Future Perspective in (Medical) Physics for Particle Therapy…

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Institut Curie, Paris, France

Primer Workshop Español en Protonterapia
Madrid, 14 Diciembre 2016

Acknowledgments: J-C.Rosenwald,
P.Lambin (Maastro), D.Verellen,
T.Lomax, G.Olivera, D.Galmarini
And many others…
France-Hadron ANR Invesstissement d'avenir
Areva, Cancéropôle

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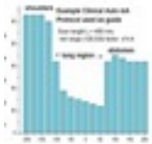
Medical Physics

The International Journal of Medical Physics Research and Practice

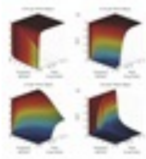
7th Nov 2013
Int Day Med Phys
Inst Curie:
Past-Present-Future

EDITOR'S PICKS

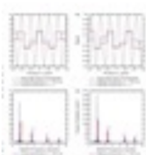
Imaging



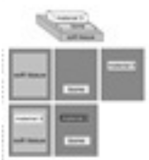
Dose equations for tube current modulation in CT scanning and the interpretation of the associated $CTDI_{vol}$



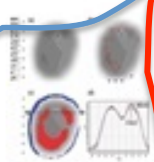
Oblique reconstructions in tomosynthesis. I. Linear systems theory



Oblique reconstructions in tomosynthesis. II. Super-resolution



Dimensionality and noise in energy selective x-ray imaging



Evaluating IMRT and VMAT dose accuracy: Practical examples of failure to detect systematic errors when applying a commonly used metric and action levels

MOST READ THIS M[ONTH]

Industry funded research

Increasing dependence on industry-funded research creates higher risk of biased reporting in medical physics

Vision 20/20: Single photon counting x-ray detectors in medical imaging

Charged particles

The more important heavy charged particle radiotherapy of the future is more likely to be with heavy ions rather than protons

MOST CITED THIS MONTH

Dosimetry of interstitial brachytherapy sources: Recommendations of the AAPM Radiation Therapy Committee Task Group No. 43

Dosimetry

BEAM: A Monte Carlo code to simulate radiotherapy treatment units

Dose Evaluations

A technique for the quantitative evaluation of dose distributions

Most read | Most cited | Latest articles | Featured articles | Review articles

July 2013

In the last 30 days

1. Optical properties of biological tissue

"Others"

2. CT : Modelling Iterative reconstruction
3. MRI analysis for brain tumor studies
4. MRI Tracer kinetic modelling
5. X-ray phase-contrast imaging

"Imaging"

6. Brachytherapy : Monte Carlo calculated doses for permanent implant in lung
7. Out-of-field dose in photon craniospinal irradiation
8. Dosimetry: when ^{60}Co is the reference quality for charged-particle and photon beams

"Dosimetry"

9. Automatic 3D ultrasound calibration in IGRT
10. Automated segmentation of pulmonary structures in CT

"Automatic tools"

Remember: "Dose evaluations " In MedPhys

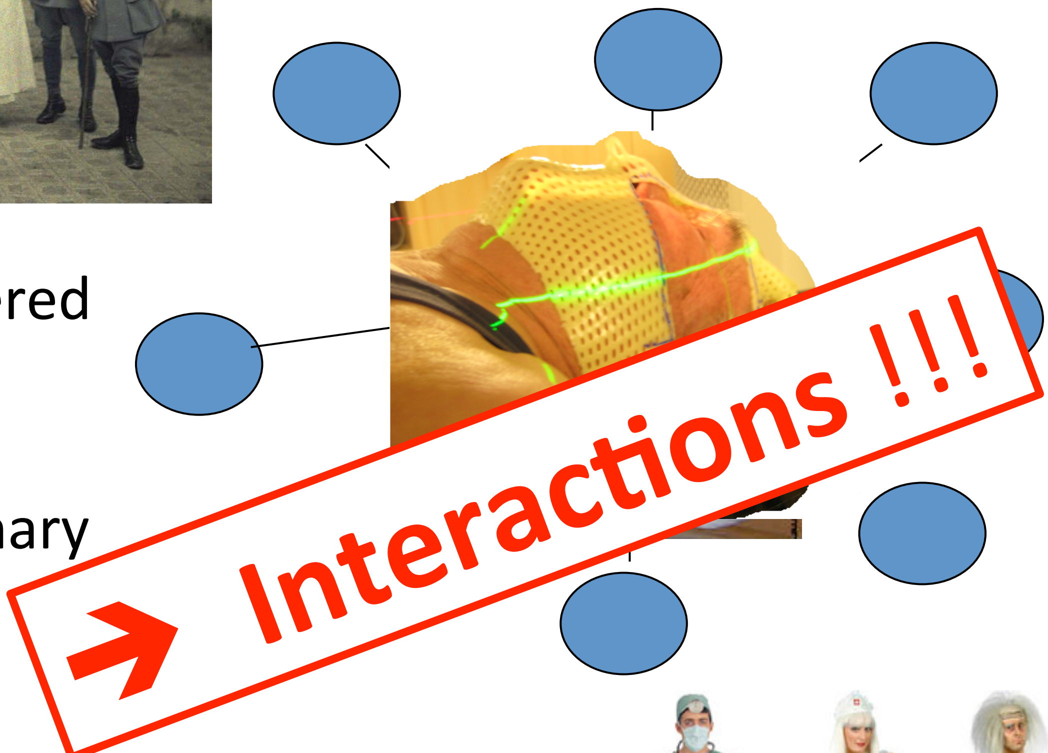
We could conclude on the importance of …

1. ***Applying efforts to imaging systems (pre-per-post treatment).***
2. ***Optimize dosimetry and models.***
3. ***Increasing role of low doses, fast evaluations and automatic tools.***
4. ***Keeping lessons from the past to the future : from cobalt through linacs, with particles getting a new place…***

… but this yet looks as a rather limited "vision"
and you are not coming to Madrid to conclude on this in 5 minutes !

Physics in medicine (ex in radiation therapy): through the history …

Patient centered
Multicentric
and …
Multidisciplinary



I Workshop Español en Protontherapia. Madrid, 14 de Diciembre 2016

Programa, Organizadores, Exponentes y Participantes :

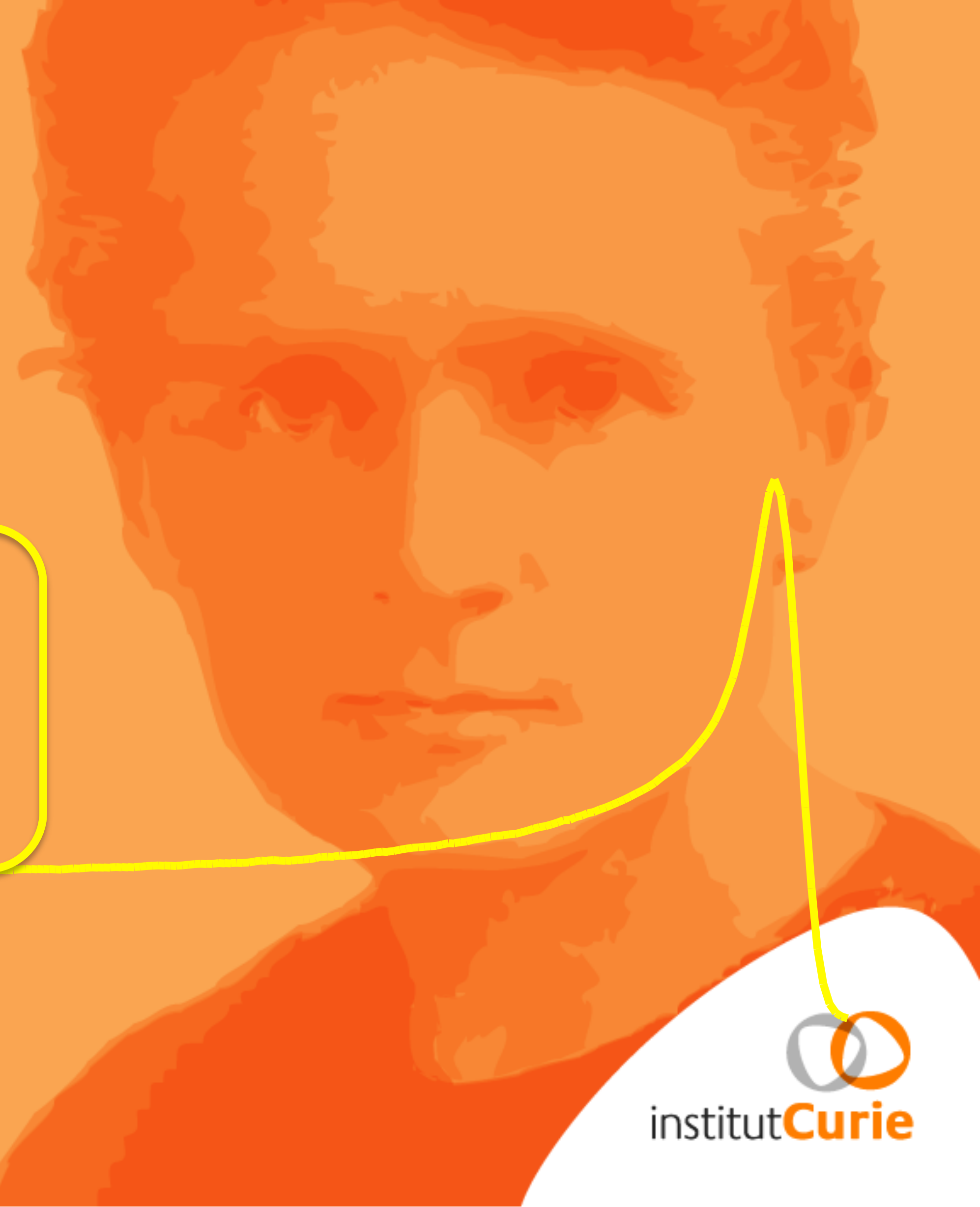
Y 200 participantes !!

→ Interactions !!!

Perspectivas futuras en Física (Médica) para la Terapia con Partículas :

“Relaciones”

Primer Workshop Español de Relaciones Humanas en Protonterapia



Future Perspective in (Medical) Physics for Particle Therapy : Interactions

Domain of interaction	Contents, Concepts and Tools	Conclusions	Key Words
1. System Technology			
2. Dosimetric issues and ancillary tools			
3. Clinical data			
4. Research and Development (biology + +)			

Menu del día (Relaciones)

Future Perspective in (Medical) Physics for Particle Therapy : Interactions

Domain of interaction	Contents, Concepts and Tools	Conclusions	Key Words
1. System Technology	# Compactness & New concepts # Heavier ions		
2. Dosimetric issues and ancillary tools			
3. Clinical data			
4. Research and Development			

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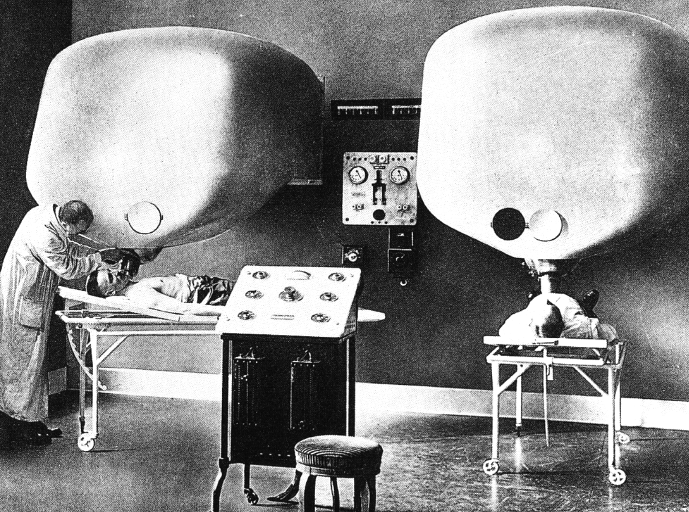
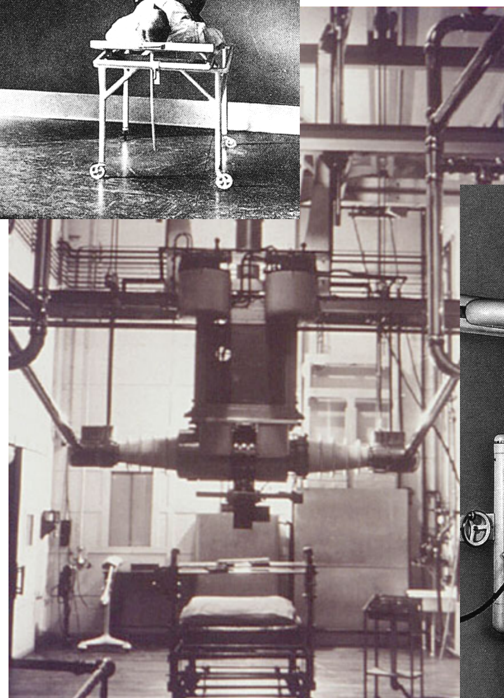
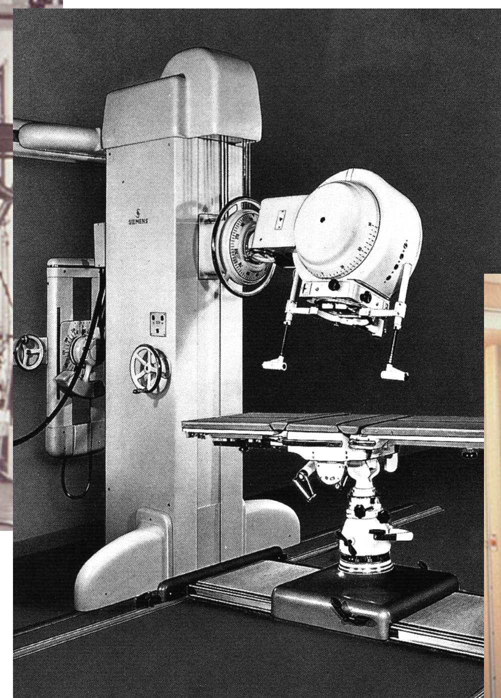
Technical evolution in external Radiation Therapy : 100 years of history



High voltage X-ray tubes Siemens 1919



600 kV circa ˜>1930…



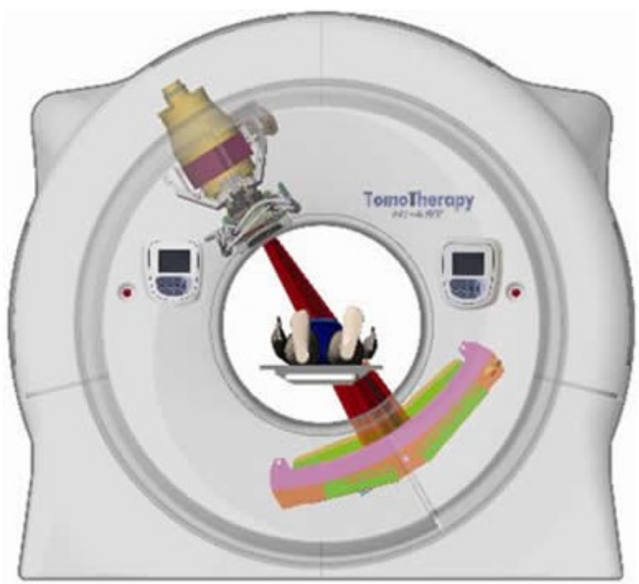
Gammatron Siemens 1956 Co-60 et Cs-137

1960 Linacs

Physics and technology: delivery systems in external radiation therapy with photons

RapidArc or equivalents (wphospitals.org)

www.cyberknife.com



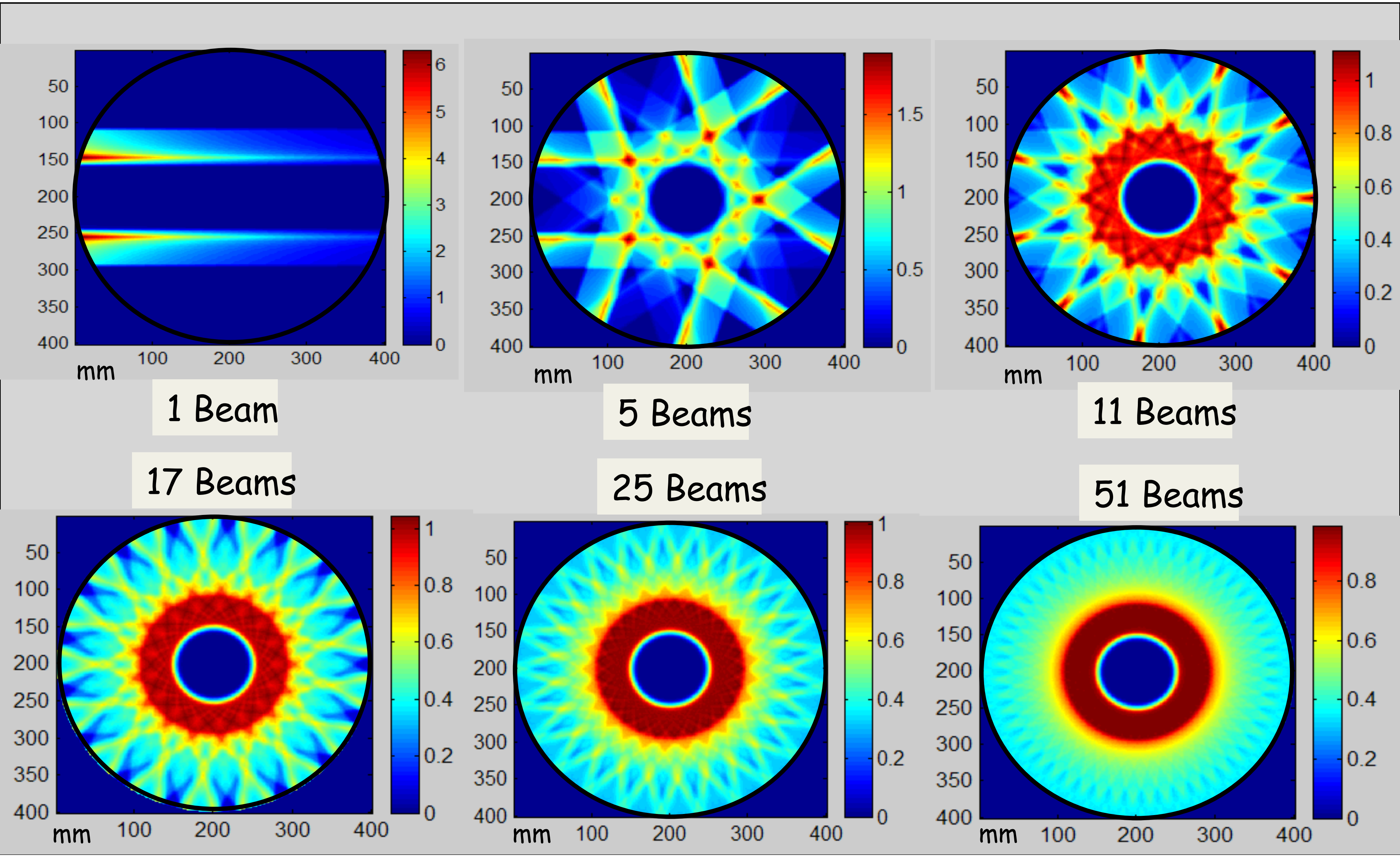
Tomotherapy

Vero

ViewRay (MRI+3Co-60 w/MLC

Linacs : → Juan Carlos

Multiplicity of incidences// changing the role of the energy

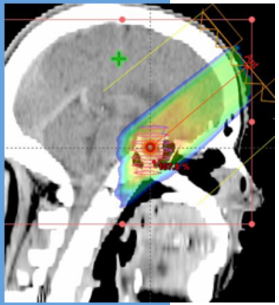


(from Tomotherapy)

Hadrontherapy : Physical selectivity and/or Radiobiological effects

* pions
* fast
& slow neutrons

(Past)

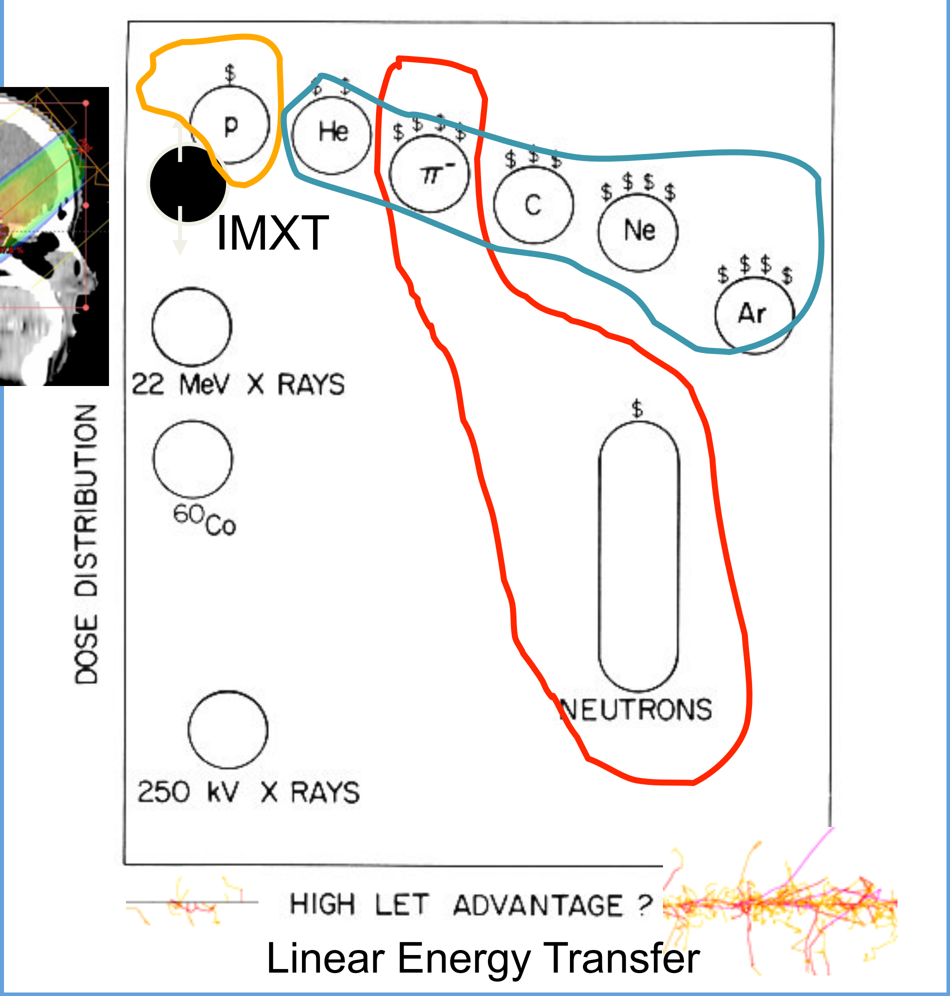


* protons

(Present)

* light and heavy ions

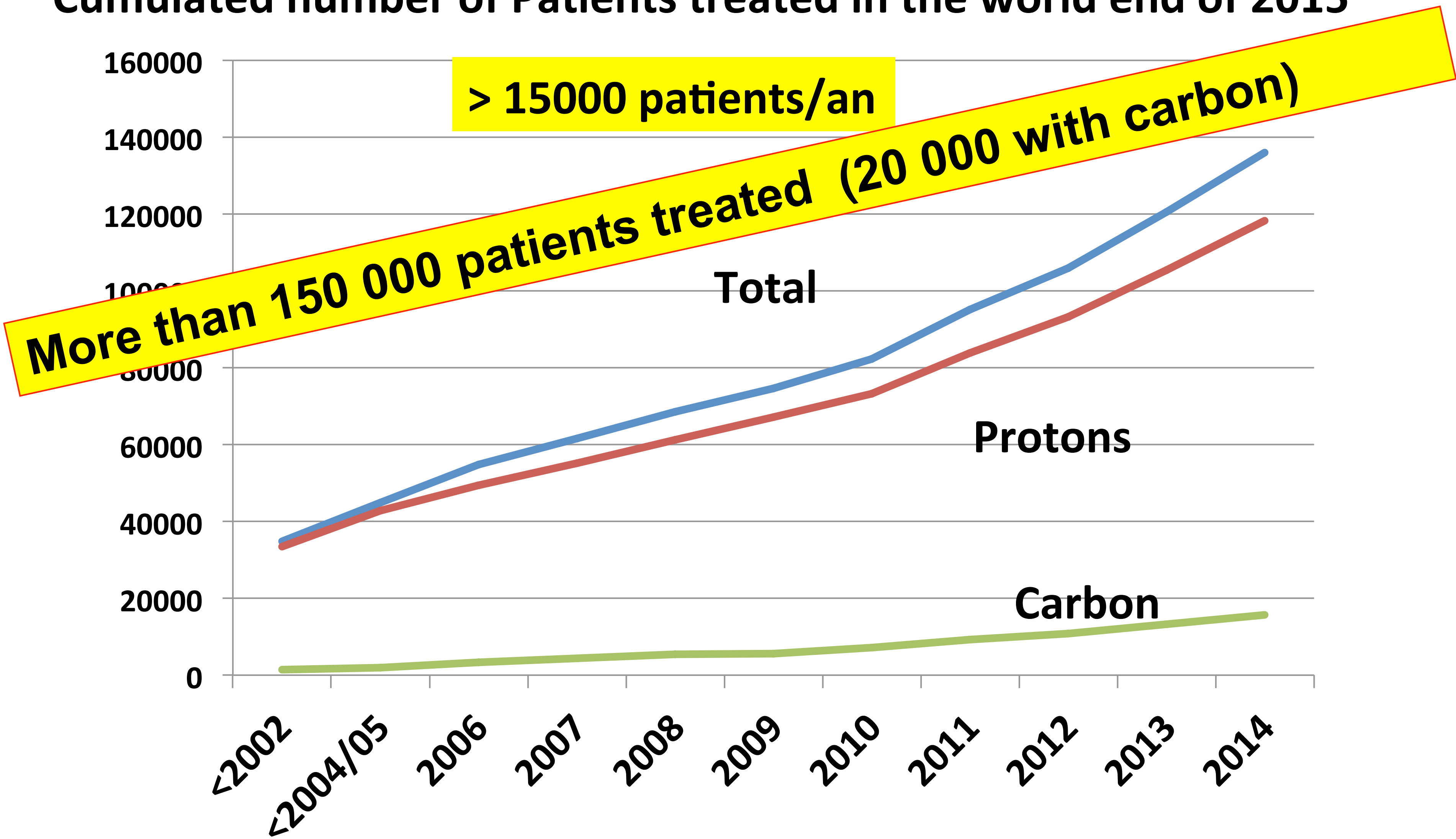
(Future ?)



