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.

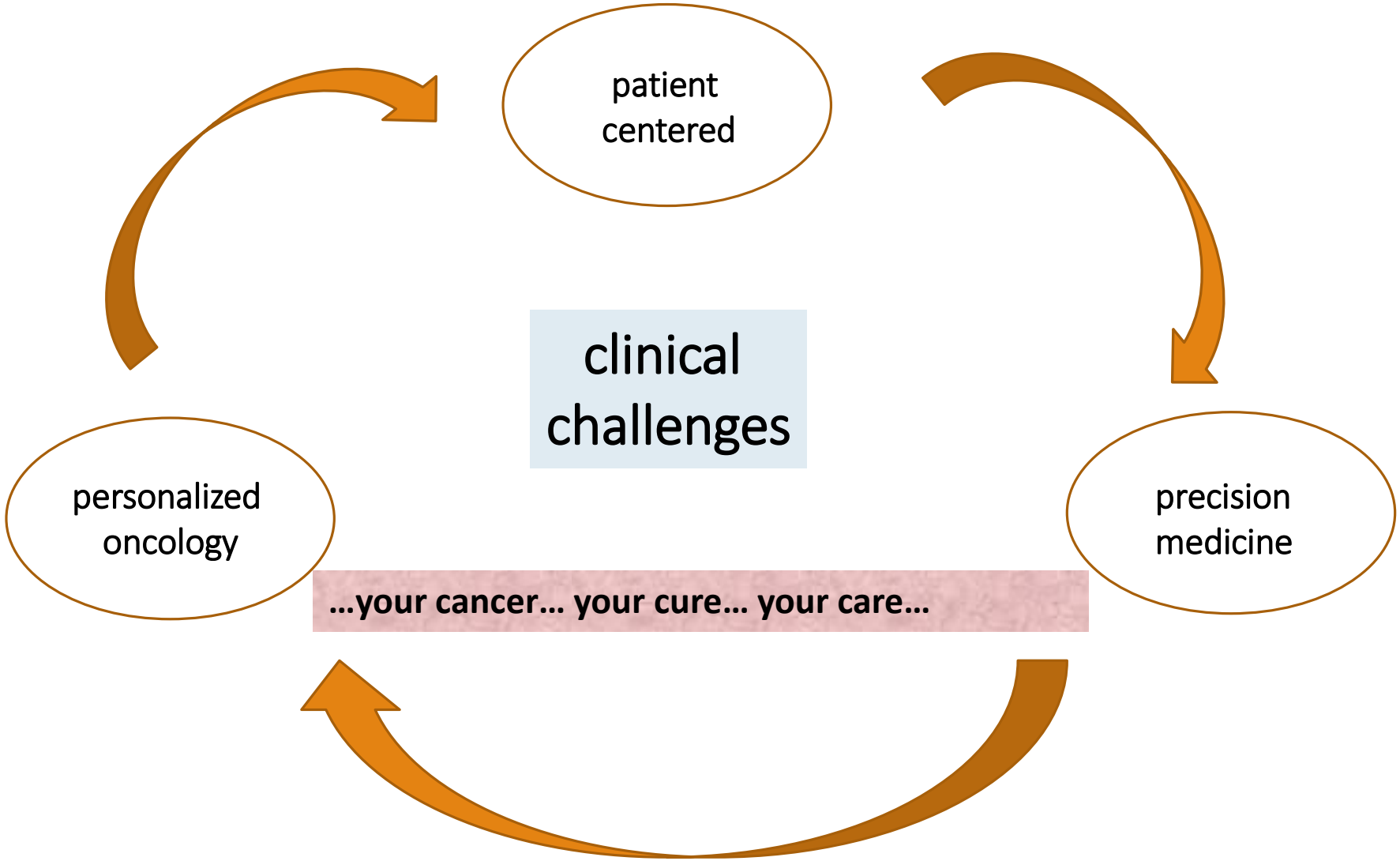
HITRIplus
Heavy Ion Therapy Research Integration

European Commission

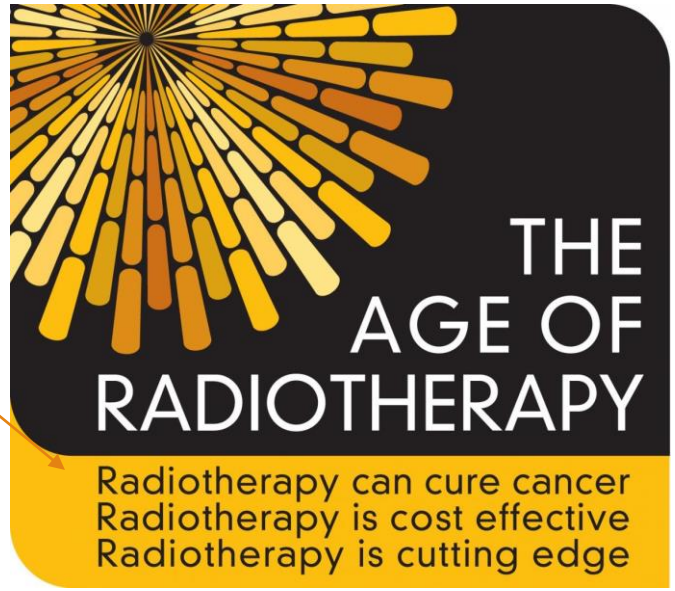
Clínica Universidad de Navarra

To apply for beamtime, please follow the instructions on this page: **https://hitriplus.eu/transnational-access/**

cancer medicine for clinicians…2022 and more**…**



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



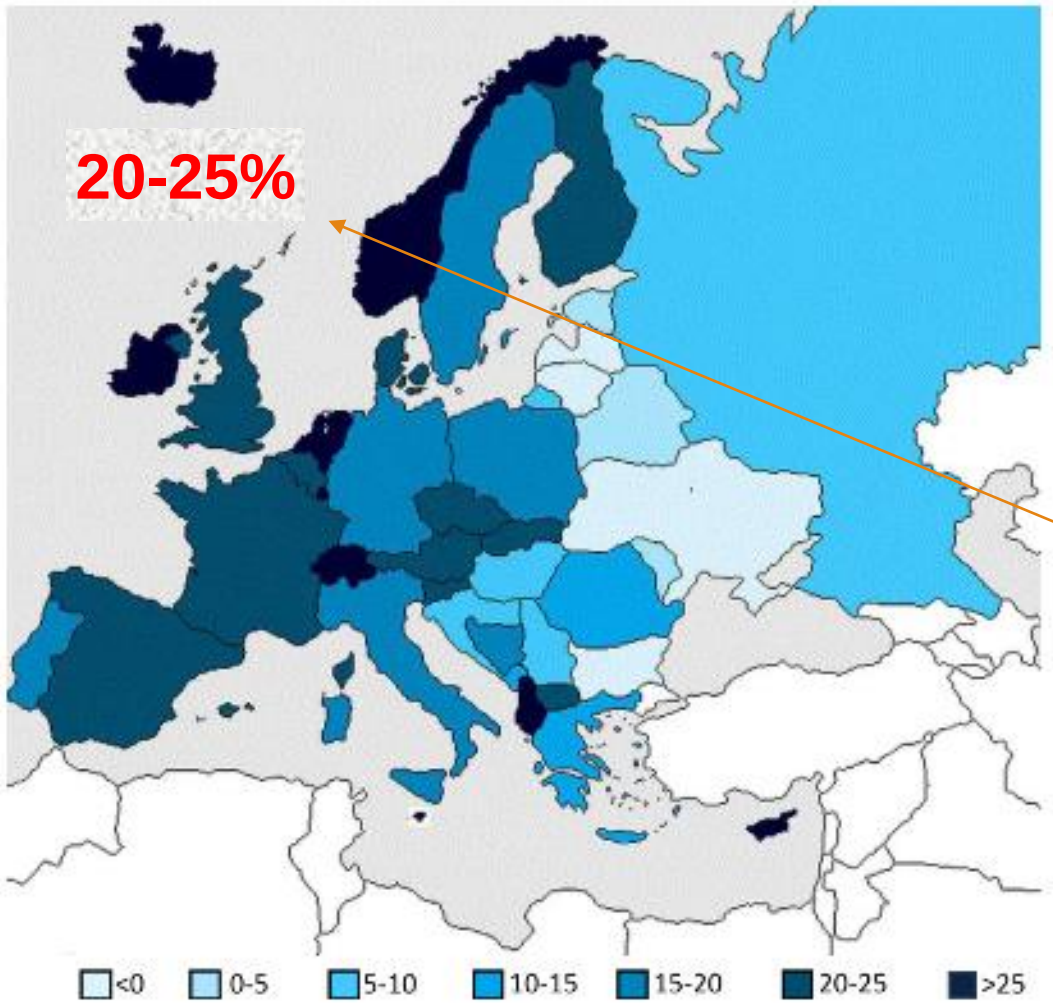


Fig. 1. Increase in new cancer patients that would require radiotherapy by 2025 by country (%).

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

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]

[a] University of Barcelona, IDIBELL, Barcelona, Spain; [b] Radiation Oncology Department, Ghent University Hospital, Ghent, Belgium; [c] CCORE Ingham Institute for Applied Medical Research, University of South New Wales, Australia; [d] Catalan Cancer Strategy, Department of Health, Generalitat de Catalunya, Barcelona, Spain; [e] Section of Cancer Surveillance, International Agency for Research on Cancer (IARC), Lyon, France; and [f] Department of Oncology, Aarhus University Hospital, Aarhus, Denmark

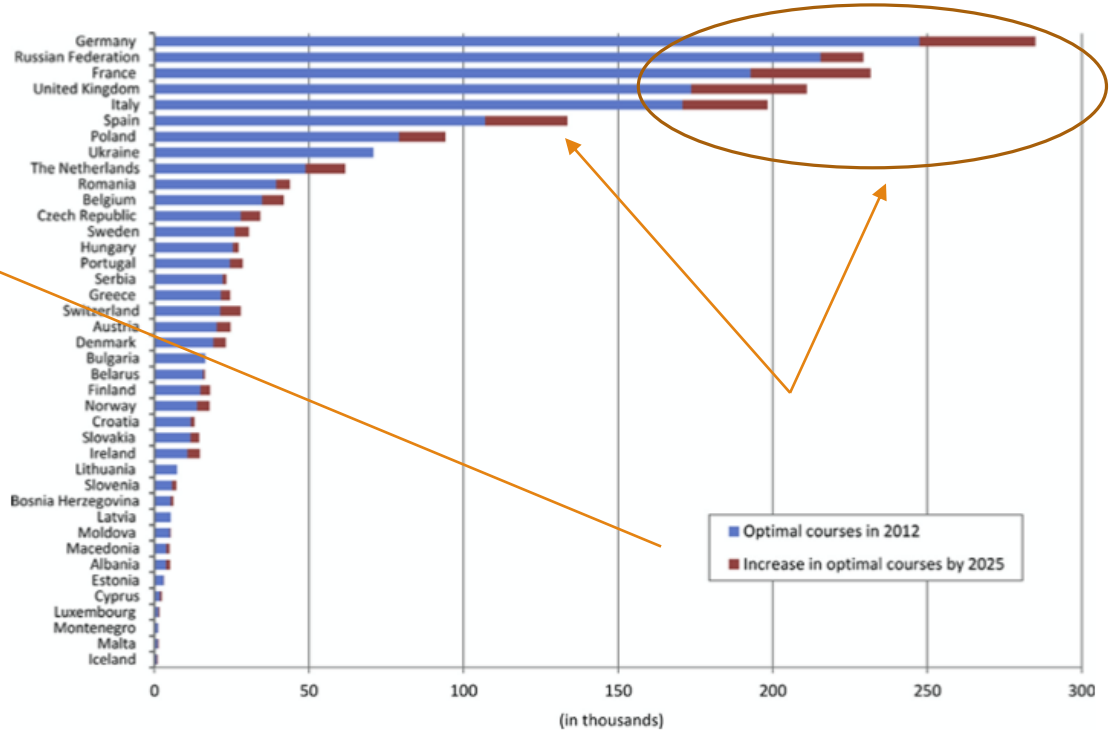
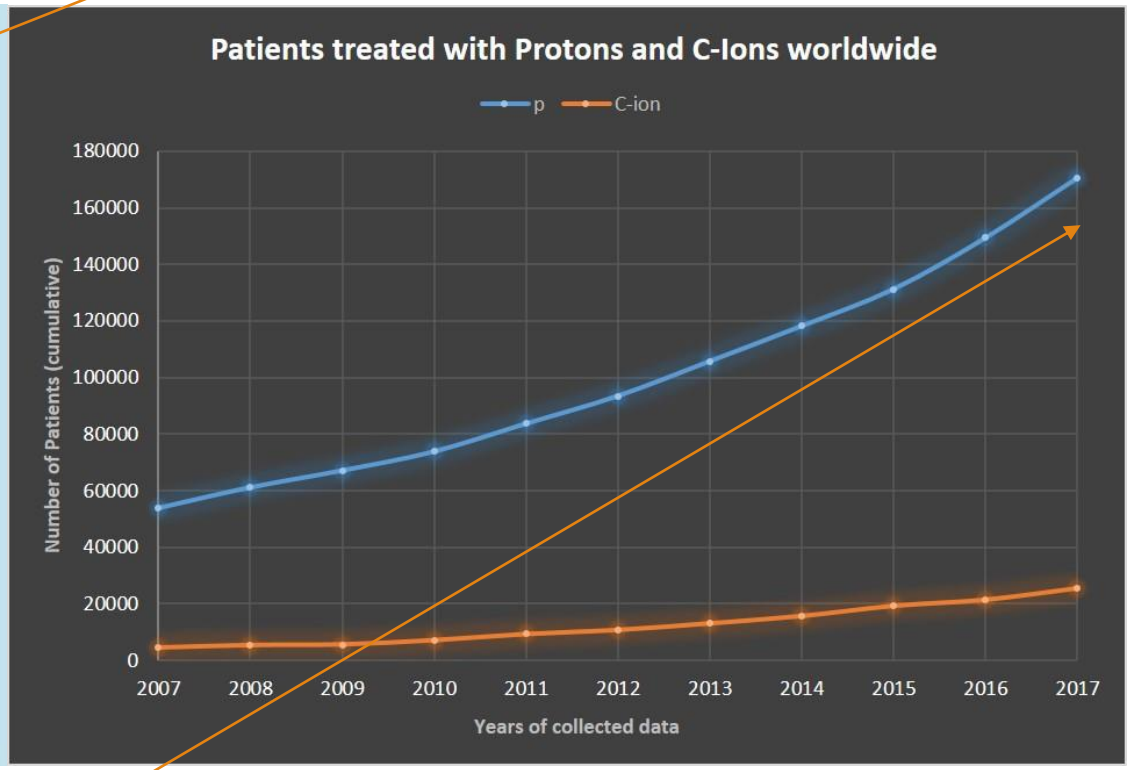


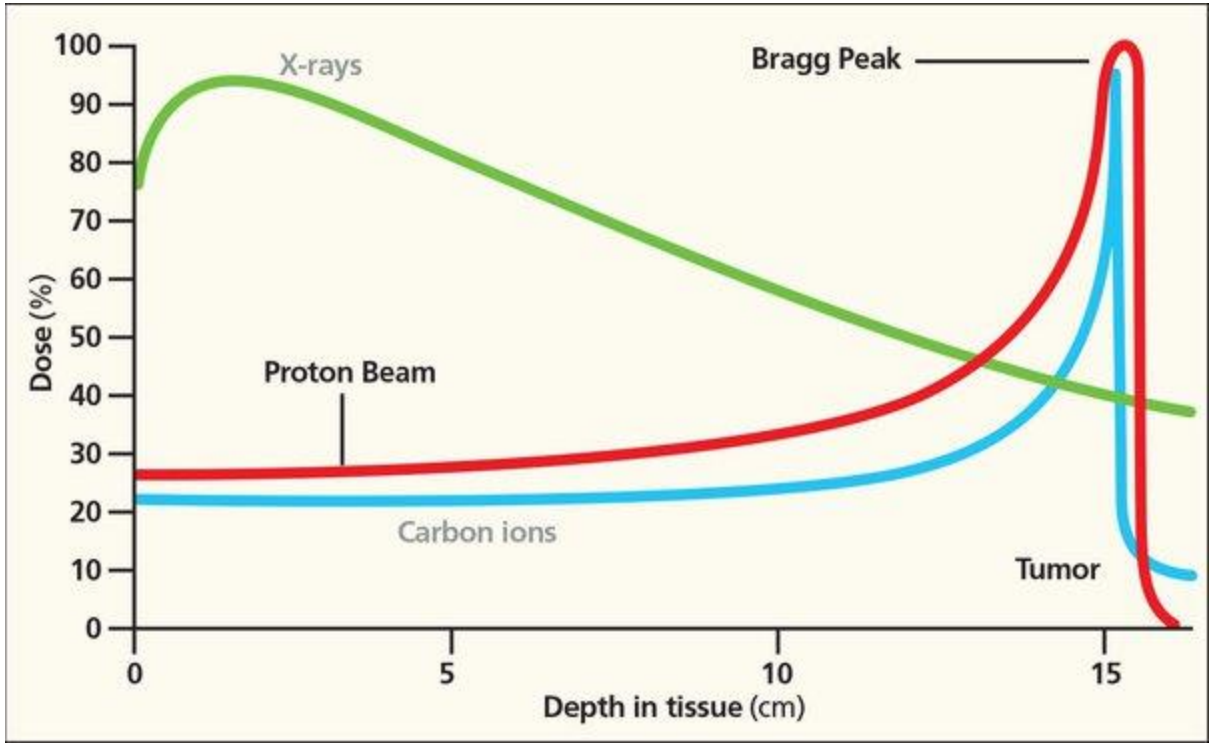
Fig. 2. Optimal number of courses of radiotherapy in 2012 and estimated absolute increase in optimal number of courses by 2025.

PTCOG website… operativos “contados a mano” en 2021 68 centros



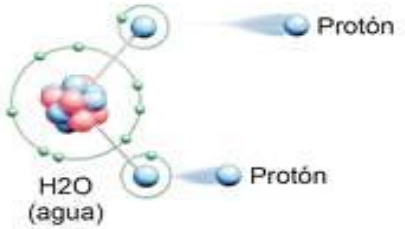
Estimados pacientes tratados en 2021….> 200.000…

Discussing *only* proton therapy arguments and data..

