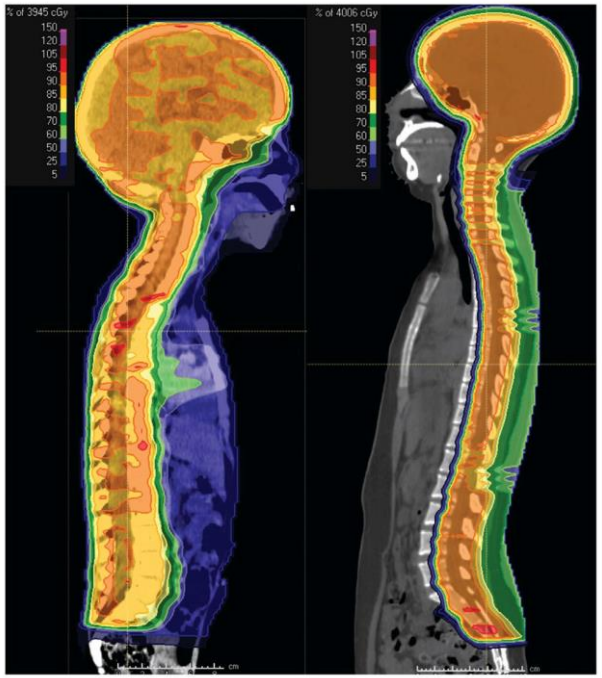
HITRI plus
Heavy Ion Therapy Research Integration

# Particle therapy clinical evidence


**DR. CAROLA LÜTGENDORF-CAUCIG**

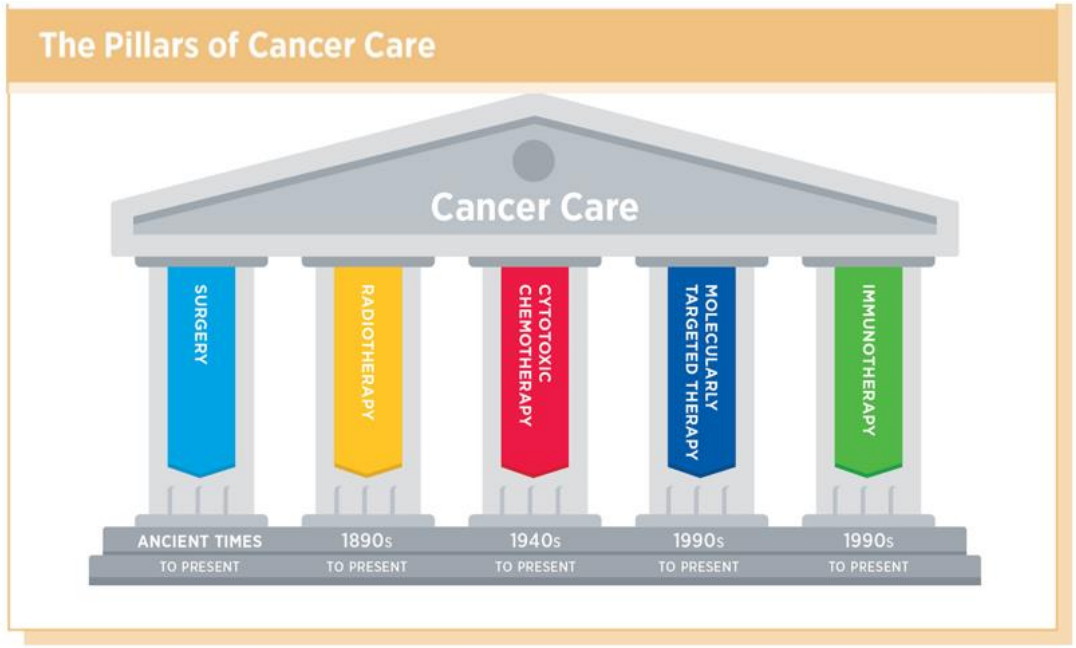
**MPH, MBA**

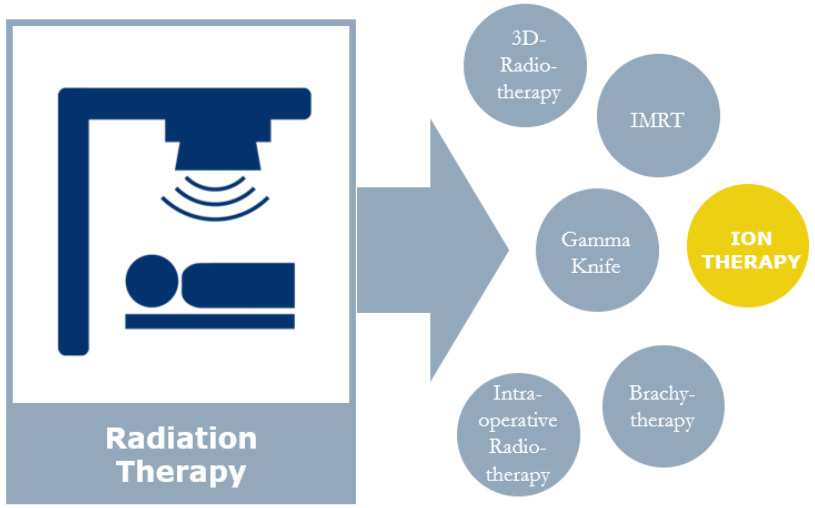


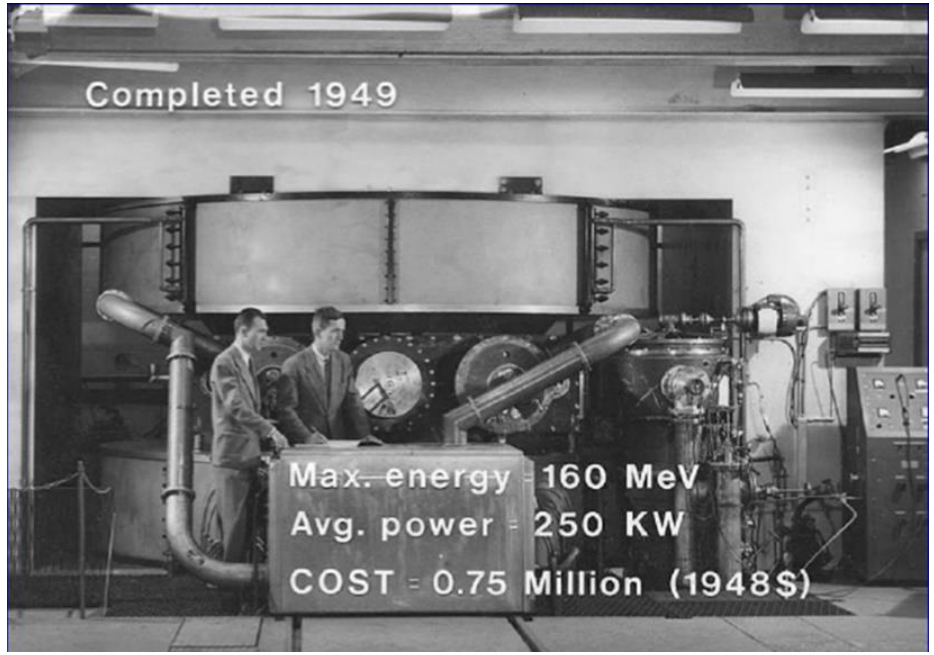
This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 101008548


Derek S. Tsang, and Samir Patel
CMAJ 2019;191:E664-E666




*American Association for Cancer Research (AACR) Cancer Disparities Progress Report 2020*

