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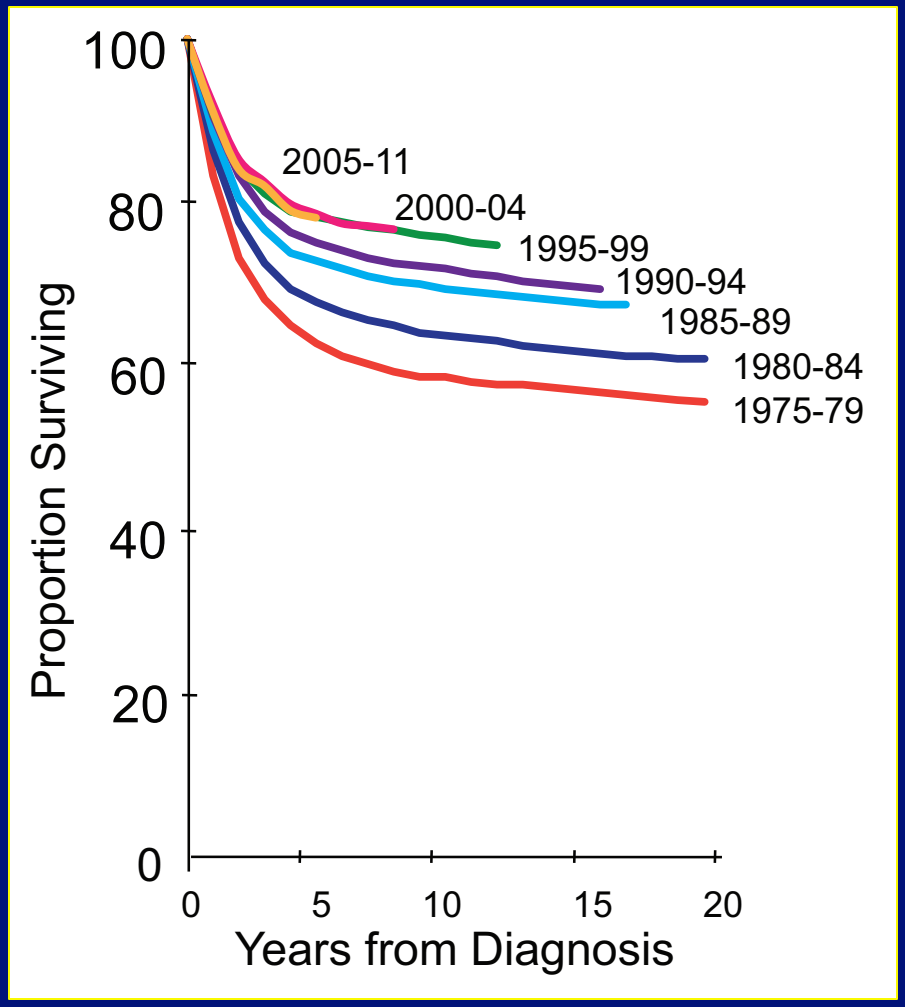
Curing Children with Cancer, But At What Cost? The Double-edged Sword of Cytotoxic Therapy and PENTEC: investigations into normal tissue dose constraints in children

Louis S. Constine, MD, FASTRO
Philip Rubin Professor of Radiation Oncology and Pediatrics
Director, Judy DiMarzo Cancer Survivorship Program
Vice Chair, Department of Radiation Oncology

No conflicts of interest

Cancer Survival, 0-14 Years of Age
SEER Program 1973-2012



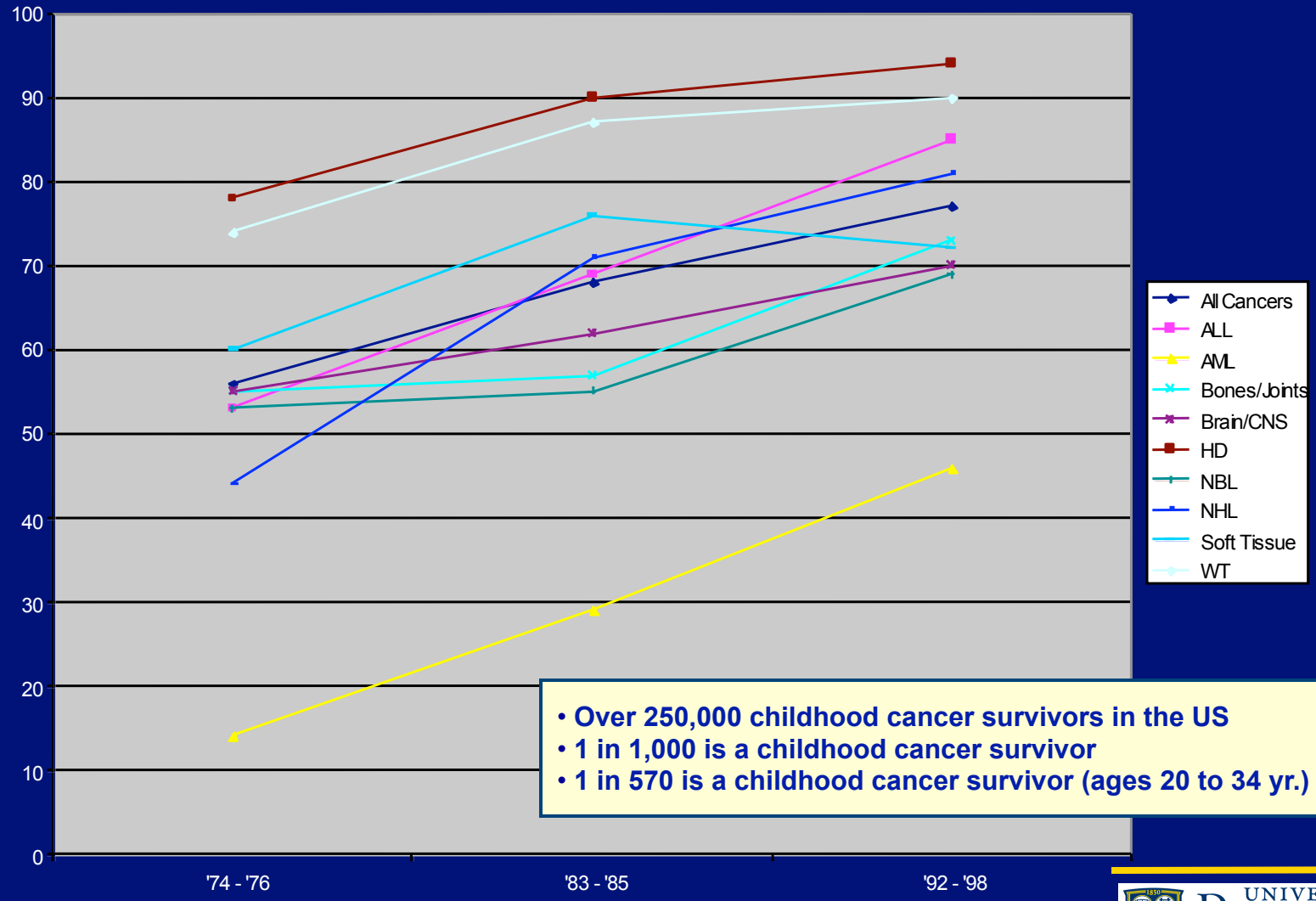
Survivorship Statistics

- >83% of children with a malignancy will achieve five-year survival
- In 2013, estimated 420,000 survivors of childhood cancer in the U.S.
- By 2020, estimated 500,000 survivors
- 1 in 750 in US is a childhood cancer survivor

Howlader N, SEER Cancer Statistics Review 1975-2012
Phillips et al, *CEBP*, 2015 NCI Office of Cancer Survivorship
Robison L. & Hudson MM, *Nature Reviews Cancer* 2014

CCSS Armstrong 2015

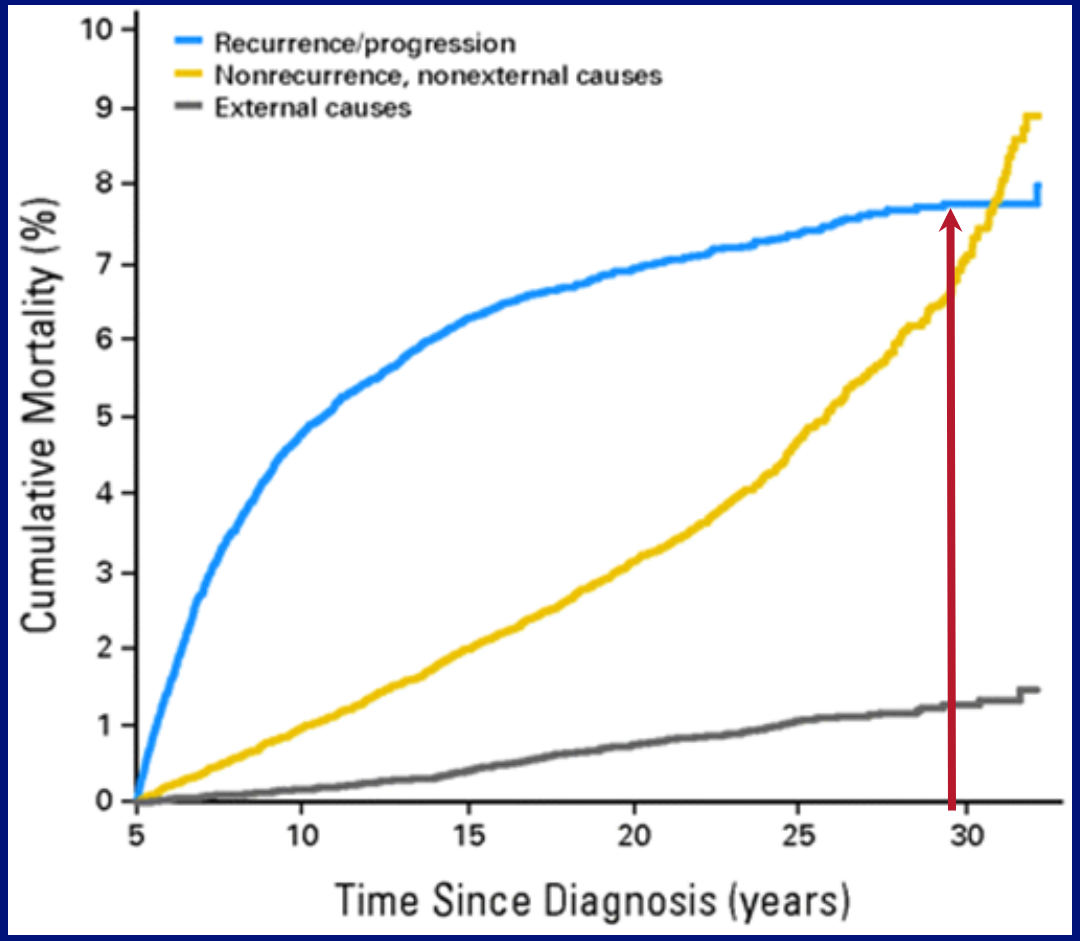
Five-Year Relative Survival Rates



- Over 250,000 childhood cancer survivors in the US
- 1 in 1,000 is a childhood cancer survivor
- 1 in 570 is a childhood cancer survivor (ages 20 to 34 yr.)

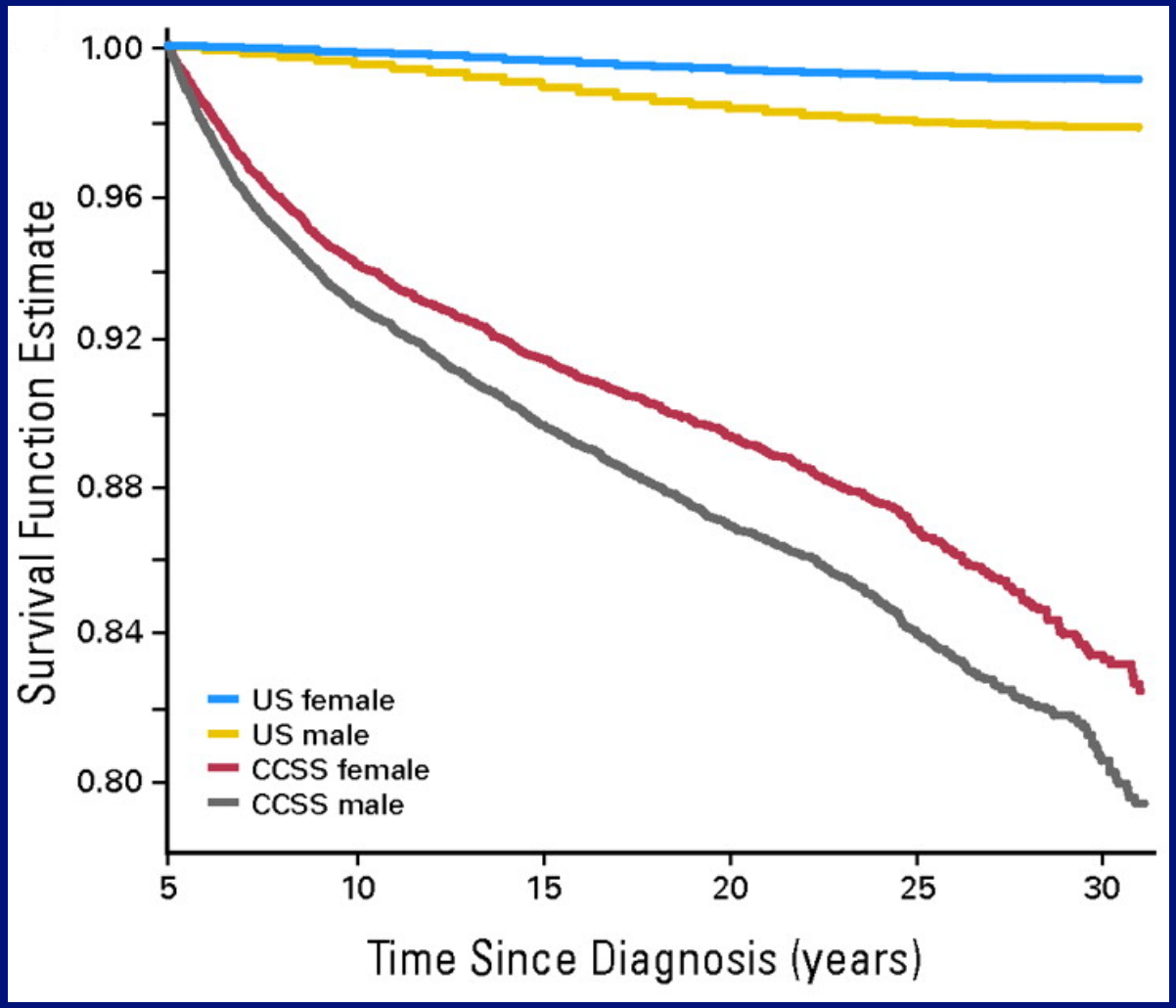
Cumulative Case-Specific Mortality

5 year survivors - Childhood Cancer Survivor Study



Armstrong GT, et al. J Clin Oncol, 2009

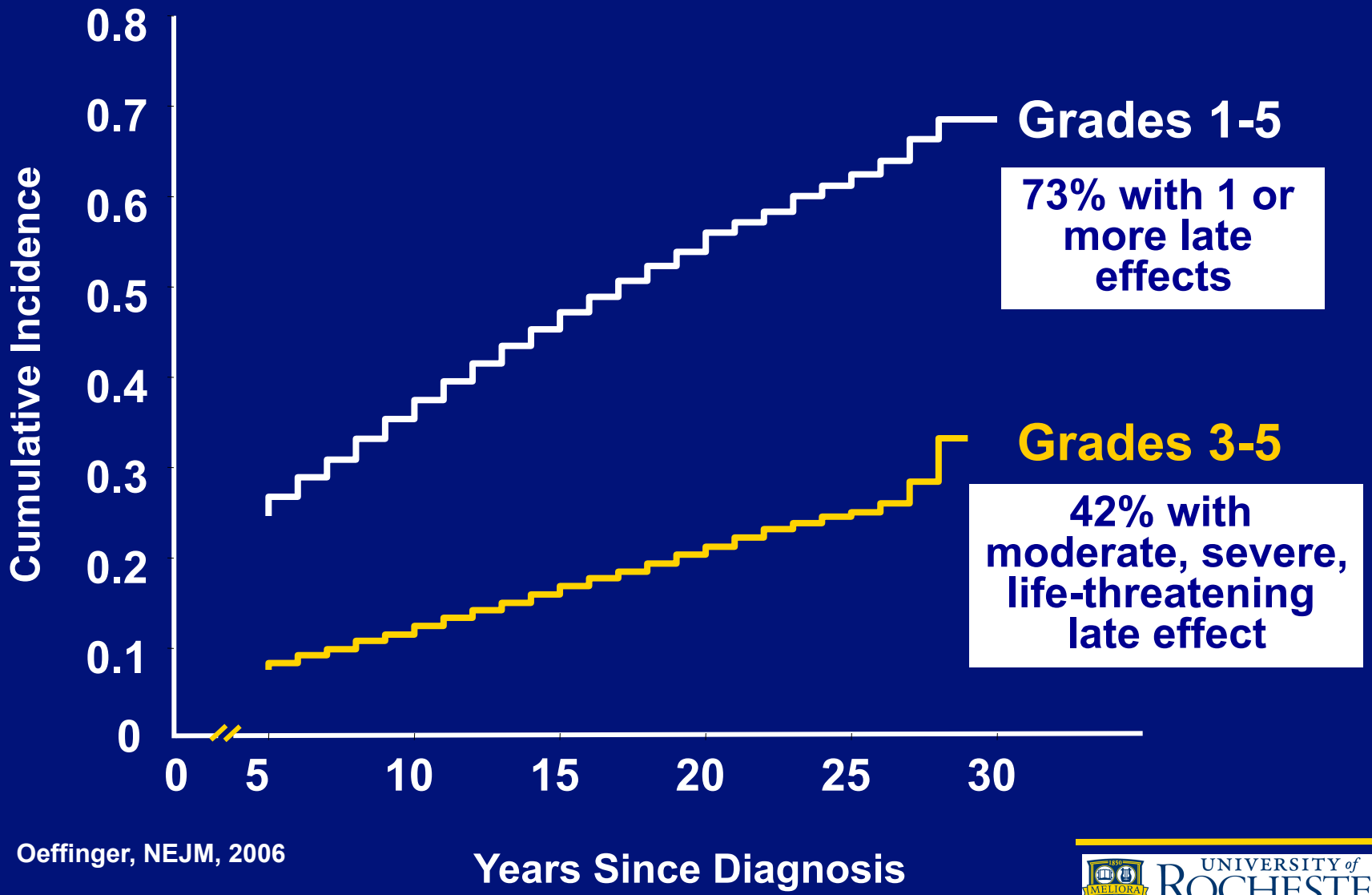
Late Mortality Among 5+ Year Survivors
Childhood Cancer Survivor Study (N=20,483)



Causes	SMR
Second cancers	15.2
Cardiac	7.0
Pulmonary	8.8

Mertens AC, et al. J Natl Cancer Inst, 2009

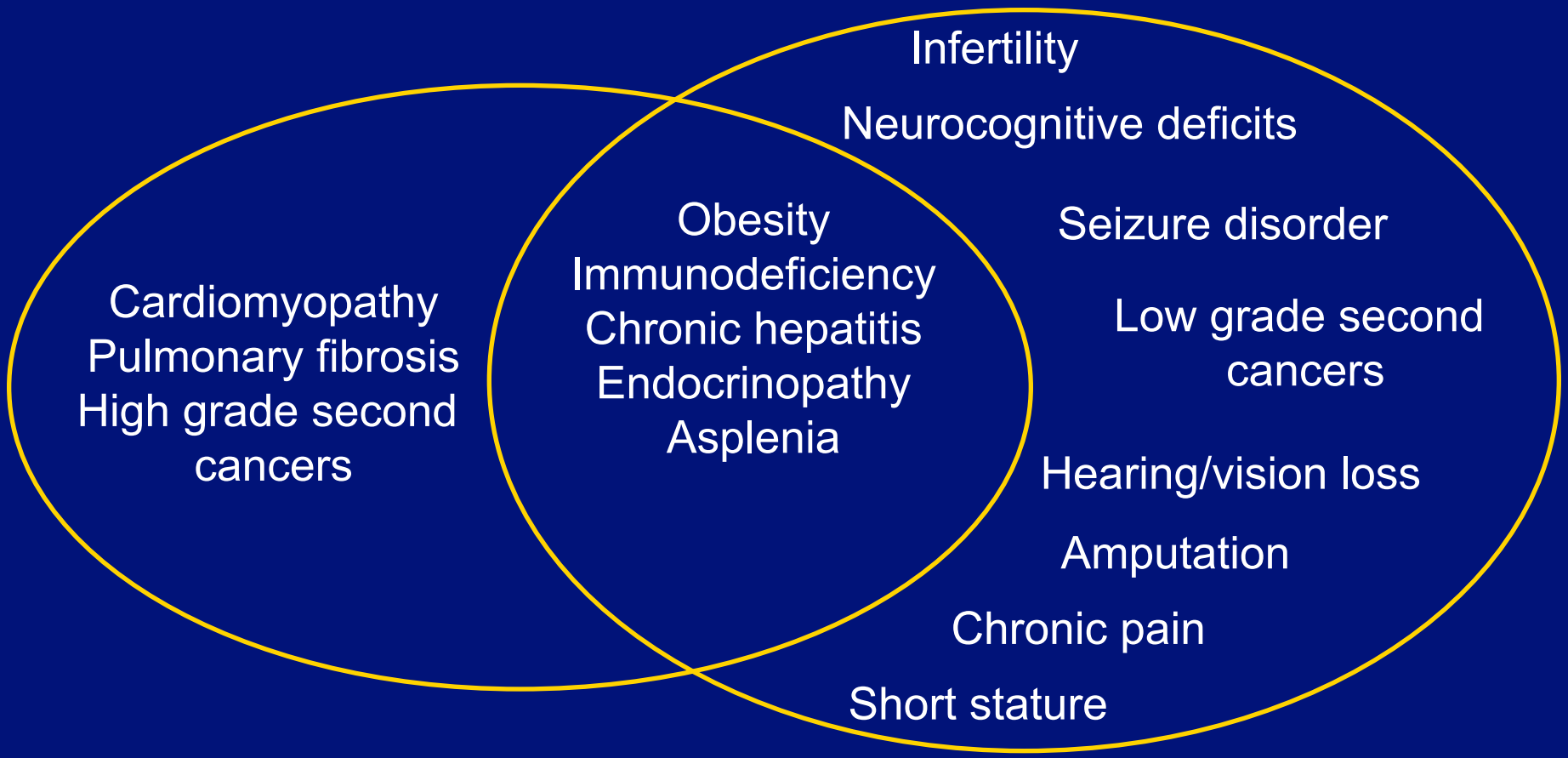
Incidence of Health Conditions in 10,397 Adults in Children's Cancer Survivor Study



Oeffinger, NEJM, 2006

Spectrum of Treatment Effects

Life-Threatening → **Life-Altering**



It’s not what you don’t know that hurts you,
It’s what you know that just ain’t so.