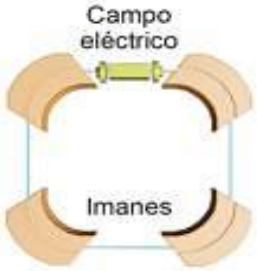


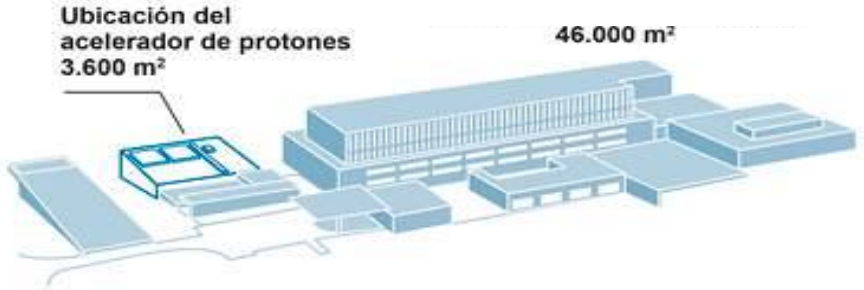
Sincrotrón

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



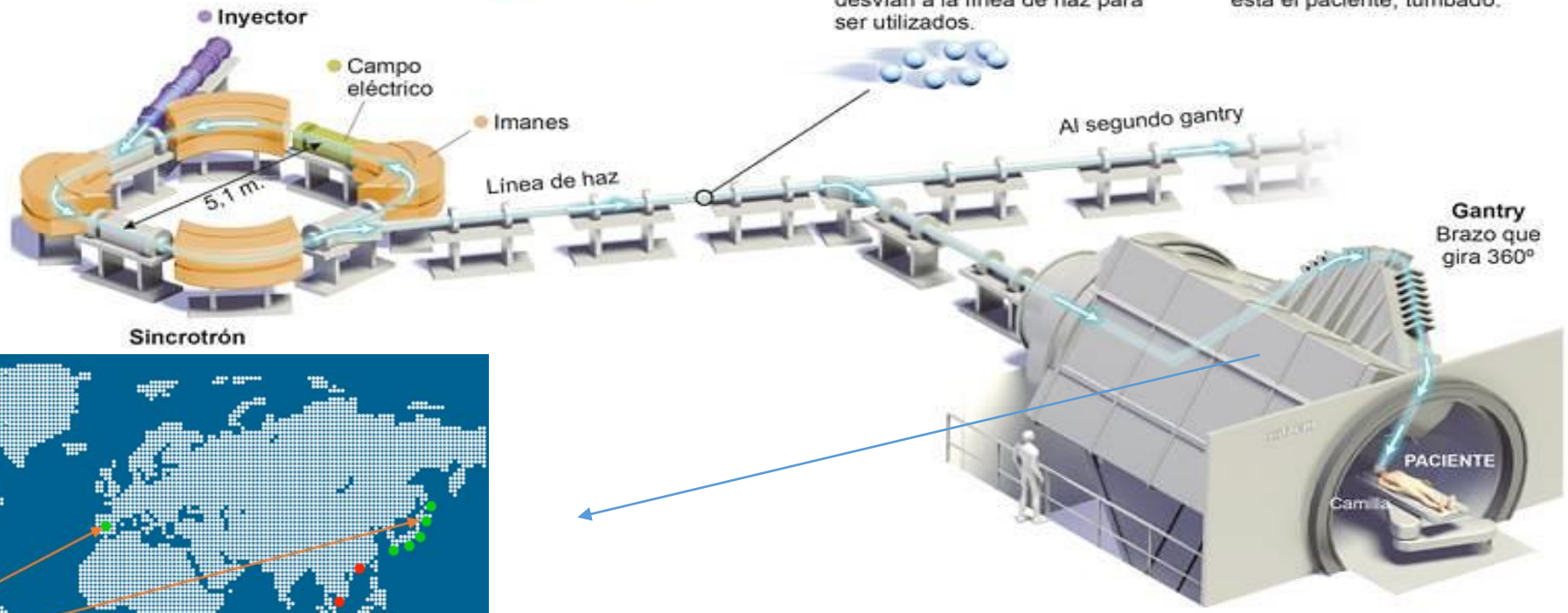
2 Sincrotrón
Cuatro imanes mueven los protones en círculo y un campo eléctrico incrementa gradualmente su velocidad.





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

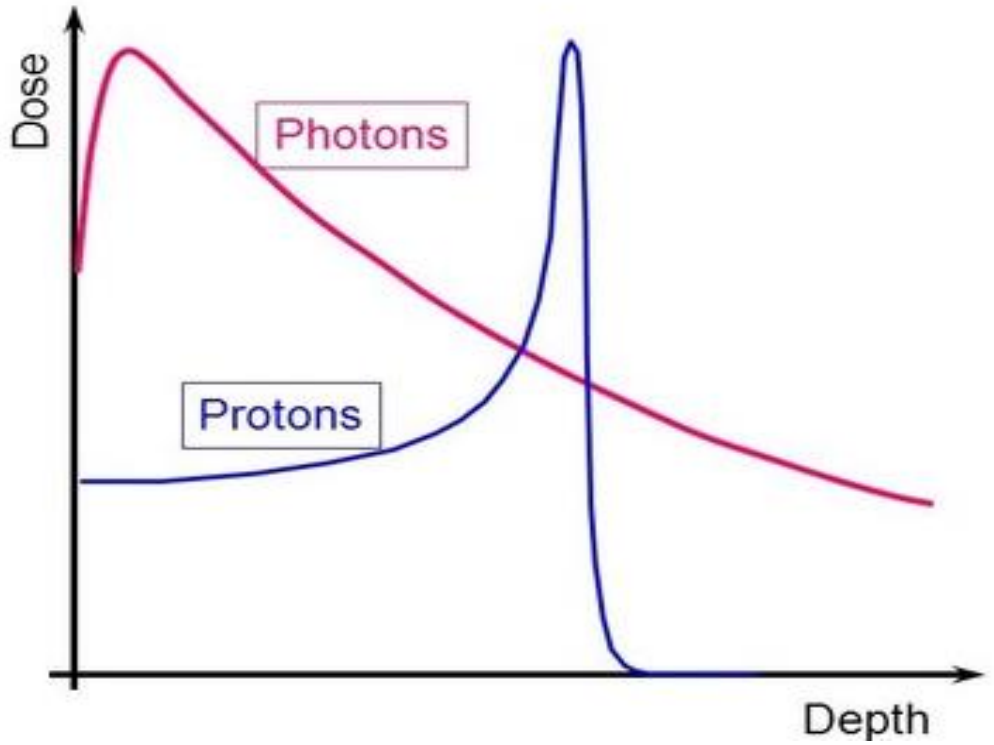
4 Gantry
Los protones llegan a uno de los dos gantrys, en cuyo centro está el paciente, tumbado.



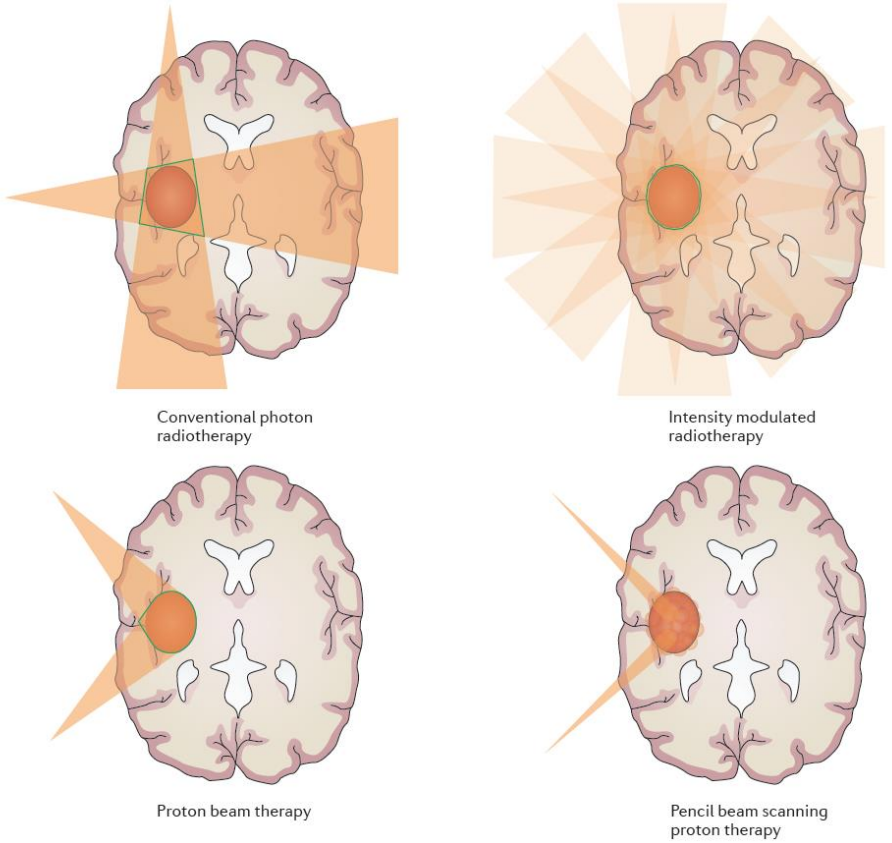
Health-Value and Proton Therapy:

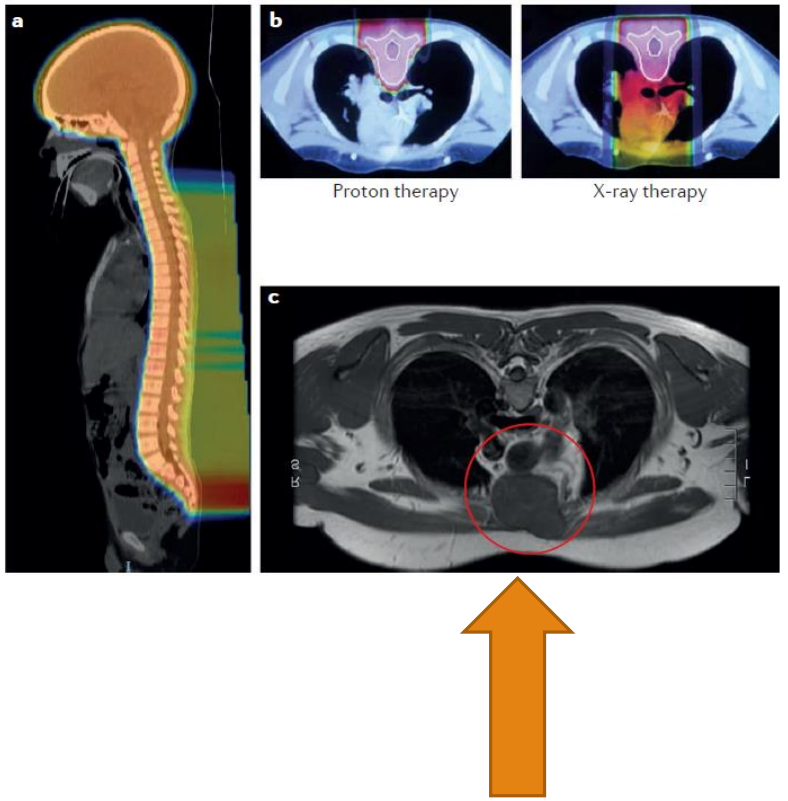
the new science of normal tissues…

Bragg Peak



Unnecesary irradiation: the medical dilema…





Sarcoma radionduced

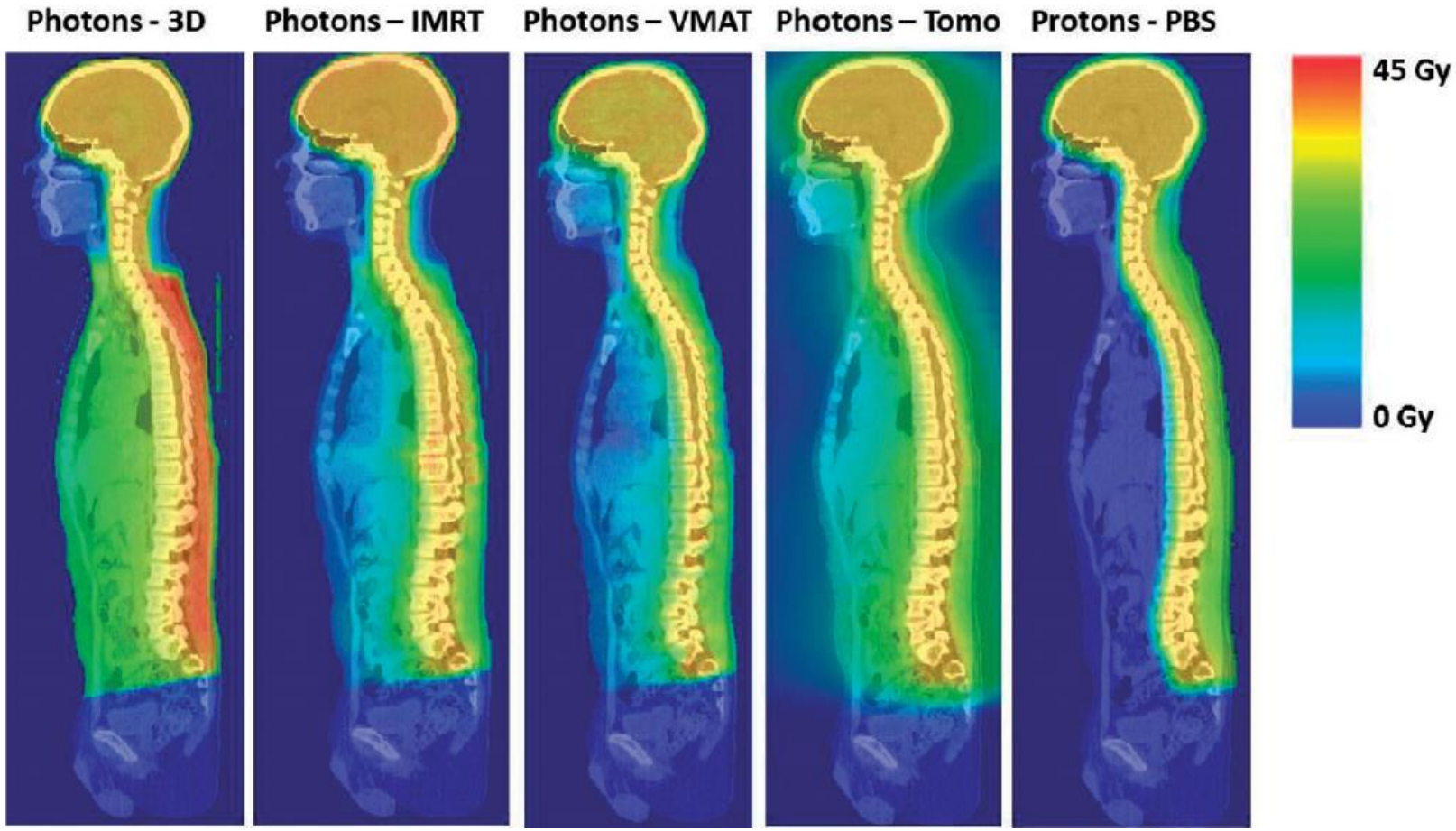
ACTA ONCOLOGICA
2018, VOL. 57, NO. 9, 1240–1249
https://doi.org/10.1080/0284186X.2018.1465588

Taylor & Francis
Taylor & Francis Group

ORIGINAL ARTICLE

OPEN ACCESS Check for updates

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

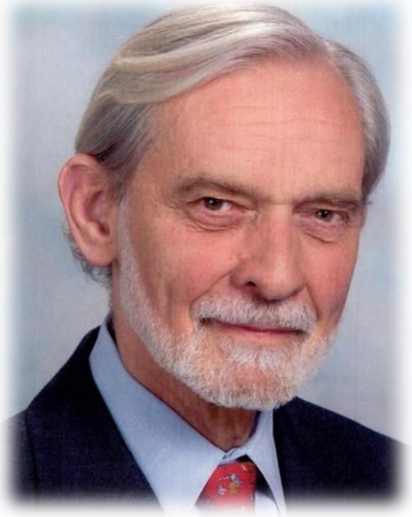


VOLUME 26 · NUMBER 2 · JANUARY 10 2008

JOURNAL OF CLINICAL ONCOLOGY | COMMENTS AND CONTROVERSIES

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?"

International Journal of Radiation Oncology biology • physics

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Clinical Investigation

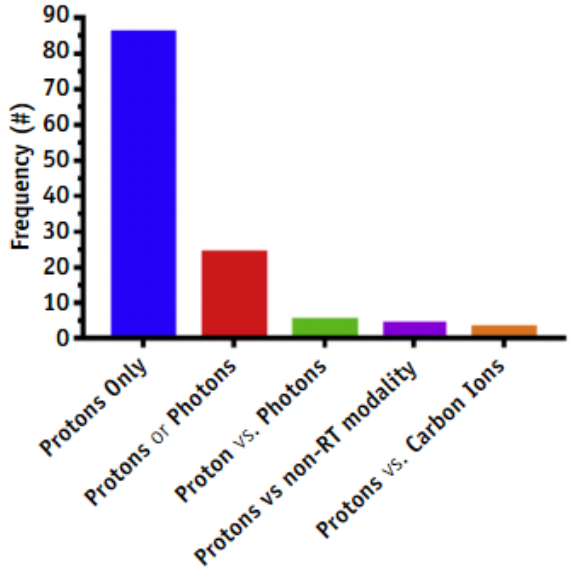
Establishing Evidence-Based Indications for Proton Therapy: An Overview of Current Clinical Trials

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*

*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*

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



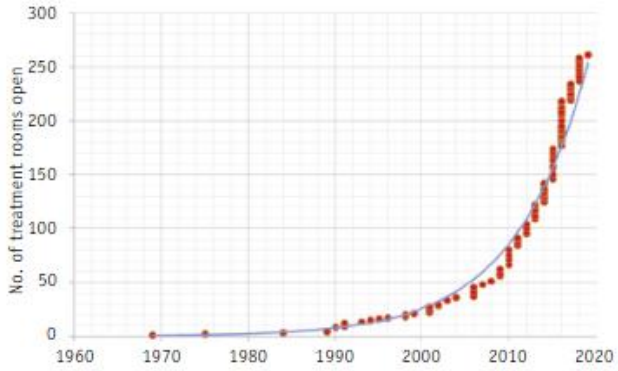


Fig. 5. Number of operating proton beam therapy rooms worldwide, 1970–present.

