

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

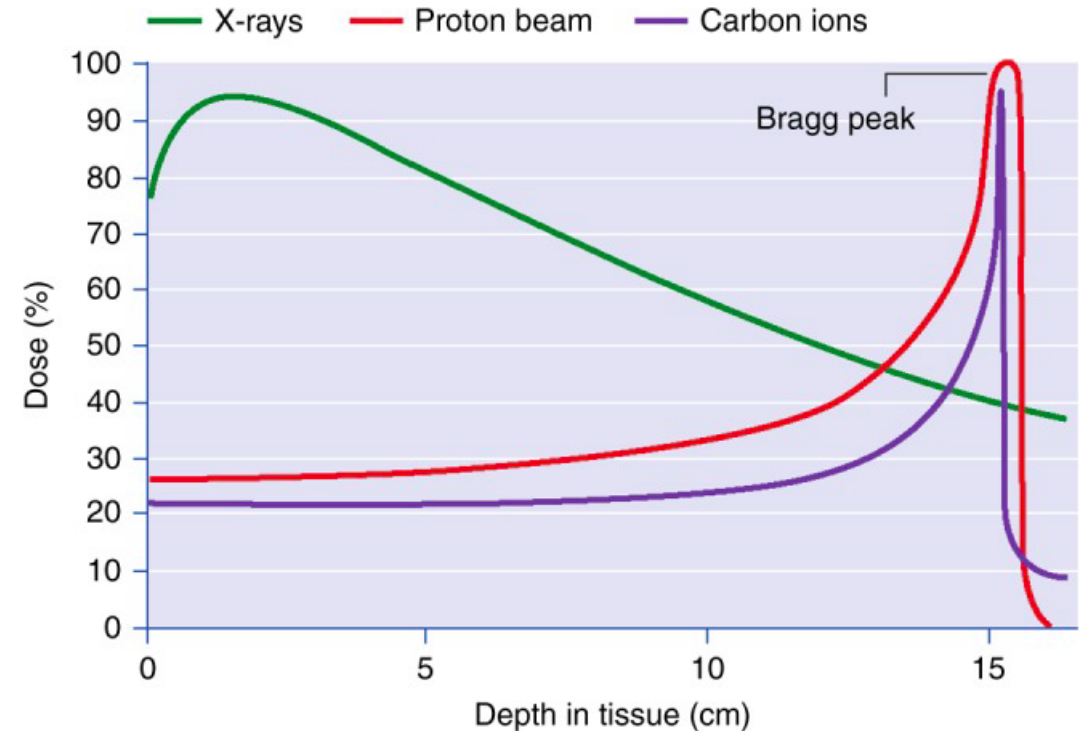
AGENDA

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



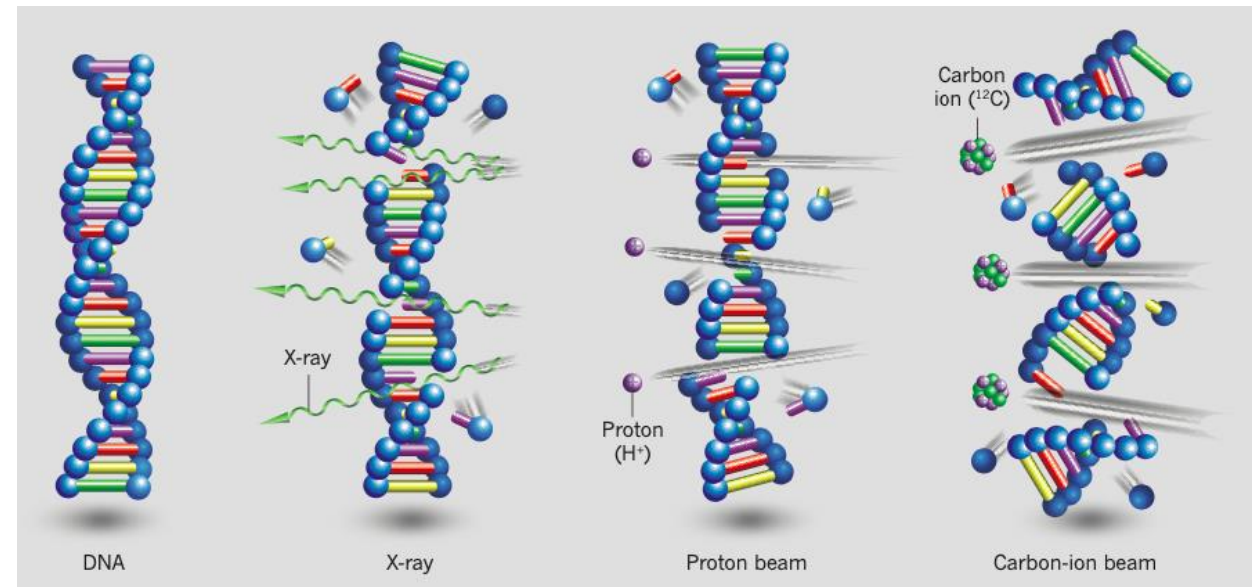
Dosimetric properties of protons and carbon ions

