Learning From the Fat Man

Understanding Second Cancer Risks for Clinical Use

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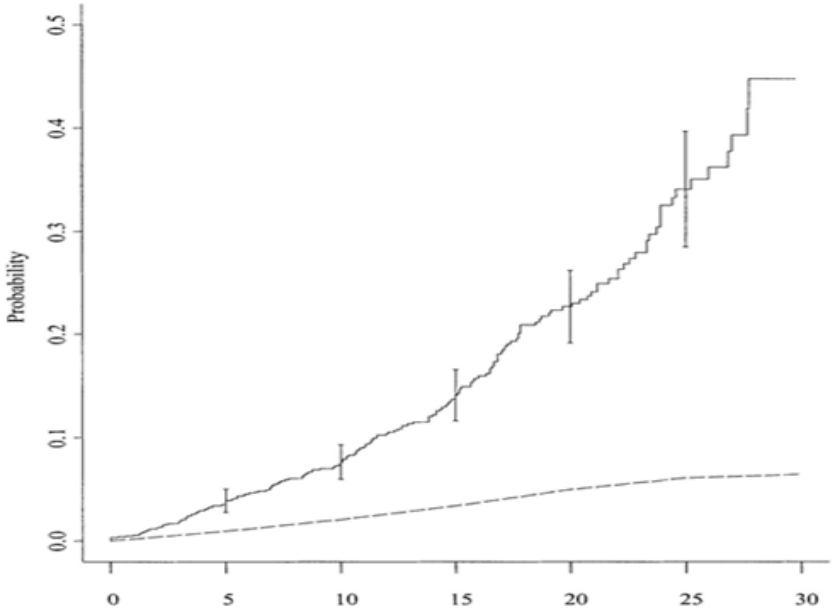
Introduction

- Second cancer risks: the clinical problem
- Conventional measures of risk and factors that influence risk
- Limitations of observational studies describing risk
- Radiobiologic modeling of second cancer risk
- Some WW2 history

Second Cancer Risk

36-40Gy Mantle RT

N = 1,319. Median Age = 25. Diagnosed 1969-1997



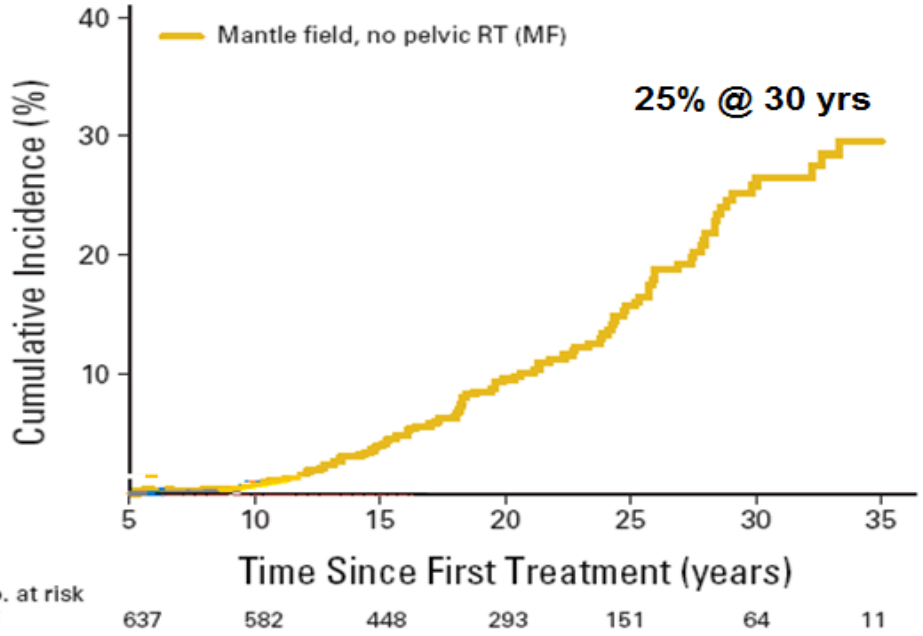
≈40% by 30 yrs

Expected rate ≈ 5%

Ng A K et al. Blood 2002;100:1989-1996

Breast Cancer Risk

40Gy Mantle RT, median age 26 at HL Dx

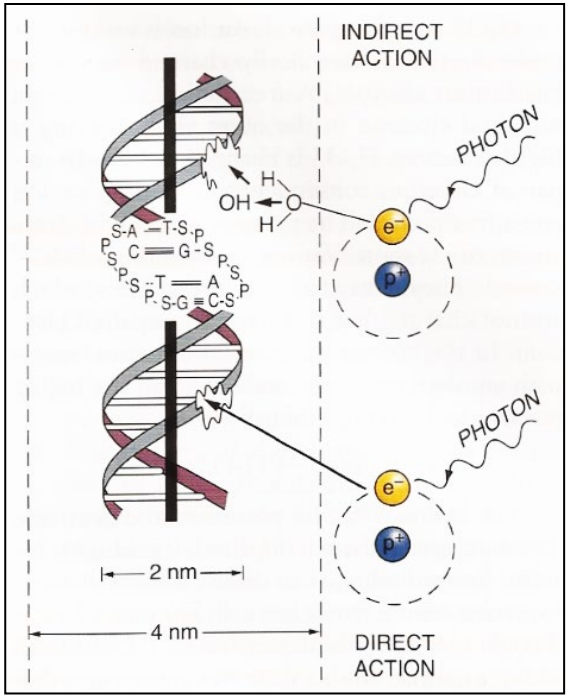


Elevated Risk of Second Cancers Seen Among Survivors

- Estimated 14-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.
- Currently ≈4800 patients aged <50 yrs received RT in Ontario annually.

Radiobiology of RT-related Second Cancer Risk

Sub-lethal DNA Damage & Telomere instability



Hall ed. Radiobiology for The Radiologist

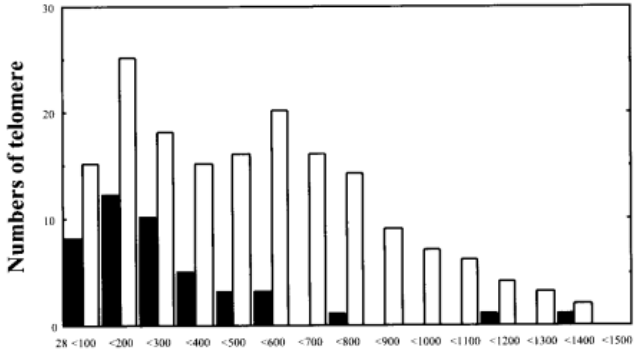
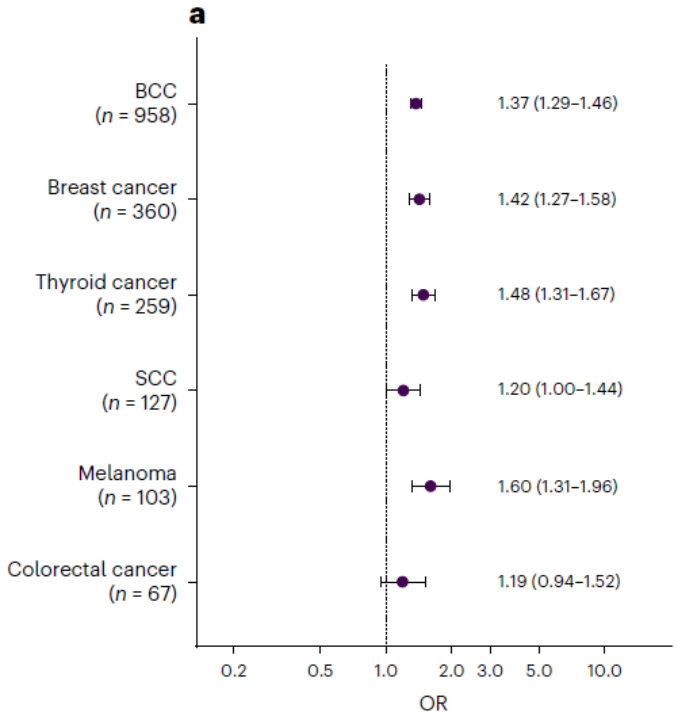
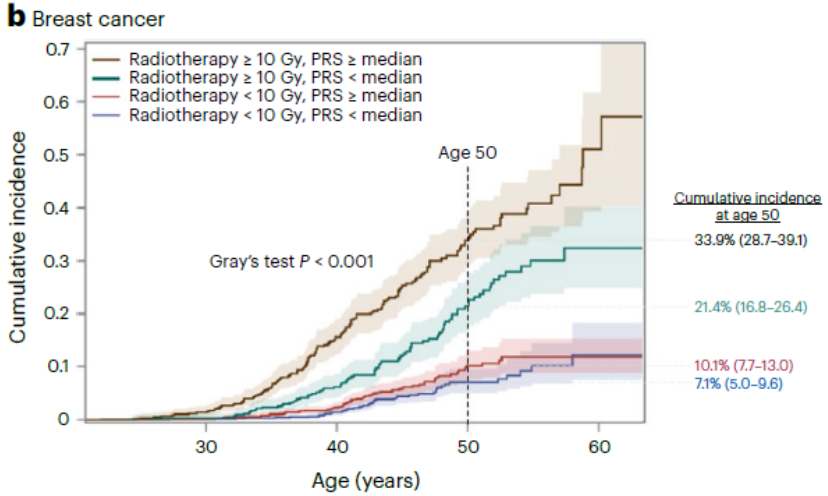


Fig. 4. Distribution of telomere fluorescence intensity in unirradiated BJ1-hTERT cells was compared with that of duplicated telomere in X-ray-surviving cells. Telomere fluorescence images were captured by IP-Lab image software, and fluorescence intensity was analyzed quantitatively by NIH image software. Open bars show the distribution of telomere fluorescence intensity in unirradiated cells. Close bars show the distribution of telomere fluorescence intensity in duplicated telomere.

J Radiat Res. 45: 105-110 (2004)

Genetic Predisposition to Second Cancers – Polygenic Risk Scores





Nature Medicine | Volume 30 | March 2024 | 690–698

Local Radiotherapy Induces Homing of Hematopoietic Stem Cells to the Irradiated Bone Marrow

Carlo Bastianutto,[1,4] Asim Mian,[1,4] Julie Symes,[1,5] Joseph Mocanu,[1,4] Nehad Alajez,[1,4] Gillian Sleep,[1,8] Wei Shi,[1,4] Armand Keating,[2,6] Michael Crump,[2,6] Mary Gospodarowicz,[3,7] Jeff Medin,[1,5] Mark Minden,[2,5,6] and Fei-Fei Liu[1,3,4,7]

Cancer Res 2007; 67: (21)