International Journal of Radiation Oncology biology • physics
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Clinical Investigation

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

Mark V. Mishra, MD,* Sameer Aggarwal, MD,†
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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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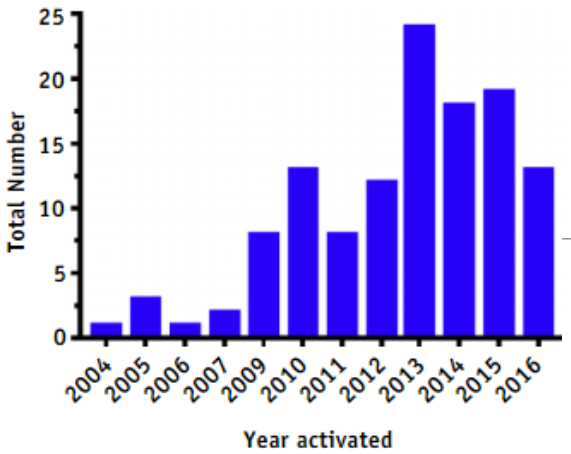
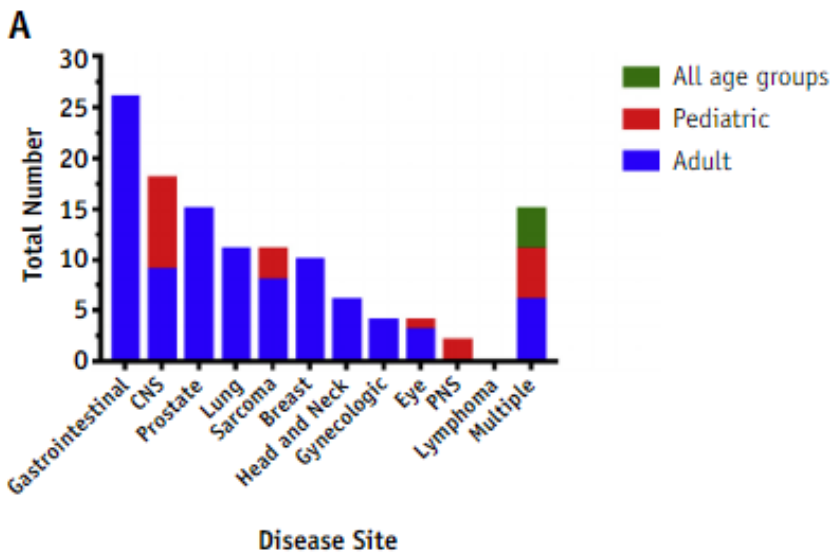
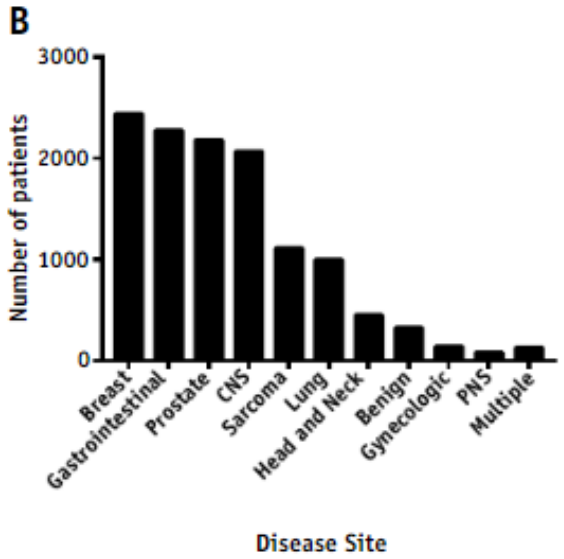


Fig. 2. Activation of clinical trials of proton beam





Recenti Prog Med 2019; 110: 566-586

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

TOM JEFFERSON[1], GIULIO FORMOSO[2], FRANCESCO VENTURELLI[2,3], MASSIMO VICENTINI[2], EMILIO CHIAROLLA[4], LUCIANA BALLINI[2,5]

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

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 CIRT[19].

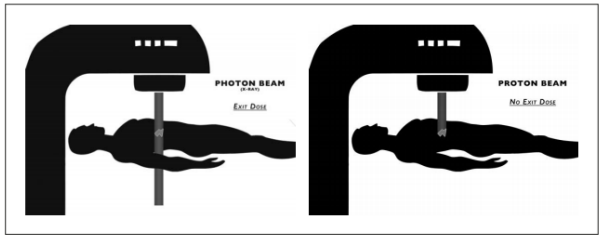


Figure 2. Proton beam stop in target and don't exit from the body (credit: Sergio Sassano).

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

Non-comparative 25 studies
Comparative 9 studies

Clinical health-value is not intuitive…

international metrics are heterogeneous

special article

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, LLD[1]; Elisabeth G.E. de Vries, MD, PhD[2]; Urania Dafni, ScD[3,10]; Elizabeth Garrett-Mayer, PhD[4]; Shannon E. McKernin[4]; Martine Piccart, PhD[5]; Nicola J. Latino[6]; Jean-Yves Douillard, MD[7]; Lowell E. Schnipper, MD[8]; Mark R. Somerfield, PhD[4]; Jan Bogaerts, ScD[6]; Dimitris Karlis, PhD[9]; Panagiota Zygoura, MSc[10]; Katerina Vervita, MD[10]; George Pentheroudakis, MD, PhD[11]; Josep Tabernero, MD, PhD[12]; Christoph Zielinski, MD[13]; Dana S. Wollins, MGC[4]; and Richard L. Schilsky, MD[4]

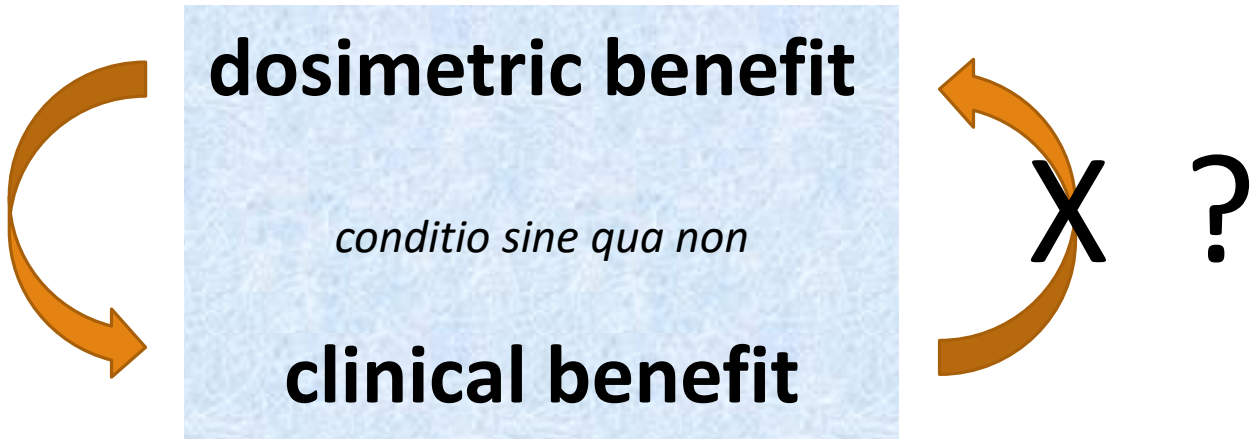
J Clin Oncol 37:336-349. © 2018 by American Society of Clinical Oncology

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



Cancer 2016;122:1483-501.

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]

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…)

National Comprehensive Cancer Network®

National Comprehensive Cancer Network

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- NCCN Categories of Preference
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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.

Quick Links

Clinicians

- NCCN Guidelines® - **FREE**
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- NCCN Biomarkers Compendium®
- NCCN Imaging AUC™
- NCCN Radiation Therapy Compendium™
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- NCCN Guidelines for Patients®

< 7 %

> 80 %

Health-Value: radiotherapy

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

Health- Value in pediatric oncology

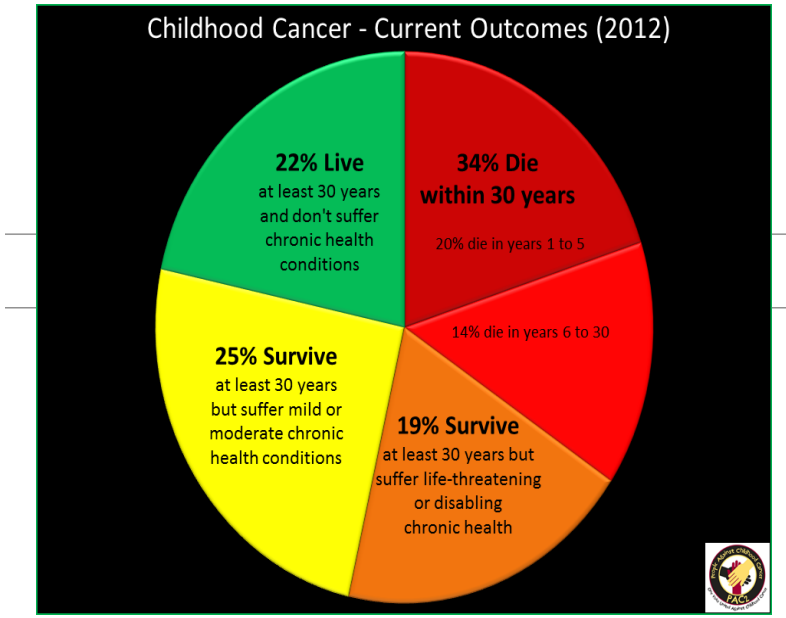
NEVER RANDOMIZED, RETROSPECTIVE, HETEROGENEOUS PROTON TECHNOLOGY

The NEW ENGLAND JOURNAL of MEDICINE

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% grado3-4 (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, PhD[3]; M. Douglas Ris, PhD[1,2]; Laura Janzen, PhD[3]; M. Fatih Okcu, MPH, MD[1,2]; David R. Grosshans, MD, PhD[4]; Vijay Ramaswamy, MD, PhD[3,5]; Arnold C. Paulino, MD[4]; David Hodgson, MD[6]; Anita Mahajan, MD[7]; Derek S. Tsang, MD, PhD[6]; Normand Laperriere, MD[6]; William E. Whitehead, MPH, MD[1,2]; Robert C. Dauser, MD[1,2]; Michael D. Taylor, MD, PhD[3,5]; Heather M. Conklin, PhD[8]; Murali Chintagumpala, MD[1,2]; Eric Bouffet, MD[3,5]; and Donald Mabbott, PhD[3,5]

J Clin Oncol 38:454-461. © 2019 9

AFFILIATIONS

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

Memphis, TN

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

Neurocognition…. Dependence…

PRT gr

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).

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

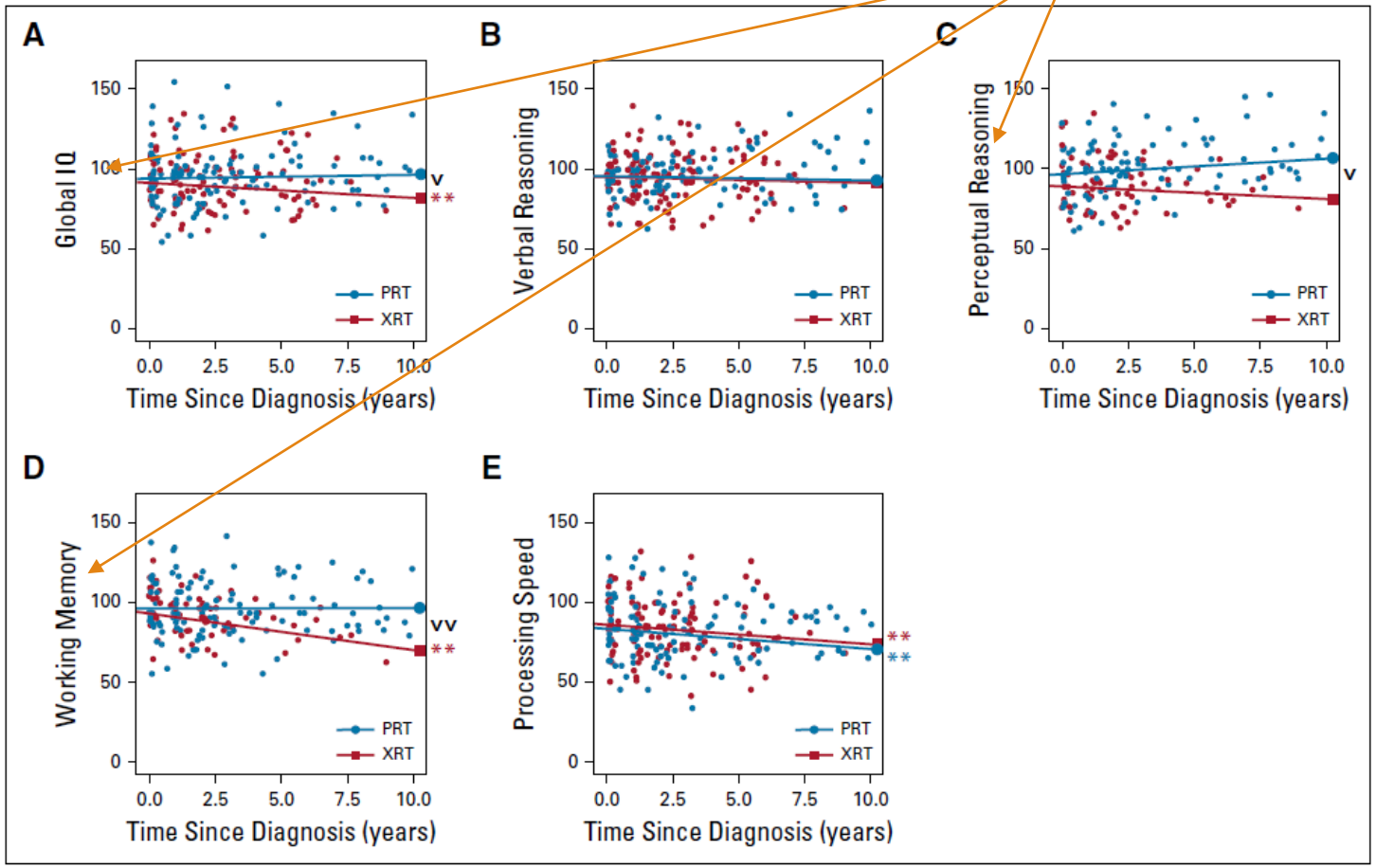


FIG 1. Change in outcomes scores over time since diagnosis by proton radiotherapy (PRT) and photon radiotherapy (XRT). (A) Global intelligence quotient (IQ). (B) Verbal reasoning. (C) Perceptual reasoning. (D) Working memory. (E) Processing speed. Bold lines are adjusted slopes showing change in neurocognitive 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

Hematologic toxicity in pediatric medulloblastoma 5

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	[illegible]	[illegible]	
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 $P < .05$.

Meduloblastoma Protons vs Photons

Clinical Investigation

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,†,‡ Matthew S. Susko, MD,§ Avani D. Rao, MD,‡ Beow Y. Yeap, ScD,‖ Antoine M. Snijders, PhD,¶ Matthew M. Ladra, MD,‡ Jennifer Vogel, MD,‡ Cierra Zaslowe-Dude, BA,* Karen J. Marcus, MD,* Torunn I. Yock, MD, MCH,† Clemens Grassberger, PhD,† Steve E. Braunstein, MD, PhD,† Daphne A. Haas-Kogan, MD,* Stephanie A. Terezakis, MD,†,# and Shannon M. MacDonald, MD†

*Department of Radiation Oncology, Brigham and Women's Hospital, Dana-Farber Cancer Institute, Boston Children's Hospital, Harvard Medical School, Boston, Massachusetts; †Department of Radiation Oncology, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts; ‡Department of Radiation and Molecular Radiation Sciences, Sidney Kimmel Comprehensive Cancer Center Johns Hopkins School of Medicine, Baltimore, Maryland; §Department of Radiation Oncology, University of California San Francisco, San Francisco, California; ‖Department of Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts; ¶Biological Systems and Engineering Division, Lawrence Berkeley National Laboratory, Berkeley, California; #Department of Radiation Oncology, University of Minnesota Medical School, Minneapolis, Minnesota

Received Jan 31, 2020. Accepted for publication Sep 22, 2020.

Immuncompetence

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

Health- Value pediatric oncology: radio-induced cancer

NEVER RANDOMIZED, RETROSPECTIVE, HETEROGENEOUS PROTON TECHNOLOGY

Cancer Science
The official journal of the Japanese Cancer Association
JCA
Volume108, Issue 3 March 2017

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

Pediatric Blood & Cancer SIOP aspho WILEY

ONCOLOGY: RESEARCH ARTICLE

Second tumor risk in children treated with proton therapy

Daniel J. Indelicato[1] | James E. Bates[2] | Raymond B. Mailhot Vega[1] |

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.

