ESTRO School

PRELIMINARY PROGRAMME
Research Masterclass in Radiotherapy Physics
Florence, Italy, 10-13 September, 2017

Sunday 10 September		
	Topic	***Speaker***
08.30 – 09.00	Welcome/Introduction to Masterclass Meeting room Giglio	B. Heijmen
09.00-09.45	Trends and research opportunities in MR imaging in radiotherapy Meeting room Giglio	Uulke van der Heide
09.45-10.30	Trends and research opportunities in PET imaging in radiotherapy Meeting room Giglio	Eirik Malinen
10.30 - 11.00	*Coffee break*	
11.00 - 11.45	Trends and research opportunities in IGRT and adaptive therapy to compensate for anatomical variations Meeting room Giglio	Mischa Hoogeman
11.45 – 12.30	Trends and research opportunities in radiotherapy dosimetry Meeting room Giglio	Hugo Palmans
12.30 - 13.30	*Lunch - Loggiato*	
13.30 - 15.00	Discussion and development of Research proposals Meeting rooms Giglio, Vescovo and Iris	All
15.00 - 15.30	*Coffee break*	
15.30 – 17.00	Discussion and development of Research proposals Meeting rooms Giglio, Vescovo and Iris	All
17.00 – 17.45	Trends and research opportunities in respiratory motion management Meeting room Giglio	Stine Korreman
19.30 -21.30	Welcome drink followed by the dinner at Restaurant La Sosta delle Contesse Via Faenza 111r – 50123 Firenze	All
	Topic	***Speaker***
09.00 - 10.30	Discussion and development of Research proposals Meeting rooms Giglio, Vescovo and Iris	All
10.30 - 11.00	*Coffee break*	
11.00 – 11.45	Trends and research opportunities in treatment planning Meeting room Giglio	Ben Heijmen
11.45 – 12.30	Trends and research opportunities in microbeam radiotherapy Meeting room Giglio	Uwe Oelfke
12.30 - 13.30	*Lunch - Loggiato*	
13.30 – 15.00	Discussion and development of Research proposals Meeting rooms Giglio, Vescovo and Iris	All
15.00 - 15.30	*Coffee break*	
15.30 – 17.30	Discussion and development of Research proposals Meeting rooms Giglio, Vescovo and Iris	All

17.30 – 18.15	Tips and tricks for writing a scientific paper and get it accepted Meeting room Giglio	Claudio Fiorino
20.00 - 21.30	Dinner at Restaurant La Sosta delle Contesse Via Faenza 111r – 50123 Firenze	All
	Topic	***Speaker***
09.00 - 10.30	Discussion and development of Research proposals Meeting rooms Giglio, Vescovo and Iris	All
10.30 - 11.00	*Coffee break*	
11.00 - 11.45	Trends and research opportunities in biophysics in RT Meeting room Giglio	Peter van Luijk
11.45 – 12.30	Trends and research opportunities in dose response modelling Meeting room Giglio	Claudio Fiorino
12.30 - 13.30	*Lunch – Loggiato*	
13.30 - 14.15	Tips and tricks for writing a successful grant proposal Meeting room Giglio	Uulke van der Heide
14.15 - 15.00	Trends and research opportunities in brachytherapy physics Meeting room Giglio	Kari Tanderup
15.00 - 15.30	*Coffee break*	
15.30 – 17.30	Discussion and development of Research proposals Meeting rooms Giglio, Vescovo and Iris	All
20.00 - 21.30	Dinner at Restaurant La Sosta delle Contesse Via Faenza 111r – 50123 Firenze	All
	Topic	***Speaker***
09.00 - 10.30	Discussion and development of Research proposals Meeting rooms Giglio, Vescovo and Iris	All
10.30 - 11.00	*Coffee break*	
11.00 - 11.45	Ion beam therapy Meeting room Giglio	Oliver Jäkel
11.45 – 12.30	Course evaluation Meeting room Giglio	All

ESTRO Research Masterclass in Radiotherapy Physics benefitted from an unrestricted educational grant from Elekta

Erasmus MC
Universitair Medisch Centrum Rotterdam

Cancer Institute

ESTRO Research Masterclass in Radiotherapy Physics
Florence, Italy, 10-13 September

Ben Heijmen

Participants

Italy	6
UK	5
Netherlands	4
Sweden	1
Denmark	1
Germany	1
Turkey	1
Israel	1
Brazil	1
Ireland	1
Poland	1
New Zealand	1
TOTAL	24

Alba Magallon	Netherlands	Rotterdam
Alberto Ciarmatori	Italy	Senigallia (Ancona)
Alex Grimwood	UK	London
Andre' Haraldsson	Sweden	Lund
Bas Schipaanboord	The Netherlands	Rotterdam
Bernardo Batista	Brazil	Sao Paulo
Davide Cusumano	Italy	Ragusa
Elisabeth Forde	Ireland	Dublin
Elisabetta Cagni	Italy	Reggio Emilia
Emily Johnstone	UK	Leeds
Jamin Martin	New Zealand	Dunedin
Janita van Timmeren	The Netherlands	Maastricht
Luisa Altabella	Italy	Milan
Lvovich Ilya	Israel	Haifa
Maria Luisa Belli	Italy	Varese
Mariaconcetta Longo	Italy	Messina
Marta Gizynska	Poland	Warsaw
Martijn Kusters	The Netherlands	Malden
Martin Menten	UK	Sutton
Nur Kodaloglu	Turkey	Ankara
Sarah Brueningk	UK	Sutton
Sarah Mason	UK	Sutton
Sofia Spampinato	Denmark	Aarhus
Toseef Khawaja	Germany	Munich

Course Director
Ben Heijmen
Medical Physicist
Erasmus Medical Centre
Rotterdam (NL)

Teachers
Claudio Fiorino
Medical Physicist
San Raffaele Scientific Institute
Milan (IT)

Mischa Hoogeman
Medical Physicist
Erasmus Medical Centre
Rotterdam (NL)

Oliver Jäkel
Medical Physicist
German Cancer Research Centre
Heidelberg University
Heidelberg (DE)

Stine Korreman
Medical Physicist
Roskilde University
Roskilde (DK)

Eirik Malinen
Medical Physicist
DNR - Norwegian Radium Hospital
Oslo (NO)

Uwe Oelfke
Medical Physicist
The Royal Marsden NHS Foundation Trust
London (UK)

Hugo Palmans
Medical Physicist
National Physical Laboratory
Teddington (UK)

Dirk de Ruysscher
Radiation Oncologist
MAASTRO
Maastricht (NL)

Kari Tanderup
Medical Physicist
Aarhus University
Aarhus (DK)

Uulke van der Heide
Medical Physicist
UMC Utrecht
Utrecht (NL)

Peter van Luijk
Medical Physicist
University Medical Centre Groningen
Groningen (NL)

ESTRO:
- Laura La Porta
- Christine Verfaillie

AIFM:
- Seranella Russo
- Mauro Iori
- Michele Stasi

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COURSE AIMS

- To improve proposals submitted by participants for a research project or a scientific paper, under the supervision of renowned scientists in a safe and friendly atmosphere.
- To highlight current trends and important unresolved issues with future research opportunities.
- To discuss general aspects of scientific research, e.g. paper and grant writing.

programme

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PROGRAMME PROJECT DISCUSSIONS

Sunday		
13.30 - 15.00	ROUND 1	*1st presentations and discussions (~30 min/project)*
15.30 - 17.00	ROUND 1	
Monday		
09.00 - 10.30	ROUND 1	*Adjust projects/pptx 1-to-1 discussions*
13.30 - 15.00	ROUND 1	
15.30 - 17.30	ROUND 1	*2nd presentations and discussions and adjust*
Tuesday		
09.00 - 10.30	ROUND 1	*Adjust projects/pptx*
15.30 - 17.30	ROUND 2	*3rd presentations and discussions*
Wednesday		
09.00 - 10.30	ROUND 2	

	1st round	2nd round
Alba Magallon	B	C
Alberto Ciarmatori	B	A
Alex Grimwood	A	C
Andre' Haraldsson	B	A
Bas Schipaanboord	A	C
Bernardo Batista	B	C
Davide Cusumano	A	C
Elisabeth Forde	C	B
Elisabetta Cagni	B	C
Emily Johnstone	A	B
Jamin Martin	C	A
Janita van Timmeren	C	A
Luisa Altabella	C	A
Lvovich Ilya	B	A
Maria Luisa Belli	C	B
Mariaconcetta Longo	C	A
Marta Gizynska	A	B
Martijn Kusters	B	A
Martin Menten	B	C
Nur Kodaloglu	A	B
Sarah Brueningk	C	B
Sarah Mason	A	C
Sofia Spampinato	C	B
Toseef Khawaja	A	B

teachers	team	room
Uwe, Mischa, Uulke, Eirik	A	Iris
Stine, Ben, Hugo, Oliver	B	Giglio
Claudio, Peter, Kari, (Dirk)	C	Vescovo

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- What is your message?
- Why would people like to know about this?

LEARNING OUTCOMES

In attending this Masterclass, participants will be able to:

- Enhance the quality of research projects concerning novelty, potential impact, urgency, and feasibility and risk.
- Effectively discuss novel research projects with colleagues to maximise scientific value.
- Discuss current trends and research opportunities in radiotherapy physics and related fields.

OTHER ADDED VALUE

- Go home with a solid project
- Develop their network by meeting new researchers from Europe and beyond and grow scientific/mentoring relationships.

ititute

Social activities

- Tonight: Welcome drink
- All days: common coffee breaks, lunches
- Each evening: common dinner
- After dinner?

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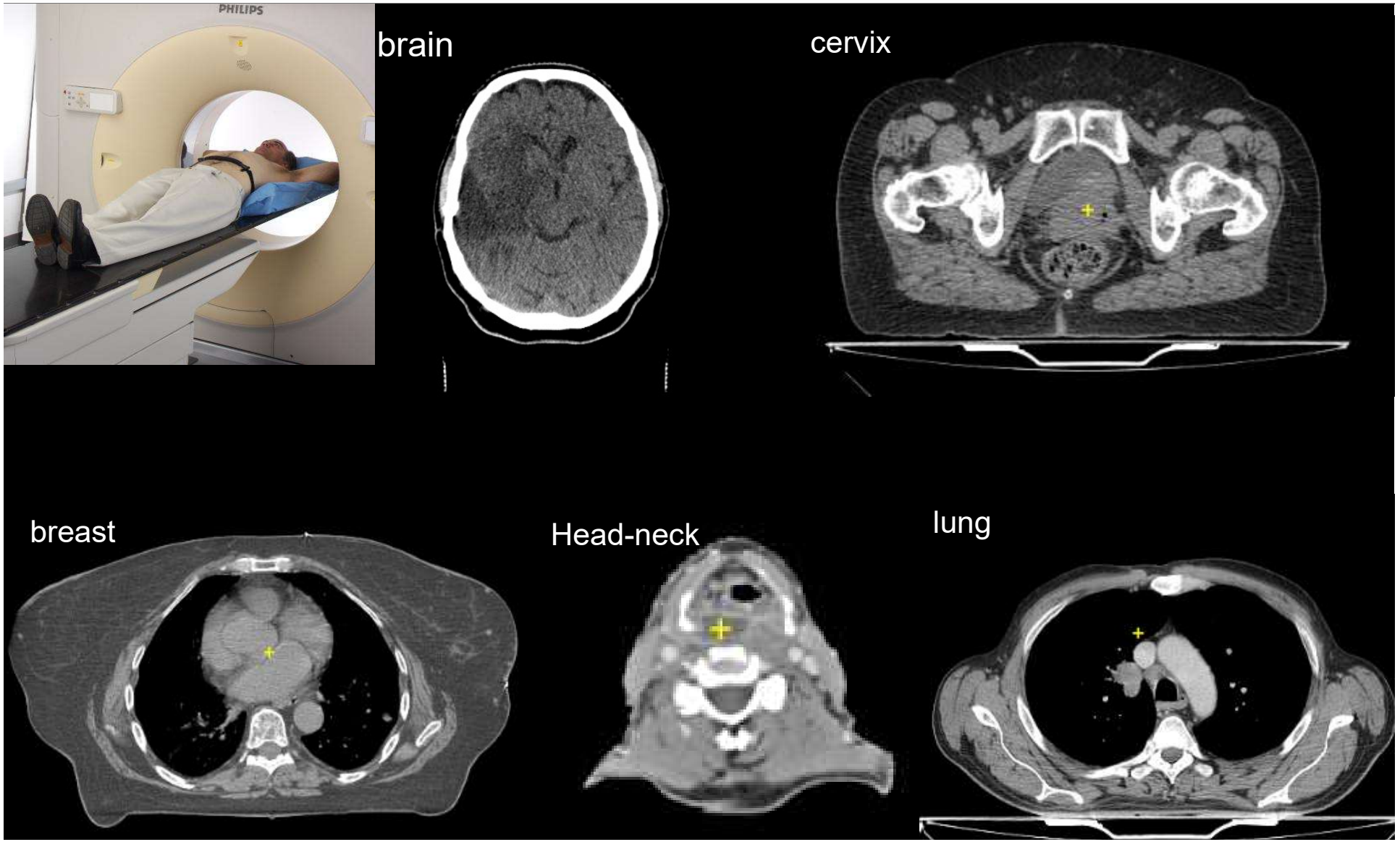
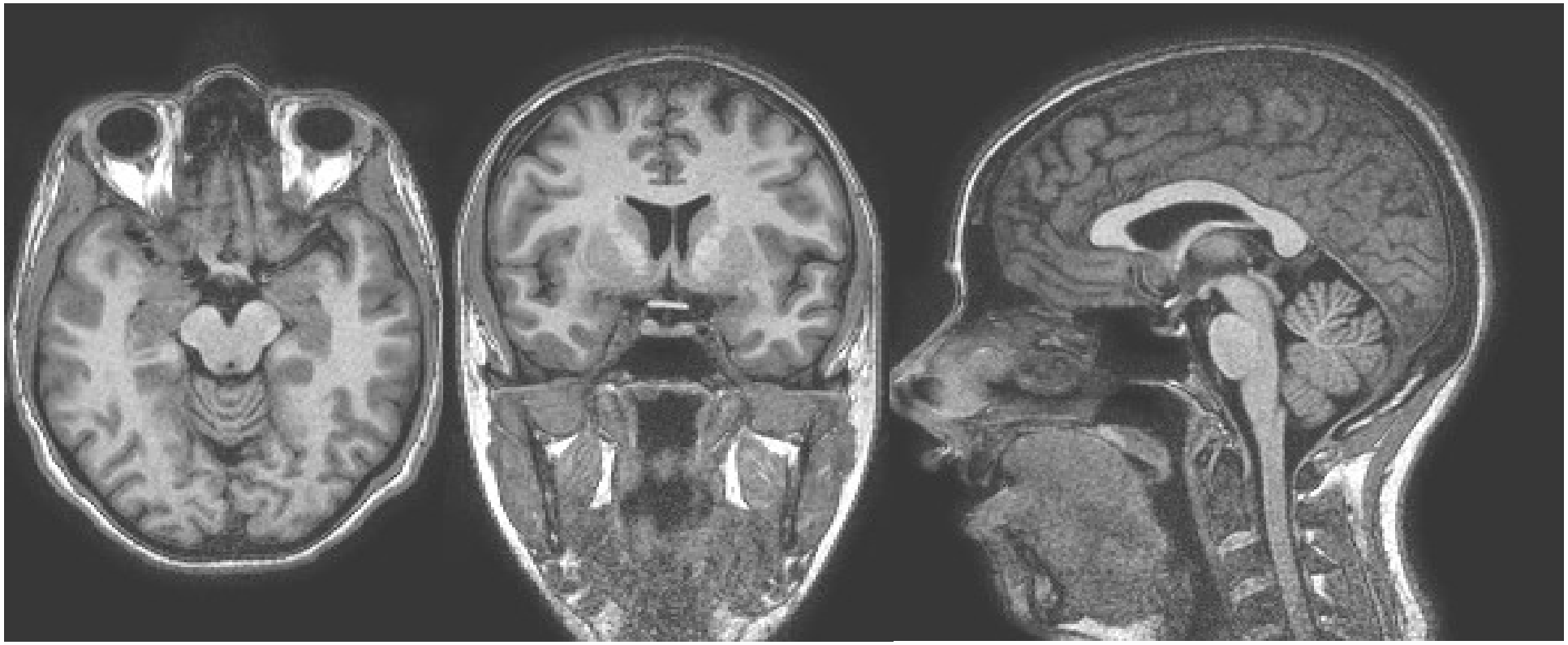
Trends and research opportunities in MR imaging in radiotherapy

Uulke A. van der Heide

Radiotherapy planning is to date based on CT images



MRI has superior soft-tissue contrast



T1 3D-TFE sequence of healthy volunteer

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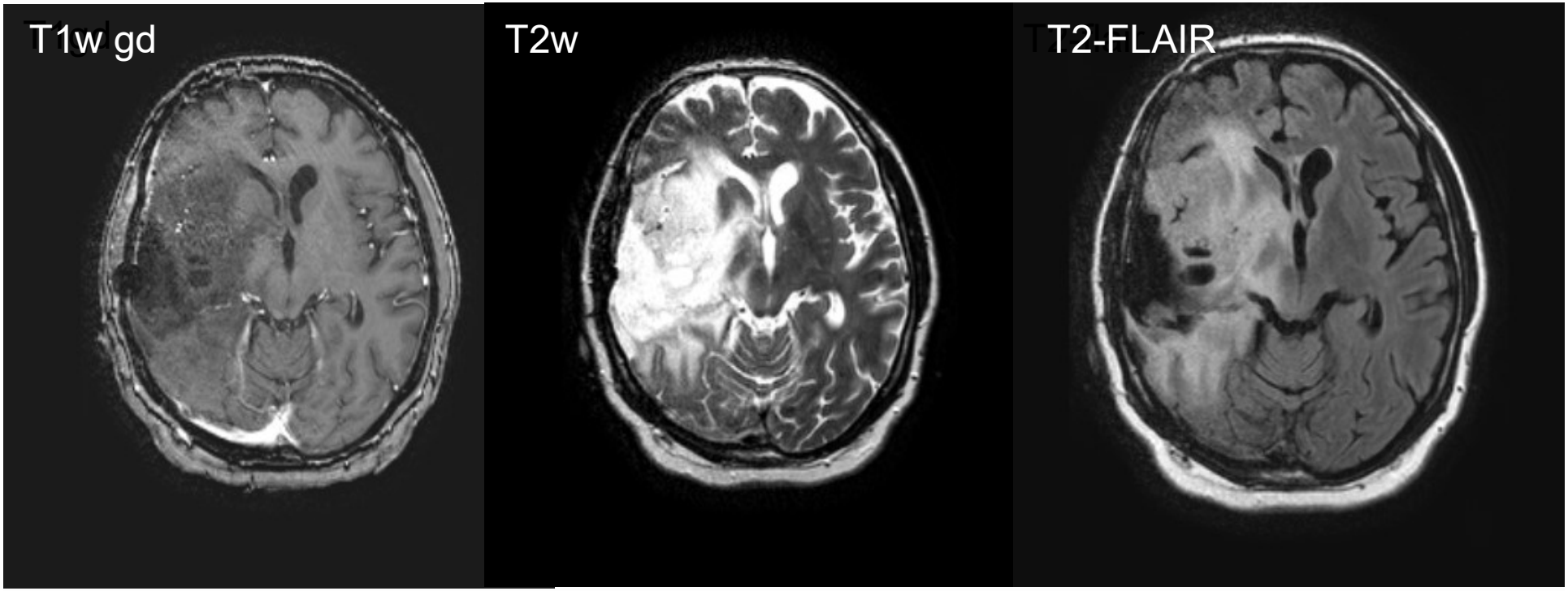
MRI has a large versatility in contrasts



patient with glioblastoma multiforme

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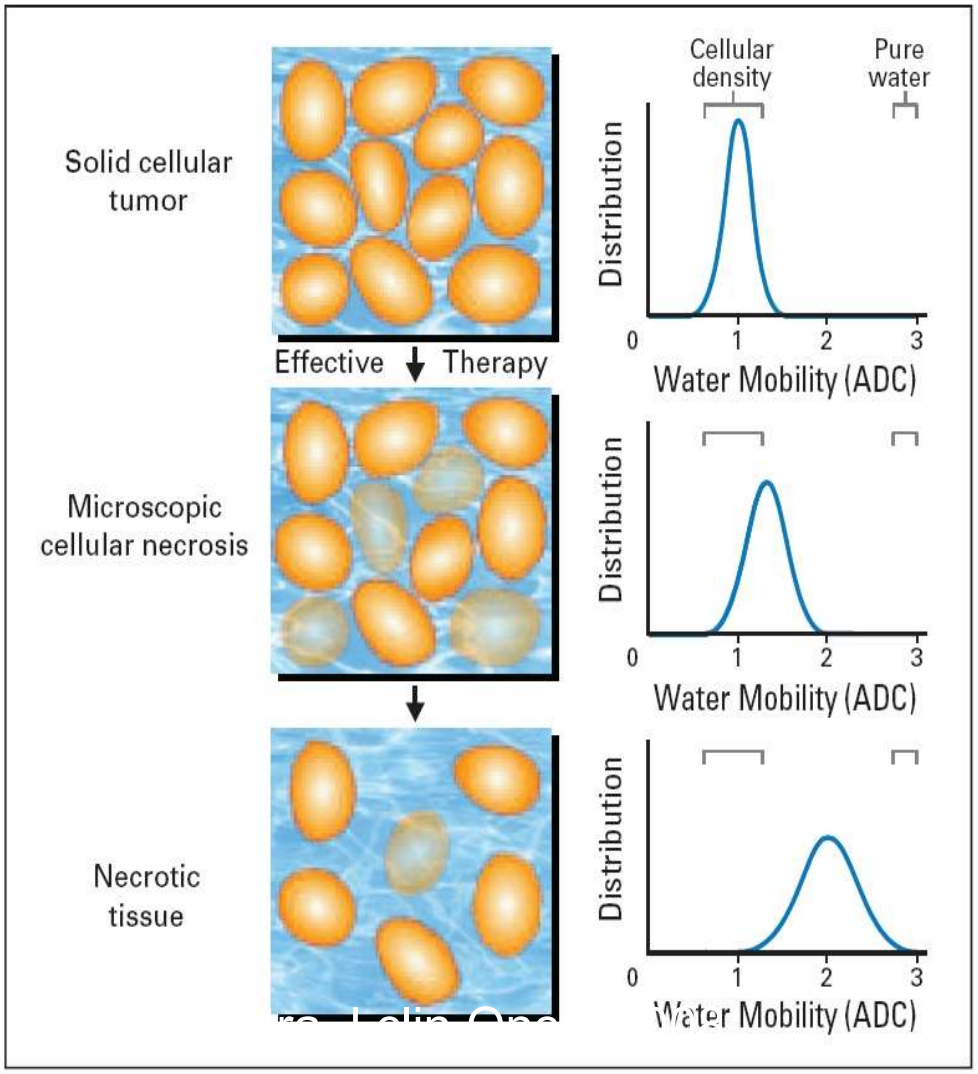
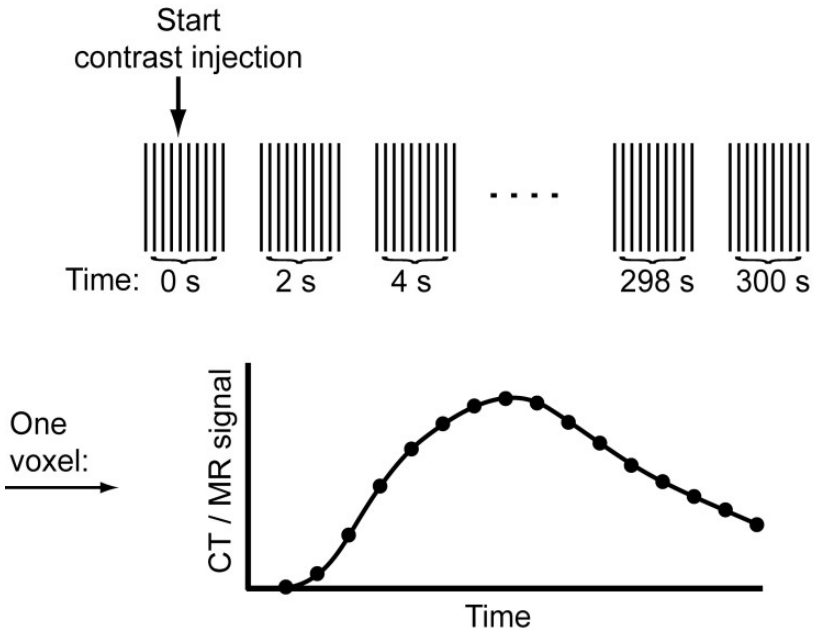
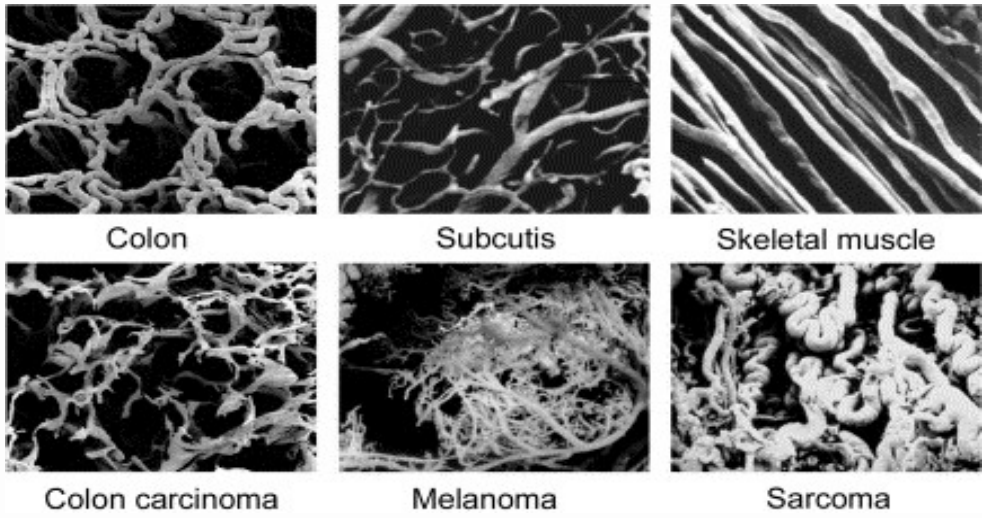
Diffusion-Weighted MRI (DWI)

- Measures the mobility of water
  - Apparent Diffusion Coefficient (ADC)
- Tissue characterization
  - high cellularity, tissue disorganisation, high extracellular space tortuosity
- Monitoring treatment response
  - vascular changes and cellular death ↑ ADC

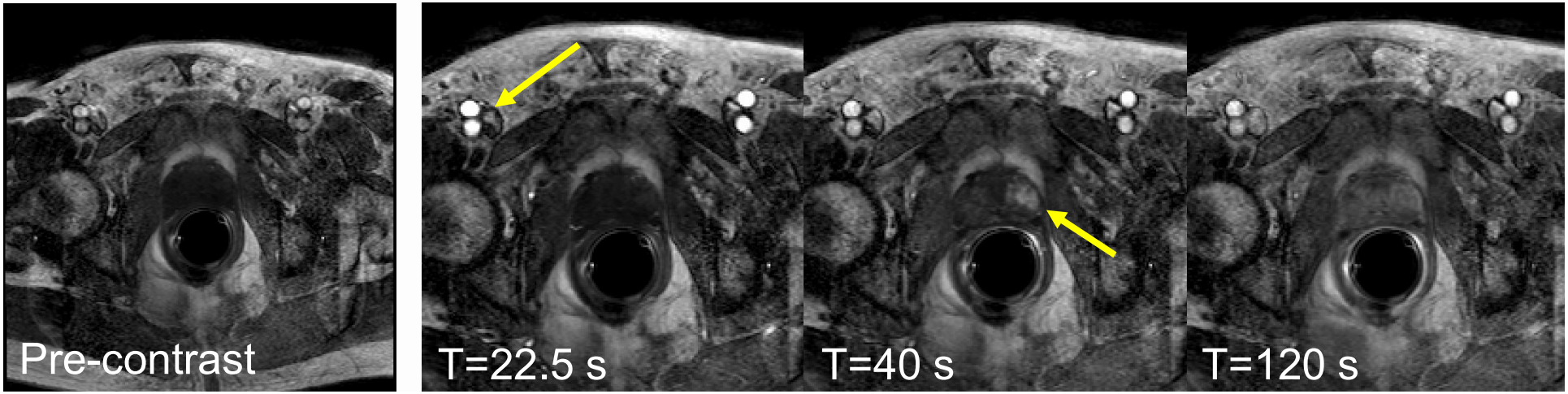


Dynamic Contrast-Enhanced (DCE) MRI





Vaupel, 2004; Semin. Radiat. Oncol. 14:198-206



functional imaging with MRI

Cell density, microanatomy

- **DWI, DTI**

Perfusion, permeability of microvasculature

- **DSC-MRI, DCE-MRI**

Cell membrane synthesis

- **MRSI (choline)**

Metabolism

- **^{31}P-MRSI**

Hypoxia

- **R2* (BOLD), MRSI (lactate)**

Mechanical rigidity

- **MR elastography (Young's modulus)**

pH

- **Chemical exchange saturation transfer (CEST) MRI**

Temperature

- **Proton resonance frequency shift imaging**

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Imaging in Radiotherapy

- Treatment planning and evaluation
- MR-guided radiotherapy

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MRI for treatment planning and evaluation

- Tumor delineation
- Tissue characterization
- Response prediction
- Assessment of response to treatment
- Geometrical accuracy
- Image registration

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Tumor delineation

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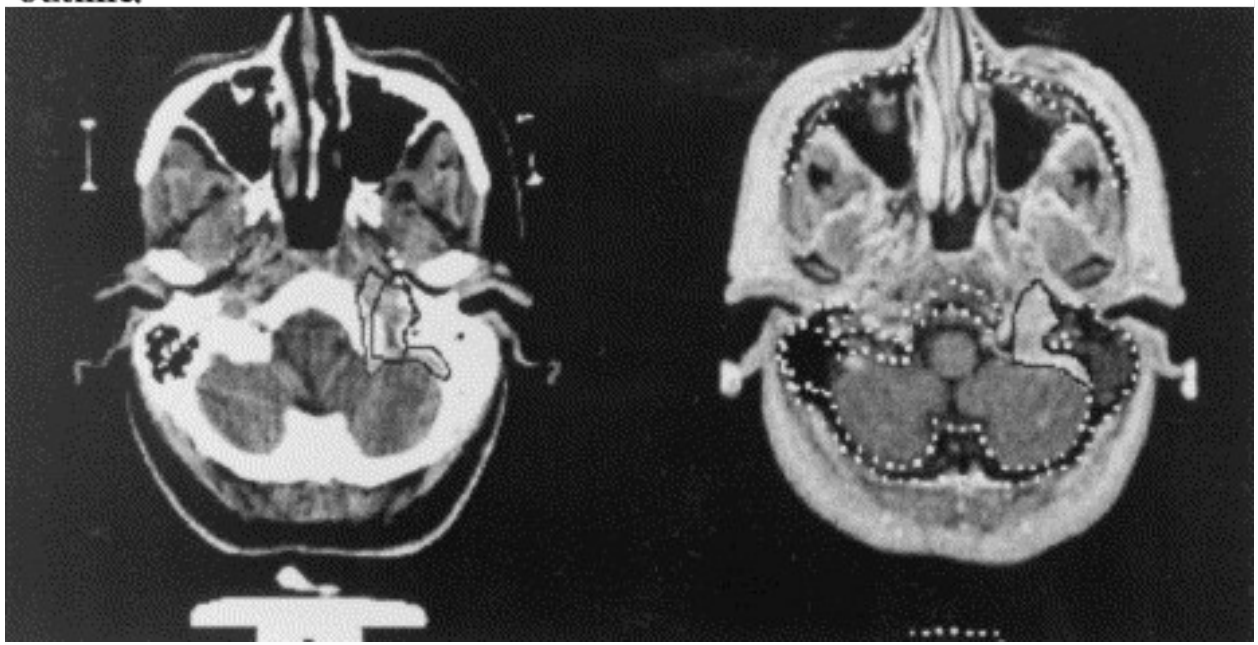
Impact of MRI on target definition

Direction	Scalar difference (mm)		Vector difference (mm)	
	Mean ± 1SD	Range	Mean ± 1SD	Range
Left	6.0 ± 7.0	0.6–29.7	3.3 ± 8.5	(−)9.1–29.7
Right	3.3 ± 2.5	0.7–13.1	(−)0.3 ± 3.8	(−)13.1–10.3
Anterior	4.9 ± 3.9	0.6–19.8	1.1 ± 5.8	(−)11.2–19.8
Posterior	4.5 ± 5.0	0.5–24.6	1.5 ± 6.4	(−)10.4–24.6

(−) indicates the extent of the MR outline is less than that of the CT outline.



CT MRI

Comparison of delineation of meningioma on CT and MRI

Improved visualization of tumor in bone leads to larger volumes on MRI

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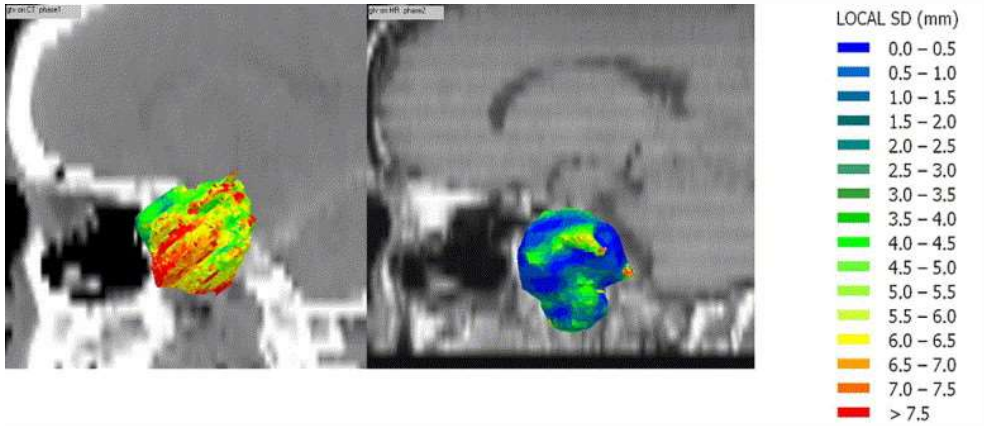
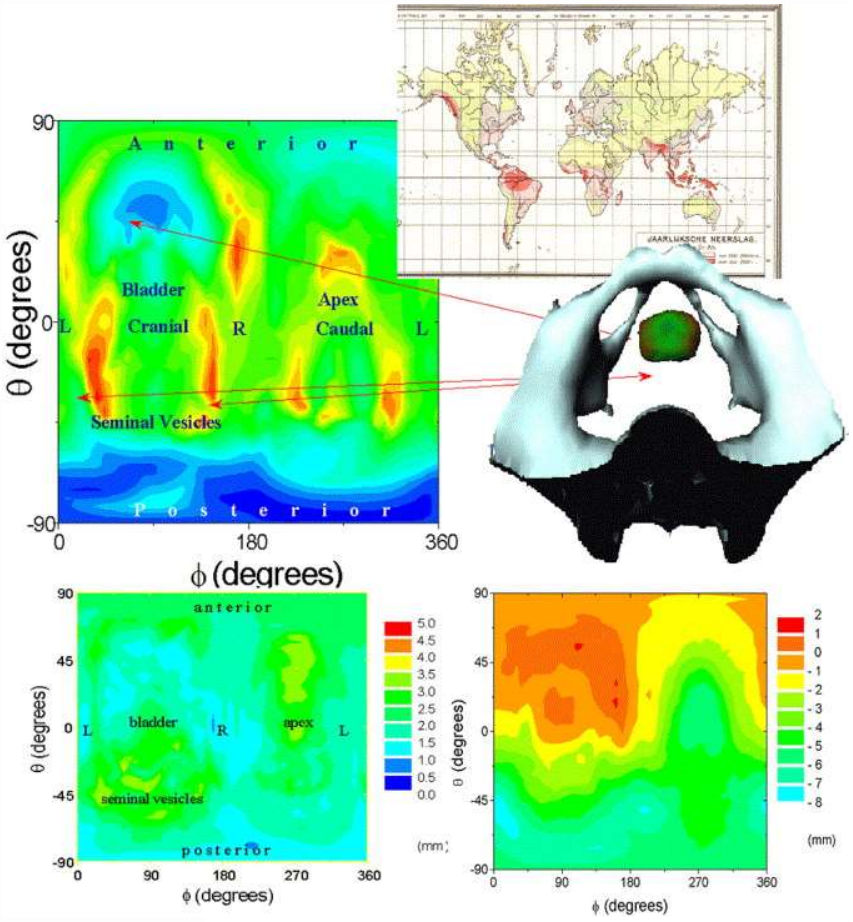
Khoo et al. 2000; Int. J. Radiat. Oncol. Biol. Phys. 46:1309-1317

Impact of MRI on target definition



Inter-observer variation

Delineation of nasopharynx tumor
Left: CT, with MRI available, not fused
Right: CT, with fused MRI

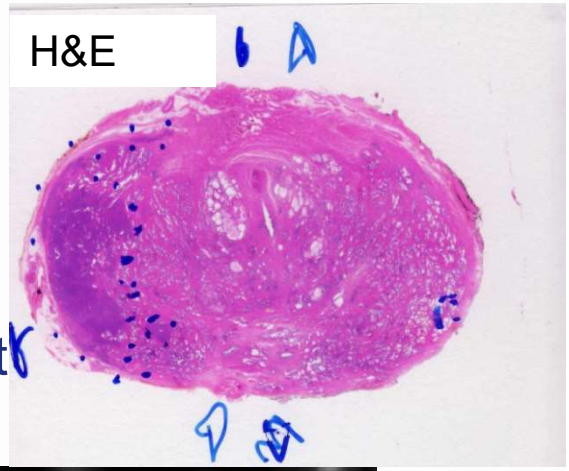


Significant differences in delineation of prostate on CT and MRI

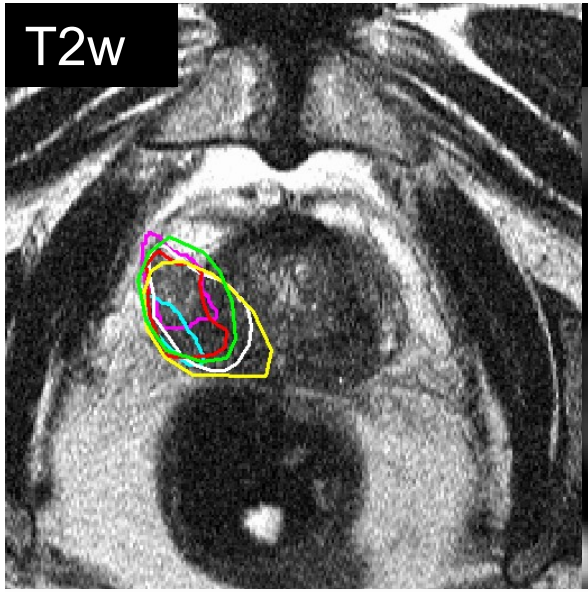
Rasch et al. 2005; Semin. Radiat. Oncol. 15:136-145

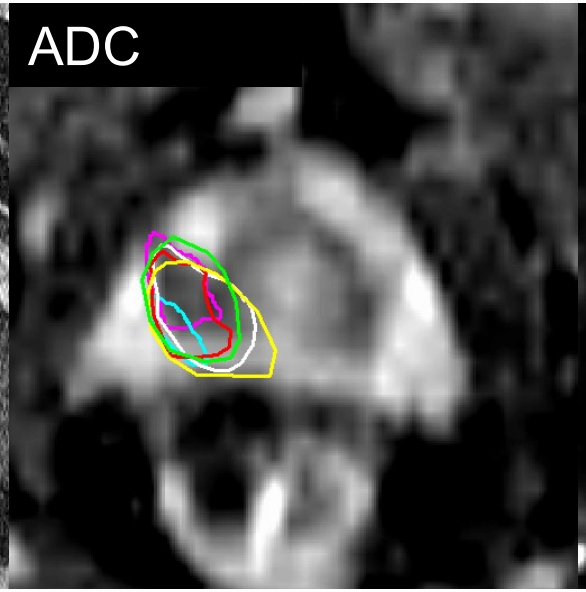
Delineation variability

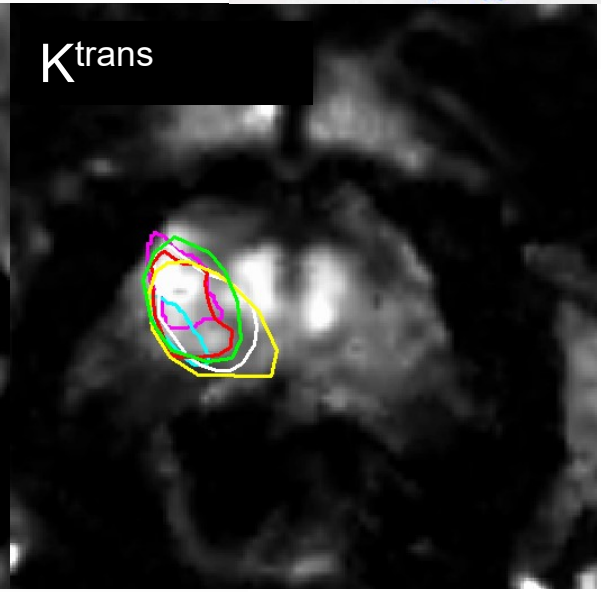
- Even when combining multiple imaging modalities, variation between observers is large



- 6 teams of a radiation oncologist and a radiologist delineated prostate tumors on mp-MRI







Steenbergen et al. Radiother Oncol. 2015;115:186-90

Tissue classification

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Computer aided tumor detection

- Tumor detection
  - Localize the tumor
- Tumor delineation
  - Identify the boundary of the tumor
- Prescription for dose painting
  - Identify the likelyhood that a voxel contains tumor;

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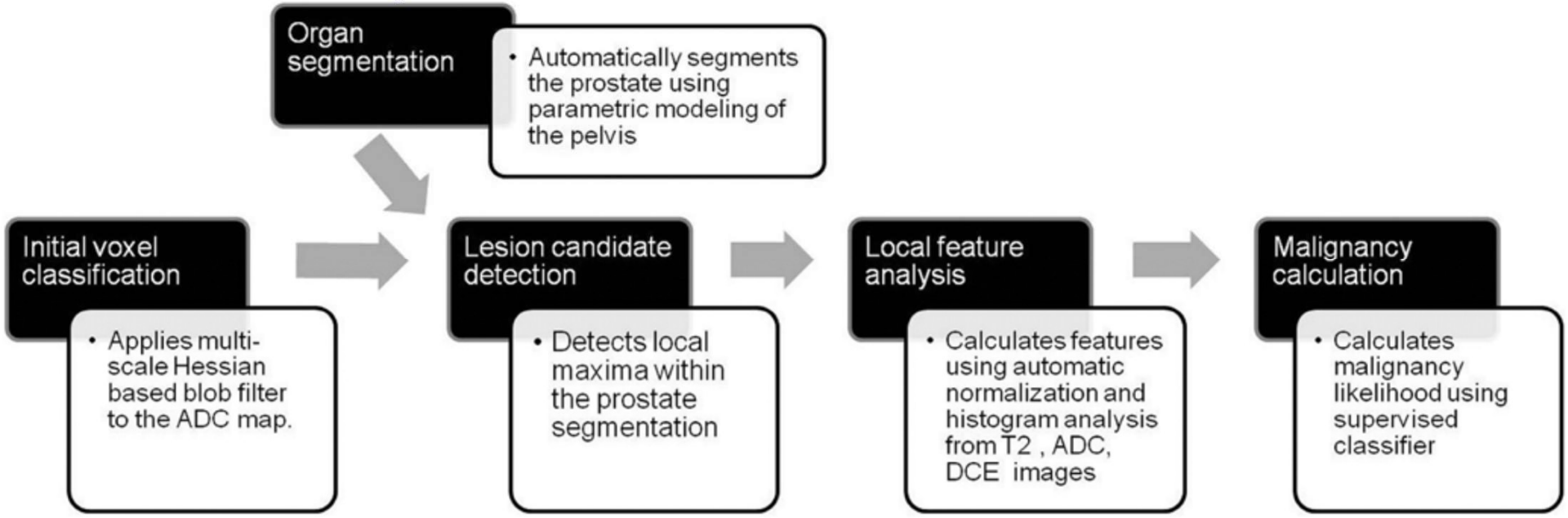
Computer aided tumor detection



- Automatic detection of cancer-suspicious regions in the prostate
- Detect all tumor regions to select the most aggressive part of the tumor

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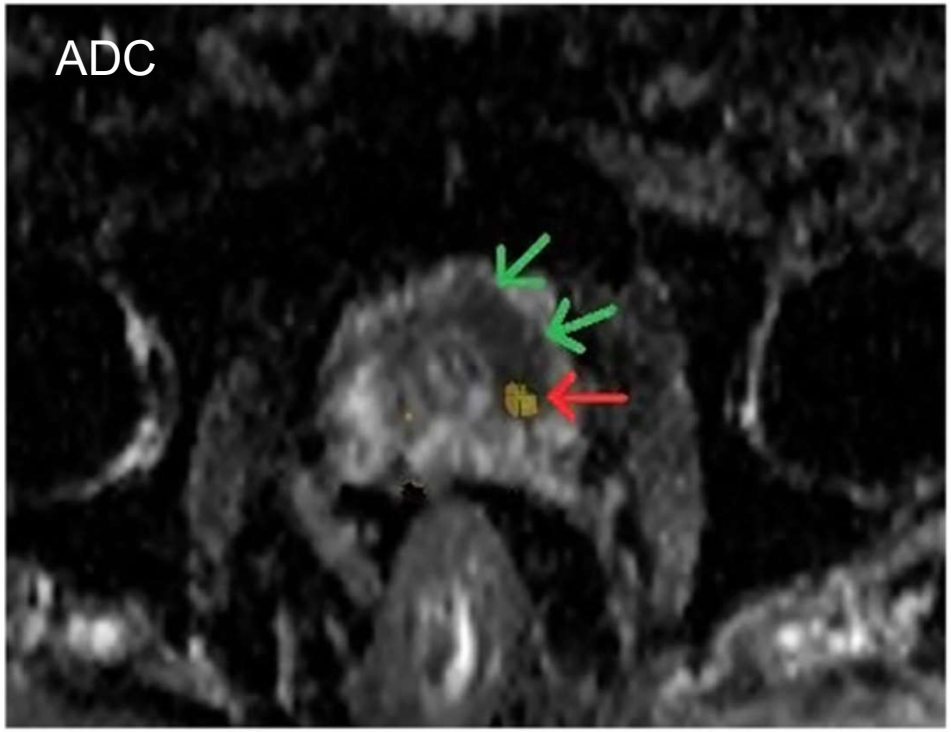
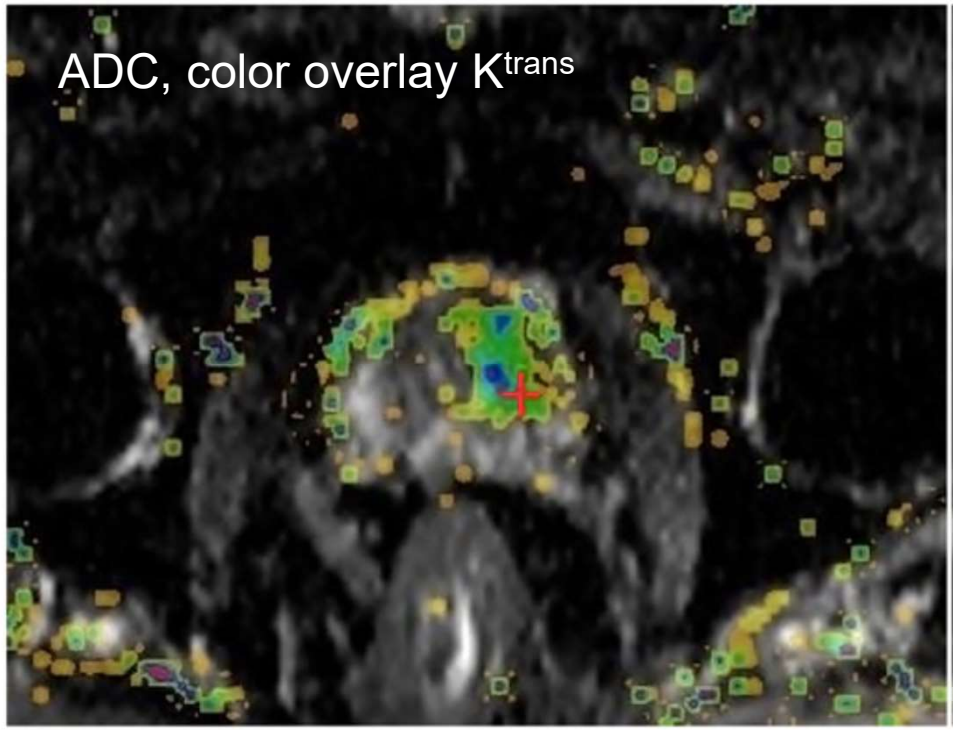
Vos et al. Phys. Med. Biol. 2012; 57:1527-1542

Computer aided tumor detection

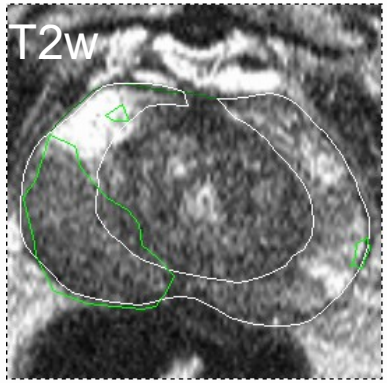


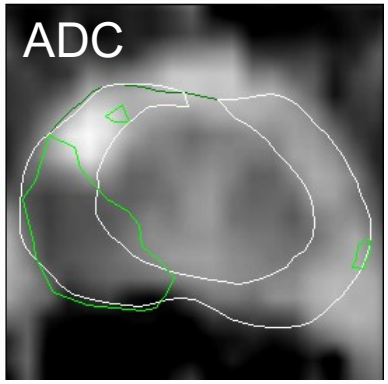


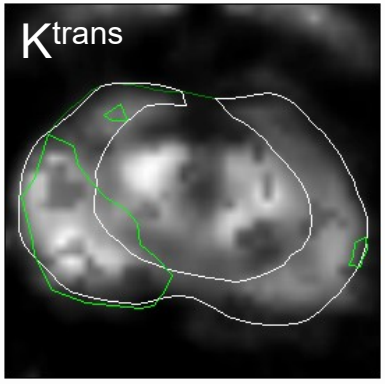
- Identify ‘blob-like regions’ in the ADC map
- Select regions within prostate
- Select lesion candidates based on peak likelyhood value
- Identify heterogeneity within tumor

Vos et al. Phys. Med. Biol. 2012; 57:1527-1542

Computer-aided detection of tumor

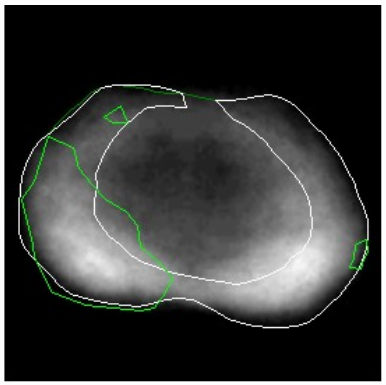






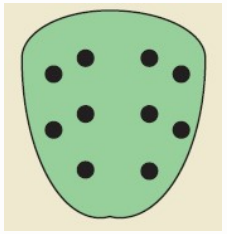
MRI data

+

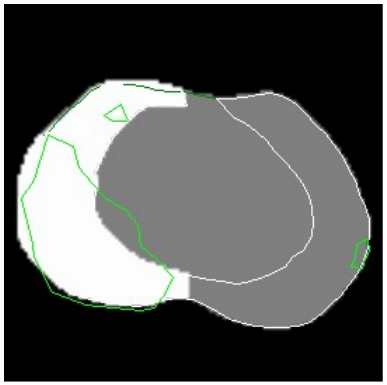


Prostate atlas based on 158 radical prostatectomy specimen *

* Zhan et al. 2007;*26*(6) 779-788



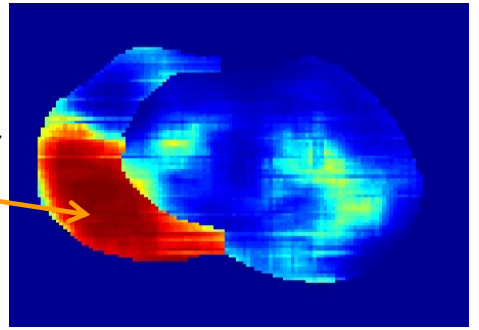
Biopsy reports

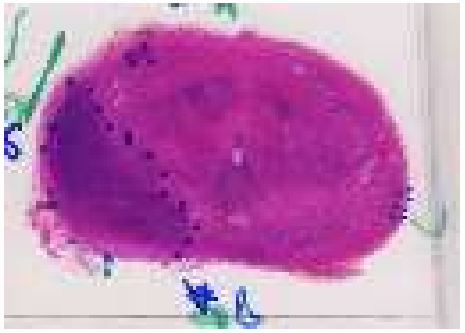


Biopsy Map

→

Detected tumor area in peripheral zone





H&E Staining Image

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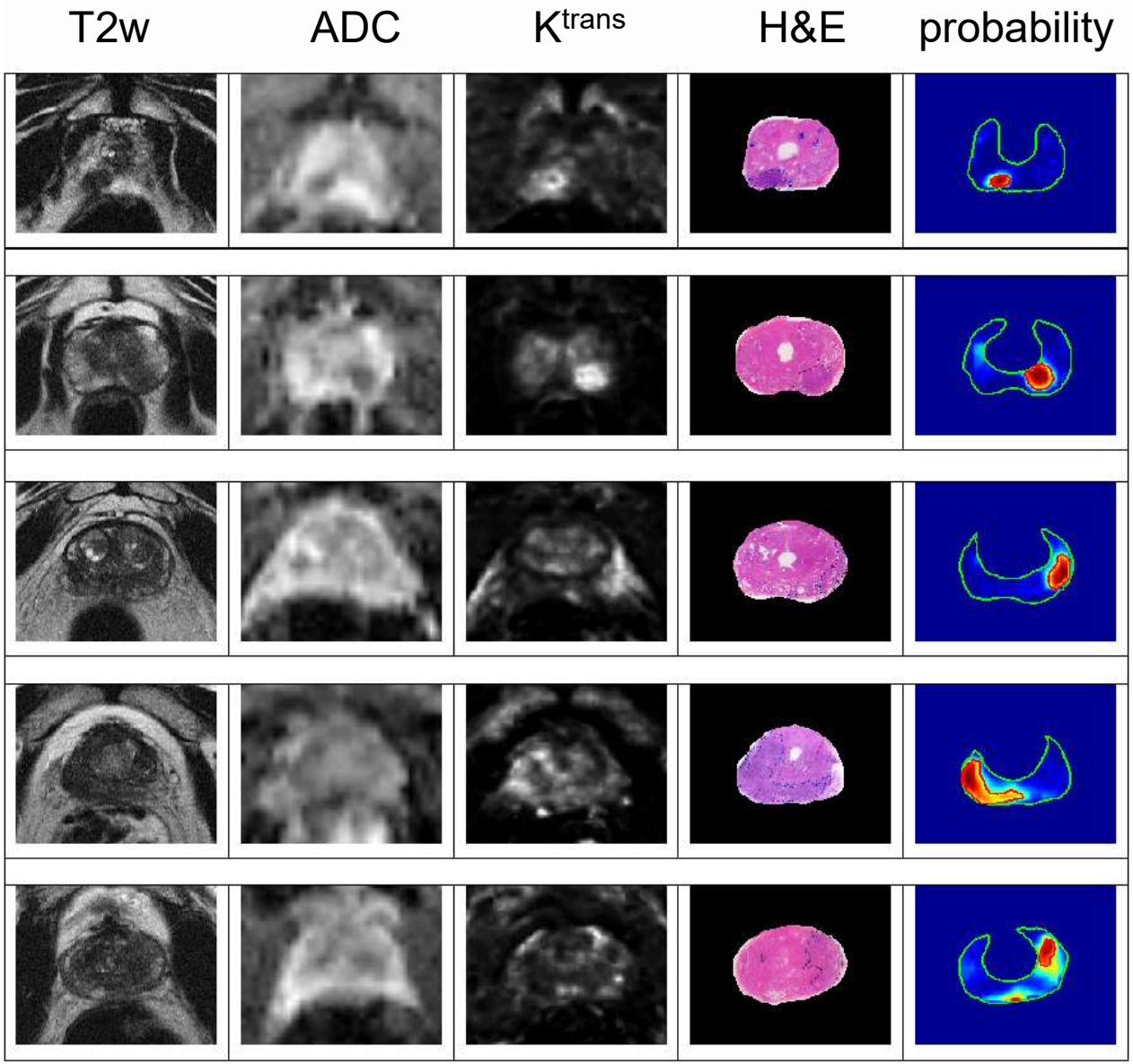
Validation of tumor probability model



AUC

- MRI: 0.70
- MRI+prevalence: 0.76
- MRI+prevalence +biopsies: 0.78

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Dinh et al. Eur J. Med. Phys. 2016 Mar;32(3):446-451; Dinh et al. Med Phys. 2017;44:949-961

Response prediction

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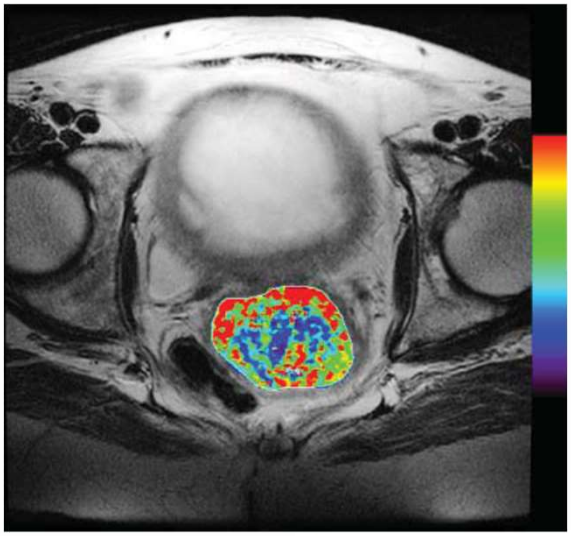
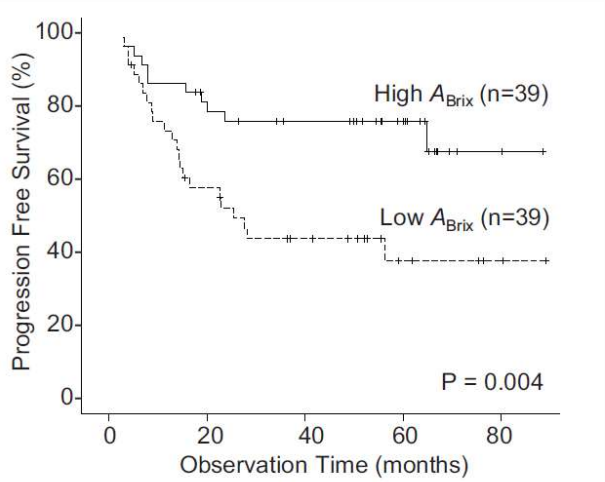
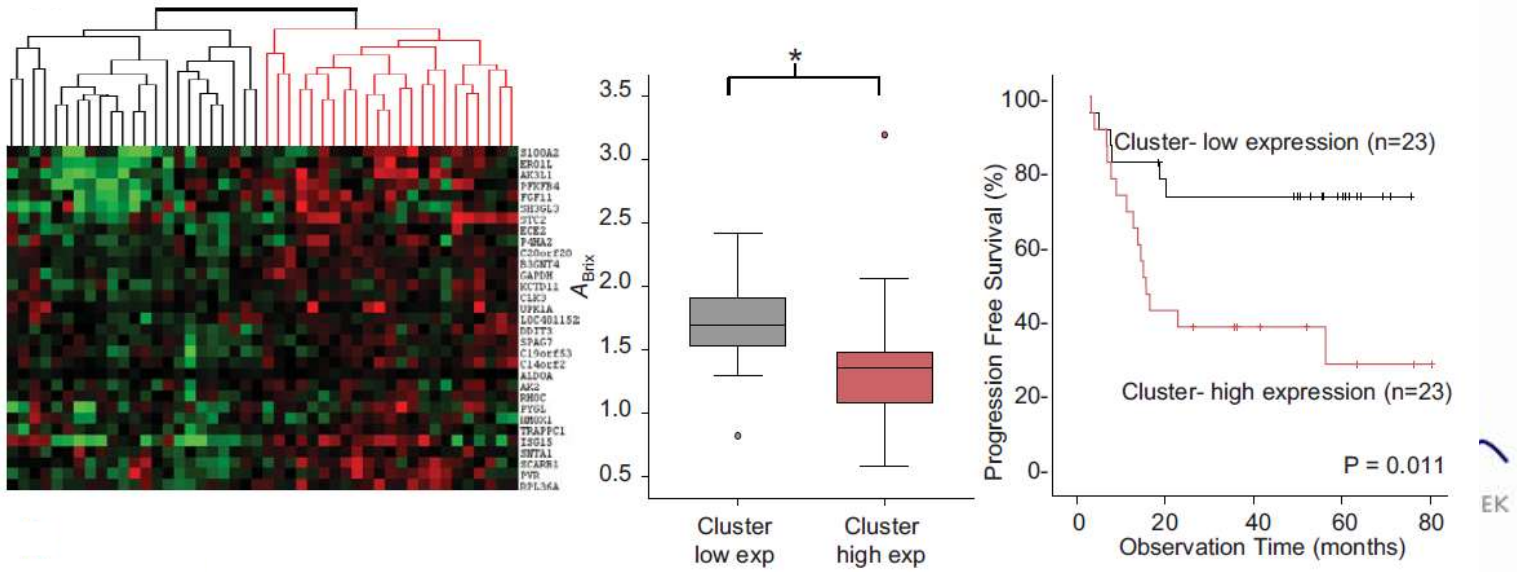
Prognostic value of DCE-MRI for outcome after CRT in cervical cancer

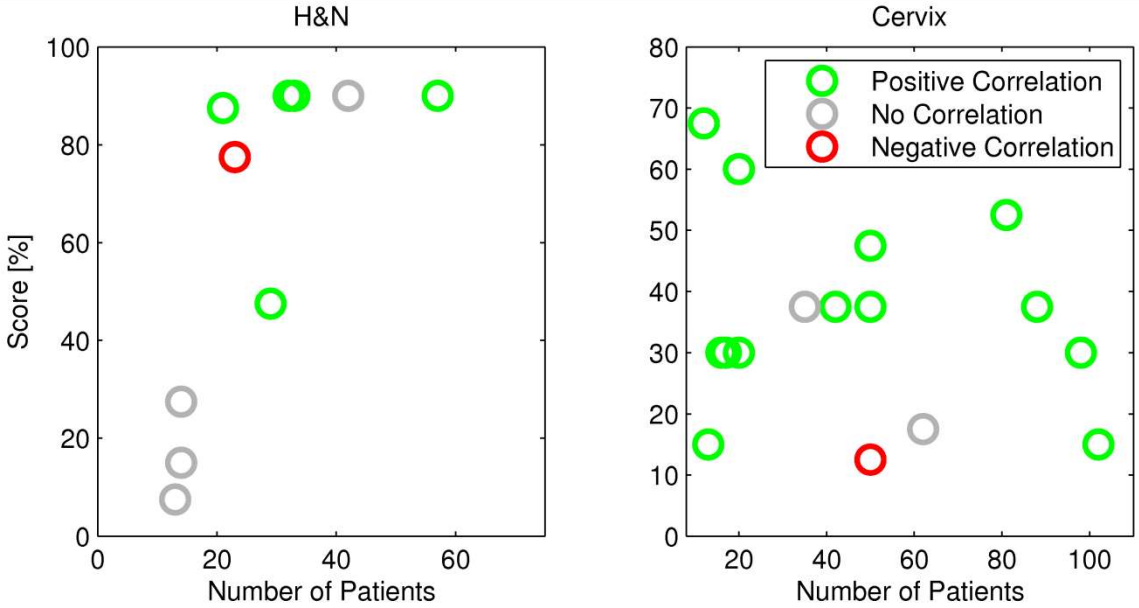






Halle et al. 2012; Cancer Res. 72:5258-5295

Variable results in response prediction



Score the degree of adherence to guidelines for DCE-MRI

- Little consensus between studies about prognostic/predictive value of imaging markers
  - Low patient numbers
  - Wide variety in imaging methods
    - Poor adherence to guidelines

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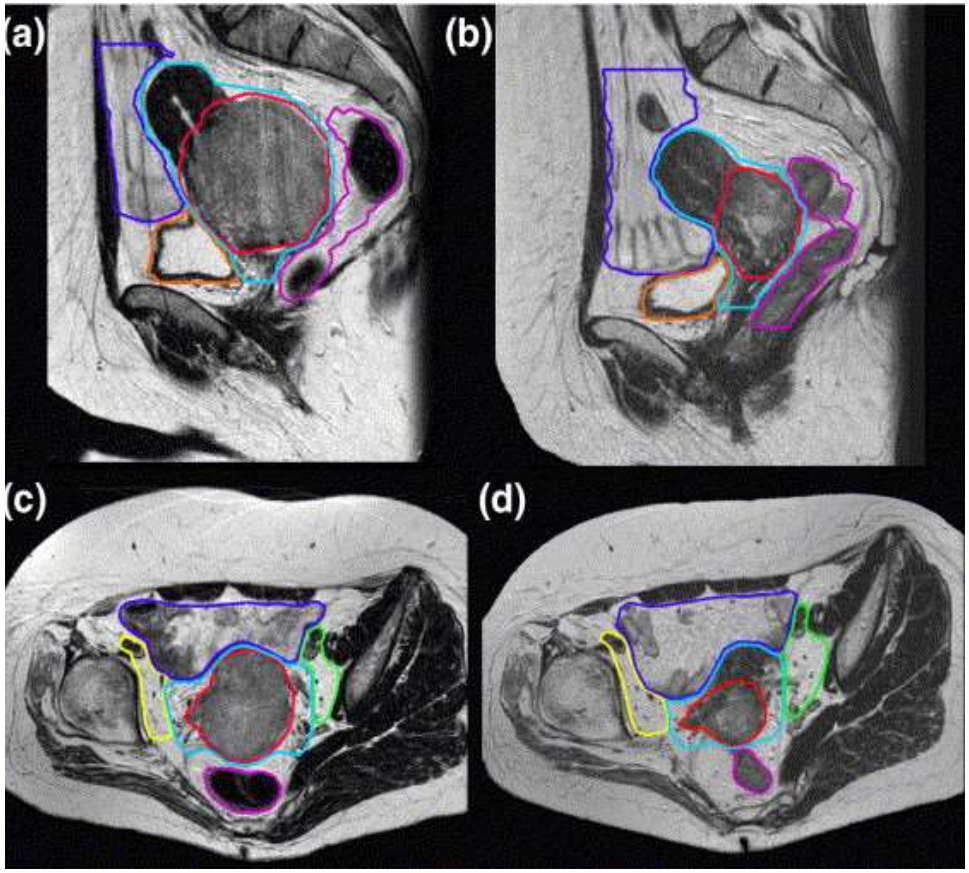
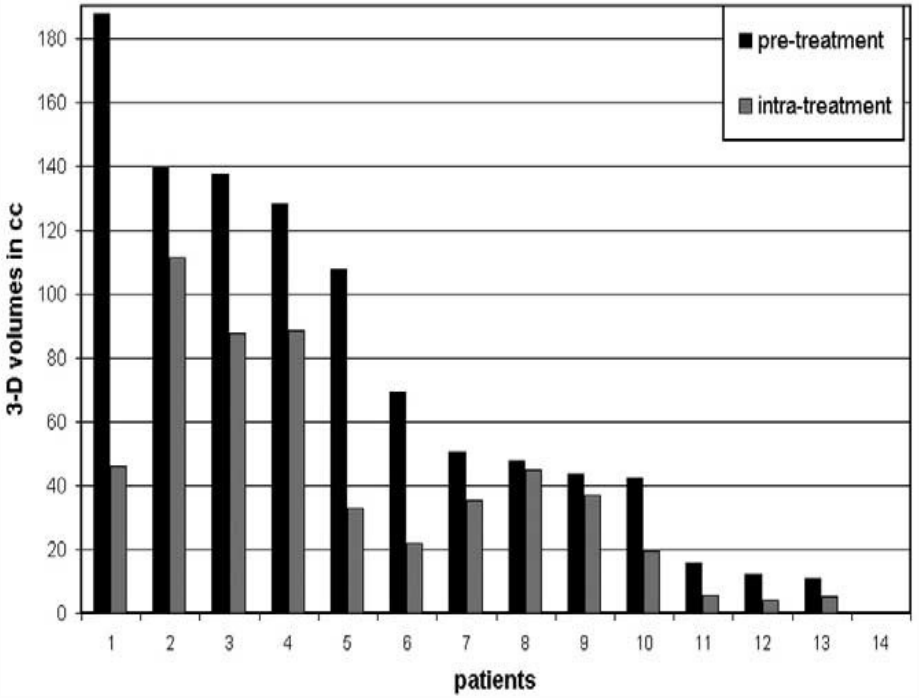
Assessment of response to treatment

Repeated MRI to monitor tumor shrinkage

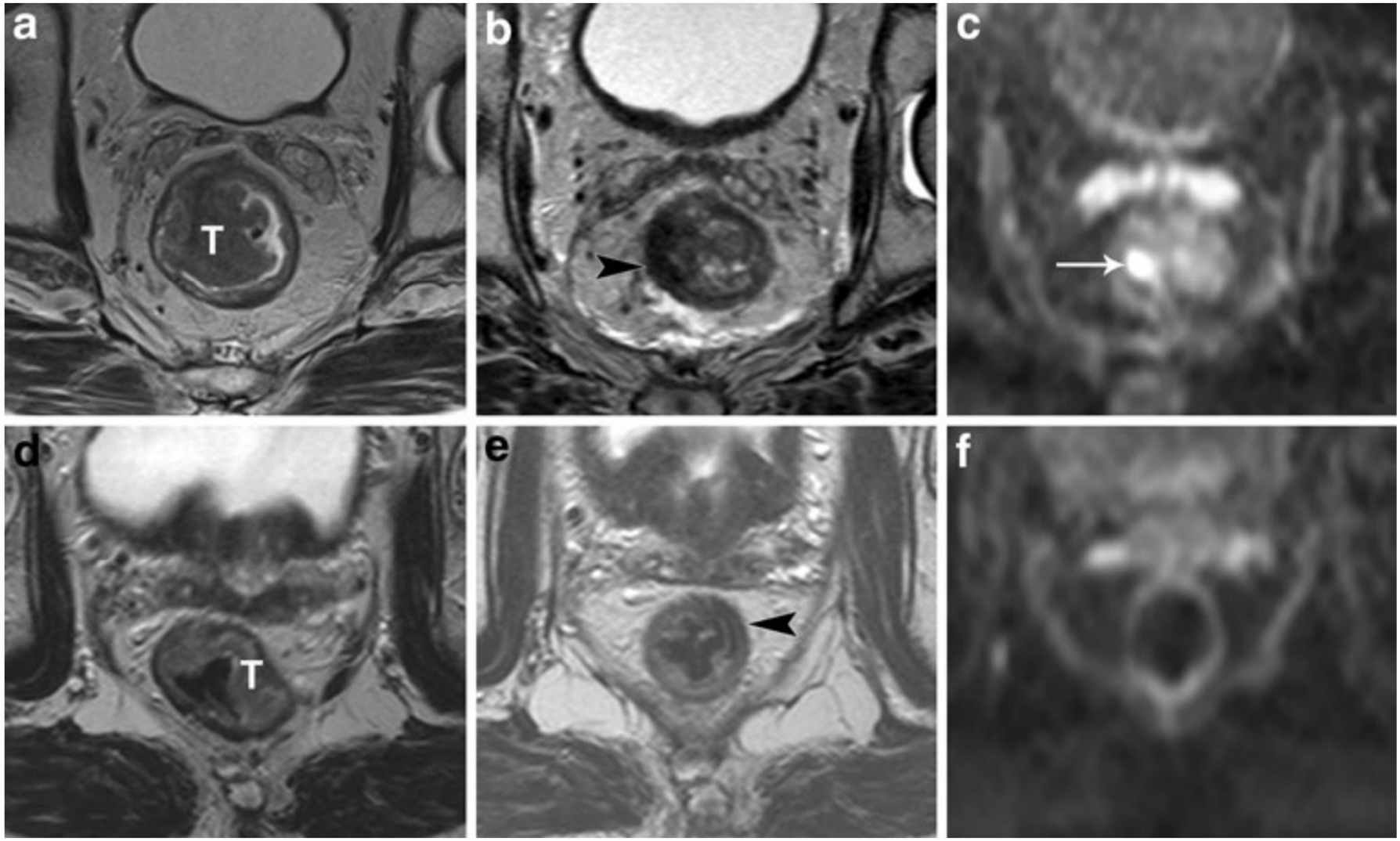




After 30 Gy, the GTVs decreased an average of 46% (6.1–100%). The TVs on the intratreatment MRI remained sufficiently covered by the 95% isodose. Repeated IMRT planning can improve the sparing of the bowel and rectum in patients with substantial tumor regression.

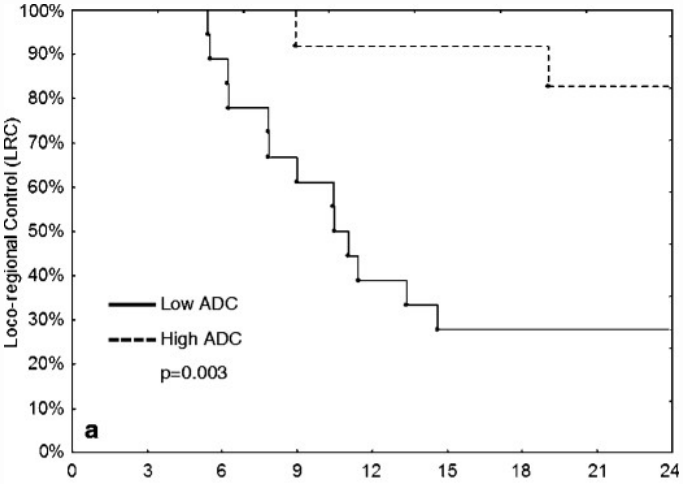
Van de Bunt L. et al. Int J Radiat Oncol Biol Phys 2006;64:189-96

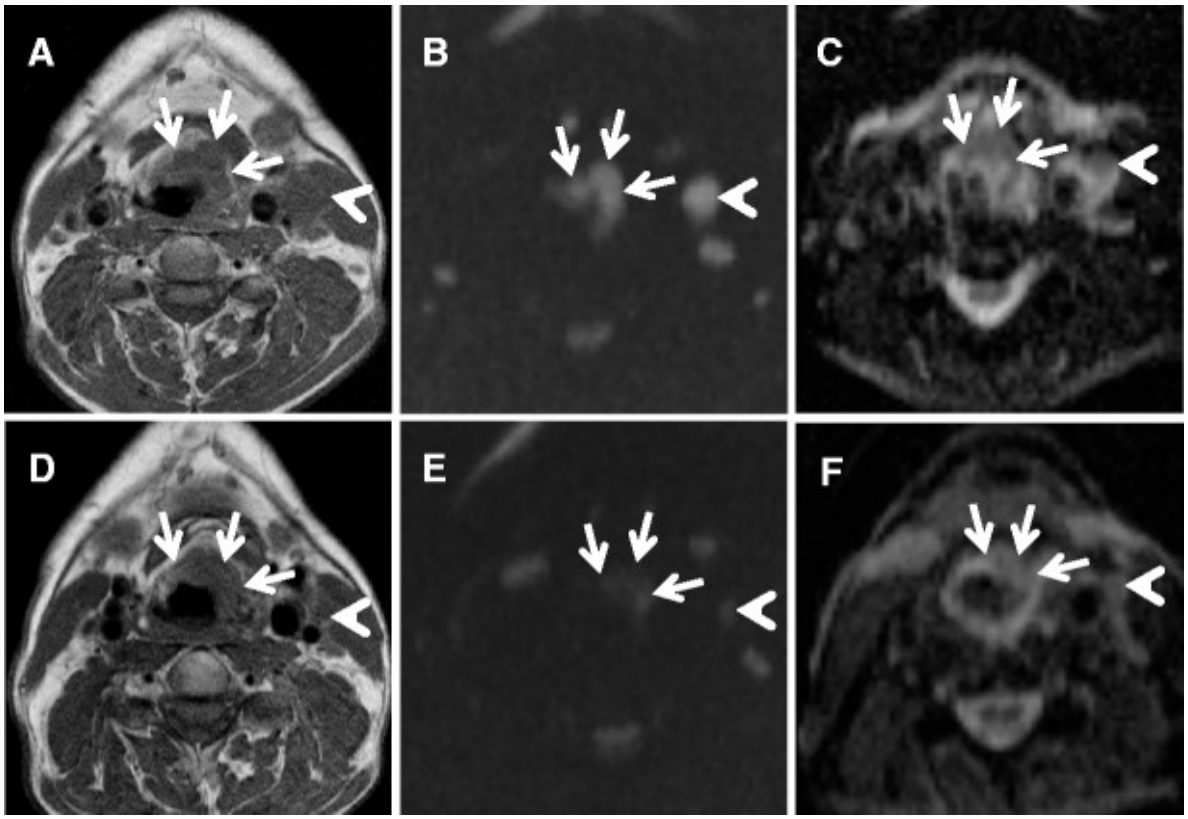
Persistent restricted diffusion indicates residual rectal cancer



Lambregts et al. Ann. Surg. Oncol. 2011;18:2225-31

Early imaging marker for response to treatment





Head-neck cancer

- >25% increase in ADC after 2 weeks of chemoradiation is associated with good loco-regional control

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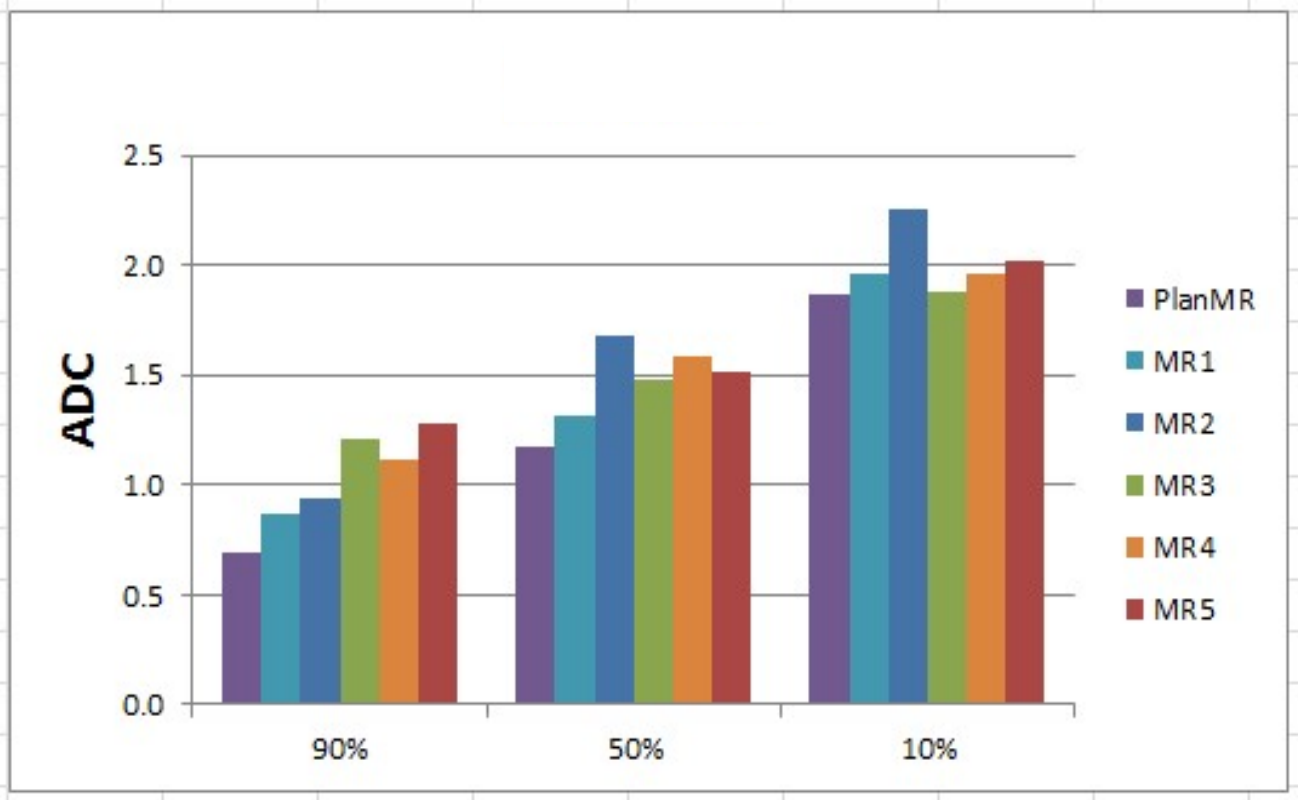
Vandecaveye et al. 2010; Eur. Radiol. 20:1703-14

Analysis of Regions of Interest



- Percentiles within a ROI show trends
- Spatial information is lost

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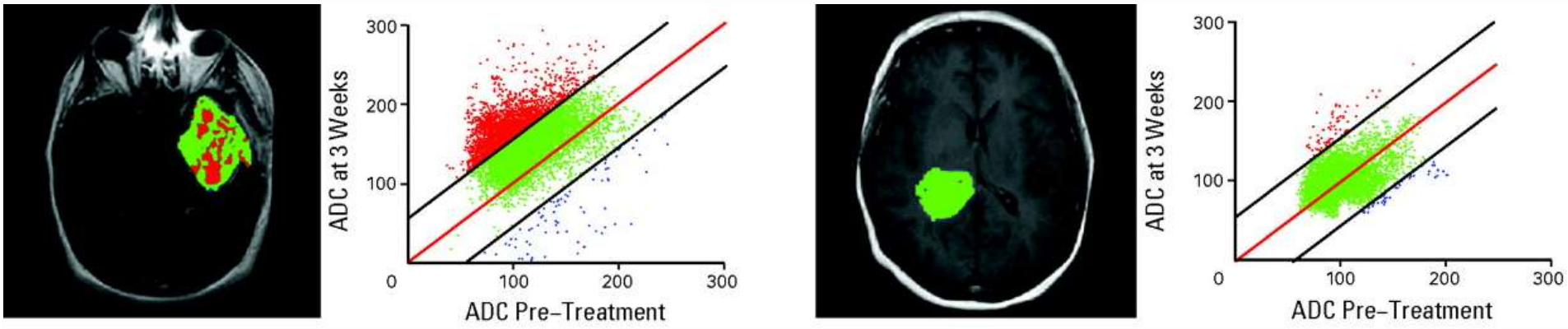
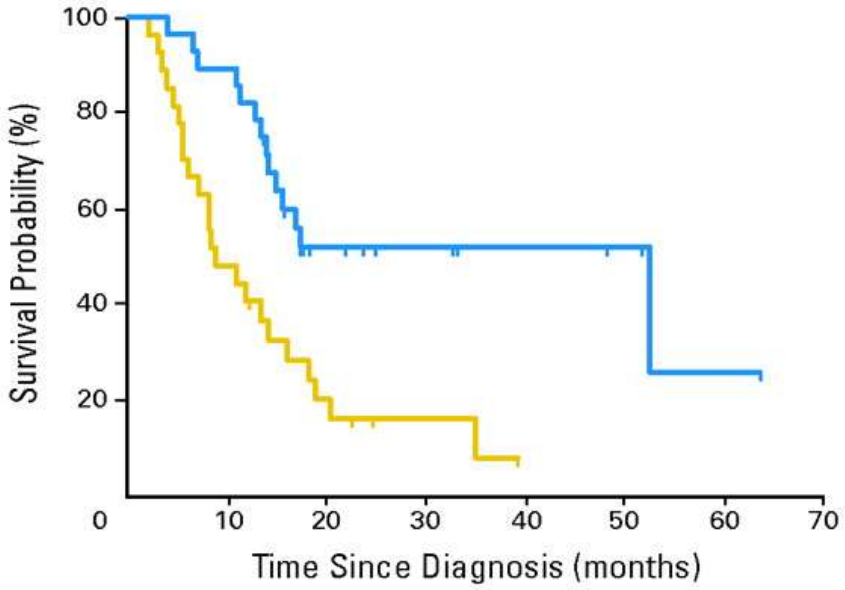
DWI as biomarker for response to treatment



High-grade glioma

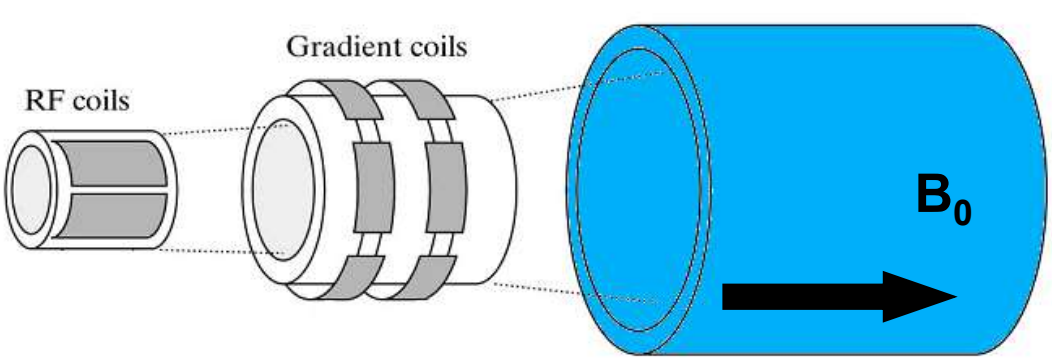
- Increase in ADC after 3 weeks of chemoradiation is predictive for patient survival

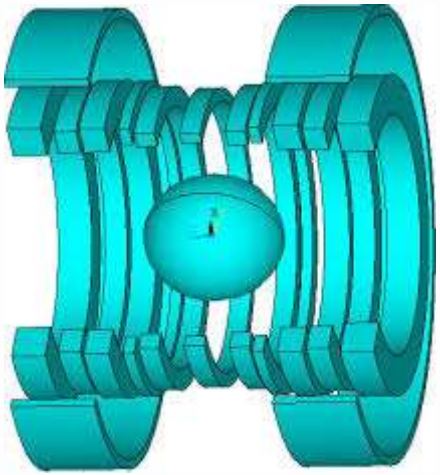


Hamstra et al. 2008; J.Clinic. Oncol. 26:3387-94

Geometrical accuracy

Homogeneity of the main magnetic field





e.g. uniformity in diameter of spherical volume DSV_{40cm} = 0.2 ppm

(at 1.5 T):
0.2 x 63.87 MHz = <u>12.8 Hz</u>

Magnet is shimmed at installation- additional (dynamic) shimming may be required

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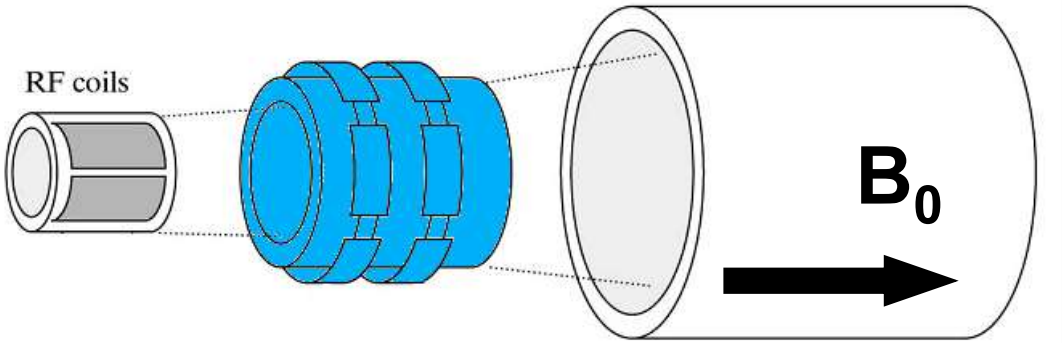
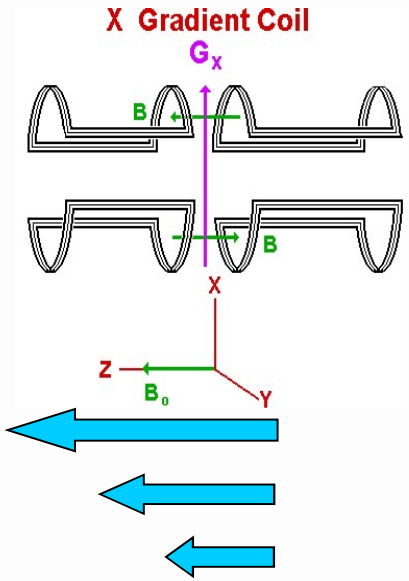
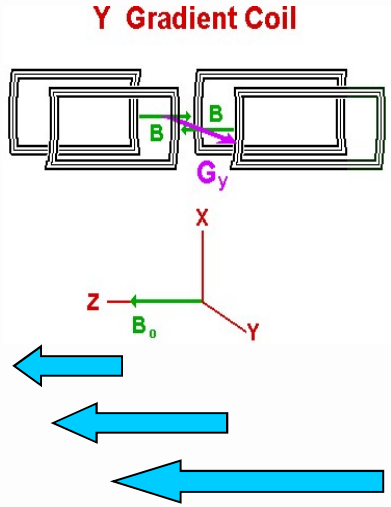
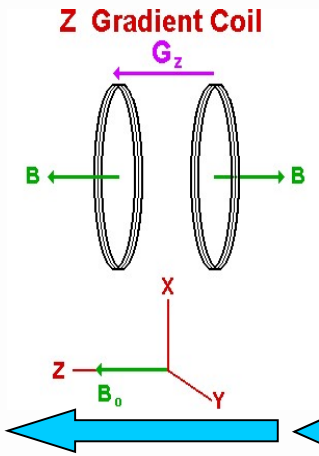
Gradient fields





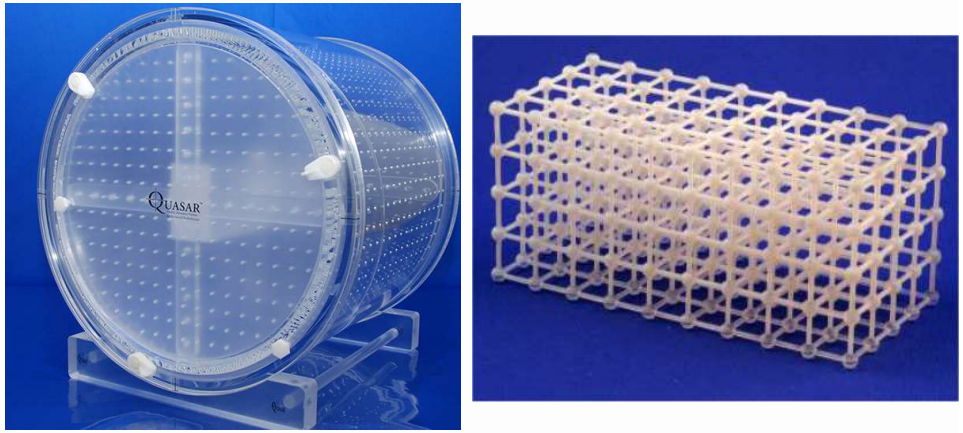




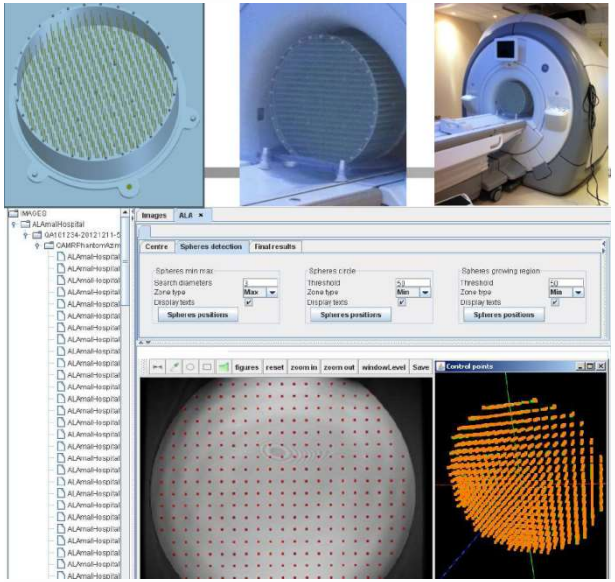
Linear changes in B_0 in each orthogonal direction

Phantoms

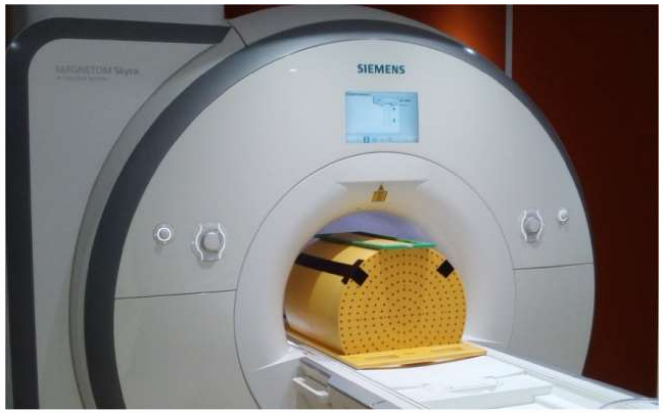
Vermandel 2014



Commercial: Quasar, Modus



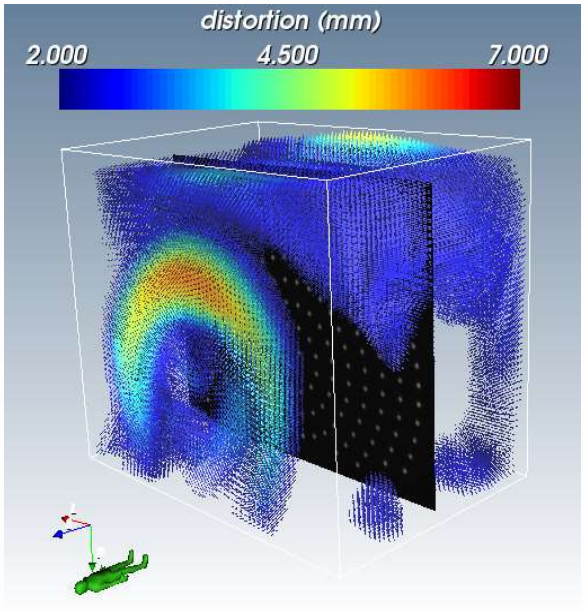
Torfeh 2015

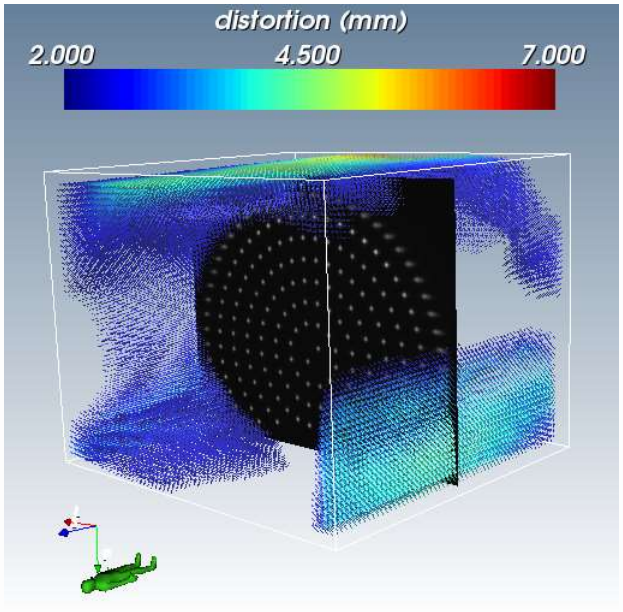


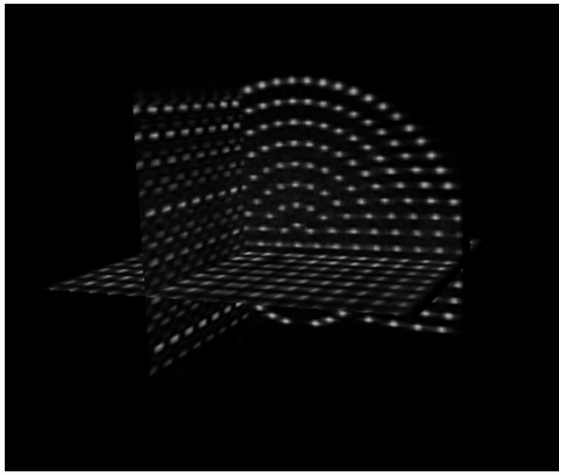
Walker 2015

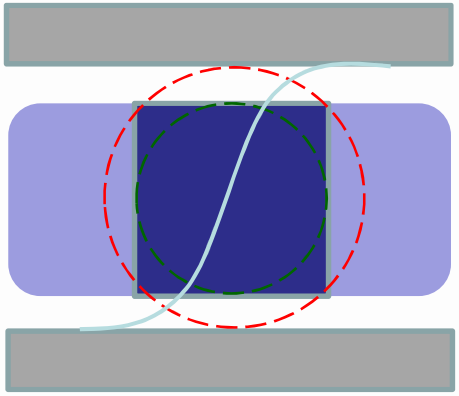
Vendor: GE

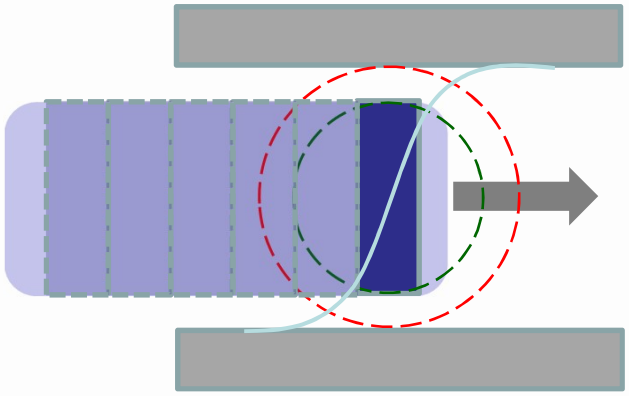
Continuous or stepped table measurement











Restrict volume

Move table through isocentre

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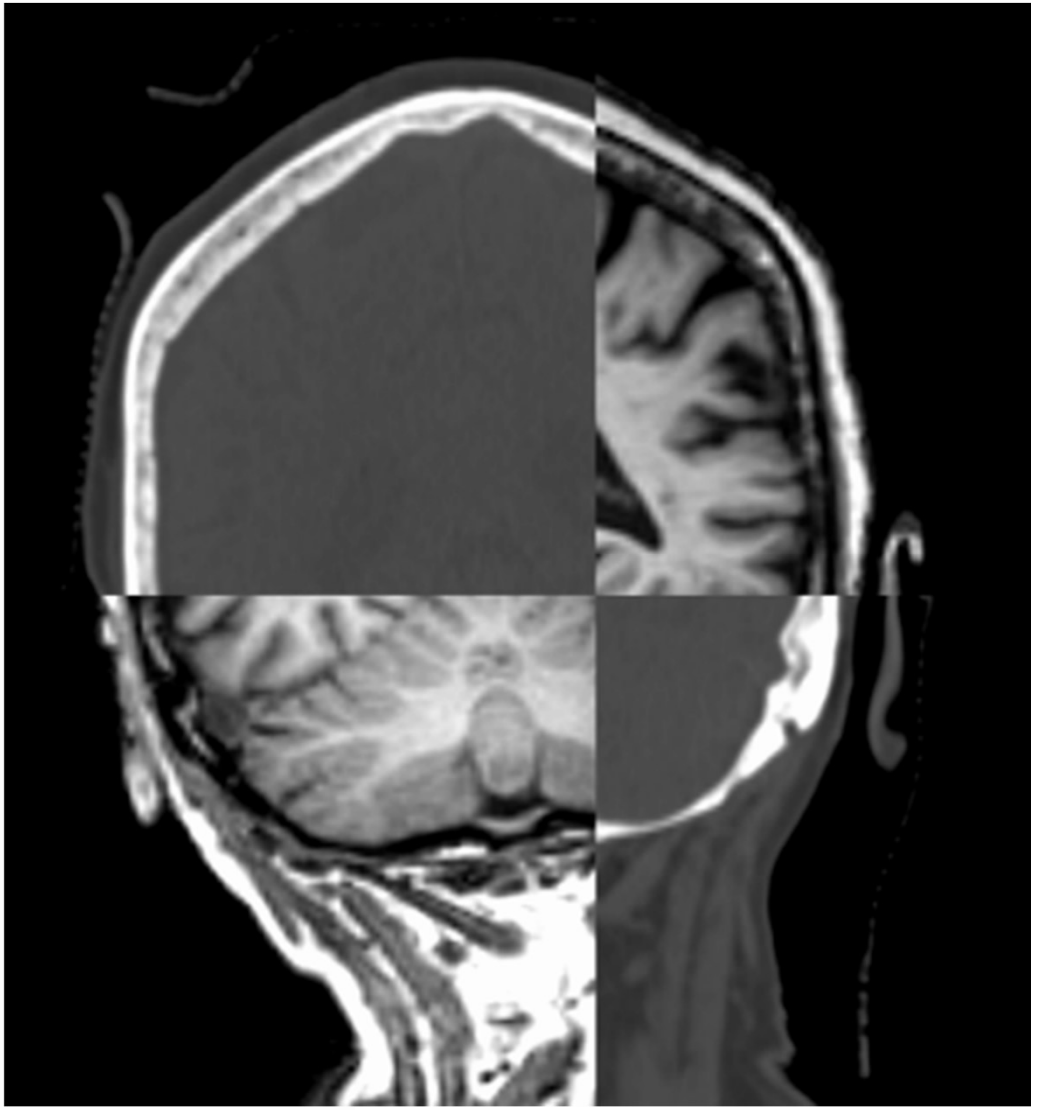
Walker et al. Med Phys 2015;42:1982-1991

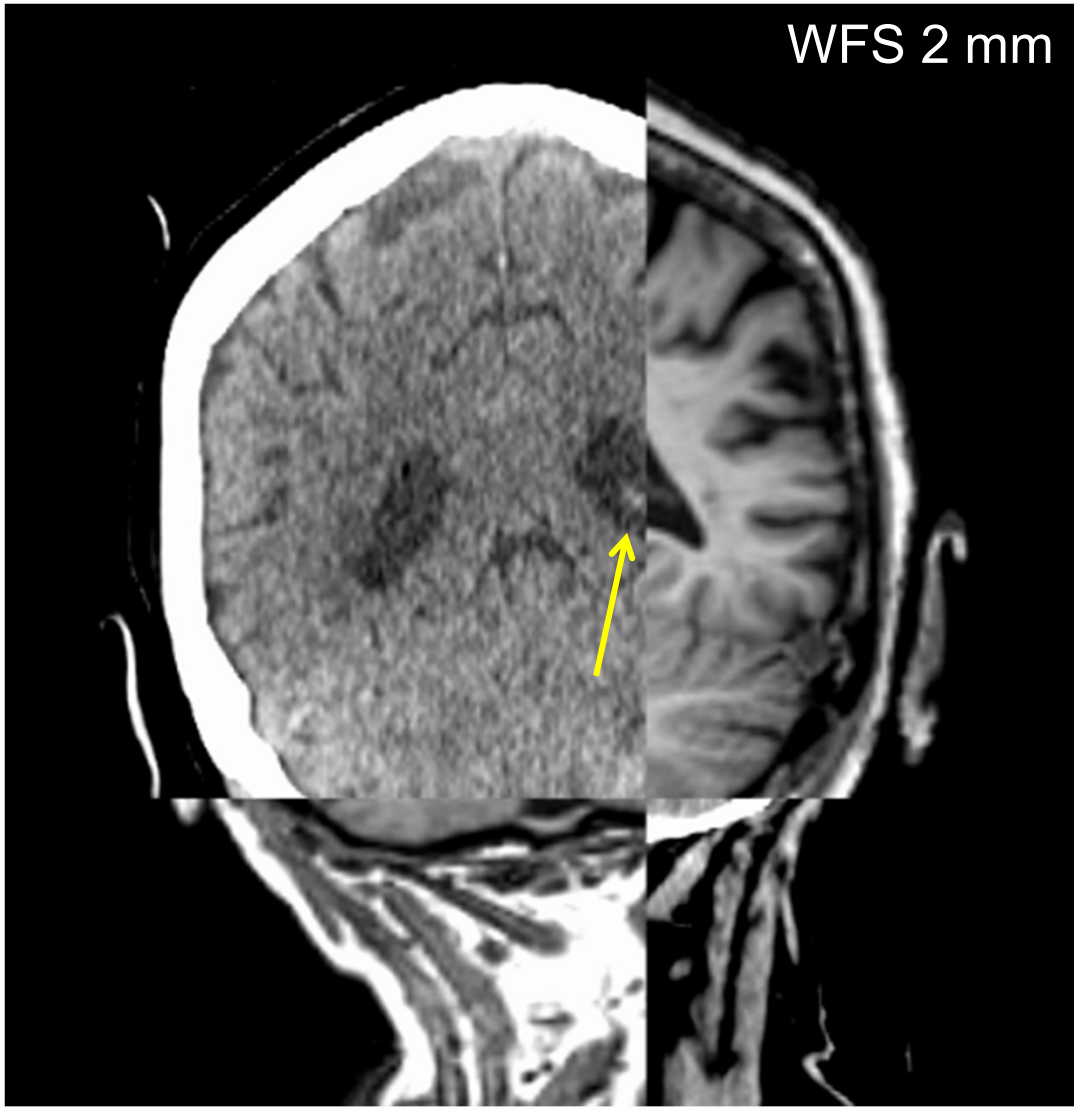
Image distortions: water-fat shift

- Cortical bone:
  - CT: bright
  - MRI: dark
- Bone marrow
  - CT grey
  - MRI: grey
- skin
  - CT: dark grey
  - MRI bright



MRI and CT of brain

- Water-fat shift (WFS)
  - The water and fat are shifted relative to each other.
  - The WFS is a parameter that can be tuned;



Water-fat shift

- Water-fat shift can be reduced, at the expense of signal
- Typically, diagnostic protocols use large WFS, to enhance signal (SNR)
- For radiotherapy, it is preferable to reduce the WFS to less than 1 pixel.

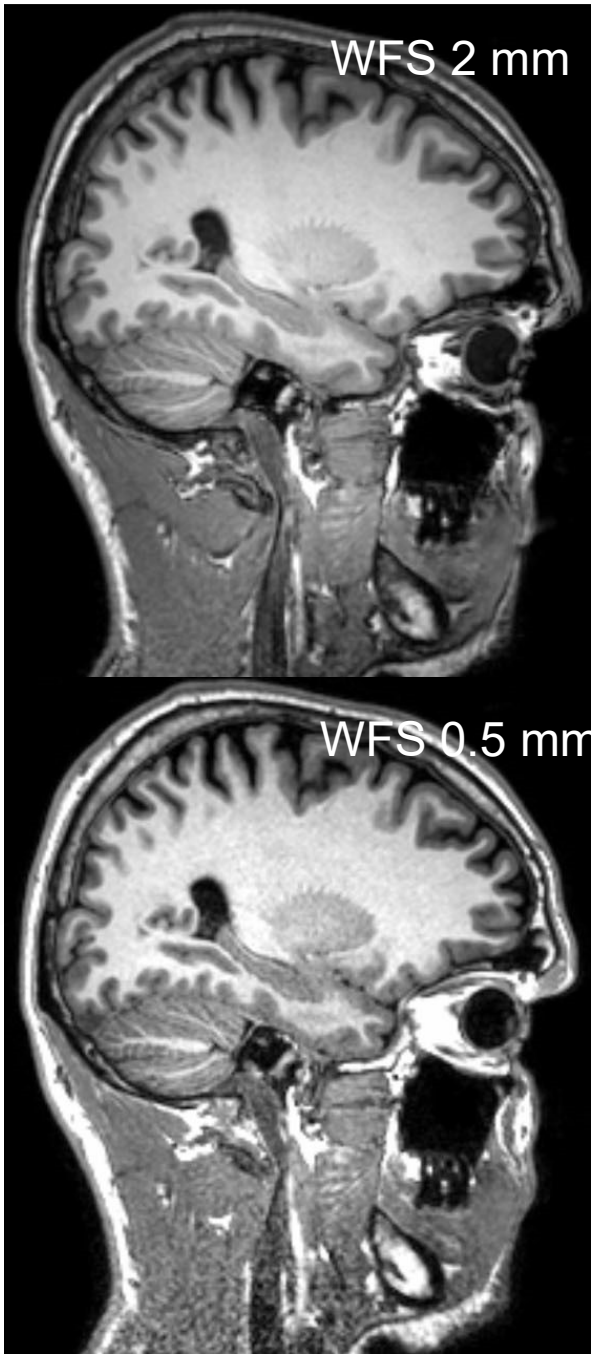


Image registration

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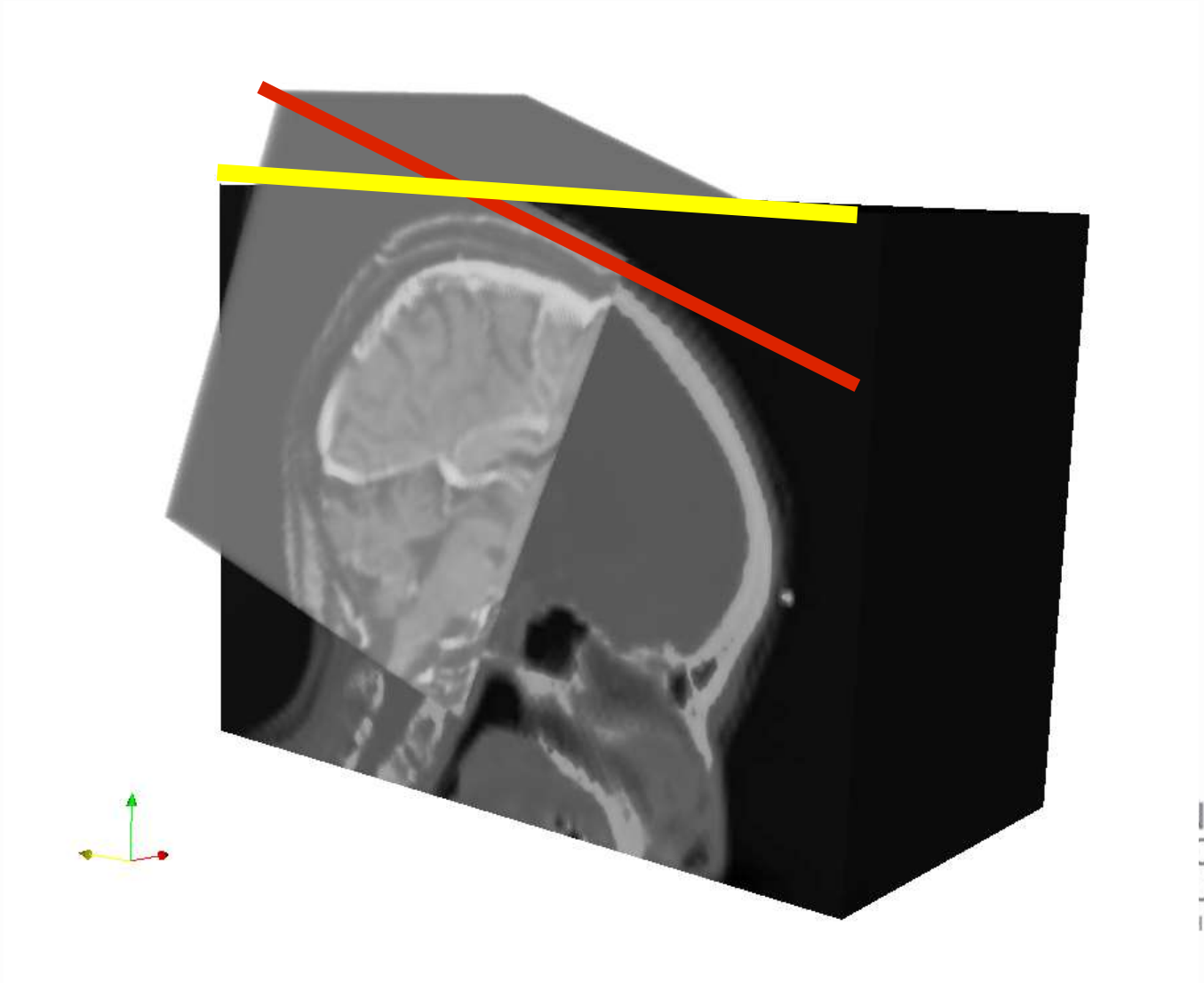
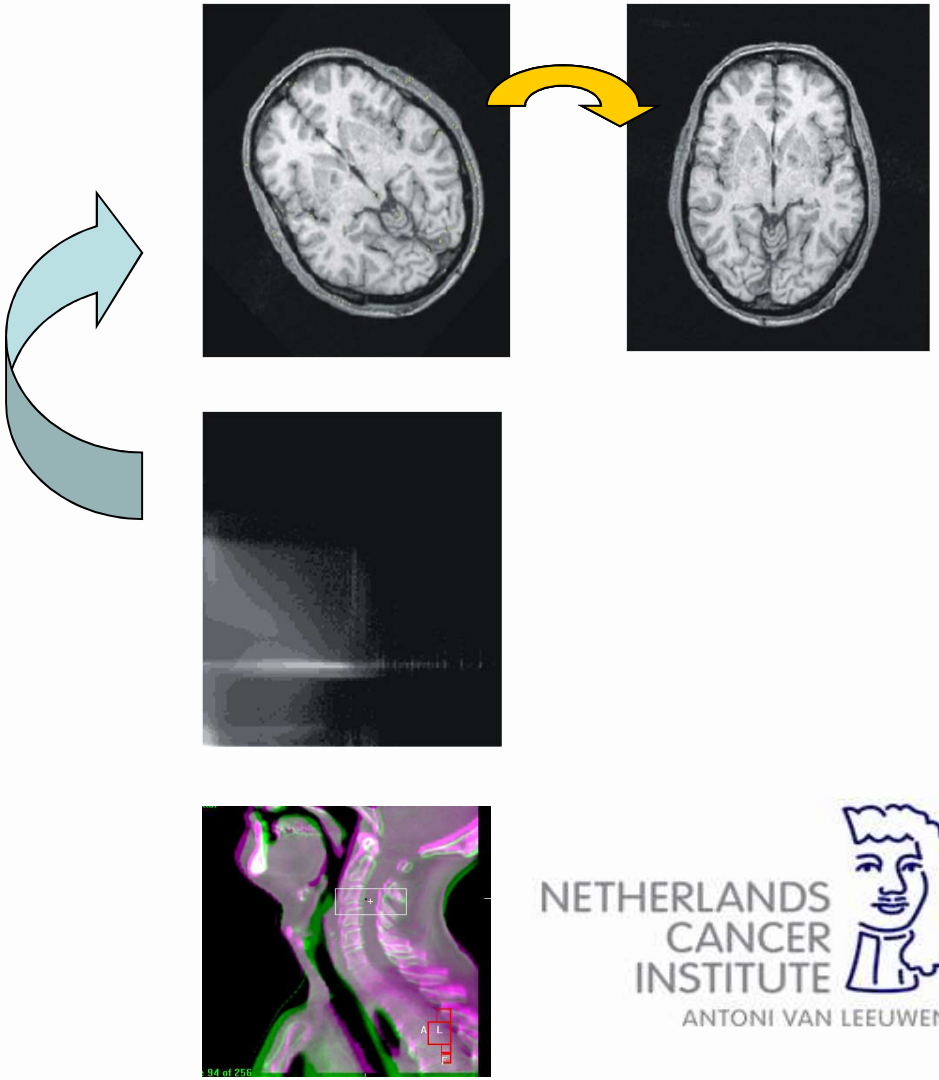
Image registration



steps of the registration process

- transformation
- similarity assessment
- visualization



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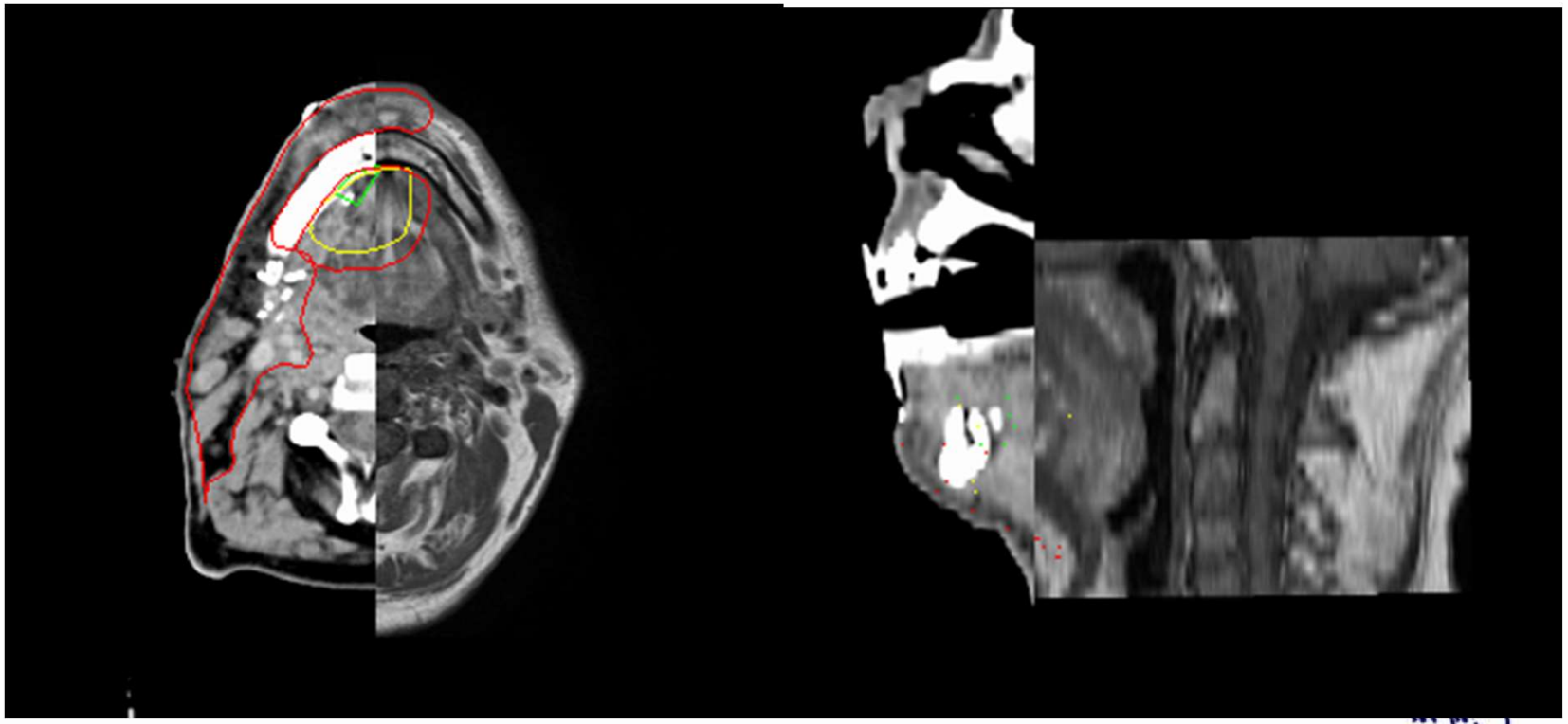
What if images don’t match?



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Research opportunities

- Delineation:
  - Which (combination of) modalities to use
  - Geometrical accuracy
  - Image registration
- Characterization
  - What kind of tumor
  - Heterogeneity
  - Relation to required dose
- Treatment response
  - Early markers
  - Prognostic/predictive value

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MRI guided radiotherapy

- MR-only simulation
- MR-guided external-beam radiotherapy
- MR-guided brachytherapy

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MRI-only simulation

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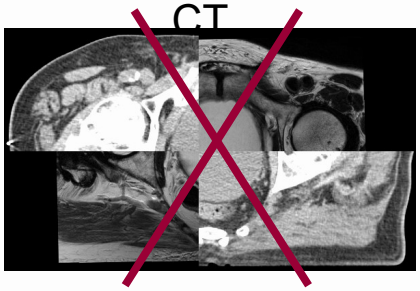
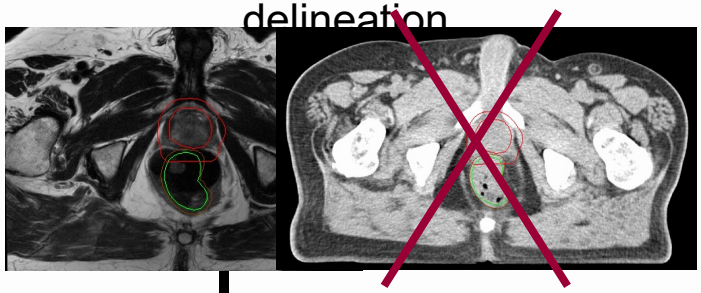
IGRT with MRI-only workflow

Pre-treatment imaging
CT + MRI/PET

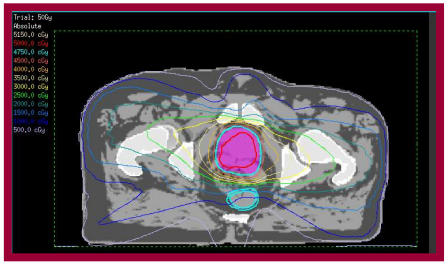
Registration MR/PET to CT



Target/OAR delineation



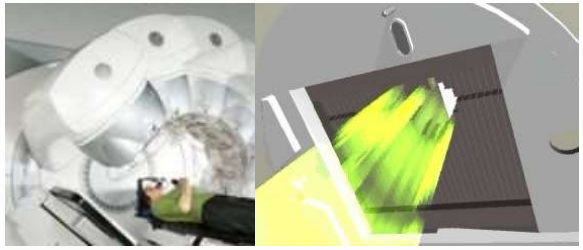
Treatment Planning



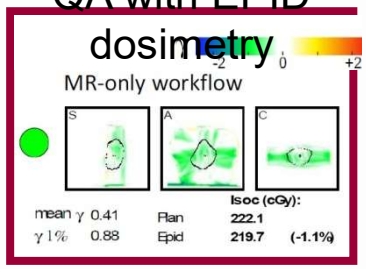
In Room Imaging

Image Registration & Correction

Treatment Delivery



QA with EPID dosimetry



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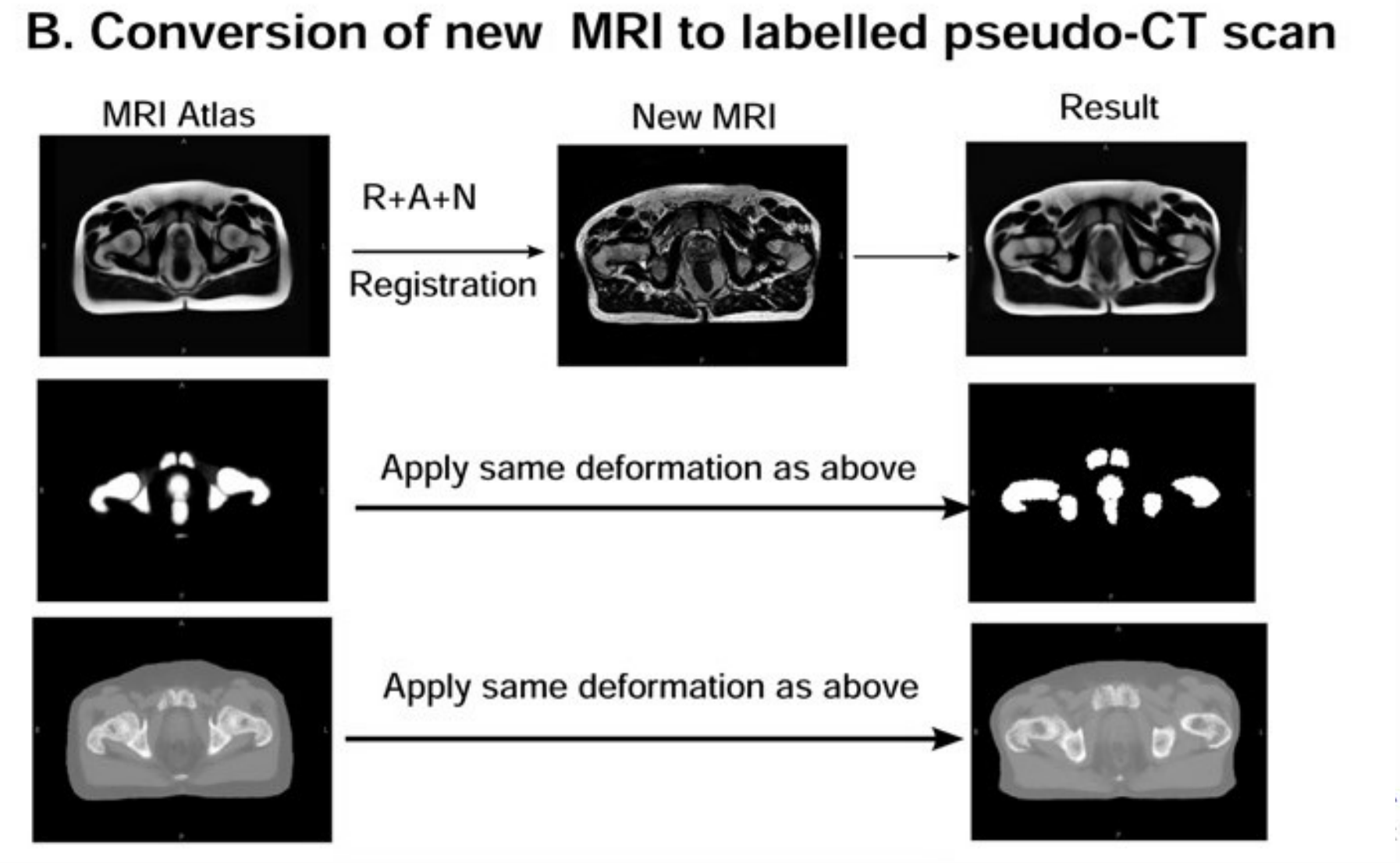
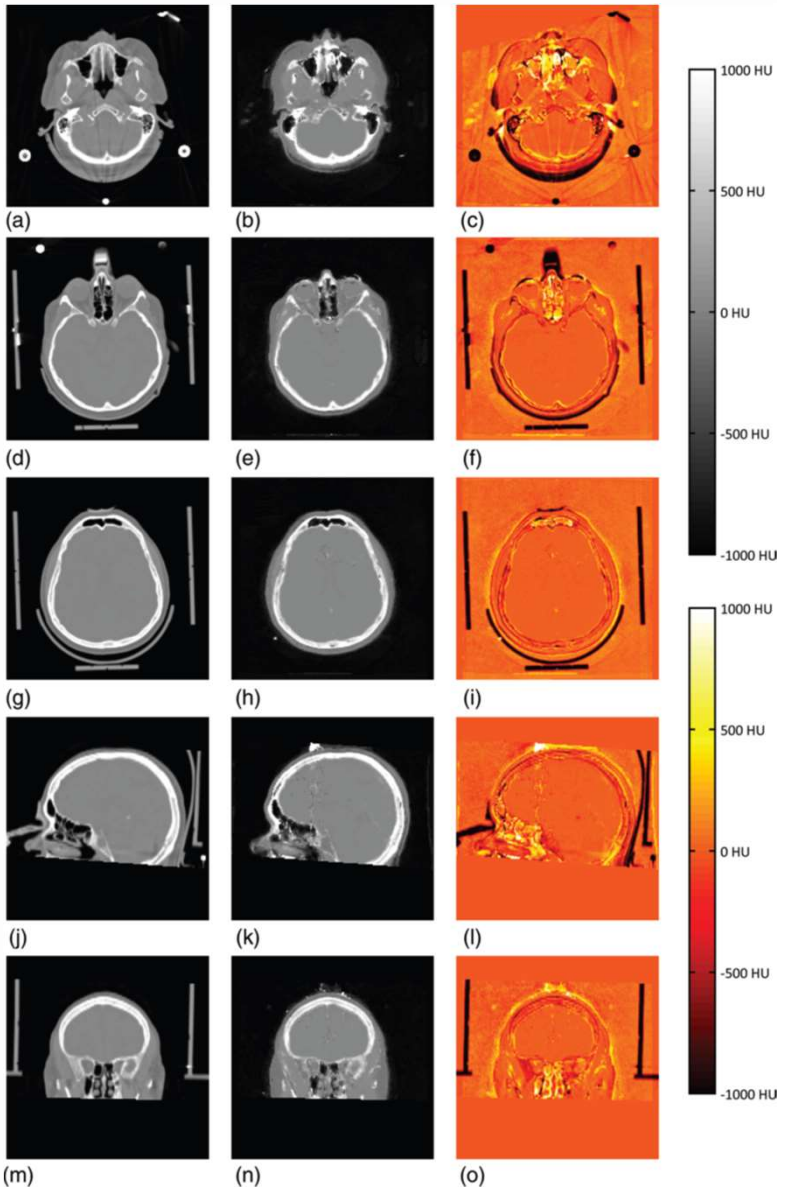
Generate Hounsfield Units from an MRI scan



Dowling et al. Int. J. Radiat. Oncol. Biol. Phys. 2012;83:e5-11

Generate Hounsfield Units from an MRI scan

- Create a Gaussian mixture regression model of HU based on
  - Two dual-echo UTE sequences (Flip Angle 10 and 60°)
  - T2-weighted 3D spin-echo sequence



Johansson et al. Med. Phys. 2011;38:2708-14

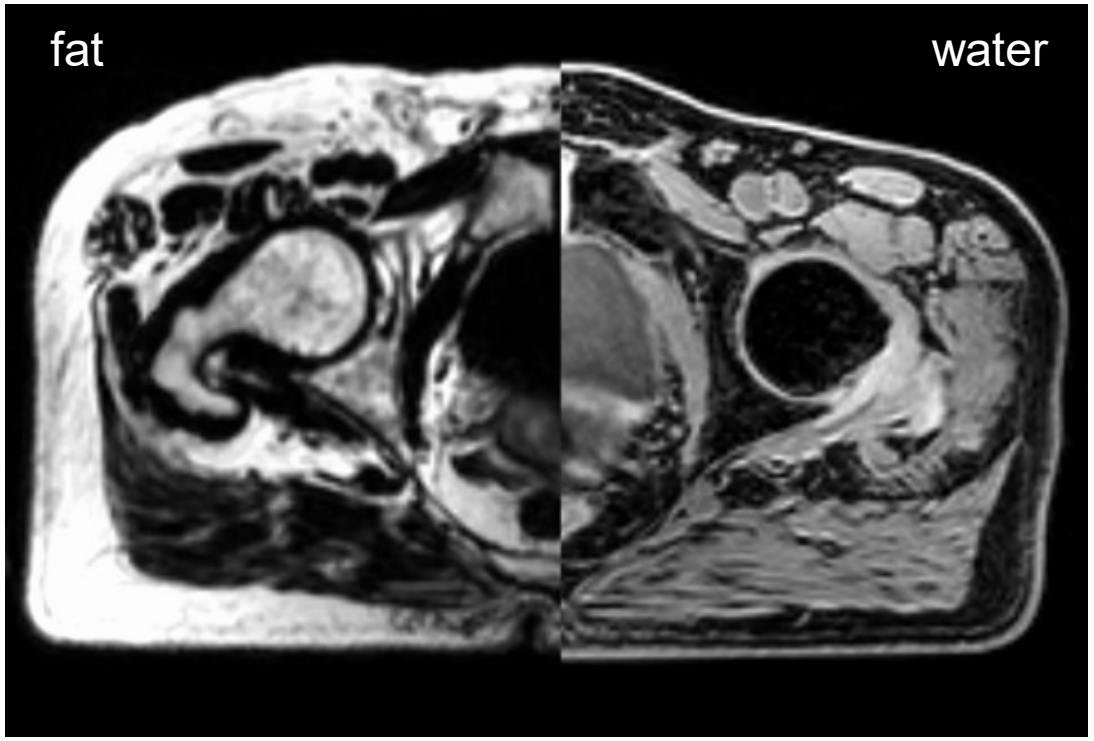
Dixon-based soft-tissue and bone classification for the Pelvis

Tissue types

- Air
- Water
- Fat
- Bony structures
  - bone marrow
  - cortical bone

Hybrid approach:

- Dixon sequence gives separate images for water and fat
- Autosegmentation separates bony anatomy



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MRI-guided radiotherapy

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state of the art image guidance: Cone-Beam CT

- Installed February, 2003
- CE marking on July, 7, 2003
- First images on July, 9, 2003
- In clinical use for bony anatomy setup on February 17, 2004

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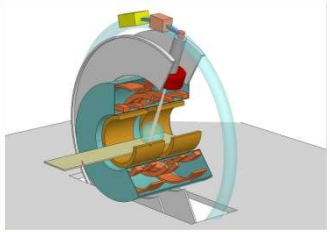
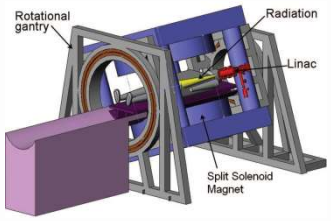
MRI guided external beam radiotherapy

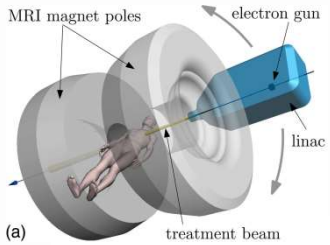
- Utrecht, The Netherlands
  - 1.5 T MRI, 6 MV linac



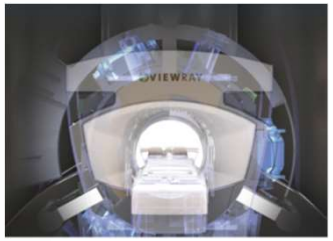
- Edmonton, Canada
  - 0.2 T MRI, 6 MV linac
  - Plan for 0.5 T or 1.0 T MRI



- Sydney Austrialia
  - 0.5 T MRI, 6 MV linac

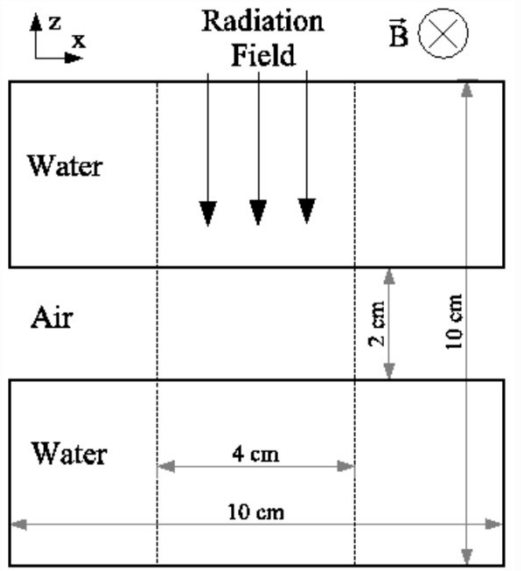


- Viewray, Cleveland, USA
  - 0.345 T MRI, 3 Co sources



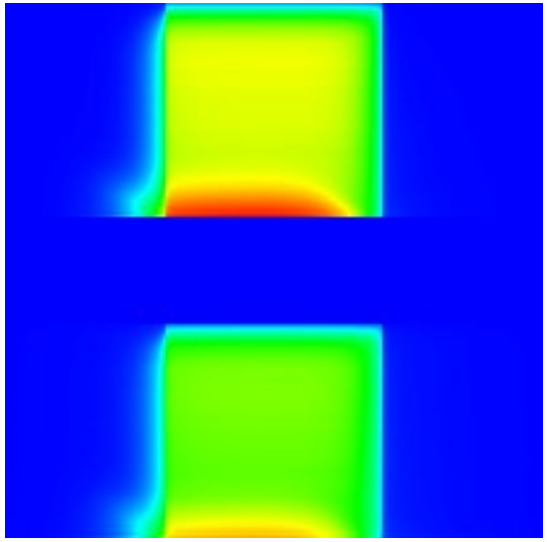
How to deal with Lorentz forces on scatter electrons

- The trajectories of scattered electrons will curve in a magnetic field
- This effect is most prominent at the interface between tissue and air ('Electron Return Effect')



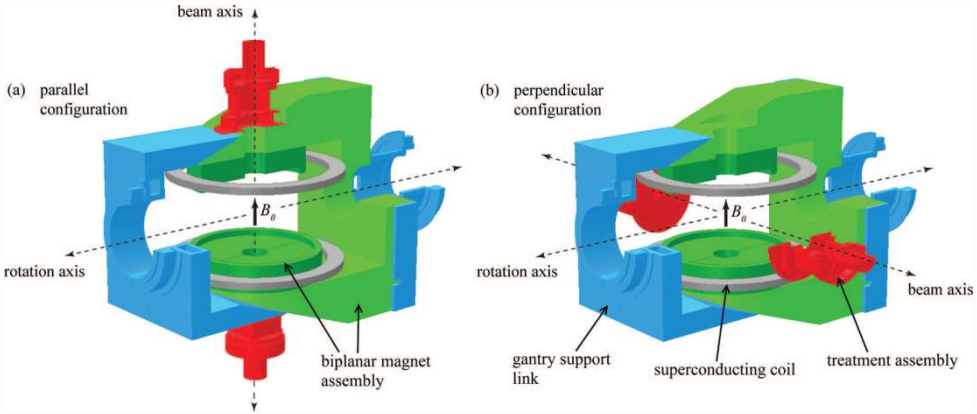
Options

1. Minimize the B_0 field
2. irradiate parallel to the B_0 field
3. choose clever beam geometries
4. Accept and incorporate in dose calculation (Monte Carlo)

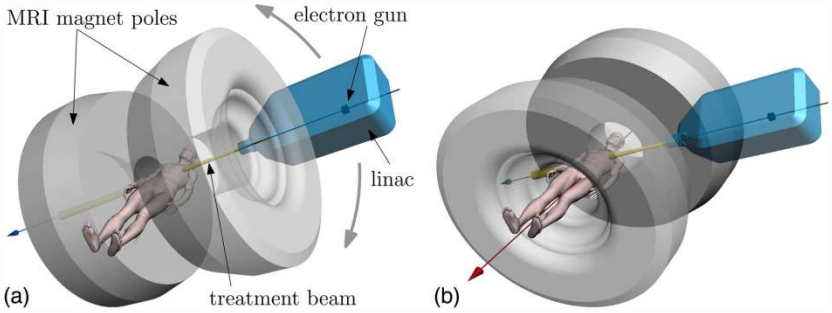


Raaijmakers et al. Phys. Med. Biol. 50, 1363 (2005);

In-line or perpendicular geometry



Keyvanloo et al. Medical Physics 39, 6509 (2012);



Constantin et al. Medical Physics 38, 4174 (2011);

In-line: scatter electrons bend around beam axis; cylinder symmetric distribution

Perpendicular: scatter electrons bend perpendicular to beam axis;

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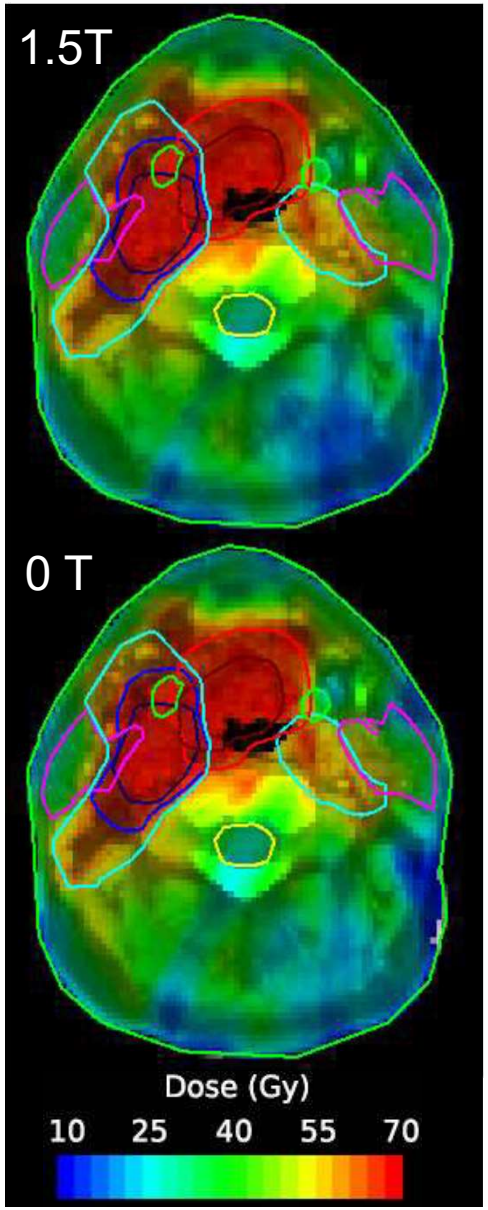
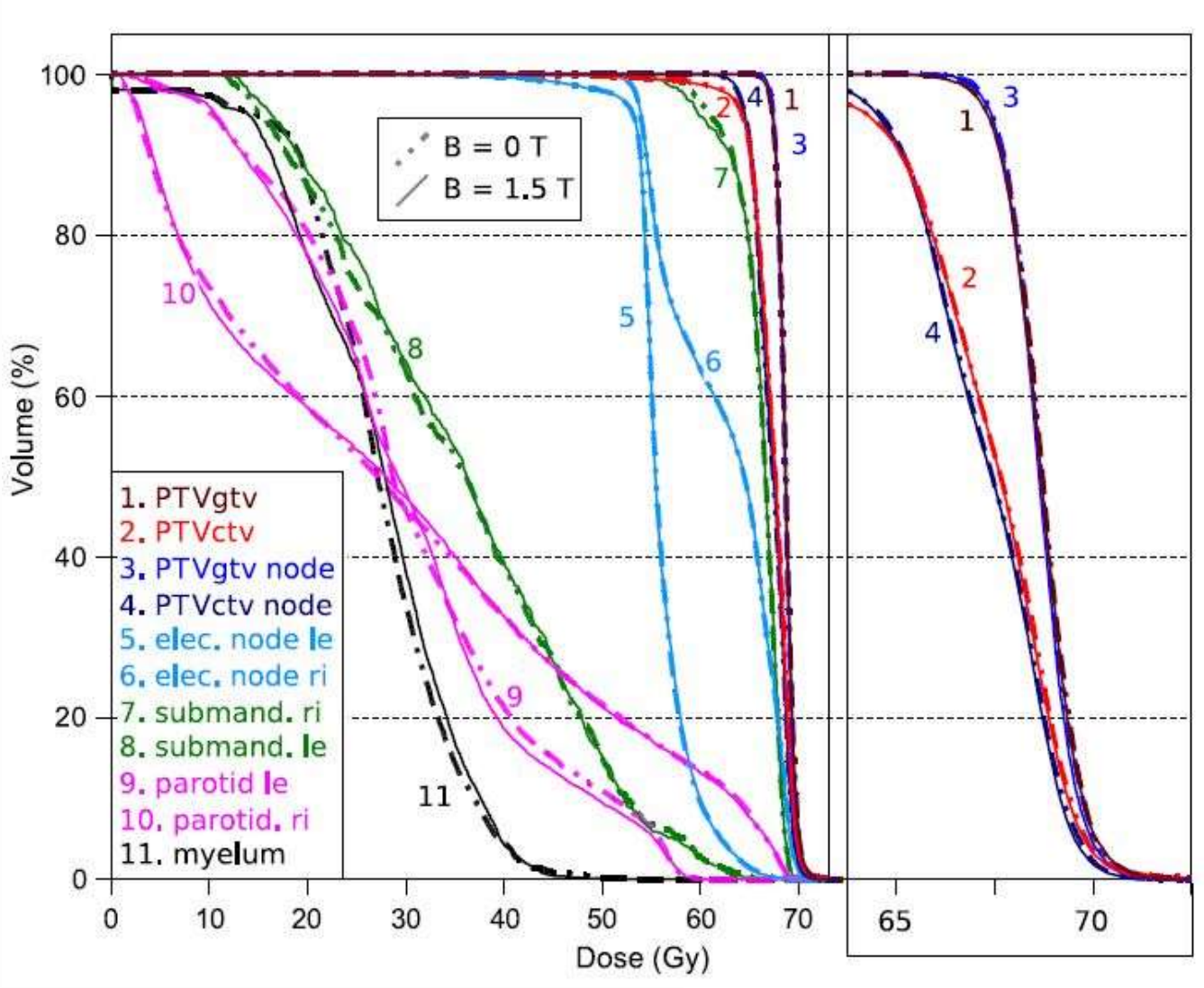
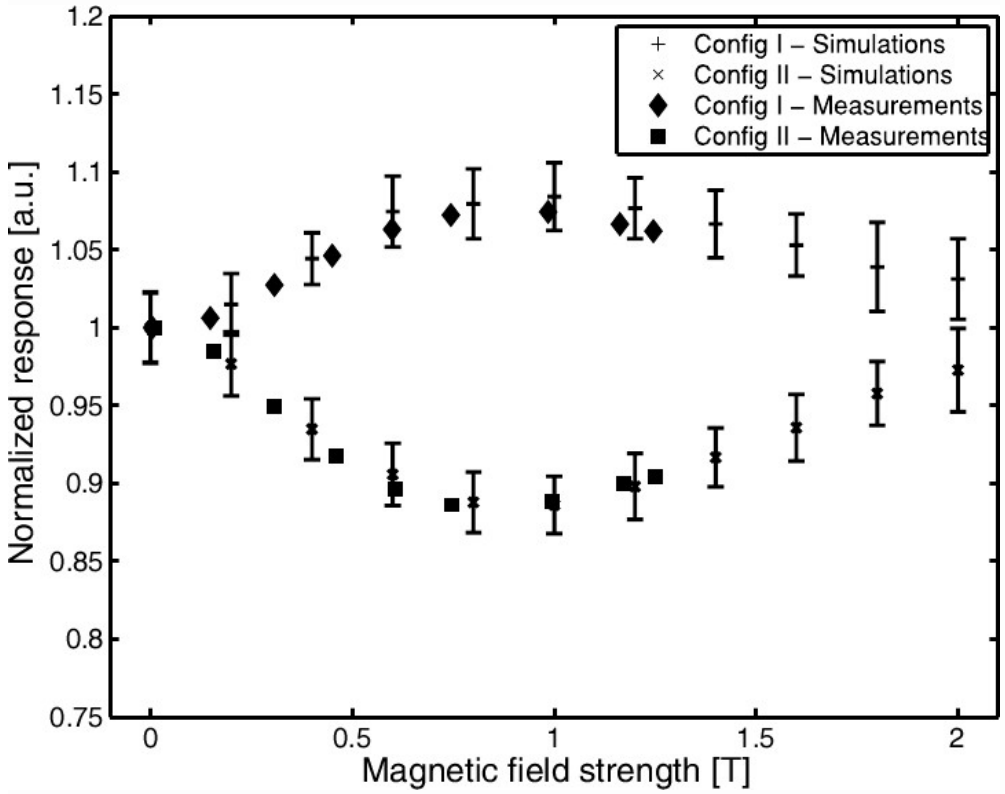
DVH for optimized dose distribution oropharynx
Comparison between B = 0 T and B = 1.5 T



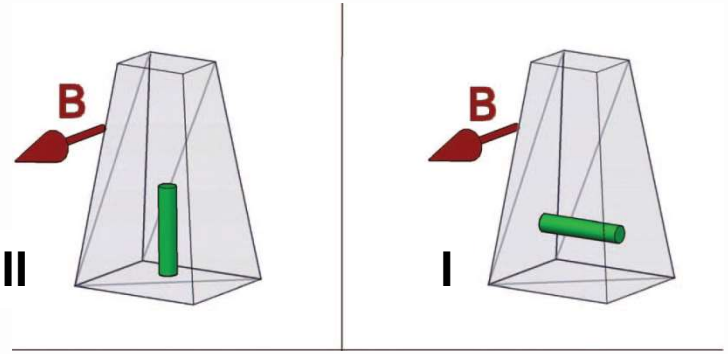


Raaijmakers et al. Phys. Med. Biol. 52, 7045 (2007)

Lorentz forces influence dosimetry in a magnetic field



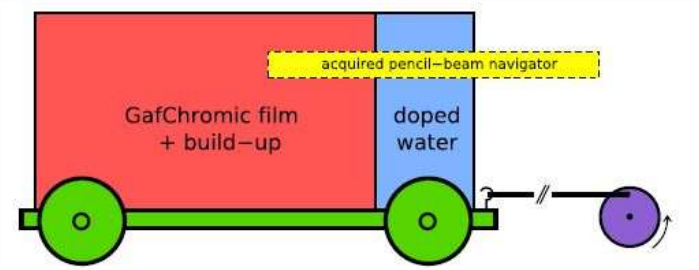
Meijsing et al. PMB 2009;54:2993-3002

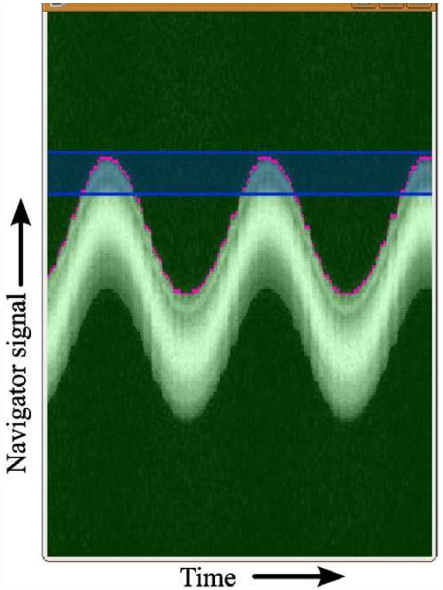


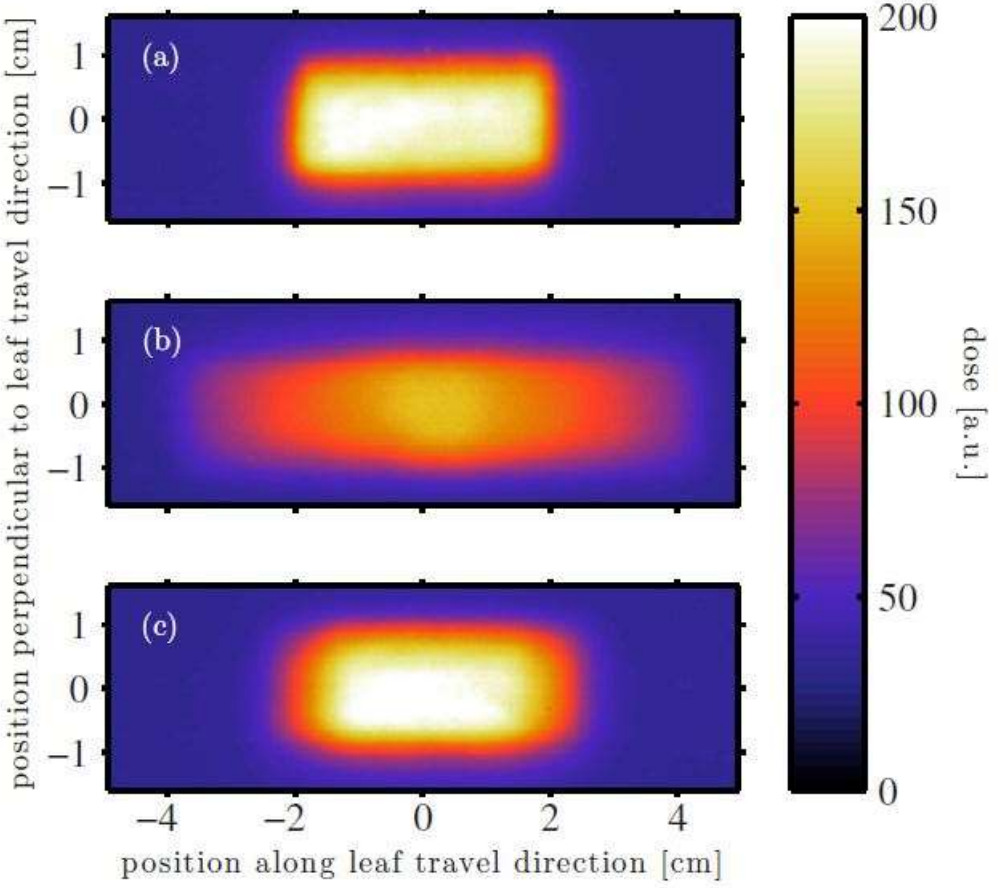
- The ion chamber response per unit fluence will depend on the orientations of
  - the beam
  - the B0 field
  - the ionization chamber