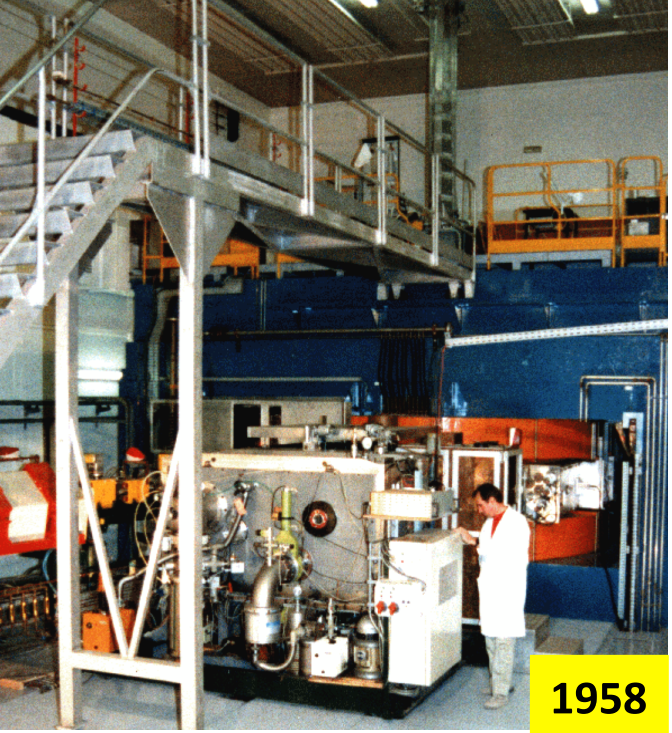
Raju & Koehler, 1980

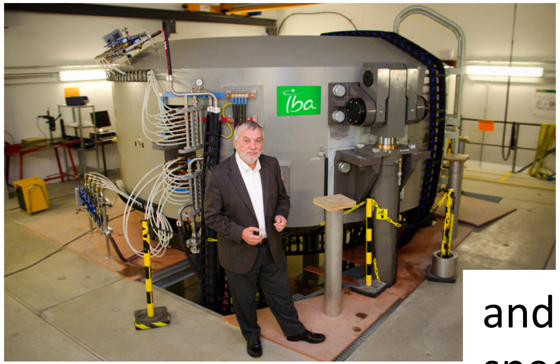
PTCOG/ M.Jermann, 2015

Cumulated number of Patients treated in the world end of 2015

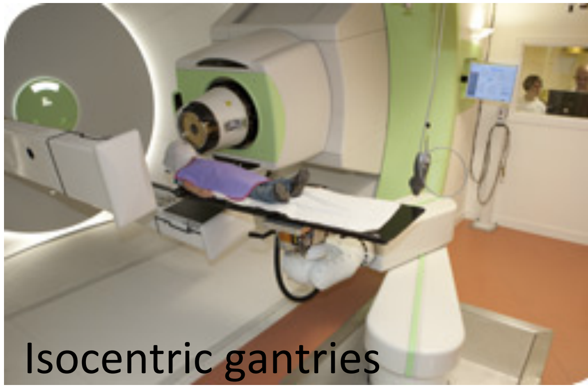


Technical evolution in hadron therapy

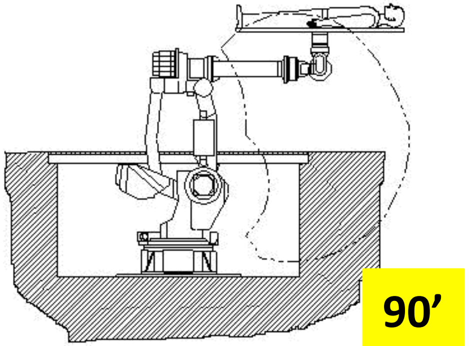




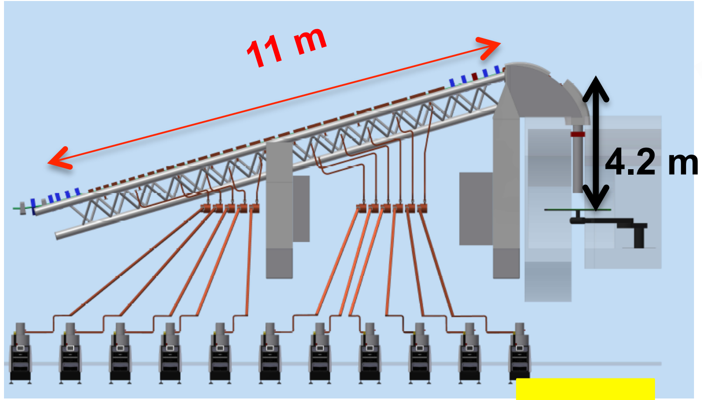
Towards compact, clinical (and cheaper?) systems



and specific tools

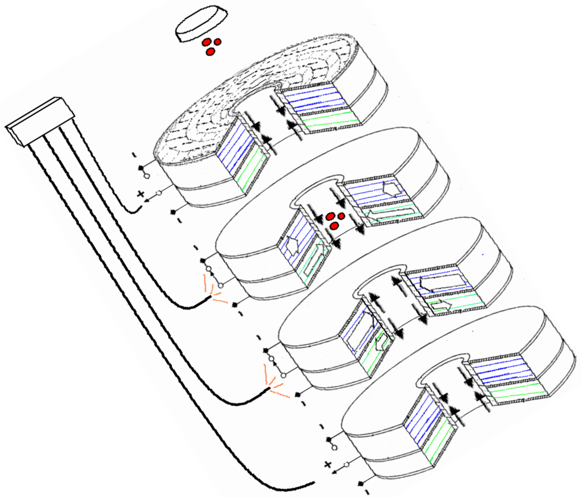


Robotics for patient positioning



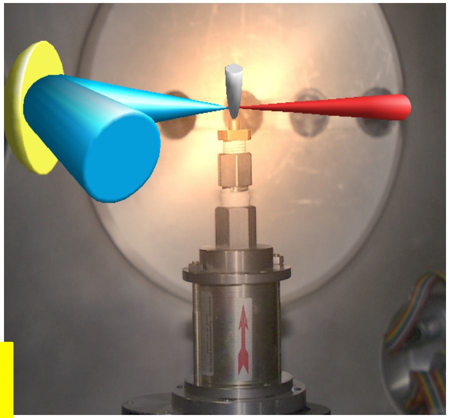
2016

Linac TULIP 30 MV/m



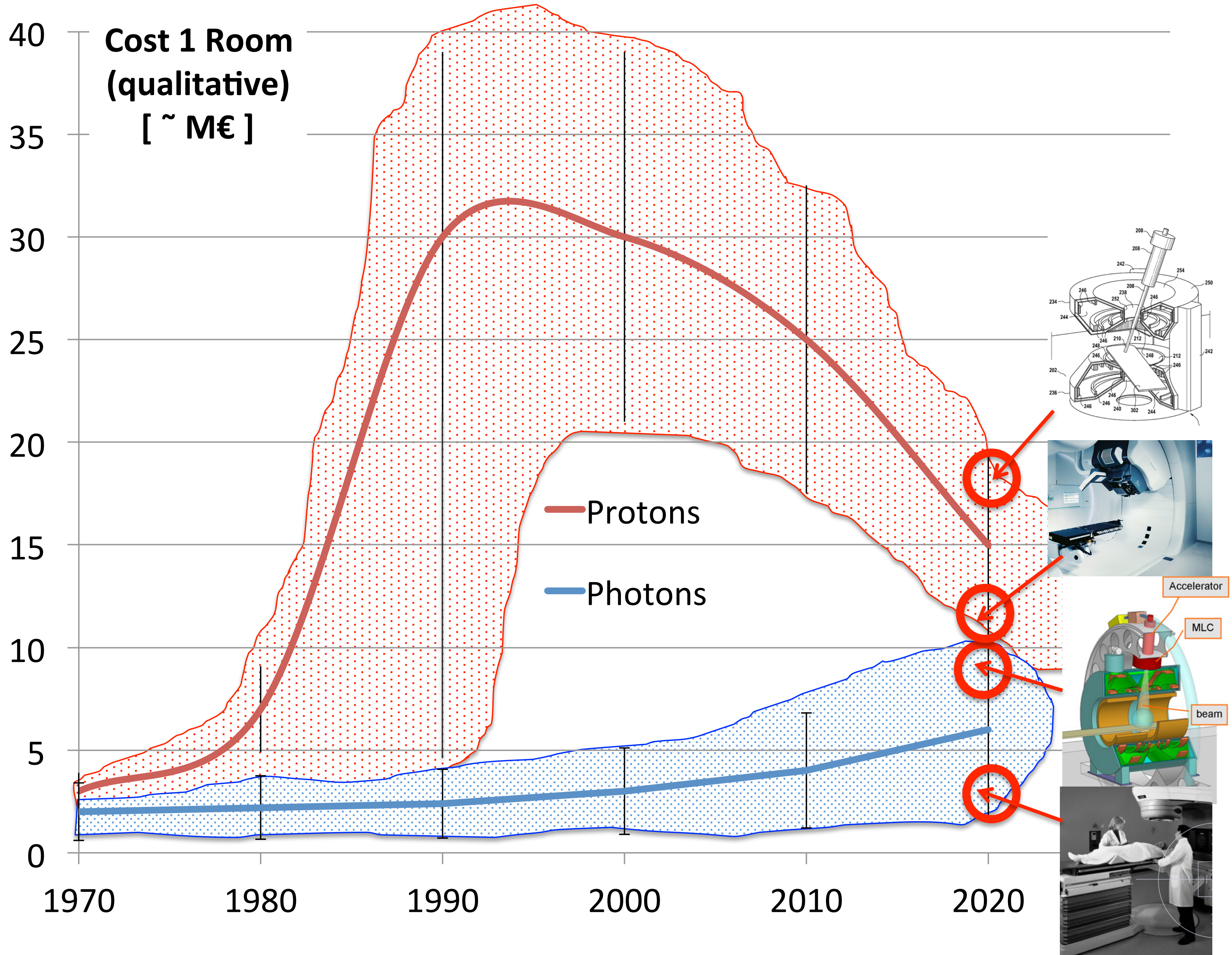
Dielectric wall accelerators

????



Laser based accelerators

Some alternatives to make it compact and cheaper



Cost 1 Room
(qualitative)
[˜ M€]
40
35
30
25
20
15
10
5
0
1970
1980
1990
2000
2010
2020
Protons
Photons
Accelerator
MLC
beam

GANTRIES

Gantry-mounted synchrotron (Phil Livdahl, 1985)

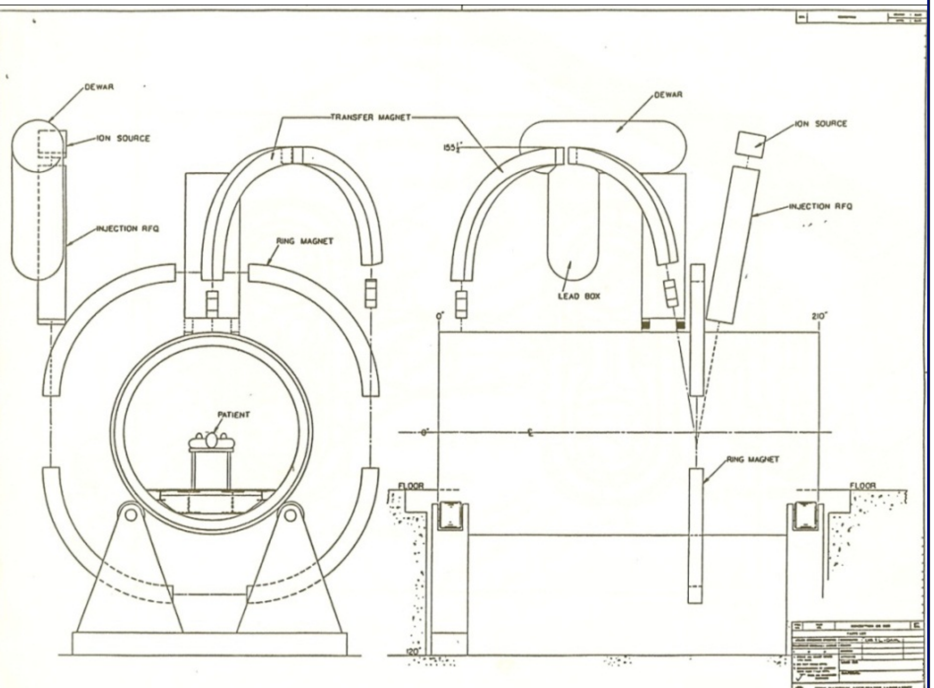


FIGURE 6

BEAM SCANNING

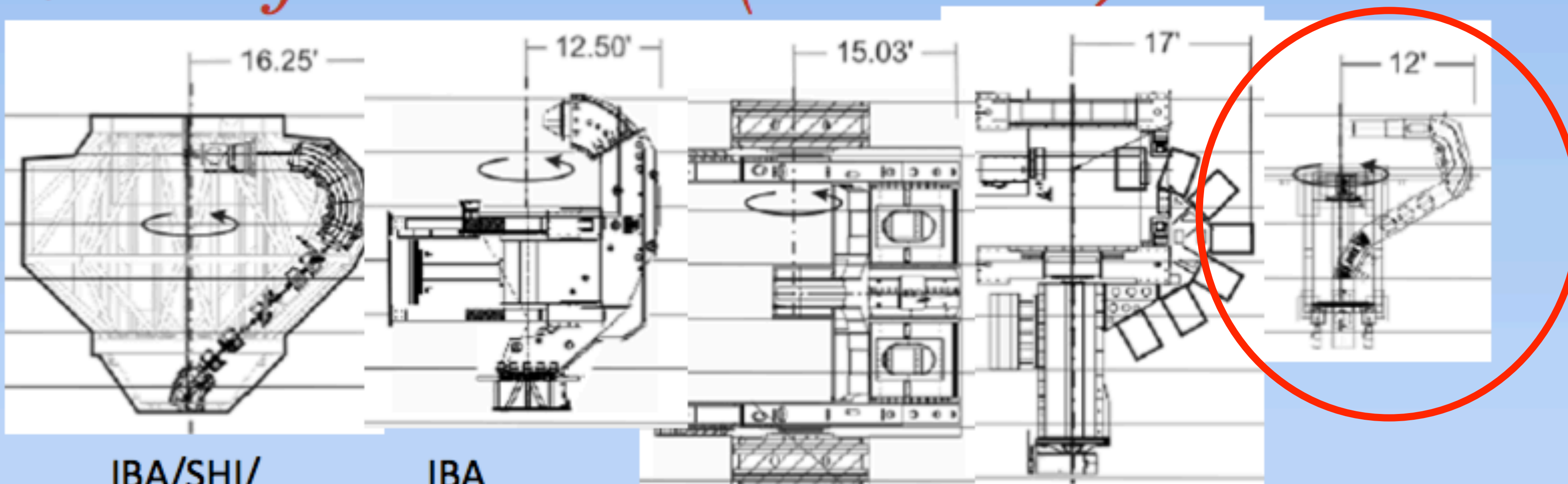
LBL, Berkeley workshop
January 19-22,1988

Preliminary Agenda for Workshop on Medical Charged-Particle Beam Scanning Systems

	Tuesday, Jan 19th	Wednesday, Jan 20th	Thursday, Jan 21st	Friday, Jan 22nd
8:30		**Plenary Session** • Charges to Working Groups - Group Leaders	**Plenary Session** • Reports, Agendae for the day - Group Leaders	**Plenary Session** • Reports, Agendae for the day - Group Leaders
≈9:30		**"Science"** 0. Basic Questions - Ludewigt / **"Engineering"** 1.1 Specifications - Renner; 1.2 Magnets - Milburn	**"Science"** 0. Basic Questions - Ludewigt; 4.0 Biology Considerations - Blakely / **"Engineering"** 1.3 Power Supplies - Nyman	**"Science"** 3.0 Treatment Planning - Petti / **"Engineering"** 2.0 Control Systems - Renner
12:00		**Lunch** Lower Cafeteria	**Lunch** Lower Cafeteria	**Lunch** Lower Cafeteria
1:00	**Registration**			
1:30		0. Basic Questions - Ludewigt / 1.2 Magnets - Milburn; 1.3 Power Supplies - Nyman	3.0 Treatment Planning - Petti / 2.0 Control Systems - Renner	
2:00	**Opening Session** • Welcome, Goals of Workshop, Organizational details - Chu • Overview of Beam Delivery Systems - Alonso • Perspectives on specific delivery options - Open • General discussions on goals, topics for working groups - Open			**Summary Session**
≈5:00	*5:00 Social Hour* *SuperHILAC*	*6:00 Dinner* *Mandarin Garden*	*8:00 Reception* *Mark Nyman's House (Sponsored by Brobeck Corp.)*	

B. Chu, PTCOG

$ize of In-Plane (& other) Gantries



IBA/SHI/
Hitachi
In-Plane

IBA
Proteus
One

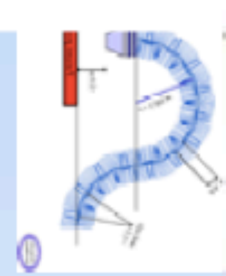
MeVIon

ProTom

ProNova

SHI Corkscrew
Note – Corkscrew gantry is 'shortest' length.

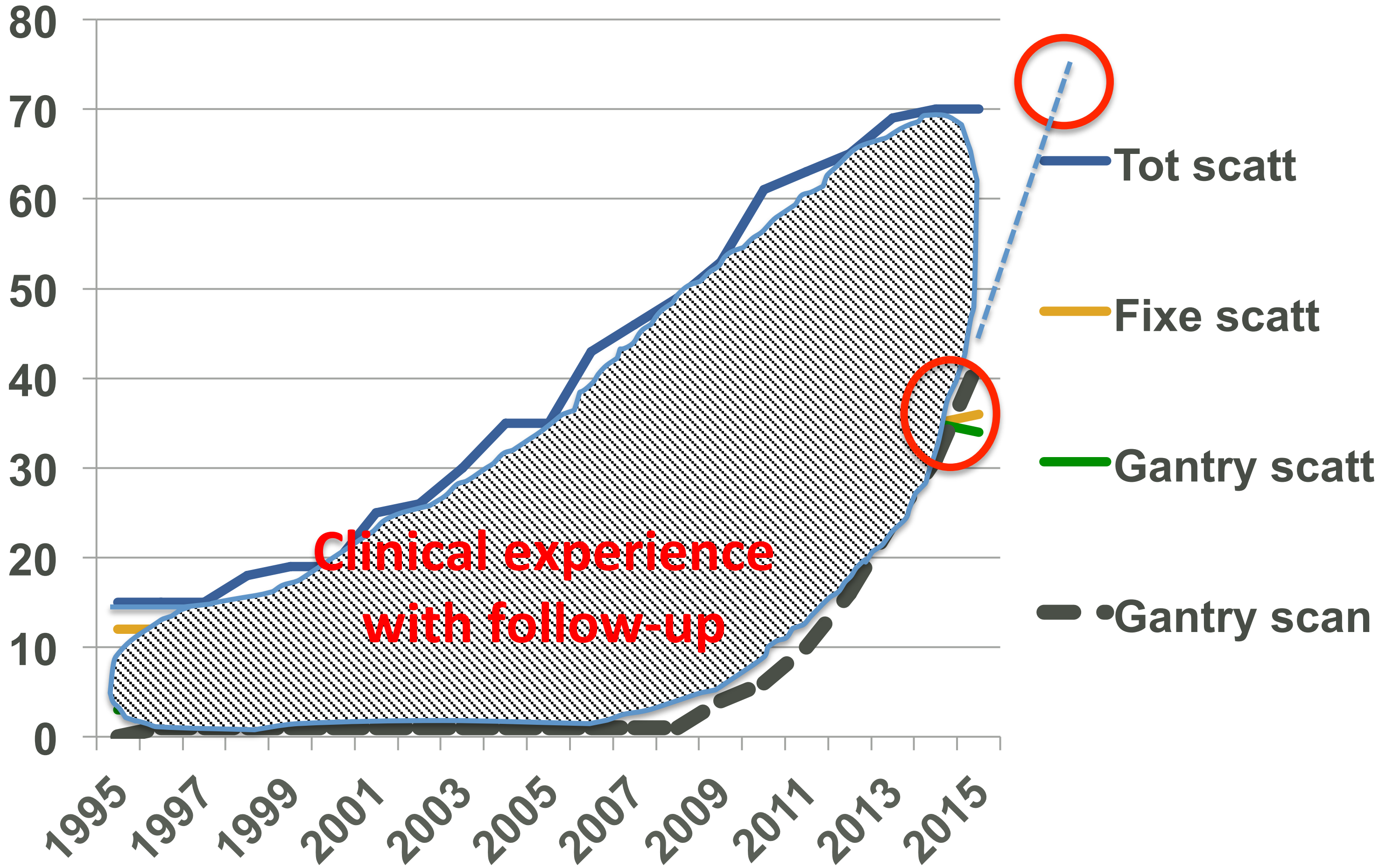
PSI 1 shortest radius



FFAG is the lightest

DOE Patents?

Number of treatment rooms in the world : scatter and scanned



M. Jermann, M. Schippers & A. Mazal PTCOG, 2015

Radiation Therapy Department Institut Curie

3 sites

9 linacs , 2 Tomotherapies, 1 Rx150kV,

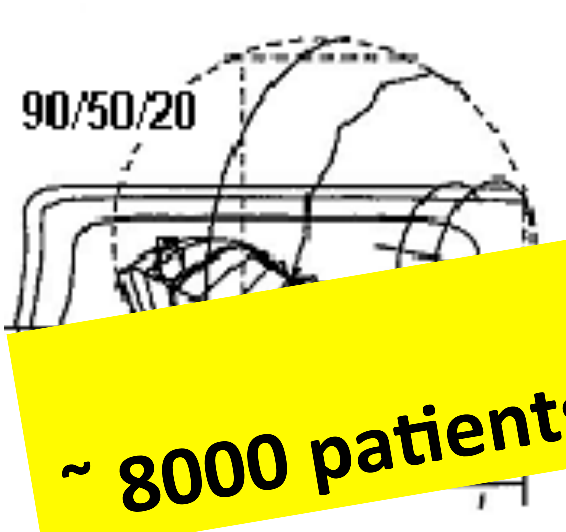
1 proton cyclotron (1 Gantry & 2 fixed rooms)

Brachytherapy   I125, PDR, HDR

5000 patients/year in RT

(**550 pats/year with protons = 11 %**) → ~10.000 fractions /year ↗

Eyes

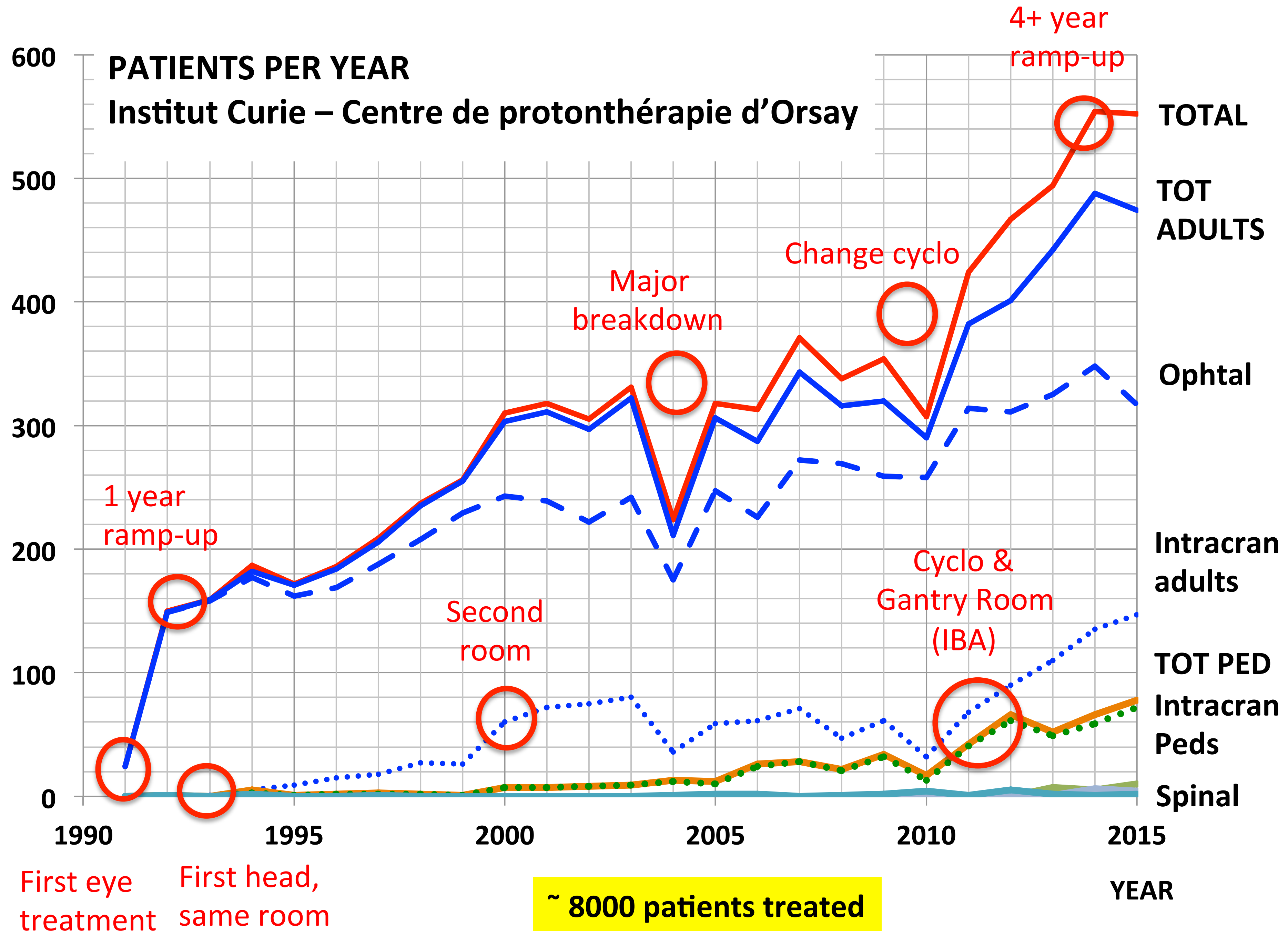


Base of Skull

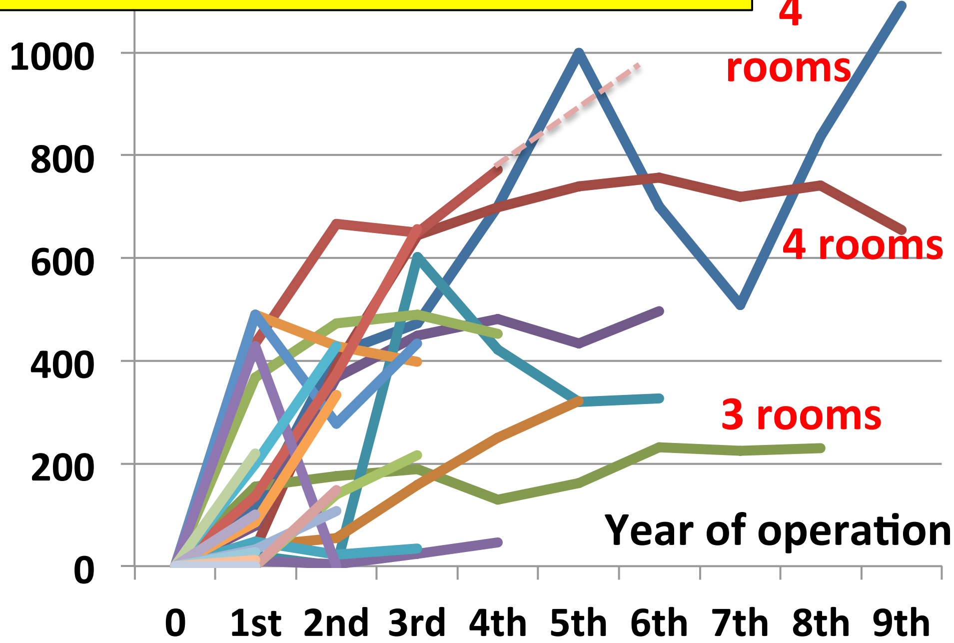
Paediatrics

End 2016:

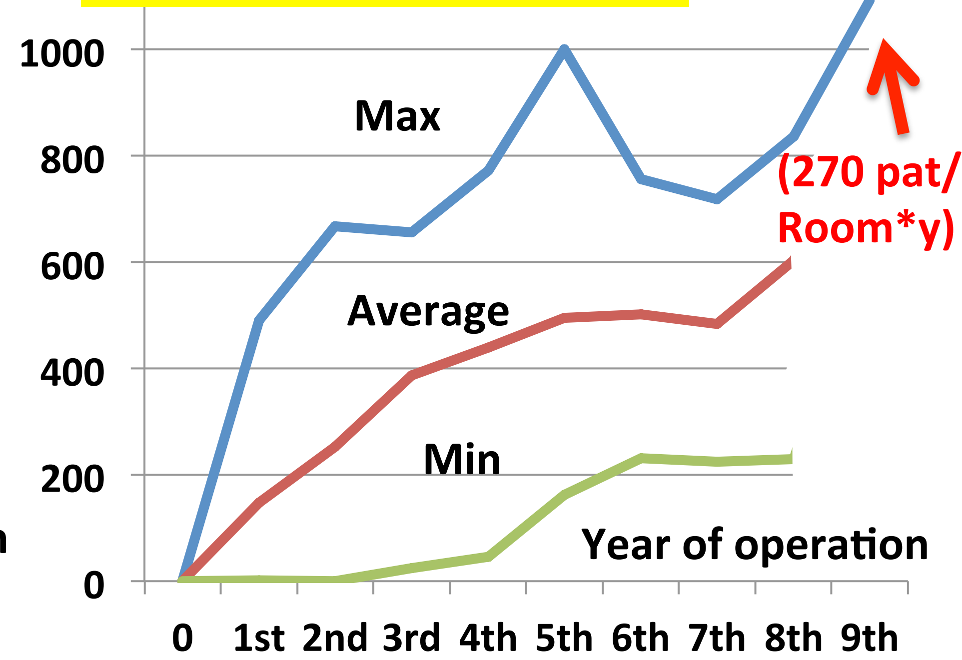
~ 8000 patients treated with protons at Curie…


PATIENTS PER YEAR
Institut Curie – Centre de protonthérapie d'Orsay
600
500
400
300
200
100
0
1990
1995
2000
2005
2010
2015
YEAR
TOTAL
TOT ADULTS
Ophtal
Intracran adults
TOT PED
Intracran Peds
Spinal
4+ year ramp-up
Change cyclo
Major breakdown
1 year ramp-up
Second room
Cyclo & Gantry Room (IBA)
First eye treatment
First head, same room
~ 8000 patients treated

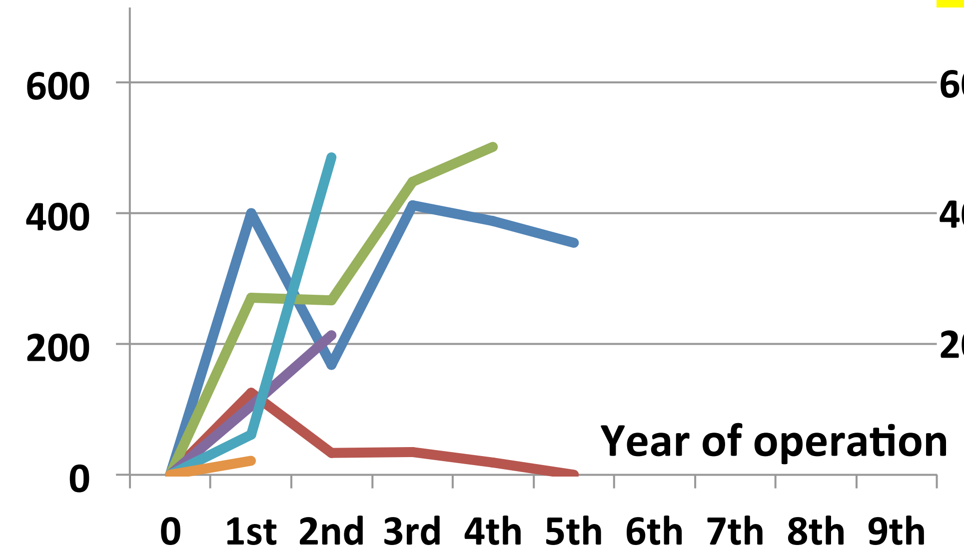
PATS PER YEAR (2005-2014)

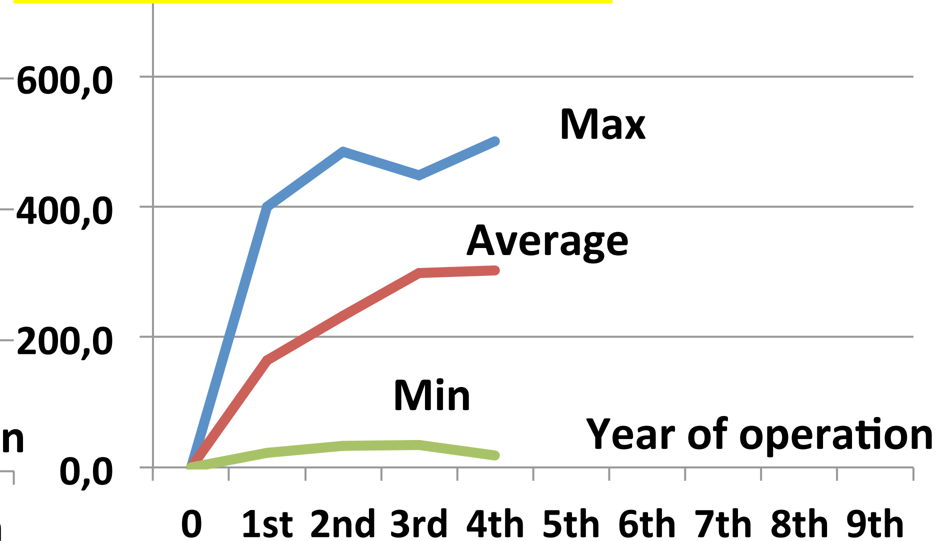


(25) New proton centers



6 New Carbon centers

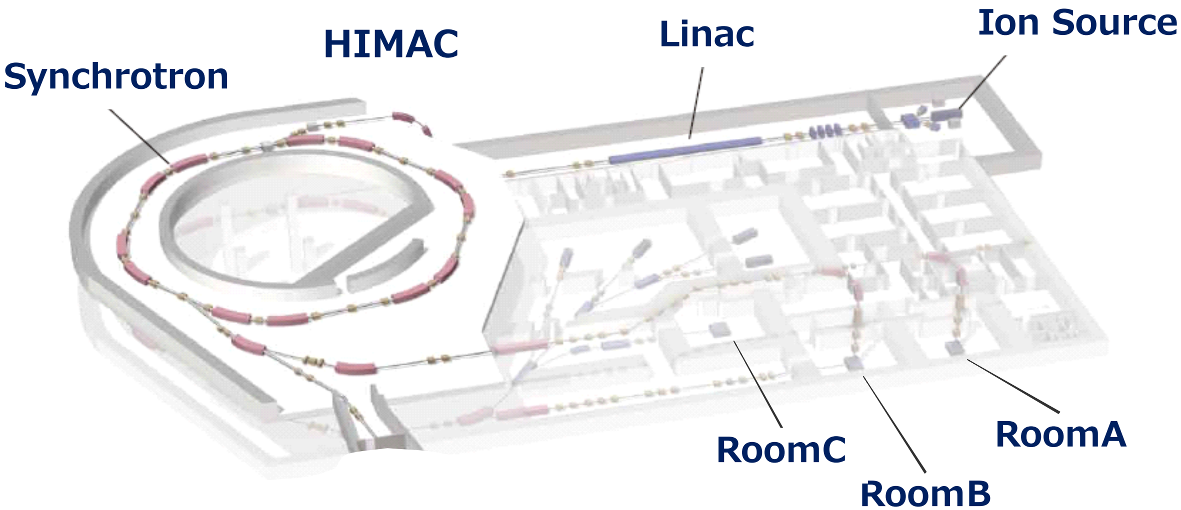




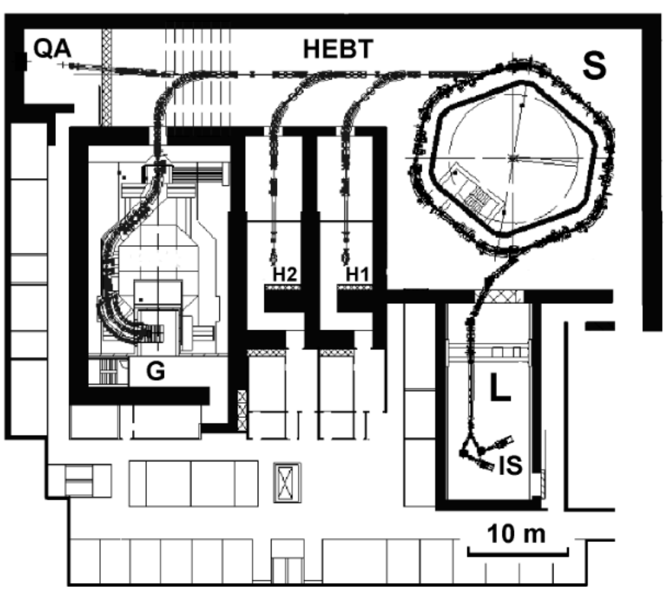
PTCOG/ M.Jermann/ A.Mazal

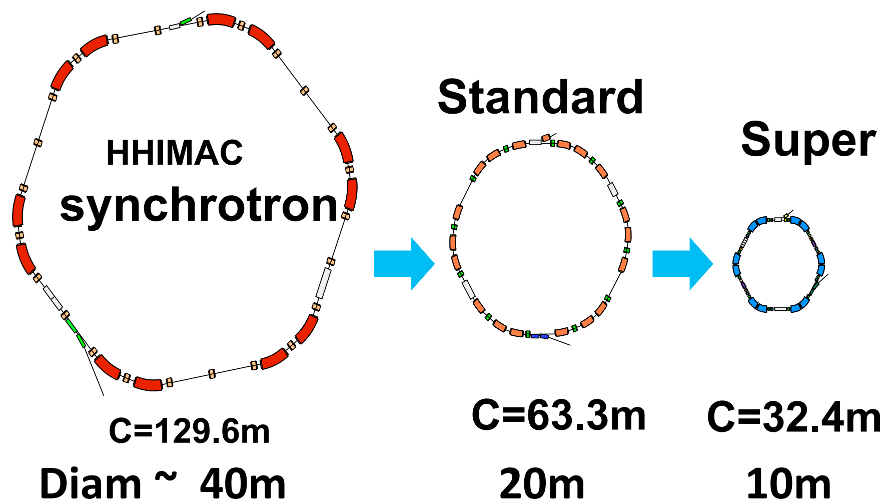
NIRS (Japan) HIMAC

Super MINMAC

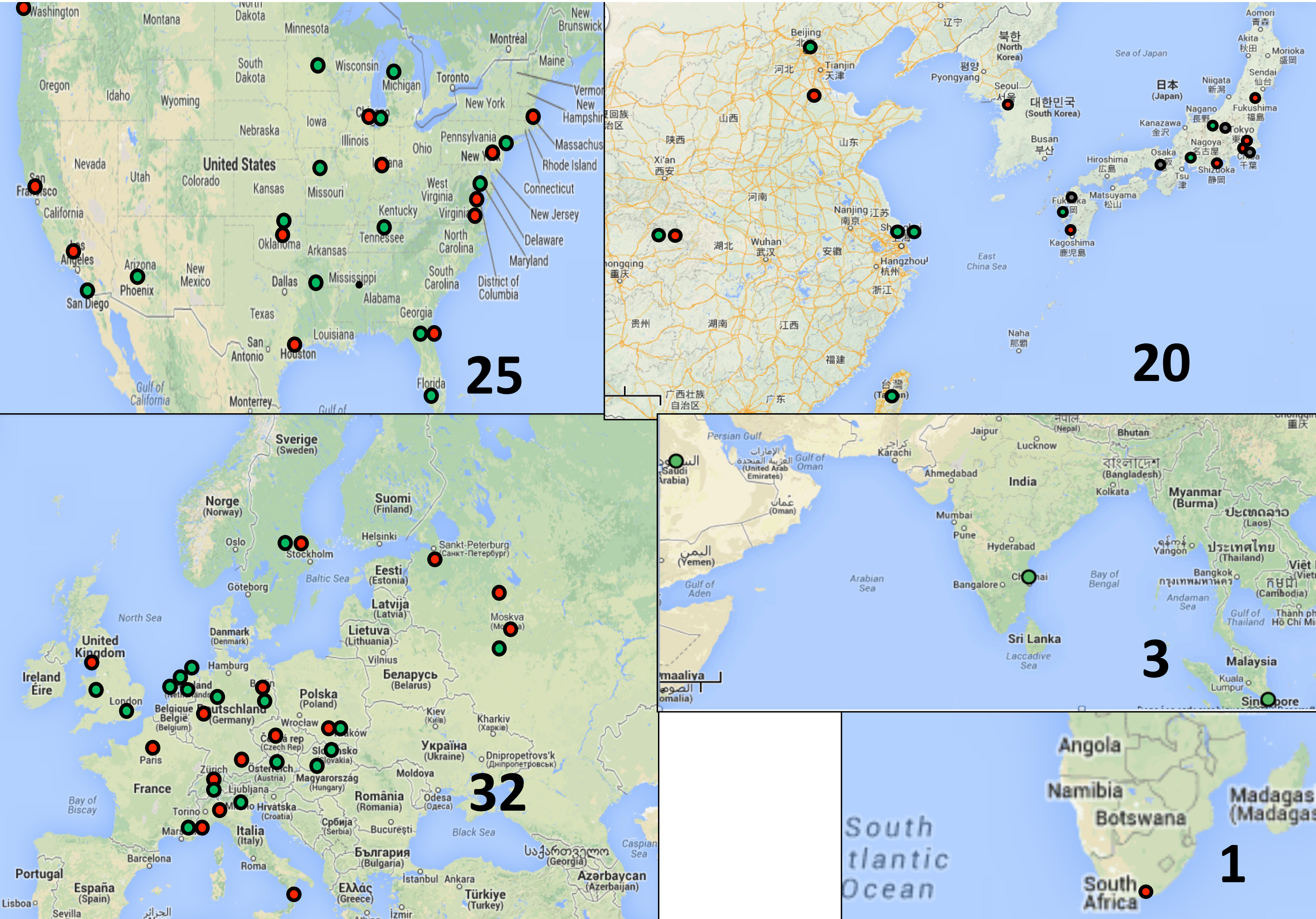


Heidelberg



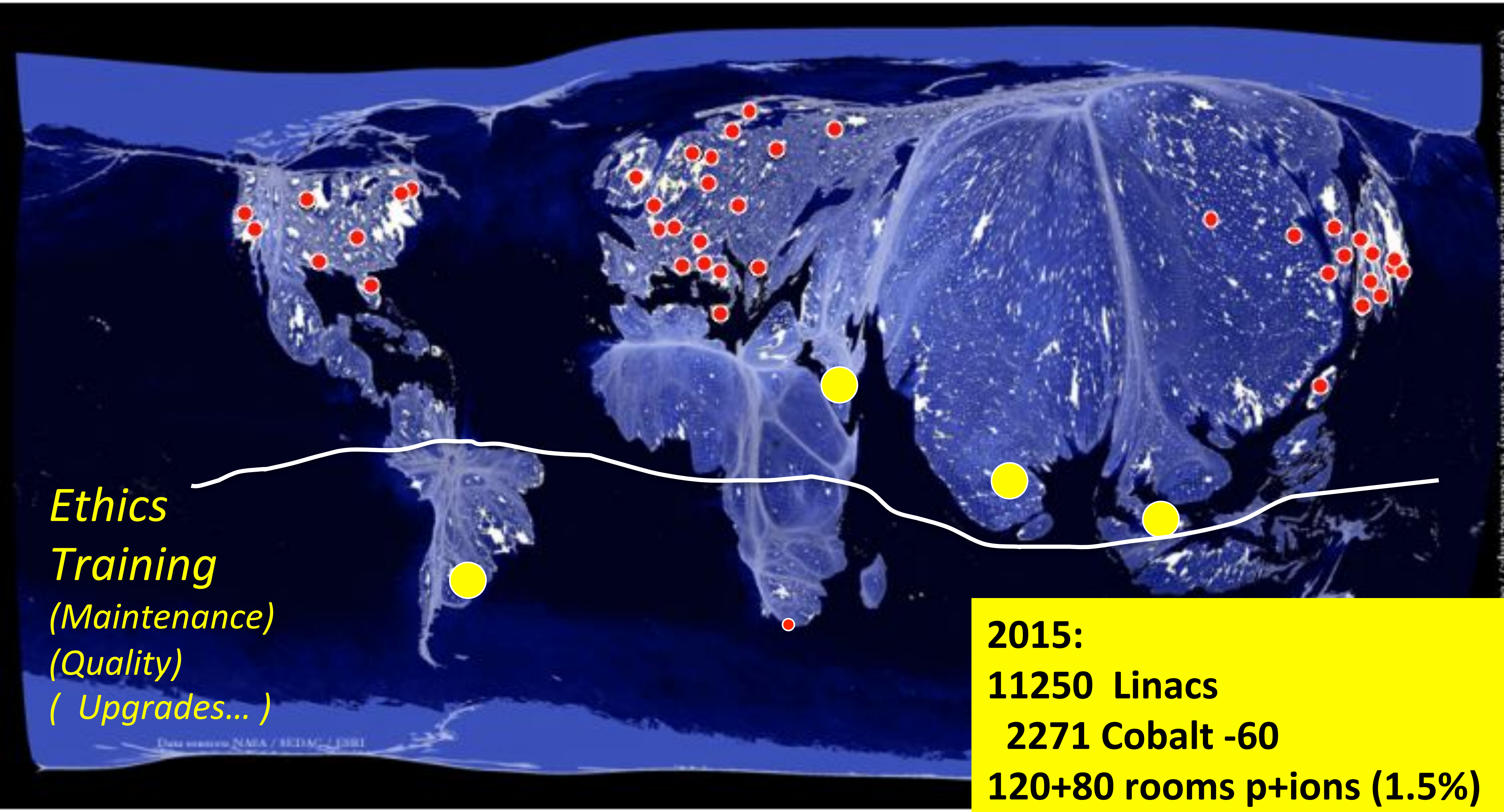


World 2015: existing (˜43) and coming (> 40) centers



Proton and Carbon-Ion Therapy Facilities Around the World

Area resized according to the nation's **population** (2010)



Original From Bill Chu, PTCOG 50, USA
Updated for this talk by AM , 2016

● In operation or under construction

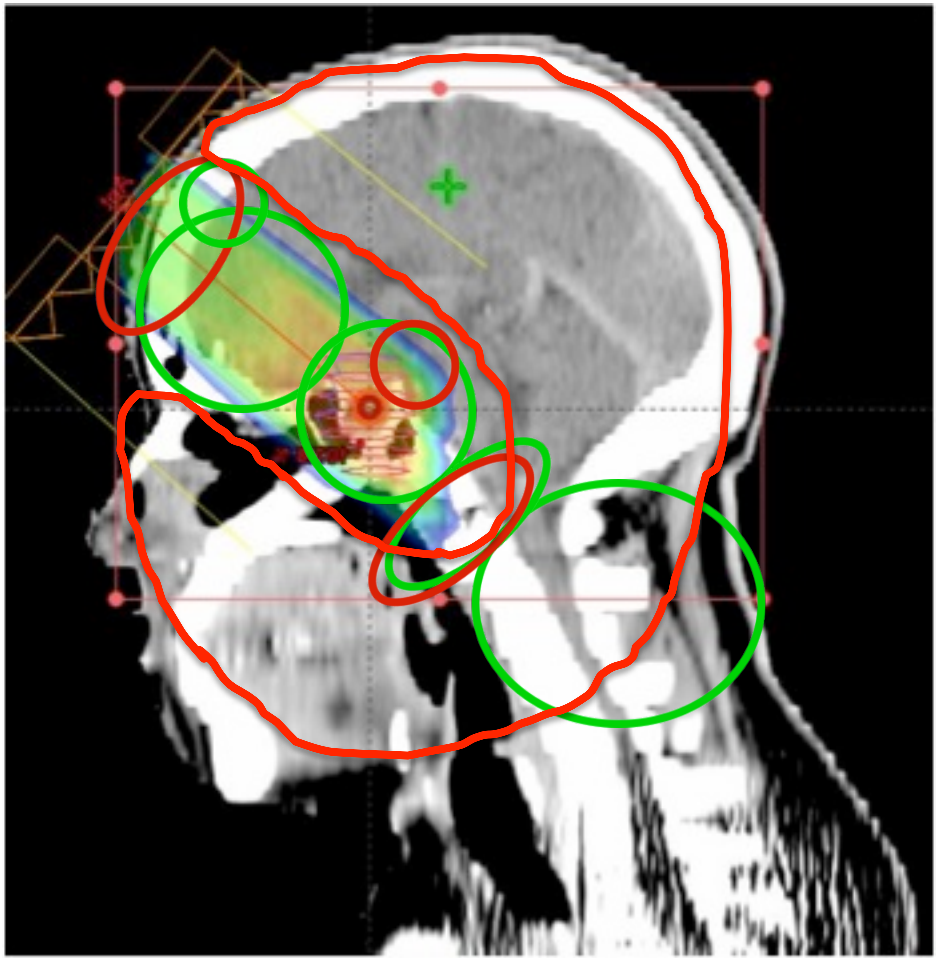
Future Perspective in (Medical) Physics for Particle Therapy : Interactions

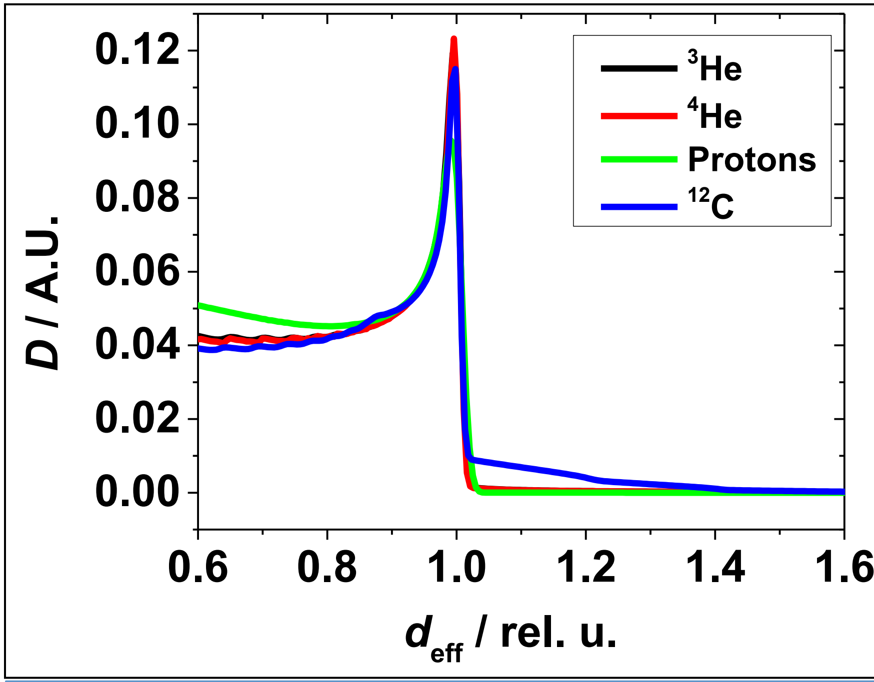
Domain of interaction	Contents, Concepts and Tools	Conclusions	Key Words
1. System Technology	**# Compactness & New concepts** **# Heavier ions**	***Technology drives cost reduction and larger accessibility. It must be evaluated in relationship with effectiveness, socioeconomic and ethical considerations.***	***→ Cost & Social***
2. Dosimetric issues and ancillary tools			
3. Clinical data			
4. Research and Development			

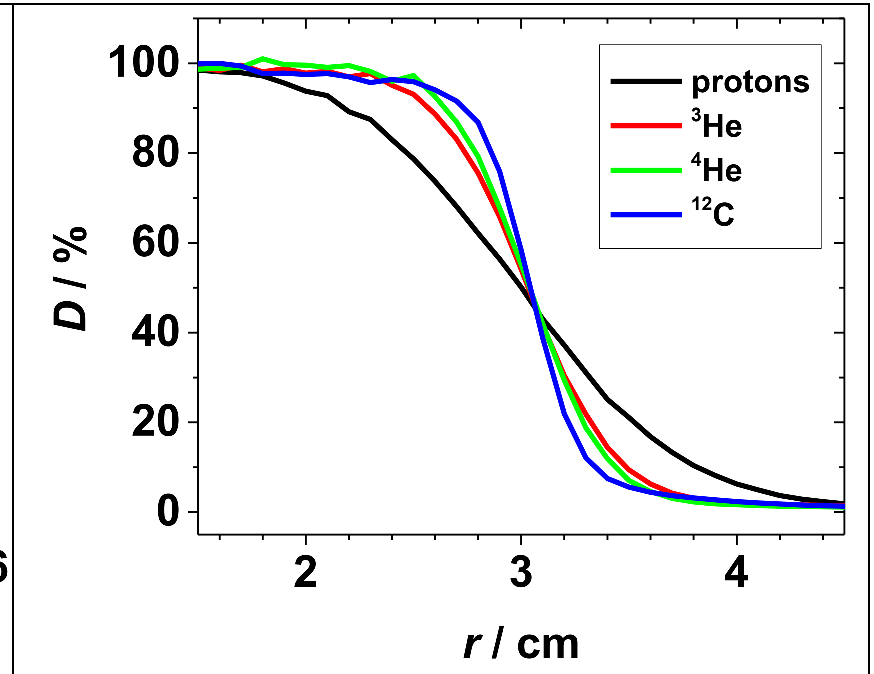
Future Perspective in (Medical) Physics for Particle Therapy : Interactions

Domain of interaction	Contents, Concepts and Tools	Conclusions	Key Words
1. System Technology	# Compactness & New concepts # Heavier ions	*Technology drives cost reduction and larger accessibility. It must be evaluated in relationship with effectiveness, socioeconomic and ethical considerations.*	→ *Cost & Social*
2. Dosimetric issues and ancillary tools	**# Entrance/Neutrons/ Penumbra/ Uncertainties** **# IGRT, IMPT,…**		
3. Clinical data			
4. Research and Development			