Cancer Science
The official journal of the Japanese Cancer Association JCA

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

No malignant secondary tumors occurred **within the irradiated field**

EPTN, PTCOCG, PROS consensus

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], Johanes A. Langendijk [f], Shannon M. MacDonald [g], Susan L. McGovern [h], Luke Pater [i], John P. Perentesis [j], Juliette Thariat [b], Beate Timmerman [k], Torunn I. Yock [g], Anita Mahajan [e]

[a] Center for Proton Therapy, Paul Scherrer Institute, ETH Domain, Villigen PSI, Switzerland; [b] Centre de lutte contre le cancer François-Baclesse, Caen, France; [c] Department of Radiation Oncology, University of Florida College of Medicine, Gainesville; [d] Department of Radiation Oncology, University of Pennsylvania, Philadelphia; [e] Department of Radiation Oncology, Mayo Clinic, Rochester, USA; [f] Department of Radiation Oncology, University Medical Center Groningen, University of Groningen, The Netherlands; [g] Department of Radiation Oncology, Massachusetts General Hospital, Boston; [h] Department of Radiation Oncology, MD Anderson Cancer Center, Houston; [i] Department of Radiation Oncology, University of Cincinnati; [j] Cincinnati Children's Hospital Medical Center, University of Cincinnati, USA; [k] WPE, University Hospital Essen, Germany

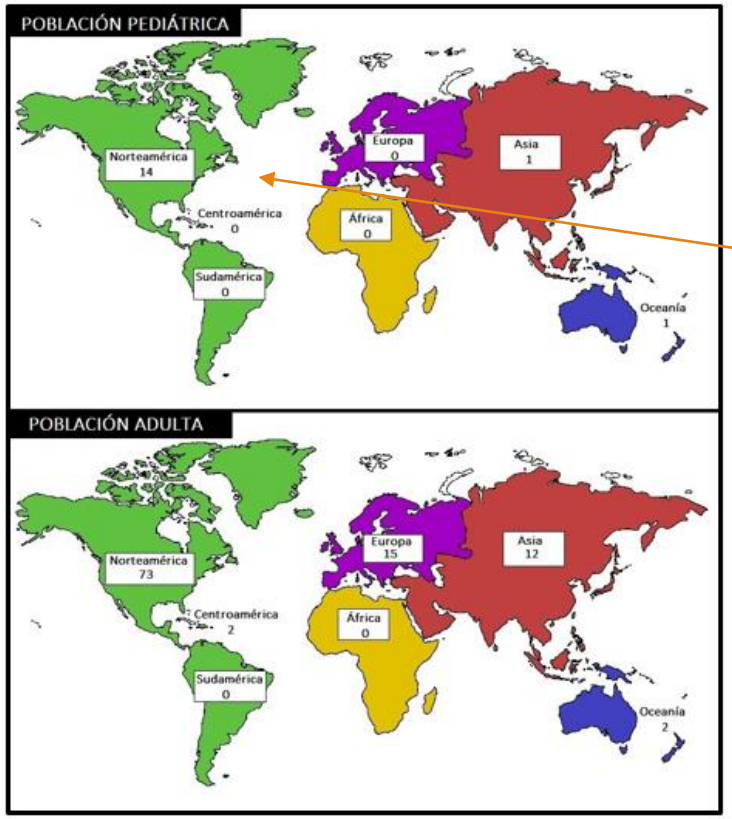
ABSTRACT

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)

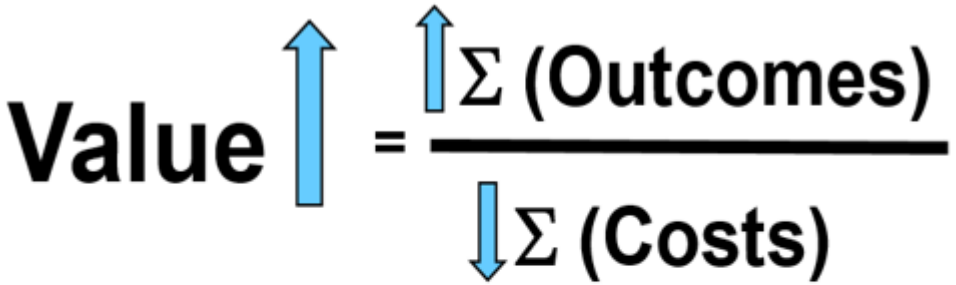
Health- Value in adult cancer models

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

Health-Value: “*costicity*”

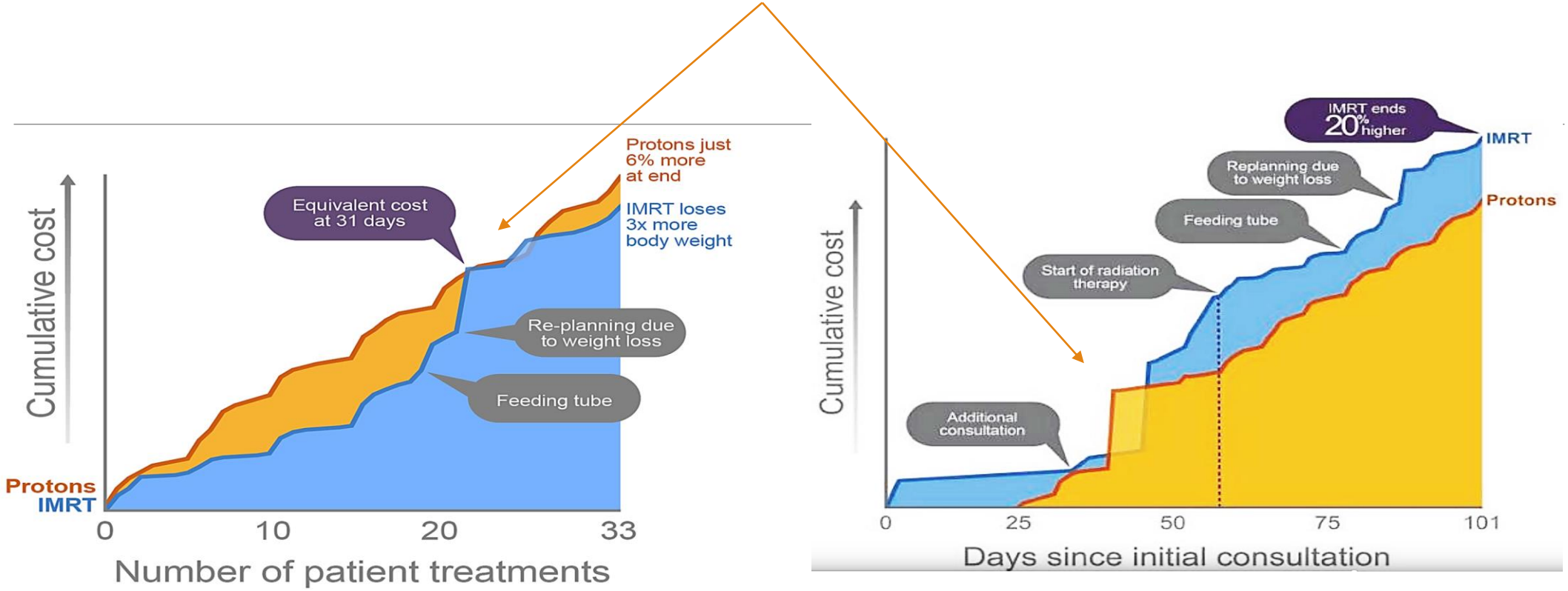
FINANTIAL TOXICITY…

Basic approach to health economy…



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, MD[1]; Matthew S. Ning, MD[1]; Dario Pasalic, MD[1]; Alexis Guzman, MBA[3]; Grace Smith, MD, PhD, MPH[1]; Emma B. Holliday, MD[1]; James Incalcaterra, PhD[3]; Adam S. Garden, MD[1]; Simona F. Shaitelman, MD[1]; G. Brandon Gunn, MD[1]; C. David Fuller, MD, PhD[1]; Pierre Blanchard, MD[1]; Thomas W. Feeley, MD[4]; Robert S. Kaplan, PhD[4]; Steven J. Frank, MD[1]

[1]Department 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.

INTERNATIONAL JOURNAL of PARTICLE THERAPY

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

Danmeng Huang, PhD[1,2]; Steven J. Frank, MD[1]; Vivek Verma, MD[1]; Nikhil G. Thaker, MD[3]; Eric D. Brooks, MD, MHS[4]; Matthew B. Palmer, MBA[5]; Ross F. Harrison, MD, MPH[6]; Ashish A. Deshmukh, PhD, MPH[2]; Matthew S. Ning, MD, MPH[1]

[1]Department 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.

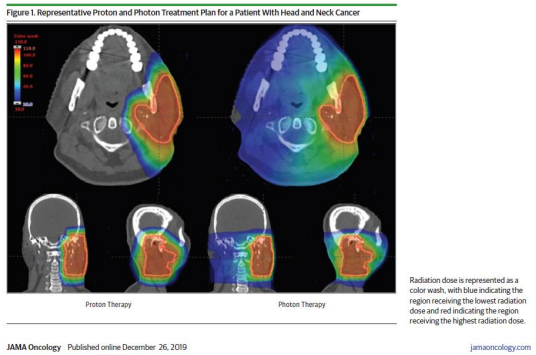
Conclusion:

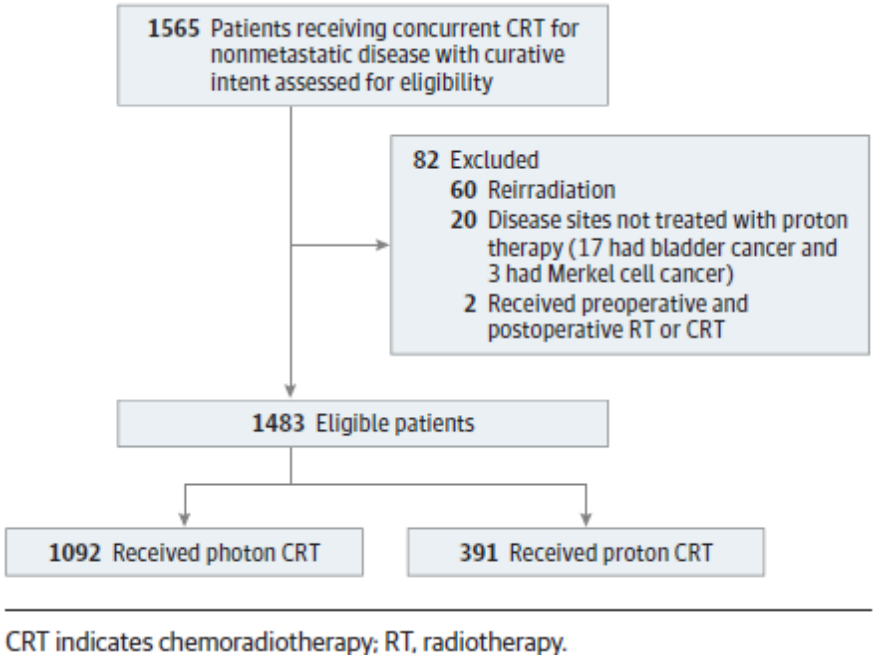
Contemporary CEMs are needed: better estimates for toxicity risks and costs associated to PBT delivery

JAMA Oncology | Original Investigation

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
Published online December 26, 2019.

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

JAMA Oncology | Original Investigation

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

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JAMA Oncol. doi:10.1001/jamaoncol.2019.4889
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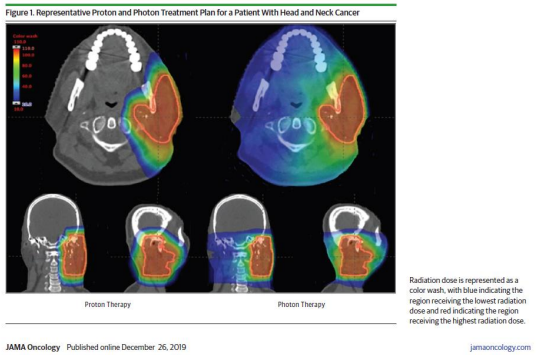

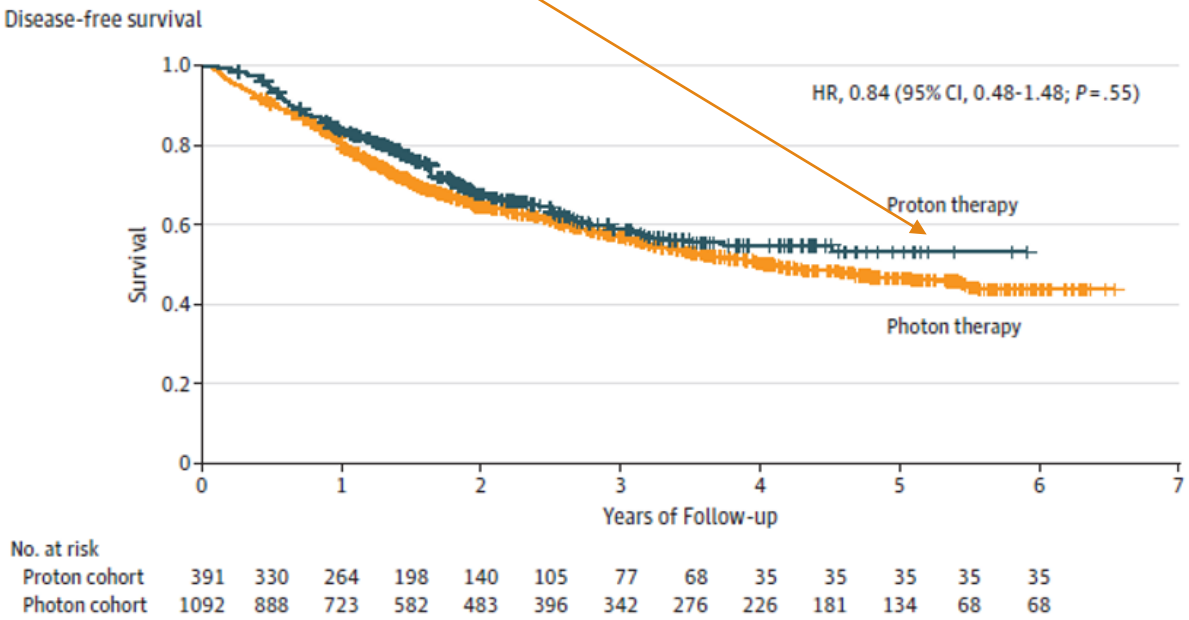

JAMA Oncology | Original Investigation

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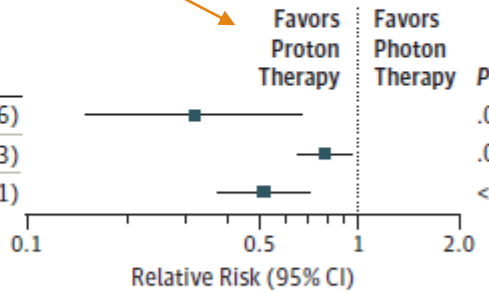
11 % vs 27 % grade 3-4 CRT toxicity

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

Outcome	Proton CRT Group (n = 391) No. of Events	Proton CRT Group (n = 391) Percentage (95% CI)	Photon CRT Group (n = 1092) No. of Events	Photon CRT Group (n = 1092) Percentage (95% CI)	Relative Risk (95% CI)	*P* Value
90-day Grade ≥3 adverse events	45	11.5% (8.3%-14.7%)	301	27.6% (24.9%-30.2%)	0.31 (0.15-0.66)	.002
90-day Grade ≥2 adverse events	290	74.2% (69.8%-78.5%)	926	84.8% (82.7%-86.9%)	0.78 (0.65-0.93)	.006
ECOG performance status decline	145	37.1% (32.3%-41.9%)	434	42.4% (39.4%-45.4%)	0.51 (0.37-0.71)	<.001



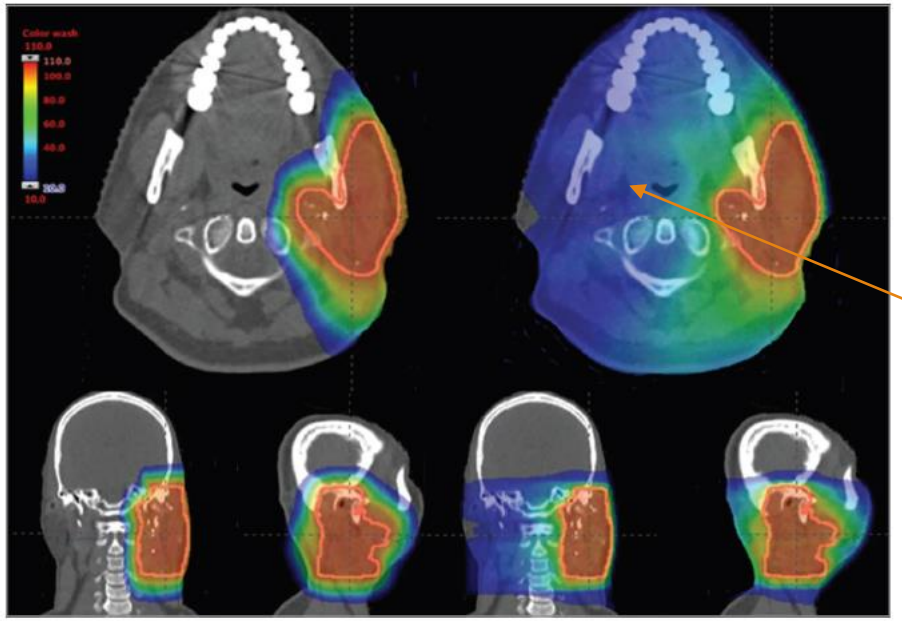
Ninety-day adverse events are measured using Common Terminology Criteria for Adverse Events, version 4 (CTCAEv4). Patients were identified with CTCAEv4 grades of at least 3 and at least 2. ECOG performance status scores range from 0 to 5, with higher scores indicating worse performance status.

JAMA Oncology | Original Investigation

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



Proton Therapy | Photon Therapy

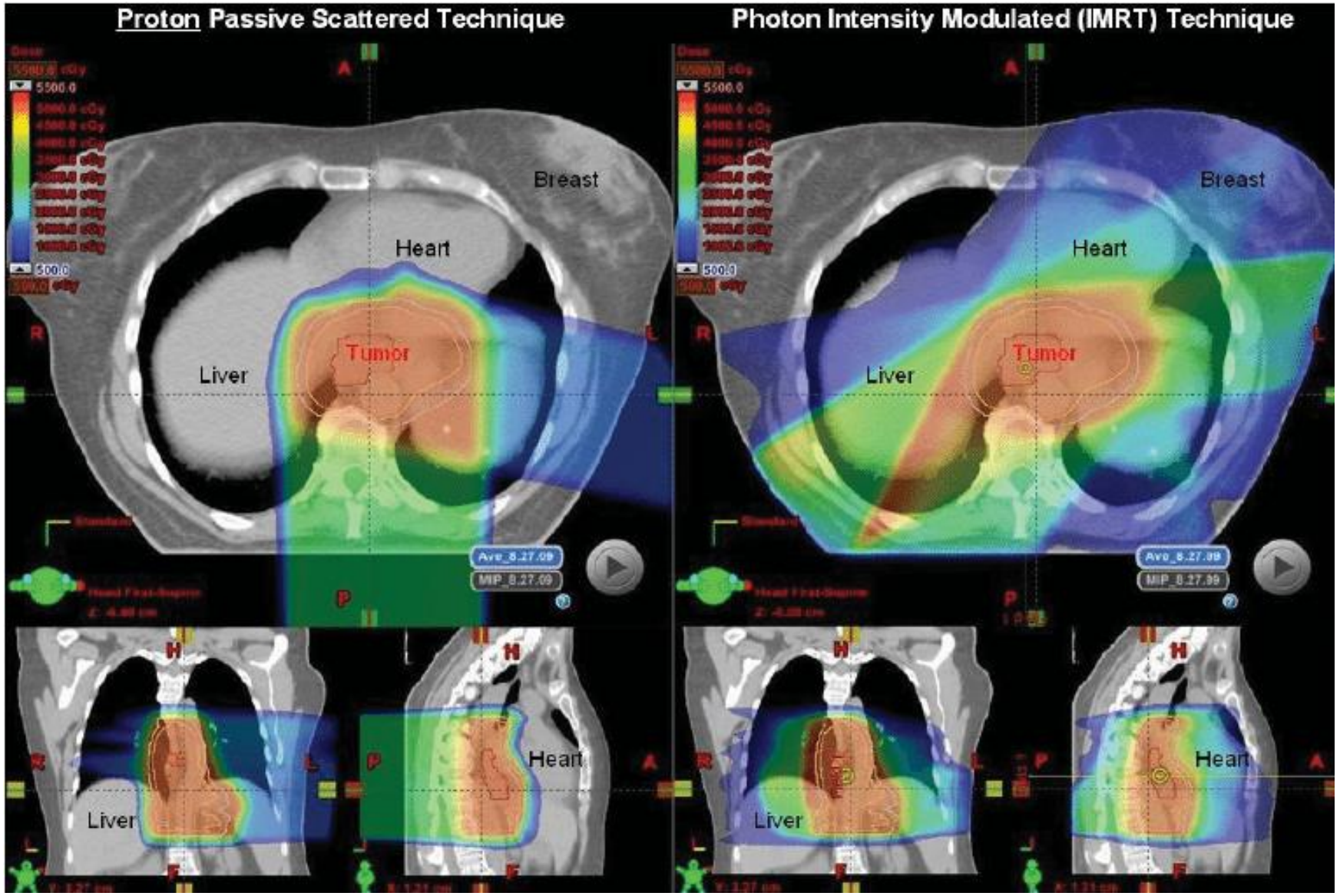
Radiation dose is represented as a color wash, with blue indicating the region receiving the lowest radiation dose and red indicating the region receiving the highest radiation dose.