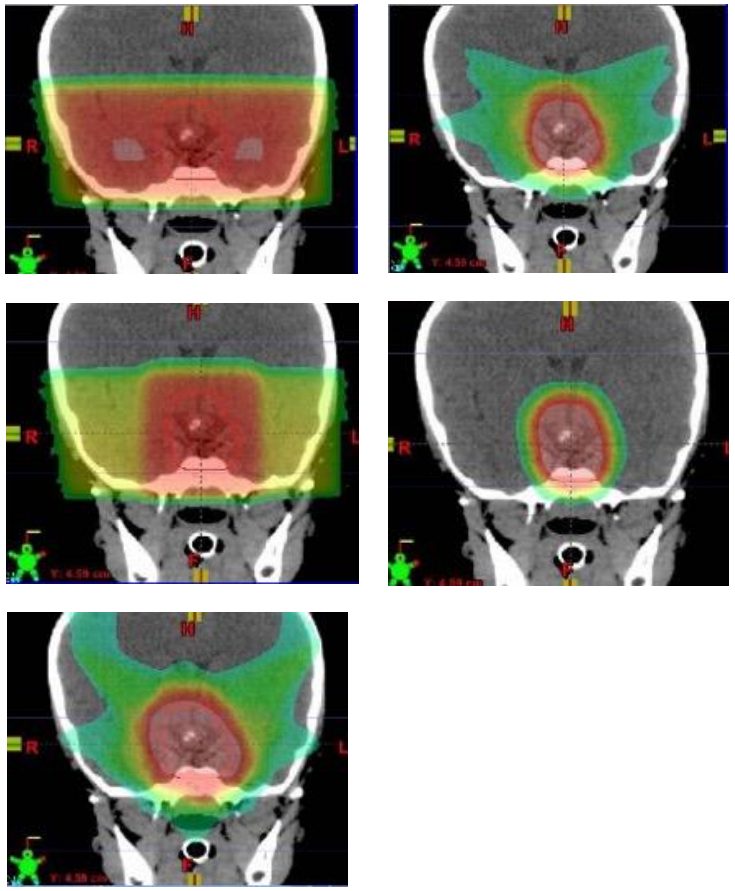


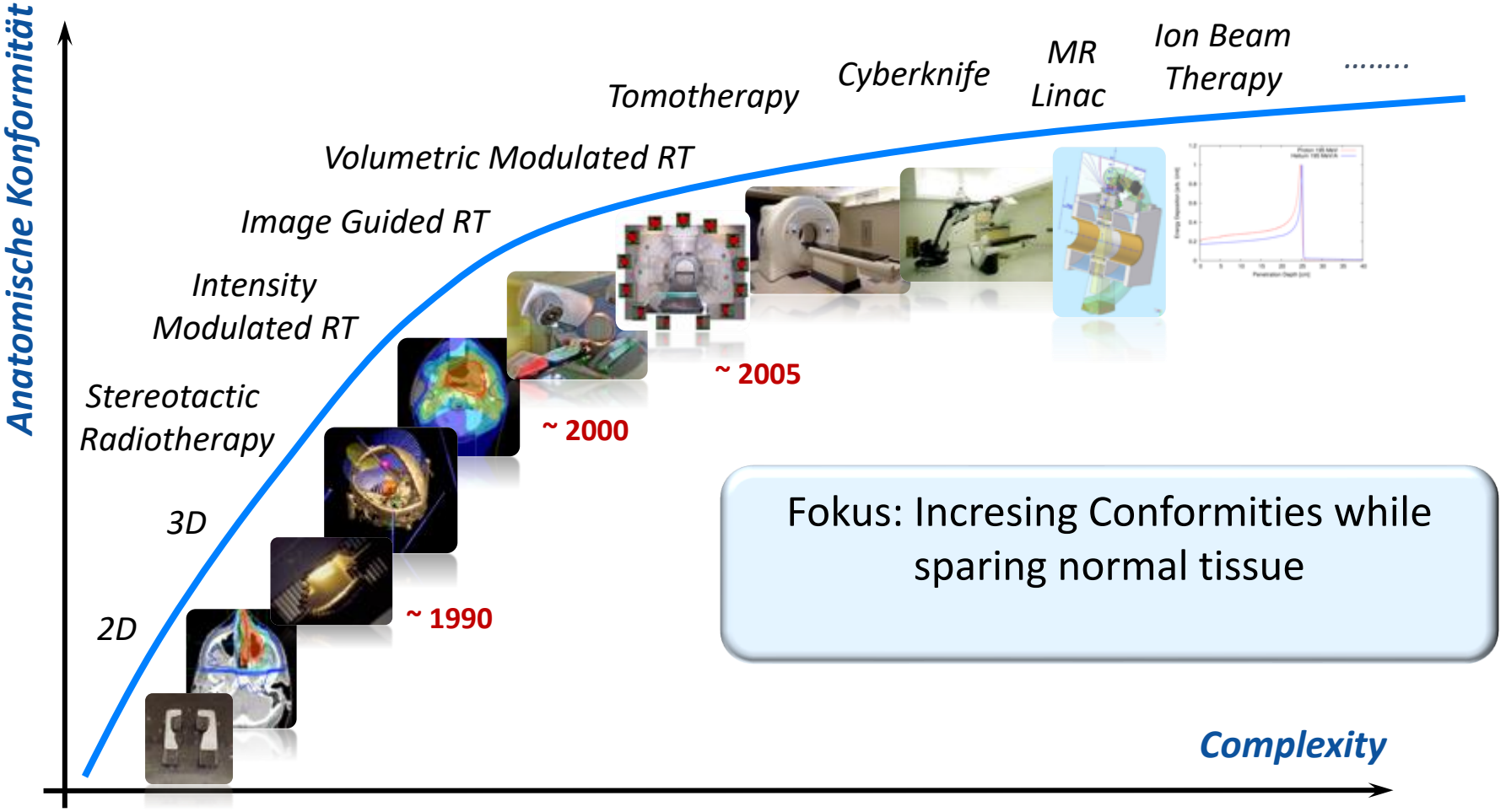




- 1929 cyclotron invented by E.O. Lawrence as a way to accelerate nuclear particles to a very high speed
- 1946 Lawrence protegee R. Wilson, professor of physics at Harvard and designer of Harvard´s Cyclotron first proposes using protons for cancer treatment
- 1954 J. Lawrence treats first patient with protons in Berkely for pituitary tumor
- 1957 first patient treated in Europe / Upsala / Sweden
- 1994The first carbon ion (C-ion) therapy center was launched at the National Institute of Radiological Science in Japan.

# Technical Evolution of Radiotherpay

*Slide courtesy Dietmar Georg*






Fokus: Incresing Conformities while sparing normal tissue

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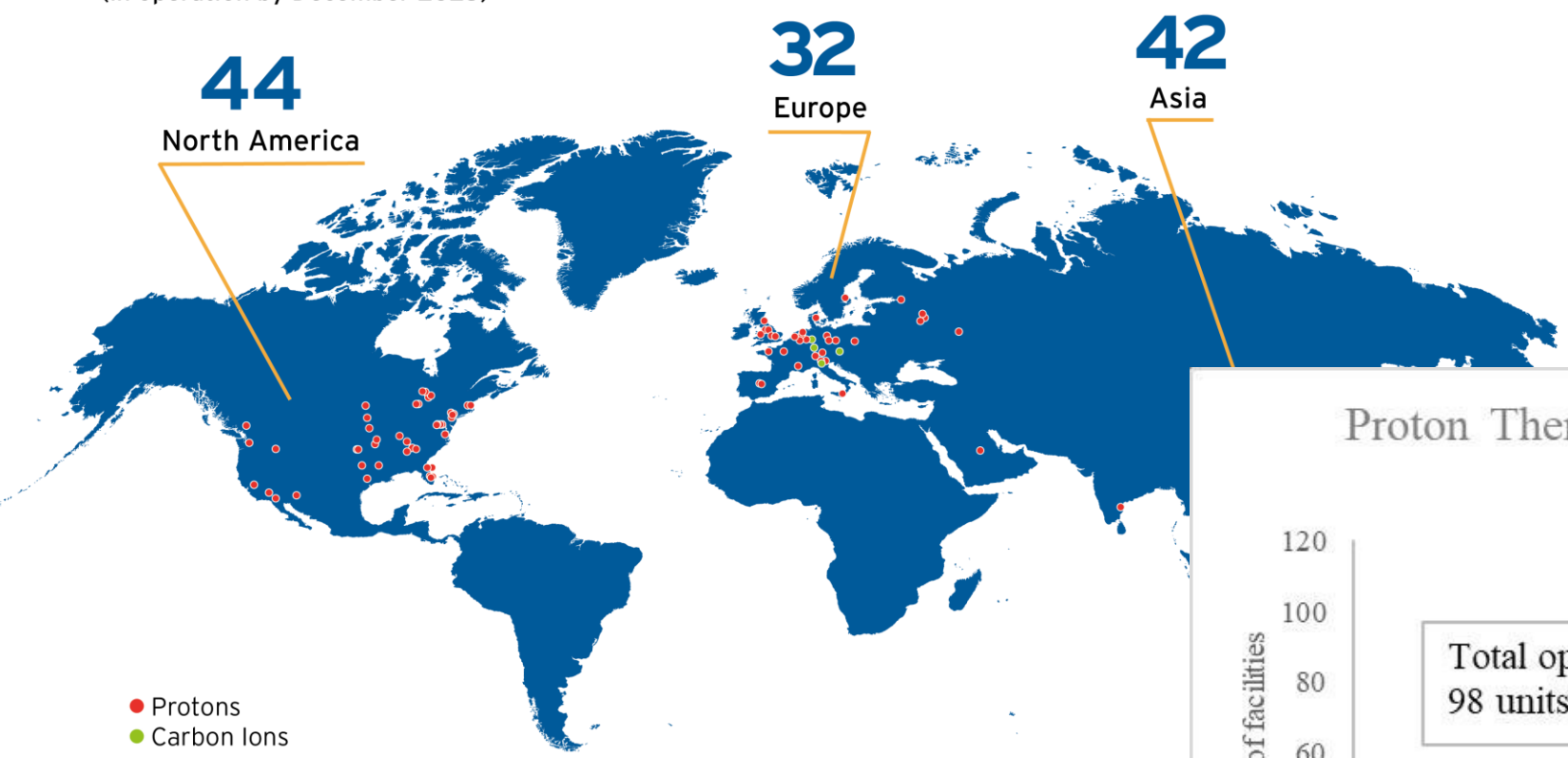
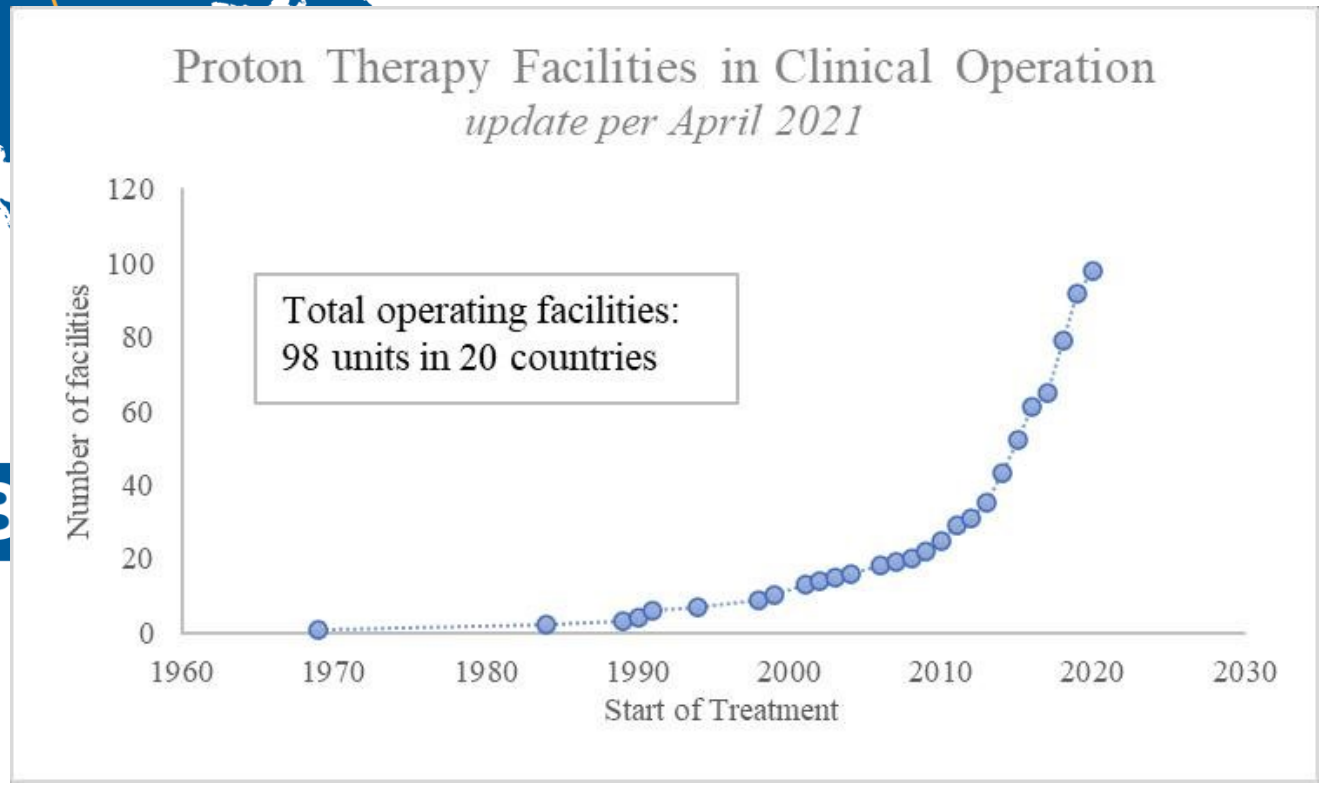
# PARTICLE THERAPY CENTERS WORLDWIDE: 118