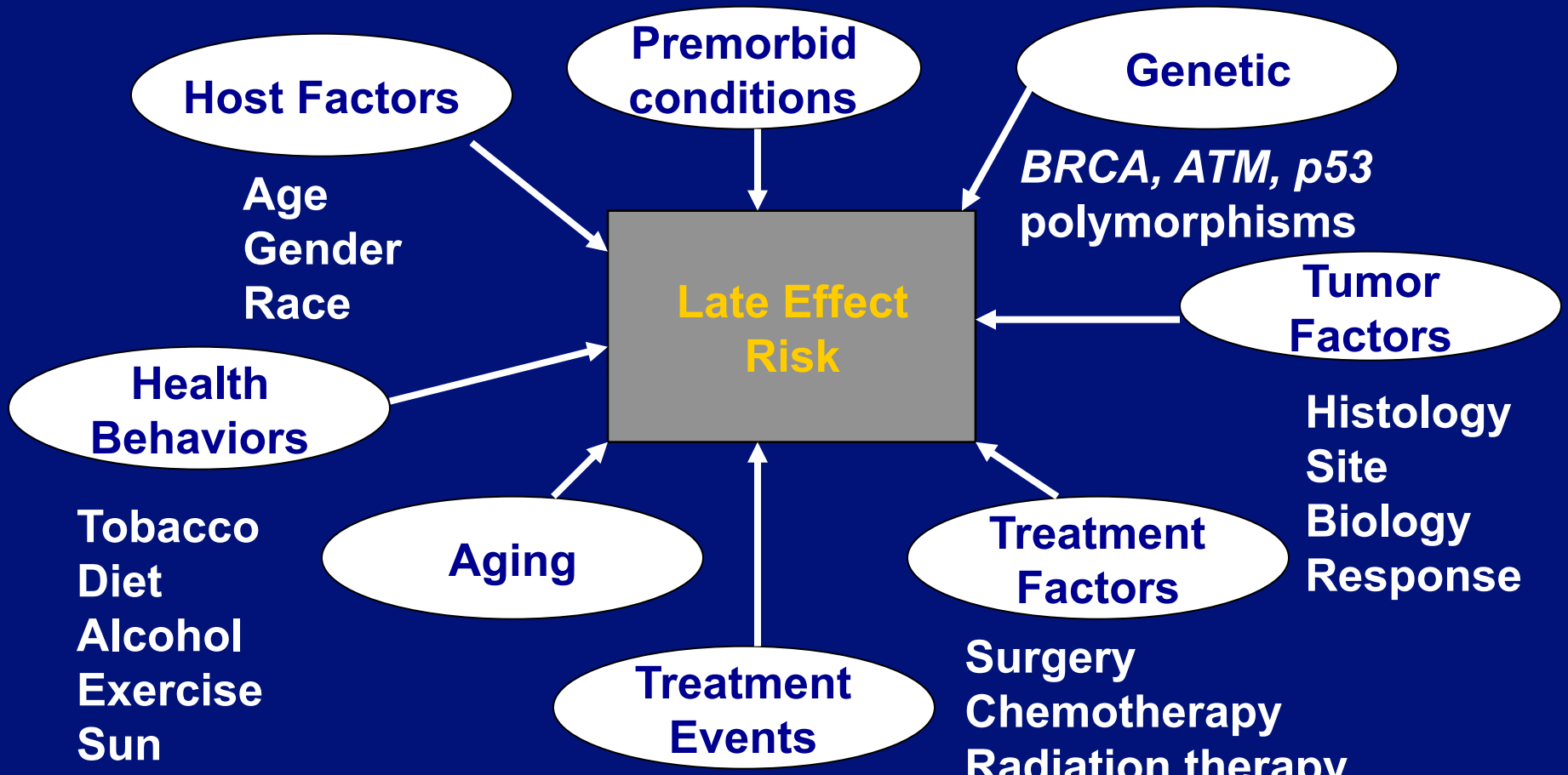
» Mark Twain

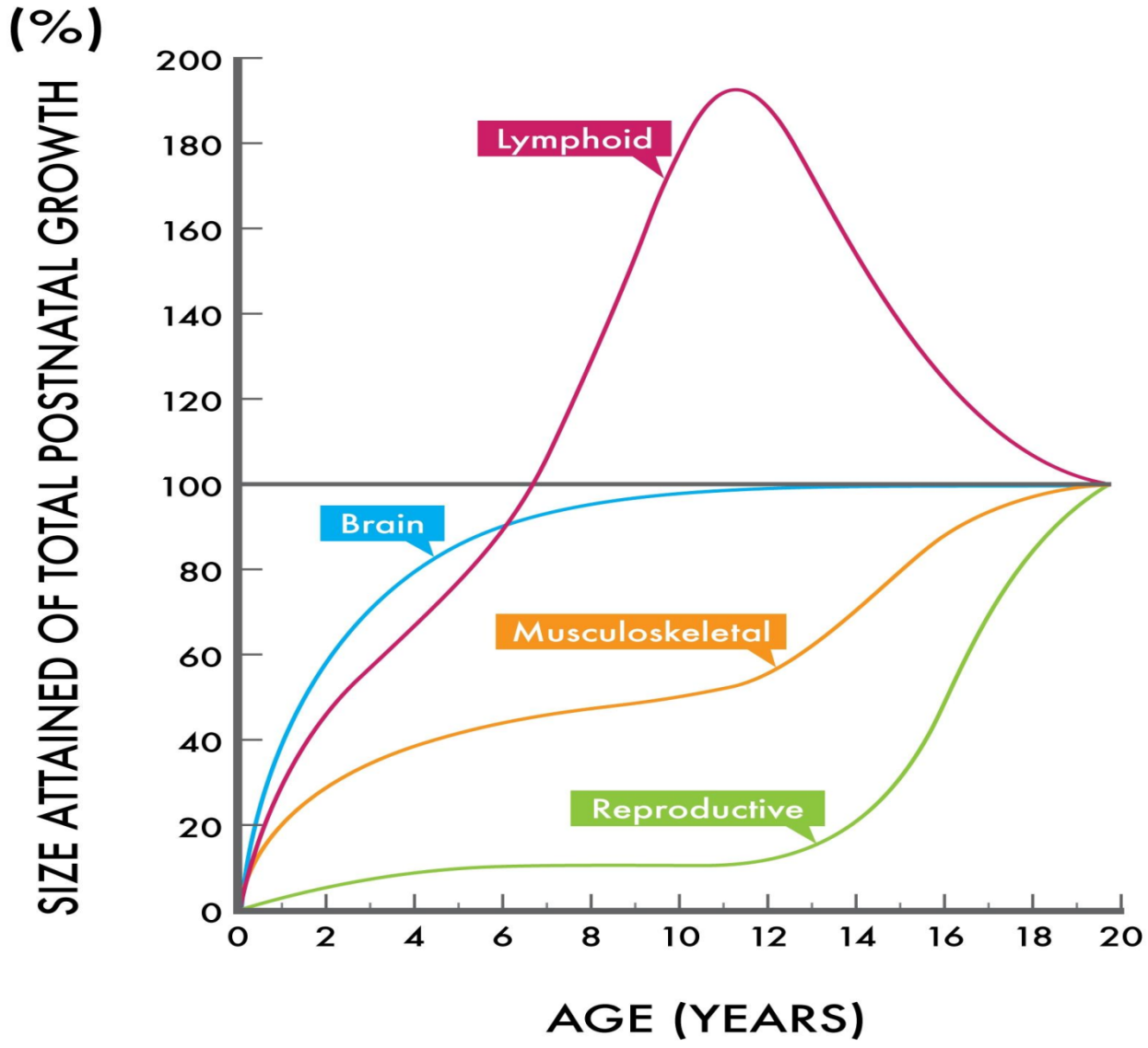
Comparative Risks after Radiotherapy: Children vs. Adults

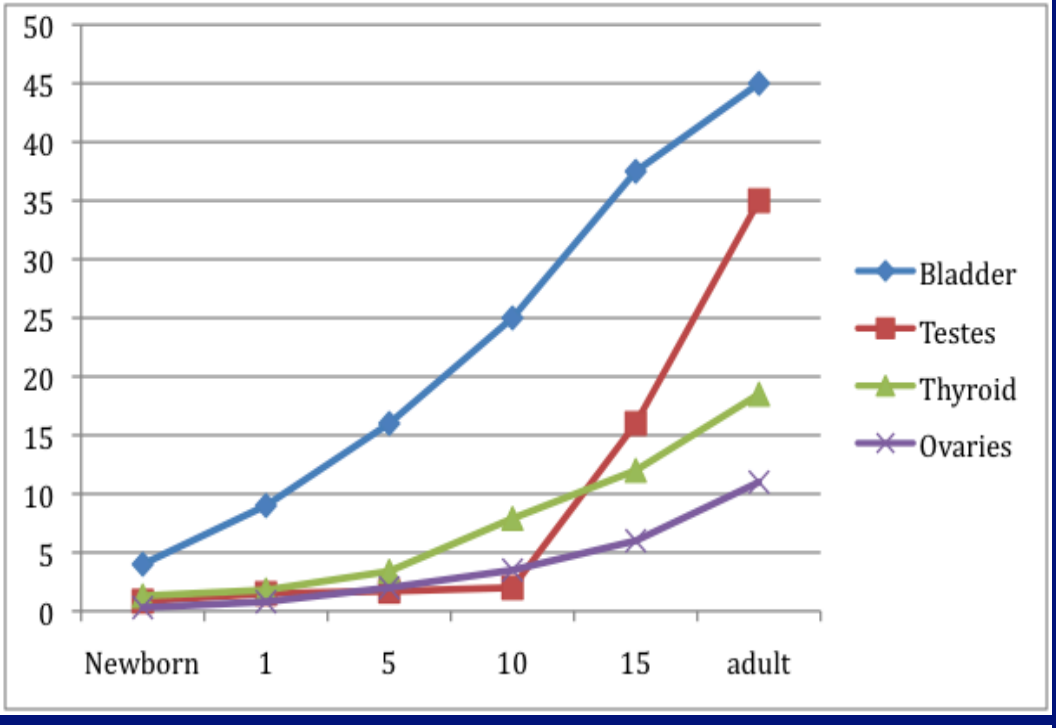
	Risk	Levels of Evidence	Comments
Brain	More	Strong	Neurocognitive reduction
Neuroendocrine	No difference	Strong	But consequences greater due to growth hormone suppression
Cataracts	More	Weak	
Cerebrovascular accident	More	Moderate	
Heart	More	Strong	Prevents myocyte hypertrophy and remodeling
Breast hypoplasia	More	Strong	Most severe during puberty
Lung	Less	Weak	Depends on endpoint: maximum capacity decreased if chest wall growth is inhibited
Thyroid hypofunction	More	Strong	
Thyroid nodules	More	Moderate	
Thyroid autoimmune	No data	Weak	
Kidney	same	weak	
Bladder	More	Strong	Bladder capacity reduced
Testes	More	Strong	Most severe during puberty
Ovaries	Less	Strong	Less sensitive to radiation at younger age
Uterus	More	Moderate	Uterine vasculature impaired
Musculoskeletal	More	Strong	Hypoplasia, deformity, osteochondroma
Immune	No data		
Marrow whole body	Less	Strong	Less available marrow when older

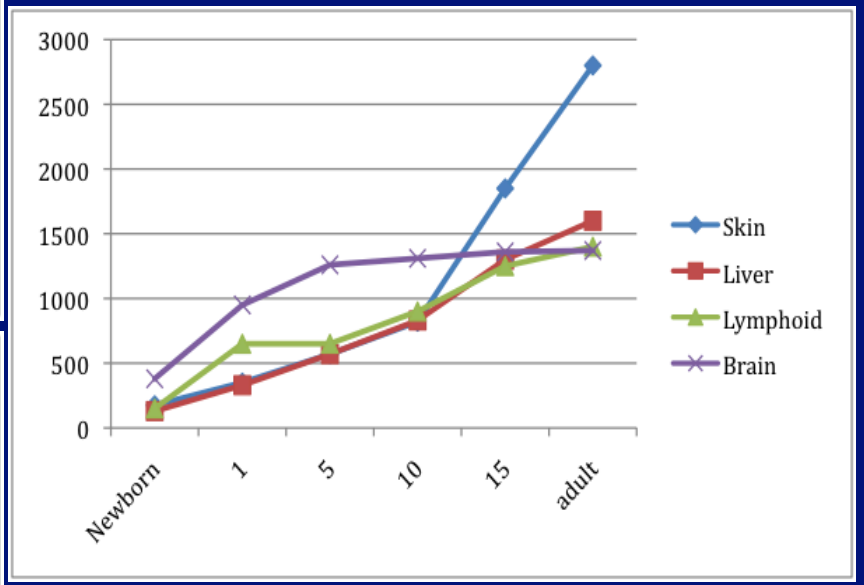
UN Scientific Committee: Constine, Mettler 2013