10 % vs 30 % grade 3-4 CRT toxicity

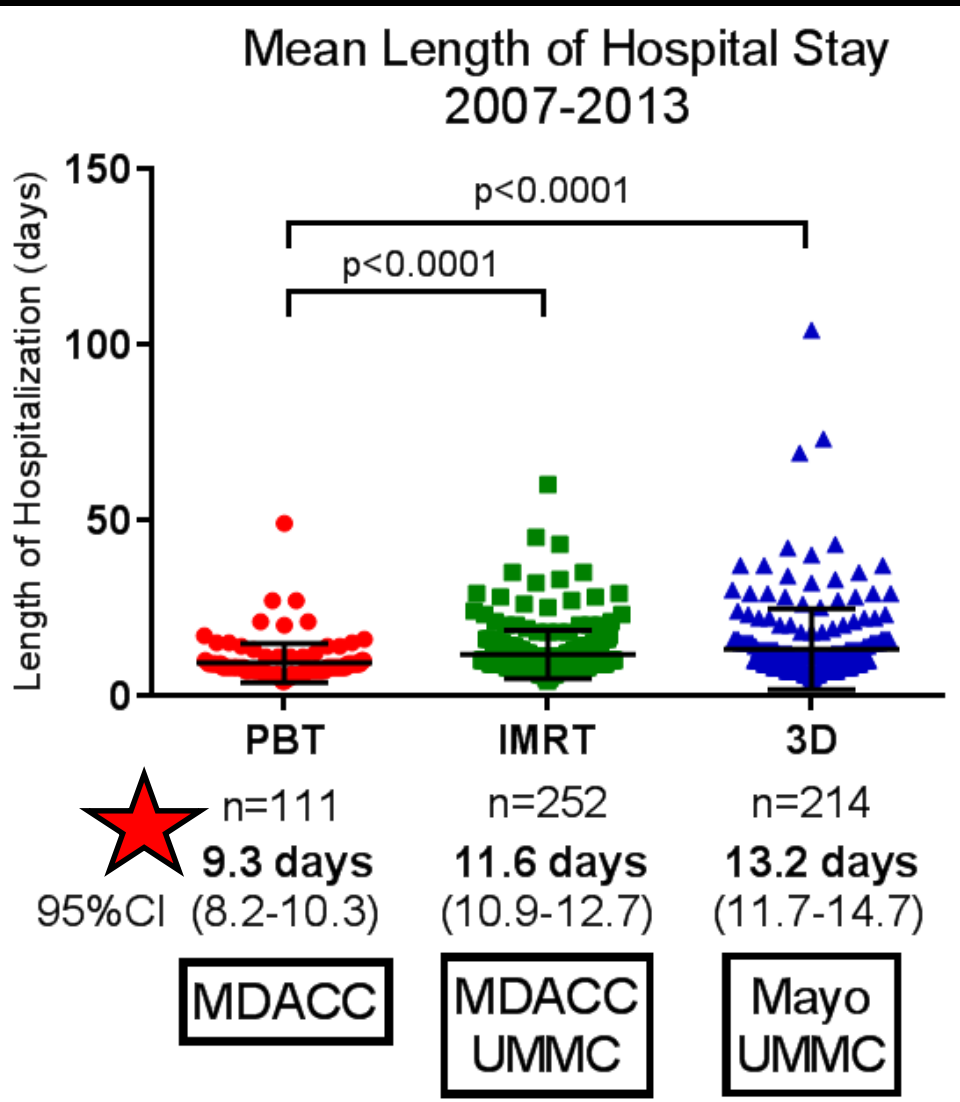
Why???

Helath-Value: "*costicity*" + survival

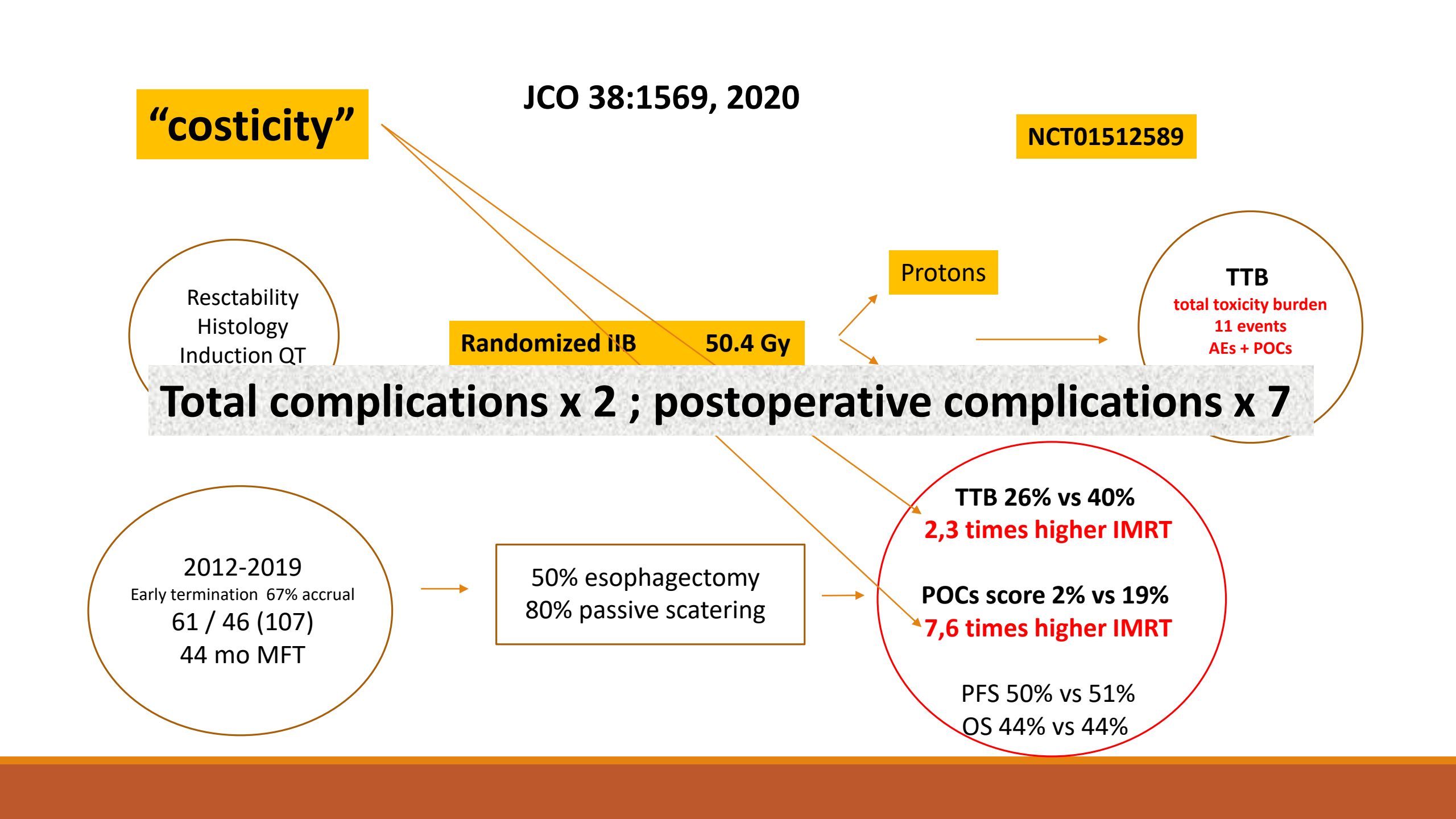
A MAJOR CONTRIBUTION… AFORDABLE CURE AND QUALITY OF LIFE


Proton Passive Scattered Technique
Photon Intensity Modulated (IMRT) Technique
Breast
Heart
Tumor
Liver
Breast
Heart
Tumor
Liver
Heart
Liver
Heart
Liver

Protons reduces hospital stay by > 2 days



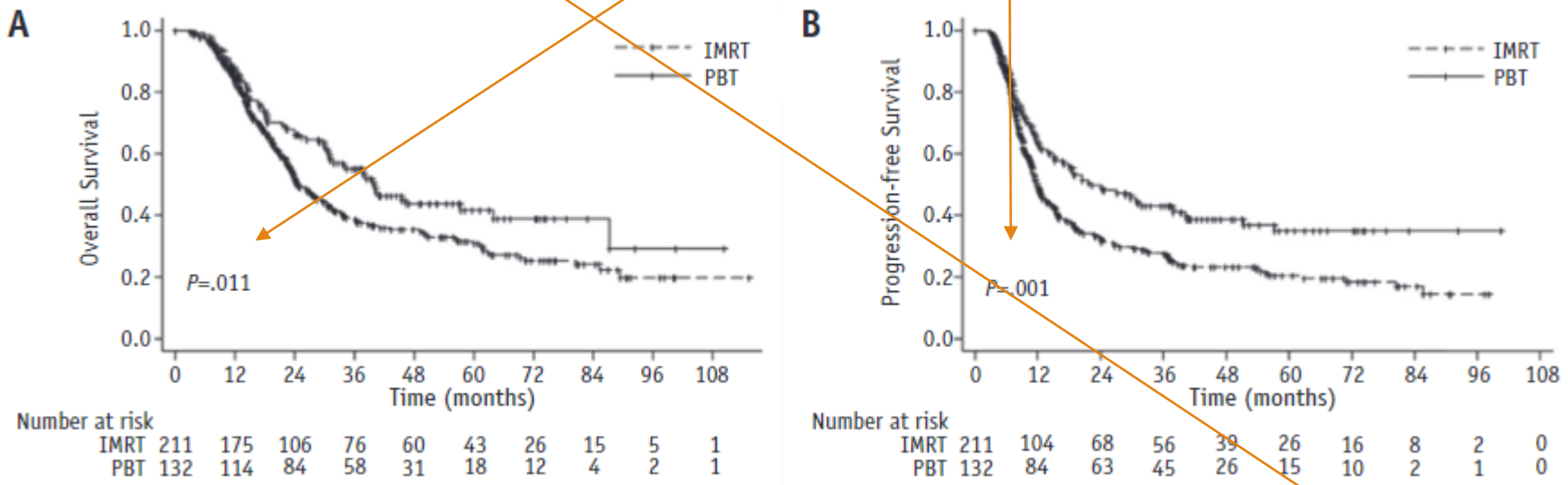
Lin SH et al., ASTRO 2015


"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

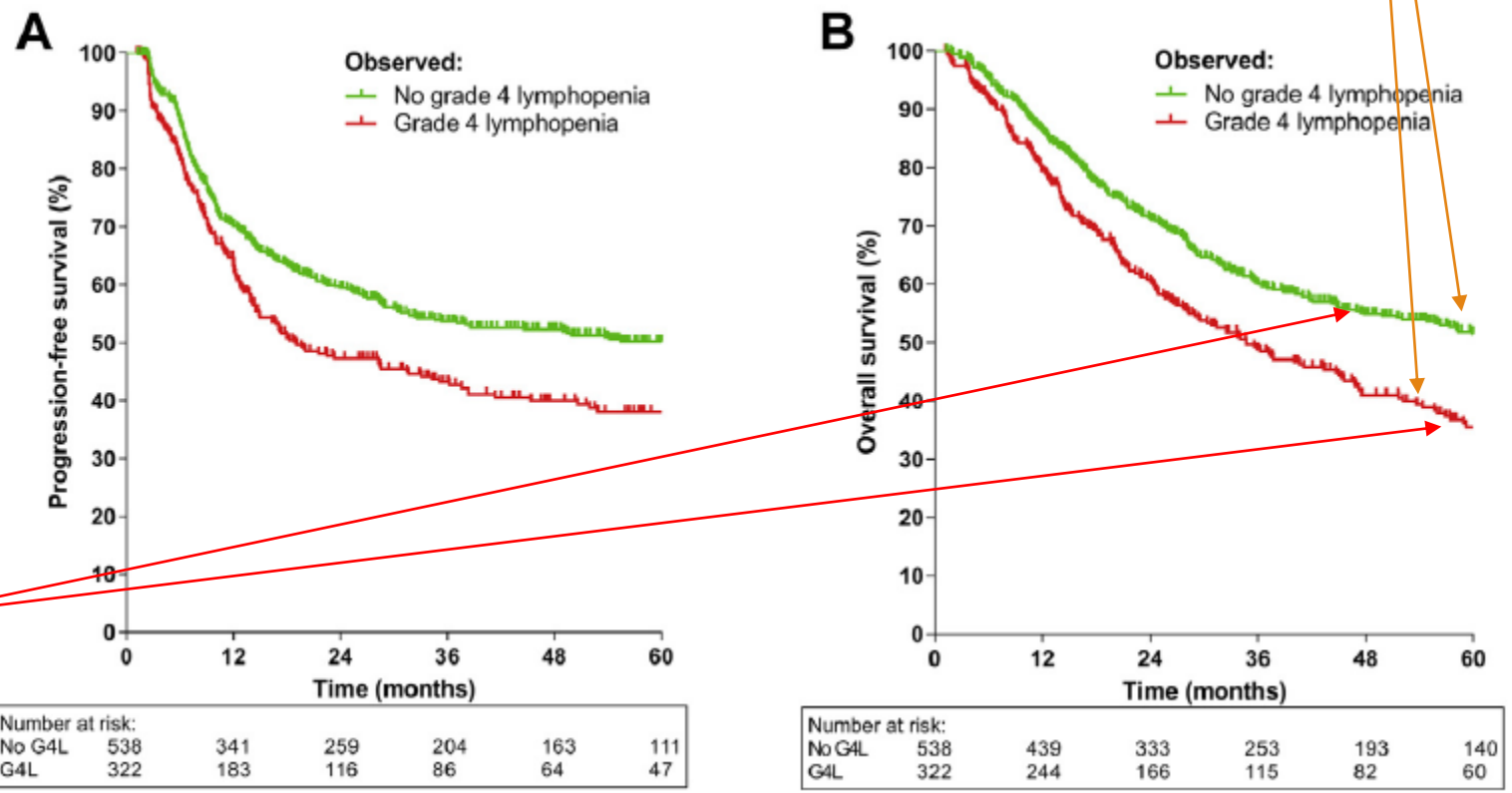
Peter S.N. van Rossum, MD, PhD,[a,b] Wei Deng, MD,[a]

Practical Radiation Oncology (2020) **10**, e16-e26

survival vs lymphopenia is… survival vs toxicity!

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

survival vs immune-competence!