(in operation by December 2023)




**104** Centers for Protons • **6** Centers for Protons & Carbon Ions • **8**

Data: PTCOG, December 2023



Doses Escalation

Pediatric and AYA

Reduction of RT induced Secondary Malignancies

Normal tissue sparing

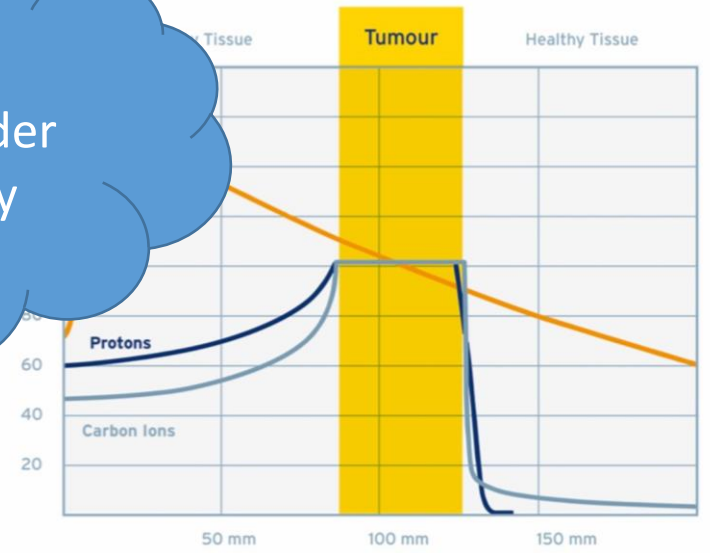
Overcome RT resistance

W Therpay?

ALARA

Reduction der RT Toxicity

Re-Irradiation

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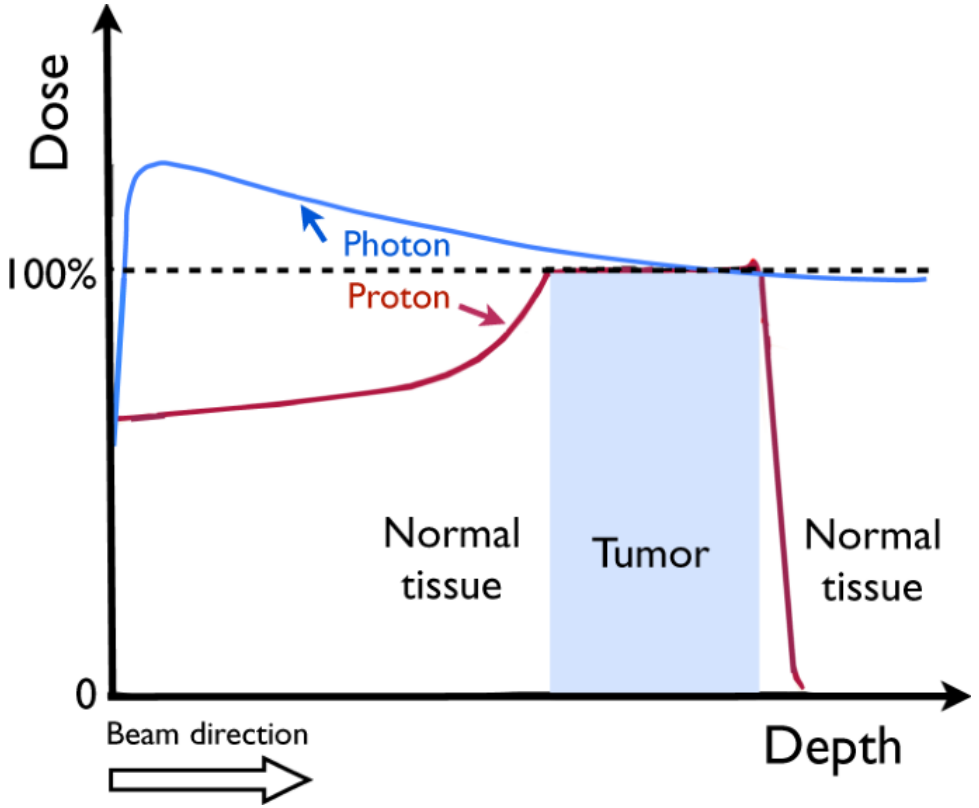
# Proton Irradiation – clinical evidence

Various national guidelines recommend proton therapy for 40 different types of cancer.

To date, protons have been successfully used in pediatric cancers and adult cancers of various localization including head-and-neck, brain, lung, liver, breast and prostate tumors.

Pediatric patients are considered to benefit most from the advantages of particle therapy, since they are particularly vulnerable to the toxic side effects of irradiation, especially from the developmental perspective.

