Particle therapy

proton-CT – a novel diagnostic tool

Dieter Roehrich
UiB

- Particle therapy – a treatment of cancer
- Bragg peak position – the critical parameter in dose planning
- Proton-CT – a novel diagnostic tool for quasi-online dose plan verification
Cancer statistics and therapies

- Radiotherapy is an important weapon in the battle against cancer
  - Contributions to successful treatment of cancer
    - 45-50% surgery
    - 40-50% radiotherapy
    - 10-15% chemotherapy

K. Peach, Heavy Ions in Science and Health workshop, Bergen, 2012
Radiotherapy with photons and hadrons

- The goal of radiation therapy is to irradiate the tumor with the prescribed dose and minimize the dose to healthy tissue.

- **Photons**
  - Electromagnetic radiation

- **Hadrons**
  - Protons and heavier nuclei, e.g. carbon nuclei.
Radiotherapy – photons vs hadrons (I)

- Treatment goal
  - Effective eradication of all tumor cells <-> avoid injury to healthy tissue
- Do we achieve the goal in the clinical routine?
Why carbon ions? (I)

History

• LBL (1975-1986)

• Japan (since 1994): NIRS, Gunma, …

• Germany (since 1997): GSI, HIT, …
Why carbon ions? (II)

- Energy loss (Bethe-Bloch) and Bragg peak

- Lateral beam profile
Radiation-induced DNA damage

C-ions are very effective – high Relative Biological Effectiveness RBE

Sparsely ionising radiation (low-LET)
- e.g. γ-rays, β-particles
  - Low concentration of ionisation events
  - electron tracks

Densely ionising radiation (high-LET)
- e.g. α-particles
  - C⁶⁺ ions
  - High concentration of ionisation events

Why carbon ions? (III)
Why carbon ions? (IV)

- Linear Energy Transfer (LET) and Relative Biological Effectiveness (RBE)

\[
LET = \frac{dE_{\text{transferred}}}{dx}
\]

\[
RBE = \frac{DOSE_{x-ray}}{DOSE_{\text{test}}}
\]
Why carbon ions? (V)

- LET and RBE
  - $\Rightarrow$ RBE ($^{12}$C, in Bragg peak): 3-4
Why carbon ions? (VI)

- Bragg peak and RBE
  - Comparison photons, protons, carbon ions

<table>
<thead>
<tr>
<th></th>
<th>Photons</th>
<th>Protons</th>
<th>Carbon ions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Integral out-of-field dose</td>
<td>1</td>
<td>0.3-0.5</td>
<td>&lt;0.3</td>
</tr>
<tr>
<td>RBE</td>
<td>1</td>
<td>1.1</td>
<td>&gt;3 (in Bragg peak)</td>
</tr>
</tbody>
</table>

Qualitative difference between photons and carbon-ions: potential improvement by 10

Integral out-of-field dose: the smaller the better (ideally 0)
RBE: the higher the better
From principal arguments to clinical studies

- Carbon ions provide a wide therapeutic window

- Confirmed by clinical results
The particle beam treatment facility - e.g. HIT
The particle beam treatment facility
Hadron facilities in operation

NuPECC, Nuclear Physics in medicine - Chapter 1 - Hadrontherapy, 2013
Clinical results

Carbon ion clinical research at NIRS (Japan)
- 57 phase I and phase II protocols since June 1994
- Number of patients enrolled for carbon ion radiotherapy at NIRS:
  - Total: 7,339
  - CP: 4,190
  - Scanning: 11 (0.1%)
  - Lacrimal gland: 22 (0.3%) CP:1
  - Abdominal lymph node: 53 (0.7%) CP:46
  - Gastrointestinal tract: 71 (1.0%)
  - Skull base: 85 (1.2%) CP:56
  - Central nervous: 106 (1.4%)
  - Eye: 128 (1.7%) CP:86
  - Gynecological region: 207 (2.8%) CP:10
  - Prostate: 1726 (23.5%) CP:1394
  - Bone & soft tissue: 903 (12.3%) CP:690
  - Head & neck: 848 (11.6%) CP:525
  - Lung: 737 (10.0%) CP:157
  - Liver: 451 (6.1%) CP:224

T. Kamada, Carbon Ion Radiotherapy at NIRS, Chiba, 2013
Clinical results (NIRS) – lung cancer

Single fraction carbon ion therapy for peripheral stage 1 non-small cell lung cancer

Local control rate (5y): 79%
Cause-spec. survival rate (5y): 75%
Overall survival rate (5y): 64%

Single dose of 36-46 Gy (n=121)

NO Grade 3 Reactions in this series

T. Kamada, Carbon Ion Radiotherapy at NIRS, Chiba, 2013
The Bragg peak position

• **Key advantage of ions: Bragg peak**
  - Relatively low dose in the entrance channel
  - Sharp distal fall-off of dose deposition (<mm)!