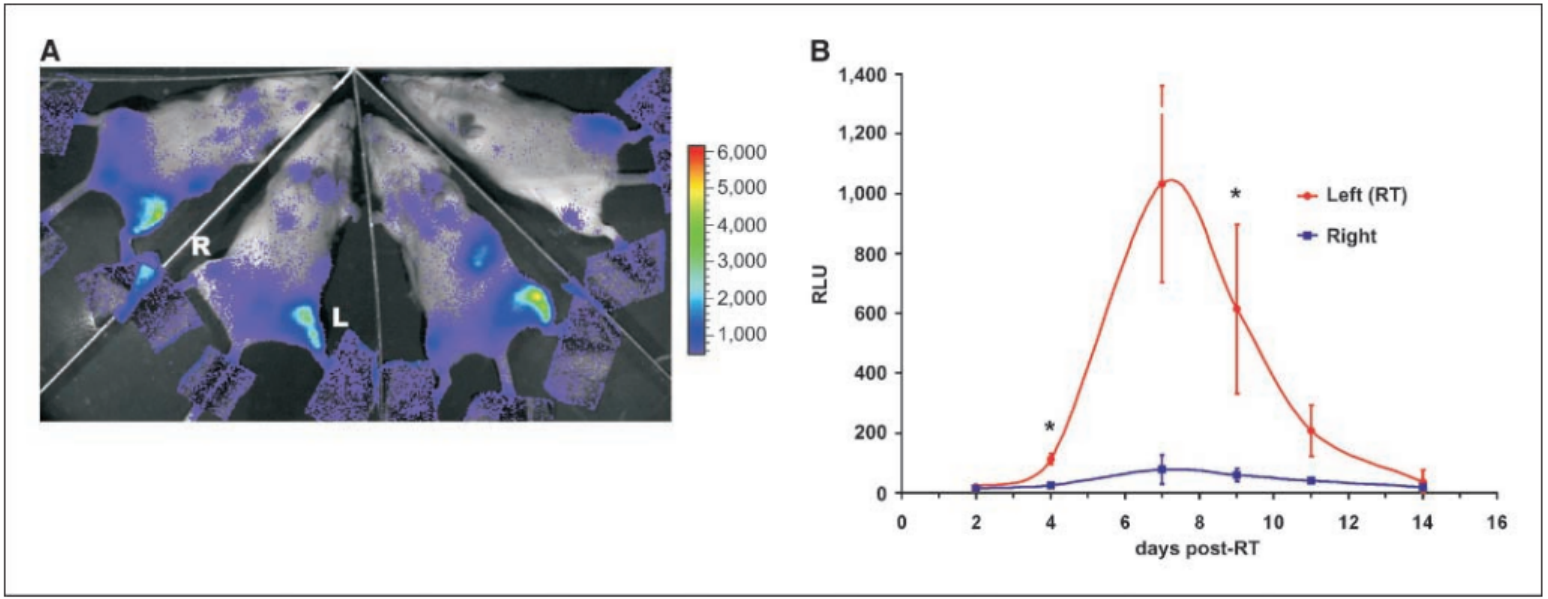


Figure 1. Recruitment of BMC to the site of local RT. *A, in vivo* imaging of luciferase expressing BMC in four representative mice 7 d after RT. Images were obtained with a CCD camera, and the BLI images were overlapped with a photographic image. *R,* right leg; *L,* left leg. *B,* relative luminescence signal intensity between the left (irradiated, *red*), and right (unirradiated, *blue*) legs of injected mice as a function of days post-RT. Mice were RT-treated on day 0 and injected with BMC on day 1. *Points,* average RLU from nine mice; *bars,* SE. *, $P < 0.01$, calculated by comparing the corresponding data time points between the left and right legs.

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.

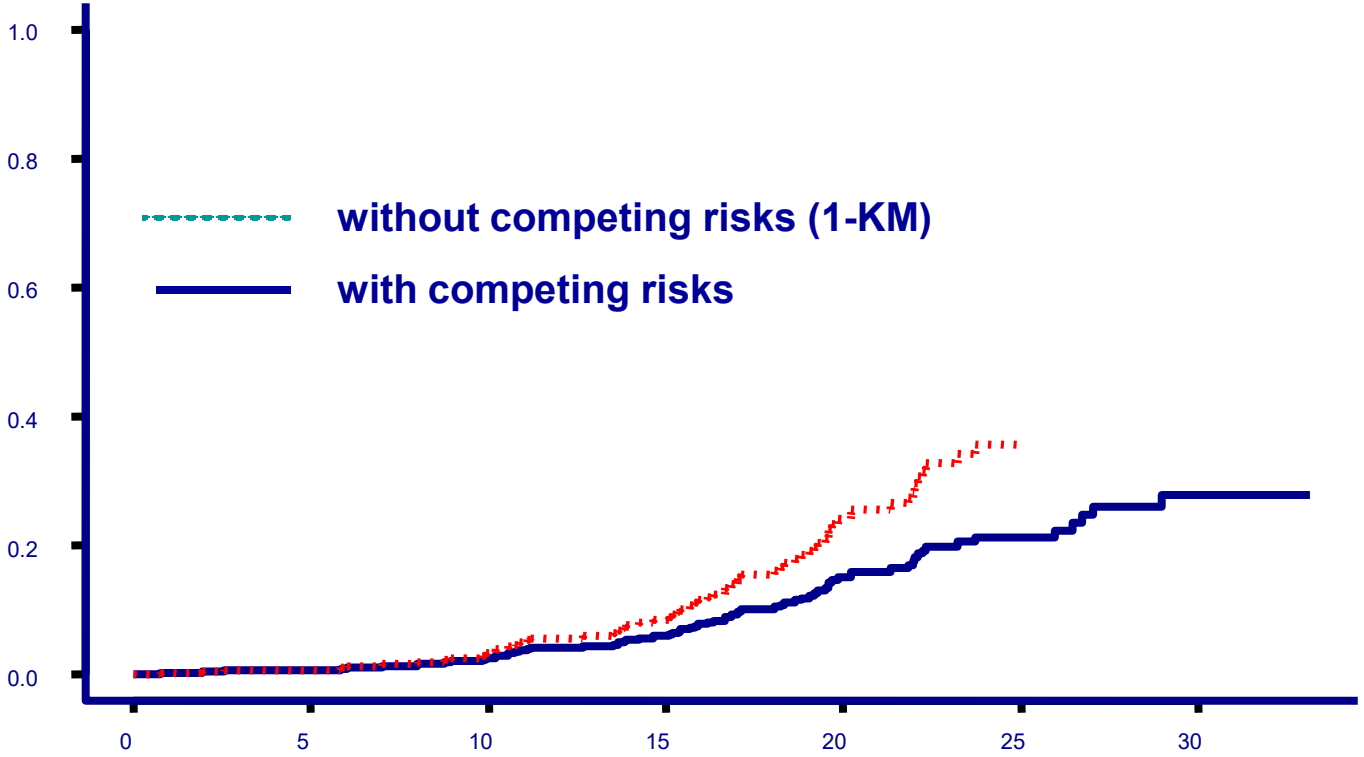
Problem with KM, SIR, AER Estimates

- 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 SMN 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.
- “Competing risks” methods are the appropriate approach.

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



Second Cancer Studies: *Caveat Emptor*

FULL TEXT ARTICLE

Incidence of Second Malignancies Among Patients Treated With Proton Versus Photon Radiation

"The use of proton radiation therapy was not associated with a significantly increased risk of secondary malignancies compared with photon therapy. Longer follow-up of these patients is needed to determine if there is a significant decrease in second malignancies. Given the limitations of the study, these results should be viewed as hypothesis generating."

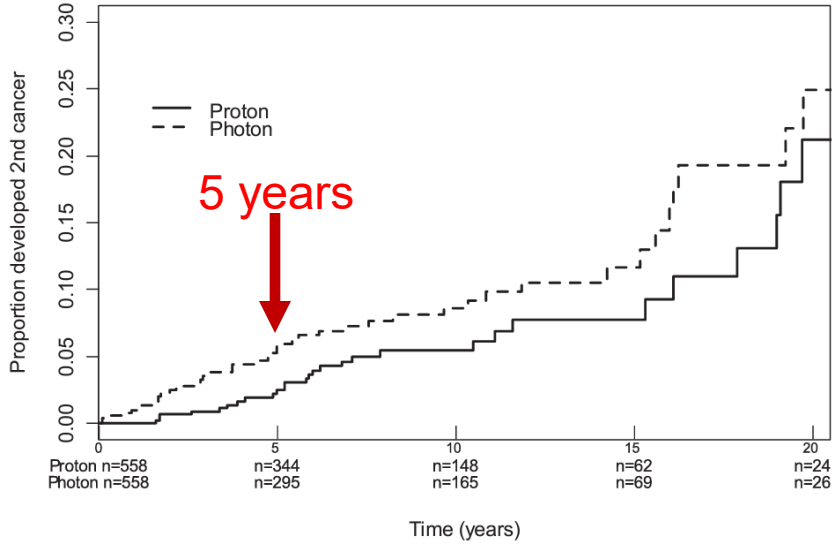
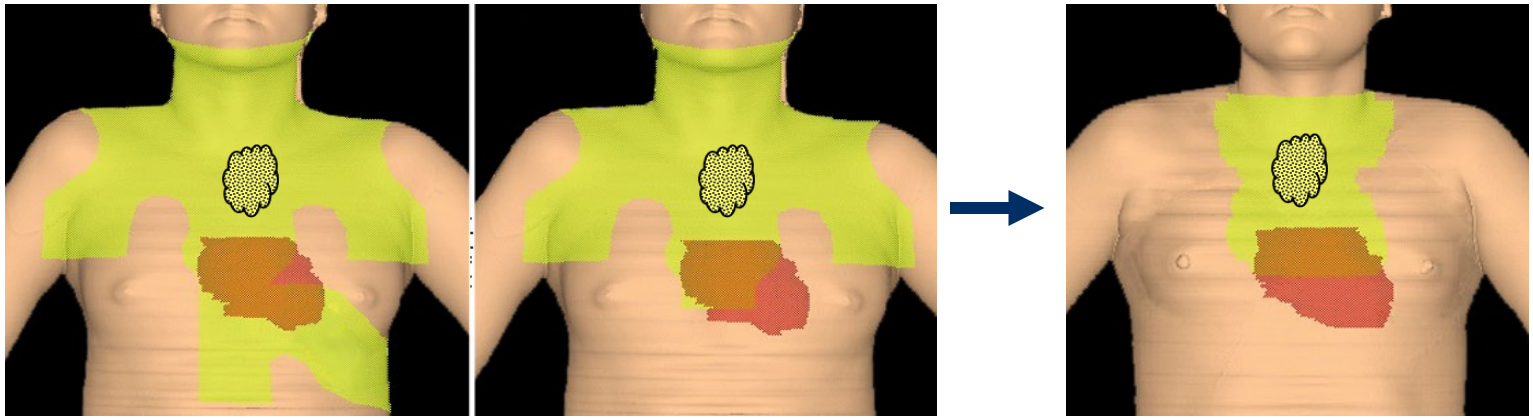


Fig. 1. Cumulative incidence curves for second cancer after radiation therapy for proton patients (solid line) and photon patients (dotted line) (log−rank $P = .085$).

