HITRI plus
Heavy Ion Therapy Research Integration

Hadron Therapy in clinical practice

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

AGENDA

- Properties of protons and carbon ions
- Hadron Therapy: when?
- Hadron Therapy: why?
- Hadron Therapy: how?
- Take home messages

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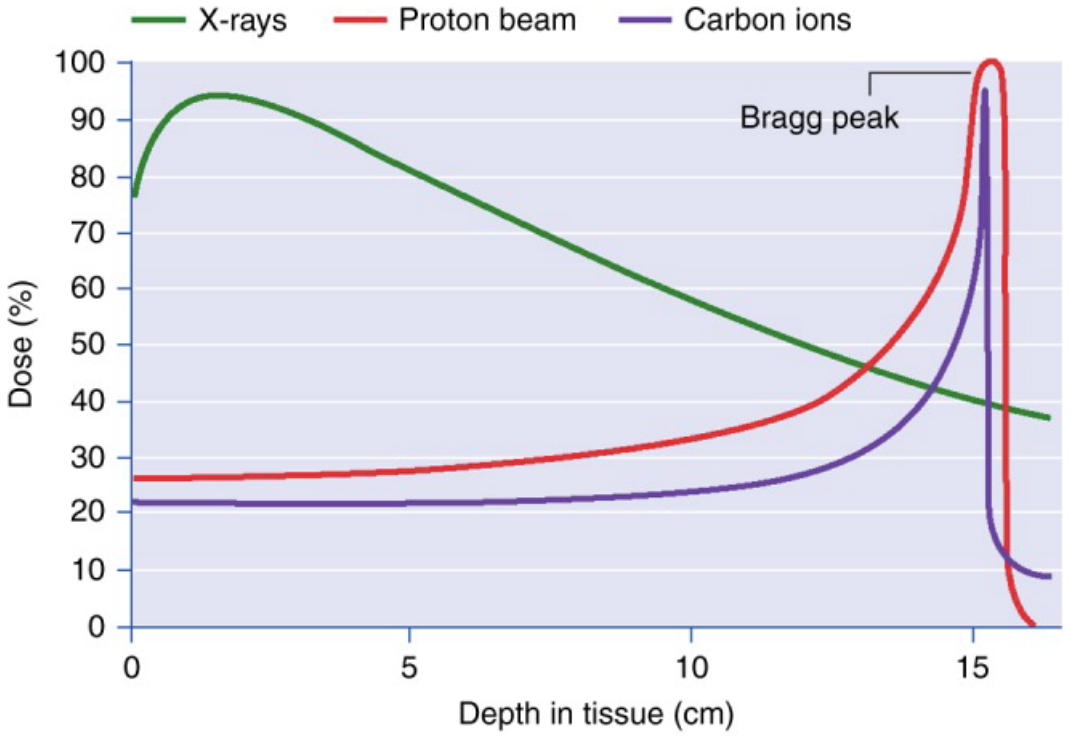
Dosimetric properties of protons and carbon ions

- Steep dose gradient
- Limited dose to the surrounding healthy tissues
- Toxicity reduction with comparable target coverage with respect to X-rays



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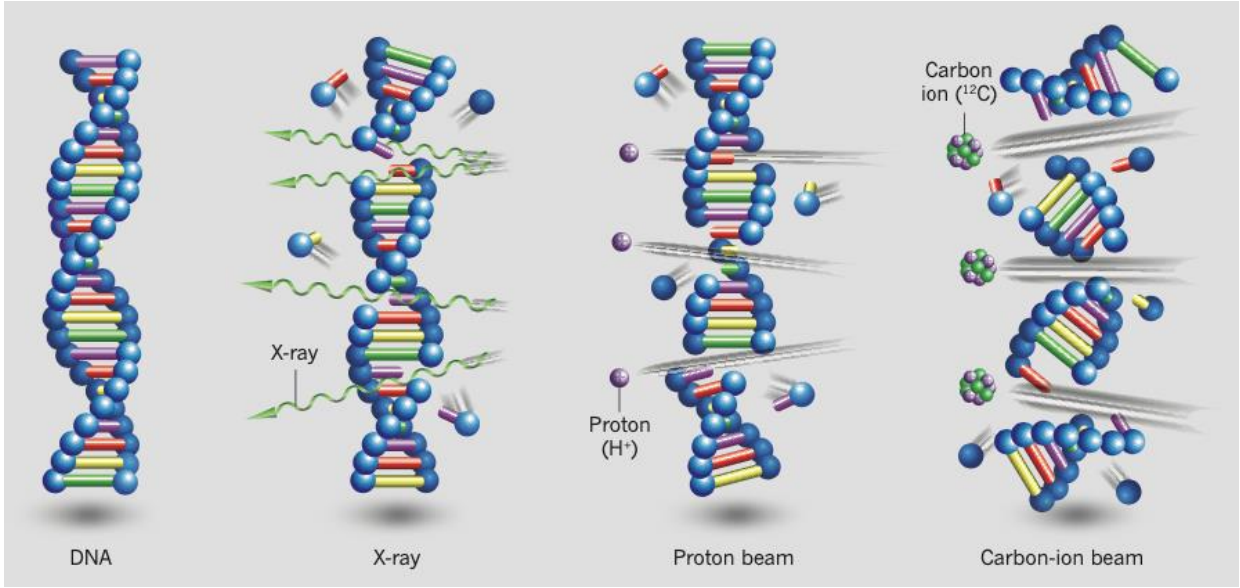
Radiobiological properties of protons and carbon ions