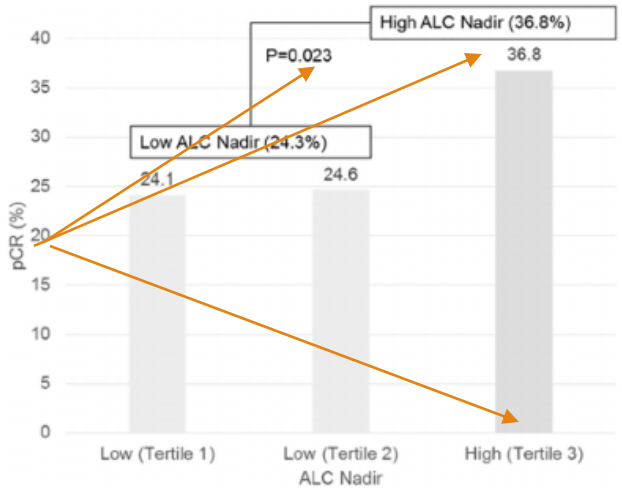


High lymphocyte count during neoadjuvant chemoradiotherapy is associated with improved pathologic complete response in esophageal cancer

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

Radiotherapy and Oncology 128 (2018) 584–590



Journal of Clinical Oncology®
An American Society of Clinical Oncology Journal
2018 Jun 20;36(18):1823-1830
ORIGINAL REPORTS | Radiation Oncology

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

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

11 clinical scenarios
5 new additions 2017

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:

- 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

6 clinical scenarios CED

JASTRO 2017

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

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?eid=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) 96.6GyE/56 fractions (2 fraction/day, edema region 50.4GyE/28 fractions)	5-7
Germ cell tumors	Local total dose 50.4-61.2GyE/28-34 fractions (Determine field of radiation from tumor site with or without spreadin Combination with whole ventricular irradiation, whole brain irradiation, or craniospinal irradiation 23.4GyE/13 fracti	8-11
Meningioma	Benign (Difficult to perform surgical resection): 54GyE/30 fractions Atypical, Anaplastic: 66.6GyE/28 fractions	12-16
Pituitary adenomas *Unresectable or postoperative remnants of recurring tumors*	54GyE/30 fractions	17-18
Craniopharyngioma *Unresectable or postoperative remnants of recurring tumors*	54GyE/30 fractions	19-22
Medulloblastoma	50-59.4GyE/25-33 fractions (craniospinal irradiation and local radiation)	23-25
Ependymoma Ad	Low grade: 50.4GyE/28 fractions Anaplastic: 60GyE/30 fractions	26-30
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	
Atypical teratoid/rhabdoid tumor		25,31
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)	
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 cauda equine	23-25, 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)	5,26,33

Disease	Radiotherapy	Ref.
Head and Neck tumors		
Squamous cell carcinoma of the nasal cavity and paranasal sinus *In cases where low doses irradiated to organs at risk cannot be ensured during X-ray radiotherapy*	Radical irradiation: 70-74GyE/35-37 fractions (standard fractionation)[a] 70.2Gy/26 fractions (reduced fractionation)[a] Postoperative irradiation: 66GyE/33 fractions[a]	34-39
Squamous cell carcinoma of the head and neck *In cases where low doses irradiated to organs at risk cannot be ensured during X-ray radiotherapy*	Radical irradiation: 70-74GyE/35-37 fractions[a] Postoperative irradiation: 66GyE/33 fractions[a] Re-irradiation: 60GyE/30 fractions	40-41
Malignant melanoma of the head and neck *Unresectable or incomplete resection*	Radical irradiation: 60-60.8GyE/15-16 fractions[b] Postoperative irradiation: 30GyE/5 fractions[b]	34,42-43
Olfactory neuroblastoma *Unresectable or incomplete resection*	Radical irradiation: 65-70.2GyE/26-32 fractions Postoperative irradiation: 66-70GyE/33-35 fractions	34,35,39 , 44,45
Adenoid cystic carcinoma *Unresectable or incomplete resection*	Radical irradiation: 65-70.2GyE/26 fractions 70.4-74.8GyE/32-34 fractions Postoperative irradiation: 66-70GyE/33-35 fractions	34,45-46
Advanced malignant salivary gland tumor *Lymph node metastasis, history of postoperative*	Radical irradiation: 65-70.2GyE/26 fractions Postoperative irradiation: X-ray therapy with proton beam boost to 66-70GyE/33-35 fractions	45-46
Non-squamous cell carcinoma of the head and nec	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 *Unresectable or inoperable cases*	Peripheral cT1-T2aN0: 66-70GyE/10 fractions[c]	47-50
	Peripheral cT2b-T3N0: 66-70GyE/10 fractions[c] 80GyE/20 fractions[c]	
	Central cT1a-T3N0: 80GyE/25 fractions[c] 72.6GyE/22 fractions[c]	
Stage II and III non-small cell lung cancer	60-66Gy/30-33 fractions 70-74Gy/35-37 fractions	51-53
Mediastinal tumor	60-66Gy/30-33 fractions 70-74Gy/35-37 fractions	29, 54-56
Gastrointestinal (GI) tumors		
Stage I to III primary esophagus cancer	60-70GyE/30-35 fractions (combined with photon therapy of 36-40Gy/20 fractions with elective field irradiation)	57-61
Locally recurrent rectal cancer *Unresectable tumor*	Close to the GI tract: 60-70GyE/30-35 fractions Not close to the GI tract: 72-75GyE/18-25 fractions	62-64
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 *Unresectable or recurrent tumors*	Porta hepatica type: 72.6-76GyE/20-22 fractions Adjacent to the digestive tract: 74-76GyE/37-38 fractions	69-73
Porta hepatic and extrahepatic cholangiocarcinom	Porta hepatic area: 70.2-72.6GyE/22-26 fractions Adjacent to the GI tract: 50-60GyE/25-30 fractions	70,74-75
Locally advanced pancreatic cancer *Unresectable or recurrent tumors*	50-56GyE/25-28 fractions (standard fractionation) 59.4GyE/33 fractions (Careful prospective multi-insitutional study is warranted) 60-67.5GyE/20-25 fraction with simultaneous boosting (Careful prospective multi-insitutional study is warranted)	76-79

Disease	Radiotherapy	Ref.
Urological tumors		
Prostate cancer Stage T1c-T4N0M0	74-78GyE/37-39 fractions (standard fractionation) 69-70GyE/28-30 fractions (reduced fractionation) 60-66GyE/20-22 fractions (reduced fractionation)	80-85
Bladder cancer Stage II-III	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
Renal cancer Stage T1-4N0M0, inoperable case	Ventral tumor: 76-79.2GyE/20-24 fractions 77GyE/35 fractions Posterior tumor: 66GyE/10 fractions	90-93
Testicular tumor *Irradiation to the para-aortic or affected common iliac artery area*	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	94-95
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, 108, 109
Metastatic tumors		
Metastatic lung tumor *Oligometastatic (≤ 3 lesions)*	Peripheral: 64GyE/8 fractions Central: 72.6GyE/22 fractions	110-111
Metastatic liver tumor *Oligometastatic (≤ 3 lesions)*	Peripheral: 64GyE/8 fractions Central: 72.6GyE/22 fractions	65, 112-114
Metastatic lymph node *Oligometastatic*	Recurrent, refractory: 64GyE/8 fractions 72.6GyE/22 fractions Adjacent to critical organs: 50-70GyEGyE/25-35 fractions	115

Proton therapy services @ CUN 2022

ASTRO updates insurance coverage recommendations for proton therapy

ARLINGTON, Va., July 12, 2017

+

+

GOBIERNO DE ESPAÑA | MINISTERIO DE SANIDAD, CONSUMO Y BIENESTAR SOCIAL

=

11 clinical scenarios
5 new additions 2017

Clínica Universidad de Navarra

Madrid, 18 de Noviembre de 2020

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 Colangiocarcinoma.
- 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 oligometastásica y oligorecurrente.

*Recomendaciones validadas por sociedades científicas:
https://www.astro.org/News-and-Publications/News-and-Media-Center/News-Releases/2017/ASTRO-updates-insurance-coverage-recommendations-f
https://seor.es/guias-clinicas/recomendaciones-de-la-seor-para-la-protonterapia-en-espana-2/

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

The REALITY, today:

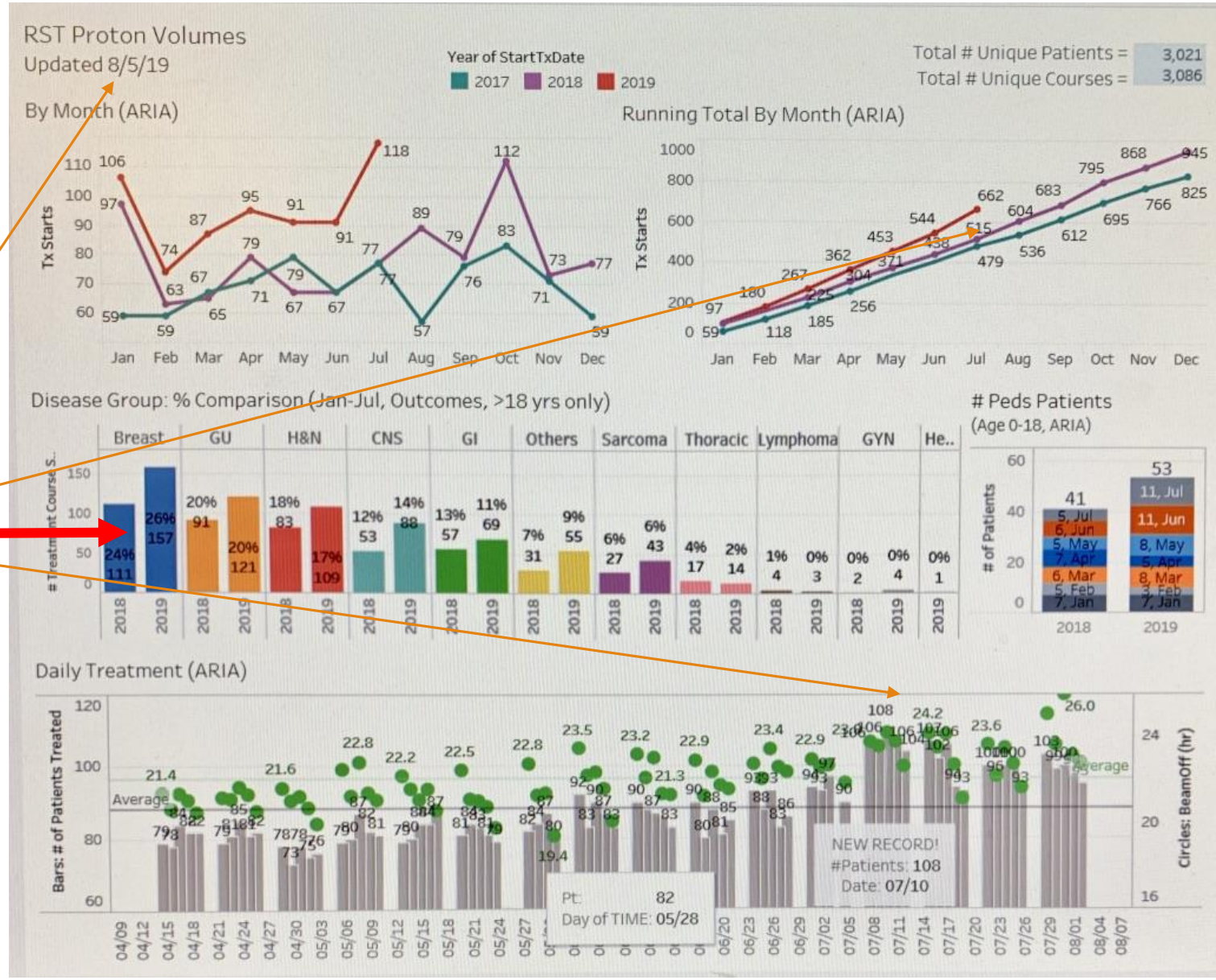
Mayo Clinic daily practice…

MAYO CLINIC

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

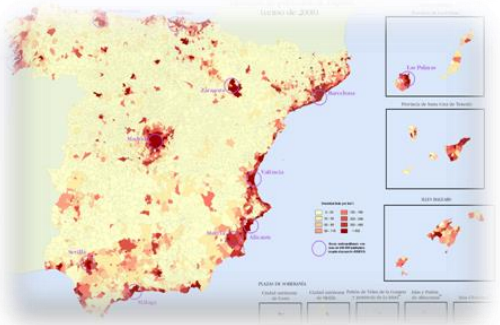
benefit = dosimetric = clinical

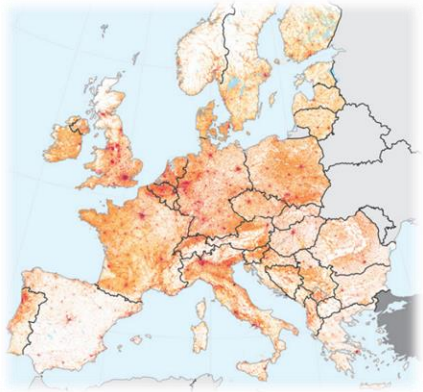


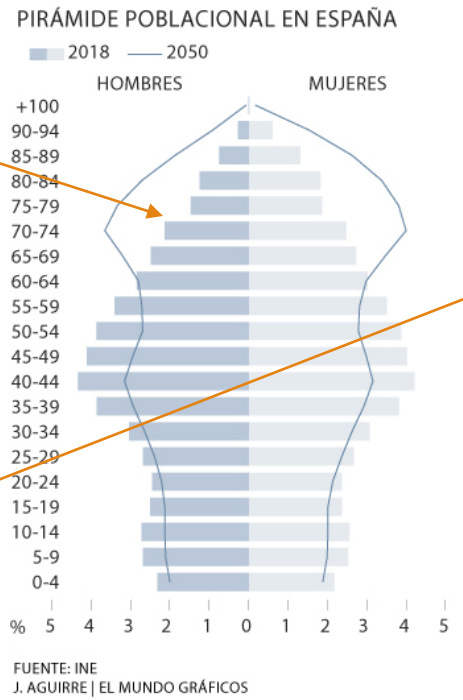
Clínica Universidad de Navarra

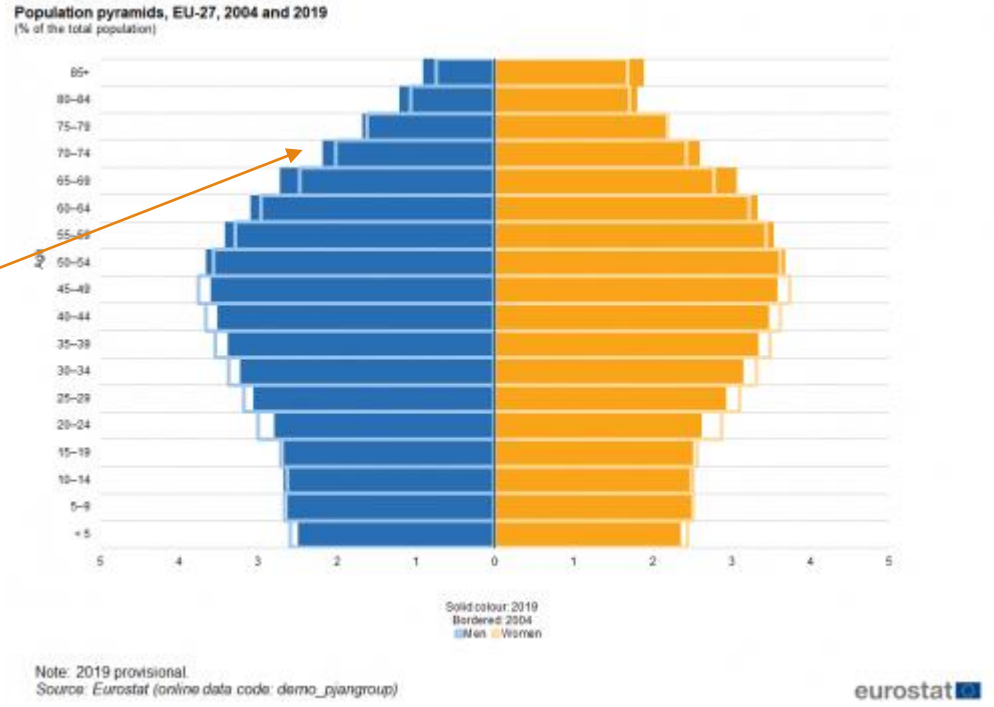
Proton therapy and social change 2022 - 2032

