2nd Divonne Brainstorming meeting on CERN Medical Applications

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Overview of Particle Therapy
Radiobiological effectiveness

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Cancer therapy

More than 75% of all cancer patients has only loco-regional extension at the time of diagnosis.

Such patients can be cured by an effective loco-regional therapy (directed towards the prinmary tumor and the associated regional lymph nodes).
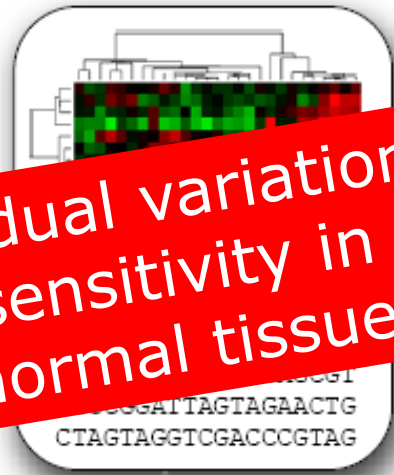
Surgery and/or radiotherapy is the key treatment modalities in this situation.

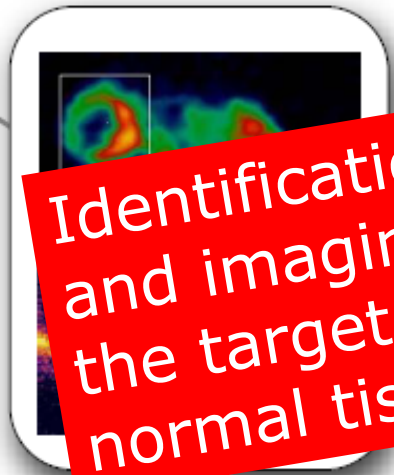# The importance of different therapeutic modalities for the cure of cancer

- Not cured 55%
- Surgery 22%
- Radiotherapy 18%
- Chemo/hormone 5%
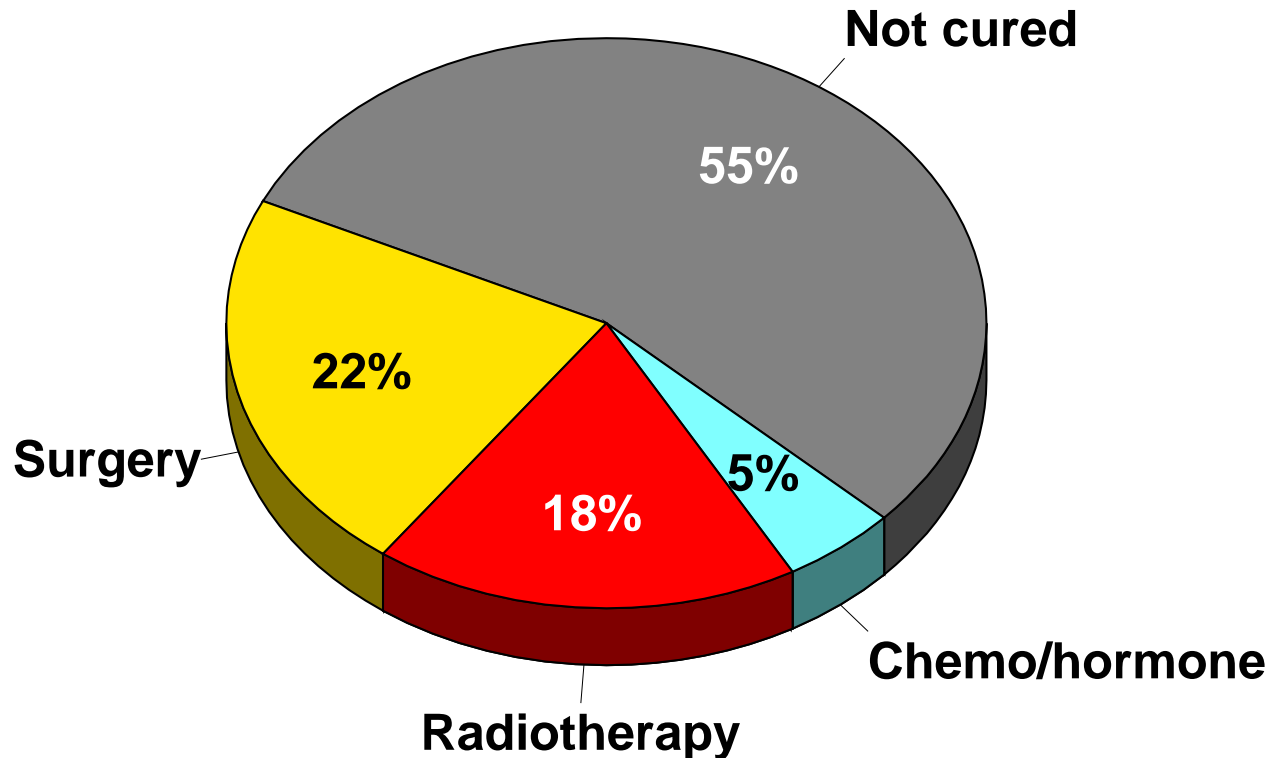
•Modified from: M. Tubiana EJC

CIRRO

Biology

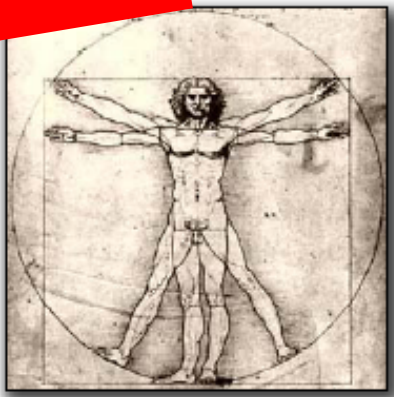Individual variation in radiosensitivity in tumors and normal tissues

Imaging

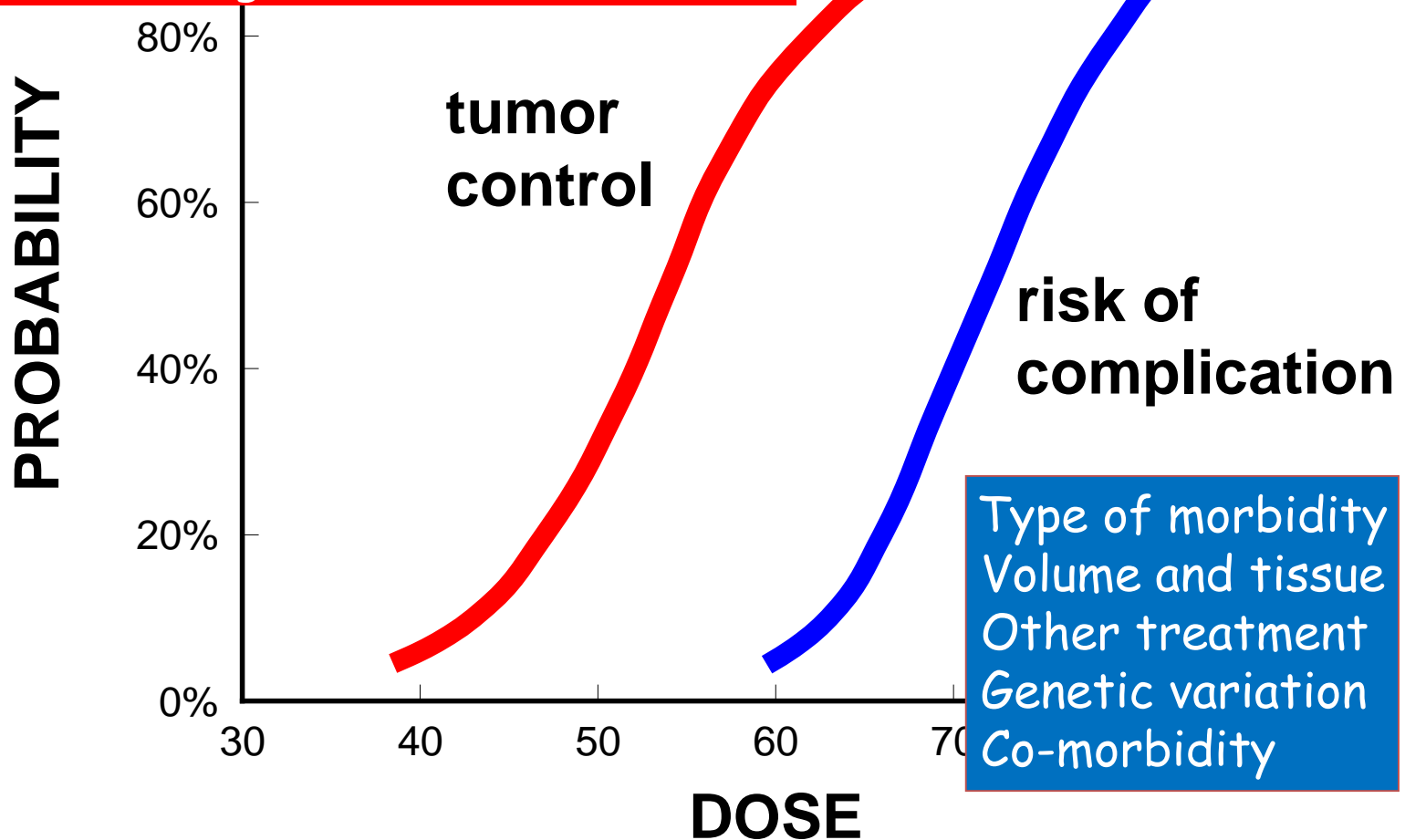Identification and imaging of the target and normal tissues