- Higher relative biological effectiveness (RBE)
- More serious DNA damage induced
- Reduced dependence on cell-cycle
- Reduced oxygen enhancement ratio (OER) in the tumor
- Higher efficacy on radioresistant clones



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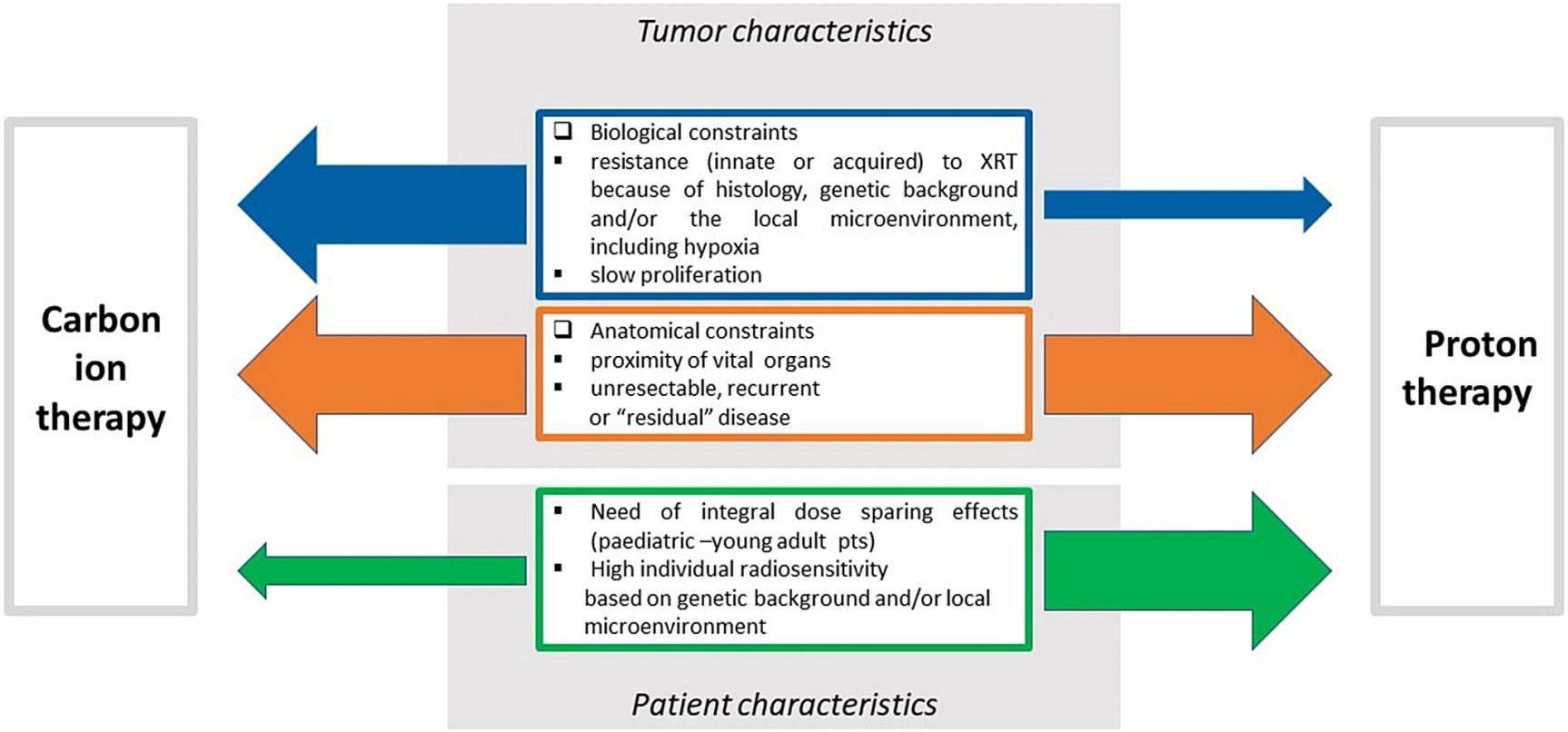
Hadron Therapy: when?

