Learning From the Fat Man

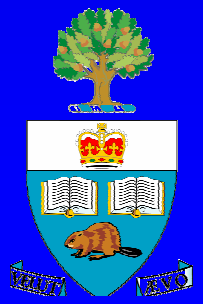
Modeling Second Cancer Risks for Clinical Use

David Hodgson MD, MPH

Department of Radiation Oncology, Princess Margaret Hospital

Department of Health Policy, Management and Evaluation,

University of Toronto.



Princess Margaret Hospital

University Health Network

Introduction

- Second cancer risks: the clinical problem
- Conventional measures of risk
- Limitations of current methods of describing risk
- Challenges to developing more useful predictors of risk
  - Age and temporal effects
  - Radiation dose-risk assocation
  - Dosimetry to 3D volumes
  - Accounting for competing risks
- Potential for modeling SC risk
- Some WW2 history

What Do These Two Have in Common?

Henry L. Stimson
US Secretary of War 1940- 45

Stephane Dion's dog

Cumulative Incidence of SC in Childhood HL Survivors

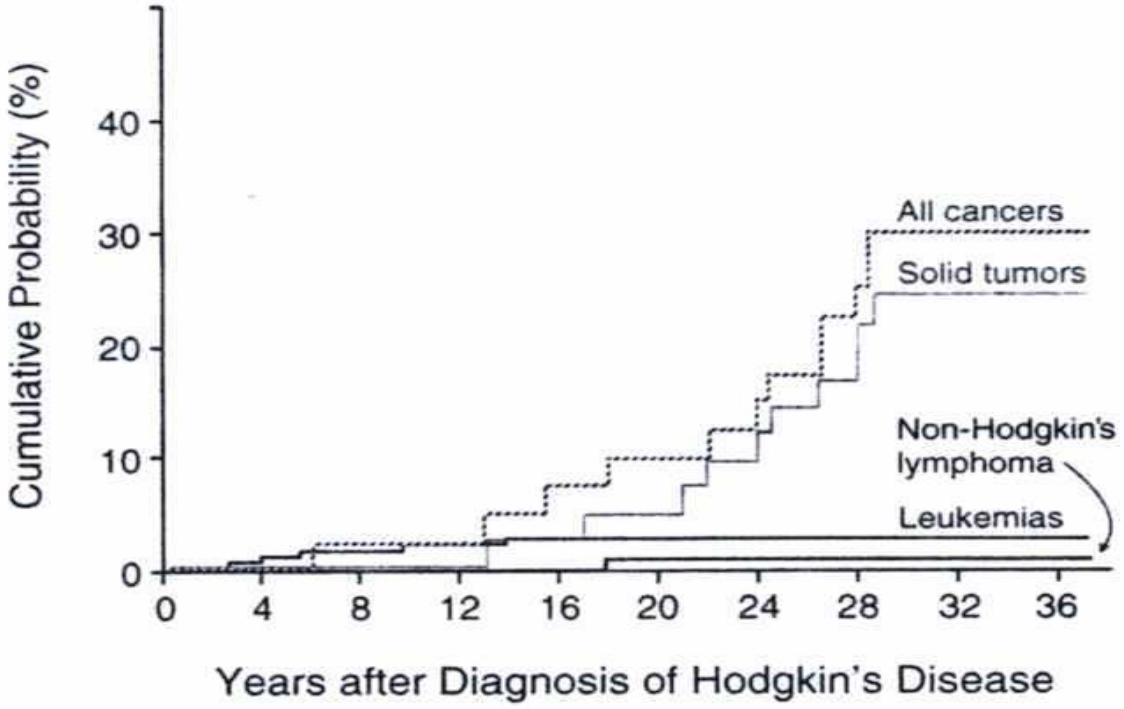


Figure 1. Cumulative Probability of Second Cancers in 1380 Patients with Hodgkin's Disease in Childhood.

NEJM 334: 745-51, 1996

Elevated Risk of Second Cancers Seen Among Survivors

- In 2004 estimated 12-million cancer survivors in North America.
- Second cancers account for ~13% of new cancers registered in SEER.
- Reported elevation in SC risk among survivors of:
  - Cervix, NHL, Nasopharyngeal, Prostate, Breast
- RT delivery may be one of the more modifiable causes of SC.
- In 2007, 4500 patients aged <50 yrs received RT in Ontario.

Conventional Measures of Risk

- Cancer survivors followed for 10-30 years after completion of treatment.
  - Cases of SC ascertained.
  - Patients censored at death or loss to follow-up.
- Standardized Incidence Ratio (SIR)
  - The ratio of the observed to the expected new cases of cancer
  - The expected number is based on the sex- and age-specific rates published for the general population.
- Absolute Excess Risk
  - (O - E)/person-years at risk.

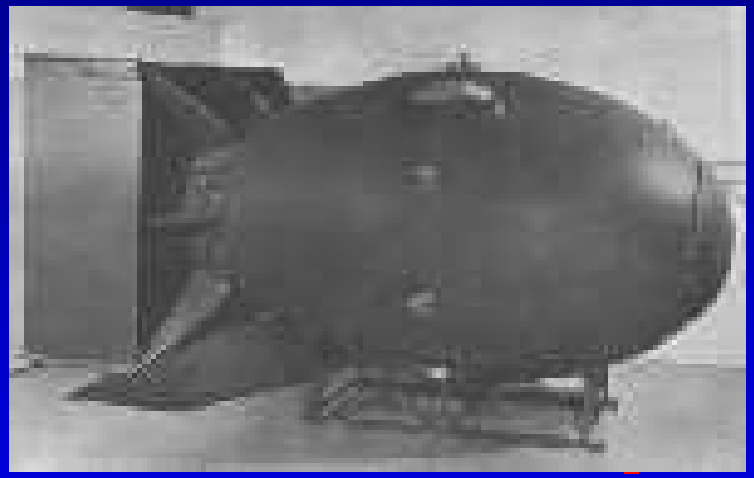
Problems With Current Approach

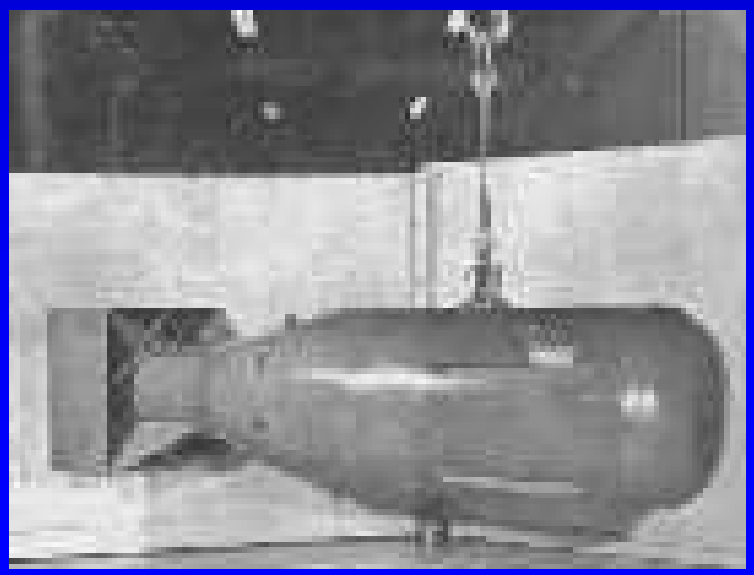
- Delay
  - Latency required to observe SC means that results apply to outdated technology/techniques
- Lack of Individual Specificity
  - Patients receiving nominally the same form of RT may have dramatically exposures
- Difficult to Interpret Clinically
  - RT reduces risk of HL relapse by ~8% at 5-years after diagnosis
  - Also associated with SIR of breast cancer = 1.8
  - So is RT worth it?

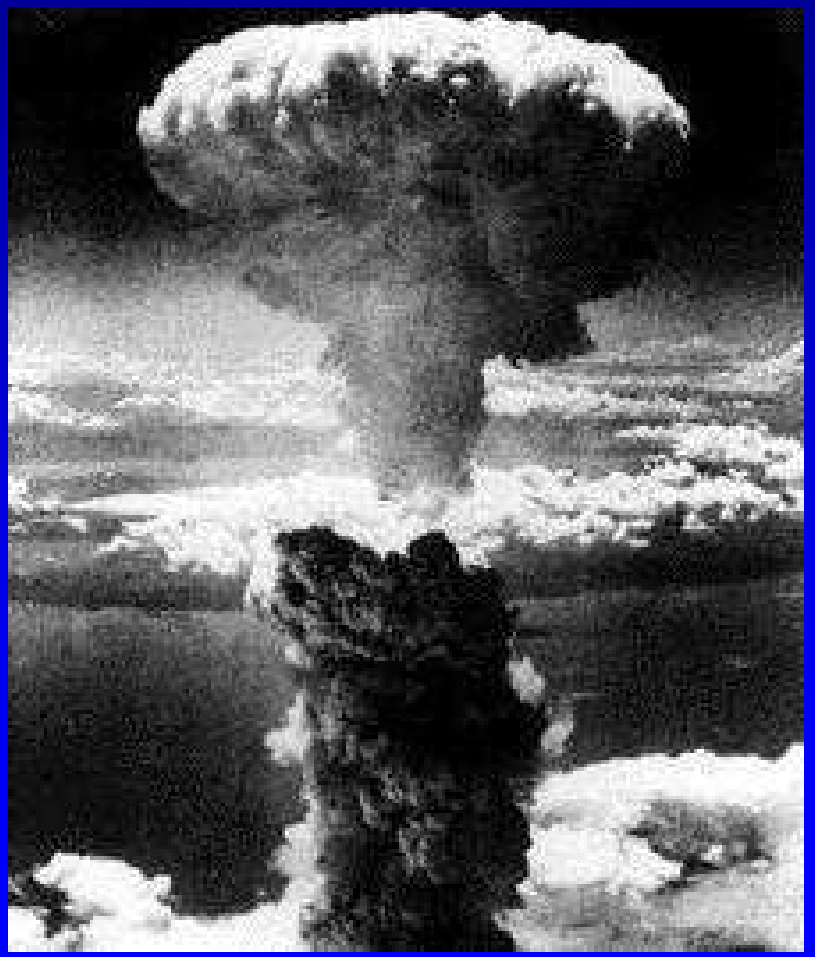
The Ideal

- Estimates of second cancer risk that are
  - Available when RT planning is occurring
    - To allow comparison of alternative RT plans
  - Individualized to facilitate patient counseling
  - Based on spectrum of dose to entire organ at risk
  - Expressed as cumulative incidence

Challenge 1: Modeling Risks Over Time After Radiation Exposure

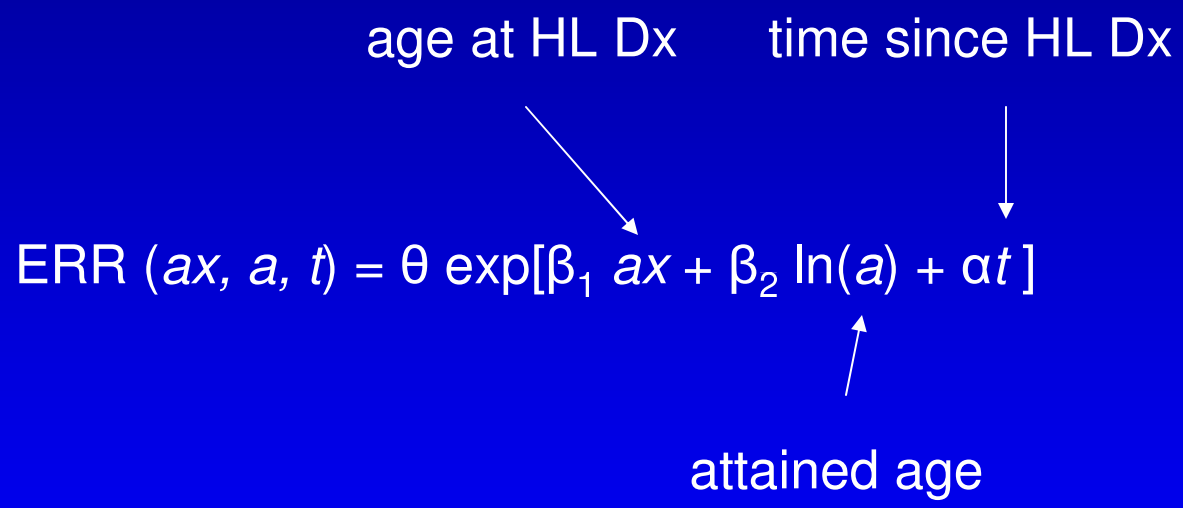






Models of Radiation Risk

"A Priori Model"