Intervention

Treatment

High precision treatment delivery

Tumor enviroment (hypoxia)
Proliferation of tumor stem cells during treatment
Intrincic (genetic) radioresitance

tumor control

risk of complication

Type of morbidity
Volume and tissue
Other treatment
Genetic variation
Co-morbidity

PROBABILITY

80%

60%

40%

20%

0%

30   40   50   60   70

DOSE

A little story

from the early days of high voltage irradiation when a new technology was just introduced

– and used with excitement.
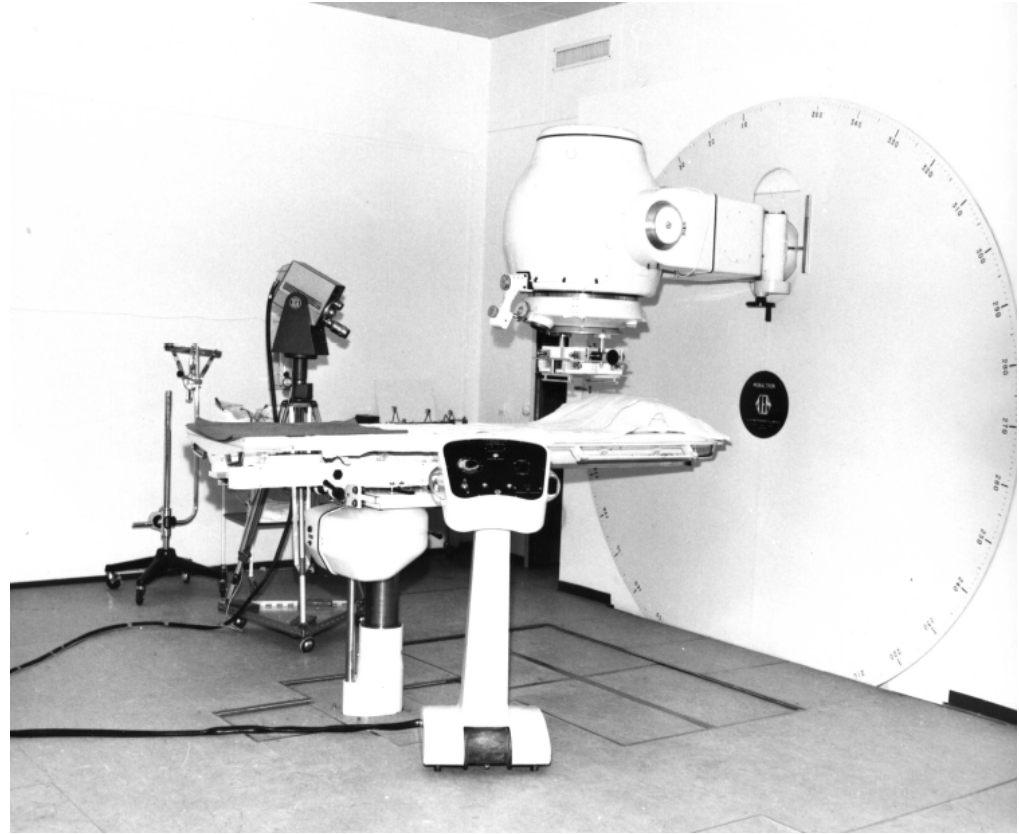
Radiotherapy of testicular cancer

Co-60 Ant.-post. fields treated on alternating days.

A few "other problems"

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Around 60% of the patients developed deleterious late effects (19% fatal) – and none were detected by routine follow up

Knap et al. Acta Oncol 2007

RT LATE EFFECTS
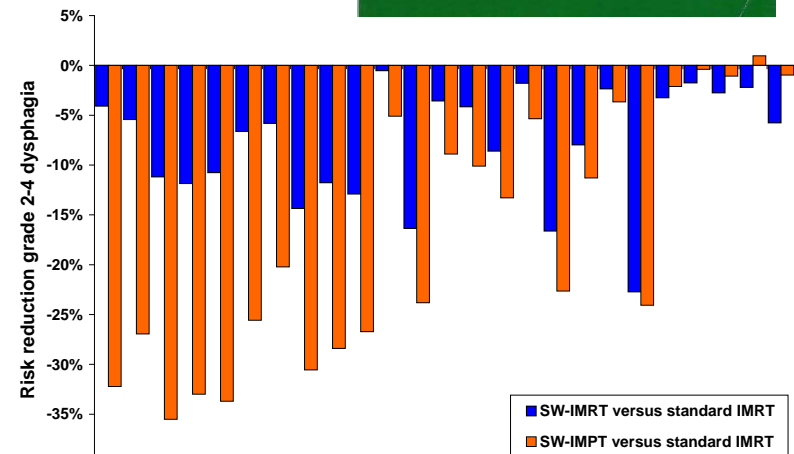
Indikations for particle therapy

- **Reduced risk for serious side effects**
- Increased tumor dose and a consequential better cure rate.

4-field 3DCRT   6-field IMRT   4-field IMPT
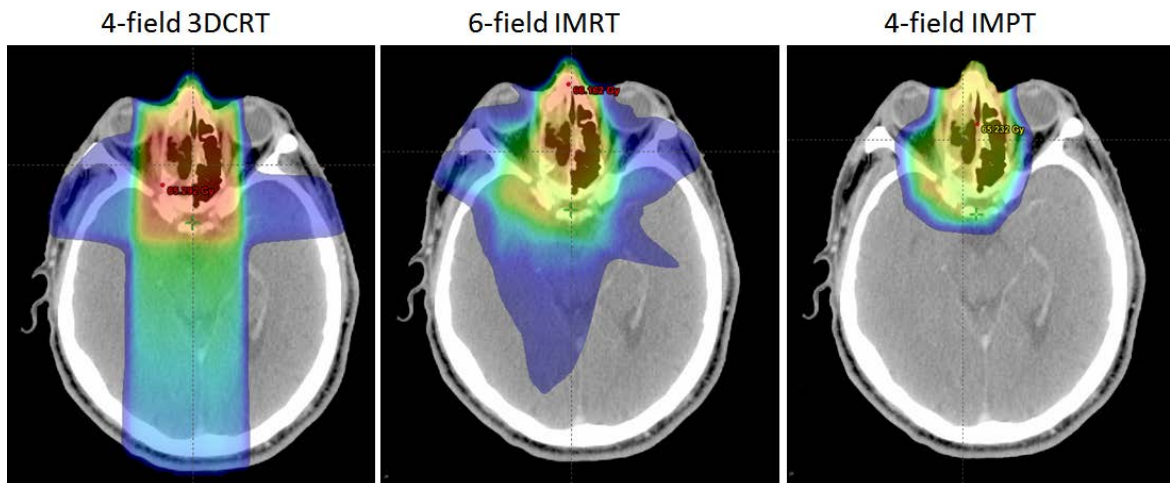
Understand the underlaying biological mechanism of (late) radiation damage with special reference to particle therapy (volume, dose, patogenesis)

