Physics in hadrontherapy:

From photons to Pan-omics, through biology for clinics, and $pecific challenge$

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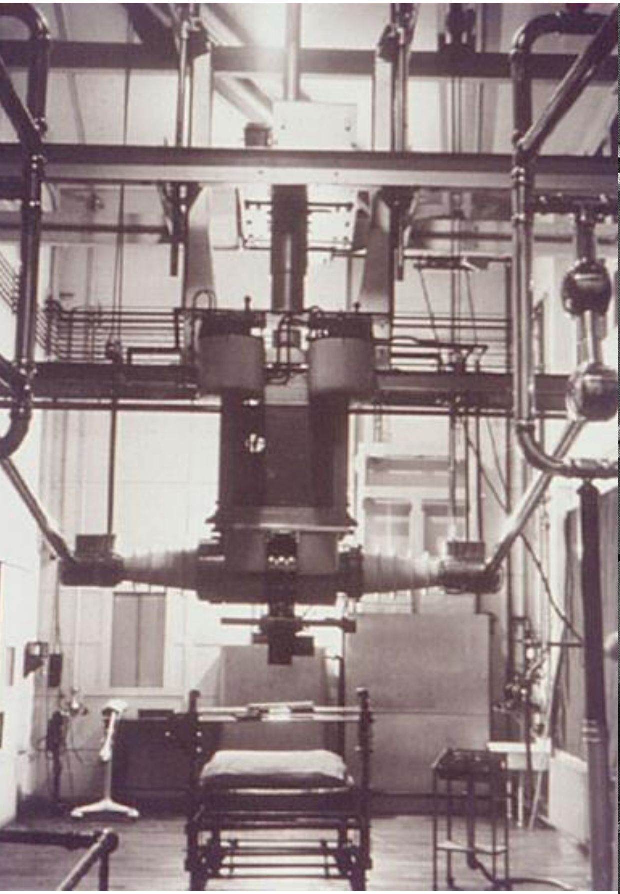
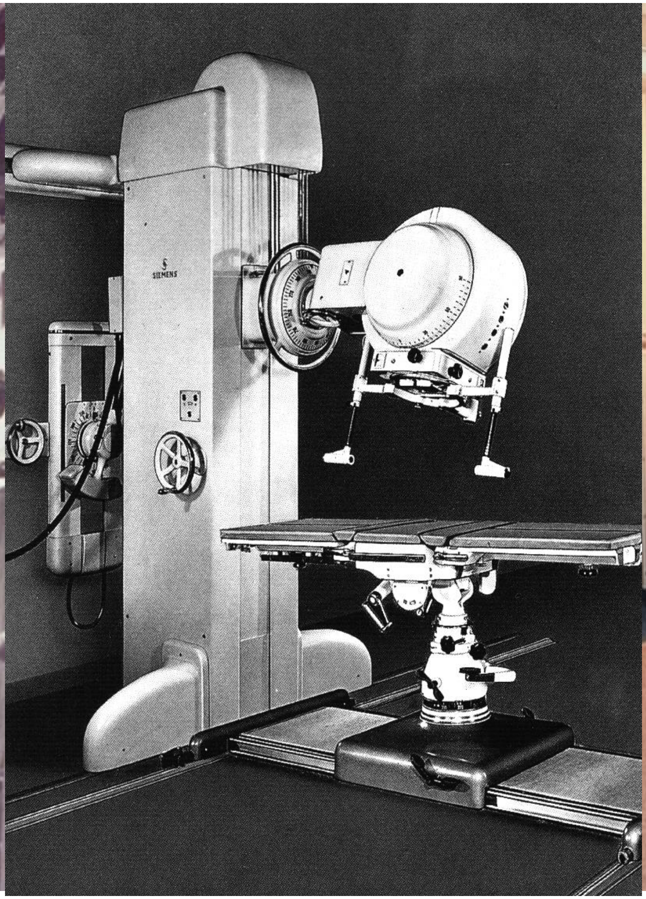
***2nd CERN brainstorming meeting
Divonne, 20th February 2016***

institutCurie

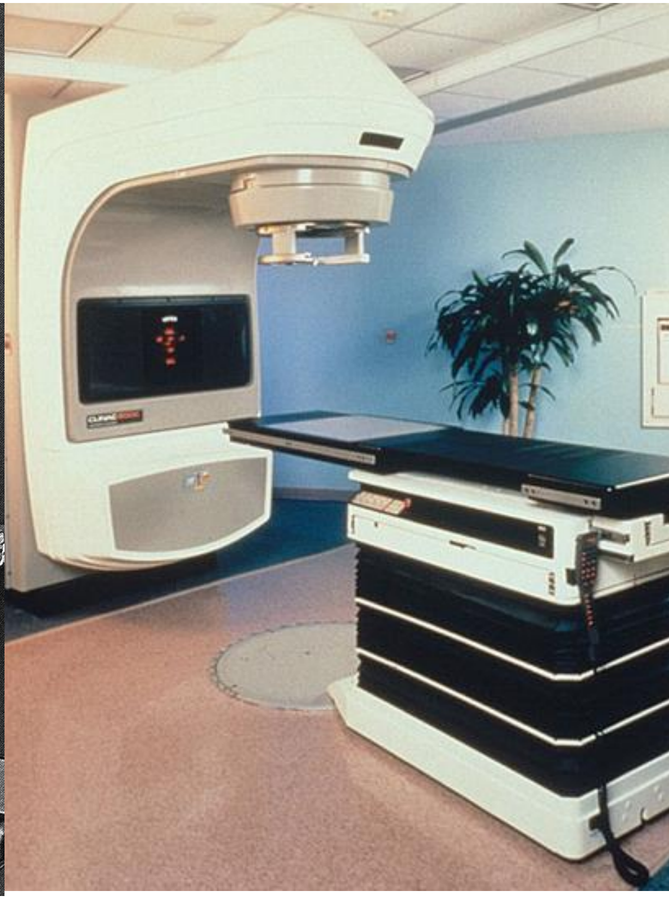
From the history of technology for radiation therapy with photons and electrons…



600 kV- Years' 30

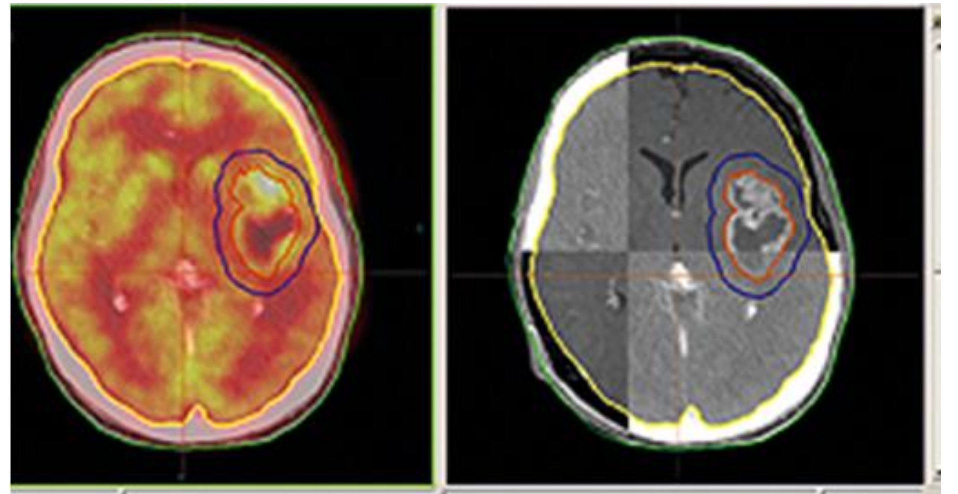


Gammatron
Siemens 1956
Cs-137 et Co-60
(1 MeV)

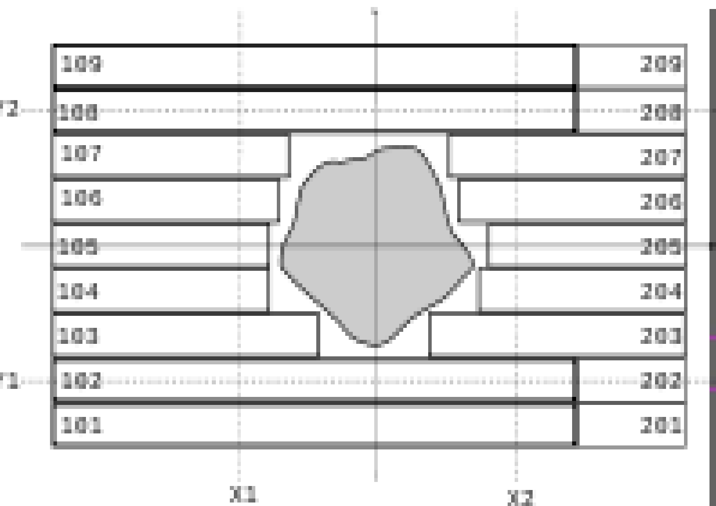


Linear Accelerators (ex.Varian)
(4-25 MV)

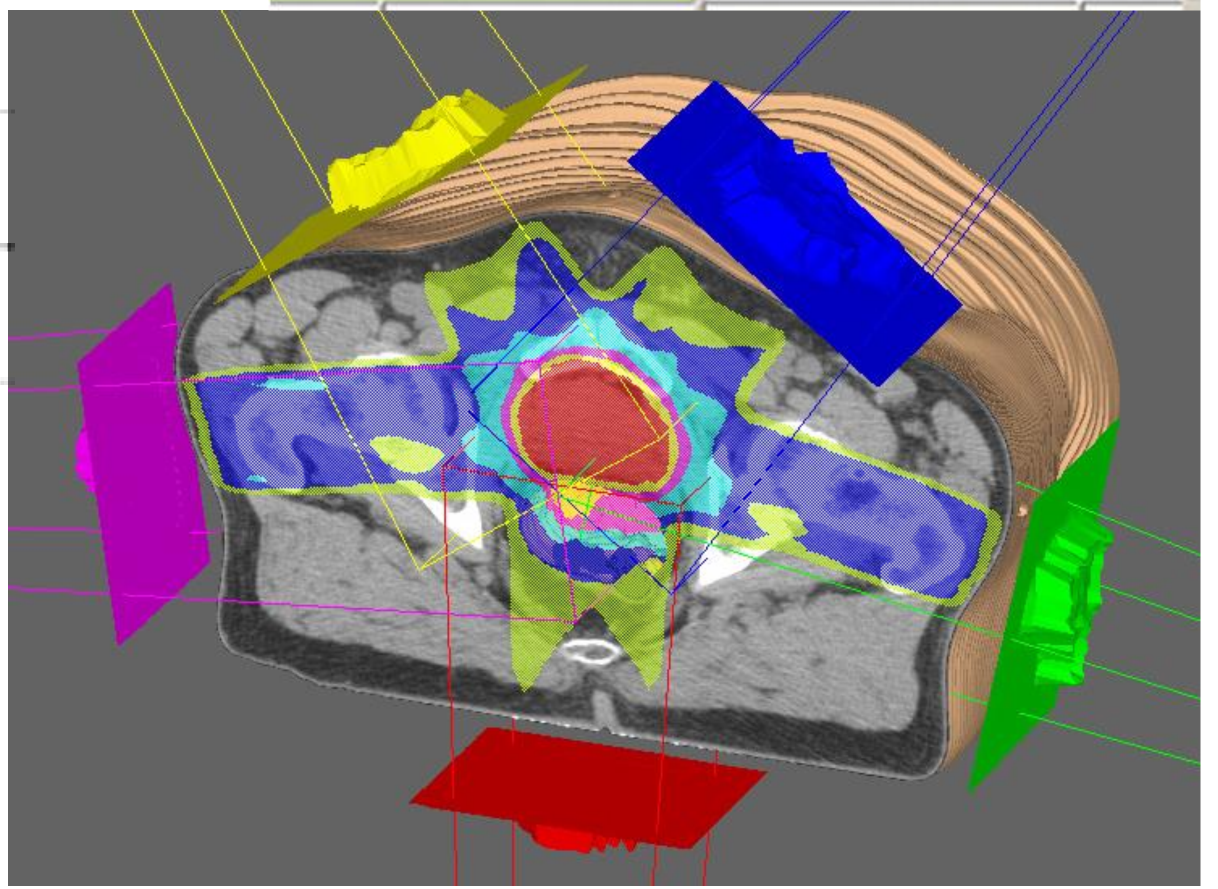
Evolution of software and hardware tools



Multimodality **imaging** including functional: registration, fast automatic segmentation,…



Multileaf_collimator
https://en.wikipedia.org/wiki/



Inverse Planning & IMRT
radiation-therapy-imrt.html
http://www.noyodecia.com/

Physics and technology: **Present delivery systems in external radiation therapy**

Varian : 4 Pi
Elekta : on line MRI

RapidArc or equivalents (wphospitals.org; www.varian.com; www. Elekta.com)

Cyber: MLC

Cyberknife
www.cyberknife.com

"state of the art" in photons ?

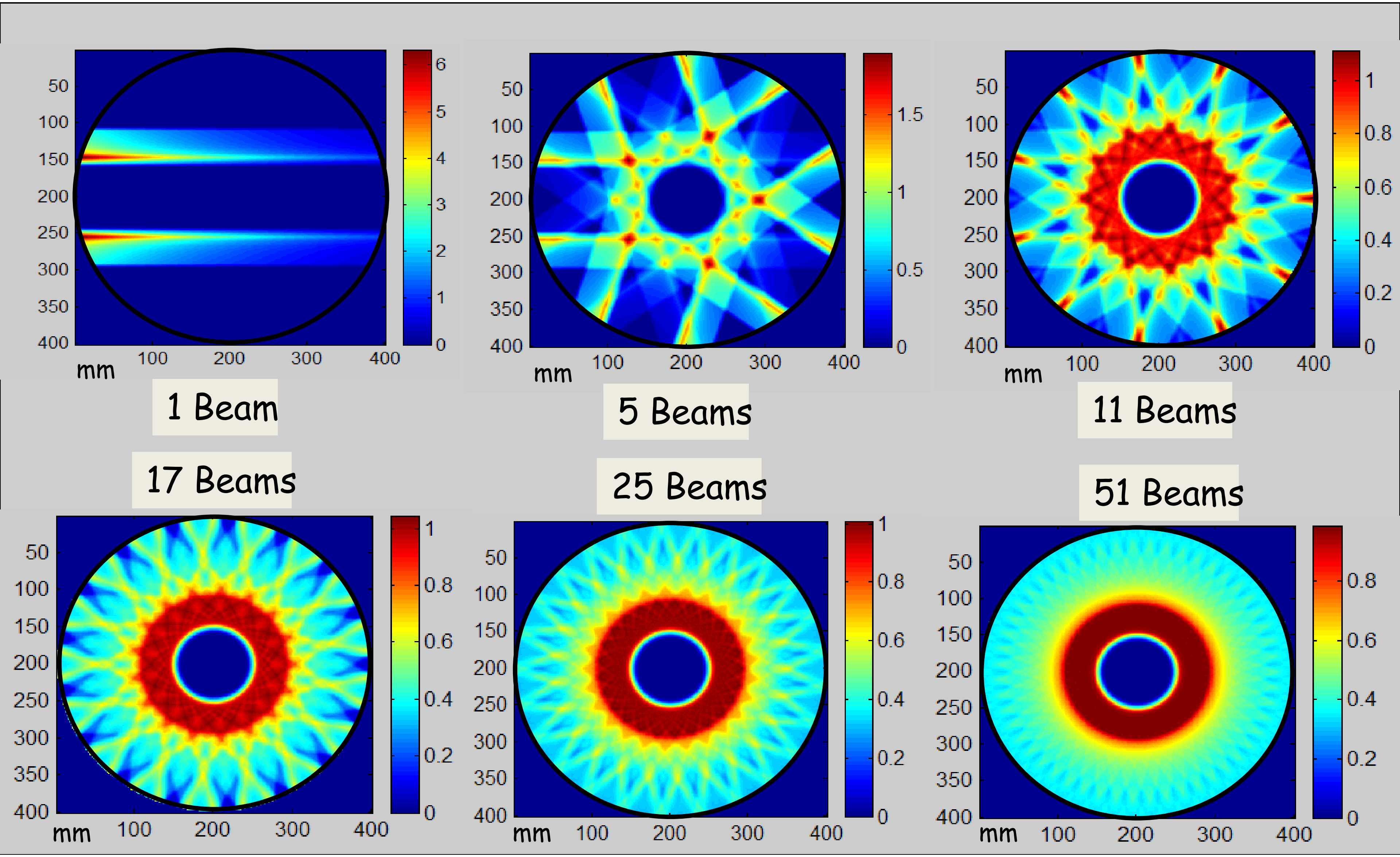
Tomo : soon

Tomotherapy
[www.tomotherapy.com]

