modern radiation treatments in lymphoma with historical studies.
- Discuss the use pharmacologic agents to help mitigate symptoms of acute toxicity from radiation therapy.

Classification of Lymphoma – Lymphoma Soup

Classification of Lymphoma – Lymphoma soup



Lymphoma Soup

- Hodgkin Lymphoma
  - Classical
  - Lymphocyte predominant
- Non-Hodgkin Lymphoma
  - Aggressive
  - Indolent

Lymphoma Staging

National Comprehensive Cancer Network®

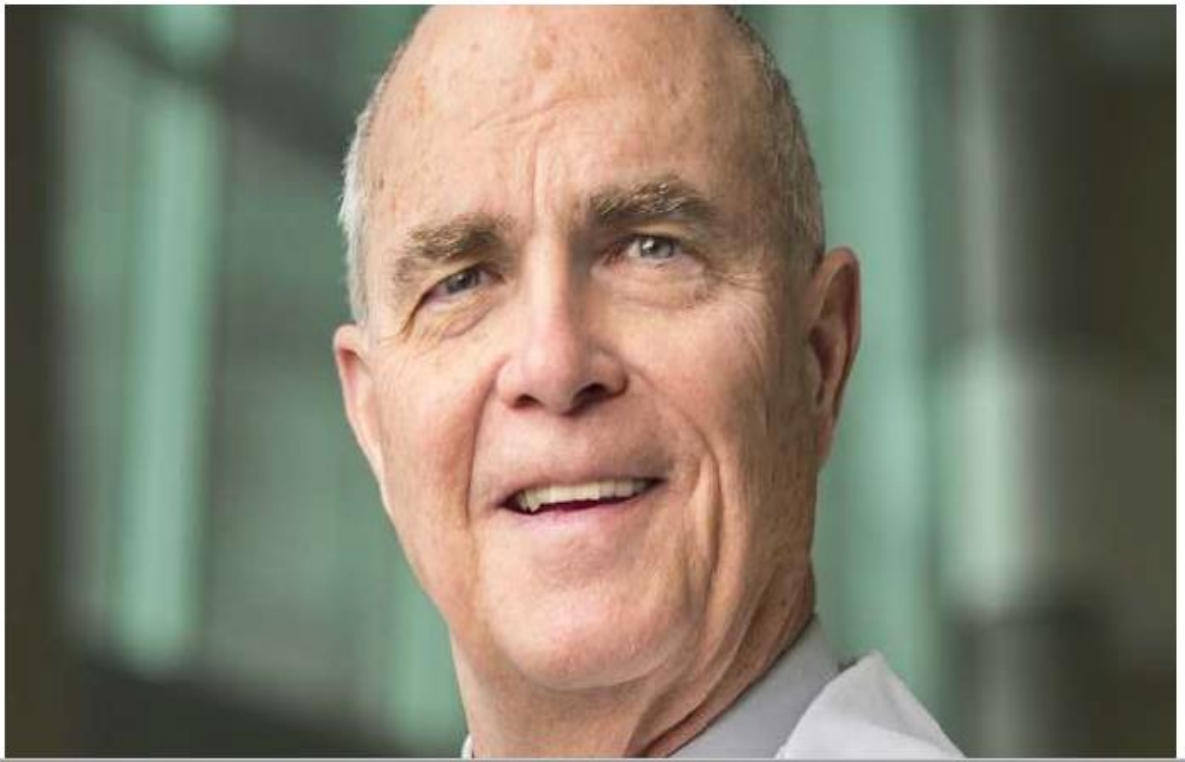
NCCN Guidelines Version 2.2019
B-Cell Lymphomas

Staging

**Lugano Modification of Ann Arbor Staging System*
(for primary nodal lymphomas)**

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

“Radiation is the Most Effective Single Agent for the Treatment of Lymphomas”



Prof. James O. Armitage

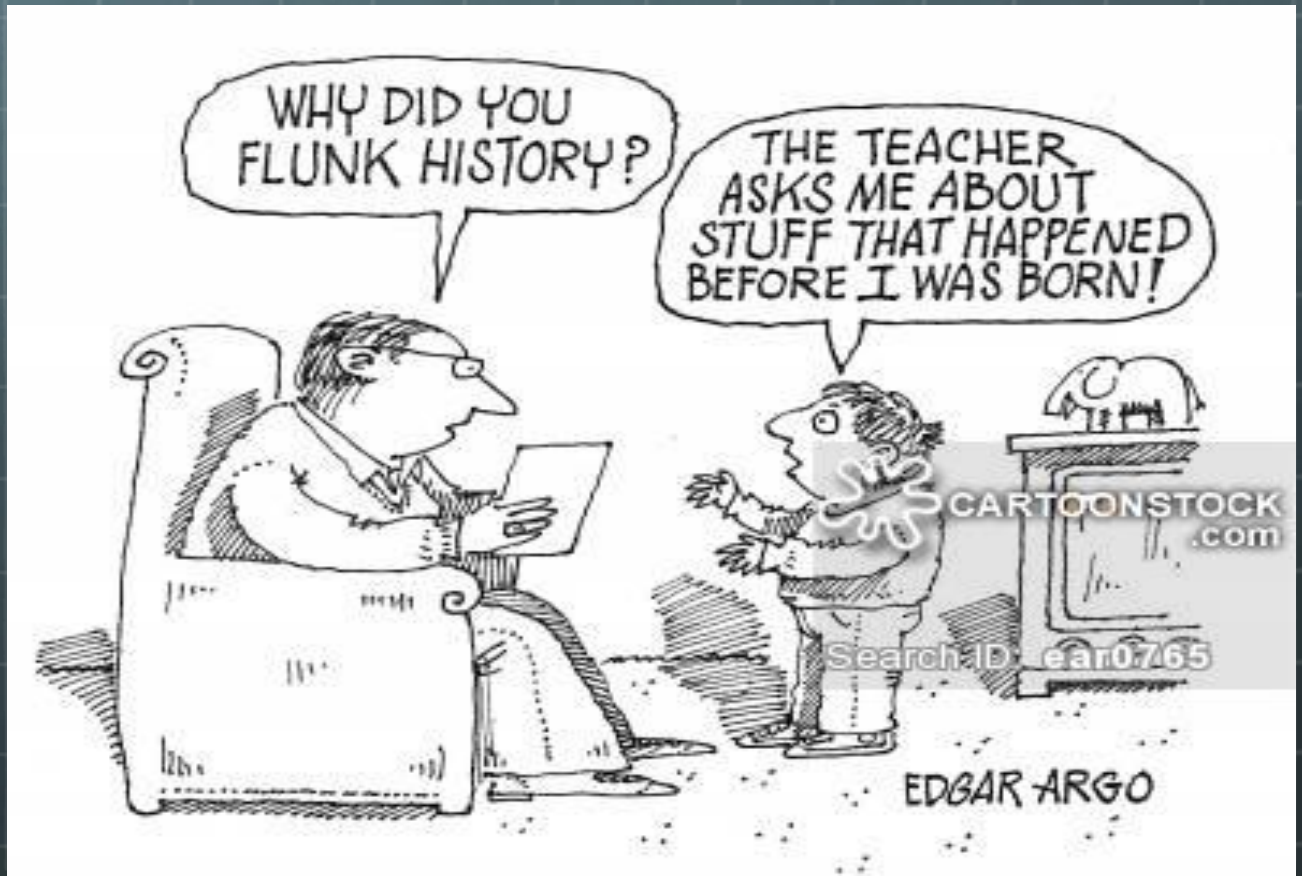
Leading Medical Oncologist and Lymphoma Expert

Past-President and Awardee of ASCO-American Society of Clinical Oncology

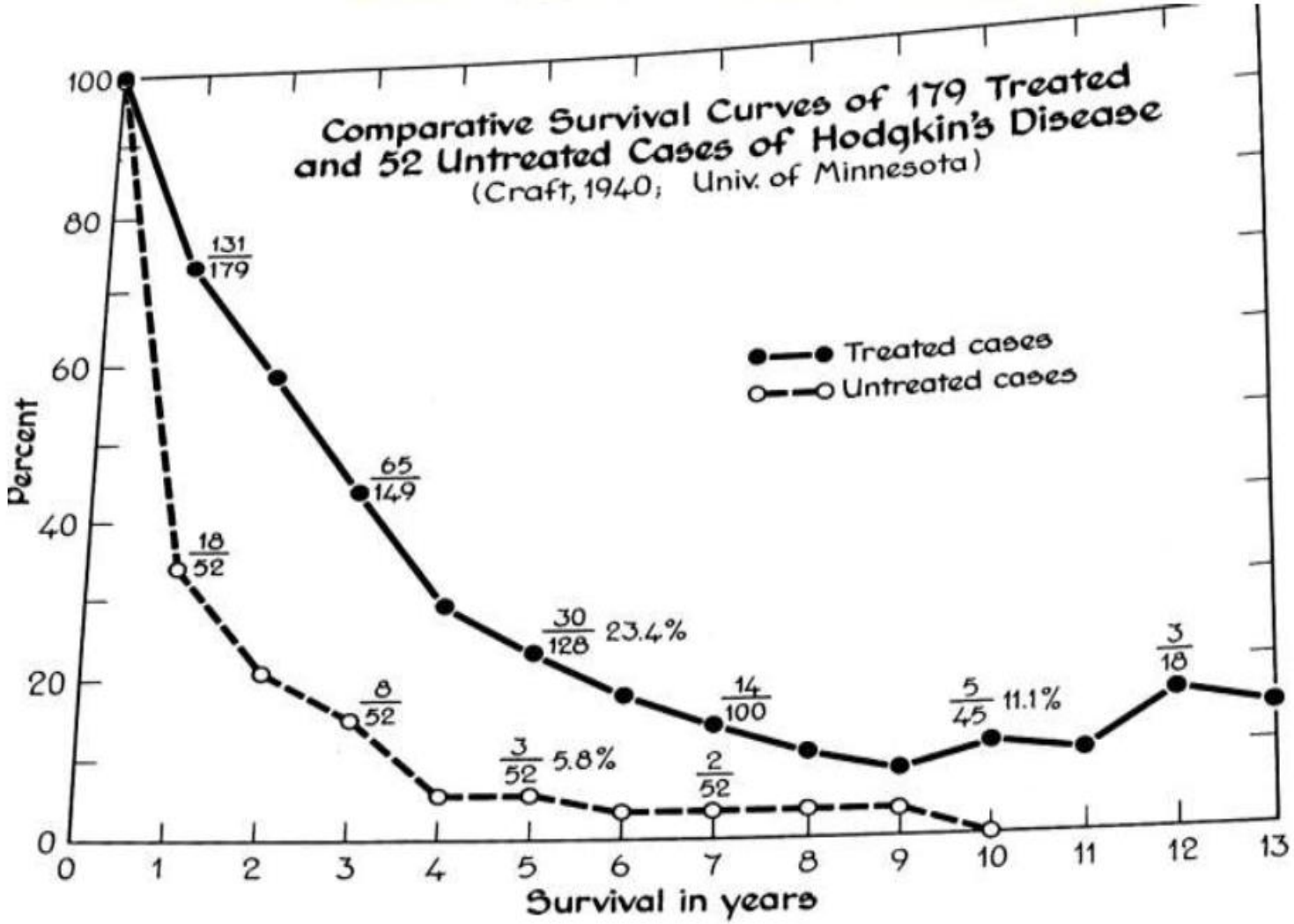
PROCRASTINATION

HARD WORK OFTEN PAYS OFF AFTER TIME,
BUT LAZINESS ALWAYS PAYS OFF NOW.

A Historical Timeline of the Use of Radiotherapy in the Treatment of Lymphoma



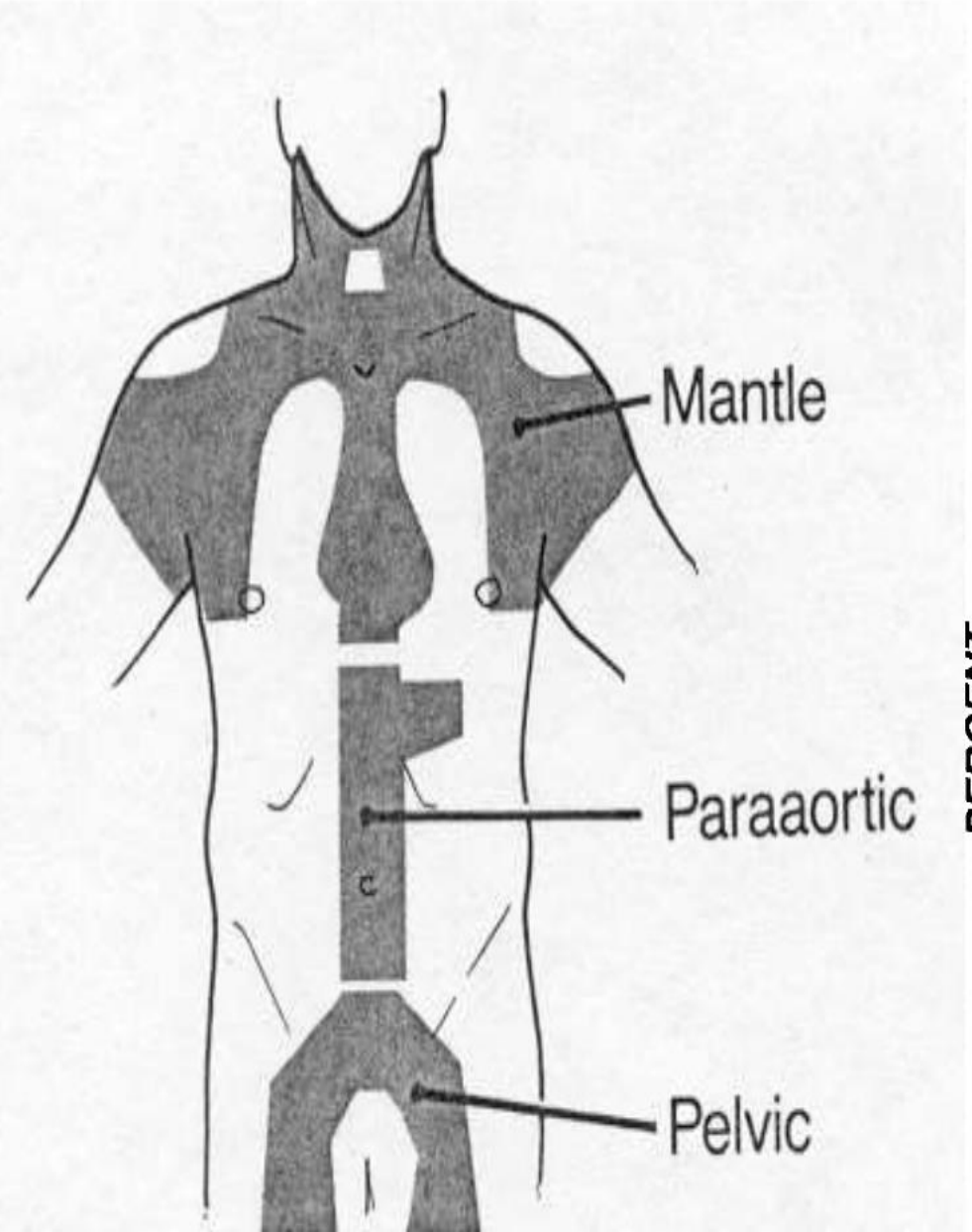
X-Ray for Hodgkin's Disease: A Great Discovery followed by Decades of Darkness

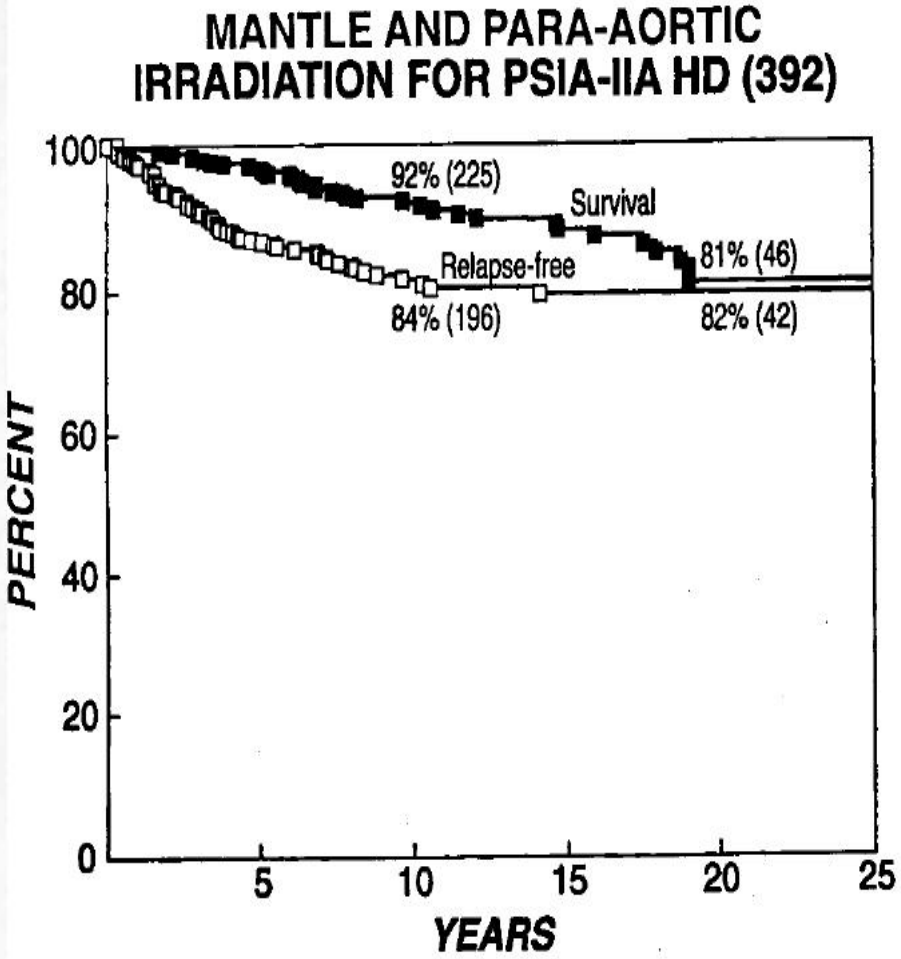


New Concepts and Better Beams

- 1925-1940: Rene **Gilbert** (Switzerland)– **"segmental radiotherapy"**- the first "extended field"- survival doubled
- 1950's: Gordon Richards and **Vera Peters** (Toronto)- ***Early stage*** *patients are* ***curable*** *with higher doses and larger fields*
- 1960's: **Henry Kaplan** (Stanford): **Radical Radiotherapy** of very large fields (Mantle, Inverted Y, Total Lymphoid Irradiation) and high doses (4400 cGy) using a megavoltage linear accelerator