IJORBP 2013

Observational Studies of Second Cancer Require Decades of Follow-up

Results Apply to Outdated Treatment

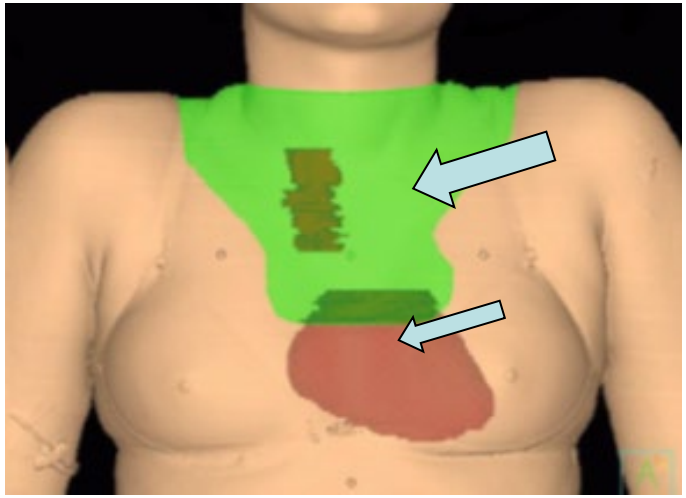


Subtotal nodal/extended-field/mantle

involved-field (IFRT)

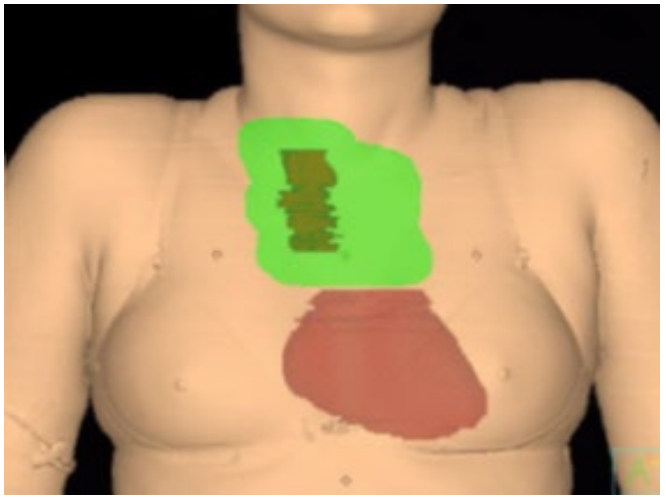
Treatment Practices Evolve

We want estimates relevant to current treatment



IFRT

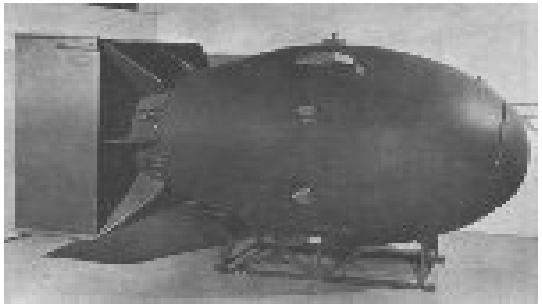
by convention treats adjacent uninvolved nodal chains

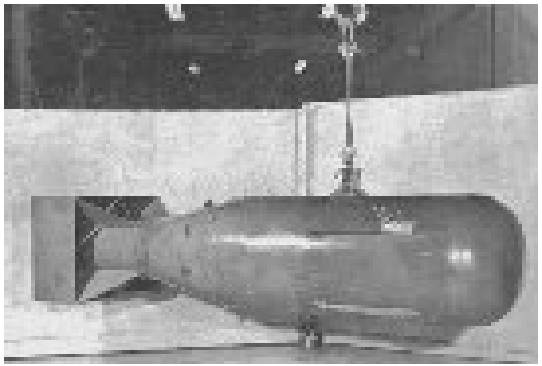


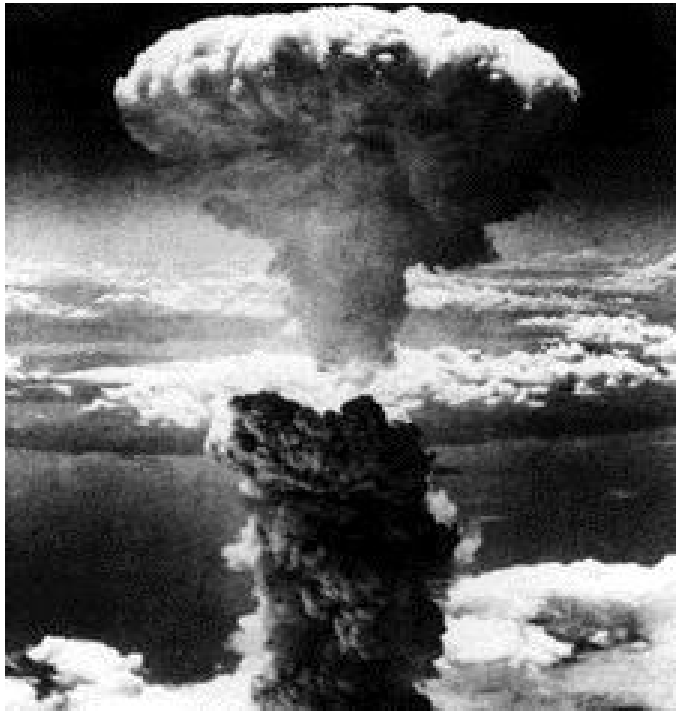
INRT

Treats only involved nodes

Challenge: Modeling Cancer Risks After Radiation Exposure







There is no Single Risk Estimate
Age at Exposure and Duration of Follow-up Significantly Affect Risk.

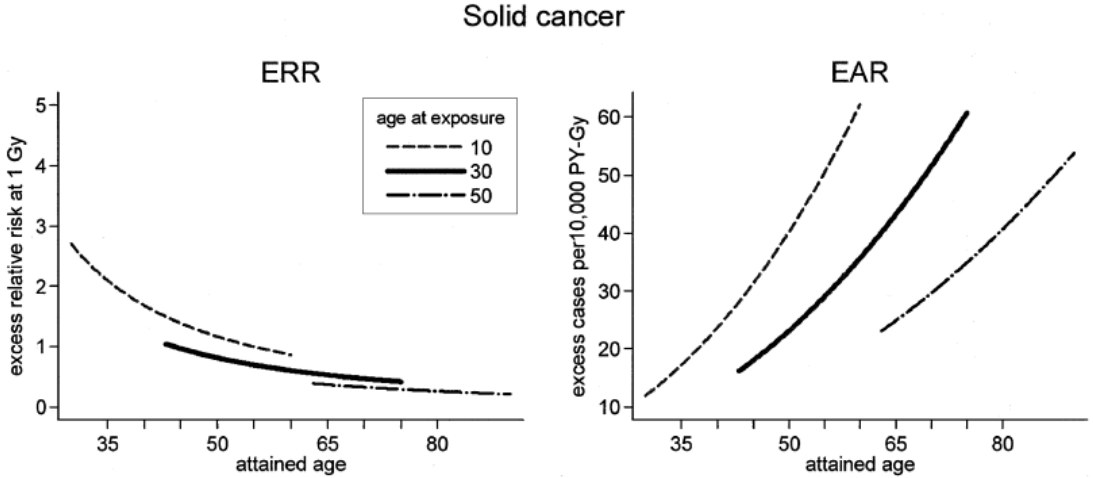
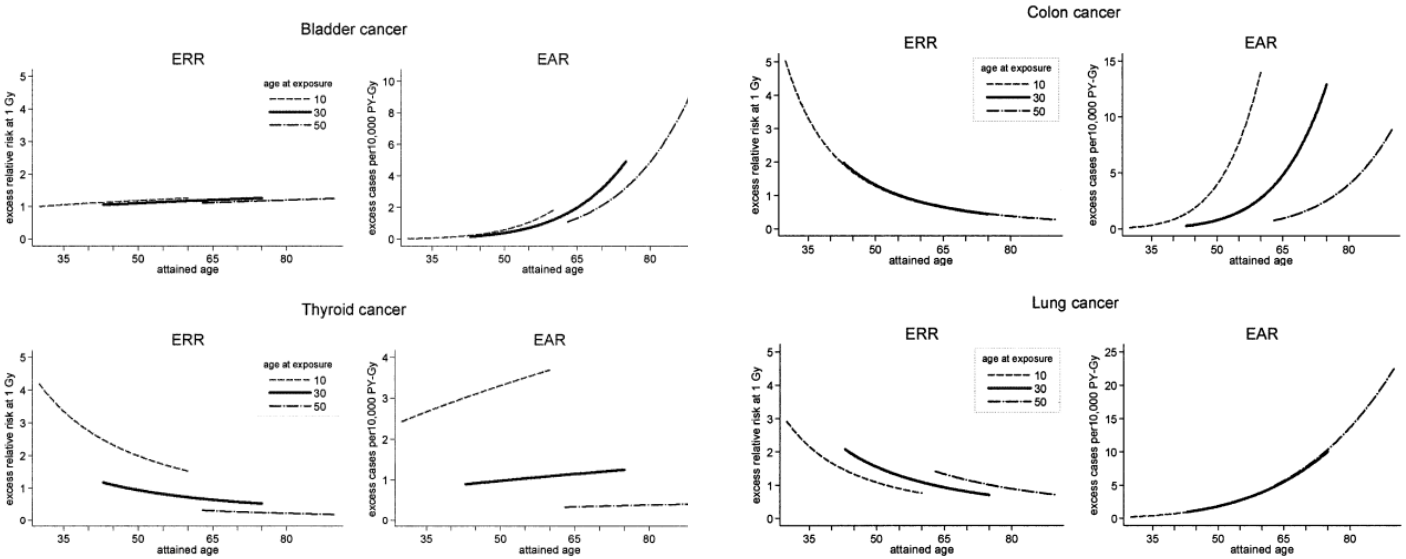


FIG. 4. Variation in solid cancer excess risks at 1 Gy with attained age for ages at exposure of 10, 30 and 50 years. The left panel presents the fitted excess relative risk (ERR) estimates while the right panel indicates excess rate (EAR) estimates. The curves are gender-averaged risks after exposure to 1 Gy.

RADIATION RESEARCH 168, 1–64 (2007)

Tissue Type Significantly Affects Risk

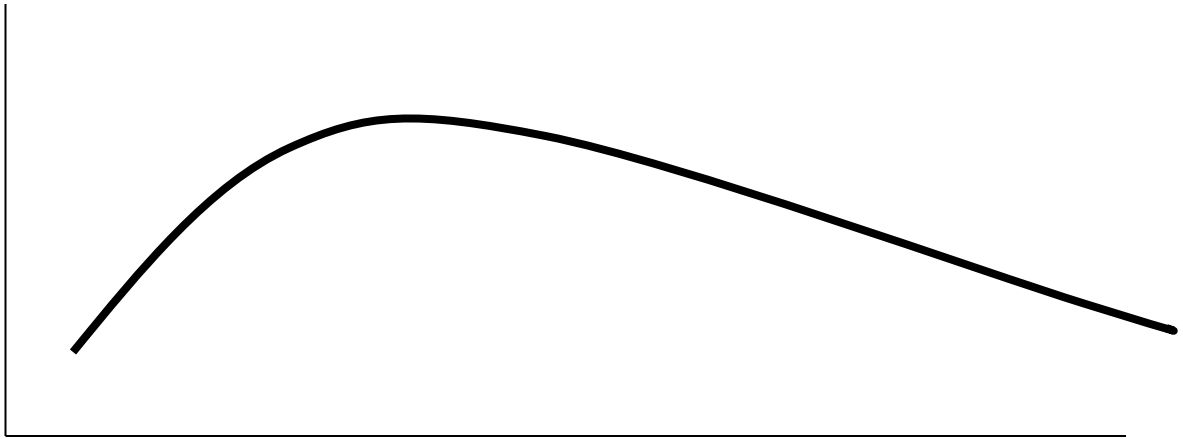


RADIATION RESEARCH 168, 1–64 (2007)

Understanding the Dose-Risk Relationship

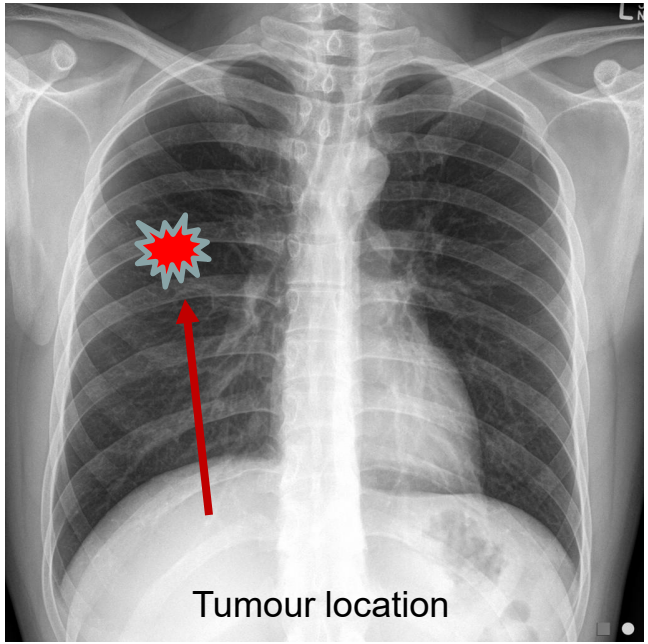
Microdosimetry / *in vivo* models of the Dose-Risk Relationship

