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Curing Children with Cancer, But At What Cost? PENTEC: Pediatric Normal Tissue Effects in the Clinic, emphasizing radiation therapy

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Director, Judy DiMarzo Cancer Survivorship Program
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No conflicts of interest

What is PENTEC?

A group of physicians (radiation and pediatric oncologists, subspecialists), physicists (clinical and modelers), epidemiologists who intend to critically synthesize existing data to:

- Develop quantitative evidence-based dose/volume guidelines 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

PENTEC session content

- How organ development complicates normal tissue radiation response in children/adolescents
- Scope of problem: normal tissue toxicity in children
- Epidemiologic considerations in understanding and synthesizing evidence
- Methodologic complexities in analyzing data: age, developmental status, dose, volume, chemotherapy interactions, on and on and on

Follow-up of children who survive cancer

Should be individually tailored but may not be necessary for all

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S O C I E T Y

MEDICINE

Young Survivors in a Deadly War

More and more young people are beating cancer, but many find that getting well is only half the battle

cer

(CO);
(SB)

Medical surveillance of long-term survivors of cancer

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Kevin C. Oeffinger, MD
Leslie L. Robison, PhD

2762 JAMA, June 27, 2007—Vol 297, No. 24 (Reprinted)

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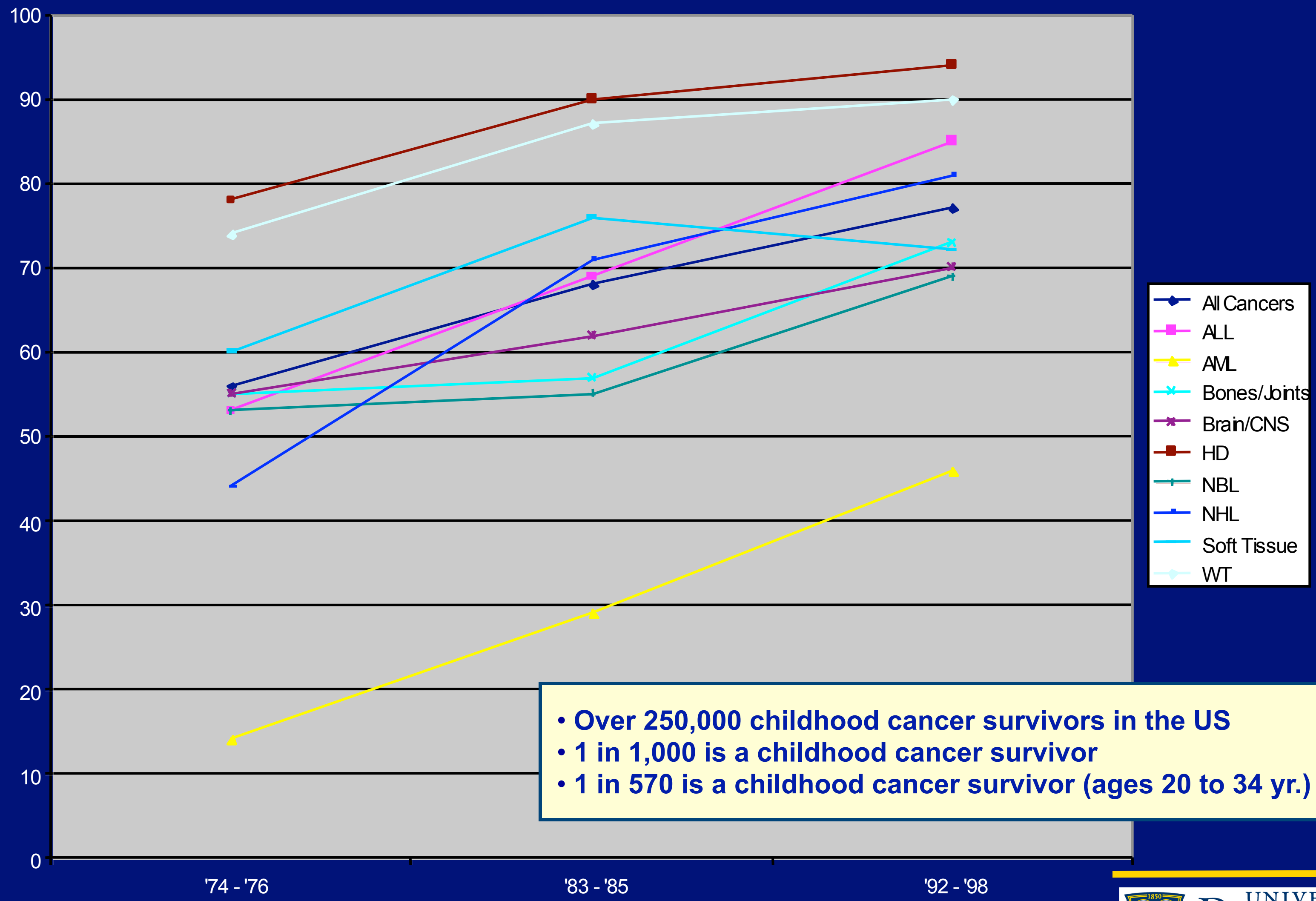
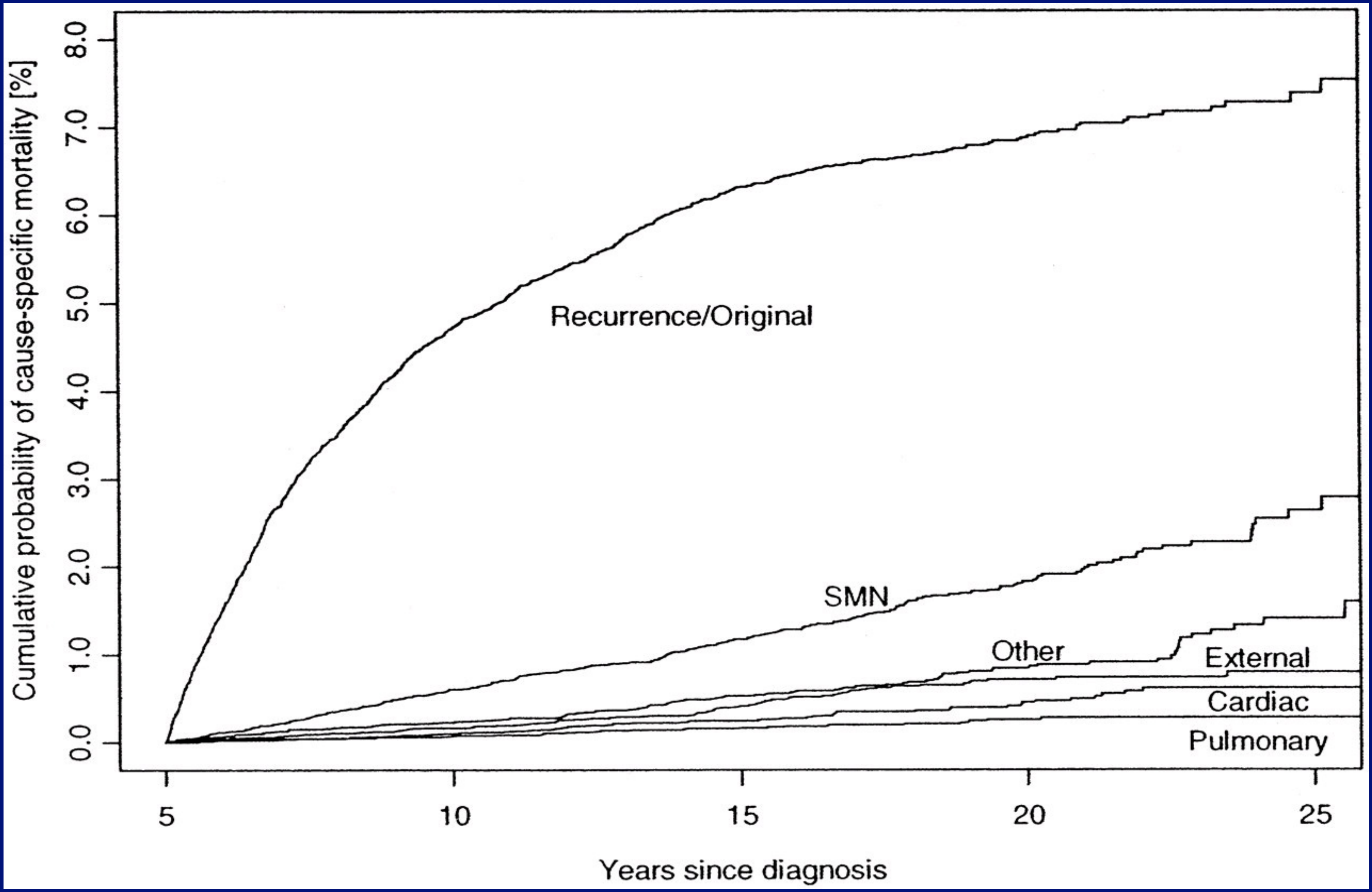
Five-Year Relative Survival Rates



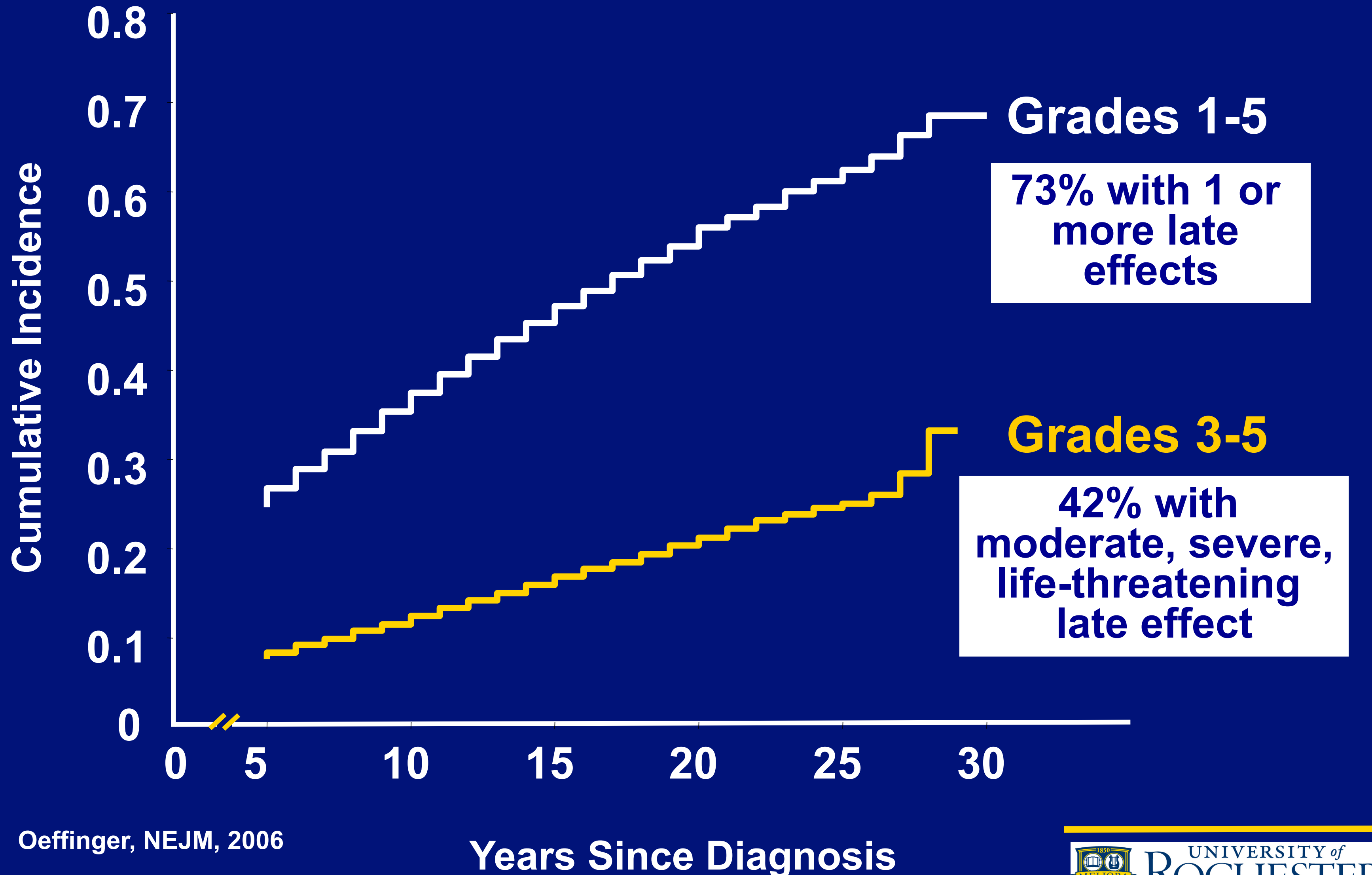
- Over 250,000 childhood cancer survivors in the US
- 1 in 1,000 is a childhood cancer survivor
- 1 in 570 is a childhood cancer survivor (ages 20 to 34 yr.)