• **Challenge**
  - Stopping power of tissue in front of the tumor has to be known – crucial input into the dose plan for the treatment
  - Stopping power is described by Bethe-Bloch formula:

\[
\frac{dE}{dx} \sim (\text{electron density}) \times \ln\left(\frac{\text{(max. energy transfer in single collision)}}{\text{(effective ionization potential)}}\right)^2
\]

• **Current practice**
  - Derive stopping power from X-ray CT
  - Problem:
    X-ray attenuation in tissue depends not only on the density, but also strongly on Z (Z^5 for photoelectric effect)
Stopping power calculation from X-ray CT

Range uncertainties

Clinical practice:
- Single energy CT: up to 7.4% uncertainty

How to deal with range uncertainties in the clinical routine?
- Increase the target volume by up to 1 cm in the beam direction
- Avoid beam directions with a critical organ behind the tumor

Unnecessary limitations -> reduce range uncertainties

Estimates for advanced dose planning:
- Dual energy CT: up to 1.7% uncertainty
- Proton CT: up to 0.3% uncertainty

A comparison of dual energy CT and proton CT for stopping power estimation
David C. Hansen,1, a) Joao Seco,2 Thomas Sangild Sørensen,3 Jørgen Breede Baltzer Petersen,4 Joachim E. Wildberger,5 Frank Verhaegen,6 and Guillaume Landry7
1) Department of Experimental Clinical Oncology, Aarhus University
Proton CT

Fig. 14. 3D rendering of the pCT-reconstructed RSP map of a pediatric anthropomorphic head phantom.

V.A. Bashkirov et al. / Nuclear Instruments and Methods in Physics Research A 809 (2016) 120–129
Proton-CT - quasi-online dose plan verification

• high energetic proton beam quasi-simultaneously with therapeutic beam
• measurement of scattered protons
  • position, trajectory
  • energy/range
• reconstruction of trajectories in 3D and range in external absorber
  • trajectory, path-length and range depend on
    • nuclear interactions (inelastic collisions)
    • multiple Coulomb scattering (elastic collisions)
    • energy loss $dE/dx$ (inelastic collisions with atom)
• MS theory and Bethe-Bloch formula of average energy loss in turn depend on electron density in the target (and ionization potentials)
  -> 3D map of electron density in target
  -> online verification of dose plan
Proton-CT - images

- Traversing proton beam creates three different 2D maps → three imaging modalities
  - Transmission map
    - records loss of protons due to nuclear reactions
  - Scattering map
    - records scattering of protons off Coulomb potential
  - Energy loss map
    - records energy loss of protons (Bethe-Bloch)

Proton-CT

High energetic proton beam traversing the target – intensity $\sim 10^9$ protons/sec

- Detector requirements
  - High position resolution (tens of $\mu m$)
  - Simultaneous tracking of large particle multiplicities
  - Fast readout
  - Radiation hardness
  - Front detector: low mass, thin sensors (50 $\mu m$)
  - Back detector: range resolution <1% of path-length

- Conceptual design
  - Extremely high-granularity digital tracking calorimeter

- Technical design
  - Monolithic Active Pixel Sensors (MAPS)
  - Planes of CMOS sensors for tracking and as active layers in a sampling calorimeter
Digital tracking calorimeter prototype (I)

Silicon-tungsten sampling calorimeter

- optimised for electromagnetic showers
- compact design 4x4x11.6 cm³
- 24 layers
  - absorbers: 3.5 mm of W (≈ 1 X₀)
    Molière radius: 11 mm
  - active layers: MAPS – MIMOSA 23*
    4 chips per layer
    -> 96 chips in total