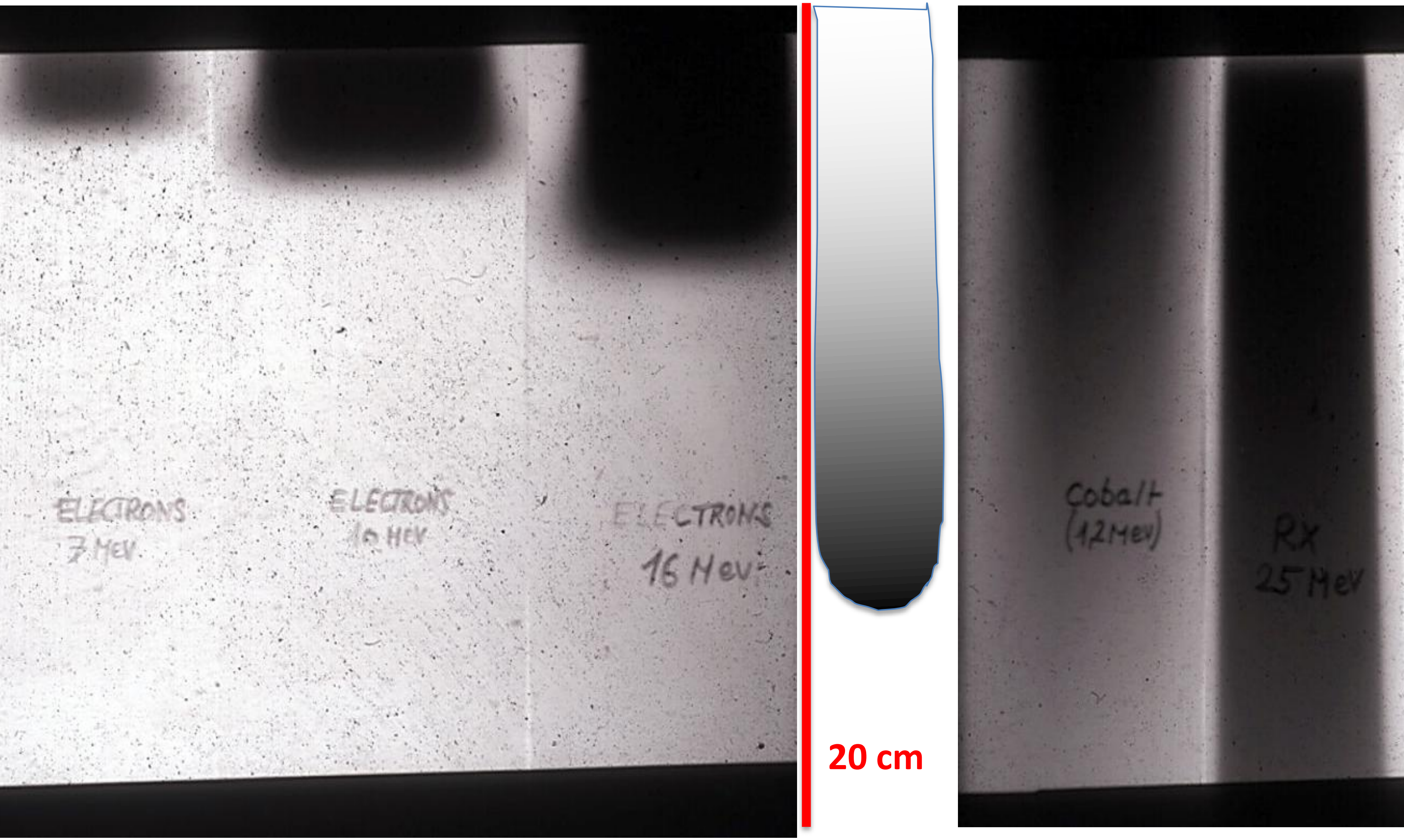
Vero
[www.brainlab.com]

ViewRay (MRI+3Co-60)
[www.viewray.com]

Multiplicity of incidences// changing the role of the energy (from Tomotherapy)



Electrons Protons/Ions Photons



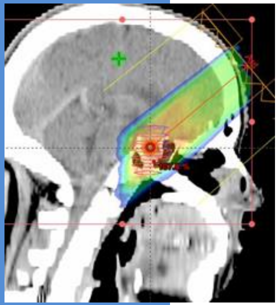
Much more than just "filling the gap"… ! :

Court J-C.Rosenwald. I. Curie

Hadrontherapy : Physical selectivity and/or Radiobiological effects

* pions
* fast
& slow neutrons

(Past)

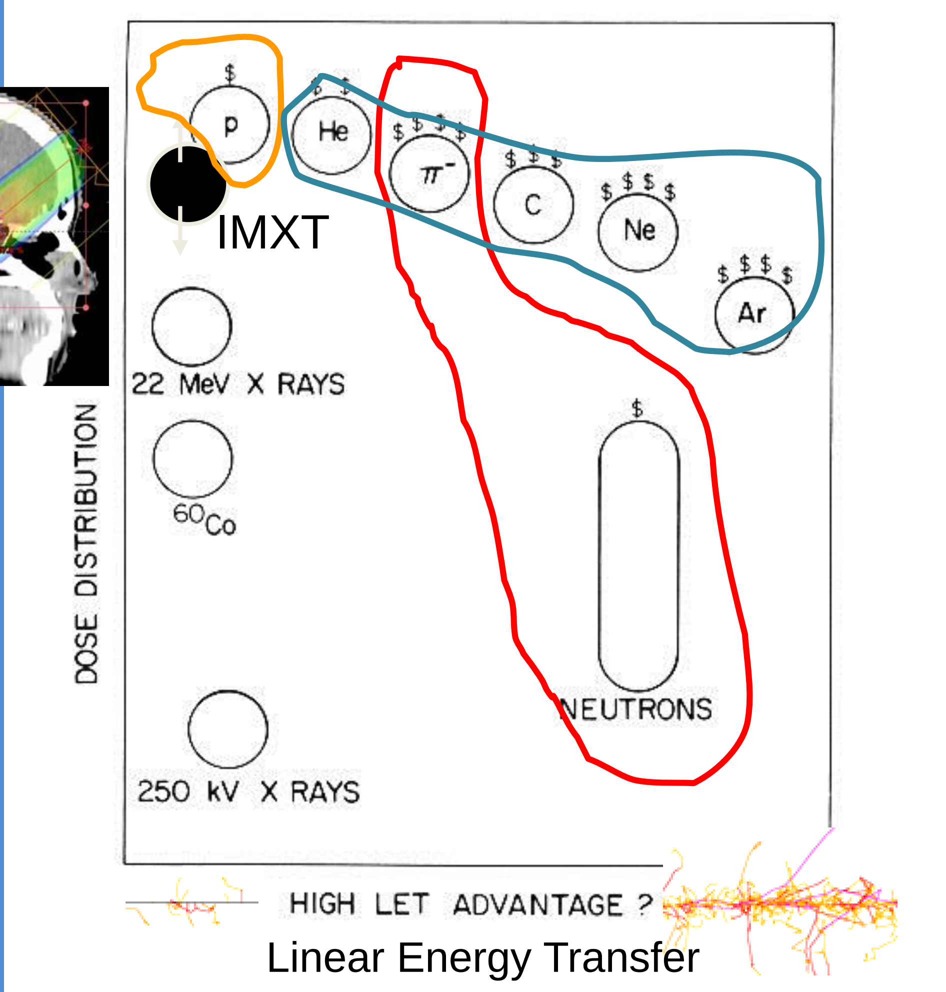


* protons

(Present)

* light and heavy ions

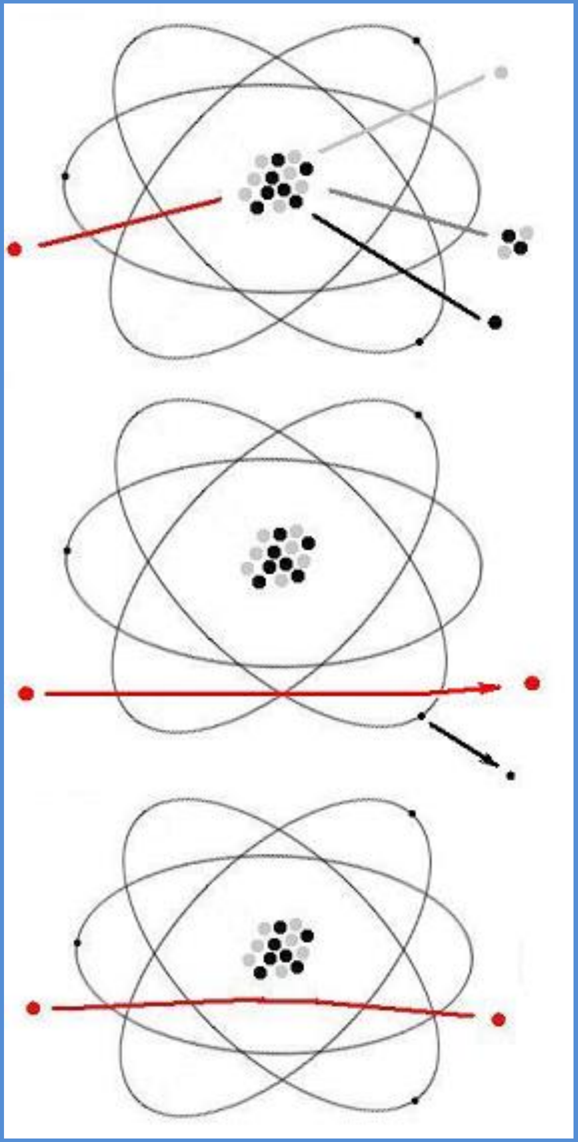
(Future ?)



A. Koehler in [Raju. 1980]

Hadrontherapy: some very basic physics

Many interactions of particles with matter … but keep 3 :

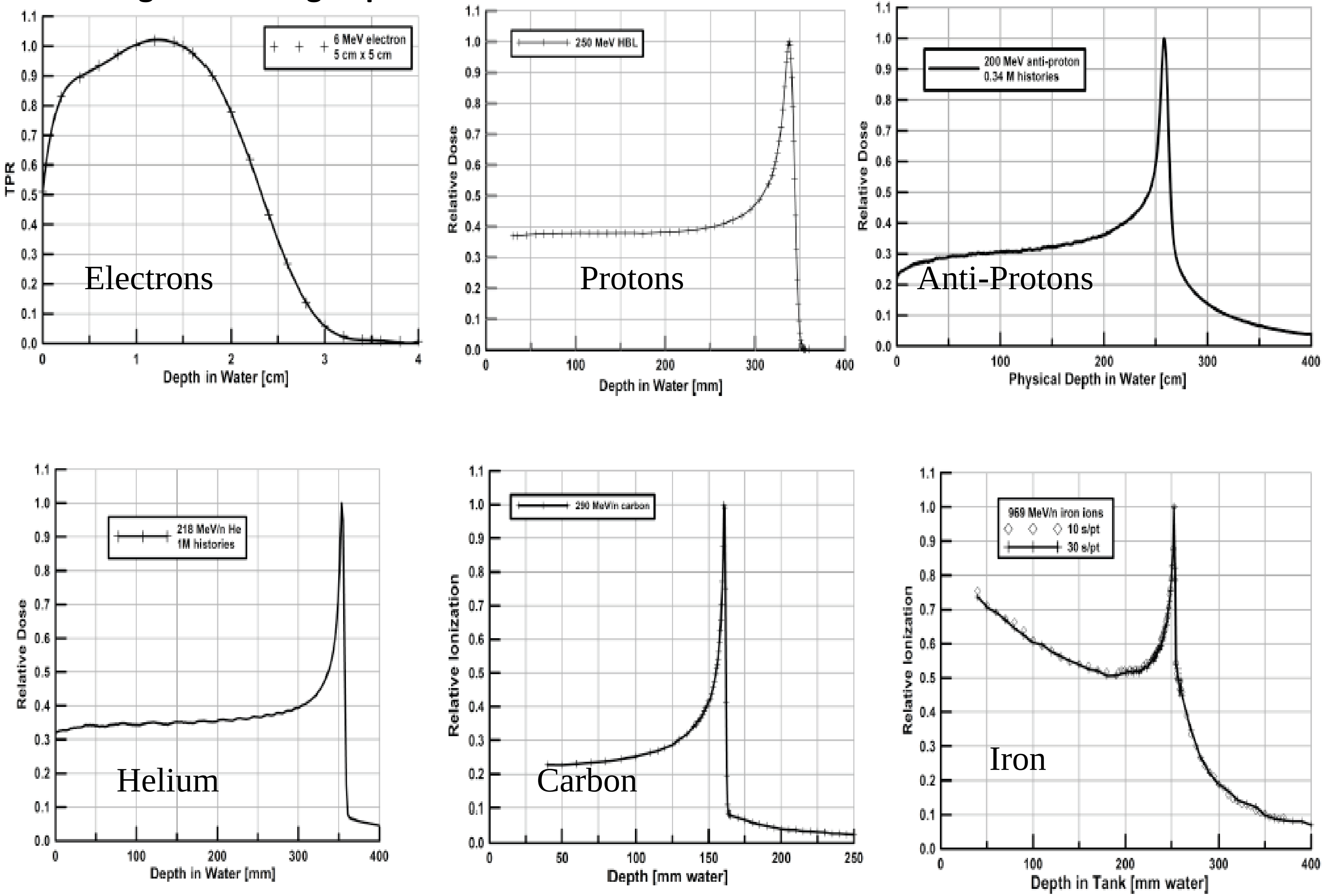


Inelastic collision w/nuclei :
neutrons, activation, fragments…

Inelastic collision with electrons: Dose

Elastic collision w/nuclei:
« multiple Coulomb scattering » :
+ Scattering foils,
- penumbra, distal edge,…

