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Risk of second cancers
Bridging epidemiology and modeling

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Workshop
Risk of secondary cancer following radiotherapy

Date: September 8-9 2016
Venue: The Royal Swedish Academy of Sciences, Stockholm, Sweden

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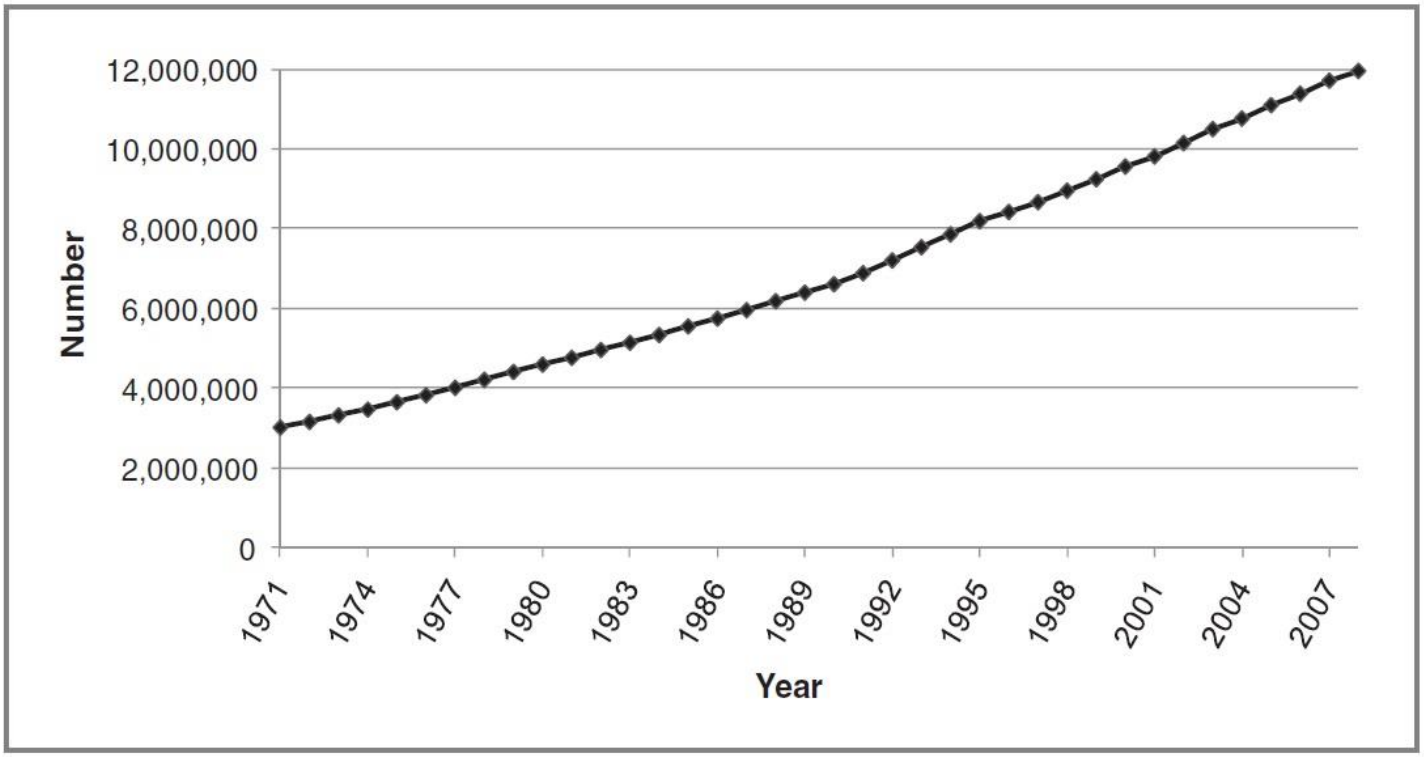
Cancer Survivors: A Booming Population

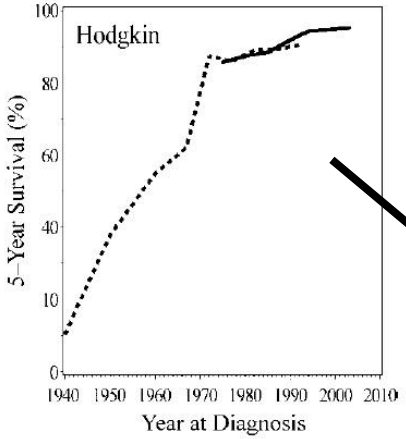


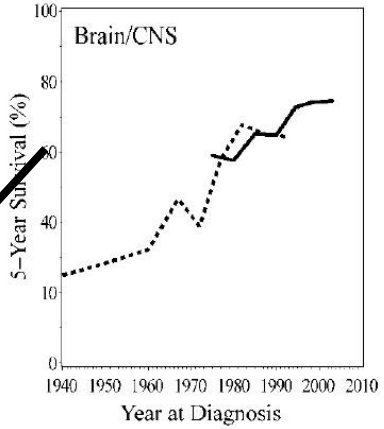
Estimated number of cancer survivors in the United States from 1971 to 2008

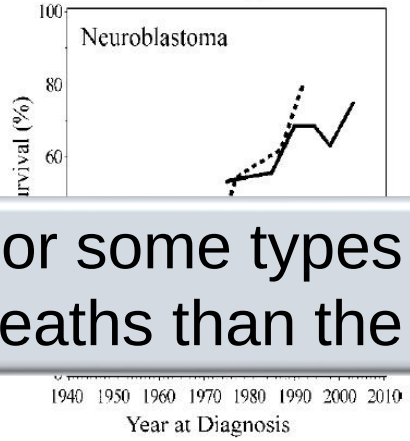
Parry C, Kent EE, Mariotto AB, Alfano CM, Rowland JH. Cancer survivors: a booming population. Cancer Epidemiol Biomarkers Prev. 2011 Oct;20(10):1996-

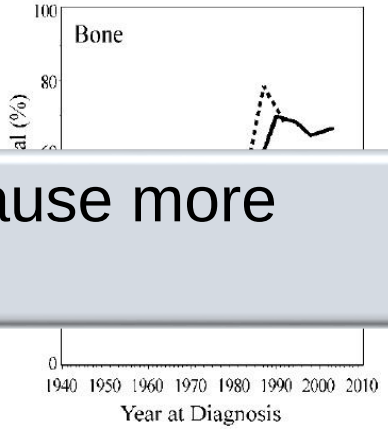
Long-term survivors of childhood cancer

5-y survival trends for children diagnosed with cancer at ages 0 to 19 y in SEER (solid lines) and Connecticut (dashed lines) areas.









Improved cure rates

For some types of cancers, secondary cancers cause more deaths than the primary cancer

Mariotto AB, et al.. Long-term survivors of childhood cancers in the United States. Cancer Epidemiol Biomarkers Prev. 2009 Apr;18(4):1033-40.

Why is there a need in predicting second cancers?

1) Increasing number of long-term cancer

2) Treating cancer as a chr

3) Distribution of adiotherapy

4) N herapy

guided radiotherapy

We should optimize our treatment plans not only by taking early and late effects into account, but also second cancer estimates

