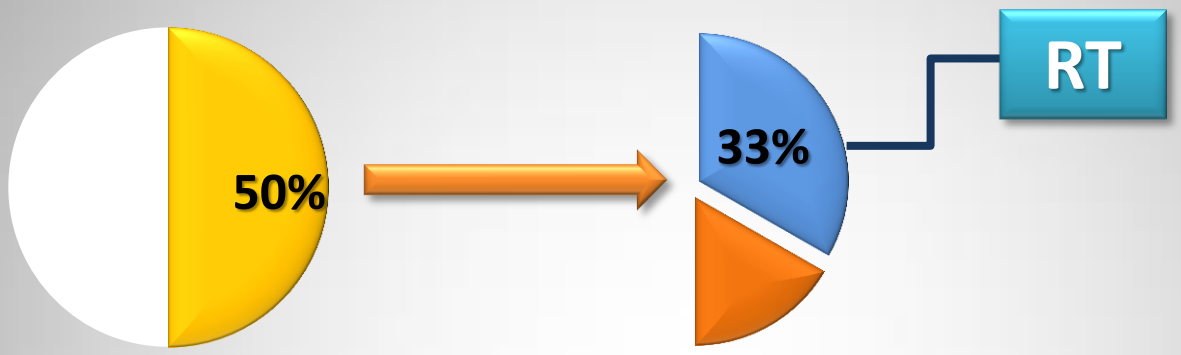
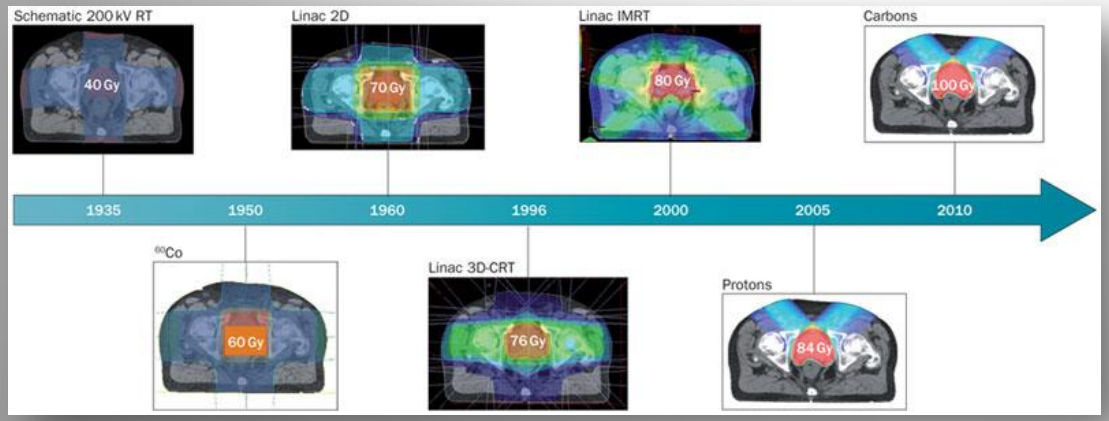
APLICACIONES CLÍNICAS DE LA PROTONTERAPIA

María Albert Antequera
CHP Castellón

Epidemiología y evolución de la RT

INCIDENCIA DEL CÁNCER[1]





Thariat, J. *et al.* (2012) Past, present, and future of radiotherapy for the benefit of patients. *Nat. Rev. Clin. Oncol.* doi:10.1038/nrclinonc.2012.203

↑ SUPERVIVIENTES

↑ Riesgo toxicidad radioinducida:

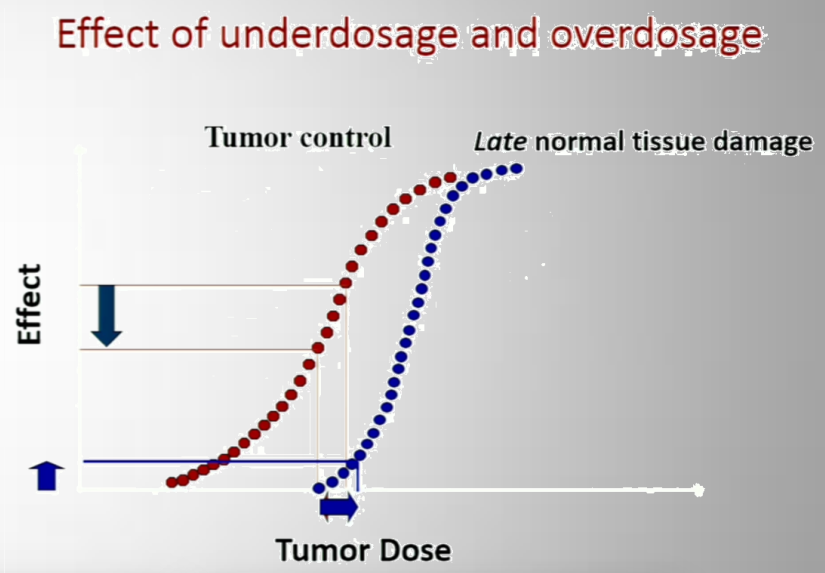
- 2as neoplasias
- Complicaciones CV, SNC, …

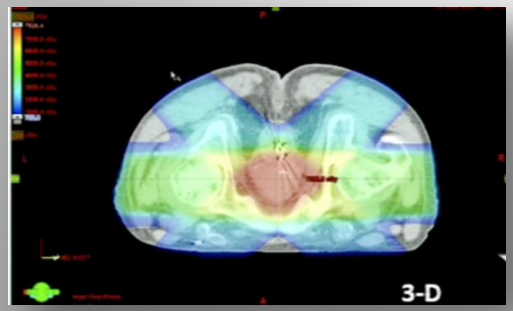
1. Newhauser WD, de Gonzalez AB, Schulte R, Lee C. A Review of Radiotherapy-Induced Late Effects Research after Advanced Technology Treatments. Front Oncol [Internet]. 2016 Feb 10 [cited 2016 Mar 7];6. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4748041/