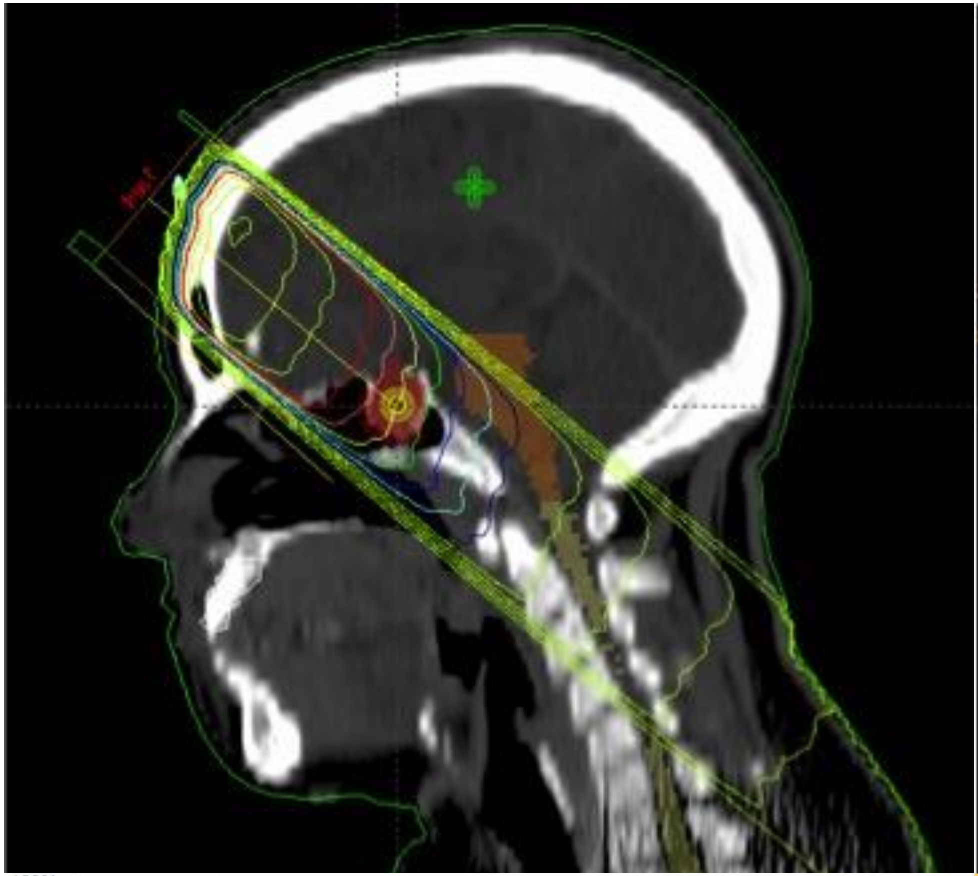
Finite Range = all charged particles

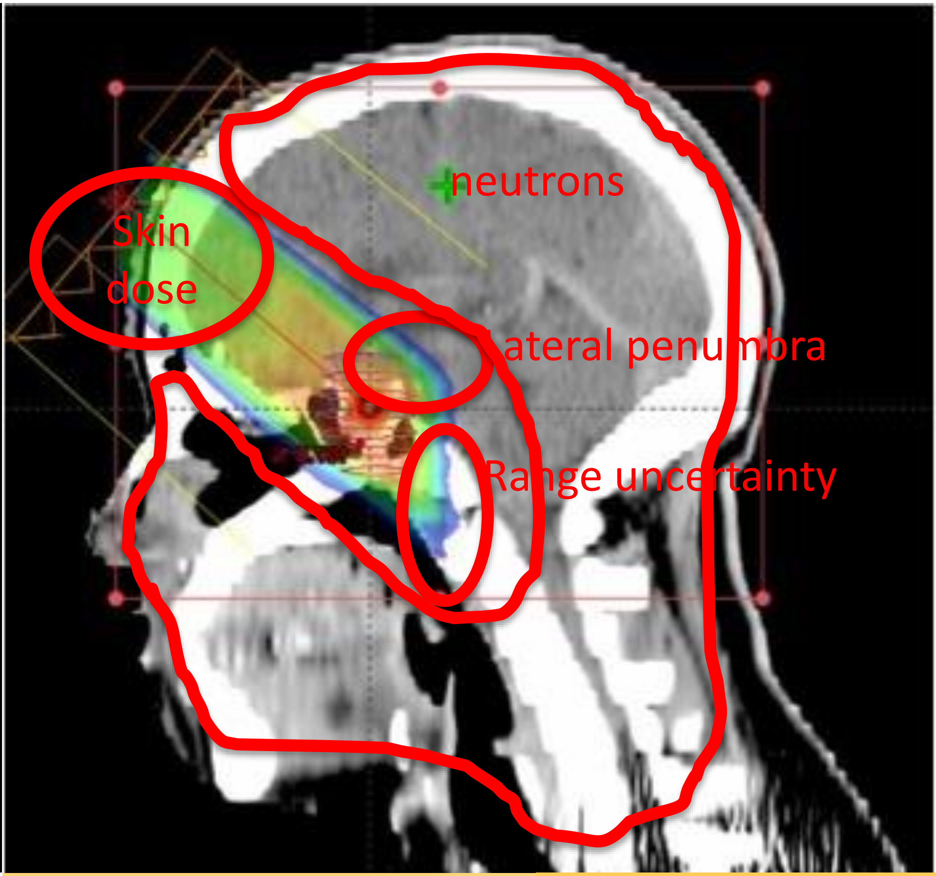


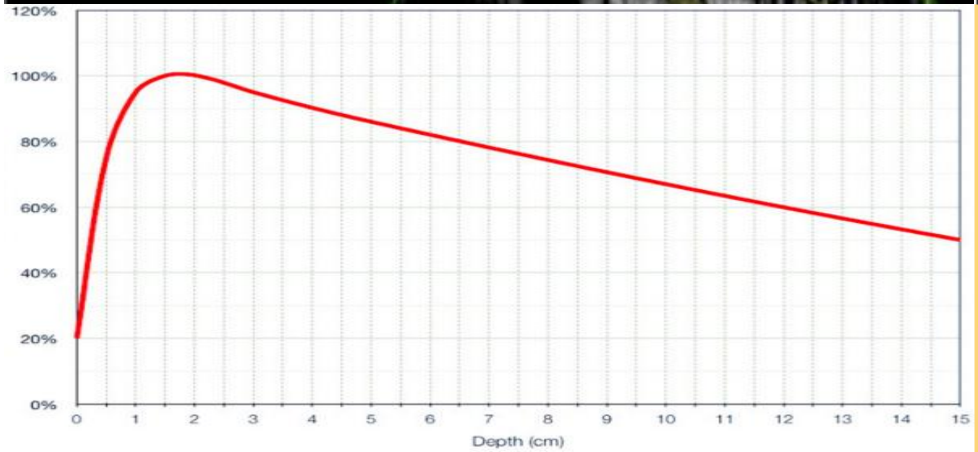
Moyers

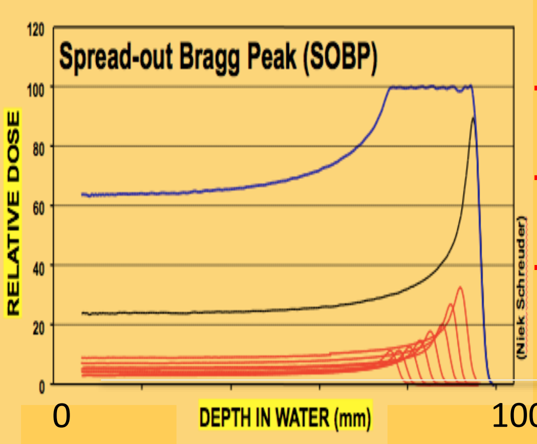
PTCOG 2008

Clinics : ex Photons vs protons (1 beam) physics advantages







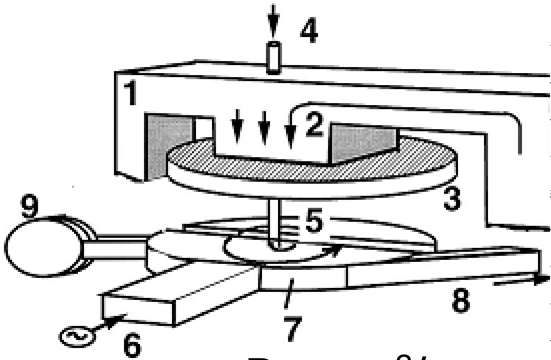


... and limits (just the physical ones

(Hadrontherapy for the physicist) :

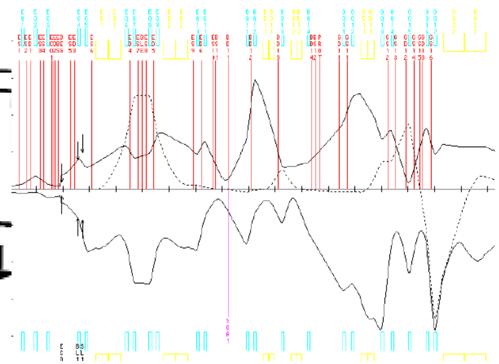
Physical "frame" to optimize the physics of hadrontherapy (some examples) :

Accelerators

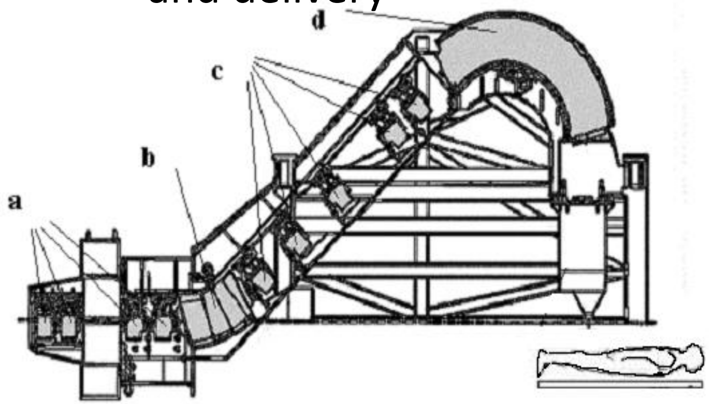


$q.v.B = mv^2/r$

Beam transport

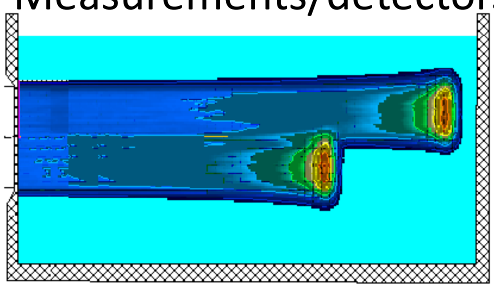


and delivery

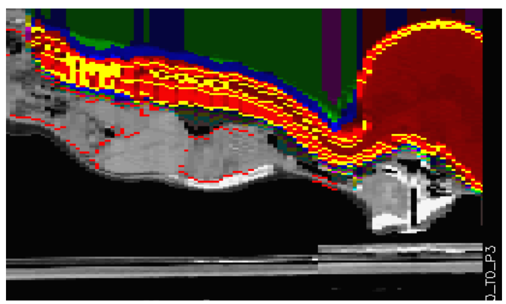


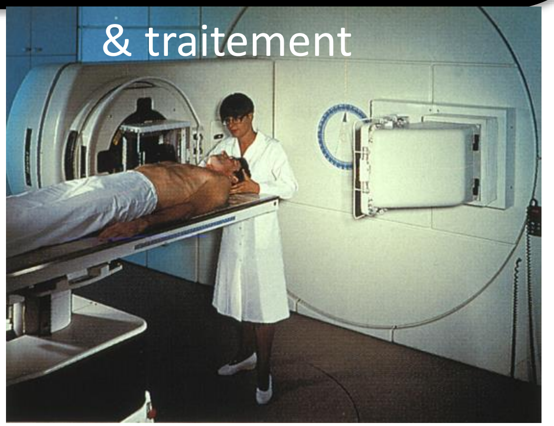
Shieding

Measurements/detectors



Models/calcs & simulations





$(dE/dx) = 4 \pi z_{eff}^2 e^4 N_A Z/A\, m_e v^2 \{ \ln (2mv^2/ I (1-\beta^2)) - \beta^2 - \Sigma(Ci/Z) \}$ Stopping Power

$\theta_0 = 14.1 \; z / p v \; \{ sqrt (L / L_R) \; (1+ \log(L /L_R) / 9) \}$ Scattering angle

2．筑波大学の陽子線治療成績

筑波大学の陽子線治療は、１９８３年以来色々な部位を対象に行われていますが、なかでも日本人に多い深部臓器がんに主体を置いているという特徴があります。表５に治療部位と治療成績を揚げました。これまでの経験で、皮膚、頭頚部、肺、食道、肝臓、子宮、膀胱、前立線などで満足すべき結果が得られています。

第６図から第14図までは、実際に陽子線で治療した患者さんの写真です。

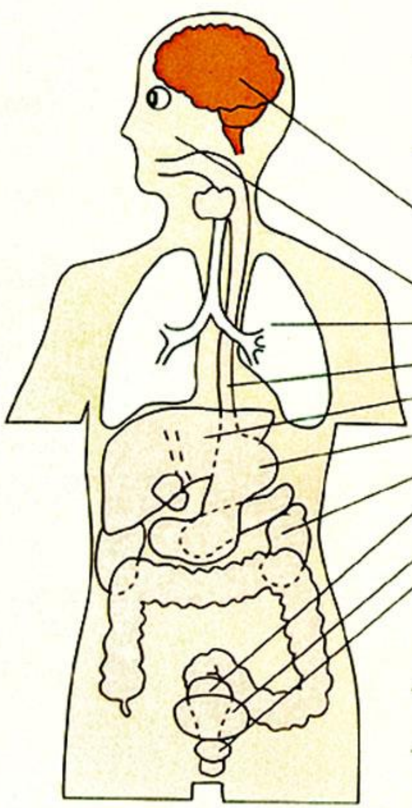
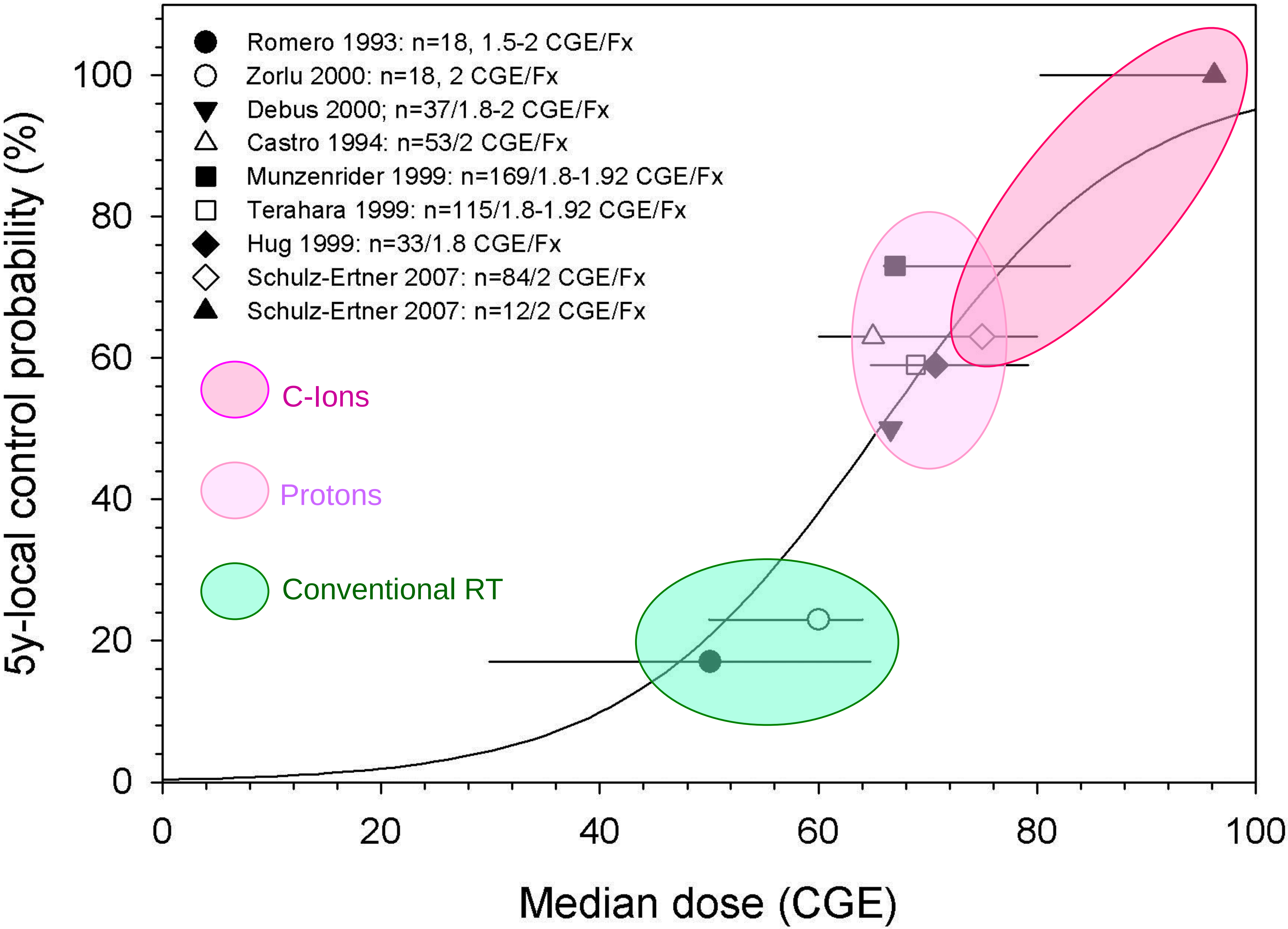


表５　筑波大学の陽子線治療結果

部位	患者数	局所治癒率推定(%)	3年生存率	後遺症
皮膚	8	7 (87.5)	87.5	0
脳 ｸﾞﾘｵｰﾑ	13	3 (23.1)	18.5	3
髄膜腫など	9	8 (88.9)	75.0	0
頭頚部	15	11 (73.3)	81.5	0
肺	19	14 (73.7)	54.1	1
食道	23	18 (78.3)	51.6	3
肝臓	30	26 (86.7)	25.5*	0
胃	5	3 (60.0)	61.0	0
腎臓	5	2 (40.0)	60.0	0
子宮	24	21 (87.5)	72.7	3
膀胱	12	8 (66.7)	62.5	2
前立腺	7	7 (100.0)	68.6	0
小児腫瘍	4	4 (100.0)	75.0	0
その他	4	3 (75.0)	100.0	1
合計	178	135 (75.8)		13(7.1%)

*肝機能良好例の3年生存率75.0%

A common goal :



Always asking for more ?