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Heavy Ion Therapy Research Integration

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 101008548

1. Matsumoto, Y.; Fukumitsu, N.; Ishikawa, H.; Nakai, K.; Sakurai, H. A Critical Review of Radiation Therapy: From Particle Beam Therapy (Proton, Carbon, and BNCT) to Beyond. J. Pers. Med. 2021, 11, 825. https://doi.org/10.3390/jpm11080825
2. Kamran, S.C., Light, J.O. & Efstathiou, J.A. Proton versus photon-based radiation therapy for prostate cancer: emerging evidence and considerations in the era of value-based cancer care. *Prostate Cancer Prostatic Dis* **22**, 509–521 (2019). https://doi.org/10.1038/s41391-019-0140-7

# Indication for Protontherapy in paediatric cancer patients

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]

**Table 1**
Inter-comparisons between the impact on toxicity of modern photon and particle therapy, in pediatric malignancies. 2005–2015 clinical experience.

| Site | # Patients | Endpoint | Results | *P* value |
|---|---|---|---|---|
| *Brain* | | | | |
| Gunther [161] | 72 | MRI changes | P < IMXRT | (.002) |
| Yock [162] | 120 | Psycho., QOL | P > XR | (.01) |
| Bishop [41] | 52 | Vision | P > IMXRT | (NS) |
| *Neuro-endocrine* | | | | |
| Eaton [137] | 77 | Ant.pituitary, height | P > XR | (.01–.001) |
| Viswanathan [163] | 31 | Ant.pituitary | P > XR+P | (.01) |
| Bishop [41] | 52 | Panhypo., obesity | P > XR | (NS) |
| *Acute* | | | | |
| Song [164] | 43 | Hemato & Digestive | P > XR | (.01) |
| Grant [8] | 24 | HN Mucosa | P > XR | (.05) |
| Rieber [165] | 83 | Skin & Mucosa | C = P + XR | (NS) |
| *Body* | | | | |
| Sethi [166] | 86 | K2 | P > XR | (.01) |
| Chung [100] | 75 | K2 | P = XR | (NS) |
| *Lung* | | | | |
| Green [167] | 303 | Restrictive syndrome | P < XR | (.001) |
| *Head & neck* | | | | |
| Böling [168] | 133 | Salivary | P < XR | (.02) |

*Abbreviations:* >: better; <worse; Ant.: anterior; C: carbon ions; HN: head and neck; Hemato: haematological; NP: not significant; Panhypo.: panhypopituitarism; Psycho.: psychological. Other abbreviations: see text.

## Conclusions

Many studies still suggest that the predominant cause for early death among cancer survivors remains the primary tumor; however, it is also known survivors have many treatment related sequelae that impair their QOL in many domains. Through almost all dosimetric and model based evaluation, clinical outcomes for PT should be favorable with an improved QOL, organ function, development with a reduction in the risk of SMNs. Several decades of

# Looking for evidence Protontherapy in paediatric cancer patients

## An Update From the Pediatric Proton Consortium Registry

*Clayton B. Hess[1], Daniel J. Indelicato[2], Arnold C. Paulino[3], William F. Hartsell[4], Christine E. Hill-Kayser[5], Stephanie M. Perkins[6], Anita Mahajan[7], Nadia N. Laack[7], Ralph P. Ermoian[8], Andrew L. Chang[9], Suzanne L. Wolden[10], Victor S. Mangona[11], Young Kwok[12], John C. Breneman[13], John P. Perentesis[13], Sara L. Gallotto[1], Elizabeth A. Weyman[1], Benjamin V. M. Bajaj[1], Miranda P. Lawell[1], Beow Y. Yeap[1] and Torunn I. Yock[1]**

frontiers in Oncology

ORIGINAL RESEARCH
published: 24 May 2018

| Institution | Open to enrollment | Patient accrual |
|---|---|---|
| Massachusetts General Hospital (Boston, MA, USA) | Jul 2012 | 478 |
| Northwestern Medicine Chicago Proton Center (Chicago, IL, USA) | Sep 2013 | 242 |
| University of Florida Health Proton Therapy Institute (Jacksonville, FL, USA) | Nov 2013 | 490 |
| Washington University (St. Louis, MO, USA) | Mar 2014 | 81 |
| M.D. Anderson Cancer Center (Houston, TX, USA) | Jun 2014 | 278 |
| University of Pennsylvania (Philadelphia, PA, USA) | Jun 2014 | 89 |
| University of Washington (Seattle, WA, USA) | Feb 2016 | 41 |
| ProCure Proton Therapy Center (Somerset, NJ, USA) | Jun 2016 | 28 |
| Mayo Clinic (Rochester, MN, USA) | Jul 2016 | 58 |
| ProCure Proton Therapy Center (Oklahoma City, OK, USA) | Oct 2016 | 13 |
| Texas Center for Proton Therapy (Irving, TX, USA) | Nov 2016 | 47 |
| Maryland Proton Therapy Center (Baltimore, MD, USA) | Apr 2017 | 9 |
| Cincinnati Children's Hospital Medical Center (Cincinnati, OH, USA) | Oct 2017 | 0 |
| TOTAL | | 1,854 |

- Since 2012 > 1800 patients entered
- 1091 CNS tumors, 632 non-CNS tumors

| Intracranial and CNS tumors | N* | % | Tumors outside the CNS | N* | % |
|---|---|---|---|---|---|
| Medulloblastoma/ PNET | 276 | 25.4 | Rhabdomyosarcoma (RMS) | 191 | 30.5 |
| Ependymoma | 214 | 19.7 | Ewing sarcoma | 105 | 16.8 |
| Glial/astrocytoma | 195 | 18 | Hodgkin lymphoma | 66 | 10.5 |
| Tumors/gangliomas | | | | | |
| Craniopharyngioma | 153 | 14.1 | Neuroblastoma | 55 | 8.8 |
| Germ cell tumor | 108 | 9.9 | Chordoma | 47 | 7.5 |
| ATRT | 27 | 2.5 | Non-rms soft tissue sarcomas (NRSTS) | 47 | 7.5 |
| Meningioma | 20 | 1.8 | Carcinoma (NOS)[F] | 42 | 6.7 |
| Vascular lesions | 20 | 1.8 | Retinoblastoma | 11 | 1.8 |
| Sarcoma | 18 | 1.7 | Osteosarcoma/bone sarcoma | 11 | 1.6 |
| Nerve sheath tumor | 9 | <1 | Chondrosarcoma | 8 | 1.3 |
| Choroid plexus | 8 | <1 | Esthesioneuroblastoma | 6 | 1.0 |
| sPineal parenchymal tumor | 7 | <1 | Wilms tumor | 6 | 1.0 |
| Pituitary tumor | 7 | <1 | Hemangioma | 6 | 1.0 |
| Neurocytoma | 4 | <1 | Melanoma | 4 | <1 |
| Leukemia | 2 | <1 | Non-Hodgkins lymphoma | 2 | <1 |
| Langerhans histiocytosis | 1 | <1 | Paraganglioma/ Pheochromocytoma | 2 | <1 |

# EVIDENCE
# REDUCED INCIDENCE OF SECONDARY MALIGNANCIES?

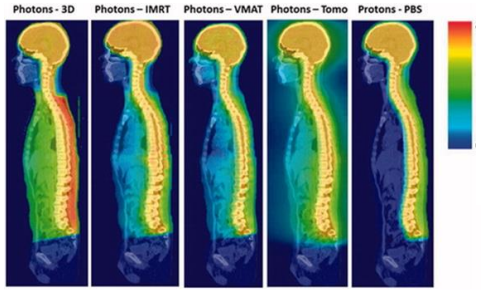
› Cancer. 2020 Aug 1;126(15):3560-3568. doi: 10.1002/cncr.32938. Epub 2020 May 19.

## Second cancer risk after primary cancer treatment with three-dimensional conformal, intensity-modulated, or proton beam radiation therapy

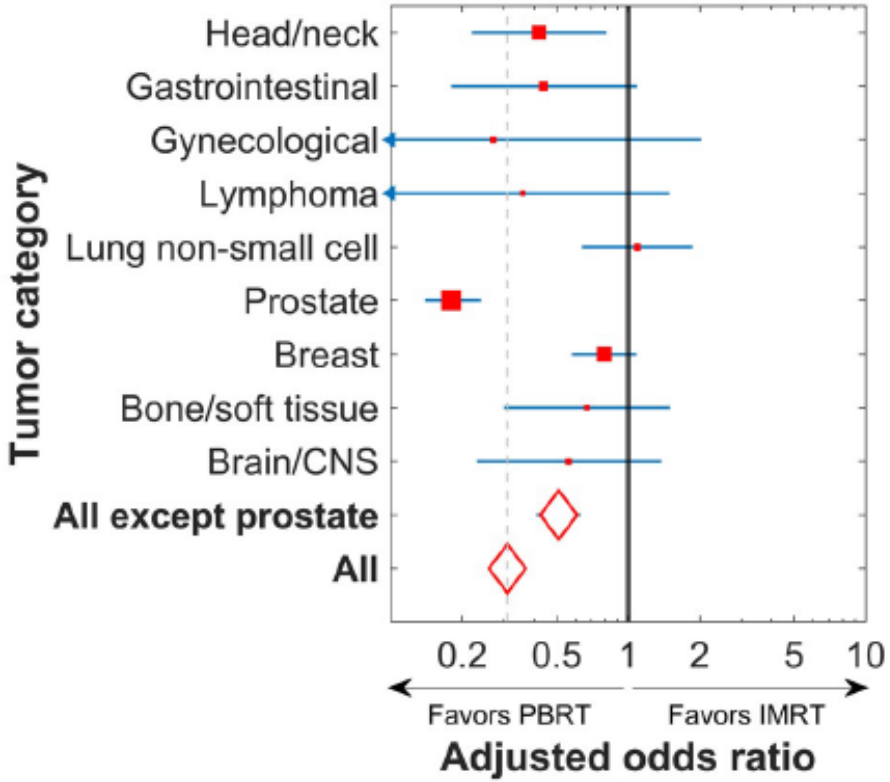
Michael Xiang [1 2], Daniel T Chang [1], Erqi L Pollom [1 2]