Cumulative Cause-Specific Mortality



Mertens JCO, 2001. 19:3163-72

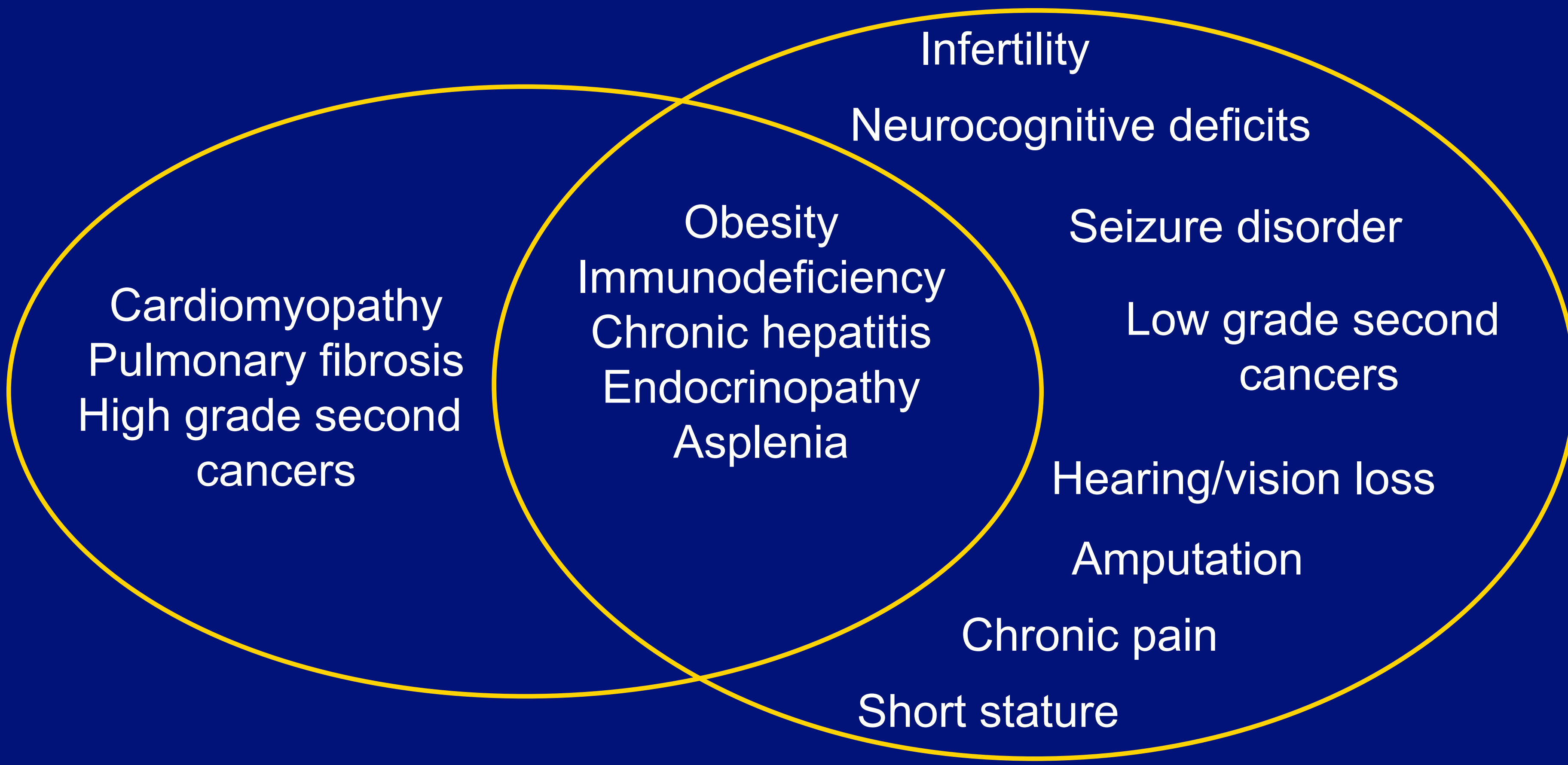
Incidence of Health Conditions in 10,397 Adults in Children's Cancer Survivor Study



Oeffinger, NEJM, 2006

Spectrum of Treatment Effects

Life-Threatening → Life-Altering



University of Rochester Medical Center

As we know, there are known knowns. There are things we know we know. We also know there are known unknowns.

» **Donald Rumsfeld**

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

Why the difference?

Children

Impairment of growth

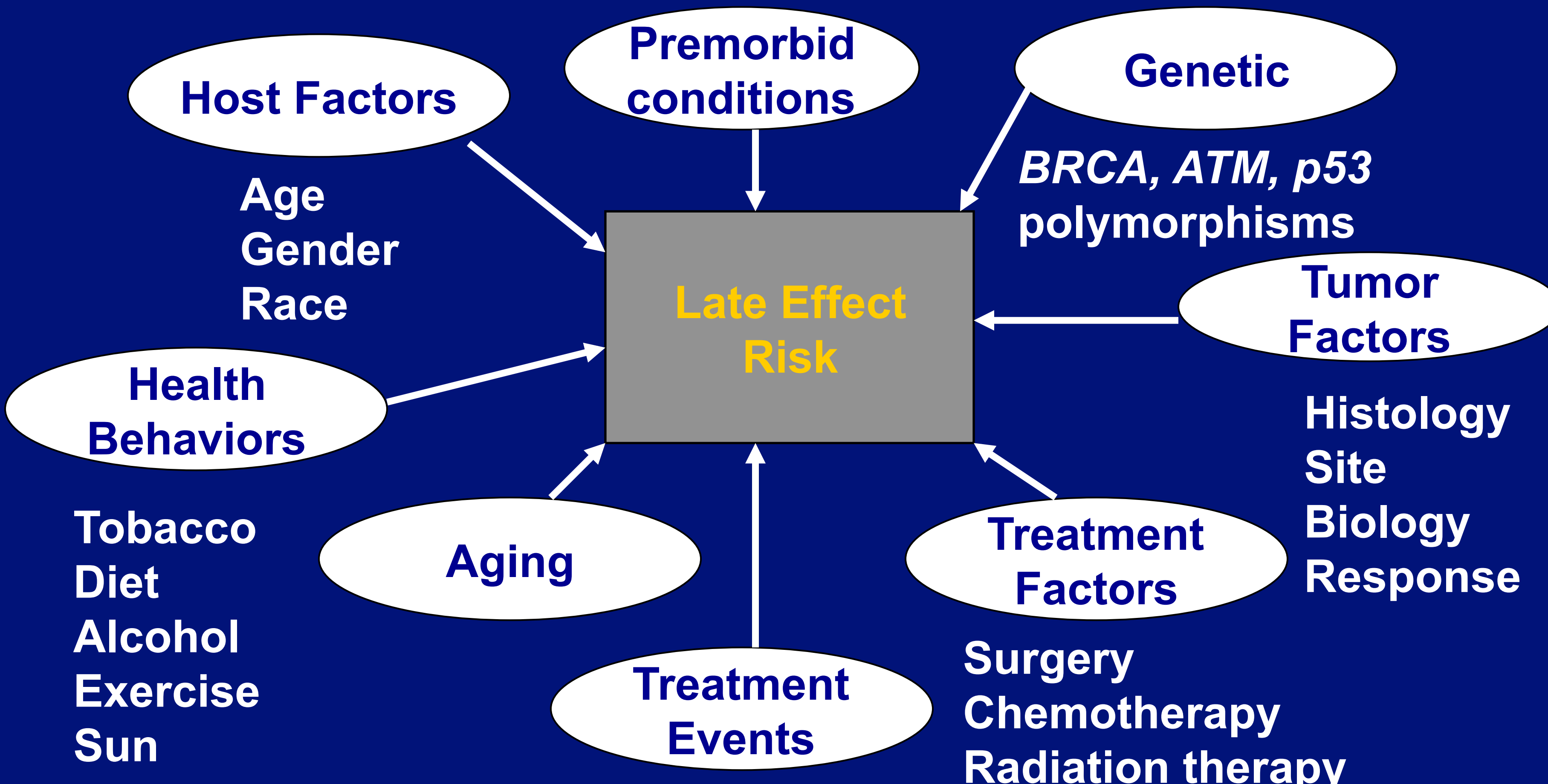
Hypoplasia and impairment of maturation

Adults

Inability to repair damage secondary to cell attrition, senescence and comorbid illness

Fibrotic and inflammatory changes

Risk-Based Survivor Care



Tolerance Radiation Doses

Single Dose (Gy) $T_{5/5}$ -$T_{5/50}$

Bone Marrow	2-10	Heart	18-20
Lens	2-10	Liver	15-20
Lung	7-10	Mucosa	15-20
Thyroid	7.5	Skin	12-20
GI tract	10-20	Testes	> 20
Kidney	10-20	Spinal Cord	20-25
Ovary	> 20-40	Brain	20-30

Fractionated dose (Gy) $T_{5/5}$ -$T_{5/50}$

Testes	1.5-2.5	Liver	35-40
Ovary	5-15	Mucosa	30-40
Lens	6-20	Skin	30-40
Bone Marrow	15-30	Heart	40-50
Kidney	23-28	GI tract	45-50
Lung	25-30	Spinal Cord	50-60
Thyroid	30-40	Brain	60-70

ALERT Volume 1, Rubin, Marks, Constine 2013

Risk of late toxicity as a function of dose and volume of radiation exposure

<table>
<tr><th></th><th></th><th>Dose (Gy)</th><th colspan="2">0</th><th colspan="2">20</th><th colspan="2">40</th><th>60</th><th>70</th></tr>
<tr><td rowspan="5">Spinal cord</td><td rowspan="5">VOLUME</td><td>0-20%</td><td colspan="4" rowspan="5"><1%</td><td colspan="2" rowspan="5"><5%</td><td colspan="2" rowspan="5">10-50%</td></tr>
<tr><td>20-40%</td></tr>
<tr><td>40-60%</td></tr>
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<tr><td>80-100%</td></tr>
<tr><td rowspan="5">Lung</td><td rowspan="5">VOLUME</td><td>0-20%</td><td rowspan="5"><5%</td><td colspan="2" rowspan="2"><5%</td><td rowspan="2"><10%</td><td rowspan="2"><20%</td><td colspan="3" rowspan="2">>20%</td></tr>
<tr><td>20-40%</td></tr>
<tr><td>40-60%</td><td colspan="2">10-20%</td><td colspan="2">30-50%</td><td colspan="3" rowspan="3">>75%</td></tr>
<tr><td>60-80%</td><td colspan="4" rowspan="2">>50%</td></tr>
<tr><td>80-100%</td></tr>
<tr><td rowspan="5">Heart</td><td rowspan="5">VOLUME</td><td>0-20%</td><td colspan="2" rowspan="5"><5%</td><td rowspan="2"><5%</td><td colspan="2" rowspan="2">5-10%</td><td colspan="3" rowspan="2">10-25%</td></tr>
<tr><td>20-40%</td></tr>
<tr><td>40-60%</td><td rowspan="3">10-15%</td><td colspan="2"><15-20%</td><td colspan="3">25-40%</td></tr>
<tr><td>60-80%</td><td rowspan="2">15-25%</td><td rowspan="2">25-40%</td><td colspan="3" rowspan="2">>40%</td></tr>
<tr><td>80-100%</td></tr>
<tr><td rowspan="5">Liver</td><td rowspan="5">VOLUME</td><td>0-20%</td><td colspan="3" rowspan="5"><1%</td><td colspan="2" rowspan="2"><5%</td><td colspan="3" rowspan="2"><25%</td></tr>
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<tr><td>80-100%</td></tr>
<tr><td rowspan="5">Kidney</td><td rowspan="5">VOLUME</td><td>0-20%</td><td colspan="2" rowspan="5"><5%</td><td colspan="2" rowspan="2">5-25%</td><td colspan="4" rowspan="2">>25%</td></tr>
<tr><td>20-40%</td></tr>
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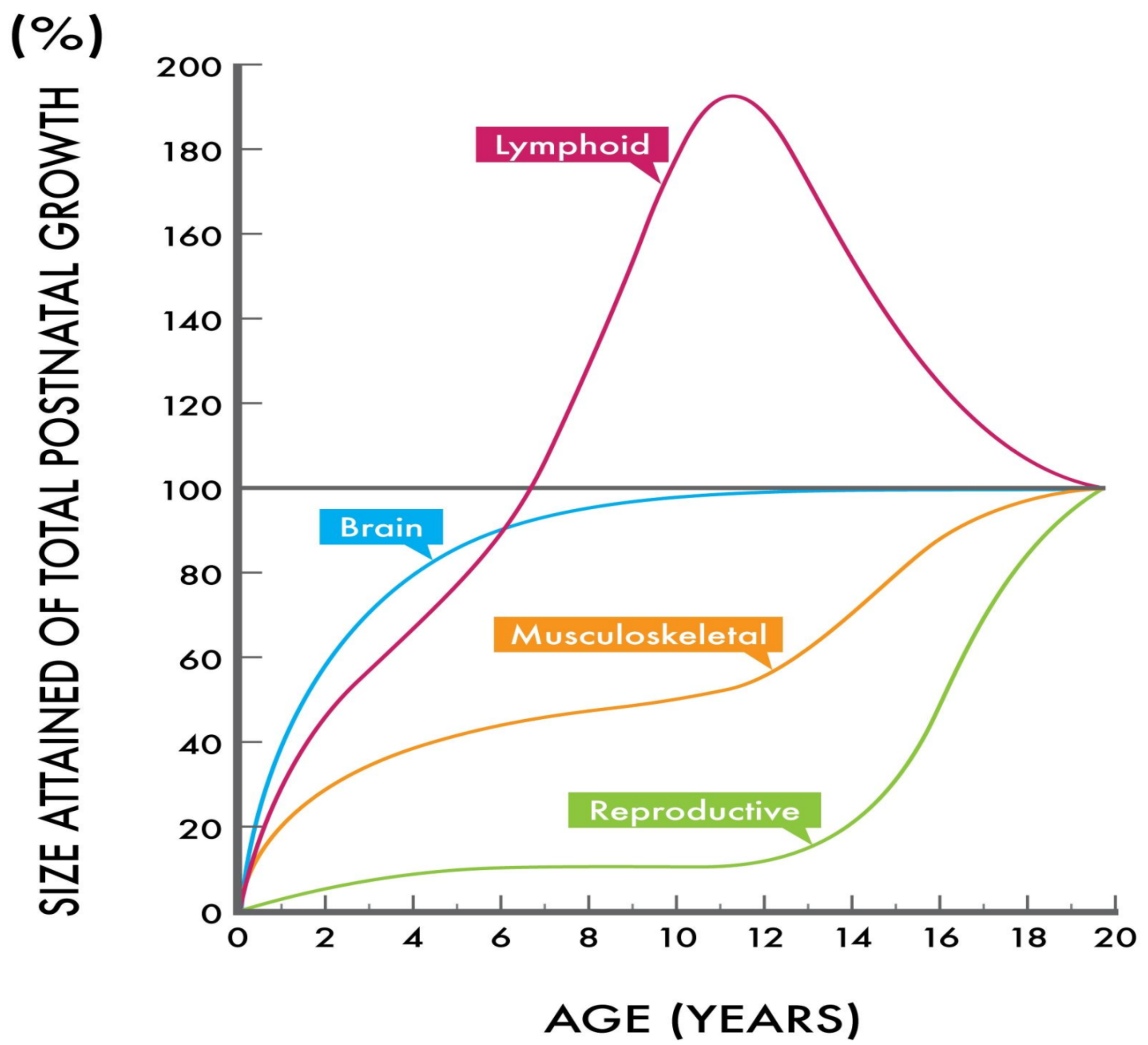
Rubin, Constine, et al LENT scoring IJROBP 1995



