

7th Seminar of HITRIplus - Health-value of particle therapy in 2022: clinical evidences and innovative opportunities, Clinica Universidad de Navarra

 jueves 5 may. 2022 17:00 → 18:00 Europe/Zurich

 ZOOM

 Manjit Dosanjh

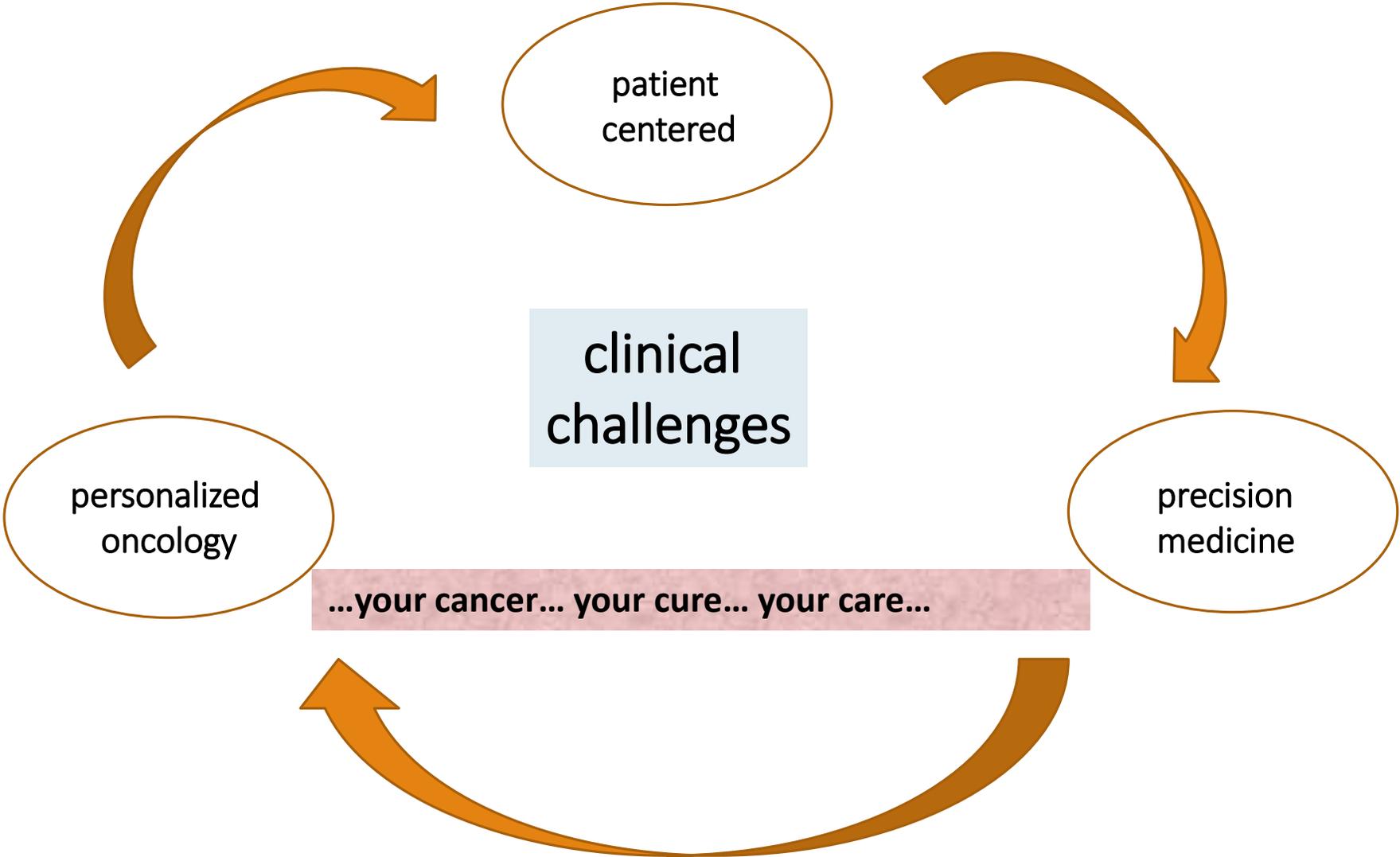
Descripción Global general scientific seminars linked to the HITRIplus project activities organised in the context of WP2 Networking, Communication, Dissemination.



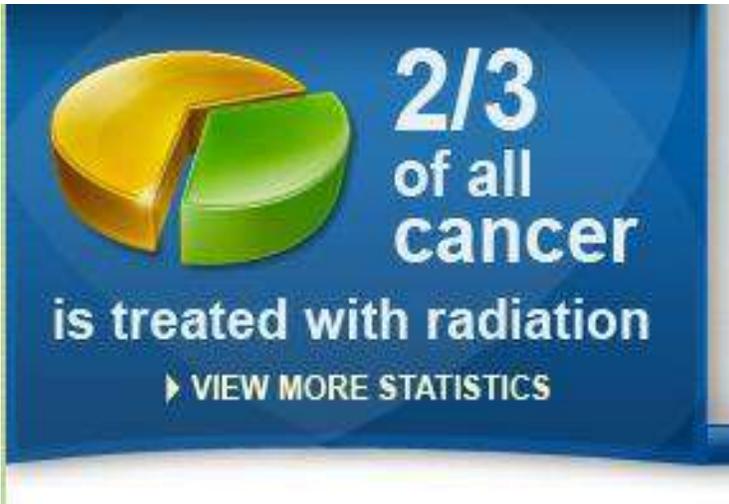
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cancer medicine for clinicians...2022 and more...



60-70% indicated; ½ for cure; 80% organ preservation; >90% + systemic therapy



THE
AGE OF
RADIOTHERAPY
Radiotherapy can cure cancer
Radiotherapy is cost effective
Radiotherapy is cutting edge

A graphic with a black background and a yellow-to-orange gradient sunburst pattern on the left. The text 'THE AGE OF RADIOTHERAPY' is in large white letters. Below it, three lines of text in a smaller white font state: 'Radiotherapy can cure cancer', 'Radiotherapy is cost effective', and 'Radiotherapy is cutting edge'. The bottom of the graphic has a yellow background.

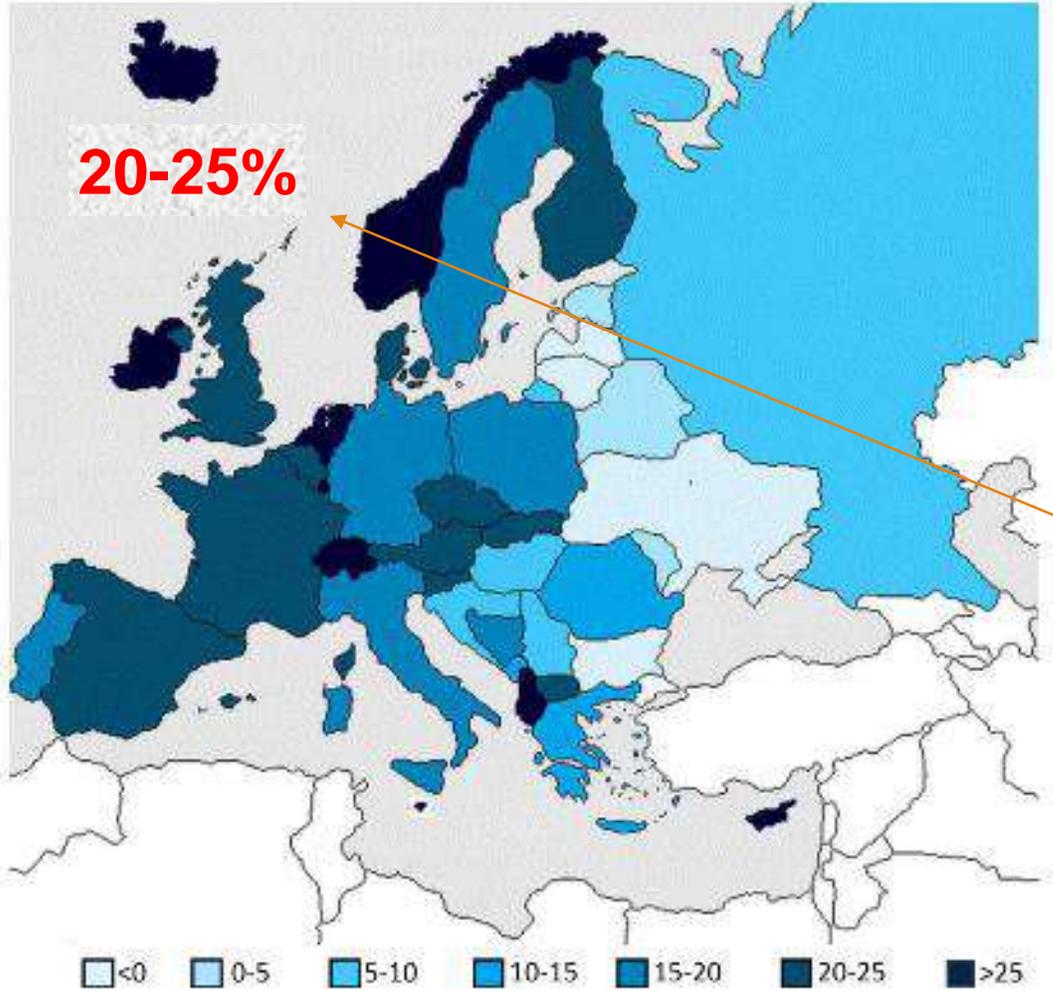


Fig. 1. Increase in new cancer patients that would require radiotherapy by 2025 by country (%).

ESTRO-HERO Analysis

How many new cancer patients in Europe will require radiotherapy by 2025? An ESTRO-HERO analysis



Josep M. Borras ^{a,*}, Yolande Lievens ^b, Michael Barton ^c, Julieta Corral ^d, Jacques Ferlay ^e, Freddie Bray ^e, Cai Grau ^f

^aUniversity of Barcelona, IDIBELL, Barcelona, Spain; ^bRadiation Oncology Department, Ghent University Hospital, Ghent, Belgium; ^cCCORE Ingham Institute for Applied Medical Research, University of South New Wales, Australia; ^dCatalan Cancer Strategy, Department of Health, Generalitat de Catalunya, Barcelona, Spain; ^eSection of Cancer Surveillance, International Agency for Research on Cancer (IARC), Lyon, France; and ^fDepartment of Oncology, Aarhus University Hospital, Aarhus, Denmark

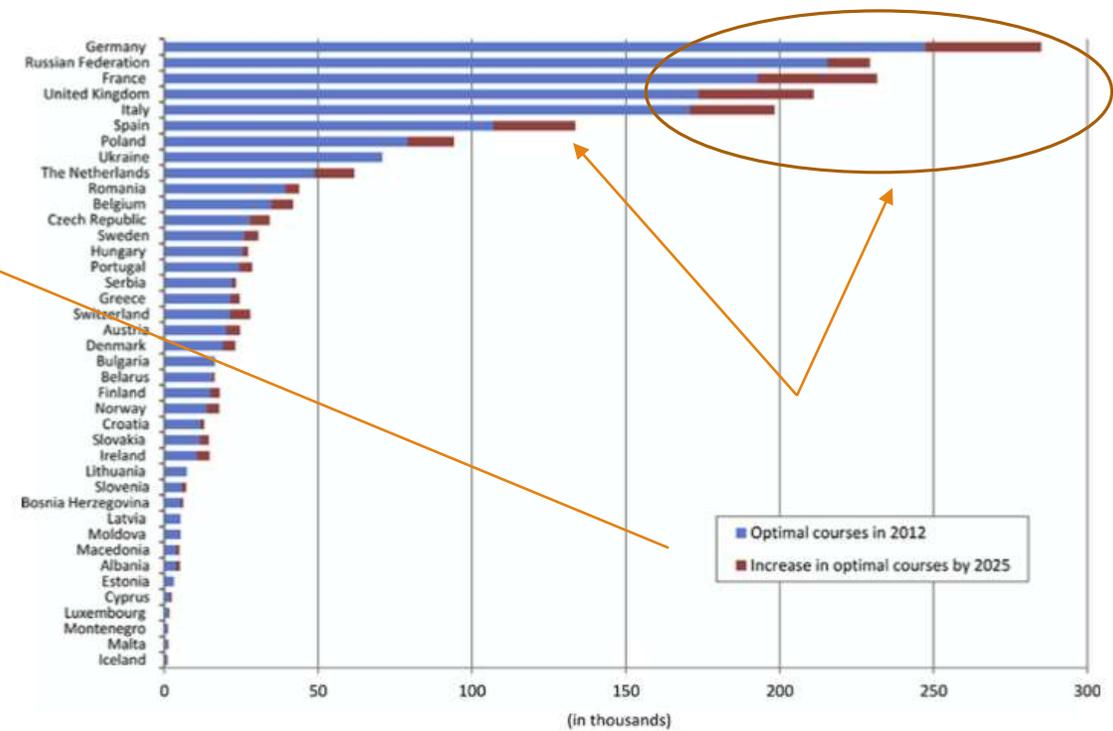
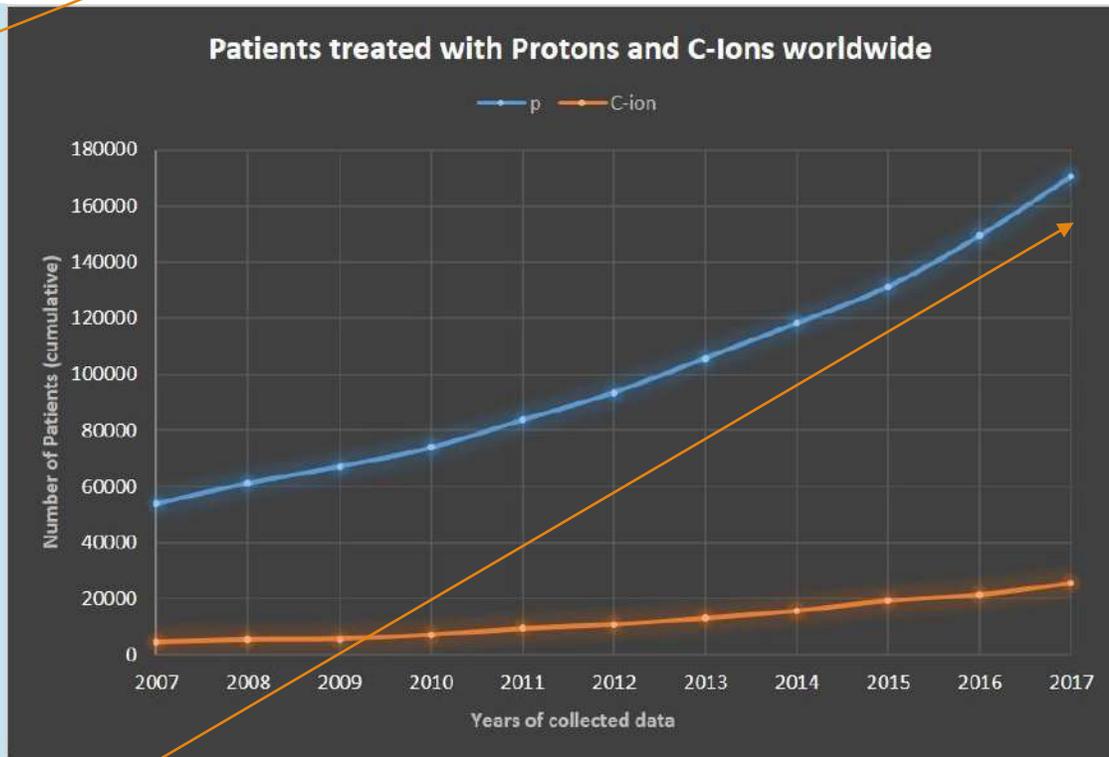


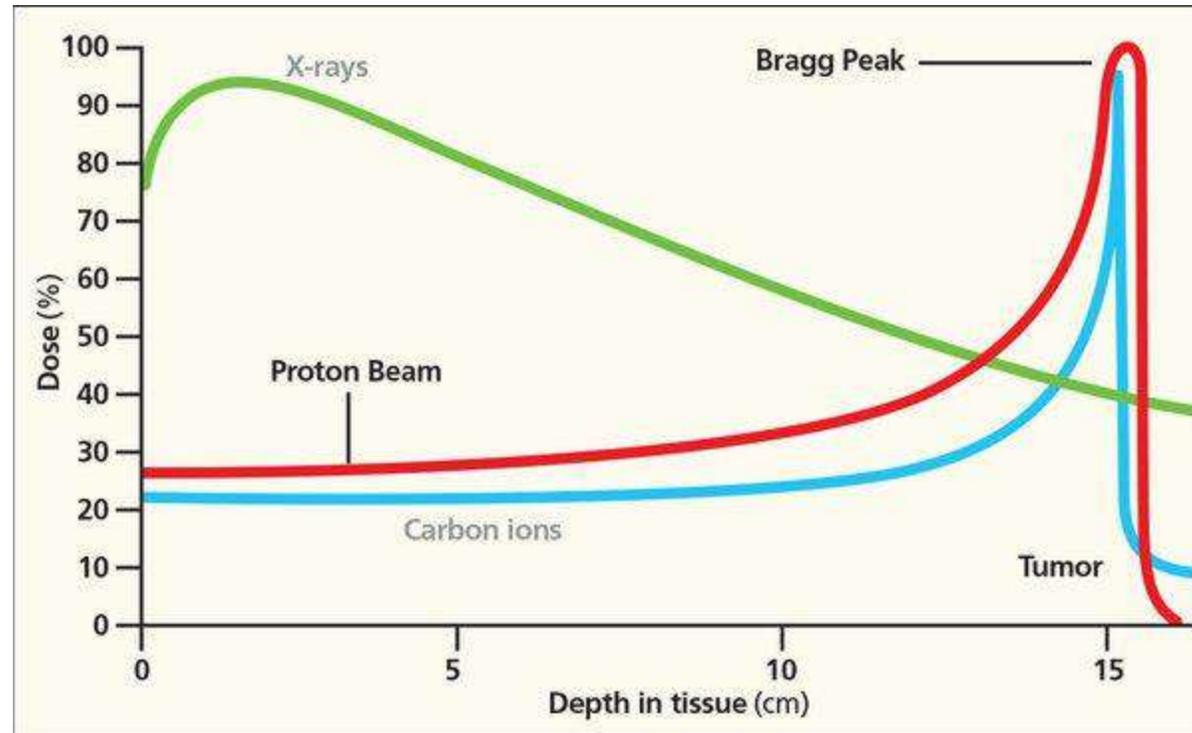
Fig. 2. Optimal number of courses of radiotherapy in 2012 and estimated absolute increase in optimal number of courses by 2025.

PTCOG website... operativos "contados a mano" en 2021 68 centros



Estimados pacientes tratados en 2021....> 200.000...

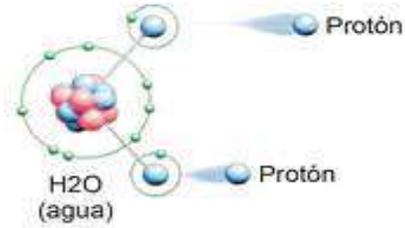
Discussing *only* proton therapy arguments and data..



Sincrotrón

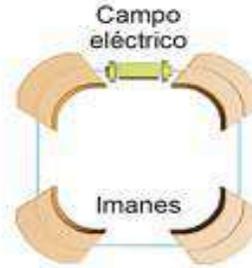
1 Inyector

Los protones se extraen de moléculas de agua y se inyectan en un acelerador lineal que los expulsa a baja velocidad.



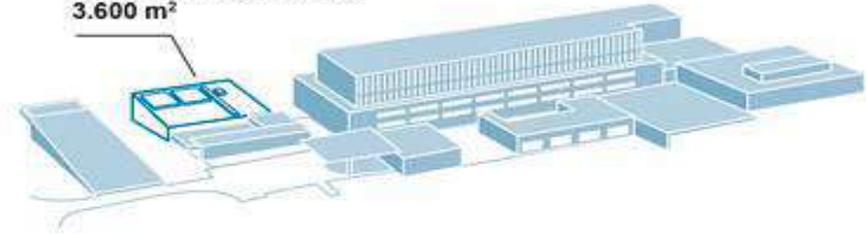
2 Sincrotrón

Cuatro imanes mueven los protones en círculo y un campo eléctrico incrementa gradualmente su velocidad.



Ubicación del acelerador de protones
3.600 m²

46.000 m²



3 Extracción

Cuando han alcanzado un 60% de la velocidad de la luz, se desvían a la línea de haz para ser utilizados.

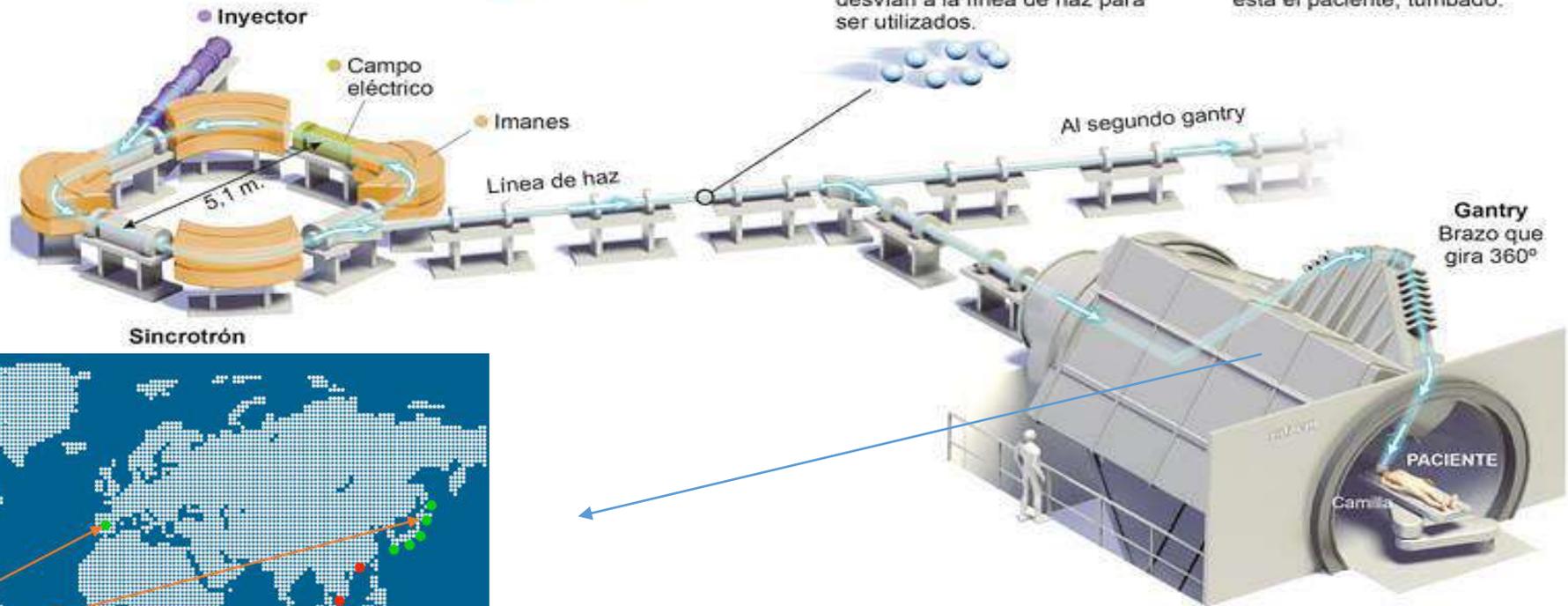


4 Gantry

Los protones llegan a uno de los dos gantrys, en cuyo centro está el paciente, tumbado.