* IPHC Strasbourg
Simulation results

Detector response

Photons and electrons (e.m. shower)

muons (MIP)

protons
Digital tracking calorimeter – rangemeter (II)

Range measuring resolution

- Energy loss measurement
  - hadron tracks:
    number of hits in a sensitive layer along the particle trajectory ("cluster size") depends (weakly) on the energy loss
• Tracking of a single proton, collecting clusters along the trajectory and fitting a Bragg curve*

Digital tracking calorimeter – rangemeter (V)

- Energy/range resolution for 188 MeV protons

H. Pettersen
Towards a clinical prototype – Bergen pCT Collaboration

• Organisation
  • UiB, HiB, HUS

• International collaboration
  • Utrecht
  • …

• Joining forces with another pCT project
  (Padova - Piero Giubilato, ERC grant iMPACT - 1.8 MEUR) – under discussion

• Financing
  • Toppforsk (26 MNOK, 5 years)
  • BFS (18 MNOK, 4 years)
  • Helse Vest

• Next steps
  • Finishing the optimisation of the design
  • Production of ALPIDE chips
Towards a clinical prototype (I)

Optimisation of the design

- geometry
- longitudinal segmentation
  - number of sensitive resp. absorber layers
- absorber
  - energy degrader, mechanical carrier, cooling medium
  - material choice: Al
  - thickness (2-4 mm)

Bragg-Kleeman fit to exp. data at 145 MeV

Fitted energy: 146.6 ± 0.7 MeV
Fitted energy: 149.5 ± 0.7 MeV
Fitted energy: 145.7 ± 3.1 MeV
Towards a clinical prototype (II)

Optimisation of the design

• sensors – MAPS
  • ALPIDE chip
    • Design team: CCNU Wuhan, CERN Geneva, YONSEI Seoul, INFN Cagliari, INFN Torino, IPHC Strasbourg, IRFU Saclay, NIKHEF Amsterdam
    • sensor for the upgrade of the inner tracking system of the ALICE experiment at CERN
    • chip size ≈ 3x1.5 cm², pixel size ≈ 28 μm, integration time ≈ 4 μs
    • on-chip data reduction (priority encoding per double column)
Towards a clinical prototype (III)

Strategy

- Modular structure – exchangeable front layers (tracking and absorber layers)
- Use the existing ALPIDE chips as sensitive layers
- R&D project to failure ALPIDE design to medical applications
  - Faster charge collection and readout: $4 \, \mu s \rightarrow < 1 \, \text{ns}$
  - Larger sensors - wafer-scale integration by stitching
- Thinner sensors (in case of tracking station between nozzle and patient)
Ongoing discussion in Norway on how many particle therapy facilities are to be build

What can we hope for in Bergen?

- Combined proton and carbon facility
- State-of-the-art technology
  - fast scanning/repainting system
  - active energy modulation
  - beam gating system
  - several treatment rooms
  - superconducting gantry for carbon ions
The End
Why carbon ions? (IV)

- Radiation-induced DNA damage

Sparsely ionising radiation (low-LET)
e.g. $\gamma$-rays, $\beta$-particles

Densely ionising radiation (high-LET)
e.g. $\alpha$-particles
$C^6^+\text{ ions}$

Low concentration of ionisation events

High concentration of ionisation events
Why carbon ions? (V)

- **LET and RBE**

**Low-LET (e.g. γ-rays)**
- 1 Gy corresponds to:
  - ~1000 electron tracks
  - ~20-40 DSB
- Relatively homogeneous

**High-LET (e.g. α-particles)**
- 1 Gy corresponds to:
  - ~2 alpha tracks
  - ~20-40 DSB
- Very non-homogeneous

Induction of double strand breaks (DSB)

Simple aberrations
FISH image

Repair

Complex aberrations

K. Peach, Heavy Ions in Science and Health workshop, Bergen, 2012
Range adaptation

range shifter

beam

Eindringtiefe

N. Saito, IRTG Lecture week, Bergen, 2011
Range adaptation

range shifter

beam

N. Saito, IRTG Lecture week, Bergen, 2011
Range adaptation

range shifter

beam

Eindringtiefe

N. Saito, IRTG Lecture week, Bergen, 2011
Range adaptation

- Range shifter
- Beam
- Air
- Bone
- Tissue

N. Saito, IRTG Lecture week, Bergen, 2011
Range adaptation
Range adaptation

- Beam
- Range shifter
- Air
- Bone
- Tissue

N. Saito, IRTG Lecture week, Bergen, 2011
Example of Electrostatic Accelerator:
Van de Graaf Accelerator
Radiotherapy with photons

