Models for the risk of secondary cancers from radiotherapy

Alexandru Dasu

The Skandion Clinic

Uppsala, Sweden

Skandionkliniken

Patient/clinician questions

- What is the (absolute) risk that the patient will get a secondary cancer from radiation treatment?

- Is the risk higher from treatment option* A than from option* B?
  - *plan, schedule, technique, modality etc.

- Due to long latency time of carcinogenesis, we have to resort to modelling to extrapolate the findings from patients treated several decades earlier.

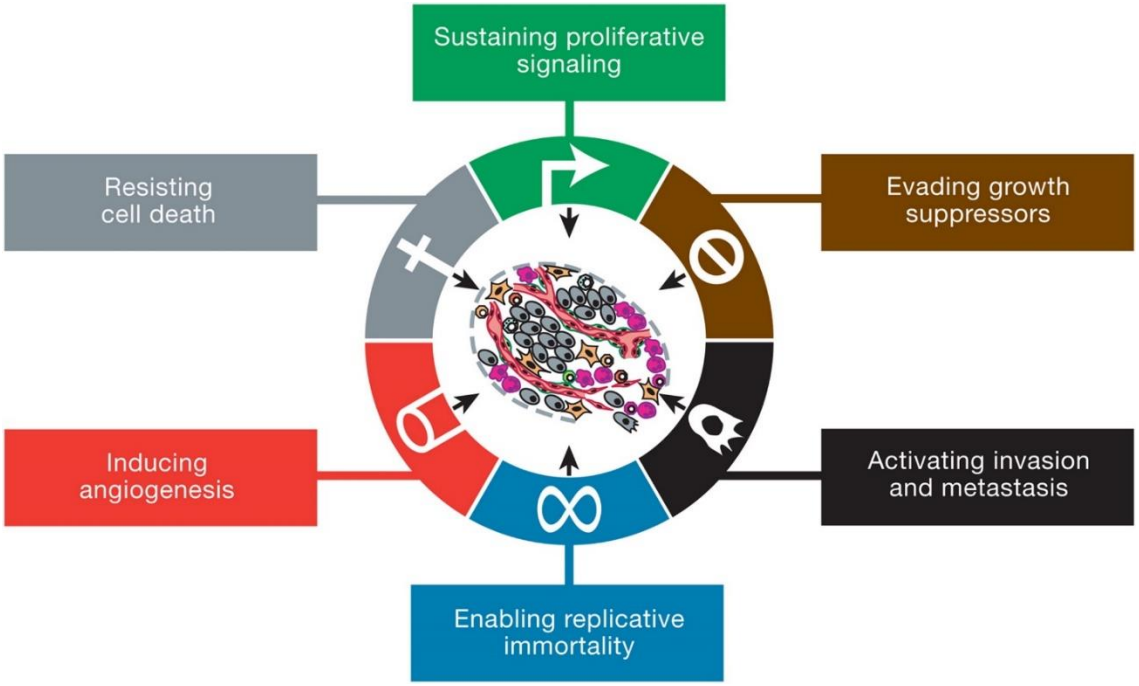
Modelling

- To simulate a process, a concept or the operation of a system (commonly with the aid of a computer).
  - Starting from ground principles and processes (mechanistic modelling)
  - Starting from observations (empirical modelling)
  - Combining observations and principles (semi-empirical/semi-mechanistic modelling)

- The aims of modelling a process are:
  - To describe it
  - To predict its outcome

Ground principles of carcinogenesis

- Carcinogenesis is the process of acquiring the hallmarks of cancer

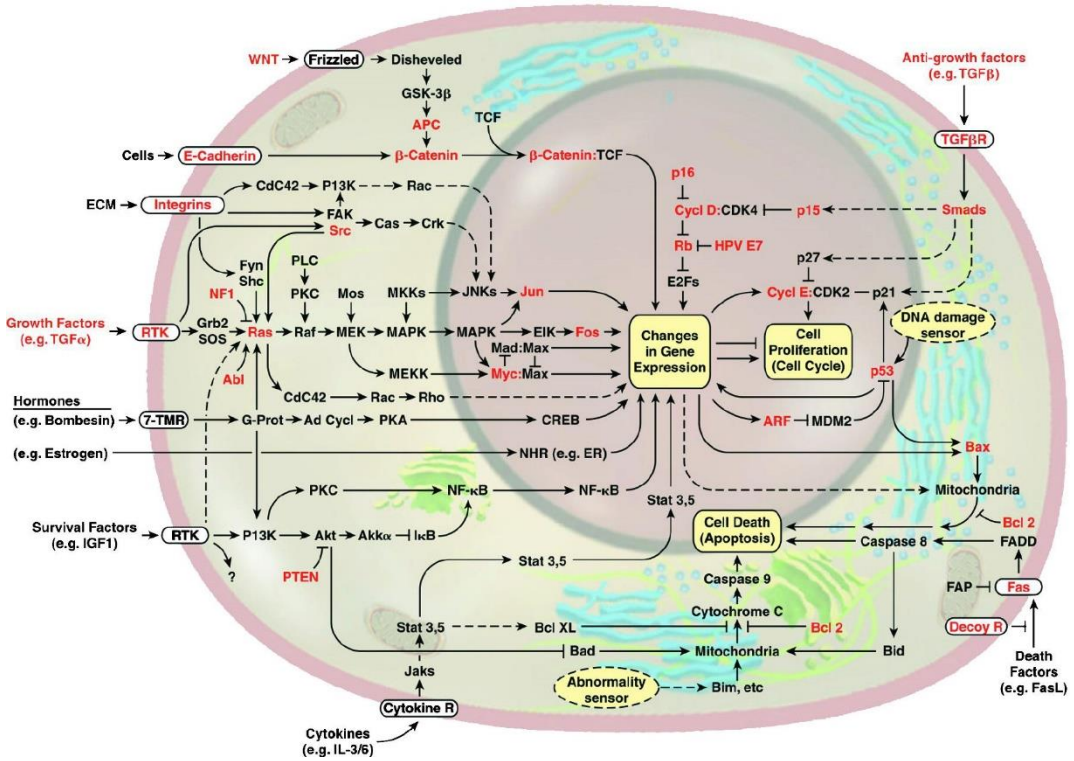


Hanahan and Weinberg (2011)

Skandionkliniken

Operation of a cell

- Intracellular signaling networks regulate the operations of the cancer cell

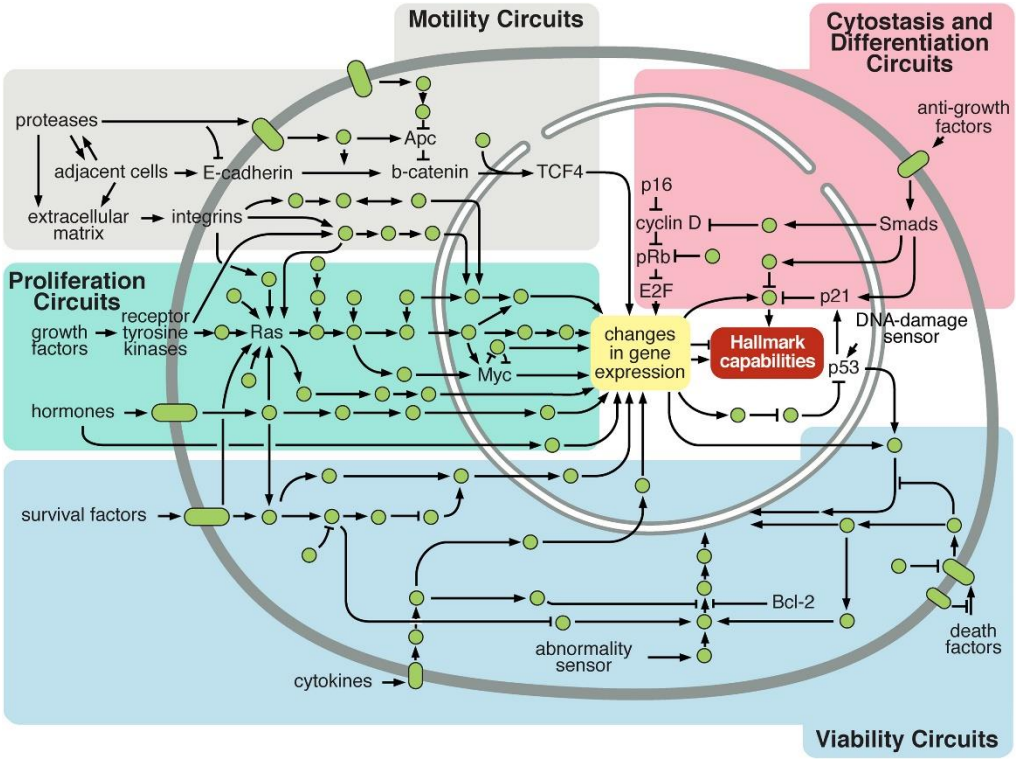


Hanahan and Weinberg (2000)

