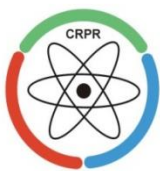




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# Risk of secondary cancer following radiotherapy



**RADIUMHEMMETS**  
FORSKNINGSFONDER



Strål  
säkerhets  
myndigheten



# Radiation therapy – a two edge sword

Radiation

=

Anti-tumour agent



Radiation

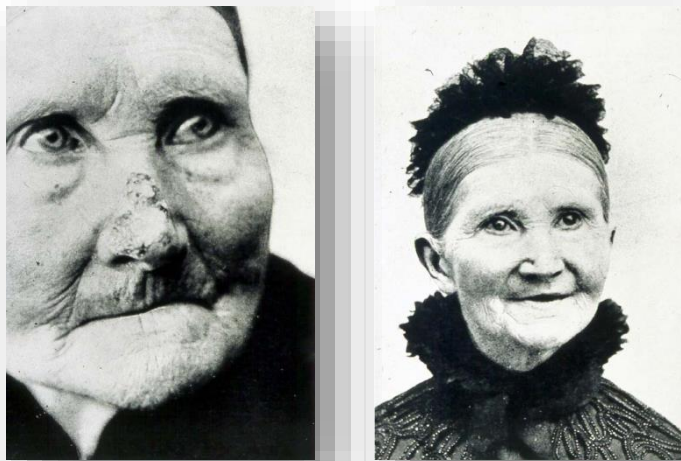
=

Carcinogenic agent



# Radiation therapy – a two edge sword

The first patient successfully treated of cancer with radiation in Stockholm in 1899 at the Stenbecks Institute



Marie Skłodowska-Curie and her daughter Irène Joliot-Curie died of leukemia probably due to their radiation exposures





# Radiation therapy – a two edge sword

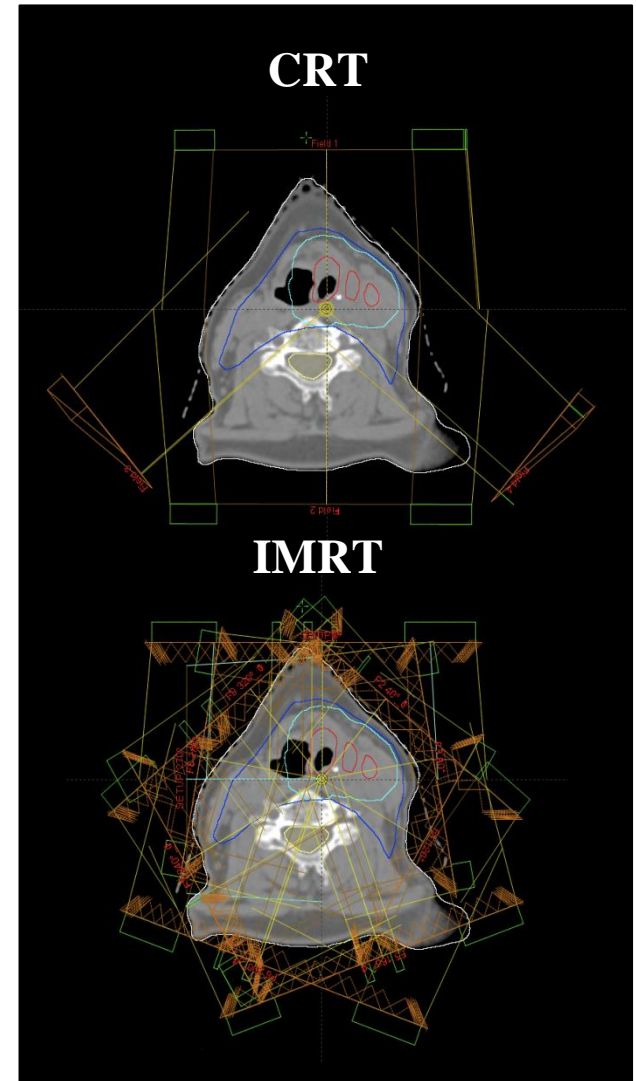
- Radiotherapy is used alone or in combination with surgery and/or chemotherapy in about **50% of the cancer treatments**
- About **5.5 million of cancer patients** worldwide receive high doses of radiation in relation to radiotherapy
- Among the cured cancer patients, 49% are cured with surgery, **40% are cured with radiotherapy** and 11% with chemotherapy
  - Late effects, including secondary cancer, become a matter of concern for the long term survivors of radiotherapy



