Stockholms universitet

Stockholm University Centre for Radiation Protection Research

SWEDISH NATIONAL COMMITTEE FOR RADIATION PROTECTION RESEARCH
THE ROYAL SWEDISH ACADEMY OF SCIENCES

European Radiation Dosimetry Group EURADOS

Workshop:
Risk of secondary cancer following radiotherapy

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

Input to epidemiological studies and dose-risk models

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Chair, EURADOS Working Group 9 Radiation Dosimetry in Radiotherapy

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Input to epidemiological studies and dose-risk models

Outline

1. Out-of-field doses
    1.1 Dose input to epidemiological studies
    1.2 The complete dose specification
    1.3 Other challenges
2. Phantoms for out-of-field measurements
    2.1 Water tanks
    2.2 BOMAB-like phantoms
    2.3 Anthropomorphic phantoms
    2.4 Comparison of phantoms
3. Analytical and Monte Carlo models
4. Options for out-of-field dosimetry
5. Measurements in proton radiotherapy facilities
6. Simplified out-of-field dose estimation
7. Future challenges and investigations

The European Radiation Dosimetry Group (EURADOS)

A self-sustainable network of more than 60 European institutions and 300 scientists active in the field of radiation dosimetry.

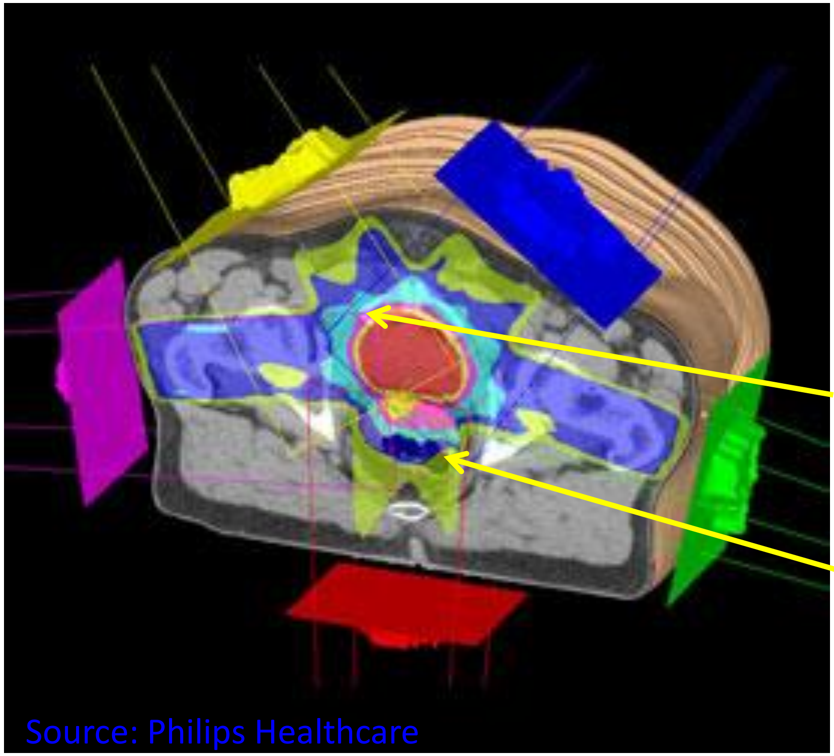
The aim: to promote research and development and European cooperation in the field of dosimetry of ionizing radiation.

Working Groups (WGs) in various dosimetric disciplines:

- Harmonization of individual monitoring
- Environmental dosimetry
- Computational dosimetry
- Internal dosimetry
- Radiation dosimetry in radiotherapy
- Dosimetry in diagnostic imaging
- Retrospective dosimetry
- Dosimetry in high energy radiation fields.

Radiotherapy

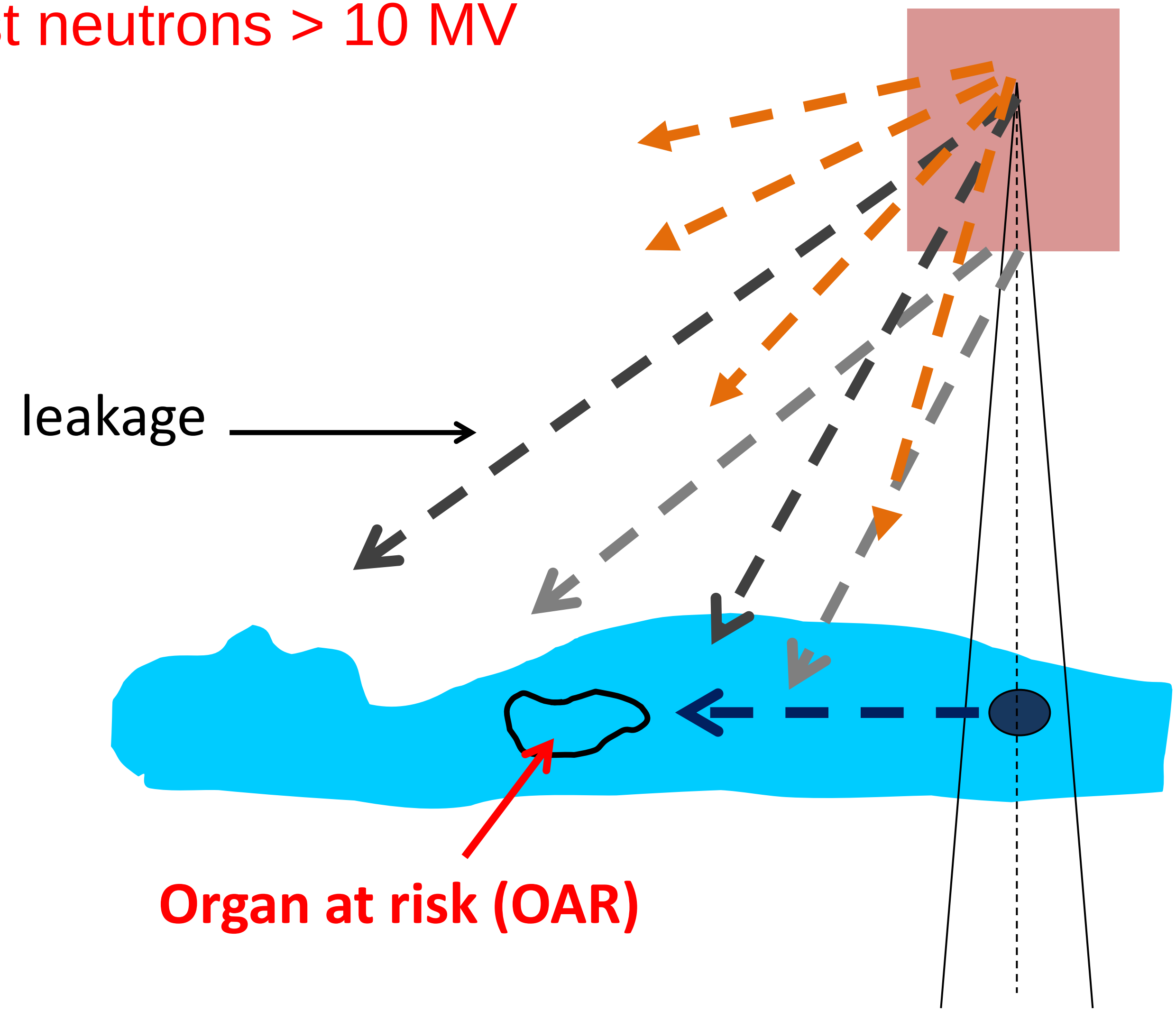
A key component of cancer therapy

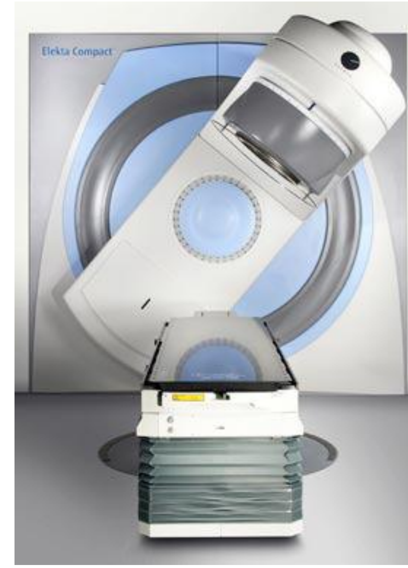


- Doses to target calculated with sufficient accuracy
- Out of field doses are less easily measured or calculated
- Epidemiological studies need (ideally) a complete dose specification

Fast neutrons > 10 MV

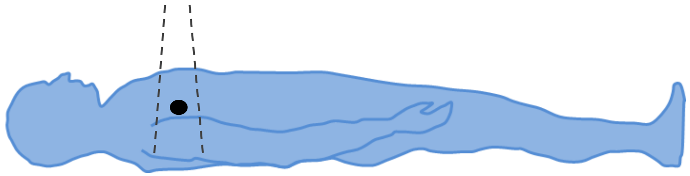
Dose input to epidemiological studies



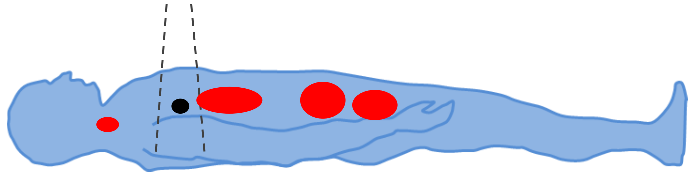


A variety of required inputs

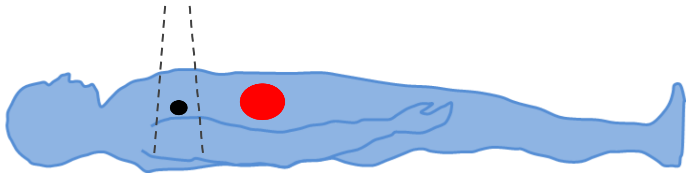
Minimal dose reconstruction :
e.g radiotherapy v. surgery



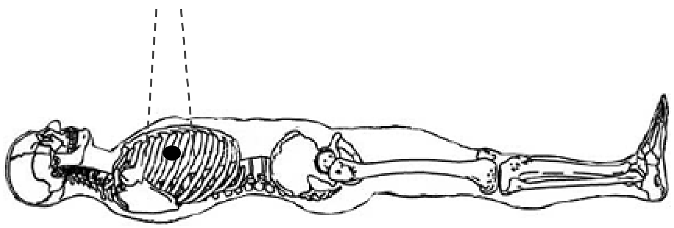
Multiple organs where second cancers arise: brain, breast, thyroid, skin………….
combined risk



Single organs : specific organ risk e.g. contralateral breast, heart



Single extended organ: active bone marrow, skin

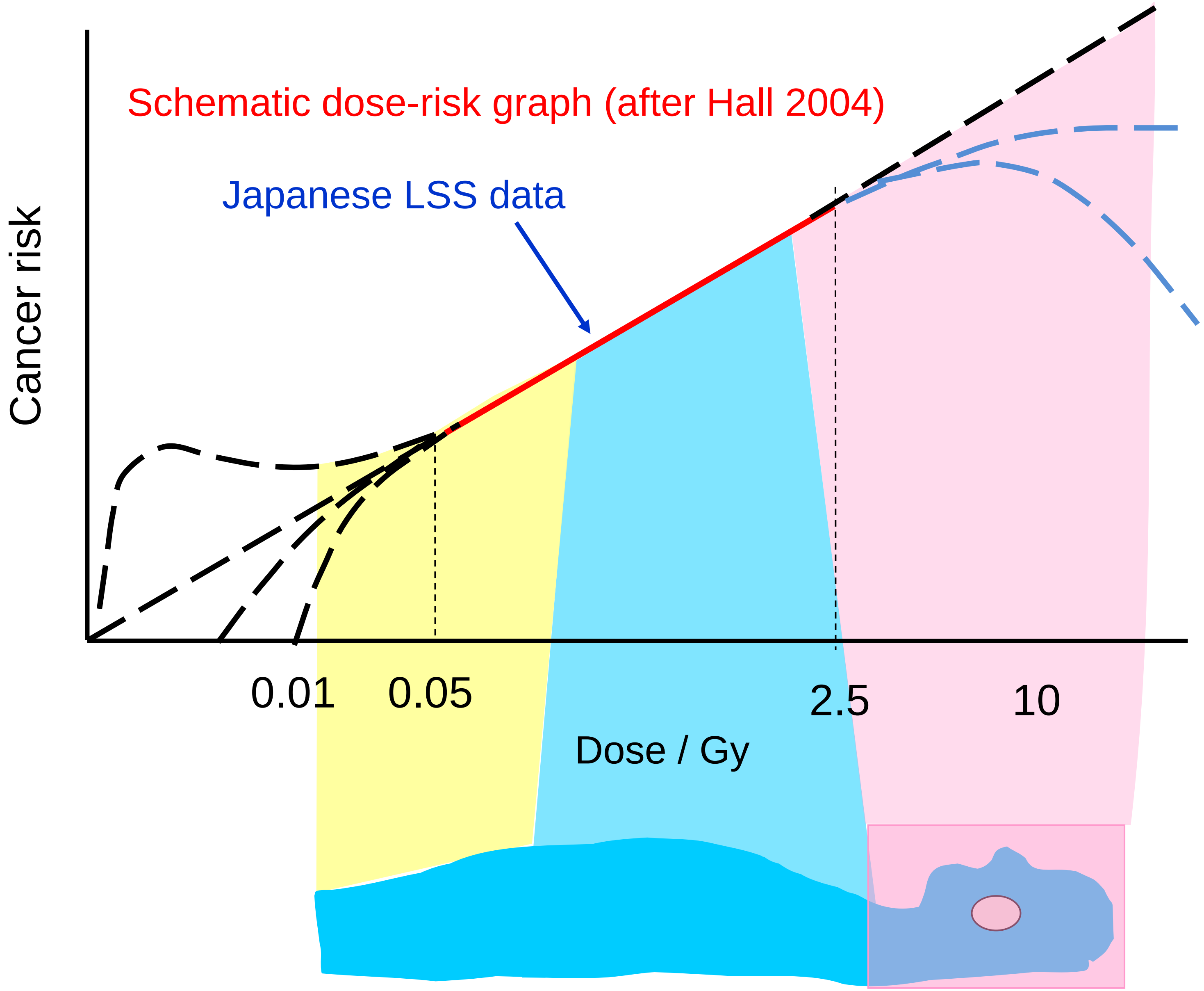


Four important attributes in the design of epidemiological studies of radiation-exposed populations*:

Attribute	Radiotherapy patient cohorts
1. Population size adequate to meet statistical power considerations * Steven L. Simon and Martha S. Linet. Health Phys. 106(2):182-195; 2014	• approximately 14 million new cancer cases per year worldwide • about half of all cancer treatments will involve radiotherapy (in the developed world) • 1.3 million radiotherapy treatments year $^{-1}$ in EU • **Very large world-wide radiotherapy patient cohort**

Attribute	Radiotherapy patient cohorts
1. Population size adequate to meet statistical power considerations	1.3 million RT treatments y^{-1} in EU
2. Large enough average dose and a wide enough dose range to derive a dose-response relationship;	**Doses vary from tens of Gy (target) to tens of mGy**

Dose input to epidemiological studies



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1. Population size adequate to meet statistical power considerations	1.3 million RT treatments y^{-1} in EU
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3. Understanding and capability to determine or reliably estimate individual doses usually required for specific organs	Radiotherapy target doses are: (i) accurately calculated and controlled (ii) delivered with rigorous supporting QA (iii) well documented ***Out-of-field doses are not so extensively measured or calculated***

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3. Understanding and capability to determine or reliably estimate individual doses usually required for specific organs	Radiotherapy target doses are accurately delivered with rigorous supporting QA, and well documented. ***Out-of-field doses are not so extensively measured or calculated***
4. Potential value of the study as determined by public health, clinical, or societal concerns.	**Clinical need and basic radiation protection requirement for risk/benefit judgements**

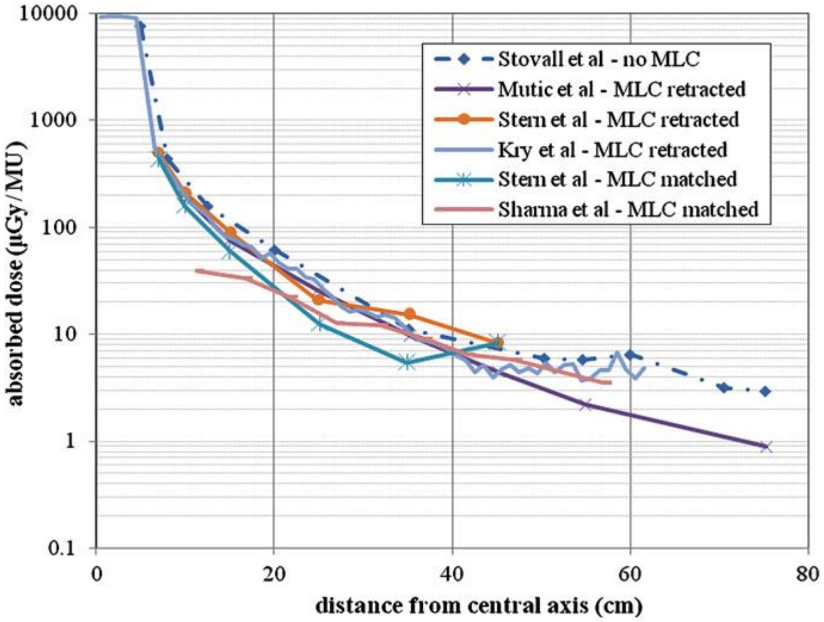
Many parameters influence the out-of-field dose:

- **RT techniques**: RT modalities
  Photon energy (neutron component > 8 MV)
  Protons + neutron component, ions
  Linac head design (leakage, wedges, MLCs)

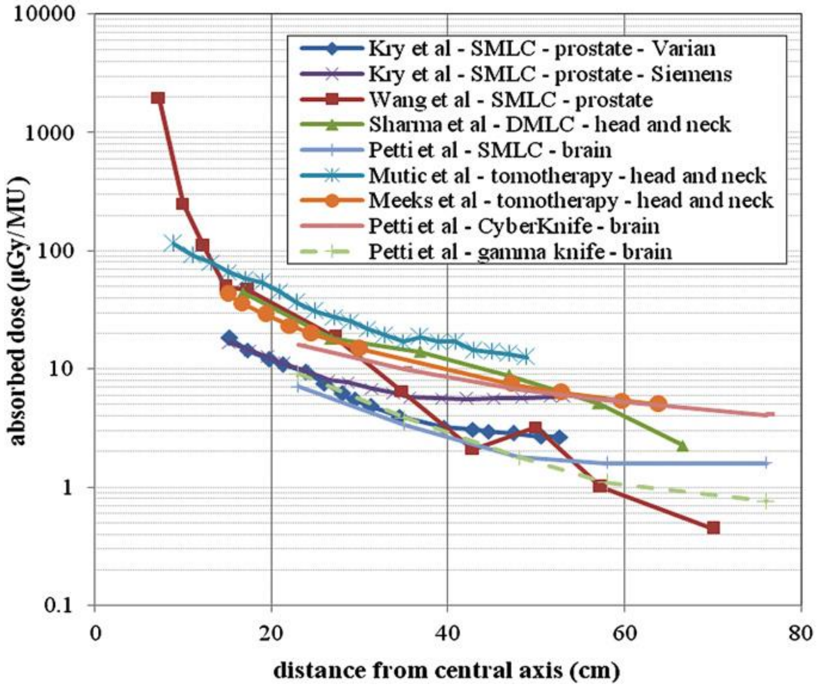
- **Concomitant imaging techniques**:
  CT, kV & MV on board imaging, radionuclide

- **Treatment planning technique** (3DCRT, IMRT, brachytherapy…)
  Target, field and organ localisation, image availability

- **Patient variability**
  age, size and shape



Out-of-field doses for 6 MV treatment plans as a function of distance from the central axis for conventional treatments (top) and IMRT and stereotactic treatments.(bottom)