Advantages and limits with particle beams in therapy



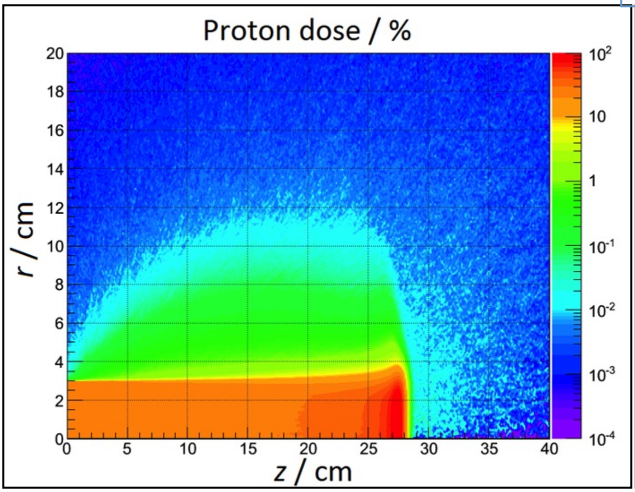


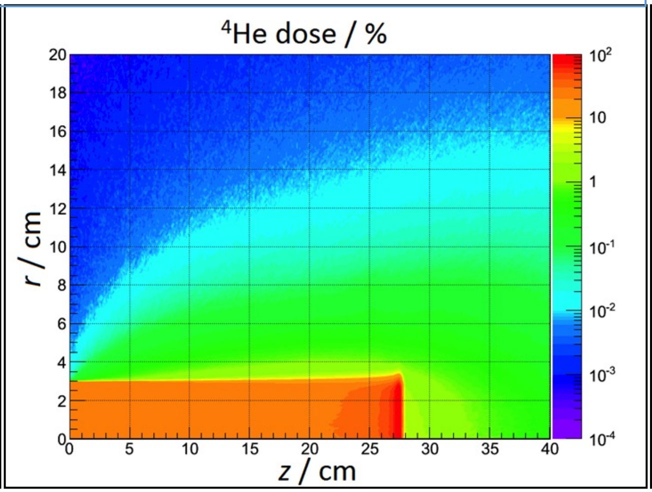


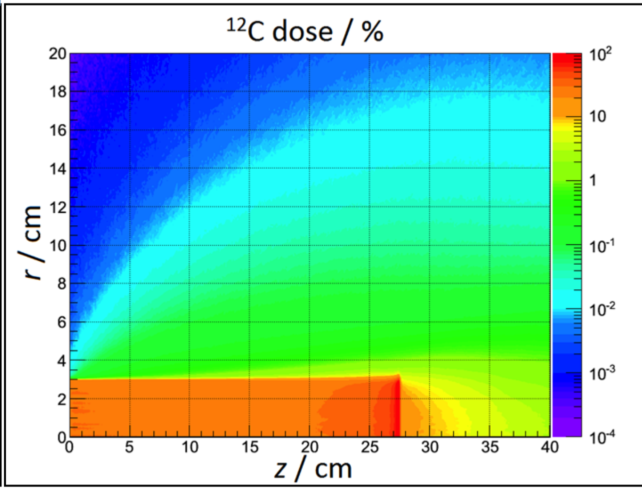
Beamlet Integral Depth Dose

Profiles of 6 cm dia field

Out-of-Field Dose

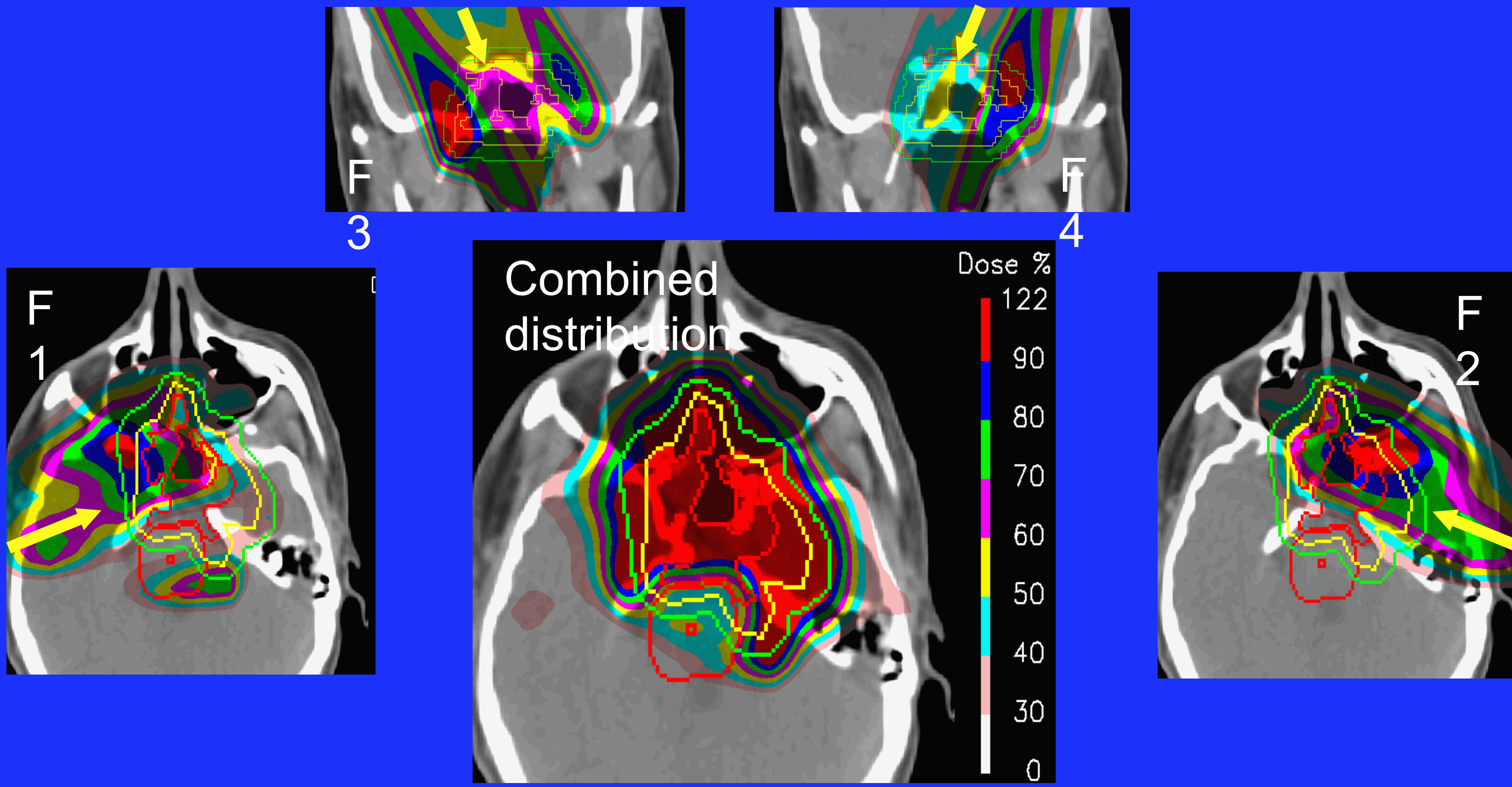






acknowledgment R. Mohan

An example IMPT plan



Note, each individual field is highly in-homogenous (in dose) across the target volume (c.f. SFUD plans)

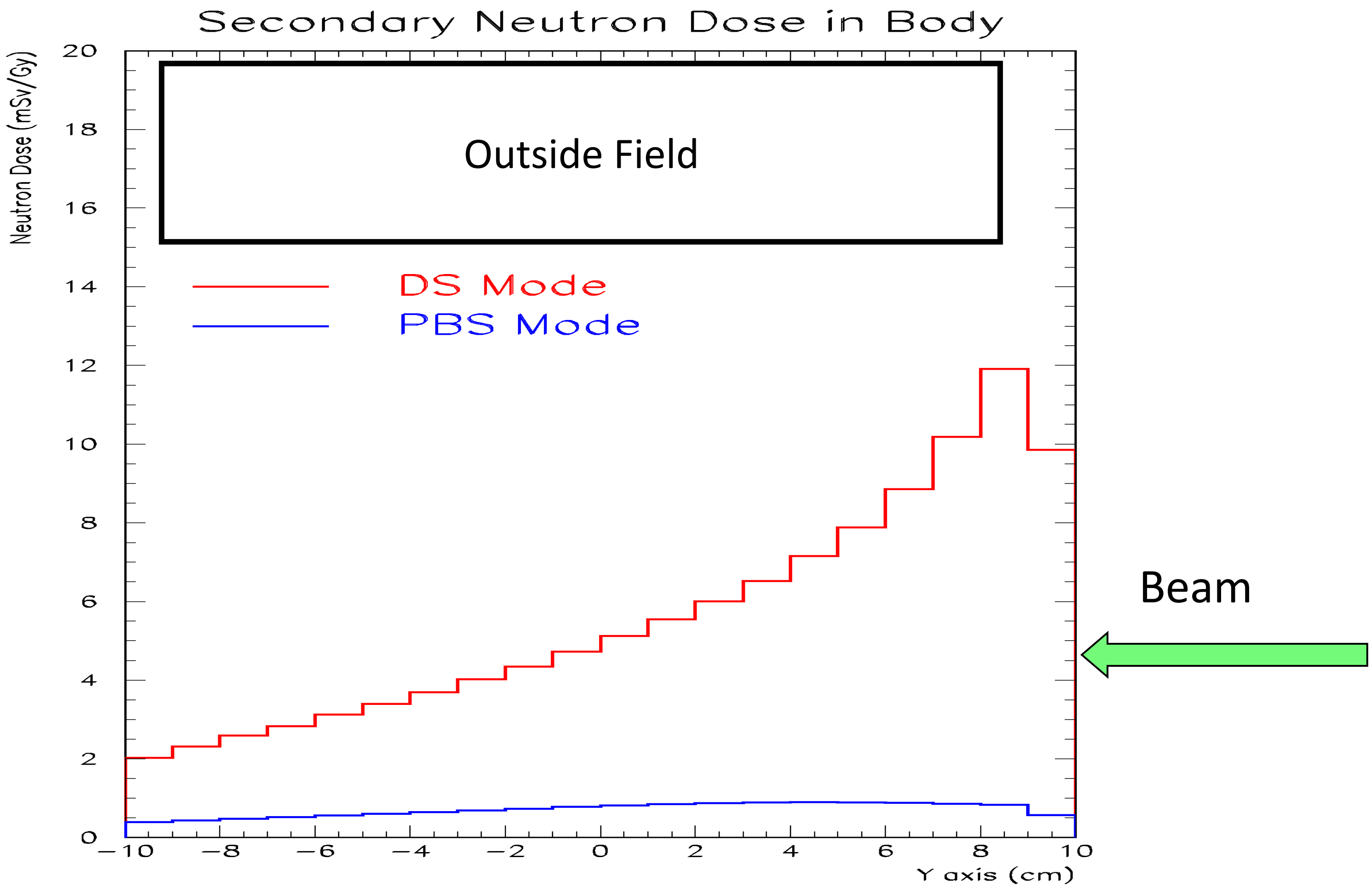
Less Hardware !

TO REDUCE ALL ASPECTS RELATED TO APERTURES AND COMPENSATORS

- CALCULATION, OPTIMISATION (air gap,…)
- WORKSHOP or OUTSOURCING
- QUALITY ASSURANCE
- DAILY SETUP
- NEUTRONS
- STORAGE
- DISPOSAL
- COST

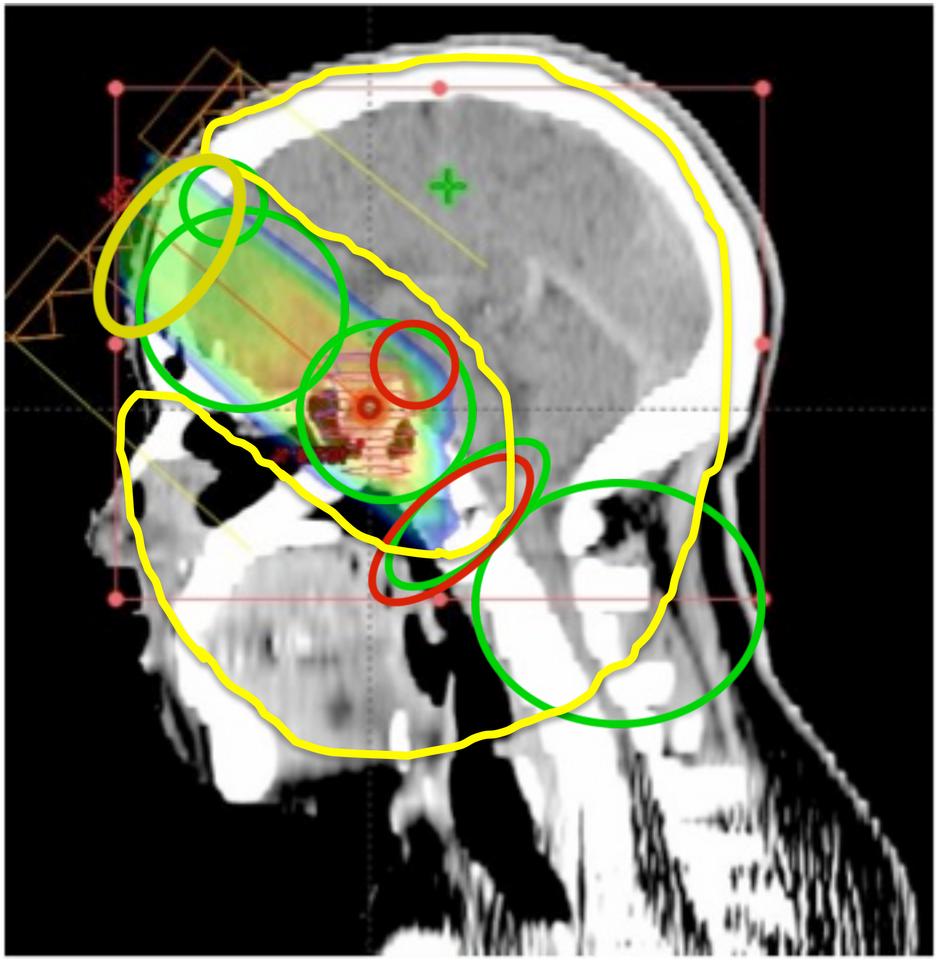
Less neutrons with PBS

Medulloblastoma Case



Fred Stickelbaut, Yves Jongen et al, IBA, 2015

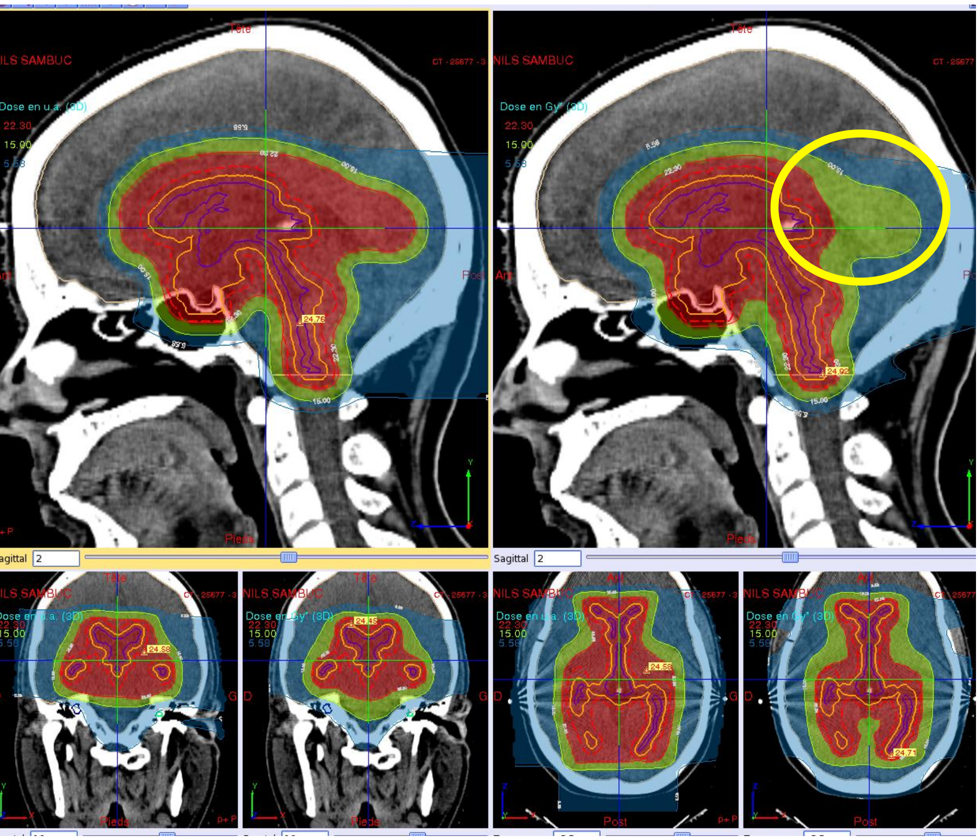
Advantages and limits with particle beams in therapy



Effect of lateral penumbra on passive and scanning systems

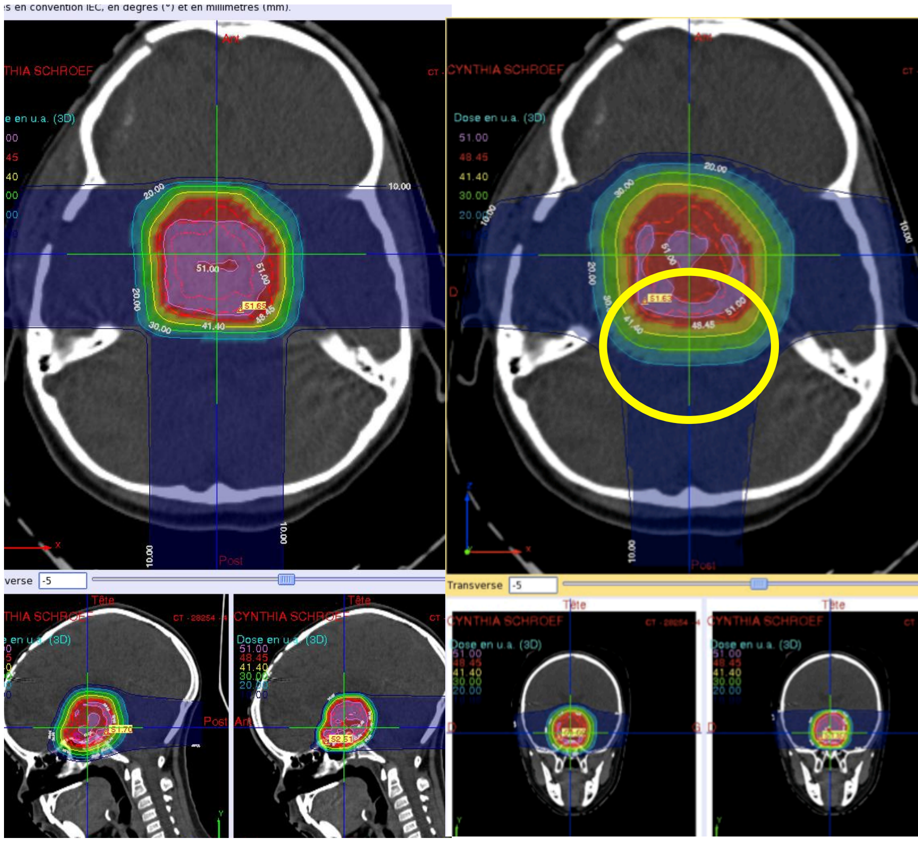
Germinoma

Double scattering | **PBS without aperture**



Craniopharyngioma

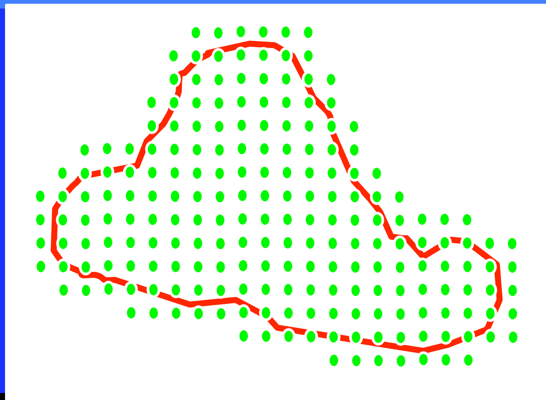
Double scattering | **PBS without aperture**