Navigators to track motion in 1D

- Very fast (~40 ms) imaging per frame is feasible in 1D
- Rather than a surrogate of the relevant motion, the actual structure can be m

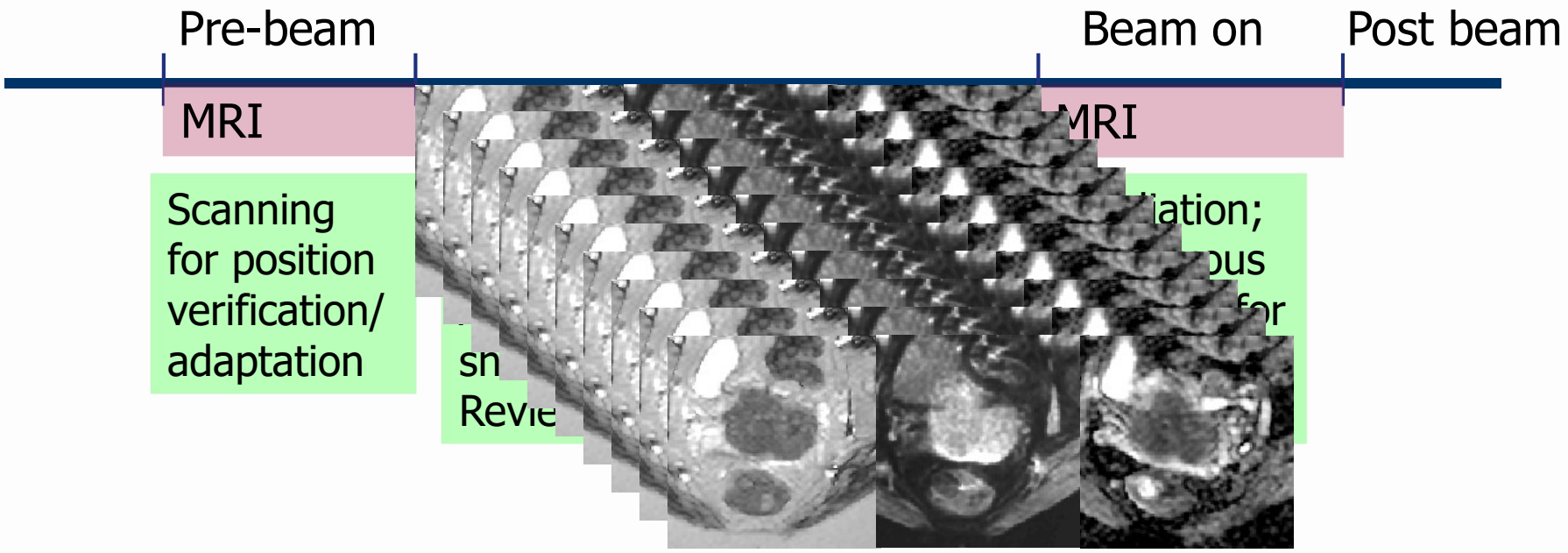






Crijns et al. Phys. Med. Biol. 56, 4815 (2011); 57, 7863 (2012)

Functional/quantitative imaging on an MR-Linac



- Frequent (daily) imaging of patients with advanced MRI techniques
- Imaging biomarker discovery

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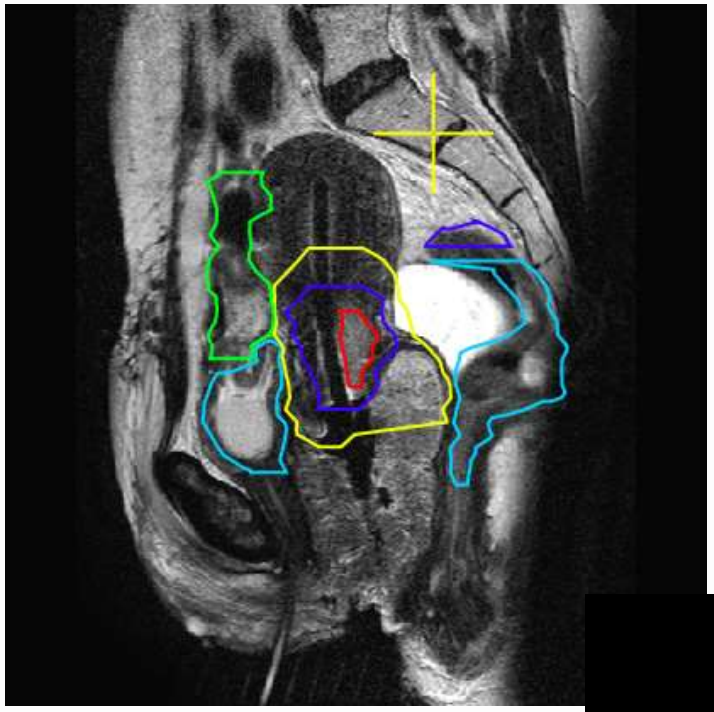
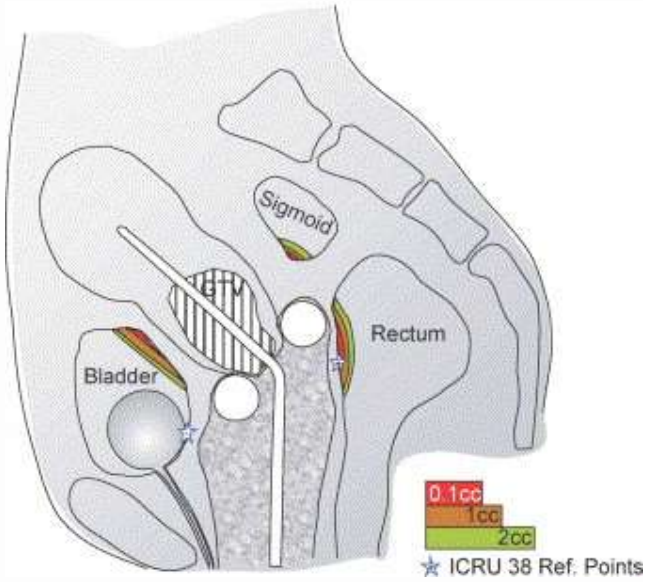
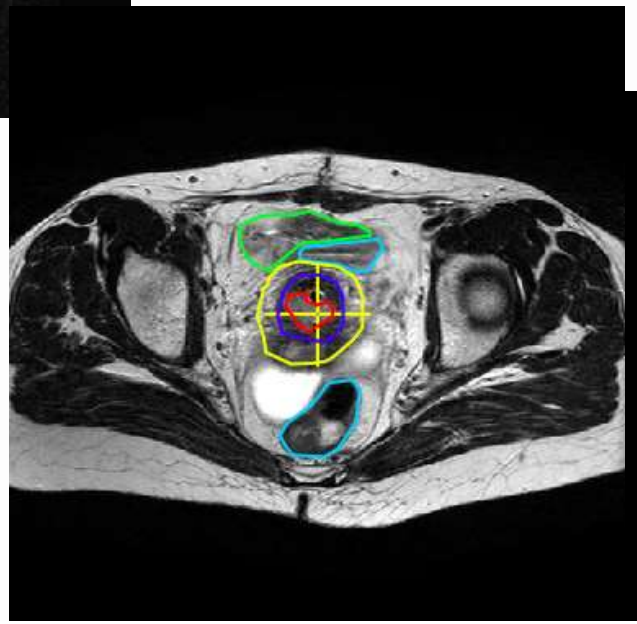
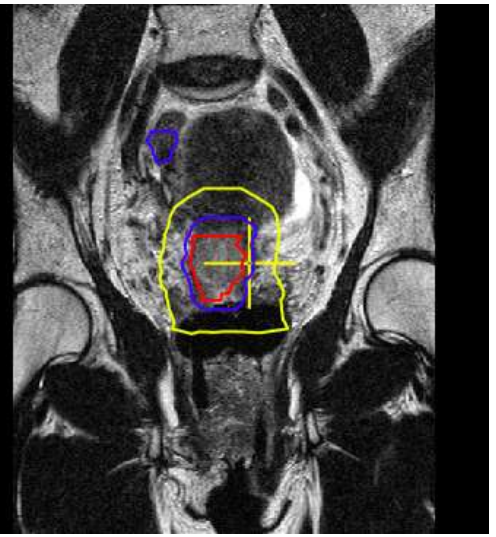
MRI-guided brachytherapy







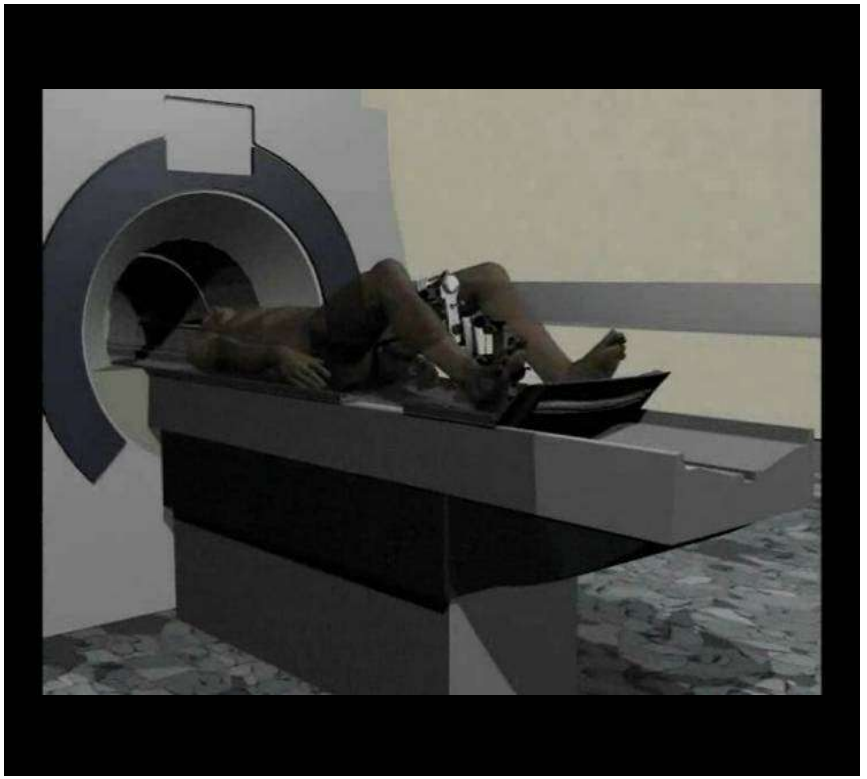


GTV
HR-CTV
IR-CTV
bladder
rectum
bowel

MRI-guided brachytherapy

Strategies:

- Register MRI with in-room imaging (US, x-rays)
  - e.g. prostate LDR
- Use MRI with applicator in situ for treatment planning, but irradiate elsewhere
  - e.g. cervix brachy
- Use MRI in shielded room: dose delivery on MRI couch



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Research opportunities

- MR-only simulation
  - Establish reliability
  - Develop technology for workflow
- MR-guided radiotherapy
  - Develop/optimize sequence for image guidance
  - Motion management
  - Automation of workflow
  - Development of new clinical applications

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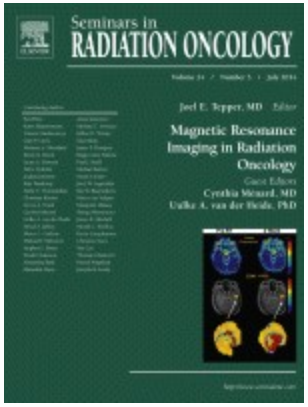
Further reading and learning on MRI in radiotherapy

ESTRO

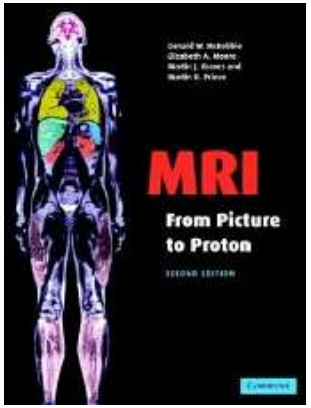
Application of imaging to radiotherapy

ISMRM ONE COMMUNITY FOR CLINICIANS AND SCIENTISTS

MRI physics and clinical application



Seminars in Radiation Oncology
July 2014



Picture to Proton (McRobbie, Moore, Graves and Prince; Cambridge University Press)

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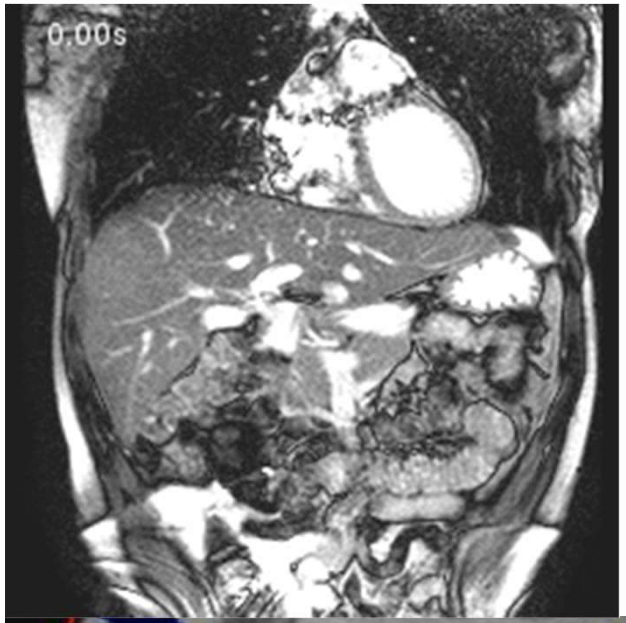
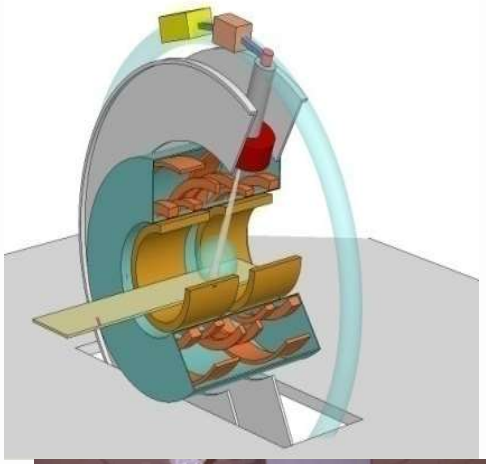
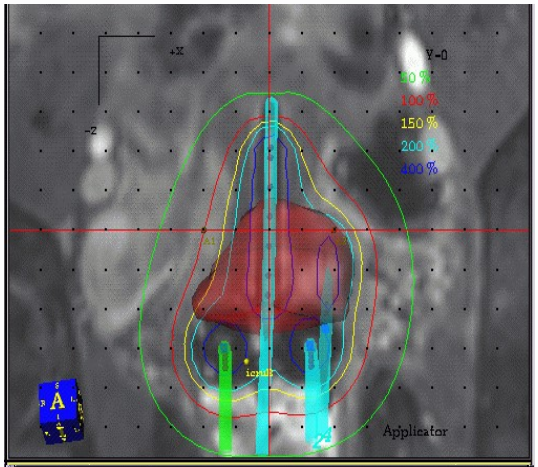
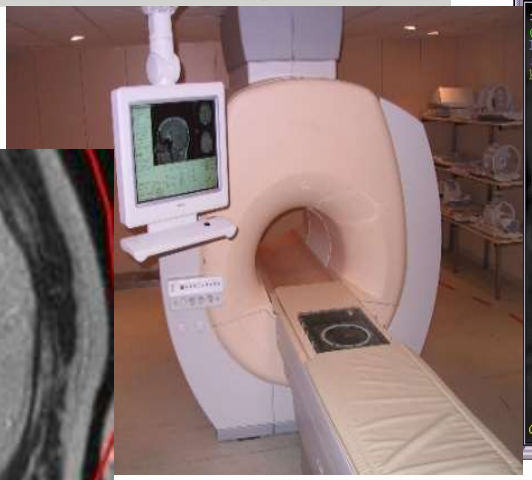
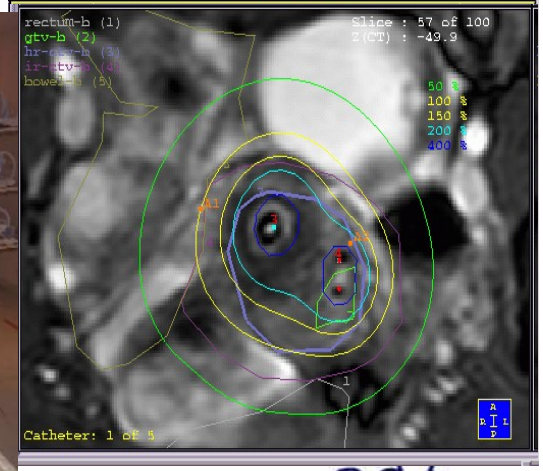
Imaging has a bright future in radiotherapy

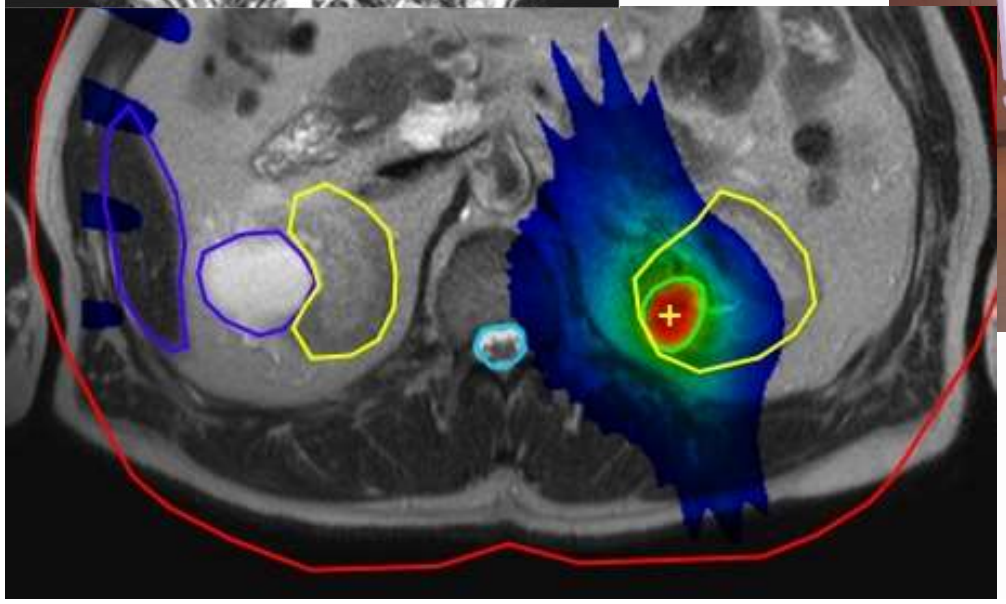












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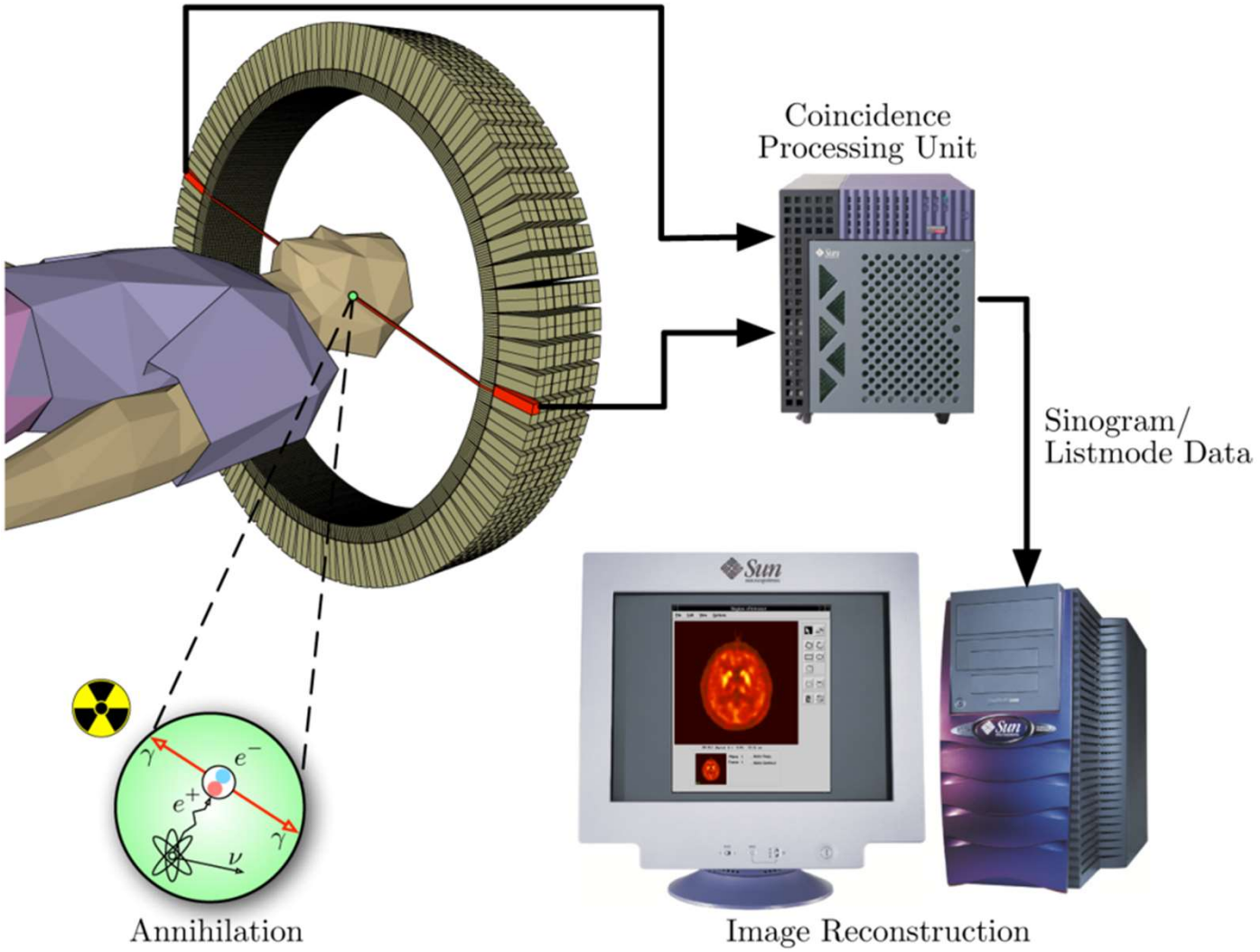
UiO : Department of Physics
University of Oslo

Oslo University Hospital

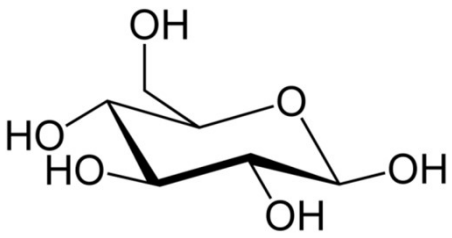
Trends and research opportunities in PET imaging in radiotherapy

Eirik Malinen

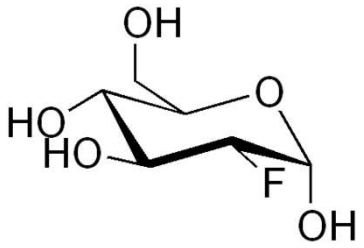
Positron emission tomography



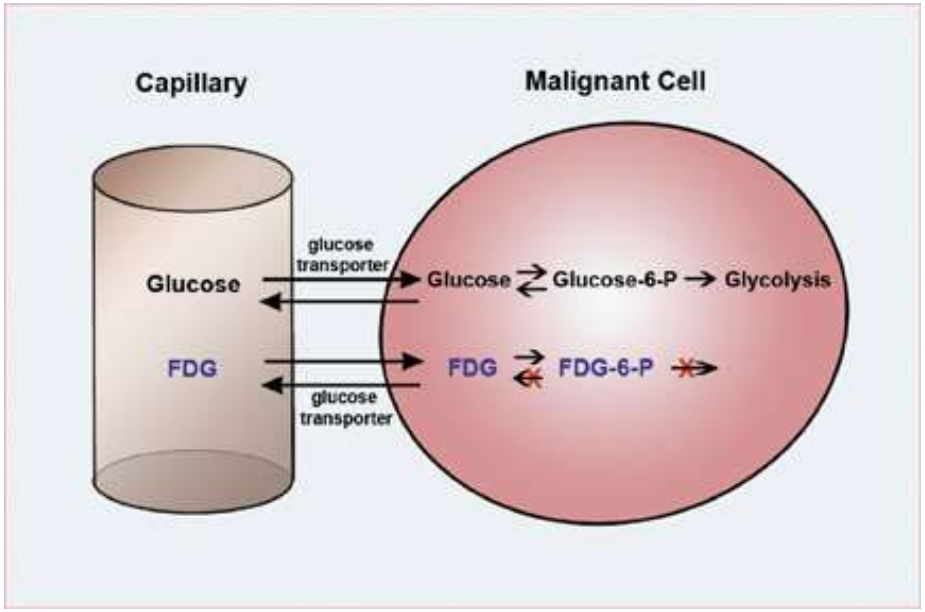
PET tracers - FDG



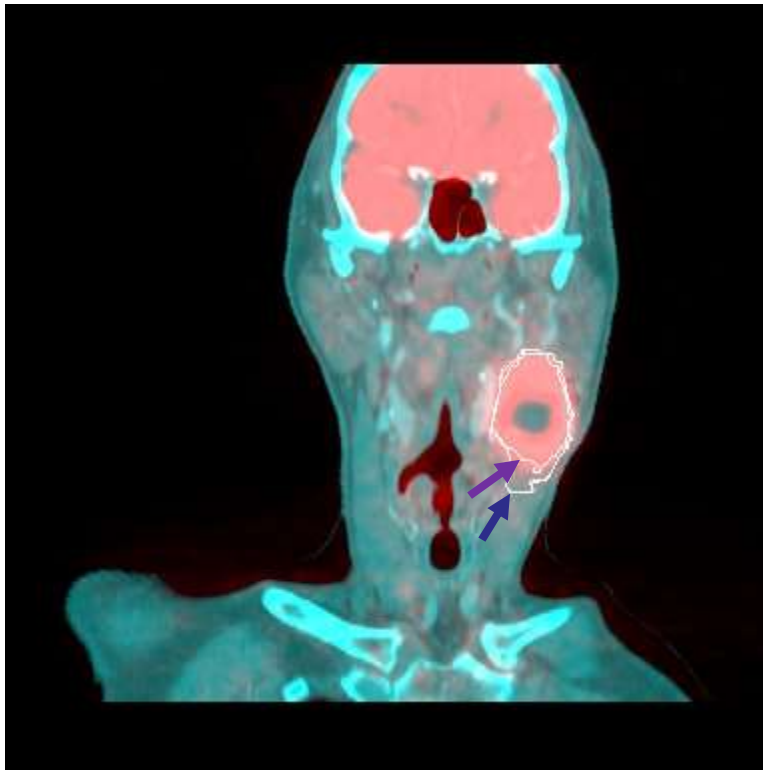
Glucose



Fluorodeoxyglucose - **18F-FDG**

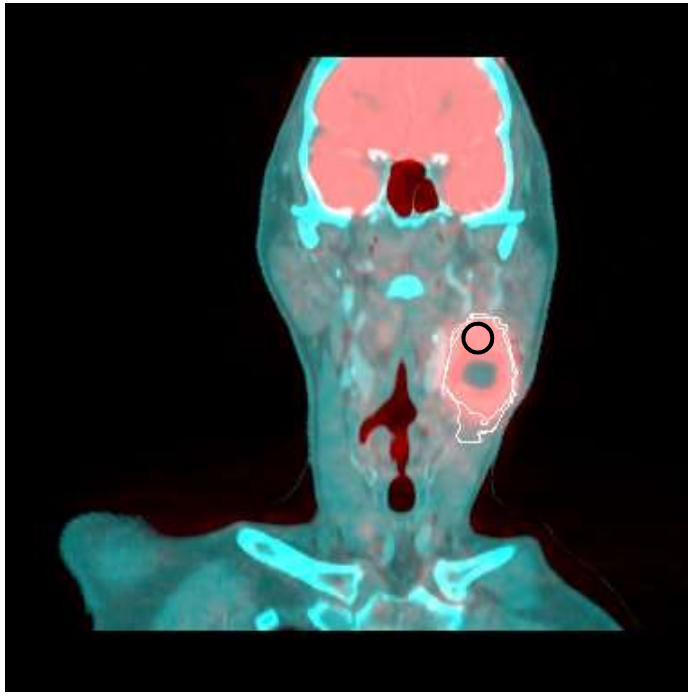


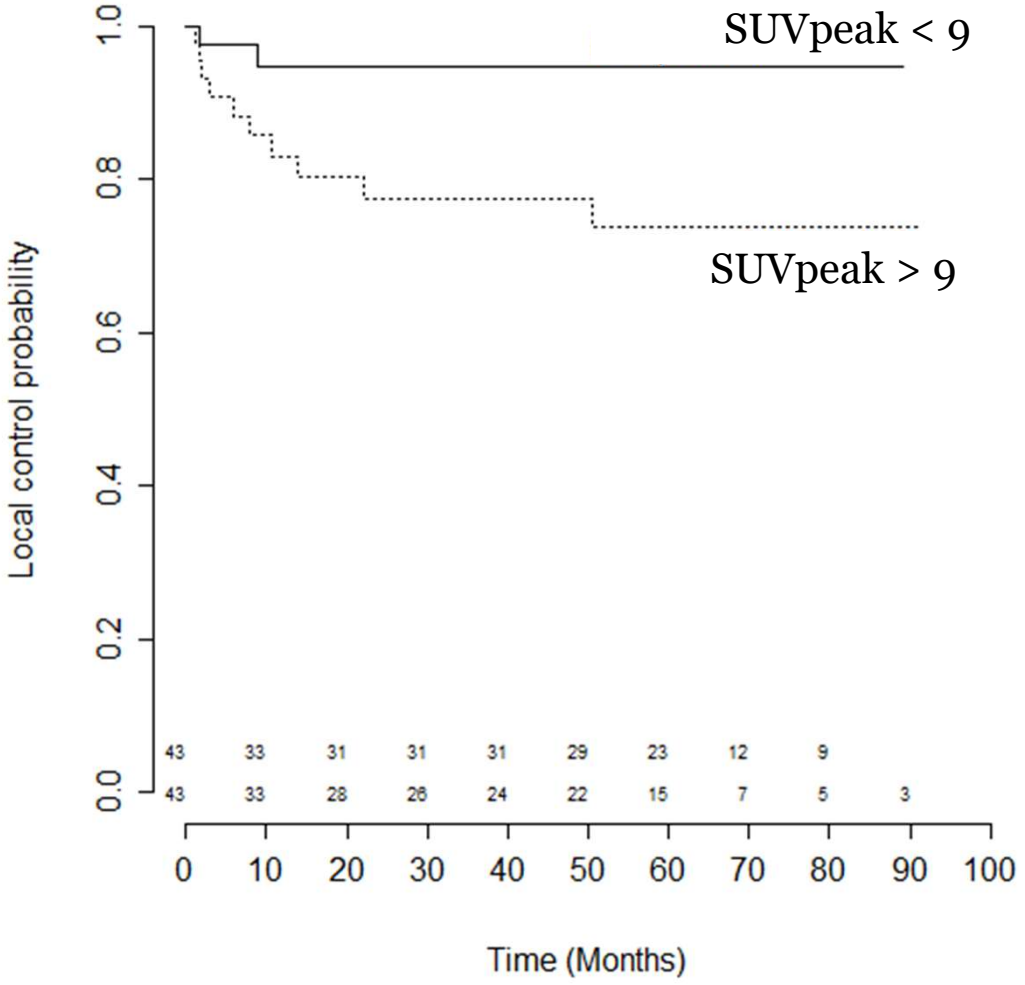
Seeing is believing…



18F-FDG PET/CT

....quantifying is proving





PET/CT in RT

Table 1 | PET–CT integration for imaging of tumor metabolism with [^{18}F]-FDG

Reference	Site of tumor	*n*	Conclusion of study	Potential applicability
Krengli *et al.* (2010)[90]	Anal cancer	27	Addition of [^{18}F]-FDG-PET–CT resulted in significant stage variation with change of treatment in a subgroup. The GTV and the CTV changed in shape and in size	Staging and target volume delineation
Ford *et al.* (2008)[93]	Breast	12	The targets using PET–CT were significantly larger than with CT alone	Target volume delineation
Kidd *et al.* (2010)[41]	Cervix uteri	83	Predicting response, pelvic recurrence risk, and disease-specific survival	Prognostic
Weber *et al.* (2001)[44] Schmidt *et al.* (2009)[45] Lordick *et al.* (2007)[49]	Esophagus	40 5 1,195	PET imaging may differentiate responding and nonresponding tumors early in the course of therapy, but this result has not been confirmed by other studies	Early response measurement with conflicting results
Madani *et al.* (2007)[48] Schinagl *et al.* (2009)[92] Geets *et al.* (2007)[95]	Head and neck	41 78 10	Adaptive IMRT with [^{18}F]-FDG-PET images has a significant impact on the delineation of GTV; however, the results depend on the PET segmentation tool used, and validation is, therefore, necessary	Target volume delineation and target boosting
Pommier *et al.* (2010)[88]	Hodgkin lymphoma	137	[^{18}F]-FDG-PET for treatment planning in Hodgkin lymphoma leads to modification of treatment and radiotherapy planning	Target volume delineation
Sasaki *et al.* (2005)[42] Hoekstra *et al.* (2005)[50] Vinod *et al.* (2010)[87] Petit *et al.* (2009)[91] Aerts *et al.* (2009)[99]	NSCLC	1,624 7 5 39 55	[^{18}F]-FDG-PET helps in the delineation of GTV [^{18}F]-FDG-PET has additional value over CT alone in monitoring response and may predict survival early during induction chemotherapy. Probability that a voxel is metabolically controlled decreased with increasing [^{18}F]-FDG uptake and tumor volume; pretreatment [^{18}F]-FDG-PET–CT identifies residual metabolically active areas	Early response measurement Prognostic/predictive target volume delineation
Jingu *et al.* (2010)[46] Janssen *et al.* (2010)[51]	Rectum	12 46	[^{18}F]-FDG-PET-guided IMRT can facilitate dose escalation and can be used to detect early metabolic responses during chemoradiotherapy	Target boosting Early response measurement
van Loon *et al.* (2008)[94]	SCLC	21	[^{18}F]-FDG-PET in limited disease SCLC changed the treatment plan in 24% of patients compared with CT	Target volume delineation
Benz *et al.* (2009)[43]	Sarcoma	50	Reduction in [^{18}F]-FDG uptake at early follow-up is a sensitive predictor of histopathological tumor response	Prognostic, early response measurement

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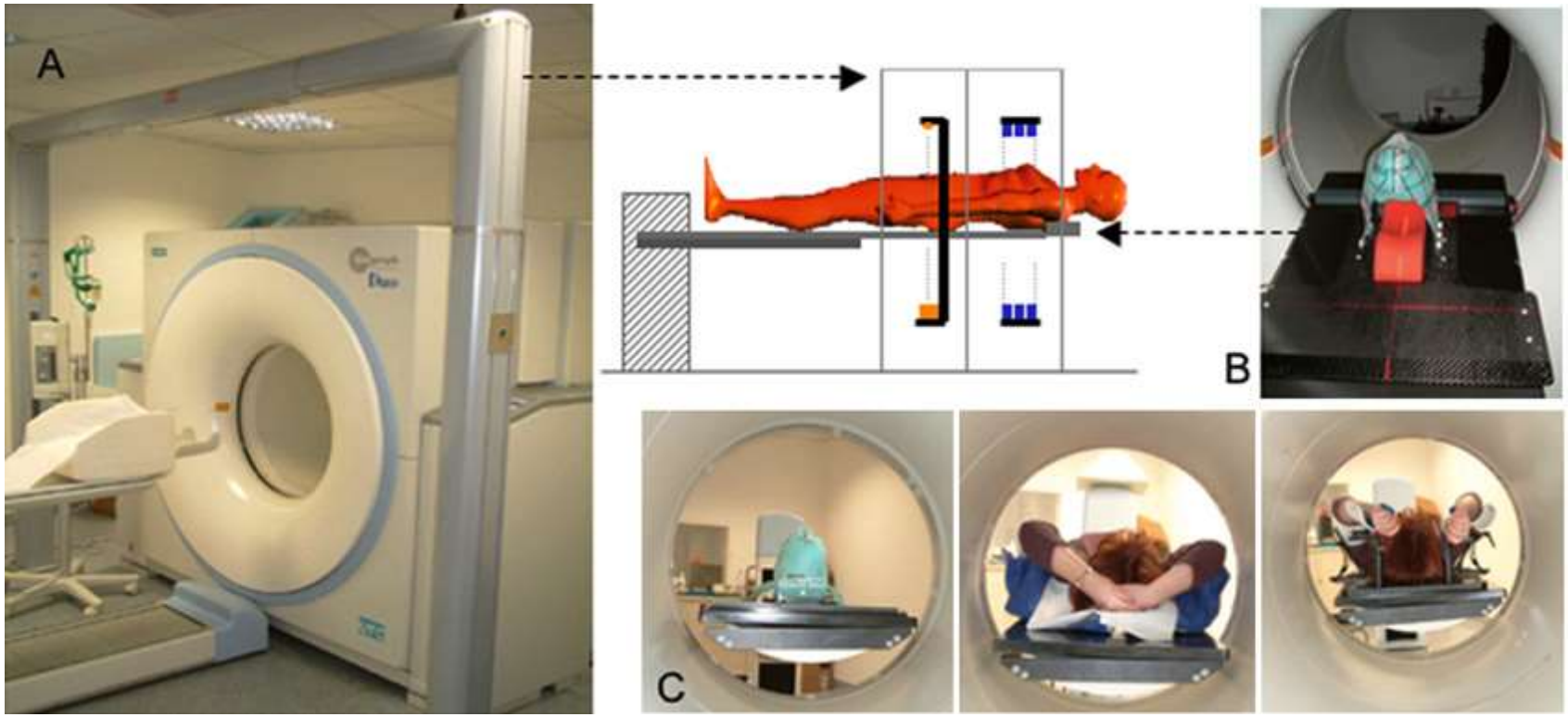
PET tracers

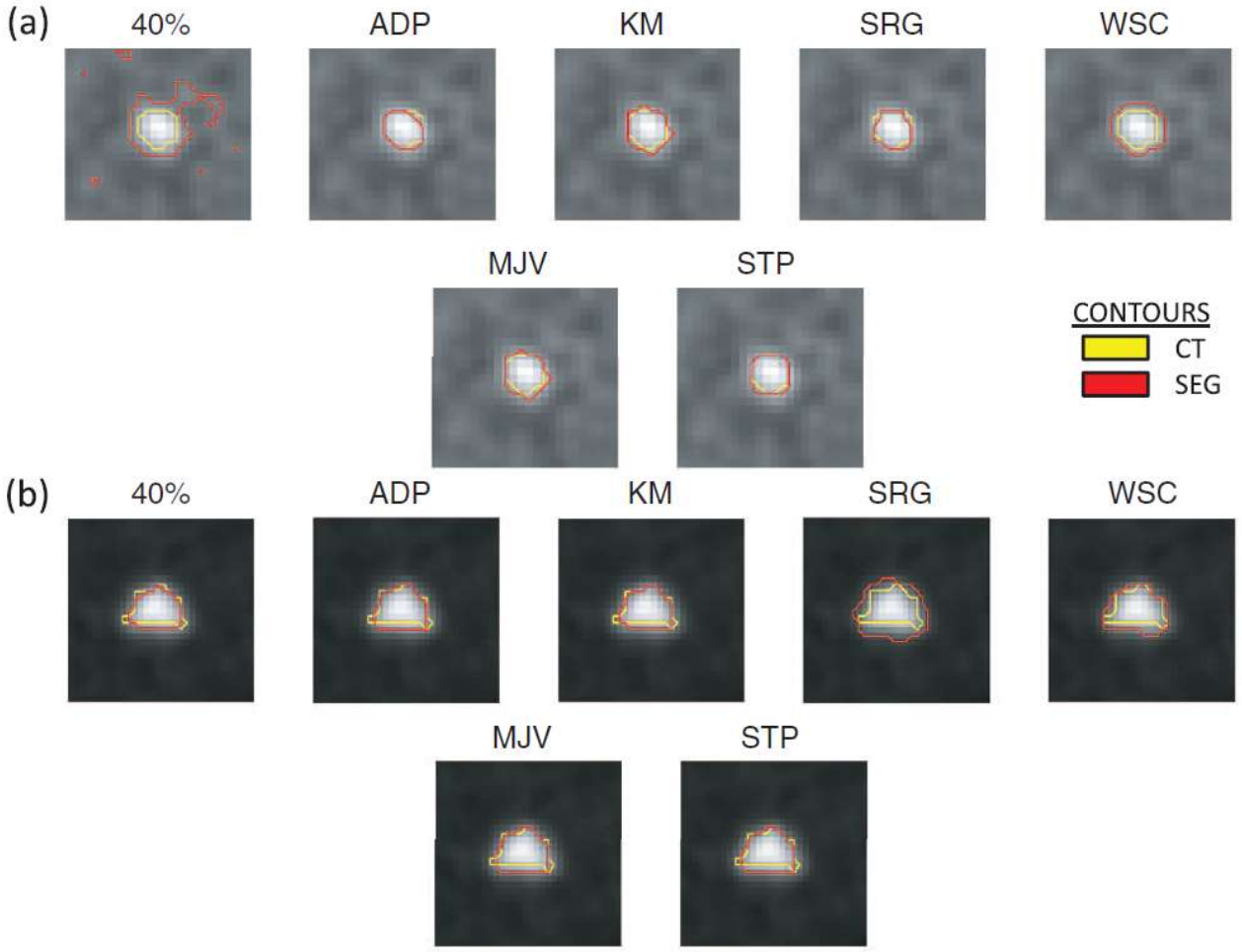
Radiopharmaceutical	Biological process	Radiation treatment planning	Therapy response monitoring of radiotherapy or chemoradiotherapy
[^{18}F]-FDG	Metabolism	13	34
[^{18}F]-FLT	Proliferation	1	2
[^{18}F]-FMISO, [^{18}F]-HX4, [^{64}Cu]-ATSM	Hypoxia	3	5
[^{18}F]-FET	Protein synthesis	0	1
[^{18}F]-NaF	Osteoblast activity	0	1
[^{64}Cu]-labeled trastuzumab	HER2 expression	0	1
[^{18}F]-FML	Apoptosis	0	3

PET/CT for RT planning



Radiotherapy & Oncology 96, issue 3 (2010)

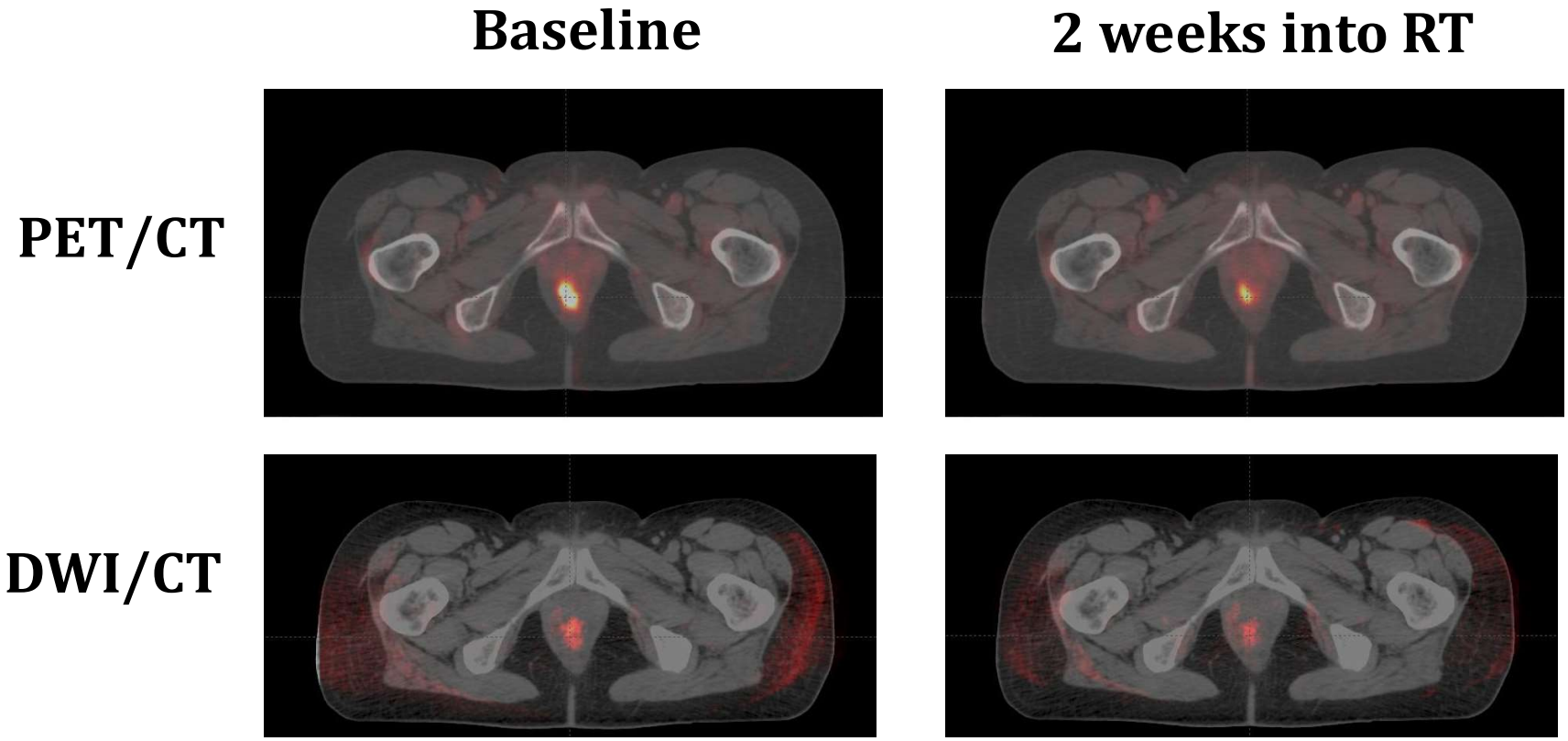
Autocontouring



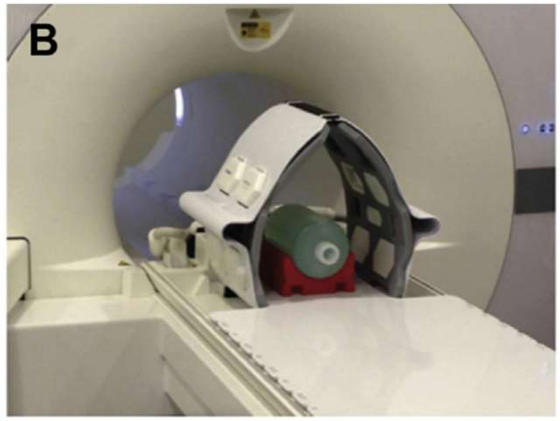
Medical Physics 40, 042501 (2013)

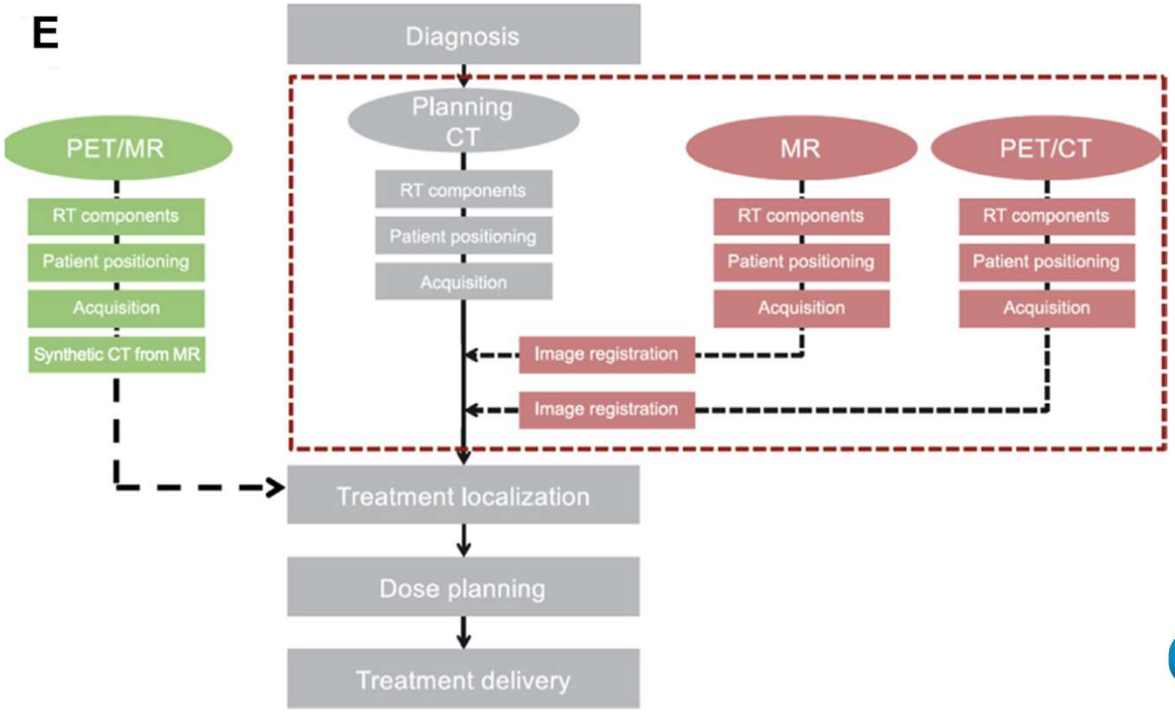
PET vs MRI

- Compare different imaging modalities



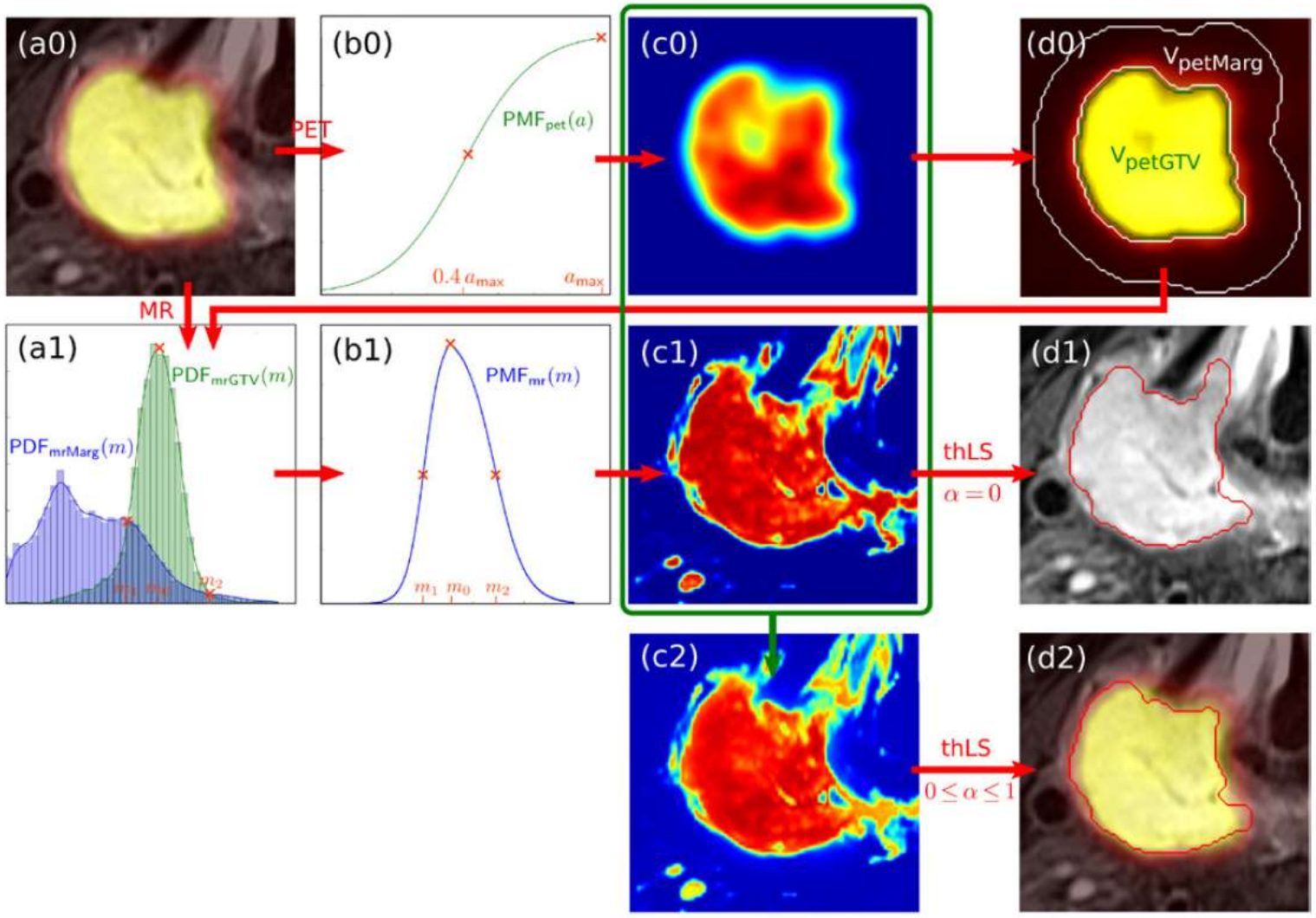
Hybrid PET/MR





Magn Reson Imaging Clin N Am
25 (2017) 377–430

PET/MR - autocontouring



Phys. Med. Biol. 60, 5399–5412 (2015)

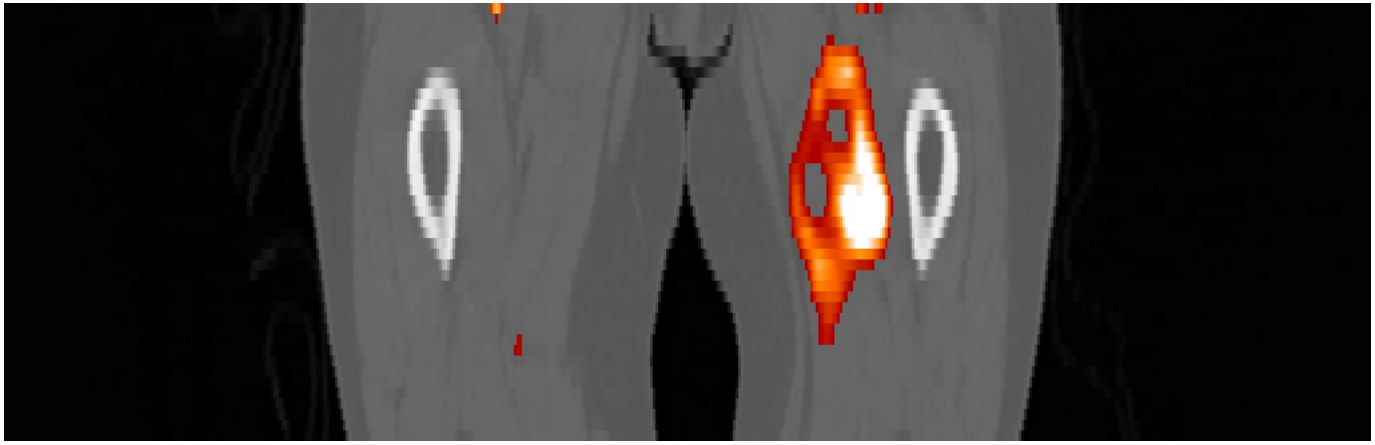
Dynamic PET

Conventional PET:

- Patient rests for 1 hour after injection
- Produces a ”static” PET image series (3D)

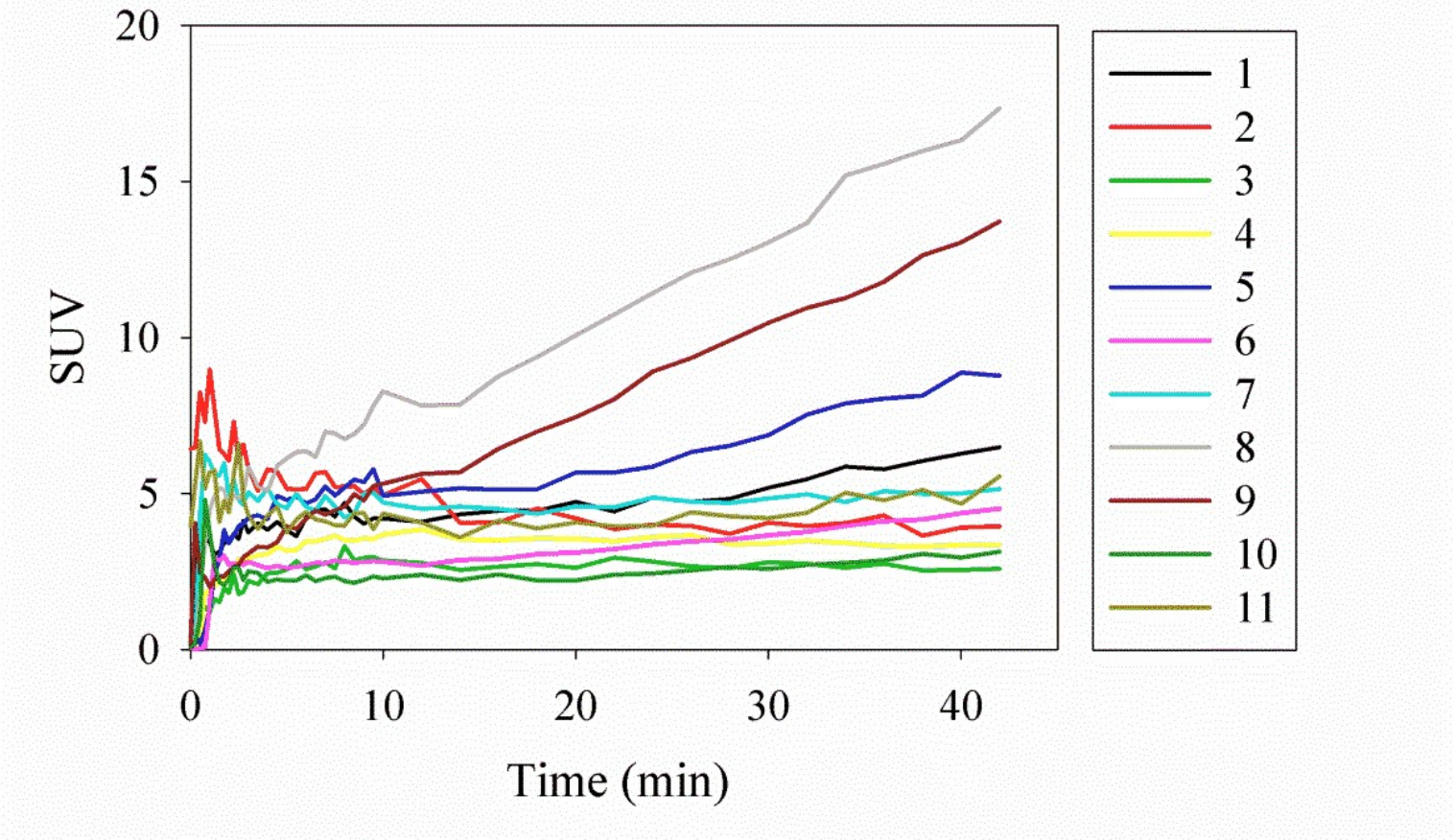
Dynamic PET

- PET-acquisition starts at the time of injection
- Produces a dynamic image series (4D)



Dynamic PET

- Soft tissue sarcomas

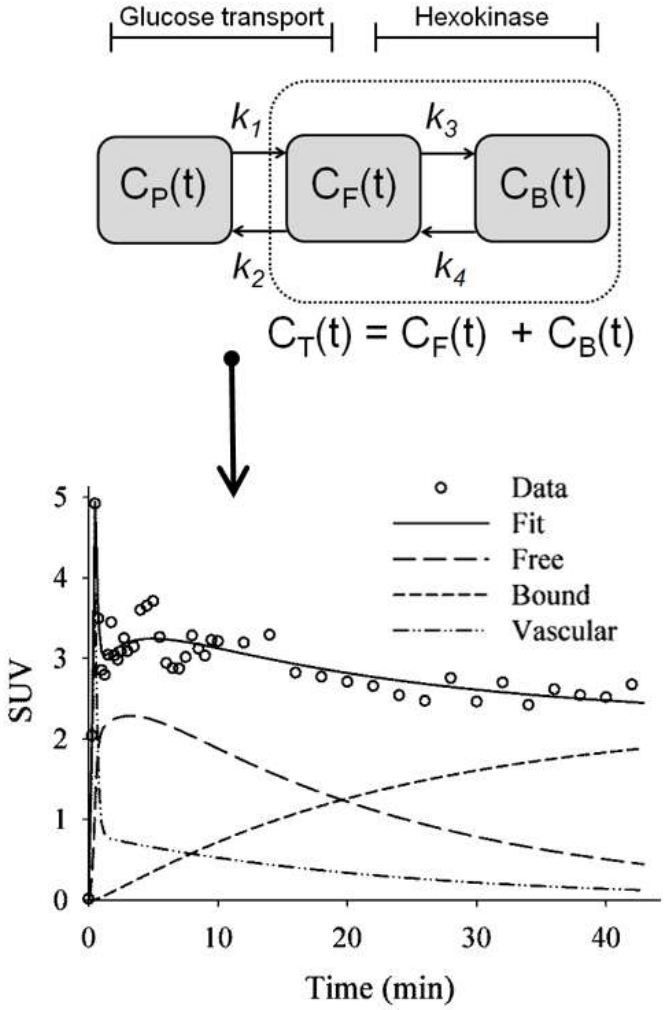


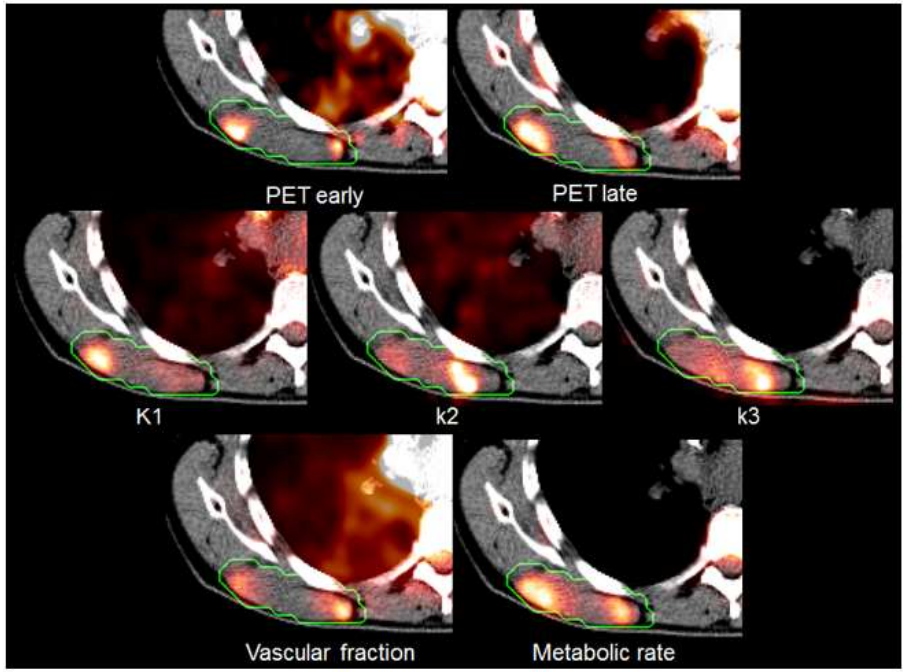
$SUV_{early} > SUV_{late}$ for 4/11 tumors

Acta Oncol. 2013 Aug;52(6):1160-7

Kinetic analysis

- Model tracer distribution in tissue



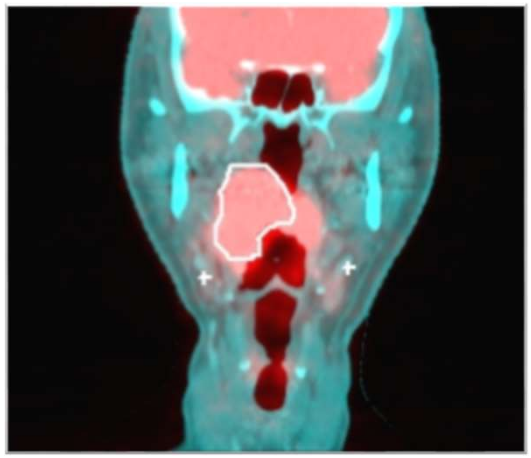


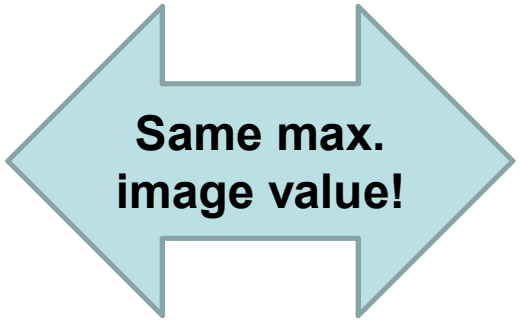
$K_1 = 0.20$
$k_2 = 0.40$
$k_3 = 0.037$
$v_p = 0.16$
$MR_{FDG} = 0.016$
$r^2 = 0.89$

Acta Oncol. 2013 Aug;52(6):1160-7

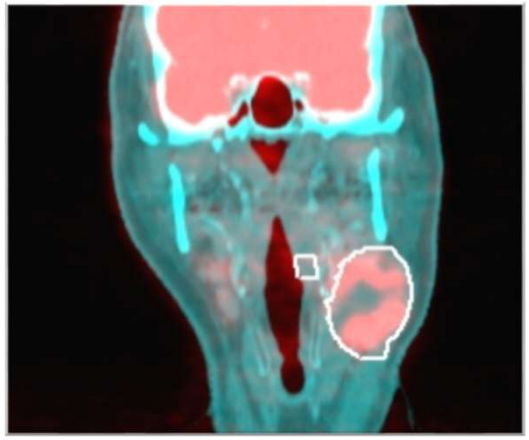
Problem

Patient 1





Patient 2

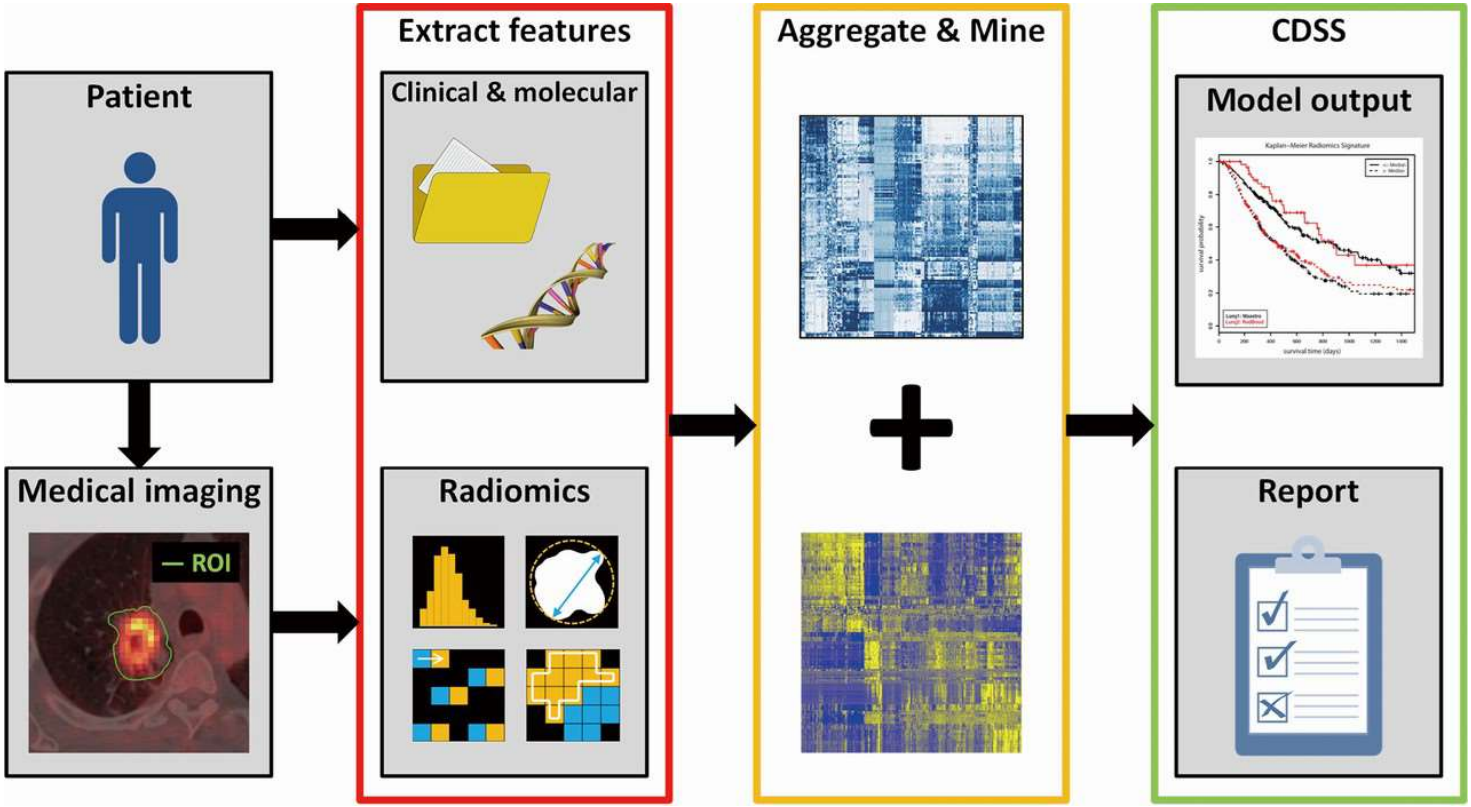


How to *quantify* differences in tumor appearance?

→ look for e.g. *texture* in images

Radiomics

- Extracting more information from medical images



Transl Cancer Res 5, 398-409 (2016)

Radiobiological modeling

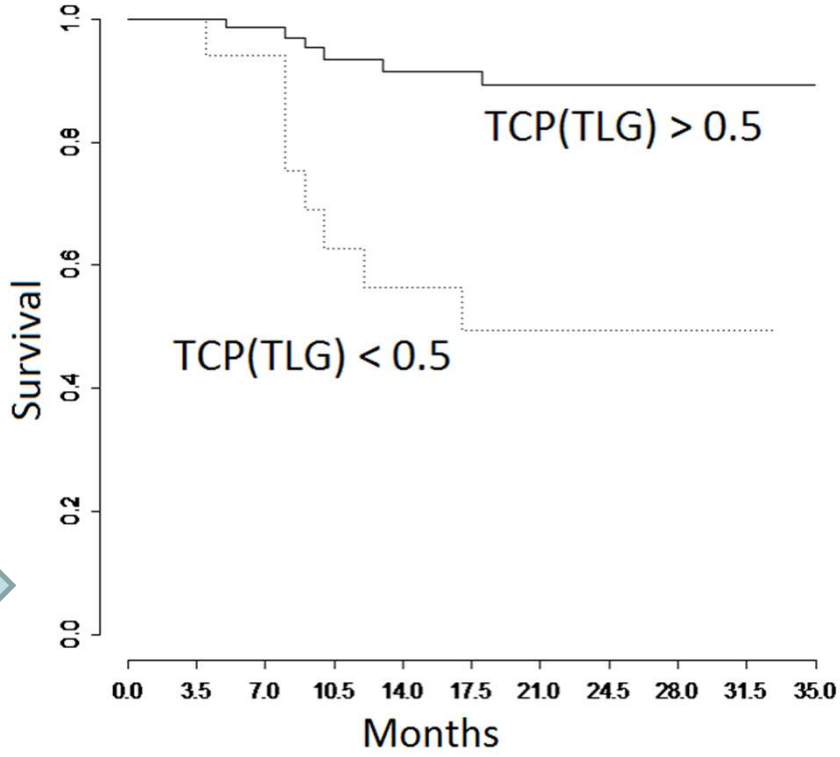
- Use images to estimate tumor radioresistance

$$\mathrm{NSC} = \rho V \mathrm{e}^{-\alpha \mathrm{nd}(1+\frac{\beta}{\alpha}\mathrm{d})}$$

$$\rightarrow \mathrm{TCP} = \mathrm{e}^{-\mathrm{NSC}}$$

$$= \exp\left\{-\rho V \mathrm{e}^{-\alpha \mathrm{nd}(1+\frac{\beta}{\alpha}\mathrm{d})}\right\}$$

Assume $\rho \sim SUV$



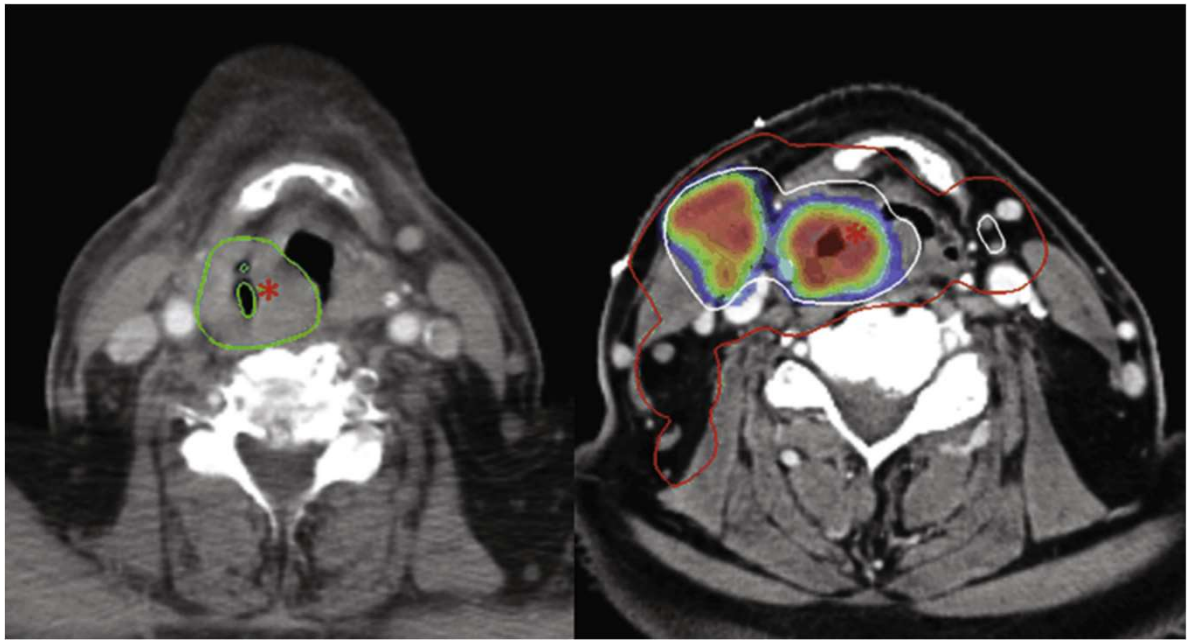
Work in progress

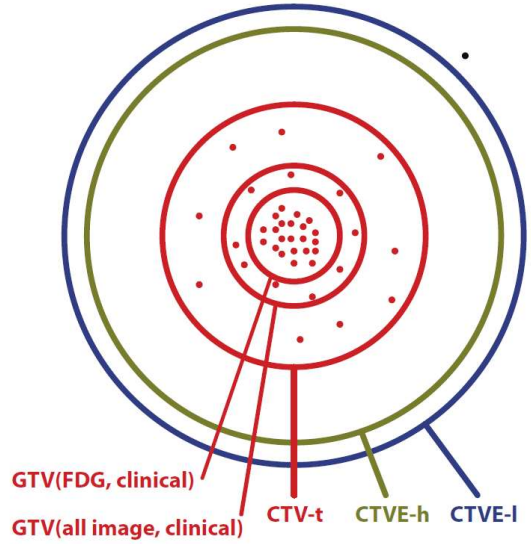
Analyzing recurrence patterns

- Where do recurrences appear? Are these reflected in uptake patterns in the primary?

CT scan of recurrent tumor

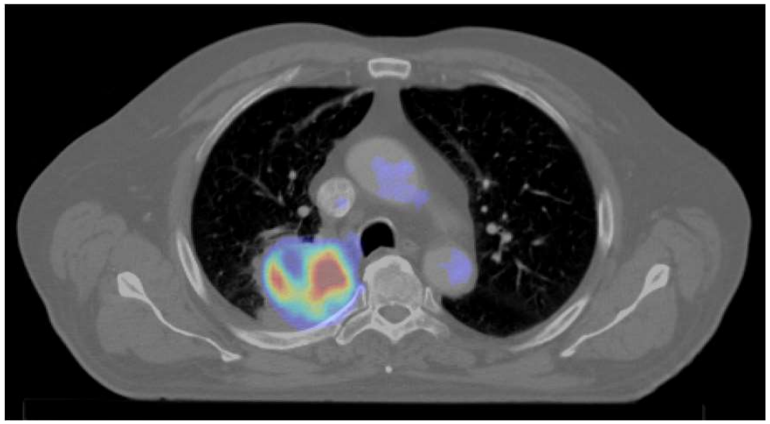
Centroid on original PET scan

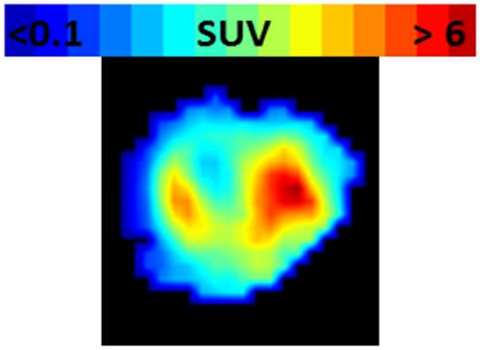




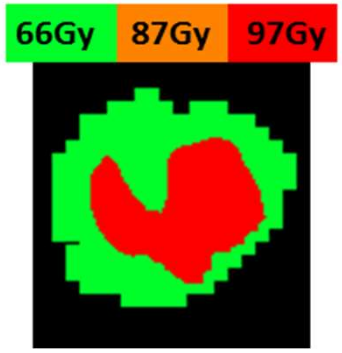
Dose painting

- Deliver dose where dose is needed

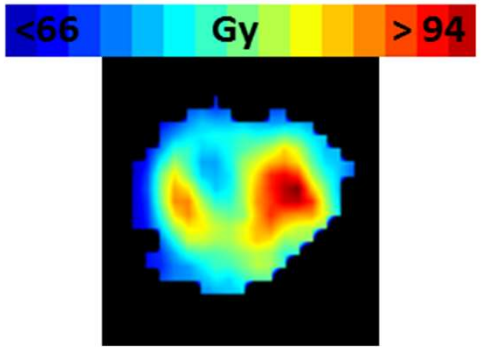




PET intensity map

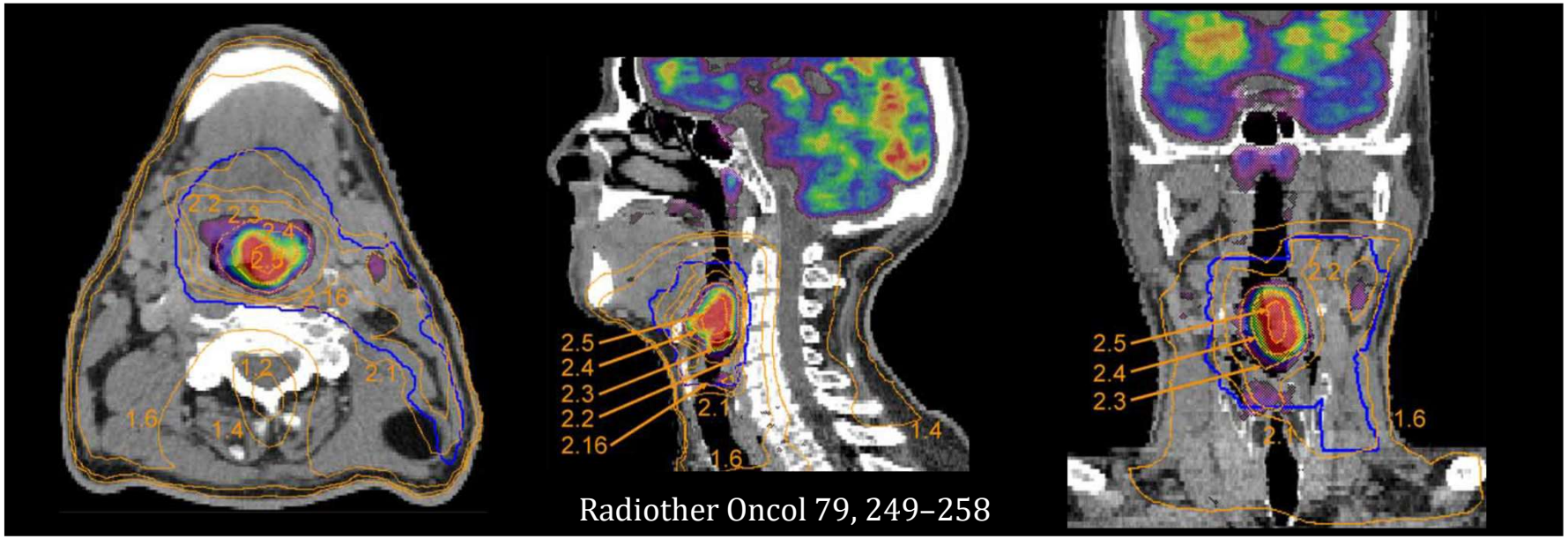


DPBC –
Dose painting
by contours



DPBN –
Dose painting
by numbers

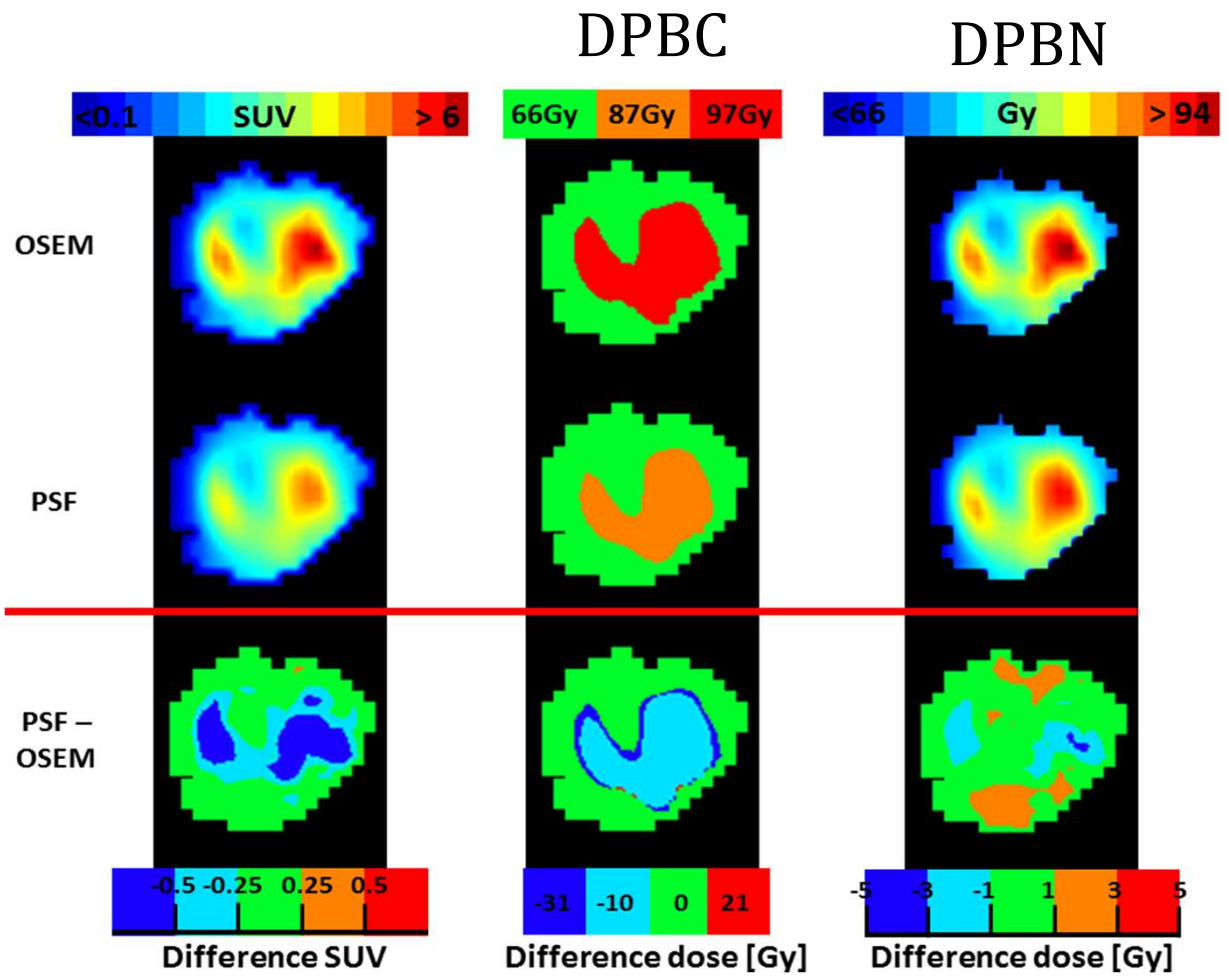
Dose painting by numbers



- Lack of clinical RT dose planning systems
- How to prescribe dose?
- What if different PET tracers are used?

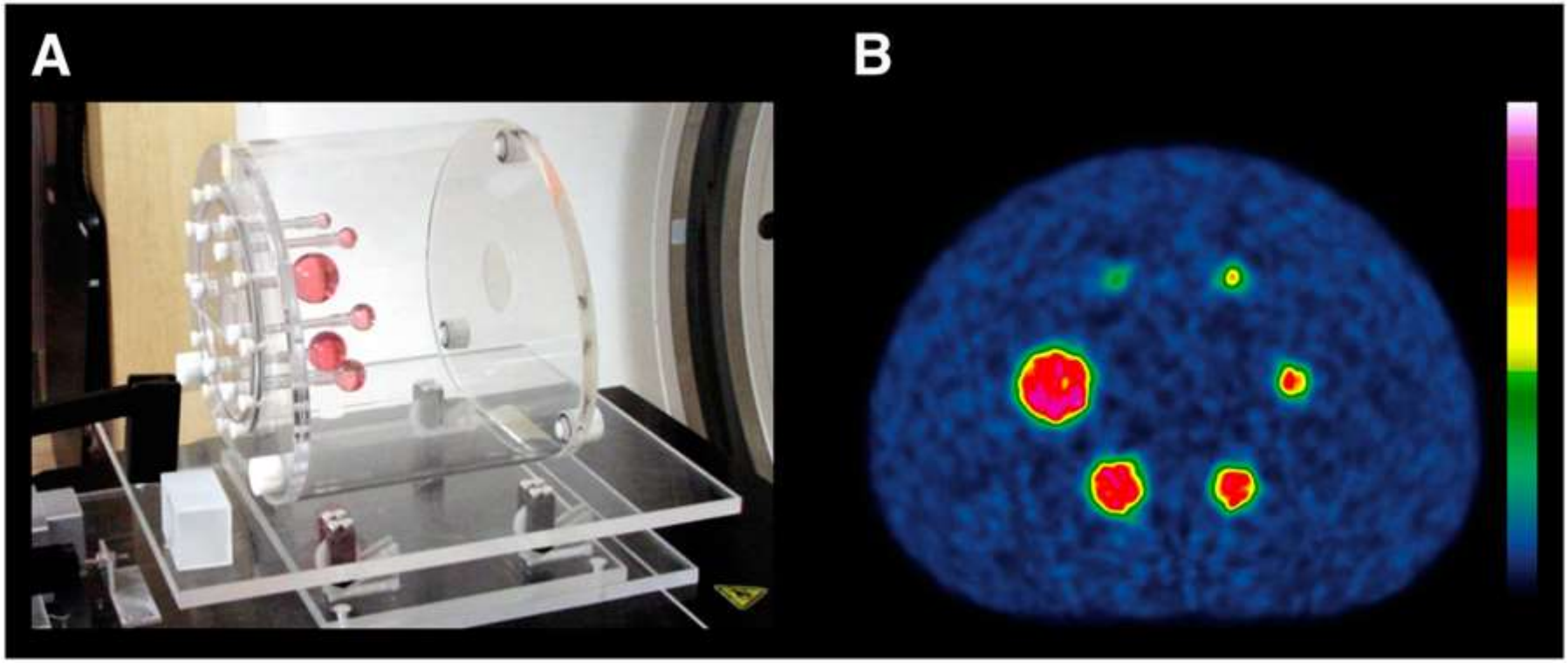
Dose painting

- Impact of PET reconstruction



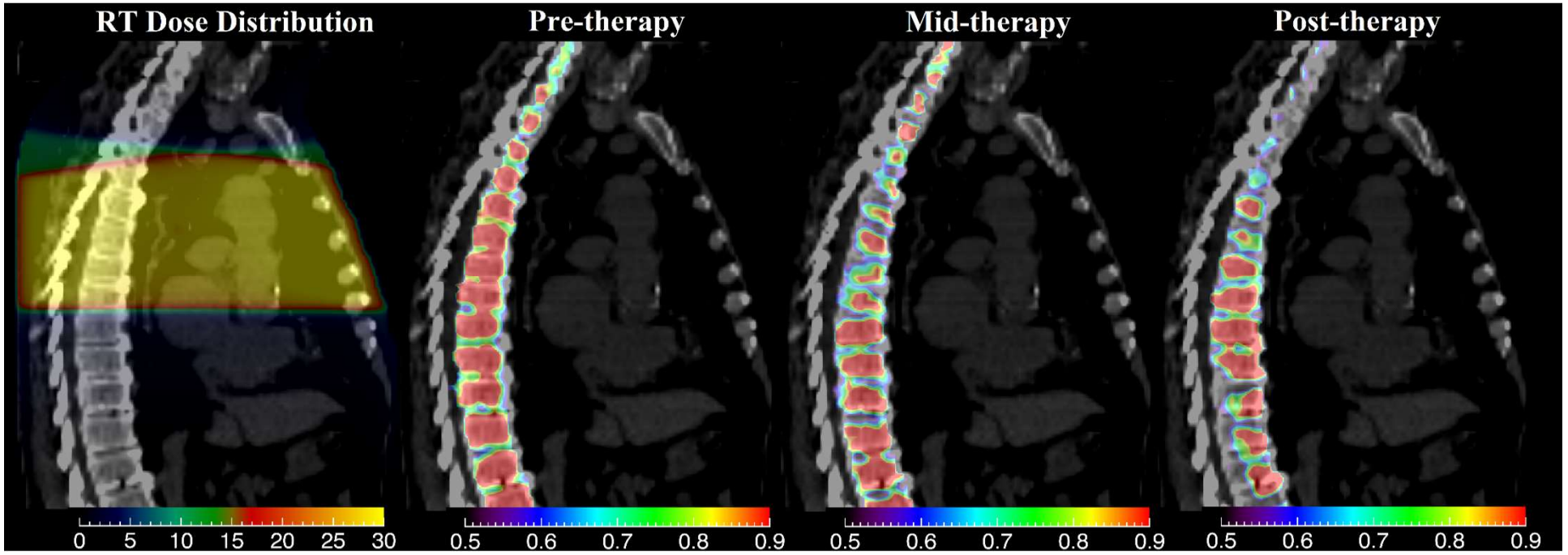
Dose painting - auditing

- What about differences between scanners?



Normal tissue function

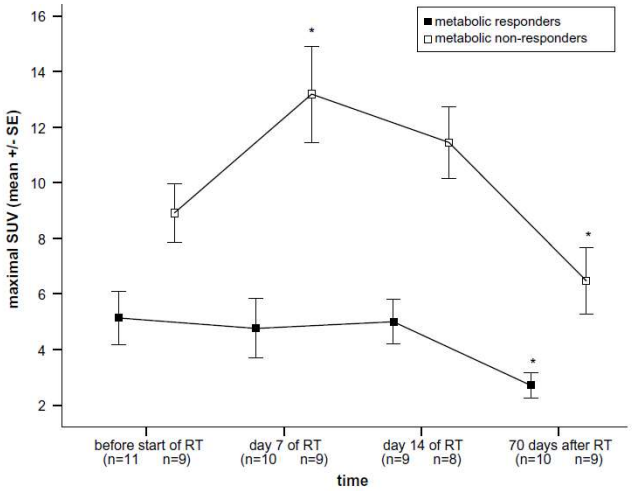
- Why only focus on the tumor?

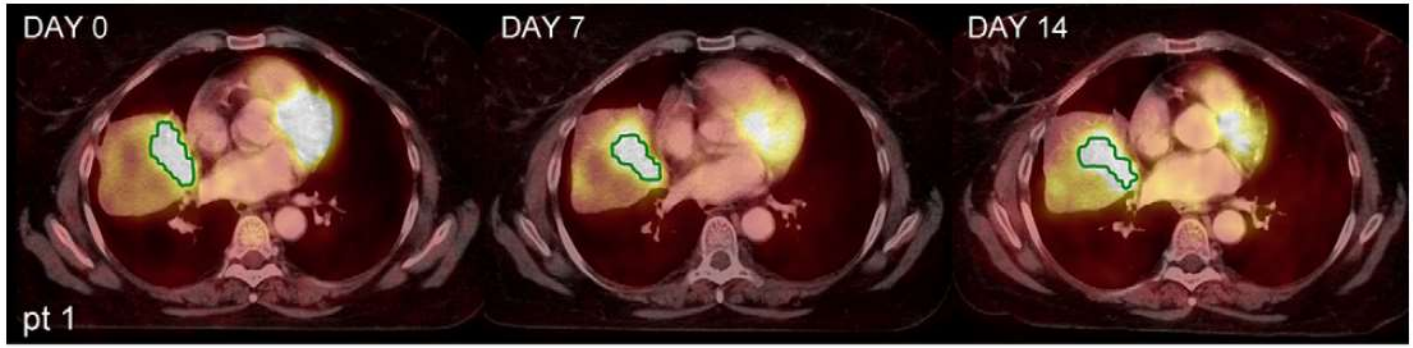


PET/CT in RT
-
success stories

^{18}F-FDG-PET of NSCLC

- Part 1: FDG as a marker of tumor resistance

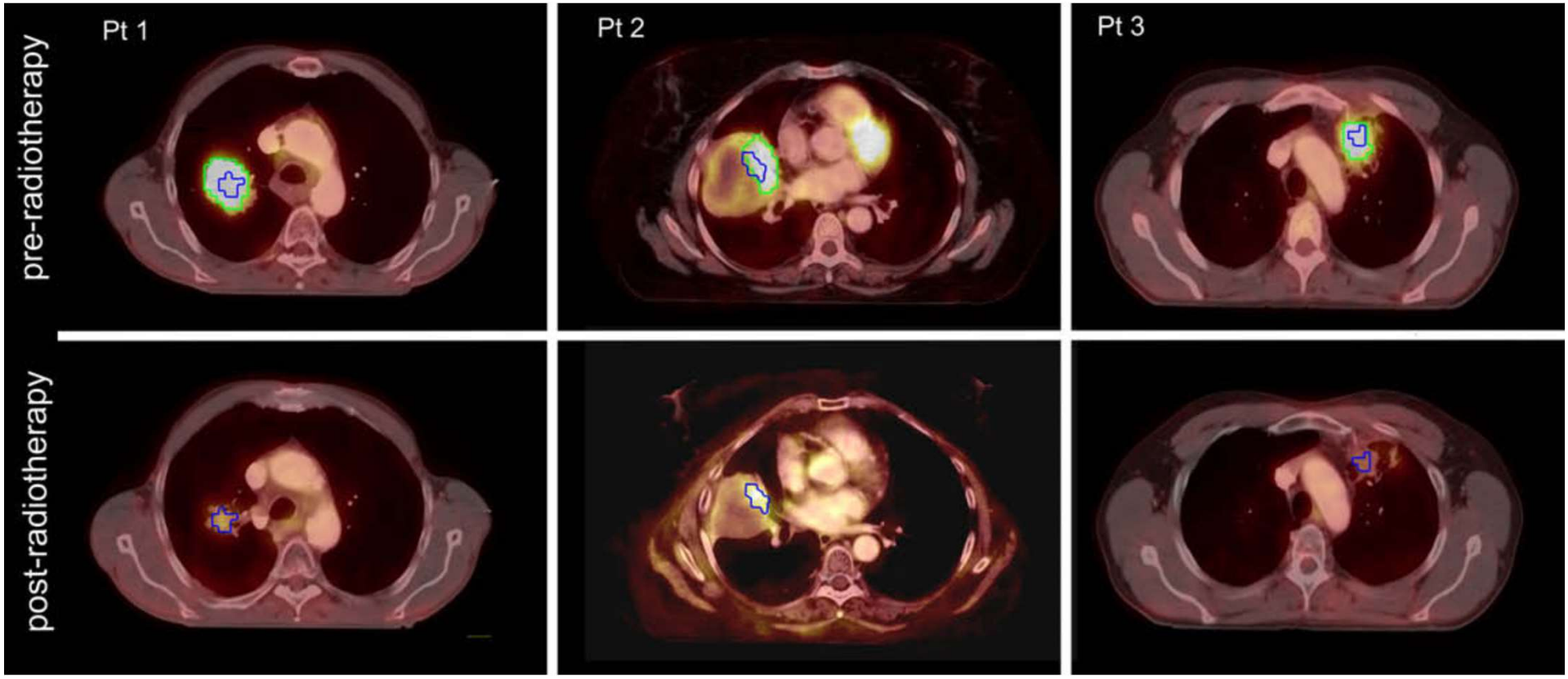




Radiother Oncol 82, 145–152
Int J Radiat Oncol Biol Phys 71, 1402-1407

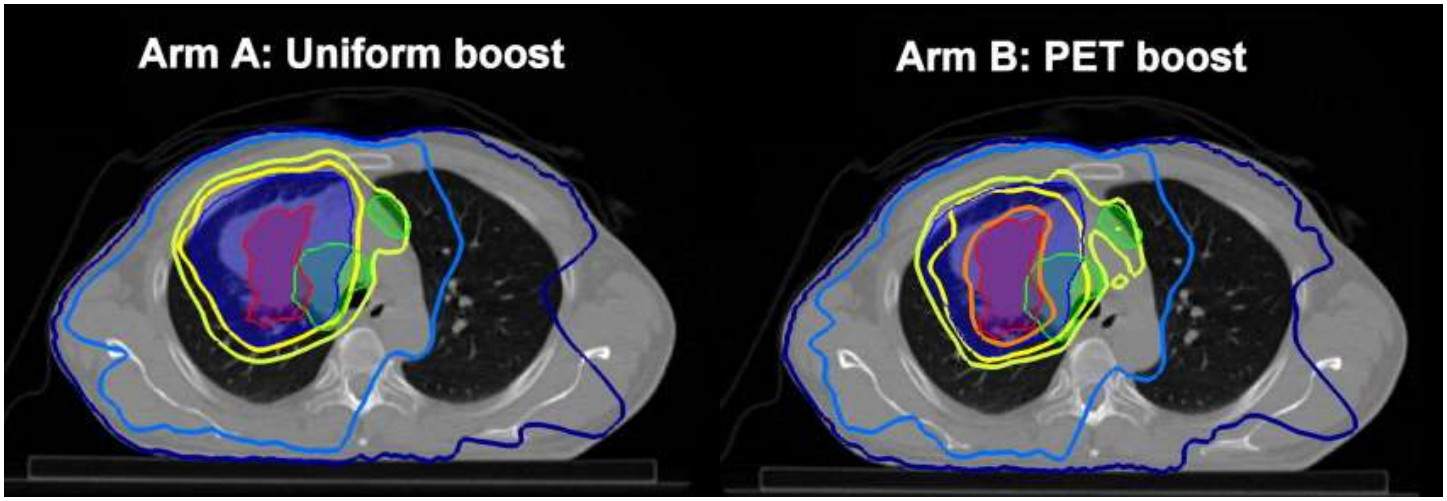
^{18}F-FDG-PET of NSCLC

- Part 2: Look at recurrence patterns



^{18}F-FDG-PET of NSCLC

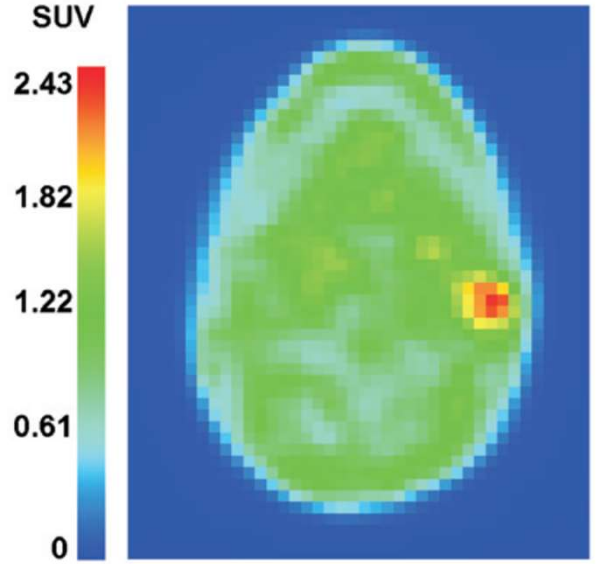
- Part 3+4: Optimize dose painting by contours; run clinical trial



Radiotherapy and Oncology 104 (2012) 67–71

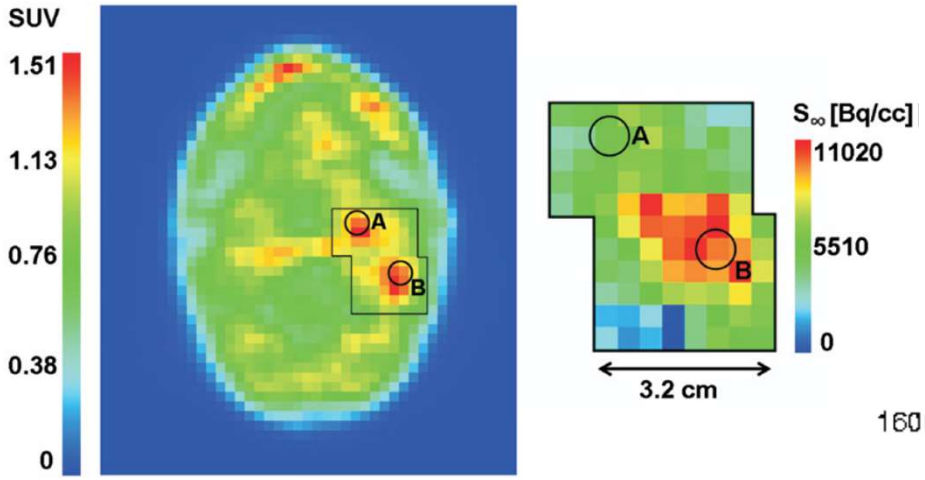
^{18}F-FMISO-PET of H&N cancer

- Hypoxia is a known cause of resistance to RT
- Use non-invasive imaging to identify hypoxic regions; escalate dose by IMRT / VMAT
- ^{18}F-FMISO accumulates in hypoxic tissues

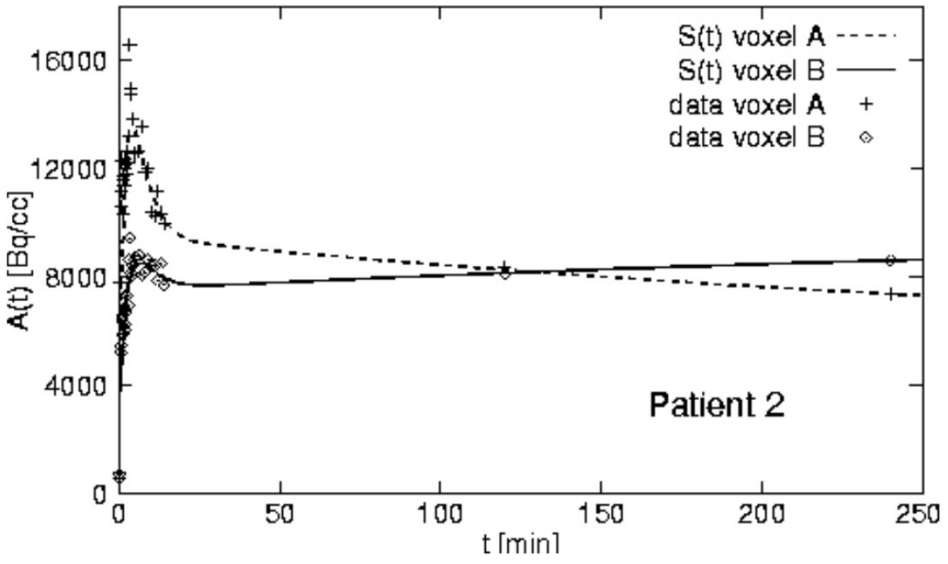


^{18}F-FMISO-PET of H&N cancer

- Part 1: Dynamic PET scanning and kinetic analysis

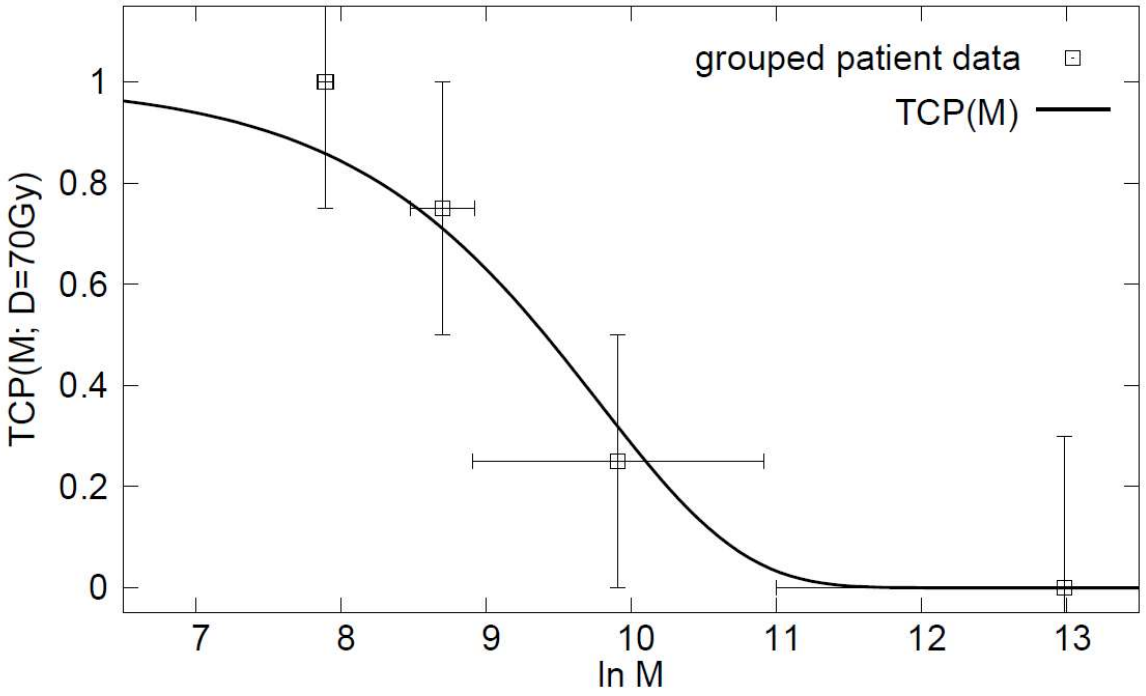


Phys. Med. Biol. 50 (2005) 2209–2224



^{18}F-FMISO-PET of H&N cancer

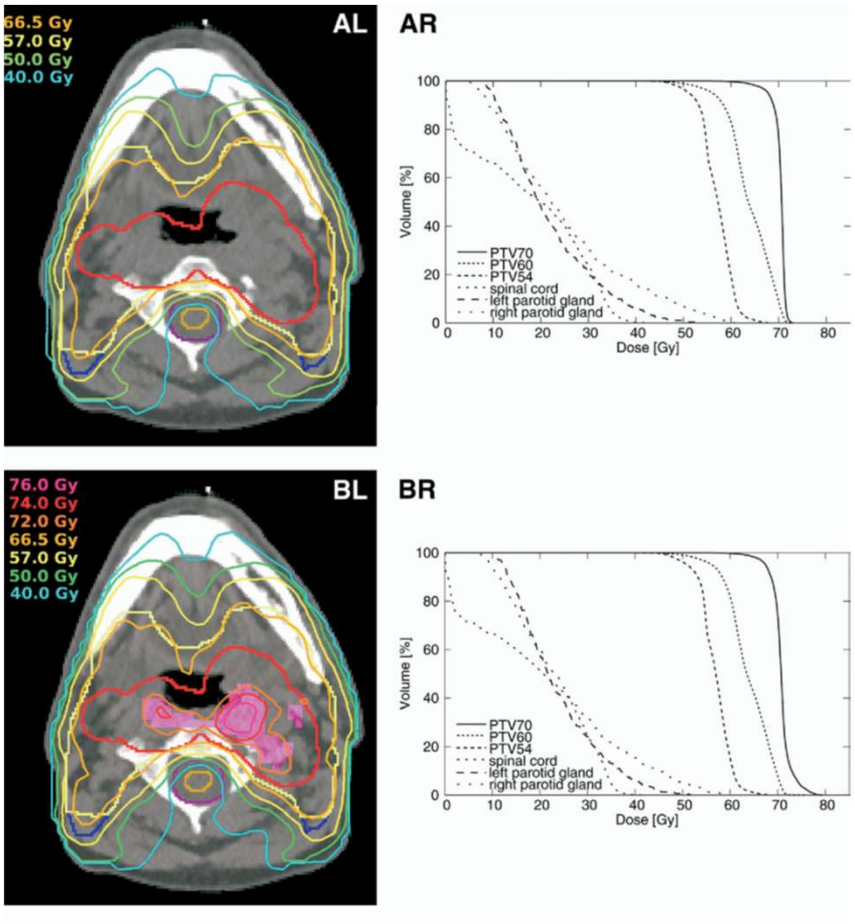
- Part 2: Clinical-follow up; derive DPET-based malignancy index



BMC Cancer 2005, 5:152

^{18}F-FMISO-PET of H&N cancer

- Part 3: Optimize hypoxia dose painting *in silico*

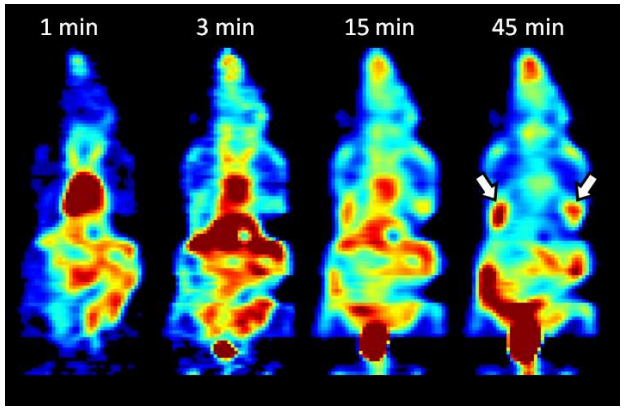


^{18}F-FMISO-PET of H&N cancer

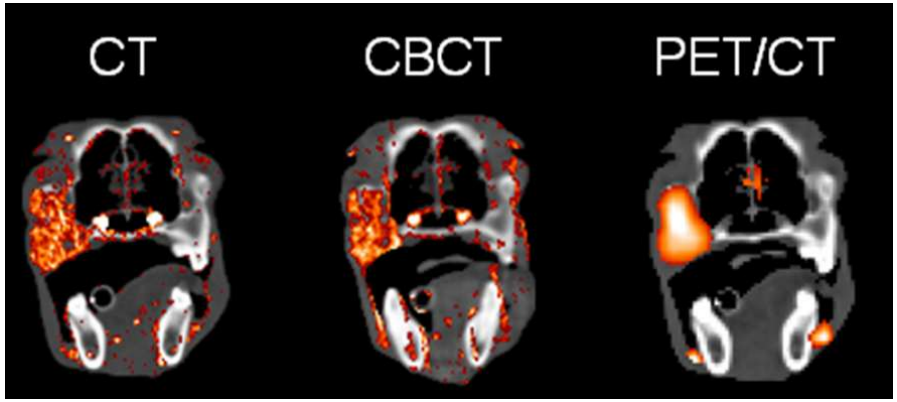
- Part 4: Start a clinical trial

Pre-clinical studies

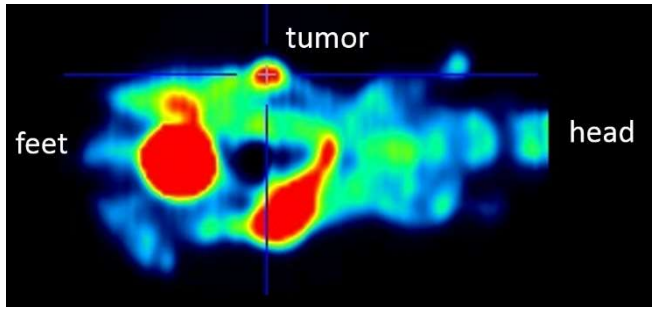
- Mouse/rats
- Dogs



Nucl Med Mol Imaging (2013) 47:173–180



Radiother Oncol 97, 521-4



Anti-1-amino-3-18F-fluorocyclobutane-1-carboxylic acid

Work in progress

- Explore PET tracers / RT strategies

Particle therapy

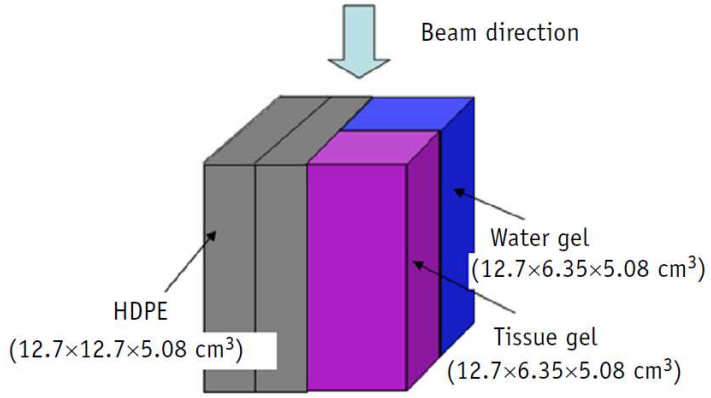
Two main directions of relevance for PET:

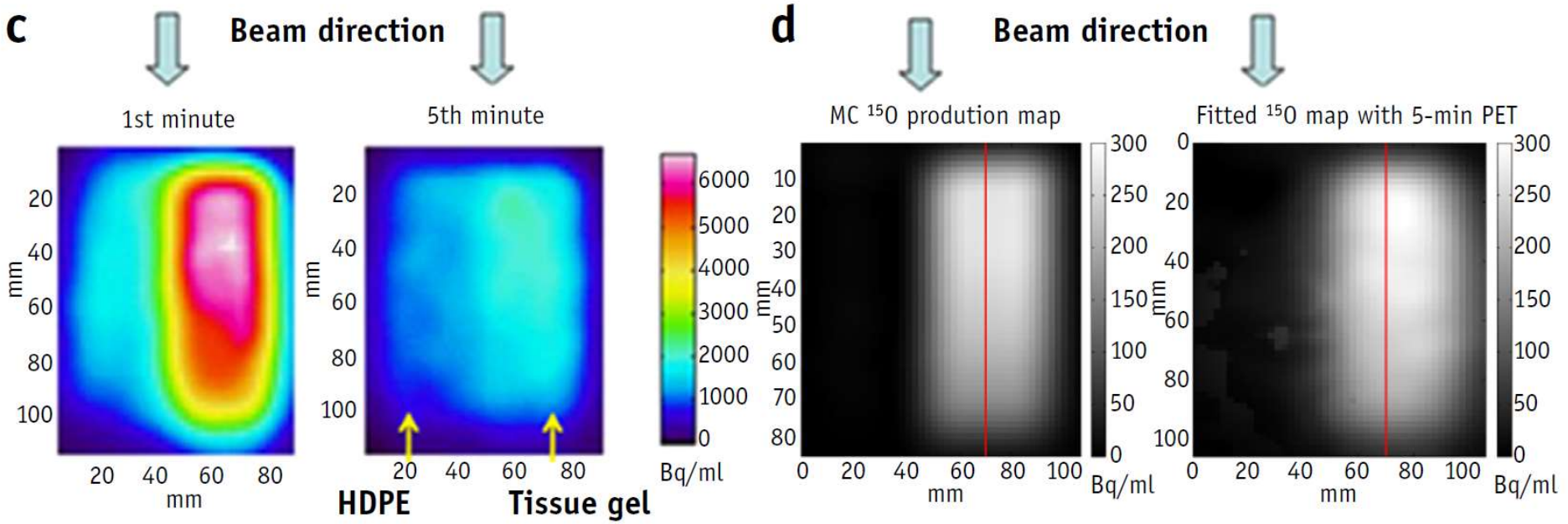
- Dose painting / ‘LET’ painting
- Dose verification

Particle therapy dose verification

- Particle range may be uncertain
- Activation of positron emitters – e.g. ^{15}O
- But activation is not proportional to dose – need Monte Carlo simulations as support
- Positron clearance both due to decay and biological washout

Range verification by DPET



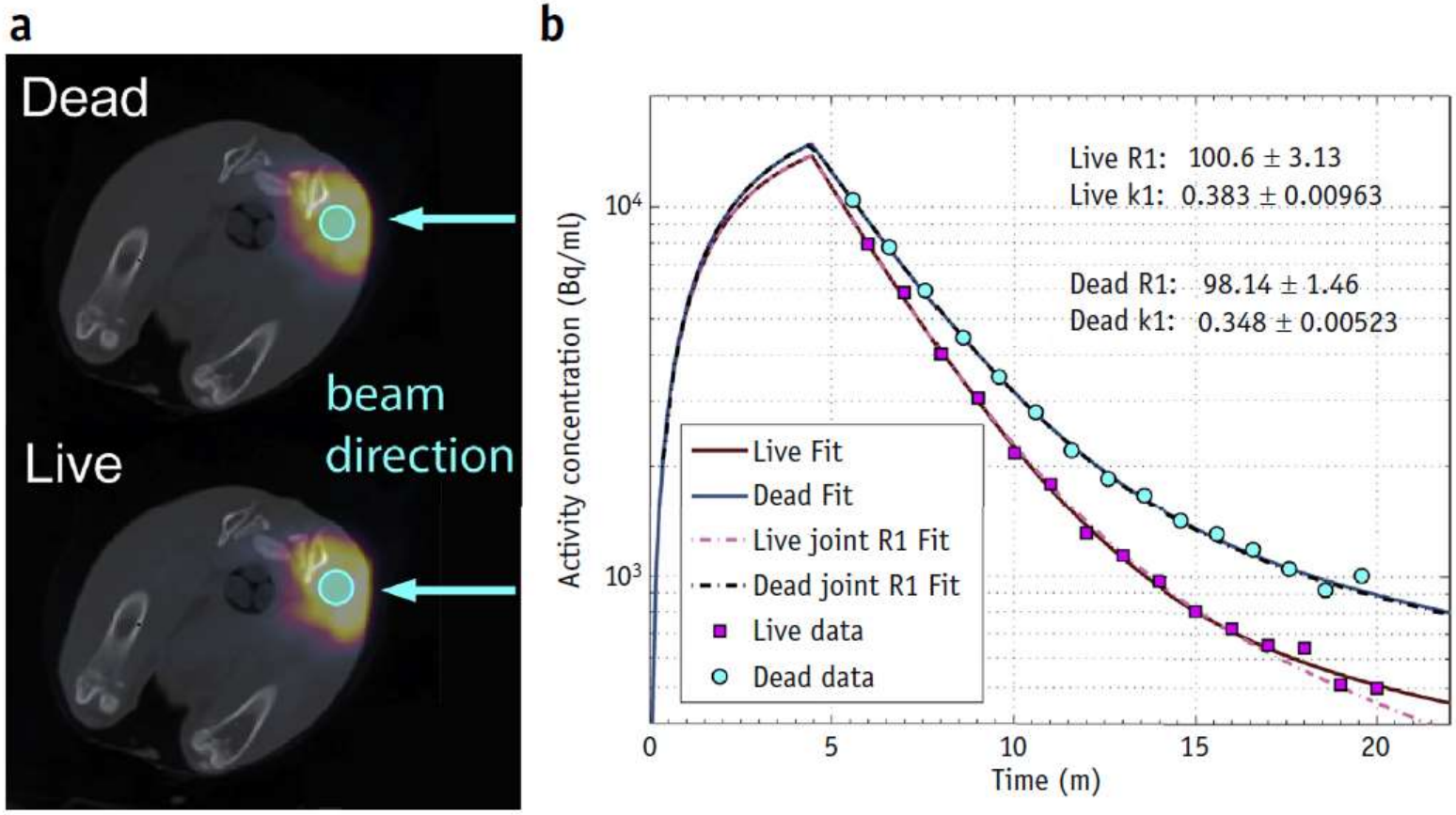


UiO : Department of Physics
University of Oslo

IJROBP 92, e453-e459 (2015)

Oslo University Hospital

Range verification by DPET



Costs

How to do PET in RT

- Use of PET in radiotherapy is a multidisciplinary effort
- Opportunities in both theoretically and clinically oriented physics-work
- Other skills: make friends with
  - Oncologist, Nuclear medicine specialist, PET physicist, Radiochemist, Biologist, IT-specialist….

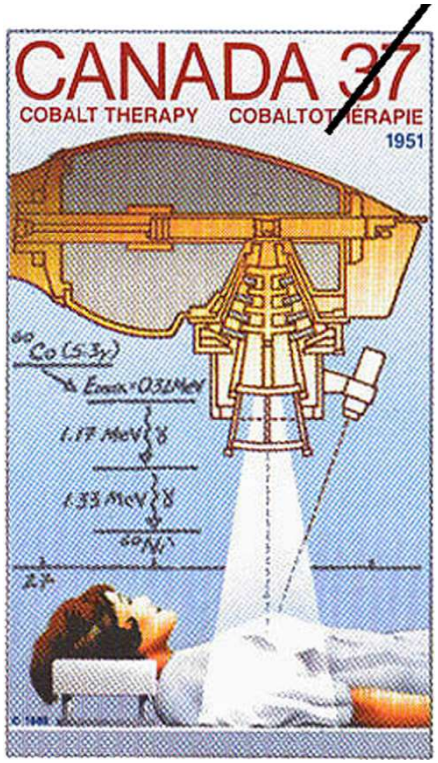
How to do PET in RT

- Expect to work on organizing the research
- Make contact with other RT centers employing PET/CT
- E.g. planning strategies – get access to PET/CT images from other institutions , explore images and strategies in own institution

Thank you for your attention!

Erasmus MC
Universitair Medisch Centrum Rotterdam

Cancer Institute



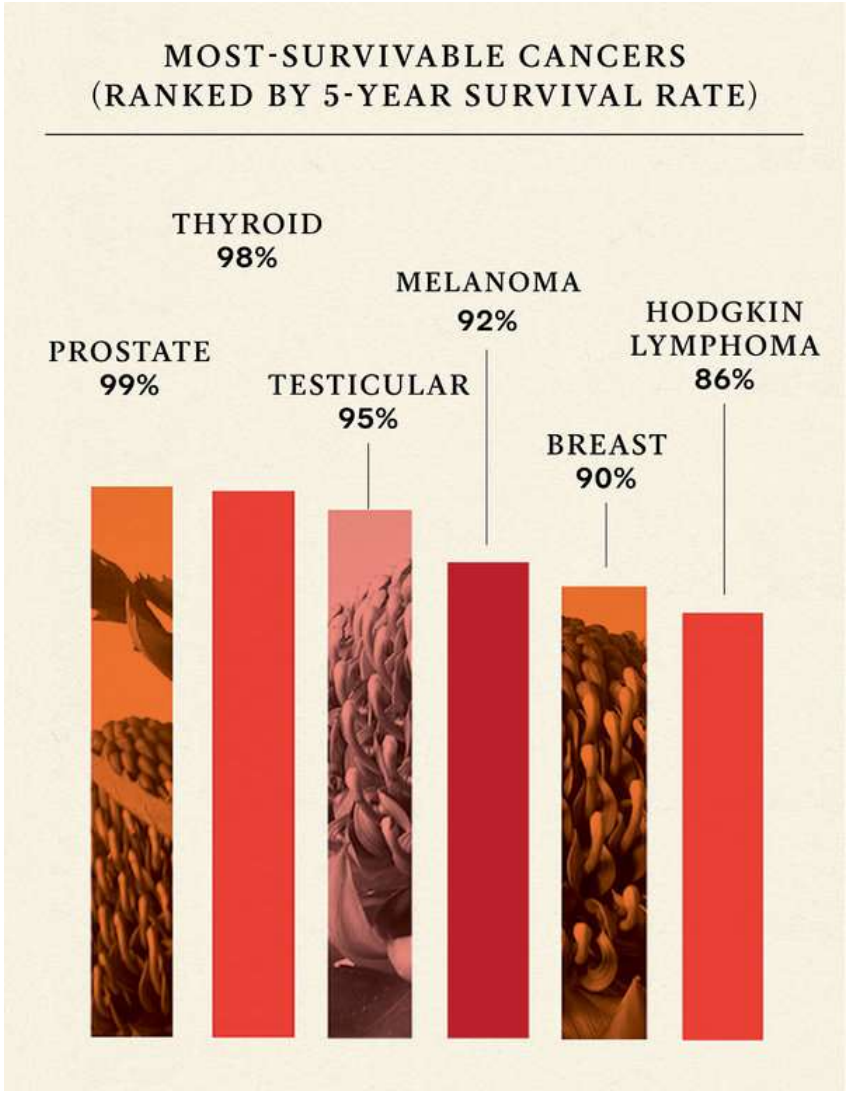
A (short) history of image-guided radiotherapy. Radiotherapy and Oncology 86 (2008) 4–13

Trends and research opportunities in IGRT and adaptive therapy to compensate for anatomical variations

Mischa Hoogeman

A Changing Landscape

- Earlier detection of cancer leading to smaller tumors with more limited and local-regional disease
- Patients live longer
- Complications are not longer acceptable



Source: NY Times; National Cancer Institute Credit Illustration by Cristiana Couceiro

A Changing Landscape

- Targeted therapies including immunotherapy extend life of cancer patients
- Com
  acce
  chronic disease

Patients want faster and less toxic treatments

Source: NY Times; National Cancer Institute Credit Illustration by Cristiana Couceiro

Precise and Selective

- **The goal is to improve Radiotherapy, i.e. increasing its value**

MRI, PET-CT, CT …

1. By improving imaging for **high-precision target definition**

IGART, IMRT, VMAT

2. By **accurately delivering dose to the defined target** deploying the optimal image-guidance and treatment planning to **each daily fraction**

3. By **offline adaptation of treatment intent** if necessary

Erasmus MC Cancer Institute

Online Adaptive Radiotherapy

Conventional

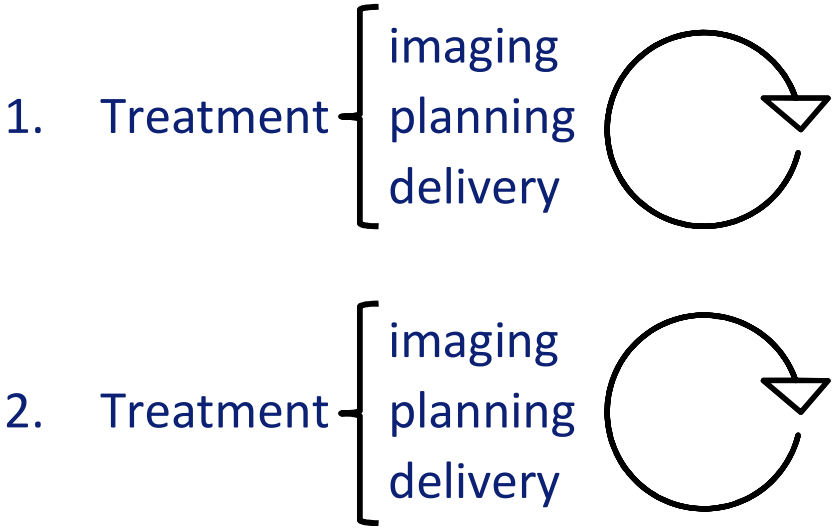
- Imaging
- Target definition
- Treatment planning

- Treatment delivery
  1. Fraction
  2. Fraction
  3. Fraction
  4. Fraction
  5. Fraction

     …
  35. Fraction

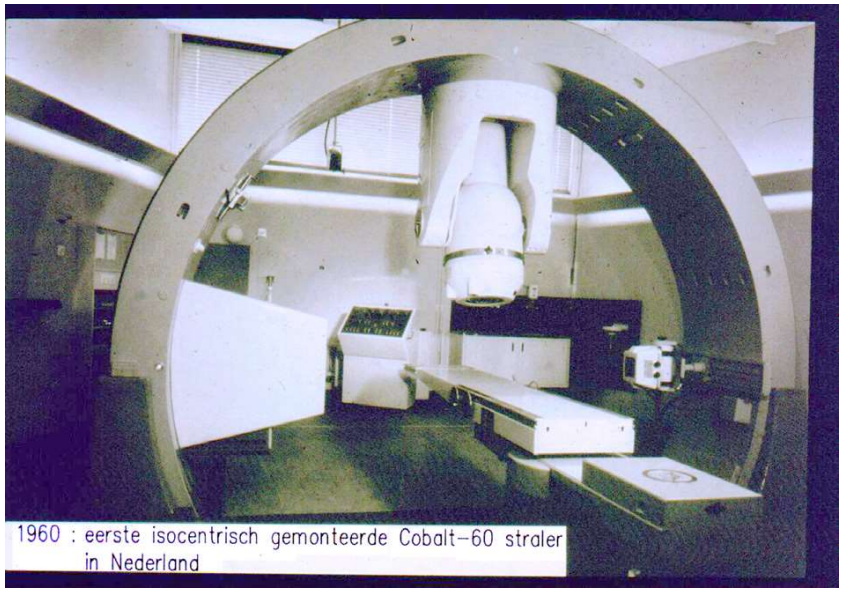
Future

- Imaging optimized for target definition
- High-precision target definition



Erasmus MC Cancer Institute

A (short) history of image-guided radiotherapy. Radiotherapy and Oncology 86 (2008) 4–13



IN-ROOM (ON-BOARD) IMAGING

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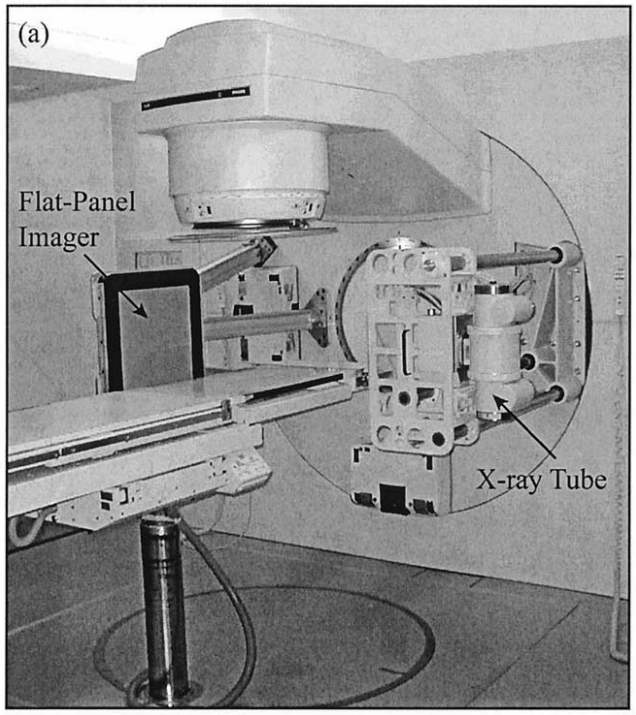
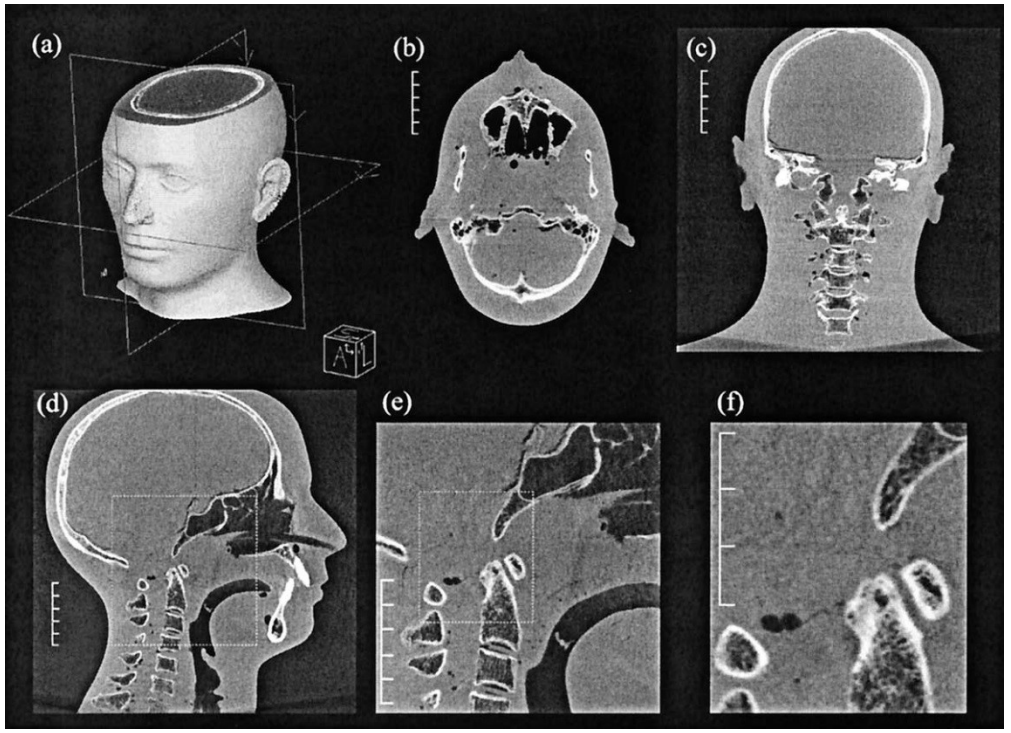
Cone-beam Computed Tomography





Jaffray DA, Siewerdsen JH, Wong JW, Martinez AA. Flat-panel cone-beam computed tomography for image-guided radiation therapy. Int J Radiat Oncol Biol Phys. 2002 Aug 1;53(5):1337-49.

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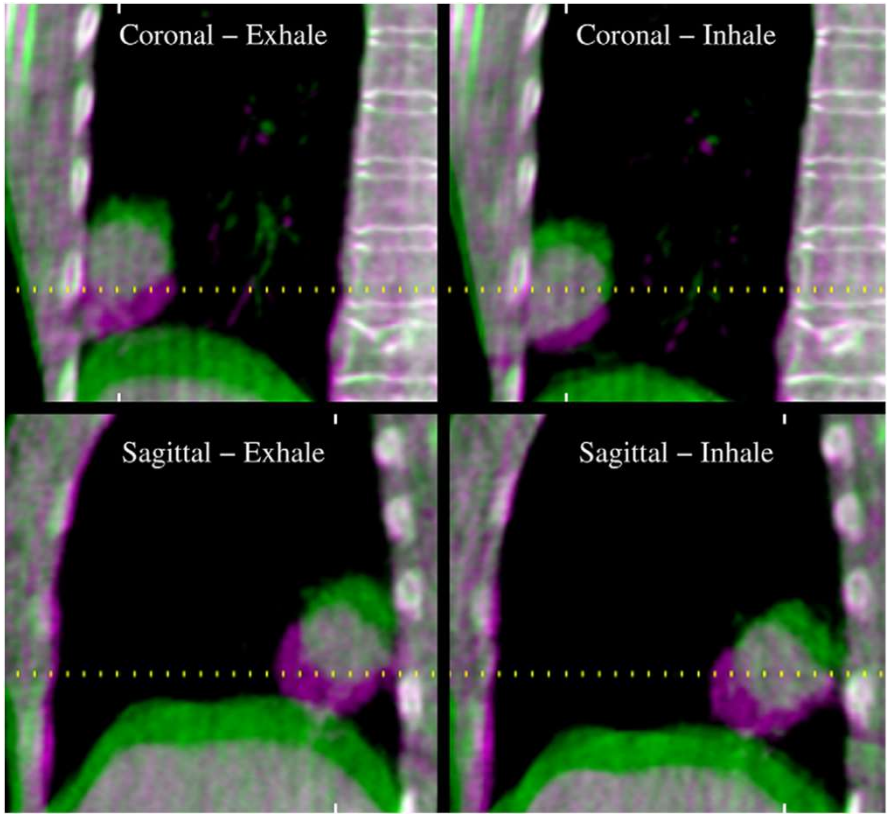
Frameless Lung SBRT and SRS

- AAPM TG 179: “Perhaps, the most important application of CBCT has been the simplification of hypofractionated, SBRT”
- IGRT on tumor, i.e. a nearly perfect inter-fraction alignment
- 4D CBCT



From: Sonke JJ, Lebesque J, van Herk M. Variability of four-dimensional computed tomography patient models. Int J Radiat Oncol Biol Phys. 2008 Feb 1;70(2):590-8.

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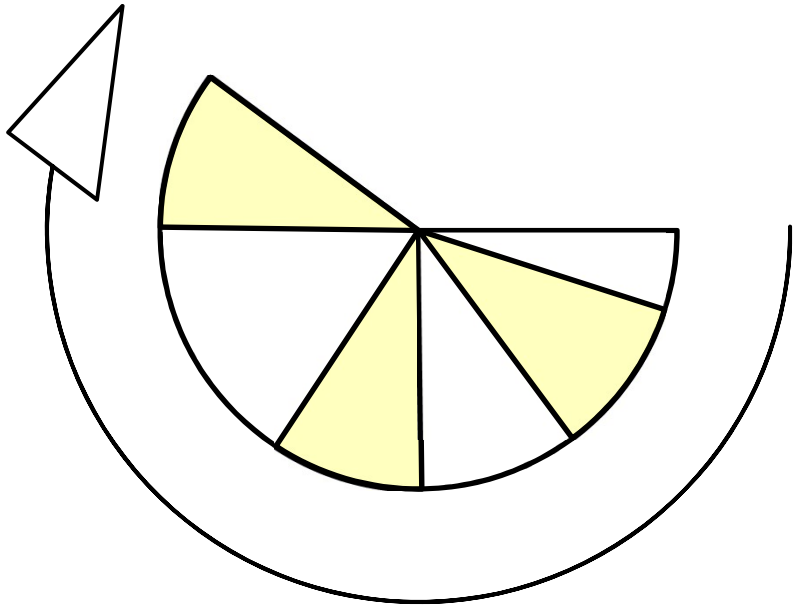
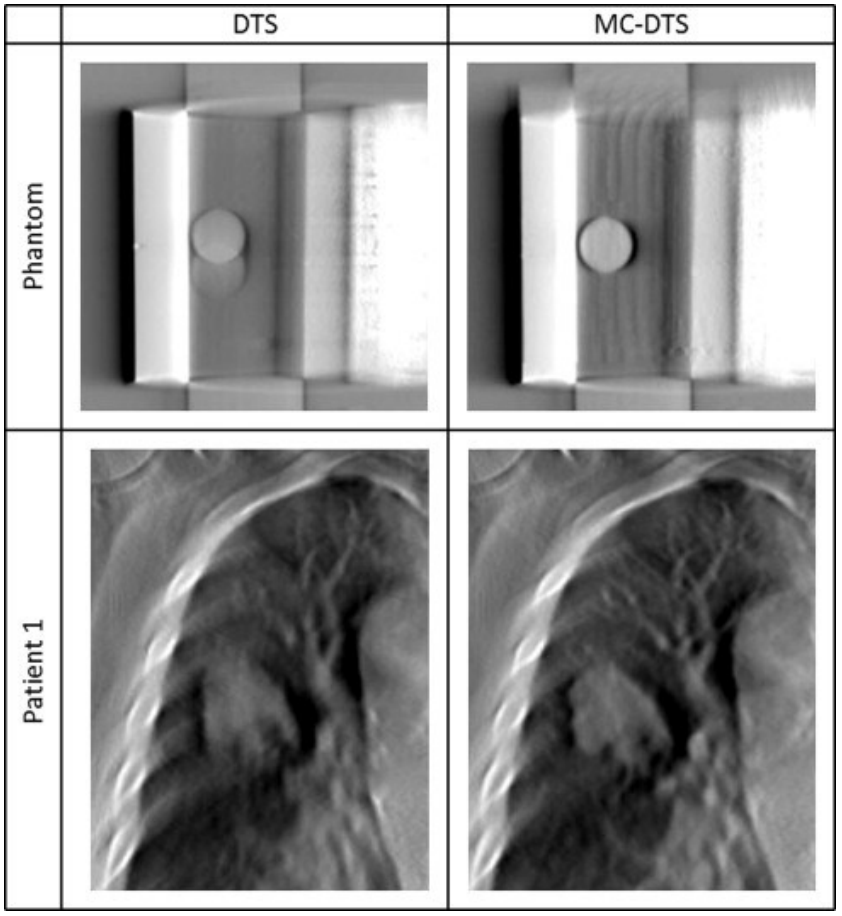
Digital Tomosynthesis for Intra-Fraction Target Verification





van der Reijden A, van Herk M, Sonke JJ. Motion compensated digital tomosynthesis. Radiother Oncol. 2013 Dec;109(3):398-403. doi:10.1016/j.radonc.2013.09.002.

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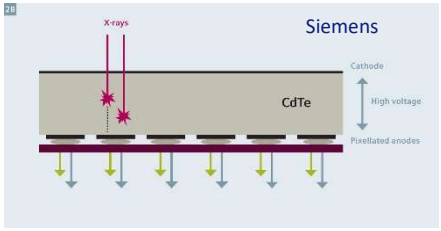
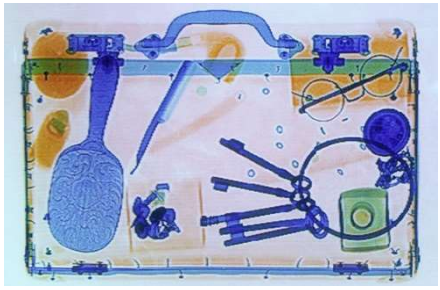
Can We Improve CBCT Image Quality?

- Anti-scatter grid
- Scatter correction software (iterative correction)
- Dual Energy CBCT

- Single photon counting (CB)CT
- Spectral or color (CB)CT





Taguchi K, Iwanczyk JS. Vision 20/20: Single photon counting x-ray detectors in medical imaging. Med Phys. 2013 Oct;40(10):100901.

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MRI-Integrated Radiotherapy Systems

ViewRay


Elekta-Philips Utrecht

Nature Reviews Clinical Oncology 9, 688-699 (December 2012) |
doi:10.1038/nrclinonc.2012.194

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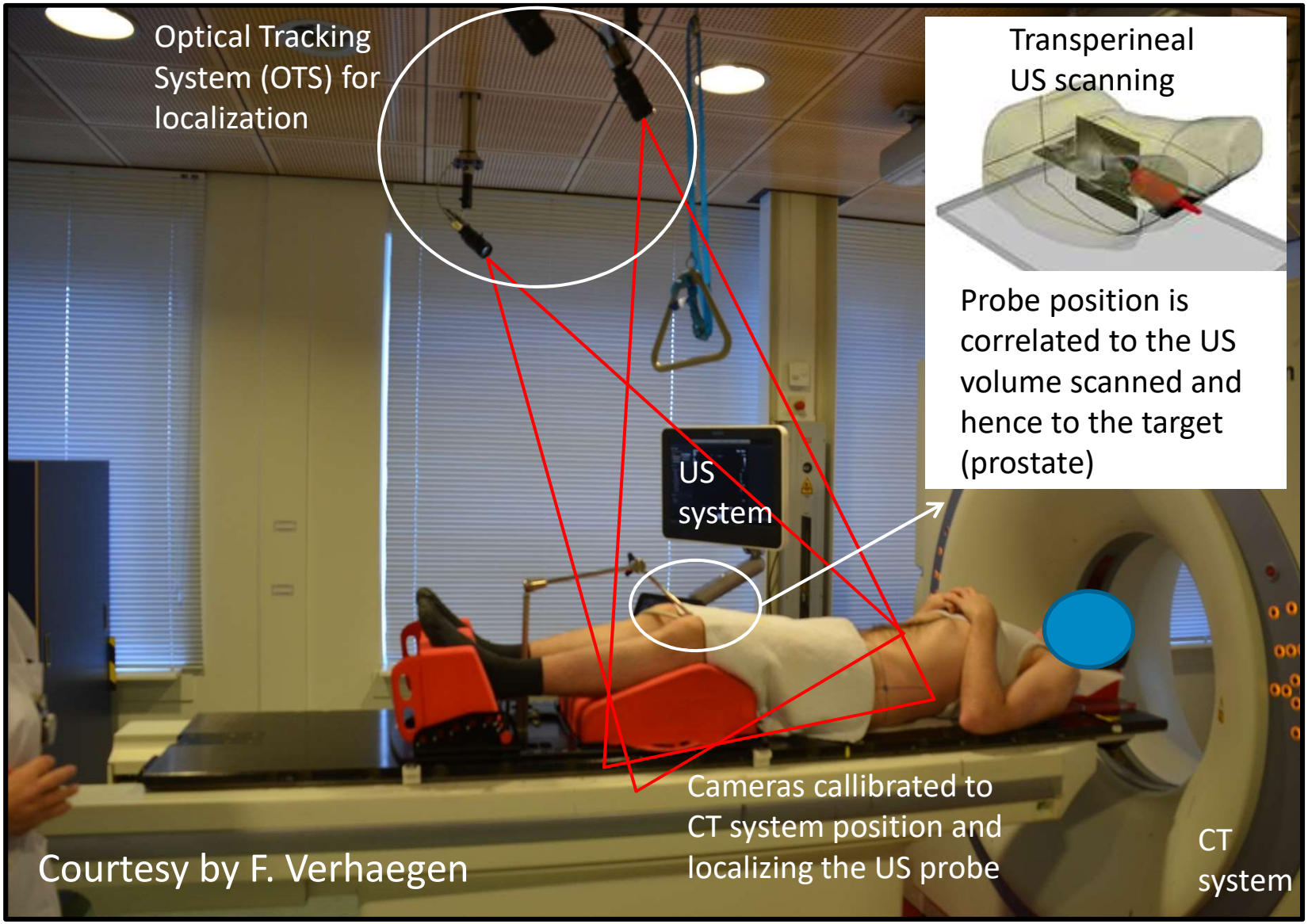
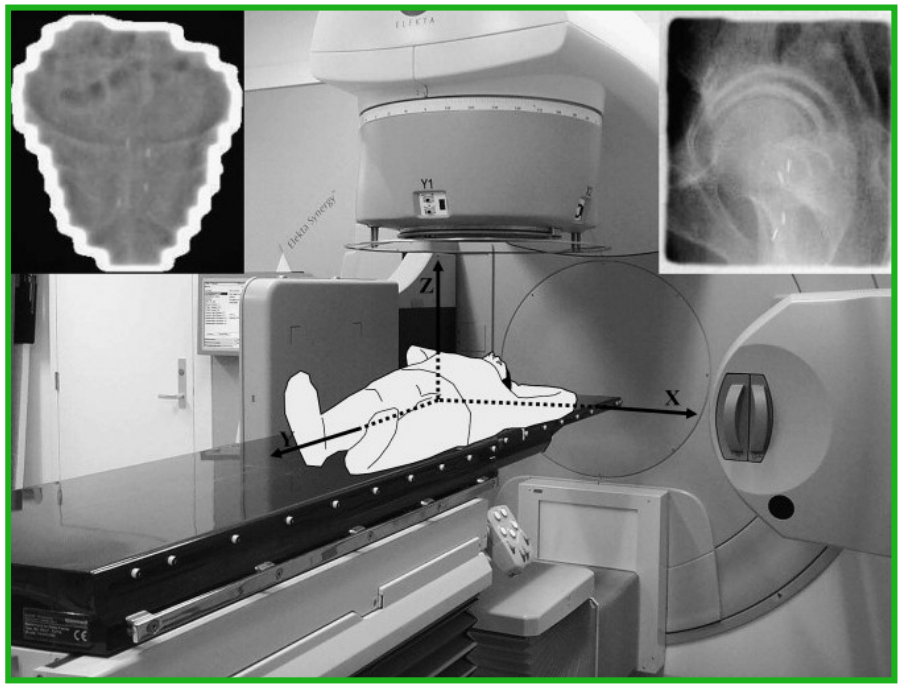
Soft-Tissue Contrast: CT on Rails



Research 4DUS system at MAASTRO Clinic (Maastricht, Netherlands)



HARDWARE TO CORRECT PATIENT OR TARGET SETUP

Mutanga et al. Stereographic Targeting in Prostate Radiotherapy: Speed and Precision by Daily Automatic Positioning Corrections Using Kilovoltage/Megavoltage Image Pairs. IJROBP 71, p. 1074-83, 2008.