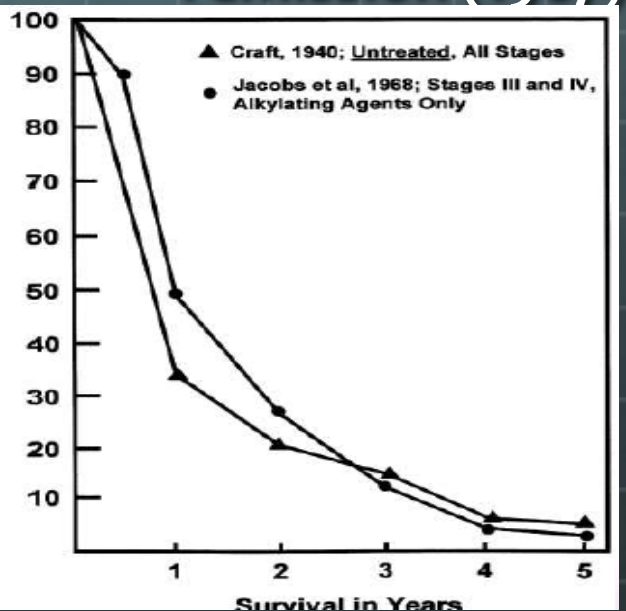
“Radical” Radiotherapy 1960-1990

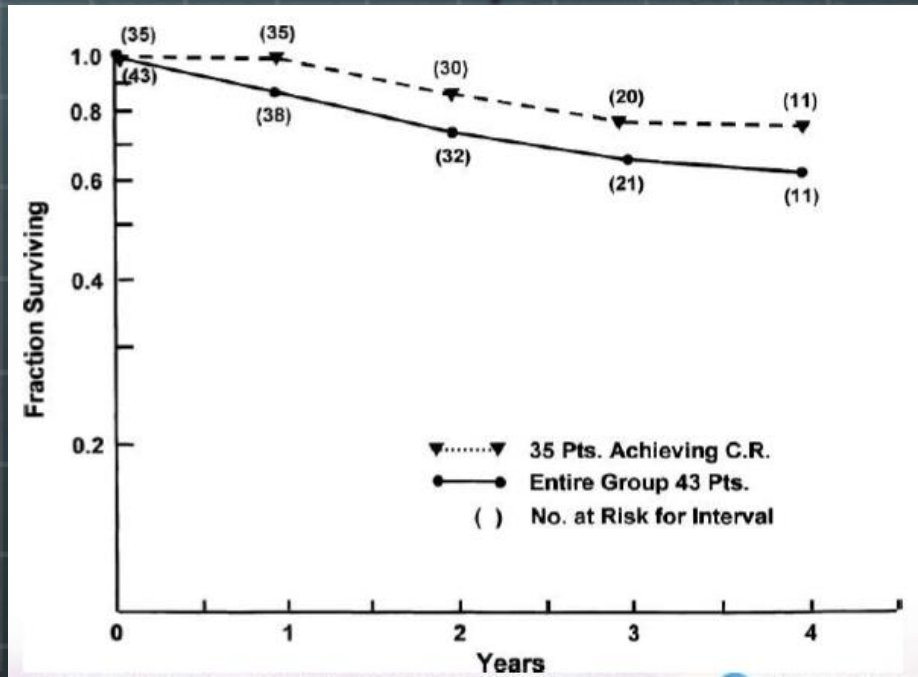




Emergence of Combination Chemotherapy

- Single Agents – Nitrogen Mustard, Chlorambucil, Vinca Alkaloids, Methotrexate – all active, but responses are very short.
- MOPP – First combination to show durable complete remission (1967)





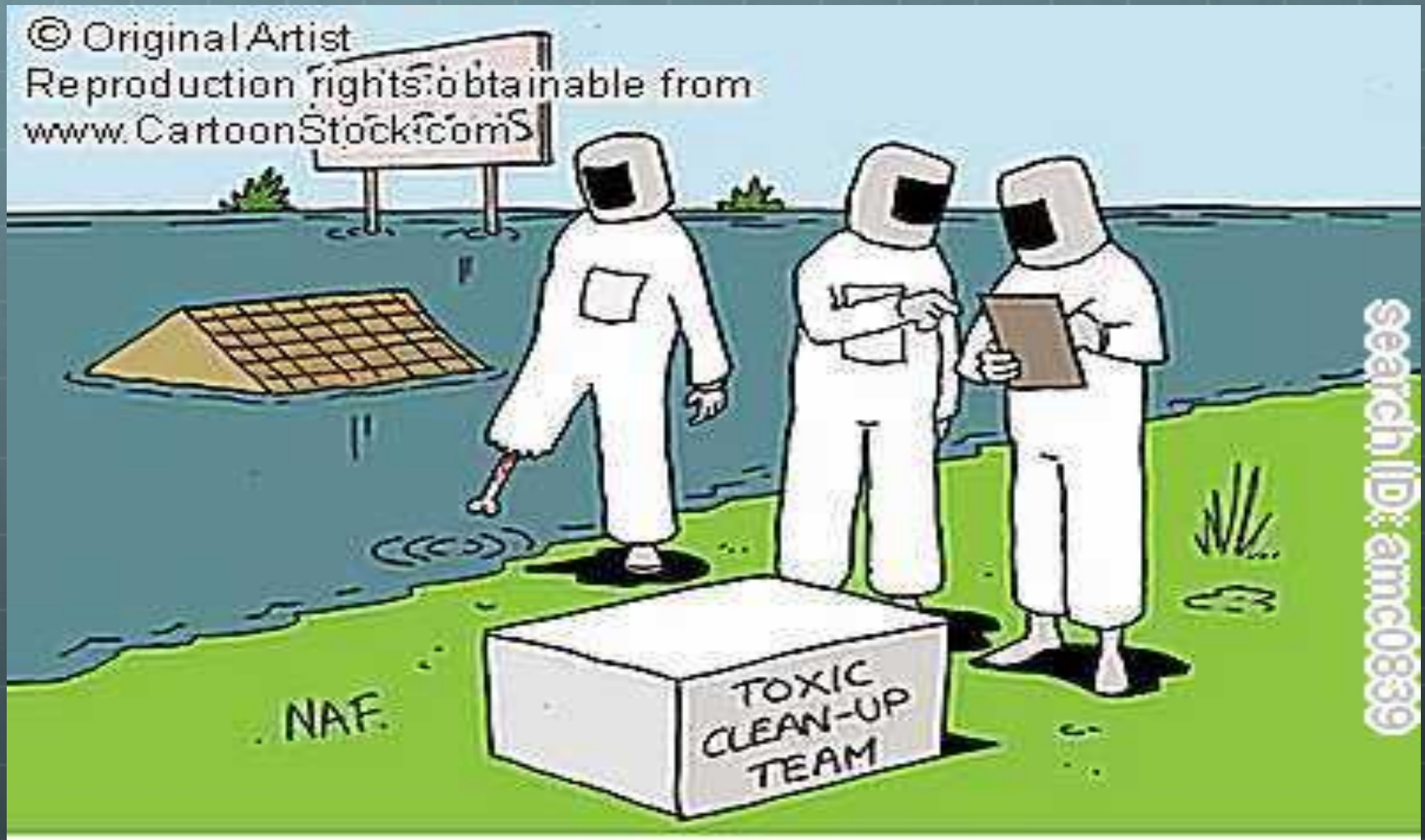
Milestones of Chemotherapy for Lymphomas

- ABVD (1975)
- ABVD/MOPP and hybrids (1980s)
- CHOP (late 1970's)
- High-Dose Salvage with ASCT (late 1980's)
- Rituximab (and radioactive anti CD-20) (1990's)
- Brentuximab vedotin
- Anti PD-1 and anti PD L-1 (immune check point inhibitors)
- CAR-T cell therapies

The Interaction between RT and Chemotherapy

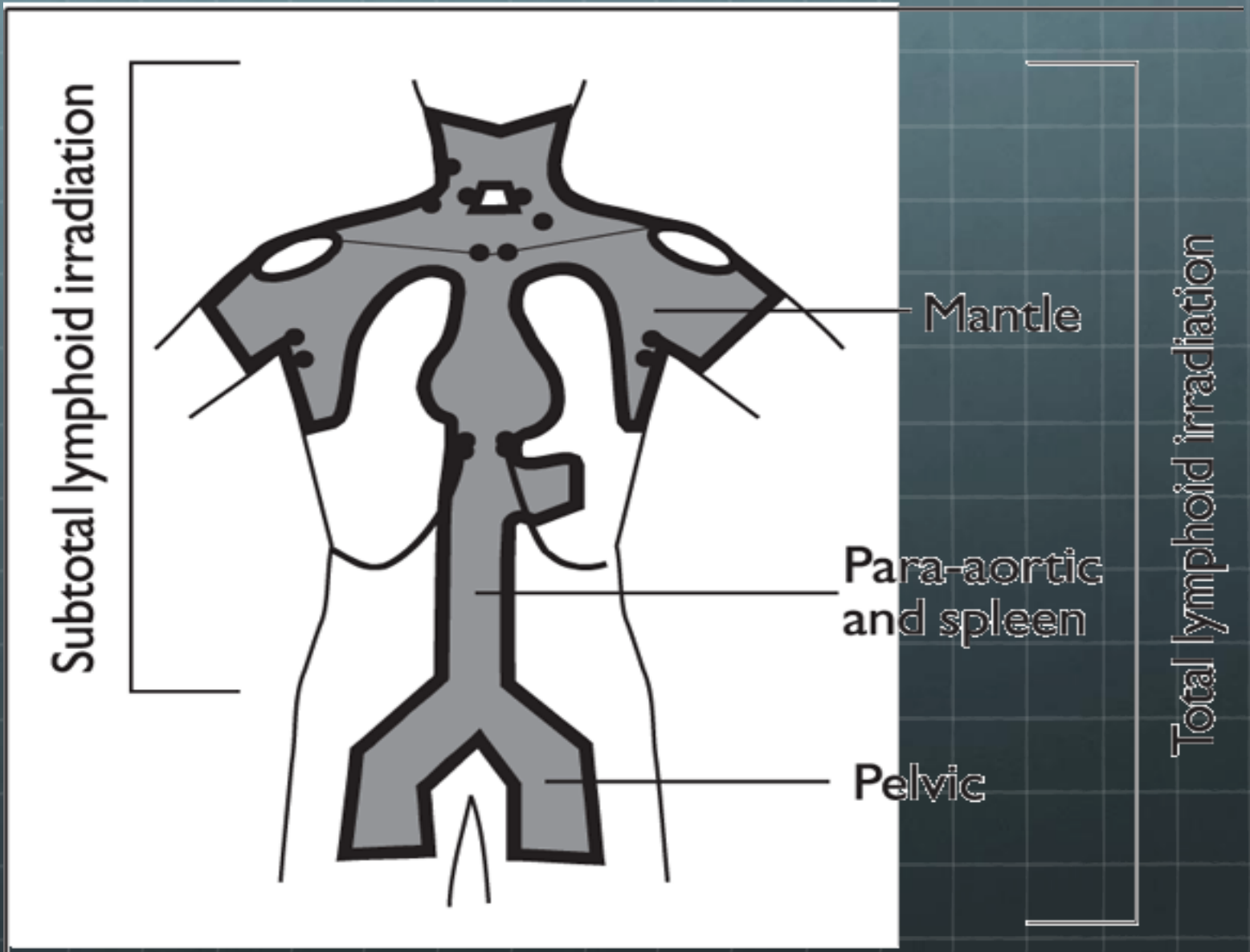
- RT is primary for early and intermediate stages – Chemo reserved for maintenance and salvage (60-70's)
- Early stage- RT alone ; RT consolidation for stages III-IV (80's)
- Maximizing treatment- All stages- maximal chemotherapy followed by RT (90's)
- Chemo alone – Avoiding RT in both HL and NHL- Questioning the need for using RT in any patient (2000's)
- Long term complications and lack of OS advantage drive anti-RT campaign
- Modern RT emerges –Reduction of field and dose (circa 2005)

External Beam Radiation Toxicity

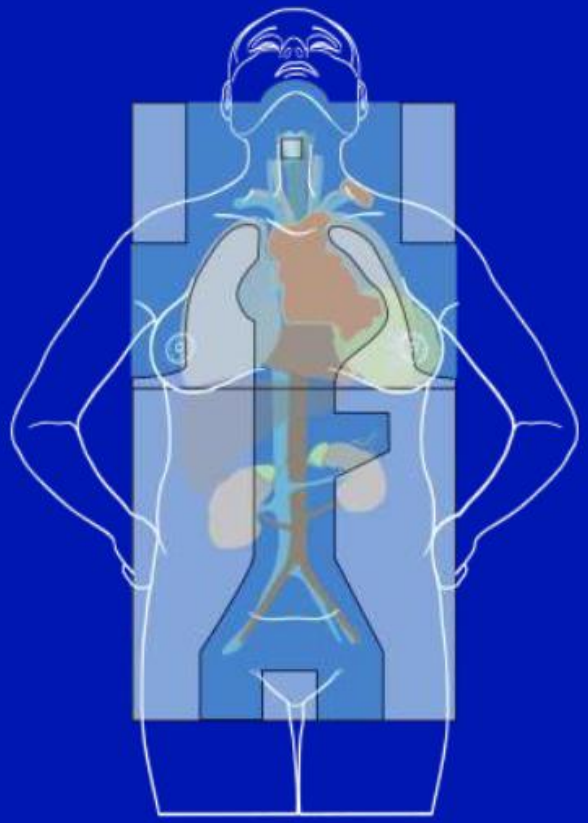


"Put a tick under 'very toxic'."

Total Nodal Irradiation

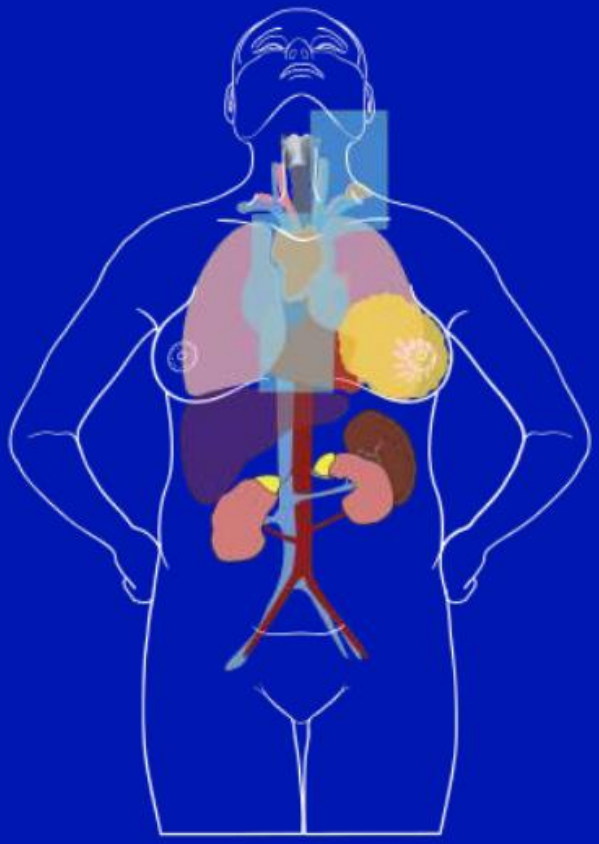


1970



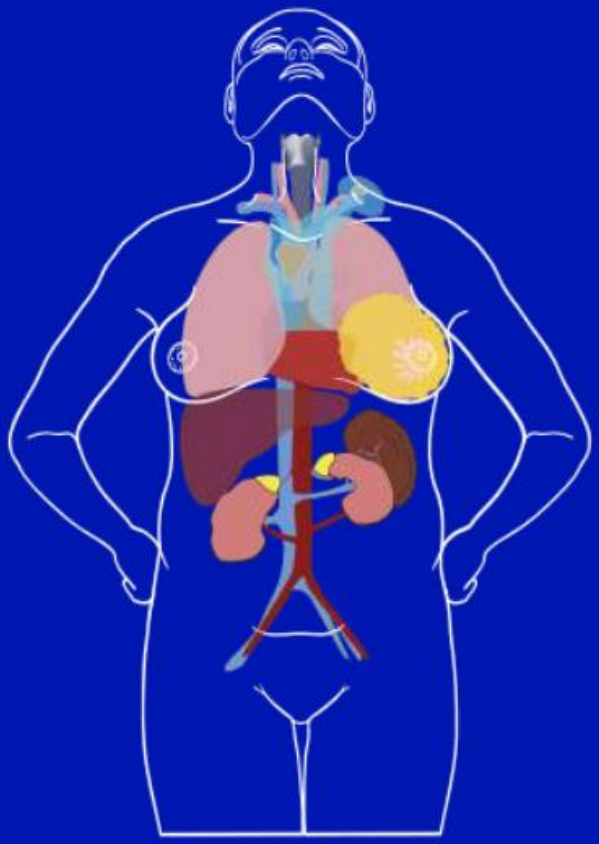
Total Lymphoid Irradiation (TLI)

1995



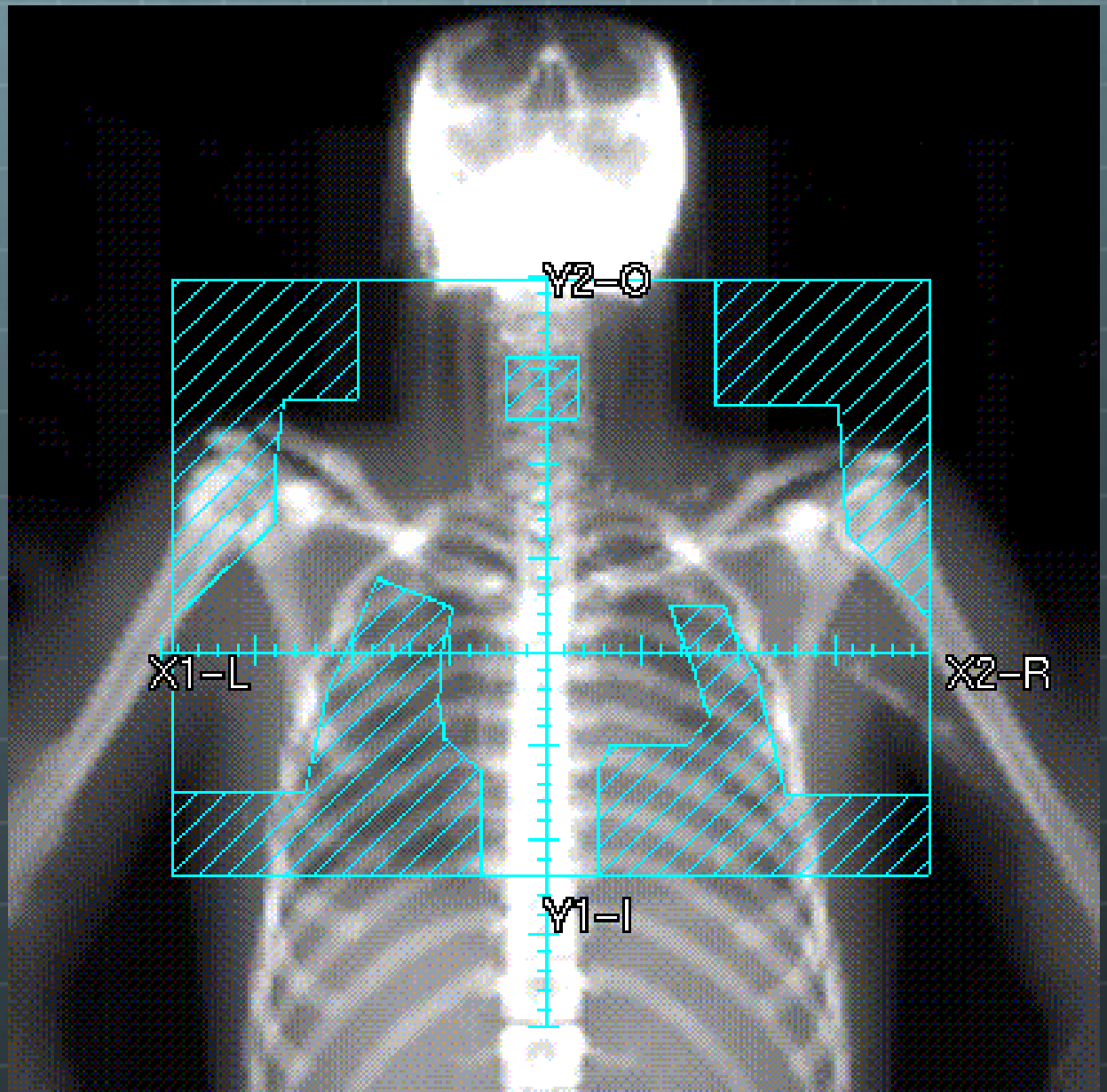
Involved-Field Radiotherapy (IFRT)

