

Protonterapia e I+D

Prontoterapia, Prototerapia, Potroterapia ?

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I.Azinovic, M.Cremades, R.Miralbell.

I+D CSN

17 Diciembre 2021

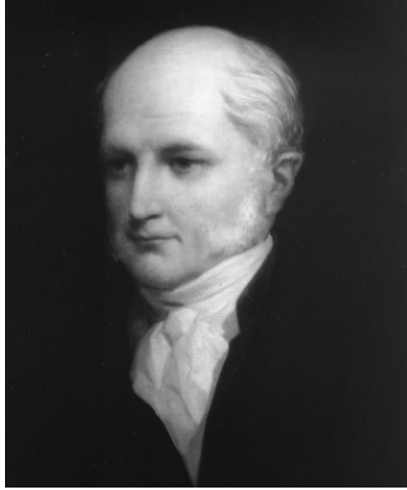
Centro de
Protonterapia

Grupo  quirónsalud

- I. Generalidades y nuestra instalación
- II. La oportunidad en España: 10 centros
- III. Investigación y desarrollo



The discovery of protons



William Prout, MD

(UK, 1785-1850)

1815

Prout's hypothesis:

In 1815, W. Prout observed that **the atomic weight of elements appeared to be whole multiples of the atomic weight of Hydrogen,**

the truly fundamental object, which he called **"Protyle"**

from Greek:

***proto* : the first *tyle*: substance**

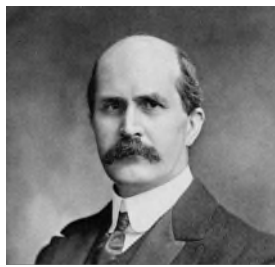
Annals of Philosophy 6, 321-30 (1815), [published anonymously]

On the Relation between the Specific Gravities of Bodies in their Gaseous State and the Weights of their Atoms.

[from David M. Knight, ed., *Classical Scientific Papers--Chemistry, Second*

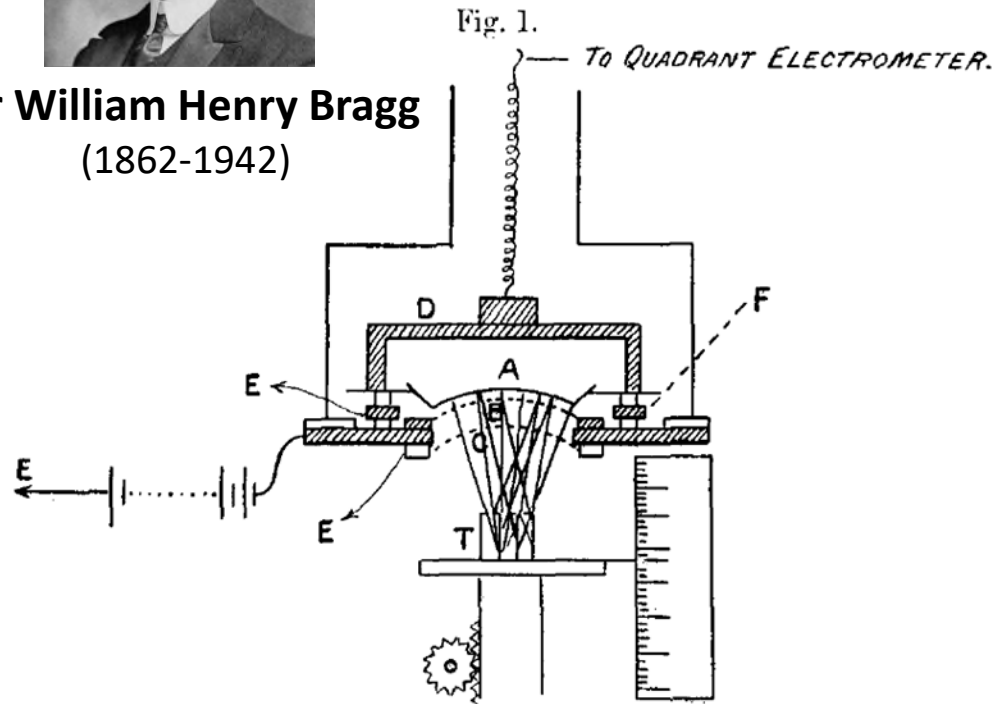
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Grupo  quirónsalud



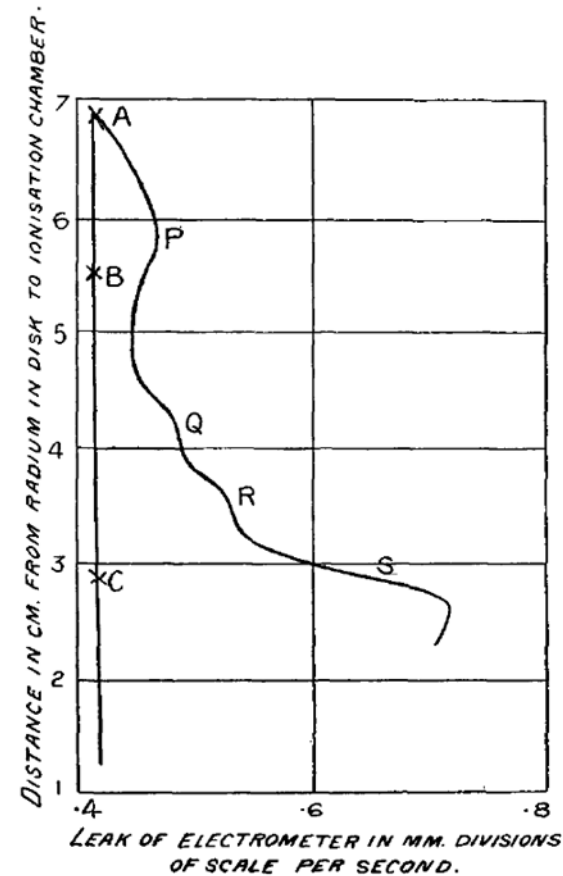
The Bragg Peak : ionisation of alpha particles

Sir William Henry Bragg
(1862-1942)



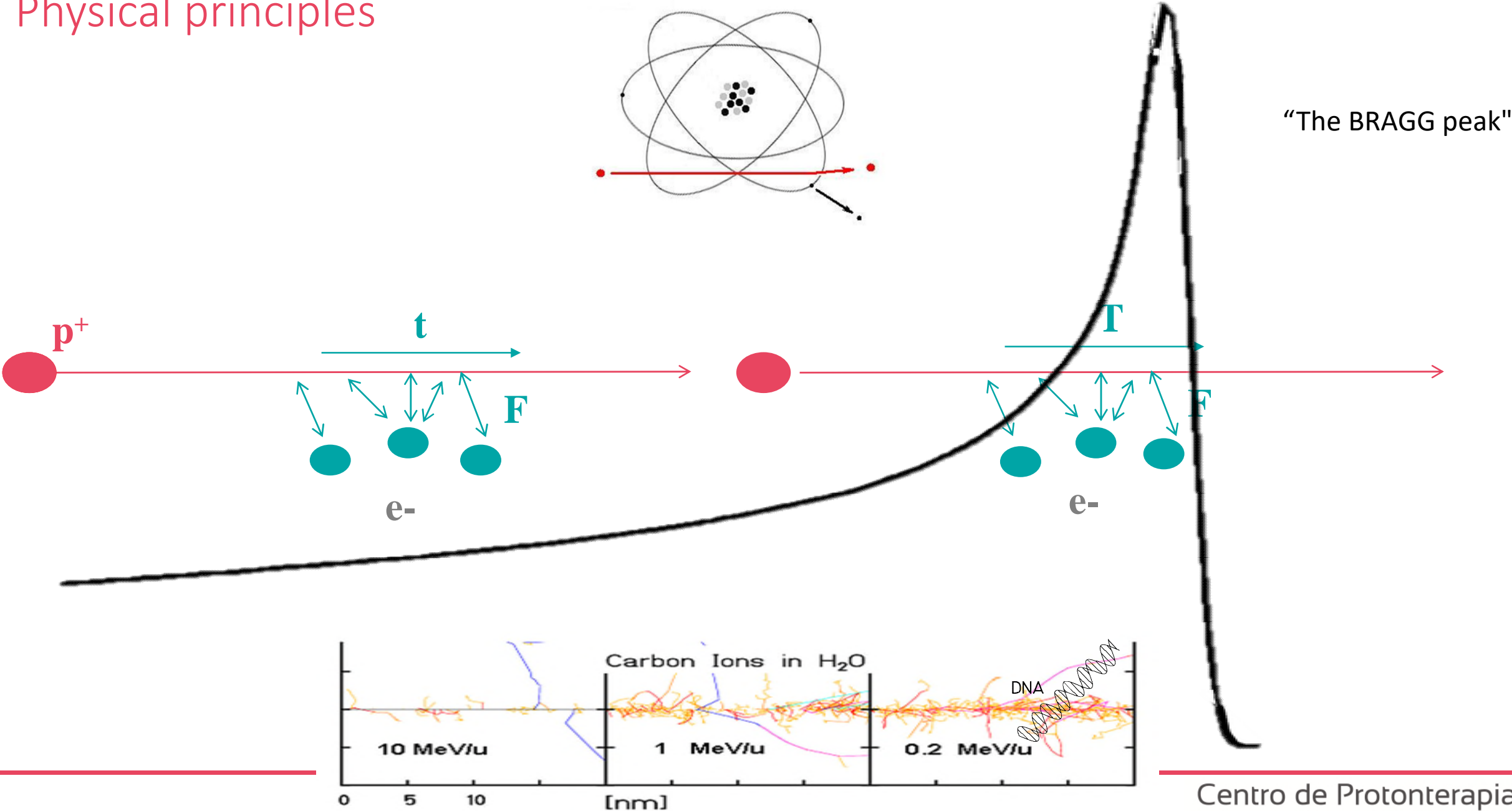
Arrangement of experiment:—Spherical ionization chamber. Conductors shaded, insulators plain. The gauze C made with B an external ionization chamber, which prevented any external ionization from entering the measuring chamber AB. It was only used occasionally, and seemed to be unnecessary.

Fig. 2.—Ionization curve of dish prepared seven days before.



- Professor W.H. Bragg M.A. (1904): LXXIII. On the absorption of α rays, and on the classification of the α rays from radium , Philosophical Magazine Series 6, 8:48, 719-725
 - W.H. Bragg M.A. & R. Kleeman (1904) LXXIV. On the ionization curves of radium , Philosophical Magazine Series 6, 8:48, 726-738

Physical principles

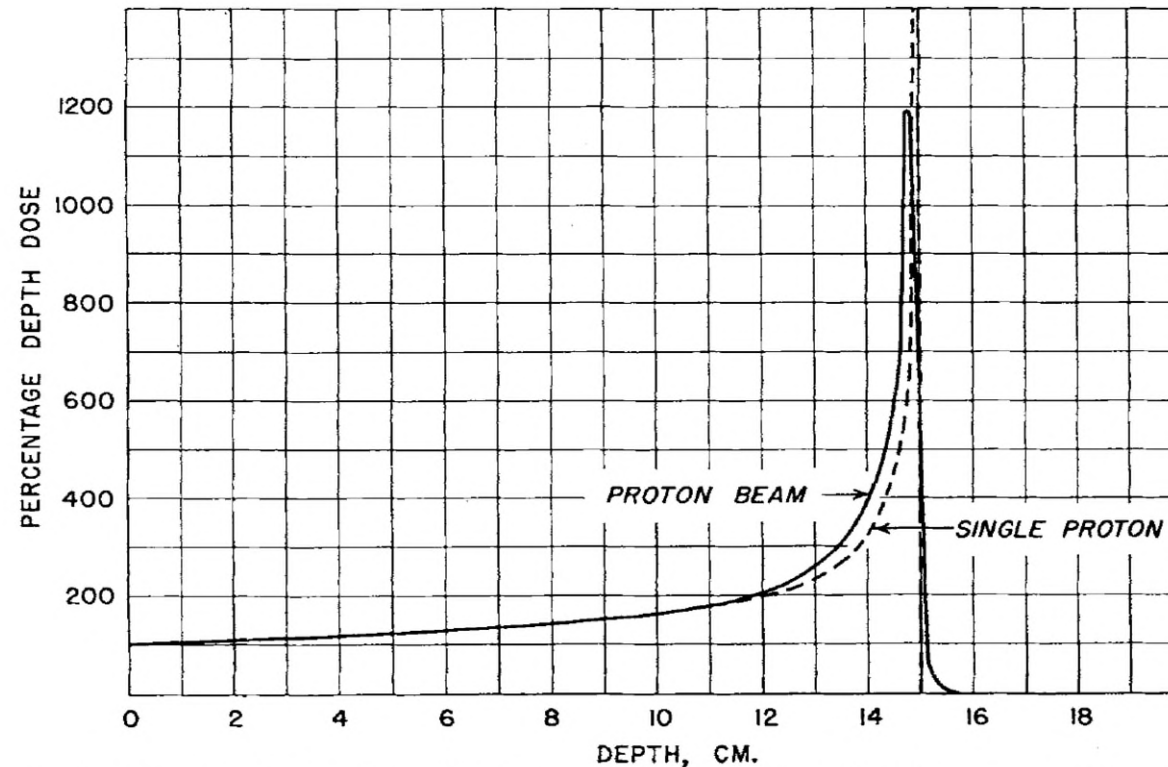


"The BRAGG peak"

Radiological Use of Fast Protons

ROBERT R. WILSON

Research Laboratory of Physics, Harvard University
Cambridge, Massachusetts



“The Bragg peak”

Fig. 2. The dotted curve shows the relative dose due to a single 140 Mev proton. The full curve shows qualitatively the depth dose curve for a beam of 140 Mev protons in tissue.



Ernest Lawrence



John.H. Lawrence

Since the 30's



The 1st cyclotron (1931)

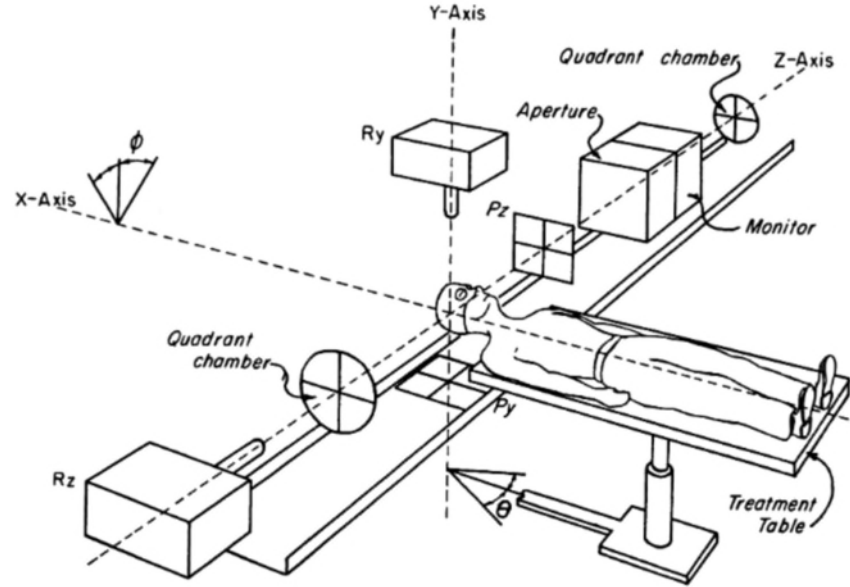


CHART 8.—A schematic drawing of the apparatus for proton irradiation of the human hypophysis

Apparatus for proton irradiation of hypophysis (and heavier ions) 1954 – 1986 -

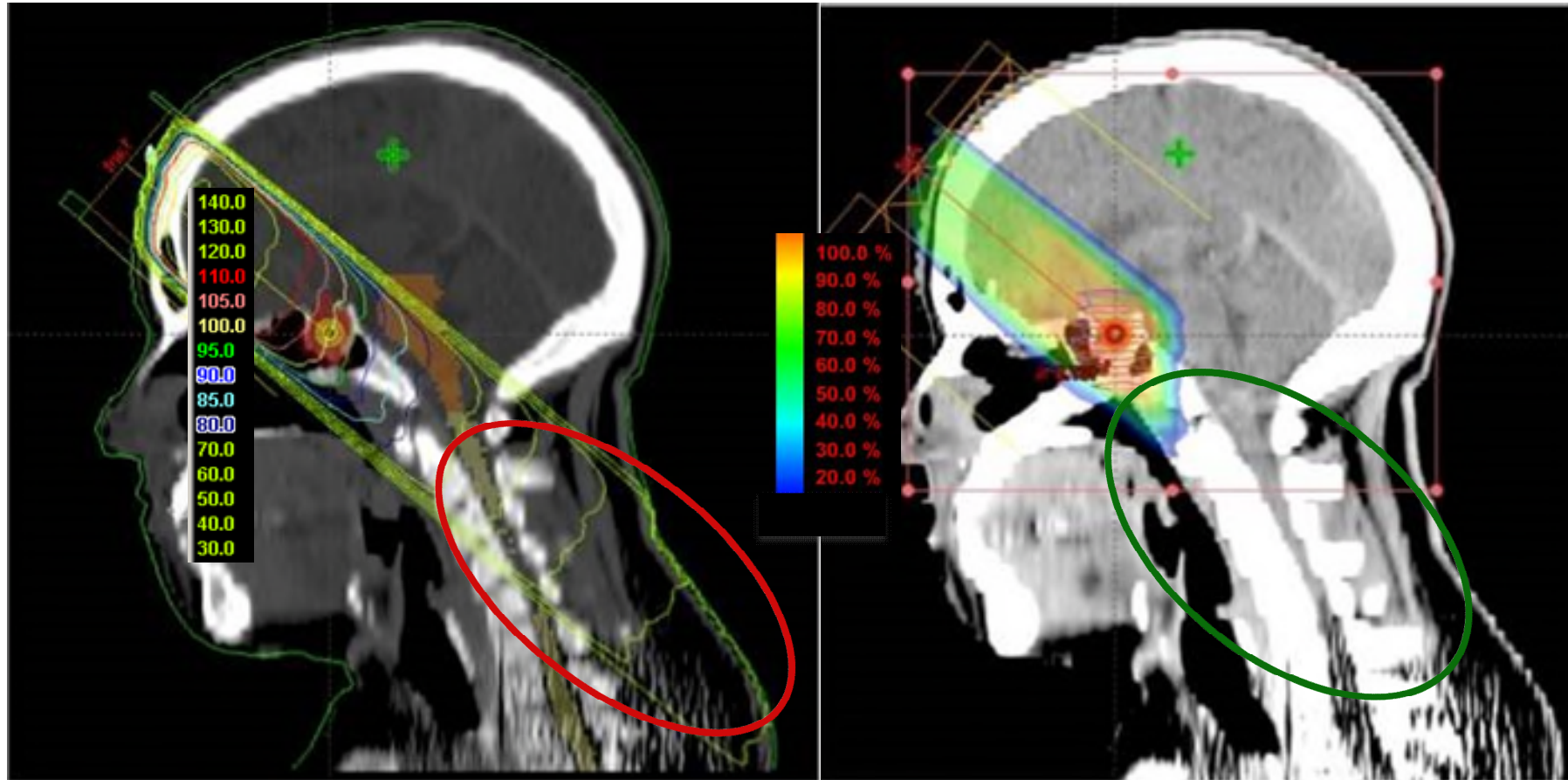
- Accelerators**
- Beam Delivery**
- Radiation Biology**
- Instrumentation**
- Planning system**
- Positioning systems**

....

