The radiobiology of hadron therapy

Prof. Marco Durante, Ph.D.
Director, BIOPHYSICS DEPARTMENT

GSI Helmholtzzentrum für Schwerionenforschung

TERA & me

- When TERA started I was in Berkely for my Ph.D.
- Later I moved to NASA and NIRS for postdoc, and was back in Italy in 1999
- At that time I became involved in the INFN ATER project, a TERA

Life Sciences in Space Research 30 (2021) 82–95

Contents lists available at ScienceDirect

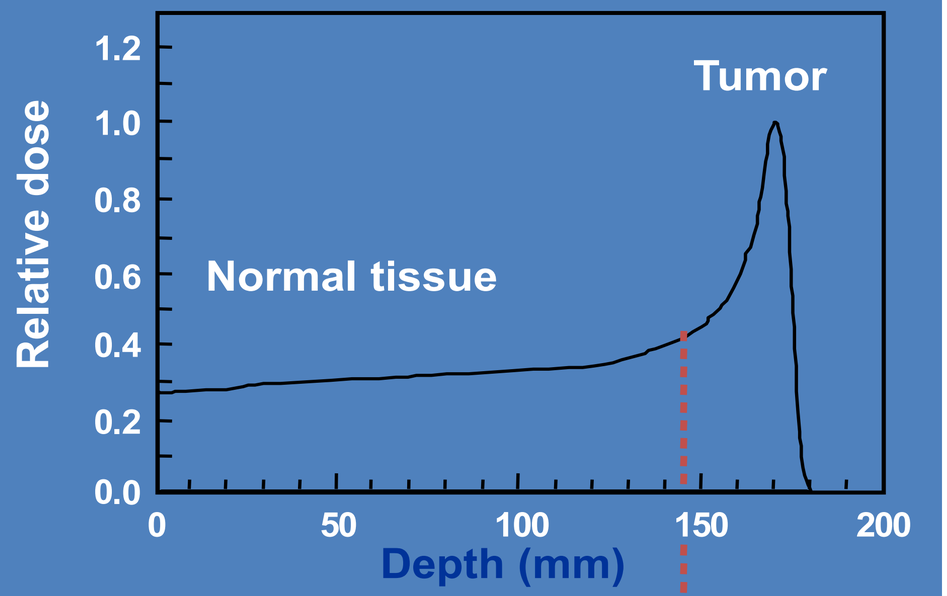
Life Sciences in Space Research

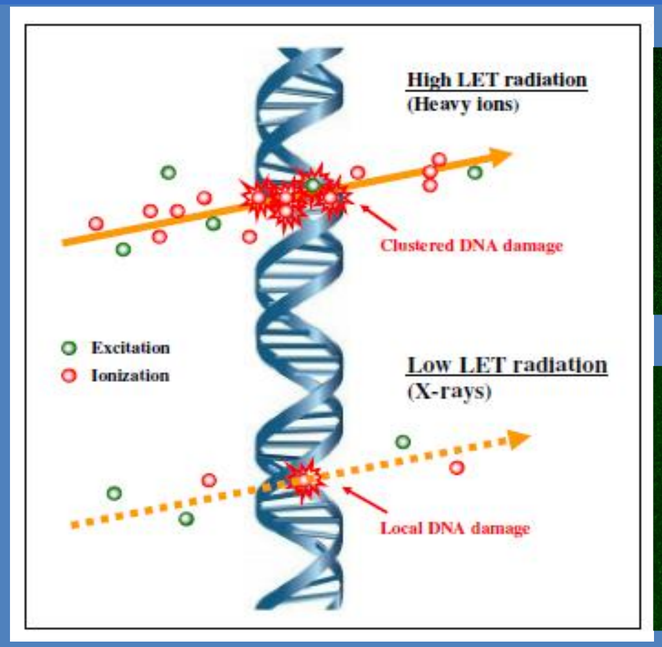
journal homepage: www.elsevier.com/locate/lssr

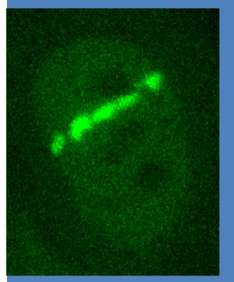
What can space radiation protection learn from radiation oncology?

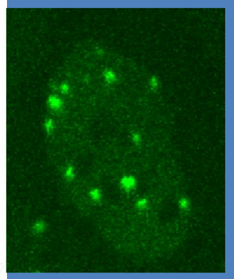
Walter Tinganelli [a], Francesca Luoni [a,b], Marco Durante [a,b,*]

[a] GSI Helmholtzzentrum für Schwerionenforschung, Biophysics Department, Darmstadt, Germany
[b] Technische Universität Darmstadt, Institut für Physik Kondensierter Materie, Darmstadt, Germany









Energy	high	low
LET	low	high
Dose	low	high
RBE	≈ 1	> 1
OER	≈ 3	< 3
Cell-cycle dependence	high	low
Fractionation dependence	high	low
Angiogenesis	Increased	Decreased
Immune effects	Weak	Strong

Potential advantages

High tumor dose, normal tissue sparing

Effective for radioresistant tumors

Effective against hypoxic tumors

Radioresistant (S) phase cells are sensitized

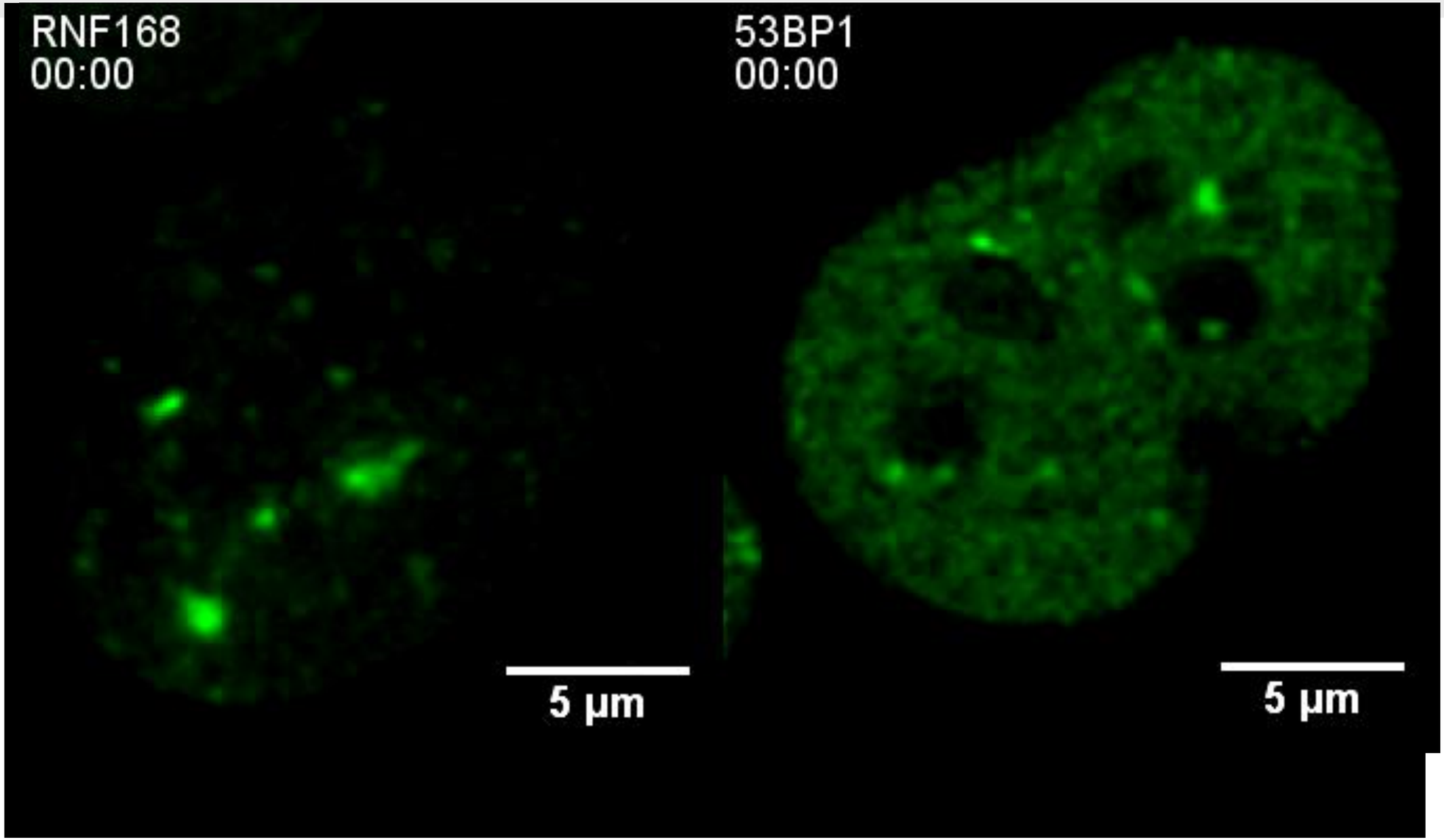
Fractionation spares normal tissue more than tumour

Reduced angiogenesis and metastatization

Systemic effects in combination with immunotherapy

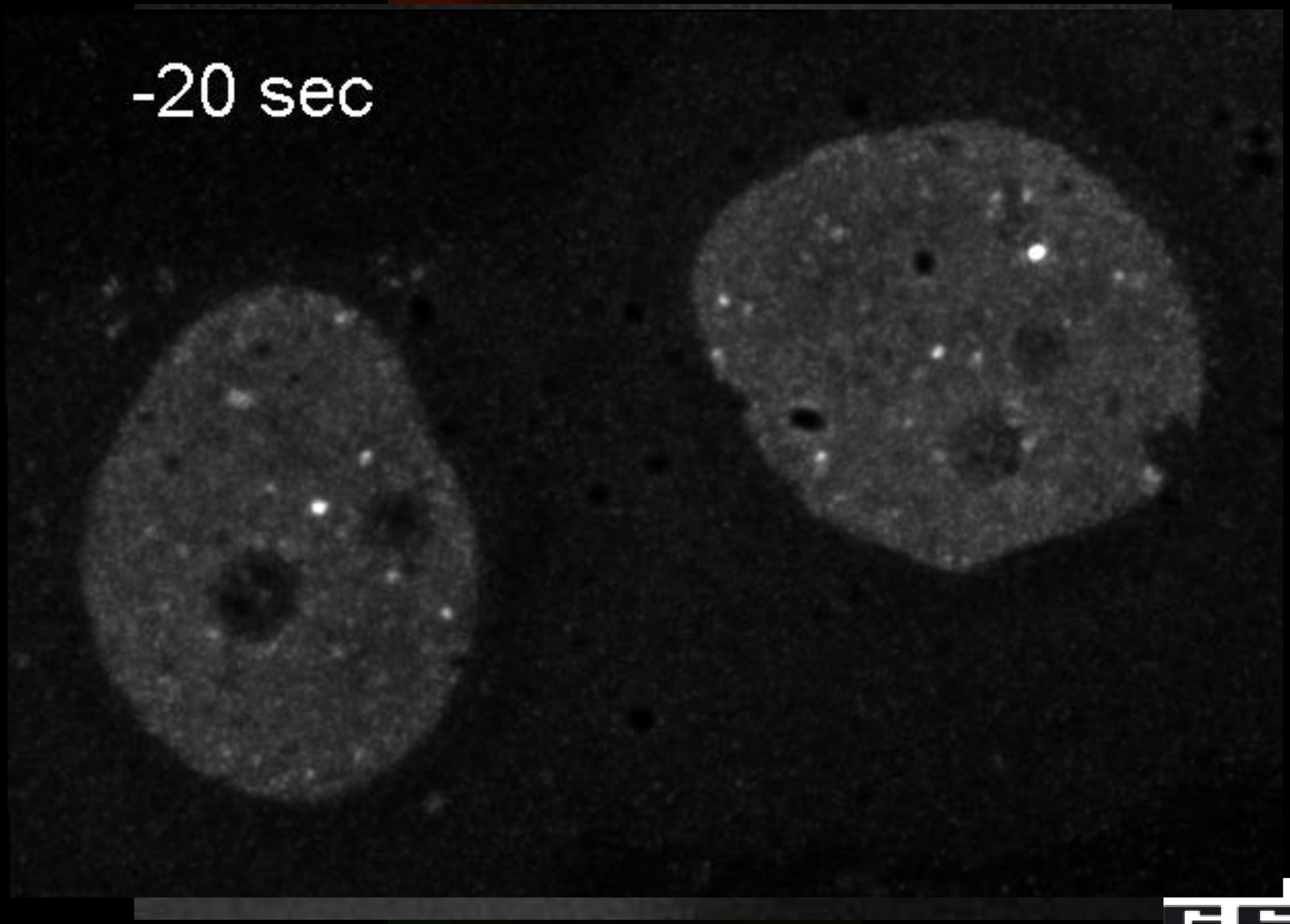
Durante & Loeffler, *Nat. Rev. Clin. Oncol*. 2010

