Hadron Therapy-UK

The goal of laser-driven ion beam radiotherapy is to develop well-controlled, reliable energetic ion beams of very high quality that can meet stringent medical requirements with respect to physical parameters and performance and therefore represent a viable alternative in an advancing state-of-the-art for radiotherapy

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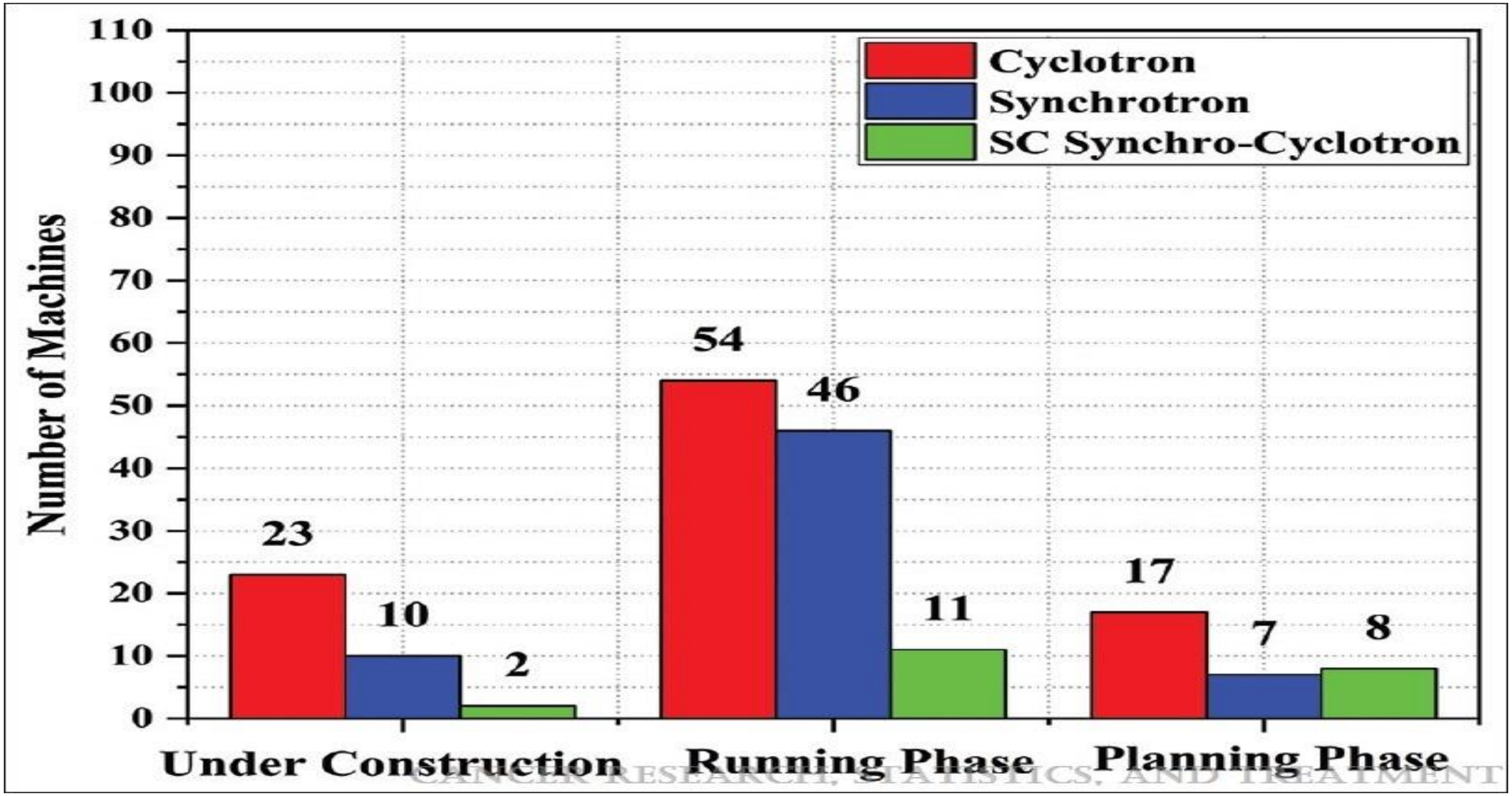
Current Status of Proton, carbon and Helium Facilities Worldwide

Status	Proton therapy	Carbon therapy	Helium therapy
Under construction	30	5	1
Running phase	99	13	0
Planning phase	32	2	0



Potential Advantages of LhARA based Ion Therapy over Conventional Ion Therapy

- Low-emittance and well-collimated beams are advantageous in proximal normal tissue-sparing.

- Highly-peaked quasi-monoenergetic beams are ideal for fast energy selection.

- High fluence and ultra-short pulse delivery should produce denser ionization track signatures (spurs, blobs, etc.) in target tumors, higher linear energy transfer, higher Bragg peak, and higher radiobiological effectiveness at the micro-level.

- Ease of generating mixed ion beams.

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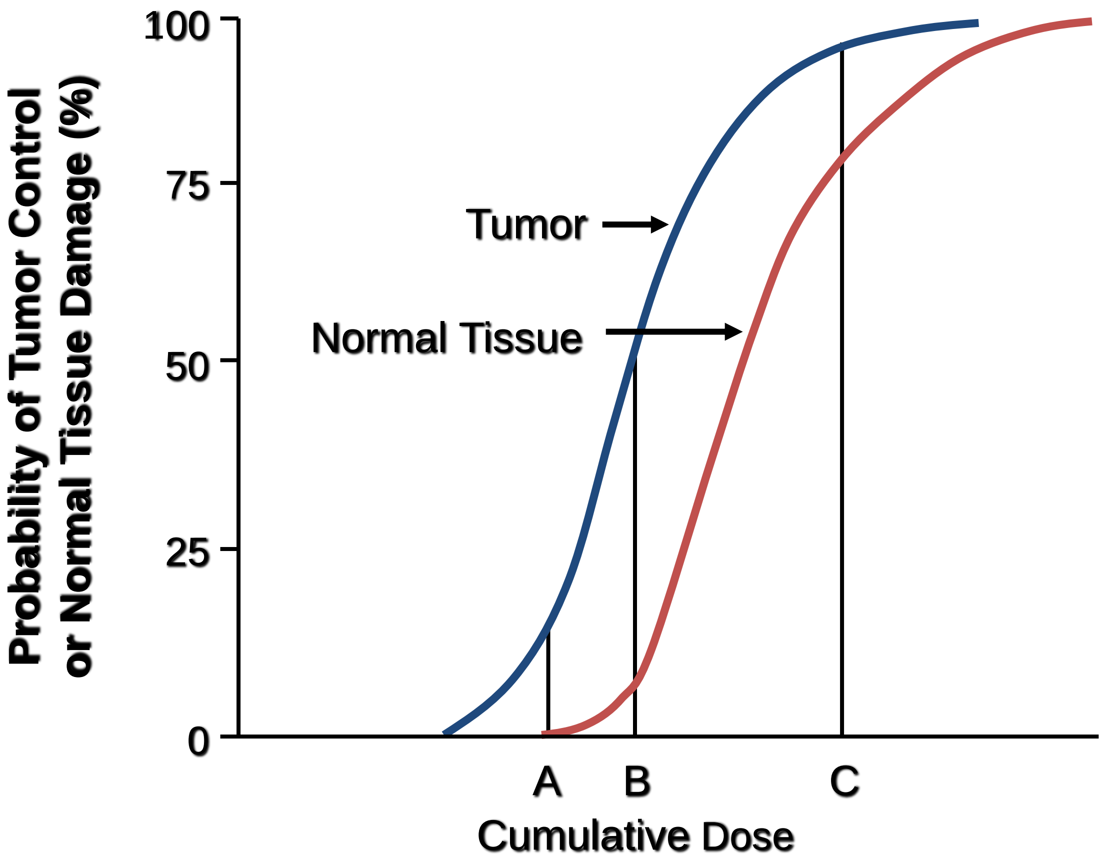
Objective: To Increase the Therapeutic Index of Radiotherapy



Hall and Giaccia, 2019

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Hadron Therapy

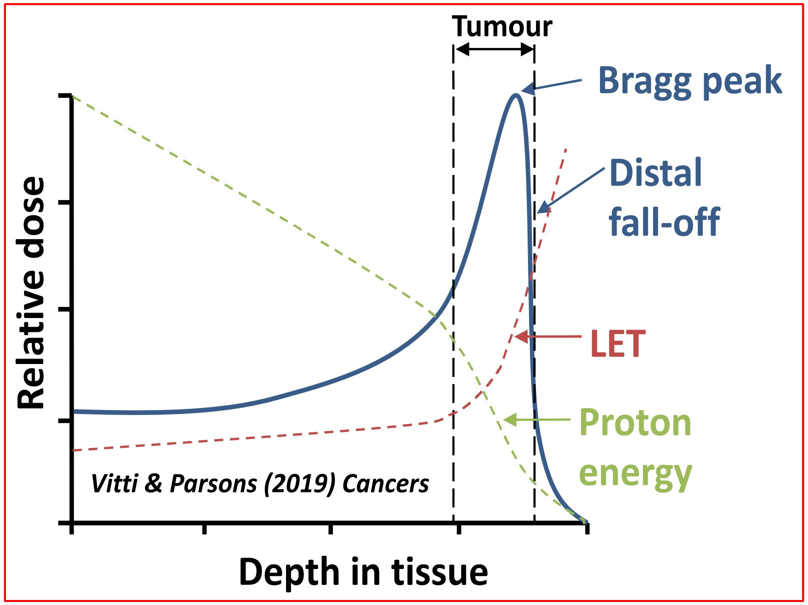
- Conventional radiation therapy
  = photons (x- or γ rays) + electrons

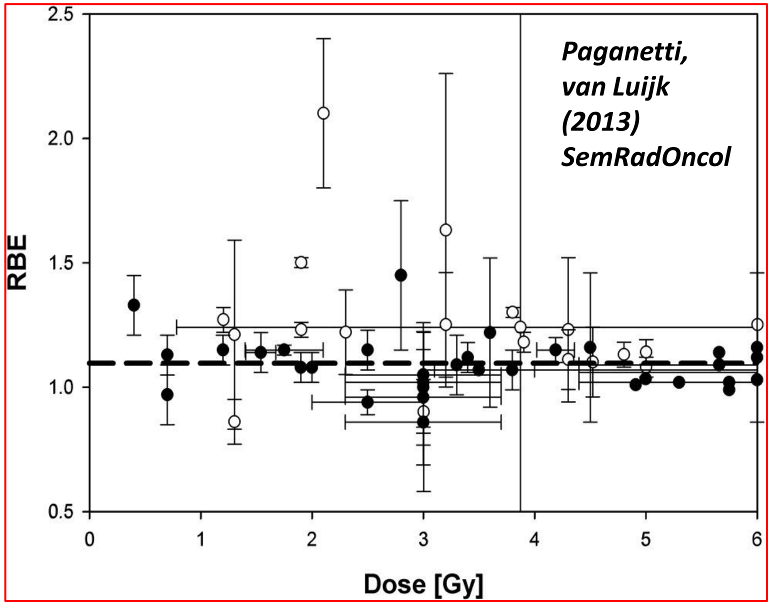
- Hadron therapy = Particle radiation therapy (particles heavier than electrons)
  – Protons
  – Carbon ions
  – Other ions (helium, neon, pions, silicon, iron, etc)

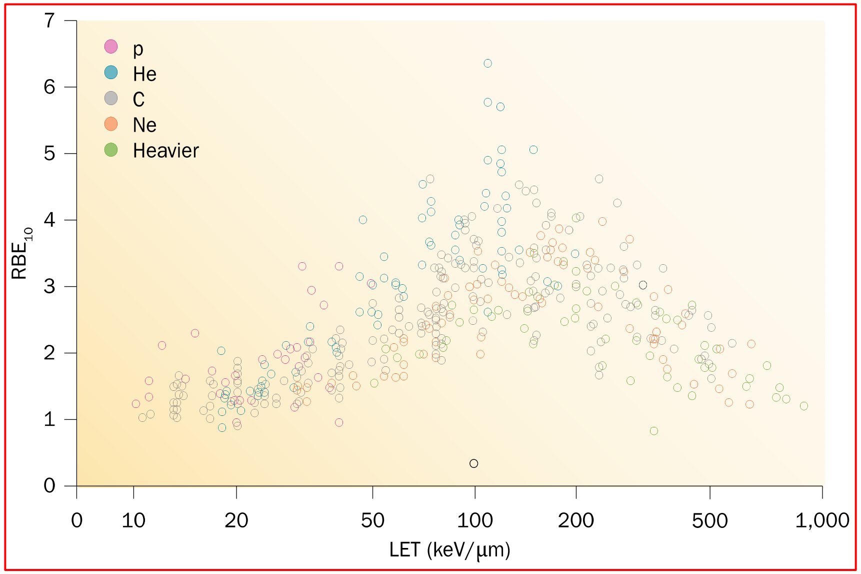
There is a strong rationale for the clinical benefit of proton and carbon therapies, but current evidence is limited

Therapy	Rationale for clinical benefit
Proton	▪ Deliver a higher, targeted radiation dose with decreased toxicity to surrounding tissue compared with photon therapy, especially near critical structures
Carbon	▪ Further increase target tissue damage with decreased secondary tissue affected compared with protons ▪ Specific potential benefit with intractable radio-resistant tumors