Health and Technology (2024) 14:1043–1050
https://doi.org/10.1007/s12553-024-00865-4

ORIGINAL PAPER

The clinical roadmap in a dual-beam hadrontherapy centre: tumour-based and patient-tailored selection criteria, management of range uncertainties and oncological patient pathway

Ester Orlandi[1,2] · Sara Lillo[2] · Anna Maria Camarda[2] · Sara Ronchi[2] · Agnieszka Chalaszczyk[2] · Lucia Pia Ciccone[2] · Marco Rotondi[2] · Maria Bonora[2] · Amelia Barcellini[2,3]



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Hadron Therapy: when?

pediatric, skull based, spinal, paranasal sinus

UNITED KINGDOM

Pediatric tumor
Most pediatric tumors, malignant and benign
Adult
Base of skull tumors (radioresistant)
Spinal and paraspinal tumors (radioresistant)
Paranasal sinus tumors with base of skull involvement

UNITED STATES

Astro Model Policy, group 1: disease sites that frequently the use of proton ocular tumors, including intraocular melanomas
Tumors that approach or are located at the base of skull, including but not limited to chordoma or 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
Hepatocellular cancer
Primary or benign solid tumors in children treated with curative intent and occasional palliative treatment of childhood tumors when at least one of the four 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
Malignant and benign primary CNS tumors
Advanced (e.g., T4) and/or unresectable head and neck cancers
Cancers of the paranasal sinuses and other accessory sinuses
Non-metastatic retroperitoneal sarcomas
Re-irradiation cases (where cumulative critical structure dose would exceed tolerance dose)

skull based, spinal, ocular, pediatric, CNS, H&N, re-irradiation, genetic syndromes

sarcoma, H&N, prostate, pediatric

JAPAN

PBT
Pediatric cancer
Bone and soft tissue sarcoma
Head and neck
Prostate
CIRT
Bone and soft tissue sarcoma
Head and neck
Prostate

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Hadron Therapy: when?

Radiotherapy and Oncology 167 (2022) 7–13

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original Article

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 Hoebers [s], Felipe A. Calvo [t], Joachim Widder [u], Fabian Eberle [v], Marco van Vulpen [w], Philippe Maingon [x], Tomasz Skóra [y], Damien C. Weber [z], Kjell Bergfeldt [aa], Jiri Kubes [ab], Johannes A. Langendijk [a]

19 European PT Centers

Lack of evidence	30%
No Reimbursement	29%
Technical limitations	20%
No patient referral	13%
Treatment capacity	3%
Other	5%

Number of patients treated in 2020							
CNS	HNC	Prostate	Breast	Lung	GI	Lymphoma	GYN
110	50	500	150	30	50	60	
100	120		60	80	50	10	
308	50	30			11	15	
300	10						
170	90				2		
41	15		40	90	23	5	
72	30		86	10		2	
153	6	13			13	10	2
70	10	80		10	20	5	
115	38		2			39	
69	61		39		3		
60	80	10			10		2
90	32					15	
88	40						
40	15	5	4	5	16	3	9
79							
60							
20	2						
20							
1965	649	638	381	225	198	164	13
46%	15%	15%	9%	5%	5%	4%	0%
100%	84%	32%	37%	32%	53%	53%	16%

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Hadron Therapy: why?

- ✓ **Childhood cancers:** reduction in normal tissue exposure and therefore in adverse effects *(Spiotto 2021, Wilson 2024, Bischoff 2024)*
- ✓ **Skull based and sinonasal malignancies:** sparing of the close critical normal tissues, e.g. brainstem and optic structures *(Grosshans 2014, Patel 2014, Iannalfi 2023)*
- ✓ **Brain tumors:** promising results in terms of cognitive preservation *(Dutz 2020, Flechl 2023)*
- ✓ **Locally advanced head and neck malignancies:** significanlty reduced toxicity *(Holliday 2015, Lin 2021, Chang 2024)*

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Hadron Therapy: why?

- ✓ **Soft tissues and bone sarcomas:** to overcome their intrinsic radioresistance, especially if unresectable or when incomplete surgery is expected *(Dong 2022, Ioakeim-Ioannidou 2024)*

- ✓ **Breast cancer:** in the presence of cardiovascular risk factors, left-sided tumors or regional nodal irradiation, and to minimize contralateral breast exposure *(Mutter 2021)*

- ✓ **Primary hepatocellular carcinoma, cholangiocarcinoma, and isolated hepatic metastases:** the normal tissue sparing allows dose escalation *(Qi 2015, Cheng 2020)*

- ✓ **Reirradiation:** safer delivery of definitive rather than palliative doses *(McDonald 2016, Lee 2023, Gaito 2023)*