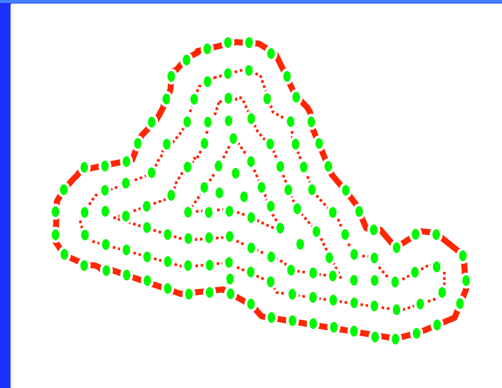


institutCurie

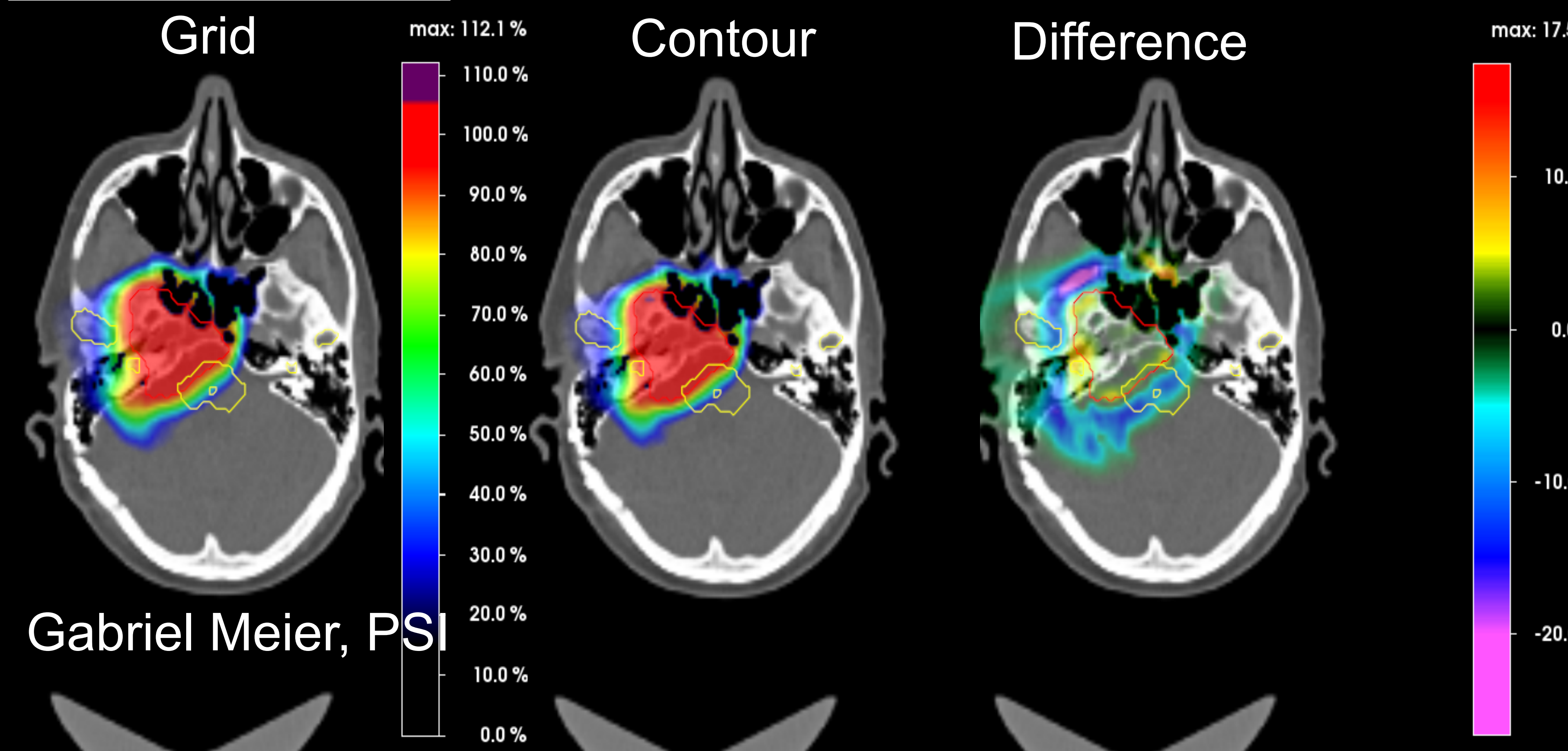
Contour scanning

PAUL SCHERRER INSTITUT



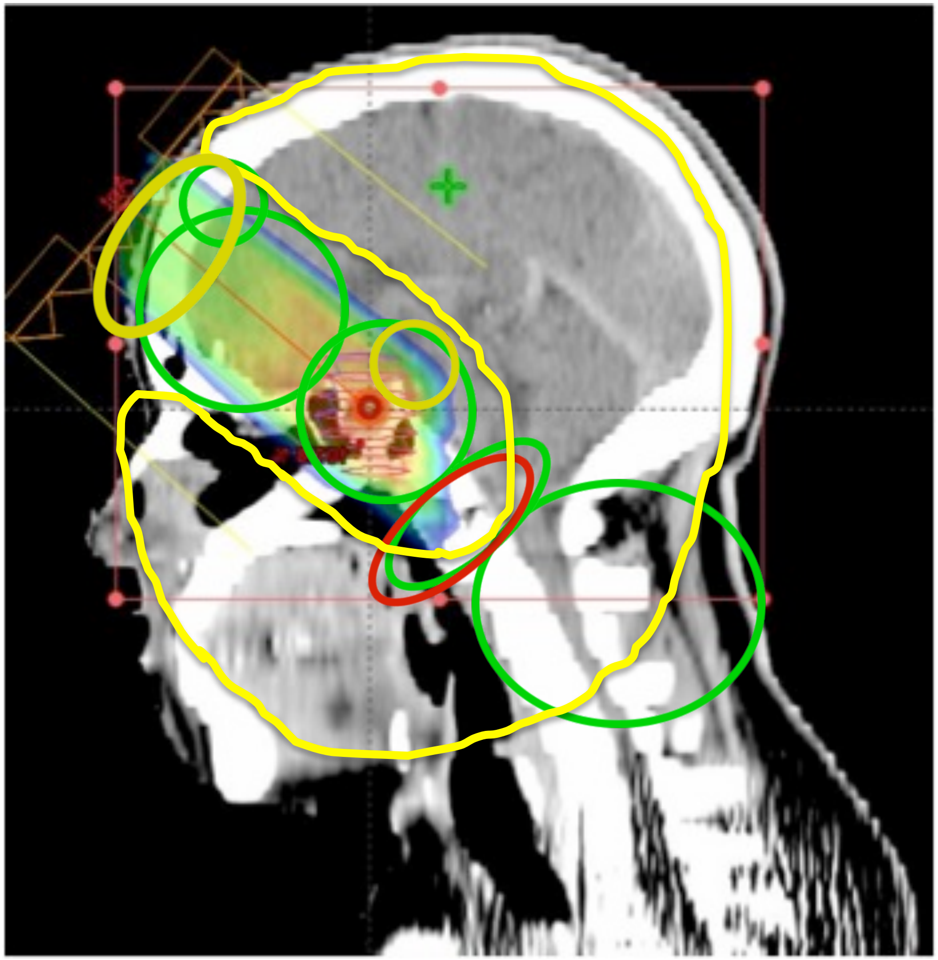


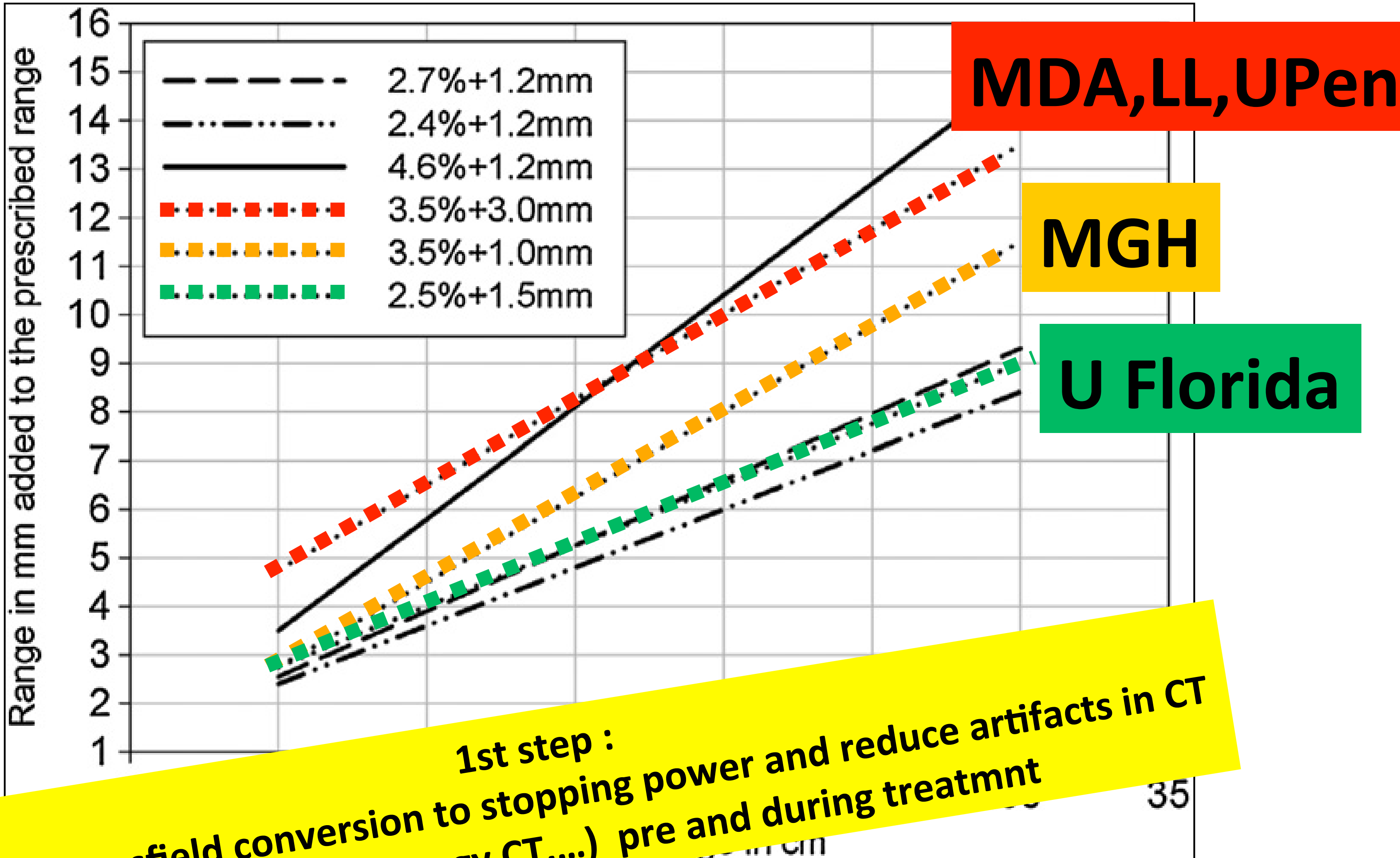
Smaller spot sizes
in the periphery ?



Gabriel Meier, PSI

Advantages and limits with particle beams in therapy



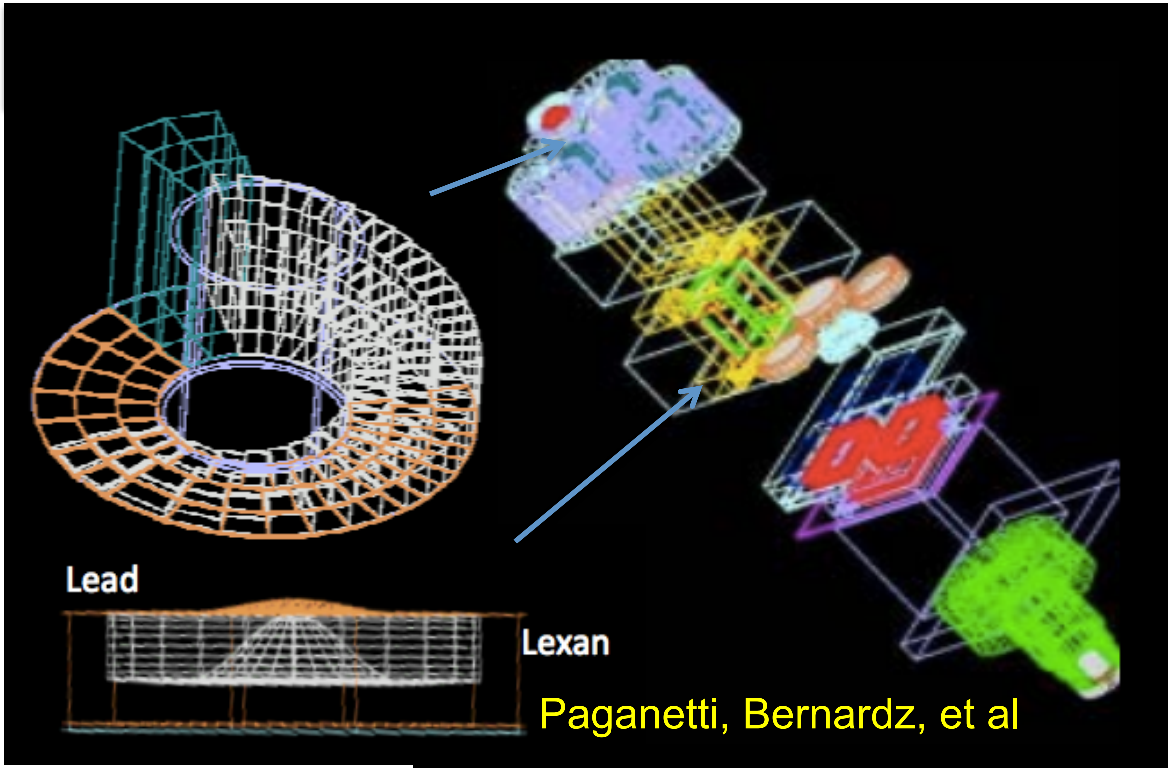


1st step :
Improve Hounsfield conversion to stopping power and reduce artifacts in CT (algorithms, Dual Energy CT,…) pre and during treatmnt

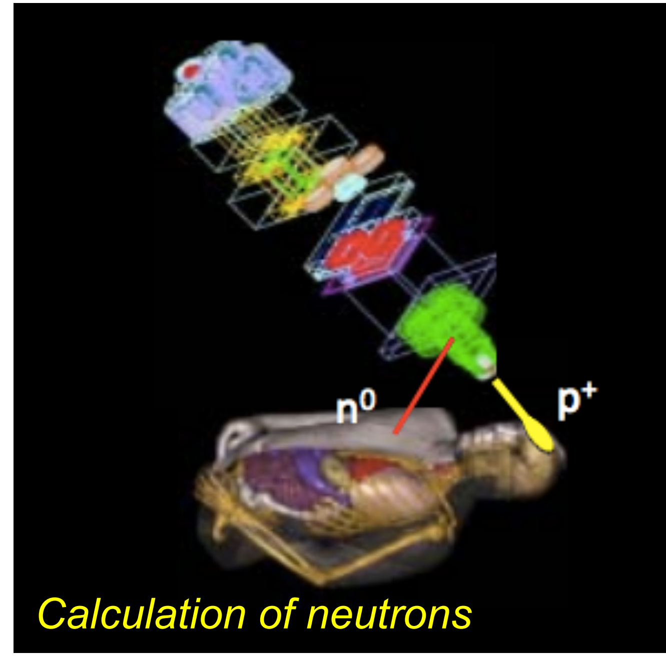
Dotted … margins in proton therapy treatment planning as currently typically … (3.5% + 1 mm), the MD Anderson Proton Therapy Center in Houston, the Loma Linda U… Medical Center and the Roberts Proton Therapy Center at the University of Pennsylvania (3.5% + 3 mm) and the University of Florida Proton Therapy Institute (2.5% + 1.5 mm). Note that these centers may apply bigger margins in specific treatment scenarios.
Dashed line: estimated uncertainty without the use of Monte Carlo dose calculation. Solid line: estimated uncertainty for complex geometries without the use of Monte Carlo dose calculation. Dashed-dotted line: estimated uncertainty with the use of Monte Carlo dose calculation.

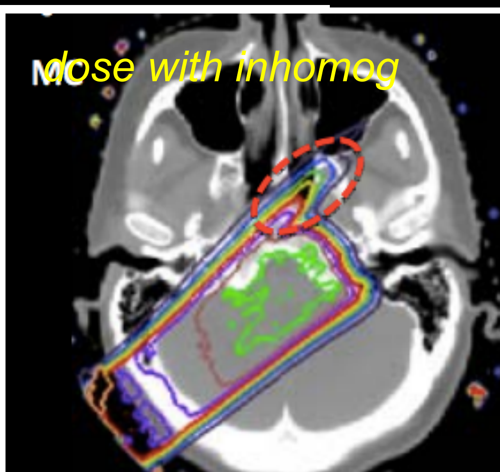
H.Paganetti , PMB 57 (2012) R99-R117 & personal comm

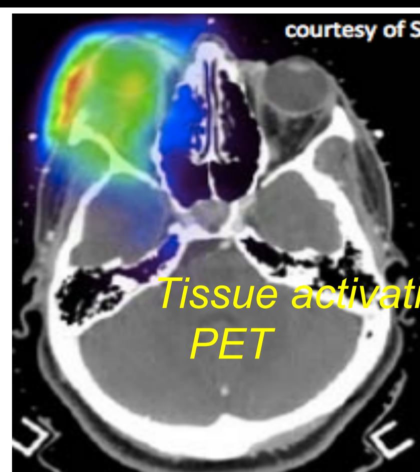
Limits in Beam models : towards Monte Carlo

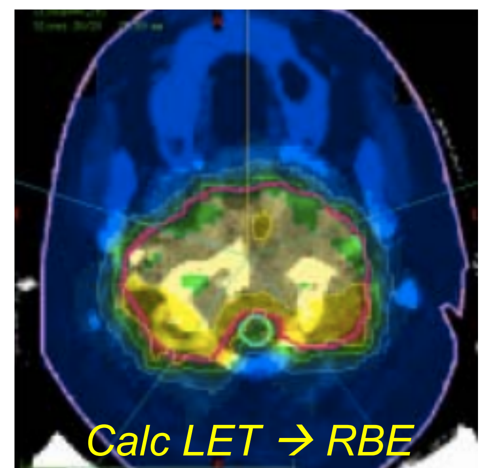


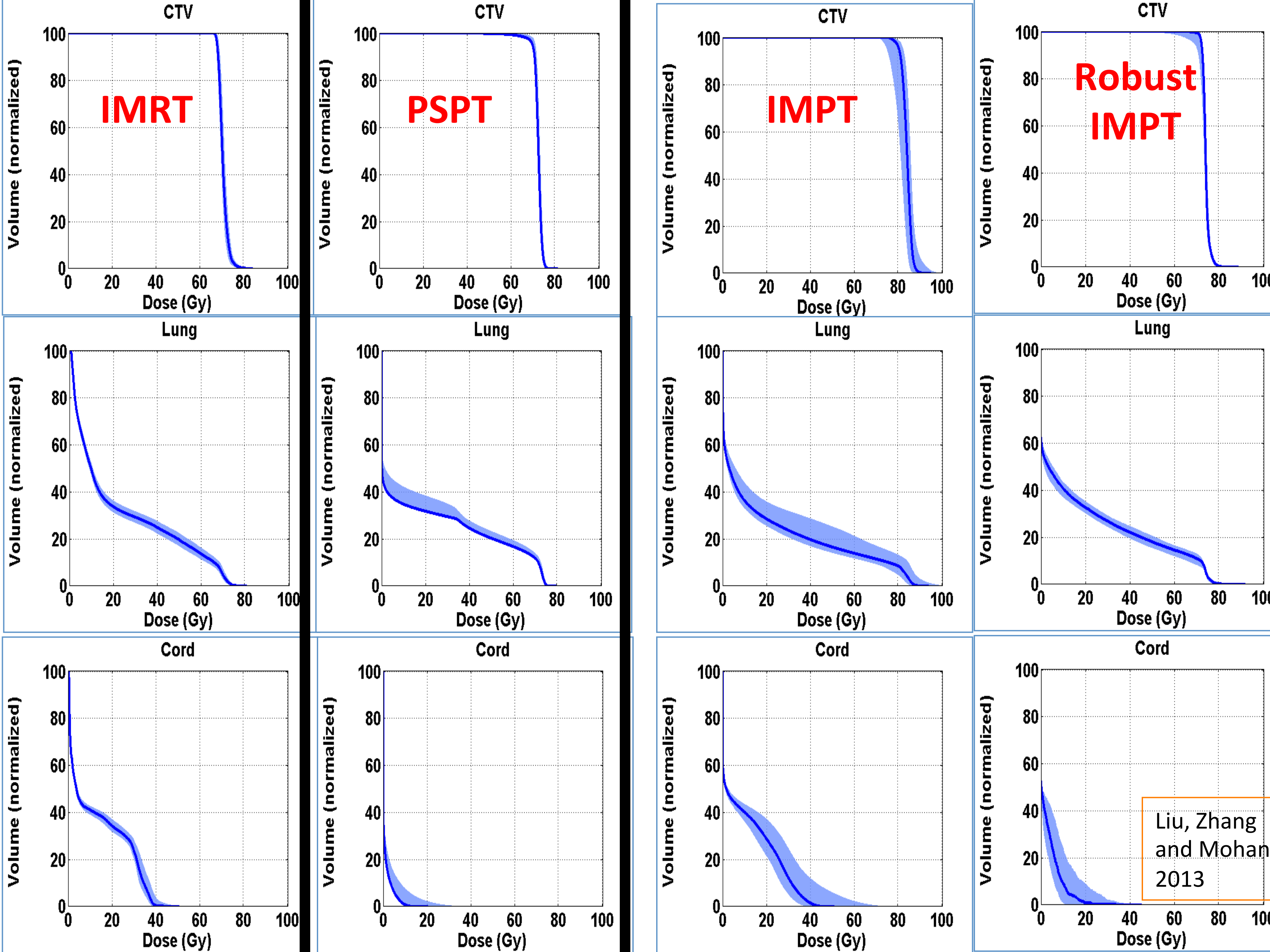
...and additional functions











CTV
IMRT
PSPT
IMPT
Robust IMPT
Lung
Cord
Volume (normalized)
Dose (Gy)
Liu, Zhang and Mohan 2013

Image guided radiation therapy

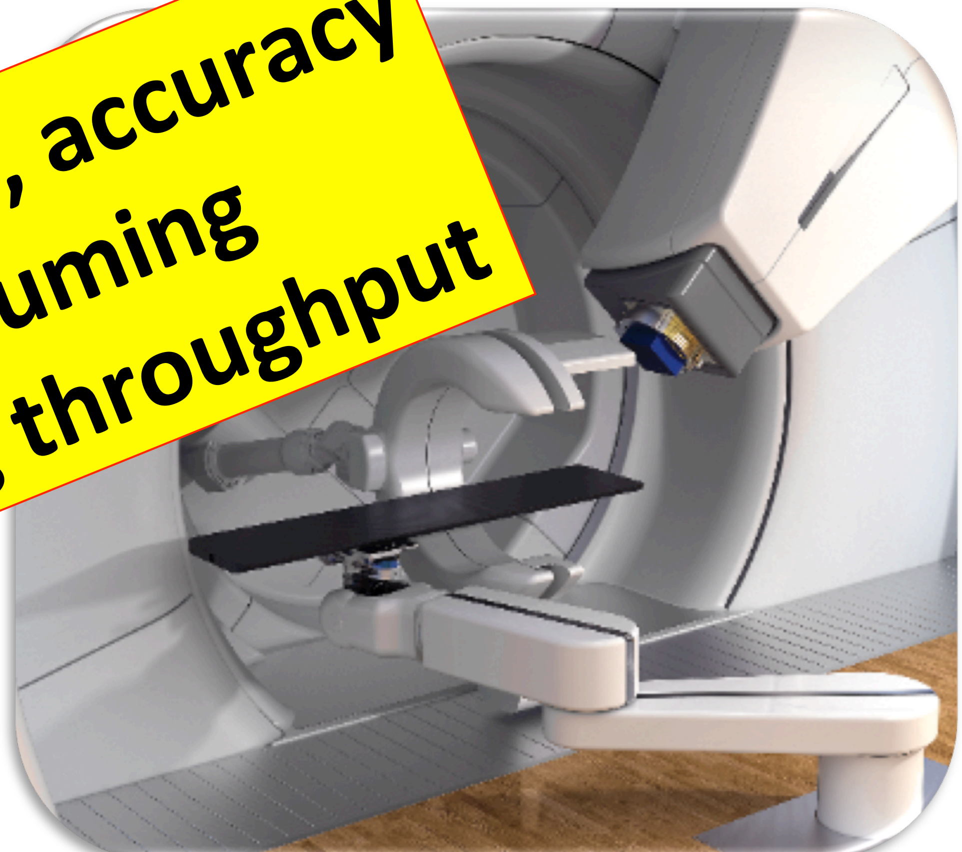
CBCT in gantry // CT in room
CBCT in the treatment Position

+ all others like in IGRT with photons !

VOLUMETRIC IMAGING - NEW DEVELOPMENTS

Key system, accuracy
Time consuming
Affecting throughput

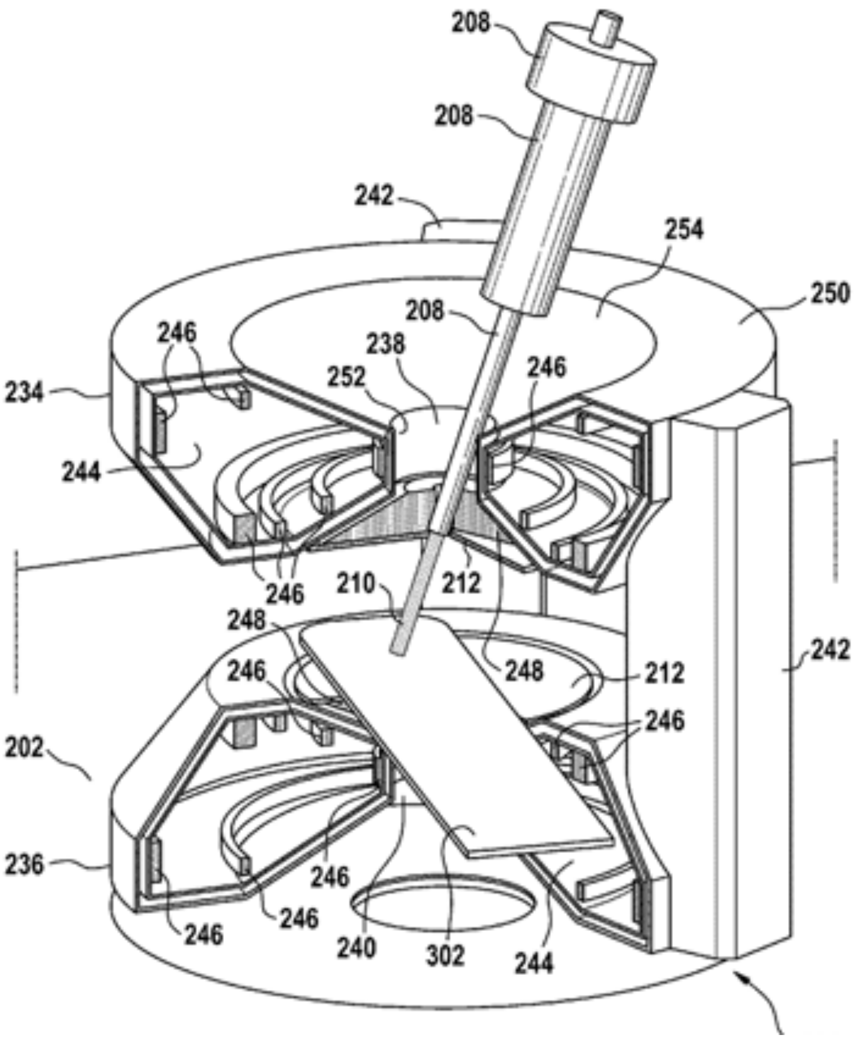
Med-Photon



ProNova

Niek Schreuder, 2014

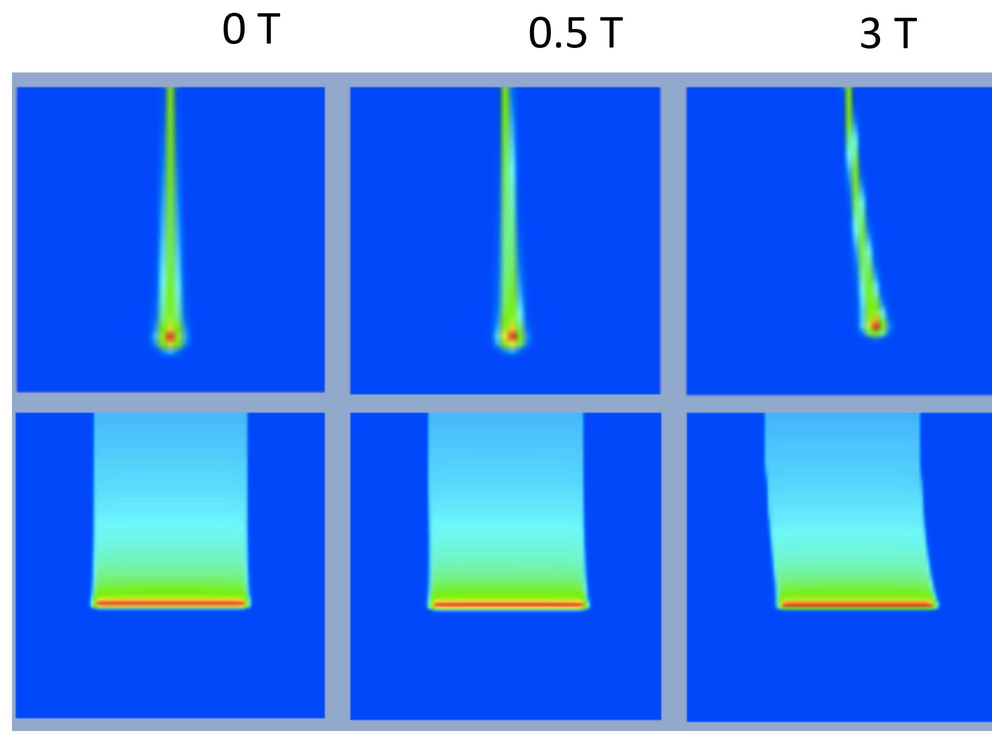
Integrating 1.5T MRI functionality with a radiotherapy accelerator   Lagendijk et al, Utrech



Patent Overweg Philips

Feasibility of MRI guided Proton Therapy:
Magnetic Field Dose Effects

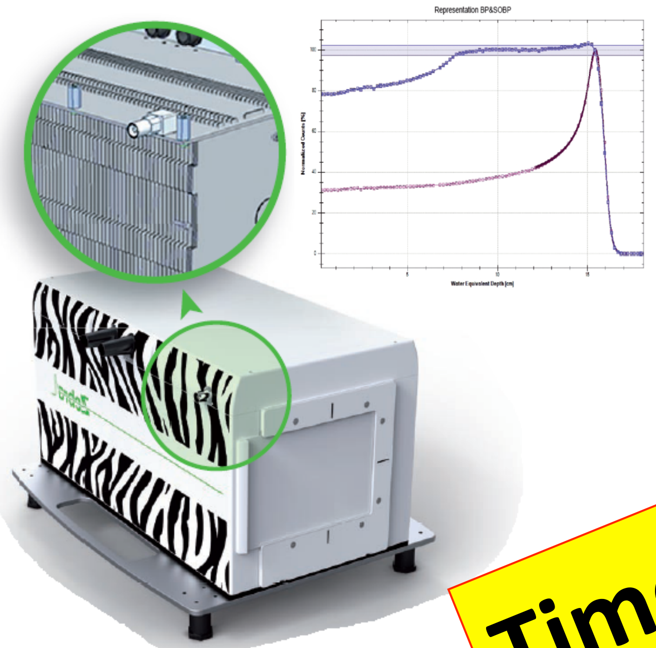
90 MeV proton beam in water



Raaymakers et al, AAPM

Multidimensional Detectors : Commissioning and Quality Assurance

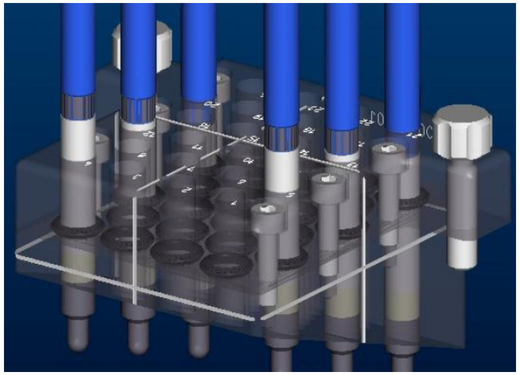
(Data from PTW and IBA dosimetry)