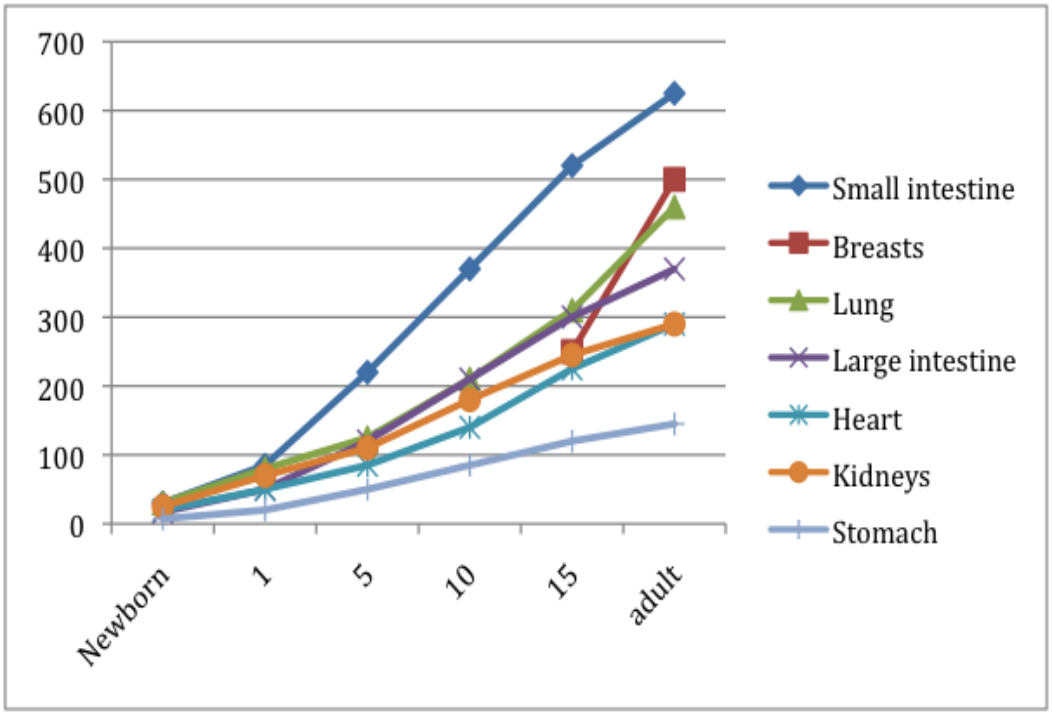
Risk-Based Survivor Care







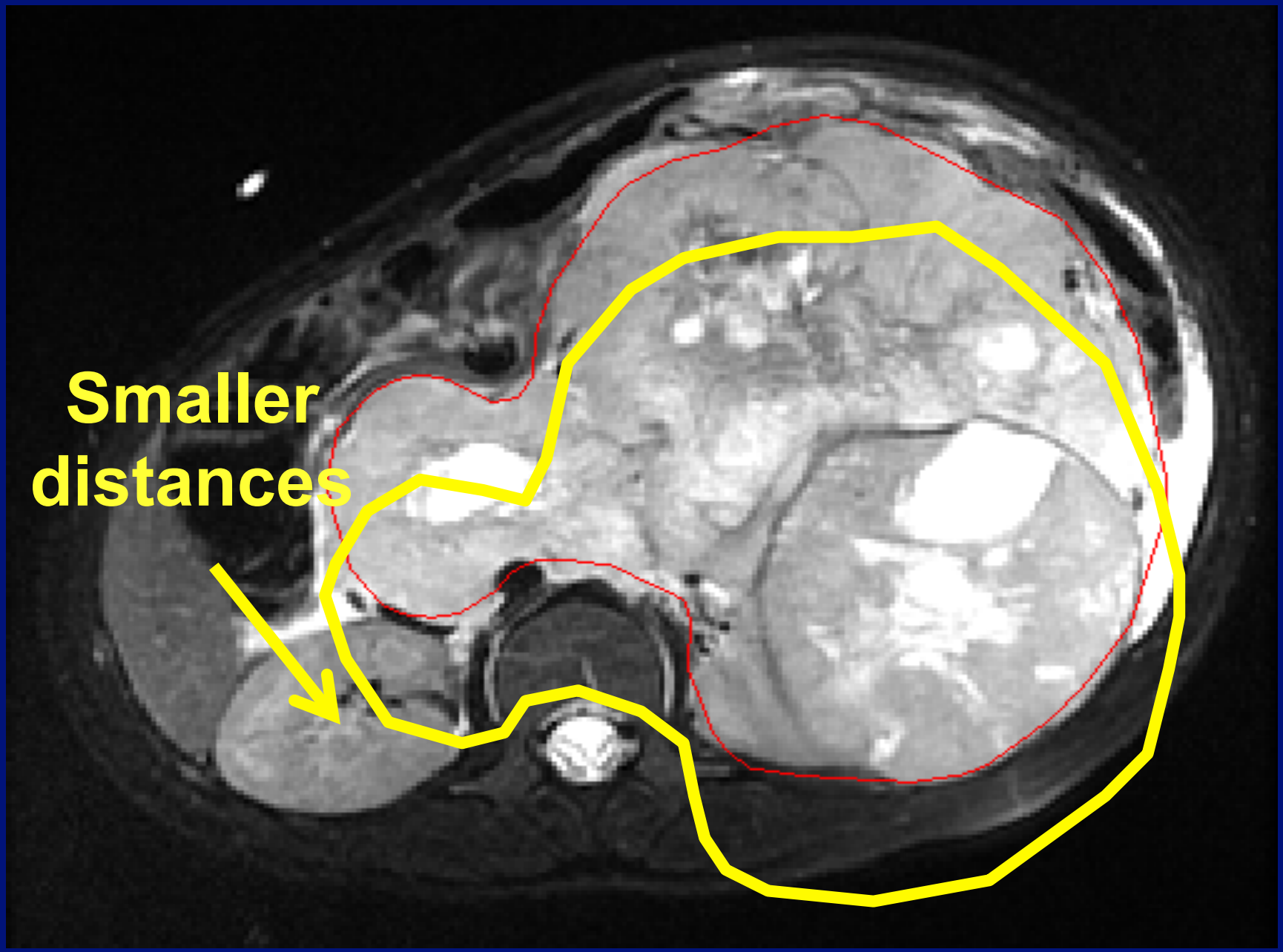




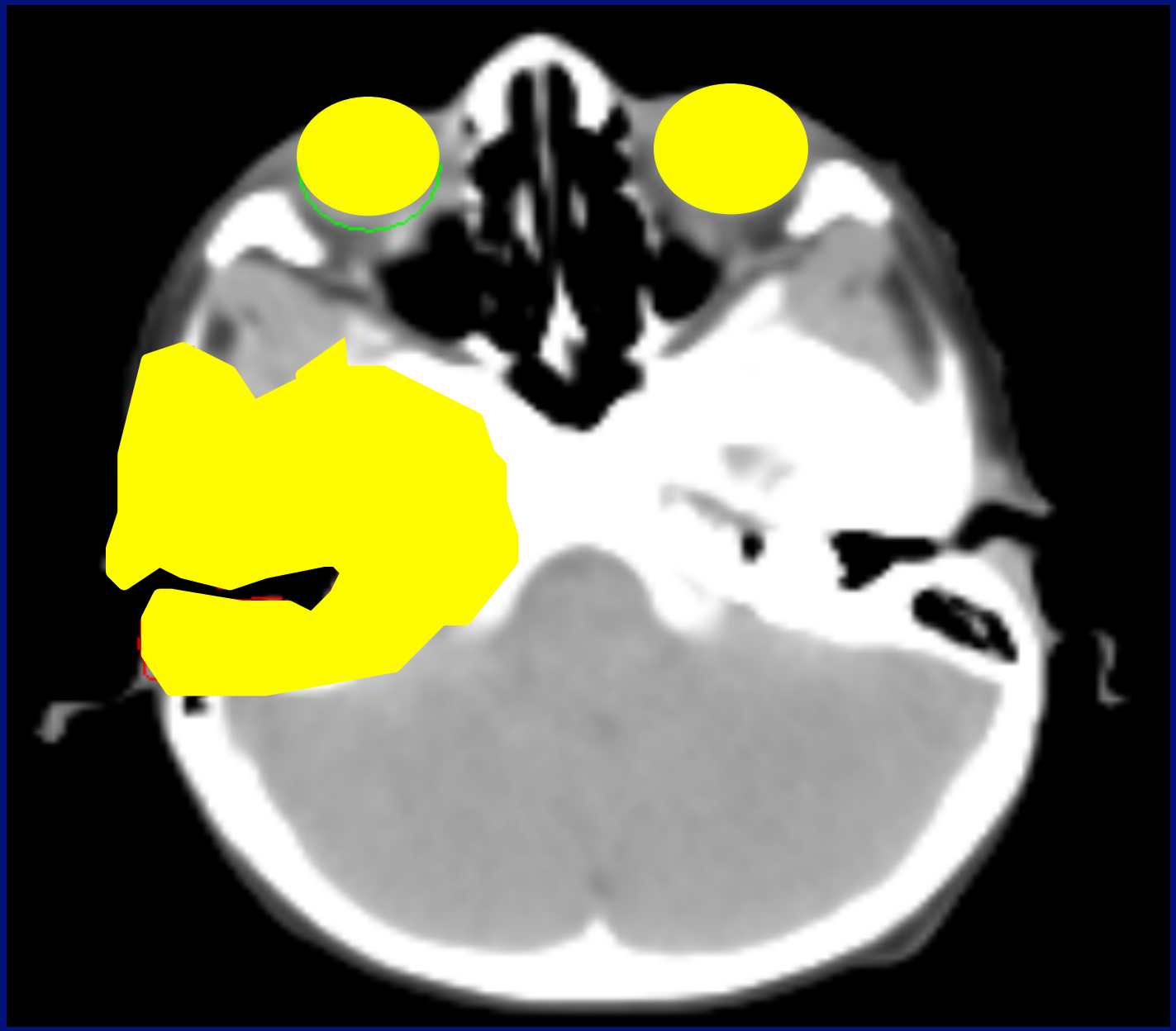
Constine, Dhakal

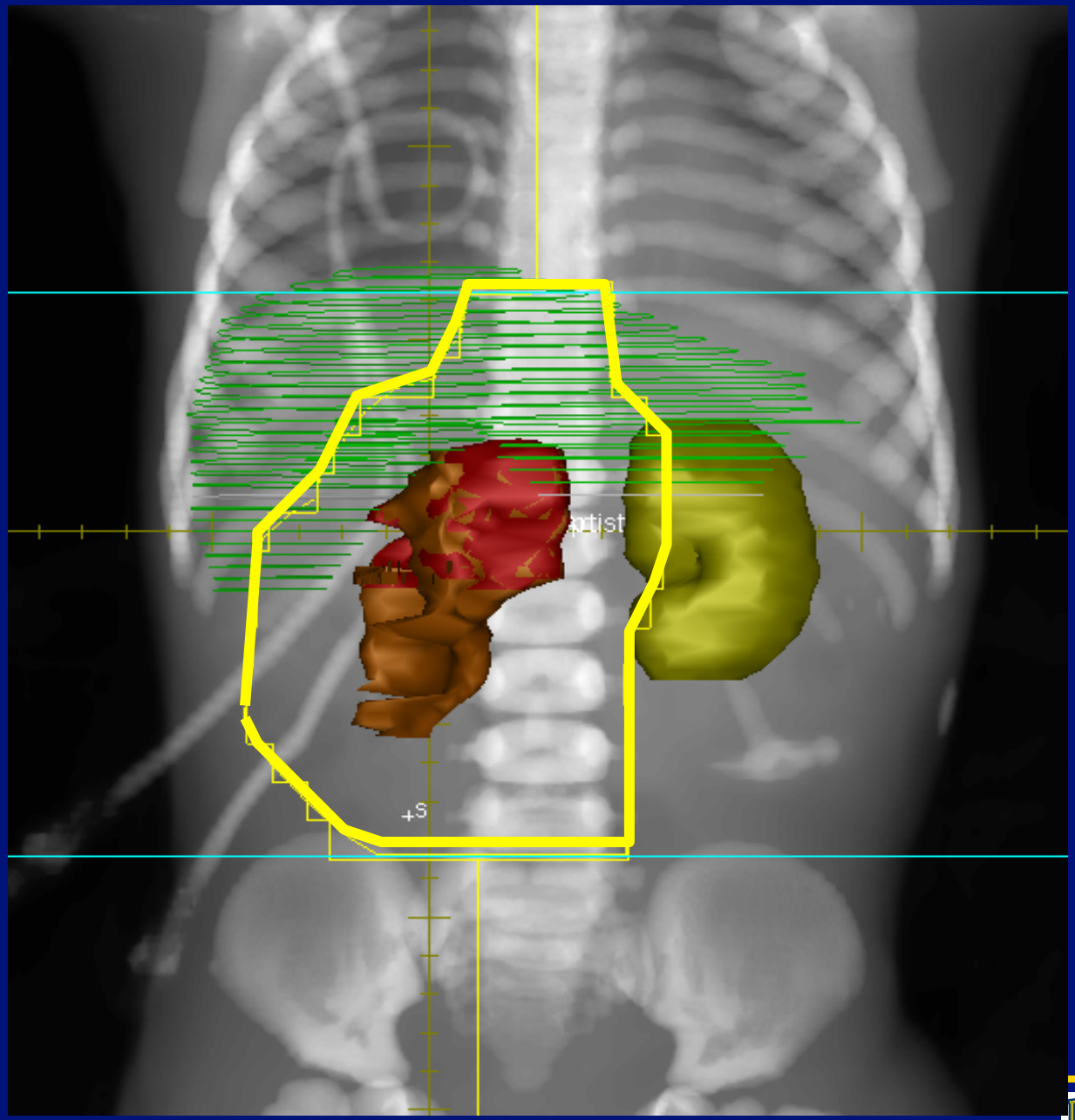
Technical issues increasing risk

- Children are little
- Things are packed in tight
- Even small RT fields treat a lot of organs



Smaller distances





Chemo?

Pre-RT **During-RT** **Post-RT**

Chemo?

Pre-RT	During-RT	Post-RT
Kids*		
All CNS, Rhabdo, Neuroblastoma	All Rhabdo, Ewings, Wilms, Medullo	All Rhabdo, Ewings, Wilms
Adults*		
Some Breast	Most ENT, Lung, GI, Gyn	GI

*Kids: most get chemo, adults, some don't:
e.g. Prostate, sarcoma, many breast, e

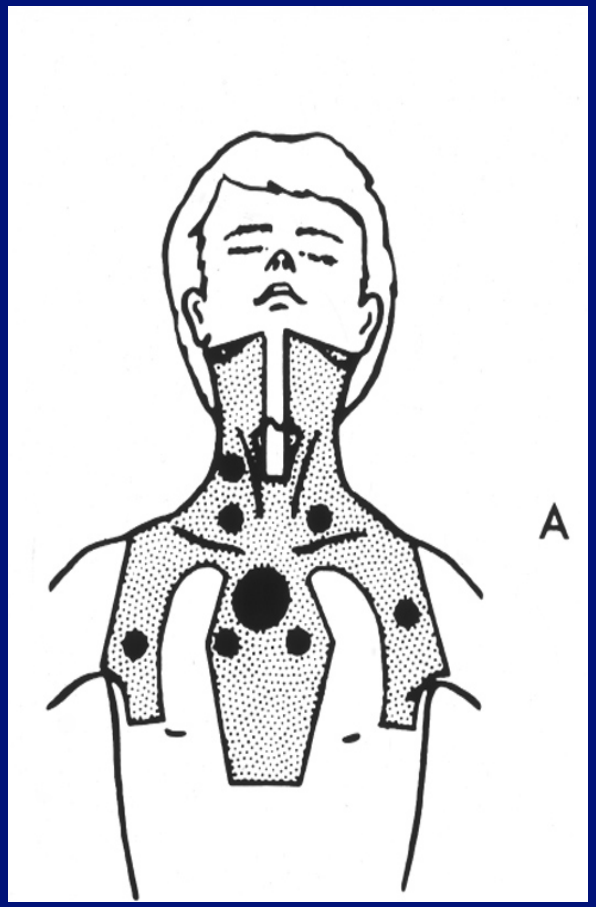
Broad Issues

Kids	Adults
Impaired Growth and development	
	Comorbid diseases
	Less reserve
Smaller size	Larger size
Long horizon	Variable horizon

Tissues at Risk for Late Toxicity

- Bone/soft tissues
- Cardiovascular
- Dental
- Endocrine
- Gastrointestinal
- Hepatic
- Hematological
- Immune system
- Nervous system
- Neuropsychological
- Ophthalmologic
- Pulmonary
- Renal
- Reproductive

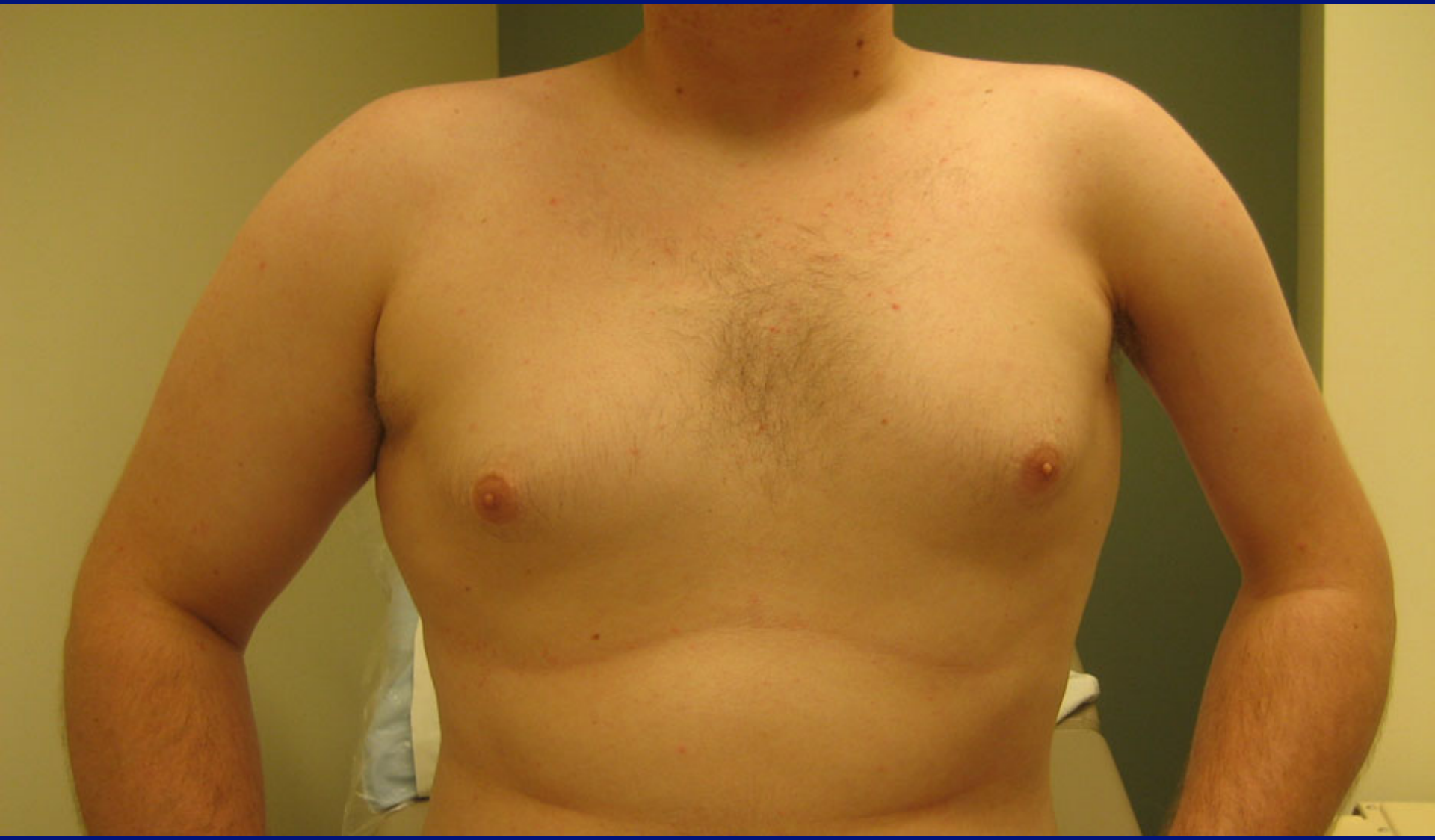
Growth Impairment



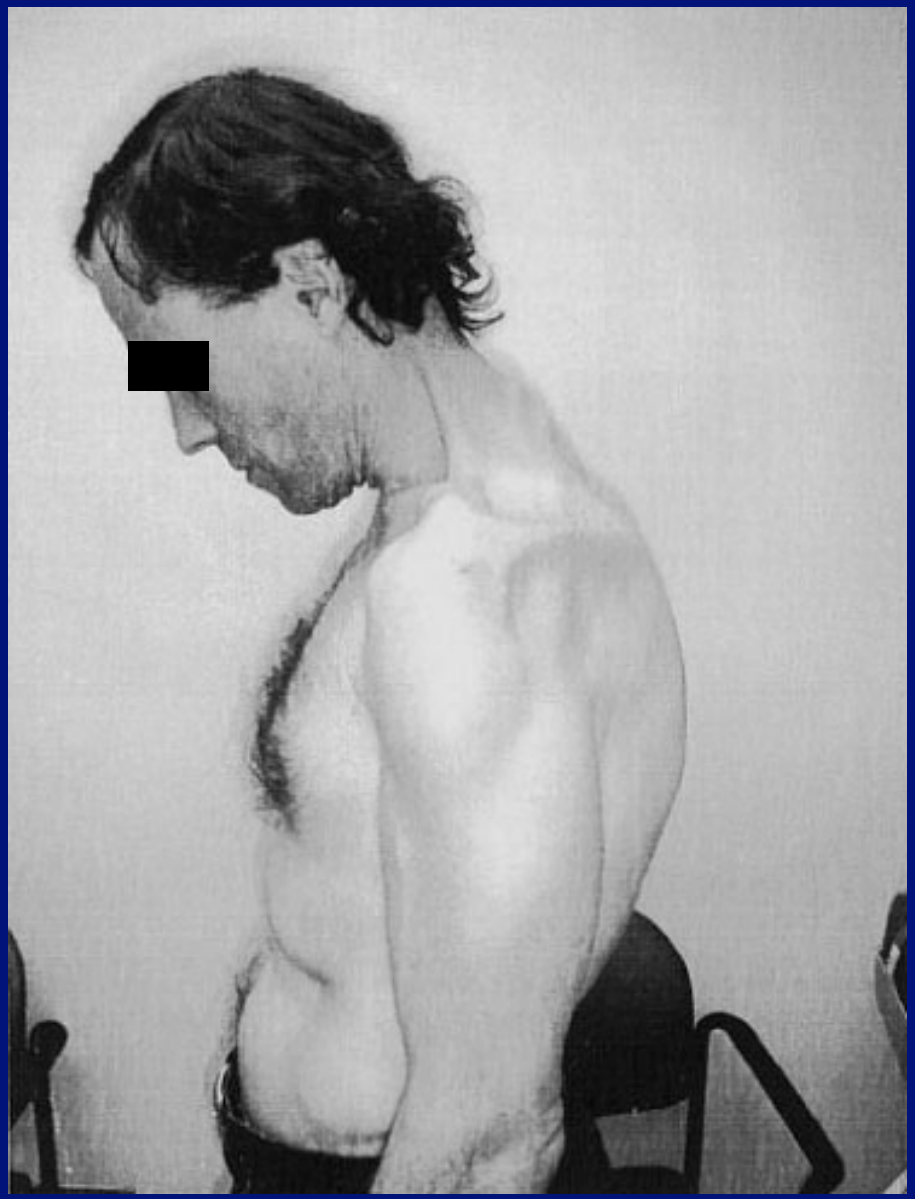
Risk factors

- Younger age (prepubertal)
- Higher dose (> 20 Gy)
- Higher daily fraction (≥ 2 Gy)
- Larger treatment field
- Epiphysis in treatment field

Radiation Treatment Sequelae with Limb-shortening and Muscle Hypoplasia

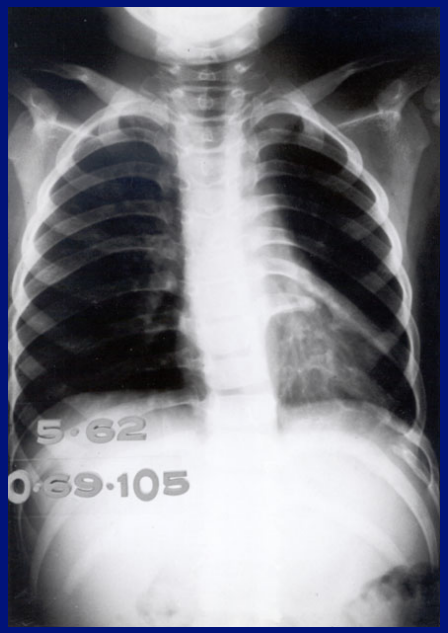


Man Treated With High-Dose Mantle RT for Hodgkin's Lymphoma



12 yrs post RT

2 yr old girl treated with high dose RT to hemi-abdomen for Wilms

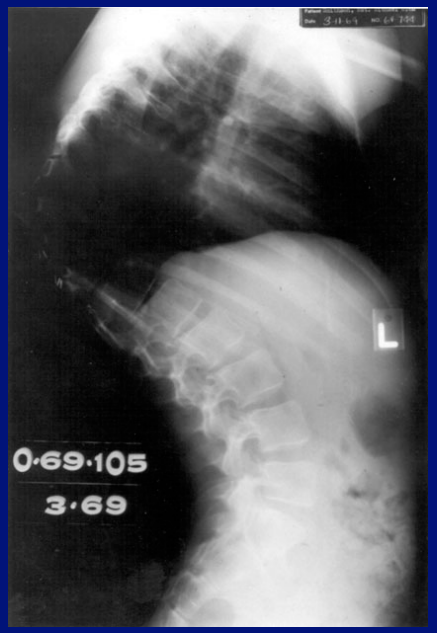


2 yrs post RT

(age 4 yrs)

4 yrs post RT

(age 6 yrs)