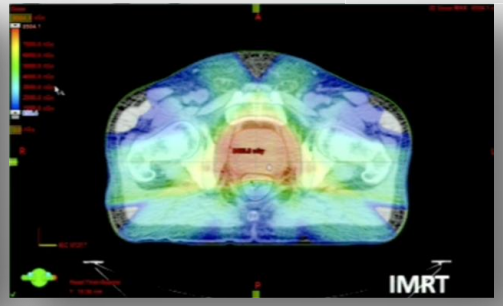
Importancia de evaluar el riesgo de efectos secundarios asociados a RT y el impacto de las nuevas tecnologías

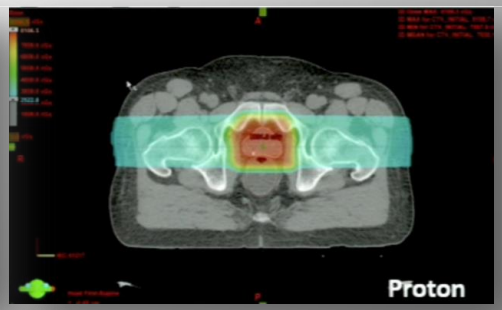
Avances en tecnología :

1. Mejorar el control local
2. ↓ dosis en tejidos sanos



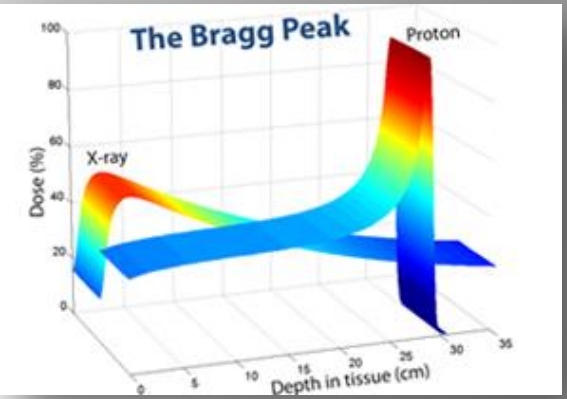






¿Por qué la protonterapia?

- **<u>Reducción de la dosis integral</u>:** ausencia de dosis de salida

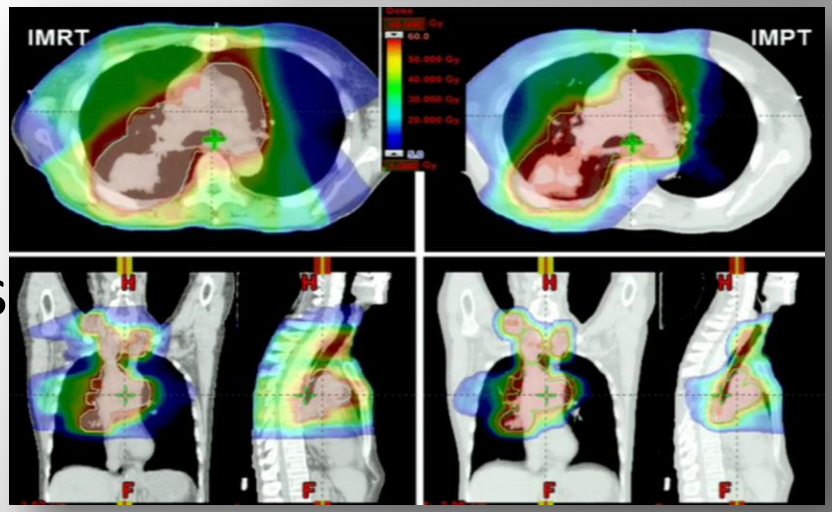


– ≠ IMRT

– Imp en tumores grandes / grande respecto al órgano / cercanos a OARs

– No riesgo ↑ de 2as neoplasias

– **Escalada de dosis ↑CL**



Buen control local con menor toxidad

Clinical equipoise

Randomized Clinical Trials

¿Son éticos?

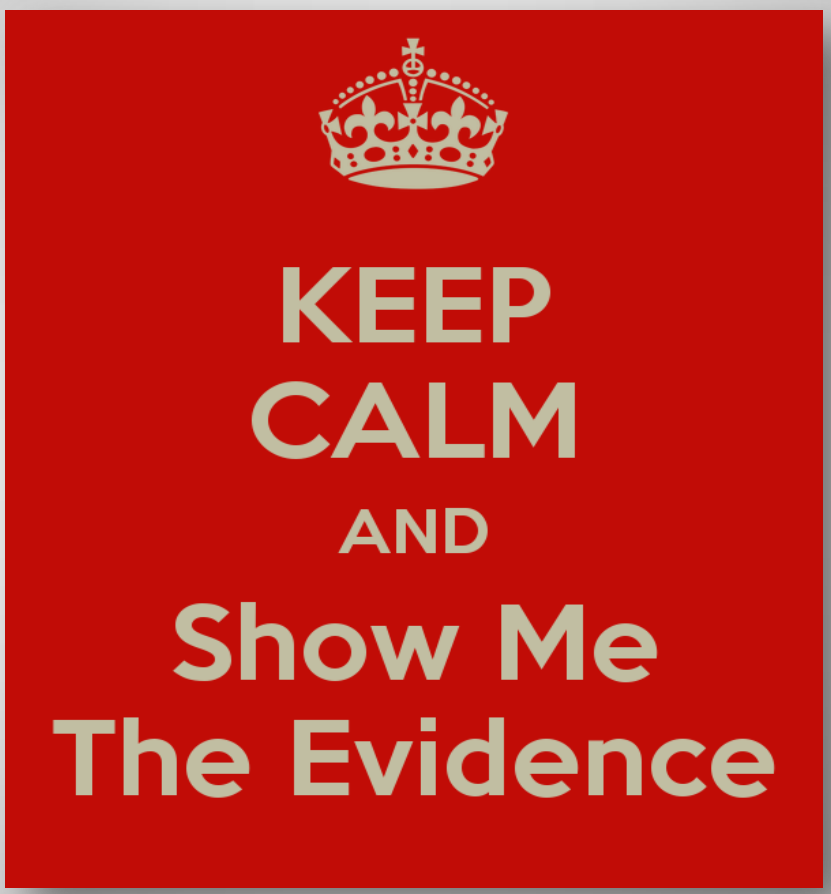
¿Inferioridad de tratamientos?