Ejemplo de cálculo de un haz dirigido a un tumor de la base del cráneo

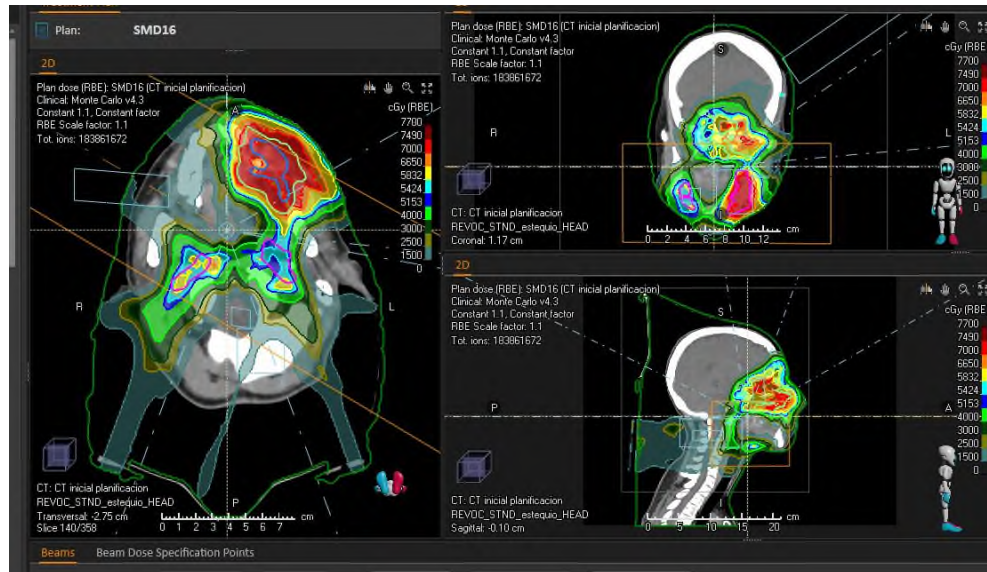
FOTONES

PROTONES

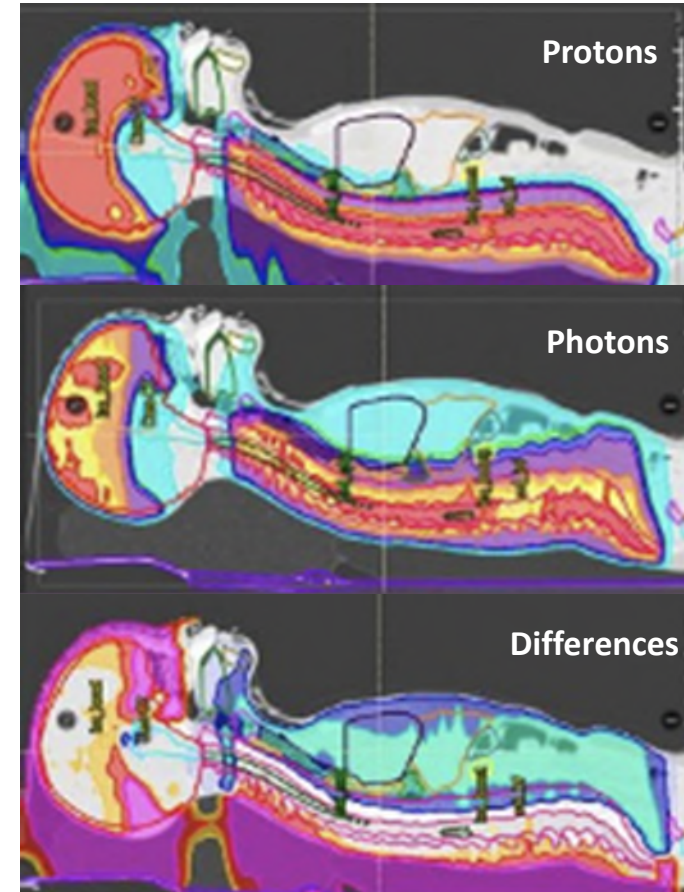


First referrals to Centro de Protonterapia Quirónsalud in Madrid: Complex cases

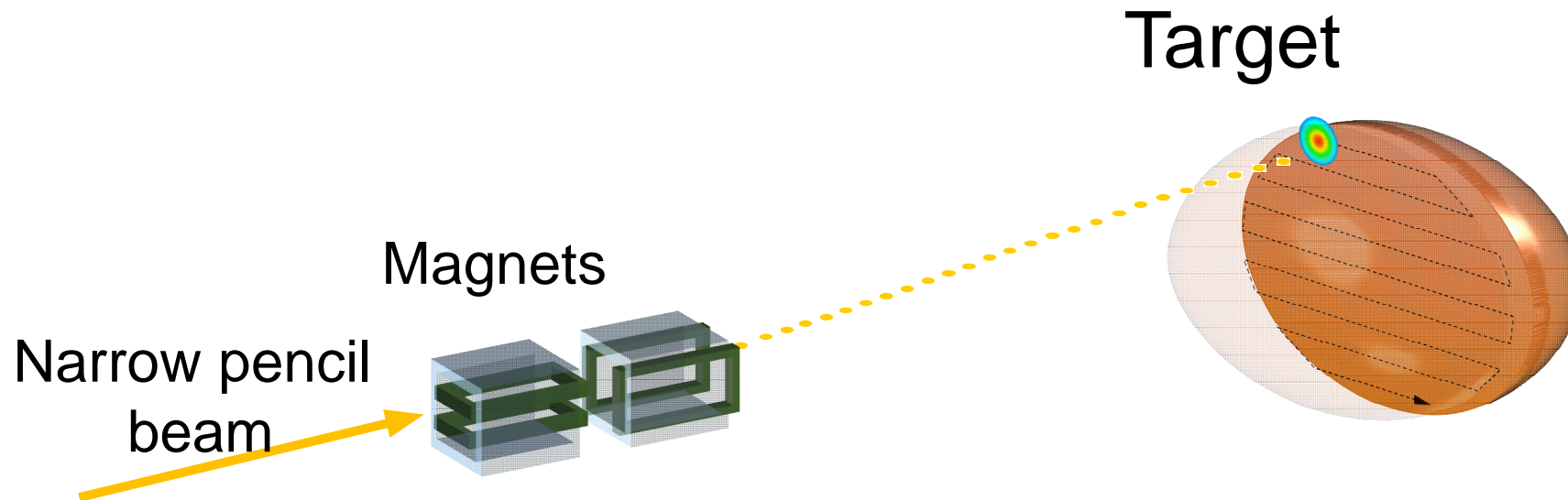
Head and Neck tumor



Craneospinal Irradiation (avoiding posterior fossa already treated)



Beam Delivery : 3D Pencil Beam Scanning

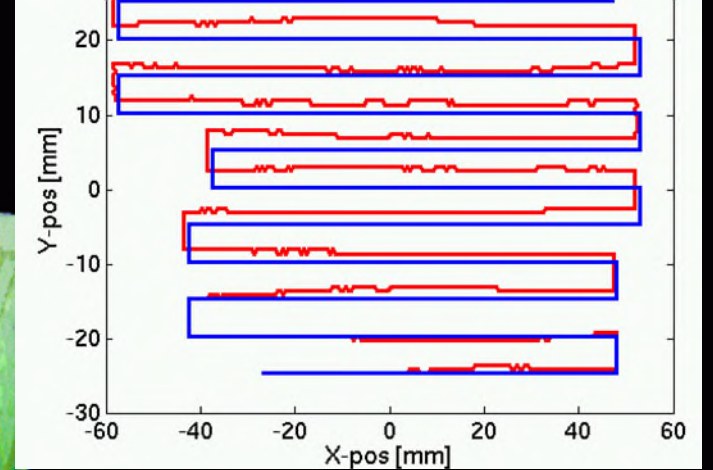
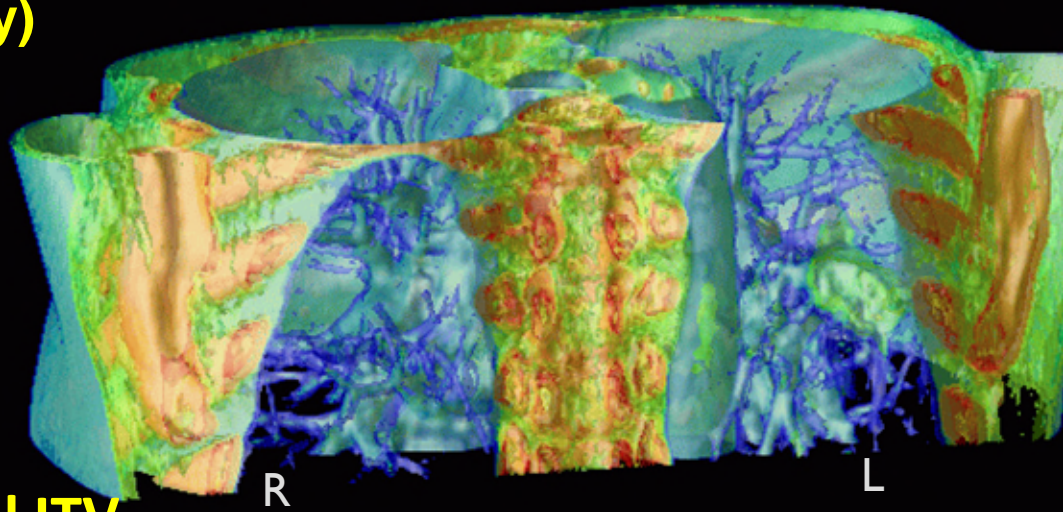


Movements and PBS (interplay)

E.Rietzel
(MGH → Siemens)

**Gating,
Residual ITV,
Tracking,
Repainting.**

Furukawa
(NIRS)
Repainting



Trofimov,
Bortfeld,
Lomax...

Fast rescan x20 times

Conventional scan

Quirónsalud Protontherapy Center

Stand-alone, opened to all public and private networks.



< 3 years

- 07/2016: Quirónsalud approves the project.
- 02/2017: **QS buys** the equipment from IBA.
 - 11/2018: Building ready & cyclotron rigging.
 - 10/2019: Acceptance of the equipment by QS.
- 12/2019: **First patient.**
- 01/2020: First general anaesthesia
- 01/2021: 1st year, 100 patients, 55% pediatrics

1 year



Centro de Protonterapia

16-01-2019

13:50

MADRID



0033

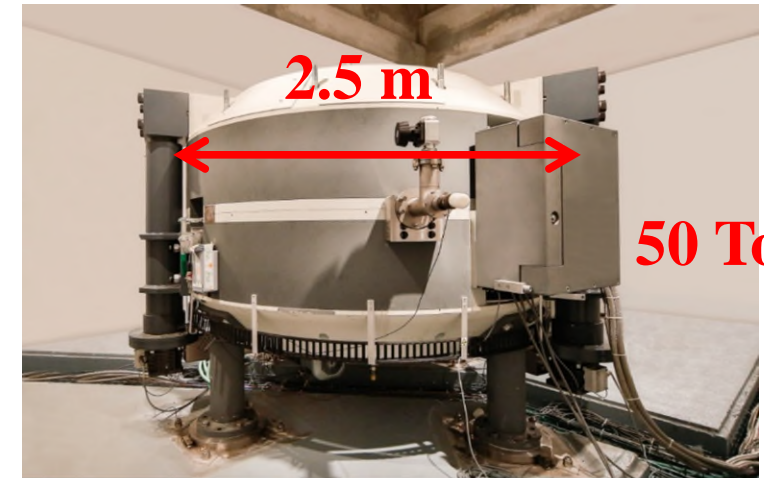
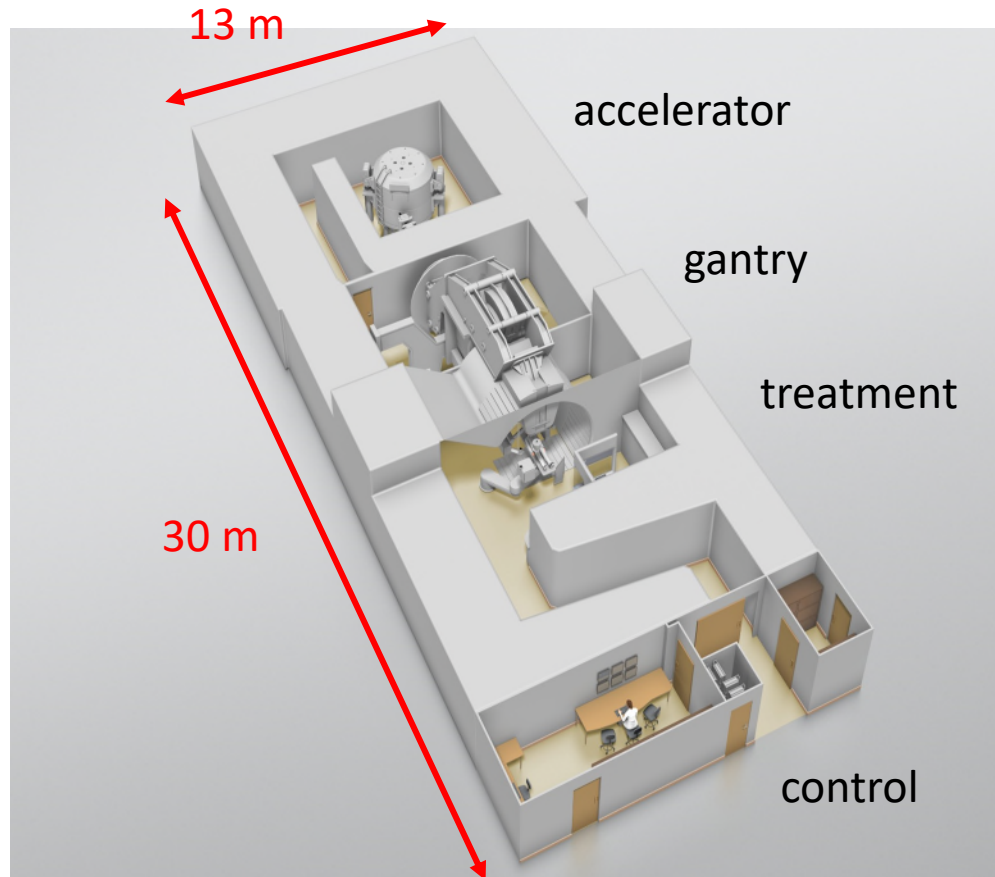
SEGUIMIENTO DE OBRAS.COM

TIMELAPSE LARGA DURACION

Architecture: stand-alone, modular



Equipment: Compact Single Protontherapy Room (Proteus One - Ion Beam Applications IBA)



Cryogenic compact synchrocyclotron



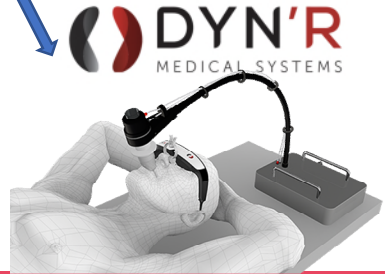
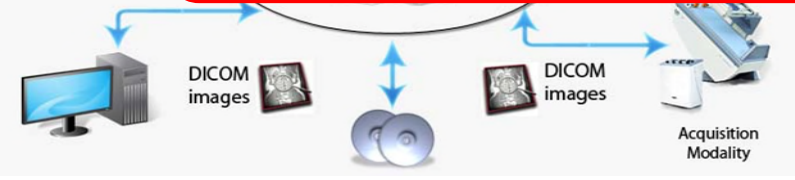
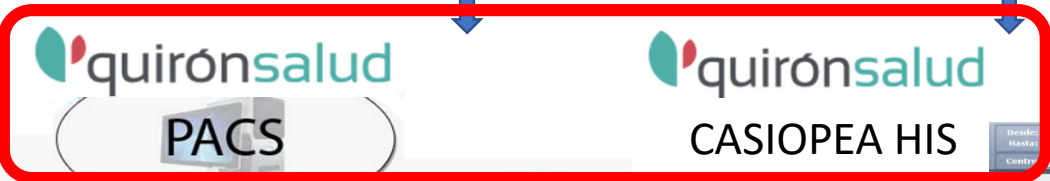
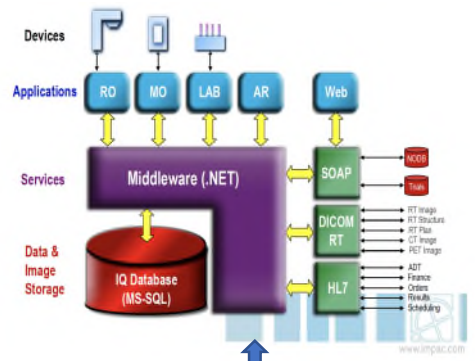
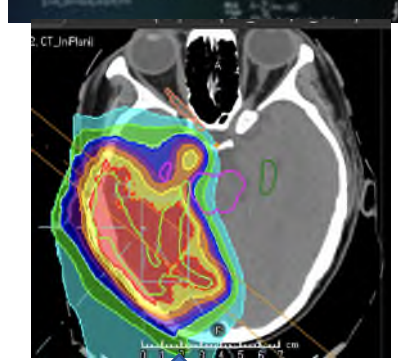
Open gantry (non-coplanar beams, anaesthesia,...)
Pencil beam scanning, Cone Beam CT
Robotic couch , rolling floor.

Protontherapy process and tools: integration

4D management

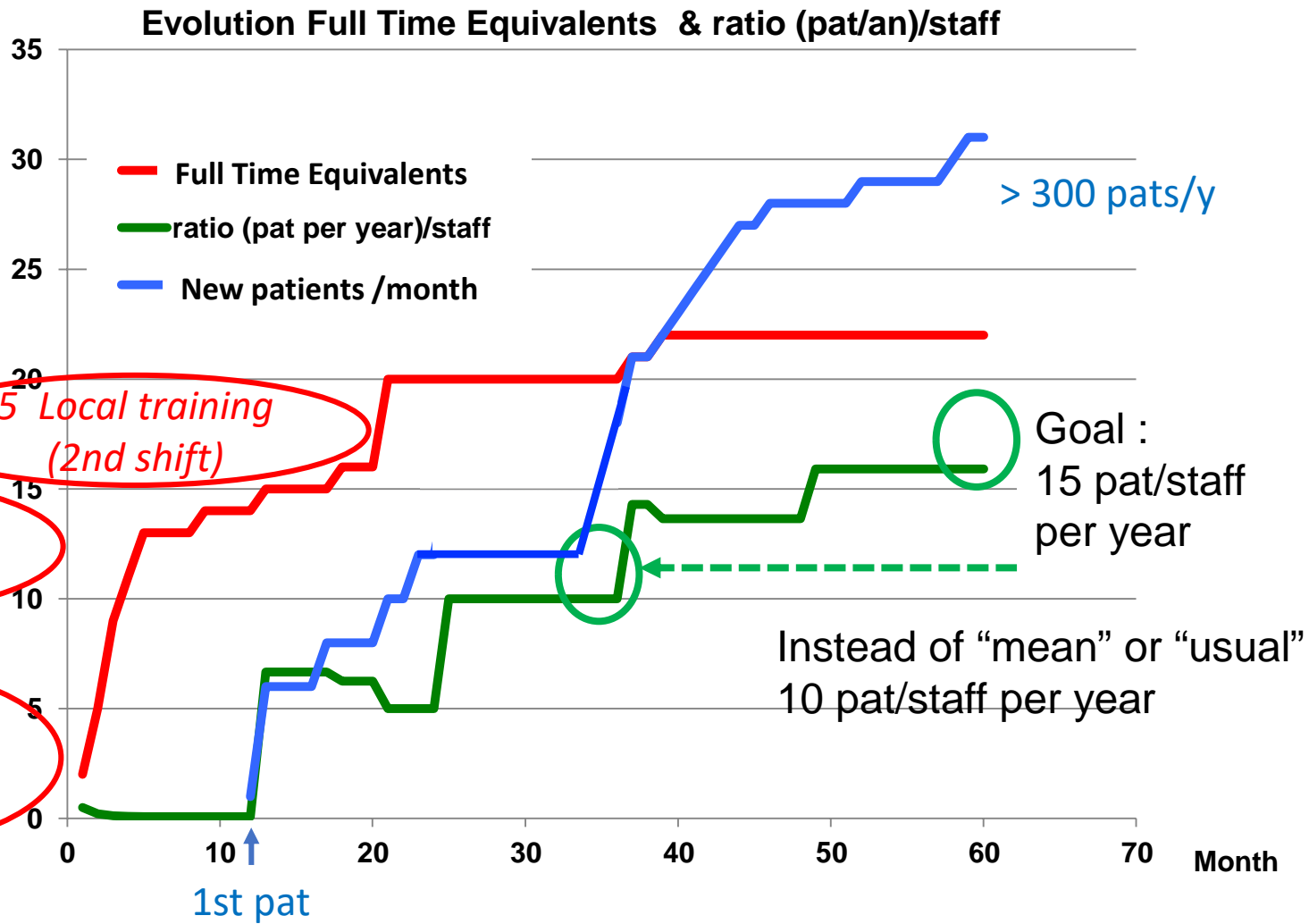


FIX positioning patients for life.®



Centro de Protonterapia

Evolution of Staff & patient rampup CPT Madrid (Usually... talking about "clinical staff")



**RECOMENDACIONES
DE LA SEOR PARA LA
PROTONTERAPIA
— EN ESPAÑA —**

ASTRO

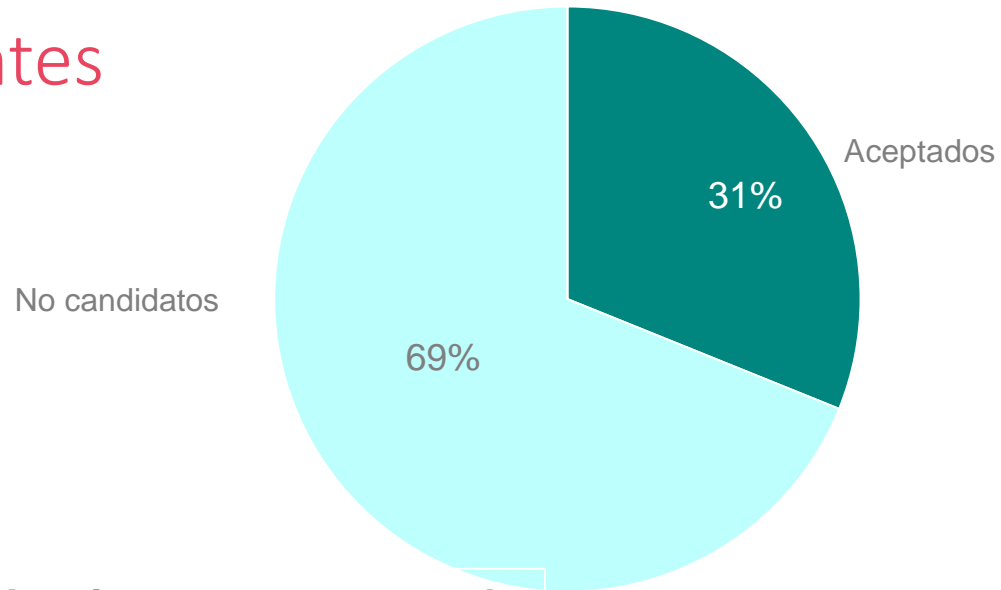
**Recomendations for Protontherapy in Spain
SEOR (Spanish Society of Oncology Radiotherapy)**

Malignant and benign primary central nervous system (CNS) tumors
Hepatocellular cancer
Advanced (e.g., T4) and/or unresectable head and neck cancers
Cancers of the paranasal sinuses and other accessory sinuses
Nonmetastatic retroperitoneal sarcomas