- retrospective cohort study using the National Cancer Database (NCDB)

- crude absolute incidence second cancer of per 100 patient-years was
  - Overall: 1.55 (95% CI, 1.53- 1.57)
  - after 3DCRT: 1.60 (95% CI, 1.57-1.62)
  - after IMRT: 1.55 (95% CI, 1.53-1.57)
  - after PBRT 0.44 (95% CI, 0.37-0.52)



Seravalli, Acta Oncologica 2018




*Risk of a second cancer diagnosis was similar after IMRT versus 3DCRT, whereas PBRT was associated with a lower risk of second cancer risk*

clinical practice guidelines

*Annals of Oncology* 25 (Supplement 3): iii113–iii123, 2014
doi:10.1093/annonc/mdu256

# Bone sarcomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

The ESMO/European Sarcoma Network Working Group*

**chordoma**

Hadrons, i.e. high-dose protons or carbon ions, are superior to photons physically and in terms of irradiation of non-target lesions, although no randomised trials are available to assess the benefit of hadrons compared with photons in chordoma. Since hadrons allow lower doses to be given to normal tissues, they should be considered the treatment of choice. Advanced

**SAcral Chordoma: a Randomized & Observational study on surgery versus definitive radiation therapy in primary localized disease (SACRO)**

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Radiotherapy and Oncology 125 (2017) 21–30

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com


Systematic review

# Systematic assessment of clinical outcomes and toxicities of proton radiotherapy for reirradiation

Vivek Verma [a], Jean-Claude M. Rwigema [b], Robert S. Malyapa [c], William F. Regine [c], Charles B. Simone II [c,*]

[a] Department of Radiation Oncology, University of Nebraska Medical Center, Omaha; [b] Department of Radiation Oncology, Mayo Clinic, Scottsdale; and [c] Department of Radiation Oncology, University of Maryland School of Medicine, Baltimore, USA

*"Although outcomes of reRT with PBT versus photons are likely not changed, especially in poor-prognostic cohorts, PBT may allow for fewer toxicities and more safely maintain functional/performance status and quality of life."*

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Received: 28 February 2023 | Revised: 8 May 2023 | Accepted: 22 May 2023
DOI: 10.1002/cncr.34965

ORIGINAL ARTICLE

# Proton beam radiotherapy versus transarterial chemoembolization for hepatocellular carcinoma: Results of a randomized clinical trial

David A. Bush MD[1] | Michael Volk MD[2] | Jason C. Smith MD[3] | Mark E. Reeves MD, PhD[4] | Samrat Sanghvi MD[1] | Jerry D. Slater MD[1] | Michael deVera MD[2]

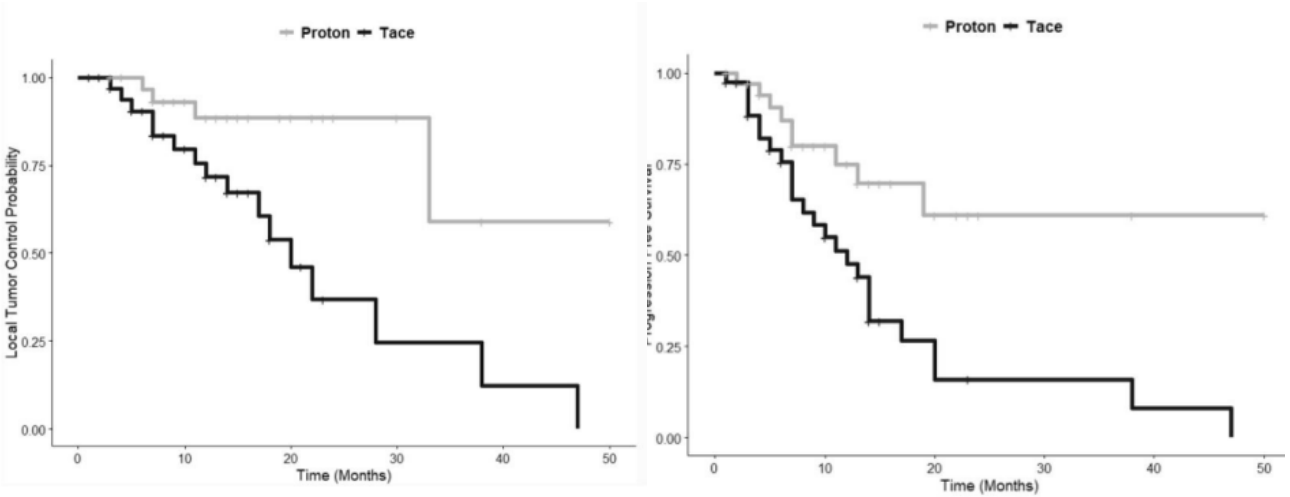



**TABLE 4** Hospitalizations (within 30 days) after PBT and TACE.

| | PBT ($n$ = 36) | TACE ($n$ = 39) | $p$ |
|---|---|---|---|
| Treatment courses | 43 | 69 | |
| Subjects hospitalized within 30 days of treatment | 2 | 62 | <.001 |
| Total days hospitalized, all patients | 24 | 166 | <.001 |
| Days hospitalized for routine post PBT/TACE observation | 0 | 53 | |

Abbreviations: PBT, proton beam radiotherapy; TACE, transarterial chemoembolization.

## Protons are better and cheaper ☺

**TABLE 3** Adverse events after PBT and TACE.

| | PBT ($n$ = 35), No. (%) | | | | TACE ($n$ = 39), No. (%) | | | | |
|---|---|---|---|---|---|---|---|---|---|
| CTCAE grade | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Grade 1 | Grade 2 | Grade 3 | Grade 4 | $p$ |
| Abdominal pain | 7 (20.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 12 (30.8) | 9 (23.1) | 2 (5.1) | 0 (0.0) | <.001 |
| Nausea | 9 (25.7) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 5 (12.8) | 5 (12.8) | 0 (0.0) | 0 (0.0) | .05 |
| Vomiting | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 3 (7.7) | 2 (5.1) | 1 (2.6) | 0 (0.0) | .1 |
| Diarrhea | 3 (8.6) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (2.6) | 0 (0.0) | 0 (0.0) | .1 |
| GI ulcer | 0 (0.0) | 0 (0.0) | 1 (2.9) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | .47 |
| GI bleed | 1 (2.9) | 0 (0.0) | 1 (2.9) | 0 (0.0) | 0 (0.0) | 1 (2.6) | 1 (2.6) | 0 (0.0) | .86 |
| Erythema (skin) | 12 (34.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | <.001 |
| Fatigue | 11 (31.4) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (5.1) | 2 (5.1) | 0 (0.0) | 0 (0.0) | <.01 |
| ALT | 4 (11.4) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 8 (20.5) | 0 (0.0) | 2 (5.1) | 0 (0.0) | .27 |
| AST | 5 (14.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 9 (23.1) | 0 (0.0) | 2 (5.1) | 0 (0.0) | .3 |
| Alkaline phosphatase | 6 (17.1) | 1 (2.9) | 0 (0.0) | 0 (0.0) | 4 (10.3) | 1 (2.6) | 0 (0.0) | 0 (0.0) | .75 |
| Total bilirubin | 4 (11.4) | 11 (31.4) | 2 (5.7) | 1 (2.9%) | 17 (43.6) | 4 (10.3) | 2 (5.1) | 2 (5.1) | <.01 |
| INR | 12 (34.3) | 2 (5.7) | 1 (2.9) | 0 (0.0) | 11 (28.2) | 4 (10.3) | 1 (2.6) | 0 (0.0) | .88 |

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CTCAE, Common Terminology Criteria for Adverse Events; GI, gastrointestinal; INR, international normalized ratio; PBT, proton beam radiotherapy; TACE, transarterial chemoembolization.