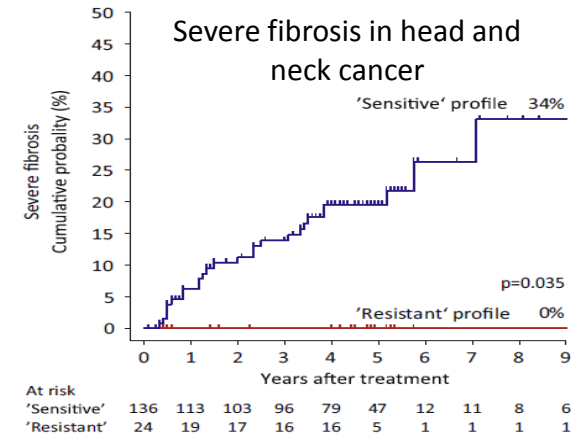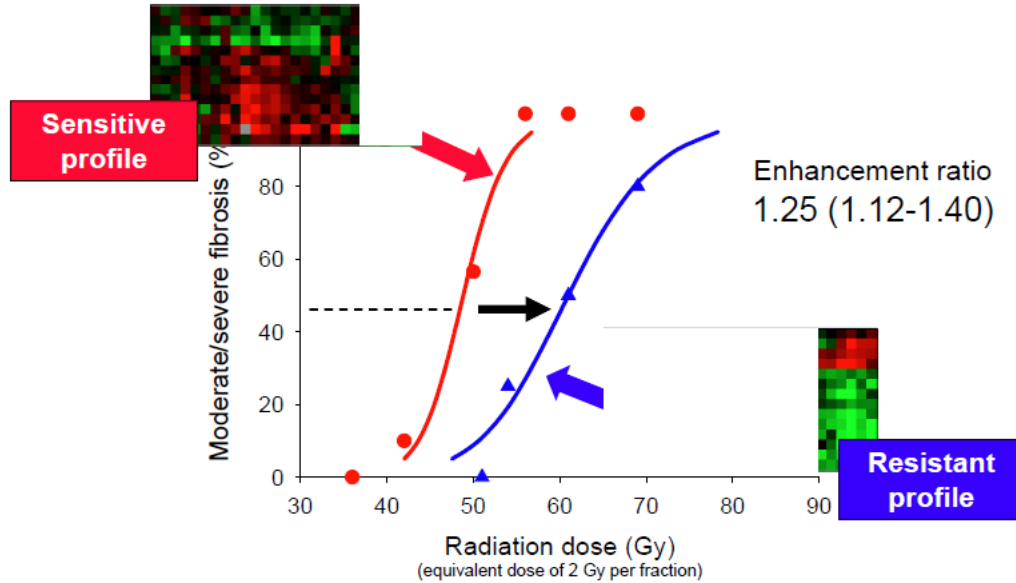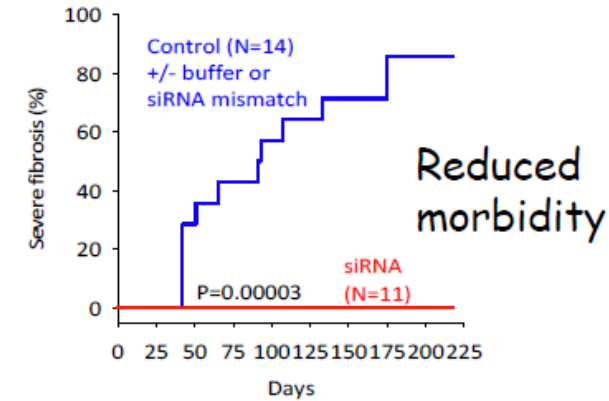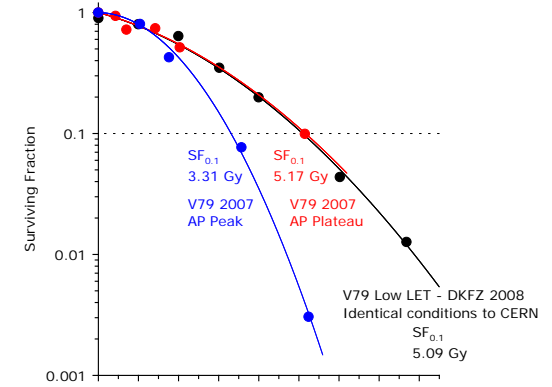# Select patients for particle therapy on that basis

(Dutch modelbased approach)
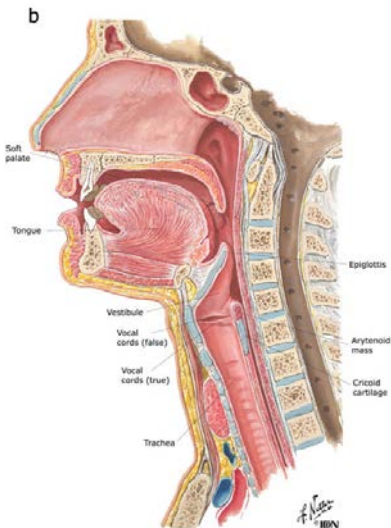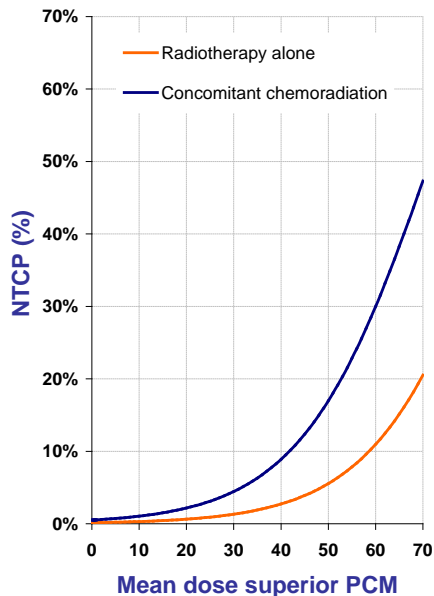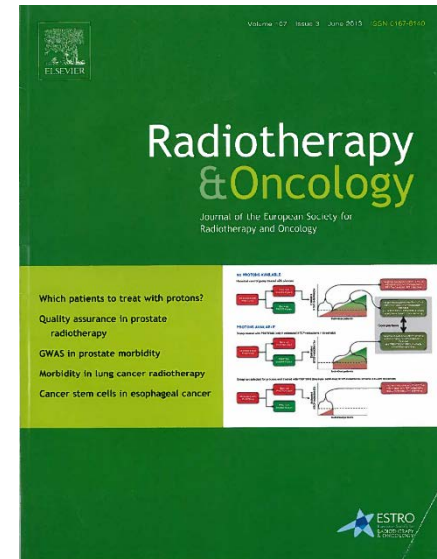
RGC ATM meta-analysis (ATM codon 1853)

Study	Tumor	Events / Total non Asp/Asp	Events / Total Asp/Asp	Odds ratio and 95% CI	Odds ratio	Lower limit	Upper limit	p-Value
AERT RADIOGEN	prostate	57 / 155	157 / 569		1.53	1.05	2.22	0.03
Canada prost	prostate	18 / 42	52 / 113		0.88	0.43	1.80	0.73
CIHR	breast	5 / 24	17 / 81		0.99	0.32	3.04	0.99
DBCG1	breast	5 / 7	18 / 34		2.22	0.38	13.08	0.38
DBCG2	breast	24 / 57	59 / 177		1.45	0.79	2.68	0.23
GENEpare	prostate	20 / 210	91 / 760		0.77	0.46	1.29	0.32
Hebron	breast	5 / 15	2 / 35		8.25	1.38	49.21	0.02
Pre START	breast	8 / 14	18 / 38		1.48	0.43	5.10	0.53
RAPPER breast	breast	77 / 201	207 / 590		1.15	0.83	1.60	0.41
RAPPER prost	prostate	13 / 84	26 / 327		2.12	1.04	4.33	0.04
Saint Pau	breast	4 / 21	9 / 75		1.73	0.47	6.29	0.41
All studies		236 / 830	656 / 2799		1.27	1.06	1.53	0.01

$SF_{0.1}$ 3.31 Gy
V79 2007 AP Peak

$SF_{0.1}$ 5.17 Gy
V79 2007 AP Plateau

V79 Low LET - DKFZ 2008 Identical conditions to CERN $SF_{0.1}$ 5.09 Gy

Control (N=14) +/- buffer or siRNA mismatch

siRNA (N=11)

P=0.00003

Reduced morbidity

Sensitive profile

Enhancement ratio 1.25 (1.12-1.40)

Resistant profile

Moderate/severe fibrosis (%)

Radiation dose (Gy)
(equivalent dose of 2 Gy per fraction)