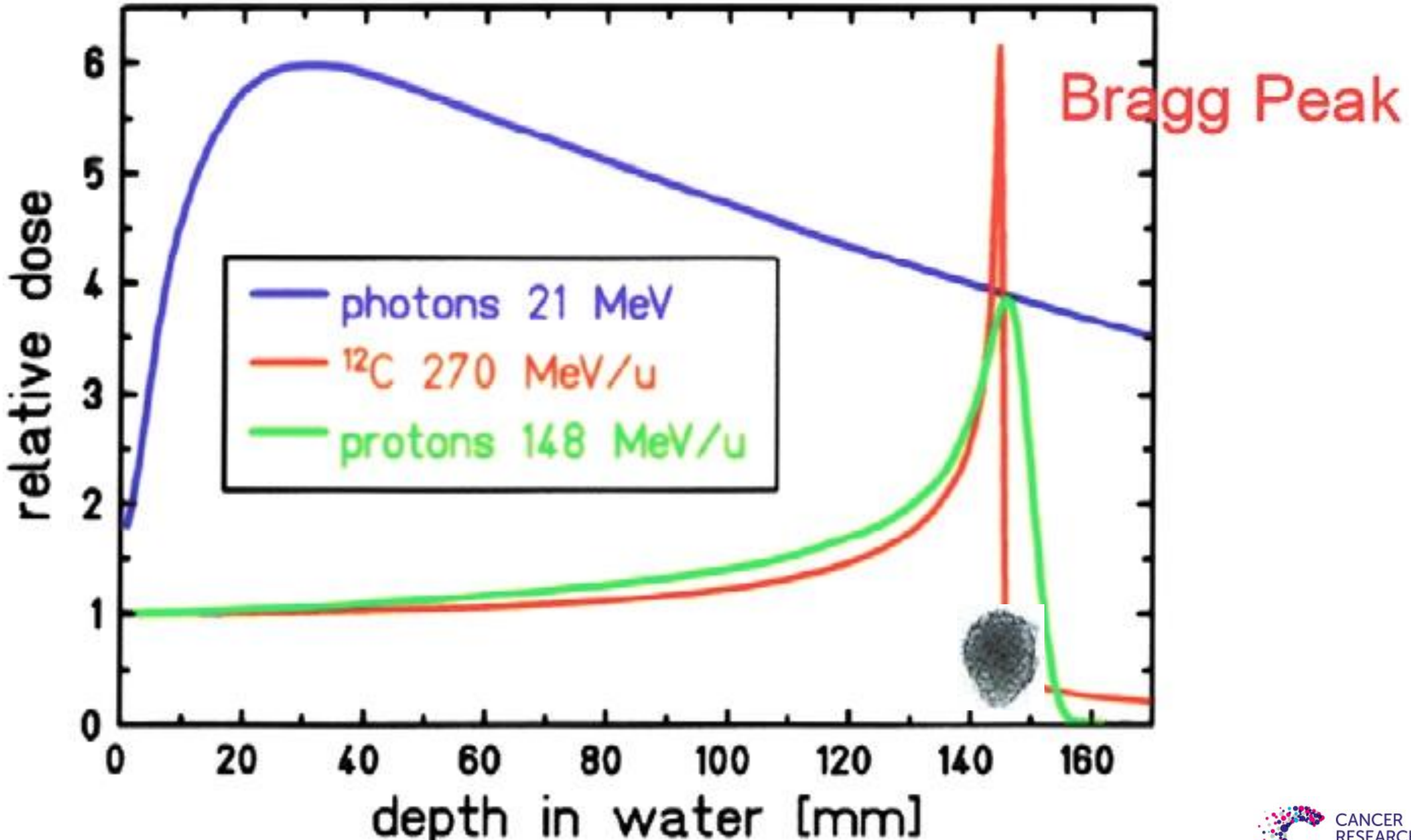
Dose-Depth Profiles







Plot of Depth-Dose Distribution of 21 MeV Photons vs 148 MeV/u Protons vs 270 MeV/u Carbon in water



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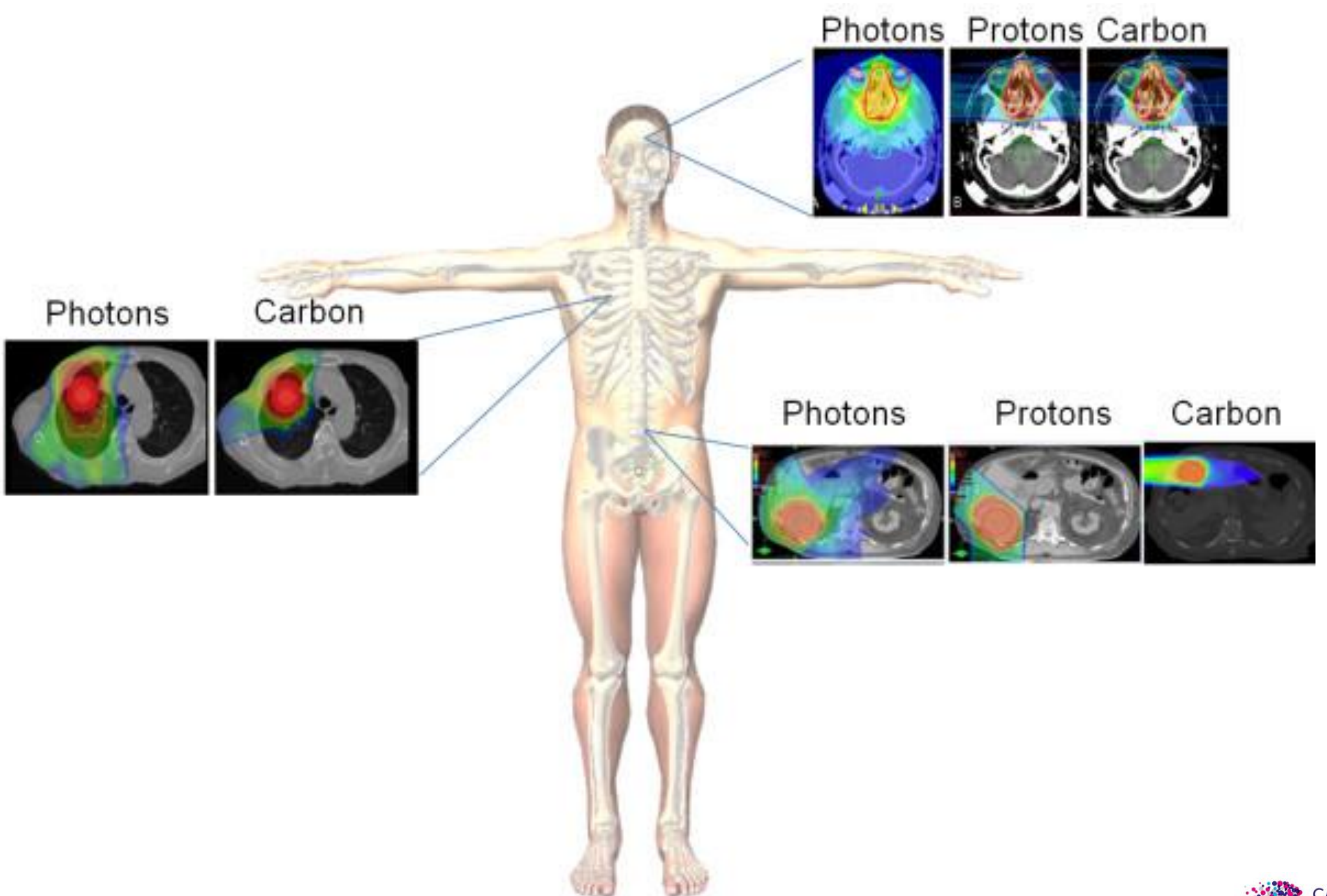
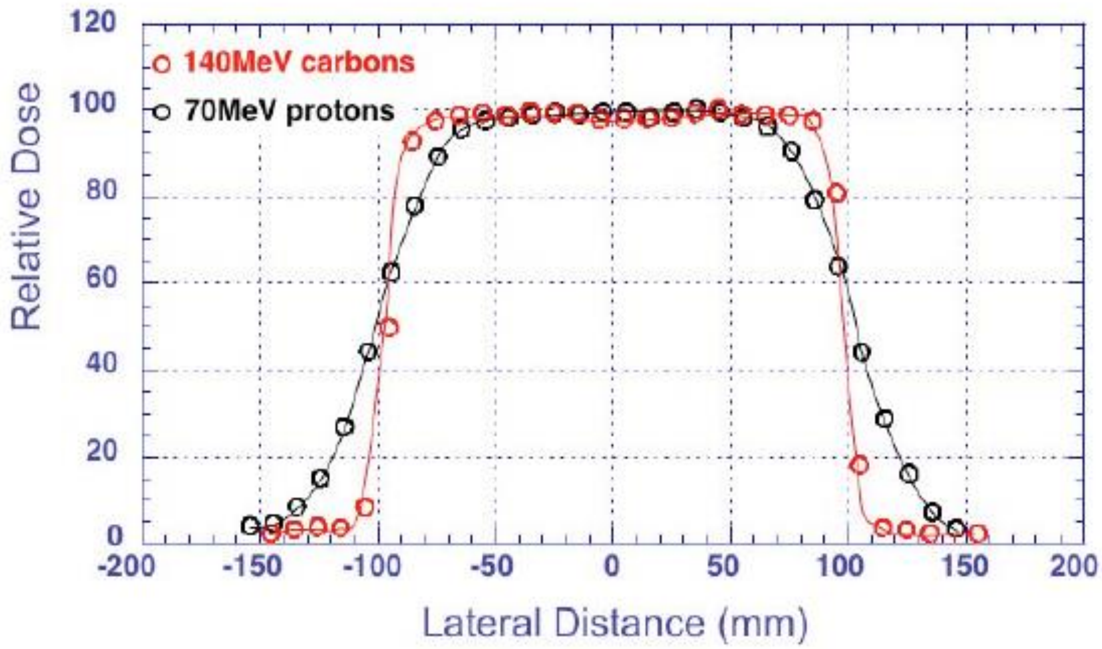
Superior Dose Distribution of Carbon Ions Compared to Protons and Photons



Carbon Ions Provide Highly Localized Tumor Deposition of Dose (Sharper Transverse Edge)



Better Localization

- Tighter deposition in depth (Bragg peak is narrower)
- Transverse deposition is more narrowly collimated
- **Less dose to the healthy tissue**

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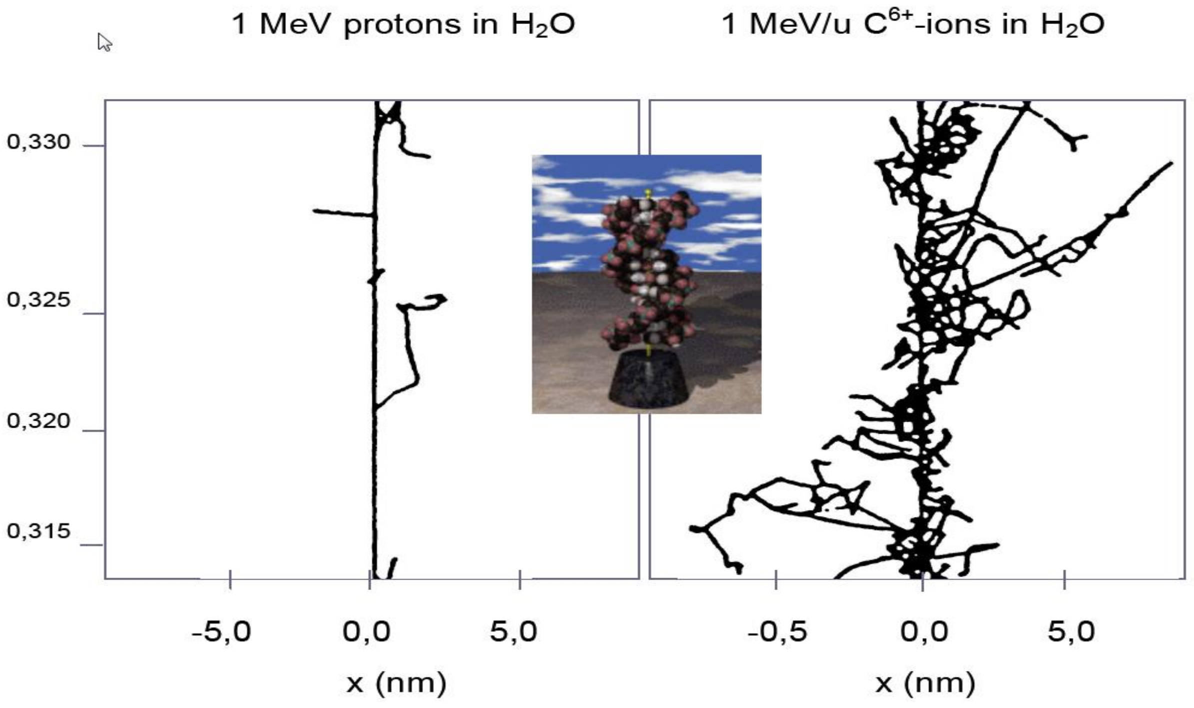
Carbon Ions Induce More Lethal Damage Per Unit Dose than Photons or Protons



