Point/Counterpoint:

The more important heavy charged particle RT of the future is more likely to be with heavy ions rather than protons

AAPM 55, Indianapolis

August 5th, 2013

Oliver Jäkel
November 2009: 1. patient treated
October 2012: Gantry treatment started
Today: > 2000 patients treated

- Flexible beam parameters: E, fwhm, Int., scan grid/mode
- Scanning Gantry
- p, He, C, O
Opening statement:

(I) With regard to Physics:
Everything that can be done with protons, can be done also with heavy ions, but in a better way.

(II) With regard to Radiobiology:
Heavier ions have the potential to significantly improve clinical results esp. for radioresistant tumors (e.g. Hypoxia, Heterogeneity, Genetic resistance …)
Physical advantages of heavier ions vs. protons

- Reduced angular scattering: sharper penumbra
- Reduced range straggling: sharper distal fall-off
- Better targeting due to better in-vivo monitoring
- There is a whole variety of heavy ions
Pencil beams for Protons vs. Helium


Helium offers excellent dose conformation, only slightly elevated RBE (~1.3); similar costs as protons.

Improved peak to plateau ratio and reduced lateral penumbra for Helium.

Helium (200MeV/u)
Clinical relevance of lateral penumbra TP for scanned beams

Carbon (O. Jäkel)  Protons (A. Trofimov)

H. Suit et al, Radiat. Oncol. 2010

Lateral penumbra alone may justify to use heavier ions
The penumbra of protons is worse than for photons at larger depth.
Reduced energy straggling

80%-20% distal fall-off

PET Imaging with ion beams

Peripheral nucleus-nucleus-collisions, low momentum transfer

\[ Z \geq 6 \] Target fragments \hspace{1cm} Projectile fragments \hspace{1cm} \[ Z < 6 \] Target fragments

\[ ^{12}\text{C}: E = 212 \text{ AMeV} \]
\[ \text{Target: PMMA} \]

\[ ^{15}\text{O}, ^{11}\text{C}, ^{13}\text{N} \ldots \]

\[ ^{11}\text{C}, ^{10}\text{C} \]

\[ ^{1}\text{H}: E = 110 \text{ MeV} \]
\[ \text{Target: PMMA} \]

\[ ^{15}\text{O}, ^{11}\text{C}, ^{13}\text{N} \ldots \]

Potential range probing with radioactive beams: C11,Ne19
In vivo PET Monitoring in C-12 vs. p-RT

Dose (TPS)

C-12

Activity (PET)

Treatment plan

Meas. activity

Combs BMC Cancer 2012

Parodi et al IJROBP 2007
Tracking of prompt protons from a Carbon beam

Measurement of peak position, beam width with 1mm resolution

Gwosch et al., PMB 2013
Biological Advantages of high LET RT

Low LET dose


Carbon tracks in nucleus

Tumor dose >> normal tissue
Effective for radioresistant tumors
Effective in hypoxic tumor cells
Which tumors might be better treated by ions?

Tumors, which are refractory to low LET irradiation

Radioresistance

Genetic alterations
- upregulated oncogenes
- mutated tumor suppressor genes
- disregulated apoptosis

Intratumoral micromilieu
- Deprivation of oxygen
- Up-regulated defense system
- High angiogenic potential

Proliferation status
- High content of quiescent cell clones
- Slow proliferation activity
LET Painting for hypoxic tumors

Planned target | SFUD | LET-Painting

DOSE

Bassler et al., Accta Oncol. 2010

F-MISO PET

LET

Scanning and IMPT offers additional degrees of freedom for adapting high LET to hypoxic areas
# Clinical Trials at HIT

see [www.clinicaltrials.gov](http://www.clinicaltrials.gov)