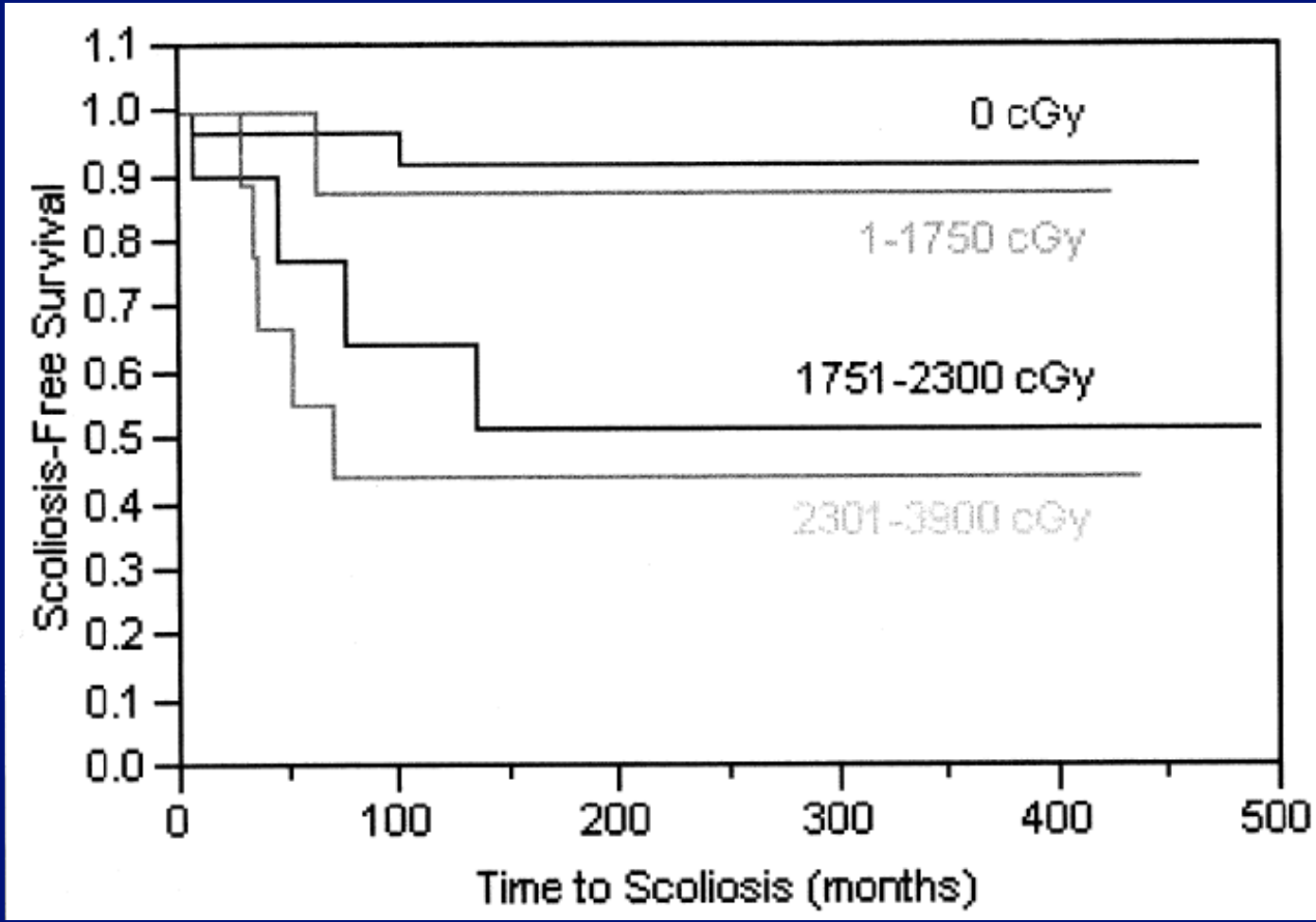
9 yrs post RT

(age 11 yrs)

9 yrs post RT

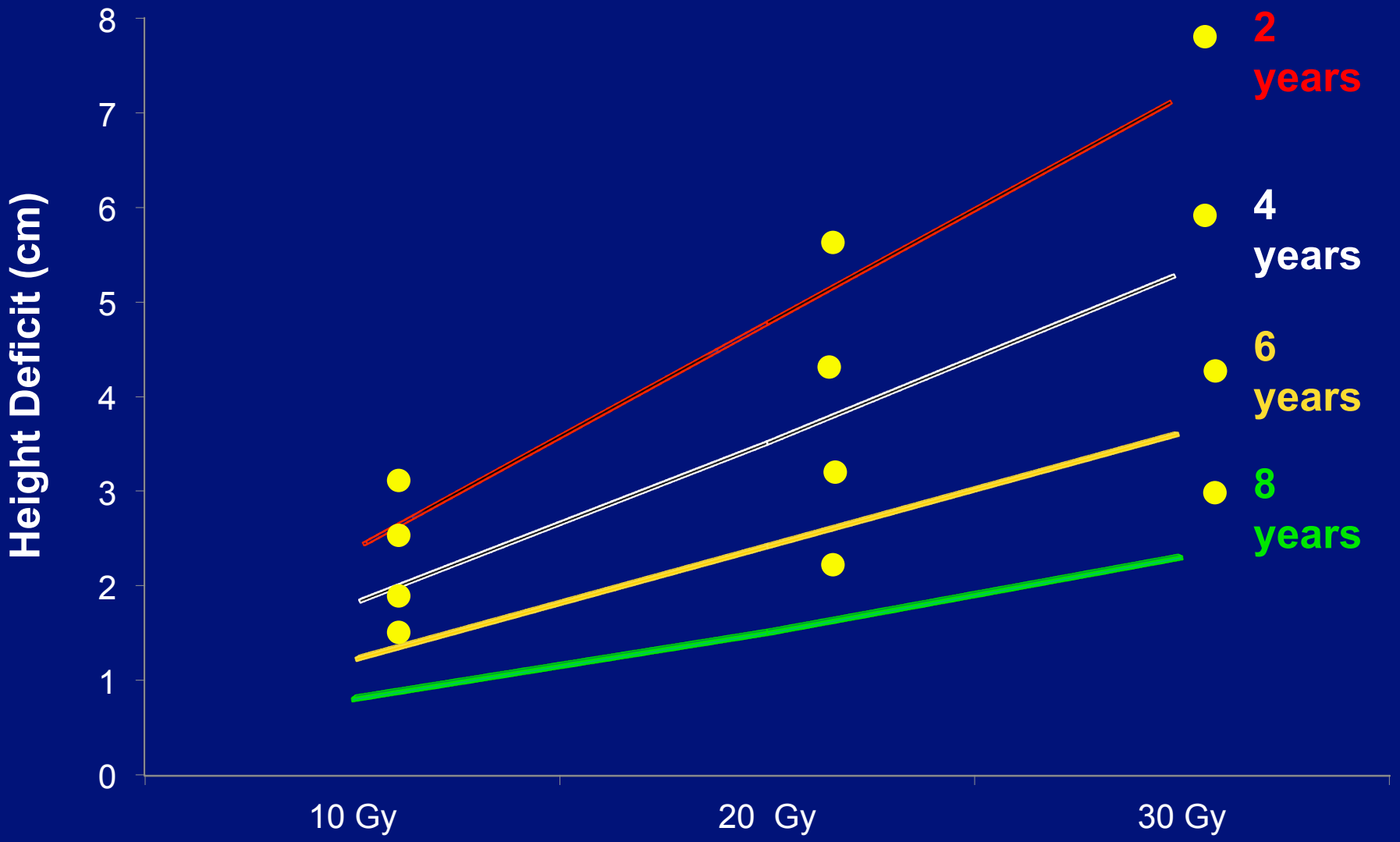
(age 11 yrs)

Scoliosis in Neuroblastoma



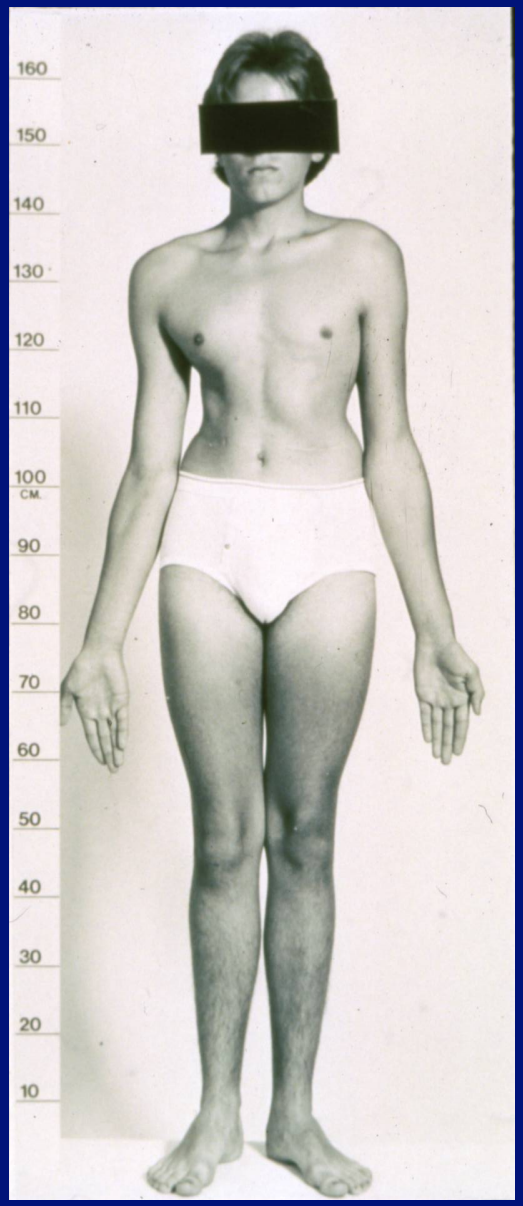
Paulino et al. IJROBP. Volume 61, Number 3, 2005

Height loss as function of age/dose after RT to lumbar spine for Wilms tumor

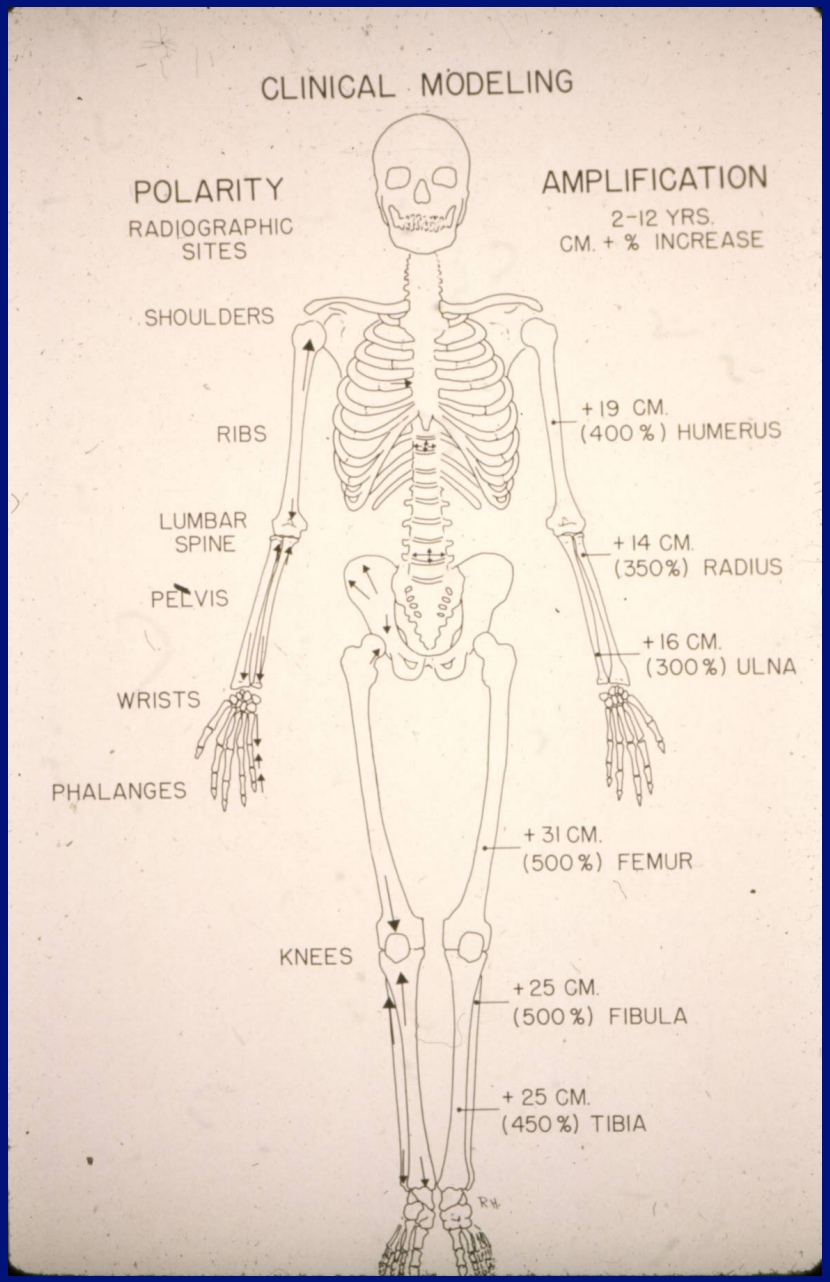


Hogeboom CJ et al. Medical and Pediatric Oncology 2001;36:295-304

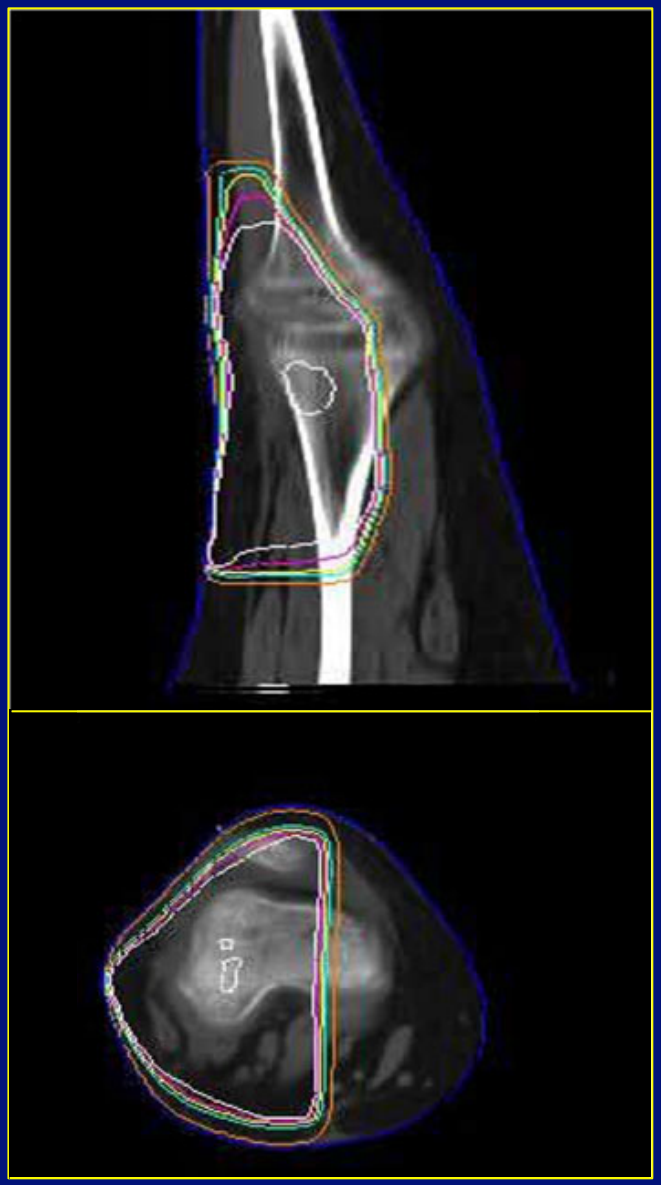
Wilm's Tumor



Bone Growth



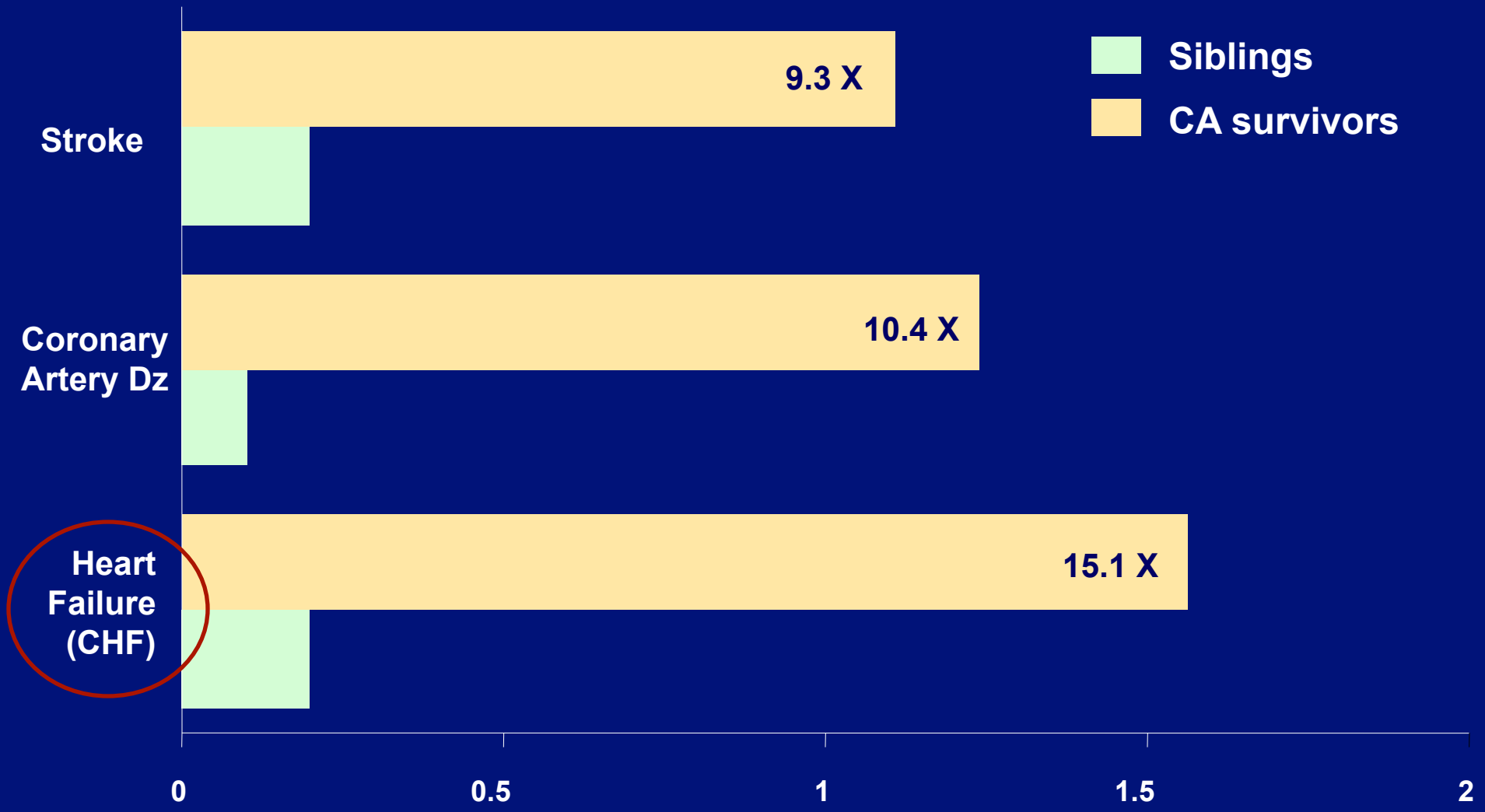
9-year-old Girl Treated With Implants and EBRT For Synovial Cell Sarcoma of Knee



3 yr post RT

Dosimetry

Cardiac Risks after Childhood Cancer: Childhood Cancer Survivor Study (CCSS)