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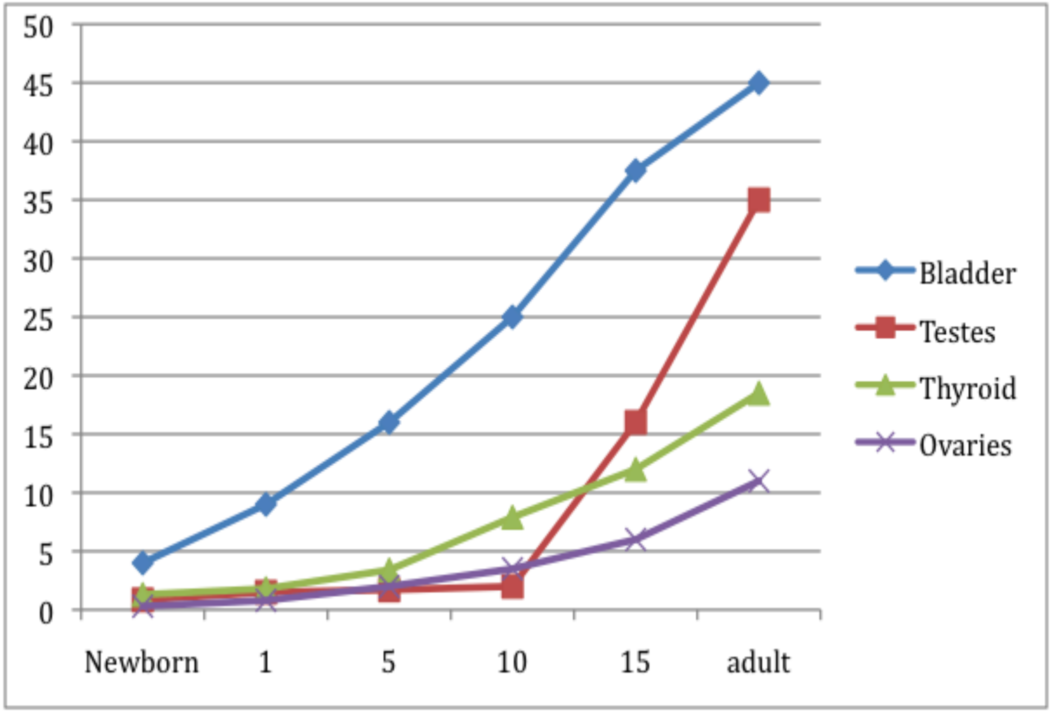
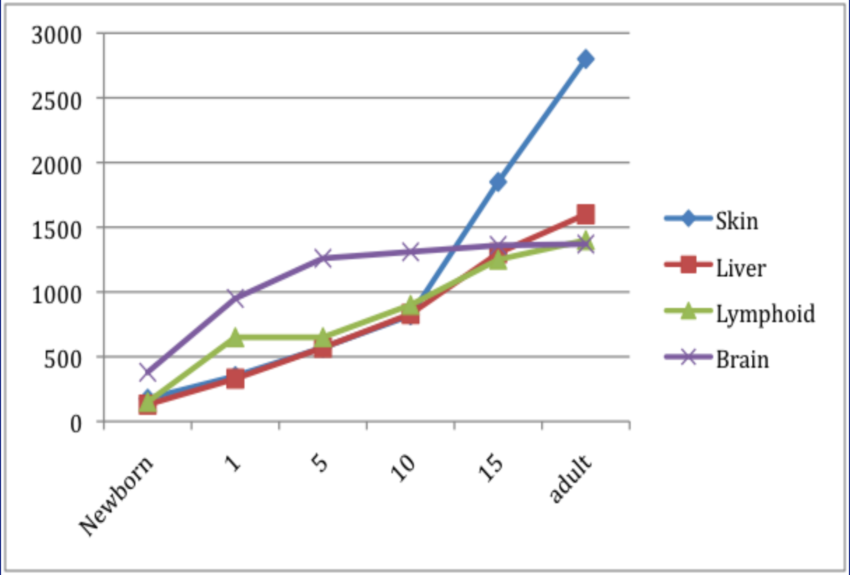
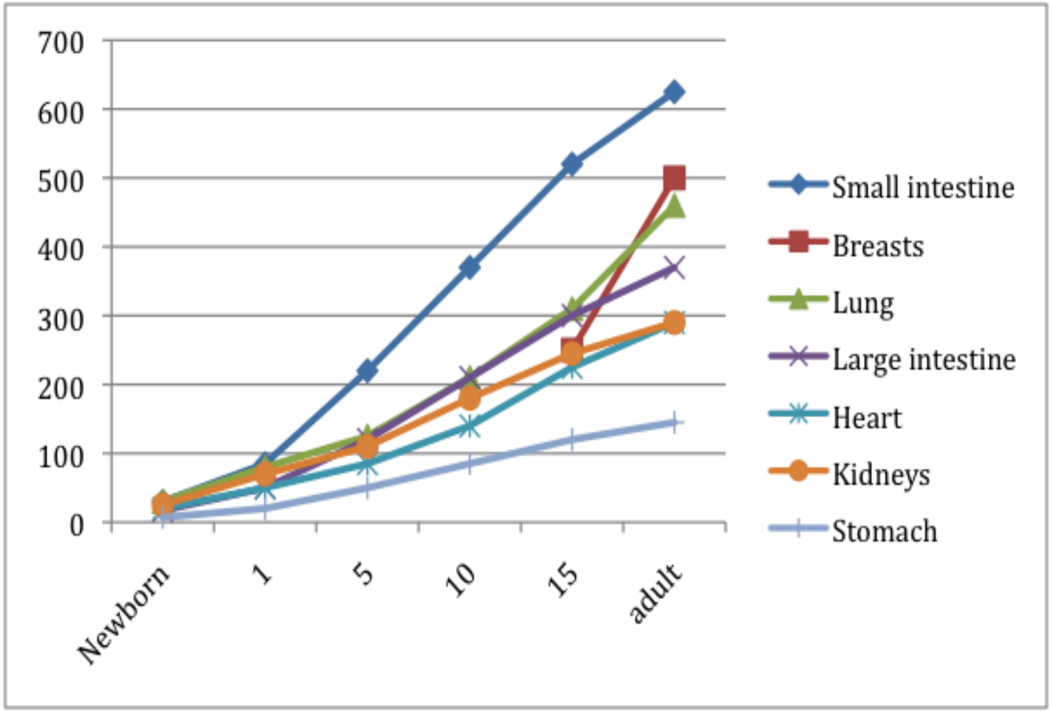






Constine, Dhakal

SAM Q1: Which is not true about the risk of late effects after radiation therapy for children compared with adults?

1. Children have an increased risk due to cell hypertrophy and hyperplasia

2. Children have a decreased risk in some normal tissues (e.g. lung) due to superior repair capacities or less base-line injury

3. Children are more sensitive than adults for most late effects with the exception of ovarian failure and bone marrow suppression

4. Children have a lower likelihood of developing second cancers because of their superior ability to repair mutations

The correct answer is:

4. Children have a lower likelihood of developing second cancers because of their superior ability to repair mutations

Ref: Constine, LS (ed) Cancer Genesis, Treatment, and Late Effects Across the Age Spectrum.

Sem Rad Onc 20(1) 2010: 78 pp

THE EFFECT OF ROENTGEN RAYS UPON THE GROWING LONG BONES OF ALBINO RATS*

I. QUANTITATIVE STUDIES OF THE GROWTH LIMITATION FOLLOWING IRRADIATION

By CHARLES L. HINKEL, M.D., Med.Sc.D.
HARRISBURG, PENNSYLVANIA

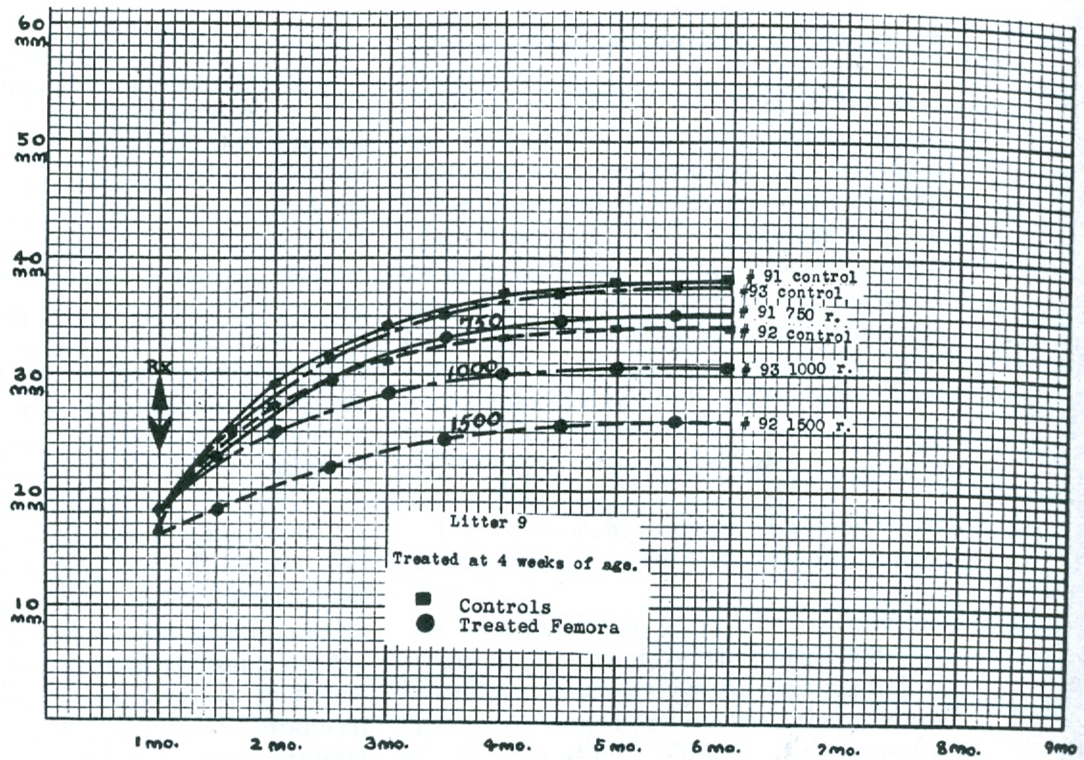


FIG. 7. *Litter 9.* Irradiated femora (●) and control femora (■) of litter 9. This shows the quantitative effects of 750, 1,000, and 1,500 r administered at one month (arrow).