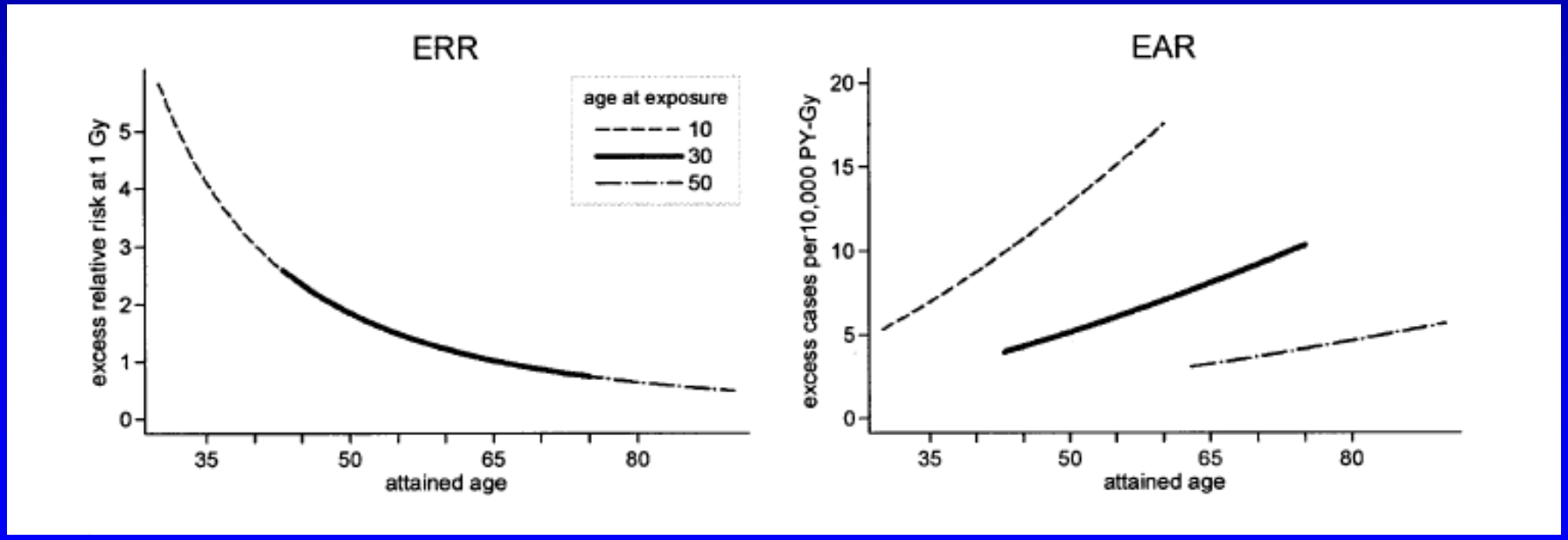


- Previously applied to:
  - A-bomb survivors (Preston Radiat Res 2003)
  - Other radiation exposures (Preston Radiat Res 2002)
  - Testicular Ca Survivors (Travis JNCI 2005)

Breast Cancer Risks
66,072 Female A-bomb Survivors
1Gy Exposure

ERR change with attained age

EAR change with attained age



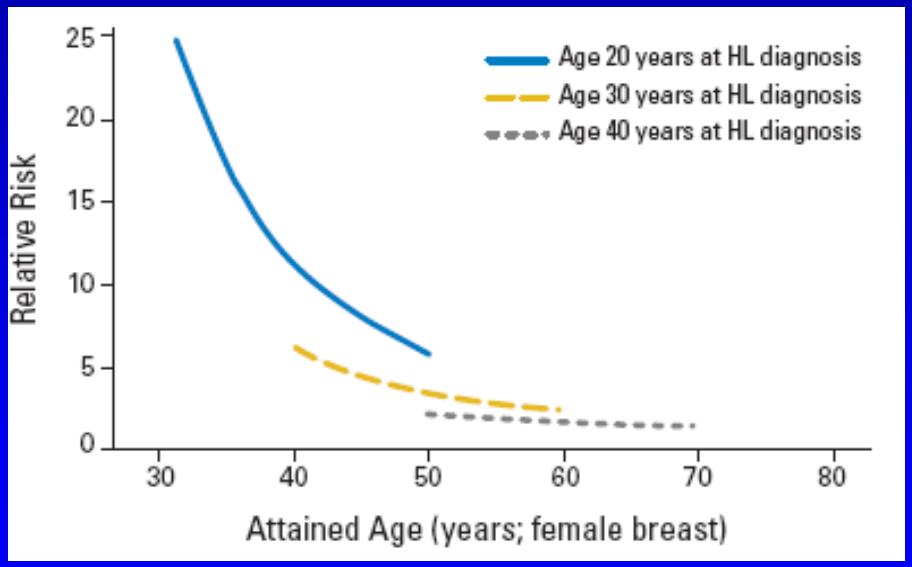
Preston et al Radiat Res 2007

Radiation Risk Model Applied to HL Cohort

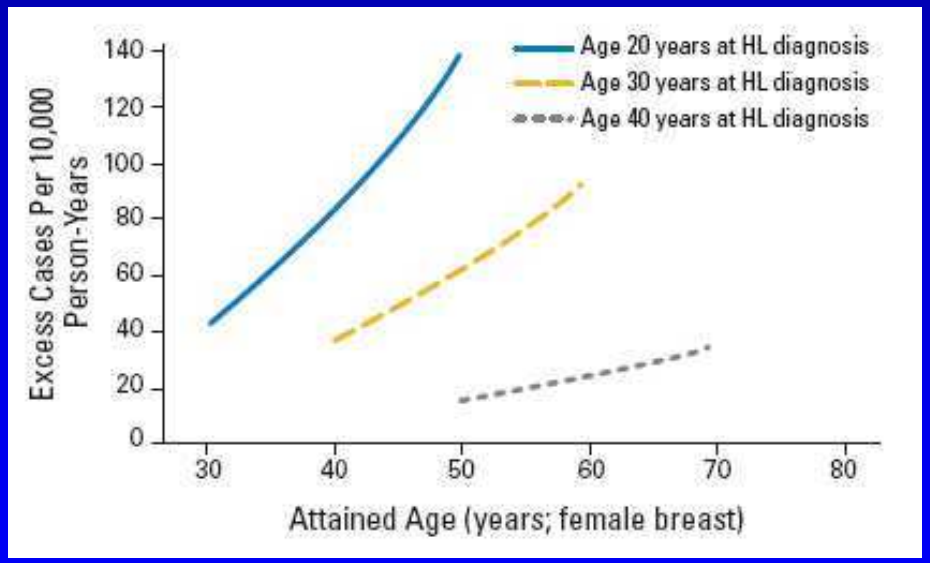
- Modeled solid cancer risk among 18,862 5-year HL survivors registered in population-based registries from North America and Europe.
- Diagnosed 1970-1997
- Study end date December 31, 2002.
- Poisson regression of ERR and EAR
  - *Risks 10+ years after diagnosis described*

Breast Cancer Risks

RR change with attained age



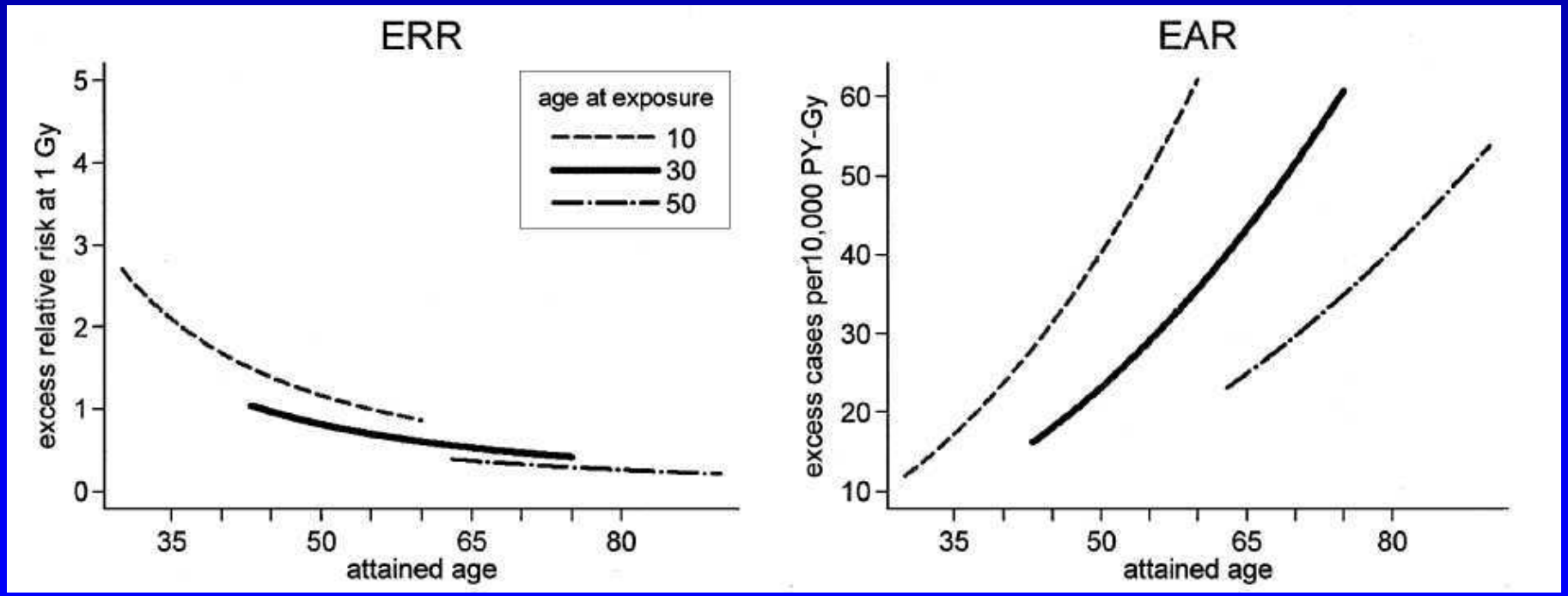
EAR change with attained age



Hodgson et al JCO 2007

Solid Cancer Risks
105,427 A-bomb Survivors
1Gy Exposure

RR change with attained age EAR change with attained age

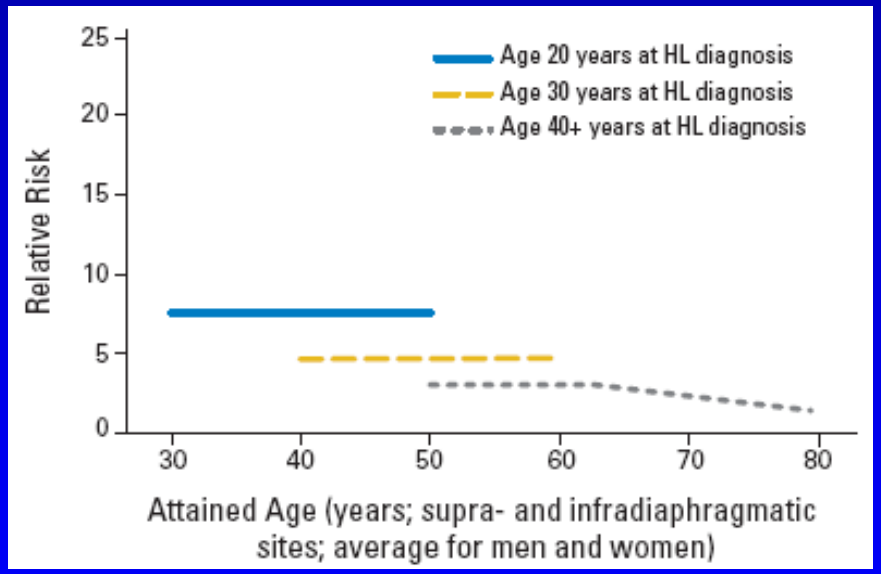


Preston et al Radiat Res 2007

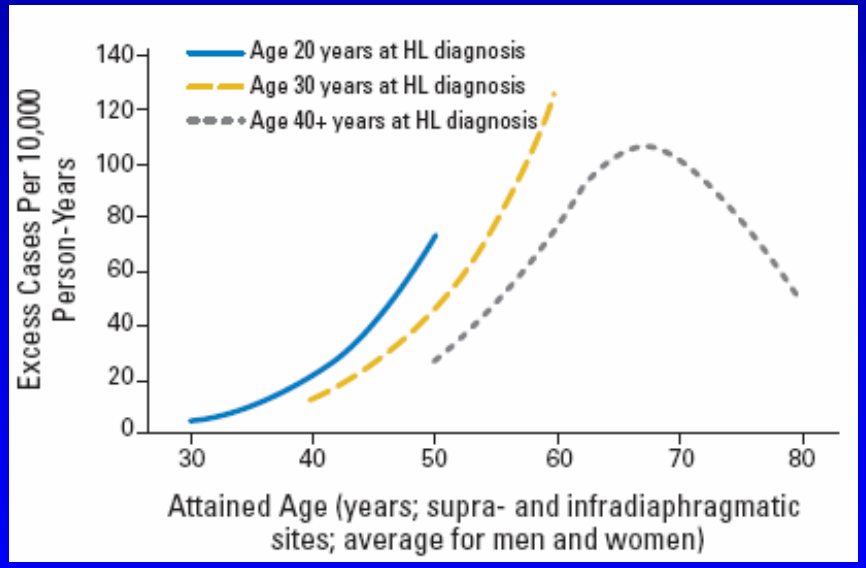
Non-Breast SC Risks

Excluding thyroid

RR change with attained age



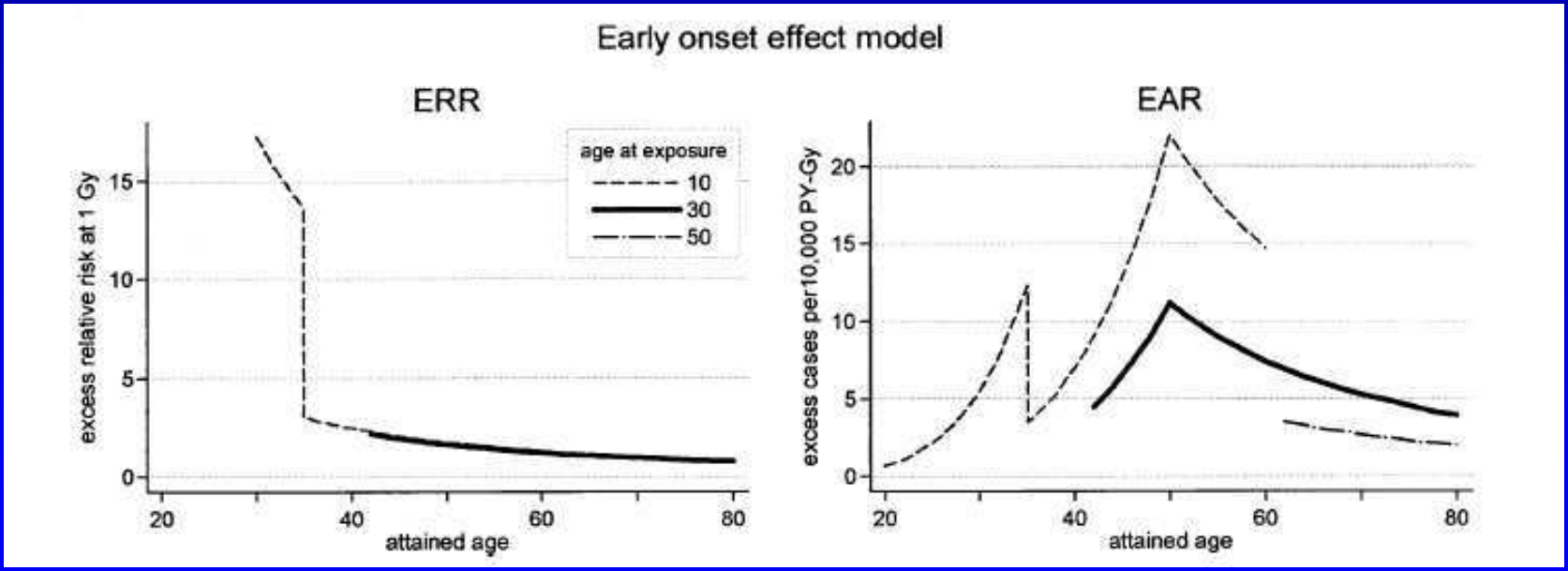
EAR change with attained age



Hodgson et al JCO 2007

But: Results Depend on Assumptions

A-bomb breast cancer risk w.”Early Onset Effect”