Skandionkliniken

Operation of a cell

- Each signaling process could be described mathematically



Hanahan and Weinberg (2011)

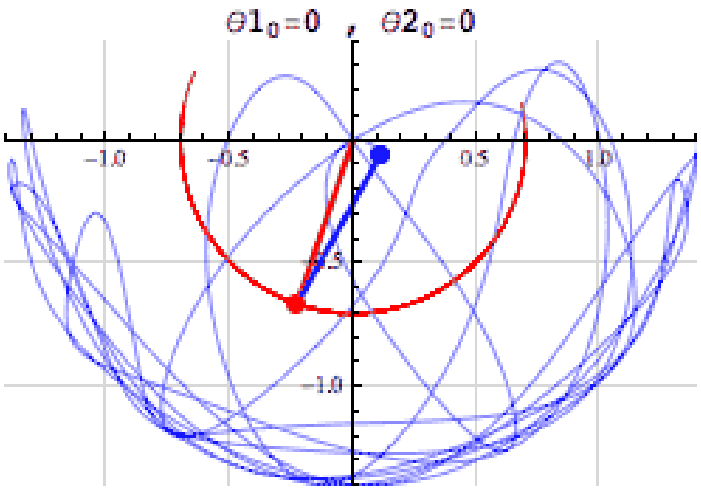
Skandionkliniken

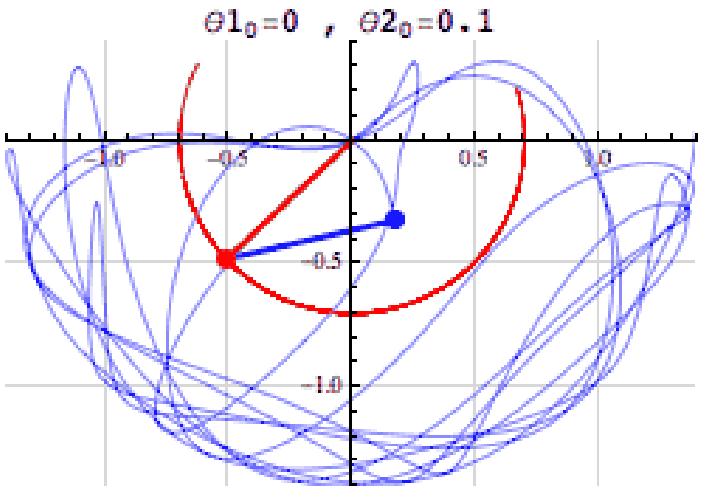
Mechanistic modelling

- Describe each signalling process by an equation.
- Equation parameters would depend on dose, but also on lifestyle and other internal and external factors (e.g., treatment related).
- The operation (and ultimately the faith) of the cell would be the solution of all these equations, tens/hundreds and many of them coupled.
- Numerical solutions could in principle be obtained.

Solving coupled differential equations

- Double pendulum: (only) 4 coupled differential equations





Skandionkliniken

Mechanistic modelling

- Parameter dependence on dose and other factors not yet known in detail.
- Multi-parameter dependencies are quite likely.
- In case of nonlinear systems, smooth (and often small) changes in parameter values or initial states could lead to sudden changes in the behaviour of the system.
- All problems are exacerbated by the number of individual processes to be modelled.
- Computation times are prohibitive.

Empirical modelling

- Describe relationships based on experimental observations.
- Correlate epidemiological observations with dose determinations.

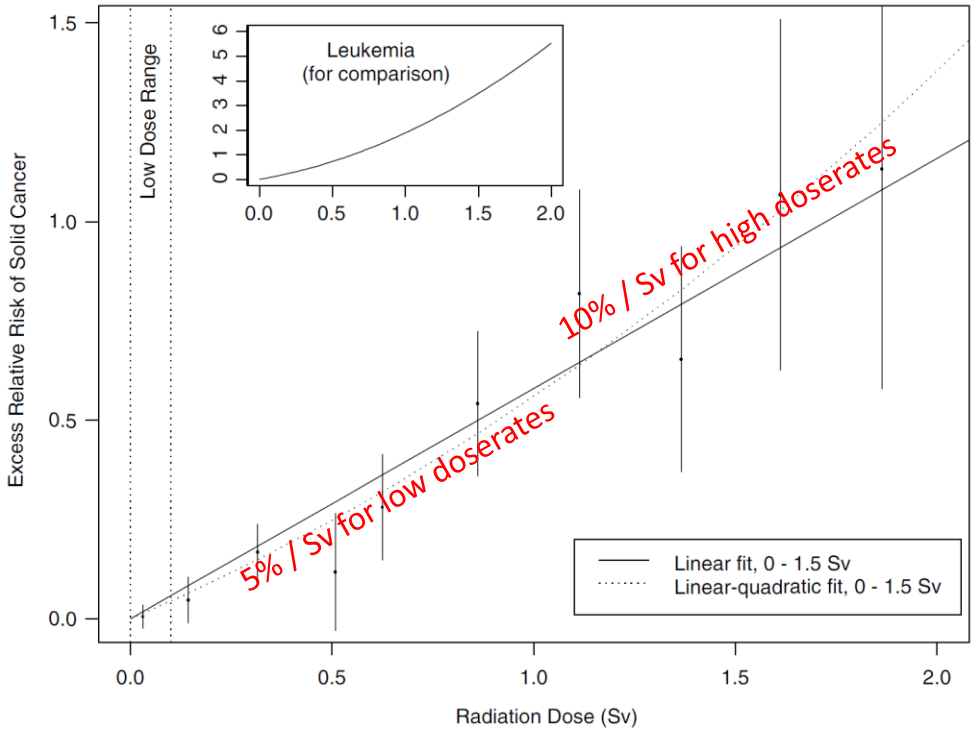
- Available epidemiological cohorts:
  - A-bomb survivors
  - Occupational irradiations
  - Medical irradiations

A-bomb survivors

- Healthy individuals
- Low doses delivered at (very) high doserates
- Combination of high energy photons and neutrons
  - Photon doses probably homogeneous
  - Neutron doses heterogeneous due to self-shielding in tissues
  - Inverse square law dependence of particle fluence with distance to epicentre

- Valuable conclusions:
  - Linear relationship between cancer induction and radiation dose up to about 2 Gy
  - Different sensitivities for various tissues
  - Variation of risk of induction with age at exposure
  - Long latency of expression

Linear no-threshold (LNT) model



BEIR VII (2006)

Alexandru Dasu

Skandionkliniken

LNT model in radiation protection

- The linear approximation of the A-bomb survivors is very much used in radiation protection (where doses are below 1-2 Gy).
- Heterogeneous irradiation is accounted for by a weighted summation of equivalent doses in affected tissues (effective dose).