DNA damage induced by X-rays



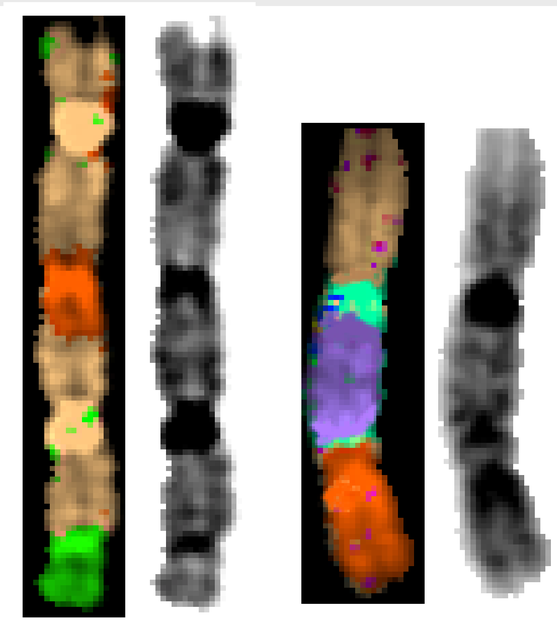
Prakash *et al., Nat. Comm. 2021*

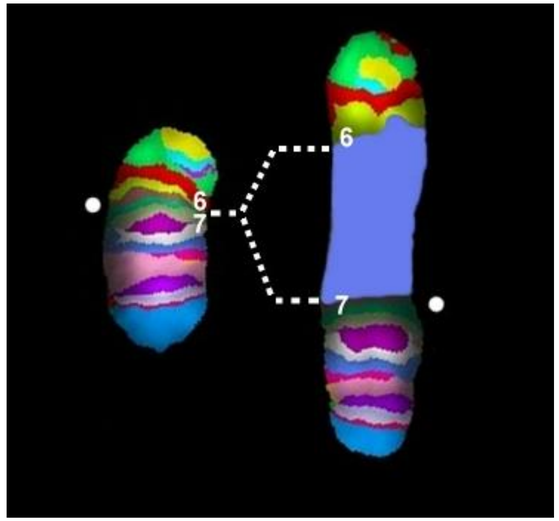
DNA damage by heavy ions

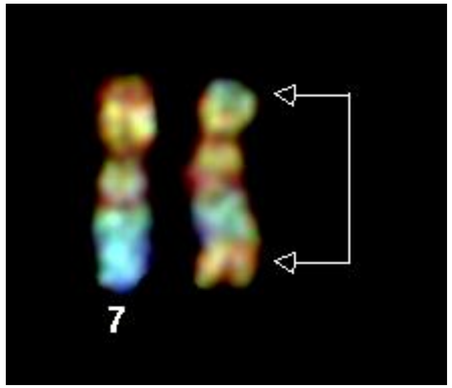


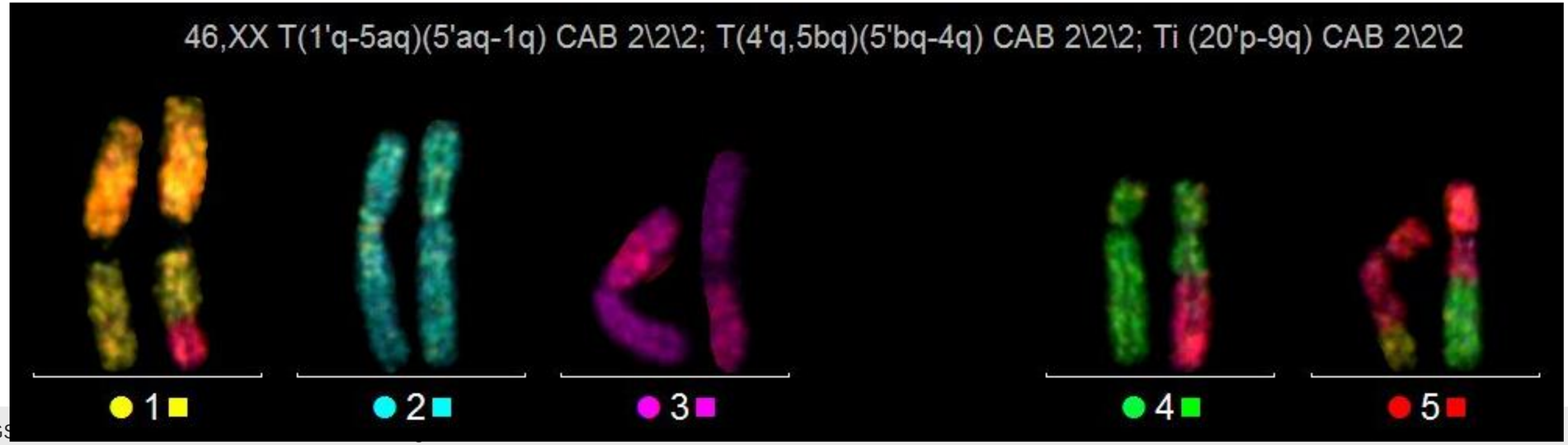
Jakob *et al., Proc. Natl. Acad. Sci. USA* 2009*; Nucl. Acids Res*. 2011

From DNA to chromosomes



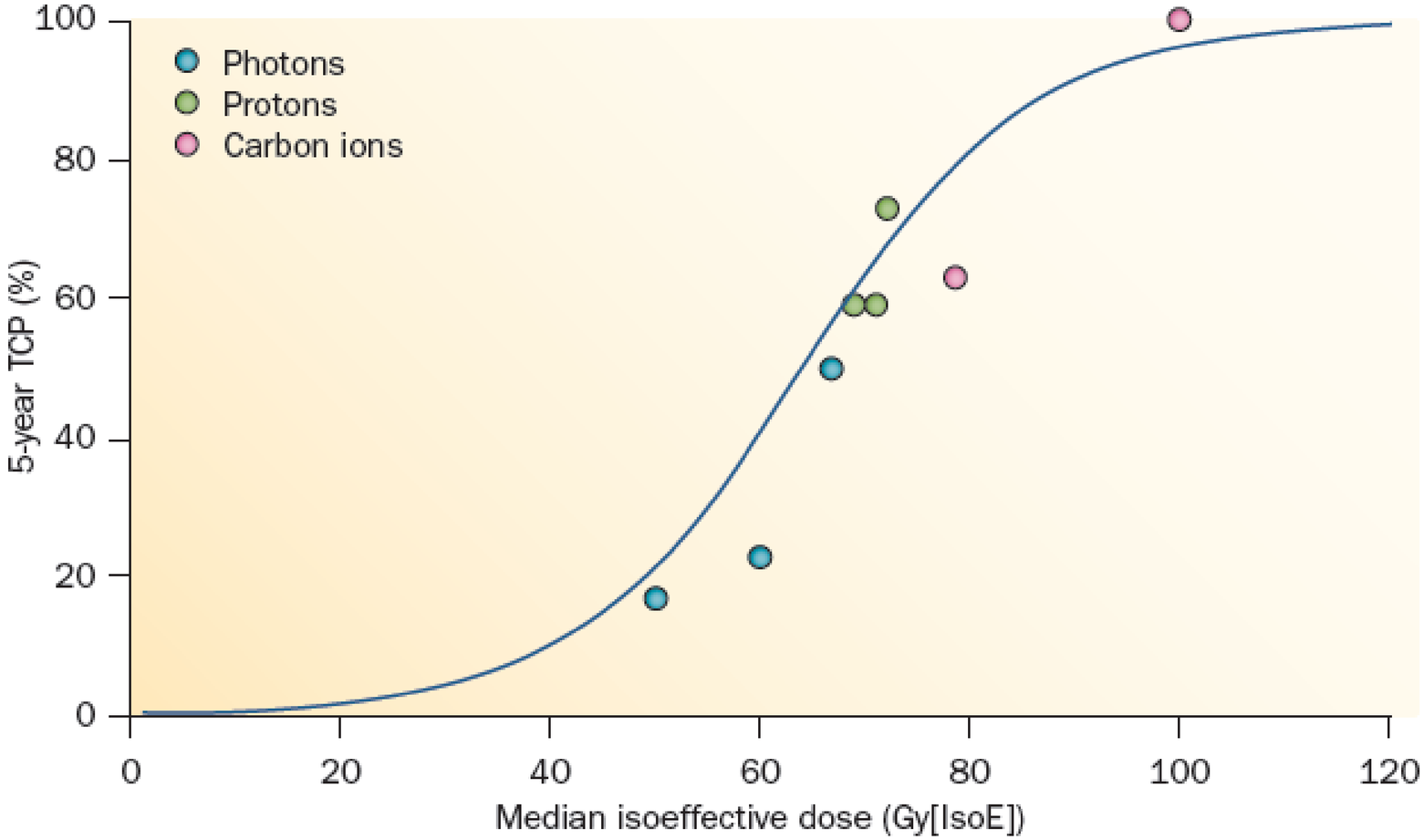






Durante *et al., Radiat. Res.* 2002

Skull-base chordoma



Loeffler & Durante, *Nat. Rev. Clin. Oncol*. 2013

Is particle therapy too expensive?

MEDICAL TECHNOLOGY

Is spending on proton beam therapy for cancer going too far, too fast?

Both the US and UK are pouring money into proton accelerators, which have been described as the world's "most costly medical devices." **Keith Epstein** asks if the investment is premature

You might think that this week's study of 12 000 patient records showing that men with prostate cancer treated with expensive proton beam therapy had more complications than patients given conventional radiotherapy would dent some people's faith in the newer treatment.[1] No clear evidence of better effectiveness exists, and it now appears that the treatment may have a downside.

But the spread of proton beam therapy for cancer has such momentum it now seems unstoppable. Millions of dollars have been invested in

former adviser to President Obama. "If the United States is ever going to control its healthcare costs, we have to demand better evidence of effectiveness and stop handing out taxpayer dollars with no questions asked."

The cost of proton therapy for prostate cancer is typically about twice as much as conventional radiation, three times as much as surgery, and four or five times as much as brachytherapy.

Who benefits?

So what is the evidence for and against the treat-

THE WALL STREET JOURNAL.

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HEALTH

Costly Cancer Therapy Dinged

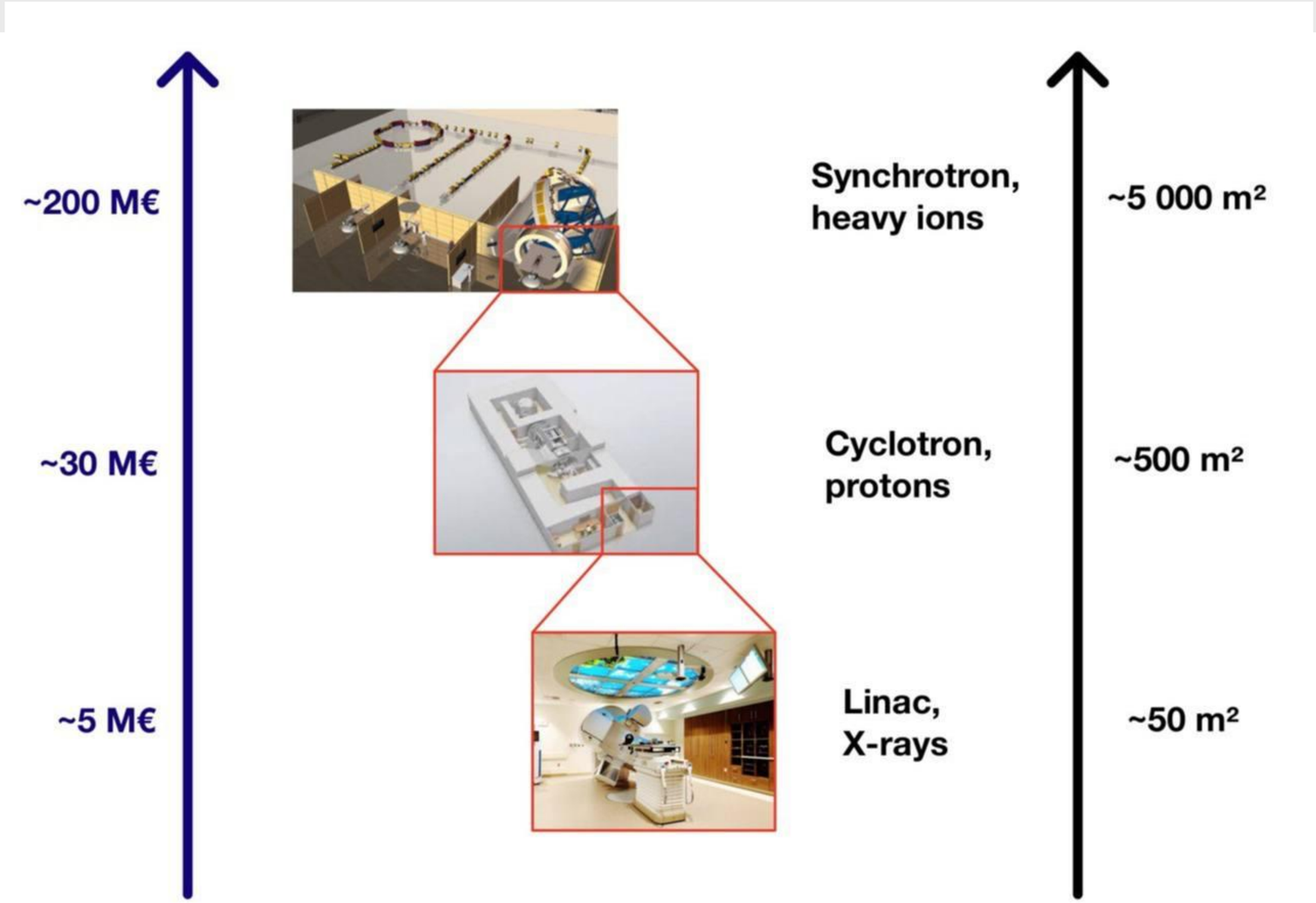
Proton-Beam Treatment for Prostate Tumors No Better Than Radiation, Study Says