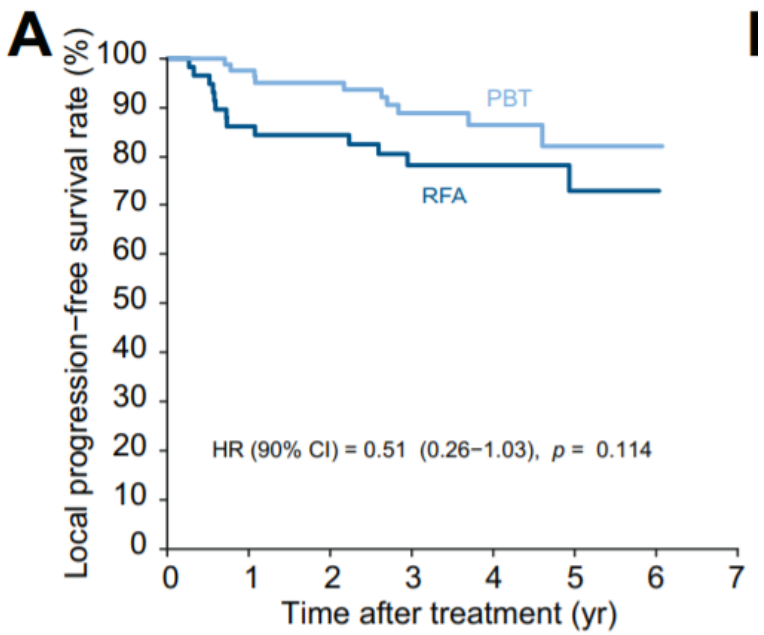
Research Article
Hepatic and Biliary Cancer

JOURNAL
OF HEPATOLOGY

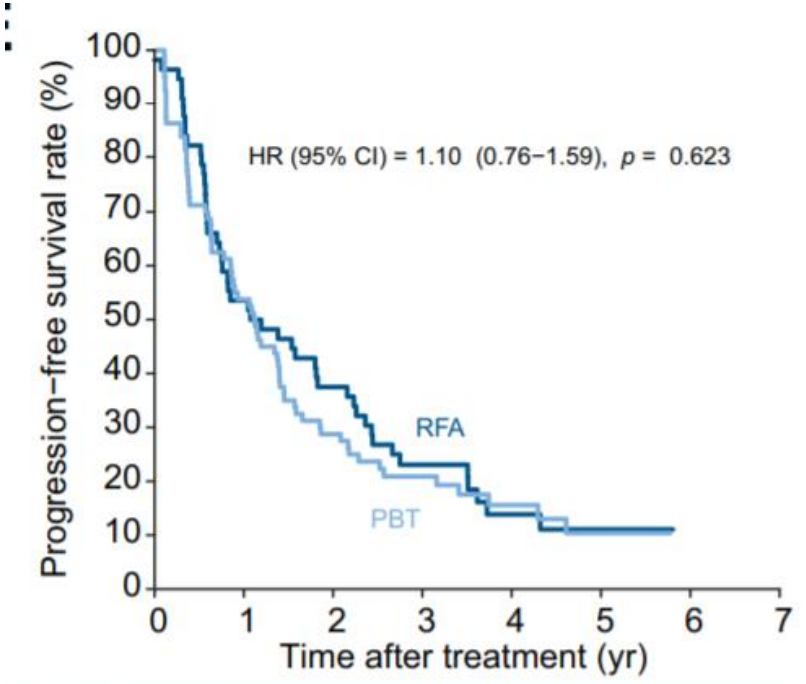
# Proton beam radiotherapy *vs.* radiofrequency ablation for recurrent hepatocellular carcinoma: A randomized phase III trial

Tae Hyun Kim[1,2,†], Young Hwan Koh[1,3,†], Bo Hyun Kim[1], Min Ju Kim[3], Ju Hee Lee[1,3], Boram Park[4], Joong-Won Park[1,*]

[1]*Center for Liver and Pancreatobiliary Cancer, National Cancer Center, Goyang, Republic of Korea;* [2]*Center for Proton Therapy, National Cancer Center, Goyang, Republic of Korea;* [3]*Department of Radiology, National Cancer Center, Goyang, Republic of Korea;* [4]*Biostatistics Collaboration Team, Research Core Center, National Cancer Center, Goyang, Republic of Korea*




| No. at Risk | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| RFA | 58 | 49 | 46 | 32 | 19 | 13 | 2 | 0 |
| PBT | 85 | 78 | 72 | 48 | 30 | 14 | 2 | 0 |




| No. at Risk | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| RFA | 56 | 30 | 21 | 10 | 5 | 4 | 0 | 0 |
| PBT | 80 | 43 | 23 | 13 | 6 | 3 | 0 | 0 |

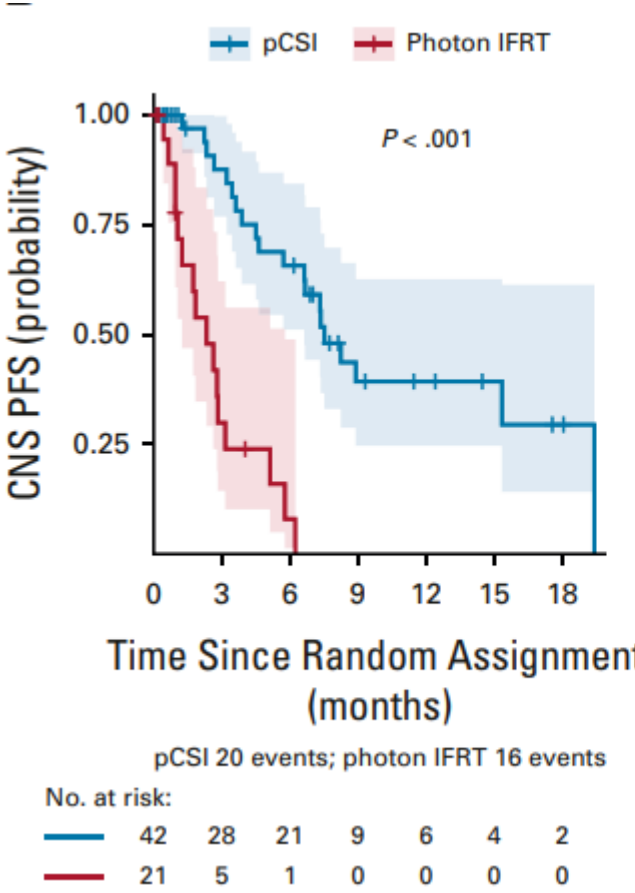
Journal of Clinical Oncology > List of Issues > Volume 40, Issue 33 >

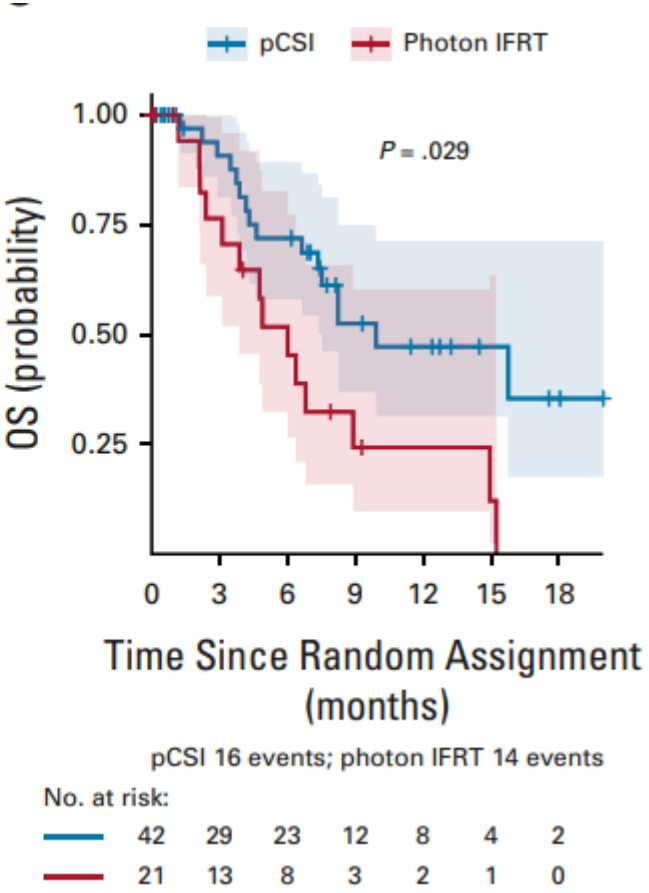
ORIGINAL REPORTS | Radiation Oncology

# Randomized Phase II Trial of Proton Craniospinal Irradiation Versus Photon Involved-Field Radiotherapy for Patients With Solid Tumor Leptomeningeal Metastasis



Jonathan T. Yang, MD, PhD[1]; N. Ari Wijetunga, MD, PhD[1]; Elena Pentsova, MD[2]; Suzanne Wolden, MD[1]; Robert J. Young, MD[3]; Denise Correa, PhD[2]; ...




**Knowledge Generated**

pCSI resulted in significantly improved CNS progression-free survival compared with IFRT in patients with metastatic non–small-cell lung cancer and breast cancer with LM, meeting the primary end point of the study, which led to early discontinuing of the trial at planned interim analysis. pCSI also showed overall survival advantage compared with IFRT with no increase in high-grade adverse events.

# Phase III randomized trial of intensity-modulated proton therapy (IMPT) versus intensity-modulated photon therapy (IMRT) for the treatment of head and neck oropharyngeal carcinoma (OPC).