Increased Biological Effectiveness:

Relative Biological Effectiveness is 2-3 times protons

- Reduces # fractionations by ~ 2: greater patient throughput/compliance
- Countermands radio-resistance: non-repairable, double-strand breaks

Production of positrons permits active monitoring using PET

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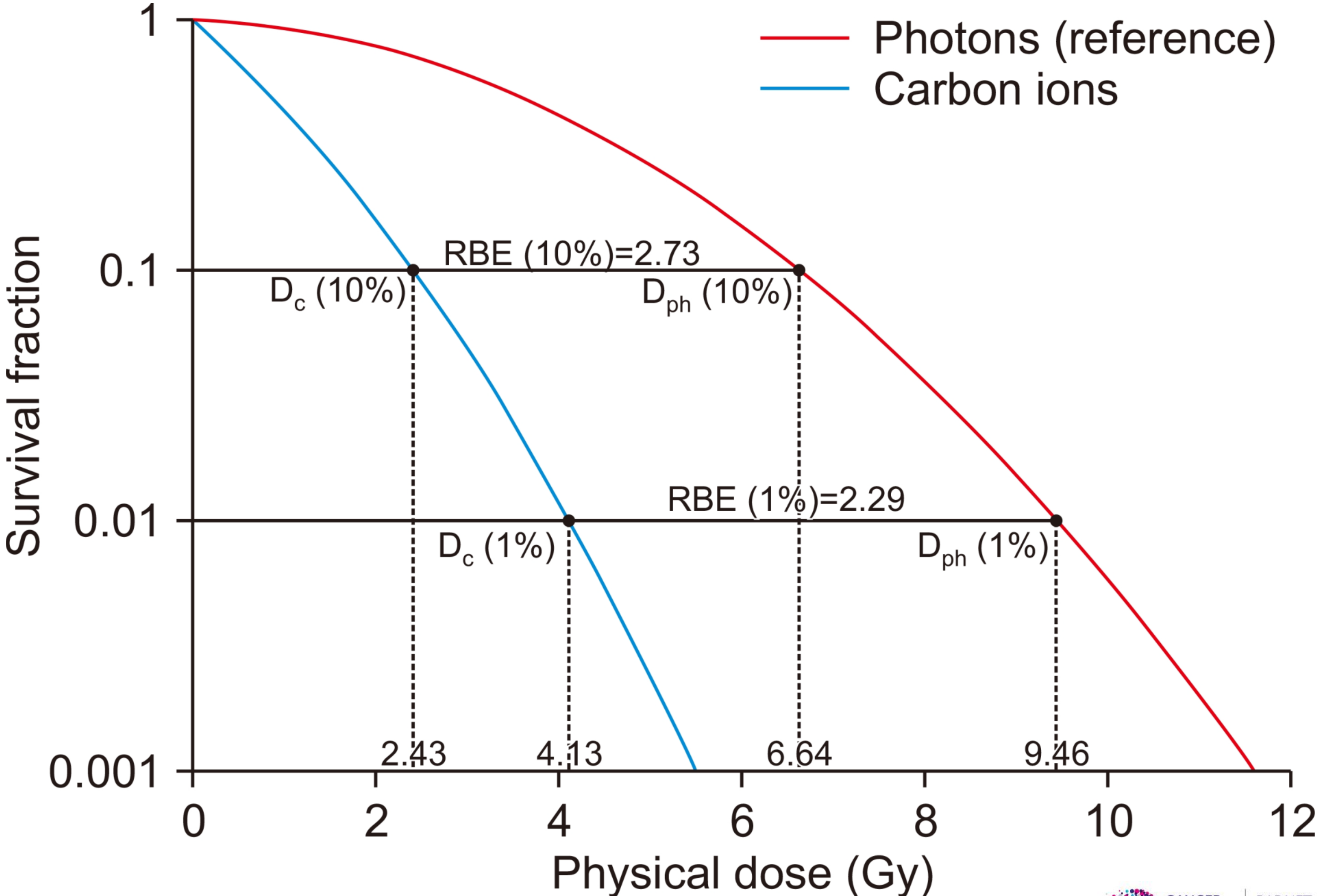
Cell Survival Based on the LQ model



Progress in Medical Physics 2020;31:1-7

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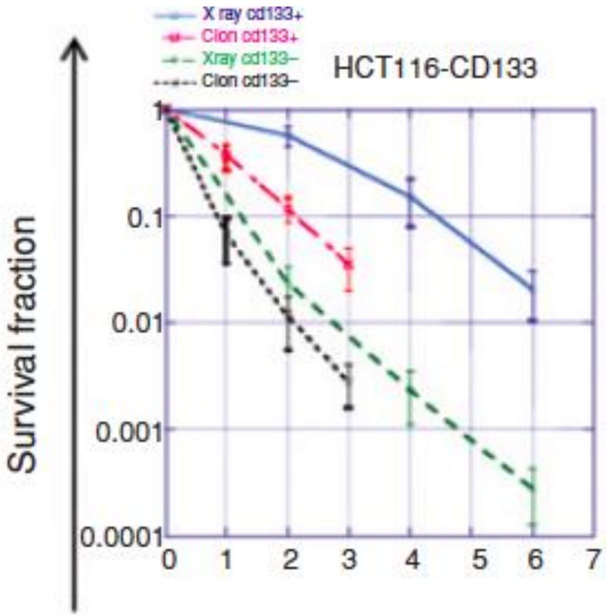
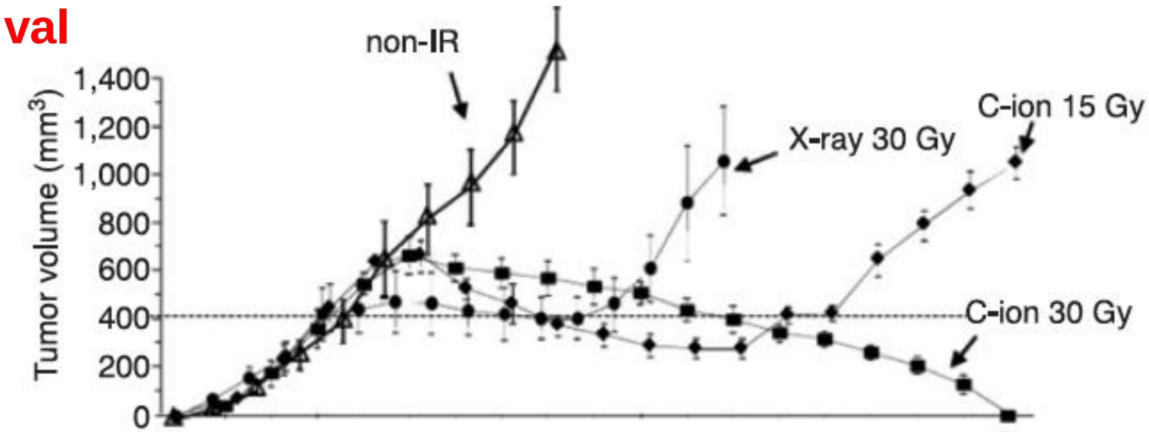
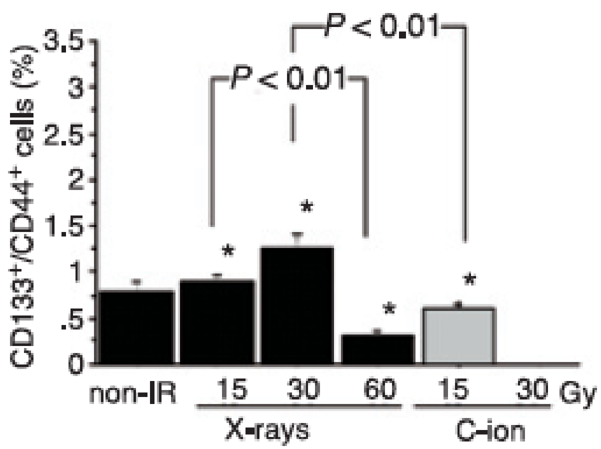
Carbon is More Effective In Killing Cancer Stem Cells

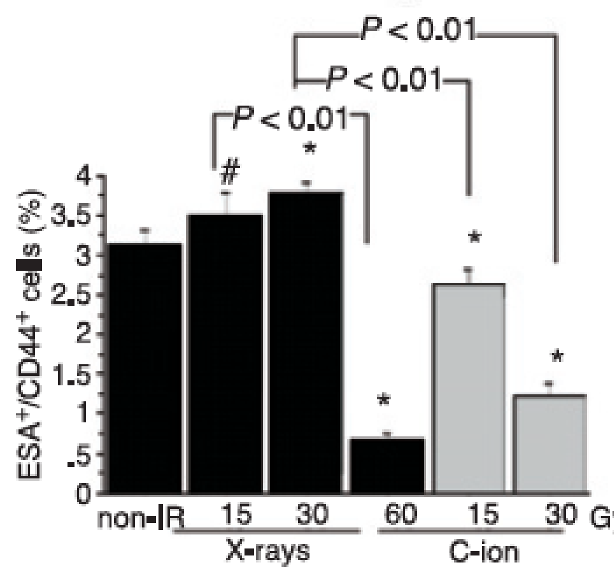
In vitro clonogenic survival



In vivo growth by beam type and dose







% putative CSC-like *in vivo* after RT

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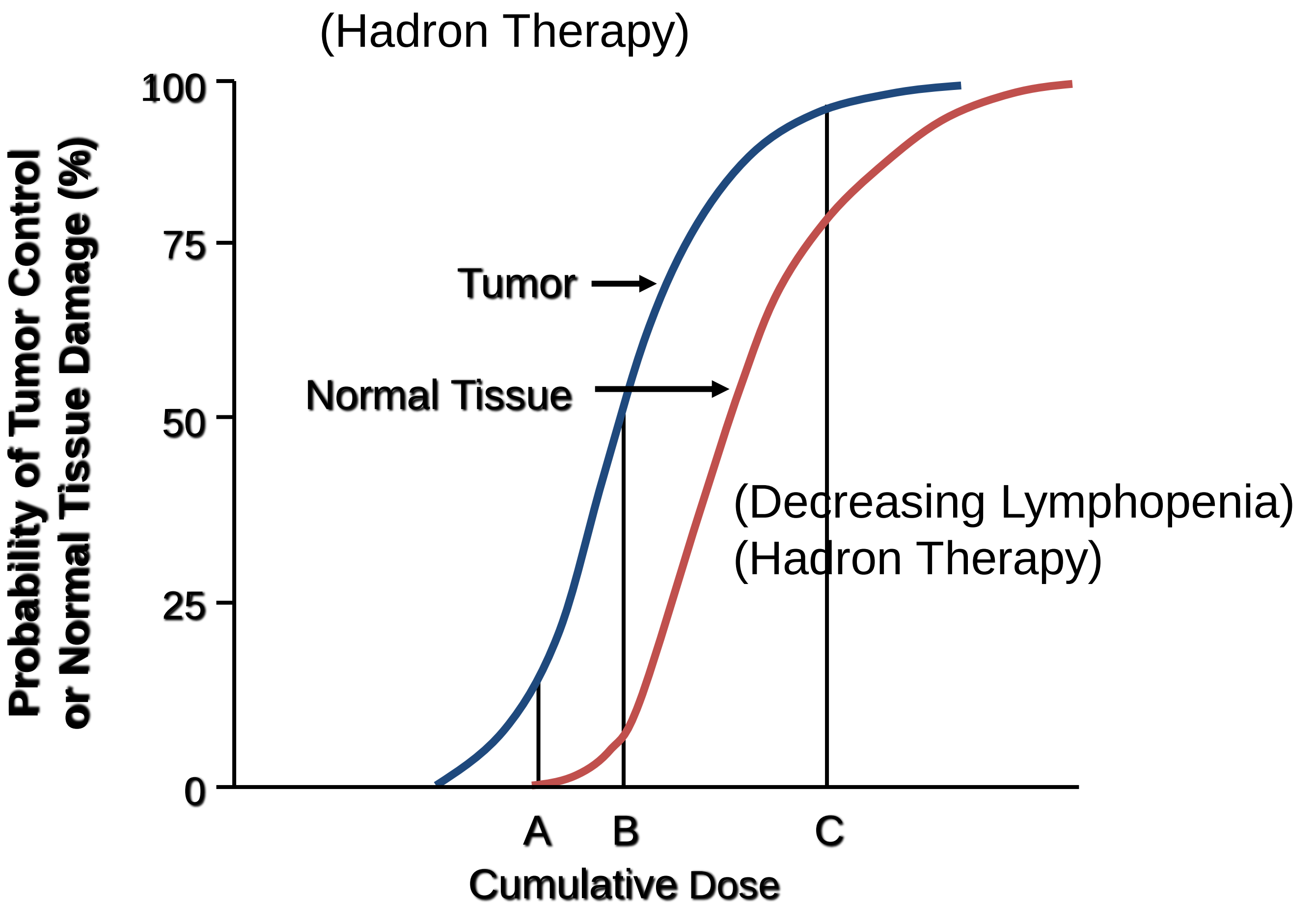
Cui X et al, Cancer Research 2011