110 centers in 2022

79 under construction or in planning stage

Particle Therapy Co-Operative Group

The cost of particle therapy



Durante, Debus & Loeffler, *Nat. Rev. Phys*. 2021

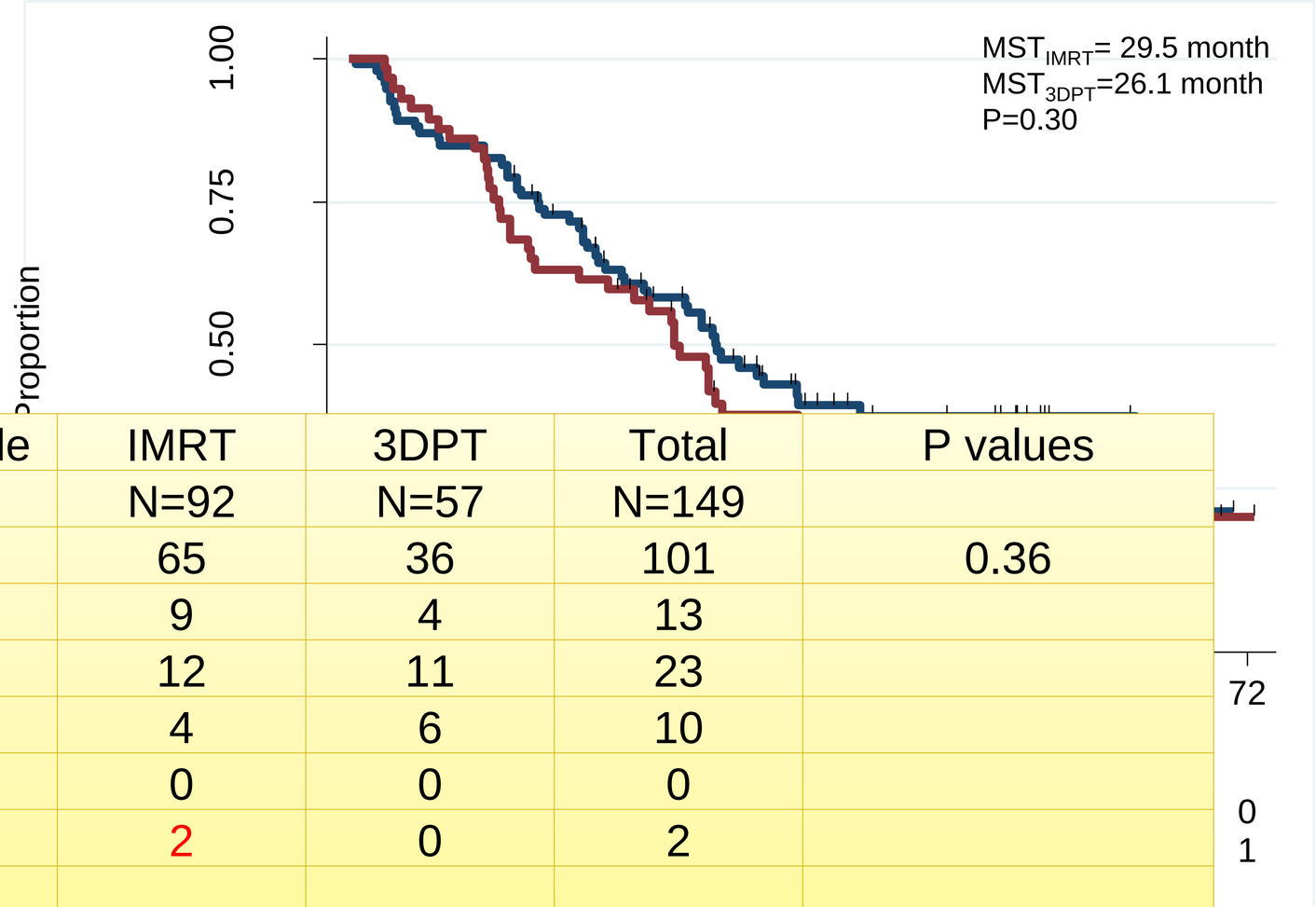
Table 1 | Ongoing randomized clinical trials comparing different radiation modalities for the same disease

Study	Institution	Phase	Condition	Radiation arm 1	Radiation arm 2
R03CA188162: IMPT vs IMRT	MDACC	III	Oropharyngeal cancer (head and neck cancer)	Protons*	X-rays*
PARTIQoL (NCT01617161): proton therapy vs IMRT	MGH	III	Low-risk or intermediate-risk prostate cancer	Protons	X-rays
NCT01512589: proton-beam therapy vs IMRT	MDACC	III	Oesophageal cancer	Protons*	X-rays*
RADCOMP (NCT02603341): pragmatic randomized trial of proton vs photon therapy	PTCORI	III	Post-mastectomy stage II or III breast cancer	Protons	X-rays
NRG BN001: dose-escalated IMRT or IMPT vs conventional photon radiation	NRG Oncology	II	Newly diagnosed glioblastoma	Protons*	X-rays*
NRG 1542: proton radiation vs conventional photon radiation‡	NRG Oncology	III	Hepatocellular carcinoma	Protons	X-rays
NCT01182753: proton radiation vs carbon-ion radiation therapy	Heidelberg University, Germany	III	Low-grade and intermediate-grade chondrosarcoma of the skull base	Protons	Carbon ions
NCT01182779: proton radiation vs carbon-ion radiation therapy	Heidelberg University, Germany	III	Chordoma of the skull base	Protons	Carbon ions
CLEOPATRA (NCT01165671): proton radiation vs carbon-ion radiotherapy	Heidelberg University, Germany	II	Primary gioblastoma	Protons*§	Carbon ions*§
IPI (NCT01641185): proton radiation vs carbon-ion radiotherapy	Heidelberg University, Germany	II	Prostate cancer	Protons	Carbon ions
ISAC (NCT01811394): proton radiation vs carbon-ion radiation therapy	Heidelberg University, Germany	II	Sacrococcygeal chordoma	Protons	Carbon ions
ETOILE (NCT02838602): carbon-ion radiotherapy vs IMRT	Lyon University Hospital, France	III	Radioresistant adenoid cystic carcinoma and sarcomas	Carbon ions	IMRT
BAA-N01CM51007-51: prospective trial of carbon-ion therapy vs IMRT	NCI	I/III	Locally advanced pancreatic cancer	Carbon ions*	X-rays*
CIPHER: prospective multicentre randomized trial of carbon-ion radiotherapy vs conventional radiotherapy	UTSW	III	Locally advanced pancreatic cancer	Carbon ions*	X-rays*

Durante, Orecchia & Loeffler, *Nat. Rev. Clin. Oncol.* 2017

RCT IMRT vs. PSPT

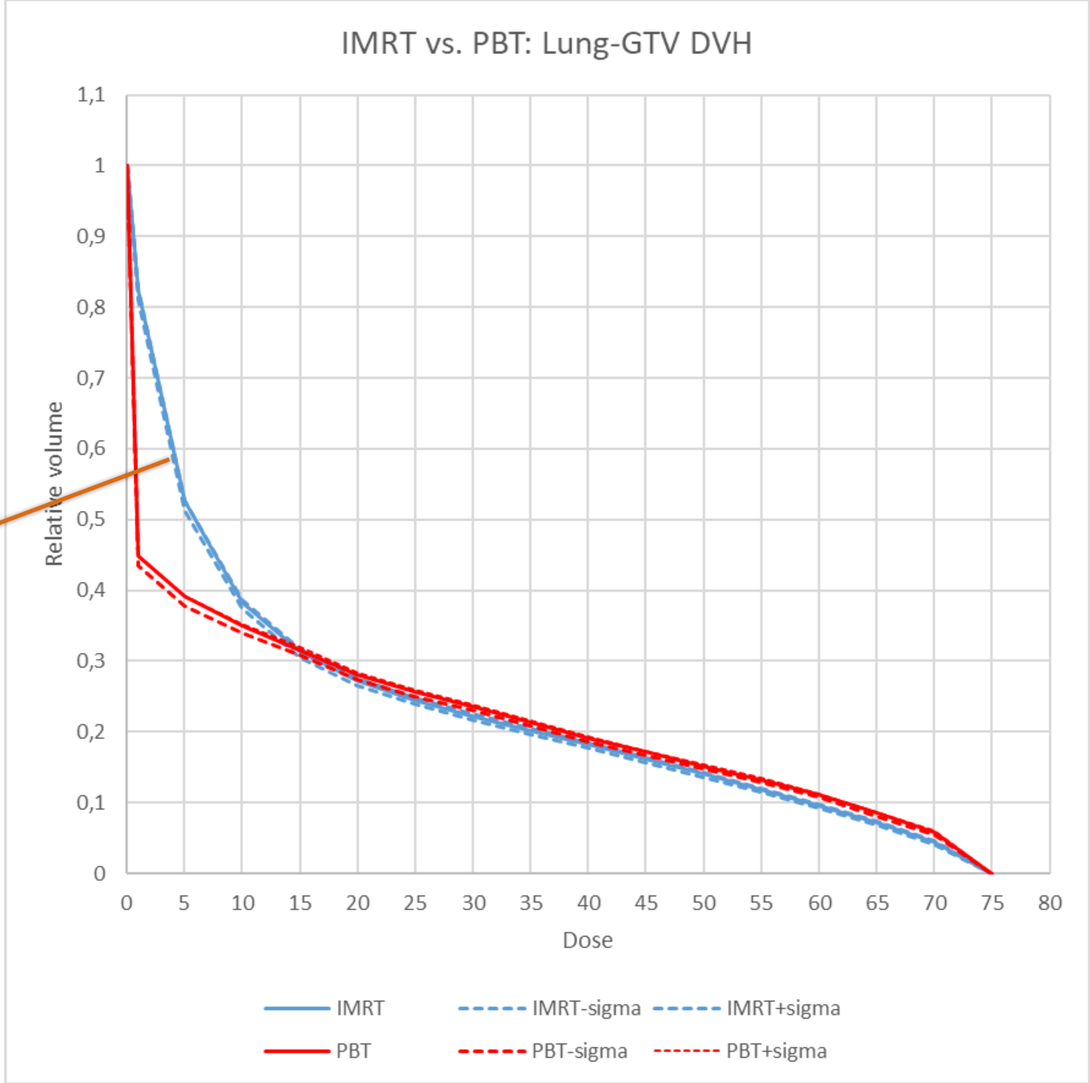
Liao *et al., J. Clin. Oncol.* 2018

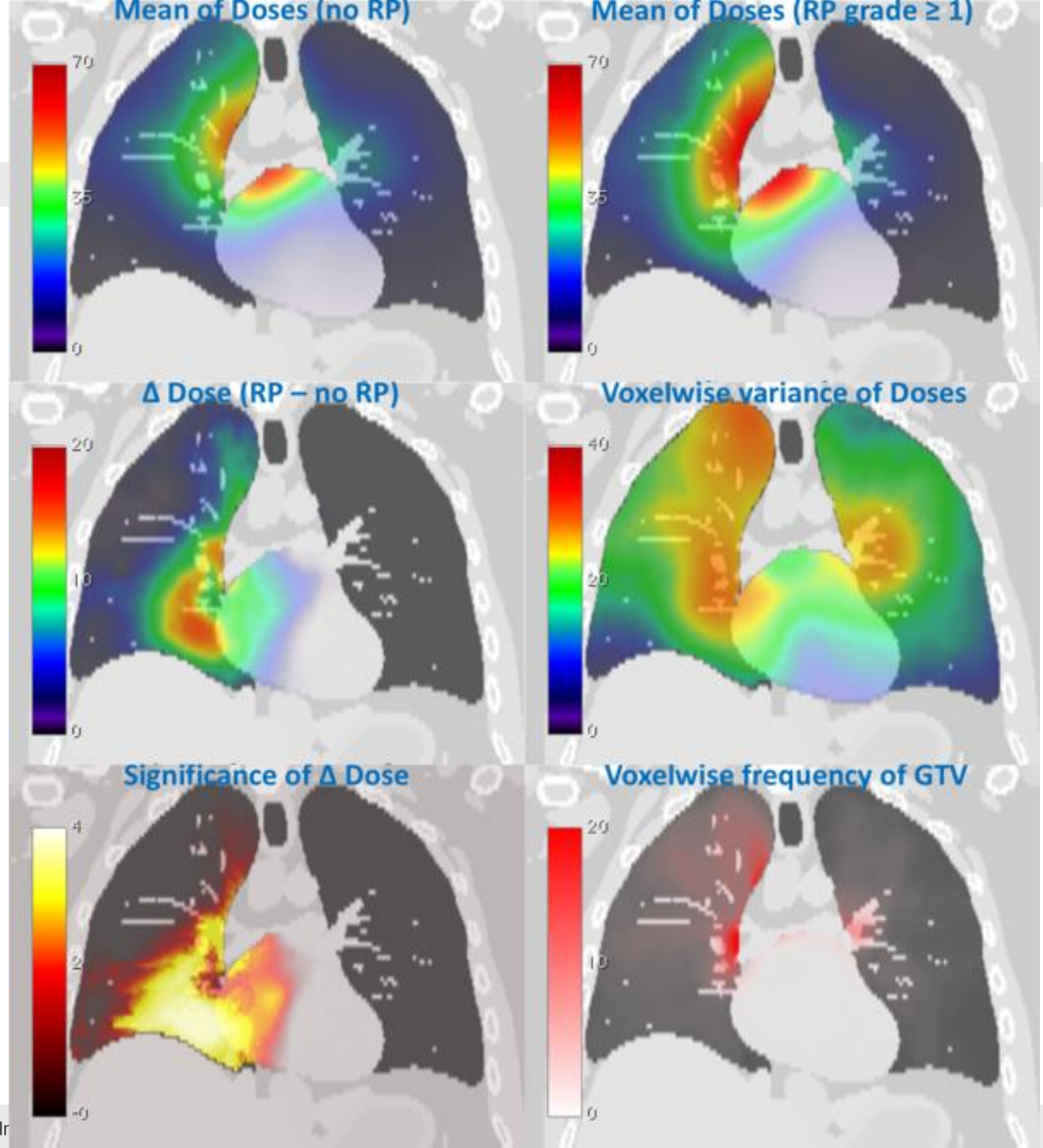


RP Grade	IMRT	3DPT	Total	P values
	N=92	N=57	N=149	
0	65	36	101	0.36
1	9	4	13	
2	12	11	23	
3	4	6	10	
4	0	0	0	
5	2	0	2	
Gr 0-2	86	51	137	0.54
Gr 3-5	6 (6.5%)	6 (10.5%)	12 (8.1%)	

DVH technique analysis

How can this low-dose difference fit the inverse RP incidence between the 2 techniques?