Steven J. Frank, Paul Busse, David Ira Rosenthal, Mike Hernandez, David Michael Swanson, Adam S. Garden, Erich M. Sturgis, Renata Ferrarotto, Gary Brandon Gunn,

**Results:** Patients (n=440) were randomized to undergo IMRT(n=219) or IMPT (n=221) at 21 institutions. The median age was 61 years and HPV/p16 was positive in 95%. IC was the initial treatment in 13% of patients. All patients were treated with CRT to 70 Gy in 33 fx with bilateral neck treatment, and post-CRT surgical lymph node dissection occurred in 8%. The median follow-up was 3.14 years. In the ITT analysis, the hazard ratio (HR) for disease progression or death at 3 y was 0.87 (95%CI 0.56,1.35); p=0.006 and the corresponding HR for death (OS) was 0.63 (95%CI 0.36-1.10) suggesting a protective affect with IMPT. In PP analysis, the PFS HR was 0.85 (95%CI 0.52,1.38); p=0.009 and HR for death (OS) was 0.60 (95%CI 0.32-1.12). In the AT analysis, PFS HR was 0.88 (95%CI 0.56,1.37); p=0.007 and the corresponding HR for death (OS) was 0.70 (95%CI 0.40-1.22). For each analysis above, the null hypothesis was rejected and IMPT was non-inferior to IMRT. PP gastrostomy-tube dependence decreased with IMPT vs. IMRT from 42% to 28% (p=0.019), and more IMPT patients sustained their nutrition with end of treatment weight loss < 5% from baseline: 24% vs 14% (p=0.037). **Conclusions:** IMPT is non-inferior to IMRT and has emerged as a standard of care CRT approach for OPC that reduces malnutrition and gastrostomy-tube dependence. Clinical trial information: NCT01893307.

Radiotherapy and Oncology 196 (2024) 110293

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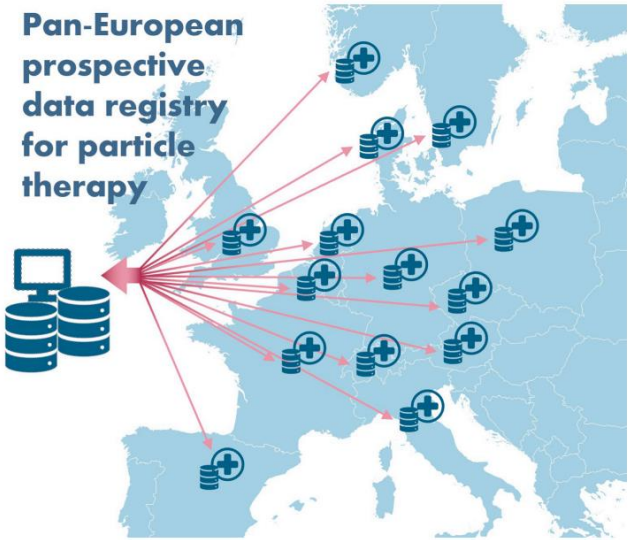
Perspective

# Towards a European prospective data registry for particle therapy

A B S T R A C T

The evidence for the value of particle therapy (PT) is still sparse. While randomized trials remain a cornerstone for robust comparisons with photon-based radiotherapy, data registries collecting real-world data can play a crucial role in building evidence for new developments. This Perspective describes how the European Particle Therapy Network (EPTN) is actively working on establishing a prospective data registry encompassing all patients undergoing PT in European centers. Several obstacles and hurdles are discussed, for instance harmonization of nomenclature and structure of technical and dosimetric data and data protection issues. A preferred approach is the adoption of a federated data registry model with transparent and agile governance to meet European requirements for data protection, transfer, and processing. Funding of the registry, especially for operation after the initial setup process, remains a major challenge.




Overview of the 3-level dataset approach.

| | Level I Basic | Level II Advanced | Level III Research |
|---|---|---|---|
| **Status** | Mandatory | Optional | Optional |
| **Standard of care** | Yes | Yes | No |
| **Description** | Minimal dataset; All evaluations should be manageable and easily implemented with current practice | More extensive dataset, but still considered standard of care; Evaluations might require extra time or specialist care | More extensive dataset in research context; Requiring medical ethical approval |
| **Items** | – Minimal baseline variables (e.g. gender, age, primary tumor site, stage)<br>– Treatment characteristics<br>– Minimal set of toxicity items<br>– Utilities (EQ-5D)<br>– Tumor control and survival<br>– PROMs | – Extensive set of baseline variables<br>– Extensive set of toxicity items<br>– Extensive set of technical treatment-related items (e.g. 3D dose distributions) | Additional diagnostic procedures at baseline and/or follow-up (e.g. imaging, functional tests, biological sampling) |
| **Implementation** | All centers can participate, even with limited resources | Limited number of centers with a similar patient mix could collect more comprehensive or detailed data; additional resources might be required | Limited number of centers having dedicated resources and infrastructure to perform clinical research / trials |

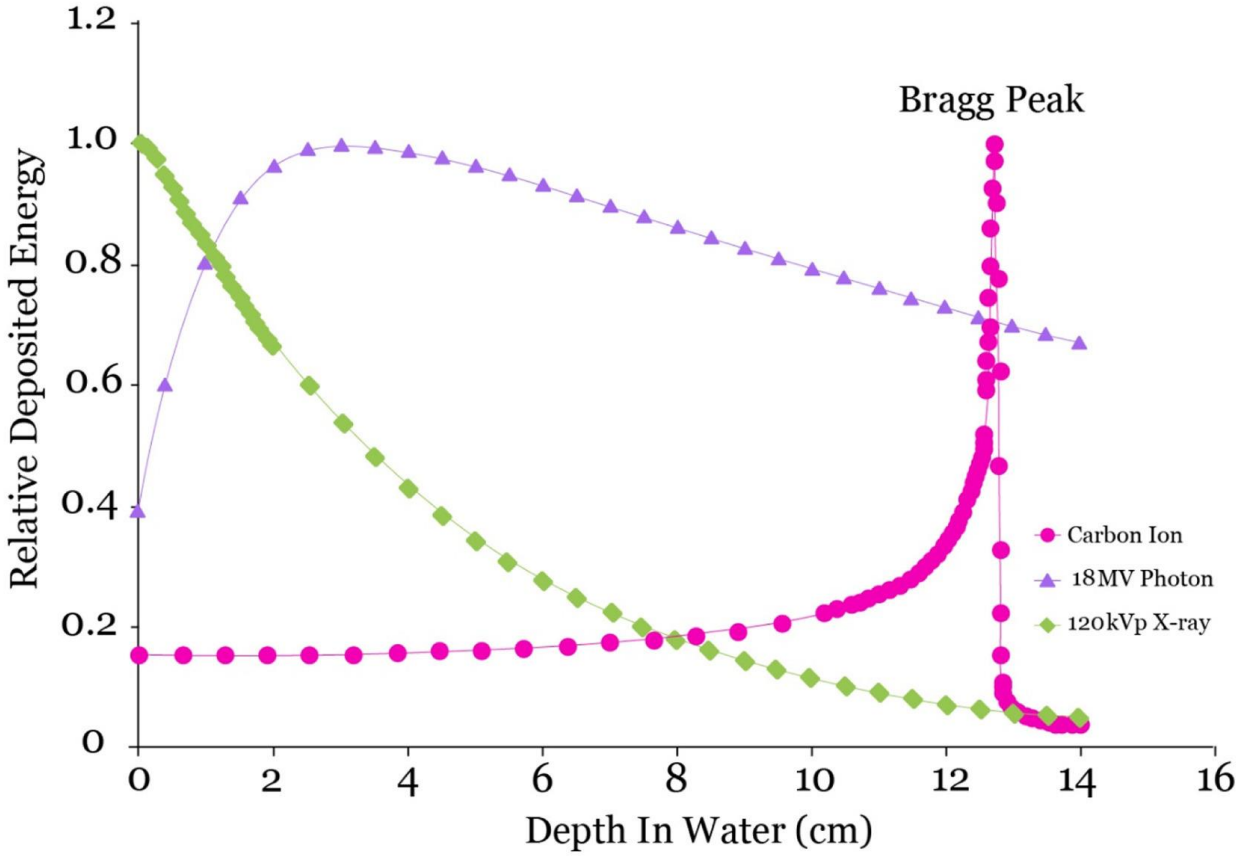
| ClinicalTrials.gov ID | Sponsor | status | TU | Study |
|---|---|---|---|---|
| NCT06846450 | Shanghai | recruting | Nasopharyngeal cancer | Phase 3 Trial Comparing IMRT or IMPT Plus CIRT for Patients with Locally Advanced NPC |
| NCT06500481 | NRG Oncology | recruiting | Leptomeningeal metastasis | A Phase III Randomized Clinical Trial of Proton Craniospinal Irradiation Versus Involved-Field Radiotherapy for Patients With Breast Cancer or Non-Small Cell Lung Cancer Leptomeningeal Metastasis (RADIATE-LM) |
| NCT05406856 | Leiden University Medical Center, Netherlands | recruting | Cervical cancer | PROTECT: On-line Adaptive Proton Therapy for Cervical Cancer to Reduce the Impact on Morbidity and the Immune System |
| NCT05350475 | University of Aarhus, Denmark | recruting | Prostate cancer | Lymph Node Radiation Therapy with Integrated Boost to Prostate for High-risk Prostate Cancer a Randomized Phase 3 Trial Comparing Photons Vs. Protons |
| NCT05190172 | Oslo University Hospital | recruting | IDH-mut Glioma | PRO-GLIO: PROton Versus Photon Therapy in IDH-mutated Diffuse Grade II and III GLIOmas (PRO-GLIO) |
| NCT05055648 | University of Aarhus | recruting | Esophageal cancer | ROton Versus Photon Therapy for Esophageal Cancer - a Trimodality Strategy (PROTECT) a Multicenter International Randomized Phase III Study of Neoadjuvant Proton Versus Photon Chemoradiotherapy in Locally Advanced Esophageal Cancer |
| NCT04607694 | Danish Head and Neck Cancer Group | recruting | Head and Neck Cancer | DAHANCA 35: A Randomized Trial of Proton Versus Photon Radiotherapy for the Treatment of Head-neck Cancer |
| NCT04525989 | Karolinska University Hospital | recruting | Rectal cancer | Preoperative Short-Course Radiation Therapy With PROtons Compared to Photons In High-Risk RECTal Cancer (PRORECT): A Prospective Randomized Swedish Phase II Trial |
| NCT03829033 | Lund University Hospital | recruting | Tonsil Cancer | Photon Therapy Versus Proton Therapy in Early Tonsil Cancer. (ARTSCAN V) |
| NCT03801876 | NRG Oncology | recruting | Esophageal Cancer | Phase III Randomized Trial of Proton Beam Therapy (PBT) Versus Intensity Modulated Photon Radiotherapy (IMRT) for the Treatment of Esophageal Cancer |
| NCT03561220 | NRG Oncology | recruting | HCC | Phase III Randomized Trial of Protons Versus Photons for Hepatocellular Carcinoma |
| NCT03164460 | M.D. Anderson Cancer Center | recruting | ReRT HnN | Phase II Randomized Trial of Stereotactic Onco-Ablative Reirradiation Versus Conventionally Fractionated Conformal Radiotherapy for Patients With Small Inoperable Head and Neck Tumors (SOAR-HN) |
| NCT02179086 | NRG Oncology | Active, not recruiting | GBM | Randomized Phase II Trial of Hypofractionated Dose-Escalated Photon IMRT or Proton Beam Therapy Versus Conventional Photon Irradiation With Concomitant and Adjuvant Temozolomide in Patients With Newly Diagnosed Glioblastoma |
| NCT01993810 | RTOG | Active, not recruiting | NSCLC | Phase III Randomized Trial Comparing Overall Survival After Photon Versus Proton Chemoradiotherapy for Inoperable Stage II-IIIB NSCLC |
| NCT01893307 | M.D. Anderson Cancer Center | Active, not recruiting | Oropharyngeal Ca | Phase III Randomized Trial of Intensity-Modulated Proton Beam Therapy (IMPT) Versus Intensity-Modulated Photon Therapy (IMRT) for the Treatment of Oropharyngeal Cancer of the Head and Neck |
| NCT01854554 | M.D. Anderson Cancer Center | Active, not recruiting | GBM | A Prospective Phase II Randomized Trial to Compare Intensity Modulated Proton Radiotherapy (IMPT) vs. Intensity Modulated Radiotherapy (IMRT) for Newly Diagnosed Glioblastoma (WHO Grade IV) |
| NCT01617161 | Massachusetts General Hospital | Active, not recruiting | n.prostata | Prostate Advanced Radiation Technologies Investigating Quality of Life (PARTIQoL): a Phase III Randomized Clinical Trial of Proton Therapy Vs IMRT for Low or Intermediate Risk Prostate Cancer |
| NCT01512589 | M.D. Anderson Cancer Center | Active, not recruiting | Esophageal Cancer | Phase IIB Randomized Trial of Proton Beam Therapy Versus Intensity-Modulated Radiation Therapy for the Treatment of Esophageal Cancer |
| NCT04190446 | Mayo Clinic | Active, not recruiting | met. Prostate cancer | A Randomized, Parallel Phase II Trial of Hypofractionated Proton Therapy or IMRT for Recurrent, Oligometastatic Prostate Cancer Involving Only Pelvic And/or Para-Aortic Lymph Nodes Following Primary Localized Treatment |
| NCT03180502 | NRG Oncology | Active, not recruiting | IDH-mut Glioma | A Phase II Randomized Trial of Proton Vs. Photon Therapy (IMRT) for Cognitive Preservation in Patients With IDH Mutant, Low to Intermediate Grade Gliomas |