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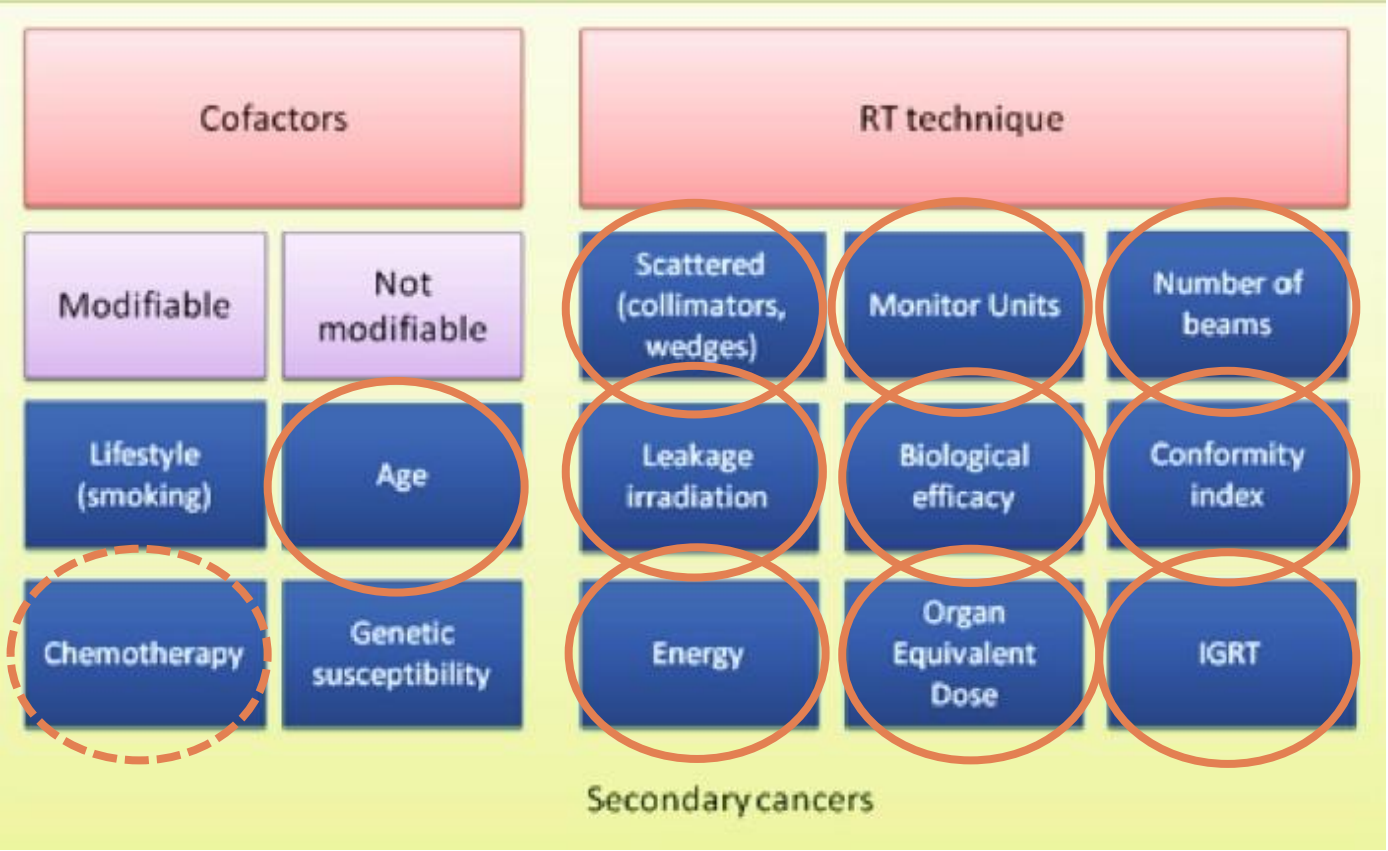
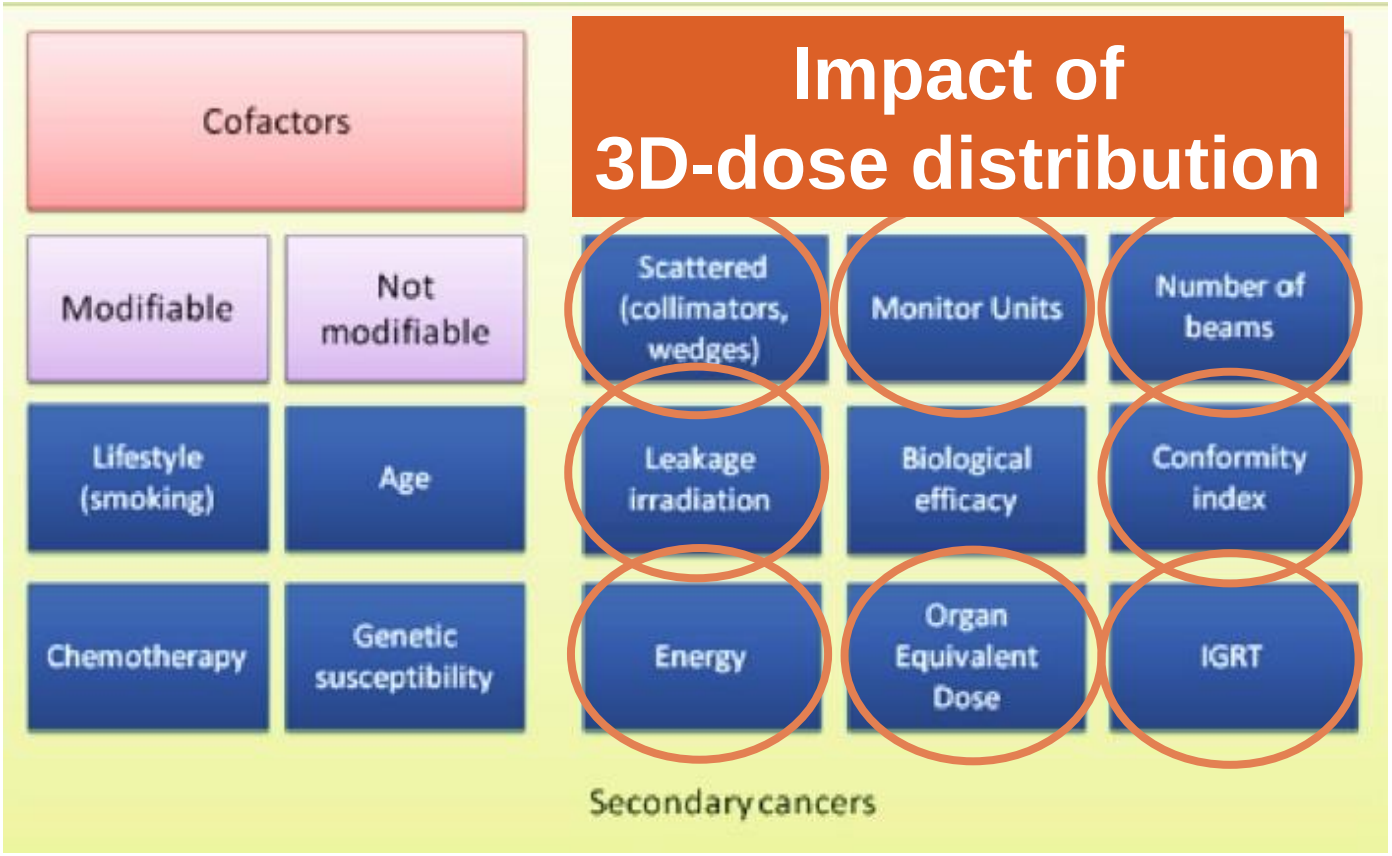
Risk factors for second cancers in modern radiation therapy



Chargari C, et al. Risk of second cancers in the era of modern radiation therapy: does the risk/benefit analysis overcome theoretical models? Cancer Metastasis Rev. 2016 35(2):277-88..

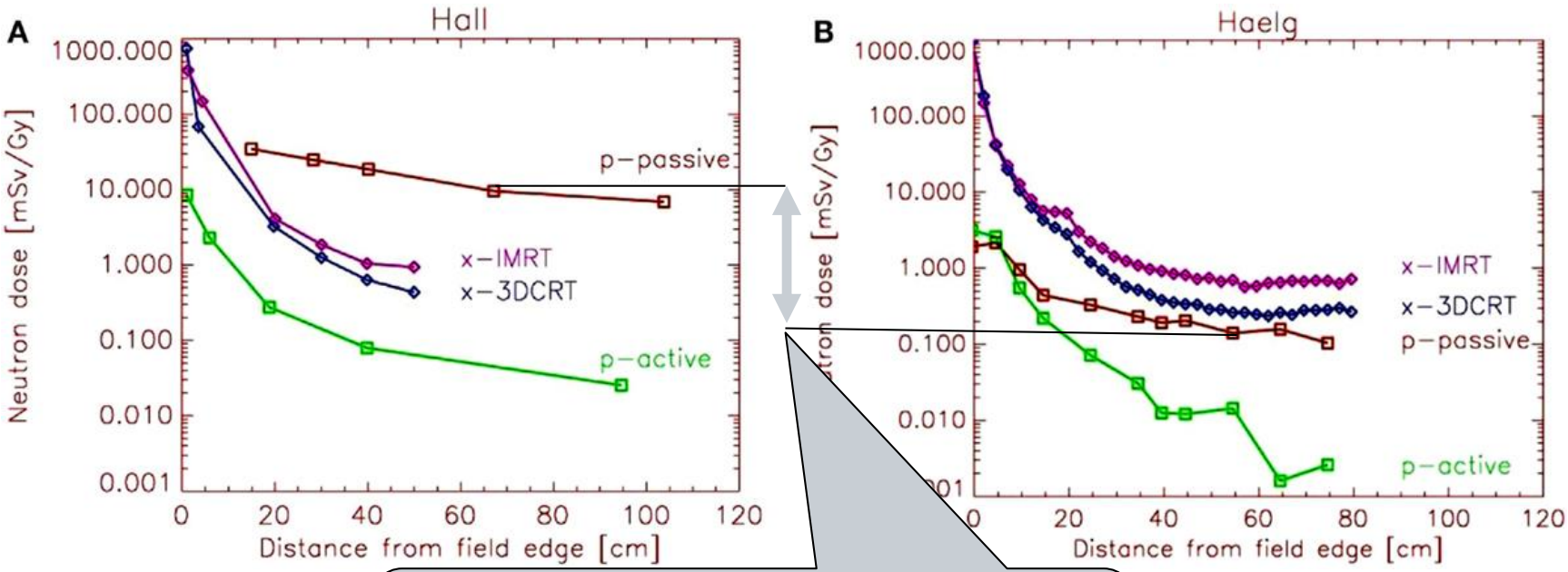
Risk factors for second cancers which impact dose-volume distribution



Chargari C, et al. Risk of second cancers in the era of modern radiation therapy: does the risk/benefit analysis overcome theoretical models? Cancer Metastasis Rev. 2016 35(2):277-88..

