Hadrontherapy
An Overview

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Chair of Radiation Oncology University of Milan & Scientific Director CNAO Foundation, Pavia

ANSTO, 8th October 2013, Sydney

Hadrontherapy

Alternative:
heavy particles radiotherapy
particle therapy
neutrontherapy, protontherapy
CIRT (Carbon Ion RT), ....

Hadrons
since 1993 .......

Hadrontherapy

Alternative:
Protons

- Proposed by Wilson in 1946 (Radiology, 1946)
- Years '50: first patients treated in Uppsala and Berkeley (Sweet WR, NEJM, 1951)
- Years '70: first patients treated in Russia and Japan
- In 1990 the first clinical centre at Loma Linda University (CA)
- First hospital-based proton-therapy centre
- First patient: 1992
- 7m synchrotron

Protontherapy: a market exists ...
Coming up: single room facility
250 MeV synchrocyclotron rotating around the patient

MEVION S250
Superconducting SC
Diameter 1.8 m

Carbon Ions

HIMAC
(Heavy Ion Medical Accelerator in Chiba)
The Hyogo ‘dual’ Centre

Mitsubishi: turn-key system
500 carbon patients

The Gunma University centre

R&D = NIRS + KEK + RIKEN
Construction: Mitsubishi
To date ..........

• Thousand and thousand and thousand of patients (>75,000) treated with protons

- Thousand and thousand of patients (>20,000) treated with neutrons

- Thousand of patients (>9,000) treated with carbon ions

\[ \text{ratio P+ / C12 = 9:1} \]

Protontherapy is booming (www.ptcog.psi.ch)
### Published Data in the years

<table>
<thead>
<tr>
<th>STUDIES YEARS</th>
<th>CLINIC</th>
<th>PHYSICS</th>
<th>BIOLOGY</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>2004-2007</td>
<td>100</td>
<td>41</td>
<td>21</td>
<td>162</td>
</tr>
<tr>
<td>2000-2003</td>
<td>46</td>
<td>29</td>
<td>18</td>
<td>93</td>
</tr>
<tr>
<td>1995-1999</td>
<td>27</td>
<td>33</td>
<td>8</td>
<td>68</td>
</tr>
</tbody>
</table>

2008-2012:
“Particle Beam Therapy”
521 papers (more than 160 related to clinic)

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In the next years there will be about 15 centres opened.
Five will offer both proton and C-ion therapy

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Europe

**Dual System C12/P+:**
- Heidelberg (D) open
- Pavia (I) open
- Marburg (D) January 2014
- Med Austron (A) October 2015
- Etoile (F) 2019?
Estimated 15,000 new eligible patients in Italy for protons

- Chordoma
- Chondrosarcoma
- Eye Melanoma
- Paediatric solid tumors

High priority
Estimated 7,000 patients with “radioresistant tumors” in Italy

About 20% of these tumors should be treated by ions

High priority

CNAO (National Center for Oncological Hadrontherapy) Syncrotron

P+ (60-250 MeV)
C-12 (400 MeV/n)
Physical Selectivity

- Inverted depth dose profile (Bragg peak)
- Defined penetration depth
- Less lateral scattering (\(1\text{H} \neq C_{12}\))
- Reduction of integral dose
Advantage of Protons

9 children primary CNS malignancies

Choclea:
average mean of 25 ± 4% of the prescribed dose from PRT; 75 ± 6% from photons

Temporal lobe:
40% of temporal lobe volume was completely excluded using protons; with photons 90% of the temporal lobe received 31% of the dose

Protons in pediatric tumors

<table>
<thead>
<tr>
<th>Protons</th>
<th>X-ray</th>
<th>IMRT</th>
<th>Proton</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTV</td>
<td>90%</td>
<td>90%</td>
<td>90%</td>
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<tr>
<td>Heart</td>
<td>18.2</td>
<td>17.4</td>
<td>0.1</td>
</tr>
<tr>
<td>Right lung</td>
<td>3.5</td>
<td>21.9</td>
<td>0.1</td>
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<tr>
<td>Esophagus</td>
<td>11.9</td>
<td>32.1</td>
<td>10.2</td>
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<tr>
<td>Stomach</td>
<td>3.7</td>
<td>20.6</td>
<td>0.1</td>
</tr>
<tr>
<td>Right kidney</td>
<td>3.3</td>
<td>29.8</td>
<td>0.1</td>
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<tr>
<td>Transvers colon</td>
<td>2.6</td>
<td>18.0</td>
<td>0.1</td>
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</tbody>
</table>
Integral Dose 3 times higher for all photon’s techniques