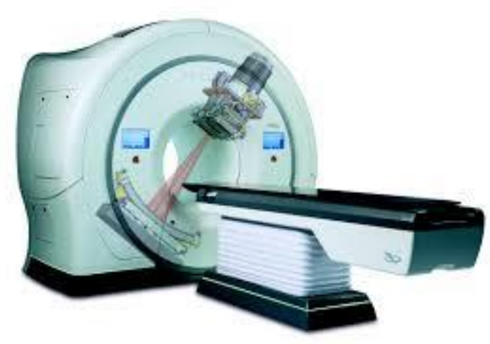


From Xu, Bednarz and Paganetti A review of dosimetry studies on external-beam radiation treatment with respect to second cancer induction. Phys. Med. Biol. 53 (2008) R193–R241

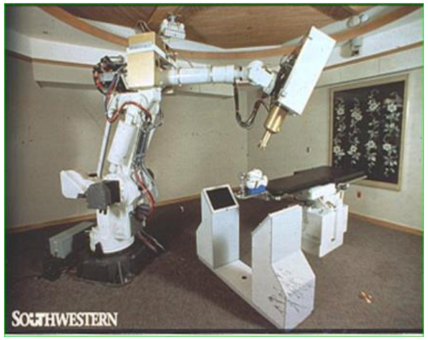
Several radiotherapy modalities:

All have different implications for out-of-field doses

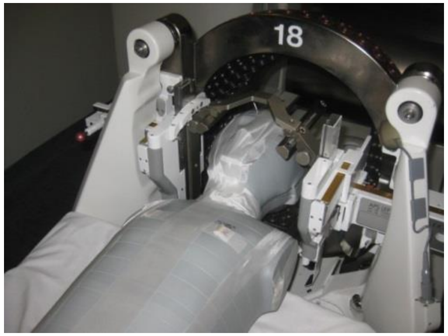
"conventional"
linear accelerator



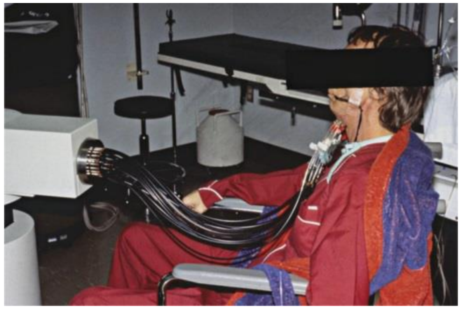
Tomotherapy



Robotic arm systems



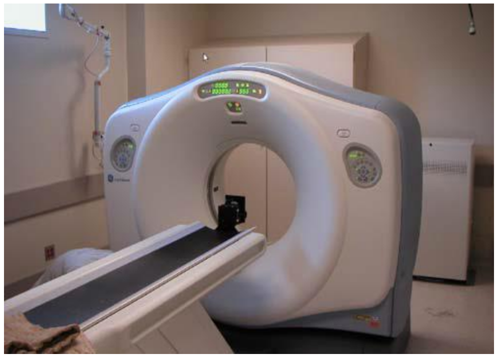
GammaKnife

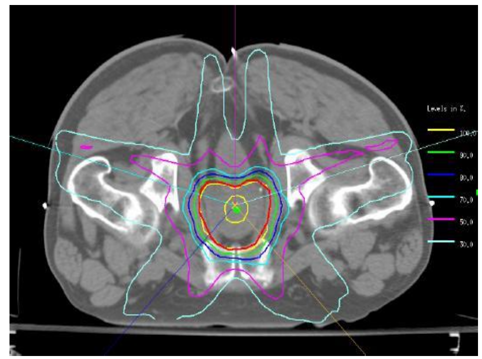


Brachytherapy

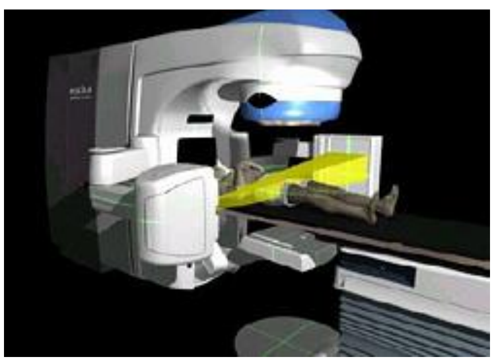
Proton therapy

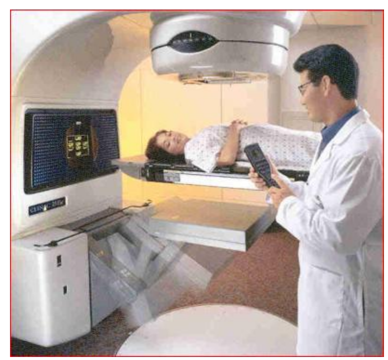
Imaging systems in radiotherapy





CT





On board imaging: kV and MV imaging systems on a linear accelerator

Dosimetry for targeted molecular radiotherapy (+ imaging)

Combination of peptide receptor radionuclide therapy with fractionated external beam radiotherapy for treatment of advanced symptomatic meningioma

Michael C Kreissl, et al. *Radiation Oncology* 2012, 7:99

Target: somatostatin receptors

PET imaging + Radiopeptide therapy + IMRT

^{68}Ga-labelled somatostatin analogues

For receptor expression and tumour delineation

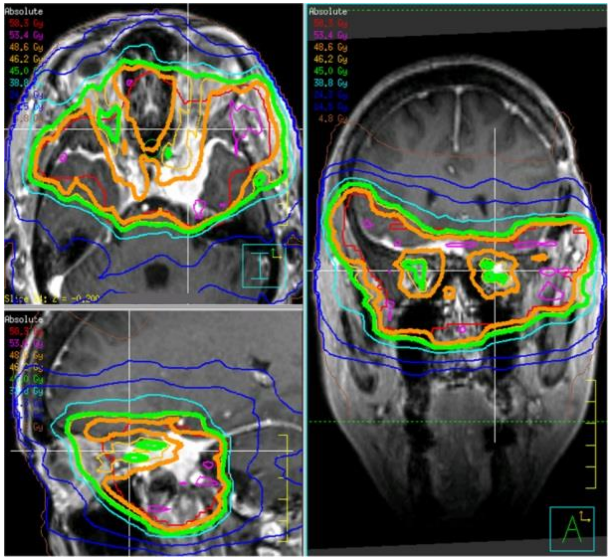
^{177}Lu-DOTATOC/-DOTATATE*

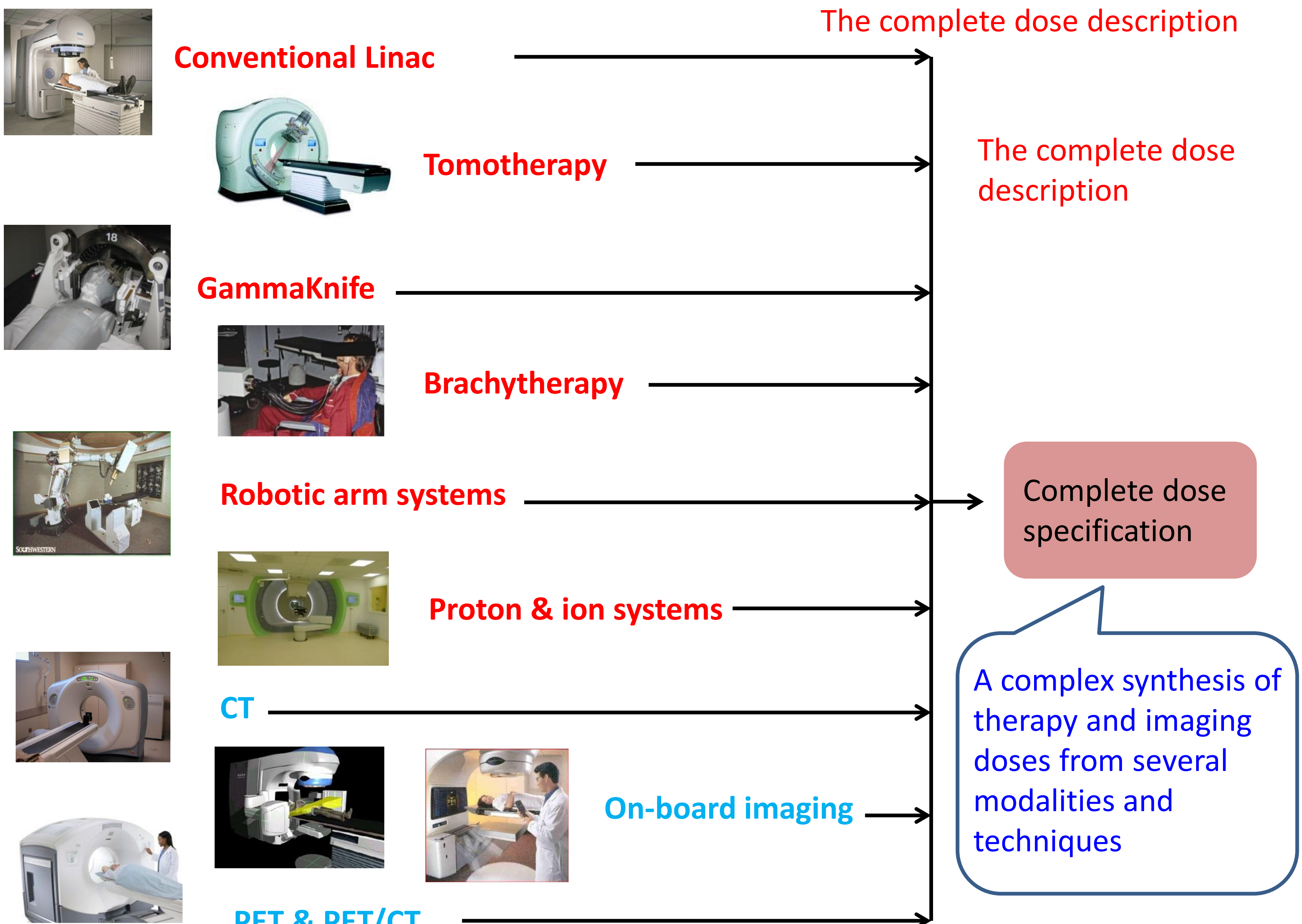
(~7 Gy)

Also SPECT/CT of head (absolute activity)

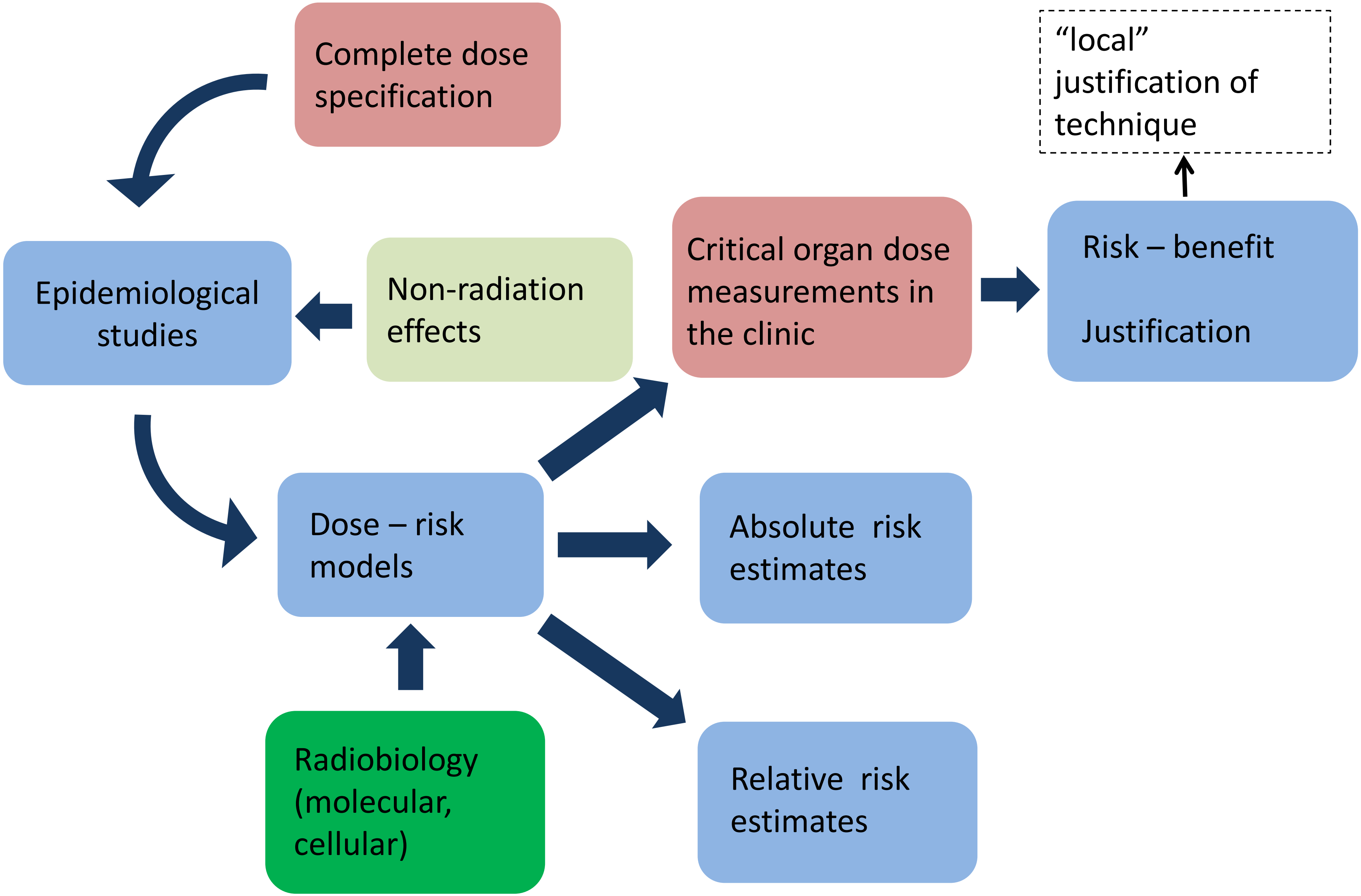
*113 and 210 keV γ & xray + 490 keV β. $T_{1/2}$ = 6.75 days

40-60 Gy

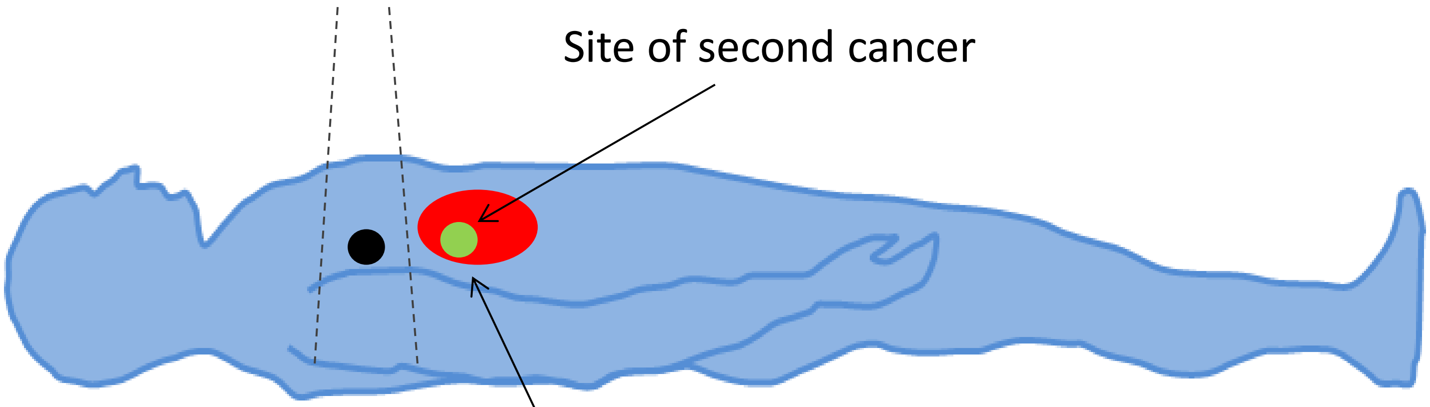



The complete dose description
Conventional Linac
Tomotherapy
The complete dose description
GammaKnife
Brachytherapy
Robotic arm systems
Complete dose specification
Proton & ion systems
A complex synthesis of therapy and imaging doses from several modalities and techniques
CT
On-board imaging
PET & PET/CT

The complete dose description



Problems of retrospective dosimetry

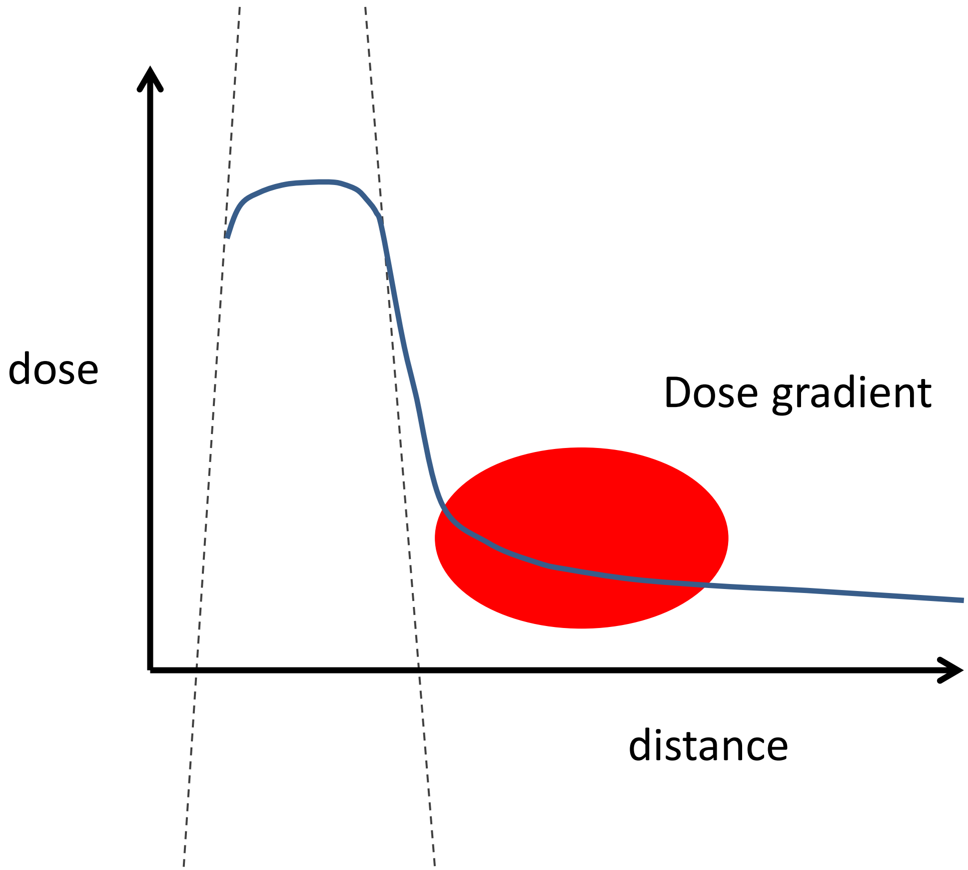


Where was this region 10 years ago?

Are the treatment plans adequate?

Are images available?