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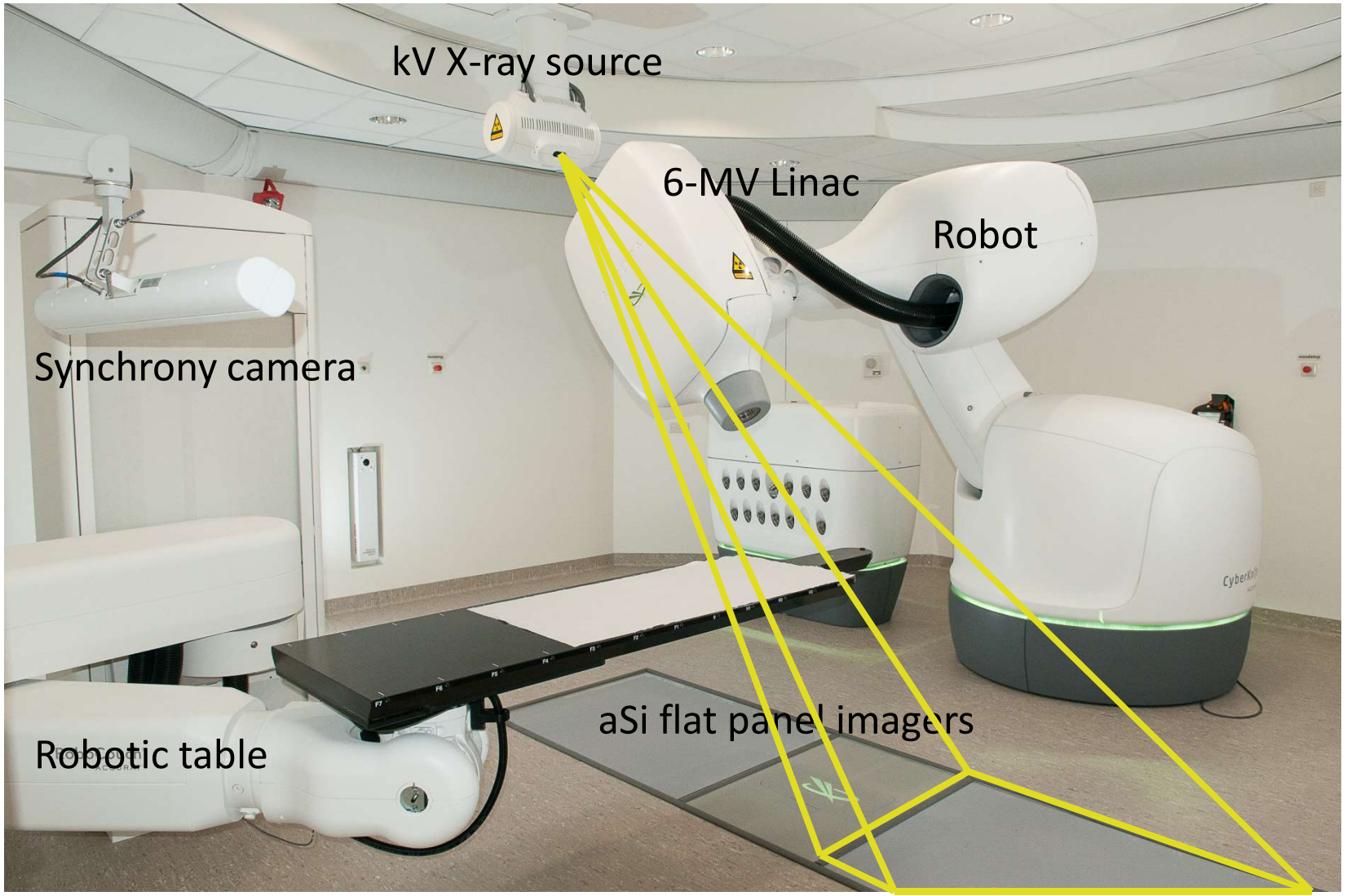
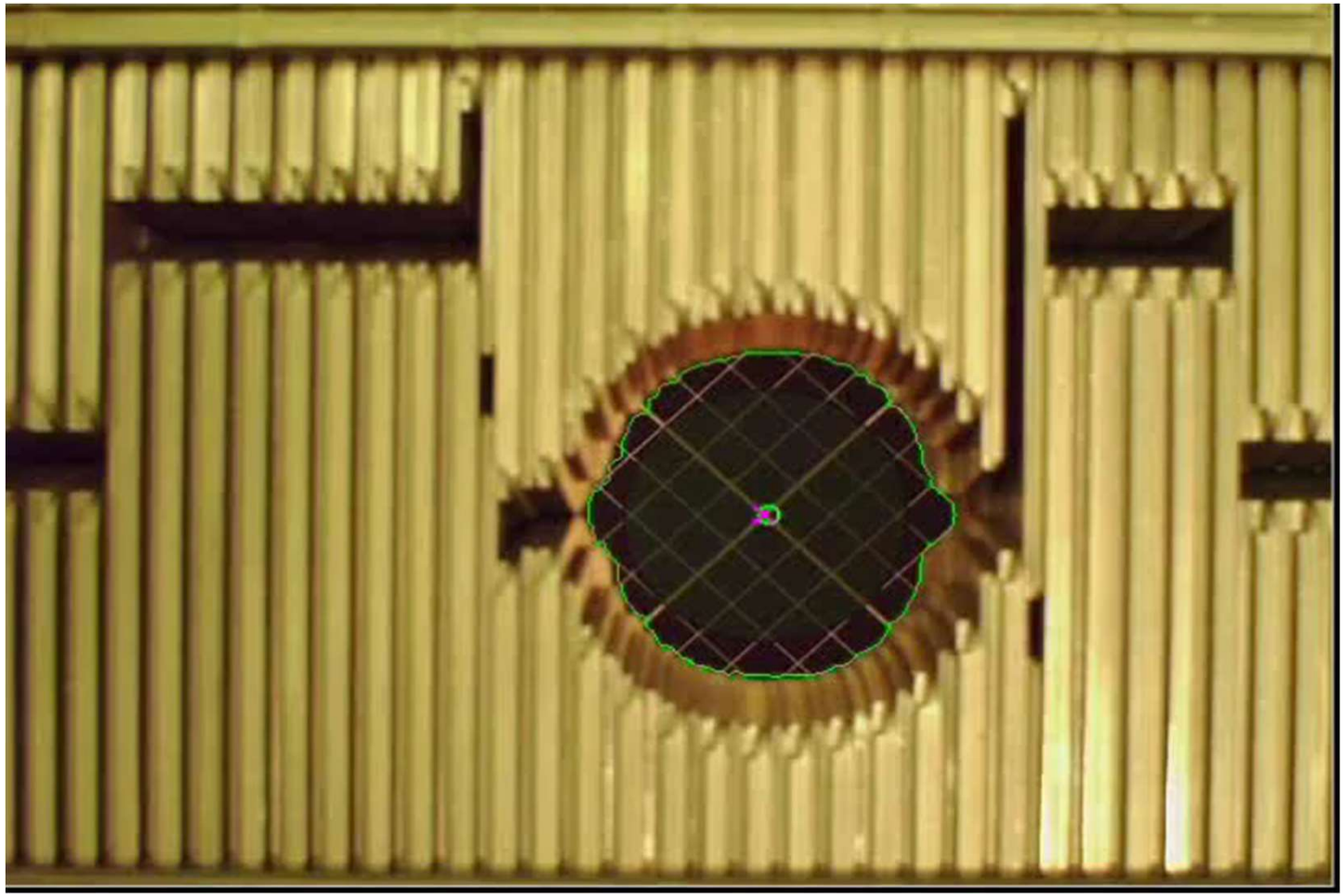
Stereoscopic Imaging and Tracking System

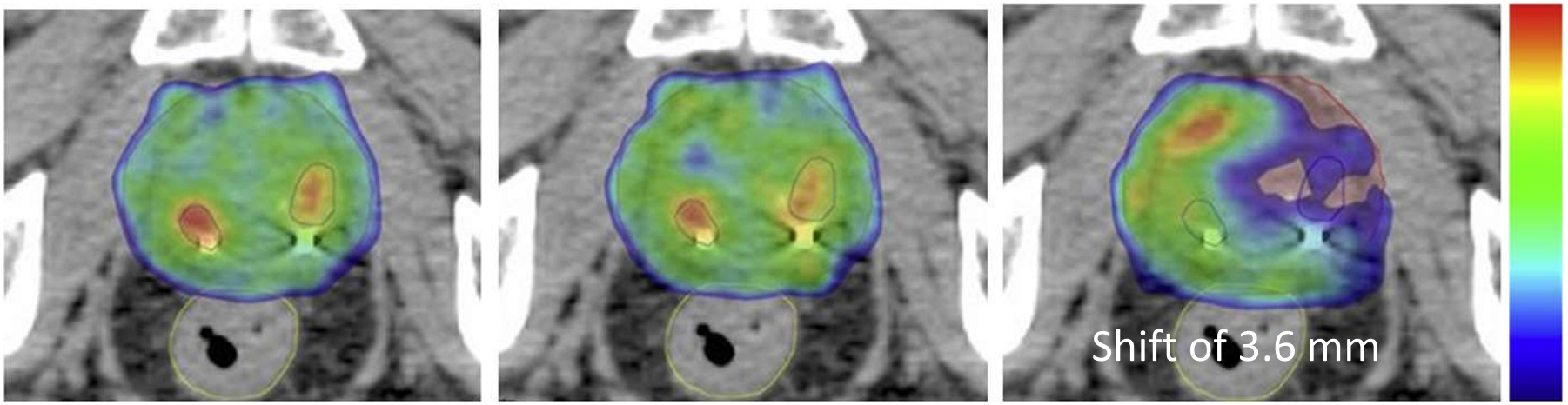


Dynamic Multileaf Collimator Tracking by Paul Keall (2007)



https://www.youtube.com/watch?v=LOETSm_HliU

Multileaf Collimator Tracking Improves Dose Delivery



- "Future research will develop and translate to clinical practice solutions to tumor rotation and deformation, including differential motion of multiple targets."

Tested in a clinical trial

Colvill E et al. Multileaf Collimator Tracking Improves Dose Delivery for Prostate Cancer Radiation Therapy: Results of the First Clinical Trial. Int J Radiat Oncol Biol Phys. 2015 Aug 1;92(5):1141-7.

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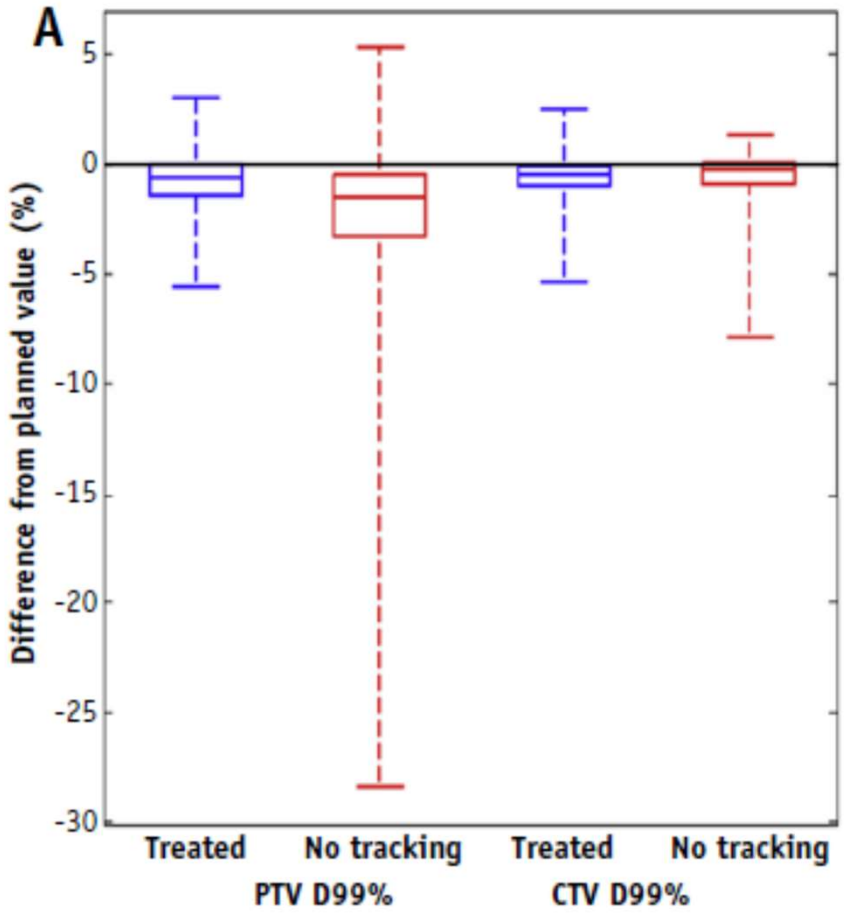
Relevance



Is this clinically relevant?

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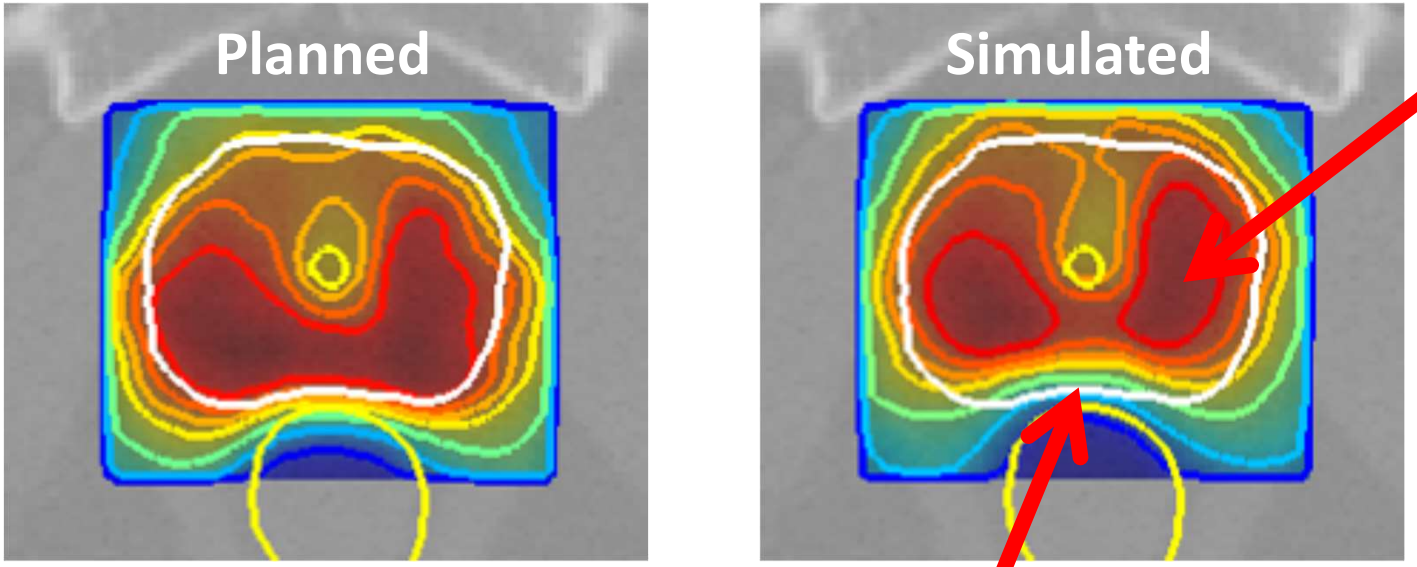
Planned Compared to Simulated Dose



Heterogeneous high dose in few fractions and small margins

van de Water S, et al. Intrafraction prostate translations and rotations during hypofractionated robotic radiation surgery: dosimetric impact of correction strategies and margins. Int J Radiat Oncol Biol Phys. 2014 Apr 1;88(5):1154-60.

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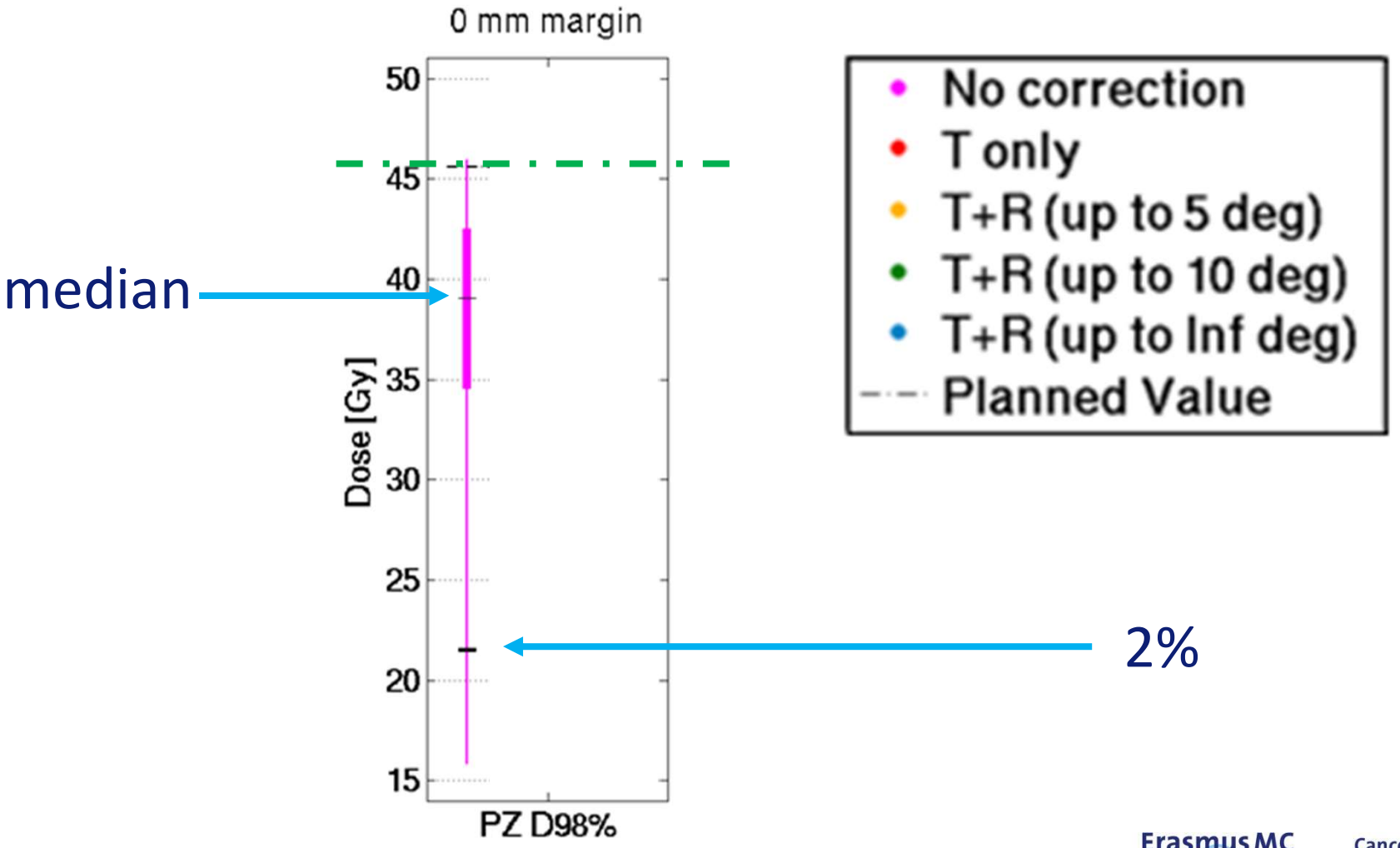
Results of the Dose to the Peripheral Zone



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Some Remarks on Classical IGRT

1. State of the art is online setup corrections for tumors that translate or rotate combined with intra-fraction monitoring or correction
2. New is to use dynamic MLC for real-time tracking
3. IGRT is still challenging for tumors that are poorly visible (abdomen) => implant fiducials or use MRI or in-room CT
4. Not discussed here is the Calypso tracking system, which puts beacons in the tumor

ADAPT TREATMENT TO ANATOMICAL CHANGES

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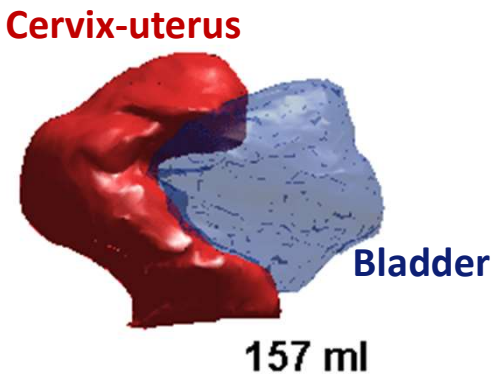
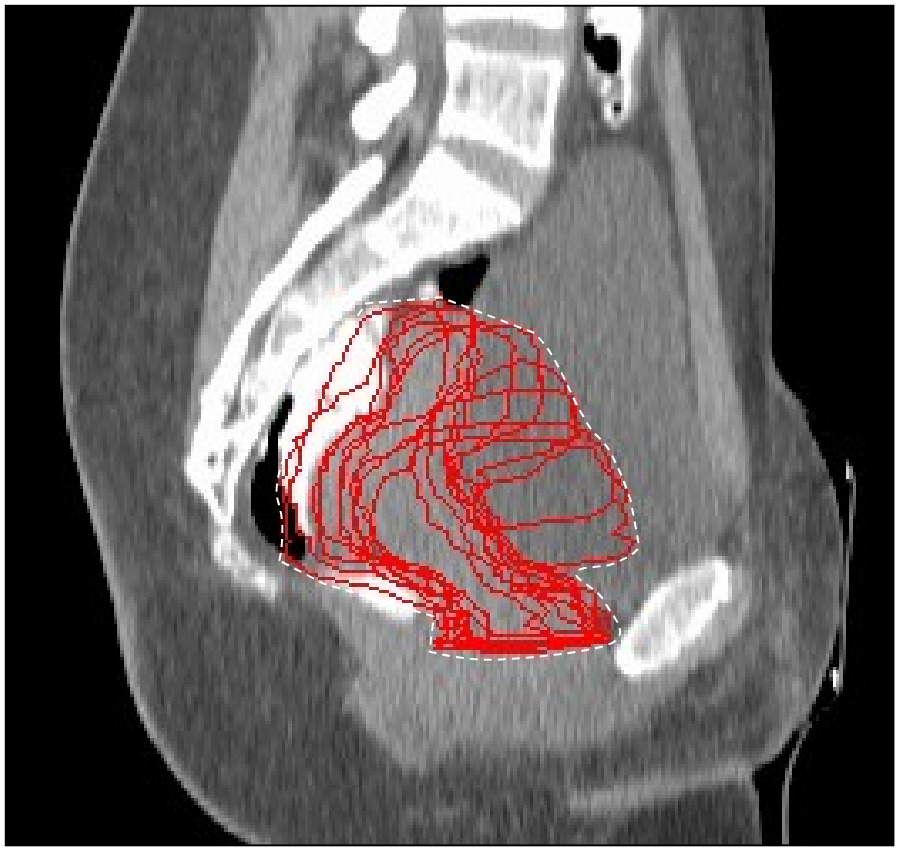
Rationale of Online Adaptive RT

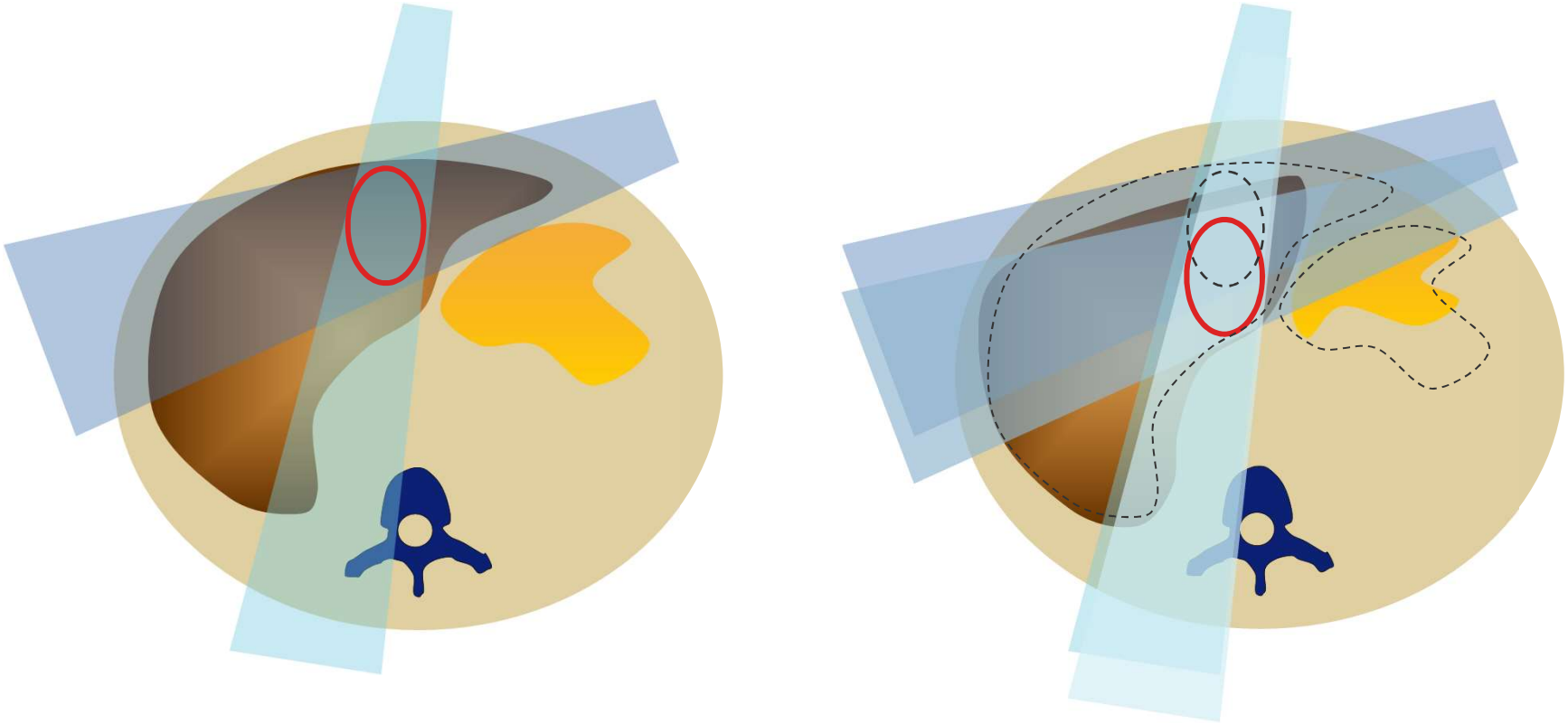
1. **Tumor perspective:** Large inter-fraction variability in target position and shape that cannot be corrected by a couch shift or rotation
2. **OARs perspective:** Due to position and shape variations of the organs at risk the treatment plan may be far from optimal for the patient's anatomy during dose delivery

Non-Rigid Organ Motion in Cervical Cancer Patients





Online Adaptive RT for Liver?



Planning

Treatment

Leinders SM, Breedveld S, et al. Adaptive liver stereotactic body radiation therapy: automated daily plan reoptimization prevents dose delivery degradation caused by anatomy deformations. Int J Radiat Oncol Biol Phys. 2013 Dec 1;87(5):1016-21.

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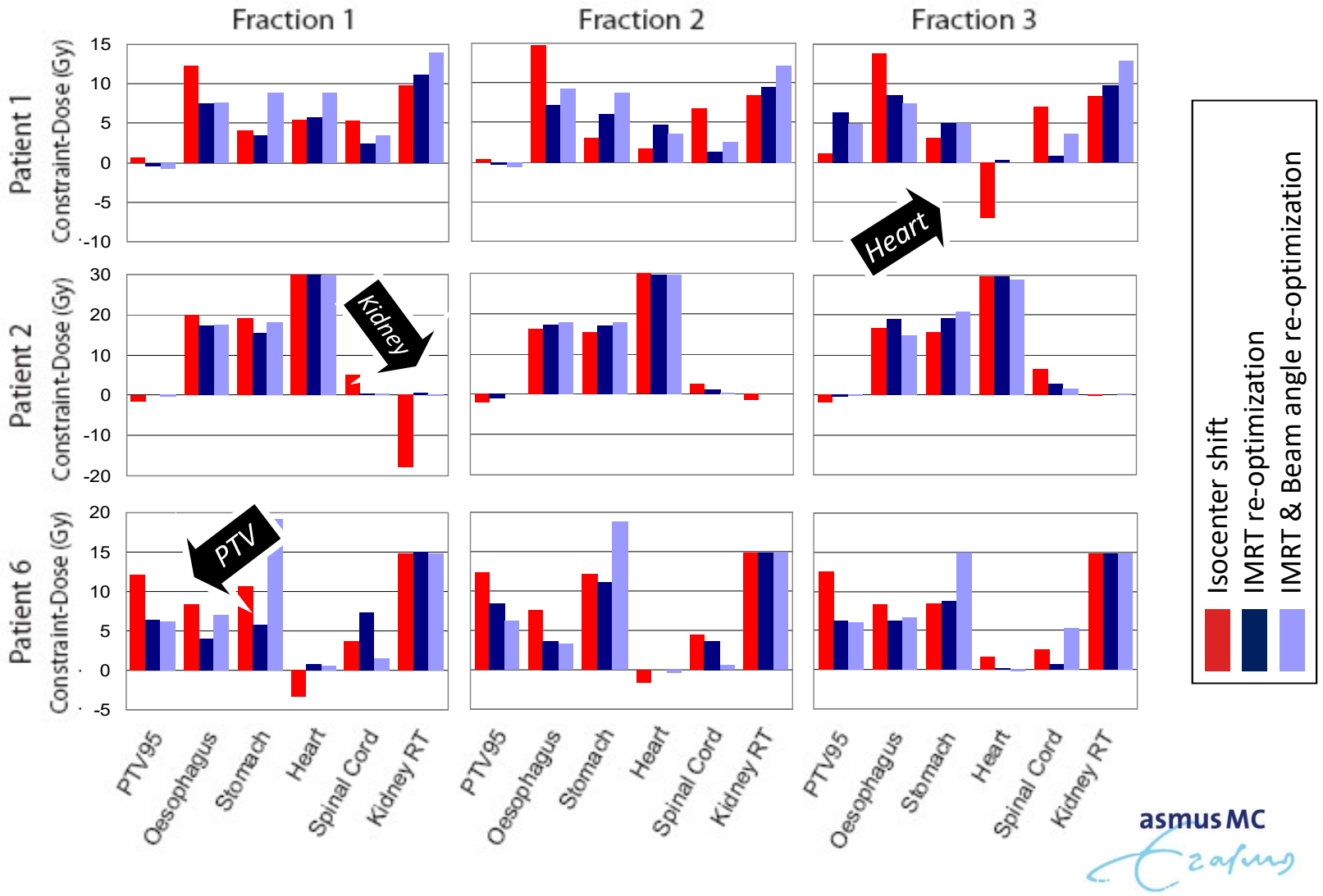
Results



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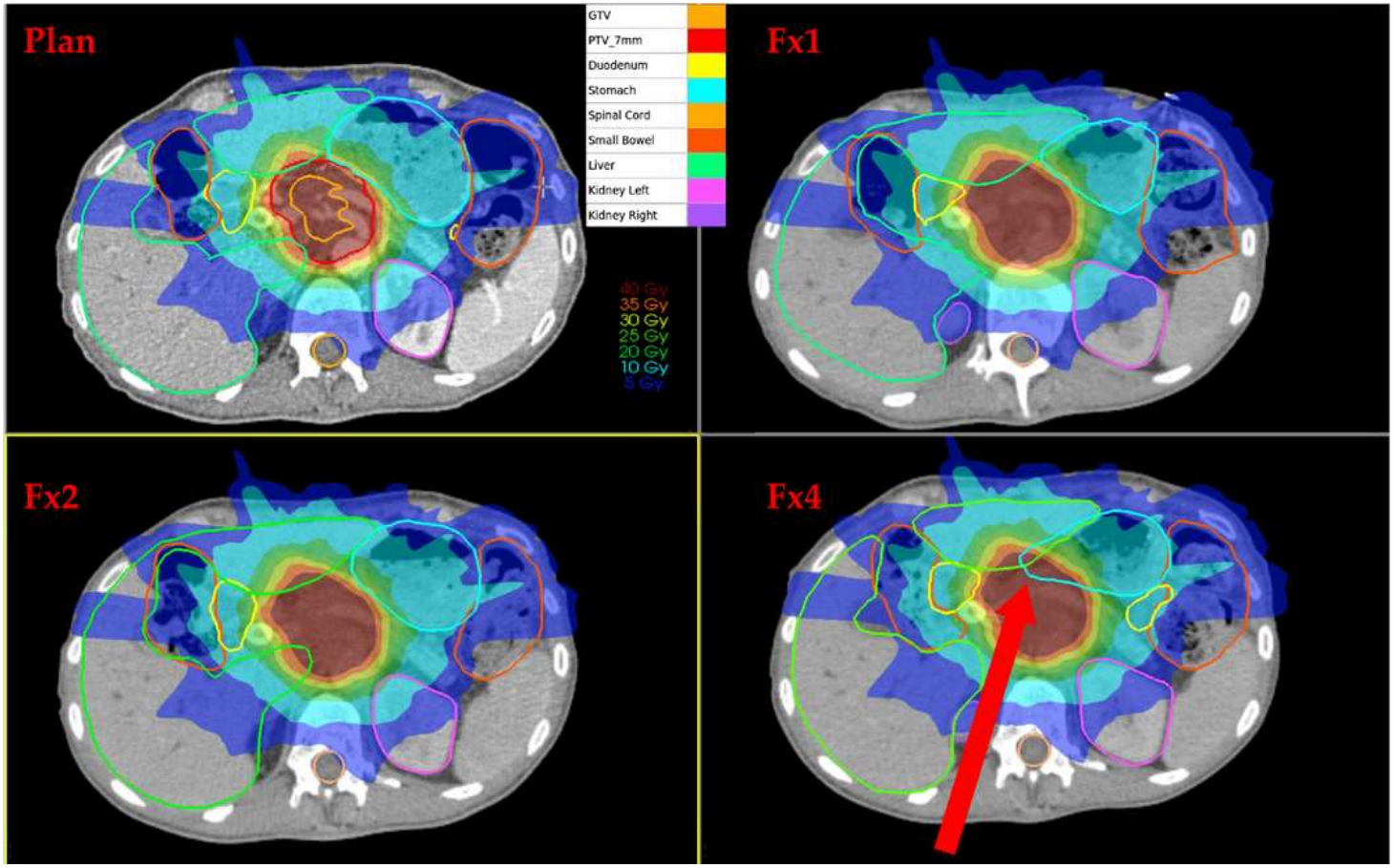
Results

- In 50% of the cases, small differences in dose delivered to the OARs were present, both favorable or unfavorable, but none of the plans was clearly better than the others

- In the other 50% of the cases, improvements of the dose-distributions could be achieved …

Patient selection!

Daily OAR Dose Variations in Pancreatic Cancer



Papalazarou C, Klop GJ, Milder MTW, Marijnissen JPA, Gupta V, Heijmen BJM, Nuyttens JJME, Hoogeman MS. CyberKnife with integrated CT-on-rails: System description and first clinical application for pancreas SBRT. Med Phys. 2017 Jun 28.

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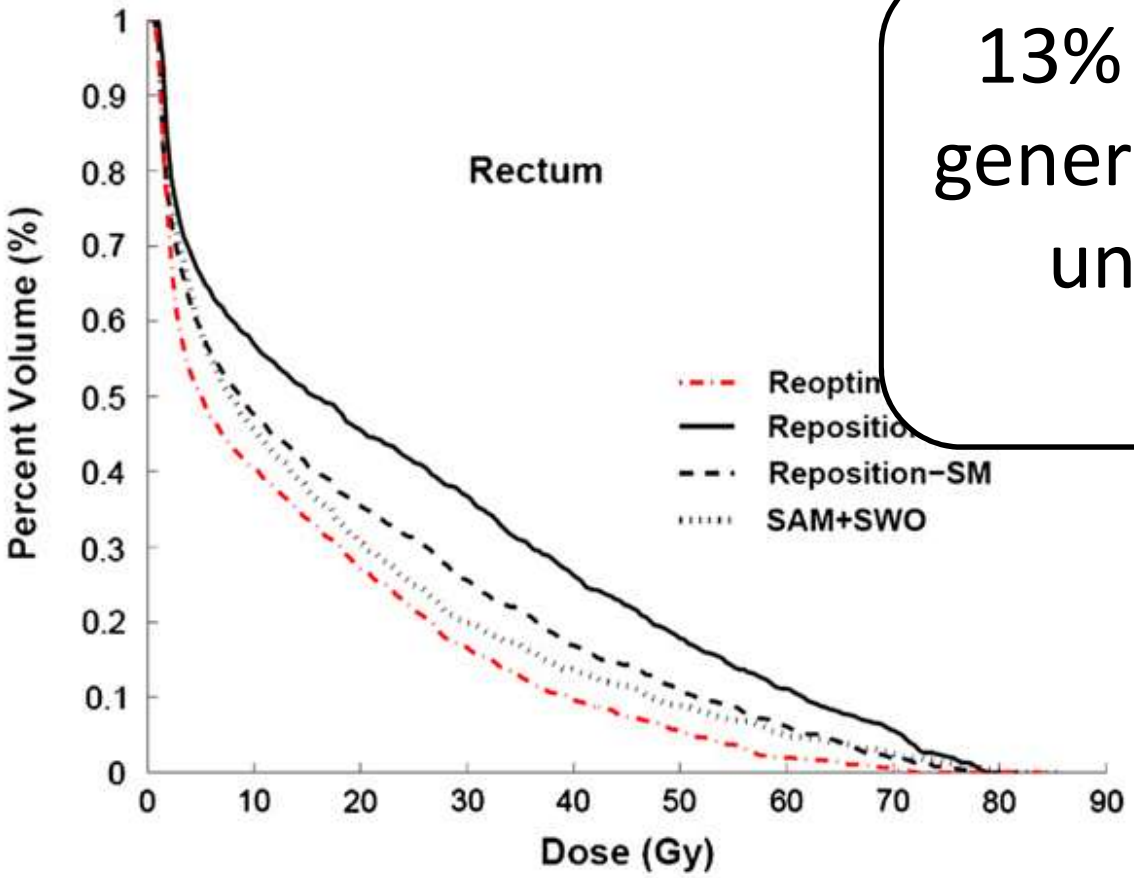
Representative Case



13% decrease in the generalized equivalent uniform dose of rectum

Ahunbay EE, Peng C, Holmes S, Godley A, Lawton C, Li XA. Online adaptive replanning method for prostate radiotherapy. Int J Radiat Oncol Biol Phys. 2010 Aug 1;77(5):1561-72. doi: 10.1016/j.ijrobp.2009.10.013.

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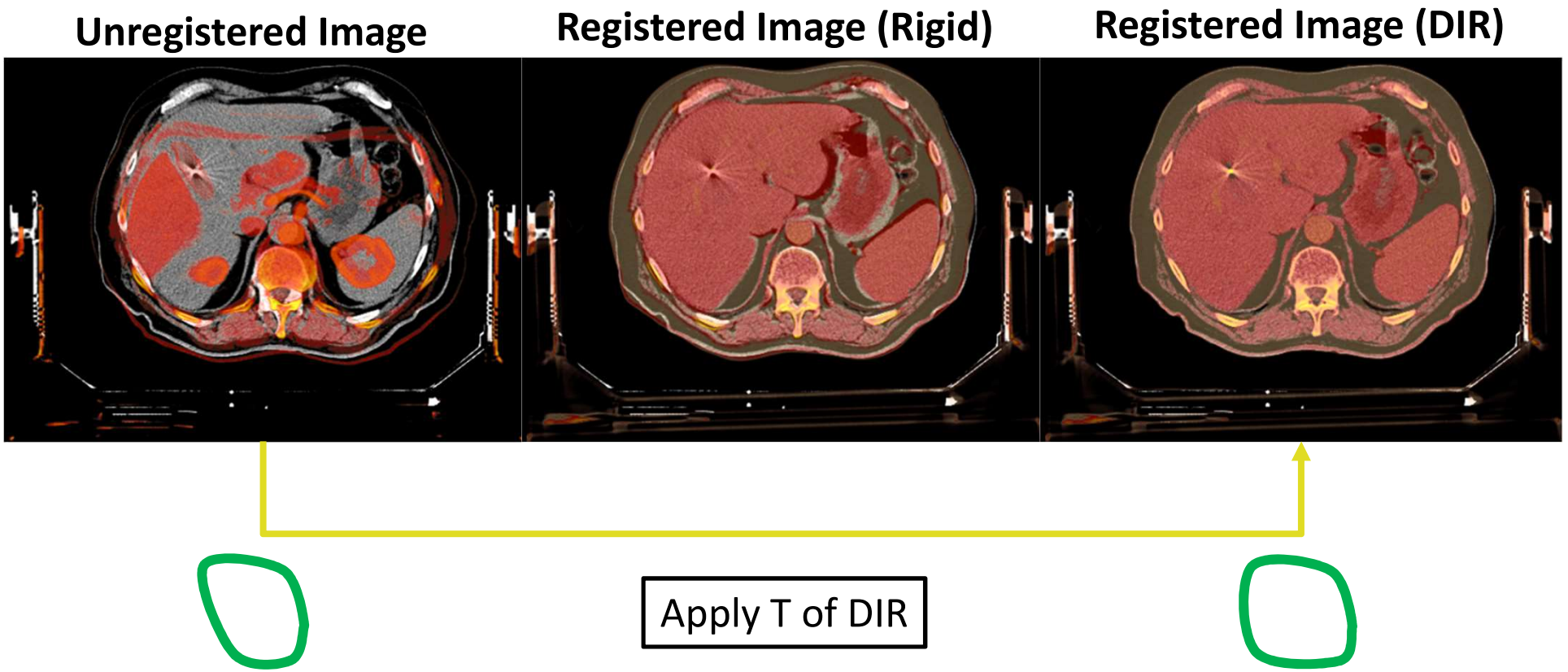
Requirements for Online Adaptive RT

- **Daily volumetric imaging (CBCT, in-room CT, onboard MRI …)**
- **Fast and robust image segmentation methods**
- **Fast re-planning**
  - Work in progress
  - MRIdian
  - Hybrid methods (e.g. aperture morphing, segment optimization)
- **Plan-library based methods**
  - Use a pre-treatment established motion model to compute configurations of the target volume and organs at risk

Fast, robust, highly automated, and failsafe

AUTO-SEGMENTATION

Auto-Segmentation by Contour Propagation



Gupta V et al.

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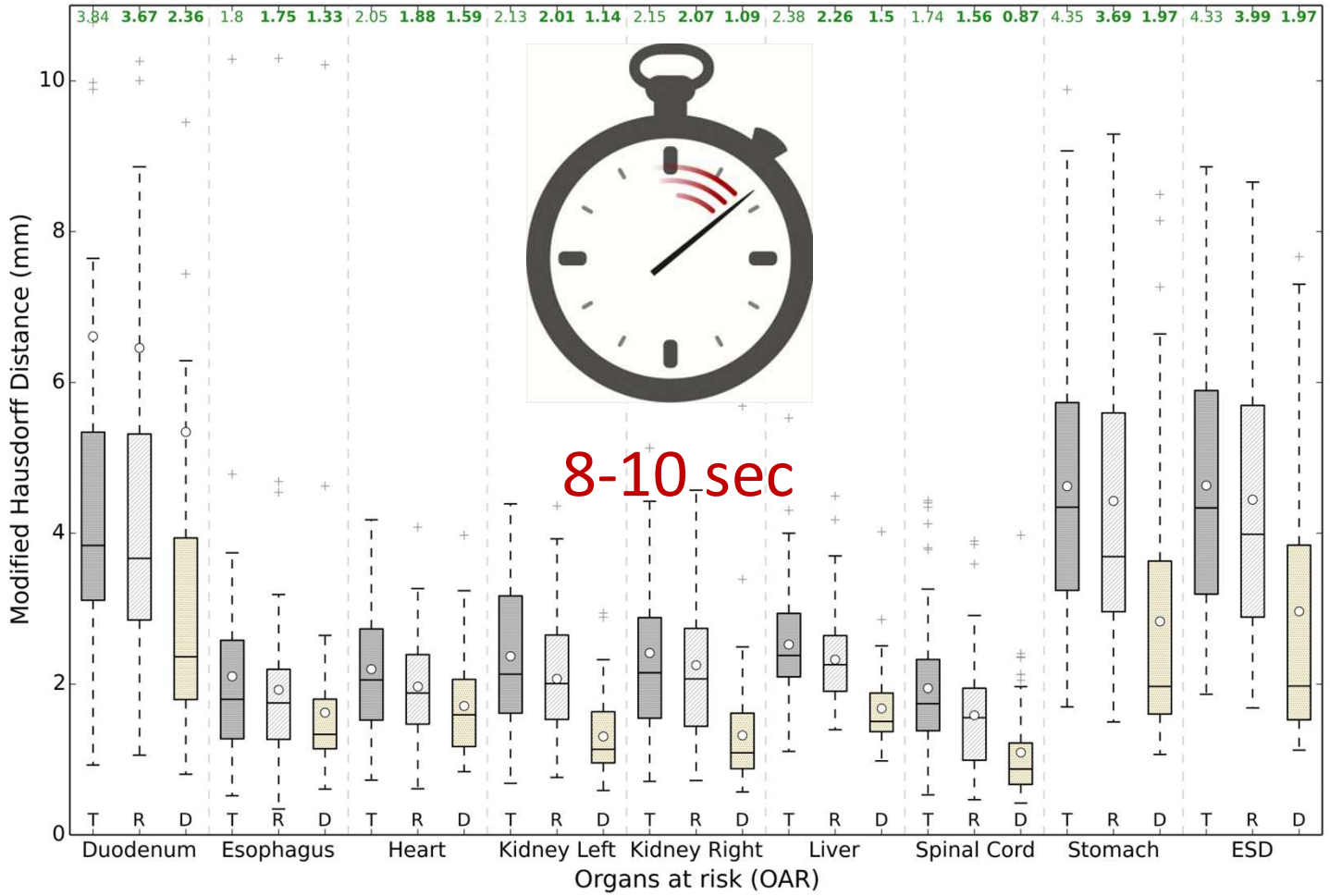
Maximum distances between gold-standard and auto contours



Gupta V et al. 2015

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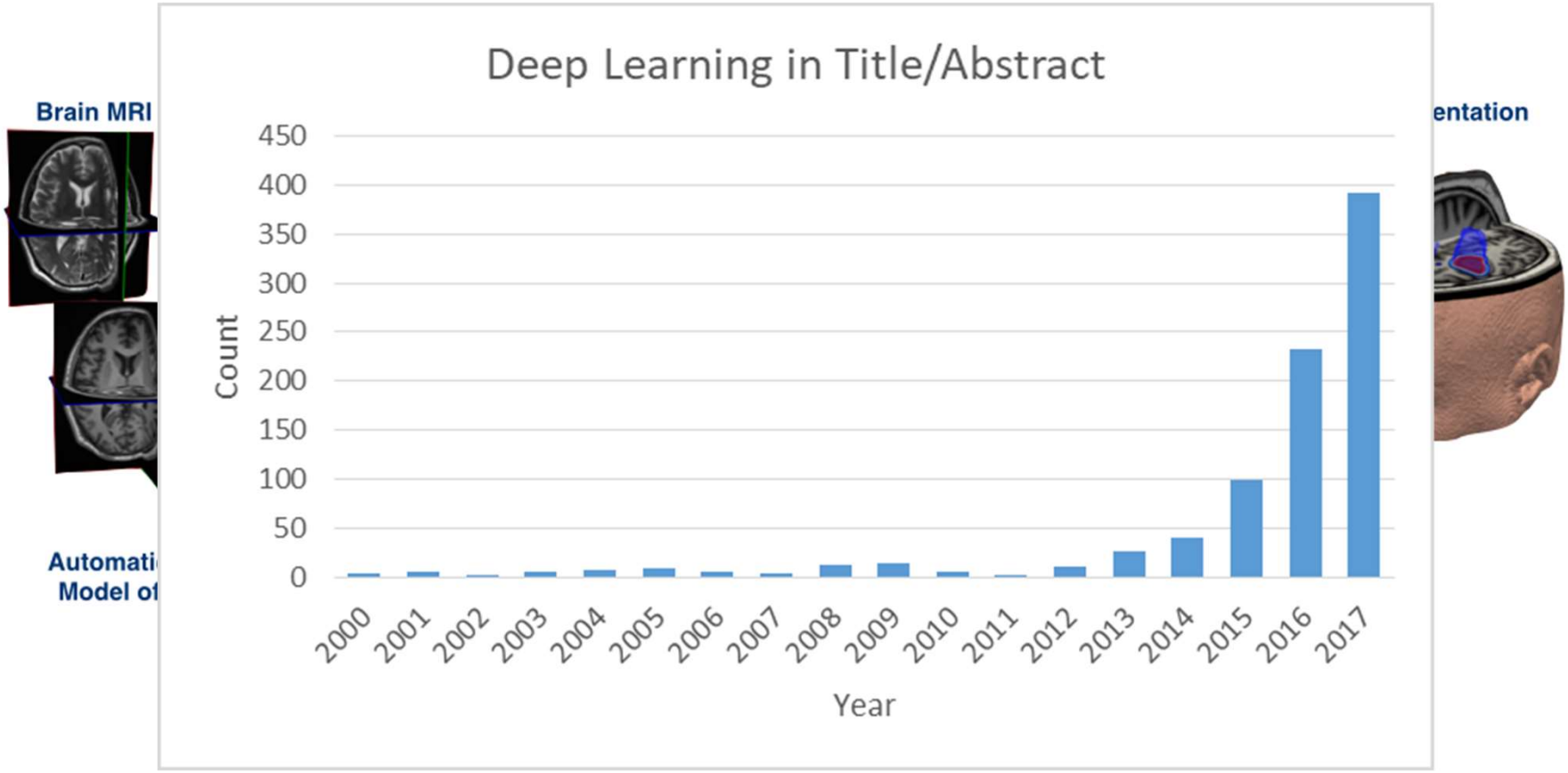
Problem Solved?

- **NO!**
- Rigorous validation based on large data sets and multiple observers
  - Open access data sets for benchmarking
- Development of tools to visually verify contoured structures and edit them quickly (human centric design)
- Development of (automatic) Quality Assurance of deformable image registrations
- Quantification of sensitivity of the re-optimized treatment plans to errors in auto-contouring
  - Define metrics and action levels, based on risk analysis

Machine Learning and Deep Learning



http://wp.doc.ic.ac.uk/bglocker/project/semantic-imaging/

Ben Glocker; Senior-Lecturer in Medical Image Computing

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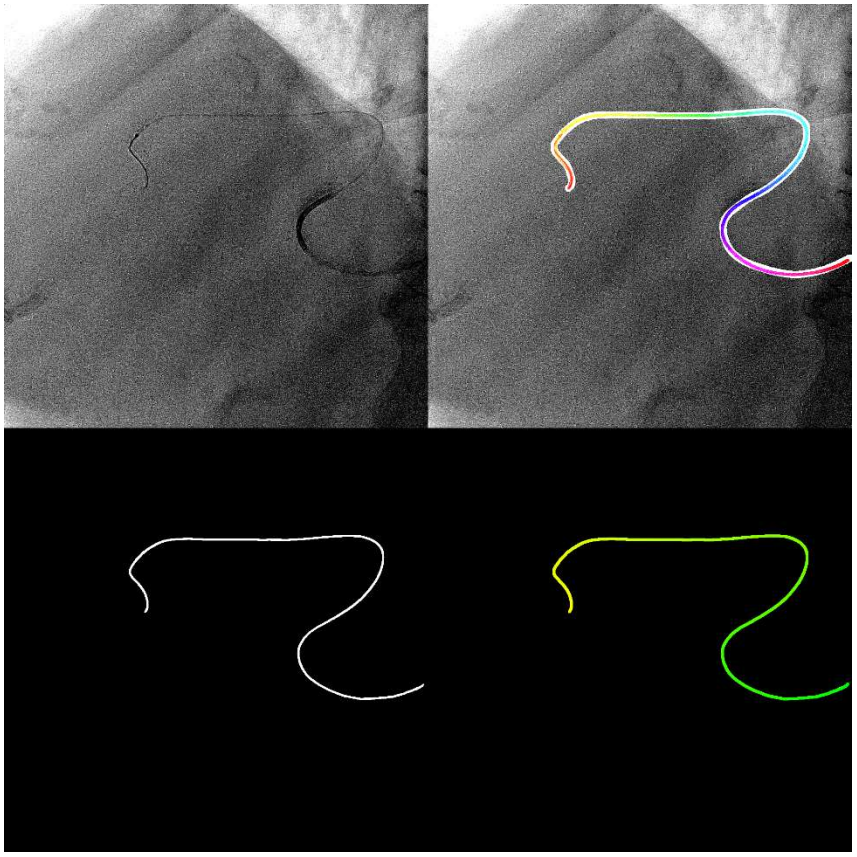
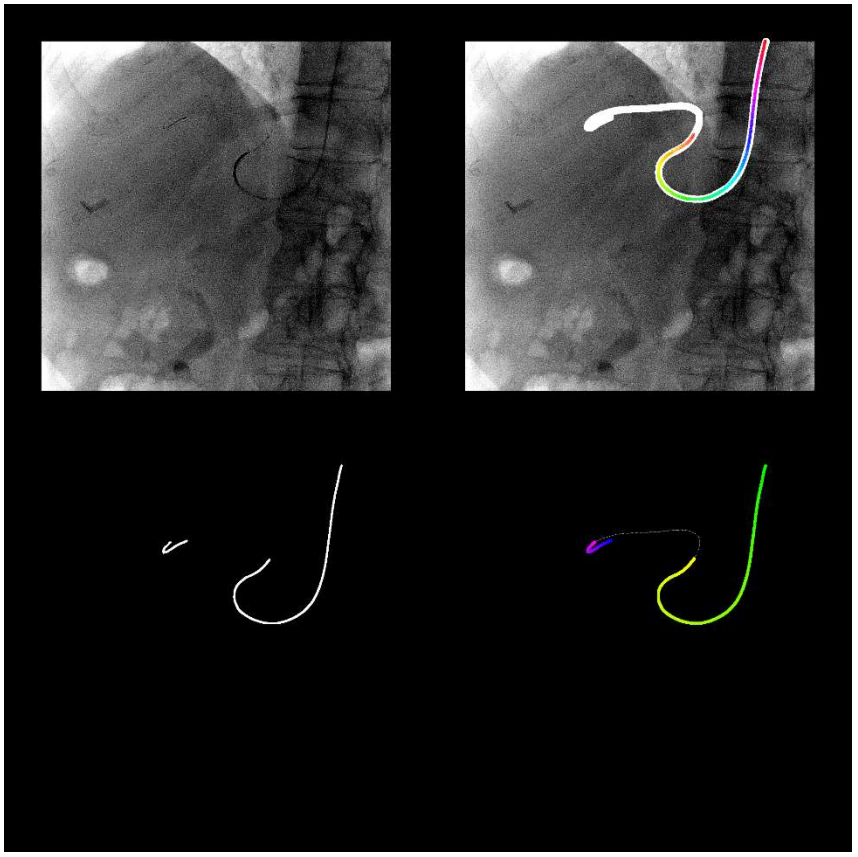
Automatic and Real-Time Catheter Segmentation in X-Ray Fluoro





Pierre Ambrosini and Theo van Walsum; BIGR – Erasmus MC

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TREATMENT PLAN ADAPTION

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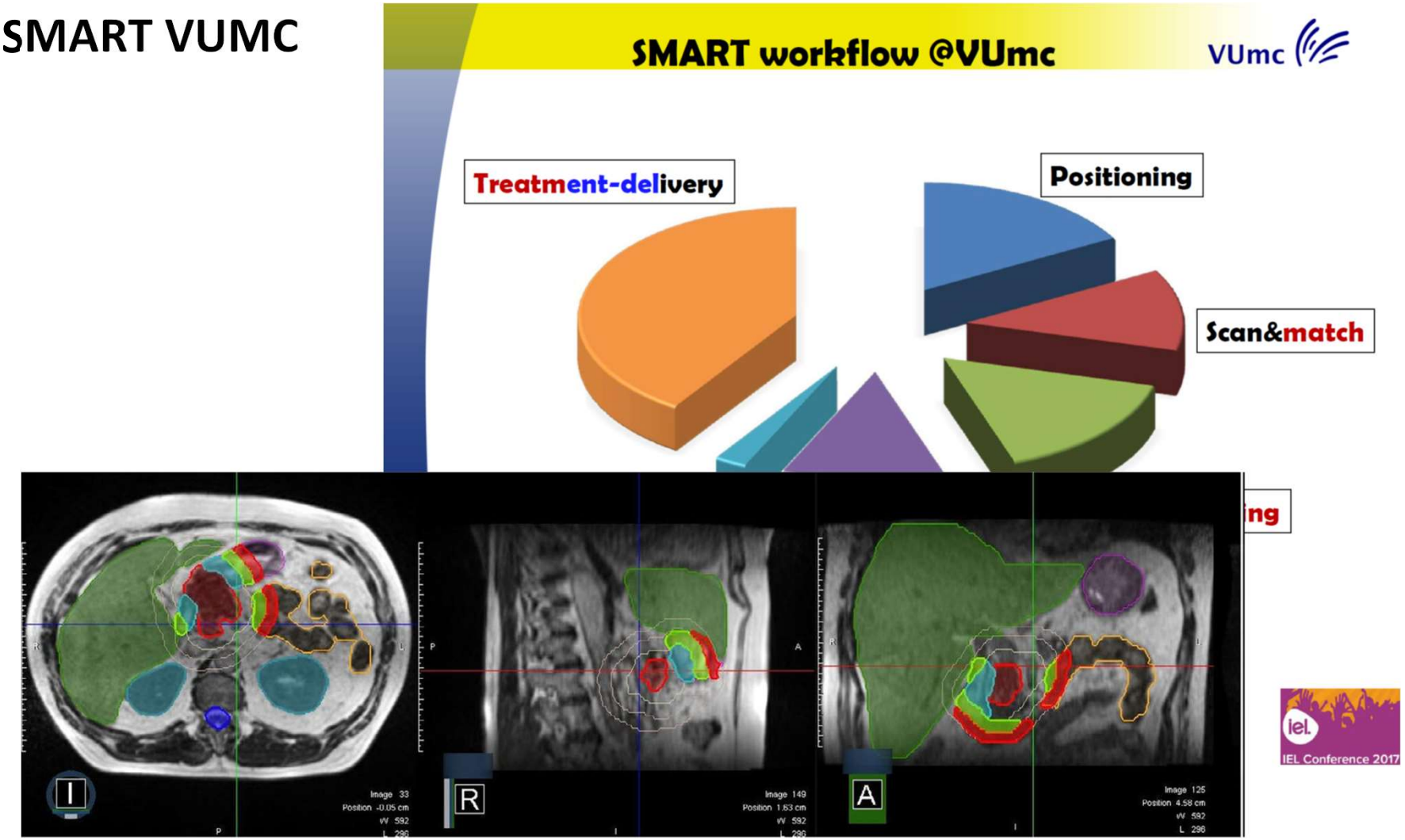
Plan Library vs. Online Re-Planning

Plan library	Online re-planning
Does not require full segmentation of target volumes and organs at risk	Requires full segmentation (and approval) of target volumes and organs at risk
No time is lost by online (re)optimization of the plan of the day	If (re)optimization time is too long intra-fractional motion will limit the precision of online adaptive approaches
Plan library approaches can be incorporated in existing radiotherapy workflows	Daily (re)optimization requires a completely new workflow
Plans stored in the plan library can be QA'd in advance	(Re)optimized plans should be QA'd on the fly
A-priori generated treatment plans do not necessarily accommodate all anatomies	Full (re)optimization will provide the most tight-fitting treatment plan
Tumor shrinkage is difficult to model a-priori and is therefore hard to incorporate in plan libraries	(Re)optimization can incorporate tumor shrinkage, but is it safe?

SMART VUMC



Bohoudi O et al. Radiother Oncol. 2017 Aug 12. Frank Lagerwaard: http://www.smartcccorp.co.uk/wp-content/uploads/2017/07/Birmingham_2017_lagerwaard.pdf

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Online Adaptive RT in Clinical Practice Using a Plan Library

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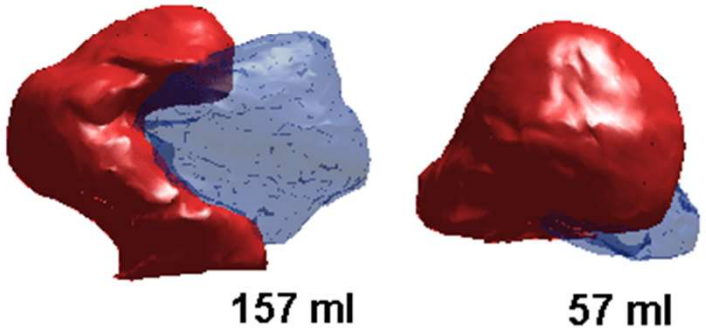
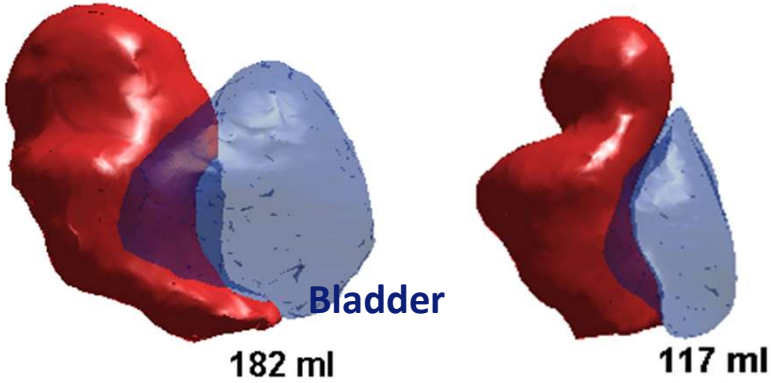
Inter-Patient Variability in Cervix-Uterus Motion



Cervix-uterus



Large and complex motion

Small motion

Bondar ML, Hoogeman MS, Mens JW, Quint S, Ahmad R, Dhawtal G, Heijmen BJ. Int J Radiat Oncol Biol Phys. 2012 Aug 1;83(5):1617-23.

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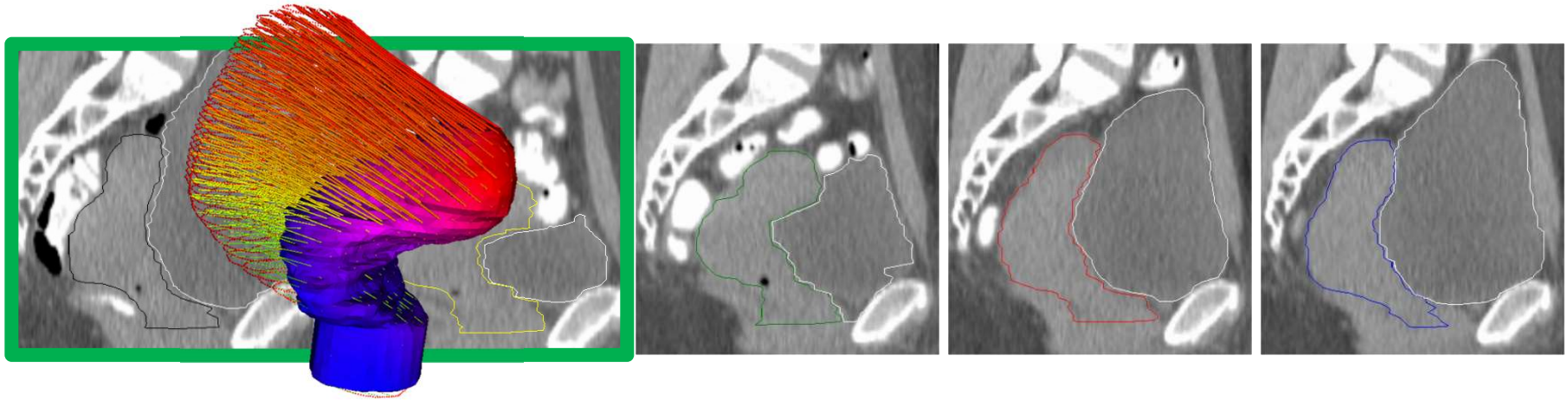
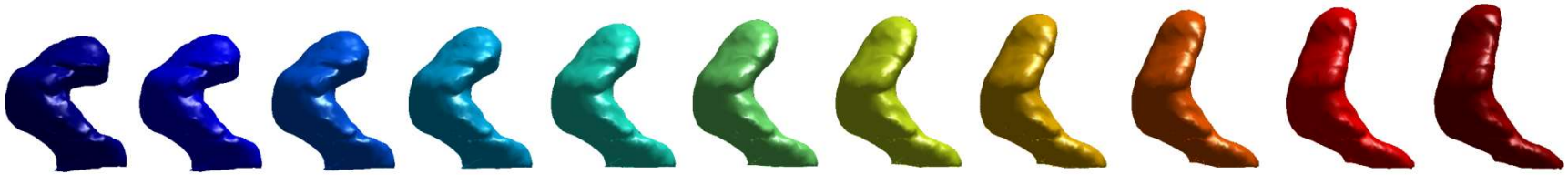
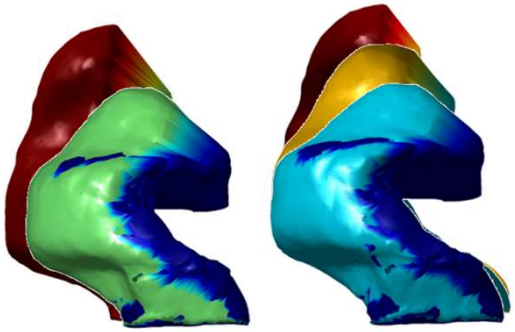
Modeling Target Motion







Input for treatment plan library

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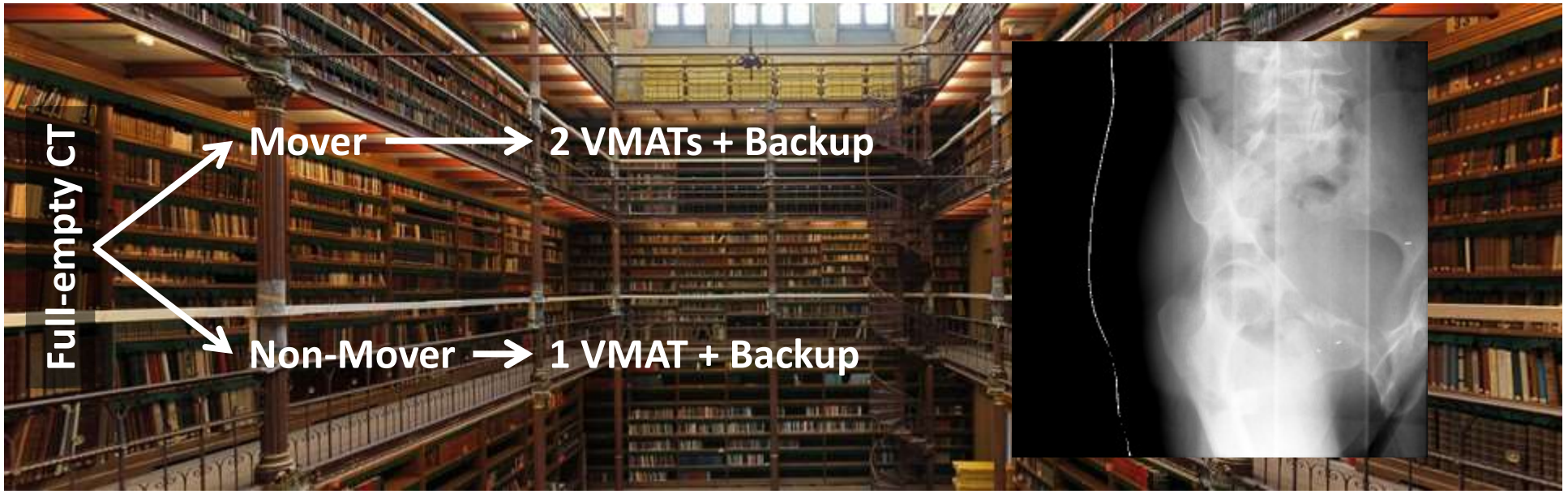
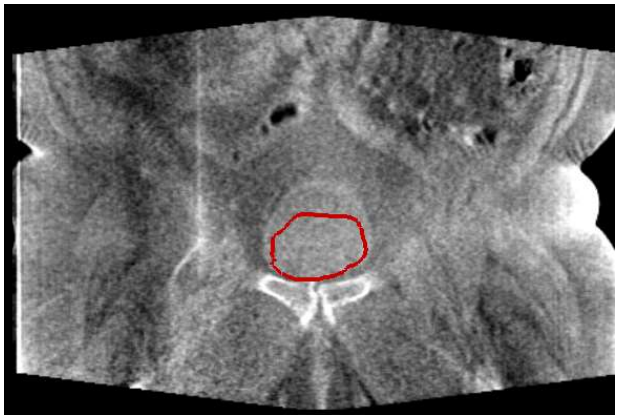
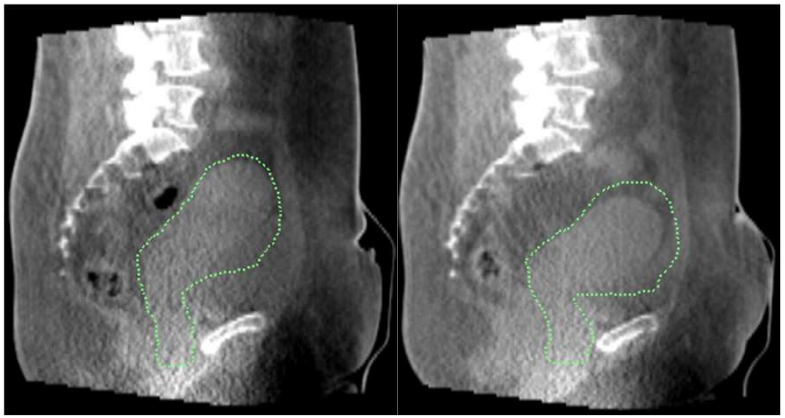
Clinical Plan Library-Based Plan-of-the-Day Protocol



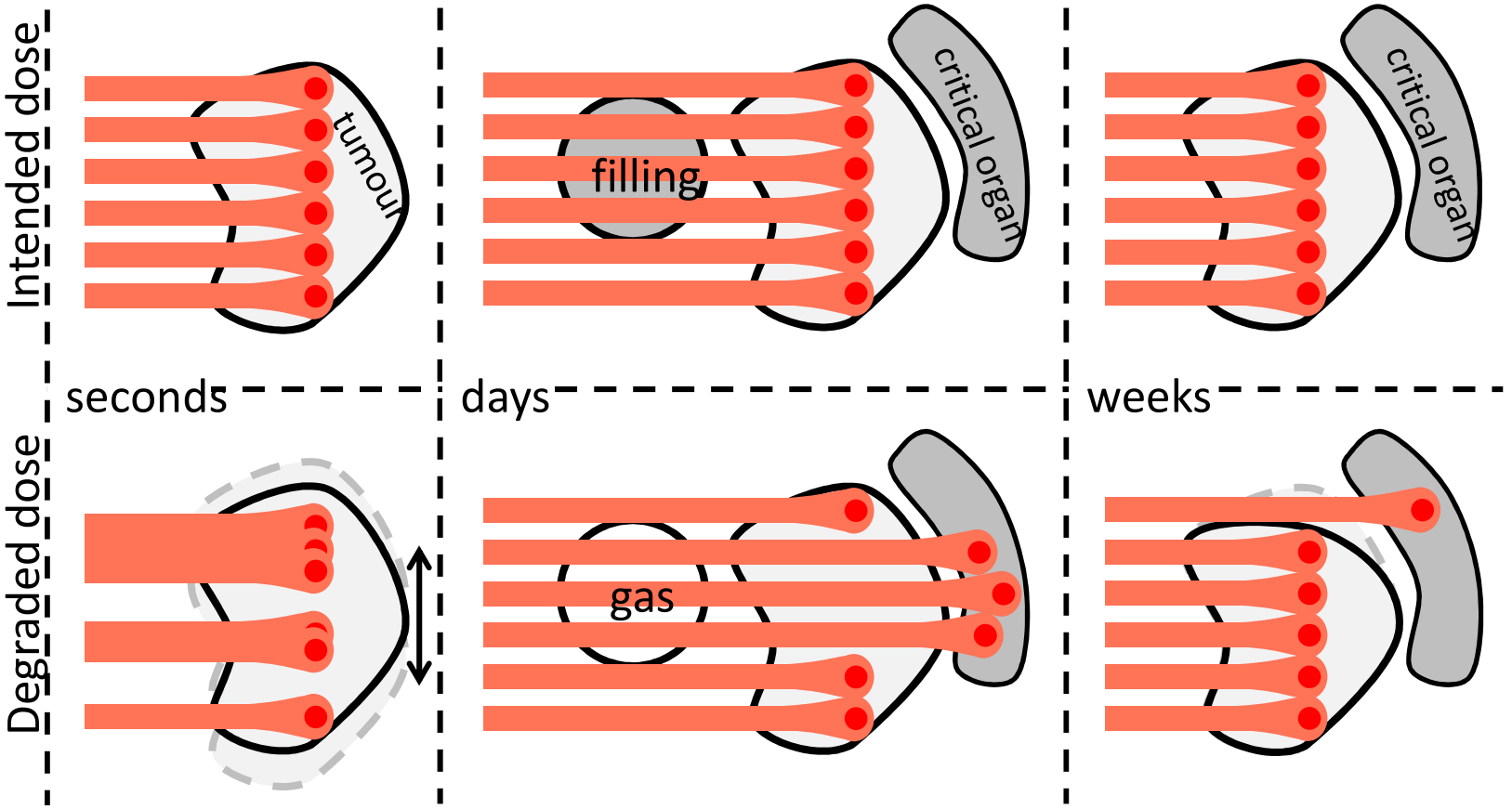




Heijkoop S et al. IJROBP 2014

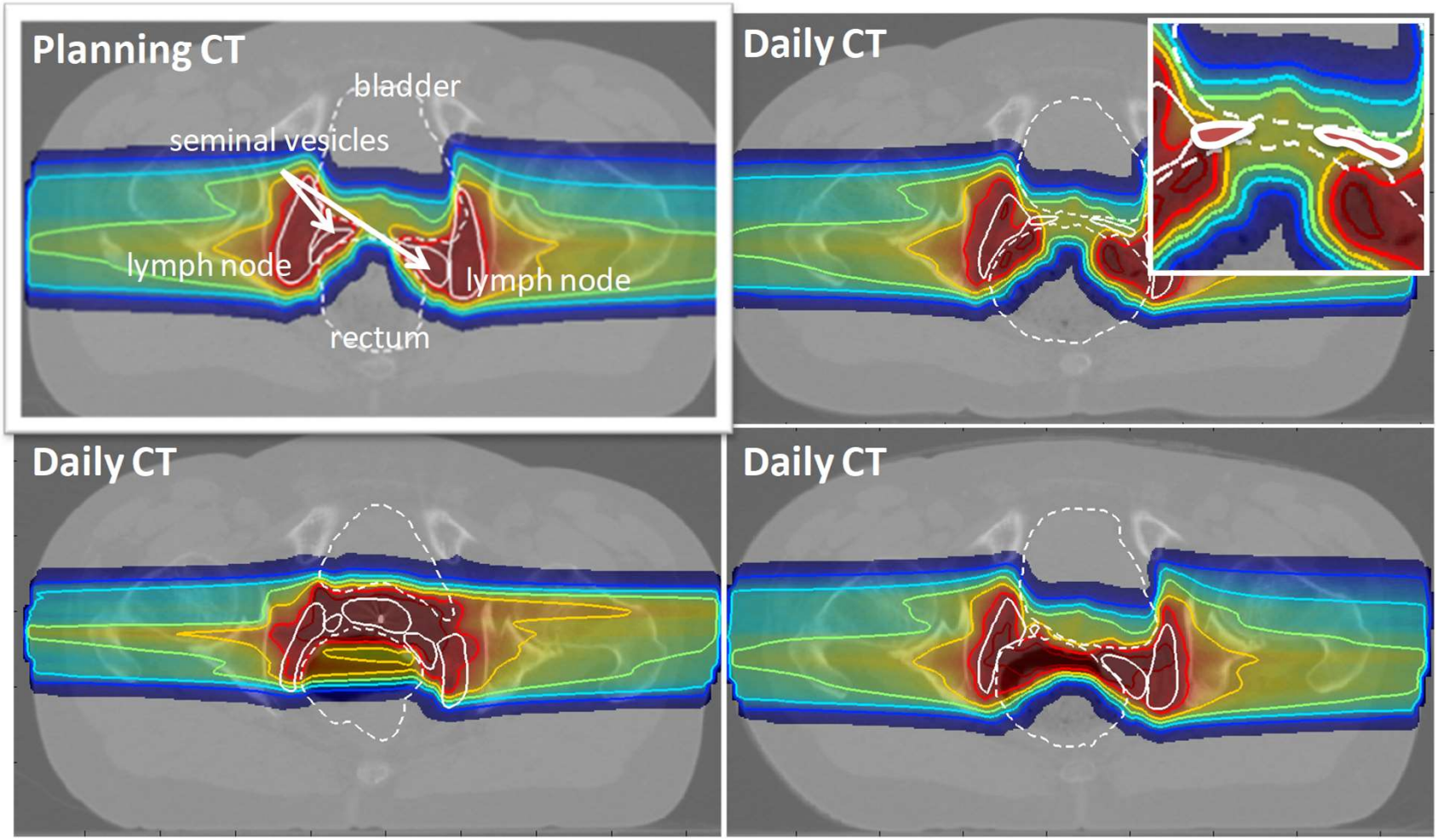

ONLINE ADAPTIVE PROTON
THERAPY

Dose Degradation in IMPT



Erasmus MC Cancer Institute

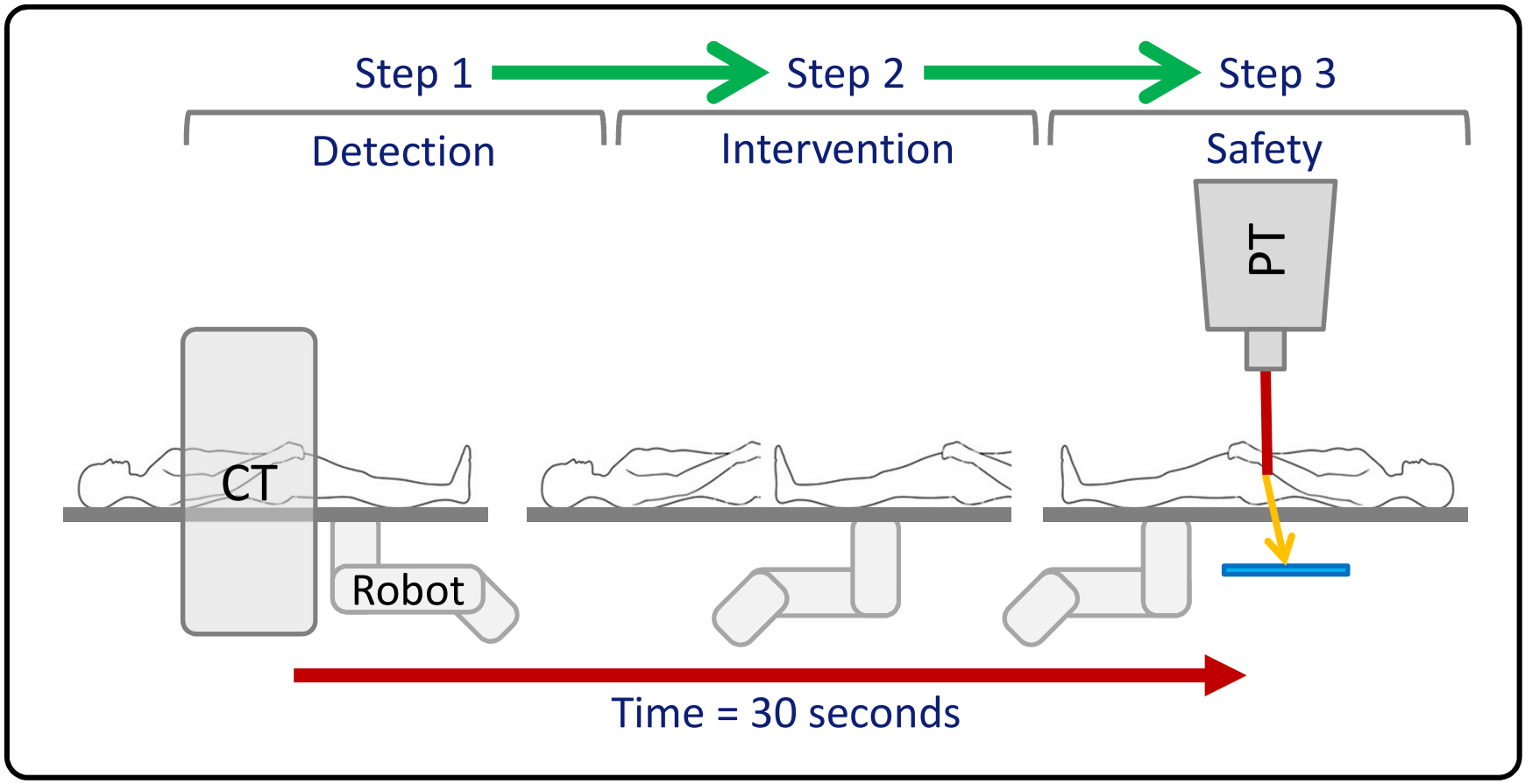
Prostate Cancer



ADAPTNOW project

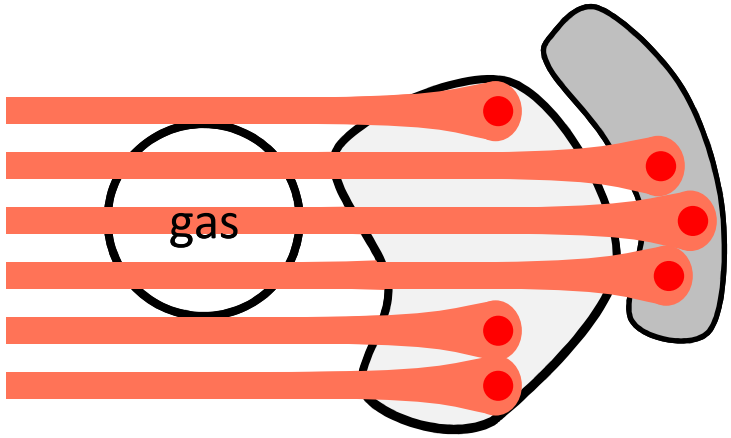
Erasmus MC Cancer Institute

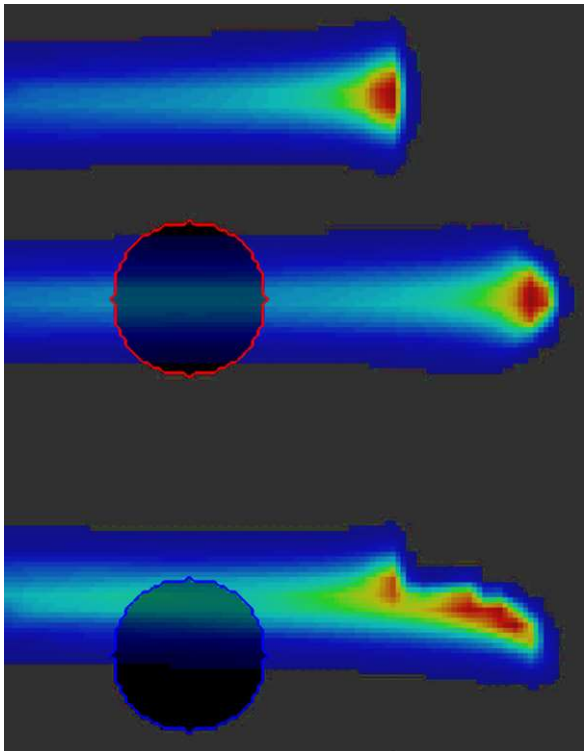
ADAPTNOW



Funded by ZonMw and co-funded by Varian

Dose Restoration





A Focused Weight Re-Optimization

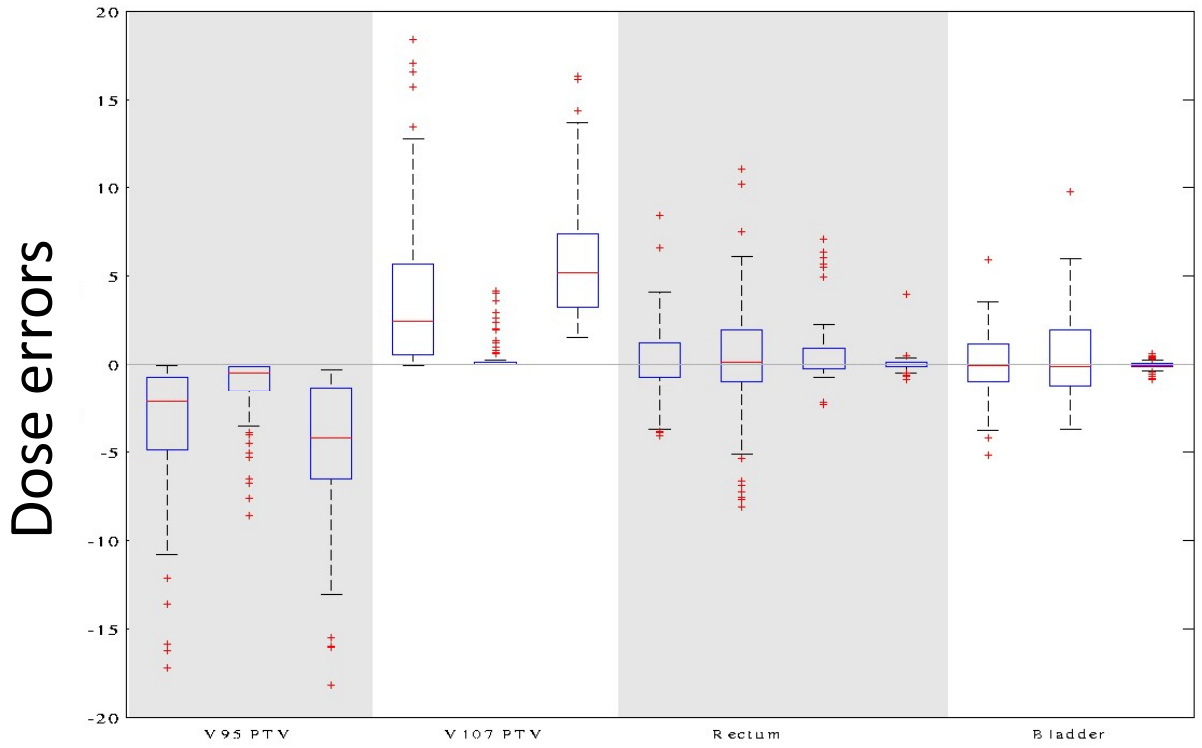
- Voxel-wise minimization of the difference between the actual dose minus and the intended dose

$$-s(\boldsymbol{f}) = \left(A\boldsymbol{f} - \boldsymbol{d}^{\boldsymbol{int}}\right)^T W\left(A\boldsymbol{f} - \boldsymbol{d}^{\boldsymbol{int}}\right) + \kappa S$$

Jagt et al. Phys Med Biol. 2017 Jun 7;62(11):4254-4272.

If we do nothing …

Degraded dose – Intended dose



Dosimetric parameters

Jagt et al. Phys Med Biol. 2017 Jun 7;62(11):4254-4272.

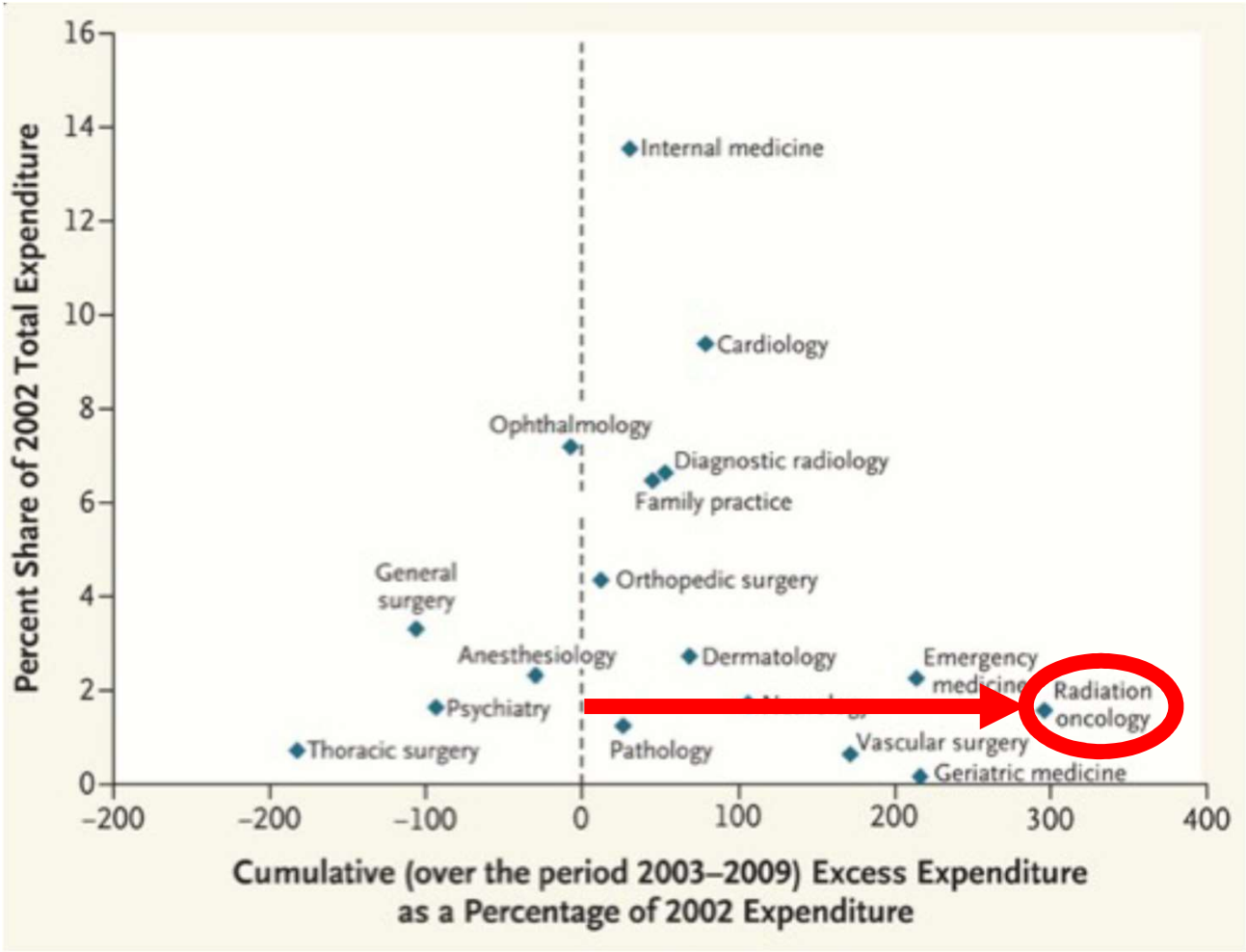
Or restore the dose … in 8 seconds

Next step is to adapt the restored dose distribution to the anatomy of the day

Jagt et al. Phys Med Biol. 2017 Jun 7;62(11):4254-4272.

FINALLY

Price of Radiotherapy Tripled



Erasmus MC Cancer Institute

Trends and research opportunities in radiotherapy dosimetry

Hugo Palmans

Dosimetry

What

- Determination of absorbed dose
- Determination of other dosimetric quantities
- Primary standards, dissemination, reference dosimetry, protocols, relative dosimetry, 4D dosimetry, in-vivo, plan verification

Importance for RT

- Dose, RBE, microdosimetry, nanodosimetry

Current status

Challenges: keeping up with modern developments sometimes hindering progress in RT

Definition of absorbed dose

ICRU Report 85 - FUNDAMENTAL QUANTITIES AND UNITS FOR IONIZING RADIATION (Revised):

The *absorbed dose*, D, is the quotient of $\mathrm{d}\bar{\varepsilon}$ by $\mathrm{d}m$, where $\mathrm{d}\bar{\varepsilon}$ is the mean energy imparted by ionizing radiation to matter of mass $\mathrm{d}m$, thus

$$D = \frac{\mathrm{d}\bar{\varepsilon}}{\mathrm{d}m}.$$

Unit: $\mathrm{J\,kg^{-1}}$

The special name for the unit of absorbed dose is gray (Gy).

How to measure

Cellular response

DNA strand breaks

Chemical yield

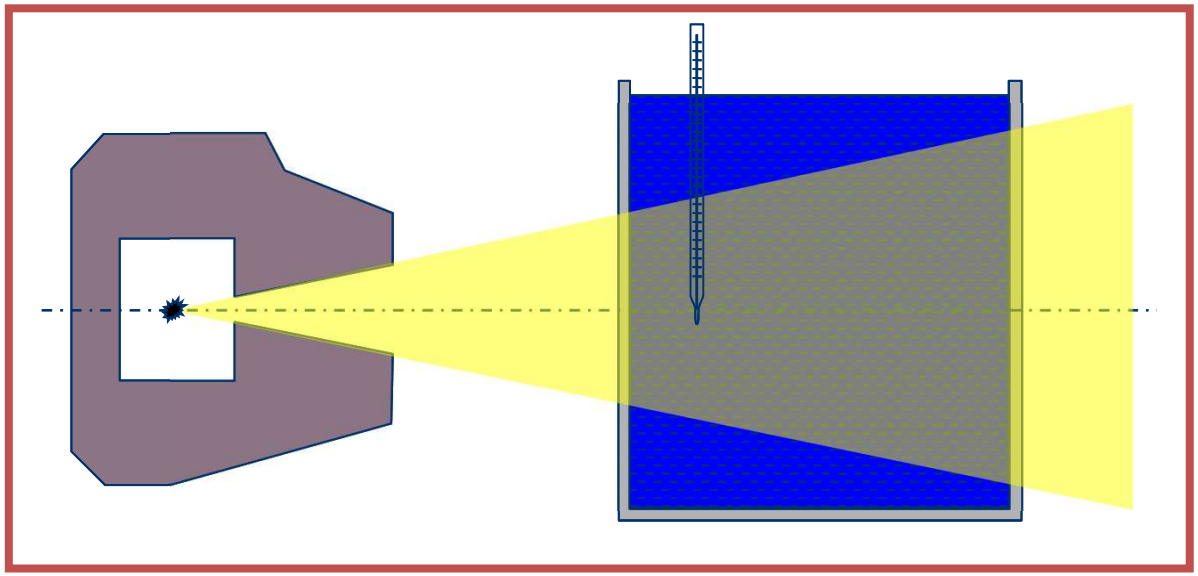
Radical yield

Ionization

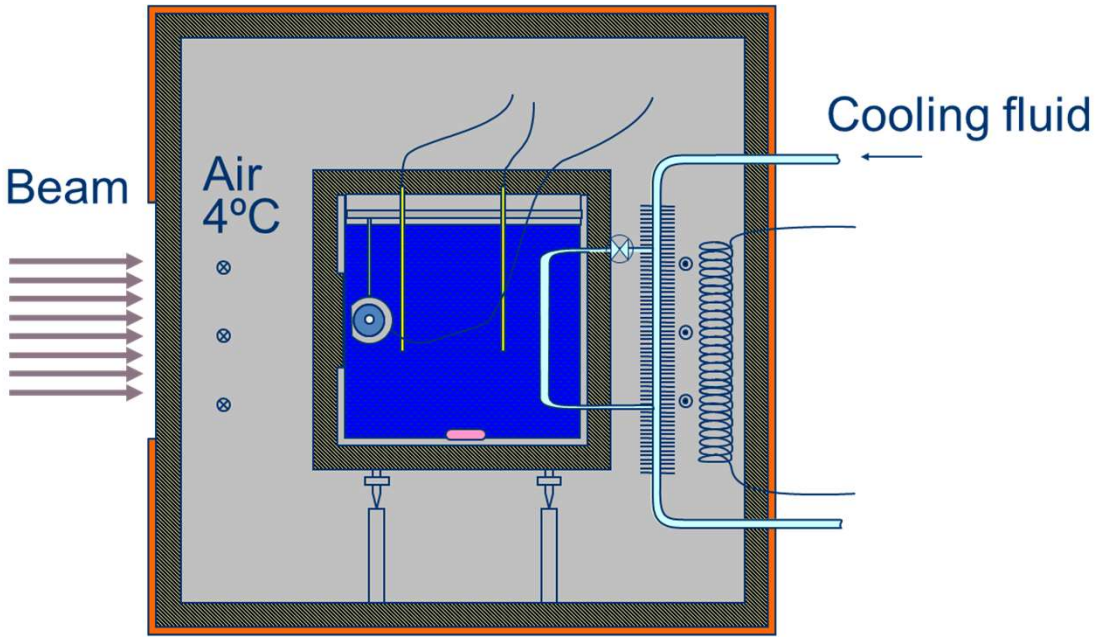
Thermalization

Calorimetry

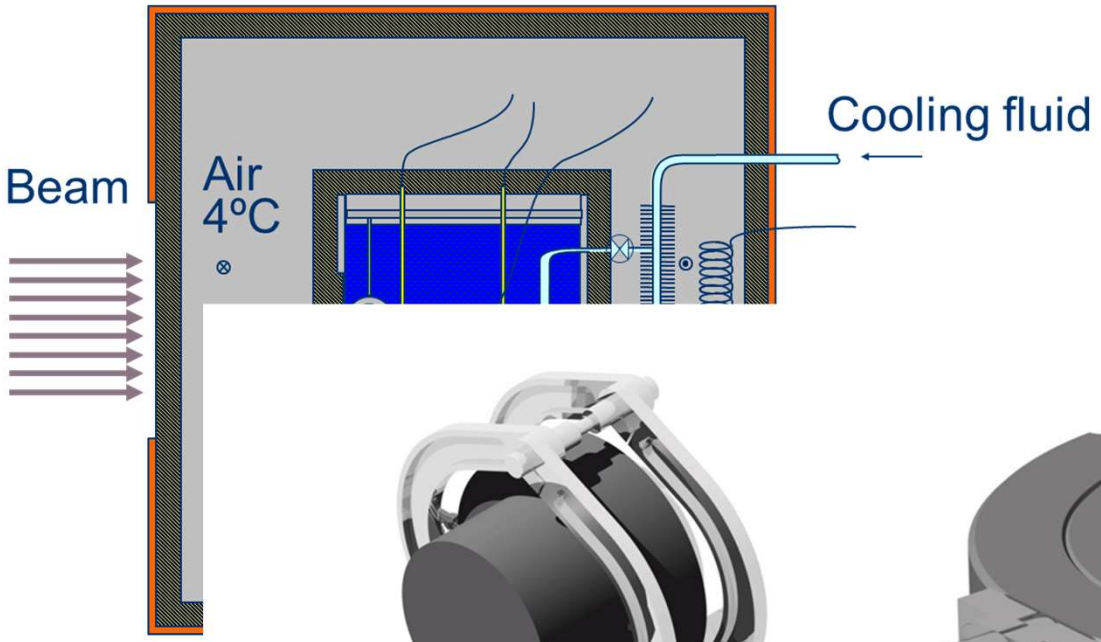
$$D_{med} = c_{med}\Delta T$$

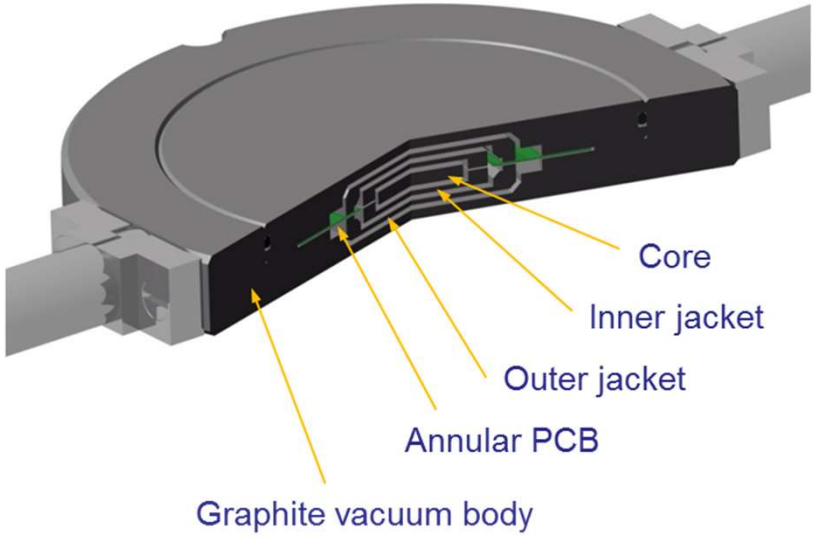


Calorimetry in practice



Calorimetry in practice





Need to diversify

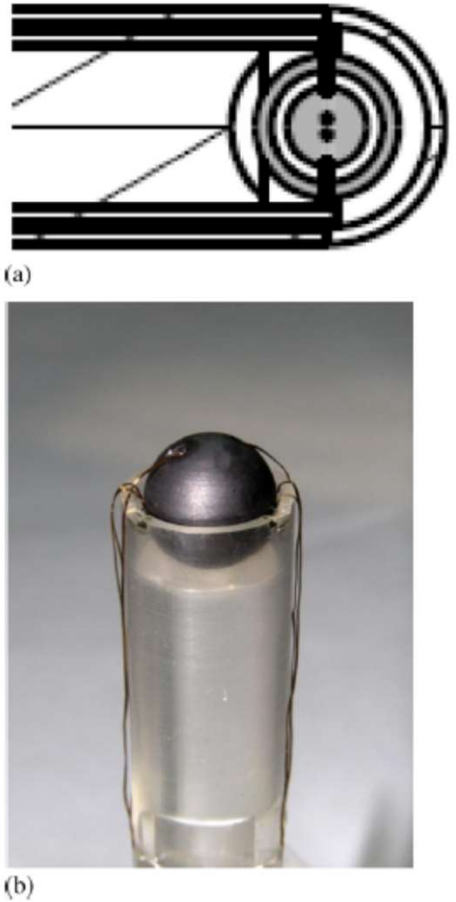
Complex fields

Scanned fields

Small fields

Dose-area-product

Brachytherapy



Duane et al 2012 Metrologia 49:S168

Need to diversify

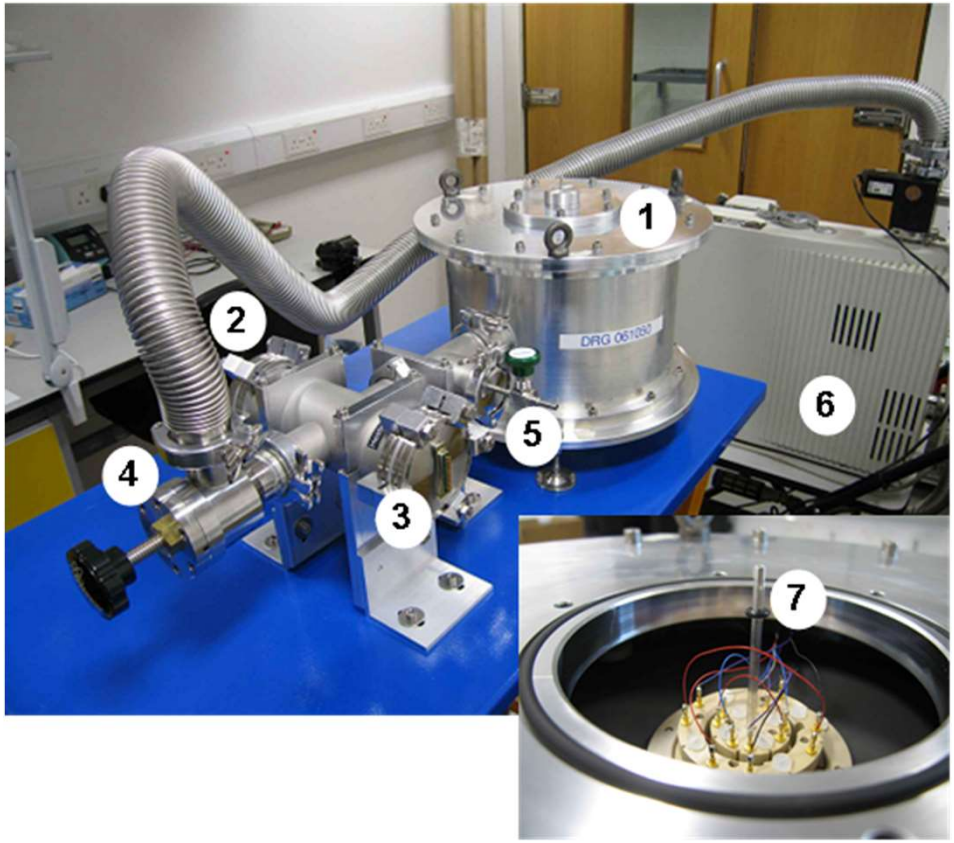
Complex fields

Scanned fields

Small fields

Dose-area-product

Brachytherapy



Sander et al 2012 Metrologia 49:S184

Need to diversify

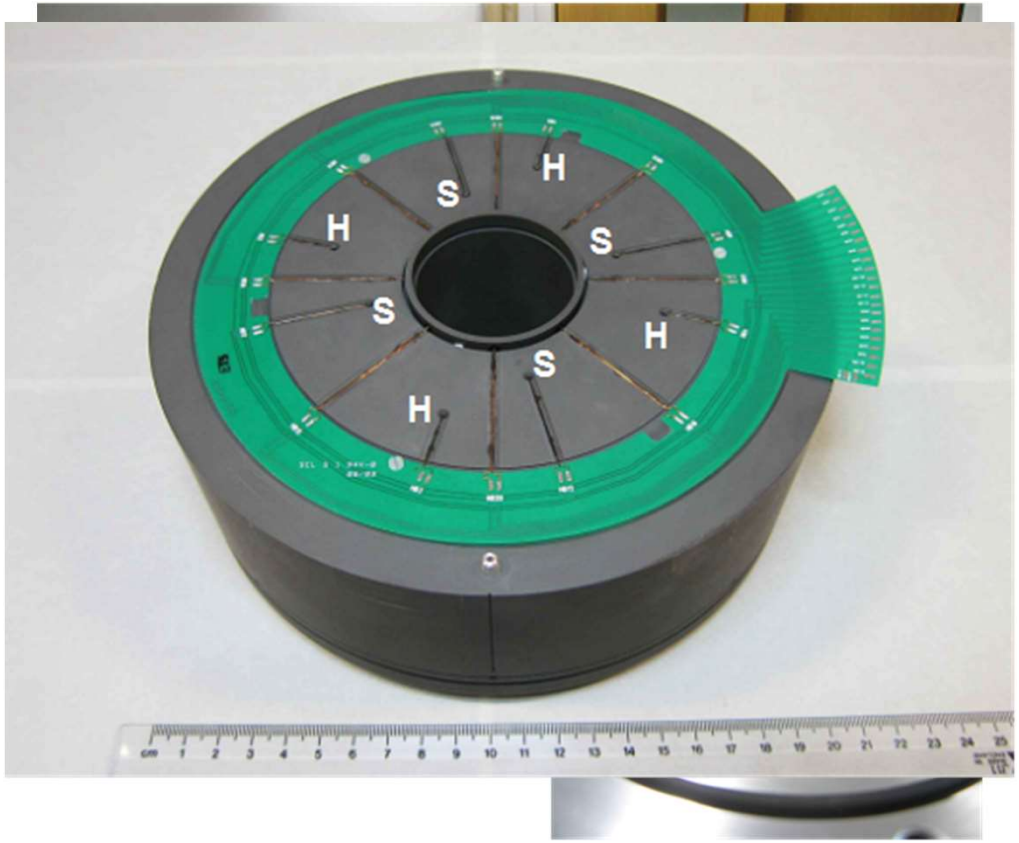
Complex fields

Scanned fields

Small fields

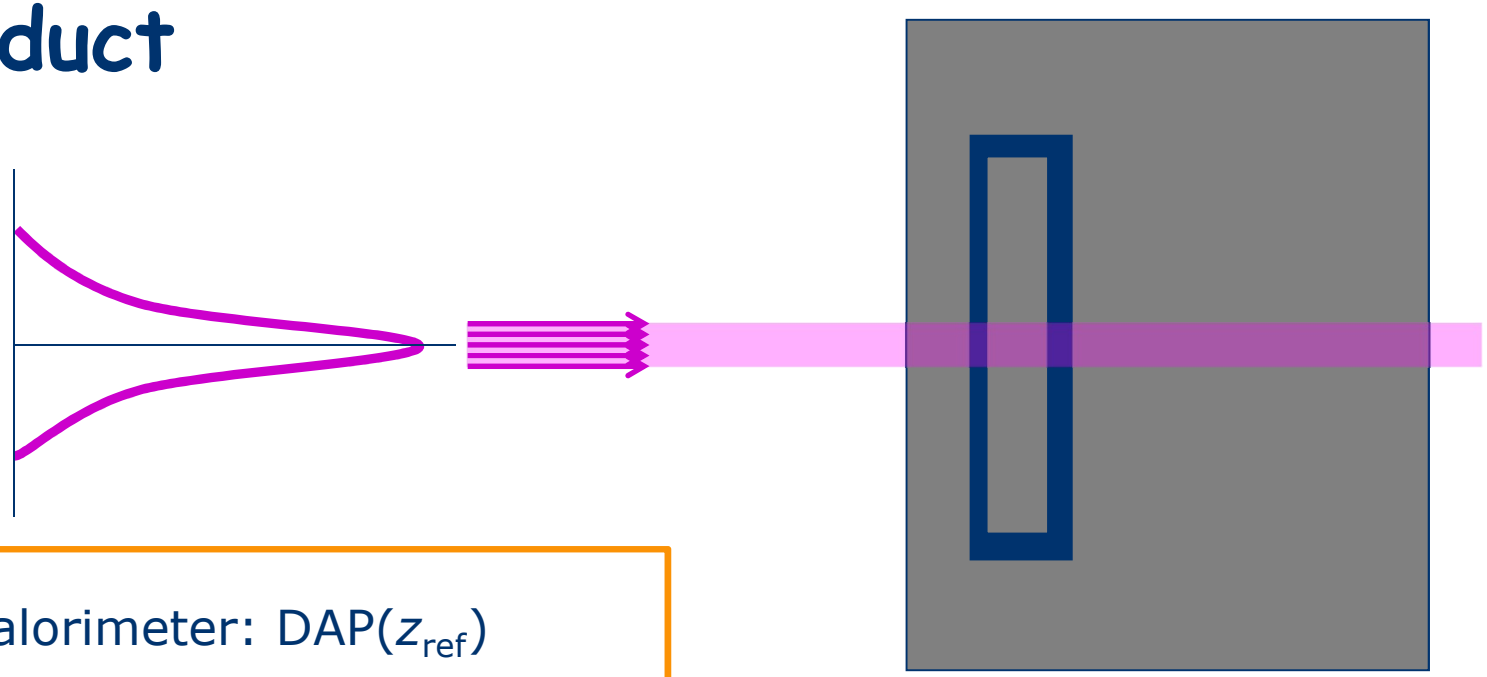
Dose-area-product

Brachytherapy



Sander et al 2012 Metrologia 49:S184

Graphite calorimetry - dose-area-product



Calorimeter: DAP(z_{ref})

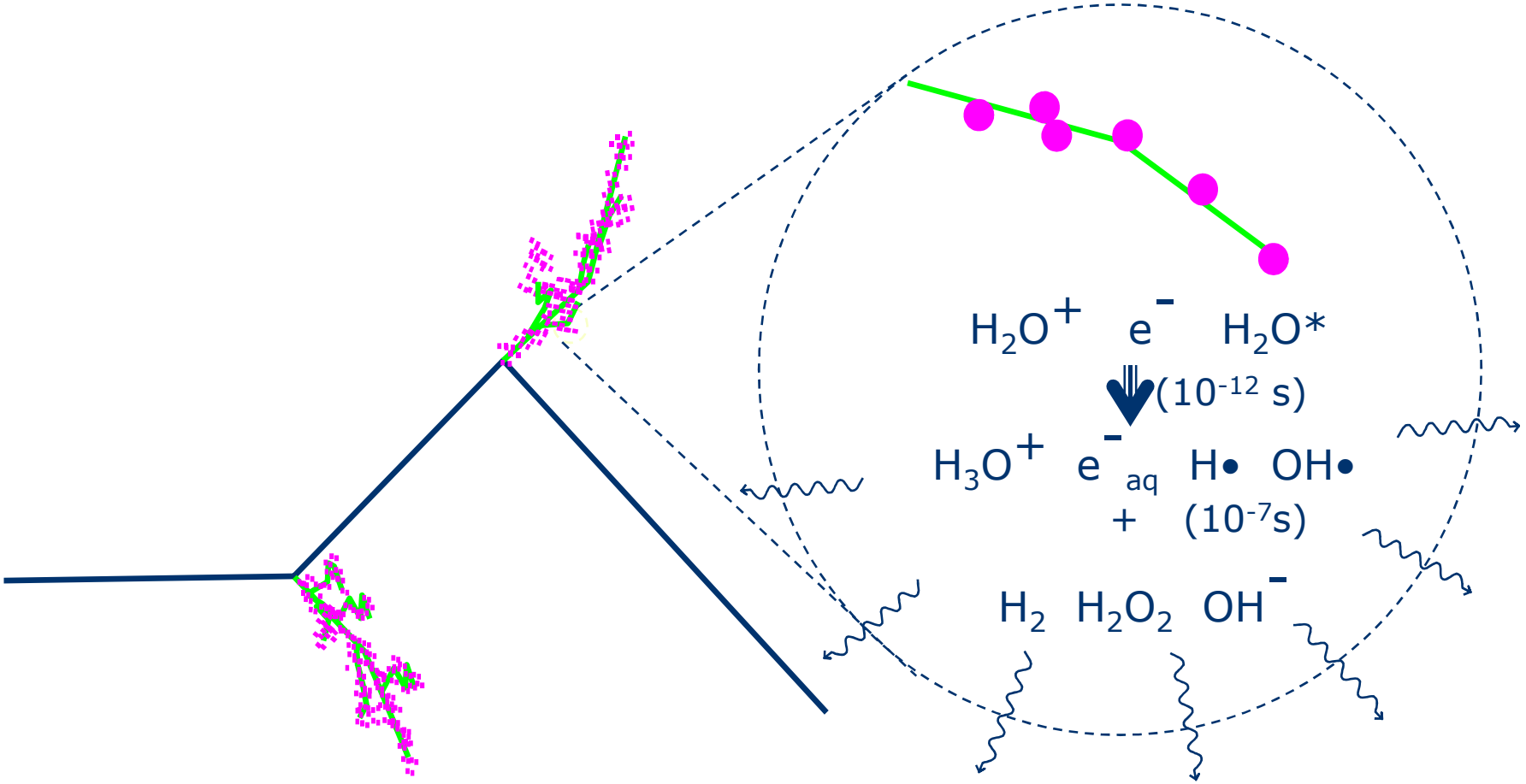
Large area ion chamber: pdd(z)

Faraday cup: N/MU

S/p: DAP(z_0 or z_{ref})

~~Integrate lateral dose profiles over all spots~~

Water calorimeter – chemical heat defect



Chemical heat defect – scanned beams

Sassowsky and Pedroni (2005) *Phys Med Biol.* 50:5381-400

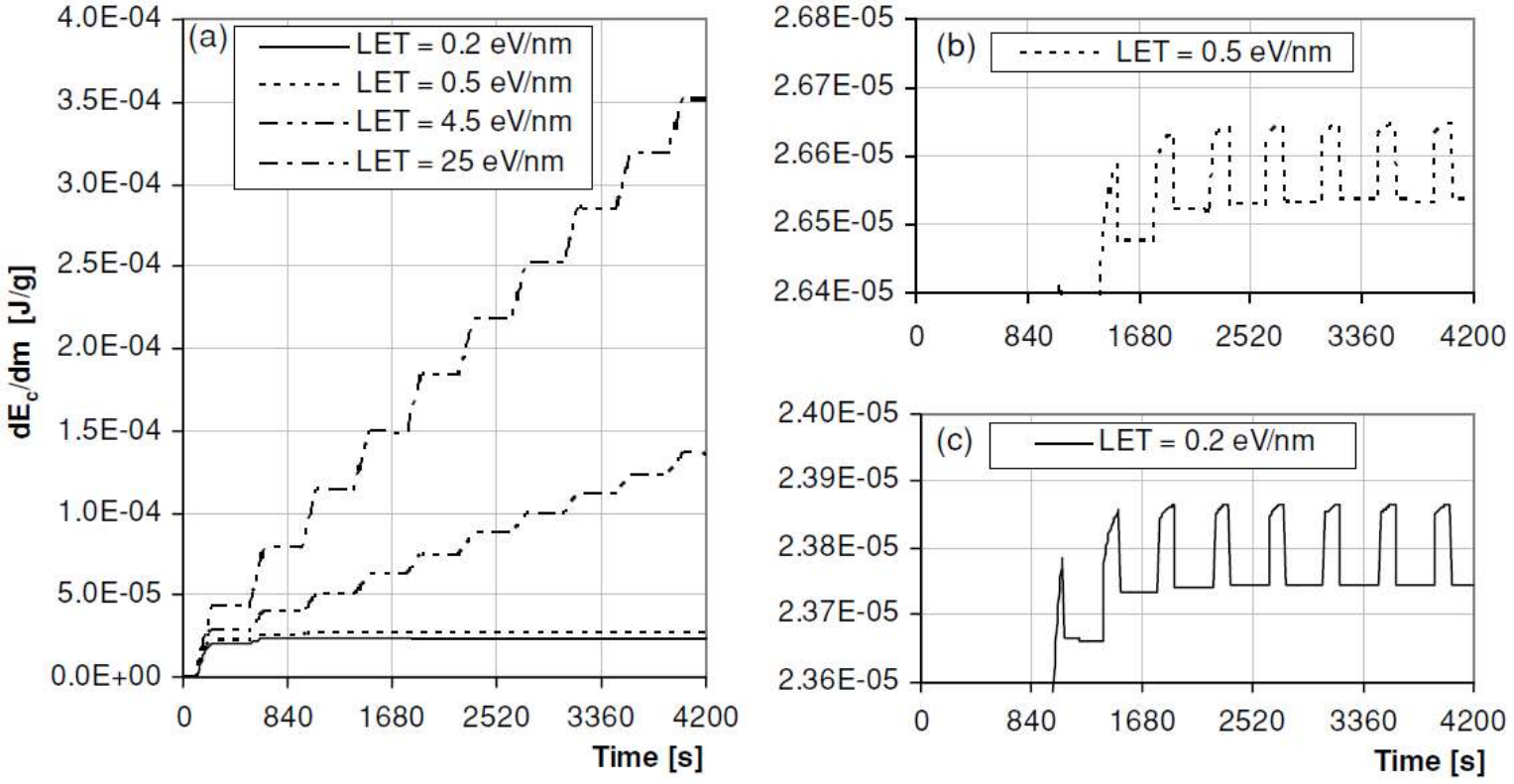


Figure 13. Calculated increase of the chemical energy per mass element as a function of time for four different LET values (a) for an N_2-saturated system. At low LET values, the system reaches a stationary state (b, c), while at higher LET values it does not. The irradiation cycle (120 s beam on time, 300 s beam off time), dose rate and aqueous system used for this simulation were the same as for figures 11 and 12.

Calorimetry - unsolved and new issues

Broad beam photons and electrons:

Protons and carbon ions:

- Chemical heat defect in water
- Lattice defects in graphite
- Dose conversion in graphite

Pencil beams: DAP calorimeter, probe Calorimeters

Complex fields: 3D integrating calorimeters

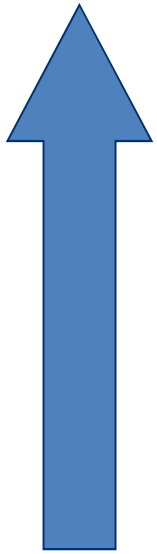
A general thought

The ideal dosimeter is the patient

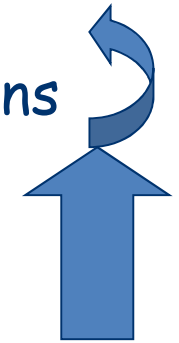
Maybe even more ideal is a phantom which is an identical copy of the patient

Then we can make ranking:

- Anthropomorphic phantoms
- Simple phantoms + anatomical features
- Simple phantom + patient-like outer dimensions
- 30 cm x 30 cm x 30 cm water phantom



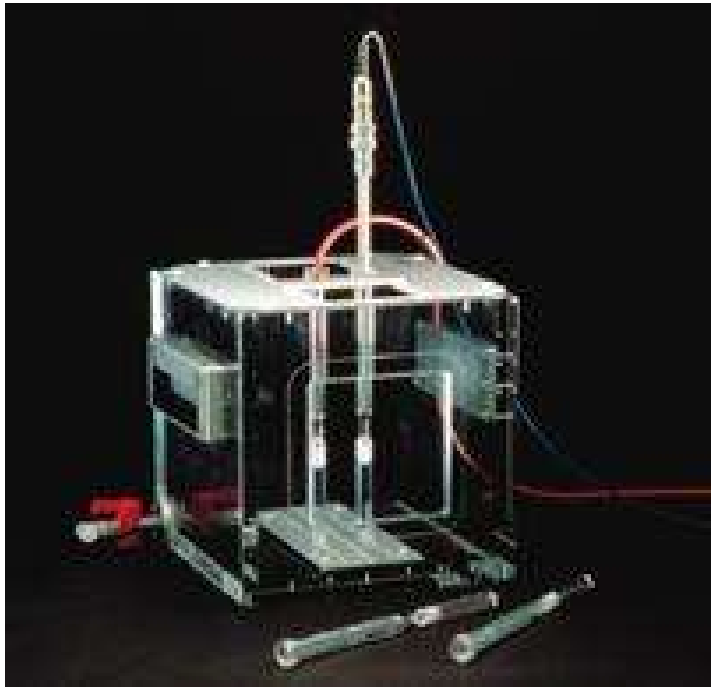
QA



Ref Dosimetry

Dosimetry for radiotherapy is done in a phantom

Because it's a good model
for the human body (???)



Dosimetry for radiotherapy is done in a phantom

Because it's a good model
for the human body (???)

Using the patient as dosimeter

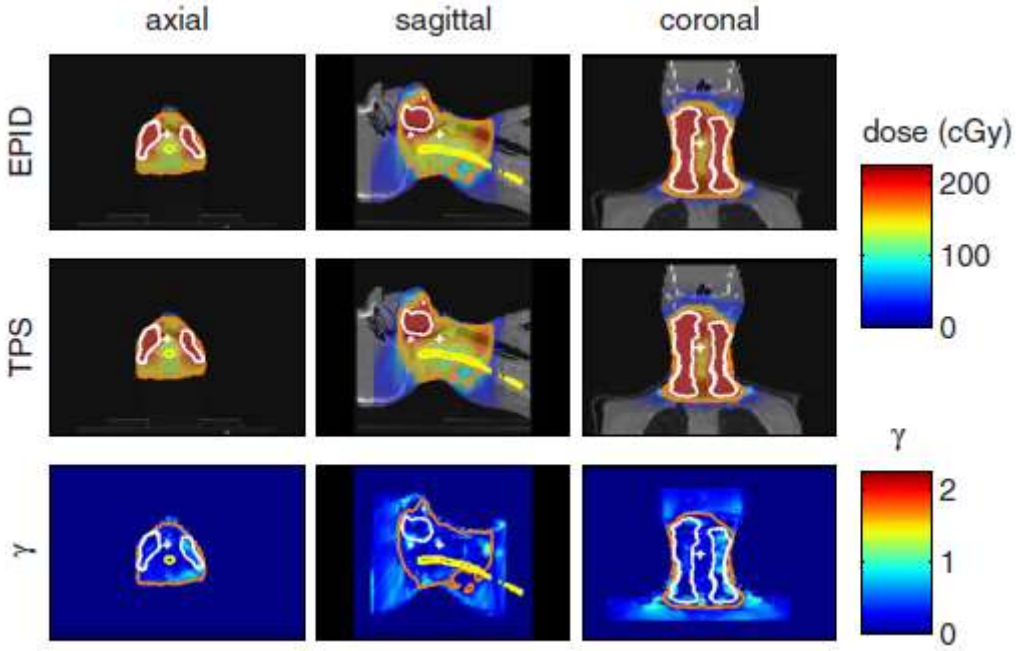
High-energy photons:

- EPID back-projection dose reconstruction

Using the patient as dosimeter

High-energy photons:

- EPID back-projec



Wendling et al 2009 Med Phys 36:3310

Using the patient as dosimeter

High-energy photons:

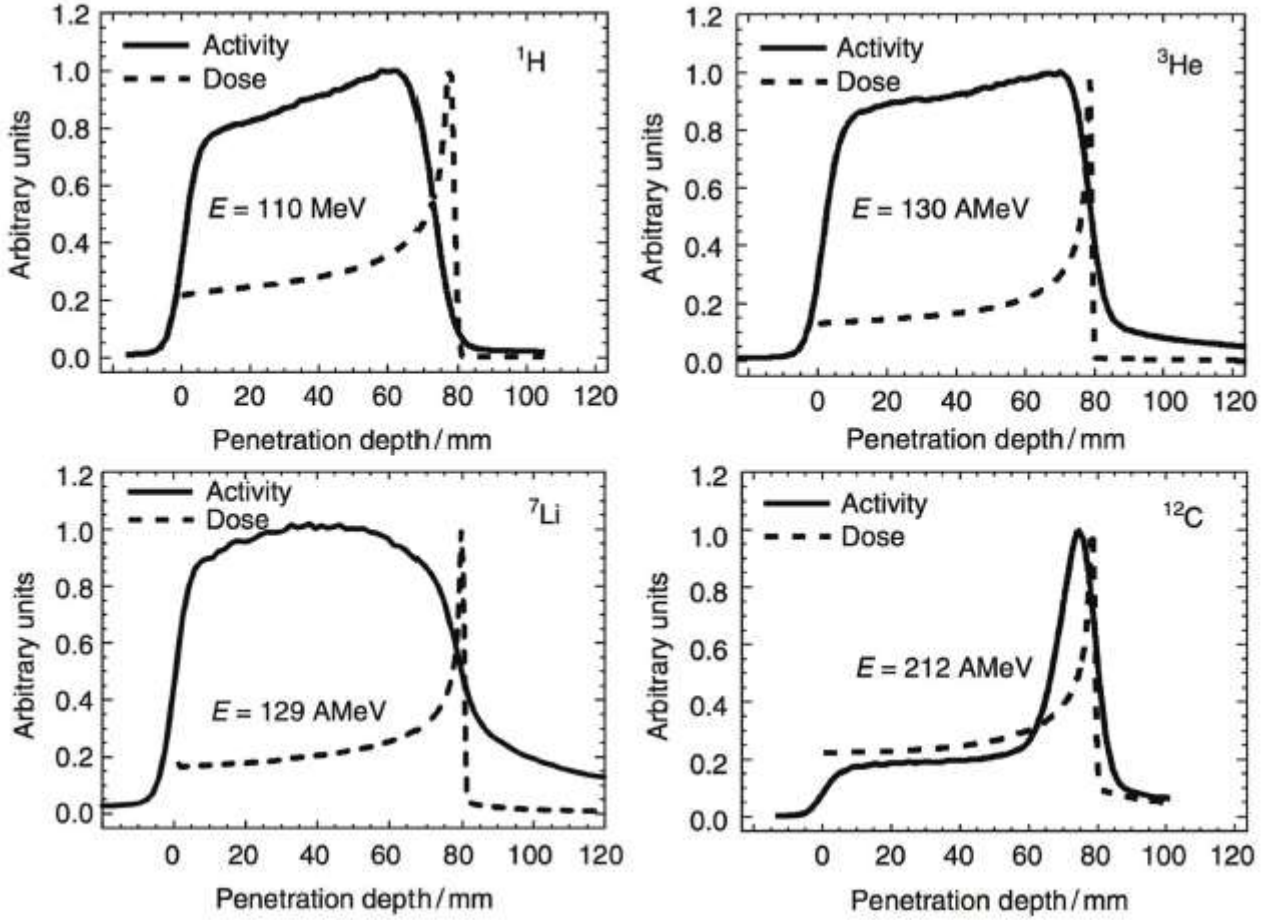
- EPID back-projection dose reconstruction

Protons and carbon ions:

- PET

Using the patient as dosimeter

- High-energy ph
  - EPID back
- Protons and car
  - PET

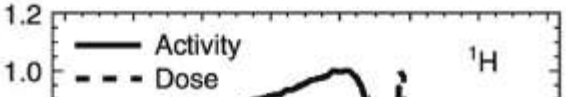


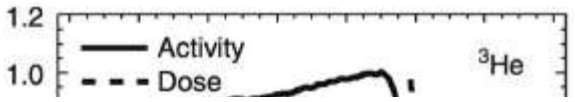
Fiedler et al 2012

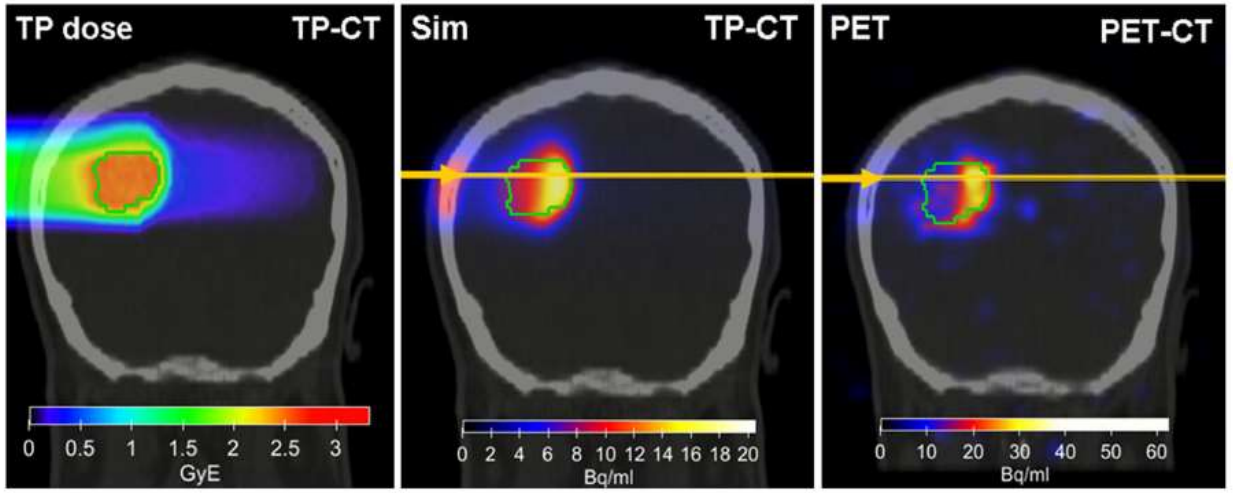
Using the patient as dosimeter

High-energy ph
- EPID back

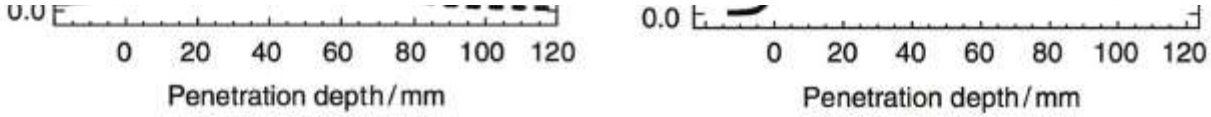
Protons and car
- PET







Bauer et al 2013 Radiother Oncol 107:218



Fiedler et al 2012

Using the patient as dosimeter

High-energy photons:

- EPID back-projection dose reconstruction

Protons and carbon ions:

- PET
- Prompt gamma

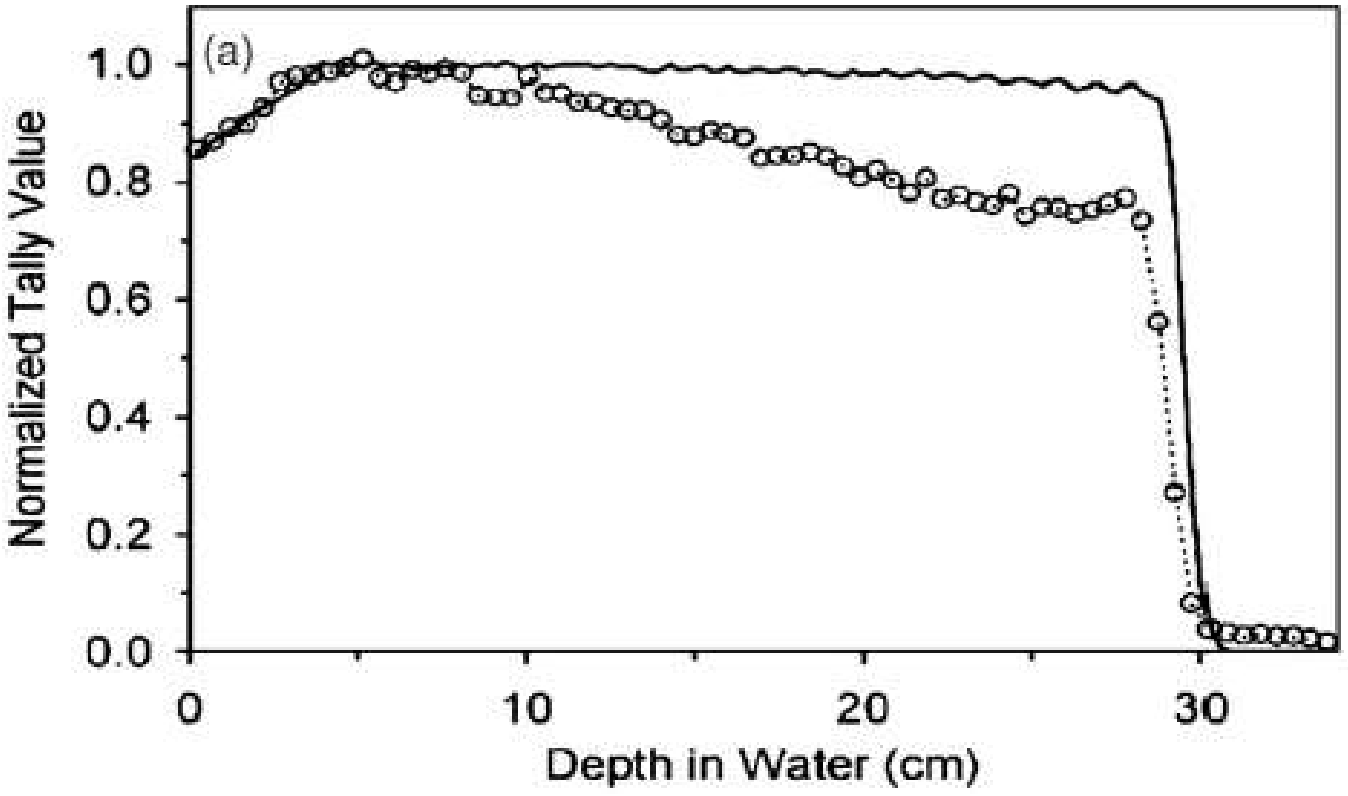
Using the patient as dosimeter

High-energy

- EPID bc

Protons and

- PET
- Prompt



Polf et al 2009 Phys Med Biol 54:731

Using the patient as dosimeter

High-energy photons:

- EPID back-projection dose reconstruction

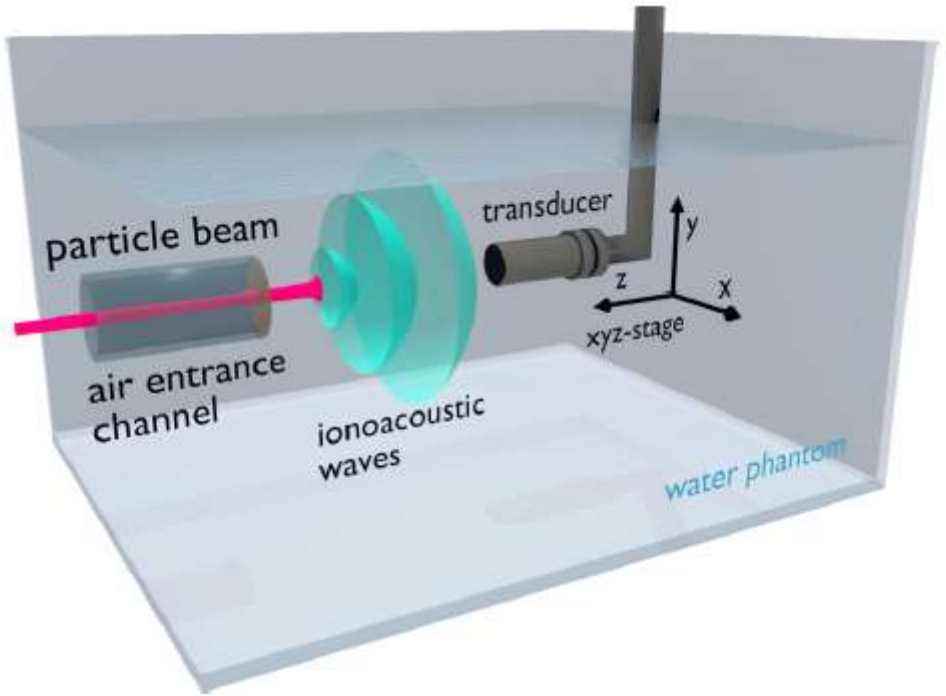
Protons and carbon ions:

- PET
- Prompt gamma
- Iono-acoustics

Using the patient as dosimeter

High-energy phot
- EPID back-pr

Protons and carbo
- PET
- Prompt gamm
- Iono-acousti

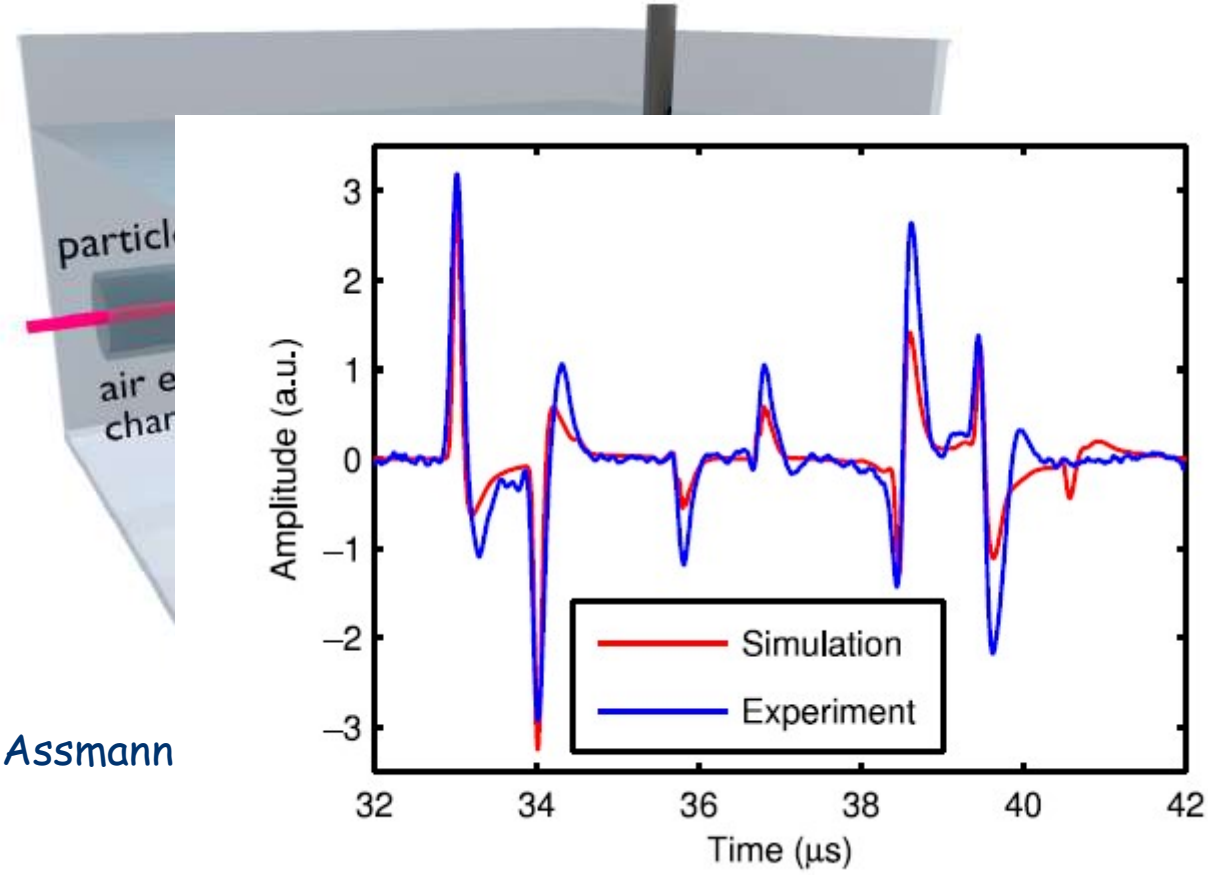


Assmann et al 2015 Med Phys 42:567

Using the patient as dosimeter

High-energy phot
- EPID back-pr

Protons and carbo
- PET
- Prompt gamm
- Iono-acousti



Assmann

NPL

PRaVDA

MedAustron

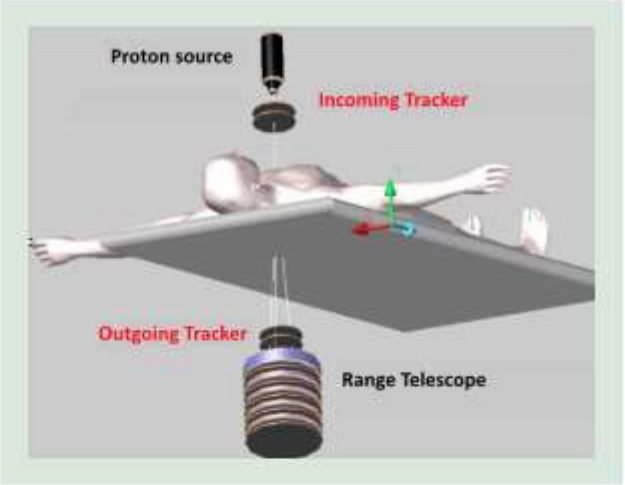
Proton Radiotherapy Verification and Dosimetry Applications

The PRaVDA (Proton Radiotherapy Verification and Dosimetry Applications) project aims to design and make the world's first fully silicon-based proton CT scanner and is funded by a Wellcome Trust Translation Scheme award of £1.6 million.

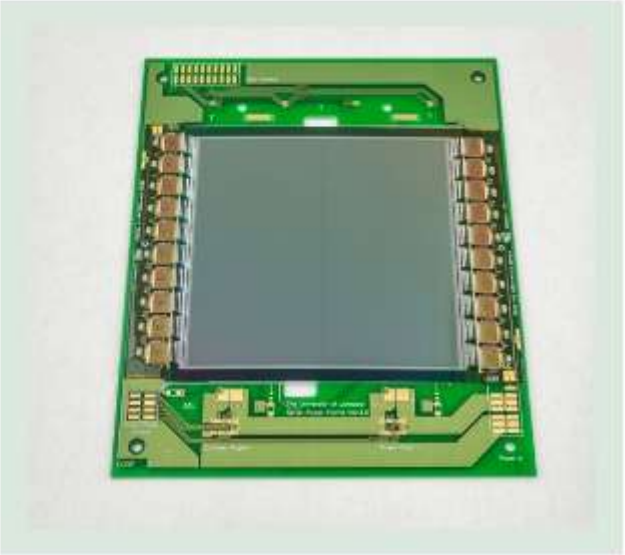
The consortium is composed of physicists from the University of Liverpool along with engineers, medical physicists and oncologists from the Universities of Birmingham, Lincoln and Surrey as well as University Hospitals in Birmingham and Coventry, and the iThemba Laboratories in Cape Town, South Africa.

The aim of the PRaVDA project is to design and make an instrument that is capable of improving particle therapy, a type of treatment for cancer carried out using charged particles such as protons or carbon ions. Such a treatment has been shown to have advantages over standard x-ray radiotherapy because of the characteristic way in which charged particles lose their energy compared with x-rays. As a result of this, many new centres offering particle therapy are currently under construction including two in the UK.

The PRaVDA instrument will make use of detector technology based on extensive research carried out for experiments at the CERN laboratory in Geneva. This technology will be used to make silicon



The PRaVDA concept



Copy of the patient

State of the art:

Phantoms with real bony structures

Usually not used as a dosimeter itself, dosimeters are inserted

Potential:

3D printing of dosimetric materials?

Anthropomorphic and simpler phantoms

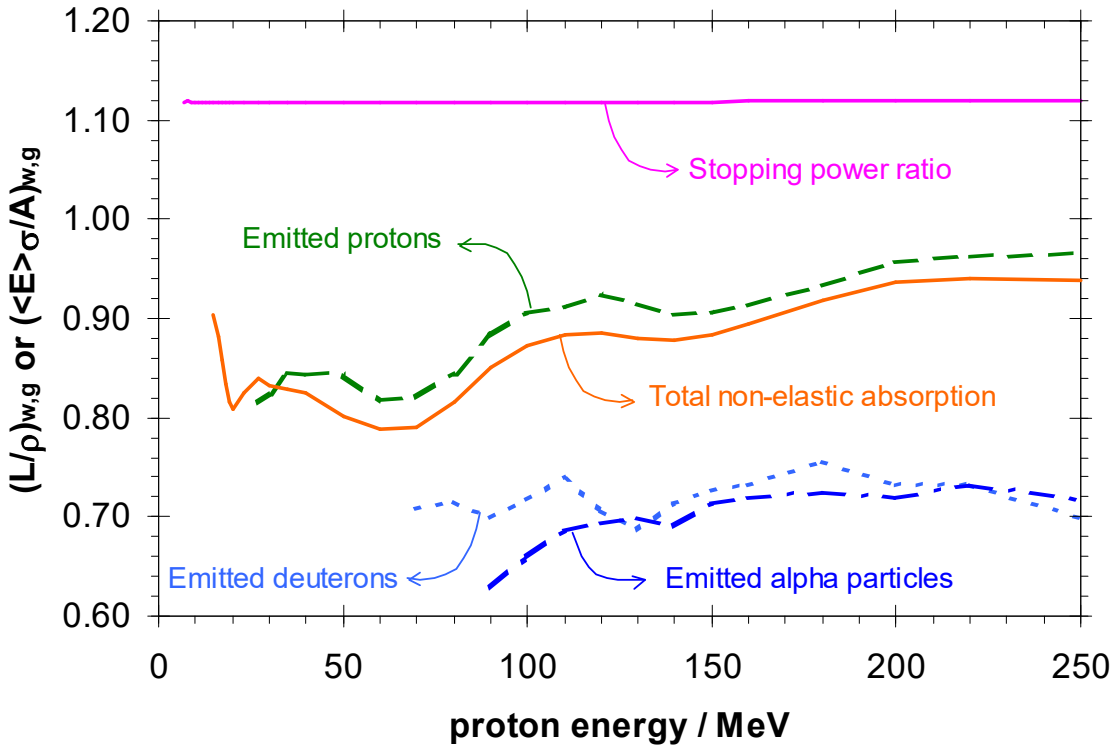
Idem, mainly dosimetric inserts

Conversion of signal to dose

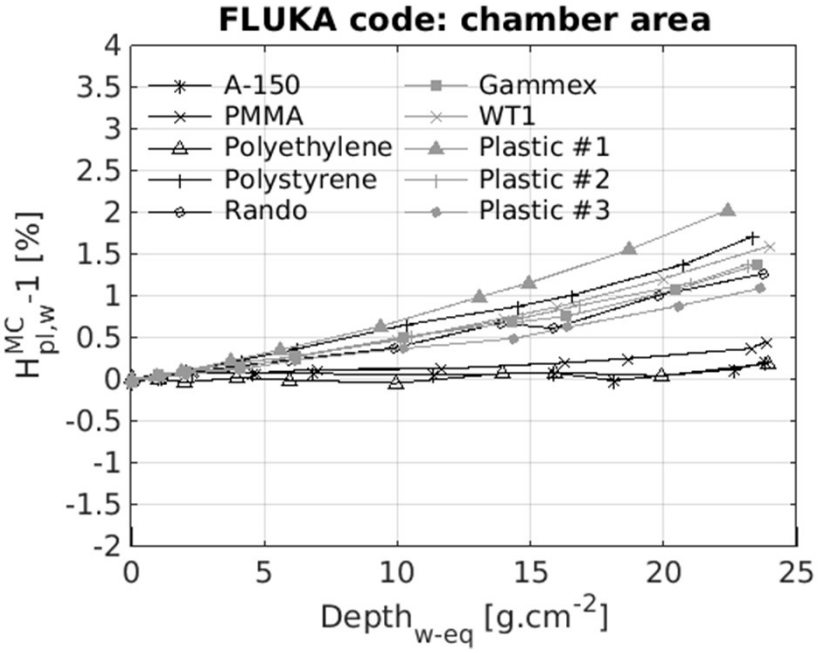
Dose to detector / dose in phantom material

Water or tissue equivalence phantom materials

$$D_w(z_w) = D_{ph}(z_{ph}) \cdot \left(\frac{S}{\rho}\right)_{ph}^{w} k_{fl}$$

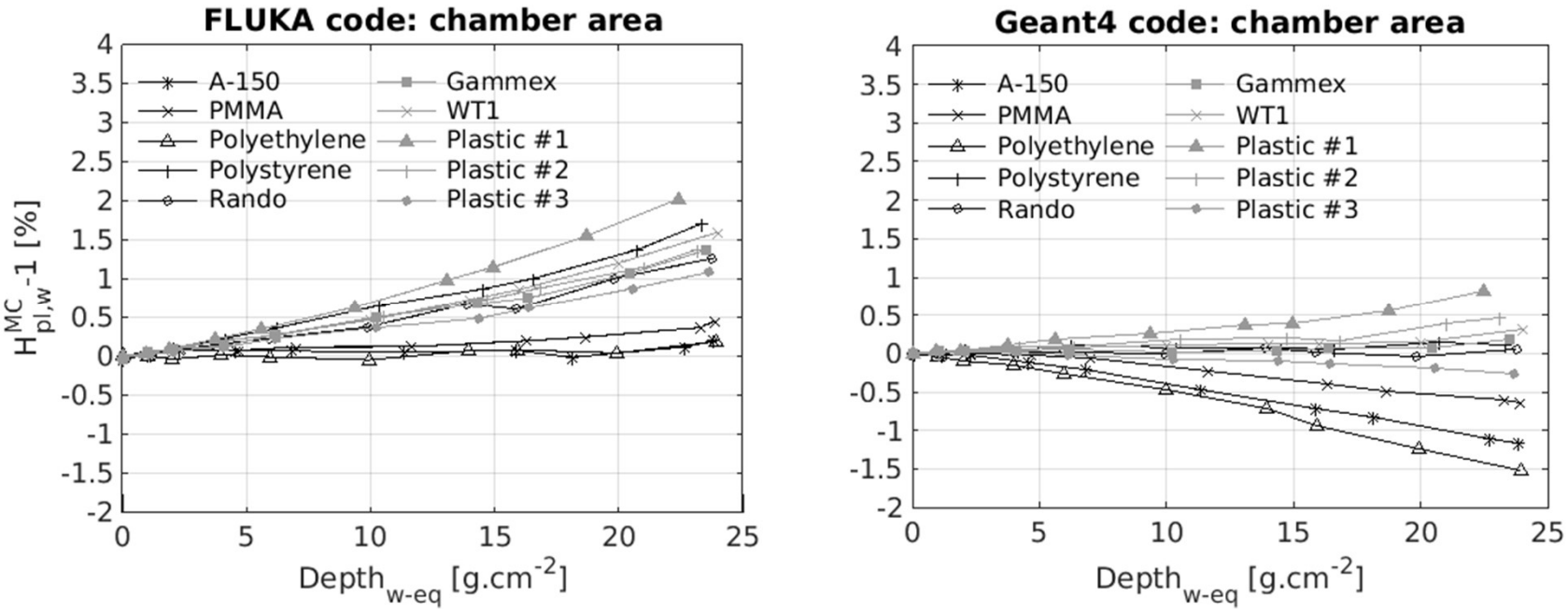


k_{fl} for low-Z phantom materials



Lourenço et al 2017 Phys Med Biol 62:3883

k_{fl} for low-Z phantom materials



Lourenço et al 2017 Phys Med Biol 62:3883

Reference dosimetry with ionization chambers

$$D_{w,Q} = M_Q N_{D,w,Q}$$

But if we have N_{D,w,Q_0} with $Q_0 \neq Q \rightarrow$

$$D_{w,Q} = M_Q N_{D,w,Q_0} k_{Q,Q_0} \qquad k_{Q,Q_0} = \frac{(W_{air})_Q (s_{w,air})_Q p_Q}{(W_{air})_{Q_0} (s_{w,air})_{Q_0} p_{Q_0}}$$

This is formalism of IAEA TRS-398

Ionometry – unresolved and new issues

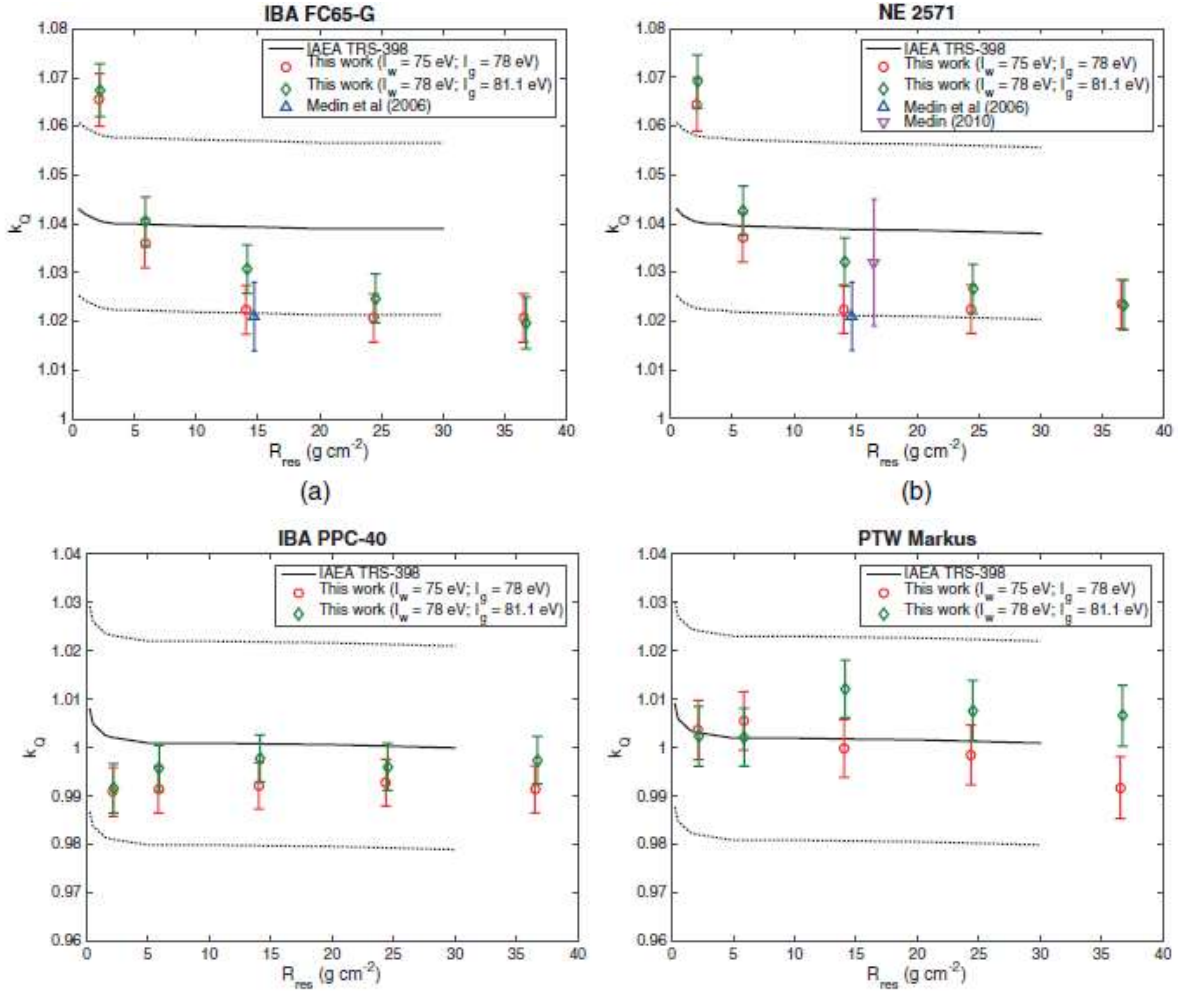
Cavity theory challenged

Ion recombination

Complex sequences

DAP

k_{Q,Q_0} for proton and ion beams



Goma et al. 2016
Phys Med Biol 61:2389

Cavity theory for ionization chambers

Fano 1954 Radiat Res 1:237-240

Note on the Bragg-Gray Cavity Principle for Measuring Energy Dissipation

U. FANO

National Bureau of Standards, Washington, D. C.

implied but perhaps never stated in full.