The Classical 2-Step Model

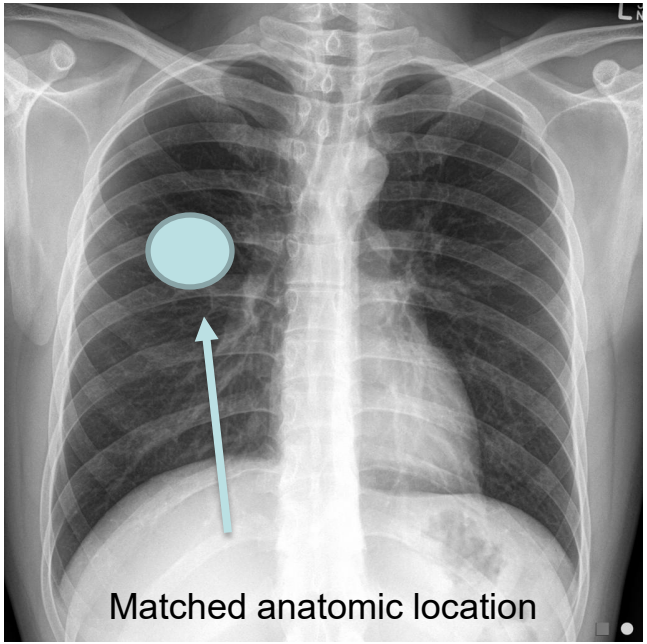


How Dose-risk Relationships are Estimated: Tissue Response vs Patient Response

Patient with Second Cancer

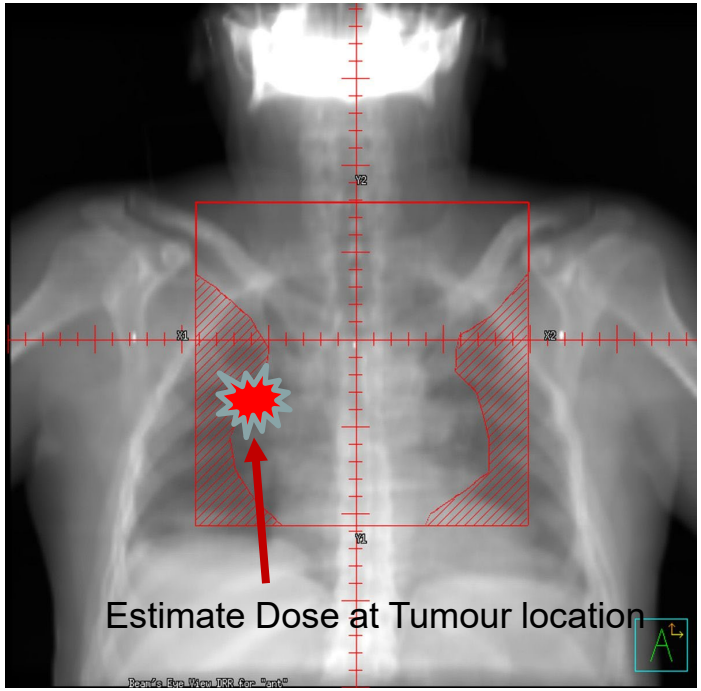


Patient w.out Second Cancer

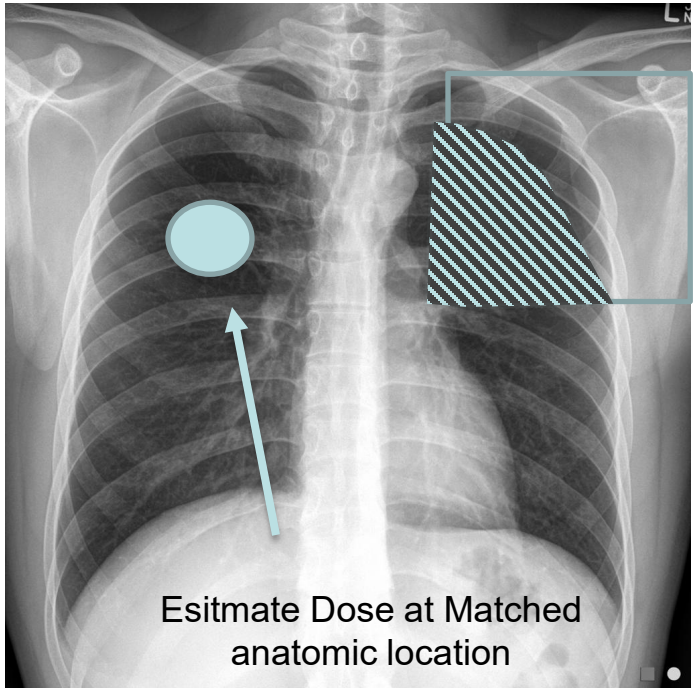


How Dose-risk Relationships are Estimated

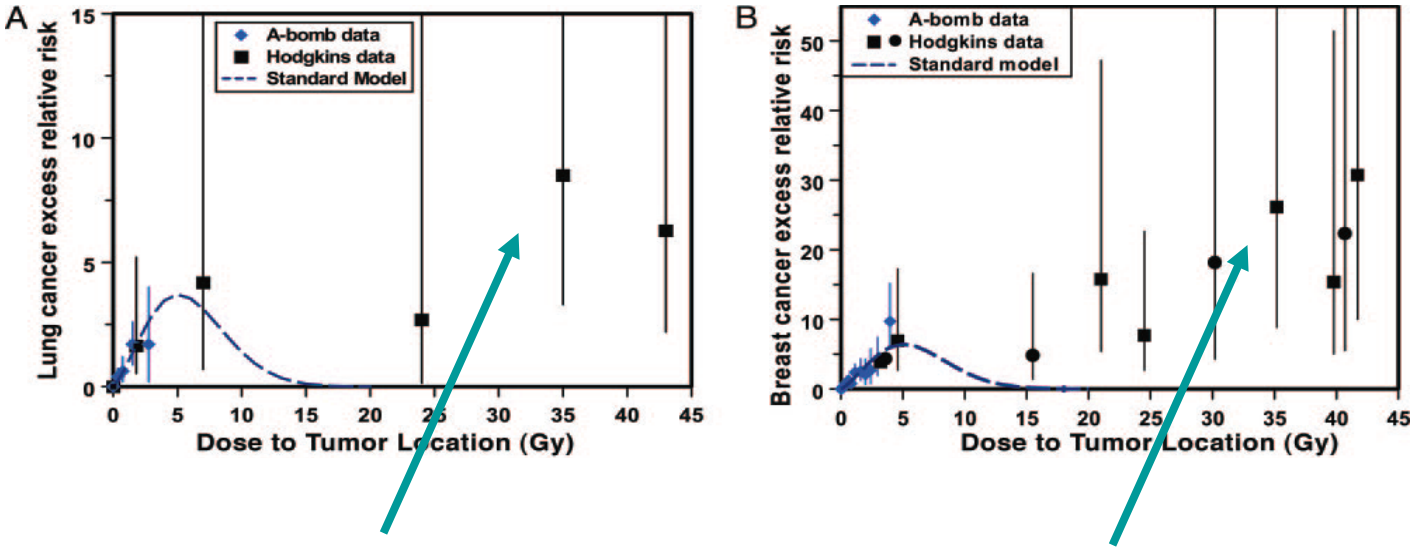
Patient with Second Cancer



Patient w.out Second Cancer



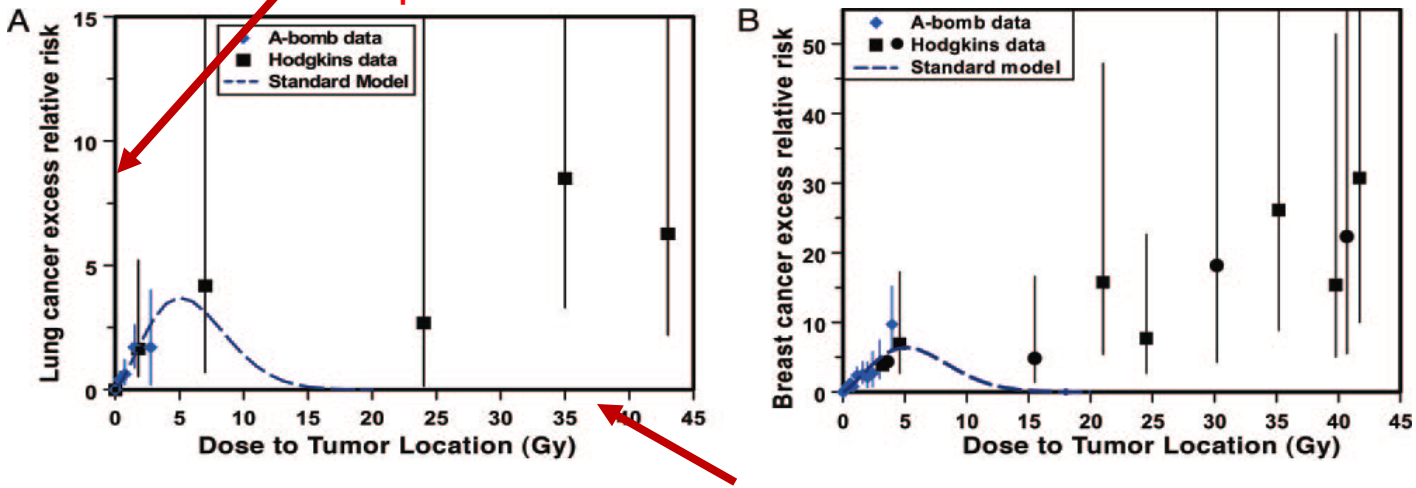
Lesson 2: Cell Killing is Not the Dominant Effect With Doses > 5Gy