<u>Tratamiento potencialmente más efectivo</u>

Investigación médica

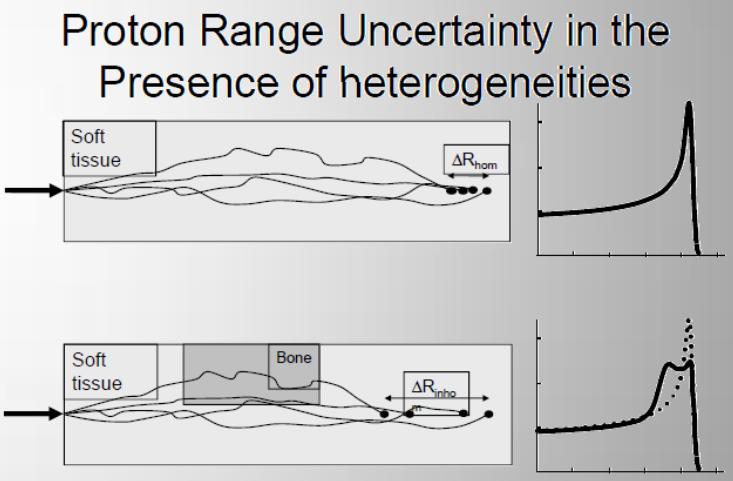
Práctica clínica

Cuidado del paciente


KEEP
CALM
AND
Show Me
The Evidence

Incertidumbres PT

- Penumbra lateral, se dispersa en profundidad
- Rango de dosis, incierto en profundidad
- Heterogeneidad de los tejidos
- Producción de neutrones
  → significado biológico

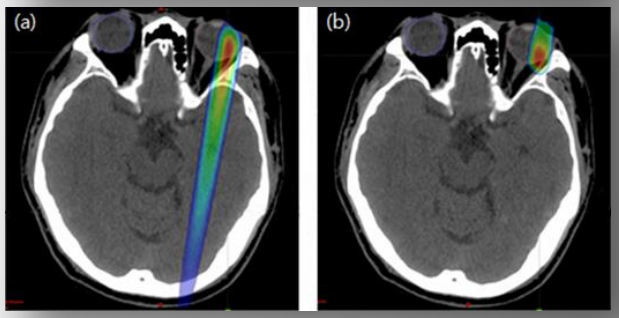


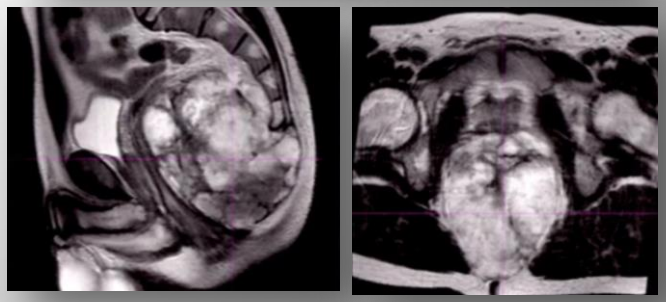
DEBATE ACTUAL

Aplicaciones clínicas[2]

- Tumores pediátricos

- Limitaciones por OARs cercanos al target:
  - Melanoma ocular
  - Neoplasias de base de cráneo
  - Cordomas
  - Condrosarcomas pélvicos y espinales





2. Doyen J, Falk AT, Floquet V, Hérault J, Hannoun-Lévi J-M. Proton beams in cancer treatments: Clinical outcomes and dosimetric comparisons with photon therapy. Cancer Treatment Reviews. 2016 Feb 1;43:104–12.

Extradurales Cordomas-Condrosarcomas

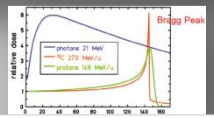
Long-Term Results of Phase II Study of High Dose Photon/Proton Radiotherapy in the Management of Spine Chordomas, Chondrosarcomas, and Other Sarcomas

Journal of Surgical Oncology 2014;110:115–122

THOMAS F. DELANEY, MD,[1]* NORBERT J. LIEBSCH, MD, PhD,[1] FRANK X. PEDLOW, MD,[2]

- Difícil RØ ➔Rt Adyuvante.
- Tumores Radioresistentes > 70Gy.
- 50Gy Límite de tolerancia de Médula espinal.
- Mal CL con cirugía radical+RT< 60 Gy (0-50%).

PROTONTERAPIA



HAY QUE DERIVAR A ESTOS PACIENTES A UNIDADES DE PROTONTERAPIA DE MANERA PRECOZ Y NO ESPERAR A LA RECIDIVA

Mediana Seg. 7,3 años:

- ✧ CL 5ª 81% 8ª 74% CL Primarios 94% y 85%. Recidivas: 11% primarios y 50% recurrentes.
- ✧ Toxicidad: Riesgo actuarial de toxicidad G3-4 en 8 a de 13%. No mielopatías. No hay efectos tóxicos neurológicos tardíos con 72,0 GyRBE vs 3 neuropatías sacras ≥ 76,6 GyRBE.

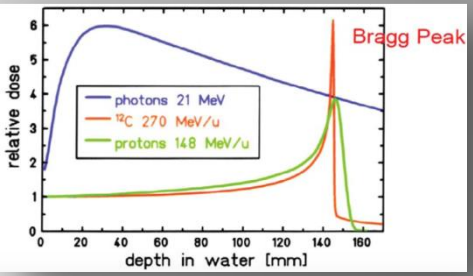
Conclusión: Buen control local con toxicidad aceptable.