Theorem: In a medium of given composition exposed to a uniform flux of primary radiation (such as X-rays or neutrons) the flux of secondary radiation is also uniform and *independent of the density* of the medium as well as of the density variations from point to point.

This theorem finds obvious application to measurements by means of thimble

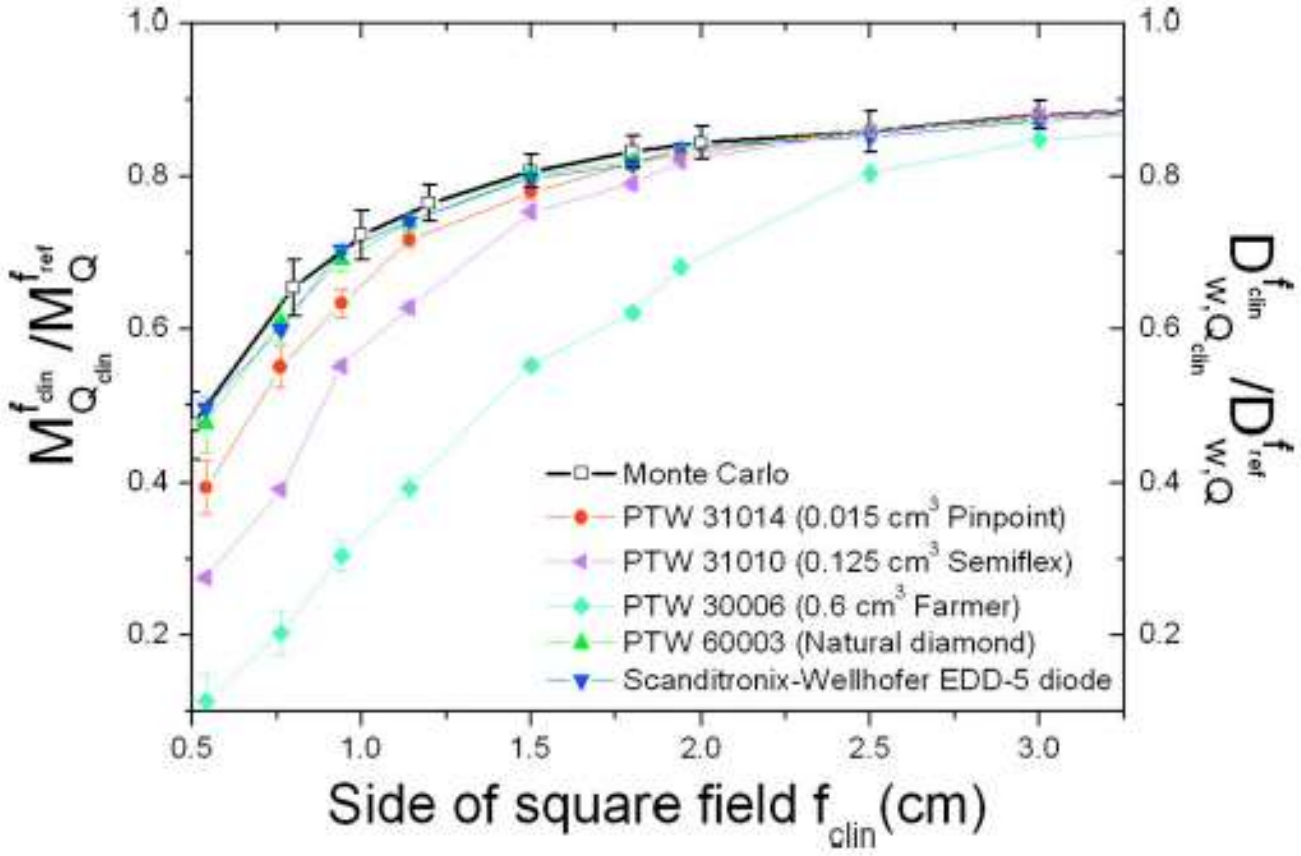
Fano conditions

Violations problematic in

- Small field dosimetry
- Presence of magnetic fields

Deviations not altered in homogeneous dose region
(Bouchard et al 2012 Med Phys 39:1473)

Small field dosimetry



Doblado et al. 2007 Phys Med 23:58-66

Small field dosimetry

Alfonso et al 2008 Med Phys 35:5179

tween the detector response in the fields f_{clin} and f_{msr} according to:

$$\Omega_{Q_{clin},Q_{msr}}^{f_{clin},f_{msr}} = \frac{M_{Q_{clin}}^{f_{clin}}}{M_{Q_{msr}}^{f_{msr}}} \cdot \left[\frac{D_{w,Q_{clin}}^{f_{clin}} / M_{Q_{clin}}^{f_{clin}}}{D_{w,Q_{msr}}^{f_{msr}} / M_{Q_{msr}}^{f_{msr}}} \right], \quad (4a)$$

or

$$\Omega_{Q_{clin},Q_{msr}}^{f_{clin},f_{msr}} = \frac{M_{Q_{clin}}^{f_{clin}}}{M_{Q_{msr}}^{f_{msr}}} \cdot k_{Q_{clin},Q_{msr}}^{f_{clin},f_{msr}}, \quad (4b)$$

showing that if the correction factor $k^{f_{clin},f_{msr}}$ is close to

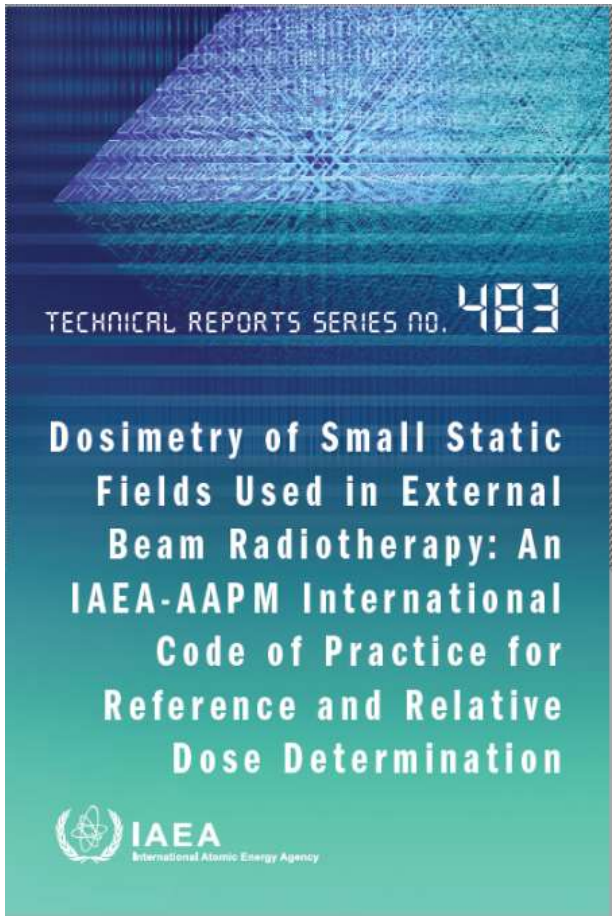
Small field dosimetry

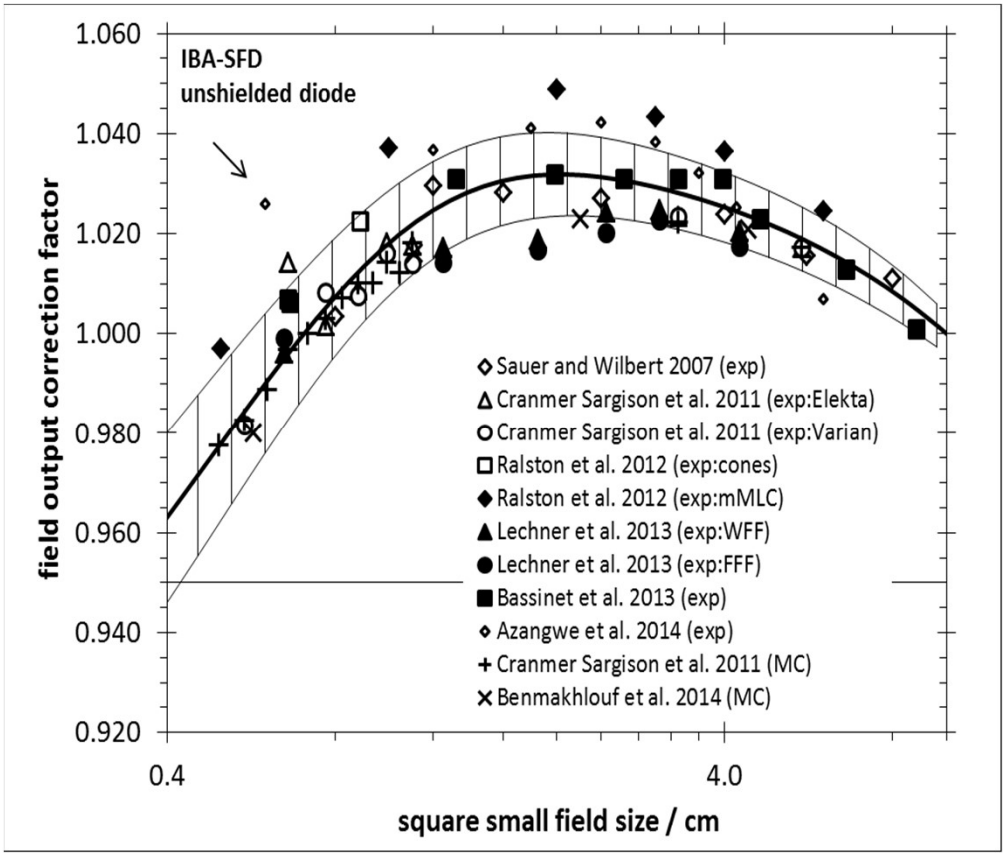
Tanny et al 2015 Med Phys 42:5370

TABLE IV. Measured $k_{Q_{clin},Q_{msr}}^{f_{clin},f_{msr}}$ for vertically mounted microionization chambers.

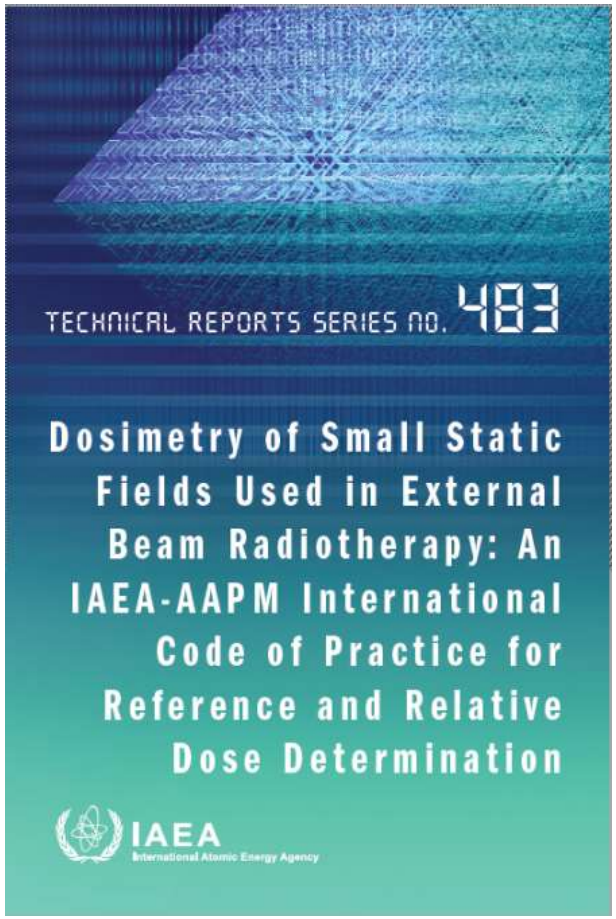
Exradin A16				Exradin A26			
F.S	6 MV	6 FFF	10 FFF	F.S	6 MV	6 FFF	10 FFF
0.6	1.077	1.083	1.058	0.6	1.120	1.126	1.092
0.8	1.034	1.042	1.027	0.8	1.045	1.054	1.041
1	1.016	1.027	1.013	1	1.020	1.027	1.020
1.2	1.013	1.020	1.009	1.2	1.014	1.016	1.011
1.4	1.013	1.018	1.006	1.4	1.012	1.013	1.007
2	1.008	1.014	1.002	2	1.006	1.008	1.001
PTW 31014				Exradin A14SL			
0.6	1.102	1.103	1.080	0.6	1.177	1.178	1.192
0.8	1.054	1.070	1.046	0.8	1.066	1.068	1.075
1	1.029	1.045	1.028	1	1.022	1.032	1.030
1.2	1.023	1.034	1.020	1.2	1.017	1.021	1.016

IAEA TRS-483


TECHNICAL REPORTS SERIES NO. 483
Dosimetry of Small Static Fields Used in External Beam Radiotherapy: An IAEA-AAPM International Code of Practice for Reference and Relative Dose Determination
IAEA
International Atomic Energy Agency


IBA-SFD
unshielded diode
field output correction factor
square small field size / cm
1.060
1.040
1.020
1.000
0.980
0.960
0.940
0.920
0.4
4.0
Sauer and Wilbert 2007 (exp)
Cranmer Sargison et al. 2011 (exp:Elekta)
Cranmer Sargison et al. 2011 (exp:Varian)
Ralston et al. 2012 (exp:cones)
Ralston et al. 2012 (exp:mMLC)
Lechner et al. 2013 (exp:WFF)
Lechner et al. 2013 (exp:FFF)
Bassinet et al. 2013 (exp)
Azangwe et al. 2014 (exp)
Cranmer Sargison et al. 2011 (MC)
Benmakhlouf et al. 2014 (MC)

IAEA TRS-483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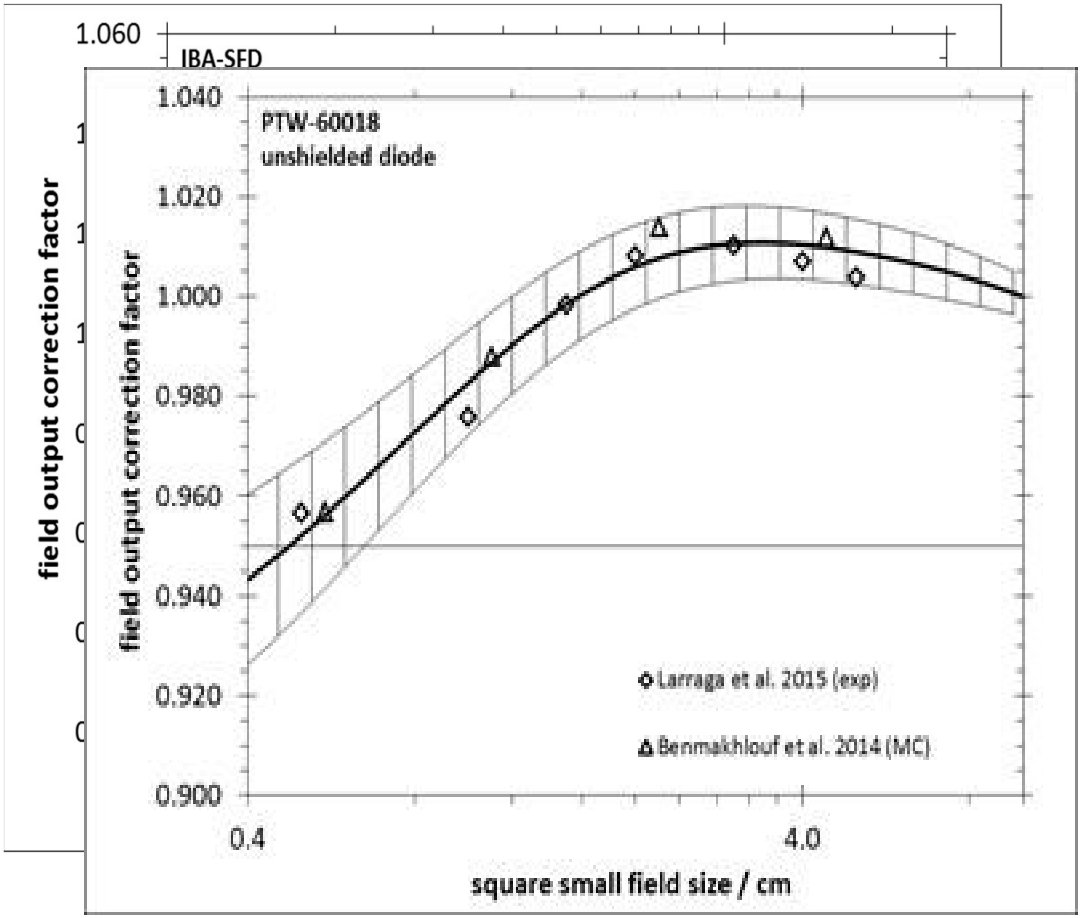
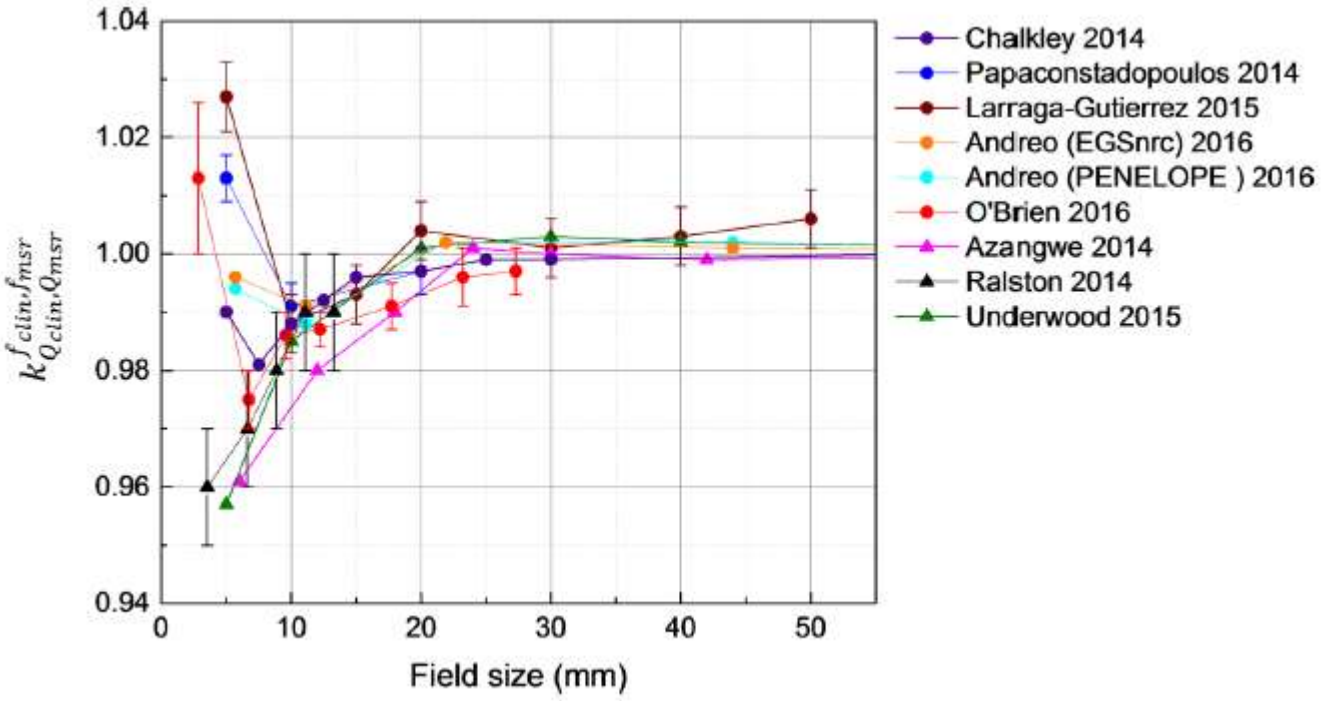

IBA-SFD
PTW-60018
unshielded diode
field output correction factor
field output correction factor
1.060
1.040
1.020
1.000
0.980
0.960
0.940
0.920
0.900
0.4
4.0
square small field size / cm
Larraga et al. 2015 (exp)
Benmakhlouf et al. 2014 (MC)

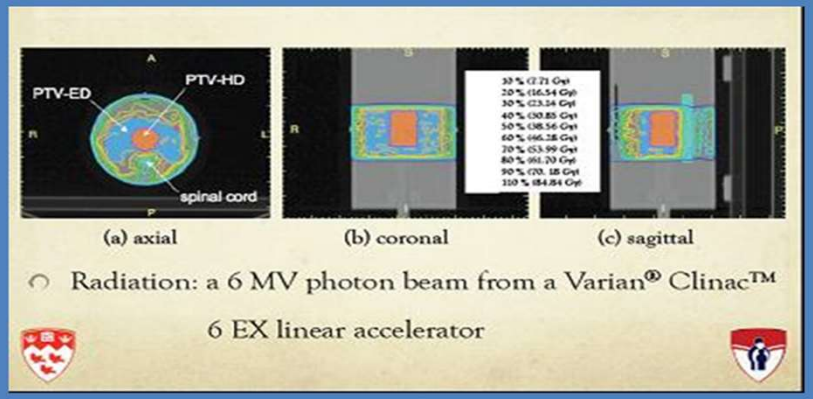
PTW-60019 microDiamond for small fields



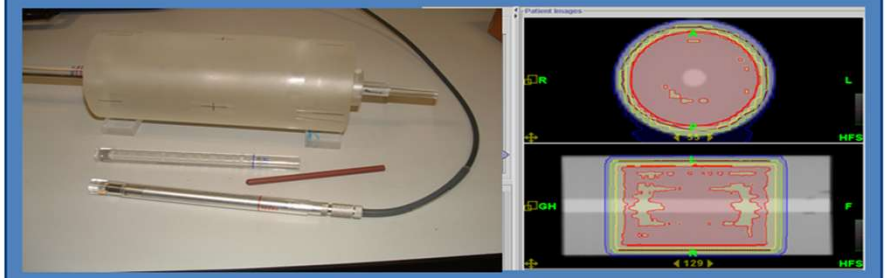
De Coste et al 2017 Phys Med Biol 62:7036

Plan class specific reference fields

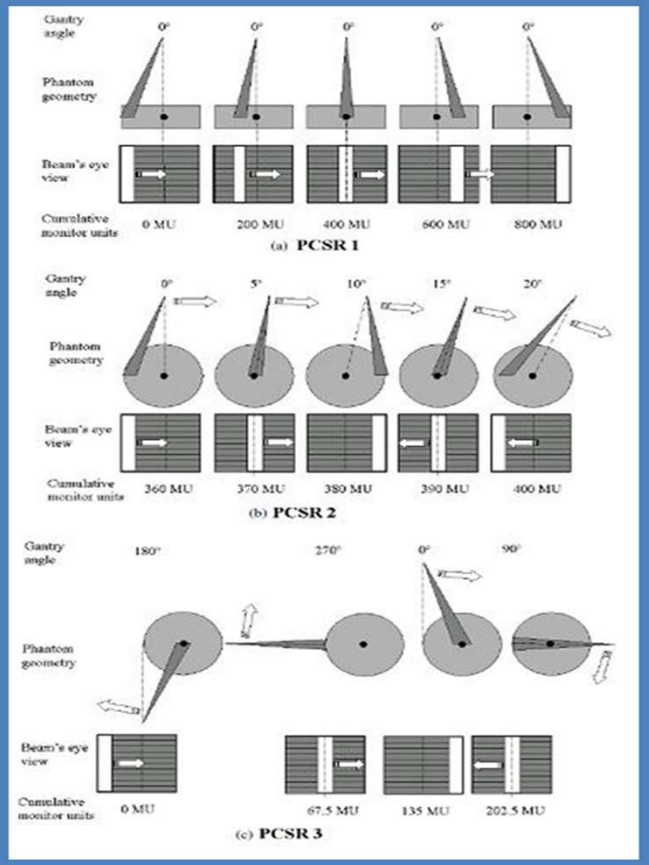
Dynamic IMRT H&N – Chung et al. 2010 Med. Phys. 37:2404-13



TomoTherapy – Bailat et al. 2009 Med. Phys. 36:3891-3896



VMAT – Rosser and Bedford 2009 Phys. Med. Biol. 54:7045-7061



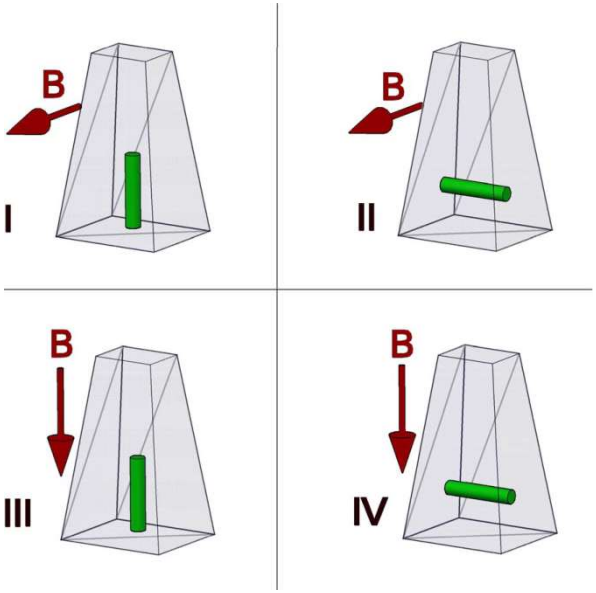
MRI-RT

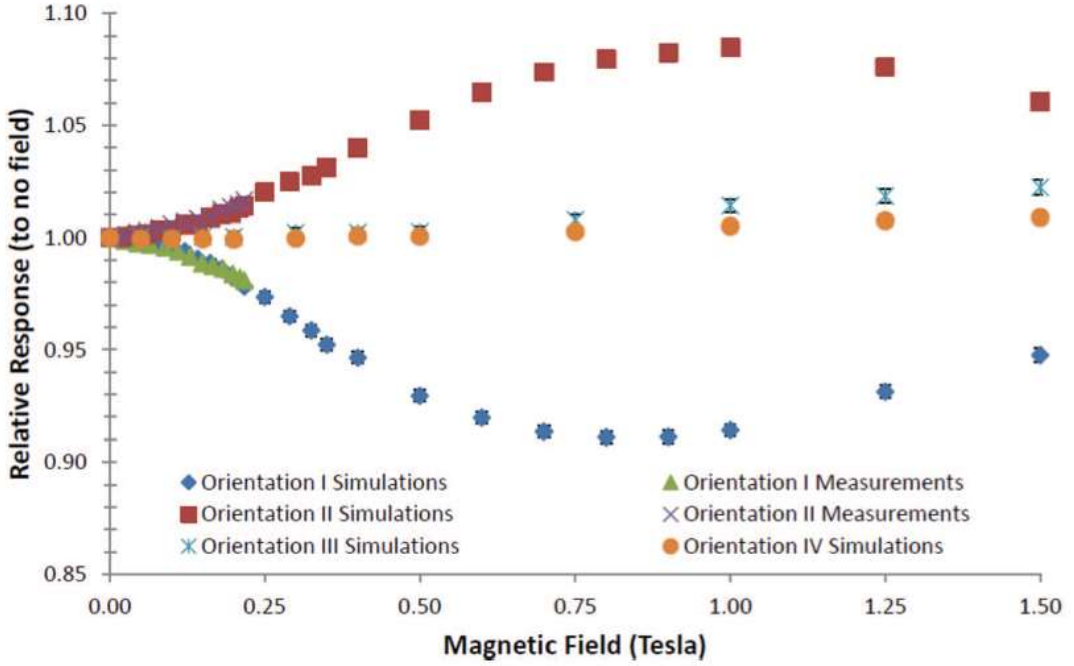
Distortion of dose distributions: small for photons, large for protons

Influence on detectors

Fundamental dosimetry and transport theories

MRI-RT: IC perturbations





Reynolds et al. 2013 Med Phys 40:042102

New Fano conditions in magnetic fields

Bouchard et al. 2015 Phys Med Biol 60:6639

4.2. Condition I: isotropic and spatially uniform sources

Theorem. *In a medium with spatially uniform atomic properties subject to a magnetic field, the particle fluences resulting from spatially uniform and isotropic primary sources are also spatially uniform and isotropic, independently of the mass density and magnetic field distributions.*

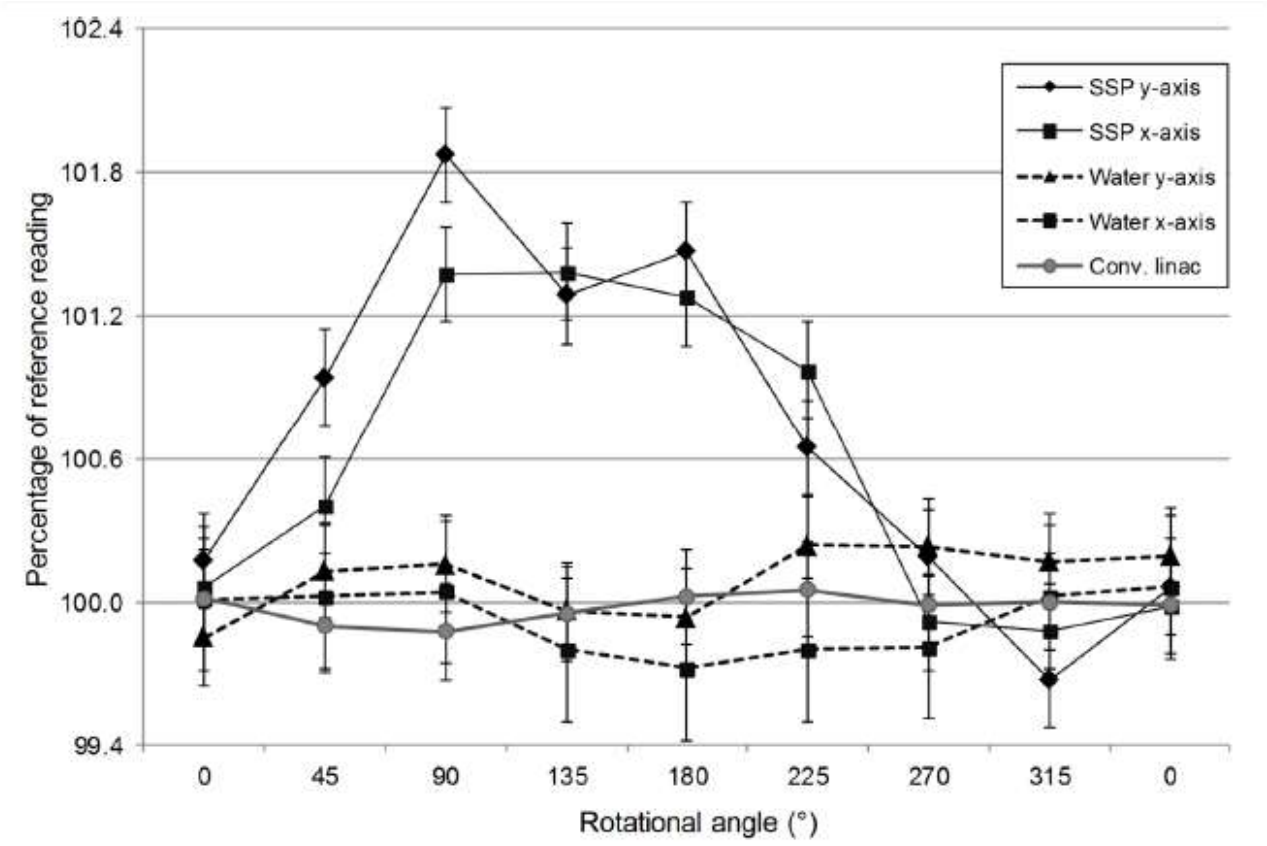
Proof. Consider a geometry with spatially uniform atomic properties such that for all interaction

4.3. Condition II: spatially uniform sources and density-scaled magnetic field

Theorem. *In a medium with spatially uniform atomic properties subject to an external magnetic field of fixed direction and with strength proportional to the mass density, the particle fluences resulting from spatially uniform primary sources are also spatially uniform, independently of the mass density distribution.*

Proof. Let us define the geometry with spatially uniform atomic properties such that for all

MRI-RT: influence of air gap in sleeve



Hackett et al. 2016 Med Phys 43:3961

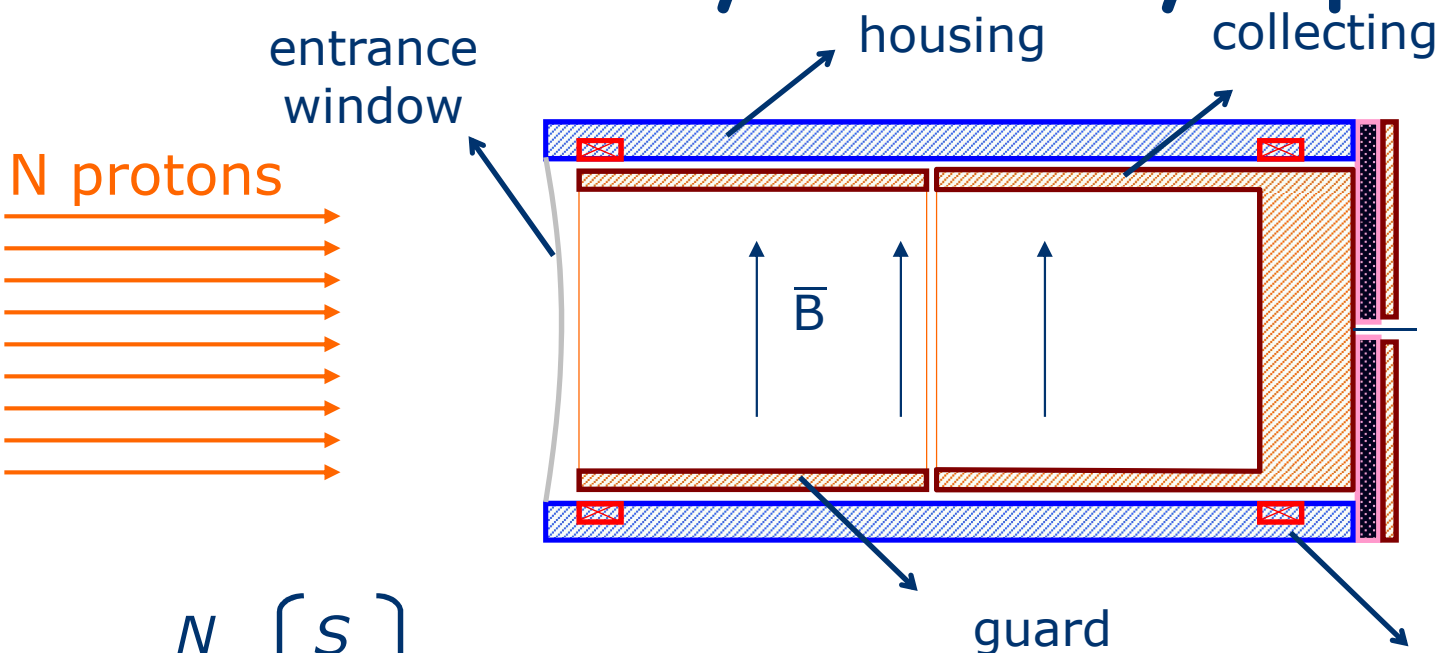
Beam monitor calibration of scanned light-ion beams

Faraday cup?

Dose-area-product with large-area plane-parallel chamber

Dose-area-product with Farmer chamber

Absolute dosimetry – Faraday cup



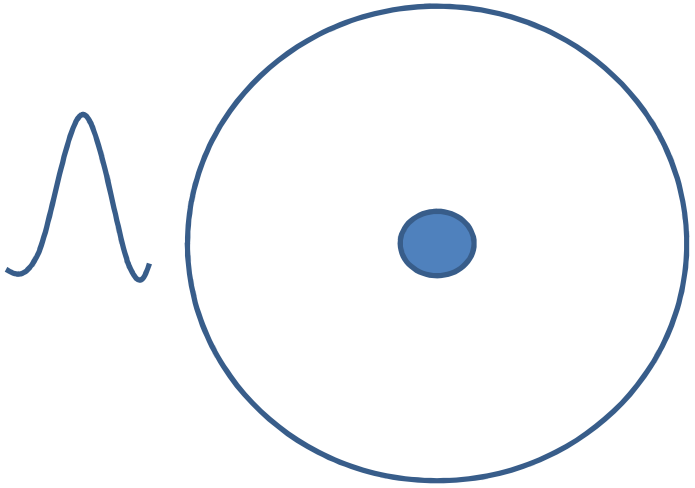
$$D_{med} = \frac{N}{A} \cdot \left[\frac{S}{\rho}\right]_{med}$$

$$DAP_{med} = N \cdot \left[\frac{S}{\rho}\right]_{med}$$

(e.g. Pedroni et al 2005, Phys Med Biol 50:541-61, Grusell et al 1995, Phys Med Biol 40:1831-40)

Reference dosimetry scanned beams

Gillin et al 2010
Med Phys 37:154

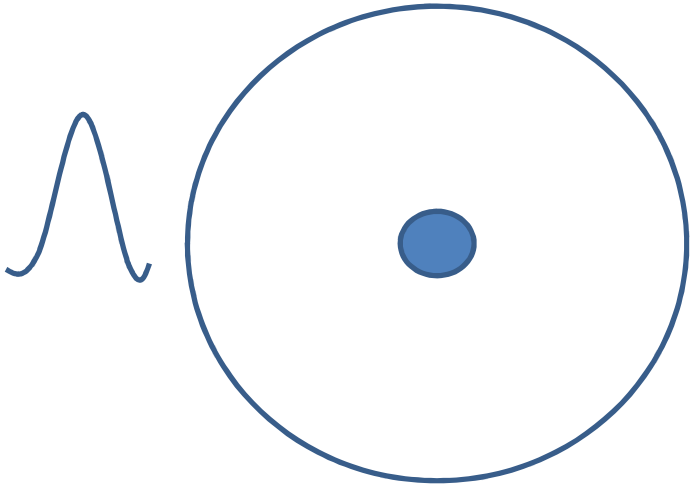


$$DAP_{w,Q}^{BP} = M_Q^{BP} N_{DAP,w,Q_0}^{BP} \kappa_{Q,Q_0}^{BP}$$

$$N = \frac{DAP_{w,Q}^{\infty}}{(S/\rho)_w} = \frac{DAP_{w,Q}^{BP}}{(S/\rho)_w} \times CF$$

Reference dosimetry scanned beams

Gillin et al 2010
Med Phys 37:154



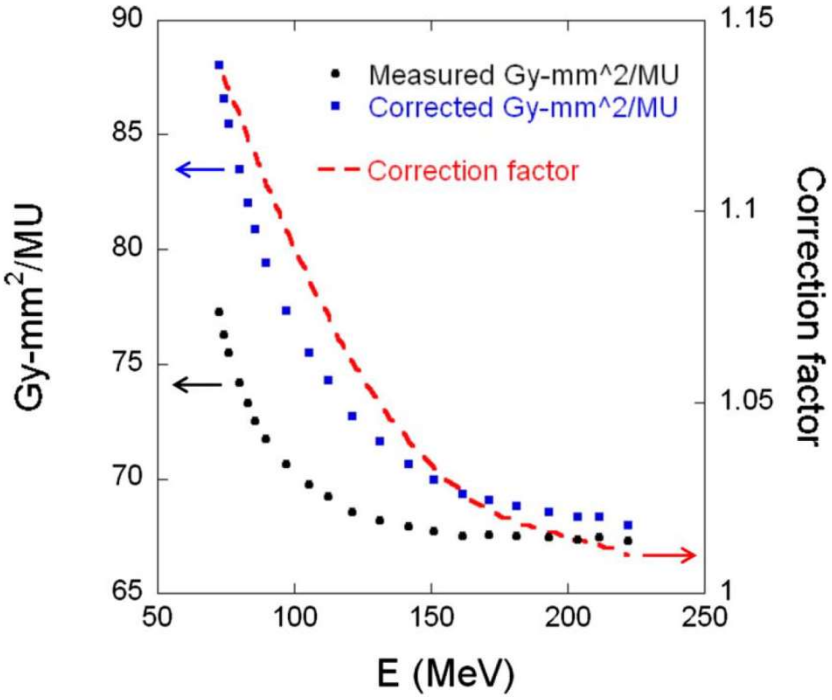


FIG. 5. Integral doses in Gy mm^2/MU at the depth of 2 cm as a function of energy. Circles are measured integral doses; squares are corrected integral doses; and dashed line is the correction factors.

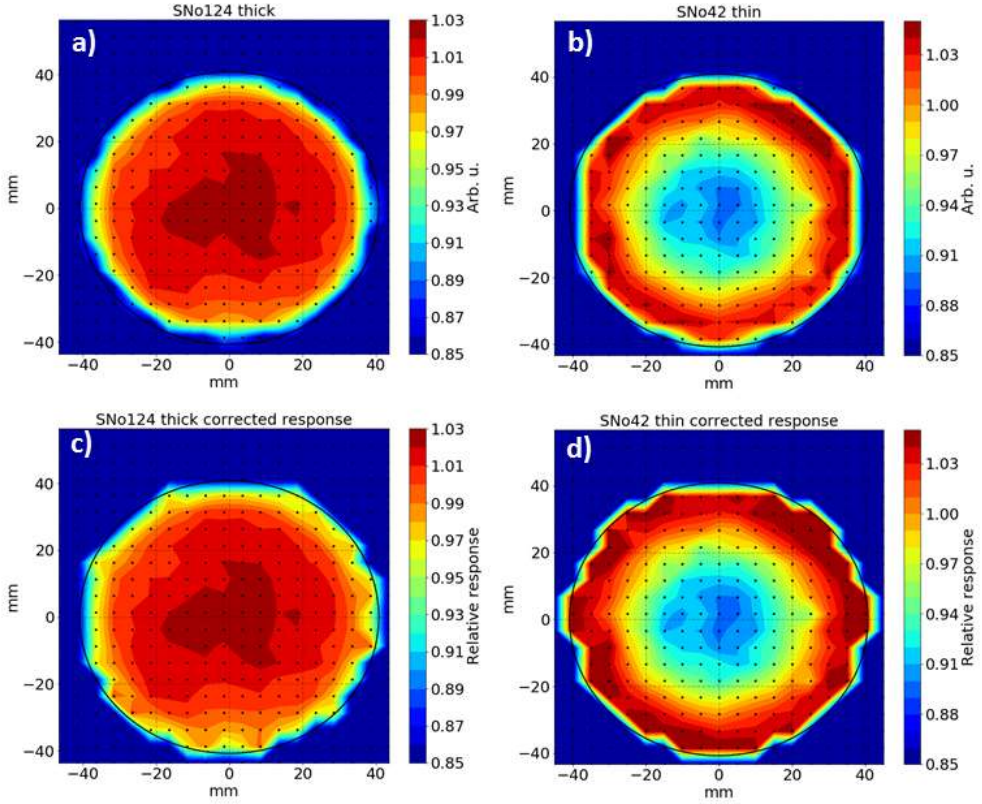
Calculation κ_{Q,Q_0}

$$\kappa_{Q,Q_0} = \frac{(W_{air})_Q (s_{w,air})_Q p_Q}{(W_{air})_{Q_0} (s_{w,air})_{Q_0} p_{Q_0}}$$

Main problem is p_{Q_0}

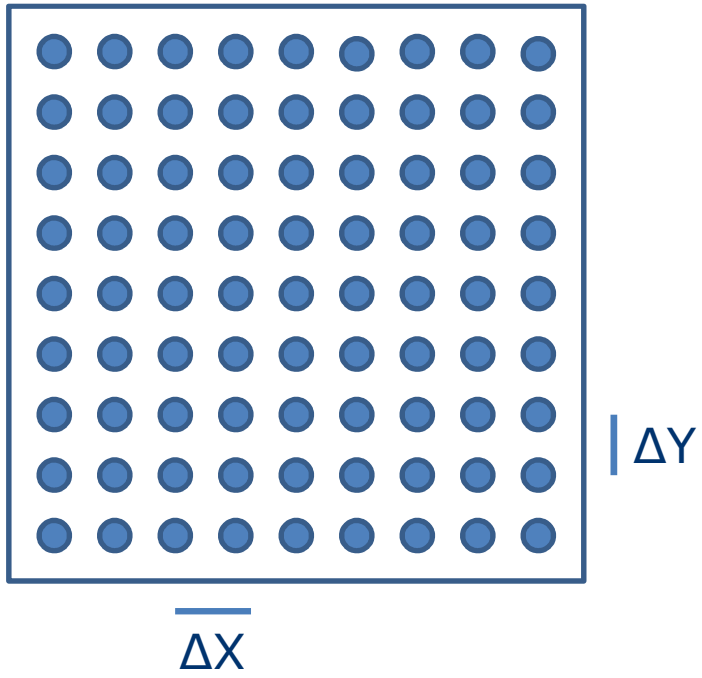
Same assumptions for photon and electrons as pp chambers ?

Large area chambers - uniformity



Reference dosimetry scanned beams

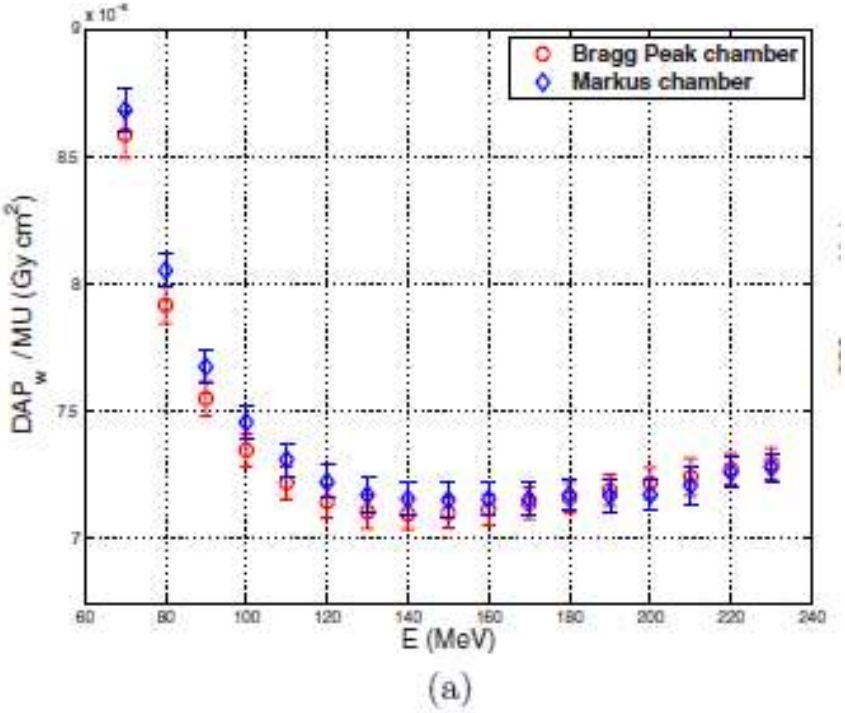
Jaekel et al Phys Med Biol 2004



$$D_{w,Q}^{cyl} = M_Q^{cyl} N_{D,w,Q_0}^{cyl} k_{Q,Q_0}^{cyl}$$

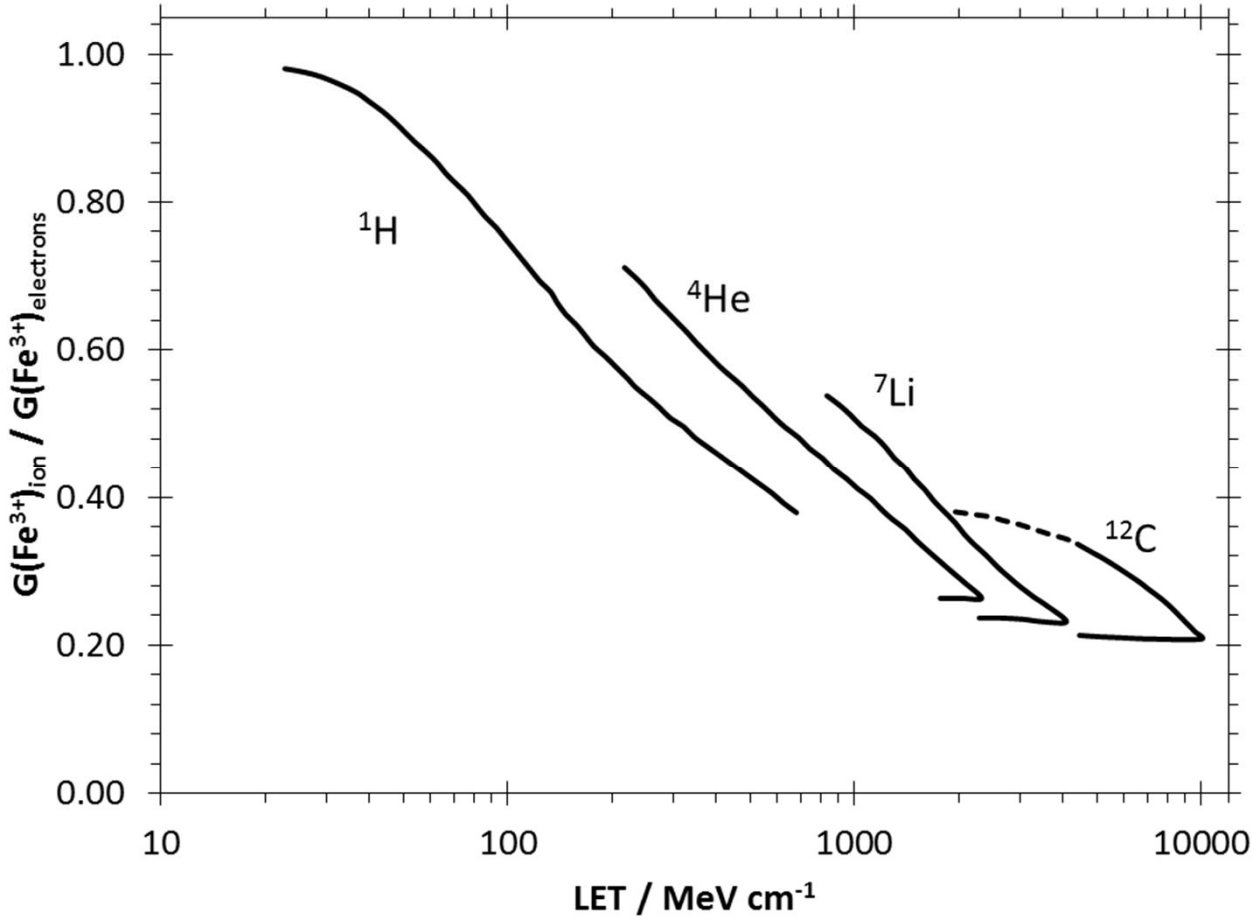
$$N = \frac{D_{w,Q}^{cyl} \Delta X \Delta Y}{(S/\rho)_w}$$

Reference dosimetry scanned beams

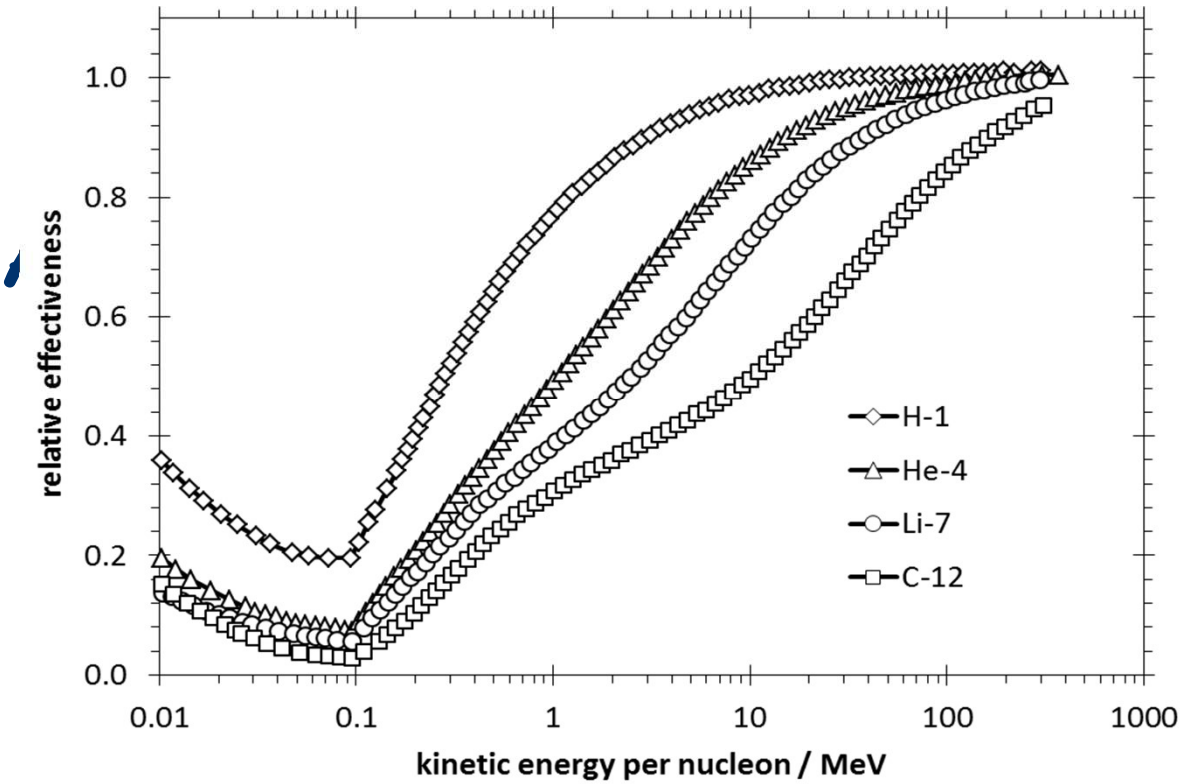


Goma et al. 2017 Phys Med Biol 62:4991

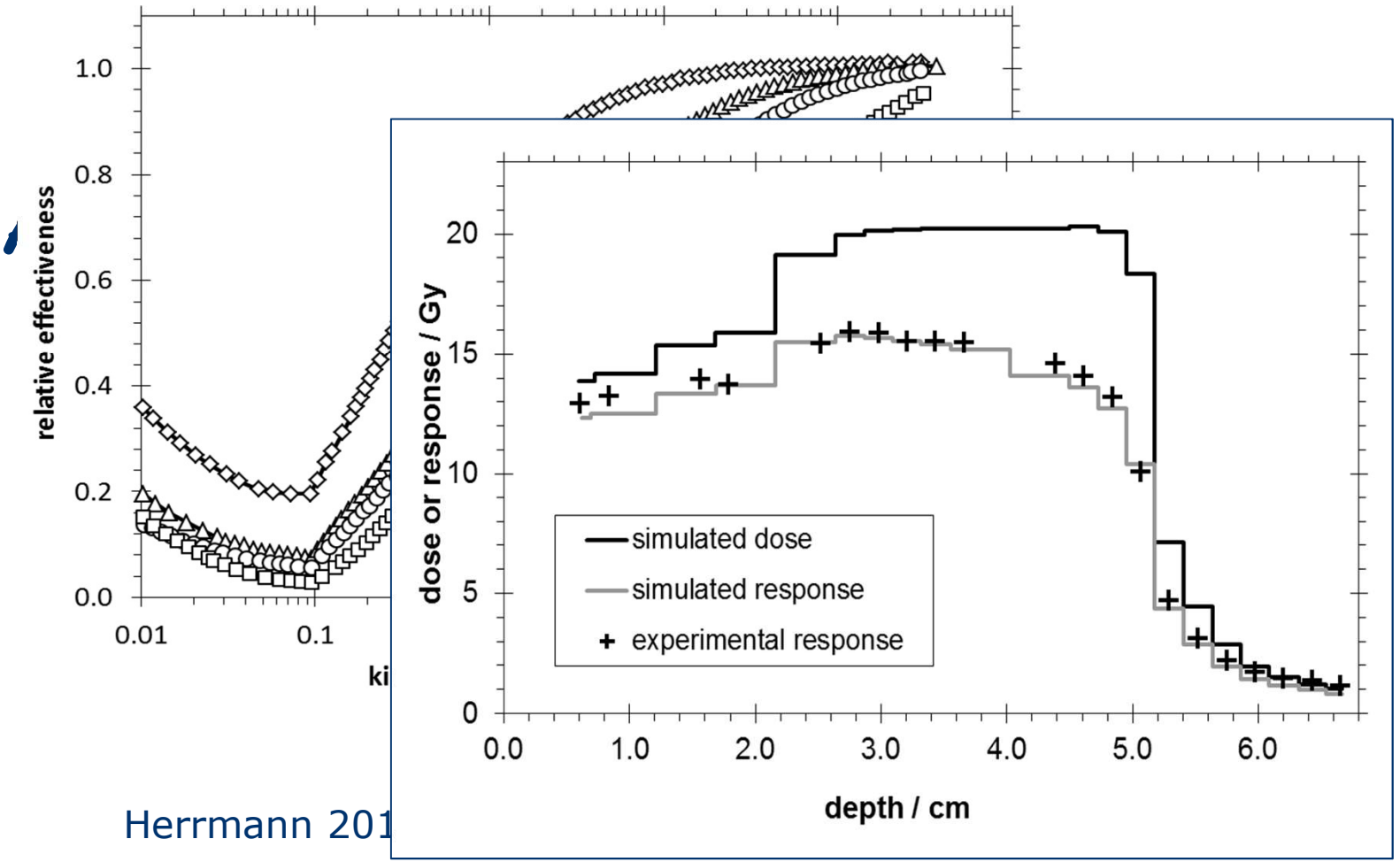
Chemical yields of the Fricke dosimeter



LaVerne and Schuler1987 J. Phys. Chem. 91:5770

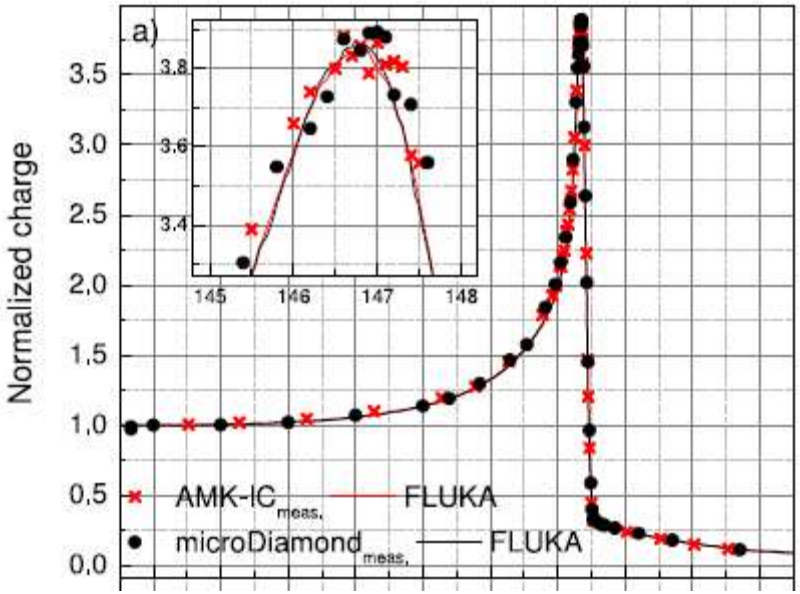


Herrmann 2012, PhD thesis Aarhus

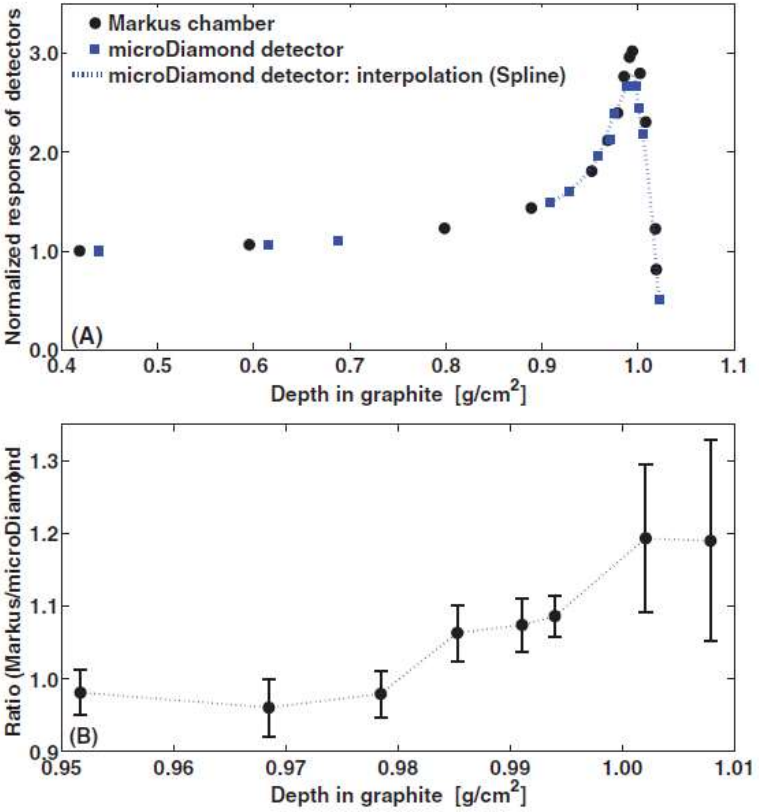


Herrmann 201

microDiamond ideal detector?

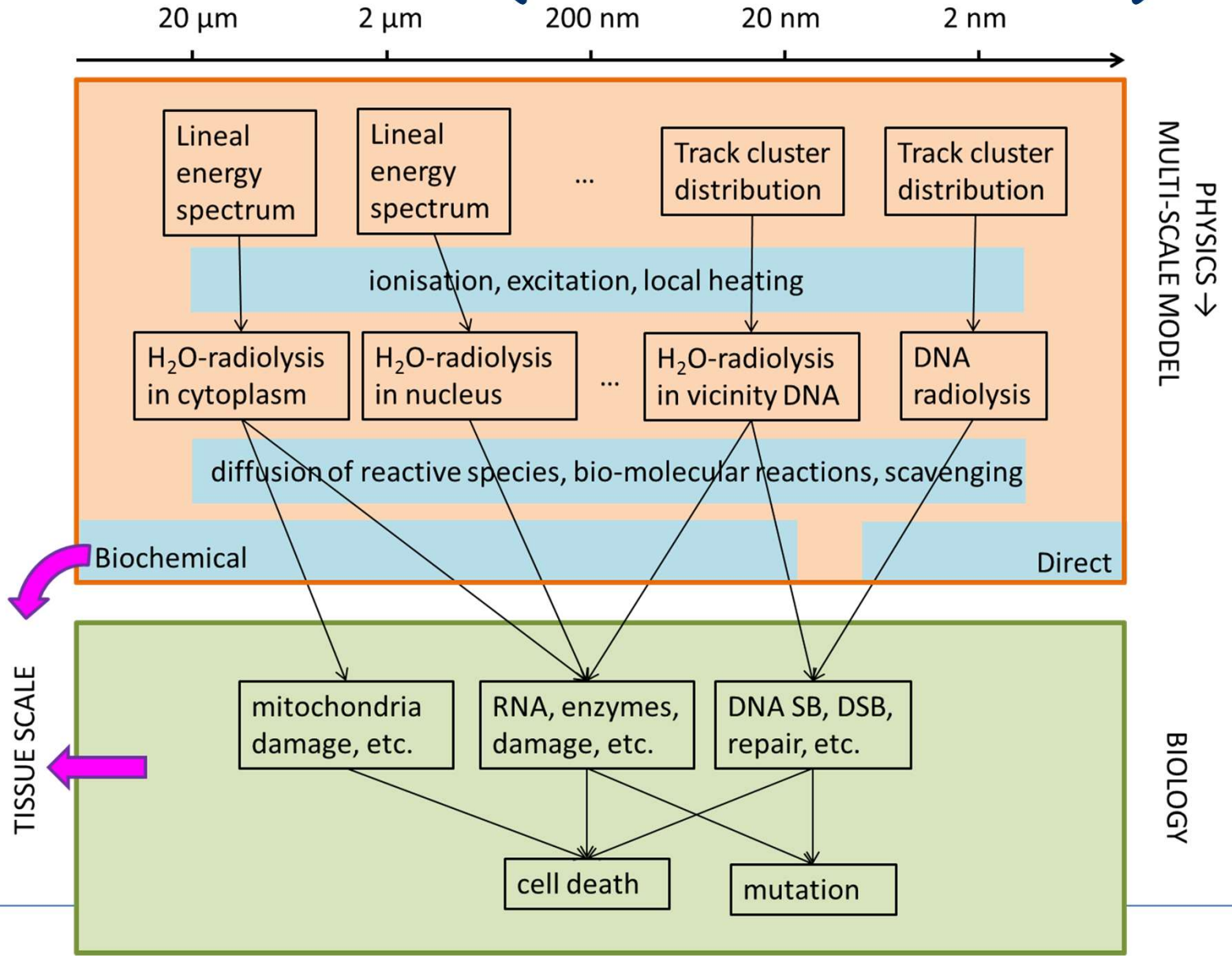


Marinelli et al 2015
Med Phys 42:2085

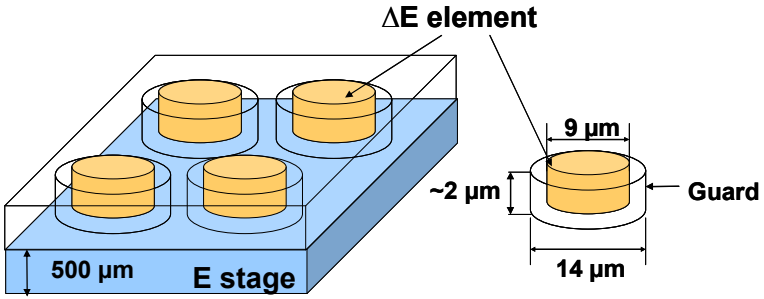


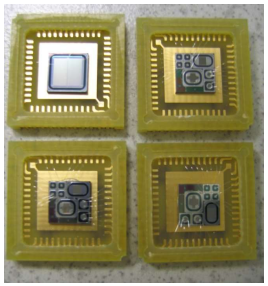
Rossomme et al 2016
Phys Med Biol 61:4551

Biologically relevant physical dosimetry - Multiscale model (BJR 88:20140392)

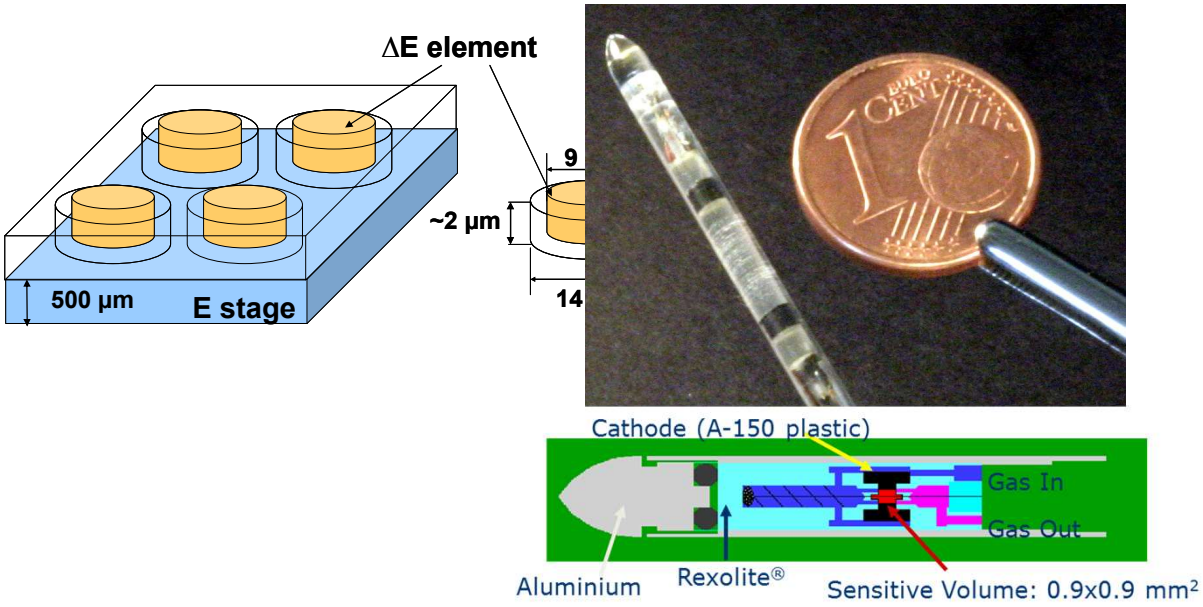


Biologically relevant physical dosimetry - Multiscale model (BJR 88:20140392)

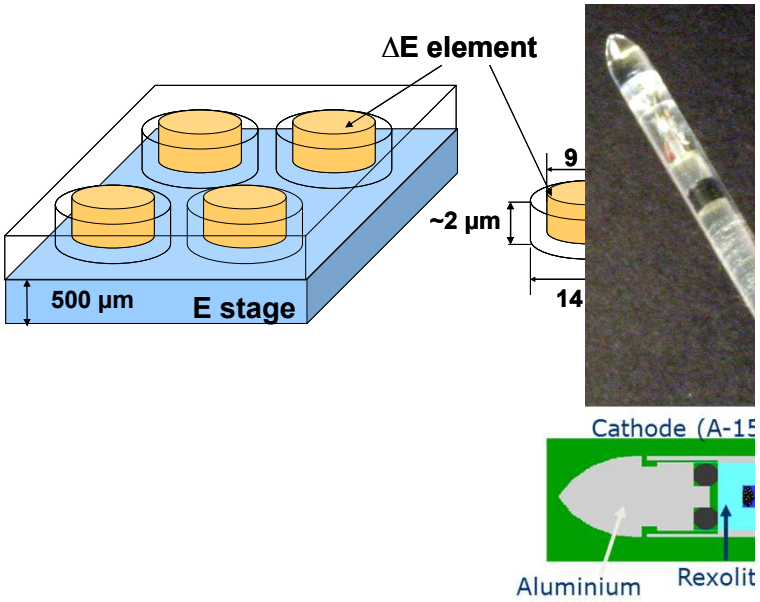


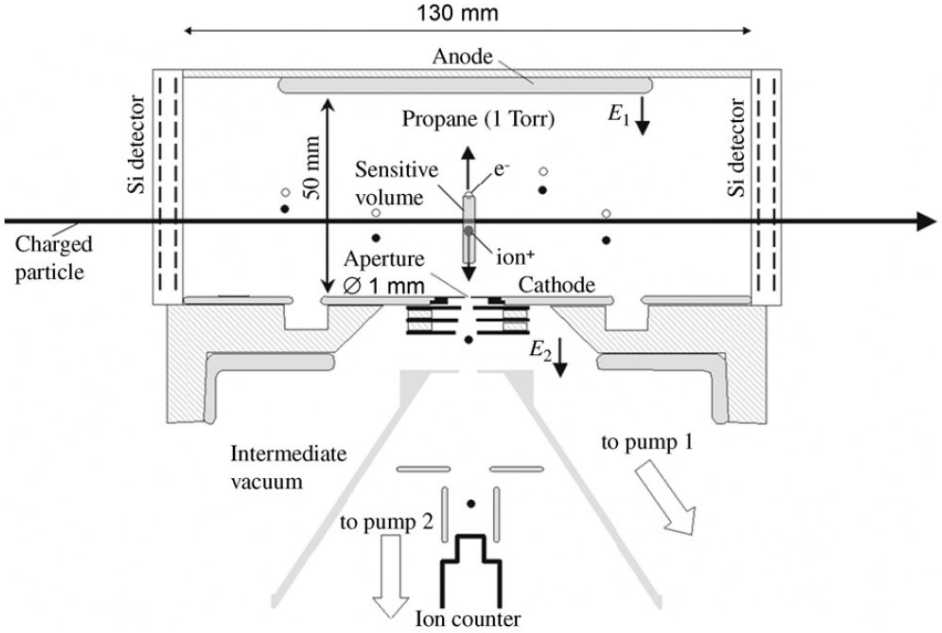


Biologically relevant physical dosimetry - Multiscale model (BJR 88:20140392)

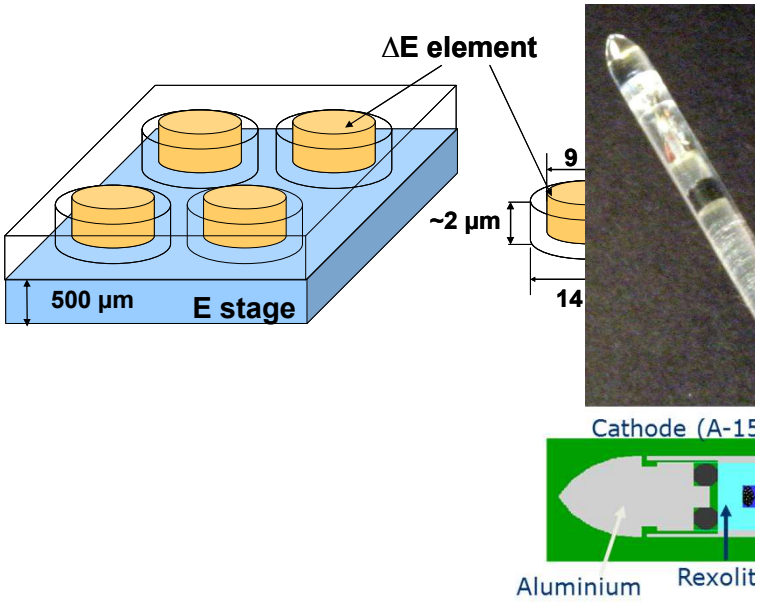


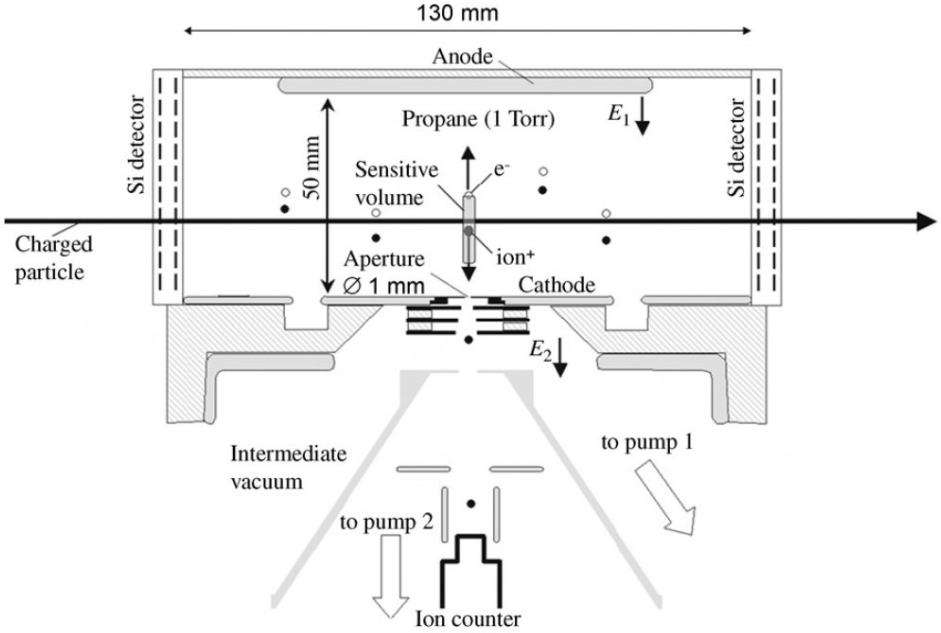
Biologically relevant physical dosimetry - Multiscale model (BJR 88:20140392)





Biologically relevant physical dosimetry - Multiscale model (BJR 88:20140392)





$$P(\Theta_{rd}|Q;D) = \iiint \sum_{\nu} P(\Theta_{rd}|\nu;\ell_N)P(\nu;\ell_N|y;\ell_M;Q;D)P(y;\ell_M|Q)\,d\ell_N d\ell_M dy$$

$$+ \iiint \iint \sum_{\nu,\mu} P\left(\Theta_{rd}\middle|\nu;\ell_N^{(1)};\mu;\ell_N^{(2)};s_{12}\right) P\left(\nu;\ell_N^{(1)};\mu;\ell_N^{(2)};s_{12}\middle|y;\ell_M;Q;D\right) P(y;\ell_M|Q)\,d\ell_N^{(1)} d\ell_N^{(2)} ds_{12} d\ell_M d$$

$$+ \cdots$$

NPL

MedAustron

BioQuaRT

EMRP

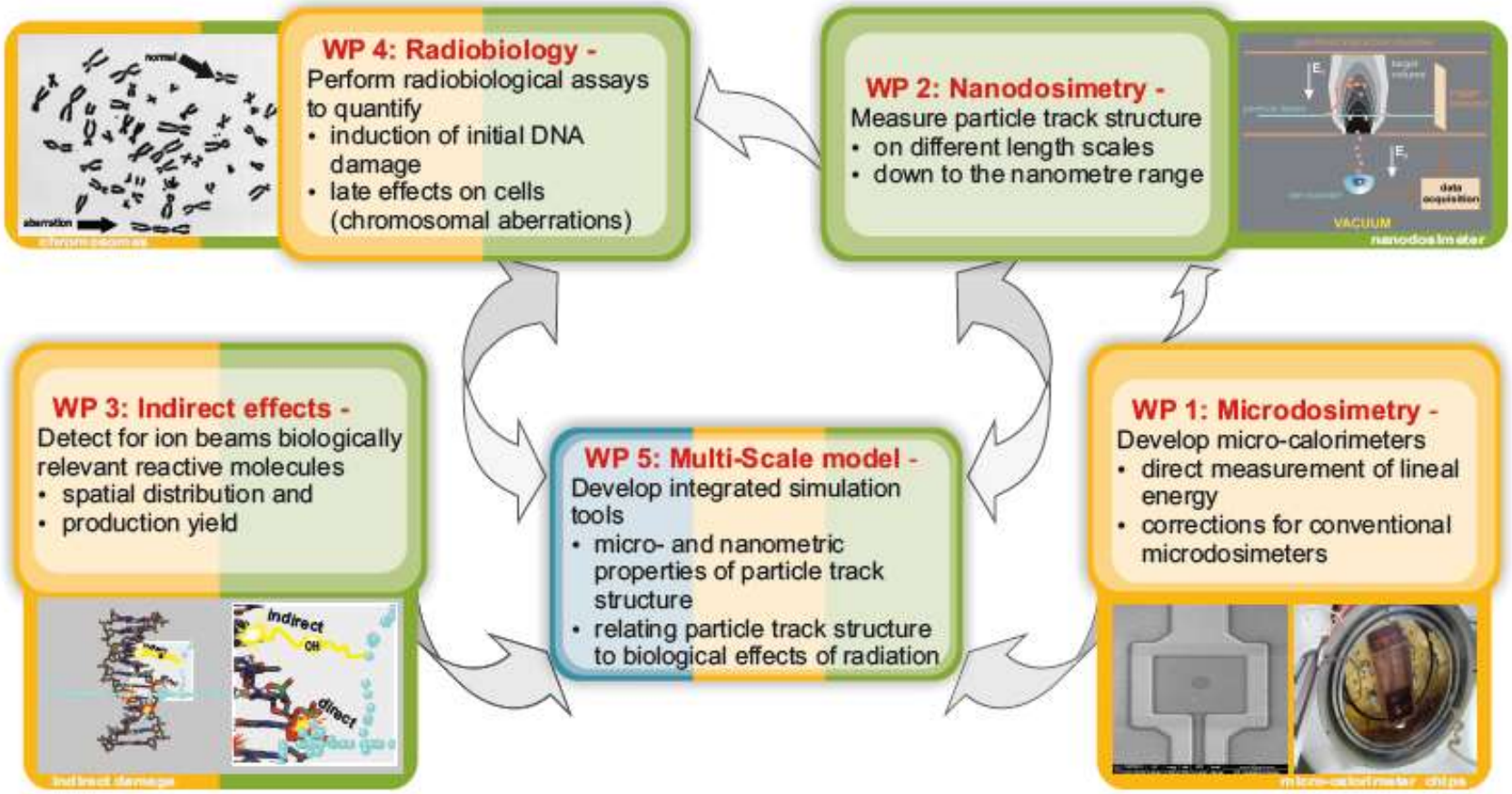
European Metrology Research Programme

Programme of EURAMET

The EMRP is jointly funded by the EMRP participating countries within EURAMET and the European Union

EURAMET

European Association of National Metrology Institutes



Conclusion

Technological progress in RT has created many new challenges in dosimetry

No primary standards for proton and ion beams

Reference dosimetry needs improvement for proton and ion beams, integrated dosimetry

2D dosimetry for particles, 3D dosimetry for IMRT

Improved point detectors for scanning, OF measurements, penumbrae, energy independence for particles

Patient specific and in-vivo dosimetry

Micro/nano dosimetry

CT to range or SPR conversion

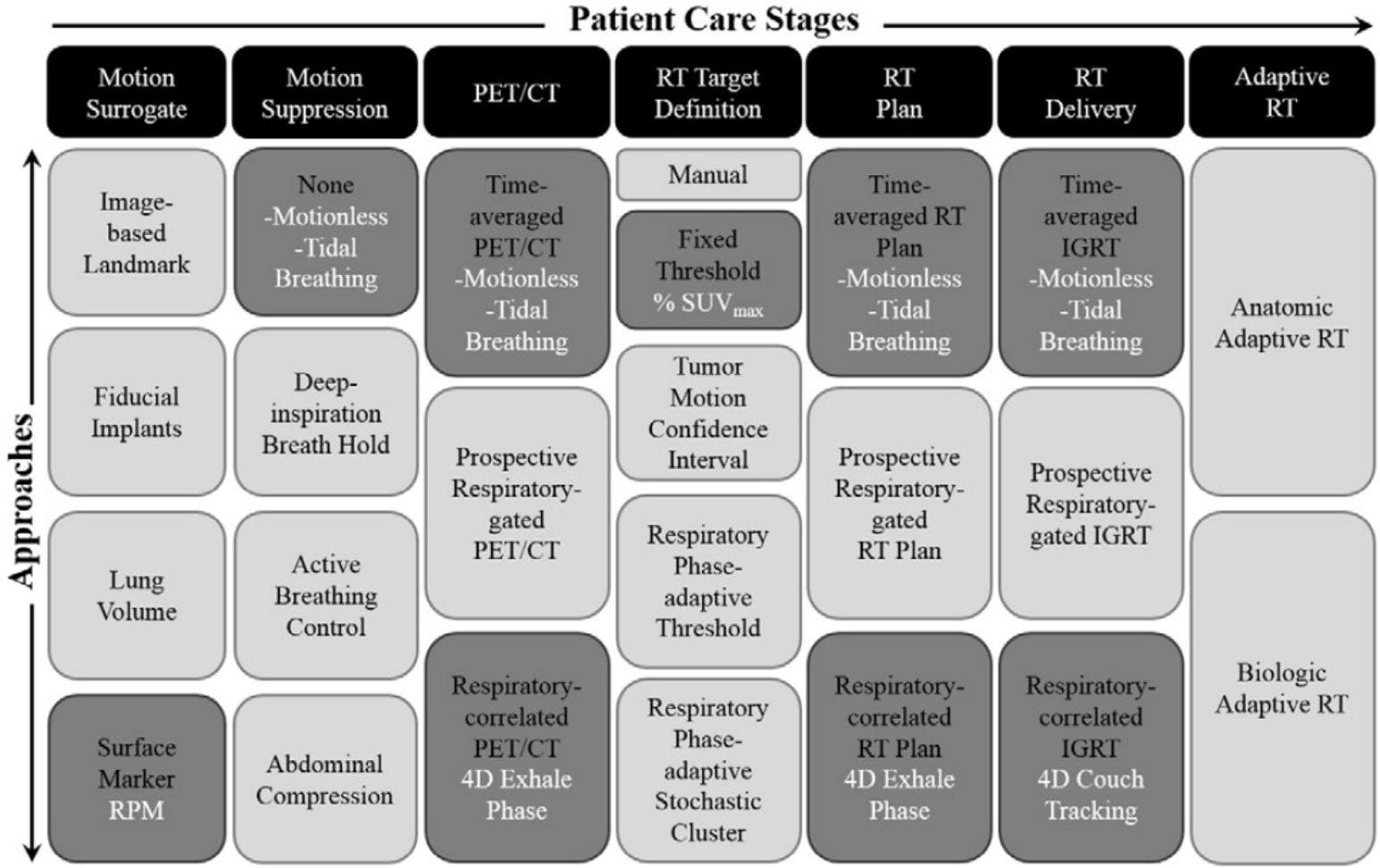
AARHUS UNIVERSITY

Trends and research opportunities in 4D radiotherapy

Stine Korreman
Aarhus University Hospital
Denmark

From so simple an idea …

”Point the beam where the target is”



Bowen et al, PMB 2015

Overview of the field

- Highly technology driven
- Highly driven by the medical physicists

- Addresses primarily medical physics issues (imaging protocols, GTV/PTV identification, beam control)

Impact

- Research and development has only increased since ~1995
- Practice changing impact has occurred with a high frequency over a short time span
- Large patient groups are now treated using motion management techniques in some form

Timeline of implementation

1984-6 First gating devices suggested

1996 Experimental gating device used for breast cancer gating

1999 Voluntary breath-hold for breast cancer used experimentally

2000 Varian RPM system released

2001 4DCT suggested

2003 Gating for breast as clinical routine

2004 Robotic tracking CyberKnife Synchrony

2005 4D CBCT

2006 Mid-ventilation phase approach suggested for lung

2009 Vero machine with tracking released

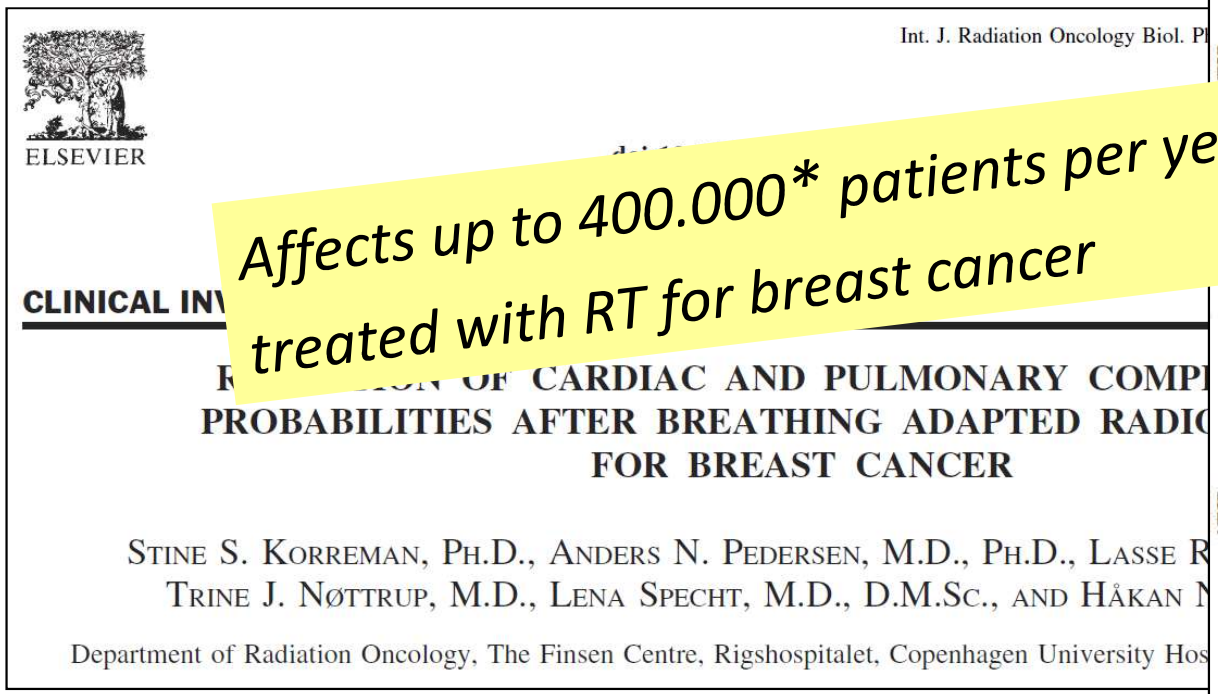
2014 First dynamic MLC tracking treatment

2014 MR guided 4D radiotherapy

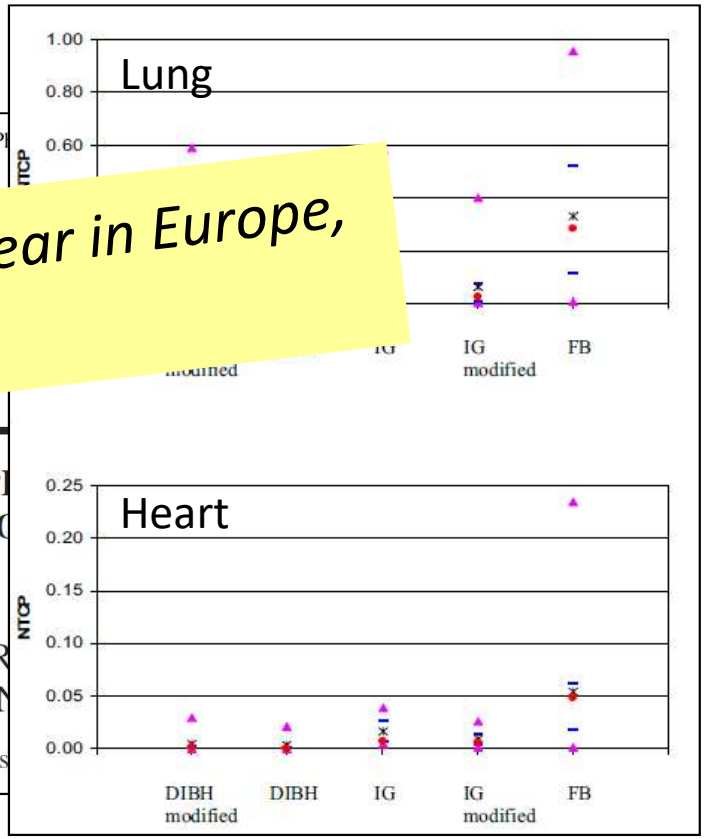
Successes of 4DRT

Treatment of breast cancer in inspiration phase of breathing.

- Clinical gain: Reduction of heart and lung toxicity.
- Dissemination: Widely implemented.



Affects up to 400.000 patients per year in Europe, treated with RT for breast cancer*



*Ideal number of evidence based RT from ESTRO-HERO

Successes of 4DRT

CT scanning for treatment planning using 4D techniques.

- Clinical gain: Better target identification, and reduced margins.
- Dissemination: Widely implemented.

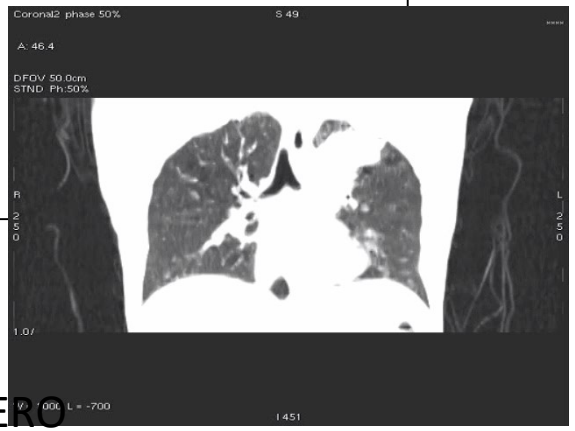
Physics in Medicine & Biology

Acquiri … tomography dataset using a… external respiratory signal

S S Vedam[1,2], P J Keall[2], V R Kini[2], H Mostafavi[3], H P Shukla[4] and R Mohan[5]

Published 16 December 2002 • Physics in Medicine & Biology, Volume 48, Number 1

Potentially affects up to 300.000 patients per year in Europe, treated with RT for lung cancer*



*Ideal number of evidence based RT from ESTRO-HERO

Successes of 4DRT

Daily setup to soft tissue for moving targets.

- Clinical gain: Smaller margins and more accurate treatment.
- Dissemination: Somewhat implemented.

Potentially affects up to 300.000 patients per year in Europe, treated with RT for lung cancer*

Medical Phys

The Internat

Radiation

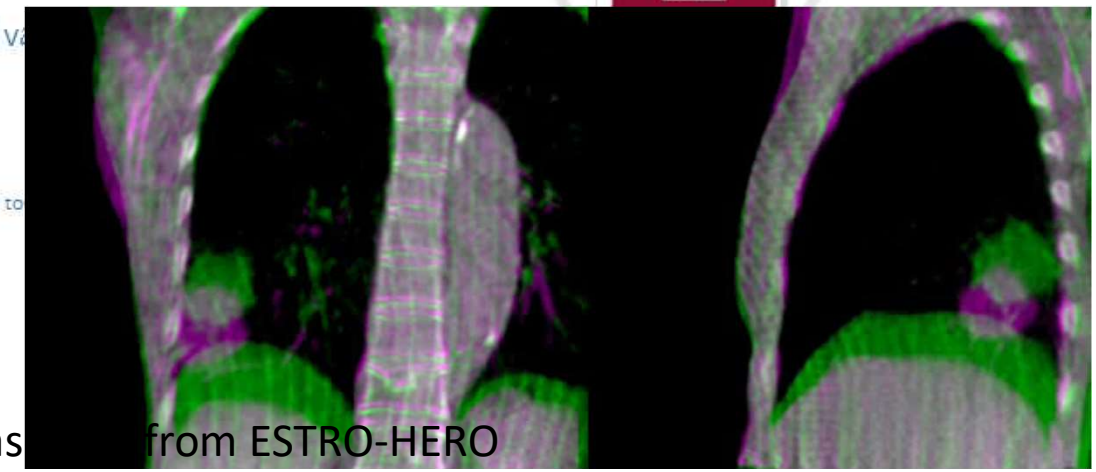
Respiratory correlated cone beam CT

Jan-Jakob Sonke, Lambert Zijp, Peter Remeijer, Marcel va

First published: 30 March 2005 Full publication history

DOI: 10.1118/1.1869074 View/save citation

Cited by (CrossRef): 326 articles Check for updates | Citation to



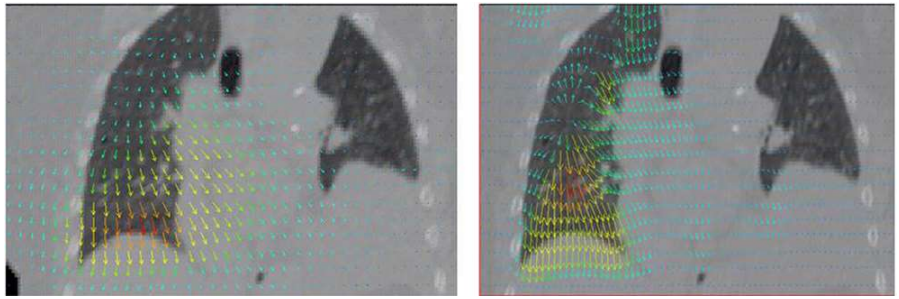
*Ideal number of evidence bas from ESTRO-HERO

Current clinical standard

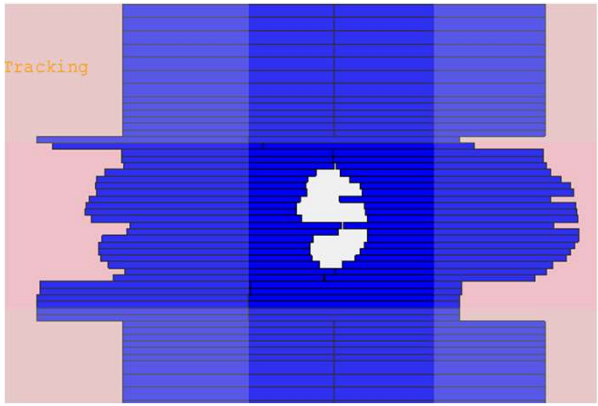
- 4DCT is standard in many modern clinics.
- Treatment planning is mostly performed to a single phase of a 4DCT.
- Delivery is almost entirely based on motion encompassing techniques – ITV or mid-ventilation approach – or on gating techniques.
- Breath-hold and/or gating techniques are mostly used for organ separation for sites including breast and mediastinal lymphoma.
- Image guidance is performed using either orthogonal x-rays or 3D cone-beam CT.

Front-line implementation

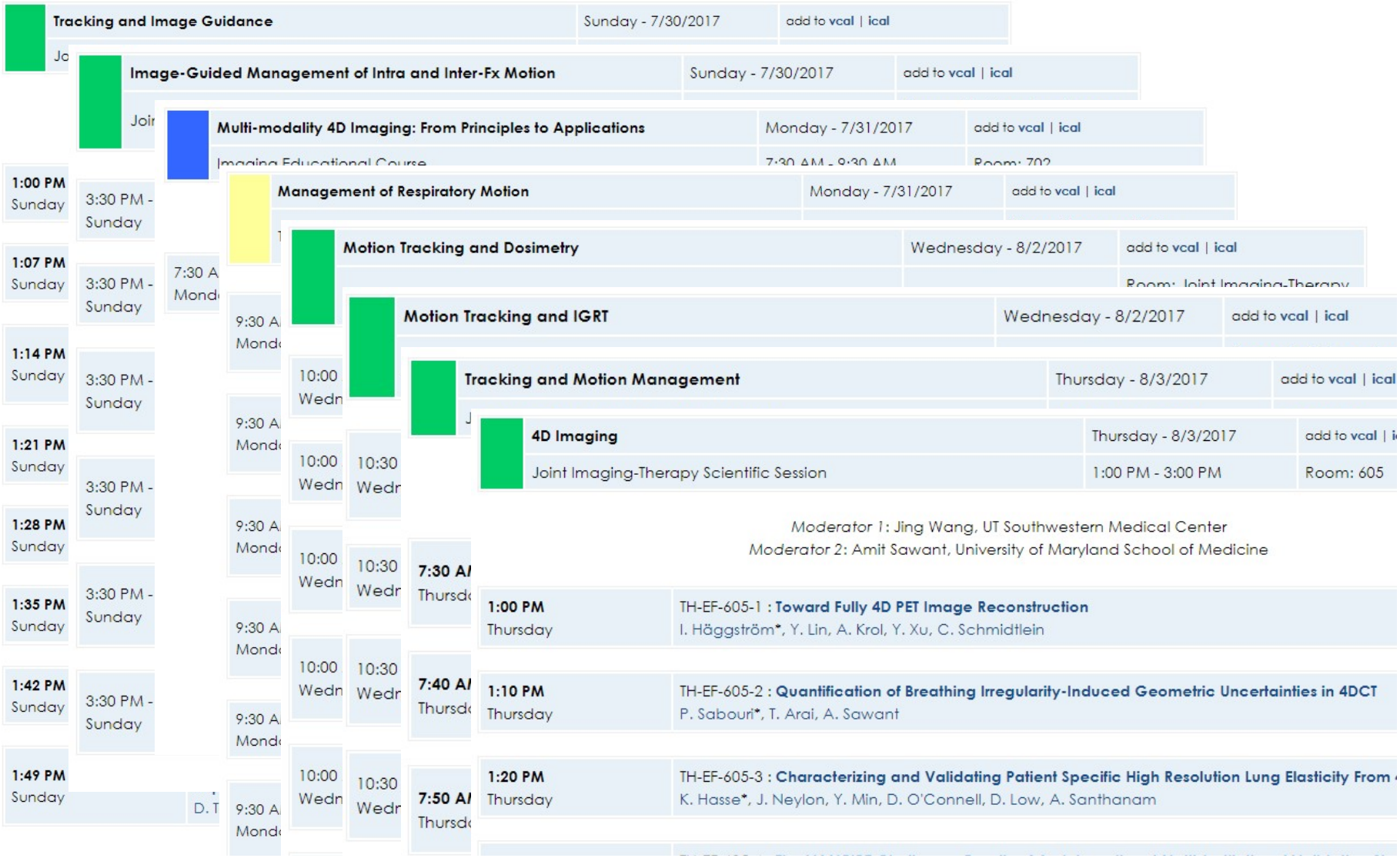
- Deformable registration of 4DCT and 4DCBCT scans.
- Planning and dose accumulation over all phases of 4D scan



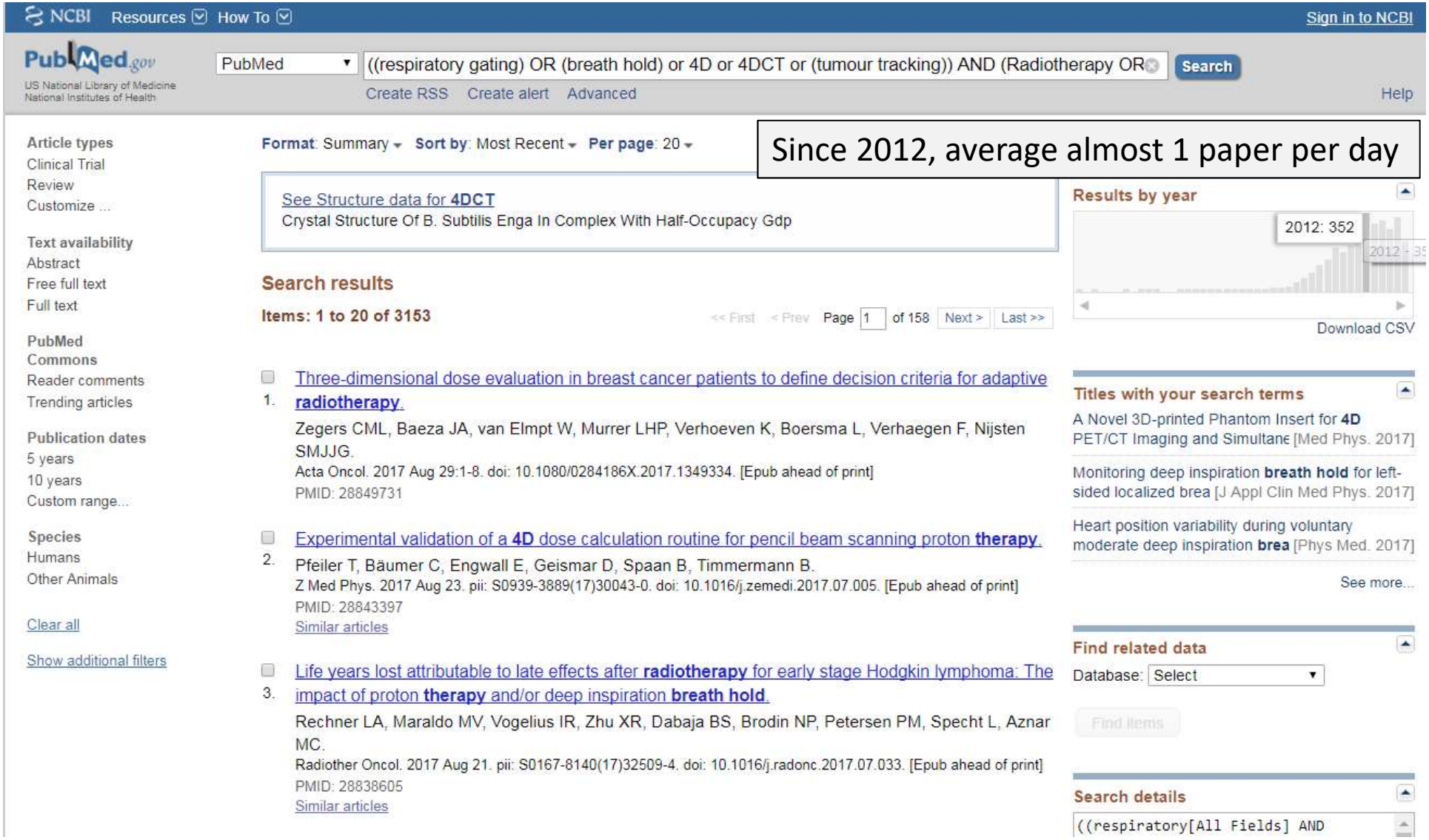
- 4D cone-beam CT scan for setup
- Adaptation with 4D dose recalculation
- Treatment with dynamic beam tracking
- 4D MR guided treatment
- Respiratory guided proton treatment



Current trends
– an AAPM 2017 snapshot



Overall research mass



Identifying research opportunities

What is already well established?

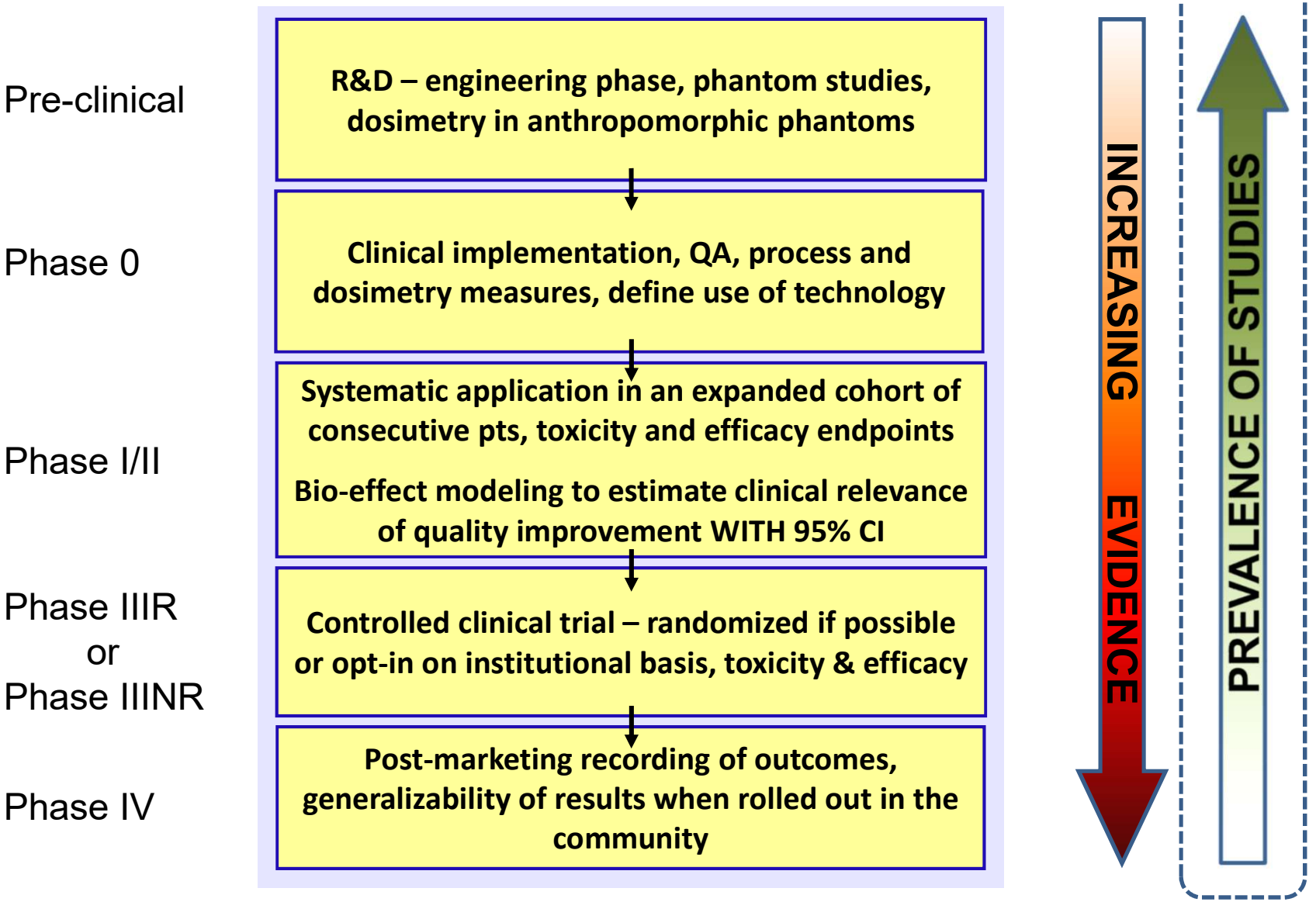
What are new unexplored issues?

Where are the opportunities for achieving clinical gain?

Clinical gain from RT research

- Delta outcome
  - Increase in TCP or OS
  - Decrease in toxicity
- Delta patients
  - Eligibility of new patient groups for RT
  - Increase in number of patients in a patient group
- Delta XX
  - Derivative effects of developments (such as new technologies useful for wider scope of applications)

Building evidence for RT



Courtesy of S. Bentzen

Types of research studies

- Development/testing of new technology
  - Soft- and hardware
- QA – devices, tools and schemes
- Mapping/quantification studies
- Treatment planning studies
- Clinical trials

New technology - hardware

- Immobilization devices
- Scanner and beam gating devices
- Respiration monitoring devices
- Breathing training devices
- Internal markers
- Beam motion drivers
- Couch motion drivers

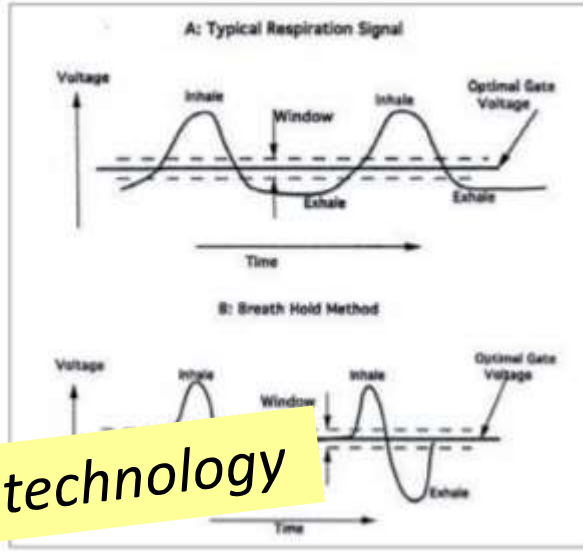
Example - First beam gating device

Physics in Medicine & Biology | 60th anniversary collection 2016

Respiration gated radiotherapy treatment: a technical study

Hideo D Kubo and Bruce C Hill

1996 *Phys. Med. Biol.* **41** 83



Groundbreaking and practice changing new technology

Abstract

In order to optimize external-beam conf… treatment must … target organs are known … This paper deals with the technical aspects … radiotherapy beam synchronously with respiration: the optimal respiration monitoring system, measurements of organ displacement and linear accelerator gating. Several respiration sensors including a thermistor, a thermocouple, a strain gauge and a pneumotachograph were examined to find the optimal sensor. The magnitude of breast, chest wall and lung motion were determined using playback of fluoroscopic x-ray images recorded on a VCR during routine radiotherapy simulation. Total dose, beam symmetry and beam uniformity were examined to determine any effects on the Varian 2100C linear accelerator due to gating.

Example – Radiobeacon internal marker

Patents | Application | Grant

System for excitation of a leadless miniature marker

US 6812842 B2

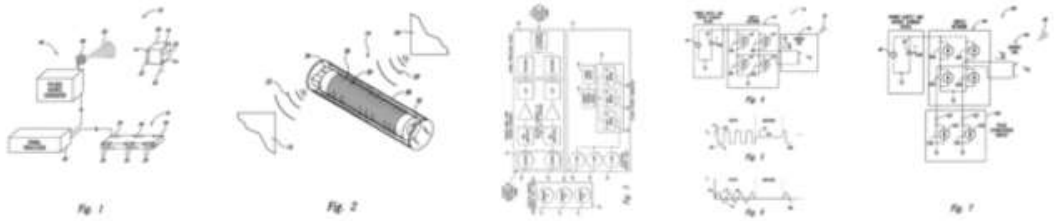
Publication number	US6812842 B2
Publication type	Grant
Application number	US 10/027,675
Publication date	Nov 2, 2004
Filing date	Dec 20, 2001
Priority date	Dec 20, 2001
Fee status	Paid
Also published as	CA2465847A1, 6 More »
Inventors	Steven C. Dimmer
Original Assignee	Calypso Medical Technol
Export Citation	
External Links:	USPTO, USPTO Assignment, Espacenet

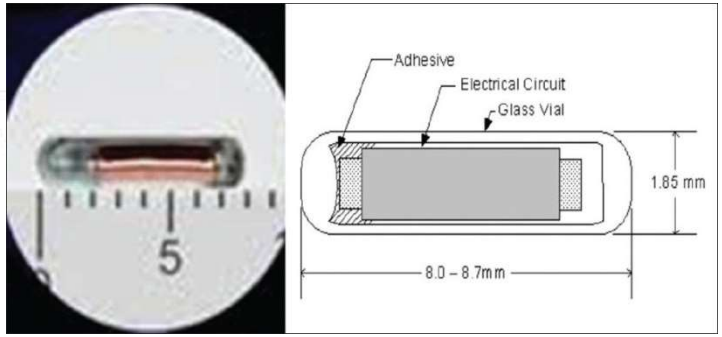
ABSTRACT

A system for generating a pulsed excitation field for excitation of a leadless marker assembly. One aspect of the system comprises a source generator assembly having a power supply, an energy storage device, a switching network and a source coil interconnected and configured to deliver a pulsed magnetic excitation signal waveform. The power supply is configured to deliver power to energize the energy storage device. The switching network is ... direct electrical current through ... on ... energy tra... the source coil; alternately transfer sto... energy from the energy storage device to the source coil and to transfer stored energy from the source coil back to the energy storage device; and the source coil being coupled to the switching network to generate a pulsed excitation signal.

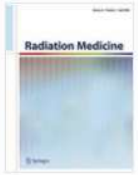
Groundbreaking new technology – not (yet) practice changing

IMAGES (6)





Example – breathing training display



Radiation Medicine
January 2008, Volume 26, Issue 1, pp 50–55

Breath-hold monitoring and visual feedback for radiotherapy using a charge-coupled device camera and a head-mounted display: system development and feasibility

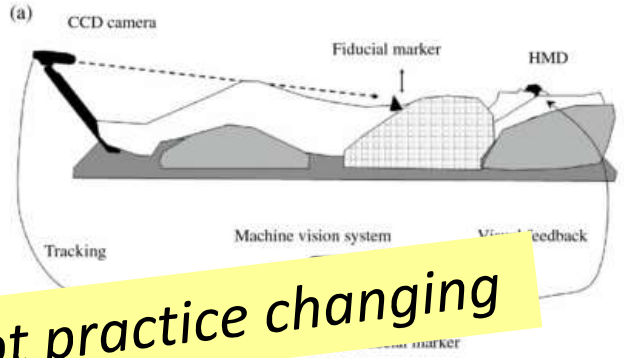
Authors | Authors and affiliations

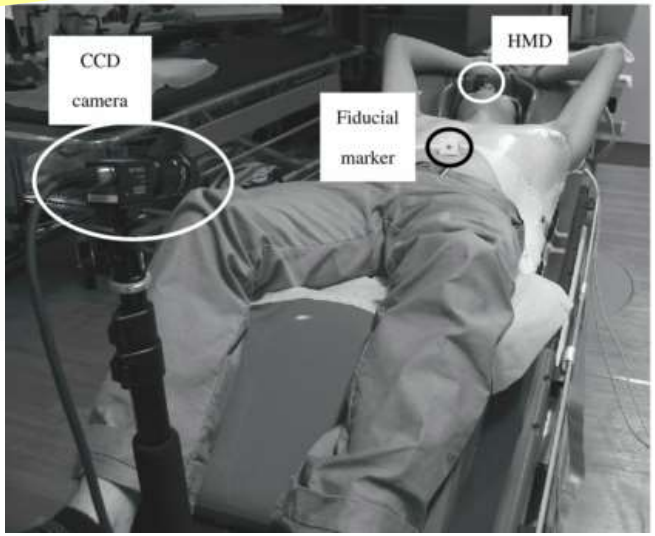
Tadamasa Yoshitake, Katsumasa Nakamura, Yoshiyuki Shioyama, Satoshi Nomoto, Saiji Ohga, Takashi Toba, Takehiro Shiinoki, Shigeo Anai, Hiromi Terashima, Junji Kishimoto, Hiroshi Honda

Technical Note
First Online: 31 January 2008

Purpose

The aim of this study was to present the technical aspects of the breath-hold technique with respiratory monitoring and visual feedback and to evaluate the feasibility of this system in healthy volunteers.



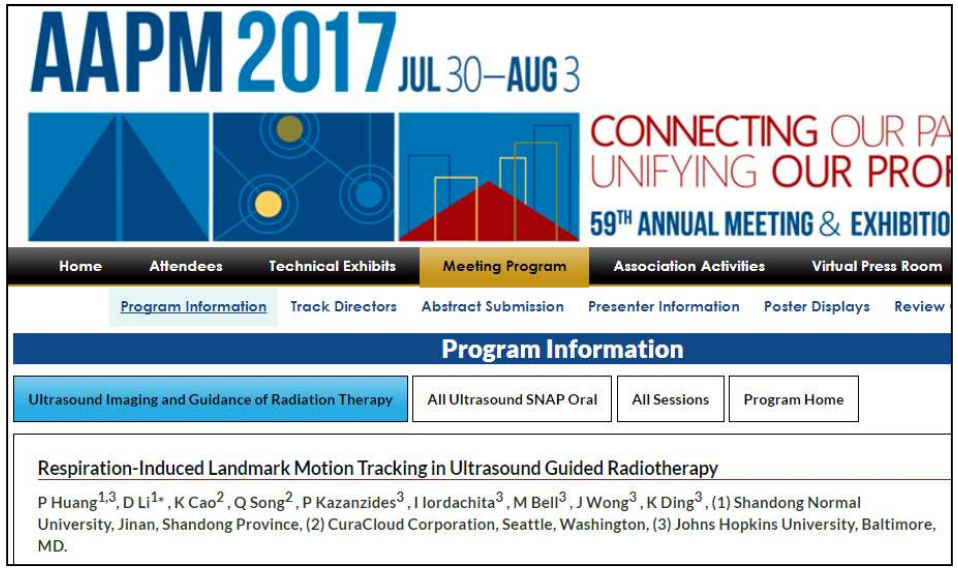


Incremental change to known technology – not practice changing

Current trends and opportunities - hardware

- Incremental improvements in hardware
  - Detectors, MLCs, dose rates, surrogate markers …

- 4D MR guided RT is a new field, calling for new developments.
- Ultrasound for 4D?



New technology - software

- Scanner protocols
- 4D scan sequence reconstruction and registration
- Deformable registration
- Landmark and marker identification and tracking in images
- Respiratory motion analysis
- 4D plan optimization
- Respiratory motion prediction

Example – 4D CT scan reconstruction

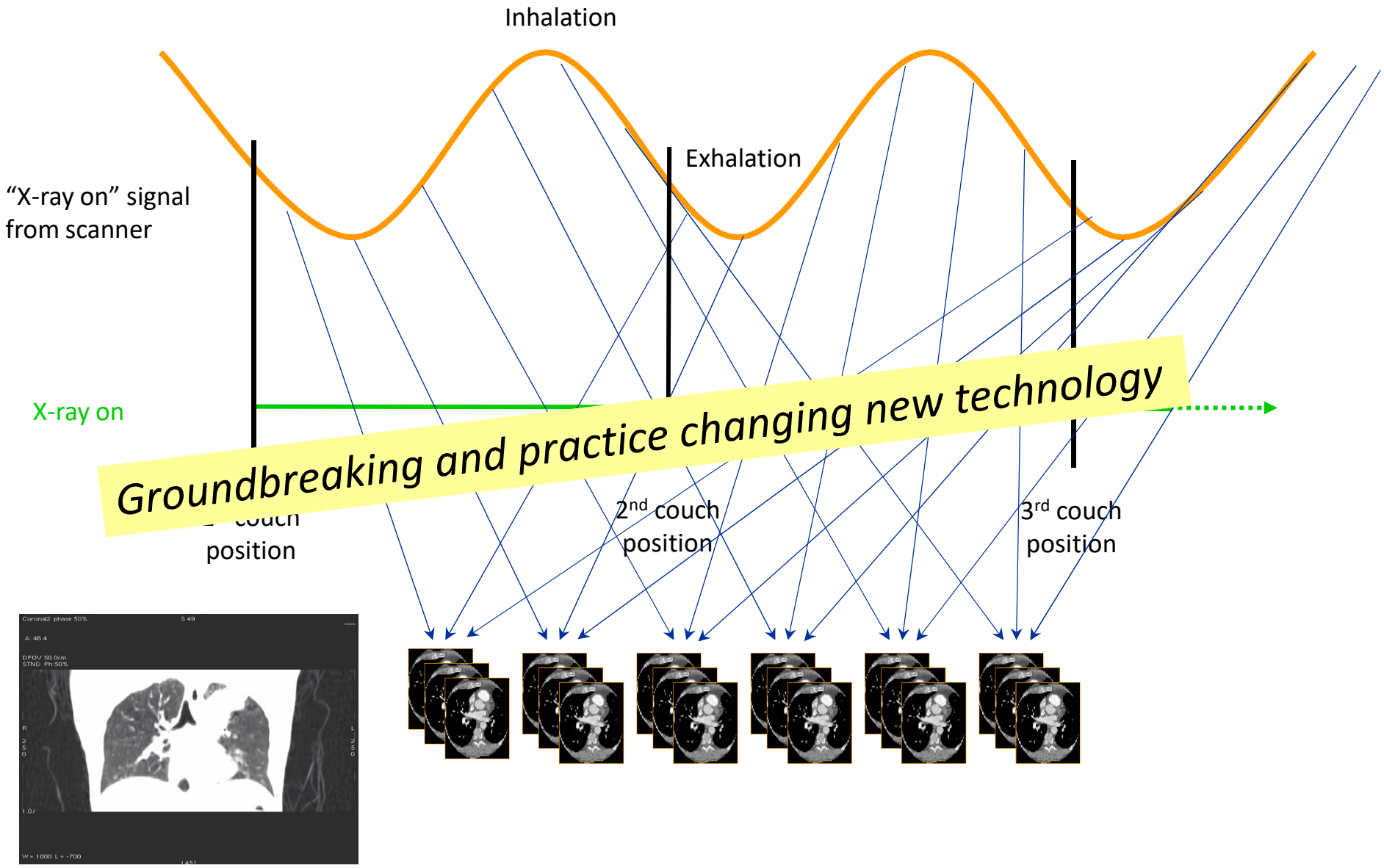
Physics in Medicine & Biology

Acquiring a four-dimensional computed tomography dataset using an external respiratory signal

S S Vedam[1,2], P J Keall[2], V R Kini[2], H Mostafavi[3], H P Shukla[4] and R Mohan[5]

Published 16 December 2002 • Physics in Medicine & Biology, Volume 48, Number 1

Example – 4D CT scan reconstruction



Example – 3D position estimation

ELSEVIER

International Journal of Radiation Oncology*Biology*Physics

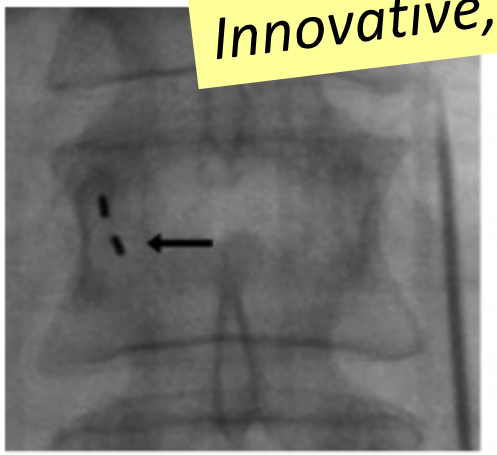
Volume 72, Issue 5, 1 December 2008, Pages 1587-1596

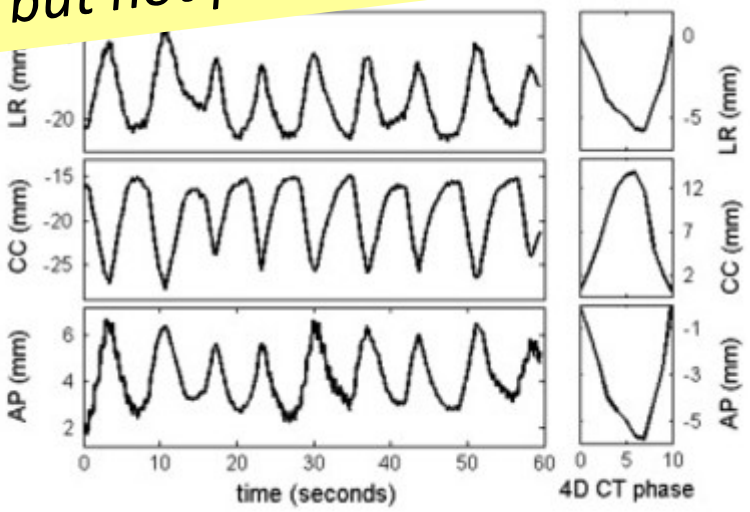
Physics Contribution

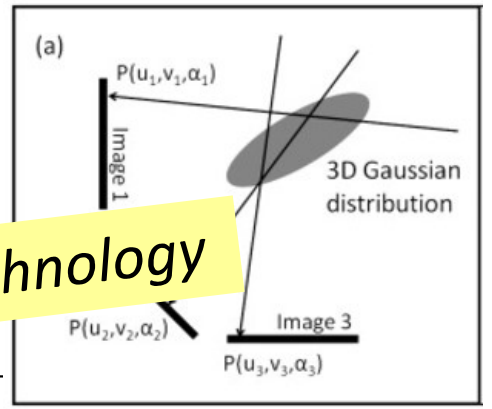
A Method to Estimate Mean Position, Motion Magnitude, Motion Correlation, and Trajectory of a Tumor From Cone-Beam CT Projections for Image-Guided Radiotherapy

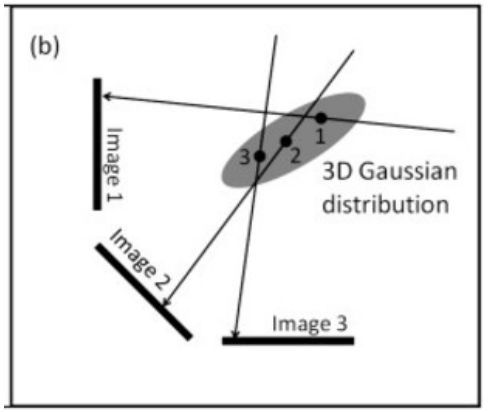
Per Rugaard Poulsen Ph.D. * †

Innovative, but not practice changing new technology









Example – markerless tumour tracking

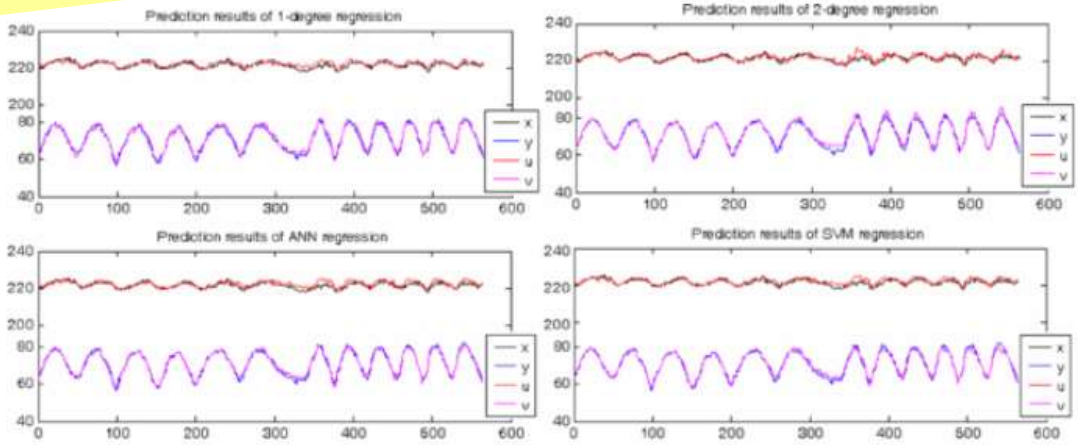
Physics in Medicine & Biology

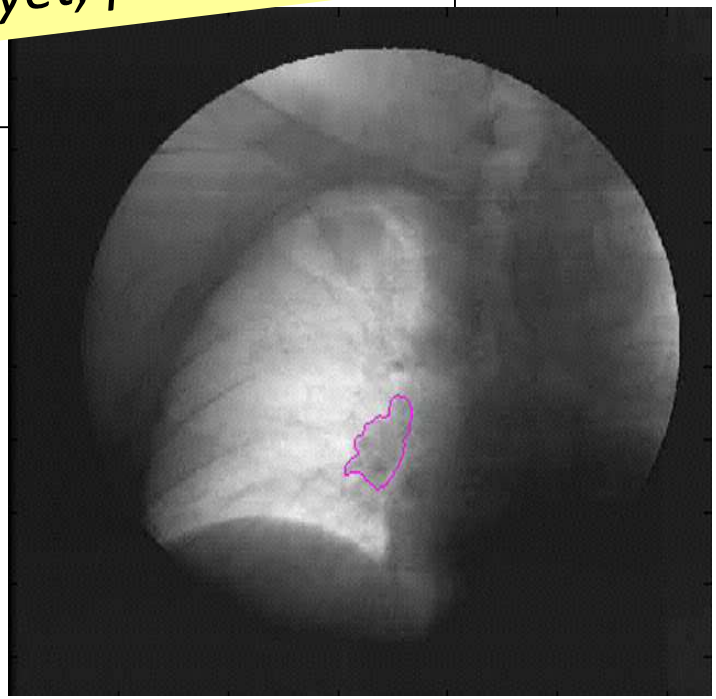
Fluoroscopic tumor tracking for image-guided lung cancer radiotherapy

Tong Lin[1,2], Laura I Cerviño[1], Xiaoli Tang[1], Nuno Vasconcelos[3]

Published 16 January 2009 • 2009

Innovative development – potentially, but not yet, practice changing





Example – 4D dose reconstruction

Physics in Medicine & Biology

PAPER • OPEN ACCESS

Assessment of MLC tracking performance during hypofractionated prostate radiotherapy using real-time dose reconstruction

M F Fast, C P Kamerling, P Ziegenhein, M J Menten, J L Bedford, S Nill and U Oelfke

Published 27 January 2016 • © 2016 Institute of Physics a

Physics in Medicine & Biology, Volume 61, Number 4

Current trends and opportunities - software

- Deformable image registration
- 4D dose reconstruction/accumulation
- Markerless tumour tracking
- Motion prediction
- Onboard treatment verification tools
- Decision making tools
- Ultrasound guidance …

QA – devices, tools and schemes

- ”Breathing” phantoms
- Time-resolved dose measurement
- Time-resolved beam delivery logs
- Risk analysis

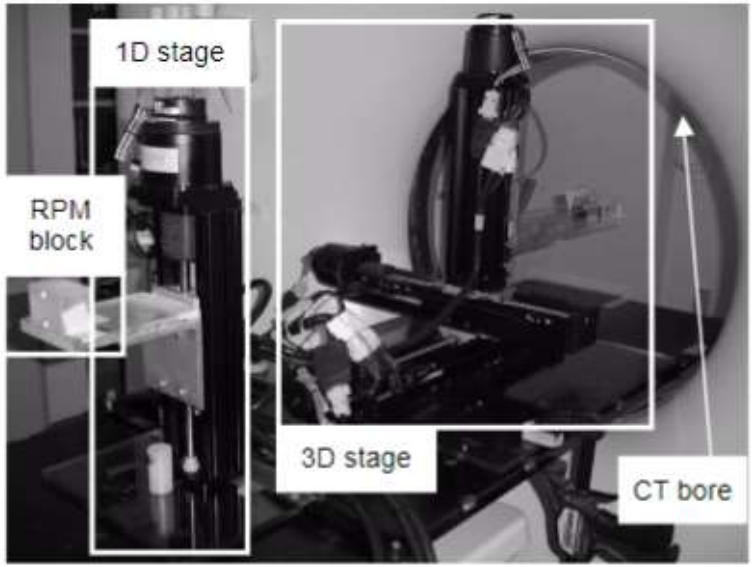
Example – 4D motion platform

SPIE 2008

Development of the 4D Phantom for patient-specific, end-to-end radiation therapy QA

K. Malinowski*[a], C. Noel[a], W. Lu[a], K. Lechleiter[a], J. Hubenschmidt[a], D. Low[a], P. Parikh[a]

[a]Washington University School of Medicine, Department of Radiation Oncology, 4511 Forest Park, Campus Box 8224, St. Louis, MO, USA 63113



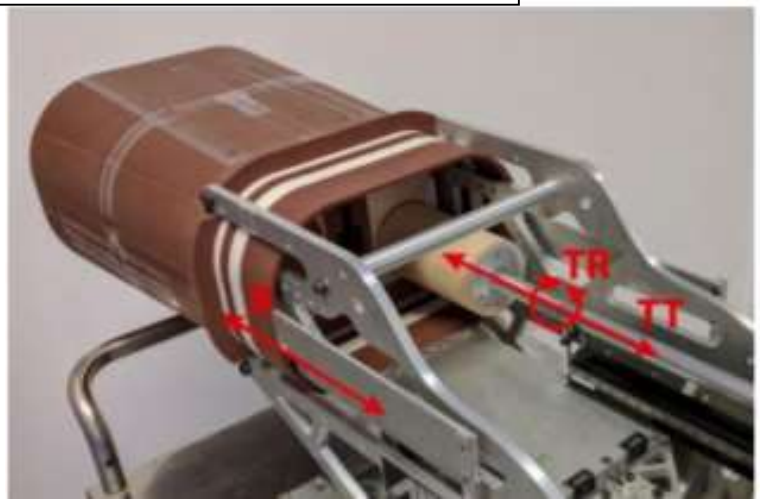
Example – anthropomorphic phantom

Physics in Medicine & Biology

ACCEPTED MANUSCRIPT

Advanced radiation dosimetry phantom (ARDOS) - a versatile breathing phantom for 4D radiation therapy and medical imaging

Natalia Kostiukhina[1], Dietmar Georg[2], Sofia Rollet[3], Peter Kuess[4], Andrej Sipaj[5], Piotr Andrzejewski[6], Hugo Furtado[7], Ivo Rausch[8], Wolfgang Lechner[9], Elisabeth Steiner[10]



Current trends and opportunities - QA

- Dosimeters with both high spatial resolution and temporal resolution.
- Utilization of 3D printing?

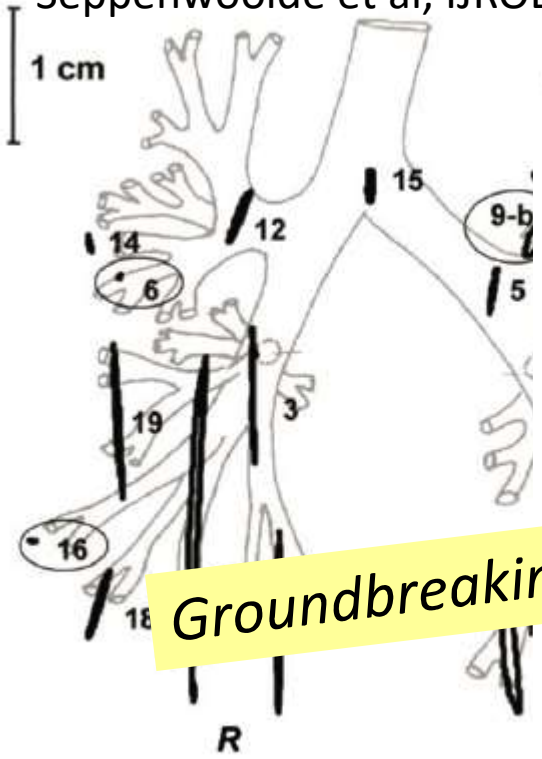
- Anthropomorphic 4D phantoms for dosimetry.

Quantification studies

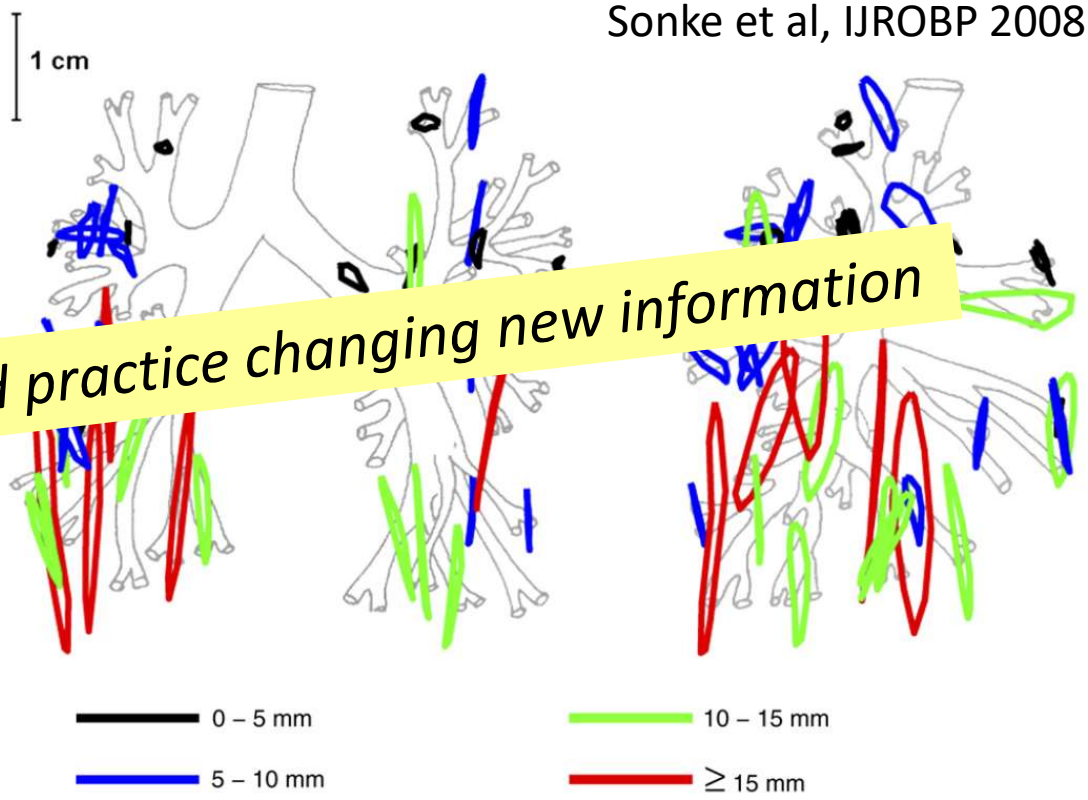
- Respiratory organ motion mapping
- Respiration pattern mapping
- Patient compliance to respiratory intervention
- Cost-effectiveness analysis

Example – 3D lung tumour motion

Seppenwoolde et al, IJROBP 2002



Sonke et al, IJROBP 2008



Groundbreaking and practice changing new information

Fig. 2. Location and shape of the average trajectory projected on coronal and sagittal views of a schematic bronchial tree (after Seppenwoolde *et al*. [23]). Only the trajectories of the 4D-CT group are shown for clarity. The 3D-CT group had similar results. Note that trajectories are not scaled to the bronchial tree. Hysteresis was frequently observed, predominantly in the sagittal plane.

Example – MLC interplay effect

Physics in Medicine & Biology

Effects of intra-fraction motion on IMRT dose delivery: statistical analysis and simulation

Thomas Bortfeld, Kimmo Jokivarsi, Michael Goitein, Jong Kung and Steve B. Jiang

Published 20 June 2002 • Physics in Medicine & Biology, Volume

Innovative idea, incremental new information

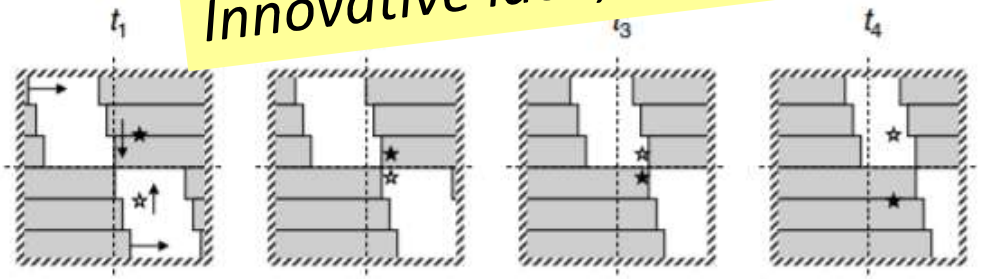
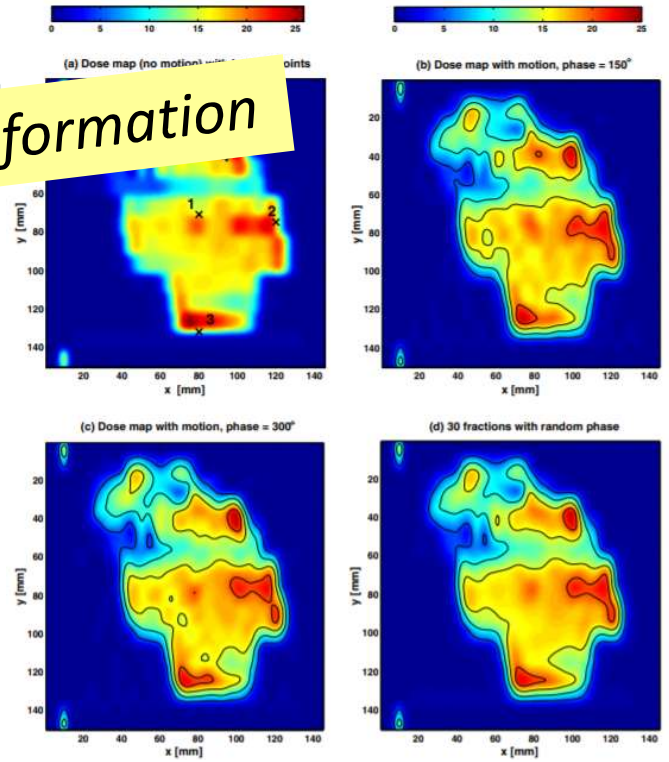


Figure 1. Illustration of the interplay between organ motion and leaf motion for the delivery of IMRT with an MLC. The leaves move from left to right. The star symbolizes a point in an organ that moves up and down. The two different versions of the star represent two different phases of the



Current trends and opportunities - quantification

- Variabilities in respiration and motion management for subpopulations.
- Multiple targets.

- Effectiveness and efficacy studies.

Treatment planning studies

- Comparison of various motion management regimes.
- Dosimetric effects of variations over treatment course.
- Initial tests for new 4D techniques.
- Demonstration of incremental improvements in application of 4D techniques.

Example – DIBH for breast

ELSEVIER

Radiotherapy and Oncology 72 (2004) 53–60

RADIOTHERAPY & ONCOLOGY
JOURNAL OF THE EUROPEAN SOCIETY FOR THERAPEUTIC RADIOLOGY AND ONCOLOGY

www.elsevier.com/locate/radonline

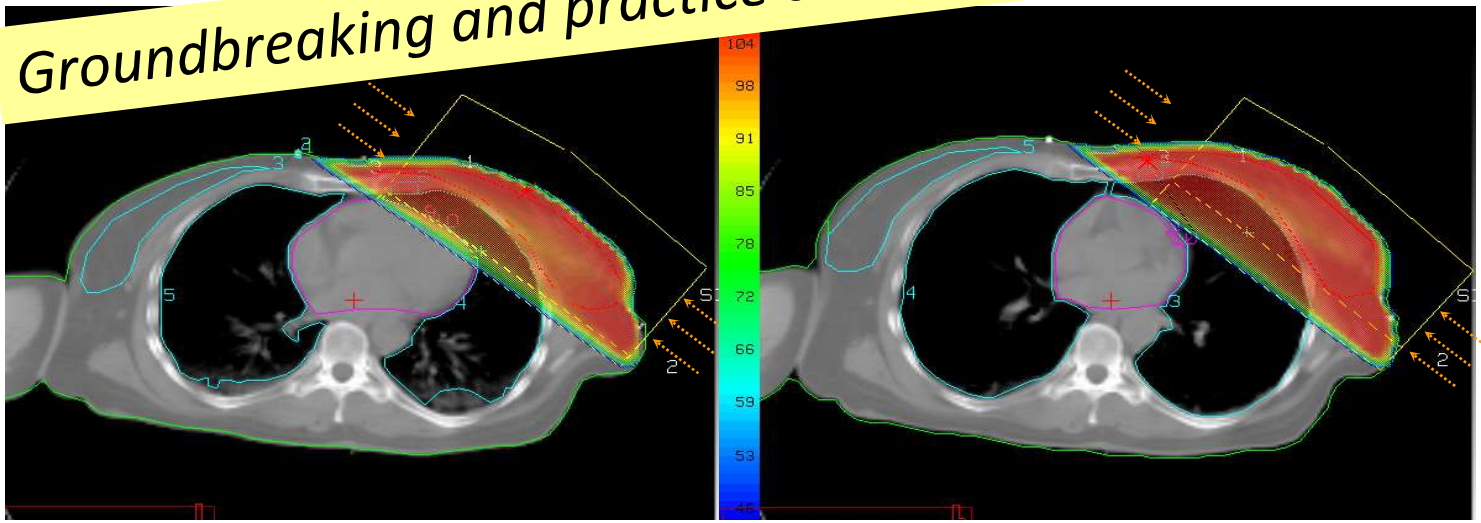
Breathing adapted radiotherapy of breast cancer: reduction of cardiac and pulmonary doses using voluntary inspiration breath-hold

Anders N. Pedersen*, Stine Korreman, Håkan Nyström, Lena Specht

Department of Radiation Oncology, The Finsen Cen

Received 30 C

Groundbreaking and practice changing new method



Example – lung dose escalation

Journal
Acta Oncologica ›
Volume 50, 2011 - Issue 6

Enter keywords, authors, DOI etc.

