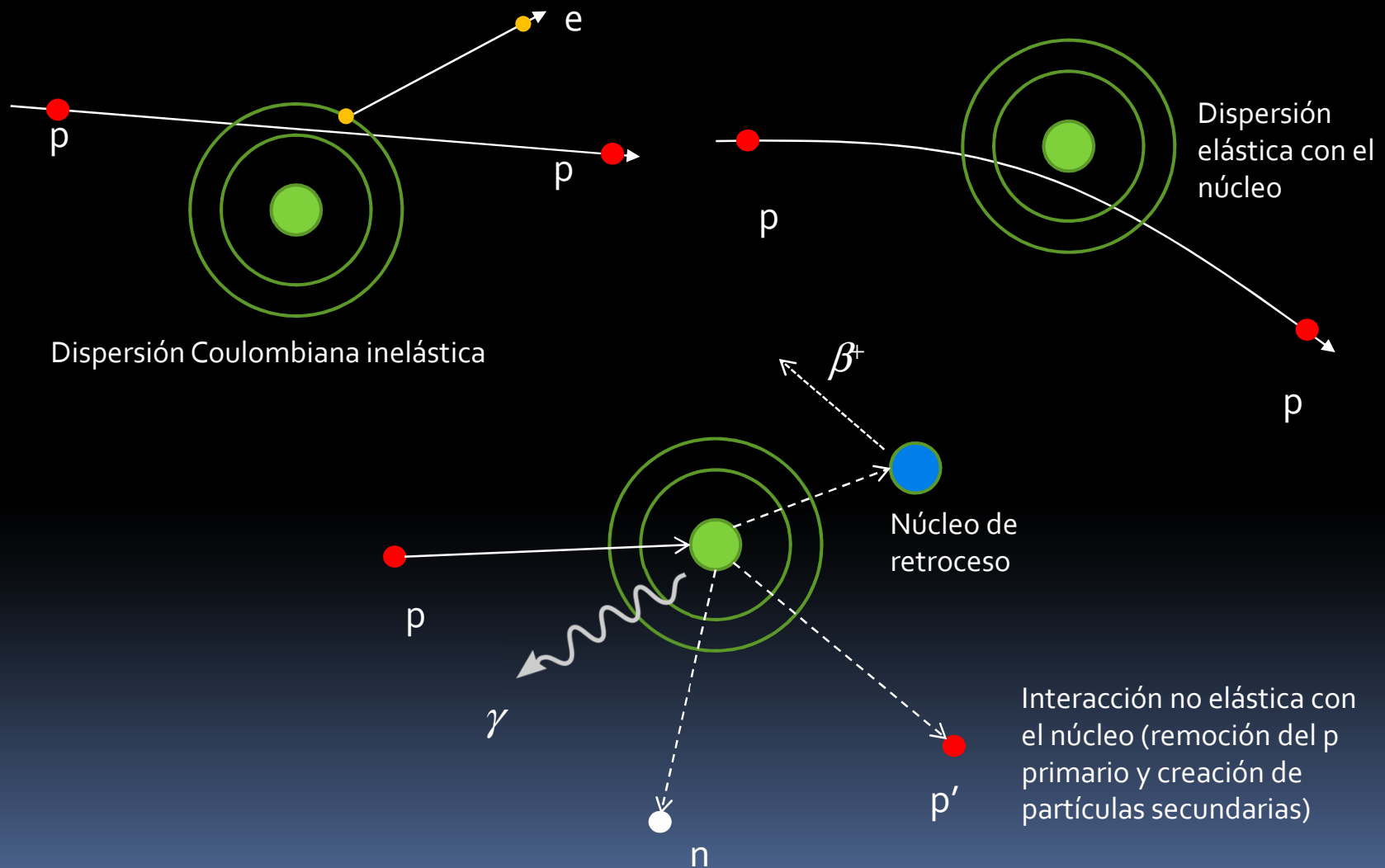


ACTIVIDADES DE INVESTIGACIÓN Y DESARROLLO EN HACES DE PROTONES PARA PROTONTERAPIA: CONTRIBUCIONES A LA CLÍNICA Y A LAS CIENCIAS BÁSICAS Y APLICADAS

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Departamento Coordinación BNCT
G. Química Nuclear y Ciencias de la Salud
GAATEN
CNEA

Protones y su interacción con los átomos y núcleos



Descripción teórica: fórmulas de Bragg-Kleeman (1905), Bohr (1915) y Bethe-Bloch (1930-33)

$$\frac{S}{\rho} = -\frac{dE}{\rho dx} \approx -\frac{E^{1-p}}{\rho \alpha p},$$

α, p dependientes del material y la velocidad de la partícula

$$\frac{S}{\rho} = -\frac{dE}{\rho dx} = 4\pi N_A r_e^2 m_e c^2 \frac{Z}{A} \frac{z^2}{\beta^2} \left[\ln \frac{2m_e c^2 \gamma^2 \beta^2}{I} - \beta^2 - \frac{\delta}{2} - \frac{C}{Z} \right]$$

Dependencias con el proyectil: carga (z^2) y velocidad (β). No depende de su masa.

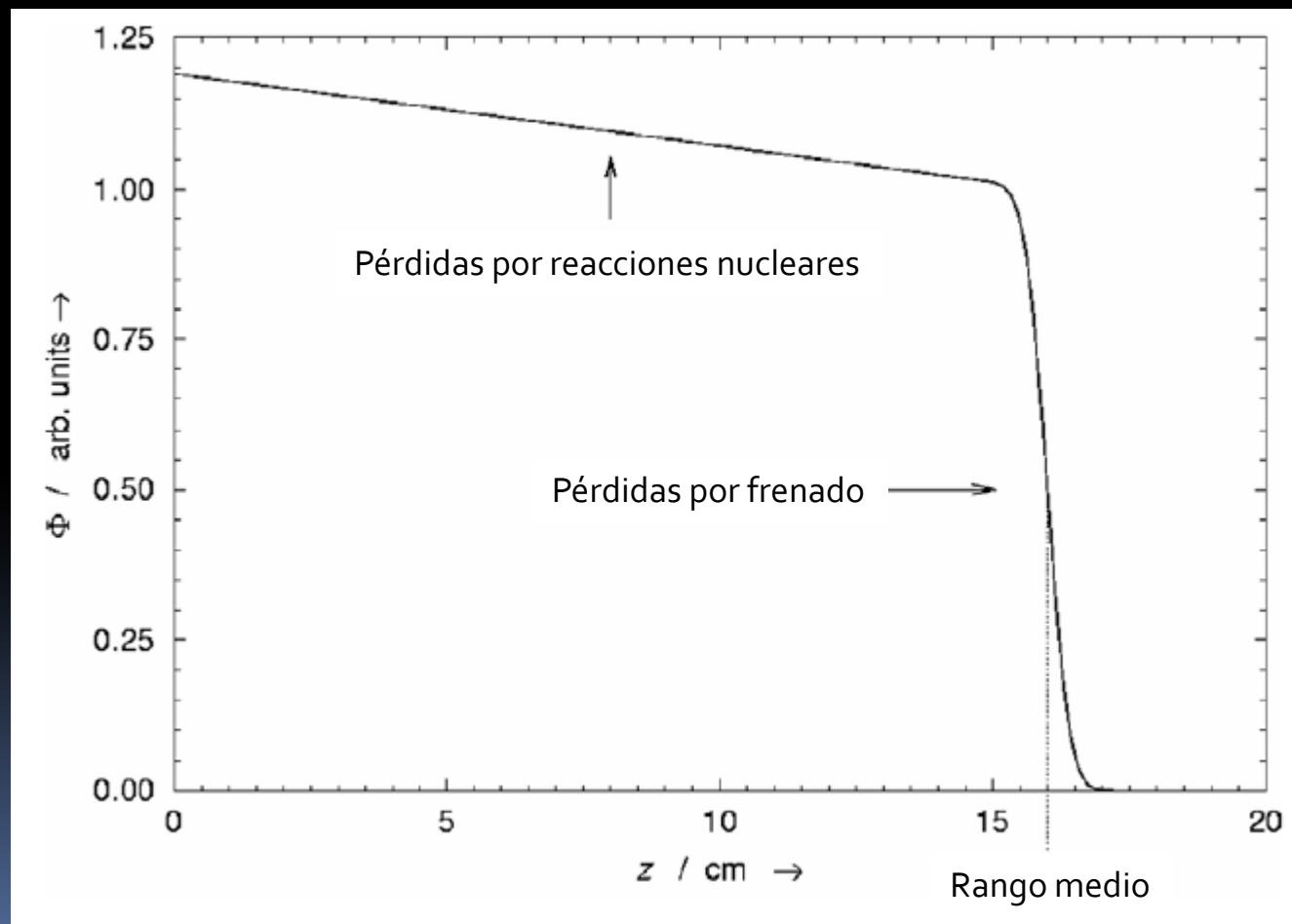
Dependencias con el material:

- Z/A (densidad electrónica). Varía en no más de un 16% (0.5 para tejido, 0.42 para materiales pesados como el plomo).
- I (Potencial de ionización).
- Correcciones por apantallamiento de los electrones más alejados y por estructura de capas atómicas.

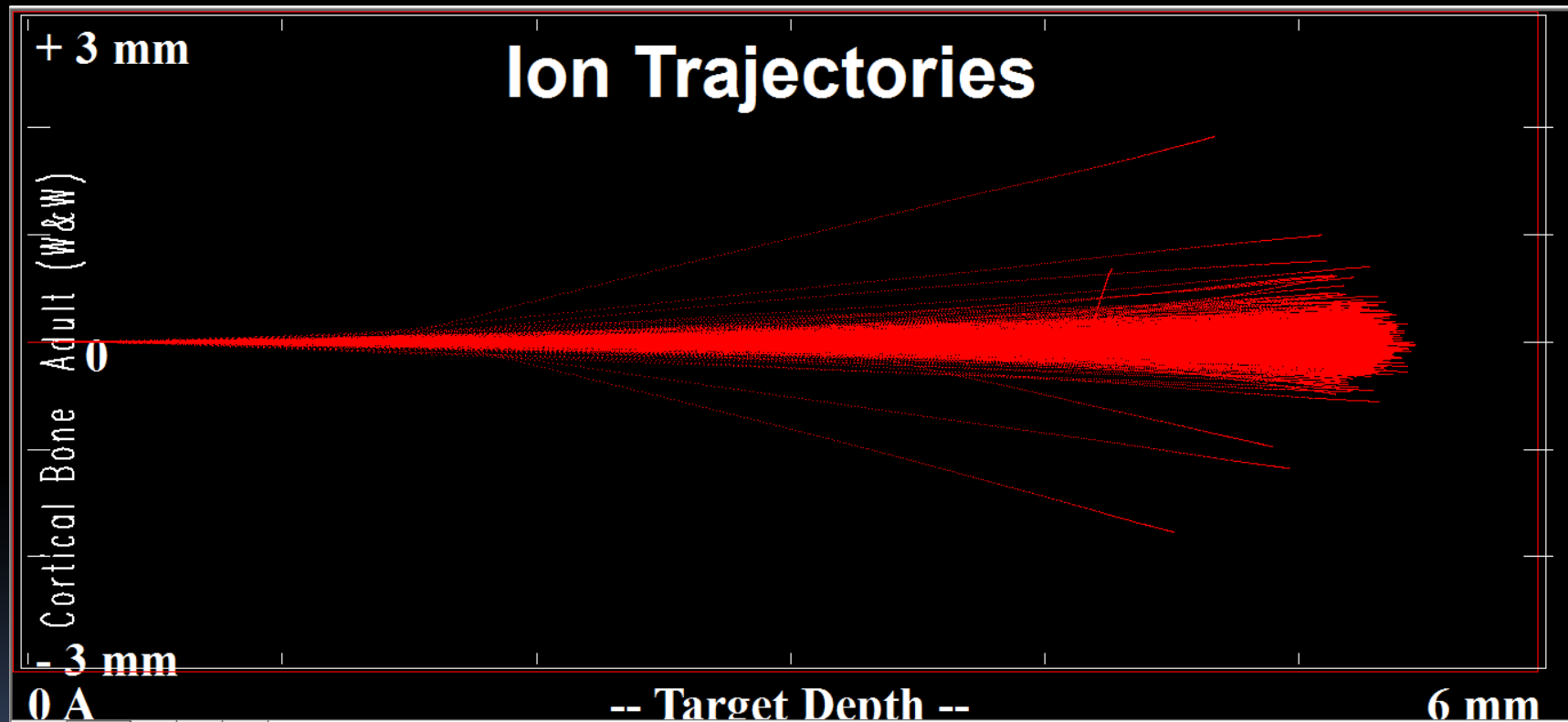
Rango

$$R(E) = \int_0^E \left(\frac{dE'}{dx} \right)^{-1} dE' \approx \sum_0^E \left(\frac{dE'}{dx} \right)^{-1} \Delta E'$$

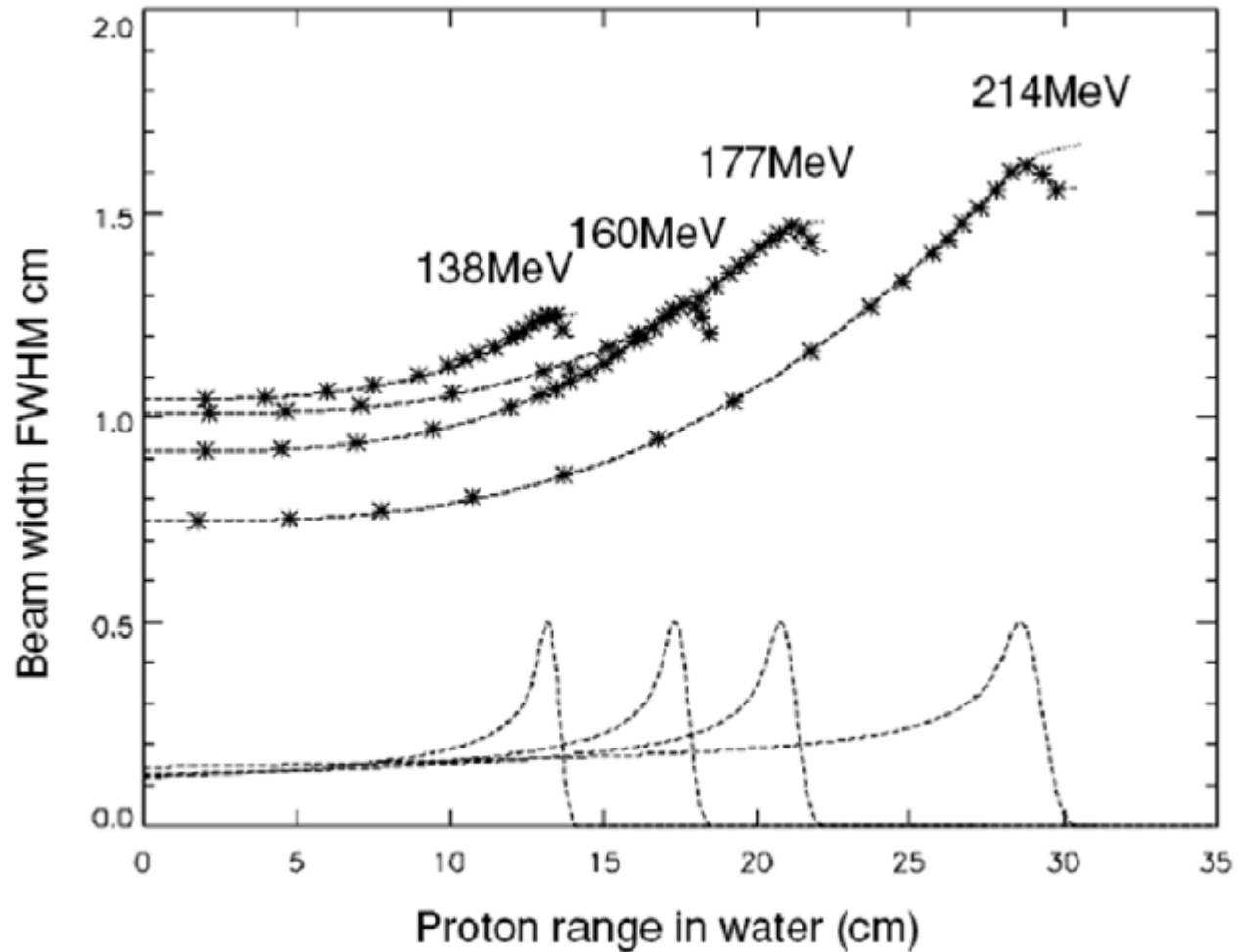
La profundidad en el material a la cual se han frenado la mitad de los proyectiles originales :