Uncertainties of the dose distribution

Has only recently been taken into consideration, as it was assumed that it can be neglected when compared to the uncertainties of the risk models



Neutron dose difference:
two orders of magnitude

Hall EJ. Intensity-modulated radiation therapy, protons, and the risk of second cancers. *Int J Radiat Oncol Biol Phys* (2006) **65**(1):1–7.
Hälg RA et al. Measurements of the neutron dose equivalent for various radiation qualities, …. *Phys Med Biol* (2014) **59**(10):2457–68.

Epidemiological studies of RT patients

Epidemiology

- Huge body of literature
- Patients treated 20 to 50 years ago
- Patients treated with techniques not used anymore
- Only few studies give insides on dose-response relationship

Extrapolate cancer risk from "old" to "new" RT

Use biophysical models

Modern treatment modalities

- IMRT / VMAT
- Protons and ions
- IGRT

Dose-response relationship from epidemiology

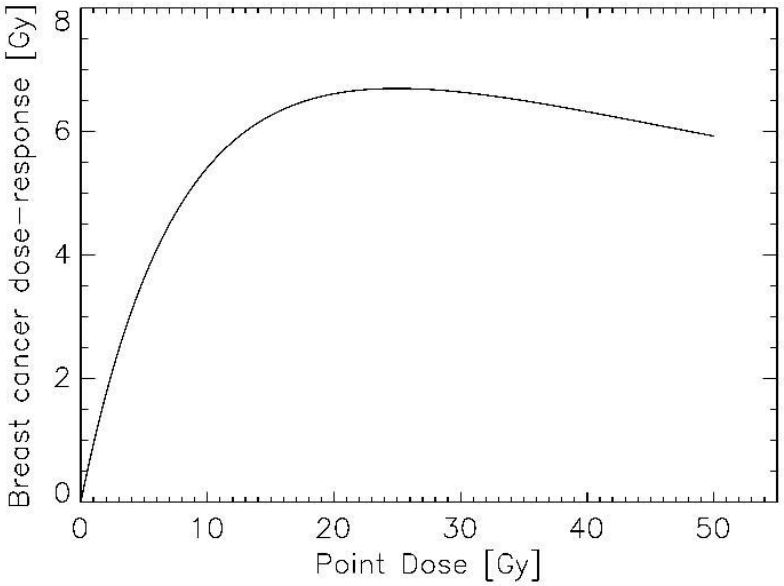
What we need

Dose-response:

Cancer risk as a function of

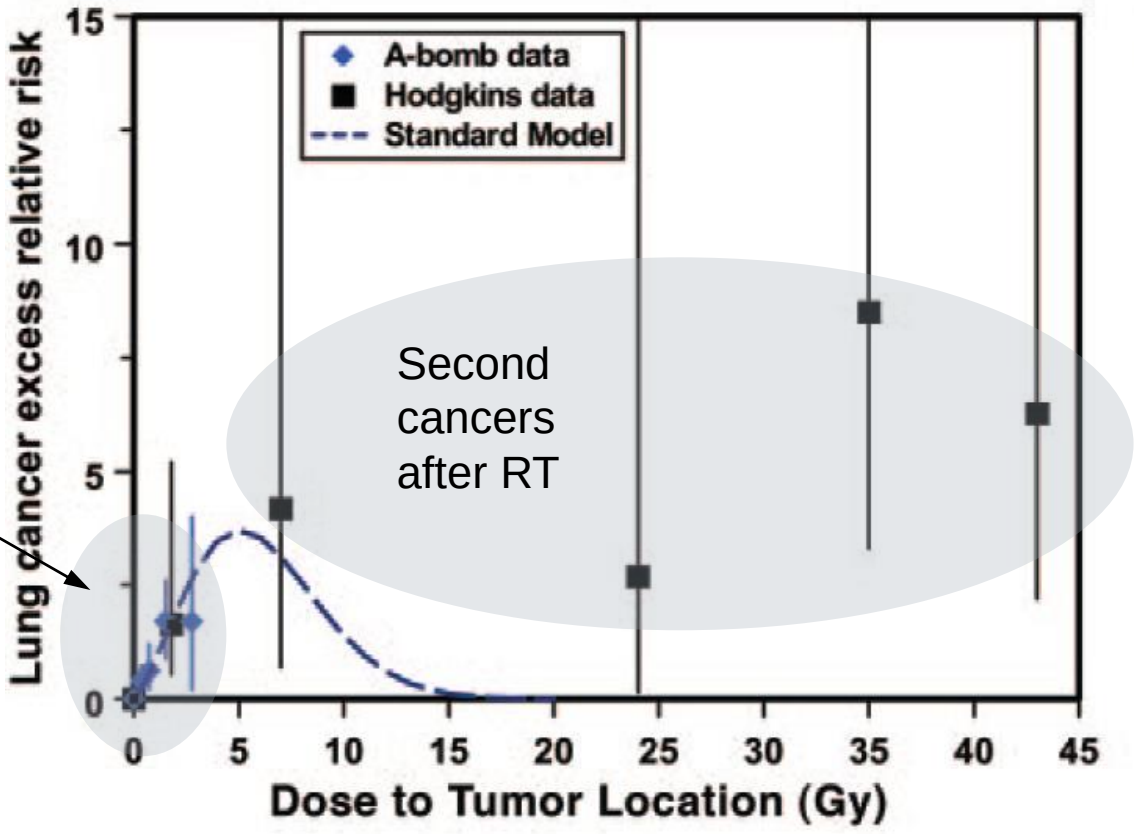
- **dose to site of second cancer**

for each organ



Standard model: “initiation + killing”