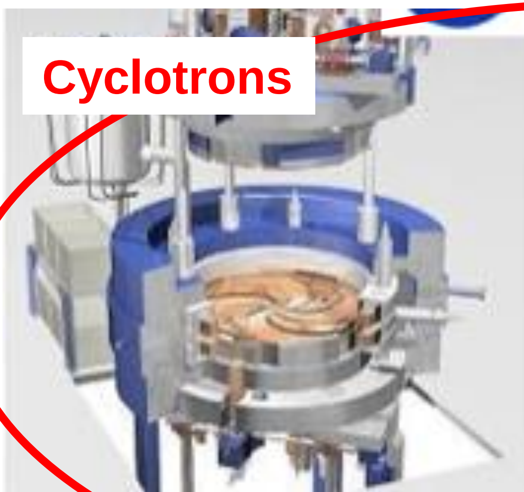
Higher Z (all ions inc radioactive)
Higher energy (radiography)
Higher intensity (dose rate)
.....

Welll… also to reduce !:

Reduce cost (size, iron, shielding,…)
Reduce uncertainties
.....

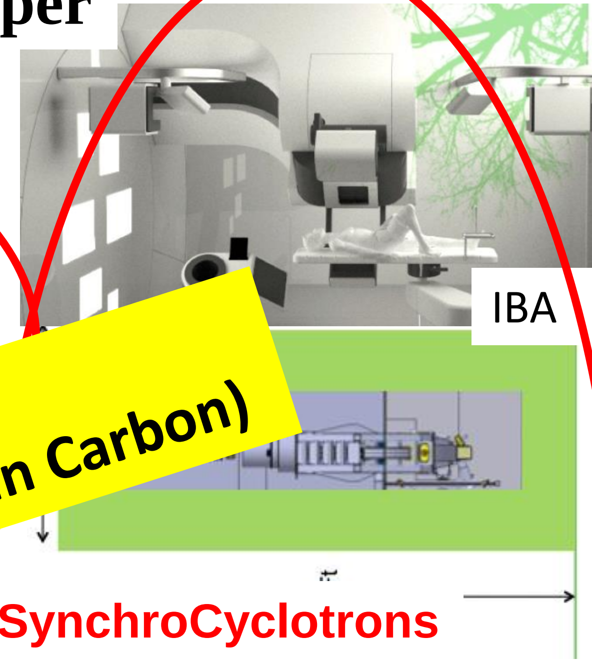
Some alternatives to make it compact and cheaper

Cyclotrons



Cryogenic
(Varian, Pronov

...no,...)



IBA

SynchroCyclotrons

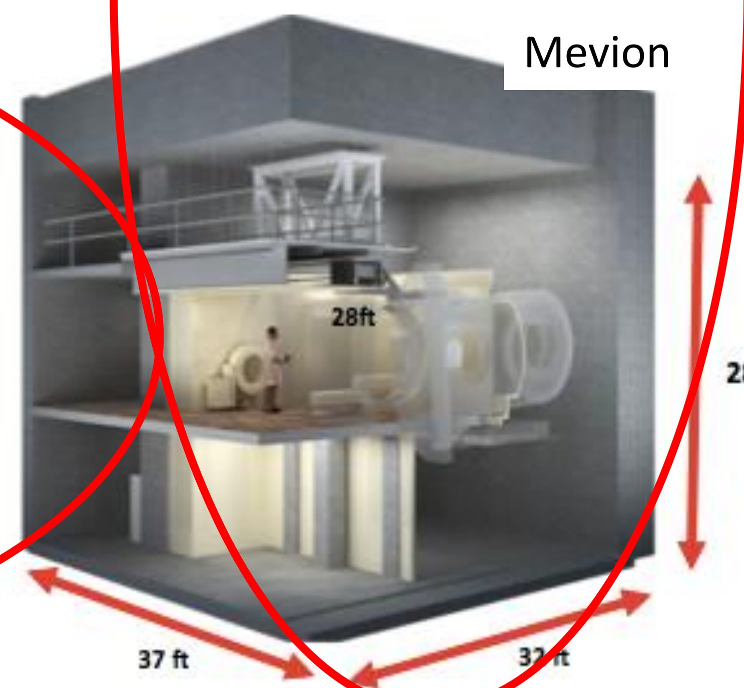
"State of the art" in protons ?
(and HIT, NIRS, Pavia, MedAustron.. In Carbon)

Synchrotrons

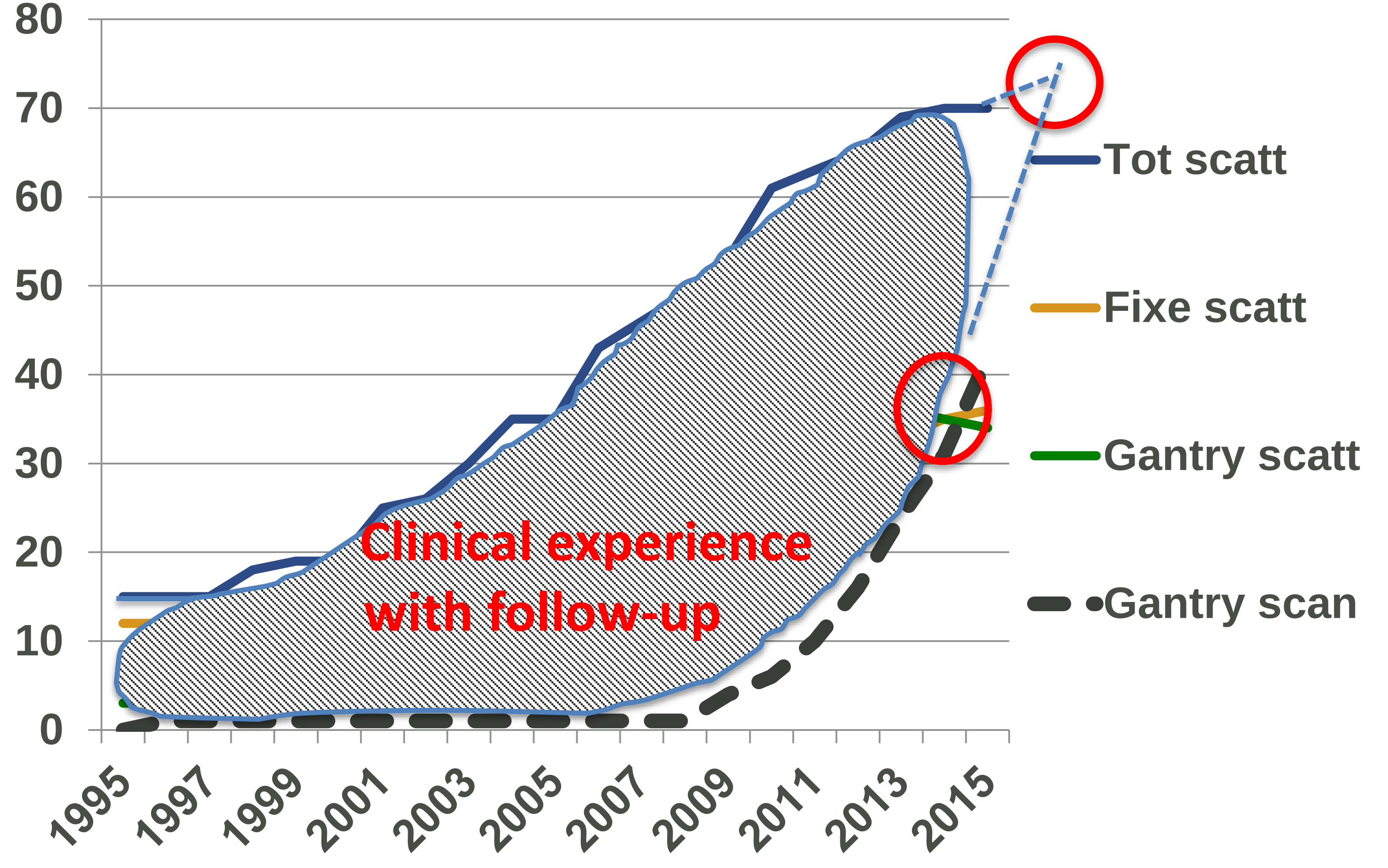
Compact synchrotron (Protom)

+ Hitachi, Mitsubishi, Toshiba,...

Mevion

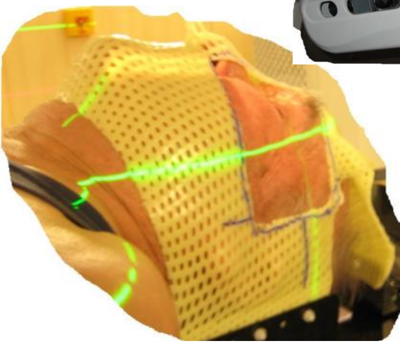


Number of treatment rooms in the world : scatter and scanned



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

IGRT



Video Surface

Vision/ Laser

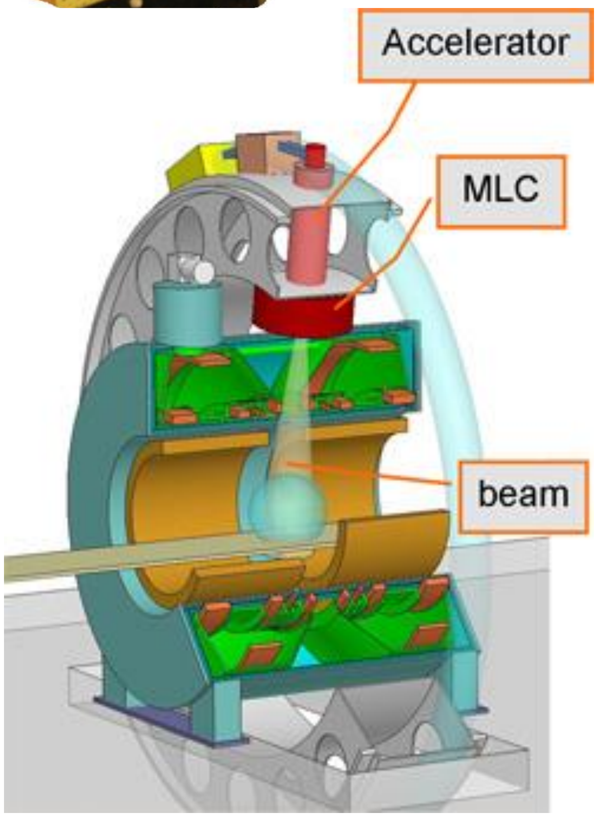
Echo

kV&fluo fixed

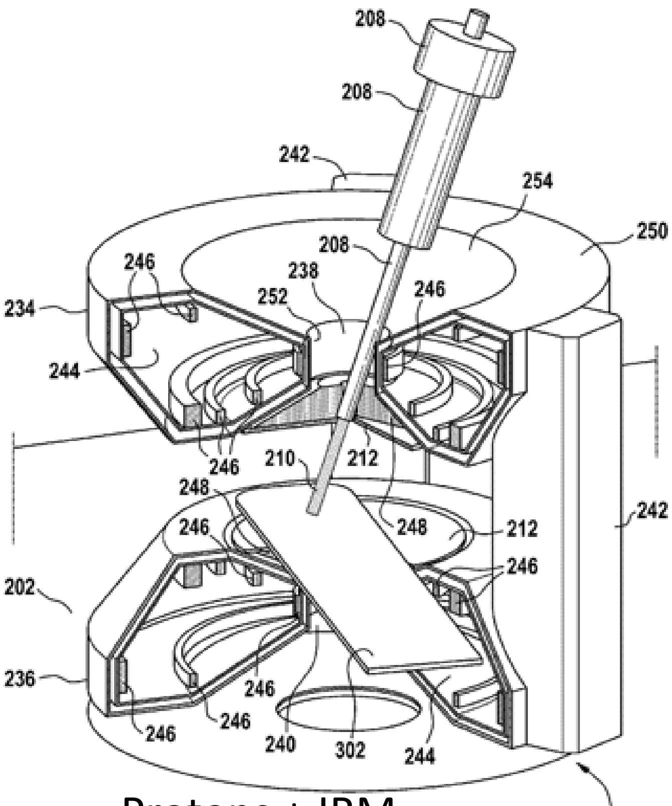
kV&Fluo/gantry

MVPortal & CBCT

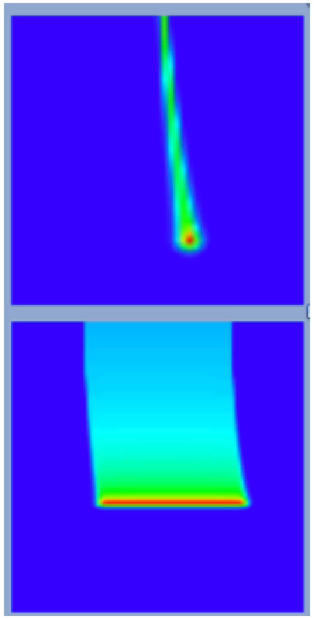
MVCT



Linac+ IRM :
www.umcutrecht.nl

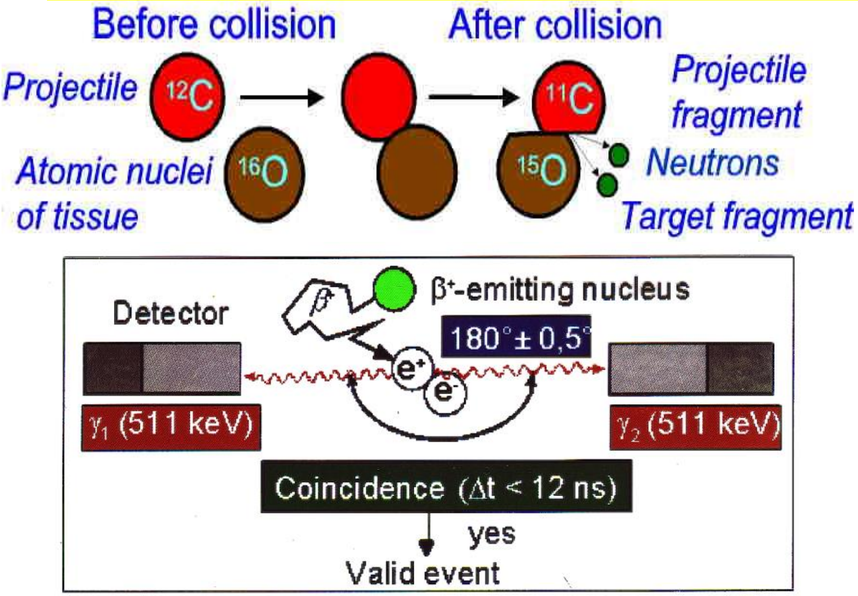


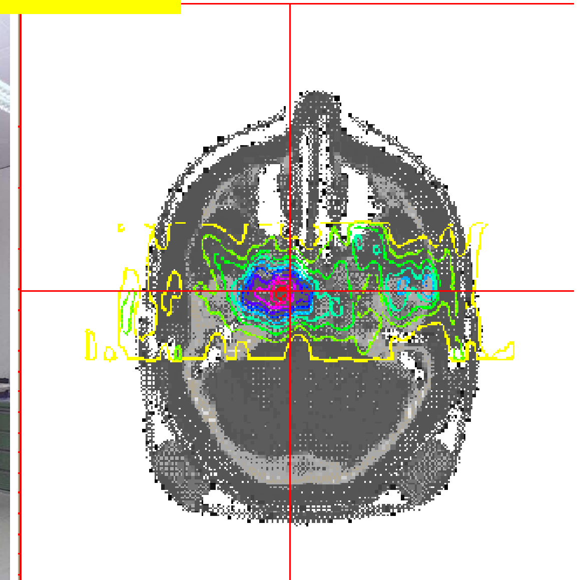
Protons + IRM
Patent Overweg Philips



Raaymakers et al, AAPM, 2014

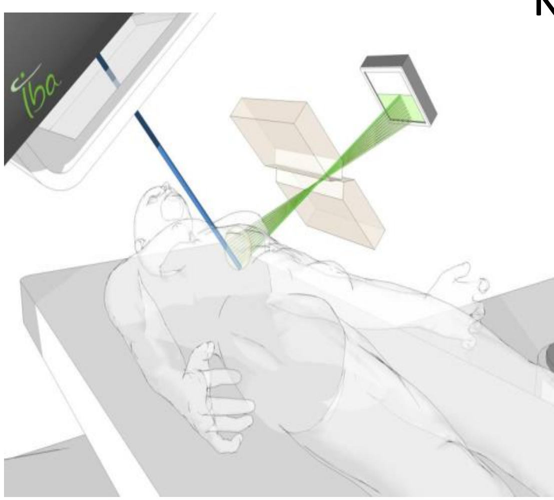
Positron Emission Tomography from patient activation with the beam