Scintillators

Time consuming
Affecting throughput

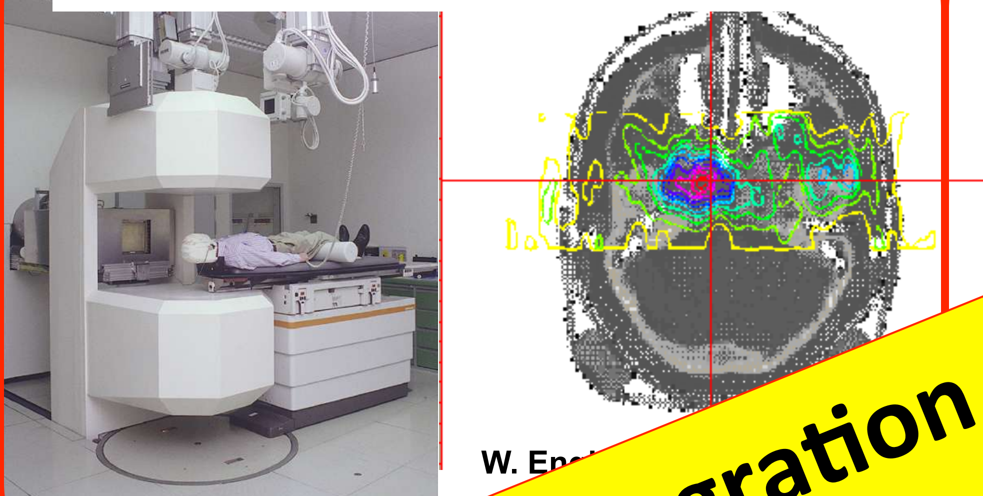
1D/2D multilayer Ion Chambers



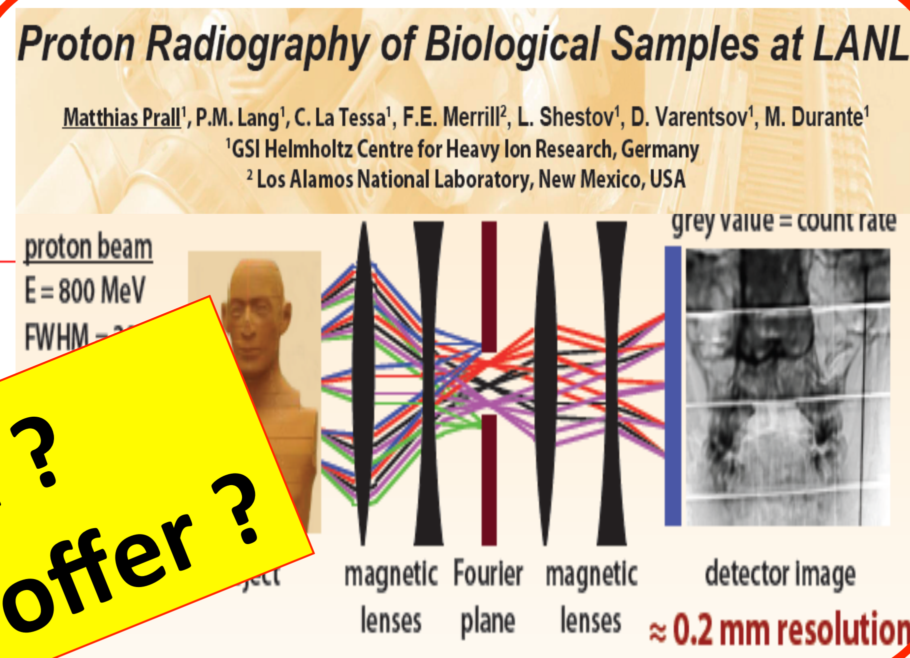
2D Arrays (chambers, semicond,…)
in solid or water phantoms

Verification of range, activation or stopping powers

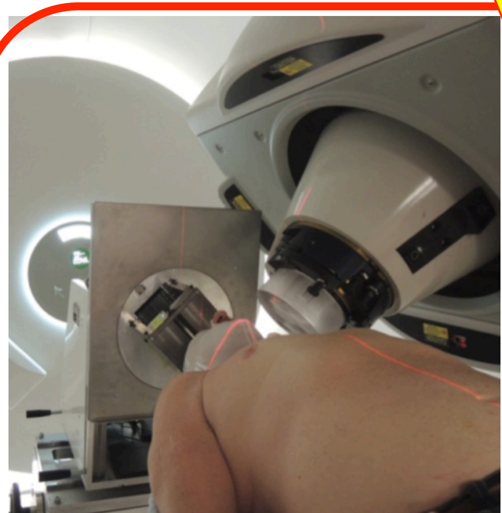
Positron Emission Tomography from patient activation with the beam

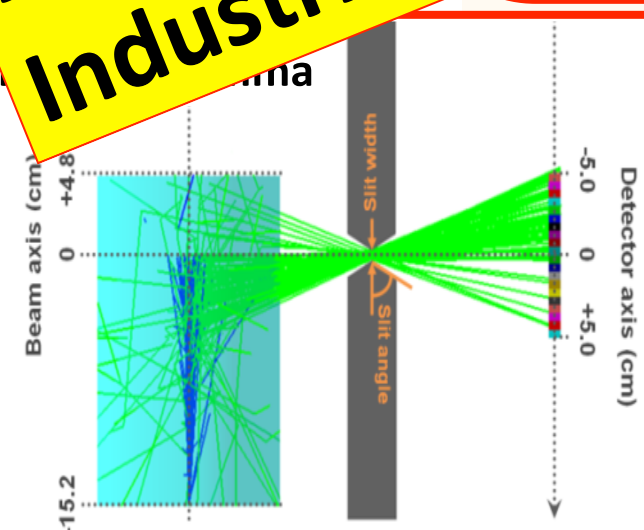


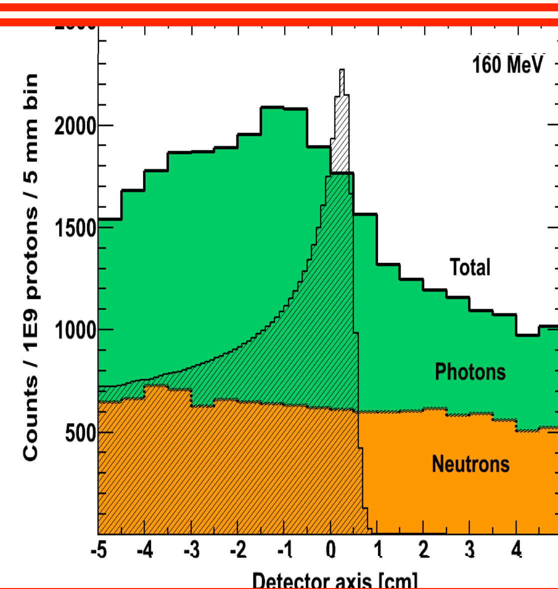
W. En...



Integration ?
Industrial offer ?

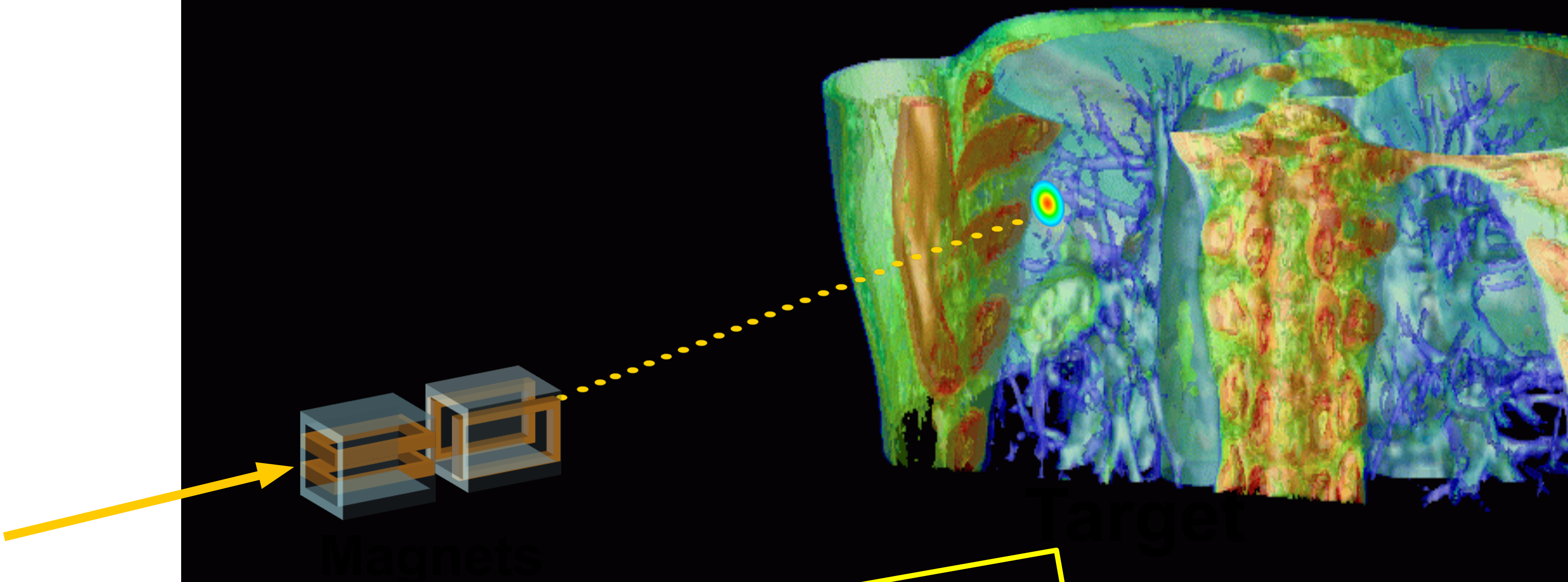






F.Roellinghoff et al, IBA & G. Pausch, Dresden

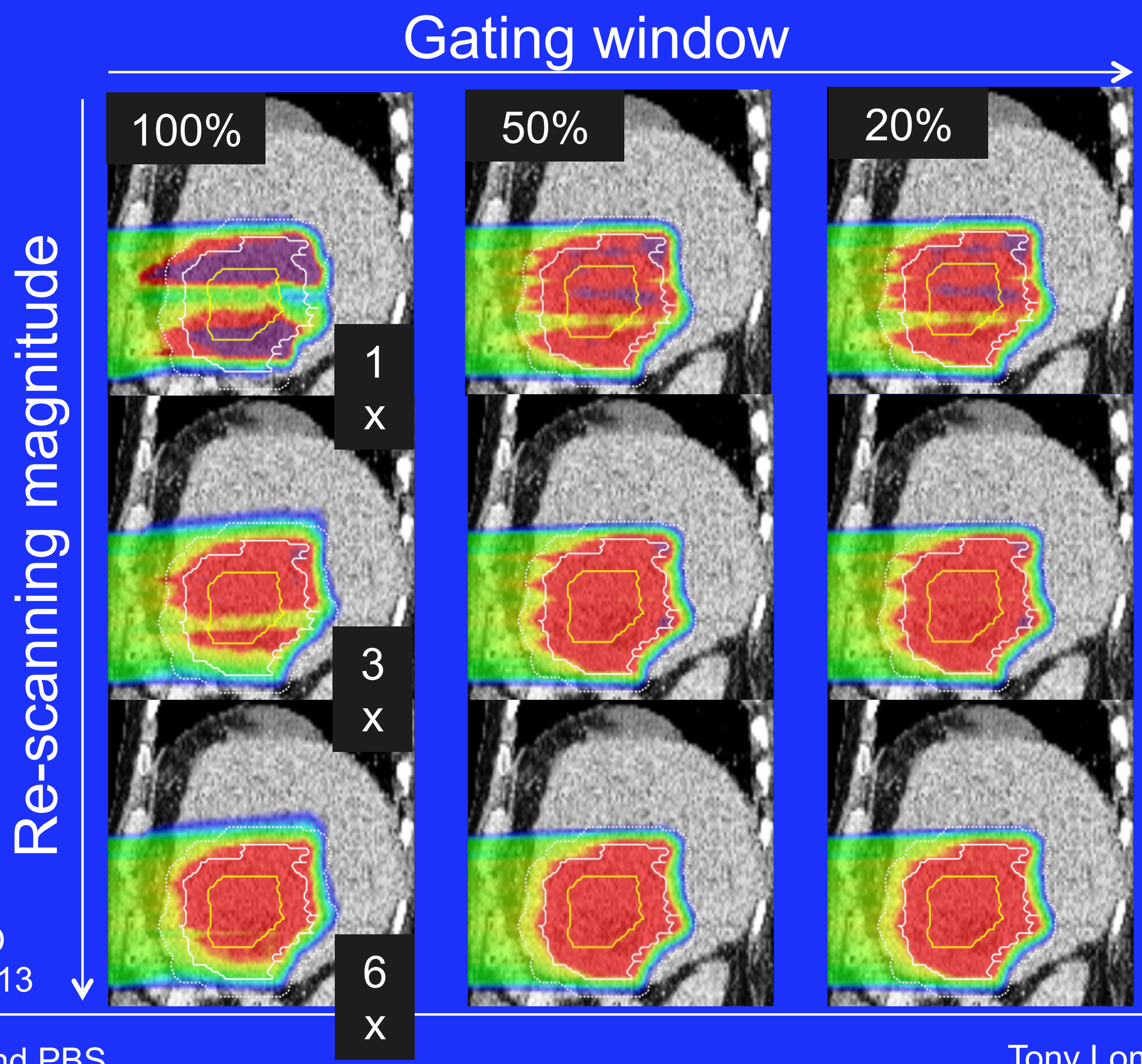
Beam Delivery : 3D Pencil Beam Scanning



"Interplay effect" !!

4D by Rietzel, Beam by Kamada

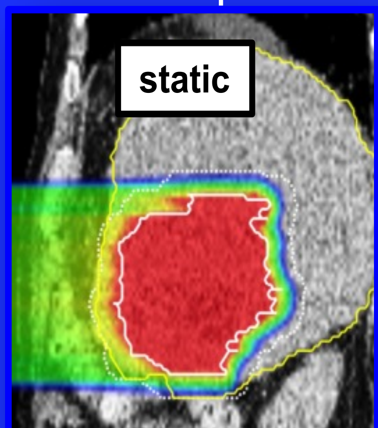
Gating and re-scanning combined



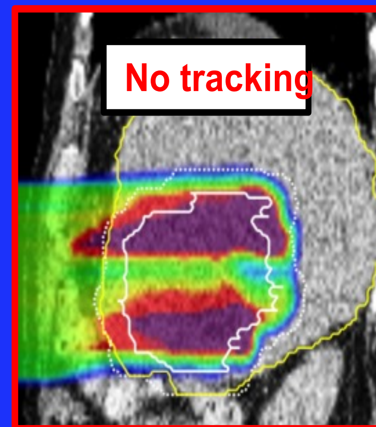
Ye Zhang, PhD thesis, PSI, 2013

Re-scanning and re-tracking compared

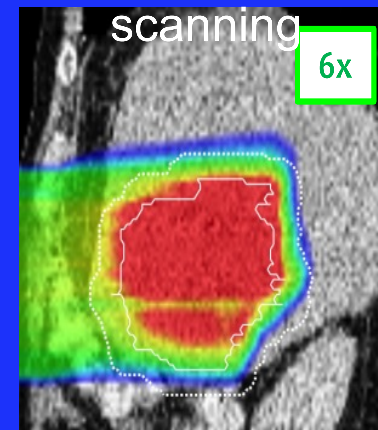
Static plan



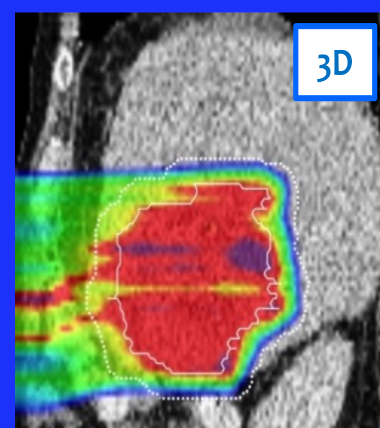
4D – no mitigation



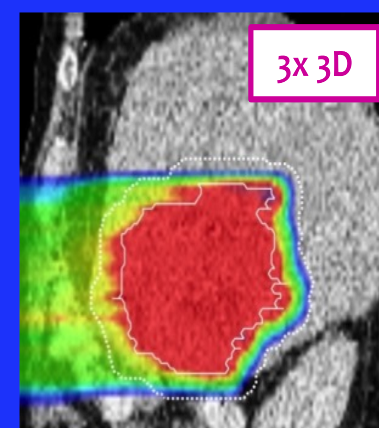
4D – 6x re-scanning



4D – tracking

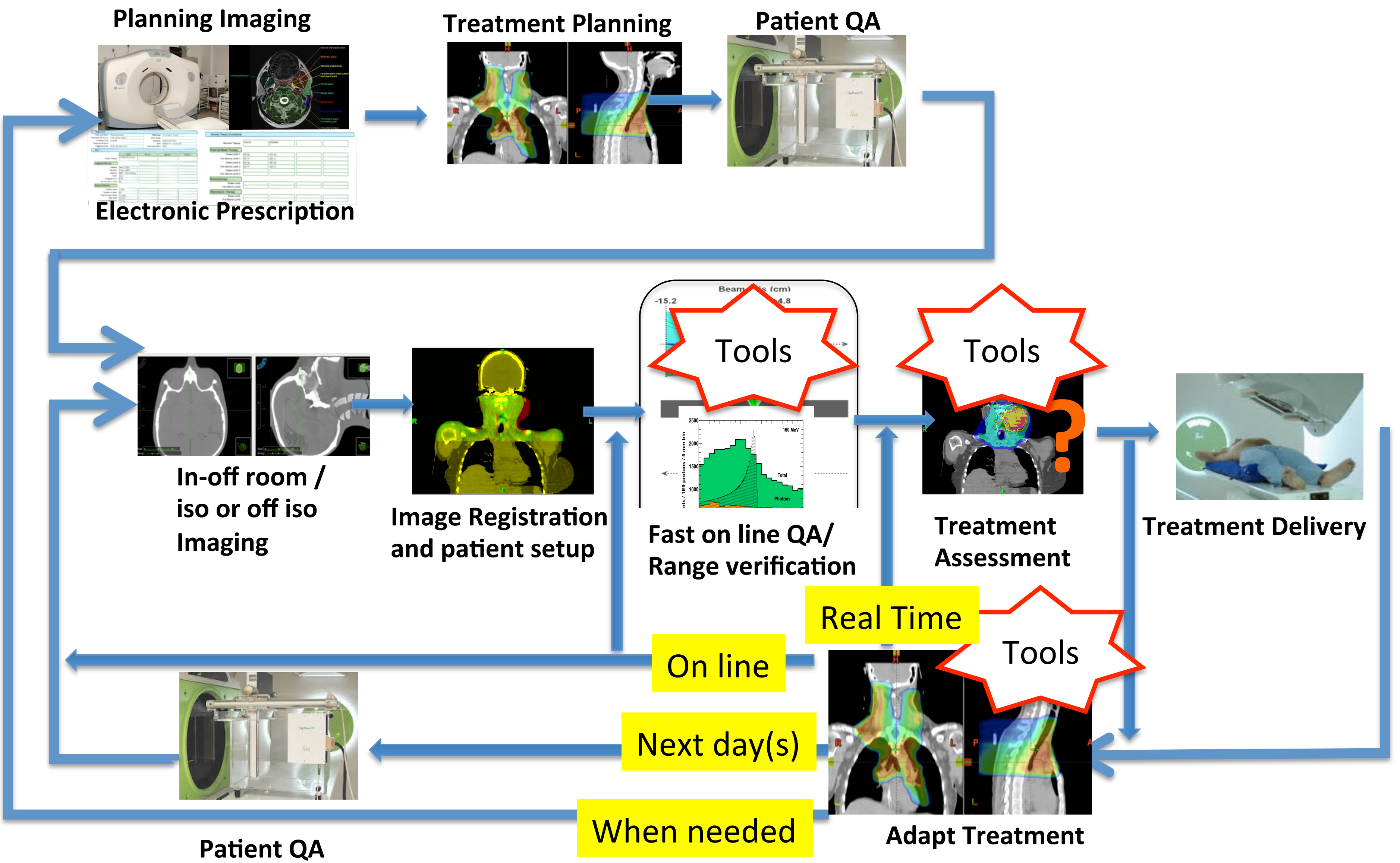


4D – 3x re-tracking



Zhang et al 2014, PMB, 59:7793-7817

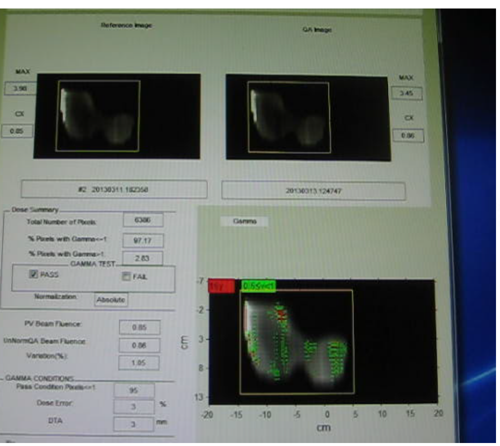
adaptive workflow

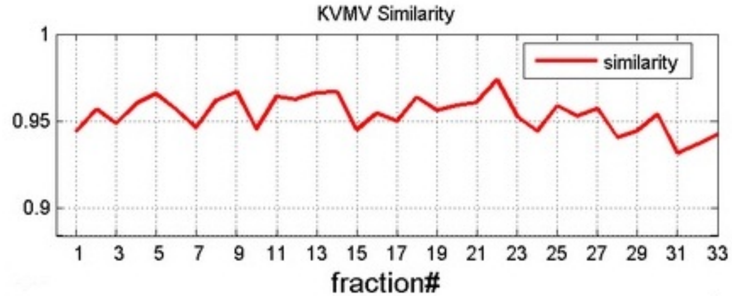


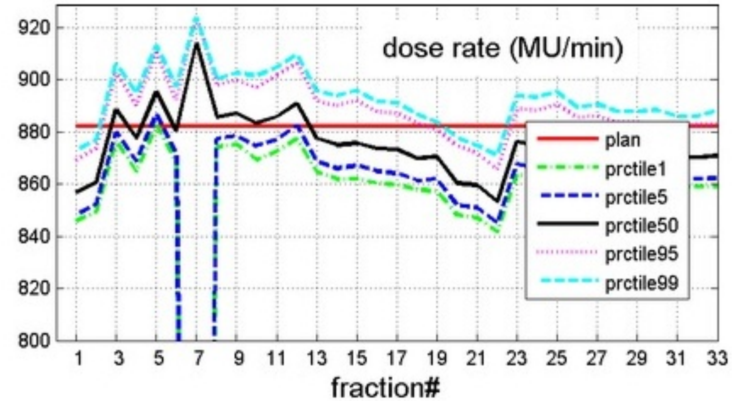
(G. Olivera, A.Mazal)

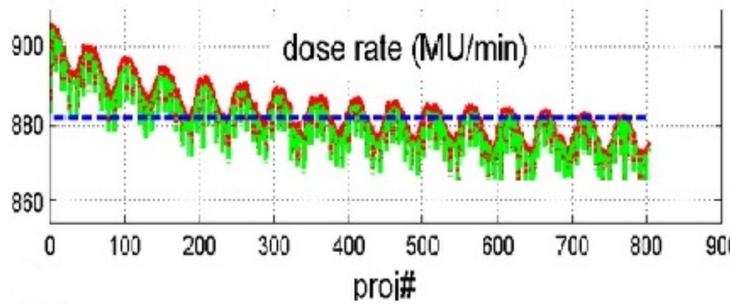
Claas Wessels,
PhD student, I.Curie

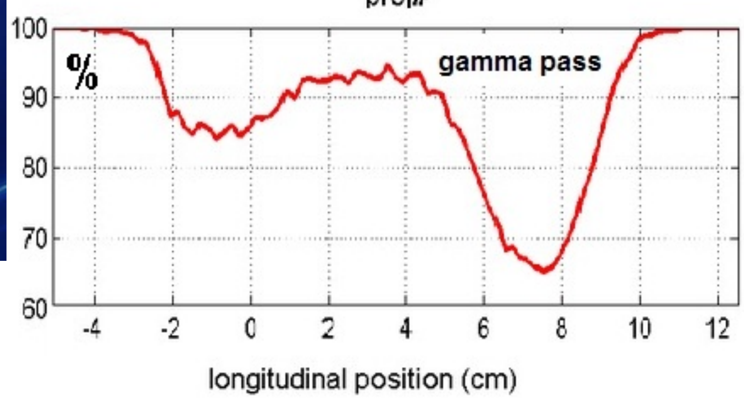
Uncertainties
In new techniques:
Rotational and protons











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1	20130826.	Yellow	Yellow	Green	
2	20130827.	Green	Yellow	Green	
3	20130828.	Yellow	Green	Yellow	
4	20130829.	Green	Green	Green	
5	20130830.	Green	Yellow	Yellow	
6	20130902.	Green	Green	Green	
7	20130903.	Yellow	Red	Red	Interr
8	20130904.	Green	Green	Green	
9	20130905.	Green	Green	Green	
10	20130906.	Yellow	Green	Green	
11	20130909.	Green	Green	Green	
12	20130910.	Green	Green	Green	
13	20130911.	Green	Green	Green	
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16	20130916.	Green	Green	Green	
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18	20130918.	Green	Green	Green	
19	20130919.	Green	Green	Green	
20	20130920.	Green	Yellow	Green	
21	20130923.	Green	Yellow	Red	Interr
22	20130924.	Green	Red	Green	
23	20130925.	Green	Green	Green	
24	20130926.	Yellow	Green	Green	
25	20130927.	Green	Green	Green	
26	20130930.	Green	Green	Yellow	
27	20131001.	Green	Green	Green	
28	20131002.	Yellow	Green	Yellow	
29	20131003.	Yellow	Green	Green	
30	20131004.	Green	Green	Green	
31	20131007.	Yellow	Green	Green	
32	20131008.	Yellow	Green	Green	
33	20131009.	Yellow	Green	Yellow	

Future Perspective in (Medical) Physics for Particle Therapy : Interactions

Domain of interaction	Contents, Concepts and Tools	Conclusions	Key Words
1. System Technology	# Compactness & New concepts # Heavier ions	*Technology drives cost reduction and larger accessibility. It must be evaluated in relationship with effectiveness, socioeconomic and ethical considerations.*	→ *Cost & Social*
2. Dosimetric issues and ancillary tools	**# Entrance/Neutrons/ Penumbra/ Uncertainties** **# IGRT, IMPT,…**	***Dosimetry and imaging tools provide macroscopic conformation. Tools are needed to warranty the accuracy and daily adaptation of treatment delivery. Mid and low doses become comparative factors.***	→ *Adaptive*
3. Clinical data			
4. Research and Development			