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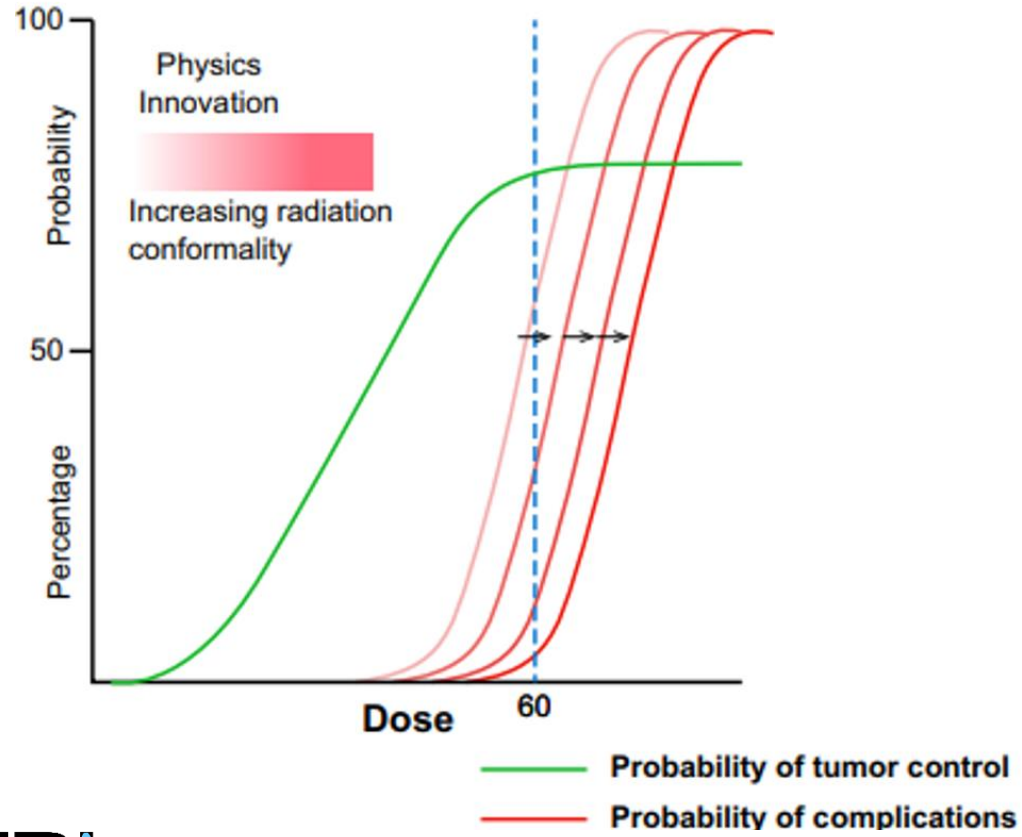
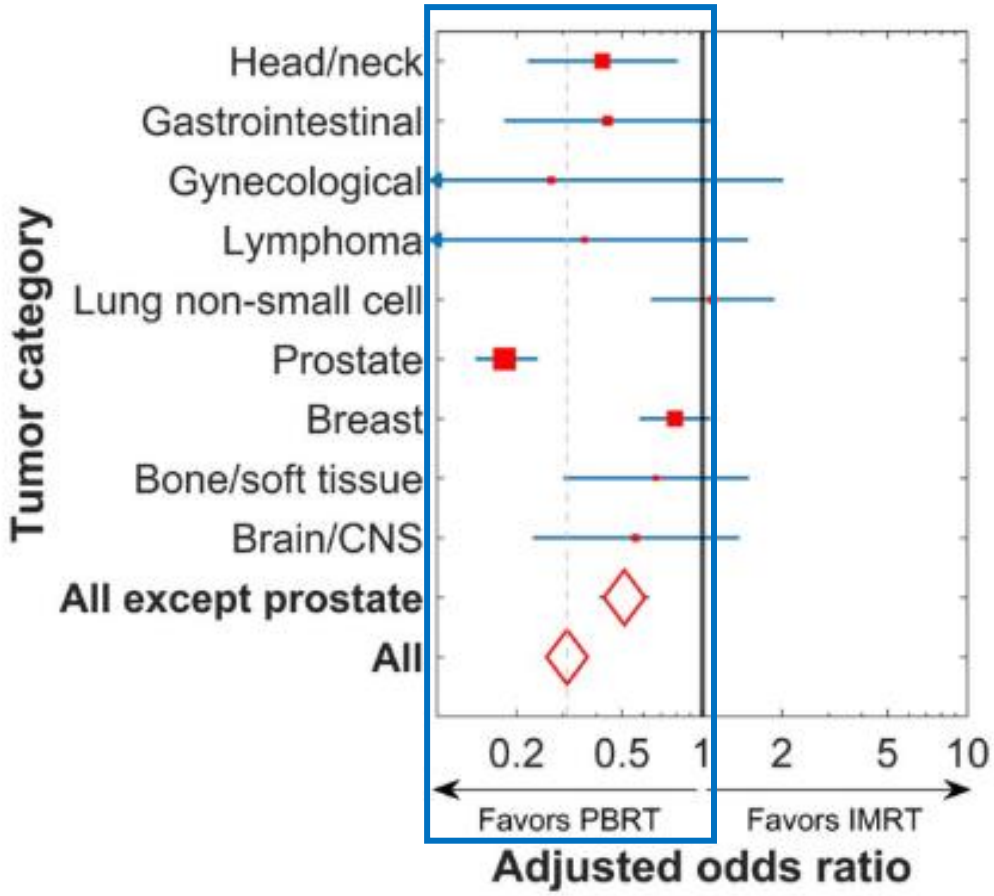
Hadron Therapy: why?
1. Reduced toxicity