- Curing cancer with multiple beams of MV X-rays
Radiotherapy – photons vs hadrons (II)

- Treatment goal
  - Effective eradication of all tumor cells <-> avoid injury to healthy tissue
- Do we achieve the goal in the clinical routine?
  - Treatment plans for cancer in the central nervous system (Medulloblastoma)
  - Dose distribution
    Ewing’s Sarcoma

K. Ytre-Hauge, PhD, Bergen, 2013
C. Stokkevåg, PhD, Bergen
S. Kvinnsland, Heavy Ions in Science and Health workshop, Bergen, 2012
Accelerator complex – ion source

- **Electron Cyclotron Resonance (ECR) source**
  - gas inside static B-field
  - inject RF-field with cyclotron frequency
  - accelerate electrons
  - ionize atoms by electron impact
  - trap plasma in sophisticated magnetic field configuration
Accelerator complex - LINACS

- Drift tube linac – Widerøe
  - Energy gain: $\Delta E = e \cdot N_{\text{gap}} \cdot V_{\text{RF}}$
  - Period length increases with velocity $l = v/2 \cdot f$
  - RF phase changes by $180^\circ$ while the particles travel inside the tubes, i.e. while the electric fields point in the “wrong direction” the particles are shielded by the drift tubes

- higher frequencies (> 10 MHz) were not practical, because then the drift tubes would act more like antennas
- when using low frequencies, the length of the drift tubes becomes prohibitive for high-energy protons, e.g. 3 m at 20 MeV
Accelerator complex – synchrotron
Accelerator complex – extraction

• Extraction
  • stable beam spot and position
  • extraction during ramping - “energy scan”, future option for tracking moving targets
Beam transport systems – beam lines

- Dose delivery to treatment rooms
  - fixed beam lines: 0°, (45°), 90°

- movable beam line - superconducting gantry

### Rotating Gantry

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ion species</td>
<td>$^{12}$C</td>
</tr>
<tr>
<td>Irradiation method</td>
<td>Scanning</td>
</tr>
<tr>
<td>Beam energy</td>
<td>430 MeV/n (max.)</td>
</tr>
<tr>
<td>Max. Field</td>
<td>$18 \times 18$ cm$^2$</td>
</tr>
<tr>
<td>Magnet</td>
<td>Superconducting Combined function</td>
</tr>
<tr>
<td>Num. of magnets</td>
<td>10</td>
</tr>
<tr>
<td>Magnetic field</td>
<td>$2.4 \sim 2.9$ T</td>
</tr>
<tr>
<td>Gantry radius</td>
<td>5.5 m</td>
</tr>
<tr>
<td>Gantry weight</td>
<td>$\sim 200$ t</td>
</tr>
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</table>
Beam delivery systems
– scanning pencil beam

- Raster scan method – scanning system
  - Deflection (x,y) of focused ion beams in fast dipole magnets

- Variation of the energy, focus and intensity in the accelerator complex and beam lines

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Haberer et al., NIM A, 1993
What remains to be done?

• Improve treatment of moving targets
  • Current method: gating
  • Future: active beam tracking

• Improve treatment planning

• Improve online verification of dose delivery

• Improve understanding of RBE

• Improve modeling the dynamics of tumor growth after irradiation

• ...
Verification of dose delivery (II)

- Quasi-online dose verification
  - proton-CT
    - high energetic proton beam (800 MeV) quasi simultaneously with therapeutic beam
    - Measurement of scattered protons: position (->multiple scattering) and energy (-> energy loss dE/dx)
    - 3D map of electron density in target -> online verification of dose plan

the principle and the prototype (UiB, Utrecht)
Clinical studies at NIRS

1) C-ion RT is successful in the not treatable by other means (radio-resistant tumors)
   - Advanced Head & Neck cancers (non-SCC)
   - Large skull base cancers
   - Post-op recurrent rectal cancer
   - Inoperable sarcoma
   - Re-irradiation after photon radiotherapy