Al segundo gantry

Gantry
Brazo que
gira 360°

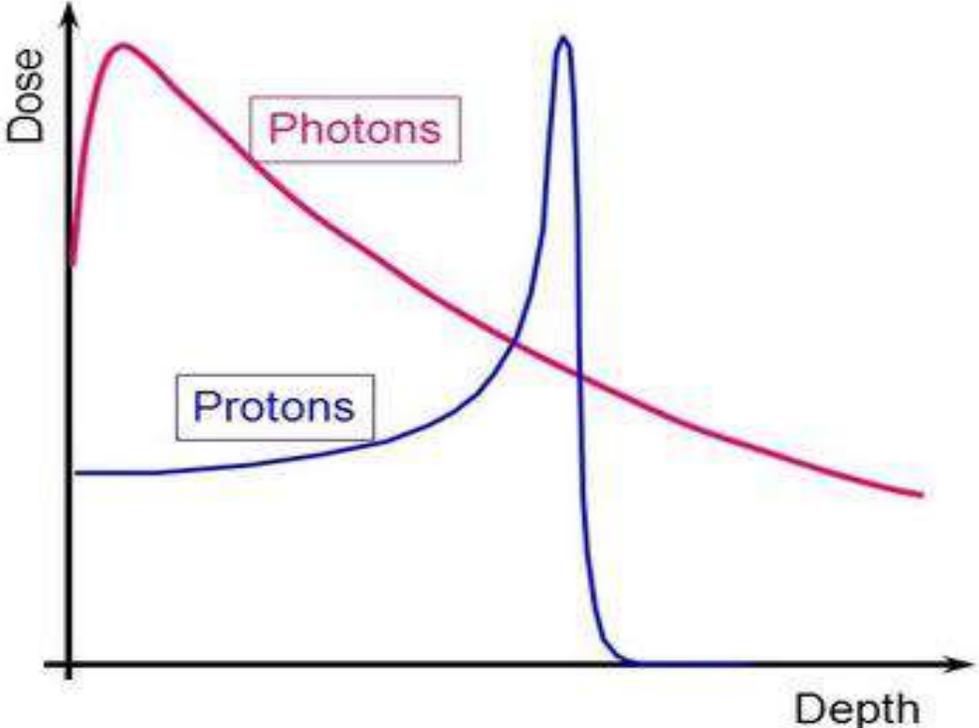


Health-Value and Proton Therapy:

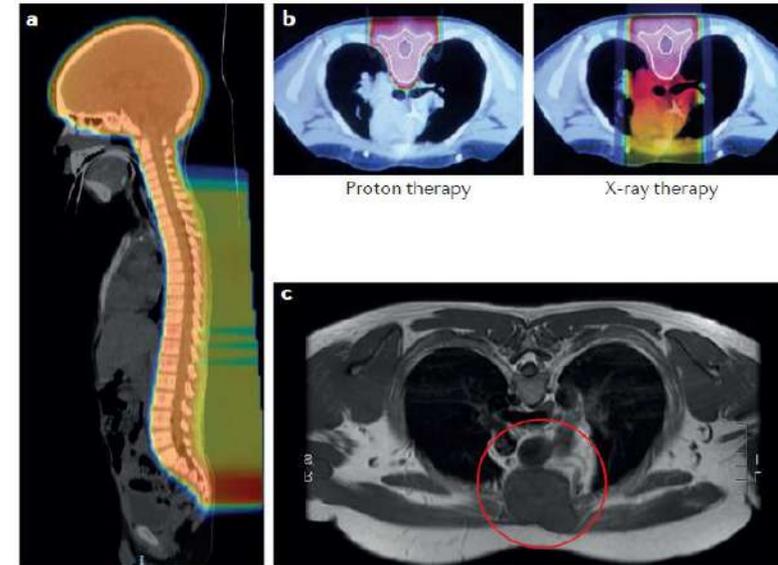
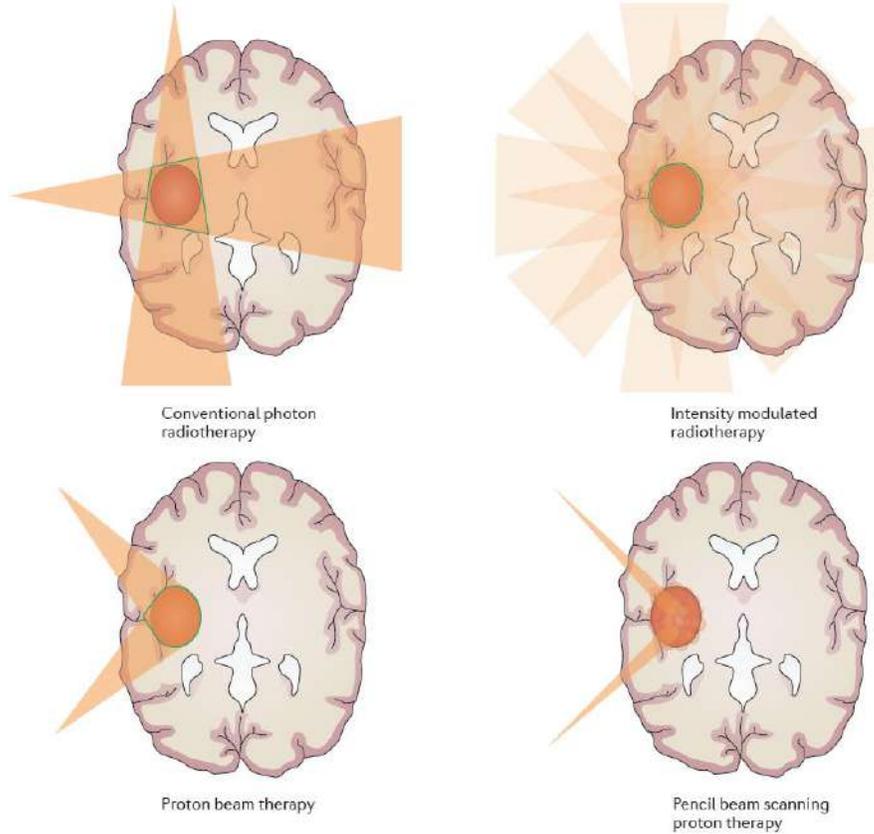
the new science of normal tissues...



Bragg Peak



Unnecessary irradiation: the medical dilemma...



Sarcoma radionduced

Dosimetric comparison of five different techniques for craniospinal irradiation across 15 European centers: analysis on behalf of the SIOP-E-BTG (radiotherapy working group)*

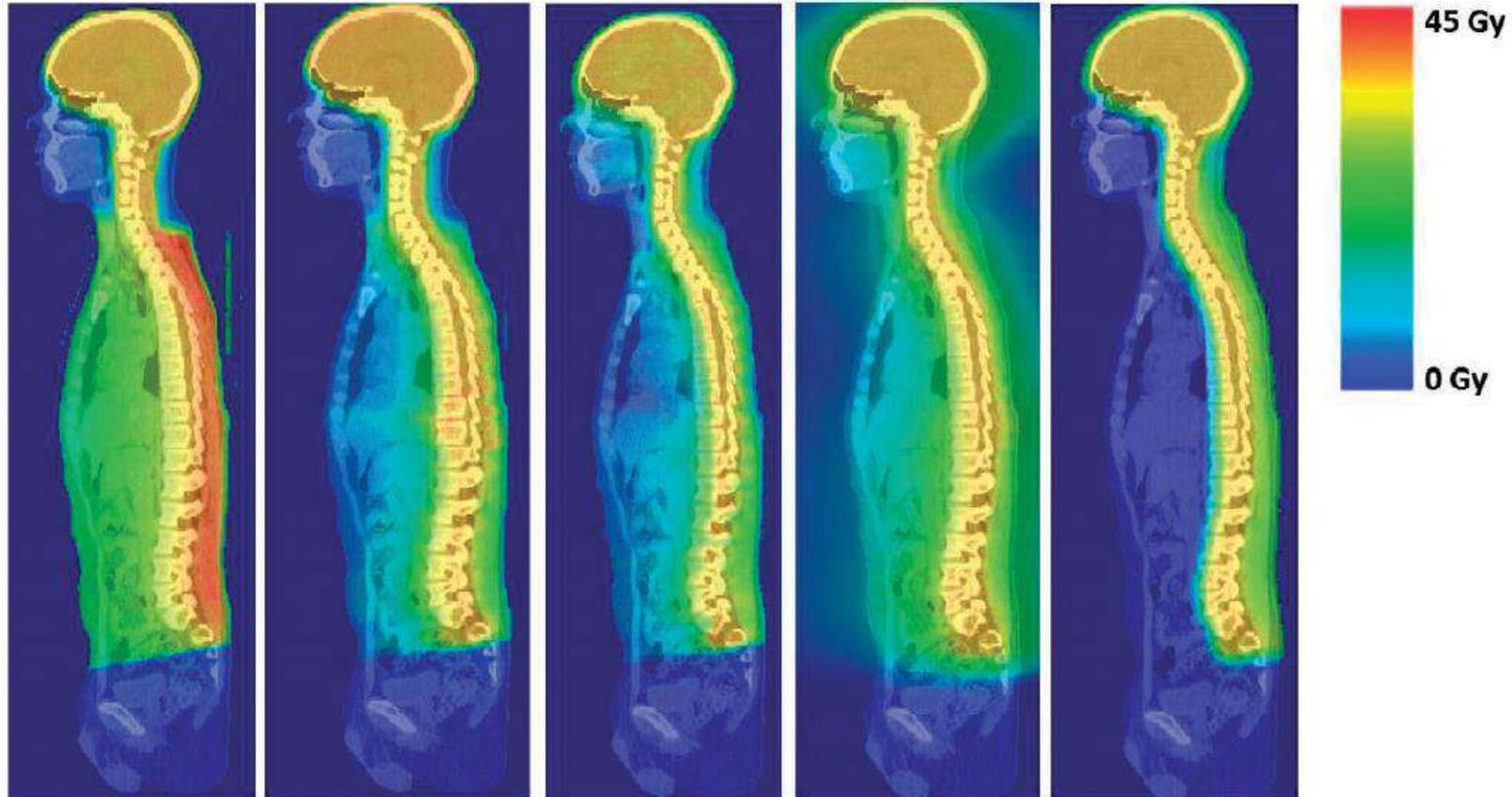
Photons - 3D

Photons – IMRT

Photons – VMAT

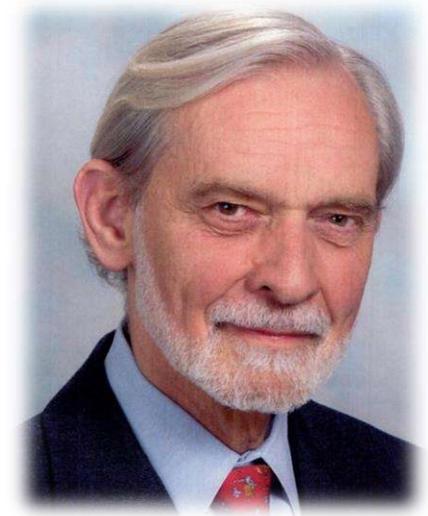
Photons – Tomo

Protons - PBS



Should Randomized Clinical Trials Be Required for Proton Radiotherapy?

Michael Goitein, *Department of Radiation Oncology, Harvard Medical School, Boston, MA*
James D. Cox, *Division of Radiation Oncology, The University of Texas M.D. Anderson Cancer Center, Houston, TX*



“Would we agree to receive **25 Gy**
to a large fraction of our brain or abdomen . . .
with no known credibly hypothesized medical benefit?”



Clinical Investigation

Establishing Evidence-Based Indications for Proton Therapy: An Overview of Current Clinical Trials

Mark V. Mishra, MD,* Sameer Aggarwal, MD,†
Soren M. Bentzen, PhD, DMSc,‡ Nancy Knight, PhD,*
Minesh P. Mehta, MD,§ and William F. Regine, MD, FACR, FACRO*

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Received Aug 30, 2016, and in revised form Oct 18, 2016. Accepted for publication Oct 31, 2016.

122 active PTB trials
42,000 patients
79 % interventional studies

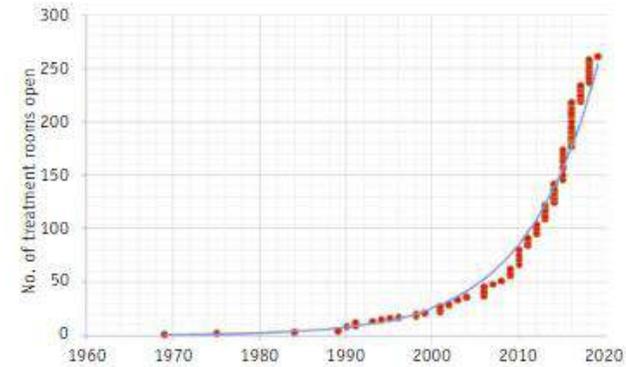
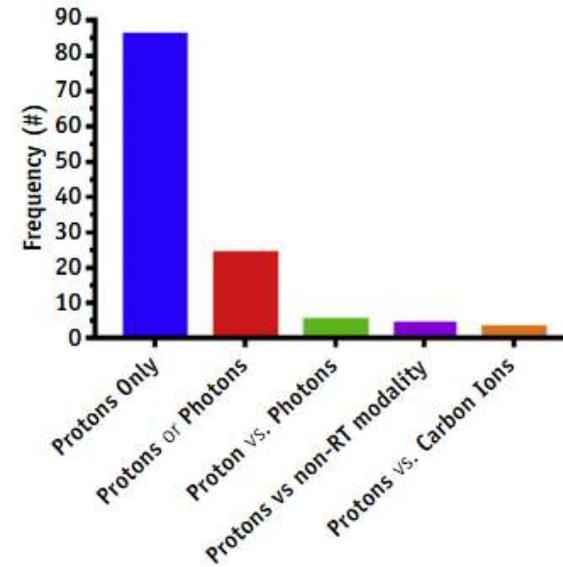


Fig. 5. Number of operating proton beam therapy rooms worldwide, 1970–present.



Clinical Investigation

Establishing Evidence-Based Indications for Proton Therapy: An Overview of Current Clinical Trials

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Departments of *Radiation Oncology, [†]Internal Medicine, and [‡]Epidemiology and Public Health, University of Maryland School of Medicine, Baltimore, Maryland; and [§]Miami Cancer Institute at Baptist Health South Florida, Miami, Florida

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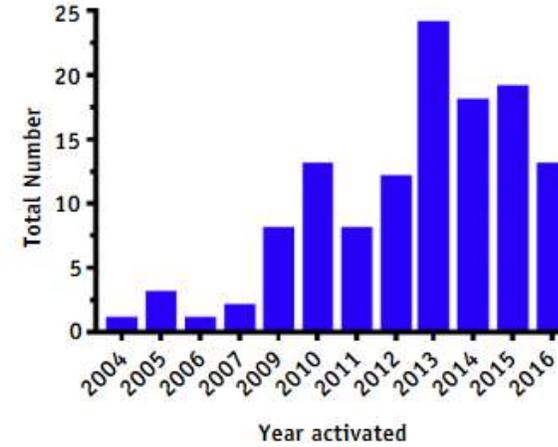
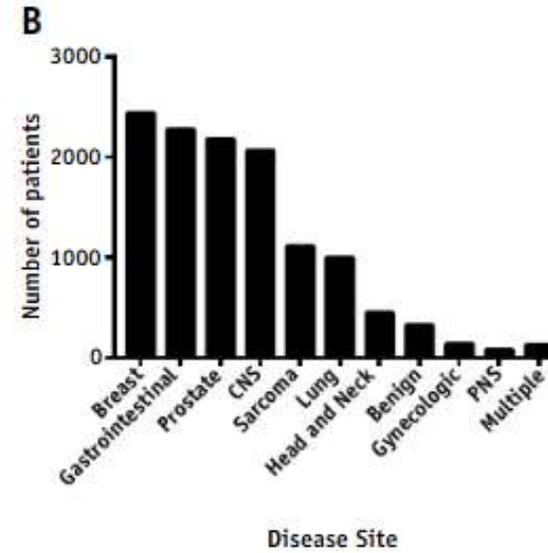
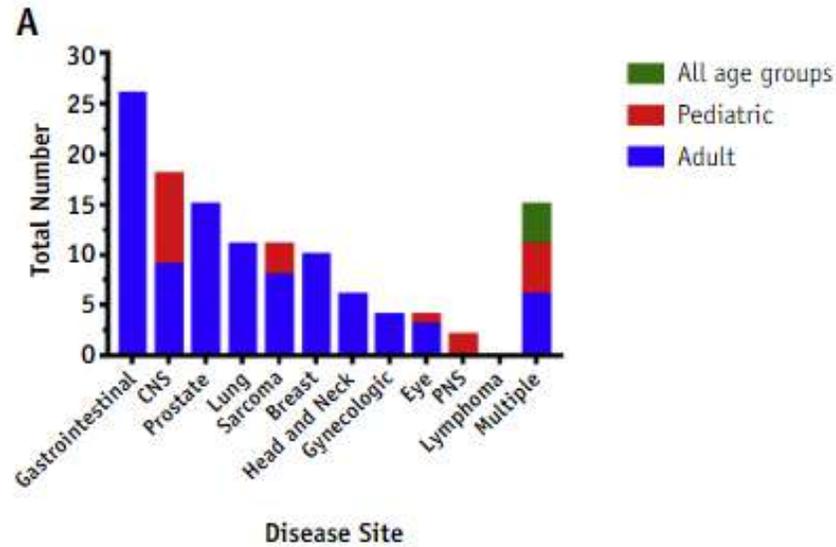


Fig. 2. Activation of clinical trials of proton beam



Hadrontherapy for cancer. An overview of HTA reports and ongoing studies

TOM JEFFERSON¹, GIULIO FORMOSO², FRANCESCO VENTURELLI^{2,3}, MASSIMO VICENTINI², EMILIO CHIAROLLA⁴, LUCIANA BALLINI^{2,5}

¹Oxford University, Newcastle University, United Kingdom; ²Azienda USL-IRCCS di Reggio Emilia; ³Clinical and Experimental Medicine PhD program, University of Modena and Reggio Emilia, Modena; ⁴Associazione Italiana Ingegneri Clinici (AIIC); ⁵Direzione Generale Cura della Persona, Salute e Welfare - Regione Emilia-Romagna.

Non-comparative 25 studies
Comparative 9 studies

CARBON ION THERAPY CENTRES

According to PTOGC to date, 13 cancer therapy centres worldwide offer CIRT, most of them are located in Asia (3 in China, 6 in Japan) and few in Europe (2 in Germany, 1 in Italy and 1 in Austria). In the next few years (2019-2023) 5 CIRT, 4 in Asia and 1 in France, are expected to come into operation.

According to the LBI HTA report, by the end of 2016, approximately 21,580 patients were recorded to have been treated with CIRT, with the majority of patients treated at HIMAC, in Chiba, Japan (10,692) followed by HIT, in Heidelberg, Germany (2,430) and HIBMC, in Hyogo, Japan (2,527). To date 2,200 patients have been treated in Italy (CNAO Pavia), most of them were funded by the Italian NHS and two thirds were treated with CIRT¹⁹.

572 | Recenti Progressi in Medicina, 110 (12), dicembre 2019

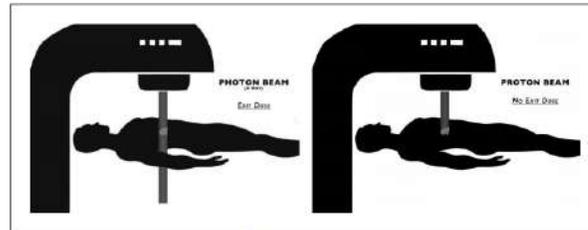


Figure 2. Proton beam stop in target and don't exit from the body (credit: Sergio Sassano).

Table 3. Availability of information in included HTA reports on CIRT and N. of ongoing non-comparative and comparative studies by clinical indications^{19,25-28*}.