Dose gradients



1. Critical organs close to the target volume are of paramount interest

- 66% of second cancers in the region -2.5 - + 5 cm from field edge
- Difficult to measure or estimate dose retrospectively in this region

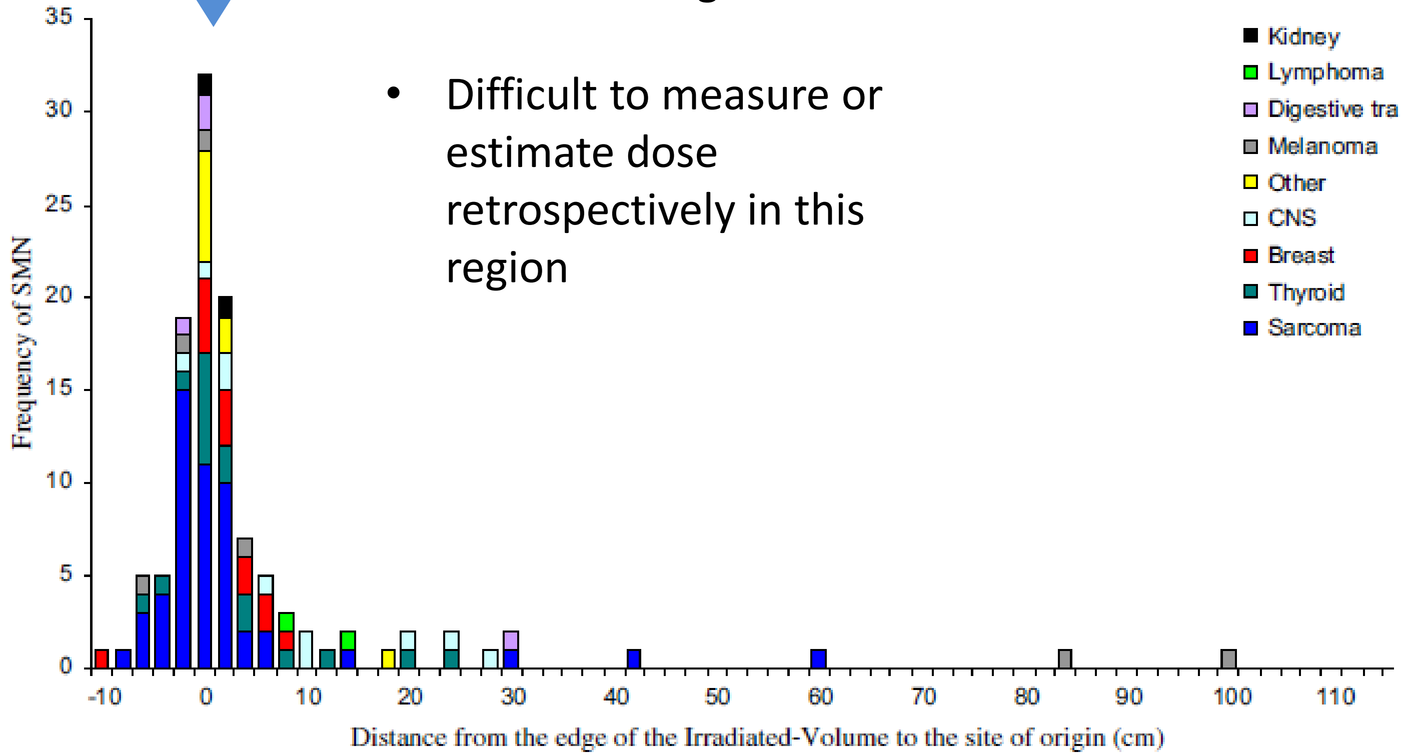
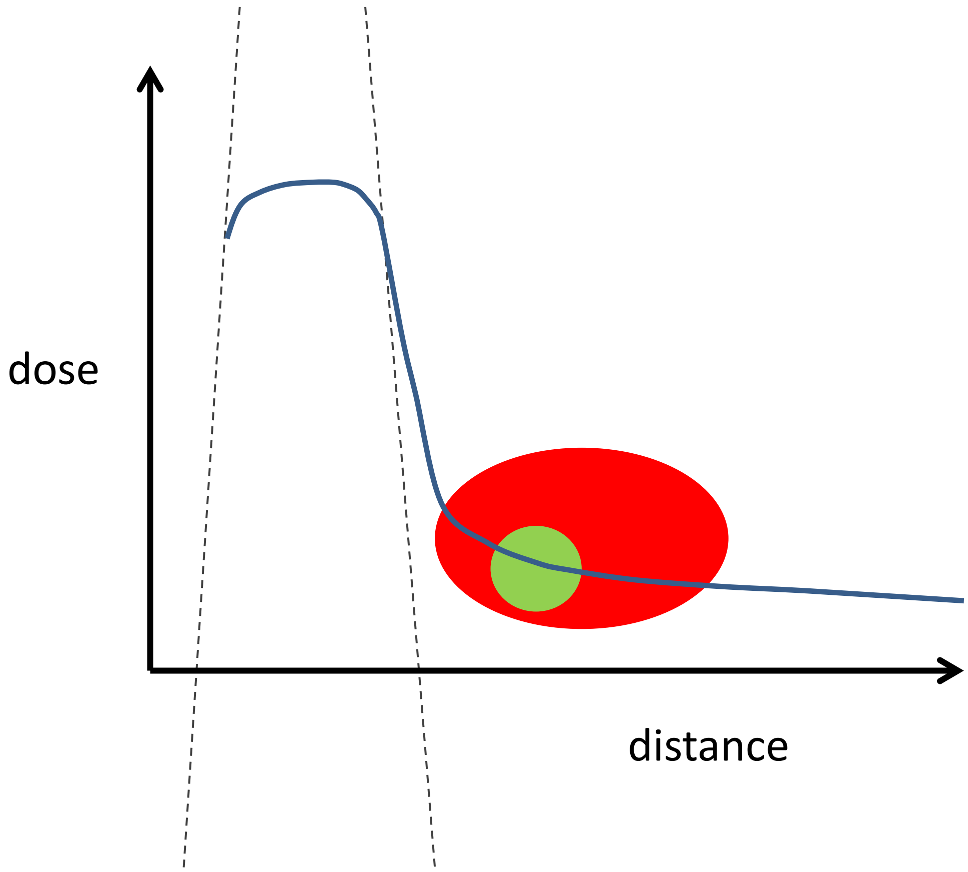


Fig. 1. Frequency distribution of the distances from the edge of the irradiated volume to the site where solid second malignant neoplasms (SMN) developed among 115 patients. The geometric limit of the closest beam path is considered to represent the limit of the irradiated volume. On the x-axis, the origin (0) is the edge of the beam path. The distances are negative from the beam edge inward and positive from the beam edge outward. CNS = brain and other nervous system tumors.

From: Diallo et al Int. J. Radiation Oncology Biol. Phys., Vol. 74, No. 3, pp. 876–883, 2009

See also: Dörr and Herrman Strahlenther Onkol 2002 178; 357-62

Dose gradients



1. Critical organs close to the target volume are of paramount interest

2. The critical organ will be in a region of dose gradient

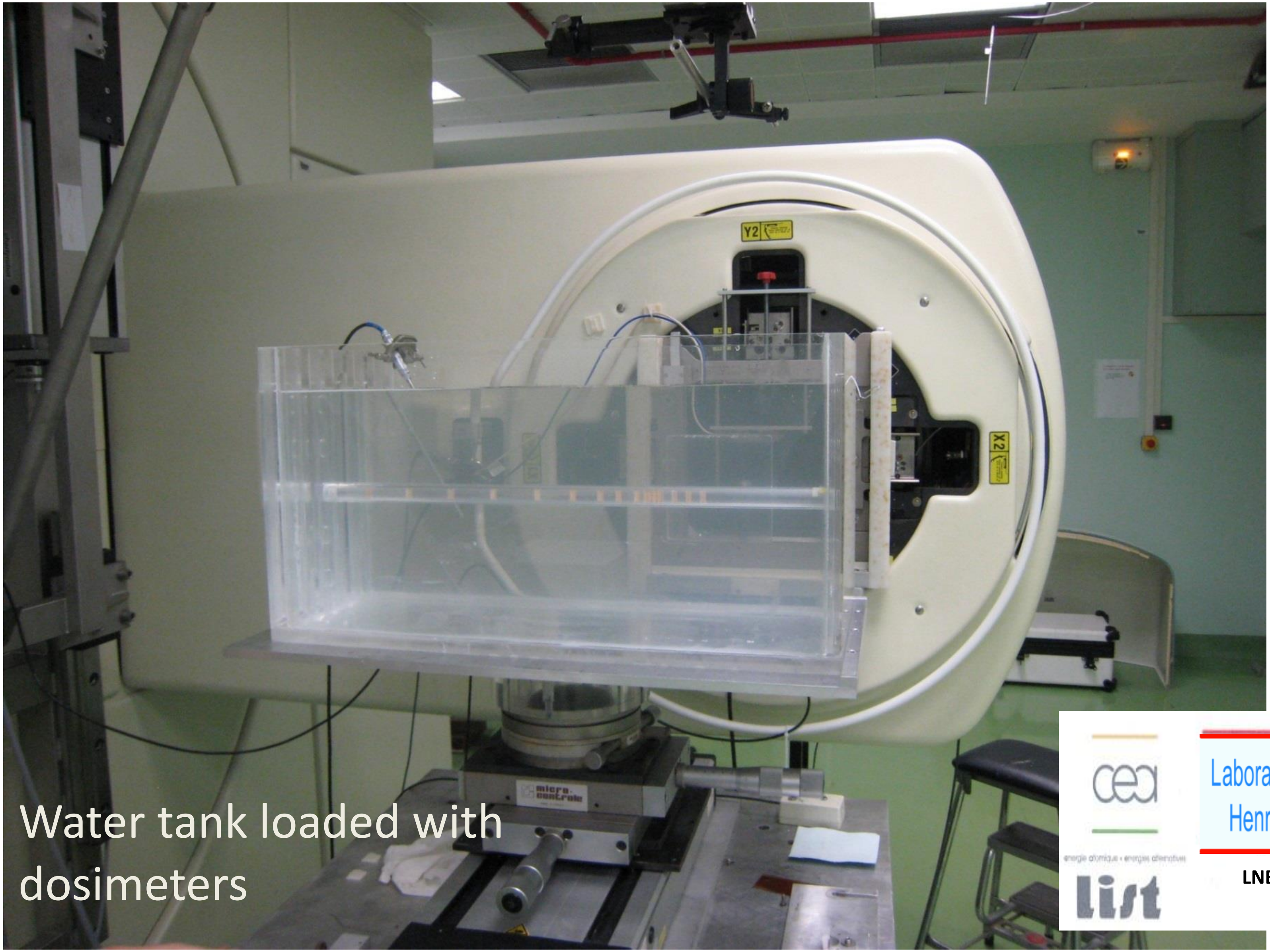
3. Mean dose may not be sufficient ; doses to sub-volumes of differing radiation sensitivity required; dose – risk relationships may be non-linear

A starting point:

Simulate the treatment using phantom measurements

Which phantom?

- Water tank
- BOMAB- like phantoms
- Anthropomorphic phantoms
- Analytical models and voxel phantoms for mathematical simulation

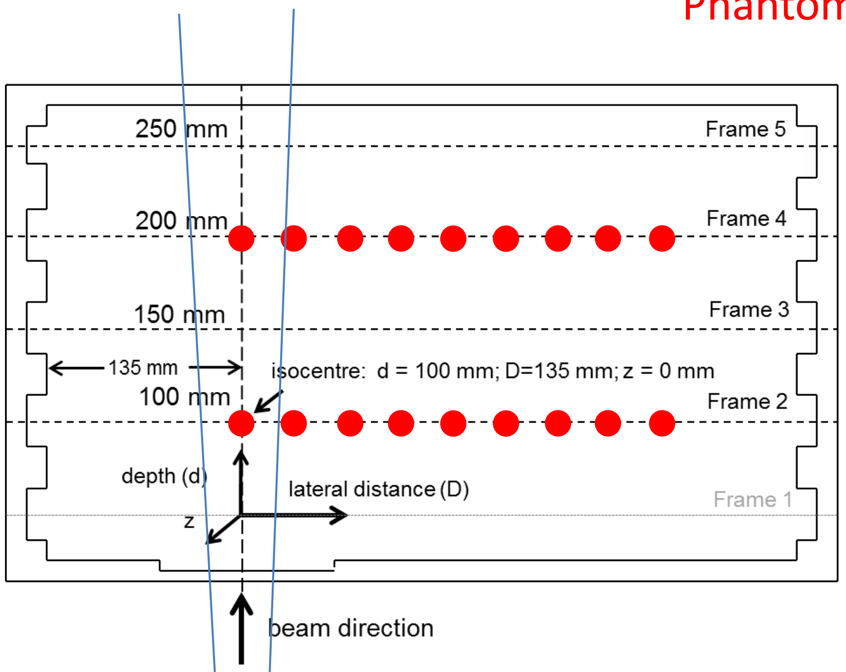


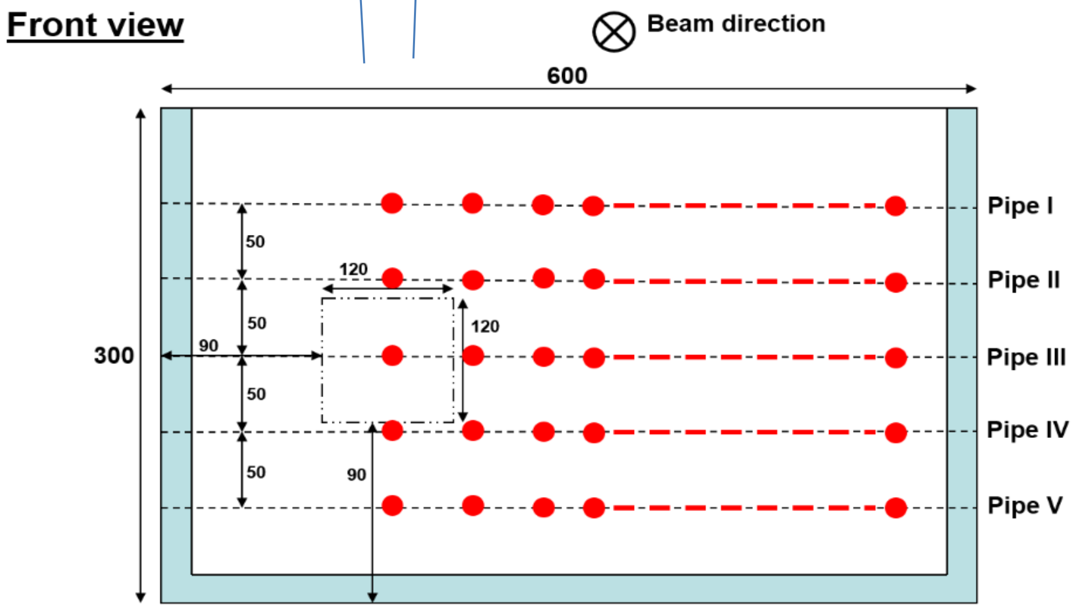
Water tank loaded with dosimeters

Laboratoire National Henri Becquerel

LNE-LNHB

Phantoms for out-of-field measurements: water tank



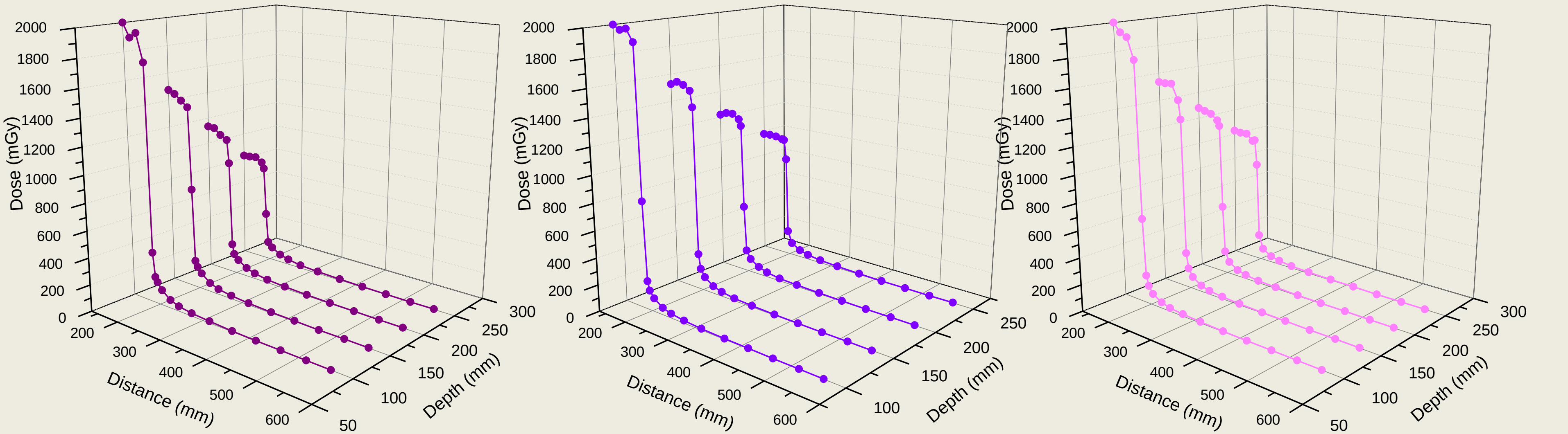


Water tank

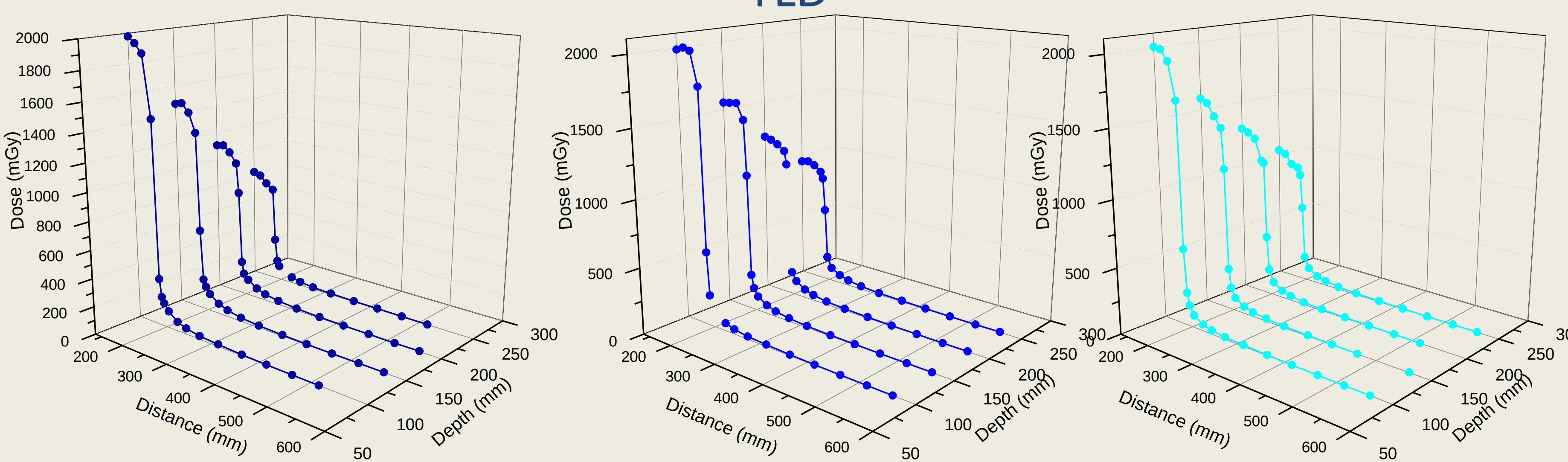
- Simple geometry
- Reproducible
- Clinically unrealistic
- Water-only medium