625
Views
13
CrossRef citations
0
Altmetric

Research Article

A planning study of radiotherapy dose escalation of PET-active tumour volumes in non-small cell lung cancer patients

Ditte Sloth Møller, Azza Ahmed Khalil, Marianne Marquard Knap

Pages 883-888 | Received 23 Mar 2011, Accepted 12 Apr 2011

Download citation

Potentially practice changing new method

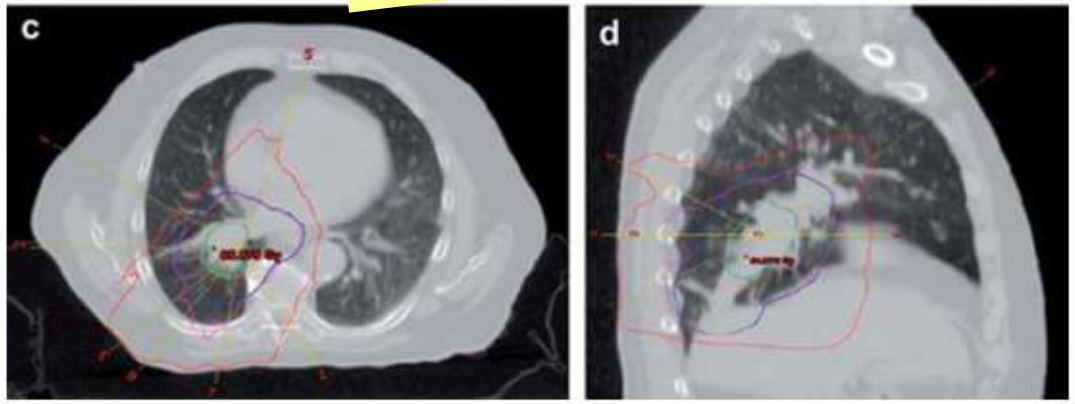
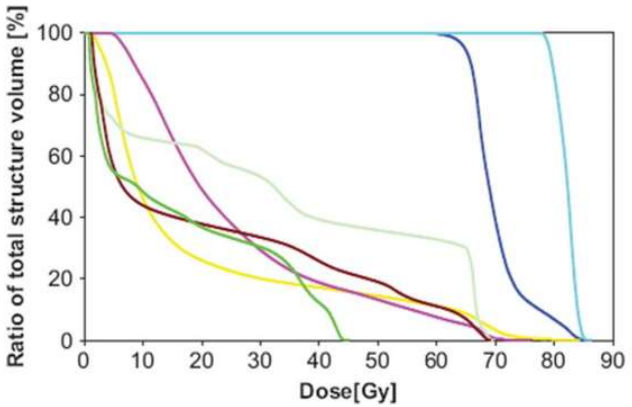


Figure 2. Dose volume histograms for case 8 of the PTV (blue), PTV-boost (cyan), heart (magenta), trachea (brown), spinal canal (green) and total lung volume (yell



Example – lymphoma DIBH

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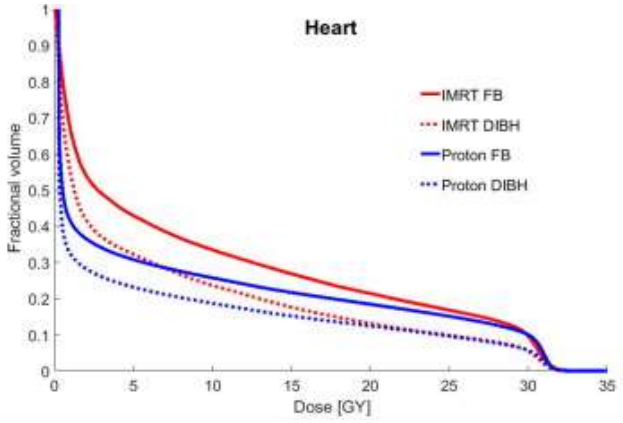
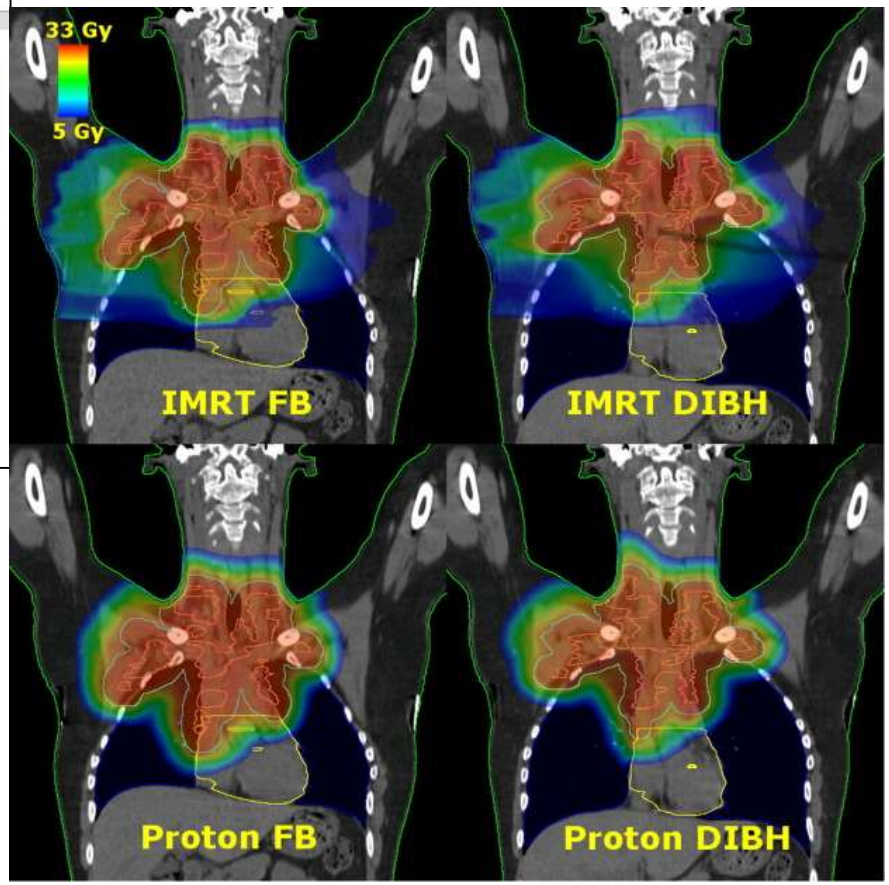
Article in Press

Life years lost attributable to late effects after radiotherapy for early stage Hodgkin lymphoma: The impact of proton therapy and/or deep inspiration breath hold

Laura Ann Rechner, Maja Vestmø Maraldo, Ivan Richter Vogelius, Xiaorong Ronald Zhu, Bouthaina Shbib Dabaja, Nils Patrik Brodin, Peter Meidahl Petersen, Lena Specht, Marianne Camille Aznar





Current trends and opportunities – treatment planning

- 4D MR guided radiotherapy
- 4D proton therapy
- New patient groups for motion management

Author bias in TP studies – a warning sign

More often than not, you will find that

- authors of a treatment planning study are all users (sometimes even vendors) of one of the techniques investigated
- the results of a treatment planning study is in favour of that technique

Clinical trials

Example – prostate 4D tracking

ELSEVIER

International Journal of Radiation Oncology*Biology*Physics

Volume 92, Issue 5, 1 August 2015, Pages 1141-1147

Physics Contribution

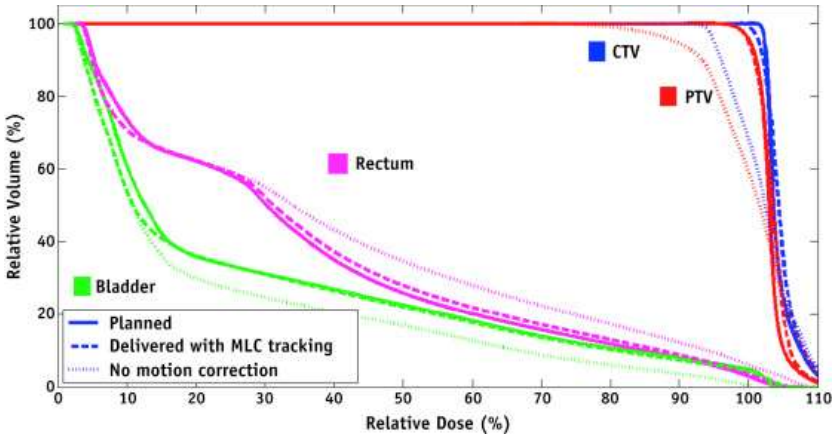
Multileaf Collimator Tracking Improves Dose Delivery for Prostate Cancer Radiation Therapy: Results of the [redacted] Trial

Phase I trial, feasibility of tracking in specific patient group

Emma C[redacted], Ricky T. O'Brien PhD *, Thomas N. Eade MBBS †, Andrew B. Kneebon[redacted], Per R. Poulsen PhD §, Paul J. Keall PhD *

Clinical trial

The first prospective clinical trial implementing Calypso-guided MLC tracking commenced in November 2013 (NCT02033343) (13). The primary endpoint of the prostate trial was the successful implementation of MLC tracking for at least 95% of all fractions. Secondary endpoints include the assessment of the delivered dose and modeling of radiobiological effects. Patients eligible for the trial were those undergoing external beam radiation therapy



Reports of trials - lung

Liao et al, ”Influence of technologic advances on outcomes in patients with unresectable, locally advanced non-small-cell lung cancer receiving concomitant chemoradiotherapy”, *Int. J. Radiat. Oncol. Biol. Phys. 2010,* **76** 775–81

Peulen H, Belderbos J, Rossi M, and Sonke JJ. Mid-ventilation based PTV margins in Stereotactic Body Radiotherapy (SBRT): a clinical evaluation. Radiother Oncol 2014;110(3):511-516.

van der Voort van Zyp NC, Prevost JB, Hoogeman MS, Praag J, van der Holt B, Levendag PC, van Klaveren RJ and others. Stereotactic radiotherapy with real-time tumor tracking for non-small cell lung cancer: clinical outcome. Radiother Oncol 2009;91(3):296-300.

Ahn SH, Han MS, Yoon JH, Jeon SY, Kim CH, Yoo HJ, and Lee JC. Treatment of stage I non-small cell lung cancer with CyberKnife, image-guided robotic stereotactic radiosurgery. Oncol Rep 2009;21(3):693-696.

Reports of trials - lung

Liao et al, "Influence of technologi… unresectable… …ung cancer receiving concomitant … *Int. J. Radiat. Oncol. Biol. Phys. 2010,* **76** 775–81

Reduced toxicity and increased overall survival with 4DCT

Peulen H, Belderbos J, Rossi M, and Sonke JJ. Mid-ventilation based PTV margi… Stereotactic Body Radiotherapy (SBRT): a clinical evaluati… 2014;110(3):511-516.

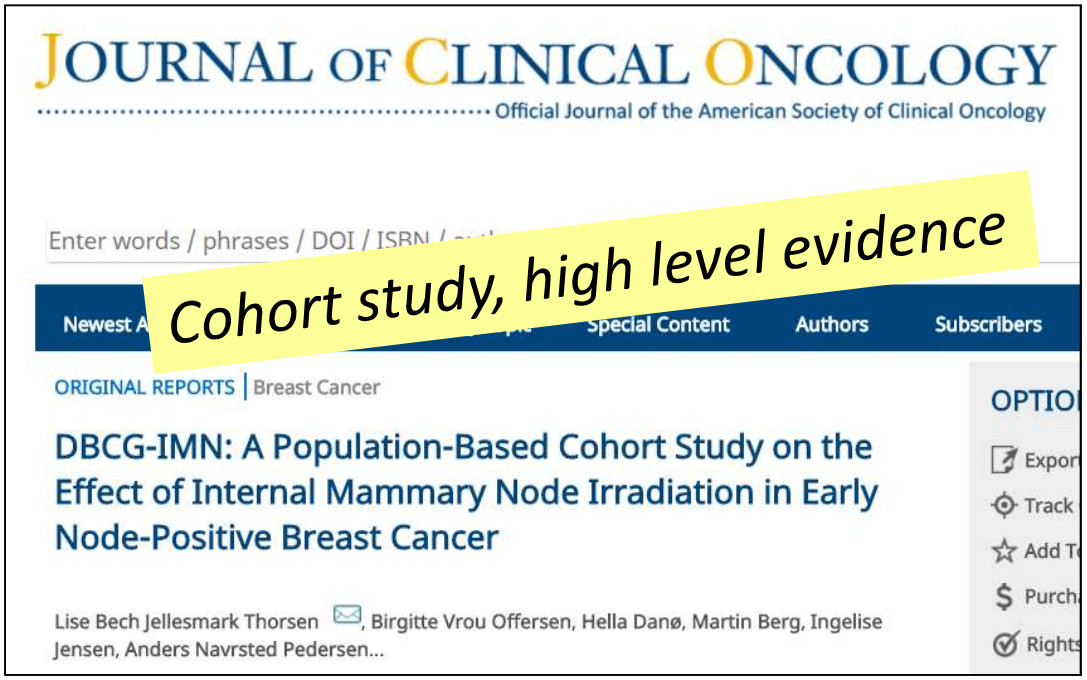
98% local control and 67% overall survival at two years

v… van Zyp NC, Prevost JB, Hoogeman MS, Praag J, van der Holt B, Levendag PC, van Klaveren RJ and others. Stereotactic radiotherapy with real-time tumor tracking for non-small cell lung cancer: clinical outcome. Radiother Oncol 2009;91(3):296-300.

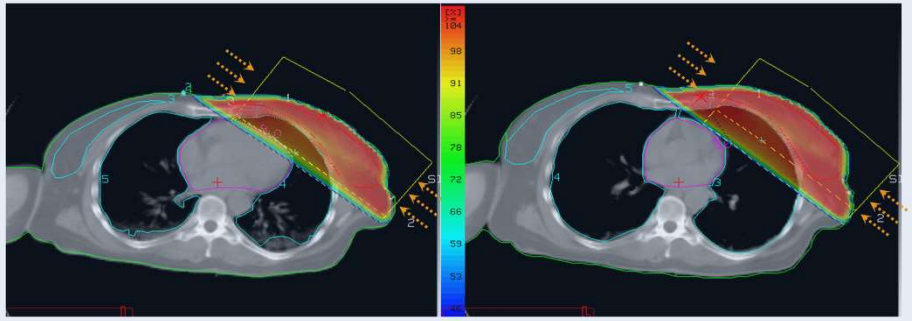
96% local control and 62% overall survival at two years

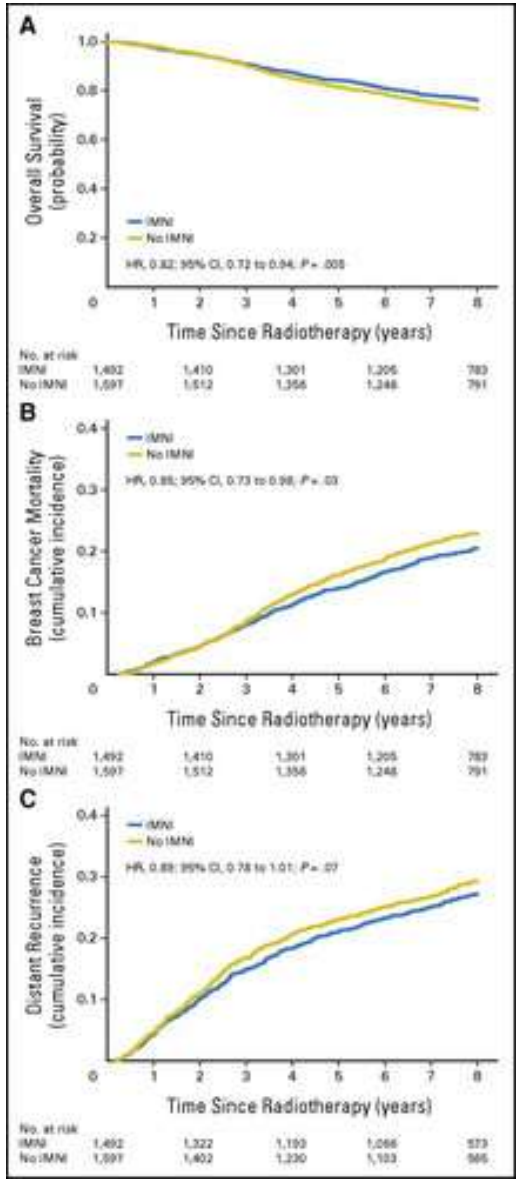
Ahn SH… …m CH, Yoo HJ, and Lee JC. Treatment of stage I n… …ung cancer with CyberKnife, image-guided robotic stereotactic radiosurgery. Oncol Rep 2009;21(3):693-696.

Example – indirect evidence breast



DIBH enables the irradiation of IMN even for patients with left-sided breast cancer:





The problem of clinical equipoise

B Freedman, NEJM 1987:

Abstract The ethics of clinical research requires equipoise — a state of genuine uncertainty on the part of the clinical investigator regarding the comparative therapeutic merits of each arm in a trial. According to this concept of "clinical equipoise," the requirement is satisfied if there is genuine uncertainty within the expert medical community — not necessarily on the part of the individual investigator — about the preferred treatment. (N Engl J Med 1987; 317: 141-5.)

Current trends and opportunities – clinical trials

- More patient groups for motion management techniques.
- Controlled clinical follow-up after 4D RT.
- Trial design to establish high level clinical evidence!

Overall - what is missing?

- 4D imaging for treatment planning using other imaging modalities than CT, i.e. PET and MR.
- Deformable image registration in 4D.
- 4D dose accumulation methods in treatment planning.
- Techniques to continuously irradiate a moving target on conventional linacs.
- Motion management for proton therapy.
- Gold standards for QA equipment and protocols.

Too much:

- Redundancy in publications
- Engineering of new devices
- Treatment planning studies

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1. Monitoring deep inspiration breath hold for left-sided localized **breast** cancer radiotherapy with an in-house developed laser distance meter system.
Jensen CA, Abramova T, Frengen J, Lund JÅ.
J Appl Clin Med Phys. 2017 Jul 29. doi: 10.1002/acm2.12137. [Epub ahead of print]
PMID: 28755403
Similar articles

2. Postmastectomy radiation therapy technique and cardiopulmonary sparing: A dosimetric comparative analysis between photons and protons with free breathing versus deep inspiration breath hold.
Patel SA, Lu HM, Nyamwanda JA, Jimenez RB, Taghian AG, MacDonald SM, Depauw N.
Pract Radiat Oncol. 2017 Jun 21. pii: S1879-8500(17)30187-X. doi: 10.1016/j.prro.2017.06.006. [Epub ahead of print]
PMID: 28734644
Similar articles

3. Selection of patients with left **breast** cancer for deep-inspiration breath-hold radiotherapy technique: Results of a prospective study.
Czeremszyńska B, Drozda S, Górzyński M, Kępka L.
Rep Pract Oncol Radiother. 2017 Sep-Oct;22(5):341-348. doi: 10.1016/j.rpor.2017.05.002. Epub 2017 Jun 30.
PMID: 28701900
Similar articles

4. An effective deep-inspiration breath-hold radiotherapy technique for left-**breast** cancer: impact of post-mastectomy treatment, nodal coverage, and dose schedule on organs at risk.
Rice L, Goldsmith C, Green MM, Cleator S, Price PM.
Breast Cancer (Dove Med Press). 2017 Jun 14;9:437-446. doi: 10.2147/BCTT.S130090. eCollection 2017.
PMID: 28652810 **Free PMC Article**
Similar articles

5. Cardiac dose-sparing effects of deep-inspiration breath-hold in left **breast** irradiation : Is IMRT more beneficial than VMAT?

Too much:

- Redundancy in publications
- Engineering of new devices
- Treatment planning studies

Too little:

- Few clinical trials
- No gold standard for technology
- Limited true 4D treatment
- New treatment technology (protons and MR-RT) awaiting 4D solutions

Room for real impact

- Enabling the routine use of putting the beam where the target is.
- Utilizing new MR-RT possibility for soft tissue based 4DRT.
- Motion management in proton therapy.

- Building of clinical evidence.

Erasmus MC
Universitair Medisch Centrum Rotterdam

Cancer Institute

Department of Radiation Oncology

See also reference list.

Trends and research opportunities in Treatment Planning

Ben Heijmen

ESTRO Research Masterclass in Radiotherapy Physics
Florence, Italy, 10-13 September 2017

Disclosures

Work in part funded by research grants from Elekta AB, and Accuray Inc.

Elekta AB is preparing commercialization of the Erasmus-iCycle approach of automated planning.

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Trends and research opportunities in Treatment Planning

Sub-fields of research on, or with planning:

- Dose calculation accuracy
- Fast dose calculation and plan optimization
- Probabilistic/robust planning (replace PTV/PRV)
- Automated planning
- Interactive (graphical) planning
- (Non-coplanar) beam angle optimization
- Pareto navigation
- Evaluation of new treatment techniques
- Automated treatment plan QA
- 'Biological' planning
- Spatio-temporal fractionation
- MR-only workflow
- Automatic image segmentation
- Deformable image registration
- Dose accumulation
- …….

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Trends and research opportunities in Treatment Planning

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- Dose accumulation
- …….

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Current treatment plans are often (much) further from optimality than we know or think!

How do I know:

- Literature
- Systematic comparisons of clinical plans with automatically generated plans using Erasmus-iCycle

✓ **Bad for patients:**
- **inadequate coverage**
- **excessive OAR dose**

✓ **Sub-optimal use of expensive resources**

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Head and Neck cancer

in 97% of cases the automatic plan was selected by physician for treatment

International Journal of Radiation Oncology biology • physics

www.redjournal.org

Physics Contribution

Toward Fully Automated Multicriterial Plan Generation: A Prospective Clinical Study

Peter W.J. Voet, RTT, Maarten L.P. Dirkx, PhD, Sebastiaan Breedveld, MSc, Dennie Fransen, RTT, Peter C. Levendag, MD, PhD, and Ben J.M. Heijmen, PhD

Department of Radiation Oncology, Erasmus Medical Center—Daniel den Hoed Cancer Center, Groene Hilledijk 301, Rotterdam 3075EA, The Netherlands

Received Jan 24, 2012, and in revised form Mar 27, 2012. Accepted for publication Apr 10, 2012

Int J Radiat Oncol Biol Phys. 2013; 85(3): 866-72.

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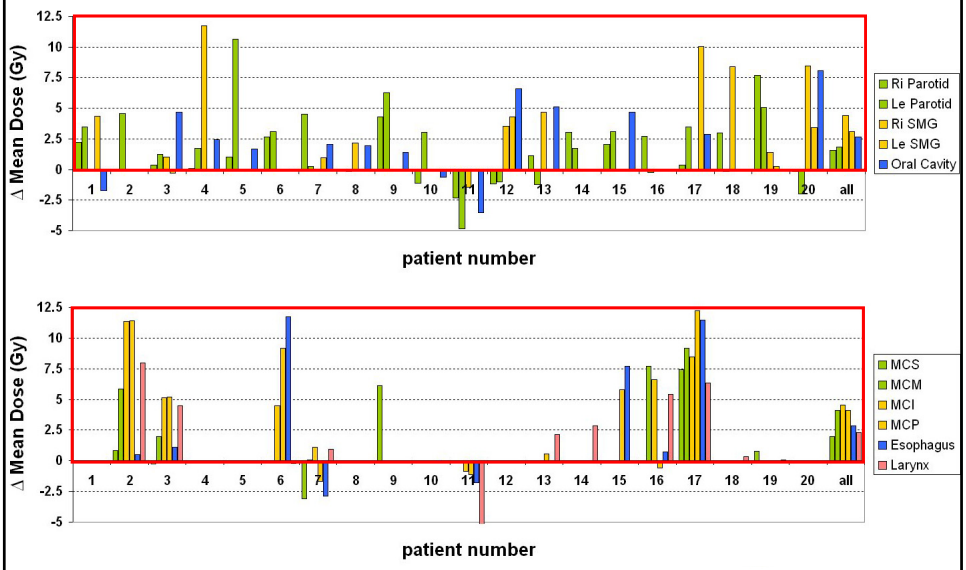
differences between automatic and manual planning in mean OAR doses

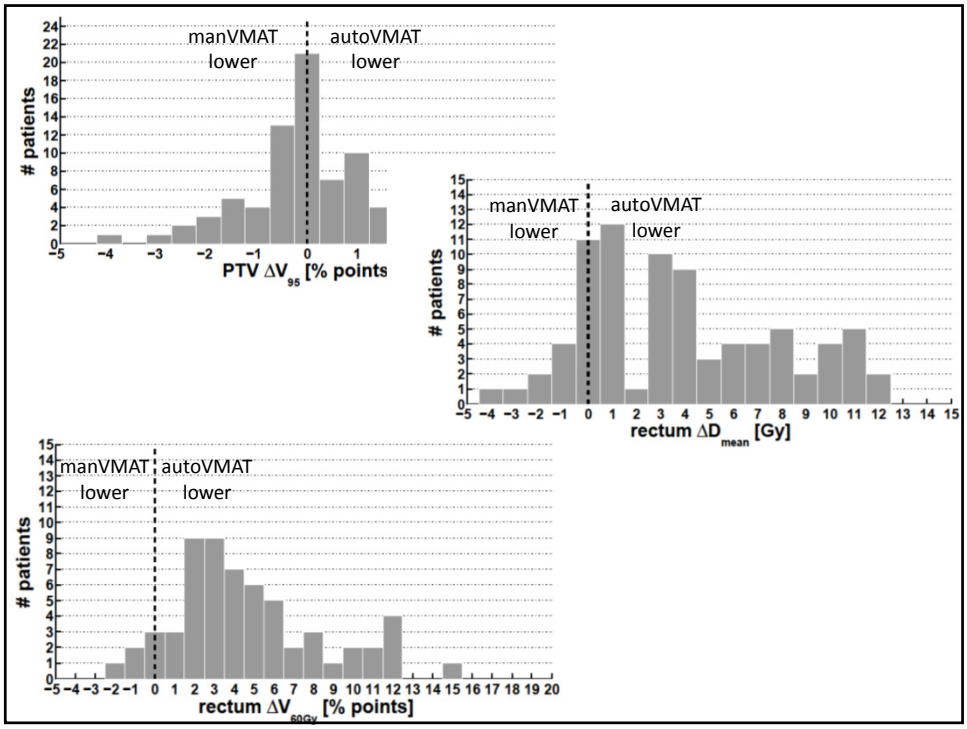


AUTOplan vs. MANplan for prostate cancer international validation

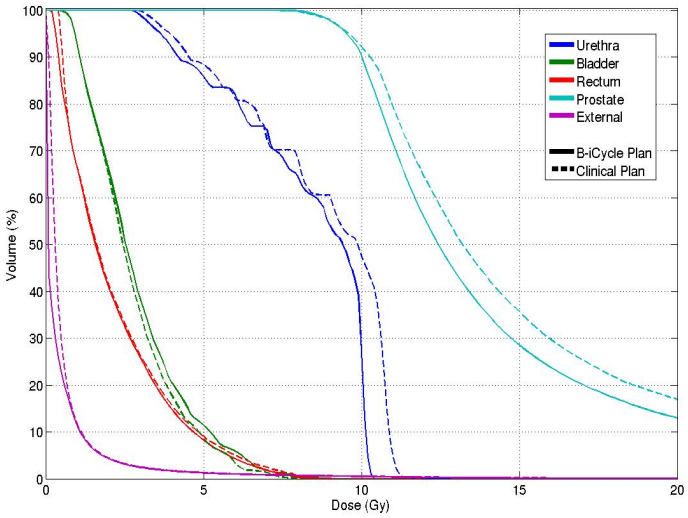
B. Heijmen[1], P. Voet[2], D. Fransen[1], H. Akhiat[2], P. Bonomo[3], M. Casati[3], D. Georg[4], G. Goldner[4], A. Henry[5], J. Lilley[5], F. Lohr[6], L. Marrazzo[3], M. Milder[1], S. Pallotta[3], J. Penninkhof[1], Y. Seppenwoolde[4], G. Simontacchi[3], V. Steil[6], F. Stieler[6], S. Wilson[5], R. Pellegrini[2], S. Breedveld[1].

[1] Erasmus MC Cancer Insitute, The Netherlands.
[2] Elekta AB, Elekta, Stockholm, Sweden.
[3] Azienda Ospedaliero-Universitaria Careggi, Florence, Italy.
[4] Medical University Vienna /AKH Wien, Radiation Oncology, Vienna, Austria.
[5] St James's Institute of Oncology- St James's Hospital, Leeds, United Kingdom.
[6] University Medical Center Mannheim - Heidelberg University, Mannheim, Germany.

Publication in preparation



Automated vs. manual planning in prostate HDR brachytherapy



Courtesy Amit Ben Antony Bennan, Sebastiaan Breedveld, Inger-Karine Kolkman-Deurloo

Issues with current planning:

- ✓ Plan quality dependents strongly on
  - skills of the planner (operator dependence)
  - allotted planning time; stop when below constraints
  - subjective preferences and priorities (within the planning protocol)
- ✓ Difficult to decide when to stop; could more iterations result in a better plan?, or really different approach?

This may compromise plan quality.

Nelms et al. Practical Radiation Oncology (2012) 2, 296–305
Berry et al. Radiotherapy and Oncology 120 (2016) 349–355
Berry et al. Practical Radiation Oncology (2016) 6, 442-449

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What is behind the issues with current planning?

- ✓ Plan generation requires solving a complex and large multi-objective problem.
- ✓ Often many (mostly conflicting) objectives.
- ✓ Trade-offs between objectives are unclear and patient-specific.
- ✓ Infinite number of (sub-optimal) solutions.
- ✓ Interactive trial-and-error planning is slow

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Current treatment plans are often (much) further from optimality than we know or think!

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Current treatment plans are often (much) further from optimality and we know!

…… this needs to be resolved!

Automated planning can be a solution.

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Systems for automated planning

- Eclipse Rapidplan Knowledge-based planning (Varian)
- Pinnacle Auto-Planning (Philips)
- 'wish-list' based lexicographic optimization
  - Erasmus-iCycle (Rotterdam) + Monaco (Elekta)
  - Raystation Plan Explorer
  - iCycle integrated in Monaco (Elekta, not yet commercial)
- Many (in-house/heuristic) systems (for single patient group)

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  - Raystation Plan Explorer
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- Many (in-house/heuristic) systems (for single patient group)

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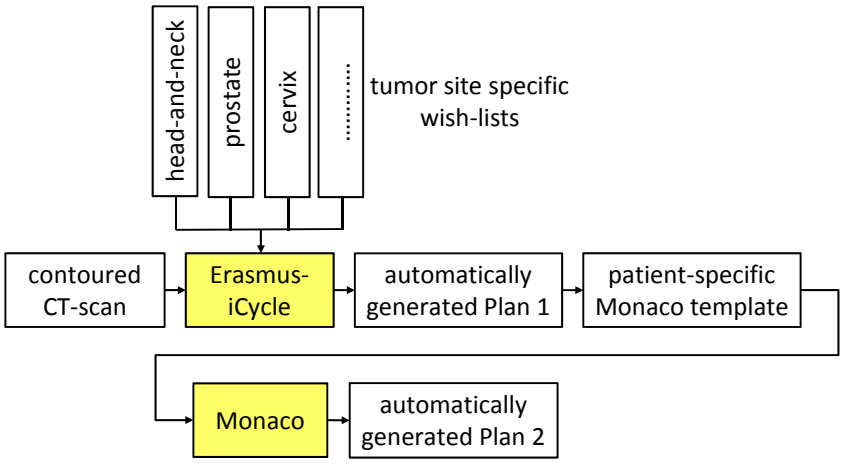
Erasmus-iCycle/Monaco

for automated, multi-criterial treatment plan generation



Erasmus-iCycle: Med Phys. 2012; 39(2): 951-963.
Monaco: Elekta AB, Stockholm, Sweden

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Prostate wishlist

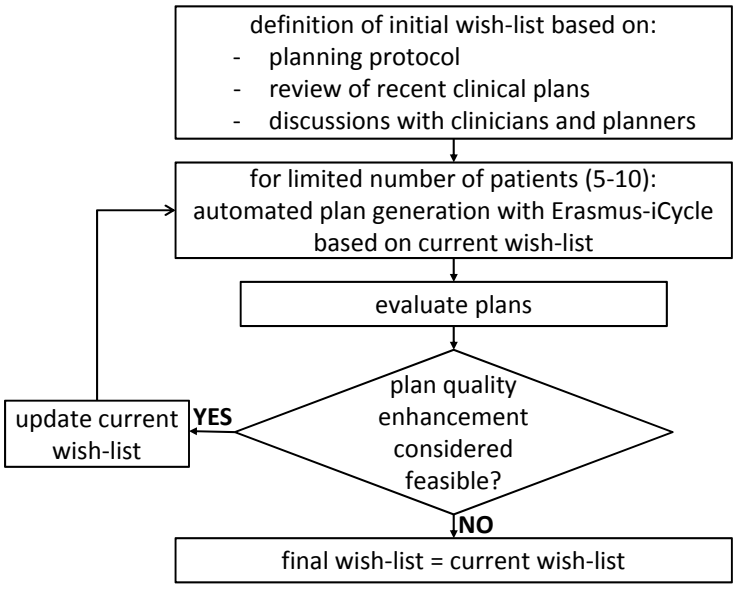
Constraints

Volume	Type	Limit
PTV	max	104% of prescribed dose
PTV shell 50 mm	max	60% of prescribed dose
Unspecified tissue	max	104% of prescribed dose
Right + Left hip	max	40 Gy

Objectives

Priority	Volume	Type	Goal
1	PTV	↓LTCP	0.5
2	Rectum	↓gEUD (parameter 12)	40% of prescribed dose
3	Rectum	↓gEUD (parameter 8)	25% of prescribed dose
4	Rectum	↓mean	33% of prescribed dose
5	External ring	↓max	40% of prescribed dose
6	PTV shell 5 mm	↓max	93% of prescribed dose
7	Anus	↓mean	10% of prescribed dose
8	PTV shell 15 mm	↓max	70% of prescribed dose
9	PTV shell 25 mm	↓max	50% of prescribed dose
10	Bladder	↓mean	60% of prescribed dose
11	Right + Left Hip	↓mean	25% of prescribed dose
12	Unspecified tissue	↓mean	10 Gy

Generation of wish-lists to improve on current plans



Erasmus-iCycle and Pinnacle Auto-Planning for plan quality enhancement with automated planning, are we done?

Not at all:

- Sequential constrained optimization
- Too slow for fast planning (1 min)
- Configuration may be really time consuming/impossible
- Include beam angle optimization
- Convex vs. non-convex cost functions
- Hard constraints?
- Pareto-optimality?
- Systems used/evaluated by very few users

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Alternatives to automated planning for plan improvement?

✓ Manual planning with super fast optimization algorithms
✓ Pareto Navigation (Raystation)
✓ Fast graphical planning
✓ …….

…. also complimentary to automated planning (not yet tested)

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Is there a future for planning studies to compare treatment techniques?

Planning studies are essential:

- often clinical studies not feasible
- get a fast answer regarding difference in plan quality, delivery time, MUs, ..
- can be hypothesis generating for clinical studies
- patient selection: protons vs. photons

Need to be done well:

- avoid bias
- enough patients
- clinically deliverable plans
- plans have to be checked by clinicians

Automated planning can help

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Bias-free treatment technique comparison

- exactly the same optimization algorithm/scheme
- exactly the same planning constraints and prioritized treatment objectives ('wish-list')

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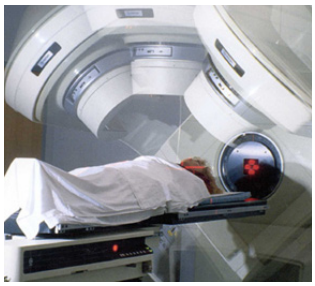
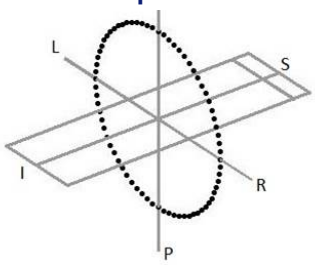
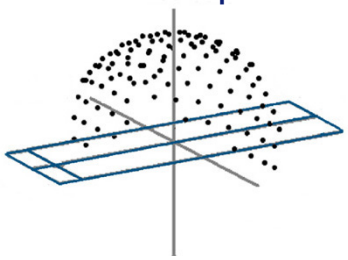
robot vs. linac for prostate SBRT



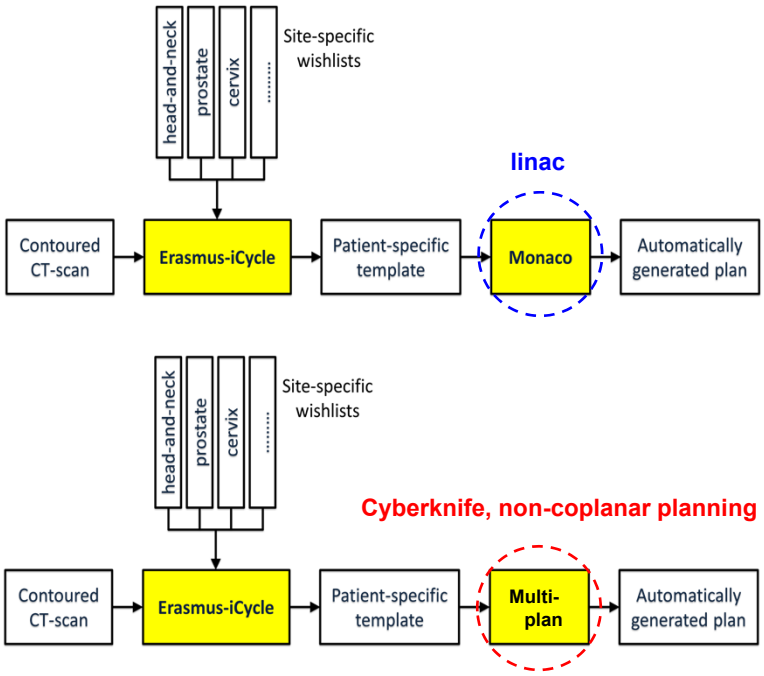
Linac: coplanar VMAT



robot: non-coplanar



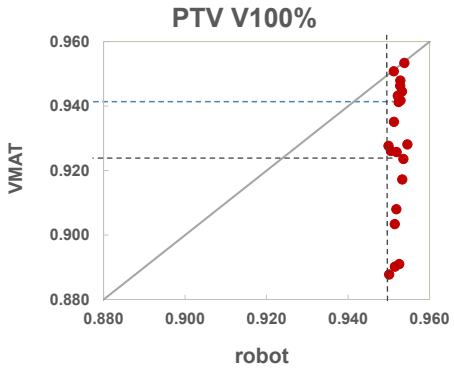
Courtesy Linda Rossi, under review



Results
PTV coverage, $V_{100\%}$

PTV	robot	VMAT	%Diff	p-value
V100% (%)	95.2	93.3	**2.0**	**0.01**

Much better tumor coverage with robot



- robot: 20/20 $V_{100\%} \geq 95\%$
- VMAT:
  - 18/20 $V_{100\%} < 95\%$
  - 11/20 $V_{100\%} < 93\%$ clinically unacceptable

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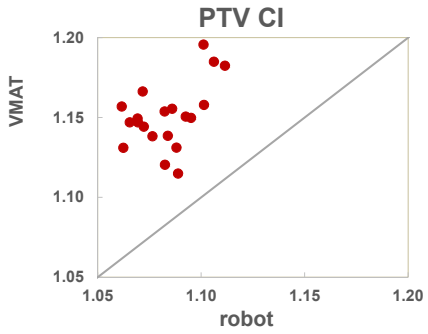
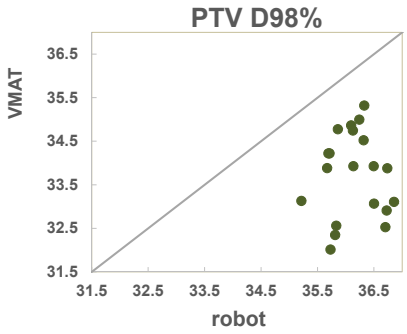
Results
Minimum PTV dose and conformity index

PTV	robot	VMAT	%Diff	p-value
CI	1.08	1.15	**5.6**	**<0.001**
D98% (Gy)	36.1	33.8	**7.2**	**<0.001**

Higher minimum tumor dose and better CI with robot

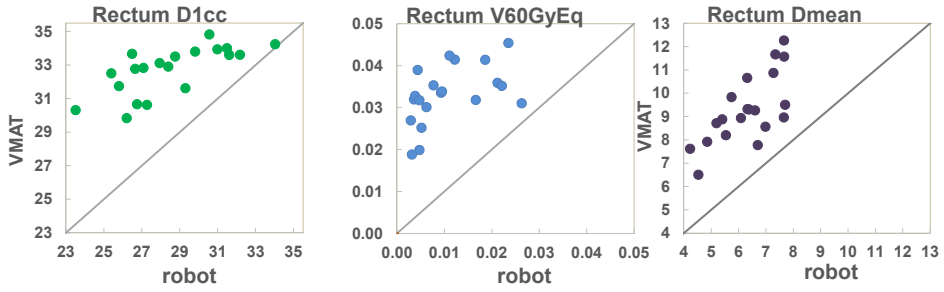




Results
Rectum

Rectum	robot	VMAT	%Diff	p-value
D1cc (Gy)	28.0	32.2	**-13.1**	**0.0001**
V60GyEq (%)	1.1	3.3	**-68.5**	**0.0001**
Dmean (Gy)	6.3	9.3	**-32.0**	**0.0001**

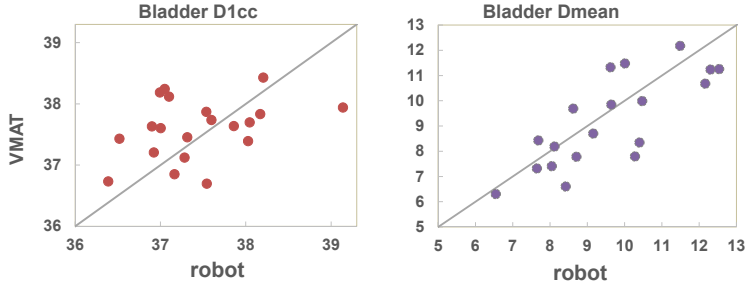
Much better rectum sparing with robot



Results
Bladder

Bladder	robot	VMAT	%Diff	p-value
D1cc (Gy)	37.4	37.6	-0.4	0.4
Dmean	9.7	9.3	5.8	0.1

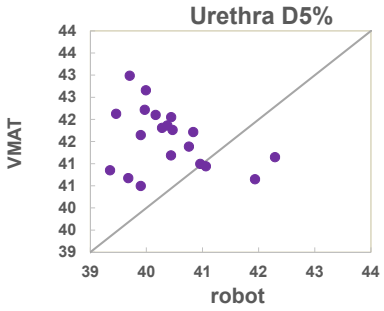
Similar bladder dose

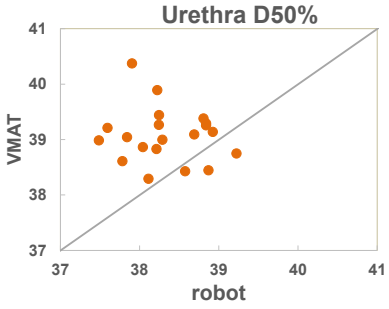


Results
Urethra

Urethra	robot	VMAT	%Diff	p-value
D5% (Gy)	40.4	41.6	**2.8**	**0.001**
D50% (Gy)	38.3	39.1	**1.9**	**<0.001**

Better urethra sparing with robot

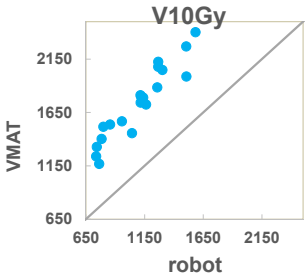


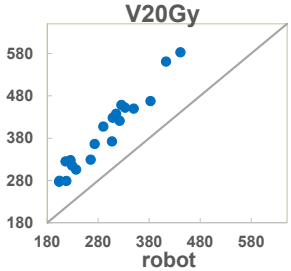


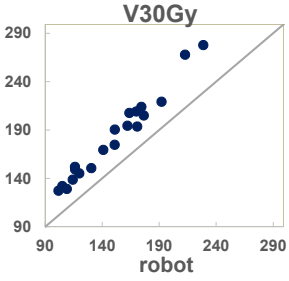
Results
Patient – dose bath

Patient	robot	VMAT	%Diff	p-value
V10Gy (cc)	1137	1789	**37**	**<0.001**
V20Gy (cc)	294	392	**25**	**<0.001**
V30Gy (cc)	150	182	**18**	**<0.001**

Reduced dose bath with robot







‘blinded’ side-by-side plan comparisons by clinician

robot vs. VMAT

	Robot better			Equal	VMAT better		
PTV	4	6	8	2			
Rectum	16	2	2				
Bladder		3	6	11			
Urethra	3	7	5	3	2		
Overall	11	8	1				

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Very clear conclusion for dosimetry!

- **Treatment time?**
- **Clinical impact?**

Erasmus MC

Another treatment technique comparison based on automated planning

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Original article

VMAT plus a few computer-optimized non-coplanar IMRT beams (VMAT+) tested for liver SBRT

Abdul Wahab M. Sharfo *, Maarten L.P. Dirkx, Sebastiaan Breedveld, Alejandra Méndez Romero, Ben J.M. Heijmen

Department of Radiation Oncology, Erasmus MC Cancer Institute, Rotterdam, The Netherlands

Radiother Oncol. 2017; 123(1):49-56

Erasmus MC

Automated planning is a health care innovation that does not increase cost!

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Improvement of dose calculation accuracy

- **Photons**: for EBRT, accuracy seems adequate (even in commercial TPS, if well implemented)
- **Electrons**:
  - Accuracy with Monte Carlo
  - Clinical urgency? #patients ↓, often manual 'planning'
  - MERT
  - Very High Energy Electrons (VHEE)
- **Brachytherapy**: Kari?
- **Protons**:
  - Range uncertainty, dual energy CT, proton beam CT …
  - Include RBE?
- **Ions**: Oliver?

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Enhance optimization- and dose calculation speed

- Make better plans
- Fast, daily on-line (re)planning for adaptive RT (MR-linac, …)
- One-stop-shot palliative treatments
- Plan approval right after contouring

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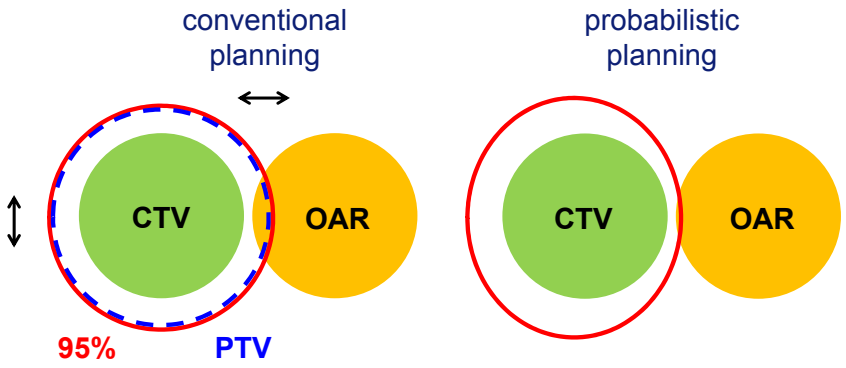
Probabilistic / robust planning to replace PTV/PRV concepts



P(98% of CTV gets dose > 95%) = 98% P(98% of CTV gets dose > 95%) = 98%

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Probabilistic / robust planning to replace PTV/PRV concepts

- Directly optimize CTV/OAR dose
- HOW:
  - cost functions include knowledge on motion

    OR
  - simultaneously optimize multiple scenario's
- If prostate moves anteriorly, then also the proximal part of the rectum
- Automatically generate high dose area around CTV
- Challenges: (individualized) motion pattern, anatomy deformation, calculation speed
- Highly relevant for IMPT (Bragg peak)

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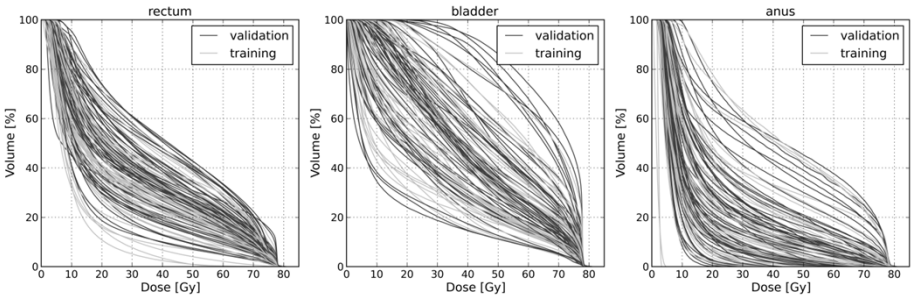
Fully automatic plan QA / plan evaluation



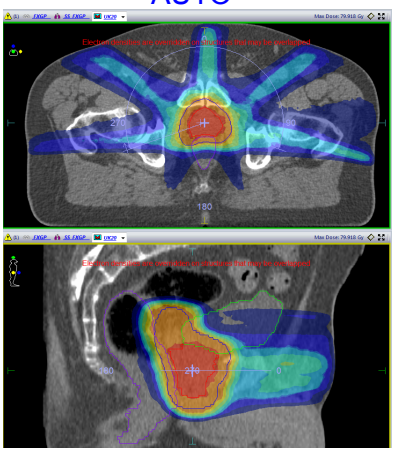
Hugh variation in prostate DVHs due to variations in anatomies (115 patients)

Can a clinician judge whether the dose distribution for an individual patient is optimal?

Courtesy Yibing Wang

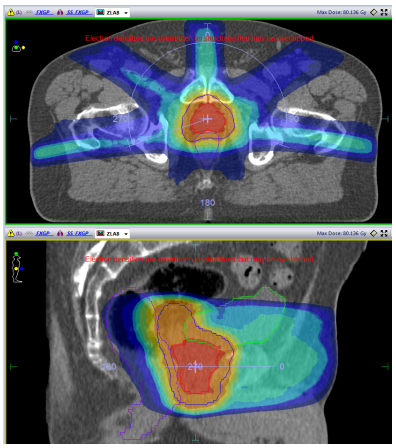
Individual plan scoring for Patient 14

AUTO



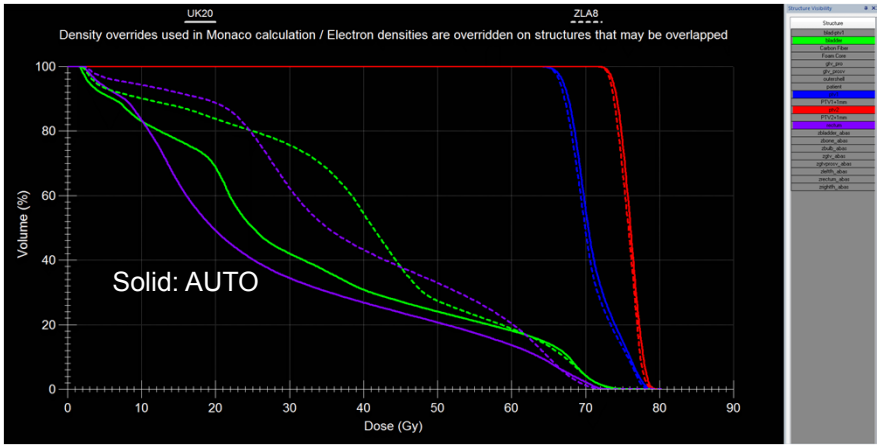
PTV	Rectum	Overall
82	78	80

CLINICAL



PTV	Rectum	Overall
80	80	81

Plan comparison for Patient 14



We need automatic plan evaluation to support clinicians with plan approval.

Machine learning for automated plan QA:

- Input: database of previously approved plans
- Create model to describe relation between anatomy and achieved dose
- Use model for new patients to check plan

Models for machine learning need improvement (e.g. high rectum dose in prostate cancer)

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Trends and research opportunities in Treatment Planning

Sub-fields of research on, or with planning:

- Dose calculation accuracy
- Fast dose calculation and plan optimization
- Probabilistic/robust planning (replace PTV/PRV)
- Automated planning
- Interactive (graphical) planning
- (Non-coplanar) beam angle optimization
- Pareto navigation
- 'Biological' planning
- Evaluation of new treatment techniques
- Automated treatment plan QA
- Spatio-temporal fractionation
- MR-only workflow
- Automatic image segmentation
- Deformable image registration
- Dose accumulation
- …….

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Automated planning – lexicographic multi-criterial optimization (iCycle)

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Knowledge-based automated planning and plan QA (overlap volume histogram, OVH, machine learning)

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ICR The Institute of Cancer Research

CANCER RESEARCH UK

in partnership with
The ROYAL MARSDEN
NHS Foundation Trust

Trends and Research Opportunities in Micro-beam Therapy (MRT)

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These are labeled: Courtesy of EBK

Furthermore, I want to thank the ICR microbeam post-docs and students:

- Stefan Bartzsch, PhD
- Harriet Steel, PhD
- Carol Box, PhD
- Mattia Donzelli

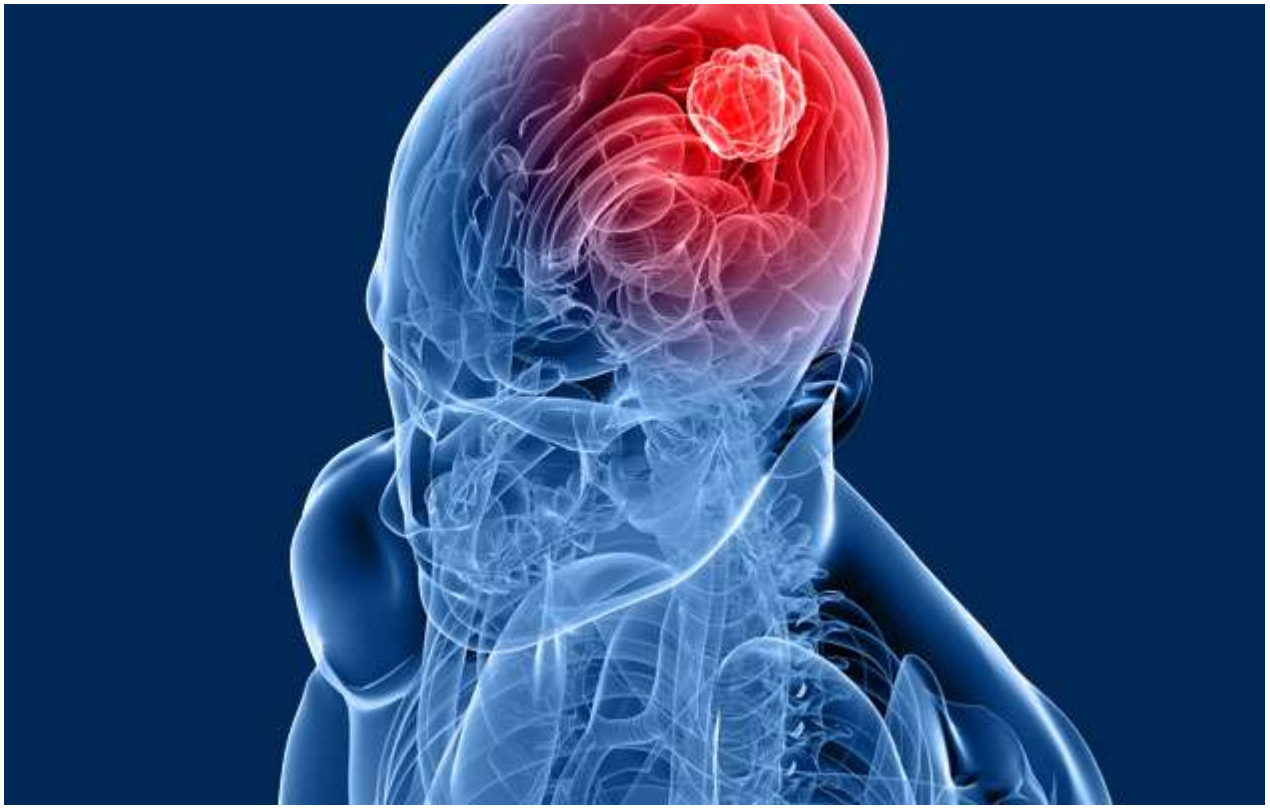
What is widening the TW in RT ?

Space … and

Time…

RT is optimized by modulation of ionizing radiation fields in space and time

Standard spatial Modulation – Binary Macroscopic scale



TIME: Fractionation – Differential Repair Potentials

Who performs micro-beam therapy?

Nobody

How does it work?

We don’t know

What is it good for?

We don’t know

What is micro-beam therapy?

The begining of MRT

An unexpected observation

1959

Tolerance of Mouse-Brain Tissue to High-Energy Deuterons

Abstract. A striking relationship between the size of the impact area of a deuteron beam and the threshold dose for a radiogenic lesion has been noted. The dose required to produce a threshold lesion in mouse brain increases from 30,000 rad with a beam 1000 μ in diameter to 1.1×10^6 rad with a beam 25 μ in diameter.

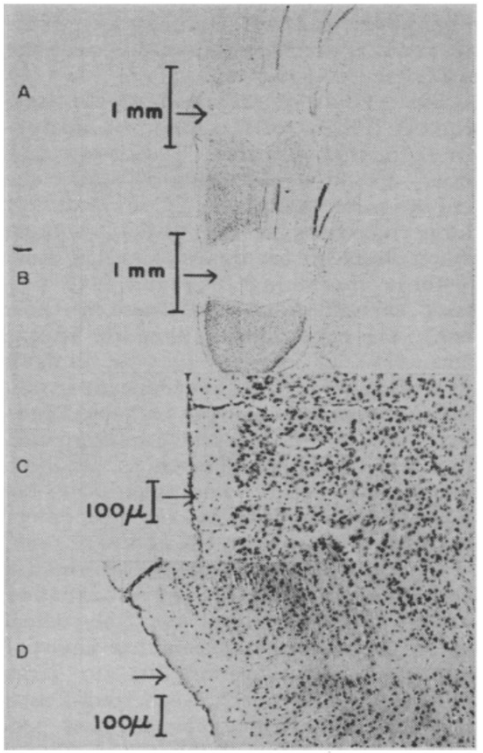
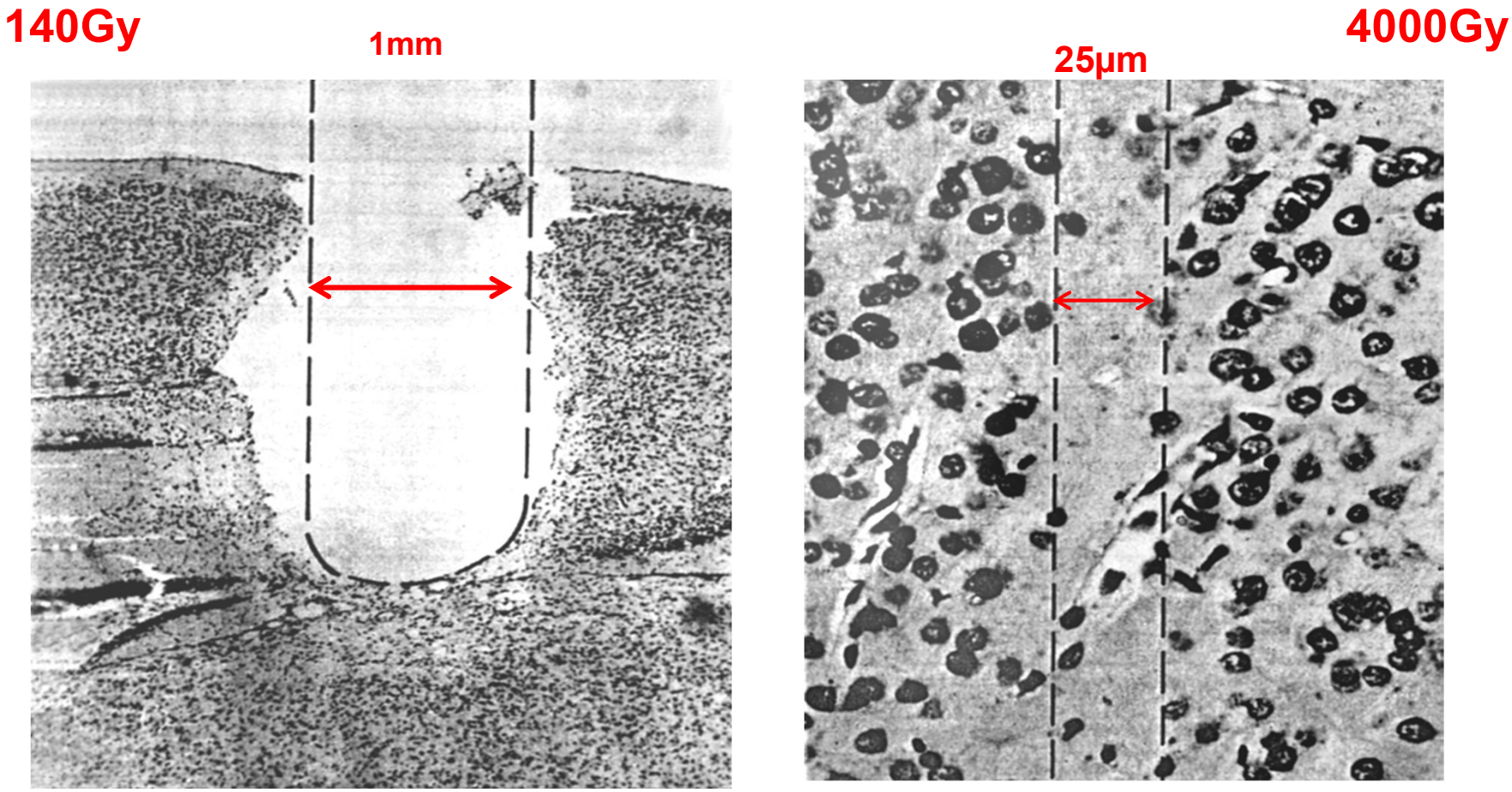


Fig. 1. Frontal sections of visual cortex of mice irradiated with deuteron beams. The arrows indicate the direction of the beam. (A) 1-mm beam, 30,000 rad, 24-day survival; (B) 1-mm beam, 60,000 rad, 24-day survival; (C) 0.025-mm beam, 1.1×10^6 rad, 6-day survival; (D) 0.025-mm beam, 1.1×10^6 rad, 48-day survival.

While investigating the effect of extraterrestrial heavy ion beams on astronauts the astonishing little effect of microbeams on tissue was found.

W Zeman, H J Curtis, E L Gebhard, and W Haymaker. Science, 1959.

The dose volume effect



22 MeV Deuteron beam; cerebral cortex of mice

Zeman et al, Radiat Res 15, 496,1961

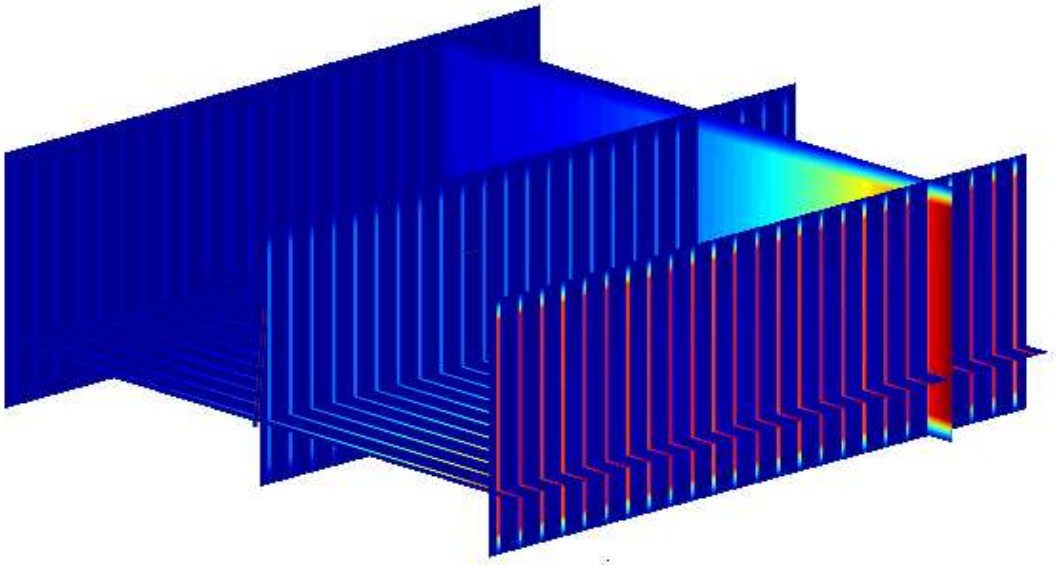
Courtesy of EBK

The begining of MRT

Generation of Microbeams

Creation of microbeams with synchrotron radiation (= photon beams):

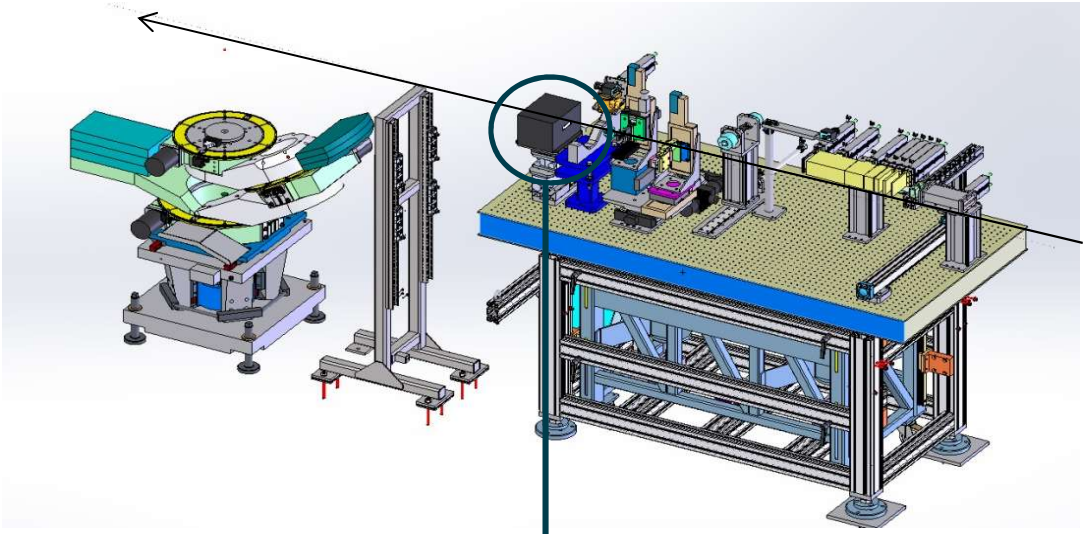
- 25-75 µm wide beams
- 100-400 µm distance (ctc)
- dose rate 16,000 Gy/s
- photon energy 40-150 keV
- even in 15 cm water depth dose gradients remain sharp

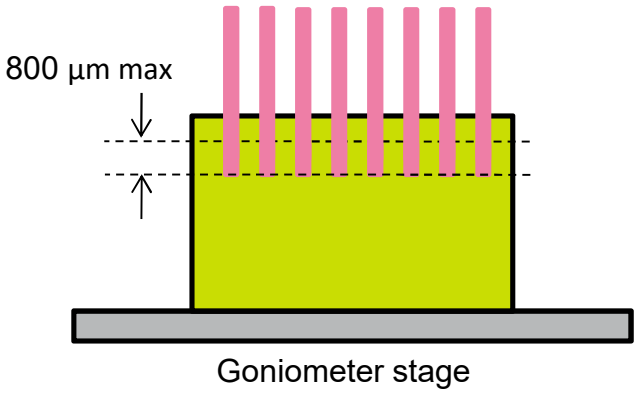


Generation and delivery of micro beams

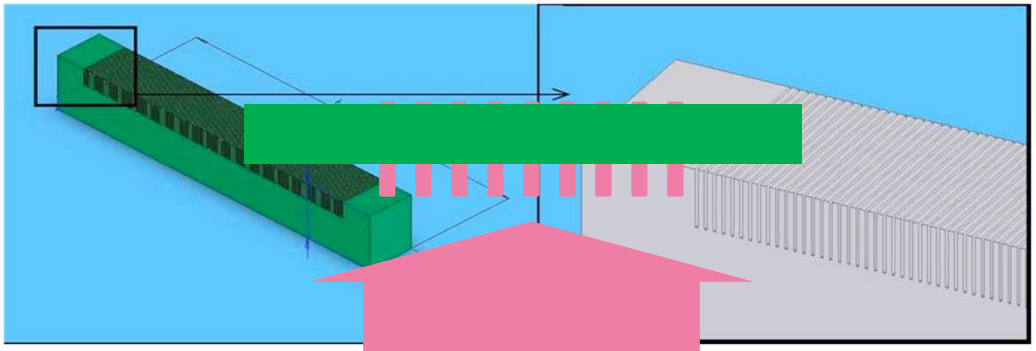
ID17

ID17 biomedical beamline at the ESRF.





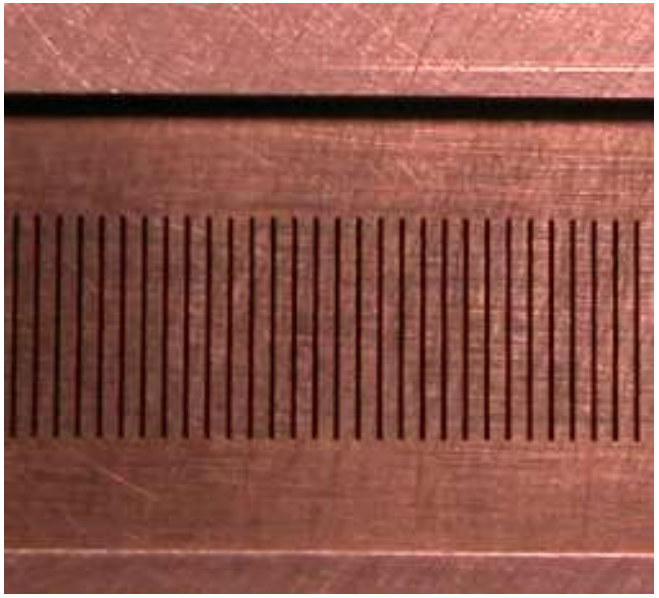
50 µm FWHM microbeams separated by 400 µm



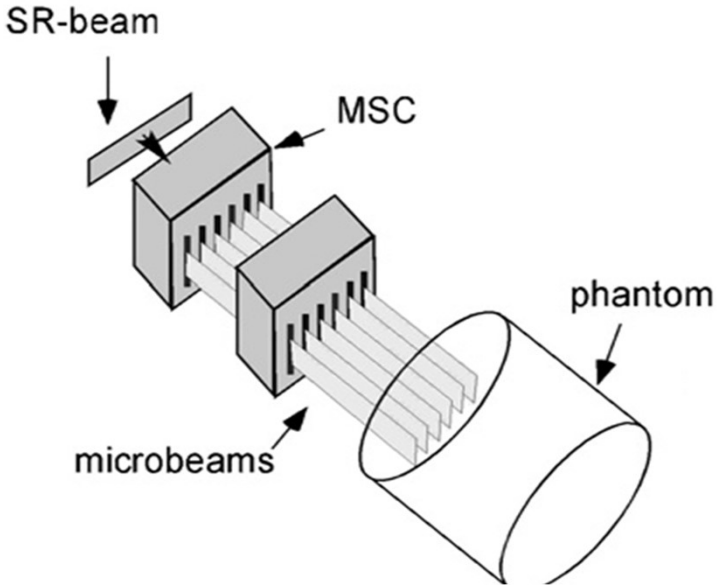
MRT Multi-Slit Collimator (MSC)

Courtesy of EBK

Generation and delivery of micro beams



Tecomet MSC, single stack



TMSC = Multislit collimator

Bräuer-Krisch et al, 2005, Rev Sci Instrum

Slatkin DN et al. Med Phys. 1992. Vol 19. p. 1395-400

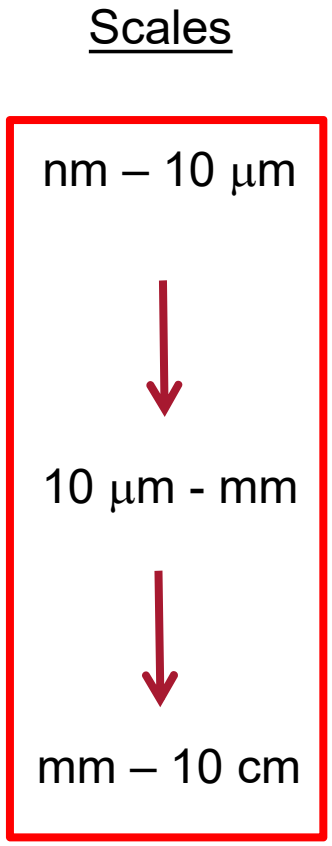
Courtesy of EBK

Therapy – Exploitation of differences – Cancer – Non-Cancer

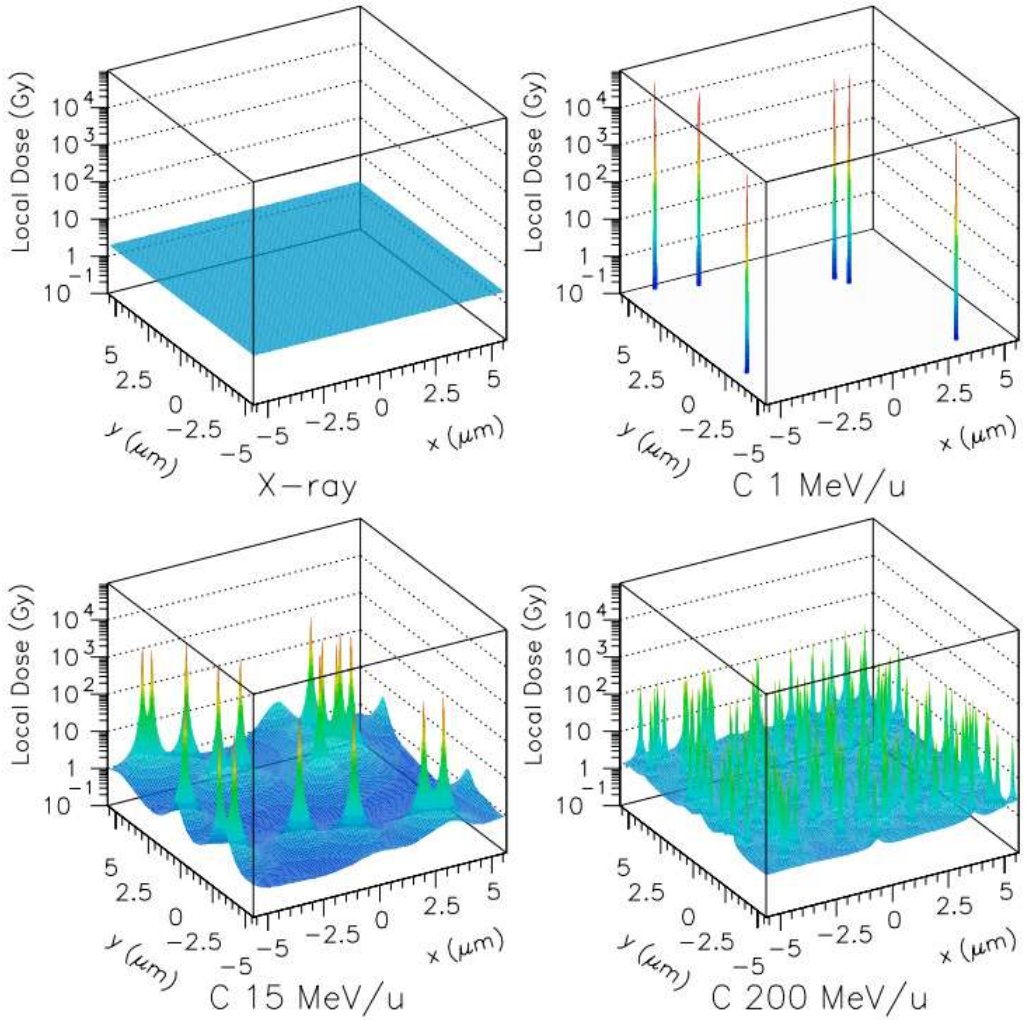
DNA - Cellular

Microenvironment

Macroscopic Lesions

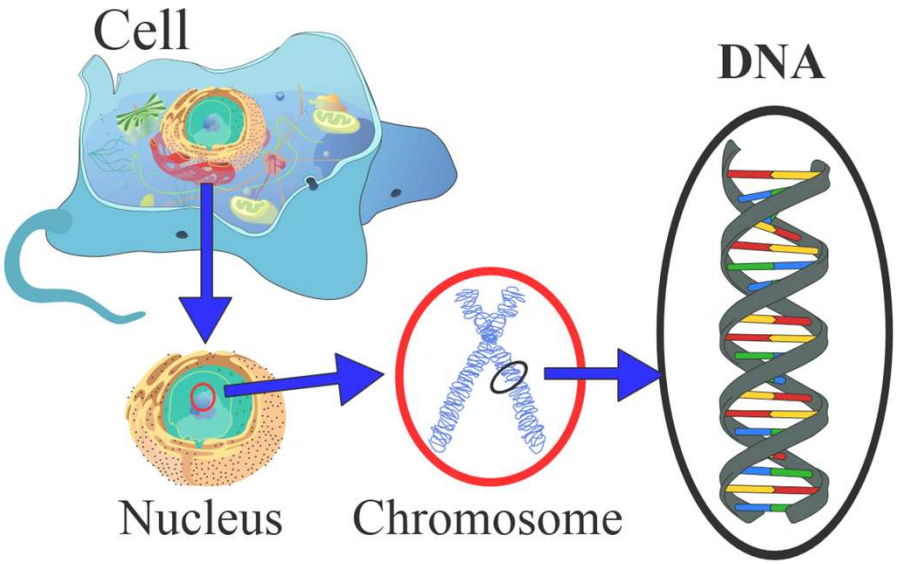


Intrinsic Modulation – Nanoscopic Scale



REVIEWS OF MODERN PHYSICS, VOLUME 82, JANUARY–MARCH 2010

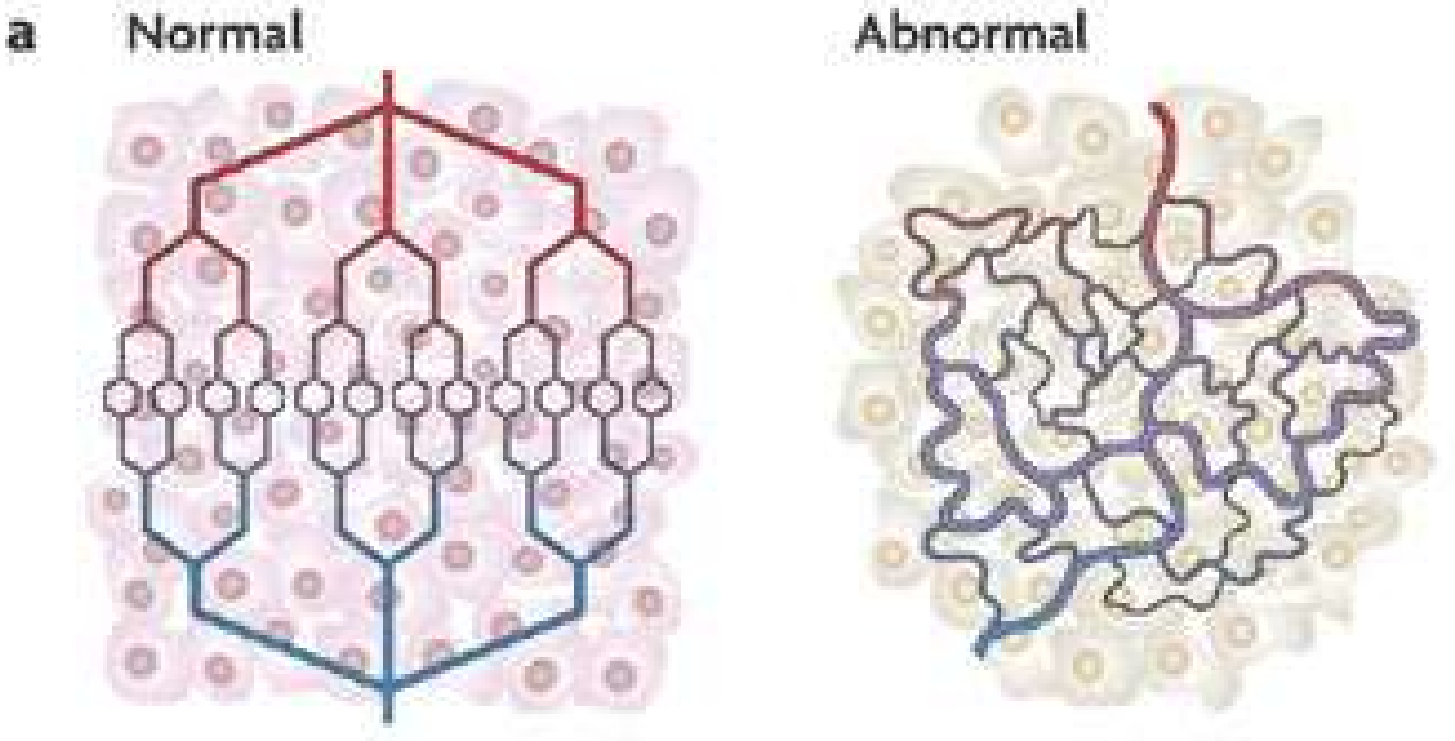
DNA as main RT target (nm)
Dose defined on microscopic scale



$$RBE^{HI}_{p} \approx \sqrt{A}$$

https://en.wikipedia.org/wiki/DNA#/media/File:Eukaryote_DNA-en.svg

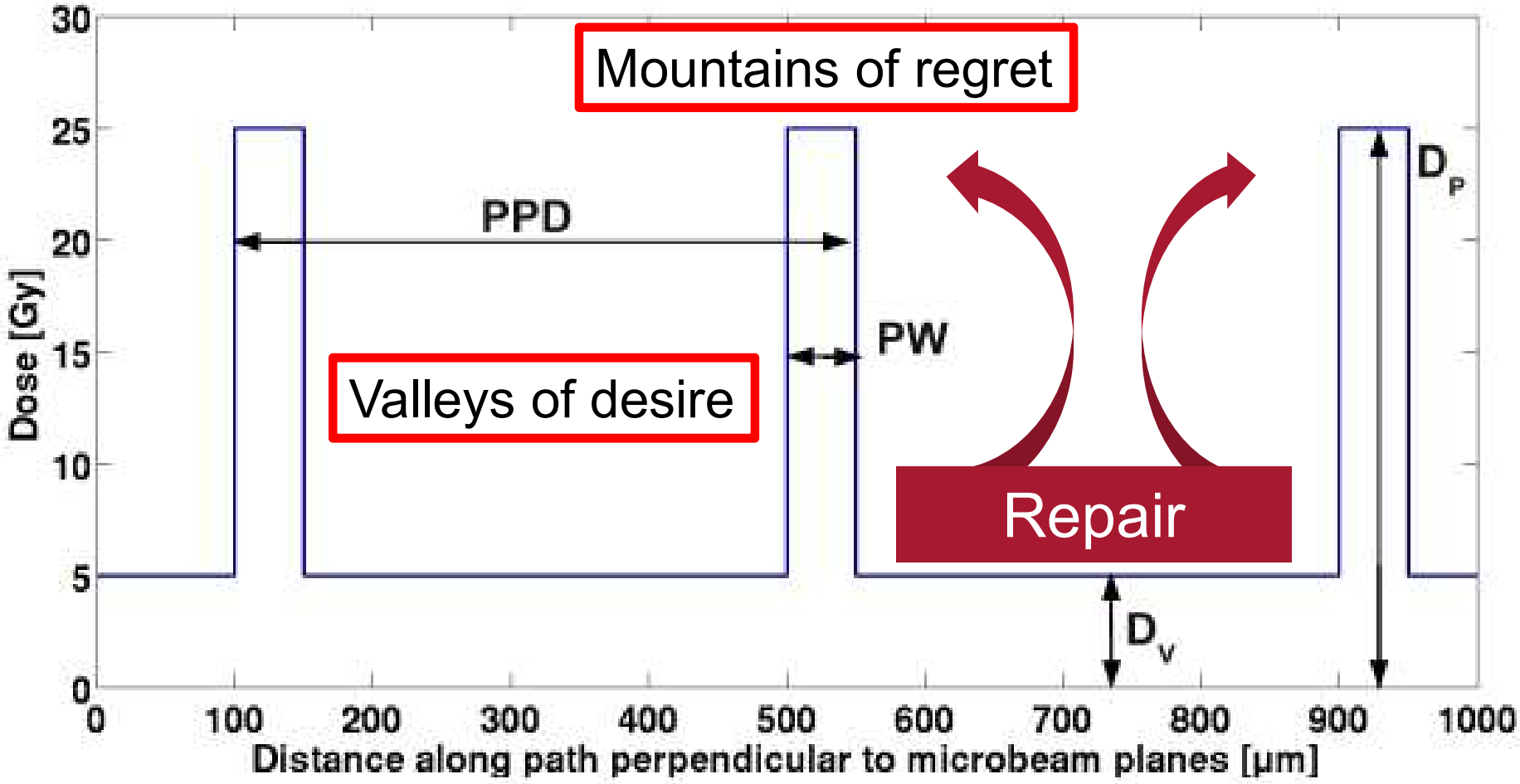
Modulation of RT on the ‘microscopic scale’



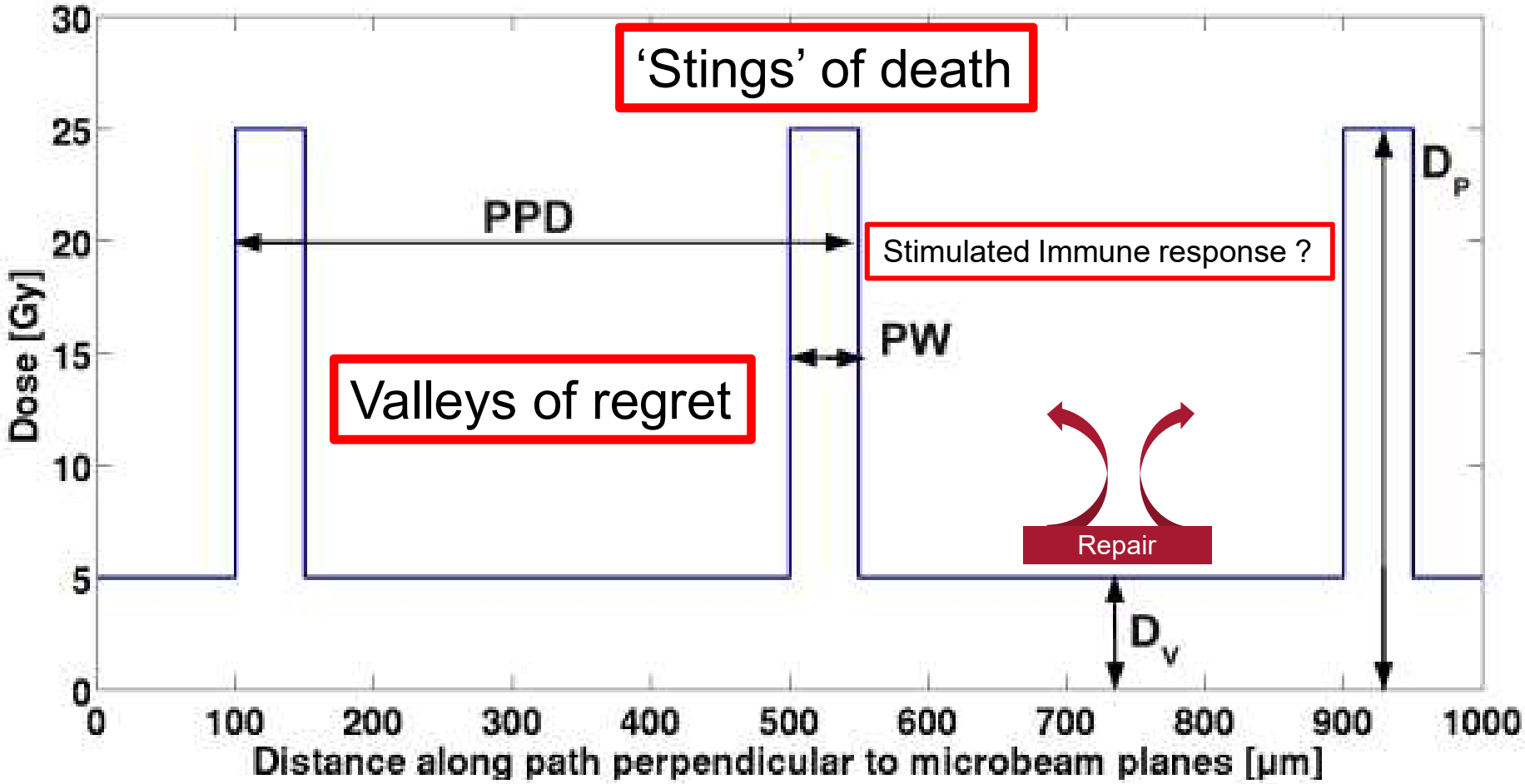
Nature Reviews Cancer 8, 579-591 (August 2008)

Idea: Harvesting of repair processes caused
by a different spatial organisation of the microenvironment

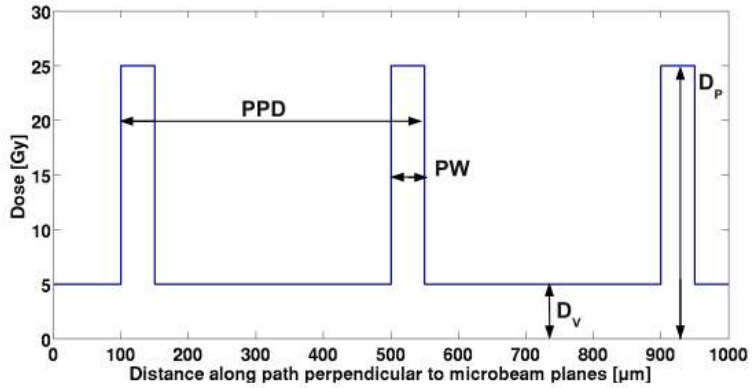
The normal tissue perspective

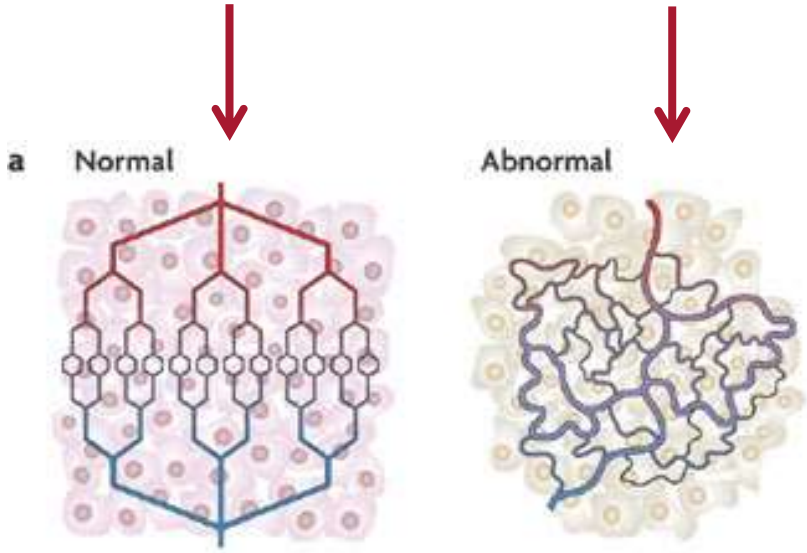


Our ‘tumour’ perspective



The grand challenge of identifying the key biological MRT ‘mechanisms’





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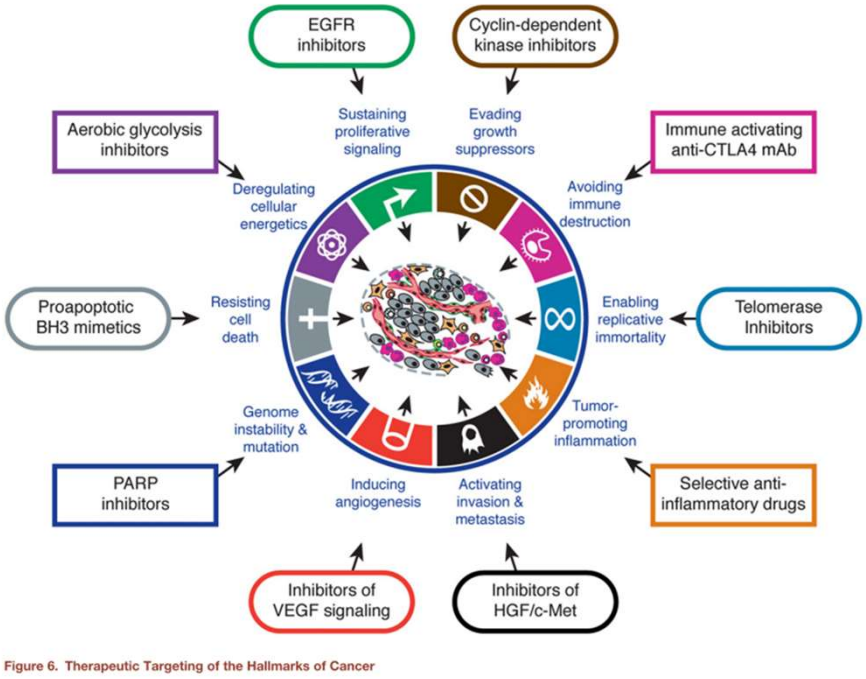


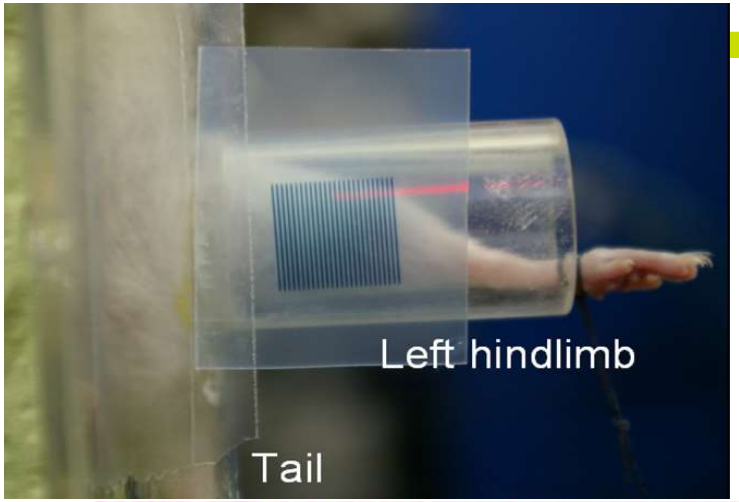
Figure 6. Therapeutic Targeting of the Hallmarks of Cancer

Pre-Clinical Evidence – Mechanisms of MRT?

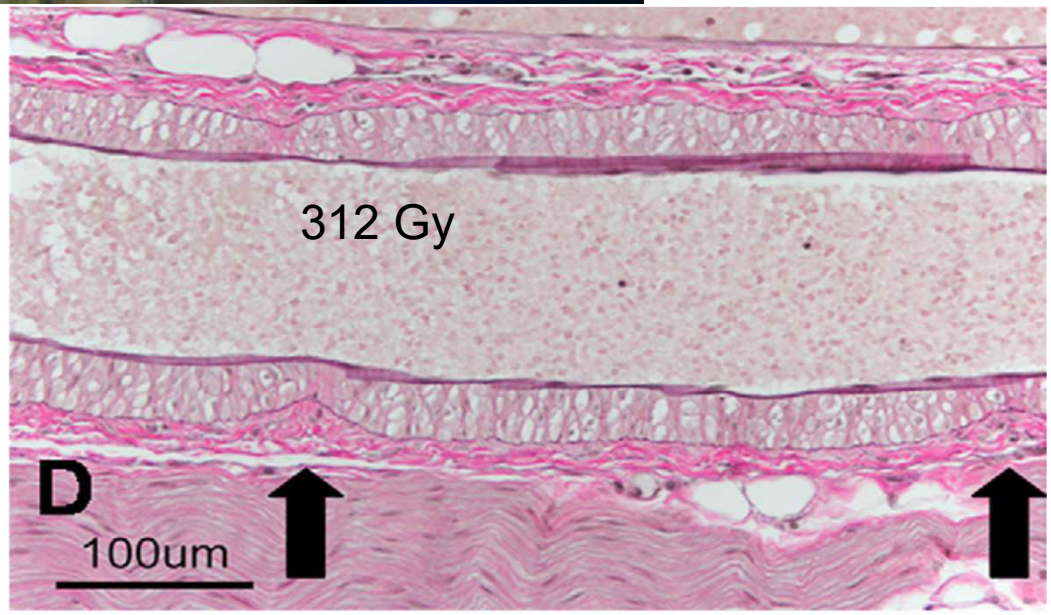
Biological Findings

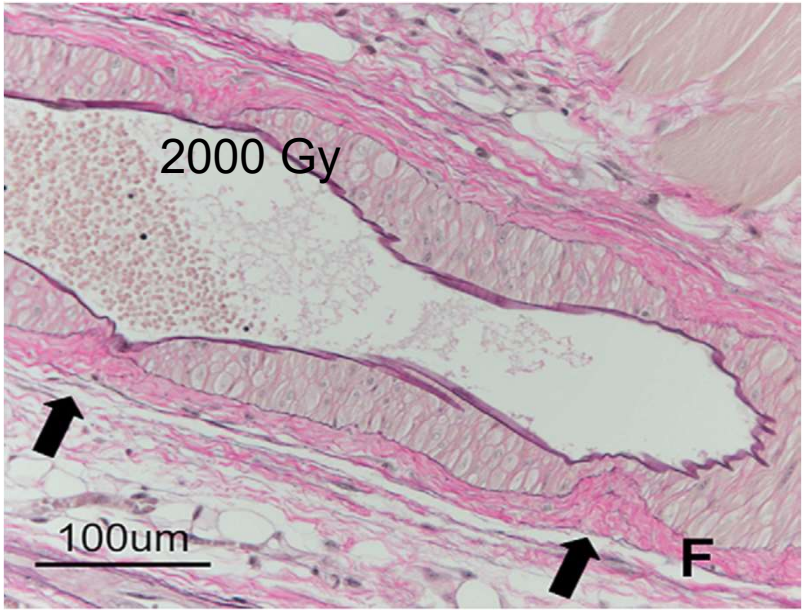
MRT and Normal tissue

OTHER TISSULAR EFFECTS STUDIED IN MICROBEAM RADIATION THERAPY (MRT)



Effects on normal vasculature





No vascular occlusion within 1 year after irradiation

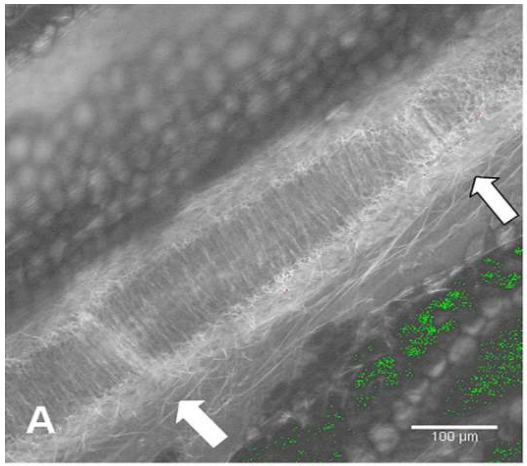
Even for 2000 Gy radiation doses

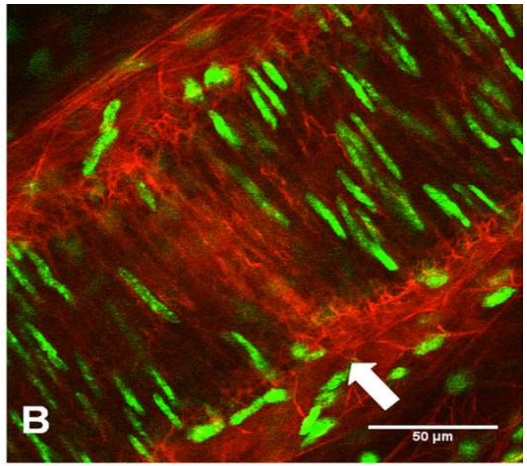
Boudewijn van der Sanden, Elke Bräuer-Krisch et al. “Tolerance of small arteries for high dose X-ray microplanar beams depends on smooth muscle cells of the normal media” Accepted by International Journal of Radiation Oncology, Biology, Physics. Ms. No. ROB-D-09-01479R2

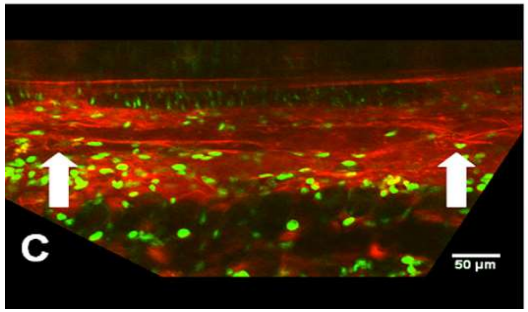
Courtesy of EBK

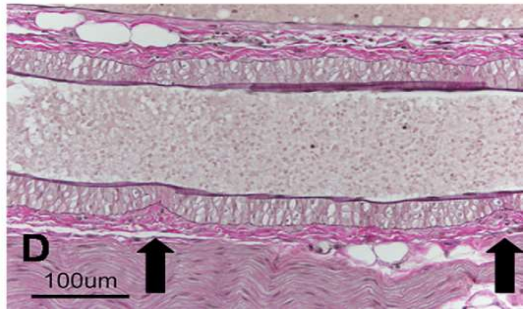
Conclusions

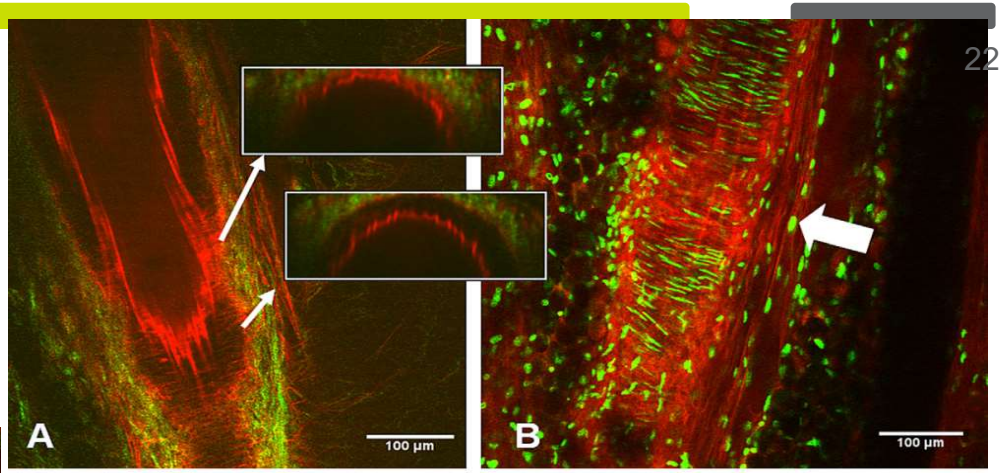
Mice hind leg arteries tolerate doses of up to 2,000 Gy delivered by spatially fractioned MPBs in a single session without occlusion development within 1 year, in contrast to the deleterious consequences of comparable doses delivered by seamless X-rays.

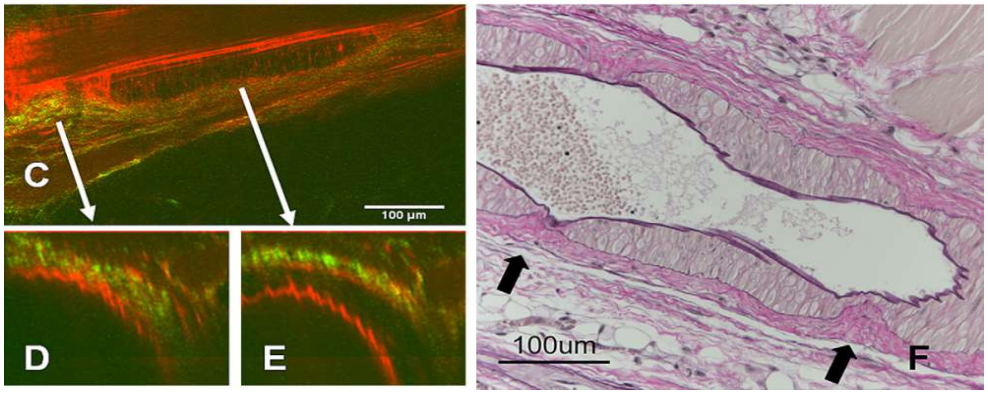










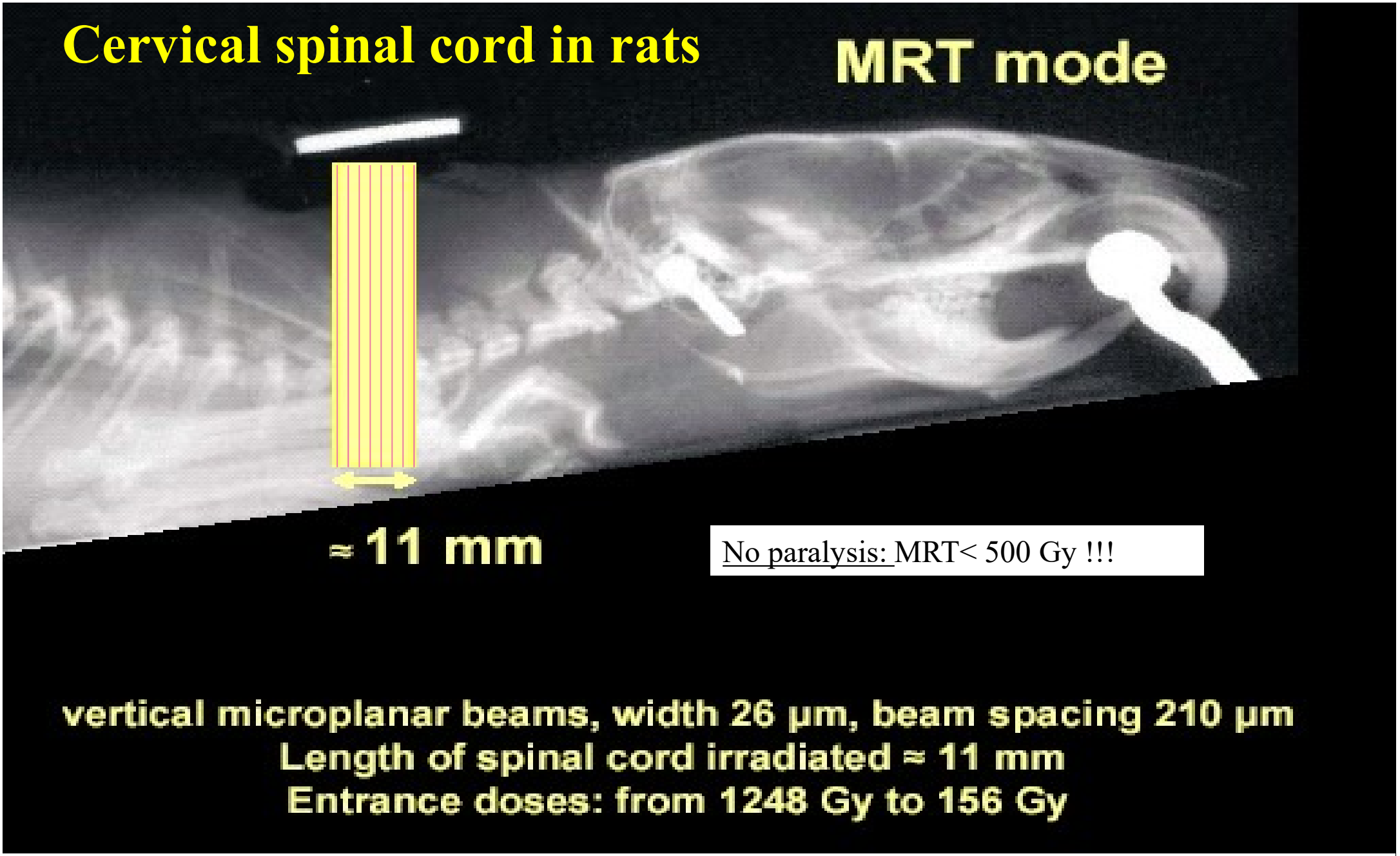


The permanent sequelae of microplanar irradiation appear to be confined.

Boudewijn van der Sanden, Elke Bräuer-Krisch et al. “Tolerance of small arteries for high dose X-ray microplanar beams depends on smooth muscle cells of the normal media ” International Journal of Radiation Oncology, Biology, Physics. Ms. No. ROB-D-09-01479R2

Courtesy of EBK

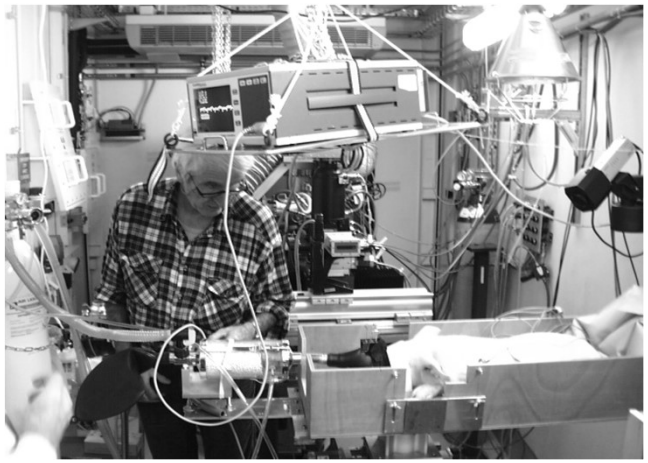
Cervical spinal cord in rats

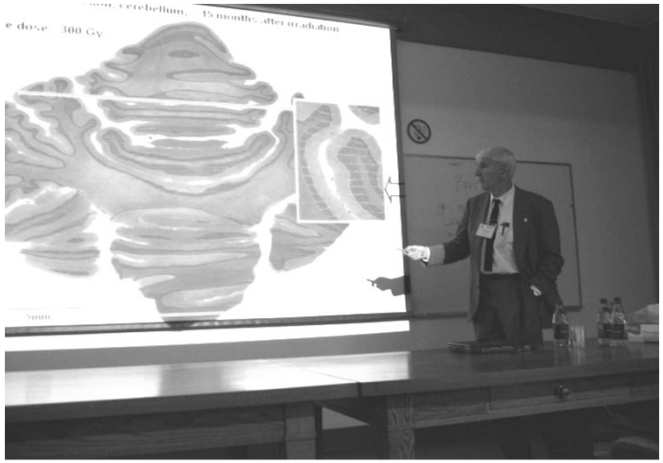


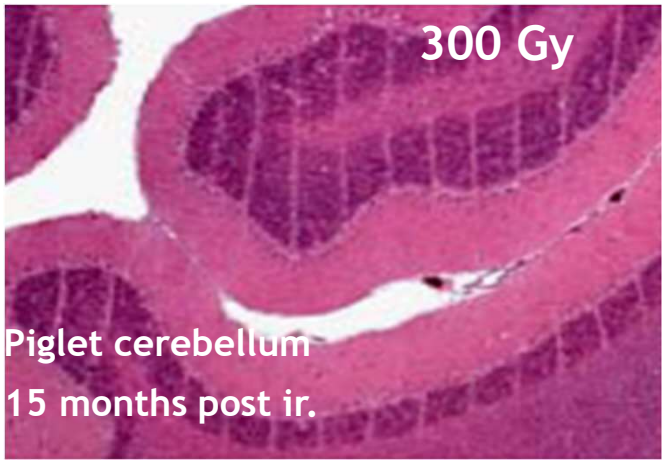
J.A. Laissue , S. Bartzsch, H. Blattmann, , Elke Bräuer-Krisch, A. Bravin, D. Dalléry, V. Djonov, A. L. Hanson, J.W. Hopewell, B. Kaser-Hotz, J. Keyriläinen, P. Laissue, M. Miura, R. Serduc, A. E. Siegbahn, D. N. Slatkin "Response of the rat spinal cord exposed to X-ray microbeams" Radiother Oncol 106, 1 (2013) 106-11

Courtesy of EBK

Normal Tissue Sparing: Piglet cerebellum







- Cell death and damages observed only along the microbeam paths
- No damage in between microbeams
- No macroscopic tissular necrosis observed as in conventional therapy

Hyp: no necrosis ↔ no damage on normal brain vasculature

Laissue *et al*. *Proceedings of SPIE*. 4508. 2003
Dilmanian *et al*. *Neuro-oncol*. 2002. Vol 4. p. 26-38
Slatkin DN *et al*. *Med Phys*. 1992. Vol 19. p. 1395-400

Courtesy of EBK

Differential Biological Effects of MRT

Damage induced by MRT depends on the ‘maturity of the vasuclar system

Example 1: Irradiation of the chorioallantoic membrane (CAM)

Example 2: Irradiation of fins of zebra fish

MB irradiation of the chorioallantoic membrane (CAM)

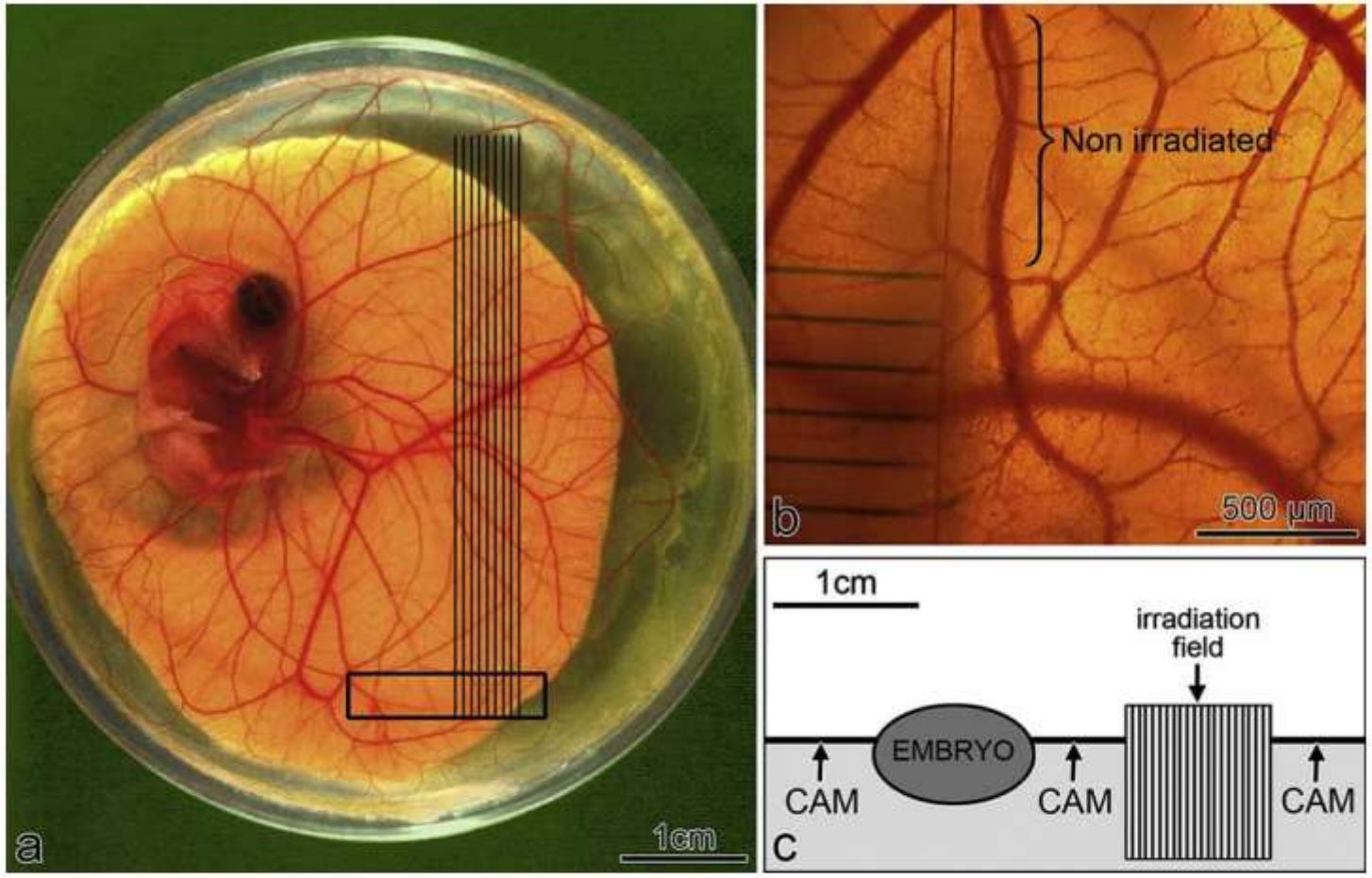
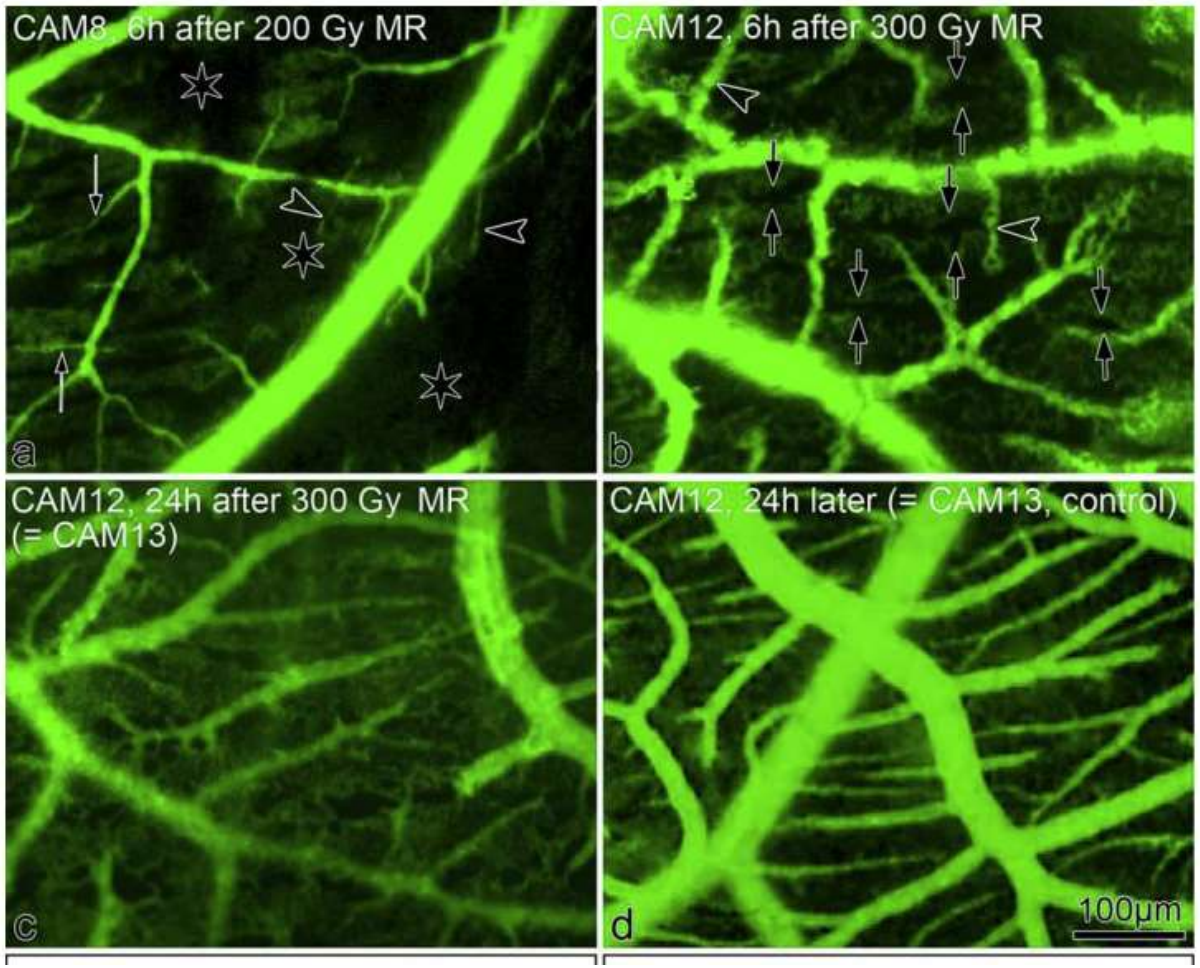


Fig. 1. CAM is shown as the thin well-vascularized membrane on the top of the shell-free cultured chick embryo. (a) Black parallel lines illustrate the MR beam conduit. (b) Black stripes on the radiochromic film indicate the entering path of the vertical microplanar beam in the irradiated region: the on-center spacing of these stripes is ~20.0 μm. (c) Schematic representation of the position of the embryo, the CAM, and the irradiation field.

Sabatasso, S et al "Microbeam radiation-induced tissue damage depends on the stage of vascular maturation" International journal of radiation oncology, biology, physics, 80, 5, 1522-32, 2011

CAM8 = 8 days mature membrane ; CAM12 = 12 days mature membrane



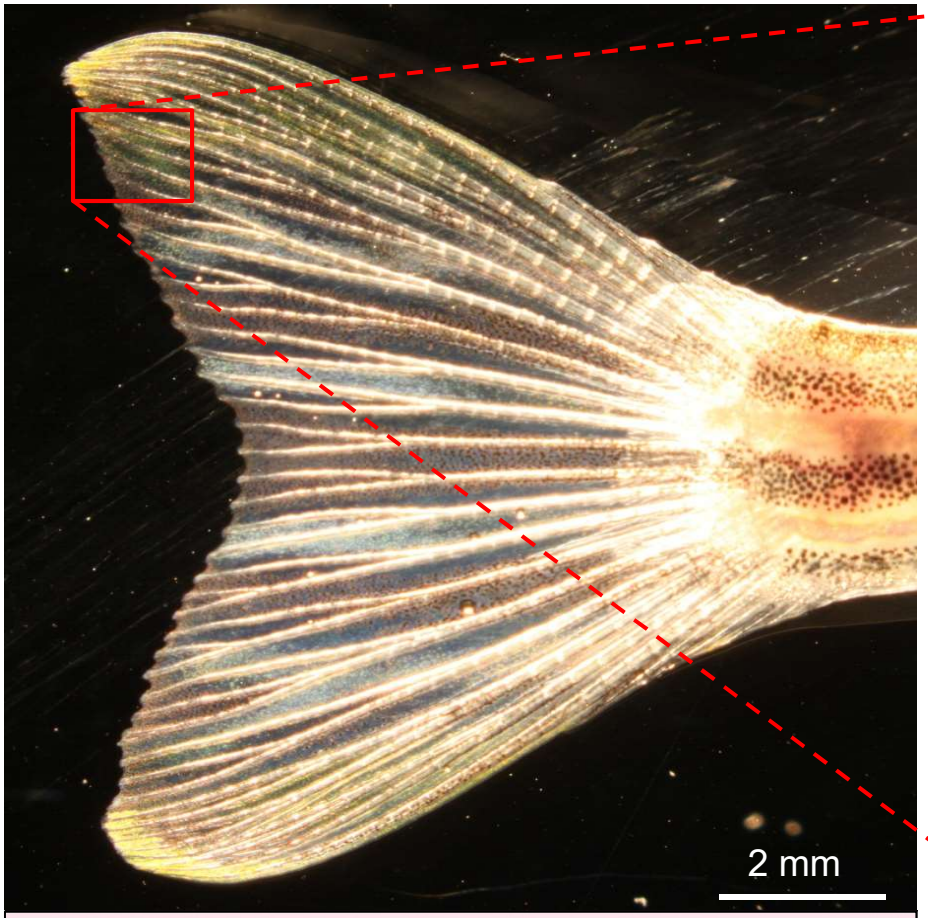
* = lack of perfusion

arrow = destruction of small supply blood vessels

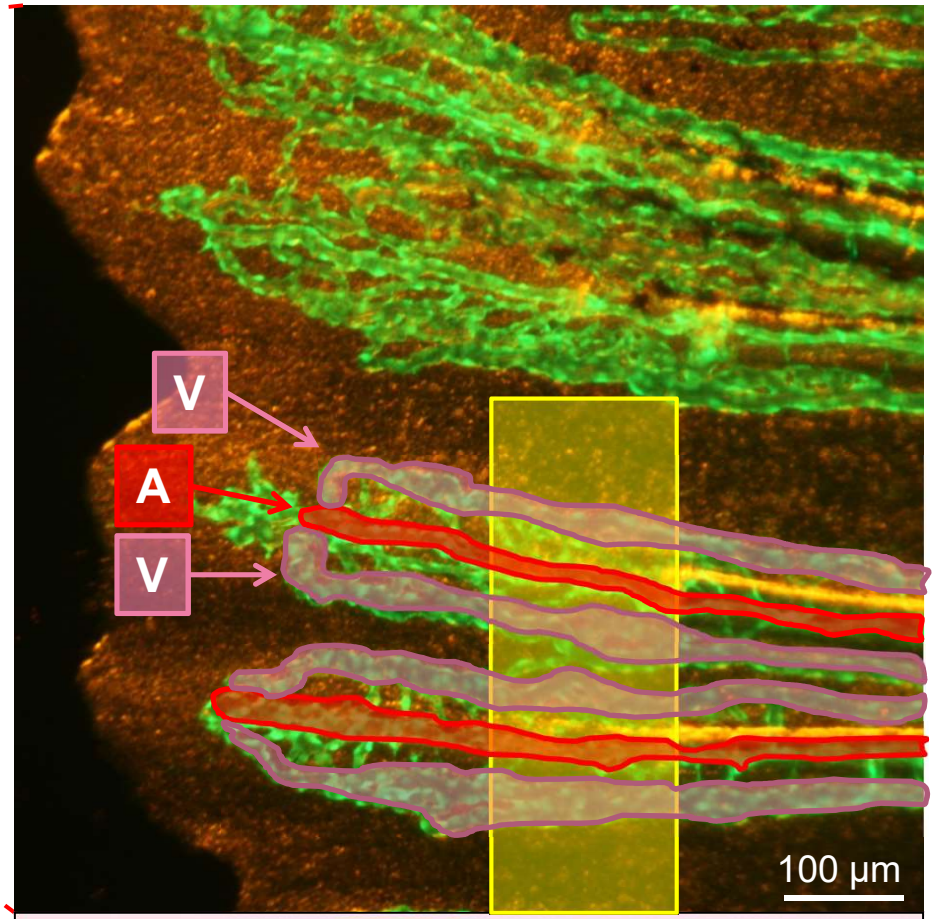
CAM12 almost recovered after 24 hours

Sabatasso, S et al “Microbeam radiation-induced tissue damage depends on the stage of vascular maturation” International journal of radiation oncology, biology, physics, 80, 5, 1522-32, 2011

MB irradiation of Zebrafish: Structure of Caudal Fin



16-18 fin rays & bifurcations

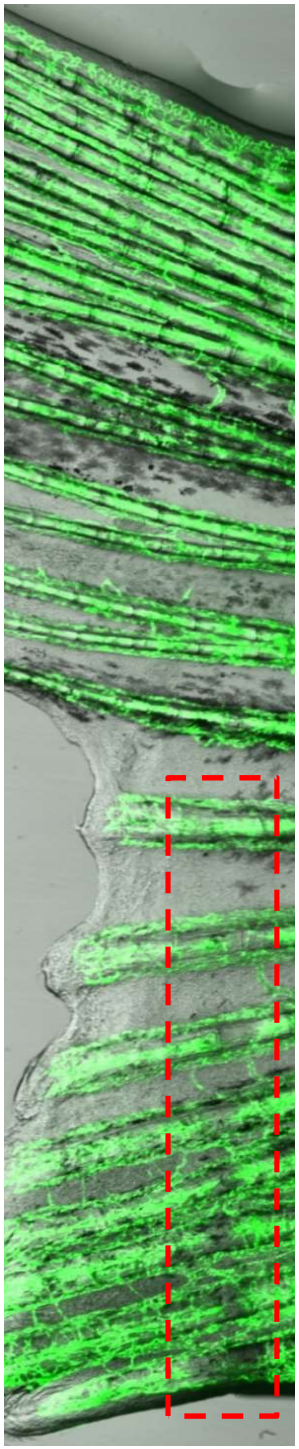


Transgenic fli1-eGFP

2 veins & 1 artery per fin ray

Daniel Broennimann, Audrey Bouchet, Christoph Schneider, Marine Potez , Raphaël Serduc, Elke Bräuer-Krisch, Werner Graber, Stephan von Gunten, Jean Albert Laissue and Valentin Djonov Synchrotron microbeam irradiation induces neutrophil infiltration, thrombocyte attachment and selective vascular damage in vivo Scientific reports, 2016

Courtesy of EBK



Beam Width 100µm, 6 hpi (hours post irradiation)

Morphology

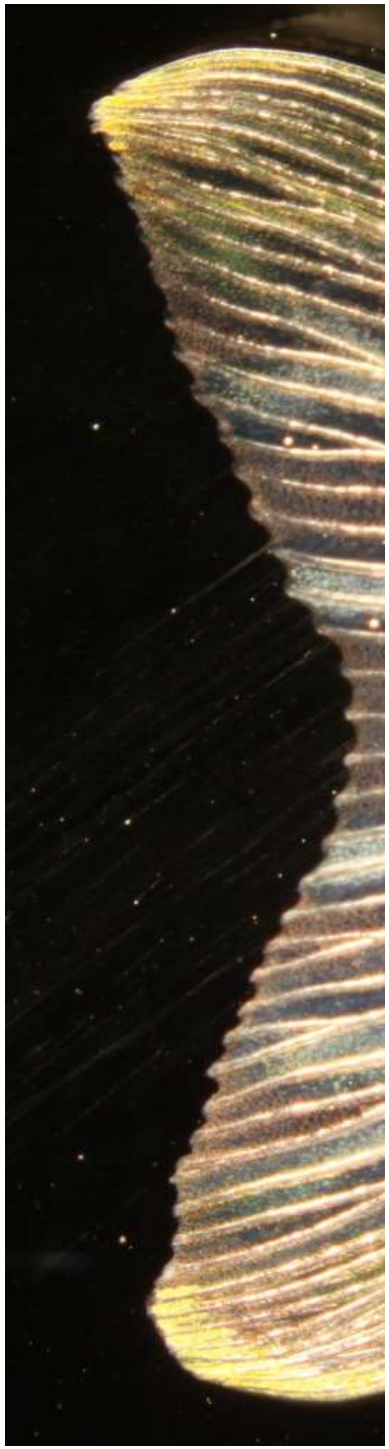
Dorsal: Non-amputated part

Ventral: Regenerated part

→ Vascular damage visible only in the immature caudal fin

→ Blood vessels are heavily damaged

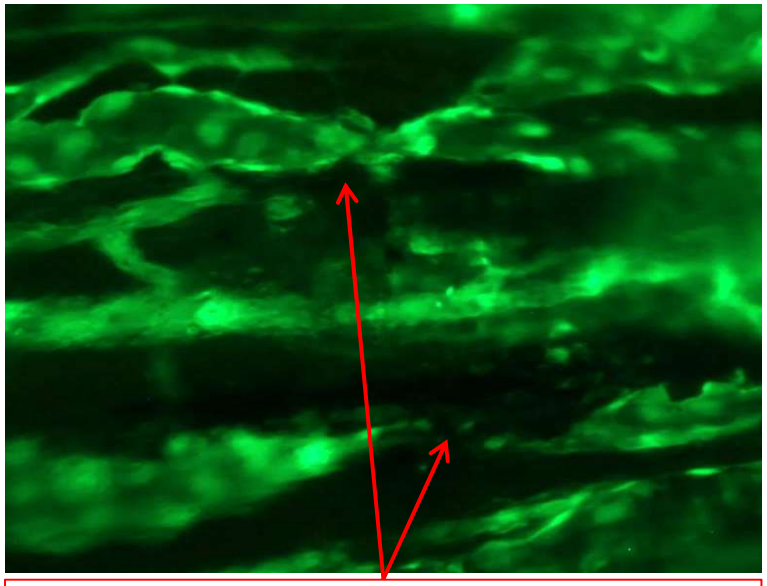
Courtesy of EBK



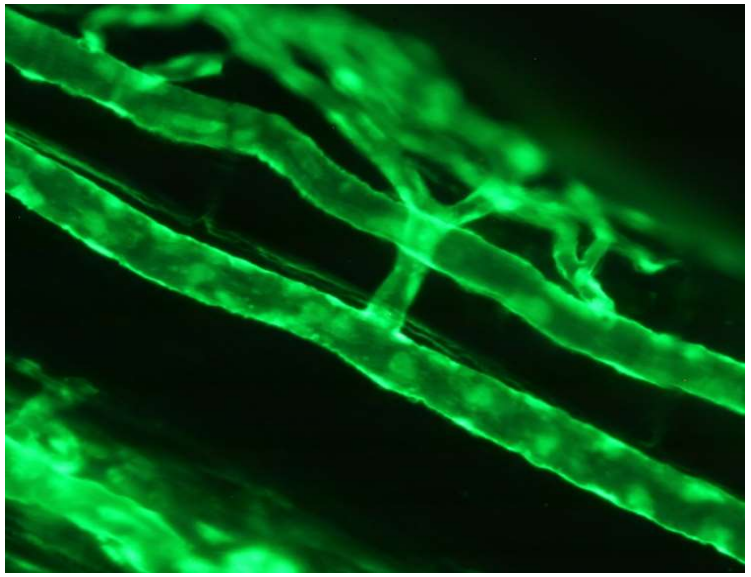
MB irradiation of Zebrafish

Beam Width 100µm, 6 hpi (hours post irradiation)

Morphology



Interrupted vessels in beampath

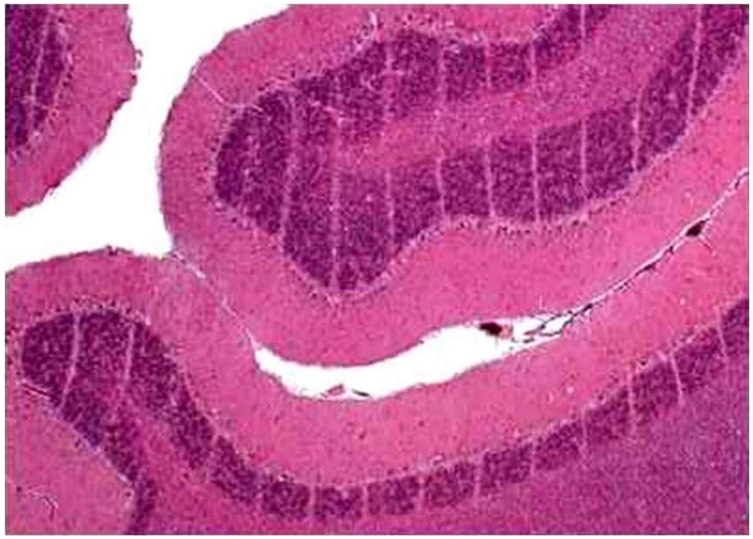


Intact vasculature

Conclusion: Zebrafish is a good model to study the sensitivity to MBs, clearly depending on the developing state of the vasculature with similarities between normal tissue vasculature and tumor vasculature.

Daniel Broennimann, Audrey Bouchet, Christoph Schneider, Marine Potez , Raphaël Serduc, Elke Bräuer-Krisch, Werner Graber, Stephan von Gunten, Jean Albert Laissue and Valentin Djonov Synchrotron microbeam irradiation induces neutrophil infiltration, thrombocyte attachment and selective vascular damage in vivo Scientific reports, 2016

Courtesy of EBK



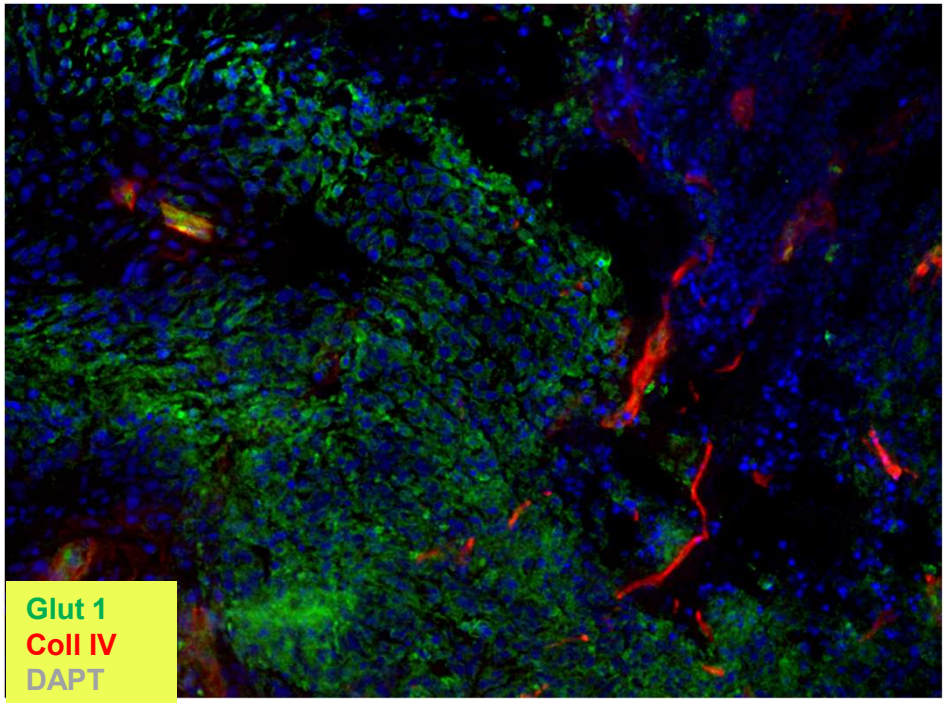
Laissue et al., 2001

Extraordinary normal tissue sparing

Cellular damage confined to microbeams

No macroscopic lesions

No changes in vascular permiability



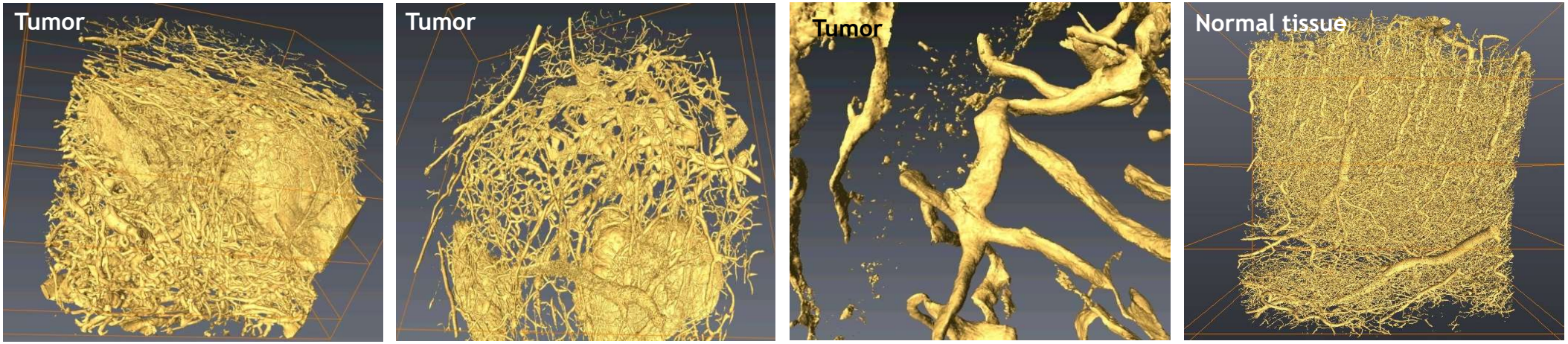
[Bouchet et al., 2010]

MRT reduces tumor blood supply

➔ tumor hypoxia

Courtesy of EBK

MRT AND BLOOD VESSEL PERMEABILITY



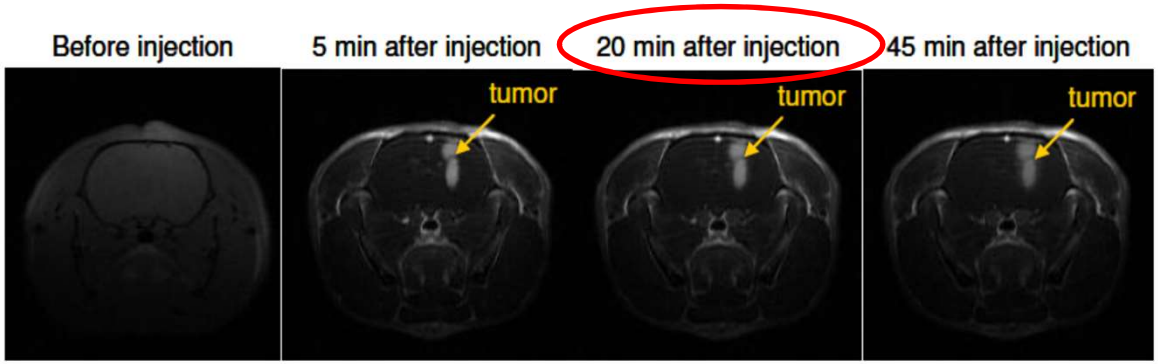
- Significant increase in tumor vessel permeability at short term after MRT (D2-5)

- No change in normal brain tissue within the same period

Specific delivery of drugs – chemical compounds to tumoral tissue

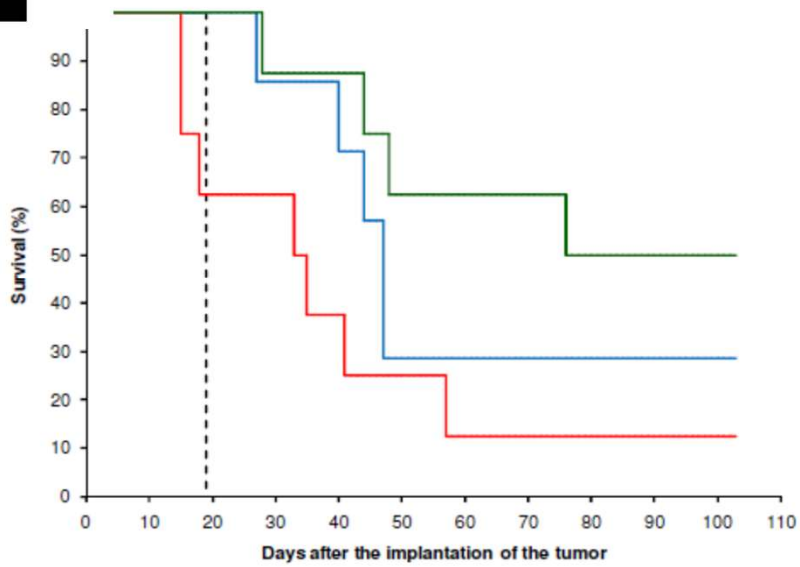
Courtesy of EBK

Microbeams and Radiosensitizer



MRI results of rat brain glioma before and 5, 20 and 45 minutes after injection of gadolinium NPs.

9LGS bearing rats, without treatment (black dashed curve, only treated by MRT (blue curve) and treated by MRT 5 minutes (red curve) and 20 minutes (green curve) after NPs intravenous injection. The MRT irradiation was done in cross fired mode: 50 micron FWHM, spacing of 211 microns. The skin entrance dose was set up at 400 Gy for the peak.



Le Duc G, Miladi I, Alric C, Mowat P, Bräuer-Krisch E, Bouchet A, Khalil E, Billotey C, Janier M, Lux F, Epicier T, Perriat P, Roux S, Tillement O. Toward an image-guided microbeam radiation therapy using gadolinium-based nanoparticles. ACS Nano. 2011 Dec 27;5(12):9566-74. Epub 2011 Nov 9.

"The High Radiosensitizing Efficiency of a Trace of Gadolinium-Based Nanoparticles in Tumors" by Dufort S, Le Duc G, Salomé M, Bentivegna M, Sancey L, Bräuer-Krisch E., Requardt H, Lux F, Coll JL, Perriat P, Roux O, Tillement O. Scientific Reports, 2016

Courtesy of EBK

MRT and interaction with the vasculary network

- Severe damage of immature and small blood vessels – no repair
- Much reduced damage at mature blood vessel systems – repair
- Tumour blood vessel networks are more immature – differential enhanced damage when compared to normal tissue
- MRT seems to ‘open’ the blood brain barrier ‘significantly’ – increased time window for efficient drug delivery

ICR The Institute of Cancer Research

CANCER RESEARCH UK

in partnership with

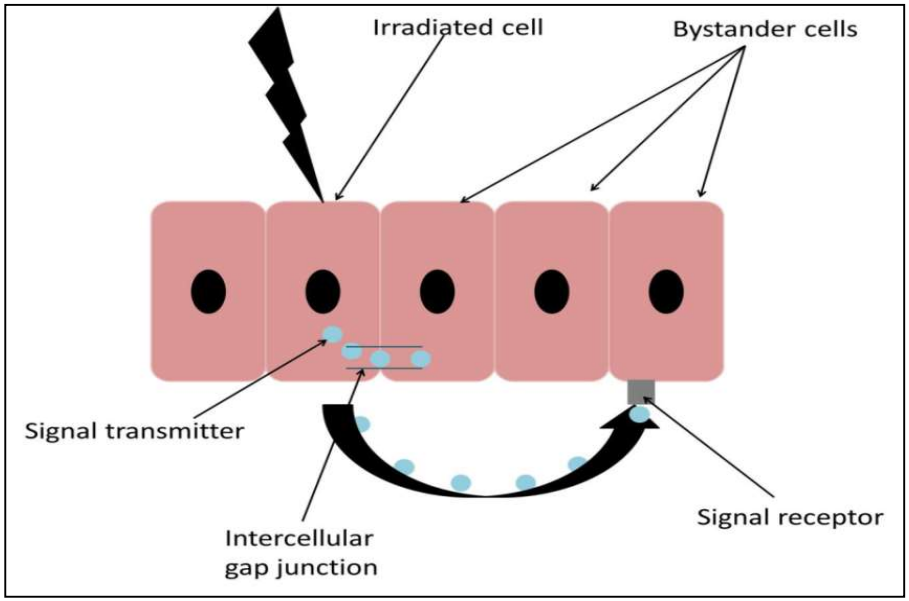
The ROYAL MARSDEN NHS Foundation Trust

Microbeam Therapy and Bystander effects?

H. Steel, C. Box, S. Bartzsch, UO

Microbeam therapy (MRT) and the bystander effect

- MRT has been shown to effectively treat tumours in vivo but has a sparing effect on normal tissues
- The mechanism underpinning MRT is not yet understood; bystander signaling has been implicated
- Not all cells are able to induce bystander effect though rapidly dividing cells, i.e. tumour cells, may be more susceptible to bystander signals
- Conflicting reports as to why some cells produce bystander signals and others don't; p53 status has been implicated



Methodology

3 human cell lines:

- MRC-5, normal lung fibroblasts
- A549, lung cancer, p53 wild-type
- NCL-H23, lung cancer, mutant p53

Irradiation:

- broadbeam
- microbeam

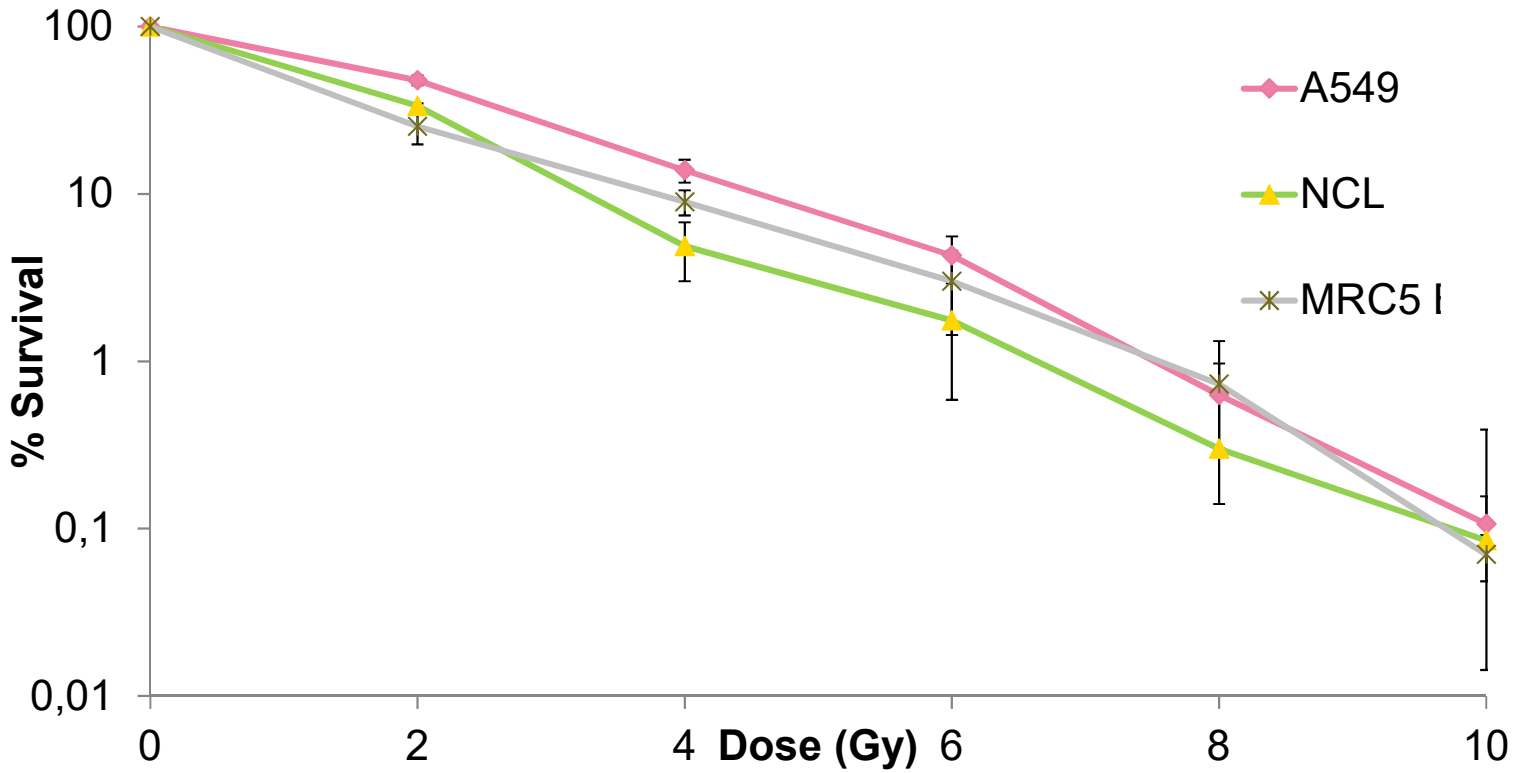
2D clonogenic assays:

- conventional measure of cell sensitivity to radiation

3D cell culture assays:

- spheroid growth curves
- cell viability assay
- image changes in spheroid morphology

Cell lines are similarly sensitive to broadbeam radiation

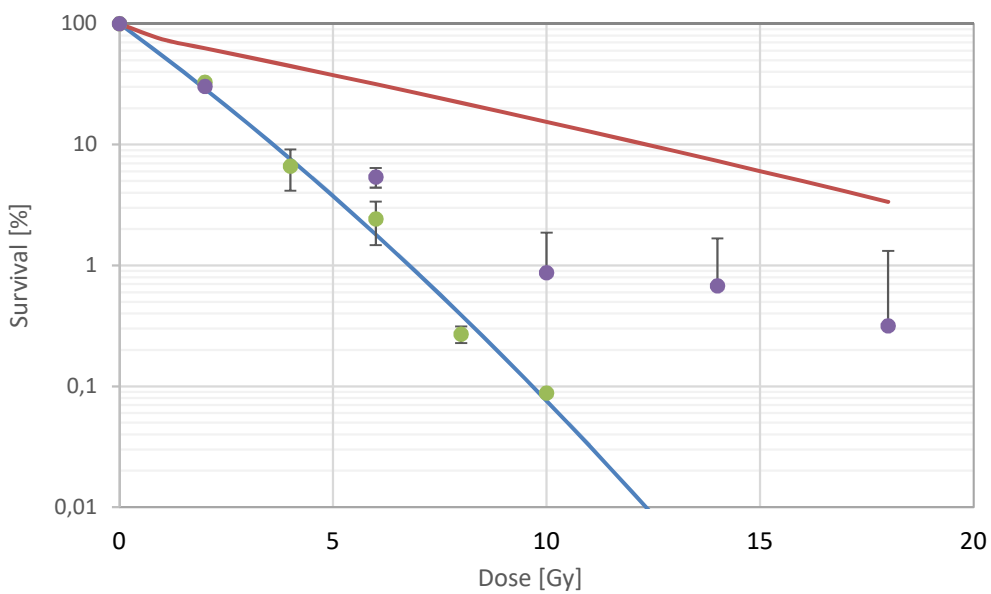


Reduced survival of cancer cells following microbeam irradiation

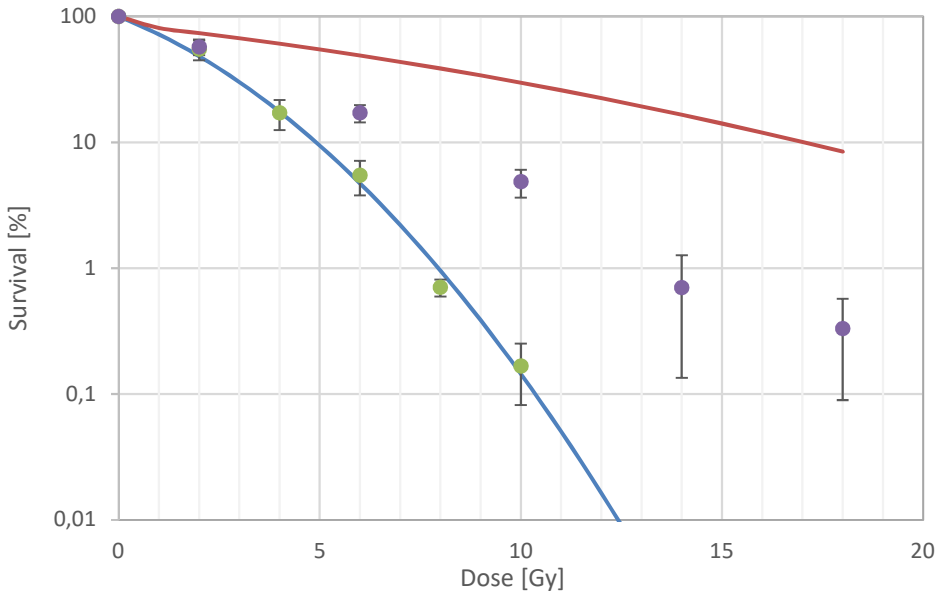
Clonogenic survival data following broad beam irradiation was fitted to a linear quadratic model

From this, survival following microbeam irradiation was predicted, assuming no communication between cells in the peaks or in the valley

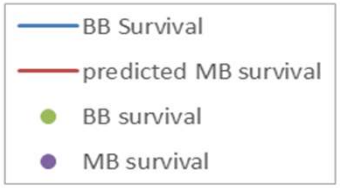
Actual microbeam survival data was then plotted



NCL-H23

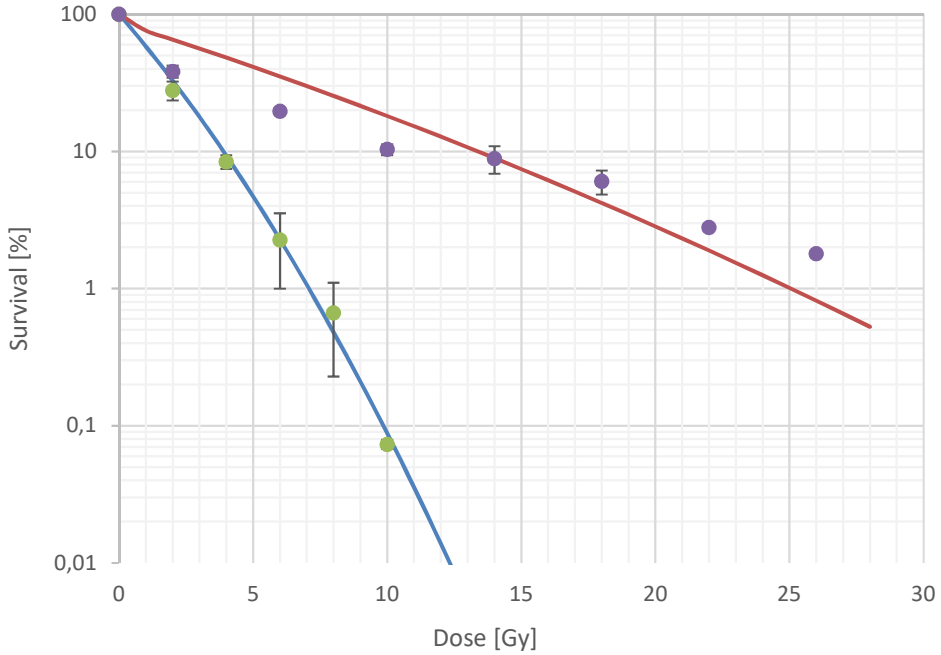


A549



This suggests that there is communication between cells

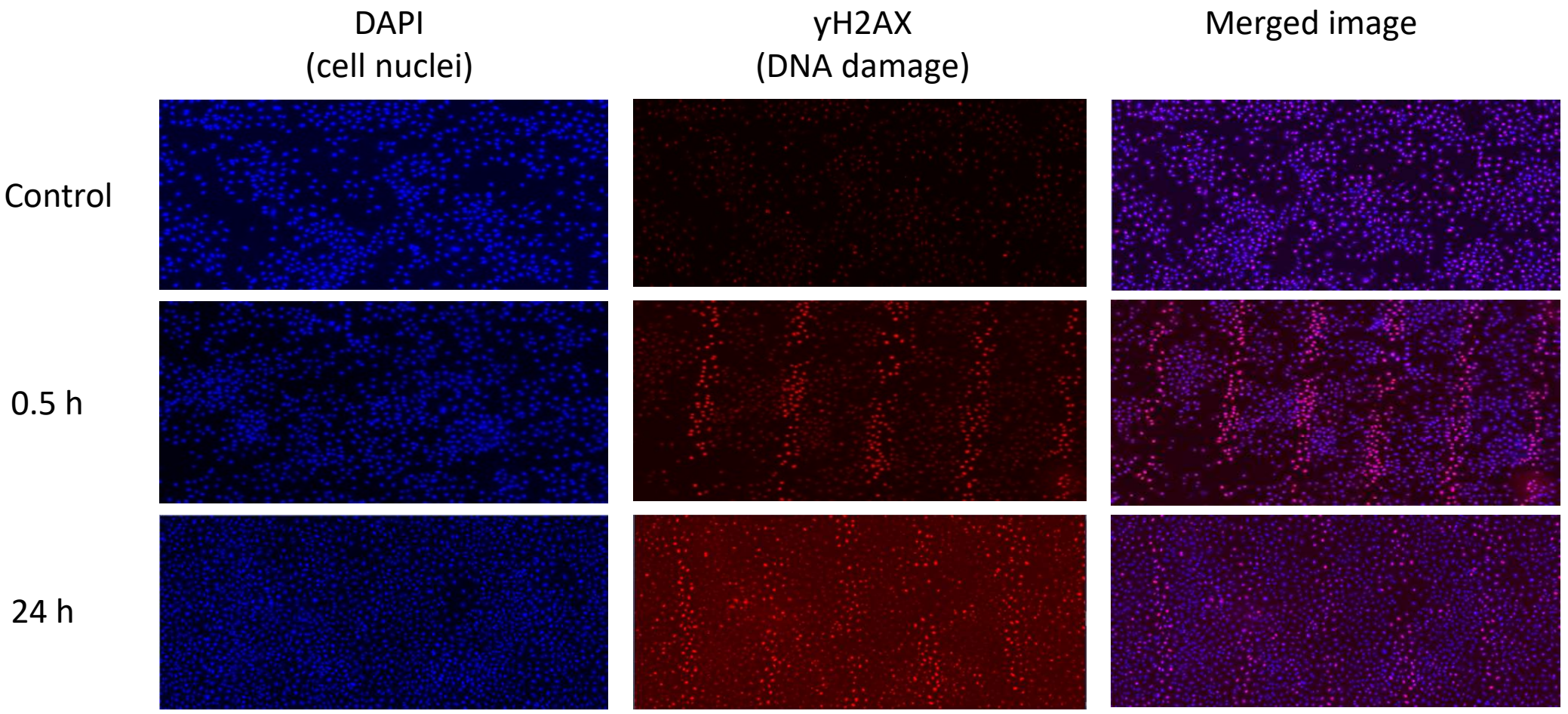
Clonogenic survival of normal cells following MRT was greater than predicted



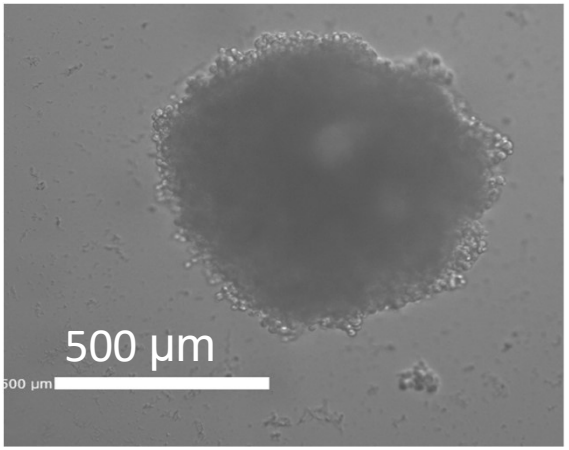
MRC-5

this suggests communication between cells does not affect normal cell survival following microbeam irradiation.