Indication	LBI 2018	CADTH 2018	CADTH 2009	Health PACT 2017	AETNA 2019	N. ongoing non comparative studies	N. ongoing comparative studies
1. Solid paediatric tumours						0	0
2. Central nervous system tumours	X					1	4
3. Sarcomas	X	X				0	2*
4. Chordomas	X	X				3	1*
5. Tumours of the head & neck region	X					6	1*
6. Cutaneous and uveal melanoma						0	0
7. Lung malignancies	X					0	0
8. Breast malignancies						0	0
9. Thyroid malignancies						0	0
10. Pancreas malignancies	X					6	1
11. Colon and rectum malignancies	X					1	0
12. Prostate malignancies at high metastathases risk	X					7	0
13. Bladder malignancies						0	0
14. Esophagus malignancies	X					0	0
15. Urinary tract malignancies						0	0
16. Gastric malignancies						0	0
17. Uterine cervical malignancies						0	0
18. Liver malignancies						7	0
19. Recurrent tumours requiring repeat treatment in areas already exposed to radiotherapy						0	0

Key: N.= number; *some studies may be repeated as they may be pertinent to different tumours

Clinical health-value is not intuitive...

international metrics are heterogeneous

Comparative Assessment of Clinical Benefit Using the ESMO-Magnitude of Clinical Benefit Scale Version 1.1 and the ASCO Value Framework Net Health Benefit Score

Nathan I. Cherny, MBBS, FRACP, FRCP, LLD¹; Elisabeth G.E. de Vries, MD, PhD²; Urania Dafni, ScD^{3,10}; Elizabeth Garrett-Mayer, PhD⁴; Shannon E. McKernin⁴; Martine Piccart, PhD⁵; Nicola J. Latino⁶; Jean-Yves Douillard, MD⁷; Lowell E. Schnipper, MD⁸; Mark R. Somerfield, PhD⁴; Jan Bogaerts, ScD⁶; Dimitris Karlis, PhD⁹; Panagiota Zygoura, MSc¹⁰; Katerina Vervita, MD¹⁰; George Pentheroudakis, MD, PhD¹¹; Josep Tabernero, MD, PhD¹²; Christoph Zielinski, MD¹³; Dana S. Wollins, MGC⁴; and Richard L. Schilsky, MD⁴

INTRODUCTION

Evaluation of the clinical benefit of any anticancer therapy depends on an objective assessment of the magnitude of improvement in meaningful clinical outcomes in the face of toxicity associated with the treatment. Both the European Society for Medical Oncology (ESMO)^{1,2} and the American Society of Clinical Oncology (ASCO)^{3,4} have developed algorithmic scales to evaluate benefit of cancer therapies. The ESMO-Magnitude of Clinical Benefit Scale (ESMO-MCBS) was developed to generate clear, valid, and unbiased grading of the magnitude of clinical benefit demonstrated in therapeutic studies that could be used for a number of purposes, including public health policy and health technology assessment, clinical decision making, medical publication, and journalism.^{1,2} The ASCO Value Framework was developed primarily as a physician-guided tool to facilitate shared decision making by patients and oncologists in selecting a high-value treatment (clinical benefit v toxicity) for an individual patient."^{3,4}

J Clin Oncol 37:336-349. © 2018 by American Society of Clinical Oncology

clinical benefit = magnitude/metrics = outcomes + toxicity



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

Vivek Verma MD¹; Mark V. Mishra MD²; and Minesh P. Mehta MBChB²

Cost-Effectiveness Analysis Registry (2000-2015) abstracts (18) Particle Therapy Co-Operative Group of North America

RESULTS:

- Cost-effectiveness for **prostate cancer** diagnosis was suboptimal.
- **The most cost-effective option are pediatric brain tumors.**
- Costs for **breast cancer** is favorable for selected patients with **left-sided cancers** at high risk of cardiac toxicity
- **NSCLC** cost-effectiveness benefits for **loco-regionally advanced**—but not early stage—tumors.
- Favourable cost-effectiveness in selected **head/neck cancer** patients at higher risk of acute mucosal toxicities.
- CONCLUSIONS: PBT offers promising cost-effectiveness. **Patient selection** is critical to assess cost-effectiveness.

Health-Value: oncology

TECHNOLOGY IS UNDER CONTROL (AGENCIES)...DRUGS ARE OUT OF CONTROL (TRIALS)...

The next decade...

In 2020-2030 Oncology **innovation** is...

cancer **cure an quality of life...**

(...not just better scientific knowledge...)



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NCCN Categories of Preference

NCCN Guidelines® Steering Committee

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NCCN Categories of Evidence and Consensus

- **Category 1:** Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
- **Category 2A:** Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
- **Category 2B:** Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.
- **Category 3:** Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise indicated.

NCCN Categories of Preference

- **Preferred intervention:** Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability
- **Other recommended intervention:** Other interventions that may be somewhat less efficacious, more toxic, or based on less mature data; or significantly less affordable for similar outcomes
- **Useful in certain circumstances:** Other interventions that may be used for selected patient populations (defined with recommendation)

All recommendations in the NCCN Guidelines are considered appropriate.

For more information on the NCCN Categories of Preference [click here](#).

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< 7 %

> 80 %

Health-Value: radiotherapy

DOSIMETRIC BENEFIT = CLINICAL BENEFIT = QUALITY OF LIFE = COST HEALTH SYSTEM

Health- Value in pediatric oncology

NEVER RANDOMIZED, RETROSPECTIVE, HETEROGENEOUS PROTON TECHNOLOGY



SPECIAL ARTICLE

Chronic Health Conditions in Adult Survivors of Childhood Cancer

Kevin C. Oeffinger, M.D., Ann C. Mertens, Ph.D., Charles A. Sklar, M.D.,
 Toana Kawashima, M.S., Melissa M. Hudson, M.D., Anna T. Meadows, M.D.,
 Debra L. Friedman, M.D., Neyssa Marina, M.D., Wendy Hobbie, C.P.N.P.,
 Nina S. Kadan-Lottick, M.D., Cindy L. Schwartz, M.D., Wendy Leisenring, Sc.D.,

> 15 años seguimiento; 72% recibieron RT

> 3.000 siblings

62% vs 27% patología en tratamiento activo

28% vs 9% grado 3-4 (severa/riesgo vital)

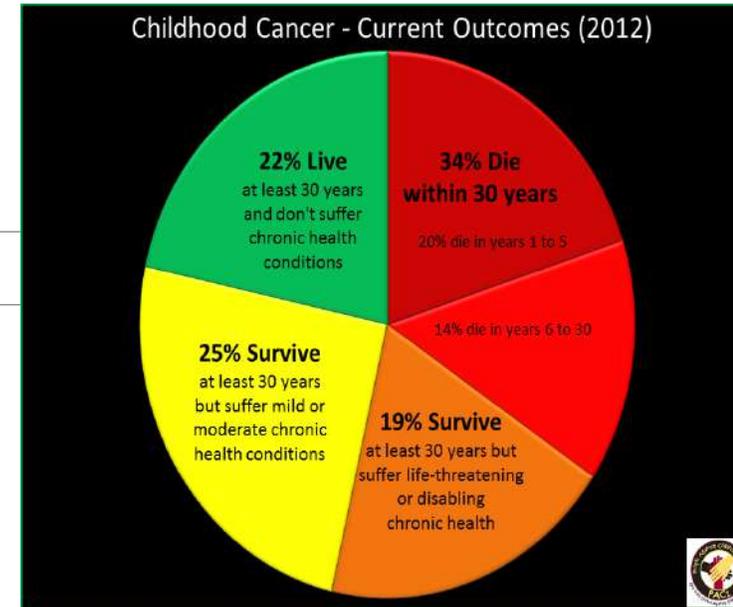


Table 2. Cancer Survivors and Siblings with a Chronic Health Condition, According to the Severity Score.*

Health Condition	Survivors (N=10,397)	Siblings (N=3034)
	no. (%)	
No condition	3887 (37.4)	1917 (63.2)
Grade 1 (mild)	1931 (18.6)	610 (20.1)
Grade 2 (moderate)	1635 (15.7)	349 (11.5)
Grade 3 (severe)	2128 (20.5)	128 (4.2)
Grade 4 (life-threatening or disabling)	653 (6.3)	30 (1.0)
Grade 5 (fatal)	163 (1.6)	NA†
Any condition‡		
Grades 1–4	6482 (62.3)	1117 (36.8)
Grade 3 or 4	2858 (27.5)	158 (5.2)
Multiple health conditions		
≥2	3905 (37.6)	397 (13.1)
≥3	2470 (23.8)	163 (5.4)

Health- Value pediatric oncology: neurocognition

NEVER RANDOMIZED, RETROSPECTIVE, HETEROGENEOUS PROTON TECHNOLOGY



Superior Intellectual Outcomes After Proton Radiotherapy Compared With Photon Radiotherapy for Pediatric Medulloblastoma

Lisa S. Kahalley, PhD^{1,2}; Rachel Peterson, PhD³; M. Douglas Ris, PhD^{1,2}; Laura Janzen, PhD³; M. Fatih Okcu, MPH, MD^{1,2}; David R. Grosshans, MD, PhD⁴; Vijay Ramaswamy, MD, PhD^{3,5}; Arnold C. Paulino, MD⁴; David Hodgson, MD⁶; Anita Mahajan, MD⁷; Derek S. Tsang, MD, PhD⁶; Normand Laperriere, MD⁶; William E. Whitehead, MPH, MD^{1,2}; Robert C. Dauser, MD^{1,2}; Michael D. Taylor, MD, PhD^{3,5}; Heather M. Conklin, PhD⁸; Murali Chintagumpala, MD^{1,2}; Eric Bouffet, MD^{3,5}; and Donald Mabbott, PhD^{3,5}

2007 and 2018 79 patients (37 PRT, 42 XRT)
same medulloblastoma protocols radiotherapy (PRT vs XRT)

PRT group **Neurocognition... Dependence...**

global intelligence quotient (IQ),
Perceptual reasoning
working memory

XRT group significant decline (all P, .05) in

global IQ,
working memory
processing speed

PRT group stable scores over time in all domains
(exception of processing speed (P = .003).

J Clin Oncol 38:454-461. © 2019 9

AFFILIATIONS

- ¹Baylor College of Medicine, Houston, TX
- ²Texas Children's Hospital, Houston, TX
- ³The Hospital for Sick Children, Toronto, ON, Canada
- ⁴The University of Texas MD Anderson Cancer Center, Houston, TX
- ⁵The University of Toronto, Toronto, ON, Canada
- ⁶Princess Margaret Cancer Centre, Toronto, ON, Canada
- ⁷The Mayo Clinic, Rochester, MN
- Memphis, TN

CONCLUSION

first study to compare intellectual trajectories
PRT vs XRT on comparable, **contemporary protocols**

PRT was associated with favorable intellectual outcomes

strongest evidence to date of an **intellectual sparing advantage**
with **PRT** in the treatment of pediatric **medulloblastoma**

Elements protected over time by protons

Kahalley et al

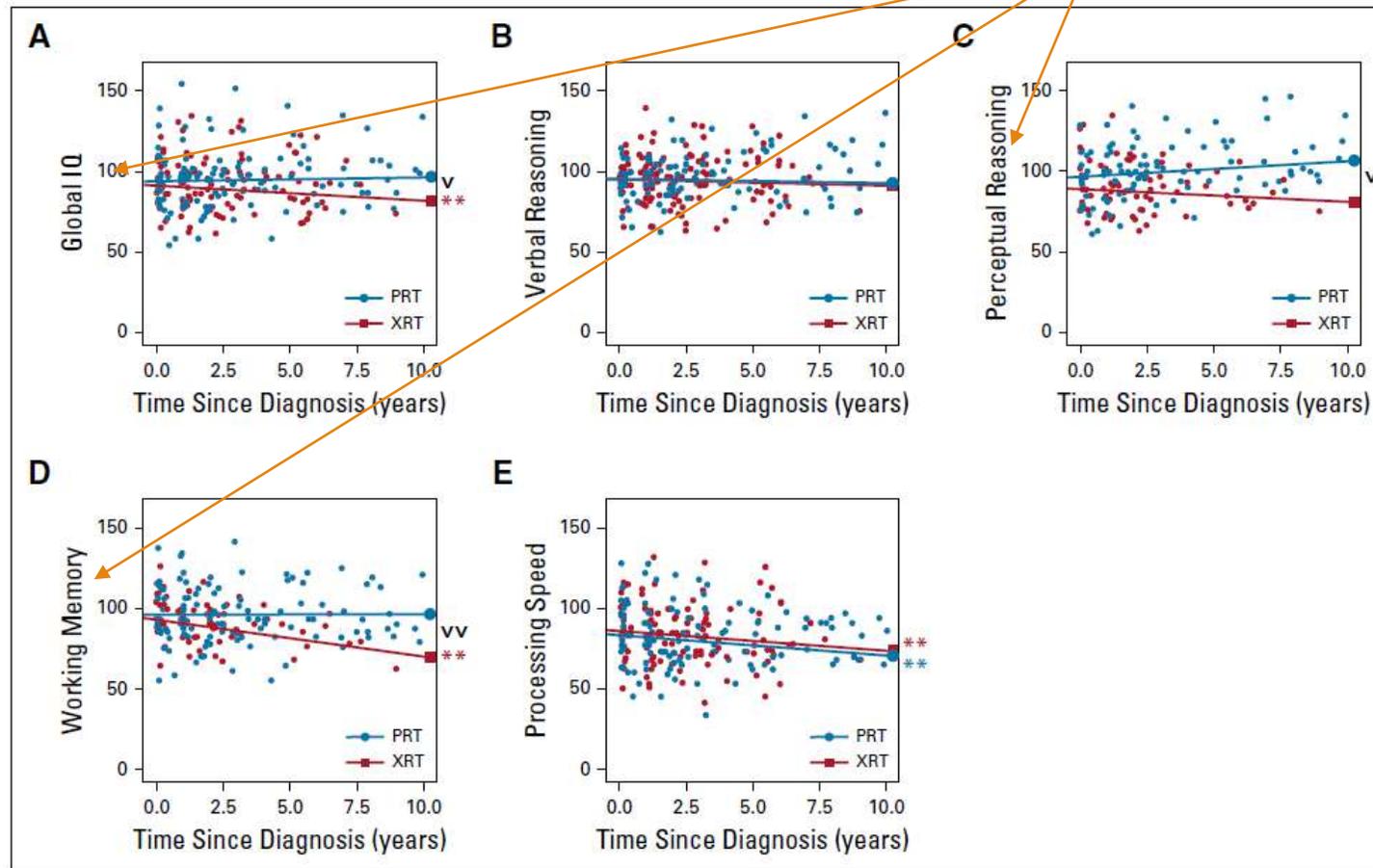


FIG 1. Change in outcomes scores over time since diagnosis by proton radiotherapy (PRT) and photon radiotherapy (XRT). (A) Global intelligence quotient (IQ). (B) Verbal reasoning. (C) Perceptual reasoning. (D) Working memory. (E) Processing speed. Bold lines are adjusted slopes showing change in neurocognitive scores over time since diagnosis as a function of treatment group. (v) Difference in slopes between PRT and XRT ($P < .05$). (**) Global IQ, working memory, and processing speed decline ($P < .01$). (vv) Difference in slopes between PRT and XRT ($P < .01$).

Health- Value pediatric oncology: hematological tolerance

NEVER RANDOMIZED, RETROSPECTIVE, HETEROGENEOUS PROTON TECHNOLOGY



Medulloblastoma Protons vs Photons

Table 2 Grades of acute hematologic toxicity of proton and photon cohorts

CTCAE grade of toxicity	Proton cohort, n (%)	Photon cohort, n (%)	P value
Leukopenia	60	37	.044*
0	2 (3.3)	0 (0.0)	
1	10 (16.7)	3 (8.1)	
2	26 (43.3)	14 (37.8)	
3	22 (36.7)	10 (27.1)	
4			
Neutropenia			
0			
1			
2			
3			
4			
Lymphopenia	59	34	<.0001*
0	0 (0.0)	0 (0.0)	
1	0 (0.0)	0 (0.0)	
2	14 (23.7)	0 (0.0)	
3	35 (59.3)	11 (32.4)	
4	10 (16.9)	23 (67.6)	
Anemia	60	37	.011*
0	4 (6.7)	0 (0.0)	
1	35 (58.3)	16 (43.2)	
2	21 (35.0)	18 (48.6)	
3	0 (0.0)	3 (8.1)	
4	0 (0.0)	0 (0.0)	
Thrombocytopenia	60	37	.066
0	43 (71.7)	20 (54.1)	
1	17 (28.3)	16 (43.2)	
2	0 (0.0)	1 (2.7)	
3	0 (0.0)	0 (0.0)	
4	0 (0.0)	0 (0.0)	

* Significance with $P < .05$.

Immunocompetence

Dana-Farber + MGH + J Hopkins + UCSF + U Minn
 < 25 y
 2000 – 2017
 No concomitant CT (only VCR)
 39.6 + boost 3D photons vs passive PT
 > 15 y VBSparing

A Multi-institutional Comparative Analysis of Proton and Photon Therapy-Induced Hematologic Toxicity in Patients With Medulloblastoma

Kevin X. Liu, MD, DPhil,* Myrsini Ioakeim-Ioannidou, MD,^{1,2} Matthew S. Susko, MD,³ Avani D. Rao, MD,⁴ Beow Y. Yeap, ScD,⁵ Antoine M. Snijders, PhD,⁶ Matthew M. Ladra, MD,⁷ Jennifer Vogel, MD,⁸ Cierra Zaslowsky-Dude, BA,⁹ Karen J. Marcus, MD,¹⁰ Torunn I. Yock, MD, MCh,¹¹ Clemens Grassberger, PhD,¹² Steve E. Braunstein, MD, PhD,¹³ Daphne A. Haas-Kogan, MD,¹⁴ Stephanie A. Terezakis, MD,¹⁵ and Shannon M. MacDonald, MD¹⁶

¹Department of Radiation Oncology, Brigham and Women's Hospital, Dana-Farber Cancer Institute, Boston Children's Hospital, Harvard Medical School, Boston, Massachusetts; ²Department of Radiation Oncology, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts; ³Department of Radiation and Molecular Radiation Sciences, Sidney Kimmel Comprehensive Cancer Center Johns Hopkins School of Medicine, Baltimore, Maryland; ⁴Department of Radiation Oncology, University of California San Francisco, San Francisco, California; ⁵Department of Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts; ⁶Biological Systems and Engineering Division, Lawrence Berkeley National Laboratory, Berkeley, California; ⁷Department of Radiation Oncology, University of Minnesota Medical School, Minneapolis, Minnesota

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Health- Value pediatric oncology: radio-induced cancer

NEVER RANDOMIZED, RETROSPECTIVE, HETEROGENEOUS PROTON TECHNOLOGY



Original Article |  Open Access |   

Long-term follow-up after proton beam therapy for pediatric tumors: a Japanese national survey

Masashi Mizumoto, Shigeyuki Murayama, Tetsuo Akimoto, Yusuke Demizu, Takashi Fukushima, Yuji Ishida, Yoshiko Oshiro, Haruko Numajiri, Hiroshi Fuji, Toshiyuki Okumura ... [See all authors](#) ▾

> 400 patients

5-, 10- and 20-year

grade 2 or higher late toxicities were 18%, 35% and **45%**

grade 3 or higher late toxicities were 6%, 17% and **17%**

Univariate analysis irradiated site (head and neck, brain) associated late toxicities

No malignant secondary tumors occurred within the irradiated field.

10- and 20-year all secondary tumors: 8% and **16%**

PBT has the potential to reduce the risk of late mortality and secondary malignancy

Radiation induced malignancies: photons vs protons

Received: 16 December 2020 | Revised: 11 January 2021 | Accepted: 12 January 2021

DOI: 10.1002/pbc.28941

ONCOLOGY: RESEARCH ARTICLE

Pediatric Blood & Cancer
aspho
The American Society of Pediatric Hematology/Oncology
WILEY

Second tumor risk in children treated with proton therapy

Daniel J. Indelicato¹ | James E. Bates² | Raymond B. Mailhot Vega¹

IMRT 10-year second malignancy of 4.3%.

peak second tumors of 31% in volumes that receive 2.5 Gy or less.

Pediatr Blood Cancer. 2015;62(2):311–316.



Original Article | Open Access | CC BY

Long-term follow-up after proton beam therapy for pediatric tumors: a Japanese national survey

Masashi Mizumoto, Shigeyuki Murayama, Tetsuo Akimoto, Yusuke Demizu, Takashi Fukushima, Yuji Ishida, Yoshiko Oshiro, Haruko Numajiri, Hiroshi Fuji, Toshiyuki Okumura ... See all authors

> 400 patients

No malignant secondary tumors occurred within the irradiated field

Proton therapy for pediatric malignancies: Fact, figures and costs. A joint consensus statement from the pediatric subcommittee of PTCOG, PROS and EPTN



Damien C. Weber^{a,*}, Jean Louis Habrand^b, Bradford S. Hoppe^c, Christine Hill Kayser^d, Nadia N. Laack^e, Johannes A. Langendijk^f, Shannon M. MacDonald^g, Susan L. McGovern^h, Luke Paterⁱ, John P. Perentesis^j, Juliette Thariat^b, Beate Timmerman^k, Torunn I. Yock^g, Anita Mahajan^e

^aCenter for Proton Therapy, Paul Scherrer Institute, ETH Domain, Villigen PSI, Switzerland; ^bCentre de lutte contre le cancer François-Baclesse, Caen, France; ^cDepartment of Radiation Oncology, University of Florida College of Medicine, Gainesville; ^dDepartment of Radiation Oncology, University of Pennsylvania, Philadelphia; ^eDepartment of Radiation Oncology, Mayo Clinic, Rochester, USA; ^fDepartment of Radiation Oncology, University Medical Center Groningen, University of Groningen, The Netherlands; ^gDepartment of Radiation Oncology, Massachusetts General Hospital, Boston; ^hDepartment of Radiation Oncology, MD Anderson Cancer Center, Houston; ⁱDepartment of Radiation Oncology, University of Cincinnati; ^jCincinnati Children's Hospital Medical Center, University of Cincinnati, USA; ^kWPE, University Hospital Essen, Germany

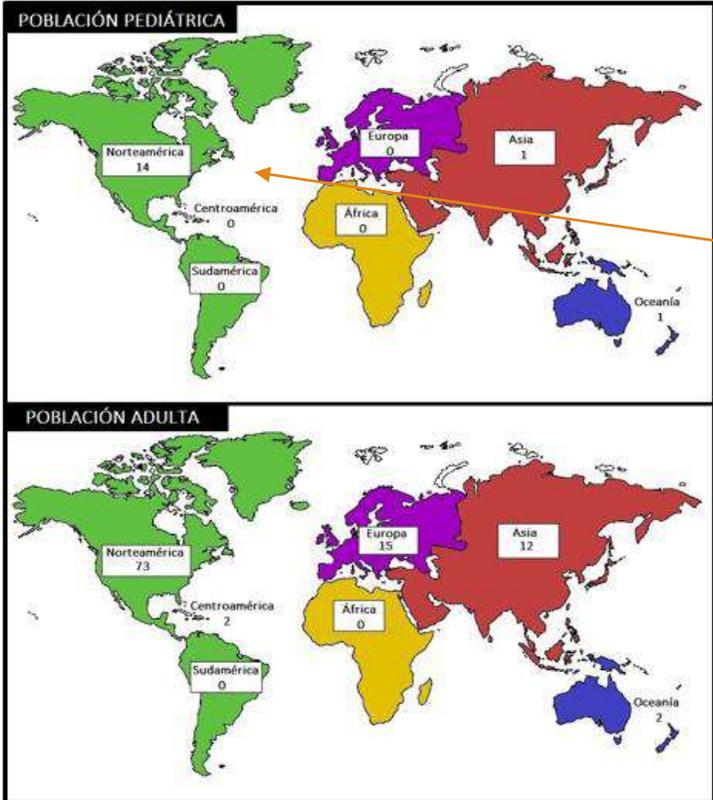
A B S T R A C T

Radiotherapy plays an important role in the management of childhood cancer, with the primary aim of achieving the highest likelihood of cure with the lowest risk of radiation-induced morbidity. Proton therapy (PT) provides an undisputable advantage by reducing the radiation 'bath' dose delivered to non-target structures/volume while optimally covering the tumor with tumoricidal dose. This treatment modality comes, however, with an additional costs compared to conventional radiotherapy that could put substantial financial pressure to the health care systems with societal implications.