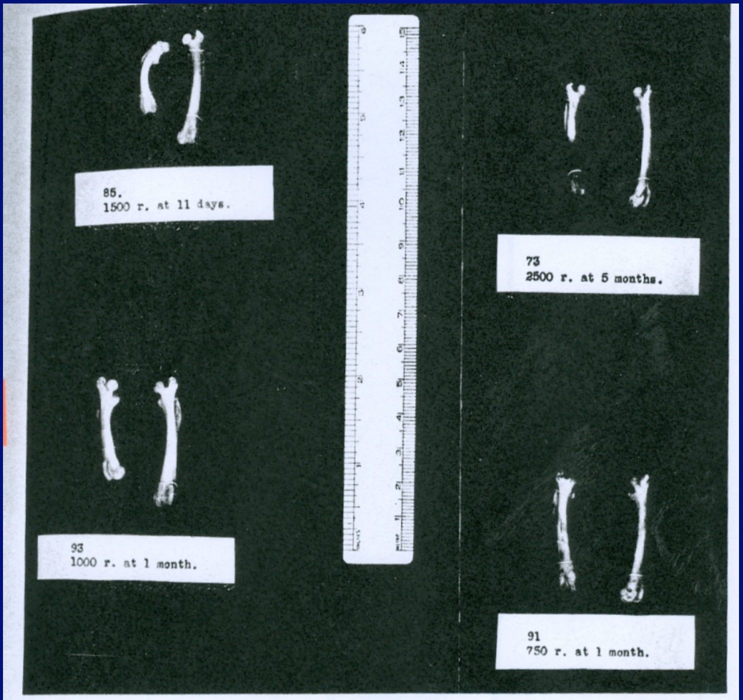
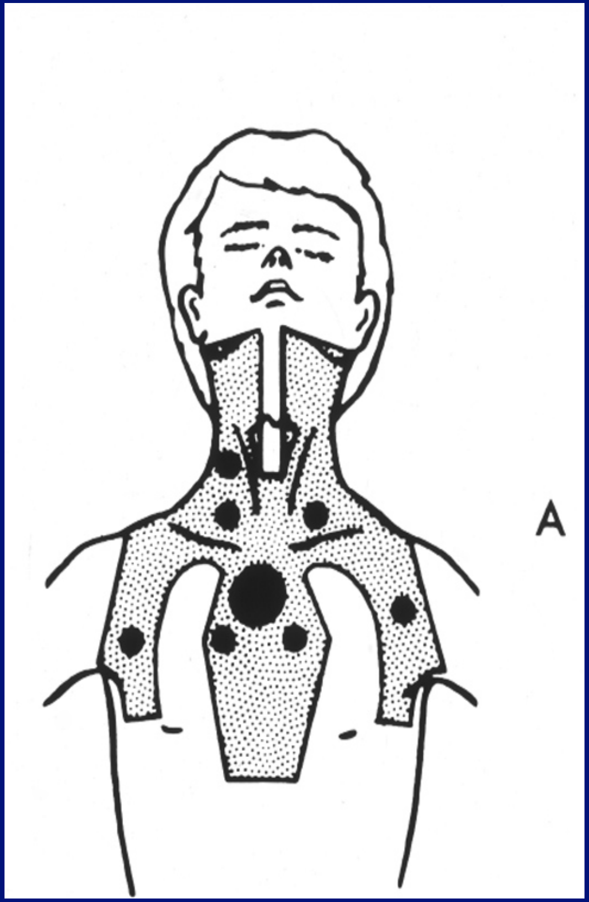


FIG. 11. *Gross Appearance of Stunted Femora.* Photograph of dissected femora from 4 animals. Rats No. 8 and No. 93 illustrate the curvature mentioned in the text. All the right femora shown here are stunted b the irradiation administered six to ten months before necropsy.

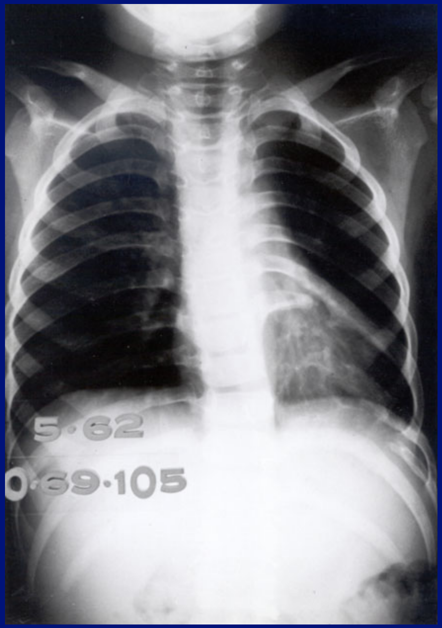
Growth Impairment



Risk factors

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

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

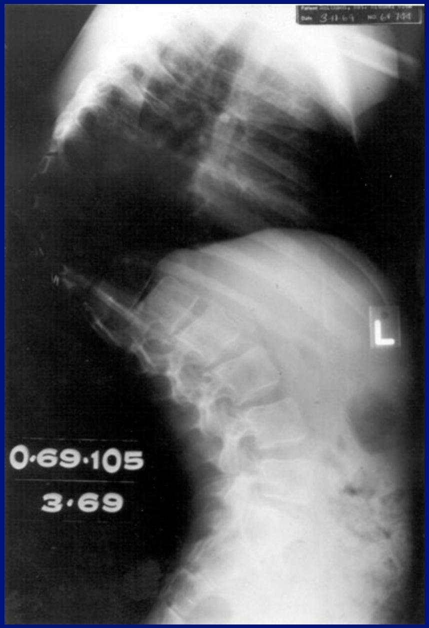


2 yrs post RT

(age 4 yrs)

4 yrs post RT

(age 6 yrs)



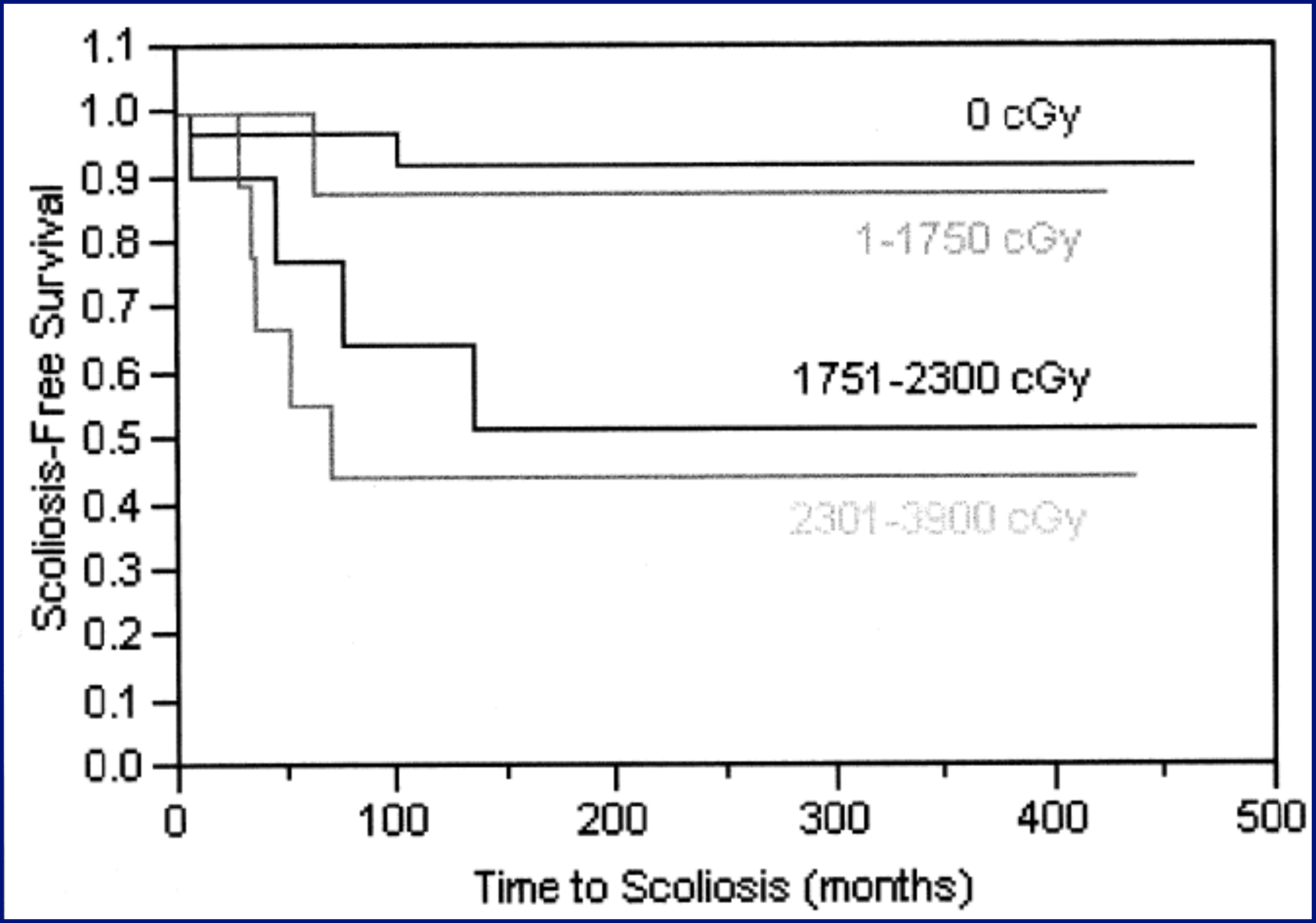
9 yrs post RT

(age 11 yrs)

9 yrs post RT

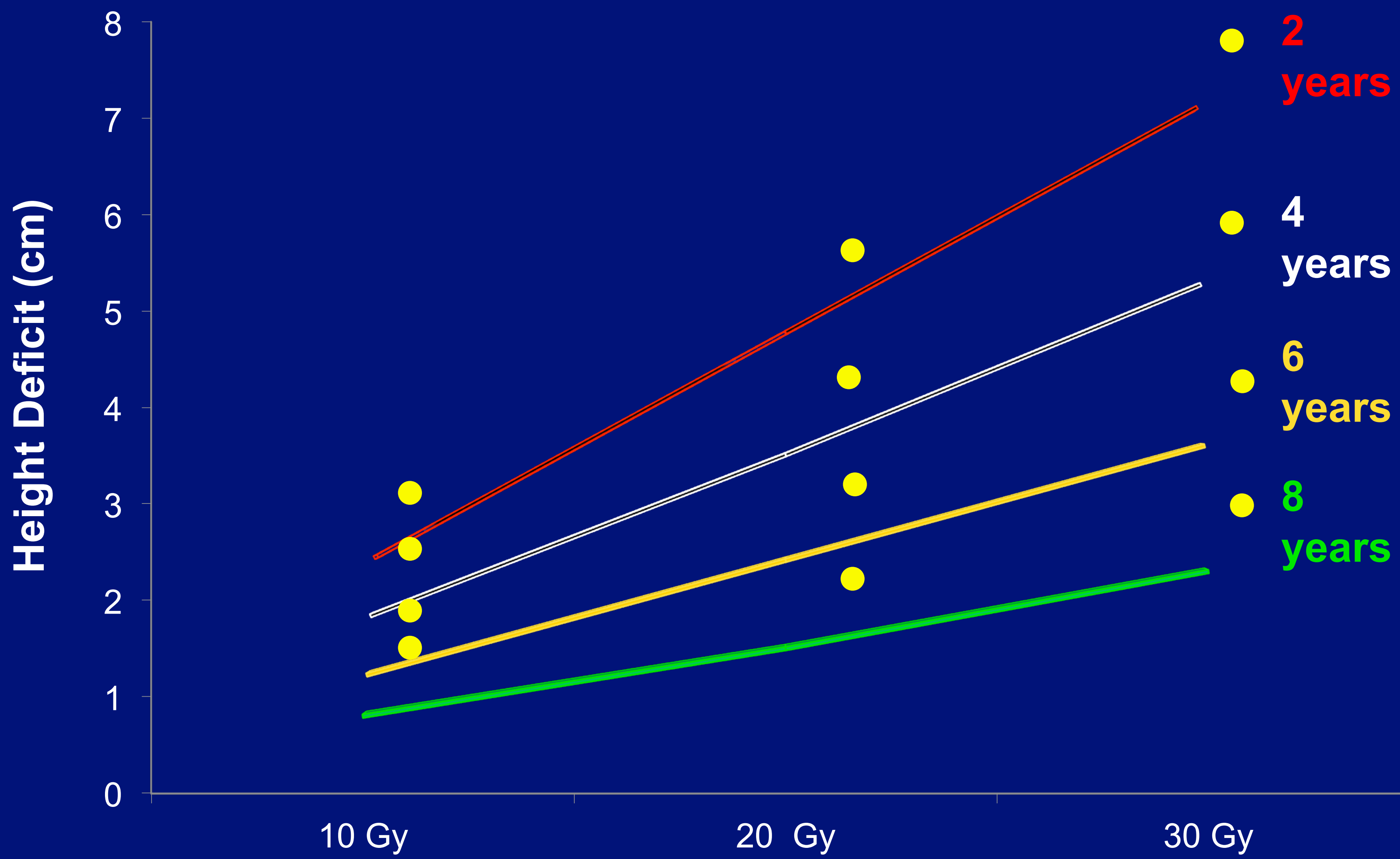
(age 11 yrs)