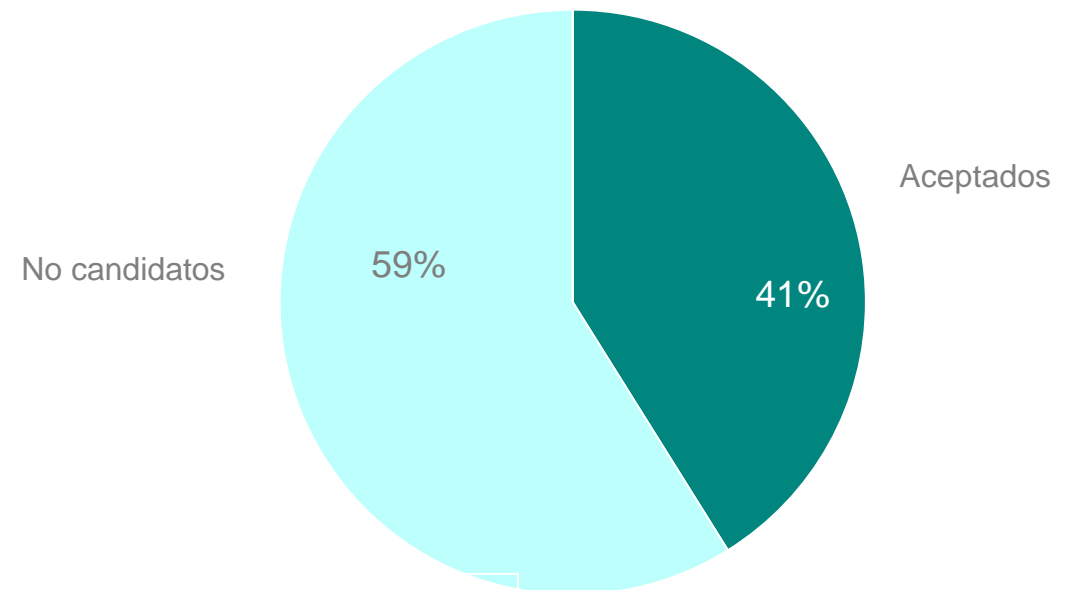
Group 1	Group 2	Group 3
Recommended	With study of quality of life and cost-benefit	Selected subgroups with study of quality of life and cost-benefit
Eyes	CNS	Breast
Base of skull	Head & Neck	Prostate
Neuroaxis	Lung	
Spinal cord and vertebral column	<p>Min 725 pats/y (3 rooms) for group I And potential ~ 18000 patients/y long term</p>	
Pediatrics		
Genetic syndroms with high risk of toxicity		
Re-irradiation		

Circuito pacientes

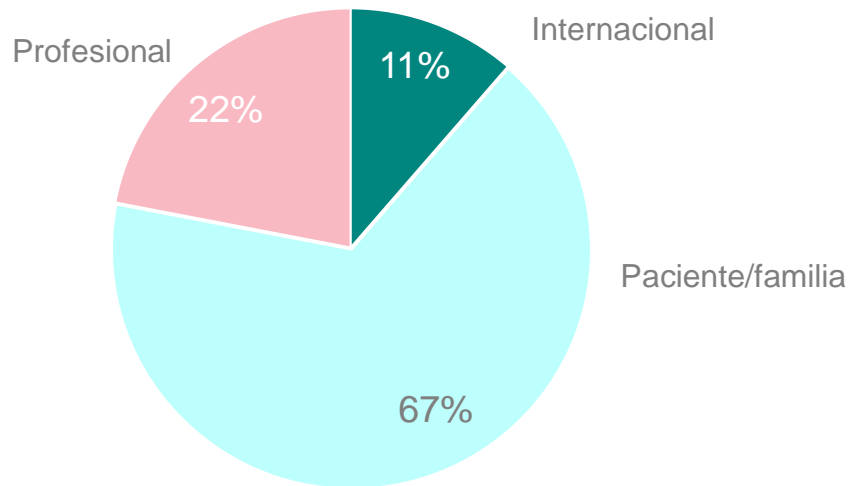
Casos primera valoración 2020



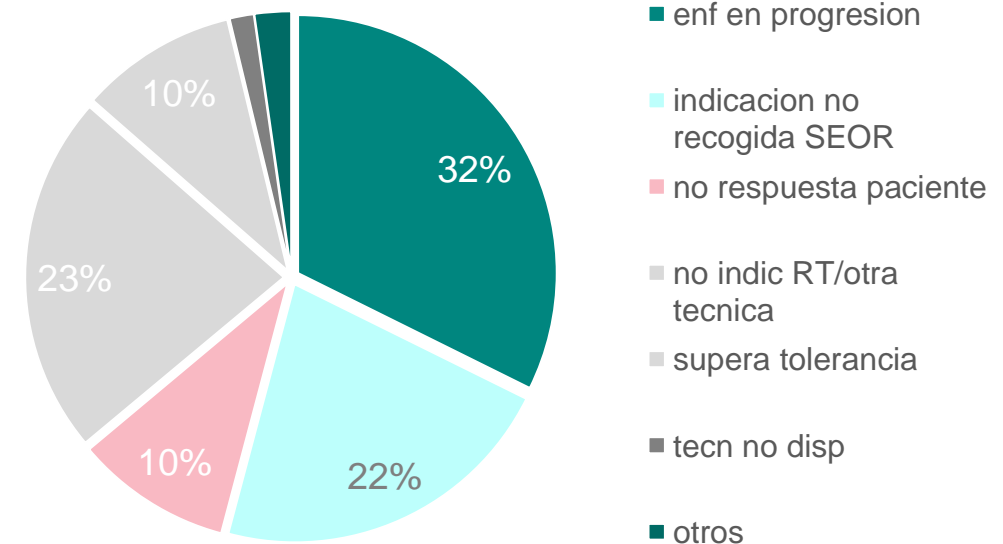
Casos primera valoración 2021



Procedencia casos no aceptados

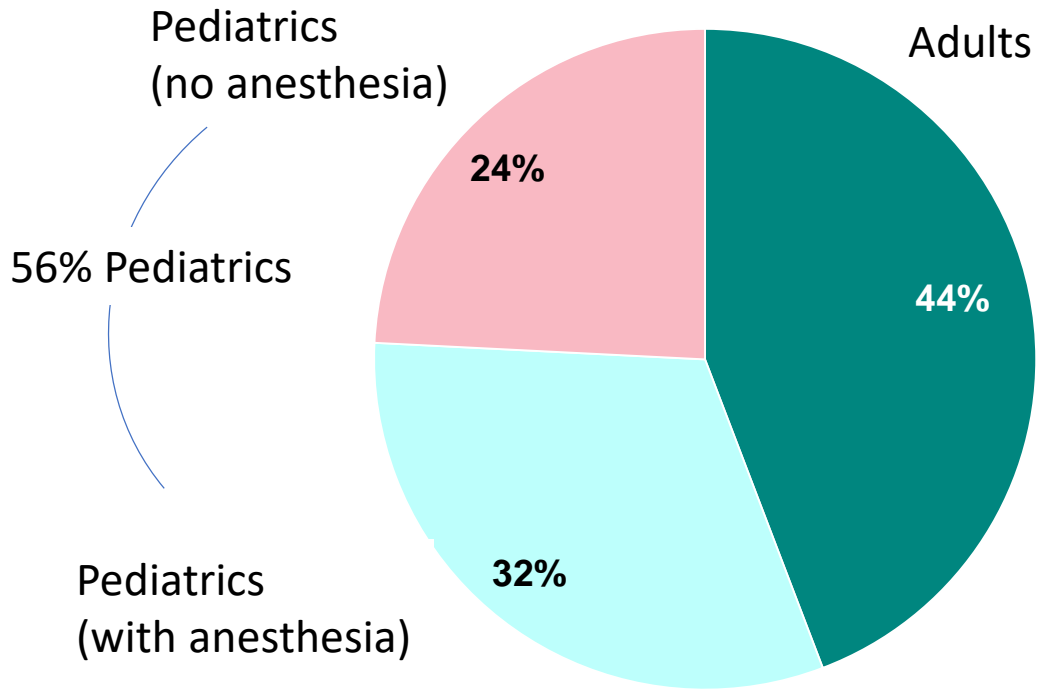


No candidatos: motivos

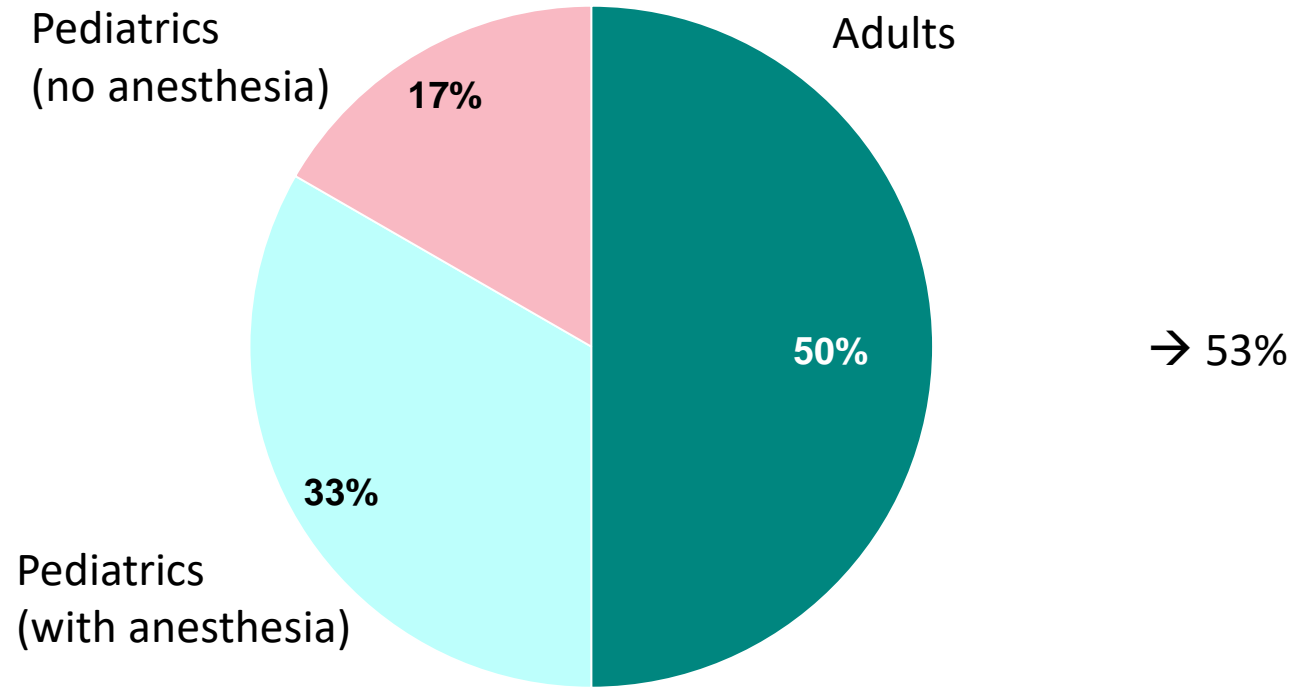


Evolution 12 to 22 months of clinical operation

Patients 1st year

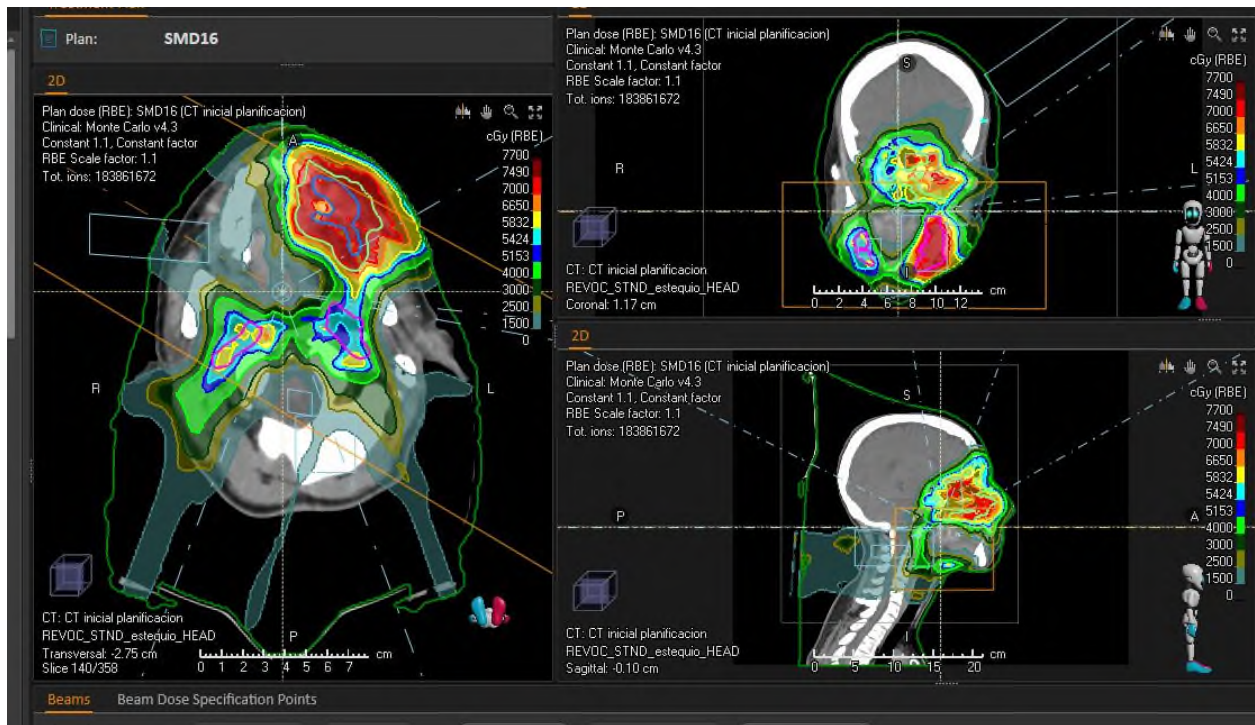


Patients 1,5 year



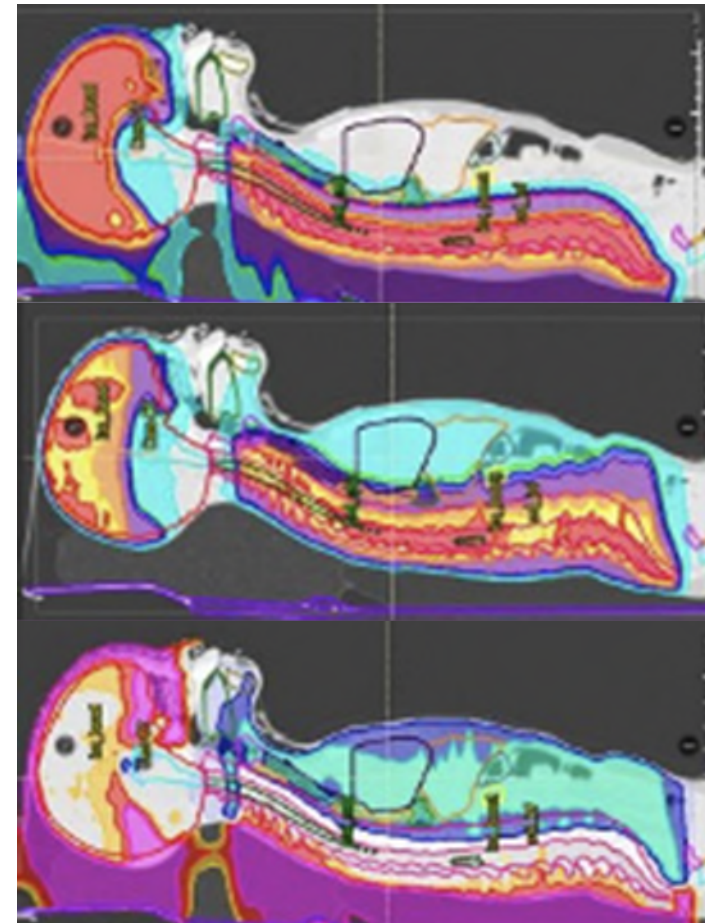
First referrals: complex cases:

Head and Neck tumor



Carcinoma Adenoide-quístico Seno Maxilar
con infiltración en base de cráneo

Craneospinal Irradiation (avoiding posterior fossa already treated)



Protons

Photons

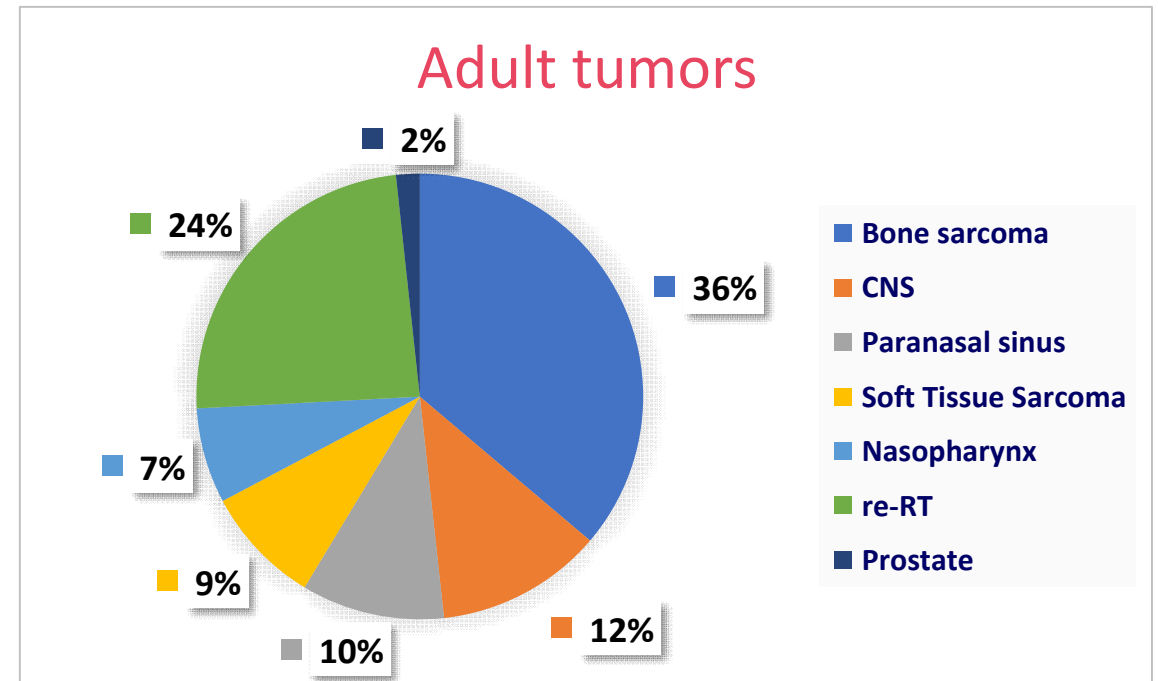
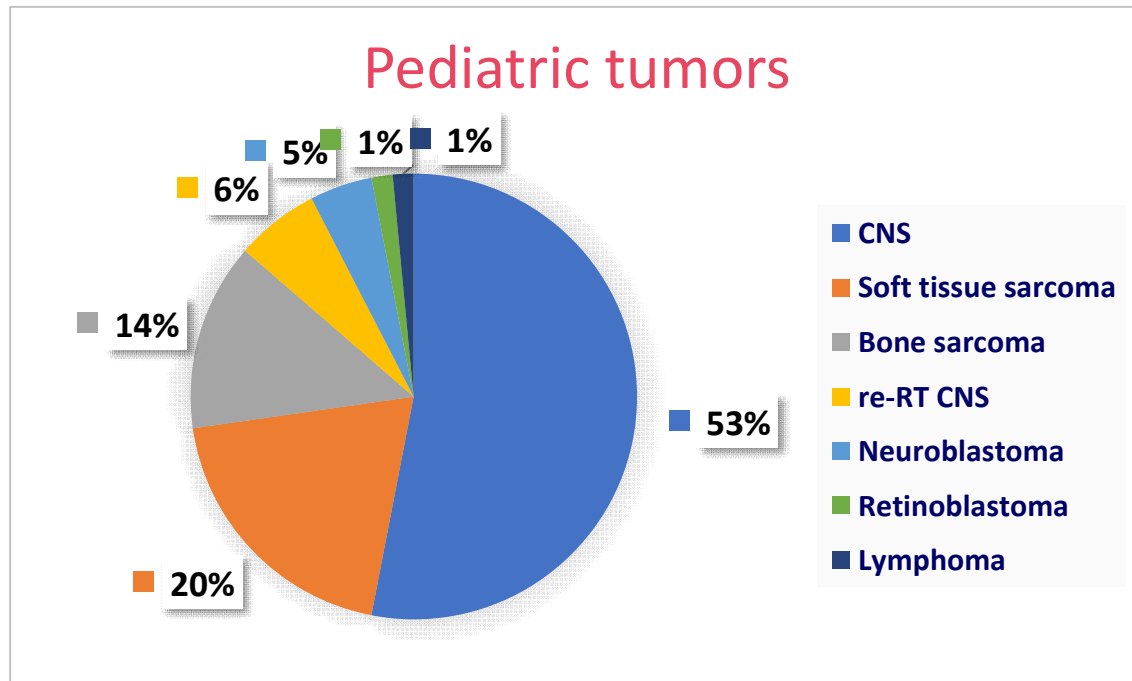
Differences