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<thead>
<tr>
<th>Trial Name</th>
<th>Status</th>
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<td>PROMETHEUS (C12 bei primärem HCC)</td>
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<td>OSCAR (inoperables Osteosarkom)</td>
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<td>IPI (C12/H1 bei Prostata Ca)</td>
<td>BFS cleared</td>
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# Carbon + GEM for loc. adv. Pancreatic Cancer

S. Yamada, NIRS, Rochester May 2nd, 2013

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<tr>
<th>Year</th>
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<th>Treatment</th>
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<th>2yr</th>
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<td>34</td>
<td>GEM+RT</td>
<td>50.4Gy</td>
<td>50%</td>
<td>12%</td>
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<td>37</td>
<td>GEM</td>
<td>-</td>
<td>32%</td>
<td>4%</td>
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<td>2010</td>
<td>50</td>
<td>GEM</td>
<td>-</td>
<td>64%</td>
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<td>Sudo</td>
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<td>34</td>
<td>S-1+RT</td>
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<td>Small</td>
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<td>28</td>
<td>GEM+BZ**+RT</td>
<td>36Gy/15fr.</td>
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<td>Schellenberg</td>
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<td>20</td>
<td>GEM+SBRT</td>
<td>25Gy/1fr.</td>
<td>50%</td>
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<td>NIRS</td>
<td>47</td>
<td>GEM+CIRT</td>
<td>45.6-55.2 GyE</td>
<td>74%</td>
<td>54%</td>
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*Bevacizumab

Incidence (Mortality) of pancreatic Ca. 2012 (US): 43 920 (37 390)
Protons are not per se superior to modern IMRT

Tomotherapy vs. IMPT (Stuschke, Radiother. Oncol, 2013)

Excess dose of IMPT in RED

Modern IMRT has come close to IMPT

The small benefit may not justify higher price for protons
Clinical potential for ion beams

- Clinical data from prospective phase I/II and phase II trials support the strong potential of heavy ions
- Randomized studies are underway
- Radiobiological research will be crucial for patient selection and targeting
- Protons offer limited benefit compared to X-rays
- Why should be stop the development with the easiest and least beneficial ion, i.e. protons?

Heavier ions will be more important than protons
... maybe not in the next few years
... maybe not in the US
“If we are satisfied, we are lost”

William J. Mayo, MD
1935

Treatment costs

Costs for p-RT in the US:
Av. Reimbursement by CMS: $35,917
Upper range for pediatric patients up to 250 000 $

Carbon RT is reimbursed in the EU with 19k€

Investment costs account for < 50% treatment costs!

Hypofractionation will change these numbers:
C-12 for lung tumors at NIRS: 10‘040 €

Cost-effectiveness is more relevant than costs!
Technical development and hypo-Fx will reduce costs
Carbon therapy in Heidelberg plus extras is cheaper than p-RT in the US ...
Carbon Gantry in clinical operation

world-wide first ion gantry

2D parallel scanning

± 180° rotation
3° / second

13m diameter
25m length
600 to rotating (145 to magnets)

MT Mechatronics
MT Aerospace

Required engineering technology is available
Btw: some providers for p-RT offer fixed beamlines ?!
Dependence of RBE on LET

855 survival curves


The spread reflects the cell types but also uncertainty of RBE
Uncertainty of RBE

\[ \text{RBE}(p) = 1.1 \text{ ??} \]

There is not a single determination of RBE(p) from clinical data.

\[ \text{RBE}(p) \text{ may have an uncertainty of } \sim 20-30\% \]

Using a model helps to reduce the uncertainty. Using a fixed RBE does not.
Normal tissue damage after carbon RT: dose response for contrast enhancement in the temporal lobes

n=59, 2002-2003, FU 2.5 years

TD5 (Dmax,V-1cm3) 68.8 ± 3.3 GyE
2/59 clinical symptoms

No signs of any increased normal tissue damage
Clinical evidence for OER effect in C-RT

Patients w. uterine cervical cancer

Reoxygenation is less important in high LET
Hypofractionated proton-RT will reduce this effect
Depth dose curves for various ions