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

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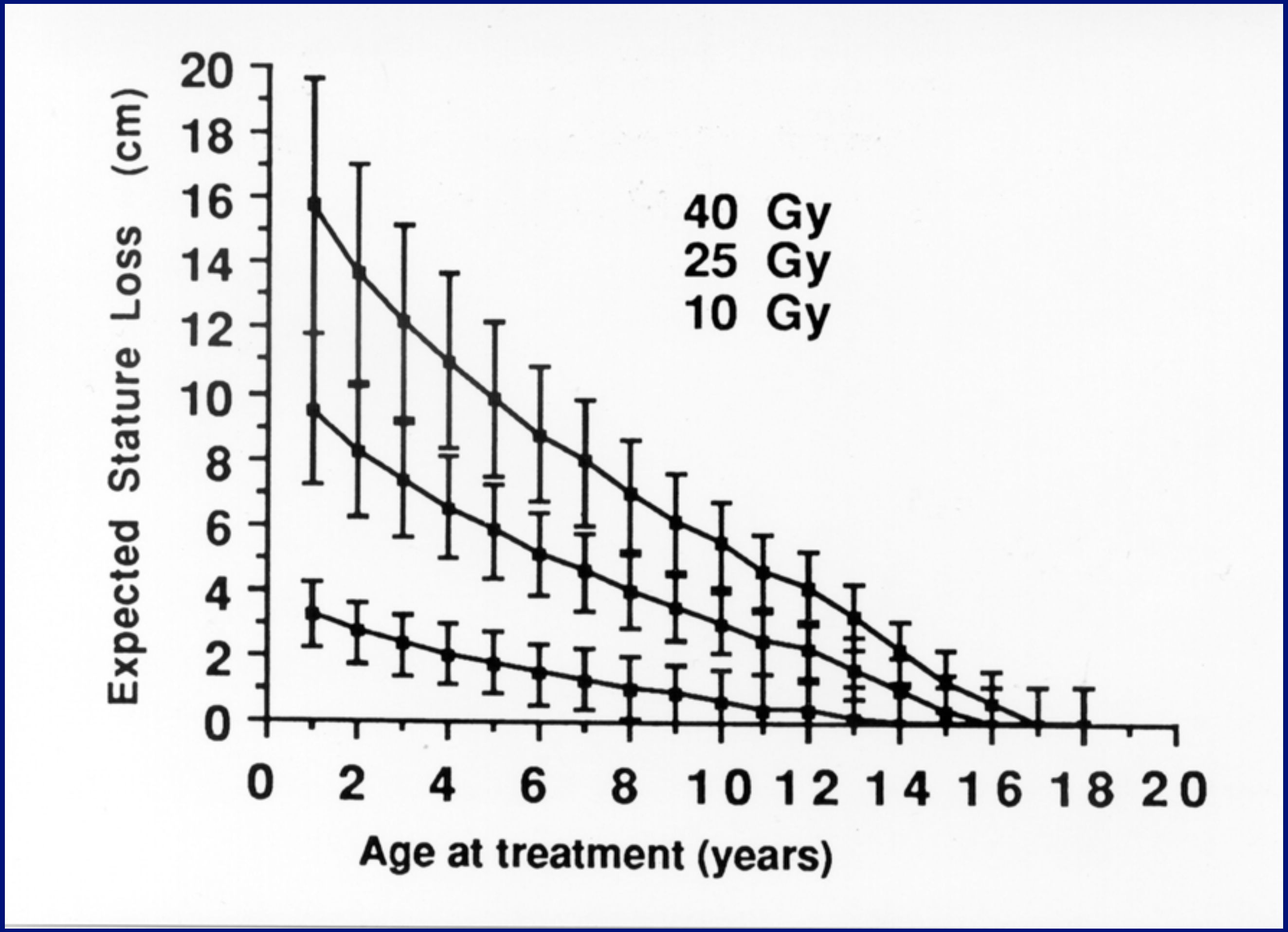
Spine Growth After RT



An example of the model for expected stature loss after radiation therapy to the spine during childhood in a hypothetical male patient treated from T10-11 to L4-5 - his Ideal Adult Stature was 176.8 cm

Silber JH, Littman PS, Meadows AT: *J Clin Oncol* 8:304-312, 1990

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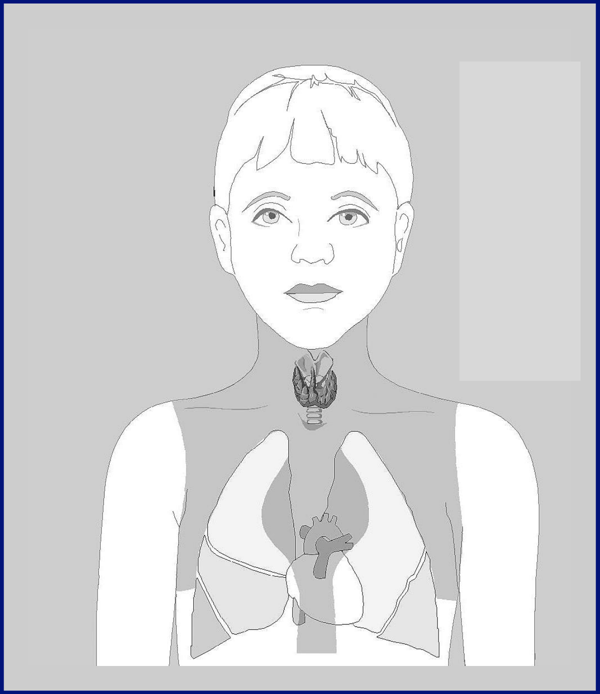
Radiation Cardiac Injury

Manifestations

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

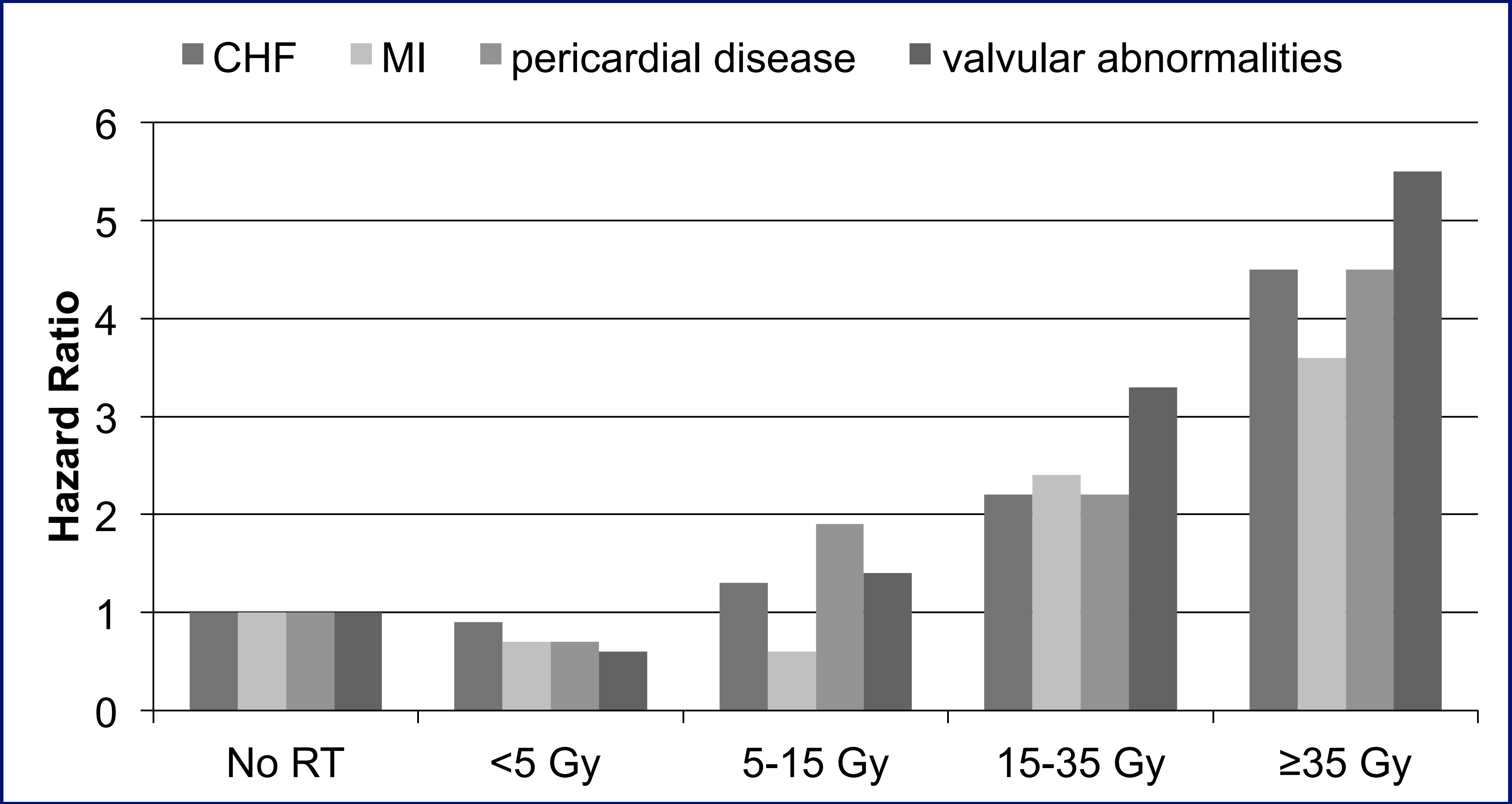


Mantle Field

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

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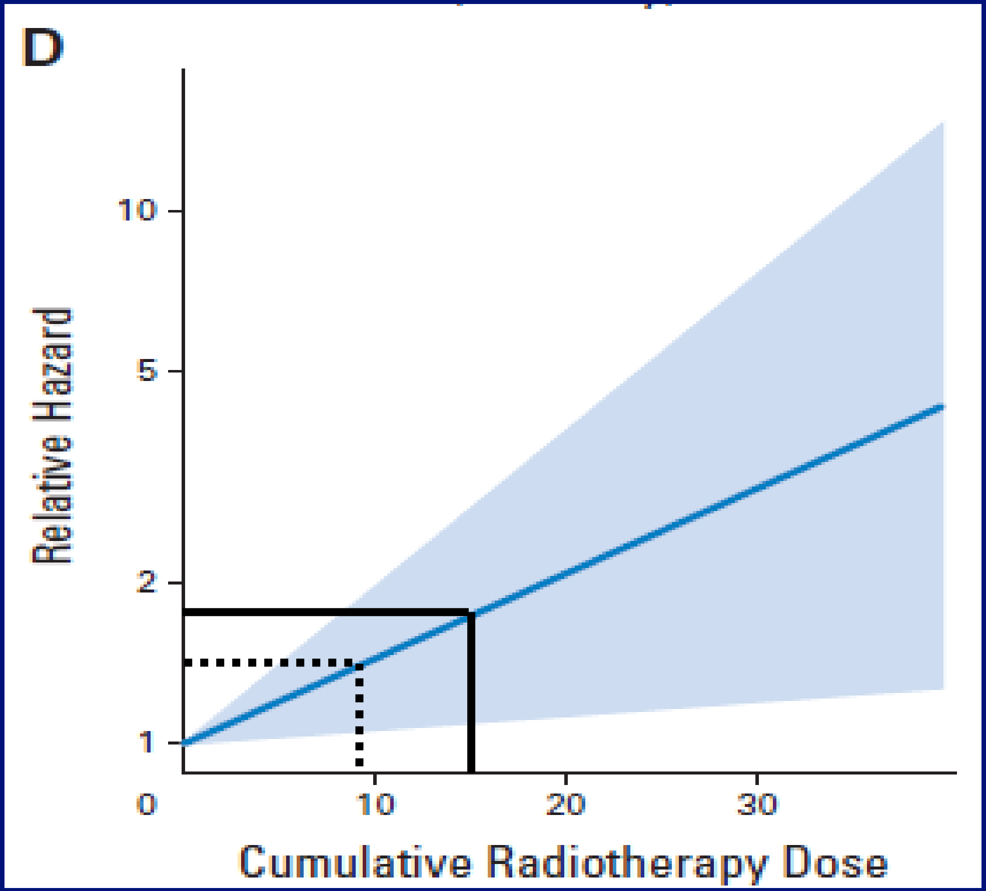
CHF Risk by Dose < 15 Gy