Objective: To Increase the Therapeutic Index of Radiotherapy



Hall and Giaccia, 2019

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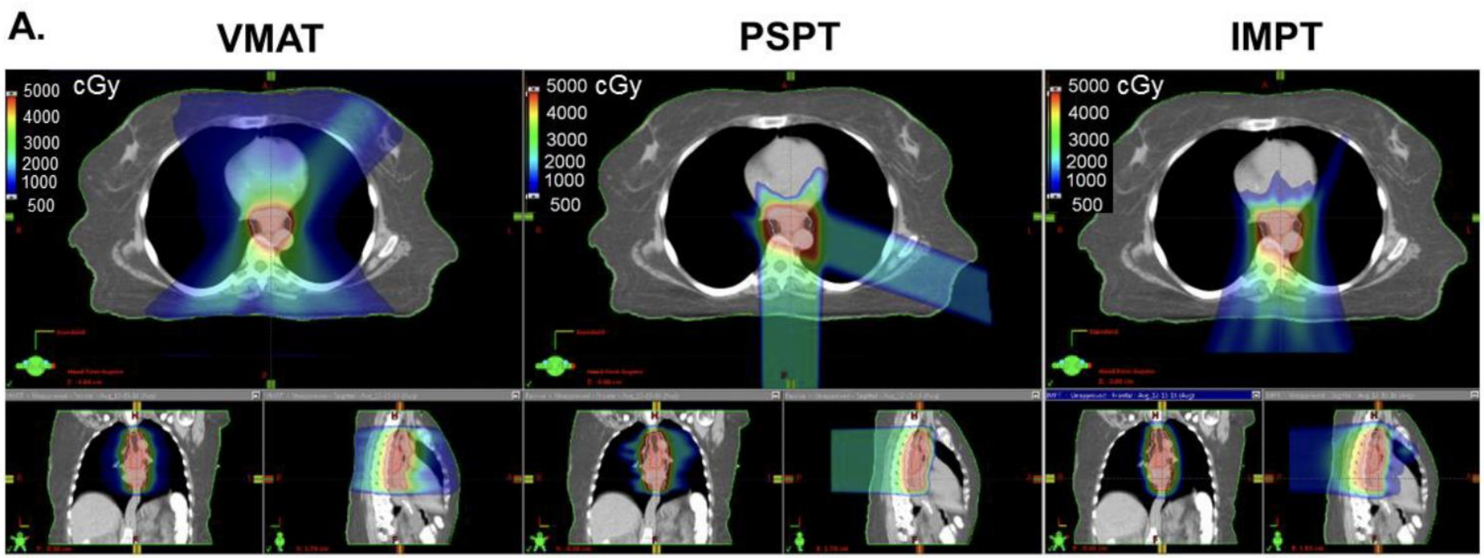
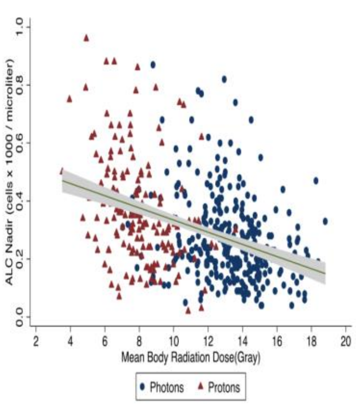
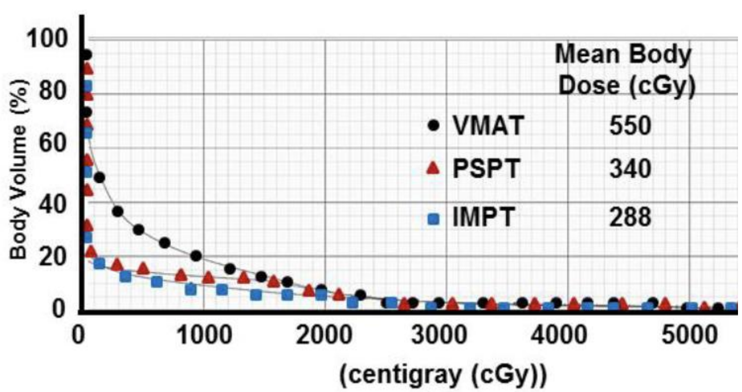
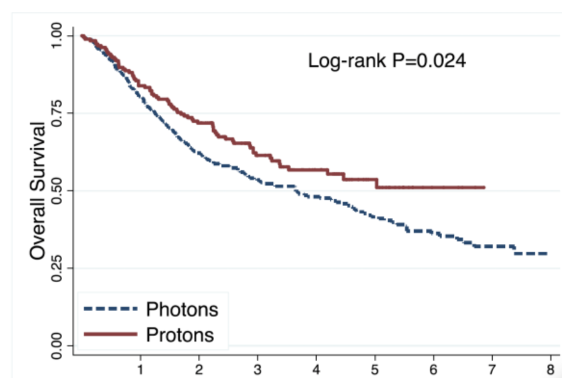
Effect of Different Therapies on Mean Body Dose and Survival









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Davuluri et al, IJROBP, 2017

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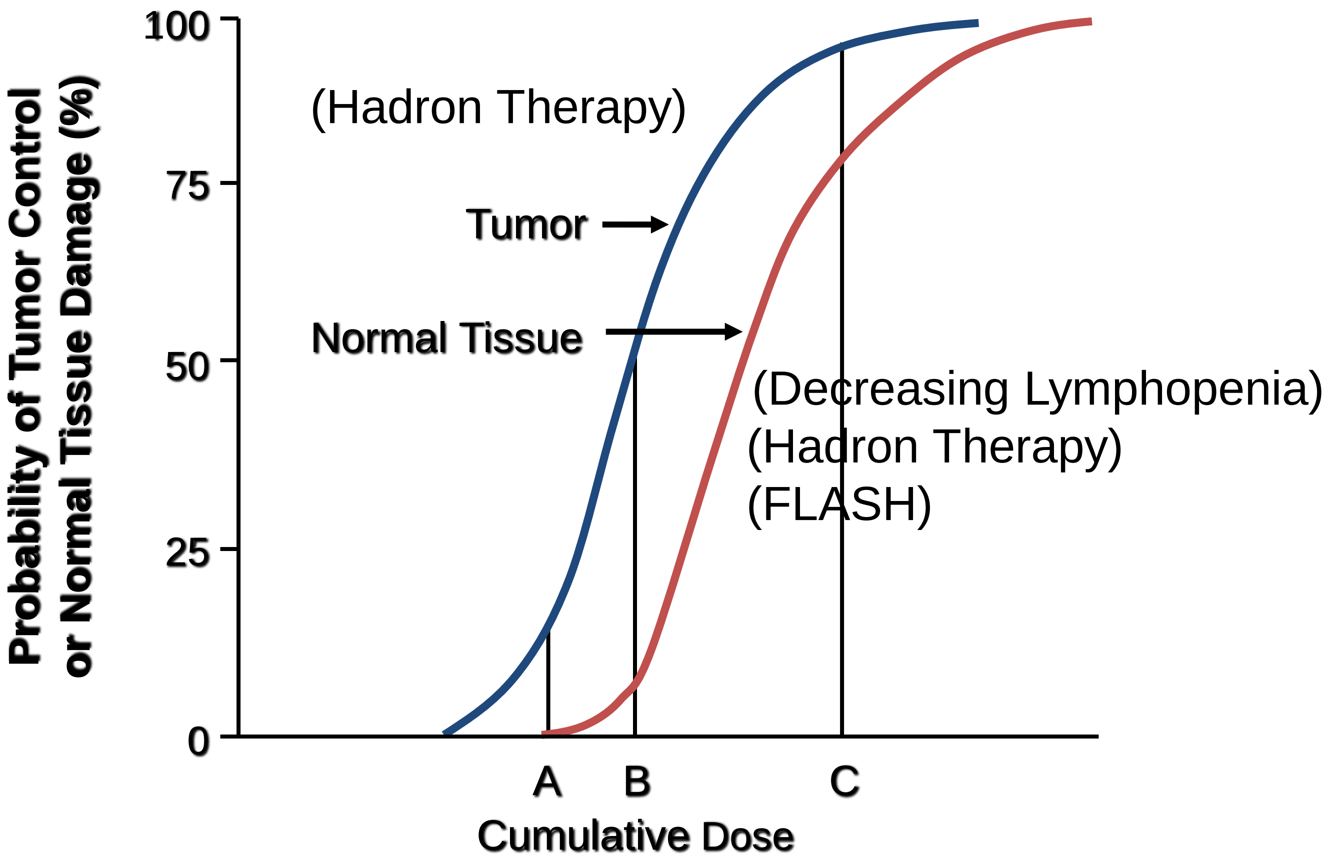

Hall and Giaccia, 2019

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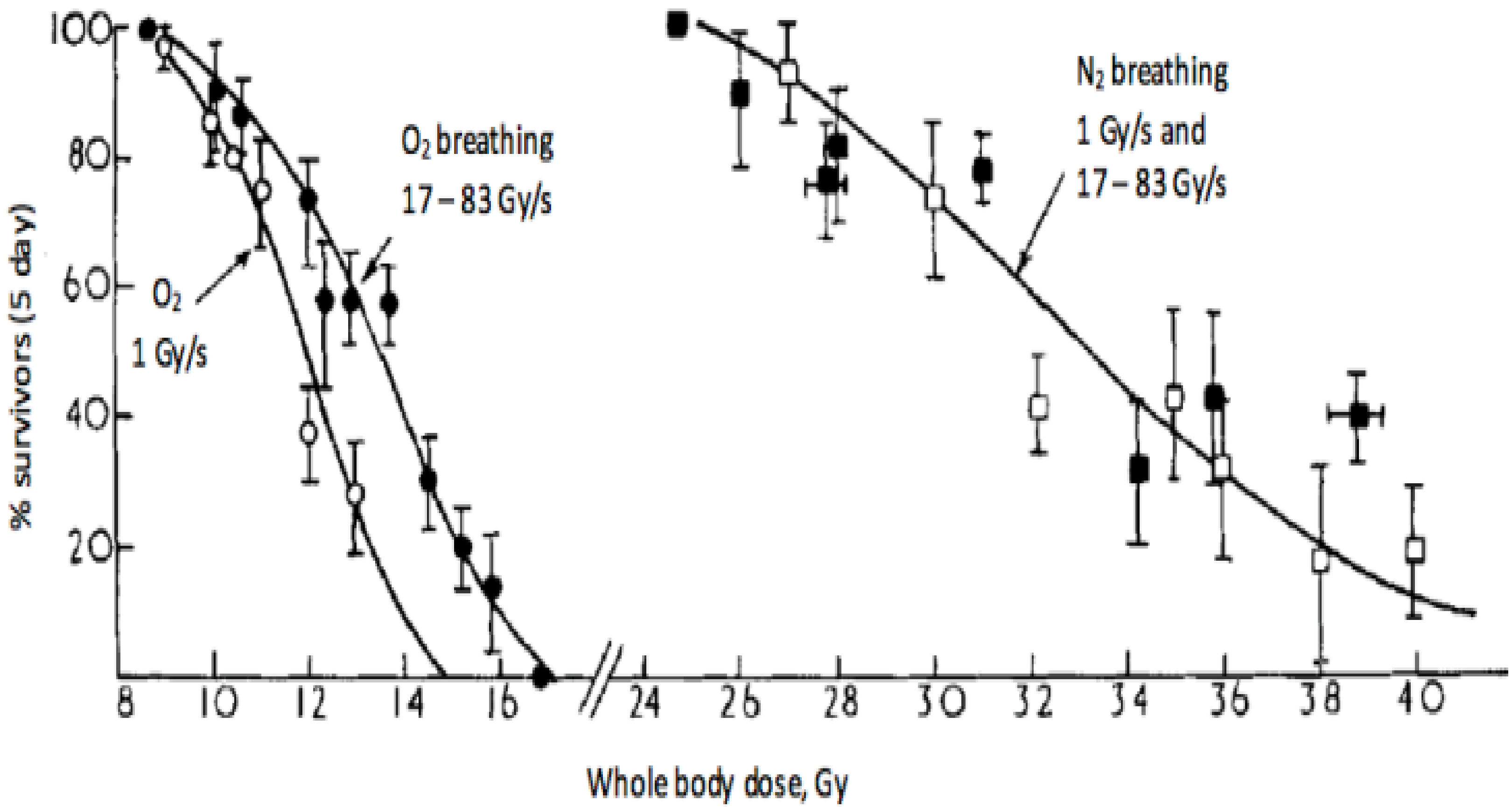
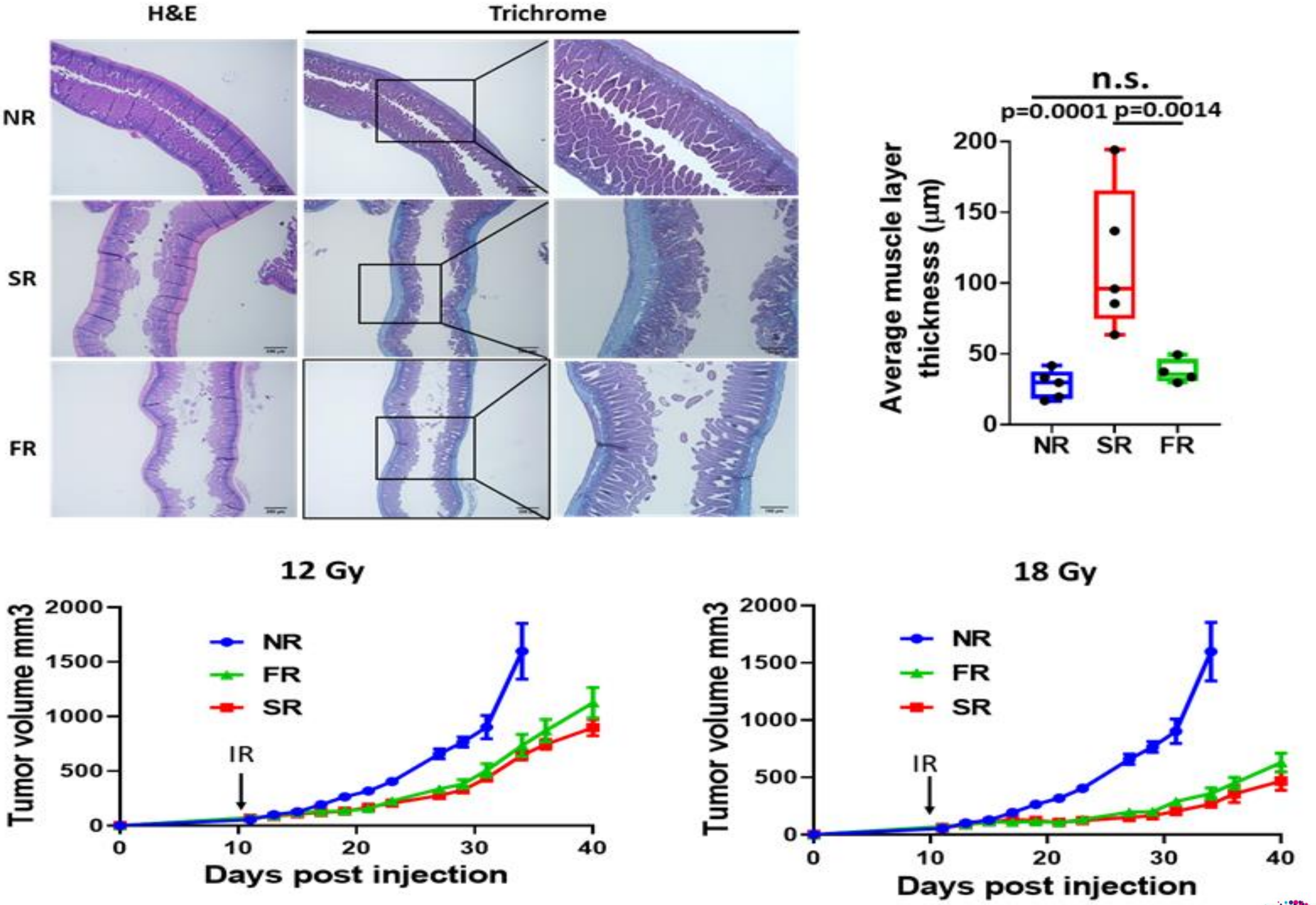
The Origins of FLASH Radiotherapy