Preston et al Radiat Res 2007

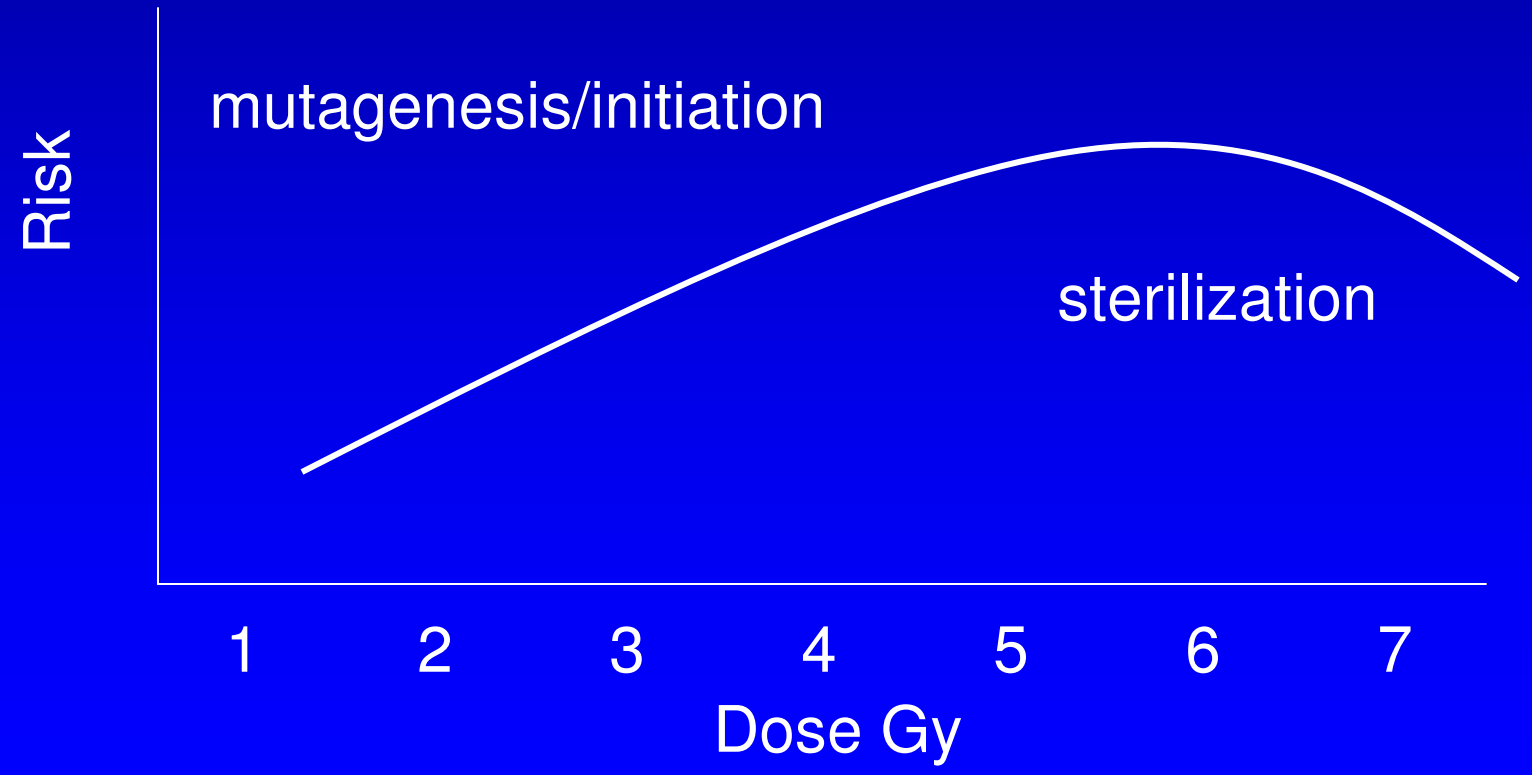
Challenge 1: Quantifying Second Cancer Risks Over Time

- A single summary SIR number is inadequate
- Risks change over time
- RR changes differently than EAR
- Risk is different for
  - patients treated at different ages
  - different organs exposed
  - males and females
- Accurate description of risk requires adjustment for age at exposure and attained age.

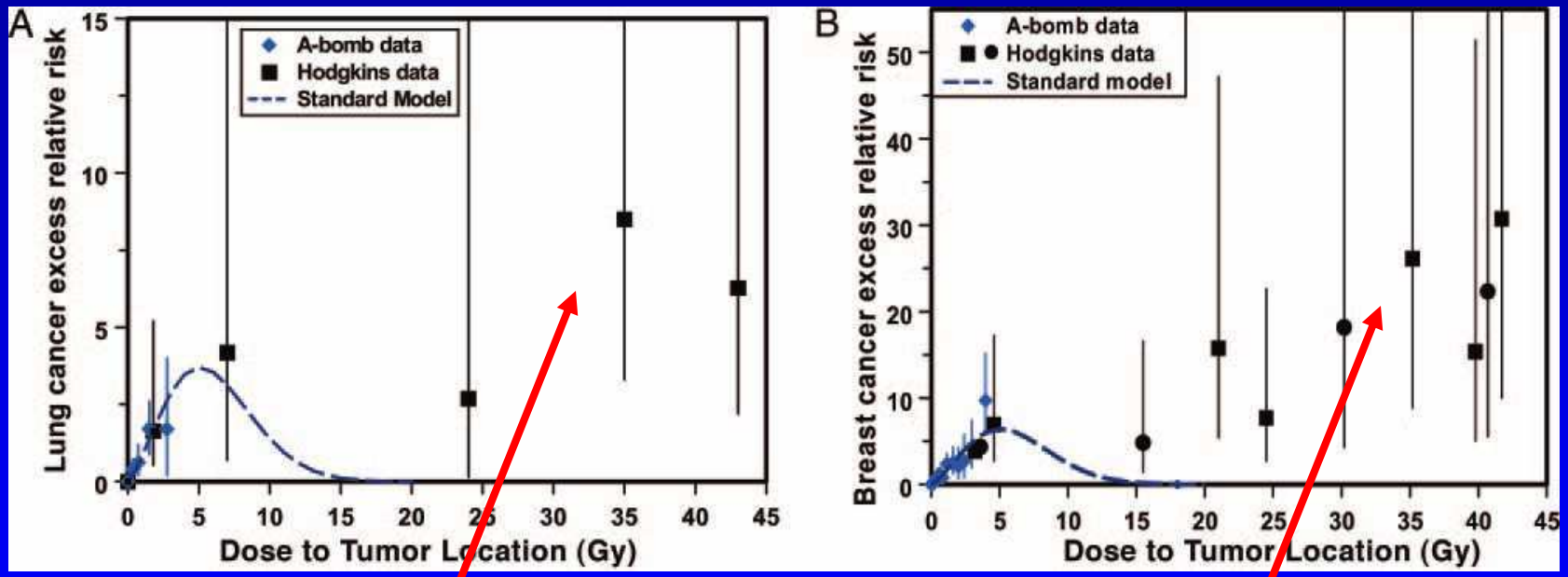
Challenge 2: Modeling the Dose-Risk Relationship

The Classical 2-Step Model

$$I^{org} = I_0{}^{org} D e^{-\alpha org D}$$

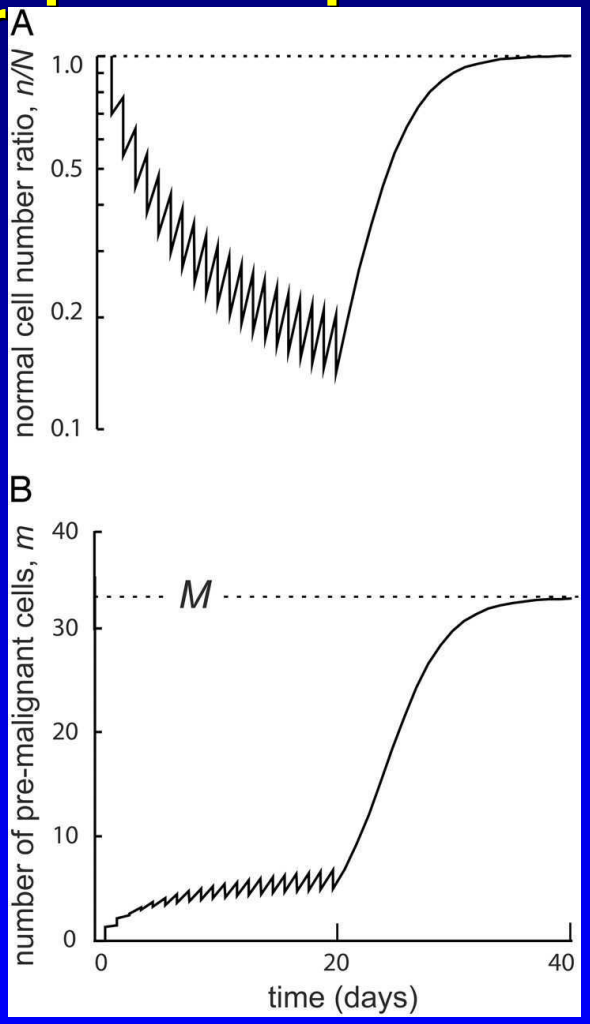


Cell Killing is Not the Dominant Effect With Doses > 5Gy



Sachs and Brenner, PNAS 2005

Initiation/Inactivation/Proliferation Model of Car



Risk of SC proportional to the number of pre-malignant stem cells created and surviving RT. Related to:

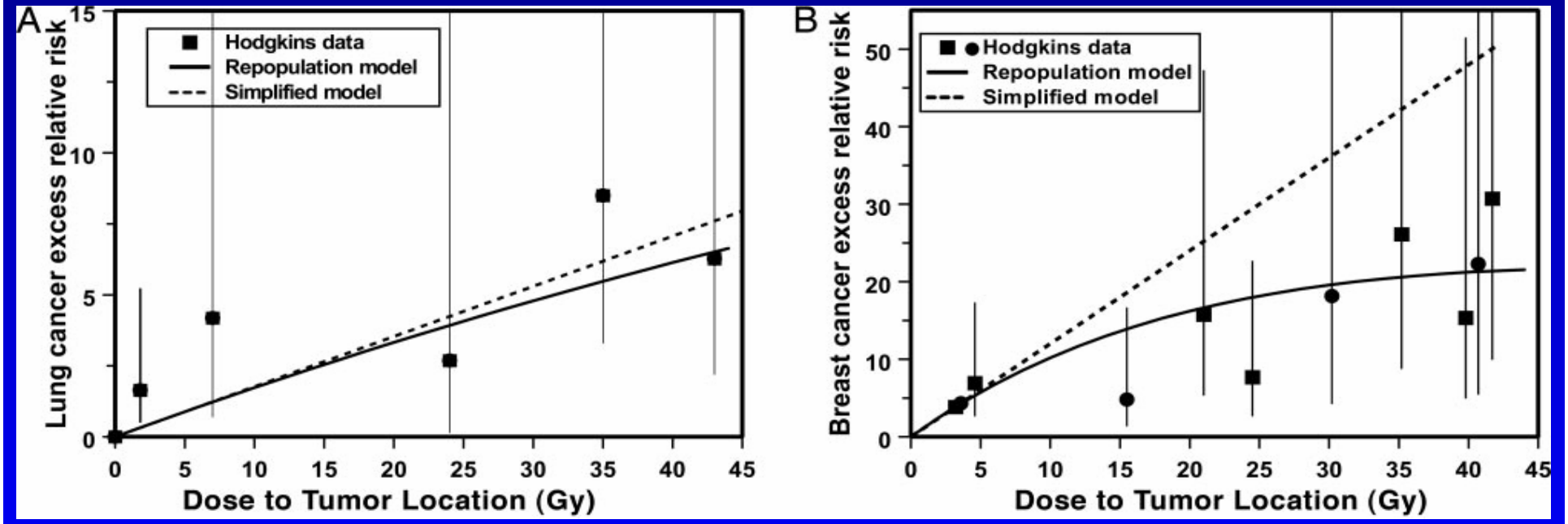
1. cell killing

2. cellular repopulation occurring between fractions and after the last fraction

3.the ratio of proliferation rate for pre-malignant cells to the proliferation rate of normal cells.