As EQD2

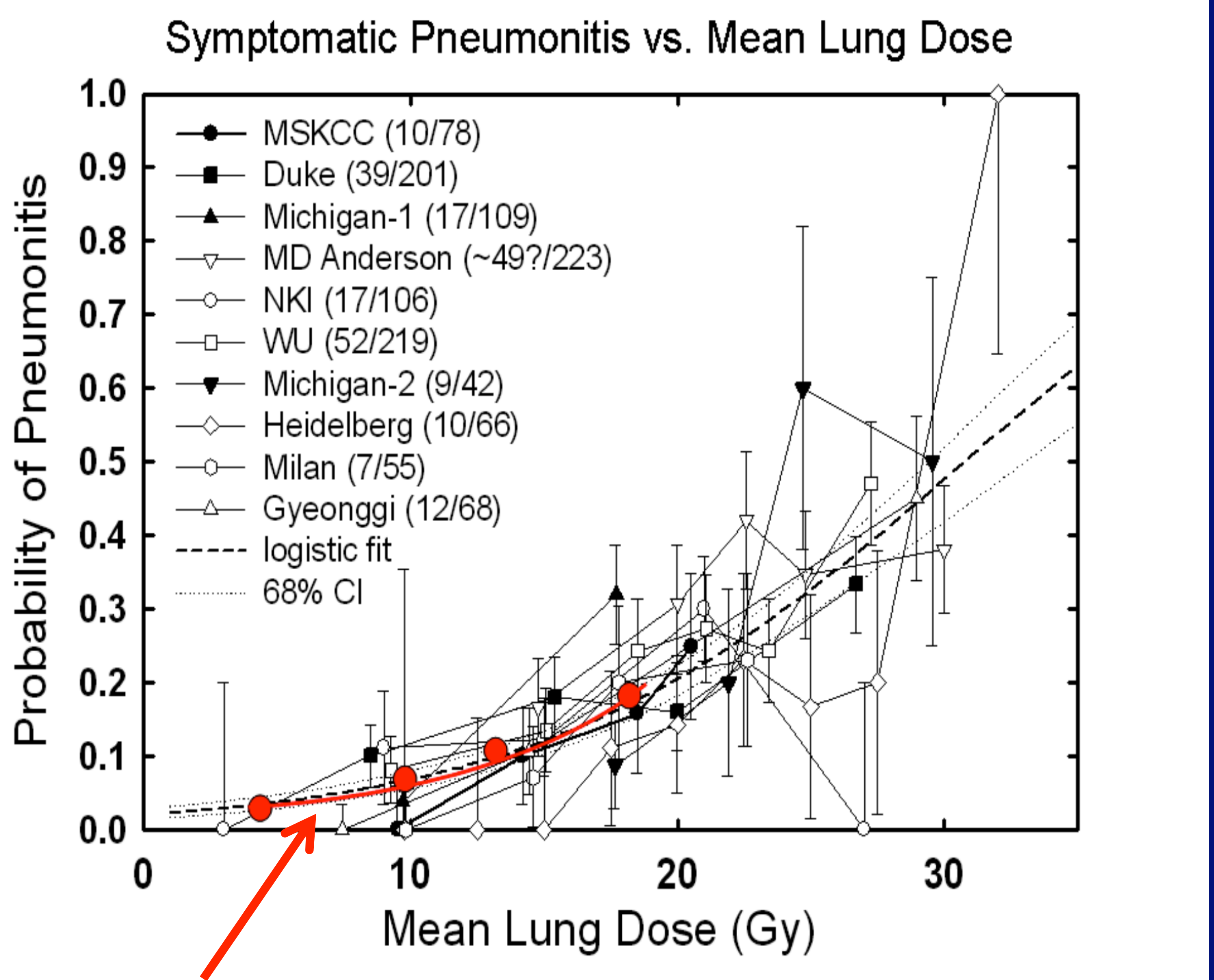
Role of TBI and Fractionation on CHF risk

TBI fractionation schedule	Physical dose (Gy)	EQD_2 (Gy)
1 x 8.0 Gy	8.0	17.6
1 x 7.5 Gy	7.5	15.75
2 x 6.0 Gy	12.0	21.6
2 x 5.0 Gy	10.0	16.0
2 x 4.5 Gy	9.0	13.5

Van der Pal HJ, et al. *J Clin Oncol*. 2012; 30:1429-37

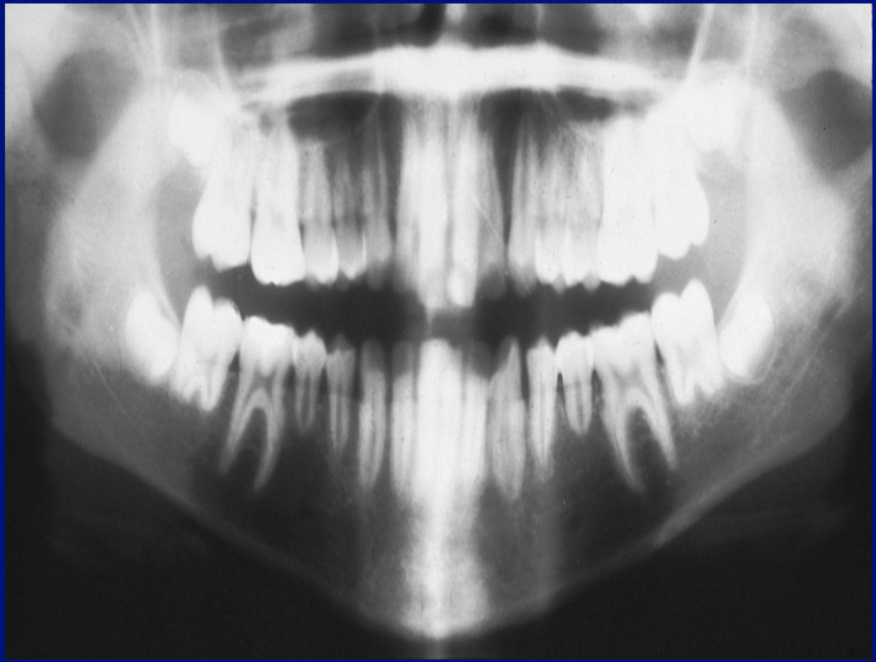
Pulmonary Dysfunction

- 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

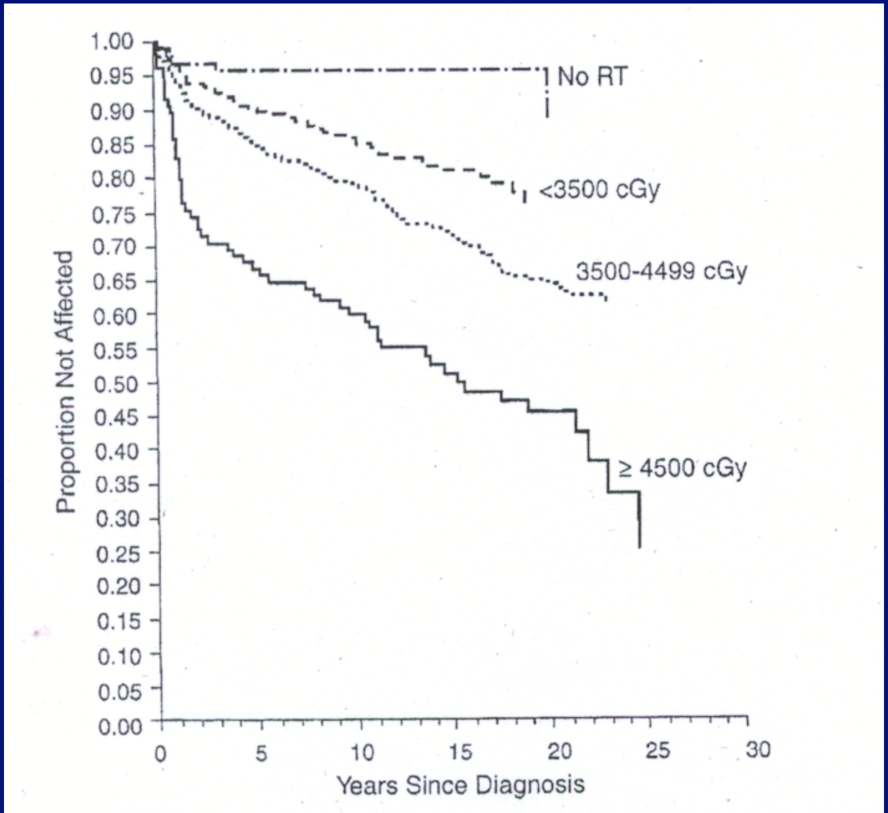
Dose thresholds are age/endpoint dependent: 10-20 Gy

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

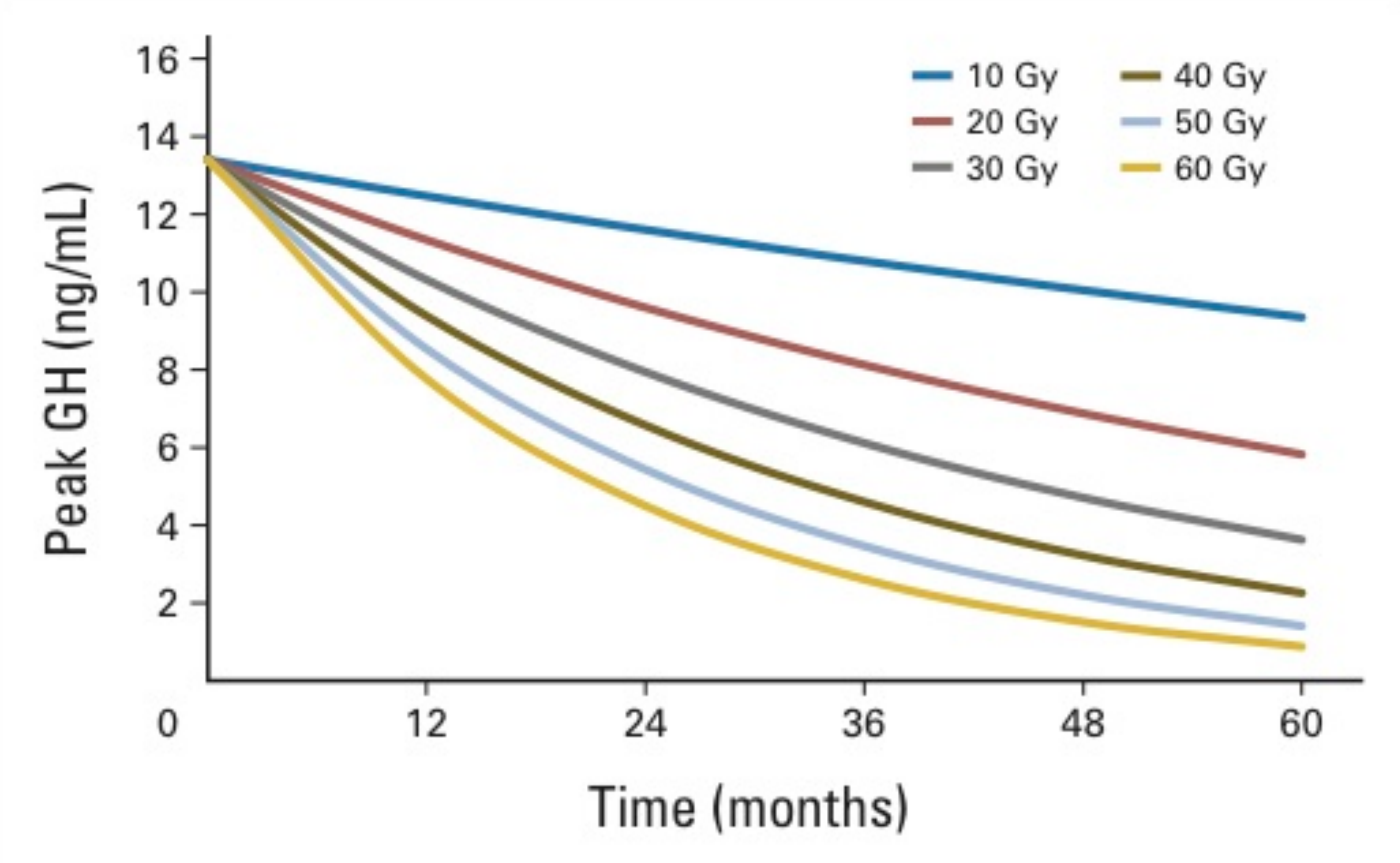


Risk Factors

- 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

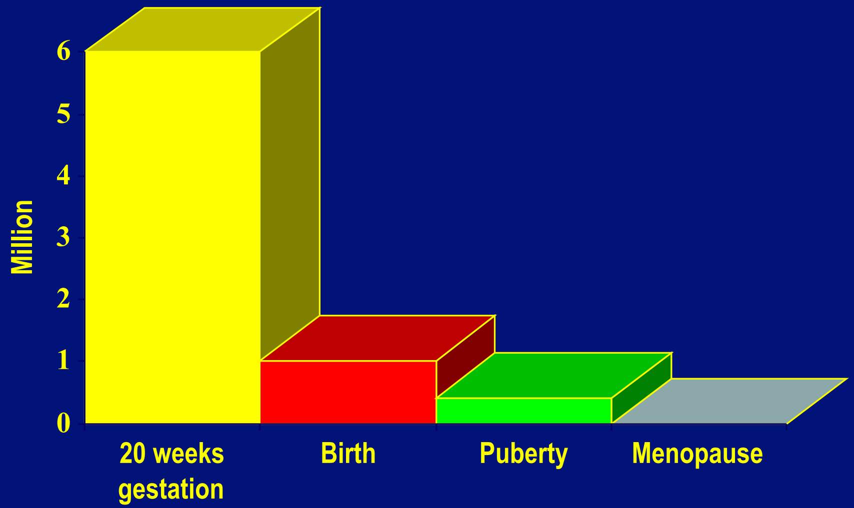
Female Gonadal Dysfunction

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



Age & Risk of Ovarian Failure

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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