DNA damage was observed in lung cancer cells in response to microbeam irradiation



3D Cell Culture



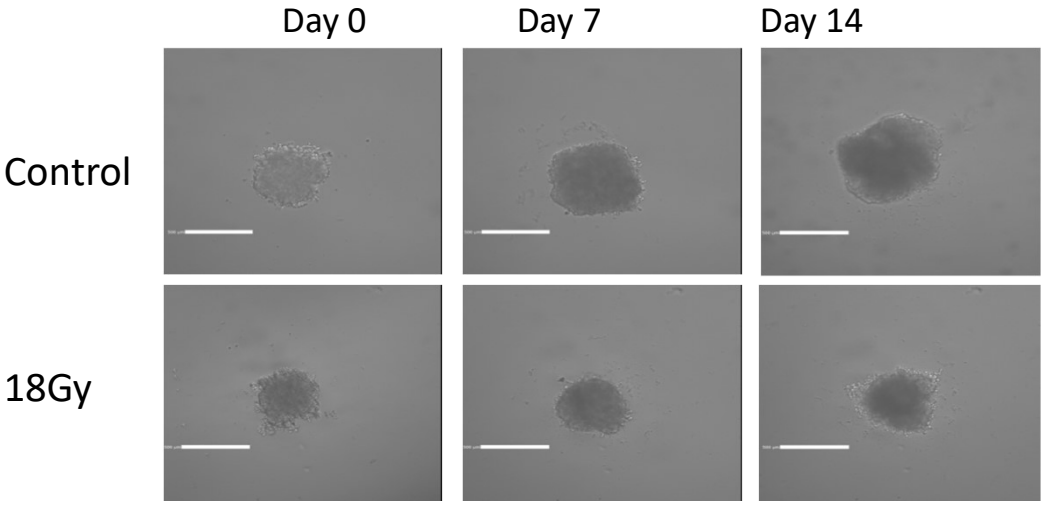
A more physiologically relevant model than 2D assays due to the presence of hypoxia, gradients of nutrients and increased cell-cell contact

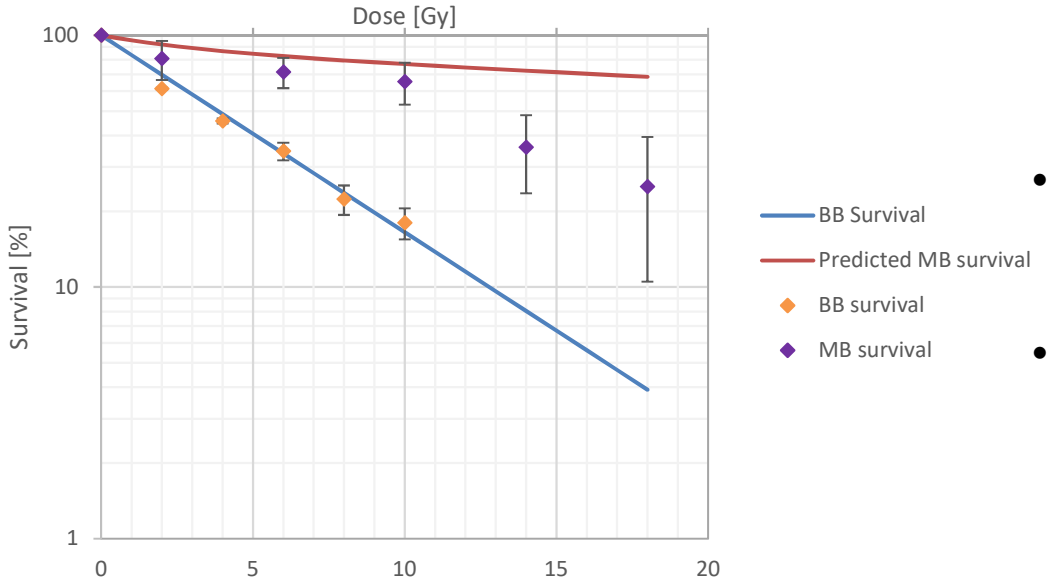
Cells added to ultra-low attachment plates form a 3D spherical structure (‘spheroid’)

Automated imaging and analysis of spheroid growth following radiation was performed with a Celigo™ cytometer

Cell viability was also measured using the Cell Titre Glo® assay (measures ATP production)

Reduced Growth and Viability of tumour spheroids following microbeam Irradiation.





- A549 Spheroids treated with Microbeam or Broadbeam Irradiation
- Growth measured using Celigo™ cytometer
- Viability measured at 14 days post treatment
- The predicted response of the spheroids to microbeam irradiation was calculated based on the assumption of no communication between cells.
- The actual viability following MB falls below the predicted
- Cell:cell communication plays a role in MB response in 3D culture

Summary

- Preliminary results indicate bystander communication between tumour cells following microbeam irradiation
- This was observed in cells grown both in 2D and in 3D (more physiologically relevant)
- Non-cancerous cells grown in 2D are able to survive MRT. Is this because they do not release bystander signals or are they less responsive to them?

Biological effects – Microbeams or high dose rate ?

MRT vs 'FLASH'

OC-0039 Unique sparing of spatial memory in mice after whole brain irradiation with dose rates above 100Gy/s

K. Petersson[1], P. Montay-Gruel[2], M. Jaccard[1], G. Boivin[2], J. Germond[1], B. Petit[2], F. Bochud[1], C. Bailat[1], J. Bourhis[2], M. Vozenin[2]

[1]*Lausanne University Hospital, Institute of Radiation Physics IRA, Lausanne, Switzerland*

[2]*Lausanne University Hospital, Department of Radiation Oncology, Lausanne, Switzerland*

RADIATION TOXICITY

Ultrahigh dose-rate FLASH irradiation increases the differential response between normal and tumor tissue in mice

Vincent Favaudon,[1,2*] Laura Caplier,[3†] Virginie Monceau,[4,5‡] Frédéric Pouzoulet,[1,2§] Mano Sayarath,[1,2¶] Charles Fouillade,[1,2] Marie-France Poupon,[1,2‖] Isabel Brito,[6,7] Philippe Hupé,[6,7,8,9] Jean Bourhis,[4,5,10] Janet Hall,[1,2] Jean-Jacques Fontaine,[3] Marie-Catherine Vozenin[4,5,10,11]

In vitro studies suggested that sub-millisecond pulses of radiation elicit less genomic instability than continuous, protracted irradiation at the same total dose. To determine the potential of ultrahigh dose-rate irradiation in radiotherapy, we investigated lung fibrogenesis in C57BL/6J mice exposed either to short pulses (≤500 ms) of radiation delivered at ultrahigh dose rate (≥40 Gy/s, FLASH) or to conventional dose-rate irradiation (≤0.03 Gy/s, CONV) in single doses. The growth of human HBCx-12A and HEp-2 tumor xenografts in nude mice and syngeneic TC-1 Luc$^+$

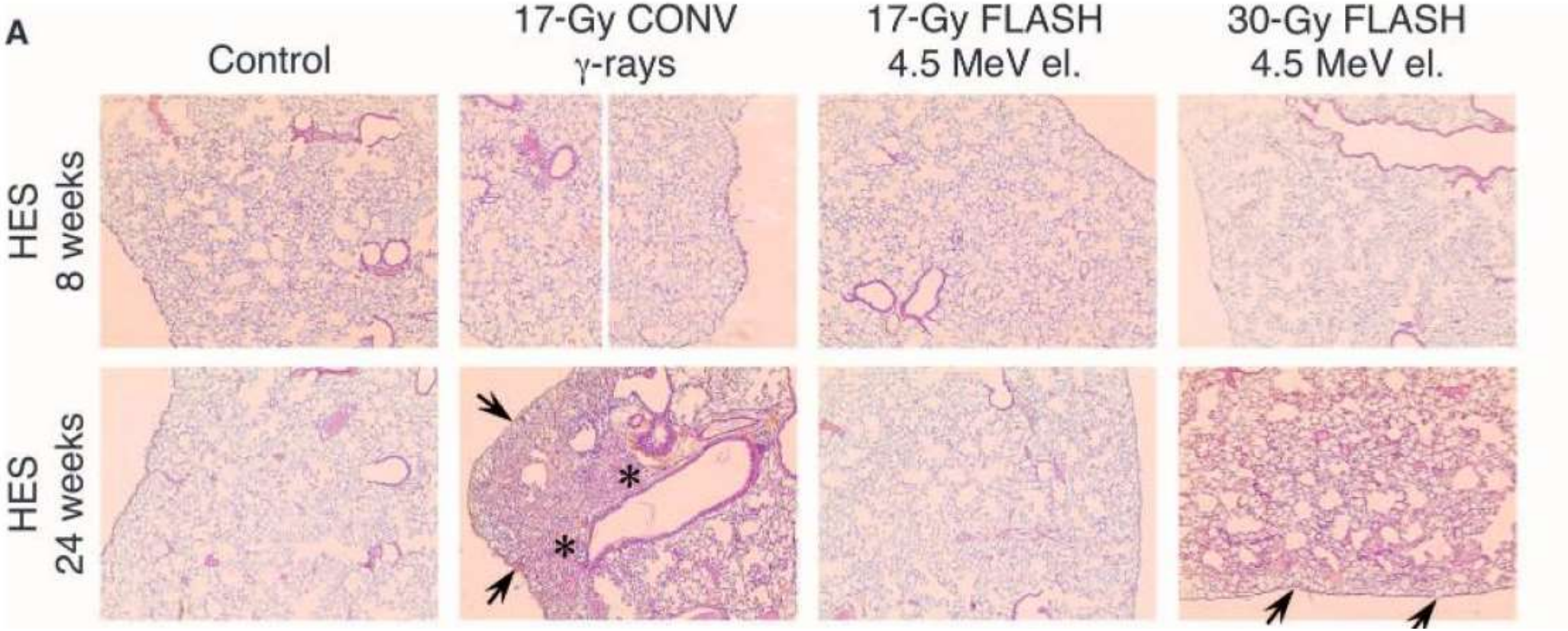


Fig. 1. Differential induction of pulmonary fibrosis by FLASH versus CONV irradiation. C57BL/6J mice were subjected to bilateral thorax exposure to CONV (g-rays or 4.5-MeV electrons, 0.03 Gy/s) or FLASH irradiation (4.5-MeV electrons, 60 Gy/s) in a single fraction and sampled at the times indicated. (A) Hematoxylin-eosin-saffron (HES) or Masson trichrome (MT) staining of lung sections (scale bar, 50 µm). Massive fibrotic lesions with subpleural fibrosis and alveolar thickening composed of fibrillar collagen were observed at 24 weeks after 17-Gy CONV, whereas 30-Gy FLASH irradiation only elicited rare fibrotic patches at this time point; arrows point to patches of subpleural fibrosis; asterisks indicate intraparenchymal fibrosis.

Limitations of microbeams

So far large synchrotrons are required to produce microbeams

Experimental time is expensive and scarce

Clinical trials are difficult and a widespread clinical use impossible

ESRF in Grenoble, France

In order to use the advantages of microbeams clinically we need to develop smaller sources!

Example for a preclinical source …

A compact microbeam source
Why do we use synchrotron radiation?

For microbeams we require

1. Parallel beams
   - To preserve sharp dose gradients
   - To guarantee high output factors

2. Photon energy of around 100 keV
   - Otherwise electron scattering will cause large beam penumbras

3. High dose rates
- To avoid dose blurring by organ motion in the micrometre range

Synchrotron radiation is characterised by a high beam brilliance, defined as

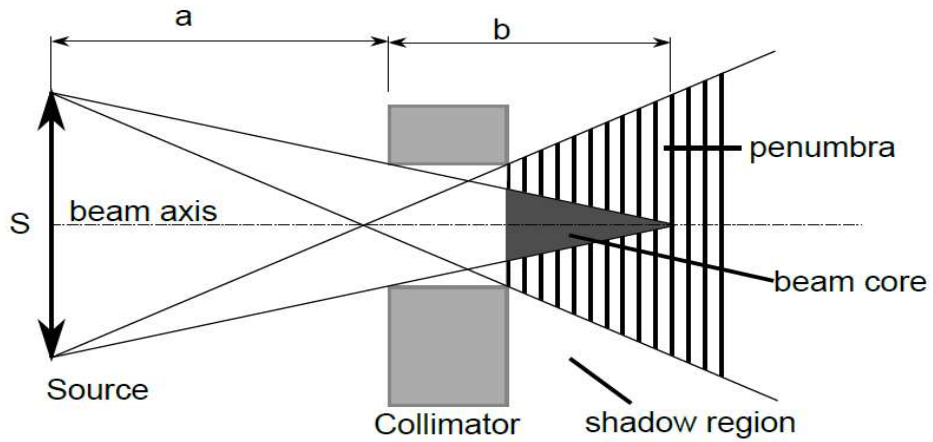
$$Brilliance = \frac{photons}{time \times angle \times area \times bandwidth}$$

A compact microbeam source

Can an x-ray tube generate microbeams?

	160 kV tube, 5 mA, small focal spot, 1 mm Al Filter	ID17 beamline at the European Synchrotron
Dose rate	1.2 Gy/s	15,000 Gy/s
Mean energy	55 keV	100 keV
Source distance	0.075 m	> 40 m

Main problems: Beam divergence, extremely low output power, geometric shadowing due to source size



A compact microbeam source

A multi-slit collimator for divergent beams

At the European Synchrotron microbeams are shaped by a multi-slit collimator with parallel slits

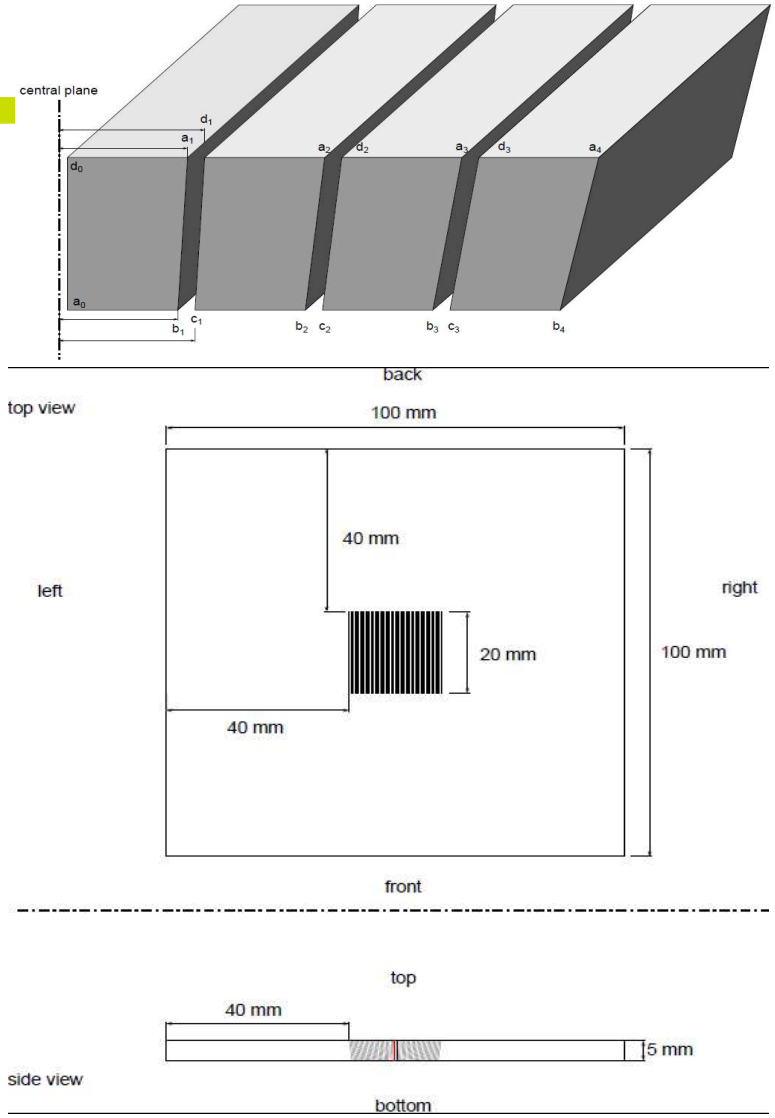
-For a divergent source, parallel slits off axis would block the beam

-Therefore slit openings need to account for the beam divergence

-We chose a plate thickness of 5 mm

-Manufacturing needs to be carried out with ±1.5’ accuracy for the inclination of each slit!

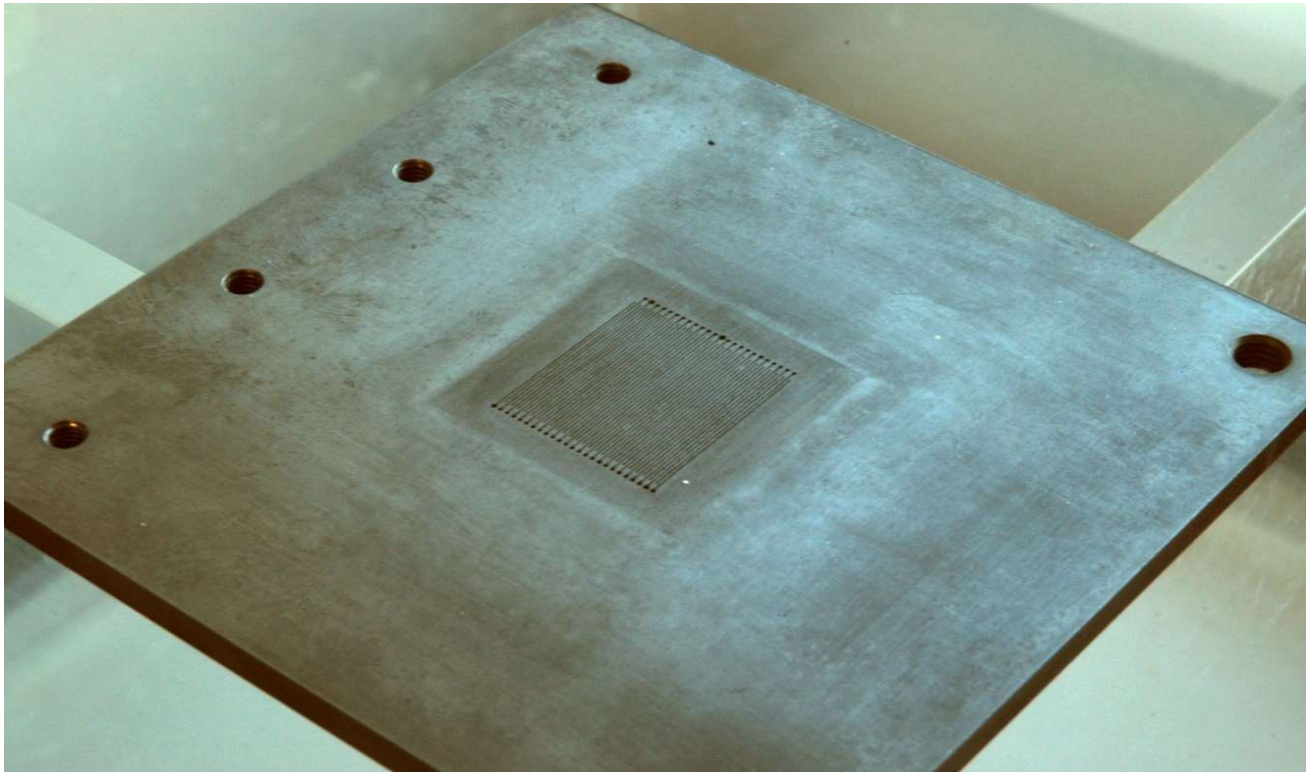
-Positioning with ±2.5 µm accuracy



A compact microbeam source
The first MSC for divergent beams

In contrast to the MSC at the ESRF: wire cutting in the centre of the plate

- Small drill holes were necessary to insert the wires
- This is the reason for the comb like design at the edges

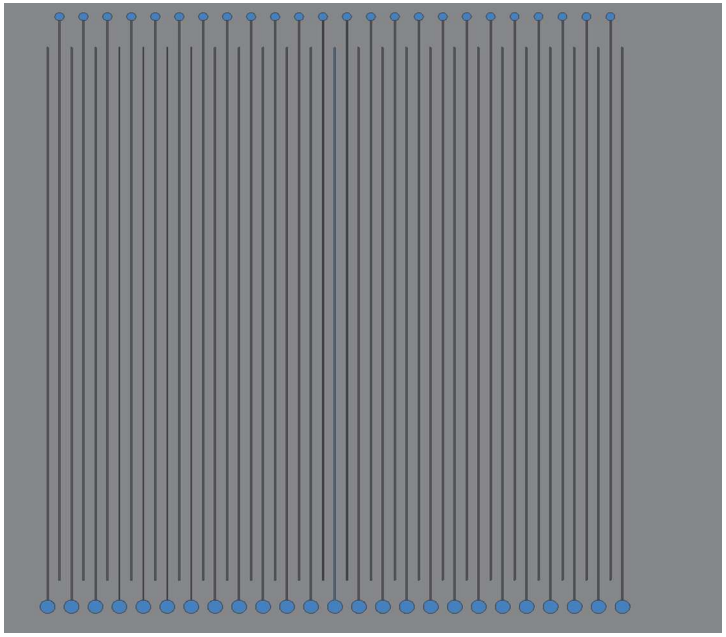


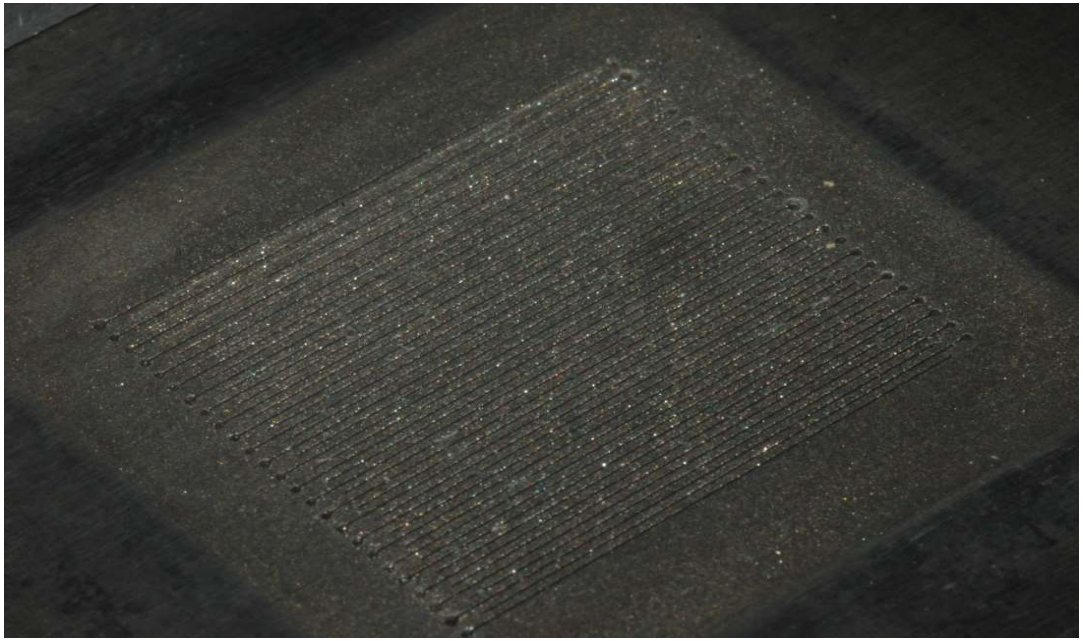
MSC at the ICR: 12 km of wire were used up for the cutting!

A compact microbeam source
Collimator fabrication

At one end of the slits: holes with 150 µm diameter drilled into the plate to start wire cutting

→ For stability reasons: alternatingly started at one side of the collimator

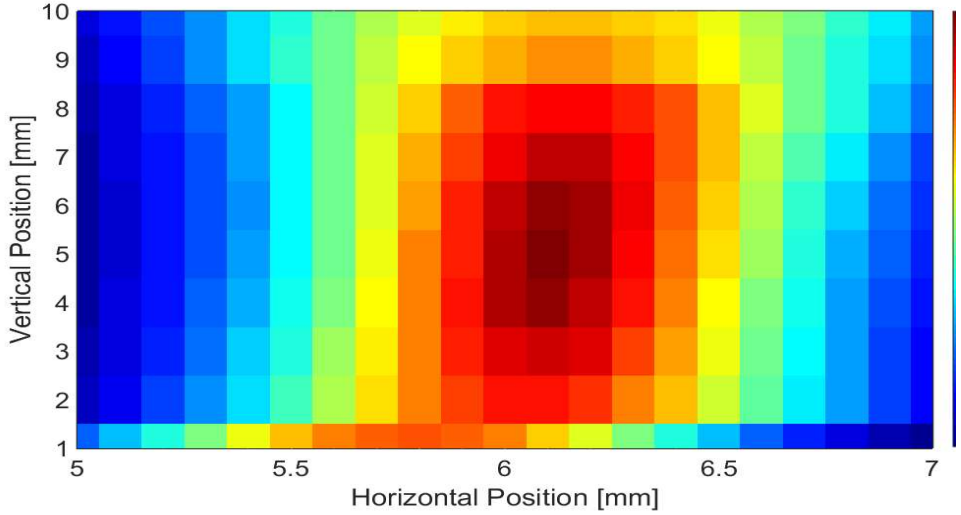




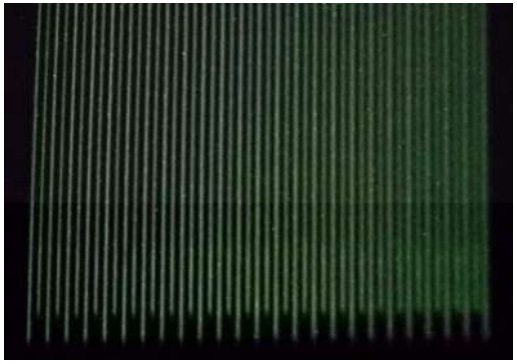
A compact microbeam source
Accurate alignment is important

The alignment between collimator and X-ray tube has to be done with high accuracy.

- Two stepping motors control the collimator postion with micrometre accuracy
- A fluorescence screen and a webcam control the output of the tube



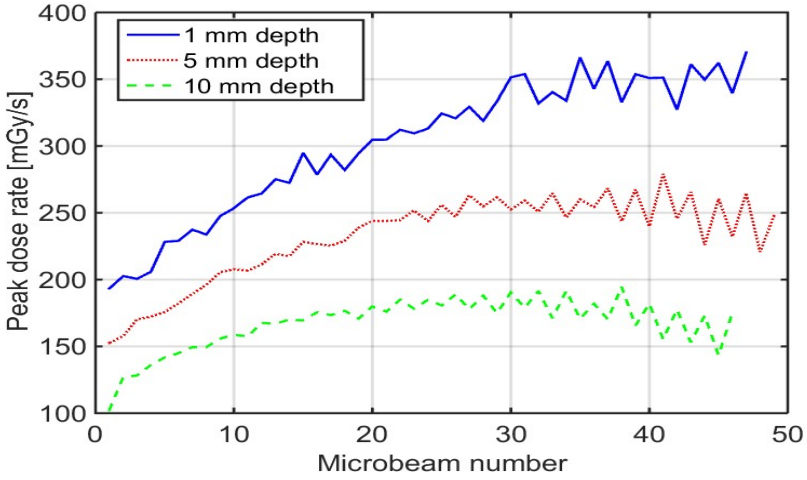
Screenshot

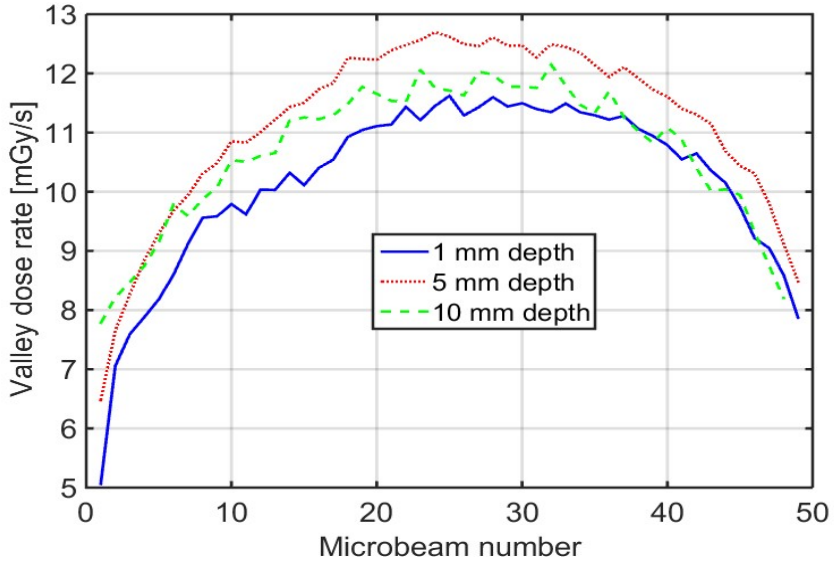


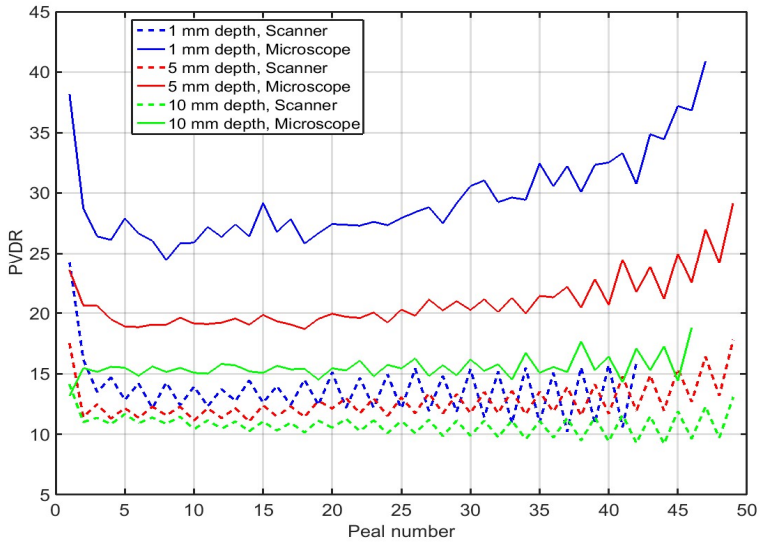
A compact microbeam source
Dosimetry

Achieved dose rates:

- 1 mm depth: 300 mGy/s
- 5 mm depth: 232 mGy/s
- 10 mm depth: 167 mGy/s



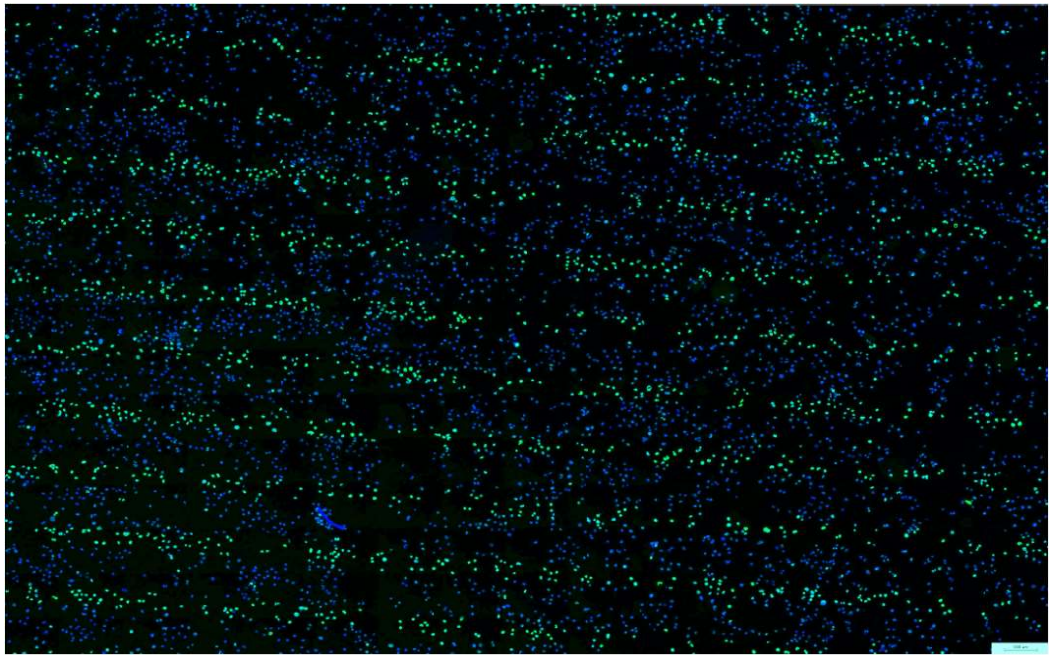




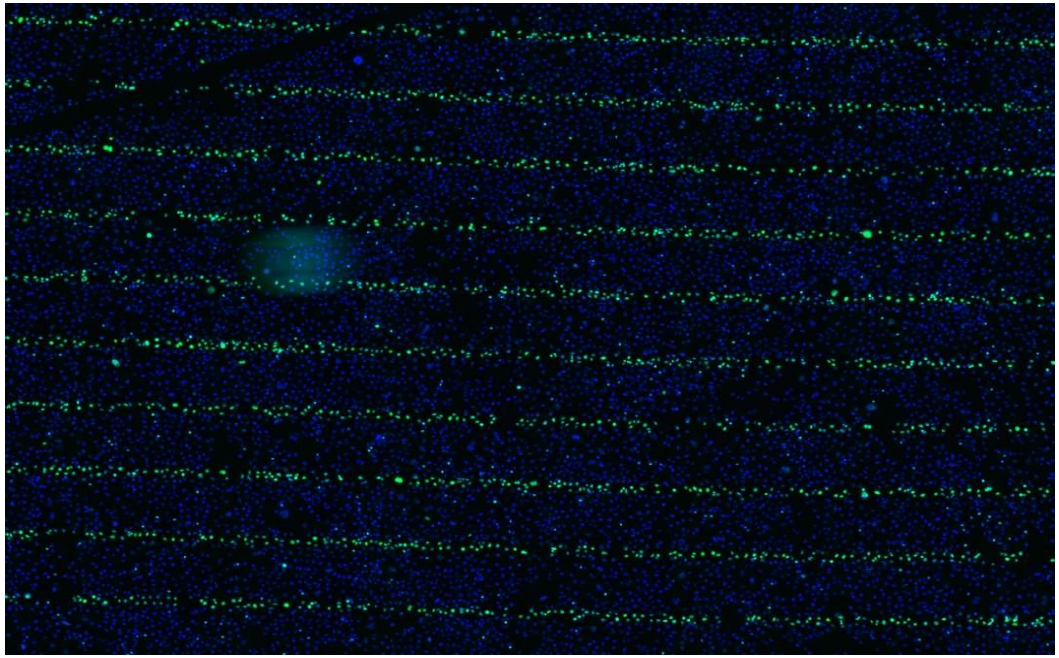
A compact microbeam source
First cell culture experiments

Fluorescence microscope images acquired from samples irradiated at

The ICR



The European Synchrotron



Solved problems – and challenges?

Solved Problems - Challenges

- ❑ Machine QA - Dosimetry
- ❑ Dose Algorithms
- ❑ Treatment Planning
- ❑ Treatment Execution
- ❑ Imaging for MRT
- ❑ Towards clinical MRT

❑ Machine QA - Dosimetry

❑ COST Initiative – ESRF driven

- Absolute doses
- Relative dose profiles

<u>A wealth of established technical solutions</u>

- Establish range of uncertainties

❑ Dose Algorithms

- Machine QA – Verification
- Treatment Planning

A wealth of established MC Solutions

- Establish range of uncertainties
- Compromise Accuracy vs Speed
- Tissue inhomogeneities

❑ Treatment Planning

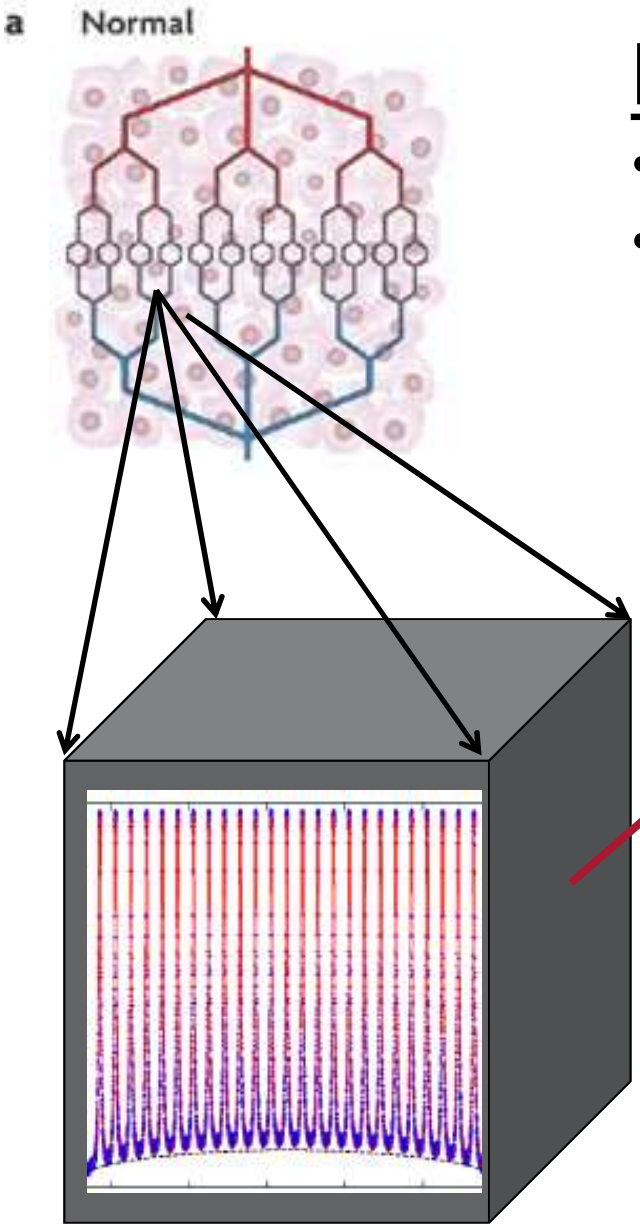
- Selection of Beam Entry Angles
- Calculation of delivered doses
- Optimization of treatment quality

<u>How do we optimize the treatments ?</u>

- Correlation of doses with biological effect (clinical endpoints)
- Definition of quality indicators

Multi-Scale Problem

- micro to mm – voxels
- voxels to organ endpoint



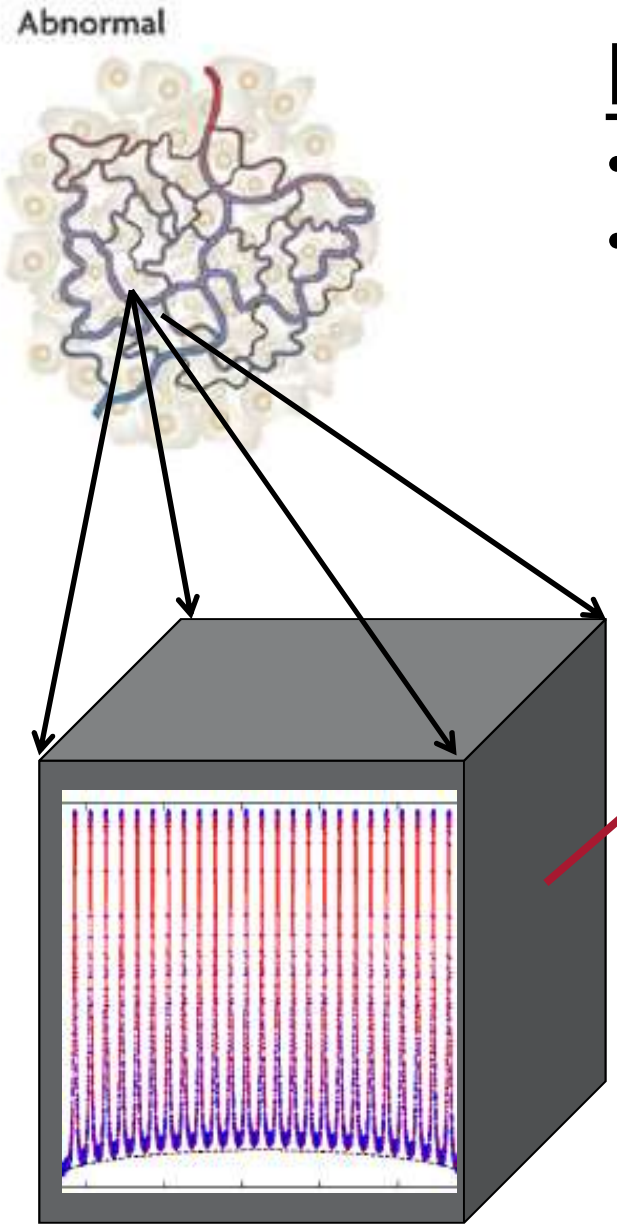
$DVH_{Voxel}(D, PW/CTC, PVDR)$

Local biological effect

Organ specific endpoint
NTCP

Multi-Scale Problem

- micro to mm – voxels
- voxels to organ endpoint



DVH_{Voxel}(D, PW/CTC, PVDR)

Local biological effect

Tumour specific endpoint
TCP

Correlation of biological effect with microscopic doses

- Design of data driven ‘microscopic’ dose reduction schemes
  - Voxel DVHs maybe a first good start
  - But next ? Tissue specific …like EUD…?
- Many data sets under varying conditions pointing in certain directions ….
- Instead of one surrogate (D) we now have 3!
- General trend: Many data – little modelling – No STM for BE

❑ Treatment Execution

- Patient QA – Image guidance
- Treatment Adaptation

<u>Development of IGRT for MRT</u>

- Seeing what to treat at time of treatment
- Risk avoidance, Optimizing benefit

Physics MasterClass ESTRO, Firenze 10-13 September 2017

Tips & tricks for writing a scientific paper and get it accepted

C. Fiorino

Medical Physics, San Raffaele Institute, Milano, Italy

OSPEDALE
SAN RAFFAELE

Summary (T&T for writing a paper and get it accepted)

- Why (the motivations)
- When (the timing)
- Where (the journal)
- Who (the roles)
- How (content, style, editing, language, tutoring, interactions between authors, with editor and reviewers, revisions…)
- After acceptance/rejection…looking for a «sense»

- Final (personal) suggestions

T&T for writing a paper and get it accepted: Why ?

- «….and get it accepted»….

……**always** start first from:

- «Is my work worthy of publication ?»

T&T for writing a paper and get it accepted: Why ?

- Publishing….from latin: «publicus»

- In italian: «pubblicare»….. from Treccani Vocabulary: making something known to everybody, making public through printing (power of the printed words)….in old Italian also «expropriate»…..
- Something (including knowledge) that from your private sphere becomes public, «forever»…strong meaning and irreversible consequences

T&T for writing a paper and get it accepted: Why ?

- **The content**

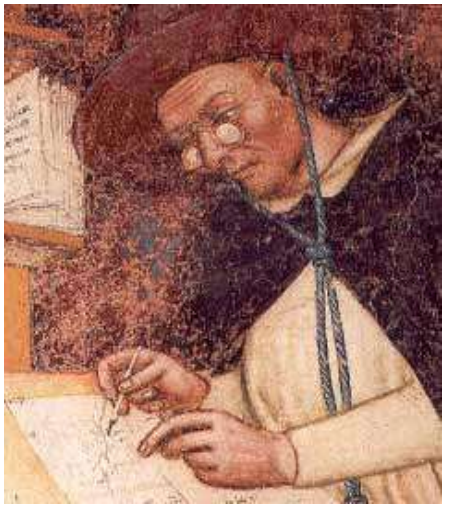
- **The context**

- Are the results sufficiently mature ?
- Are they new ?
- Are they relevant ?

- Is the work within a «long-term» project ?
- It is before/after a series of papers
- My chief wants to publish it
- I need to demonstrate that we are «productive»
- Time constraints (human resources, student fellowship, funding,…)

T&T for writing a paper and get it accepted: Why ?

- You have to be fully convinced about the motivations
- Discuss with your collaborators and the main responsible/PI of the project
- Agreement with the whole team (internal and external collaborators)
- It is not a shame to postpone to write a paper or to retire a manuscript if you realize that its publication is not really motivated (for instance after the first report of Reviewers)



T&T for writing a paper and get it accepted: When ?

- Timing for writing and submitting a paper is a crucial issue
- If possible, better to have a publication plan following the development of a project
- Balancing the needs to be «fast» and the maturity of data/results (publishing should not be a competitive run)
- Putting deadlines to avoid to go too slow
- Evaluate the scientific context to give timing priorities
- Resources

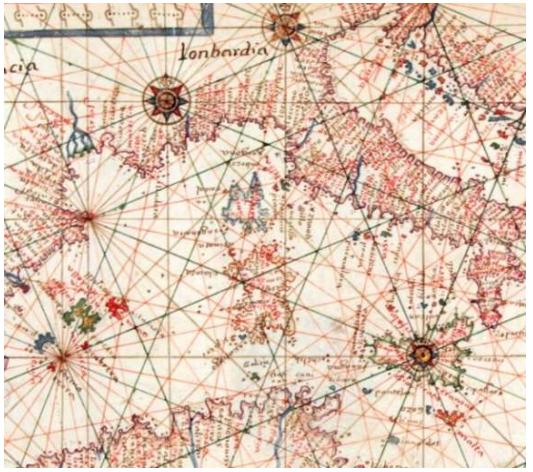
T&T for writing a paper and get it accepted: When ?

- The case of the multiplication of papers….
- Writing too many (clone) papers from the same data set is a bad (and widespread) practice
- Honestly evaluate the overlap with your previous works and the relevance/novelty of the content if it is worthy of a new publication

- ….on the other hand, don’t put too many (variegated) results in the same paper if they may be better splitted in two….

T&T for writing a paper and get it accepted: Where ?

- The choice of the proper journal is crucial
- Submitting a «good paper» to the wrong journal followed by a rejection is a damage due to the delay of your research (and discourage, de-motivate….)
- Submitting a «bad paper» to the wrong journal followed by acceptance may hide the visibility and/or decrease the reputation of your group
- Discuss before with the responsible and the contributors (never a waste of time)
- «Experience is master of life»…making mistakes as part of a process of the author's growth

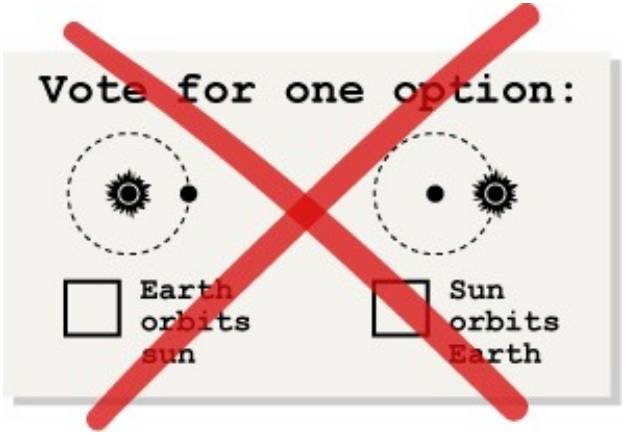


T&T for writing a paper and get it accepted: Where ?

- Getting oriented in the possible choices evaluating pro's and con's (Reputation in the field, IF, audience, speed of publication, access, history..)
- Rank your work and start with the «best affordable» journal
- Think about backup solutions in case of rejection, defining the lowest acceptable level
- Publishing is much easier than in the past, but what about quality ?

T&T for writing a paper and get it accepted: Where ?

- Pro's and con's of the multiplication of journals (especially open access)
- «Right to publish» *vs* selection of the best science
- Best science will be more defined by citations/impact instead of publishing in itself: «…get it accepted»…replaced by «….get it cited» !!!!!
- Is the current explosion of RT/MP journals justified by a corresponding increase of «science» (???)
- Risks of «liquid science» (auto-referral, creation of relative values, unpredictable consequences…)



Undsci.berkeley.edu

SCIENCE IS NOT DEMOCRATIC

«…rejecting a paper…»: the actual risks of open access

- Risks of «liquid science» (auto-referral, creation of relative values, unpredictable consequences….)

- Last Editorial of J Overgaard on the Green

The recent years have seen dramatic increase the number of new open access journals, which through claims of "peer review" evaluations, accept basically any manuscript for money and at the same time dramatically downgrade the concept of peer review. Despite using the same vocabulary, this no longer necessarily implies serious scholarly scrutiny. In a world where anybody can establish a scientific journal within hours through accessible software on the internet, it is important for the publishing houses to ensure that manuscripts, which once submitted to (and rejected from) one of their more established "old-fashioned" journals, remain accessible for their other journals. Consequently, the established publishers and societies have created an increasing number of downstream open access journals. ESTRO is indeed following that path and has this year established three such journals, to

Editorial

So long, Farewell, Au revoir, Auf Weidersehen

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T&T for writing a paper and get it accepted: Who ?

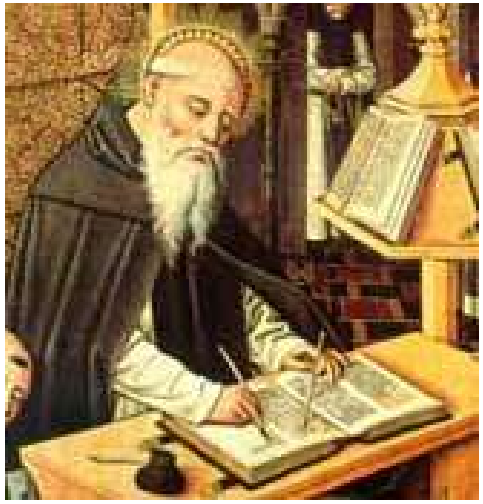
- First author should be the one who drives the manuscript preparation and, in general, should write the major part and coordinate the other contributions (in agreement/together with the senior author/PI)
- Deciding the first author based on the real commitment in leading the study
- Co-authors: who contributed in some way (not strictly making measurements, writing sections or analyzing data…). Sometime it is challenging….name position.
- Crucial role of the corresponding author

T&T for writing a paper and get it accepted: Who ?

- Papers as steps of a project: planning roles and responsabilities regarding autorship
- Facilitating cooperation (a published paper is never an accomplishment of a single person !)
- Conflicts should not be hidden but solved with shared rules
- Avoiding/limiting internal competition (n° of manuscripts with first name should reflect the real value of the researcher), giving opportunities…
- Needs of governance by a responsible senior (typically last author), …possibly wise…☺

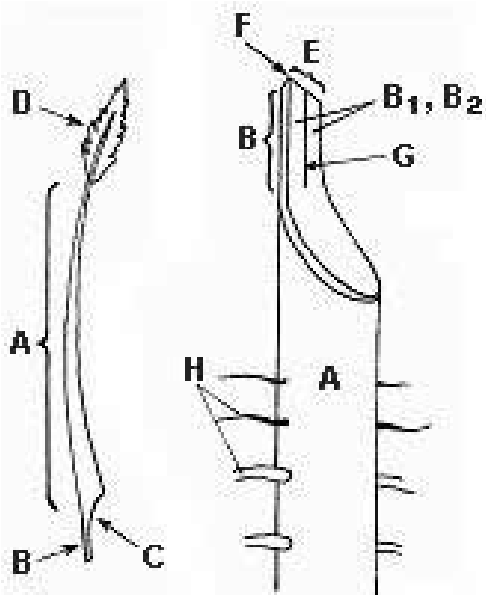
T&T for writing a paper and get it accepted: How ?

- <u>Content and style: generalities</u>
- The scientific writing is not the most natural way to communicate. You need to learn it !
- Trial and error process
- Big help from experienced people around you (including your tutor/mentor/PI)
- Being precise and concise (this ability is largely variable among young writers…☺)
- Avoid to fly out the proper area, keep far from linguistic ambiguities, be clear in what you want to say (selecting priorities, emphasis,…)



T&T for writing a paper and get it accepted: How ?

- <u>Content and style: Building the manuscript</u>
- Put the proper content in the proper section (Intro, M&M, Results, Discussion, Conclusions)
- Underline the relevant results of your study in terms of novelty and addition to what has already been published/or valuable confirmation
- Dont' omit the weak/critical points and discuss the limits of your work; demonstrate to be able to put your work in the scientific context
- Dont' extrapolate too much from your results (appropriate conclusions)
- Essential, updated and complete bibliography



T&T for writing a paper and get it accepted: How ?

- Editing and language
- How to get started…. after discussions, plan the structure of the paper then start to write with inspiration without pausing…then come back and refine, refine, refine….(word limits is an issue but you can work later on it)
- Incorporation of parts written by co-authors and their harmonization.
- Language issues (english is not the first language for most of us), particularly difficult for latin guys (still more for non-europeans)
- Cultural issues (depending on the country and culture, less or more difficult to learn to write a scientific paper)

T&T for writing a paper and get it accepted: How ?

- Editing and language
- Title, abstract and Figure/Table legends are the most important parts of a paper (>90% of the readers has no time to read the whole text)
- Put here your main messages in a clear and concise way (!)..give a character to your results
- Abstract and Title are more easily accessible and are read/downloaded in literature search (..the business card of your work)

T&T for writing a paper and get it accepted: How ?

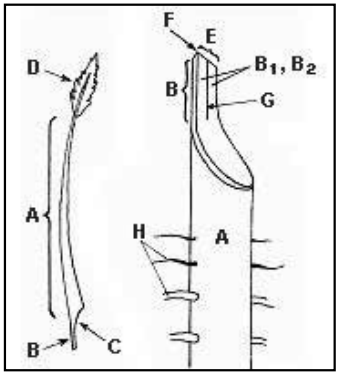
- Tutoring, interactions between authors,
- Need of governance, importance of the full agreement before submission of the final text
- Good mentor is a key point
- Discussing controversial points with the co-authors especially in case of critical suggestions/corrections
- Reputation of the last/corresponding author(s) may help

T&T for writing a paper and get it accepted: How ?

- Interactions with editor and reviewers, managing revisions
- Respecting the position of the Reviewers, taking their suggestions as an opportunity to improve the work
- Making the best to incorporate suggestions, if possible
- In case of controversial points, discuss with the other leading authors and decide.
- Misunderstanding are always possible
- Interaction with expert reviewers is an important experience for a young researcher

Main criteria for rejection

- Main «Strict rejection» criteria
- Ill posed question, out of field topic
- Unclear Aims
- Uncorrected methods (…often Insufficient statistics/number), outdated issue/results
- Repetition (if no relevance in confirming other results)
- Unrelevant for the field/audience
- Ethical problems
- Lack of scientific style
- Strong linguistic lack

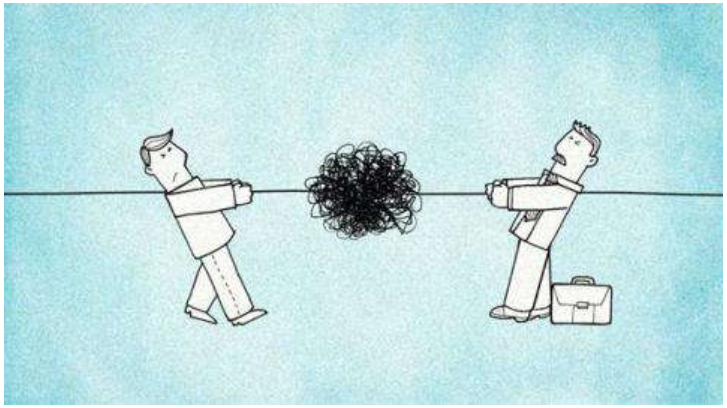


Main criteria for rejection

- Main criteria in rejecting a paper (if considered for review)
- Novelty (is there any new results/idea ?)
- Relevance (Are the results relevant for the readers?)
- Impact on the audience (what is the impact on the field, including practical applications and/or further scientific developments ?)
- Uncorrect/inappropriate methods
- Lack of Statistics/numbers
- Style (scientificity, clarity, linearity…)
- Not discussing/Ignoring the literature
- outdated literature
- Language (typically, bad English)

T&T for writing a paper and get it accepted: How ?

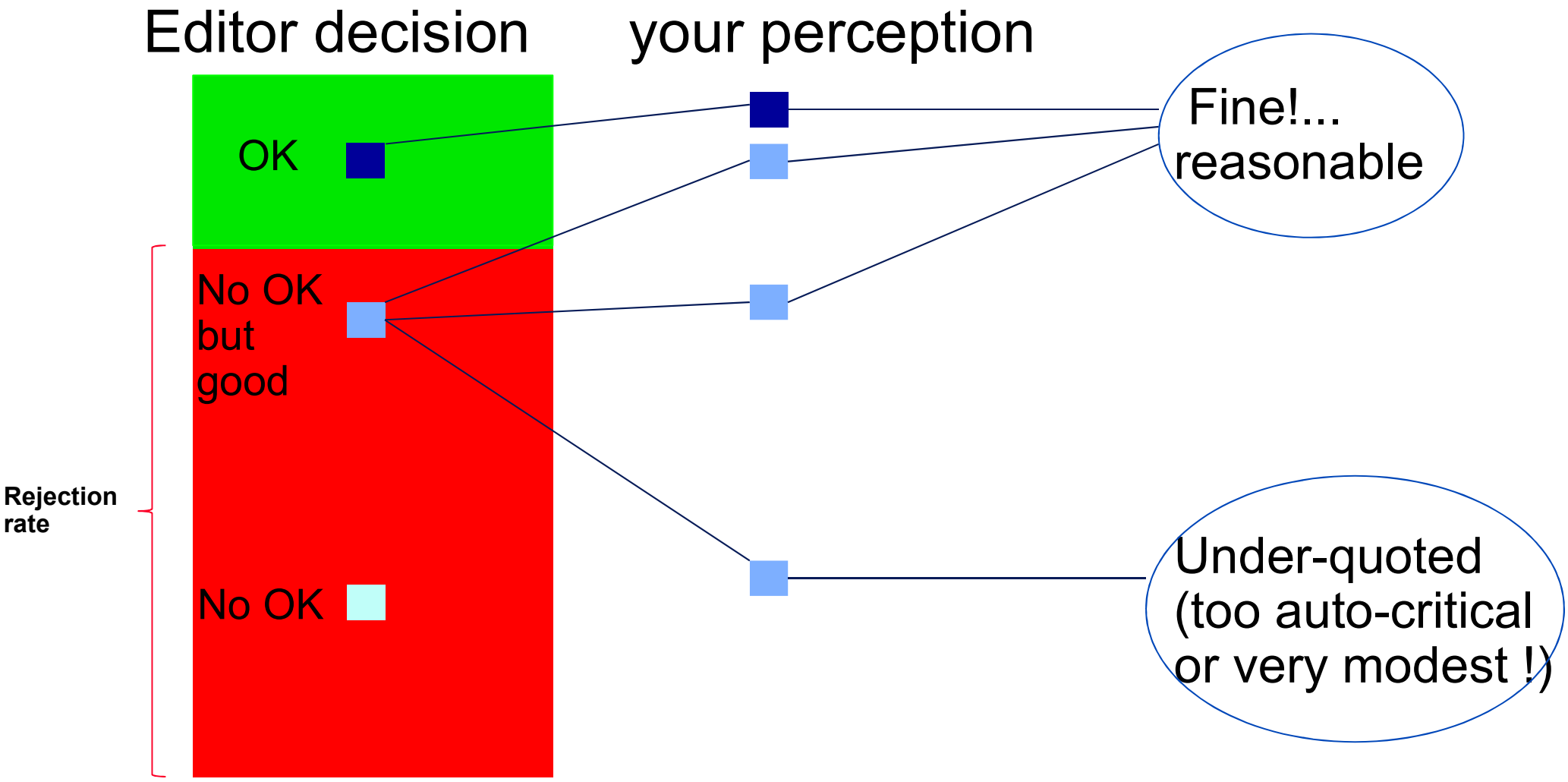
- Interactions with editor and reviewers, managing revisions
- Evaluate the possibility to retire the submission in case of «difficult» major revision (wasting time ?)…recognizing the limits and lacks of your work and exploiting the experience to improve….
- …or, stand up and explain your reasons underlining the positive aspects deriving from the publication of your work and/or the negative ones if it would not be published
- …in any case, ask for a rapid decision



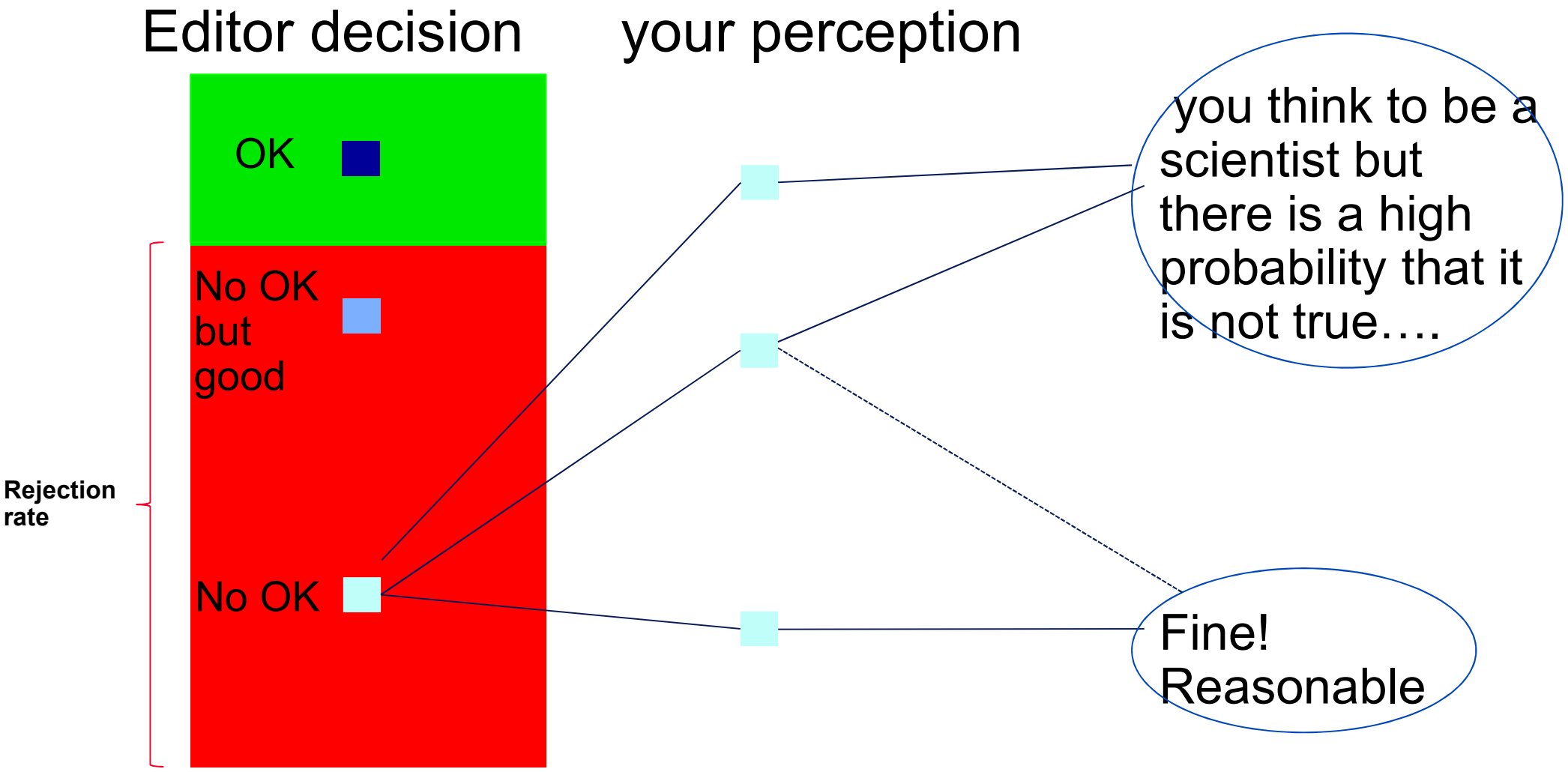
After acceptance/rejection….looking for a sense

- Big party in case of acceptance…☺
- In case of rejection, don't discourage: a rejected paper may be more important than an accepted paper
- Rejection is the «normality» for the best journals (for instance: rejection rates of best RT journals are around 80%)
- Follow plan B to re-arrange and re-submit (if it makes sense…), depending on the severity of the criticisms
- Giving sense to the experience…sharing in the group and with your tutor/PI

After acceptance/rejection….looking for a sense

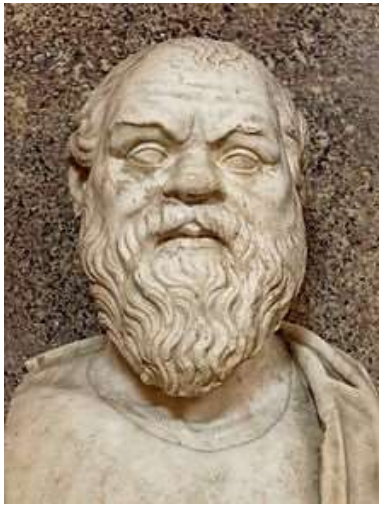


After acceptance/rejection….looking for a sense



Final (personal) suggestions to young «writers»

- Mixing ambition (to make science, to help suffering people, to contribute to the field, to find something new……) and modesty (…I have always a lot to learn, …«Scio nihil scire», Socrates, V° Century BC)
- Writing and publishing a paper is the natural way how humans share scientific knowledge nowdays….then, I should have something valuable to write (good science always first !)
- A good paper can never results from a poor research……first good ideas and work, then publish ……!
- The publication (or the rejection) of a paper is <u>always</u> a positive experience

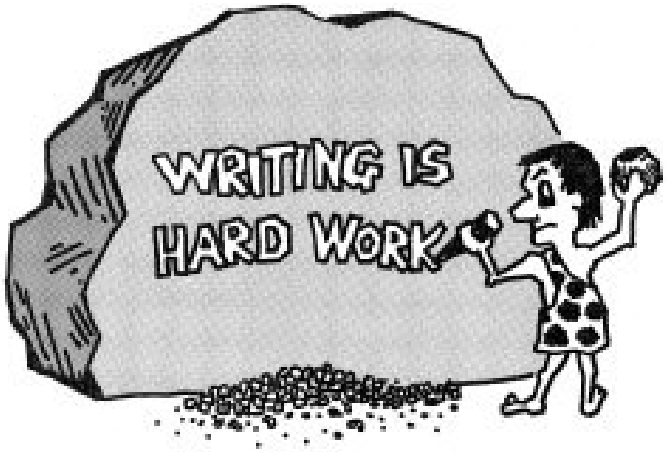


Final (personal) suggestions to young «writers»

- Favourable environment and good mentors/tutors are a key point
- …but this is not enough
- You need talent, motivation, patience, perseverance, modesty, ability to cooperate
- Writing a paper is never the result of the efforts of one single person
- Writing a paper is an art that needs to be learned and continously updated, applied and improved…needs time (…years….)

«Writing a paper is an art that needs to be learned and continously updated, applied and improved…needs time (…years….)»

….a good motivation to start early…..!



Grazie !

Trends & research opportunities in biophysics in RT

Peter van Luijk

Department of Radiation Oncology
University Medical Center Groningen / University of Groningen
Groningen
The Netherlands

Trends? Opportunities?

The grant that marked the beginning of my career:

Criteria

The assessment criteria are:

- quality of the researcher
- quality, innovative character and academic impact of the research proposal, and
- knowledge utilisation

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You

I'm already part of the field
You bring new ideas!

Easy: Radiotherapy = application

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I'm already part of the field
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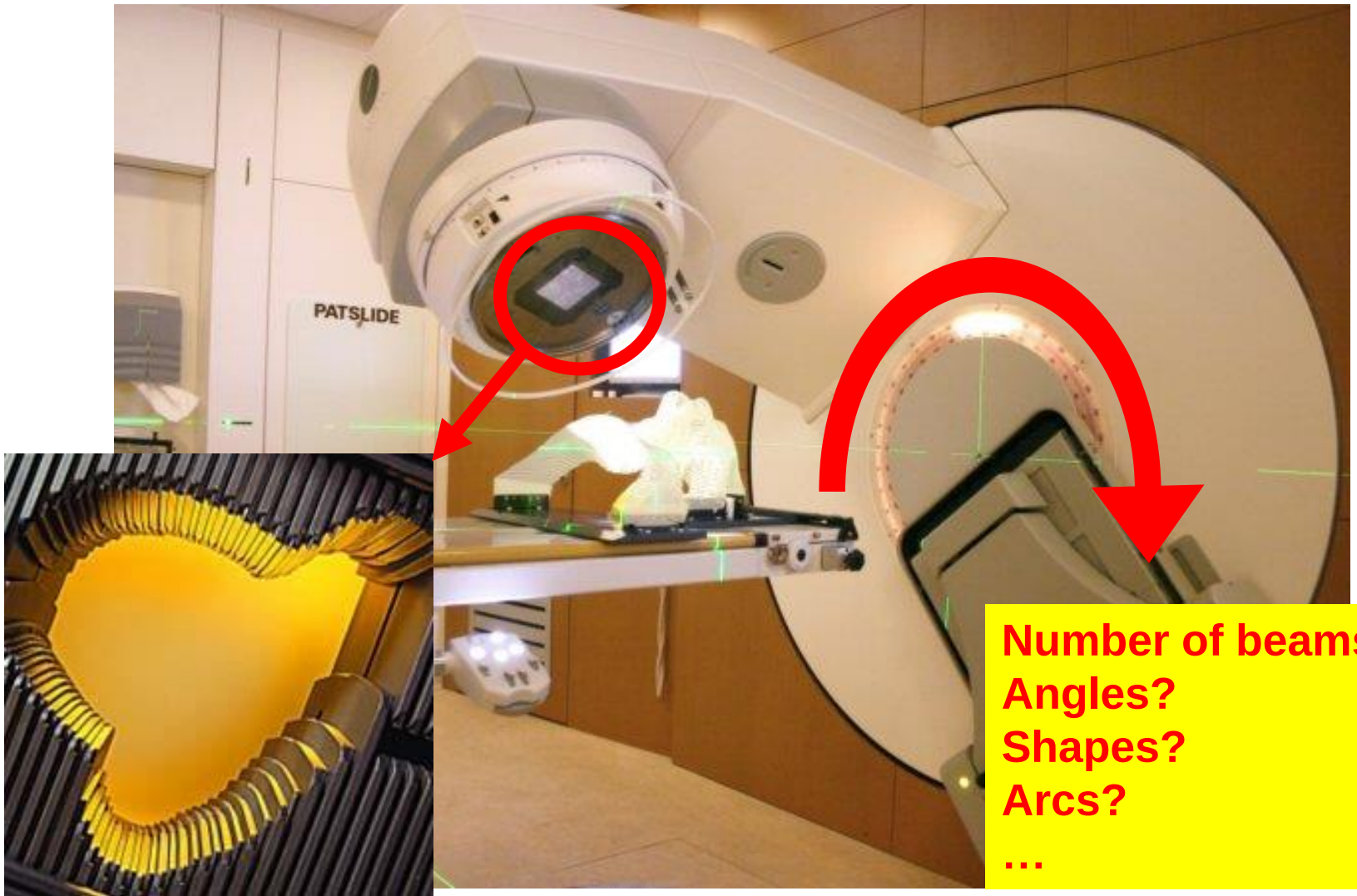
Easy: Radiotherapy = application

What should I talk about?!

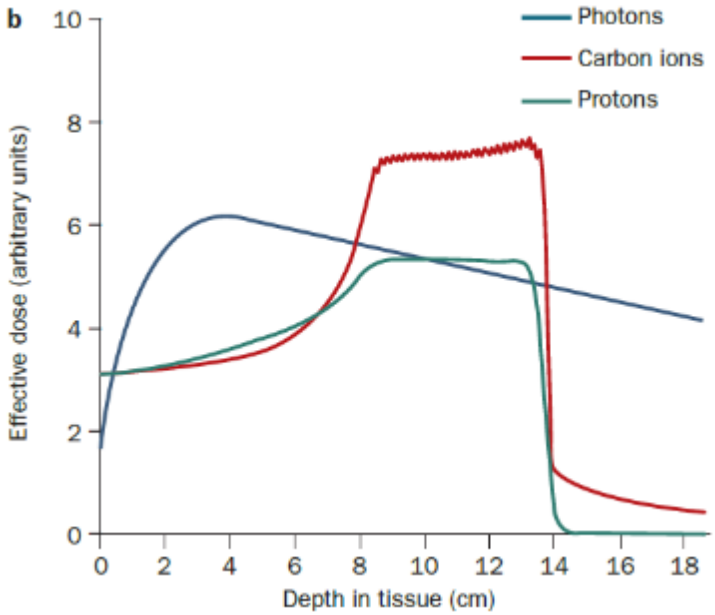
Aim

- What is the role of biophysics in radiotherapy?
- Provide a brief overview of topics in the field
- Identify what would make me enthusiastic for new research in these areas

Radiotherapy: Technology



Radiotherapy: Technology



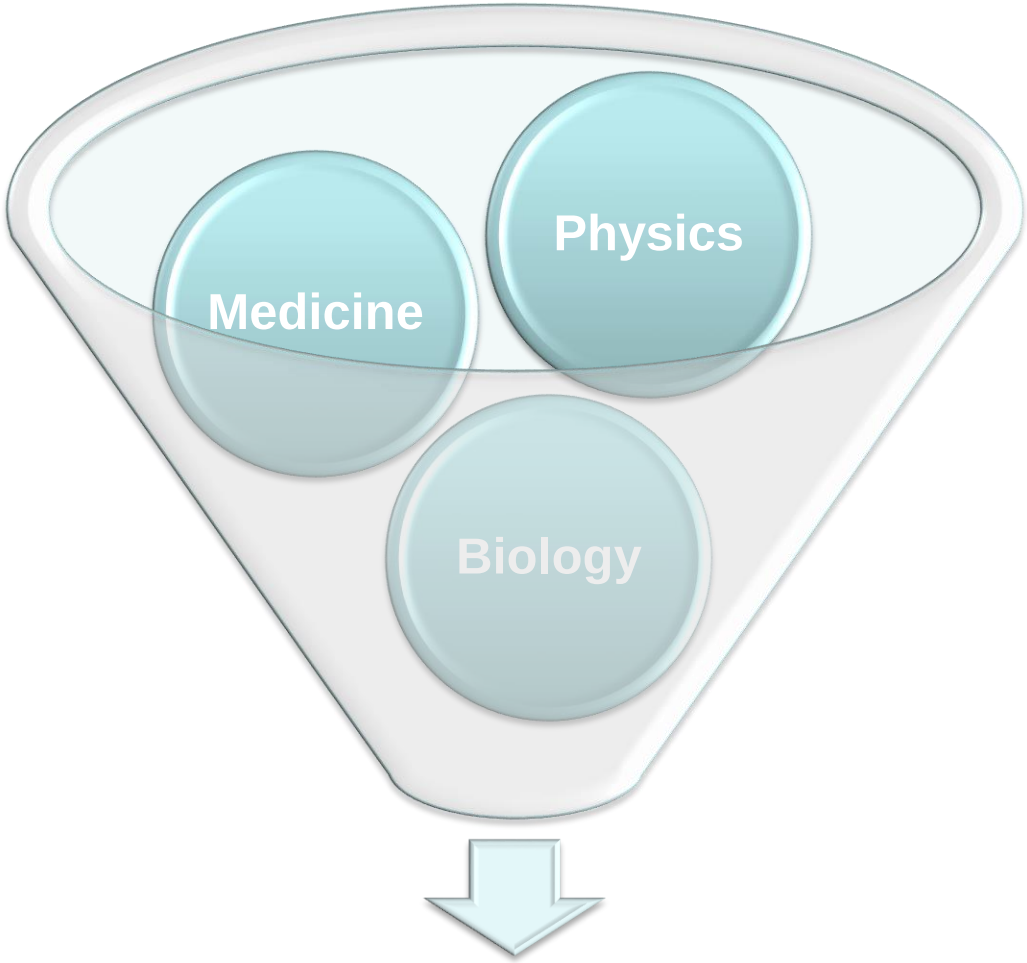
Or maybe particles?
But… which?
And by which technology?
RBE?!?

Durante M et al. Nat Rev Clin Oncol. (2010)

Radiotherapy: Biology

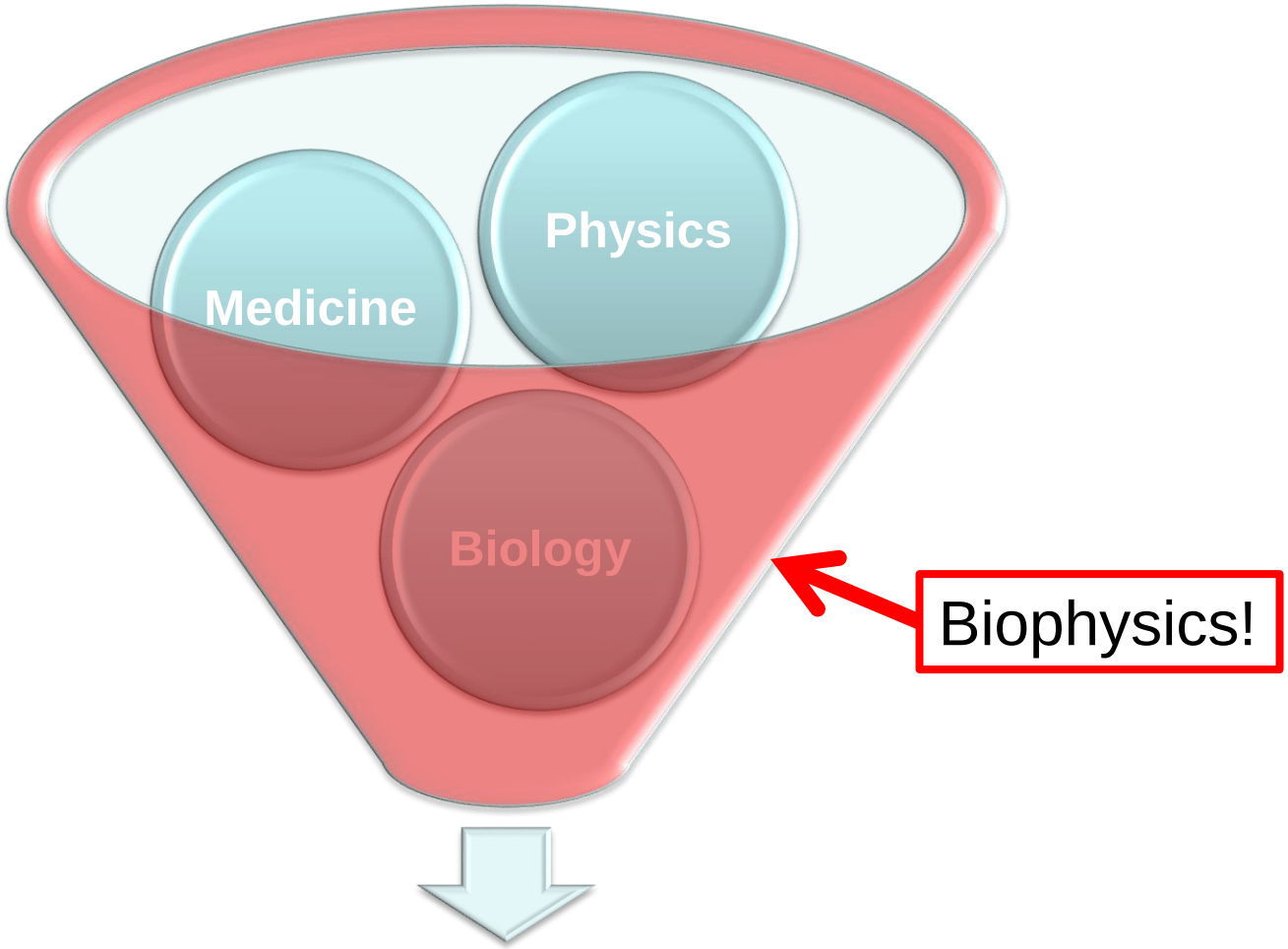
- Heterogeneity
  - Hypoxia (non-uniform, temporal variation, …)
  - Proliferation
  - …
- And the patient surrounding it?!
  - Genetic background
  - Other patient factors
  - Co-morbidity
  - …

Radiotherapy



Radiation Oncology

Radiotherapy



Radiation Oncology

Biophysics in radiotherapy

- Imaging: see also lectures by Uulke, Eirik
  - Outcome, rather than its associates!
  - Tissue properties, organ function, cell markers
- Outcome modeling: see also lecture of Claudio
  - Tumor
  - Normal tissues
    - “Volume” effects
    - “RBE” effects when using particles
- Facilitating medicine / biology
  - Specialized irradiation facilities
  - Quantitative analysis of e.g. pathology, imaging, …
  - Analysis of large amounts of data

Biophysics in radiotherapy

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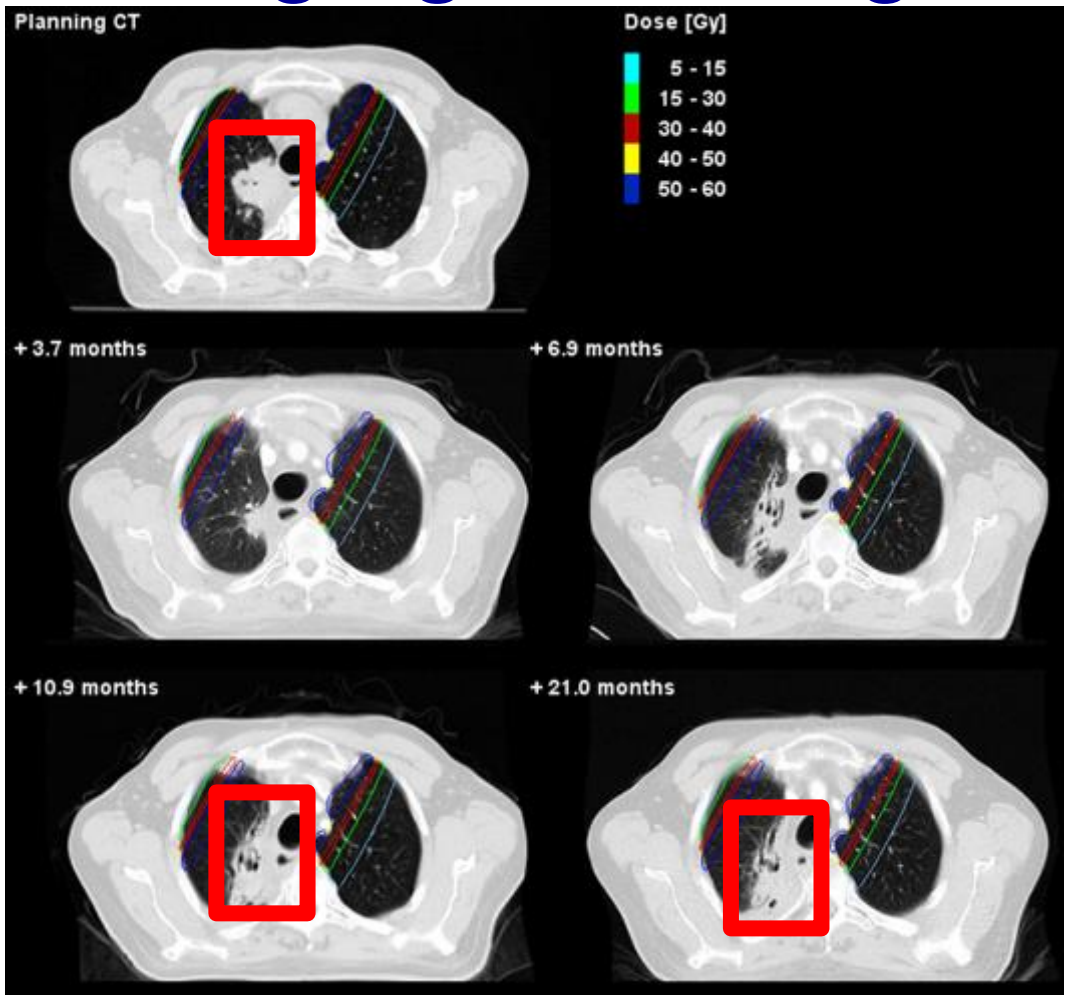
  - Analysis of large amounts of data

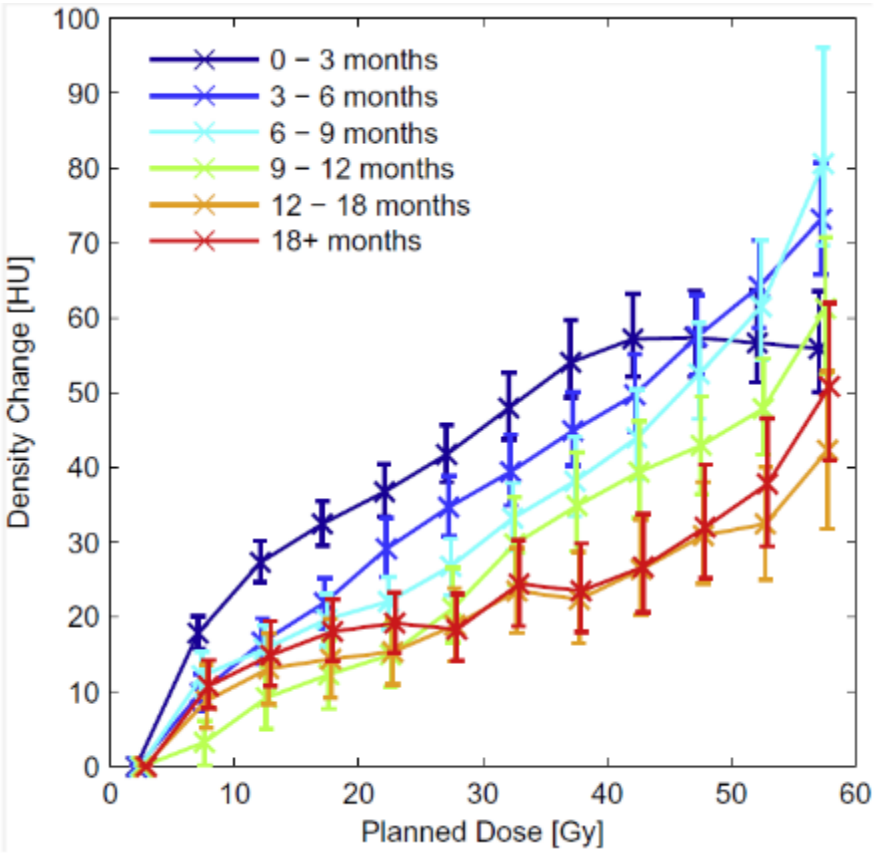
Imaging: CT/Lung

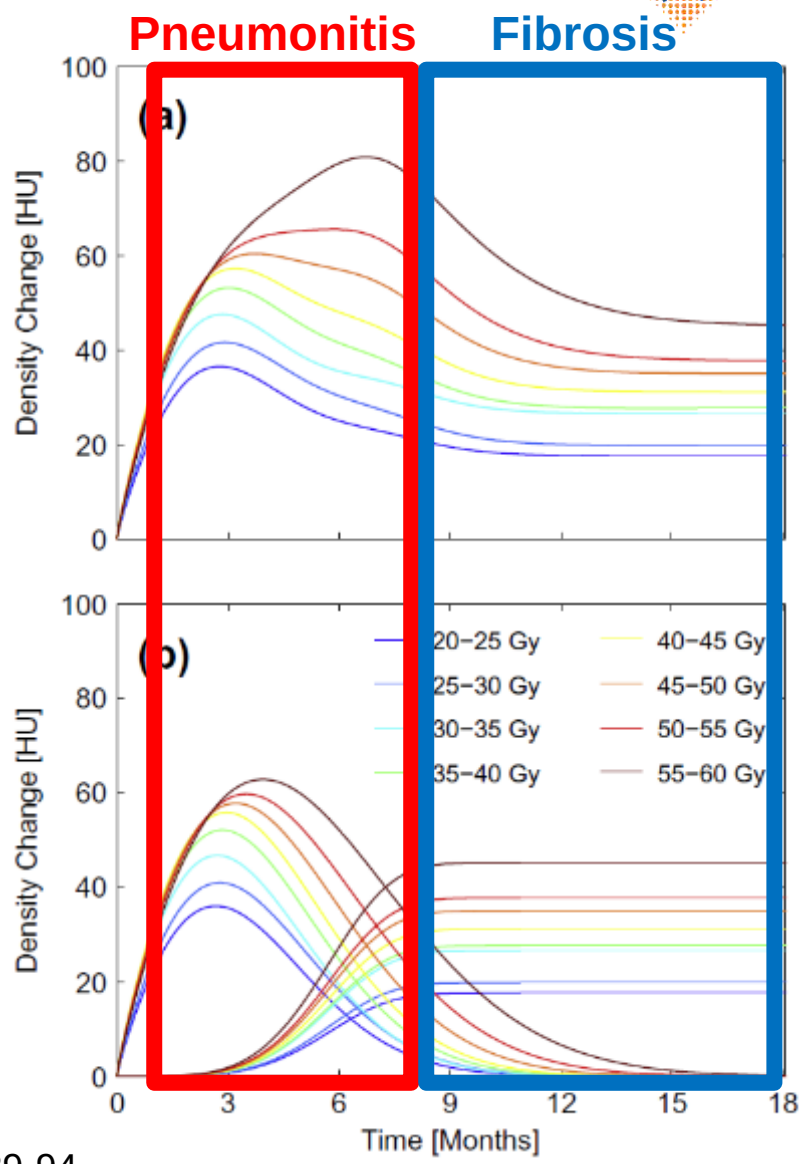


- Register pre- and post-treatment CT
- Calculate local change in number of HU

E.C.J. Phernambucqa et al. Lung Cancer 74 (2011) 451– 456

Imaging: CT/Lung

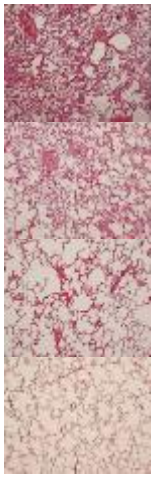


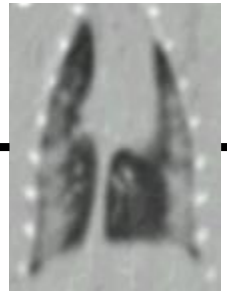


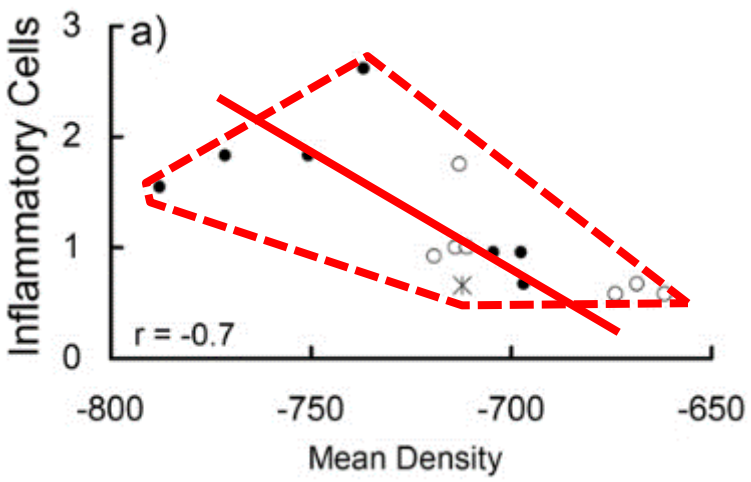
One number, different pathologies:
What does it mean?
Can they be compared?

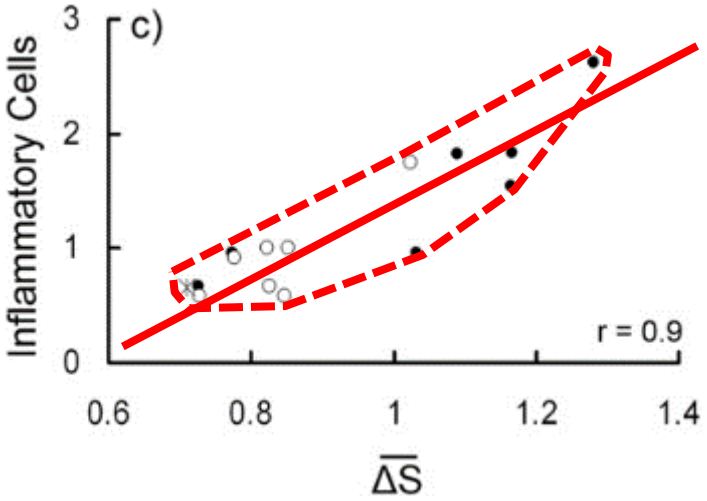
U. Bernchou et al. Radiother Oncol. 2013 Oct;109(1):89-94.

Imaging: CT/Lung





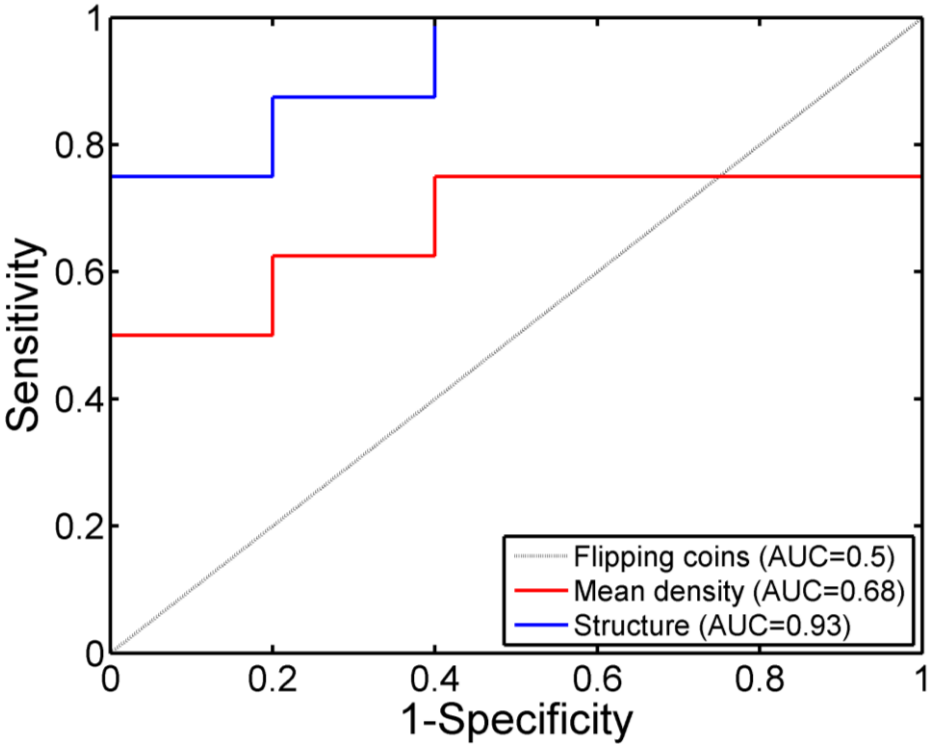




G. Ghobadi et al. Int J Radiat Oncol Biol Phys. 2010

Imaging: CT/Lung

Post-RT CT as predictor of physician score > SWOG 1



Mean density

Threshold	Sensitivity	Specificity
6 HU	75%	60%
11 HU	63%	80%

Structure

Threshold	Sensitivity	Specificity
1.1	88%	80%
1.3	75%	100%

G. Ghobadi et al. Radiother Oncol. 2015

Imaging

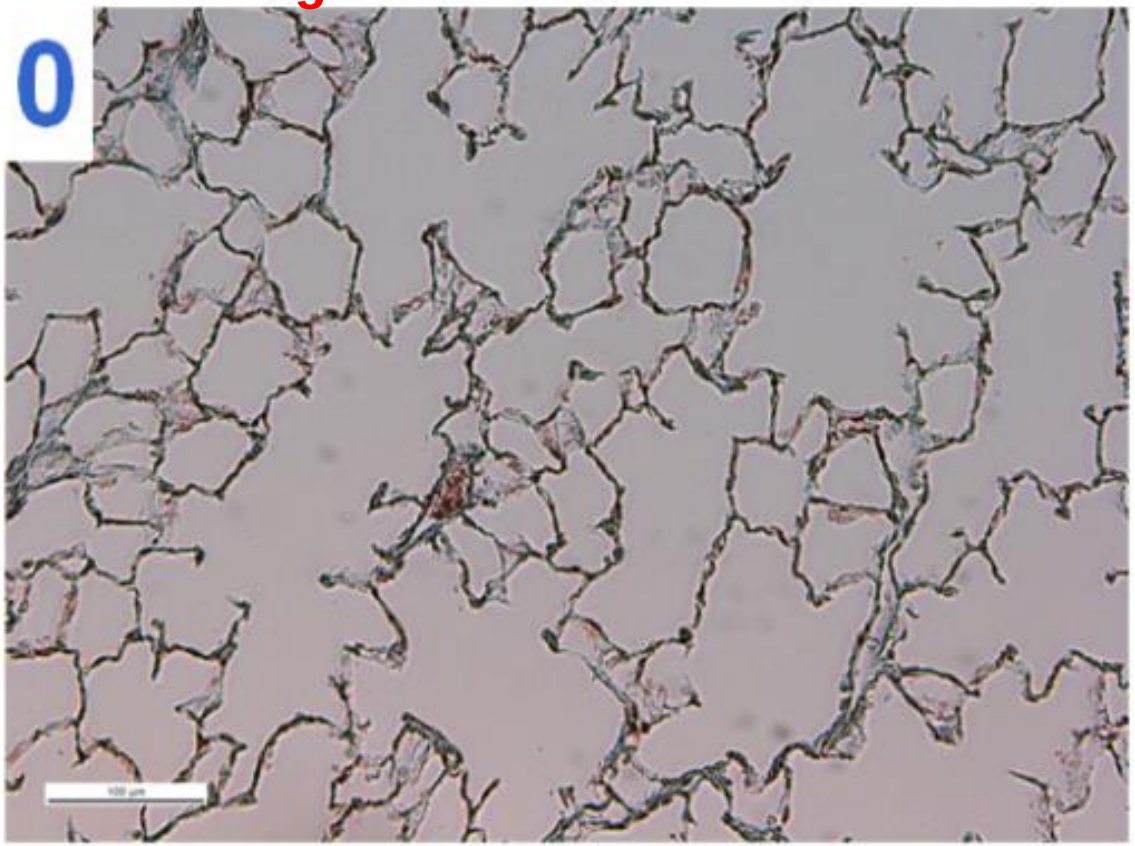
- Characterized relation to pathology, but still association-based
- Alternatives / combinations
  - Directly image cell markers (PET, …)
  - Direct imaging of (functional) consequences (PET, MRI, CT(?), Echo,…)
  - ???
- Opportunities
  - “Import” imaging from other fields
  - Develop techniques to image endpoints unique for radiation responses
  - Validate readouts in animal / in vitro models by specific modulation of the pathology

Radiomics

- Increased use of available information!
- Risks
  - Large numbers of signatures / limited patient numbers
- Link to biology by
  - Pre-selecting signatures based on mechanistic hypothesis?
  - Independently validate findings by looking at biological models?

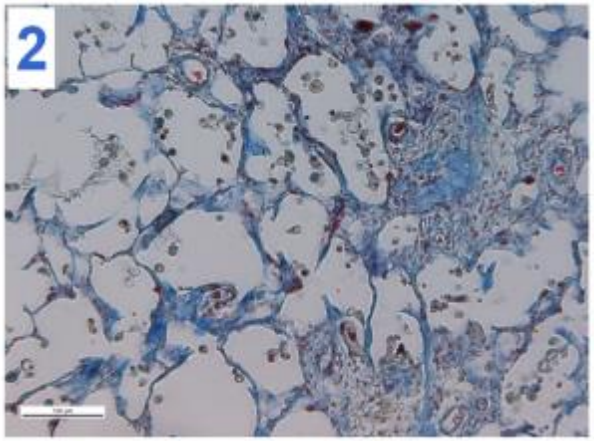
Change in density?

Normal lung tissue



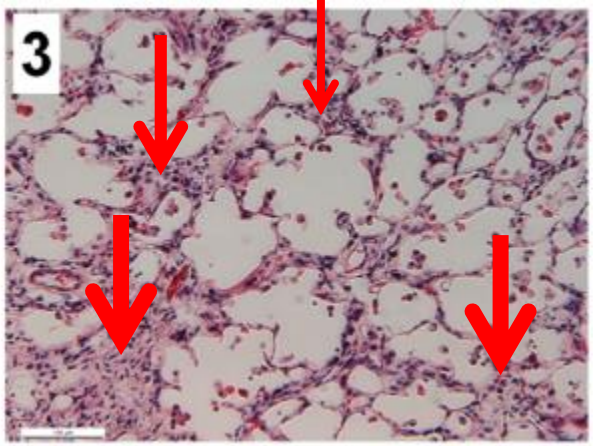
Change in density?

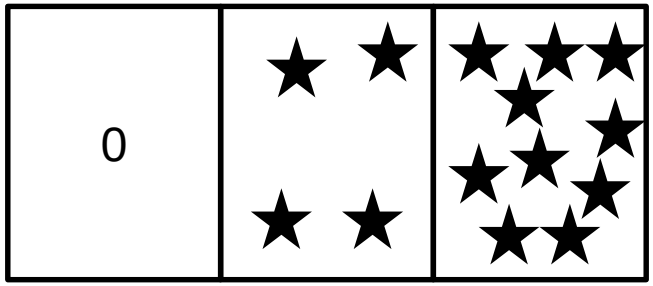
Fibrosis



Change of local value
e.g.: regional mean!

Inflammation





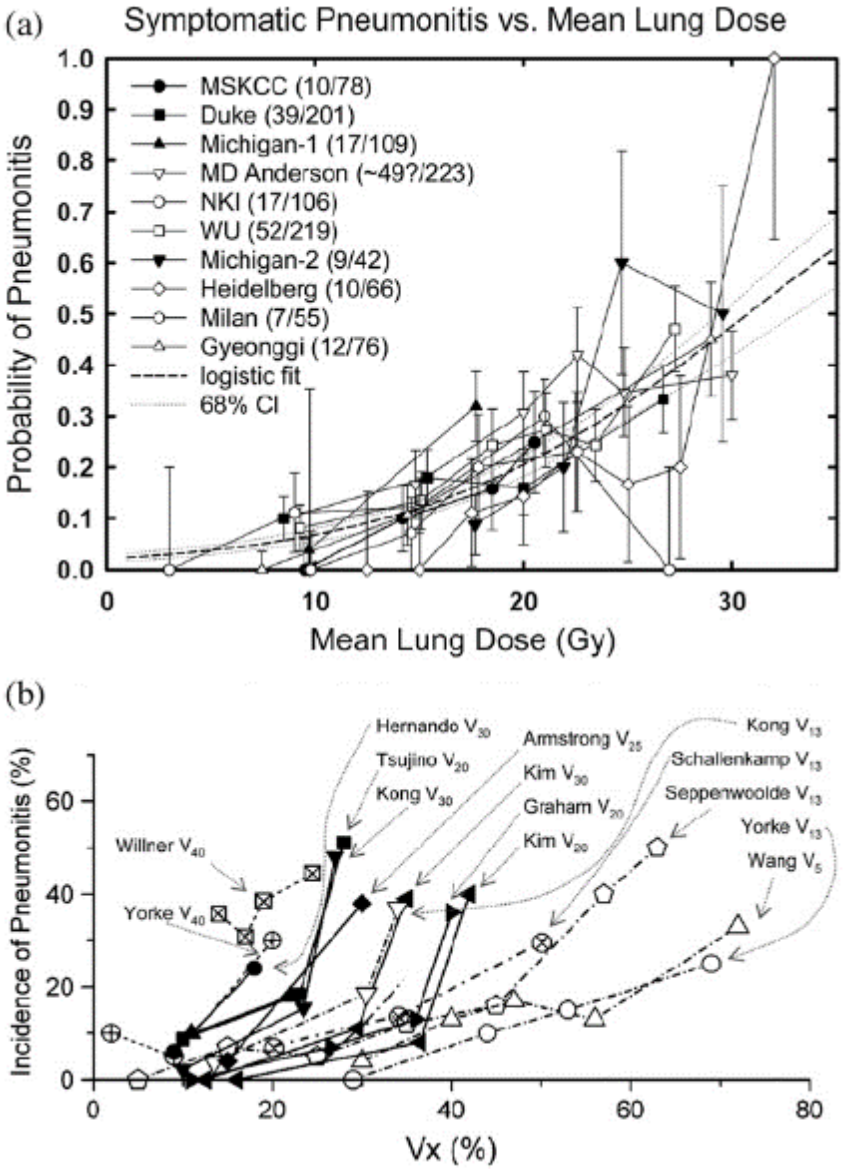
Change in pattern / uniformity!
e.g.: regional standard deviation

ΔS

Biophysics in radiotherapy

- Imaging: see also lectures by Uulke, Eirik
  - Outcome, rather than its associates!
  - Tissue properties, organ function, cell markers
- Outcome modeling
  - Tumor
  - Normal tissues
    - “Volume” effects
    - “RBE” effects when using particles
- Facilitating medicine / biology
  - Specialized irradiation facilities
  - Quantitative analysis of e.g. pathology, imaging, …
  - Analysis of large amounts of data

Biophysics: modeling

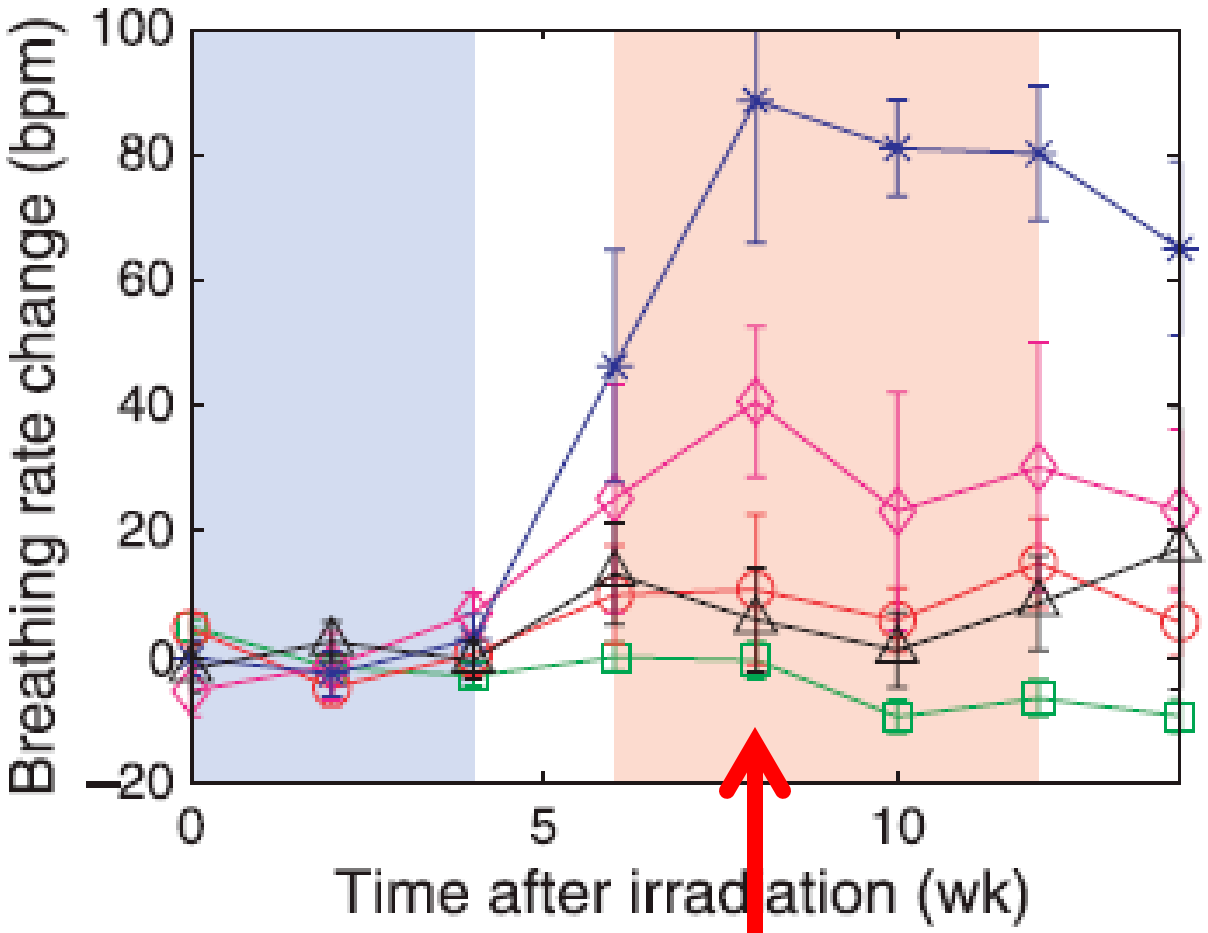


L.B. Marks et al. Int J Radiat Oncol Biol Phys. 2010

Biophysics: modeling

- Aim at:
  - Understanding mechanisms
    - A fitted model:
      - will improve use of current treatments
    - Understanding a mechanism could:
      - change modeling approaches
      - treatments
      - impact other medical disciplines
  - True multi-disciplinarity (Epidemiology, Biology, Radiology, Other medical disciplines, …)

Heart and lung interaction

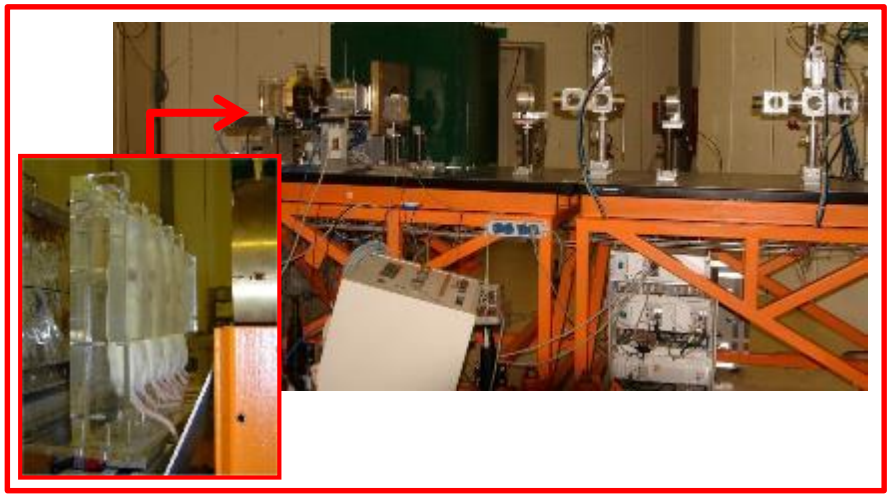


Heart damage after 8 weeks?

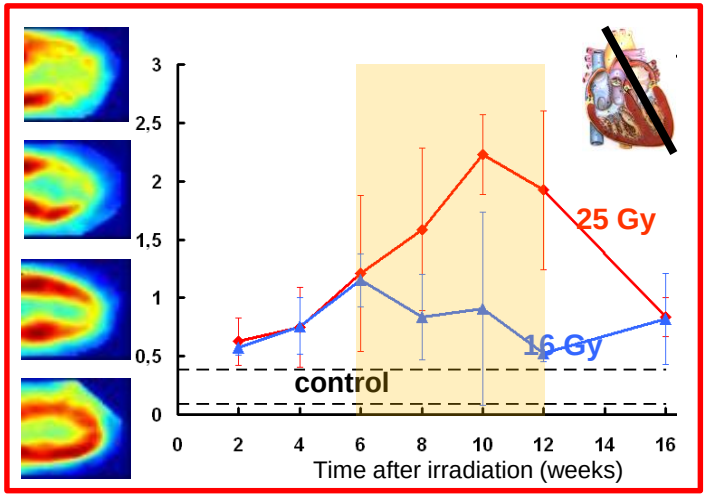
van Luijk et al. Cancer Res. 2005;65:6509-11

Heart and lung interaction

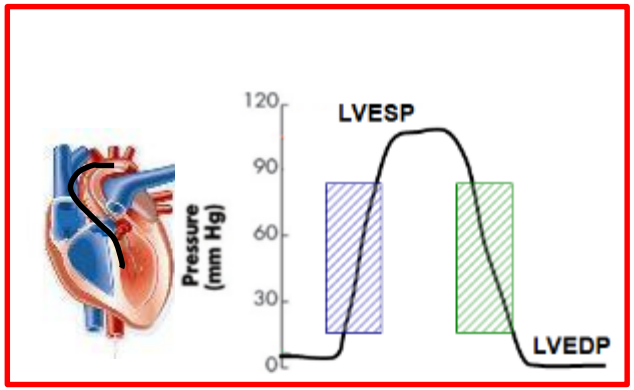
High-precision animal irradiation



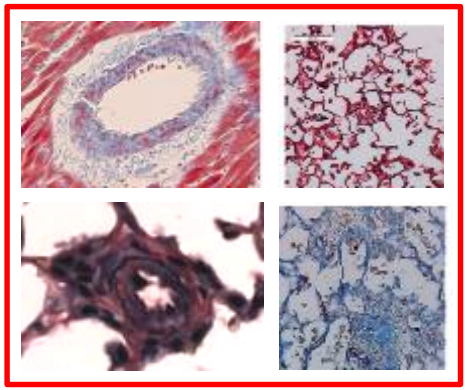
Imaging



Cardiology / Physiology



Histology



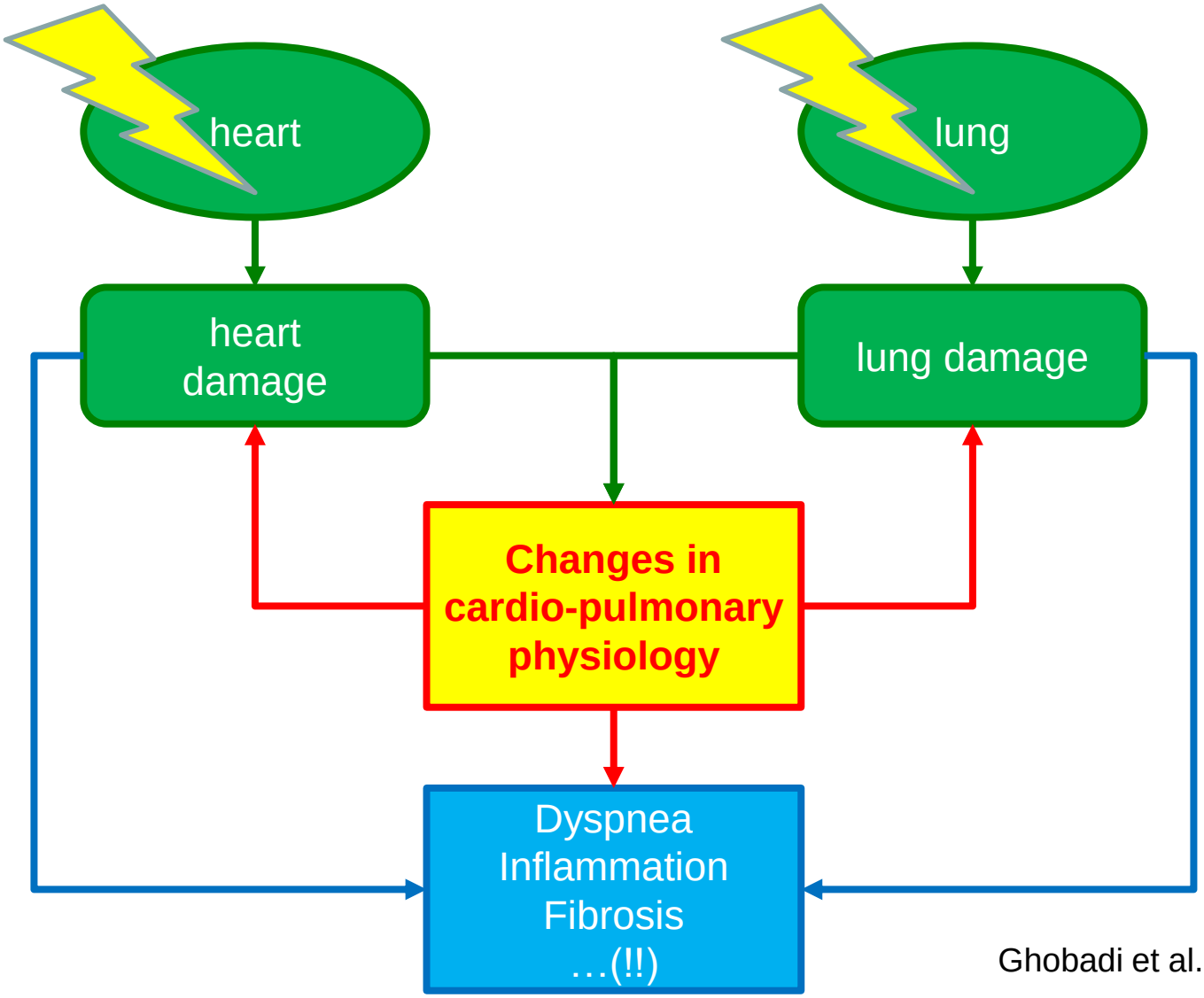
Persistent PhD student

Gazaleh Ghobadi

Ghobadi et al. Thorax 2012

Ghobadi et al. Int J Radiat Oncol Biol Phys. 2012

Heart and lung interaction



Ghobadi et al. Thorax 2012

Ghobadi et al. Int J Radiat Oncol Biol Phys. 2012

Heart and lung interaction

Acta Oncologica, 2010; Early Online, 1–10

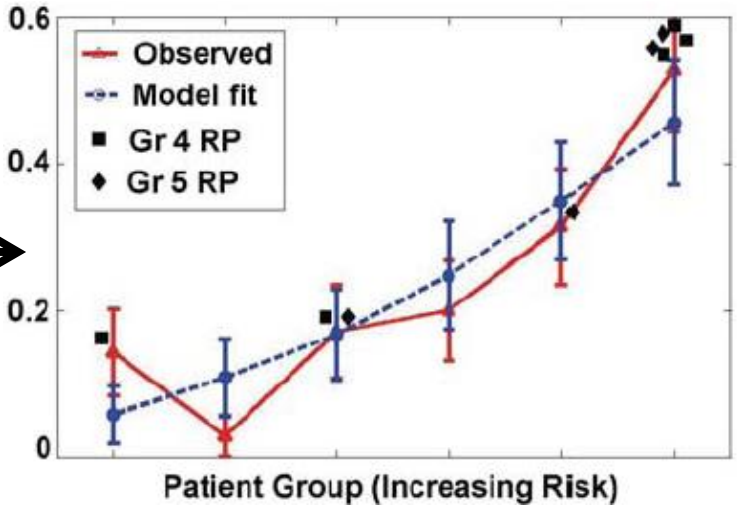
ORIGINAL ARTICLE

Heart irradiation as a risk factor for radiation pneumonitis

ELLEN X. HUANG[1], ANDREW J. HOPE[2], PATRICIA E. LINDSAY[2], MARCO TROVO[3], ISSAM EL NAQA[1], JOSEPH O. DEASY[1] & JEFFREY D. BRADLEY[1]

[1]*Department of Radiation Oncology, Mallinckrodt Institute of Radiology, Washington University School of Medicine, St. Louis, Missouri, USA,* [2]*Princess Margaret Hospital, Toronto, ON, Canada and* [3]*National Cancer Institute, Aviano, Italy*

Model variable	Spearman (Rs)	Significance (p)
D10_H, D35_L, MaxD_L	0.266	<0.0001
D35_L, MaxD_L	0.201	<0.001
V20_L	0.173	<0.01
MLD (Mean Lung Dose)	0.17	<0.01



Huang EX et al. Acta Oncol. 2011;50(1):51-60

Heart and lung interaction

Is there an impact of heart exposure on the incidence of radiation pneumonitis? Analysis of data from a large clinical cohort

SUSAN L. TUCKER[1], ZHONGXING LIAO[2], JEFFREY DINH[2], SHELLY X. BIAN[2], RADHE MOHAN[3], MARY K. MARTEL[3] & DAVID R. GROSSHANS[2]

[1]*Department of Bioinformatics and Computational Biology, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA,* [2]*Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA and* [3]*Department of Radiation Physics, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA*

Abstract

Background. The goal of the present study was to determine, in a large clinical cohort, whether incidental radiation exposure to the heart during definitive radiotherapy of inoperable non-small cell lung cancer (NSCLC) detectably increased the risk of radiation pneumonitis (RP) beyond that resulting from radiation exposure to lung. *Material and methods.* Data were analyzed from all patients who received definitive three-dimensional (3D) concurrent radiotherapy or intensity-modulated radiotherapy for the treatment of NSCLC over a 10-year period at our institution, except those who had previous lung cancer or for whom radiation treatment plans were unavailable for calculation of heart and lung dose-volume histograms (DVHs). Parameters computed from heart and lung DVHs included mean lung dose (MLD), effective lung dose computed using volume parameter $n = 0.5$ (D_{eff}), mean heart dose (MHD), percentage of heart receiving >65 Gy (V65), and minimum dose to the hottest 10% of heart (D10). Univariate and multivariate normal-tissue complication probability (NTCP) models were used to analyze incidence of Grade ≥ 2 or Grade ≥ 3 RP as a function of these and other parameters. *Results.* The study cohort included 629 patients, with crude rates of Grade ≥ 2 RP and Grade ≥ 3 RP of $N = 263$ (42%) and $N = 124$ (20%), respectively. Univariate NTCP models based on dosimetric lung parameters (MLD and D_{eff}) fit the data better than models based on univariate heart parameters (heart D10, heart V65 or MHD). In multivariate modeling, incorporation of heart parameters did not significantly improve the fit of RP risk models based on lung parameters alone ($p > 0.38$ in each case). *Conclusions.* In this large clinical cohort, there was no evidence that incidental heart exposure during radiotherapy of NSCLC had a detectable impact on the occurrence of moderate or severe RP.

Tucker SL et al. Acta Oncol. 2014

In patients?

Modeling the risk of radiation-induced lung fibrosis: Irradiated heart tissue is as important as irradiated lung

Laura Cella [a,*], Vittoria D'Avino [a], Giuseppe Palma [a], Manuel Conson [a,b], Raffaele Liuzzi [a], Marco Picardi [c], Maria Cristina Pressello [d], Genoveva Ionela Boboc [e], Roberta Battistini [f], Vittorio Donato [e], Roberto Pacelli [a,b]

[a] *Institute of Biostructure and Bioimaging, National Research Council (CNR);* [b] *Department of Advanced Biomedical Sciences, Federico II University School of Medicine;* [c] *Department of Clinical Medicine and Surgery, Federico II University School of Medicine, Naples;* [d] *Department of Health Physics, S. Camillo-Forlanini Hospital, Rome;* [e] *Department of Radiation Oncology, S. Camillo-Forlanini Hospital, Rome; and* [f] *Department of Hematology, S. Camillo-Forlanini Hospital, Rome, Italy*

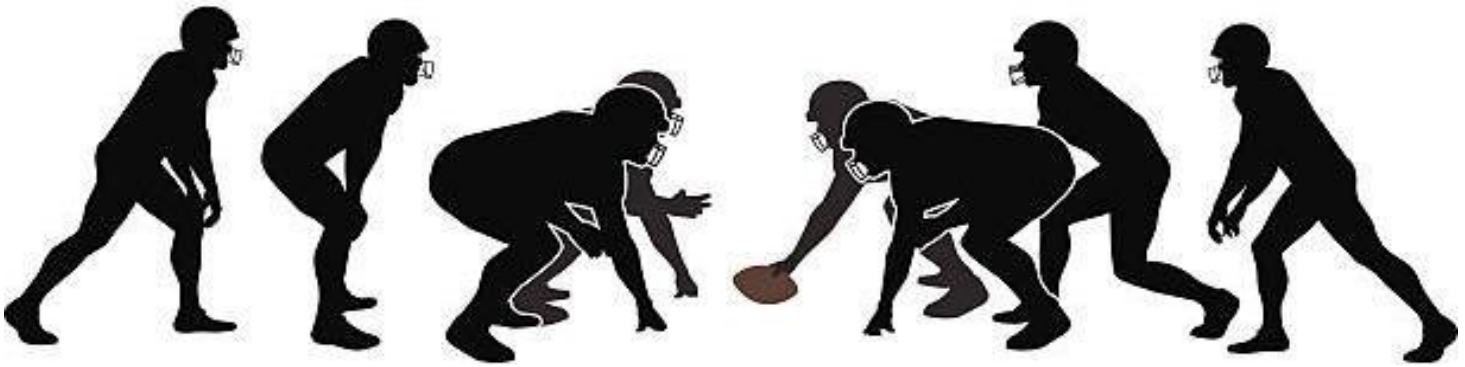
Purpose: We used normal tissue complication probability (NTCP) modeling to explore the impact of heart irradiation on radiation-induced lung fibrosis (RILF).

Materials and methods: We retrospectively reviewed for RILF 148 consecutive Hodgkin lymphoma (HL) patients treated with sequential chemo-radiotherapy (CHT-RT). Left, right, total lung and heart dose–volume and dose–mass parameters along with clinical, disease and treatment-related characteristics were analyzed. NTCP modeling by multivariate logistic regression analysis using bootstrapping was performed. Models were evaluated by Spearman *Rs* coefficient and ROC area.

Results: At a median time of 13 months, 18 out of 115 analyzable patients (15.6%) developed RILF after treatment. A three-variable predictive model resulted to be optimal for RILF. The two models most frequently selected by bootstrap included increasing age and mass of heart receiving >30 Gy as common predictors, in combination with left lung V5 (*Rs* = 0.35, AUC = 0.78), or alternatively, the lungs near maximum dose $D_{2\%}$ (*Rs* = 0.38, AUC = 0.80).

Conclusion: CHT-RT may cause lung injury in a small, but significant fraction of HL patients. Our results suggest that aging along with both heart and lung irradiation plays a fundamental role in the risk of developing RILF.

Tucker SL et al. Acta Oncol. 2014



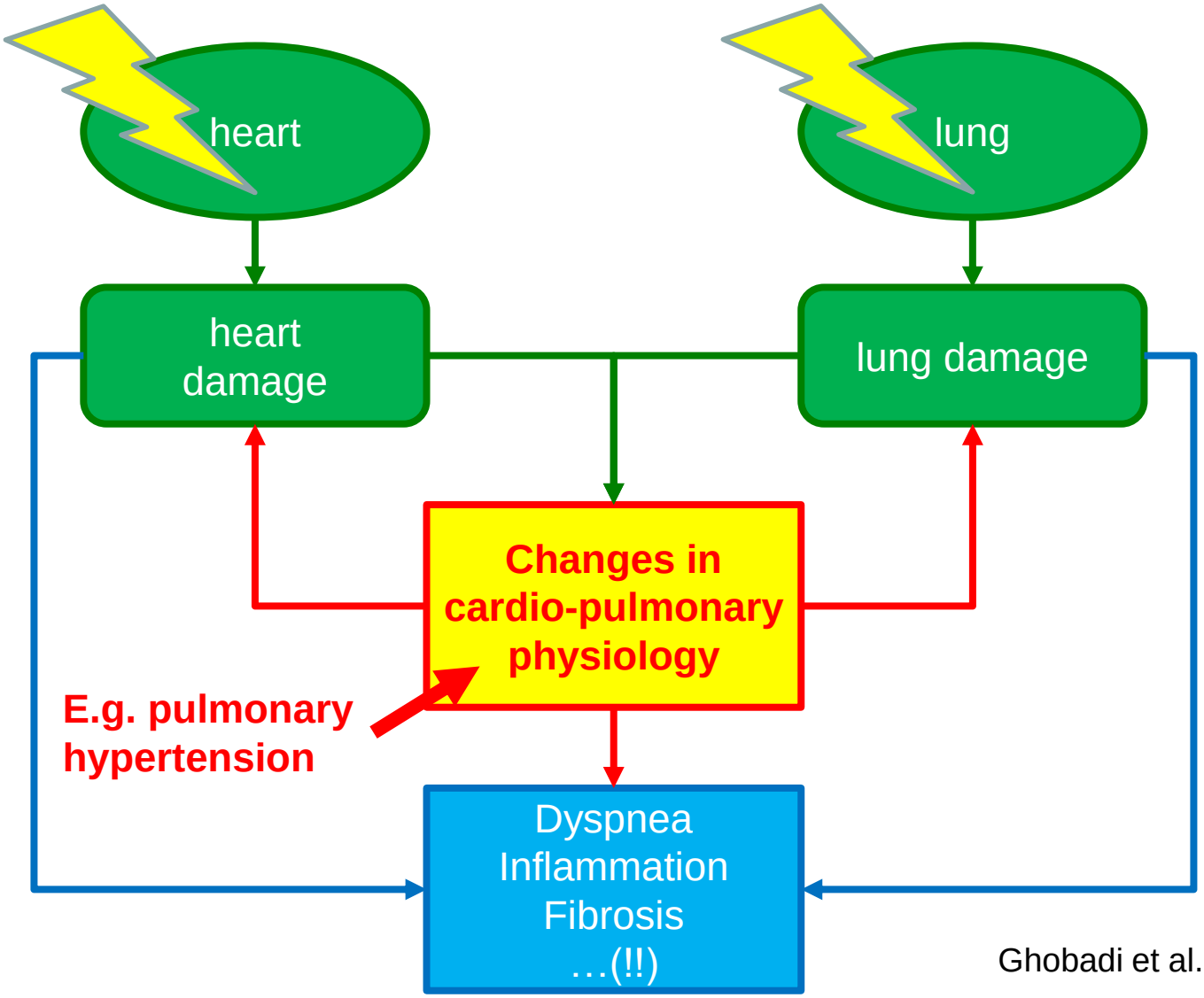

2
90:00
1

????????

Translation via modeling??

- Models represent correlations
- Correlations do not proof a mechanism
  - Cardiac dose metric may correlate to another (lung) dose metric that was not considered
- Lack of correlation does not proof / reject a mechanism
  - Power?
  - Population/treatment characteristics?
  - Was the relevant dose metric considered and did it vary sufficiently?
  - Medication?

Heart and lung interaction



Ghobadi et al. Thorax 2012

Ghobadi et al. Int J Radiat Oncol Biol Phys. 2012

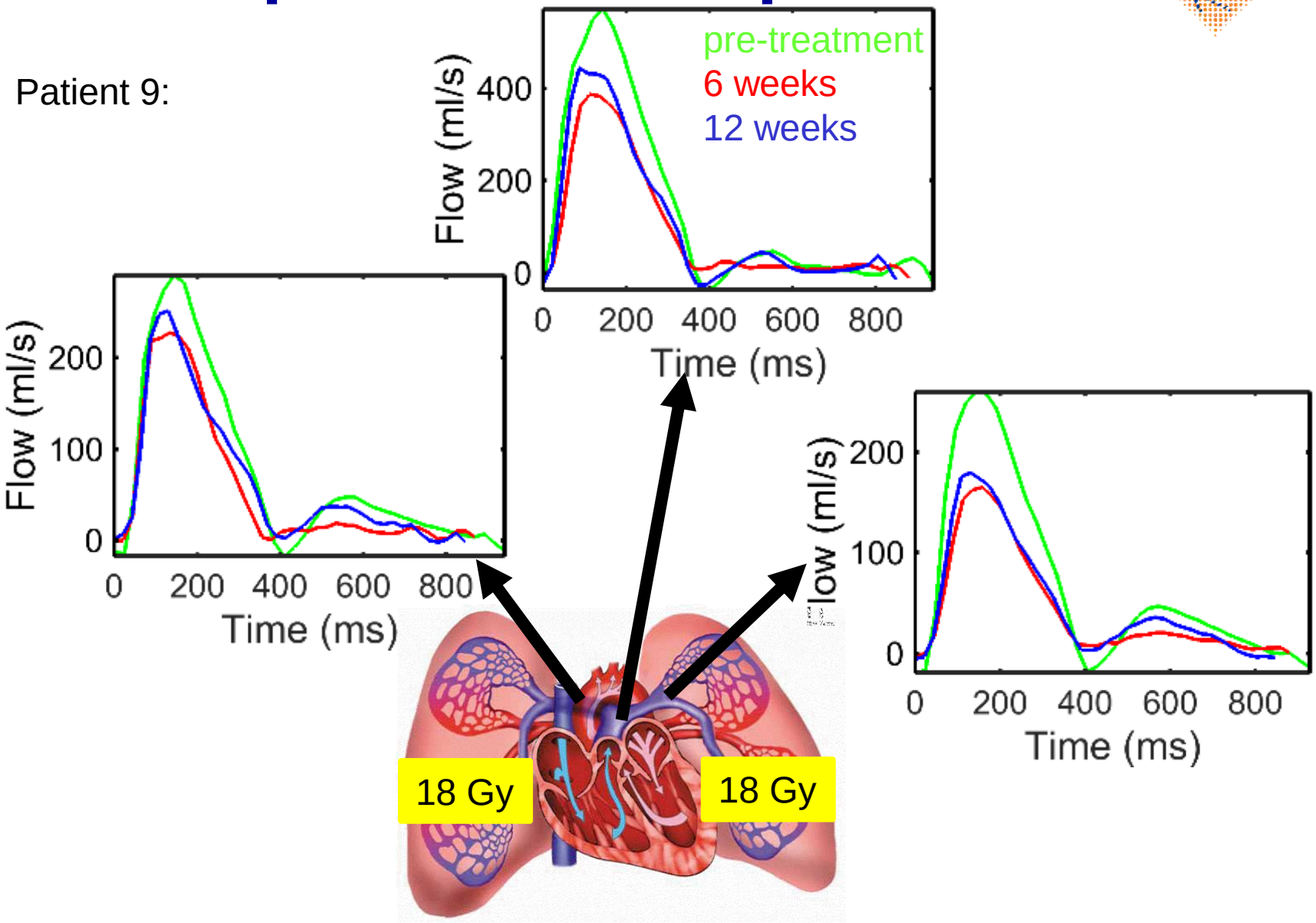
Specific, prospective test

- Can thoracic radiotherapy cause pulmonary hypertension?
- Prospective series: 9 NSCLC patients
  - Velocity-encoded MRI
    - Pre-treatment
    - 6 weeks after treatment
    - 12 weeks after treatment
  - Pulmonary blood flow in pulmonary arteries

ClinicalTrials.gov Identifier: NCT02377934

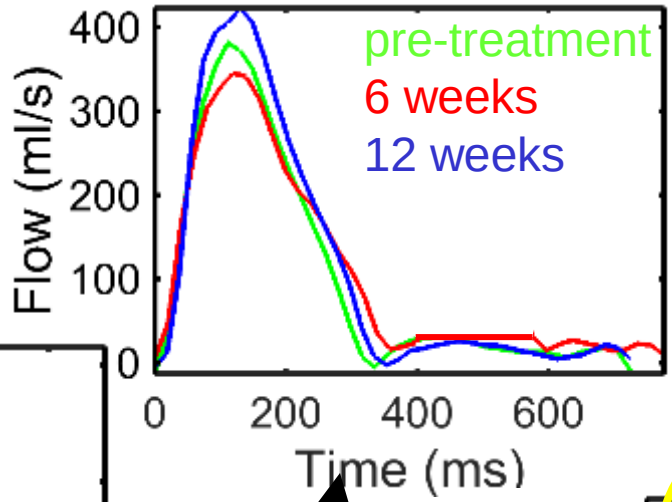
Flow profile – example 1

Patient 9:

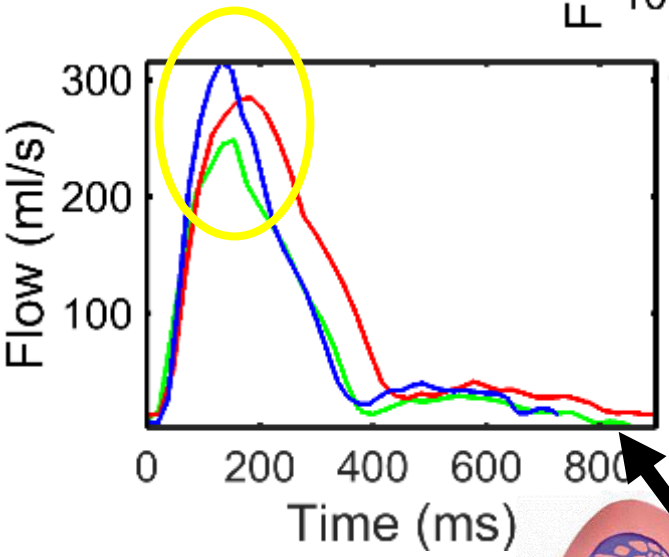


Flow profile – example 2

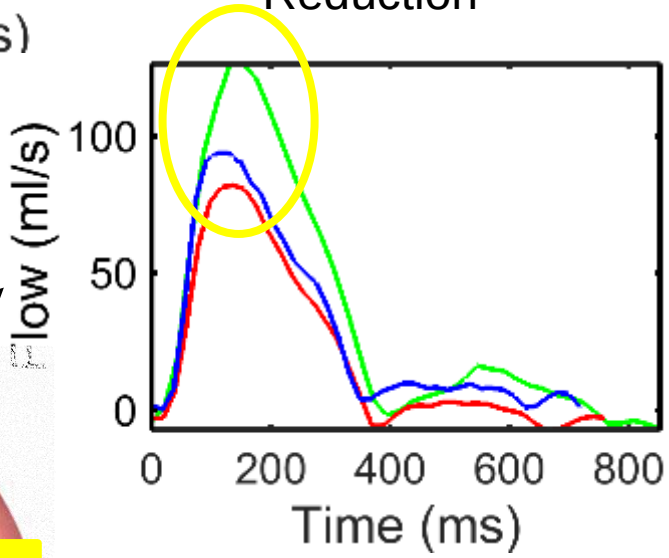
Patient 5:

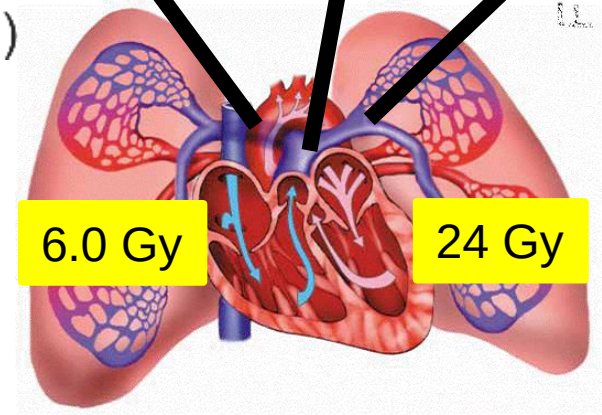


Compensation

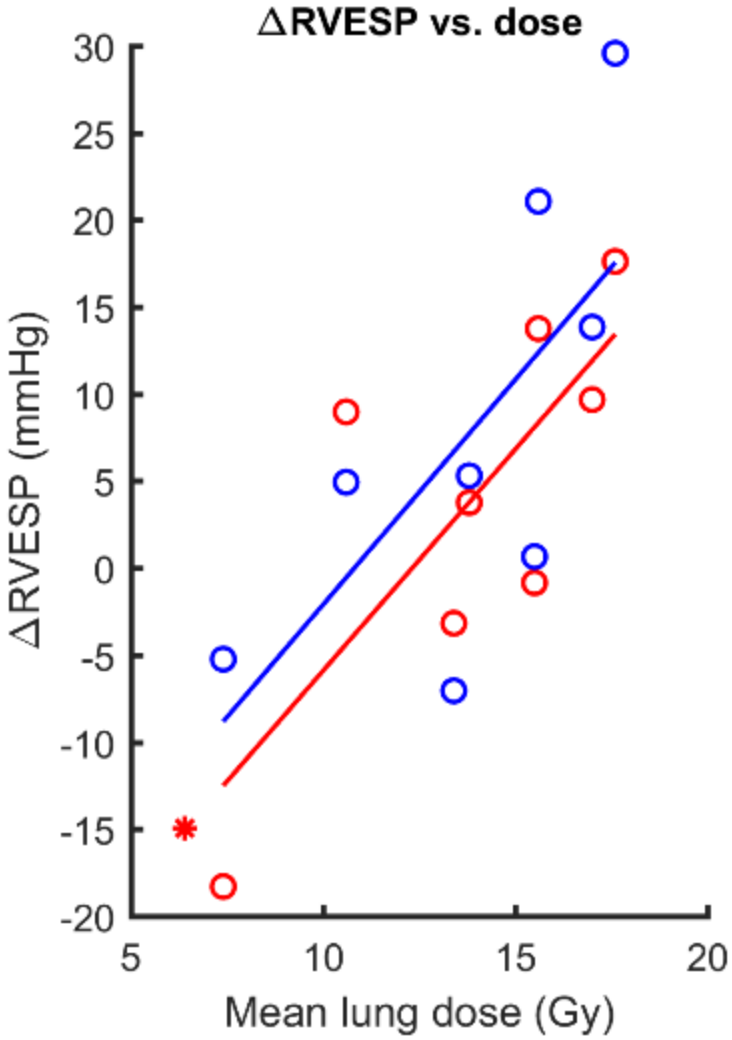


Reduction





Estimated pressure increase



- Main branch
- Estimate based on a model developed in echocardiography
- Dose dependent increase in pulmonary artery pressure!

Ultrasound-based model from: Yared, et al. J Am Soc Echocardiogr 2011;24:687-92

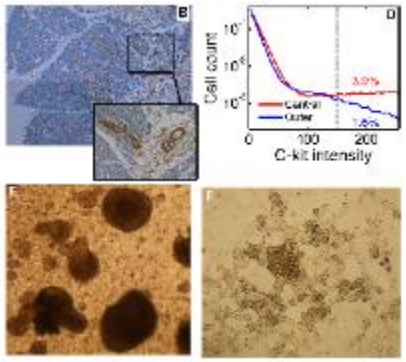
Biophysics: modeling

- Aim at:
  - Understanding mechanisms
    - A fitted model:
      - will improve use of current treatments
    - Understanding a mechanism could:
      - change modeling approaches
      - treatments
      - impact other medical disciplines
  - True multi-disciplinarity (Epidemiology, Biology, Radiology, Other medical disciplines, …)

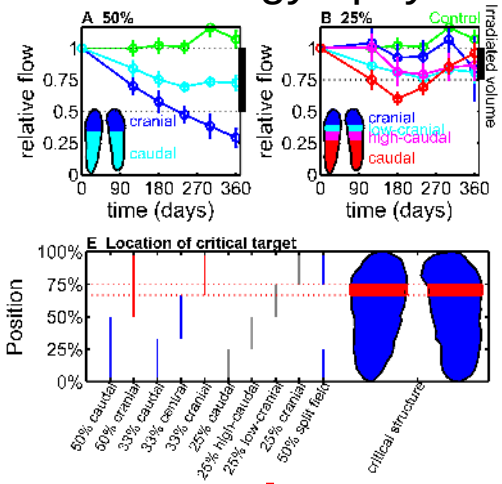
Heart-Lung work:
- Calls for changes in optimization of thoracic RT (consider heart dose)
- Identified new, serious, toxicity: Pulmonary hypertension
- Yielded the 1st animal model for human pulmonary arterial hypertension

Critical target in parotid

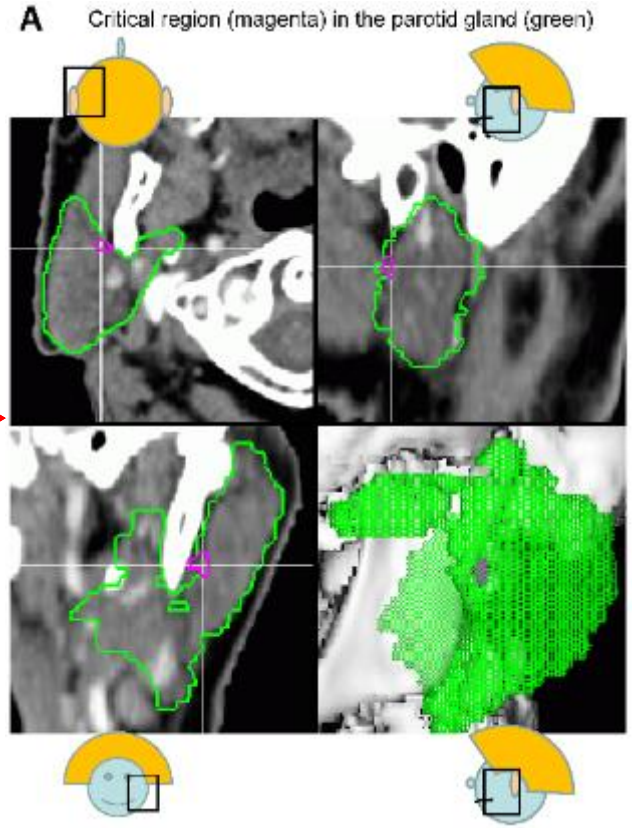
Stem cell biology



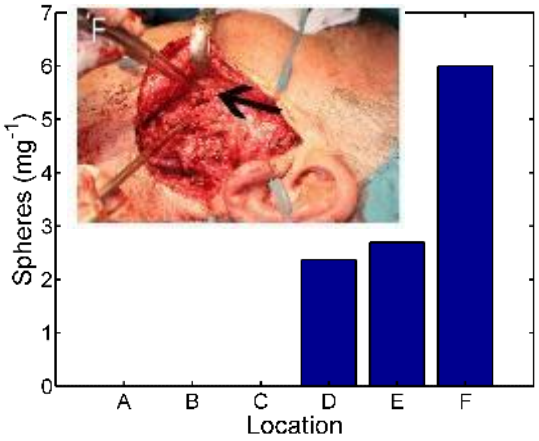
Radiobiology / physics



Radiation Oncology



H&N surgeon



Van Luijk et al. Sci Transl Med. 2015 7(305):305ra147

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  - True multi-disciplinarity (Epidemiology, Biology, Radiology, Other medical disciplines, ...)