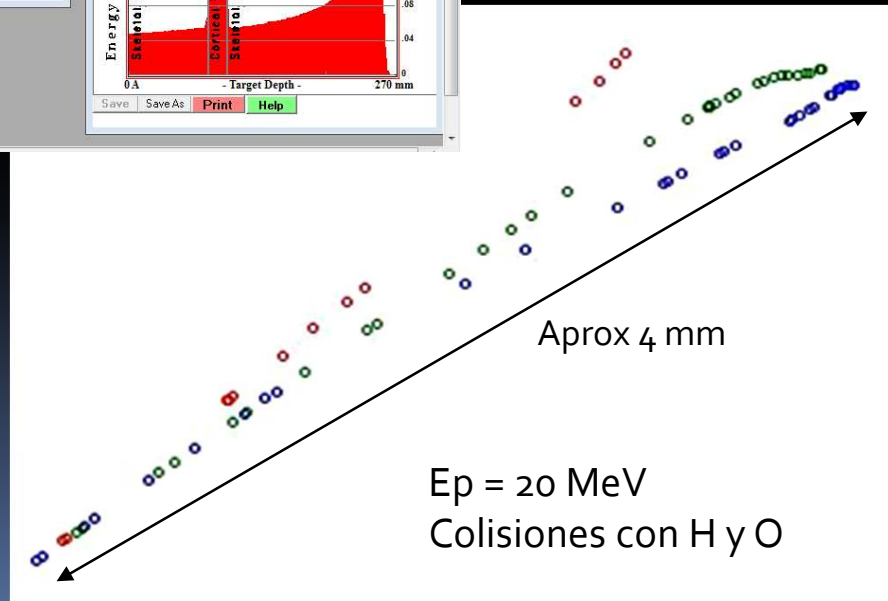
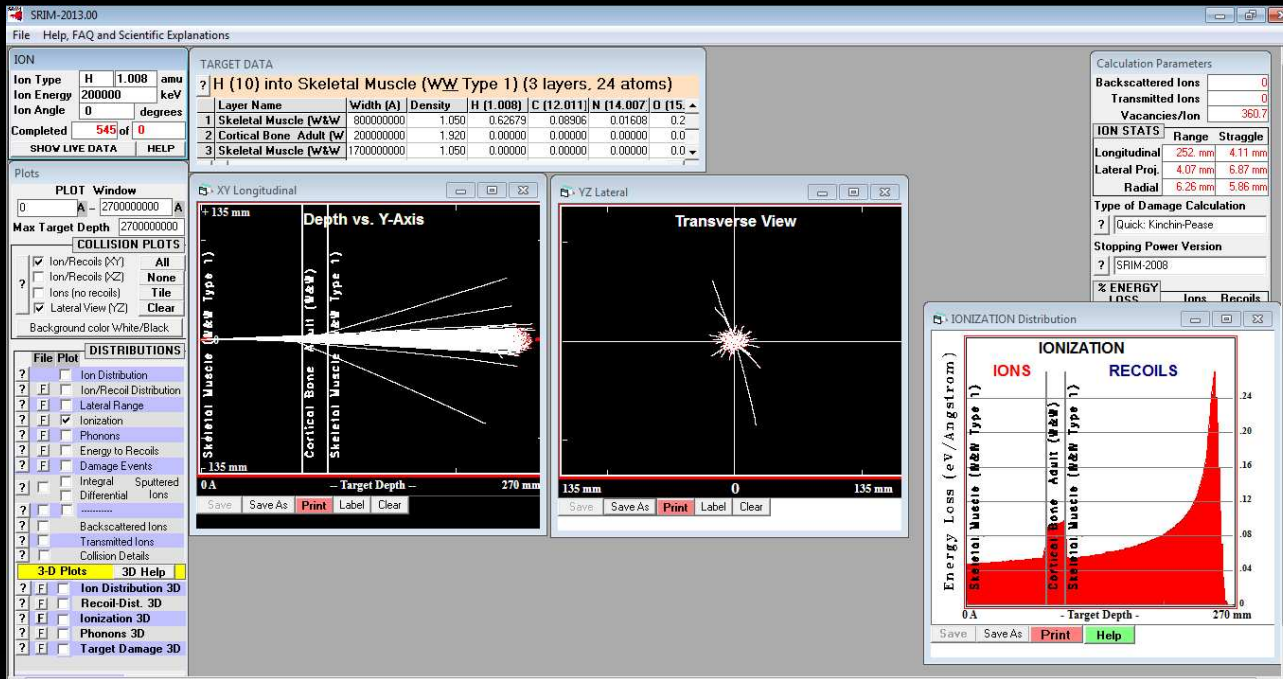
Haz de protones de 30 MeV, incidiendo en hueso cortical humano (TRIM 2008)



Penumbra de un haz colimado debido a Scattering Múltiple Coulombiano (MCS)



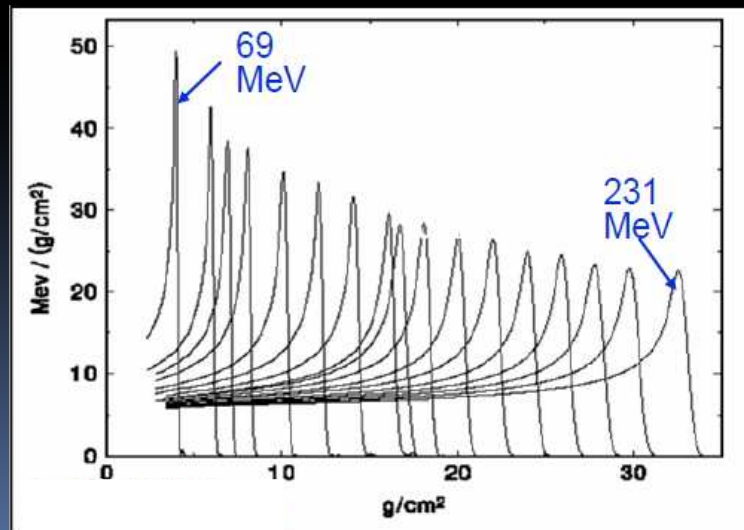
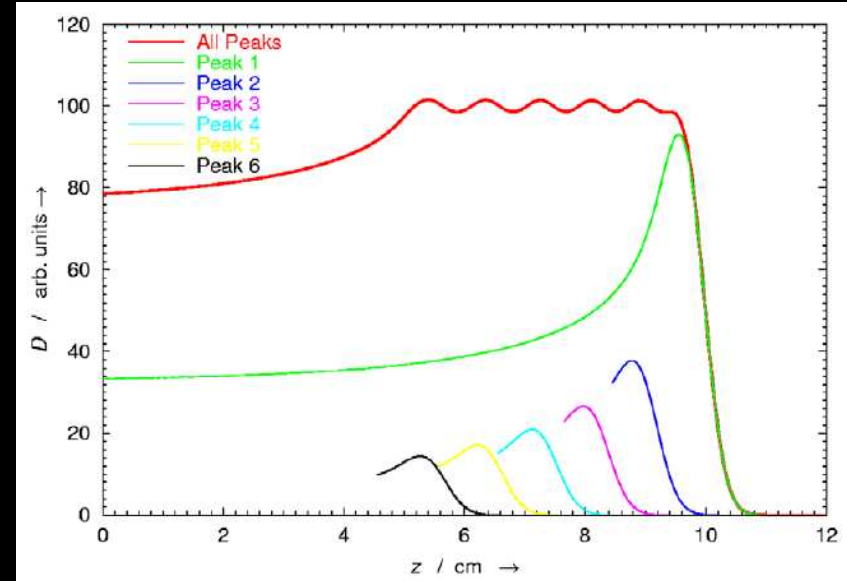
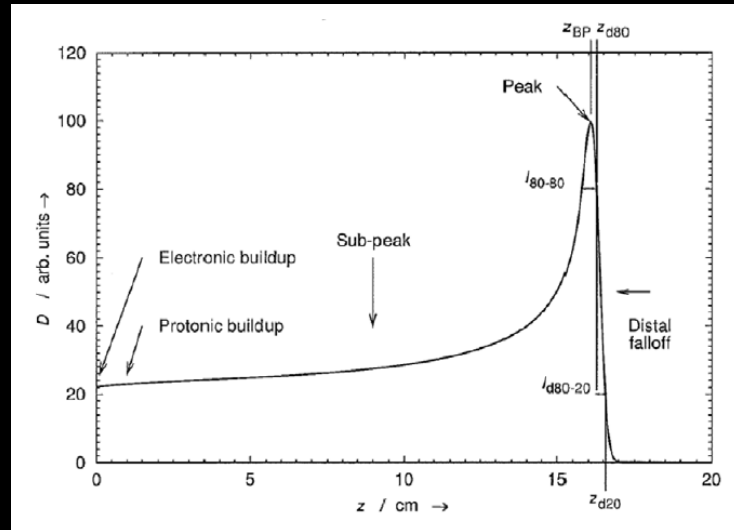
Simulaciones de haces de protones en materiales biológicos



Resumen de las interacciones y sus consecuencias

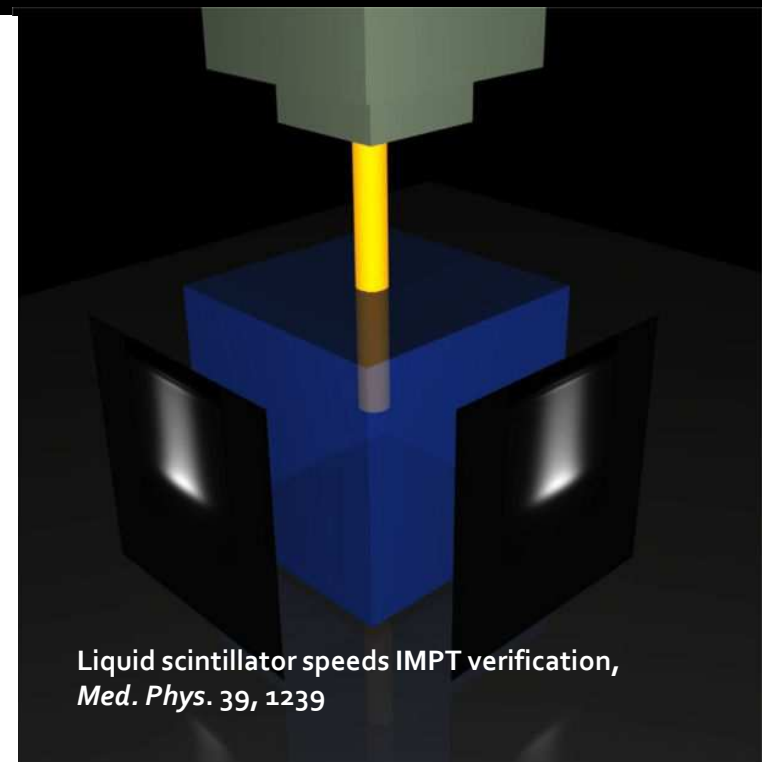
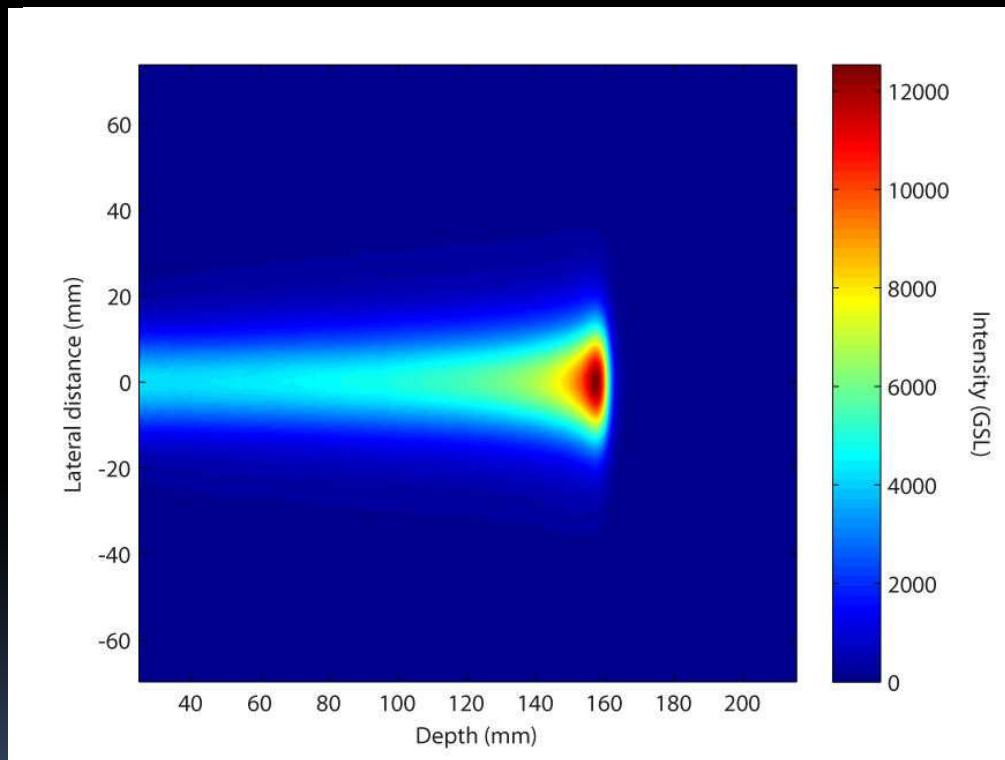
| Tipo de Interacción | Blanco | Principales ejectiles | Acción sobre el proyectil | Consecuencias dosimétricas |
|------------------------------------------|---------------------|---------------------------------------------------------------------------------|------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------|
| Dispersión Coulombiana Inelástica | Electrones atómicos | Protón primario Electrones ionizantes | Pérdida de energía cuasi-continua | Determina el rango en el tejido |
| Dispersión Coulombiana Elástica | Núcleo atómico | Protón primario Núcleo de retroceso | Cambio en la trayectoria | Determina la penumbra lateral (MCS) |
| Reacciones Nucleares No elásticas | Núcleo atómico | Protones secundarios Iones (núcleo de retroceso) Neutrones Rayos gamma | Remoción del protón primario del haz | Cambios en la fluencia del haz primario Neutrones errantes Prompt gammas y aniquilación de positrones para detección in vivo |
| Bremsstrahlung | Núcleo atómico | Protón primario Fotón de Bremsstrahlung | Pérdida de energía Cambio en la trayectoria | Despreciable |

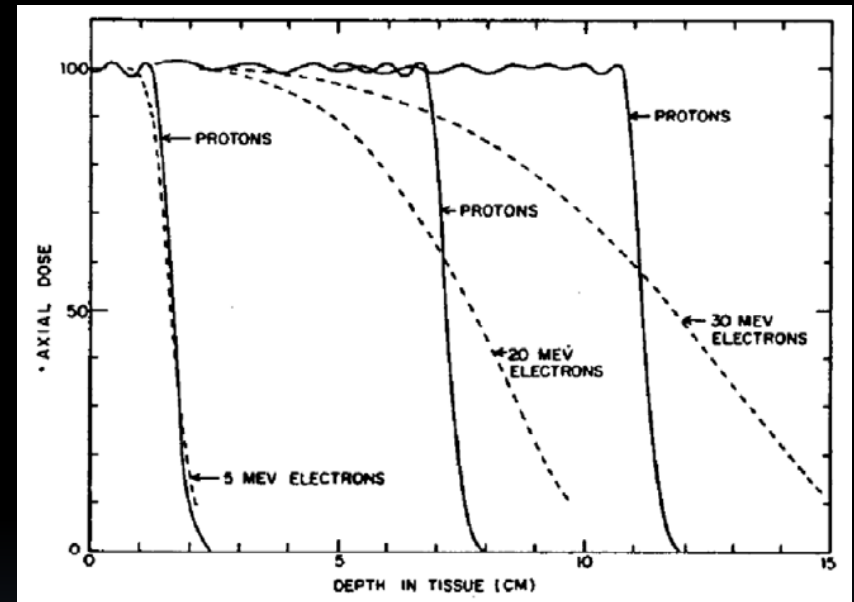
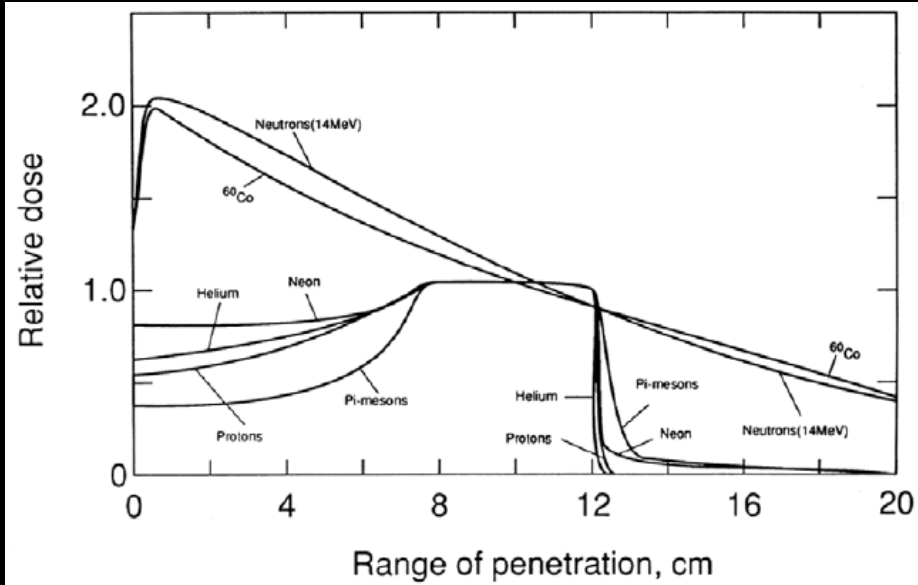
Pico de Bragg “Prístino” y “Extendido” (SOBP, Spread-Out Bragg Peak)



...sin embargo, estas dependencias en profundidad asumen la validez de condiciones de CPE (Equilibrio de Partículas Cargadas), debido a electrones dispersados por colisiones y a protones que sufren MCS... o sea, valen para un haz extenso lateralmente.