Sachs and Brenner, PNAS 2005

Lesson 2: Cell Killing is Not the Dominant Effect With Doses > 5Gy

Relative risk of developing cancer at a specific anatomic site

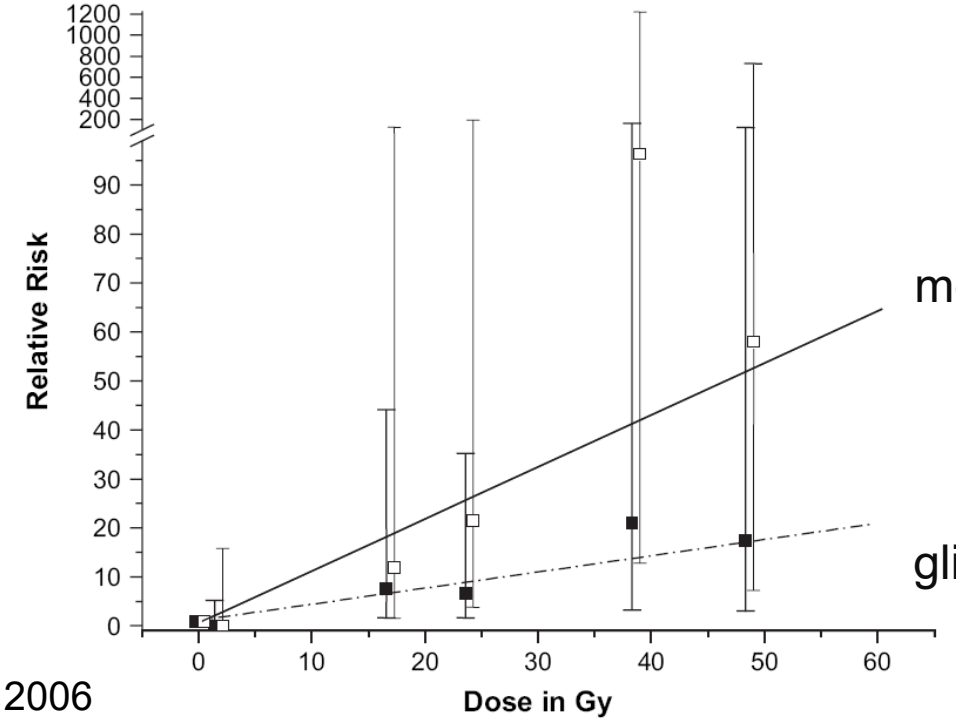


Dose at a specific anatomic site

Sachs and Brenner, PNAS 2005

Dose-Risk for RT-induced CNS Tumours

CCSS 14,361 5 –year survivors



Neglia et al JNCI, 2006

Breast Cancer Dose-Risk Relationship

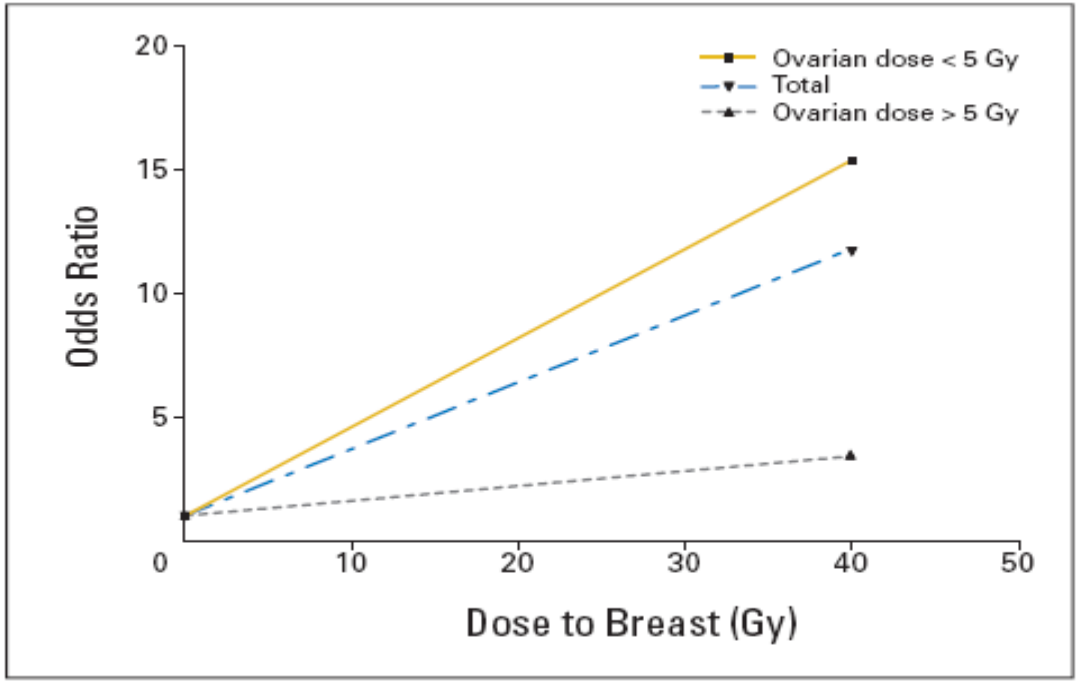


Fig 2. Fitted breast cancer risk by radiation dose to the breast and ovary.

Inskip et al JCO 2009

RT Dose and Thyroid Cancer Risk

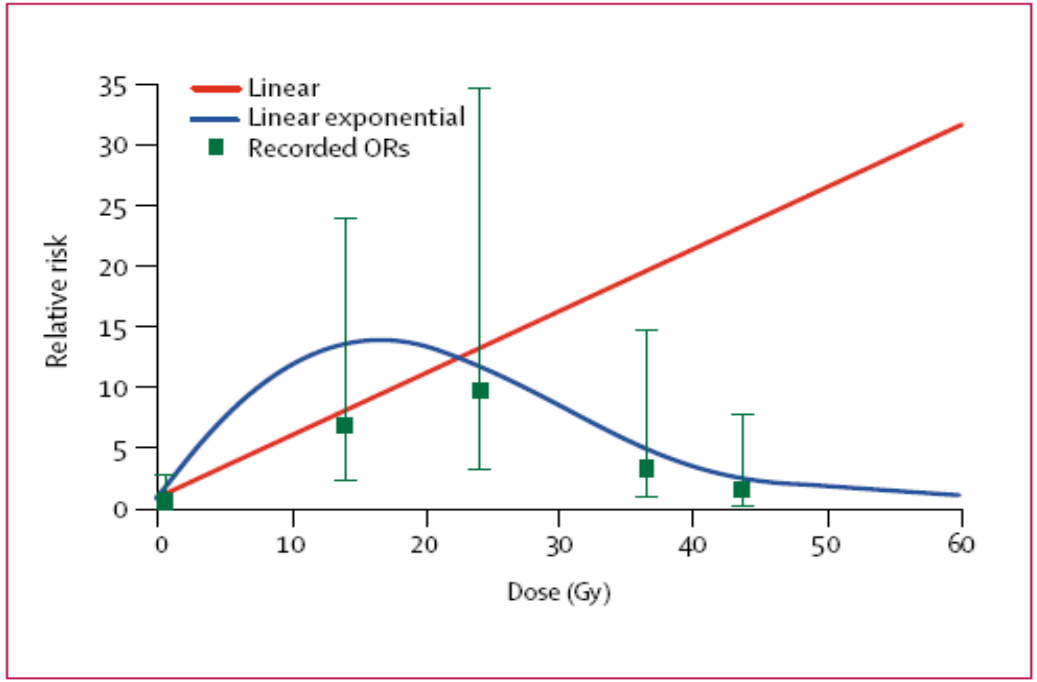
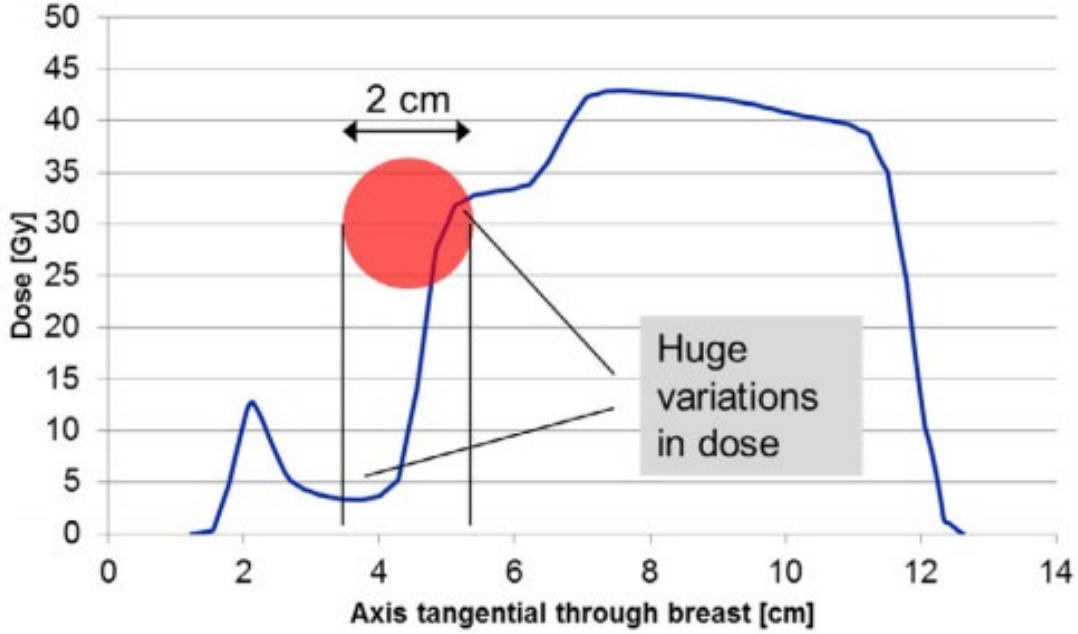


Figure 1: Thyroid-cancer risk by radiation dose in cases and controls after adjustment for first cancer

Sigurdson et al, Lancet 2005

Second Cancer Studies: *Caveat Emptor*

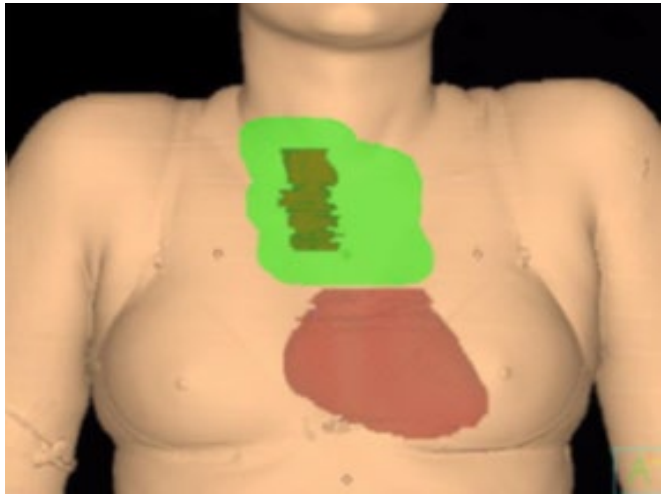
Uncertainty in Dose Estimation

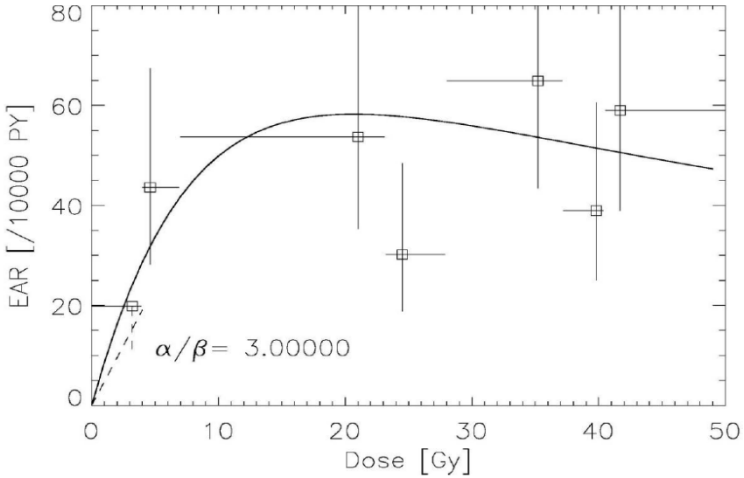


U. Schneider, L. Walsh / Physica Medica 42 (2017) 228–231

Modelling Second Cancer Risk Based on Radiotherapy Dosimetry

Schneider Organ Equivalent Dose (OED) model
(age at exposure, attained age, sex, tissue, volume, dose)

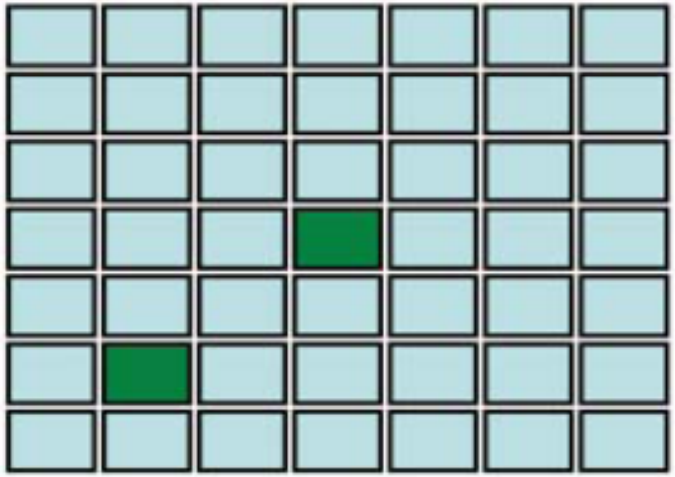




Schneider. *Genes*, 2011

Induction of Pre-Malignant Stem Cells:
A Multi-step Model of SC Induction with Local Cell Migration