2) Promising results are obtained in C-ion hypofractionated RT (common cancers)
   - Lung cancer (Single irradiation)
   - Liver cancer (Single & Two fractions)
   - Pancreatic cancer (8~12 fractions)
   - High risk prostate cancer (12~16 fractions)

T. Kamada, Carbon Ion Radiotherapy at NIRS, Chiba, 2013
Clinical results (NIRS) – skull base chordoma (I)

Pre-treatment  Dose distribution  67 months later

T. Kamada, Carbon Ion Radiotherapy at NIRS, Chiba, 2013
### Clinical results (NIRS) – skull base chordoma (II)

**Clinical characteristics of the reported cases of skull base chordoma**

<table>
<thead>
<tr>
<th></th>
<th>Authors</th>
<th>N</th>
<th>Median dose</th>
<th>Median f/u (y)</th>
<th>Local control rate (%)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>N</td>
<td></td>
<td></td>
<td>3-y</td>
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<tr>
<td><strong>Photon</strong></td>
<td>Catton et al. 1996</td>
<td>24</td>
<td>50</td>
<td>5.2</td>
<td>23</td>
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<tr>
<td></td>
<td>Romero et al. 1993</td>
<td>18</td>
<td>50</td>
<td>3.1</td>
<td>17</td>
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<tr>
<td></td>
<td>Forsyth et al. 1993</td>
<td>39</td>
<td>50</td>
<td>8.3</td>
<td>39</td>
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<tr>
<td></td>
<td>Magrini et al. 1992</td>
<td>12</td>
<td>58</td>
<td>6</td>
<td>25</td>
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<tr>
<td><strong>Proton (+/- photon)</strong></td>
<td>Munzenrider et al. (MGH) 1999</td>
<td>169</td>
<td>66-83</td>
<td>3.4</td>
<td>73</td>
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<tr>
<td></td>
<td>Noel et al. (CPO) 2003</td>
<td>100</td>
<td>67</td>
<td>2.6</td>
<td>86 (2y)</td>
</tr>
<tr>
<td></td>
<td>Igaki et al. (Tsukuba) 2004</td>
<td>13</td>
<td>72</td>
<td>5.8</td>
<td>67</td>
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<tr>
<td></td>
<td>Ares et al. (PSI) 2009</td>
<td>42</td>
<td>73.5 (mean)</td>
<td>3.2</td>
<td>81</td>
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<tr>
<td><strong>Helium</strong></td>
<td>Castro et al. (LB) 1994</td>
<td>53</td>
<td>65</td>
<td>4.3</td>
<td>63</td>
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<tr>
<td><strong>Carbon</strong></td>
<td>Shults-Ernter et al. (GSI) 2007</td>
<td>96</td>
<td>60 (mean)</td>
<td>2.6</td>
<td>81</td>
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<tr>
<td></td>
<td>Present study</td>
<td>44</td>
<td>60.8</td>
<td>4.8</td>
<td>91</td>
</tr>
</tbody>
</table>

T. Kamada, Carbon Ion Radiotherapy at NIRS, Chiba, 2013
Protokoll frå føretaksmøte
Helse Vest RHF

27. september 2013

Føretaksmøtet la til grunn at alternativet med etablering av mindre, regionale protonanlegg er eit godt alternativ for raskt å kunne tilby protonbehandling i Noreg og på lengre sikt mogeleg etablering av eit felles karbonanlegg i Noreg.

Føretaksmøte vedtok:

Norwegian prospects (II)

What can we hope for in Bergen?

- Combined proton and carbon facility
- State-of-the-art technology
  - fast scanning/repainting system
  - active energy modulation
  - beam gating system
  - several treatment rooms
  - superconducting gantry for carbon ions
Digital tracking calorimeter – rangemeter (IV)

- Validation of sensor simulation
  - Cluster sizes vs energy deposition - cluster sizes are larger than expected

 Cluster Size response for layer 1

 Cluster Size response for layer 4

 Number of Hits
Digital tracking calorimeter – rangemeter (V)

- Mean cluster size vs layer (range) for different beam energies
  - clear Bragg peak
  - 170 MeV: Bragg peak close to sensitive layer 5
  - 180 MeV: Bragg peak located inside absorber
  - 190 MeV: Bragg peak located between sensitive layer 6 and 7

-> to be compared with MC