VB analysis of dose differences (RP grade ≥ 1)

Conclusion 1:

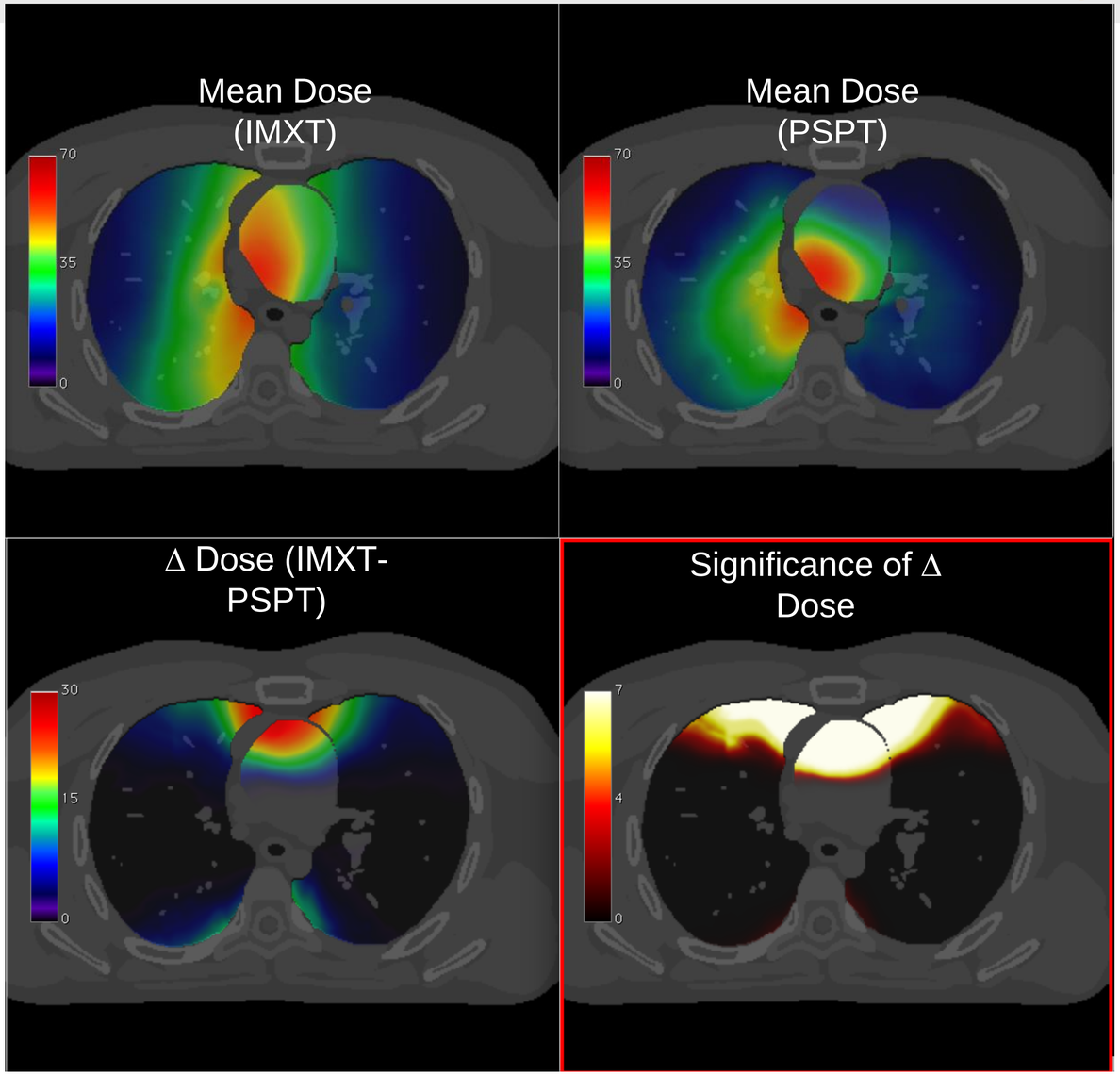
the lower parts of the lungs and the heart play a prominent role in the development of RP

VB analysis: IMXT vs PSPT

Conclusion 2

The dose difference between X-rays and protons was mostly localized in the upper region of the lungs,which is not correlated to RP

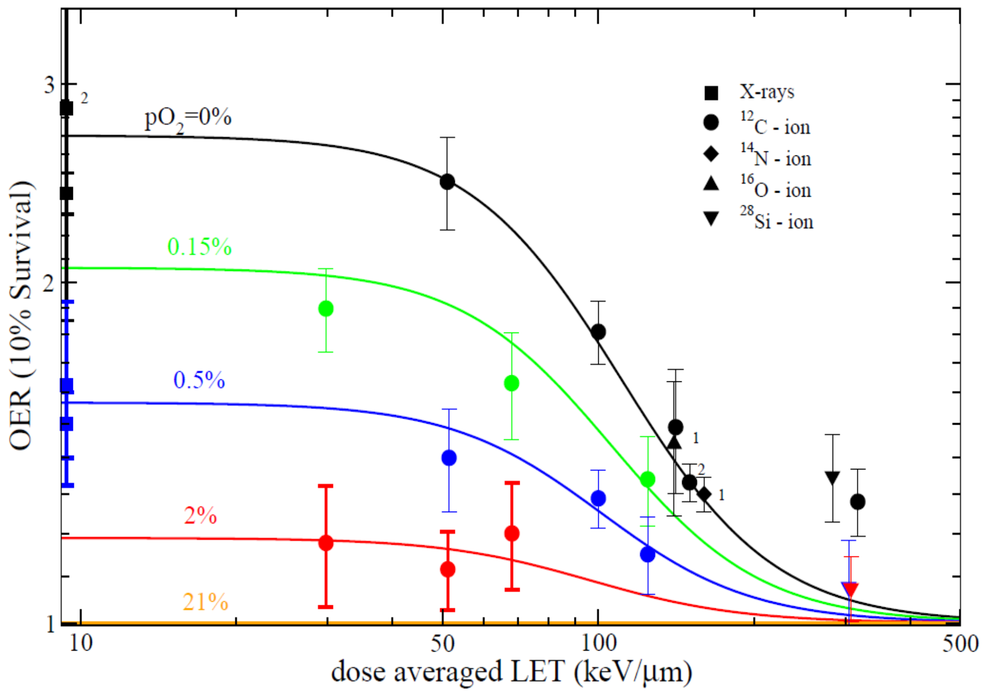
Palma *et al., Int. J. Radiat. Biol. Oncol. Phys.* 2019

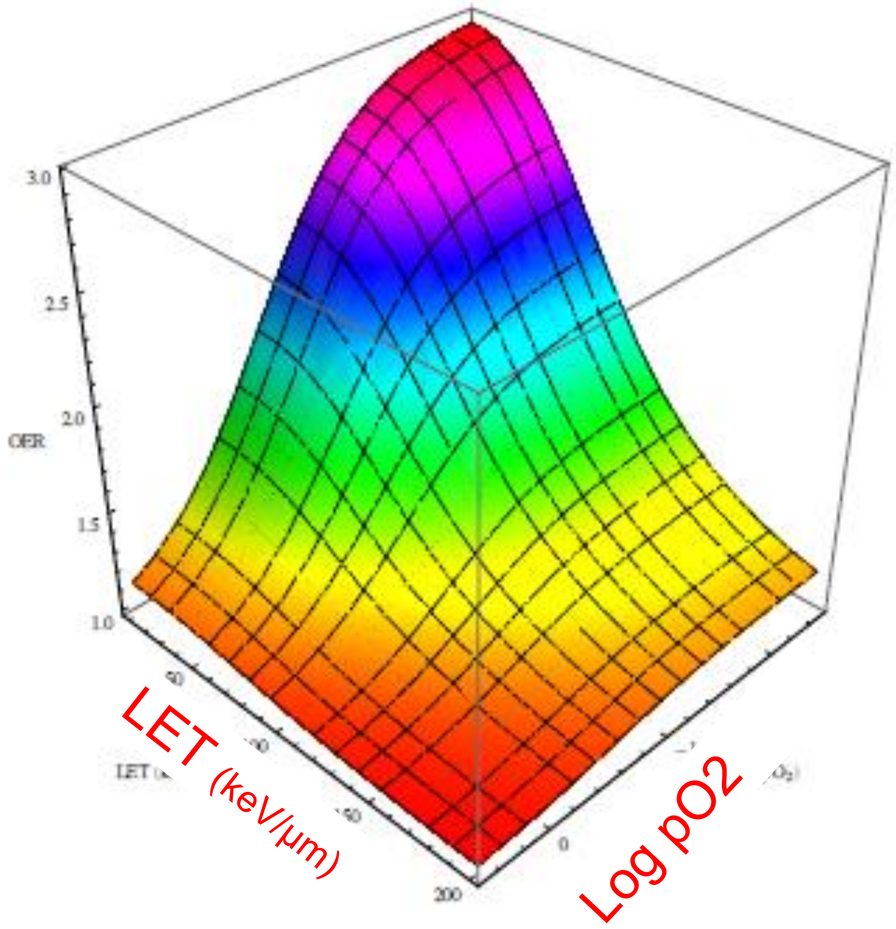


Need for more translational research

Heavier ions can be effective against hypoxic tumors

$$OER(\overline{L},p) = \frac{b(aM+\overline{L}^3)/(a+\overline{L}^3)+p}{b+p}$$

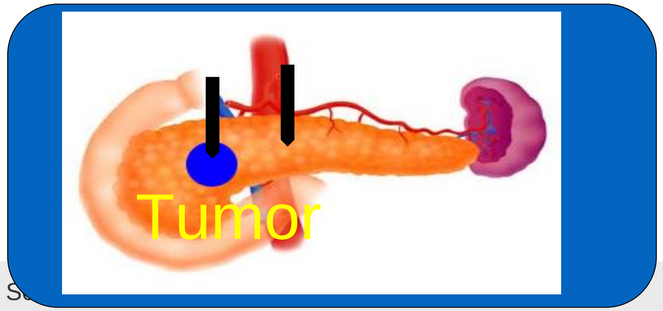




Tinganelli *et al., Sci. Rep*. 2015

pO_2 measurements in pancreatic tumors and normal pancreatic tissue

	Tumor		Normal Tissue	
Patient	Med pO2	%<2.5mmHg	Med pO2	%<2.5mmHg
1	3.1	35	47.3	9
2	0	94	46.6	0
3	2.7	43	24.3	0
4	3.4	24	67.4	0
5	0.9	95	51.6	0
6	2	54	69.8	7
7	5.3	68	82.7	0

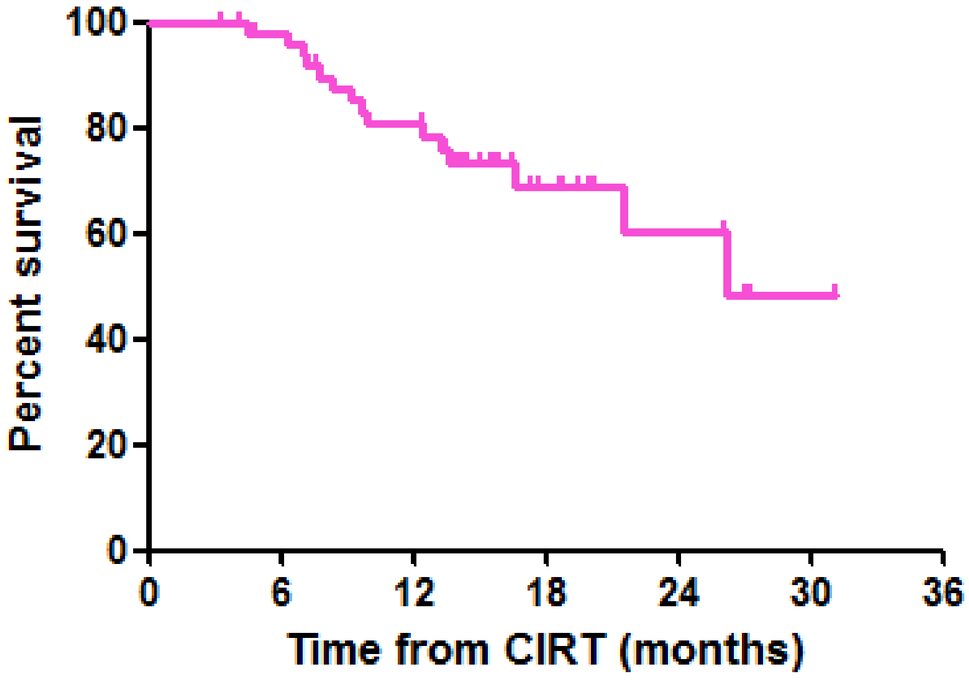


(Koong AC, IJROBP 48, 2000)

Overall survival

Median follow-up time: 13.6 (2.8–37.9) months

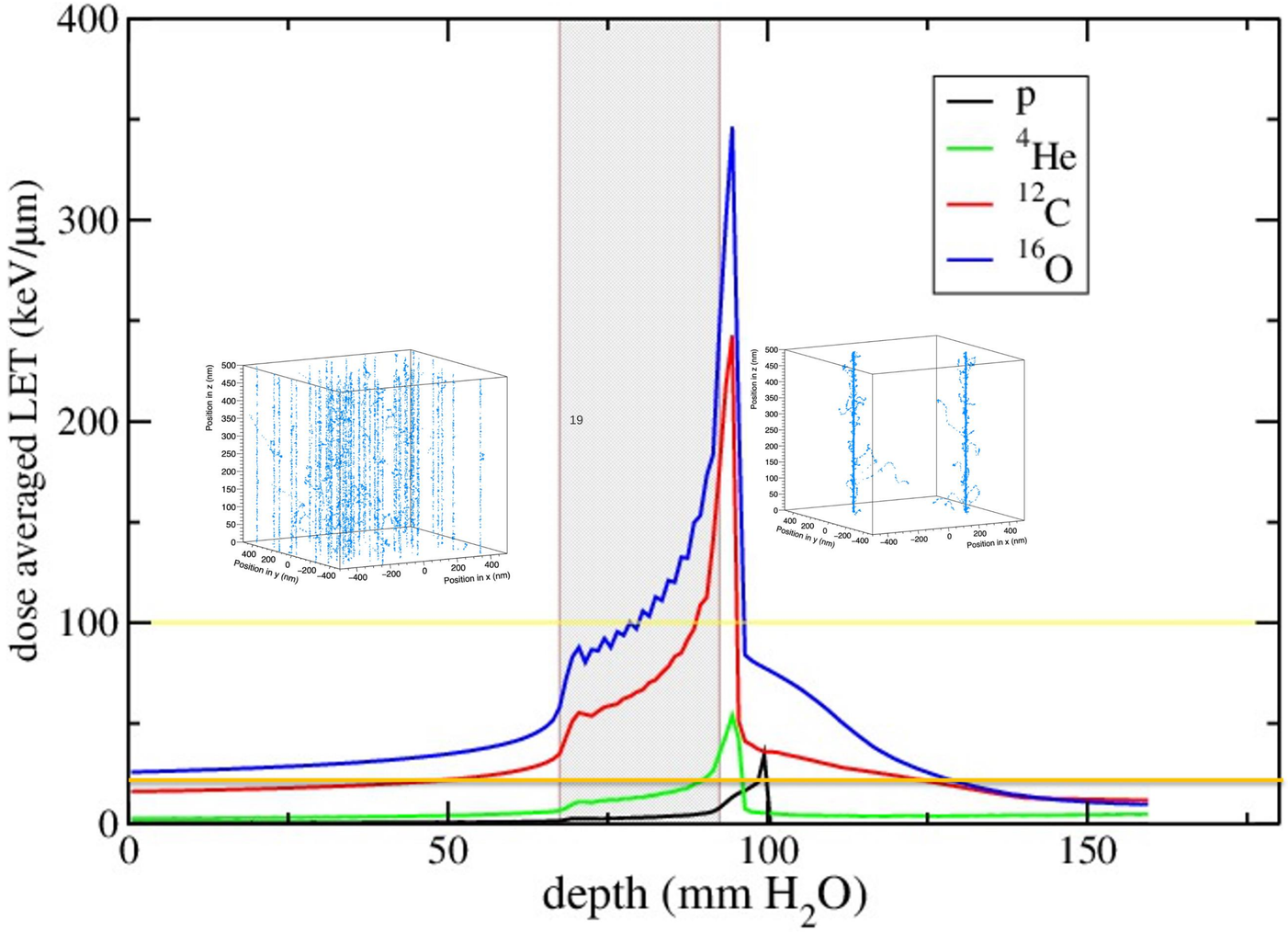
J-CROS 1403-CROS
（Japan Carbon-ion Radiation Oncology Study Group)
55.2 Gy(RBE)/12fr (n=52)



	1y	2y	MST
55GyE	81%	60%	26.2M

Kawashiro et *al.*, *Int. J. Radiat. Oncol. Biol. Phys*. 2018

Is LET high enough?