There is no tail for Helium
The dose in the tail is 10-20%

Kantemiris
Med Phys 38, 2011
Fragmentation of Carbon ions
400MeV/u in water

Most of the particles in the tail are protons!
Dose and RBE are included in the TPS
No clinical observation questioning this approach
Clinical evidence for protons

*For brain tumors, despite reduced integral doses, no reduction of adverse events could be demonstrated.*


*There are only a few sites potentially to benefit from the use of Proton Beam Therapy.*

The report of ASTRO’s emerging technology committee: *An evidence based review of proton beam therapy*”

*Proton Beam Therapy is not associated with an increased risk for secondary malignancies*“

Chung et al. IJROBP 2013 Incidence of 2nd malignancies of patients treated with p and photons

There is little clinical evidence for protons Are they cost-effective ??
Clinical evidence for Carbon ions
Skull base chordoma

C12 as primary RT: 60-70 Gye in 20 Fx

Open question: high LET or high conformity?
Clinical evidence for Carbon ions  
Adenoid cystic carcinoma  
Local Control Rate after IMRT vs. IMRT+C12 (54Gy+ 18 Gye)

[Schulz-Ertner et al., Cancer 2004]

Open question: can Chemo-RT reduce distant metastasis?
Availability of Ion Beam RT is increasing worldwide

Japan: Tokyo Bay, Yokohama, Obu-City
France, China (2), South Korea, Thailand, Russia
HIT in the middle of a unique campus

- Physics institute
- Internal medicine
- German Cancer Research center
- Surgical clinic
- Natl. Cancer Center
- Dep. Radiat. oncology
- Women's hospital
- Children's hospital
- Medical Physics
Neutron production Carbon vs. protons


At the same beam line, n-doses are lower for Carbon
Out of field dose


Scanned Carbon offers lowest out-of-field dose
Ion beam Therapy in Japan
Patient Distribution Enrolled in Carbon Ion Therapy at NIRS (Treatment: June 1994 ~ July 2011)

- **Prostate**: 1382 (20.9%) CP: 1057
- **Bone & Soft tissue**: 901 (13.6%) CP: 666
- **Head & Neck**: 763 (11.5%) CP: 440
- **Lung**: 695 (10.5%) CP: 118
- **Liver**: 443 (6.7%) CP: 213
- **P/O rectum**: 341 (5.2%) CP: 274
- **Eye**: 114 (1.7%) CP: 72
- **GYN**: 170 (2.6%) CP: 1
- **Pancreas**: 175 (2.6%) CP: 1
- **CNS**: 105 (1.6%) CP: 538
- **Skull Base**: 81 (1.2%) CP: 52
- **PA L/N**: 69 (1.0%) CP: 62
- **Lacrical**: 23 (0.3%)
- **Scanning**: 8 (0.1%)
- **Re-irradiation**: 75 (1.1%) CP: 16
- **Miscellaneous**: 1208 (18.3%) CP: 538
- **Total**: 6,619
  - **Clinical Practice**: 3,509
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More than 50 phase I and phase II protocols have been conducted at NIRS since 1994.
FIG. 9. (Color online) Bragg curve for 670 MeV/u $^{20}$Ne ions in water measured at GSI (circles) and calculated contributions of primary ions, secondary and tertiary fragments. Adapted from Sihver et al. (1998).

No conformation of high LET to the target region
Which is the best ion for RT?

RBE for a fractionated irradiation of jejunal crypt cells of mice (SOBP of 8 cm)


The differential RBE peak/plateau is optimal for Li...O
Radioactive beams: Pet imaging with Ne-19

Idea:

• Use Ne-19 for range probing
• Use Ne-20 for treatment

Images: Courtesy of Bill Chu, Berkeley
Scattering at inhomogeneities

Scattered dose behind an inhomogeneity (bone) in water

Image: Weber 2009
Mayo Clinic
Light Ion Therapy Program – Phase II

Structure

New Frontiers: Making the case for bringing carbon ion radiation therapy to American cancer patients

April 4, 2012

Join us April 26-27 for New Frontiers in Cancer Treatment: A Focus on Photon and Carbon Ion Radiation Therapy. The symposium, hosted by CSU and the College of Veterinary Medicine and Biomedical Sciences, will be held in Fort Collins at the Hilton Hotel.