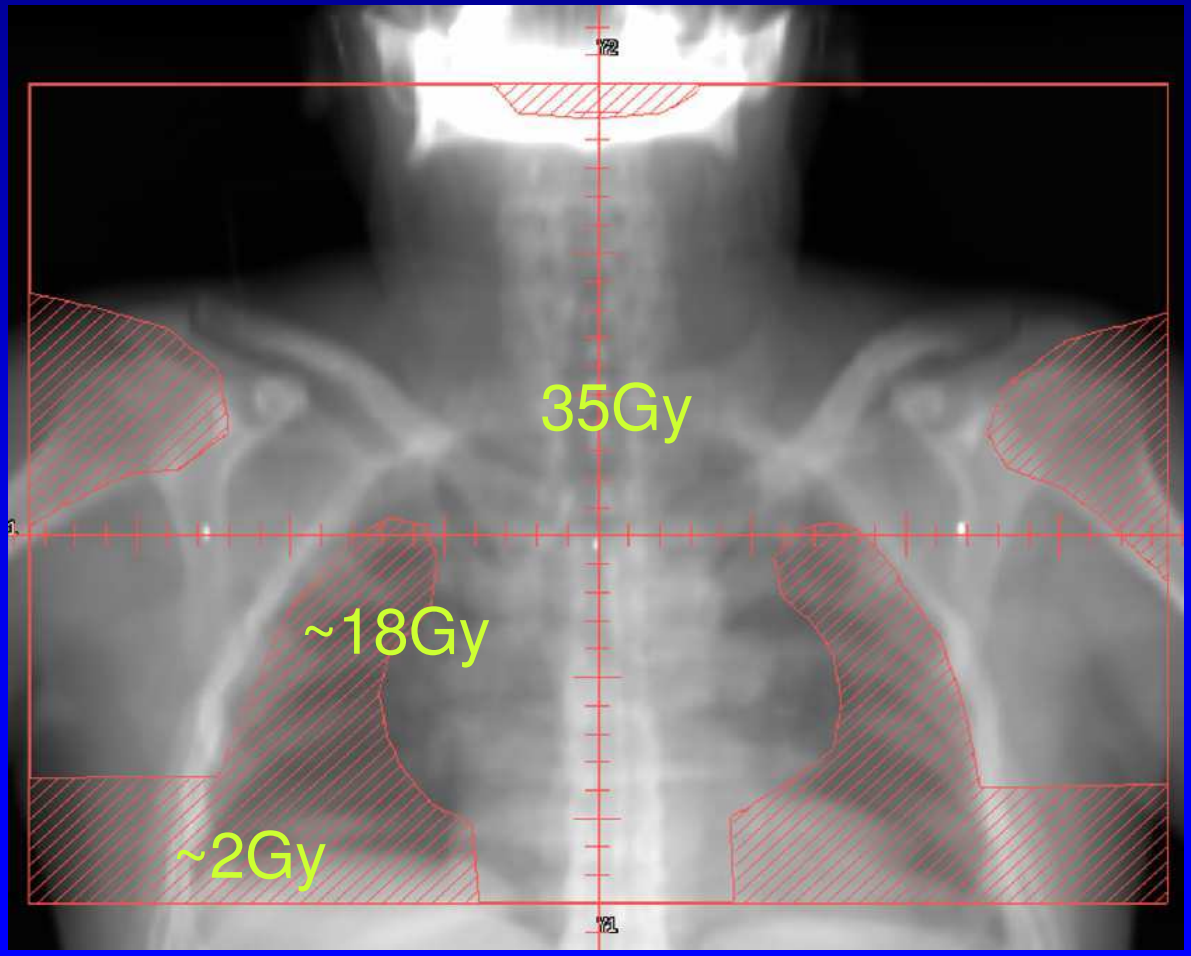
Sachs, Rainer K. and Brenner, David J. (2005) Proc. Natl. Acad. Sci. USA 102, 13040-13045

Model Predictions More Consistent With Observed SC Risk

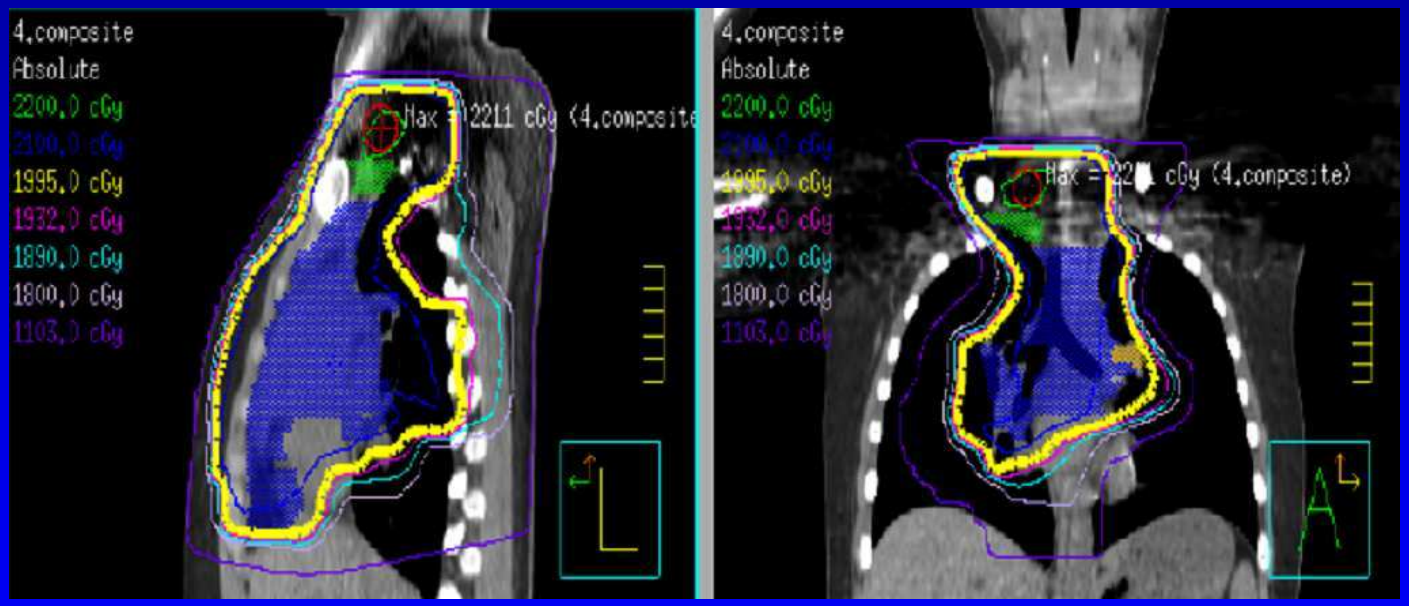


Sachs and Brenner. PNAS 102, 13040-13045, 2005

Challenge 3: Moving from 2D Point Doses to Volumetric Dosimetry



Challenge 3: Moving from Point Doses to Volumetric Dosimetry



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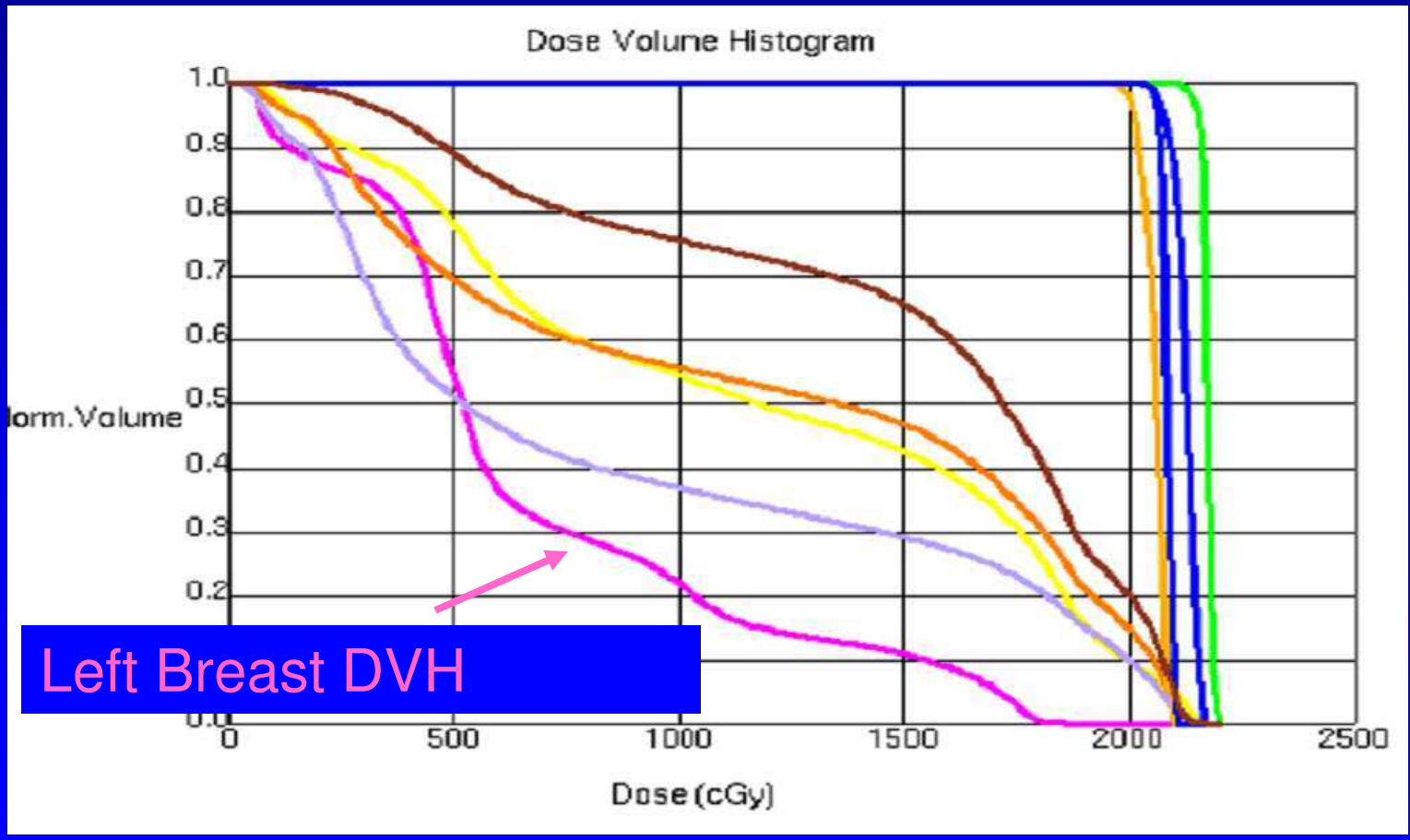
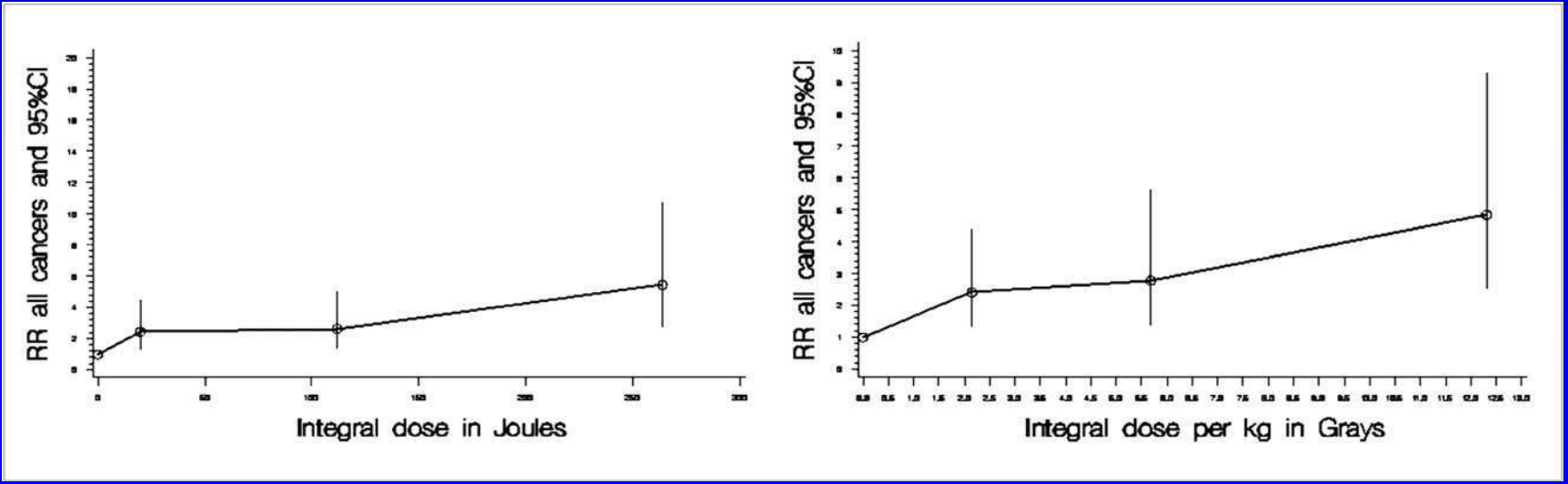


Integral Dose as a Risk of SC

- Integral dose = E deposited in the body
  = dose x mass
- Proportional to area under DVH curve