# Risk of SMN

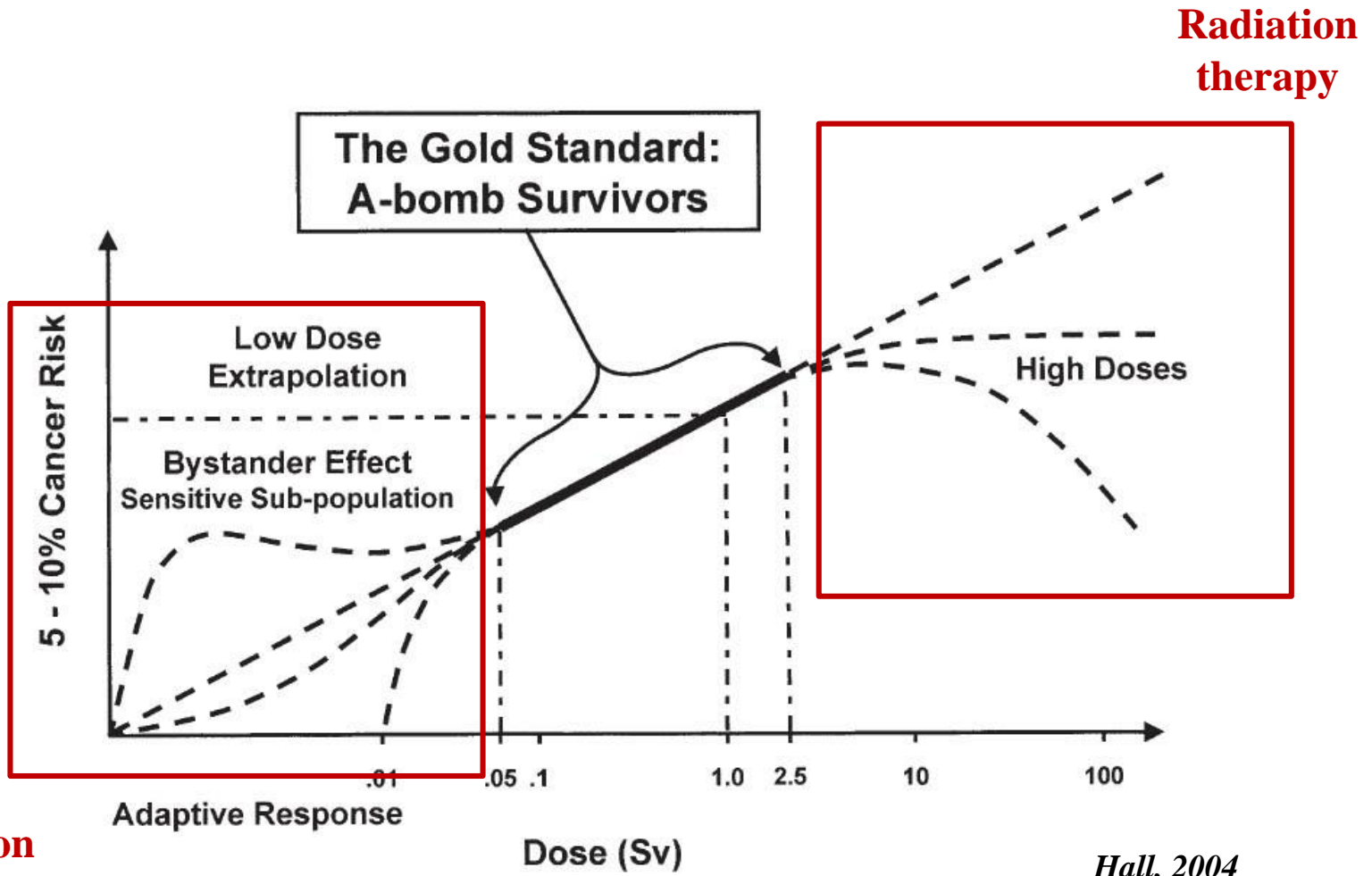
- How dangerous is a particular type of treatment ?
- Is the risk from one type of RT treatment larger than the risk from another RT treatment?