- Intended to bridge the gap between microdosimetry studies and epidemiologic studies
- Based on Kinetics of Stem Cell Repopulation
- Initiation



Shuryak, Sachs, Brenner. Radiation Protection Dosimetry (2011)

A Multi-step Model of SC Induction

- Radiation:
  - Initiation
  - Cell Killing

Shuryak, Sachs, Brenner. Radiation Protection Dosimetry (2011)

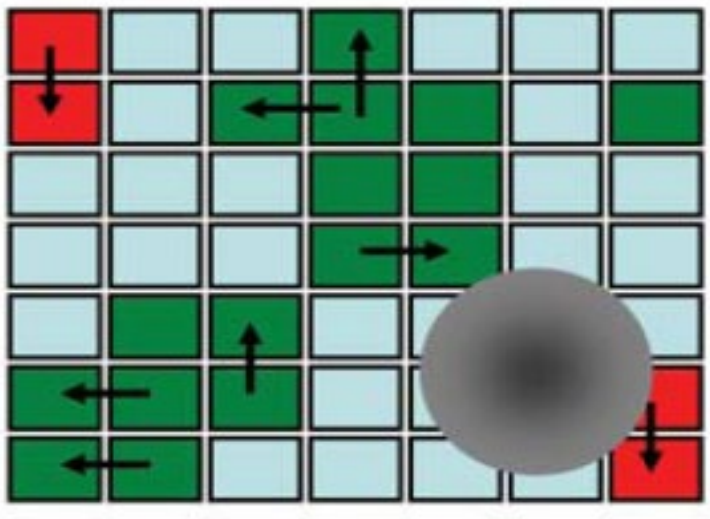
A Multi-step Model of SC Induction

Repopulation of Stem Cell Compartments

Progression

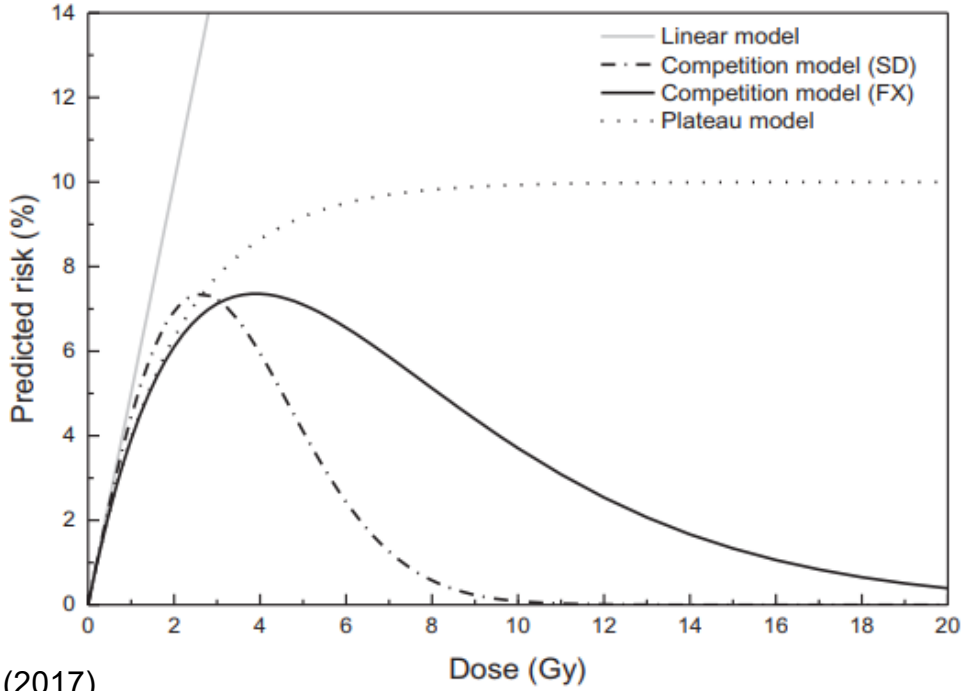
Tissue Repair

Malignant Transformation



Shuryak, Sachs, Brenner. Radiation Protection Dosimetry (2011)

Although Linear Dose-risk Models Dominate, There is not Unanimous Agreement



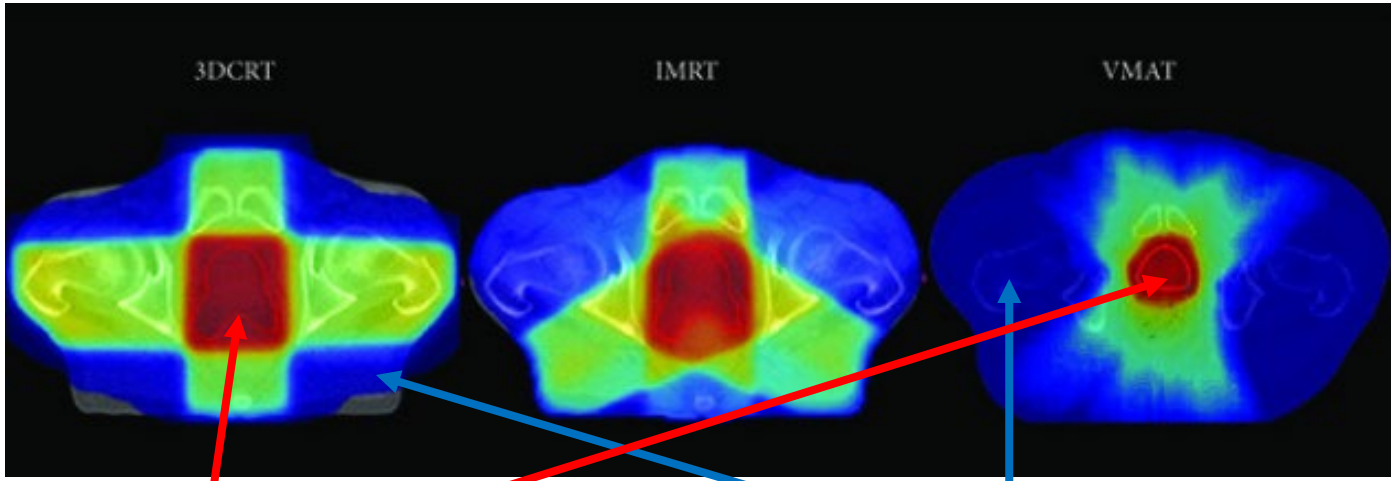
Dasu A, Toma-Dasu I. Phys. Med. (2017)

Fig. 1. Illustration of the dose-risk dependence for risk models used in radiation therapy.

Key Elements of Schneider OED Model

1. **Dose-Response** : The OED model incorporates different dose-response relationships to predict cancer risk. These include:
    - **Linear Model**: Assumes a direct proportionality between dose and cancer risk, applicable at low doses.
    - **Linear-Exponential Model**: Accounts for cell killing effects at higher doses, reducing cancer risk due to the elimination of mutated cells.
    - **Plateau Model**: Reflects a balance between cell killing and repopulation effects, often seen in fractionated radiation schemes.
2. **Organ-Specific Parameters**: The model uses organ-specific parameters derived from data on atomic bomb survivors and radiotherapy patients. These parameters include:
    - **α (alpha)**: Represents the initial slope of the dose-response curve.
    - **β (beta)**: Reflects the quadratic component of cell killing.
    - **R (repopulation parameter)**: Accounts for tissue recovery and repopulation.
3. **Fractionation and Cell Sterilization**: The model considers the impact of fractionation on cancer risk by incorporating the dose per fraction and total dose. Cell sterilization effects are also accounted for, particularly at higher doses.
4. **Application in Radiotherapy Planning**: Schneider's OED model is used to compare cancer risks associated with different radiotherapy techniques, such as intensity-modulated radiotherapy (IMRT) and volumetric modulated arc therapy (VMAT).

Does it Matter if Dose-Risk is Linear or Non-Linear: Implications for Transition to IMRT and VMAT



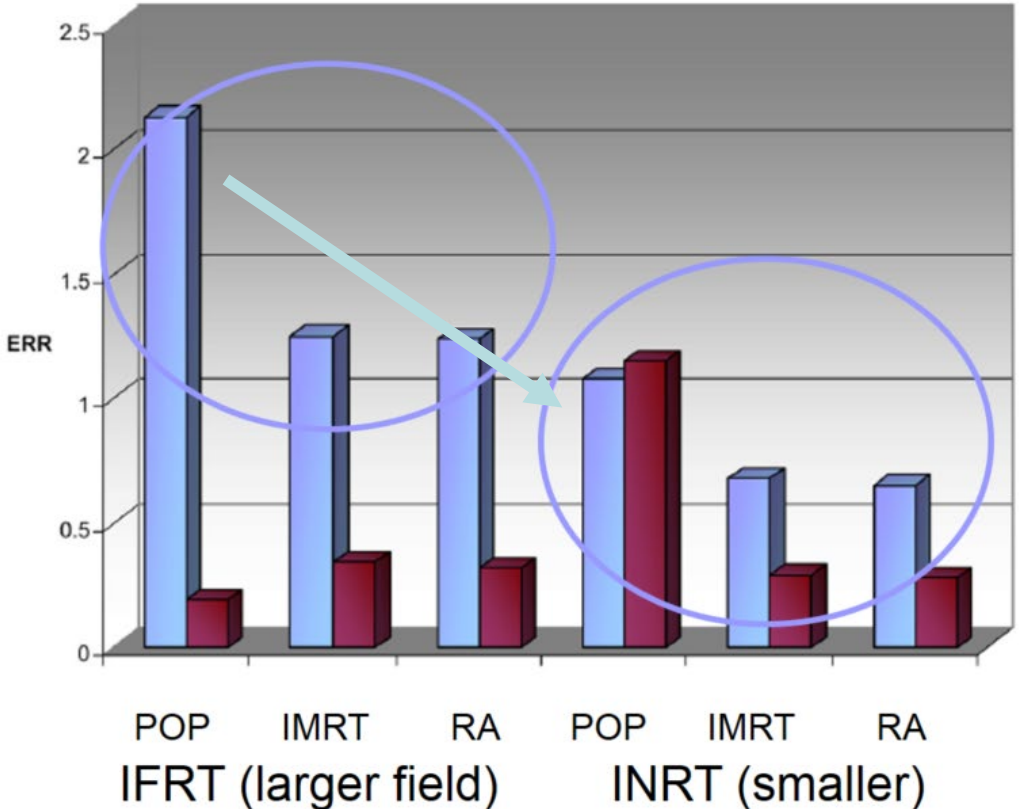
High dose volume decreases

Low dose volume increases

DOI:10.1155/2016/6829875

Does It Matter if Dose-Risk is Linear or Non-Linear?