2008

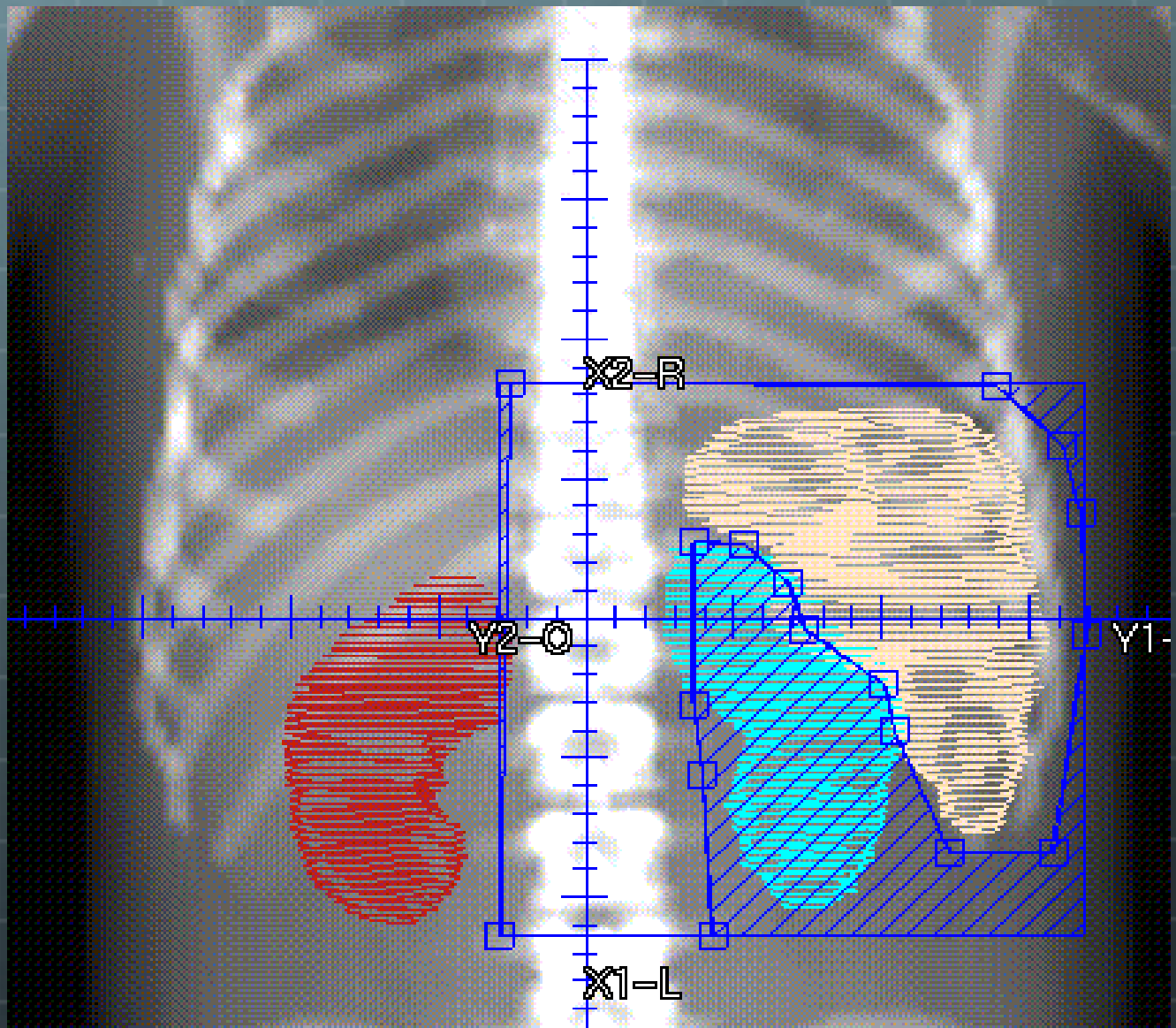


Involved Node Radiotherapy (INRT)

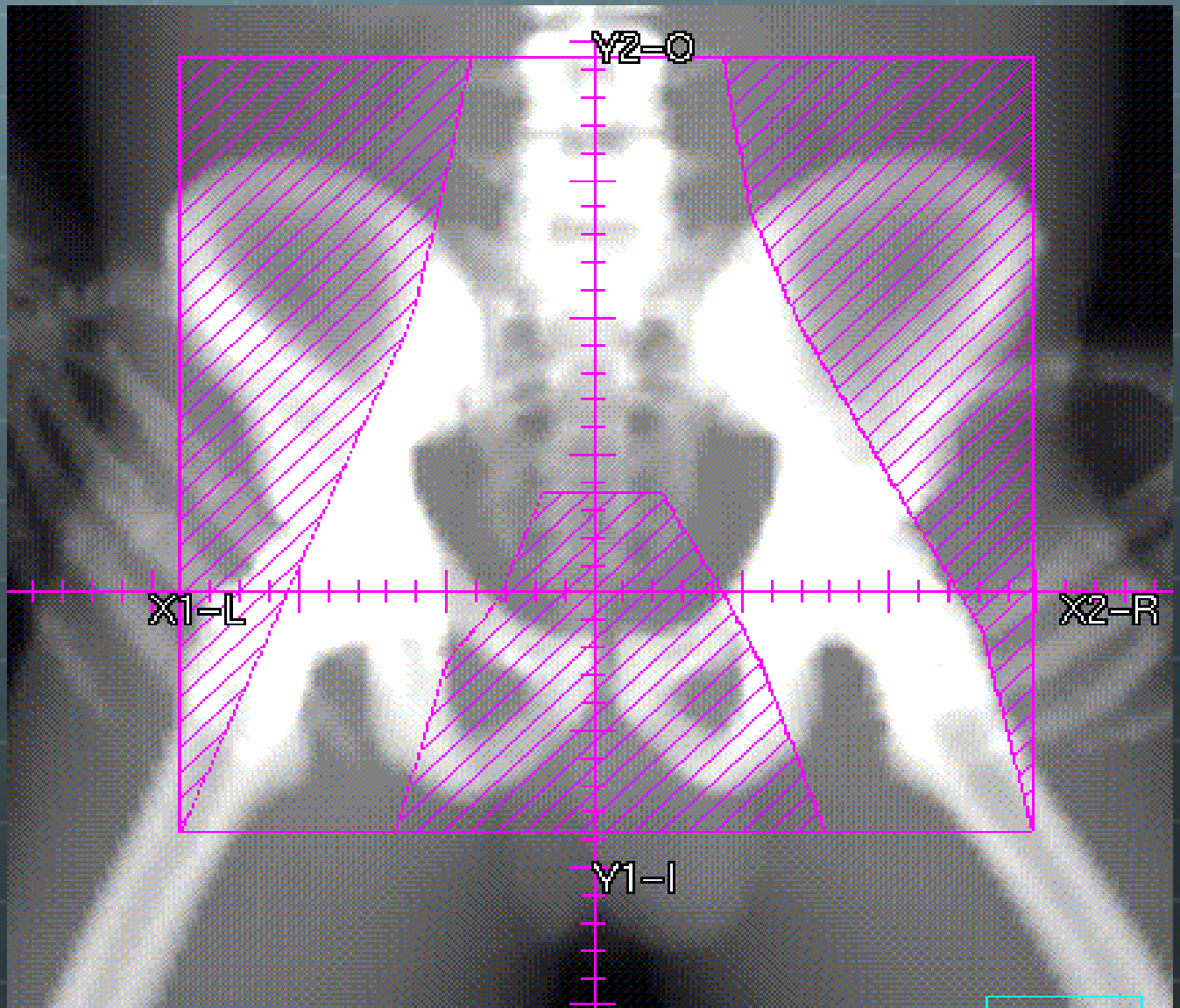
Mantle



Para-aortic/splenic



Pelvic Nodal



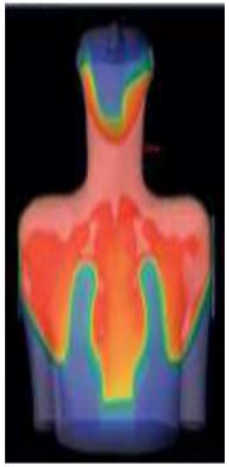
The Use of RT for Lymphomas has Continuously Diminished

- More effective chemotherapy regimens
- Efforts to develop and introduce new systemic agents
- Strong Pharma industry driving clinical trials
- Association of radiation with toxicity (as a result of radical RT techniques of the 60s and 70s)

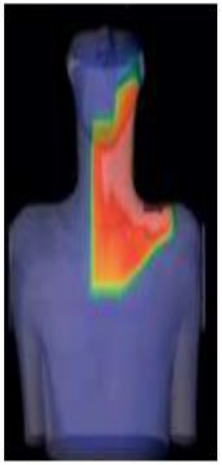
RT-related Late Complications: Overplaying a Risk -that has mostly disappeared- into a Scare that Persists

- Long-term HL data bases of Radical RT disclosed concerning second cancer risks and coronary artery disease
- This concern has been extended (with no data support) to NHL
- BC risk has become mostly irrelevant for modern RT volume and dose
- Studies that supported mortality were flawed and mis-represented (EORTC advanced-stage and HD-6)
- Many ignore lethal risks of (more) chemotherapy (cardiac and pulmonary) as well as neurological deficits (vincristine, Brentuximab)

RT: Reducing Volume and Reducing Dose



Mantle: 60's-80's

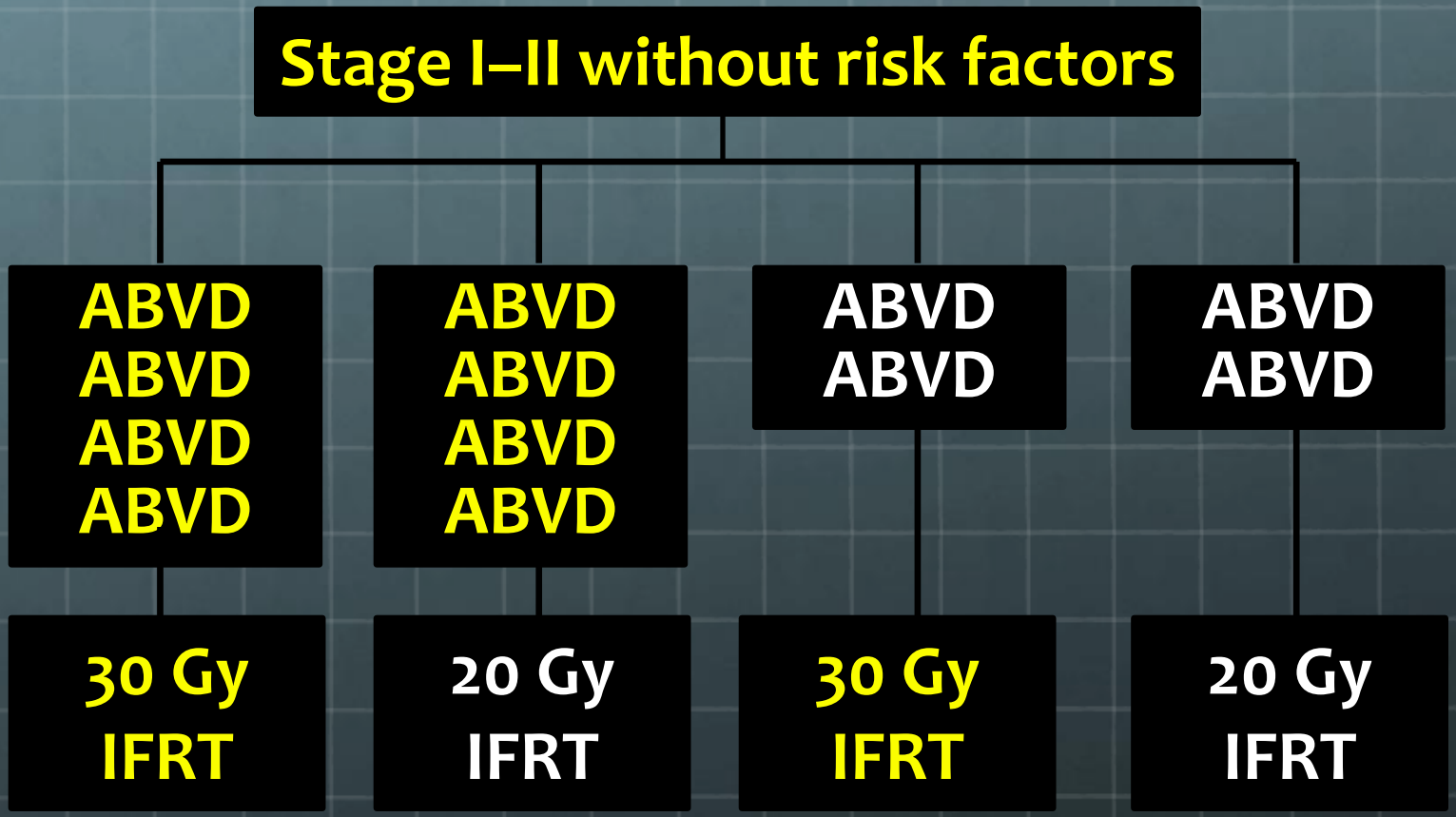


Involved field: 90's

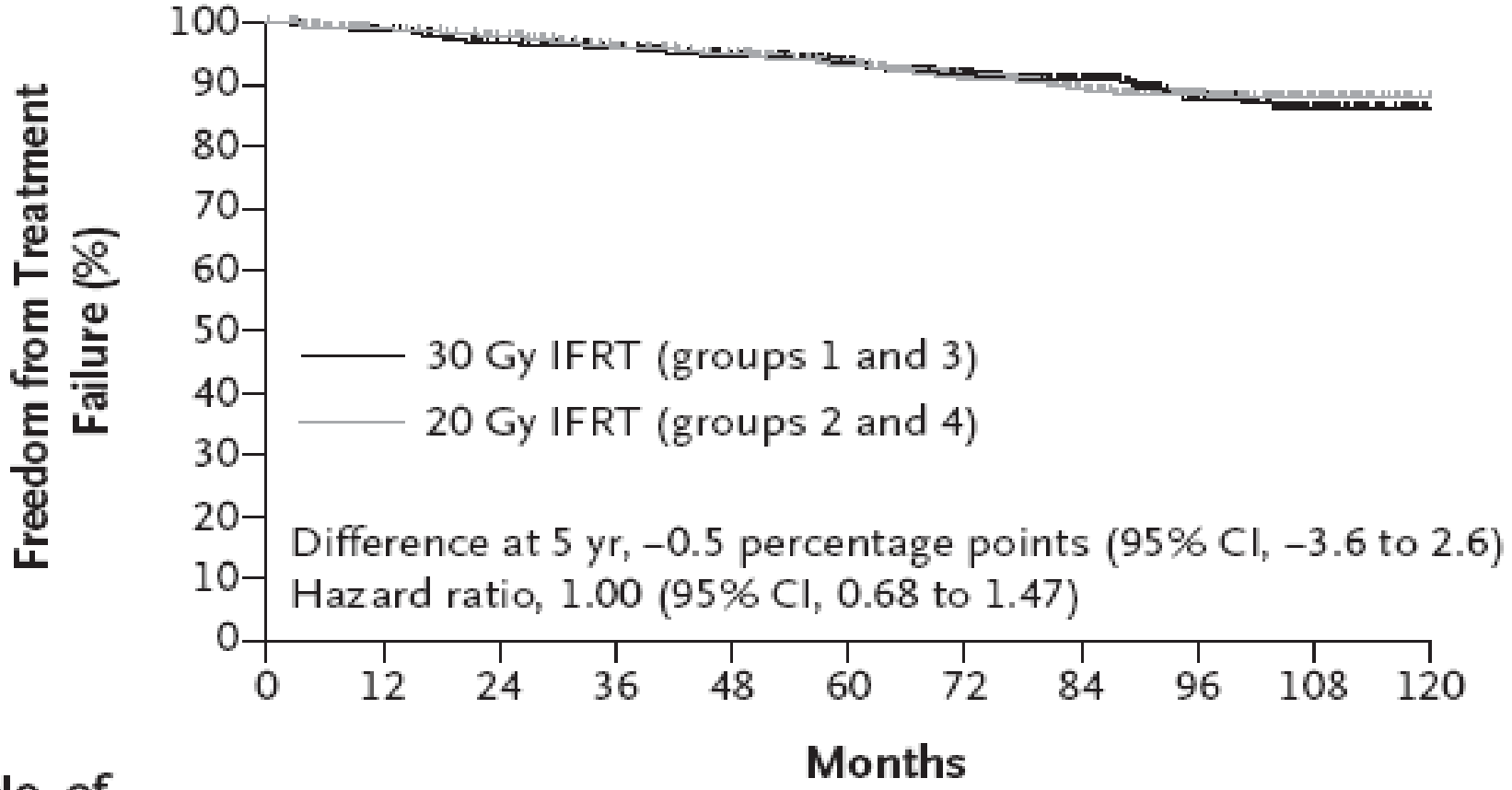
Involved site: current

Hodgkin	Aggressive	Indolent
44 Gy	45-55 Gy	45 Gy
20 Gy	30 Gy	24 Gy (4 Gy)