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





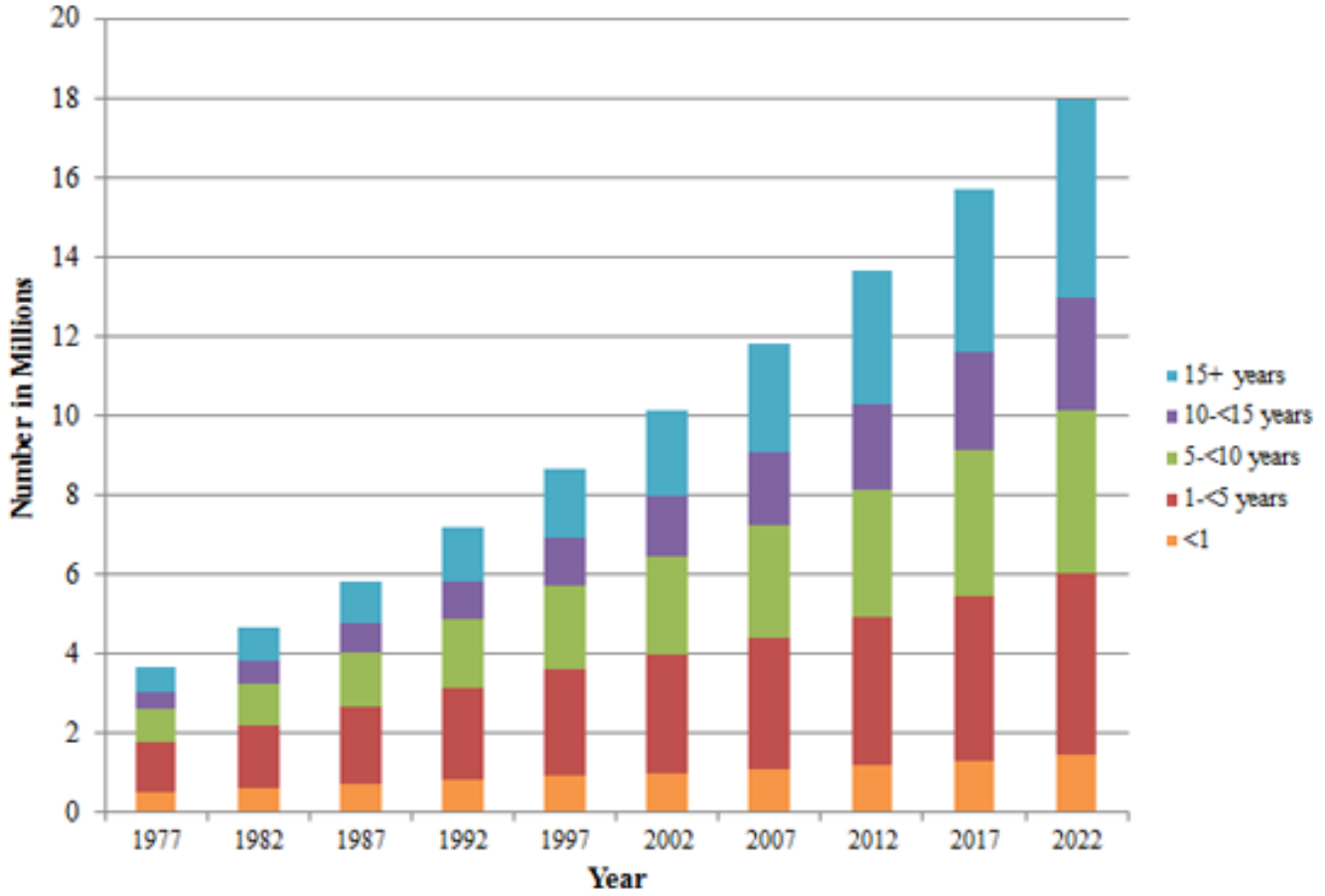




Normal tissues that are not *that* normal: comorbidities…

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

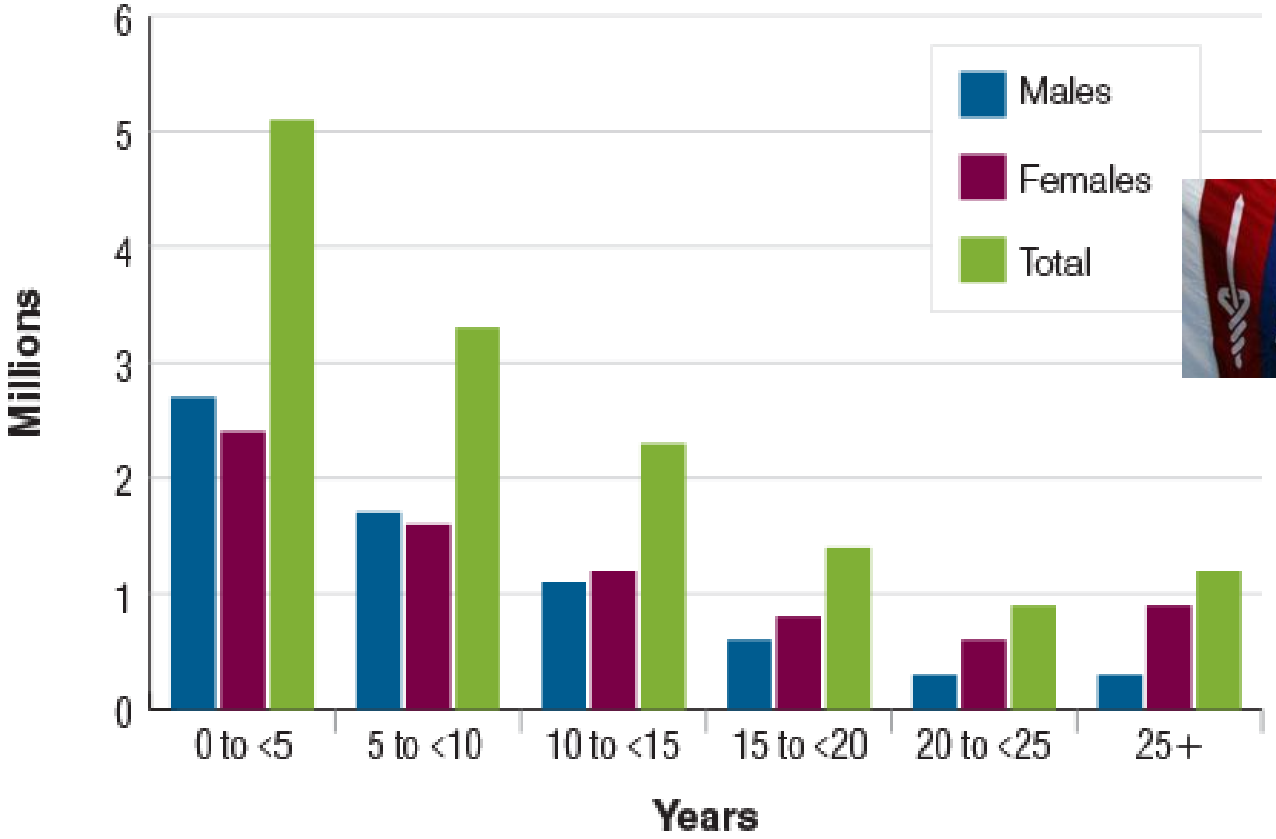
Estimated and projected number cancer survivors in the United States from 1977-2022 by years since diagnosis



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.

“Suvivors” : male *vs* female

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



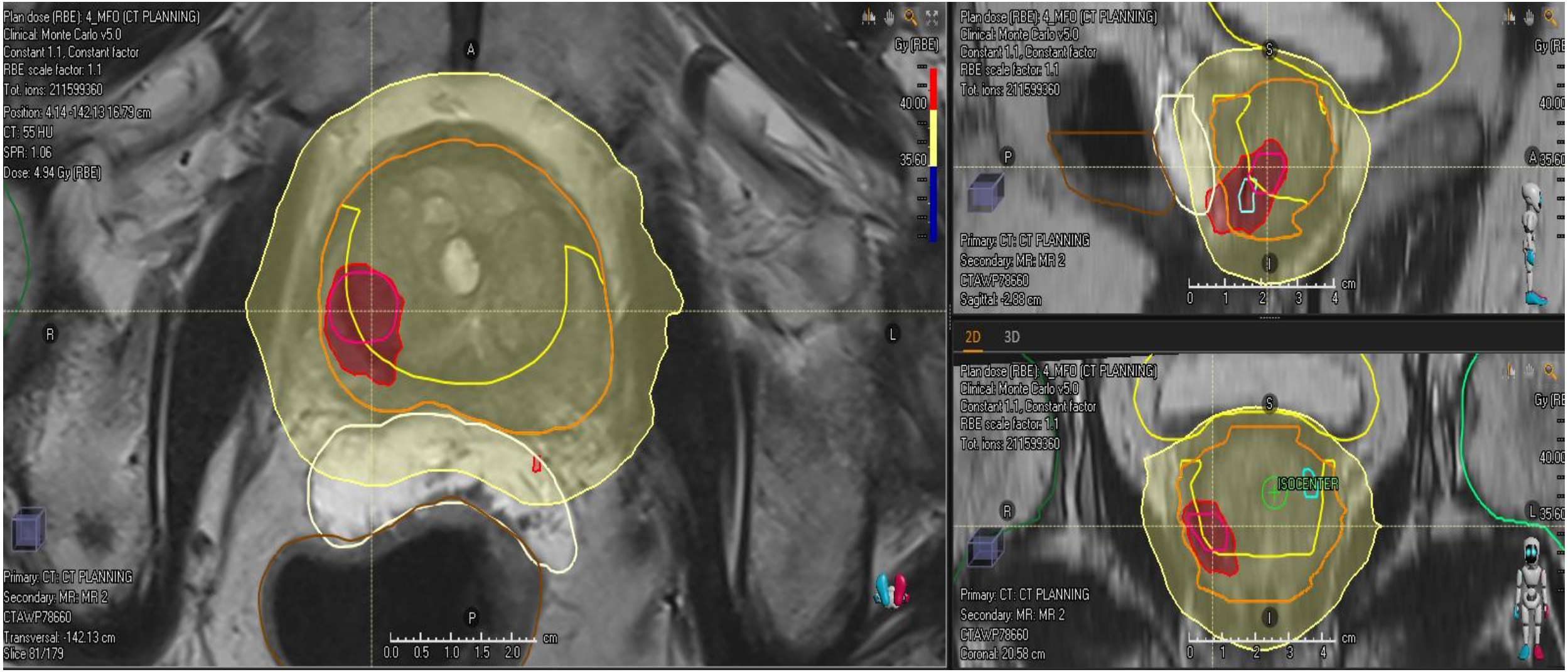
The REALITY, today:

Opportunities in clinical practice…

PT in context: interdisciplinar oncology; opportunities 2022

Cancer Center
Universidad
de Navarra

Caring · Researching
Innovating · Educating



CTV Prostate & Intraboost CTV HR

Impact factor 2017… 244.585

CA CANCER J CLIN 2017;67:65–85

Radiotherapy Combination Opportunities Leveraging Immunity for the Next Oncology Practice

Fernanda G. Herrera, MD[1,2]; Jean Bourhis, MD, PhD[3]; George Coukos, MD, PhD[4,5]

[1]Radiation Oncologist, University Hospital of Lausanne (CHUV), Lausanne, Switzerland; [2]Instructor, University Hospital of Lausanne (CHUV), Lausanne, Switzerland; [3]Professor, Chief of Radiation Oncology Service, University Hospital of Lausanne (CHUV), Lausanne, Switzerland; [4]Professor, Director, Department of Oncology, University Hospital of Lausanne (CHUV), Lausanne, Switzerland; [5]Director, 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-

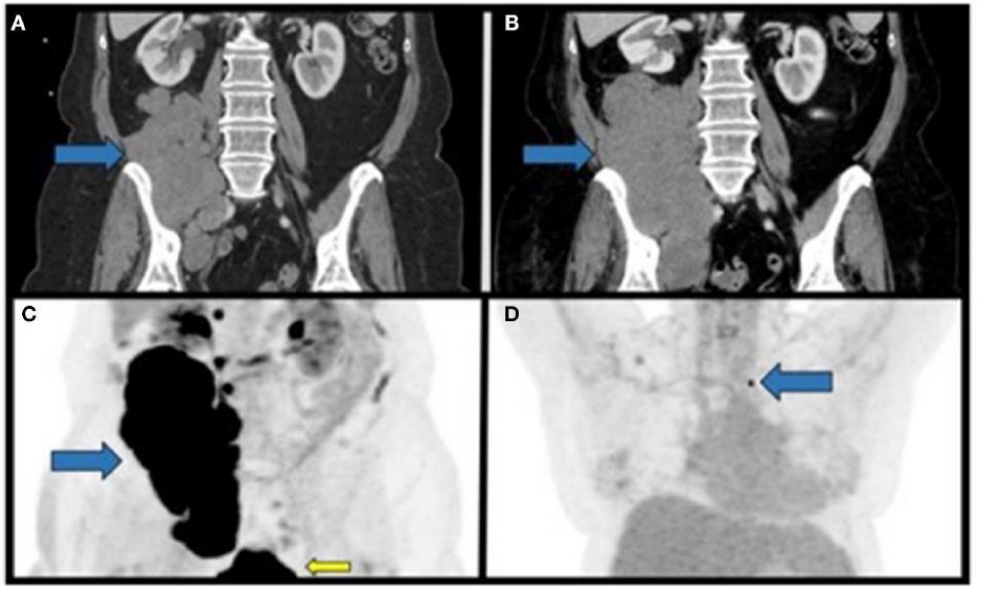
CASE REPORT
published: 26 September 2019
doi: 10.3389/fonc.2019.00922

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

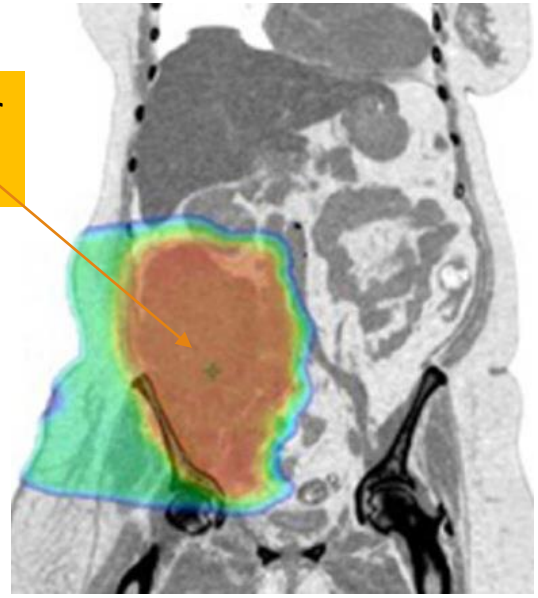
Randall J. Brenneman[1], Nima Sharifai[2], Benjamin Fischer-Valuck[3], Comron Hassanzadeh[1], Jeffrey Guzelian[4], John S. A. Chrisinger[2], Jeff M. Michalski[1], Peter Oppelt[5] and Brian C. Baumann[1]

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

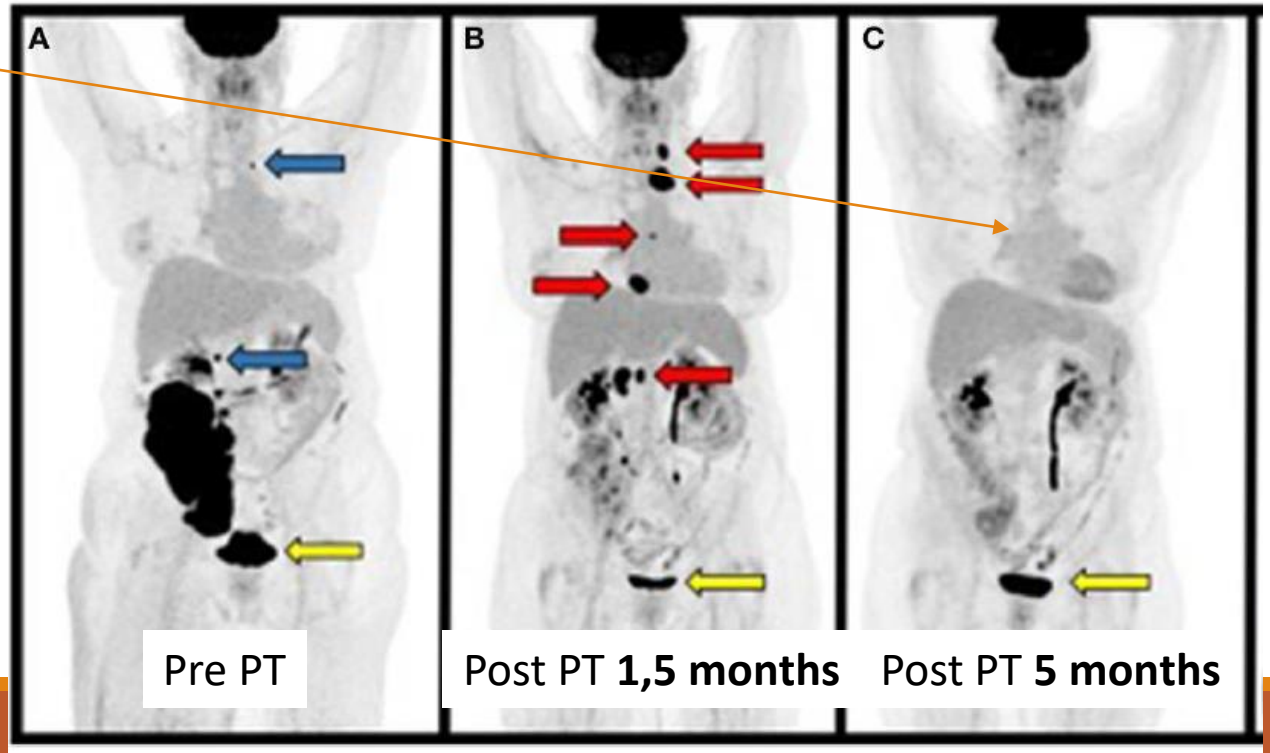
frontiers in Oncology



50 CGyE/25 fr **protons**



18 months NED



unclassified round cell sarcoma with INI1 loss

PD-L1 expression >/=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

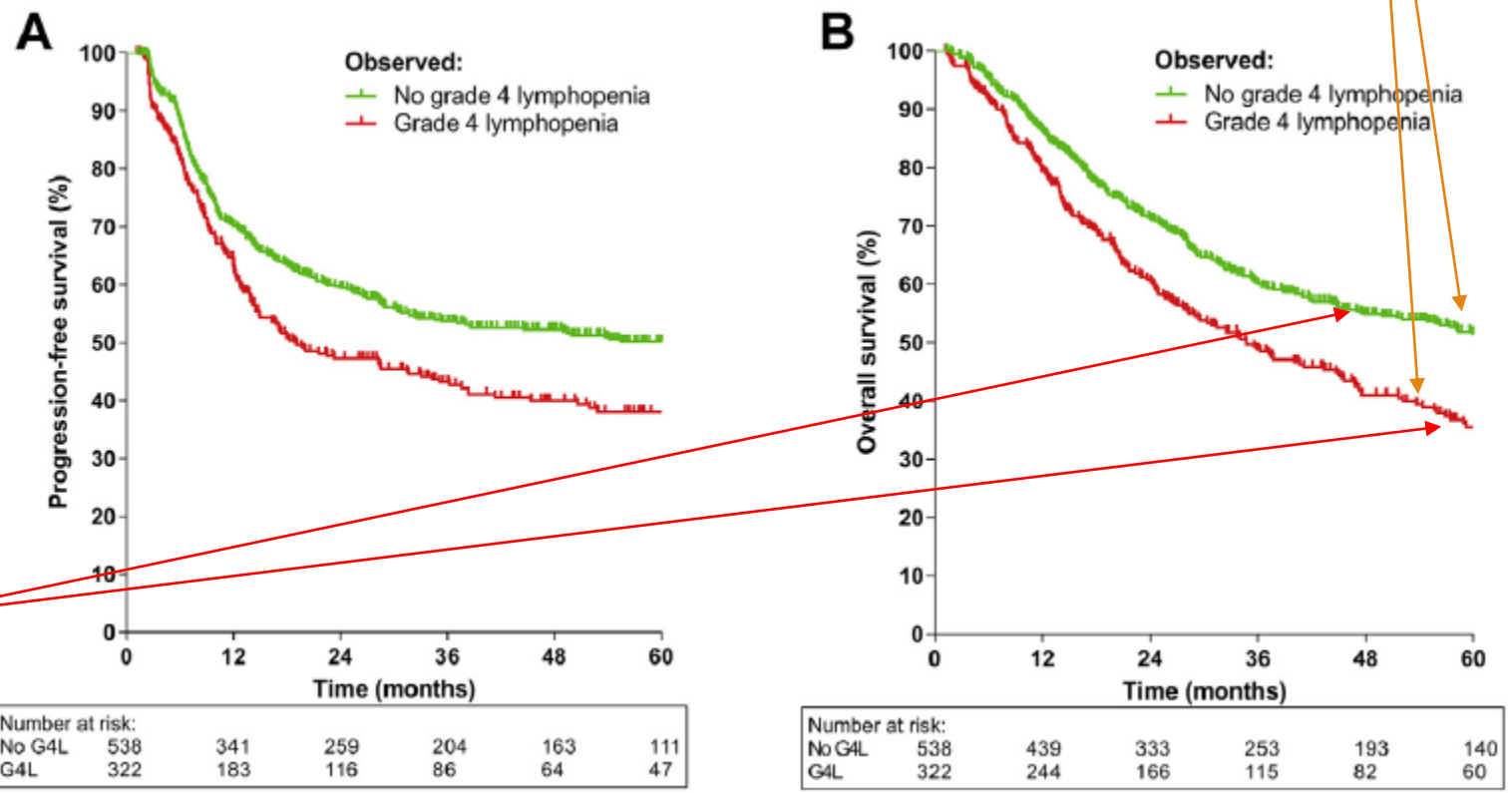
Peter S.N. van Rossum, MD, PhD,[a,b] Wei Deng, MD,[a]

Practical Radiation Oncology (2020) **10**, e16-e26

survival vs lymphopenia is… survival vs toxicity!

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

survival vs immune-competence!