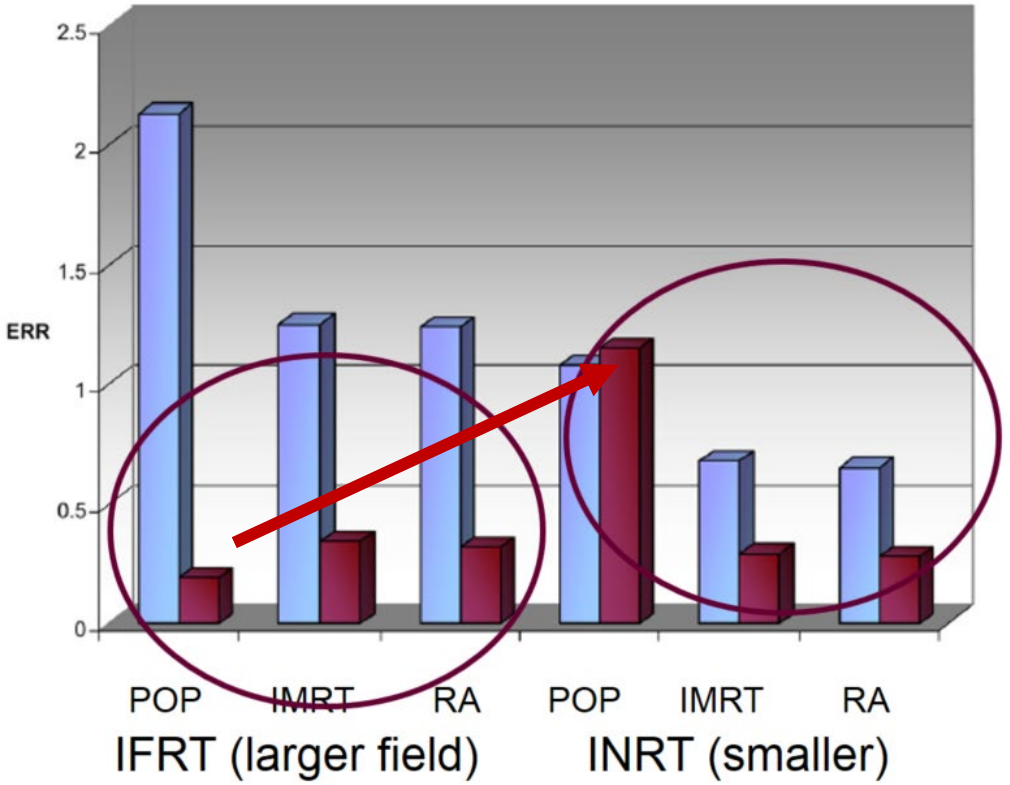
Linear models predict that smaller mediastinal fields reduce risk of breast cancer, and that IMRT has lower risk



Int. J. Radiation Oncology Biol. Phys., Vol. 81, No. 2, pp. 490–497, 2011

Does It Matter if Dose-Risk is Linear or Non-Linear?

Non-linear models predict smaller fields will increase breast cancer risk, especially POP, and that IMRT may be worse with larger volumes



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Int. J. Radiation Oncology Biol. Phys., Vol. 81, No. 2, pp. 490–497, 2011

Does Matter If Dose-Risk is Linear or Non-Linear?

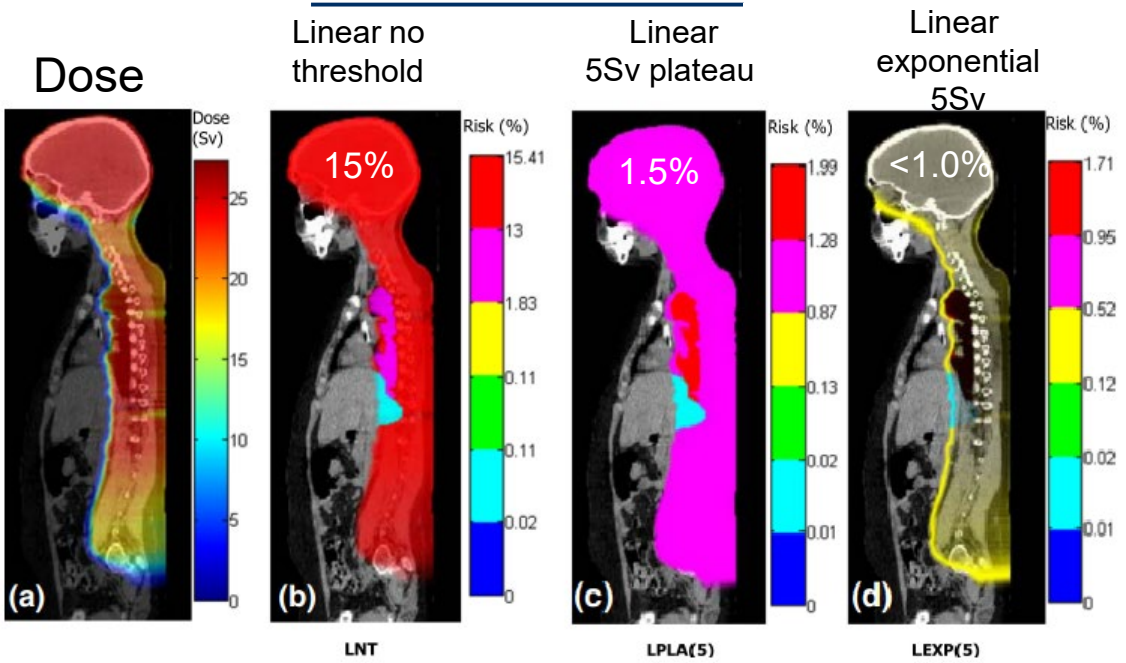
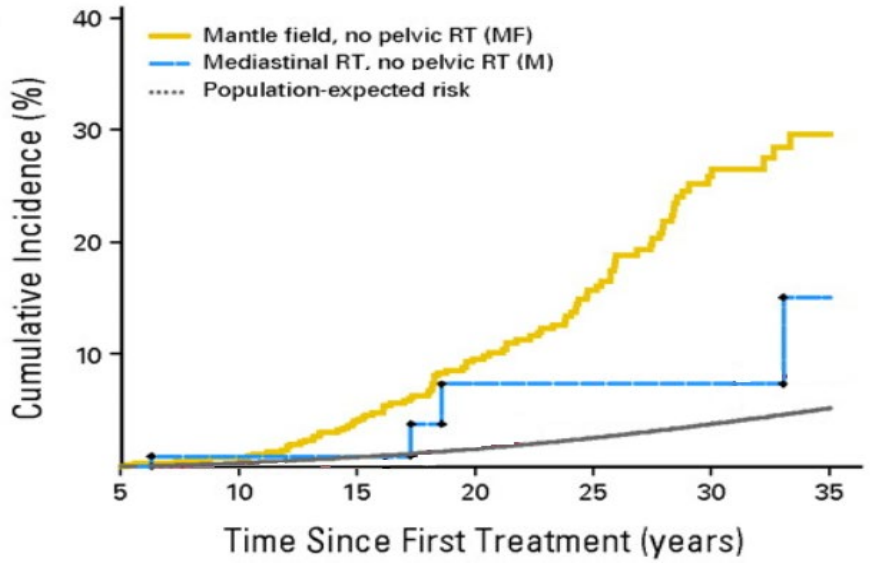
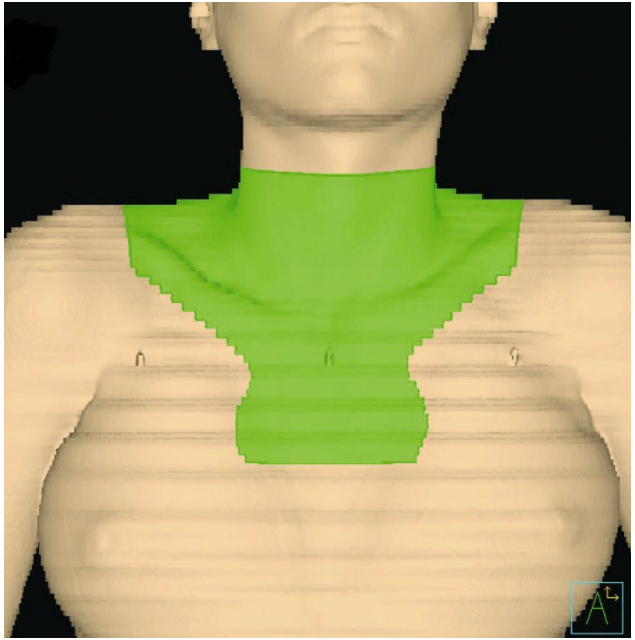


Figure 4 Visualization of **(a)** equivalent dose and **(b)**, **(c)**, and **(d)** lifetime risks of second cancer incidence based on different dose-risk relationships (LNT: linear non-threshold model, LPLA(5): linear plateau model with bending point at 5 Sv, LEXP(5): linear exponential model with bending point at 5 Sv) on a sagittal slice for a 13-year-old girl who received proton CSI.

Zhang et al. Radiation Oncology (2015) 10:107
DOI 10.1186/s13014-015-0404-x

Dose-Volume-Risk: Breast Cancer Risk in Hodgkin Lymphoma Survivors

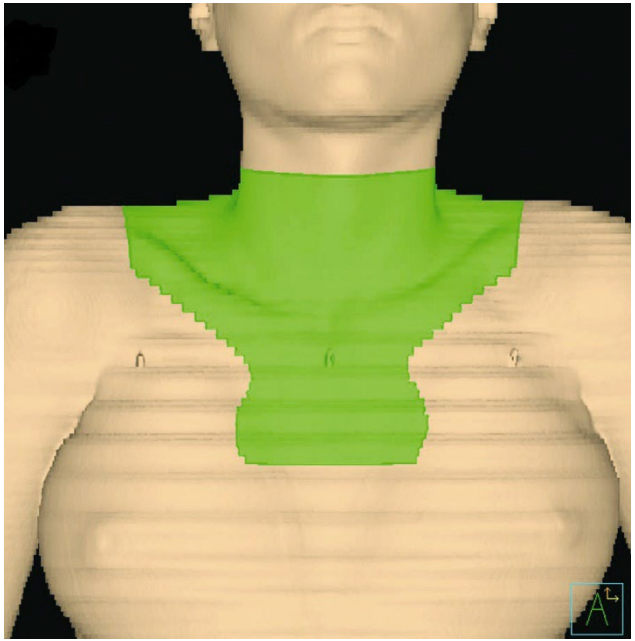




De Bruin M L et al. JCO 2009;27:4239-4246

Dose-Volume-Risk: Breast Cancer Risk in Hodgkin Lymphoma Survivors

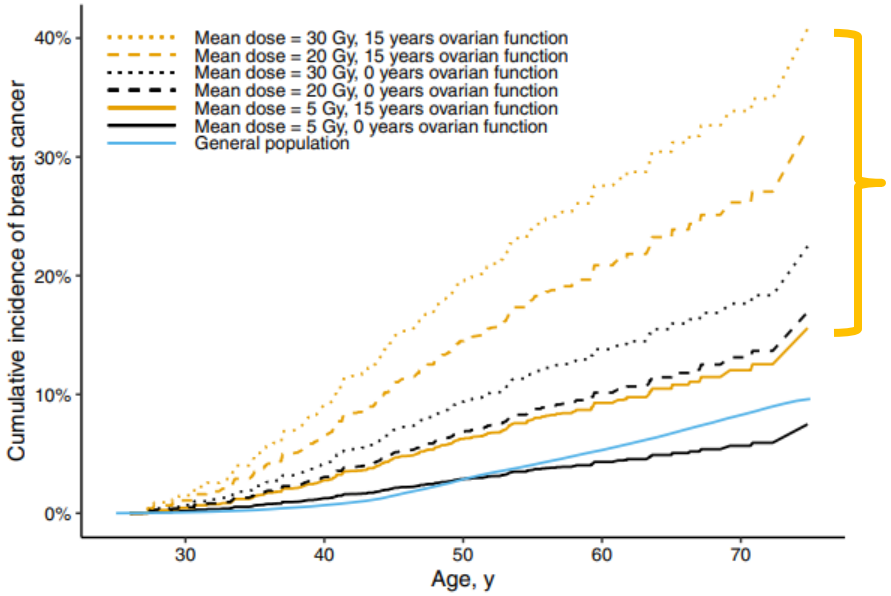
Second Cancer Site	Relative Risk Compared to Mantle
Any Solid	0.64 (0.49-0.83)
Female Breast	0.38 (0.19-0.72)
Lung	0.88 (0.54-1.43)
Gastrointestinal	0.56 (0.26-1.19)



N Engl J Med 2015;373:2499-511

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

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



Increasing risk with increasing RT dose

Applies to the "whole patient" ie useful for counselling patients about risk

Figure 2. Cumulative incidence of breast cancer for a 5-year survivor of Hodgkin lymphoma treated at age 20 years, according to mean breast dose and duration of intact ovarian function. Case-control data were combined with information from the Hodgkin lymphoma survivors cohort (37), and cumulative incidence estimates were based on model (M1). Death and other cancers (except those treated with surgery only) were treated as competing events.