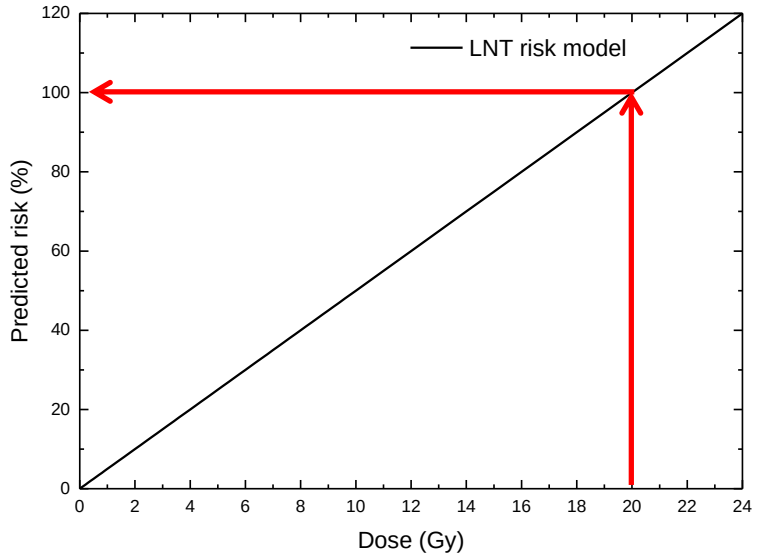
- Nominal risk coefficients should be applied to whole populations and not to individuals.
- The model is not recommended for epidemiological evaluations.
- The use of effective dose for assessing the exposure of patients has severe limitations that must be considered when quantifying medical exposure.
- Organ or tissue doses, not effective doses, are required for risk-benefit assessments or evaluating the probability of cancer induction in exposed individuals.

Medical irradiations

- Specific age and health distributions
- Diagnostic irradiations
  - Low doses and low doserates (in case of repeated exposures)
  - Heterogeneous doses
- Therapeutic irradiations
  - Wide range of doses extending to well above A-bomb survivors
  - Very heterogeneous dose distributions
  - Fractionated irradiation

LNT model in radiotherapy

- It is mathematically unsustainable at very large doses



- Risk relationships/models are non-linear in dose
  - However, whatever the model, it must reduce in the first approximation (low doses) to the dependence derived from A-bomb survivors.

Skandionkliniken

LNT model in radiotherapy

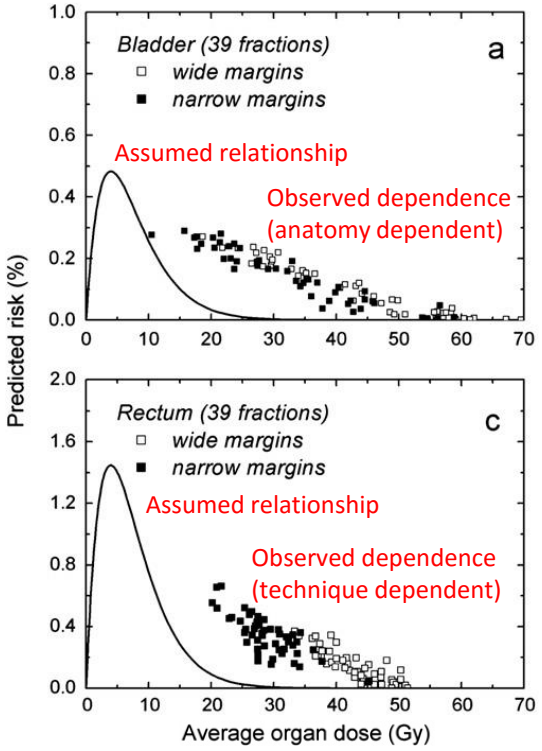
- Two main approaches have been used to apply the LNT model to radiotherapy:

- Separate primary and scatter contribution and apply the LNT model only to the latter
  - Underrepresents the risk as the contribution of primary radiation is neglected
  - The approach predicts large changes in relative risk

- Apply the LNT model to all, but therapeutic doses
  - Overrepresentation of the risk from (fairly) large doses
  - Erroneous identification of average/integral doses as indicators of risk

Empirical non-linear models

- Non-linear relationships hamper finding purely empirical correlations
- Average dose is no longer a risk indicator
- Confounding factors
  - Dose uncertainties due to gradients
  - Dose heterogeneities due to anatomy
  - Dose heterogeneities due to technique
  - Fractionated delivery
    - Repair
    - Proliferation
  - Effect of adjuvant treatments



Dasu et al (2011)

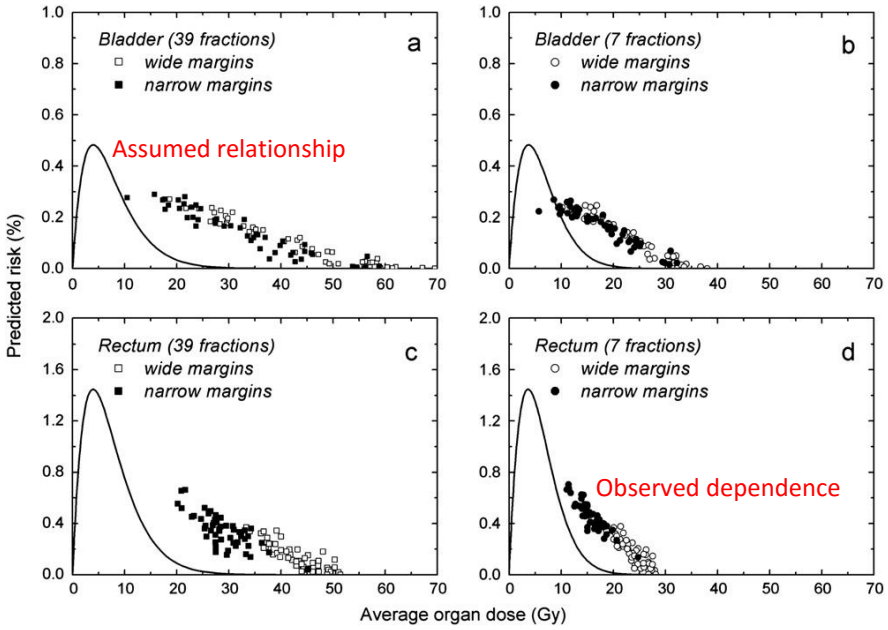
Alexandru Dasu

Skandionkliniken

Empirical non-linear models

- Non-linear relationships hamper finding purely empirical correlations

- Confounding factors
  - Dose uncertainties due to gradients
  - Dose heterogeneities due to anatomy
  - Dose heterogeneities due to technique
  - Fractionated delivery
    - Repair
    - Proliferation
  - Effect of adjuvant treatments



Dasu et al (2011)

Alexandru Dasu

Skandionkliniken

Semi-mechanistic models

- Simplify the number of processes that have to be simulated
- Model predictions based on the evolution of these processes
- Attune the model to epidemiological data
  - In the first approximation (low doses) the model must reduce to the linear relationship derived from A-bomb survivors
- Identify important correlations to be expected from epidemiological data
- Iterate

Radiation action

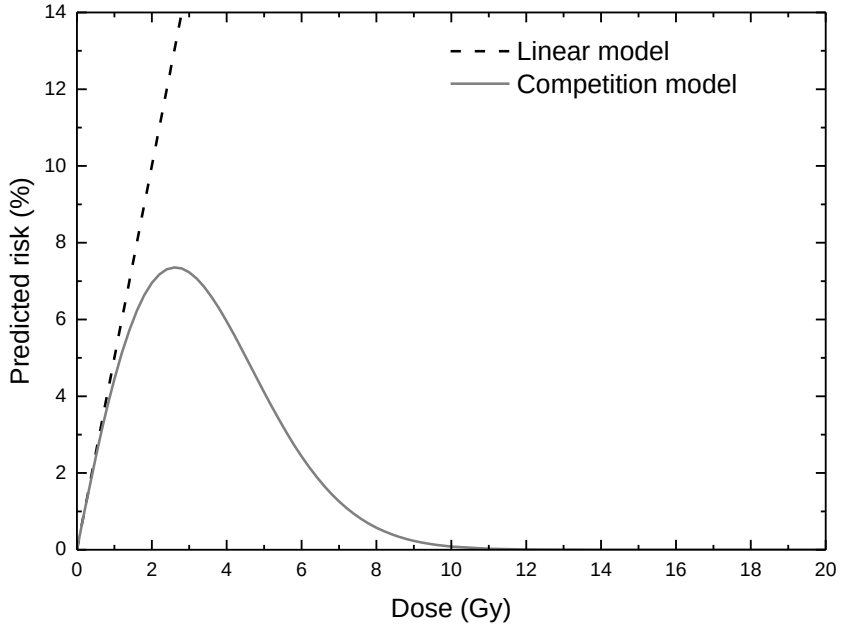
- Ionising radiation causes DNA damage
- Repair removes most of the damage
- Misrepair leads to mutations
  - Viable mutations
  - Lethal mutations
- Cells with lethal mutations cannot survive
- Gray (1965): There is a competition between mutation and killing