PT was associated with a lower risk of second cancer

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Lin SH, Int J Radiat Oncol Biol Phys. 2021 / Xiang M, Cancer. 2020

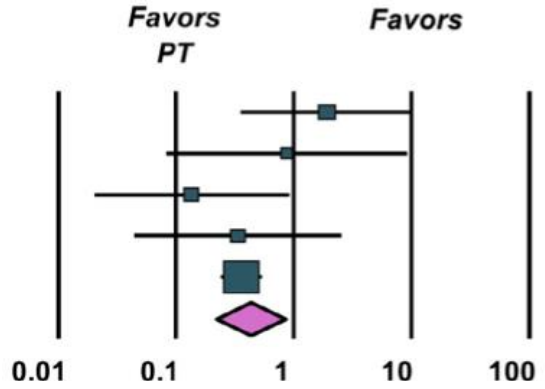
Hadron Therapy: why?
2. Potential improved outcomes

Review > Head Neck. 2024 Jul 15. doi: 10.1002/hed.27877. Online ahead of print.

Efficacy and safety of proton therapy versus intensity-modulated radiation therapy in the treatment of head and neck tumors: A systematic review and meta-analysis

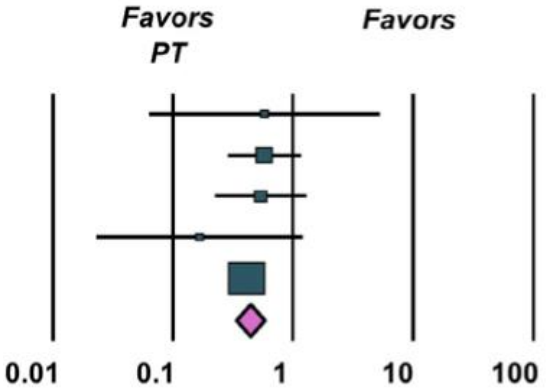
Srivatsa Surya Vasudevan [1], Haya Deeb [2], Anuhya Katta [3], Lindsay Olinde [1], John Pang [1], Ameya A Asarkar [1], Sanford Katz [4], Cherie-Ann O Nathan [1 5]

11 studies, 3087 pts (606 PT + 2481 IMRT)



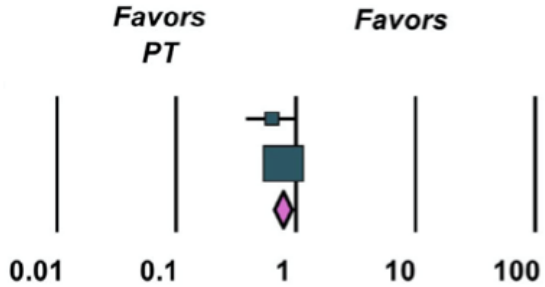
1-year OS

P=0.02



2-year OS

P<0.0001



5-year OS

P=0.004

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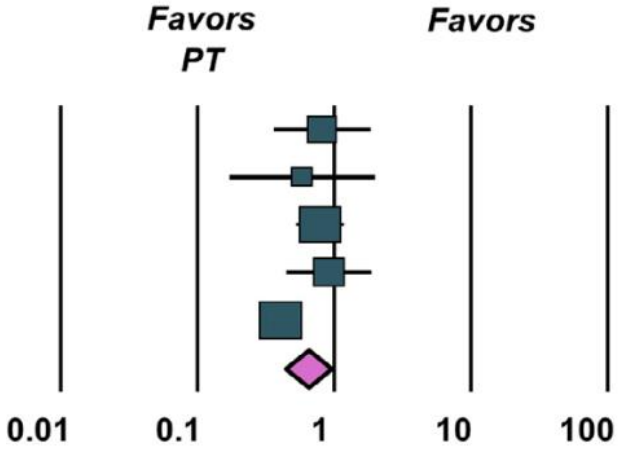
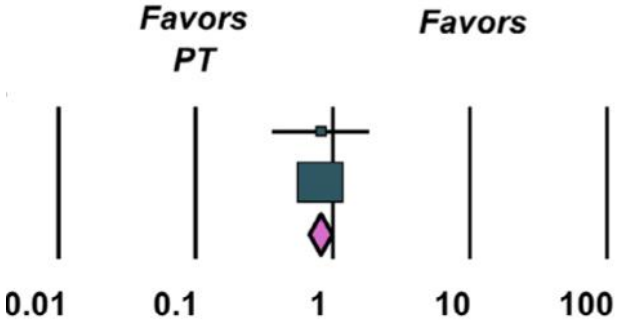