➤ **We need risk estimates!**





# Risk of radiation induced cancer





# Gold standard – A-bomb survivors

- About 100000 persons of all ages and both sexes have been followed after the A-bombings of the Japanese cities of Hiroshima and Nagasaki.
- The appearance of cancers has been carefully recorded.
- A wide range of doses has been available.
- The irradiations were generally with a mixture of low and high LET radiation.
- The photon doses were generally uniform, those from neutrons were not.





# Radiation-induced cancer in humans

- A large part of the data on cancer induction comes from epidemiological studies on earlier human irradiations.
  - Accidental irradiations:
    - Japanese survivors of A-bomb attacks
    - Survivors from nuclear accidents
  - Professional irradiations:
    - Uranium miners, dial painters, radiologists
  - Medical irradiations:
    - Patients irradiated for tinea capitis, enlarged thymus or tonsils, or ankylosing spondylitis, frequent radiology patients (tuberculosis)
    - **Survivors of cancer treatments**
- The doses and dose-rates of each category generally differ from those used in RT.





# Radiation-induced cancer in humans

- A non-negligible excess of cancer incidence has been observed in long-term survivors.
  - **A linear risk relationship between 0.05 and 2.5 Sv**
- Extrapolations of risks from general populations to radiotherapy patients are not straightforward.
  - Age distribution and the genetic features of the patients may differ from the general population.
- Best risk estimates would probably be obtained from long term survivors of radiotherapy.
  - Control populations might be difficult to establish.

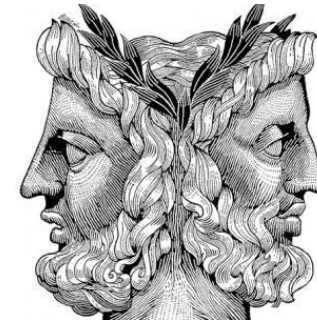


# Risk estimations from RT survivors

## SARCOMA ARISING IN IRRADIATED BONE

*Report of Eleven Cases*

WILLIAM G. CAHAN, M.D.,<sup>†</sup> HELEN Q. WOODARD, PH.D.,  
NORMAN L. HIGINBOTHAM, M.D., FRED W. STEWART, M.D.,  
and BRADLEY L. COLEY, M.D.



*Cancer*, 1:3-29, 1948

- Criteria that were used to establish the link between sarcomas and the previous irradiations:
  1. There was no evidence (microscopic or radiological) of the malignancy in the initial bone.
  2. The sarcomas must have appeared in the area included in the RT beam.
  3. The second tumour must have appeared a long time after the irradiation.
  4. The sarcomas must have been proved histologically.