Severe fibrosis in head and neck cancer

'Sensitive' profile   34%

'Resistant' profile   0%

p=0.035

Years after treatment

| At risk									
'Sensitive'	136	113	103	96	79	47	12	11	8	6
'Resistant'	24	19	17	16	16	5	1	1	1

Functional imaging

- Tumour delineation using mono-clonal antibodies and nanotech-nology

- Radioresistant sub-volumes and functional imaging

- Validation of clinical imaging findings with pathology and patterns of failure

- Imaging of normal tissue function

Hypoxia staining (bound pimonidazole)

Clinical PET voxel

4 mm

4 mm

T/M 1:8

T/M 1:2

Autoradiogram showing bound (hypoxia) and unbound FAZA
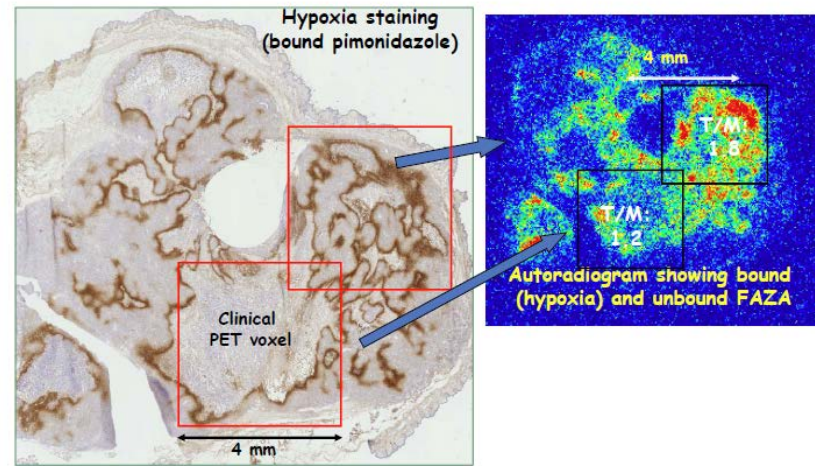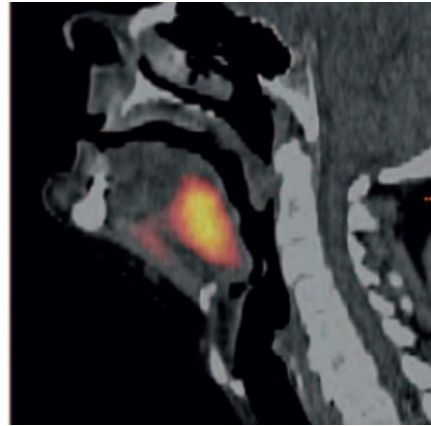
Our current problem/situation is that we can hit a target with a better precision than we can imagine it! – in fact: lack of precision in imaging is (one of) our achilles heel(s).
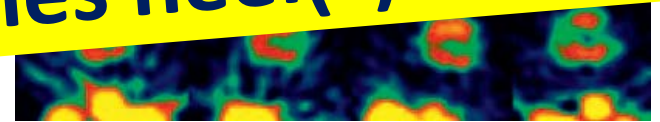
Why radiobiology?

- Gained knowledge from photon irradiation cannot necessarily be directly transferred to particles/protons

- Particles may show unique molecular and cellular responses compared to photon radiation

  - Complexity of the DNA damage

  - Differential gene expression

  - Epigenetic modulation

  - Effect on cell cycle

  - Hypoxia

RBE – the weakest link


Must be clarified to secure optimal particle therapy

Sørensen, Overgaard og Bassler, Acta Oncol; 2011
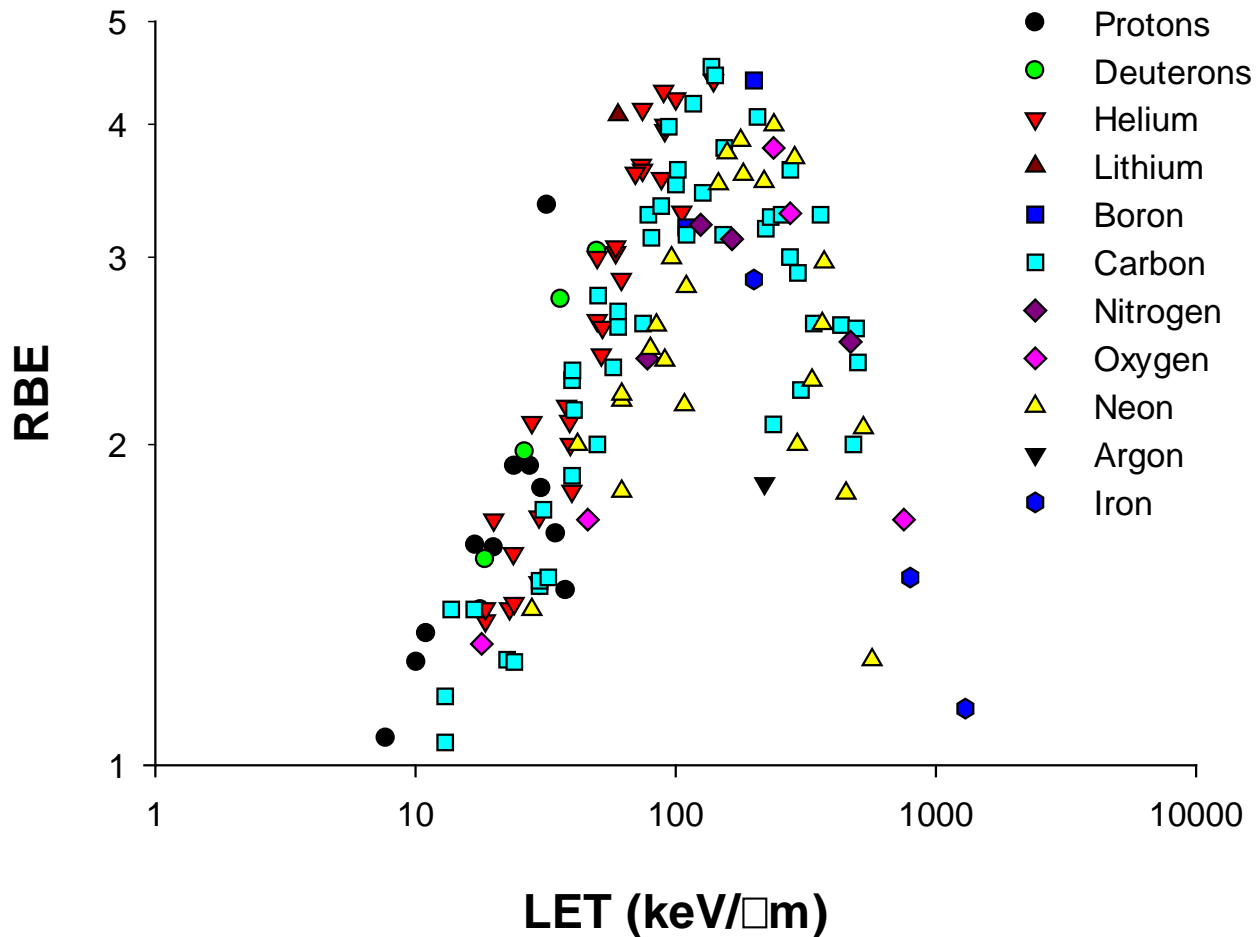
Radiobiology - needed projects

We need (and are short of data related to):

- **RBE in a range of clinically relevant treatment schedules and tumor/normal tissue models**

- Combination with other treatments

- Radiogenomics: individualisation, risk of normal tissue damage
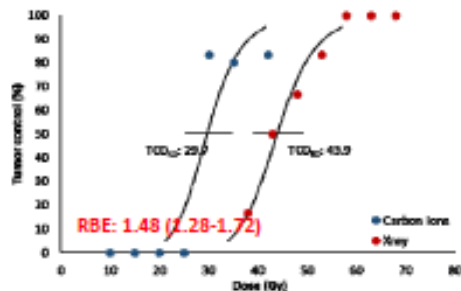
In vivo RBE - Carbon Ion

