The radiobiology of hadron therapy

SYMPOSIUM
30TH ANNIVERSARY OF THE TERA FOUNDATION
15 SEPTEMBER 1992 - 15 SEPTEMBER 2022

Symposium held as a hybrid event. Registration is mandatory at the link below.

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

GSI Helmholtzzentrum für Schwerionenforschung
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 promoted project for funding hadron therapy research in Italy

I was very much inspired by the TERA activity and that program played a decisive role in the development of my career.

On May 27-31, 2000, TERA organized with NASA the 1st International Workshop on Space Radiation research, first of a long serie of meetings about cross-fertilization between two apparently distinct disciplines.

What can space radiation protection learn from radiation oncology?

Walter Tinganelli, Francesca Luoni, Marco Durante

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

DNA damage induced by X-rays

Prakash et al., Nat. Comm. 2021
DNA damage by heavy ions

-20 sec

From DNA to chromosomes

Durante et al., Radiat. Res. 2002
Skull-base chordoma

Is particle therapy too expensive?

110 centers in 2022
79 under construction or in planning stage
The cost of particle therapy

<table>
<thead>
<tr>
<th>Study</th>
<th>Institution</th>
<th>Phase</th>
<th>Condition</th>
<th>Radiation arm 1</th>
<th>Radiation arm 2</th>
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</thead>
<tbody>
<tr>
<td>R03CA188162: IMPT vs IMRT</td>
<td>MDACC</td>
<td>III</td>
<td>Oropharyngeal cancer (head and neck cancer)</td>
<td>Protons*</td>
<td>X-rays*</td>
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<tr>
<td>PARTIO-L (NCT01617161): proton therapy vs IMRT</td>
<td>MGH</td>
<td>III</td>
<td>Low-risk or intermediate-risk prostate cancer</td>
<td>Protons</td>
<td>X-rays</td>
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<tr>
<td>NCT01512589: proton-beam therapy vs IMRT</td>
<td>MDACC</td>
<td>III</td>
<td>Oesophageal cancer</td>
<td>Protons*</td>
<td>X-rays*</td>
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<tr>
<td>RADCMP (NCT02503341); pragmatic randomized trial of proton vs photon therapy</td>
<td>PTCORI</td>
<td>III</td>
<td>Post-mastectomy stage II or III breast cancer</td>
<td>Protons</td>
<td>X-rays</td>
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<tr>
<td>NRG BN001: dose-escalated IMRT or IMPT vs conventional photon radiation</td>
<td>NRG Oncology</td>
<td>II</td>
<td>Newly diagnosed glioblastoma</td>
<td>Protons*</td>
<td>X-rays*</td>
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<tr>
<td>NRG 1542: proton radiation vs conventional photon radiation?</td>
<td>NRG Oncology</td>
<td>III</td>
<td>Hepatocellular carcinoma</td>
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<td>X-rays</td>
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<td>NCT01182753: proton radiation vs carbon-ion radiation therapy</td>
<td>Heidelberg University, Germany</td>
<td>III</td>
<td>Low-grade and intermediate-grade chordoma and sarcoma of the skull base</td>
<td>Protons</td>
<td>Carbon ions</td>
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<td>NCT01182779: proton radiation vs carbon-ion radiation therapy</td>
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<td>Chordoma of the skull base</td>
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<td>Carbon ions</td>
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<td>CLEOPATRA (NCT01165671): proton radiation vs carbon-ion radiotherapy</td>
<td>Heidelberg University, Germany</td>
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<td>Primary glioblastoma</td>
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<td>Carbon ions*</td>
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<td>IPI (NCT01641135): proton radiation vs carbon-ion radiotherapy</td>
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<td>Prostate cancer</td>
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<td>Carbon ions</td>
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<td>ISAC (NCT01311394): proton radiation vs carbon-ion radiation therapy</td>
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<td>Sacrococcygeal chordoma</td>
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<td>Carbon ions</td>
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<tr>
<td>ETOILE (NCT02383602): carbon-ion radiotherapy vs IMRT</td>
<td>Lyon University Hospital, France</td>
<td>III</td>
<td>Radioresistant adenoid cystic carcinoma and sarcomas</td>
<td>Carbon ions</td>
<td>IMRT</td>
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<tr>
<td>BAA-N01:CM1007-51: prospective trial of carbon-ion therapy vs IMRT</td>
<td>NCI</td>
<td>I/III</td>
<td>Locally advanced pancreatic cancer</td>
<td>Carbon ions*</td>
<td>X-rays*</td>
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<td>CIPHER: prospective multicentre randomized trial of carbon-ion radiotherapy vs conventional radiotherapy</td>
<td>UTSW</td>
<td>III</td>
<td>Locally advanced pancreatic cancer</td>
<td>Carbon ions*</td>
<td>X-rays*</td>
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</tbody>
</table>