6 MV 12 MV 20 MV

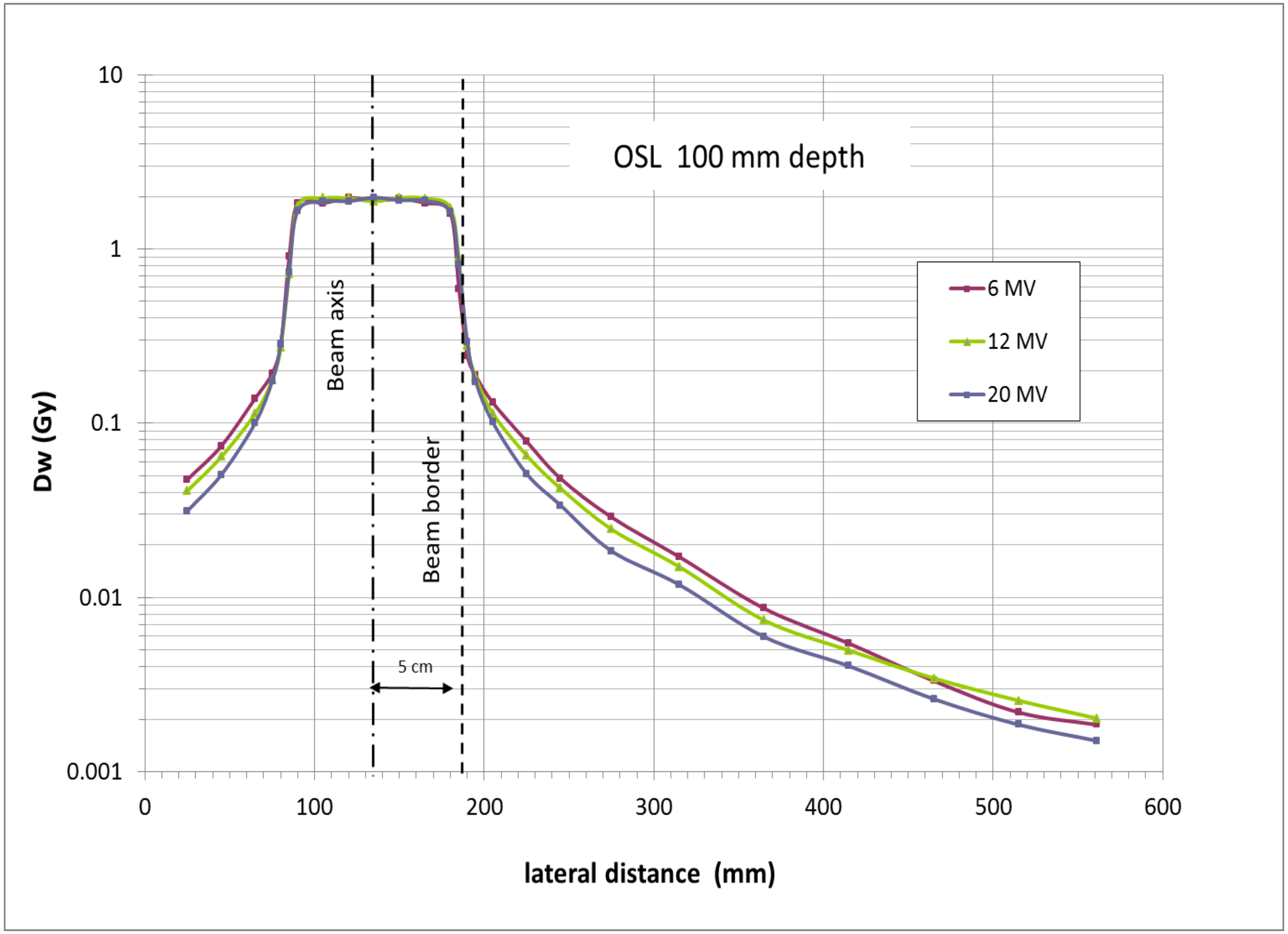
RPL



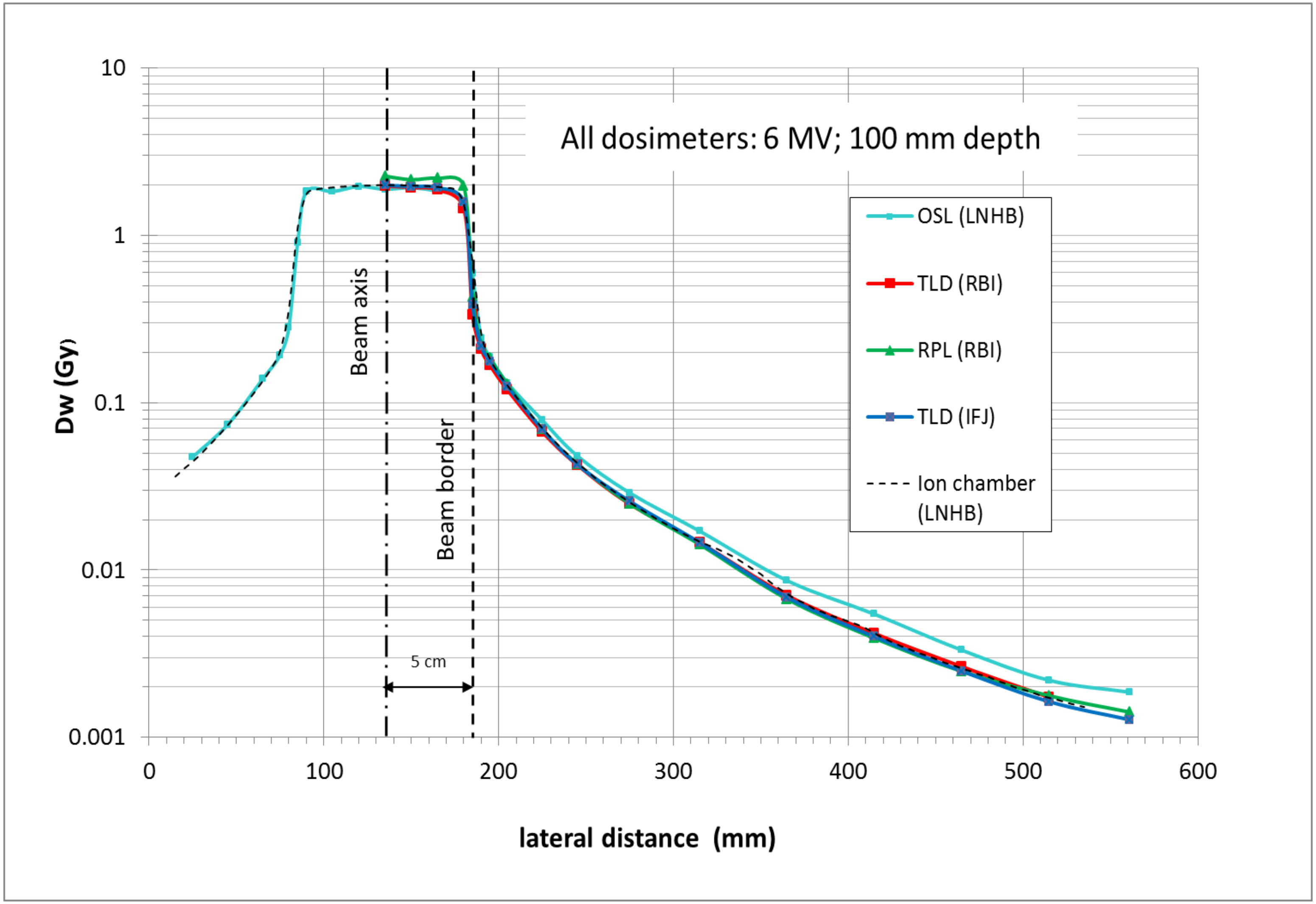
TLD



Phantoms for out-of-field measurements: water tank



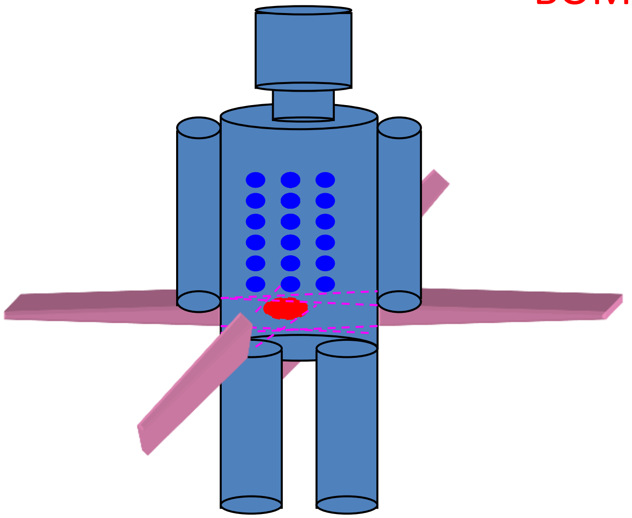
Phantoms for out-of-field measurements: water tank



The BOttle MAnnikin ABsorber phantom (BOMAB)

Phantoms for out-of-field measurements:

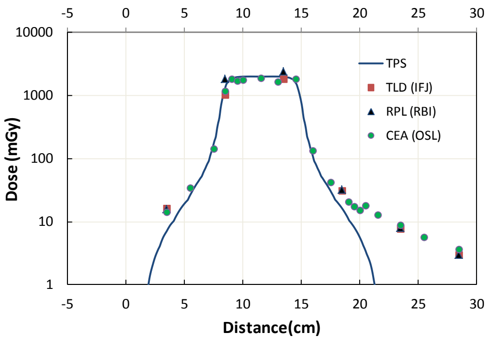
BOMAB phantoms



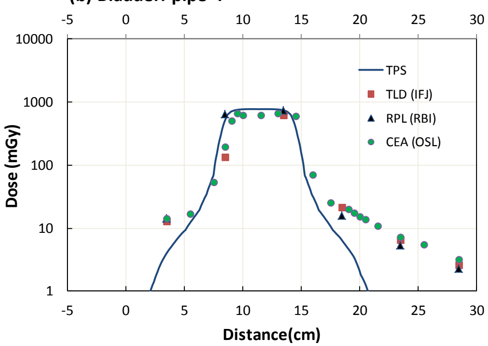
Phantoms for out-of-field measurements: BOMAB phantoms

15 MV 5-field CRT: UHSC Pisa

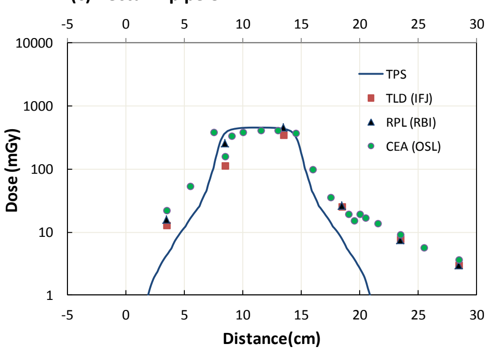
(a) PTV: pipe 1



(b) Bladder: pipe 4

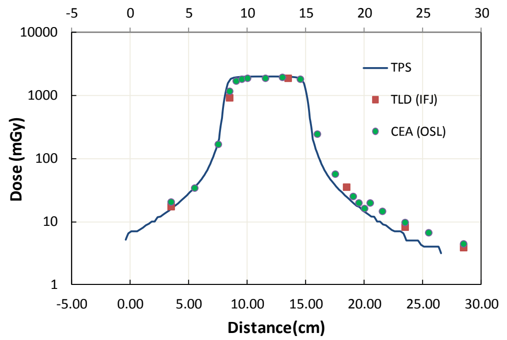


(c) Rectum: pipe 5

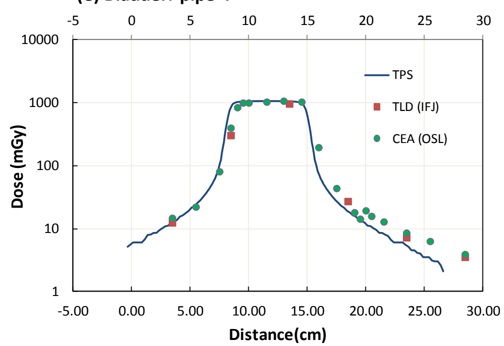


18 MV 4-field CRT: IFJ Krakow

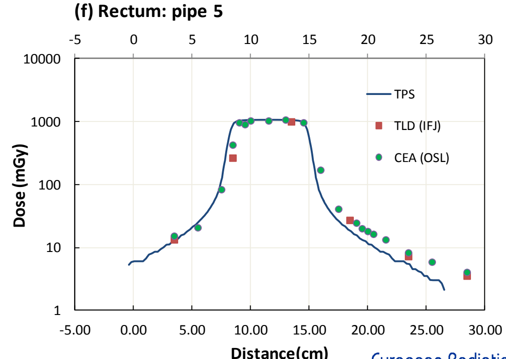
(d) PTV: pipe 1

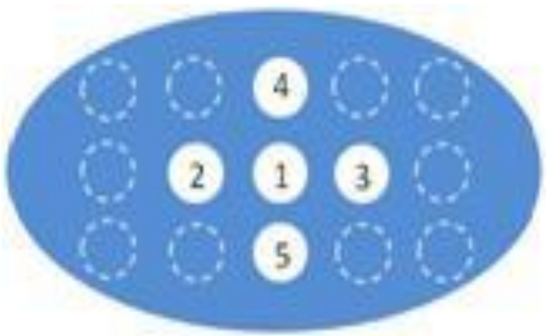


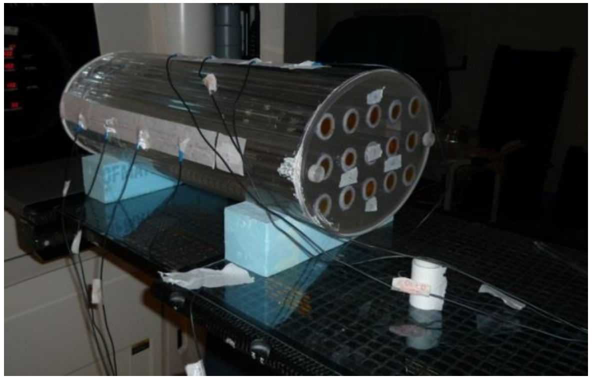
(e) Bladder: pipe 4



(f) Rectum: pipe 5





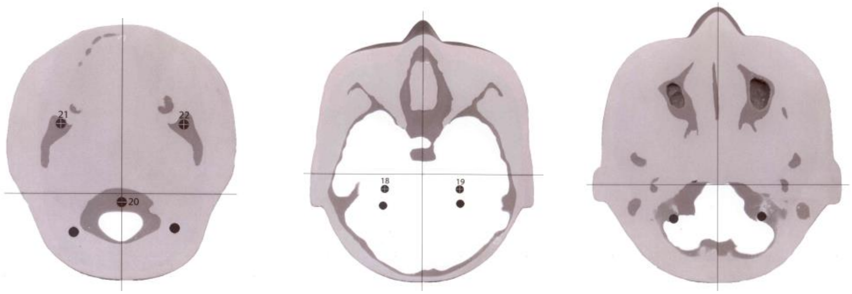


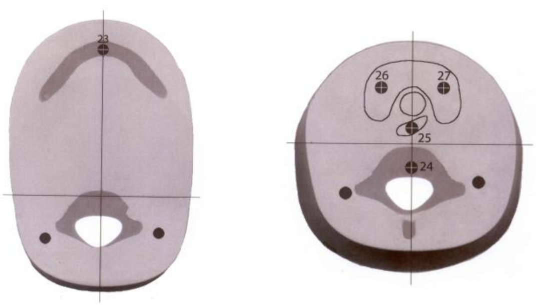
Centre of Oncology, Krakow: Varian Eclipse v8.6

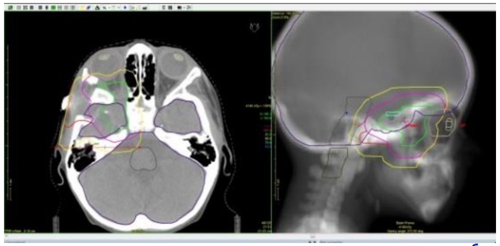
University Hospital of Santa Chiara, Pisa: CMX XiO 4.40.05

Measuring out-of-field doses from a paediatric brain tumour treatment (photons)

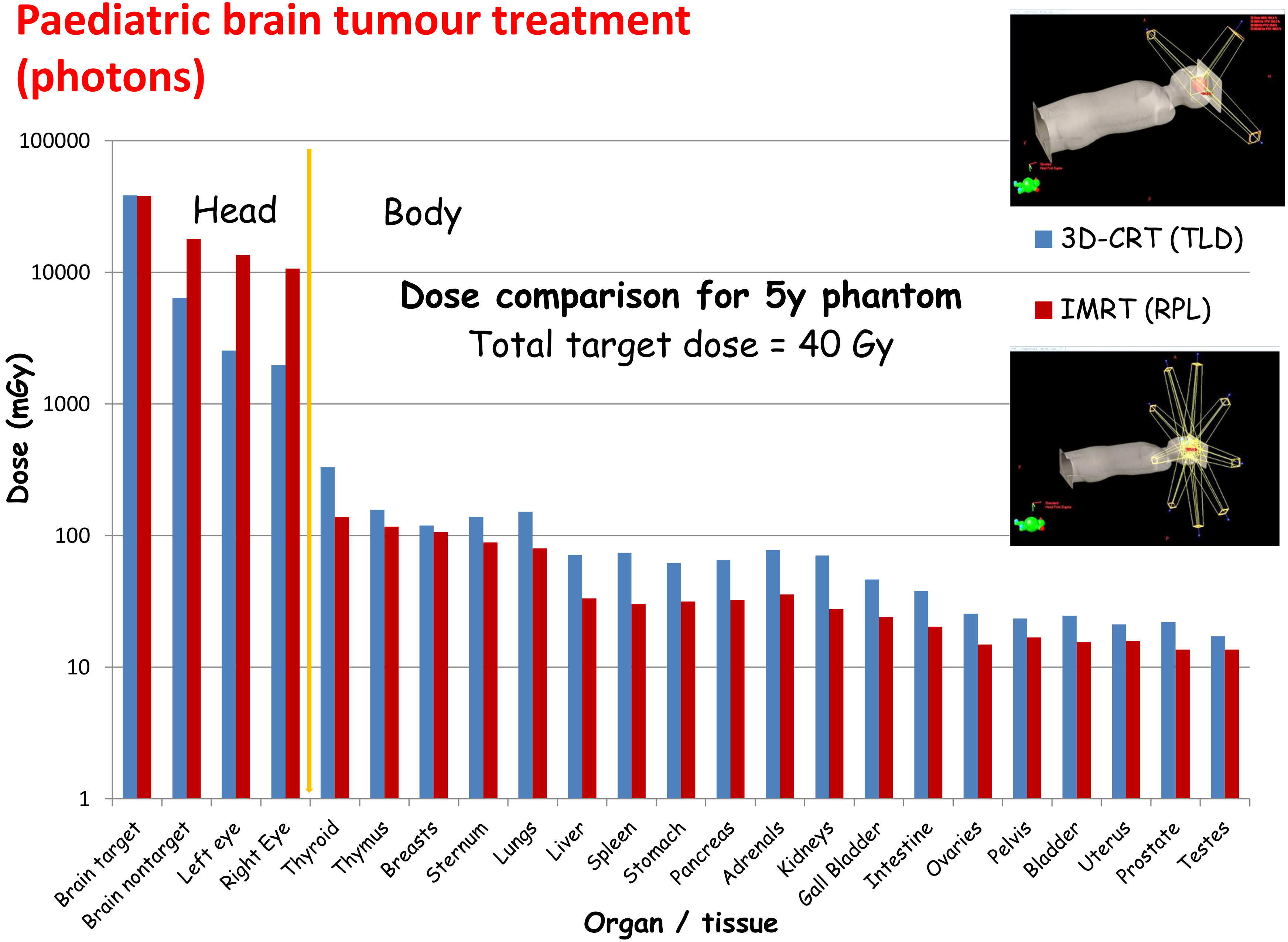
Institute of Nuclear Physics (IFJ) and Centre of Oncology, Krakow
Ruđer Bošković Institute, Clinical Hospital for Tumours & Clinical Hospital Centre, Zagreb