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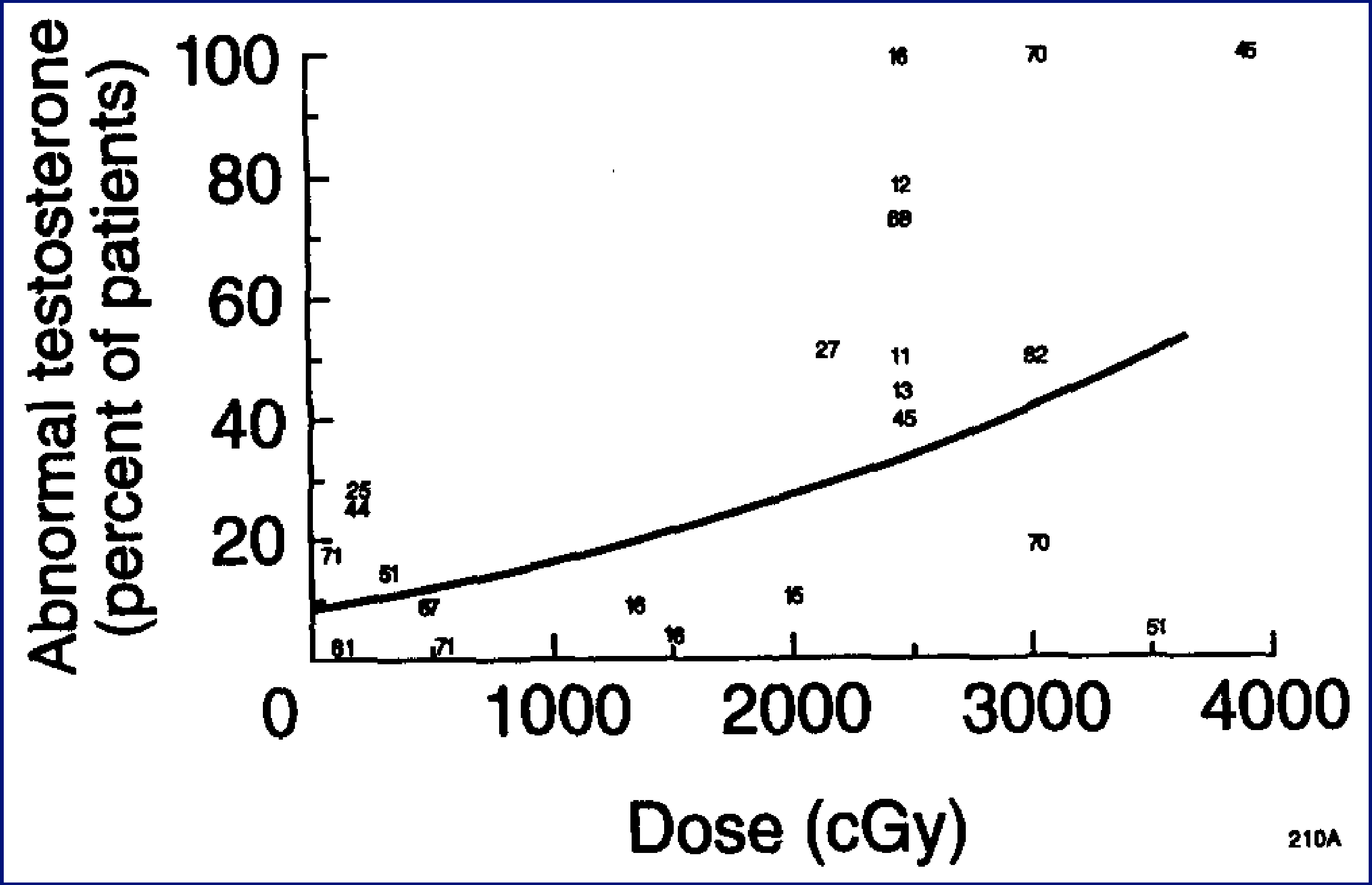
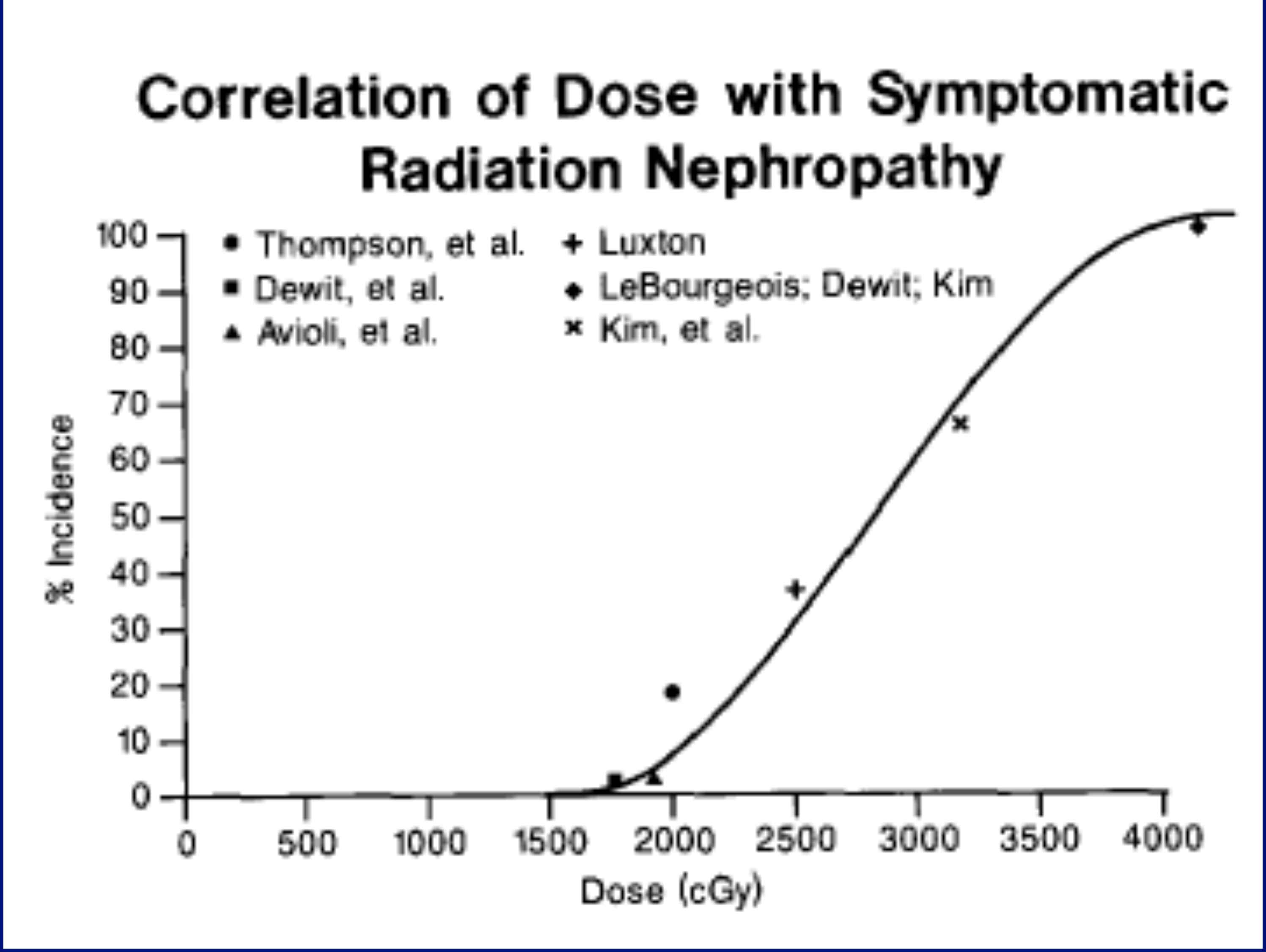
Abnormal Testosterone Value vs Radiation Dose to Testicles

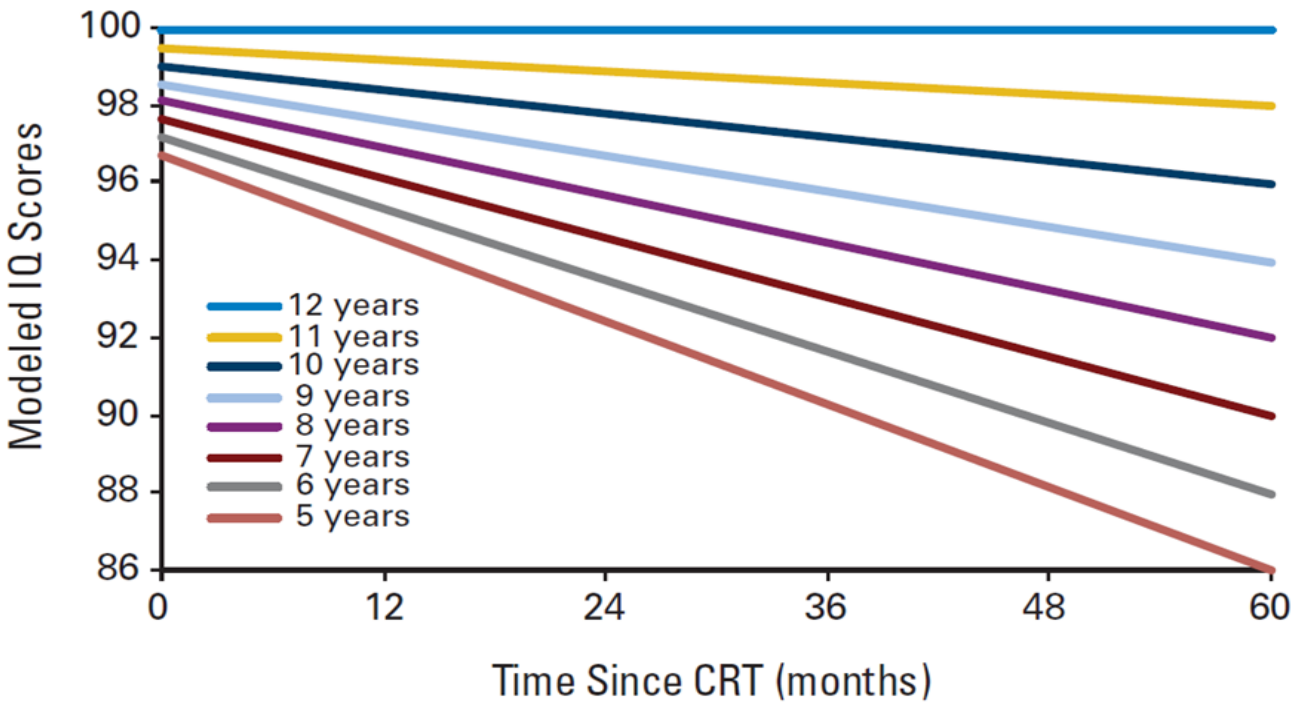


Izard M, Rad & Onc; 34:1 (1995)

Bilateral Whole Kidney RT – non TBI



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.

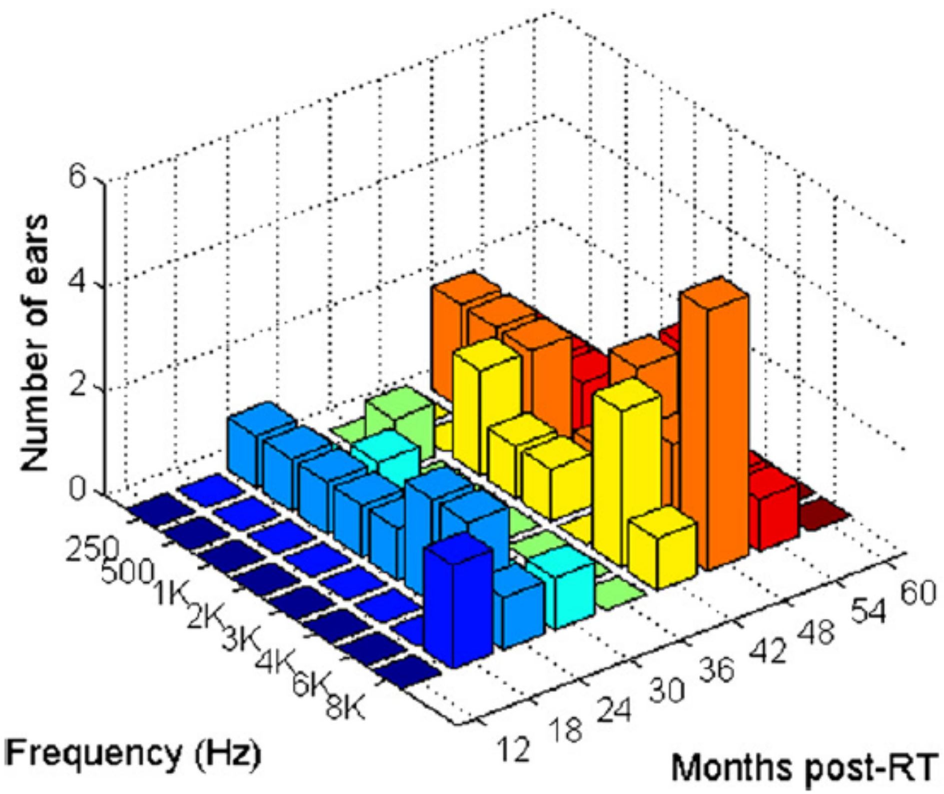


Fig. 5. Histogram of hearing loss onset. RT = radiotherapy.