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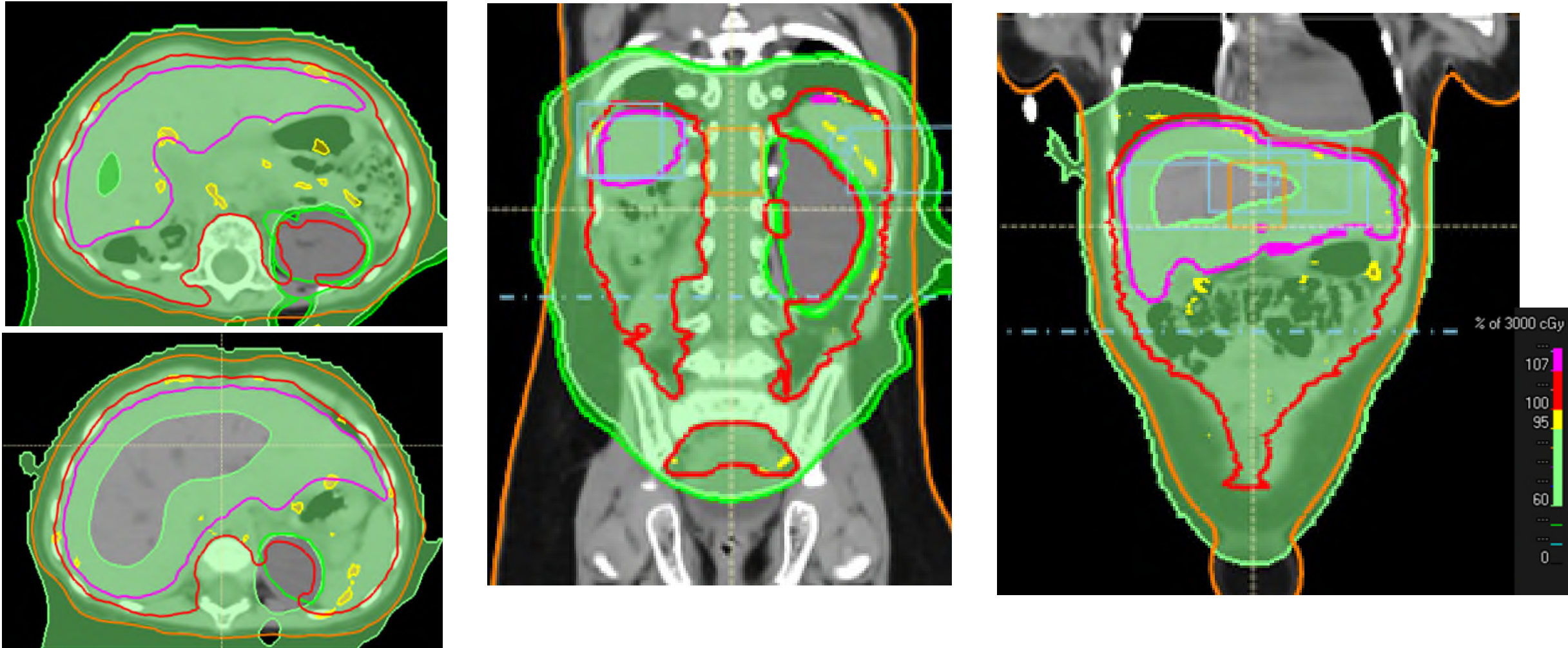
Pacientes Pediátricos y Adultos – Distribución patologías

Primeros 124 pacientes con más de 3 meses de seguimiento

C.Ares SEOR 2021



Irradiación peritoneal total



Niño de 2 años – rabdomiosarcoma abdominal con rotura tumoral y hemoperitoneo

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Outcome – Pacientes Pediátricos (n=66)

→ Seguimiento Medio 8,5 meses (rango, 3 – 17,8 meses)

• Vivos sin evidencia de enfermedad	56	(84,8%)
• Vivos con Recidiva local (in-field)	2	(3%)
○ Supratentorial ETMR (Embryonal tumor with multilayered rosettes)		
○ Supratentorial ATRT (Atypical Teratoid Rhabdoid Tumor)		
• Vivos con Progresión metastática	4	(6%)
○ Progresión leptomenígea		
▪ Re-RT ependymoma (2)		
▪ Metastatic Germ Cell Non-Germinoma (1)		
▪ CNS relapse Neuroblastoma (1)		
• Exitus	4	(6%)
○ Skull Base ATRT – recidiva local		
○ Ewing Sarcoma – enfermedad M1 con Control local		
○ Rhabdomyosarcoma parameníngeo - enfermedad M1 (diseminación leptomenigea) con Control local		
○ Medulloblastoma M3 – progresión enfermedad leptomenígea		

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Outcome – Pacientes Adultos (n=58)

→ Seguimiento Medio 7,9 meses (rango, 3 – 19,3 meses)

• Vivos sin evidencia de enfermedad	51	(87,9%)
• Recidiva local (in-field)	5	(8,6%)
○ CNS – DMLG		
○ Carcinoma escamoso senos paranasales		
○ Re-RT cordoma		
○ Re-RT glioblastoma		
○ Osteosarcoma Base de Cráneo		
• Progresión metastática con control local	2	(3,4%)
• Exitus	3	(5,2%)
○ M1 Sarcoma Ewing		
○ M1 Cordoma indiferenciado		
○ Progresión local Osteosarcoma Base de Cráneo		

Toxicidades Pacientes adultos

	Acute Toxicities	Late Early Toxicities
Dermatitis		
	G3 4	0
	G2 17	0
	G1 14	3
Alopecia		
	G2 7	0
	G1 1	1
Xerostomia		
	G1 2	4
Mucositis		
	G3 5	0
	G2 11	0
	G1 6	0
Conjunctivitis		
	G2 1	0
	G1 3	0
Citopenia		
	G2 1	0
	G1 2	0
Fatigue		
	G1 5	1
Nauseas /Vomits		
	G3 1	0
	G1 3	0
Rectitis		
	G1 1	0
Worsening paresis VI cranial nerve		
	G1 1	
Trigeminal neuralgia		
	G3 0	1
Trismus		
	G2 0	1

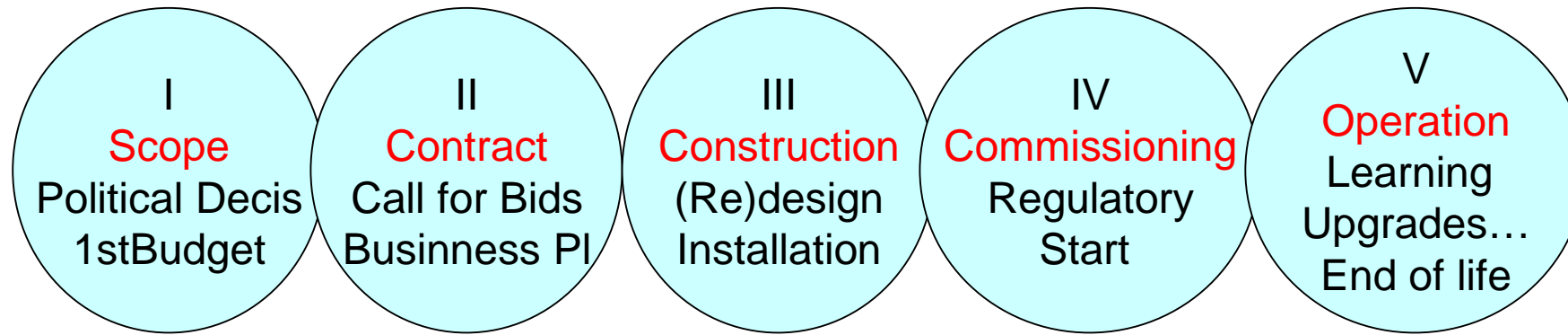
Pacientes pediátricos

	Acute Toxicities	Late Early Toxicities
Dermatitis		
	G3 3	0
	G2 4	0
	G1 38	0
Alopecia		
	G2 34	0
	G1 5	3
Maudarosis		
	G2 3	2
Mucositis		
	G3 2	0
	G2 3	0
	G1 5	0
Conjunctivitis		
	G2 1	0
Laryngitis		
	G1 1	0
Citopenia		
	G3 4	0
Leukoencephalopathy Brainstem		
	G3 0	3
	G1 0	1

Una oportunidad para España ! 10 centros públicos de protonterapia



Phases of a project



I. Scope

Public or private? Who is the driver?

Protons only or other ions?

Clinical only or **with research**?

Non profit, **self maintained**, high or mid benefits?

Open patient mix or limited **recognized indications**?

Hospital based or **independent site**?

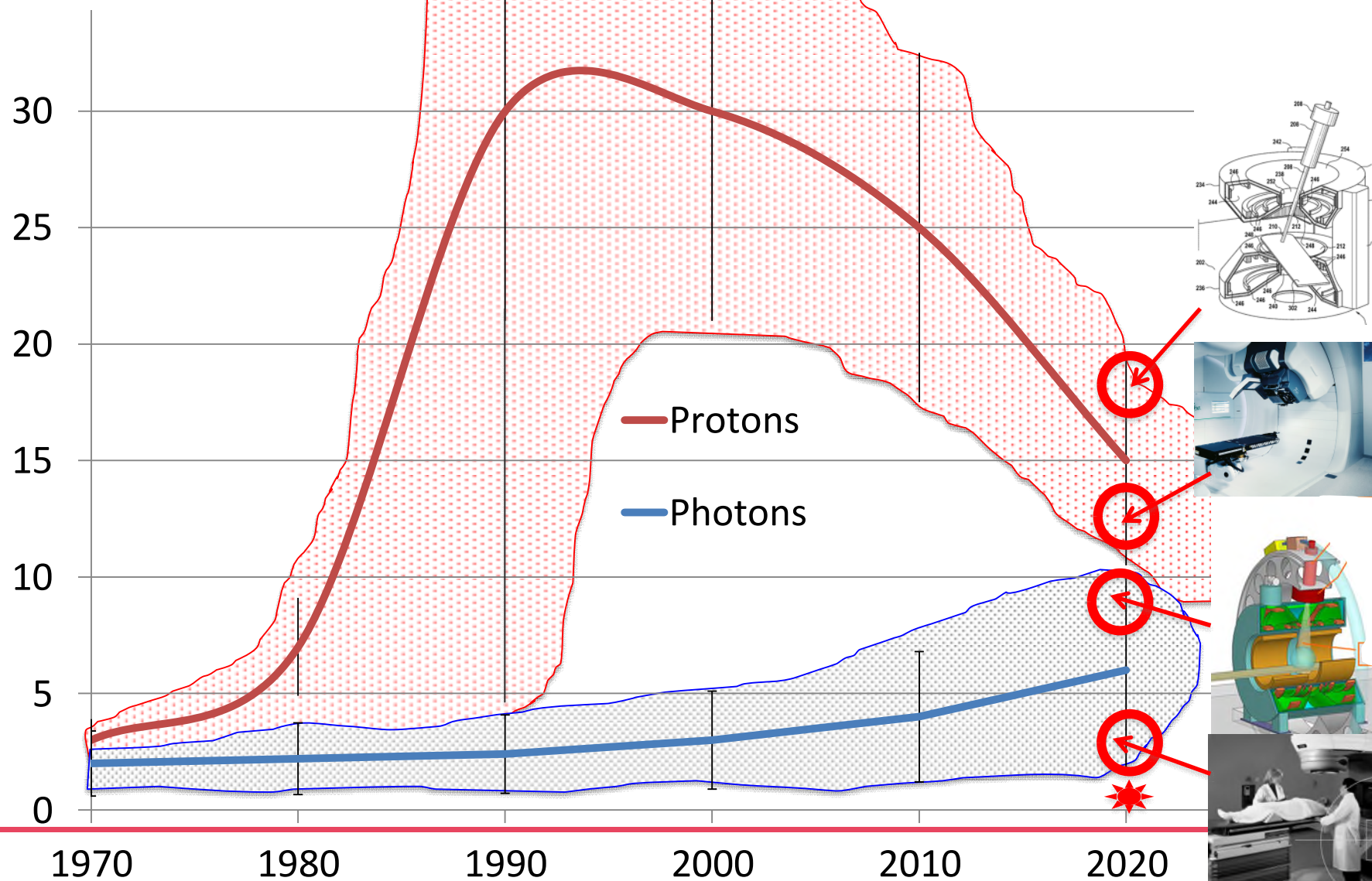
Single room or multiple rooms?

Open or closed gantry?

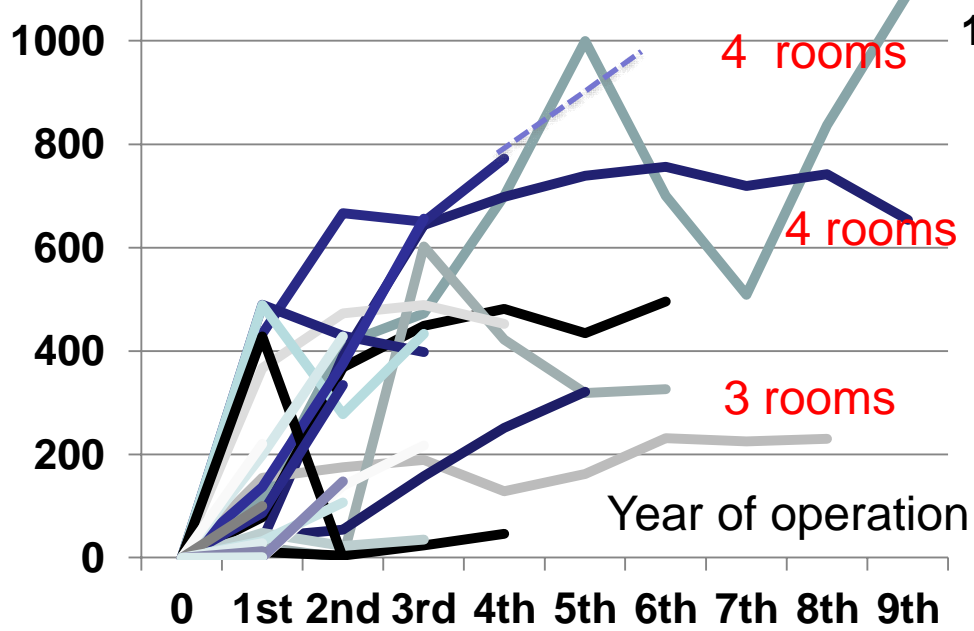
(Utopical linear approach)

Cost 1 Room (technology)
(qualitative)
[~ M€]

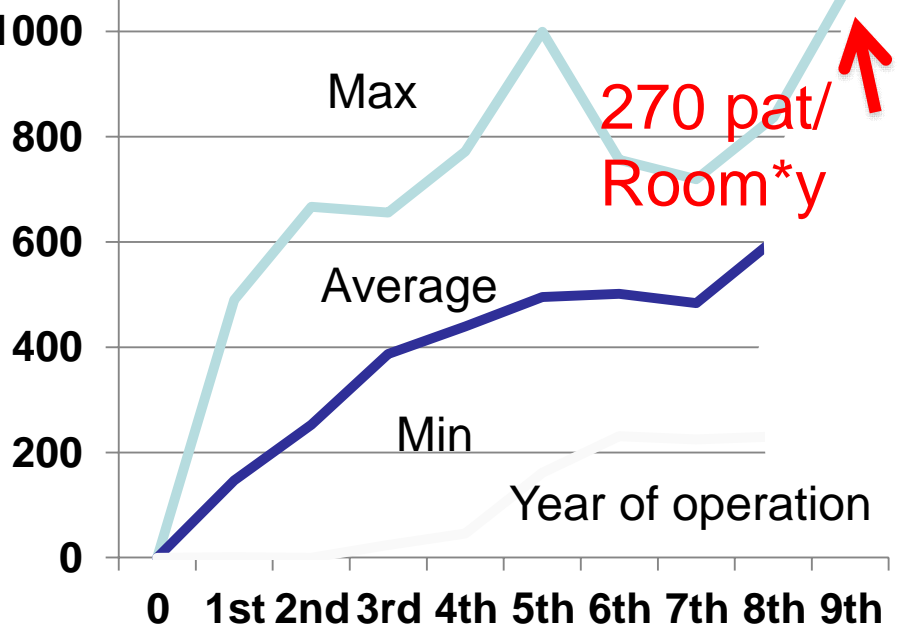
EQUIPMENT COST
(<50% of total)



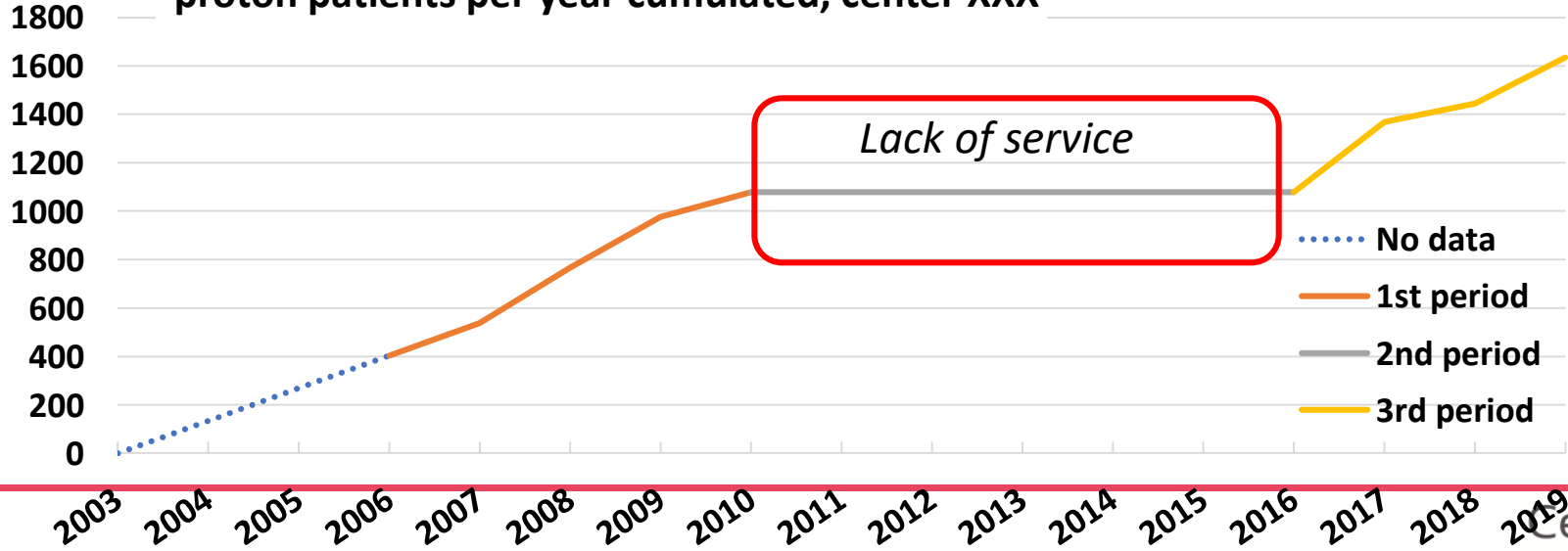
PATS PER YEAR (2005-2014)