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



Radiobiological properties of protons and carbon ions

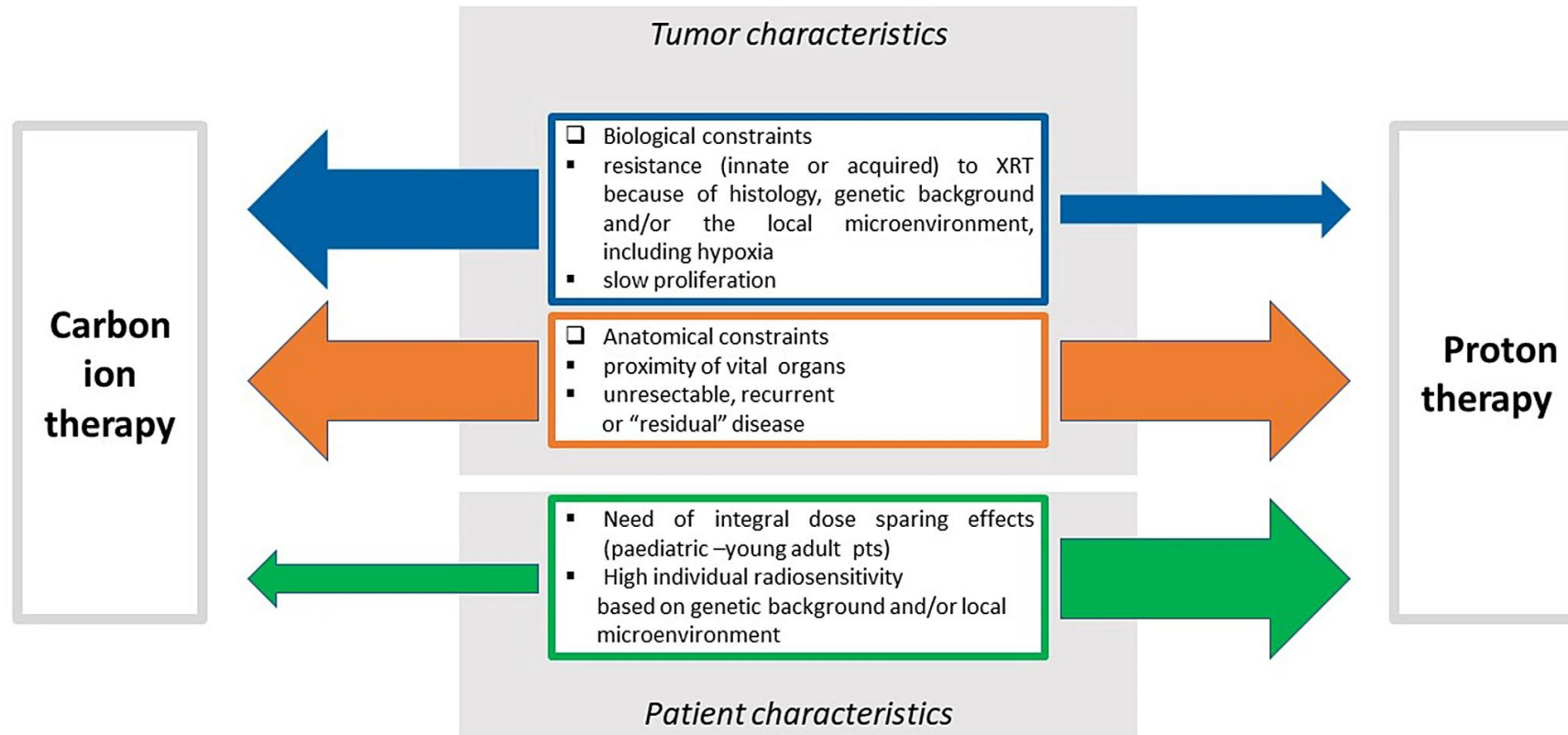
- Higher relative biological effectiveness (RBE)
- More serious DNA damage induced
- Reduced dependence on cell-cycle
- Reduced oxygen enhancement ratio (OER) in the tumor
- Higher efficacy on radioresistant clones



Hadron Therapy: when?