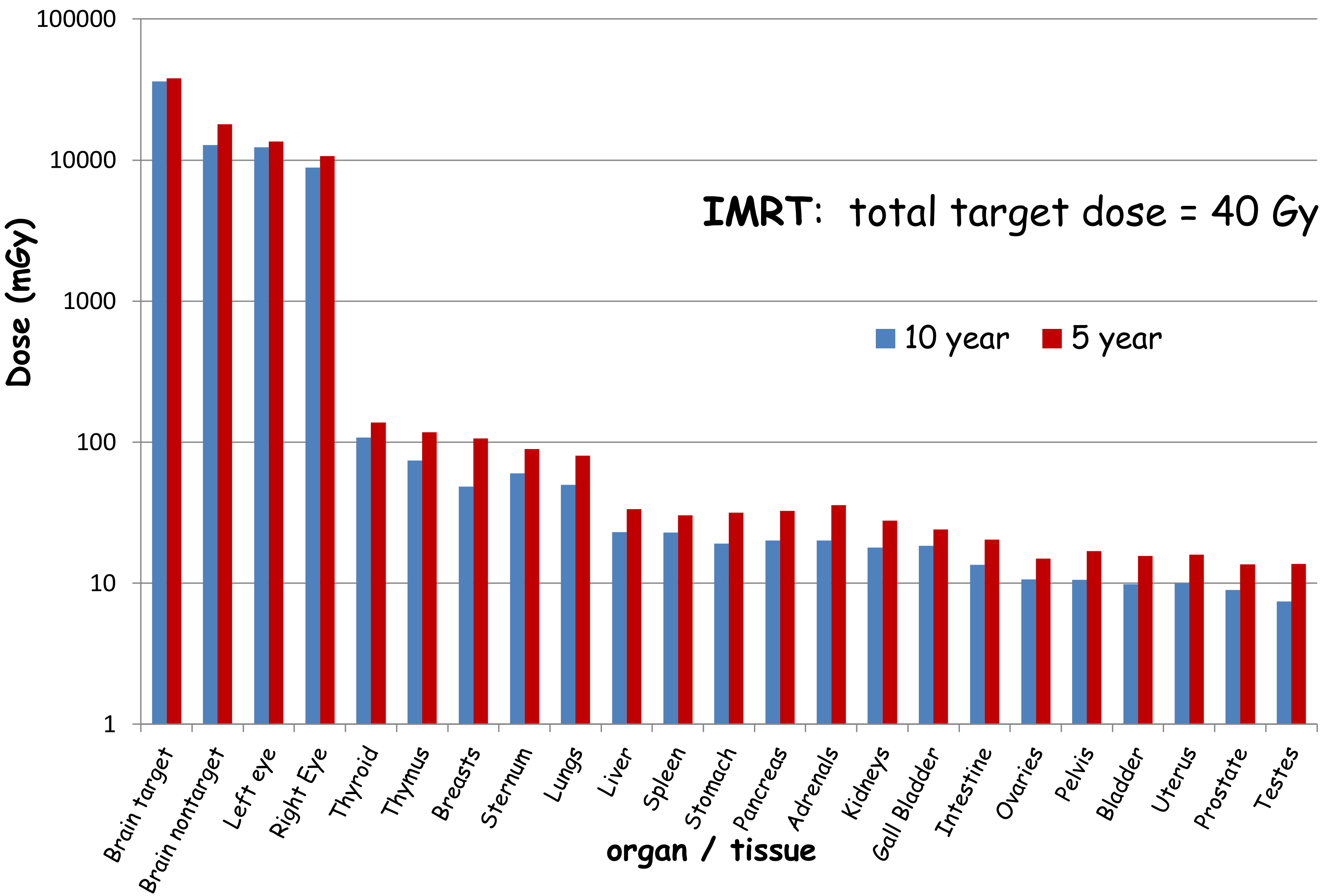


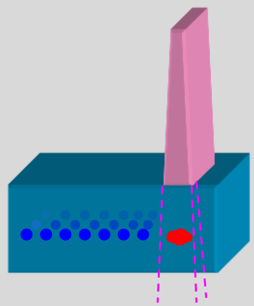
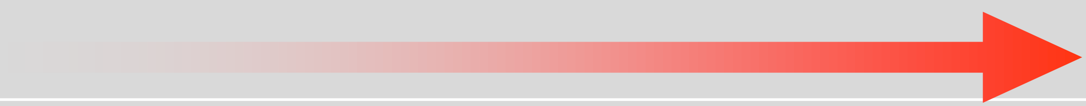


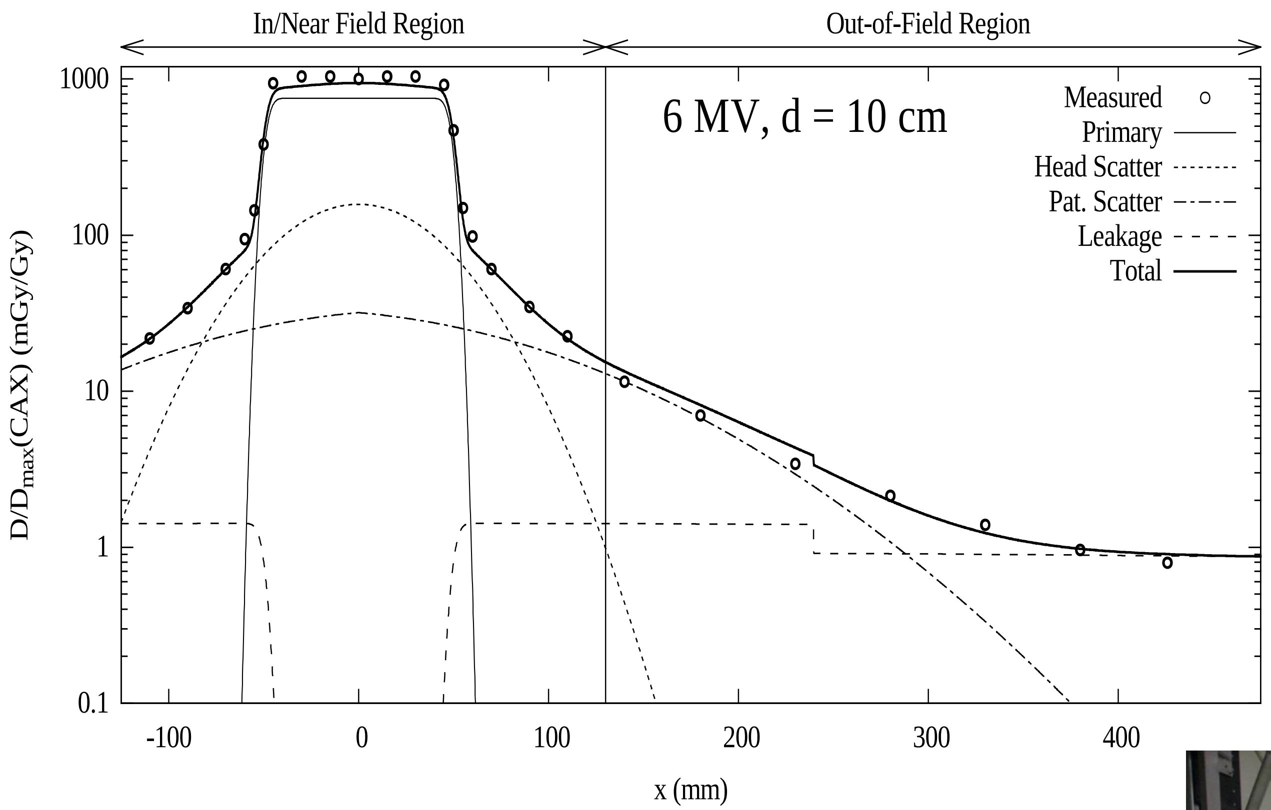
Paediatric brain tumour treatment (photons)



Paediatric brain tumour treatment (photons)

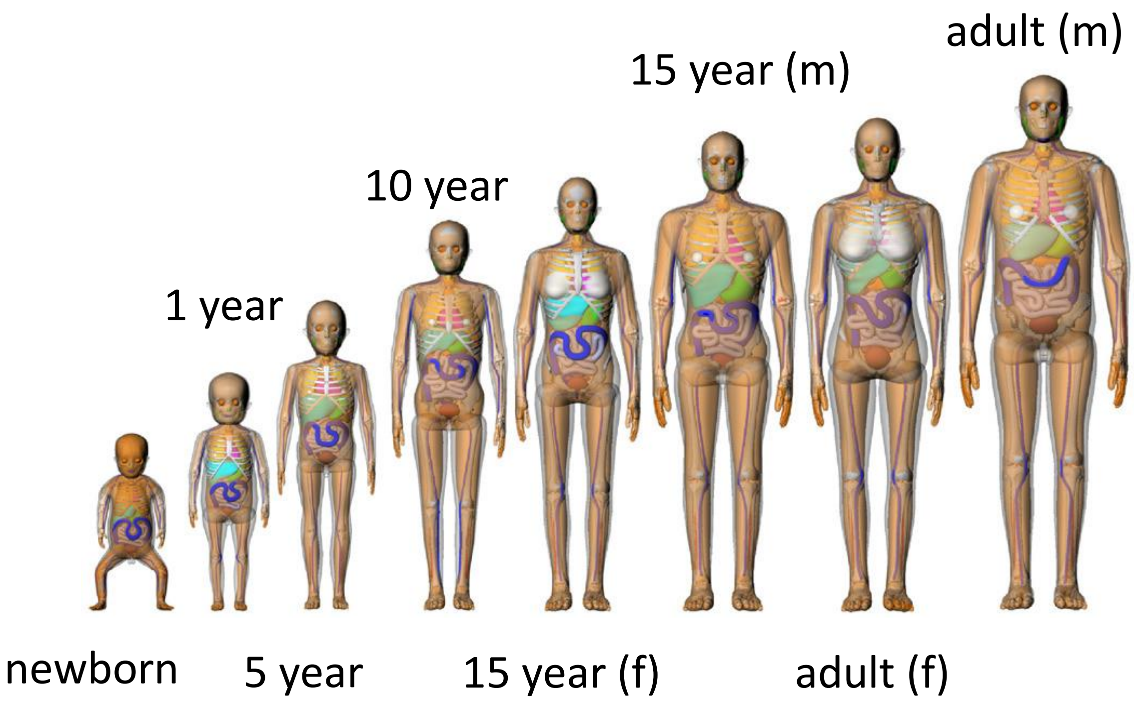


	Water tank	BOMAB	anthropo-morphic	patient
				
clinical realism				
generality				
accuracy of risk estimation				
measurement difficulty				
facility for dosemeter comparison				



Measured and calculated relative absorbed doses for 6 MV beam and 10 cm depth in water from the EURADOS dataset, following training of the model

WG9 collaboration with Prof. Wayne Newhauser, Chris Schneider et al, Mary Bird Perkins Cancer Center & Louisiana State University, USA



> TPS > plan simulated treatments

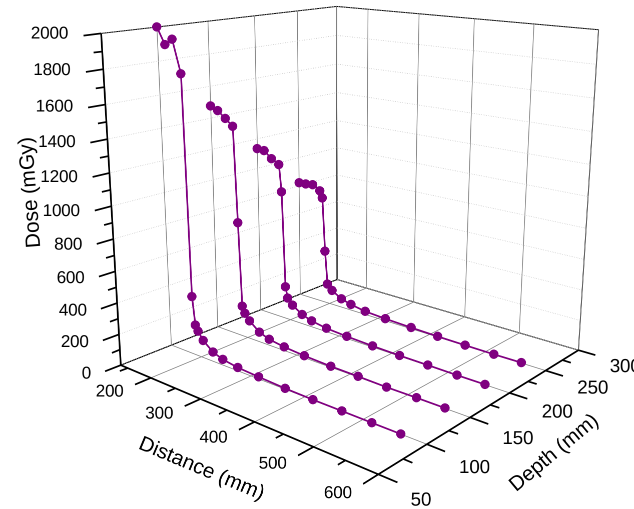
> Monte Carlo (XVMC) > plan simulation

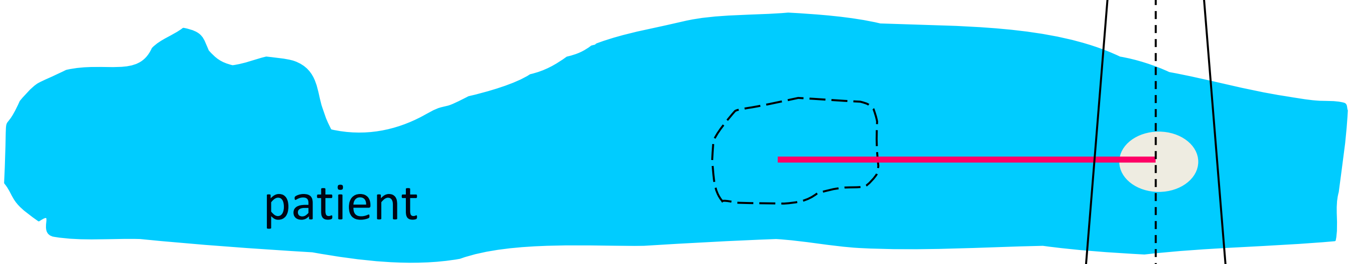
A series of hybrid voxel phantoms representing paediatric and adult reference individuals.

Lee et al. Reconstruction of organ dose for external radiotherapy patients in retrospective epidemiologic studies. Phys. Med. Biol. 60 (2015) 2309–2324

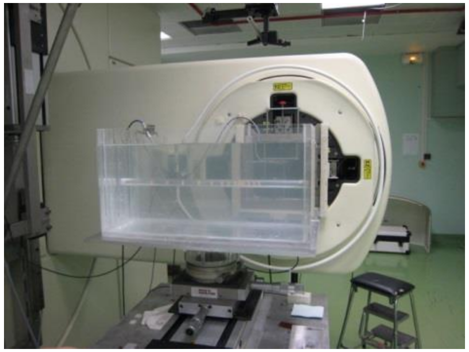
Options for out-of-field dosimetry

- No image of organ
- No TPS calculation
- Organ shape and extent uncertain
- Estimate nominal distance to organ
- Use approximate dose-distance relationships from water tank data

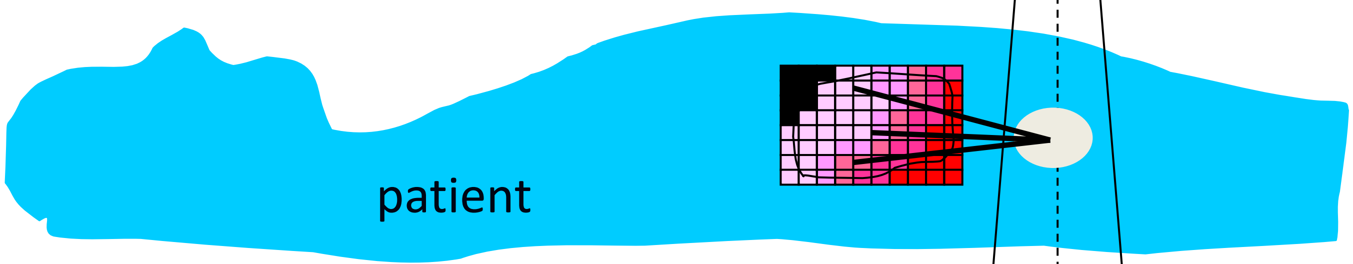


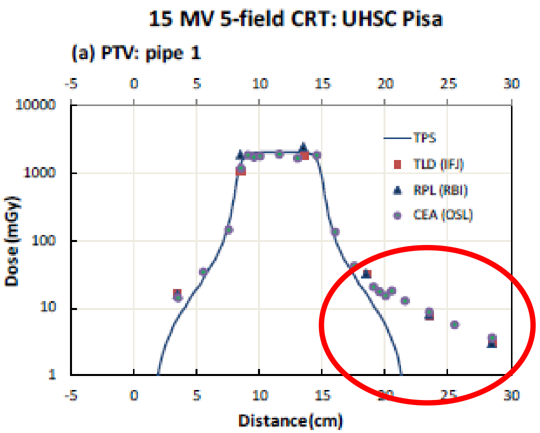


See: Stovall et al. 2006 Dose reconstruction for therapeutic and diagnostic radiation exposures: use in epidemiological studies. Rad. Res. 166, 141-157



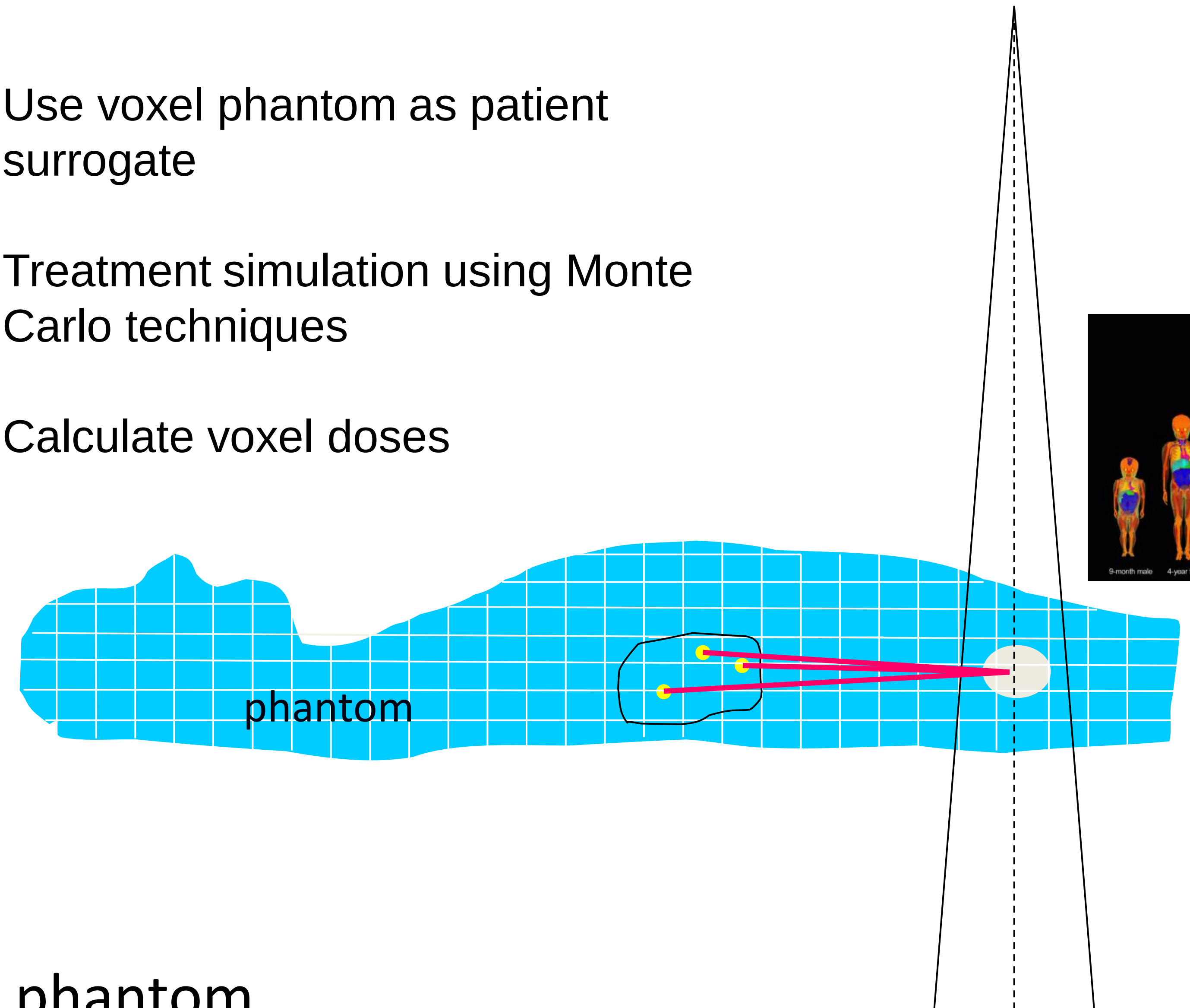
- Known location and extent of OAR (CT, MRI…..)
- Known dose distribution (from TP system) in organ
- Calculate voxel doses

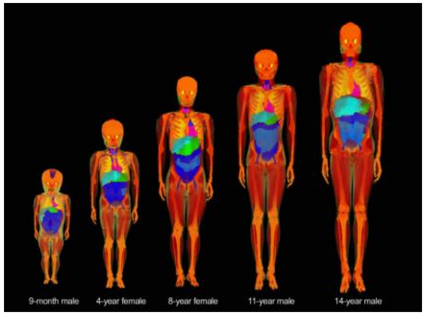




BUT – check the TPS with measurements

- Use voxel phantom as patient surrogate
- Treatment simulation using Monte Carlo techniques
- Calculate voxel doses