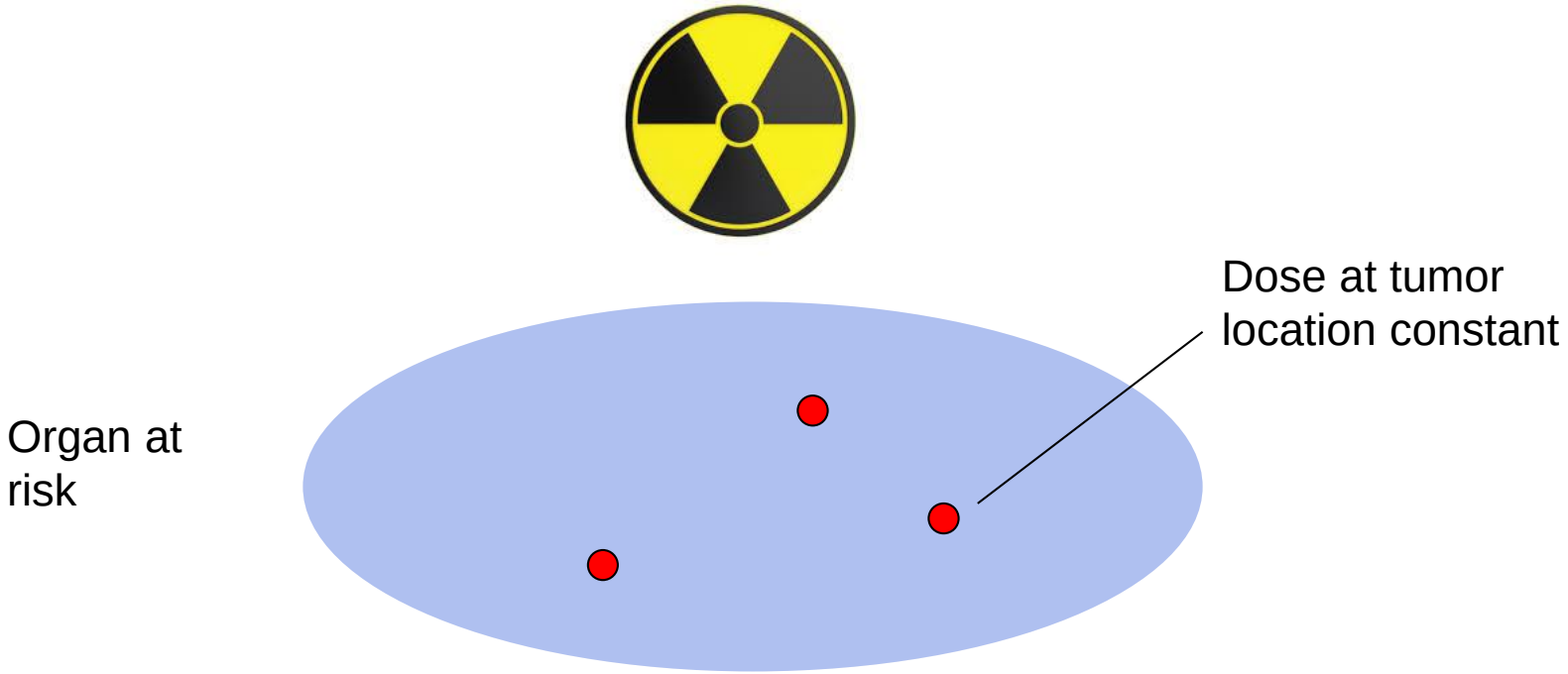
A-bomb survivor data



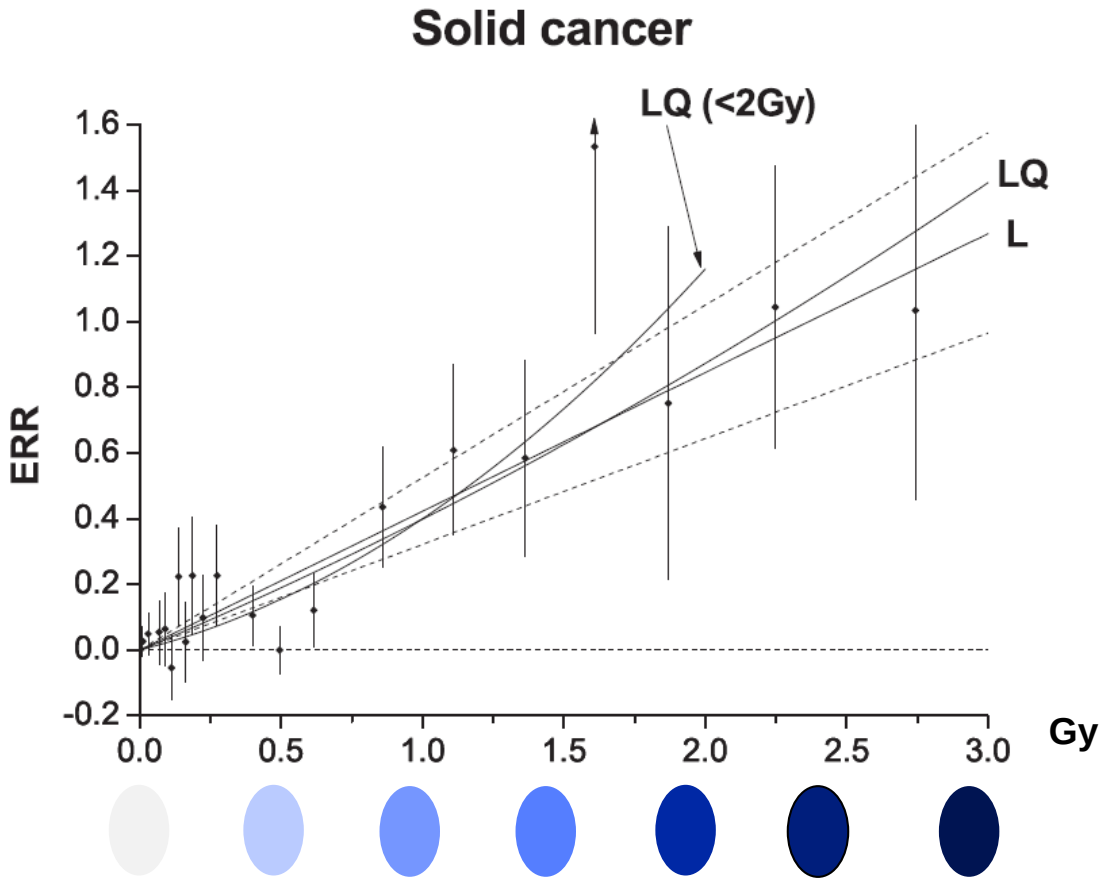
Conclusion: repopulation of normal tissue between dose fractions must be considered

Sachs RK, Brenner D. Solid tumor risks after high doses of ionizing radiation. PNAS 2005 102(37): 13040–13045.

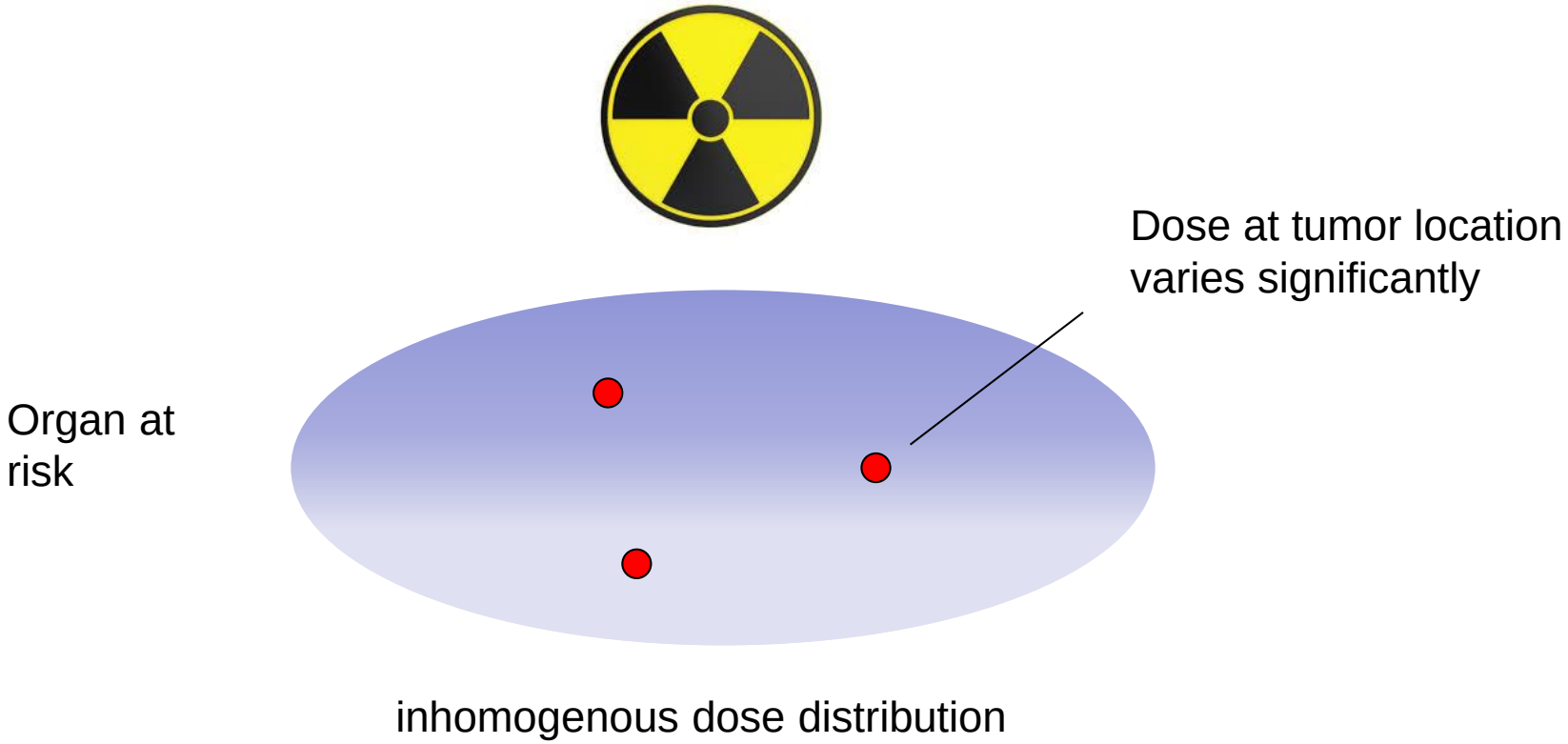
Stratifications of cancer risk as a function of dose to the tumor location: A-bomb survivors



Stratifications of cancer risk as a function of dose to the tumor location: A-bomb survivors



Stratifications of cancer risk as a function of dose to the tumor location: RT patients



Determination of dose: RT patients

Fact: a detected second tumor is already **a few cm** in size

Table 5 Tumor size according to FH of BC. I. All patients; II. Tumors found by self-examination

	MD (95 % CI)	*p* value
All patients		
Degree of relationship		
0. no FH: 26.4 mm		
1. First-degree FH: 19.3 mm		
2. Second-degree FH: 26.3 mm		

Additional uncertainties:

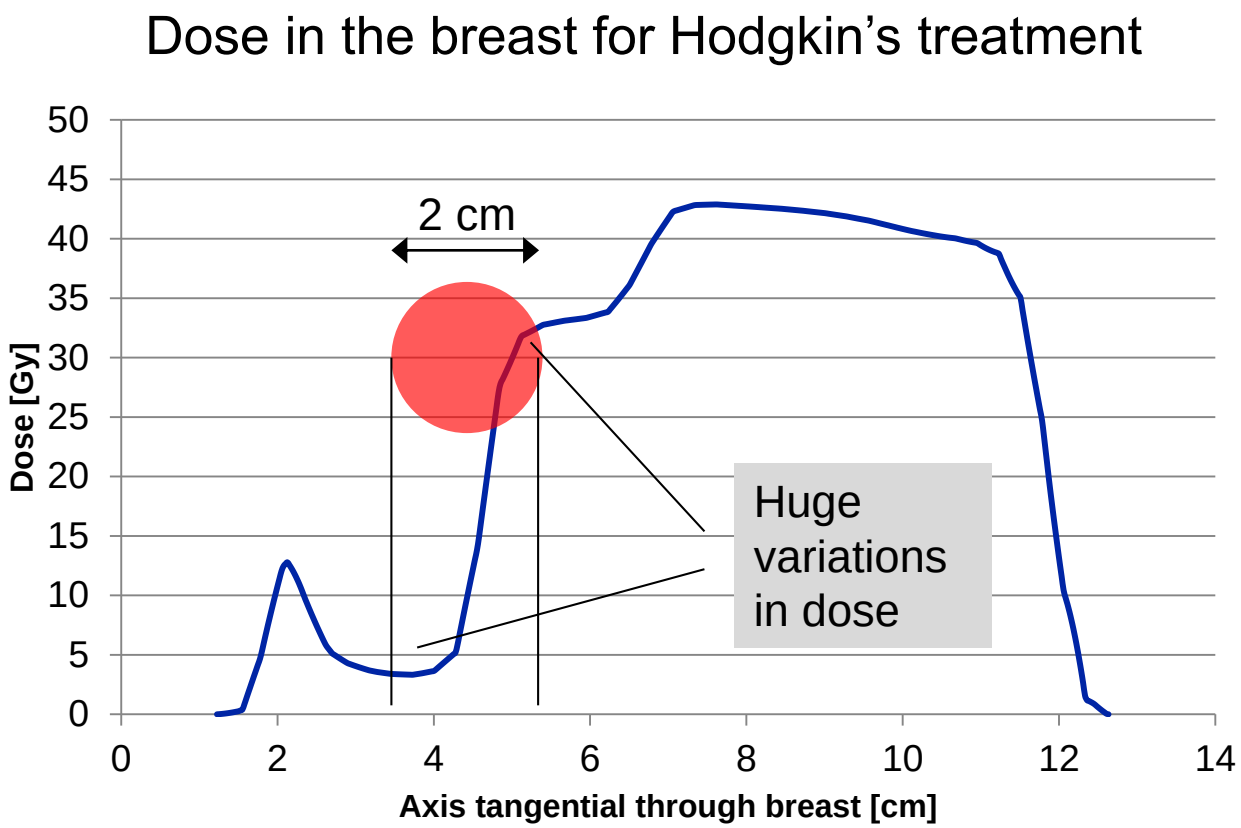
- ❑ Patient positioning
- ❑ Internal organ motion
- ❑ Anatomical changes
- ❑ Dose calculation

….

Schwab FD et al. Impact of breast cancer family history on tumor detection and tumor size in women newly-diagnosed with invasive breast cancer. Fam Cancer. 2014 13(1):99-107.

Determination of dose: Point dose

Point dose estimates are related to huge errors



Stratifications of cancer risk as a function of dose to the tumor location

Table 2. Risk of Breast Cancer Among Young Women Diagnosed With Hodgkin Disease, by Treatment*

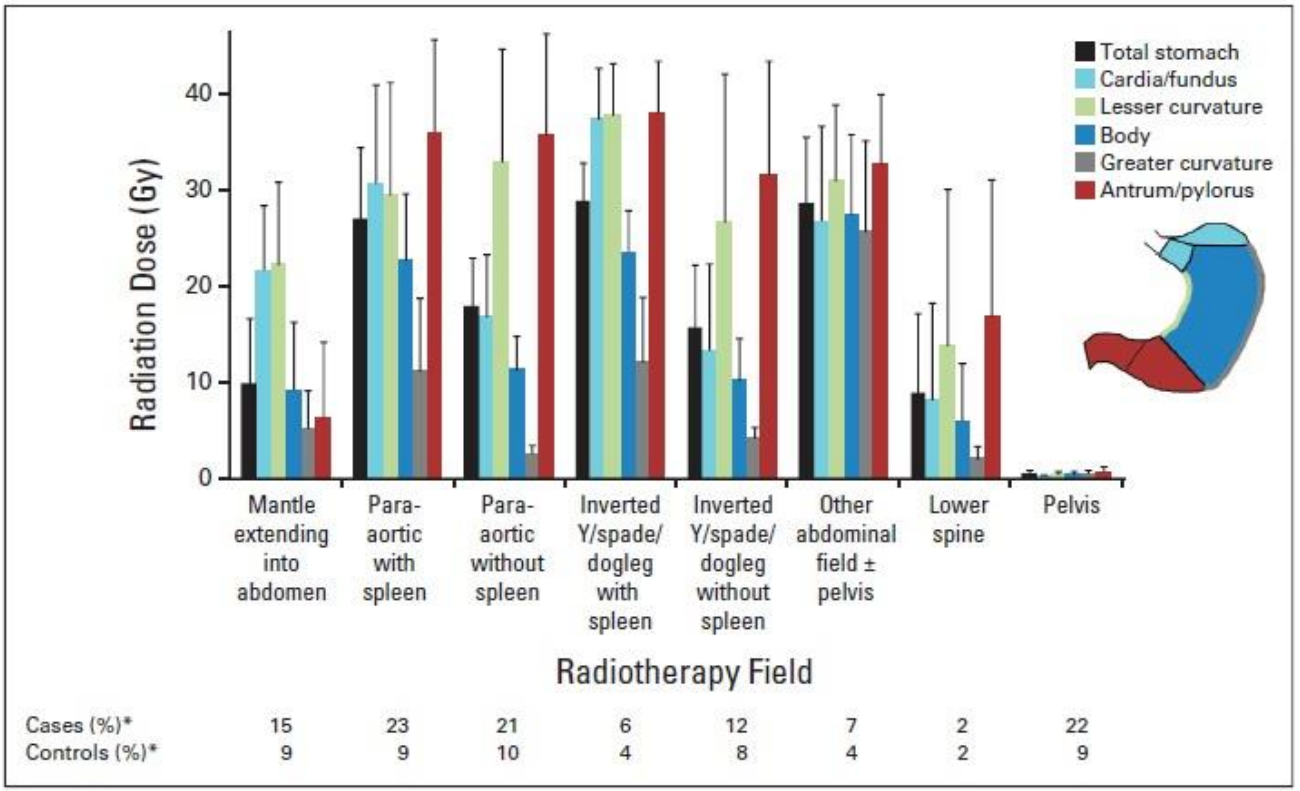
	No. (%)			
	Cases (n = 105)	Matched Controls (n = 266)	RR (95% CI)	*P* Value
Radiation Delivered to Specific Location in Breast†				
Dose, median (range), Gy				
3.2 (0-3.9)	15 (14.7)	76 (29.5)	Reference	
4.6 (4.0-6.9)	13 (12.7)	30 (11.7)	1.8 (0.7-4.5)	.21
21.0 (7.0-23.1)				008
24.5 (23.2-27.9)				22
35.2 (28.0-37.1)				001
39.8 (37.2-40.4)				02
41.7 (40.5-61.3)	17 (16.7)	29 (11.2)	8.0 (2.6-26.4)	<.001

Huge dose intervals:
~ 15 Gy

Travis LB, Hill DA, Dores GM, Gospodarowicz M, et al.. Breast cancer following radiotherapy and chemotherapy among young women with Hodgkin disease. JAMA. 2003 290(4):465-75.

Determination of dose: RT patients

- Analyses of radiotherapy risks using mean dose to the stomach tumor location
- Evaluation of risk for the whole organ (e.g. case-control)



Morton LM, Dores GM, Curtis RE, et al. Stomach cancer risk after treatment for hodgkin lymphoma. J Clin Oncol. 2013 Sep 20;31(27):3369-77.

Dose-response relationship from epidemiology

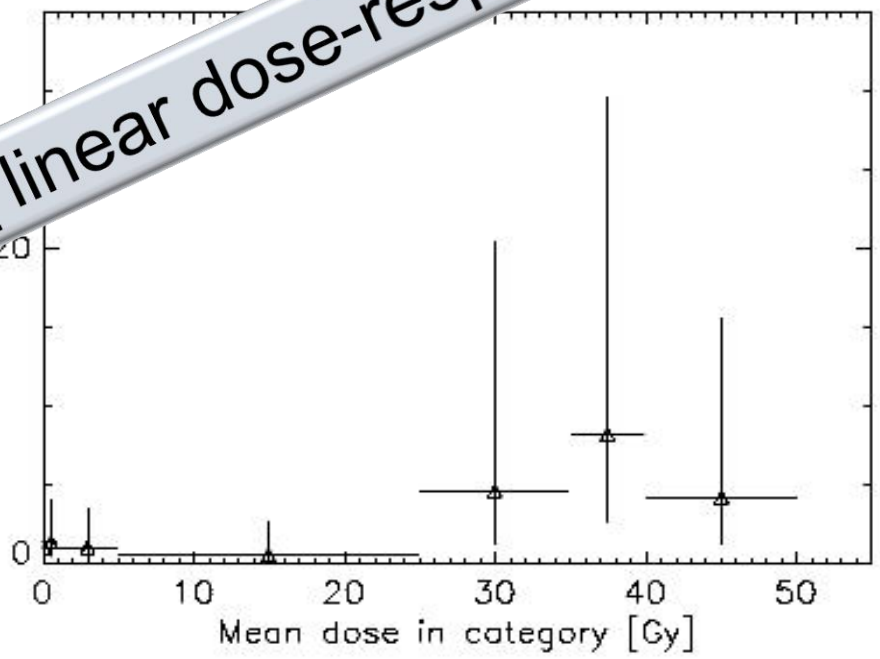
What we get

Dose-response:

Cancer risk as a function of

- ❑ **average dose in huge dose categories**
- ❑ **averaged dose c… different tr… techni…**
- ❑ **…dose in a large …t of the organ**

Average dose implies linear dose-response



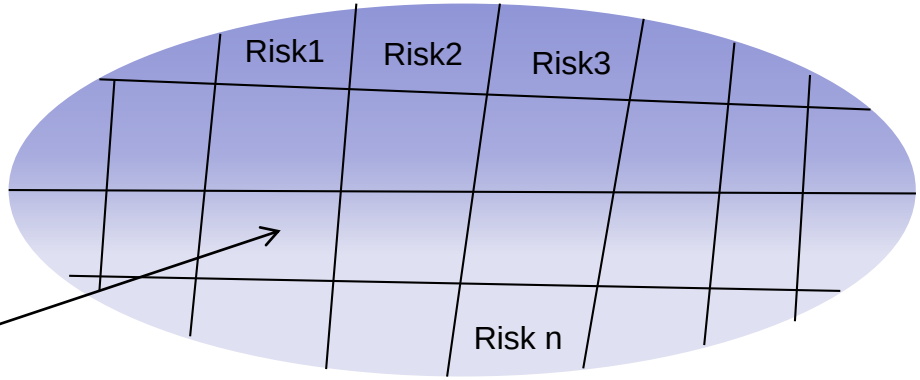
How to deal with inhomogeneous dose distributions in epidemiology

Problem:

Which dose do we assign to the "comparison organs" in the people who did not get cancer?

How to deal with inhomogeneous dose distributions in epidemiology

- Organ sub-division into sections where the dose is known



- Get the risks in these "organ sections" first
- Combine these risks to get the total organ risks.

Persons without cancer would provide "multiple comparisons" - one for each cancer free organ section

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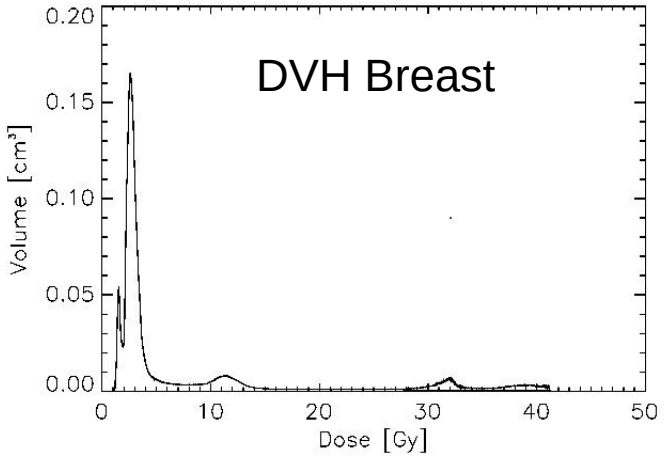
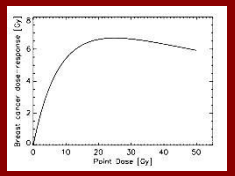
Dose-response without dose stratification: Reduction of the DVH

Epidemiology:

- ❑ organ specific risk
  e.g. Breast EAR = 10.5*
  O/E = 2.0 CI95(1.8-2.3)
- ❑ 3D-dose distribution or dose reconstruction



Apply dose-response model



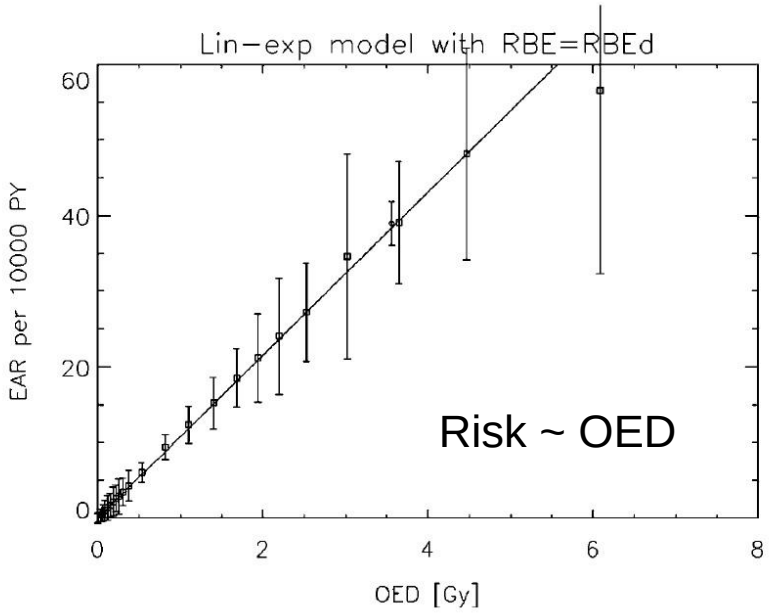
Reduction of DVH into risk a equivalent variable: **OED** (similar to EUD-concept)

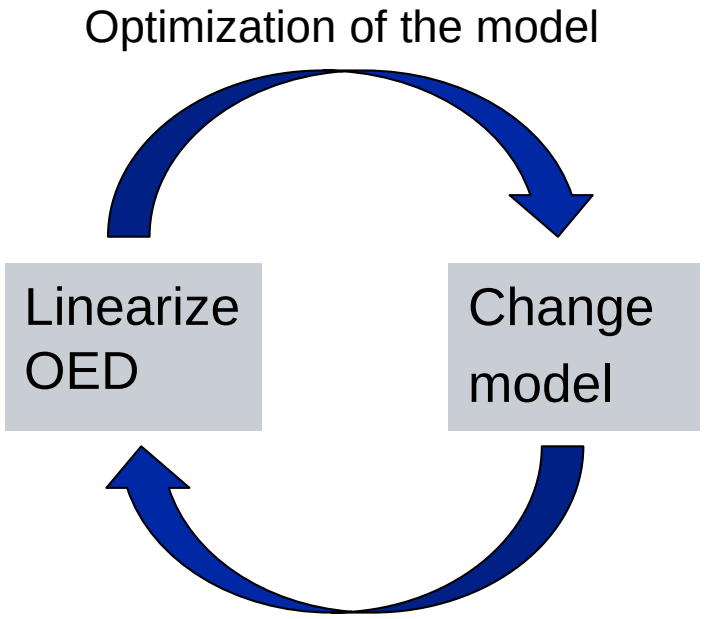
*Dores GM, et al. Second malignant neoplasms among long-term survivors of Hodgkin's disease: a population-based evaluation over 25 years. J Clin Oncol. 2002 20(16):3484-94.

Reduction of the DVH: Hodgkin - Breast

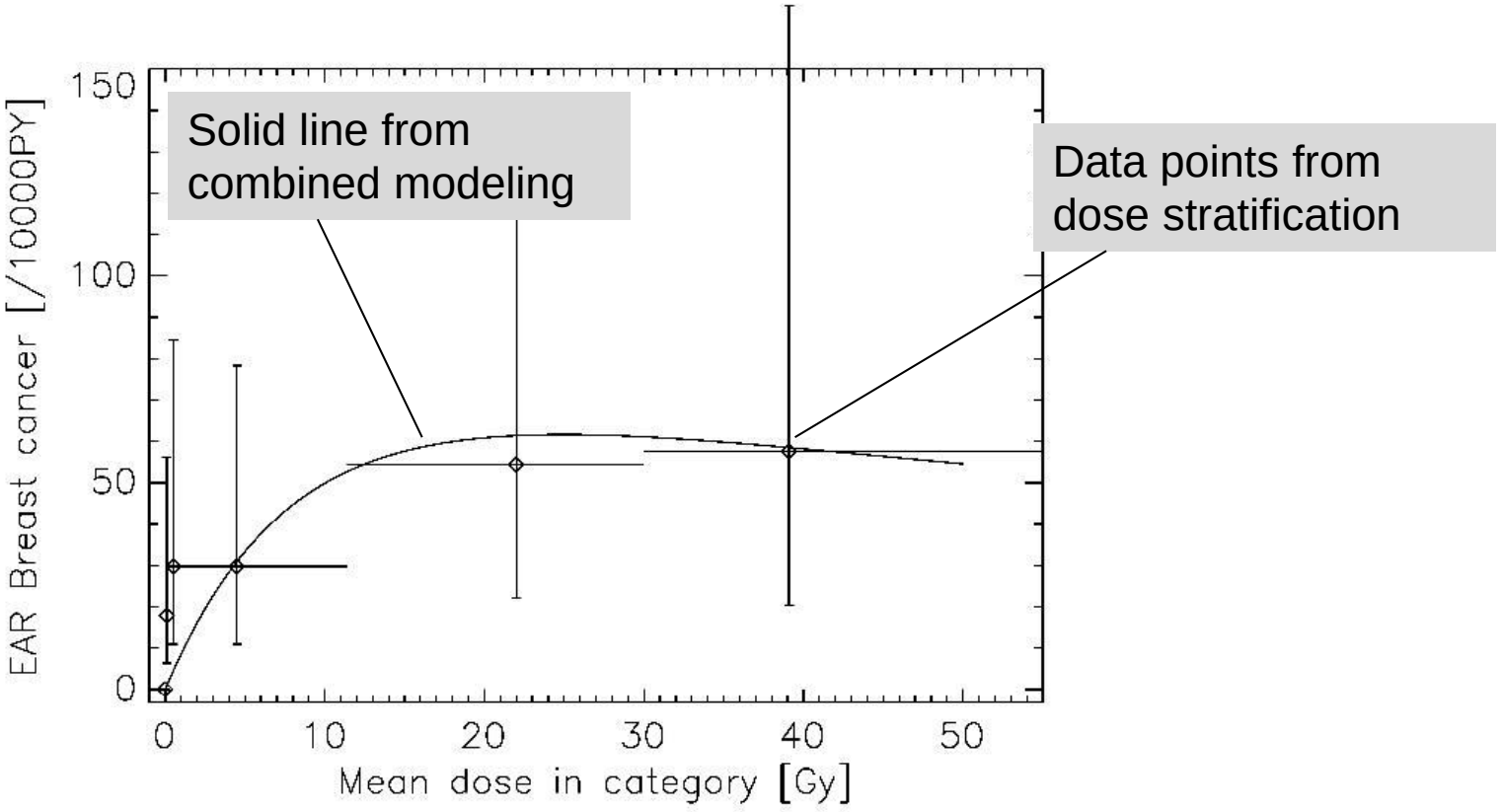
Epidemiology:

- Combination with A-bomb survivor data



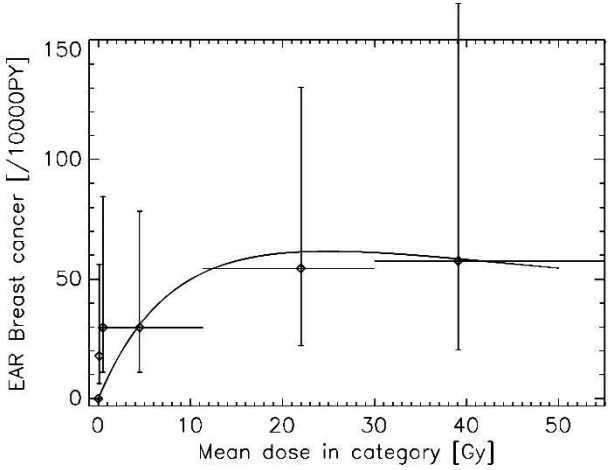


Result: optimized dose-response relationship without dose averaging

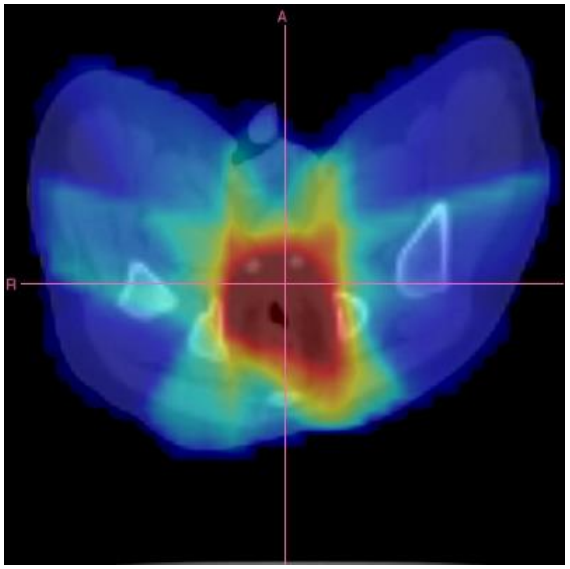


Inskip PD, Robison LL, Stovall M, Smith SA, Hammond S, Mertens AC, Whitton JA, Diller L, Kenney L, Donaldson SS, Meadows AT, Neglia JP. Radiation dose and breast cancer risk in the childhood cancer survivor study. J Clin Oncol. 2009 Aug 20;27(24):3901-7.

Result: optimized dose-response relationship without dose averaging

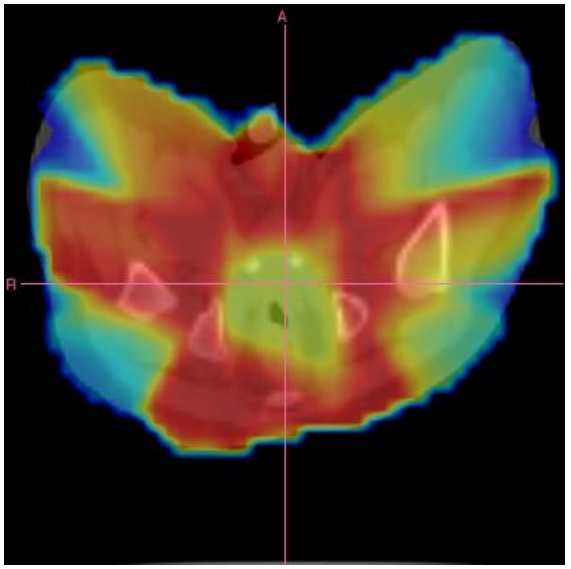


IMRT Dose

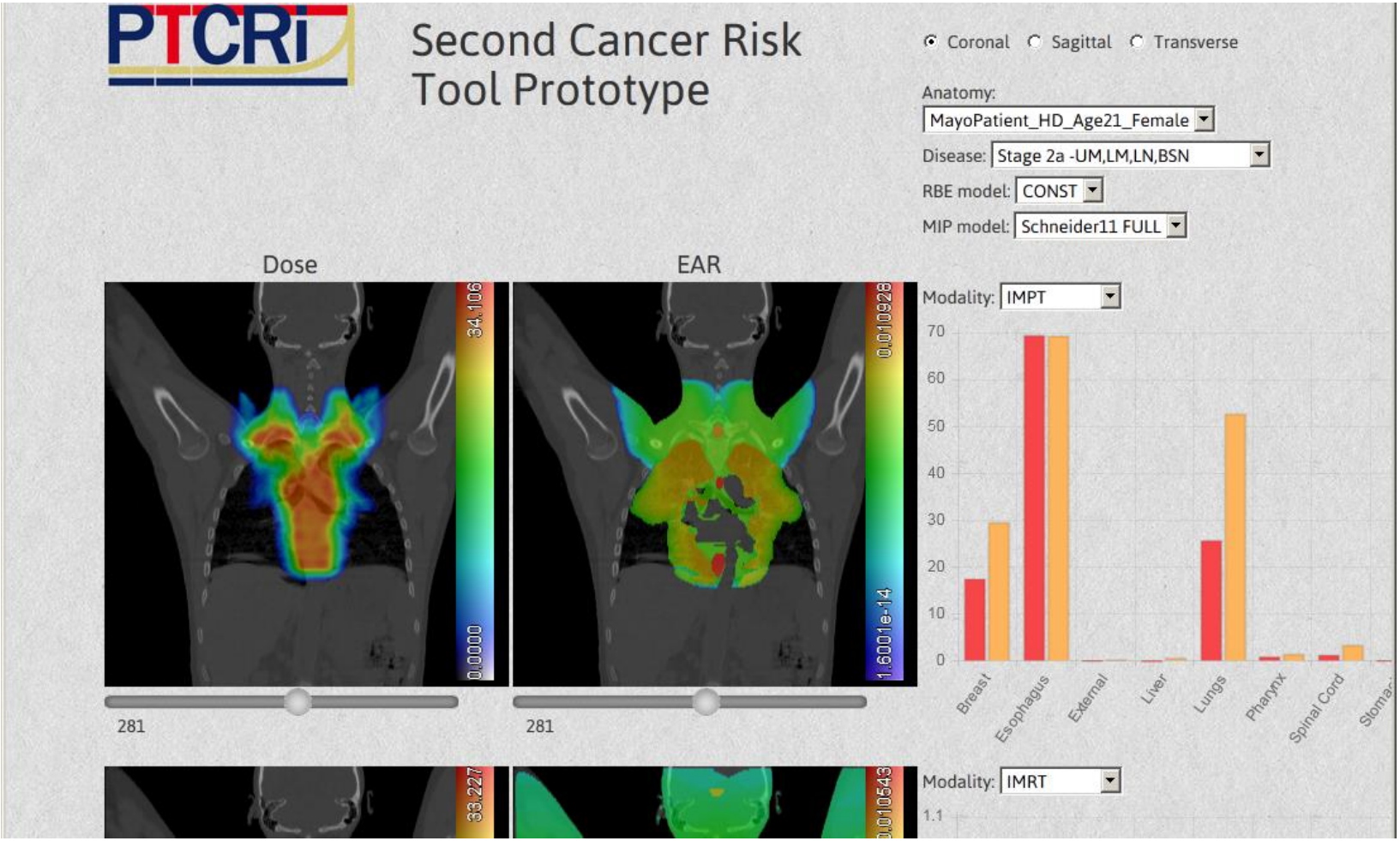


Convert DOSE to RISK

IMRT Risk



Second cancer web-tool from the University of Oxford



Timlin C, Warren DR, Rowland B, Madkhali A, Loken J, Partridge M, Jones B, Kruse J, Miller R. 3D calculation of radiation-induced second cancer risk including dose and tissue response heterogeneities. Med Phys. 2015 Feb;42(2):866-76.