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 Lillo² · Anna Maria Camarda² · Sara Ronchi² · Agnieszka Chalaszczyk² · Lucia Pia Ciccone² · Marco Rotondi² · Maria Bonora² · Amelia Barcellini^{2,3}



Hadron Therapy: when?

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)

pediatric, skull based, spinal, paranasal sinus

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

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

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

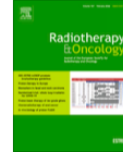
Hadron Therapy: when?

Radiotherapy and Oncology 167 (2022) 7–13



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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 Burnetⁱ, Vincent Gregoire^j, Valentin Calugaru^k, Esther G.C. Troost^{l,m,n,o,p,q,r}, Frank Hoebbers^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?

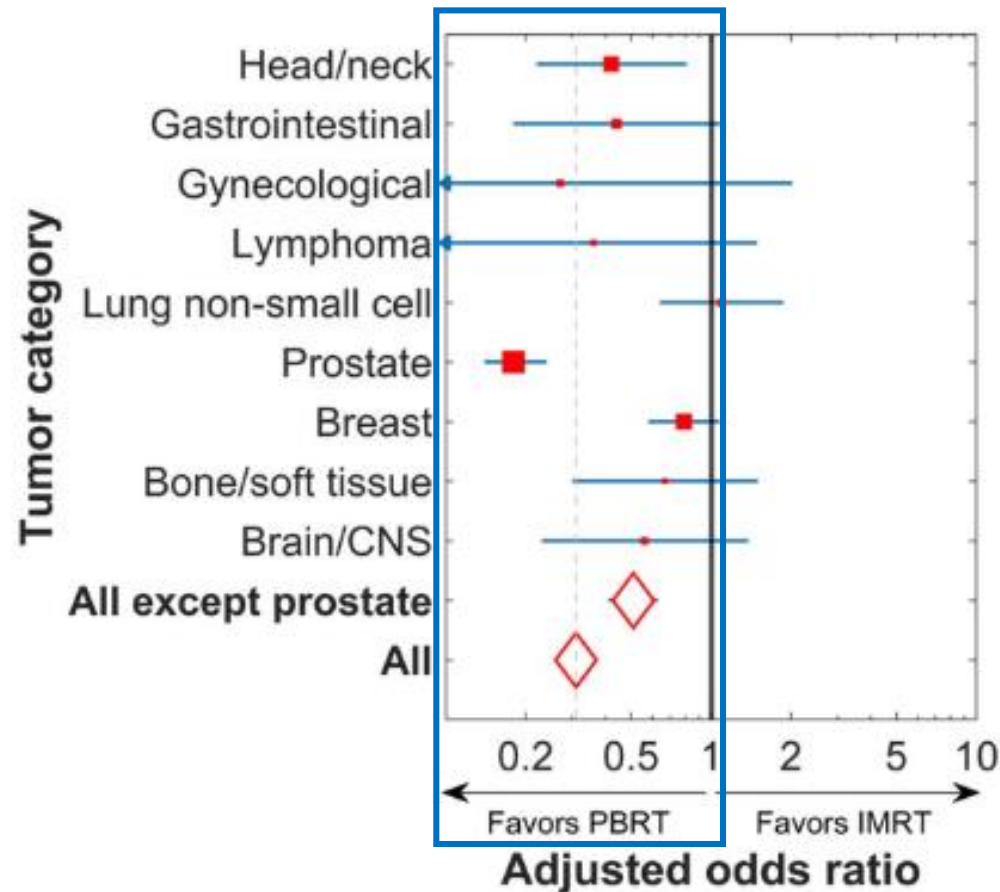
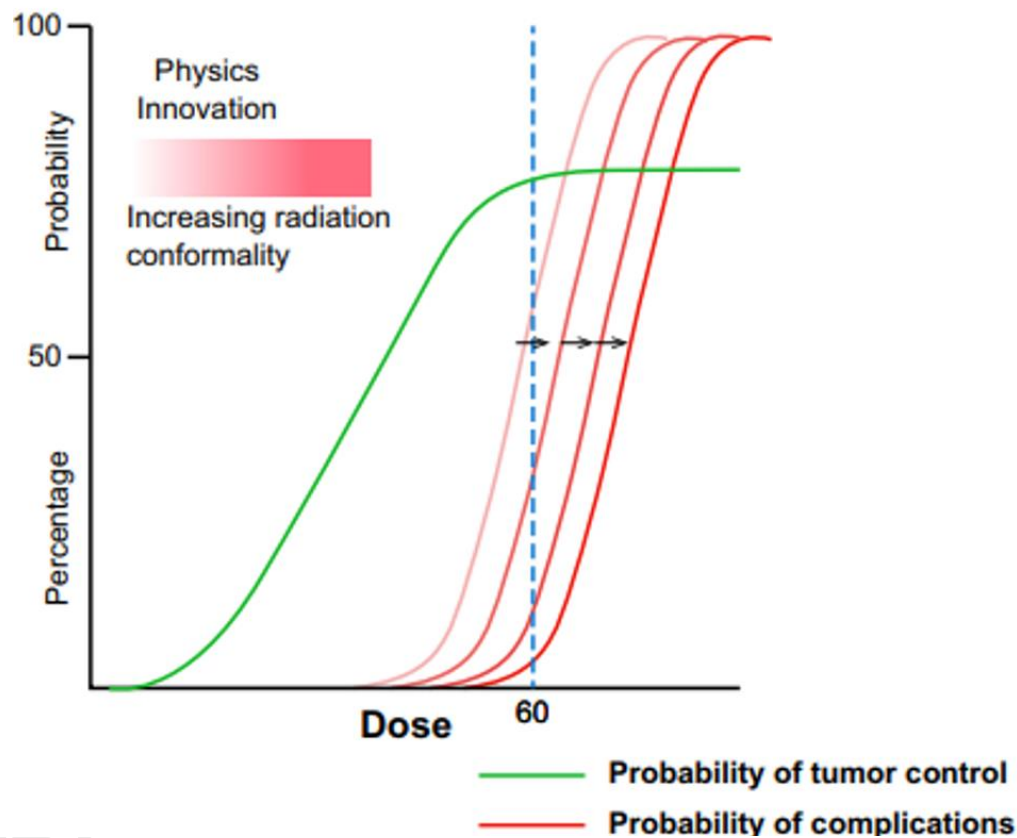
- ✓ **Childhood cancers:** reduction in normal tissue exposure and therefore in adverse effects (*Spiotto 2021, Wilson 2024, Bischoff 2024*)
- ✓ **Skull based and sinonasal malignancies:** sparing of the close critical normal tissues, e.g. brainstem and optic structures (*Grosshans 2014, Patel 2014,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