Normal tissue damage, acute effects

Percentage of mice with score 3.5 (moist desquamation of entire skin area) per dose group within 40 days after irradiation
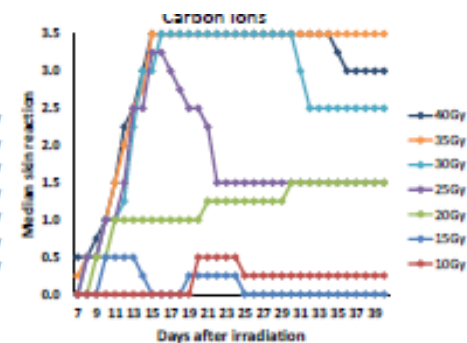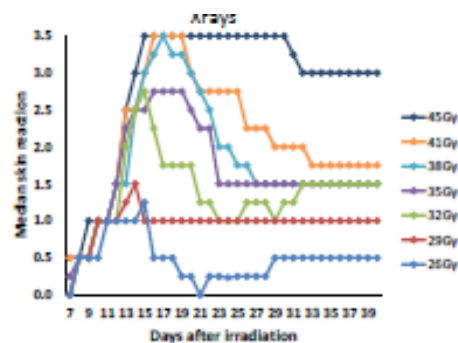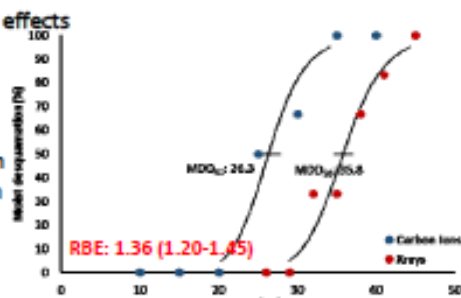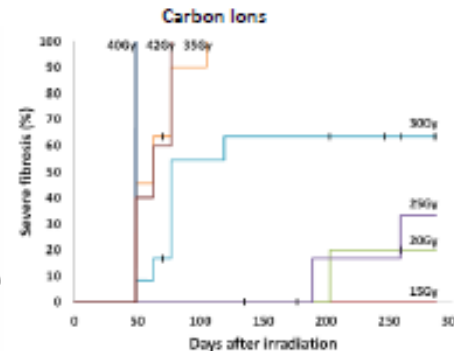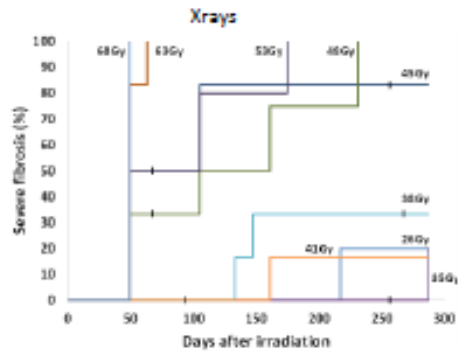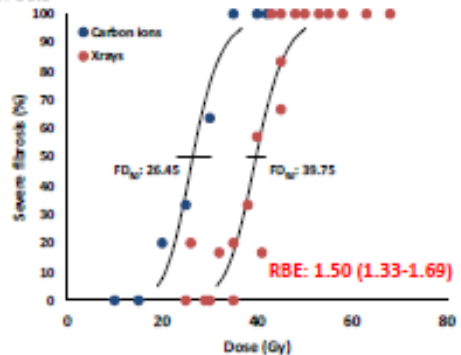
Tumour control

Percentage of mice in each dose group with complete disappearance of the tumor within 90 days after irradiation
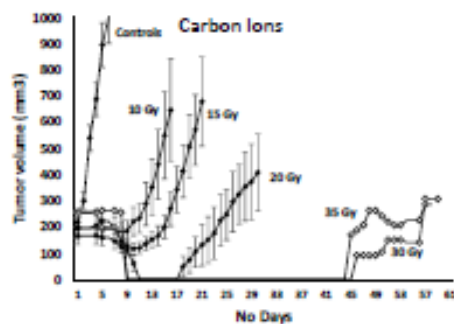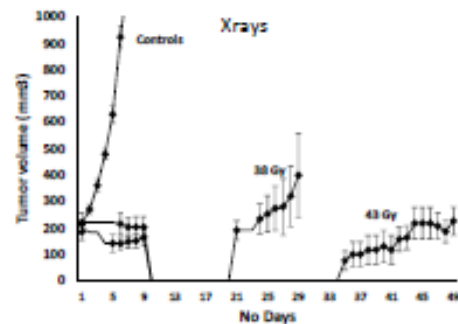
Normal tissue damage, late effects

Percentage of mice in each dose group developing fibrosis within 280 days after irradiation

Sørensen et al 2016

In proton beam therapy, it is current practice in the majority of centres to assume an RBE value of 1.1 for protons, relative to photons, for all clinical conditions. A 'generic' RBE value of 1.1 is recommended.[2]

Journal of the ICRU

ICRU REPORT 78

Prescribing, Recording, and Reporting Proton-Beam Therapy

OXFORD JOURNALS
OXFORD UNIVERSITY PRESS

IAEA

ICRU

TECHNICAL REPORTS SERIES NO. 461

Relative Biological Effectiveness in Ion Beam Therapy

Jointly sponsored by the IAEA and ICRU

IAEA   ICRU

IAEA
International Atomic Energy Agency

In the case of protons, where use of a generic RBE of 1.1 is recommended:

$$D_{RBE} = 1.1 \times D. \qquad (2.1)$$

Because it is simple and easy – not because it is right
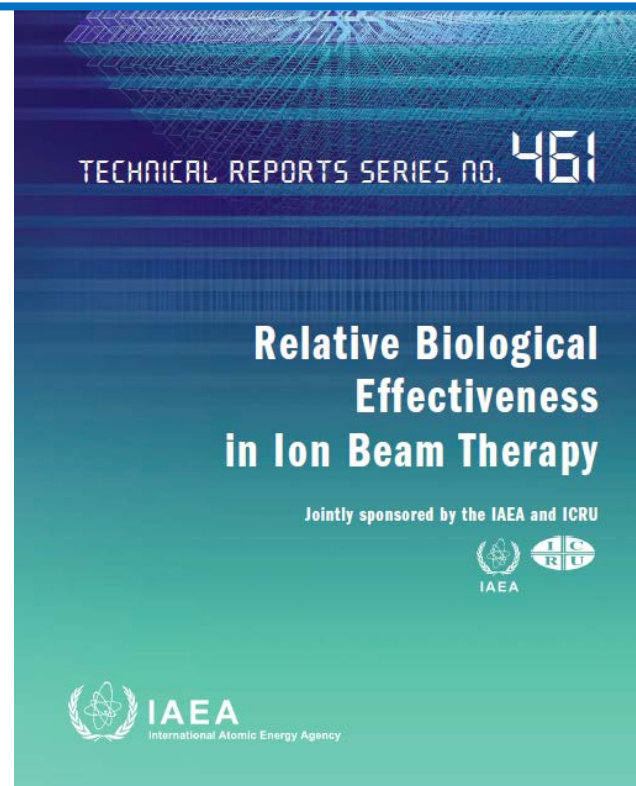
But (proton) RBE is not a single figure, because it is influenced by many factors, e.g:

LET
SOBP (distal end)
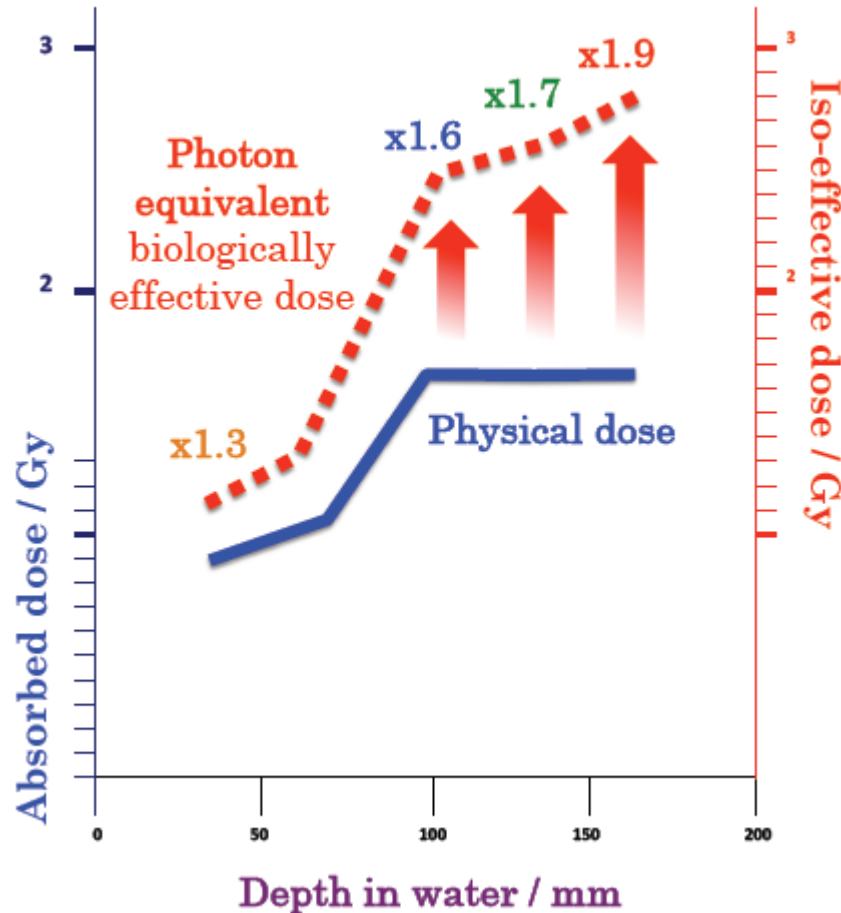Dose and fractionation
Cells and tissue type (alpha/beta)
Endpoint
etc…