Hornsey S, Bewley DK. Hypoxia in mouse intestine induced by electron irradiation at high dose-rates. *Int J Radiat Biol Relat Stud Phys Chem Med.* 1971;19(5):479-483.

Flash-Proton Radiotherapy Highly Effective in Controlling Pancreatic Tumor Growth and Reduces Normal Tissue Toxicity



Koumenis et al. 2022

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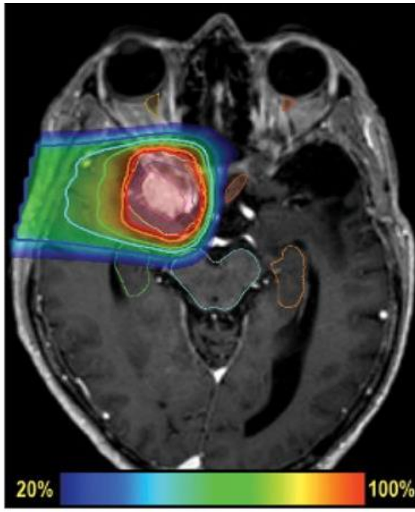
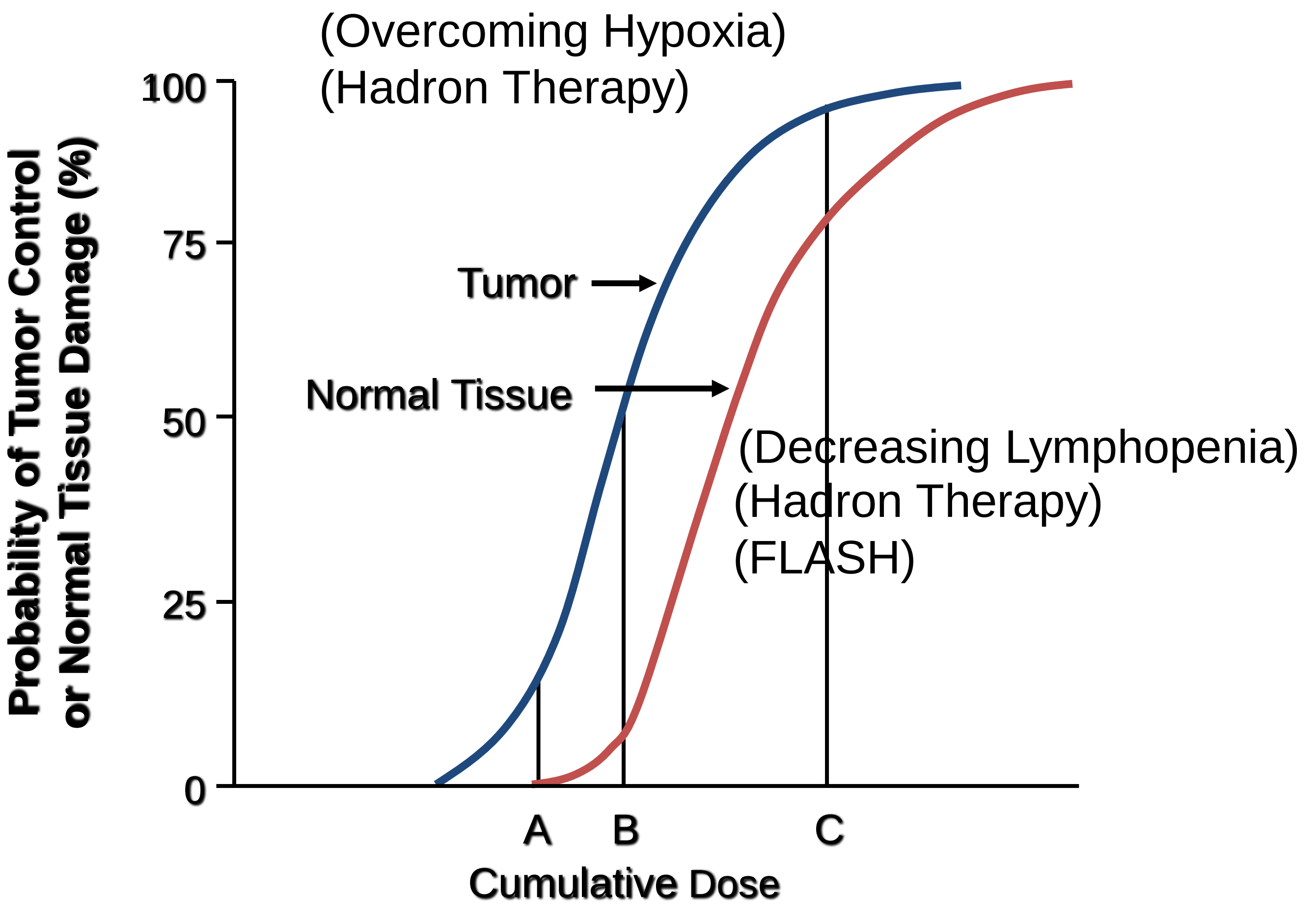
Treating Deep-Seated Tumours with Proton-FLASH

- Problems/challenges:
    - Scanning/scattering needed to cover the target volume
        – Dose rate decreases!
    - Several beam energies needed to cover the target volume in depth
        – Dose rate decreases!
    - Several beams needed for dose conformity
        – Dose rate decreases!
        – Takes time to change beam angle.



Proton radiation beam

Objective: To Increase the Therapeutic Index of Radiotherapy



Hall and Giaccia, 2019

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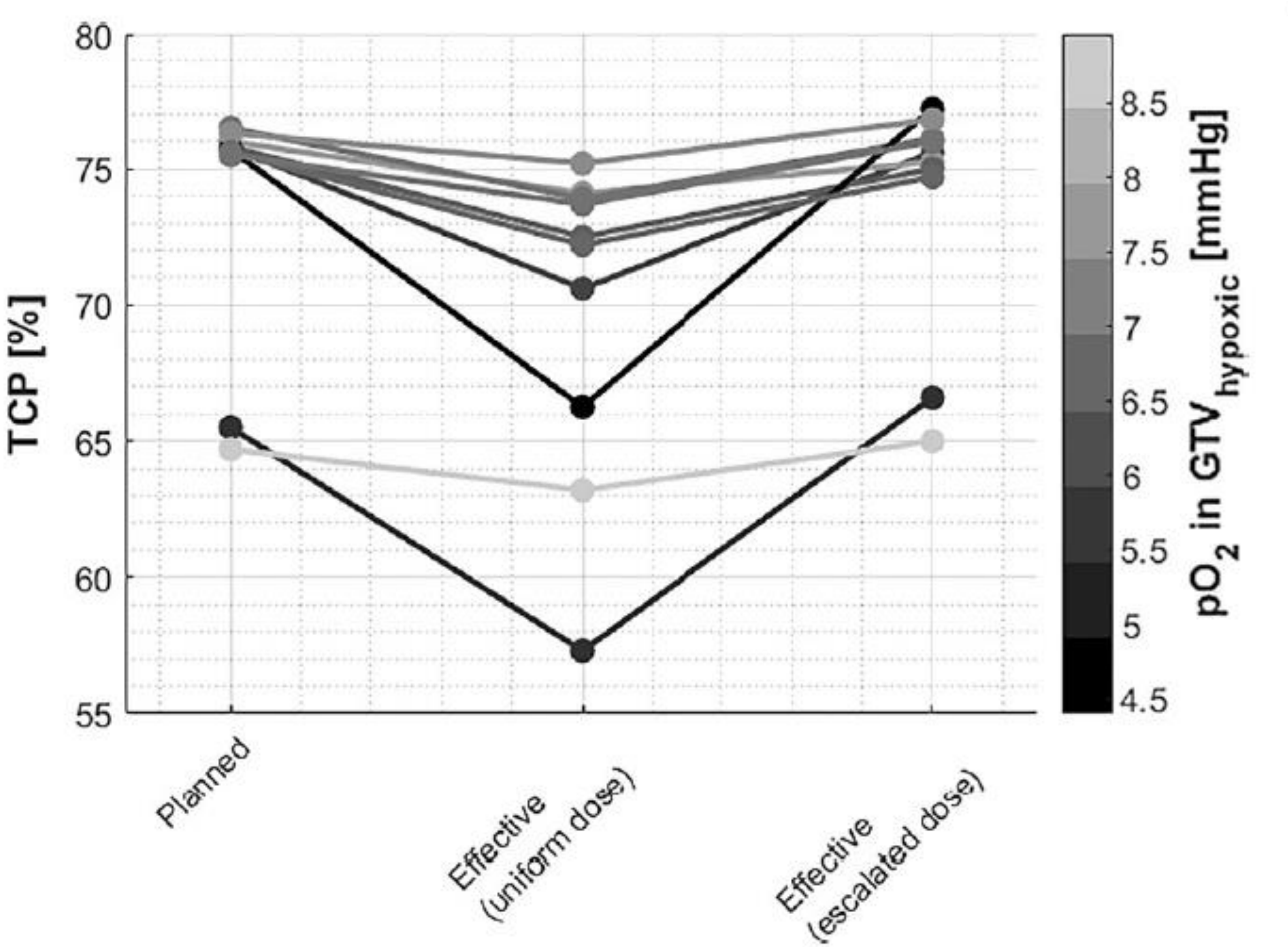
TCP for Individual Patients Treated with Protons