# CARBONS (CIRT) CLINICAL EVIDENCE

Offers ballistic and radiobiological advantages over conventional photon-based radiotherapy, making it an effective option in case of rare, radioresistant, and difficult-to-treat tumors.

CIRT has distinctive radiobiological hallmarks exerting 2–3-fold higher relative biological effectiveness (RBE) against intrinsic radioresistant tumours.

To date, 55 clinical studies including CIRT for adult and pediatric solid neoplasms have been registered on the www.clinicaltrials.gov website and ***three phase III trials*** are currently recruiting patients to test CIRT versus photon or PBT as standard treatment for unresectable or incompletely resected radioresistant tumors, such as axial chordoma, adenoid cystic carcinoma, sarcomas  and for recurrent head and neck (H&N) cancers.





1. Orlandi E, et al.. The Role of Carbon Ion Therapy in the Changing Oncology Landscape-A Narrative Review of the Literature and the Decade of Carbon Ion Experience at the Italian National Center for Oncological Hadrontherapy. Cancers (Basel). 2023 Oct 20;15(20):5068.
2.. Fereshteh et al Review of Recent Improvements in Carbon Ion Radiation Therapy in the Treatment of Glioblastoma Koosha.Advances in Radiation Oncology, 2024. Volume 9, Issue 5, 101465

# Summary

- Particle therapy is „young“ compared to traditional photon therapy
- At the present time, the clinical superiority of protons compared with photons is clearly established in pediatric populations and in rare situations when normal structures in close proximity to the treatment target
- Clinical evidence in terms of long term results on outcome and toxicity is underway to determine the role of particle therapy



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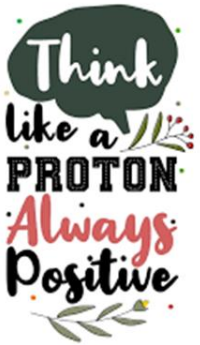



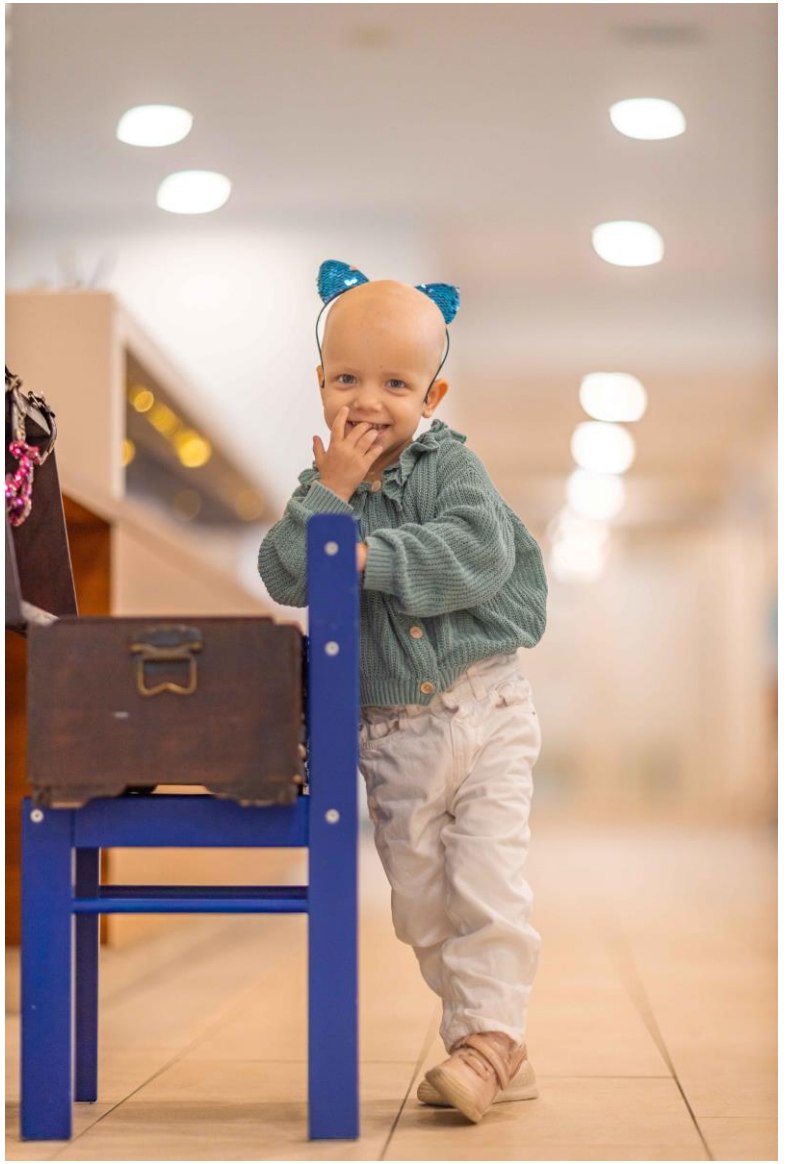

HITRI
Heavy Ion Therapy Research Integration

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