Parotid gland work:
- Identified a critical target for radiation response
- Calls for changes in modeling of response /sparing a new structure
- Could change use of technology / change technology
- Implications for stem cell transplantation treatment

Biophysics: modeling

- Aim at:
  - Understanding mechanisms
    - A fitted model:
      - will improve use of current treatments
    - Understanding a mechanism could:
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      - treatments
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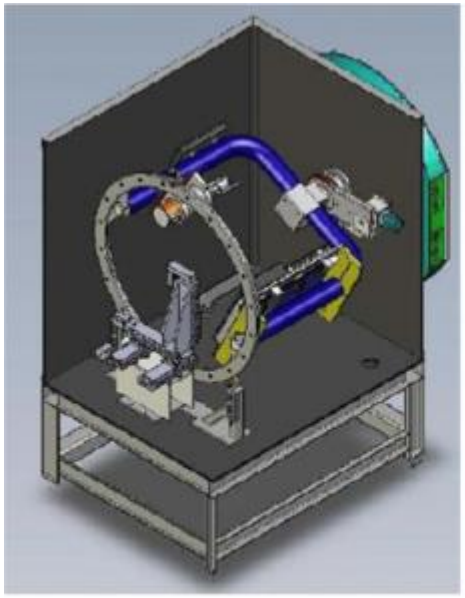
  - True multi-disciplinarity (Epidemiology, Biology, Radiology, Other medical disciplines, …)

Biophysics in radiotherapy

- Imaging: see also lectures by Uulke, Eirik
  - Outcome, rather than its associates!
  - Tissue properties, Cell markers
- Outcome modeling
  - Tumor
  - Normal tissues
    - “Volume” effects
    - “RBE” effects when using particles
- Facilitating medicine / biology
  - Specialized irradiation facilities
  - Quantitative analysis of e.g. pathology, imaging, …
  - Analysis of large amounts of data

Specialized irradiation facility

High-precision, “clinically relevant” small animal irradiators



Opportunities

- In vivo radiobiology was rare because it required customized solutions to be developed in the lab
- Broad availability makes it easy to perform and should make it more accessible to physicists interested in multidisciplinary approaches to e.g. response modelling.

“Clinically relevant”

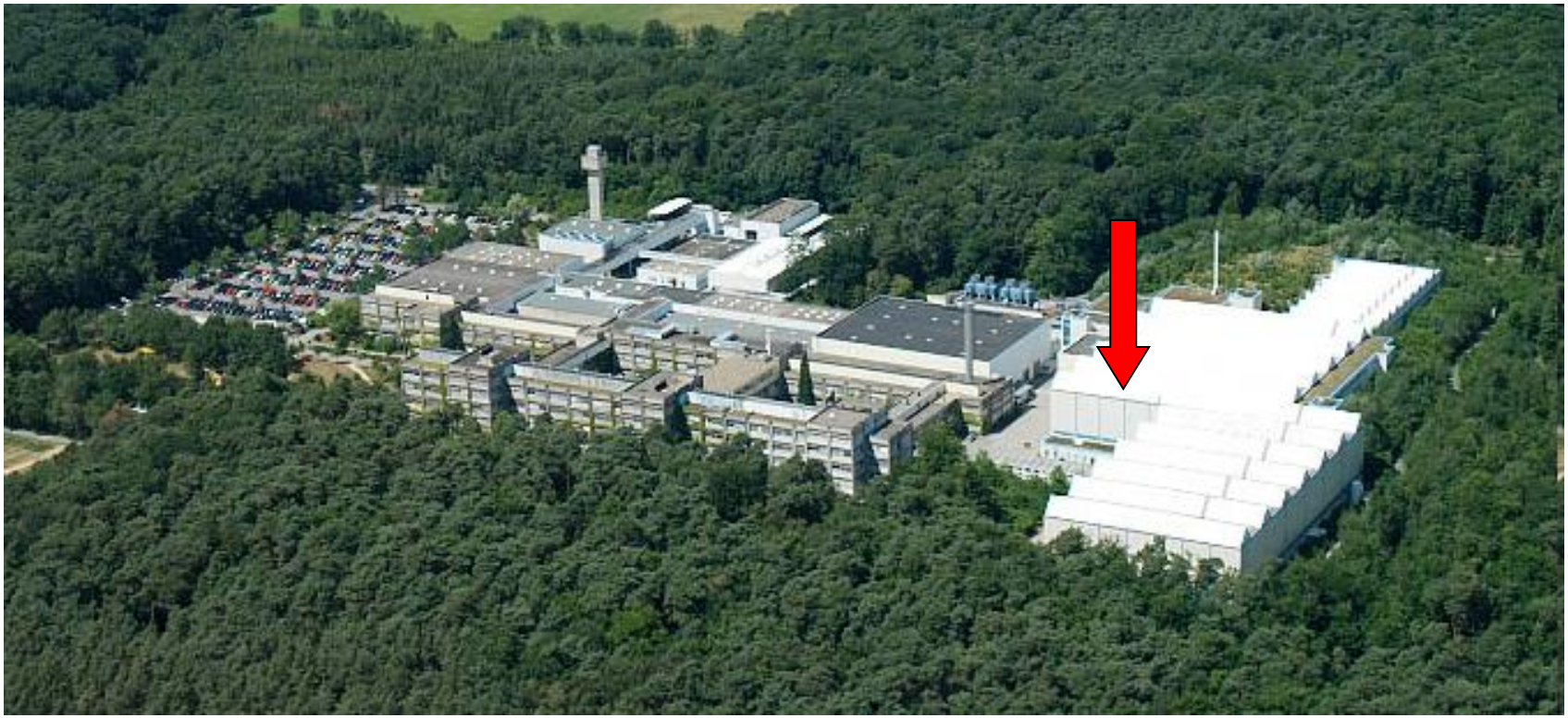
- Clinical-grade
  - Imaging
  - Treatment planning
  - Delivery

“Clinically relevant” ?

- Clinical-grade
  - Imaging
  - Treatment planning
  - Delivery
- But …
  - It’s a rodent!
  - Dose distributions scale, but biology doesn’t!
  - Biology WILL differ at differing scales
  - Scaled clinical dose distributions will poorly model clinical effects!
- Think carefully about your study design!!

Specialized irradiation facility

GSI Darmstadt: Clinical-grade high-energy carbon ions



Specialized irradiation facility

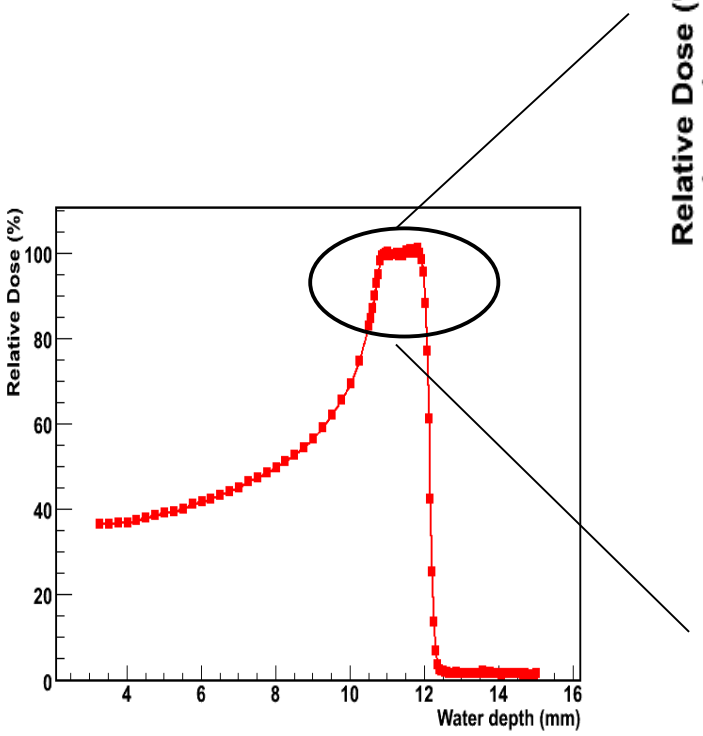
High-precision, high-LET cell irradiation (carbon ions)

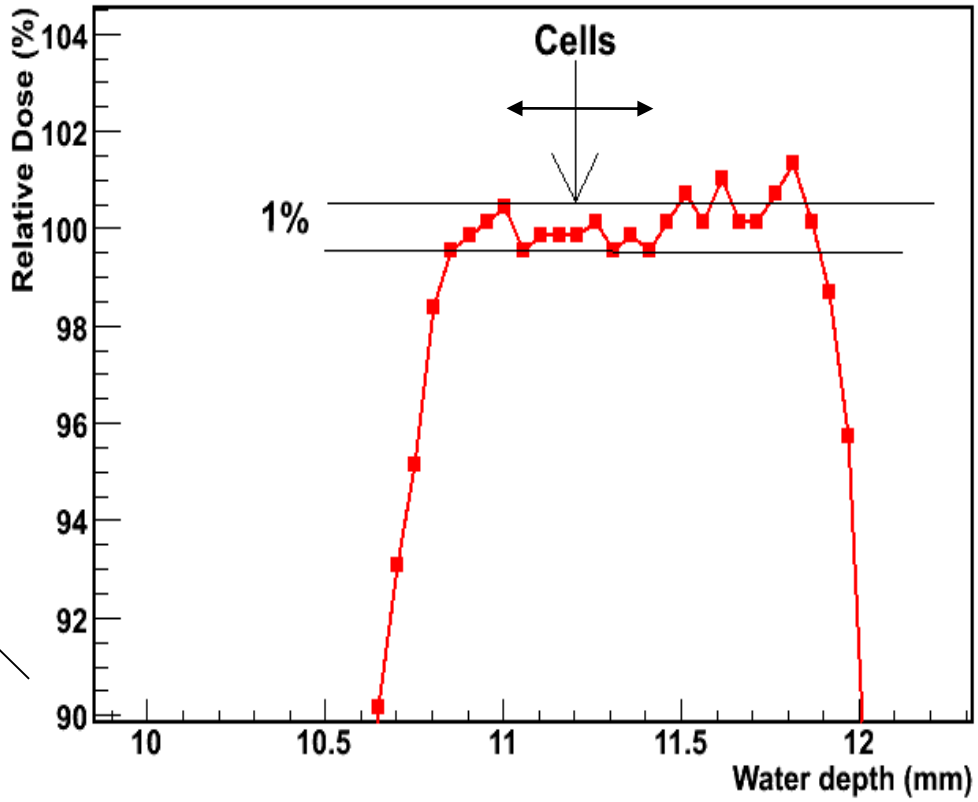
Van Goethem et al. Med Phys. 2011 Jan;38(1):256-63

Specialized irradiation facility

Spread Out Bragg Peak

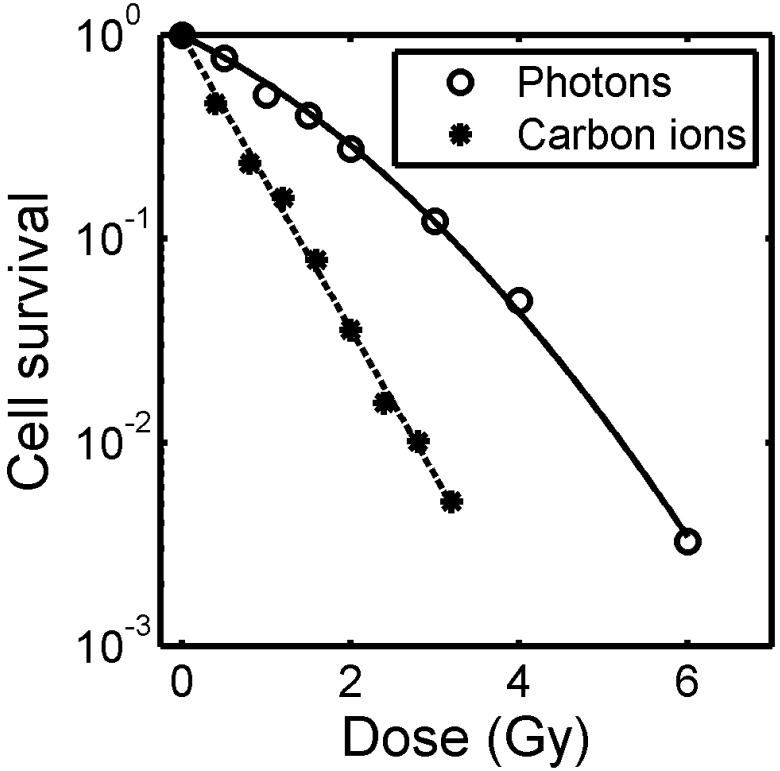
- modulation 1.35 mm
- flatness ~1%
- LET: 189 +/- 15 keV/µm





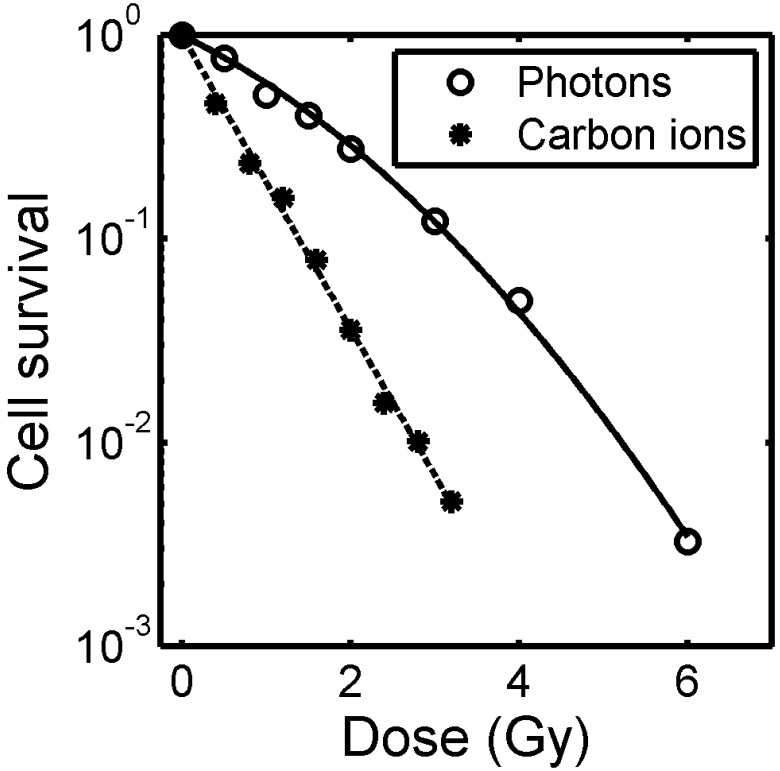
Van Goethem et al. Med Phys. 2011 Jan;38(1):256-63

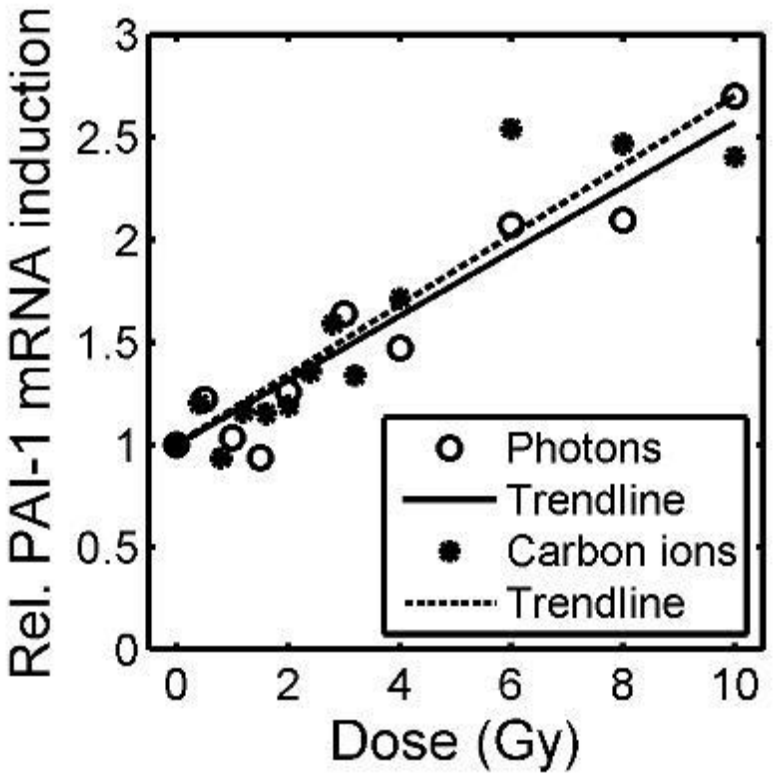
Specialized irradiation facility



Niemantsverdriet et al. Int J Radiat Oncol Biol Phys. 2012 Jul 15;83(4):1291-7

Specialized irradiation facility





Niemantsverdriet et al. Int J Radiat Oncol Biol Phys. 2012 Jul 15;83(4):1291-7

Aim

- What is the role of biophysics in radiotherapy
- Provide a brief overview of topics in the field
- Identify what would make me enthusiastic for new research in these areas

Research combining knowledge, tools and expertise from multiple disciplines to solve questions in radiotherapy

Physics MasterClass ESTRO, Firenze 10-13 September 2017

Trends and research opportunities in dose response modelling

C. Fiorino

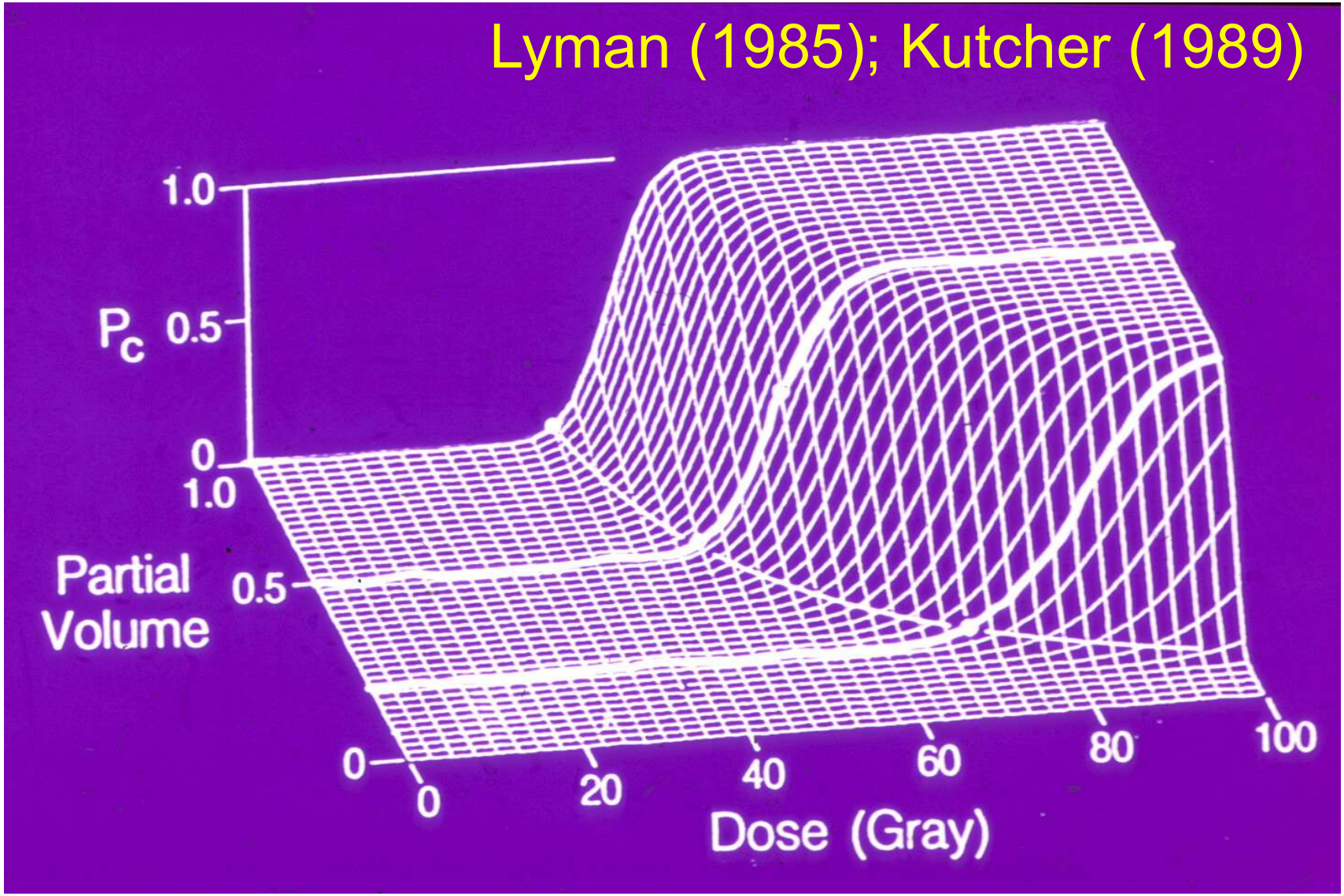
Medical Physics, San Raffaele Institute, Milano, Italy

OSPEDALE
SAN RAFFAELE

Summary

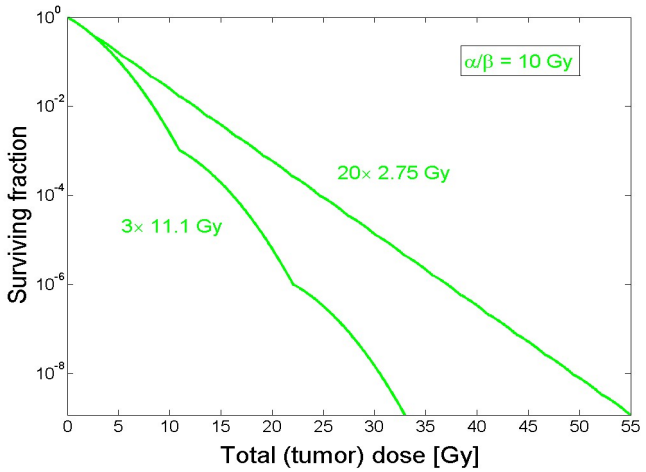
- The long tradition of MP in the field of outcome/toxicity modeling
- Why medical physicists have been relevant in the field ?
- Why are they still more important today (and tomorrow) ?
- MP & personalized RT (big data issues...)
- Major trends of R&D for MP in predictive modeling in RT
- Final remarks

Quantitative Predictive Models in RT: a long tradition

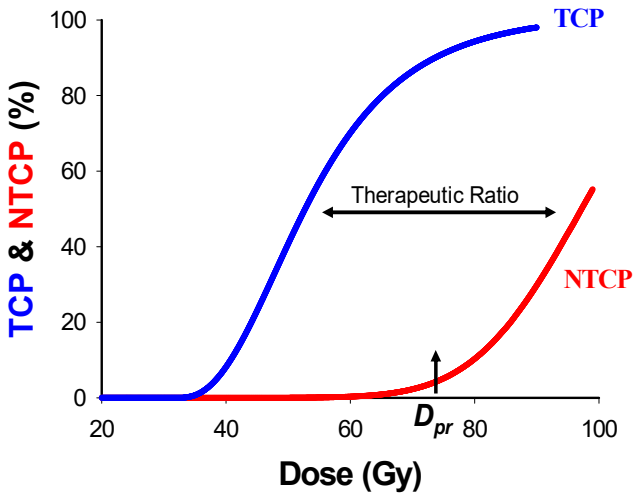


Modelling tumour response: a long successful story

- Fit of Clinical Data on local control/survival
- Models of fractionation (LQ)
- Population-based TCP models
- Incorporating repopulation, hypoxia, functional imaging information…
- Incorporation of dose distribution heterogeneity, Dose painting and response's models for resistant sub-volumes…
- Models of tumour progression and regression
- Models of secondary cancer induction



For a given fraction size

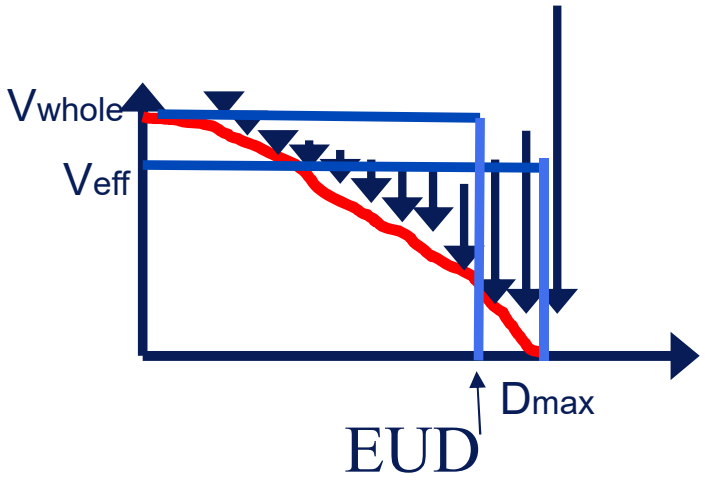


Modelling normal tissues response: a long successful story

- Assessment and modeling of dose-volume effects
- Quantitative (organ-based) relationships
- NTCP models through DVH reduction (LKB, gEUD….)
- Mechanistic models
- Impact of fractionation (LQ-based and updates…)
- Milestones of Emami/Burman paper (1991) and QUANTEC Supplement (2009)

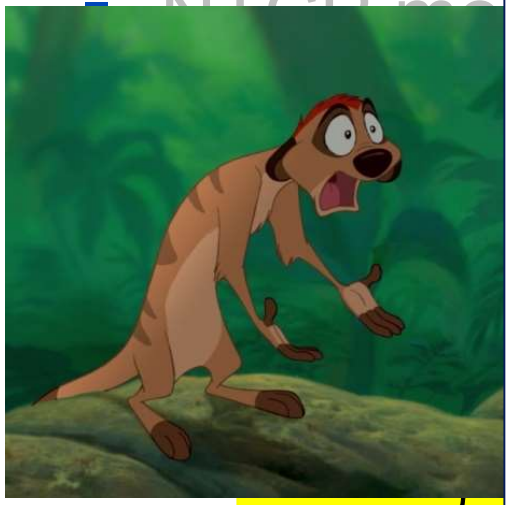
$$EUD = \left(\sum_i v_i * (D_i)^{1/n} \right)^n$$

n ≈ volume effect



Modelling normal tissues response: a long successful story

- Assessment and modeling of dose-volume effects
- Quantitati
- NTCP mo



$$EUD = \left(\right.$$

$n \approx$ vo

- Quantitative analyses dealing with the relationship between dosimetric data (for instance DVH) and toxicities are heavily present in our Journals and their scientific impact is high…..!
- Considering all papers published in the last 10 years in the Green or Red Journal (n=10.500), 3/20, 8/50 and 12/100 most cited papers come from the field of quantitative modelling of toxicity

……from ESTRO lecture: "How to bring QUANTEC into the 21° century ?» Turin 2016

EUD

Dmax

Predictive models in RT & MP: a successful story

Why ?

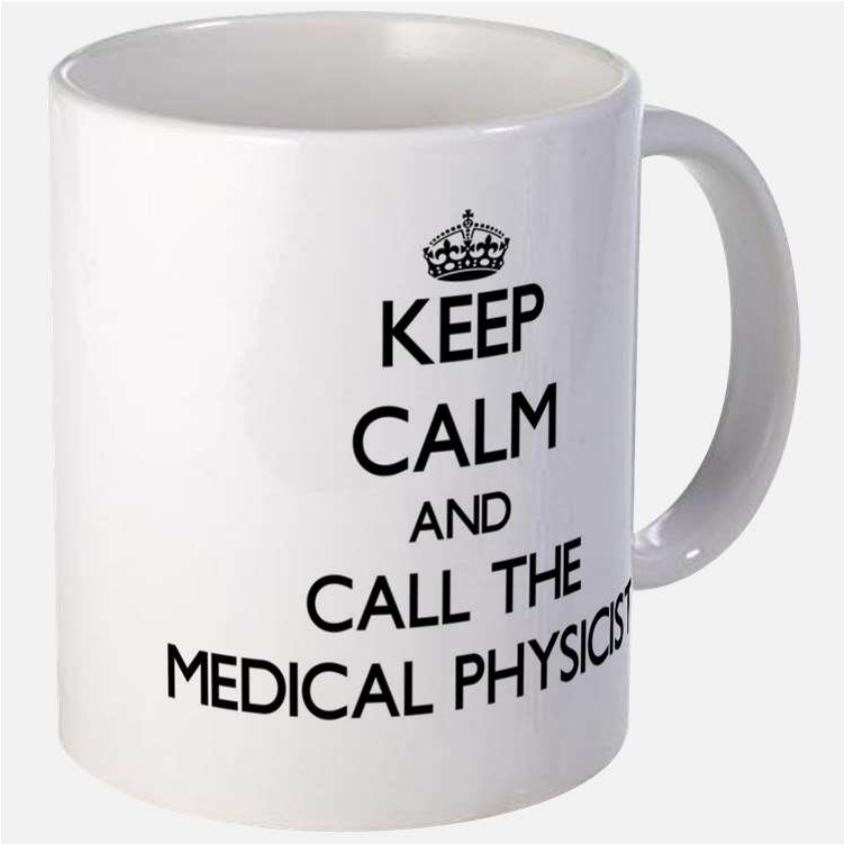
Predicting is a medical physics peculiarity

Is there still space for medical physicists to contribute to these challenging developments as they have done over past decades? The question is provocative and the answer is obvious since the prediction of what may happen, given some "boundary conditions", is an innate interest of physicists and, specifically, of medical physicists.

Physics Corner, ESTRO Newsletter March-April 2015

Predictive models in RT & MP: a successful story

Why ?

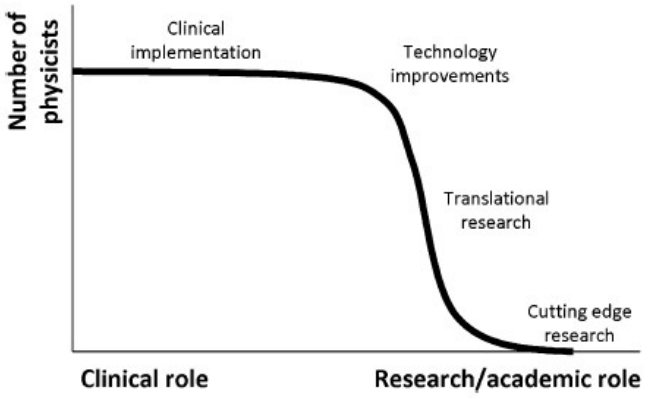


Predictive models in RT & MP: a successful story

Why ?

Last 25 years: the golden age of technology revolution of RT ! ….

more and more expectancies from biology, omics, data, models…..predict to personalize



Bortfeld & Jeraji, BJR 2011

Predictive models in RT & MP: a successful story

Why ?

Mathematics

Informatics

Oncology

Radiation physics

Patient Data

Omics

Imaging &
image analysis

Radiology

Bioengineering

Radiobiology

Particle physics

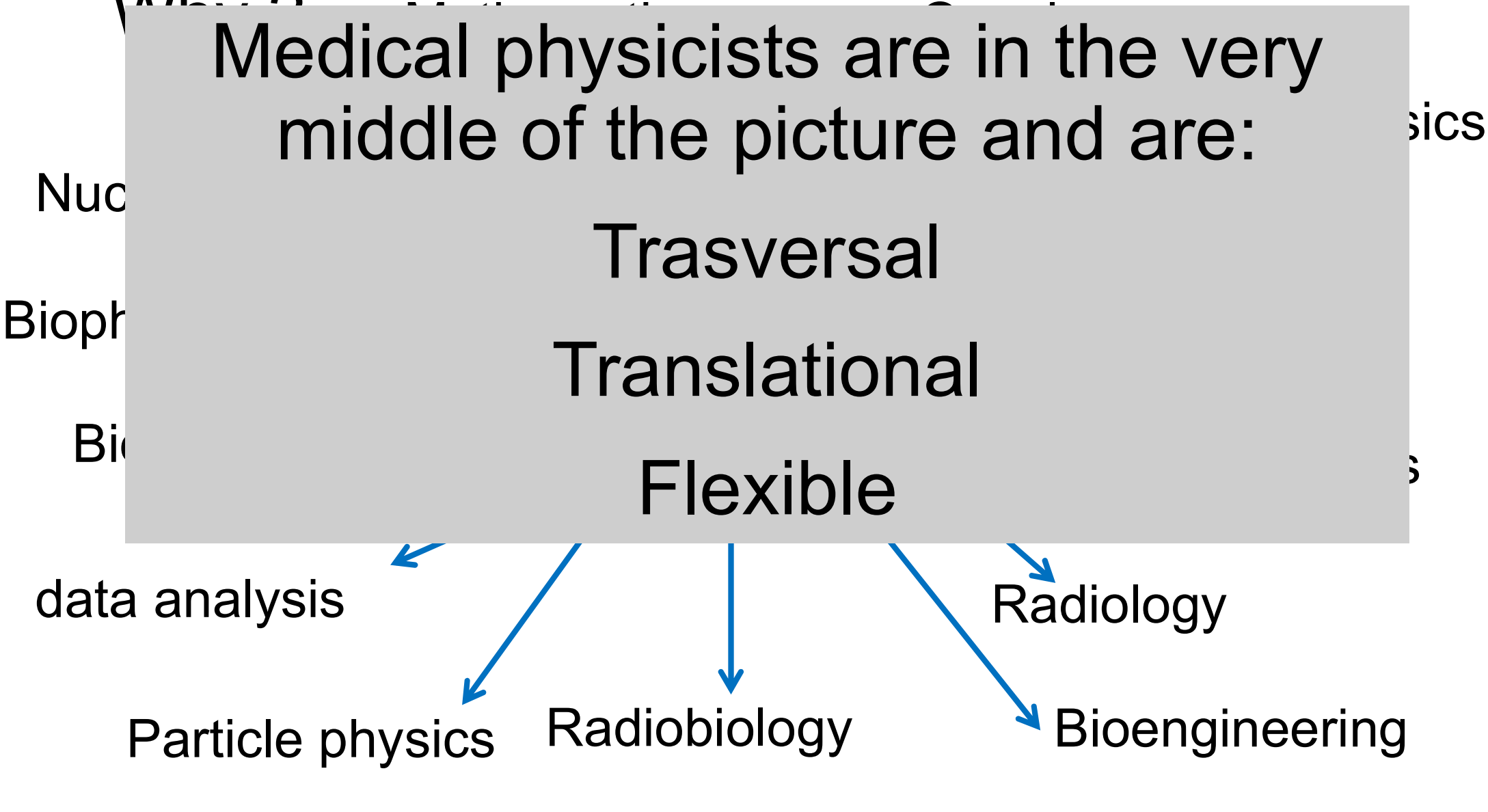
data analysis

Biostatistics

Biophysics

Nuclear Medicine

Predictive models in RT & MP: a successful story



«glorious past», …..challenging present and future (?)

- Development of predictive models: one of the 4 major strategic topics of research for RT in the next years !!!!

ESTRO Vision 2012

ESTRO 2012 Strategy Meeting: Vision for Radiation Oncology

Vincenzo Valentini *[1,4,5], Jean Bourhis [2,4,5], Donal Hollywood [3,4,5]

European Society for Radiotherapy and Oncology (ESTRO), Brussels, Belgium

(c) To enable the above improvements in clinical care, ESTRO will, through its congress, special meetings, educational courses and journal(s), support the future development of radiation oncology, emphasising and supporting the need for the following:

- New approaches to adaptive radiotherapy integrating novel developments in biology, imaging, technology, and the assessment of tumour response and patient outcome.
- Innovative research and development on the potential future use of novel biological modifiers of tumour and normal tissue response.
- The development of validated predictive models of treatment outcome based on complex databases comprising clinical, biologic, genetic, imaging, dosimetric and population data.
- The continued development of quality programmes, including clinical audit and comprehensive safety systems in Radiation and Clinical Oncology that maintain the principles of providing the highest quality of patient care and treatment in a safety-aware enviroment.

«glorious past», …..challenging present and future (?)

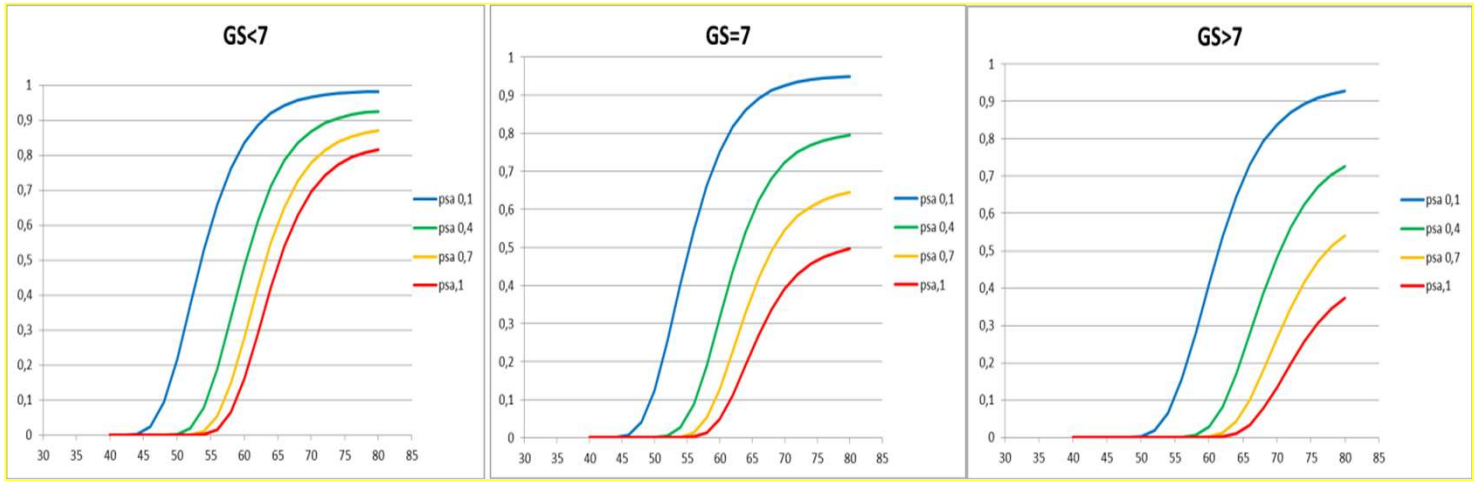
- The key point of the coming time: Personalized Radiation Oncology (see next talk….)

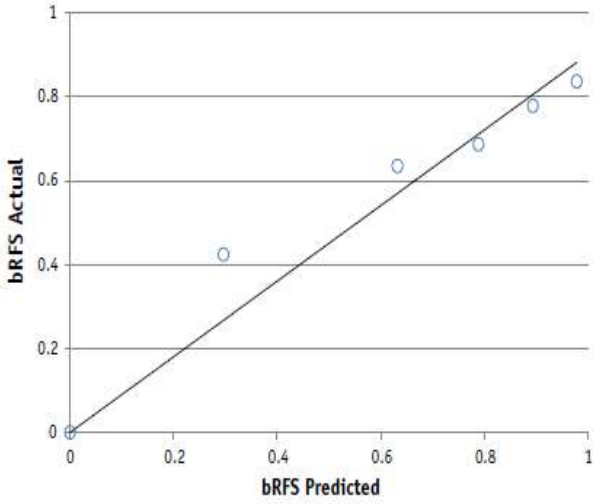
- Mechanistic models: from understanding mechanisms building models that may predict the response

- Phenomenological models: from (big) data and observation, finding correlation and assessing predictors; creating conjectures (not causality, hypothesis generating)

Modified from T. Rancati

«Mechanistic» models





K to depend linearly on PSA. Thus, formula 5 becomes:

$$bRFS = (1 - B \times PSA) \times \left(1 - \exp\left(-\alpha_{eff} D\right)\right)^{C \times PSA} \quad (6)$$

The parameter B represents the reduction of bRFS caused by clonogens outside the irradiated volume for PSA = 1. A limitation of formula 6 is that for a large PSA

Predicting the 5-Year Risk of Biochemical Relapse After Postprostatectomy Radiation Therapy in ≥PT2, pN0 Patients With a Comprehensive Tumor Control Probability Model

Claudio Fiorino, PhD,* Sara Broggi, PhD,* Nicola Fossati, MD,† Cesare Cozzarini, MD,‡ Gregor Goldner, MD,§ Thomas Wiegel, MD,‖ Wolfgang Hinkelbein, MD,¶ R. Jeffrey Karnes, MD,# Stephen A. Boorjian, MD,# Karin Haustermans, MD,** Steven Joniau, MD,†† Federica Palorini, PhD,* Shahrokh Shariat, MD,‡‡ Francesco Montorsi, MD,† Hein Van Poppel, MD,†† Nadia Di Muzio, MD,‡ Riccardo Calandrino, PhD,* and Alberto Briganti, MD†

Int J Radiat Oncol Biol Phys 2016

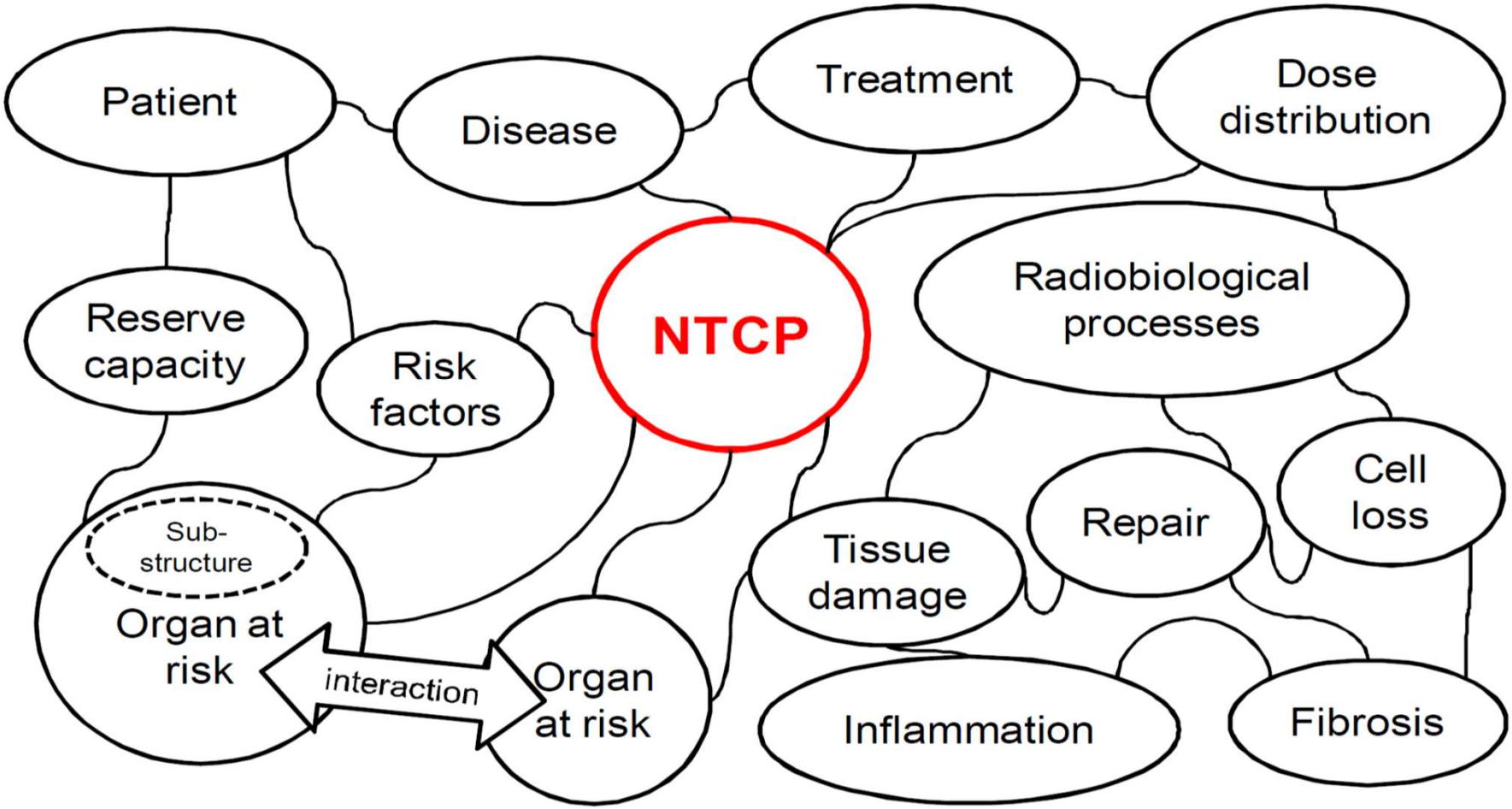
Table 1 Best-fit values of the parameters of the K_lin_GS_3- groups model

bRFS	α_{eff} (Gy^{-1})	B	C
GS < 7			
Best-fit value	0.262	0.307	10^7
95% confidence level	0.251-0.273	0.180-0.434	-
GS = 7			
Best-fit value	0.247	0.492	10^7
95% confidence level	0.241-0.253	0.387-0.597	-
GS > 7			
Best-fit value	0.235	0.500	10^7
95% confidence level	0.230-0.240	0.402-0.598	-

Abbreviations: bRFS = biochemical recurrence-free survival; GS = Gleason score.

Table based on formula 6 and grouping patients according to 3 GS groups.

What determines NTCP?



TOO MANY UNKNOWN DETAILS

Courtesy of Arjen van der Schaaf, ESTRO Vienna 2014

Phenomenological models

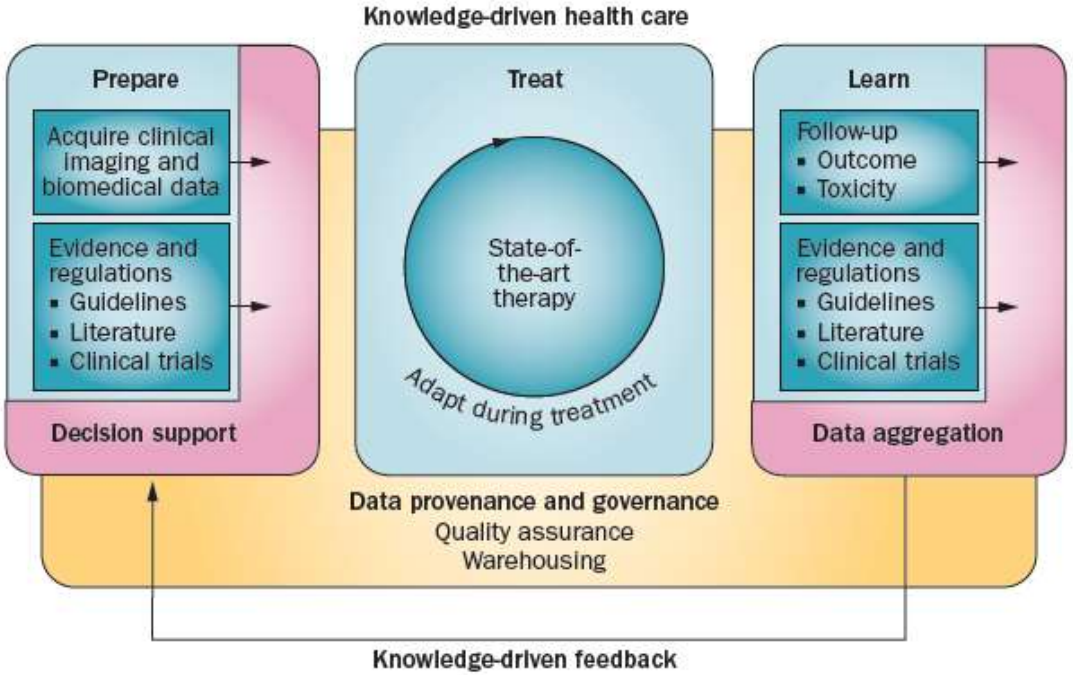
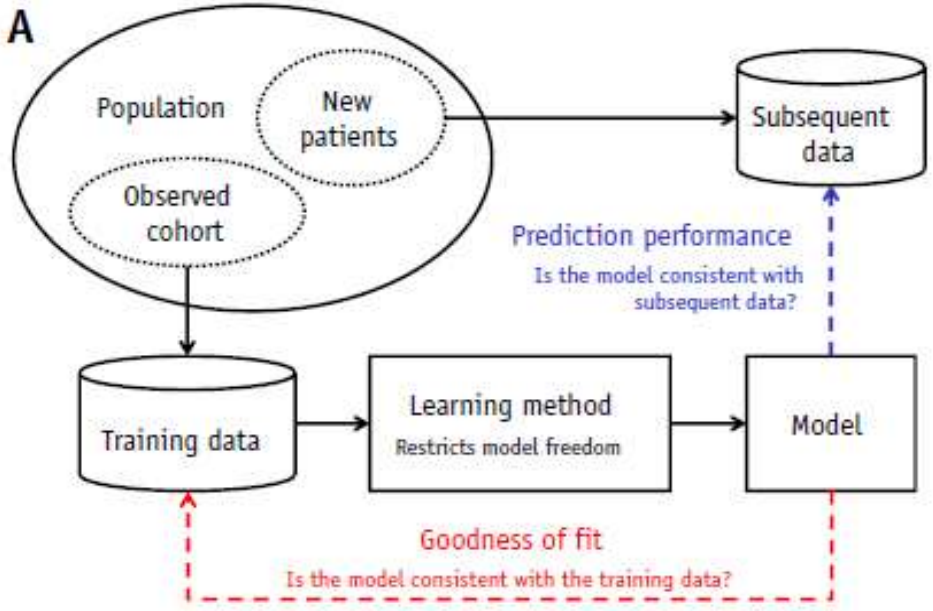


Figure 5 | Knowledge-driven health-care principles using a clinical decision-support system in conjunction with standard evidence and regulations to choose the optimal treatment. In learning from follow-up data, knowledge is fed back to improve the clinical decision-support system and adapt regulations.

Predicting outcomes in radiation oncology —multifactorial decision support systems

Philippe Lambin, Ruud G. P. M. van Stiphout, Maud H. W. Starmans, Emmanuel Rios-Velazquez, Georgi Nalbantov, Hugo J. W. L. Aerts, Erik Roelofs, Wouter van Elmpt, Paul C. Boutros, Pierluigi Granone, Vincenzo Valentini, Adrian C. Begg, Dirk De Ruysscher and Andre Dekker

Lambin Nat Rev Clin Oncol 2013



EDITORIAL

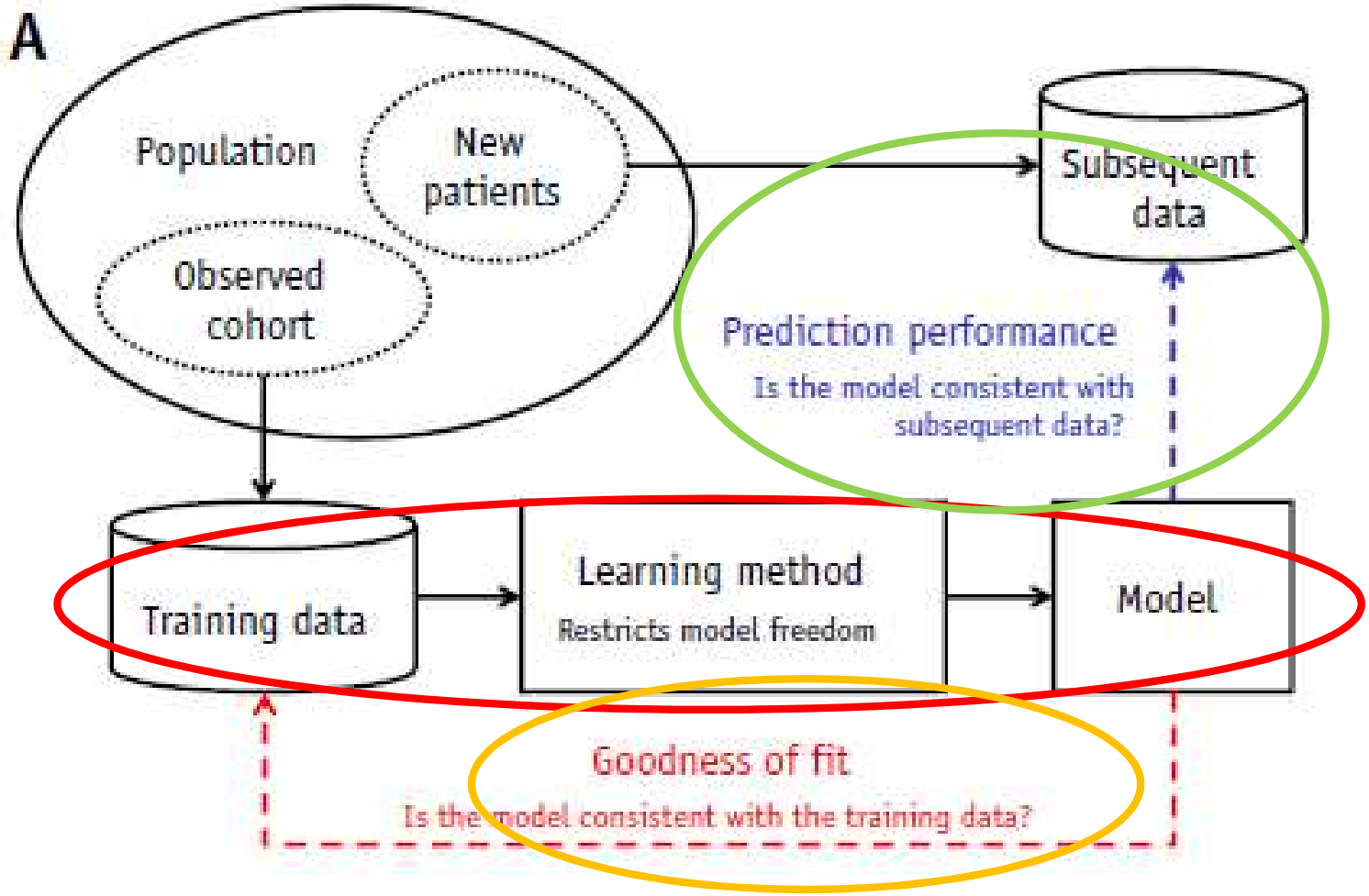
Embracing Phenomenological Approaches to Normal Tissue Complication Probability Modeling: A Question of Method

A. van der Schaaf, PhD,* J.A. Langendijk, MD, PhD,* C. Fiorino, and T. Rancati, PhD†

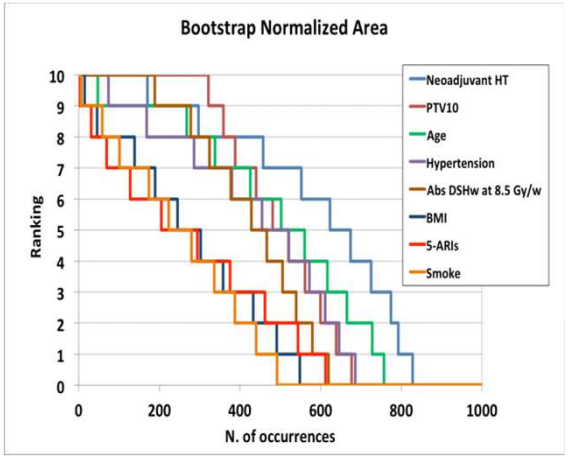
*Department of Radiation Oncology, University of Groningen, University Medical Center Groningen, The Netherlands; †Medical Physics, San Raffaele Scientific Institute, and ‡Prostate Cancer Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

Received Sep 30, 2014, and in revised form Oct 7, 2014. Accepted for publication Oct 9, 2014.

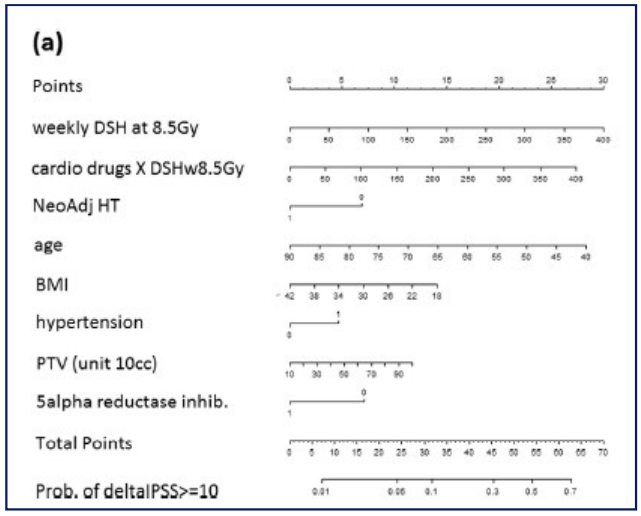
Van der Schaaf Red J 2015

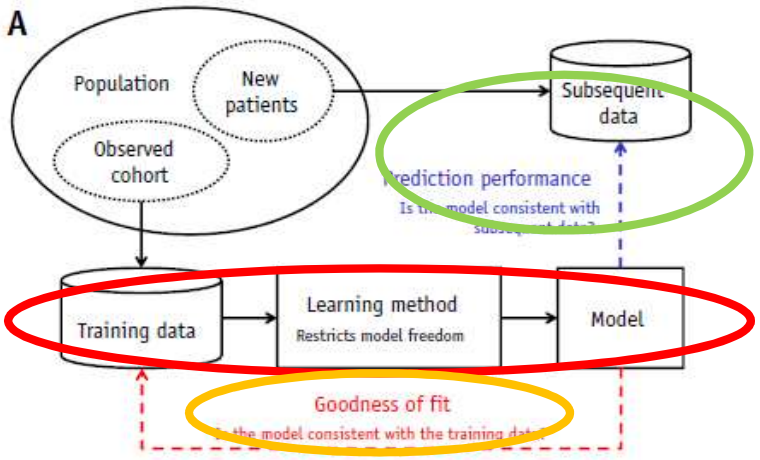

A
Population
New patients
Observed cohort
Subsequent data
Prediction performance
Is the model consistent with subsequent data?
Training data
Learning method
Restricts model freedom
Model
Goodness of fit
Is the model consistent with the training data?

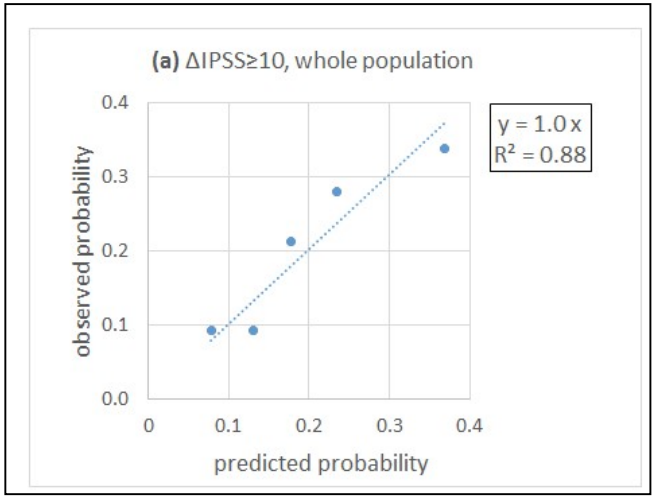
Variables selection



Parameters





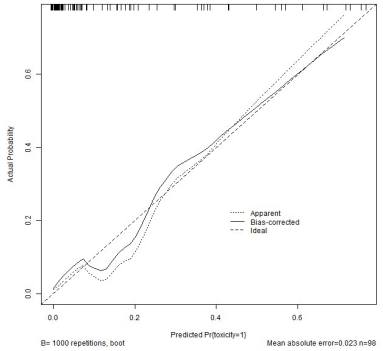


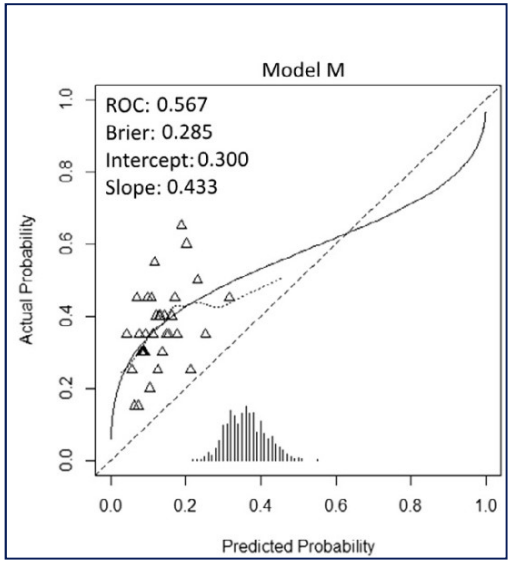
Model's performance

Palorini et al. R&O 2016

Yahia et al. R&O 2016

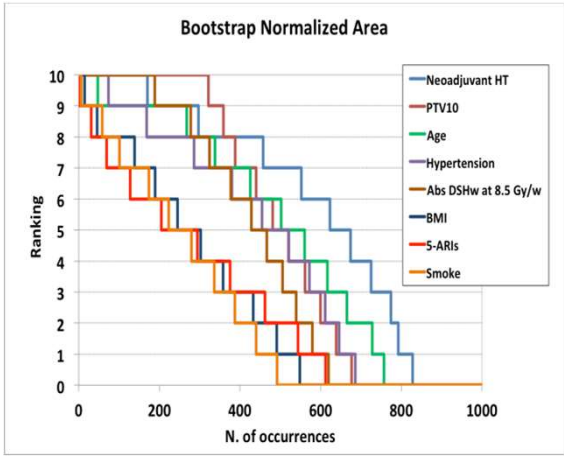
Internal validation



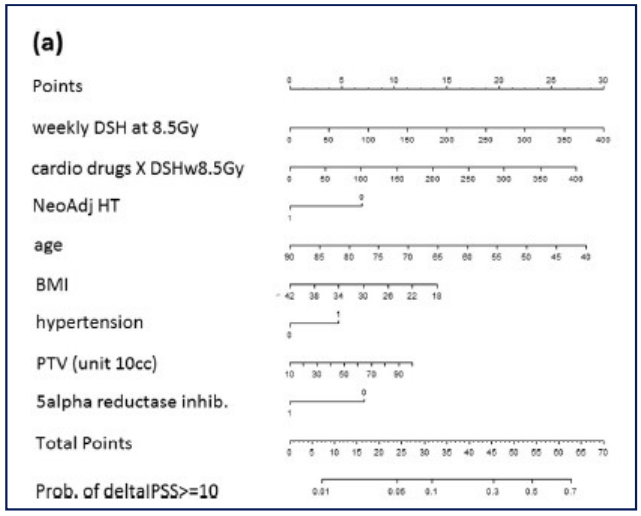


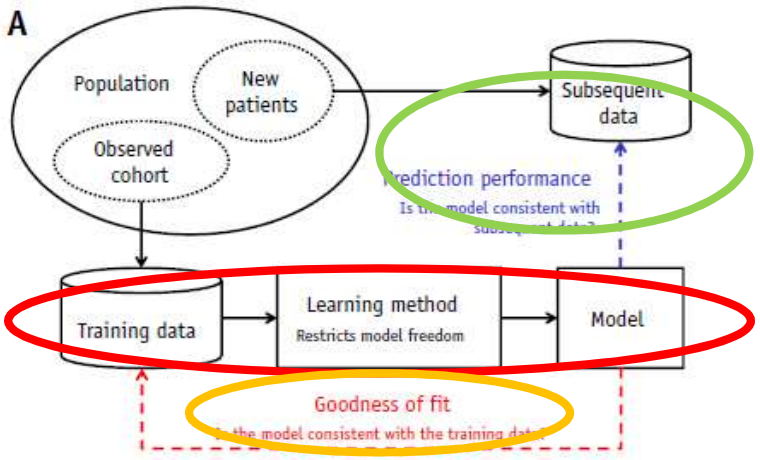
External validation

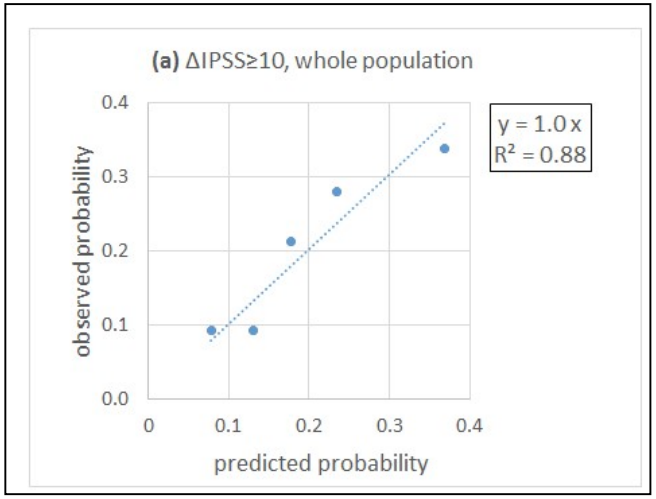
Variables selection



Parameters

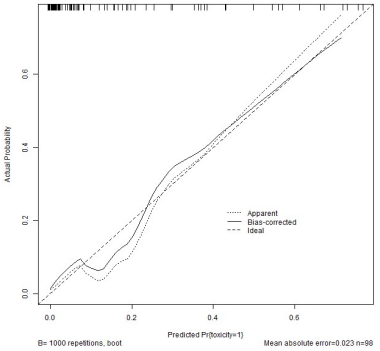


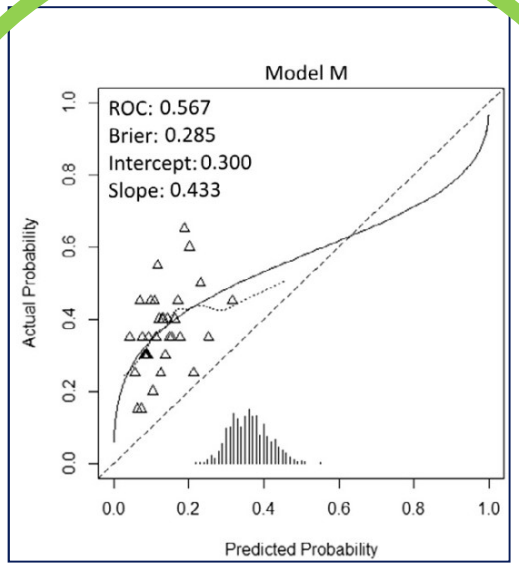




Model's performance

Internal validation





External validation

Palorini et al. R&O 2016

Yahia et al. R&O 2016

Validating Phenomenological models: a key point

- The ideal predictive model should:

Adequately fit the data (no under or overfit !)

Giving correct predictions outside the original (training) data set on new (validation) data sets

More external validations means more confidence in applying the model (…and negative results reduce it)

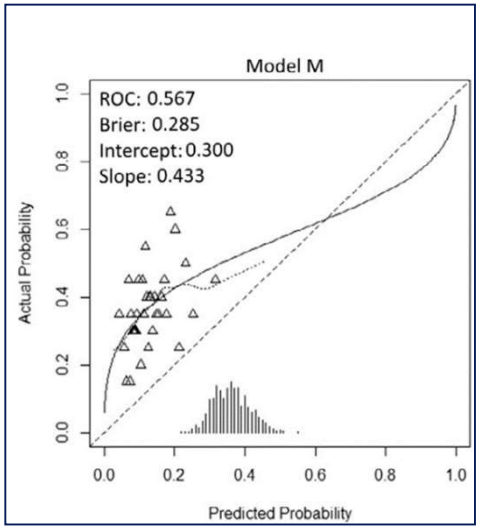
Different degrees of generalization of the model based on the type of validation (range of doses, delivery technique, temporal, geographical,……)

Heavy lacks of available predictive models with (satisfactory) external validation !

Need of much more efforts to accomplish accurate and well assessed validation studies

(c) To enable the above improvements in clinical care, ESTRO will, through its congress, special meetings, educational courses and journal(s), support the future development of radiation oncology, emphasising and supporting the need for the following:

- New approaches to adaptive radiotherapy integrating novel developments in biology, imaging, technology, and the assessment of tumour response and patient outcome.
- Innovative research and development on the potential future use of novel biological modifiers of tumour and normal tissue res
- The development f validated predictive models t treatment outcome ba comprising clinical, biologic, genetic, imaging, dosimetric and population data.
- The continued development of quality programmes, including clinical audit and comprehensive safety systems in Radiation and Clinical Oncology that maintain the principles of providing the highest quality of patient care and treatment in a safety-aware enviroment.



External validation

Phenomenological models & “big data”

- Powerful potentials for developing and validating models (!!)
- “Cloud-like” approach to data collection is coming…
- Property and legal issues, difficulty in sharing experience
- Developing/accepting/sharing common languages/methods
- Cultural issues…..

QUANTEC: VISION PAPER

IMPROVING NORMAL TISSUE COMPLICATION PROBABILITY MODELS: THE NEED TO ADOPT A “DATA-POOLING” CULTURE

Clinical studies of the dependence of normal tissue response on dose-volume factors are often confusingly inconsistent, as the QUANTEC reviews demonstrate. A key opportunity to accelerate progress is to begin storing high-quality datasets in repositories. Using available technology, multiple repositories could be conveniently queried, without divulging protected health information, to identify relevant sources of data for further analysis. After obtaining institutional approvals, data could then be pooled, greatly enhancing the capability to construct predictive models that are more widely applicable and better powered to accurately identify key predictive factors (whether dosimetric, image-based, clinical, socioeconomic, or biological). Data pooling has already been carried out effectively in a few normal tissue complication probability studies and should become a common strategy.

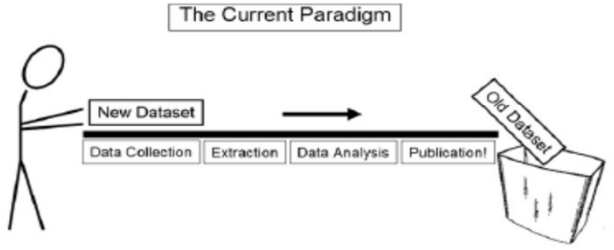


Fig. 2. “The current (data-loss) paradigm.” Data are effectively lost to the wider scientific community after publication. Capturing key datasets in query-able data repositories would accelerate the discovery of causative factors and increase the accuracy of parameter estimates.

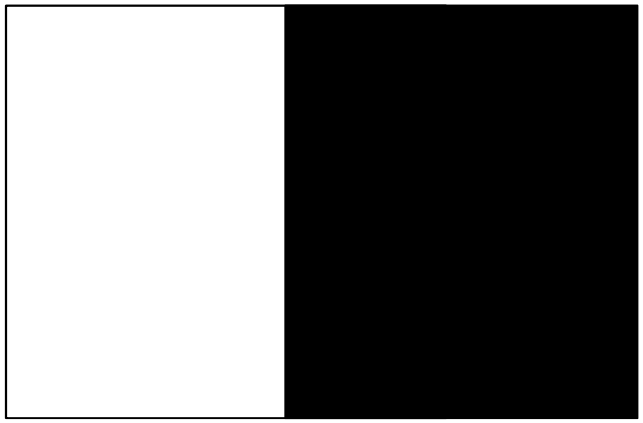
Deasy et al. QUANTEC

Phenomenological models & “big data”

- Powerful potentials for developing and validating models (!!)

…….Big difference between

survival/control *vs* Toxicity (and QoL)



(interplay between quantity and quality of data ?)

- Big Data….Big issues for MP ??

Classical statistical analyses

n° variables:

10^0 - 10^1

Advanced Predictive models

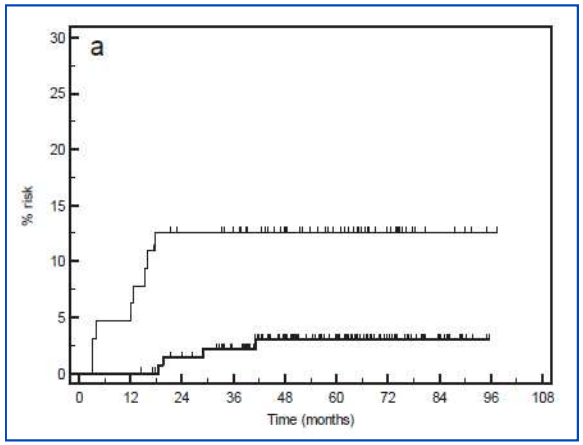
n° variables:

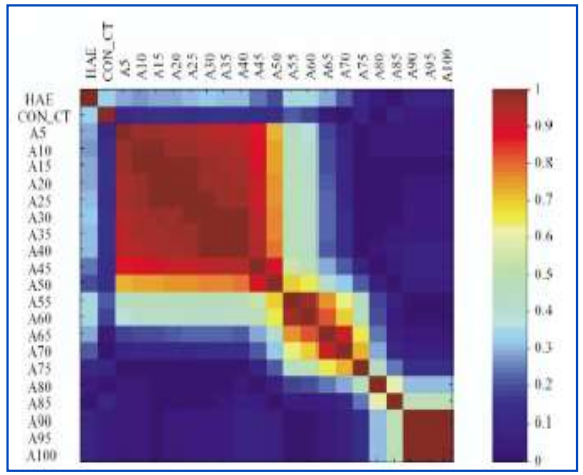
10^1 - 10^3

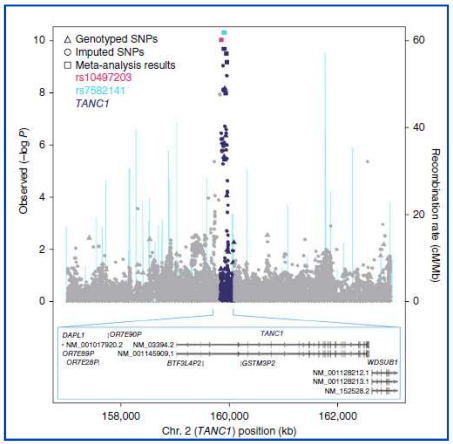
Wide-Genes predictors search

n° variables:

10^4 - 10^7







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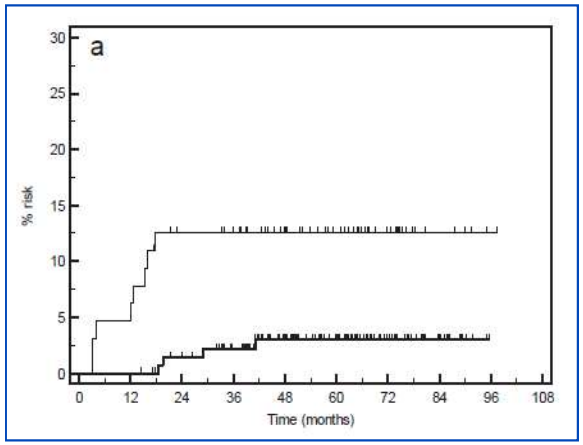

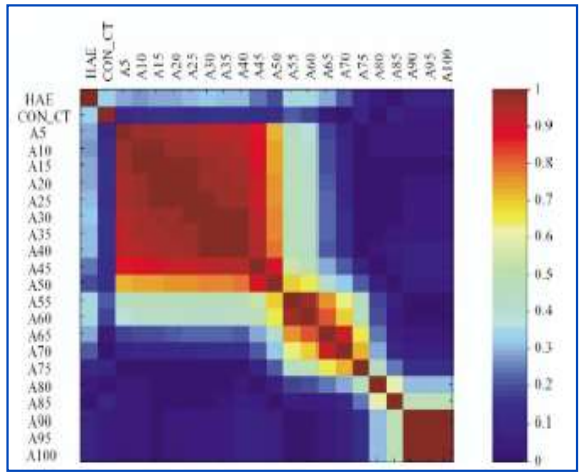

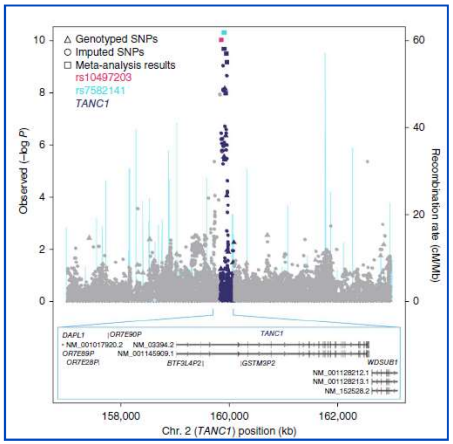

- Big Data….Big issues for MP ??

Integrating genomics into predictive models

Searching impact of genomics on residuals of the models

Classical statistical analyses

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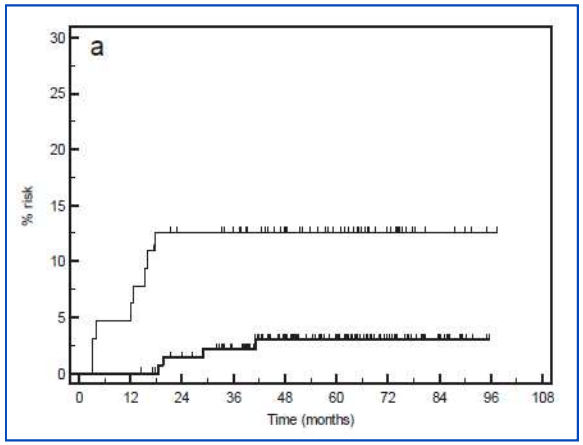
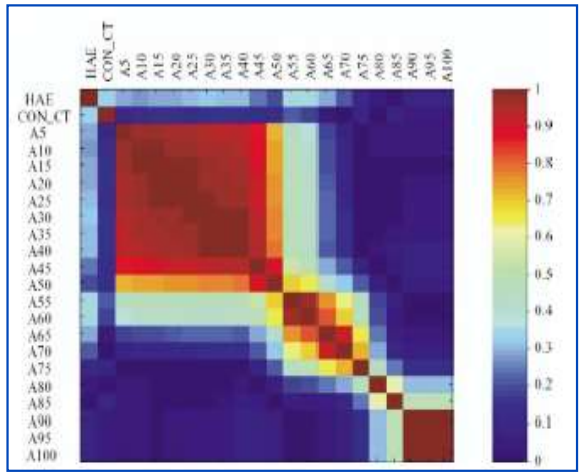
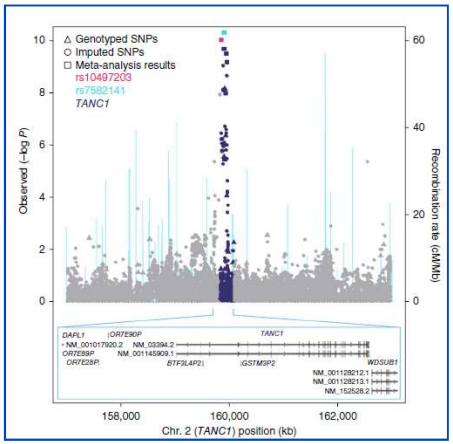






- Big Data….Big issues for MP ??

MULTIDISCIPLINARITY !

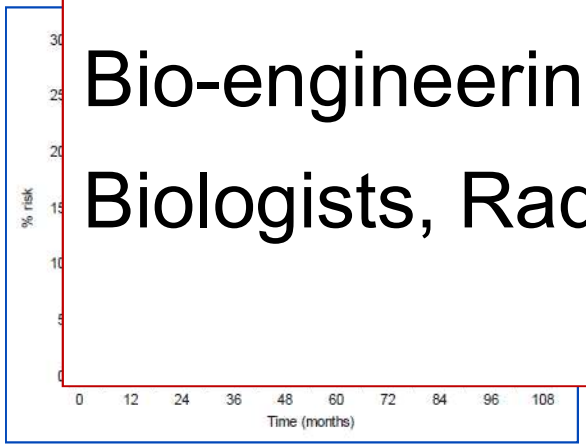
MP AS MEMBER OF A TEAM

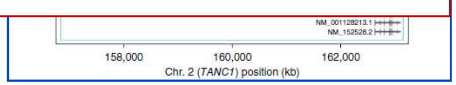
Radiation Oncologists,

Statisticians, Bio-informatics, Data managers

Bio-engineering, Mathematicians

Biologists, Radiobiologists ……



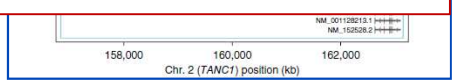


- Big Data….Big issues for MP ??

COOPERATION

(Clinical) MP SHOULD HAVE
A PIVOTAL ROLE IN FACILITATING
PROSPECTIVE DATA COLLECTION

(Italian experience: AIROPROS, DUE01, IHU…)



Major trends and research opportunities in predictive modelling with relevant contribution from MP: Tumor

- Including pre-RT (omic) individual characteristics on T response (radiomic, genomic, proteinomic, metabolomic,…) in predictive models
- Incorporation of individual response (volume and functional characteristics) by imaging during/after RT
- T progression, angiogenesis, resistance mechanisms…
- Interaction with drugs/agents
- Damage and repair mechanisms in ablative RT and heavy Hypo
- Heavy particles
- Clinical trials exploring individualized strategies for dose prescription
- Pre-clinical (mouse) models
- Interaction immune response and RT

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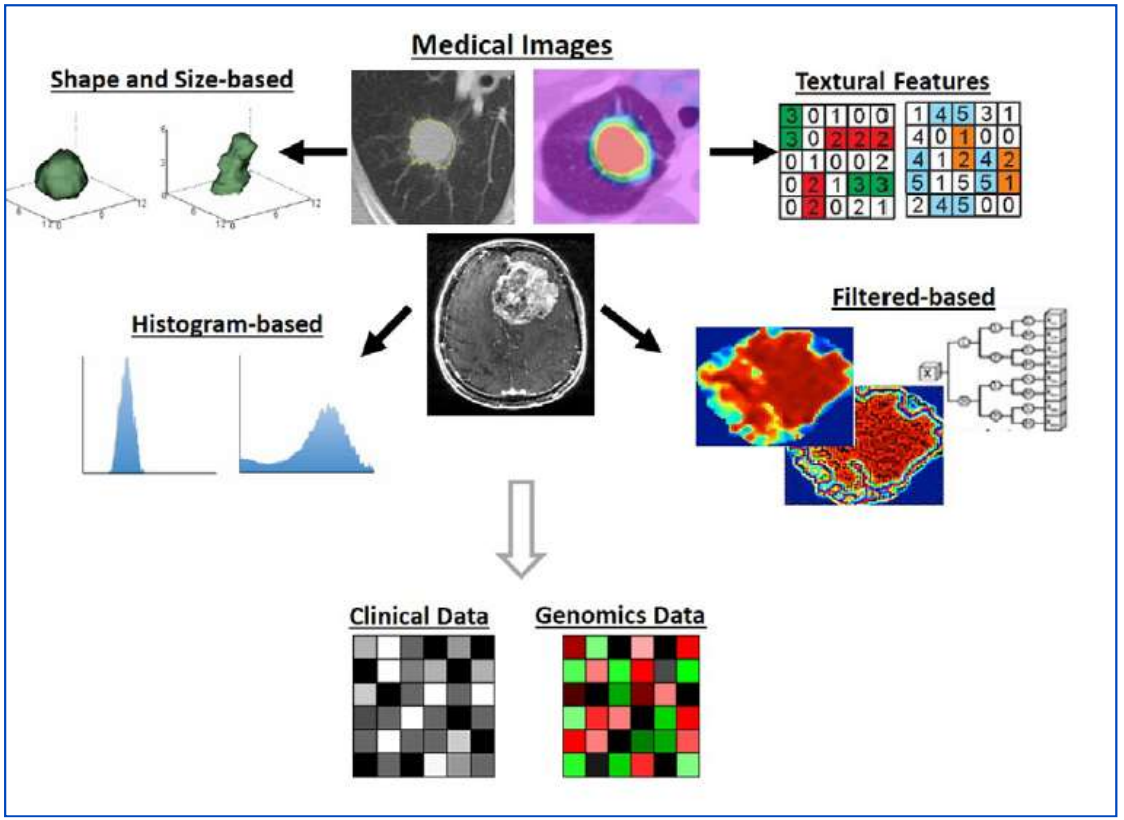
Radiomics & predictive modeling in RT

- Feature extraction and combination
- Inter-modality issues (CT, PET, MRI, US….)
- Robustness of the features
- Meaning of the features…phenomenological approaches
- Feature selection and incorporation in predictive models
- Validation (?)



Yip & Aerts, pmb 2016

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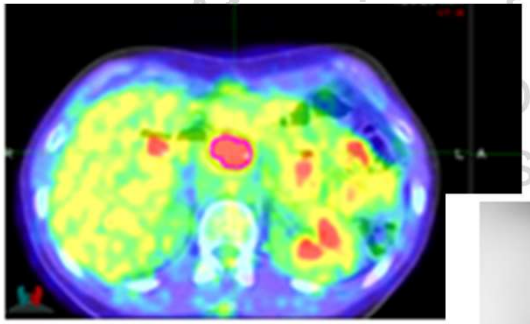
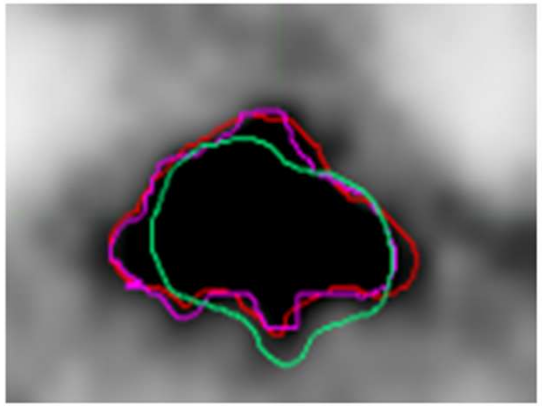
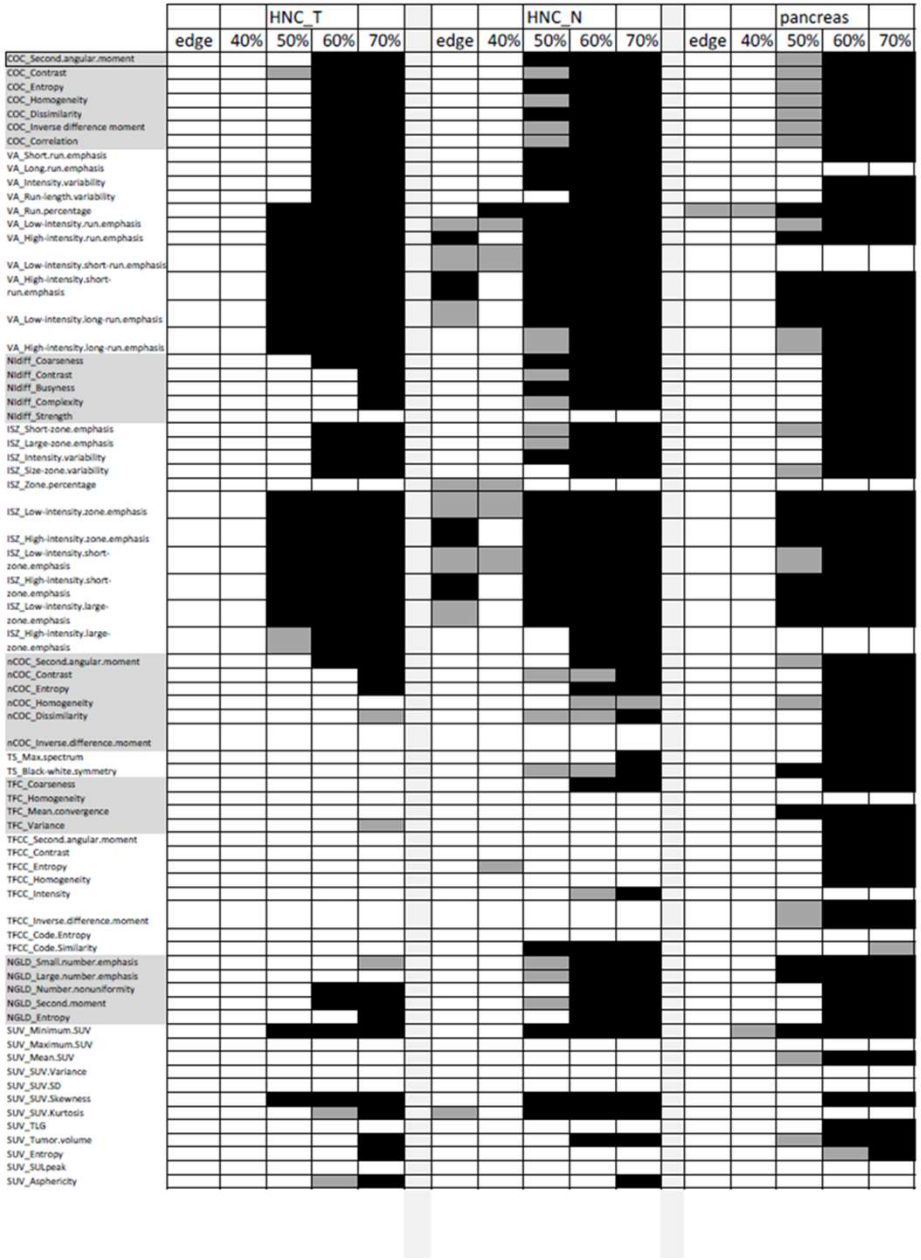




Belli et al, Submitted



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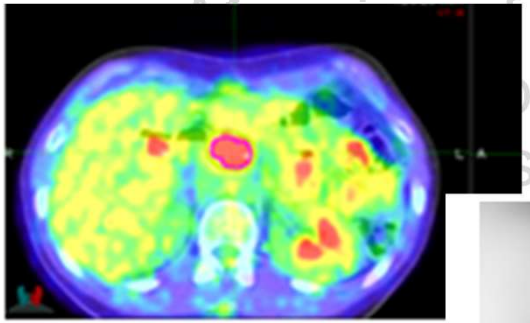

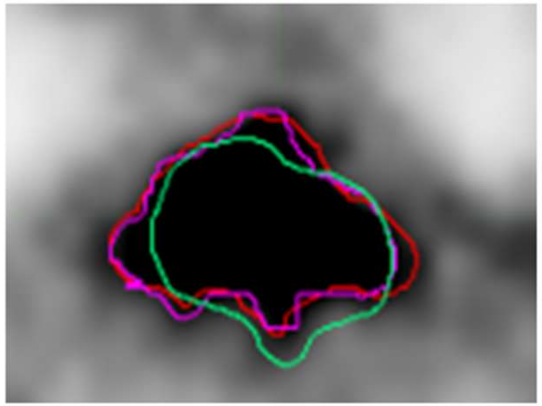

Belli et al, Submitted

ELSEVIER

Seminars in RADIATION ONCOLOGY

Quantitative Imaging in Radiation Oncology: An Emerging Science and Clinical Service

David Anthony Jaffray, PhD,[*,†,‡,§,¶] Caroline Chung, MD,[*,‡] Catherine Coolens, PhD,[*,†,‡,¶] Warren Foltz, PhD,[*,†,‡] Harald Keller, PhD,[*,†,‡] Cynthia Menard, MD,[*,†,‡] Michael Milosevic, MD,[*,‡] Julia Publicover, MSc,[†] and Ivan Yeung, PhD[*,†,‡]

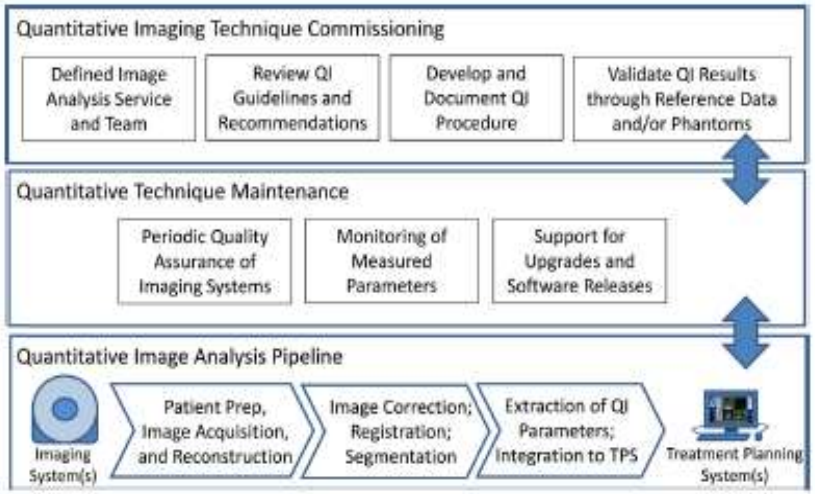

Figure 3 As a treatment modality that relies on spatial integrity and quantitative imaging for accurate dose calculation, quantitative integration of imaging into radiation oncology practice should be part of good practice. The development of a robust and reproducible pipeline of imaging procedure documentation, system commissioning, quality assurance, imaging data collection, image analysis, and integration into the treatment process should be established within the radiation oncology process for data used to effect the desired treatment. As a direct input to the treatment prescription and planning process, the image analysis pipeline should have a means to document and store the provenance of the data and its derivatives. (Color version of figure is available online.)

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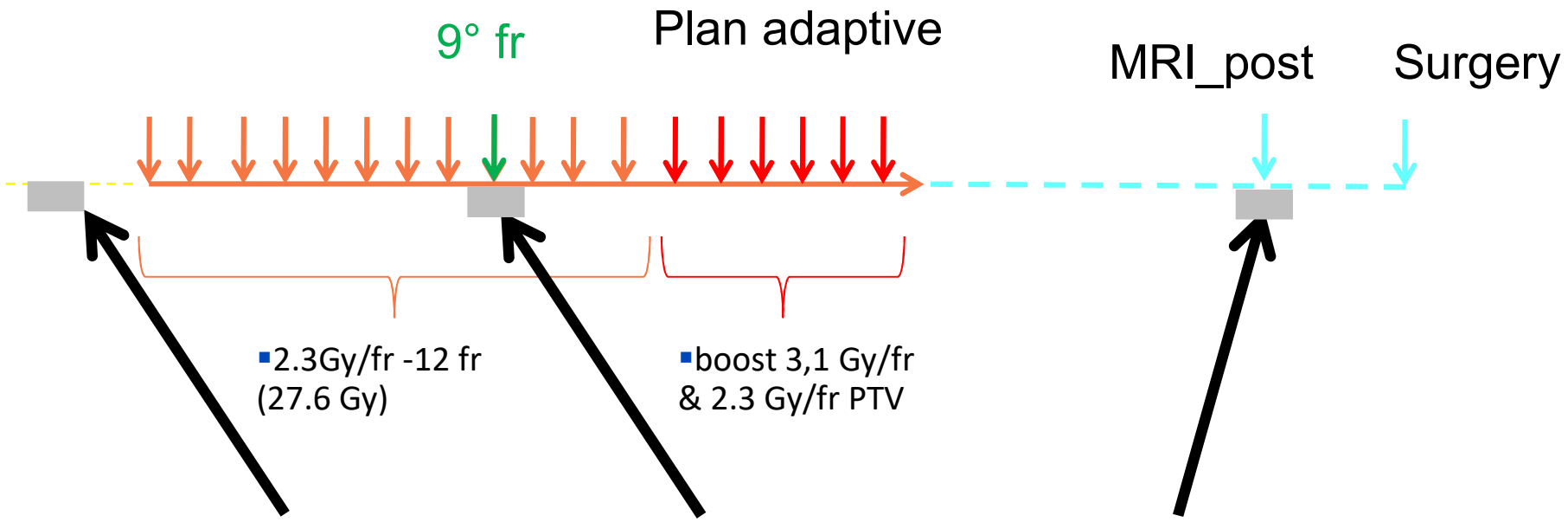
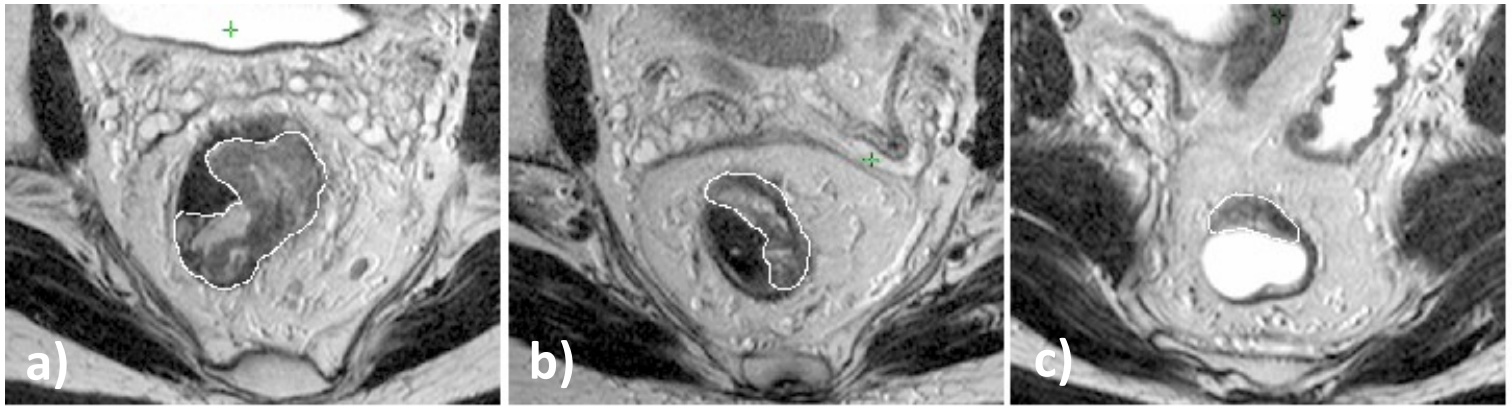
Incorporating T regression for individual predictions: pCR in neo-adjuvant RT-chemo for rectal cancer



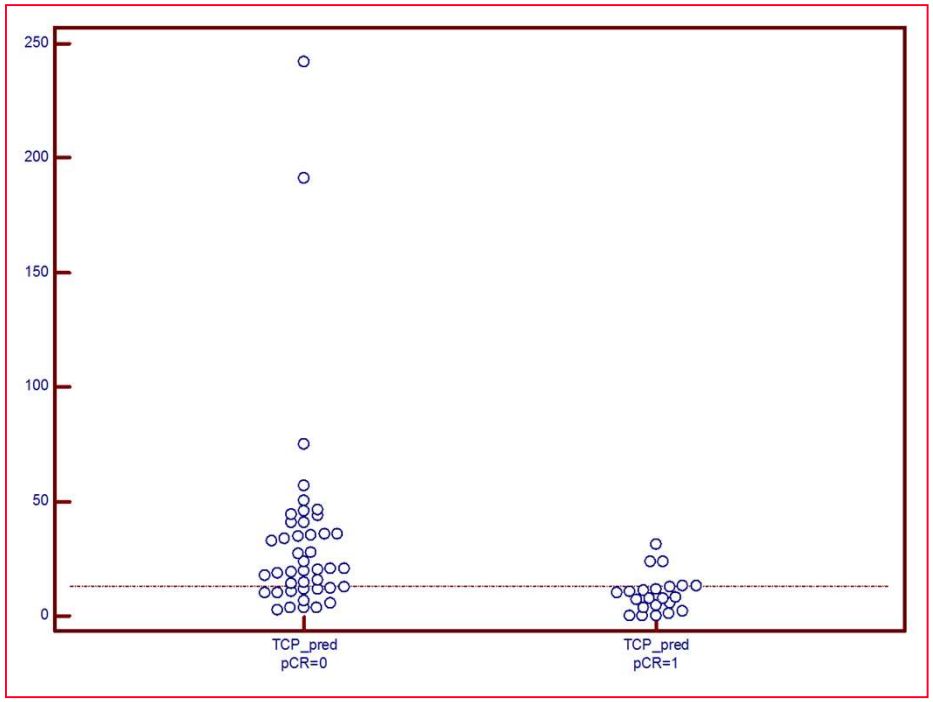


MRI pre mid post

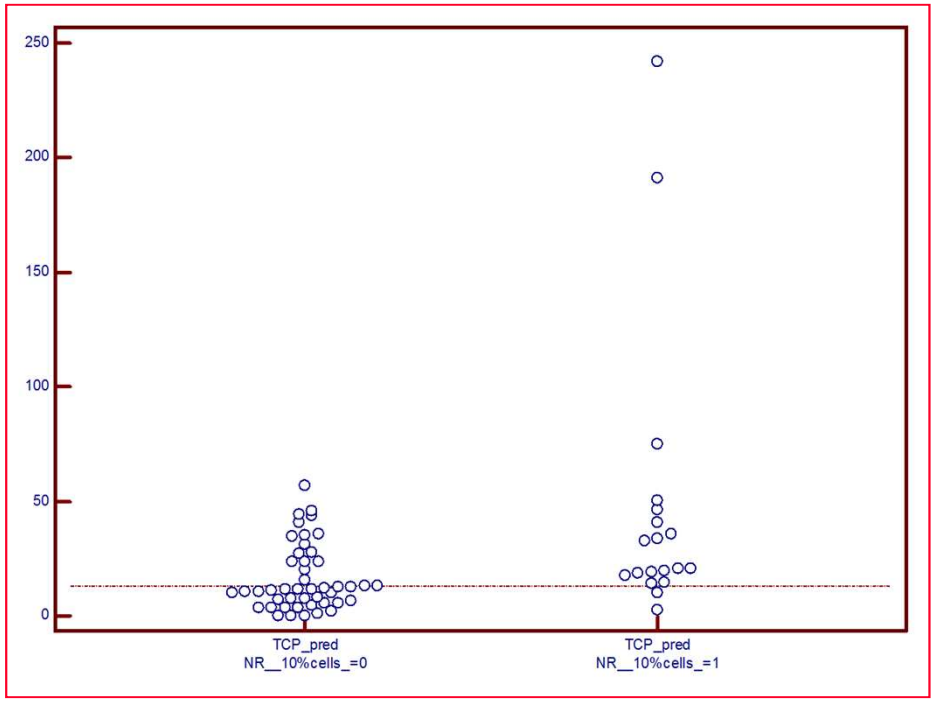
Incorporating T regression for individual predictions: pCR in neo-adjuvant RT-chemo for rectal cancer

$$TCP = \left(1 - \frac{N}{N_0}\right)^{N_0} \quad \Rightarrow \quad TCP\_mid \approx \left(1 - \frac{V\_mid}{V\_pre}\right)^{V\_pre} \quad \Rightarrow$$

TCP figure of merit : -ln(TCP_mid)



Complete remission
AUC: 0.81



Not responding (≥10% vital cells)
AUC: 0.75

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$$TCP = \left(1 - \frac{N}{N_0}\right)^{N_0} \Rightarrow TCP\_mid \approx \left(1 - \frac{V\_mid}{V\_pre}\right)^{V\_pre} \Rightarrow$$

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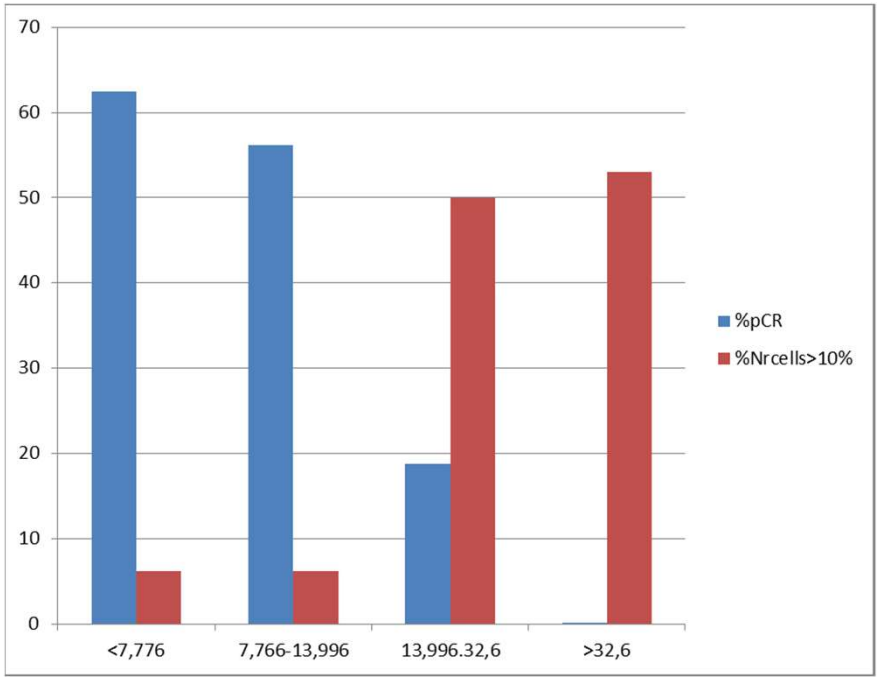
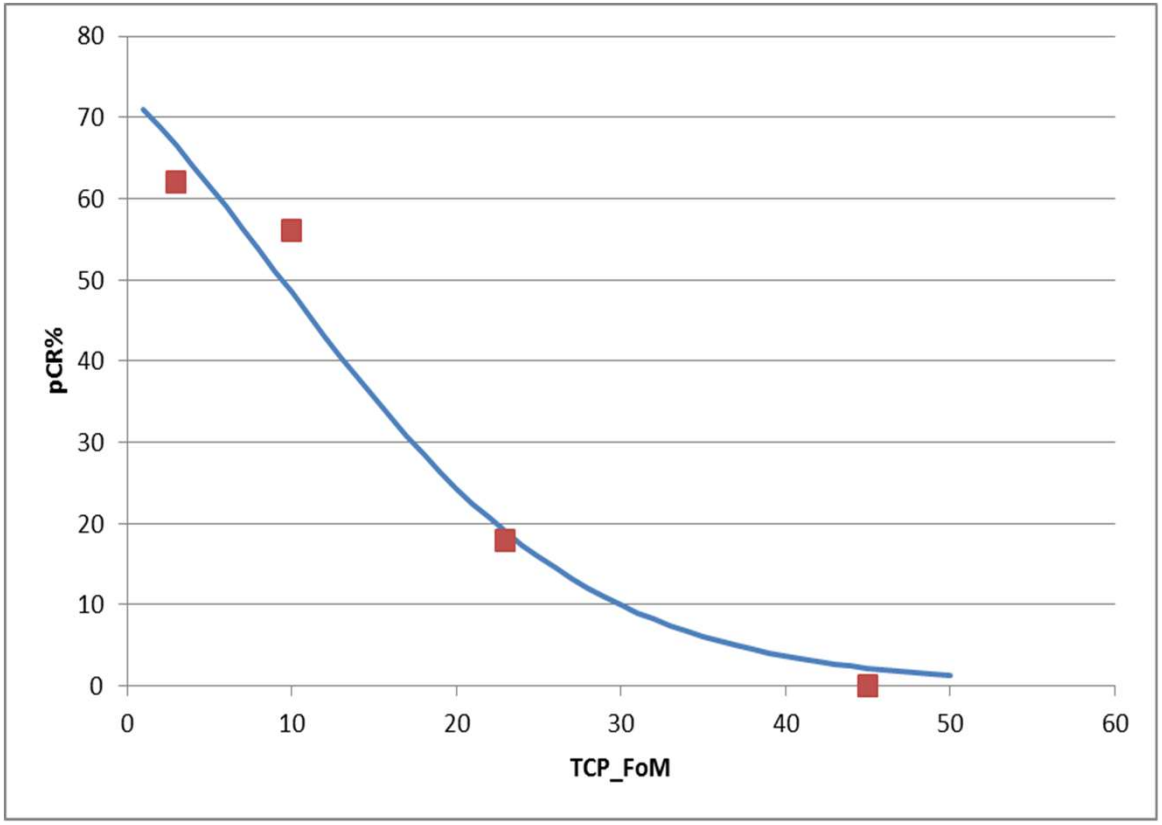


Negative Predictive Value
NPV= TN/(TN+FN):

pCR: 90 %
Not responding: 94%



Manuscript in preparation

Major trends and research opportunities in predictive modelling with relevant contribution from MP: Normal tissues

- Incorporation of clinical and «omics» predictors into dose-volume (phenomenological) models: methods for variable selection, robustness assessment, validation
- Data-sharing and data-mining issues
- Objective, image-based scoring of toxicity (morphological and functional changes)
- Involvement into data analysis/modelling of clinical trials/Institutional series
- Overcoming organ-based approach of dose-volume modelling (considering the 3D dose distribution, similarity/dissimilarity comparisons, multi-structure models…)
- Incorporation of delivered dose into models (replacing planned doses)

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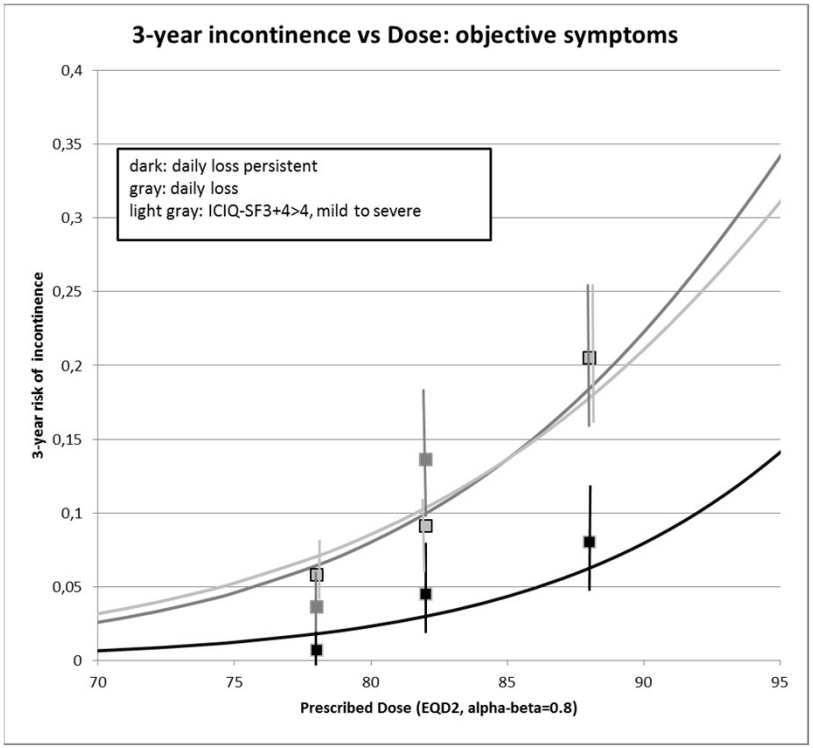
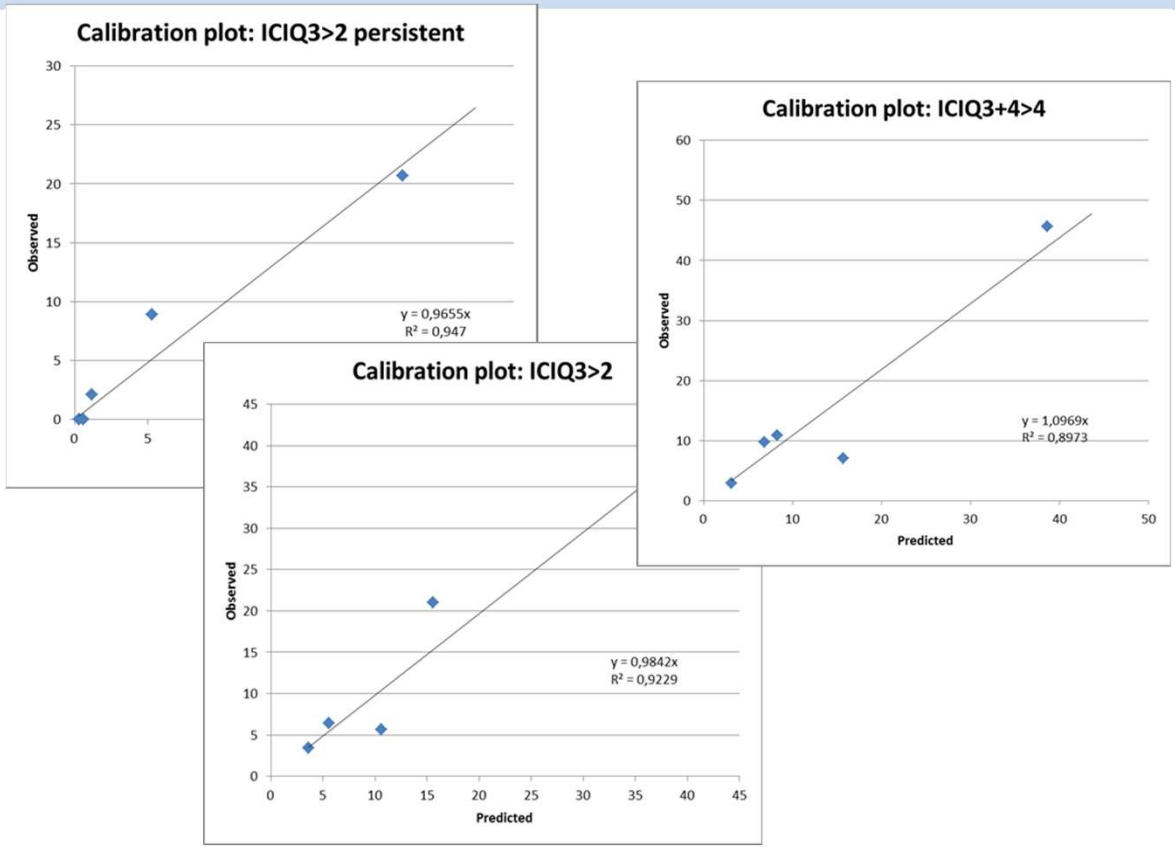


Fitting (Multi-variable models)



Performances evaluation + bootstrap-based internal validation

Ex: modeling dose-effect of 3-year patient-reported urinary incontinence (ICIQ questionnaire); 298 prospectively followed pts (DUE01 trial) treated with Conventional and moderate Hypo fractionation

Cozzarini et al. In press R&O

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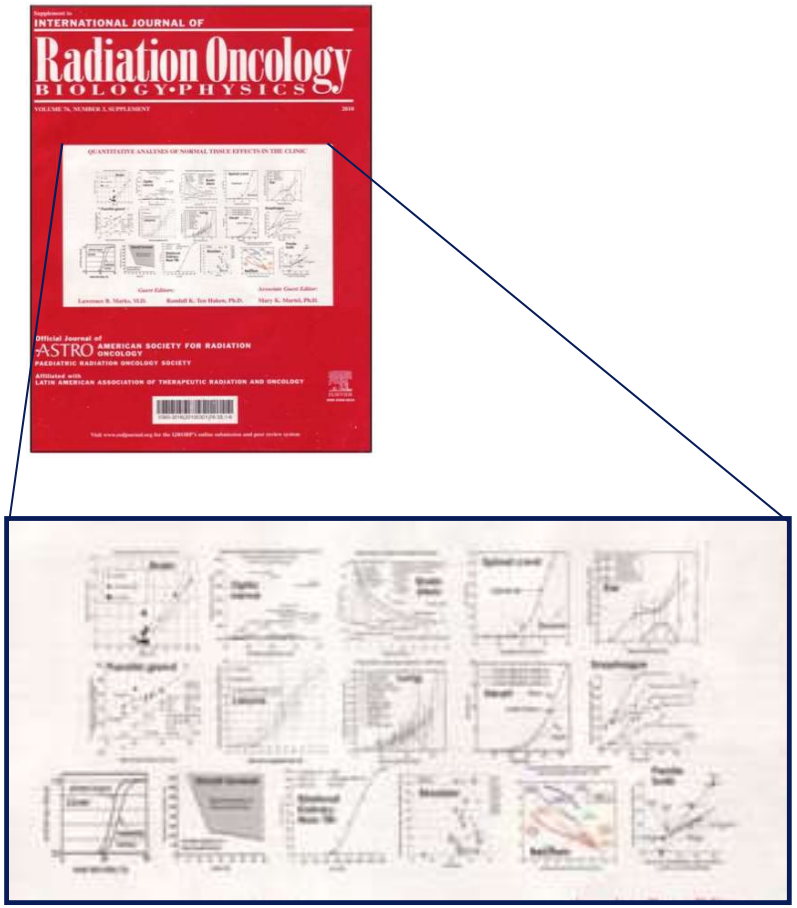
Overcoming organ-based approach of dose-volume modelling

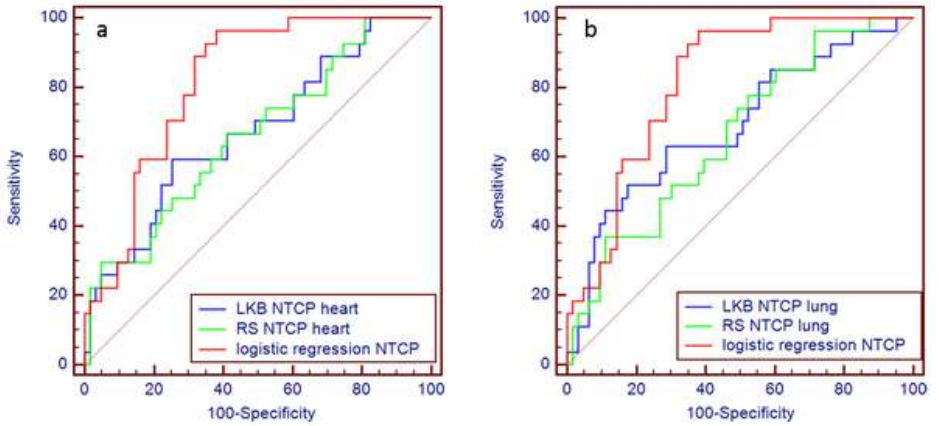
- Organ-based…an intuitive and natural way to describe radiotherapy-induced effects
- Organs as «independent and homogeneous entities» is a robust and practically usable approximation for most end-points
- Supported the translation from «qualitative» to «quantitative» RT ….knowledge condensed into organ constraints/EUDs/NTCPs
- Successful in reducing toxicities by guiding RT to «safely» deliver treatments respecting organ-based constraints
- Conserving a «flavour» of Radiobiology (....serial and parallel-like organs…)
- «Easy» incorporation in multi-variable phenomenological models

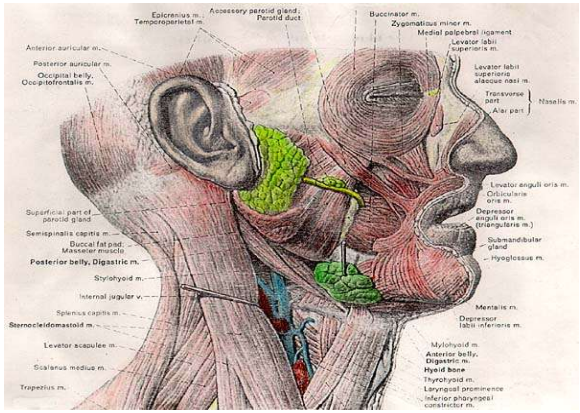


Overcoming organ-based approach of dose-volume modelling

- The organ-based DVH approach is clearly a (useful) "hard constraint" not reflecting the real world in many situations:
- 1) Symptoms may depend on the dose received by multiple organs
- 2) Organs are not "homogenous entities" from the point of view of their response to radiation and their functions

Cella et al. PlosOne2014, Complication Probability Models for Radiation-Induced Heart Valvular Dysfunction: Do Heart-Lung Interactions Play a Role?.





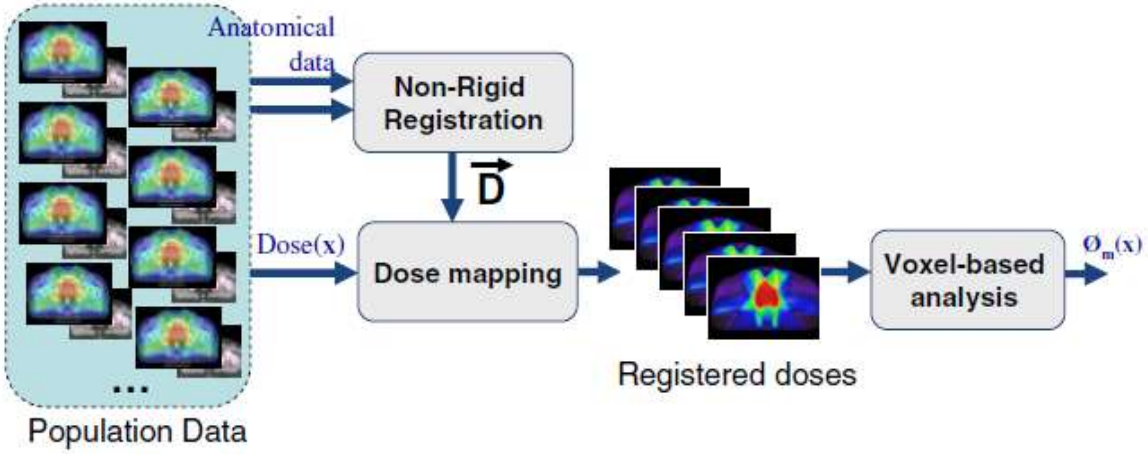
Organs are not “homogenous entities” from the point of view of their response to radiation and their functions…

- **“forward”** approach: making hypothesis/assumptions and segmenting organs in pre-defined substructures (for instance: brain segmented in sub-regions according to their functionality)
  - Simple extension of the organ-based approach (multiplication of organs/structures)
  - Pro’s: testing well assessed functional hypothesis functional , possibly easy to accomplish
  - Con’s: loosing part of the spatial information
- **“backward”** approach: without any additional hypothesis, directly looking to the differences of the dose distributions between patients with vs without toxicity
  - Generalized approach trying to take the whole spatial information into account
  - Pro’s: «full» search of spatial effects, ...potentially hypothesis-generating
  - Con’s: challenging, need of large numbers, how translate this information in «constraints»?

3D (backward) methods: challenges and limits

- The idea: translating individual dose distributions on “template” patient(s)
- Assessing rules for imaging/dose deformation
- Searching predictors through “voxel-wise” dissimilarity measurement

- Potential for identify regions whose irradiation better discriminate pts with/wout tox (control/relapse)
- Robustness of the results mainly depends on the way the deformation is applied and/or on the integrity of the correspondence among patients



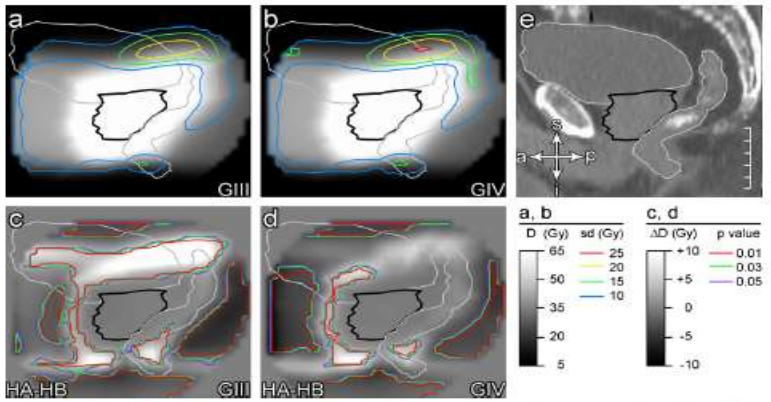


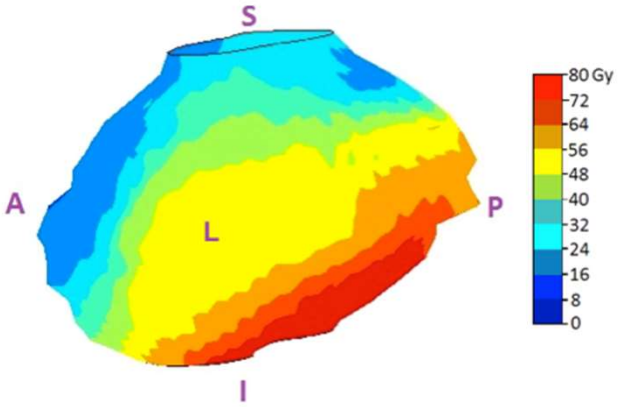
Fig. 1. (a, b) The average planned dose over the patients of both hospitals in group III (a) and group IV (b), mapped onto the anatomy of a representative patient in sagittal view (e). Colored contours indicate the standard deviation of the dose. The mapping was based on delineated prostate contours (black line). (c, d) The difference in average dose between hospitals A and B for treatment groups III and IV. Colored contours indicate the *p* values acquired by performing a *t*-test in every point.

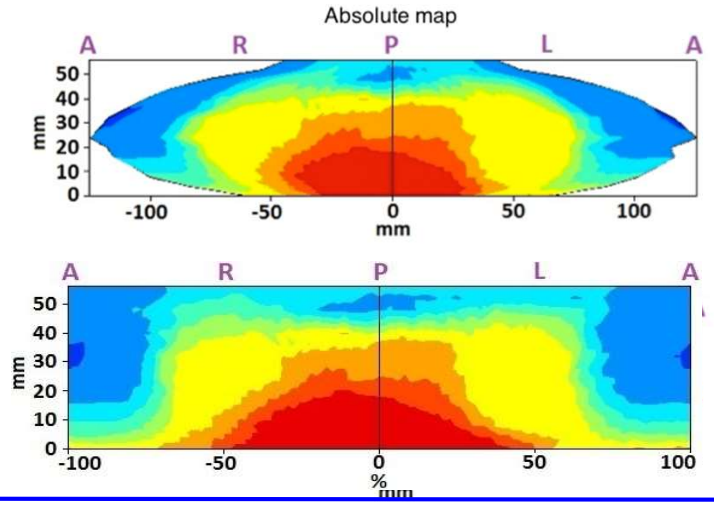
Acosta et al. pmb 2013

Witte et al. IJROBP 2010

Ex: 2D pixel-wise analysis of bladder dose-surface maps (hollow organ)

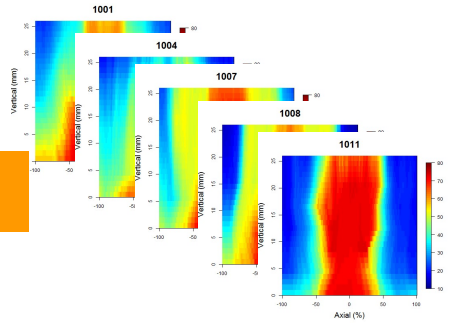
- Cutting and unfold bladder to generate dose surface maps



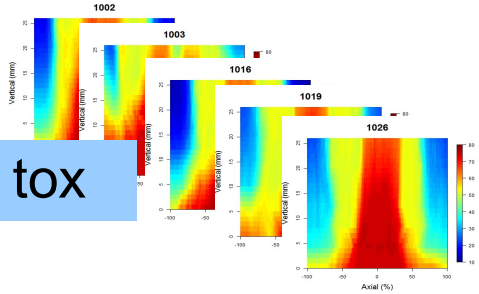


- Aligning maps on the same frame

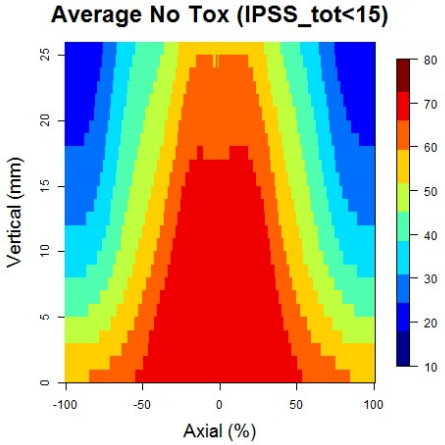
Pts with tox

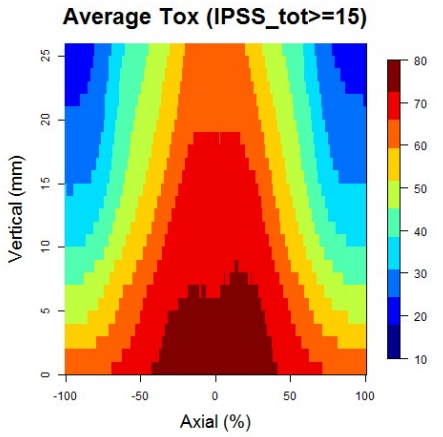


Pts witout tox



- Comparing maps with/wout tox

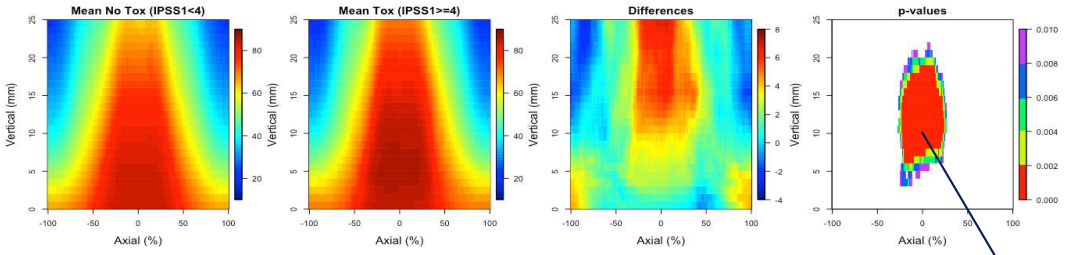




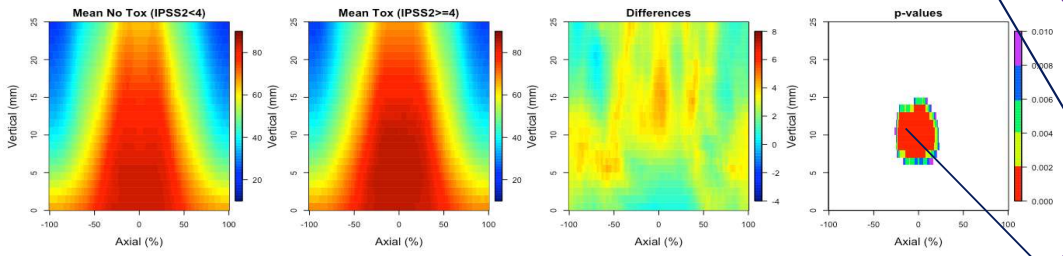
Palorini et al R&O 2016, Improta et al. 2016

HYPO PATIENTS

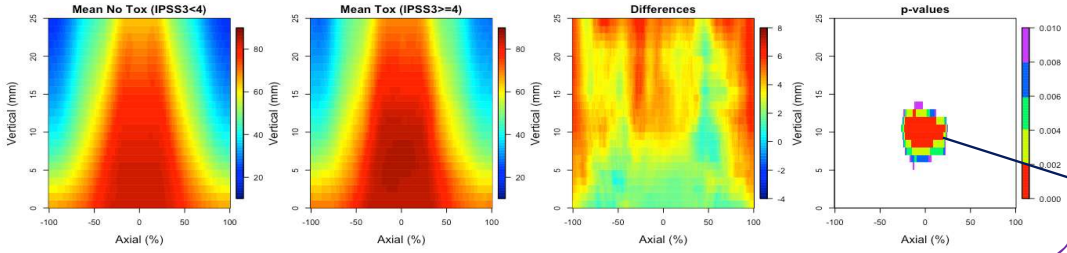
Feeling of incomplete emptying (19/194)



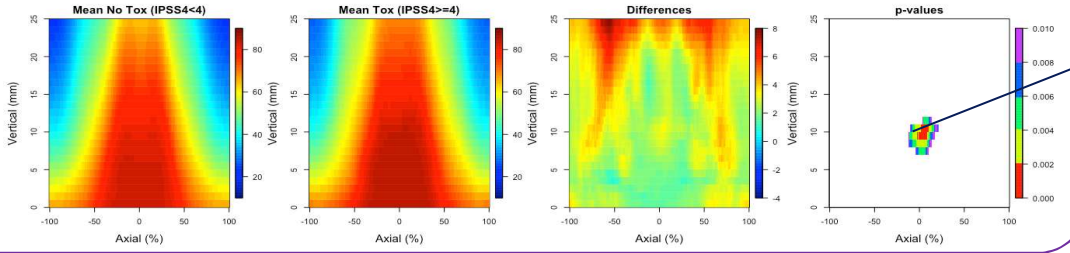
Frequency (41/195)



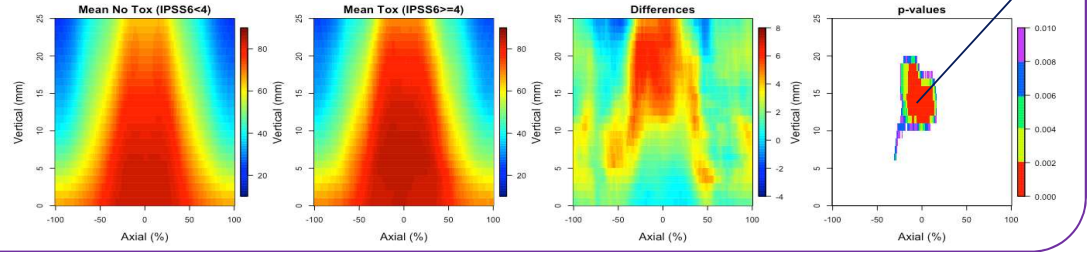
Intermittency (23/203)

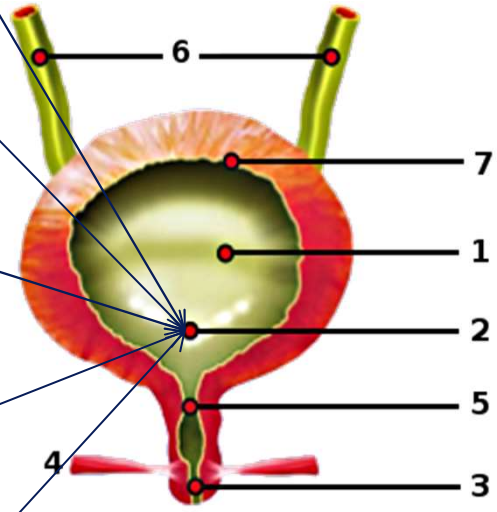


Urgency (32/195)



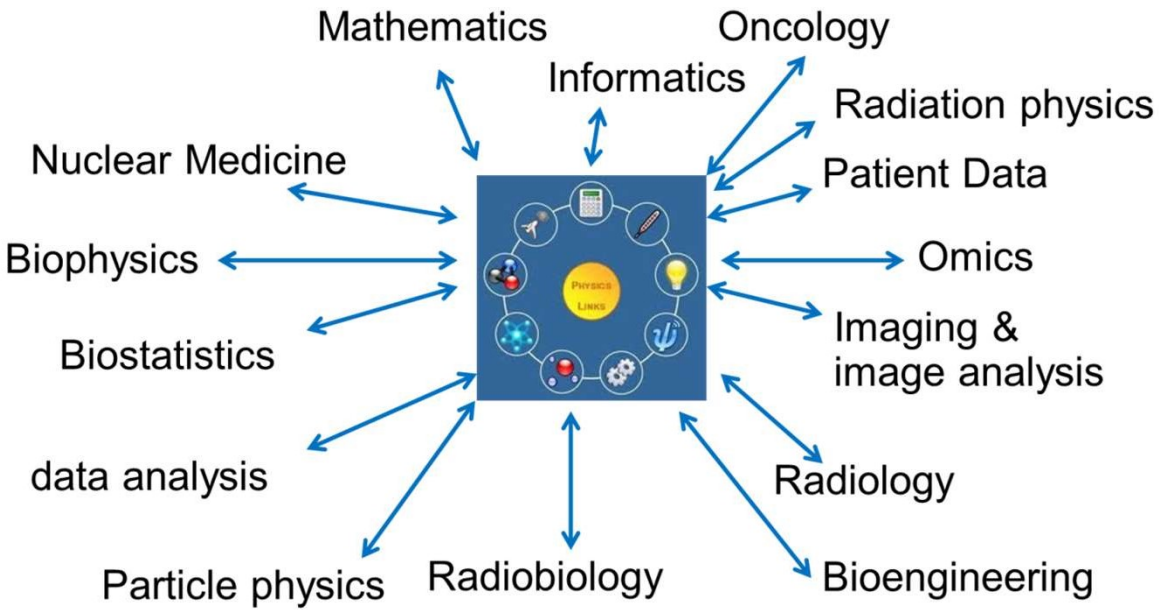
Straining (21/210)





2: Trigone

Concluding remarks: the future of MP in the field of predictive modeling…..



Medical physicists are in the very middle of the picture and are:

Trasversal

Translational

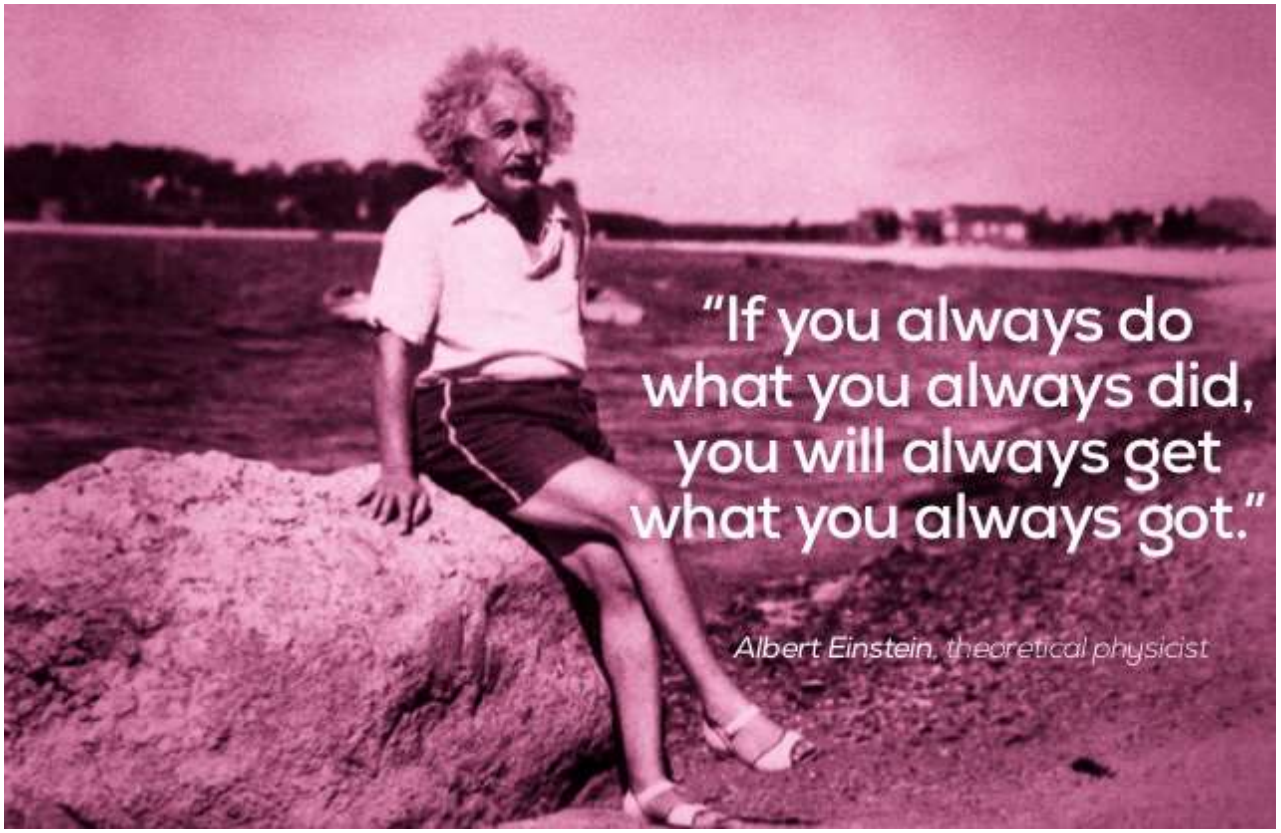
Flexible

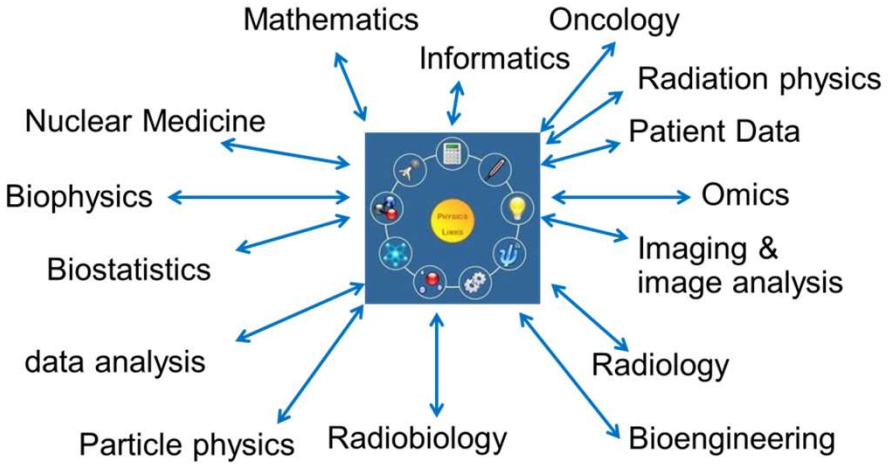
and… skilled in rigorously applying the scientific method, with a long tradition in RB/modeling and clinical data analysis

Concluding remarks: the future of MP in the field of predictive modeling…..

Huge potentials for RT medical physics in contributing to a rapidly emerging field in many ways, …..need for medical physicists to be reactive and pro-active and to rebuild/hybridize skills and competencies in multi/inter-disciplinary environments

Concluding remarks: the future of MP in the field of predictive modeling…..





Acknowledgments

- MP & RT Dept, OSR: S Broggi, GM Cattaneo, ML Belli, I Improta, P Mangili, L. Perna, F Palorini, R Raso, C Sini, N di Muzio, A Fodor, I Dell'Oca, P Passoni, C Cozzarini…

- RX, NM, Uro Dept OSR: A Briganti, F Decobelli, M Picchio

- T. Rancati, G Gagliardi, AE Nahum, M Ebert, E Oniukka, A. Cicchetti, M Alber, T Bortfeld, L Muren, G Rizzo, E Scalco, M Schwarz, G Sanguineti, A. van der Schaaf, V Valentini, R Valdagni …….and many others…

Grazie !!

Tips and tricks for writing a successful grant proposal

Uulke A. van der Heide

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Introduction

- There are several components to a strong grant application.
  - the subject must be creative, exciting, and worthy of funding.
  - the project must be developed through a rigorous, well-defined experimental plan.
  - you must make sure that the information is presented in clear language and that your application follows the rules and guidelines detailed in the grant application kit

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http://www.ninds.nih.gov/funding/write_grant_doc.htm

Key components to a succesful grant application

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Good research starts with the right question

"My project is simply this. I want to find out once and for all whether there's any truth in the belief that money can't buy happiness."

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Key questions to ask when reviewing a scientific paper

- Is it new?

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Key questions to ask when reviewing a scientific paper

- Is it new?
- Is it true?

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Key questions to ask when reviewing a scientific paper

- Is it new?
- Is it true?
- And why should I care?

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Key questions to ask when reviewing a grant application

- Novelty

New?

- Feasibility
- Risk

Can it be done?

- Address a relevant scientific/clinical question
- Potential impact
- Urgency

Why should I care?

Is it new

- Review literature (also older literature)
- Google the topic
- Assess what others in the field are working on
- Why did nobody address this question before?
  - or did they and failed?

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Feasibility

Is the workplan solid?

- What are the risks in your methodology?
- What are contingencies if a step in the project fails?
- Timing?
- Preliminary work?
- Sufficient budget?

Feasibility, contingencies

- Think about organization of your project
  - What if a step in your plan of investigation fails?

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Feasibility, contingencies

- Think about organization of your project
  - Assess risk and develop contingency plans
  - Show preliminary results for the risky parts

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Preliminary work

- Establish if the problem is real
- Establish that you can handle the most risky elements in your project
- Establish your credentials, capacity to actually carry out the project

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Preliminary work

- Establish if the problem is real
- Establish that you can handle the most risky elements in your project
- Establish your credentials, capacity to actually carry out the project

Preliminary work is not unfinished work, raw data

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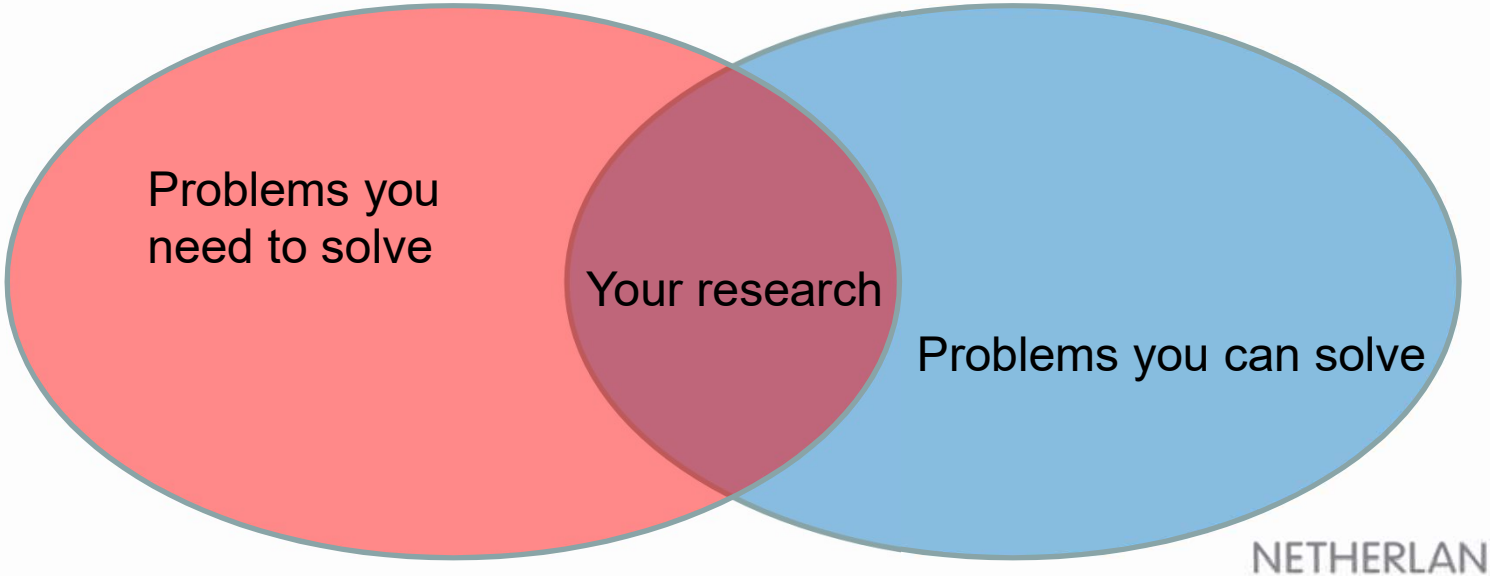
Feasibility

Why are you the right person to carry out the workplan

- Show your expertise (CV, preliminary work)
- Show the expertise of your institute/network of collaborators
- Show that you have specialist help where needed
- Show what sets you apart from your competition

Why should I care

- Relevancy
  - The fact that you CAN answer a question doesn't mean that you should



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Why should I care

- Urgency
  - If everything you propose succeeds, how is it going to impact the field?
  - How does it fit in the developments in the field?
  - Why does your project require funding NOW and not 5 years ago, or 5 years from now?

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- Most reviewers feel that a good grant application is driven by a strong hypothesis. The hypothesis is the foundation of your application. Make sure it's solid. It must be important to the field, and you must have a means of testing it.
- Provide a rationale for the hypothesis. Make sure it's based on current scientific literature. Consider alternative hypotheses. Your research plan will explain why you chose the one you selected.
- A good hypothesis should increase understanding of biologic processes, diseases, treatments and/or preventions.
- Your proposal should be driven by one or more hypotheses, not by advances in technology (i.e., it should not be a method in search of a problem). Also, avoid proposing a "fishing expedition" that lacks solid scientific basis.
- State your hypothesis in both the specific aims section of the research plan and the abstract.

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http://www.ninds.nih.gov/funding/write_grant_doc.htm

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http://www.ninds.nih.gov/funding/write_grant_doc.htm

WRITING A GRANT PROPOSAL

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Strategic planning

- Have a strategy for a grant application
  - Select the funding agency/call for proposals
  - Strengthen your CV
  - Do literature research
  - Generate preliminary results
  - Write the grant application

- Build a track record
  - Applying for many small grants may be better than for one big one

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The funding agency

- Select the appropriate funding agency / program
  - Public/private/charity
- Find out which criteria are used to assess your proposal
  - What does the funding organization want
    - High-risk / safe implementation
  - This is not always explicit. Talk to people who may know
    - Call the program officer to find out

Government/international bodies	Basic, translational, clinical, applied
Charities/foundations	Specific problems/diseases
Industry	Commercial interest; restrictions on publications?

The funding type

- Select the appropriate funding agency / program
- Find out how much can be funded and what can be done
  - Your salary? Other salaries? Investments?

Government/international bodies	Basic, translational, clinical, applied
Charities/foundations	Specific problems/diseases
Industry	Commercial interest; restrictions on publications?

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CV

- What is requested by the funding agency?
  - Grant application for junior scientists
  - Program grant for consortium of established groups
- Do you have publications that show your expertise?
- Do you have international collaborations
  - Worked for a while in other countries

It may be better to wait a year to build a better CV

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Generate preliminary results

- The purpose of preliminary results is
  - To show that critical steps in your plan of investigation are likely feasible
  - To show your expertise and the expertise of your institute

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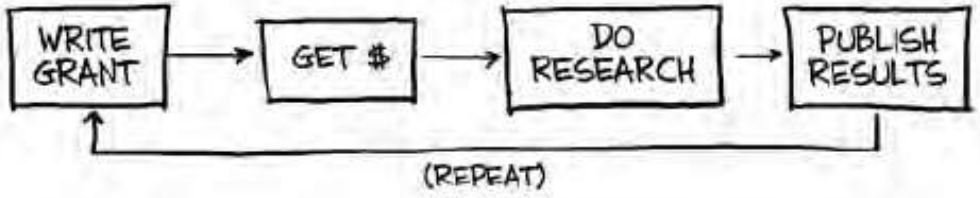
Piled Higher and Deeper *by Jorge Cham* www.phdcomics.com

THE GRANT CYCLE

HOW IT'S SUPPOSED TO WORK:



HOW IT REALLY WORKS:

WWW.PHDCOMICS.COM

title: "The Grant Cycle" - originally published 5/8/2011

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Write the grant application

- Choose a clear and concise title; use the right buzz words as they are used to select reviewers
- The abstract is the most critical part of the application
- Formulate a clear and relevant goal, be specific
  - Avoid phrases like ‘want to improve insight into …’
  - Pose a testable hypothesis
  - Provide numbers (power calculation!)
- Design a plan of investigation that can achieve that goal
- Sell, but don’t oversell
- Be specific.