Durante, Debus & Loeffler, *Nat. Rev. Phys*. 2021

Local failure maps with dose-averaged LET in CIRT

Contents lists available at ScienceDirect

Clinical and Translational Radiation Oncology

journal homepage: www.elsevier.com/locate/ctro

Original Research Article

Influence of dose-averaged linear energy transfer on tumour control after carbon-ion radiation therapy for pancreatic cancer ☆

Yasuhito Hagiwara [a,b], Tapesh Bhattacharyya [a], Naruhiro Matsufuji [c], Yuka Isozaki [a], Hirotoshi Takiyama [a], Kenji Nemoto [b], Hiroshi Tsuji [a], Shigeru Yamada [a,d,*]

Radiotherapy and Oncology 163 (2021) 209–214

Contents lists available at ScienceDirect

Radiotherapy and Oncology

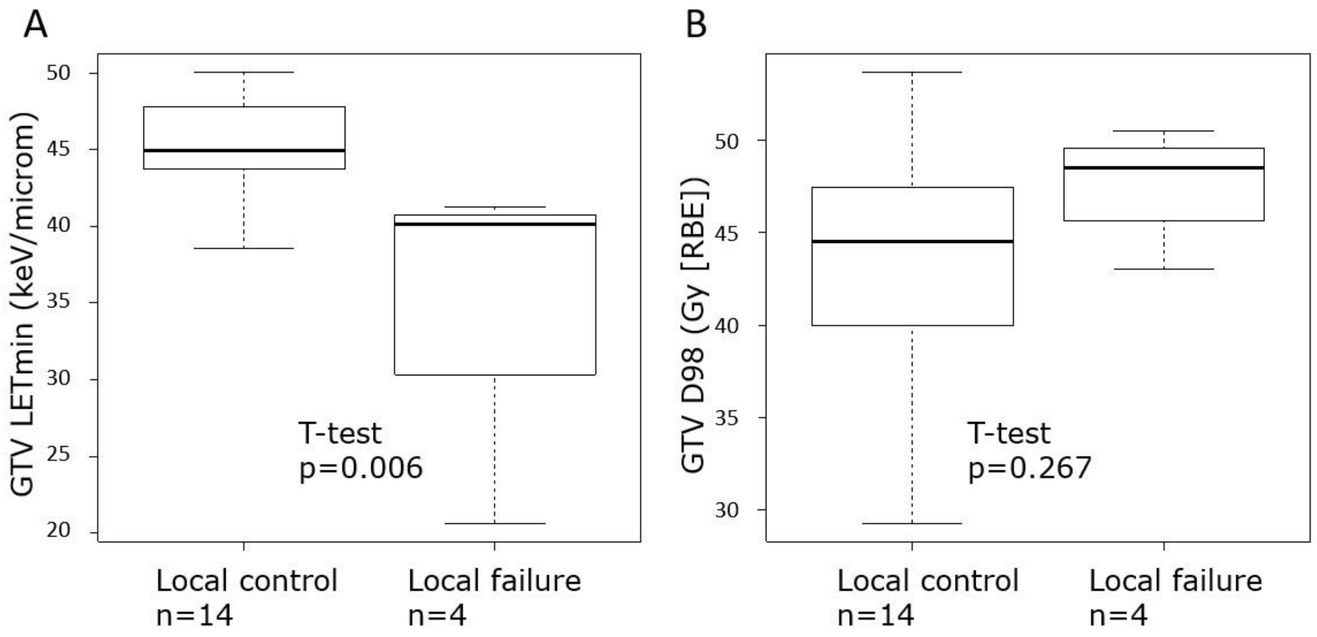
journal homepage: www.thegreenjournal.com

Original Article

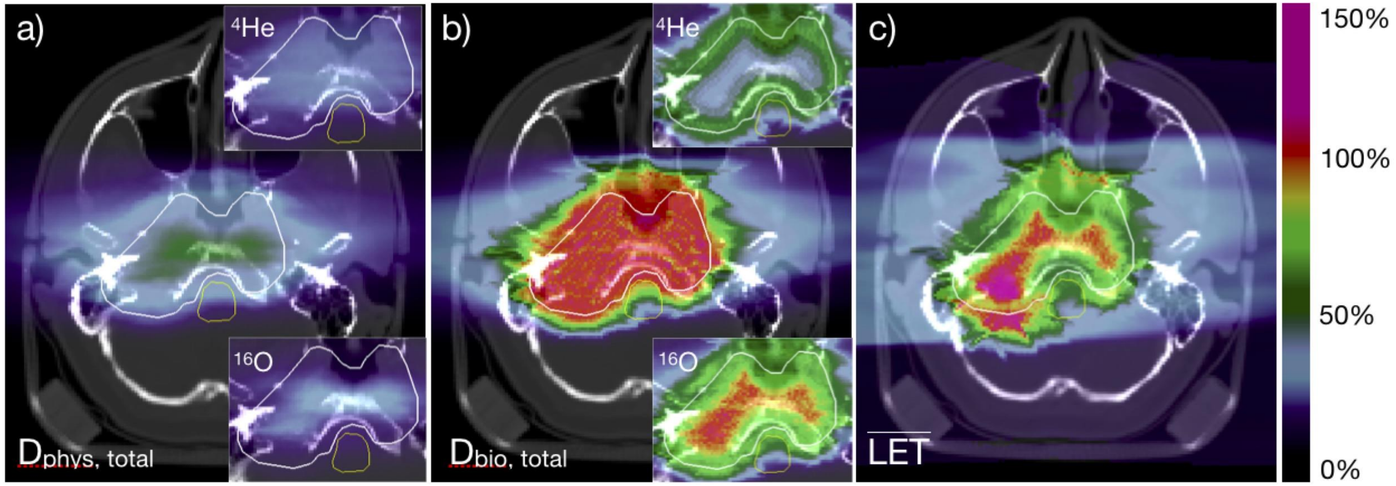
How LEM-based RBE and dose-averaged LET affected clinical outcomes of sacral chordoma patients treated with carbon ion radiotherapy

Silvia Molinelli [a,*], Giuseppe Magro [a], Andrea Mairani [b], Albina Allajbej [c], Alfredo Mirandola [a], Agnieszka Chalaszczyk [a], Sara Imparato [a], Mario Ciocca [a], Maria Rosaria Fiore [a,1], Ester Orlandi [a,1]

[a] Fondazione CNAO, Pavia, Italy; [b] Heidelberg Ion Beam Therapy Center (HIT), Germany; [c] Istituto Nazionale dei Tumori, Milano, Italy



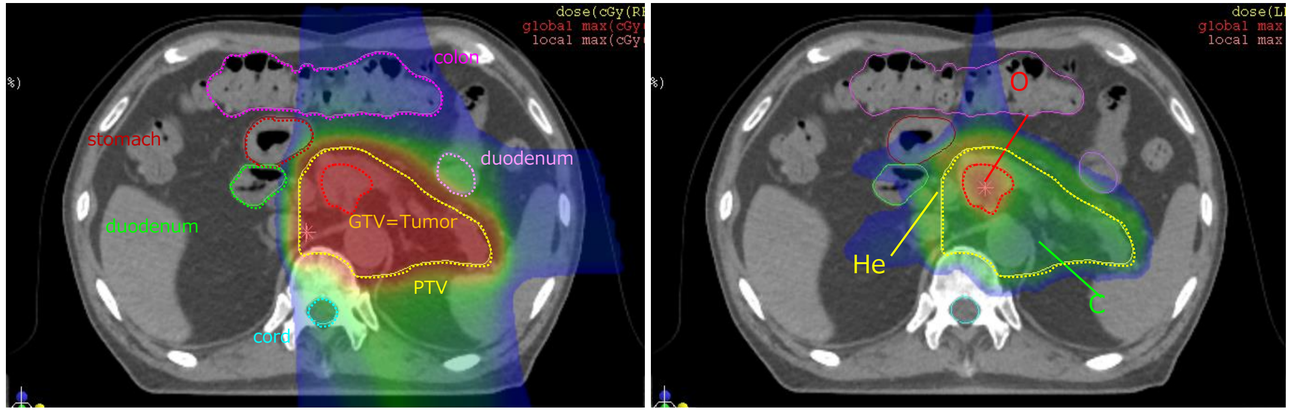
LET-painting with multi-ion treatment



Sokol *et al.*, *Phys. Med. Biol*. 2019

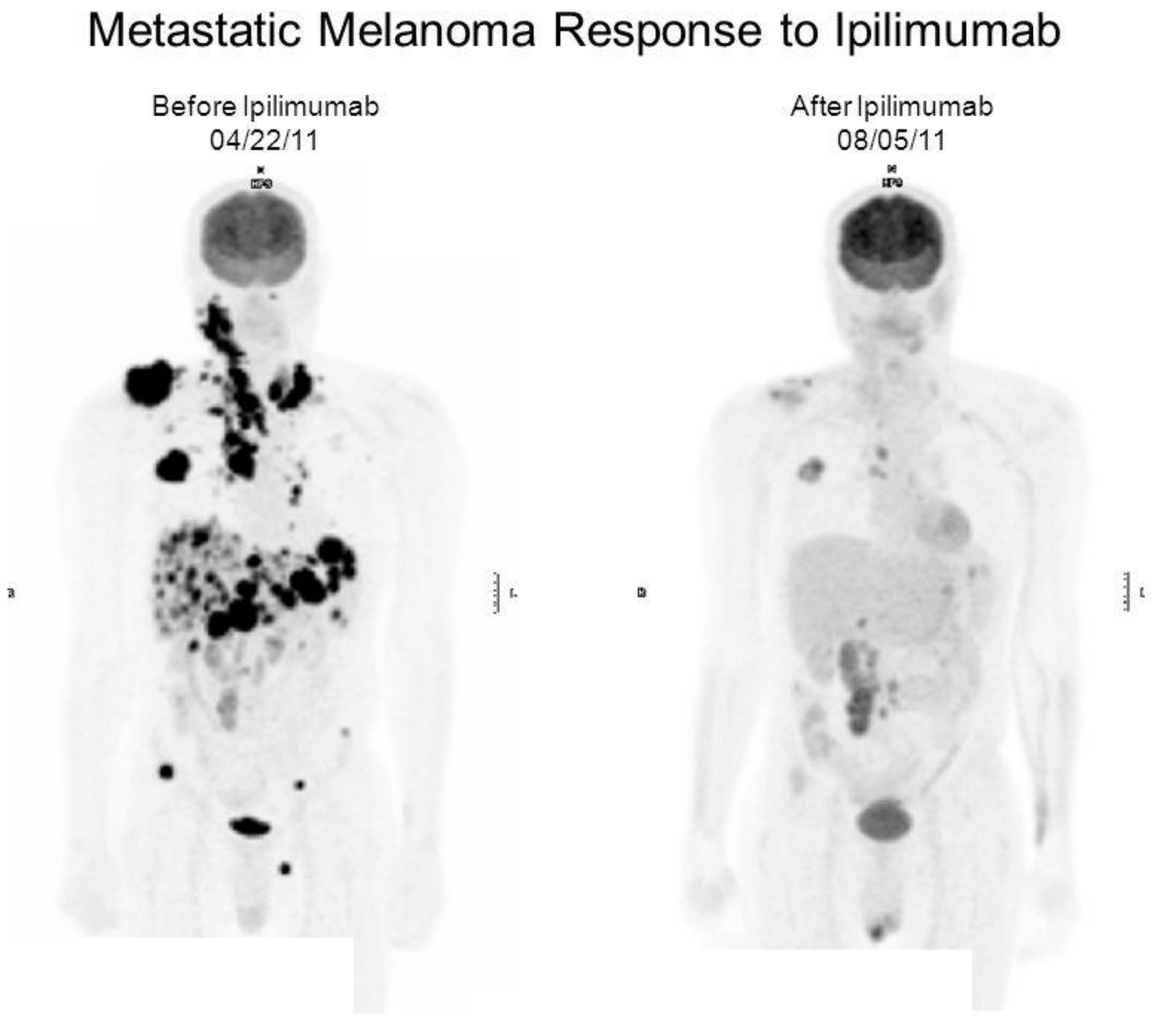
DOSE (Multi-ion : He, C, O)

LET (Multi-ion : He, C, O)

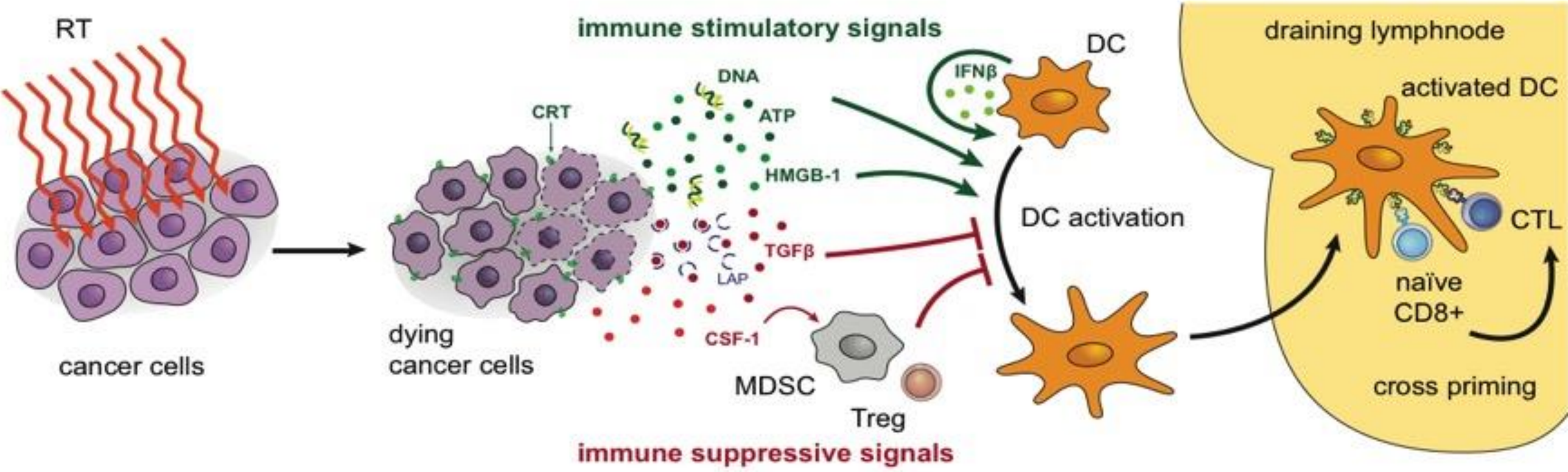


Inaniwa *et al.*, *Phys. Med. Biol*. 2021

The big question: shall we need radiotherapy *at all* in the future?