Dose Reduction in Hodgkin Lymphoma – GHSG HD10

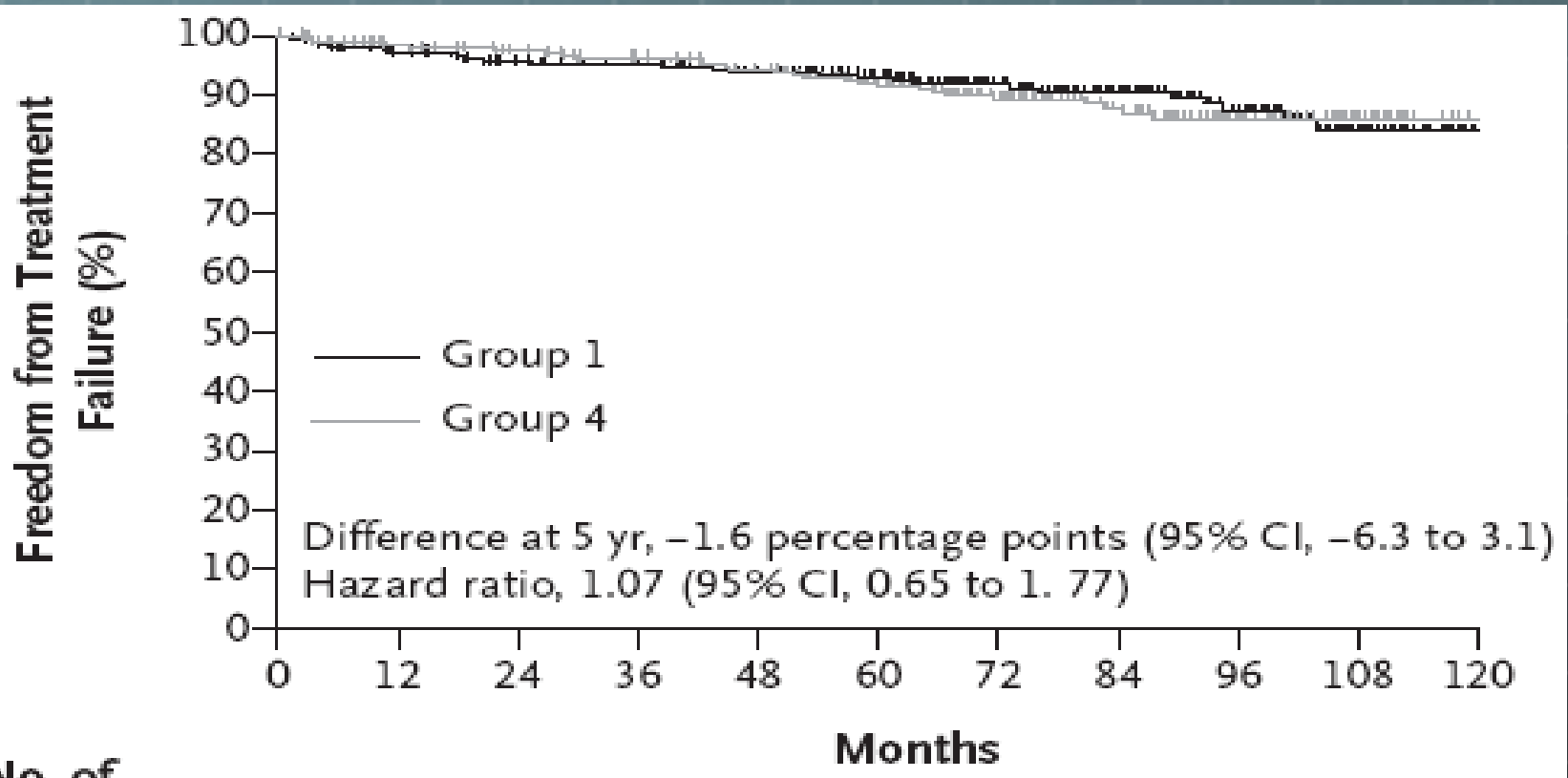


GHSG HD10 Results



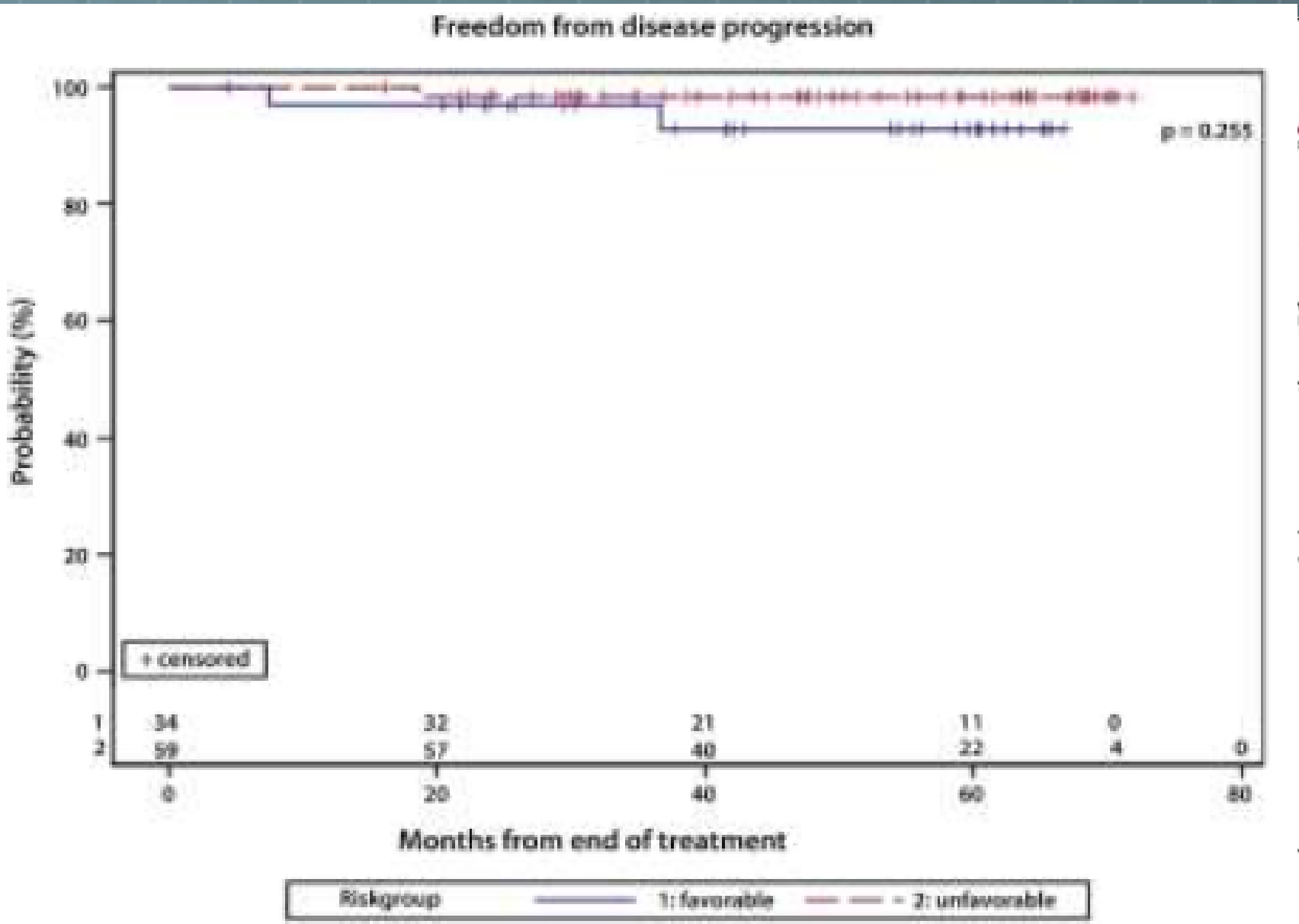
No. of Patients at Risk											
30 Gy IFRT	575	553	526	499	471	426	328	235	139	61	8
20 Gy IFRT	588	550	531	502	478	411	314	215	123	50	7

GHSG HD10 Results



No. of Patients at Risk											
Group 1	298	277	264	255	239	217	167	121	74	35	3
Group 4	299	275	265	252	239	199	151	110	66	28	4

Reducing RT volume



Toxicity of Radiotherapy

Toxicity of Radiotherapy

Acute Toxicity

- Dependent on:
  - Region Irradiated
  - Tissue Type
  - Total Dose
- Characterized by stem cell divisional inhibition
- Transient/short-term

Late Toxicity

- Dependent on:
  - Region Irradiated
  - Tissue type
  - Dose per fraction
  - Total Dose
- Characterized by parenchymal cell loss, fibrosis and vascular injury
- Progressive
- Irreversible

Acute Toxicity

- Radiation dermatitis (skin erythema)
  - Moisturizing creams, topical antibiotics for open skin
- Mucositis
  - Pain control, numbing mouth rinses (magic mouthrinse)
- Esophagitis
  - PPI (omeprazole), topical lidocaine, carafate, Pain control
- Gastritis/Enteritis (nausea, vomiting, diarrhea)
  - Antiemetics (Zofran, Compazine)
  - Imodium
- Hematologic toxicity
  - Close followup, precautions

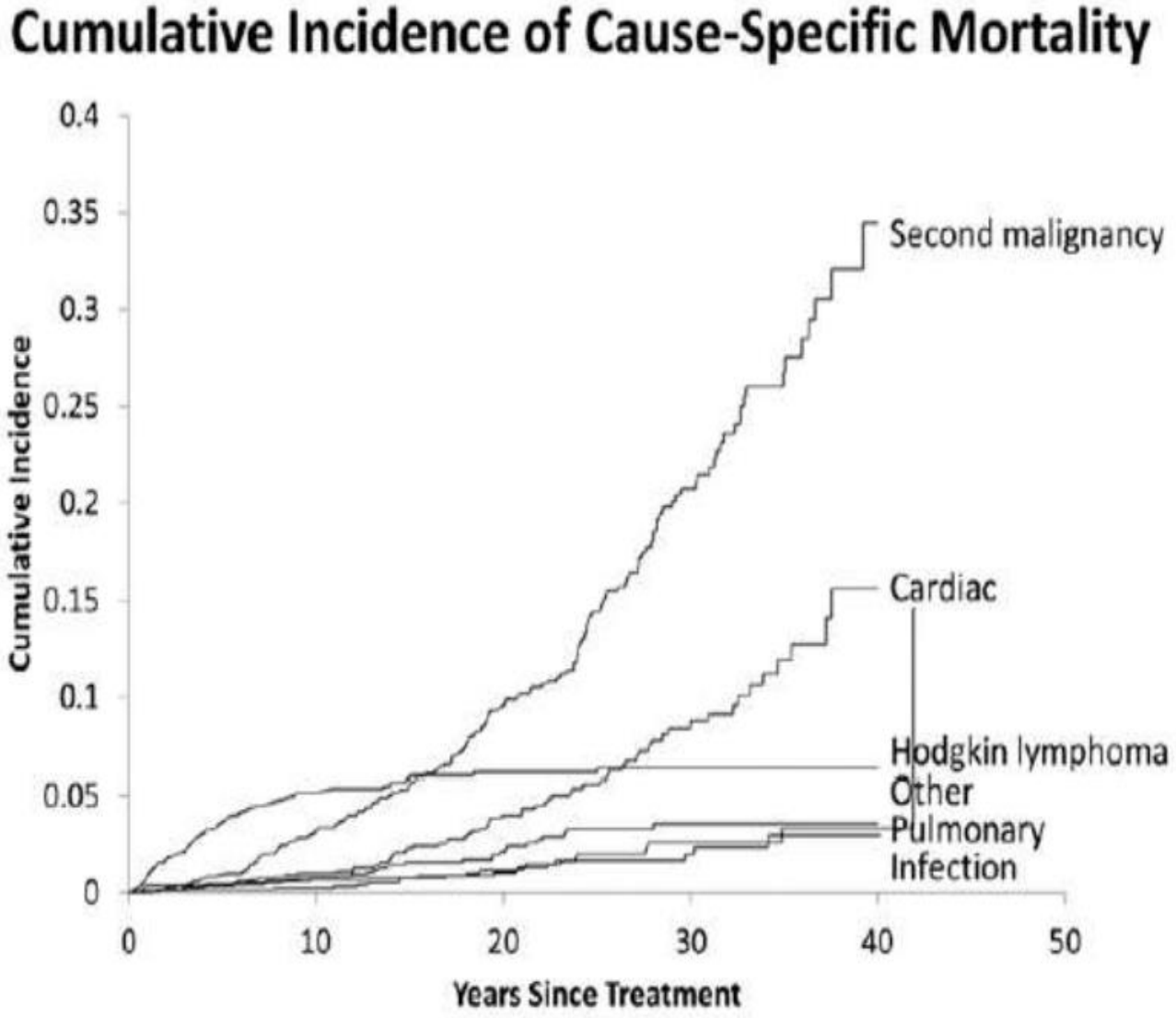
Radiation Dermatitis

Radiation Mucositis

Late Toxicity – The Driving Force Behind the Decline in use of Radiotherapy

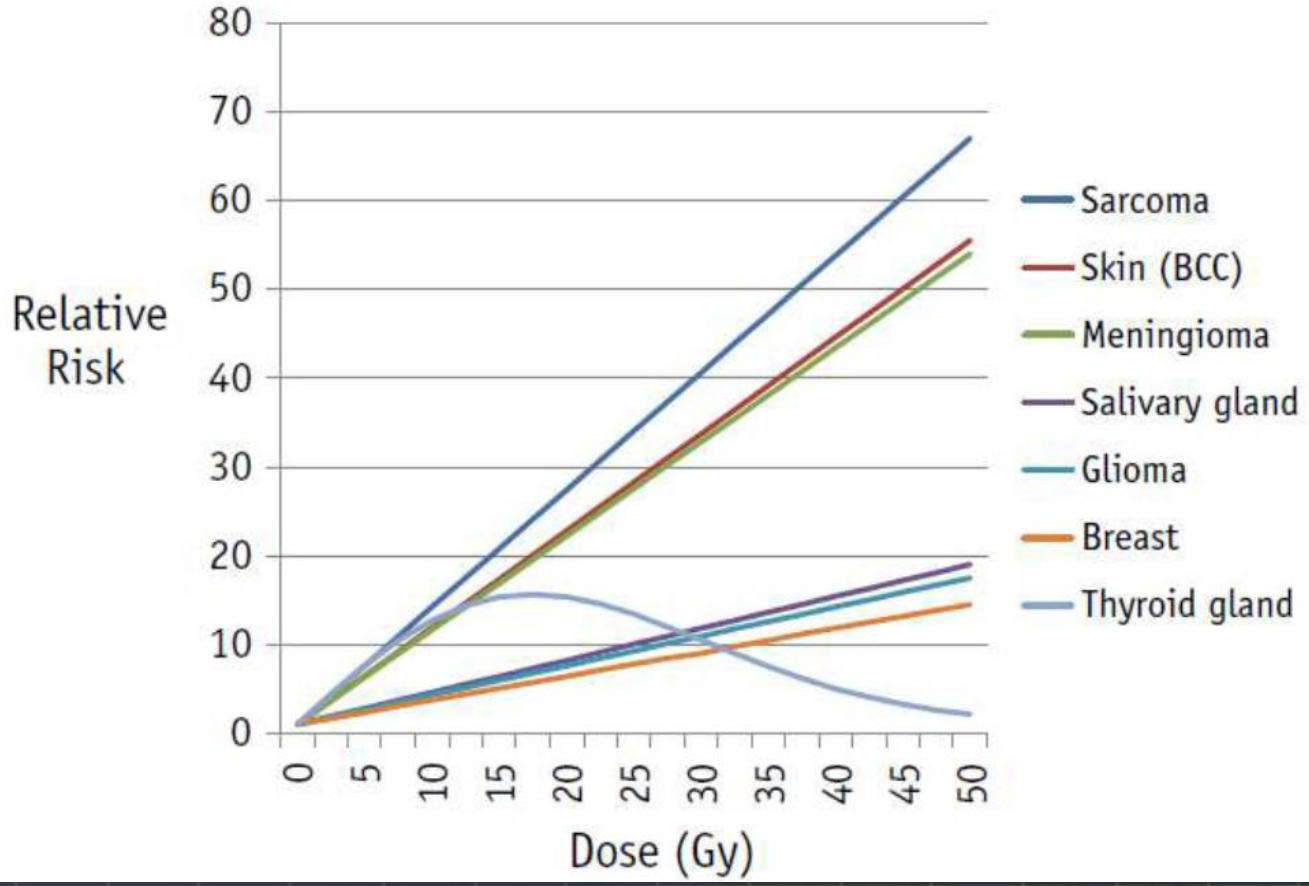
- Skin fibrosis
- Hypothyroidism
- Cardiotoxicity
- Pulmonary fibrosis/pneumonitis
- Stricture/obstruction (esophagus, bowel)
- Vascular damage (telangiectasia, vessel fibrosis, accelerated atherosclerosis)
- Fertility (recommend ovarian transposition, sperm banking if at risk)
- Necrosis
- Secondary malignancies (breast, thyroid, lung)