In this review we assess the data available to the oncology community of PT delivered to children with cancer, discuss on the urgency to develop high-quality data. Additionally, we look at the advantage of combining systemic agents with protons and look at the cost-effectiveness data published so far.

© 2018 Elsevier B.V. All rights reserved. Radiotherapy and Oncology 128 (2018) 44–55

Clinicaltrials.gov... proton therapy... active 2020



Pediatric (all observational)

Health- Value in adult cancer models

FEW RANDOMIZED, RETROSPECTIVE BUT ALSO PROSPECTIVE, HETEROGENEOUS PROTON TECHNOLOGY,
CONCOMITANT CHEMOTHERAPY

Health-Value: “*costicity*”

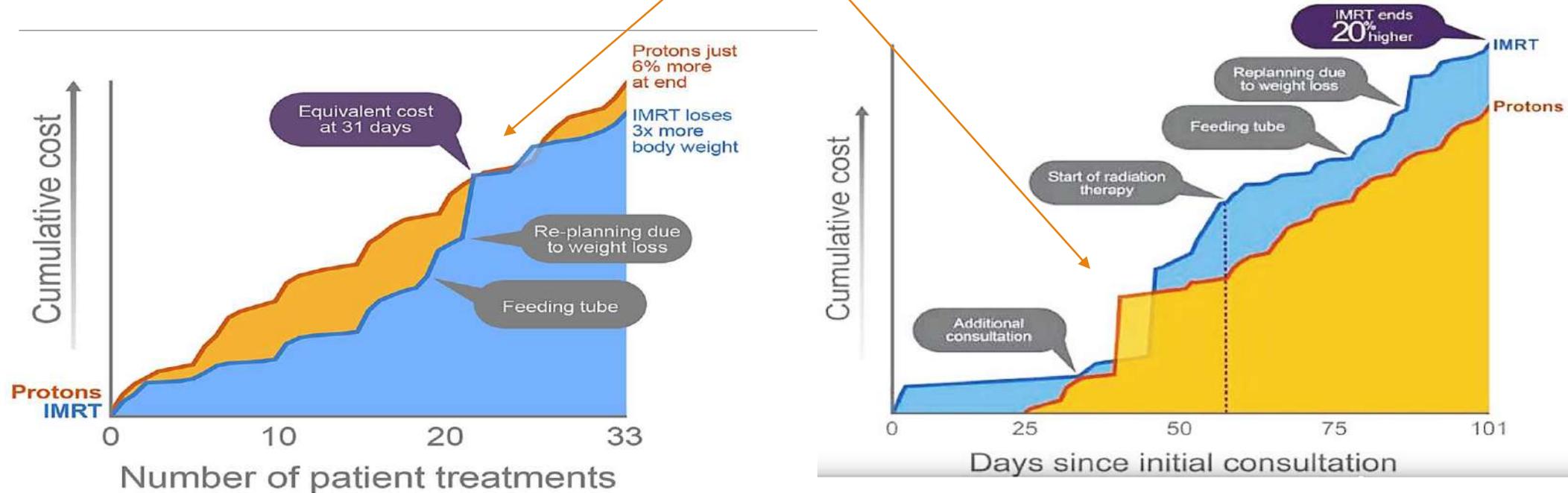
FINANTIAL TOXICITY...

Basic approach to health economy...

$$\text{Value} \uparrow = \frac{\uparrow \Sigma (\text{Outcomes})}{\downarrow \Sigma (\text{Costs})}$$

Thaker N et al. *Oncology Payers* 2014

Health Value



Decreased cost of after treatment delivery...



Activity-Based Costing of Intensity-Modulated Proton versus Photon Therapy for Oropharyngeal Cancer

Nikhil G. Thaker, MD^{1,2}; David Boyce-Fappiano, MD¹; Matthew S. Ning, MD¹; Dario Pasalic, MD¹; Alexis Guzman, MBA³; Grace Smith, MD, PhD, MPH¹; Emma B. Holliday, MD¹; James Incalcaterra, PhD³; Adam S. Garden, MD¹; Simona F. Shaitelman, MD¹; G. Brandon Gunn, MD¹; C. David Fuller, MD, PhD¹; Pierre Blanchard, MD¹; Thomas W. Feeley, MD⁴; Robert S. Kaplan, PhD⁴; Steven J. Frank, MD¹

¹Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

clinicopathologic factors to match 25 patients with OPC **IMPT in 2011-12** vs 25 patients **IMRT in 2000-09**.

single-fraction costs **2.79** times higher IMPT vs IMRT (owing to higher equipment costs),

average full cycle cost of IMPT **1.53** times higher than IMRT, the initial cost increase is mitigated by:
reductions in costs in non-RT supportive health care services.

Conclusions: **a subset of IMRT patients had similar costs to IMPT patients, owing to greater use of supportive care resources.**

Multidimensional patient outcomes and TDABC provide vital methodology for defining the value of radiation therapy modalities.



Cost-Effectiveness Models of Proton Therapy for Head and Neck: Evaluating Quality and Methods to Date

Danmeng Huang, PhD^{1,2}; Steven J. Frank, MD¹; Vivek Verma, MD¹; Nikhil G. Thaker, MD³; Eric D. Brooks, MD, MHS⁴; Matthew B. Palmer, MBA⁵; Ross F. Harrison, MD, MPH⁶; Ashish A. Deshmukh, PhD, MPH²; Matthew S. Ning, MD, MPH¹

¹Department of Radiation Oncology, University of Texas MD Anderson Cancer Center, Houston, TX, USA

Results:

only 4 formal CEMs specific to PBT for HNC had been published (**2005, 2013, 2018, 2020**).

The parameter inputs cohort models generally referenced older literature,

exclusion of clinically relevant complications

applying numerous hypothetical assumptions for toxicity states,

incorporating inputs from theoretical complication-probability models (limited availability of direct clinical evidence).

Case numbers of cohorts low

structural design of models inadequately reflected the natural history of HNC.

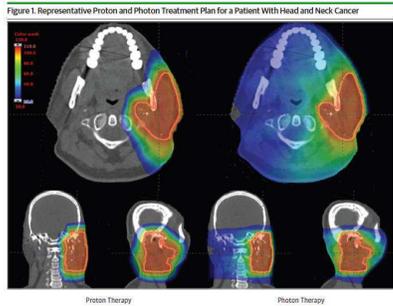
cost inputs were incomplete and referenced to historic figures.

Conclusion:

Contemporary CEMs are needed: better estimates for toxicity risks and costs associated to PBT delivery

Comparative Effectiveness of Proton vs Photon Therapy as Part of Concurrent Chemoradiotherapy for Locally Advanced Cancer

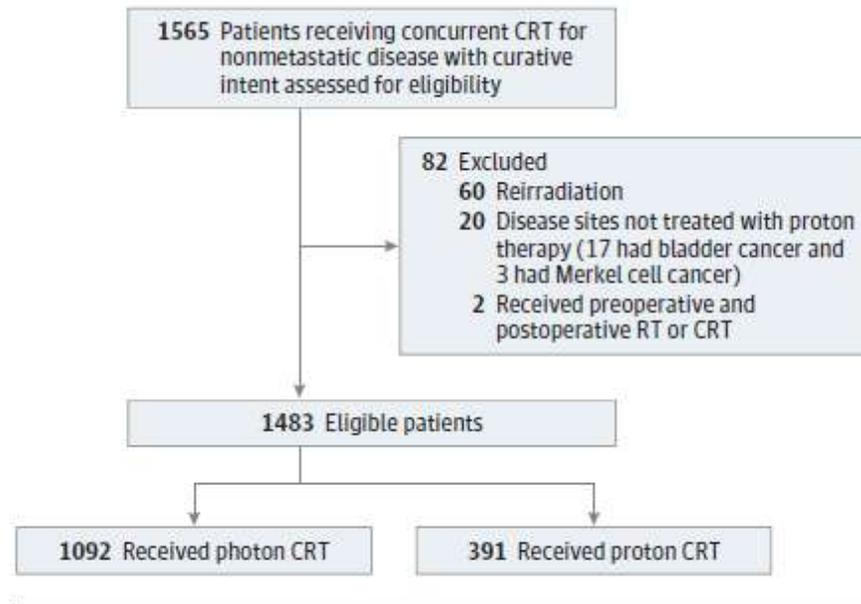
Brian C. Baumann, MD; Nandita Mitra, PhD; Joanna G. Harton, MS; Ying Xiao, PhD; Andrzej P. Wojcieszynski, MD; Peter E. Gabriel, MD, MSE; Haoyu Zhong, MSc; Huaizhi Geng, PhD; Abigail Doucette, MPH; Jenny Wei, BS; Peter J. O'Dwyer, MD; Justin E. Bekelman, MD; James M. Metz, MD



Radiation dose is represented as a color wash, with blue indicating the region receiving the lowest radiation dose and red indicating the region receiving the highest radiation dose.

JAMA Oncology Published online December 26, 2019

jamaoncology.com



CRT indicates chemoradiotherapy; RT, radiotherapy.

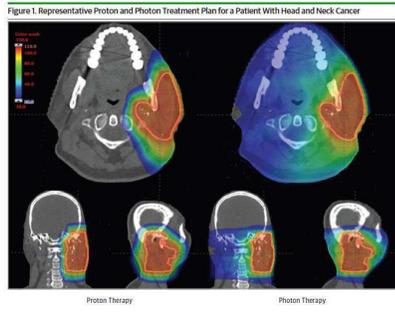
JAMA Oncol. doi:10.1001/jamaoncol.2019.4889
Published online December 26, 2019.

COSTICITY... the cost of toxicity... intensive chemoradiation

Comparative Effectiveness of Proton vs Photon Therapy as Part of Concurrent Chemoradiotherapy for Locally Advanced Cancer

Brian C. Baumann, MD; Nandita Mitra, PhD; Joanna G. Harton, MS; Ying Xiao, PhD; Andrzej P. Wojcieszynski, MD; Peter E. Gabriel, MD, MSE; Haoyu Zhong, MSc; Huaizhi Geng, PhD; Abigail Doucette, MPH; Jenny Wei, BS; Peter J. O'Dwyer, MD; Justin E. Bekelman, MD; James M. Metz, MD

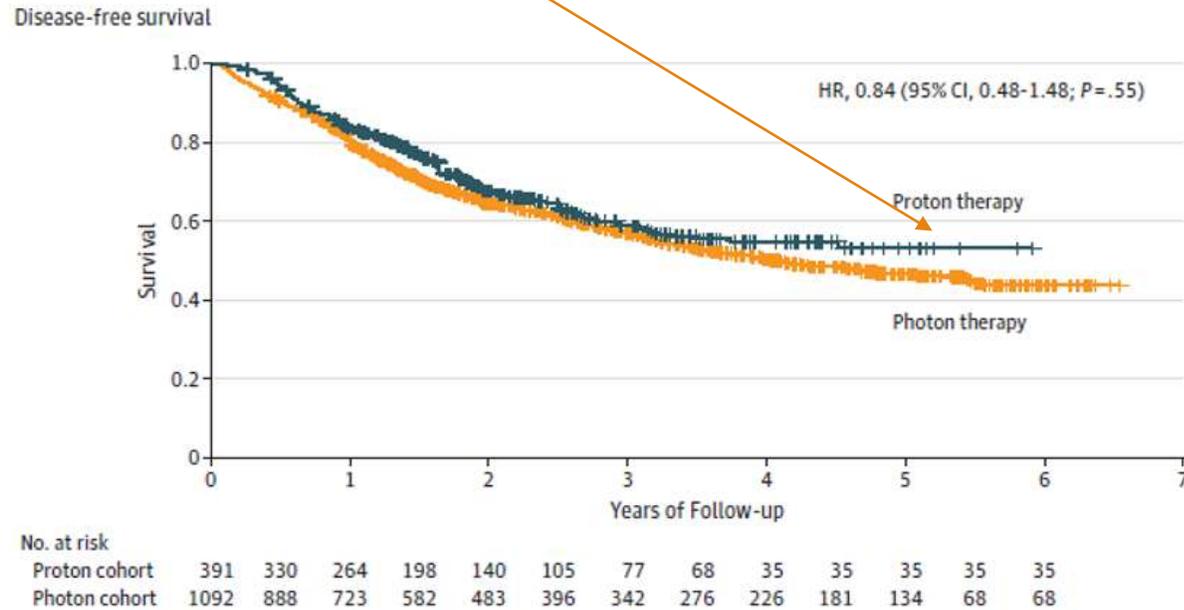
JAMA Oncol. doi:10.1001/jamaoncol.2019.4889
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Comparative Effectiveness of Proton vs Photon Therapy as Part of Concurrent Chemoradiotherapy for Locally Advanced Cancer

JAMA Oncol. doi:10.1001/jamaoncol.2019.4889
 Published online December 26, 2019.

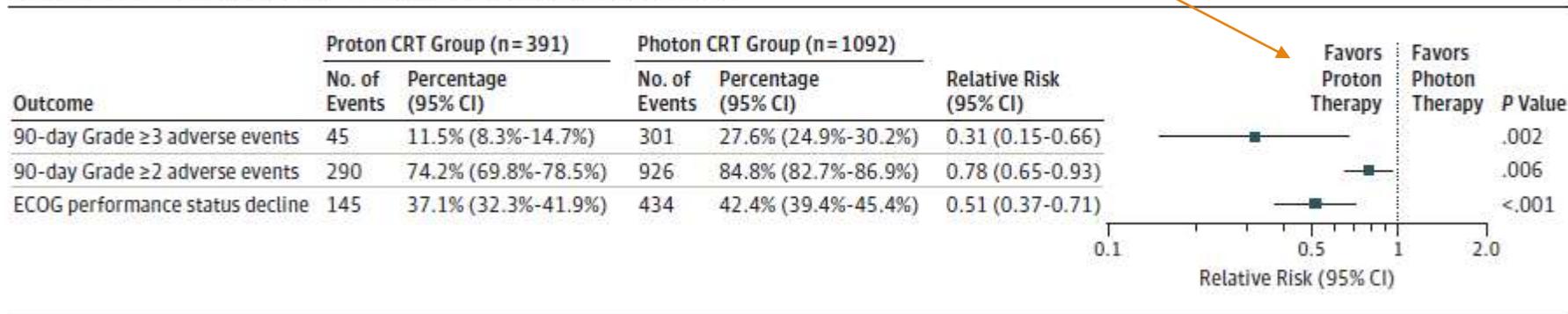
Brian C. Baumann, MD; Nandita Mitra, PhD; Joanna G. Harton, MS; Ying Xiao, PhD; Andrzej P. Wojcieszynski, MD; Peter E. Gabriel, MD, MSE; Haoyu Zhong, MSc; Huaizhi Geng, PhD; Abigail Doucette, MPH; Jenny Wei, BS; Peter J. O'Dwyer, MD; Justin E. Bekelman, MD; James M. Metz, MD

11 % vs 27 % grade 3-4 CRT toxicity

Research Original Investigation

Proton vs Photon Therapy as Part of Concurrent Chemoradiotherapy for Locally Advanced Cancer

Figure 3. Adverse Events and Decline in Eastern Cooperative Oncology Group (ECOG) Performance Status for Proton vs Photon Chemoradiotherapy (CRT) and Propensity Analysis Results

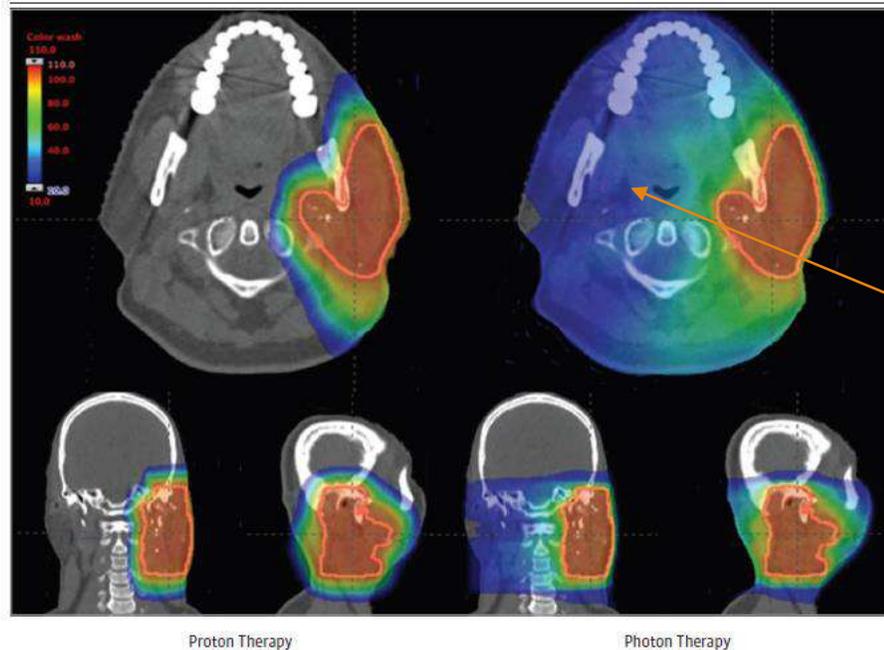


Ninety-day adverse events are measured using Common Terminology Criteria for Adverse Events, version 4 (CTCAEv4). Patients were identified with CTCAEv4 grades of at least 3 and at least 2. ECOG performance status scores range from 0 to 5, with higher scores indicating worse performance status.

Comparative Effectiveness of Proton vs Photon Therapy as Part of Concurrent Chemoradiotherapy for Locally Advanced Cancer

Brian C. Baumann, MD; Nandita Mitra, PhD; Joanna G. Harton, MS; Ying Xiao, PhD; Andrzej P. Wojcieszynski, MD; Peter E. Gabriel, MD, MSE; Haoyu Zhong, MSc; Huaizhi Geng, PhD; Abigail Doucette, MPH; Jenny Wei, BS; Peter J. O'Dwyer, MD; Justin E. Bekelman, MD; James M. Metz, MD

Figure 1. Representative Proton and Photon Treatment Plan for a Patient With Head and Neck Cancer



10 % vs 30 % grade 3-4 CRT toxicity

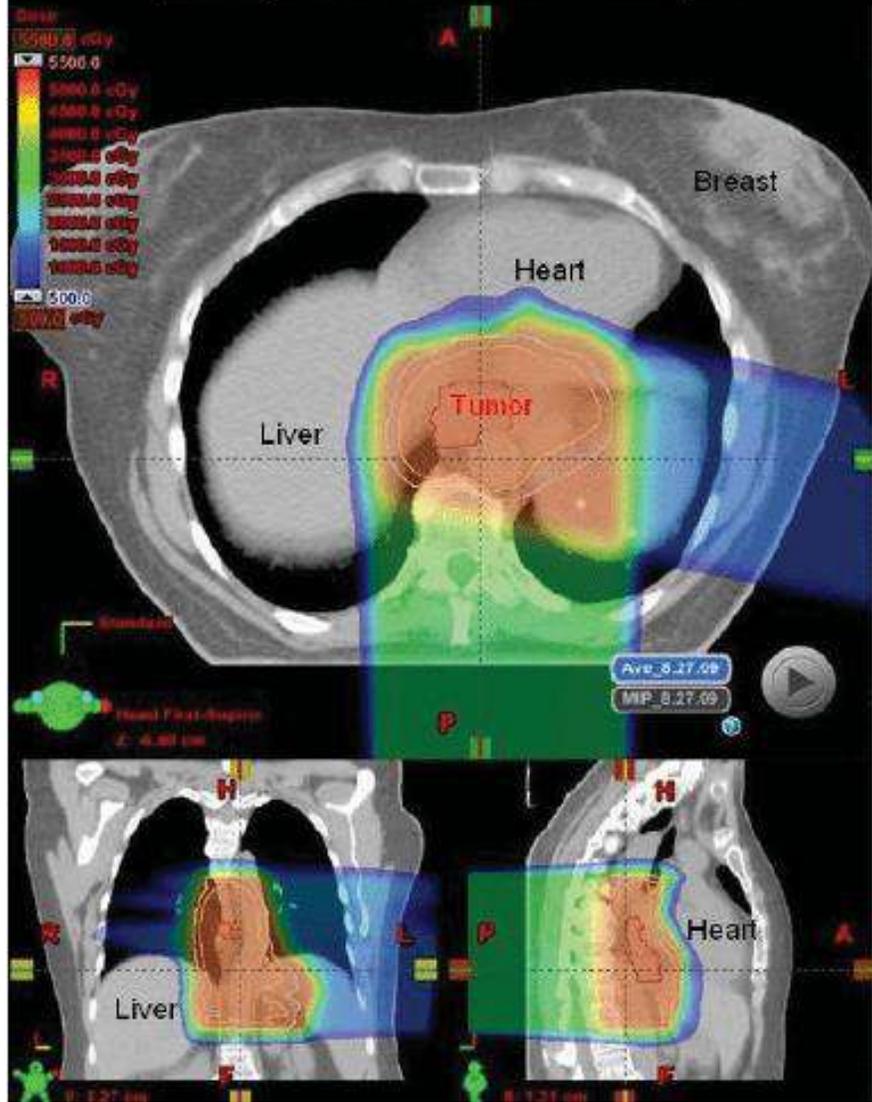
Why???

Radiation dose is represented as a color wash, with blue indicating the region receiving the lowest radiation dose and red indicating the region receiving the highest radiation dose.