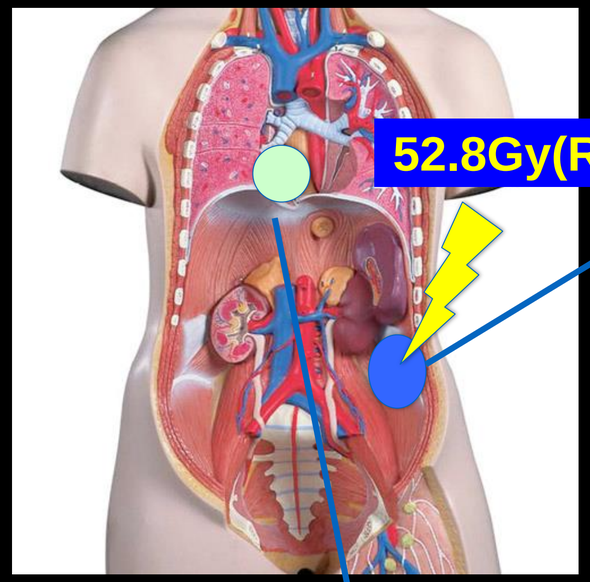


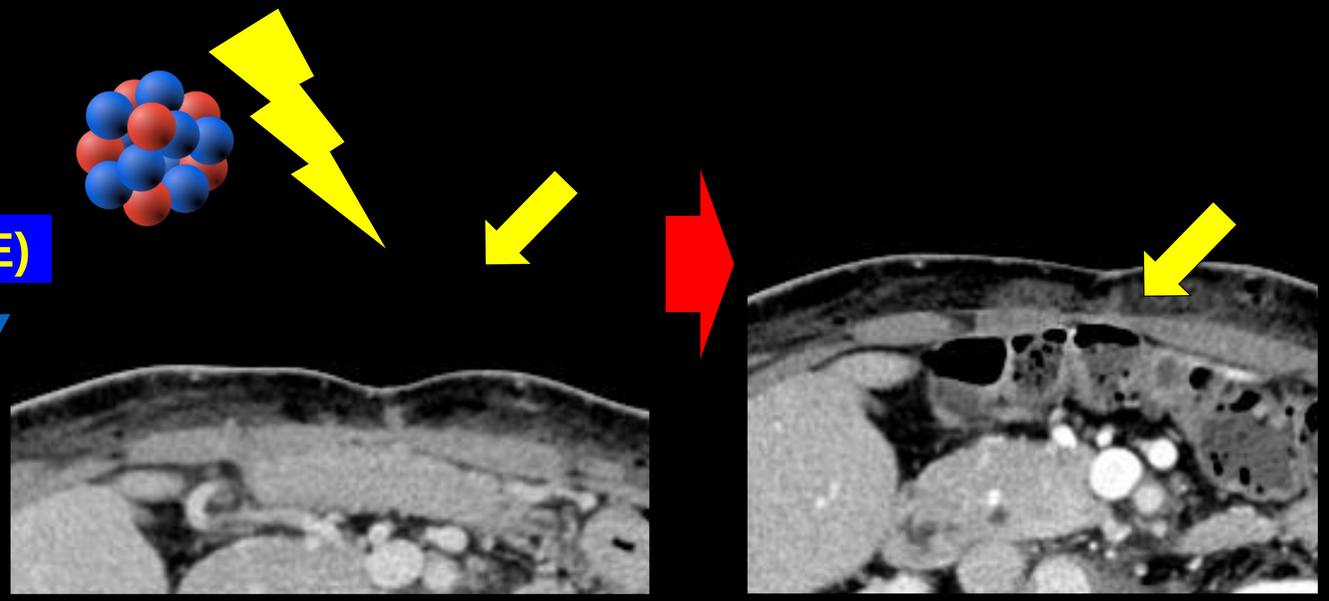
Radioimmunotherapy



Formenti & Demaria, *Lancet Oncol*. 2009

53 year old male pancreatic cancer recurrence after surgery



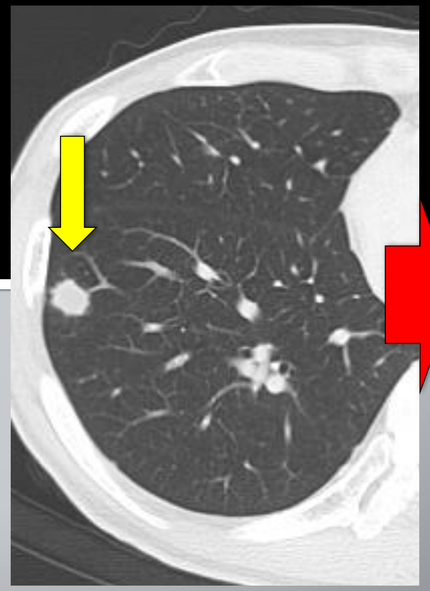


Paraaortic lymph node metastasis

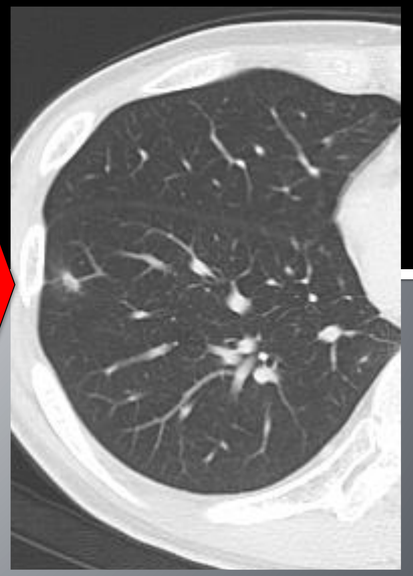
nivolumab180mg/
2weeks

Lung metastasis

6 months after C-ions



Lung metastasis



6 months after C-ions

Particle therapy + immunotherapy

Does Heavy Ion Therapy Work Through the Immune System?

Marco Durante, PhD,* David J. Brenner, PhD,† and Silvia C. Formenti, MD‡

*Trento Institute for Fundamental Physics and Applications-National Institute for Nuclear Physics, University of Trento, Trento, Italy; †Center for Radiological Research, Columbia University Medical Center, New York, New York; and ‡Department of Radiation Oncology, Weill Cornell Medical College, New York, New York

Received Aug 10, 2016, and in revised form Aug 21, 2016. Accepted for publication Aug 25, 2016.

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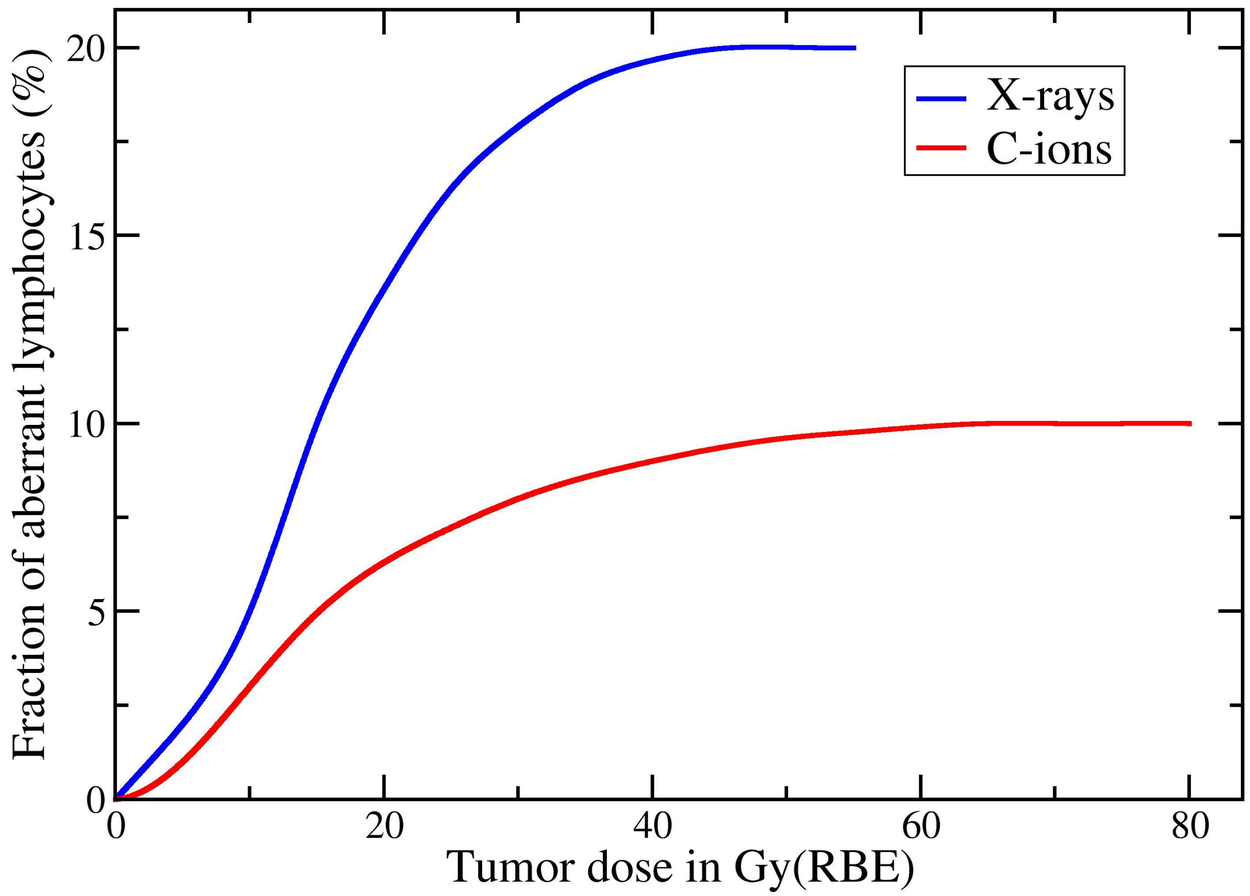
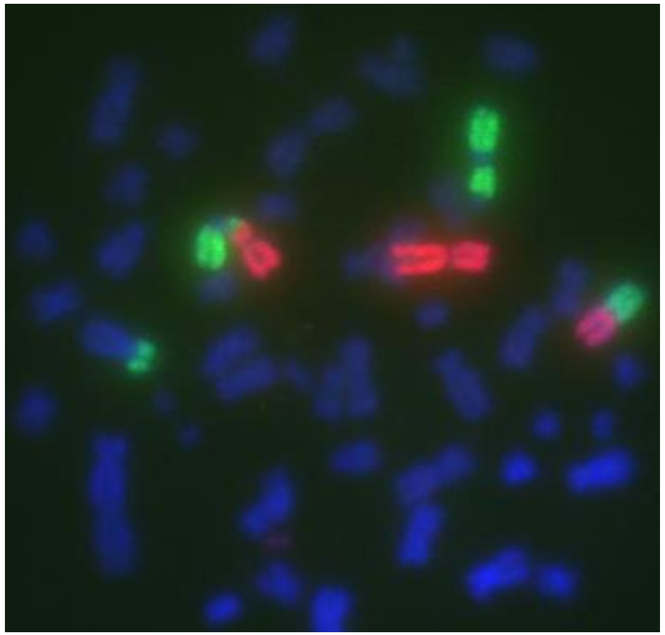
Physical advantages of particle therapy for immunology