Oeffinger KC, et al. *N Engl J Med* 2006; 355: 1572

Anthracycline Cardiac Injury

Cardiac myocyte injury

Reduced LV wall thickness

Elevated LV afterload

Depressed LV performance

Cardiomyopathy

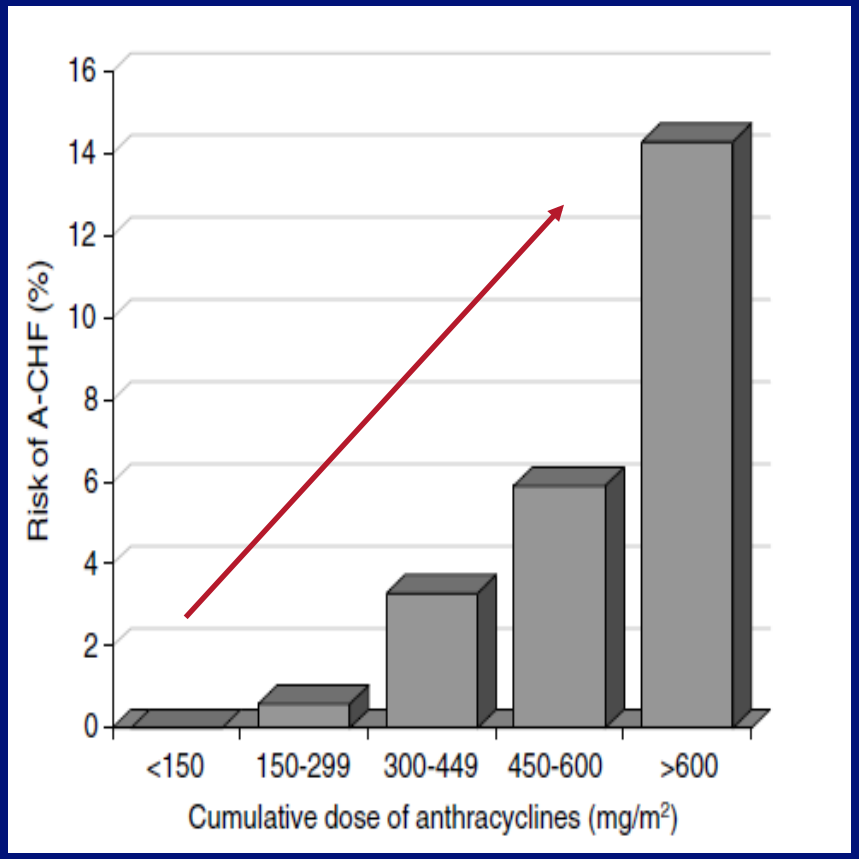
Risk Factors

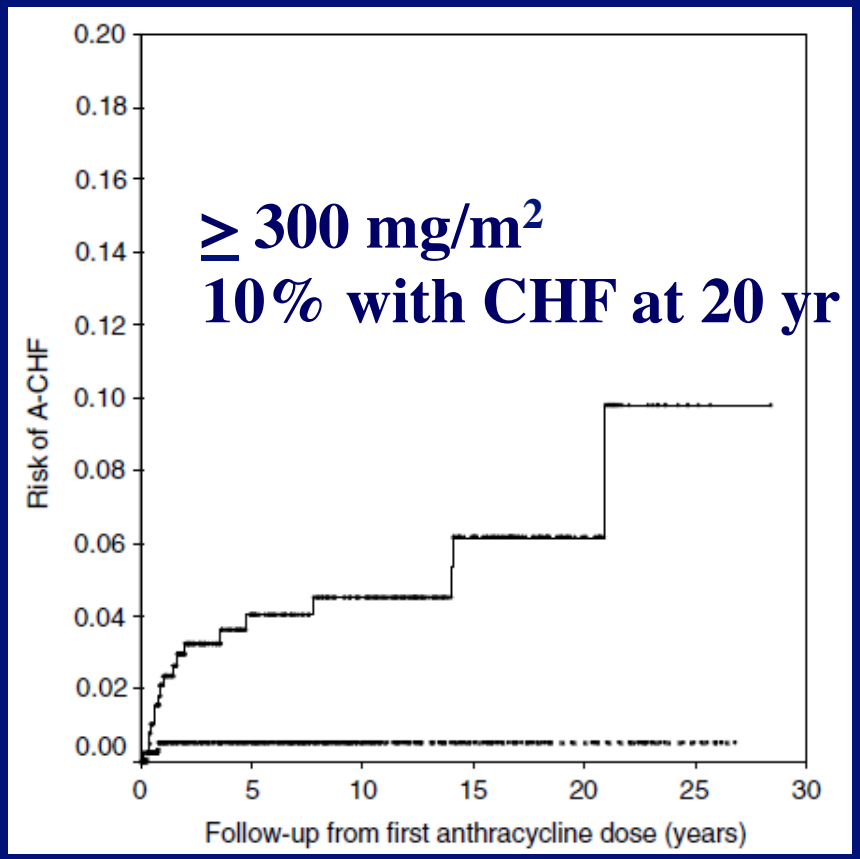
Younger age (< 5 y)
Female sex
African American
Higher dose (> 250/m2)
Use of chest radiation
Longer time from Rx

Manifestations

Cardiomyopathy
Congestive heart failure
Arrhythmia
Sudden death

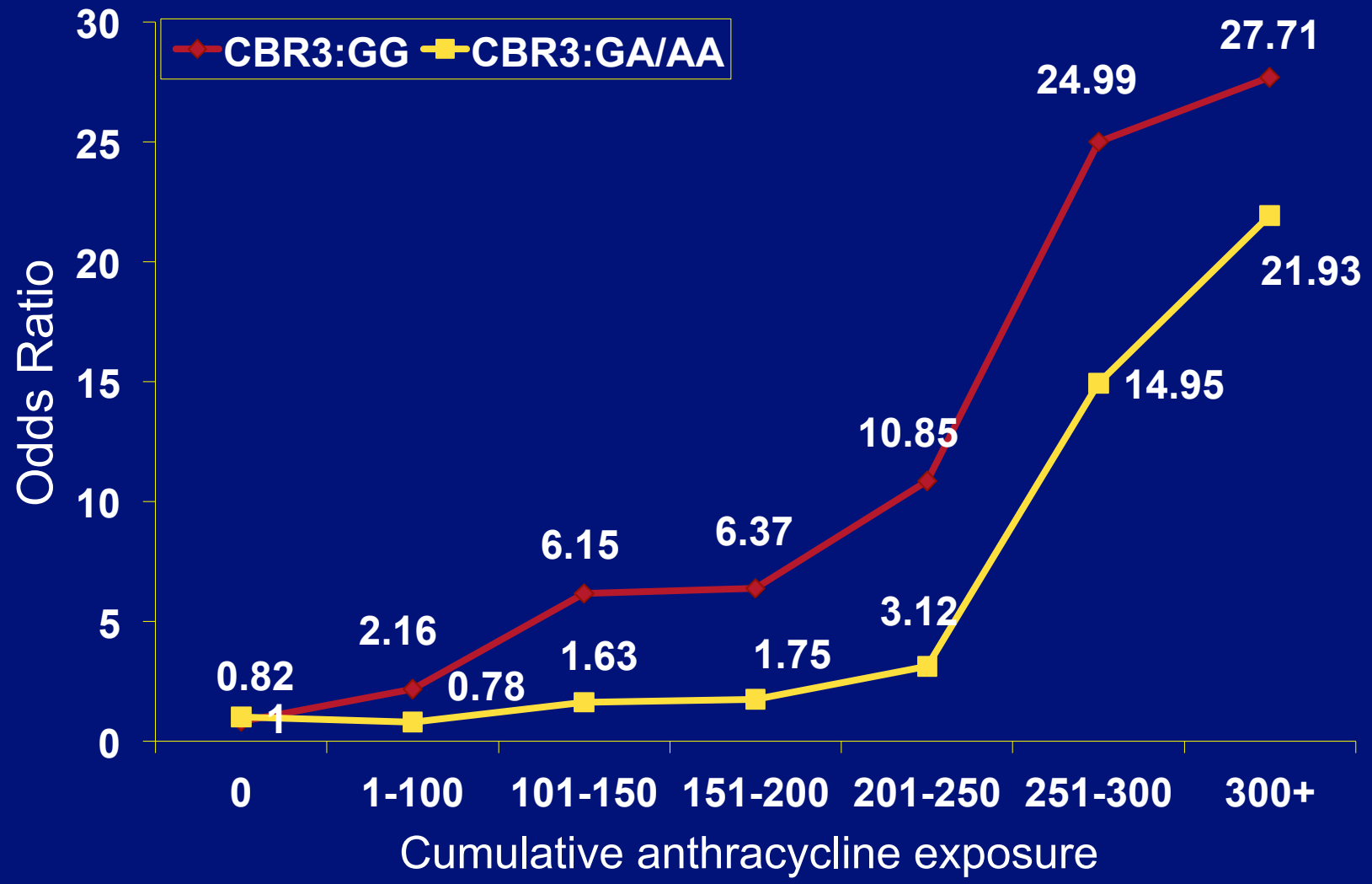
Anthracycline-Induced CHF
830 survivors; 8.5 yrs mean follow-up





van Dalen EC, et al. Eur J Cancer, 2006 (and Kremer LC, J Clin Oncol 2001)

Anthracyclines and risk of cardiomyopathy, stratified by patients' *CBR3* genotype status



Blanco et al. J Clin Oncol, 2012

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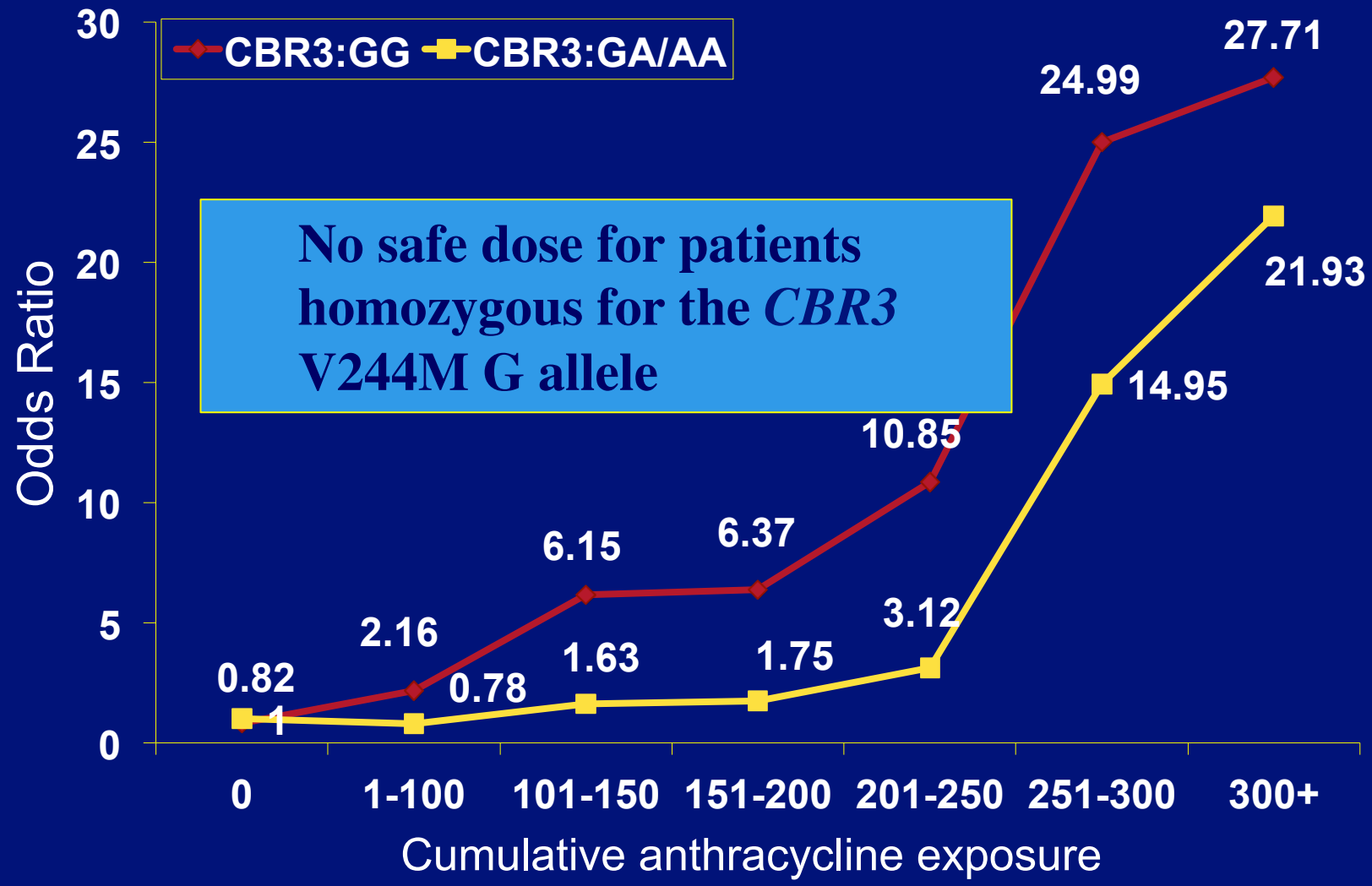
Anthracyclines and risk of cardiomyopathy, stratified by patients' *CBR3* genotype status

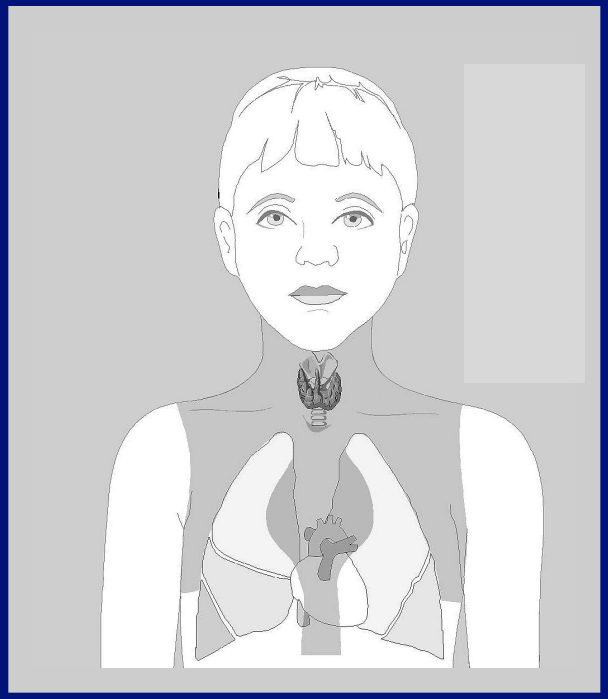


Blanco et al. J Clin Oncol, 2012

Radiation Cardiac Injury

Manifestations

- Restrictive cardiomyopathy
- Premature CAD
- Myocardial infarction
- Valvular disease
- Autonomic dysfunction
- Conduction defects

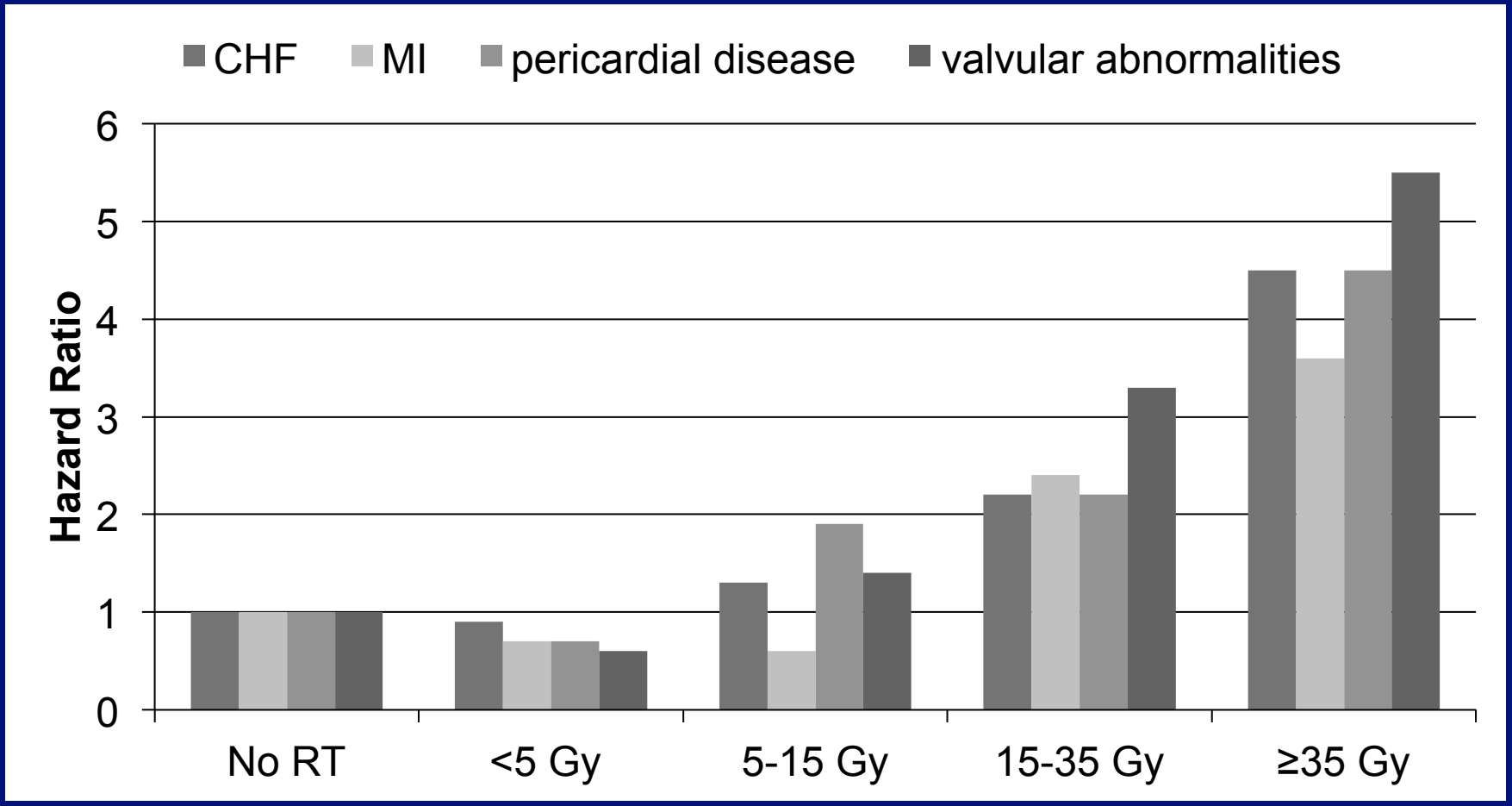


Mantle Field

Risk Factors

- Younger age (< 5 y)
- Higher dose (> 35 Gy)
- Higher daily fraction (≥ 2 Gy)
- Larger volume of heart in field
- Anteriorly weighted field
- Subcarinal shielding
- Longer time from RT
- Use of cardiotoxic chemoRx

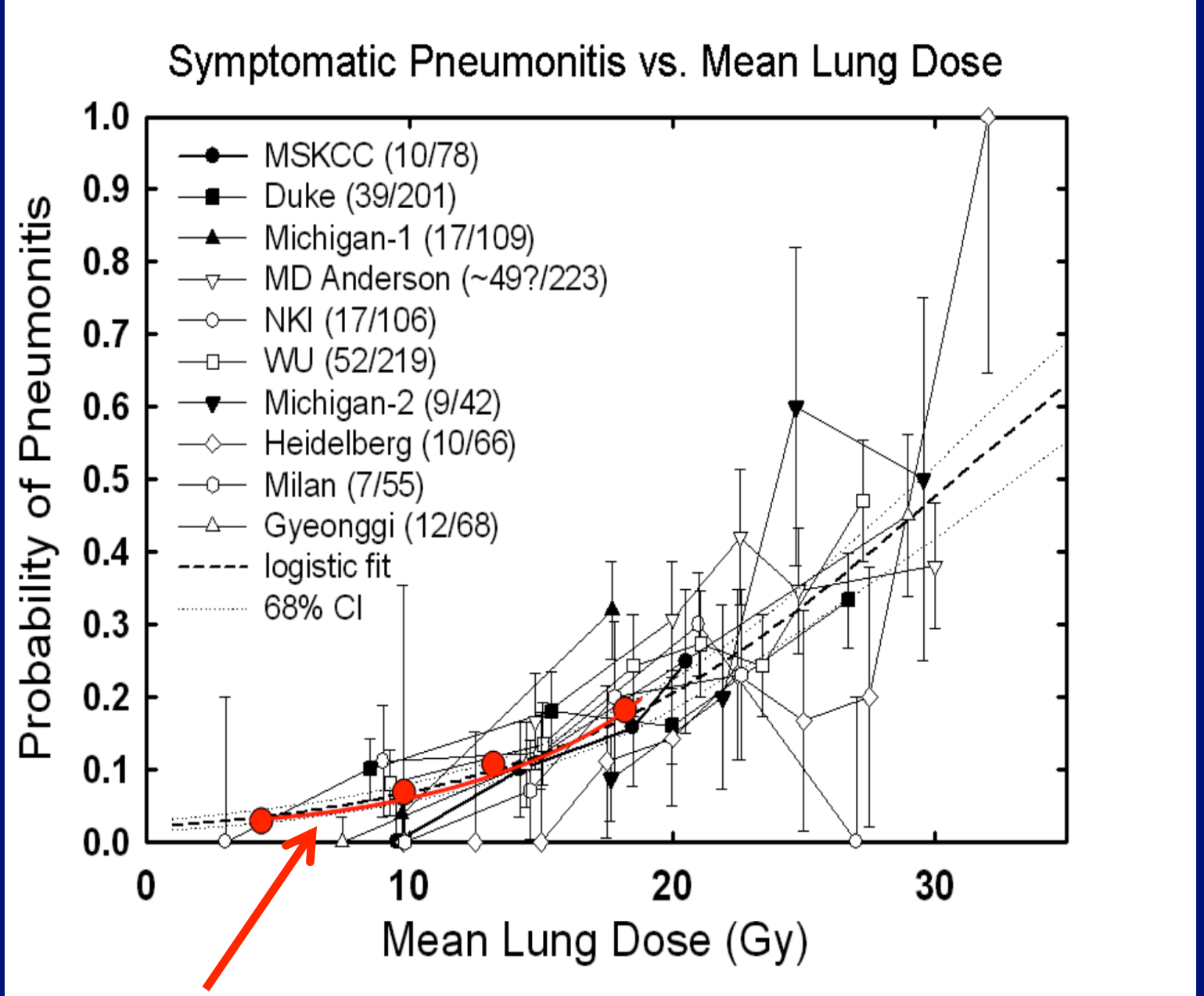
Incidence of CVD vs RT Dose to Heart (Childhood Cancer Survivors)