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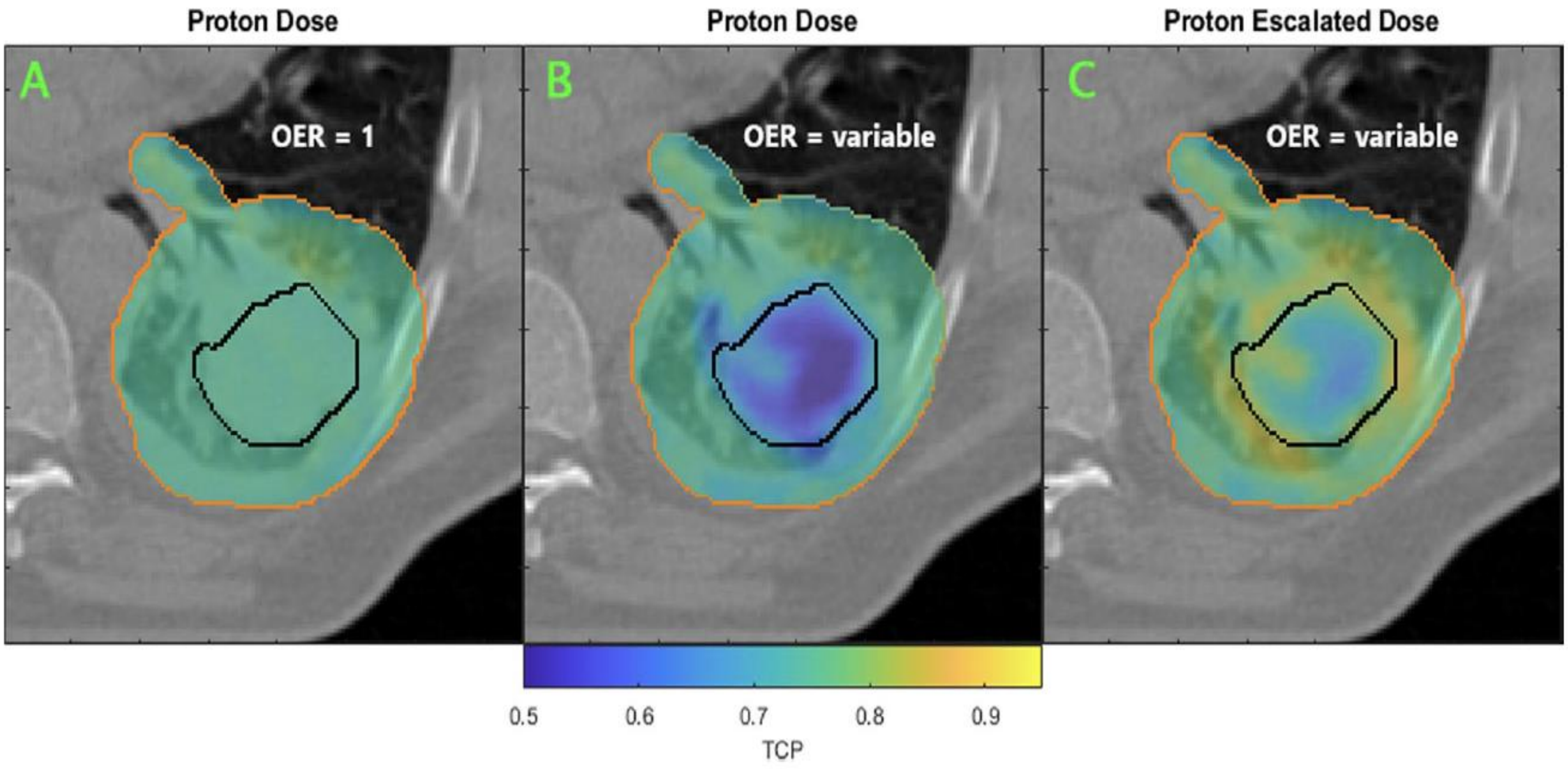
Kothe et al, Radiat Oncol, 2021

Voxel-wise TCP Calculation and Overcoming Hypoxia with Proton Escalation



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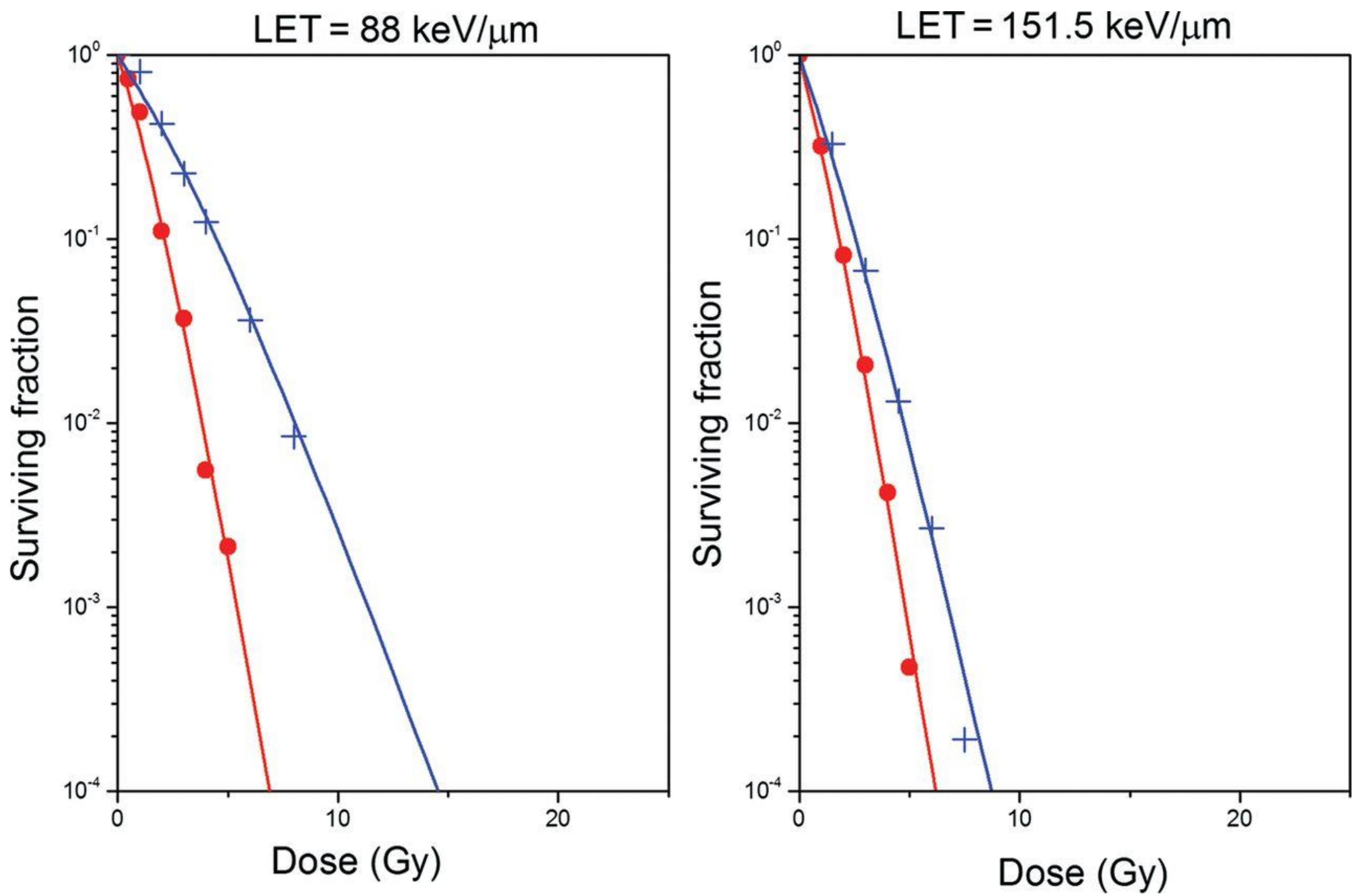
Kothe et al, Radiat Oncol, 2021

Survival of Cells Irradiated with Carbon Ions in Oxic (red curves) and Hypoxic conditions (blue curves) for Two Different LETs



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Antonovic L et al. J Radiat Res 2013;54:18-26

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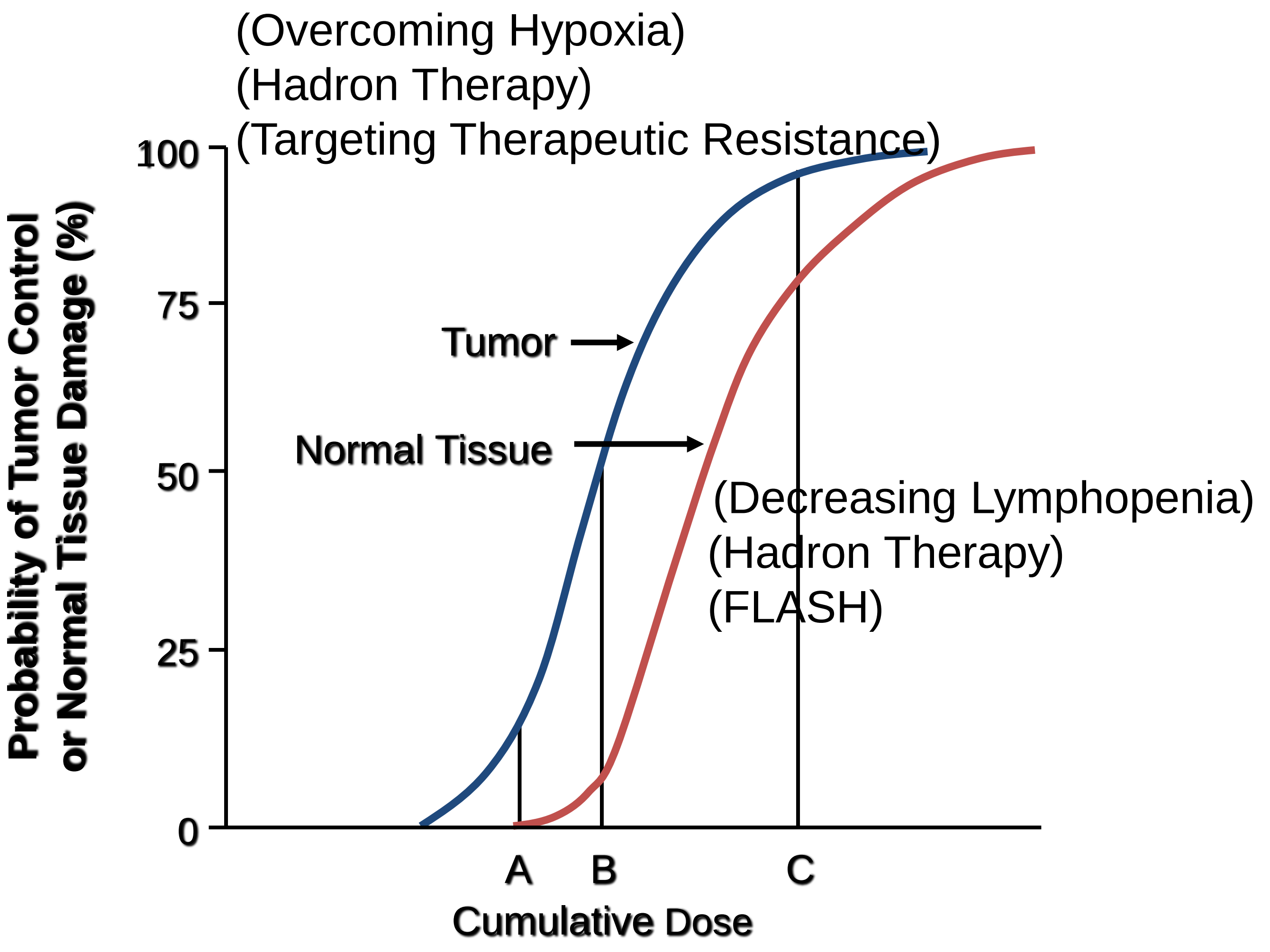
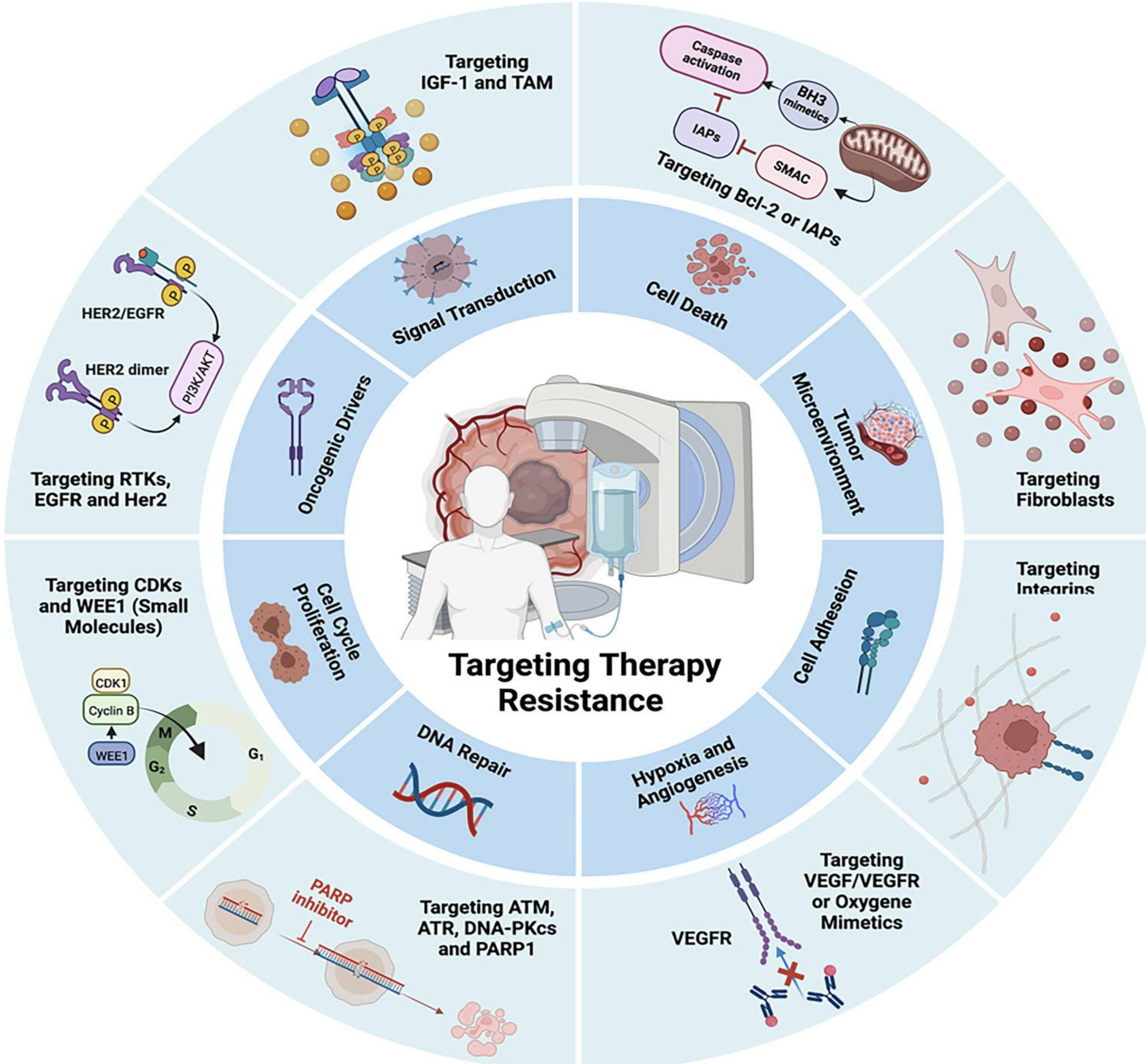


Hall and Giaccia, 2019

Schematic representation of molecular mechanisms associated with treatment resistance in solid tumors and molecular targeting approaches for cancer chemo- and radiation sensitization.