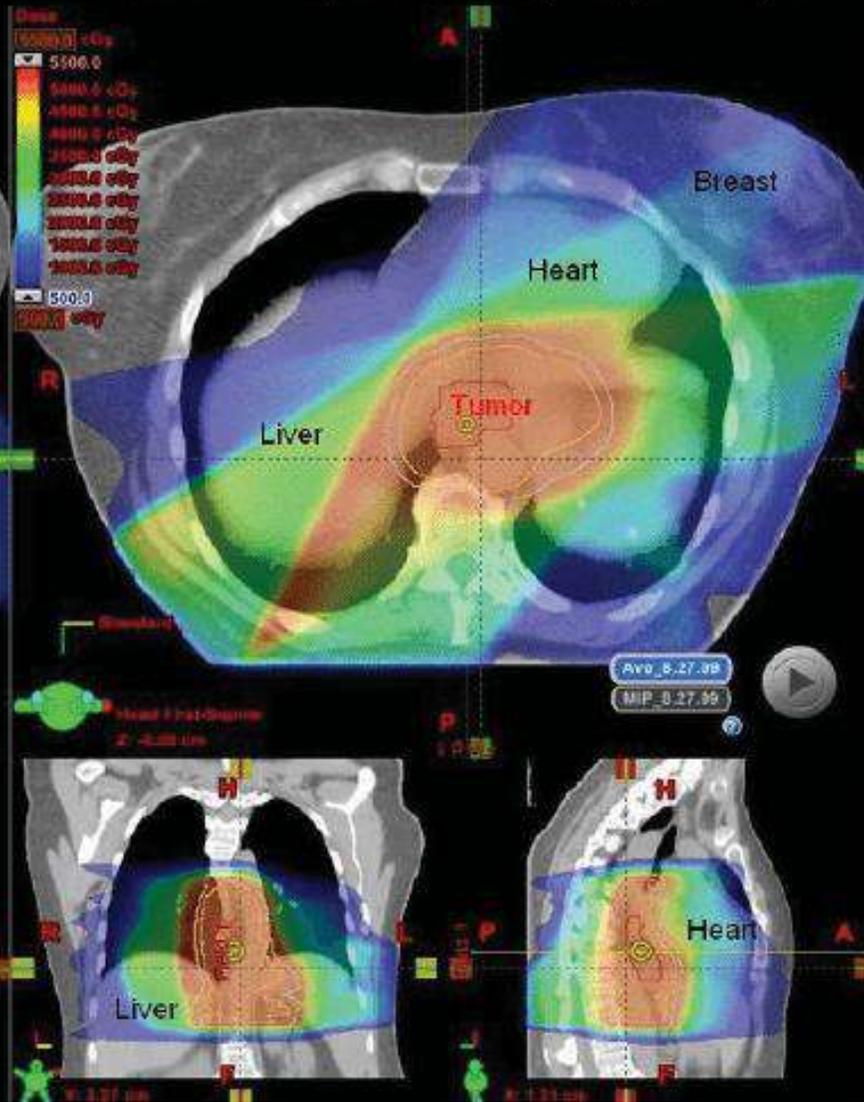
Health-Value: “*costicity*” + survival

A MAJOR CONTRIBUTION... AFFORDABLE CURE AND QUALITY OF LIFE

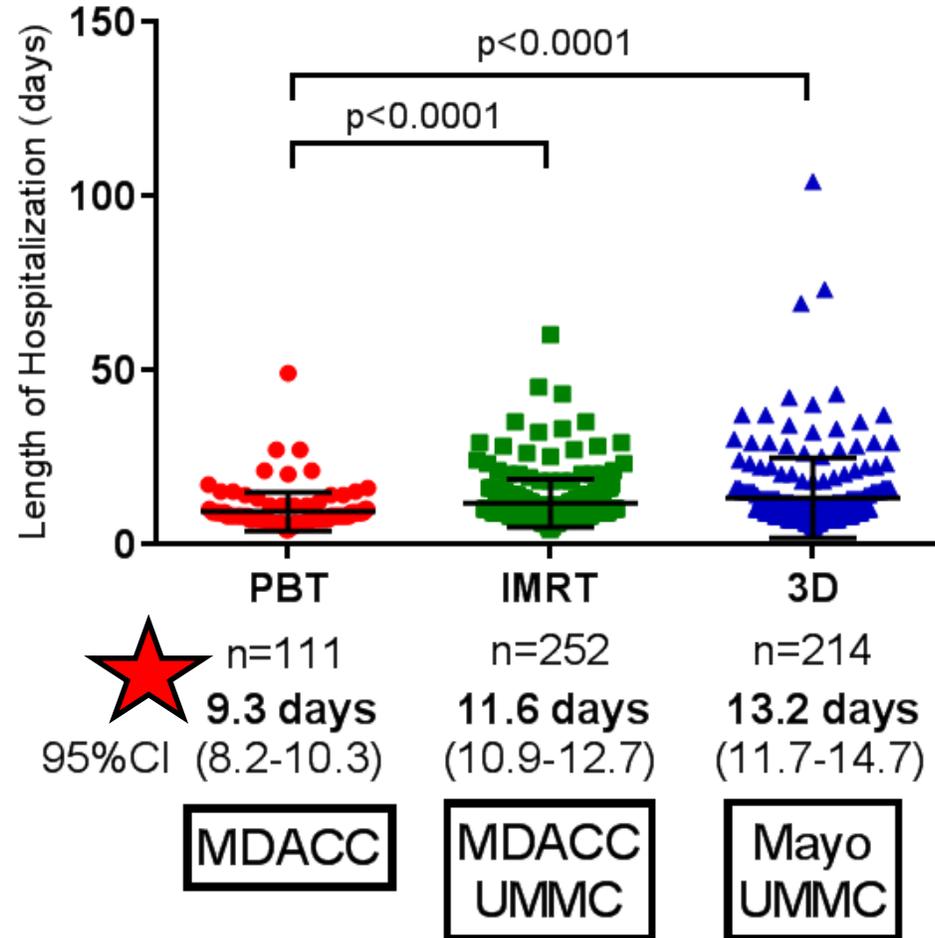
Proton Passive Scattered Technique



Photon Intensity Modulated (IMRT) Technique



Mean Length of Hospital Stay 2007-2013



Protons reduces hospital stay by > 2 days



“costicity”

JCO 38:1569, 2020

NCT01512589

Resctability
Histology
Induction QT

Randomized IIB 50.4 Gy

Protons

TTB
total toxicity burden
11 events
AEs + POCs

Total complications x 2 ; postoperative complications x 7

2012-2019
Early termination 67% accrual
61 / 46 (107)
44 mo MFT

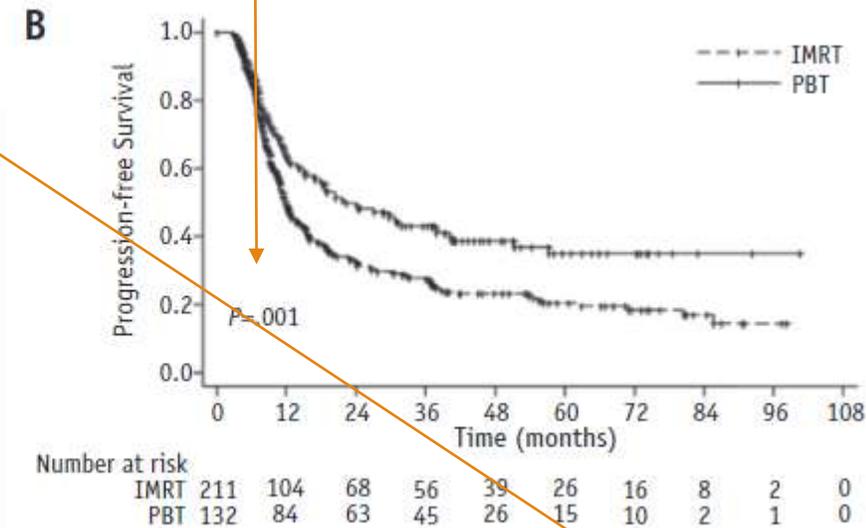
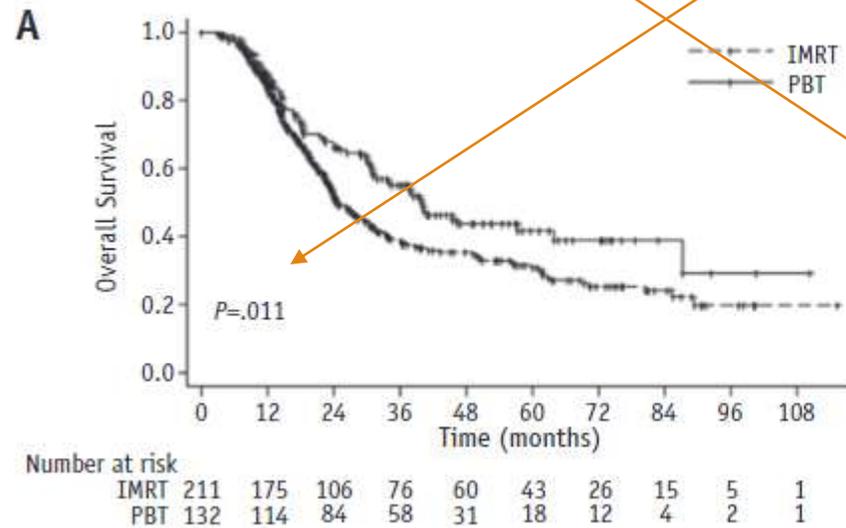
50% esophagectomy
80% passive scatering

TTB 26% vs 40%
2,3 times higher IMRT
POCs score 2% vs 19%
7,6 times higher IMRT
PFS 50% vs 51%
OS 44% vs 44%

Comparative Outcomes After Definitive Chemoradiotherapy Using Proton Beam Therapy Versus Intensity Modulated Radiation Therapy for Esophageal Cancer: A Retrospective, Single-Institutional Analysis

Mian Xi, MD,^{*,†} Cai Xu, MD,^{*,†} Zhongxing Liao, MD,^{*}

Benefit in cancer control and patient survival



protons vs photons: extreme difficult model!

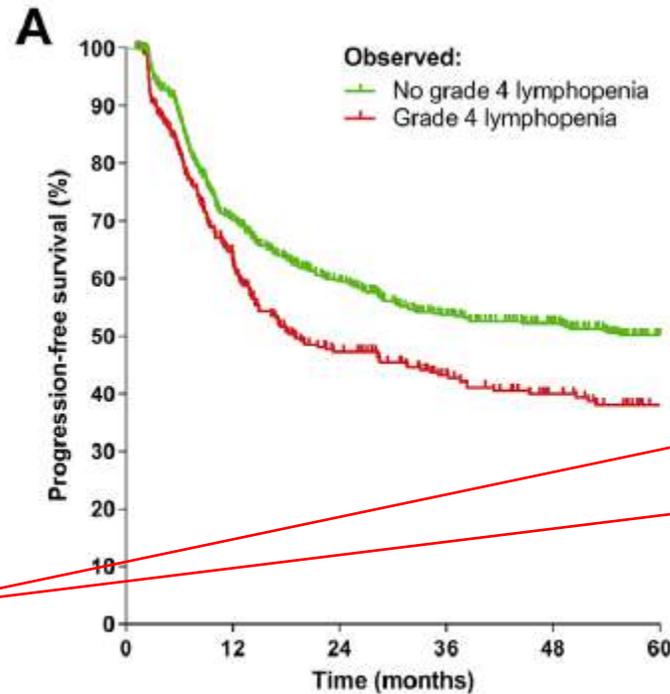
Prediction of Severe Lymphopenia During Chemoradiation Therapy for Esophageal Cancer: Development and Validation of a Pretreatment Nomogram

Peter S.N. van Rossum, MD, PhD,^{a,b} Wei Deng, MD,^a

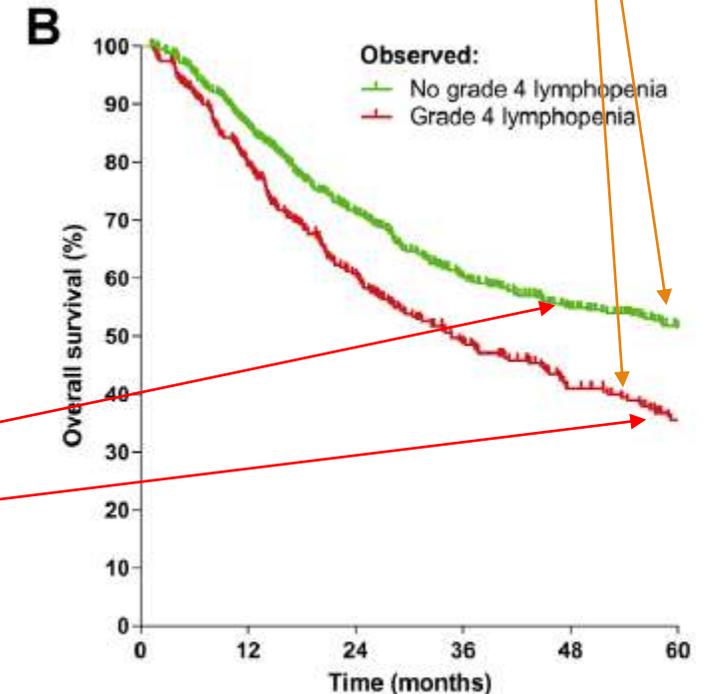
survival vs lymphopenia is... survival vs toxicity!

Practical Radiation Oncology (2020) 10, e16-e26

Lymphopenia	grade 4	no-G4
Proton therapy	65 (20.2)	232 (43.1)
IMRT	257 (79.8)	306 (56.9)



Number at risk:						
No G4L	538	341	259	204	163	111
G4L	322	183	116	86	64	47



Number at risk:						
No G4L	538	439	333	253	193	140
G4L	322	244	166	115	82	60

survival vs immune-competence!

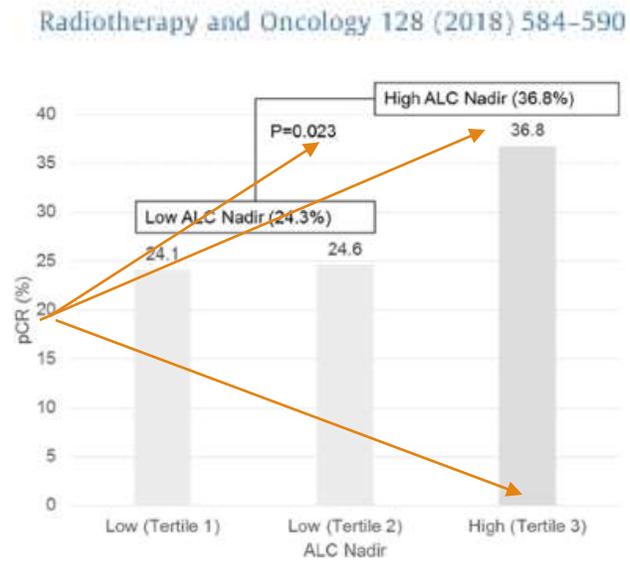


High lymphocyte count during neoadjuvant chemoradiotherapy is associated with improved pathologic complete response in esophageal cancer



Penny Fang^a, Wen Jiang^a, Rajayogesh Davuluri^c, Cai Xu^a, Sunil Krishnan^a, Radhe Mohan^b, Albert C. Koong^a, Charles C. Hsu^{c,*}, Steven H. Lin^{a,*}

^a Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center; ^b Radiation Physics, The University of Texas MD Anderson Cancer Center, Houston; and ^c Department of Radiation Oncology, The University of Arizona, Tucson, United States



Comparative Toxicities and Cost of Intensity-Modulated Radiotherapy, Proton Radiation, and Stereotactic Body Radiotherapy Among Younger Men With Prostate Cancer

[Hubert Y. Pan](#), [Jing Jiang](#), [Karen E. Hoffman](#), [Chad Tang](#), [Seungtaek L. Choi](#), [Quynh-Nhu Nguyen](#),

693 proton therapy patients matched to **3,465 IMRT**

Proton therapy patients group had:

lower risk of composite urinary toxicity (33% v 42% at 2 years; $P < .001$)

Erectile dysfunction (21% v 28% at 2 years; $P < .001$)

Risk of bowel toxicity (20% v 15% at 2 years; $P = .02$)

younger men with prostate cancer, **proton radiation** was associated with **significant reductions in urinary toxicity** but increased bowel toxicity

The REALITY, today:
recommendations...

ASTRO, ESTRO, SEOR...Minister of Health...

ASTRO updates insurance coverage recommendations for proton therapy

ARLINGTON, Va., July 12, 2017



11 clinical scenarios
5 new additions 2017

Group 1 indications, or the clinical scenarios that frequently support the use of proton therapy based on medical necessity and published clinical data, were updated with five additions and one modification. Group 1 indications, with additions marked by asterisks, include:

- Malignant and benign primary central nervous system (CNS) tumors*
- Advanced (e.g., T4) and/or unresectable head and neck cancers*
- Cancers of the paranasal sinuses and other accessory sinuses*
- Nonmetastatic retroperitoneal sarcomas*
- Reirradiation cases where cumulative critical structure dose would exceed tolerance dose*
- Hepatocellular cancer (no longer required to be treated in a hypofractionated regimen*)
- Ocular tumors, including intraocular melanomas
- Tumors that approach or are located at the base of skull, including but not limited to chordoma and chondrosarcomas
- Primary or metastatic tumors of the spine where the spinal cord tolerance may be exceeded with conventional treatment or where the spinal cord has previously been irradiated
- Primary or benign solid tumors in children treated with curative intent and occasional palliative treatment of childhood tumors when one of the criteria noted above apply
- Patients with genetic syndromes making total volume of radiation minimization crucial, such as but not limited to NF-1 patients and retinoblastoma patients

ASTRO updates insurance coverage recommendations for proton therapy

ARLINGTON, Va., July 12, 2017



The policy recommends coverage for Group 2 indications if the patient is enrolled in either an Institutional Research Board (IRB)-approved study or in a multi-institutional registry adhering to Medicare requirements for **Coverage with Evidence Development (CED)**. These indications also represent the disease sites for which evidence is accumulating and may support future Group 1 coverage. While the policy specifies that no indications are deemed inappropriate for CED, it also specifies several systems for Group 2 indications:

6 clinical scenarios CED

- Non-T4 and resectable head and neck cancers (previously all head and neck malignancies*)
- Nonmetastatic prostate cancer (previously grouped with genitourinary carcinomas*)
- Breast cancer*
- Thoracic malignancies, including nonmetastatic primary lung and esophageal cancers
- Abdominal malignancies, including nonmetastatic primary pancreatic, biliary and adrenal cancers
- Pelvic malignancies, including nonmetastatic rectal, anal, bladder and cervical cancers

JASTRO 2017

125 proton references
 35 sites / histologies / stages
58 % hypofractionated schemes
 45 % pediatric cancer

Disease	Radiotherapy	Ref
Urological tumors		
Prostate cancer	74-78GyE/37-39 fractions (standard fractionation)	60-83
Stage T1c-T4N0M0	69-70GyE/28-30 fractions (reduced fractionation) 60-66GyE/20-22 fractions (reduced fractionation)	
Bladder cancer	Whole bladder irradiation 40-41.4Gy/20-23 fractions then add local irradiation: Close to the GI tract: 19.8-25.2GyE/10-14 fractions (Total dose: 59.8-66.6GyE/30-37 fractions) Not close to the GI tract: 33-36.6GyE/10-11 fractions (Total dose: 73-78GyE/30-34 fractions)	86-89
Stage II-III		
Renal cancer	Ventral tumor: 76-79.2GyE/20-24 fractions 77GyE/35 fractions Posterior tumor: 66GyE/10 fractions	90-92
Stage T1-4N0M0, inoperable case		
Testicular tumor	Stage I: 19.8-25.2GyE/10-14 fractions Stage IIA (lymph node diameter < 2 cm; N1): 28.8-30.6GyE/15-17 fractions Stage IIB (2 cm ≤ lymph node diameter < 5 cm; N2): 36GyE/18-20 fractions	91-95
Irradiation to the para-aortic or affected common iliac artery area		
Gynecological tumors		
Locally advanced cervical cancer or endometrial cancer	59.4GyE/33 fractions (lymph node metastasis) 50.4GyE/28 fractions (elective regional lymph node)	96-97
Bone and soft tissue tumors		
Chordoma, Chondrosarcoma	Adjacent to critical organs: 63-70.4GyE/26-39 fractions Not adjacent to critical organs: 70.4GyE/16 fractions (4 times/week)	98-106
Osteosarcoma	Adjacent to critical organs: 70.2-70.4GyE/26-32 fractions Not adjacent to critical organs: 70.4GyE/16 fractions (4 times/week)	99, 104, 106, 107
Other rare bone and soft tissue tumors	Adjacent to critical organs: 65-80GyE/26-32 fractions (combination with X-ray therapy is acceptable) Not adjacent to critical organs: 70.4GyE/16 fractions (4 times/week)	99, 104, 106, 109
Metastatic tumors		
Metastatic lung tumor	Peripheral: 64GyE/8 fractions Central: 72.6GyE/22 fractions	110-111
Oligometastatic (< 3 lesions)		
Metastatic liver tumor	Peripheral: 64GyE/8 fractions Central: 72.6GyE/22 fractions	65, 112-114
Oligometastatic (< 3 lesions)		
Metastatic lymph node	Recurrent, refractory: 64GyE/8 fractions 72.6GyE/22 fractions	115
Oligometastatic	Adjacent to critical organs: 50-70GyE/25-35 fractions	

English Translation of JASTRO treatment policy of proton beam therapy. Ver 1.0 at 2016 May (https://www.jastro.or.jp/particle_beam/detail.php?cid=00002)
 This treatment policy can be changed at any time without notice.