# Risk estimations from RT survivors

RADIATION RESEARCH **116**, 3-55 (1988)

## Radiation Dose and Second Cancer Risk in Patients Treated for Cancer of the Cervix

JOHN D. BOICE, JR.,<sup>1,2</sup> GÖRAN ENGHOLM,<sup>3</sup> RUTH A. KLEINERMAN,<sup>2</sup>  
MARIA BLETTNER,<sup>2,3</sup> MARILYN STOVALL,<sup>4</sup> HERMANN LISCO,<sup>5</sup>

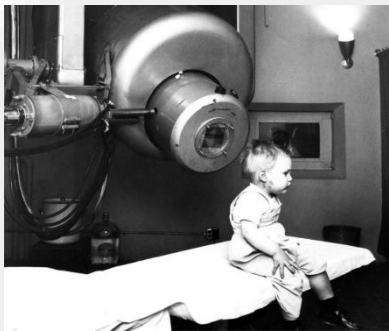
Data from 150000 patients  
from 20 clinics treated  
over 40 years

- Patients treated before 1960s received mainly orthovoltage radiotherapy
  - Patients treated after 1965 received mainly megavoltage radiotherapy
  - Dose determinations in phantoms representing ‘the average patient’
  - At most 5% of the second cancers could be attributed to radiation treatment
- Challenge: Use results to make predictions for patients treated nowadays with VMAT and particle therapy



# Risk estimations from RT survivors

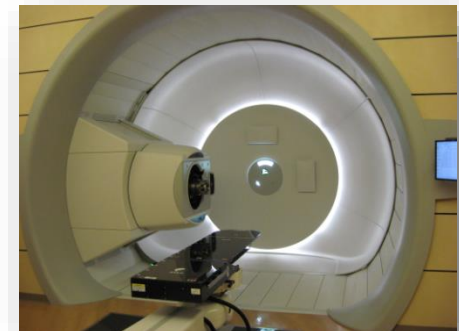
**Early linear accelerator**



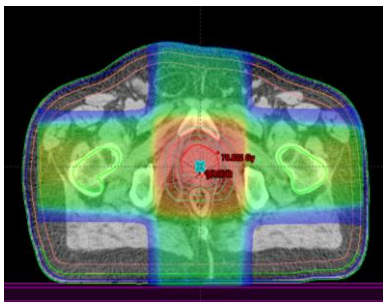
**Modern linear accelerator**



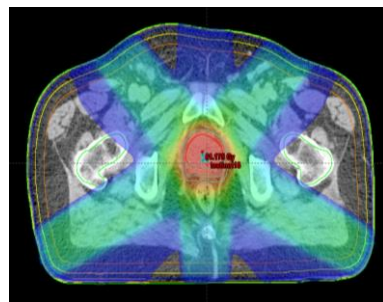
**Proton gantry**



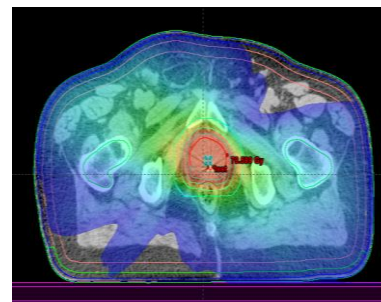
- Irradiation techniques have changed over the years.
  - The relevance of the results from 30-year old treatments to modern techniques?



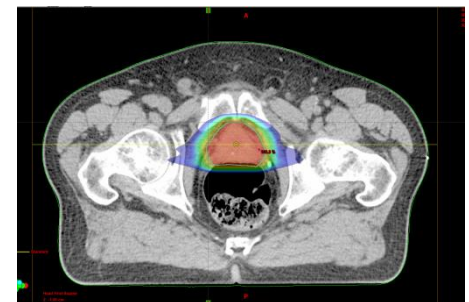
**3D-CRT**



**IMRT**



**VMAT**



**IMPT**



# Risk of SMN – epidemiological challenges

- Design of the study
  - Prospective studies - follow a group of patients treated at a single institution and compare the occurrences of second cancers with those from an appropriate control group
    - Avoid major differences in terms of treatment protocol or uncertainties in dose recording
    - Small numbers of patients
  - Retrospective studies - based on data from one or more cancer registries
    - Large populations could be studied
    - Heterogeneities in protocols and dose recording
- Avoidance of the confounding factors related to the radiobiological aspects