Competition model

- UNSCEAR (1993, 2000): LQ model is used to describe mutation and killing

$$\text{Risk} = \left(\alpha_1 D + \beta_1 D^2\right) \exp\left[-\left(\alpha_2 D + \beta_2 D^2\right)\right]$$

  - In the first approximation, *Risk* = $\alpha_1 \cdot D$
  - α_1 is the linear coefficient derived from A-bomb survivors



Alexandru Dasu

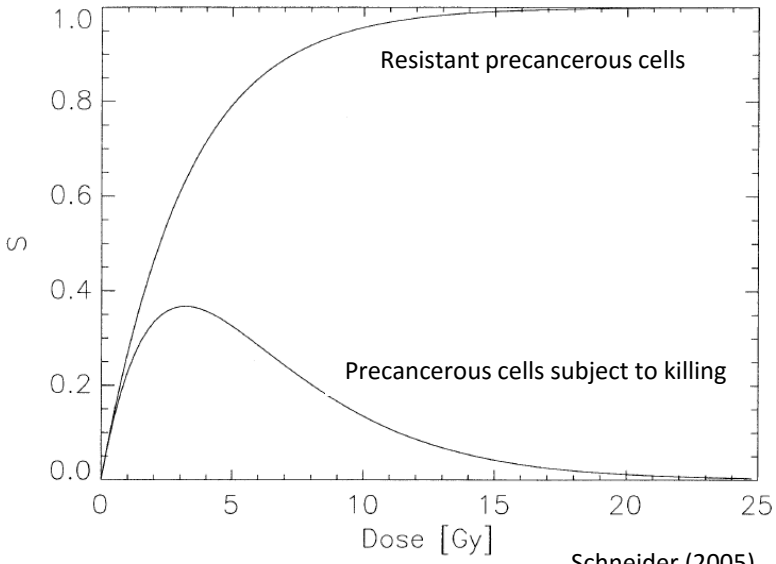
Skandionkliniken

Precursor cancer model

- Davis (2004): radiation acts upon a population of precancerous cells

$$\text{Risk} = \frac{cn}{a} \times \left(1 - e^{-aD}\right)$$

  - In the first approximation, *Risk = cn·D*
  - *cn* is the linear coefficient derived from A-bomb survivors



Schneider (2005)

$$S_1 = \frac{cn}{a}\left(1 - e^{-aD}\right)$$

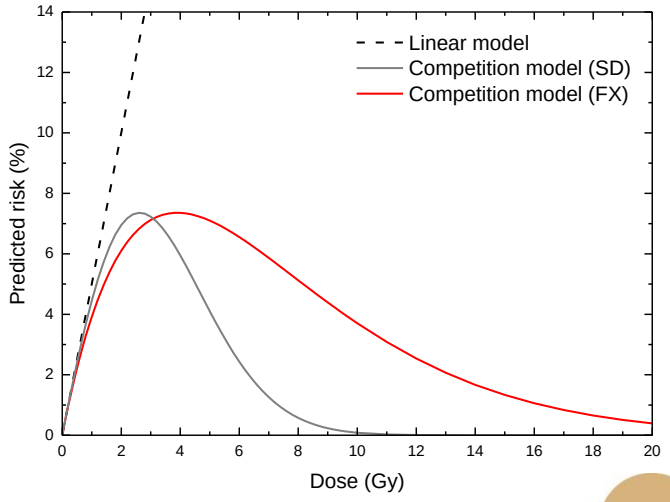
$$S_2 = cnD\ e^{-aD}$$

Effect of interfraction repair

- Repair influences directly the amount of DNA damage
  - More repair opportunities, less mutations
- Fractionation influences the number of mutations

$$\text{Risk} = \left(\alpha_1 D + \frac{\beta_1 D^2}{n}\right) \exp\left[-\left(\alpha_2 D + \frac{\beta_2 D^2}{n}\right)\right]$$ (Dasu et al 2005)

- In the first approximation, *Risk* = $\alpha_1 \cdot D$



Alexandru Dasu

Skandionkliniken

Proliferation models

- Sachs and Brenner (2005): Compensatory proliferation amplifies the number of mutated cells
  - Competition between normal and mutated cells

$$n^+(k) = SPn^-(k), \quad [1]$$

where

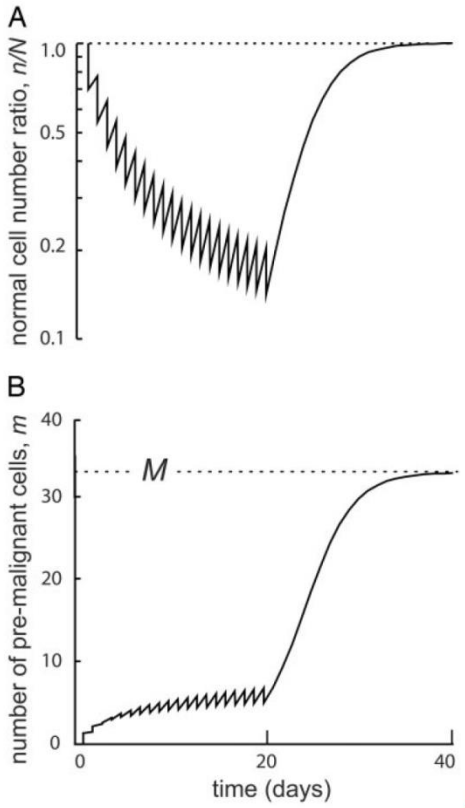
$$S = \exp(-\alpha d) \text{ and } P = \exp(-\gamma d) \approx 1-\gamma d;$$

$$m^+(k) = S[m^-(k) + (1-P)n^-(k)]; \quad [2]$$

$$n^-(k+1) = N/\{1 - e^{-\lambda T}[1 - N/n^+(k)]\}; \quad [3]$$

$$m^-(k+1) = m^+(k)[n^-(k+1)/n^+(k)]^r. \quad [4]$$

$$\mathrm{ERR} = N[\exp(\gamma D) - 1]B$$



- In the first approximation, *Risk = γNB·D*

Alexandru Dasu

Skandionkliniken

Proliferation models

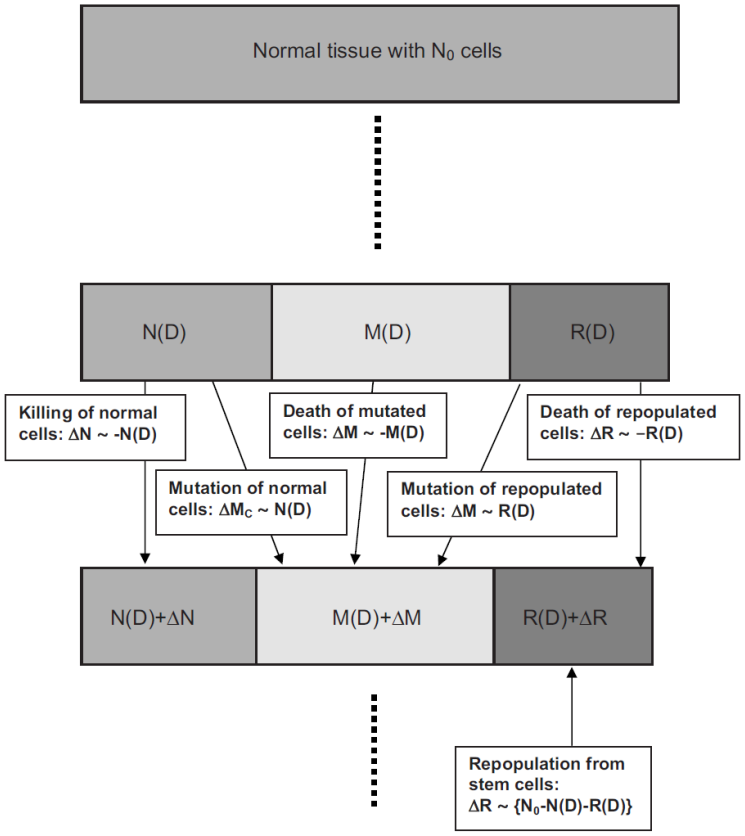
- Schneider (2009): Risk response depends on tissue proliferation capacity
- Different dose response functions for sarcomas and carcinomas