Disease	Radiotherapy	Ref
Brain and spinal cord tumors		
Glioma	Low grade: 54GyE/30 fractions High grade: 60GyE/30 fractions	1-4
Glioblastoma	60GyE/30 fractions (a part may be combined with X-ray therapy) 66.4GyE/36 fractions (2 fractionally, skewer region) 50.4GyE/28 fractions	5-7
Germin cell tumors	Local total dose 50.4-61.2GyE/28-34 fractions (Determine field of radiation from tumor site with or without spread) Combination with whole ventricular irradiation, whole brain irradiation, or craniospinal irradiation 23.4GyE/13 fractions	8-11
Meningioma	Benign (Difficult to perform surgical resection): 54GyE/30 fractions Atypical, Anaplastic: 66.6GyE/28 fractions	12-16
Pituitary adenomas	54GyE/30 fractions	17-18
Unresectable or postoperative remnants of recurring tumors		
Craniospharyngioma	54GyE/30 fractions	19-22
Unresectable or postoperative remnants of recurring tumors		
Medulloblastoma	50-59.4GyE/25-33 fractions (craniospinal irradiation and local radiation)	23-25
Ependymoma	A) Low grade: 50.4GyE/28 fractions Anaplastic: 60GyE/30 fractions Children (3 years or older): Low grade: 50.4GyE/28 fractions Anaplastic: 59.4GyE/33 fractions Children (under 3 years of age): Low grade: 50.4GyE/28 fractions Anaplastic: 54GyE/30 fractions	26-30
Atypical teratoid/rhabdoid tumor	Children (3 years or older): 54GyE/30 fractions (Craniospinal irradiation or local radiation: 36GyE/20 fractions + local irradiation 18GyE/10 fractions) Children (under 3 years of age): 54GyE/28 fractions (Craniospinal irradiation or local radiation: 23.4GyE/13 fractions + local irradiation 27GyE/15 fractions)	25, 31
Primitive neuroectodermal tumor	Local total dose: 55.8GyE/31 fractions (Craniospinal irradiation or local radiation: 36GyE/20 fractions + local irradiation 19.8GyE/11 fractions) 45GyE for spinal cord metastasis 50.4GyE for canda equine	25-25, 32
Other brain tumors	Decide on treatment plans, the irradiation methods, doses, and number of fractions through case evaluation at the cancer committee with several specialists (evaluation based on age, tumor pathology, and location)	3, 26, 33

Disease	Radiotherapy	Ref
Head and Neck tumors		
Squamous cell carcinoma of the nasal cavity and paranasal sinus	Radical irradiation: 70-74GyE/35-37 fractions (standard fractionation) ¹ 70.2GyE/26 fractions (reduced fractionation) ¹ In cases where low doses irradiated to organs at risk cannot be ensured during X-ray radiotherapy Postoperative irradiation: 66GyE/33 fractions ⁴	24, 29
Squamous cell carcinoma of the head and neck	Radical irradiation: 70-74GyE/35-37 fractions ⁴ In cases where low doses irradiated to organs at risk cannot be ensured during X-ray radiotherapy Postoperative irradiation: 66GyE/33 fractions ⁴ Re-irradiation: 60GyE/30 fractions	40-41
Malignant melanoma of the head and neck	Radical irradiation: 60-60.8GyE/15-16 fractions ³ Unresectable or incomplete resection Postoperative irradiation: 40GyE/4 fractions ³	34, 42-43
Olfactory neuroblastoma	Radical irradiation: 65-70.2GyE/26-32 fractions Unresectable or incomplete resection Postoperative irradiation: 66-70GyE/33-35 fractions	34, 35, 30, 14, 45
Adenoid cystic carcinoma	Radical irradiation: 65-70.2GyE/26 fractions Unresectable or incomplete resection 70.4-74.8GyE/32-34 fractions Postoperative irradiation: 66-70GyE/33-35 fractions	34, 45, 46
Advanced malignant salivary gland tumor	Radical irradiation: 65-70.2GyE/26 fractions Lymph node metastasis, history of postoperative Postoperative irradiation: X-ray therapy with proton beam boost to 66-70GyE/33-35 fractions	43-46
Non-squamous cell carcinoma of the head and neck	Radical irradiation: 65-70.2GyE/26 fractions 70.4-74.8GyE/32-34 fractions Postoperative irradiation: 66-70GyE/33-35 fractions	35-36, 45

Disease	Radiotherapy	Ref
Lung and mediastinal tumors		
Stage I and cT2b-3N0 lung cancers	Peripheral cT1-T2a/b: 66-70GyE/10 fractions ² Peripheral cT2b-T3N0: 66-70GyE/10 fractions ² Unresectable or inoperable cases 80GyE/20 fractions ² Central cT1a-T3N0: 80GyE/25 fractions ² 72.6GyE/22 fractions ²	47-50
Stage II and III non-small cell lung cancer	60-66Gy/30-33 fractions 70-74Gy/25-37 fractions	51-53
Mediastinal tumor	60-66Gy/30-33 fractions 70-74Gy/25-37 fractions	29, 34, 36
Gastrointestinal (GI) tumors		
Stage I to III primary esophagus cancer	60-70GyE/30-35 fractions (combined with photon therapy of 30-40Gy/20 fractions with elective field irradiation)	57-61
Locally recurrent rectal cancer	Close to the GI tract: 60-70GyE/30-35 fractions Unresectable tumor Not close to the GI tract: 72-75GyE/18-25 fractions	63-64
Hepatobiliary tumors		
Hepatocellular cancer	Peripheral type: 66GyE/10 fractions Porta hepatica type: 72.6-76GyE/20-22 fractions Adjacent to the GI tract: 74-76GyE/37-38 fractions	65-68
Intrahepatic cholangiocarcinoma	Porta hepatica type: 72.6-76GyE/20-22 fractions Unresectable or recurrent tumors Adjacent to the digestive tract: 74-76GyE/37-38 fractions	69-71
Porta hepatic and extrahepatic cholangiocarcinoma	Porta hepatica area: 70.2-72.6GyE/22-26 fractions Unresectable or recurrent tumors Adjacent to the GI tract: 50-60GyE/25-30 fractions	70, 72-73
Locally advanced pancreatic cancer	50-56GyE/25-28 fractions (standard fractionation) Unresectable or recurrent tumors 59.4GyE/33 fractions (Careful prospective multi-institutional study is warranted) 60-67.5GyE/20-25 fraction with simultaneous boosting (Careful prospective multi-institutional study is warranted)	76-79

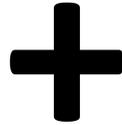
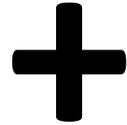
Proton therapy services @ CUN 2022



Madrid, 18 de Noviembre de 2020

ASTRO updates insurance coverage recommendations for proton therapy

ARLINGTON, Va., July 12, 2017



CARTERA DE SERVICIOS PROTONTERAPIA CUN MADRID *

- Tumores malignos y benignos pediátricos y en adolescentes.
- Tumores del sistema nervioso central (SNC) primarios malignos y benignos.
- Cáncer de cabeza y cuello avanzado y/o irresecables.
- Cáncer de senos paranasales.
- Cánceres de glándulas salivares.
- Tumores malignos cutáneos extensos.
- Tumores orbitarios.
- Tumores de base del cráneo.
- Cordoma y condrosarcoma.
- Tumores de esqueleto axial y paraespinales.
- Cáncer de mama: post-mastectomía y reconstrucción inmediata.
- Cáncer de mama en pacientes con patología severa cardiopulmonar.
- Cáncer de pulmón avanzado de localización central o con extensión pared torácica.
- Tumores mediastínicos: linfoma, timoma y tumores germinales.
- Mesotelioma maligno.
- Cáncer de esófago.
- Cáncer Hepatocelular y Coliángiocarcinoma.
- Cáncer de páncreas.
- Sarcomas óseos.
- Sarcomas de partes blandas retroperitoneales, centrales y de extremidades.
- Cáncer de próstata en pacientes frágiles.
- Cáncer pélvico avanzado con previsión de tolerancia desfavorable.
- Reirradiaciones.
- Síndromes genéticos con susceptibilidad a la radiación.
- Enfermedad oligometastática y oligorecurrente.

11 clinical scenarios
5 new additions 2017

Resolución de 30 de noviembre de 2020, de la Dirección General de Cartera Común de Servicios del Sistema Nacional de Salud y Farmacia, por la que se hacen públicos los acuerdos de la Comisión de prestaciones, aseguramiento y financiación de 14 de julio de 2020 en relación a la técnica de protonterapia en la cartera común de servicios del Sistema Nacional de Salud.

*Recomendaciones validadas por sociedades científicas:
<https://www.astro.org/News-and-Publications/News-and-Media/Case/News-Bulletin/2017-ASTRO-Updates-insurance-coverage-recommendations-for-proton-therapy>
<https://www.es.es/areas-clinicas/recomendaciones-de-la-seor-para-la-protonterapia-es-espana-2/>

The REALITY, today:

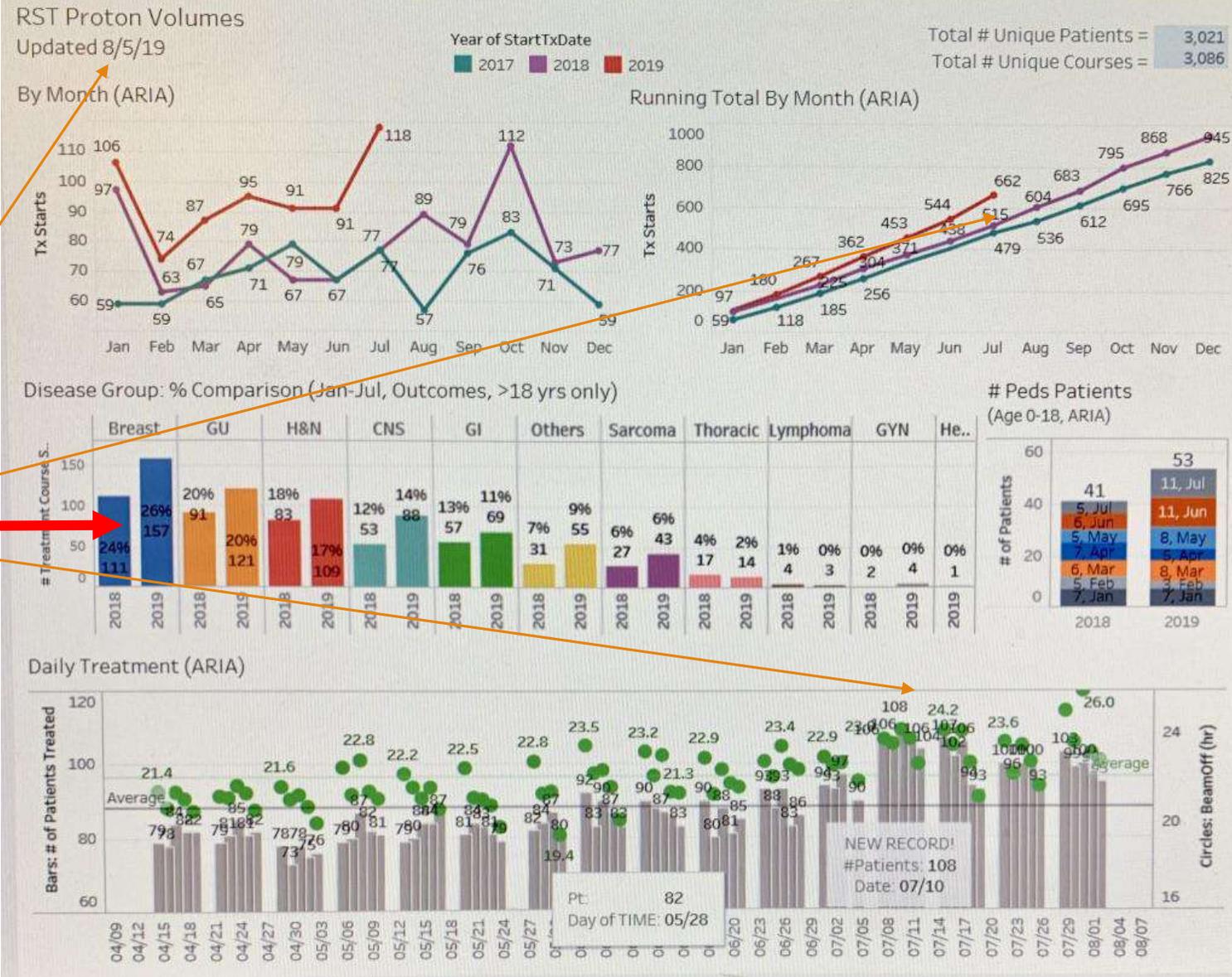
Mayo Clinic daily practice...



Un día cualquiera del verano 2019
...en Mayo Clinic Rochester...

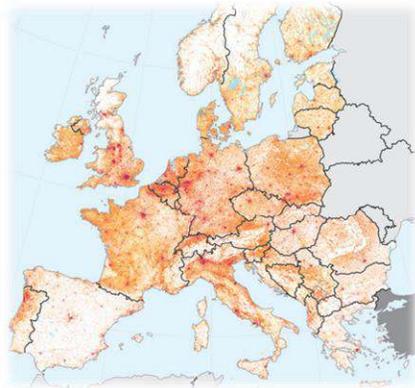
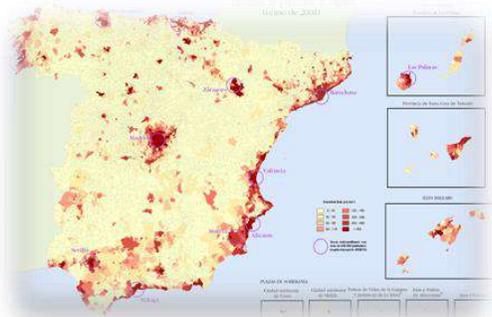
Protonterapia con sincrotrón 4 salas
100 pacientes al día
1000 pacientes al año
25% pediátricos 10% nonagenarios

benefit = dosimetric = clinical

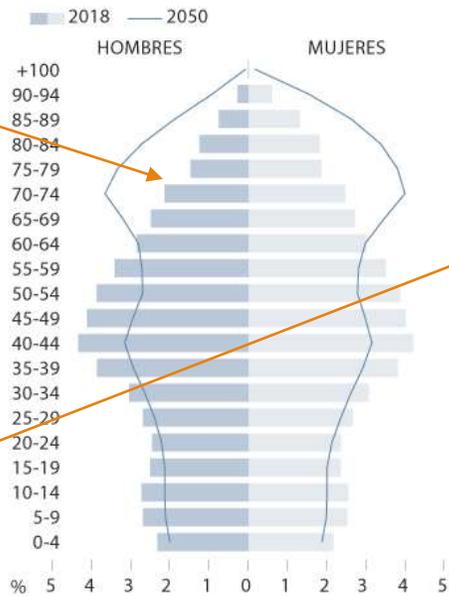


Proton therapy and social change 2022 - 2032

Demographic change and health-value system: impact in proton therapy

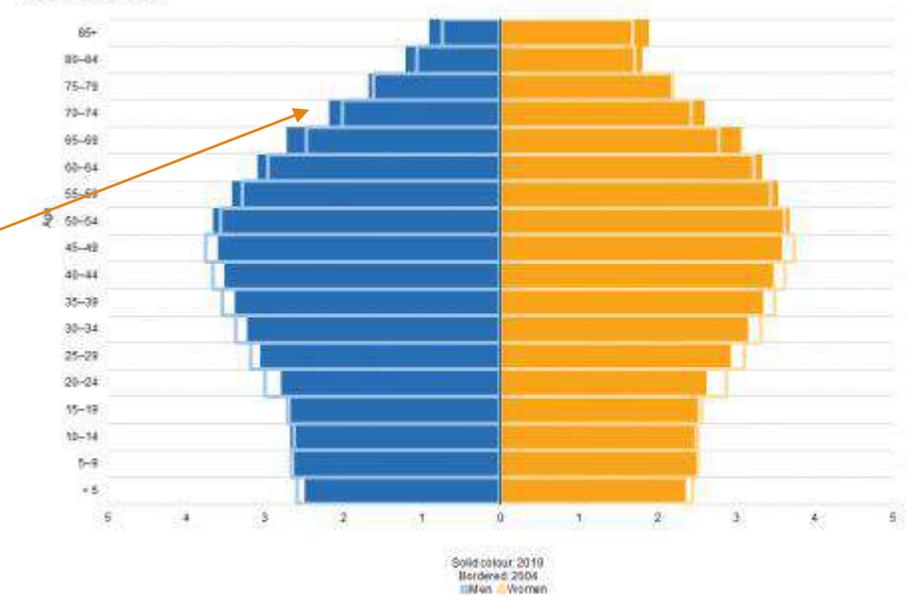


PIRÁMIDE POBLACIONAL EN ESPAÑA



FUENTE: INE
J. AGUIRRE | EL MUNDO GRÁFICOS

Population pyramids, EU-27, 2004 and 2019
(% of the total population)



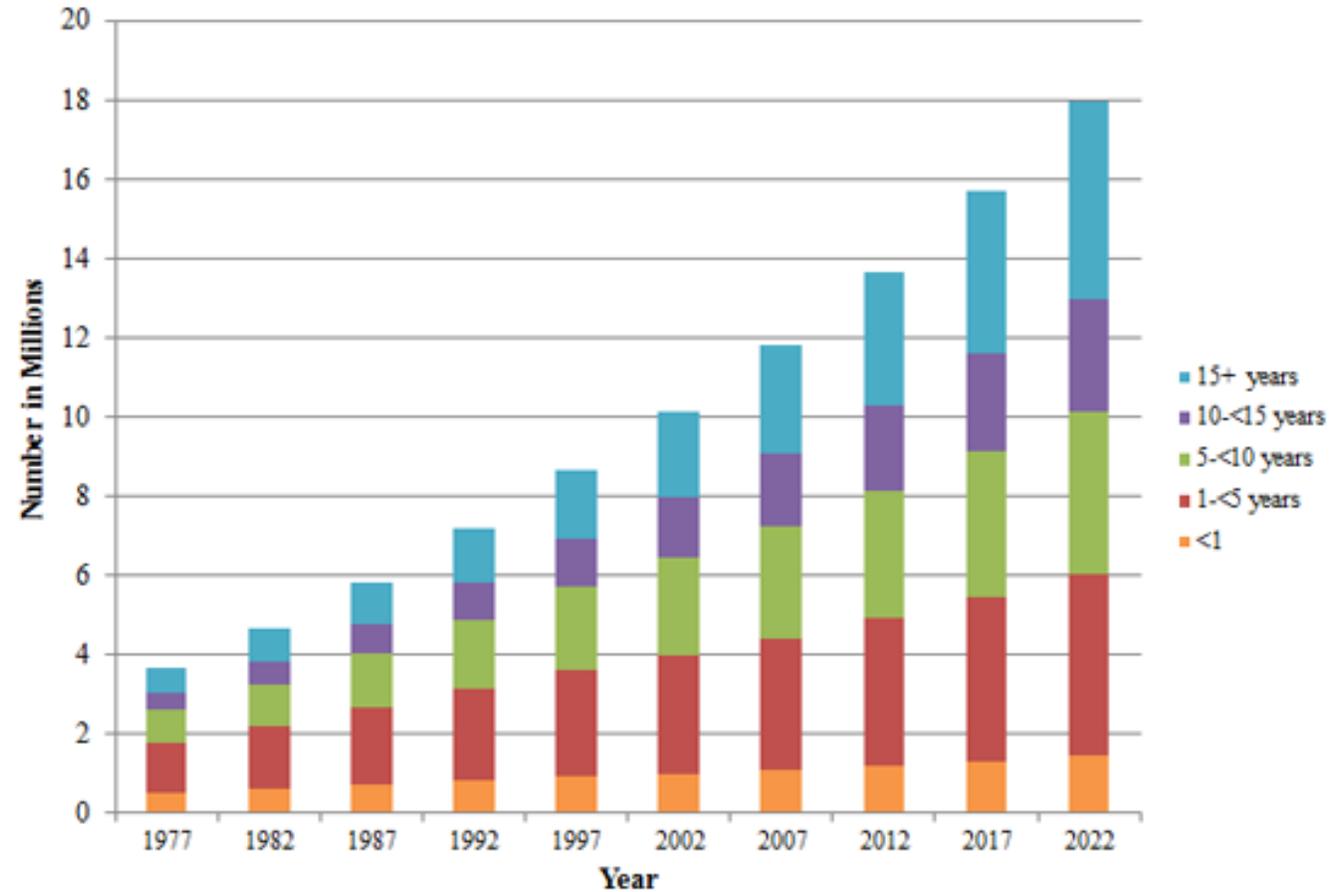
Note: 2019 provisional
Source: Eurostat (online data code: demo_pygroup)

eurostat

Normal tissues that are not *that* normal: comorbidities...

Survivors ... unexpected!...toxic?...social dependence?

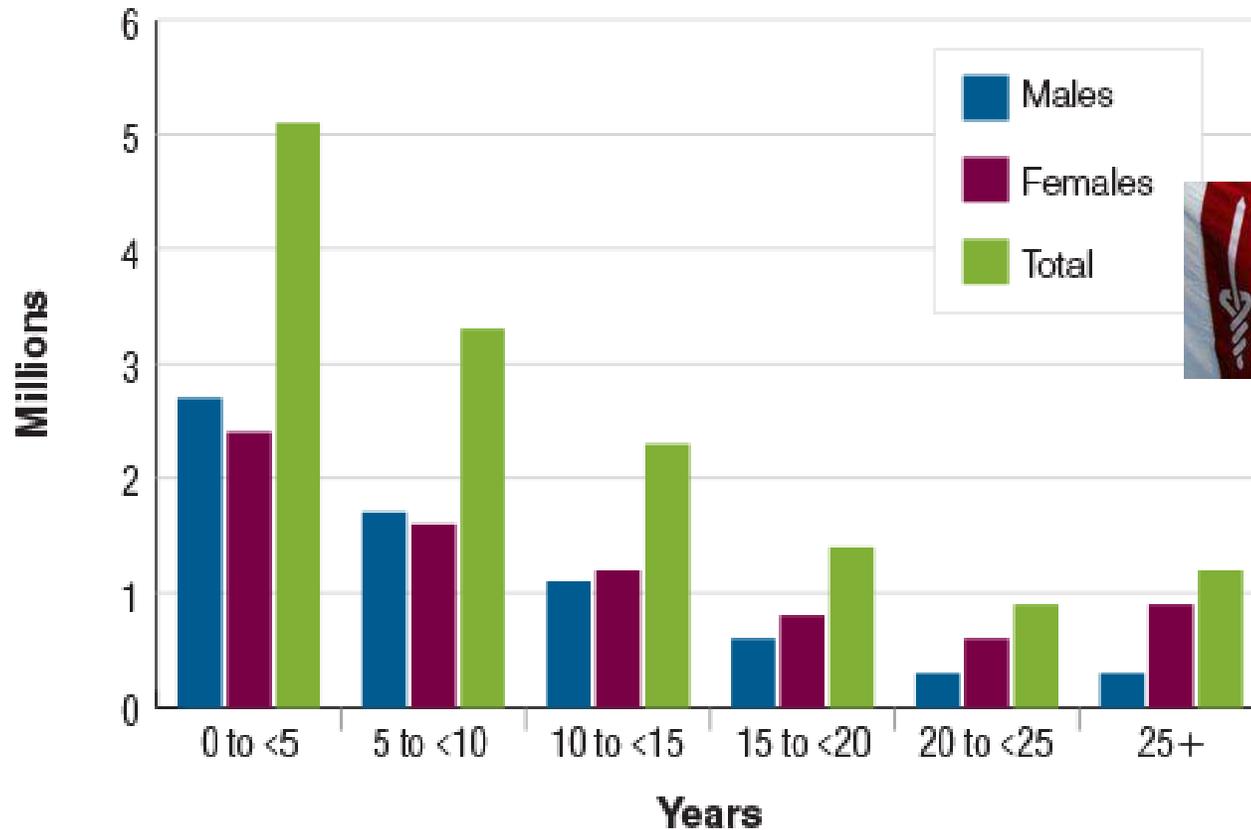
Estimated and projected number cancer survivors in the United States from 1977-2022 by years since diagnosis



de Moor JS, Mariotto AB, Parry C, Alfano CM, Padgett L, Kent EE, Forsythe L, Scoppa S, Hachey M, and Rowland JH. Cancer Survivors in the United States: Prevalence across the Survivorship Trajectory and Implications for Care. *Cancer Epidemiol Biomarkers Prev.* 2013 Apr;22(4):561-70. doi: 10.1158/1055-9965.EPI-12-1356. Epub 2013 Mar 27.