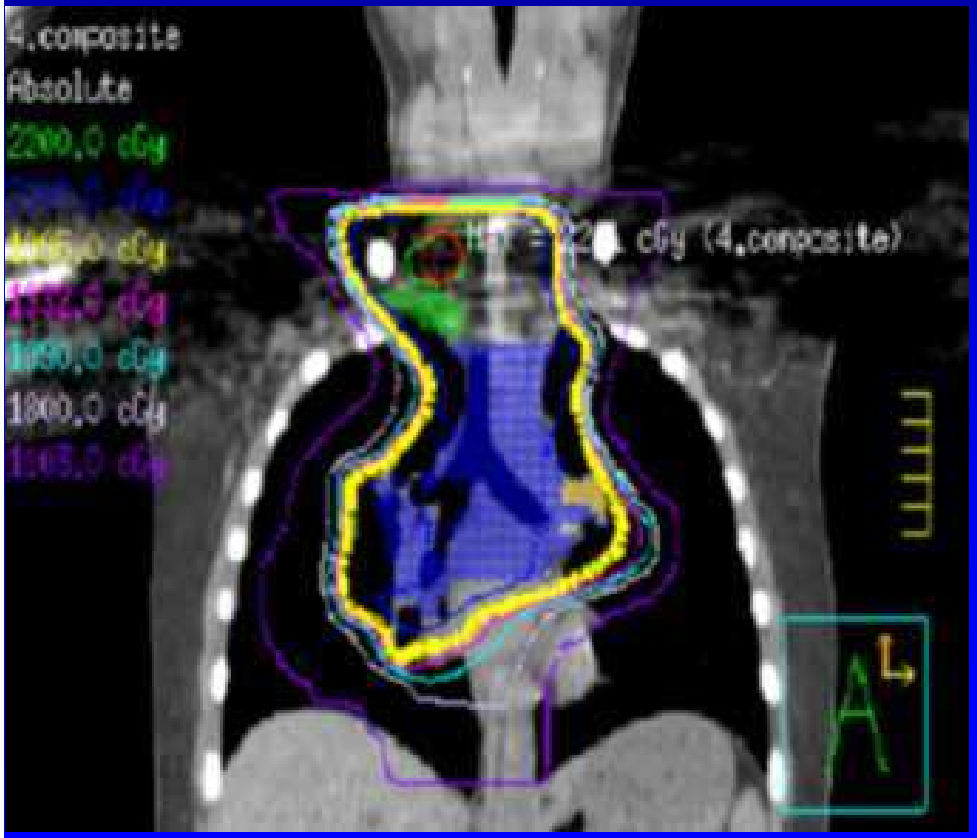


Nguyen et al. IJORBP, 2008

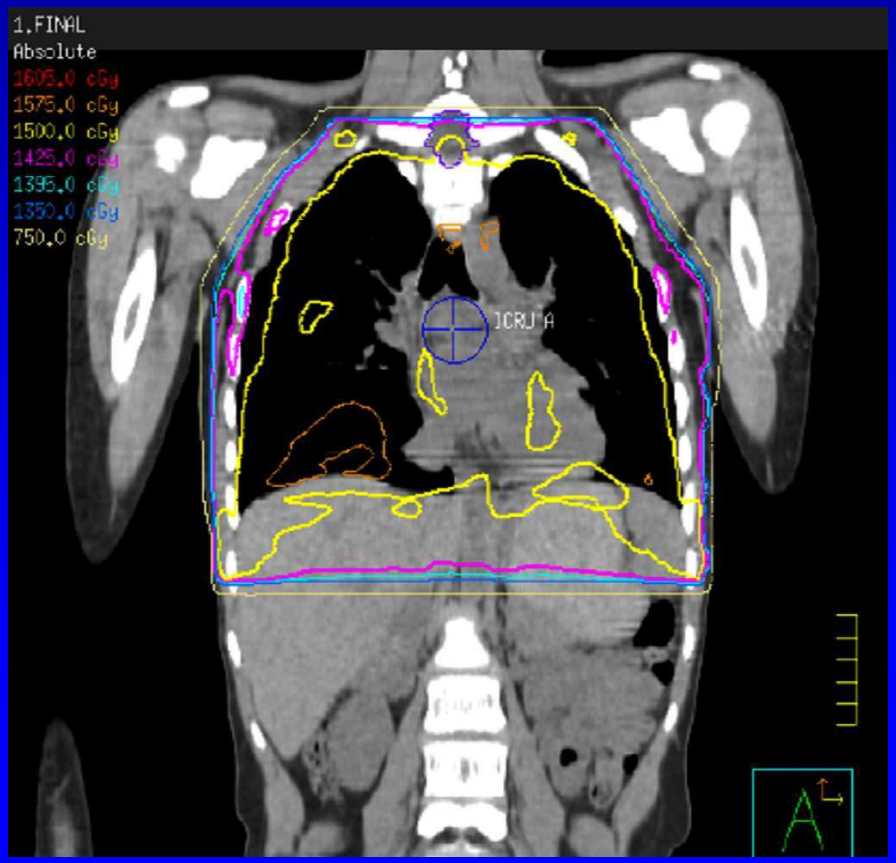
Problem with Integral Dose

- Very different dose distributions, same integral dose to lungs

21Gy to mediastinum



15Gy to both lungs



Problem with Integral Dose

- Limited range of integral doses, limited discriminatory power between patients, reduced predictive value

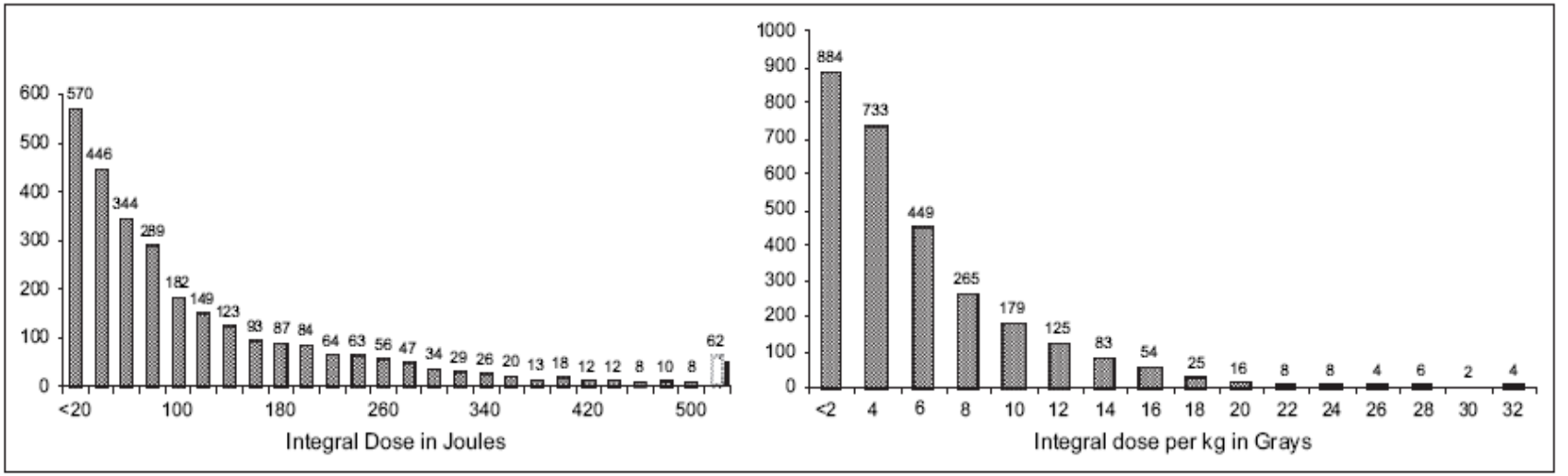


Fig. 1. Distribution of the integral dose restricted to the irradiated fields (left panel) and the integral dose per kilogram (right panel): number of patients per dose unit.

Nguyen et al. IJORBP, 2008

Challenge 4: Competing Risks of Death In Long Term Survivors

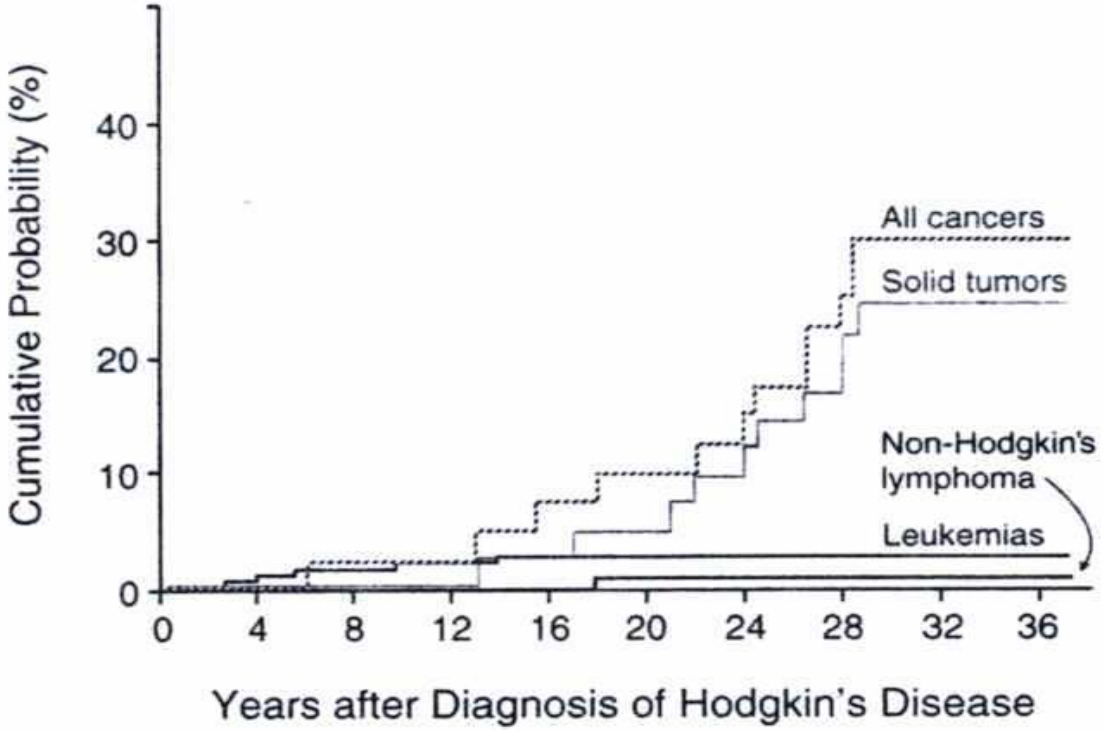


Figure 1. Cumulative Probability of Second Cancers in 1380 Patients with Hodgkin's Disease in Childhood.

NEJM 334: 745-51, 1996

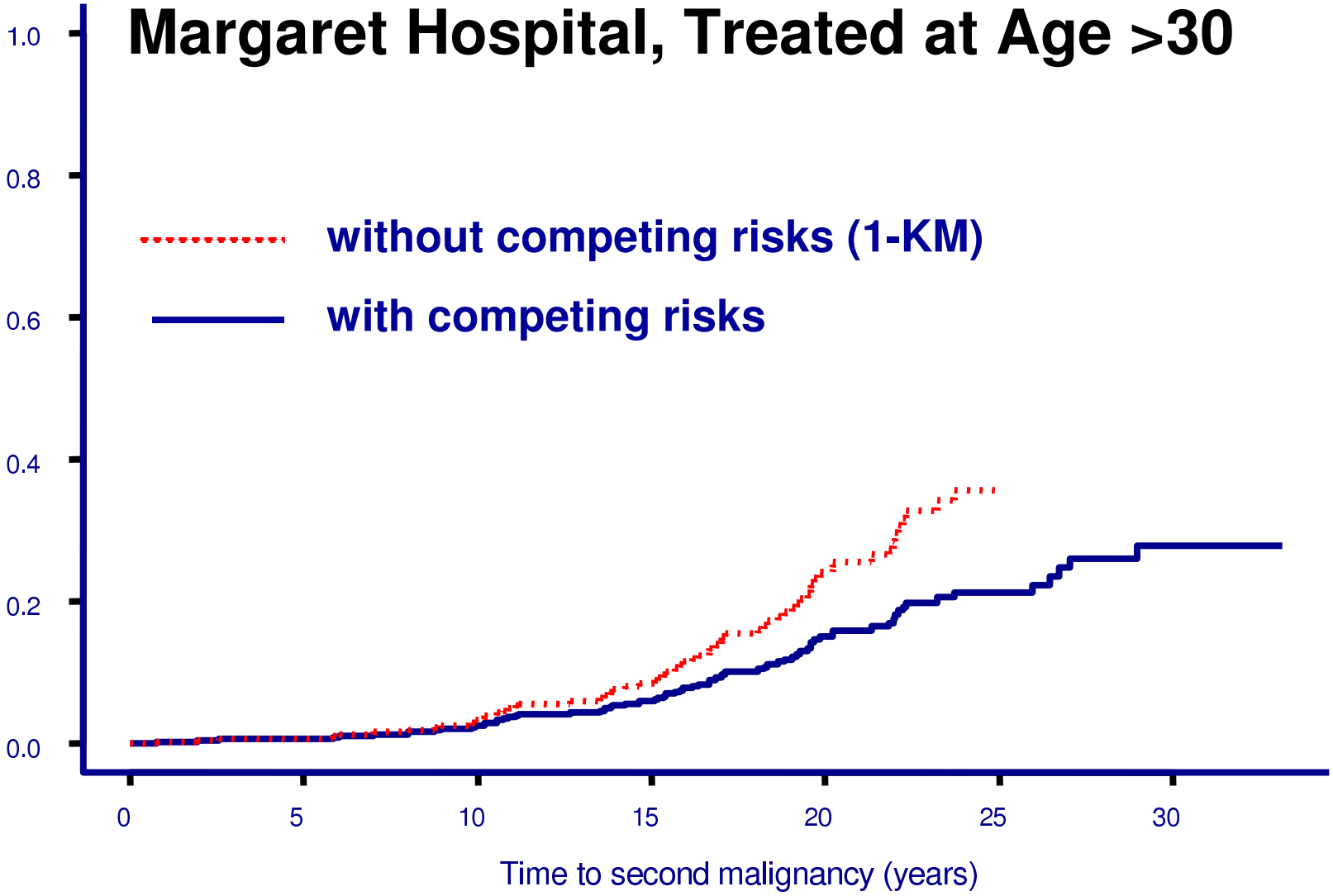
Problem with KM, SIR, AER Estimates

- Kaplan-Meier method was developed to estimate overall survival, where the event (death) is inevitable.
- It assumes that censored patients are as likely to develop the event as those who remain in the analysis.
- aka “non-informative censoring”.