RCT IMRT vs. PSPT

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

<table>
<thead>
<tr>
<th>RP Grade</th>
<th>IMRT N=92</th>
<th>3DPT N=57</th>
<th>Total N=149</th>
<th>P values</th>
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<tbody>
<tr>
<td>0</td>
<td>65</td>
<td>36</td>
<td>101</td>
<td>0.36</td>
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<tr>
<td>1</td>
<td>9</td>
<td>4</td>
<td>13</td>
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</tr>
<tr>
<td>2</td>
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</tr>
<tr>
<td>3</td>
<td>4</td>
<td>6</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>5</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td></td>
</tr>
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</table>

Gr 0-2     86         51         137         0.54
Gr 3-5     6 (6.5%)   6 (10.5%)  12 (8.1%)

MST_{IMRT}= 29.5 month
MST_{3DPT}=26.1 month
P=0.30
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
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.

Need for more translational research
Heavier ions can be effective against hypoxic tumors

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

# pO2 measurements in pancreatic tumors and normal pancreatic tissue

<table>
<thead>
<tr>
<th>Patient</th>
<th>Tumor Med pO2</th>
<th>%&lt;2.5mmHg</th>
<th>Normal Tissue Med pO2</th>
<th>%&lt;2.5mmHg</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>3.1</td>
<td>35</td>
<td>47.3</td>
<td>9</td>
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<td>2</td>
<td>0</td>
<td>94</td>
<td>46.6</td>
<td>0</td>
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<td>2.7</td>
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<td>67.4</td>
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<tr>
<td>5</td>
<td>0.9</td>
<td>95</td>
<td>51.6</td>
<td>0</td>
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<tr>
<td>6</td>
<td>2</td>
<td>54</td>
<td>69.8</td>
<td>7</td>
</tr>
<tr>
<td>7</td>
<td>5.3</td>
<td>68</td>
<td>82.7</td>
<td>0</td>
</tr>
</tbody>
</table>

(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)


<table>
<thead>
<tr>
<th>Time from CIRT (months)</th>
<th>Percent survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>1y</td>
<td>55GyE 81%</td>
</tr>
<tr>
<td>2y</td>
<td></td>
</tr>
<tr>
<td>MST</td>
<td>55GyE 60%</td>
</tr>
<tr>
<td>26.2M</td>
<td></td>
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</tbody>
</table>
Is LET high enough?

Local failure maps with dose-averaged LET in CIRT
**LET-painting with multi-ion treatment**


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

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

Metastatic Melanoma Response to Ipilimumab

Before Ipilimumab
04/22/11

After Ipilimumab
08/05/11
Radioimmunotherapy

53 year old male pancreatic cancer recurrence after surgery

nivolumab 180 mg/2 weeks

Paraortic lymph node metastasis

Lung metastasis 6 months after C-ions

52.8 Gy (RBE)
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.
Physical advantages of particle therapy for immunology

Esophageal cancer lymphopenia

Correlation Coefficient -0.3721, $P < 0.0016$


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

Assessment of superficial nodules after fixation in Bouin’s solution


NC = negative control
CPI = checkpoint 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.

Potential for widening the therapeutic window

![Chart showing therapeutic window with FLASH RT](image-url)
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
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

FLASH with Carbon ions


- HIT $\approx 5 \times 10^8$ ions per spill
  $\Rightarrow 8$ Gy $|$ 50 Gy/s for $10 \times 10$ mm$^2$

- GSI $> 5 \times 10^9$ ions per spill (reliable)
  $\Rightarrow 18$ Gy $|$ 100 Gy/s for $20 \times 20$ mm$^2$
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

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

Donald Rumsfeld (1932-2021)
Secretary of Defense 2001-2006
Thank you very much!

www.gsi.de/biophysik
Thank you!