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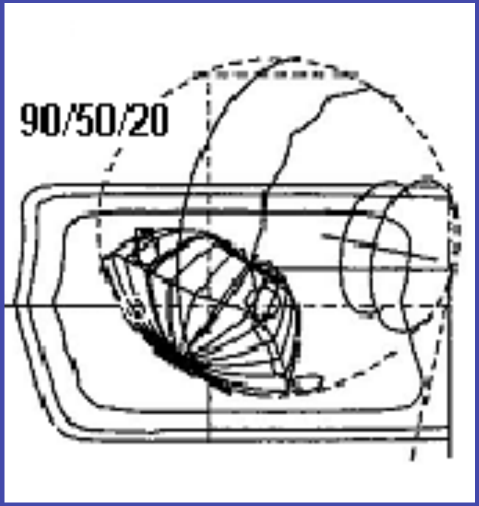
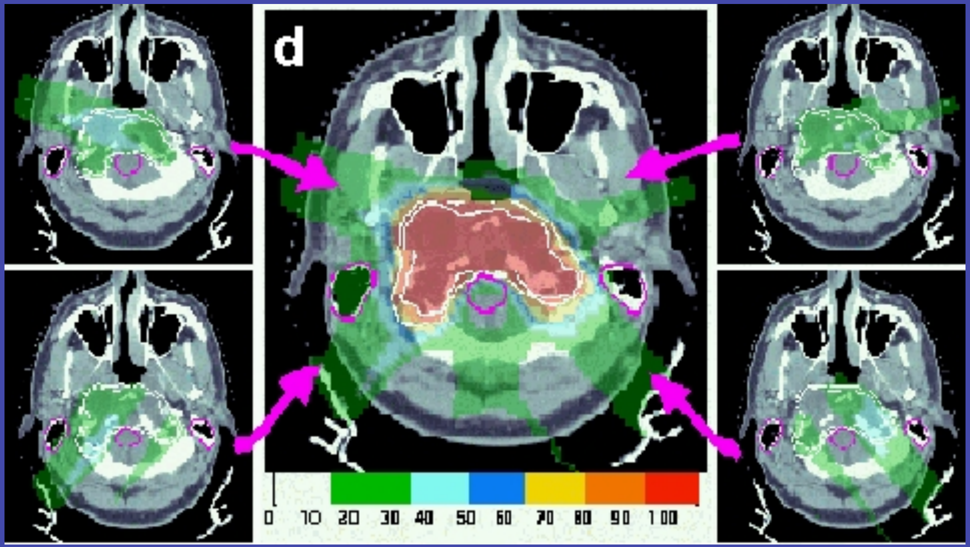
4. Research and Development			

CLINICAL SPECS (I)

« Accepted » Clinical Indications (protons):



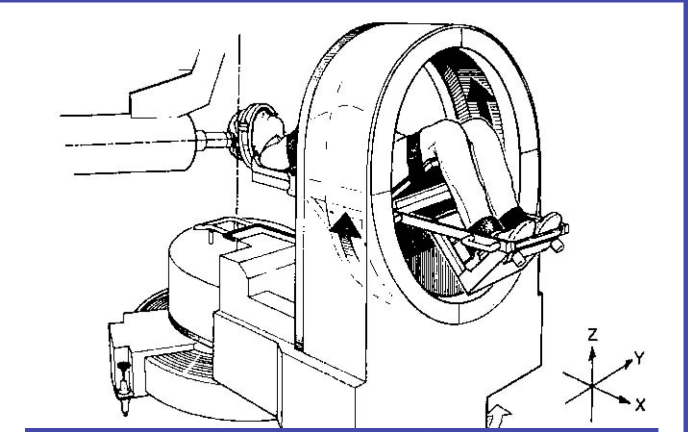
Uveal Melanoma



Base of the skull Chordomas & chondrosarcomas

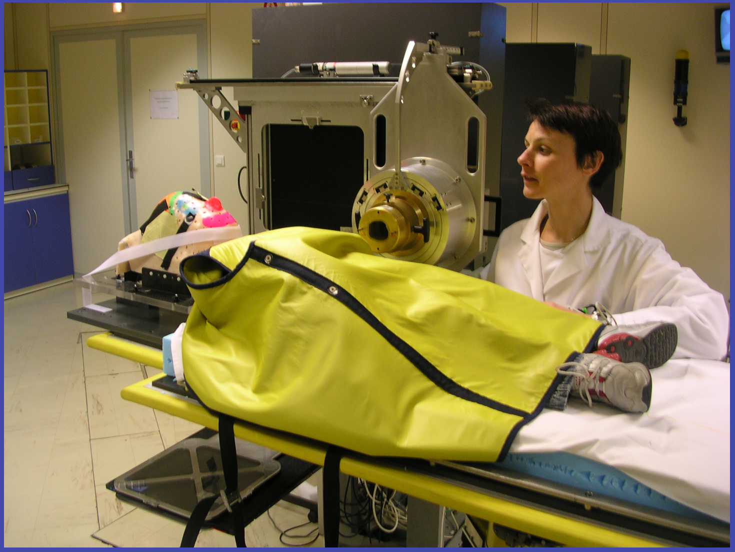
IMPT, Trofimov, Bortfeld (Boston), Lomax (PSI)

Radiosurgery (M. Boussiere, Boston)



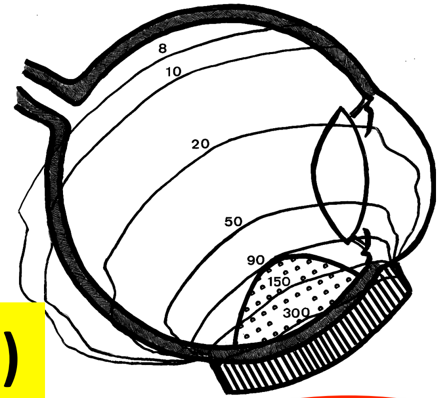
Dedicated lines?

Pediatrics

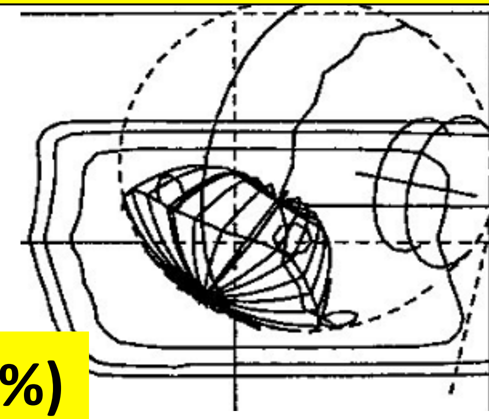


Classical and rare locations :
371 EYE treatments with radiation therapy, Institut Curie, 2015

I-125 Plaques



Protons



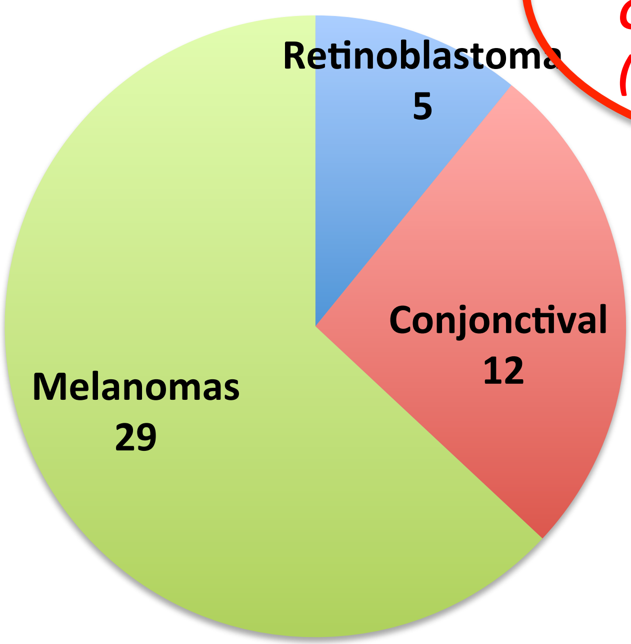
Total = 46 (12%)

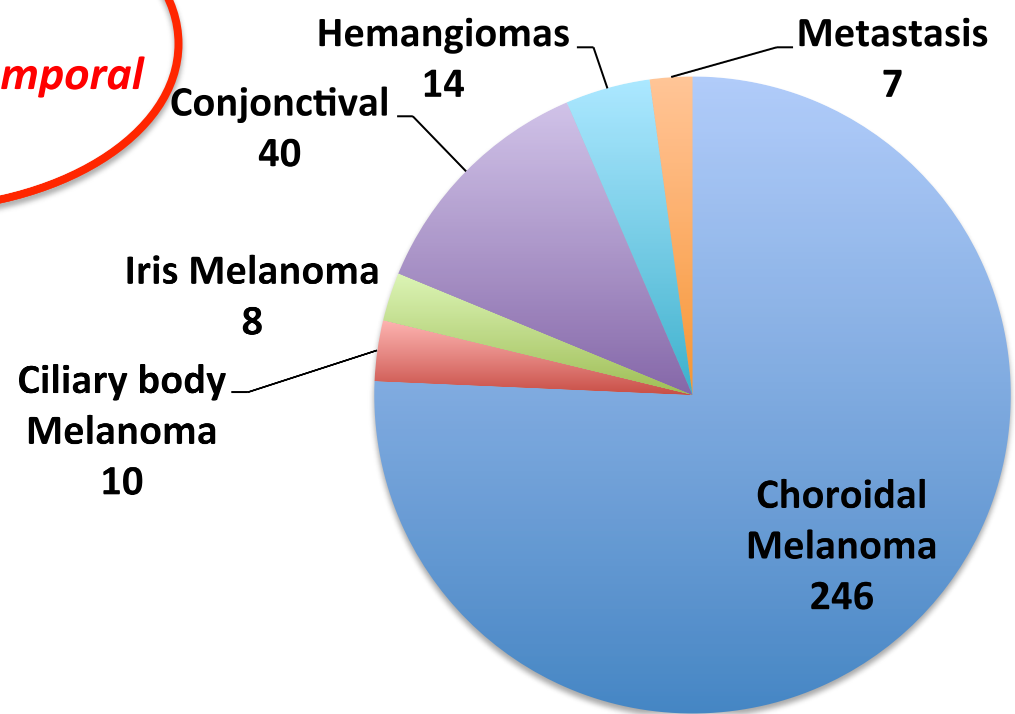
Total Melanomas = 29 (10%)

Total = 325 (88%)

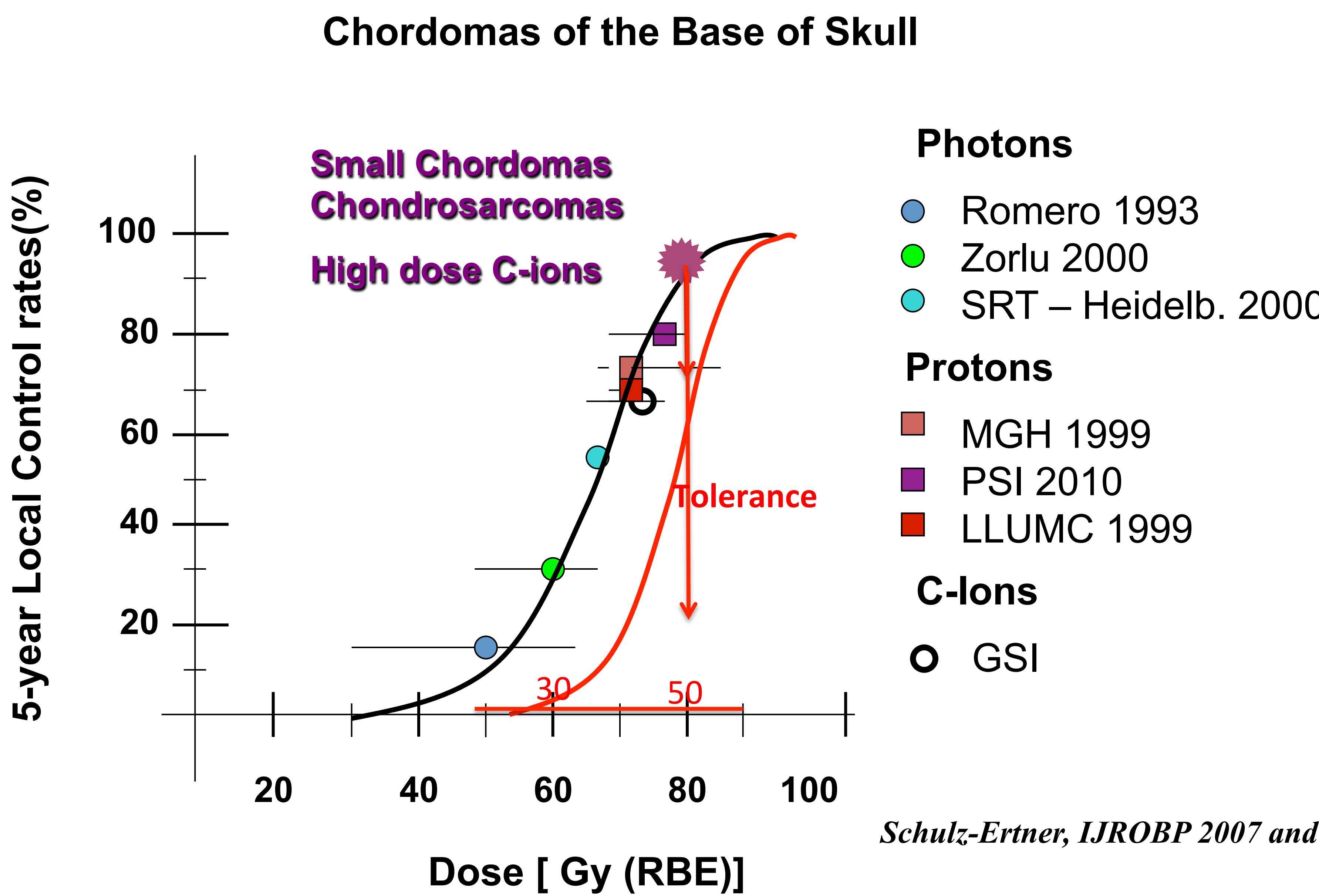
Total Melanomas = 264 (90%)

Petit Ant
Grand Ant-Temporal
(lacrimal)



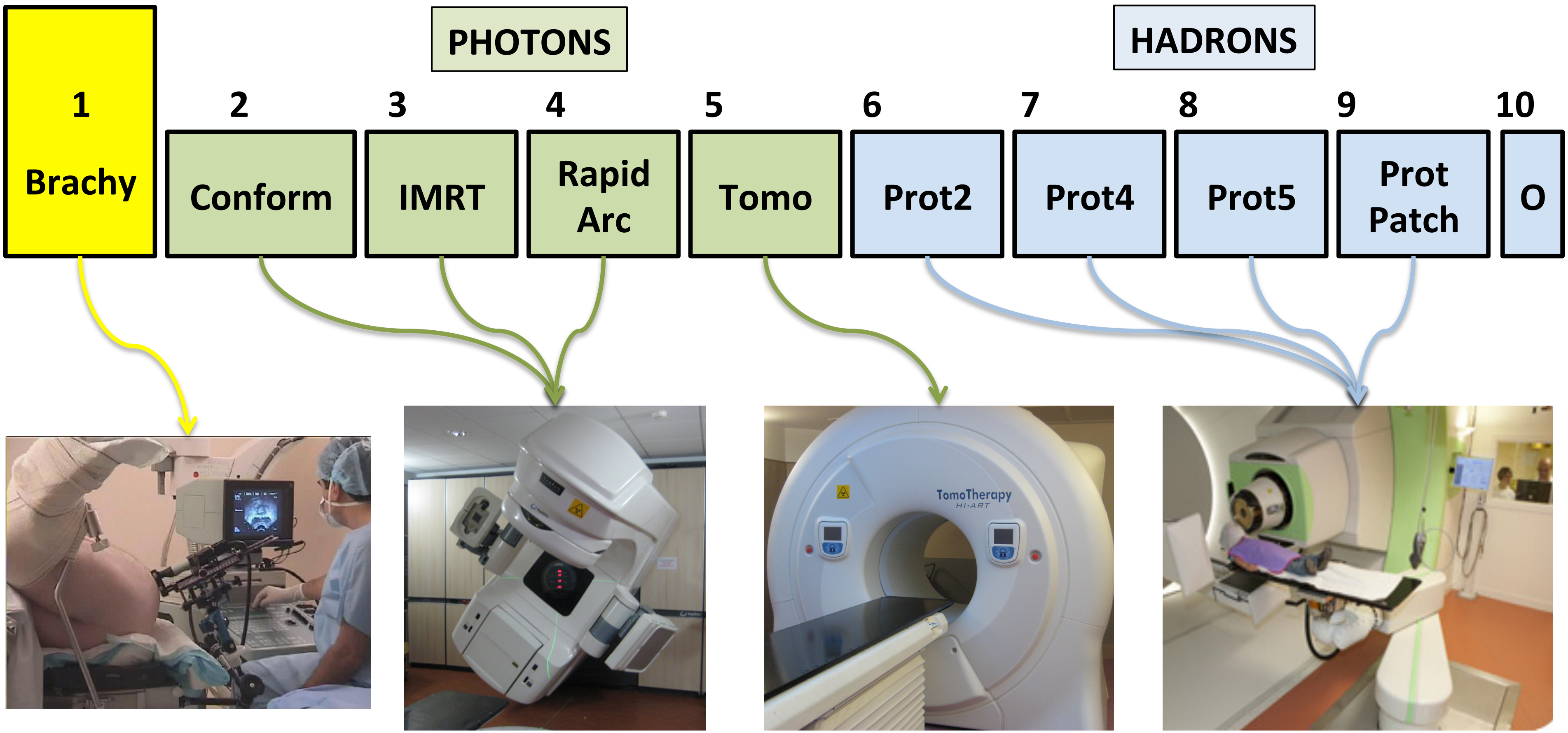


Local control
(photons, protons, carbon…)



Schulz-Ertner, IJROBP 2007 and

PROSTATE : Dosimetric comparisons for all cases: systems available at Institut Curie



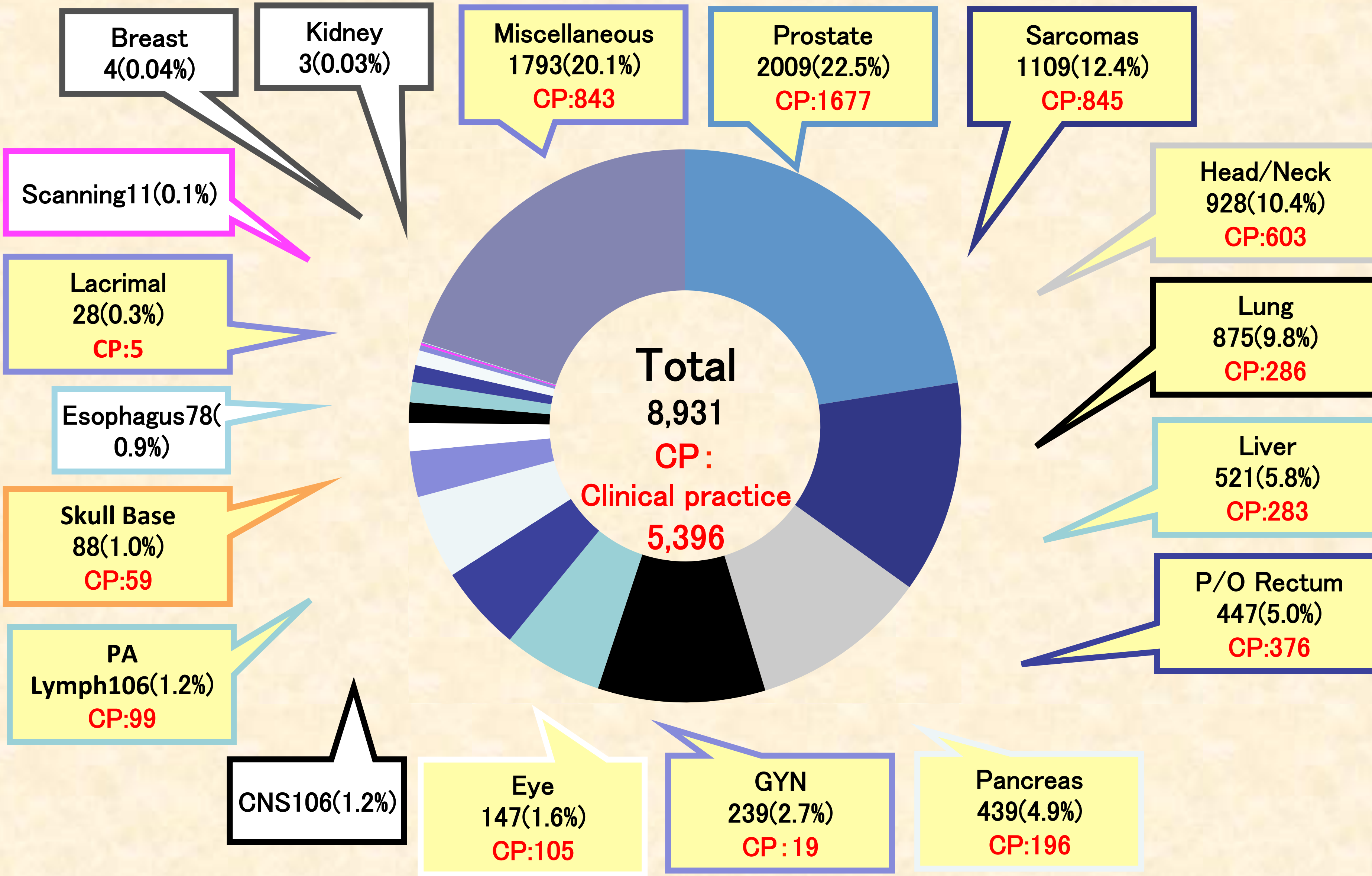
Transperineal Interstitial
Permanent implant
I-125 seeds

LinacVarian

Tomotherapy HD

IBA protontherapy

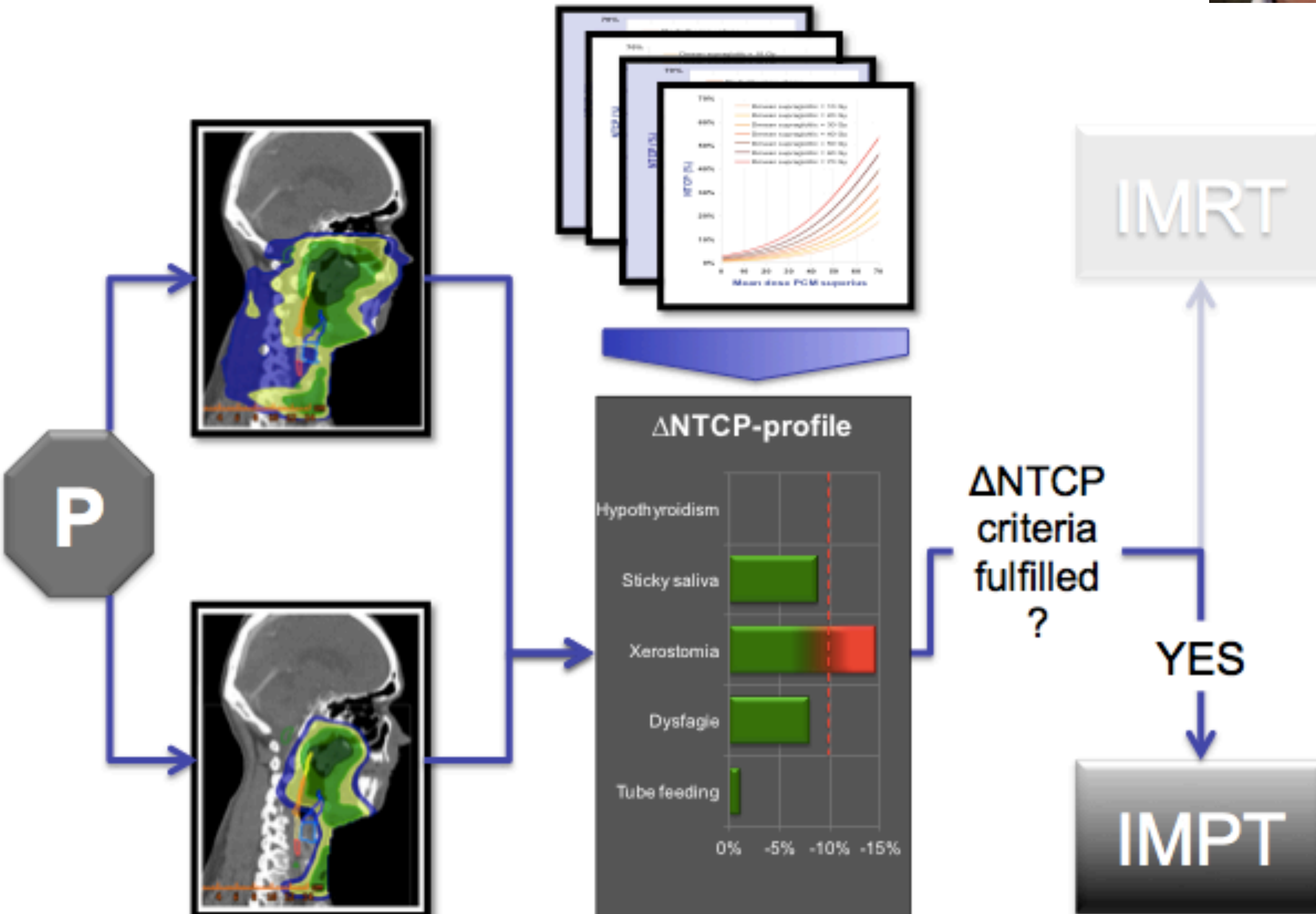
Patient Distribution Enrolled in Carbon Therapy at NIRS (Treatment: June 1994～March 2014)



Johannes (Hans) A. Langendijk UMC Groningen

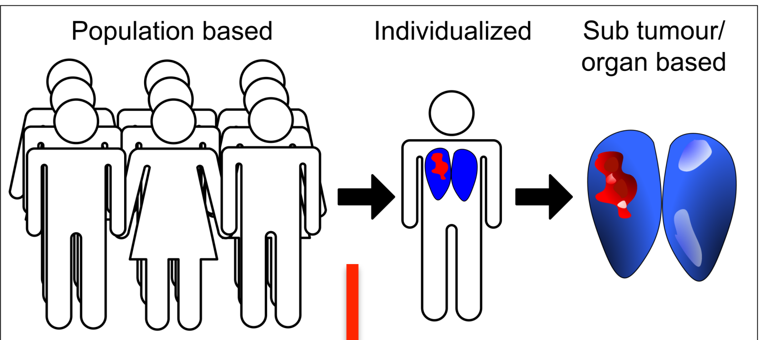
Model-based selection

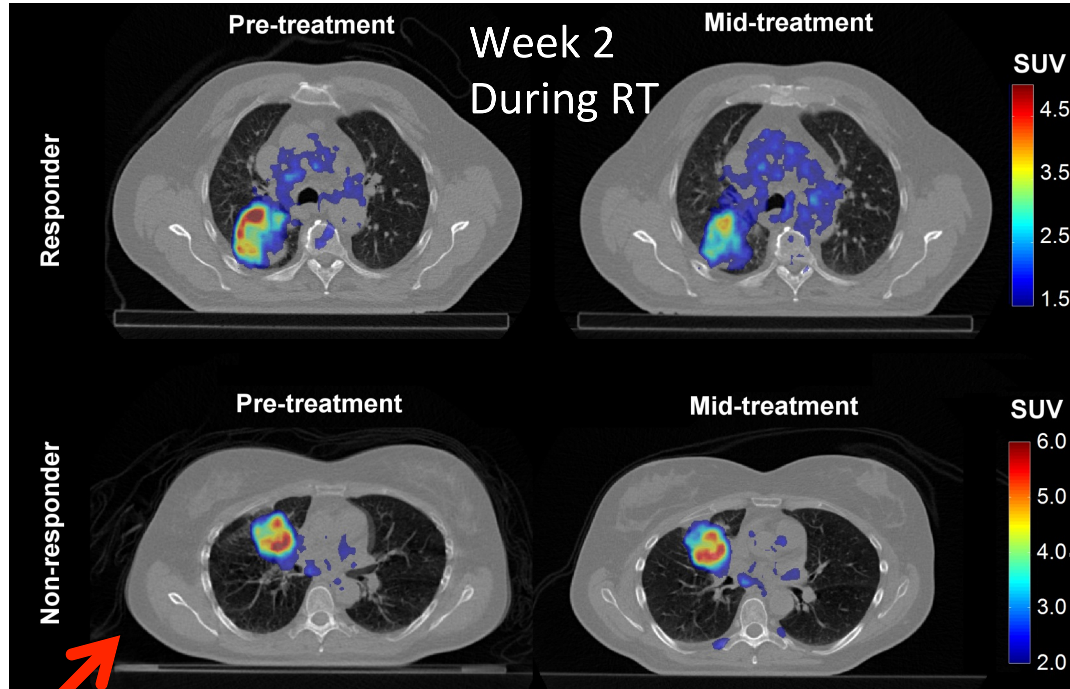
Decision support system



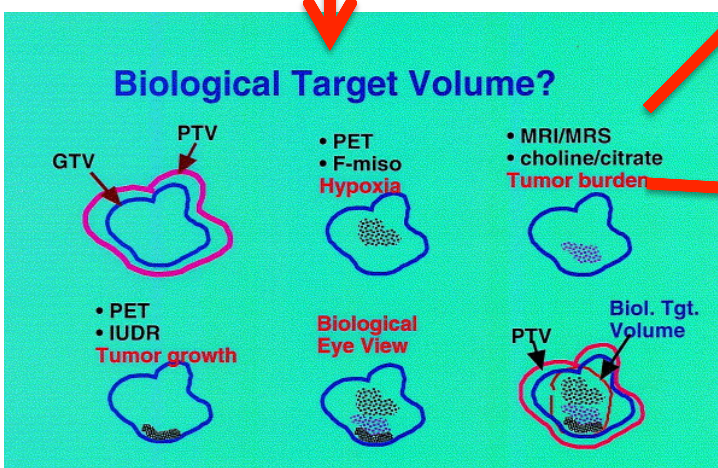
PET Guided Radiotherapy

Philippe Lambin,
Maastro, Belgium





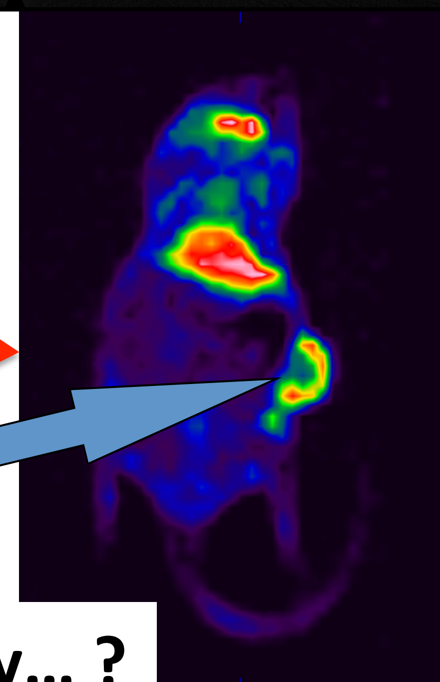
Van Elmpt et al



Ling et al

Drug Uptake
89Zirconium – Cetuximab

« Cold spot »:
Less Drug Uptake
(GTV_{LDU})



Aerts et al

From Dosimetry to Biometry… ?