¿Cómo lucen estos perfiles para haces delimitados lateralmente?





TERAPIA CON HACES DE PROTONES

Historia breve

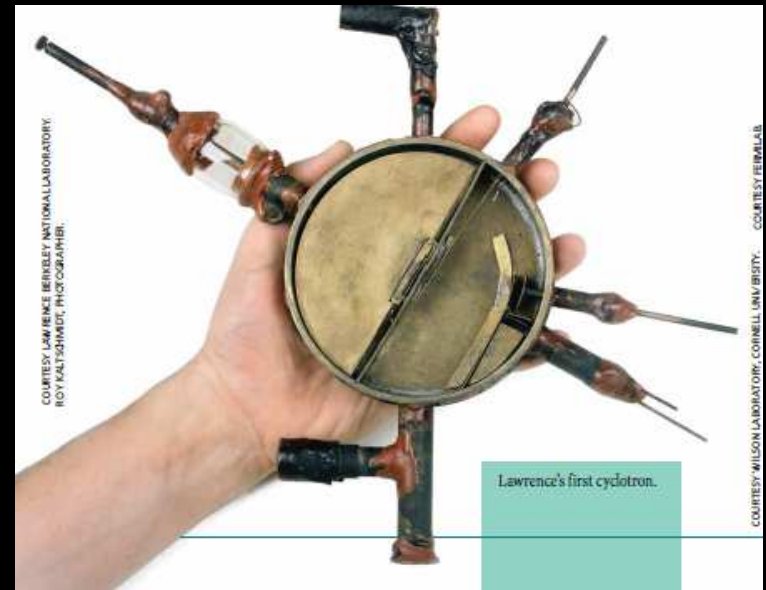
El origen tecnológico de esta modalidad de tratamiento del cáncer se remonta a 1930, cuando Ernest Lawrence, en la Universidad de California, Berkeley inventa el primer ciclotrón...

En 1946, Robert Wilson (físico que había trabajado en el proyecto Manhattan y estudiante de Lawrence), propone el uso de protones para el tratamiento del cáncer.

En el año 1954 se lleva a cabo la primera irradiación de una paciente con metástasis de cáncer de mama en la glándula pituitaria, en el Berkeley's Donner Laboratory.

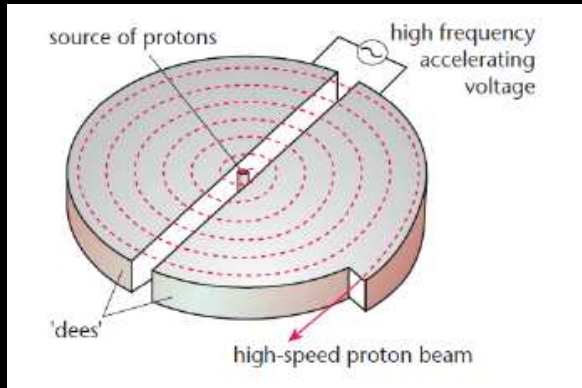
En 1990 MGH y Loma Linda comienzan a aplicar protonterapia basada en hospitales.

En 2010 se comienza a aplicar la técnica de PBS (Proton Beam Scanning) lentamente reemplazando la técnica de scattering pasivo.



Acelerador de protones a 80 keV usando menos de 1 kV en electrodos semicirculares de 13 cm de diámetro

Ciclotrones



- Fuente de partículas
- Imanes
- Generador de RF
- Sistema de extracción



Radio $m v/q B$
 Masa $m = \gamma m_0$
 Período $2\pi m/q B$



Aumentar el período con el radio y mantener constante el campo

ó

Mantener constante el período y aumentar radialmente el campo



Disminuir la RF con el radio => Sincrociclotrones: pulsados (500 a 1000 Hz)
 T ambiente o superconductores

Aumentar el campo con el radio => **Ciclotrones Isócronos: haz continuo**

La energía de extracción es fija

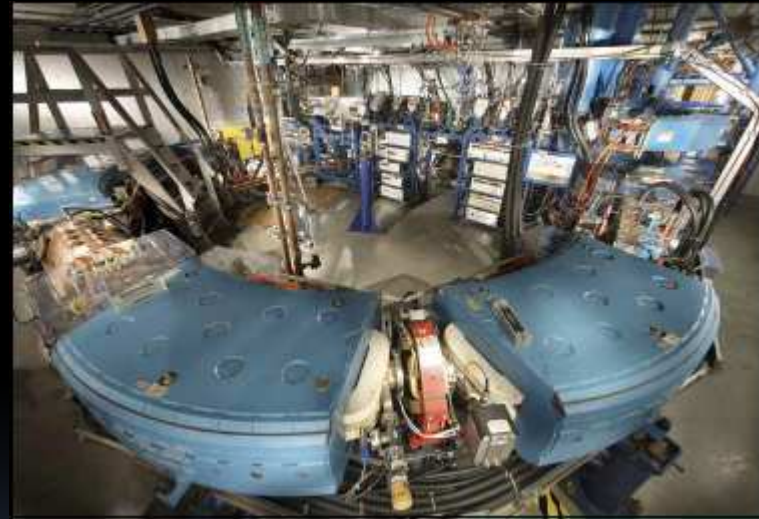
Sincrotrones

Son de radio fijo.

- Fuente de partículas
- Aceleradores auxiliares
- Cavidades resonantes de radiofrecuencia
- Elementos magnéticos (dipolos, cuadrupolos)



Sincrotrón del CNAO, Pavia, Italia



Sincrotrón de Loma Linda
University Medical Center, CA, USA

La energía de extracción es ajustable

Futuros desarrollos

Dielectric Wall Accelerator

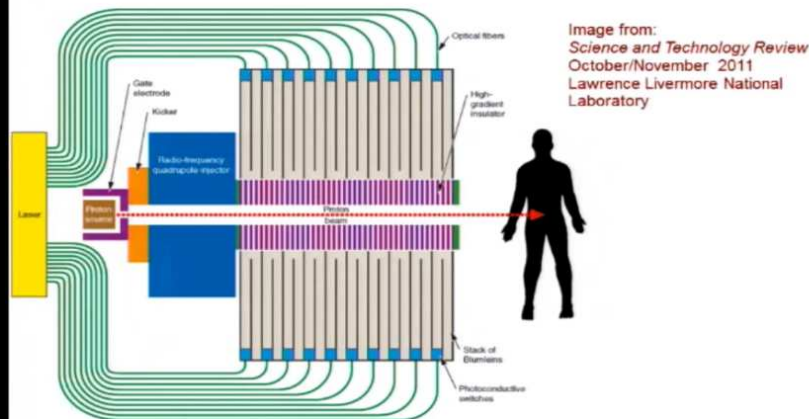
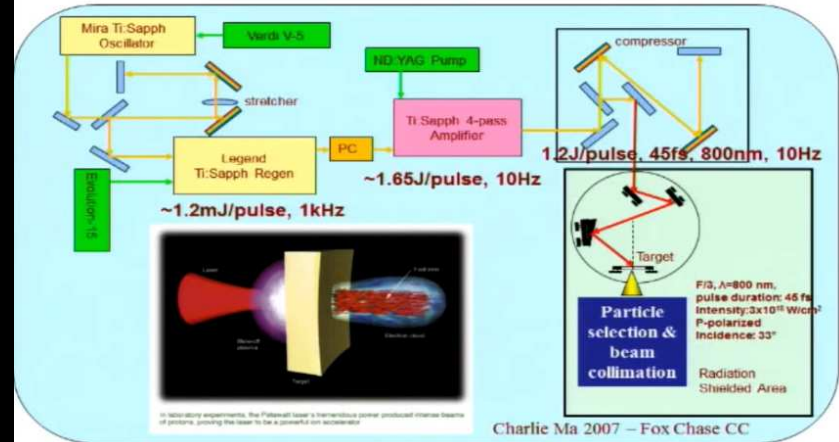


Image from:
Science and Technology Review
October/November 2011
Lawrence Livermore National
Laboratory

<https://str.llnl.gov/OctNov11/caporaso.html>

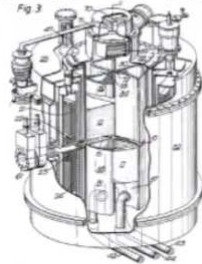
Laser Based Proton Accelerator



Charlie Ma 2007 – Fox Chase CC

Yokeless Magnet

US Patent 8,443,781



- Oxford Instruments' Yokeless Cyclotron Patent .
- "There is no iron yoke for the magnet and the weight and size are consequently much reduced and the cyclotron is highly transportable."
- The design was for a 17 MeV proton cyclotron.
- MIT Paper:

Variable Energy Acceleration in a Single Iron-Free Synchrocyclotron.

Radovinsky, A.L., Minervini, J.V., Michael P.C., Bromberg, L., Miller, C.E.
September 5, 2013

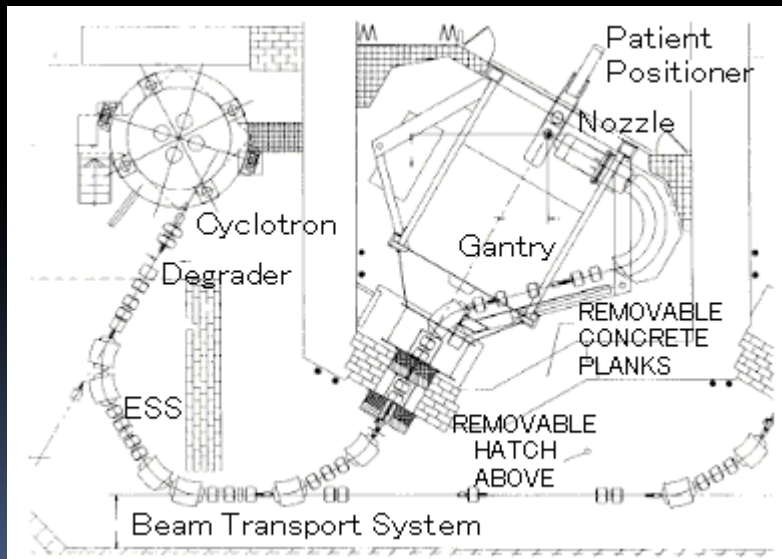
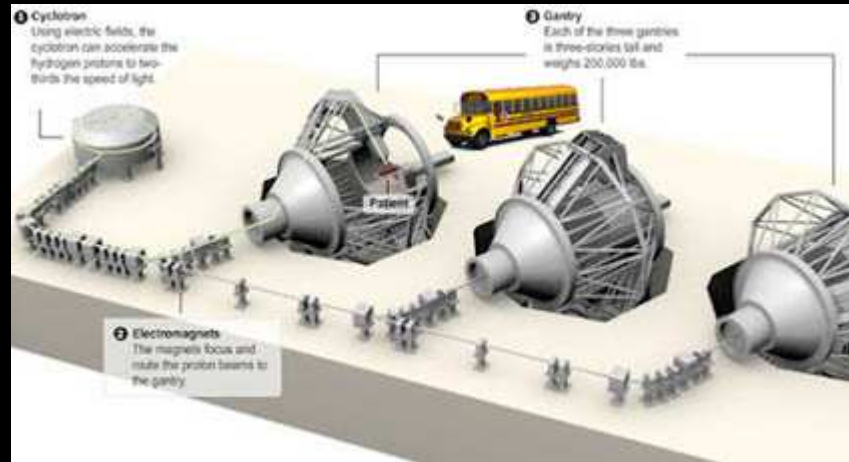


Plasma Science and Fusion Center
Massachusetts Institute of Technology
PSFC/RR-13-9



CNAO (CENTRO NAZIONALE DI ADRONTERAPIA ONCOLOGICA), PAVIA, ITALIA

CENTROS DE HADRONTERAPIA (PROTONES Y 12-C)





Facilidades de Protonterapia en operación (al 01-Abril-2015)

Ref. PTCOG

| COUNTRY | WHO, WHERE | PARTICLE | S/C/SC* MAX. ENERGY (MeV) | BEAM DIRECTIONS | START OF TREATMENT | TOTAL PATIENTS TREATED | DATE OF TOTAL |
|----------------|--------------------------|----------|---------------------------------|-------------------------|-----------------------|------------------------------|------------------|
| Canada | TRIUMF, Vancouver | p | C 72 | 1 horiz. | 1995 | 182 | Dec-14 |
| Czech Republic | PTC Czech r.s.o., Prague | p | C 230 | 3 gantries, 1 horiz. | 2012 | 357 | Dec-14 |
| China | WPTC, Wanjie, Zi-Bo | p | C 230 | 2 gantries, 1 horiz. | 2004 | 1078 | Dec-14 |
| China | IMP-CAS, Lanzhou | C-ion | S 400/u | 1 horiz. | 2006 | 213 | Dec-14 |
| China | SPHIC, Shanghai | p | S 250 | 3 horiz. | 2014 | 13 | Dec-14 |
| China | SPHIC, Shanghai | C-ion | S 430/u | 3 horiz. | 2014 | 22 | Dec-14 |
| England | Clatterbridge | p | C 62 | 1 horiz. | 1989 | 2626 | Dec-14 |
| France | CAL, Nice | p | C165 | 1 horiz. | 1991 | 5205 | Dec-14 |
| France | CPO, Orsay | p | S 250 | 1 gantry, 2 horiz. | 1991 | 7004 | Dec-14 |
| Germany | HZB, Berlin | p | C 250 | 1 horiz. | 1998 | 2525 | Dec-14 |
| Germany | RPTC, Munich | p | C 250 | 4 gantries, 1 horiz. | 2009 | 2307 | Dec-14 |
| Germany | HIT, Heidelberg | p | S 250 | 2 horiz., 1 gantry** | 2009, 2012 | 824 | Dec-14 |
| Germany | HIT, Heidelberg | C-ion | S 430/u | 2 horiz., 1 gantry** | 2009, 2012 | 1723 | Dec-14 |
| Germany | WPE, Essen | p | C 230 | 4 gantries***, 1 horiz. | 2013 | 139 | Dec-14 |
| Germany | PTC, Uniklinikum Dresden | p | C 230 | 1 gantry | 2014 | first patient | Dec-14 |
| Italy | INFN-LNS, Catania | p | C 60 | 1 horiz. | 2002 | 350 | Dec-14 |
| Italy | CNAO, Pavia | p | S 250 | 3 horiz., 1 vertical | 2011 | 111 | Dec-14 |
| Italy | CNAO, Pavia | C-ion | S 480/u | 3 horiz., 1 vertical | 2012 | 318 | Dec-14 |
| Italy | APSS, Trento | p | C 230 | 2 gantries, 1 horiz. | 2014 | 5 | Dec-14 |

* S/C = Synchrotron (S) or Cyclotron (C) or SynchroCyclotron (SC)

** with beam scanning

*** with spread beam and beam scanning

**** degraded beam

***** with beam scanning, Gantry 1 since 1996, Gantry 2 since 2013

Facilidades de Protonterapia en operación (al 01-Abril-2015)