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Uncertainties of risk models

$$EAR(D, df, agex, agea, s) = \beta(s) \cdot \mu(agex, agea, s) \cdot OED(D, df)$$

95 CI
EAR ≈ 100%

If you really need absolute risks

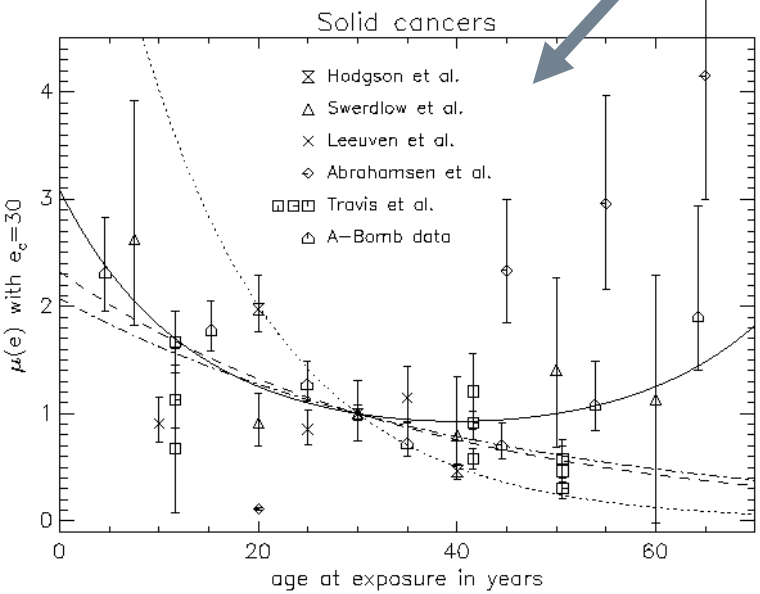
95 CI
OED ≈ 10%

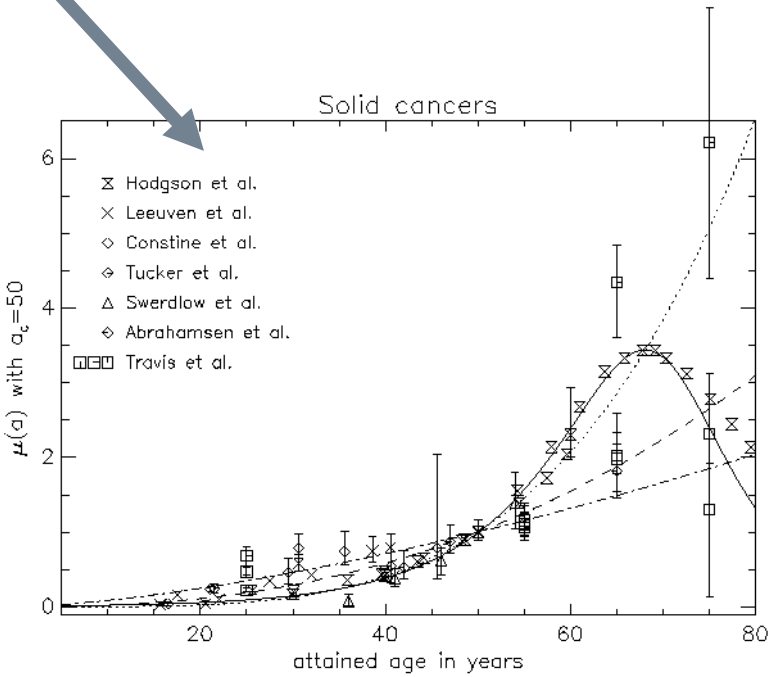
If you want to compare risks for one patient: treatment planning

Nguyen J, Moteabbed M, Paganetti H. Assessment of uncertainties in radiation-induced cancer risk predictions at clinically relevant doses. Med Phys.2015 Jan;42(1):81-9.

Risk variation with age

$$\mu(agex, agea, s)$$





- Significant variation of risk with age
- important for children

Schneider U, Walsh L. Age at exposure and attained age variations of cancer risk in the Japanese A-bomb and radiotherapy cohorts. Med Phys. 2015 Aug;42(8):4755-61.

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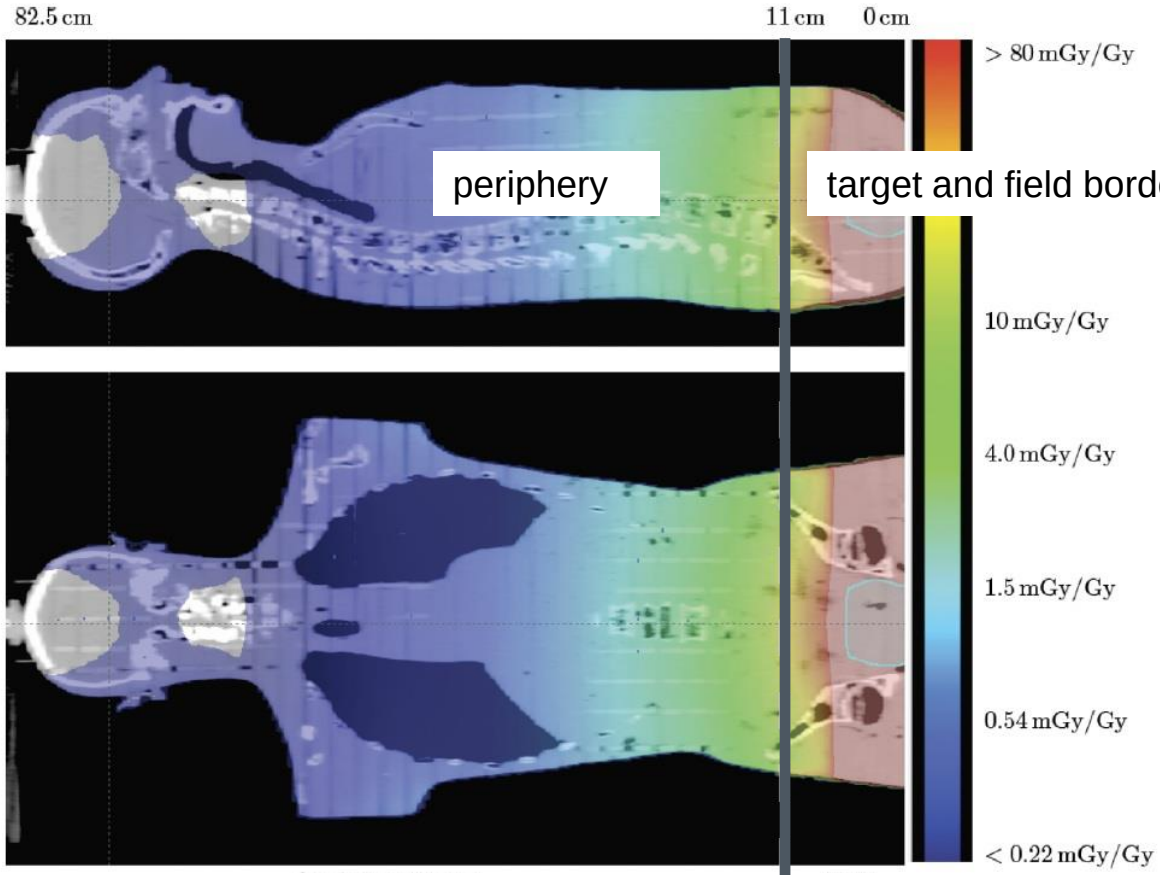
Uncertainties of the dose distribution



Analytical model / Monte Carlo | TPS

Dose models:	large error (20-50%)	small error (3%)
Risk models:	small error	large error

Hauri P, et al. A general model for stray dose calculation of static and intensity-modulated photon radiation. Med Phys. 2016 43(4):1955.

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Conclusions I

- The number of cancer survivors is increasing
- Modern radiotherapy is changing the distribution of dose in the patient
- Epidemiological studies provide risk data for "old-fashioned RT"

Models of second cancer risk:
Extrapolate cancer risk from "old" to "new" RT

Conclusions II

- Epidemiology: Analysis of the 3D-dose distribution
  (avoid dose averaging)
- Epidemiology and inhomogeneous dose distributions:
  Dose stratification calculating risk in organ sections
- Epidemiology and modelling:
  - avoid dose stratification
  - use of DVH and models together with epidemiology
- Fractionation effects: animal experiments and epidemiology
- Neutrons and ions: RBE with regard to cancer induction

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Thank you for your attention!

Acknowledgement:

- Roger Hälg, Pascal Hauri and the Radiotherapy Division of Hirslanden
- Linda Walsh and the Medical Physics research group @ University of Zürich

SEVENTH FRAMEWORK PROGRAMME

Schweizerische Eidgenossenschaft
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Confederazione Svizzera
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ligue suisse contre le cancer
lega svizzera contro il cancro