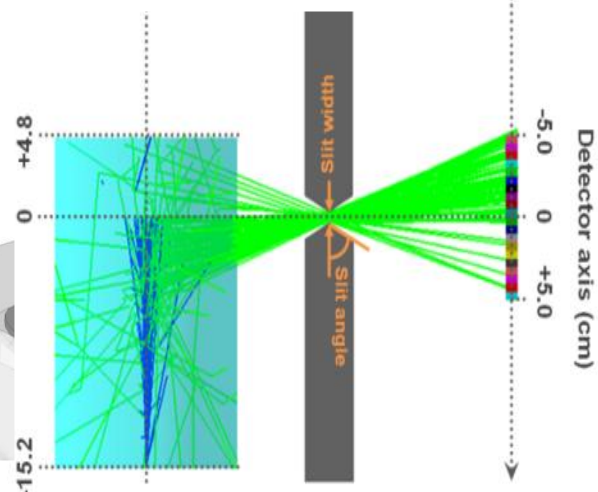


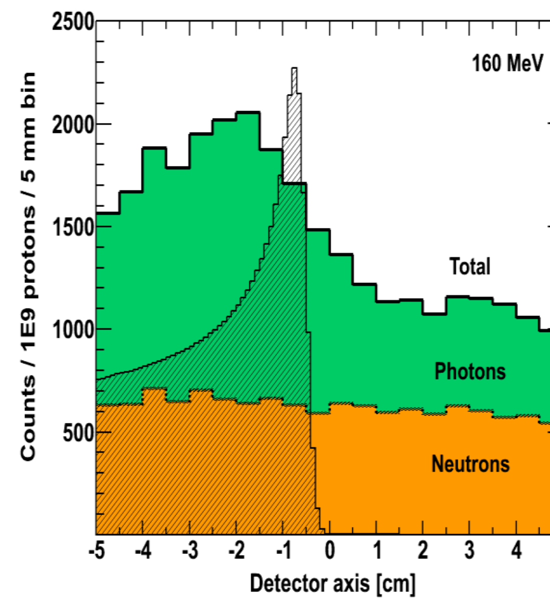
W. Enghardt et al

Prompt Gamma



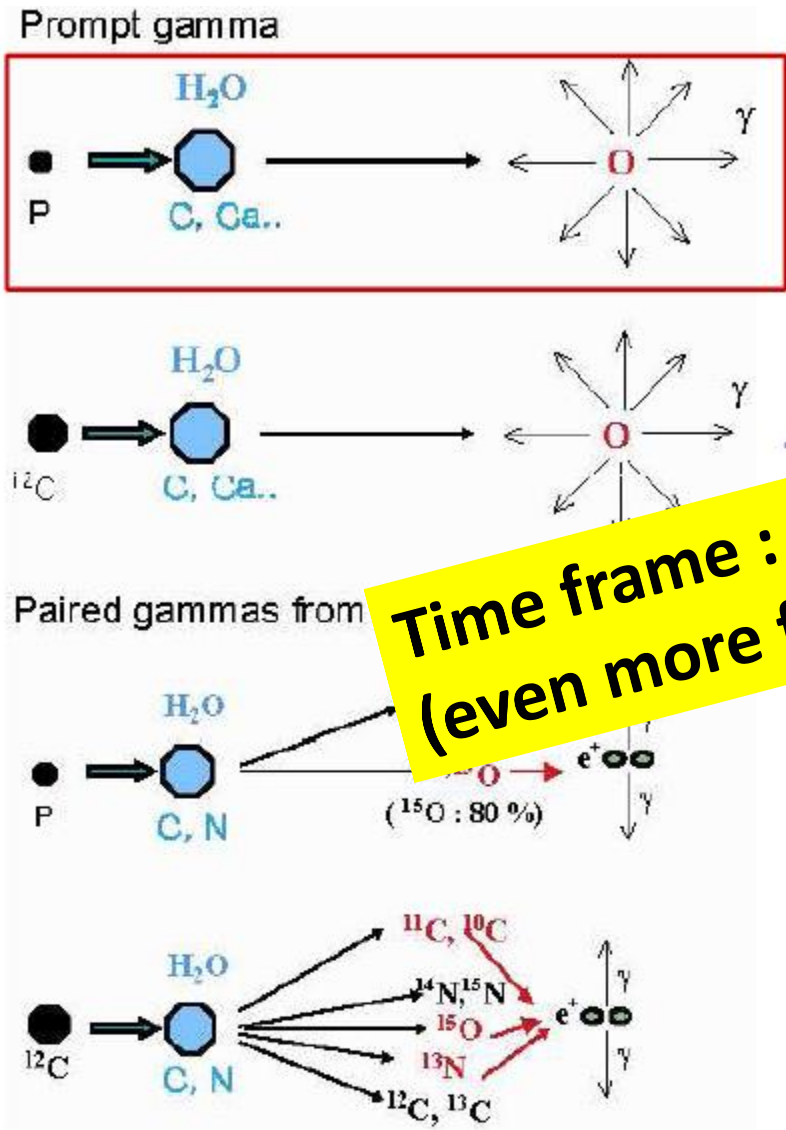
Knife-edge slit camera





D.Prieels, F.Roellinghoff,…..

« *Instead of using positron emission, could we use prompt γ ?* » Y. Jongen (2001)



Time frame : 15 years !
(even more for scanning…)

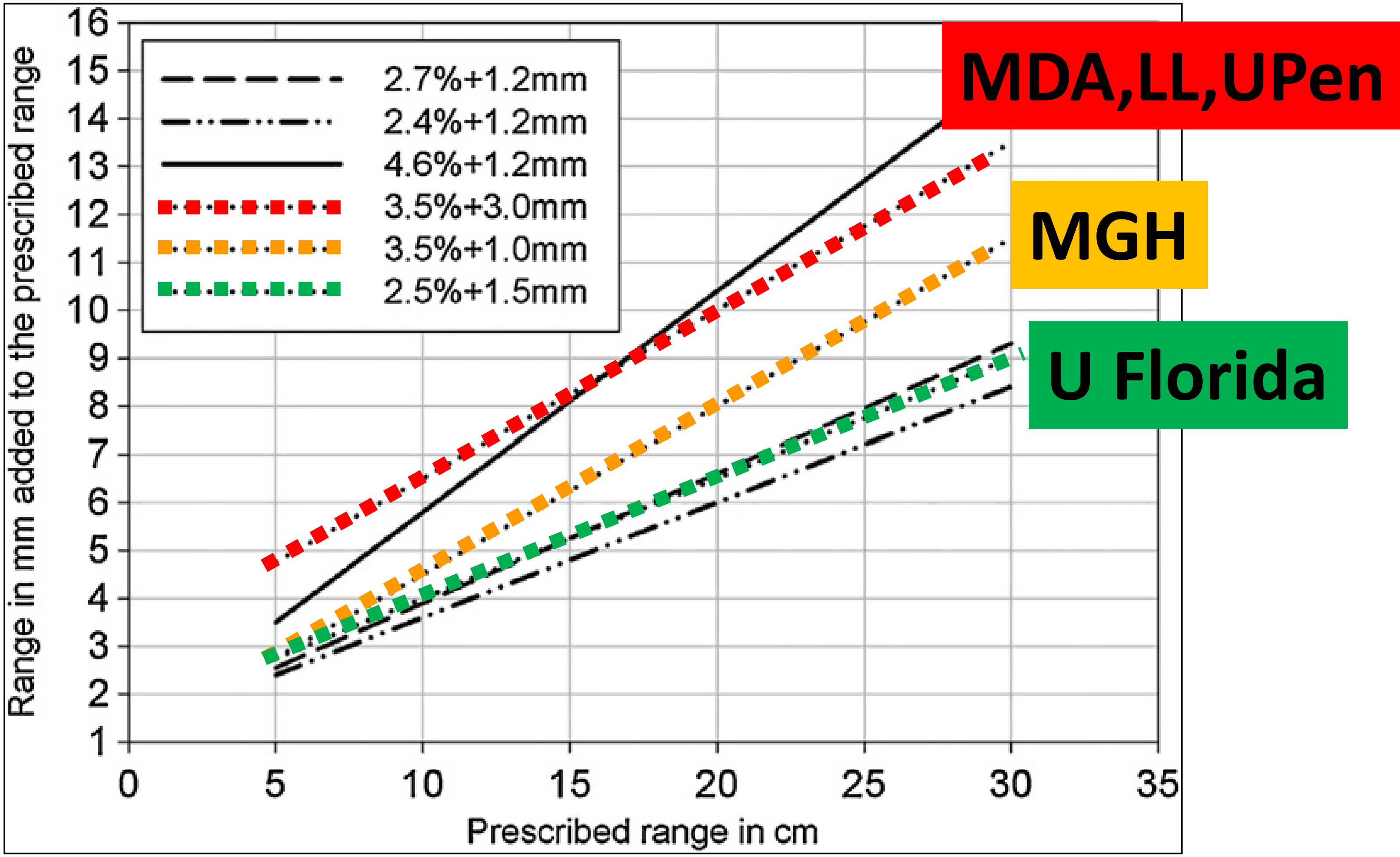
E (MeV)	Transition	Reaction	Mean Life (s)
0.718	$^{10}B^{*0.718} \to$ g.s.	$^{12}C(p,x)^{10}B^*$	1.0×10^{-9}
		$^{12}C(p,x)^{10}C(\varepsilon)^{10}B^*$	27.8
		$^{16}O(p,x)^{10}B^*$	1.0×10^{-9}
0.937	$^{18}F^{*0.937} \to$ g.s.	$^{16}O(^3He,p)^{18}F^*$	6.8×10^{-11}
1.022	$^{10}B^{*1.740} \to {}^{10}B^{*0.718}$	$^{12}C(p,x)^{10}B^*$	7.5×10^{-15}
		$^{16}O(p,x)^{10}B^*$	7.5×10^{-15}
1.042	$^{18}F^{*1.042} \to$ g.s.	$^{16}O(^3He,p)^{18}F^*$	2.6×10^{-15}
1.635	$^{14}N^{*3.948} \to {}^{14}N^{*2.313}$	$^{14}N(p,p^*)^{14}N^*$	6.9×10^{-15}
2.000	$^{11}C^{*2.000}$ [illegible]	$^{12}C(p,x)^{11}C^*$	1.0×10^{-14}
2.124	[illegible]	$^{12}C(p,x)^{11}B^*$	5.5×10^{-15}
[illegible]	[illegible]	$^{14}N(p,p^*)^{14}N^*$	9.8×10^{-14}
		$^{16}O(p,x)^{14}N^*$	9.8×10^{-14}
[illegible]	[illegible]	$^{16}O(p,p^*)^{16}O^*$	1.8×10^{-13}
[illegible]	[illegible]	$^{40}Ca(p,p^*)^{40}Ca^*$	2.9×10^{-11}
[illegible]	[illegible] $\to$ g.s.	$^{12}C(p,p^*)^{12}C^*$	6.1×10^{-14}
		$^{14}N(p,x)^{12}C^*$	6.1×10^{-14}
		$^{16}O(p,x)^{12}C^*$	6.1×10^{-14}
4.444	$^{11}B^{*4.445} \to$ g.s.	$^{12}C(p,2p)^{11}B^*$	5.6×10^{-19}
		$^{14}N(p,x)^{11}B^*$	5.6×10^{-19}
5.105	$^{14}N^{*5.106} \to$ g.s.	$^{14}N(p,p^*)^{14}N^*$	6.3×10^{-12}
		$^{16}O(p,x)^{14}N^*$	6.3×10^{-12}
5.180	$^{15}O^{5.181} \to$ g.s.	$^{16}O(p,x)^{15}O^*$	$< 4.9 \times 10^{-14}$
6.129	$^{16}O^{*6.130} \to$ g.s.	$^{16}O(p,p^*)^{16}O^*$	2.7×10^{-11}
6.916	$^{16}O^{*6.917} \to$ g.s.	$^{16}O(p,p^*)^{16}O^*$	6.8×10^{-15}
7.115	$^{16}O^{*7.117} \to$ g.s.	$^{16}O(p,p^*)^{16}O^*$	1.2×10^{-14}
15.10	$^{12}C^{*15.11} \to$ g.s.	$^{12}C(p,p^*)^{12}C^*$	1.5×10^{-17}

B. Kozlovsky et al., Astrophysics J., Suppl. Ser. **141** (2002

Courtesy John Wong Kim (AAPM 2009)

D. Prieels, F. Stichelbaut, F. Roellinghoff et al, IBA et ENVISION

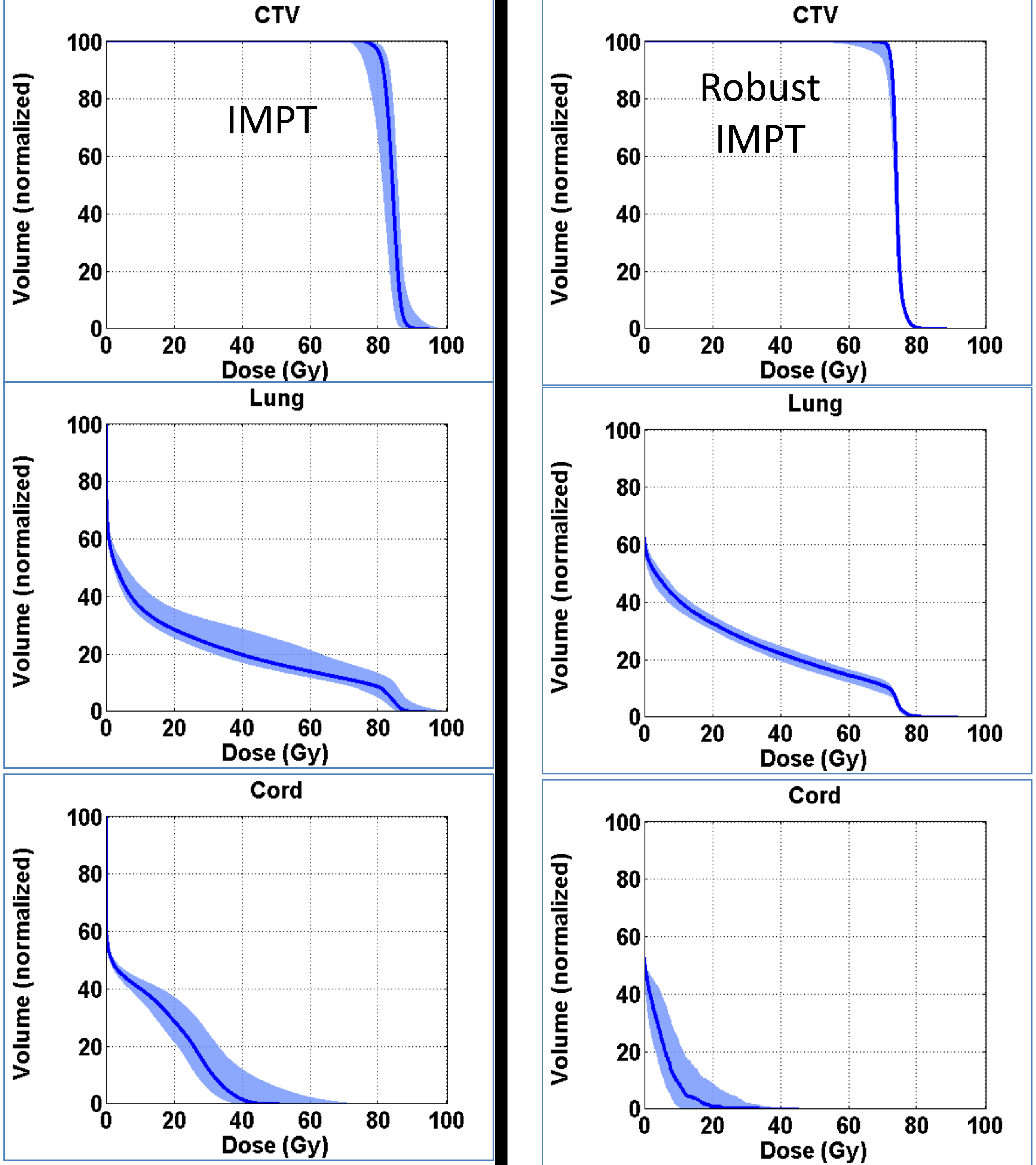
	Classes of uncertainties	Eliminate / Mitigate / Take in charge
	PATIENT PREPARATION AND IMAGING	
1	Patient immobilisation & contention devices	Minimise & Homogeneous material in beam path
2	CT calibration, QA, use and constancy	Methods, frequency, evaluation,...
3	CT conversion Hounsfield to Stopping power	Stoichiometric, analytical, data base, double Energy CT,...
4	CT grid size	Tests, compromises
5	CT artifacts (eg metals)	Acquisition parameters, MVCT, Double Energy CT, others...
6	Protocols for image acquisition	Conceive, Compromises, Verify use, human error, evolut
7	Movement management, breath holding, gating,...	4D CT, breath holding, gating, (tracking), repainting,...
8	Patient imaging and correlations for tumor volume delineation	Image & correlation QA
9	Target & critical organs delineation	MD experience & goals, protocols, procedures, tools
	TECHNOLOGY: DEVICES & MEASUREMENTS	
10	Facility Commissioning (eg beam data)	Detectors, redundancies, small tolerances, interlocks
11	Beam on line range monitoring and feedback	Detectors, fast feedback and/or interlocks
12	Measuring errors : devices, procedures, human errors	Detectors, check lists, automatic tools and filters
	CALCULATIONS IN THE PREPARATION PHASE	
13	Range calculation algorithms	Improve & validate algorithm; comparisons and tests;
14	Compensator calculation, optimisation, fabrication, validation	Improve algorithm; Quality Control, smearing, drill size,
15	Dose calculation models (including multiple scattering and biological effects)	Improve algorithm; Quality Control, compensate, reoptimise,..
16	Management of Inhomogeneities (lung, metals, ...)	Improve algorithms; tests, avoid incidences, reject cases,...
17	Accessories in beam path (eg table, masks, ...)	Avoid or Verify, measure, model, test,...
	TRANSFER AND TREATMENT	
18	Patient specific QA on range	Detectors, redundancies,tolerances, stats, models
19	Accessories in beam path (eg table, masks, ...)	Avoid or verify
20	Patient setup	Immobilise, margins, IGRT (CBCT, orthogonal X, vision, ...)
21	Management of movements	Immobilise, margins, gate, track, repaint, monitor range
22	Changes in anatomy	in room - off room imaging, monitor range
23	Beam modifiers choice (compensator and others)	Check lists, test, interlocks, imaging, monitor range
24	Beam modifiers setup (compensator and others)	Fixations, verification, monitor range
25	Beam delivery (pattern, position, interruptions,...)	Monitoring, testing
26	Delivered Range (abs value, reproducibility,...)	QA, monitor range