$$N(D) = N_0 e^{-\alpha' D},$$

$$R(D) = \frac{N_0}{\alpha' + \xi}\{\xi - \alpha' e^{-\alpha' D} - \xi e^{-\alpha' D} + \alpha' e^{-(\alpha'+\xi)D}\},$$

$$M_C(D) = \frac{\mu N_0 e^{-\alpha' D}}{\alpha' + \xi}\left\{\frac{\alpha'}{\xi} - \frac{\xi}{\alpha'} + \frac{\xi}{\alpha'} e^{\alpha' D} - \frac{\alpha'}{\xi} e^{-\xi D}\right\},$$

$$M_S(D) = \frac{\mu N_0 e^{-\alpha' D}}{\alpha' + \xi}\left\{\frac{\alpha'}{\xi} - \frac{\xi}{\alpha'} + \frac{\xi}{\alpha'} e^{\alpha' D} - \alpha' D - \xi D - \frac{\alpha'}{\xi} e^{-\xi D}\right\}.$$

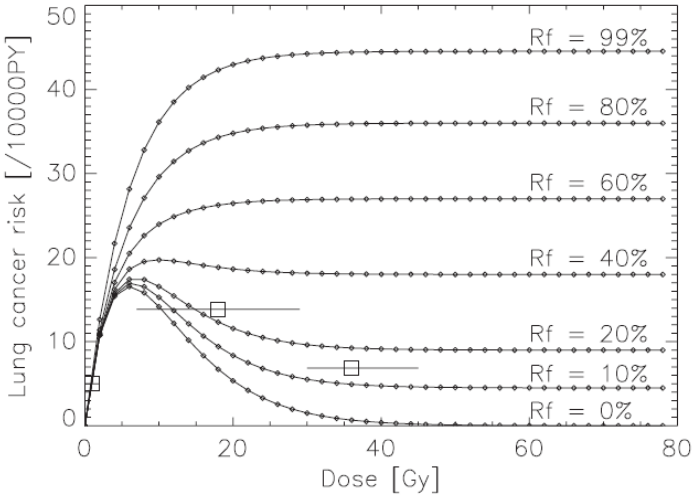


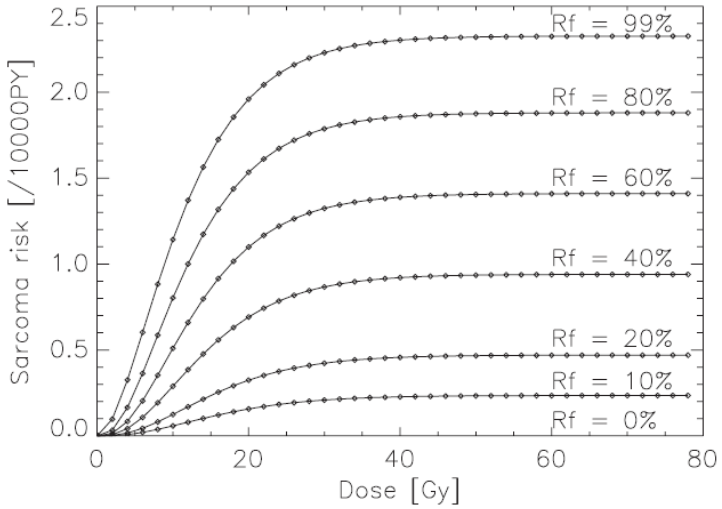
Alexandru Dasu

Skandionkliniken

Proliferation models

- In the first approximation: $M_C(D, \xi \to 0, d_f = D \to 0) = \mu N_0 D$
- If proliferation and cell kill are negligible: $M_C(D, \alpha' = 0, \xi \to 0) = \frac{\mu_C N_0}{\alpha'}(1 - e^{-\alpha' D})$





Schneider (2009)

Individualised models

- There is a large diversity in the patients and tissues subjected to radiation
  - Most models refer to the 'average patient'

- Tissue/organ differences
- Gender differences
- Age
- Size
- Adjuvant effects (hormonal or chemo-therapy)
- Genetic effects
- Lifestyle factors

Tissue/organ differences

TABLE 12-2 Committee's Preferred ERR and EAR Models for Estimating Site-Specific Solid Cancer Incidence and Mortality[a]

Cancer Site	No. of Cases	ERR Models				EAR Models			
		β_M[b] (95% CI)	β_F[b] (95% CI)	γ[c]	η[d]	β_M[e] (95% CI)	β_F[e] (95% CI)	γ[c]	η[d]
Stomach	3602	0.21 (0.11, 0.40)	0.48 (0.31, 0.73)	–0.30	–1.4	4.9 (2.7, 8.9)	4.9 (3.2, 7.3)	–0.41	2.8
Colon	1165	0.63 (0.37, 1.1)	0.43 (0.19, 0.96)	–0.30	–1.4	3.2 (1.8, 5.6)	1.6 (0.8, 3.2)	–0.41	2.8
Liver	1146	0.32 (0.16, 0.64)	0.32 (0.10, 1.0)	–0.30	–1.4	2.2 (1.9, 5.3)	1.0 (0.4, 2.5)	–0.41	4.1 (1.9, 6.4)
Lung	1344	0.32 (0.15, 0.70)	1.40 (0.94, 2.1)	–0.30	–1.4	2.3 (1.1, 5.0)	3.4 (2.3, 4.9)	–0.41	5.2 (3.8, 6.6)
Breast[f]	952	—	0.51 (0.28, 0.83)	0	–2.0	—	9.4 (6.7, 13.3)	–0.51	3.5, 1.1[g]
Prostate	281	0.12 (<0, 0.69)	—	–0.30	–1.4	0.11 (<0, 1.0)	—	–0.41	2.8
Uterus	875	—	0.055 (<0, 0.22)	–0.30	–1.4	—	1.2 (< 0, 2.6)	–0.41	2.8
Ovary	190	—	0.38 (0.10, 1.4)	–0.30	–1.4	—	0.70 (0.2, 2.1)	–0.41	2.8
Bladder	352	0.50 (0.18, 1.4)	1.65 (0.69, 4.0)	–0.30	–1.4	1.2 (0.4, 3.7)	0.75 (0.3, 1.7)	–0.41	6.0 (3.1, 9.0)
Other solid cancers	2969	0.27 (0.15, 0.50)	0.45 (0.27, 0.75)	–0.30	–2.8 (–4.1, –1.5)	6.2 (3.8, 10.0)	4.8 (3.2, 7.3)	–0.41	2.8
Thyroid[h]		0.53 (0.14, 2.0)	1.05 (0.28, 3.9)	–0.83	0				

NOTE: Estimated parameters with 95% CIs. PY = person-years.

BEIR VII (2006)

Tissue/organ differences

- Organ size varies between patients.

Table 1. Liver Diameter in the MCL in Individual Age Groups

Age, y	n (%)	Liver Diameter, cm	
		Mean ± SD	Median (Range)
18–25	250 (12.0)	13.6 ± 1.5	13.4 (9.5–17.2)
26–35	514 (24.7)	13.7 ± 1.6	13.6 (10.0–18.5)
36–45	402 (19.3)	14.0 ± 1.6	14.0 (9.4–18.8)
46–55	308 (14.8)	14.2 ± 1.7	14.1 (10.2–19.9)
56–65	343 (16.5)	14.4 ± 1.8	14.4 (10.6–19.8)
≥66	263 (12.7)	14.1 ± 2.0	14.0 (10.0– 21.3)
Total	2080 (100.0)	14.0 ± 1.7	13.9 (9.4–21.3)

Kratzer et al (2003)

- Larger organs mean more cells that could be mutated.
- Risk calculations for individual patients should account for differences in organ size from the average patient.