so even we do not talk about it – is the situation rather complex,
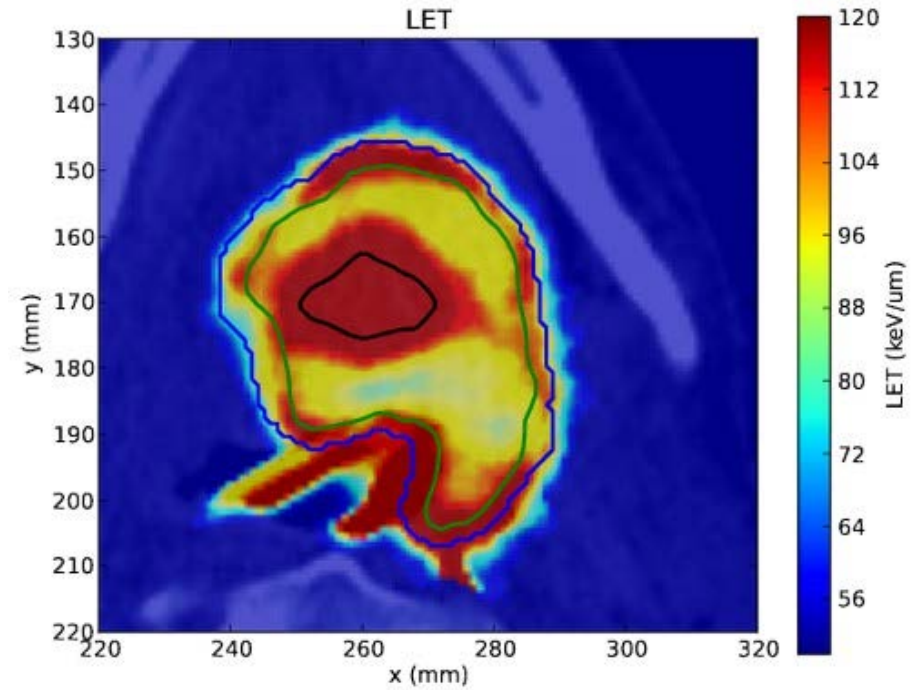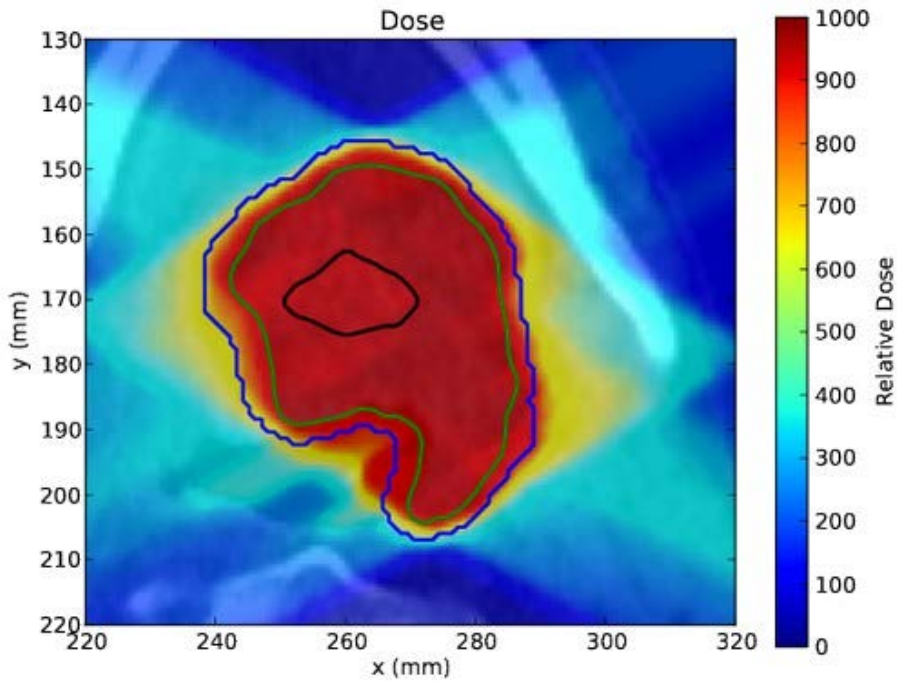
RBE - painting

Carbon ions

Gueulette *et al* 2010

- **A homogeneous biologically effective dose requires an inhomogeneous physical dose distribution – even for protons**

# LET-painting : Oxygen-16 ions

Motivation

Need for radiobiological research with ion beams:

– Protons and Carbon ions *in clinical use*

  • Improved dose distribution, but limited understanding of all effects

  • Other ions than p and C could be better suited (for certain cases)

– *Radiobiology of new ions*: Incoherent sets of data (radiobiological and clinical) observed under different conditions: cell survival for *different ions*/LET/doses, bystander effects, RBE …

Focus

1. "Provides particle beams of different types and energies: *Exotic ions* **?**

2. Only for comparison: X-rays, protons carbon ions… **?**

Tools: Classical cellular models

Courtesy: D. Słonina (Centre of Oncology, Krak
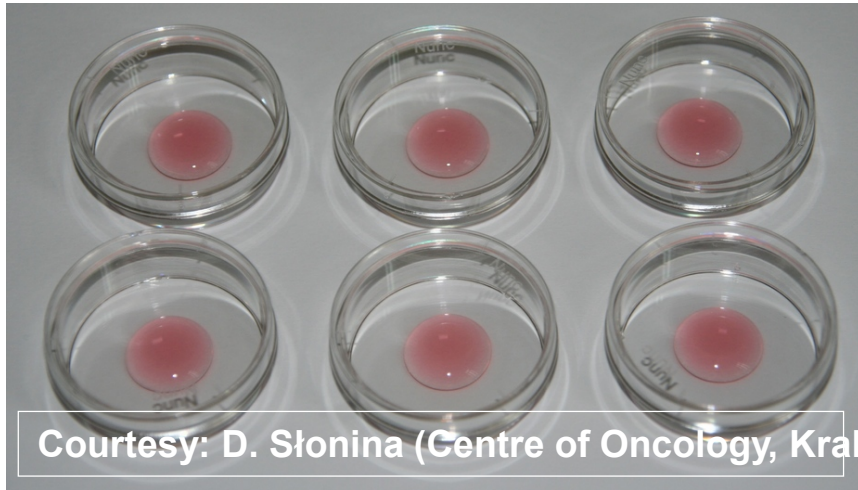
Cells (1x10^5) in 400 µl of medium, plated as a drop in the centre of a 35 mm Petri dish and left overnight to adhere (cells occupied an area ~ 1cm^2)

Markus ionization chamber

Buildup plates (plexiglass)