Dotted lines: typically applied range uncertainty margins in proton therapy treatment planning as currently typically applied at the MGH (3.5% + 1 mm), the MD Anderson Proton Therapy Center in Houston, the Loma Linda University 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.

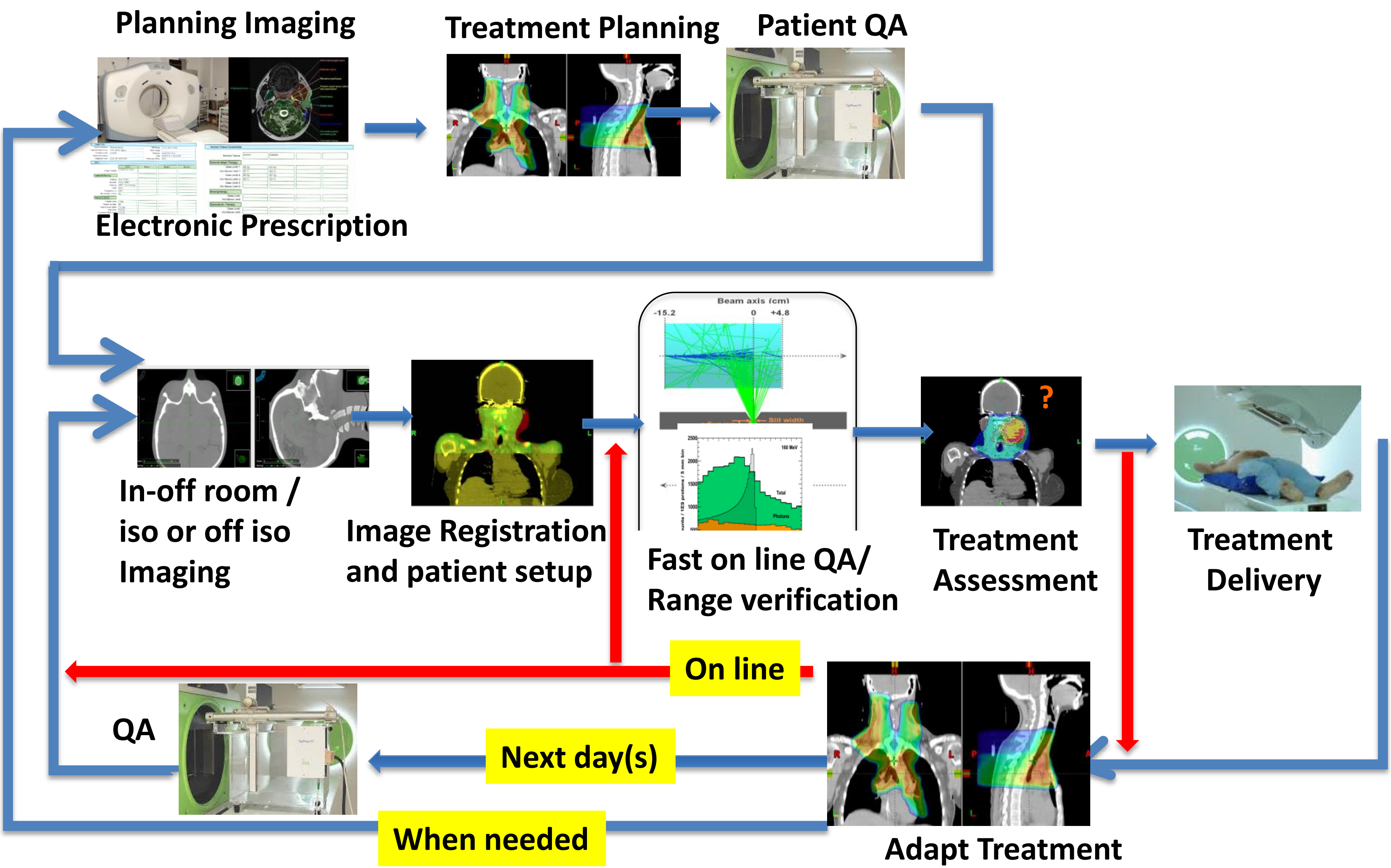
H.Paganetti , PMB 57 (2012) R99-R117 & personal comm

ROBUST OPTIMISATION



Liu, Zhang and Mohan, 2012

IMRT and proton pencil beams in adaptive workflow

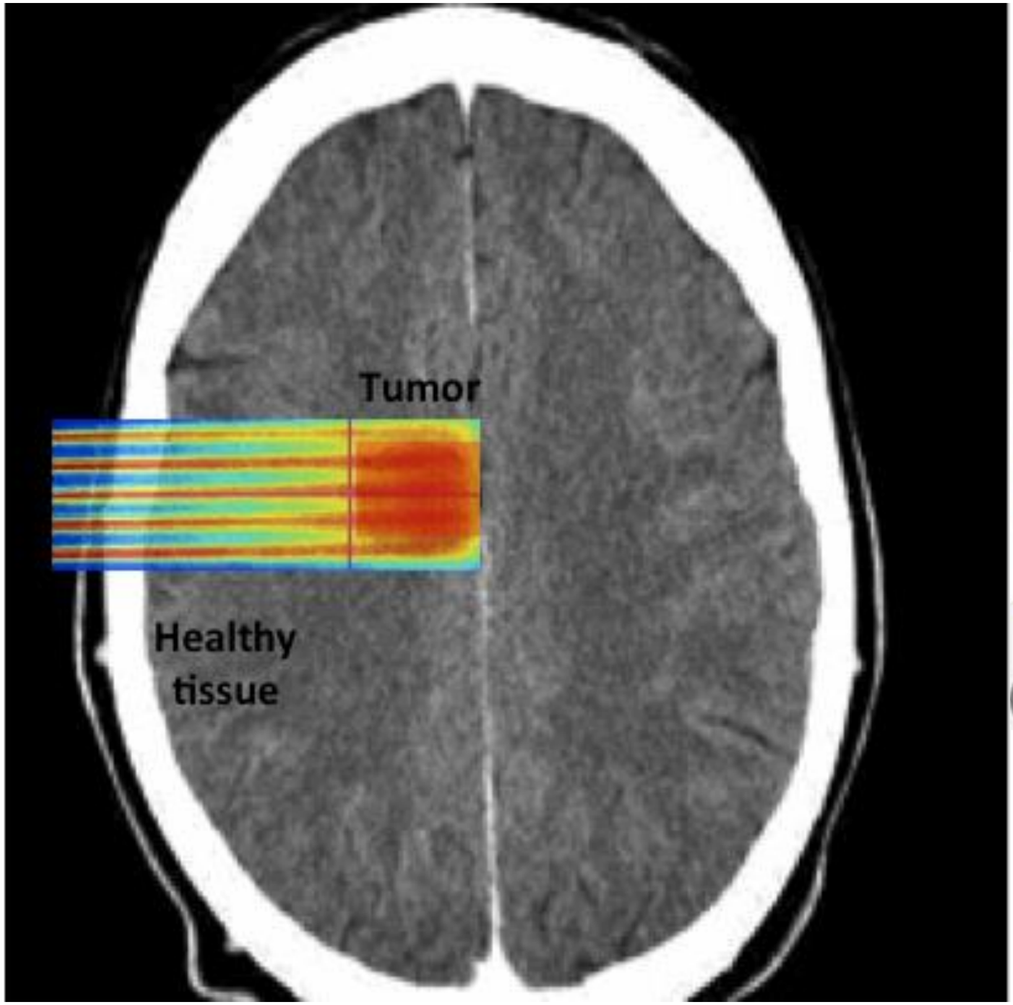


G.Olivera/ D.Galmarini / A.Mazal

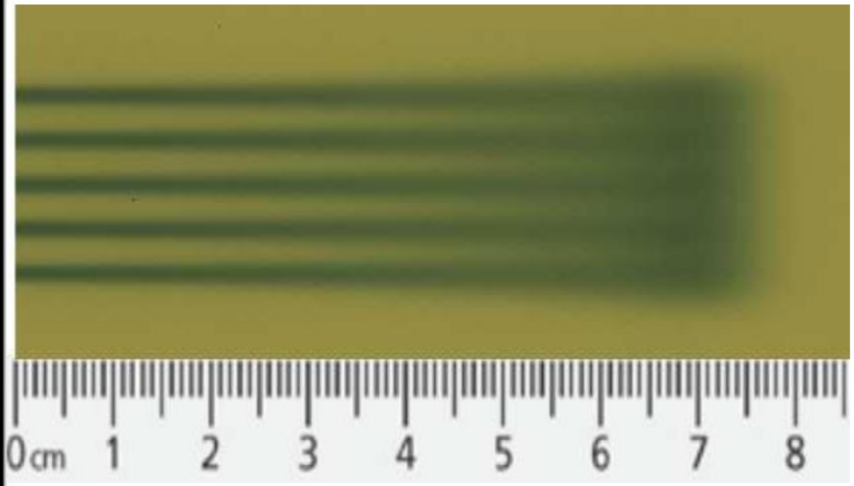
Proton MiniBeam Radiation Therapy (pMBRT)

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…

From synchrotron irradiation

(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%)