# Risk of SMN – radiobiological challenges

- Several radiobiological factors may influence the risk estimates from the survivors of RT leading to differences in predictions from the A-bomb survivors
  - Genetic susceptibility
    - Mutated ATM gene
    - Mutations in BRCA genes
  - Age-related radiosensitivity
  - Hormonal mechanisms
  - HPV infection status
  - Non-targeted effects
    - Bystander effect
    - Abscopal effect
- Differential RBE for radiation induced mutations and cell killing



# Risk of SMN – dosimetrical challenges

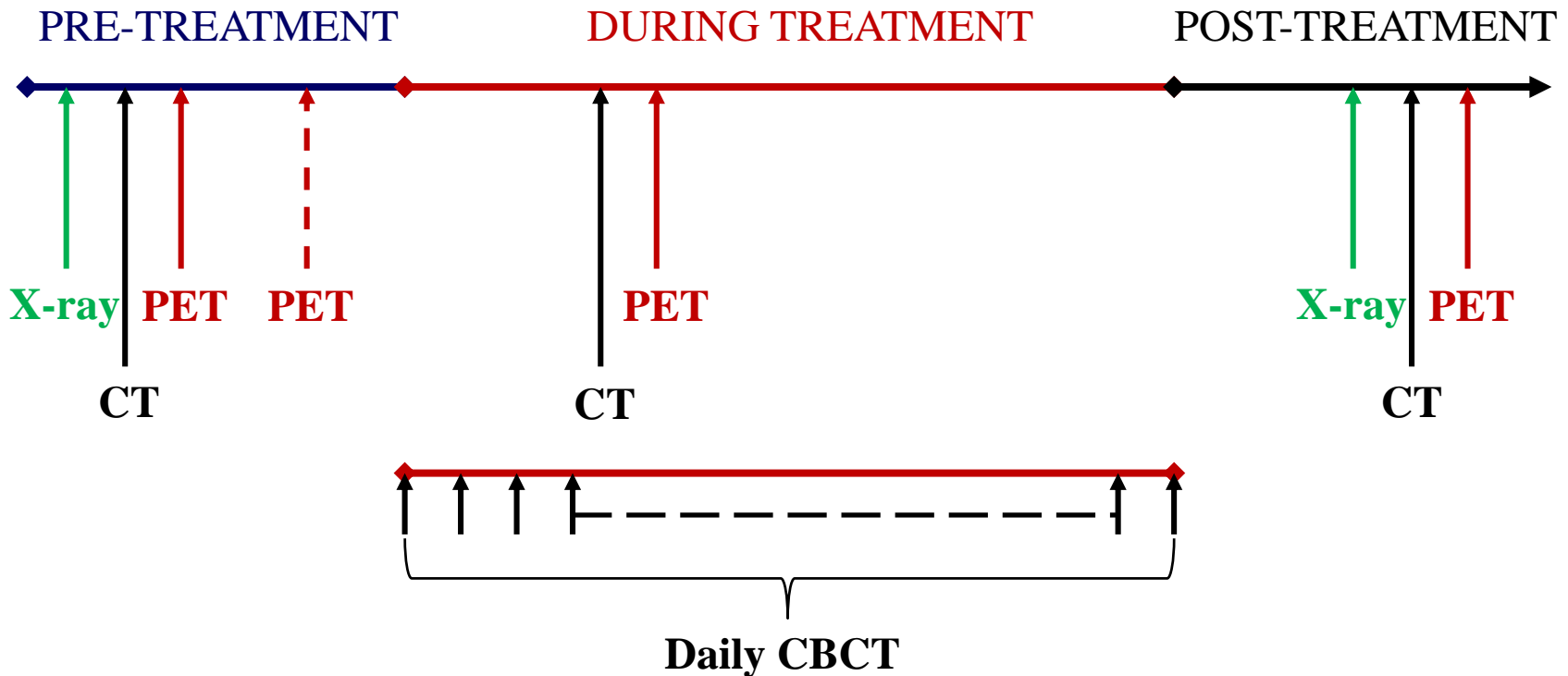
- Generally SMN occur near the RT fields.
- Most TPSs do not provide accurate calculation of the dose outside the treatment field:
  - Primary photons leakage and scattering
  - Neutrons produced through  $(\gamma, n)$
  - Scattered primary protons
  - Neutrons produced in proton nuclear interactions
  - Secondary particles due to inelastic nuclear interactions
  - Secondary particles (n,  $\gamma$ ,  $e^-$ , p,  $\pi$ ,  $^2\text{H}$ ,  $^3\text{H}$ ,  $^3\text{He}$ ,  $^4\text{He}$ ,  $^6\text{Li}$ ,  $^7\text{Li}$ ,  $^{10}\text{B}$ ,  $^{11}\text{B}$ ,  $^{10}\text{C}$ ,  $^{11}\text{C}$ ) due to fragmentation processes of the primary ions