There are three in Japan, one in China and one in Germany. In the next five years, Japan will add two more, China will add two more, Italy had just completed construction on one, two are under construction in Germany, and one is under
Mayo Clinic
Light Ion Therapy Program – Phase II

Technical Specifications

- **Ions** – Protons, Carbon, (He? Li? O?)
- **Beam** – Pencil beam scanning, 50-450 MeV/nucleon
- **Range** – from 1 g/cm² to 30 g/cm² in H₂O
- **Field size** – 30x30 cm²
- **Rooms** – Three rooms with robotic patient positioners, two with fixed horizontal and oblique angle beams and single room with a small field, fixed horizontal beam. (New gantry technology?)
The Rationale for Oxygen: OER

OER as function of LET


Oxygen maybe more used for hypoxic areas
Re-oxygenation

- Will not work for hypo-fractionated Tx
- Less important for Carbon (increased vascular damage; antiangiogenic effects, decreased latency)
- Other factors also important intratumor heterogeneity (stem cells, highly repairing subpopulations enhanced metabolism)
Thank you!

Check out our online Master program: [http://www.apmr.uni-hd.de](http://www.apmr.uni-hd.de)

Beam team

Research team

Joseph Castro, MD, UCSF Radiation Oncologist, who conducted the LBNL clinical trials.

Treatment plan for a lesion in the Esophagus using Neon beams (Chen, IJROBP 1979)
Depth dose distributions of RT beams

- Similar absorbed dose for protons and Carbon
- Lower biological effective dose for Carbon
- Small tail of fragments behind the BP of Carbon
Influence of Scattering in Tissue

Protons: 220 MeV

20 cm

50 mm
Influence of Scattering in Tissue

Carbon Ion
380 MeV/u

20 cm

50 mm
LET Painting for hypoxic tumors

Bassler et al. LET painting increases TCP n hypoxic tumors. Acta Oncol 2013
COSMIC Study: Response

At treatment planning

FU @ 6 weeks after C12
Clinical evidence for OER effect in C-RT

Patients w. uterine cervical cancer

Reoxygenation is less important in high LET Hypofractionated proton-RT will reduce this effect
GEM + CIRT for locally advanced Pancreatic Cancer

<table>
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<th>Total dose</th>
<th>n</th>
<th>12mo</th>
<th>24mo</th>
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<tr>
<td>45.6 GyE&lt;</td>
<td>47</td>
<td>67%</td>
<td>58%</td>
</tr>
<tr>
<td>43.2 GyE</td>
<td>24</td>
<td>68%</td>
<td>28%</td>
</tr>
<tr>
<td>Overall Survival</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>45.6 GyE&lt;</td>
<td>47</td>
<td>74%</td>
<td>54%</td>
</tr>
<tr>
<td>43.2 GyE</td>
<td>24</td>
<td>71%</td>
<td>21%</td>
</tr>
</tbody>
</table>

Incidence / Mortality of pancreatic tumors 2012 (US): 43 920 / 37 390
Treatment verification for gated Tx

Initial TP  4 weeks after RT  12 weeks after RT

RT: 4 x 10Gy (RBE)
Prometheus study

D. Habermehl

Activation study Using PET-CT @ HIT
(J. Bauer)
Arguments against protons

Proton RT is less robust as photon plans and may lead to worse coverage in reality.

Photon RT has made great progress, so that the benefit of proton becomes less important.

Given the higher price, protons may not offer enough benefit for the higher price.

Cheap single room, passive beam facilites may yield sub-optimal results.