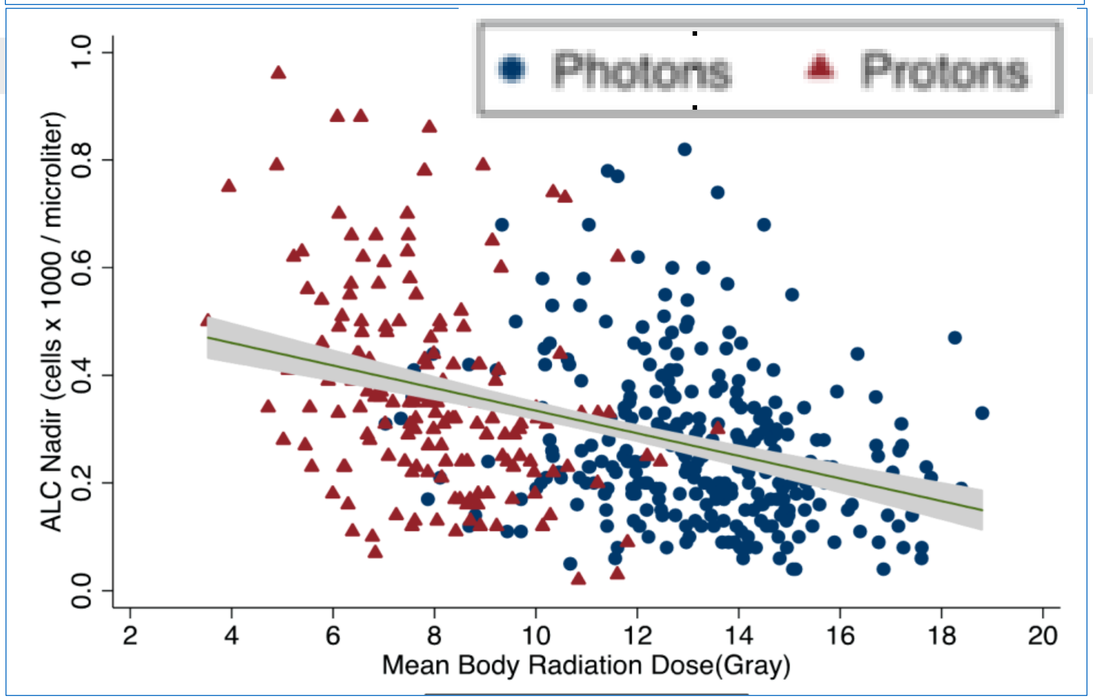




Durante *et al.*, *Nat Rev. Clin. Oncol.* 2017

Esophageal cancer lymphopenia

Correlation Coefficient -0.3721, P< 0.0016



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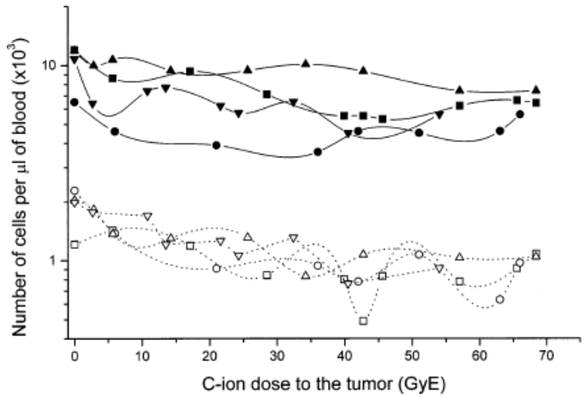
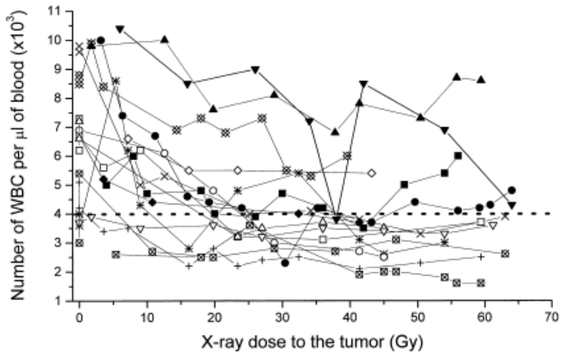
Davuluri *et al.*, *Int. J. Radiat. Oncol. Biol. Phys*. 2017

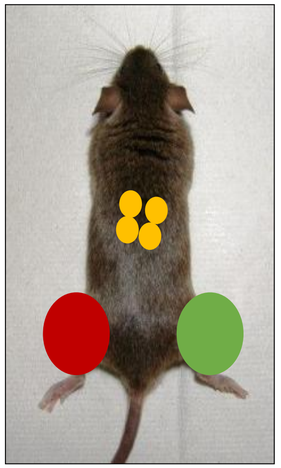




NIRS

Durante *et al.*, *Int. J. Radiat. Oncol. Biol. Phys*. 2000

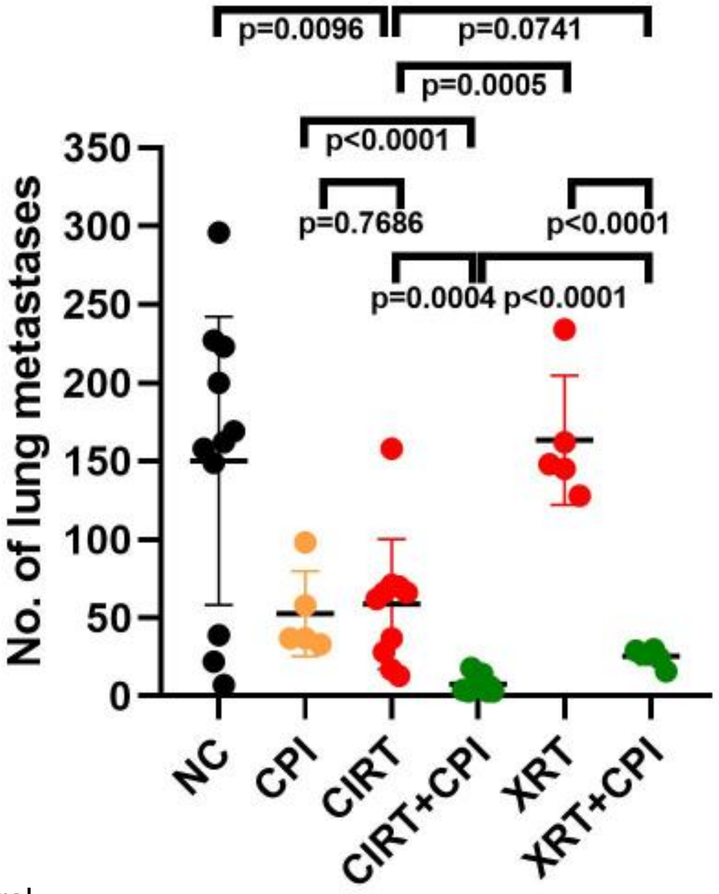
Preclinical results on C-ion radiotherapy (CIRT) + checkpoint inhibitors (CPI)



CIRT+CPI

Negative control

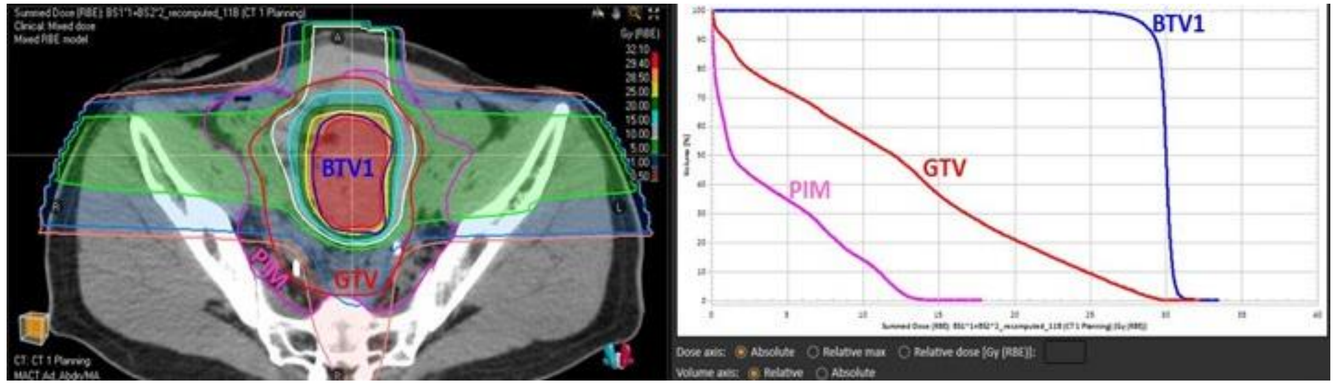
Assessment of superficial nodules after fixation in Bouin's solution



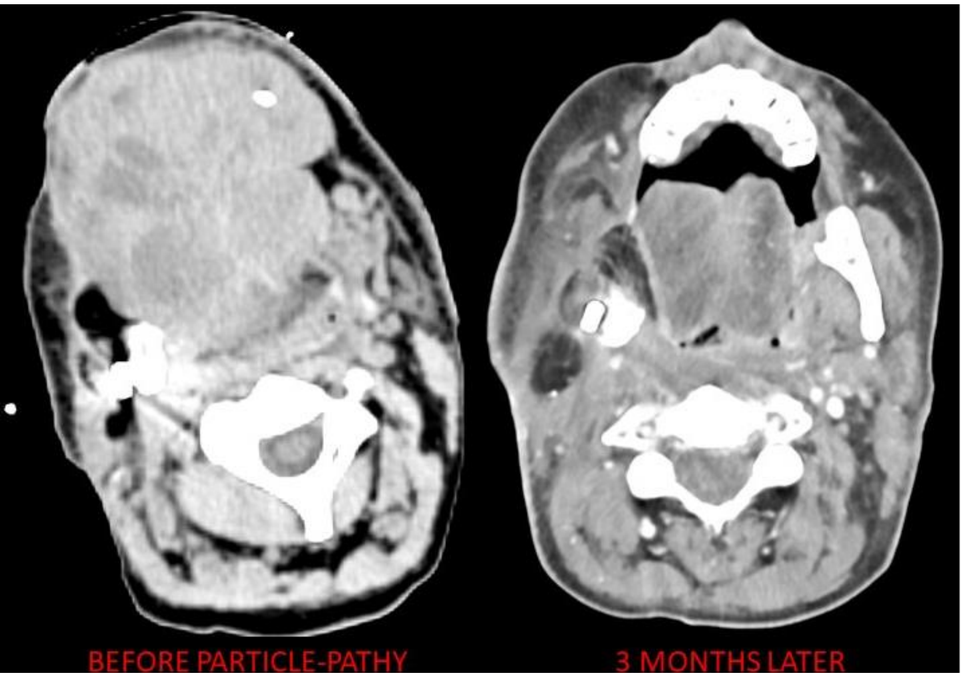
Helm et al., *Int. J. Radiat. Oncol. Biol. Phys.* 2021

NC = negative control
CPI = check point inhibitors only
CIRT = C-ions only, 10 Gy
XRT = photons, 10 Gy

Particle-PATHY
(PArtial Tumour irradiation targeting HYpoxic segment)



For large, bulky tumors, targeting the bystander tumour volume (BTV) in the GTV and spare the peritumoral immune microenvironment (PIM)



Squamous cell bulky tumour of the oral cavity re-irradiated in C-ion PATHY following failure of 70 Gy IMRT

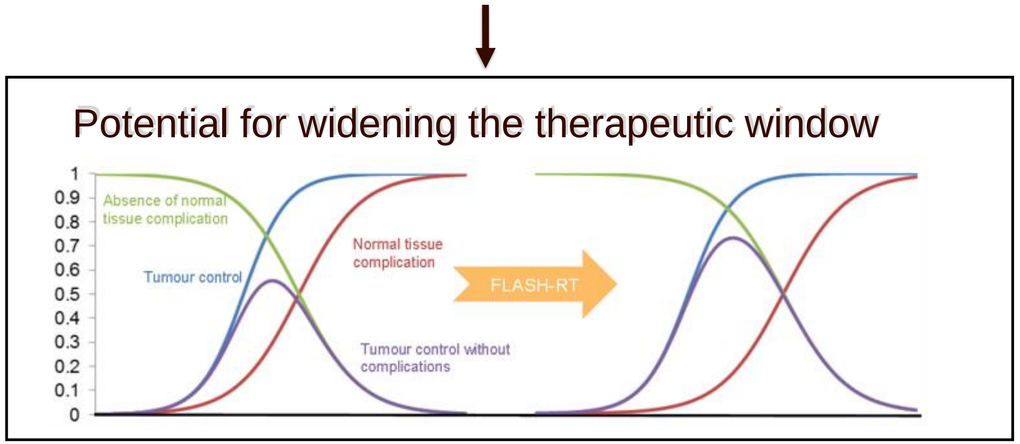
Tubin *et al.*, *Cancers* 2022

FLASH RT: what's that

- FLASH Radiotherapy, is a novel approach of radiotherapy using ultra-high dose rate

(>40 Gy/s overall dose rate, for a total irradiation time <100 ms , but much higher rates (up to 10^9 Gy/s) during each pulse)

aiming to get **unchanged tumor control** and **protection in the normal tissue.**



Ultra-high dose rate (FLASH)