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

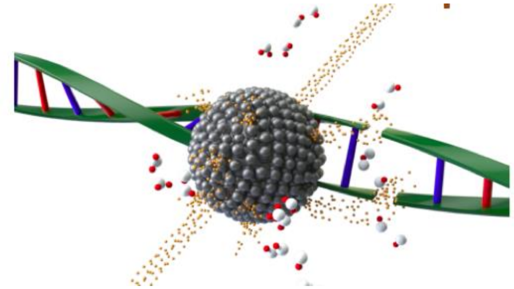
From irradiations with photons

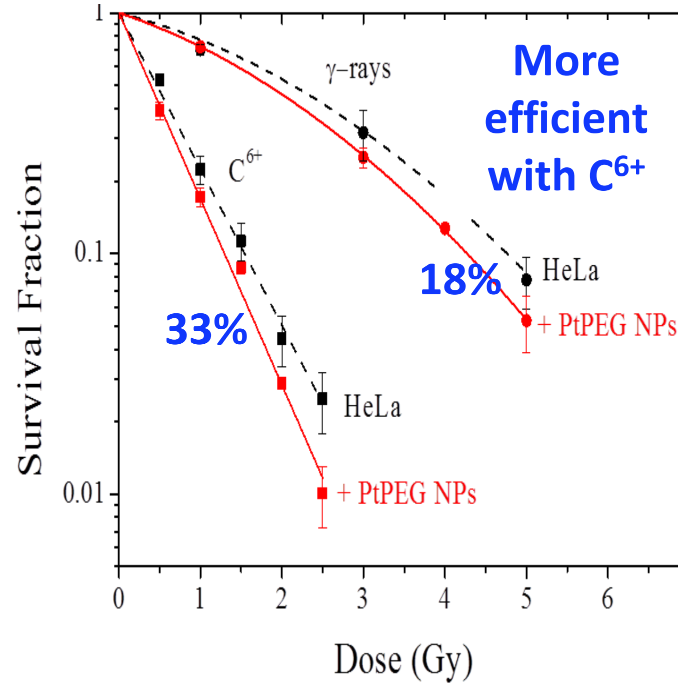
ISMO

Sandrine LACOMBE

Erika PORCEL

UNIVERSITÉ PARIS SUD

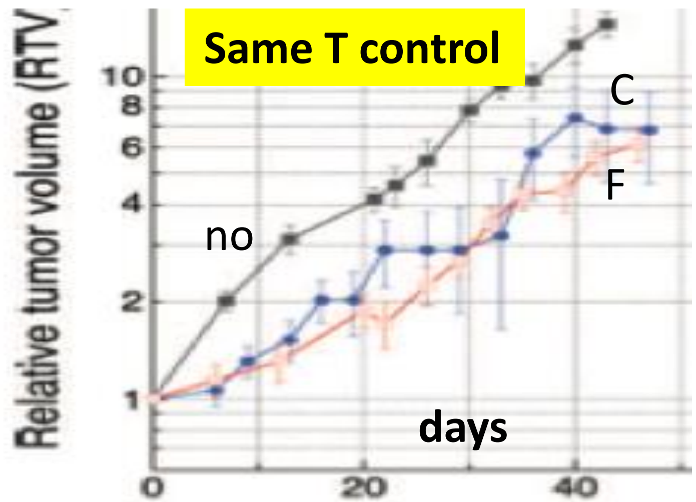


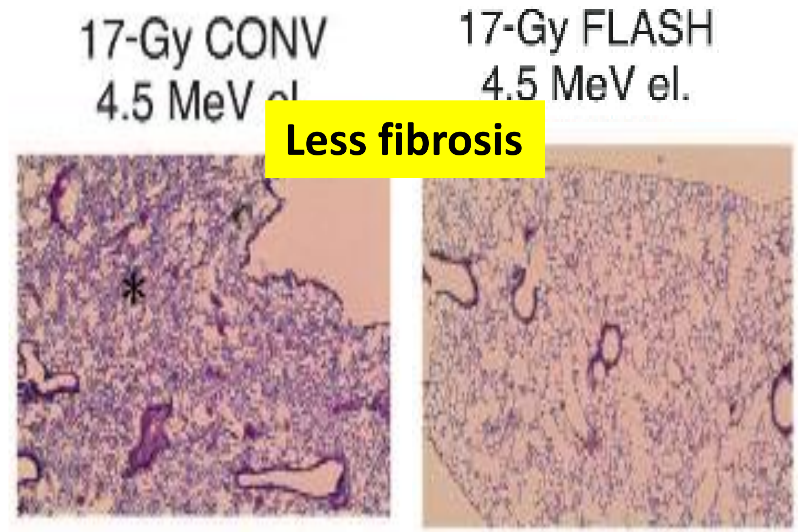


Porcel et al, 2010, 2014
Jong-Ki Kim et al // for protons 2012

"FLASH –Effect" Ultrahigh dose-rate FLASH irradiation

Favaudon et al, Sci Transl Med 16 July 2014



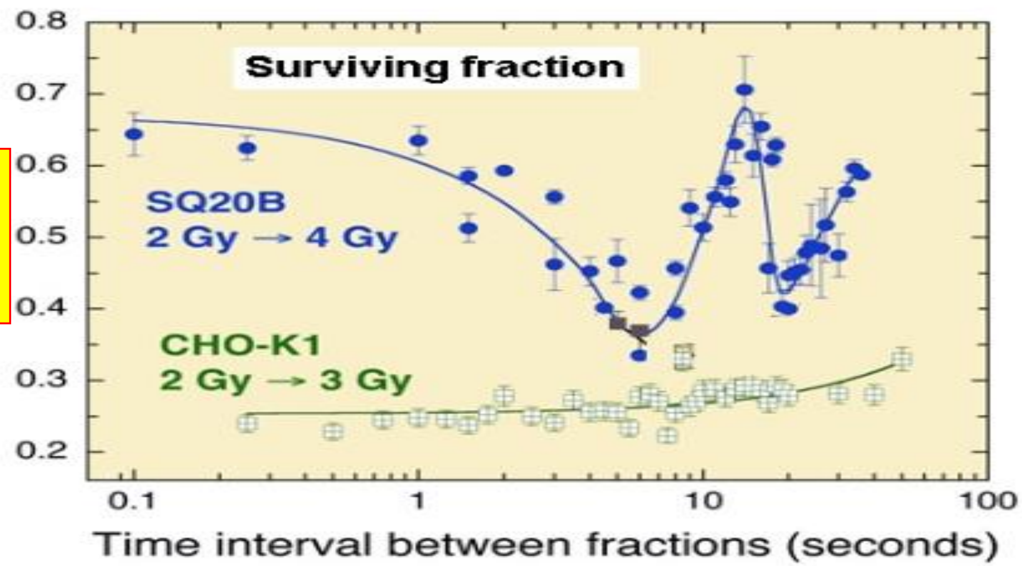


Vincent Favaudon

"W-Effect": Early cell response to split-dose irradiation

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

From irradiations with electrons



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Which research with light ions for therapy ? (and what to do in a research line?)

WORK IN PROGRESS

Thanks to :
G.SantaCruz, K.Parodi, D.Auvergne, F.Pouzoulet (building a table…)
D.Verellen, T.Lomax, T.Bortfeld (personal exchanges future of Medical Physics)
…..

Technical accelerators, beam transport and shaping, robotics, imaging, integration

1 Accelerator for all ions including radioactive beams
2 High energies (eg. radiography), very high intensities (eg. pulses 100Gy/sec)
3 Reduction in size, in cost (cryogenics), increase reliability, maintenability (modularity, ..)
4 Gantries reduced in size and cost (cryogenics, multiple magnets, ironless,…)
5 Pencil beam technology multiple spot sizes, fast continuous scanning, fast Energy switching, optimized IMPT
6 Development of proton micro-beams: quantitative PIXE analysis, micromachining
7 Ministrips beams, mini & micro beams for therapy
8 Integrated IGRT (IGPT) double Energy CT, MRI, PET, vision, ultrasound, OCT
9 Compensating filters and field delimiters, multileaf collimators
10 Beams for special applications: functional radiosurgery, ophtalmology, pediatrics …
11 Shielding, radiation protection
12 Robotics systems for patient positioning
13 Scanned beam technology, irradiation techniques with IM…
14 Proton tomography
15 Data for dosimetry from PET & SPECT (st… …tion, ..)

Nuclear Physics, Instrumentation, Nuclea… …ciences

16 Beam monitoring (positioning, dose, ..) and … …sis (breakdowns, misfunctioning, ..)
17 Detectors dosimetry: Calorim, Faraday, chambers, counters, Hodoscopes, Compton, solid state, diamants, CCD, scintill, Gafchr, alanine, TLDs
18 Analysis of detectors saturation, quenching, recombination, dosimetry in presence of strong magnetic fields
19 Detectors for low dose imaging, organ movements, pencil beam scanning
20 Detectors for "biometry" (LET, RBE,…)
21 Online range monitoring (PET, gamma prompt, charged secondaries, proton radiography, acoustic, ..): towards "actual delivered dose"
22 Radiation protection and patient radiation "vigilance" measurements and models on neutron production & attenuation
23 Radiation damage studies by high energy particles, hydrogen damage data for nuclear reactors and nuclear power plants.
24 MRI, PET and SPECT techniques based on proton-induced reactions for retrospective assessment of treatment.
25 Space science (spectra, radiation protection, detectors, ..)

>60 lines not exhaustive and still not "filtered"
Some presented in the previous slides…

Medical physics – treatment planning, do[...]simetry, QA,…

27 Image registration, elastic deformations, voxelized models, automatic contouring (Atlas, knowledge based, …)
28 Models, measurements and application of nuclear data for dose calculations.
29 Fast (full) Monte Carlo calculations and deterministic transport techniques.
30 Immobilisation systems, fiducial markers, metallic implants, balloons, tissue spacers
31 Microdosimetry and Nanodosimetry, Tissue-Equivalent Proportional Counter…
32 Interphase dosimetry
33 Proton range calculations with inhomogeneities
34 Passive and scanned beam lateral penumbra and far low…
35 Hardware and algorithms for very fast calculations
36 QA of TPS, intercomparisons between different treatme…
37 Small section beams, production and studies about charg…
38 IMPT, Dose-based and biological-based optimization, LET…
39 Time-dependent treatments, target movement, simulatio…
40 Automated planning with fast, knowledge based, robust (b…
41 Integrated Adaptive therapy, Data mining tools, knowledge…
42 Risk based QA & tools; "No" QA (integrated and time efficie…
43 "No effort" commissioning, class solutions
44 Ancillary tools – collision models, apertures and pencil beam, combined treatments and retreatments

Biology and pre-clinical – Beams, devices, data and models for Radiobiology, Biophysics and Pre-clinical…

45 Development of particle micro-beams on single cells and tissu (intravital microscopy)
46 Cell studies: DNA damage, non-targeted effects, cell survival, repair, stem cells…
47 RBE studies = f(ion, energy, model, …), Alpha-Beta parameters
48 Oxygen effect, hypoxia, oxidative stress, redox, reactive…
49 Dose, dose-rate, (hypo) fractionnation effects
50 pMBRT mini beams
51 Radiosensitizers and radioprotectors.
52 Activation C11, O15, Be7, biological effect assessment
53 Nanoparticles and radiation – physics, dosimetry, biochemi…
54 Mechanistic models of radiation action in living tissues and…
55 Positioning devices for small animal experiments.
56 In-vivo animal models, tumor control, effect on healthy tissu…
57 New targets for Particle beam therapy
58 Mixed particle irradiation and combination with other advanc…
59 PAN-omics and particle therapy, biological targets, Protein bio…
60 Big Data in Radiation Oncology, expert knowledge decision too…

Clinical Research

XXXXXXX

Health Economy

XXXXXXX

CERN : "Accelerators, Detectors, Computers"

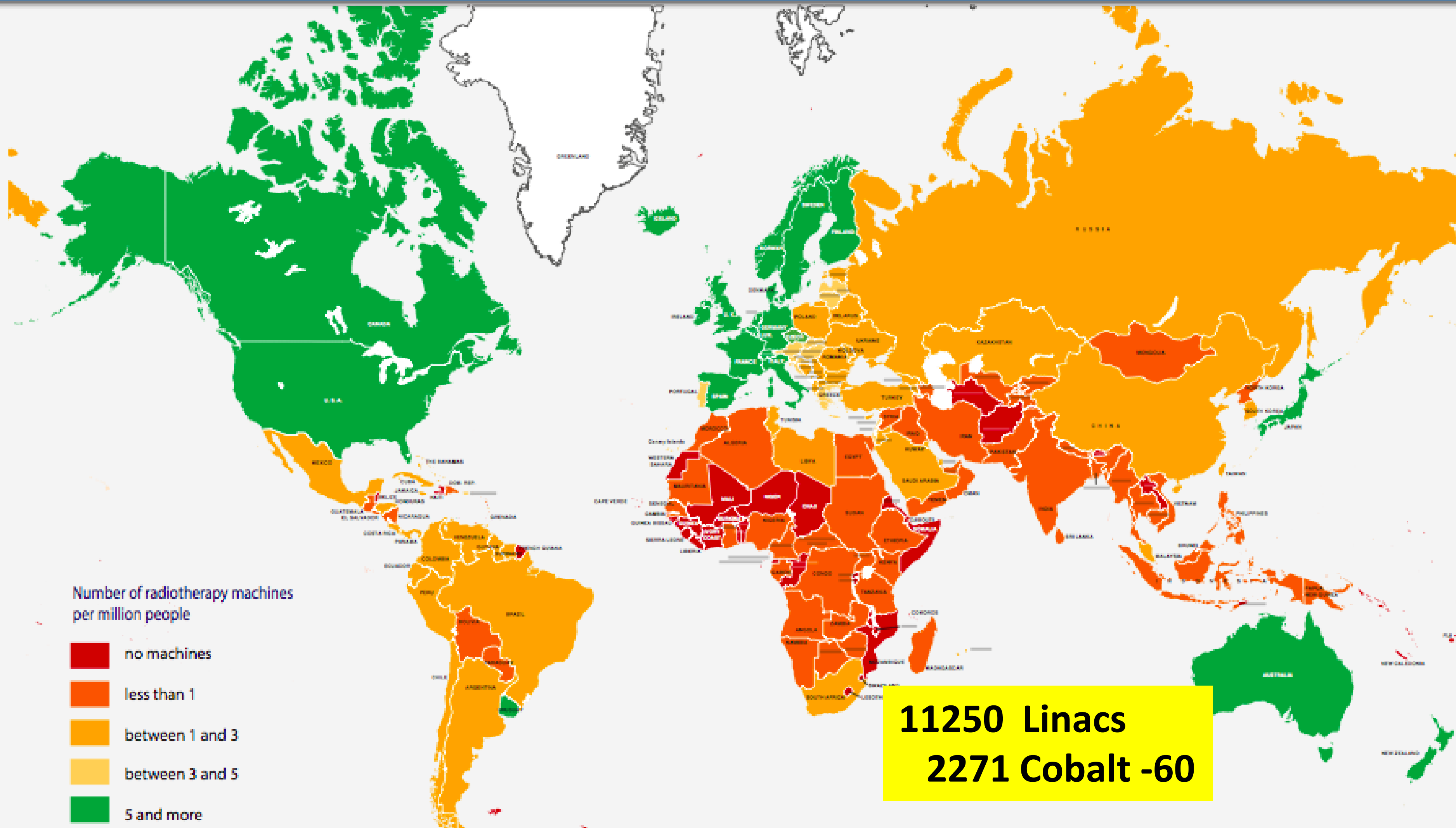
- ✓ Medpix Chips
- ✓ Fluka Monte Carlo
- ✓ Medical molecular Imaging & Nuclear Medecine
- ✓ Radioisotopes
- ✓ OpenMed BioLeir

But today when users talk about "Clinical, Biology, Medical Physics, Industry…"

- ✓ Animals
- ✓ Cells
- ✓ State of the art of Industrial solutions
- ✓ State of the art of other research institutions
- ✓ Clinical data, trials and research
- ✓ Health Economy and world status