Adapted from Mulrooney, BMJ 2009

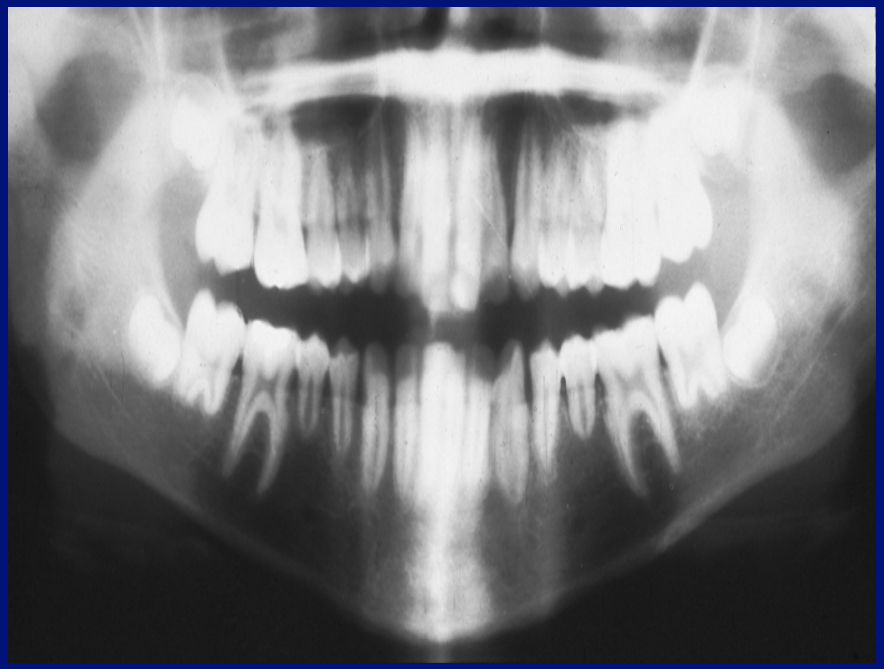
Pulmonary Dysfunction

- Paramediastinal fibrosis
- Pulmonary fibrosis
- Restrictive lung disease
- Pneumothorax



Krasin,Constine, Friedman, Marks. Sem Rad Onc 20:21, 2010

Dental Abnormalities After RT



- Tooth/root agenesis
  - Adontia
  - Microdontia
- Root thinning or shortening
- Enamel dysplasia

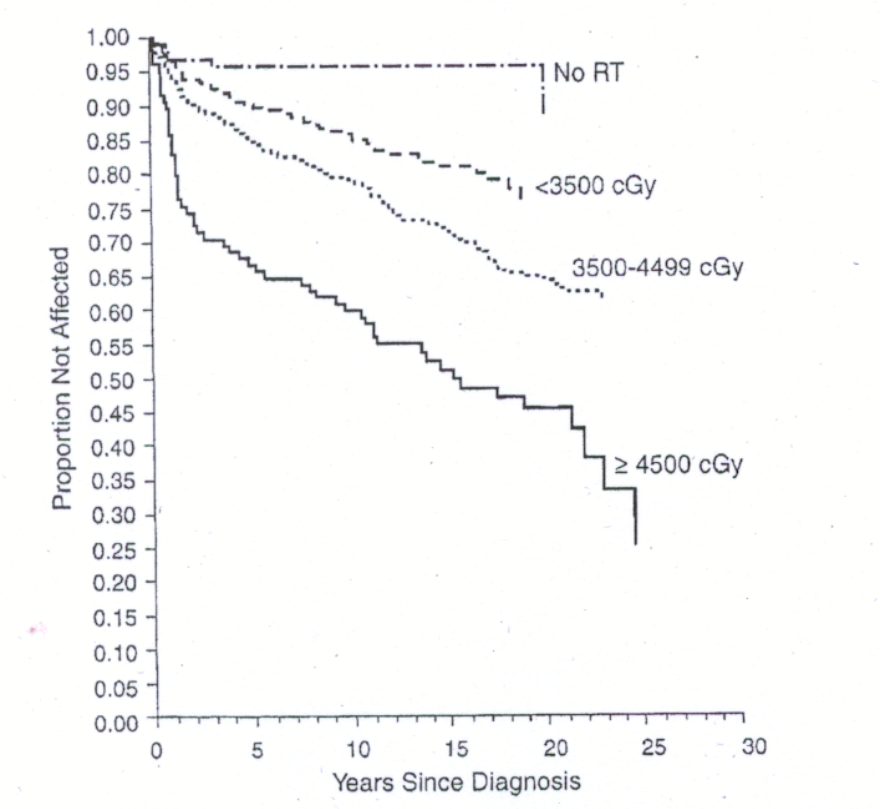
Dose thresholds are age/endpoint dependent: 10-20 Gy

Dental Abnormalities After Radiation

- Salivary gland dysfunction
- Xerostomia
- Dental caries
- Periodontal disease

Dose thresholds relate to salivary gland dysfunction: 20-40 Gy dependent on volume, bilateral v unilateral

Hypothyroidism

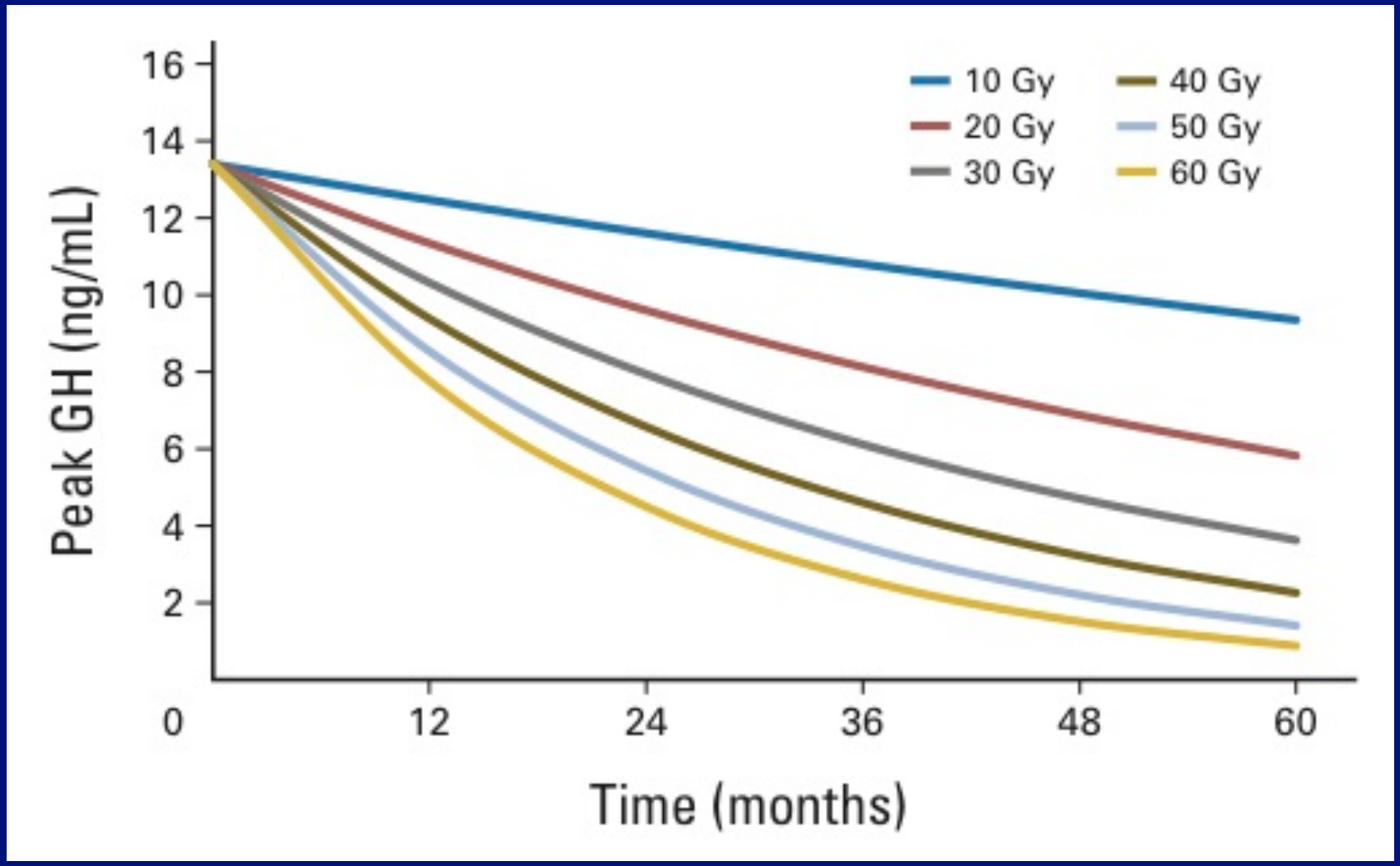


Risk Factors

- Female sex
- Older age (> 15 y)
- Higher radiation dose
  - 30% if 35-44 Gy
  - 50% if > 45 Gy
- Time < 5 y from Dx

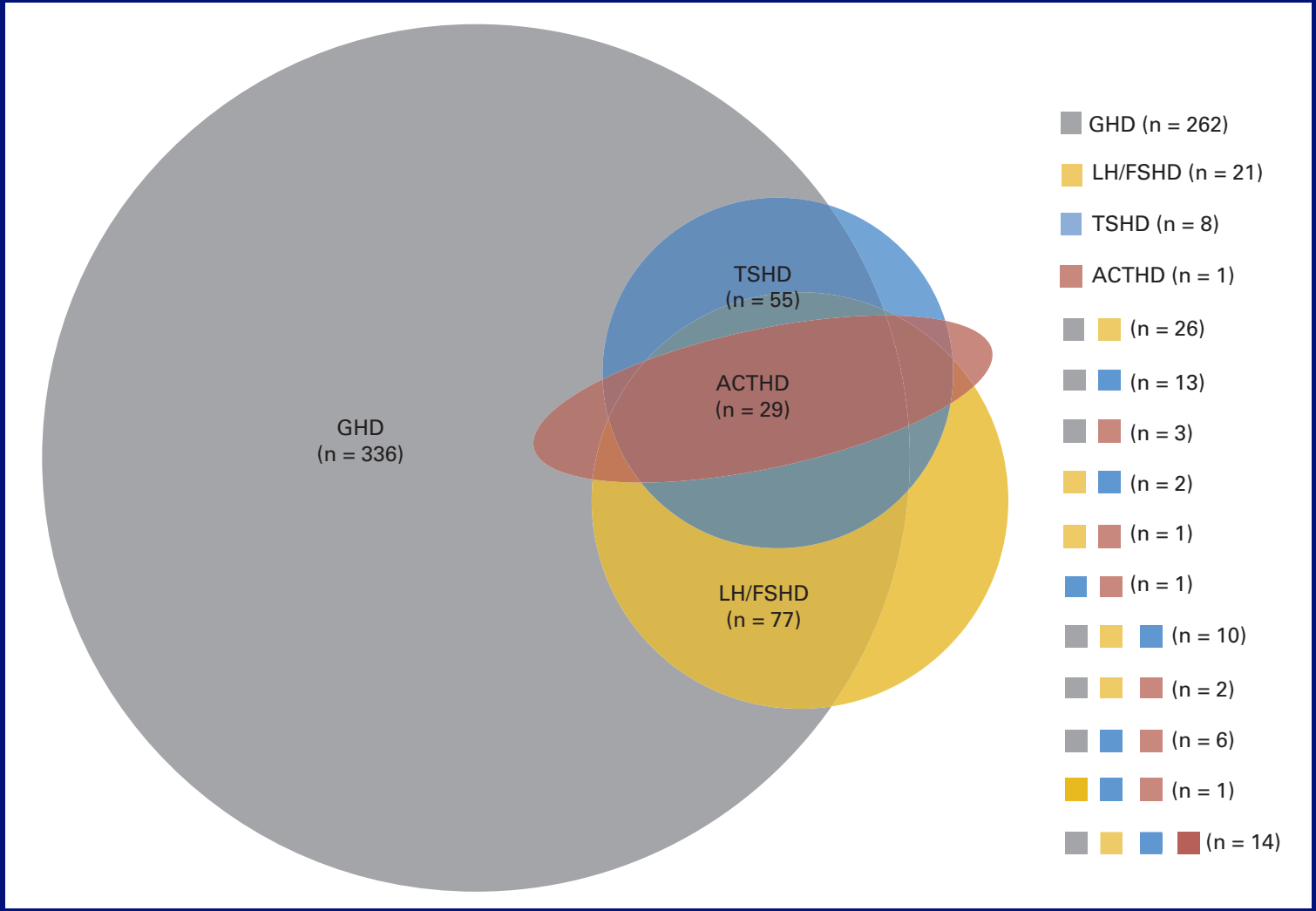
Sklar et al, JCEM 2000

Peak Growth Hormone according to hypothalamic mean dose and time from irradiation



Merchant et al, JCO 29:4776, 2111

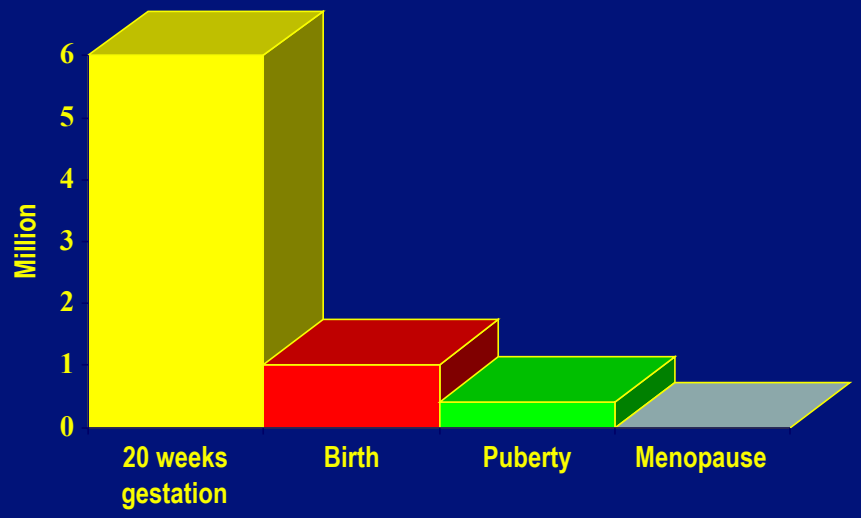
Relative Proportions and Overlap Among Anterior Pituitary Deficiencies Following Cranial Radiotherapy



ACTHD, adrenocorticotropic hormone deficiency
GHD, growth hormone deficiency
LH/FSHD, luteinizing hormone/follicle-stimulating hormone deficiency
TSHD, thyroid-stimulating hormone deficiency

Chemaitilly et al
J Clin Oncol 33:2015

Female Gonadal Dysfunction



Age & Risk of Ovarian Failure

Manifestations:

- Delayed/arrested puberty
- Infertility/early menopause

Risk factors:

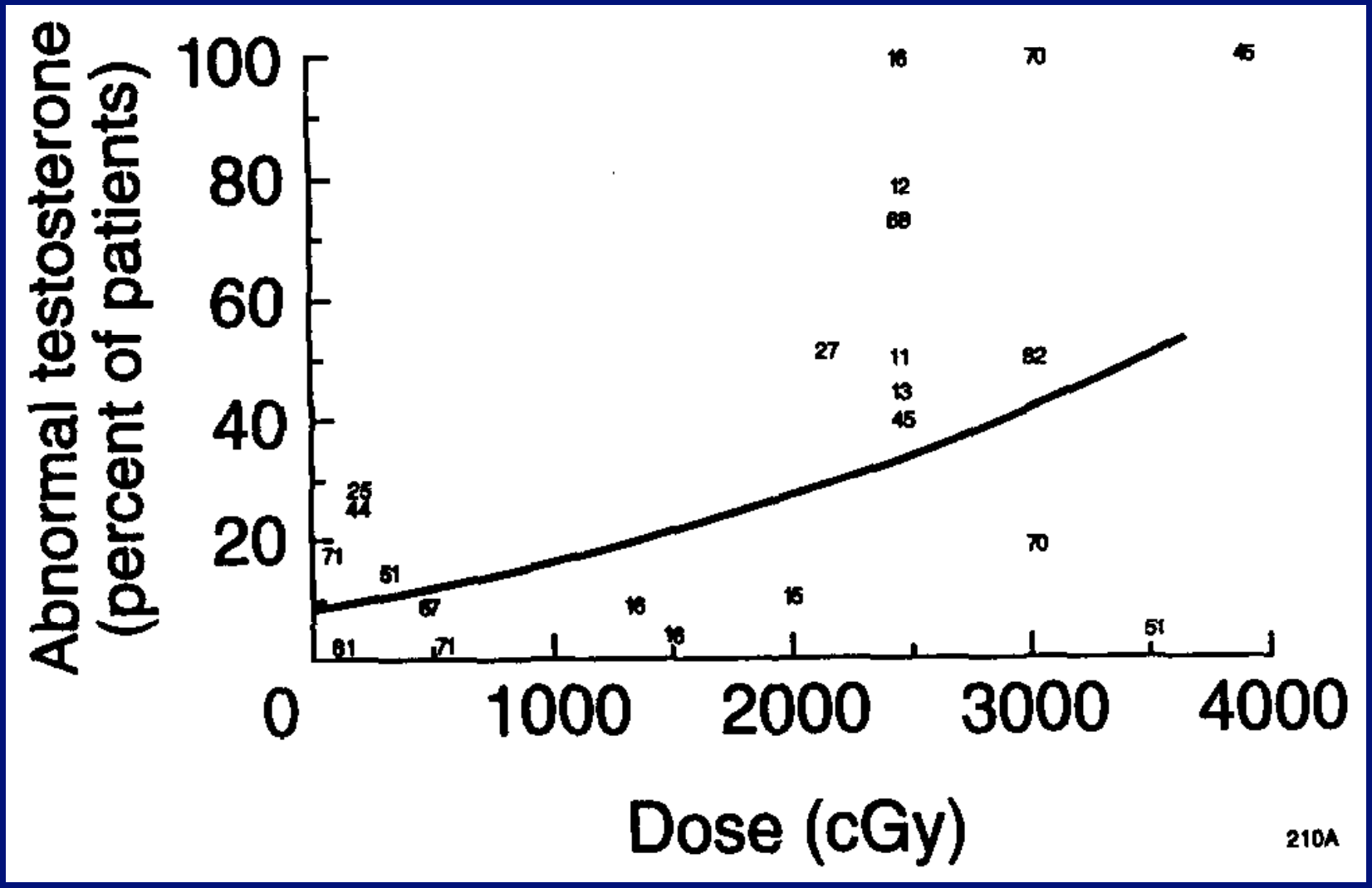
- Older age
- High doses of alkylators
- > 6-10 Gy radiation to pelvis (permanent if > 20 Gy)
- Gonadal radiation combined with alkylators

Effect of Fractionated Testicular Radiation on Sperm Count

Rounded Dose (Gy)	Effect post-RT	Recovery
0.1 – 0.3	Temporary oligospermia	
0.3 – 0.5	Temporary aspermia at 4-12 months	Full recovery by 48 months
0.5 – 1.0	100% temporary aspermia from 3 – 17 months	Recovery begins at 8–38 months
1.0 – 2.0	100% temporary aspermia from 2 – 15 months	Recovery begins at 9–20 months
2.0 – 3.0	100% temporary aspermia beginning at 1-2 months (a certain percentage will suffer permanent aspermia)—large daily fractions	Recovery begins in some cases at 12–14 years
	100% aspermia beginning at about 2 months —small daily fractions	No recovery observed up to 40 months