HUA et al. IJROBP 72:892, 2008

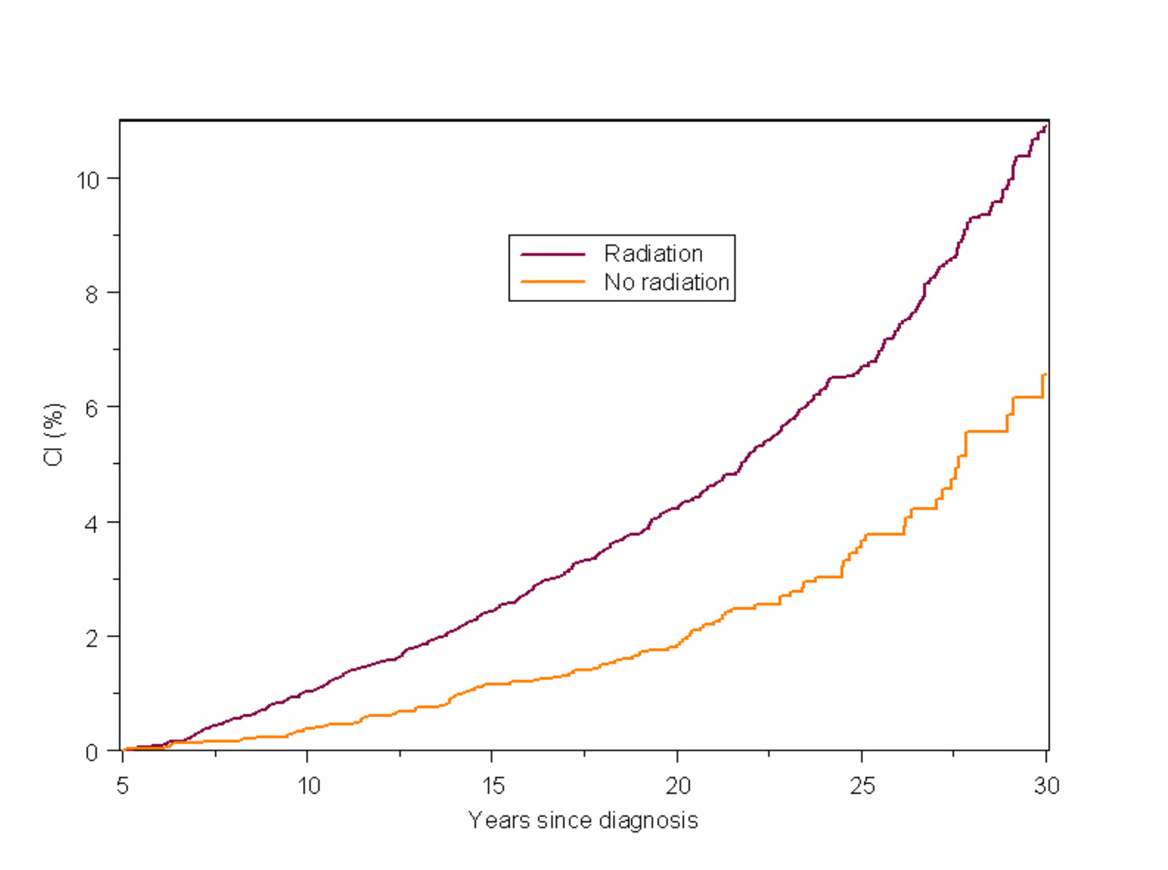
Secondary Acute Myeloid Leukemia

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

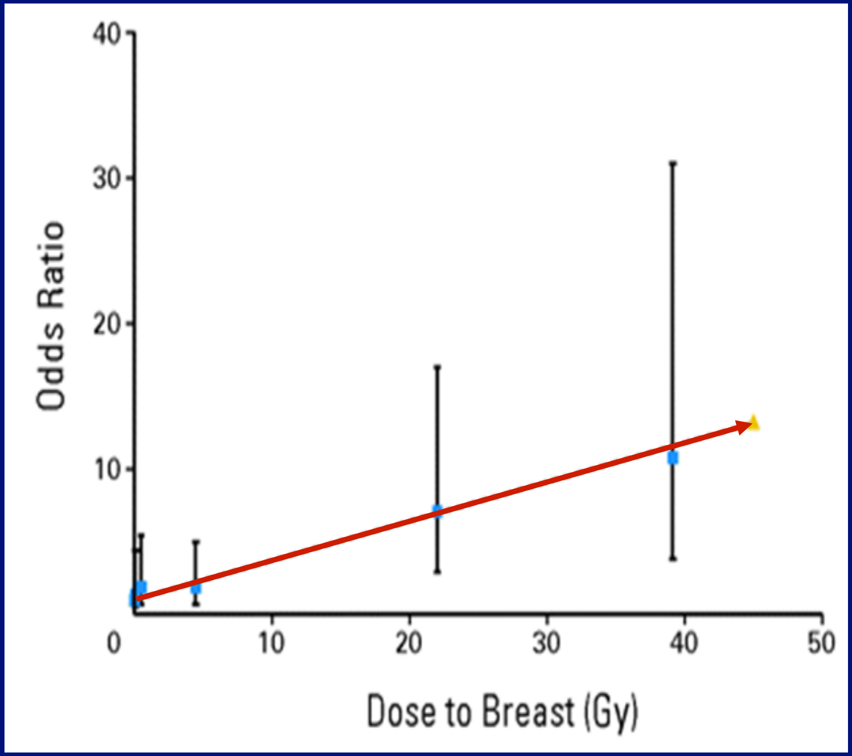
CHILDHOOD CANCER SURVIVOR STUDY (CCSS)

Second and Subsequent Malignancies

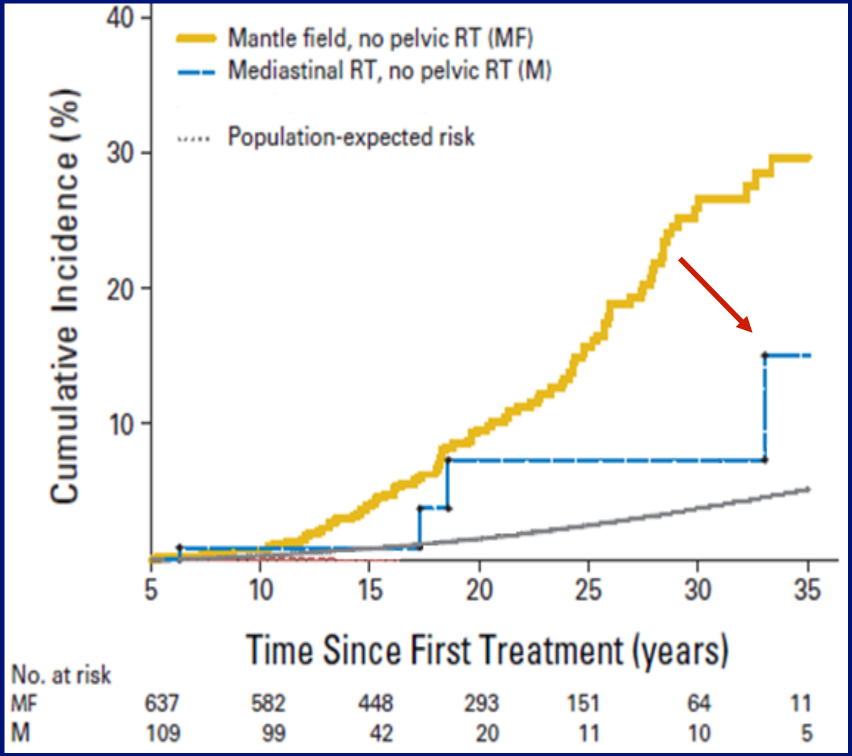
Cumulative incidence by exposure to radiotherapy



Breast cancer risk, dose and volume, Childhood cancer survivors



Inskip PD, et al. J Clin Oncol, 2009



De Bruin ML, et al. J Clin Oncol, 2009

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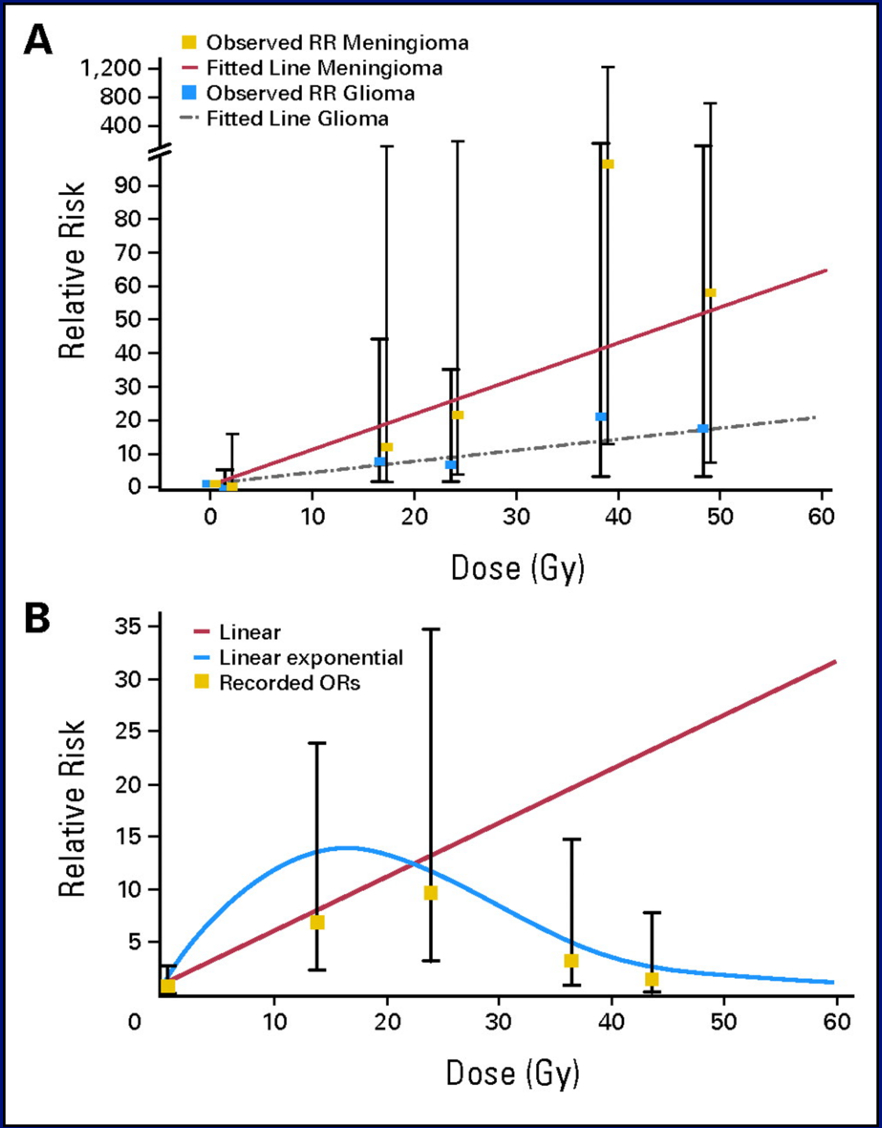
Dose-response Relations Between RT Dose and Relative Risk (RR) of Second Neoplasms

CNS SMNs

Thyroid SMNs



Neglia JNCI 98:1528, 2006

Ronckers Rad Res, 166:618, 2006

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

SAM Q2 Which is true about SMNs in children following radiation therapy

1. SMNs increase in incidence for the first 20 years after RT, and then taper
2. SMNs increase according to radiation dose in all tissues except for the breast
3. The radiation volume is not relevant to the incidence of SMNs, since dose is the dominant factor
4. Acute leukemias are more likely due to radiotherapy than to chemotherapy

The correct answer is:

4. Acute leukemias are more likely due to radiotherapy than to chemotherapy

Ref: : Travis LB, Ng AK, …Constine LS, Boice JD Jr. NCRP SC-17: Second malignant neoplasms and CVD after radiotherapy, Report 170. April 2012.

Make everything as simple as possible, <u>but</u> not simpler.

Or

Make everything as simple as possible, <u>if</u> not simpler.

» Albert Einstein