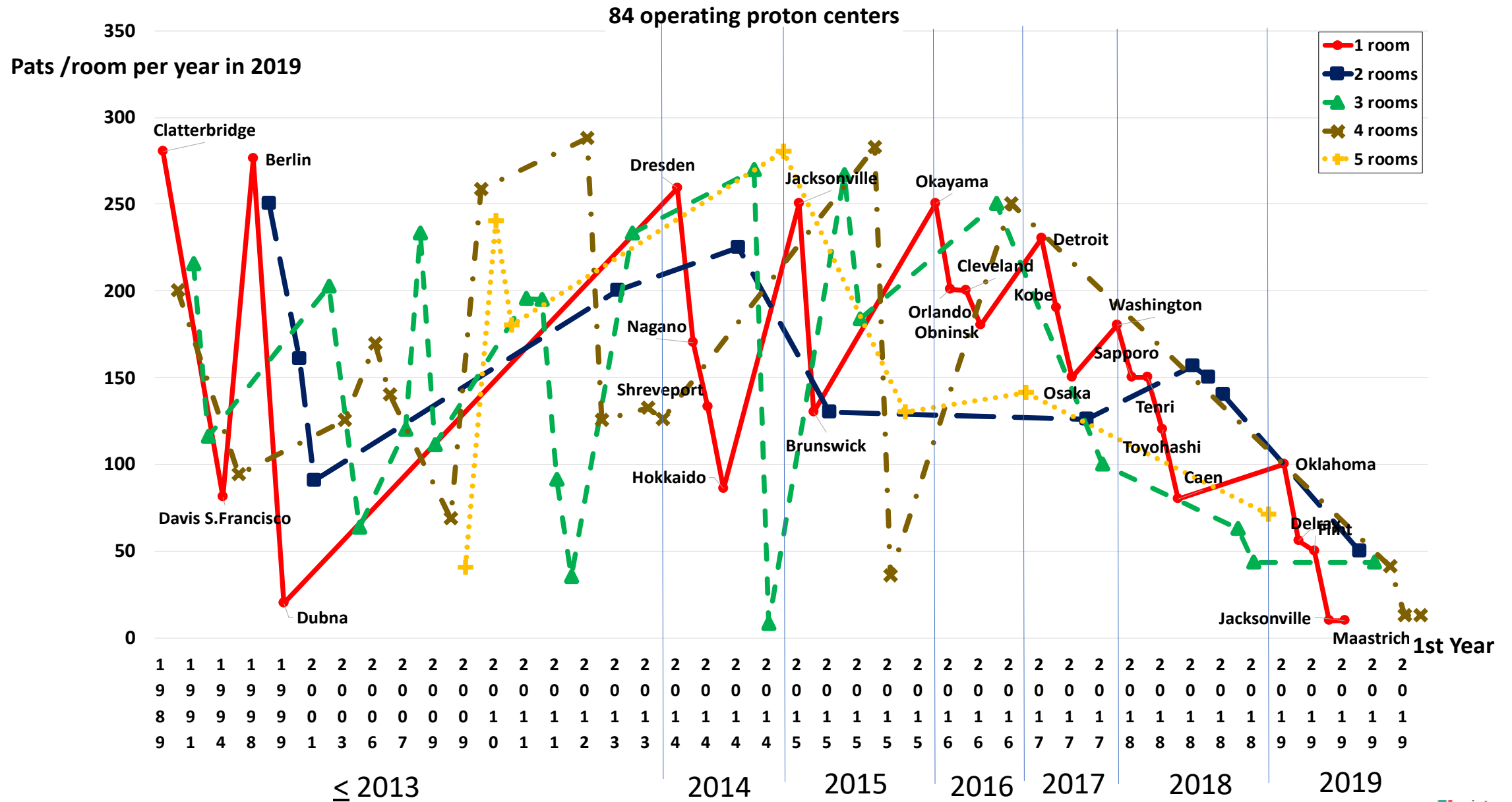
(25) New proton centers



proton patients per year cumulated, center XXX

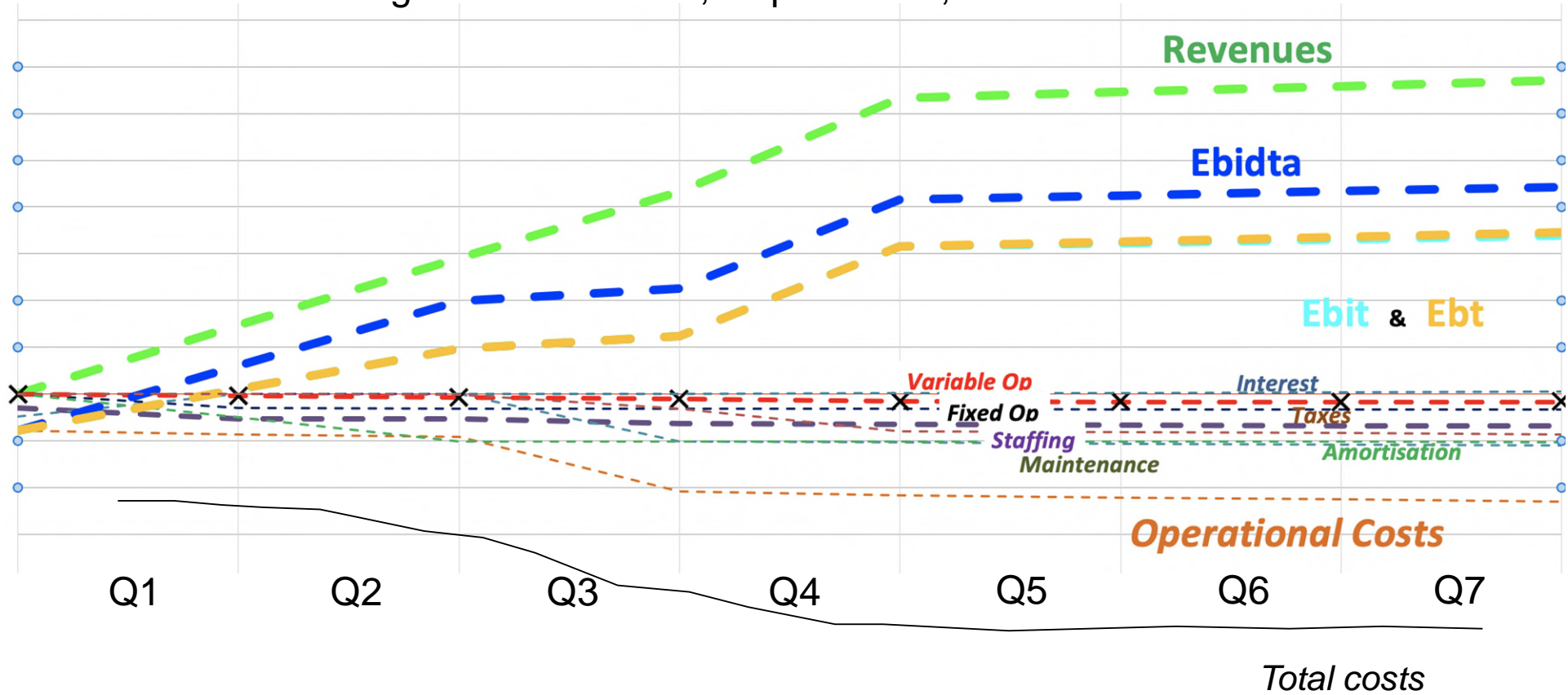


WORLD : patients per room per year in 2019



THE IMPORTANCE OF A REALISTIC BUSINESS PLAN
(THIS IS NOT A GOOD ONE)

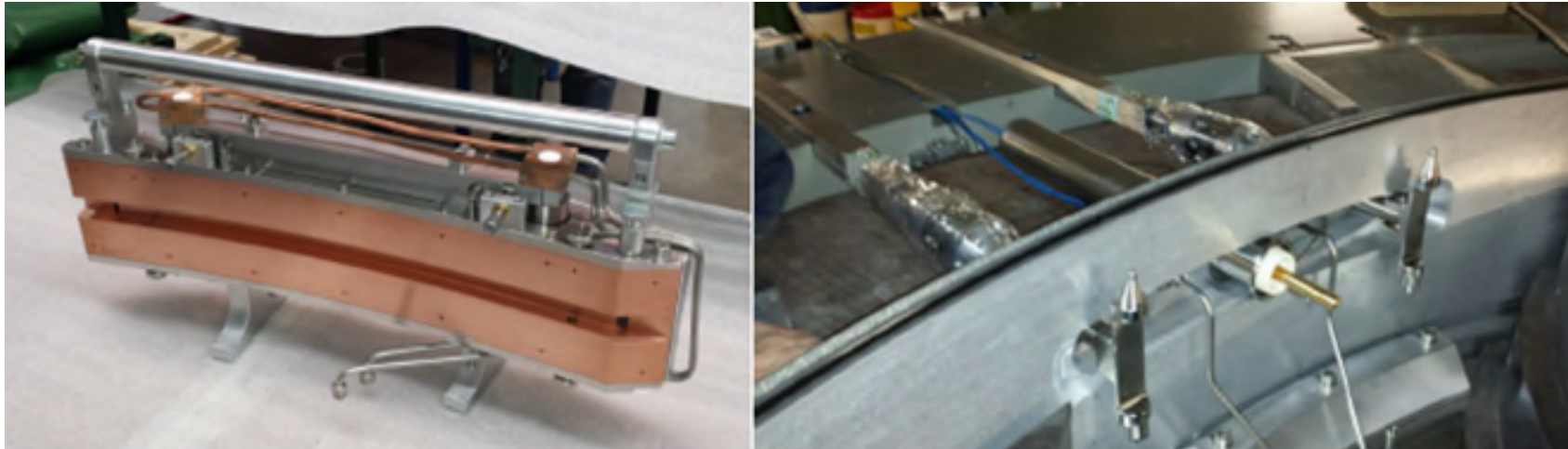
EBIDTA : Earnings Before Interest, Depreciation, Taxes and Amortization



Updates and upgrades ... : if you want to keep your facility 5, 10, 15... years

**Examples of upgrades:
need to know the (short term) roadmap**

- *New version of the deflector*
- *Rolling floor*
- *CBCT*
- *Gamma prompt*
- *Moving organs*
- *Arcttherapy*
- *Ophtalmic line*
- *Radiosurgery*
- *Flash....*



S.Meyroneinc. Curie Training Course, 2018 & A. Mazal 2020

BJR 2020

PROTON THERAPY SPECIAL FEATURE: REVIEW ARTICLE

Proton therapy delivery: what is needed in the next ten years?

¹ANDRIES N. SCHREUDER, M.Sc. (Med) and ²JACOB SHAMBLIN, PhD

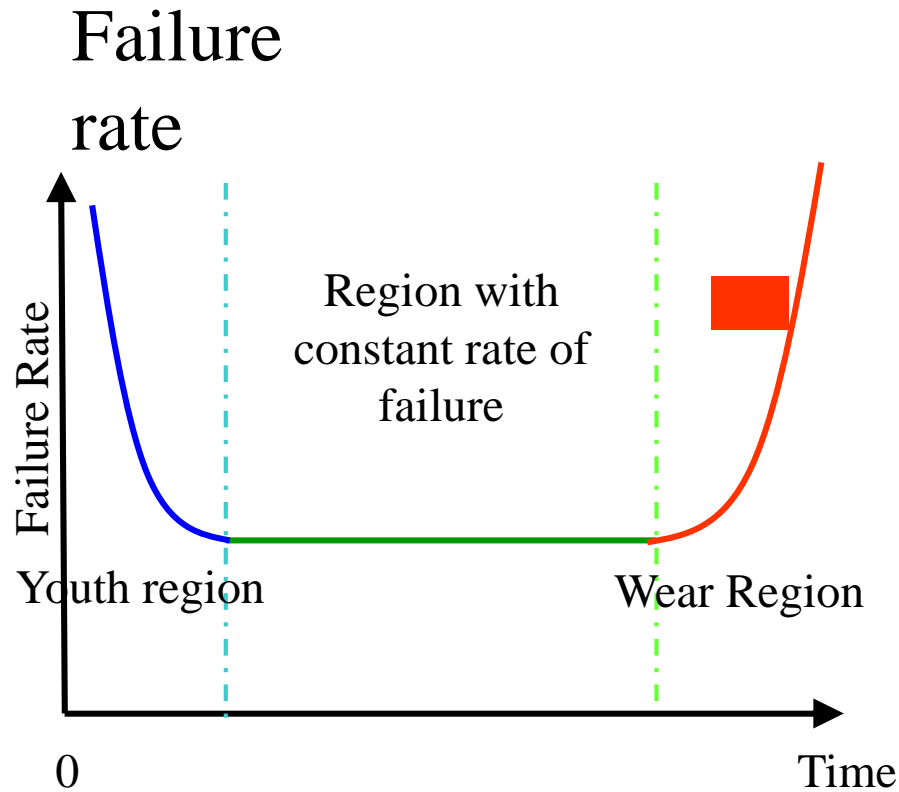
¹Provision Center for Proton therapy - Knoxville, 6450 Provision Cares way, Knoxville, TN 37909, USA

²ProNova Solutions, LLC, 330 Pellissippi Place, Maryville, TN 37804, USA

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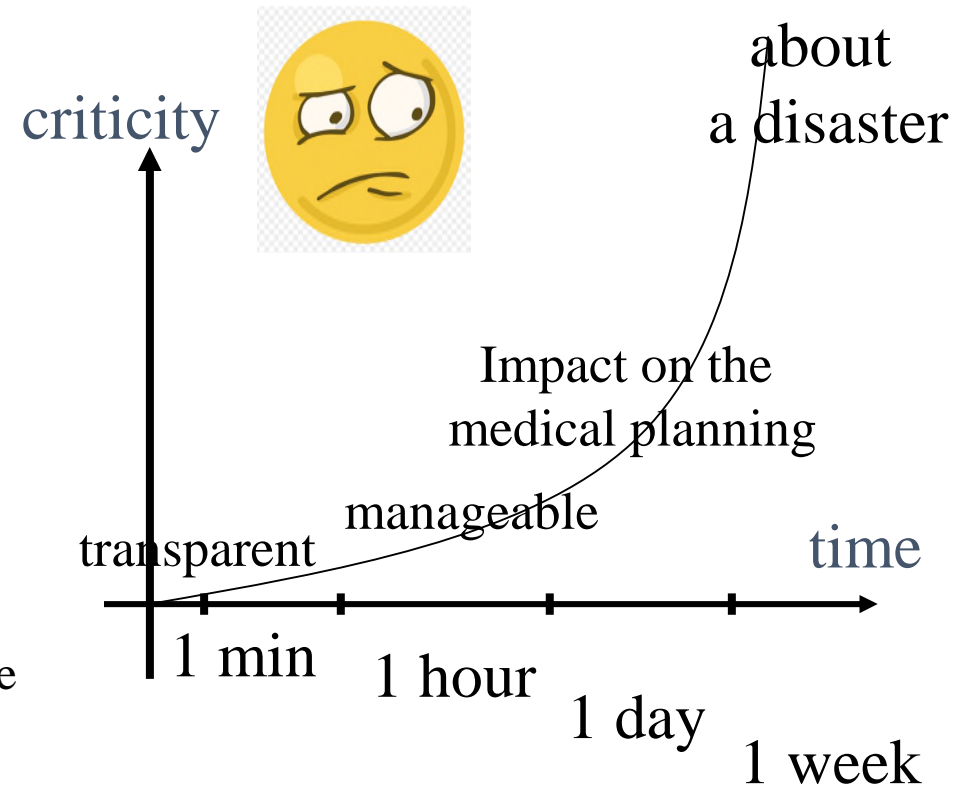
Grupo  Quirónsalud

The reliability bath curve



And this shape happens also in every planned stop!

Criticality of breakdowns



Erreur de fractionnement 1 fx de 13 Gy au lieu de 4x 4,3 Gy

Le 22 décembre 2011, le centre Antoine Lacassagne à Nice a déclaré à l'Autorité de [sûreté nucléaire](#) (ASN) un incident relatif à une erreur de fractionnement de la [dose](#) délivrée lors du traitement d'une pathologie oculaire d'un patient par protonthérapie^[1].

Le patient a reçu une dose de 13 grays lors de la première séance du traitement alors que le protocole thérapeutique planifié prévoyait la réalisation de quatre séances de 4,3 grays chacune. À la suite de la détection de cette erreur, une seconde séance de 1 [gray](#) a été réalisée. L'incident ne consiste donc pas en un dépassement de la dose totale prévue mais à une erreur dans le fractionnement de la dose délivrée, qui a entraîné une exposition aiguë du cristallin lors de la première séance.

Classement ASN-SFRO de l'incident



Erreur de volume 1 fx regard pas correct

Le 19 juin 2013, le Centre de protonthérapie d'Orsay a informé l'Autorité de [sûreté nucléaire](#) (ASN) d'un incident survenu lors du traitement d'un œil d'un patient.

Cet événement s'est produit lors de la première séance d'un traitement qui en comptait 4. Lorsque l'équipe a examiné les images de la position de l'œil à l'issue de la séance, elle a constaté que l'œil du patient n'avait pas été placé correctement et qu'une [dose](#) avait été délivrée en dehors du volume prévu.

Classement ASN-SFRO de l'incident



Erreur de lateralité 10 fx 2,2 Gy paupière droite

Le 7 octobre 2019, le centre de lutte contre le cancer (CLCC) de Caen a déclaré à l'ASN un incident survenu dans le service de [radiothérapie](#). Lors d'un traitement par protonthérapie, un patient a reçu 10 séances de traitement de 2,2 [Gy](#) sur la paupière droite, au lieu de la paupière gauche. Le traitement initial prévoyait 28 séances de 2,2 Gy au niveau de la paupière gauche pour une [dose](#) totale de 61,6 Gy.

Classement ASN-SFRO de l'incident



2009

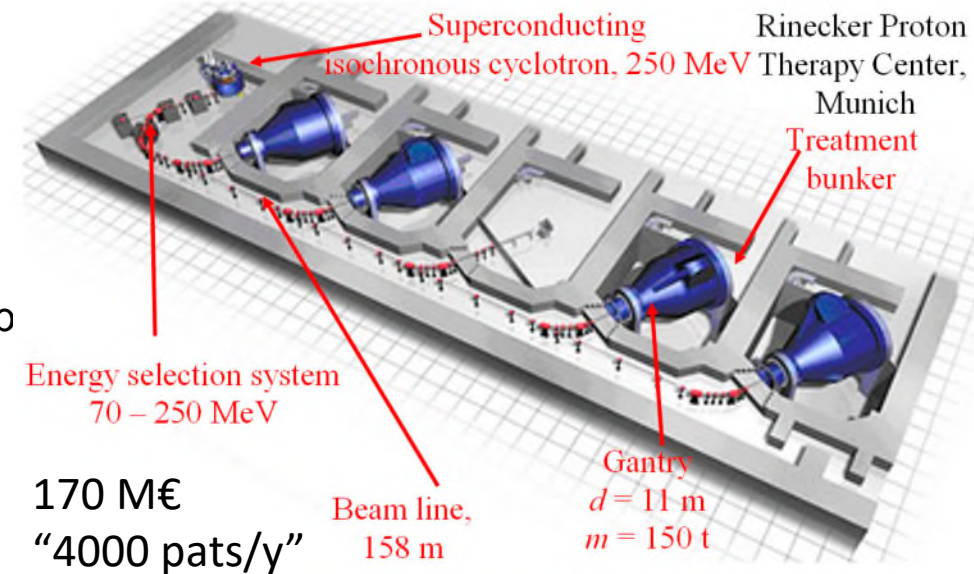


Leading Varian-Equipped Proton Therapy Center Treats 100th Patient

Oncology 11 de March de 2010

MUNICH, March 11 /PRNewswire-FirstCall/ --

Clinicians at the Rinecker Proton Therapy Center (RPTC) in Munich have treated their 100th patient using advanced proton therapy systems supplied by Varian Medical Systems (NYSE: VAR).



170 M€

“4000 pats/y”

Case 5) First proton therapy overdose reported

- Rinecker Proton Therapy Center (RPTC), Munich, Germany
- Overdose reported to patient treated last summer.
- Press reports indicate the prostate cancer patient after 15 daily treatments mistakenly received a daily dose of **63Gy** instead of 3Gy!
- The patient has severe problems (blood in the urine) and cannot sit
- Incident was blamed on “human error” and two employees were fired.
- Additional software installed to prevent this problem from happening again.

Bankruptcy 2017-2019

The operating company and the property company had to file for bankruptcy in 2017 due to insufficient capacity utilization. However, operations were initially continued by the insolvency administrators with the support of the technology and service partner for the proton facility, Varian Germany, and only stopped at the end of 2019.

~~ACCEL~~



~~MITSUBISHI ELECTRIC~~



~~Iba~~

COMPANIES



VARIAN
medical systems



HITACHI
Inspire the Next



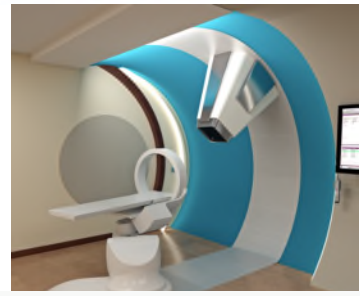
Optivus
The Proton Therapy Company



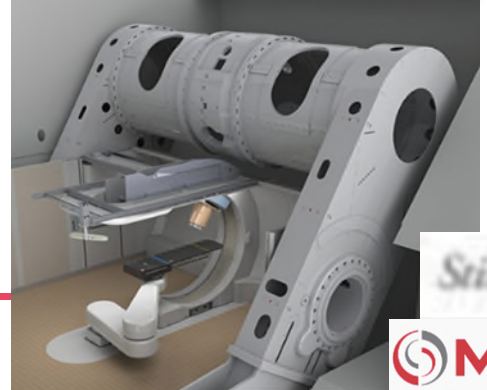
SIEMENS



PRONOVA



PROTOM
proton therapy technologies



Still/River

MEVION
medical systems

Protonterapia
Grupo Quirónsalud

**R&D
Projects
Orsay
(2018)**

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

Medical physics : treatment planning, dosimetry, QA,...

1 **Accelerator for all ions including radioactive beams**

27 Image registration, elastic deformations, voxelized models, automatic contouring (

2 High energies (eg. radiography), very high intensities (eg. pulses 100Gv/cm²)

28 Models, measurements and application of nuclear data for dose calculations.

3 Reduction in size, in cost (cryogenics), increase in reliability, maintenance

Fast (full) Monte Carlo calculations and deterministic transport techniques.

4 **Gantries reduced in size and cost (compact)**

1. Technical :
accelerators
magnets,
robots,
imaging,
electronics...

**2. Nuclear
Physics,
Instrumentation
Materials,
...**

**3. Medical
physics
Dosimetry,
models, QA**

5 Pencil beam technology : multiple beams

6 Development of proton microbeams

7 Ministrips beams, mini & microbeams

8 Integrated IGRT (IGPT) : double beam

9 Compensating filters and field shaping

10 Beams for special applications

11 Shielding, radiation protection

12 Robotics system

13 Scanned beam

14 Proton tomography

15 Data for dosimetry

7. Others

IMPT

tissue composition, ...)

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Biology and pre-clinics devices, data and models for Radiobiology, Biophysics

Proton beams on single cells and tissue (intravital microscopy)

targeted effects, cell survival, repair, stem cells in radiotherapy

(DNA, ...), Alpha-Beta parameters

stress, redox, reactive oxygen species. Necrosis signaling

effects

... effect assessment

... physics, dosimetry, biochemical effects

... action in living tissues and cells. Tumor and normal

... animal experiments.