- Ardenfors et al (2014): Multiply the risk for the average patient with the ratio of individual organ volume to average organ volume.

Age dependent models

- A-bomb survivor data yielded information regarding the variation of the risk with age at exposure and attained age.

$$\mathrm{EAR} = \beta_s \cdot d \cdot \exp[\gamma e + \varepsilon \log(a)].$$

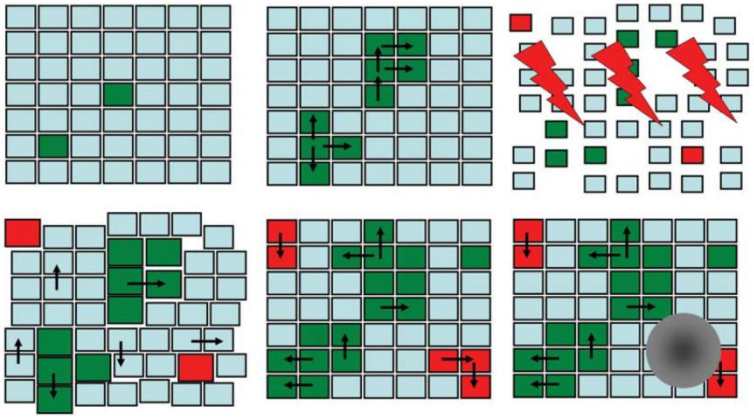
where β_s is the risk coefficient in the LNT model (Pierce et al 1996).

- The model was used in subsequent risk evaluations from A-bomb survivors (Preston et al 2004, 2007).

- Schneider and Walsh (2008) adapted the model for various other expressions of the risk model.

Age dependent models

- Shuryak et al (2009): radiation initiates, promotes, or kills pre-malignant cells; a pre-malignant cell generates a clone, which, if it survives, quickly reaches a size limitation; the clone subsequently grows more slowly and can eventually generate a malignant cell; the carcinogenic potential of pre-malignant cells decreases with age.



$$
\begin{aligned}
\mathrm{ERR} &= [(Q_1 Q_2 + Q_3)/Q_4] - 1, \quad \text{where} \\
Q_1 &= (1 + YD)/\left[1 + YD\left(1 - \exp\left[-\delta T_y\right]\right)\right]; \\
Q_2 &= [(\exp[bT_x] - 1)Sf(Z, D) + bXISf(D)]\exp\left[bT_y\right]; \\
Q_3 &= \exp\left[bT_y\right] - 1; \\
Q_4 &= \exp\left[b\left(T_x + T_y\right)\right] - 1
\end{aligned} \tag{15}
$$

Other differences

- Accounting for individual differences (genetic predisposition, disease- or treatment-induced aspects, lifestyle factors)

Other differences

- Accounting for individual differences (genetic predisposition, disease- or treatment-induced aspects, lifestyle factors) is still…

Risk evaluations for treatment plans

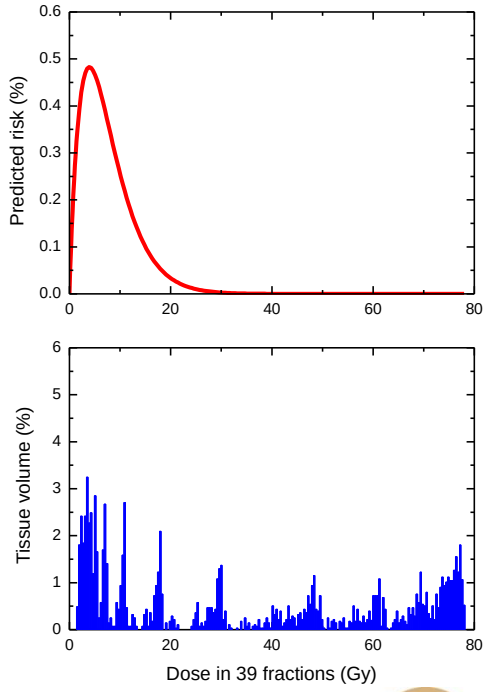
- Predictions of risk could be used for further evaluation and ranking of plans in radiation therapy.
- Risks for particular organs or tissues
- Total risk for the patient
- Distributions of risks

Heterogeneous irradiations

- Dose response models assume uniform irradiations of tissues which is seldom the case in radiation therapy.

- Dasu et al (2005): the risk is the weighted average of partial risks throughout the volume of interest.

$$\text{Total risk} = \frac{\sum_i v_i \times \text{Risk}\,(D_i)}{\sum_i v_i}$$



- Leads to an absolute quantification of the risk

Alexandru Dasu

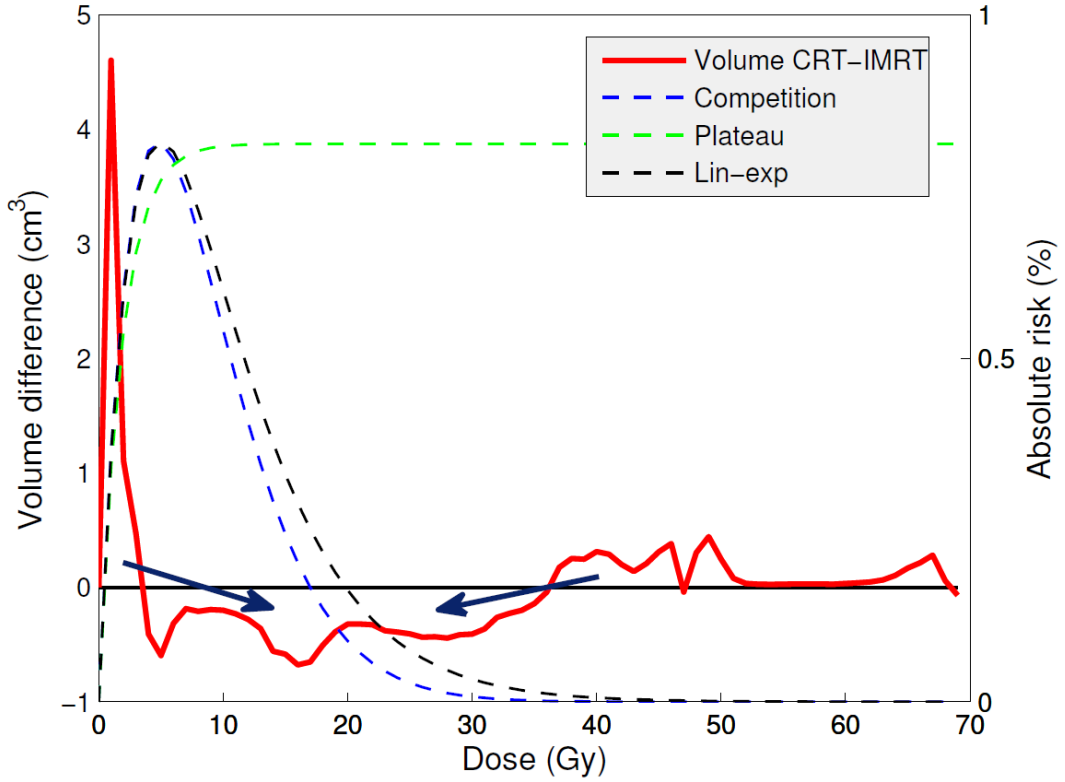
Skandionkliniken

Organ equivalent dose (OED)

- Absolute risk determinations are subject to parameter uncertainties.
- Schneider et al (2005): Dividing the total risk for a tissue to the linear risk coefficient leads to the equivalent uniform dose that results in the same risk:
- $OED=Risk/\alpha_1$
- OED could be used for evaluations of relative changes in risk, avoiding uncertainties in absolute risk determinations.