Clínica Universidad de Navarra

Proton therapy today in Europe (2021)

clinical practice in adults…questionaire 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 Burnet [i], Vincent Gregoire [j], Valentin Calugaru [k], Esther G.C. Troost [l,m,n,o,p,q,r], Frank Hc
Felipe A. Calvo [t], Joachim Widder [u], Fabian Eberle [v], Marco van Vulpen [w], Philippe 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 centras treating that tumor site			100%	84%	32%	37%	32%	53%	53%	16%			

ACTIVIDAD DE LA

Unidad de Protonterapia

Cancer Center Universidad de Navarra | Clínica Universidad de Navarra

Pacientes

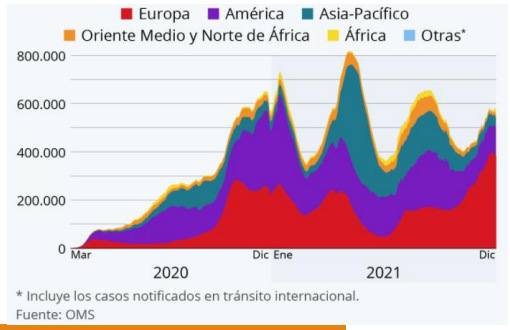
365 **267** adultos y **98** niños
(desde 14 meses hasta los 87 años)

TRATAMIENTOS FINALIZADOS: **317**

TRATAMIENTOS EN CURSO: **27**
21 en planificación

18 países de 4 continentes

España
262 pacientes
17 C.C.A.A.



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

Tumores

23 **tipos de tumores** diferentes:

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

La técnica

65.233 **movimientos del gantry**

31.579 **disparos**

98,0% **disponibilidad de uso de haz**

MAR 2022

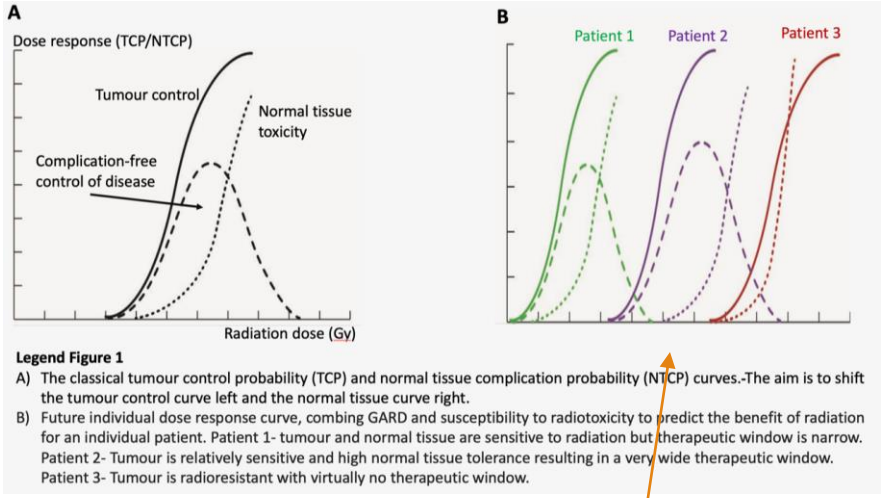
Original Article

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

Aimee L. McNamara [a,*,1], 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]

[a] Department of Radiation Oncology, Massachusetts General Hospital & Harvard Medical School, Boston; and [b] University of Texas MD Anderson Cancer Center, Houston, USA

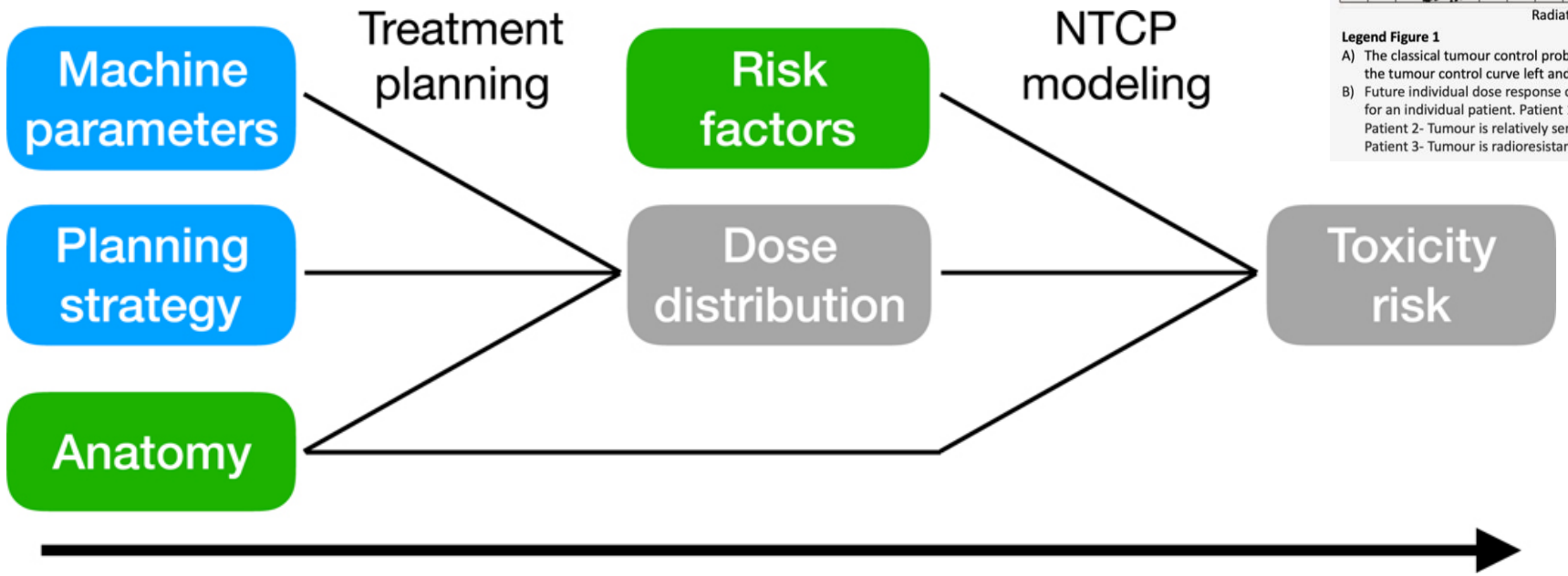
$$\Delta NTCP = NTCP_{Photons} - NTCP_{Protons}.$$



Legend Figure 1

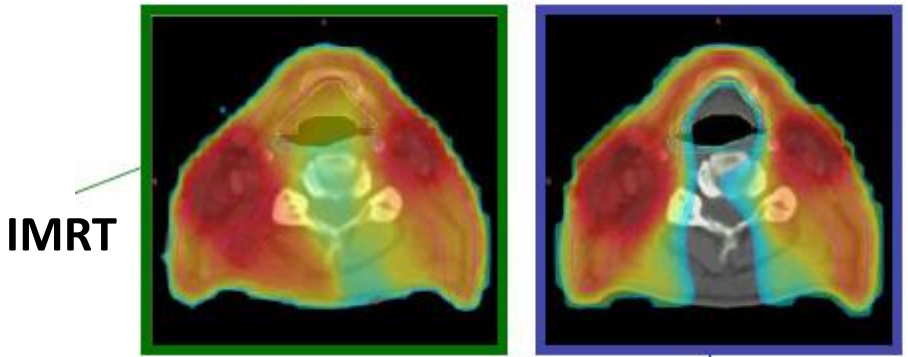
A) The classical tumour control probability (TCP) and normal tissue complication probability (NTCP) curves.-The aim is to shift the tumour control curve left and the normal tissue curve right.

B) Future individual dose response curve, combing 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.



Comorbidity scales

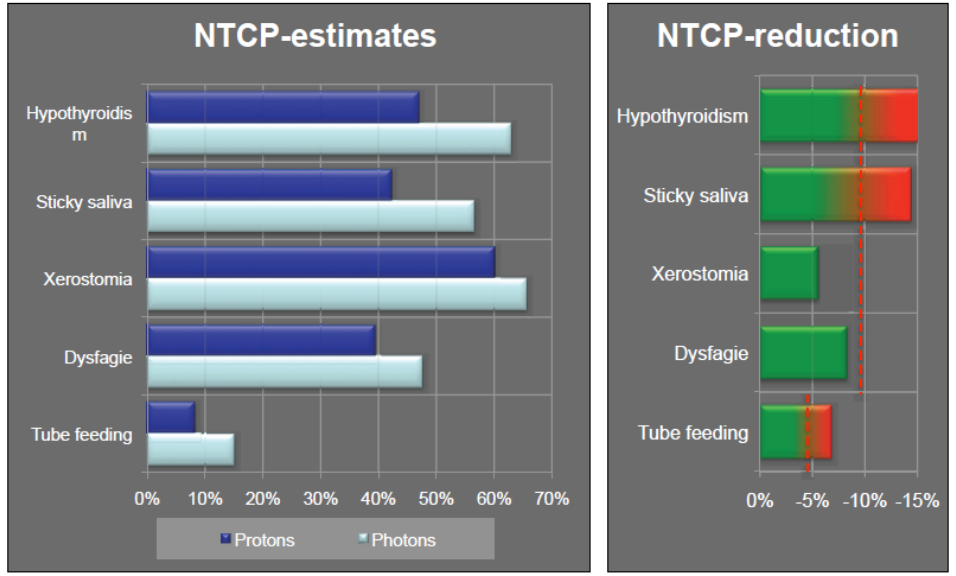
Models for individual risk estimations:



university of groningen

ΔNTCP selection

Comprehensive Individual TOxicity Risk profiles (CITOR-profile)



work in progress

Journal of Medical Imaging and Radiation Oncology •• (2020) ••–••

RADIATION ONCOLOGY—ORIGINAL ARTICLE

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

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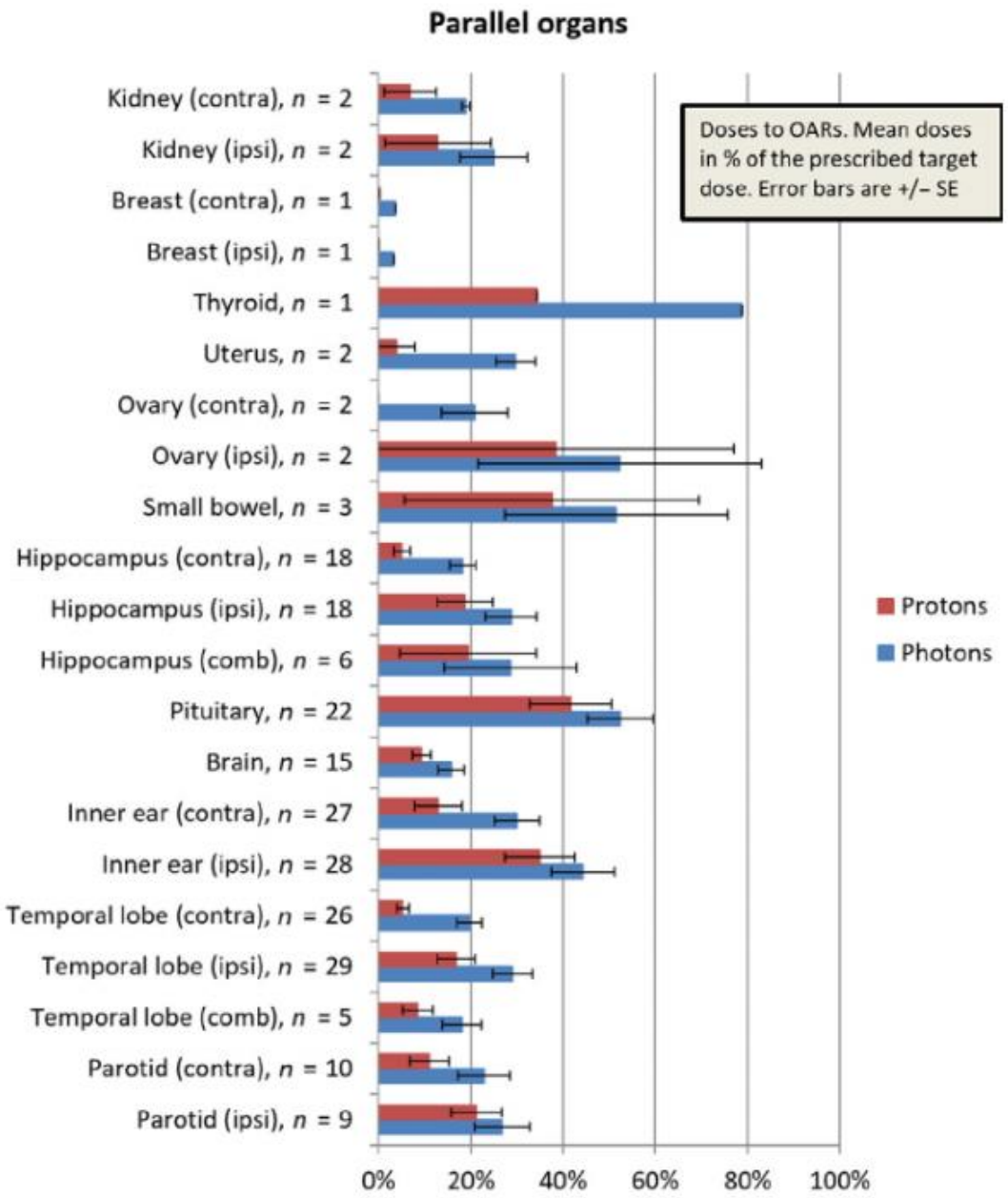
4 School of Health Sciences, University of South Australia, Adelaide, South Australia, Australia

January 2016 and December 2018

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

Commonwealth funding for PBT via the Medicare Medical Treatment Overseas Program (MTOP)
Proton versus photon treatment planning is a pre-requisite for the MTOP application



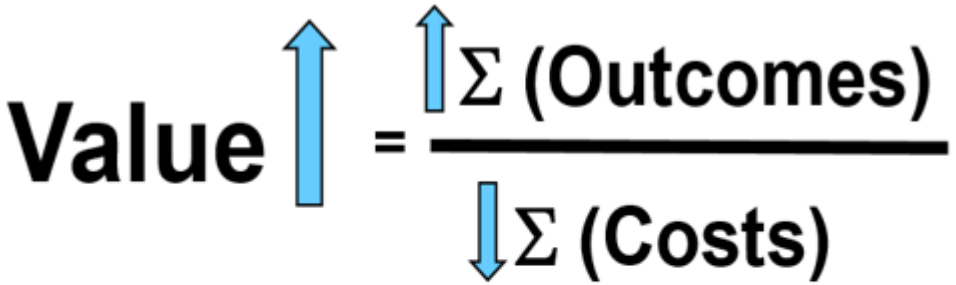
rgans at risks (OARs). Mean doses in % of the prescribed target dose. Error bars are ± SE.

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… 360º models



Thaker N et al. *Oncology Payers* 2014

INTERNATIONAL JOURNAL of PARTICLE THERAPY

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

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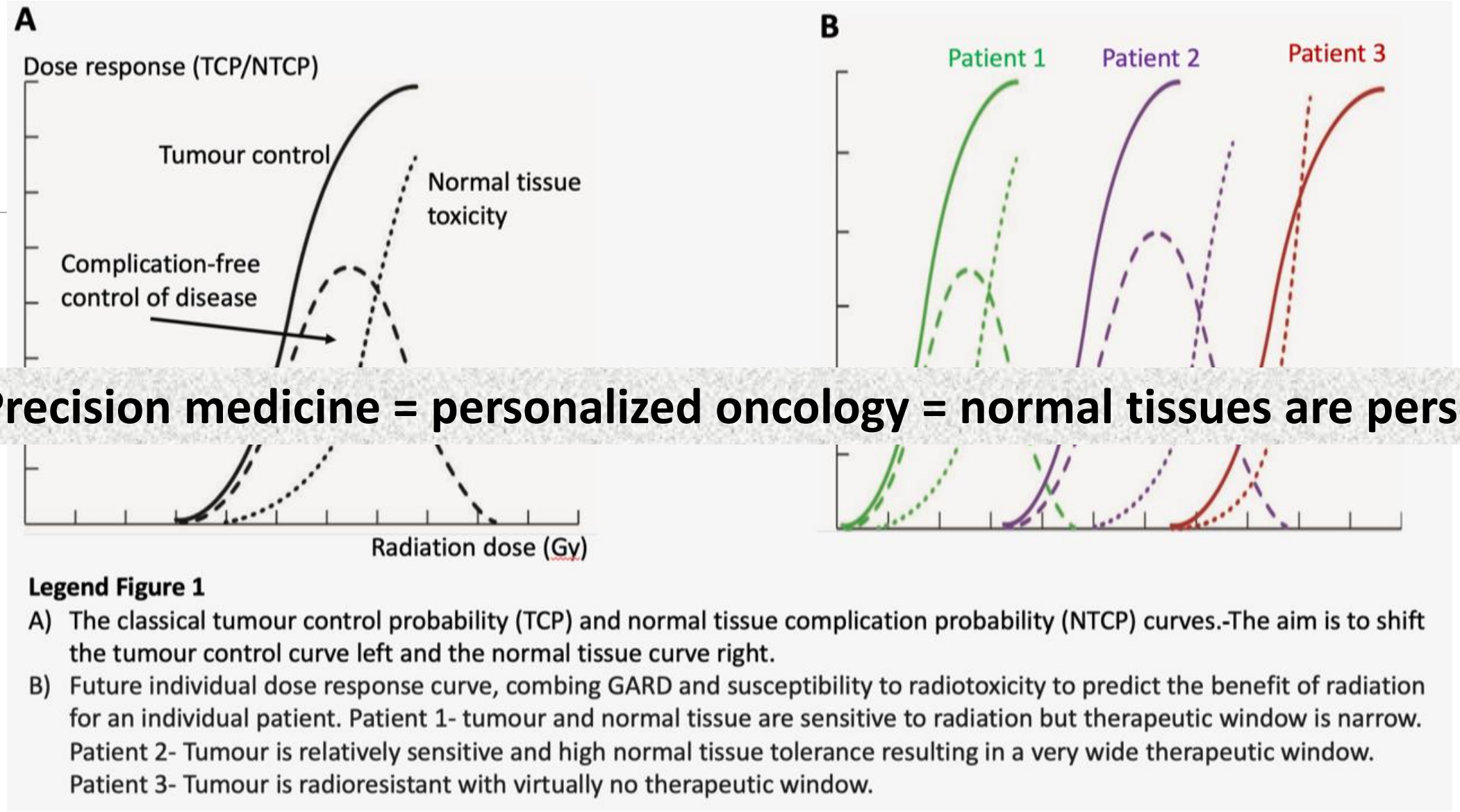
Cancer-related **financial toxicity impacts** head and neck cancer patients and survivors.
Economic implications of proton therapy—dimensions of "financial toxicity"—need to be addressed.
The value of proton therapy for head and neck cancer: empiric comparisons of patients' and survivors'
lost productivity
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, combing 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 360º analytical models based in medical and demographic dinamics

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