MDAnderson: Destacan el beneficio de la PT adyuvante precoz vs Rescate. Spine 2015 *"in press"*

Extradurales

Cordomas-Condrosarcomas

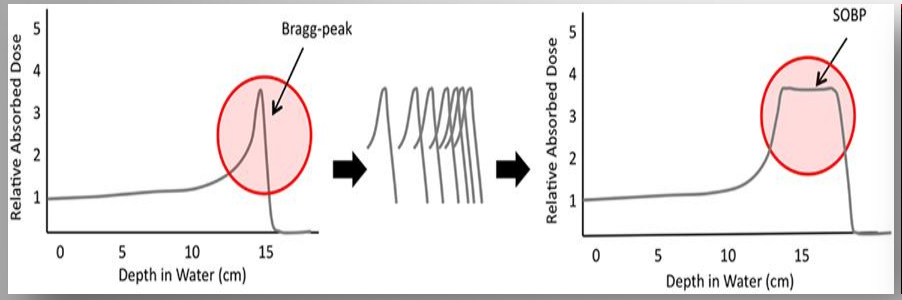
Otras estrategias…

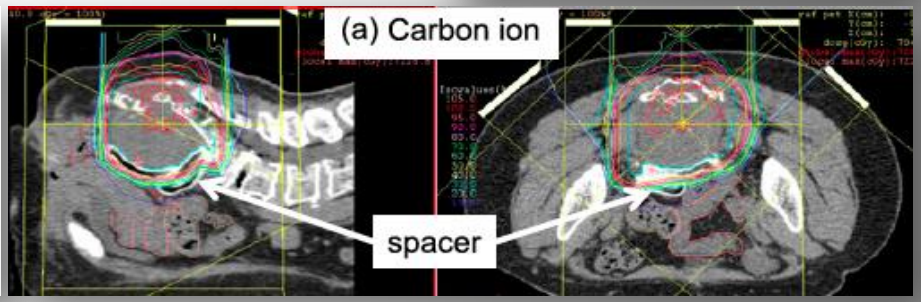


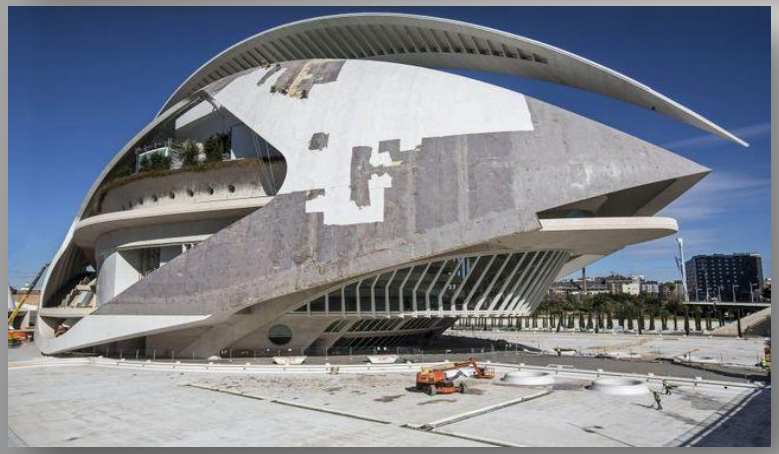
- **<u>Iones Carbono:</u>** CL 76-**94**% a 3-5 años

(Kamada 2002, Imai 2010, Mima 2014)

20 VECES MAS LETALES QUE LOS PROTONES





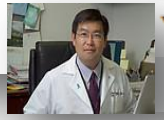


382,5 millones de euros

119 millones de euros

(50% U. Heidelberg y 50% Gobierno Alemán)

Preliminary Results of High-Dose Single-Fraction Radiotherapy for the Management of Chordomas of the Spine and Sacrum



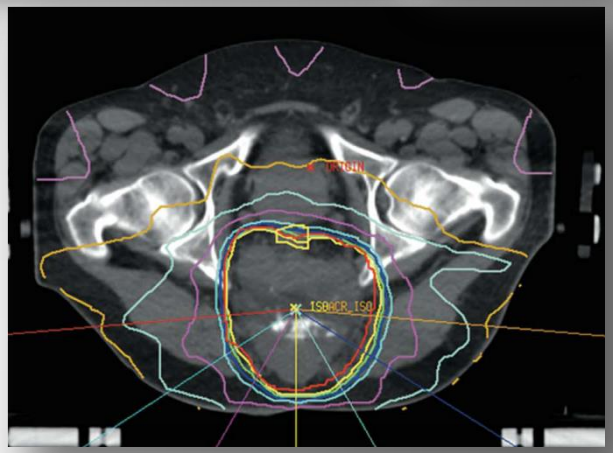
Yoshiya Yamada, MD†

Neurosurgery 73:673–680, 2013

SRS 24Gy/1Fx: 21p Primario y 3 Mts:

- **13 Neoadyuvante**
- Previsto:

SRS➔Cirugía➔Estudio AP



RESULTADOS: Mediana seguimiento 24m:

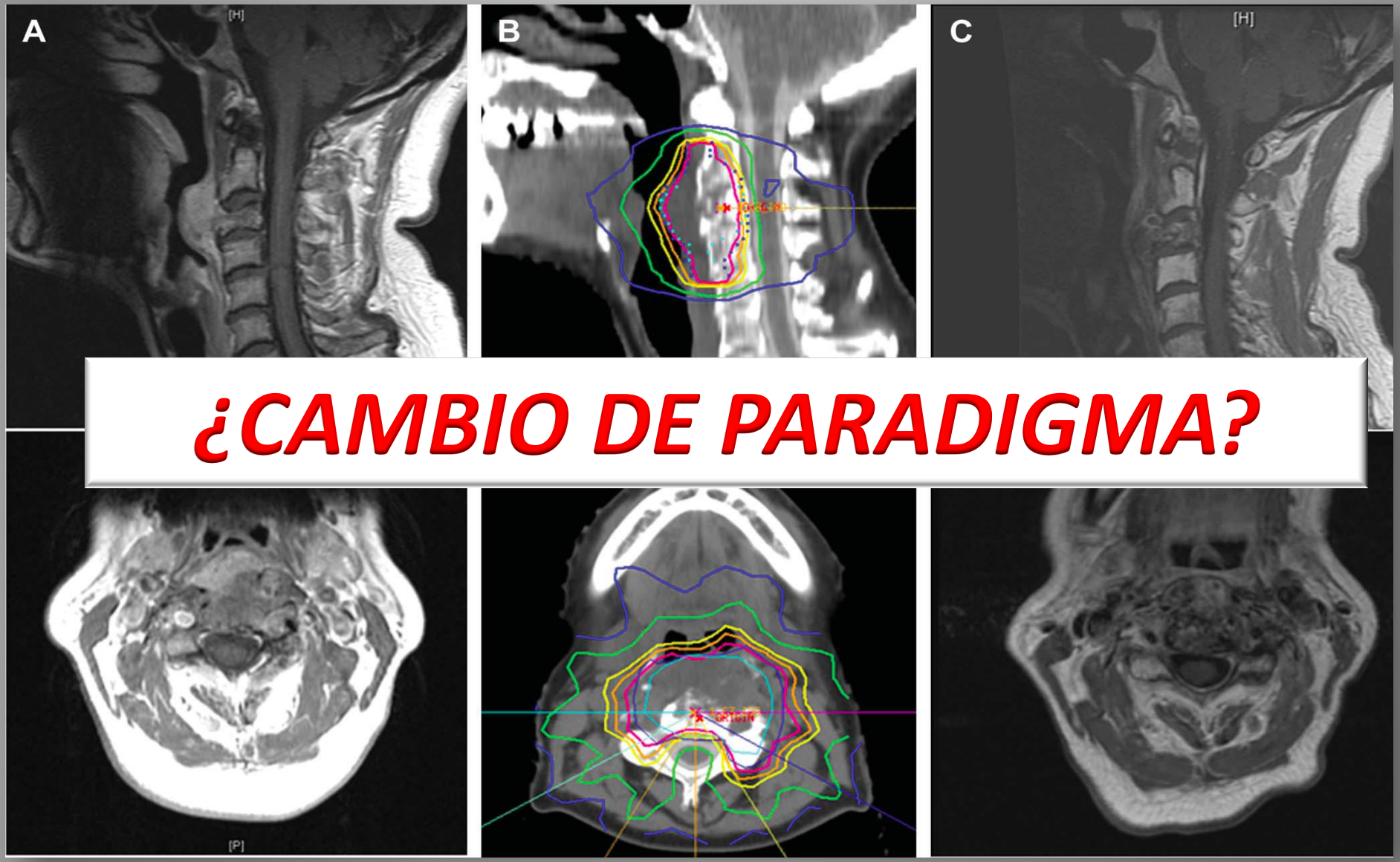
- 23 p. (95%) RMN: enfermedad estable o **respuesta!!!**
- 1 P. RMN: Progresión Radiologica a los 11 meses.
- Sólo 6/13 de los pacientes neoadyuvantes fueron operados➔ **Rechazo del paciente** dada la Respuesta Clínica y Radiológica!!!
- Complicaciones: 1 neuropatía ciática 1 parálisis de cuerda vocal.

CONCLUSION: HDSF-SRS da un buen CL con baja morbilidad.

TABLE 4. Pathological Outcomes[a]

Patient	Level	Time From SRS, mo	Extent of Necrosis, %	Follow-up, mo
1	L2	2	Conventional chordoma	60
2	L3	4	>90	46
3	Sacrum	4	>90	32
4	Sacrum	5	50	19
5	Sacrum	5	5	13
6	Sacrum	8	>90	40

SE REQUIERE MAYOR SEGUIMIENTO



¿CAMBIO DE PARADIGMA?

Comentarios de RadOnc & Protonterapia & Cirujanos:

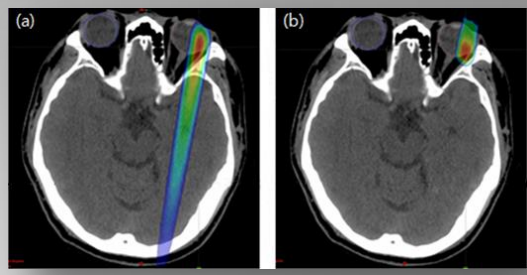
Joshua Lawson San Diego, California

Thomas F. DeLaney Boston, Massachusetts

Stefano Boriani Bologna, Italy

Opción de futuro que se podrían plantear con Protones

Melanoma uveal



- >95% de los tumores oculares
- Tratamiento → Quirúrgico: - enucleación
  → Conservador con RT: ↓mortalidad
  - Placa BQT
  - **Protonterapia**

- Prevenir mtx
- Conservar el ojo
- Mantener fx

Overview

Clinical Outcomes of Proton Radiotherapy for Uveal Melanoma

V. Verma*, M.P. Mehta†

*Department of Radiation Oncology, University of Nebraska Medical Center, Omaha, NE, USA
†Department of Radiation Oncology, University of Maryland Medical Center, Baltimore, MD, USA

Received 15 September 2015; received in revised form 20 December 2015; accepted 5 January 2016

5ª: CL >90%...10-15ª; SG 70-85%: SLmtx y SCE 75-90%

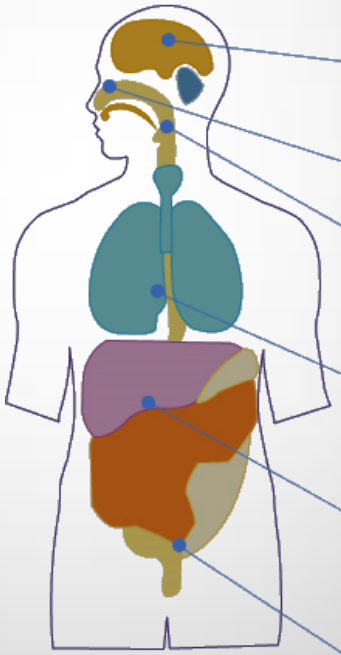
↓60-70% Agudeza visual post-PT (>20/200)