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*)

Hadron Therapy: why?

1. Reduced toxicity



PT was associated with a lower risk of second cancer

Hadron Therapy: why?

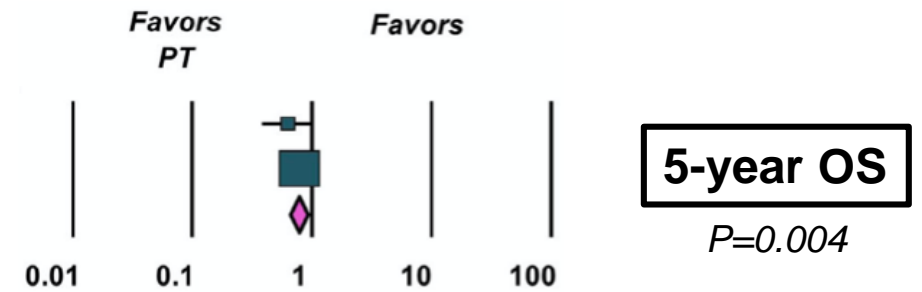
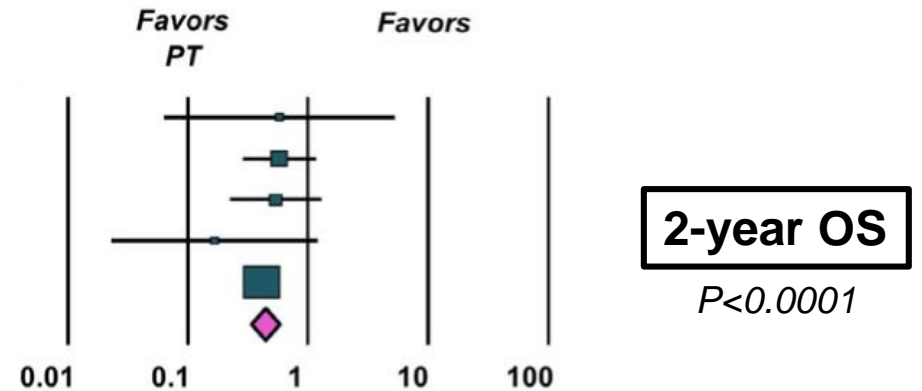
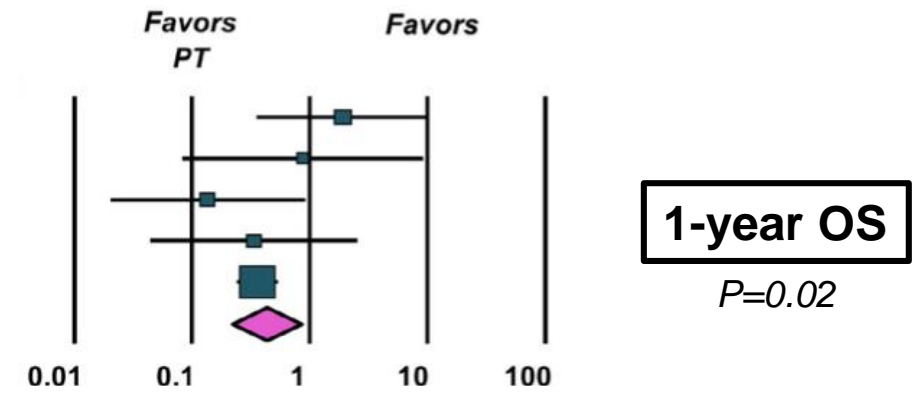
2. Potential improved outcomes