Patient risk evaluations

- Multi-model evaluations



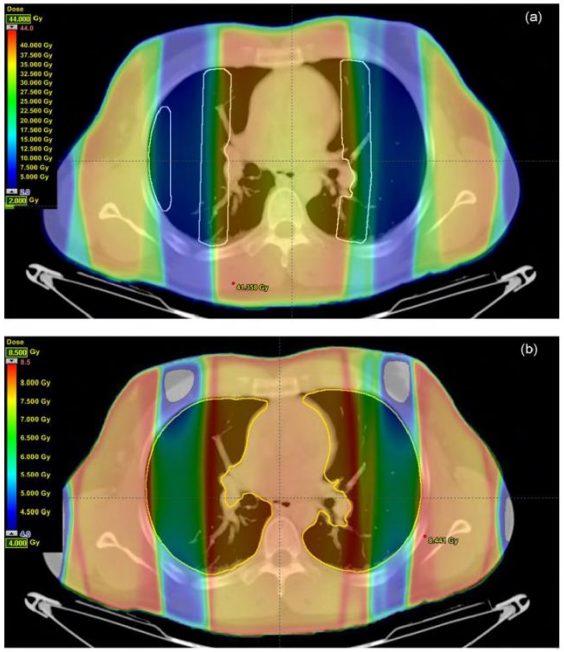
Ardenfors et al (2014)

Alexandru Dasu

Skandionkliniken

Risk Equivalent Dose (RED)

- Schneider (2010, 2011): Dose distributions could be transformed into their associated risk equivalent dose (RED) distributions.



- As different tissues may have different sensitivities, there could be discontinuities at tissue interfaces.

Secondary dose contributions

- Primary radiation is only one contributor to radiation burden to tissues.
- Other contributors to the radiation burden:
  - Head leakage
  - Scatter radiation
  - Doses from imaging procedures
- Non-linear dose response models mean that risk components are not additive.
- $Risk(d_1+d_2+d_3+\ldots) \neq Risk(d_1)+Risk(d_2)+Risk(d_3)+\ldots$

Leakage and scatter dose contributions

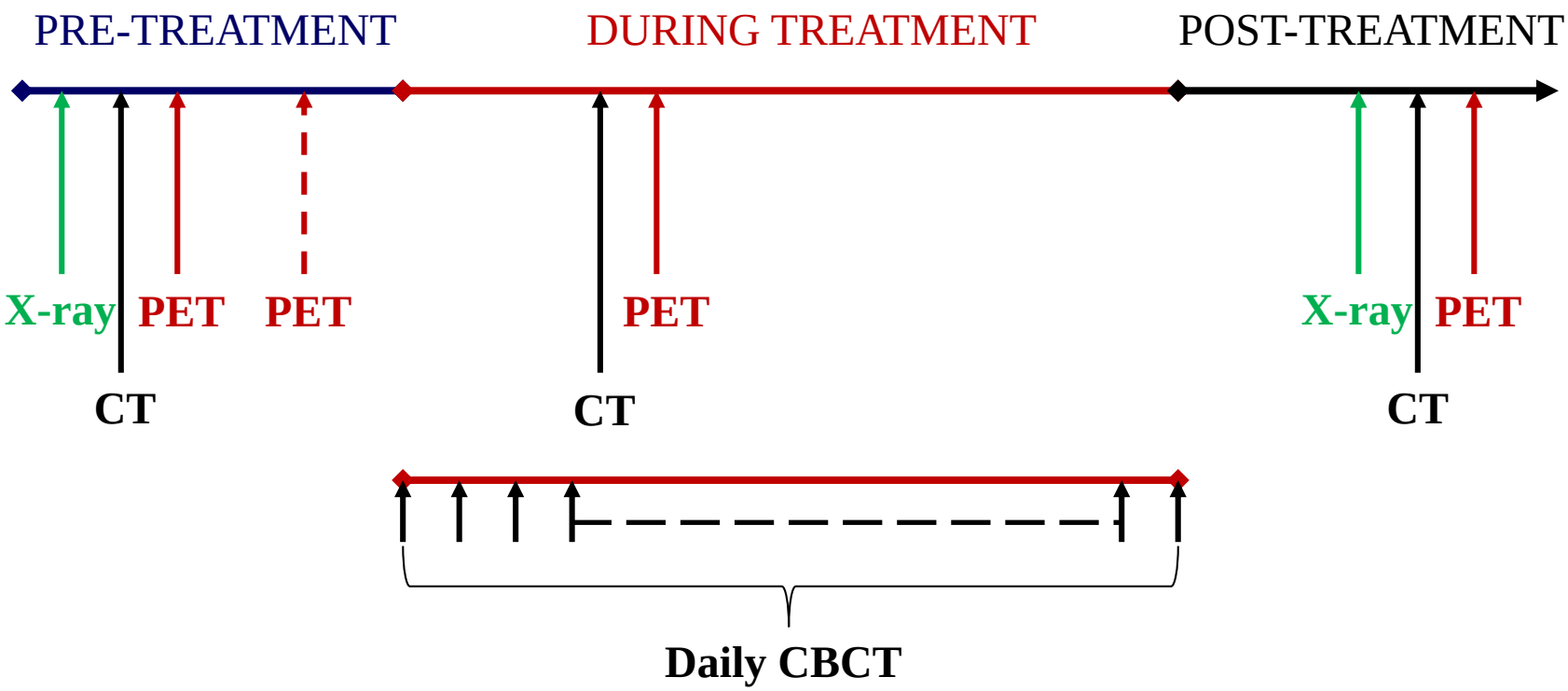
- Leakage radiation increases with the number of MU.
- The amount of scatter radiation depends on many factors, including radiation modality and field size.
  - Extrapolation from 3D-CRT to IMRT is not straightforward

Table I. Doses from TLD measurements in an anthropomorphic phantom. Doses per MU are presented per fraction, average total doses and the corresponding ratios correspond to doses per MU per fraction multiplied with 34 fractions and the mean number of MUs employed for each treatment technique.

Distance from PTV (cm)		Dose per MU (mGy)		Av. Tot. Dose (Gy)		Av. Tot. Dose Ratio (IMRT/CRT)
IMRT	CRT	IMRT	CRT	IMRT	CRT	
−1.2	−0.7	1.72	7.61	51.2	64.6	0.8
4.1	4.6	0.05	0.19	1.5	1.6	1.0
9.2	9.7	0.03	0.08	0.8	0.6	1.2
14.5	15.0	0.02	0.05	0.6	0.4	1.6

Ardenfors et al (2014)