→PT: excelente tto. para el melanoma uveal

Posibles aplicaciones de los PT

↓Dosis en tejidos sanos
↑Dosis en el tumor

- A estudio: próstata, mama…
- Otras indicaciones a considerar: Reirradiación



Pediatric Tumors
- glioma, medulloblastoma and other primitive neuroectodermal tumors, germinoma, retinoblatoma, soft tissue sarcoma, skull base chordoma and chondrosarcoma
- recurrent cancer and other : selective

Central nervous System (Brain & Spinal Cord)
- glioma
- pituitary adenoma
- chordoma
- vestibular schwannoma
- meningioma
- optic glioma

Orbit(Eye)
- choroidal melanoma
- retinoblastoma
- lacrimal gland tumor

Head & Neck
- nasopharyngeal cancer
- oropharyngeal cancer
- hypopharyngeal cancer
- oral cavity cancer
- unresectable or recurrent cancer

Thorax and Breast
- lung cancer : selective
- breast cancer : selective
- esophageal cancer : selective
- unresectable or resurrent cancer

Abdomen
- liver cancer : selective
- pancreatic cancer : selective
- rectal cancer
- unresectable or recurrent cancer

Pelvis and Extremities
- prostate cancer
- cervical cancer
- chordoma
- soft tissue sarcoma
- unresectable or recurrent cancer

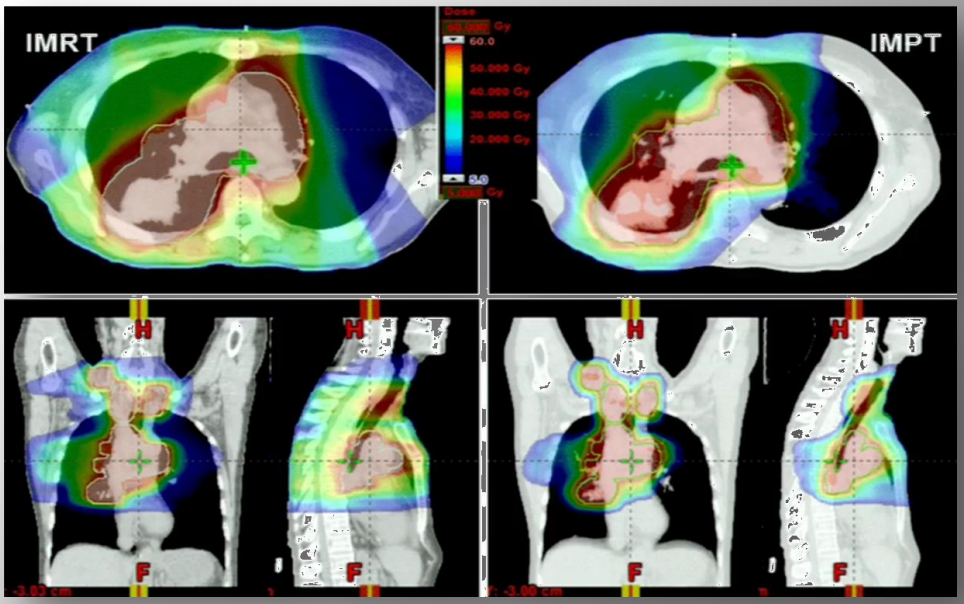
Ca Pulmón no microcítico

↑ Dosis en tumor → **↑ CL y Supervivencia[3]**

- RTOG 0617: escalada de dosis de 60 a 74 Gy con RT conformada con fotones ± Cetuximab.

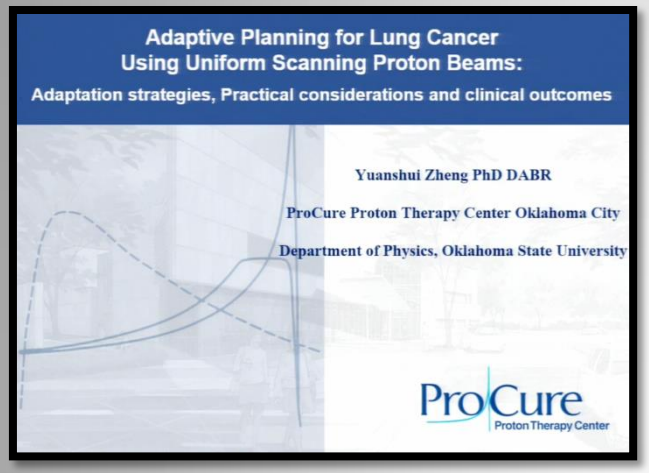
Resultados:

- ↓ tasa supervivencia con 74 Gy
- **Dmedia corazón:** factor pco independiente de SG



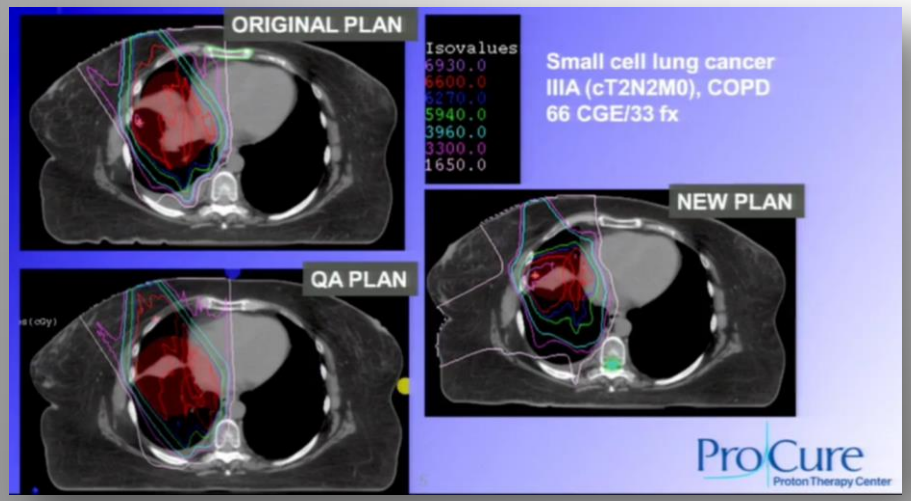
3. Partridge M, Ramos M, Sardaro A, Brada M. Dose escalation for non-small cell lung cancer: analysis and modelling of published literature. Radiother Oncol. 2011 Apr;99(1):6–11.