# Risk of SMN – dosimetrical challenges

- Accounting for radiation burden associated to the imaging modalities
- Example: ARTFORCE H&N trial → Small optimised doses adding up to the RT doses







# Risk of SMN – a multidisciplinary approach

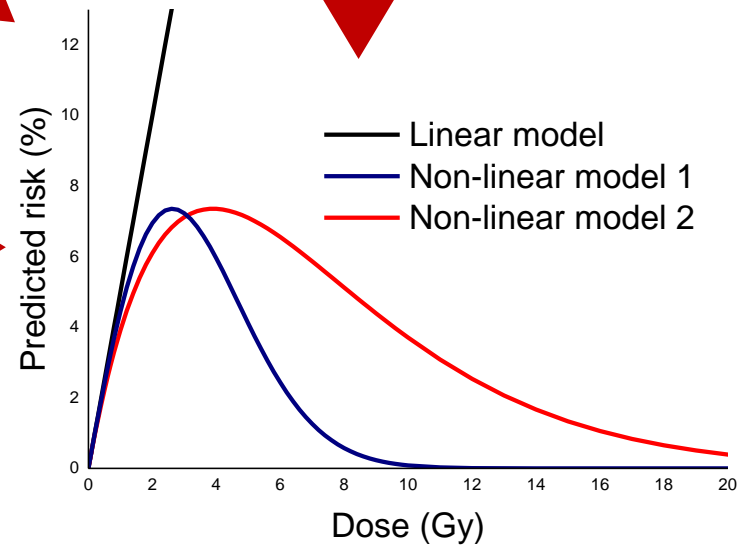
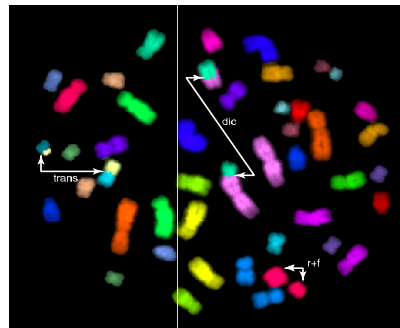
**Epidemiology**



**Dosimetry**



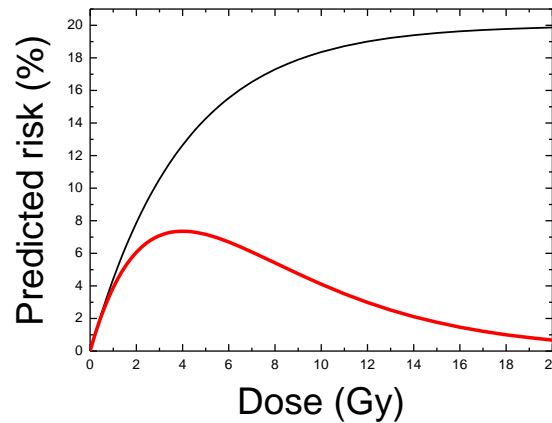
**Radiobiology**





# Risk of SMN – a multidisciplinary approach

- More advanced models have to be developed based on findings of epidemiological studies accounting for the radiobiological and dosimetric challenges.