... tumor control, effect on healthy tissues, vascular reactions,

... targets for particle beam therapy

... ed particle irradiation and combination with other advanced therapies

... AN-omics and particle therapy, biological targets, Protein biomarkers

Big Data in Radiation Oncology, expert knowledge decision tools

Clinical Research

All locations

Health Economy
Cost benefit and quality of life

Nuclear Physics, Instrumentation

16 Beam monitoring (position, intensity)

17 Detectors dosimetry: Calorimeters

18 Analysis of detectors saturation

19 Detectors for low dose imaging

20 **Detectors for "biometry" (L**

21 **Online range monitoring (PET, ...)**

22 Radiation protection and patient radiation

23 Radiation damage studies by high energy particles, hydrogen damage

24 MRI, PET and SPECT techniques based on proton-induced reactions for retrospective

25 Space science (spectra, radiation protection, detectors, ...)

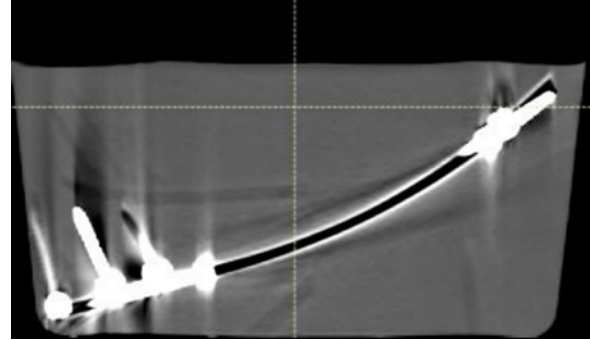
26 Hardening and response of electronics components, anesthesia equipment, implant

Use of Double Energy Spectral CT

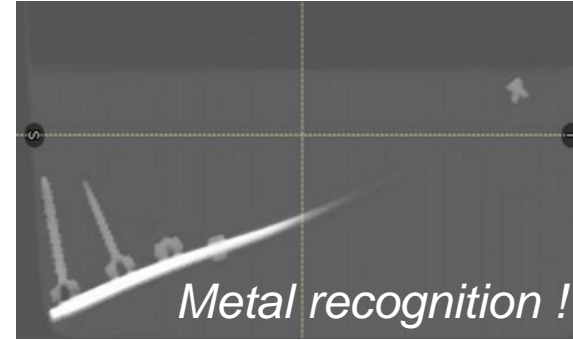
General Electric Revolution



Standard



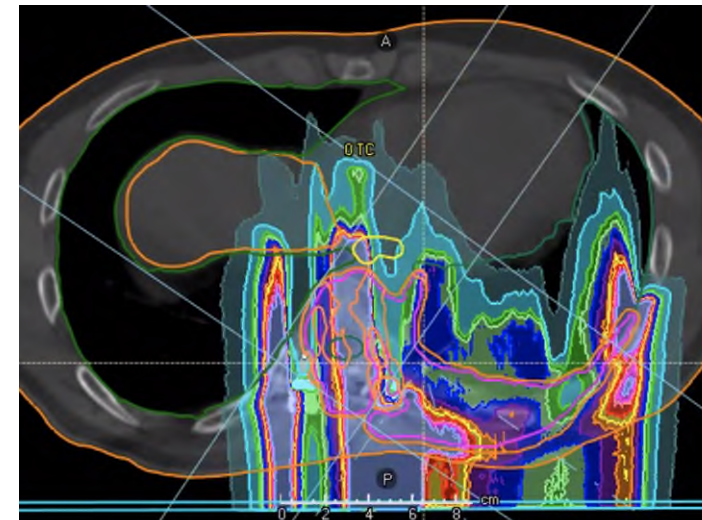
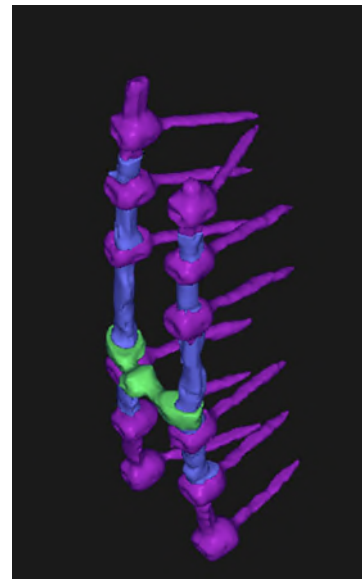
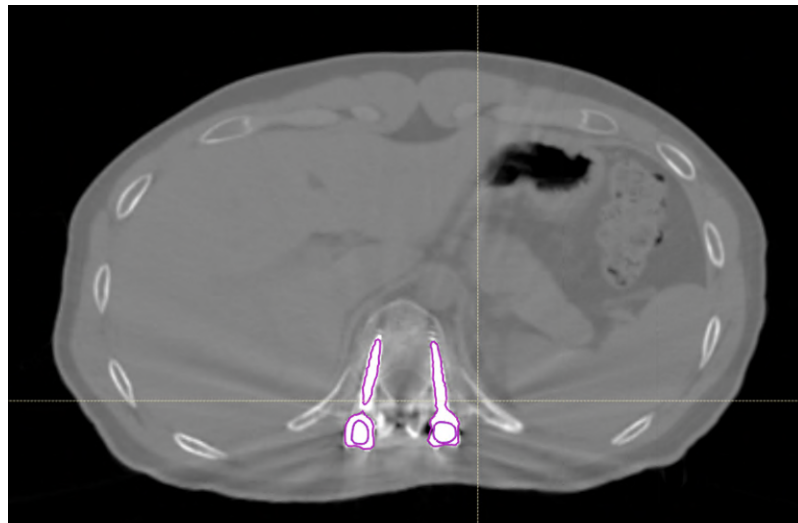
Artifacts, Hounsfield, Double E



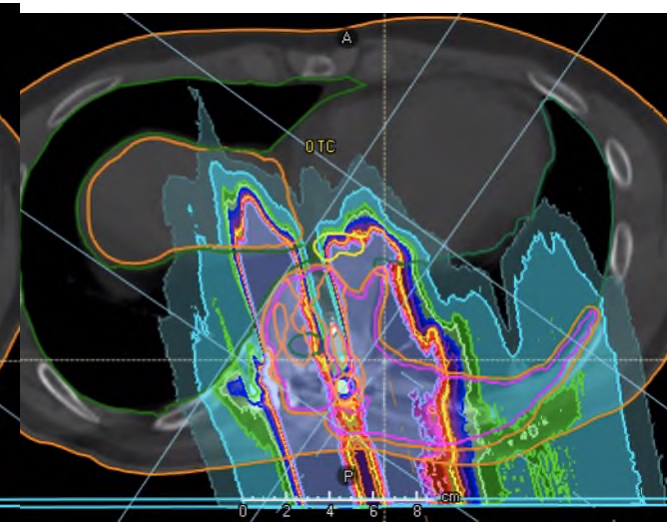
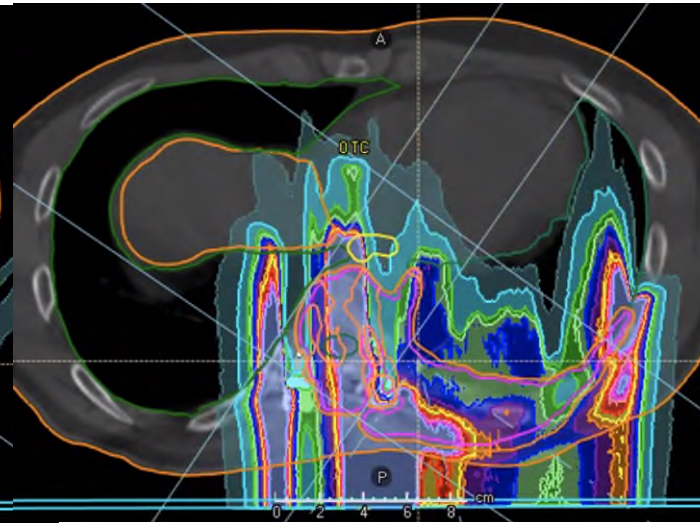
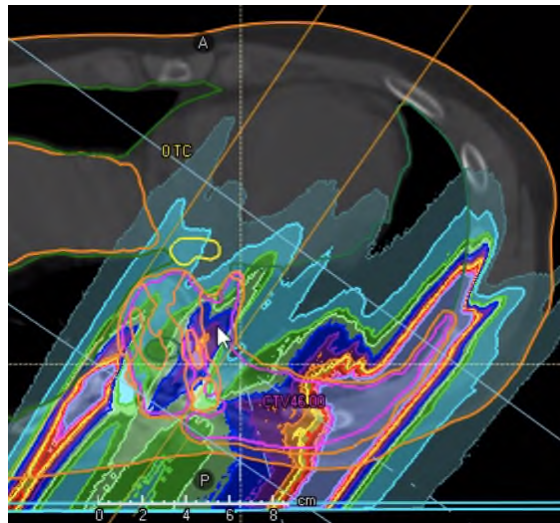
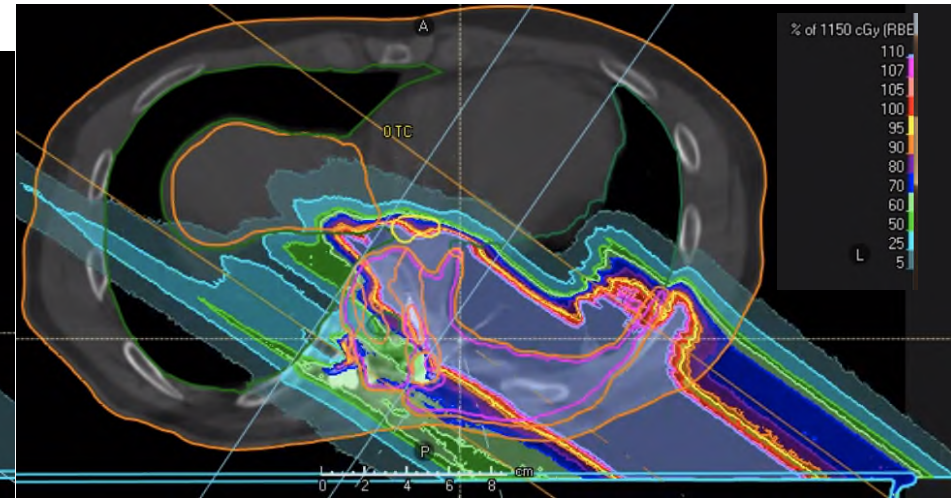
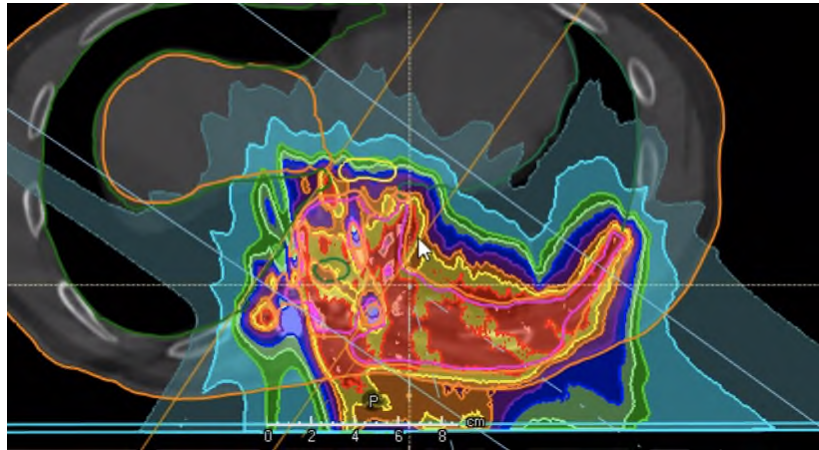
Juan Antonio
Vera Sanchez

High accuracy calculations

RaySearch



Planning taking into account metals:
Avoidance or accurate calculation

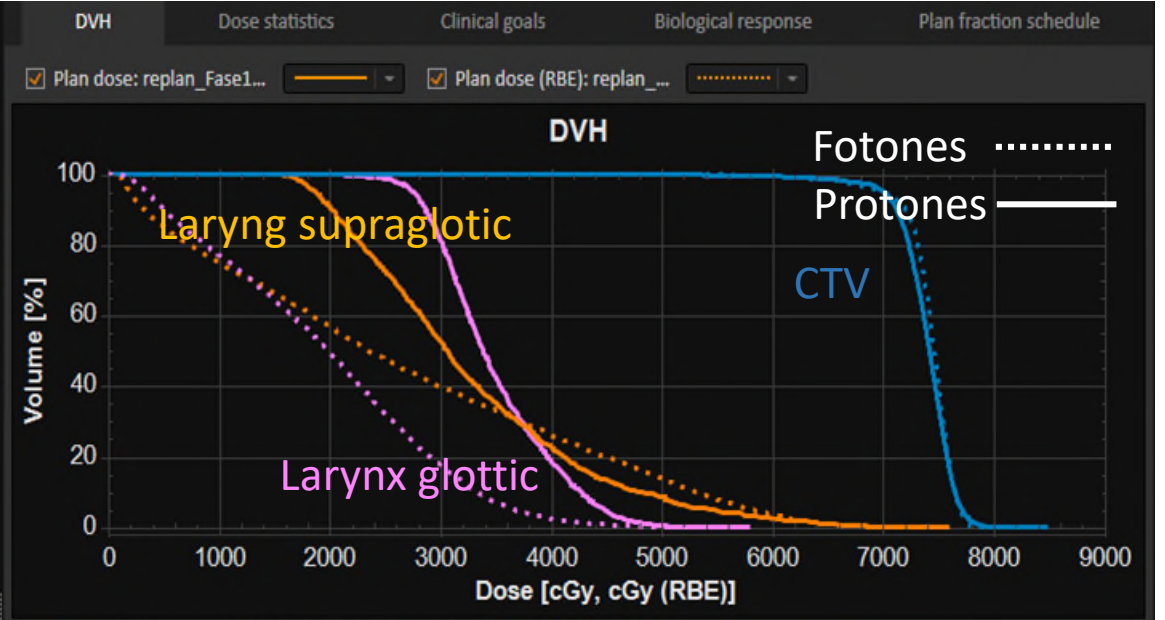
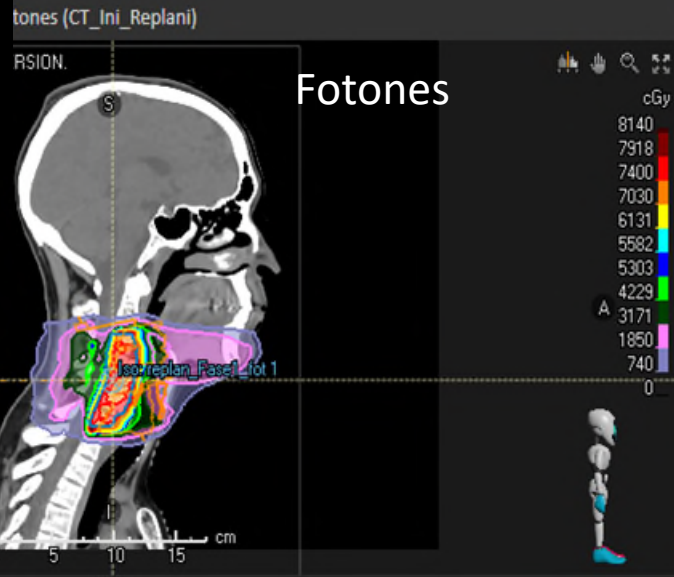


Juan María
Pérez
Moreno

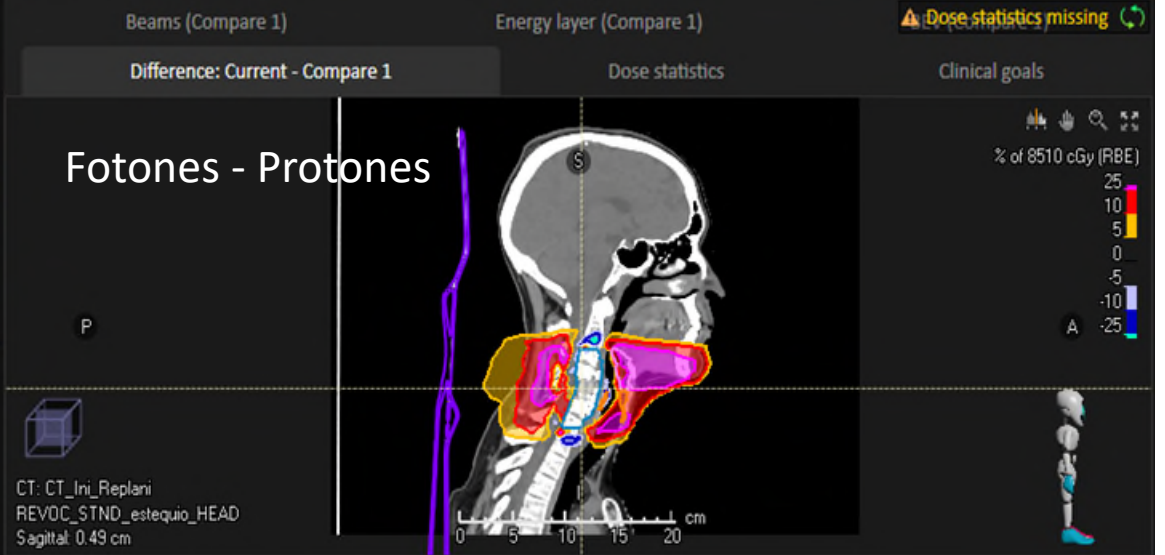
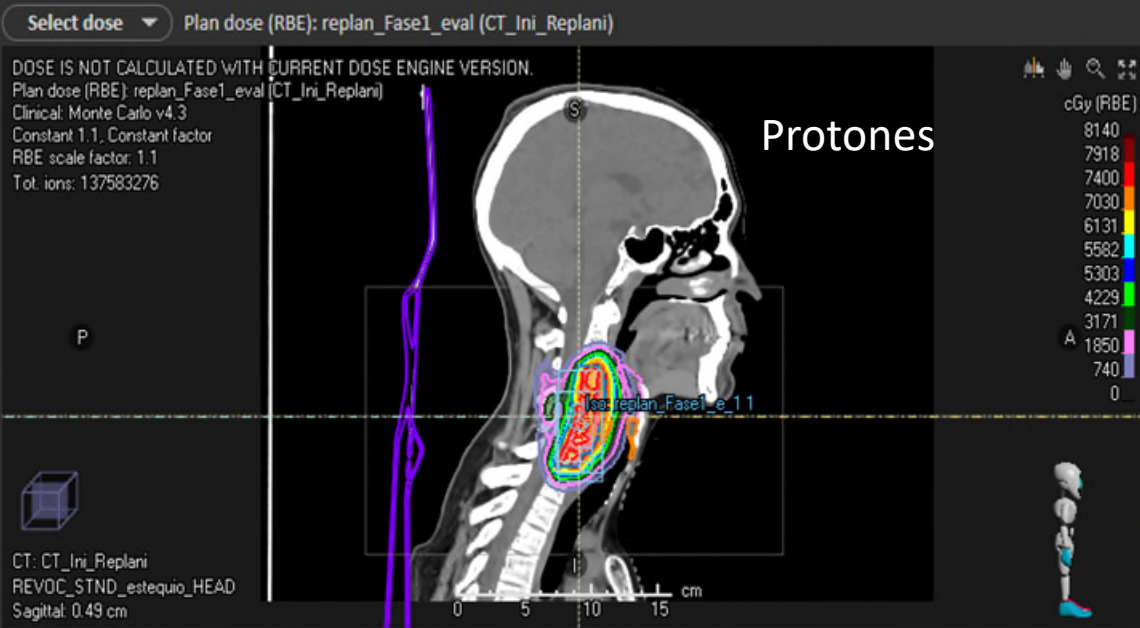
Comparative Planning



Fernando Cerrón Campoo



Dose axis: Absolute Relative max Relative dose [cGy, cGy (RBE)]:
Volume axis: Relative Absolute

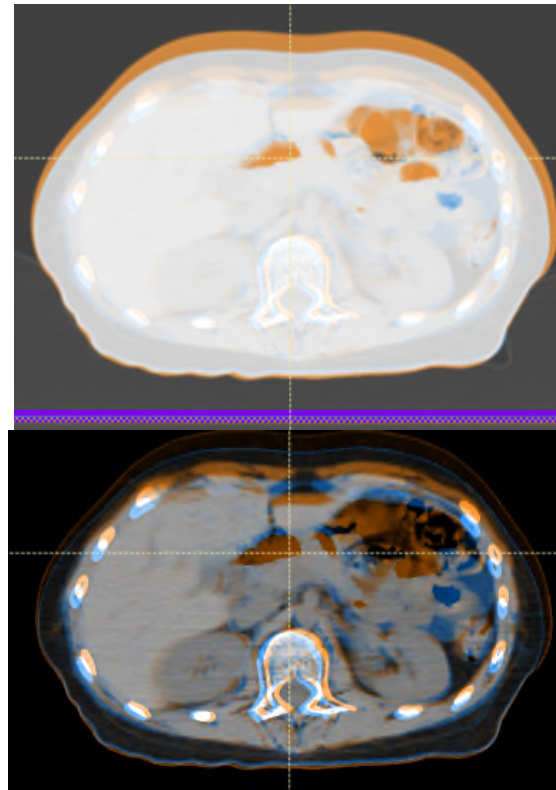


Protontherapy process and tools:

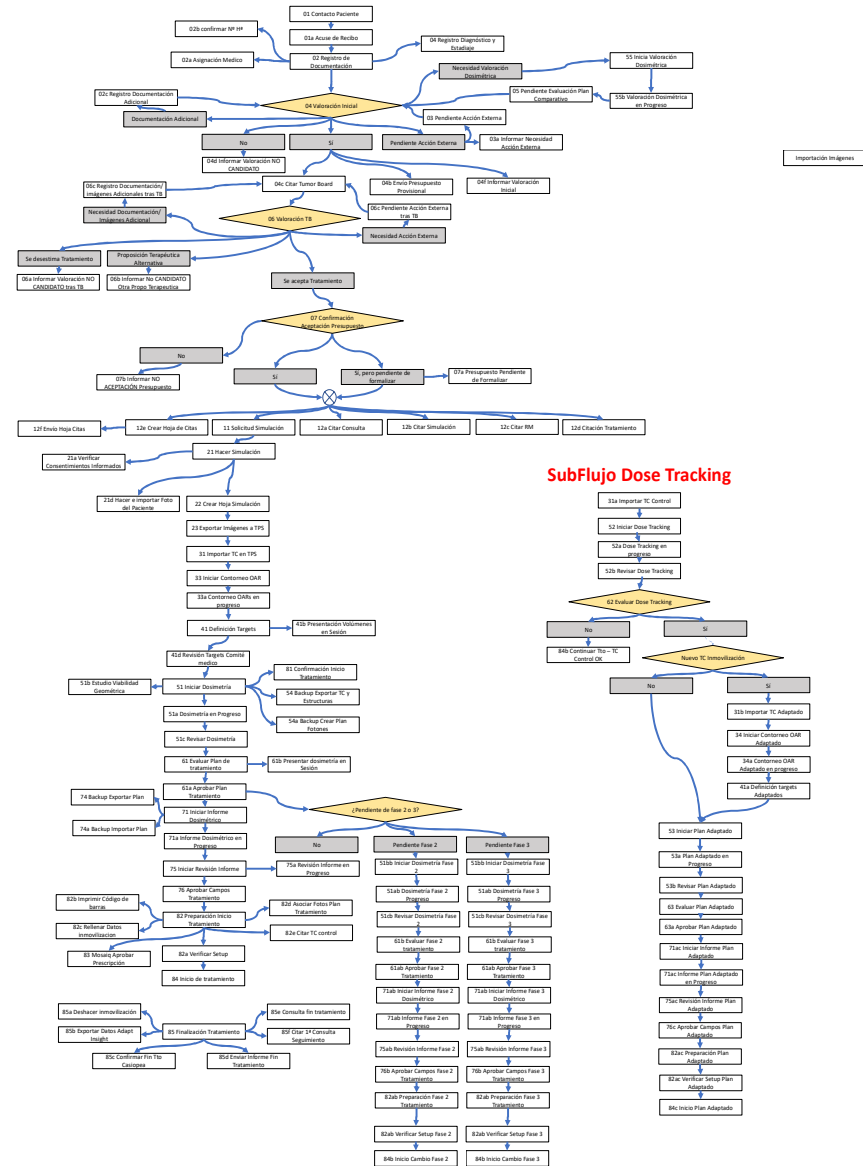
A comprehensive QA approach for **Integration**, with tracking of the process and end-to-end tests including the **weekly dose adaptation**



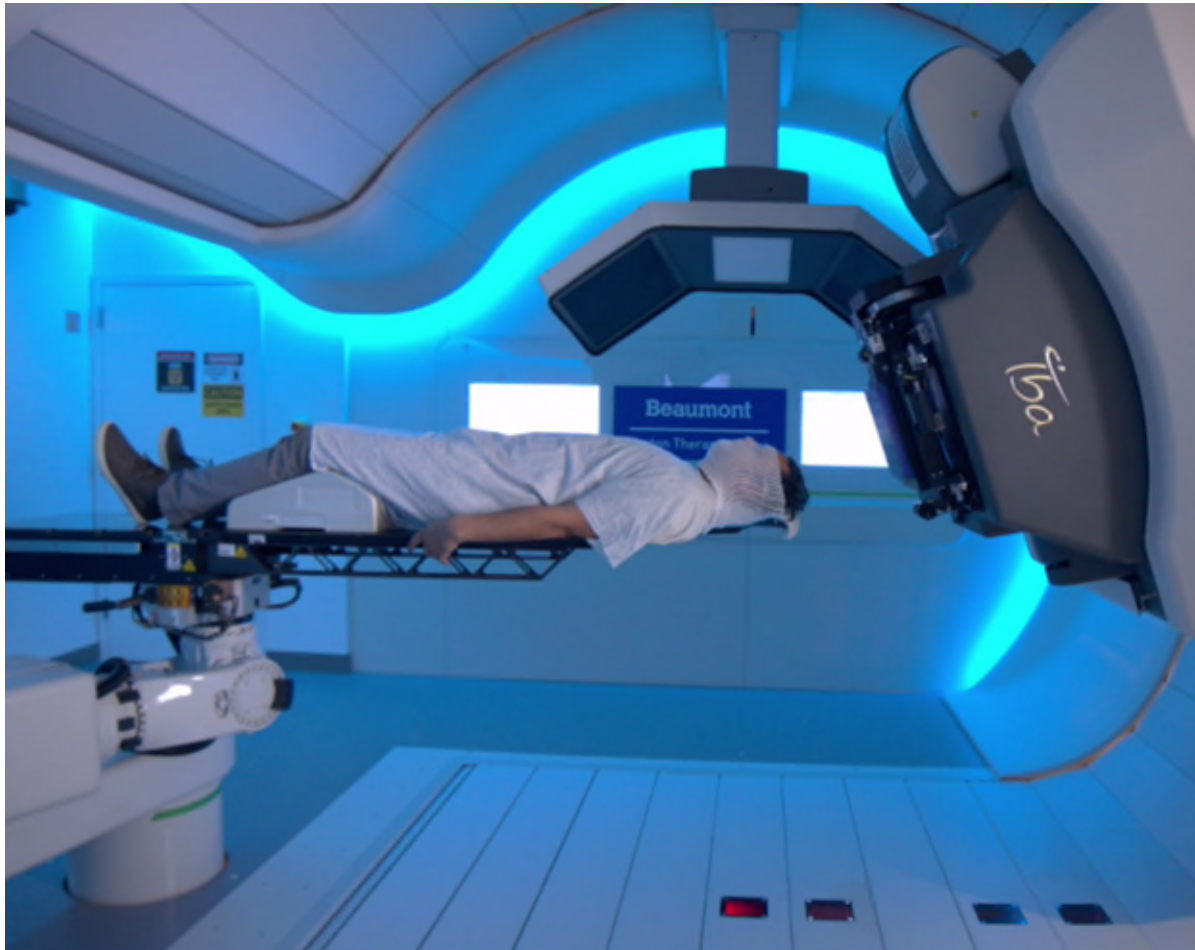
Juan Castro



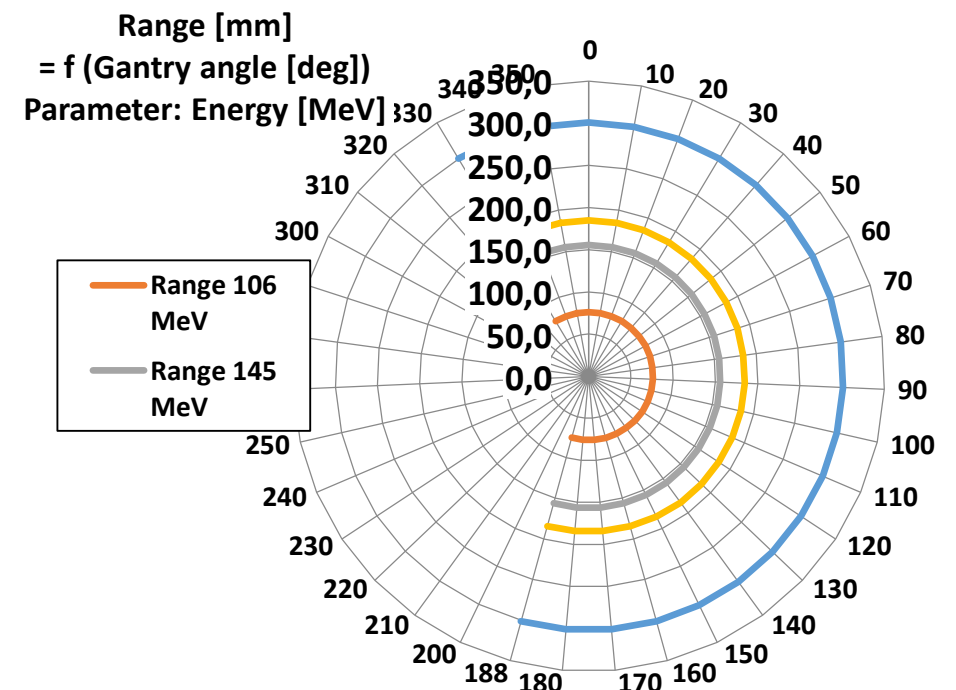
QA of Workflow (eg in Mosaiq)



I+D: hacia proton arco terapia?

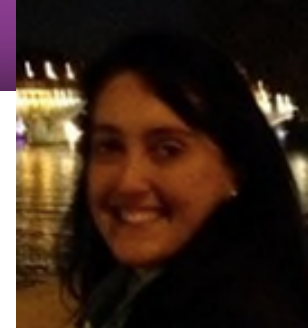


Stability of Energy (Range) vs Gantry Angle



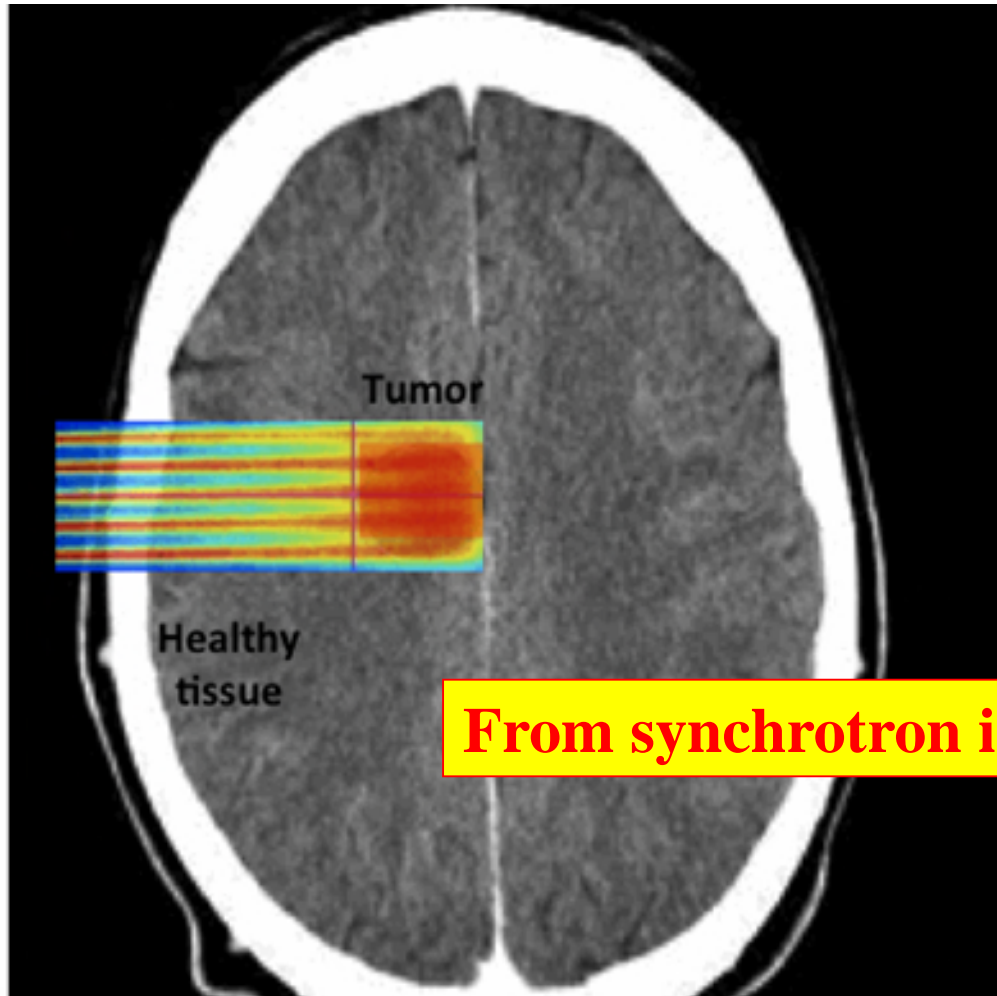
Delta range vs 0 deg : ± 0.5 %

Proton MiniBeam Radiation Therapy (pMBRT)

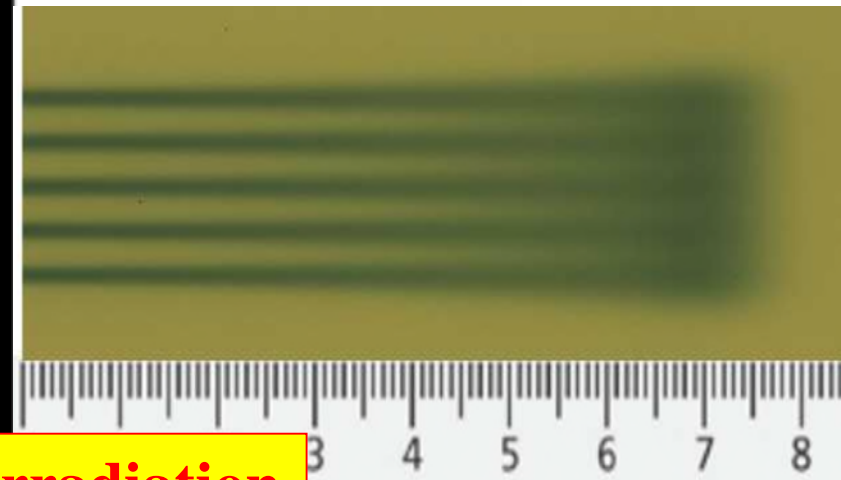


Theoretical concept :
Y. Prezado et al., Med. Phys. 2013

Experimental beam CPO
since 2014



Spatial distribution



From synchrotron irradiation

2014





V. Favaudon

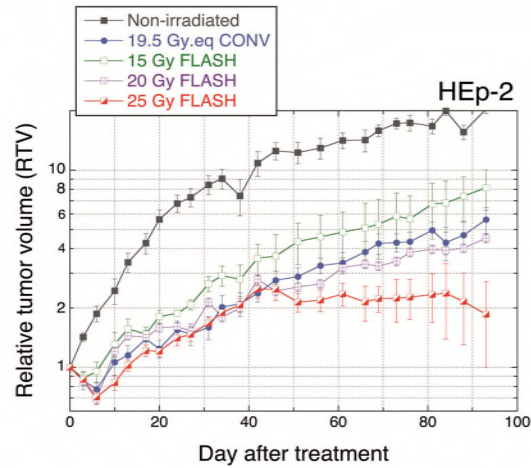


“FLASH –Effect” Ultrahigh dose-rate FLASH irradiation

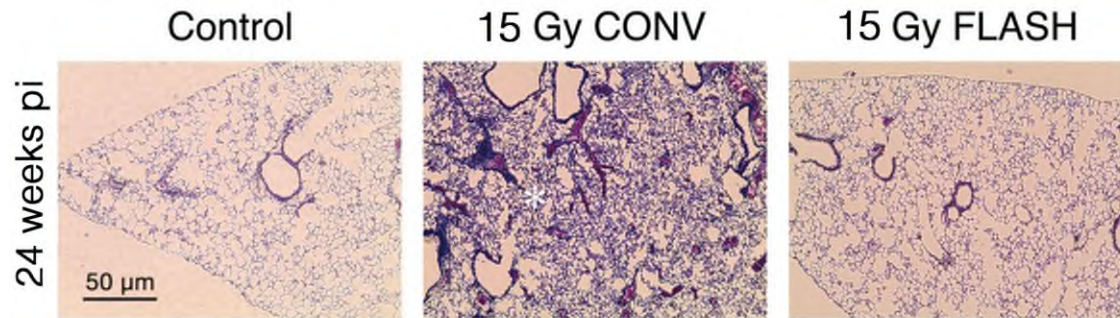
2014

Sci Transl Med 6: 245ra93, 16 July 2014

Total dose in < 0,5 sec



➤ FLASH spared normal lung tissue from radio-induced fibrosis.



Visualisation of collagen invasion (Masson trichrome staining)

➤ FLASH as efficient as CONV on inhibition of the growth of tumor xenografts.

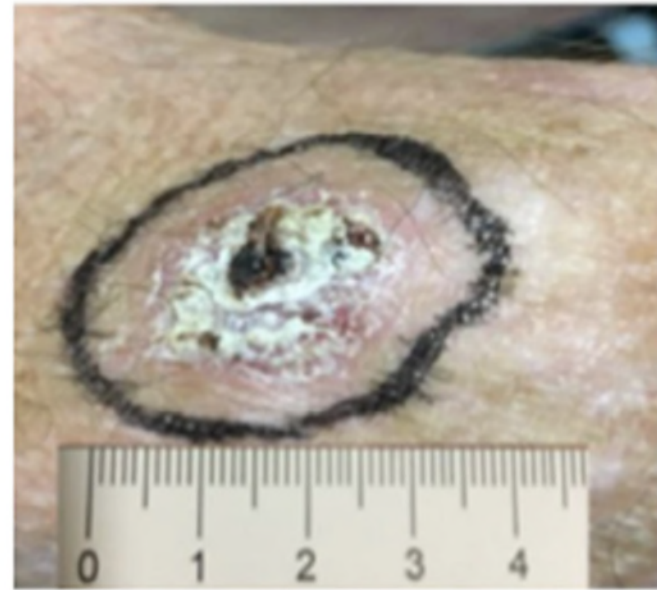
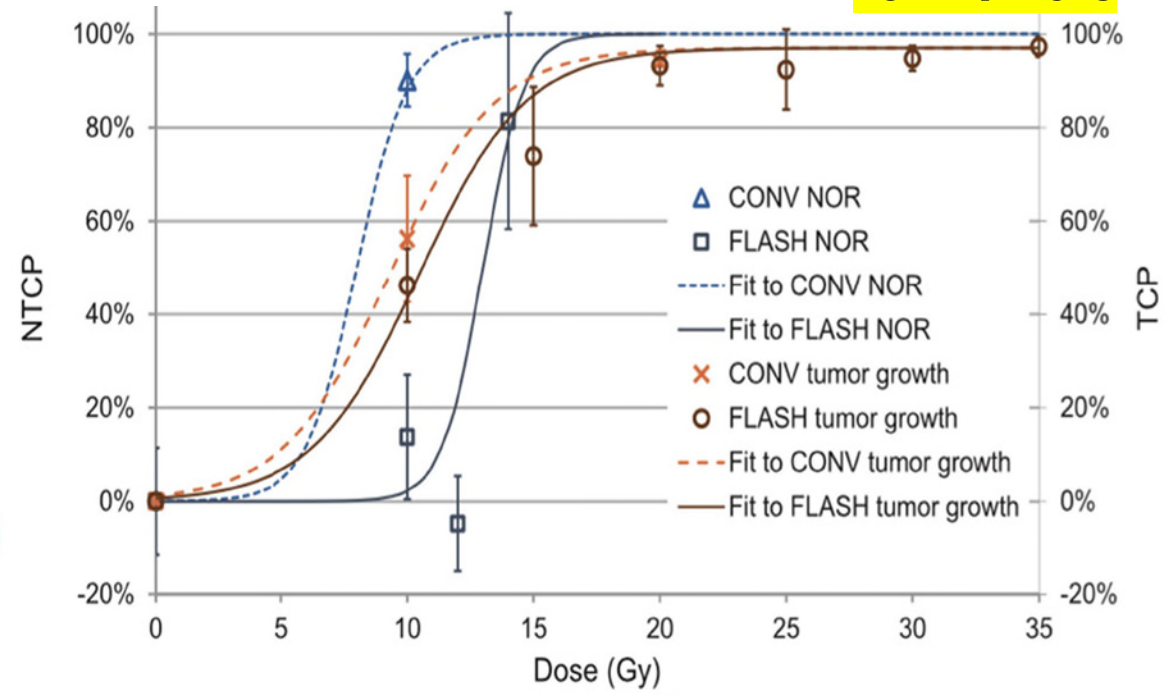
Same T control

Less fibrosis

2014 → 2019



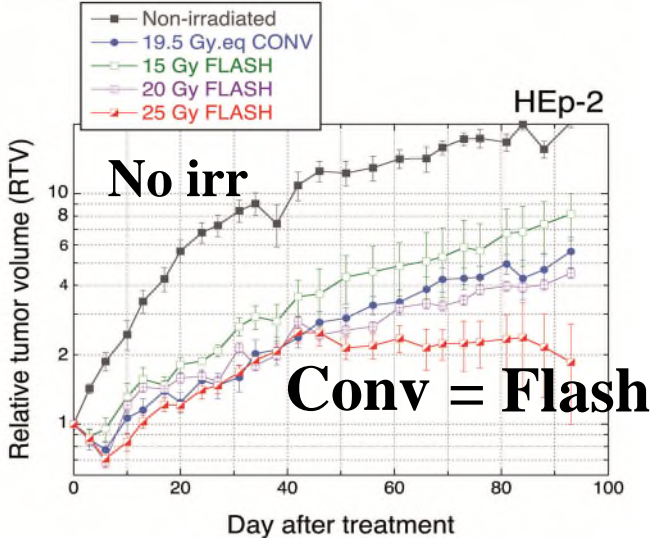
a b
c



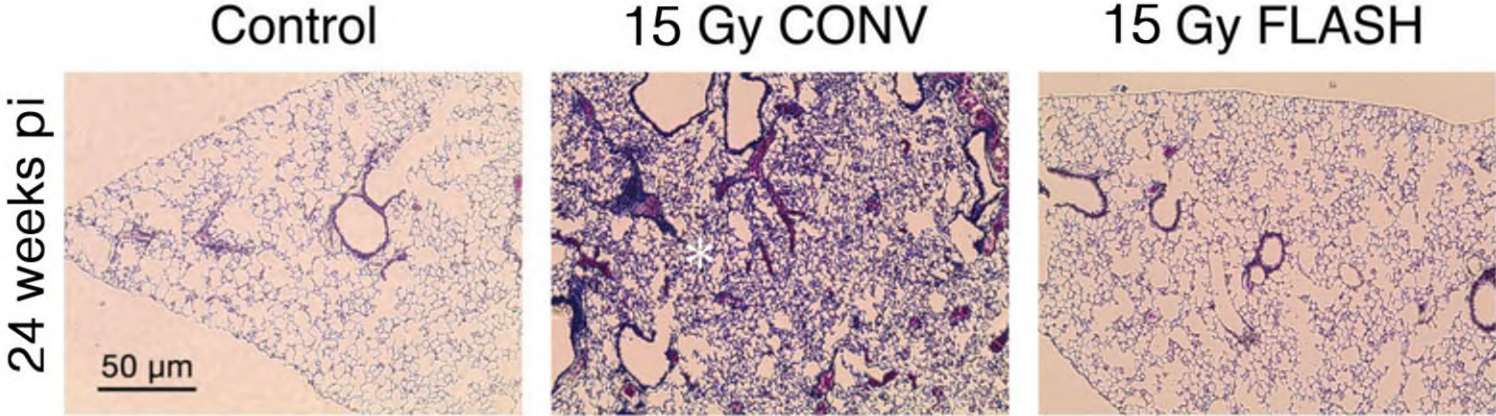
Bouhris et al, 2019

R&D: "FLASH", all the treatment in less than 0.5 sec !