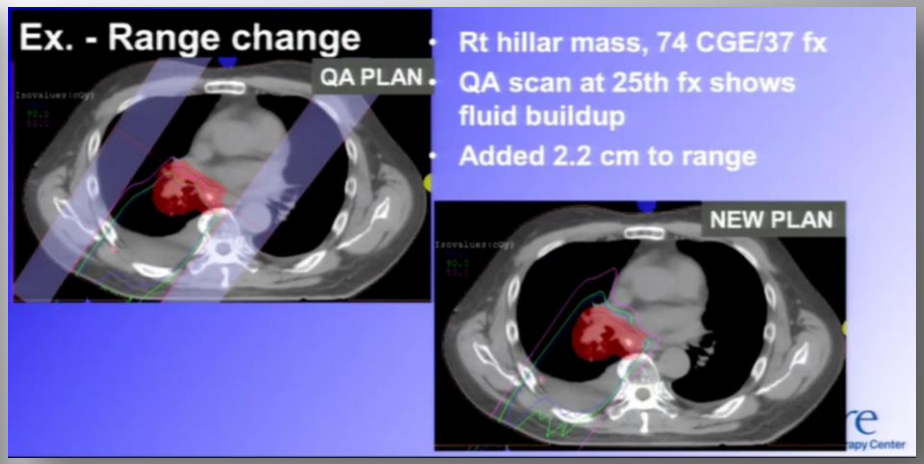
RT adaptativa con protones en Ca Pulmón



PT muy sensibles a cambios de densidad de tejidos

Necesaria la adaptación
para mantener una distribución de dosis óptima



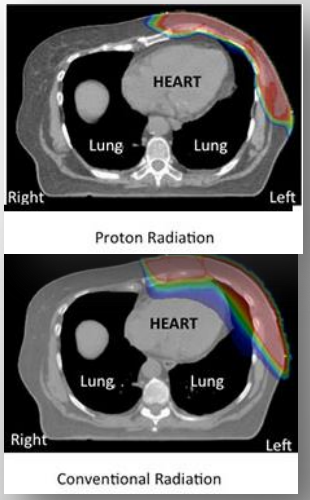


Ca Mama

- Ca mama izquierda: ↑ toxicidad cardiaca
- Riesgo de 2as neoplasias:
  - Áreas ganglionares afectas
  - < 60 años

- **PCORI**: Estudio clínico randomizado para E. II y III de cáncer de mama con afectación áreas ganglionares (axila/FSC)

n= 1.716 pacientes → Protonterapia / Tto. fotones

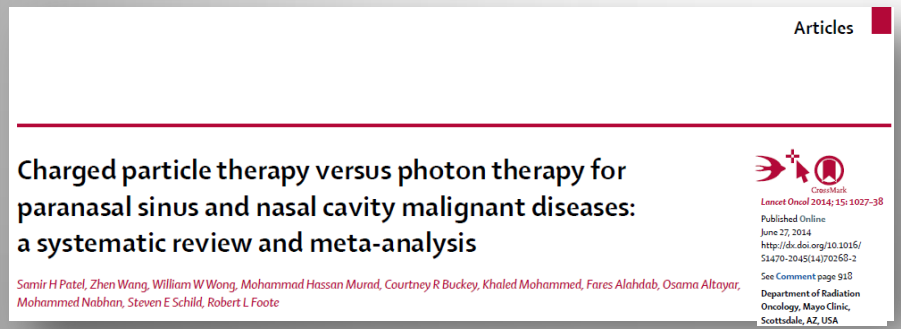


Durante el seguimiento evaluan:
Control tumoral, tox. cardiaca, CV

PT → Menor dosis en corazón, pulmones y grandes vasos, con control tumoral similar a técnicas avanzadas de fotones.

Ca Cabeza y Cuello

- Superioridad dosimétrica PT : ↓dosis en gländ. salivares, médula, tronco, estructuras de base de cráneo, esófago, laringe.
- **Carcinoma de nasofaringe, seno paranasal y cavidad nasal**



Articles

Charged particle therapy versus photon therapy for paranasal sinus and nasal cavity malignant diseases: a systematic review and meta-analysis

Samir H Patel, Zhen Wang, William W Wong, Mohammad Hassan Murad, Courtney R Buckey, Khaled Mohammed, Fares Alahdab, Osama Altayar, Mohammed Nabhan, Steven E Schild, Robert L Foote