Ref. PTCOG

| COUNTRY | WHO, WHERE | PARTICLE | S/C/SC* MAX. ENERGY (MeV) | BEAM DIRECTIONS | START OF TREATMENT | TOTAL PATIENTS TREATED | DATE OF TOTAL |
|--------------|-----------------------------------------------|----------|---------------------------------|--------------------------------|-----------------------|------------------------------|------------------|
| Japan | HIMAC, Chiba | C-ion | S 800/u | horiz.***, vertical*** | 1994 | 8841 | Dec-14 |
| Japan | NCC, Kashiwa | p | C 235 | 2 gantries*** | 1998 | 1560 | Dec-14 |
| Japan | HIBMC, Hyogo | p | S 230 | 1 gantry | 2001 | 4652 | Dec-14 |
| Japan | HIBMC, Hyogo | C-ion | S 320/u | horiz., vertical | 2002 | 2146 | Dec-14 |
| Japan | PMRC 2, Tsukuba | p | S 250 | 2 gantries | 2001 | 3416 | Dec-14 |
| Japan | Shizuoka Cancer Center | p | S 235 | 3 gantries, 1 horiz. | 2003 | 1757 | Dec-14 |
| Japan | STPTC, Koriyama-City | p | S 235 | 2 gantries, 1 horiz. | 2008 | 2797 | Dec-14 |
| Japan | GHMC, Gunma | C-ion | S 400/u | 3 horiz., 1 vertical | 2010 | 1486 | Dec-14 |
| Japan | MPTRC, Ibusuki | p | S 250 | 3 gantries | 2011 | 1317 | Dec-14 |
| Japan | Fukui Prefectural Hospital PTC, Fukui City | p | S 235 | 2 gantries, 1 horiz. | 2011 | 428 | Dec-13 |
| Japan | Nagoya PTC, Nagoya City, Aichi | p | S 250 | 2 gantries, 1 horiz. | 2013 | 627 | Dec-14 |
| Japan | SAGA-HIMAT, Tosu | C-ion | S 400/u | 3 horiz., vertical, 45 deg. | 2013 | 547 | Dec-14 |
| Japan | Aizawa Hospital PTC, Nagano | p | C 235 | 1 gantry | 2014 | first patient | Oct-14 |
| Poland | IFJ PAN, Krakow | p | C 60 | 1 horiz. | 2011 | 85 | Dec-14 |
| Russia | ITEP, Moscow | p | S 250 | 1 horiz. | 1969 | 4368 | Dec-14 |
| Russia | St.Petersburg | p | S 1000 | 1 horiz. | 1975 | 1386 | Dec-12 |
| Russia | JINR 2, Dubna | p | C 200**** | 1 horiz. | 1999 | 1069 | Dec-14 |
| South Africa | NRF - iThemba Labs | p | C 200 | 1 horiz. | 1993 | 524 | Dec-14 |
| South Korea | NCC, Ilsan | p | C 230 | 2 gantries, 1 horiz. | 2007 | 1496 | Dec-14 |
| Sweden | Svedberg Lab., Uppsala | p | C 200 | 1 horiz. | 1989 | 1431 | Dec-14 |
| Switzerland | CPT, PSI, Villigen | p | C 250 | 2 gantries****, 1 horiz. | 1984, 1996, 2013 | 7364 | Dec-14 |

Facilidades de Protonterapia en operación (al 01-Abril-2015)

Ref. PTCOG

| COUNTRY | WHO, WHERE | PARTICLE | S/C/SC* MAX. ENERGY (MeV) | BEAM DIRECTIONS | START OF TREATMENT | TOTAL PATIENTS TREATED | DATE OF TOTAL |
|----------|-------------------------------------------------------------|----------|---------------------------------|---------------------------------------|-----------------------|------------------------------|------------------|
| USA, CA. | J. Slater PTC, Loma Linda | p | S 250 | 3 gantries, 1 horiz. | 1990 | 18362 | Dec-14 |
| USA, CA. | UCSF, San Francisco | p | C 60 | 1 horiz. | 1994 | 1729 | Dec-14 |
| USA, MA. | MGH Francis H. Burr PTC, Boston | p | C 235 | 2 gantries***, 1 horiz. | 2001 | 8107 | Sep-14 |
| USA, IN. | IU Health PTC, Bloomington | p | C 200 | 2 gantries***, 1 horiz. | 2004-2014 | 2200 | Dec-14 |
| USA, TX. | MD Anderson Cancer Center, Houston | p | S 250 | 3 gantries***, 1 horiz. | 2006 | 5838 | Dec-14 |
| USA, FL. | UFPTI, Jacksonville | p | C 230 | 3 gantries, 1 horiz. | 2006 | 5376 | Dec-14 |
| USA, OK. | ProCure PTC, Oklahoma City | p | C 230 | 1 gantry, 1 horiz, 2 horiz/60 deg. | 2009 | 1690 | Dec-14 |
| USA, PA. | Roberts PTC, UPenn, Philadelphia | p | C 230 | 4 gantries, 1 horiz. | 2010 | 2522 | Dec-14 |
| USA, IL. | Chicago Proton Center, Warrenville | p | C 230 | 1 gantry, 1 horiz, 2 horiz/60 deg. | 2010 | 1782 | Dec-14 |
| USA, VA. | HUPTI, Hampton | p | C 230 | 4 gantries, 1 horiz. | 2010 | 1200 | Dec-14 |
| USA, NY. | ProCure Proton Therapy Center, New Jersey | p | C 230 | 4 gantries | 2012 | 1168 | Dec-14 |
| USA, WA. | SCCA ProCure Proton Therapy Center, Seattle | p | C 230 | 4 gantries | 2013 | 420 | Dec-14 |
| USA, MO. | S. Lee Kling PTC, Barnes Jewish Hospital, St. Louis | p | SC 250 | 1 gantry | 2013 | 149 | Dec-14 |
| USA, TN. | Provision Center for Proton Therapy, Knoxville | p | C 230 | 3 gantries | 2014 | 100 | Aug-14 |
| USA, CA. | Scripps Proton Therapy Center, San Diego | p | C 250 | 3 gantries, 2 horiz. | 2014 | 220 | Dec-14 |
| USA, LA. | Willis Knighton Proton Therapy Cancer Center, Shreveport | p | C 230 | 1 gantry | 2014 | 28 | Dec-14 |
| USA, FL. | Ackermann Cancer Center, Jacksonville | p | SC 250 | 1 gantry | 2015 | 1 | Apr-15 |



Systematic review

An evidence based review of proton beam therapy: The report of ASTRO's emerging technology committee

Aaron M. Allen^{a,*}, Todd Pawlicki^b, Lei Dong^c, Eugene Fourkal^d, Mark Buyyounouski^d, Keith Cengel^e, John Plastaras^e, Mary K. Bucci^c, Torunn I. Yock^f, Luisa Bonilla^a, Robert Price^d, Eleanor E. Harris^g, Andre A. Konski^h

^a Davidoff Center, Tel Aviv University, Israel; ^b University of California, San Diego, La Jolla, USA; ^c M.D. Anderson Cancer Center, University of Texas, Houston, USA; ^d Fox Chase Cancer Center, Philadelphia, USA; ^e University of Pennsylvania, Philadelphia, USA; ^f Massachusetts General Hospital, Boston, USA; ^g H. Lee Moffit Cancer Center, Tampa, USA; ^h Wayne State University Medical Center, Detroit, USA

A B S T R A C T

Proton beam therapy (PBT) is a novel method for treating malignant disease with radiotherapy. The purpose of this work was to evaluate the state of the science of PBT and arrive at a recommendation for the use of PBT. The emerging technology committee of the American Society of Radiation Oncology (ASTRO) routinely evaluates new modalities in radiotherapy and assesses the published evidence to determine recommendations for the society as a whole. In 2007, a Proton Task Force was assembled to evaluate the state of the art of PBT. This report reflects evidence collected up to November 2009. Data was reviewed for PBT in central nervous system tumors, gastrointestinal malignancies, lung, head and neck, prostate, and pediatric tumors. Current data do not provide sufficient evidence to recommend PBT in lung cancer, head and neck cancer, GI malignancies, and pediatric non-CNS malignancies. In hepatocellular carcinoma and prostate cancer and there is evidence for the efficacy of PBT but no suggestion that it is superior to photon based approaches. In pediatric CNS malignancies PBT appears superior to photon approaches but more data is needed. In large ocular melanomas and chordomas, we believe that there is evidence for a benefit of PBT over photon approaches. PBT is an important new technology in radiotherapy. Current evidence provides a limited indication for PBT. More robust prospective clinical trials are needed to determine the appropriate clinical setting for PBT.

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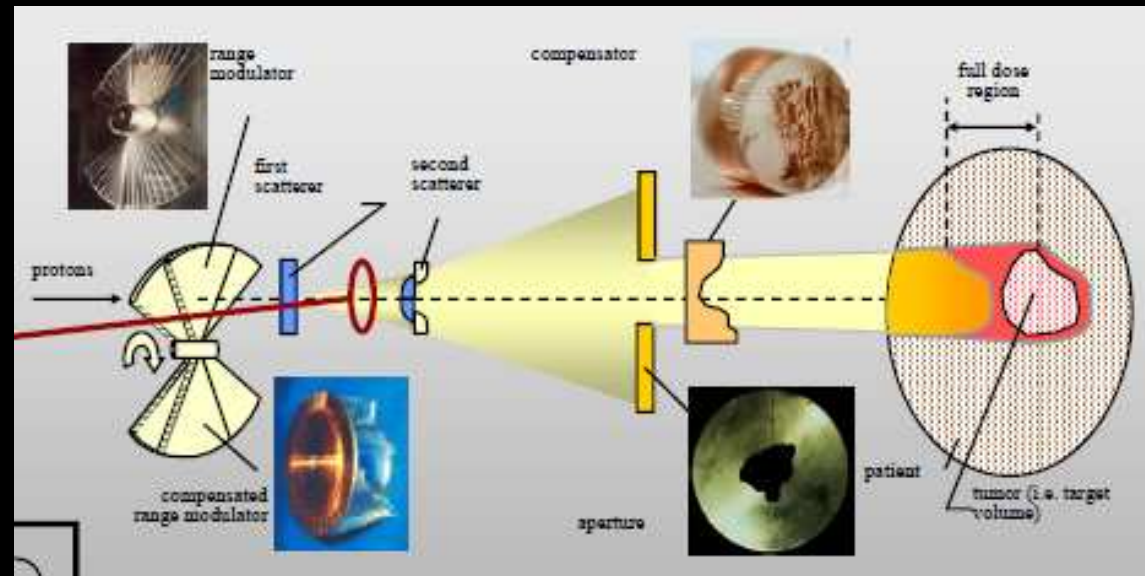
Radiotherapy and Oncology 103 (2012) 8–11



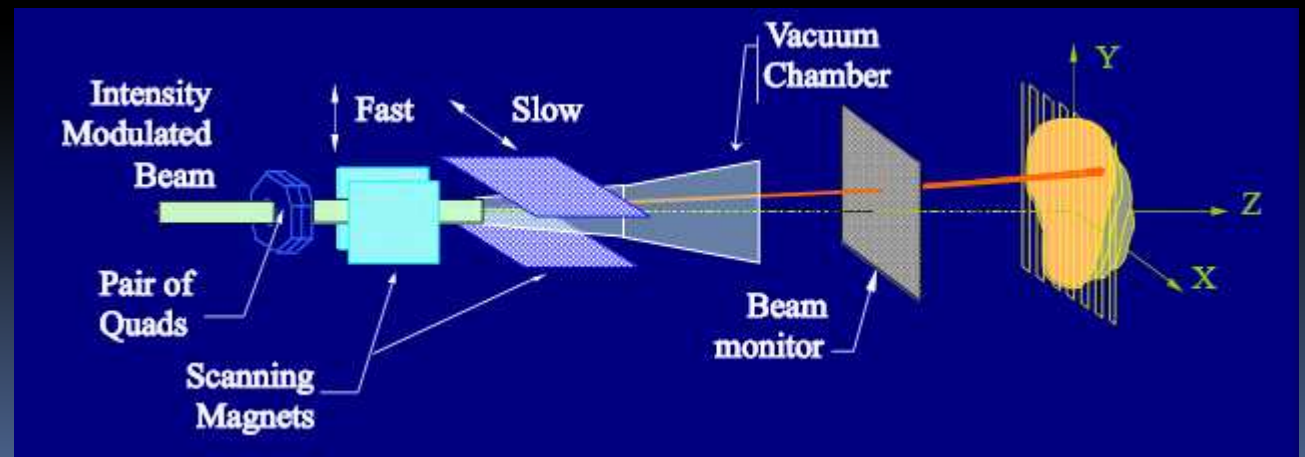
TÉCNICAS DE IRRADIACIÓN

Estrategias para la conformación de dosis en tumor

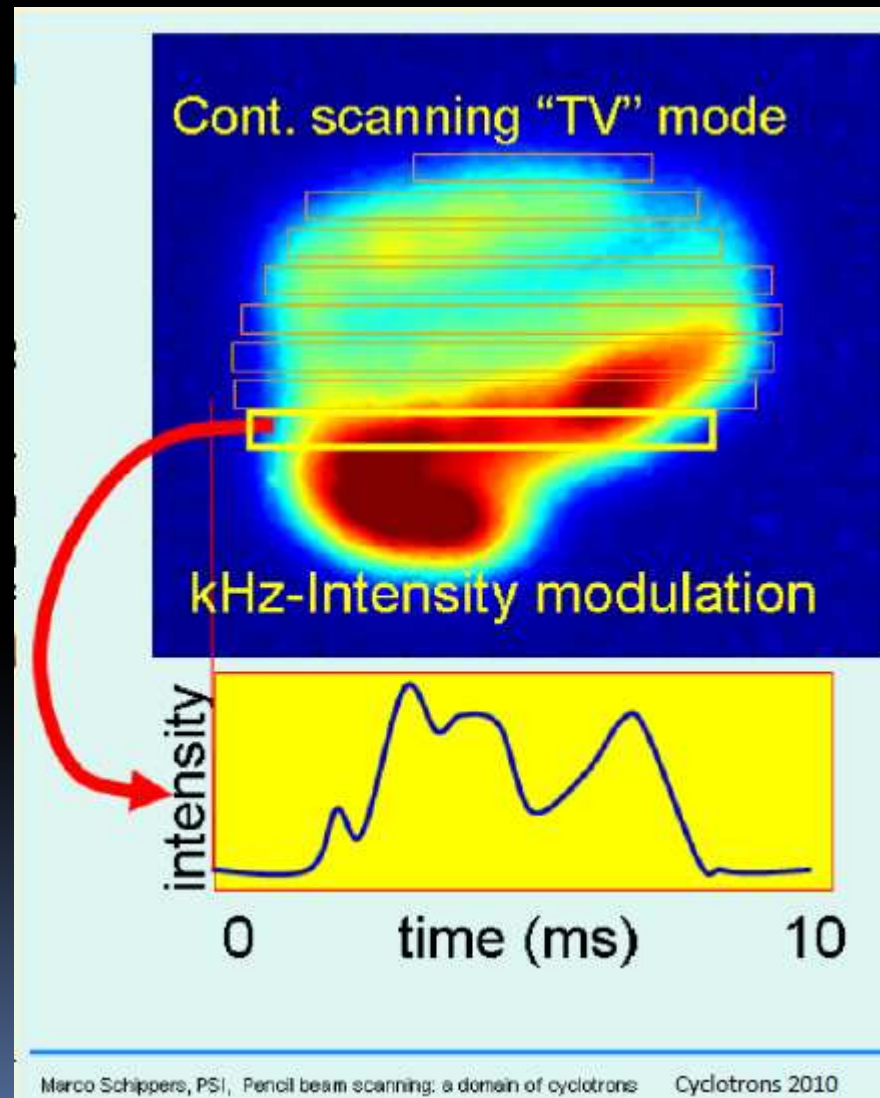
Passive Scattering



Scanning
(Uniform and Pencil Beam)

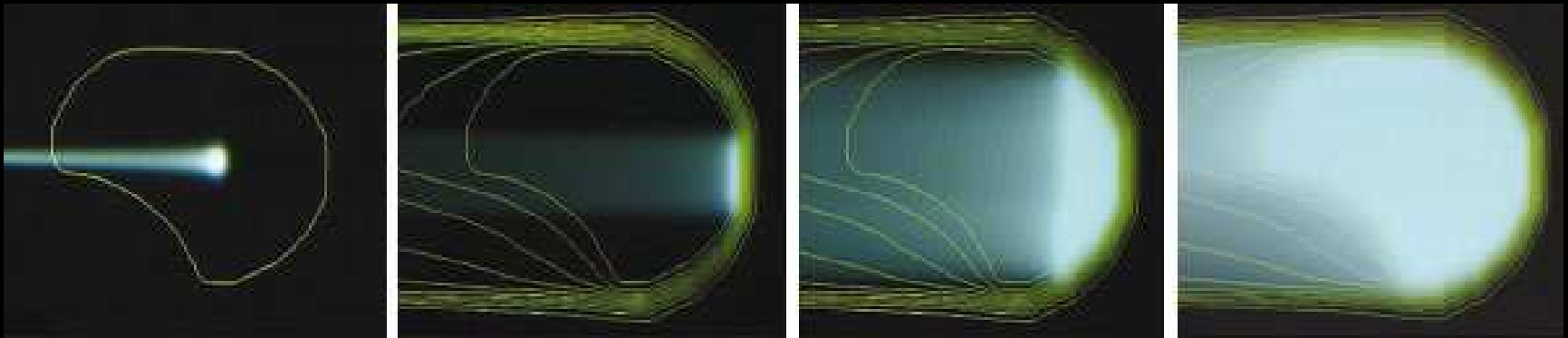


IMPT



PBS:

Conformalidad de Dosis tanto distal como proximal



Films en fantomas E. Pedroni and T Lomax, PSI

Típicamente se requieren

10.000 PBs

5 variables (Intensidad, rango (energía), sección, x , y)

PBS: Pros y Cons

PROs

- Mejor conformación de dosis en el borde proximal del volumen target
- Permite la implementación de IMPT (Intensity Modulated Proton Therapy)
- Produce muchos menos neutrones
- Puede tratar campos extensos sin tener que recurrir a la superposición
- Puede tratar tumores en localizaciones más profundas
- Elimina la necesidad de delimitadores personalizados o bolus
- Ofrece mejores planes de tratamiento

CONs

- Los tiempos de entrega de haz son mayores, debido a la selección de E
- Targets en movimiento (PBS posee una estructura temporal)
- Requiere una E mínima (70 a 100 MeV)
- La aplicación de la técnica en forma estándar es relativamente nueva (2011)

Contribuciones a la Clínica

MODELO DEL PACIENTE

Incertezas en el Rango según las imágenes

Artefactos (Head and Neck)

Variaciones Inter-fracciones: cambios anatómicos (vejiga, recto, cambios en el tumor), movimiento de órganos.