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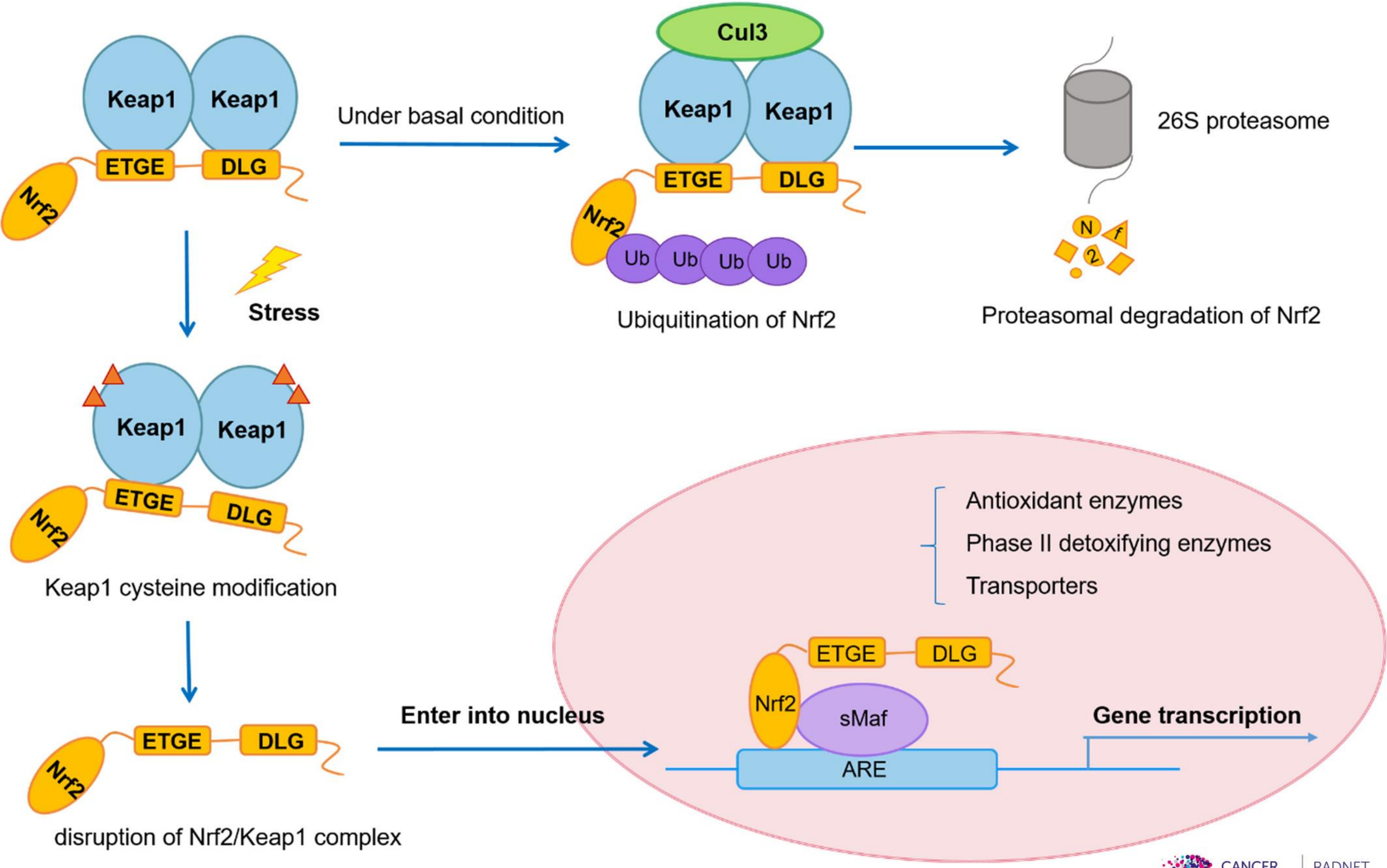
Modified from Viktorsson et al, Strahlenther Onkol, 2023

Keap-Nrf2 Pathway



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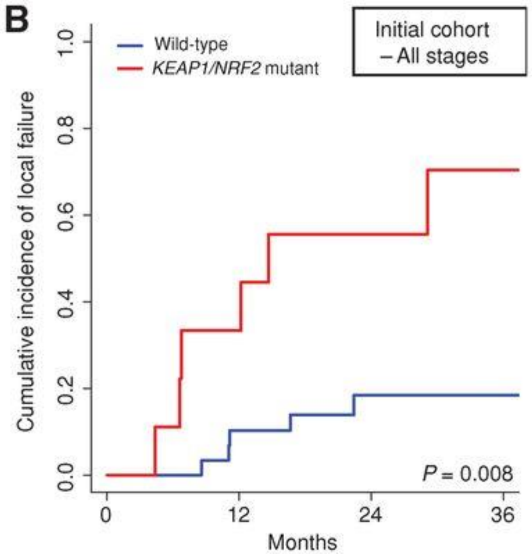
KEAP1/NRF2 Mutation Status Predicts Local Failure after Radiotherapy in Human NSCLC

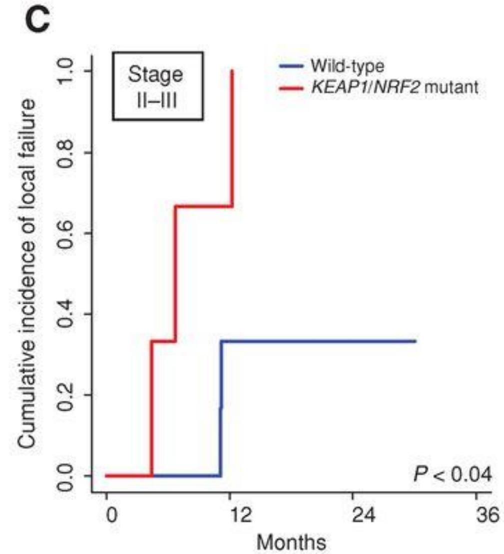
A

		Wild-type (*n* = 33)	*KEAP1/NRF2* mutant (*n* = 9)	*P*
Sex	M	9 (27%)	5 (56%)	0.23
	F	24 (73%)	4 (44%)	
Median age, years (range)		70 (42–91)	66 (56–91)	0.45
Median follow-up, mo. (range)		24 (6–53)	25 (7–63)	0.47
Histology	SCC	5 (15%)	1 (11%)	0.85
	Adenoca	25 (76%)	7 (78%)	
	Other	3 (9%)	1 (11%)	
Stage	I	22 (67%)	5 (56%)	0.54
	II	6 (18%)	1 (11%)	
	III	5 (15%)	3 (33%)	
Median tumor volume, mL (range)		16.2 (0.8–569.8)	16.1 (1.0–218.5)	0.48
Radiation type	SABR	25 (76%)	6 (67%)	0.68
	CFRT	8 (24%)	3 (33%)	
Chemotherapy	Yes	7 (21%)	3 (33%)	0.66
	No	26 (79%)	6 (67%)	

B



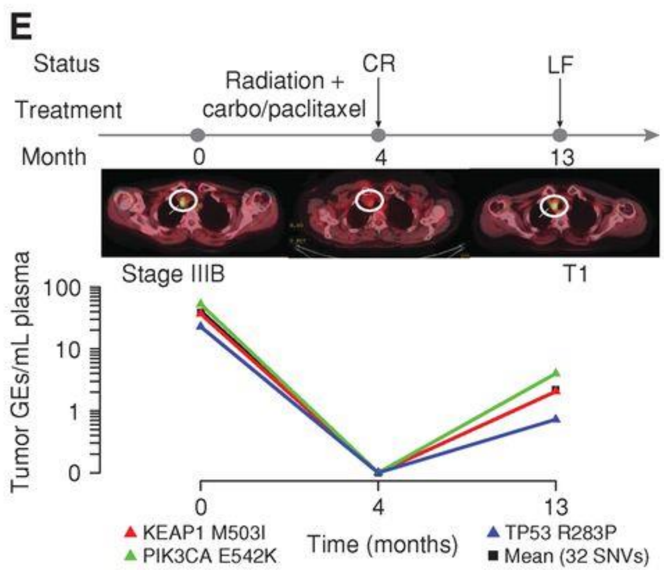
C



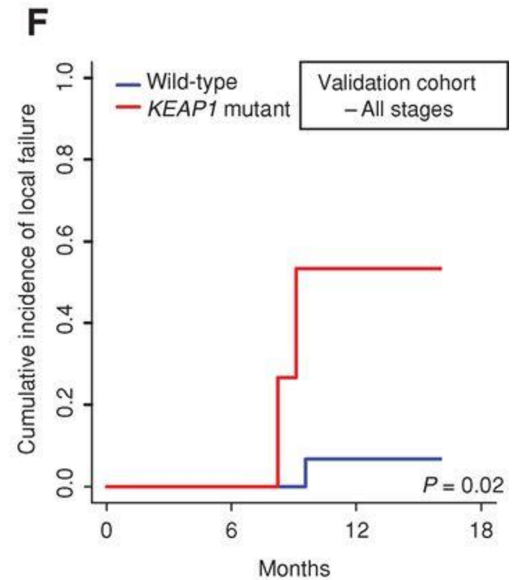
D

Patient	Age	Sex	Stage	*KEAP1* mutations: Tumor variant	*KEAP1* mutations: ctDNA variant (%AF)
T1	56	F	IIIB	M503I	M503I (3.38%)
T2	56	F	IIIB	R483C	R483C (0.44%)
T11	46	F	IIA	Wild-type	Wild-type
T13	81	F	IB	Wild-type	Wild-type
T14	78	M	IB	Wild-type	Wild-type
T23	51	F	IIIA	Wild-type	Wild-type
T35	48	F	IIIB	Wild-type	Wild-type

E



F



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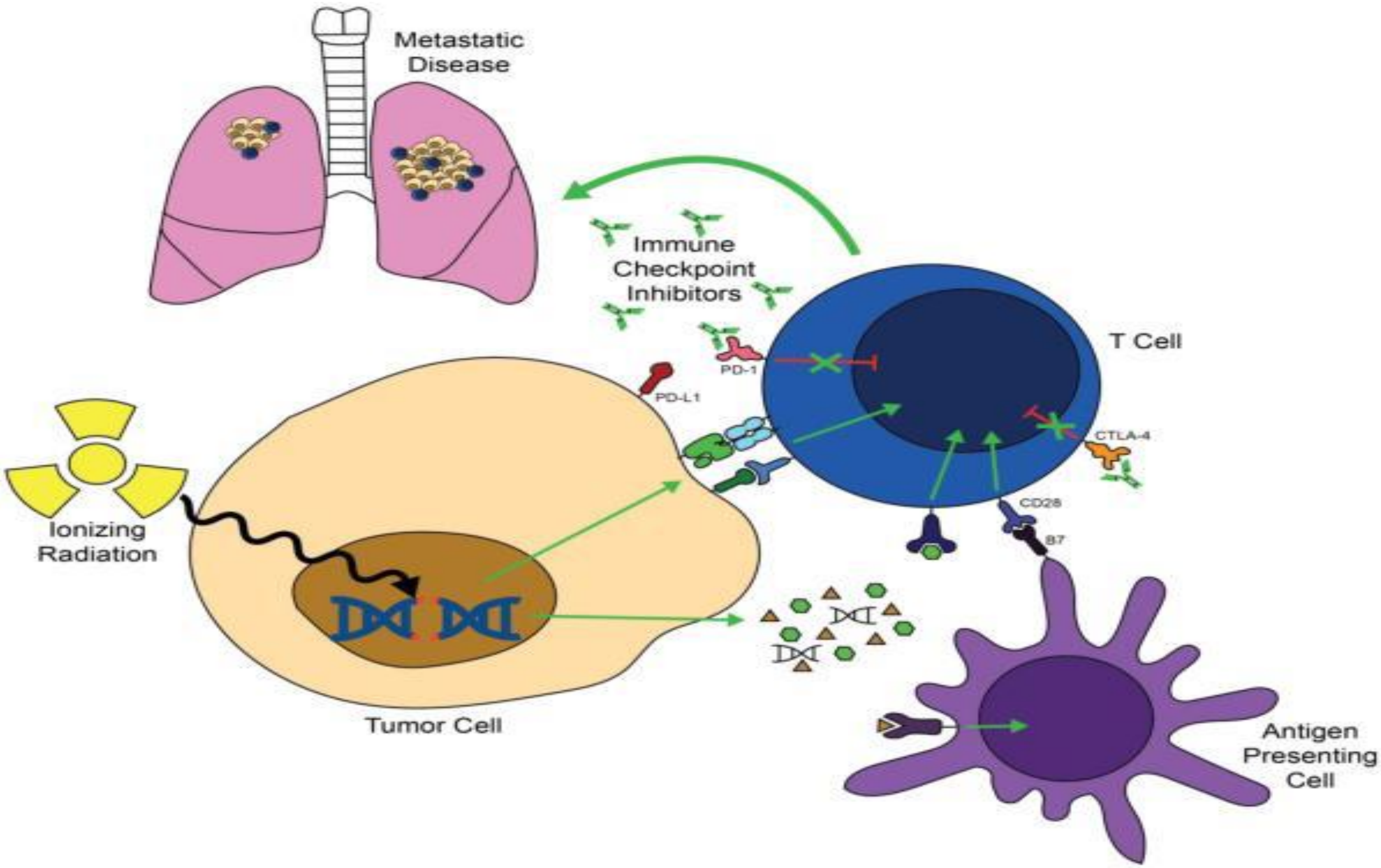
Youngtae Jeong et al. Cancer Discov 2017;7:86-101