“Survivors” : male vs female

Estimated Number of US Cancer Survivors by Sex and Years Since Diagnosis (as of January 1, 2014)



The REALITY, today:

Opportunities in clinical practice...

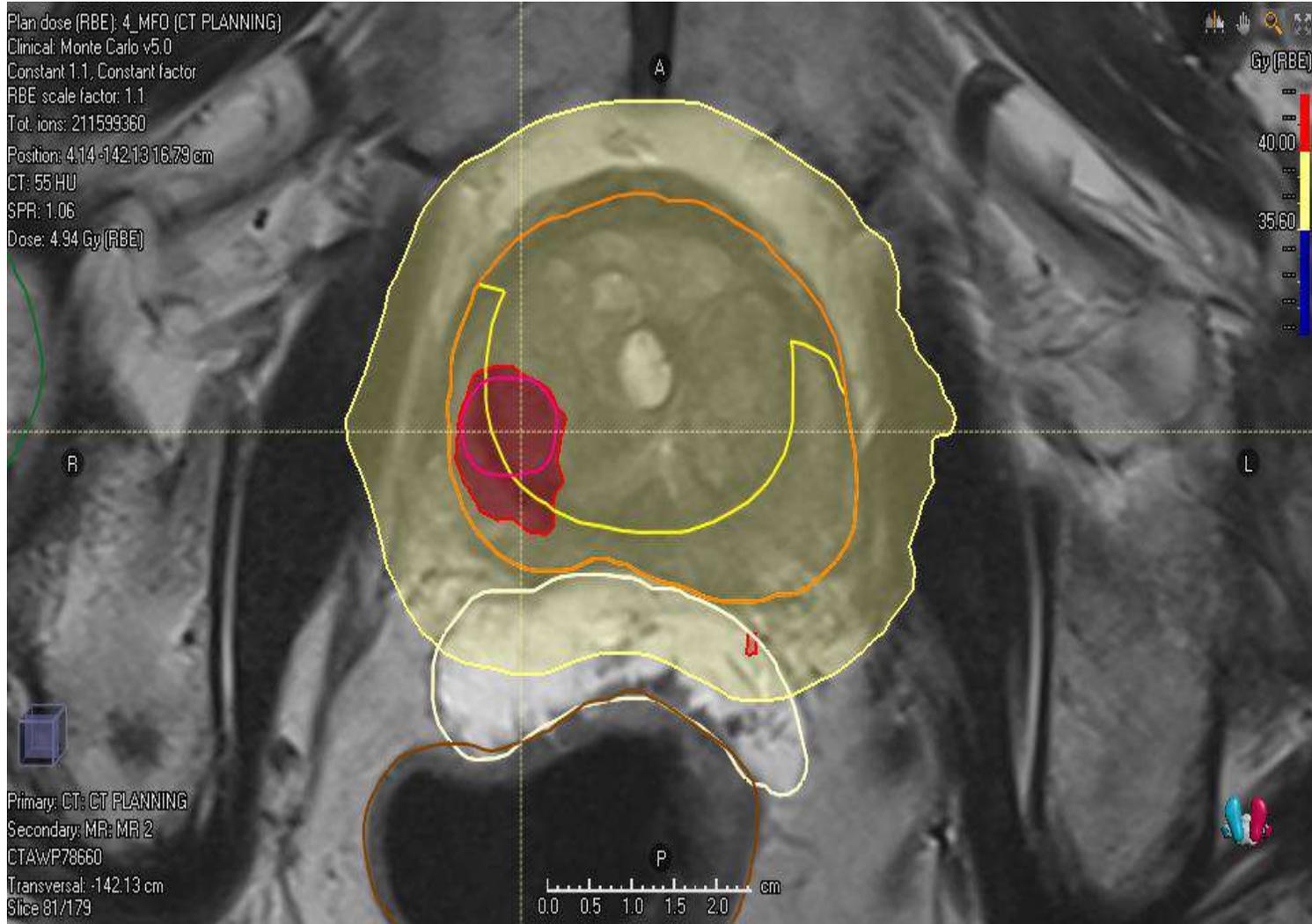
PT in context: interdisciplinary oncology; opportunities 2022



Cancer Center
Universidad
de Navarra

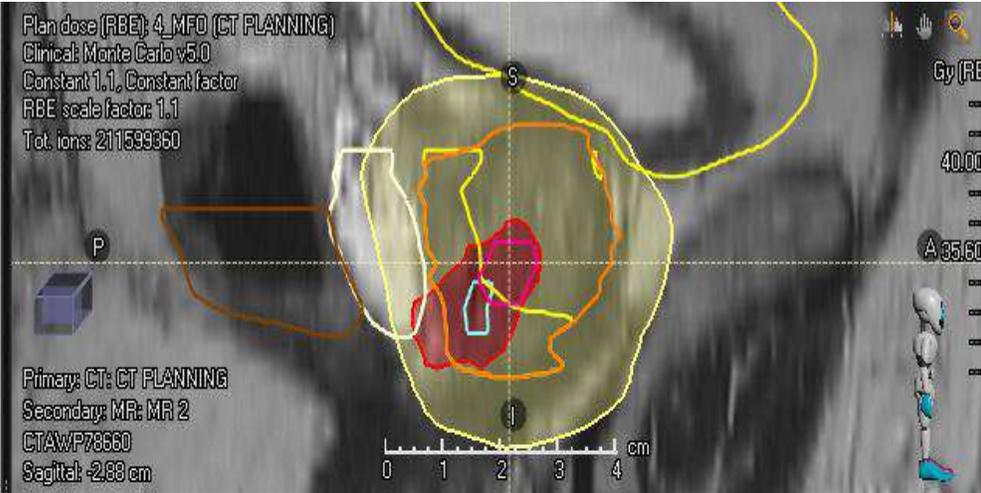
*Caring · Researching
Innovating · Educating*

Plan dose (RBE): 4_MFD (CT PLANNING)
Clinical: Monte Carlo v5.0
Constant 1.1, Constant factor
RBE scale factor: 1.1
Tot. ions: 211599360
Position: 4.14 -142.13 16.79 cm
CT: 55 HU
SPR: 1.06
Dose: 4.94 Gy (RBE)



Primary: CT: CT PLANNING
Secondary: MR: MR 2
CTAW/P78660
Transversal: -142.13 cm
Slice 81/179

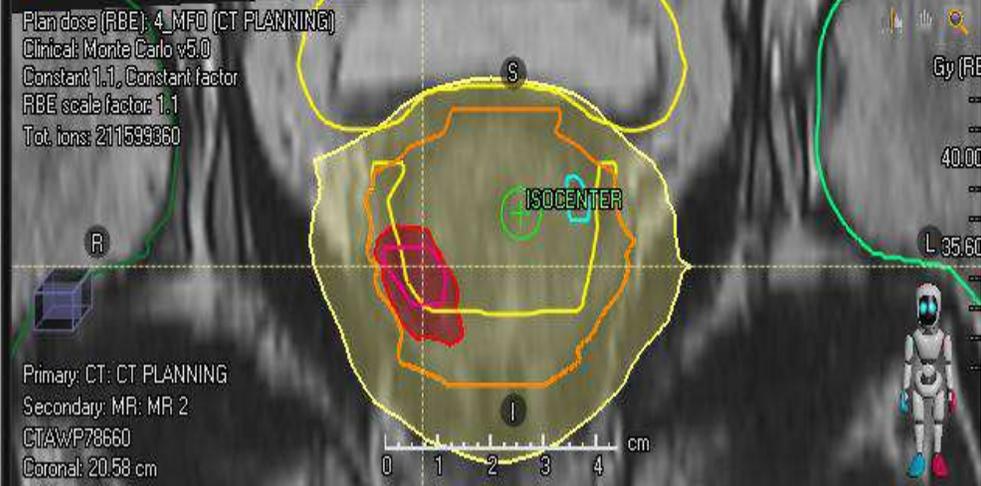
Plan dose (RBE): 4_MFD (CT PLANNING)
Clinical: Monte Carlo v5.0
Constant 1.1, Constant factor
RBE scale factor: 1.1
Tot. ions: 211599360



Primary: CT: CT PLANNING
Secondary: MR: MR 2
CTAW/P78660
Sagittal: -2.68 cm

2D 3D

Plan dose (RBE): 4_MFD (CT PLANNING)
Clinical: Monte Carlo v5.0
Constant 1.1, Constant factor
RBE scale factor: 1.1
Tot. ions: 211599360



Primary: CT: CT PLANNING
Secondary: MR: MR 2
CTAW/P78660
Coronal: 20.58 cm

CTV Prostate & Intraboastr CTV HR

Radiotherapy Combination Opportunities Leveraging Immunity for the Next Oncology Practice

Fernanda G. Herrera, MD^{1,2}; Jean Bourhis, MD, PhD³; George Coukos, MD, PhD^{4,5}

¹Radiation Oncologist, University Hospital of Lausanne (CHUV), Lausanne, Switzerland; ²Instructor, University Hospital of Lausanne (CHUV), Lausanne, Switzerland; ³Professor, Chief of Radiation Oncology Service, University Hospital of Lausanne (CHUV), Lausanne, Switzerland; ⁴Professor, Director, Department of Oncology, University Hospital of Lausanne (CHUV), Lausanne, Switzerland; ⁵Director, Ludwig Institute for Cancer Research, University of Lausanne Branch, Lausanne, Switzerland

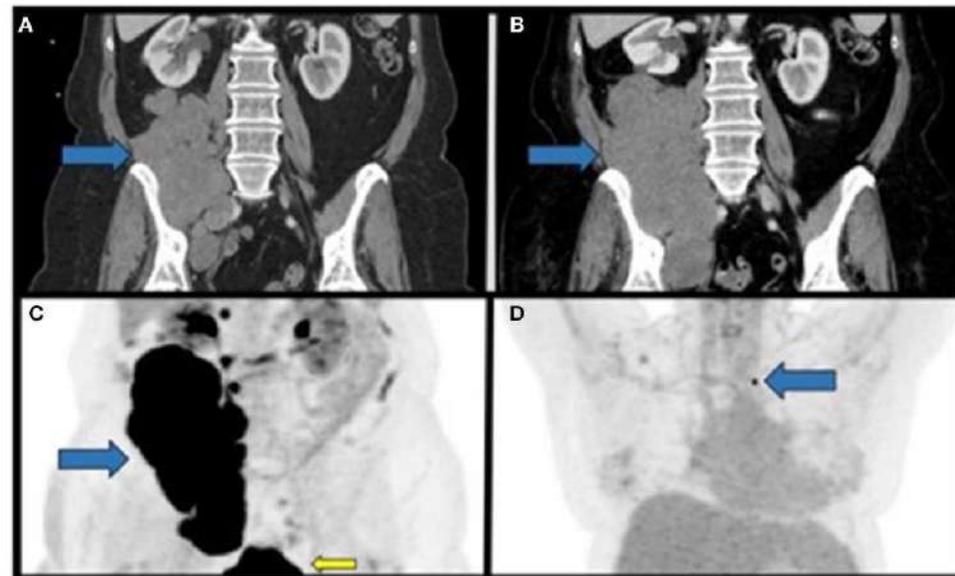
ABSTRACT: Approximately one-half of patients with newly diagnosed cancer and many patients with persistent or recurrent tumors receive radiotherapy (RT), with the explicit goal of eliminating tumors through direct killing. The current RT dose and schedule regimens have been empirically developed. Although early clinical studies revealed that RT could provoke important responses not only at the site of treatment but also on remote, nonirradiated tumor deposits—the so-called “abscopal effect”—the underlying mechanisms were poorly understood and were not therapeutically exploited. Recent work has elucidated the immune mechanisms underlying these effects and has paved the way for developing combinations of RT with immune therapy. In the wake of recent therapeutic breakthroughs in the field of immunotherapy, rational combinations of immunotherapy with RT could profoundly change the stan-

Abscopal Effect Following Proton Beam Radiotherapy in a Patient With Inoperable Metastatic Retroperitoneal Sarcoma

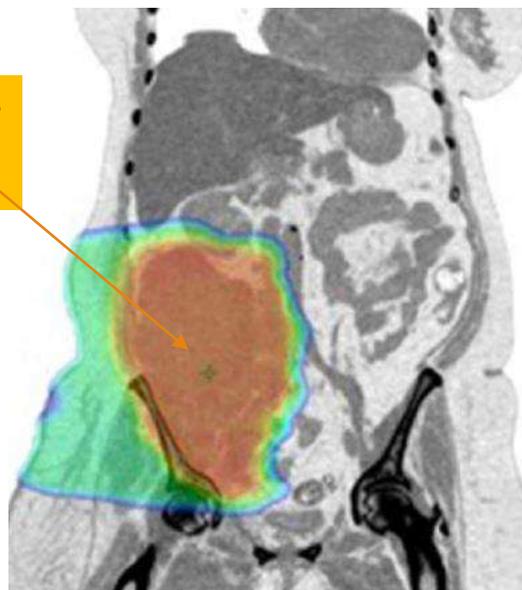
Randall J. Brennehan¹, Nima Sharifai², Benjamin Fischer-Valuck³, Comron Hassanzadeh¹, Jeffrey Guzelian⁴, John S. A. Chrisinger², Jeff M. Michalski¹, Peter Oppelt⁵ and Brian C. Baumann^{1*}

¹ Department of Radiation Oncology, Washington University School of Medicine, St. Louis, MO, United States, ² Department

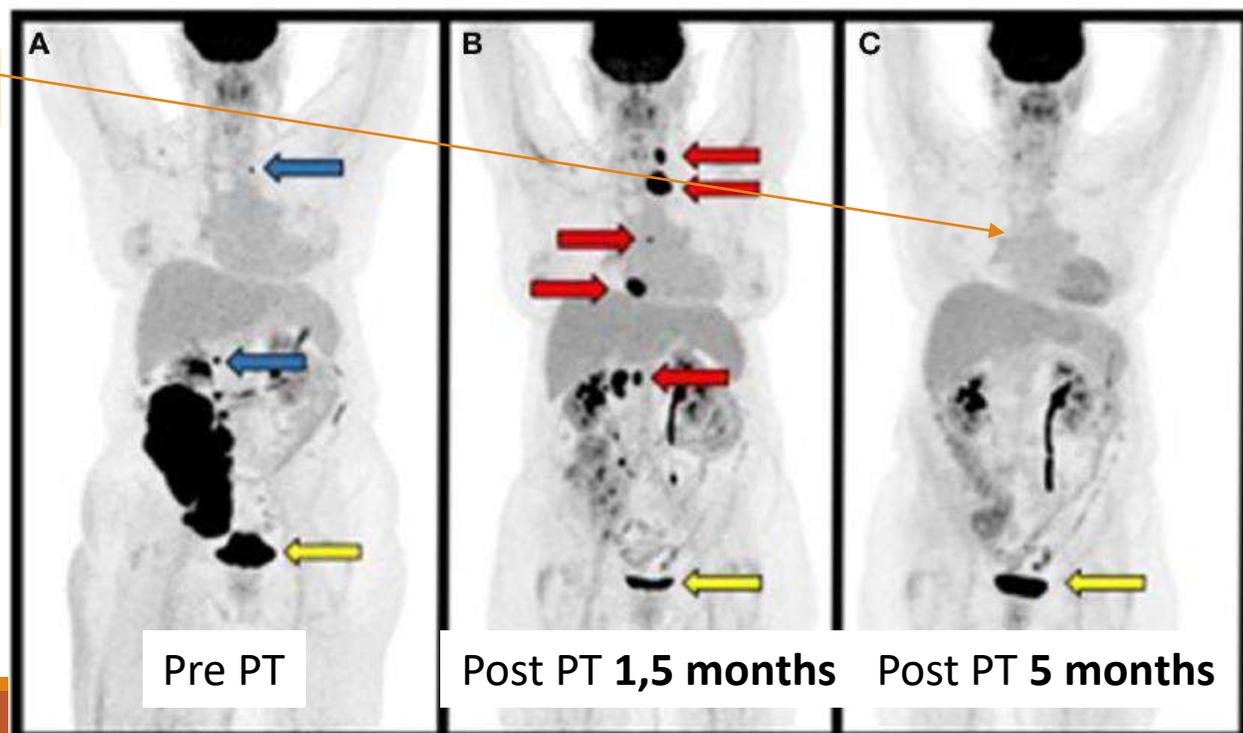
CASE REPORT
published: 26 September 2019
doi: 10.3389/fonc.2019.00922



50 CGyE/25 fr protons



18 months NED



unclassified round cell sarcoma with INI1 loss

PD-L1 expression $\geq 1\%$
TILs (CD4 10% positive, CD8 2% positive; 5:1ratio)

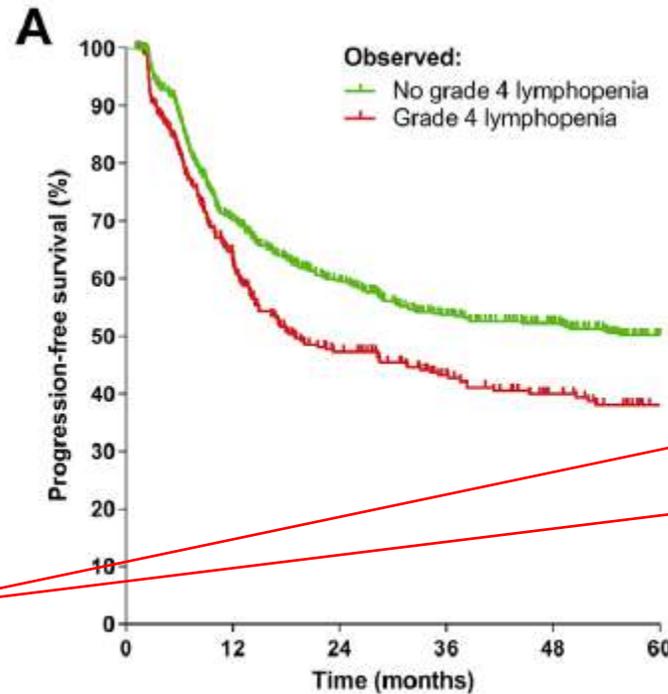
Prediction of Severe Lymphopenia During Chemoradiation Therapy for Esophageal Cancer: Development and Validation of a Pretreatment Nomogram

Peter S.N. van Rossum, MD, PhD,^{a,b} Wei Deng, MD,^a

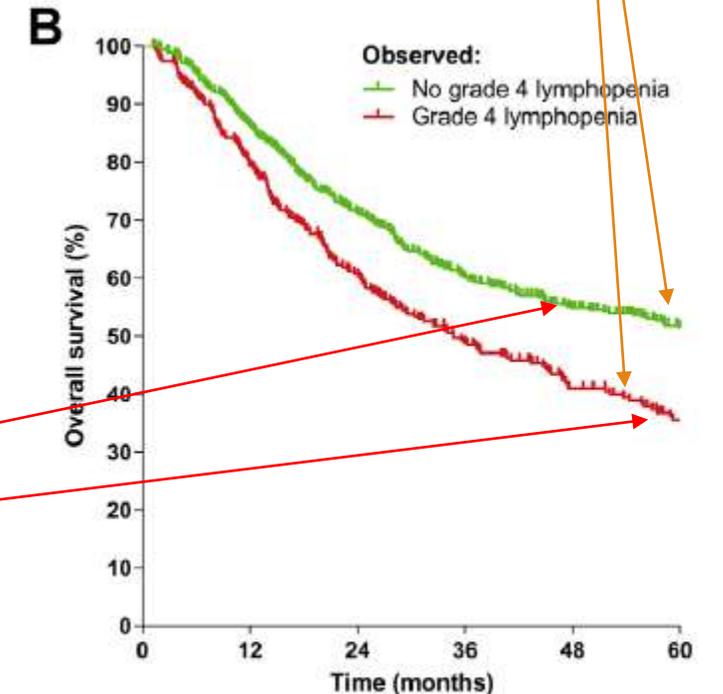
survival vs lymphopenia is... survival vs toxicity!

Practical Radiation Oncology (2020) 10, e16-e26

Lymphopenia	grade 4	no-G4
Proton therapy	65 (20.2)	232 (43.1)
IMRT	257 (79.8)	306 (56.9)



Number at risk:						
No G4L	538	341	259	204	163	111
G4L	322	183	116	86	64	47



Number at risk:						
No G4L	538	439	333	253	193	140
G4L	322	244	166	115	82	60

survival vs immune-competence!