Top causes of death in HL survivors



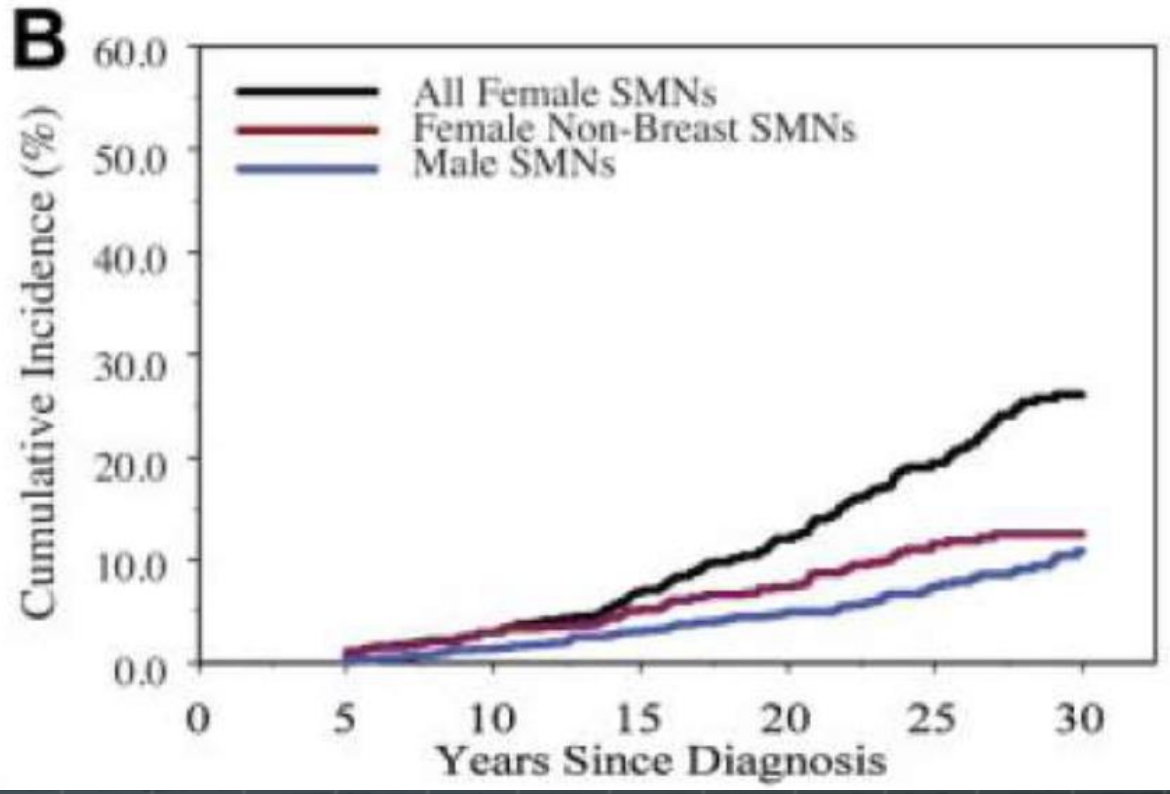
Secondary Malignancies

2nd Cancer and RT dose relationship

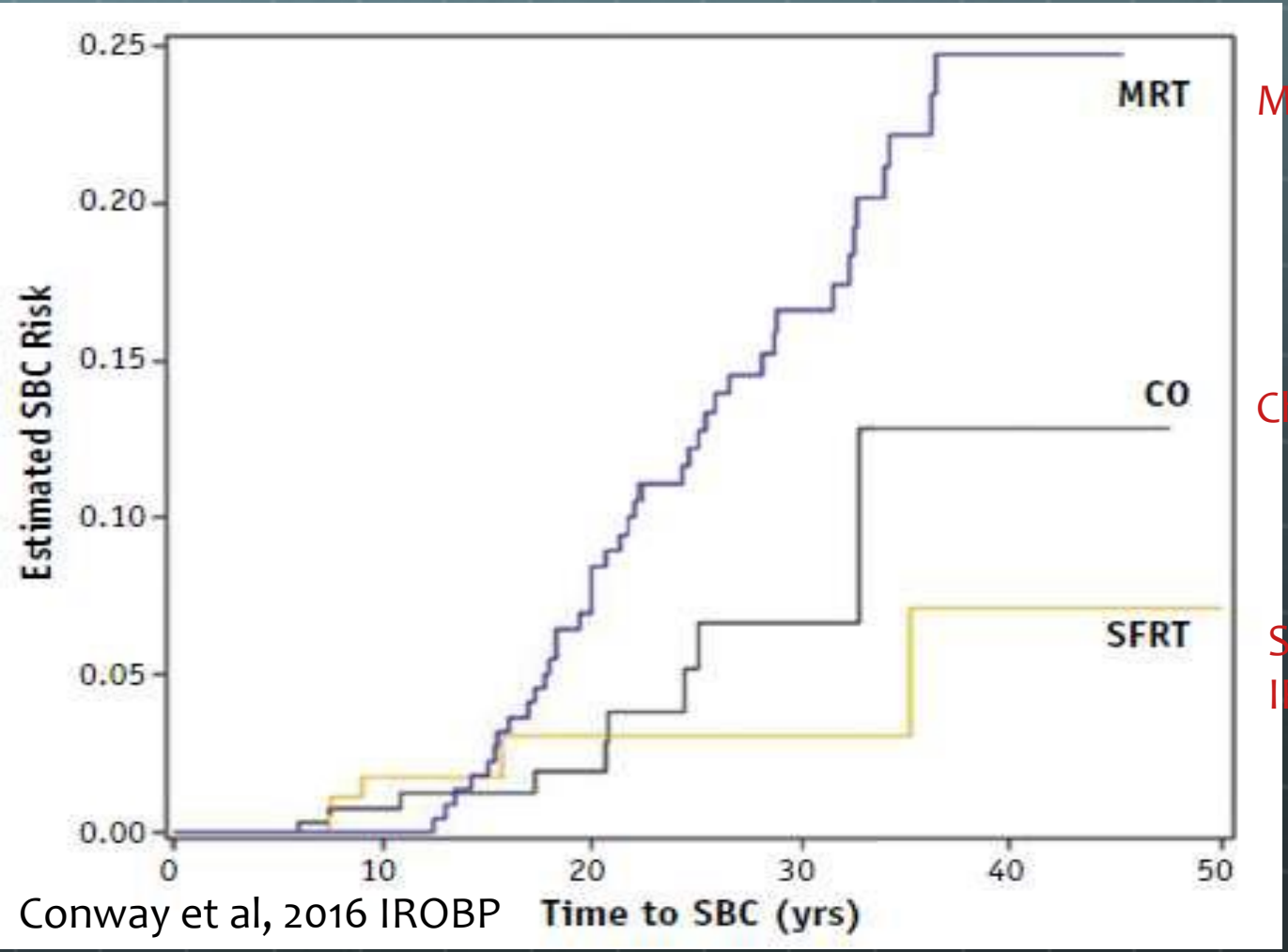


Inskip et al IJROBP 201

Second malignancies- Breast Cancer



Less 2nd Breast Cancer Risk with Smaller Fields



Mantle Field RT

Chemotherapy only

Small Field RT - IFRT, ISRT, INRT

Conway et al, 2016 IROBP

Second Breast Cancer- RT relationship

Dose to breast where 2nd cancer developed	<22 years old		22-30 years old	
	RR	P-value	RR	P-value
< 4 Gy	Reference		Reference	
4-23 Gy	2.2 (0.8-6.7)	0.13	2.9 (0.98-9.8)	0.05
23-37 Gy	3.3 (1-11.7)	0.046	3.3 (098-13.3)	0.05
37.2-61.3	5.2 (1.3-23.7)	0.02	4.5(1.2-20.1)	0.03

Suggests minimizing V4 of the breast in treatment planning

Travis et al JAMA 2003

2nd Lung Cancer

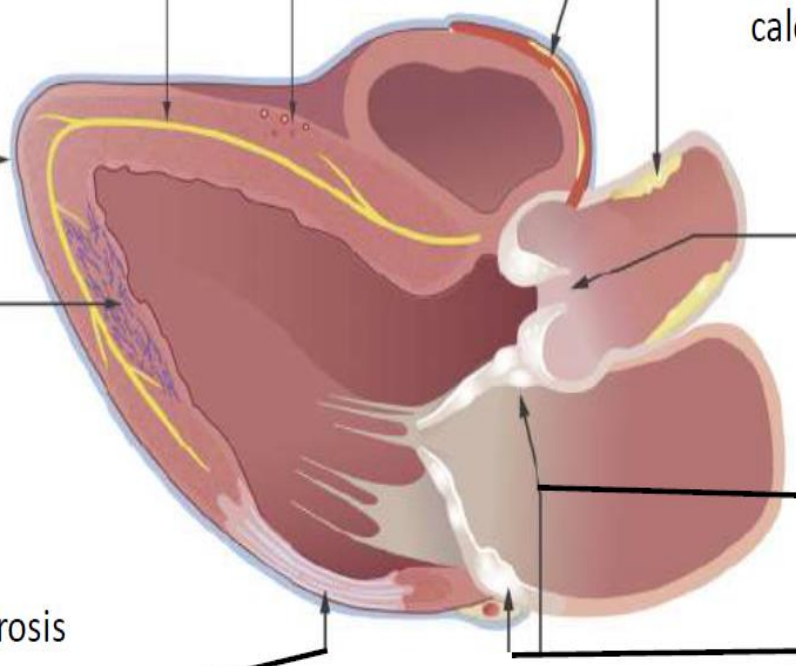
RT dose > 5 Gy	Non-Smoker, light, other	Moderate- heavy smoker
No	RR- 1.0	RR-6.0 (1.9-20.4) P=0.002
Yes	RR- 7.2 (2.9-21.2) P<0.001	RR-20.2 (6.8-68) P<0.001

Travis et al JNCI 2002

Radiation Related Cardiotoxicity

- 20+ years follow up need with large data sets
- Data complicated by anthracycline use (doxorubicin)
- More common with larger historical fields (mantle field)

RT related Cardiac disease



Vasculopathy
Microvascular disease

Coronary artery disease

Conduction System disease

Macrovascular disease including calcification of the ascending thoracic aorta

Pericardial disease

Valvular heart disease-
Valve leaflet thickening, calcification, and restriction

Calcification and thickening of aortomitral curtain

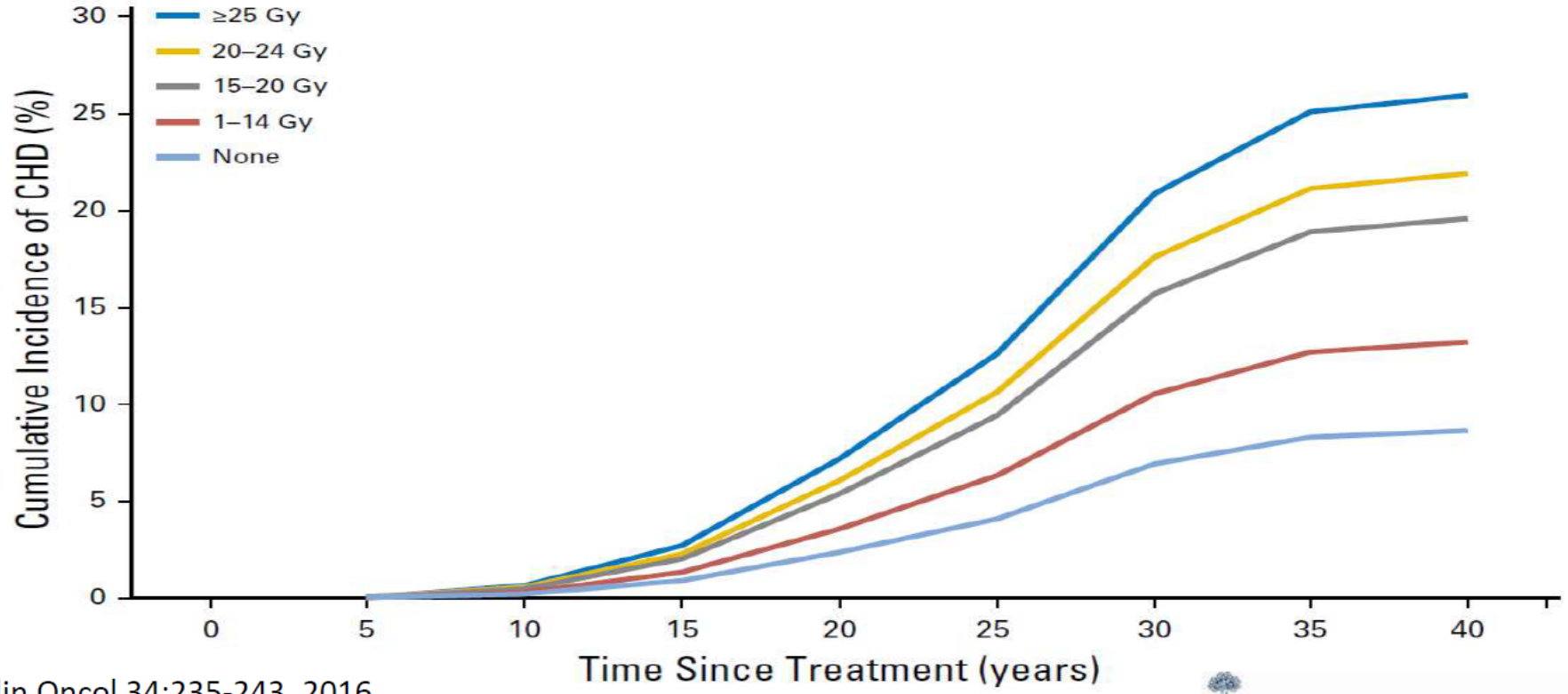
Myocardial Disease
Non-ischemic myocardial fibrosis

Mitral annular calcification

Ischemic myocardial scar

Desai JACCI 2018

Increasing Heart Dose = Increasing Late Cardiac Morbidity

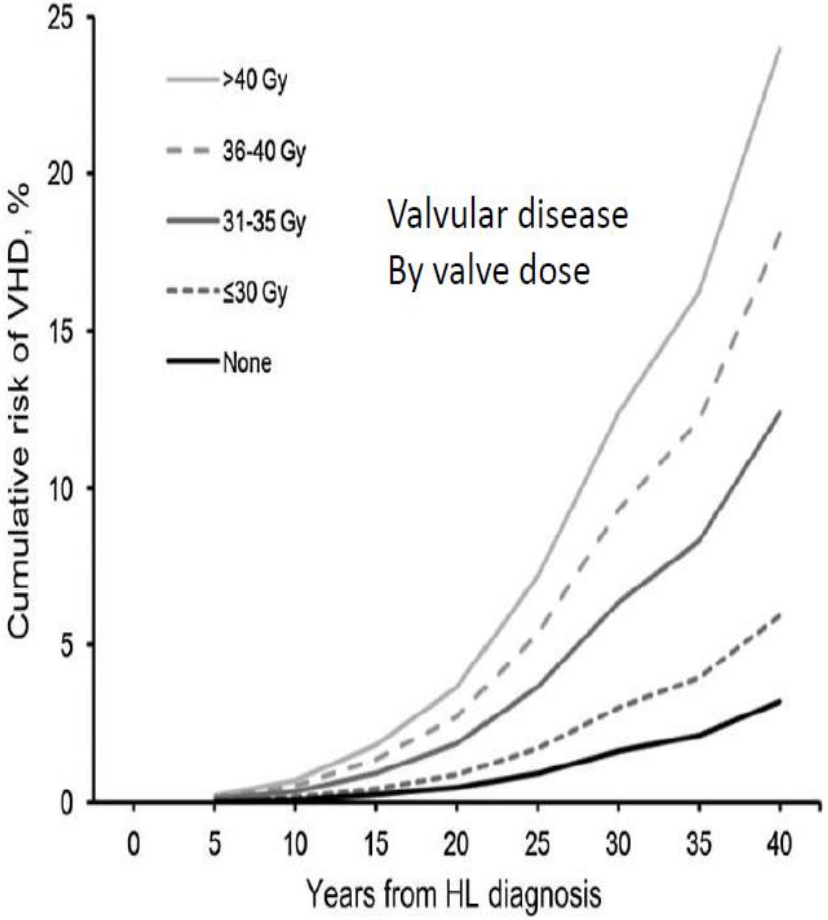


Clin Oncol 34:235-243, 2016

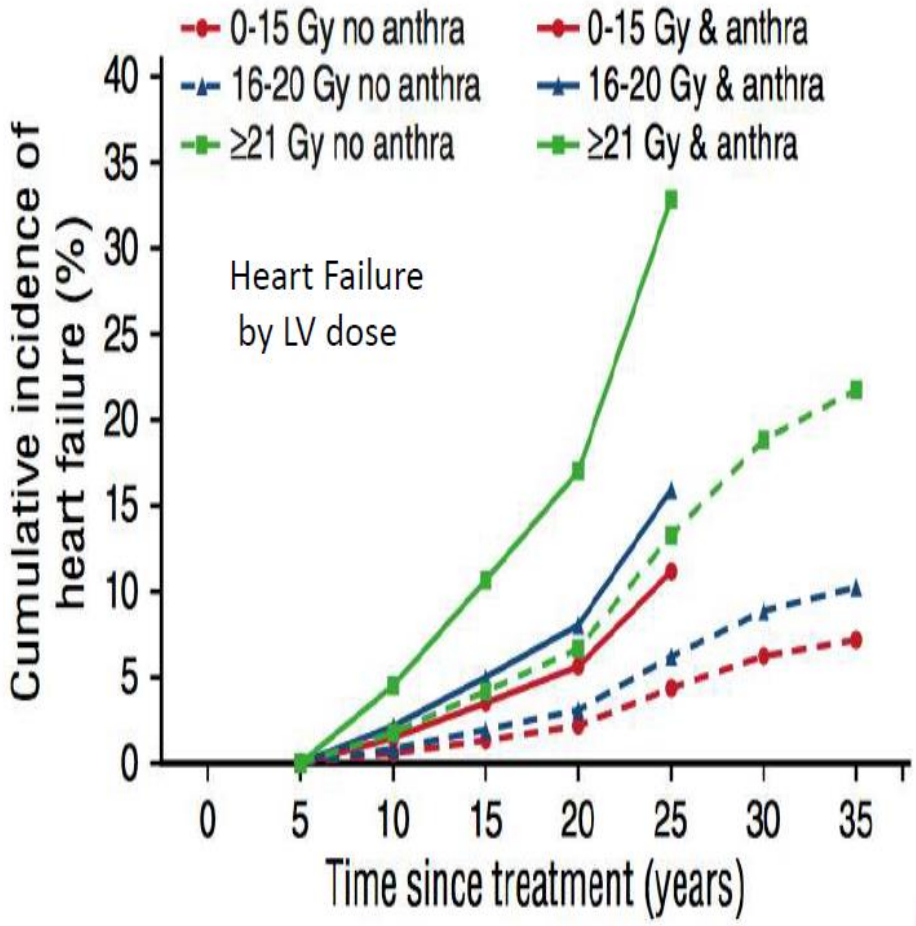
Radiation Oncology
UNIVERSITY OF TORONTO