CÁLCULOS

Incertezas en el rango debido a la conversión Hounsfield a RSP.

Aproximaciones en los cálculos analíticos-numéricos.

Planificación inversa

Monte Carlo: **Librerías de datos nucleares**, reducción de varianza, etc.

DOSIS ISOEFECTIVA

Hipótesis de validez de los RBEs. Dependencias con el espectro de energía lineal.

Variaciones en la calidad del haz en el tiempo.

QA y QC, PROTECCIÓN RADIOLÓGICA

Penumbra lateral y longitudinal, Estabilidad en energía

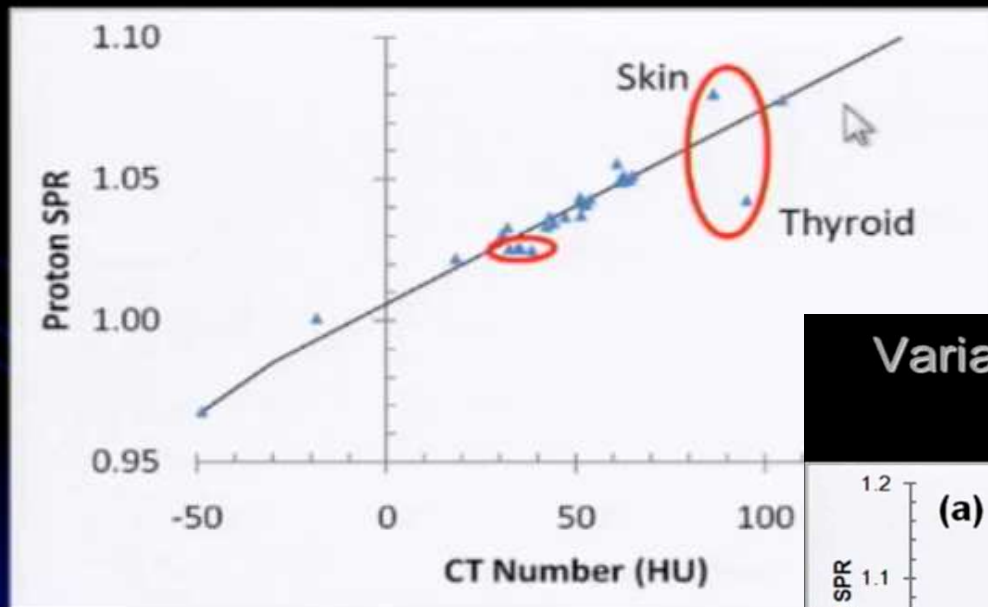
Monitoreo on-line del posicionamiento del haz

Producción de neutrones, dosis ambiente

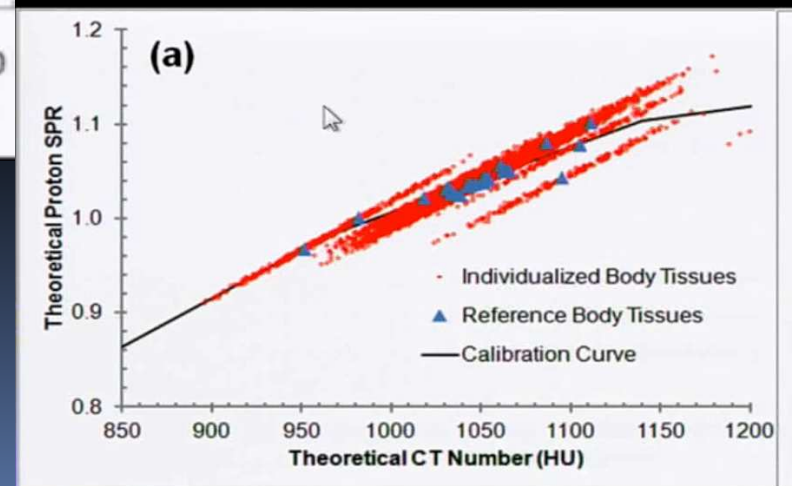
Degeneración CT => SPR

$$HU(\rho_1, Z_1) = HU(\rho_2, Z_2)$$

$$SPR(\rho_1, Z_1) \neq SPR(\rho_2, Z_2)$$

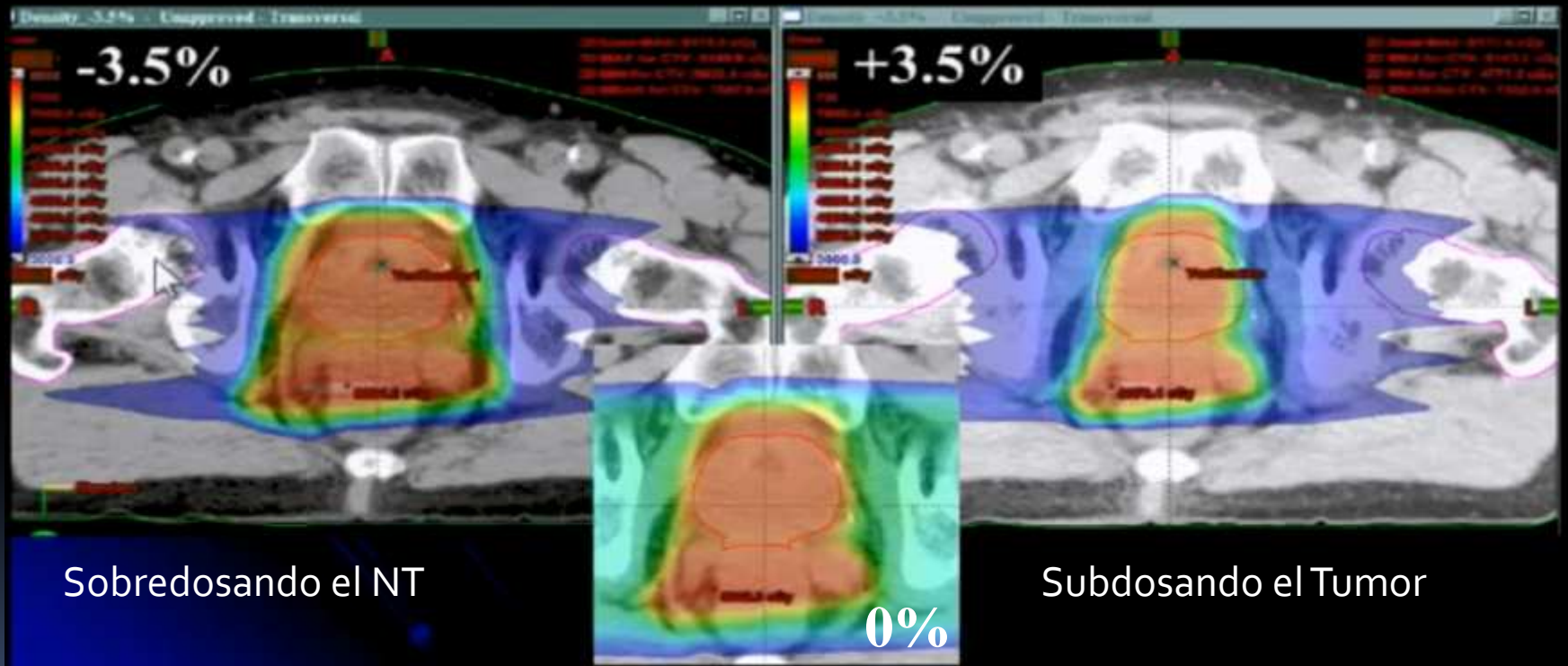


Variations in Human Tissue Composition



Incertezas en el Rango

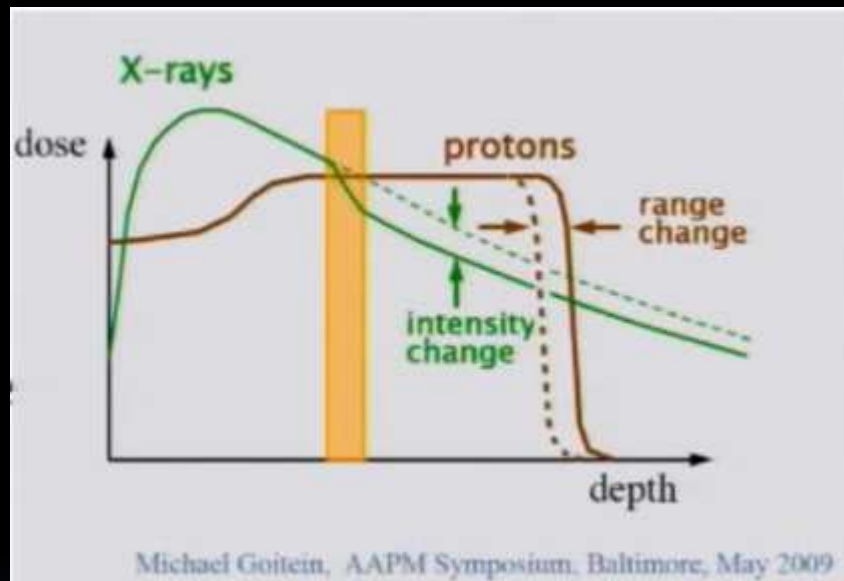
Producen un impacto significativo en la distribución de dosis



Importancia clínica de las incertezas en el rango

- Targets próximos a estructuras críticas
- Aplicación de dosis únicas o pocas fracciones (hipofraccionamiento)
- Reirradiación cuando los tejidos normales ya han alcanzado previamente su límite de tolerancia

Mitigar los efectos de las incertezas en el rango y en la dosis



Objetivo: lograr incertezas en el rango del orden del 1%

- Hay un buen conocimiento del rango de p en agua para todas las E
- Sin embargo, se necesita conocer esta cantidad en tejidos (pulmón, blandos, hueso)
- Pequeñas variaciones en la densidad y composición conllevan variaciones importantes en la dosis

LA POSICIÓN DE CADA PICO DE BRAGG ES ALTAMENTE SENSIBLE A DIFERENCIAS EN EL SP

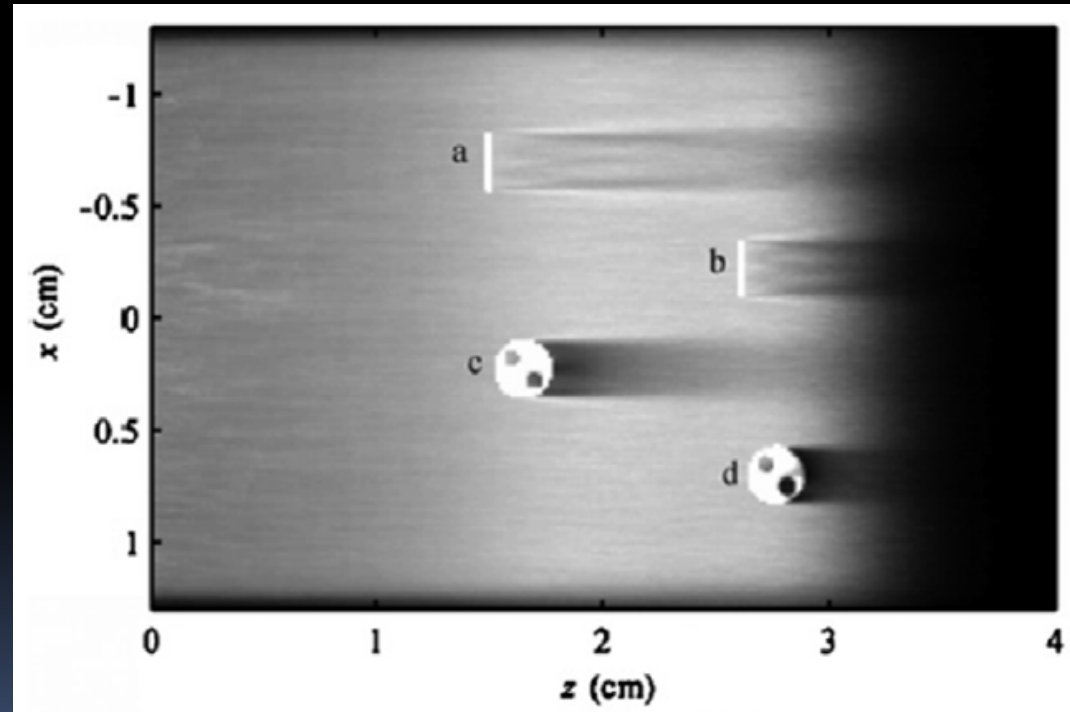
PBS: DESDE 100% OVERLAP HASTA GAPS ENTRE CAPAS

M. Yang et al, PMB 2012

| Uncertainty Sources | | Relative Range Uncertainties (2σ) | | |
|-----------------------------------------------------------------------------|-------------------------------------------|--------------------------------------------|-------------|-------------|
| | | Lung | Soft | Bone |
| Inherent uncertainty in the presence of human tissue composition variations | | 0.4% | 2.0% | 3.0% |
| CT# Related | Modeling errors in predicted CT numbers | 7.5% | 1.5% | 1.1% |
| | CT imaging uncertainties | 6.7% | 1.1% | 3.1% |
| RSP Related | Uncertainties in mean excitation energies | 0.2% | 0.6% | 0.7% |
| | RSP variations with proton energy | | 0.3% | 0.8% |
| Total | | 10.1% | 2.9% | 4.5% |

MCS y marcadores fiduciales implantados en el paciente: ejemplo de la influencia en la dosimetría