Snout   Beam
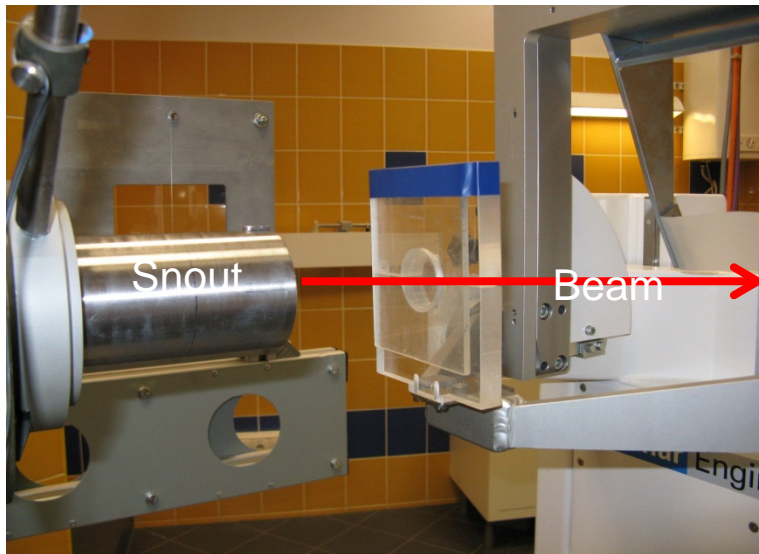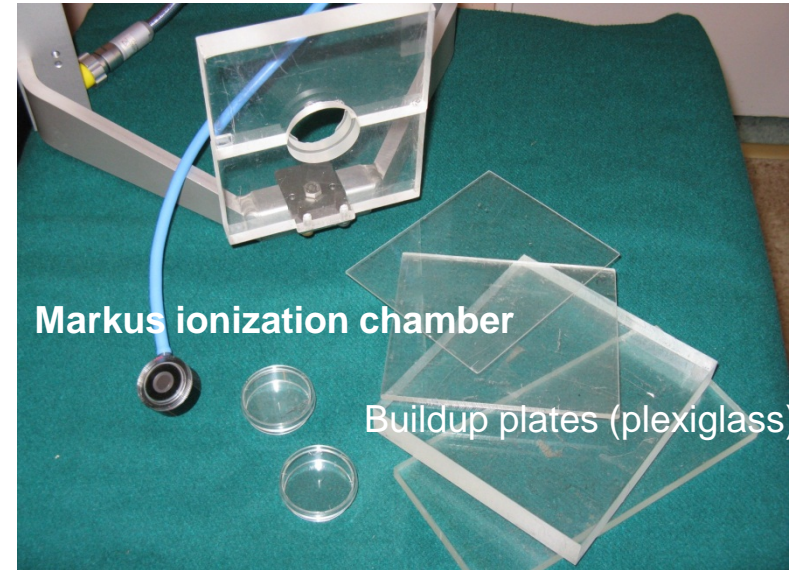
Ions: H, He, Li, Be, B, C, N, O, Ne, Ar, Fe, Pb, U ??
Energy: 5 – 70 MeV/amu ??
Range in water: 0.1 – 30 cm
Beam c/s: 0.5 - 15 cm (flat dose distr.)
Dose rates: 1-10 Gy/min.
Horizontal and vertical (up) beams
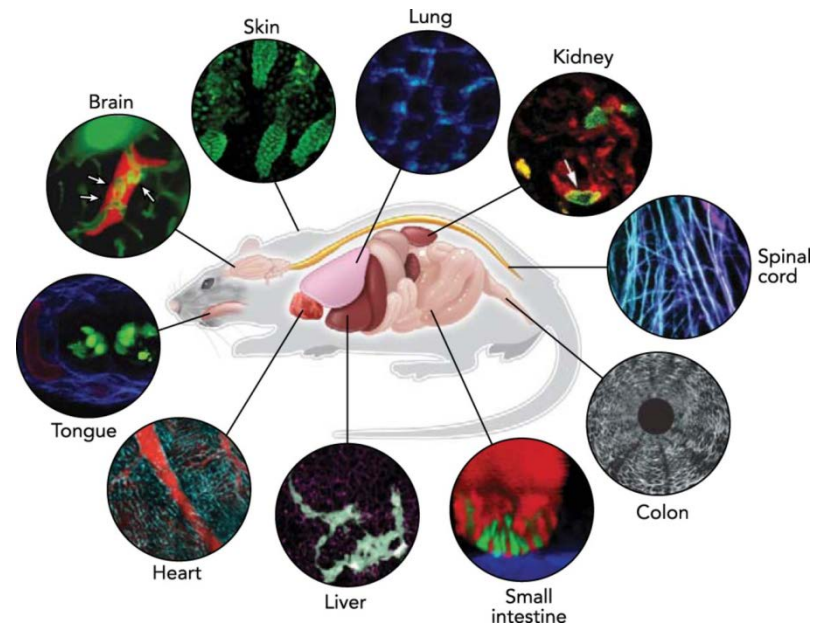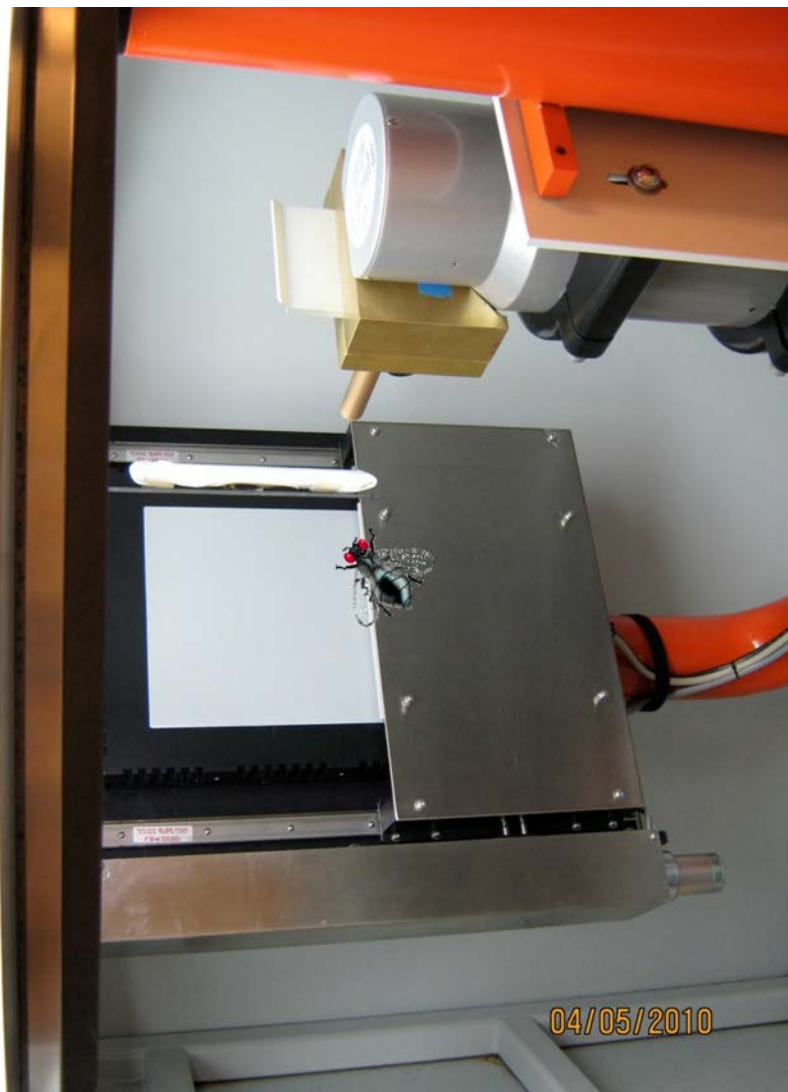Dosimetry: protocol/to be developed