Cardiac Outcomes and Substructre RT Dose

- Cutter et al JNCI 2015



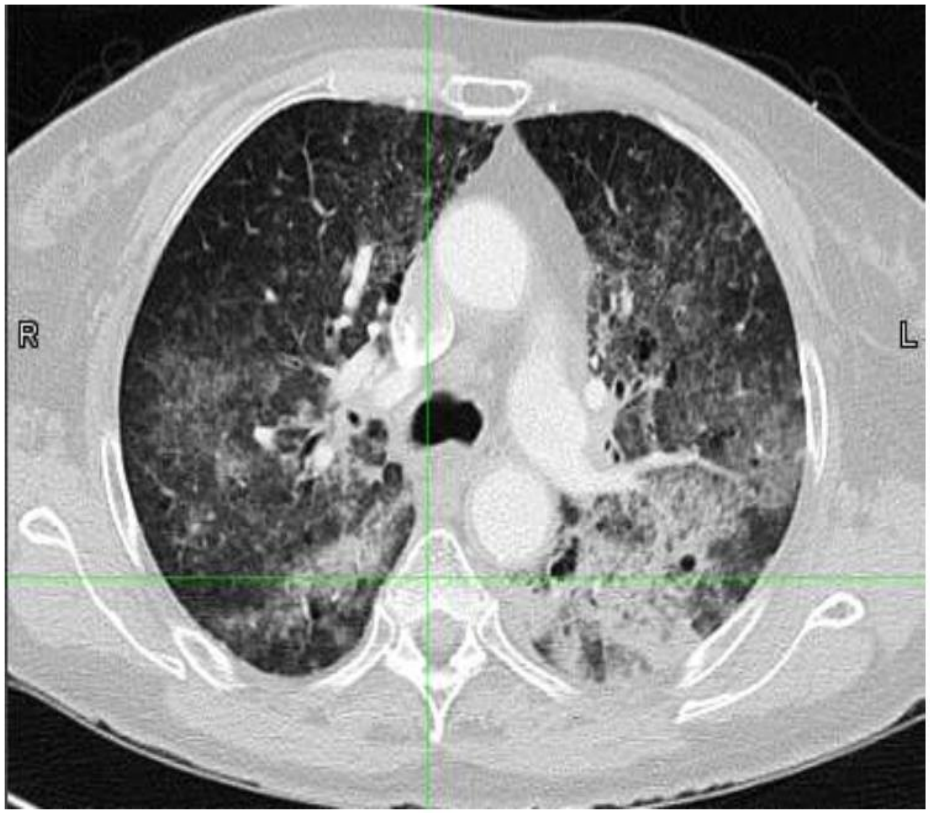
- Van Nimwegen et al Blood 2017

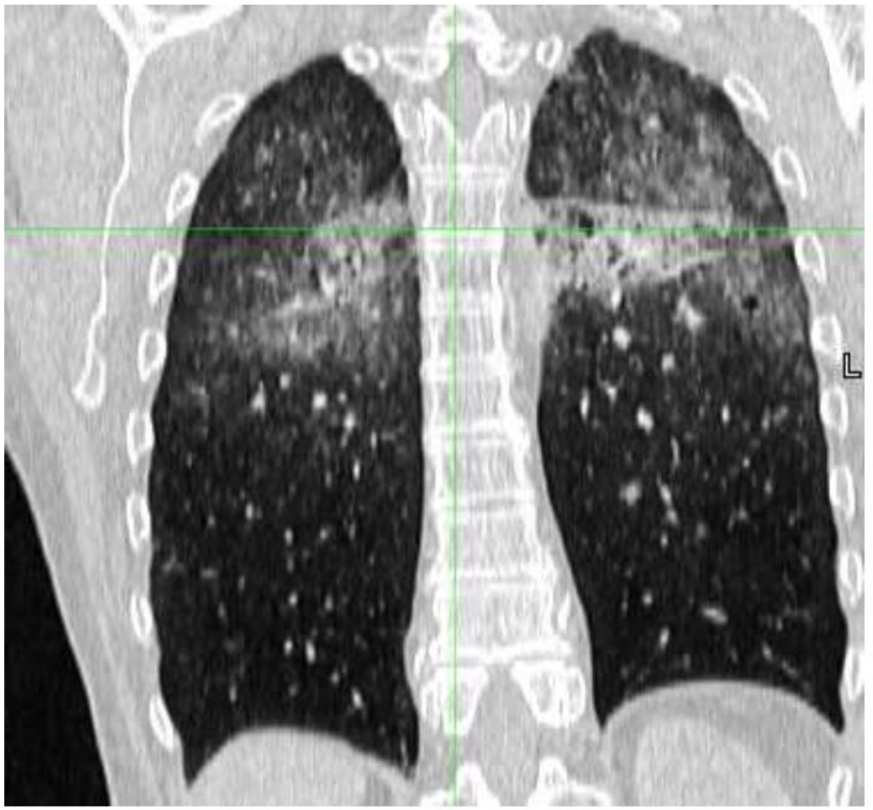


Radiation Pneumonitis

- Inflammatory condition of the lungs related to radiation exposure. Directly correlates with radiation dose and volume of the lung exposed to radiation.
- Occurs 1-6 months after treatment
- Symptoms: Dry cough, shortness of breath
- Very low rates with modern day consolidative treatment (<5%).
- Higher rates when used as salvage after multiple lines of systemic therapy and stem cell transplant (up to 15%)
- Treatment with steroids
- 1-3% of cases will be fatal

Radiation Pneumonitis

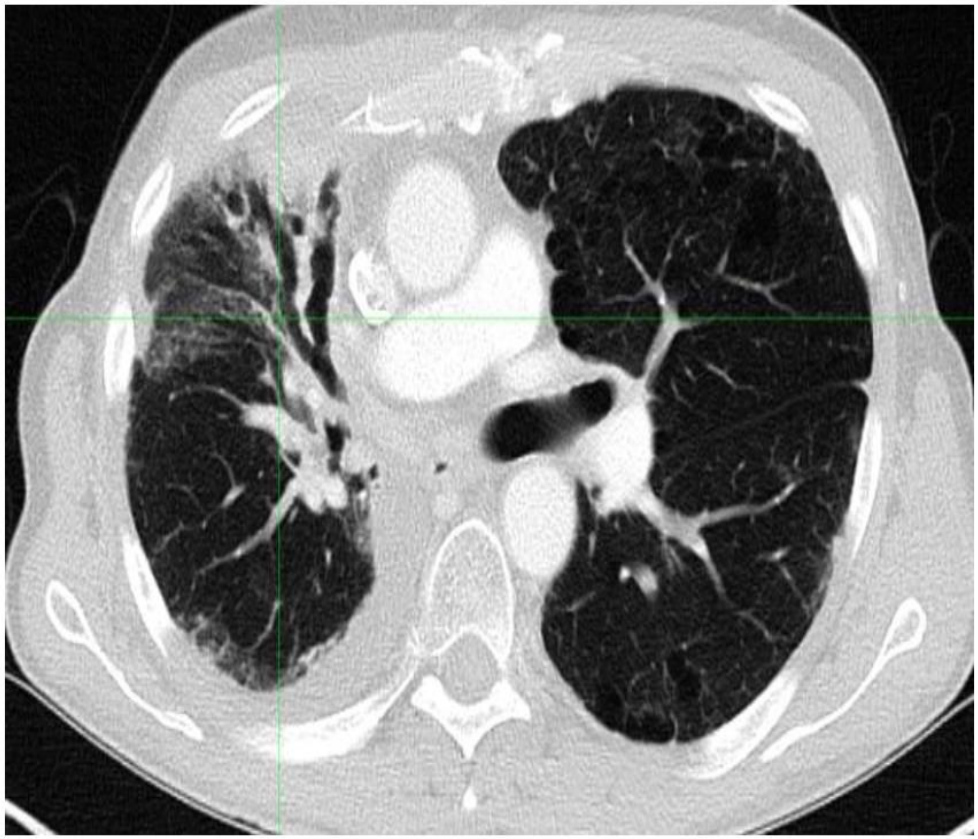


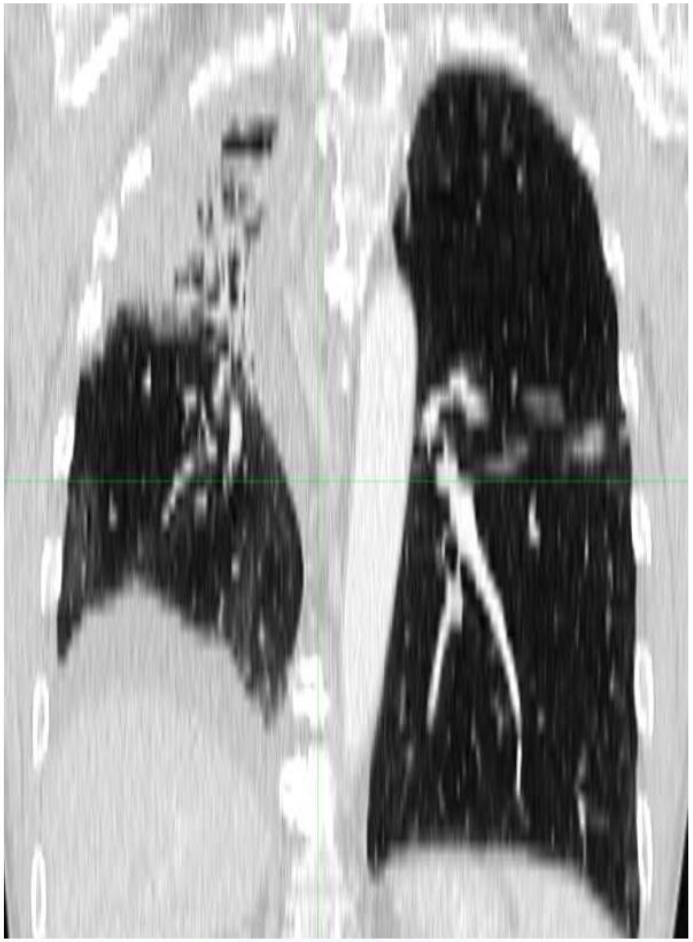


Pulmonary Fibrosis

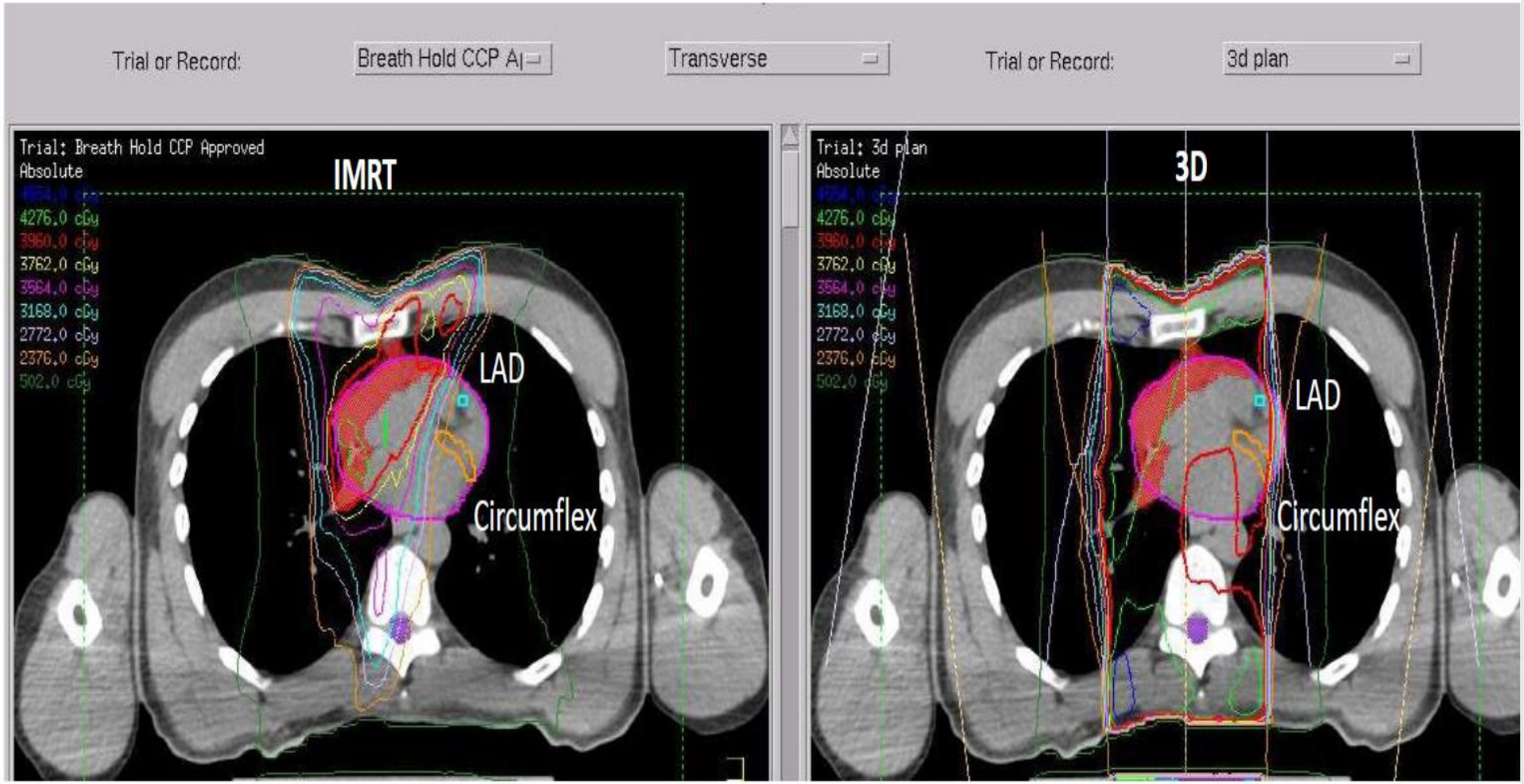
- Mostly subclinical in modern era, more common in historical era
- Current literature suggests <5% risk
- Chronic
- Increased shortness of breath and long-term oxygen requirement
- Smoking dramatically increases the risk

Radiation Pulmonary Fibrosis



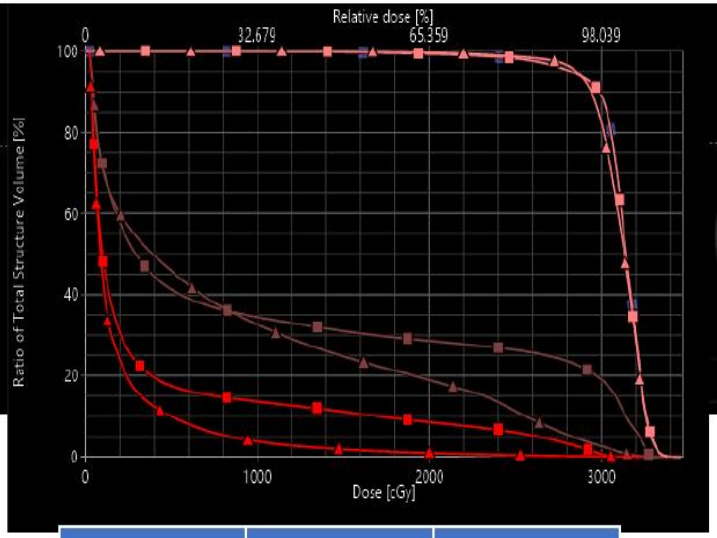


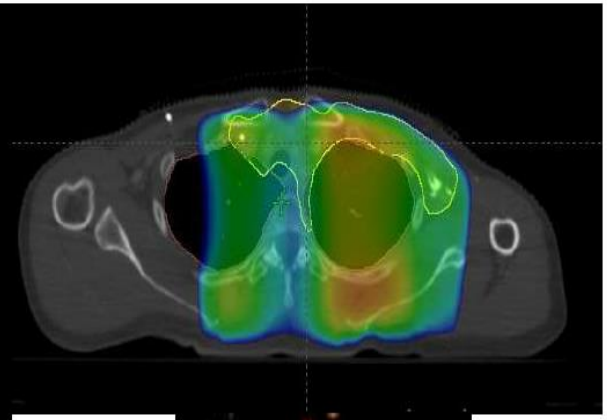
Reducing Toxicity - IMRT

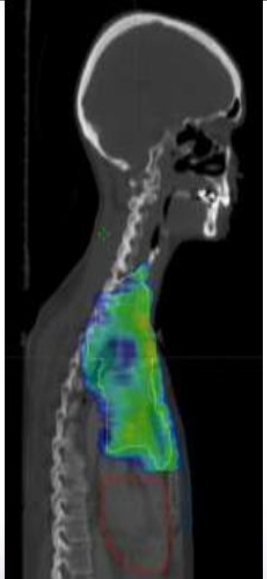


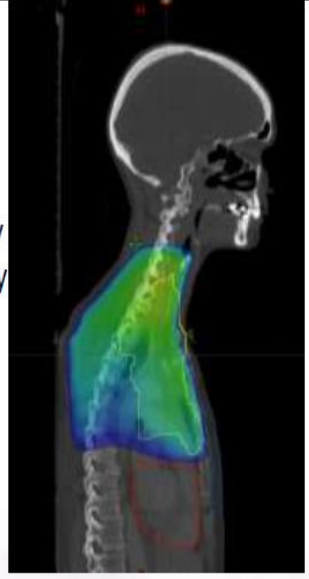
Reducing Toxicity – IMRT/VMAT

DIBH: VMAT vs. 3D









	VMAT	3D
Lung V20	19%	28.6%
Lung V10	33%	34%
Lung V5	50%	*42%*
MLD	8.67 Gy	10.8 Gy
MHD	4.5 Gy	7.2 Gy

L Breast MD: 6.1 Gy
R Breast MD: 2.1 Gy

Reducing Toxicity

ACTIVE BREATHING CONTROL (ABC) FOR HODGKIN'S DISEASE: REDUCTION IN NORMAL TISSUE IRRADIATION WITH DEEP INSPIRATION AND IMPLICATIONS FOR TREATMENT

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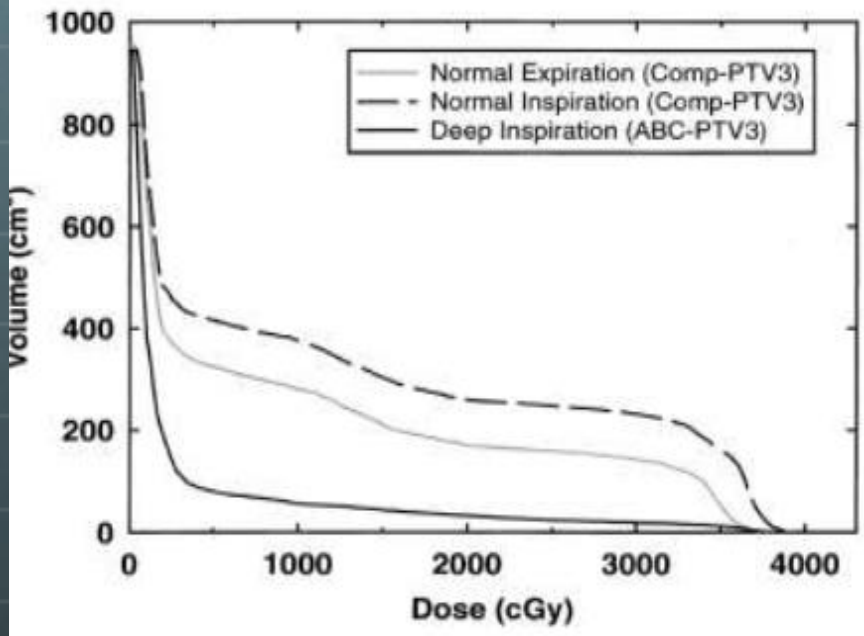
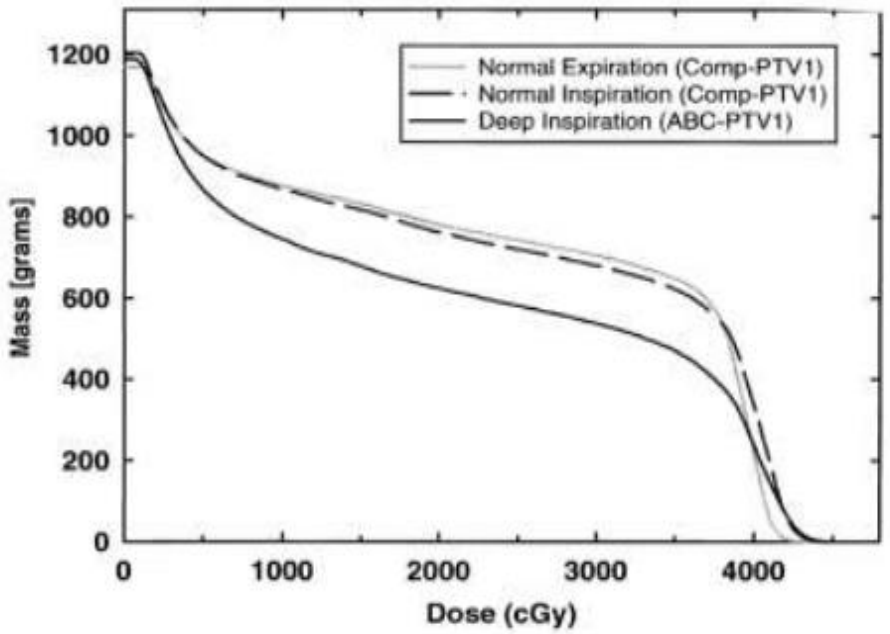