Same T control

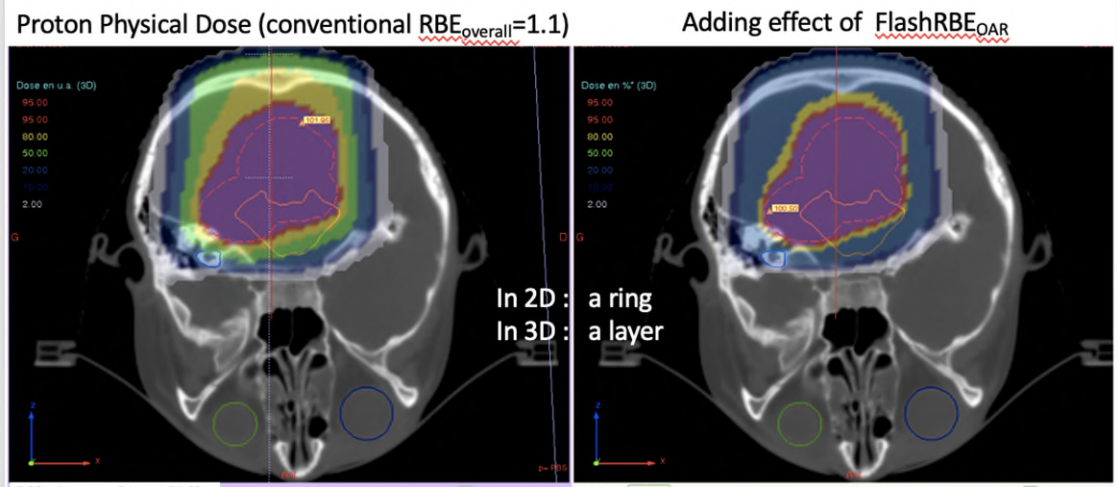


Less fibrosis in lung



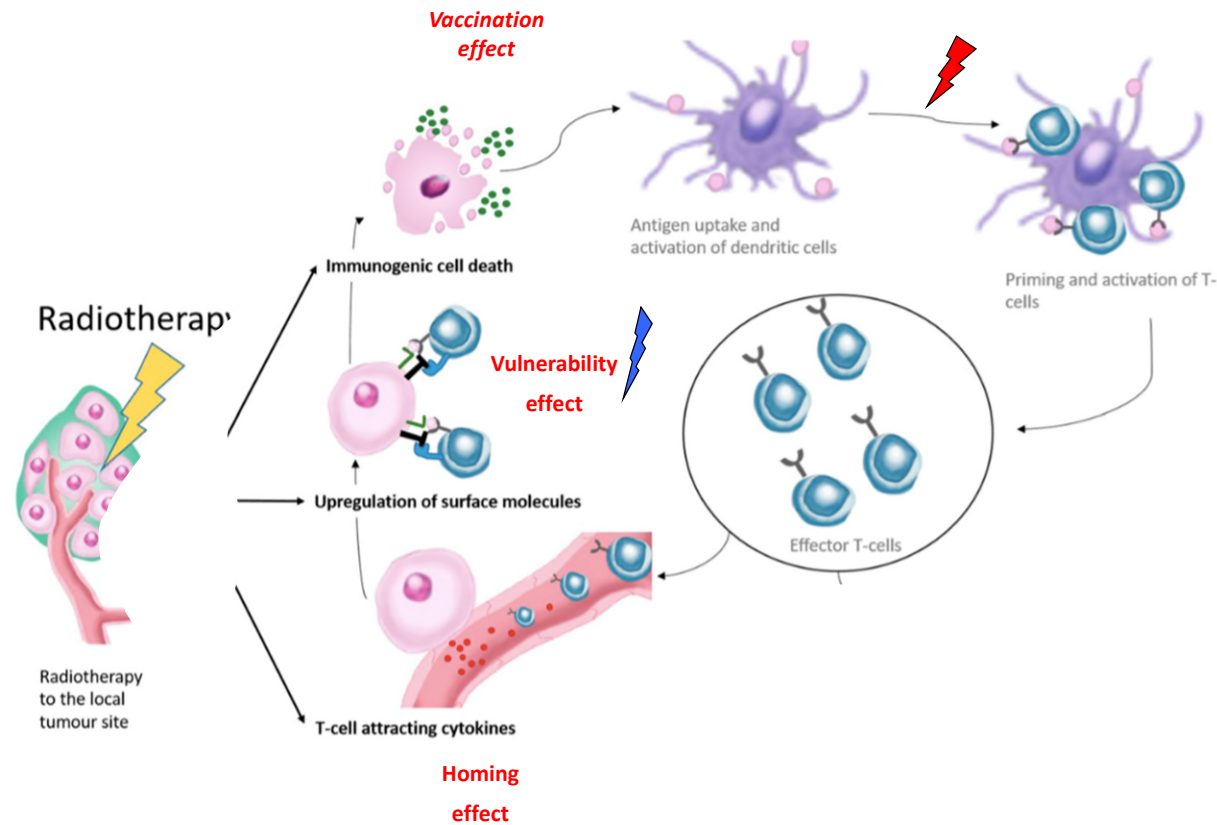
V. Favaudon et al. Sci Transl Med 16 July 2014

Potential with protons



Combining radiotherapy with immunotherapy: the past, the present and the future

Van Limbergen EJ (P.Lambin) et al. Br J Radiol 2017; 90



Lymphocytes:

- Cytotoxic CD8+
- Progenitor T-helper CD4+
- Effector Th1
- Regulatory Treg

Failures:

- Foreignness : not enough antigens
- Not enough lymphocytes
- Hampered tum. cell infiltration by T
- T-cells checkpoints

Immunotherapy:

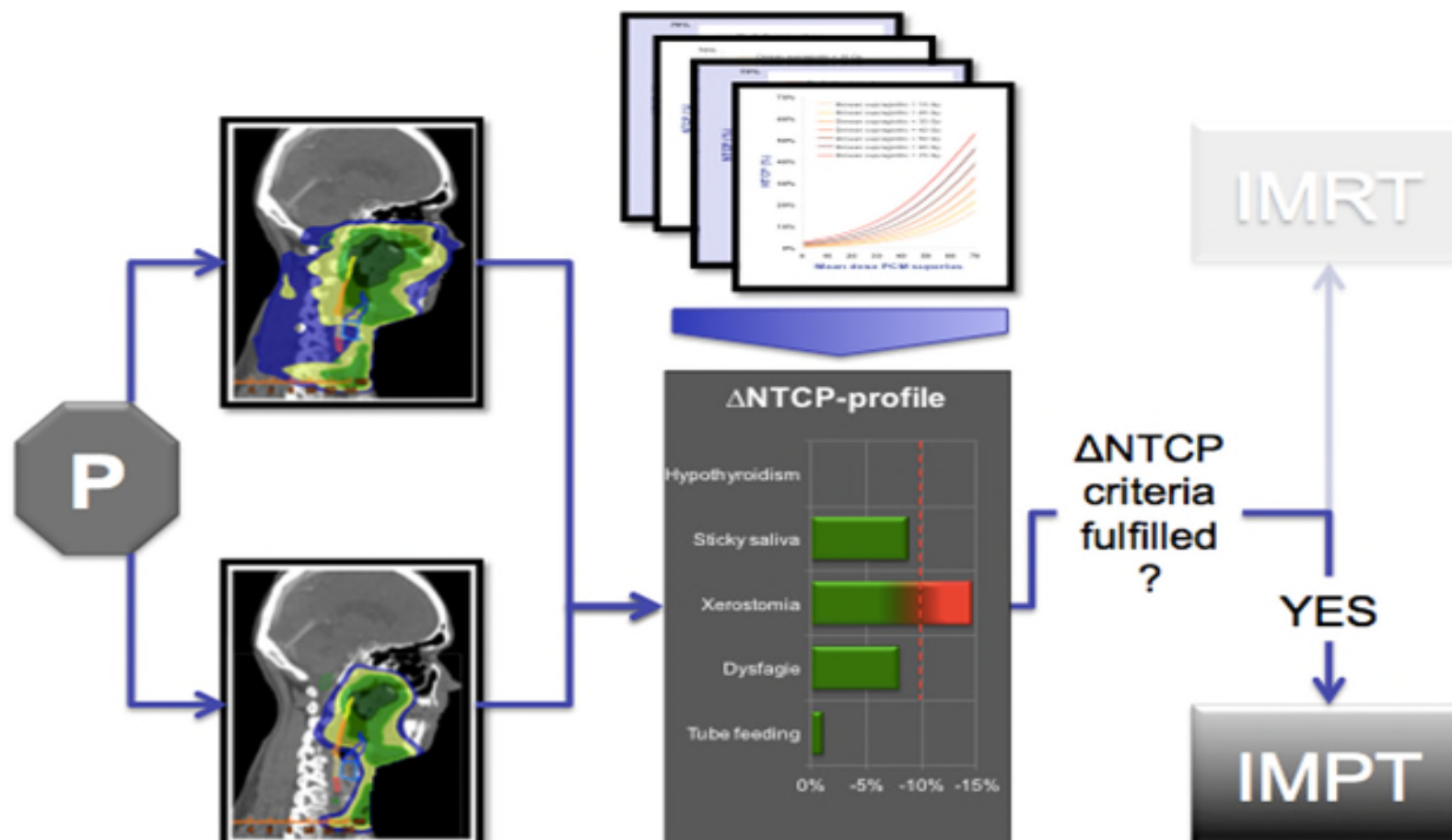
- ...
- Checkpoints inhibitors
- Ipilimumab CTLA-4
- Nivolumab PD-1/PD-L1





Model-based selection

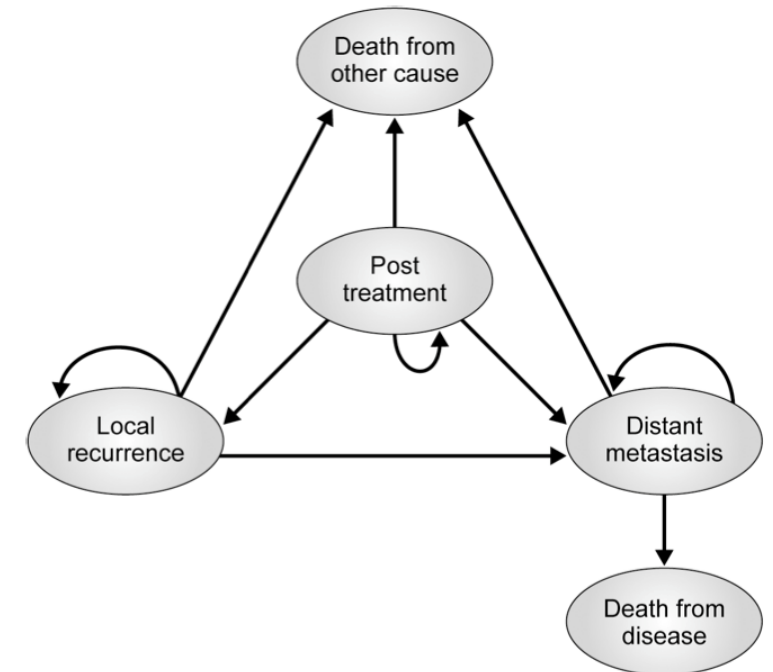
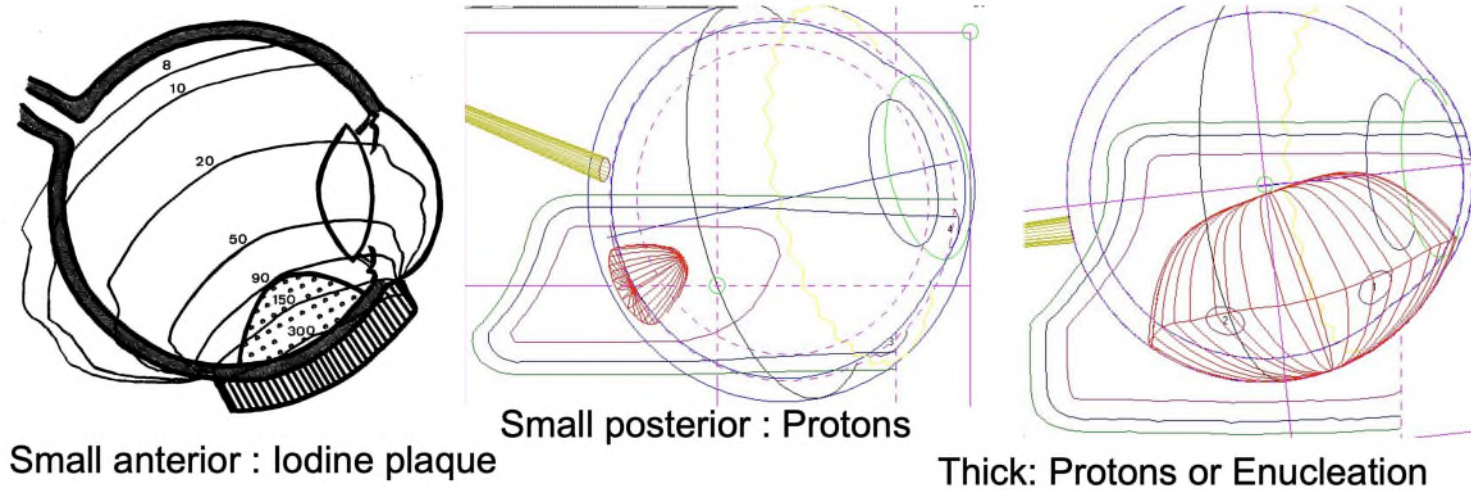
Decision support system



<https://indico.cern.ch/event/522875/contributions/2324902/attachments/1347512/>

Cost-Effectiveness of proton Beam Therapy for Intraocular Melanoma

(a) Plaques vs protons vs enucleation

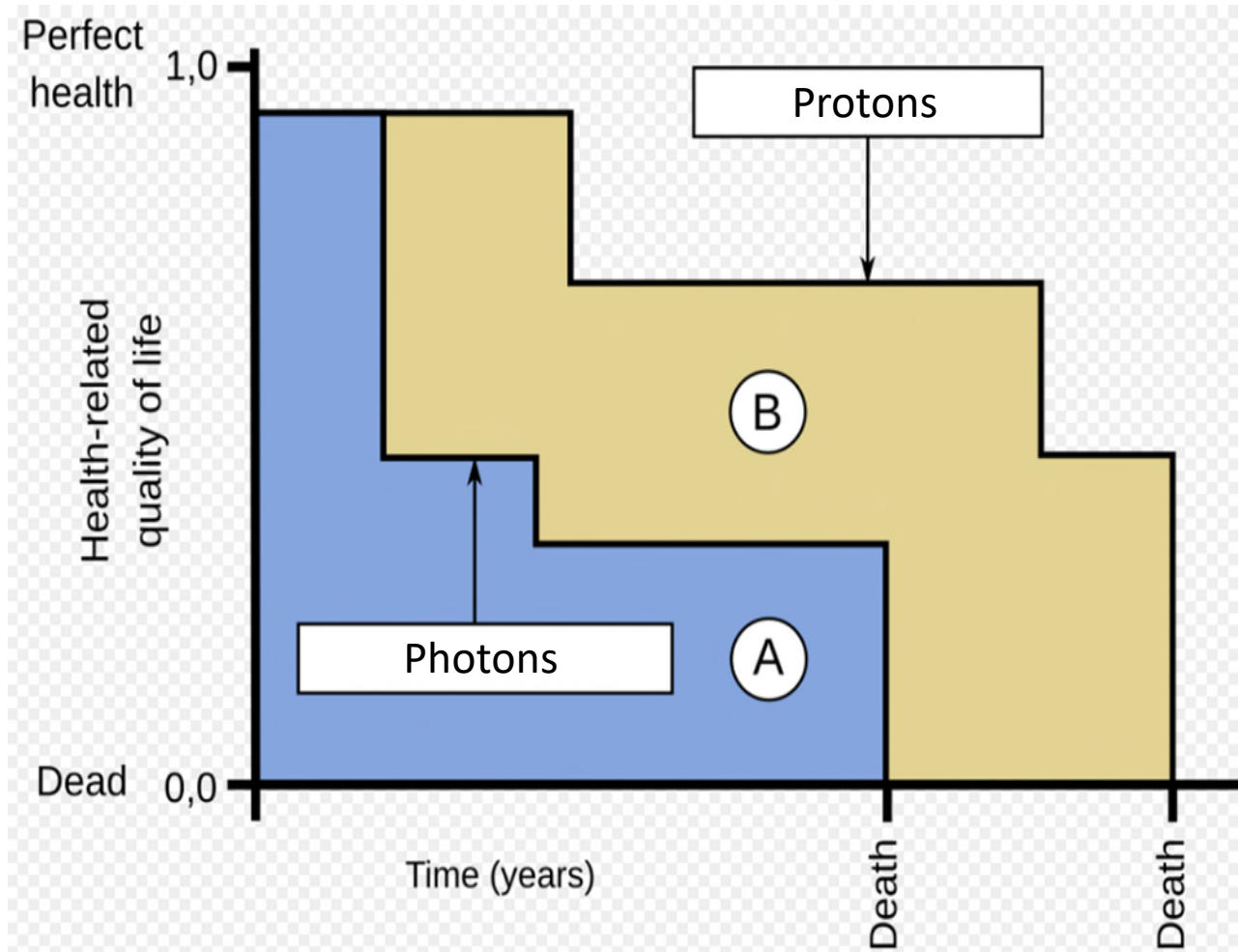


(b) Markov Model :

Ovals signify the differing health states.
Arrows indicate pathways.

Responsibility: work on cost-benefit and Qualys :

opportunity in a single center to collect all costs and data on clinical follow up



Cost-benefit / Qualy
See data collection extracts for different clinical indications treated with proton therapy compared with alternative techniques in: *Verma et al, Cancer, 2016*

Research, development, educational and training

6 Nat Research Cooperations

- Complutense
- Autonoma Madrid
- Ciemat
- Rey Juan Carlos
- IFIC Valencia
- Quiron: Fundación Jimenez Diaz

6 Educational Agreements

- 7 + 2 Physician residents
- 4 + 2 Physicist residents
- 2 PhD physics (G-URJC) + masters
- 1 MD observership (Santander)
- Nebrija University training
- San Juan de Dios: Therapists

24 Scientific Publications

- 20 published (5 as CPT)
- 2 in Press
- 2 submitted or in progress

➤ Ensayos clínicos Internacionales: 4
PROTECT (esófago), SACRO,
SIOPE-ependymoma II y PNET-5

6 Industrial Agreements

- IBA + IBA dosimetry
- GE
- Qfix
- VisionRT
- RaySearch

Meetings

Conferences + + +
PTCOG in 2023

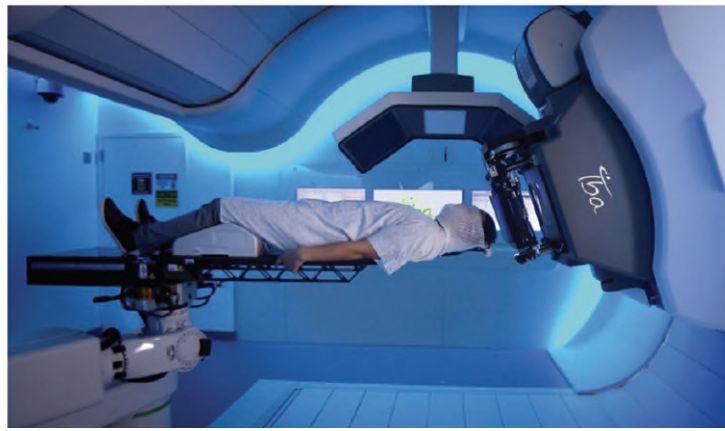
3(+3) Internat Cooperations

- Ministry of Health Israel
- University of Georgia
- Argentinian Proton Center
- ...

➤ Becas concedidas por ministerio: 2

- 1) URJC & CPT (Juan Antonio Vera)
“Protonterapia Adaptativa
Mediante Inteligencia Artificial
- 2) U.Valencia Prompt Gamma

*1st publication submitted in group + Complutense+ Autónoma:
Biological and mechanical synergies to deal with proton therapy
pitfalls: minibeam, FLASH, arcs and gantryless rooms. A Mazal, JA
Vera Sanchez, D Sanchez-Parcerisa, Jose Manuel Udias, S España, V
Sanchez-Tembleque, LM Fraile, P Bragado, A Gutierrez-Uzquiza, N
Gordillo, G Garcia, J Castro Novais, JM Perez Moreno, L Mayorga
Ortiz, A Ilundain Idoate, M Cremades Sendino, C Ares, R Miralbell, N
Schreuder . In : Proton Therapy in Cancer Treatments: Clinical
Evidence and Controversies. Eds J.Doyen, B.Timmermann, A.Lomax
Frontiers in Oncology - section Radiation Oncology*



¡GRACIAS POR CUIDARME!

27-9-21

("Thanks to take care of me")

ro de Protonterapia

Grupo  quirónsalud

¡¡ VISITEN
NUESTRO
CENTRO !!



Centro de Protonterapia

Grupo  quirónsalud