Implication for SC Estimates

- In many analyses, patients are censored at the time of relapse, death from HL or any death occurring before the late effect of interest.
- The assumption of non-informative censoring implies that these dead patients are as likely to develop the late effect as the surviving patients(!)
- The result is an overestimation of the cumulative incidence of the late effect.
- Also true for SIR and AER which censor at time of death.

Cumulative Incidence of Second Cancer in Hodgkin Lymphoma Survivors at Princess Margaret Hospital, Treated at Age >30



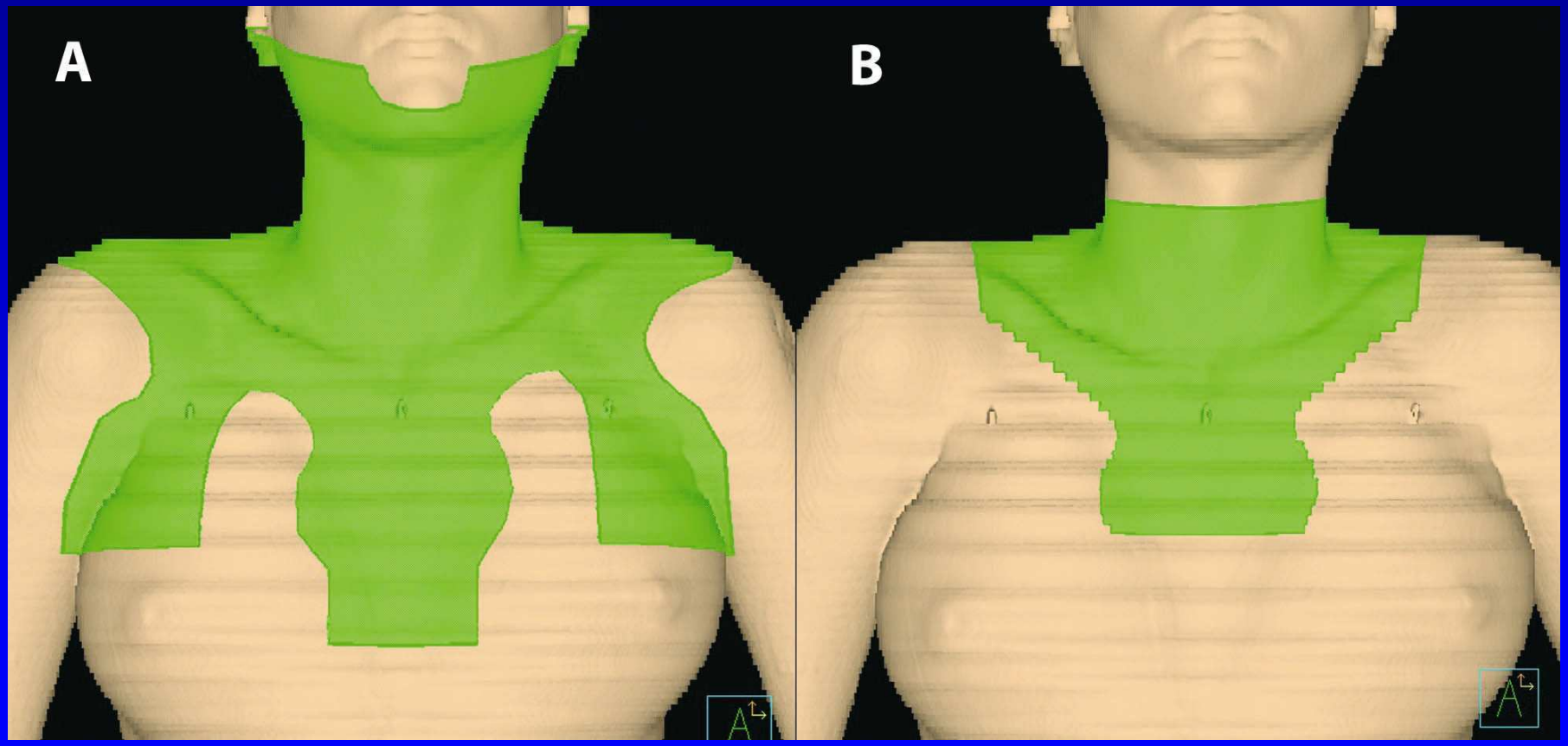
Preliminary Attempt to Address Some of These Issues

To estimate the excess relative risk (ERR) and cumulative incidence of secondary lung and breast cancer following

1. Full Mantle RT 35Gy (historic)
2. IFRT 35Gy (current)
3. IFRT 20Gy (future)

using 3D volumetric dose data and contemporary radiobiologic models of carcinogenesis.

Modeling Second Cancer Risk
Full Mantle vs. IFRT



Methods

- 3D dosimetry data (for each voxel) to lung and breast tissue obtained from CT planning dataset.
- Initiation/Inactivation/Proliferation model applied to dosimetry data to establish risk associated with each voxel/dose combination. Overall risk is volume average.
- For each patient ERR calculated for each of 3 planning scenarios
  - 35Gy mantle
  - 35Gy IFRT
  - 20Gy IFRT
- Competing risks estimates of cumulative incidence calculated.

Patient Characteristics

- 38 patients consecutively treated patients with mediastinal HL
- 22 females, 16 males
- median age 27 years (range 14- 58yrs).

Reduction in Normal Tissue Dose With Transition From Mantle to IFRT

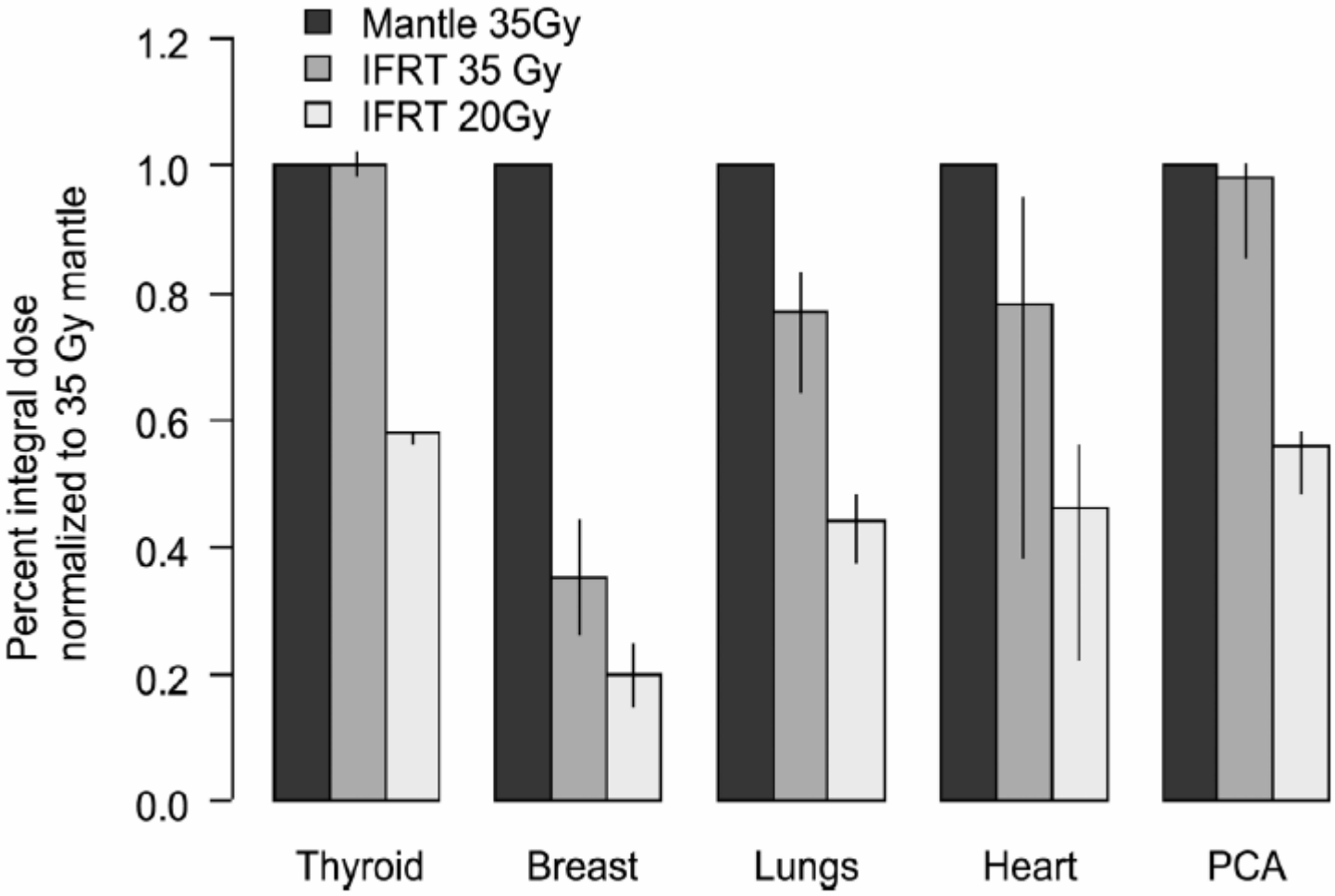
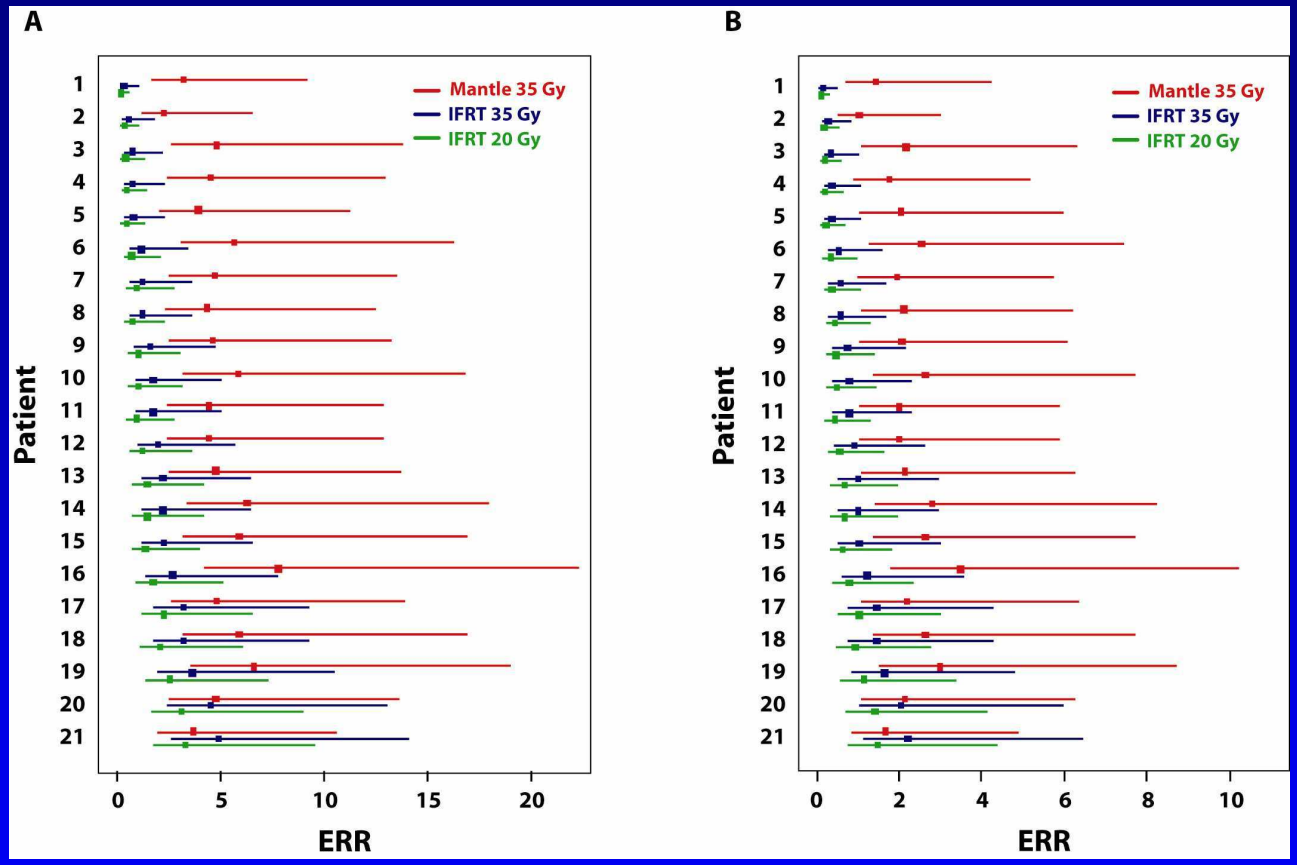