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 Vasudevan¹, Haya Deeb², Anuhya Katta³, Lindsay Olinde¹, John Pang¹, Ameya A Asarkar¹, Sanford Katz⁴, Cherie-Ann O Nathan^{1,5}

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



Hadron Therapy: why?

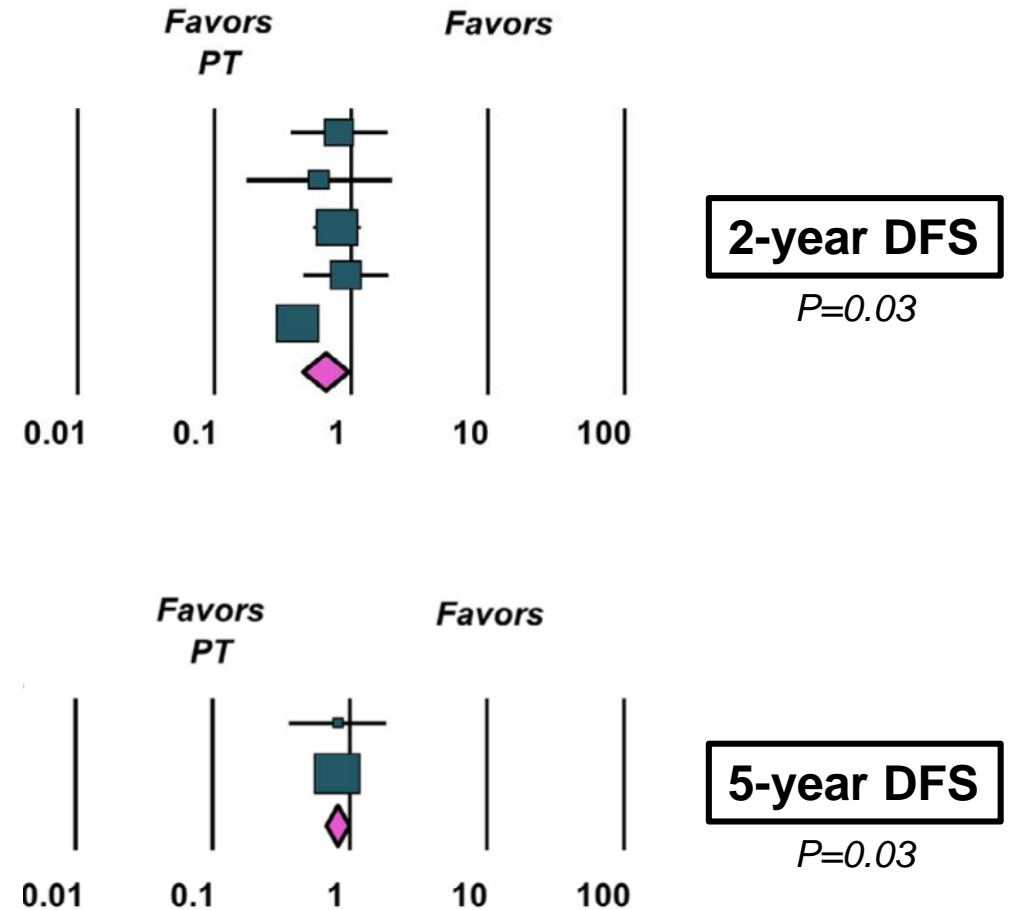
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Hadron Therapy: why?