2-year DFS

P=0.03



5-year DFS

P=0.03

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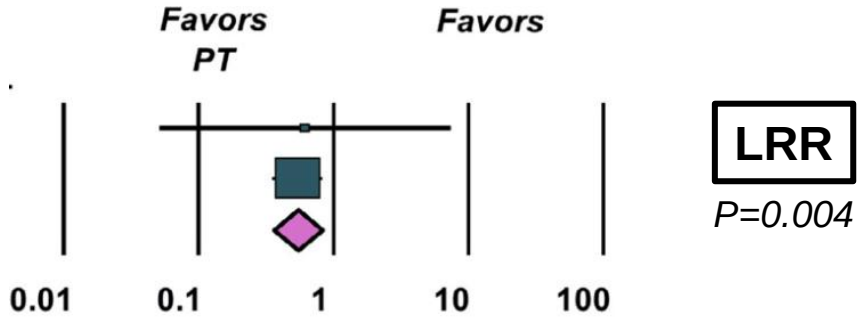

11 studies, 3087 pts (606 PT + 2481 IMRT)

To be confirmed…

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Hadron Therapy: why?
3. Multimodal approaches

2015

Clinical Investigation

COSMIC: A Regimen of Intensity Modulated Radiation Therapy Plus Dose-Escalated, Raster-Scanned Carbon Ion Boost for Malignant Salivary Gland Tumors: Results of the Prospective Phase 2 Trial

Alexandra D. Jensen, MD, MSc,* Anna V. Nikoghosyan, MD,* Karen Lossner,* Thomas Haberer, PhD,† Oliver Jäkel, PhD,† Marc W. Münter, MD,* and Jürgen Debus, MD, PhD*

International Journal of Radiation Oncology biology • physics

2024

CLINICAL INVESTIGATION

Combined Photon and Carbon Ion Radiation Therapy for Sinonasal Malignancies: Results of the HIT—SNT Prospective Phase 2 Trial

Katharina Weusthof, MD,*,†,‡ Thomas Held, MD,*,†,‡ Kristin Lang, MD,*,†,‡ Zoe E. Rachel,† Semi B. Harrabi, MD,*,†,‡ Karim Plath, MD,§ Christian Freudlsperger, MD,‖ Klaus Herfarth, MD,*,‡ Jürgen Debus, MD, PhD,*,†,‡ Thomas Haberer, PhD,‡ Marc Münter, MD,¶ Alexandra D. Jensen, MD,# and Sebastian Adeberg, MD*,†,‡,**,††,‡‡

- **Carbon ion boost** 24 GyRBE + IMRT 50 Gy
- The rationale is that the **number of tumor cells and hypoxia level** are at their greatest extent at the beginning of therapy
- One of the goals is the **early targeting of stem cells**
- Further research is needed to optimize **patient selection**

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Hadron Therapy: why?
3. Multimodal approaches