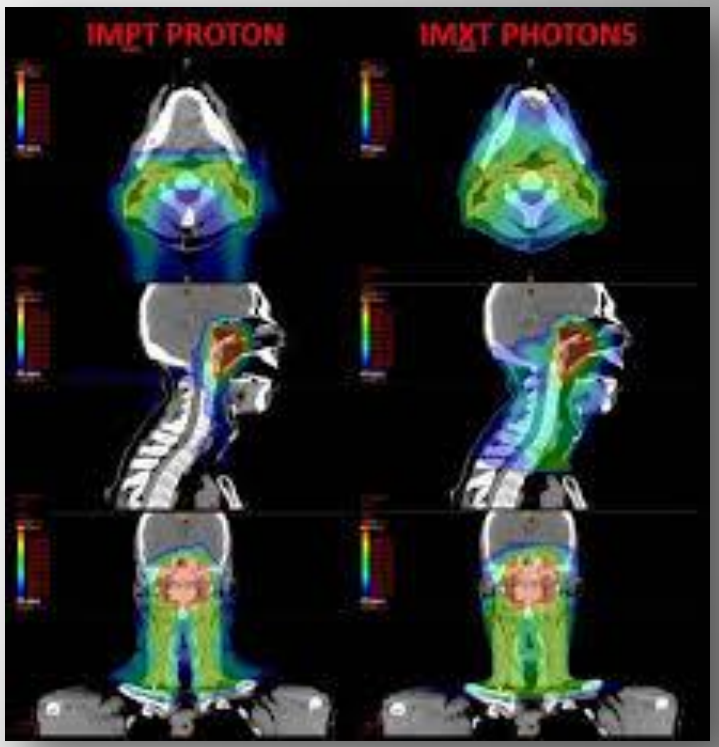
CrossMark

Lancet Oncol 2014; 15: 1027–38

Published Online June 27, 2014 http://dx.doi.org/10.1016/S1470-2045(14)70268-2

See Comment page 918

Department of Radiation Oncology, Mayo Clinic, Scottsdale, AZ, USA



↑Supervivencia libre de progresión local

- mejor cobertura CTV
- mejor comportamiento RB

Ca Próstata

Proton Versus Intensity-Modulated Radiotherapy for Prostate Cancer: Patterns of Care and Early Toxicity

James B. Yu, Pamela R. Soulos, Jeph Herrin, Laura D. Cramer, Arnold L. Potosky, Kenneth B. Roberts, Cary P. Gross

Manuscript received May 15, 2012; revised September 24, 2012; accepted September 25, 2012.

Correspondence to: James B.Yu, MD, Yale University School of Medicine, Department of Therapeutic Radiology, 40 Park St, LL511-SMILOW, New Haven,

Although PRT is substantially more costly than IMRT, there was no difference in toxicity in a comprehensive cohort of Medicare beneficiaries with prostate cancer at 12 months post-treatment.
J Natl Cancer Inst 2013;105:25–32

PT: ↓Dmedia a recto y vejiga.

ClinicalTrials.gov

18 Estudios en fase de reclutamiento

→ Caracterizar la ventaja de los protones vs fotones

→ BQT vs PT…

International Journal of Radiation Oncology biology • physics
www.redjournal.org

Physics Contribution

Dosimetric Considerations to Determine the Optimal Technique for Localized Prostate Cancer Among External Photon, Proton, or Carbon-Ion Therapy and High-Dose-Rate or Low-Dose-Rate Brachytherapy

Dietmar Georg, PhD,*,† Johannes Hopfgartner, MSc,*,† Joanna Gòra, MSc,* Peter Kuess, MSc,*,† Gabriele Kragl, PhD,* Daniel Berger, MSc,*,† Neamat Hegazy, MD,* Gregor Goldner, MD, PhD,*,† and Petra Georg, MD, PhD*,†

*Department of Radiation Oncology and †Christian Doppler Laboratory for Medical Radiation Research for Radiation Oncology, Medical University of Vienna/Allgemeines Krankenhaus der Stadt Wien, Vienna, Austria

Received Aug 8, 2013, and in revised form Nov 19, 2013. Accepted for publication Nov 22, 2013.

Brachytherapy techniques were clearly superior in terms of BW, RW, and normal tissue sparing, with lowest values for HDR-BT. © 2014 Elsevier Inc.

RE-IRRADIACIÓN

- Con fotones→ menor dosis, volumen más pequeño. Peor CL.
- Con protones→ altas dosis, respetando OARs. Mejor CL.

  - Cordomas (16p, 2ª CL 85%, SG 80%)[6]
  - Ca pulmón (31 p, 1ª SG 47%, SLP 28%, 3p tox G3)[7]
  - T. cerebrales (26p, SGmedia 18.3 meses, 2 RNecrosis)[8]

→Mejor CL , SG y menor toxicidad.

6. McDonald MW, Linton OR, Shah MV. Proton therapy for reirradiation of progressive or recurrent chordoma. Int J Radiat Oncol Biol Phys. 2013 Dec 1;87(5):1107–14.
7. McAvoy SA, Ciura KT, Rineer JM, Allen PK, Liao Z, Chang JY, et al. Feasibility of proton beam therapy for reirradiation of locoregionally recurrent non-small cell lung cancer. Radiother Oncol. 2013 Oct;109(1):38–44.
8. Mizumoto M, Okumura T, Ishikawa E, Yamamoto T, Takano S, Matsumura A, et al. Reirradiation for recurrent malignant brain tumor with radiotherapy or proton beam therapy. Technical considerations based on experience at a single institution. Strahlenther Onkol. 2013 Aug;189(8):656–63.

Coste-efectividad PT

Review Article

A Systematic Review of the Cost and Cost-Effectiveness Studies of Proton Radiotherapy

Vivek Verma MD[1]; Mark V. Mishra MD[2]; and Minesh P. Mehta MBChB[2]

- Próstata ✗
- T. cerebrales pediátricos ✓
- Mama: izquierda, ↑riesgo tox. cardiaca ✓
- Pulmón NSLCC: localmente avanzado ✓
- C & C : ↑riesgo de mucositis aguda ✓
- T. oculares: similar PT, BQT, enucleación ≈

Selección de pacientes

Mensaje final…

- **Beneficios claros del tratamiento con protones** en determinadas indicaciones.
  - Tumores pediátricos
  - Cordomas y condrosarcomas
  - Tumores oculares
  - Otros a estudio…

- RT adaptativa: papel importante en el tratamiento con PT.
  Las variaciones inter/intra-fracción tienen más consecuencias.

Necesidad de centros de tratamiento con protones en un país que se considere desarrollado

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