Combining Ion Therapy with Immune Checkpoint Inhibitors



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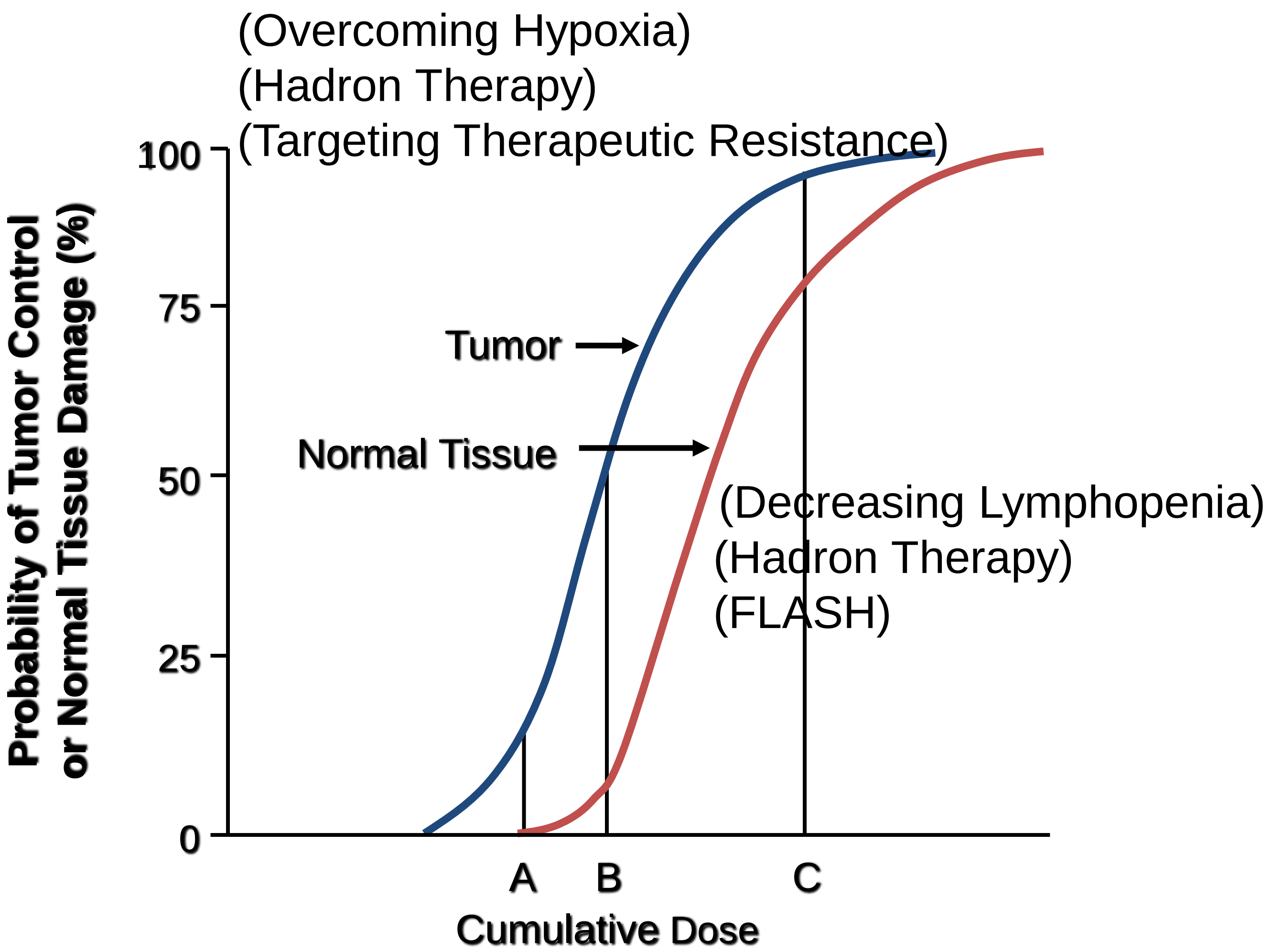

Hall and Giaccia, 2019

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Clinical Data for Carbon

Tumor Site	# Studies	# Pts	Results
Occular	2	114	Similar to proton
CNS	4	218	Similar to proton
Prostate	3	1384	Excellent results for high risk, less toxicity than proton/photon
HCC	1	64	High local control
Lung (NSCLC)	2	129	Maybe better than proton
HNC	1	236	High LC – ACC, melanoma
Chordomas	3	38	Similar to proton

Ongoing Trials for Carbon

Tumor	Phase	N	Design	Endpoint	Site
Prostate	II	90	Carbon vs. Proton	Toxicity	Heidelberg
Skullbase Chondrosarc	III	154	Carbon vs. Proton	LPFS	Heidelberg
Skullbase Chrodoma	III	319	Carbon vs. Proton	LPFS	Heidelberg
Salivary Gland CA	I	54	IMRT + Carbon boost	Safety	Heidelberg
HCC	I	33	Carbon	MTD	Heidelberg
GBM	II	150	CRT + Carbon vs. Proton boost	1 yr OS	Heidelberg, RTOG
HNC	II	50	TPF + RT + Cetux + Carbon Boost	LRC	Heidelberg

What LhARA Needs to Achieve for Clinical Acceptance

- LhARA has to deliver a defined number of ions within the therapeutic energy range with sufficiently stable and reproducible ion beam parameters.
- LhARA's beam transport and delivery system is required for cleaning the beam from undesired particles and for ensuring beam energy, beam intensity, beam direction and field size to deliver a prescribed dose to the patient
- Clinical application of LhARA in radiation therapy demands precise dosimetric control.
- Current dose delivery in clinical irradiation uses one of the two procedures, pencil beam scanning or a scattering technique. The new time structure of LhARA's beams with low pulse repetition frequency requires a new strategy for dose delivery, because the dose has to be delivered within at least the same (or possibly shorter) treatment time by a much lower number of pulses compared to conventional ion beams.
- the laser based acceleration leads to pulses with an outstandingly high pulse dose rate close to the source which may result in an altered radiobiological response. A different radiobiological effectiveness also needs more effort to implement in the treatment planning system

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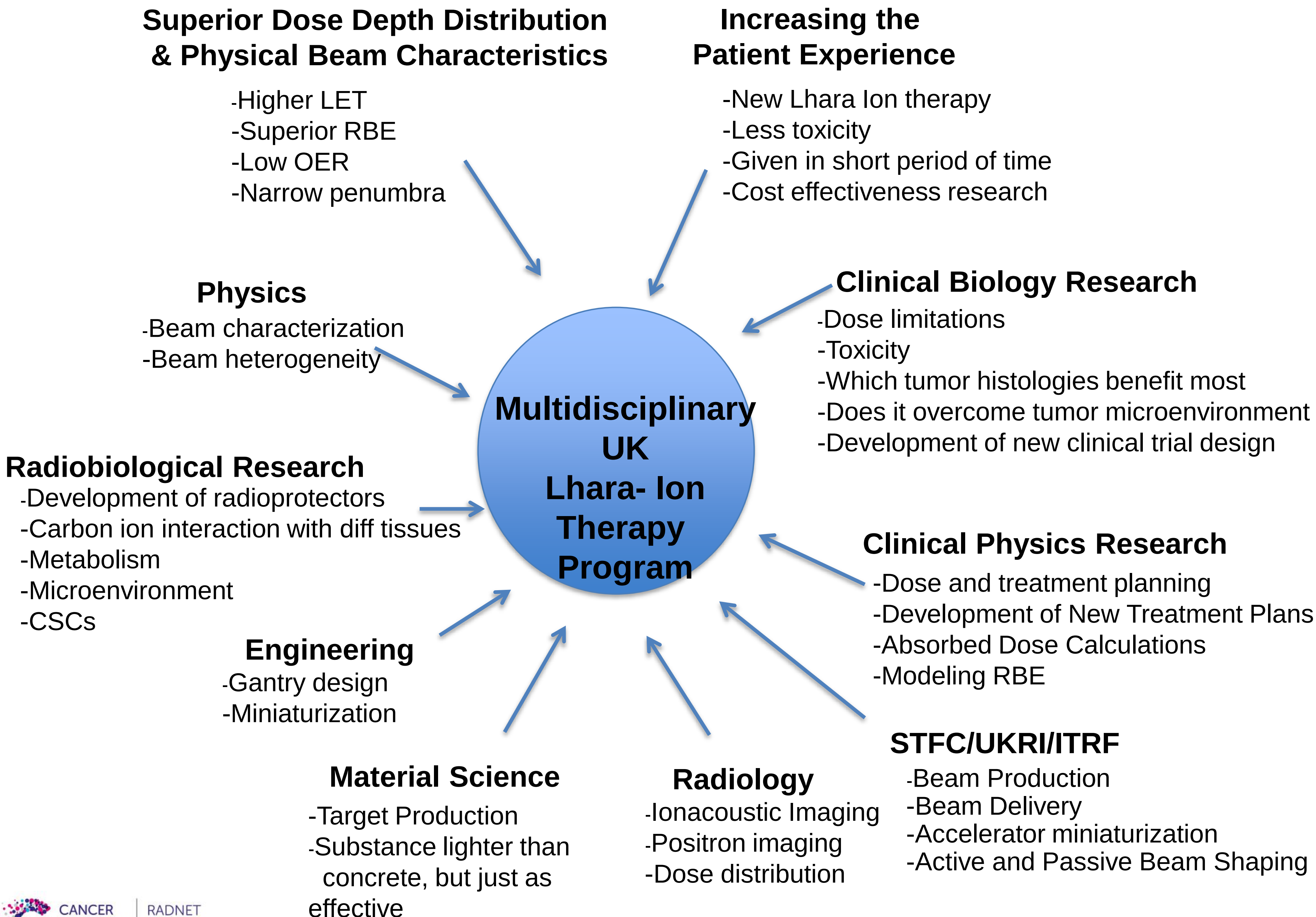

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Imperial College London

CCAP Centre for the Clinical Application of Particles

ICR The Institute of Cancer Research

Medical Research Council

UKRI Oxford Institute for Radiation Oncology

University of Oxford

JAI John Adams Institute for Accelerator Science

LhARA Laser-hybrid Accelerator for Radiobiological Applications

Imperial College Academic Health Science Centre

Cancer Research UK | Imperial Centre

NHS Imperial College Healthcare NHS Trust

Manchester 1824 The University of Manchester

University of Birmingham

University of Liverpool

NHS University Hospitals Birmingham NHS Foundation Trust

NHS The Clatterbridge Cancer Centre NHS Foundation Trust

NHS The Christie NHS Foundation Trust

institut Curie

Queen's University Belfast

Swansea University Prifysgol Abertawe

UCL Medical Physics & Biomedical Engineering

University Clinical Accelerator Industry Laboratory

Partners

Netherlands Cancer Institute Antoni van Leeuwenhoek

Hampton University Proton Therapy Institute Fighting Cancer, Saving Lives

University of Strathclyde Glasgow Department of Physics

Royal Holloway University of London

Lancaster University

UKRI Science and Technology Facilities Council

ASTeC

Daresbury Laboratory

Particle Physics Department

ISIS Neutron and Muon Source

CLF central laser facility

University of Birmingham | Cyclotron Facility | Positron Imaging Centre

INFN Catania

The Cockcroft Institute of Accelerator Science and Technology

CERN

Corerain 鲲云科技

LEO Cancer Care

Maxeler Technologies Maximum Performance Computing

The Rosalind Franklin Institute

NPL National Physical Laboratory