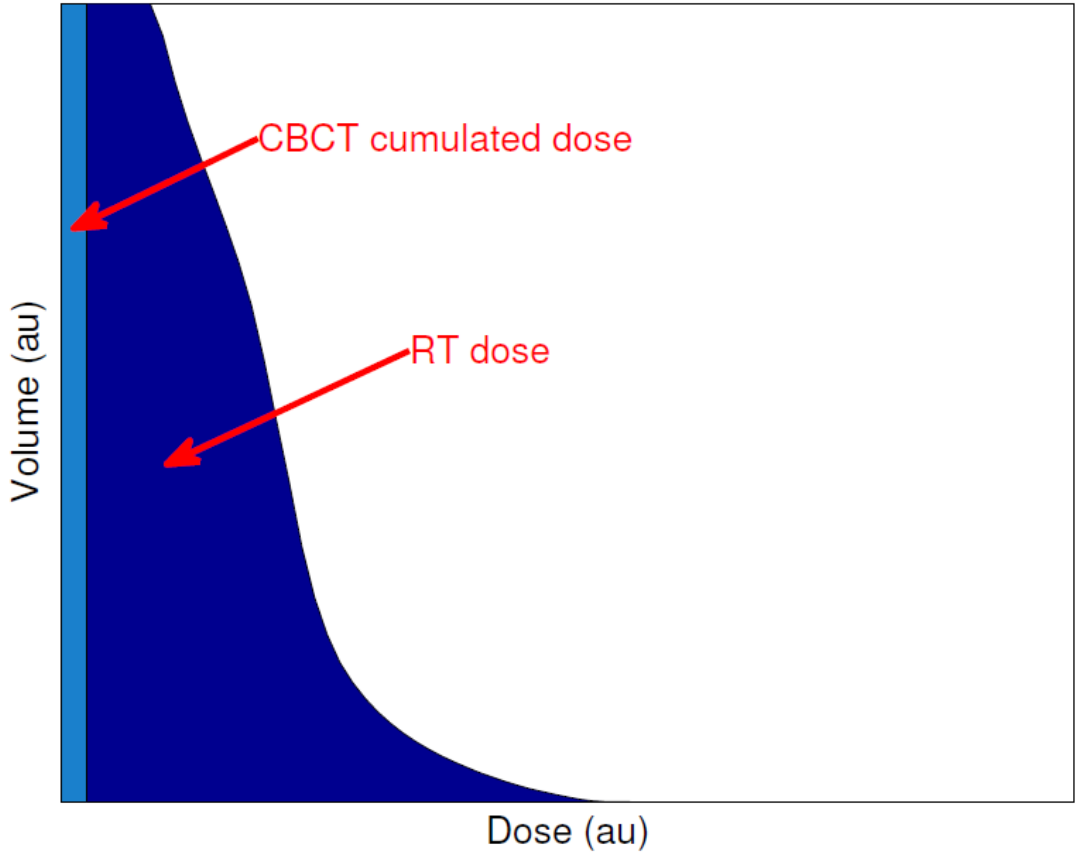
Imaging dose contributions



Alexandru Dasu

Skandionkliniken

Imaging dose contributions



Ardenfors (2011)

Skandionkliniken

Imaging dose contributions

Table II. Average lifetime risk contributions from IMRT and CRT treatments (RT), scatter to the lungs, and cone-beam CT imaging.

	Competition model		Plateau model		Lin-exp model	
Risk	IMRT	CRT	IMRT	CRT	IMRT	CRT
RT without imaging	0.49%	0.61%	1.13%	1.11%	0.51%	0.64%
RT + weekly imaging	0.50%	0.62%	1.14%	1.12%	0.52%	0.65%
RT + daily imaging	0.53%	0.65%	1.17%	1.15%	0.55%	0.68%
Scatter radiation	0.58%	0.51%	0.99%	0.93%	0.58%	0.51%
Total[a]	1.08%	1.14%	2.13%	2.05%	1.10%	1.16%
Spread of total risk values	0.91–1.29%	0.91–1.48%	1.82–2.51%	1.72–2.43%	0.92–1.30%	0.93–1.50%

[a]Sum of RT with weekly imaging and scatter radiation.

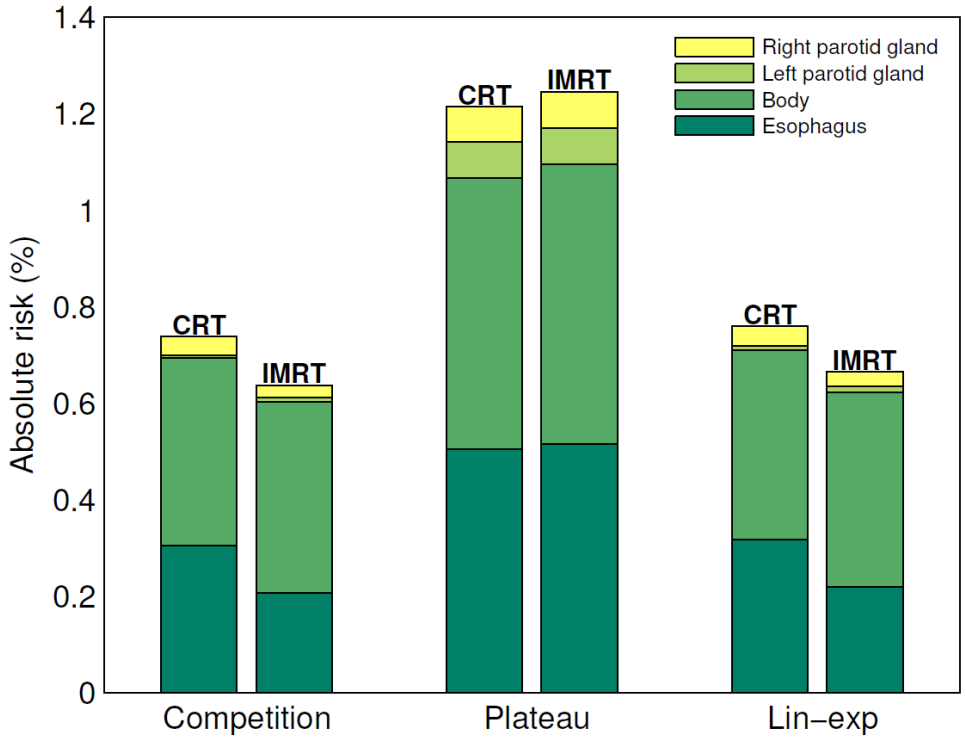
Ardenfors et al (2014)

Alexandru Dasu

Skandionkliniken

Patient risk evaluations

- Total risk for the patient could be more informative.



Ardenfors et al (2014)

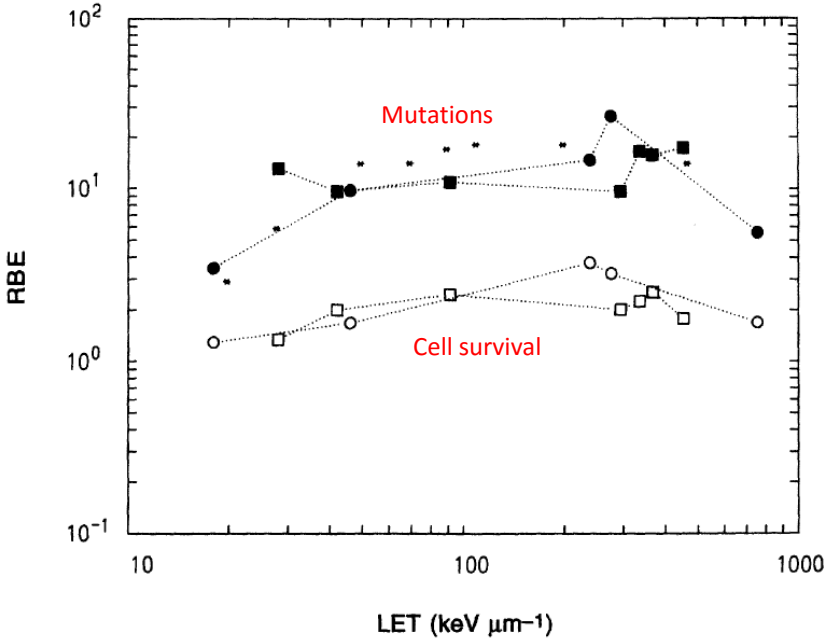
- Dose redistribution might lead to risk redistribution.

Alexandru Dasu

Skandionkliniken

Risks from particle therapy

- Risk models could be adapted for particle therapy by accounting for the radiobiological effectiveness of the radiation.
- $$Risk = \left(\alpha_1 RBE_{\alpha_1} D + \frac{\beta_1 RBE_{\beta_1} D^2}{n}\right) \times exp\left(\alpha_2 RBE_{\alpha_2} D + \frac{\beta_2 RBE_{\beta_2} D^2}{n}\right)$$



Stoll et al (1995)

Alexandru Dasu

Skandionkliniken

Conclusions

- Several models with increasing complexity are available for risk evaluation.
  - Further complexity layers could be added depending on future findings.
- Risk models could be used for extrapolating epidemiological knowledge to new radiotherapy techniques.
- Any risk model should be in agreement with epidemiological findings.
- A promising application is the optimisation of treatments from the point of view of associated risks.
  - This requires the balancing of deterministic and stochastic effects as both influence the quality of life (or disability) of the patient.

Acknowledgments

- Oscar Ardenfors

- Dan Josefsson

- Iuliana Toma-Dasu

- Irena Gudowska

Alexandru Dasu

Skandionkliniken

Thank you!

Skandionkliniken