9 mo post-RT

3 years post-RT

CONV

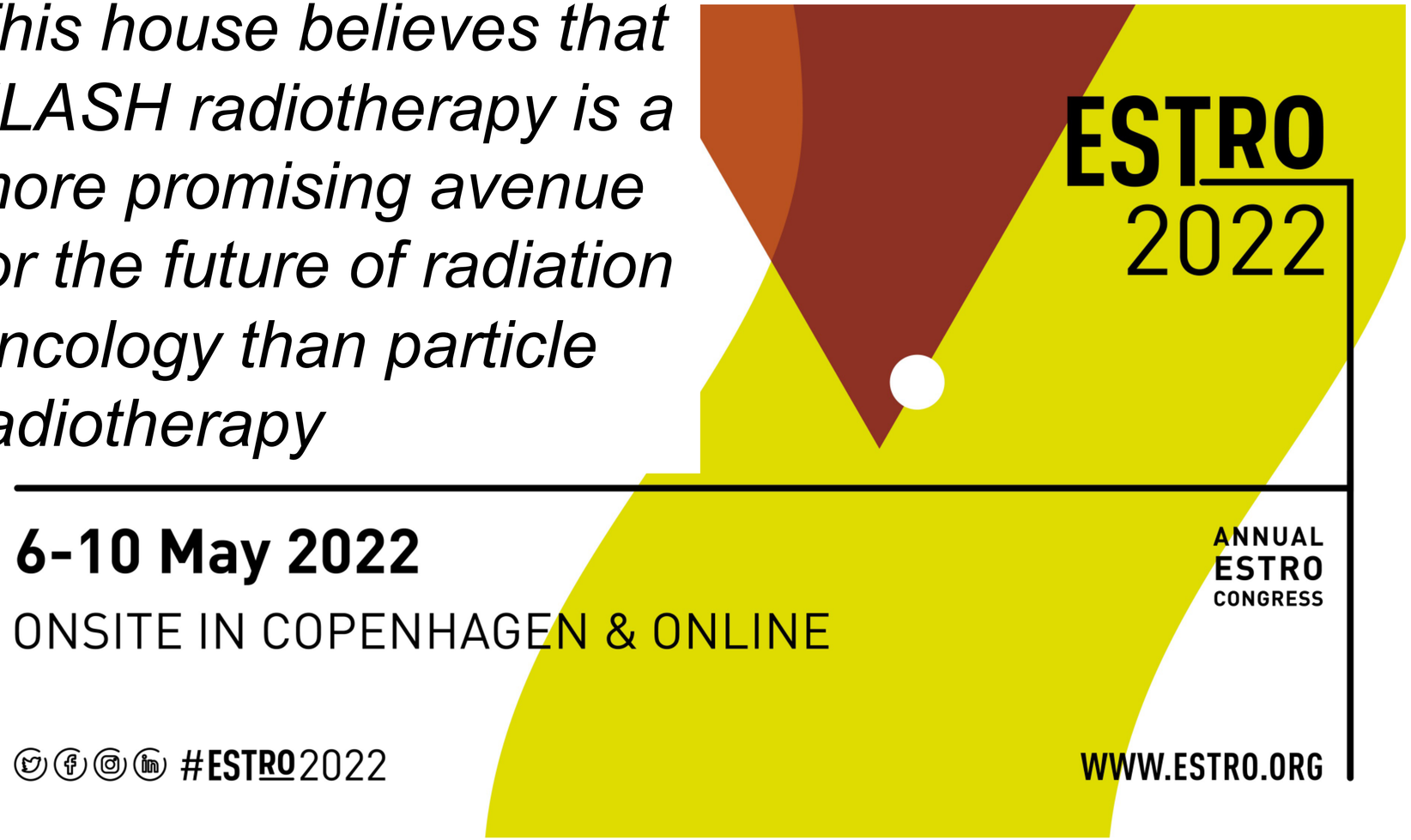
FLASH

34Gy 31Gy 28Gy 34Gy 31Gy 28Gy

Vozenin *et al., Clin. Cancer Res*. 2019

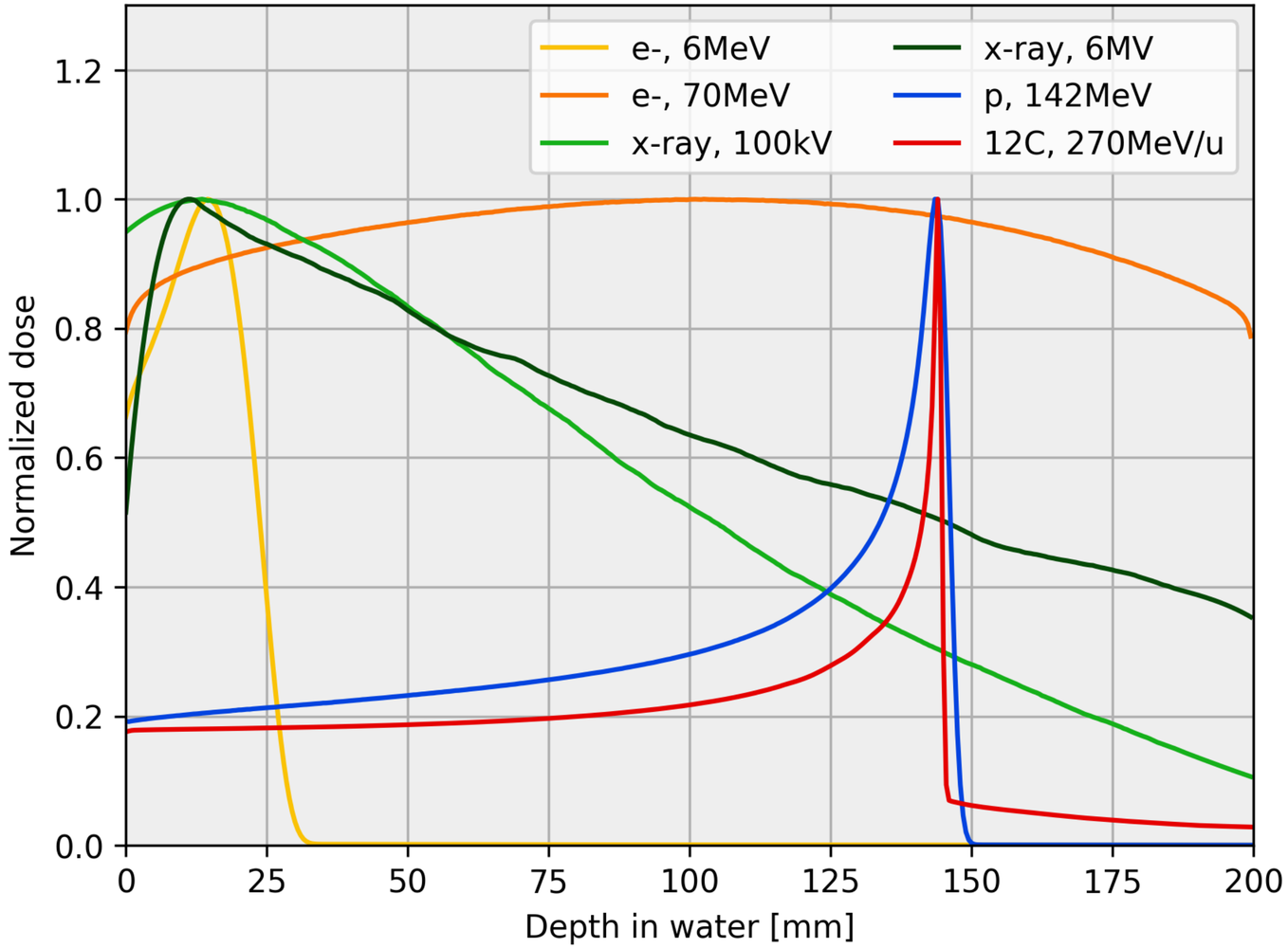
FLASH and particle therapy

This house believes that FLASH radiotherapy is a more promising avenue for the future of radiation oncology than particle radiotherapy



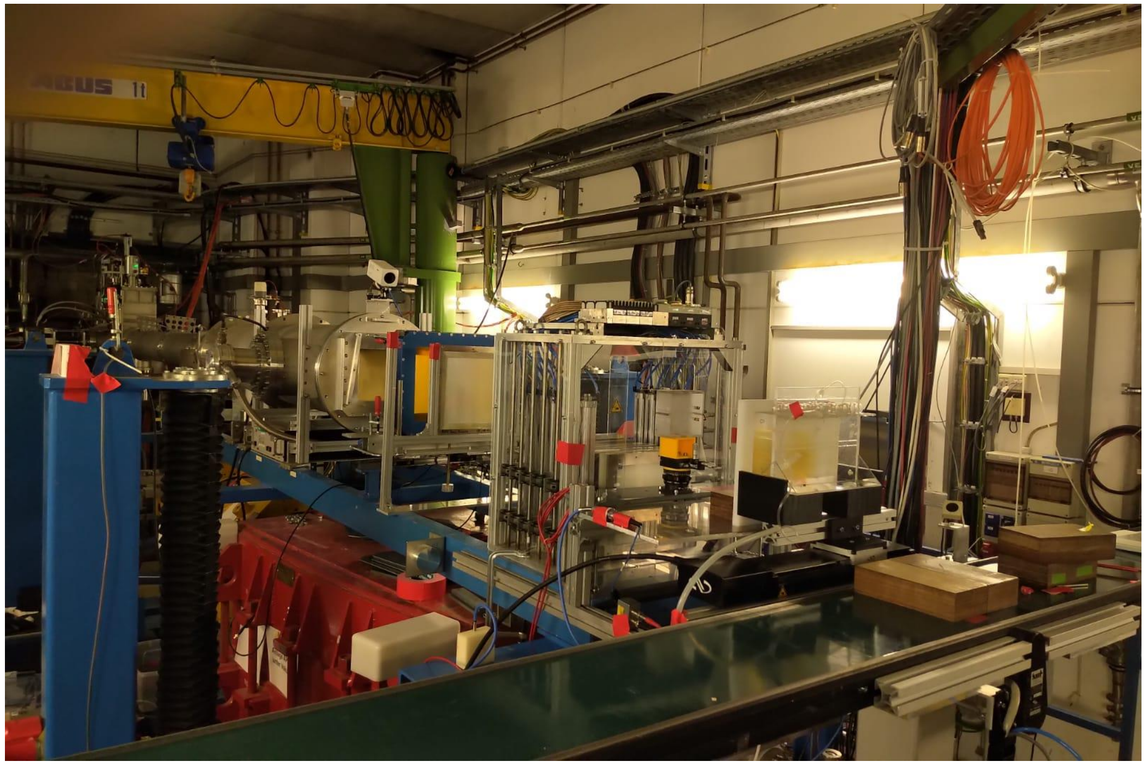
This house believes that riders are more important than horses for the future of equestrian show jumping

FLASH radiation modalities



Vozenin, Bourhis & Durante, *Nat. Rev. Clin. Oncol*. 2022

FLASH with Carbon ions

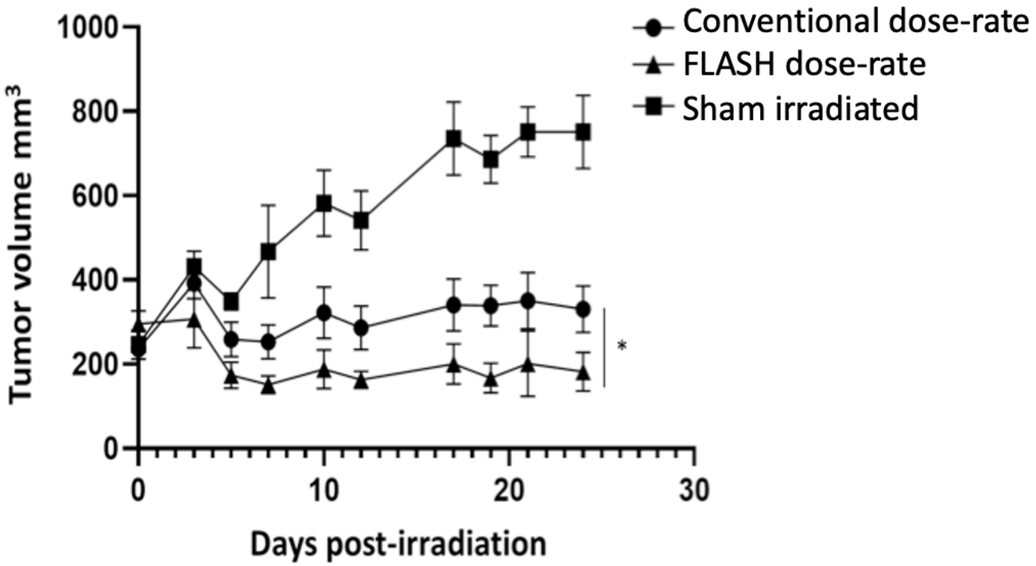


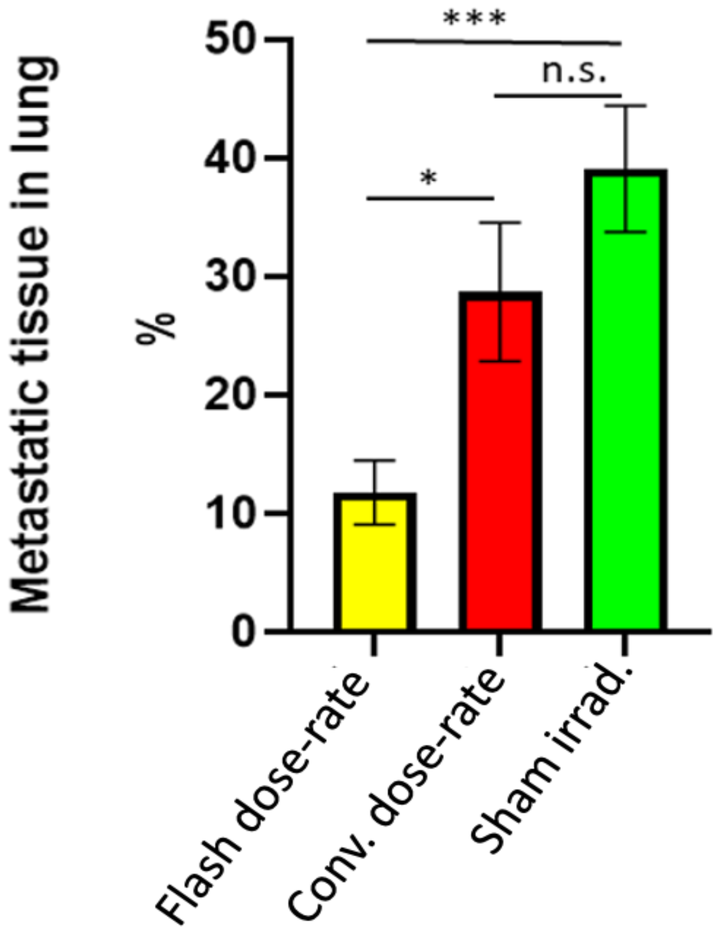
- HIT ≈ 5×10^8 ions per spill
  ⇨ 8 Gy | 50 Gy/s for 10 × 10 mm^2

- GSI > 5×10^9 ions per spill (reliable)
  ⇨ 18 Gy | 100 Gy/s for 20 × 20 mm^2

Tinganelli *et al., Int. J. Radiat. Oncol. Biol. Phys*. 2021

FLASH with C-ions and immune response





Tinganelli *et al.*
Radiother. Oncol. 2022

Summary

1. Charged particle therapy is generally considered the most advanced radiotherapy technique
2. However, the cost effectiveness is not demonstrated
3. Phase-III clinical trials are complicated by ethical, economical, and design (dose distribution, particle Z, RBE, fractionation)
4. Radiobiology suggest trials addressing high-NTCP sites, hypoxic tumors and systemic response (with immunotherapy)
5. New beam delivery systems such as FLASH may be a further benefit of heavy ion therapy
6. Research at accelerators can provide breakthrough in particle therapy: collaboration is needed

How TERA changed me

Donald Rumsfeld (1932-2021)

Secretary of Defense 2001-2006

In life, there are:

- **Known Knowns**: things that we know that we know
- **Known Unknowns**: things that we know that we do not know
- **Unknown Unknowns**: things that we do not know that we do not know

Thank you very much!

www.gsi.de/biophysik

Thank you!

TERA
Fondazione per Adroterapia Oncologica

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