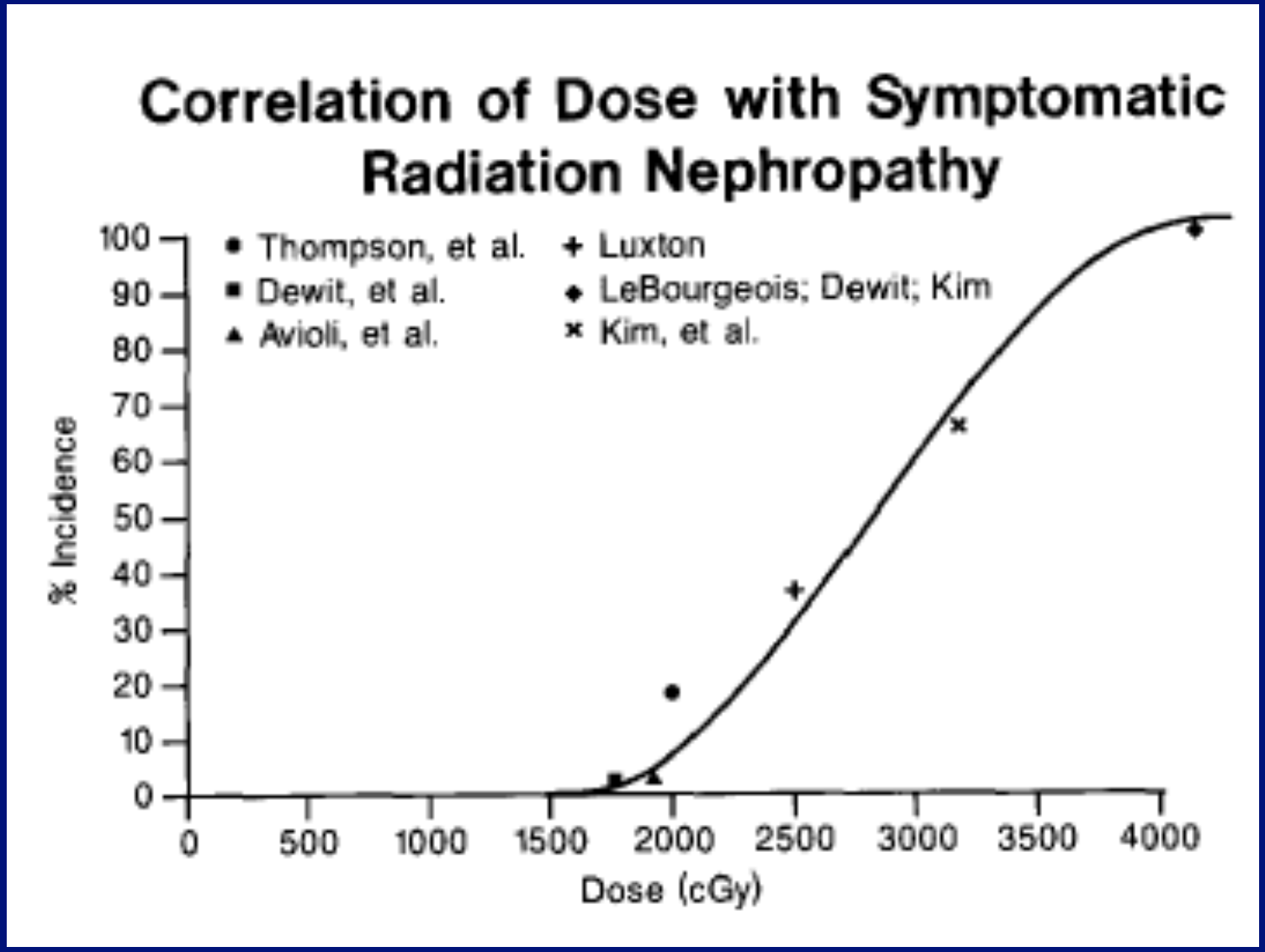
Ash P; Brit J Radiol; 53:271; 1980

Abnormal Testosterone Value vs Radiation Dose to Testicles

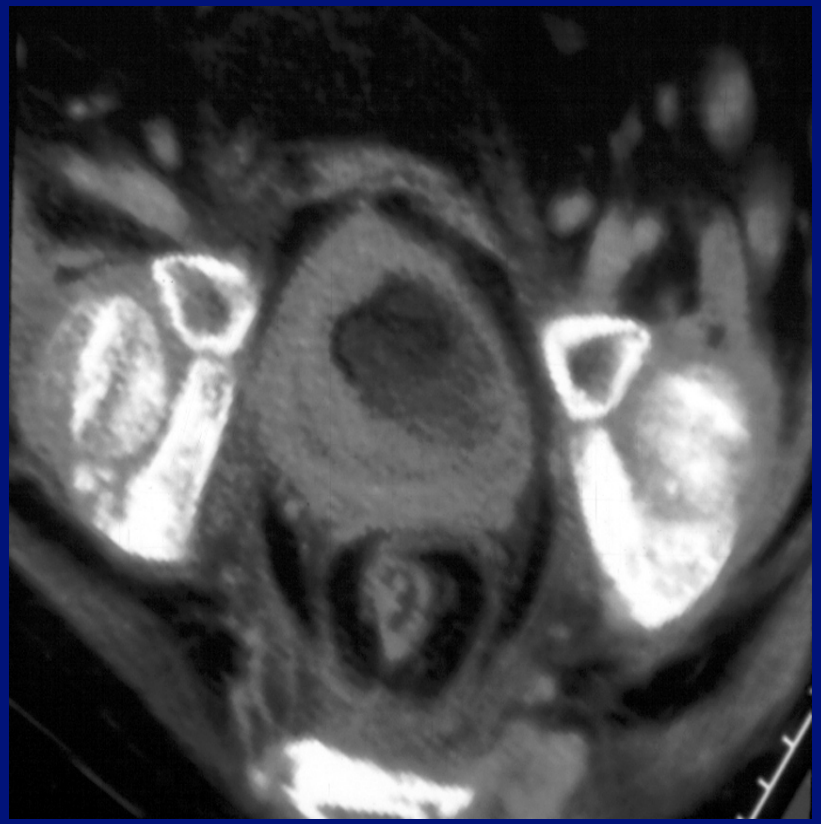


Izard M, Rad & Onc; 34:1 (1995)

Bilateral Whole Kidney RT – non TBI

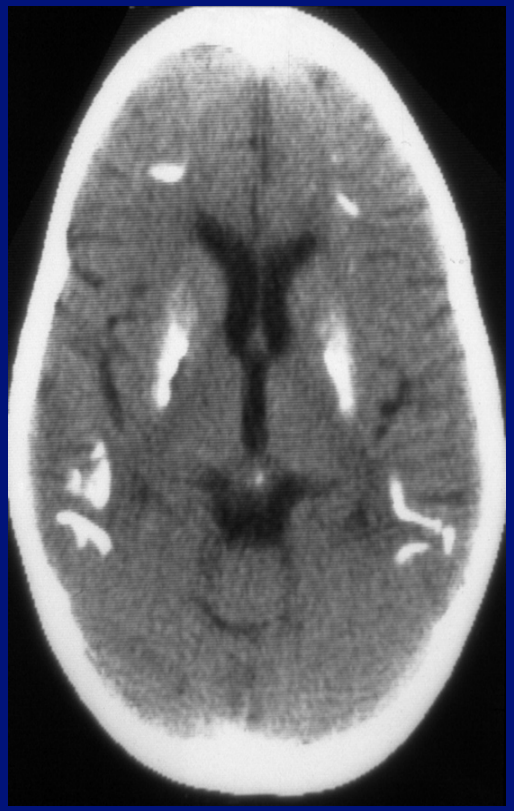


Bladder Complications

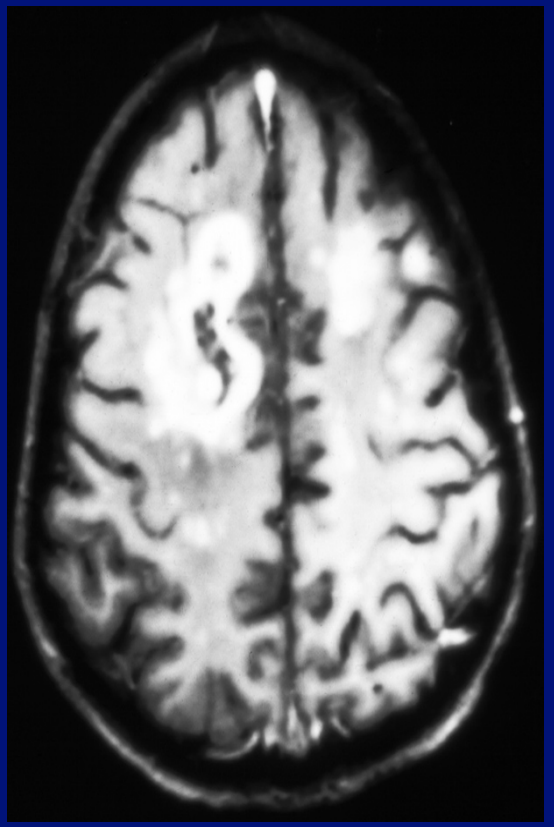


- Hemorrhagic cystitis
- Bladder fibrosis
- Dysfunctional voiding
- Urinary incontinence
- Bladder carcinoma

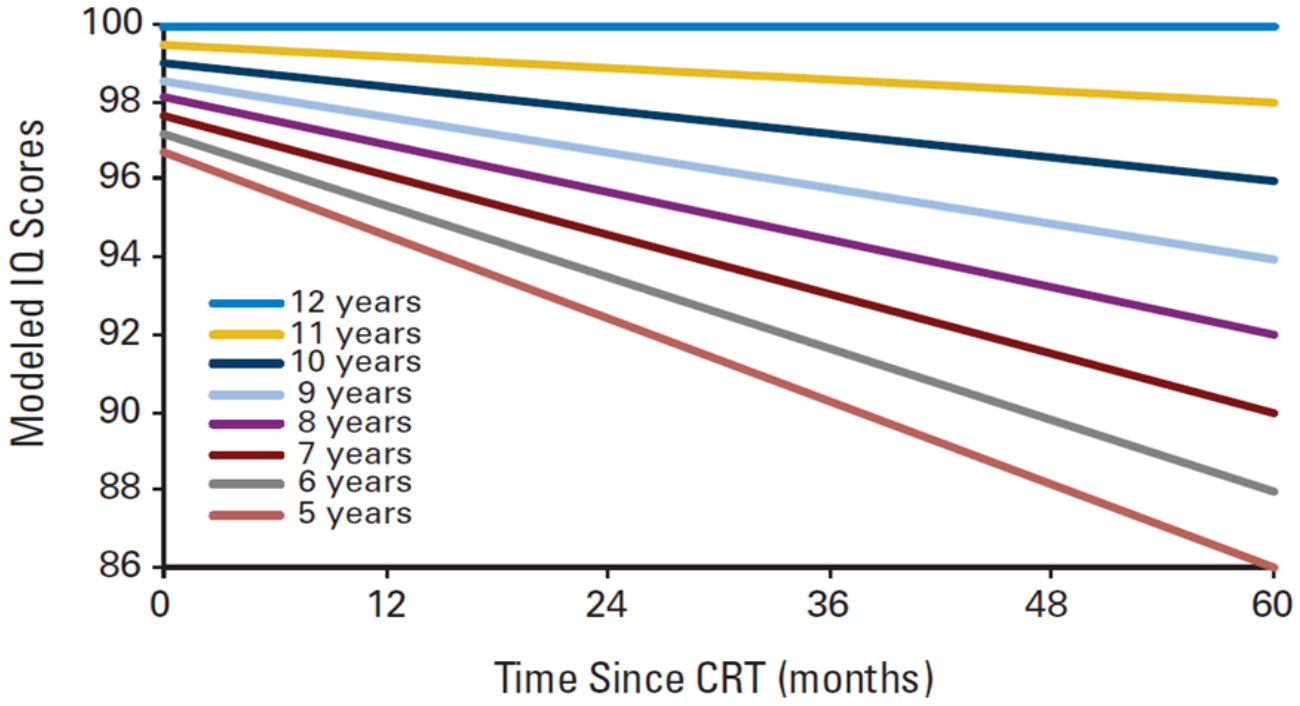
Neuroimaging Abnormalities



- Brain atrophy
- Encephalomalacia
- Cerebral lacunes
- Dystrophic calcification
- Leukoencephalopathy
- Necrosis/gliosis



IQ After Conformal RT for Low Grade Glioma



n = 78
54 Gy
10mm margin

Merchant TE, J Clin Oncol 2009; 27:3691

Hearing loss

- 78 children, 155 ears after RT for BT: 14% hearing loss at 3-5 yrs

Table 1. Incidence of hearing loss for 155 ears of 78 pediatric patients with brain tumor

	Mean cochlear dose (Gy)						
Frequency (Hz)	≤30	35	40	45	50	55	60*
High (6,000 and 8,000 Hz)	0	2	4	5	11	24	37
Intermediate (2,000, 3,000, and 4,000 Hz)	0	0	0	1	5	13	21
Low (250, 500, and 1,000 Hz)	0	0	0	1.5	10	16	22

Incidence of hearing loss expressed as percent.
* Linearly extrapolated to 60 Gy.

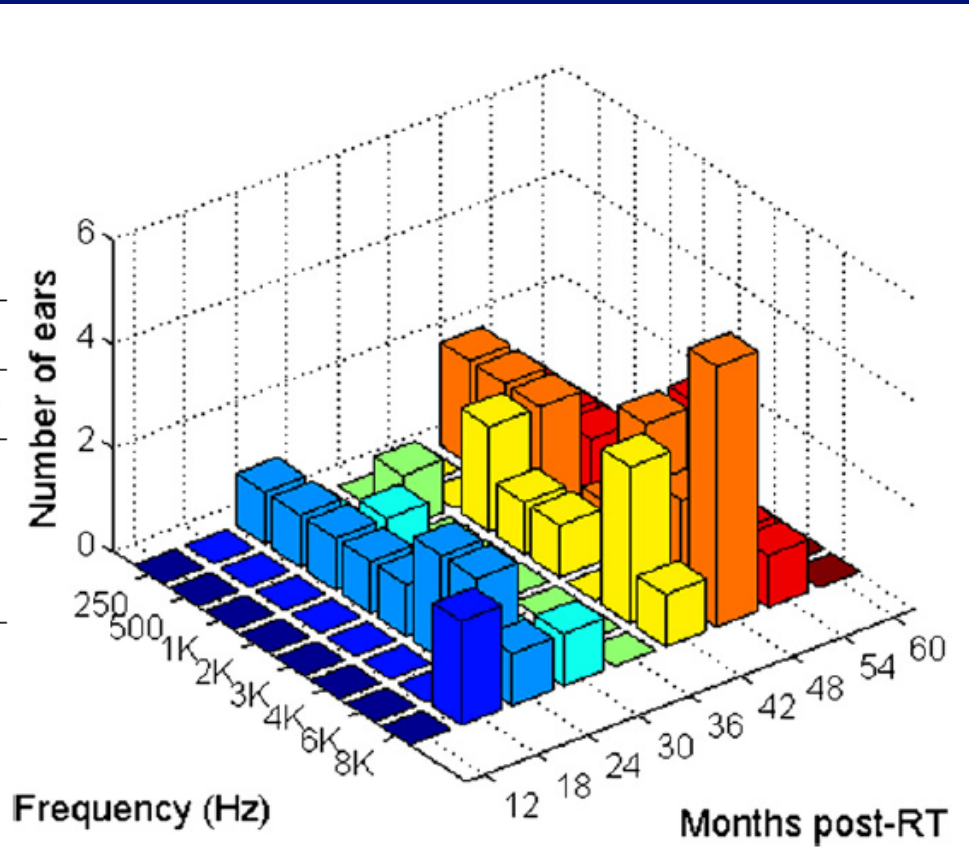


Fig. 5. Histogram of hearing loss onset. RT = radiotherapy.

HUA et al. IJROBP 72:892, 2008

Subsequent Neoplasms

- Overall risk of 5%-12% by 25 years
- Higher risk in specific subgroups
- Determinants of risk:
  - Presence of cancer gene mutation
  - Cancer treatment exposures
  - Environmental factors
  - Lifestyle practices

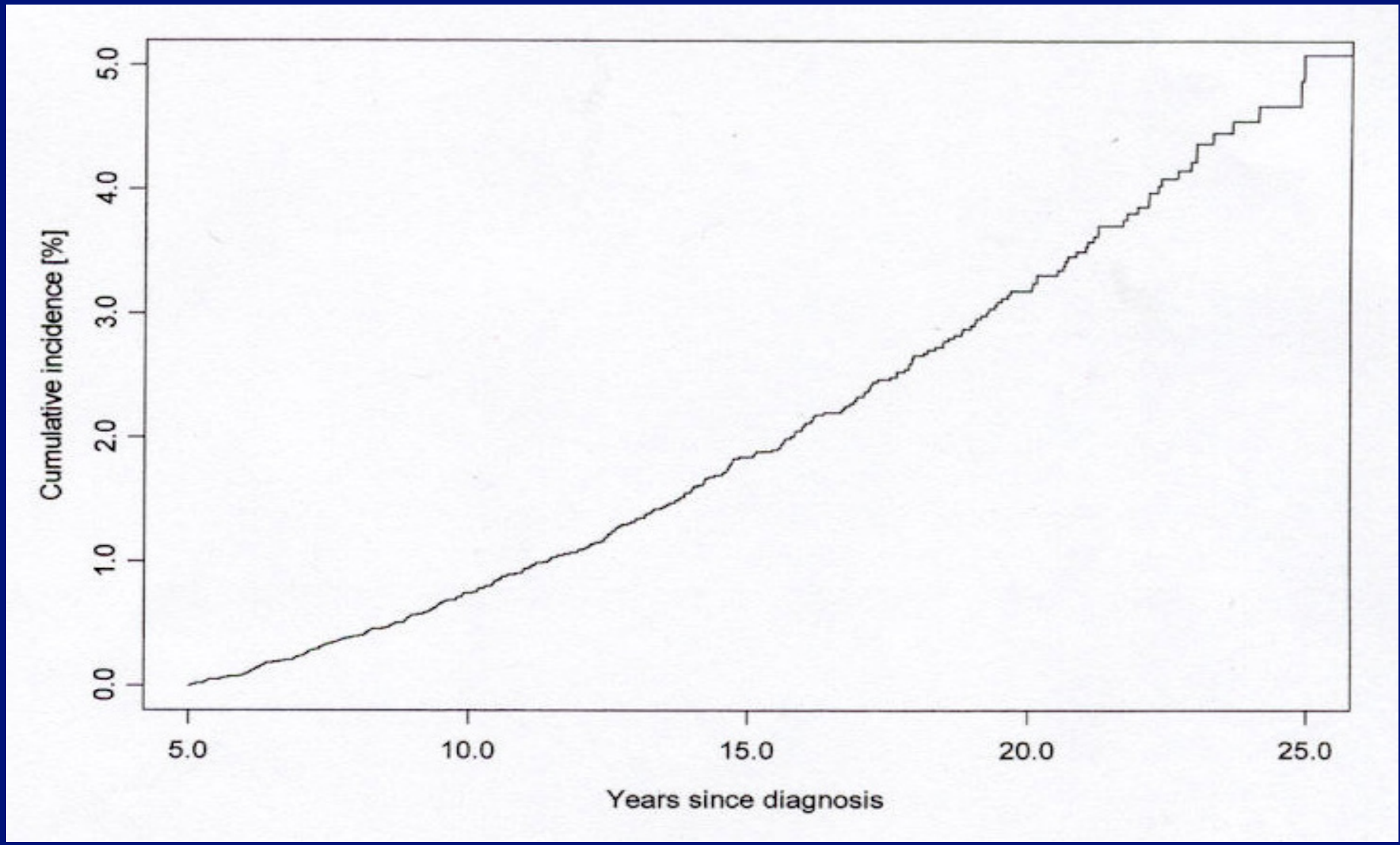
Secondary Acute Myeloid Leukemia

- Brief latency: 3 to 10 years
- Risk related to chemotherapy
  - Alkylating agents
  - Epipodophyllotoxins
- No additional risk after radiation

Second Solid Tumors

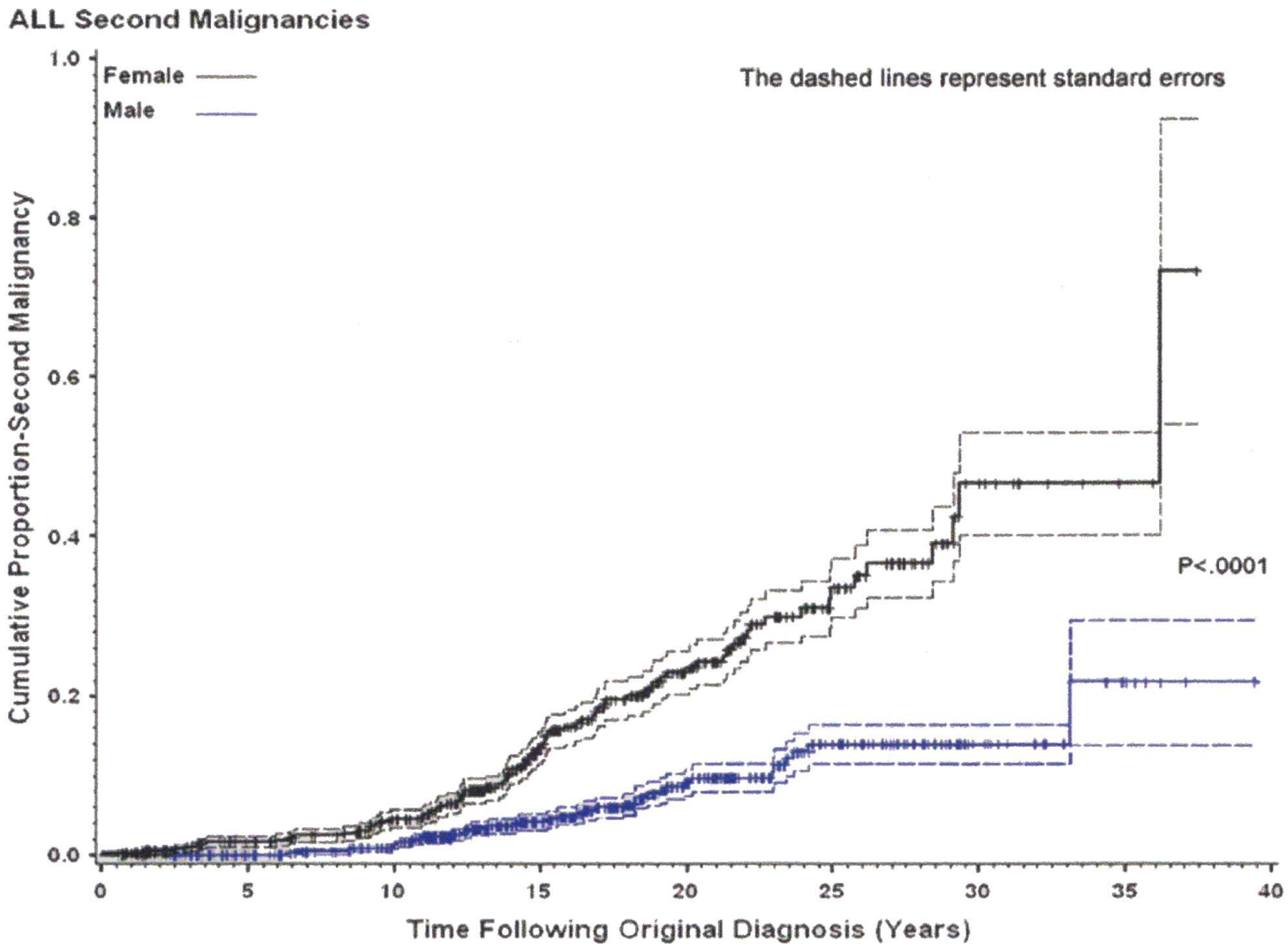
- Long latency period (> 10 years)
- Primarily associated with radiation
- Risk for specific histologies can be enhanced by chemotherapy
- Adult tumor histologies predominate
- Higher risk with cancer gene mutations