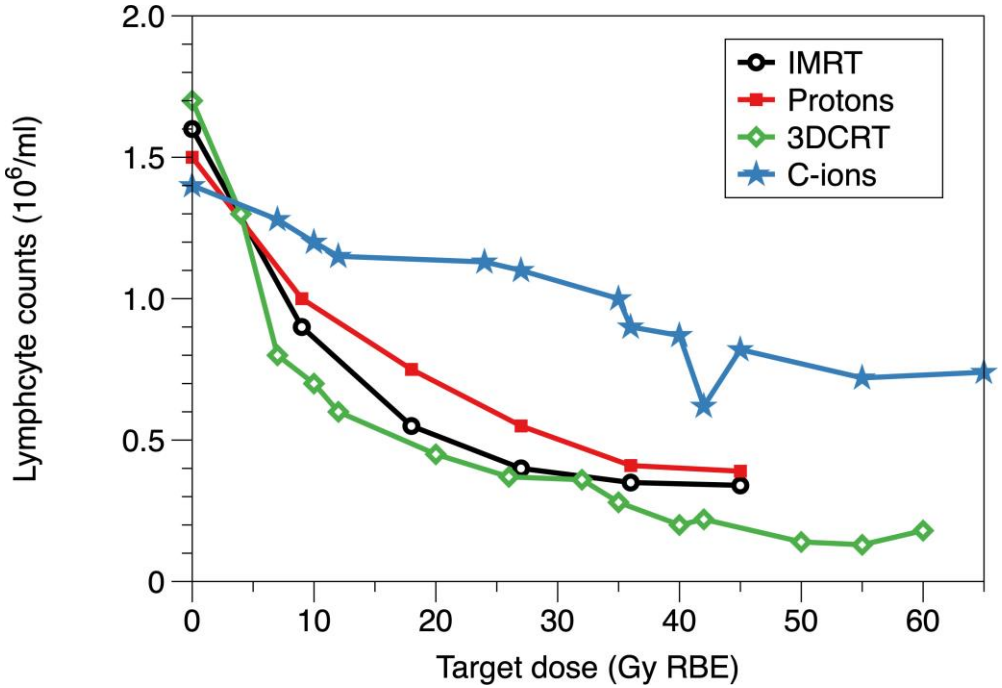
Review > Int Rev Cell Mol Biol. 2023:376:1-36. doi: 10.1016/bs.ircmb.2023.01.001.
Epub 2023 Feb 15.

Are charged particles a good match for combination with immunotherapy? Current knowledge and perspectives

A Helm [1], C Totis [1], M Durante [2], C Fournier [1]

In vitro:
- increased release of **immune-stimulating cytokines**
- greater impact on **antigen release**
- long-term inhibition of **cell migration**

In vivo:
- reduced **damage to blood lymphocytes** compared to X-rays



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Hadron Therapy: why?
3. Multimodal approaches

1. NSCLC, HNSCC, melanoma and urothelial carcinoma
2. At least 2 measurable target lesions

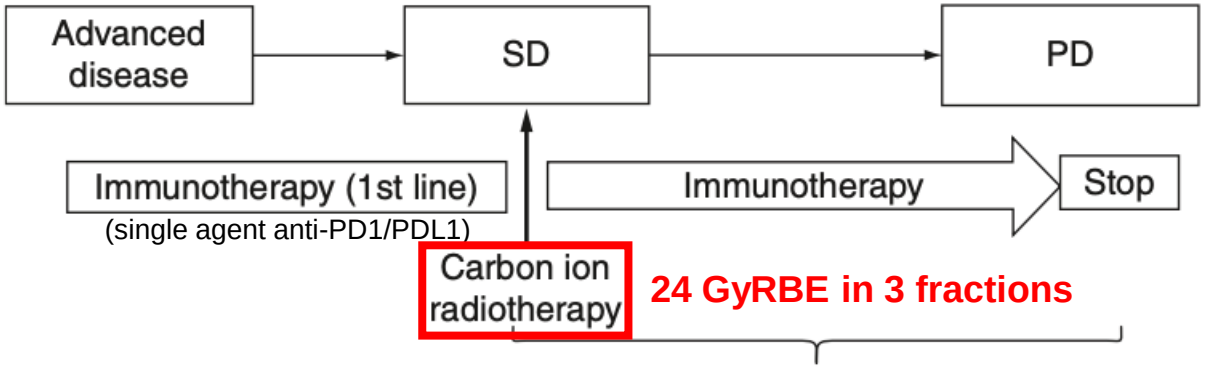
Primary endpoint:
- objective response rate (ORR) according to RECIST, at least 8 weeks after CIRT

Secondary endpoints:
- toxicity according to CTCAE version 5.0
- PFS
- OS

Future Oncol. (2023) 19(3), 193–203

Immune checkpoint inhibitors and Carbon iON radiotherapy In solid Cancers with stable disease (ICONIC)

Stefano Cavalieri[1,2], Viviana Vitolo[3], Amelia Barcellini*[,3,4], Sara Ronchi[3], Angelica Facoetti[5], Chiara Campo[6], Catherine Klersy[7], Silvia Molinelli[8], Francesco Agustoni[4,9], Virginia Valeria Ferretti[7], Annalisa De Silvestri[7], Marco Platania[10], Michele Del Vecchio[10], Marco Durante[11], Alexander Helm[11], Claudia Fournier[11], Filippo de Braud[2,10], Paolo Pedrazzoli[4,9], Ester Orlandi‡[,3] & Lisa Licitra‡[,1,2,6]