Proton therapy today in Europe (2021)

clinical practice in adults...questionnaire of activity



Current practice in proton therapy delivery in adult cancer patients across Europe

Makbule Tambas^{a,*}, Hans Paul van der Laan^a, Roel J.H.M. Steenbakkers^a, Jerome Doyen^b, Beate Timmermann^{c,d}, Ester Orlandi^e, Morten Hoyer^f, Karin Haustermans^g, Petra Georg^h, Neil G Burnetⁱ, Vincent Gregoire^j, Valentin Calugaru^k, Esther G.C. Troost^{l,m,n,o,p,q,r}, Frank Hejblum^s, Felipe A. Calvo^t, Joachim Widder^u, Fabian Eberlein^v, Marco van Vulpen^w, Dhillipa Maingon^x

Radiotherapy and Oncology 167 (2022) 7–13

Dosimetric benefit
=
Clinical benefit

Centres	Gantry (n)	Treatment start	Number of patients treated in 2020										N of tumor sites treated in that centre
			CNS	HNC	Prostate	Breast	Lung	GI	Lymphoma	GYN	Total (n)	Total (%)	
Centre_1	3	2012	110	50	500	150	30	50	60		950	22%	7
Centre_2	2	2018	100	120		60	80	50	10		420	10%	6
Centre_3	4	2013	308	50	30			11	15		414	10%	5
Centre_4	2	2014	300	10							310	7%	2
Centre_5	4	2011	170	90				2			262	6%	3
Centre_6	1	2019	41	15		40	90	23	5		214	5%	6
Centre_7	2	2018	72	30		86	10		2		200	5%	5
Centre_8	4	2015	153	6	13			13	10	2	197	5%	6
Centre_9	1	2014	70	10	80		10	20	5		195	5%	6
Centre_10	2	2015	115	38		2			39		194	5%	4
Centre_11	3	2019	69	61		39		3			172	4%	4
Centre_12	2(3)*	2016	60	80	10			10		2	162	4%	5
Centre_13	3	1984-2018	90	32					15		137	3%	3
Centre_14	2	2011, 2016	88	40							128	3%	2
Centre_15	1	2020	40	15	5	4	5	16	3	9	97	2%	8
Centre_16	3	2018	79								79	2%	1
Centre_17	1	1991, 2016	60								60	1%	1
Centre_18	1	2020	20	2							22	1%	2
Centre_19	1	2018	20								20	0%	1
Total (n)	43		1965	649	638	381	225	198	164	13	4233		
Total (%)			46%	15%	15%	9%	5%	5%	4%	0%		100%	
% of centres treating that tumor site			100%	84%	32%	37%	32%	53%	53%	16%			

ACTIVIDAD DE LA Unidad de Protonterapia

Pacientes

365 **267** adultos y **98** niños
(desde 14 meses hasta los 87 años)



TRATAMIENTOS
FINALIZADOS:
317

TRATAMIENTOS
EN CURSO:
27
21 en planificación

18 países de 4
continentes

Tumores



23 tipos de tumores
diferentes:

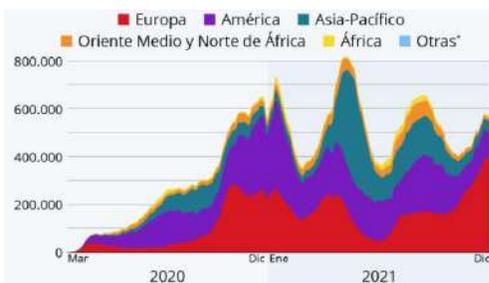
- | | | |
|-------------------|-----------------|---------------------------|
| Base de cráneo | Hepatocarcinoma | Próstata |
| Condrosarcoma | Hipófisis | Pulmón |
| Cordomas | Mama | Rabdomiosarcoma |
| Craneofaringiomas | Meduloblastomas | Recto |
| Ependimoma | Nasofaríngeos | Reirradiaciones |
| Esófago | Oligometástasis | Sarcoma cerebral |
| Ginecológicos | Órbita | Sarcoma de partes blandas |
| Gliomas | Para-espinales | |

La técnica

65.233 movimientos
del gantry

31.579 disparos

98,0% disponibilidad
de uso de haz



* Incluye los casos notificados en tránsito internacional.
Fuente: OMS

Original Article

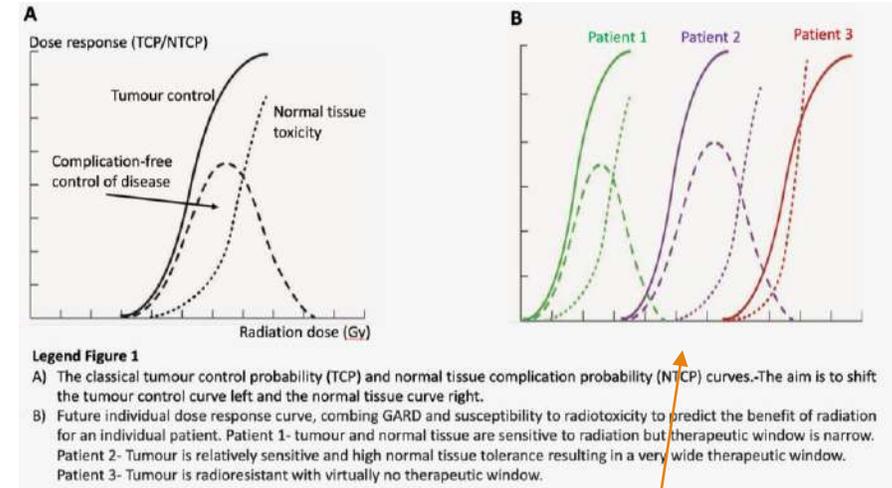
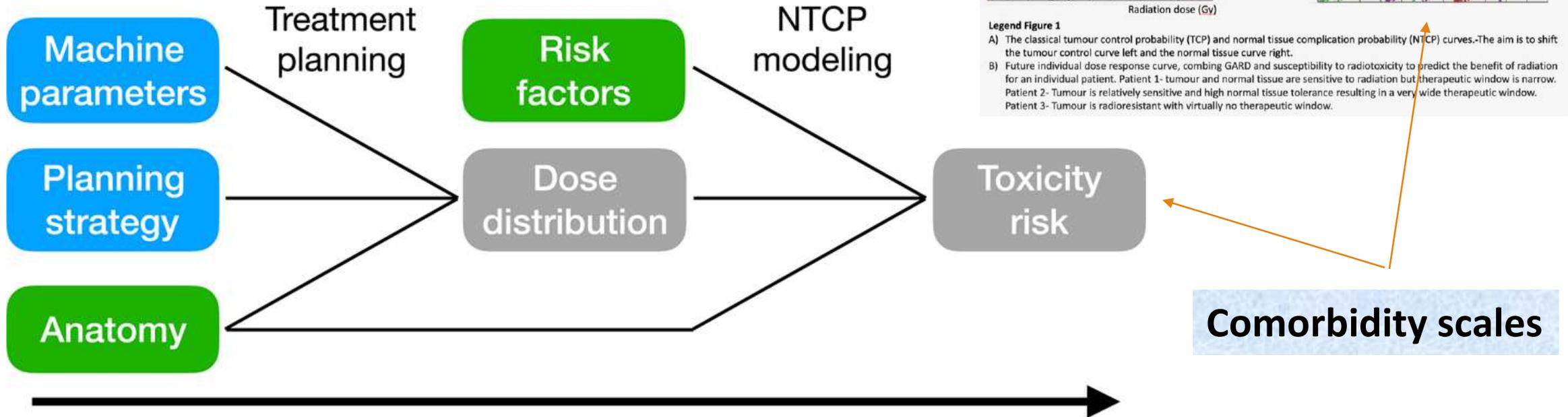
Perspectives on the model-based approach to proton therapy trials: A retrospective study of a lung cancer randomized trial



Aimee L. McNamara ^{a,*}, David C. Hall ^{a,1}, Nadya Shusharina ^a, Amy Liu ^b, Xiong Wei ^b, Ali Ajdari ^a, Radhe Mohan ^b, Zhongxing Liao ^b, Harald Paganetti ^a

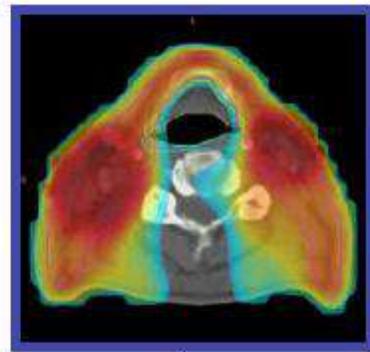
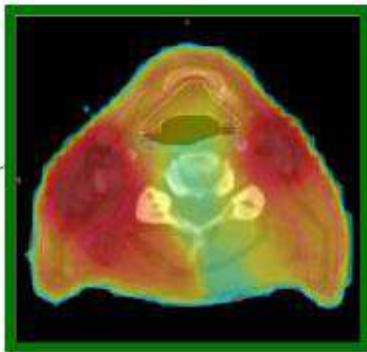
^aDepartment of Radiation Oncology, Massachusetts General Hospital & Harvard Medical School, Boston; and ^bUniversity of Texas MD Anderson Cancer Center, Houston, USA

$$\Delta NTCP = NTCP_{Photons} - NTCP_{Protons}$$



Models for individual risk estimations:

IMRT



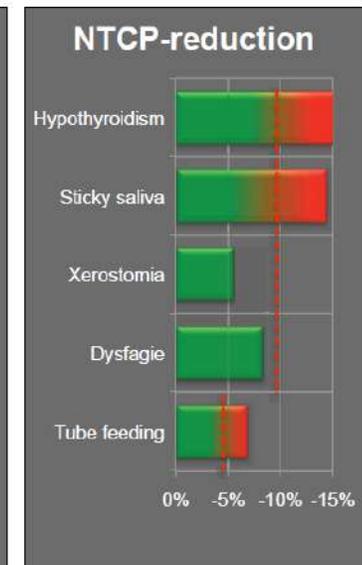
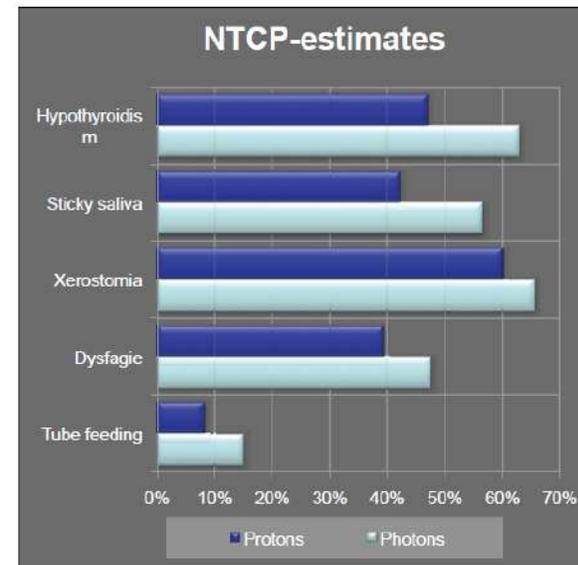
IMPT



university of
 groningen

Δ NTCP selection

Comprehensive Individual TOxicity Risk profiles
(CITOR-profile)



work in progress

RADIATION ONCOLOGY—ORIGINAL ARTICLE

Comparative proton versus photon treatment planning for the Medicare Medical Treatment Overseas Program: The Royal Adelaide Hospital experience

Yvonne Hu,^{1,*}  Raymond Dalfsen,¹ Scott N Penfold,^{1,2} Peter Gorayski,¹ Hui Chin Tee,¹ Michael Penniment^{1,3} and Hien Le^{1,4}

1 Department of Radiation Oncology, Royal Adelaide Hospital, Adelaide, South Australia, Australia

2 Department of Physics, University of Adelaide, Adelaide, South Australia, Australia

3 School of Medicine, University of Adelaide, Adelaide, South Australia, Australia

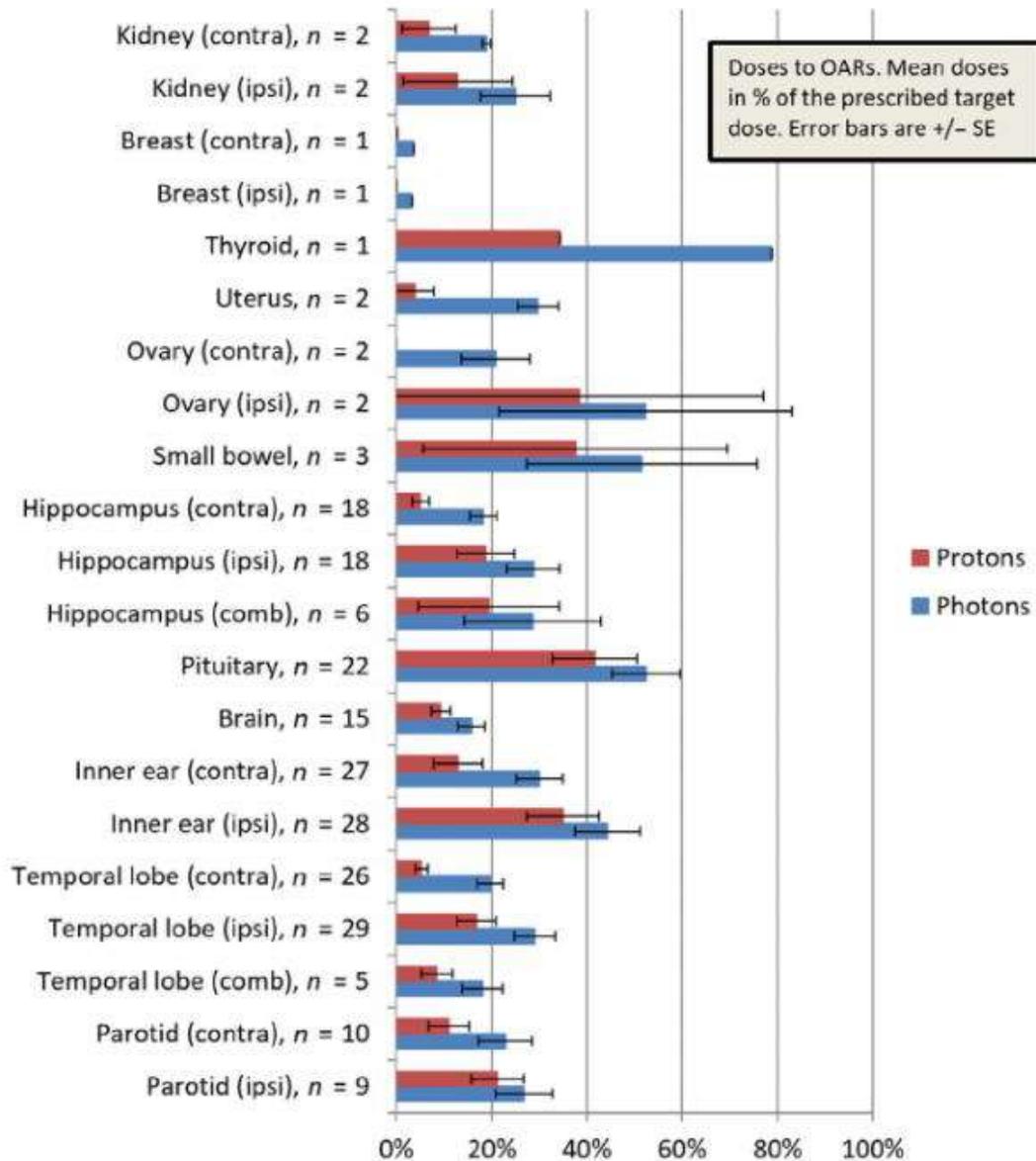
4 School of Health Sciences, University of South Australia, Adelaide, South Australia, Australia

January 2016 and December 2018

chordoma (10)
craniopharyngioma (7)
ependymoma (6)

Commonwealth funding for PBT via the Medicare Medical Treatment Overseas Program (MTO) is a pre-requisite for the MTO application

Parallel organs



significant reduction in **dose** to *parallel* OARs

IMPT over VMAT

- ipsilateral parotid ($P = 0.004$)**
- contralateral parotid ($P = 0.01$)
- ipsilateral temporal lobe ($P < 0.001$)
- contralateral temporal lobe ($P < 0.001$)
- ipsilateral inner ear ($P < 0.001$)
- contralateral inner ear ($P < 0.001$)
- brain ($P < 0.001$)
- pituitary ($P = 0.007$)
- combined hippocampi ($P = 0.031$)**
- ipsilateral hippocampus ($P < 0.001$)
- contralateral hippocampus ($P < 0.001$)

Basic approach to health economy... 360° models

$$\text{Value} \uparrow = \frac{\uparrow \Sigma (\text{Outcomes})}{\downarrow \Sigma (\text{Costs})}$$

Thaker N et al. *Oncology Payers* 2014



Financial Toxicity in Head and Neck Cancer Patients Treated With Proton Therapy

Grace L. Smith, MD, PhD, MPH^{1,2}; Ya-Chen Tina Shih, PhD²; Steven J. Frank, MD¹

¹Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

²Department of Health Services Research, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Cancer-related **financial toxicity impacts** head and neck cancer patients and survivors. Economic implications of proton therapy—dimensions of “financial toxicity”—need to be addressed. The value of proton therapy for head and neck cancer: empiric comparisons of patients’ and survivors’ **lost productivity disability after treatment.**

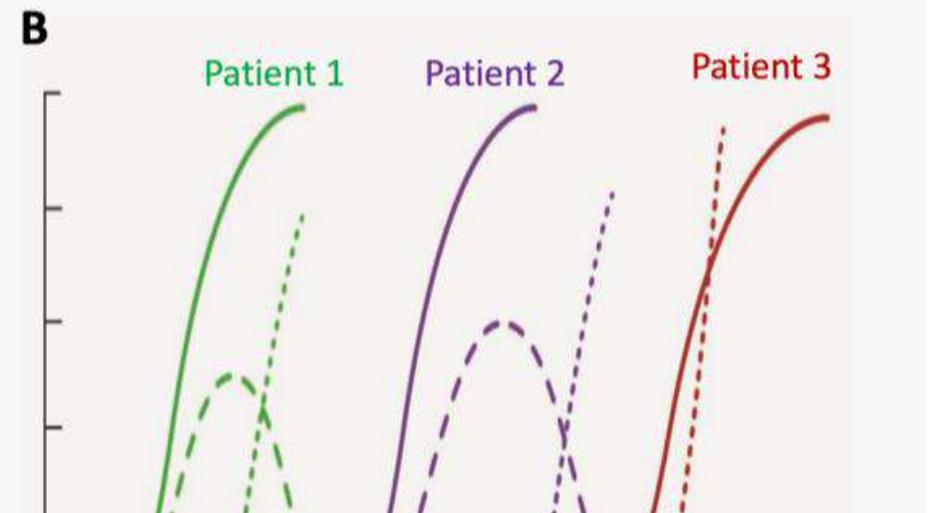
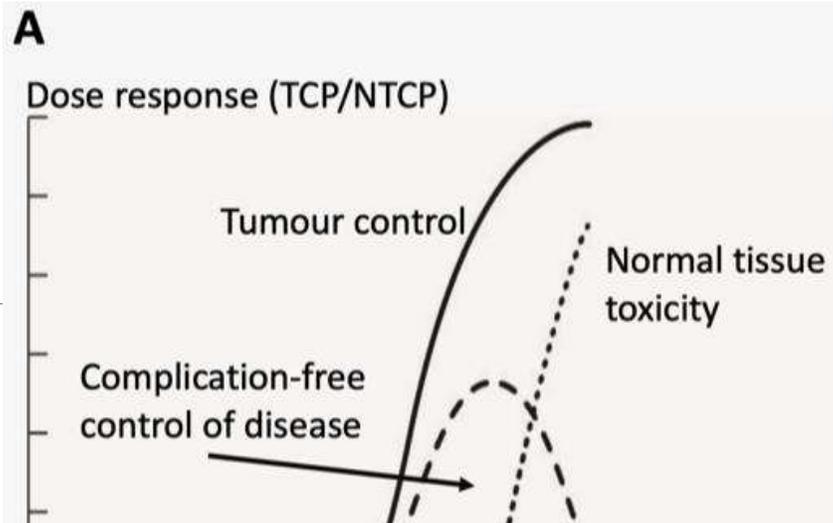
A cost-of-illness framework for evaluation comprehensively identifying the value of proton therapy incorporating financial toxicity in evaluation.

Overall, **financial toxicity burdens remain understudied** in head and neck cancer patients from a patient-centered perspective

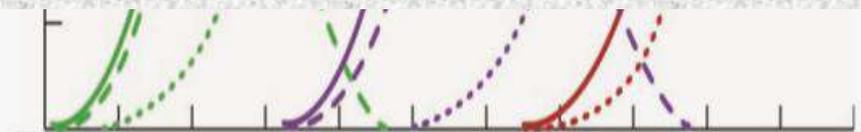
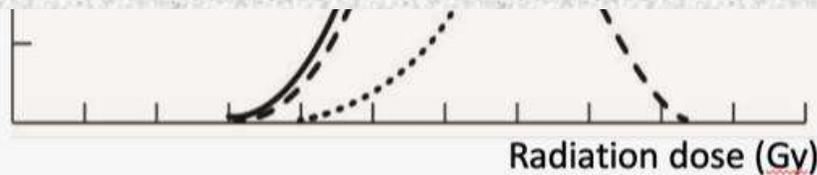
The evidence base for optimal selection and rationale for payer coverage

Cancer care delivery: proactive screening for financial toxicity and **early financial navigation in vulnerable patients:**

- engaging stakeholders,
- improving oncology provider team cost communication,
 - expanding policies to promote price transparency
 - expanding insurance coverage for proton therapy



Precision medicine = personalized oncology = normal tissues are personal



Legend Figure 1

- A) The classical tumour control probability (TCP) and normal tissue complication probability (NTCP) curves.-The aim is to shift the tumour control curve left and the normal tissue curve right.
- B) Future individual dose response curve, combining GARD and susceptibility to radiotoxicity to predict the benefit of radiation for an individual patient. Patient 1- tumour and normal tissue are sensitive to radiation but therapeutic window is narrow. Patient 2- Tumour is relatively sensitive and high normal tissue tolerance resulting in a very wide therapeutic window. Patient 3- Tumour is radioresistant with virtually no therapeutic window.

Health-Value estimations for particle therapy do need a 360° analytical models based in medical and demographic dynamics



Clínica
Universidad
de Navarra

Prof. Dr. Felipe A. Calvo Manuel
Co-director Oncology Department
Chair Prof. & Head of Radiation Oncology Department
Research & Education Coordination

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fcalom@unav.es