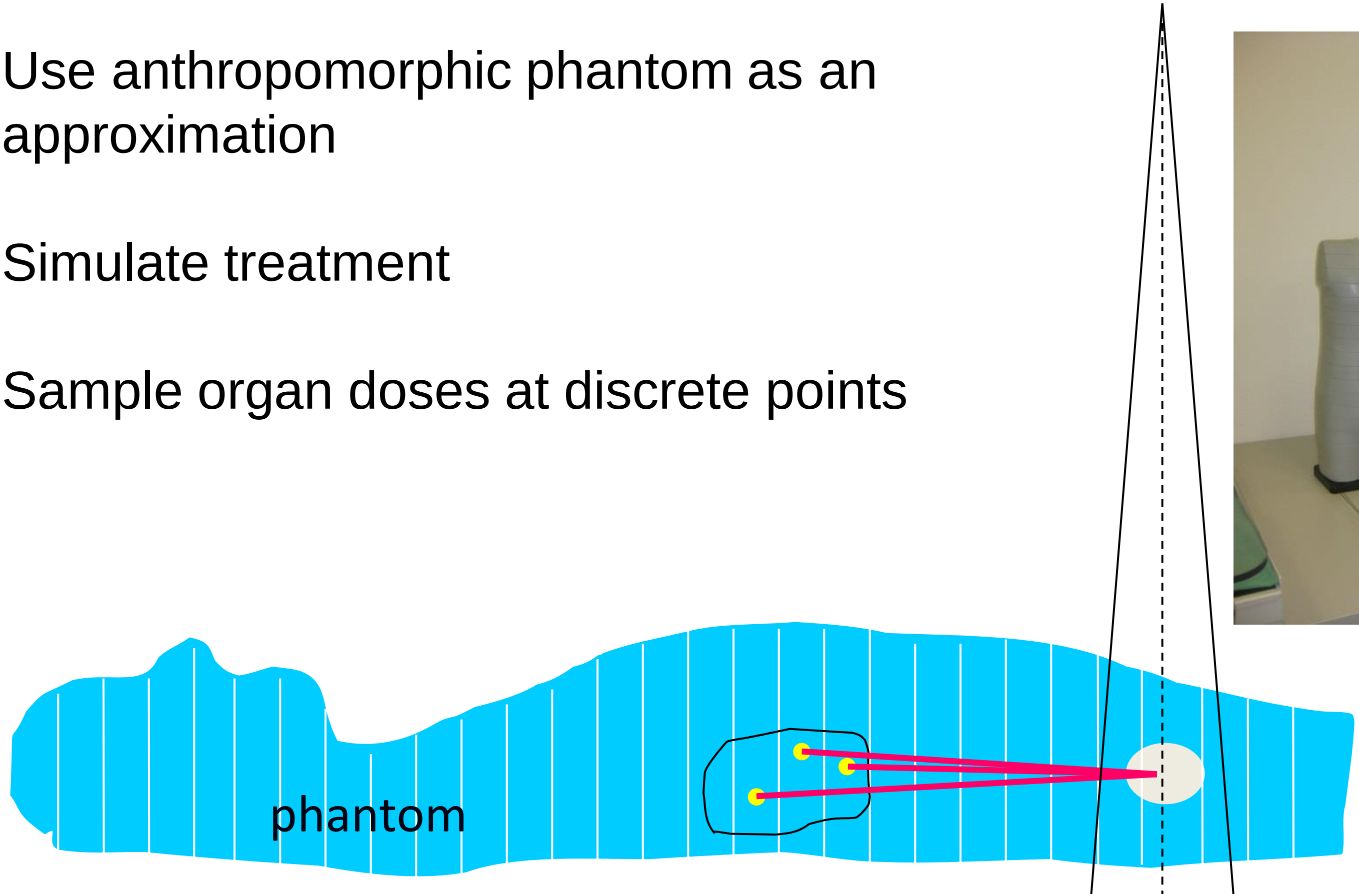




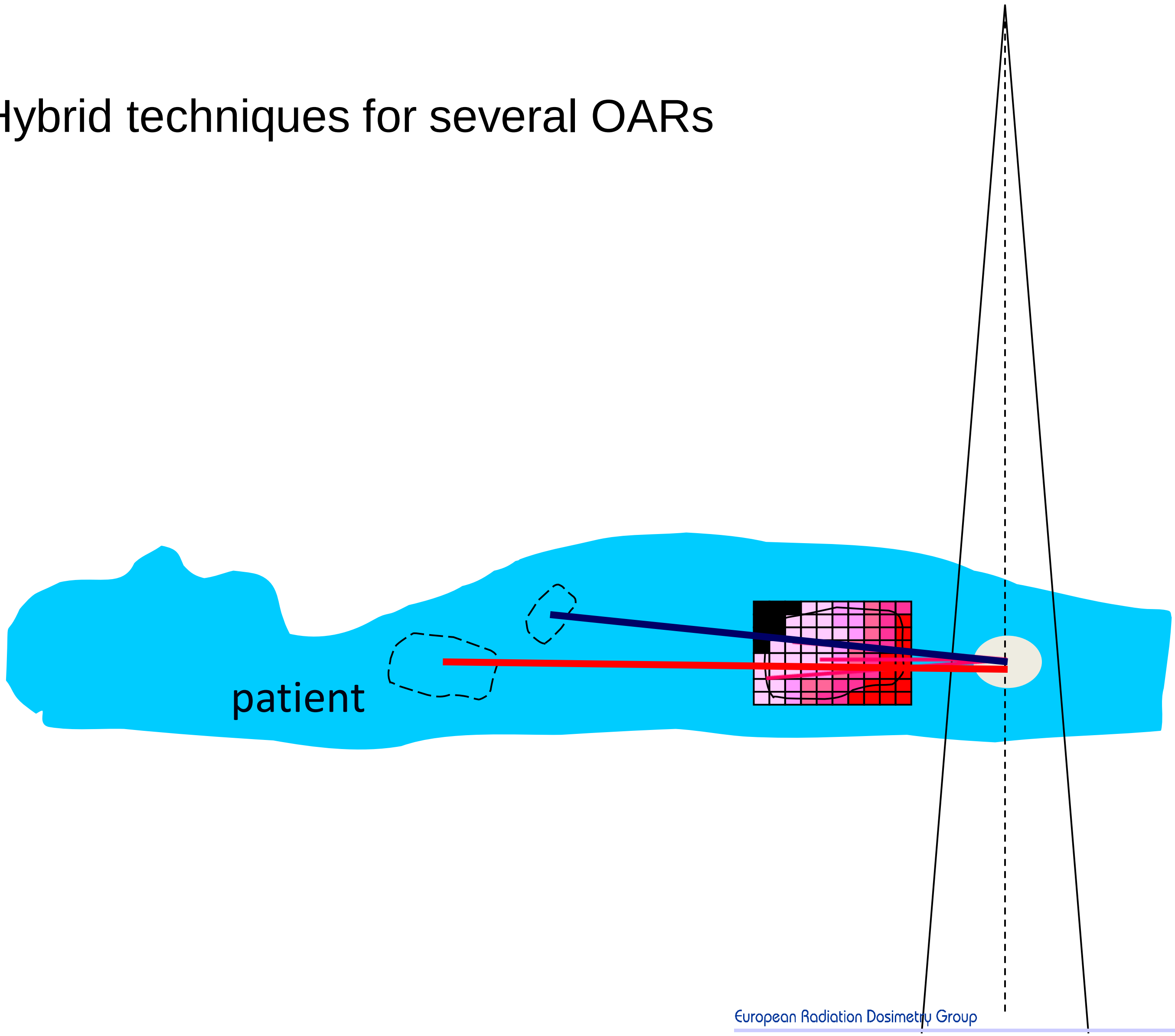
voxel phantom

Options for out-of-field dosimetry

- Use anthropomorphic phantom as an approximation
- Simulate treatment
- Sample organ doses at discrete points



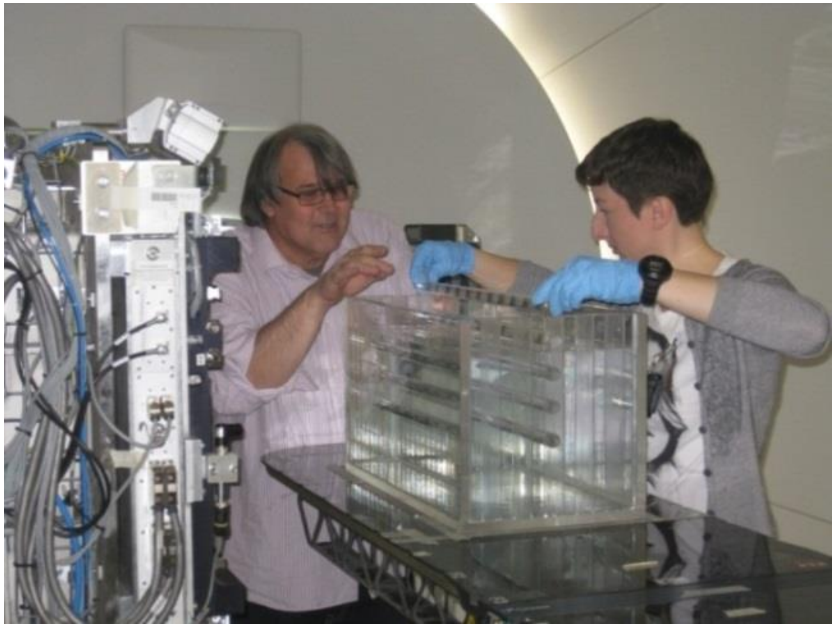
- Hybrid techniques for several OARs

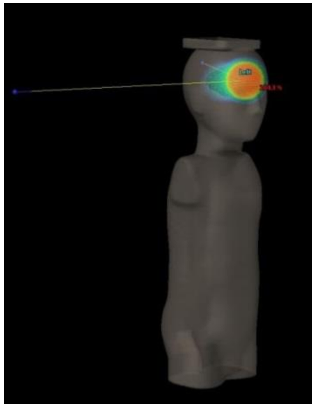


Proton therapy dosimetry:

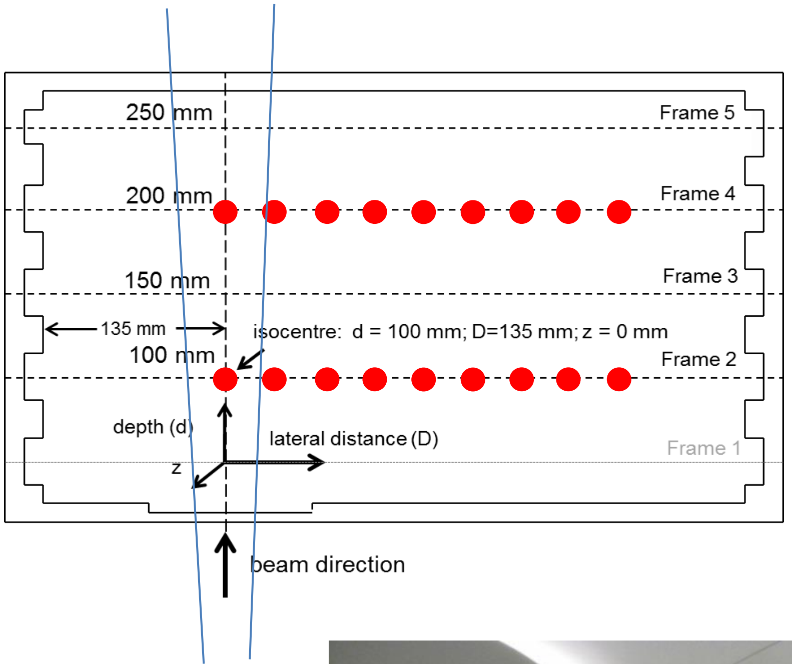
Institute of Nuclear Physics (IFJ), Krakow
Proton Therapy Centre, Trento

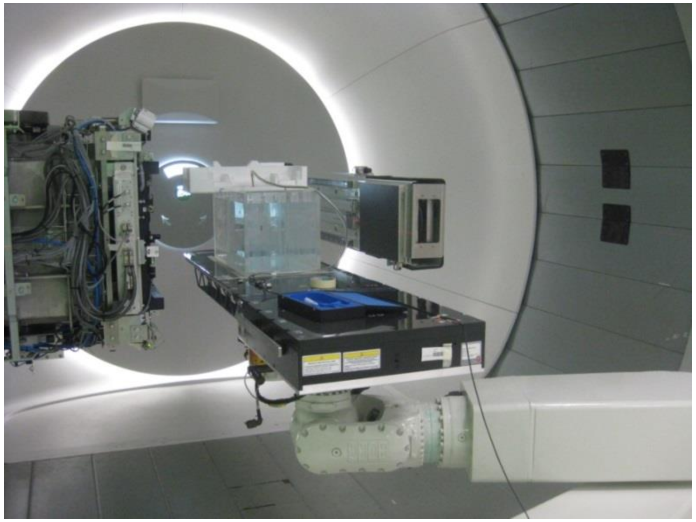
- Out-of-field doses in a water tank
- Brain tumour treatment simulation
- Environmental neutron measurements with a variety of dosemeters

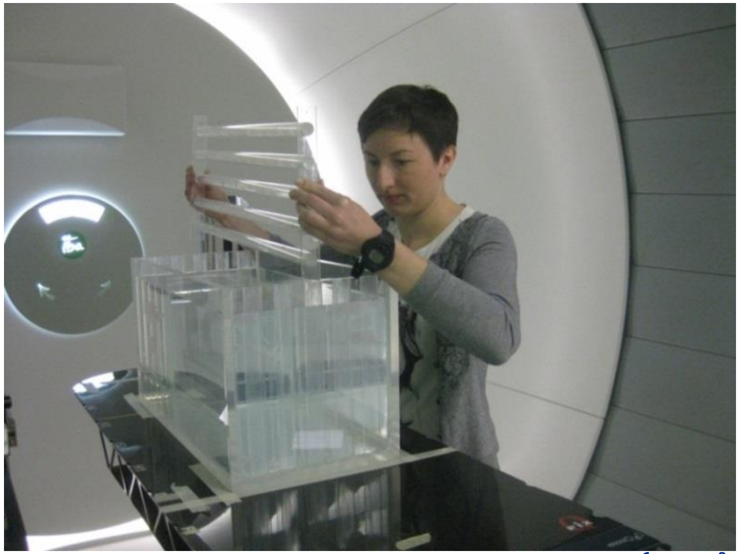




Water tank measurements:
Trento Proton Therapy Centre





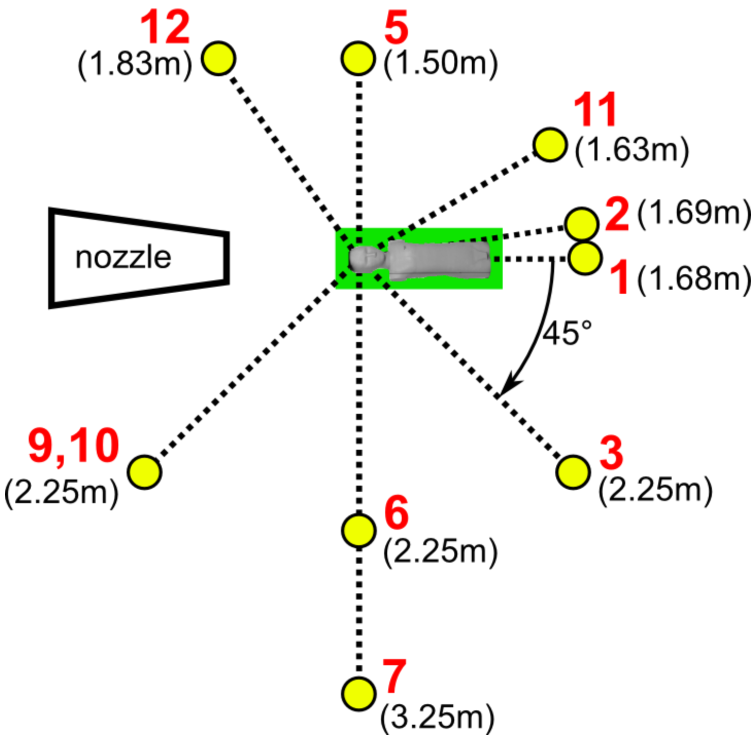


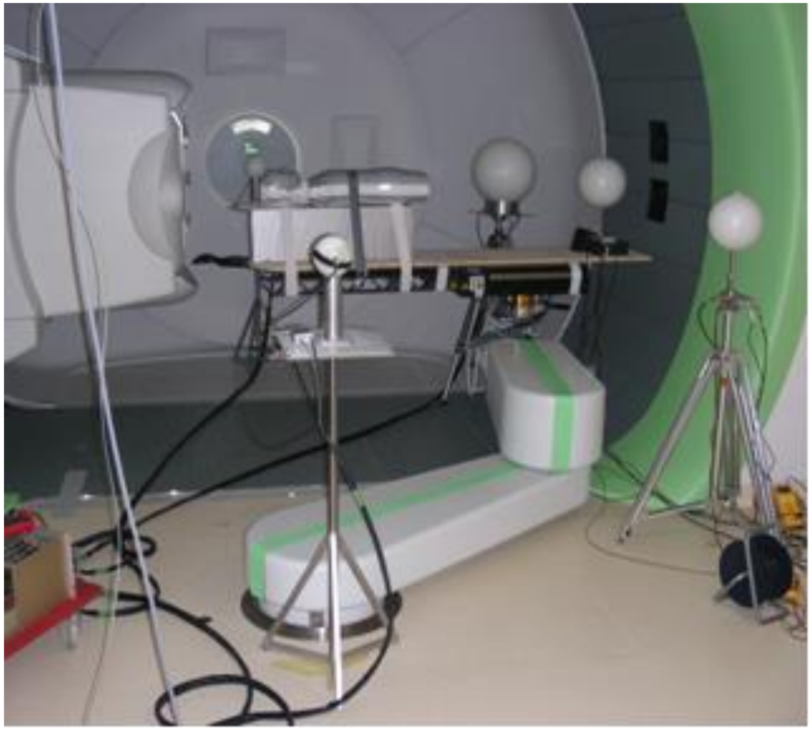
Detectors

Proton radiotherapy facilities

Detector type	Participant	Material	Form	Dimensions (mm)	Z_{eff}	Reader
MTS-7 (IFJ PAN, Poland)	IFJ PAN NPI ASCR	^{7}LiF: Mg, Ti,	pellet	F 4.5×0.9	8.14	IFJ: RA’94 TL Reader-Analyser (Mikrolab) RA’94 NPI: TOLEDO 654 reader (Vinten)
MTS-6 (IFJ PAN, Poland)	IFJ PAN NPI ASCR	^{6}LiF: Mg, Ti	pellet	F 4.5×0.9	8.14	
MTS-N (IFJ PAN, Poland)	NPI ASCR NRPI	^{nat}LiF: Mg, Ti	pellet	F 4.5×0.9	8.14	
TLD-700 (Harshaw)	RBI	^{7}LiF: Mg, Ti	pellet	F 4.5×0.9	8.14	modified TOLEDO 654 reader (Vinten)
RPL GD-352M (with Sn filter) (ATGC)	RBI	Ag activated Phosphate glass	rod holder	F1.5 × 12 F4.3 × 14.5	12.04	automatic reader Dose Ace (FGD-1000)
RPL GD-302M (without filter) (ATGC)	RBI	Ag activated Phosphate glass	rod holder	F 1.5 ×12 F2.8 × 13.0	12.04	
PADC	NPI ASCR NRPI	$C_{12}H_{18}O_7$				
PADC	UAB	$C_{12}H_{18}O_7$				