Figure 3
Proportional reduction in integral dose to normal tissues

Radiation Oncology **2007, 2:13**

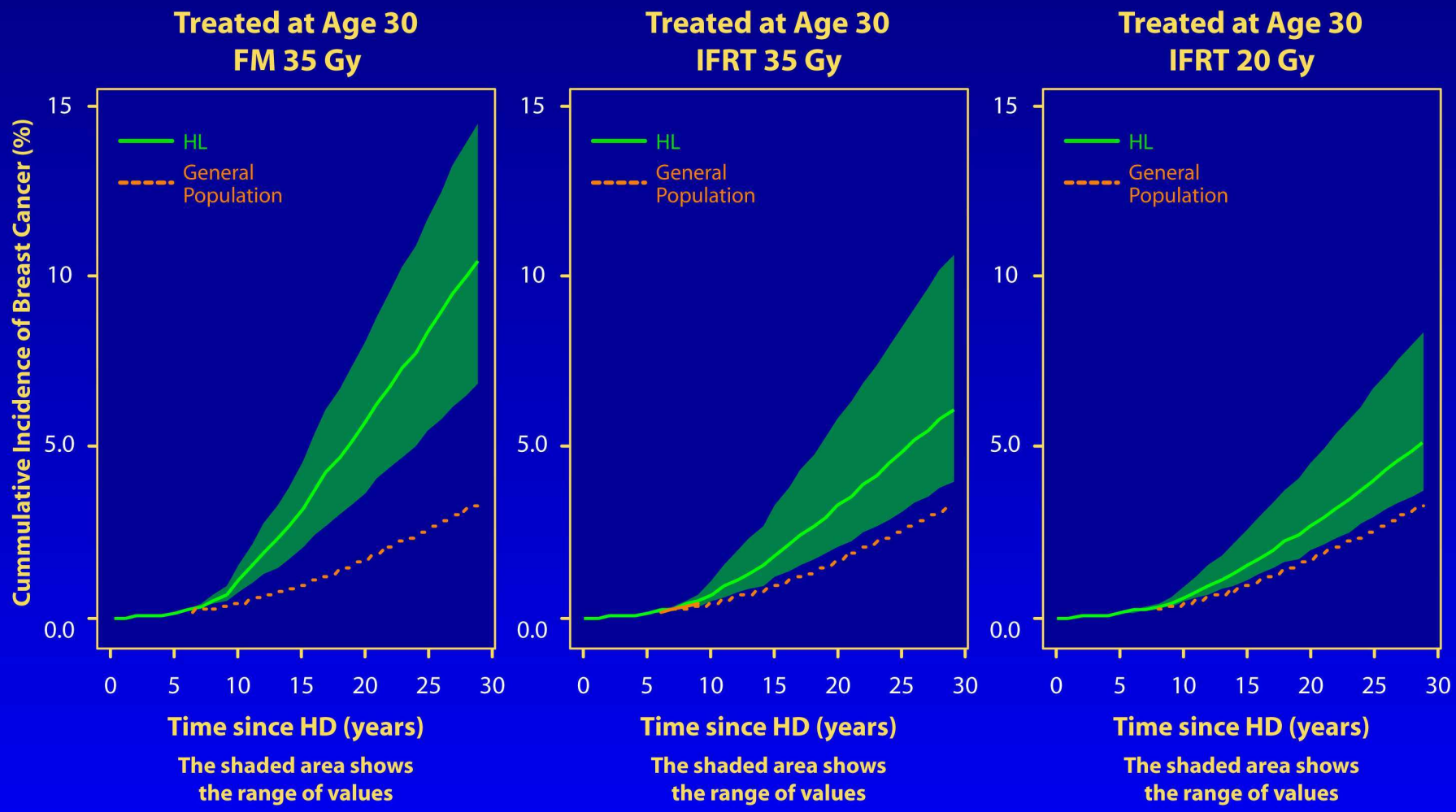
Reduction in ERR of Breast Cancer



Age 20 at RT
median ERRs
4.8 (35Gy mantle)
1.8 (35Gy IFRT)
1.1 (20Gy IFRT)

Age 30 at RT
median ERRs
2.1 (35Gy mantle)
0.8 (35Gy IFRT)
0.5 (20Gy IFRT).

Reduction in Cumulative Incidence of Breast Cancer- Age 30 at RT



Hodgson et al , Cancer 2007

Reduction in ERR of Lung Cancer

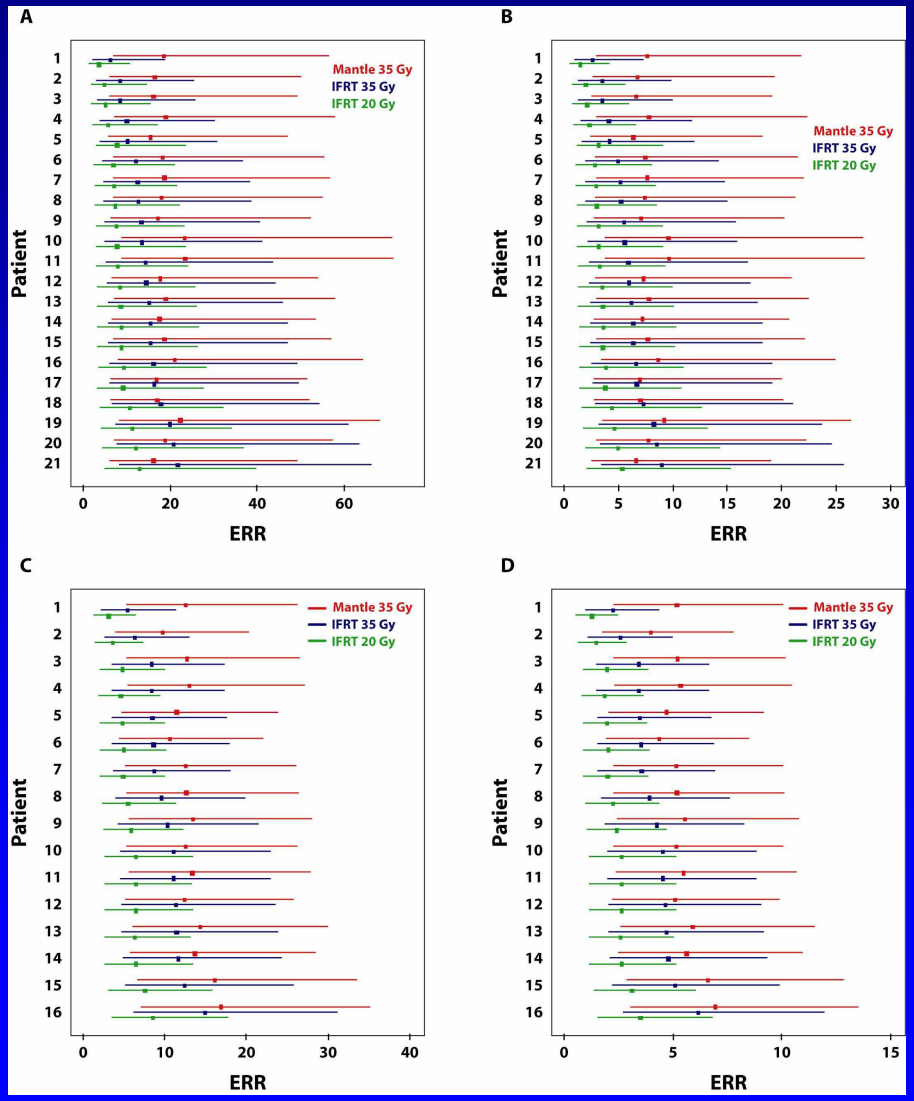


Figure 4. Individual patients' ERR estimates of lung cancer among non-smoking HL survivors.

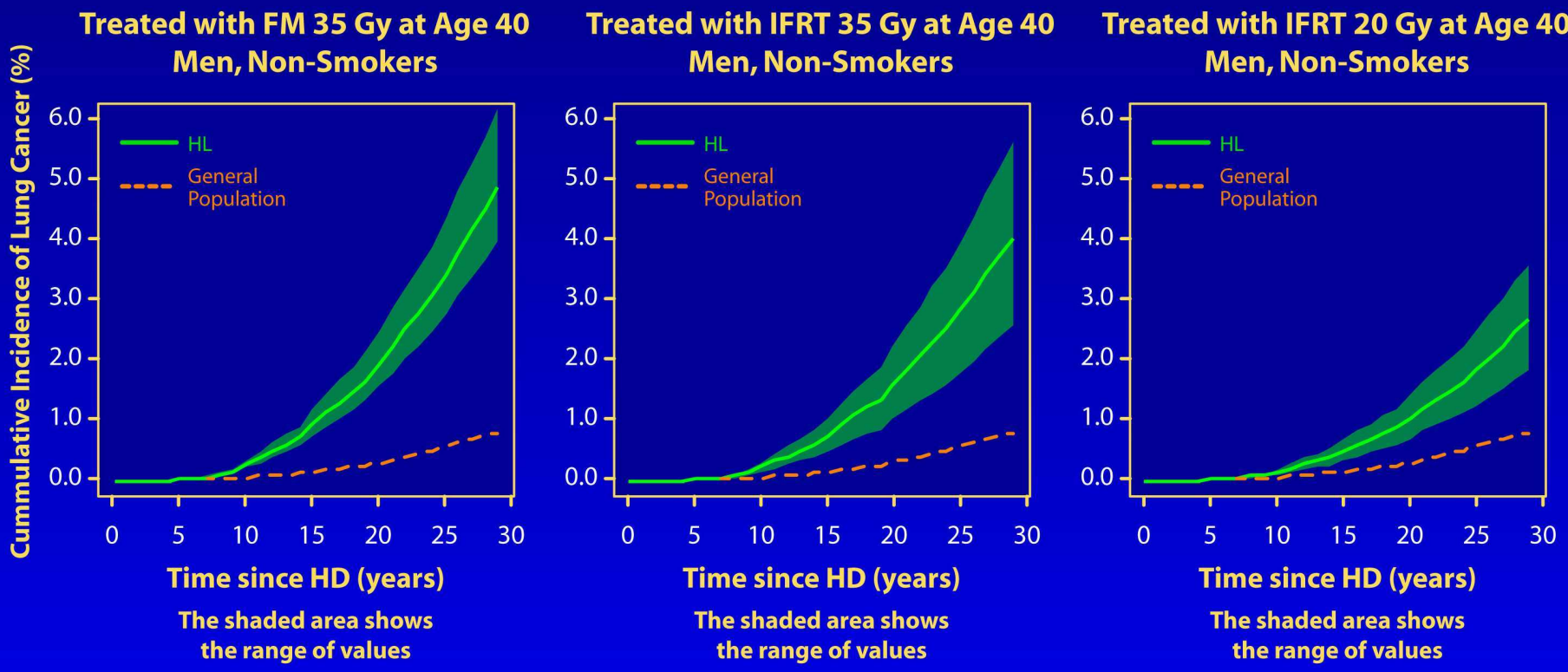
A. Females age 20: median ERRs: 18.0, 14.2 , and 7.8;

B. Females age 30: median ERRs: 7.4, 5.8, and 3.2

C. Males age 20: median ERRs: 12.6, 9.9, and 5.6;

D. Males age 30: median ERRs: 5.2, 4.1, and 2.3.

Reduction in Cumulative Incidence of Lung Cancer: Males age 40



Hodgson et al , Cancer 2007

Summary

- Data are emerging regarding the dose-risk response of different tissues within the therapeutic range.
  - Different tissues have different response
- Contemporary models can be applied to 3D RT dosimetry data to create plausible estimates of SC risk.
  - Account for temporal and age-associated variation in risk
  - Account for competing risks.

Other Considerations

- Radiation is not the only cause of SC in HL patients.
  - Chemotherapy, genomic instability
  - Requires consideration in modeling work
- Reconstruction of 3D dosimetry from 2D planning data to analyze old cases.
- Very wide confidence intervals on risk estimates limits clinical utility.
- There is ongoing (and planned) work to address these issues.

Conclusions

- The planets are aligning:
  - 3D volumetric dosimetry is easy to obtain
  - Modeling of radiation-induced cancer risk as a function of time, age, and sex is entering clinical application
  - Understanding of dose-risk relationship for doses in the therapeutic range is advancing.

Conclusions

- Put together, these advances offer the possibility of:
  - Allowing oncologists to create RT plans that minimize the risk of SC
  - Counsel patients and create screening programs based on quantitative estimates of SC
  - Facilitate the rational design of clinical trials that aim to reduce late effects

What Do These Two Have in Common?