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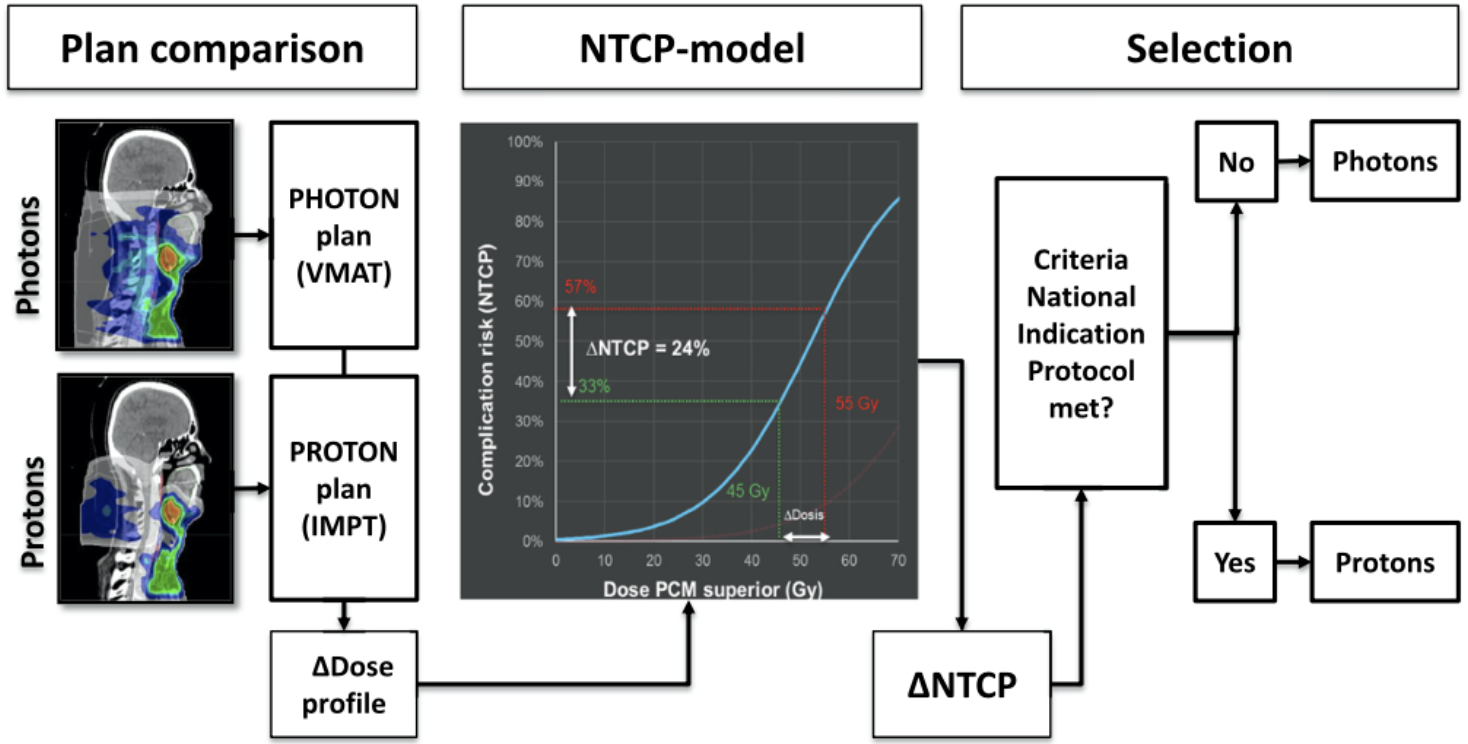
Hadron Therapy: how?

1) *Model-Based Approach (MBA)*



2) *Trials within Cohorts*
3) *Generalized Pairwise Comparison*
4) *Propensity Score Analysis*

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Hadron Therapy: how?

Contents lists available at ScienceDirect
Radiotherapy and Oncology 2024
journal homepage: www.thegreenjournal.com

Perspective

Towards a European prospective data registry for particle therapy

5) Prospective data registries

Registry of the European Reference Network on Rare Adult Solid Cancer "EURACAN"

European Reference Network for rare or low prevalence complex diseases
Network Adult Cancers (ERN EURACAN)

RARITY

AIR Study

AIOCC Italian Registry on Head and Neck Carcinoma

HITRI*plus*

REGAL

Heavy **I**on **T**herapy **R**esearch **I**ntegration plus

HITRI*plus*
Heavy Ion Therapy Research Integration

CNAO
REGistry Tri**AL**
(NCT05203250)

REGAL

HITRI*plus*
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Take home messages

1. Hadron therapy appears to be a safe, effective and feasible treatment method, which has shown **advantages over photon therapy**

2. Hadron therapy has the potential to reduce radiation exposure, which should **reduce late radiation-induced toxicities**

3. It is crucial to **better select patients**

4. The development of **clinical registries** might help to elucidate current uncertainties

5. National and International **multidisciplinary cooperation** is of utmost importance

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THANK YOU!

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