Heart Dose



Lung Dose

Magnitude of The Dose Reduction: Lung

	Princess Margaret (N = 47)[1]	Rigshospitalet (N = 22)[2]	Institut Gustave Roussy (N =28)[3]	University of Muenster (N =11) [4]
Mean Lung Dose	11Gy→9.5Gy (18%)*	8.5 Gy → 7.2 Gy (15.3%)	11.8Gy →9.4Gy* (20.3%)	9.88Gy→ 5.87Gy* (40.58%)
V20	28% → 22%*		21% →15%	19.05→ 14.12
% pts improving	95.7%	86.4% used DIBH plan	NS	NS

* DIBH had greater effect on lung dose reduction than transition to ISRT or use of IMRT

1. Practical Radiation Oncology (2014) 4, 174–180.
2.Acta Oncol. 2015 Jan;54(1):60-6.
3. IJORBP 82 (4): 1522–1527, 2012.
4. Strahlenther Onkol (2015) 191:717–725

Magnitude of the Dose Reduction: Heart

	Princess Margaret (N = 47, mediastinal)[1]	Rigshospitalet (N = 22, supraDx)[2]	Institut Gustave Roussy (N =28,)[3]	University of Muenster (N =11) [4]
Mean Heart Dose	14.3Gy → 11.8Gy (10.3%)*	6.0 Gy→3.9 Gy (35%)	8.4 Gy→ 7.1Gy (15.5%)	5.74 →3.95* (31.2%)
Heart V20	38% → 29%	15% → 4.1%	NS	NS
% pts improving	78.7%	86.4% used DIBH plan	NS	NS

* Transition from IFRT to ISRT had greater effect: approx 7Gy reduction in mean heart dose

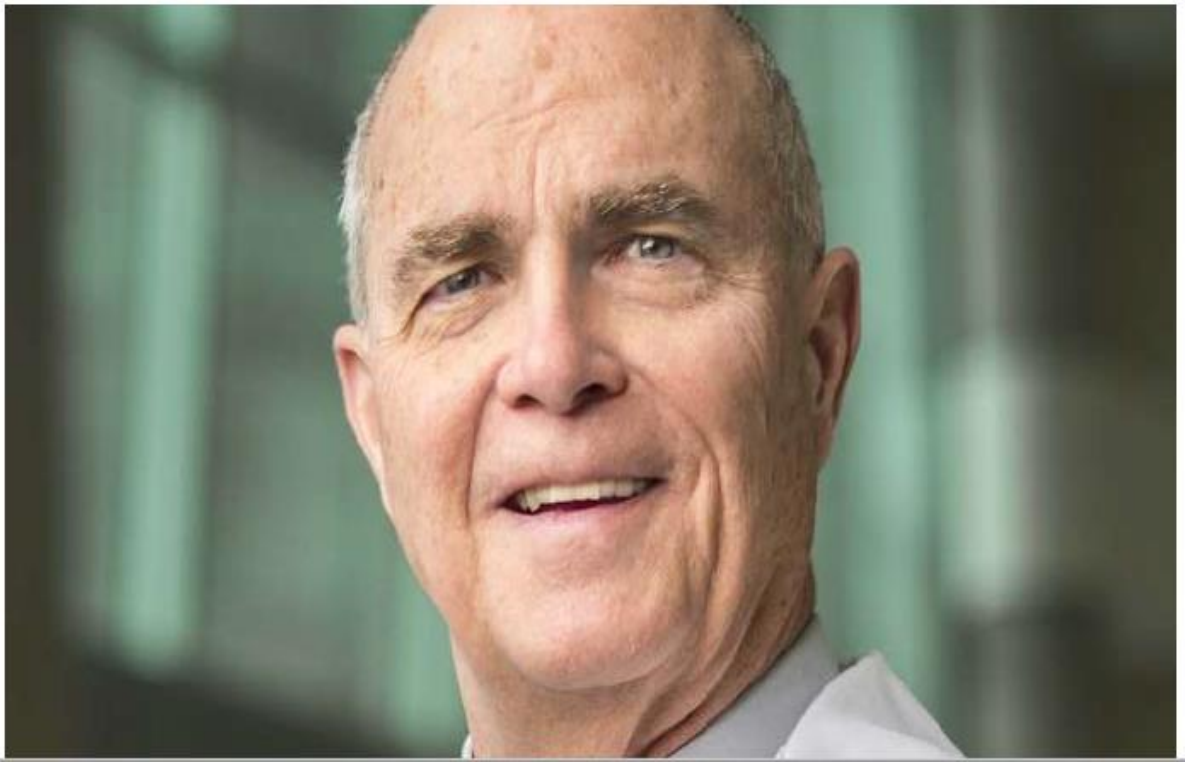
1. Practical Radiation Oncology (2014) 4, 174–180. 2.Acta Oncol. 2015 Jan;54(1):60-6.
3. IJORBP 82 (4): 1522–1527, 2012. 4. Strahlenther Onkol (2015) 191:717–725

Respiratory Gating - DIBH

Toxicity Reduction in Lymphoma - Summary

- Reduced dose
- Reduced treatment volume (extended field RT → involved field RT → Involved site/involved nodal RT)
- Improved treatment planning techniques – IMRT
- Deep inspiration breath hold/respiratory gating with monitoring at treatment

“Radiation is the Most Effective Single Agent for the Treatment of Lymphomas”



Prof. James O. Armitage

Leading Medical Oncologist and Lymphoma Expert

Past-President and Awardee of ASCO-American Society of Clinical Oncology

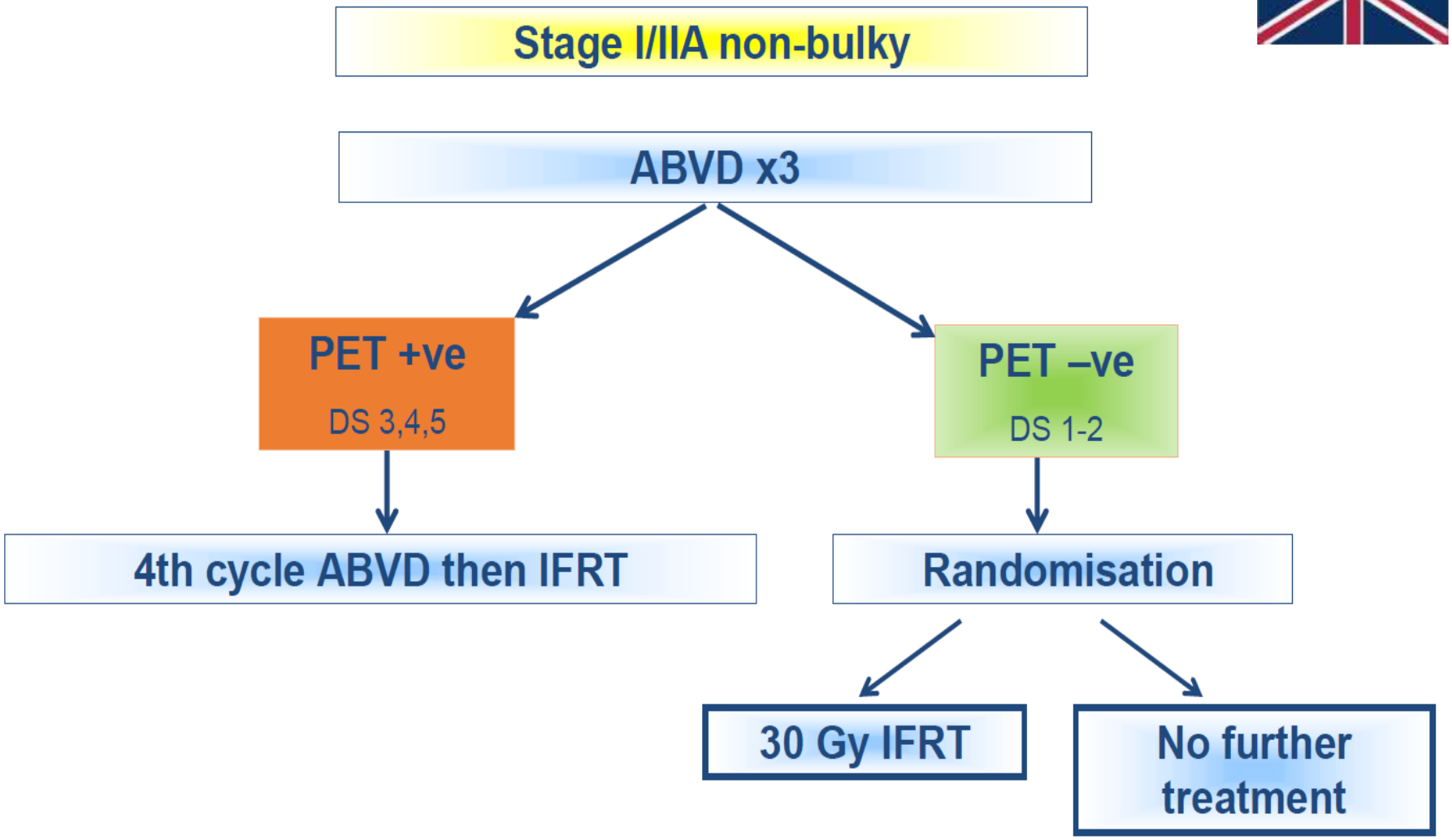
RT-related Late Complications: Overplaying a Risk -that has mostly disappeared- into a Scare that Persists

- Long-term HL data bases of Radical RT disclosed concerning second cancer risks and coronary artery disease
- This concern has been extended (with no data support) to NHL
- BC risk has become mostly irrelevant for modern RT volume and dose
- Studies that supported mortality were flawed and mis-represented (EORTC advanced-stage and HD-6)
- Many ignore lethal risks of (more) chemotherapy (cardiac and pulmonary) as well as neurological deficits (vincristine, Brentuximab)

Should We Really Try to Eliminate RT

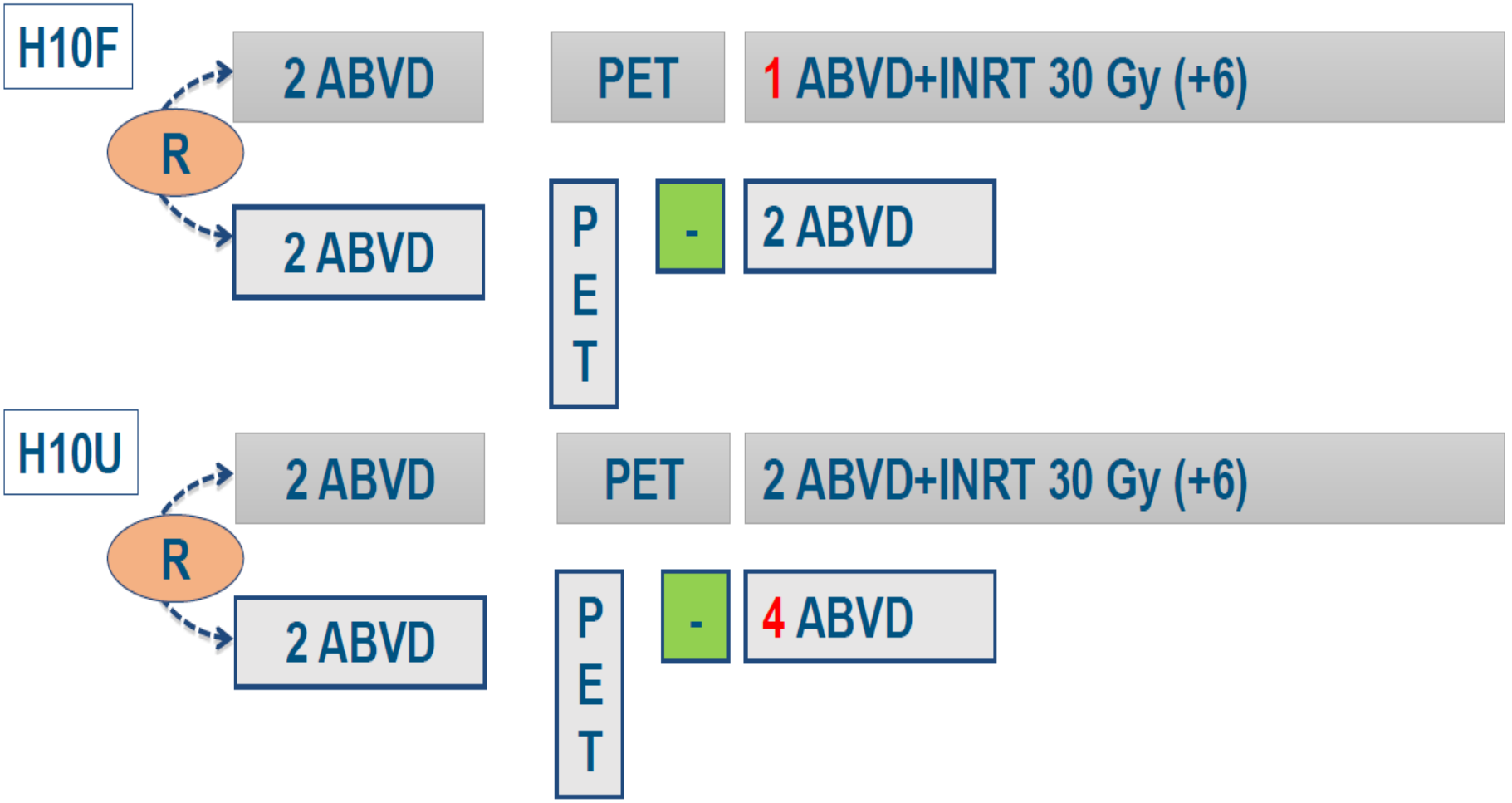
- EORTC H9F – 700+ patients with early stage favorable HL and complete response to chemo, randomized to 1 of 3 arms:
  - Arm A: IFRT 36Gy
  - Arm B: IFRT 20Gy
  - Arm C: Observation
- Increased failures w/o RT at 4 years
  - Arm A: 87% event free survival
  - Arm B: 84%
  - Arm C: 70%
  - Overall survival 98% in all arms

UK NCRI RAPID trial

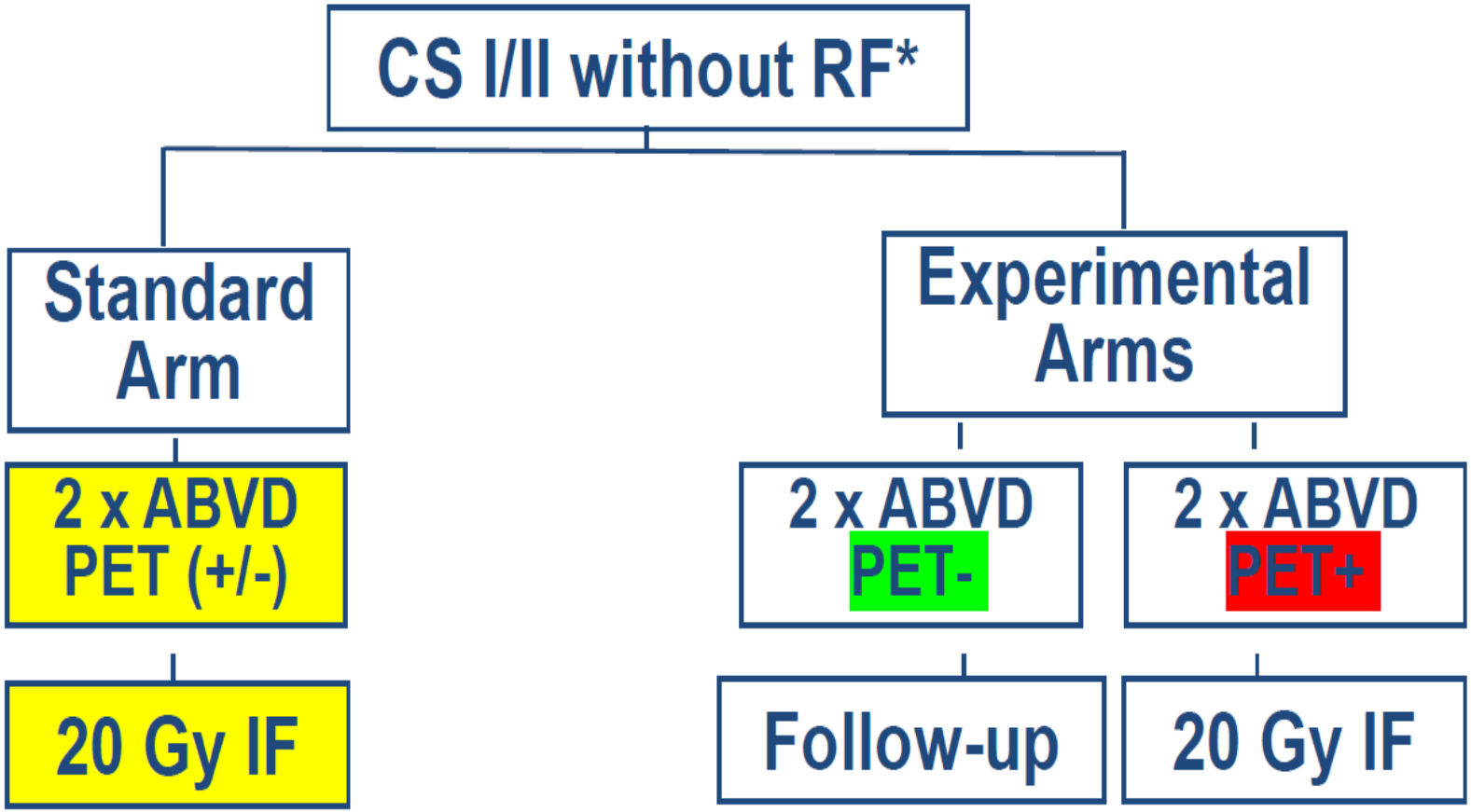


Radford J et al; NEJM (2015) 372;17:1598-1605

EORTC/LYSA/FIL H10 Study – PET-



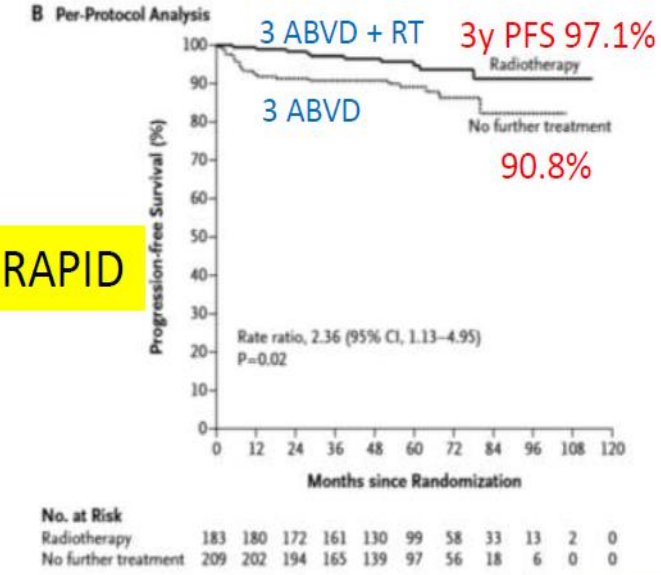
GHSG HD16 (Early Fav)



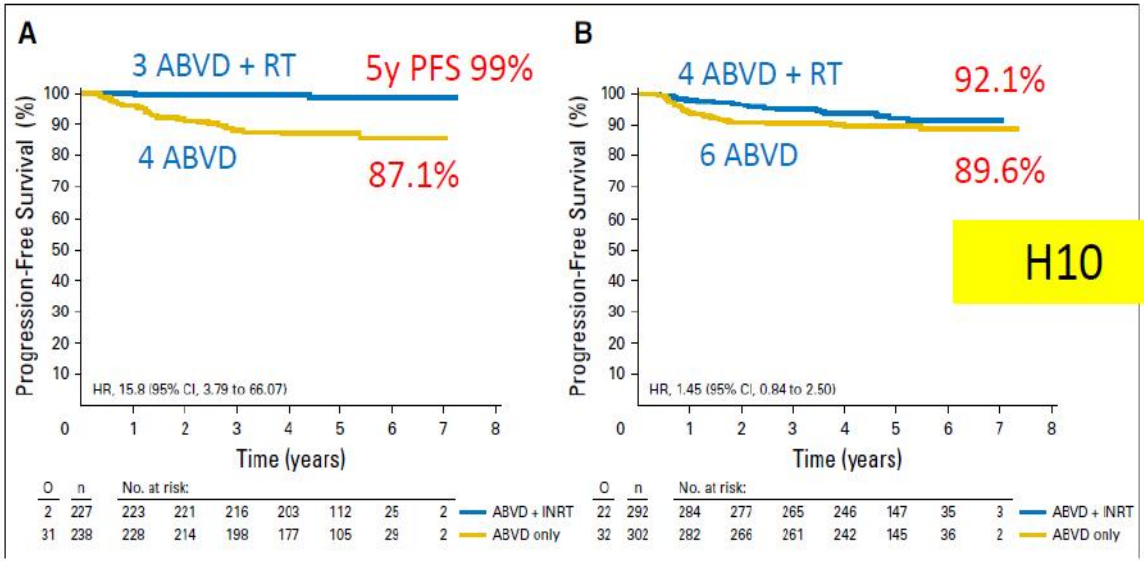
*a) large mediastinal mass; b) extranodal disease; c) high ESR; d) 3 or more areas

Can Radiotherapy be Admitted After a Negative Pet Scan?