Tools: Animal experiments: Cancer models

- Subcutaneous murine, rat, syngeneic, human, PDX tumor models
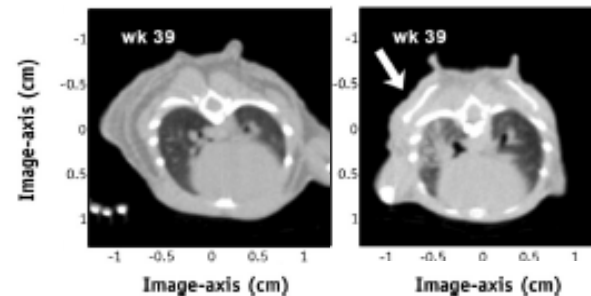- Orthotopic lung, brain human modelspneumonitis and fibrosis)
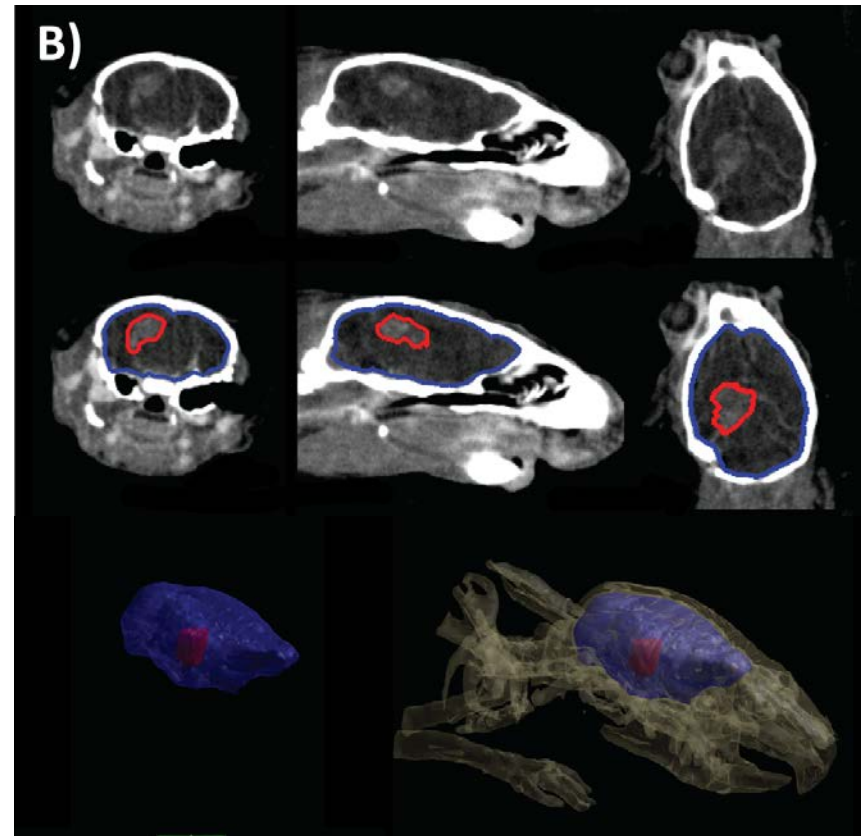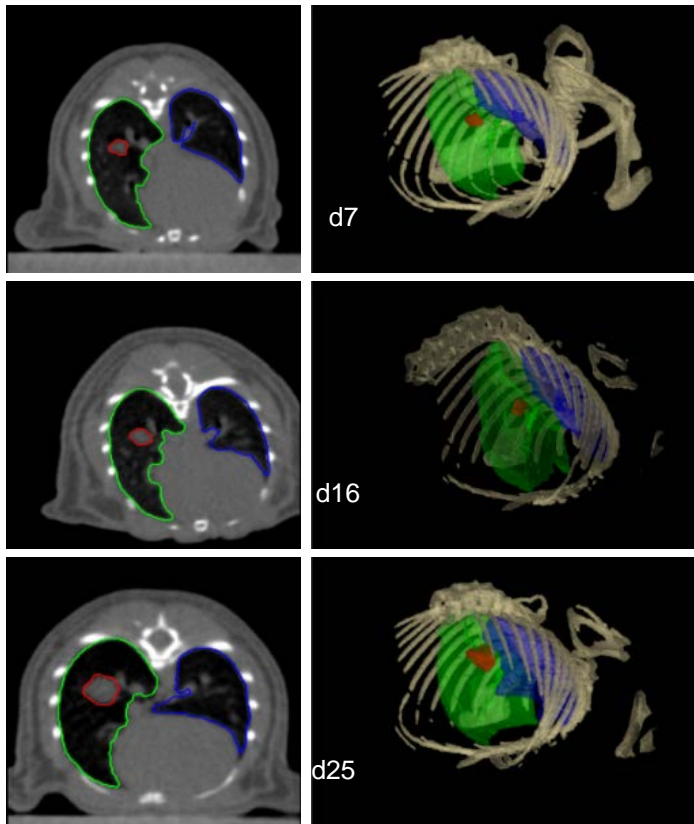
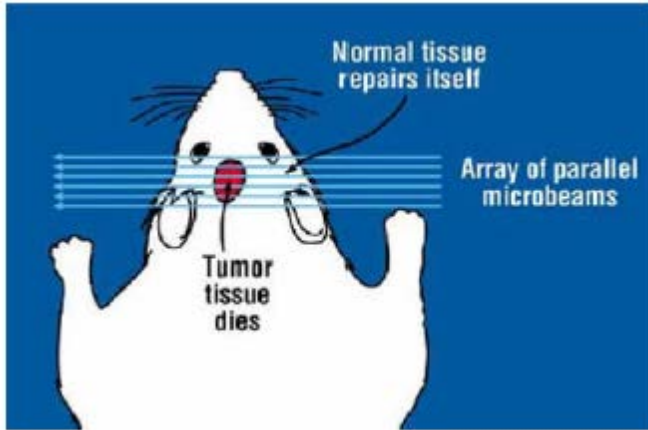Test immunological effects, dose/RBE painting strategies, genetic defects…

Tools: Normal tissues (in vivo models)

- Normal tissue radiation-induced toxicity models (gut mucosa, lung pneumonitis and fibrosis)
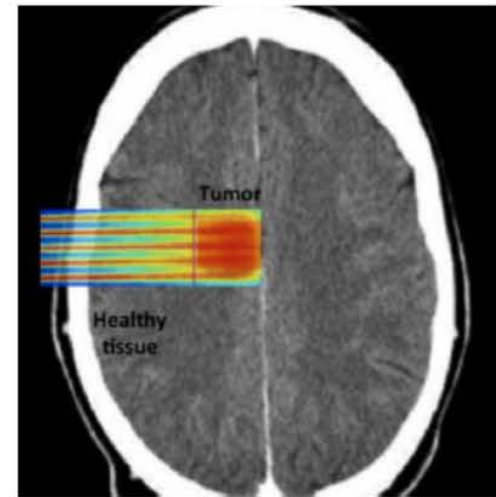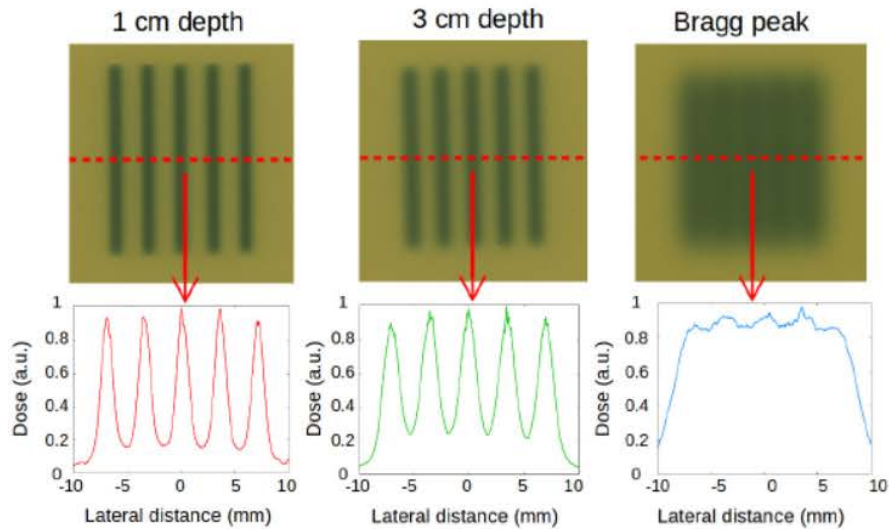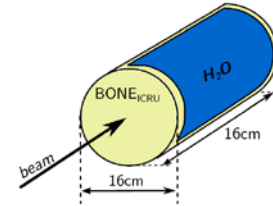
Tools: Animal models e.g. microbeams

Normal tissue repairs itself

Array of parallel microbeams

Tumor tissue dies

Proton microbeams

(Kłodowska et al. Physica Med. 2015,

(FLUKA MC)

c-t-c distance

$BONE_{ICRU}$ H_2O

beam   16cm   16cm

1 cm depth   3 cm depth   Bragg peak

Dose (a.u.)   Lateral distance (mm)

Dose (a.u.)   Lateral distance (mm)

Dose (a.u.)   Lateral distance (mm)

Tumor

Healthy tissue
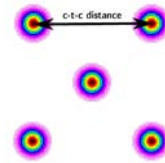
The scenario

We have no good long-term clinical data – and can just wait and hopefuly trust that we do not make harm.

It is most likely that we either under- or overdose our treatments – but only time will show.

We need guidence – but are simply **short of good experimental studies in relevant animal model systems which can yield data from especially late responding tissues treated with relevant fractionation.**

The scenario

Particle - especially proton - therapy is becoming a part of modern radiotherapy

The (potential) benefit must be explored in an academic environment (with the best armamentarium - (there are no room for political short cuts) - aimed to generate the needed evidence.

We think we have more knowledge, than we have.

But we can only achive that through (large) international *collaboration*