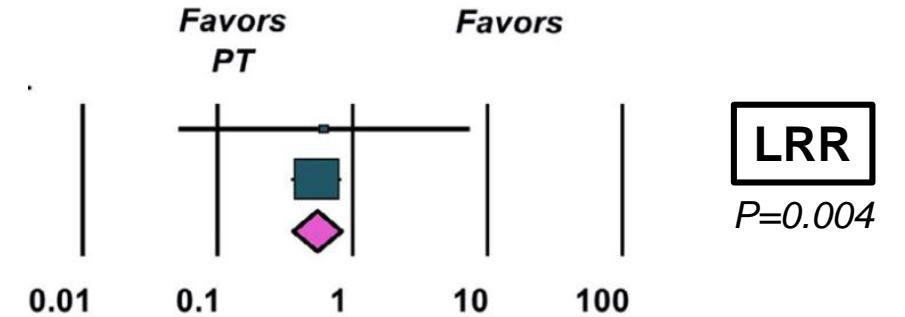
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11 studies, 3087 pts (606 PT + 2481 IMRT)



To be confirmed...

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**

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

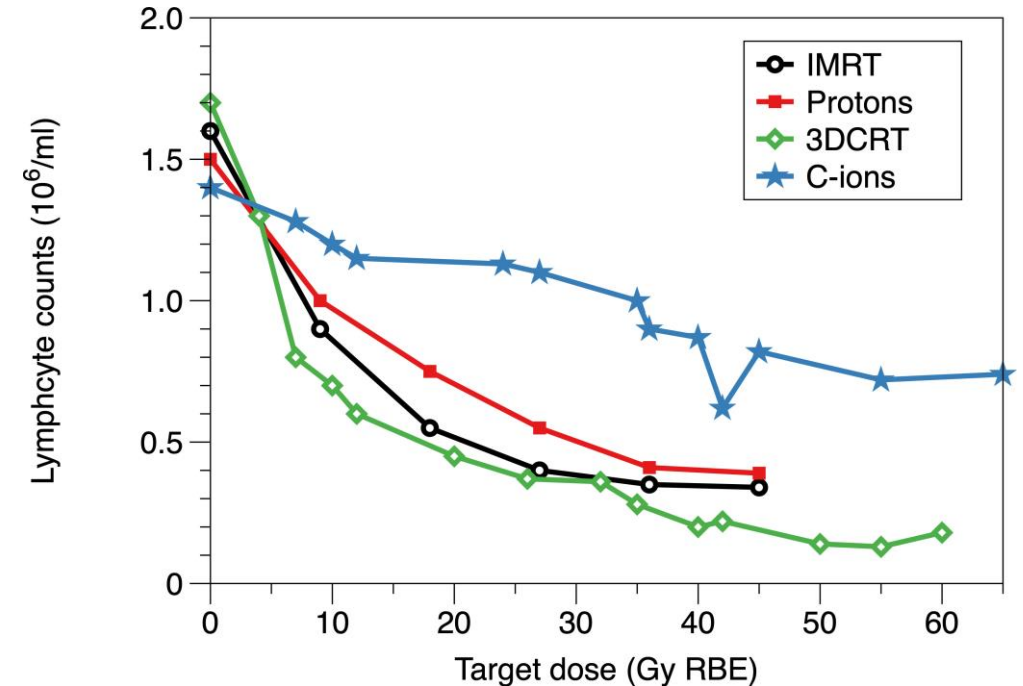
A Helm¹, C Totis¹, M Durante², C Fournier¹

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



Hadron Therapy: why?

3. Multimodal approaches

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 Vitolo³ , Amelia Barcellini^{*,3,4}, Sara Ronchi³ , Angelica Facoetti⁵, Chiara Campo⁶, Catherine Klersy⁷, Silvia Molinelli⁸, Francesco Agustoni^{4,9}, Virginia Valeria Ferretti⁷, Annalisa De Silvestri⁷, Marco Platania¹⁰, Michele Del Vecchio¹⁰, Marco Durante¹¹, Alexander Helm¹¹, Claudia Fournier¹¹, Filippo de Braud^{2,10}, Paolo Pedrazzoli^{4,9}, Ester Orlandi^{†,3}  & Lisa Licitra^{†,1,2,6}