Future Perspective in (Medical) Physics for Particle Therapy : Interactions

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4. Research and Development			

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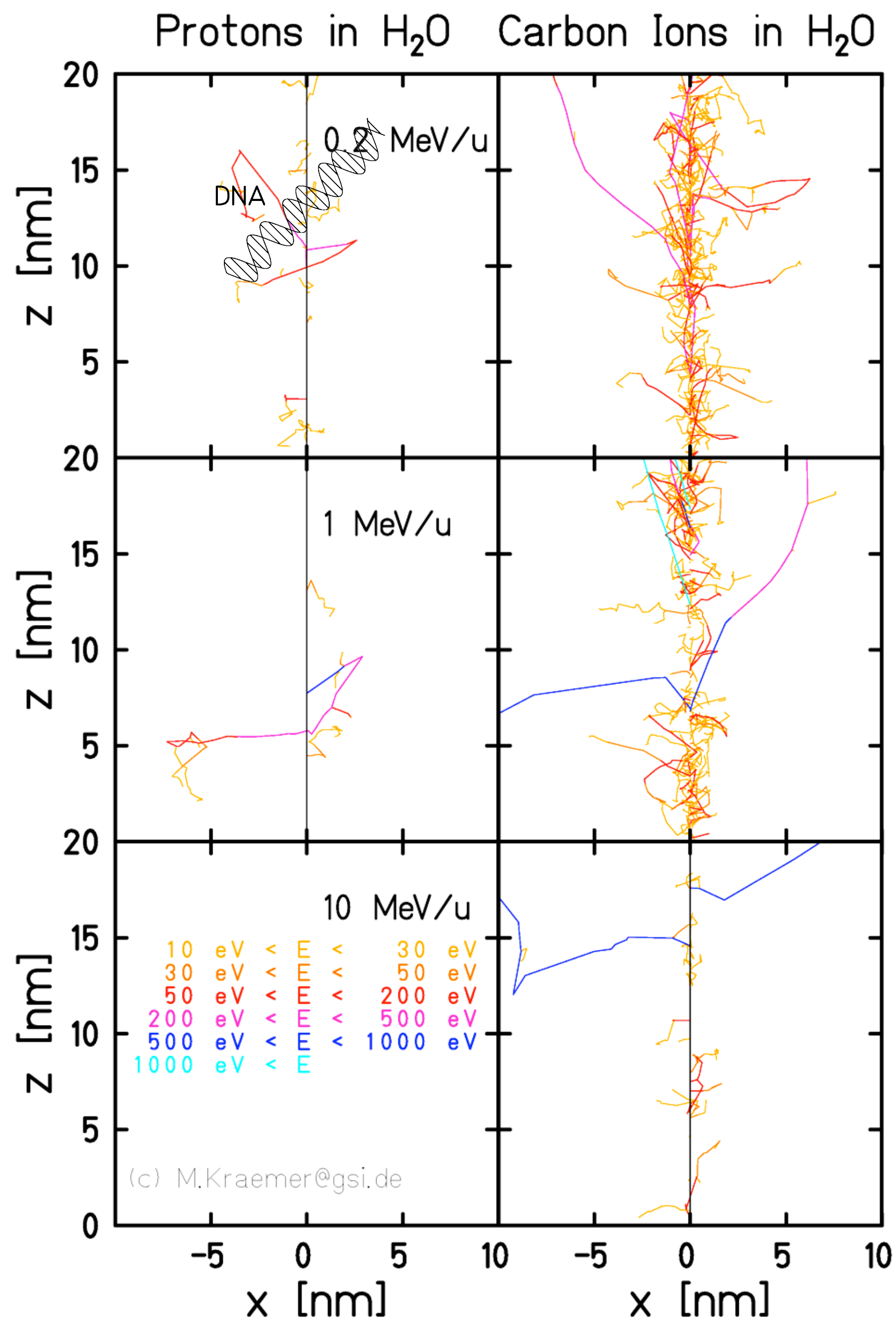
4. Research and Development	**# Models : from LET to RBE, BTV, TCP, NTCP, ….** **# Special techniques: microstrips, nano, flash,…**		

Radiation Biology:

Dose distribution
in
nanometer scale

Concept of RBE

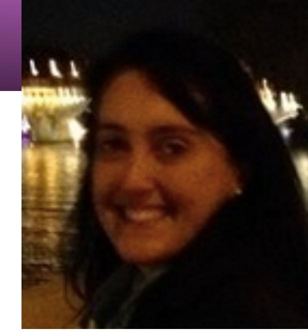


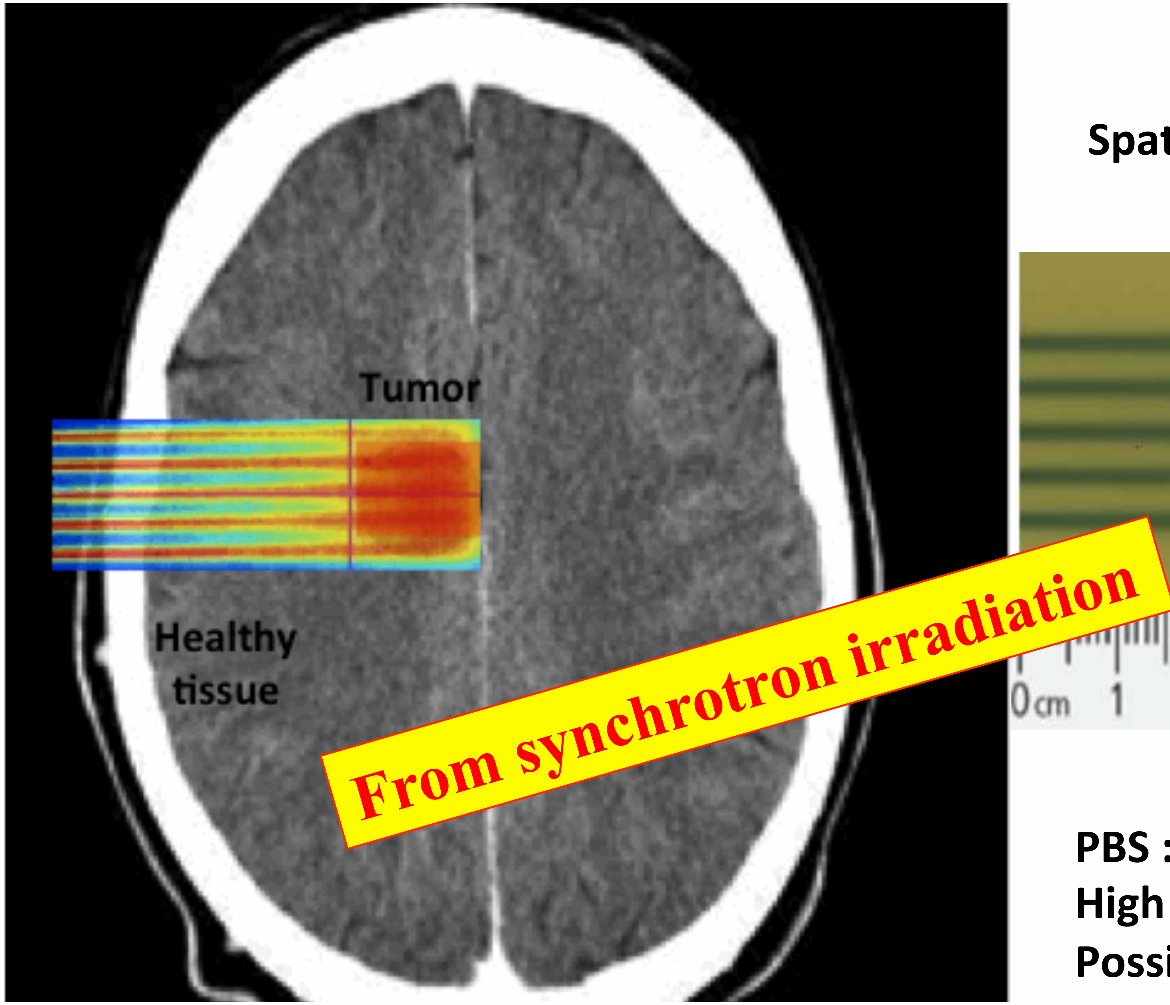
M. Kraemer

Proton MiniBeam Radiation Therapy (pMBRT)

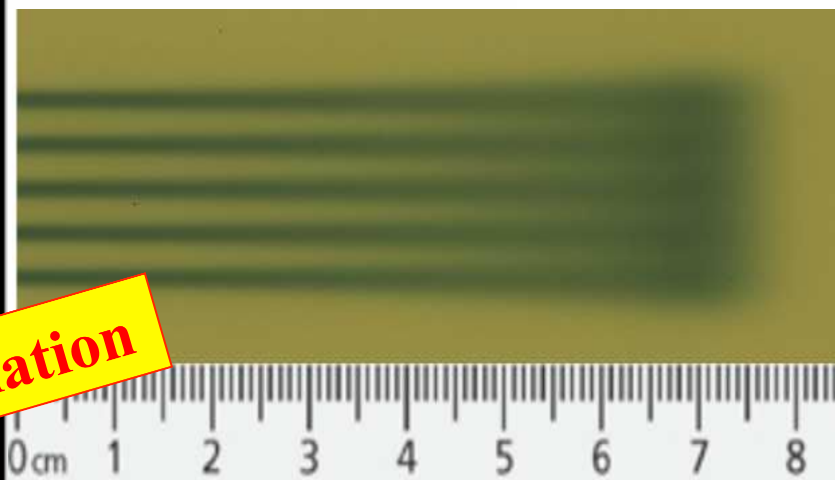
Theoretical concept :
Y. Prezado et al., Med. Phys. 2013

Experimental beam :
CPO Mai-Juin 2014





Spatial distribution



PBS : without collimators,
High peak-valley ratio, no neutrons
Possibility to modulate intensity…

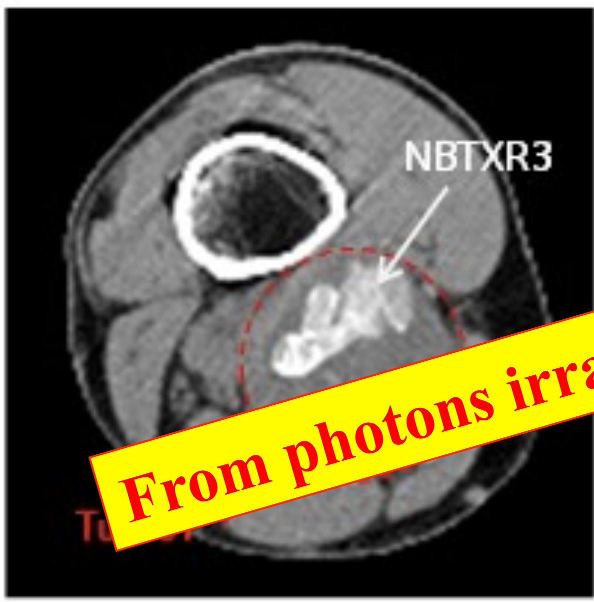
(France Hadron)

Painting target volumes injected with nanoparticles ?

Phase I : NBTXR3 + 50 Gy Rx

CT scan - 24h post IT injection- Day 2

Myxoid liposarcoma
Tumor volume: 1814.4 cc
NBTXR3 volume: 45 mL (2.5%)



From photons irradiation

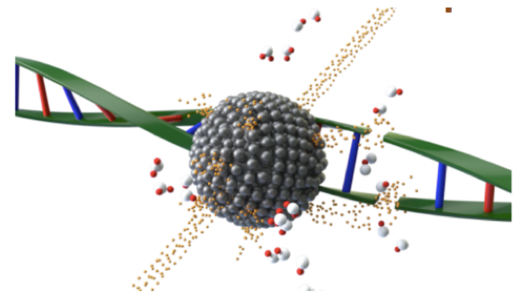
ASCO, 2014
http://www.nanobiotix.com/news/release/

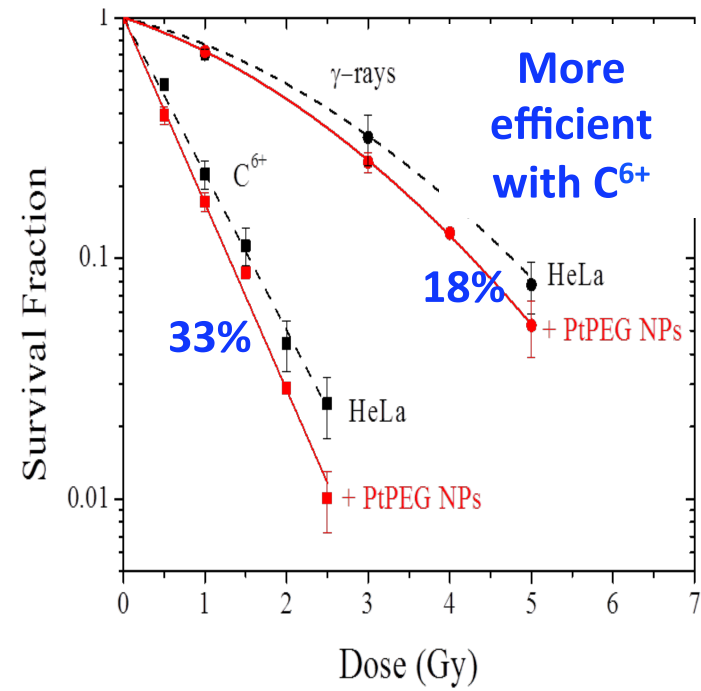
ISMO

Sandrine LACOMBE

Erika PORCEL

UNIVERSITÉ PARIS SUD



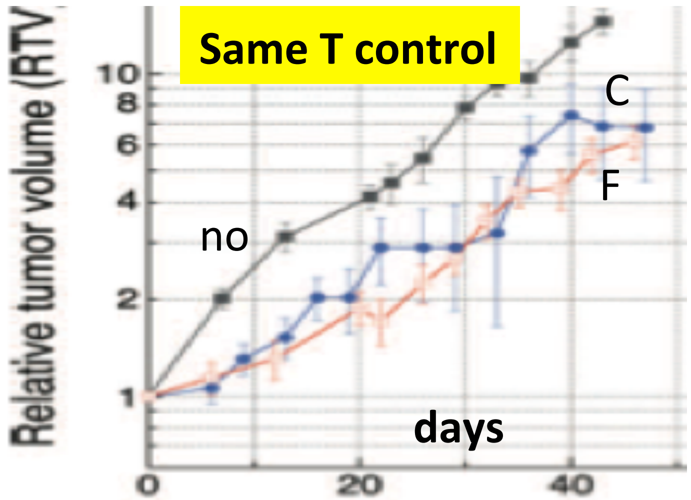


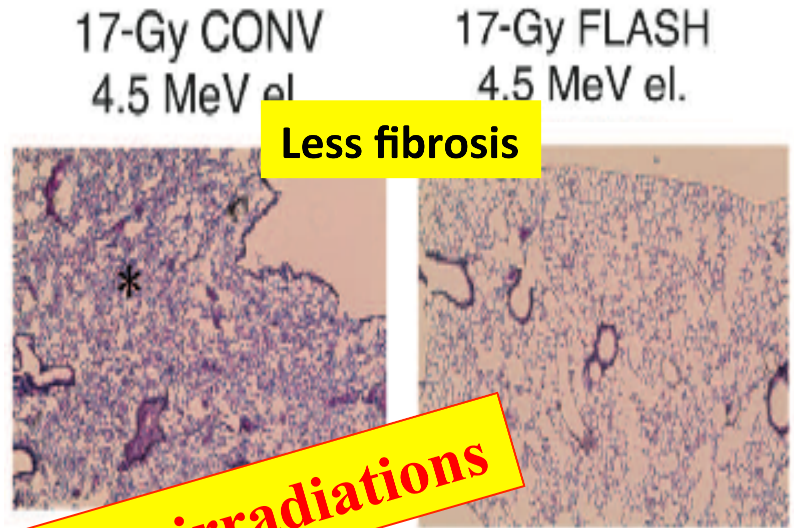
Porcel et al, Nanomedicine: Nanotechnology, Biology and Medicine 2014

Jong-Ki Kim et al // in vivo protons
2012 Phys. Med. Biol. 57 8309

“FLASH –Effect” Ultrahigh dose-rate FLASH irradiation

Sci Transl Med 16 July 2014



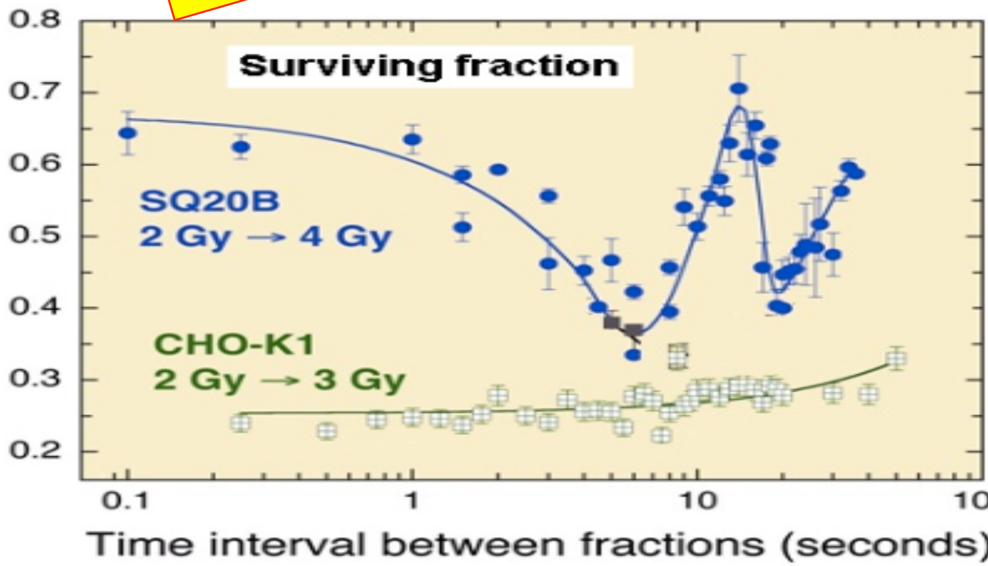


Vincent
Favaudon

From electrons irradiations

“W-Effect”: Early ce… …se to split-dose irradiation

Ponette et al. (2000) Int J Ra… …l 76: 1233-43 - Fernet et al. Int J Radiat Biol 76: 1621-29



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Future Perspective in (Medical) Physics for Particle Therapy : Interactions

Domain of interaction	Contents, Concepts and Tools	Conclusions	Key Words
1. System Technology	# Compactness & New concepts # Heavier ions	*Technology drives cost reduction and larger accessibility. It must be evaluated in relationship with effectiveness, socioeconomic and ethical considerations.*	→ *Cost & Social*
2. Dosimetric issues and ancillary tools	# Entrance/Neutrons/ Penumbra/ Uncertainties # IGRT, IMPT,…	*Dosimetry and imaging tools provide macroscopic conformation. Tools are needed to warranty the accuracy and daily adaptation of treatment delivery. Mid and low doses become comparative factors.*	→ *Adaptive*
3. Clinical data	# Series, knowledge based and trials (from silico to randomized) # Genomics, panomics	*Clinical data (large series of patients, clinical trials and personalized approaches) is required to find the place of particle therapy.*	→ *Big (Clinical) Data*
4. Research and Development	**# Models : from LET to RBE, BTV, TCP, NTCP, ….** **# Special techniques: microstrips, nano, flash,…**	***Research in Radiation Biology is required to understand the effects and optimize new approaches. It is mandatory for the use of heavy ions.***	→ ***(Radio) Biology***

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Photons : "classical"

Jan Brueghel: L'ouïe

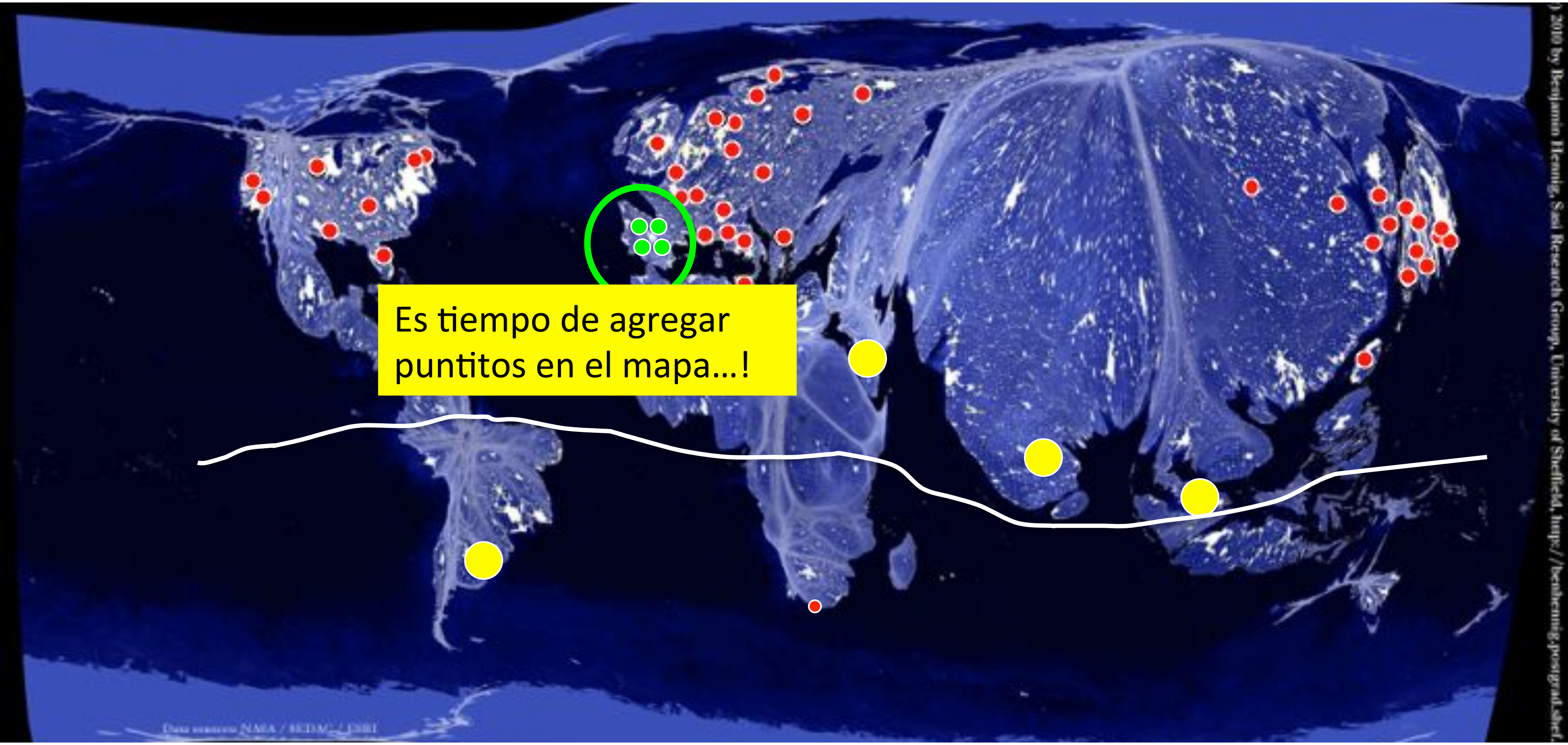
Protons:
"State of the art
in conformation"

Magritte :
Femme à la fenêtre

Ions:
"biological
Avant-garde"
"

Picasso :
La table
devant la fenêtre

Between photons and ions, the perspective of physics is in agreement with a "proton therapeutic window" (5%?, 10%?, 50 %?) that will evolve and still needs to be optimized



Original From Bill Chu, PTCOG 50, USA
Updated for this talk by AM , 2016

Perspectivas futuras en Física (Médica) para la Terapia con Partículas :

"Relaciones"

Primer Workshop Español de Relaciones Humanas en Protonterapia

GRACIAS!

PREGUNTAS ?

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