Incidence: Second Malignancies



Neglia, 2001

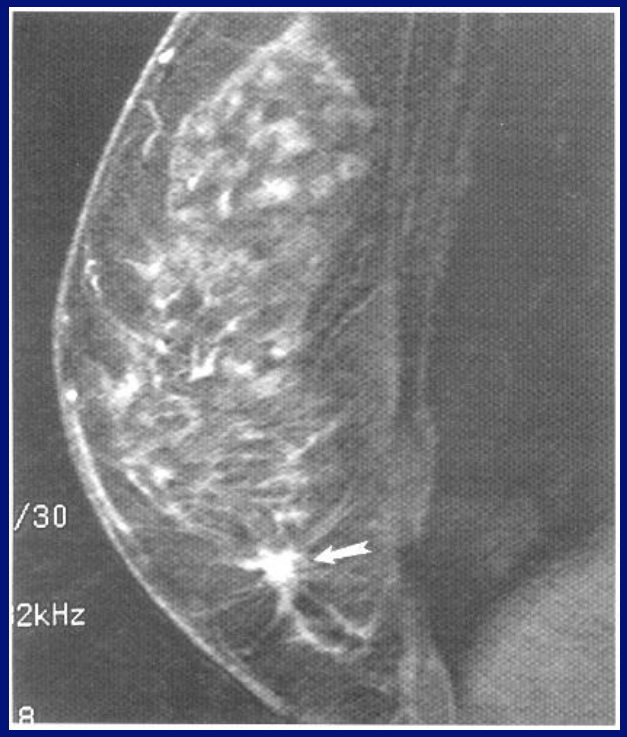
Cumulative Proportion of Second Malignancies After Hodgkin Lymphoma According to Gender



Constine, et al IJROBP 72:24, 2008

Children's Oncology Group

Mammogram and breast MRI annually, starting at the age of 25 or 8 yrs after chest radiation

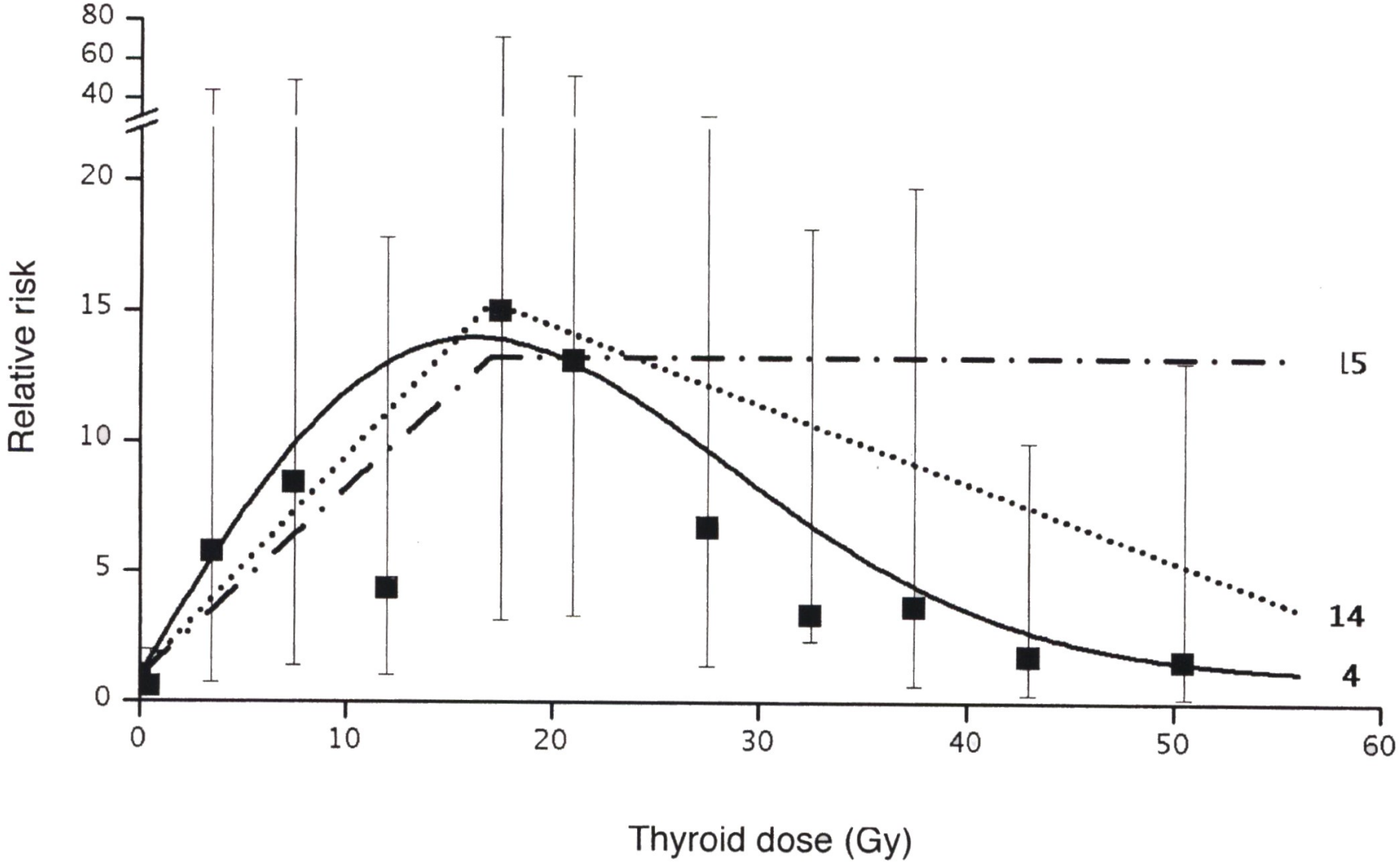


International Meeting for Harmonization of Health Screening and Surveillance Guidelines for Childhood Cancer Survivors

Secondary Breast Cancer

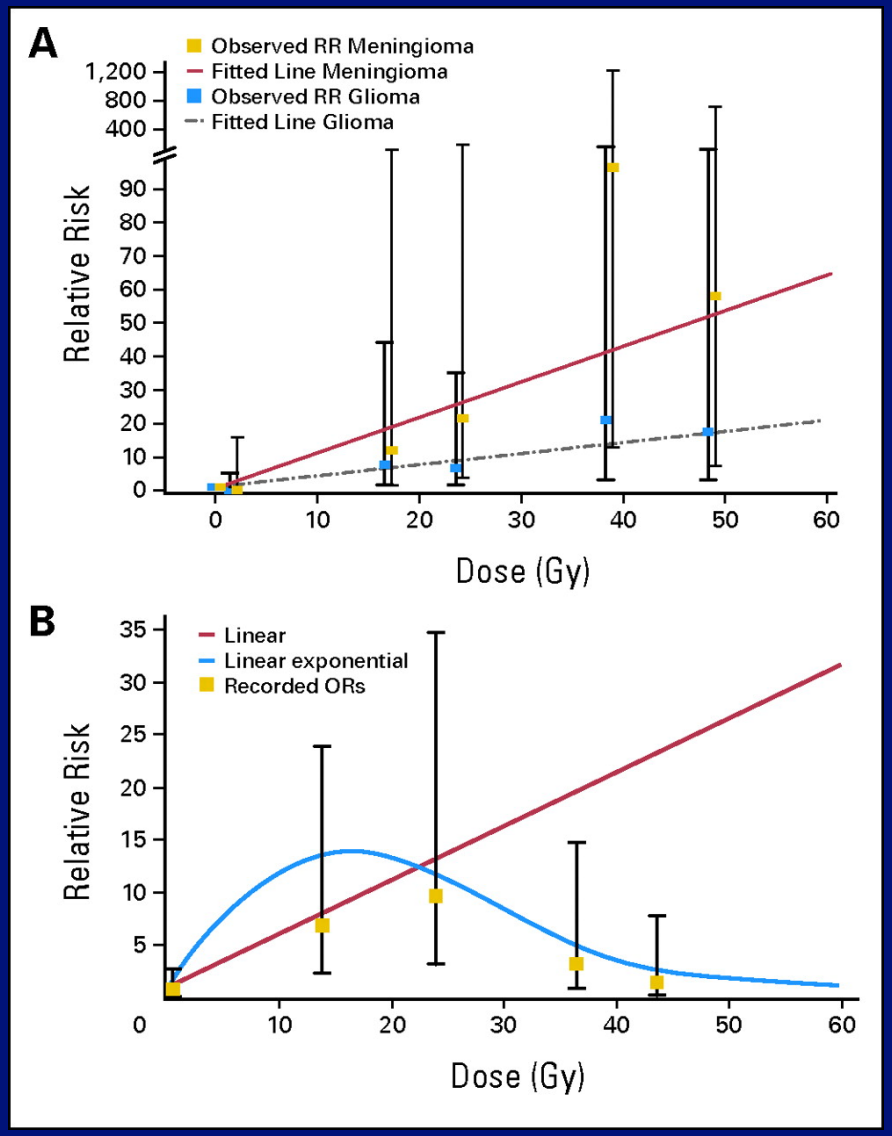
Amsterdam, the Netherlands

Secondary Thyroid Malignancy After RT



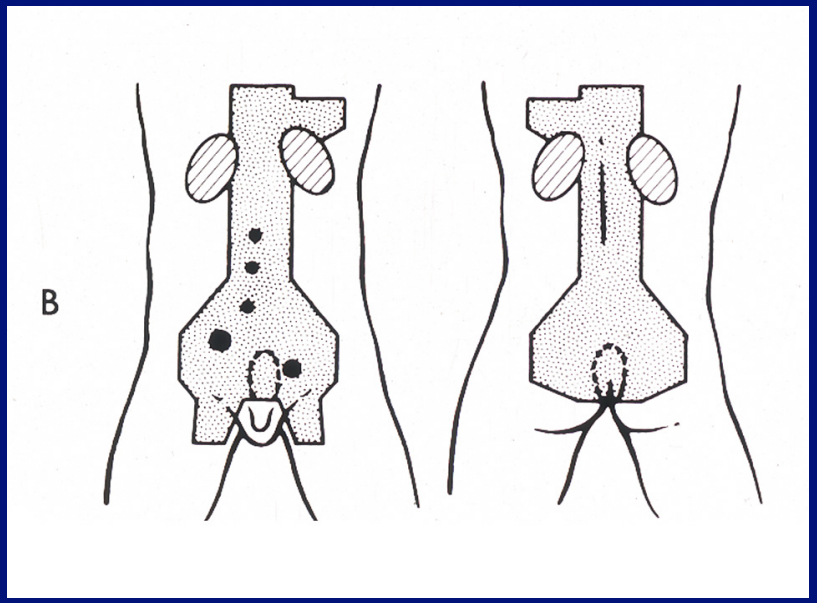
Ronckers et al, Rad Res, 166:618, 2006

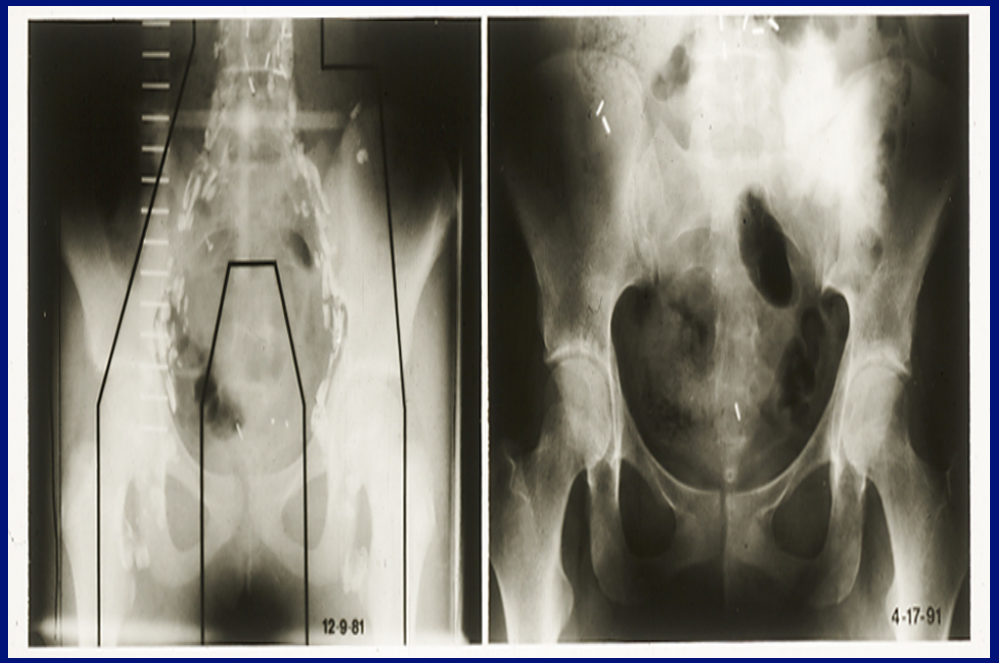
Dose-response Relations Between RT Dose and Relative Risk (RR) of Second Neoplasms



Meadows, A. T. et al. J Clin Oncol; 27:2356-2362 2009

Solid Tumors After Radiation





Conclusions About Late Effects

- Risk depends on tissues and age of patient
- Late effects are dose and modality specific
- Most late effects may be anticipated
- Combined therapy may have additive effects

Make everything as simple as possible, but not simpler.

Or

Make everything as simple as possible, if not simpler.

» Albert Einstein

PENTEC

Pediatric Normal Tissue Effects in the Clinic

Curing Children with Cancer, But At What Cost? PENTEC: Pediatric Normal Tissue Effects in the Clinic, An International Collaboration

Louis S. Constine, MD, FASTRO
Philip Rubin Professor of Radiation Oncology and Pediatrics
Director, Judy DiMarzo Cancer Survivorship Program
Vice Chair, Department of Radiation Oncology

No conflicts of interest

UNIVERSITY of ROCHESTER MEDICAL CENTER

What is PENTEC?

Physicians (radiation and pediatric oncologists, subspecialists), physicists (clinical and modelers), and epidemiologists critically synthesizing existing data to:

- Develop quantitative evidence-based dose/volume guidelines, as impacted by developmental status, to inform RT planning and improve outcomes
- Describe relevant physics issues specific to pediatric radiotherapy
- Propose dose-volume-outcome reporting standards to inform future RT guidelines

What PENTEC will include

Introductory Reports

- Introduction to scientific issues
- Summary of Pediatrics NTCP data and models
- Pediatric bio-developmental considerations
- Pediatric physics aspects
- Epidemiologic considerations
- Improving NTCP and modeling in pediatrics
- Contrasting Pediatrics vs. Adult QUANTEC

Working Groups

Cranial/Brain Stem	***A. Mahajan***
Head/Neck	***A. Paulino***
Stroke	***S. MacDonald***
Endocrine	***G. Wheeler***
Hearing	***T. Yock***
Eye	***J. Buchsbaum***
Thyroid	***M. Milano***
Pulmonary	***MF. McAleer***
Breast	***K. Marcus***
Cardiac	***D. Hodgson***
Gastrointestin. tract	***J. Bradley***
Kidney/bladder	***A. Liu***
Testes/male fertility	***B. Hoppe***
Female Genital	***C. Hill***
Muscle/Skin/Bone	***N. Esiashvili***
Spinal Cord	***N. Laack***
SMN	***K. Roberts***
TBI	***K. Dusenbery***

Visionary Reports

- Methodology for accurate data acquisition on radiation dose distribution
- Biomarkers and surrogate endpoints
- Pediatric imaging issues
- Secondary malignancy as impacted by evolution of technology
- Recommendations for reporting and gathering data—to cooperative groups
- Future directions

Content of organ-specific reports

- Required sections:
  - Anatomy & developmental dynamics
  - Clinical significance
  - Endpoints & Toxicity Scoring
  - Challenges defining volumes: pediatric image issues
  - Review of Dose Volume Response data/risk factors
  - Recommended dose volume (Dose per fraction)
  - Toxicity scoring recommendations
  - Contrast Pediatric & Adult NTCP data
  - Future Investigations

PENTEC Methodology Overview

1. **Identify and select evidence**

   Uniform data extraction

2. **Quantitative and descriptive synthesis**

   Expert opinion Consensus

3. **Conclusions and recommendations**

Identify and Select Evidence

PICO

P	Childhood Cancer Patients
I	Radiotherapy
C	Internal control group (no RT) or general population
O	Musculoskeletal development

Research question

What is the association between radiation dose/volume and the risk impairment of __"endpoint"__ ?

Search filters

RT pentec AND skeletal problems AND children; Limits: Humans

Search results, PubMed, date 2014.09.08

1. **Identify and select evidence**

   Uniform data extraction

2. **Quantitative and descriptive synthesis**

   Expert opinion Consensus

Synthesis

Heterogeneity

- Radiation exposure assessment
  - Radiation technique
  - Prescribed vs. absorbed (measured) dose
  - Volume, fractionation

- Covariates
  - Age at RT / attained age
  - Chemotherapy/Surgery/SCT/other treatments

- Follow-up
  - Duration
  - Completeness

- Outcome
  - Definition of endpoints
  - Methodology for assessment

Anticipated Hurdles and Potential Solutions for Modeling

Ideal dataset: associates dose/volume for an organ with a specific endpoint, impacted by age at RT and interval to endpoint.

Anticipated problems:

1. Reports containing dose/volume data are limited and may not have adequate spread for reliable curve fitting
2. Definitions of endpoints across institutions may vary (e.g. hearing loss thresholds; various cognitive and behavioral outcome measures)
3. Data only reports age range and median (or mean), or lumps all patients into one group, or arbitrarily divides into different groups (e.g. young vs. old)

Anticipated Hurdles and Potential Solutions for Modeling (continued)

4. Dose-fractionation schemes or dose rates vary
5. Extent of irradiation or dose distribution varies (whole lungs vs. partial lungs; proton vs. photon)
6. Many organs were exposed, or no organ-specific dose data were reported (e.g. TBI)
7. Chemo regimens and surgical techniques evolved (confounding factors)

Identify and select evidence

Uniform data extraction

Quantitative and descriptive synthesis

Expert opinion Consensus

3. Conclusions and recommendations

Conclusions and Recommendations

Conclusions

- What we know
- And what we don't know yet

Recommendations

- Constraints
- Impact of covariates
- Outcome definitions
- Research priorities to answer clinical questions

PENTEC Steering Committee

• Louis S Constine *Chair* (University of Rochester)	Louis_Constine@urmc.rochester.edu
• Søren Bentzen: (University of Maryland)	SBentzen@som.umaryland.edu
• Cécile Ronckers: (Emma Children's Hospital)	C.M.Ronckers@amc.uva.nl
• Sughosh Dhakal: (University of Rochester)	Sughosh_dhakal@urmc.rochester.edu
• Chia-Ho Hua: (St. Jude)	Chia-Ho.Hua@STJUDE.org
• David Hodgson: (University of Toronto)	David.Hodgson@rmp.uhn.on.ca
• Melissa Hudson: (St. Jude)	Melissa.Hudson@stjude.org
• Andrew Jackson: (MSK Cancer Center)	jacksona@mskcc.org
• Leontien Kremer: (Emma Children's Hospital)	L.C.Kremer@amc.uva.nl
• Larry Marks: (University of North Carolina)	marks@med.unc.edu
• Mary Martel: (MD Anderson)	mmartel@mdanderson.org
• Michael Milano: (University of Rochester)	Michael_Milano@urmc.rochester.edu
• Arthur Olch: (Univ of S.CA)	AOlch@chla.usc.edu
• Marilyn Stovall: (MD Anderson)	mstovall@mdanderson.org
• Jackie Williams: (University of Rochester)	Jackie_Williams@urmc.rochester.edu
• Tim Schultheiss: (City of HopeMedicalCenter)	Schultheiss@coh.org
• Ellen Yorke: (MSK CancerCenter)	Yorkee@mskcc.org

We are working hard:

- To cure children with cancer
- To minimize late effects

And we are making progress!