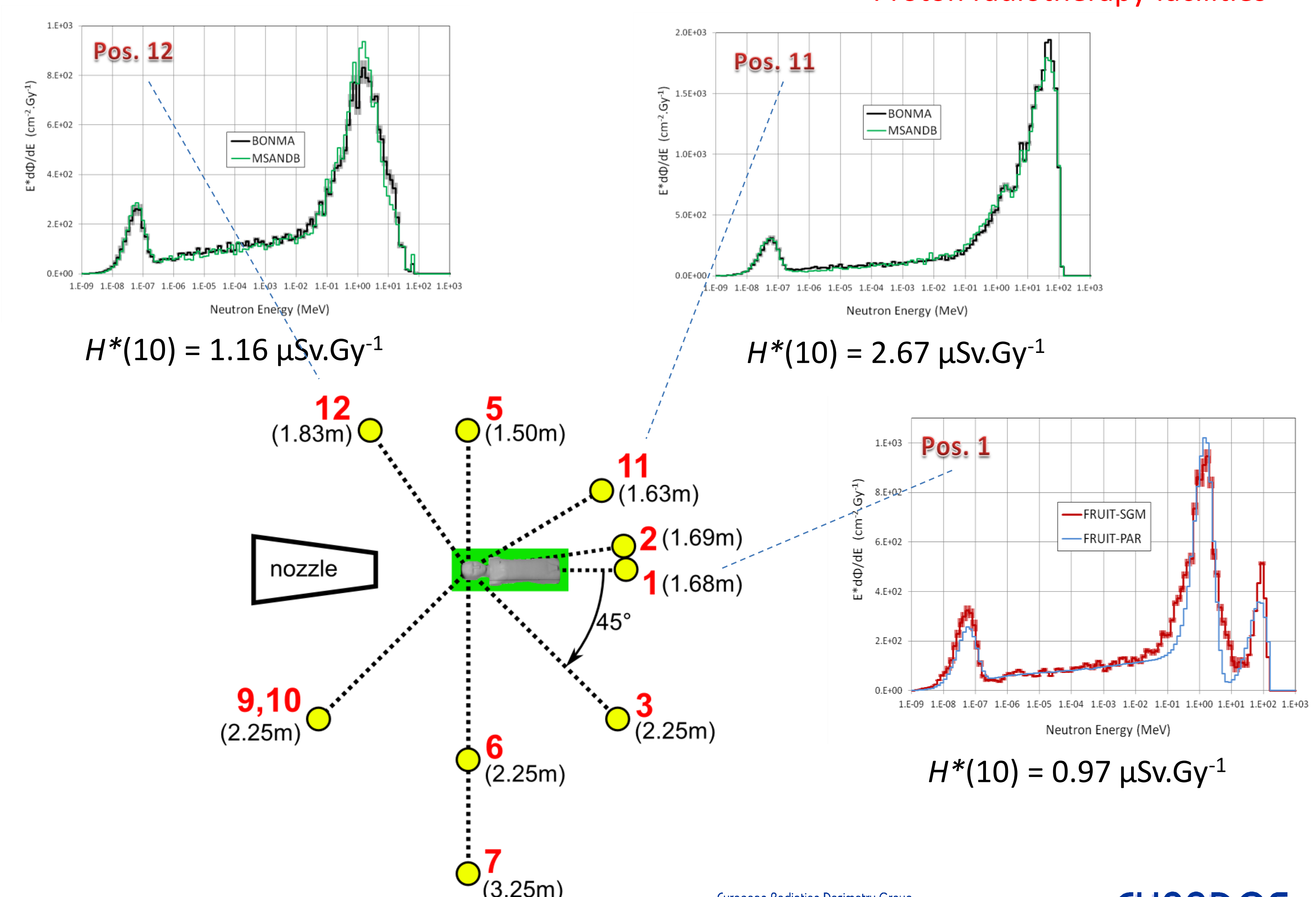
IFJ PAN: Institute of Nuclear Physics, Krakow, Poland
NPI ASCR: Nuclear Physics Institute, Řež, Czech Republic
NRPI: National Radiation Protection Institute, Prague, Czech Republic
RBI: Ruđer Bošković Institute, Zagreb, Croatia
UAB: Universitat Autònoma de Barcelona, Spain



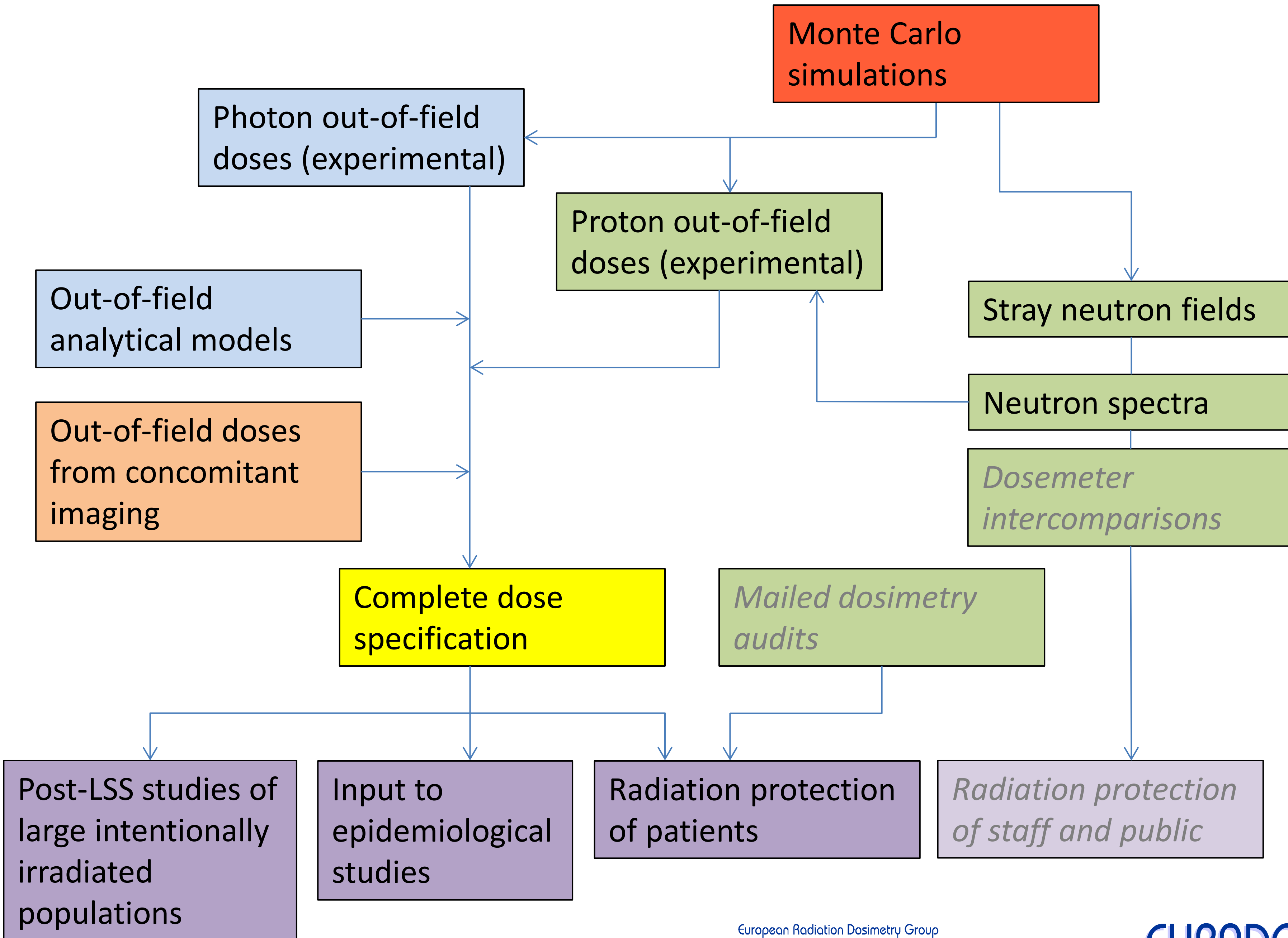


Schematic view of ten measurement positions around a 10-year-old paediatric phantom and experimental setup with Bonner spheres within the gantry room in the Bronowice Cyclotron Centre, Institute of Nuclear Physics, Krakow.

A comprehensive spectrometry study of stray neutron radiation field in scanning proton therapy. Mares et al. Phys. Med. Biol. 61 (2016) 4127–4140


Pos. 12
BONMA
MSANDB
E*dΦ/dE (cm-2.Gy-1)
Neutron Energy (MeV)
H*(10) = 1.16 µSv.Gy-1
Pos. 11
BONMA
MSANDB
E*dΦ/dE (cm-2.Gy-1)
Neutron Energy (MeV)
H*(10) = 2.67 µSv.Gy-1
12 (1.83m)
5 (1.50m)
11 (1.63m)
2 (1.69m)
1 (1.68m)
nozzle
45°
9,10 (2.25m)
3 (2.25m)
6 (2.25m)
7 (3.25m)
Pos. 1
FRUIT-SGM
FRUIT-PAR
E*dΦ/dE (cm-2.Gy-1)
Neutron Energy (MeV)
H*(10) = 0.97 µSv.Gy-1

Pathways to the complete dose specification



European Radiation Dosimetry Group EURADOS

Pathways to the complete dose specification

Input to epidemiological studies and dose-risk models

Complete dose specification

↓

Input to epidemiological studies

↓

Risks of non-cancer effects

Cardiovascular disease

e.g. pericardial & myocardial disease, valvular defects, coronary artery disease (from breast & Hodgkin's RT)

Other organs

Digestive, lung, eye, thyroid, liver, kidney, cognitive/neurological effects …

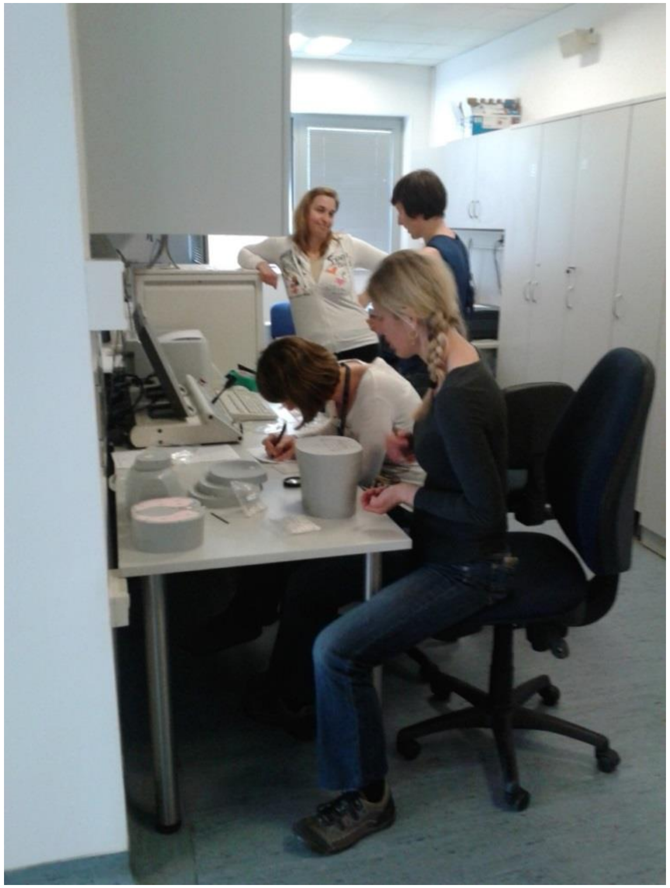
Second cancer risks

(especially in children and young adults)

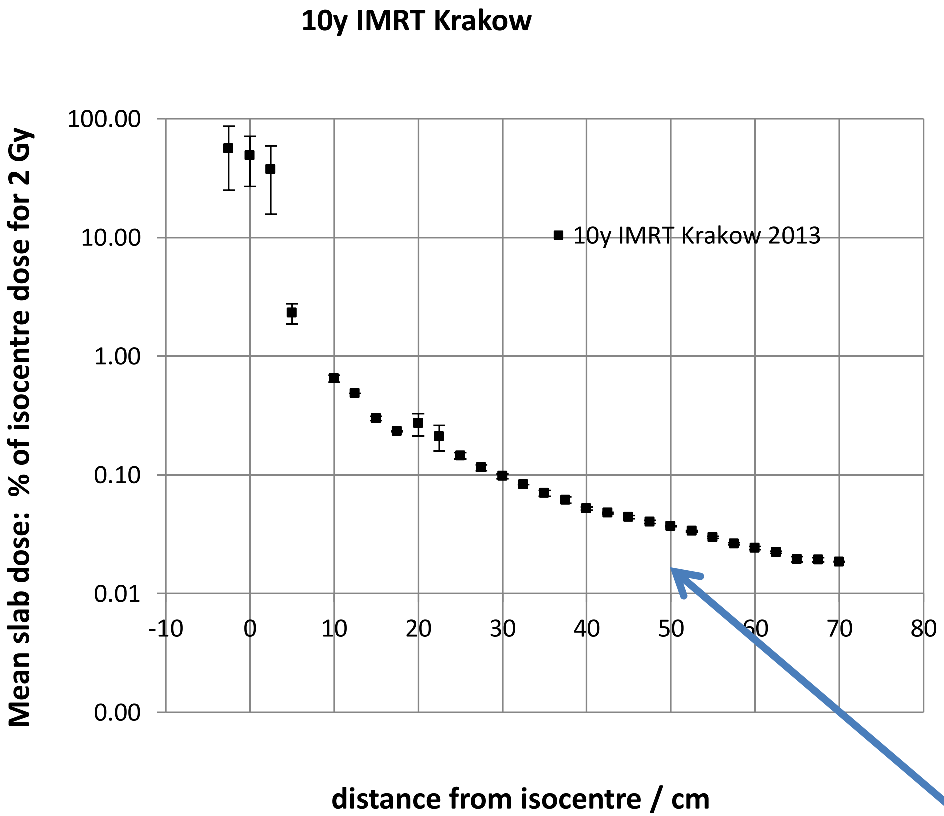
Risks to the irradiated foetus

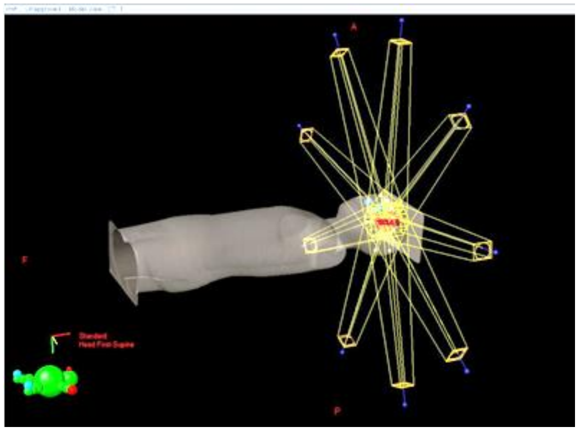
A practical question:

Can we simplify anthropomorphic phantom measurements?