Availability of **RADIATION THERAPY**

Number of Radiotherapy Machines per Million People 2012

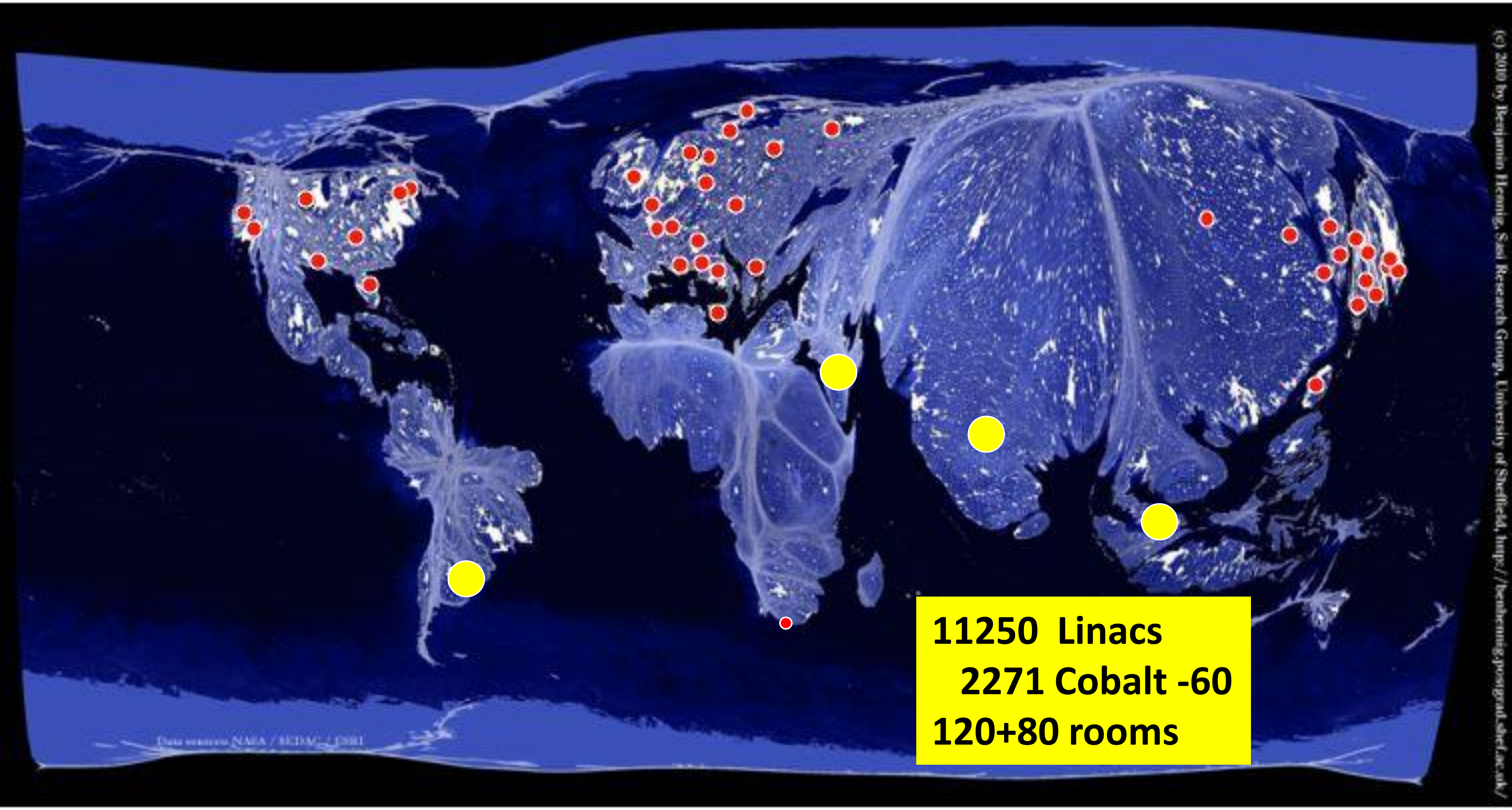


For more information: *http://www-naweb.iaea.org/nahu/dirac/*
dirac@iaea.org

Source: *DIRAC (Directory of Radiotherapy Centres), 2012 / IAEA*

Proton and Carbon-Ion Therapy Facilities Around the World

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

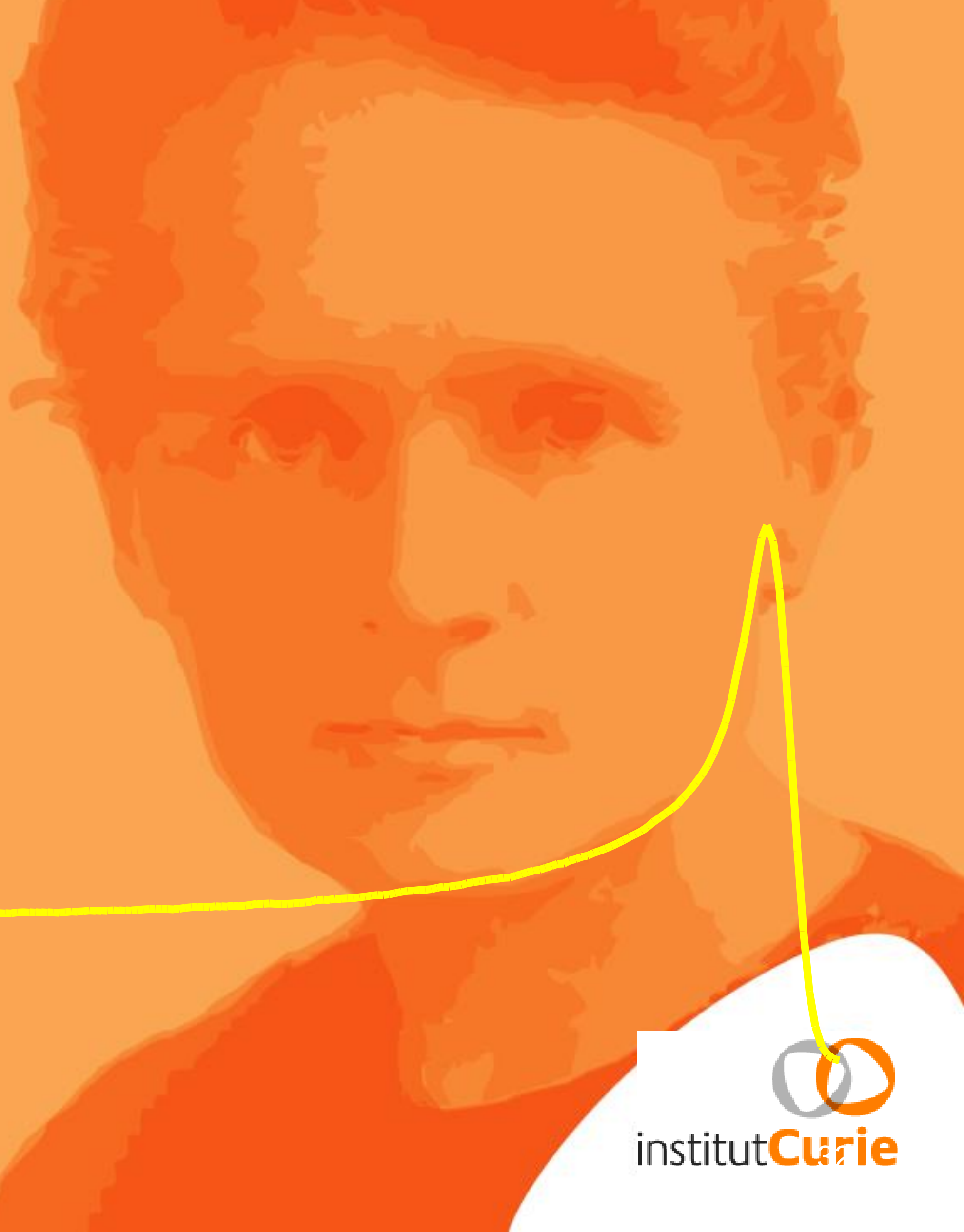


• In operation or under construction

From Bill Chu, PTCOG 50, USA

Physics in hadrontherapy:

From photons to Pan-omics,
through biology for clinics,
and $pecific challenge$



THANK YOU !

2nd CERN brainstorming meeting
Divonne, 20th February 2016

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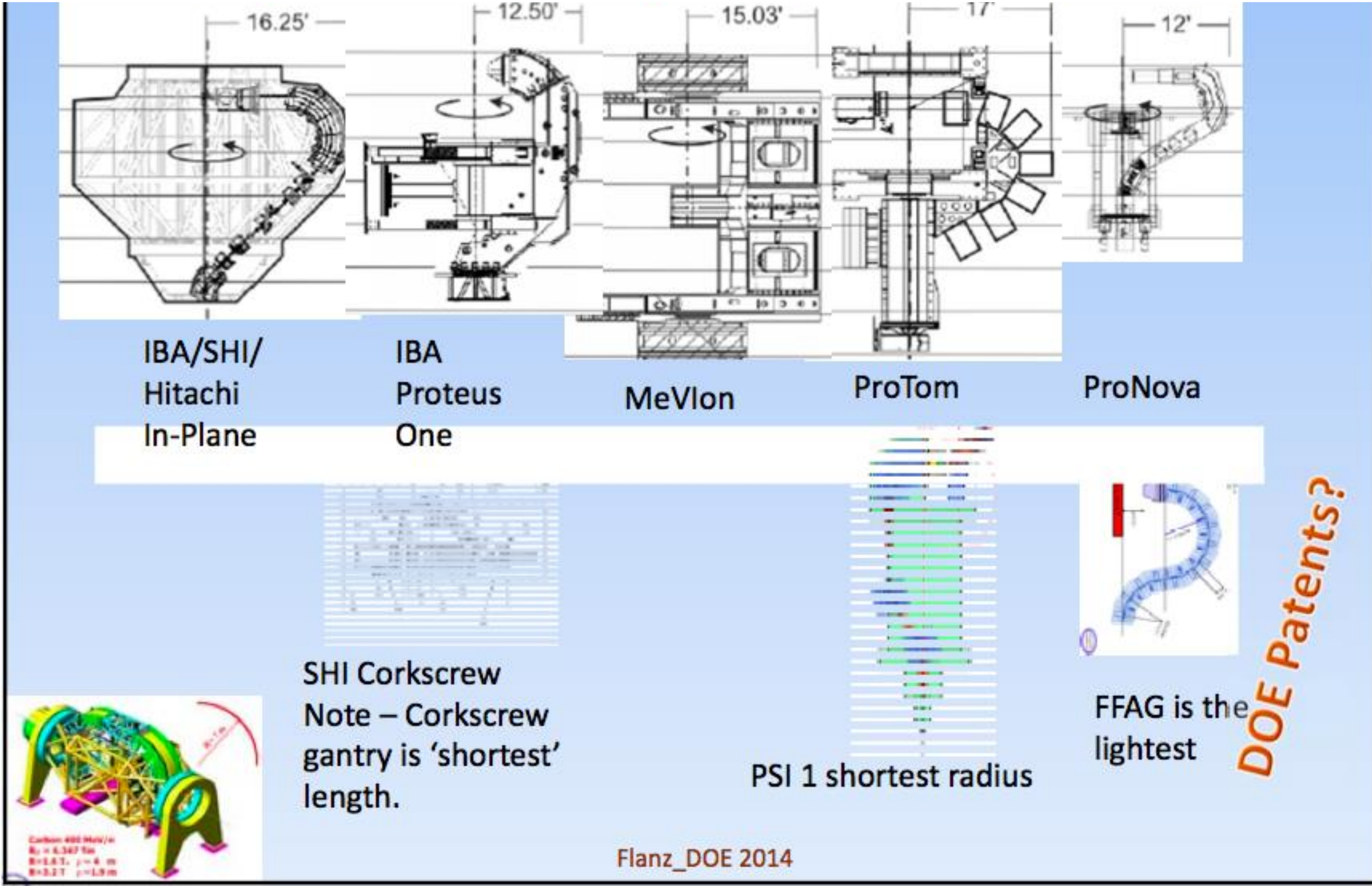
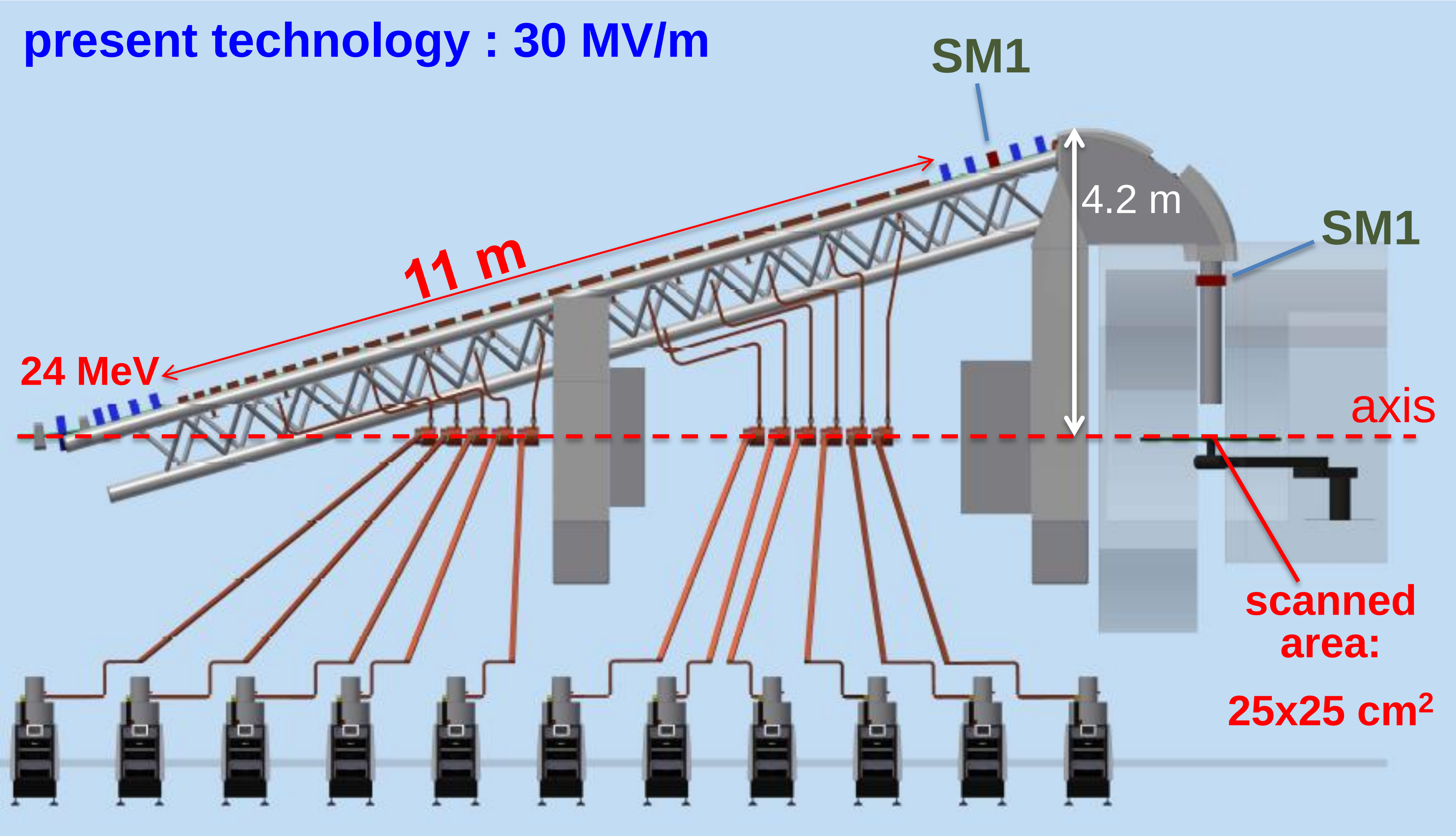
Desarrollo de brazos isocéntricos más compactos (y baratos)

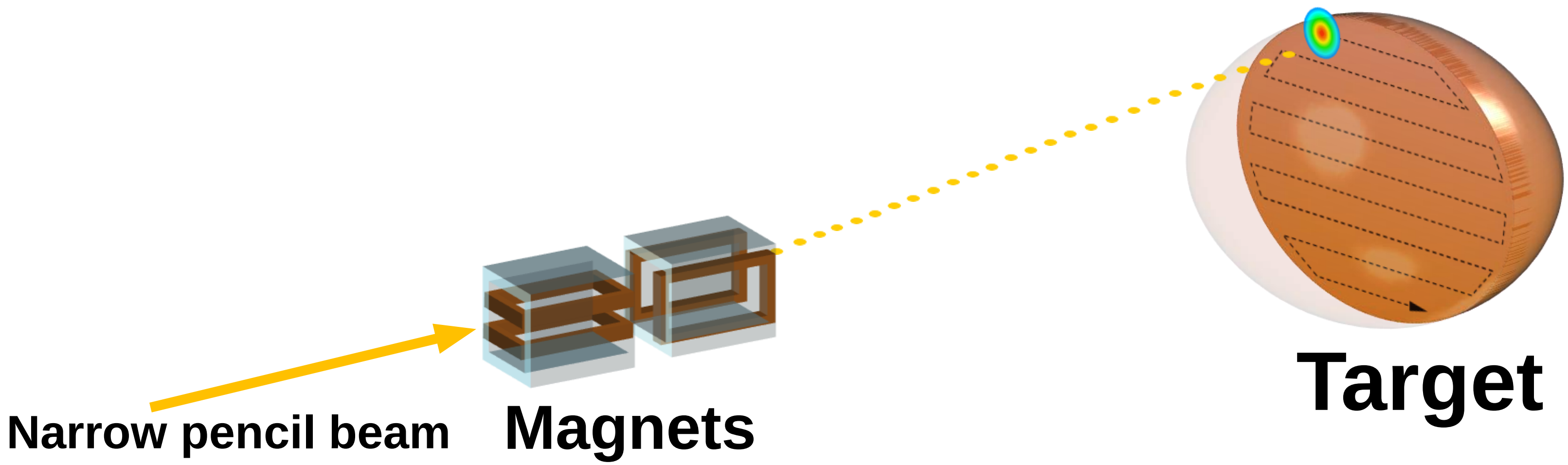


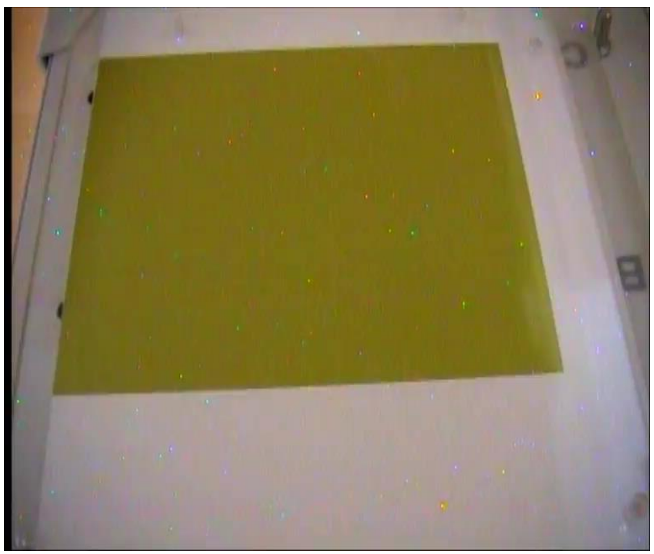
TULIP at 3 GHz with E_0 = 30 MV/m



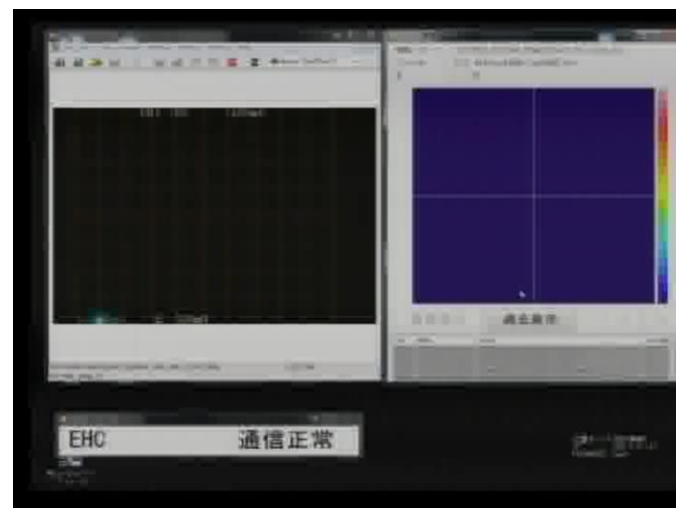
Courtoisie : Amaldi et al

Beam Delivery : 3D Pencil Beam Scanning





Range shifted by changing beam energy (or absorbers)



Kamada, PTCOG 2014