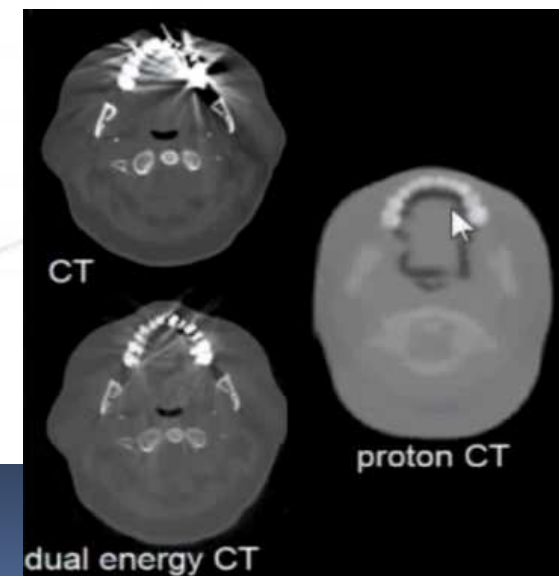
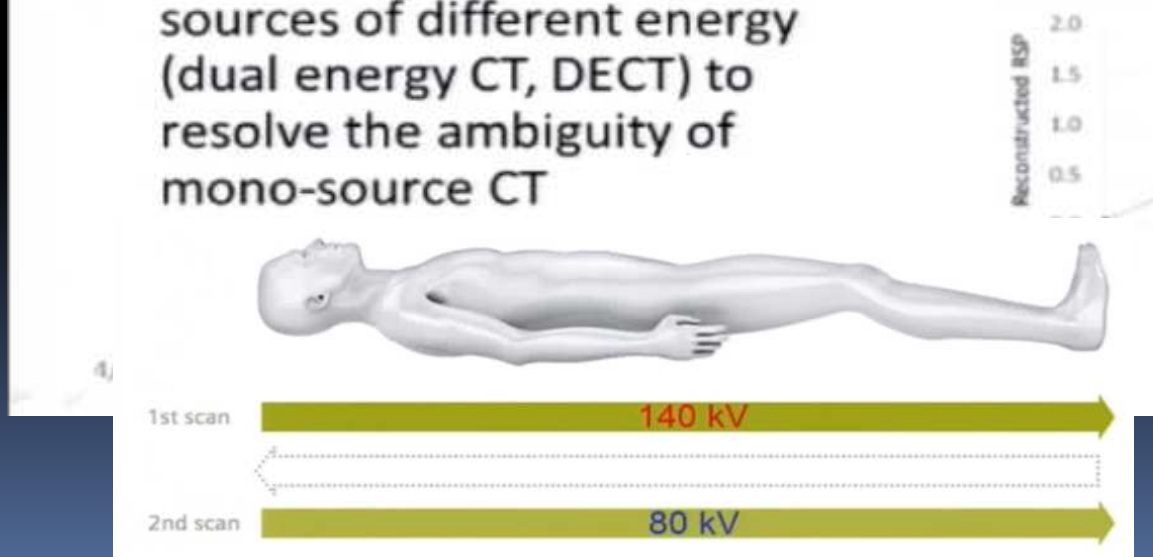
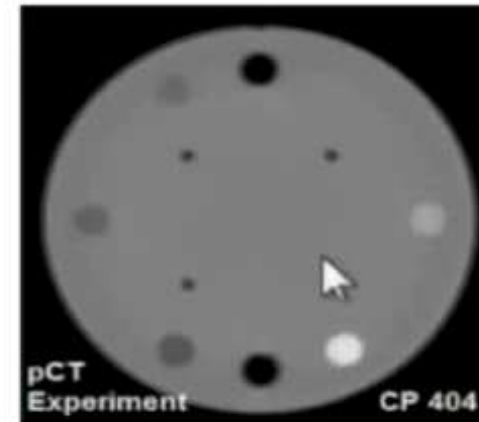
Utilizados para la alineación guiada por imágenes de los pacientes en protonterapia, con el objetivo de mejorar la cobertura del tumor y/o la protección de tejidos normales



Distribución 2D de dosis, simulación por Monte Carlo, de marcadores implantables de tantalio, orientados paralela o transversalmente al haz. Rangos típicos para tratamiento de melanoma uveal. *Phys. Med. Biol.* 52, 2937-52 (2007)

Novel Imaging Technologies Addressing CT-Related Range Uncertainties

- Range uncertainties due to conversion of x-ray CT units to relative stopping power (RSP) would best be solved by using protons for imaging (proton CT)
- Another possibility is to use CT scanning with two x-ray sources of different energy (dual energy CT, DECT) to resolve the ambiguity of mono-source CT



Tomografía con protones

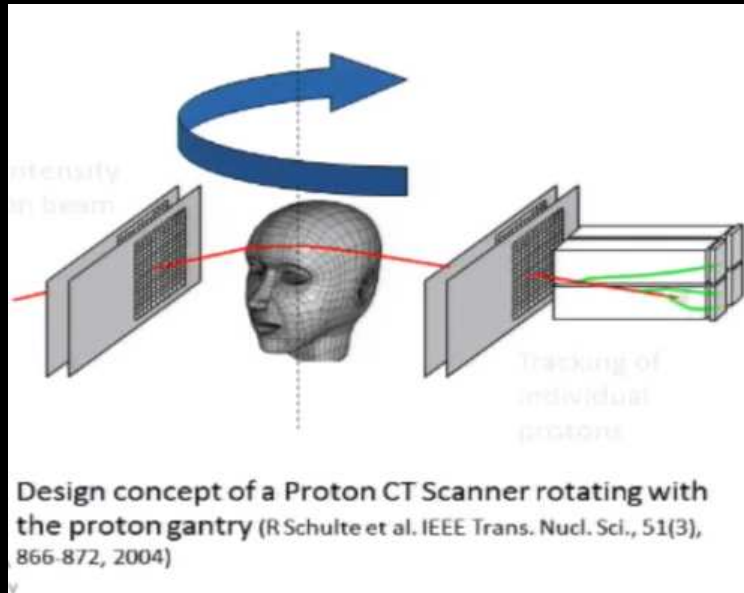


Figure 4.1: Test beam setup for range detector at ProCure Proton Therapy Center at Central DuPage Hospital.

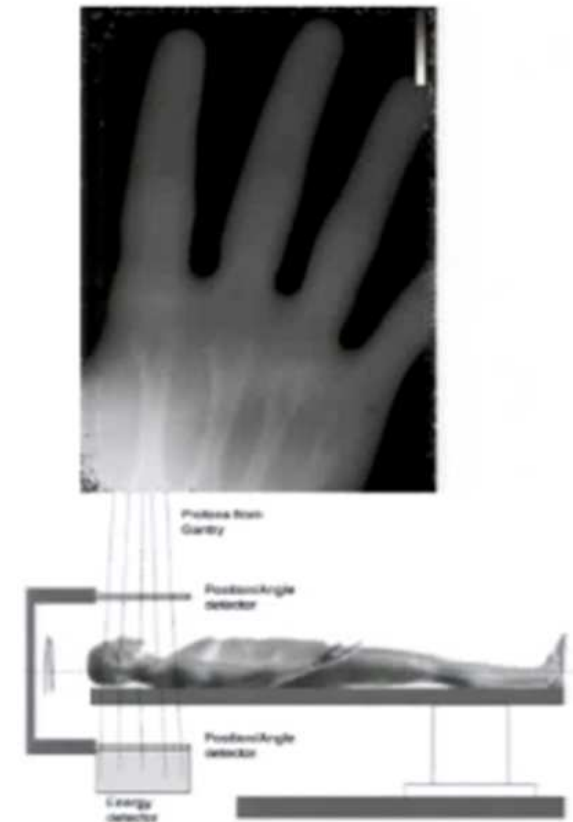


Fantoma pediátrico, R. Schulte et al.

CT con protones: alineamiento y verificación

Proton Radiography and CT

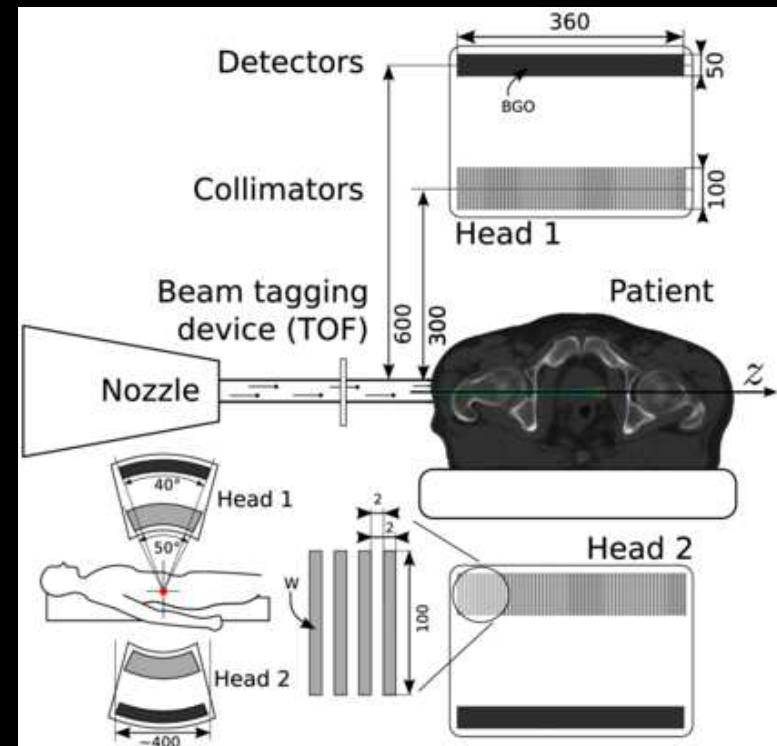
- As proton imaging can be integrated into a proton gantry, it can also be used for alignment and plan verification
- Proton radiography can be used to verify correct position and integrated path length distribution
- A proton CT/radiography system is under development, but a few years away



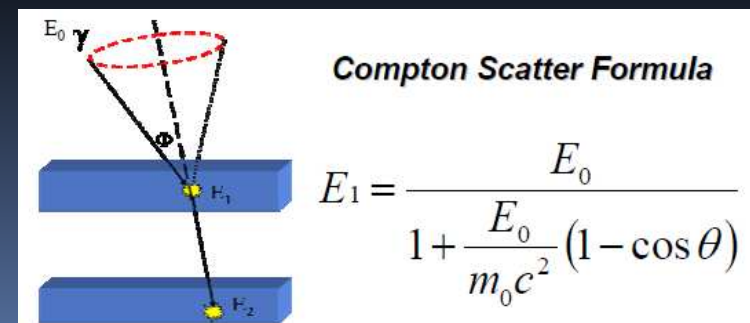
Prompt-gamma

- Gamma-prompt de reacciones de captura con los elementos del tejido a bajas energías de protones.
- Pueden ser utilizados para el monitoreo in vivo durante el tratamiento en la zona del tumor.
- La intensidad y perfil están relacionados fuertemente con la dosis entregada y la posición del pico de Bragg.

- Cámaras Compton en desarrollo



P Gueth *et al* 2013 *Phys. Med. Biol.* 58 4563



Positron Emission Tomography

- PET debido a reacciones nucleares con los elementos del tejido

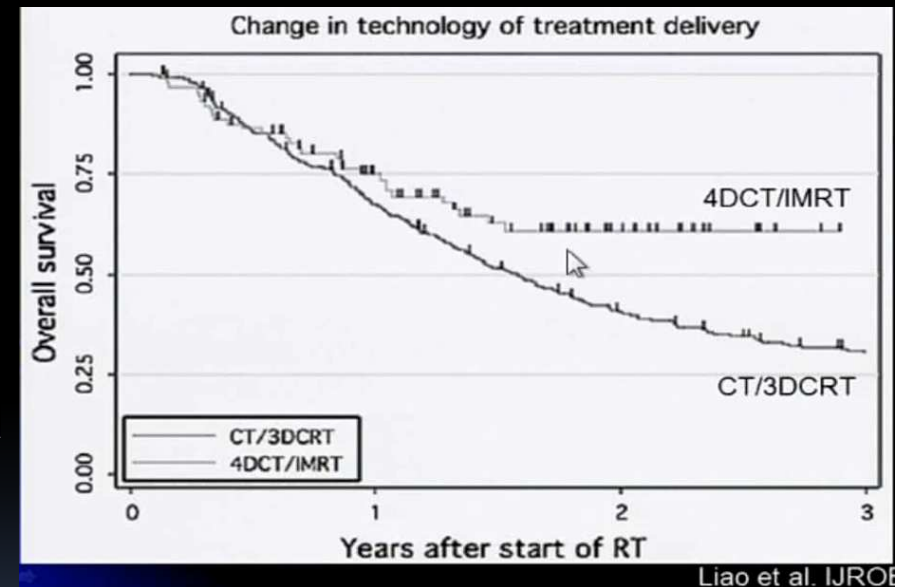
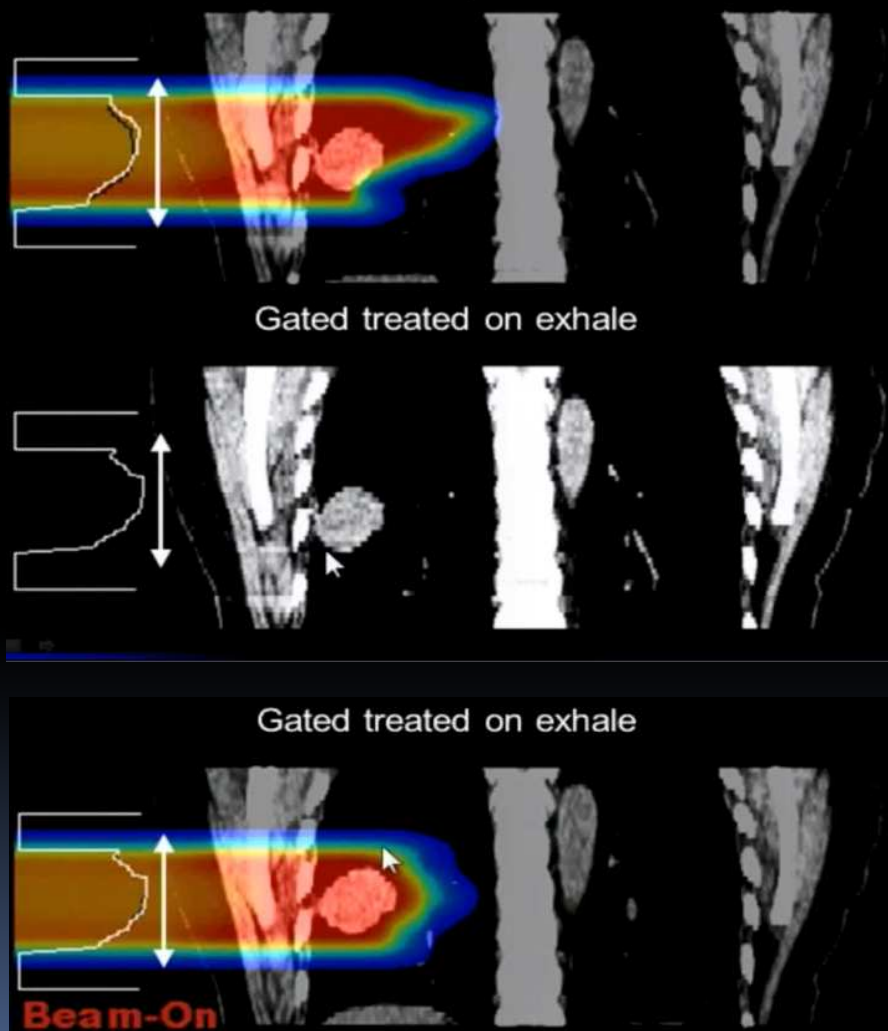
Table 1. Major nuclear reaction channels for proton induced positron emitter productions.

| Radionuclide | Half live (min) | Nuclear reaction channels / Threshold energies (MeV) |
|-----------------|-----------------|---------------------------------------------------------------------------------------------------------------------------------------|
| ^{15}O | 2.037 | $^{16}\text{O}(p,pn)^{15}\text{O}/16.79$ |
| ^{11}C | 20.385 | $^{12}\text{C}(p,pn)^{11}\text{C}/20.61,$ $^{14}\text{N}(p,2p2n)^{11}\text{C}/3.22,$ $^{16}\text{O}(p,3p3n)^{11}\text{C}/59.64$ |
| ^{13}N | 9.965 | $^{16}\text{O}(p,2p2n)^{13}\text{N}/5.66,$ $^{14}\text{N}(p,pn)^{13}\text{N}/11.44$ |
| ^{30}P | 2.498 | $^{31}\text{P}(p,pn)^{30}\text{P}/19.7$ |
| ^{38}K | 7.636 | $^{40}\text{Ca}(p,2p2n)^{38}\text{K}/21.2$ |