Weber DC et al, Radiat Oncol, 2009; 4:34

Chordoma: Base of Skull

- Base of skull chordomas account for ~1/3 of chordomas
PT in Skull Base Chordomas and Chondrosarcomas

<table>
<thead>
<tr>
<th>Reference</th>
<th>Institution</th>
<th>Pts</th>
<th>Histology</th>
<th>RT</th>
<th>GTV</th>
<th>Dose, mean (CGE)</th>
<th>5-y LC</th>
<th>F-up (Months)</th>
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</thead>
<tbody>
<tr>
<td>Hug et al, 1999</td>
<td>LLUMC</td>
<td>58</td>
<td>C (33)</td>
<td>X+p</td>
<td>9%</td>
<td>71.9 (66.6-79.2)</td>
<td>67</td>
<td>7.75</td>
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<td></td>
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<td>CS (25)</td>
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<tr>
<td>Munzenrider et al., 1999</td>
<td>MGH</td>
<td>290</td>
<td>C</td>
<td>X+p</td>
<td>NA</td>
<td>72 (70–75.6)</td>
<td>73</td>
<td>4.1</td>
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<td>Munzenrider et al. 1999</td>
<td>MGH</td>
<td>220</td>
<td>C</td>
<td>X+p</td>
<td>NA</td>
<td>72 (70–75.6)</td>
<td>73</td>
<td>4.1</td>
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<tr>
<td>Igaki et al, 2004</td>
<td>Tsukuba</td>
<td>136</td>
<td>C</td>
<td>X+p</td>
<td>NA</td>
<td>72 (70–75.6)</td>
<td>73</td>
<td>4.1</td>
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<tr>
<td>Noel et al, 2005</td>
<td>CPO</td>
<td>100</td>
<td>C</td>
<td>X+p</td>
<td>23 cm³ (1-125 cm³)</td>
<td>Median 67.0 (60.8-71.0)</td>
<td>86</td>
<td>4.8 (1-87)</td>
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<tr>
<td>Noel et al, 2004</td>
<td>CPO</td>
<td>26</td>
<td>Cs</td>
<td>X+p</td>
<td>NA</td>
<td>Median 67.0 (22-70)</td>
<td>91</td>
<td>3.4 (3-74)</td>
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<tr>
<td>Ares C et al, 2009</td>
<td>PSI</td>
<td>42</td>
<td>C (42)</td>
<td>X+p</td>
<td>≤25 mL, n=24 (C), n=15 (CS)</td>
<td>73.5 for C (87-74)</td>
<td>87</td>
<td>3.8 (14-92)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CS (22)</td>
<td></td>
<td>&gt; 25 mL, n=18 (C), n=7 (CS)</td>
<td>68.4 for CS (83-74)</td>
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</tbody>
</table>

5-y Local Control
Chordoma 59-81%
Chondrosarcoma 79-98%
The potential benefit of radiotherapy with protons in head and neck cancer with respect to normal tissue sparing: a systematic review of literature

Groningen & Maastricht, The Netherlands

- 14 in silico planning comparative (ISPC) studies
- Protons have the potential for a significantly lower normal tissue dose, while keeping similar or better target coverage
- Probability of reducing >25% salivary flow with IMRT is 22%, and with IMPT 9%
- Probability of reducing grade 2-4 swallowing dysfunction is reduced by 8.8% with IMRT, and by 17.2% with IMPT

The results of these ISPC studies should be confirmed in properly designed clinical trials
Biological Effectiveness (C12)

10 – 20 keV/μm = 100 – 200 MeV/cm =
20 – 40 eV/(2 nm)
Which tumors might benefit of high LET particles?

- Radioresistant for genetic alteration
- Up-regulated oncogenes
- Mutated tumor suppressor genes
- Dis-regulated apoptosis

- Radioresistant for intratumoral micromilieu
- Deprivation of oxygen
- Up-regulated defense system
- High angiogenetic potential

- Radioresistant for proliferation status
- High content of quiescent cell clones
- Slow proliferation activity

Carbon ion RT at NIRS

ACC 57.6GyE/16fr/4 wks

Pre RT 24 Months
5-year LC rate

Overall 68 %
MMM 75 %
ACC 73 %
Adenoca. 73 %
Papillary Adenoca. 61 %
SCC 61 %
Sarcomas 24 %
(with Max 64 GyE)

Mizoe J et al, Radiother Oncol, 2012

Carbon ion RT at NIRS

Bone and soft-tissue sarcoma

Pre RT 70.4 GyE/16f./4 wks 5 years
Table 4. Comparisons of overall survival and local control of sarcomas of the adult head and neck.