JNCI J Natl Cancer Inst (2022) 114(9): djac125. https://doi.org/10.1093/jnci/djac125

Increasing Applications of SMN Modelling

Predicted cardiac and second cancer risks for patients undergoing VMAT for mediastinal Hodgkin lymphoma

Orla A. Houlihan[1,8] · Georgios Ntentas[2,3,4] · David J. Cutter[2,5] · Patricia Daly[1,6,7] · Charles Gillham[1,6,7] · Orla McArdle[1] · Frances K. Duane[1,6,7]

Received: 6 October 2022 / Accepted: 29 November 2022 / Published online: 31 December 2022

PAPER

Applications of a patient-specific whole-body CT-mesh hybrid computational phantom in second cancer risk prediction

Erika Kollitz[1], Moritz Roew[1], Haegin Han[2], Marco Pinto[1], Florian Kamp[3,4,9], Chan Hyeong Kim[2], Marco Schwarz[5,6,9], Claus Belka[4], Wayne Newhauser[7,8], Katia Parodi[1,10] and George Dedes[1,10]

Determining Out-of-Field Doses and Second Cancer Risk From Proton Therapy in Young Patients—An Overview

Maite Romero-Expósito[1,2], Iuliana Toma-Dasu[2,3] and Alexandru Dasu[1,4]*

[1] The Skandion Clinic, Uppsala, Sweden, [2] Oncology Pathology Department, Karolinska Institutet, Stockholm, Sweden, [3] Medical Radiation Physics, Stockholm University, Stockholm, Sweden, [4] Medical Radiation Sciences, Department of Immunology, Genetics and Pathology, Uppsala University, Uppsala, Sweden

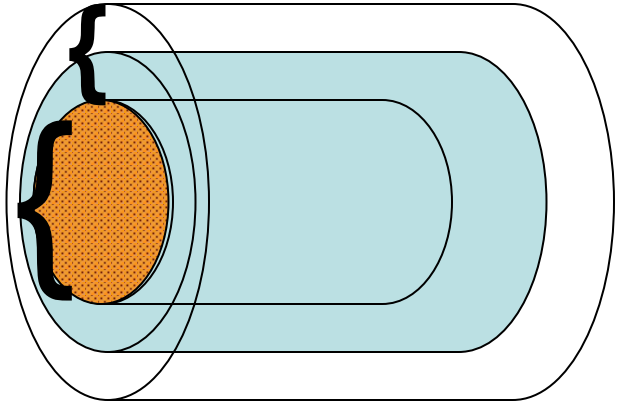
"Intermediate Dose":

Is the Risk Related to the Dose, or the Volume?

Irradiating cylinder 10cm diameter, 20cm length

Volume +/- 1cm from edge = 1257 cc

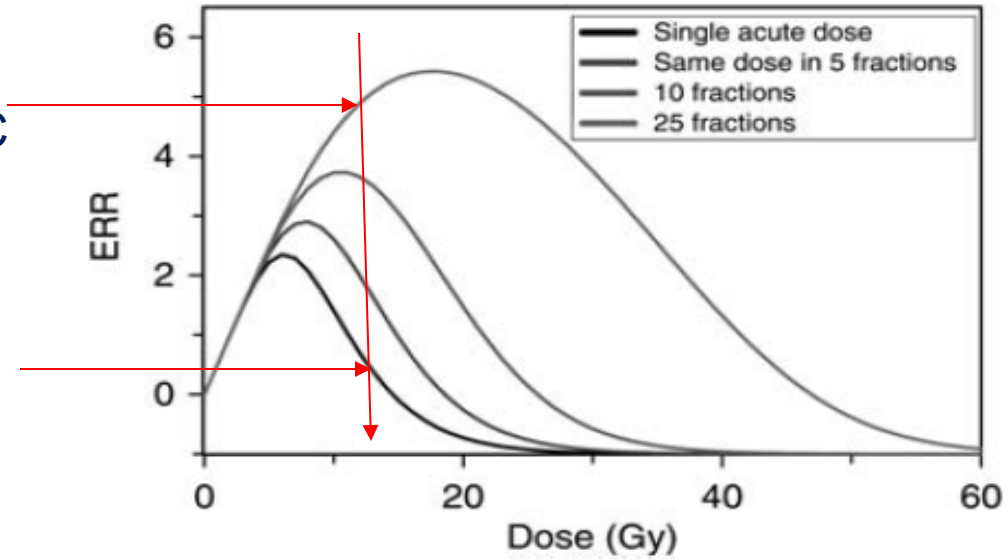
Volume >1 cm inside edge = 1005 cc



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 larger than the high dose volume

Predicted Impact of Fractionation on Second Cancer Risk: More Fractions More Risk (!)

Model predicts that for a given dose, SC risk *increases* with increasing fractionation.



Shuryak, Sachs, Brenner. Radiation Protection Dosimetry (2011)

Modifiers of Dose-Risk Relationship:

Breast Cancer Risk is Affected by Endogenous Estrogen

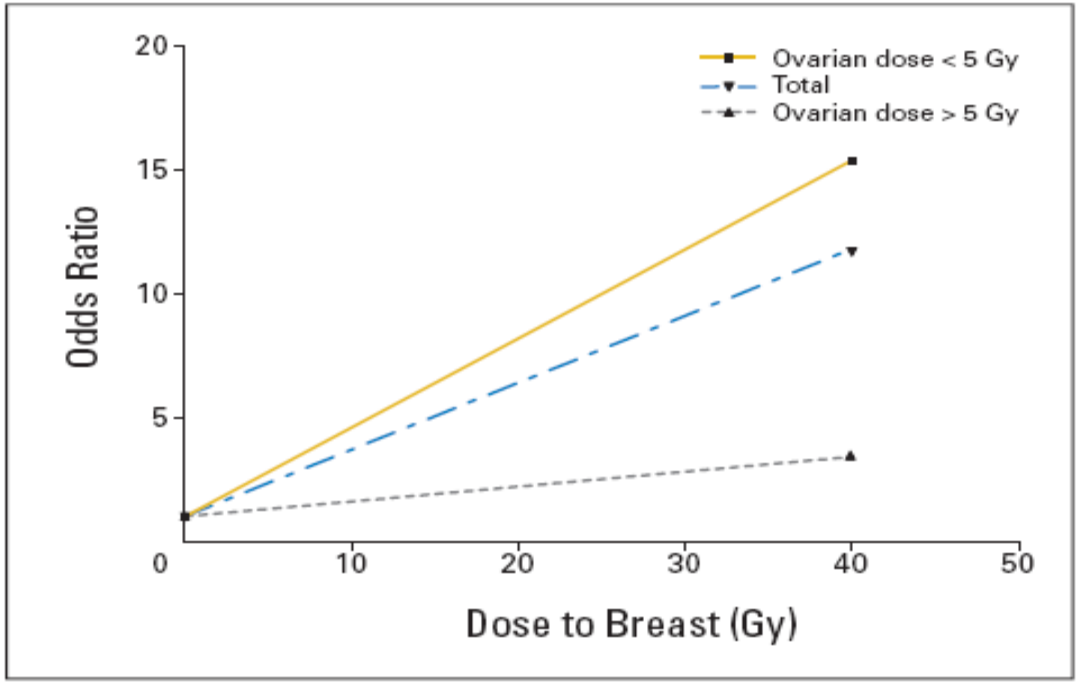
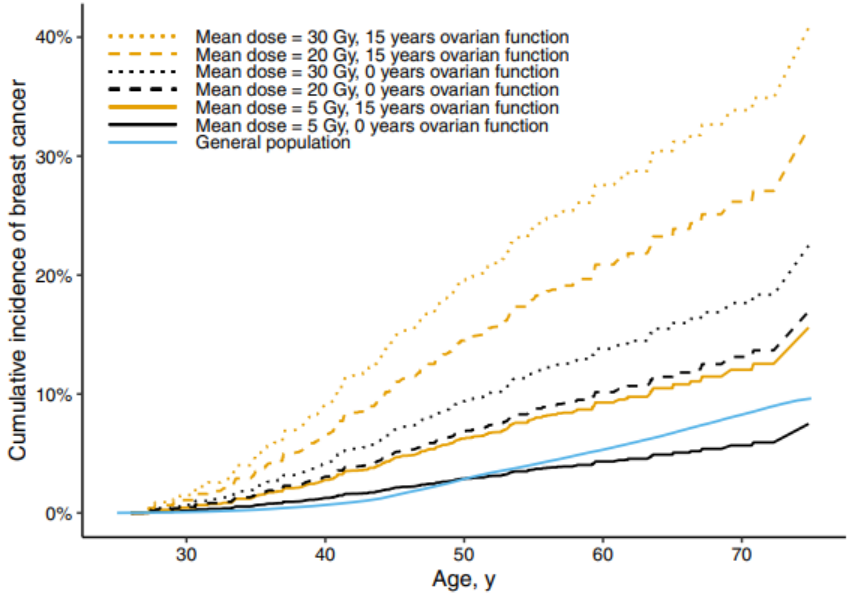


Fig 2. Fitted breast cancer risk by radiation dose to the breast and ovary.

Inskip et al JCO 2009

Non-RT Modifiers of Second Cancer Risk
Estrogenic Promotion of Breast Cancer



Increasing risk with increasing duration of ovarian function (5Gy)

Figure 2. Cumulative incidence of breast cancer for a 5-year survivor of Hodgkin lymphoma treated at age 20 years, according to mean breast dose and duration of intact ovarian function. Case-control data were combined with information from the Hodgkin lymphoma survivors cohort (37), and cumulative incidence estimates were based on model (M1). Death and other cancers (except those treated with surgery only) were treated as competing events.

JNCI J Natl Cancer Inst (2022) 114(9): djac125. https://doi.org/10.1093/jnci/djac125

What About Diagnostic (CT Scan) Doses?

	Head Scan			Abdomen/Pelvis Scan		
	Solid Cancer			Solid Cancer		
Age, y	Girls	Boys	Leukemia	Girls	Boys	Leukemia
Lifetime Attributable Risk of Cancer per 10 000 CT Scans						
<5	17.5	7.4	1.9	33.9	14.8	0.8
5-9	1.6	2.4	0.9	25.8	13.7	0.7
10-14	1.1	2.1	0.5	27.2	13.1	1.0
No. of CT Scans Leading to 1 Case of Cancer (Rounded to the Nearest 10)						
<5	570	1350	5250	300	670	12 170
5-9	6130	4150	11 660	390	730	14 470
10-14	9020	4660	21 160	370	760	10 380

Abbreviation: CT, computed tomography.

JAMA Pediatr. 2013;167(8):700-707

Summary

- Most data suggest a linear increasing relationship between organ dose and risk of second cancer up to 40-60Gy.
  - Exceptions are leukemia and thyroid cancer.
- Confidence intervals on these estimates are wide.
  - These models leave considerable uncertainty in the prediction of absolute risk for any individual, but are useful for predicting the relative potential benefit of RT changes to groups of patients treated in different ways.

Summary

- Radiation is not the only cause of SC in HL patients.
  - Chemotherapy, genomic instability
  - Requires further consideration in modeling work.
- Diagnostic exposures are a public health problem
  - But limited risk for individual patients
  - ALARA

Thank You

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2. A Review of Radiotherapy-Induced Late Effects Research after Advanced Technology Treatments Front Oncol 2016 Feb 10;6:13. doi: 10.3389/fonc.2016.00013.
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Questions?

Thank you!

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