Theranostics 2013, Vol. 3, Issue 10



Movimientos de órganos: gating respiratorio

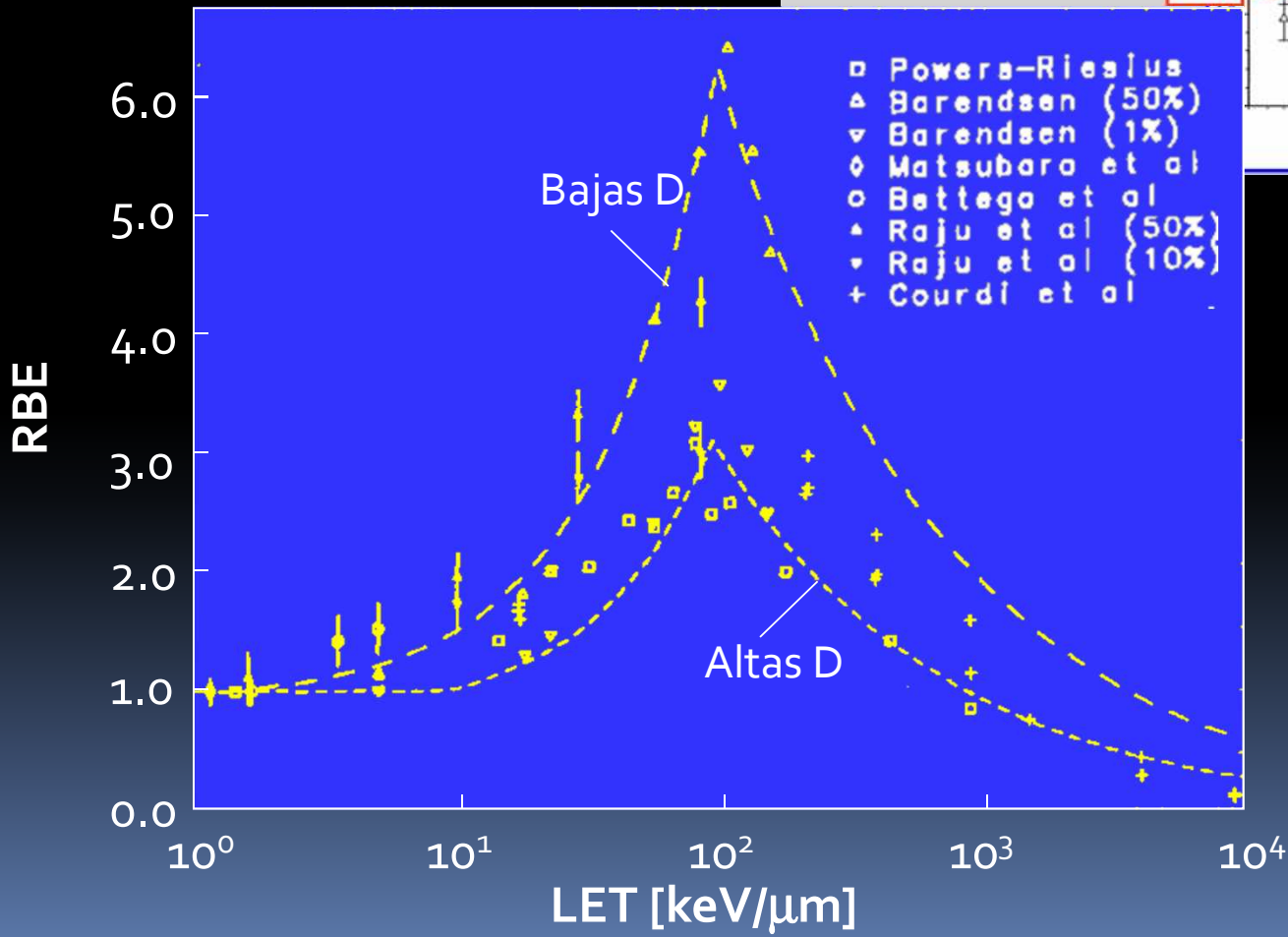
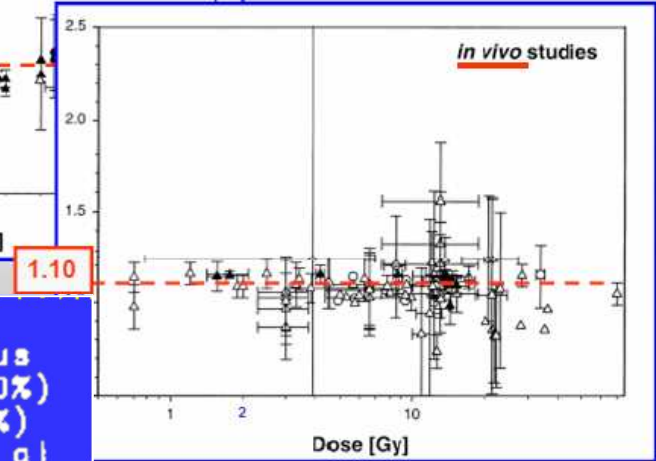
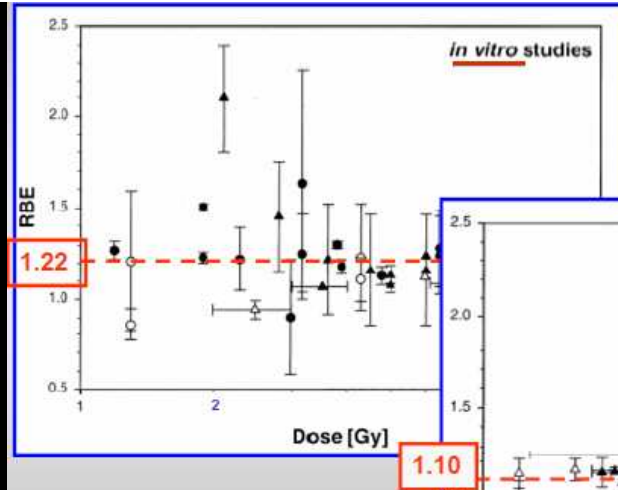


Relative Biological Effectiveness (RBE)

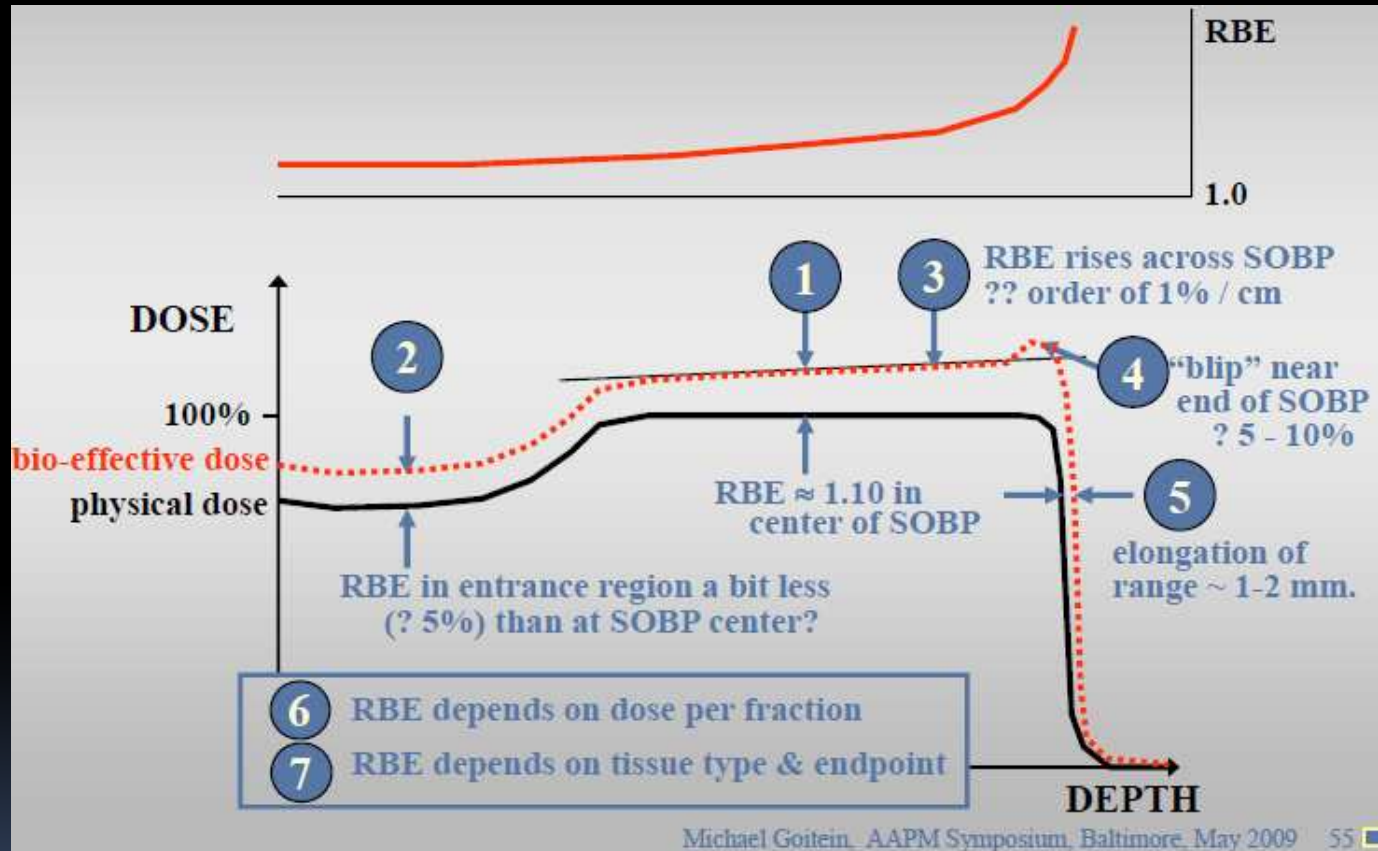
(RBE clínico = 1.1)

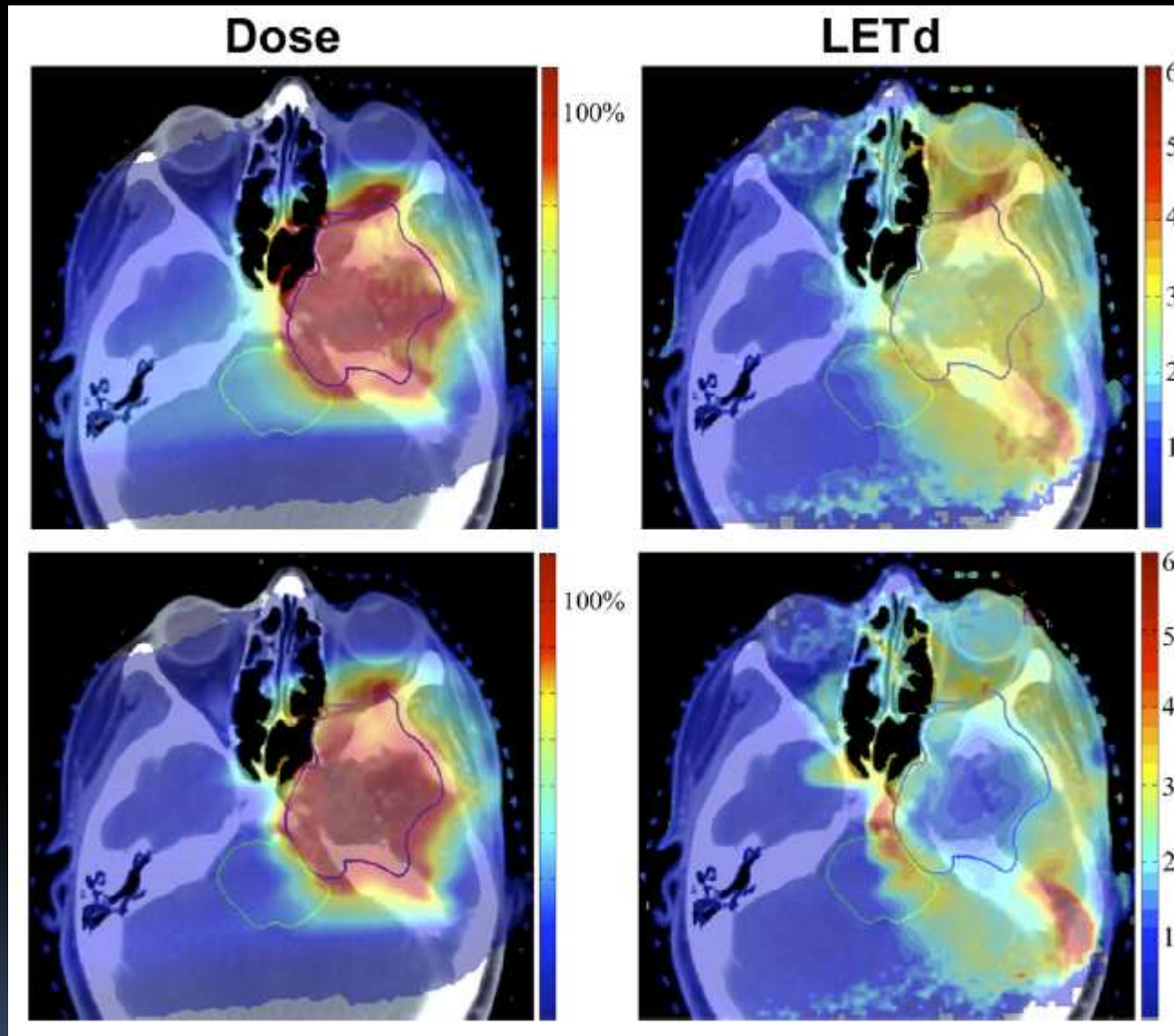
- RBE clínico: 1 Gy dosis p \equiv 1.1 Gy dosis γ
- RBE vs. profundidad no es constante
- RBE depende de
 - dosis
 - tasa de dosis
 - Calidad de la radiación (LET, energía lineal)
 - capacidad de reparación
 - efecto oxígeno
 - sistema biológico (cell type)
 - endpoint clínico (respuesta temprana, efectos tardíos)

RBEs



RBEs

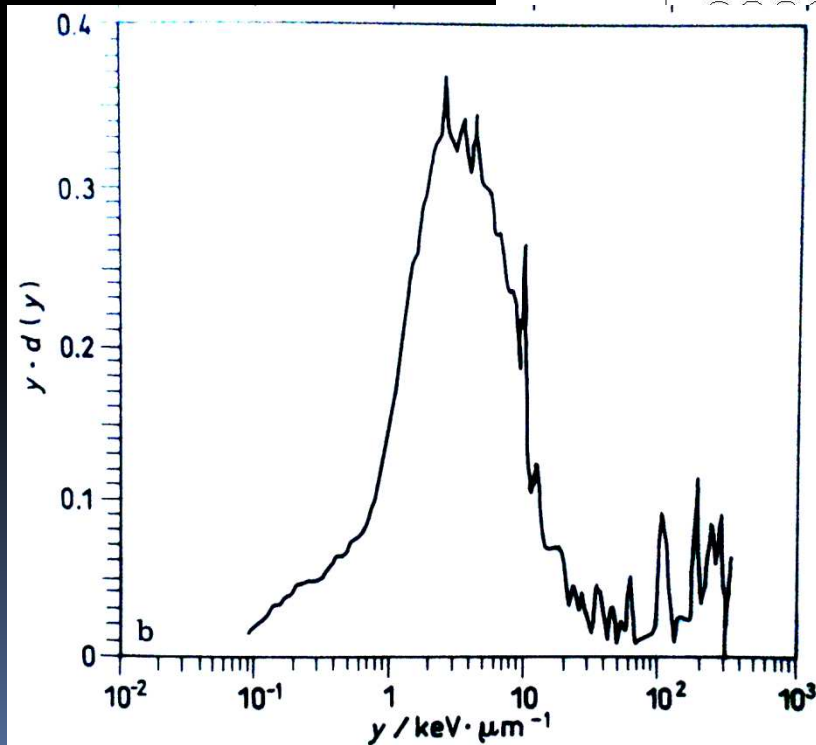
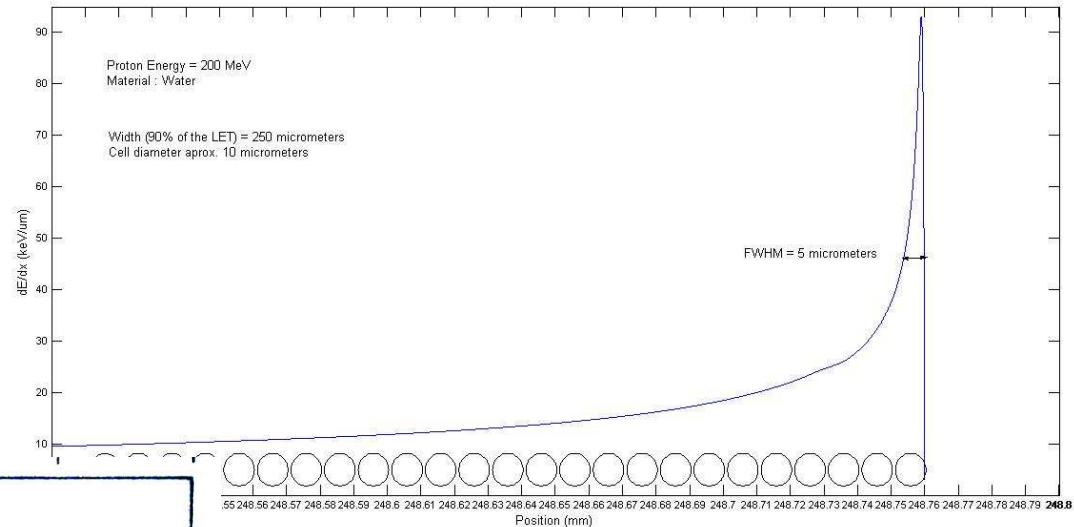




Biological Considerations When Comparing Proton Therapy With Photon Therapy

Harald Paganetti, PhD,* and Peter van Luijk, PhD†

Microdosimetría en haces de protones



Espectro microdosimétrico de un haz de protones de 160 MeV. Contribuciones a la dosis debidas a rayos delta (0.1 keV/um a 1 keV/um), protones primarios (1 keV/um a 80 keV/um) y partículas resultantes de reacciones no elásticas con núcleos del tejido (desde 100 keV/um hasta 300 keV/um).