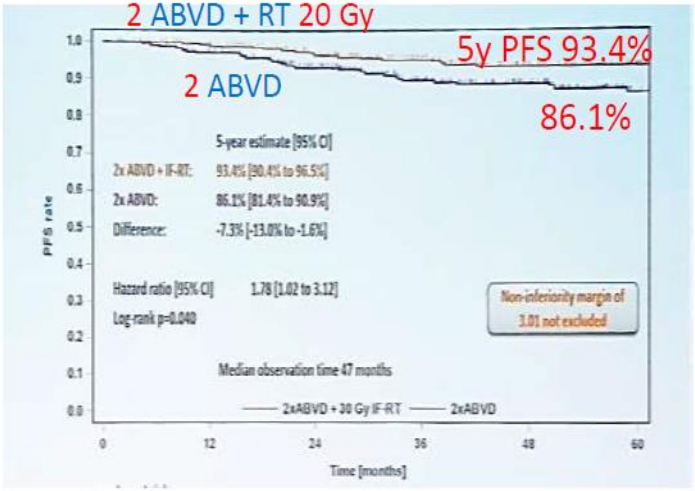
RAPID



H10



HD16

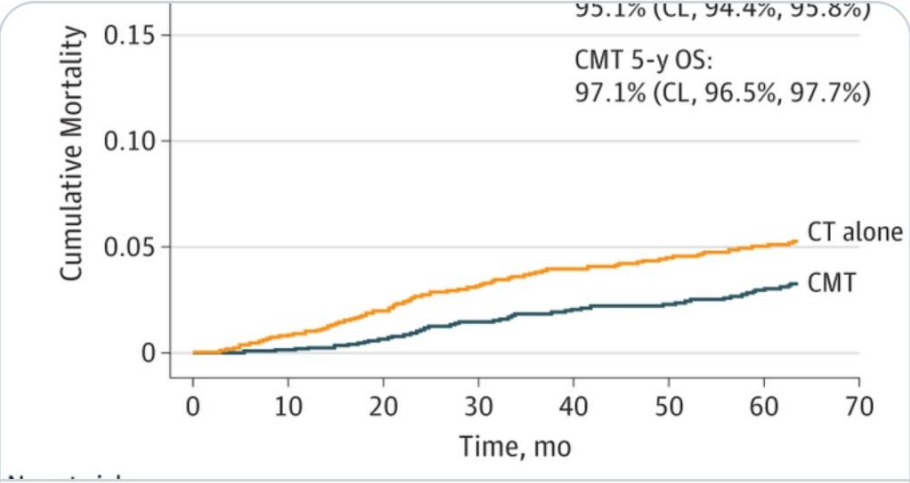


Negative PET
does not =
no microscopic disease

Shane Stecklein, MD, PhD on T...
https://mobile.twitter.com

Tweet

Bias against #radiotherapy for early-stage #Hodgkin #lymphoma is costing lives. All patients should be referred to a #radonc to discuss treatment.



Combined Therapy vs Chemotherapy Alone and Overall Survival in Early-Stage Pediatric Hodgkin...
jamanetwork.com

SEER Analysis – Improved Overall Survival with RT

- 13,420 stage I-II DLBCL pts treated 1988-2004
- 41% received RT, 59% did not
- Results:
  - RT associated with significantly increased DSS (HR 0.82, $p<0.0001$) and OS (HR 0.86, $p<0.001$)

Indolent NHL

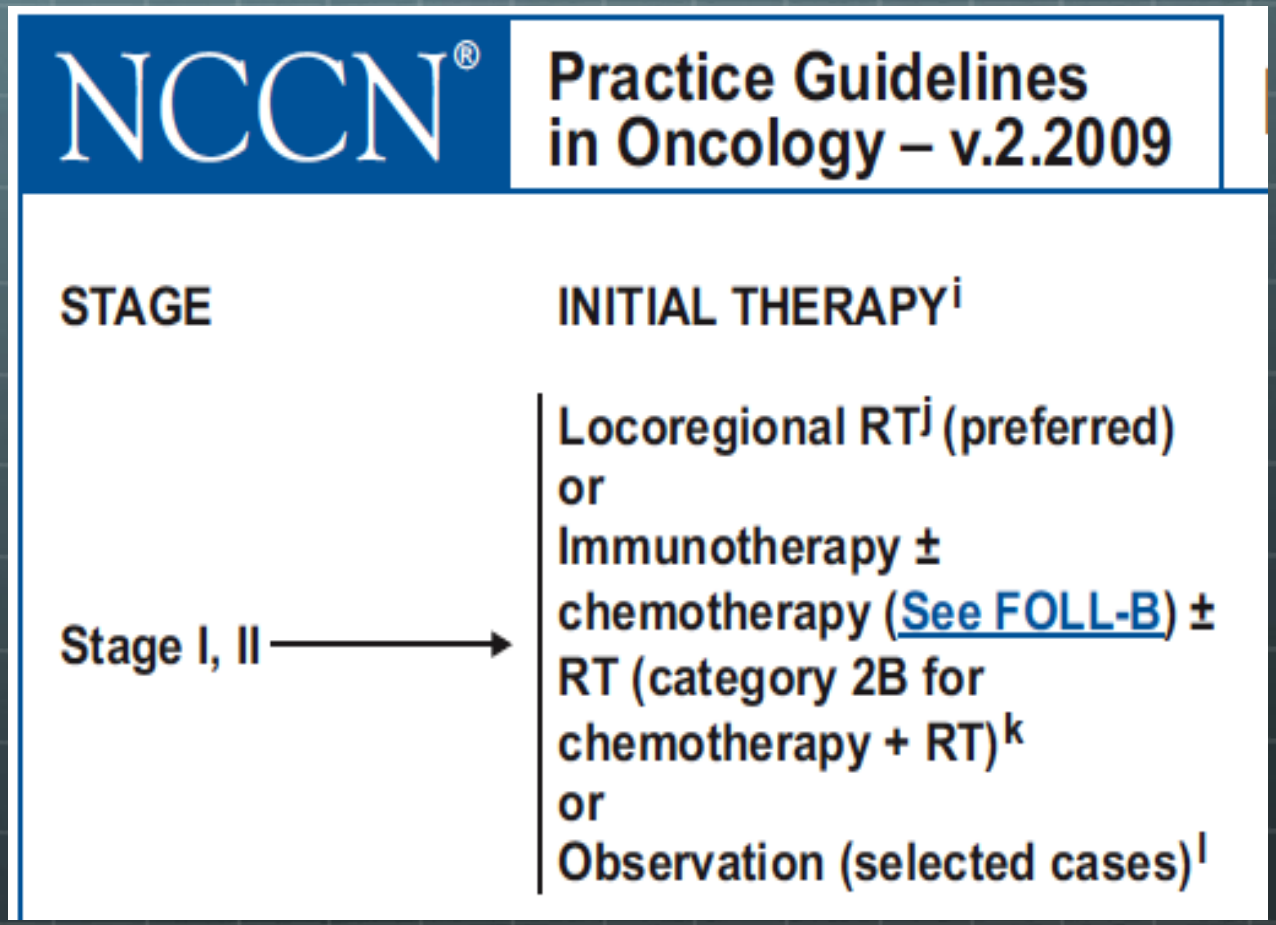
- Follicular NHL (grades I-II)
- MALT lymphoma
- Marginal zone
- Small lymphocytic lymphoma

Indolent NHL – Role of RT

- Early stage
  - Can treat definitively with RT alone
  - Great local control
  - Many relapses systemically
- Advanced stage
  - Not curable with current treatment approaches
  - Role of RT limited to:
    - Treatment of symptomatic bulky disease/palliation
    - Disease progression/transformation
    - Very low doses can be used

Follicular Lymphoma - 2009

- Classic example of indolent lymphoma



NCCN® Practice Guidelines in Oncology – v.2.2009

STAGE	INITIAL THERAPY[i]
Stage I, II →	Locoregional RT[j] (preferred) or Immunotherapy ± chemotherapy (See FOLL-B) ± RT (category 2B for chemotherapy + RT)[k] or Observation (selected cases)[l]

Follicular Lymphoma - 2019

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2019
Follicular Lymphoma (grade 1-2)

NCCN Guidelines Index
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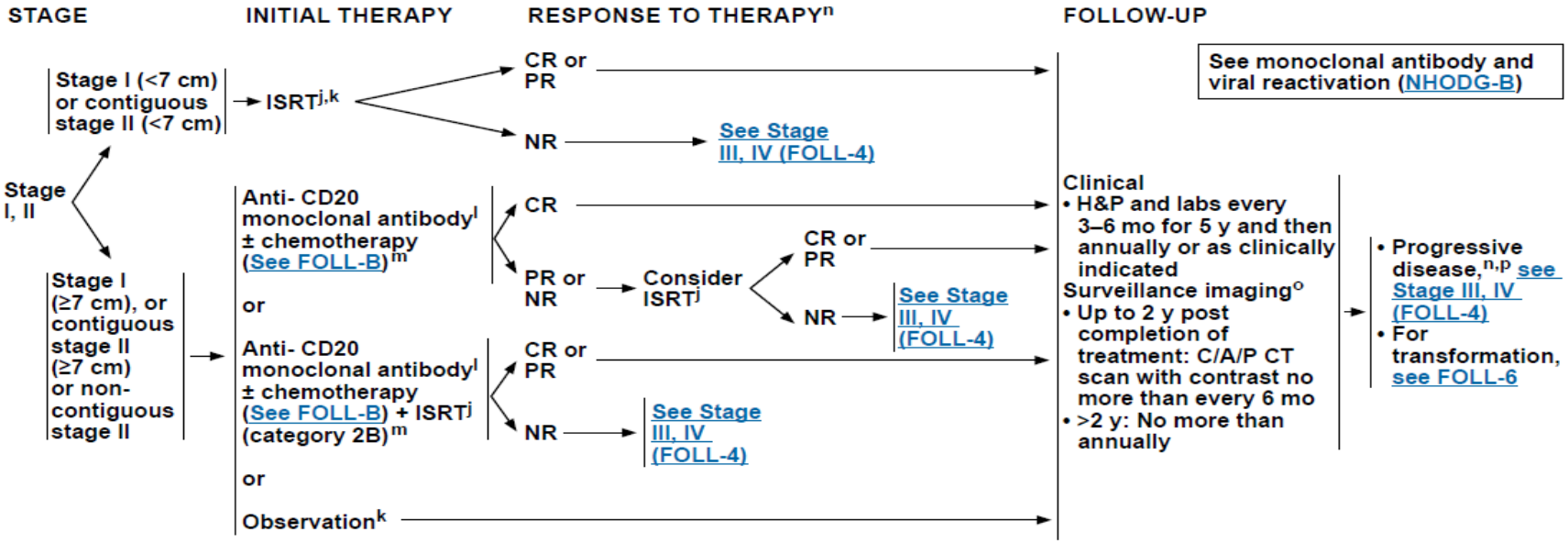
Discussion



[j] See Principles of Radiation Therapy (NHODG-D).

[k] Observation may be appropriate in circumstances where potential toxicity of involved-site RT (ISRT) outweighs potential clinical benefit.

[l] Anti-CD20 monoclonal antibodies include rituximab or obinutuzumab. Obinutuzumab is not indicated as single-agent therapy.

[m] Initiation of chemotherapy or more extended RT can improve failure-free survival (FFS), but has not been shown to improve overall survival. These are options for therapy.

[n] See Lugano Response Criteria for Non-Hodgkin's Lymphoma (NHODG-C). PET/CT scan should be interpreted via the PET Five Point Scale (FPS).

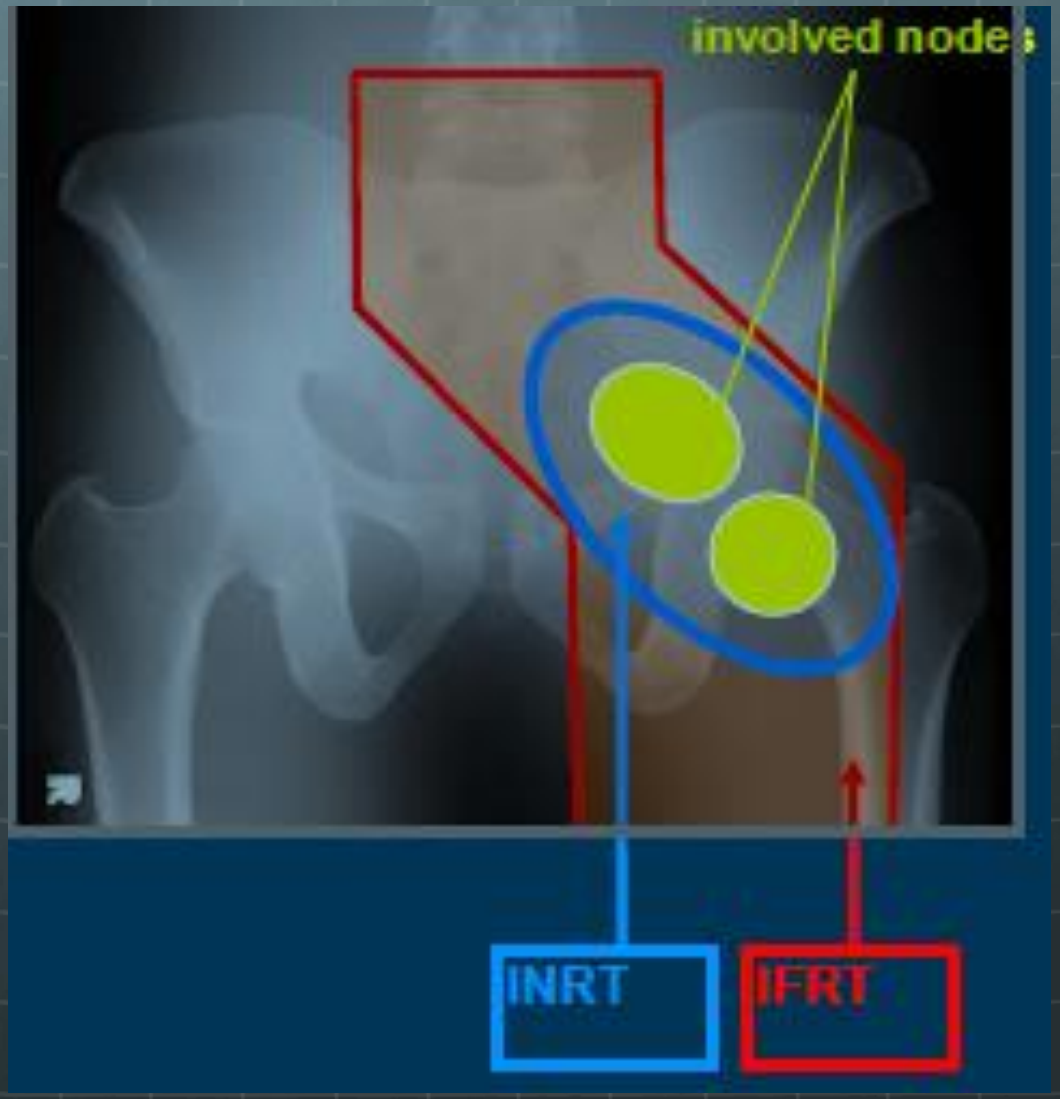
[o] Imaging should be performed whenever there are clinical indications. For surveillance imaging, see Discussion for consensus imaging recommendations.

[p] Consider possibility of histologic transformation in patients with progressive disease, especially if LDH levels are rising, single site is growing disproportionately, extranodal disease develops, or there are new B symptoms. If clinical suspicion of transformation, FDG-PET may help identify areas suspicious for transformation. FDG-PET scan demonstrating marked heterogeneity or sites of intense FDG avidity may indicate transformation, and biopsy should be directed biopsy at the most FDG-avid area. Functional imaging does not replace biopsy to diagnose transformation. If transformation is histologically confirmed, treat with anthracycline-based therapy. See Management of Transformation (FOLL-6).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

RT for Follicular Lymphoma

- Involved Field RT vs Involved Nodal RT
  - 24-30 Gy for rapidly responding disease
  - 30-36 Gy for slowly regressing disease



Evidence for RT Alone

Center	# Pts	Stage	FFR at 10 y
PMH	460	I-II	51%
BNLI	208	I	49%
Stanford	177	I-II	44%
RMH	58	I-II	43%

Questions???