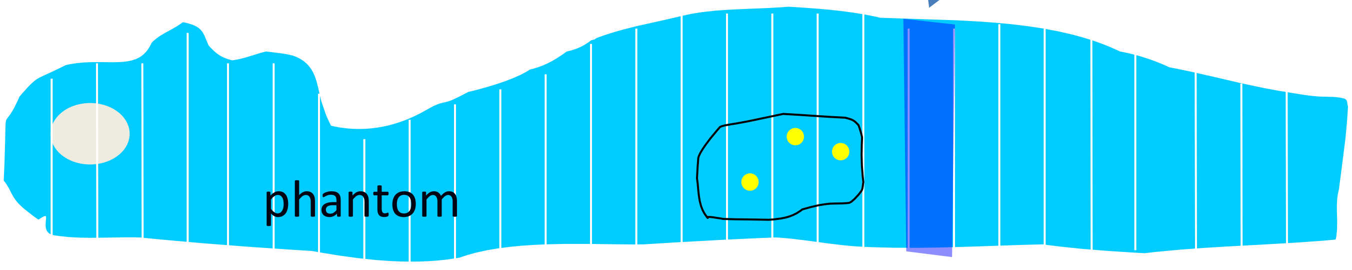


Simplified out-of-field dose estimation



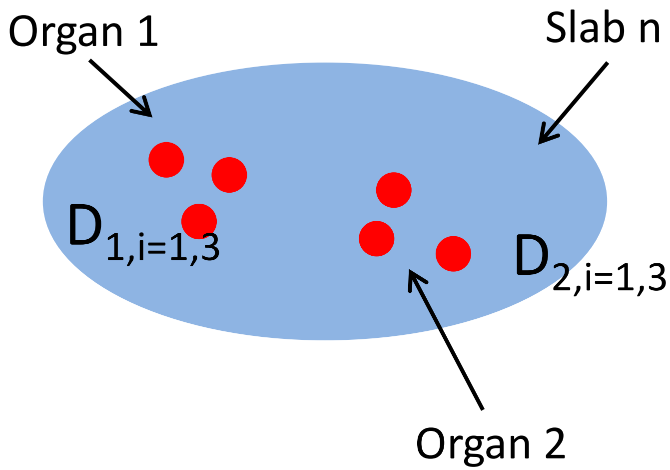


Mean slab dose



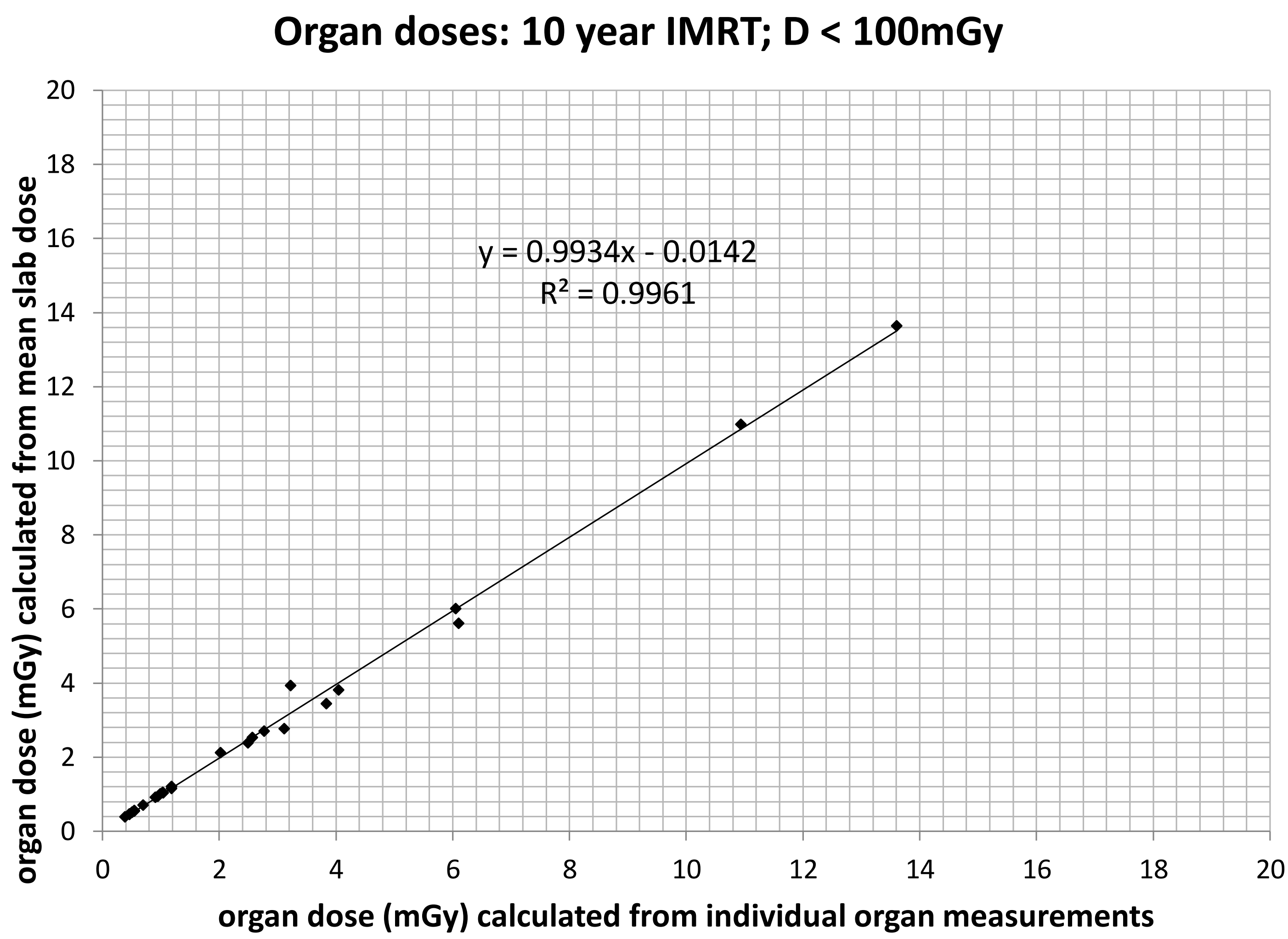
Distance from isocentre

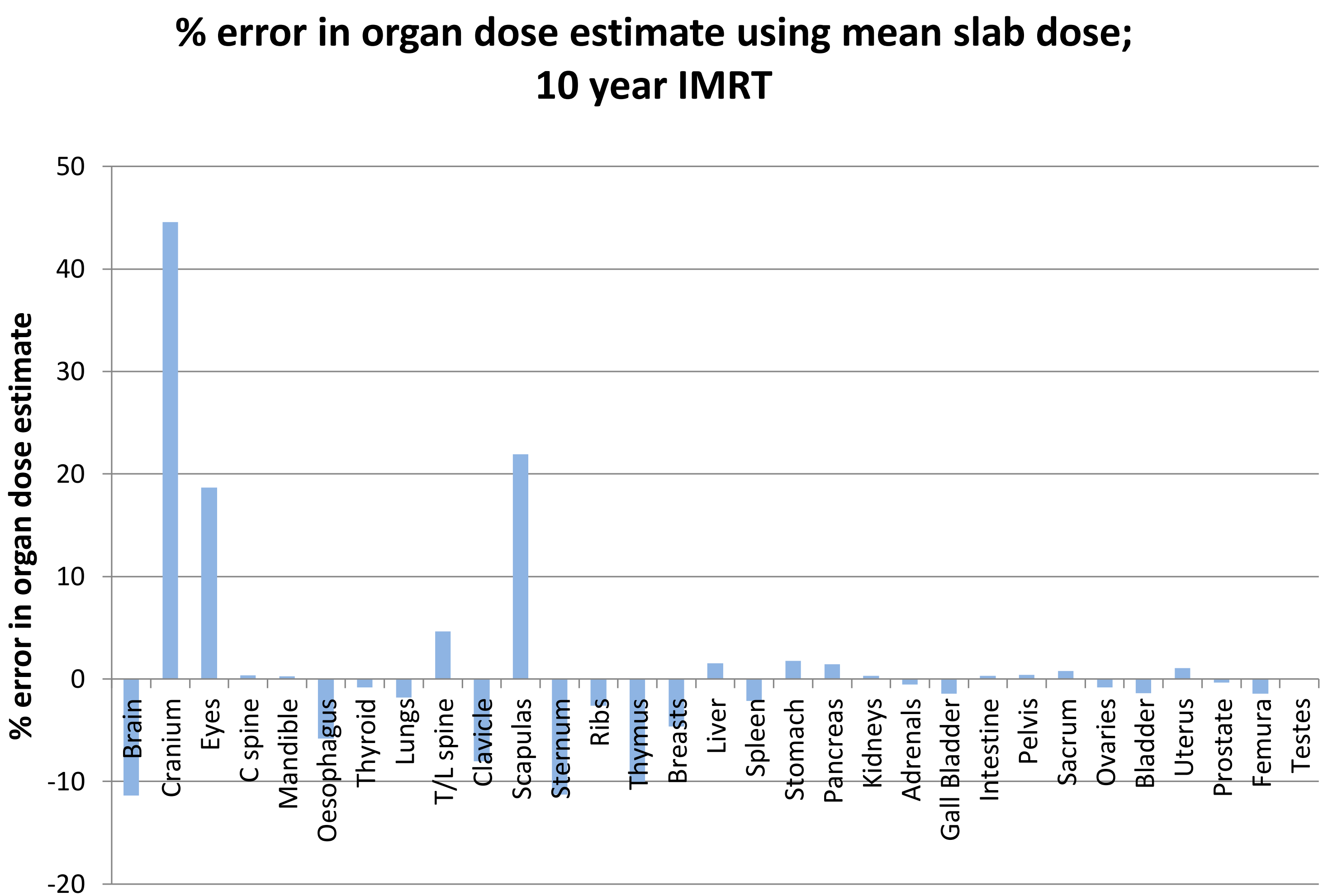
Mean slab dose



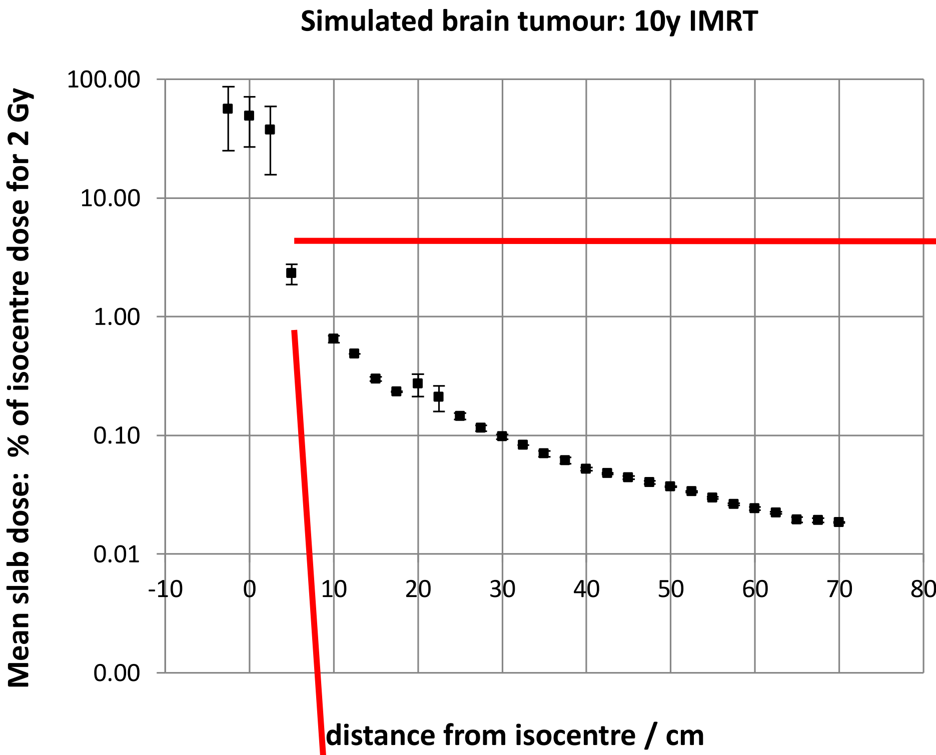
Replace individual dose measurements with the mean slab dose

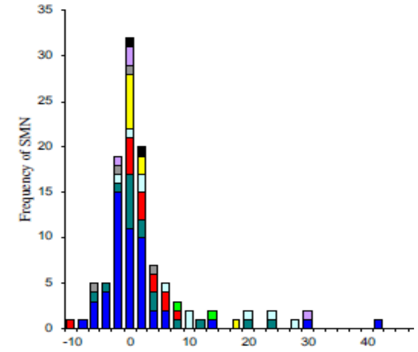
Example	
Mean dose to organ 1, from measurements, $\bar{\boldsymbol{D}}$	Mean dose to organ 1 based on mean slab dose,
$$\bar{D} = \frac{1}{3}\sum_{i=1}^{3} D_{1,i}$$	$$\bar{D}_{slab} = \frac{1}{6}\left[\sum_{i=1}^{3} D_{1,i} + \sum_{i=1}^{3} D_{2,i}\right]$$


Organ doses: 10 year IMRT; D < 100mGy
y = 0.9934x - 0.0142
R² = 0.9961
organ dose (mGy) calculated from mean slab dose
organ dose (mGy) calculated from individual organ measurements
0
2
4
6
8
10
12
14
16
18
20

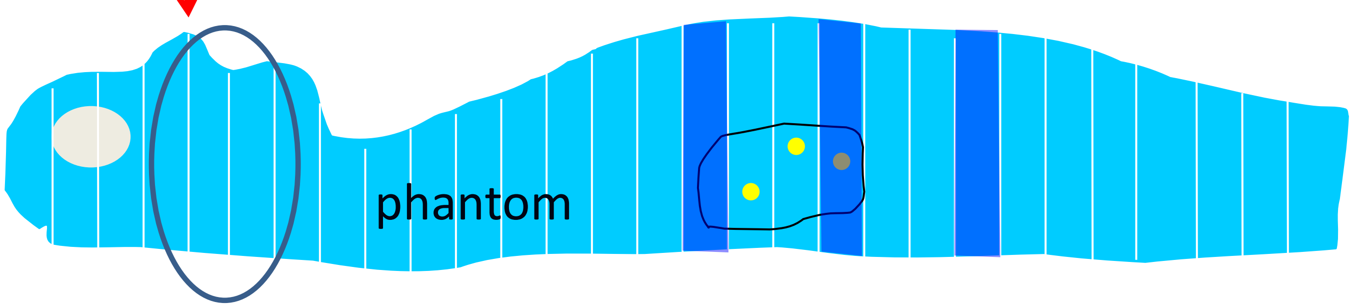

% error in organ dose estimate using mean slab dose;
10 year IMRT
% error in organ dose estimate
50
40
30
20
10
0
-10
-20
Brain
Cranium
Eyes
C spine
Mandible
Oesophagus
Thyroid
Lungs
T/L spine
Clavicle
Scapulas
Sternum
Ribs
Thymus
Breasts
Liver
Spleen
Stomach
Pancreas
Kidneys
Adrenals
Gall Bladder
Intestine
Pelvis
Sacrum
Ovaries
Bladder
Uterus
Prostate
Femura
Testes

Simplified out-of-field dose estimation





For remote organs, measure smaller number of slabs and interpolate?

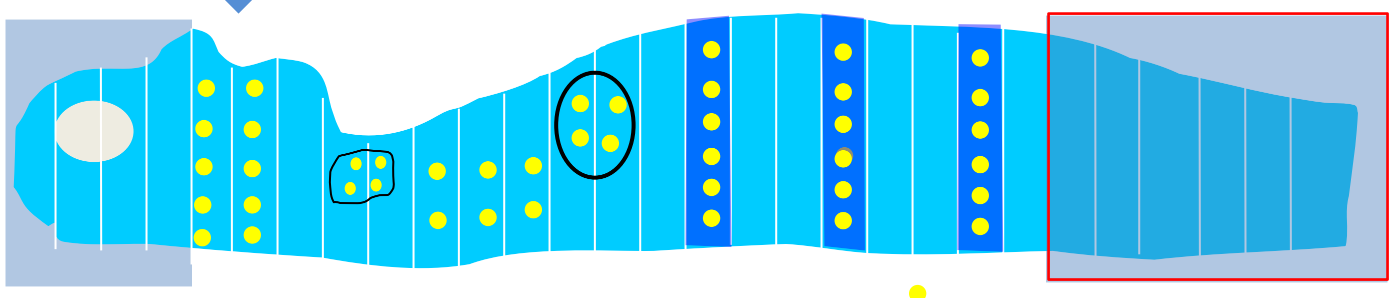


More measurements in this region

Simplified out-of-field dose estimation

- More measurements in this region
- TPS calculations more uncertain
- Validated models

- Organ doses and risk still significant
- If slab dose is uniform, measure mean slab dose and interpolate?



- Use validated TPS
- High dose region
- Accurate dosimetry but uncertain risks

- Slab dose non-uniform
- Specific organ dosimetry
- Validated models

- Low dose region
  Dose estimate sufficient?

General

- Radiotherapy: the opportunity to study late effects of human irradiation

- Radiotherapy offers:
  - a very large worldwide patient cohort
  - planned, controlled and documented irradiations
  - wide range of doses to out-of-field organs

Out-of-field dosimetry

- Basic technology for whole body dosimetry is available:
  - established anthropomorphic phantoms
  - established dosimetry using TLD, RPL, OSL, PADC and bubble detectors
  - some simplification of dosimetry methodology is possible

BUT

- Limited number of measurements per organ
- Insufficient spatial resolution
- Time consuming
- Specific to phantom used

Out-of-field dosimetry

Future developments….

- Mixed field dosimetry in proton and ion radiotherapy
- Small neutron detectors for in-phantom measurements
- Measurements in dose gradients
- Dosimetry of critical sub-structures in OARs

Out-of-field absorbed dose models

Future developments….

- Development of coherent and more widely applicable out-of-field models, verified by measurements
- Refinement and extension of TPS algorithms within a few cm of the field edge

See also in submitted abstracts:

Madkhali et al. The effect of mean dose or voxel-wise calculation in prediction of radiation-induced secondary cancers

Sanchez-Nieto et al Second cancer modelling: a necessary complement to the treatment planning systems

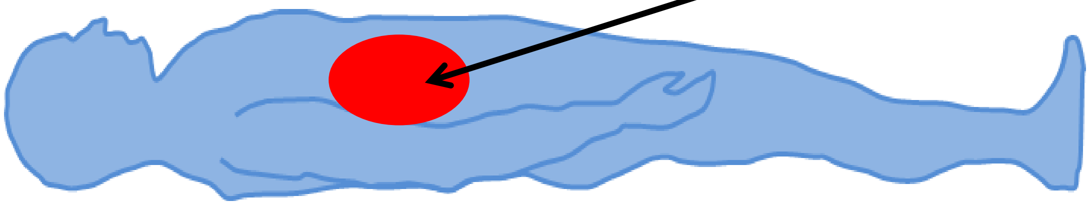
The complete dose specification

- Synthesis of the total dose to radiotherapy patients from all sources for input to epidemiological studies (i.e. out-of-field organ doses from therapy and concomitant imaging procedures) should be developed

Dose-risk models

- The refinement of dose-risk models is important to guide the development of appropriate organ dosimetry (spatial requirements, accuracy….)

The radiation protection case (low doses)

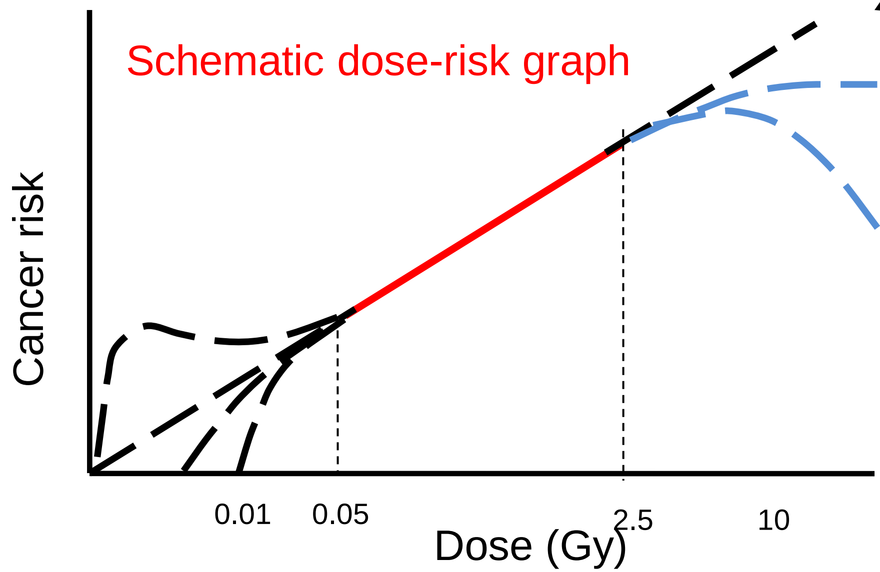


Mean absorbed dose

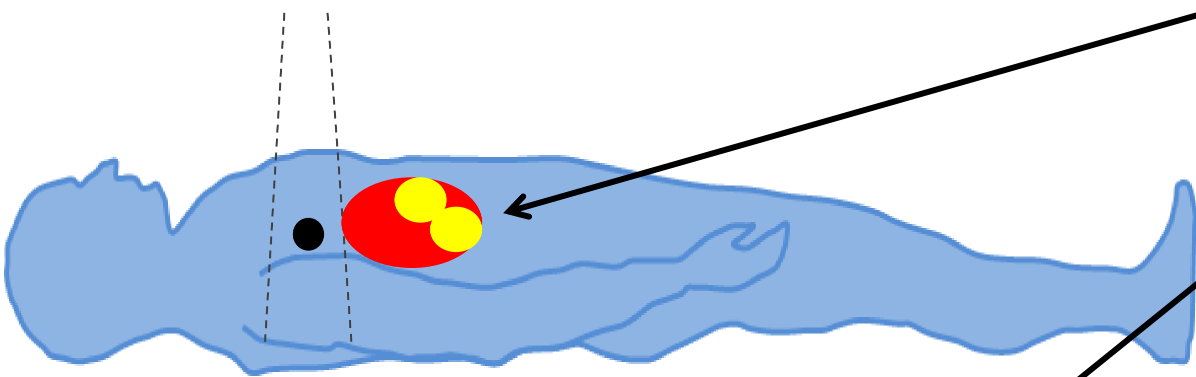
Equivalent dose

Effective dose

Linear dose-risk function



The radiotherapy case (high dose)

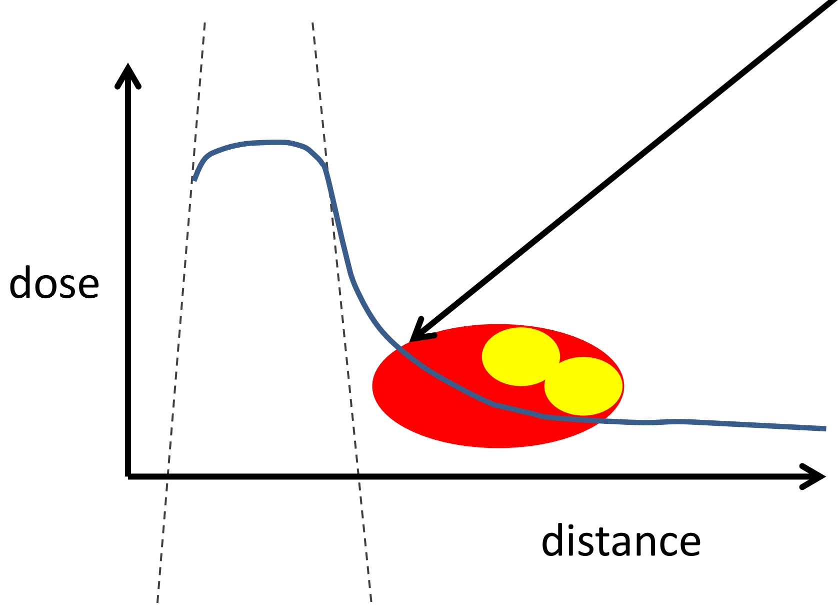


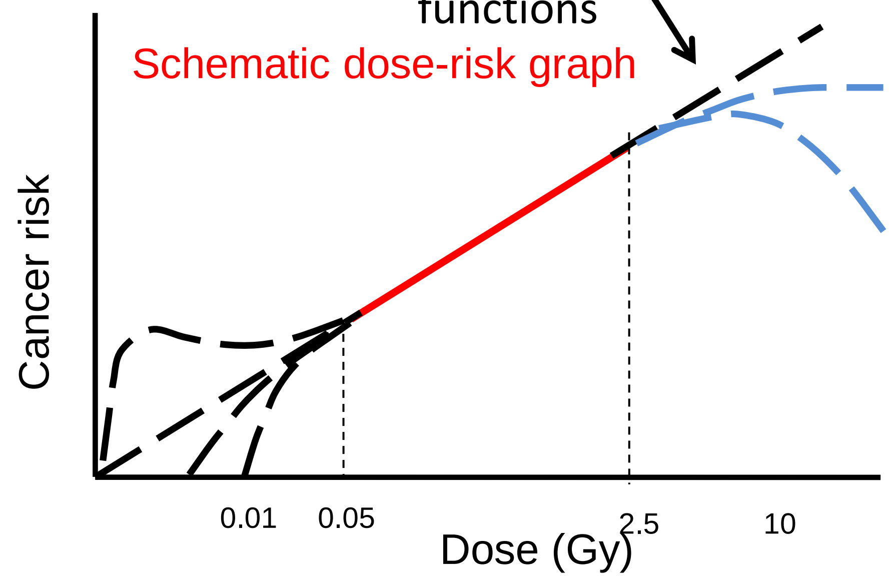
Critical sub-structures (brain & cardiac arteries, GI tract, breast)

Dose gradients

Fractionation

Non-linear dose – risk functions





Risk estimates based on mean dose to the critical organ or tissue:

- acceptable in the context of radiation protection of the population
- not generally applicable for individual medical exposures
- equivalent dose and effective dose are not applicable in radiotherapy

Therefore we need to develop a dosimetry system which takes into account – simultaneously

- **organ sub-structure dosimetry**
- **dose heterogeneities**
- **non-linear dose response**

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