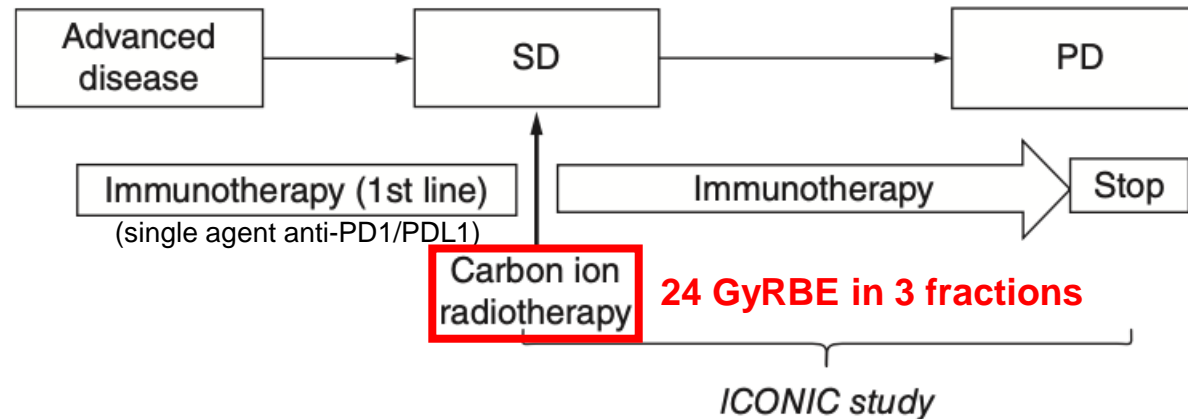
1. NSCLC, HNSCC, melanoma and urothelial carcinoma
2. At least 2 measurable target lesions

Primary endpoint:

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

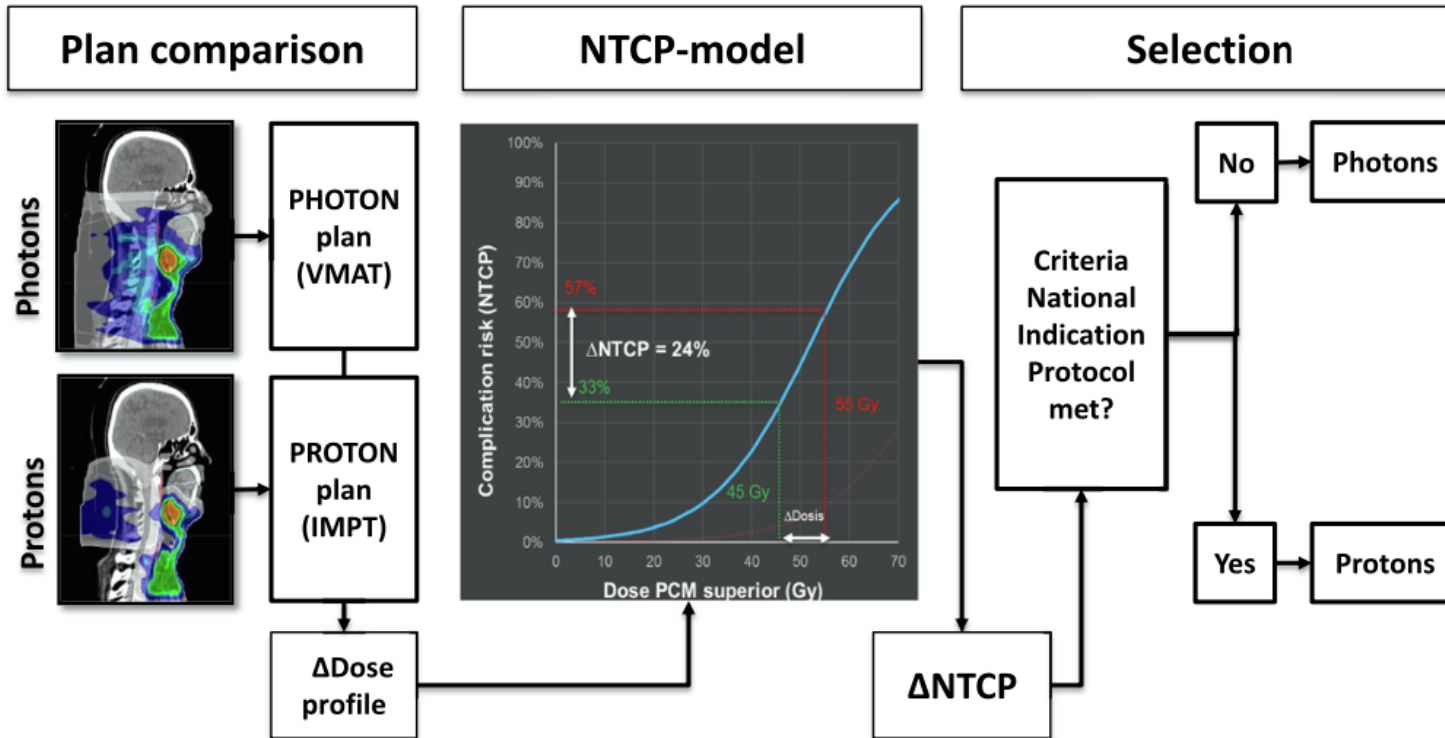
Secondary endpoints:

- toxicity according to CTCAE version 5.0
- PFS
- OS



Hadron Therapy: how?