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Write the grant application

- Read **AND FOLLOW** the guidelines of a particular call for proposals as a small error may kill an application
- Check if letters of support/commitment are required
- Use the spelling checker
- Involve colleagues you want to participate in the project well in time
- Ask someone/(preferably more people) with experience, but not involved in your project to review your proposal before submitting it

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Final remarks

- You can apply for multiple grants at the same time, but never use two or more grants to fund the same work!
- You can reject an awarded grant, but put it on your CV

- Pitfalls:
  - Too little focus, too ambitious
  - Technology driven research
  - No contingency plan
  - Level of detail
  - ‘me too’ research

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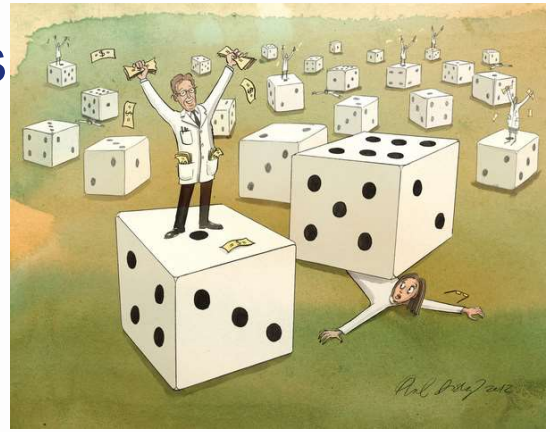
Final remarks

- The success rate of grant applications varies between funding agencies
  - The majority of grants is rejected initially
- Resubmit the grant, taking the advice of the reviewers
  - Stay positive
  - More preliminary work
  - Improved CV
  - But that's also true for your competion



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Hot research topics in brachytherapy

ESTRO Master Class in Radiotherapy Physics
Florence, September 2017

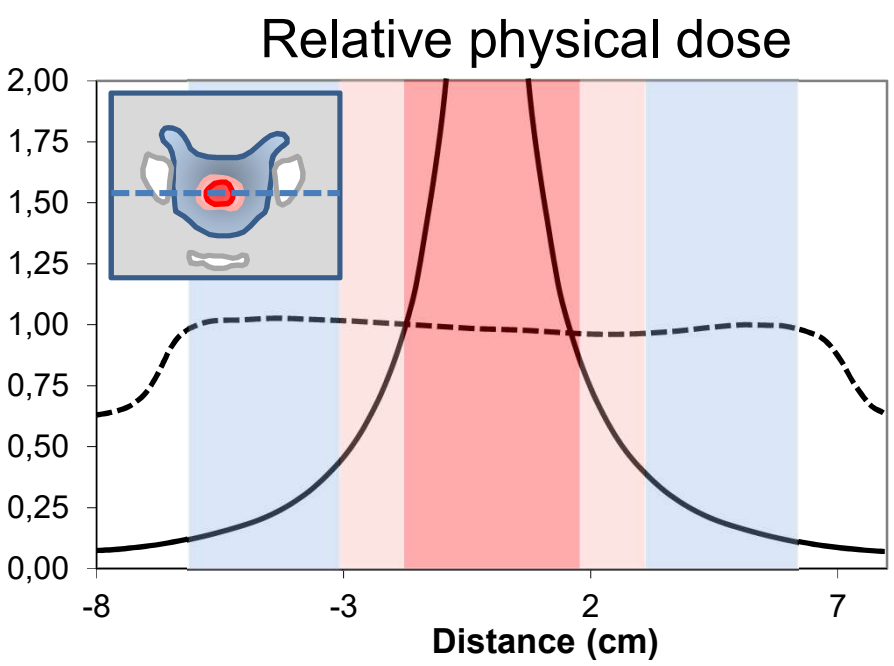
PhD Kari Tanderup, Aarhus University/Aarhus University Hospital

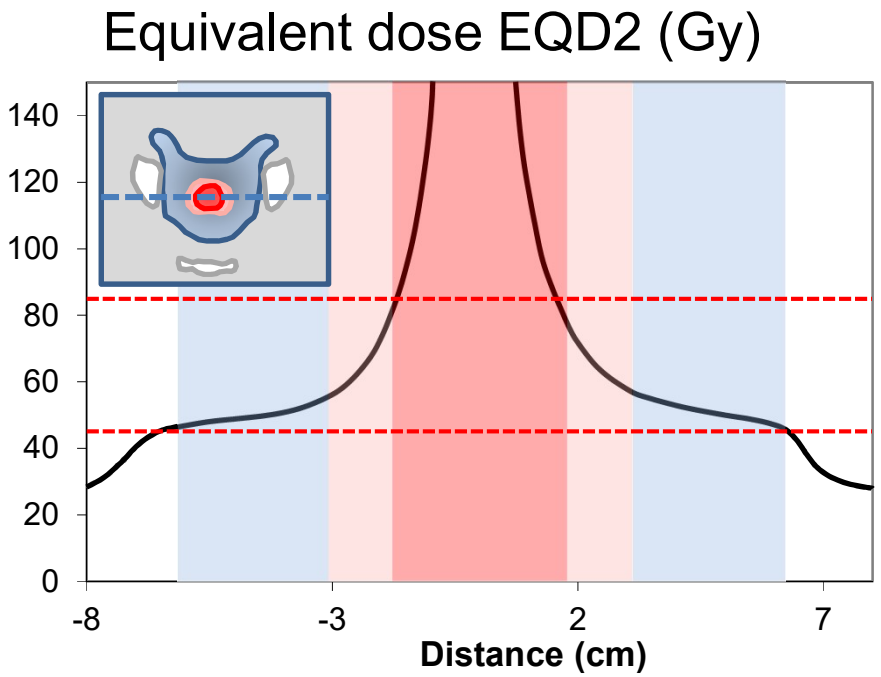
Aarhus University Hospital

AARHUS UNIVERSITY

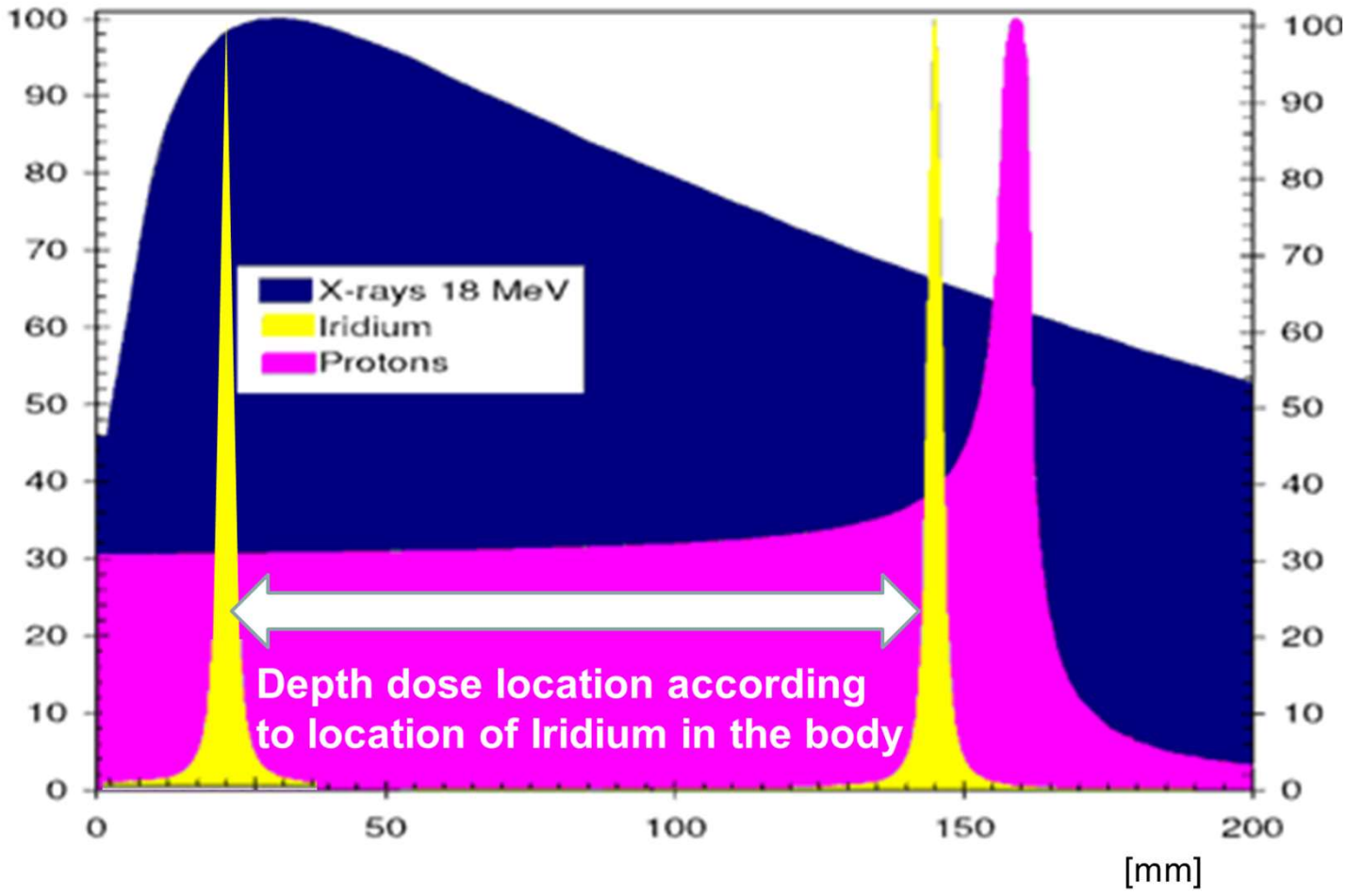
Why is brachytherapy hot?

- **High, intermediate, low doses within mm**
- **Dose gradients**
  - **~5-30% pr mm at the target edge (e.g. 6% at point A)**
- **Hypofractionation**





Bragg peak and brachy peak



Modified from Kovacs, Lübeck

Major applications of brachytherapy

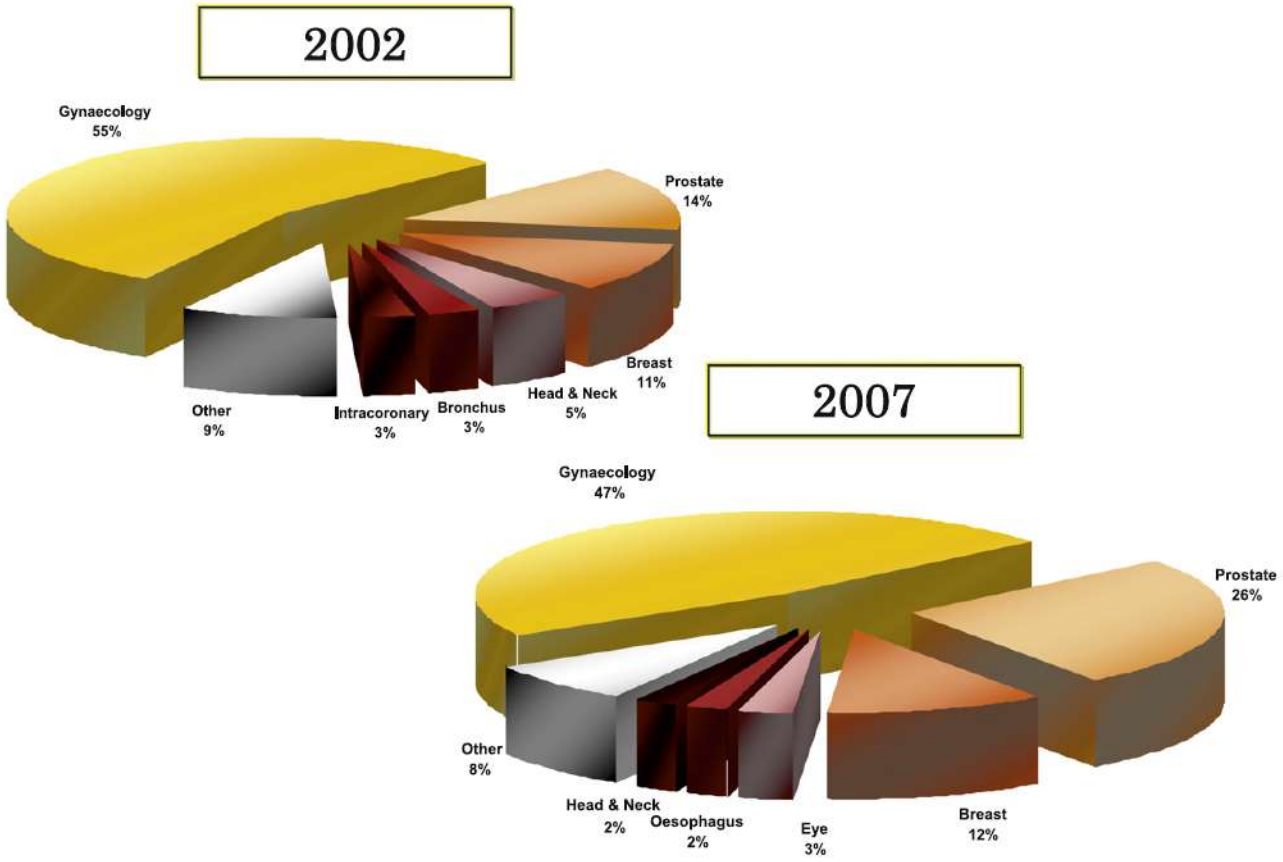
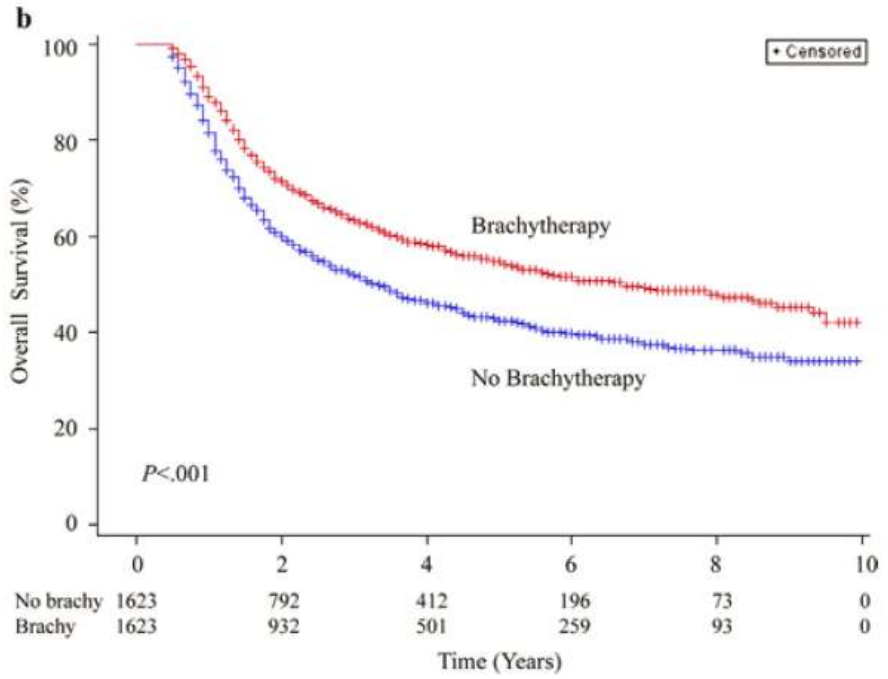


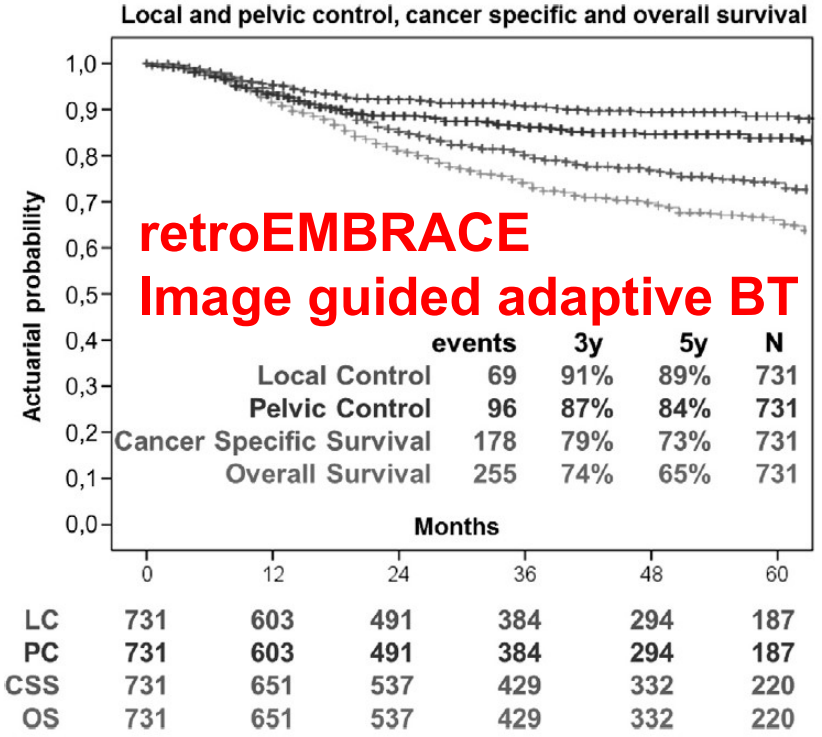
Fig. 3. Most common treatment localizations, group I (2002 vs. 2007).

Guedea et al, RO (97), 2010, 514-520

Importance of BT and image guidance in cervix cancer



Han et al, IJROBP, 87(1), 111-119, 2013



Sturdza et al, Radiother Oncol, 120, 428-433, 2016

International Journal of Radiation Oncology biology • physics

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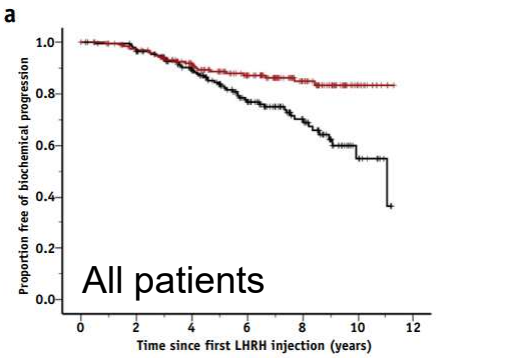
EDITORIAL

Curative Radiation Therapy for Locally Advanced Cervical Cancer: Brachytherapy Is NOT Optional

Kari Tanderup, PhD,*,† Patricia J. Eifel, MD,‡ Catheryn M. Yashar, MD,§ Richard Pötter, MD,‖ and Perry W. Grigsby, MD*

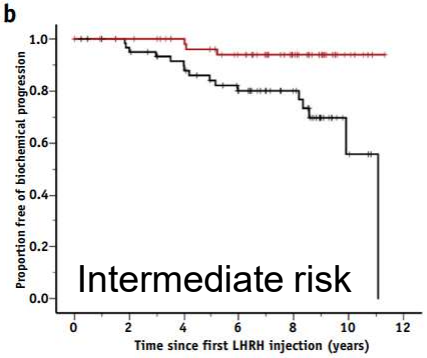
Potential of BT in prostate cancer

- **ASCENDE-RT**
- **Randomised**
- **High and intermediate risk prostate cancer**
- **398 pts**
- **Arm 1: Pelvic 46Gy EBRT + EBRT boost to 78Gy**
- **Arm 2: Pelvic 46Gy EBRT + LDR boost**



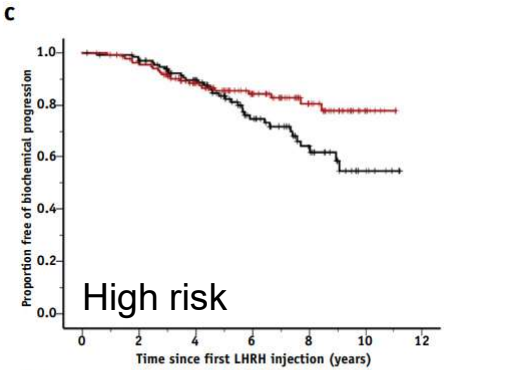
Numbers at risk:

Time (yrs)	0	2	3	4	5	6	7	8	9	10
DE-EBRT	200	186	168	145	119	93	74	52	27	11
LDR-PB	198	184	168	147	127	106	86	59	38	14



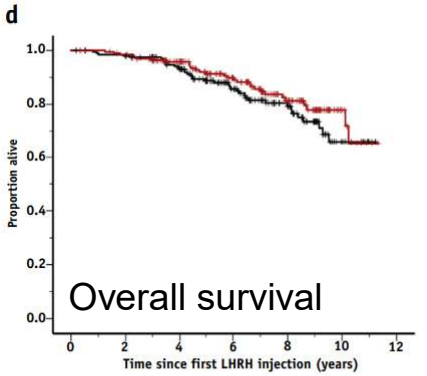
Numbers at risk:

Time (yrs)	0	2	3	4	5	6	7	8	9	10
DE-EBRT	63	57	54	49	43	38	30	25	12	4
LDR-PB	59	55	54	50	47	42	35	26	7	6



Numbers at risk:

Time (yrs)	0	2	3	4	5	6	7	8	9	10
DE-EBRT	137	129	114	96	76	55	44	27	15	7
LDR-PB	139	128	114	97	80	64	51	33	21	8



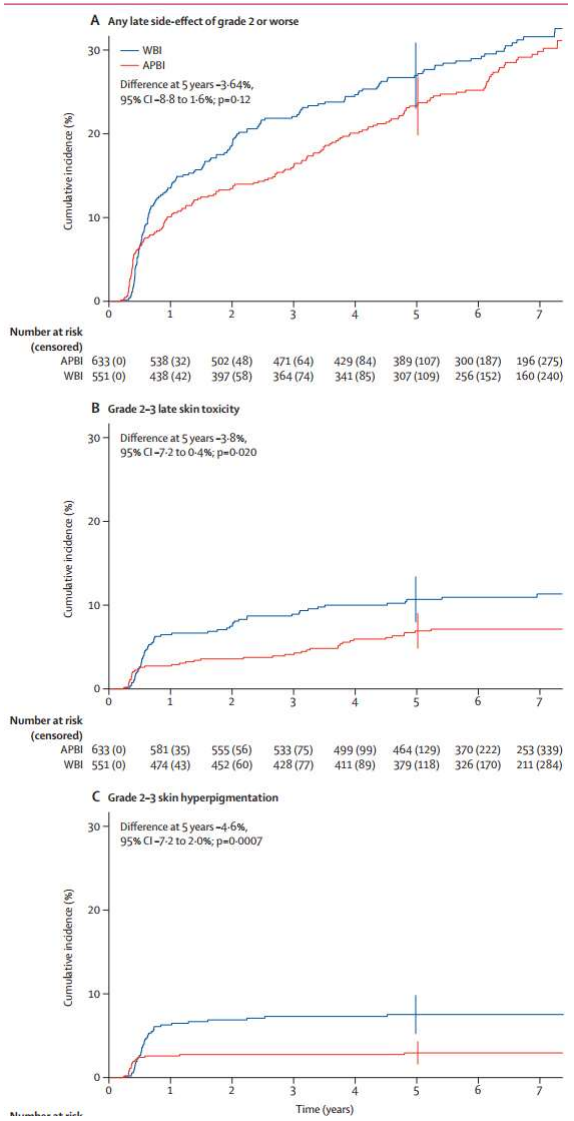
Numbers at risk:

Time (yrs)	0	2	3	4	5	6	7	8	9	10
DE-EBRT	200	192	184	161	134	109	85	66	40	16
LDR-PB	198	191	182	160	137	116	94	65	41	15

Morris et al, IJROBP, 98(2), 275-285, 2017

Potential of BT in breast cancer

- GEC ESTRO trial
- Randomised
- Stage 0-IIA breast cancer
- 1328 pts
- Arm 1: Whole breast EBRT 50Gy + 10Gy boost
- Arm 2: Accelerated Partial Breast Irradiation (APBI) with brachytherapy



Polgar et al, Lancet Oncology, 18(2), 259-268, 2017

Research topics in brachytherapy

- Dosimetry
- Dose calculation
- Imaging and target definition
- Treatment technology
  - Applicators/implantation
  - Sources/Afterloaders
- Treatment delivery verification
- Clinical outcome

What is hot?

Uncertainty budget cervix

- **What are the major contributors to uncertainties in the current workflow?**
- **How do we improve on precision and accuracy?**

Table 1
Uncertainty budget (SD) for one intracavitary brachytherapy fraction. The overall uncertainty for the entire treatment course is depending on the fractionation schedule and level of verification.

	Target (HR CTV D90)	OARs (D_{2cm^3})
Source strength	2%	2%
Dose and DVH calculation	3%	3%
Dwell position uncertainty (reconstruction and source positioning)	4%	4%
DVH addition across fractions (previously called "worst case assumption")	NA	1%[a]–?%
Contouring (inter-observer)	9%	5–11%
Intra- and inter-fraction (intra-application) uncertainties[b] (5)	11%	20–25%
Total[c]	12%	21–26%

[a] For the bladder and likely rectum, whereas it has not been evaluated for sigmoid.
[b] Per se including intra-and inter-observer contouring variations.
[c] Contouring uncertainties included through intra- and inter-fraction uncertainties.

Tanderup et al, RO Vol 107, 2013

Uncertainty prostate LDR

- **Largest contributors for LDR prostate:**
  - **Dose calculation uncertainties**
  - **Anatomical changes**

Table 4
Example 4 – LDR ^{125}I sources for permanent prostate BT.

Category	Typical level (%)	Assumptions
Source strength	3	PSDL traceable calibrations
Treatment planning	4	Reference data with the appropriate bin width
Medium dosimetric corrections	5	No consideration is given for calcifications or their composition in the patient
Inter-seed attenuation	4	An advanced dose calculation formalism may indicate source models and orientations cause the largest effects
Treatment delivery imaging	2	US QA performed according to AAPM TG-128
Target contouring uncertainty	2	Using CT or CT + T2 imaging
Anatomy changes between dose delivery and post-implant imaging	7*	Post-implant imaging using CT, with a scalar correction factor for edema correction
Total dosimetric uncertainty ($k = 1$)	**11**	For treatment delivered without excreted seeds

* Estimated value based on expert discussion.

Kirisits et al, RO Vol 110, 2014 199-212

Research topics in brachytherapy

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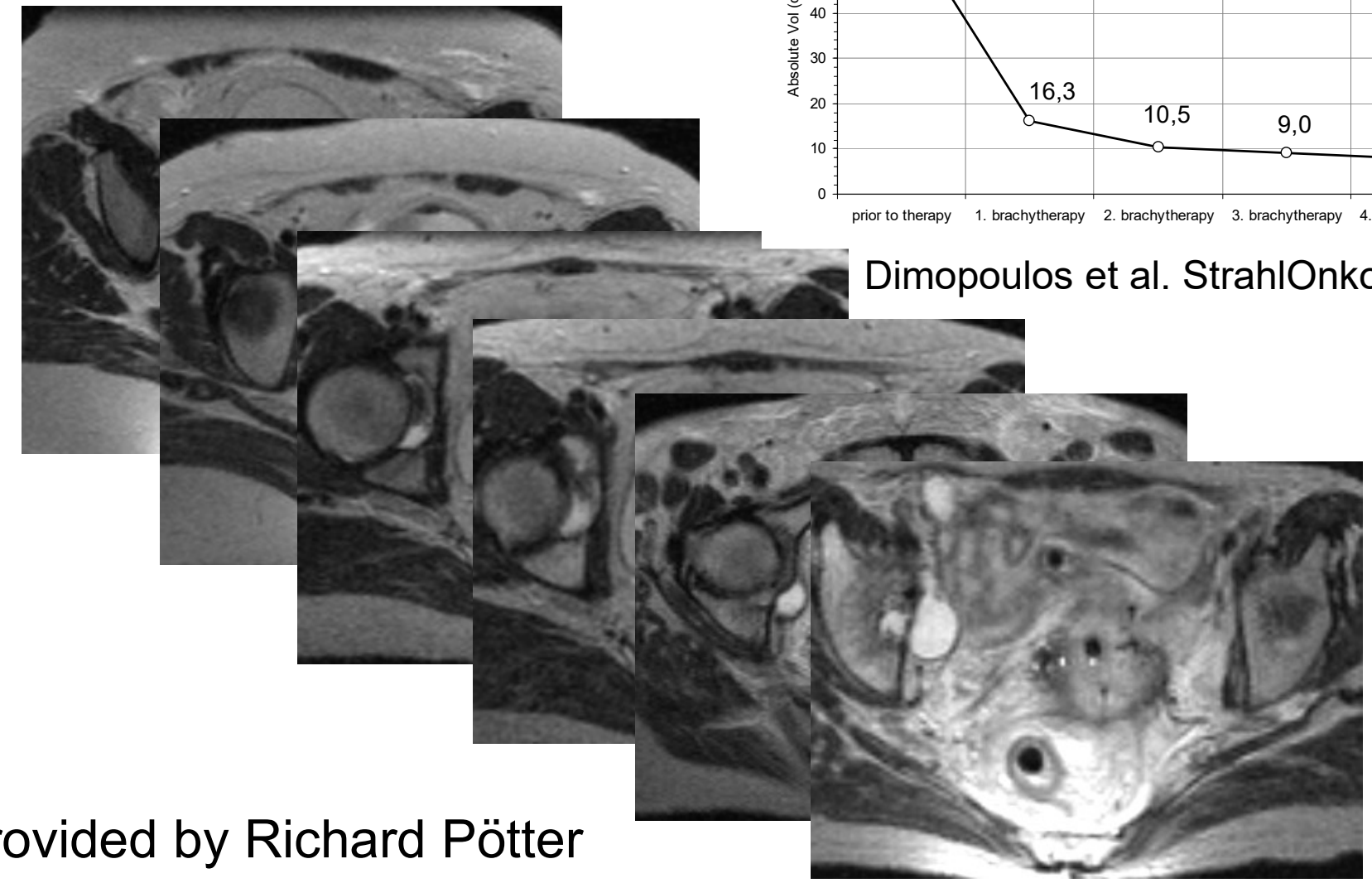
Imaging during RT in cervix cancer
Pattern of response (4D)

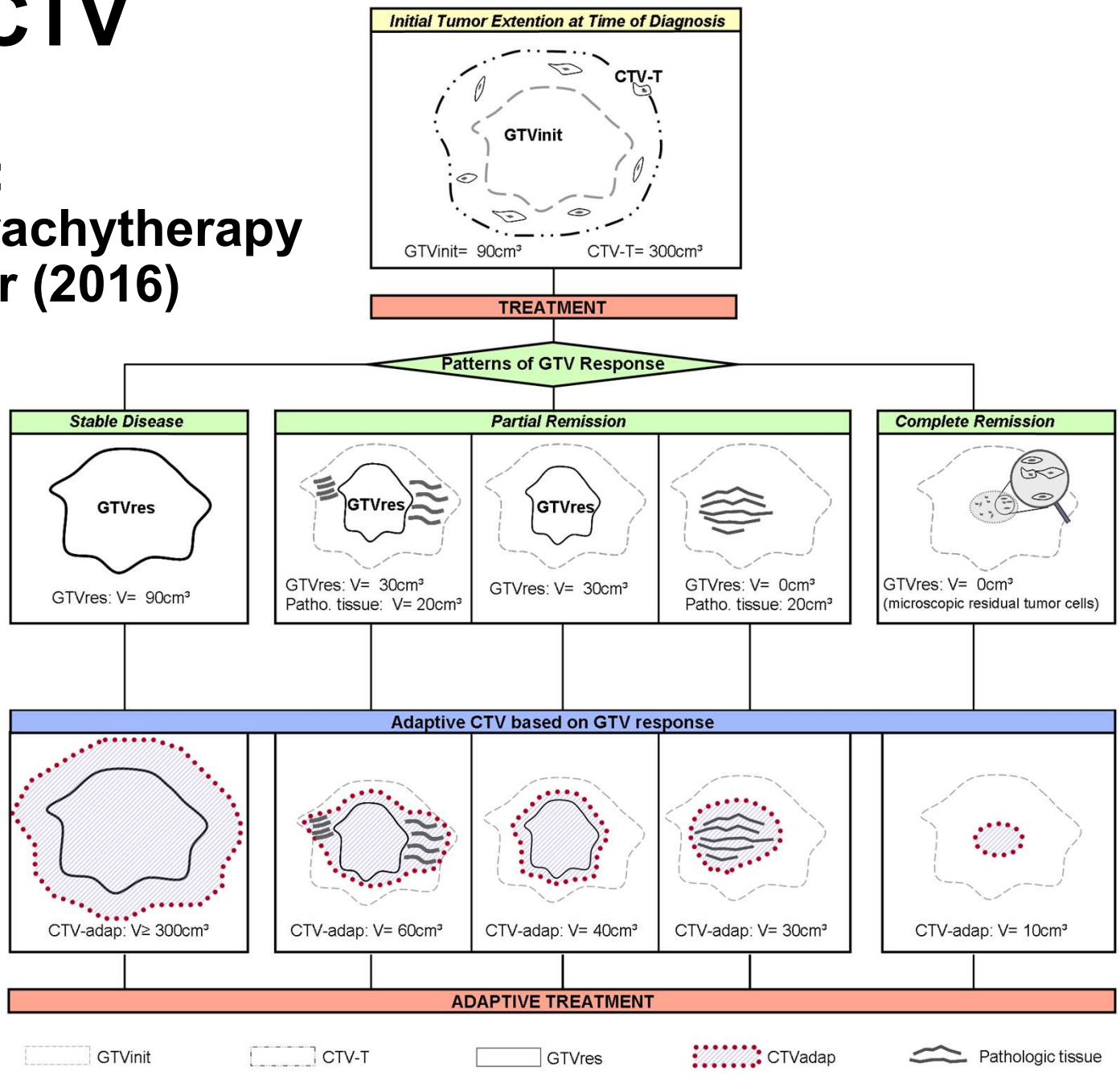


Dimopoulos et al. StrahlOnkol 2008

Provided by Richard Pötter

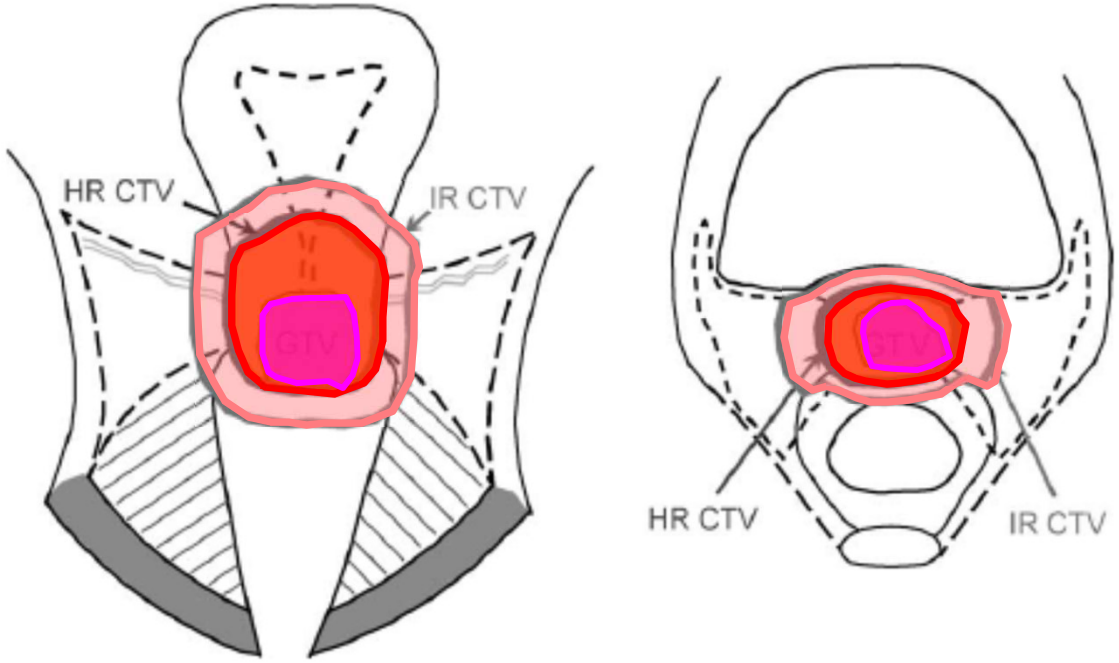
Adaptive CTV

ICRU report 89: Intracavitary brachytherapy in cervix cancer (2016)



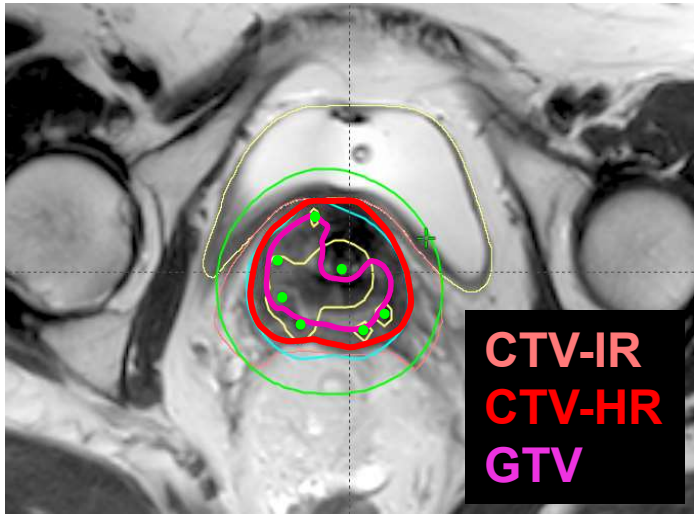
Risk adapted target concept

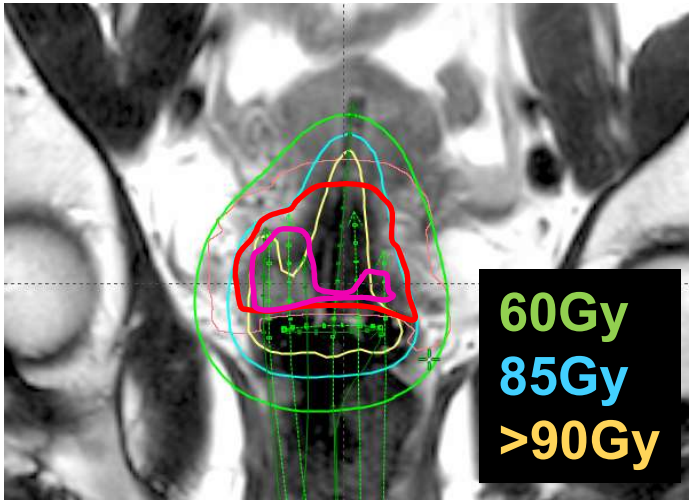
- $\underline{GTV_{res}}$: Macroscopic tumor at BT
- $\underline{CTV_{HR}}$: GTV_{res} + cervix + extra-cervical extension at BT
- $\underline{CTV_{IR}}$: Tumor at diagnosis

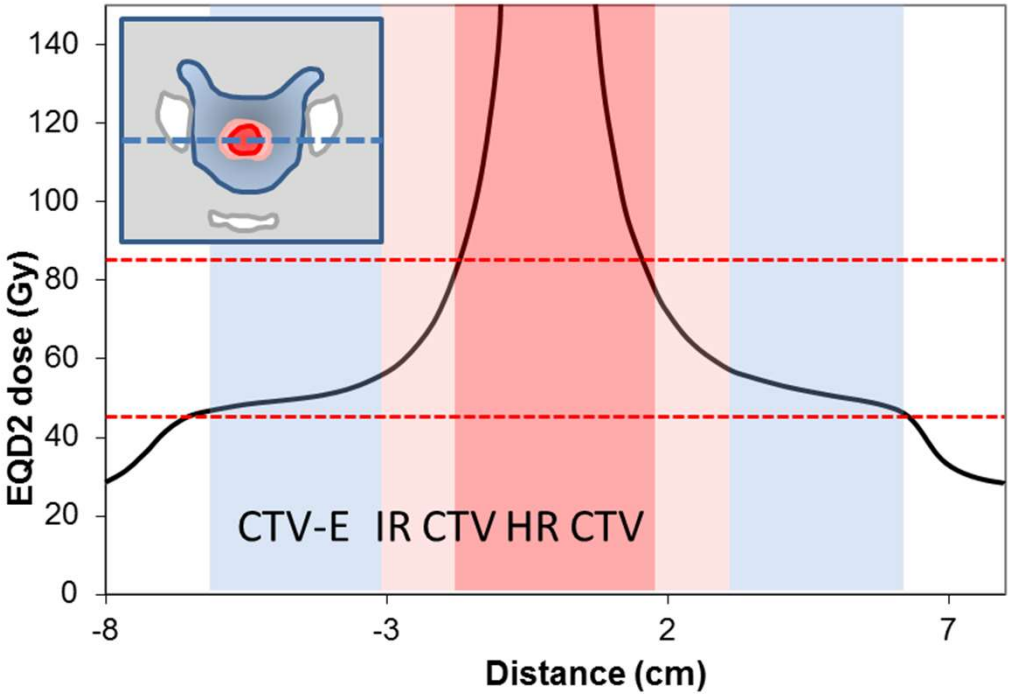


Haie-Meder et al, Radiother Oncol. 2005 Mar;74(3):235-45

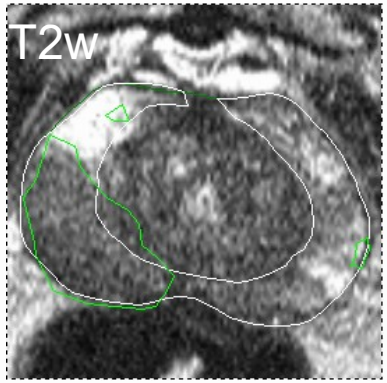
Risk adapted dose prescription

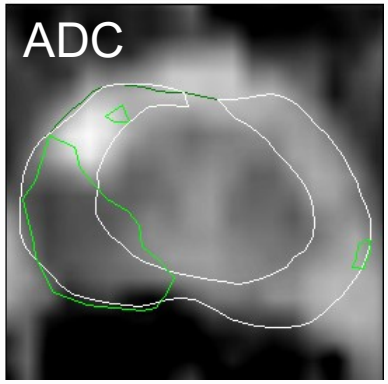


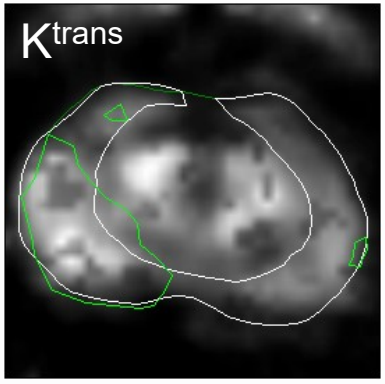




Computer-aided detection of tumor in prostate cancer

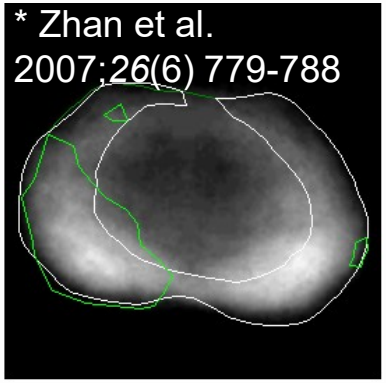




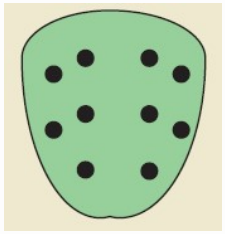


MRI data

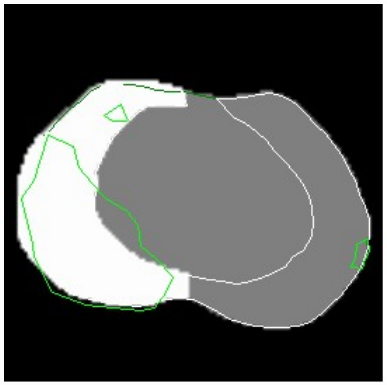
+



Prostate atlas based on 158 radical prostatectomy specimen *



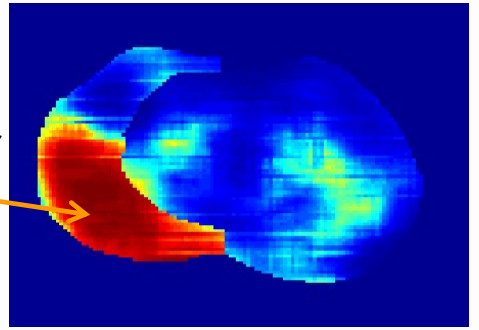
Biopsy reports

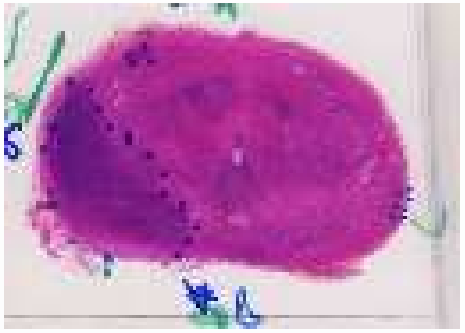


Biopsy Map

Courtesy Uulke van der Heide

Detected tumor area in peripheral zone



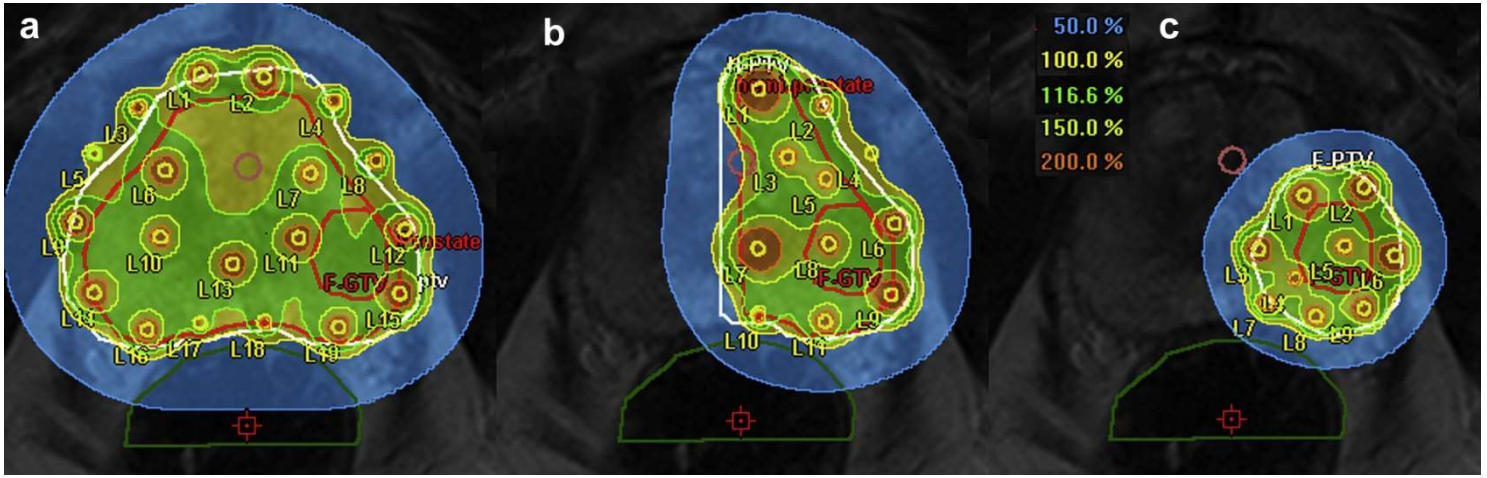


H&E Staining Image

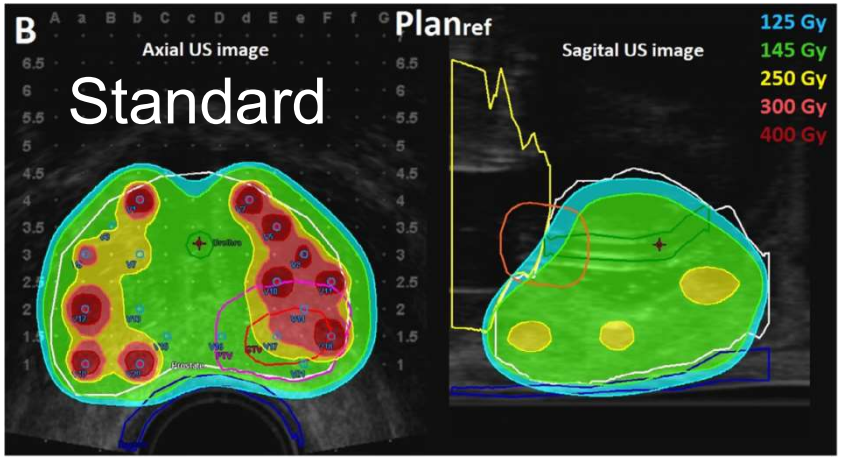
NETHERLANDS CANCER INSTITUTE
ANTONI VAN LEEUWENHOEK

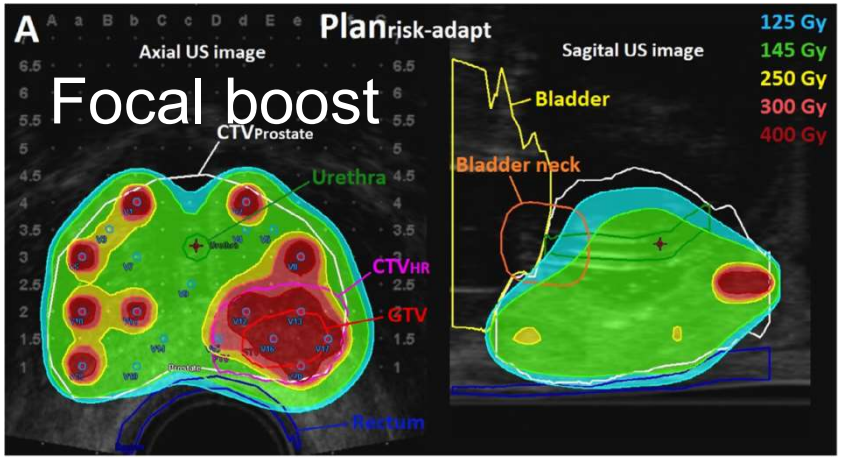
Dinh et al. Med Phys. 2017;44:949-961

Focal treatment/boosting with brachytherapy



J.Mason et al, Brachytherapy, vol 13, 611-617, 2014





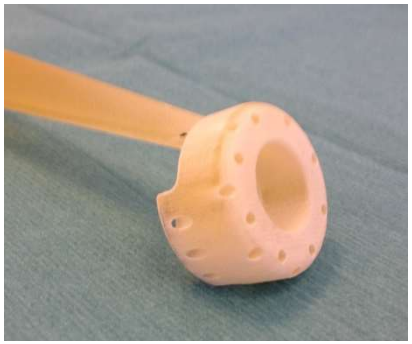
S. Rylander et al, RO, vol 115, 308-313, 2015

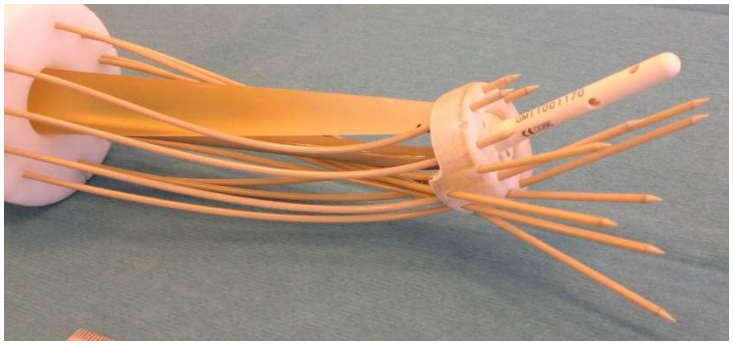
Research topics in brachytherapy

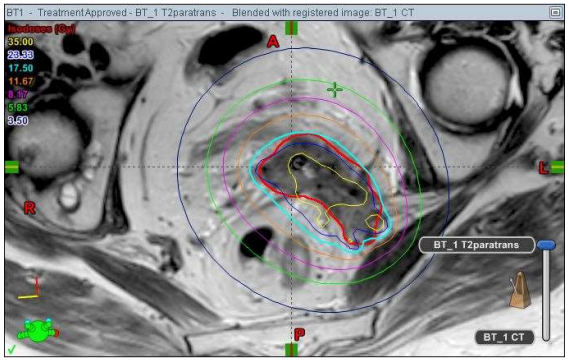
- Dosimetry
- Dose calculation
- Imaging
- Treatment technology
  - Applicators/implantation
  - Sources/Afterloaders
- Treatment delivery verification
- Clinical outcome

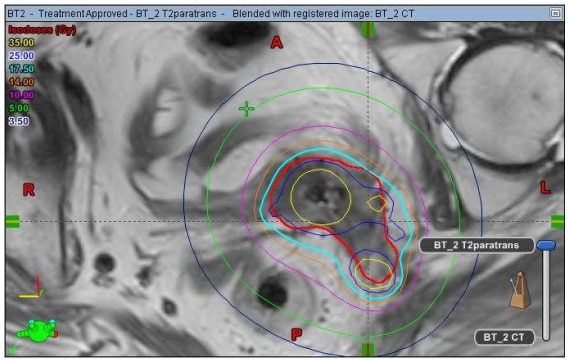
Applicators: can we reach the target?

- **Individualised applicators based on imaging**
- **3D printed applicators**





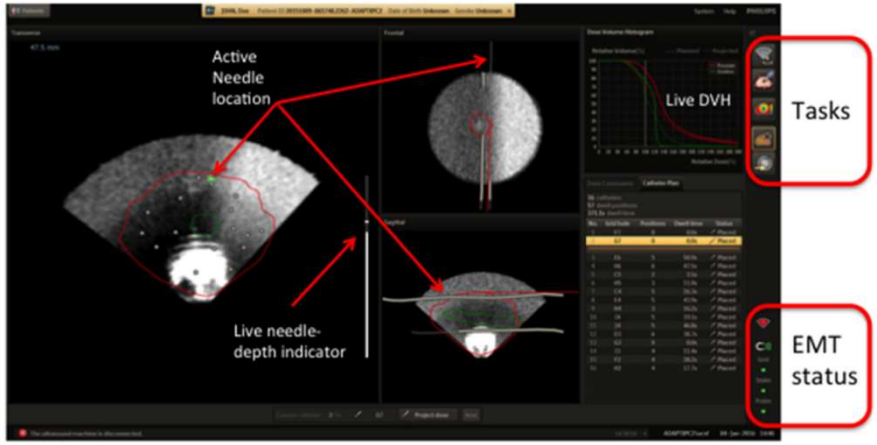


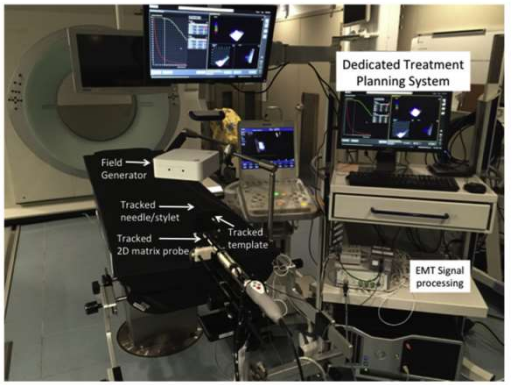


Lindegaard et al. Radiother Oncol. 2016 Jan;118(1):173-5

Navigation and tracking

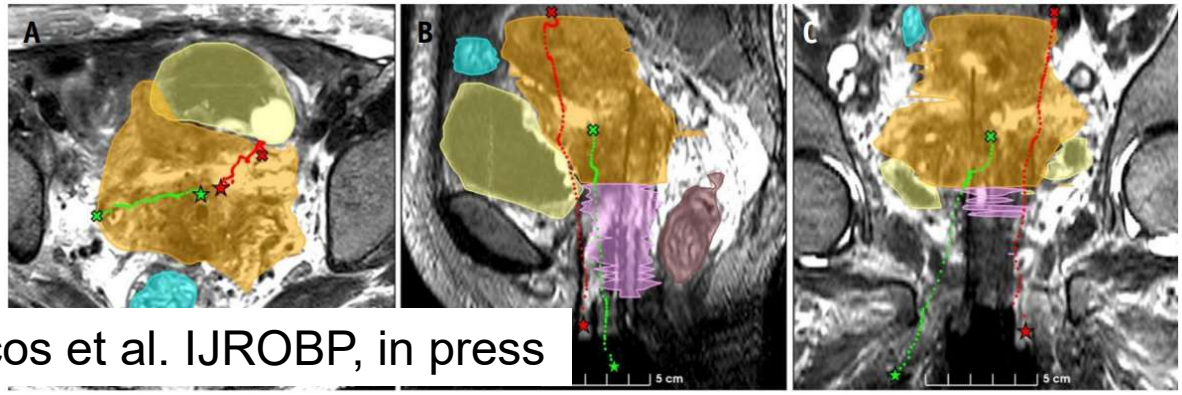
Electromagnetic (EM) tracking



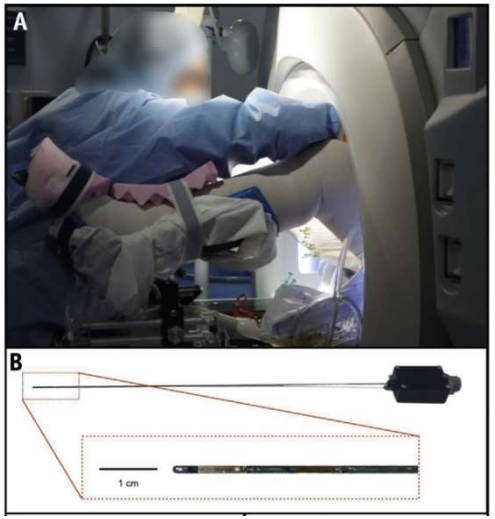


Beauliea et al. Brachytherapy, in press

Tracking on MRI with RF coil

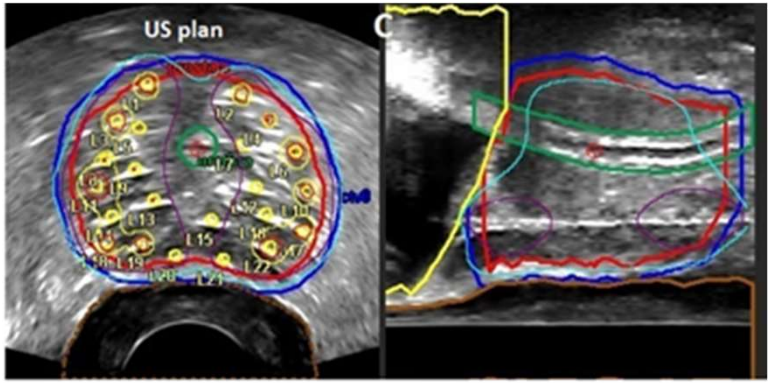


Arcos et al. IJROBP, in press

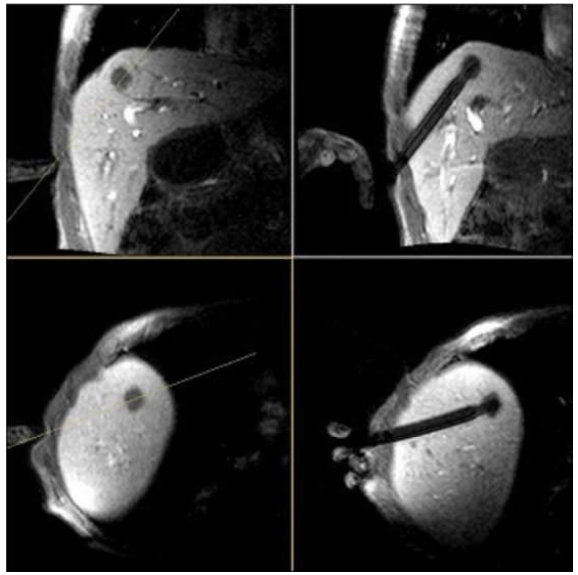


”On-board / In-room imaging” for BT: Imaging during catheter implantation

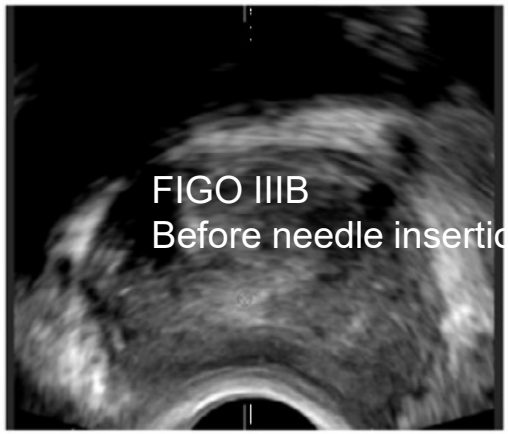
- **US guided prostate**

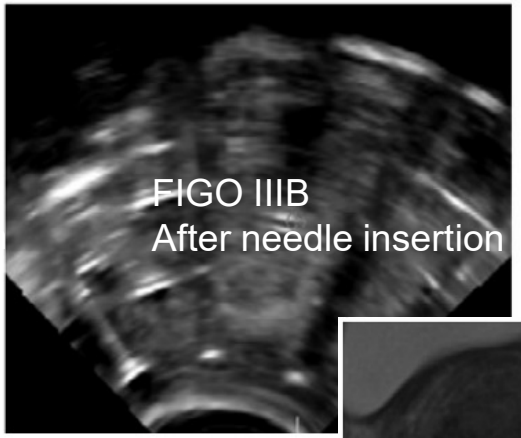


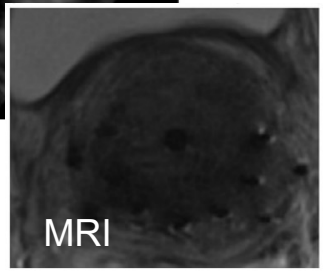
- **MRI guided liver BT**



- **Gyn cervix: US guidance**







Ricke et al, Semin Radiat Oncol. 2011 21:287-93

Schmid et al, Radiother Oncol, 120 (2016), 467-472

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Treatment verification: importance for BT

- **Risk of errors (high compared to EBRT):**
  - **Manual procedures: errors in reconstruction of catheters, applicator length, applicator-afterloader connection, etc.**
  - **Mechanical equipment: obstructed transfer tubes and applicators, machine failure, etc.**
- **High impact of errors/uncertainties:**
  - **High dose gradients**
  - **Hypofractionation schemes**
- **Challenge: Low patient volume (compared to EBRT):**
  - **Resource investment limitations**
  - **Small clinics: Reduced expertise and experience**

How much is *in vivo* dosimetry utilised?

- **Patterns of care study Europe (2007)*:**
  - ***in vivo* dosimetry available in 23% of centers**
- **French survey of 15 centers by Estelle Spasic (2017)**:**
  - ***in vivo* dosimetry not performed in any center**
- **74% of departments would like to do *in vivo* dosimetry given an appropriate technique was available**

*F Guedea et al, **"Patterns of care for brachytherapy in Europe: Updated results"**, Radiotherapy and Oncology 97 (2010) 514–520.

** Estelle Spasic, Institute Curie, Paris, personal communication

Why is in vivo dosimetry not systematically used?

Routine rectal diode in vivo dosimetry, Aarhus University Hospital:

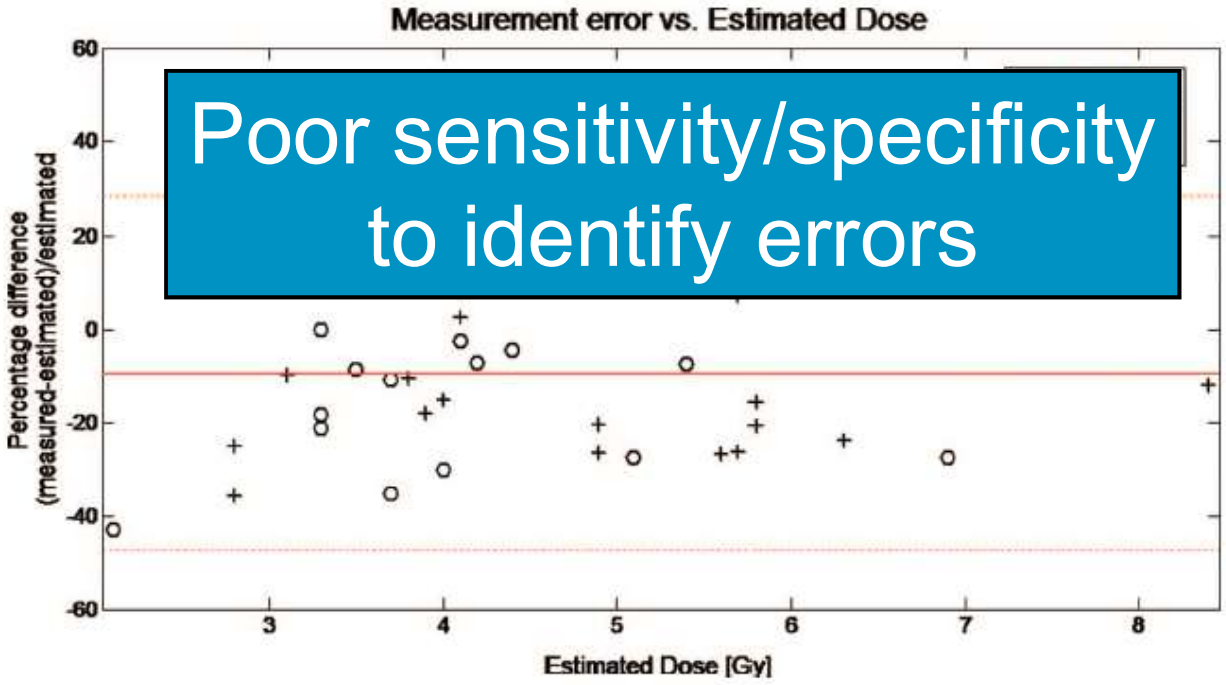


FIG. 1. Rectal IVD in PDR ^{192}Ir cervix cancer BT with tandem ring applicator for BT fractions 1 (BT1) and 2 (BT2). Dashed lines indicate bounds of the 95% prediction interval.

Tanderup, Beddar, Andersen, Kertzscher, Cygler. In vivo dosimetry in brachytherapy, Med Phys 40(7), 2013

How often do errors happen?

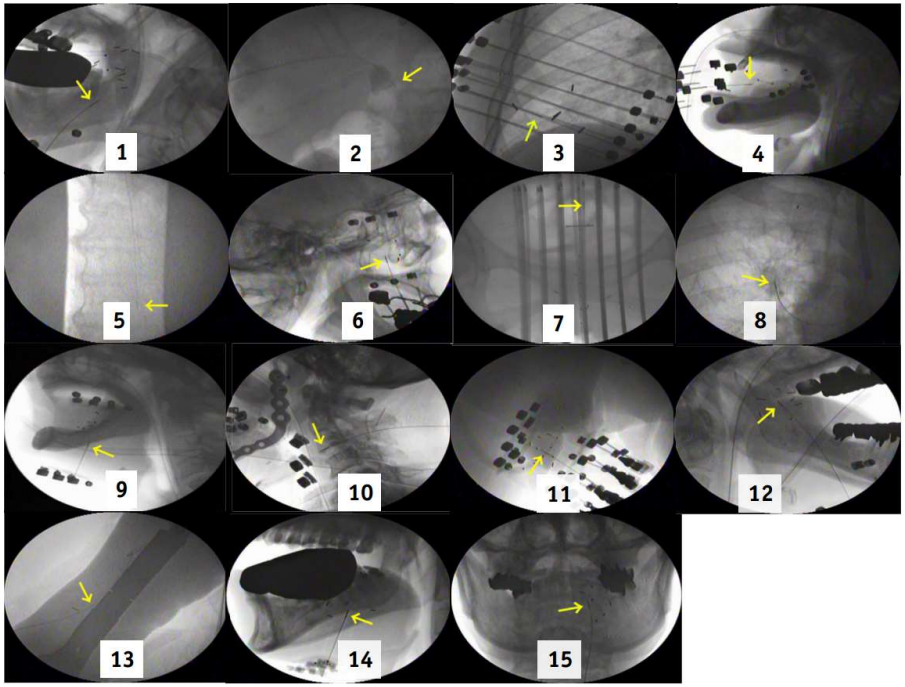
Results of questionnaire after GEC ESTRO treatment verification seminar, Brussels 2014

Have you ever encountered any errors/events or major deviations in brachytherapy delivery?

1. Applicator movement
2. Incorrect connection, wrong catheter length, wrong reconstruction
3. Wrong catheter direction, wrong needle depth
4. Wrong patient, swopped reconstruction
5. None
6. None
7. Incorrect connection, wrong applicator length
8. Incorrect connection, wrong applicator length
9. Incorrect connection, wrong reconstruction, afterloader malfunction, applicator movement

”On-board / In-room imaging” for BT: Imaging of source progression

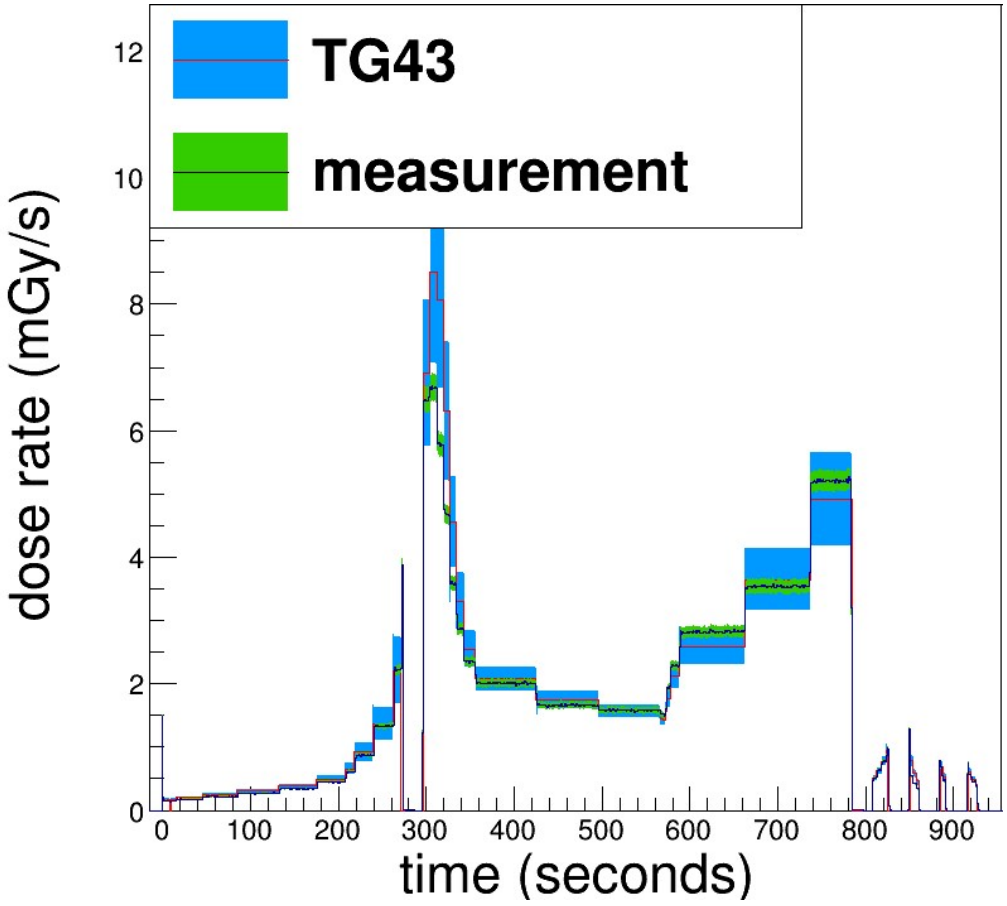
- Real-time flouroscopy of source
- Flouroscopy during 2031 treatment sessions in 370 patients
- 2/2031 errors detected (0.1%)
- Affected 2/370 (0.5%) of pts
  - Swapped guide tubes
  - Wrong applicator length



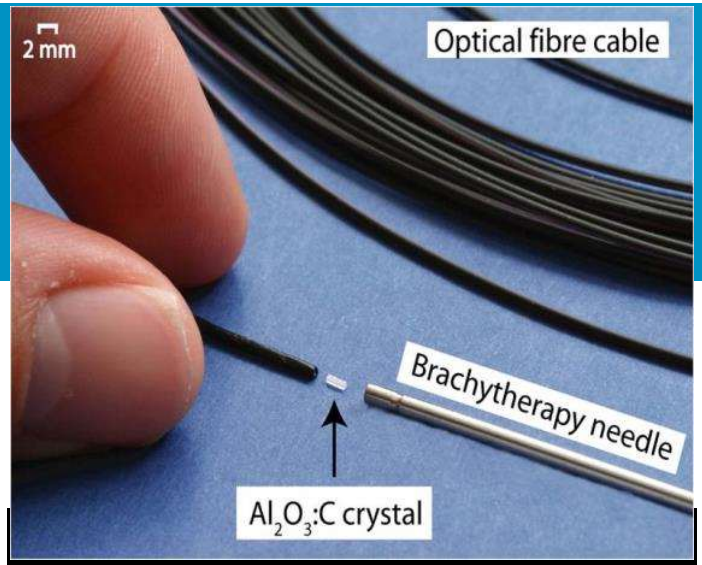
Nose et al, Int J Radiation Oncol Biol Phys, Vol. 97, No. 4, pp. 858-865, 2017

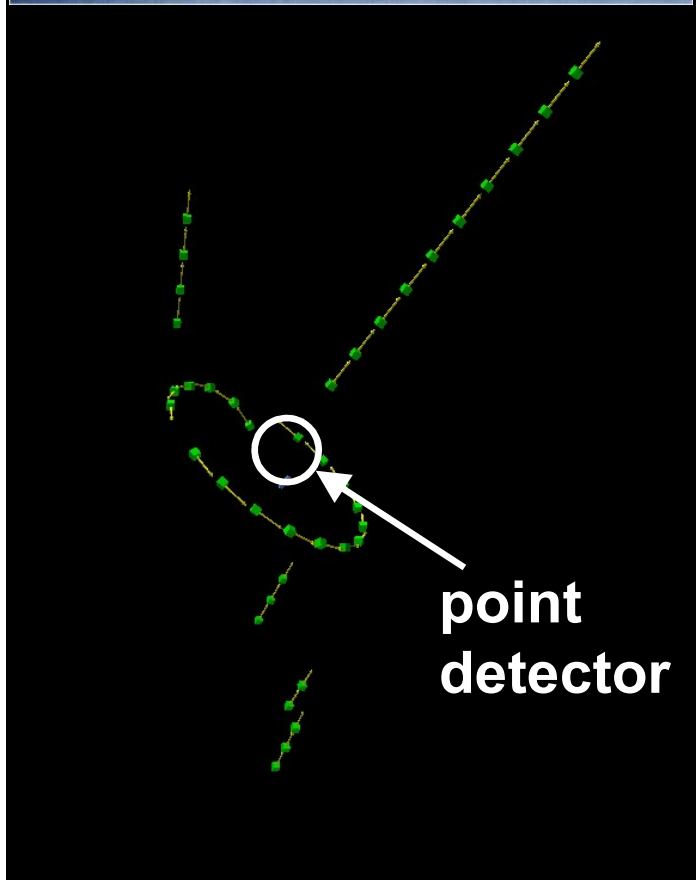
Real-time *in vivo* dosimetry

Footprint of source progression!



Kertzscher et al, Med Phys, 2014





Research topics in brachytherapy

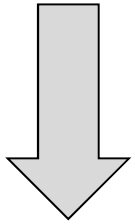
- Dosimetry
- Dose calculation
- Imaging
- Treatment technology
  - Applicators
  - Sources/Afterloaders
- Treatment delivery verification
- Clinical outcome

New sites and applications

- **Sites which can be treated with both EBRT or BT:**
  - **Prostate**
  - **Breast**
  - **Rectum**
  - **Bladder**
  - **Head and Neck**
  - **Liver**
- **Clinical trials**
- **Training and centralisation**

Towards best clinical RT practice

- **Understanding clinical outcome**
  - **What is the magnitude and pattern?**
  - **What are the risk factors?**



- **Improving RT practice**
  - **Can we change practice?**
  - **Interventional trial**

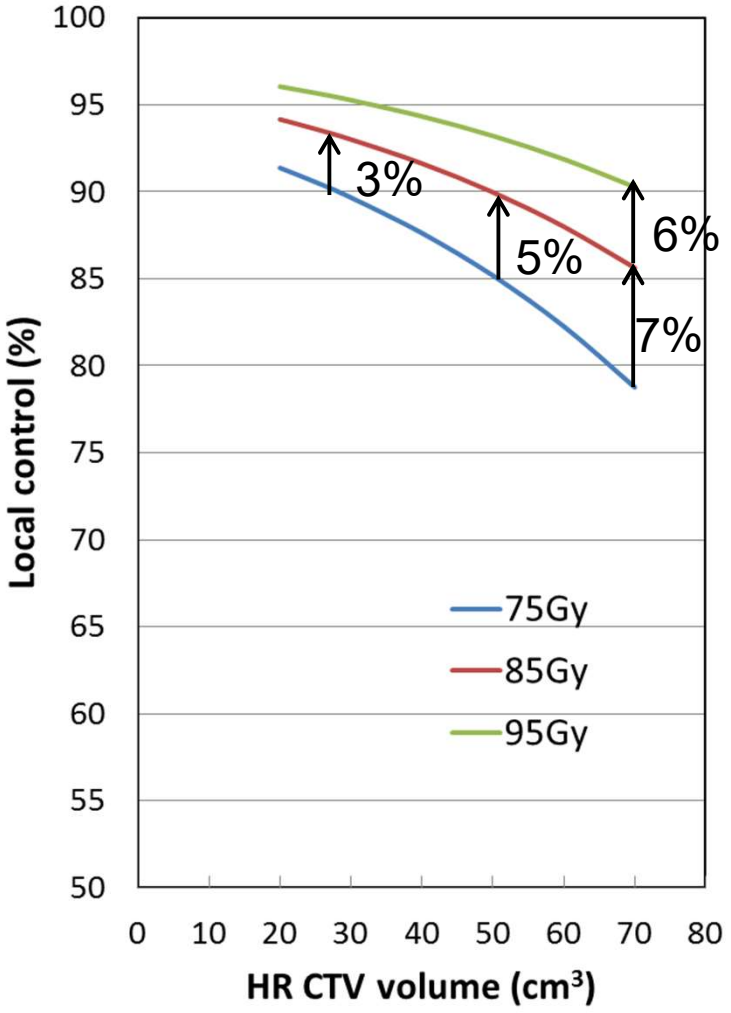
Dose and volume effect for target

Data from retroEMBRACE study

Effect of dose, volume and time:

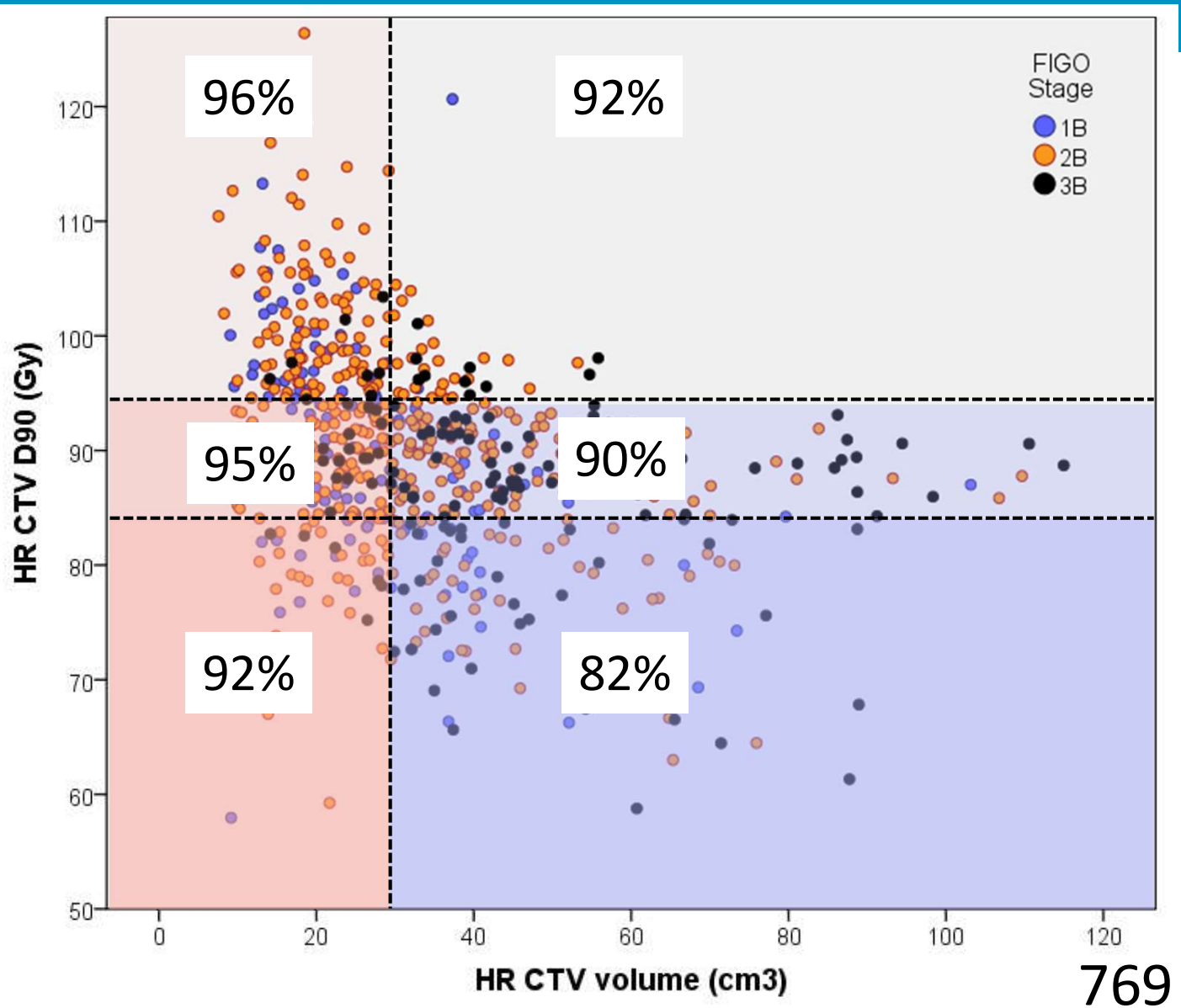
Dose:	**10Gy → ~ 5% LC**
Time:	**7 days ~ 5Gy**
Volume:	**10cm³ ~ 5Gy**

Local control at 3 years



Tanderup et al Radiother Oncol, Vol 120, 2016

Is our current practice appropriate?

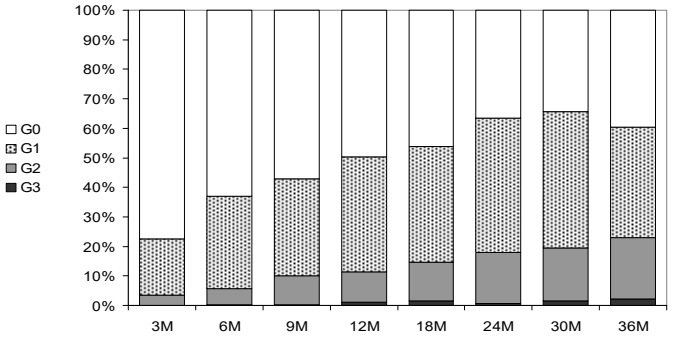


769 pts EMBRACE

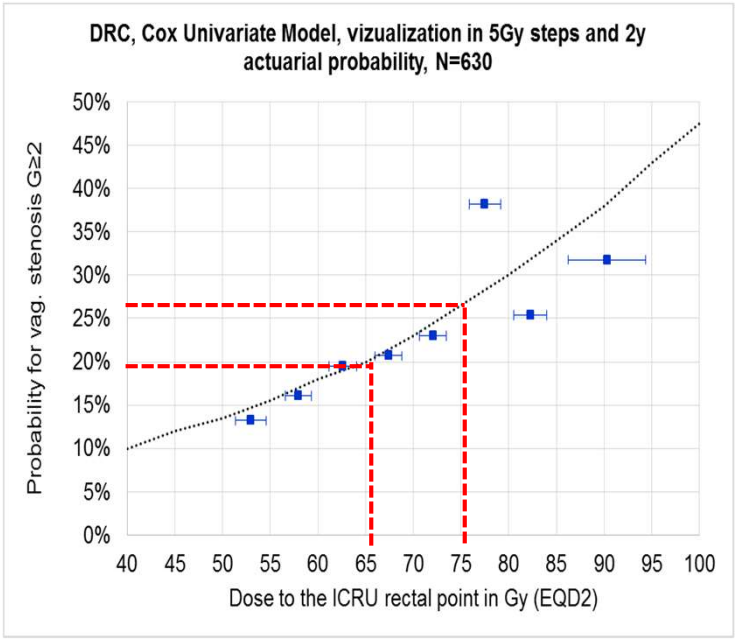
Vaginal stenosis
ICRU recto-vaginal point (630 pts)

- Significant impact of EBRT dose (45Gy versus 50Gy)
- Significant impact of BT ICRU recto-vaginal dose

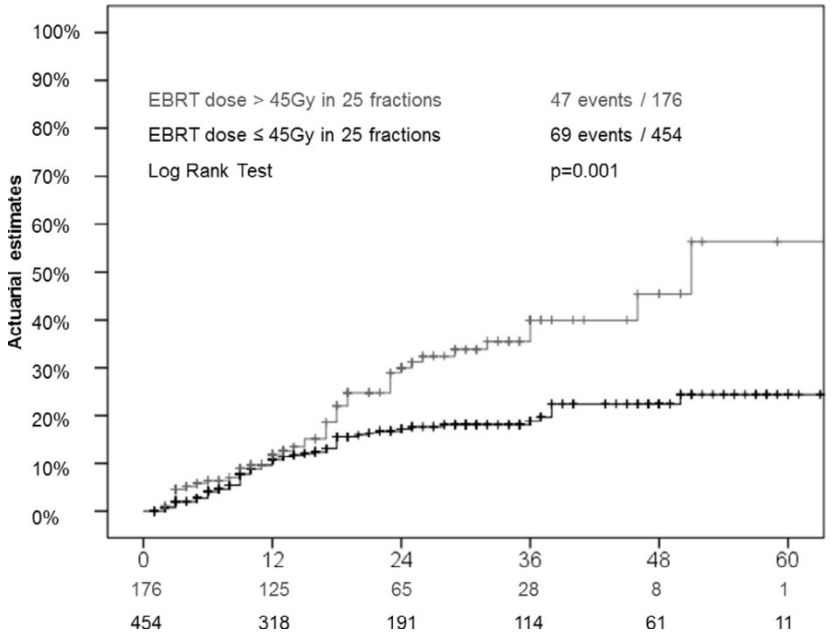
Prevalence vaginal stenosis



Kirchheiner K et al IJROBP 2014 May 1;89(1):88-95

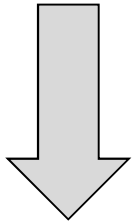


Kirchheiner K et al RO, 118 (2016) 160–166



Towards best clinical RT practice

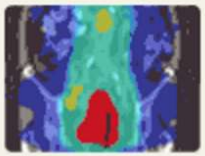
- **Understanding clinical outcome**
  - What is the magnitude? Vaginal stenosis prevalence is 20% of pts
  - What are the risk factors? EBRT and BT dose



- **Improving RT practice**
  - Can we change practice? 45Gy EBRT and BT dose de-escalation
  - Interventional trial? EMBRACE II + validation

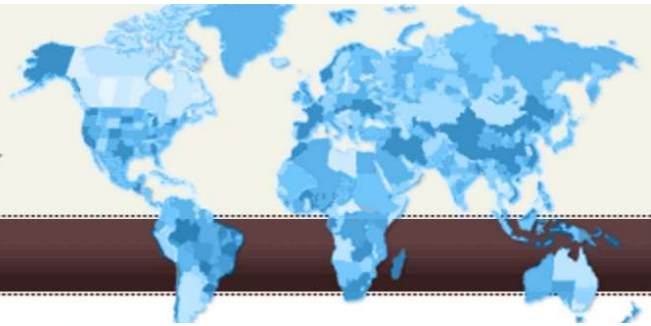
EMBRACE II interventions

- Increased use of IC/IS technique in BT
- Reduction of vaginal source loading
- Systematic utilisation of IMRT
- Utilisation of daily IGRT (set-up according to bony structures)
- EBRT target concept related to the primary tumour; concepts for OAR contouring
- EBRT dose prescription and reporting
- Adaptation of EBRT nodal elective CTV according to risk of nodal and systemic recurrence
- Systematic application of simultaneous chemotherapy
- Reduction of overall treatment time



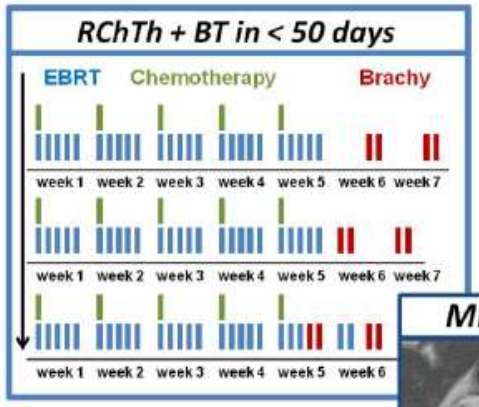
EMBRACE-II

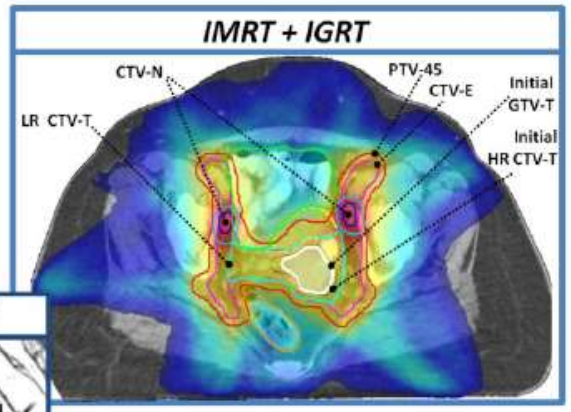
{ Image guided intensity modulated External beam radiochemotherapy and
MRI based adaptive BRAchytherapy in locally advanced CErvical cancer }

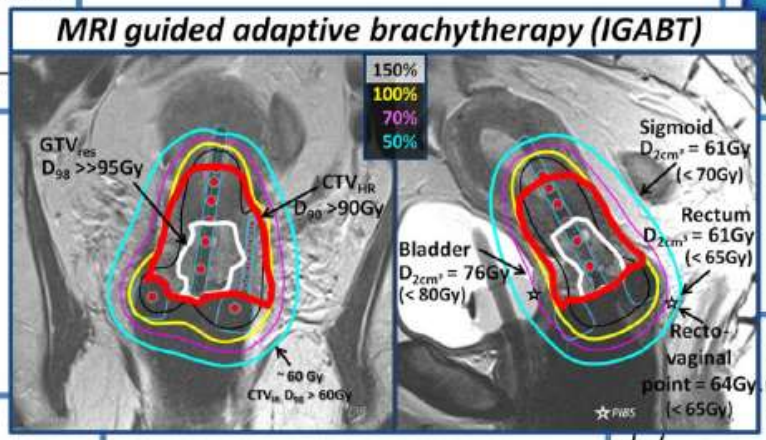


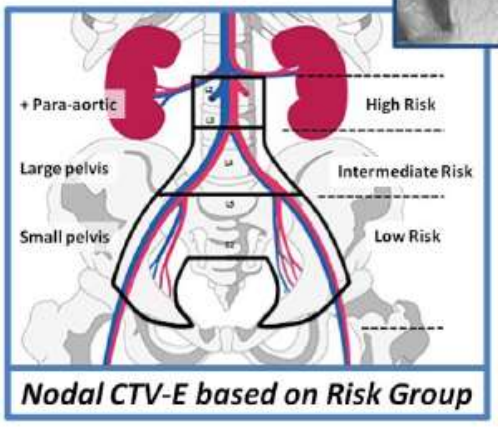
About Embrace | Contacts | Participation | Data entry | Tools | Members info | Admin | Logout

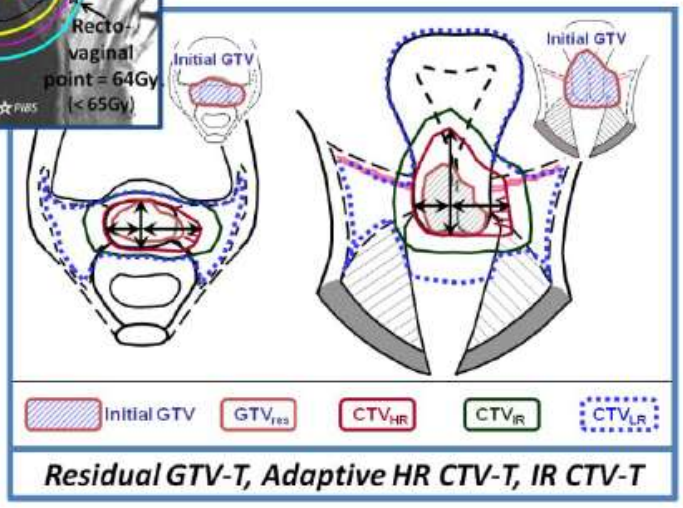
Accrual since March 2016











These are my favourites...

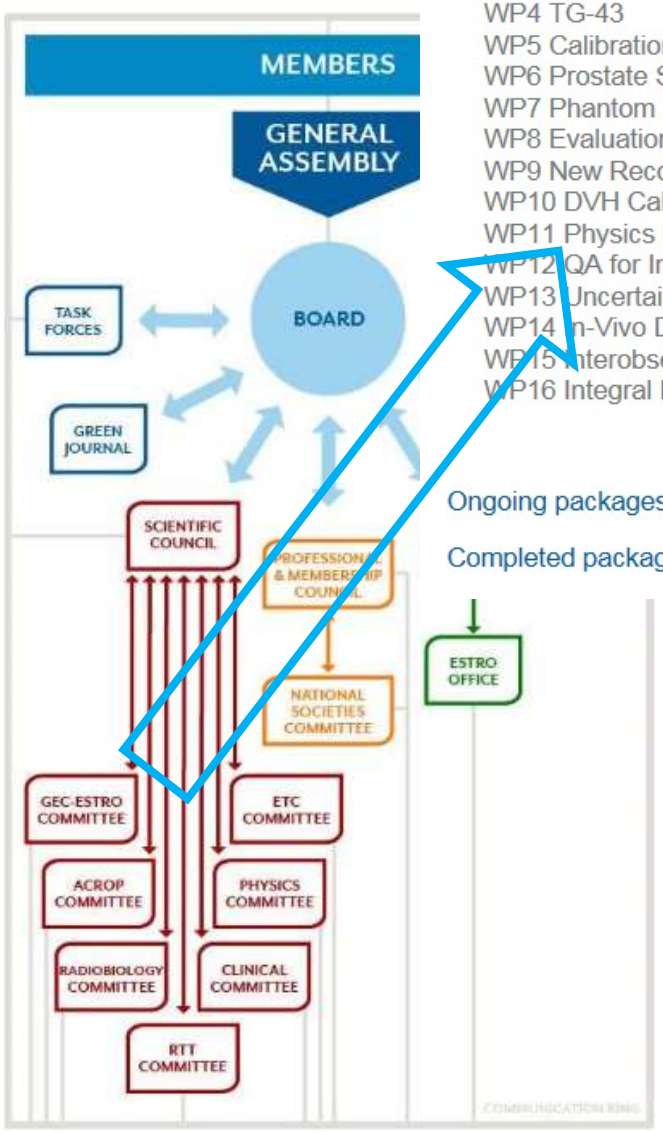
- Dosimetry
- Dose calculation
- Imaging and target definition
- Treatment technology
  - Applicators/implantation
  - Sources/Afterloaders
- Treatment delivery verification
- Clinical outcome

ESTRO

WORKING PACKAGES

The activities of the BRAPHYSQS work group have been organised into the following 16 working packages:

WP1 Dose Delivery Audit
WP2 Geometric Reconstruction Audit
WP3 QA Recommendations
WP4 TG-43
WP5 Calibration Facility For 125I
WP6 Prostate Survey Practices
WP7 Phantom Studies for Physics Part
WP8 Evaluation of Clinical Part
WP9 New Recommendations
WP10 DVH Calculation Evaluation
WP11 Physics Data for Radiation Protection
WP12 QA for Implant Dosimetry in LDR and HDR
WP13 Uncertainties in Brachytherapy
WP14 In-Vivo Dosimetry
WP15 Interobserver Variability Study
WP16 Integral Doses in Brachytherapy



Ongoing packages

Completed packages

ONGOING PACKAGES

WP4 - TG43
The TG43 data of "conventional" brachytherapy sources -mainly 137Cs and 192Ir sources- are collected by the group at the University of Valencia. New sources or new source data can be added. Data are also included on low-energy photon emitting brachytherapy sources (125I, 103Pd) that comply with the prerequisites of AAPM TG-43. If consensus datatsets coud be obtained by the AAPM, these are incoluded on the estro web page. The contents are supervised by a BRAPHYQS expert team. A new entrance to the Braphyqs website data can be accessed.
The BRAPHYQS group has written a short introductory text to the TG-43 data site with explanation on use and background information. Research data -which means: non-validated sets of TG43 data- will stay available using the 2nd website still located at the University of Valencia: http://www.uv.es/braphyqs. Transfer of the data from the http://www.uv.es/braphyqs site to this site has been done.
José Pérez Calatayud, member of BRAPHYQS is chair of the AAPM Brachytherapy Subcommittee Working Group on High Energy Brachytherapy Dosimetry (HEBD-WG). In this position, he represents the ESTRO community, reflected in an ESTRO's co-sponsorship of the manuscripts under preparation in the WG (title of this manuscript: "Dosimetric prerequisites for routine clinical use of photon emitting brachytherapy sources with average energy higher than 50 keV"; by Zuofeng Li et al., Med Phys. Dec 2007; 34:37-40). Facundo Ballester, also member of BRAPHYQS occupies the position of vice chair in the HEBD-WG of the AAPM. It is hoped and expected that the work of the BRAPHYQS group will lead to a full consensus on the data of the Low-Energy Interstitial Brachytherapy Dosimetry (LIBD) subcommittee as well of the High Energy Brachytherapy Dosimetry (HEBD), with an internet presentation of such data using links from the ESTRO site to USA counterparts and vice versa.

WP5 - Calibration Facility for 125I
Calibration facilities for 125I and 103Pd sources with easy access for European institutes are lacking. Actually, in the world only NIST provides the user with a calibration facility and recently PTB Braunschweig (H.J. Selbach) has opened a WAFAC type 125I calibration facility. The purpose of the taskgroup is to further stimulate European primary and secondary standard labs in co-operation within EUROMET to develop such standards for these low-energy sources. Following a previous contact with PTB by Alex Rijnders, Jack Venselaar and Tony Aalbers (NMI NL), a small mini-symposium in parallel to the ESTRO 25 meeting in Leipzig (Oct 2006) was organized. Invitations were sent to representatives of different EU and USA labs and ABS (on behalf of BRAPHYQS, Jack Venselaar, Alex Rijnders, Heikki Toelli, Taran Paulsen Hellebust and José Pérez-Calatayud). The meeting was successful and it was agreed that there is a need for cooperation between labs and "customers". Several ideas were discussed and will be brought to the attention of the board of EURAMET. The EURAMET project T2.J06 is a project of European standard laboratories with the goal to establish dose-to-water calibration in brachytherapy. BRAPHYQS is cooperating with the EURAMET T2.J03 project group, offering the expertise of BRAPHYQS to this project. As chair of BRAPHYQS F.-A. Siebert is invited to the EURAMET meetings.

WP9 - New recommendations
The survey on implant techniques (see at 6 & 8) will lead to a re-evaluation of existing recommendations on the procedures: dose prescription, margins, quality tools, etcetera. The recommendations may include seed implantation and HDR implantation techniques. Carl Salembier reported the first ideas during the GEC-ESTRO meeting in Budapest, May 2005. A manuscript is submitted for a publication in Radiothera & Oncol (title: "Tumour and Target Volumes in Permanent Prostate Brachytherapy; a supplement to the GEC/ESTRO/EAU recommendations on prostate brachytherapy", Carl Salembier et al). Radiother & Oncol 2007; 83:3-10). This is part of the Probate group (Carl Salembier, Peter Hoskin et al).

WP12 - QA for Implant Dosimetry in LDR and HDR

WP13 - Uncertainties in Brachytherapy

WP14 - In-Vivo Dosimetry

WP16 - Integral Doses in Brachytherapy
The goal of this work package is to give an overview of the integral doses in brachytherapy with the background of secondary cancer risk, and to bring the results in relation to other treatment options like photon, proton and heavy ion radiotherapy. Because this project is not only a physical task it is defined as a joint project between BRAPHYQS and PROBATE. Until now a literature overview was collected. Shortly Monte Carlo Calculations will be performed to evaluate the physical background in more details.

Thanks for listening

Good luck in choosing your hot research topics!

Trends and Research Opportunities in Light Ion Beam Therapy

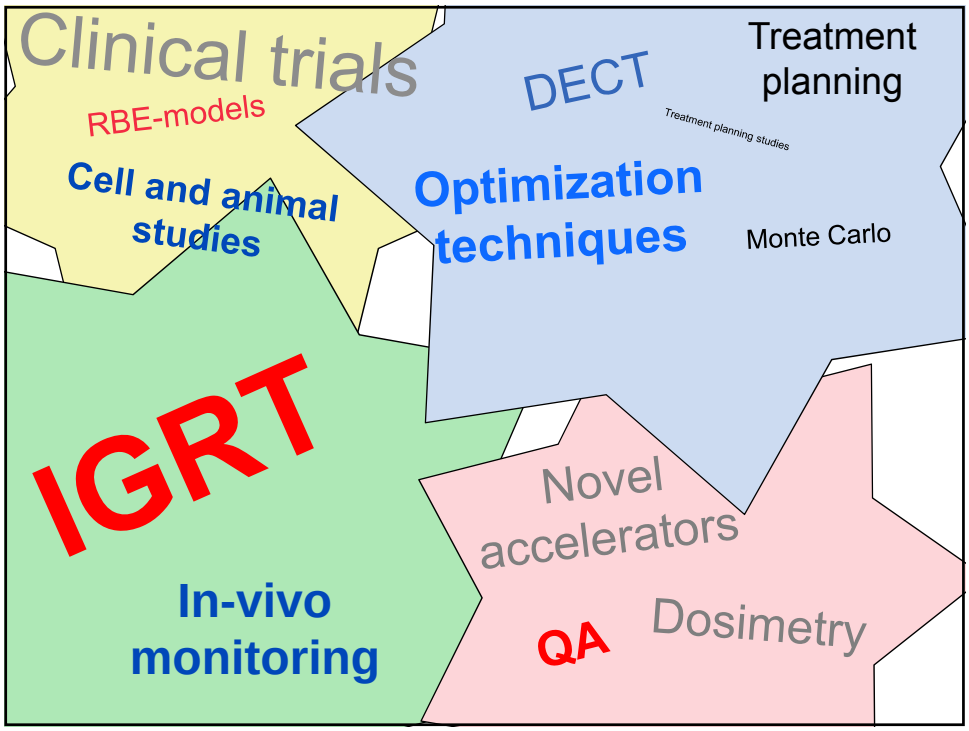
ESTRO Masterclass in Physics, Florence 2017

Oliver Jäkel

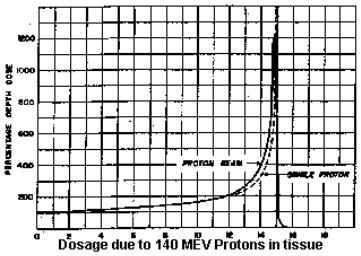
HIT Heidelberger Ionenstrahl-Therapiezentrum

dkfz. GERMAN CANCER RESEARCH CENTER IN THE HELMHOLTZ ASSOCIATION

50 Years – Research for A Life Without Cancer

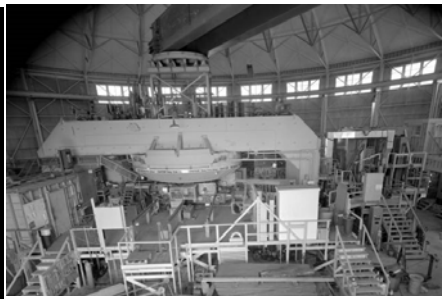


From the Bragg Peak to Radiotherapy



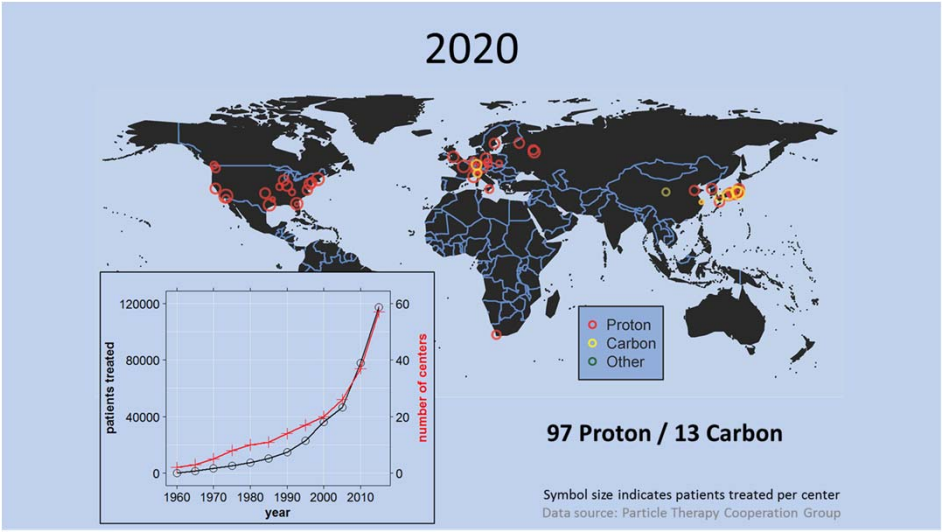
Robert Wilson

"Radiological use of fast protons," Radiology, 1946



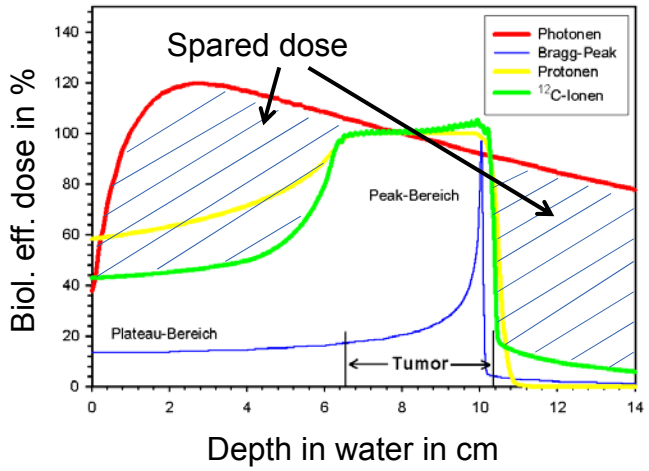
1955: 1. proton RT, 1957: 1. He-RT; 1977: 1. RT with Ne, N, O, C, Si, Ar

Exponential growth of proton RT
A proton bubble ?



Carbon ion facilities are a rare species

Clinical depth dose



- Ions show significant reduced integral dose
- Zero (Little) dose behind the tumor

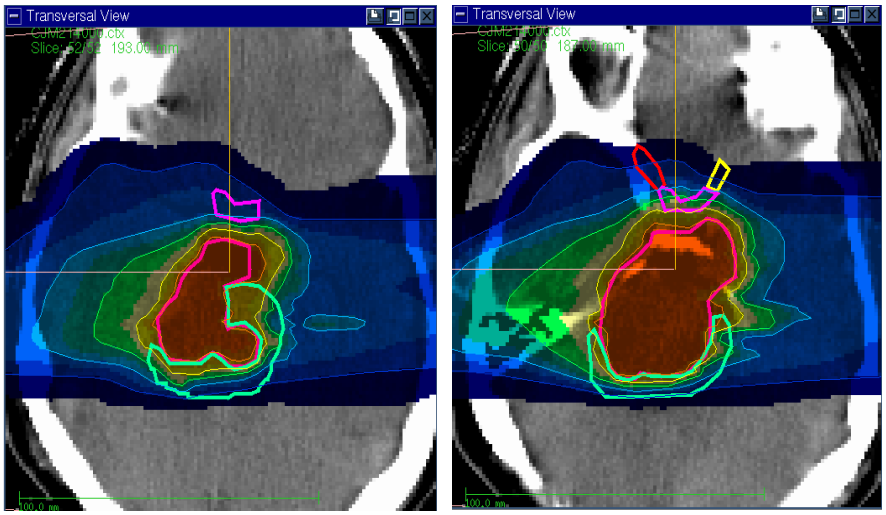
Beam delivery systems

▪Passive irradiation

▪Scanning irradiation

Still 50% of all rooms are equipped with passive systems

The dose conformation potential: Carbon ion RT of skull base chordomas



Excellent sparing of normal tissue and highly effective RT

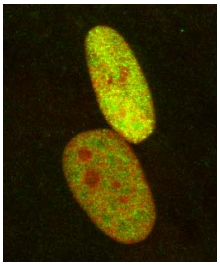
The meaning of high LET

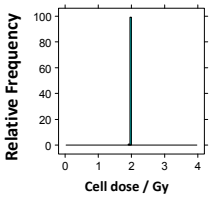
Max. energy of secondary electrons: $W_{\max} \cong 2m_e c^2 \left(\frac{\beta^2}{1-\beta^2} \right)$

Secondary electrons / deposition patterns

Photons

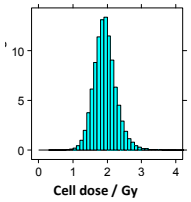
$\overline{E}_{e^-} \approx$ MeV





‚Sea of Electrons'

M. Scholz et al., Rad. Res., 2001



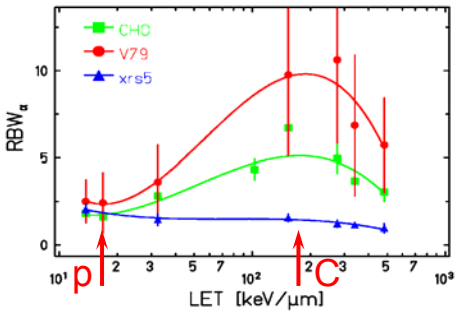
Ions

$\overline{E}_{e^-} \approx$ (k)eV

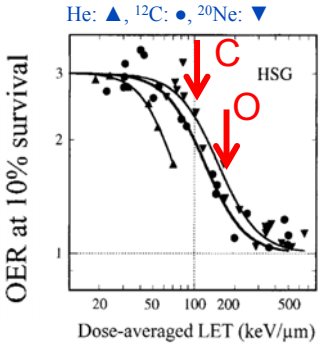
Micro-dosimetry

Rahmanian et al., PMB 62, 2017

Dependence of RBE and OER on LET



Weyrather Int. J. Rad. Biol. (1999),

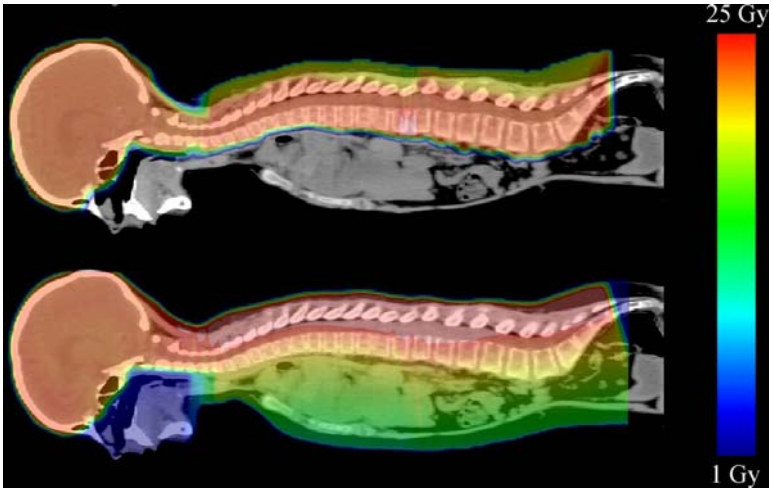


Furusawa Rad. Res. (2000)

- Increased RBE for high LET in resistant tumors.
- Improved outcome for high LET in hypoxic tumors.
- Benefit for Carbon as compared to protons

The clinical relevance of has not been shown yet.

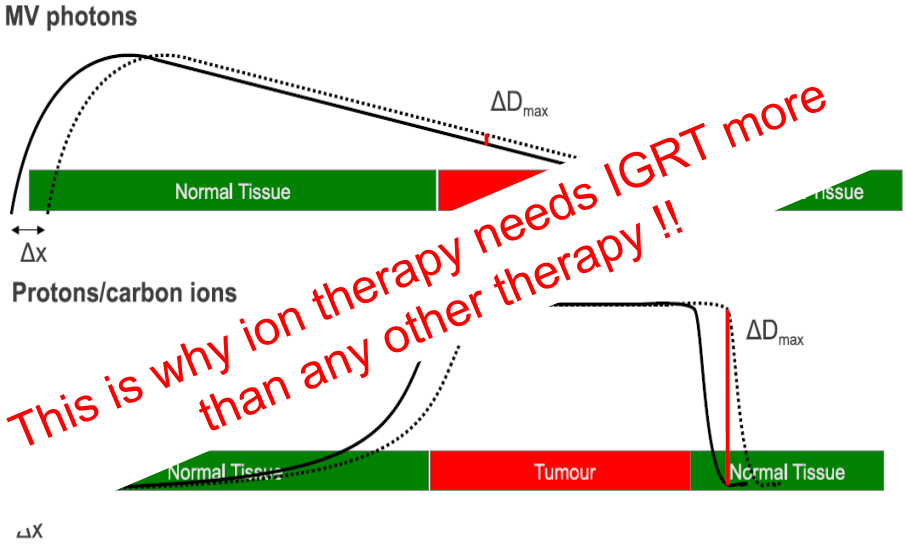
Proton RT for Medulloblastoma treatments



Stokkevåg et al. *Acta Oncol* **2014**

Finite range of protons reduces dose to dose reduction in heart, lung, intestine, mediastinum

Additional problem: Range uncertainty



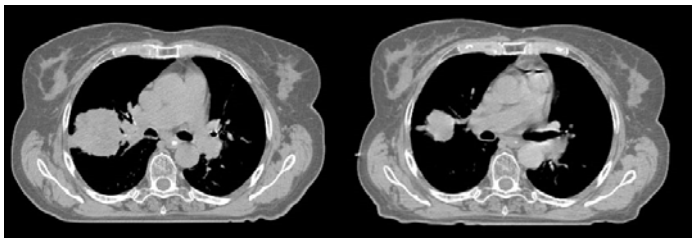
This is why ion therapy needs IGRT more than any other therapy !!

Small uncertainties in density may result in larger dose uncertainties as compared to MV photons

Lung Tumor shrinkage during p-therapy

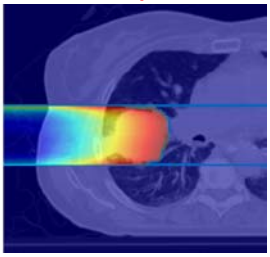
Initial Planning CT
GTV 115 cc

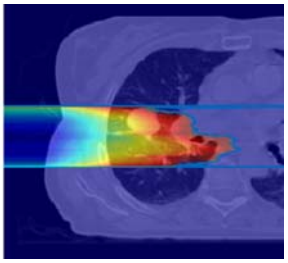
5 weeks later
GTV 39 cc



Beam stops at distal edge

Beam overshoot

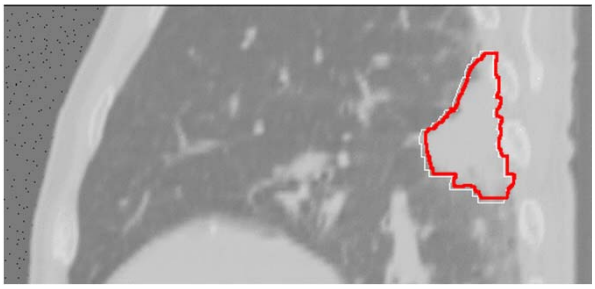




Courtesy of S. Mori, G. Chen, MGH, Boston

Need for replanning and adaption during course of RT

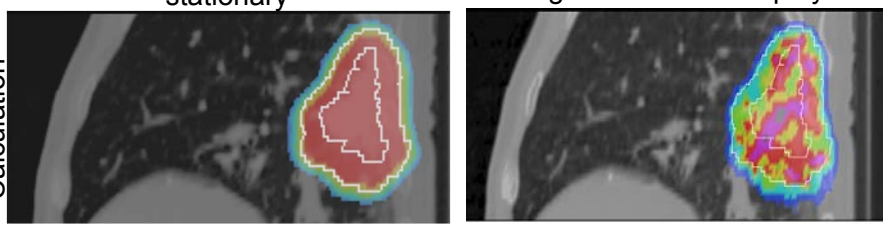
Organ motion in scanned beams



stationary

organ motion→interplay

Calculation



Rietzel and Bert, GSI, 2006/2007

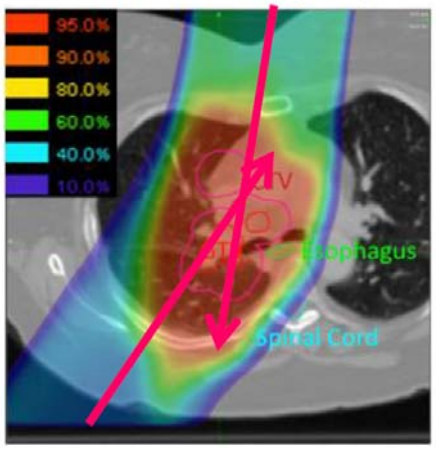
Scanning will generally not lead to a homogeneous dose for moving organs

Thomas Bortfeld

Example: Lung

Breathing and range uncertainties

State of the art (2016)



Much work is put in the development of motion mitigation and in-vivo monitoring (prompt gamma, PET, etc.)

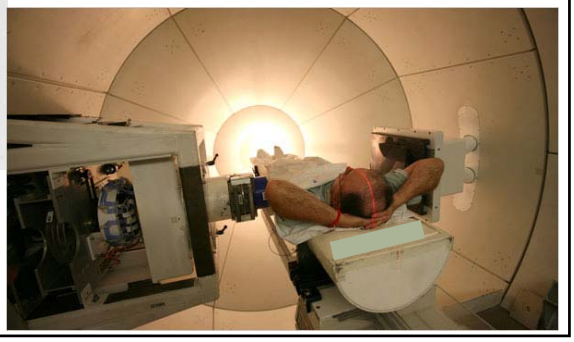
We are not making use of the full potential of particle therapy.

MASSACHUSETTS GENERAL HOSPITAL
RADIATION ONCOLOGY

Image guidance in light ion RT

Light ion RT has always been IGRT

Michael Goitein using orthogonal x-rays to position a patient at the Harvard Cyclotron facility in Boston in the 1970's



Unfortunately, 40 years later, we're still doing it more or less the same way

Motion mitigation techniques

New Delivery techniques:

- Gating
- Fast rescanning
- Tracking, Gated retracking, …
- Simulated scattering
- Very fast delivery

Gantry 2 at PSI

4D Treatment Planning strategies:

- Calculate accumulated dose
- Optimize treatment parameters
- Robust optimization

M. Bangert, PMB 2013

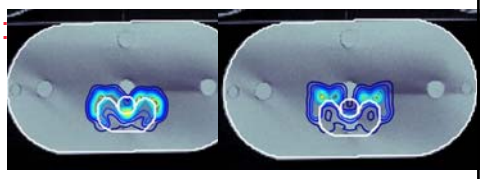
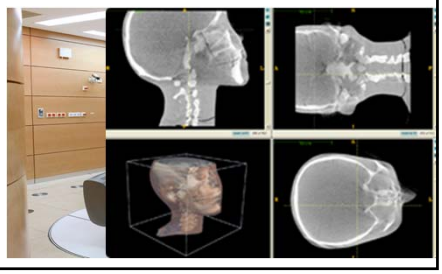


Image guided p-RT (lacking behind)

- Cone beam CT
- CT on rails
- Ultrasound guidance
- Optical systems
- MR guidance



Only recently manufacturers offer CBCT

Rationale for IGPT

- Particle therapy is lacking proper IGRT (mostly orth. X-rays)
  - **– this is not sufficient !**
- Only some recent facilities have X-ray CBCT
  - **– probably not sufficient ?**
- Proton RT is clearly indicated for pediatric patients
  - **– can we justify the additional imaging dose ?**

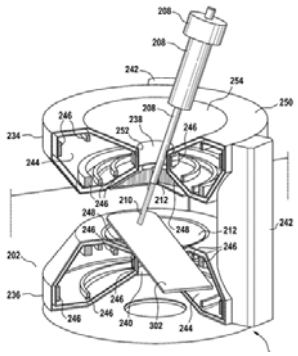


CT on rails at PSI, Dresden, Trento; Novel DECT system at MedAustron; Robotic C-arm at HIT

IGPT is more important than IGRT !

Why not go straight to MRgPT ?

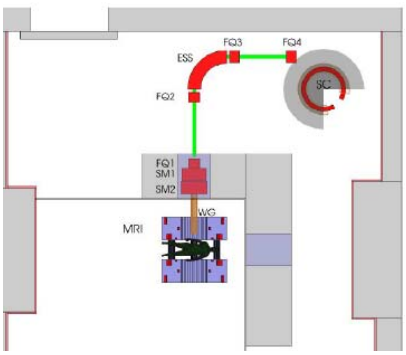
How about a real hybrid system?



Hybrid MRI proton system, patent by J. Overweg 20110230754, Philips, Germany, 2012.

Not very convincing…

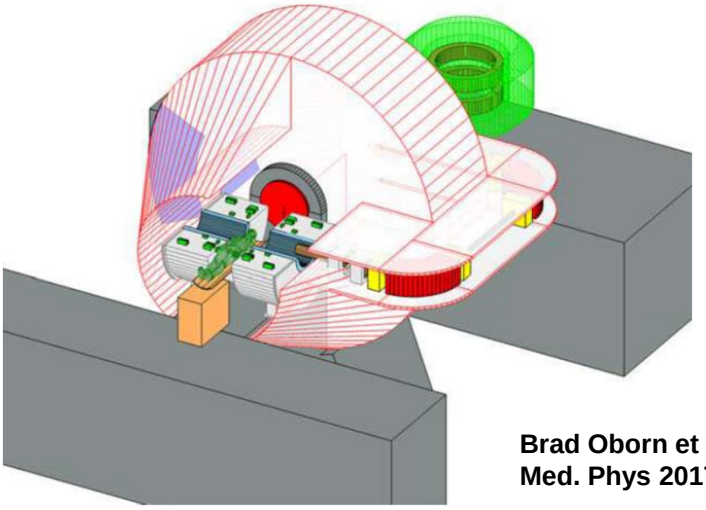
Bunker layout at Ingham Inst., Sydney



Including an MRI in a proton gantry is technically non-trivial

Current designs look at fixed beam-lines

Hybrid system: MRI in a rotating gantry



Brad Oborn et al.
Med. Phys 2017

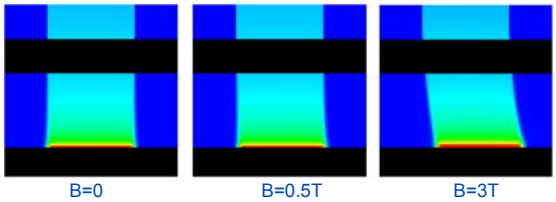
At least one vendor is seriously investigating this possibility

Dose calculation – deflection of primaries

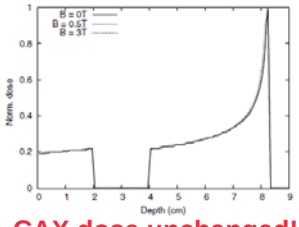
B Raaymakers et al., Phys. Med. Biol. 2008
Feasibility of MRI guided proton therapy: magnetic field dose effects,

90 MeV protons

Air

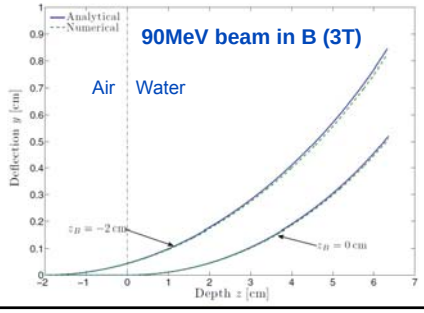


B=0 B=0.5T B=3T



CAX dose unchanged!

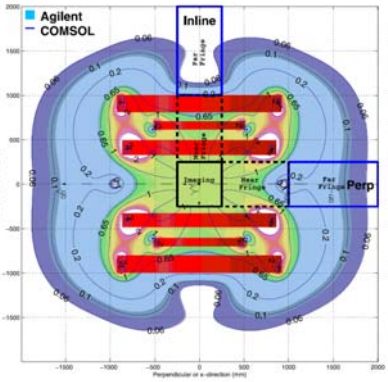
Wolf and Bortfeld, Phys. Med. Biol. 2012



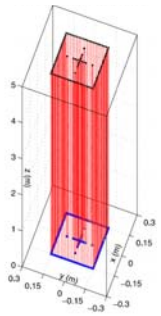
- Simple Monte Carlo and numerical studies of proton beam deflection
- Deflection is predictable
- Deflection is moderate, needs correction
- No electron return effect

Dose calculation incl. MR specific fringe fields

B Oborn, Med. Phys. 2015



p(90 MeV, B=0)



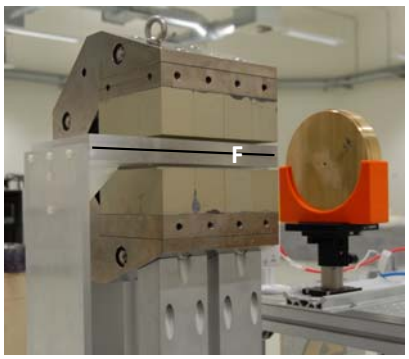
Beam scanning important to correct online for the effects!

To do: Simulation including scanning magnets

No optimization yet

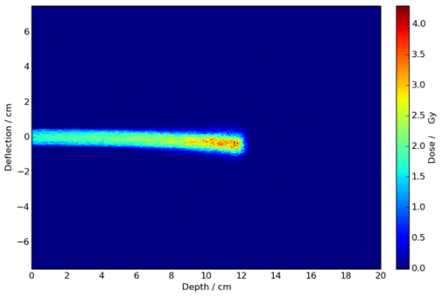
Fast beam trajectory prediction in heterogeneous media
Experimental proof-of-principle: First *„in magneto“* film dosimetry in slab phantom Hoffmann *et al.*, HZDR at OncoRay (Dresden)

Measurement setup



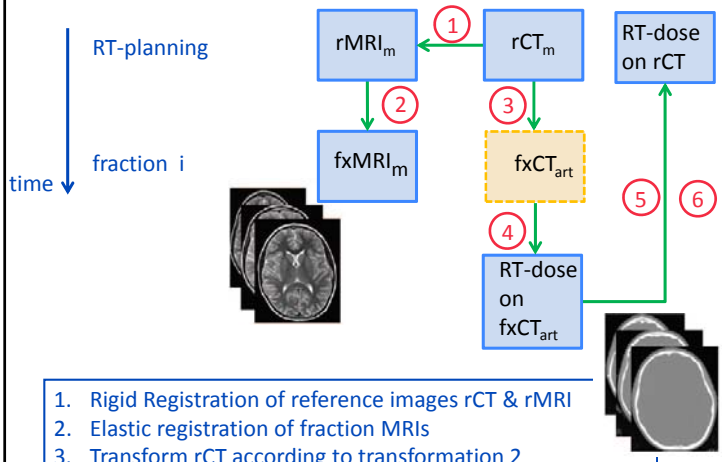
Y = yoke
M = permanent magnets (1 T)
F = film in PMMA slab phantom
C = collimator (∅5 mm)

Monte Carlo simulation



EBT3 film measurement

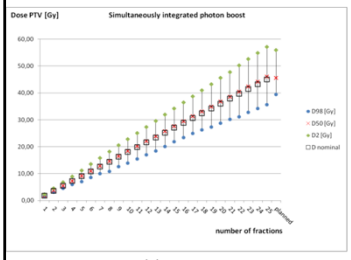
Pseudo CTs based on daily MRI and reference CT
Offline MR-gudidance



K. Kraus et al. Phys. Med. Biol. 2017

1. Rigid Registration of reference images rCT & rMRI
2. Elastic registration of fraction MRIs
3. Transform rCT according to transformation 2
4. Recalculate dose on artificial fraction CT fxCT$_{art}$
5. Transform dose back to reference rCT
6. Sum up fraction doses

Dose accumulation in the patient

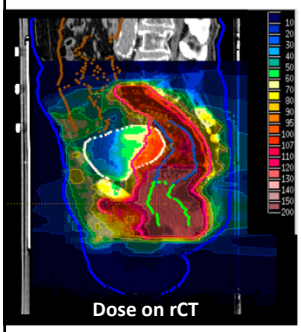


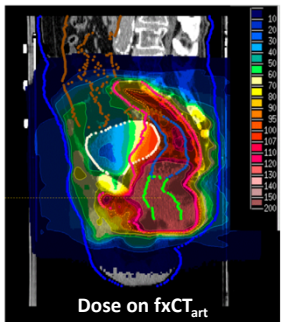
(a)

*

- Simultaeous integrated boost (SIB) IMRT
- Accumulation of Dose on fxCT$_{art}$ in 25 Fx

Small deviation from nominal total dose





Nominal (static) dose vs. accumulated fractions doses

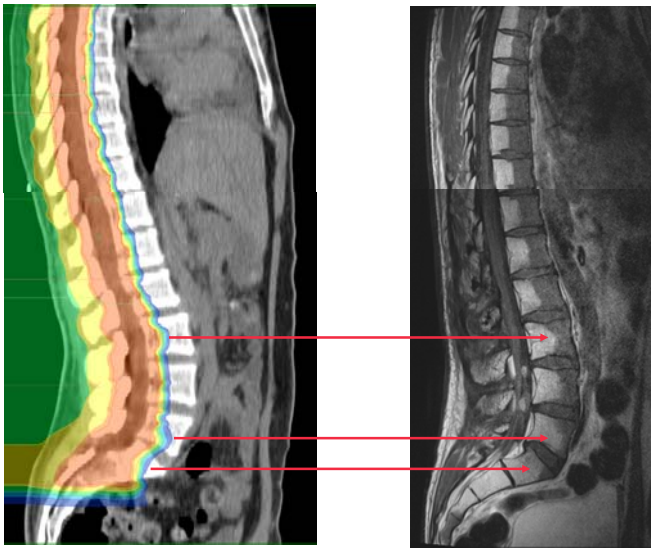
Deviations at the PTV border

K. Kraus et al. Phys. Med. Biol. 2017

Offline MRI would be a good starting point

Tissue changes in MRI post RT: Craniospinal pRT

Treatment planning CT and dose



T1-w MRI 6 months after pRT

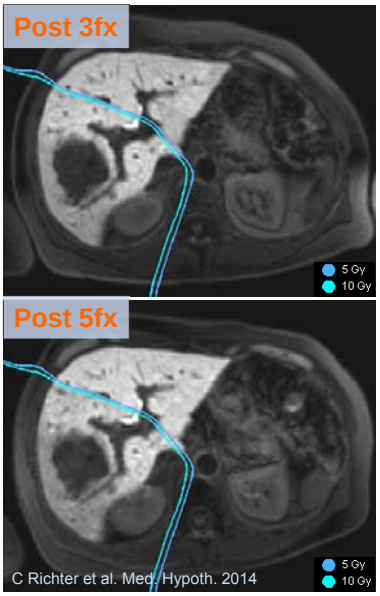
HIT patient

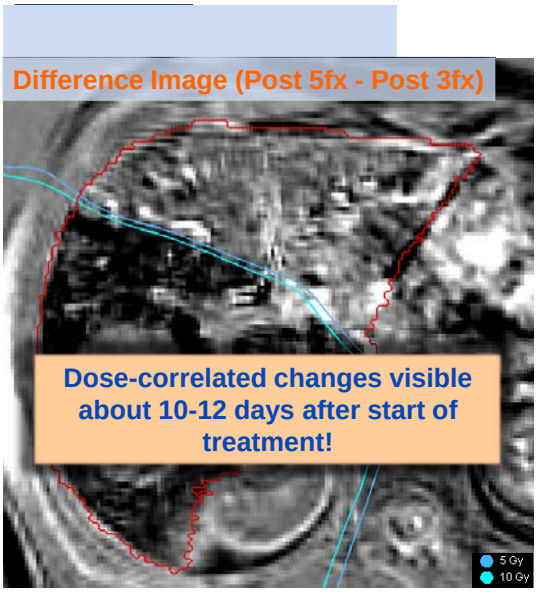
Changes in fat signal in irradiated part of vertebral bodies,

Distal dose fall off can be visualized – how early ??

Described already in Krejcarek, Yock, et al. IJROBP 2007;68(3):646-649

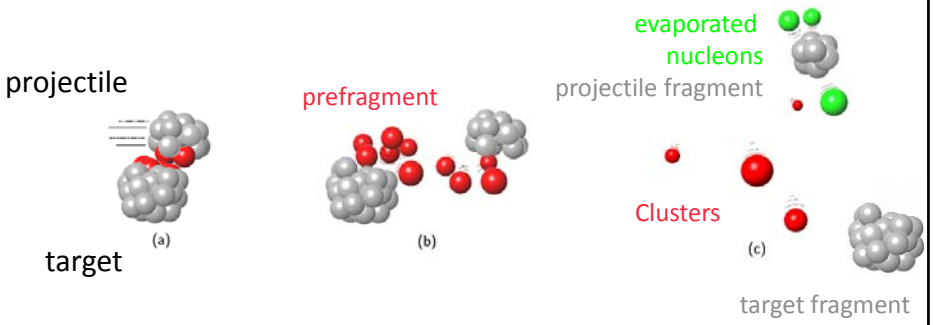
MRI for response assessment during p-RT?





Not in all patients though – to be investigated

Secondary radiation for in-vivo imaging of proton/ion beam RT

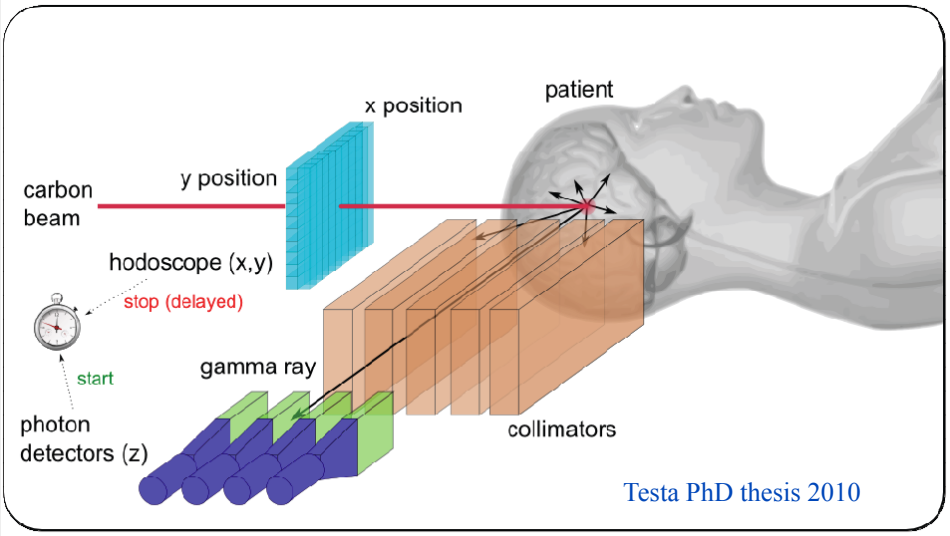


Radioactive nuclei: decay slow, half lives: s/h

De-excitation of nuclei: γ-emission, fast ~10^{-12}- 10^{-9}s

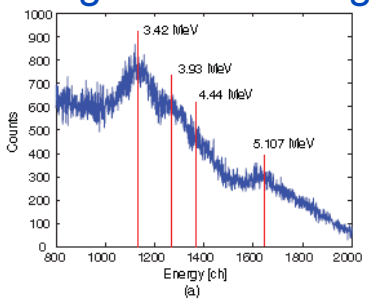
Evaporation of light ions: p, n, α, very fast ~10^{-12} s

Prompt γ-imaging principle



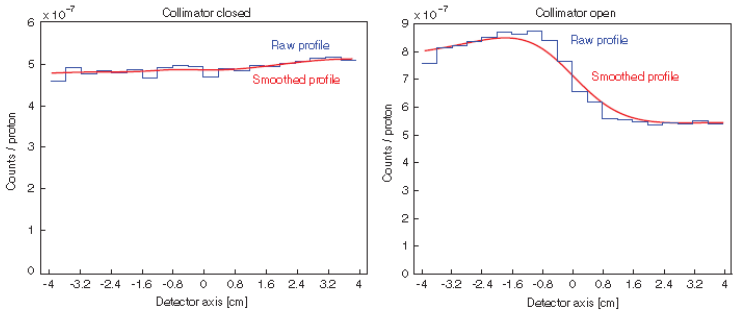
Collimators and attached scintillation counters for various depths:
Problem: low detection efficiency, no "tracking"
Alternatives: Compton camera (electronic collimation)

Signal and Background for 160 MeV protons



Spectrum measured for 100MeV protons w/o collimator – high energy!

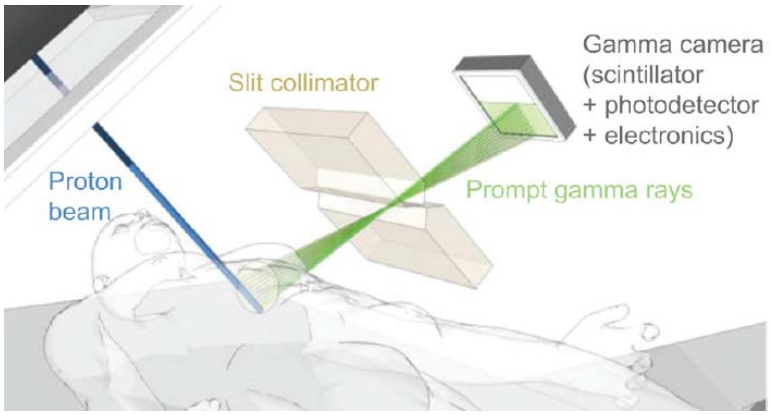
High count rates and large background (gammas and neutrons)



Signal and Background for 160 MeV protons

Fast electronics, smart signal processing needed

Prompt γ-emission: commercial design

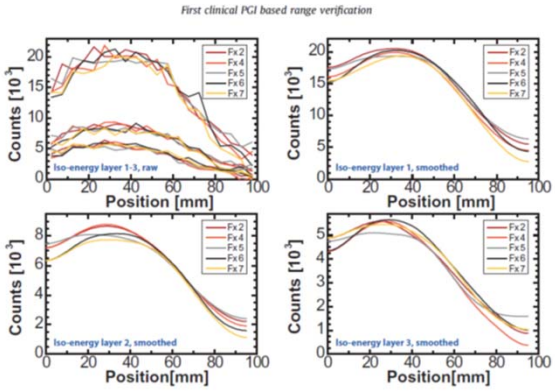


I. Perali et al, PMB 59, 2014

Slit camera (4cm tungsten) approach:
1D projection of prompt gammas along beam path on a segmented scintillator (no TOF)

First clinical application

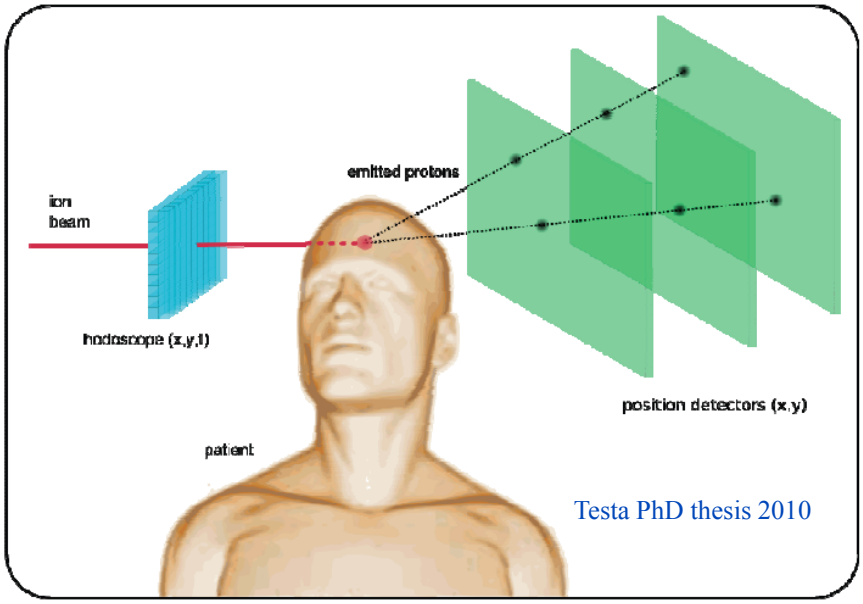
Richter et al., Radiother. Oncol. 2016



Potential improvements:

- **Improved collimator, segmented detectors**
- **Fast scintillators for TOF (sep. neutrons)**
- **Include spectral information (reduce background)**

Interaction vertex imaging (IVI)

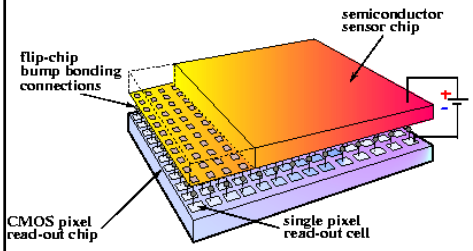


Testa PhD thesis 2010

Timepix (Medipix) as a tracking monitor

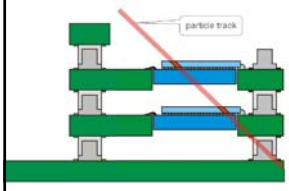
Semiconductor-based detector

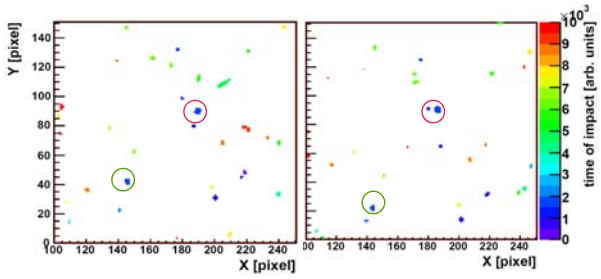
Work by M. Martisikova



- **particle position**
  area: 1.4 x 1.4 cm^2
  256 x 256 pixels
- **time of arrival**

1. detector layer 2. detector layer

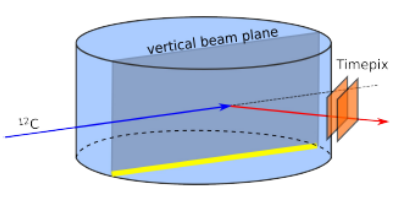


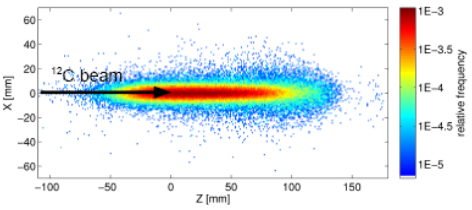


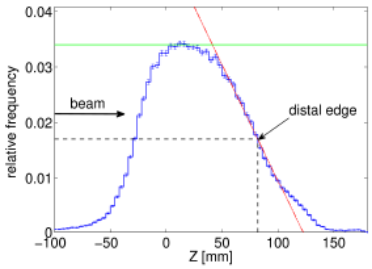
3D voxel detector based on Timepix, P. Soukup et al. 2011 JINST 6 C01060

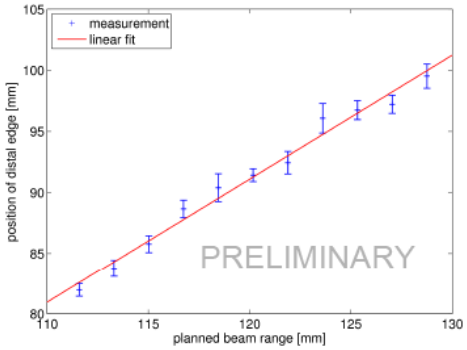
Tracking secondary charged particles with ~100% efficiency

Range determination using prompt protons









K. Gwosch, PMB 2013

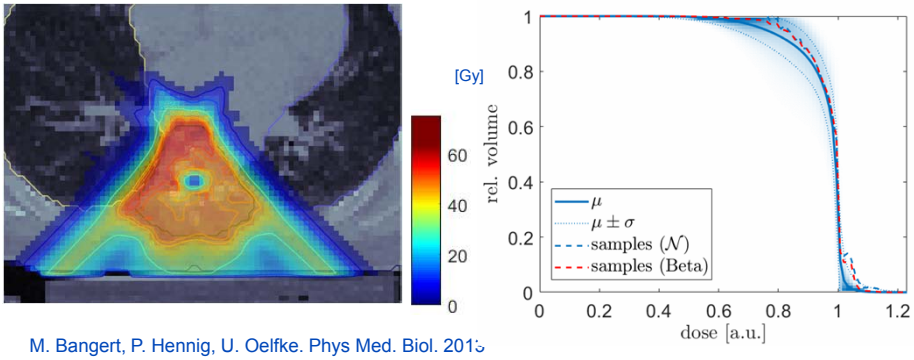
Range/position monitoring: ~1-2mm; Beam width: ~2mm

Larger detector needed for high res. images at low dose

Probabilistic p-TP for robust optimization

Analytical approach for uncertainty quantification and minization in particle therapy

Systematic errors: 3.5% Range, 1mm Setup
Random errors: 1mm range, 2mm Setup



M. Bangert, P. Hennig, U. Oelfke. Phys Med. Biol. 2013

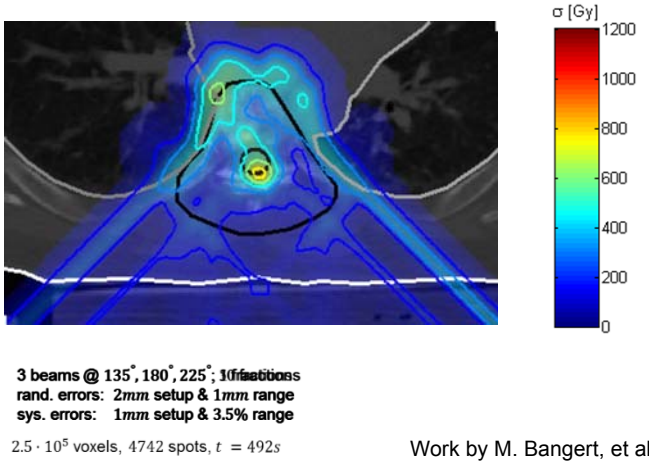
N. Wahl, et al. Phys. Med. Biol. 2017

Robust optimization allows for increased probability for coverage, smaller PTV, higher robustness

Probabilistic proton dose calculation accounting for fractionation

- Random and systematic uncertainties

30 fractions



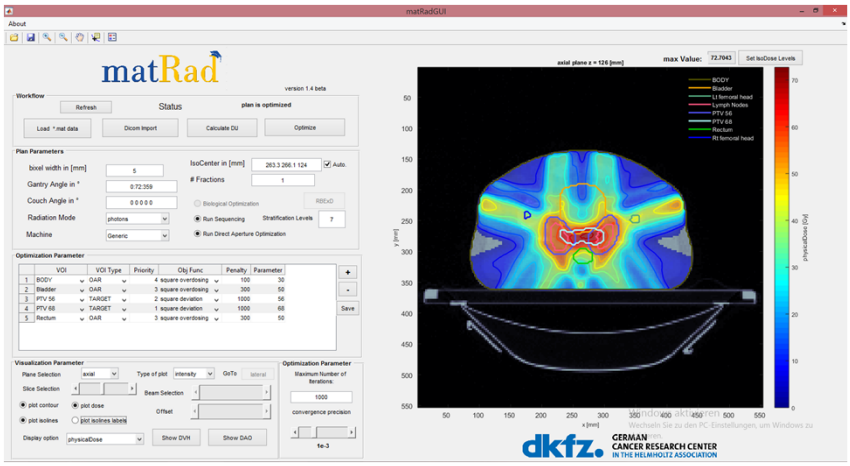
3 beams @ 135°, 180°, 225°; 10 fractions
rand. errors: 2mm setup & 1mm range
sys. errors: 1mm setup & 3.5% range

$2.5 \cdot 10^5$ voxels, 4742 spots, $t = 492s$

Work by M. Bangert, et al.

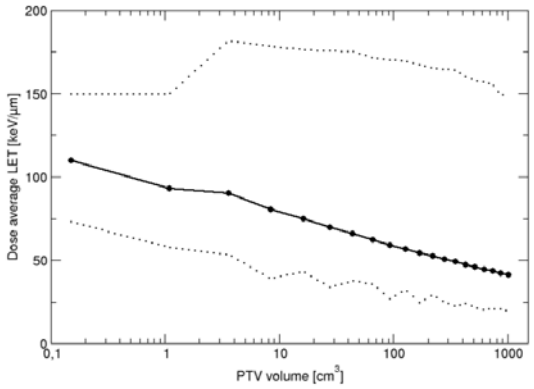
No yet implemented in any commercial TPS

matRad Open source toolkit for TP based on MATLAB



http://e0404.github.io/matRad/

The problem with high LET

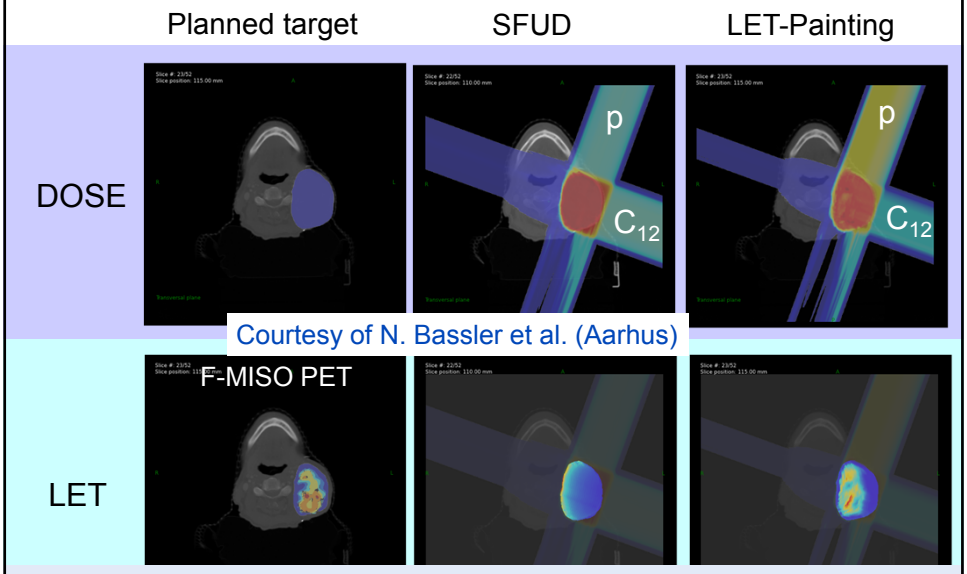


N. Bassler, O. Jäkel, et. al., Acta Oncologica 49 (2010), 1170

- The larger the PTV, the lower the average LET
- With SFUD, the highest LET is always at the distal end, i.e. in normal tissue

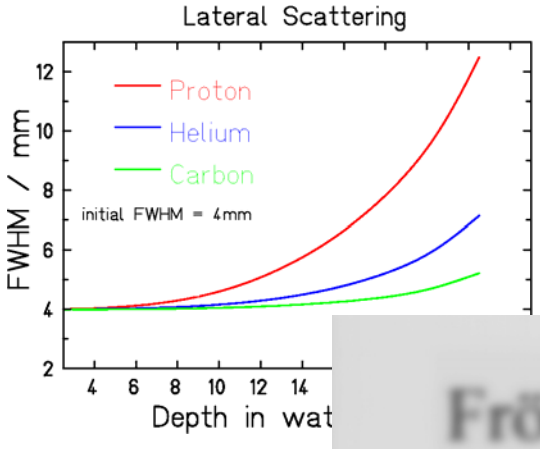
Optimize boost volumes for high LET
Use LET as additional degree of freedem

LET Painting for hypoxic tumors



Scanning and IMPT offers additional degrees of freedom for plan optimization (LET, beam width, scan path, …)

Outlook: Helium to replace protons ?

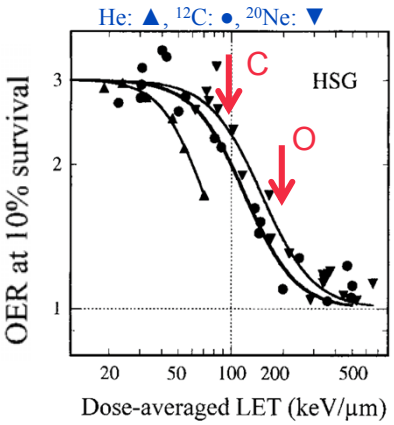


He may replace p's:
- reduced penumbra
- similar biology

He beams commissioned at HIT in Dec 2013

Heavier ions: Rationale for Oxygen

OER as function of LET



Furusawa et al Rad. Res. (2000)

Rasterscan @ HIT-R+D-Room

Oxygen maybe more effective esp. for hypoxic tumors