- Epidemiological studies in turn may benefit from theoretical modelling that could highlight aspects of potential interest.



# How do we communicate the risk?

- Risk of radiation SMN can be expressed in multiple ways: numbers vs probabilities, absolute values, RR, ERR, attributable risk percent, *etc.*

- Example:

Risk predictions based on a competition risk model accounting for fractionation and dose heterogeneity throughout the irradiated organ and comparisons with clinically observed results  
(Dasu *et al* 2011)

| Organ                    | Bladder                   |
|--------------------------|---------------------------|
| Risk of SMN              | <b>0.28%</b>              |
| Clinically observed risk | 0.15-0.32%                |
| Reference                | Boice <i>et al</i> (1995) |

- The values are quite similar to the risk of mortality from surgery for prostate cancer (0.2-0.6%).

***“You could either die from surgery now or from radiation-induced cancer in 20 years.”***



# Optimised RT accounting for risk of SMN

- Radiation induced SMN is regarded as the price to pay for the effectiveness of radiation therapy.
  - When risk of SMN represents a too high a price to pay?
  - The answer requires a complex analysis of the competing risks.
- An important prerequisite for the development of a second cancer is the successful treatment of the primary tumour.
- RT treatment plans should be optimised with respect to risk of SMN.



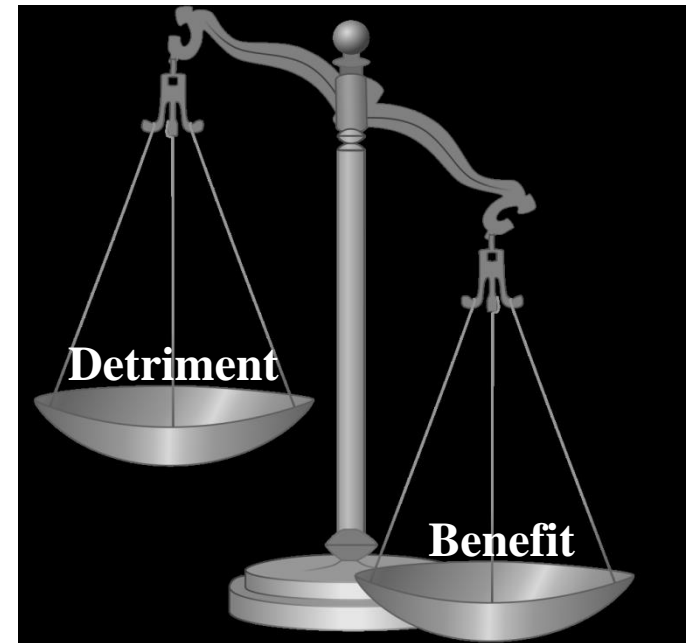


# Optimised RT accounting for risk of SMN

- The optimisation process must include the **Benefit** as well as both *stochastic* and *deterministic* effects since both of them influence the quality of life of the patients.
- Optimisation will require the conversion of the *frequency of stochastic effects* and the *incidence and severity of the deterministic effects* and the into a common metric

**=> Detriment**

- The concept of detriment will ease comparisons between effects with different latencies, severities and patterns of appearance and, together with the benefit, their balancing during the optimisation process.





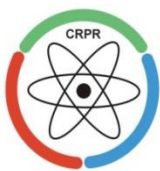
# Radiation therapy – a two edge sword

- Estimating the risk of cancer following irradiation is not an easy task.
- Today we have more questions than answers...

...but now I trust that many of these questions will find their answers by the end of our workshop.



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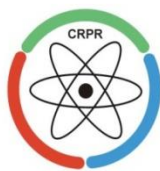
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