1) Model-Based Approach (MBA)



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

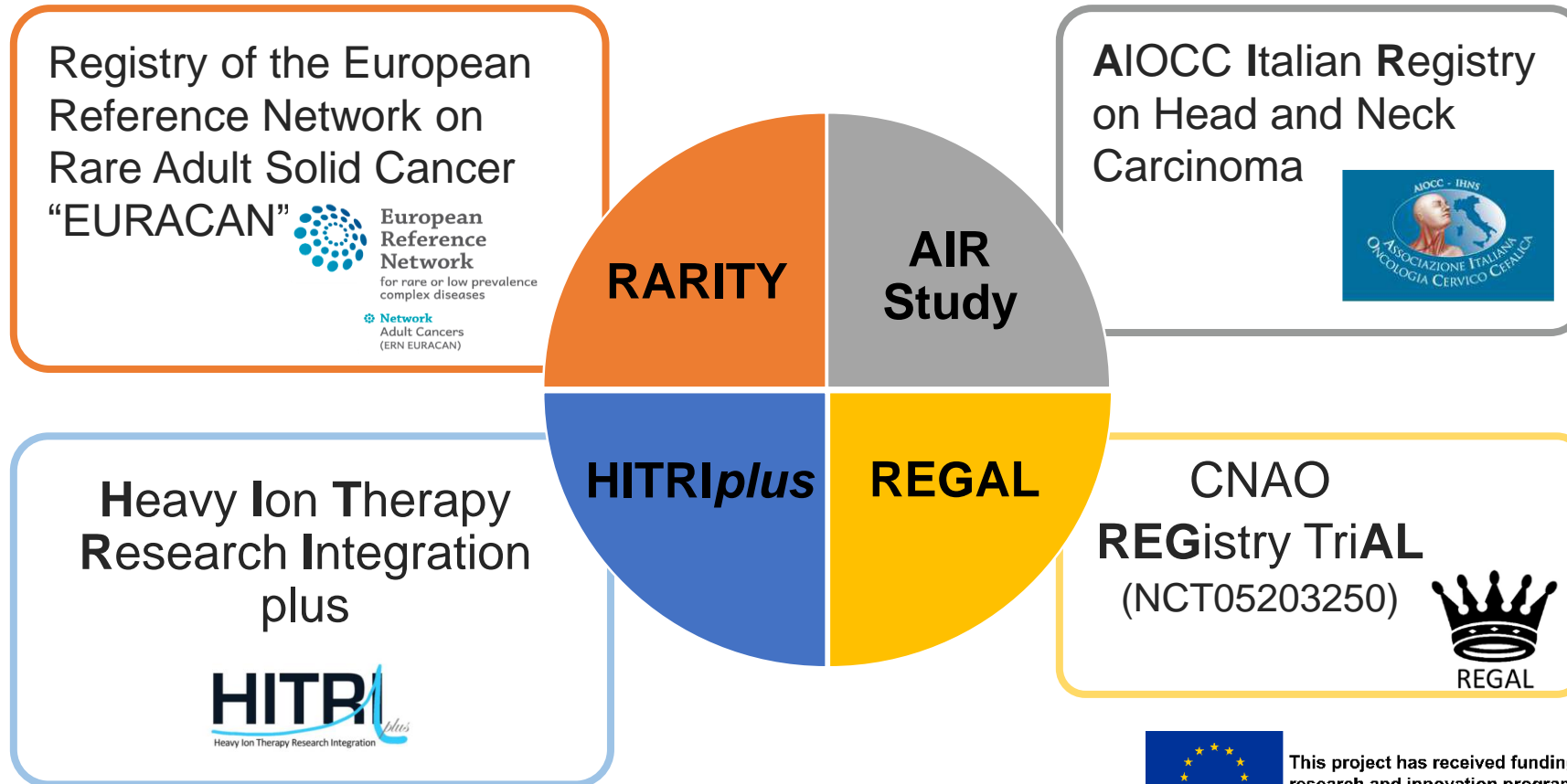
Hadron Therapy: how?

Perspective

Towards a European prospective data registry for particle therapy

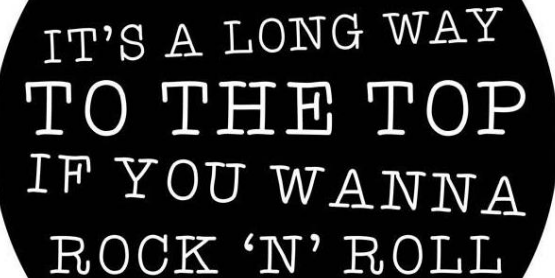


5) Prospective data registries



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



IT'S A LONG WAY
TO THE TOP
IF YOU WANNA
ROCK 'N' ROLL

THANK YOU!