Henry L. Stimson
US Secretary of War 1940- 45

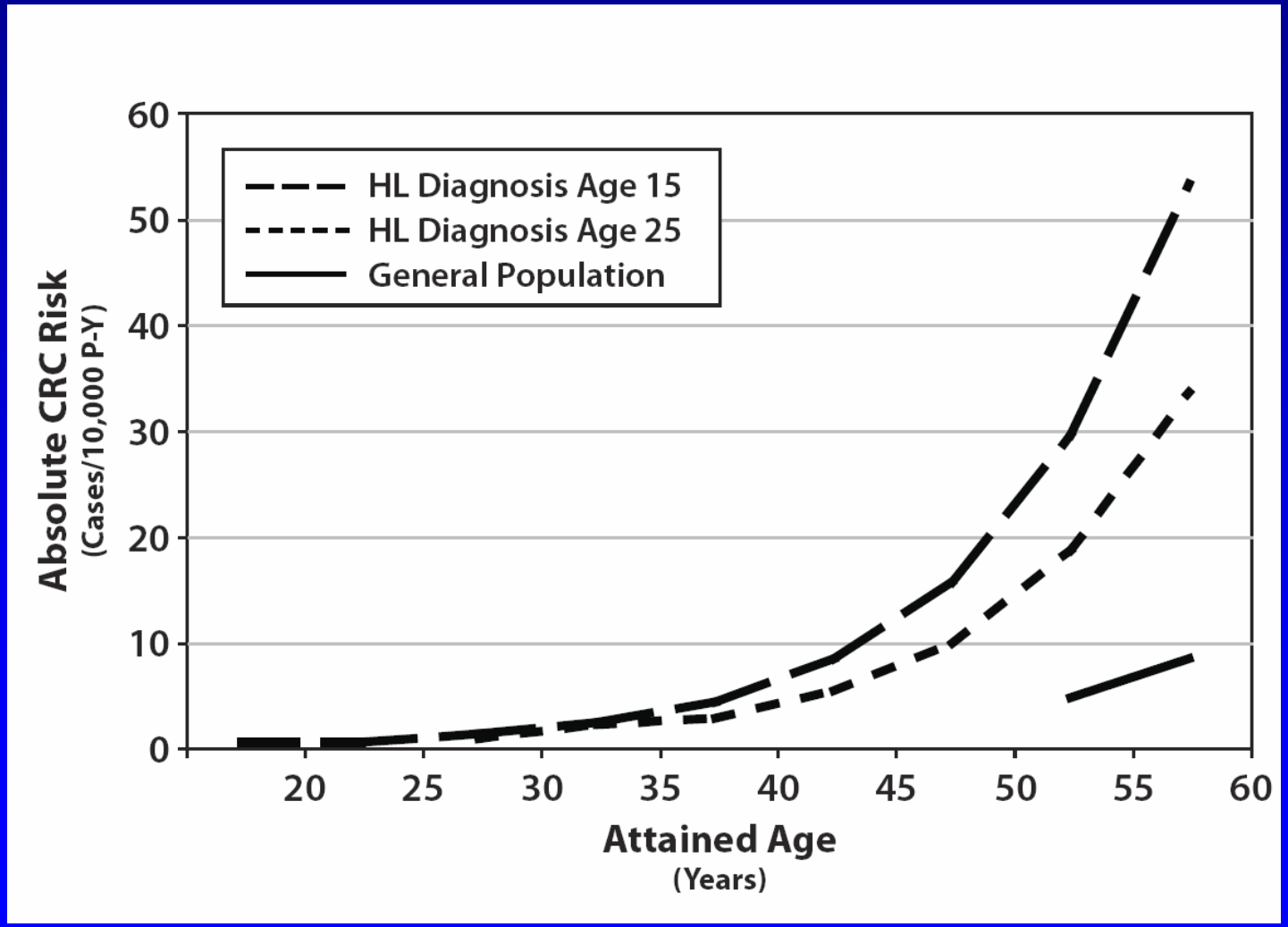
Stephane Dion's dog

Kyoto

For Lovers, not Fighters

Other Uses of Modeling SC Risk

Developing Guidelines For Follow-up



Importance for Estimating SC Risk

- Study modeling SC risk associated with photon v. proton RT for lymphoma
- Lifetime risk estimated as:

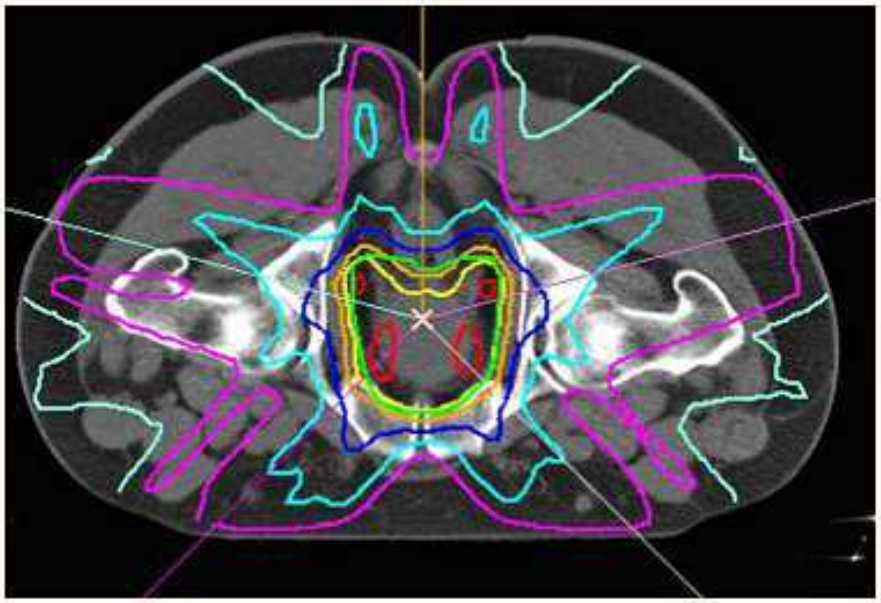
$$CI = (M_{HH} /100)*R$$

- Where M_{HH} = published estimates of excess cancers per 10^4 patients per year.
- R = residual life expectancy (=50 years).

Schneider et al Rad Res 2000

RT Related Second Cancers:

Not Just for Childhood Cancer Survivors

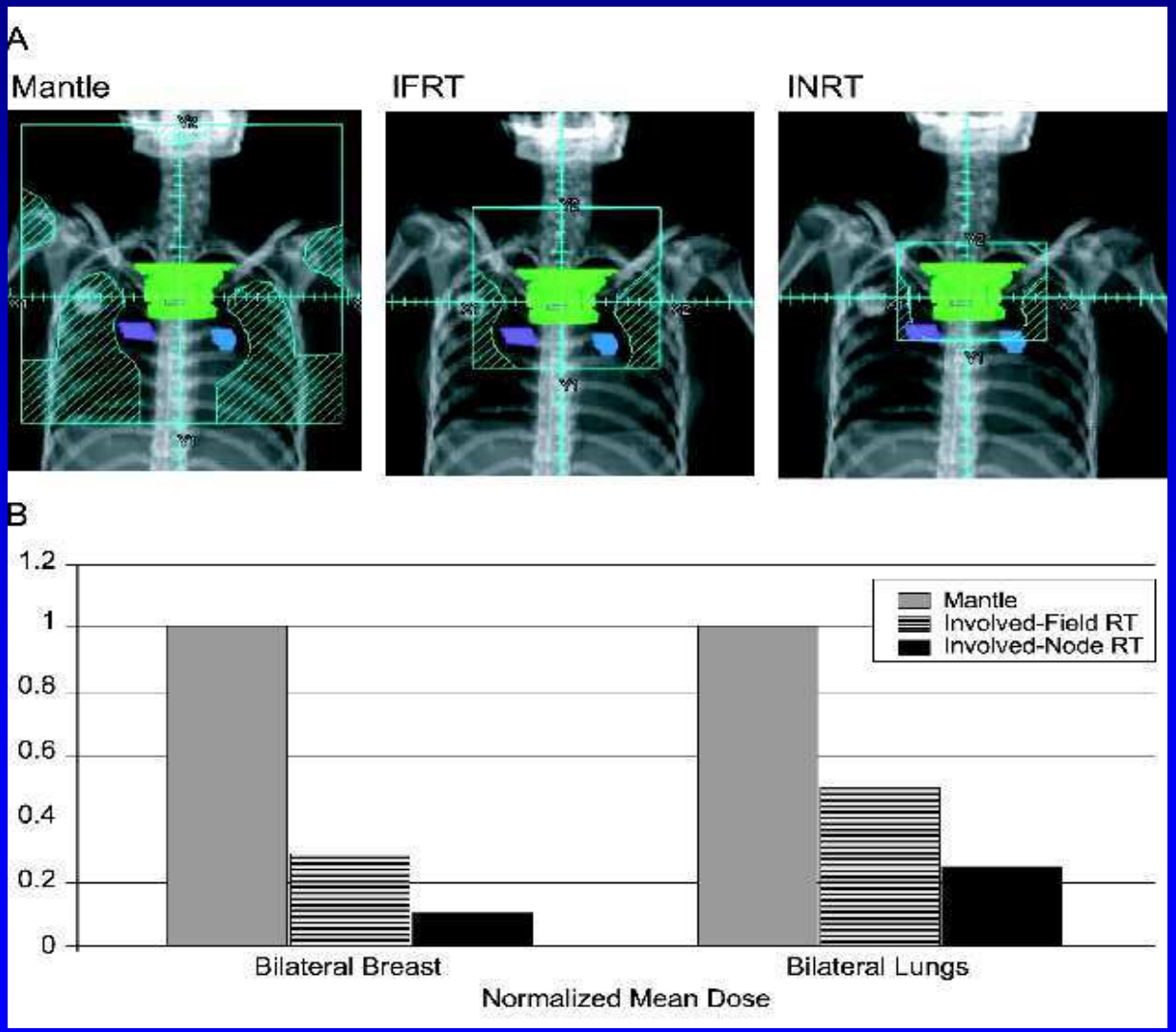


The automatic radiation planning algorithm results in beamlet intensities that produce equal-dose contours. The prostate (center) receives a high dose, while nearby tissue receives a low dose.

Image by Rensselaer/Richard Radke

From: Machine Learning Could Speed Up Radiation Therapy for Cancer Patients

Predicting Benefits of Potential Future Modifications to RT: Involved Node RT

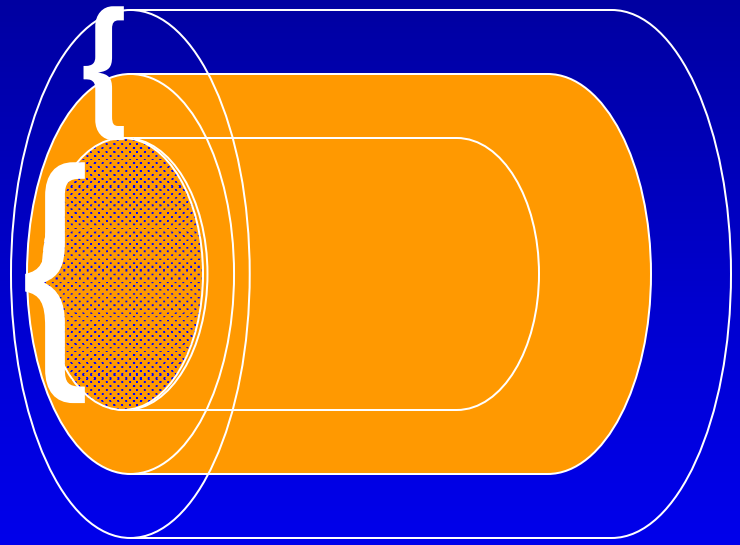


The Myth of "Intermediate Dose"?

Irradiating cylinder 10cm diameter, 20cm length

Volume +/- 1cm from edge = 1257 cc

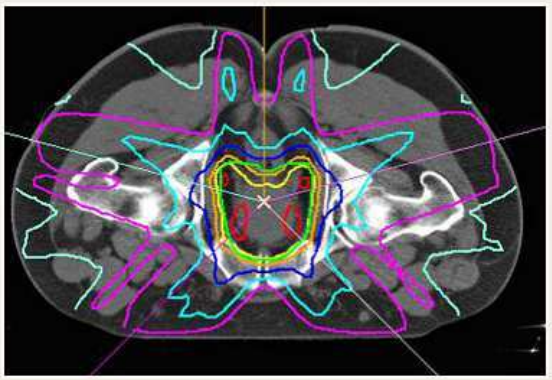
Volume >1 cm inside edge = 1005 cc



SCs occurring randomly in the irradiated volume may be expected to occur more often in the "intermediate dose" volume not because of lesser cell killing, but because it is often larger than the high dose volume

Other Clinical Considerations

- Absolute risk, not RR is the clinically relevant measure
- Confidence intervals around risk estimates are large.



The automatic radiation planning algorithm results in beamlet intensities that produce equal-dose contours. The prostate (center) receives a high dose, while nearby tissue receives a low dose.

Image by Rensselaer/Richard Radke

The Problem of Large Uncertainty in Risk Estimates

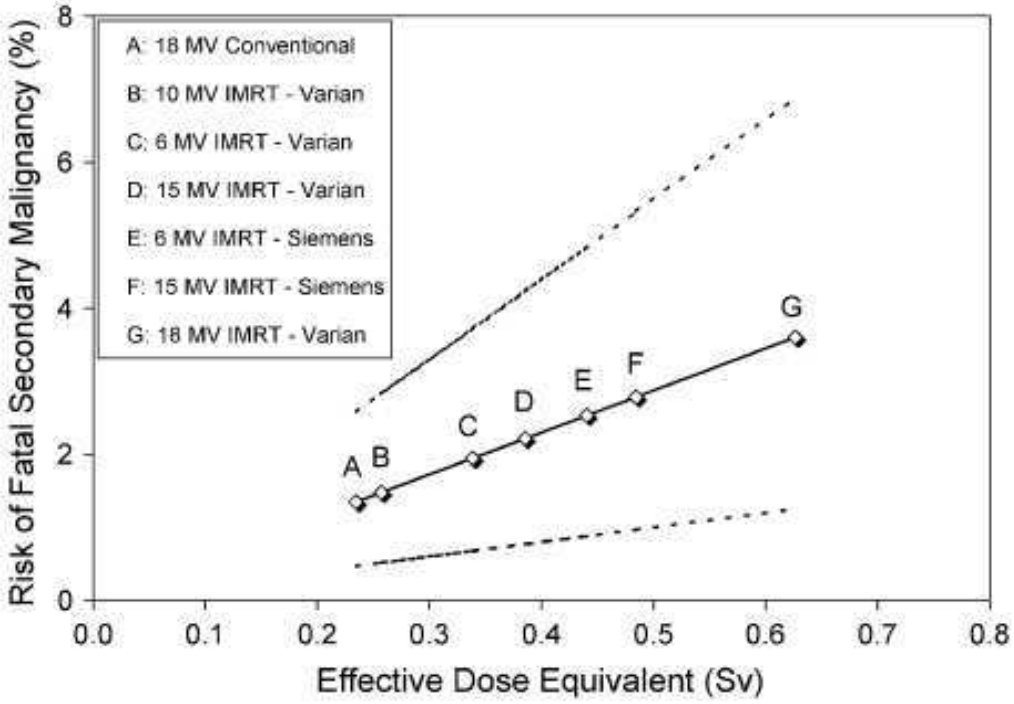


Fig. 1. Calculated risk of fatal secondary malignancy as a function of second-cancer low-dose effective dose equivalent of secondary fatal malignancies. The solid line is the EPA risk model for second cancer (10), the dashed lines are the 90% confidence intervals, and the points along the line are the data from Table 3.

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