Rossi and Zaider, Microdosimetry and its Applications (1996)

Radiación “errante”

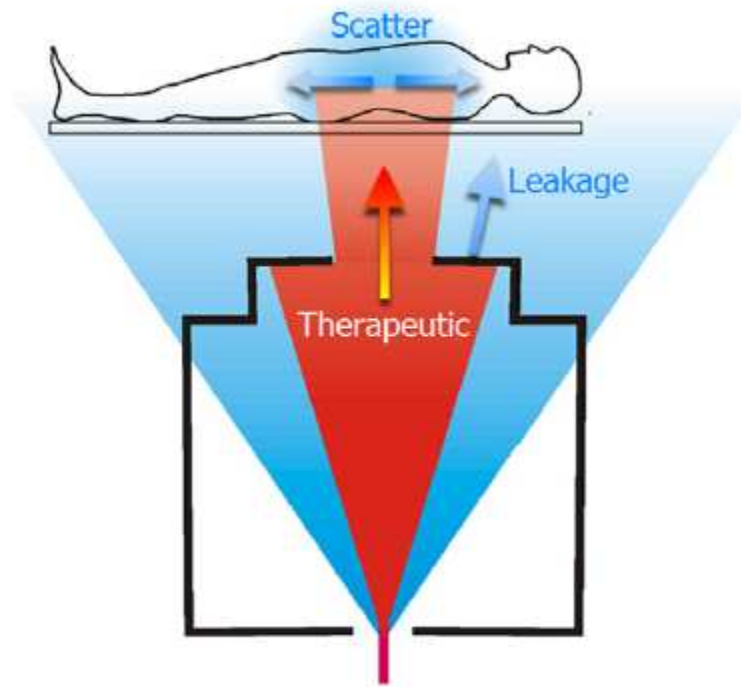
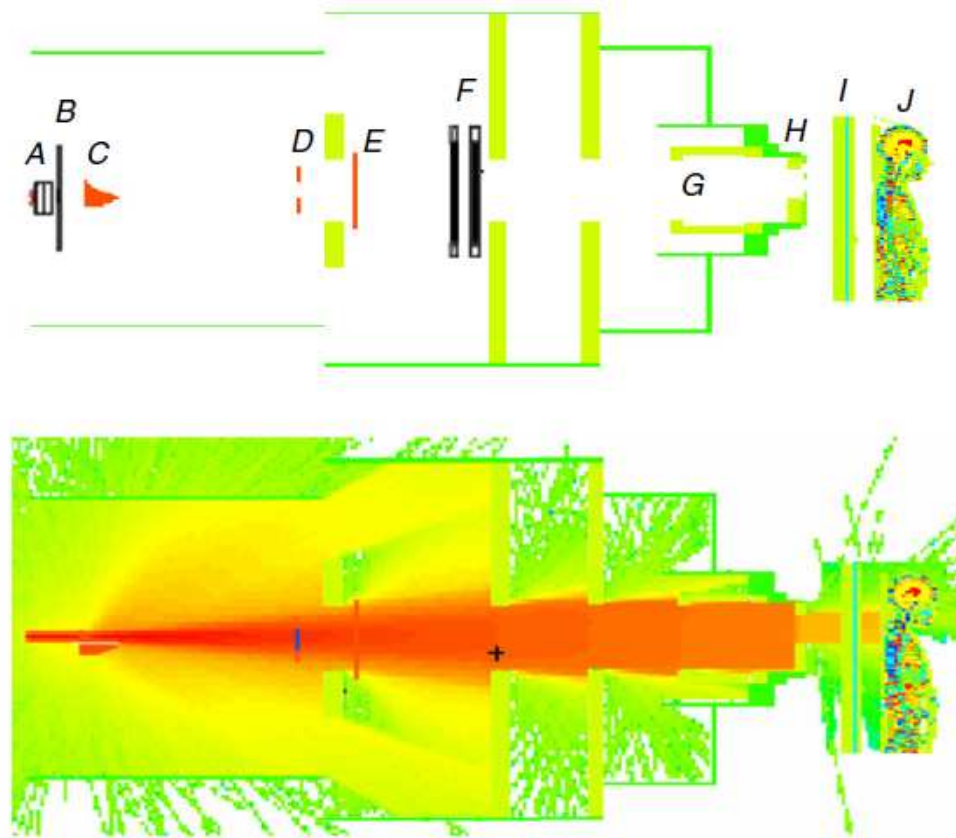
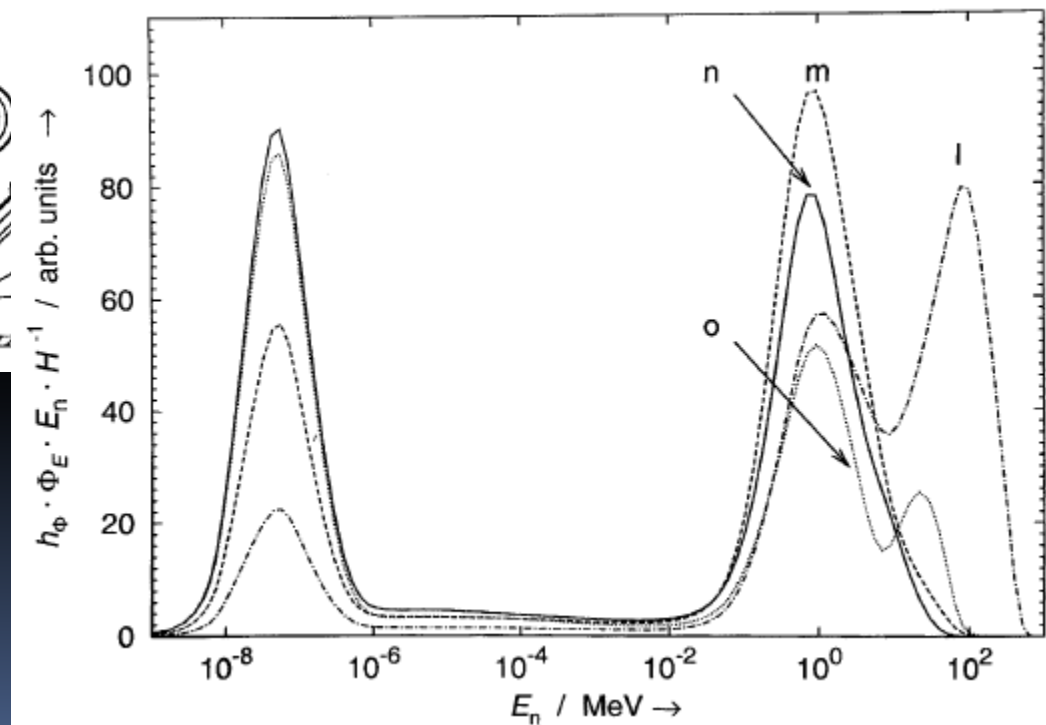
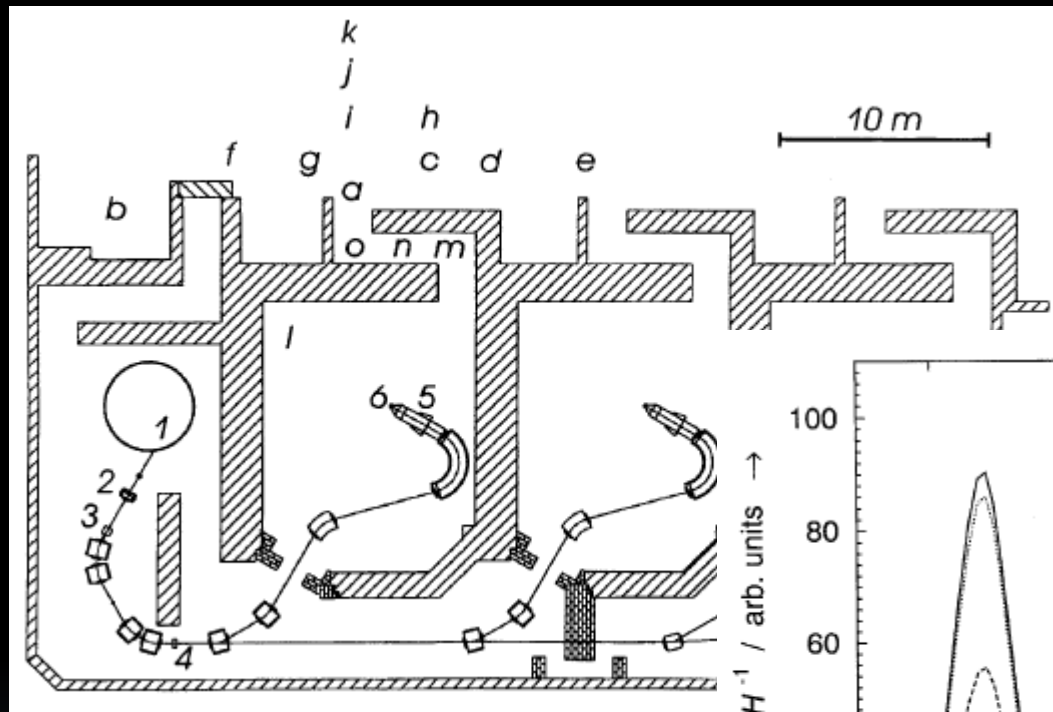


Figure 19. (Upper) Geometric model of proton therapy unit and the voxelized phar oriented for the superior spinal proton field. The beam delivery system include vacuum window (A), a beam profile monitor (B), a range modulator wheel (C), a scatterer (D), a range shifter assembly (E), backup and primary monitors (F), the source (G), the range compensator (H), the treatment couch (I), and the patient (J) (reproduced with permission from Zhang *et al* 2013a). (Lower) Simulated proton transport through the proton therapy unit and the patient.

Cálculo de equivalentes de dosis por neutrones por Monte Carlo

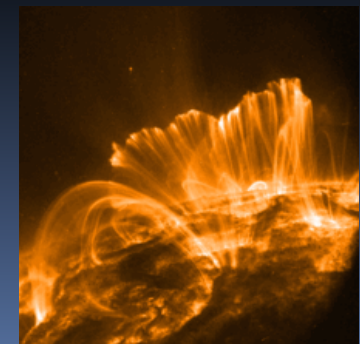
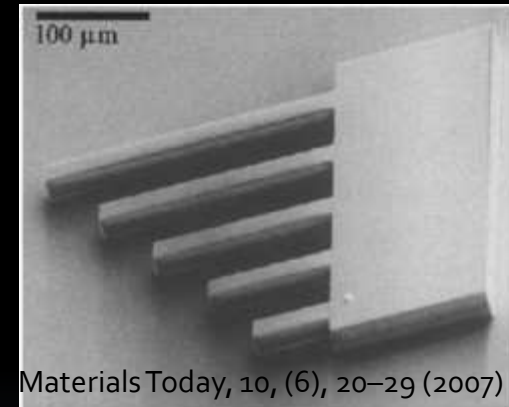


Temas generales de I&D

- **Dispositivos asociados a la tecnología de aceleradores.**
- **Instrumentación nuclear para protones.**
 - Detectors for proton imaging, ionization chambers, proportional counters, Compton cameras, solid state detectors, CCD cameras, scintillating plates, Gafchromic films, alanine detectors, TLDs.
- **Imagenología de protones**
 - proton tomography, determination of physical parameters for macroscopic dosimetry (relative proton stopping powers, tissue elemental compositions) from proton-induced PET and SPECT.
- **Dosimetría Computacional y Planificación de Tratamientos.**
 - Voxelized models.
 - Application of nuclear data for dose calculations.
 - Intercomparisons with different treatment planning systems, Monte Carlo calculations and deterministic transport techniques.

Temas generales de I&D

- **Investigación en Física nuclear y ciencias de materiales**
 - nuclear reactions induced by energetic protons
 - radiation damage studies by high energy particles, hydrogen damage .
- **Desarrollo de micro-haces de protones:**
 - quantitative PIXE analysis, micromachining.
 - delivery of defined numbers of protons on single cells to avoid Poisson statistics.
- **Física Espacial y Solar:**
 - Coronal Mass Ejections and proton emissions
 - Satellite damage by solar protons
 - Production of atmospheric neutrons



Temas generales de I&D

- **Radiobiología y Biofísica de las Radiaciones**
 - live-cell studies of radiation-induced DNA damage, study of radiation-induced non-targeted effects.
 - Cell survival, repair, dose-rate and fractionation treatment schemes. Radiosensitizers and radioprotectors.
 - Assessment of Tumor Control Probability and Normal Tissue Complication Probability parameters.
- **Microdosimetría y Nanodosimetría**
 - Tissue-Equivalent Proportional Counters (TEPC)
 - Track structure (wall-less ion counter)
 - W-values for proton in water
 - Mechanistic models of radiation action in living tissues and cells.
- **Ensayos pre-clínicos con animales**
 - In-vivo animal models, tumor control and normal tissue toxicity,
 - new targets for PBT, combination with other advanced therapies. BNCT + PBT.



In the space currently filled with scaffolding (top), the Proton Therapy Center's massive gantries will aim

CENTER TO PLAY LEADING ROLE IN RESEARCH

Research will play an integral role in the new facility. One of the gantries will be dedicated exclusively to research and development – making it the only fully dedicated proton research gantry in the world, says **John Perentesis, MD**, Executive Co-Director of the **Cancer and Blood Diseases Institute**. This gives a cross-campus team of scientists from Cincinnati Children's and five colleges of the University of Cincinnati unprecedented access to an emerging technology.

Experts in cancer biology, genomics, particle physics, and engineering have already begun studying ways to refine and expand the use of proton therapy. Projects include studying the biological effects of proton radiation across differing types of tumors and tissues, cancer stem cell research, and developing new therapies. Other projects will evaluate and sharpen imaging technology and computer tracking systems. Longer-term clinical studies will track outcomes and identify ideal dose levels for various cancers and age ranges, Perentesis says.

The Proton Therapy Center also will anchor a new inpatient and outpatient oncology treatment center at the Liberty Campus, developed in conjunction with the UC College of Design, Art, Architecture and Planning and its Live Well Collaborative.

"Our objective is to use 21st century technology to transform and extend the compassionate and supportive environment that families and patients already experience when receiving cancer care here, from initial diagnosis all the way through to survivorship," Perentesis says.

Resumen del estado del conocimiento (Goitein, AAPM, 2009)



SUMMARY

INTERACTIONS OF PROTONS

proton penetration



Coulomb scattering



nuclear interactions



dosimetry



inhomogeneities



TREATMENT PLANNING

use of imaging



image registration



changes with time



broad- & pencil-beam algorithms



Monte Carlo dosimetry calculation



uncertainties: calcn. and allowance for



IMPT: understanding



IMPT: solutions



optimization: search techniques



optimization: dose-based



optimization: biology-based



robust optimization



TECHNOLOGY

current sources of protons



future sources of protons



scattered beam technology



scanned beam technology & IMPT



scattered beam: depth characteristics



scanned beam: depth characteristics



scattered beam: lateral penumbra



scanned beam: lateral penumbra



immobilization & motion management



patient support systems



throughput, integration & workflow



RADIOBIOLOGY

RBE value(s)



tissue response: data



tissue response: models



treatment strategies based on biology



CLINICAL TRIALS

randomized protons vs. X-rays



case-controlled protons vs. X-rays



BNCT: 14 de Octubre de 2015



¡GRACIAS!