<table>
<thead>
<tr>
<th>Institution/year</th>
<th>Histology</th>
<th>Treatment</th>
<th>MOP (mo)</th>
<th>5-year LC (%)</th>
<th>5-year OS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSCMCC (12)</td>
<td>Soft-tissue sarcoma</td>
<td>Surgery ±X-ray ± chemo</td>
<td>112</td>
<td>139</td>
<td>45</td>
</tr>
<tr>
<td>RMH (21)</td>
<td>Soft-tissue sarcoma</td>
<td>Surgery ±X-ray ± chemo</td>
<td>103</td>
<td>50</td>
<td>47</td>
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<tr>
<td>MGH (22)</td>
<td>Soft-tissue sarcoma</td>
<td>Surgery ±X-ray ± chemo</td>
<td>46</td>
<td>50</td>
<td>69</td>
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<tr>
<td>UCSF (23)</td>
<td>Soft-tissue sarcoma</td>
<td>Surgery ±X-ray ± chemo</td>
<td>65</td>
<td>64</td>
<td>66</td>
</tr>
<tr>
<td>NCI (24)</td>
<td>Osteosarcoma</td>
<td>Surgery ±X-ray ± chemo</td>
<td>496</td>
<td>—</td>
<td>—</td>
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<tr>
<td>NIRS (current study)</td>
<td>Bone and soft-tissue sarcoma</td>
<td>Carbon ion RT</td>
<td>27</td>
<td>37.0</td>
<td>80.4</td>
</tr>
</tbody>
</table>

Abbreviations: LC = 5-year local control rate; MOP = median observation period; MSCMCC = M. Sklodowska-Curie Memorial Cancer Center; NCI = national cancer institute; NIRS = National Institute of Radiological Sciences; OS = 5-year overall survival; RMH = Royal Marsden Hospital; UCSF = university of california san francisco.
Malignant mucosal melanoma in head and neck

<table>
<thead>
<tr>
<th>Author</th>
<th>No.</th>
<th>Tumor location</th>
<th>Treatment modalities</th>
<th>5-year OS</th>
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</thead>
<tbody>
<tr>
<td>Gilligan</td>
<td>28</td>
<td>Sinonasal</td>
<td>Radiotherapy</td>
<td>18</td>
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<tr>
<td>Shibuya</td>
<td>28</td>
<td>Upper jaw</td>
<td>Radiotherapy +/- surgery</td>
<td>25</td>
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<tr>
<td>Shah</td>
<td>74</td>
<td>Head and neck</td>
<td>Surgery +/- radiotherapy</td>
<td>22</td>
</tr>
<tr>
<td>Chaudhry</td>
<td>41</td>
<td>Head and neck</td>
<td>Surgery +/- radiotherapy +/- chemotherapy (BCG, melphalan)</td>
<td>28</td>
</tr>
<tr>
<td>Lund</td>
<td>58</td>
<td>Sinonasal</td>
<td>Surgery +/- postoperative radiotherapy +/- chemotherapy</td>
<td>28*</td>
</tr>
<tr>
<td>Pandey</td>
<td>60</td>
<td>Head and neck</td>
<td>Surgery +/- radiotherapy +/- chemotherapy</td>
<td>32</td>
</tr>
<tr>
<td>Chang</td>
<td>163</td>
<td>Head and neck</td>
<td>Surgery +/- radiotherapy +/- chemotherapy</td>
<td>35</td>
</tr>
<tr>
<td>Patel</td>
<td>59</td>
<td>Sinonasal and oral</td>
<td>Surgery +/- postoperative radiotherapy +/- chemotherapy</td>
<td>35</td>
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<tr>
<td>Stern</td>
<td>42</td>
<td>Sinonasal and oral</td>
<td>Surgery +/- radiotherapy +/- chemotherapy +/- immunotherapy</td>
<td>40</td>
</tr>
<tr>
<td>Guzzo</td>
<td>48</td>
<td>Head and neck</td>
<td>Surgery +/- radiotherapy +/- chemotherapy +/- immunotherapy</td>
<td>21</td>
</tr>
<tr>
<td>Wada</td>
<td>31</td>
<td>Head and neck</td>
<td>Surgery +/- radiotherapy +/- chemotherapy</td>
<td>33*</td>
</tr>
<tr>
<td>NIRS-1(9602)</td>
<td>100</td>
<td>Head and neck</td>
<td>Carbon ion radiotherapy</td>
<td>36</td>
</tr>
<tr>
<td>NIRS-2(0007)</td>
<td>82</td>
<td>Head and neck</td>
<td>Carbon ion radiotherapy +/- chemotherapy</td>
<td>62</td>
</tr>
</tbody>
</table>

Hadron Therapy: What is happening at CNAO?
Main Tasks:

- Dosimetry characterisation
- Radiobiology characterisation
- Patient treatment

Proton Radiobiology

3 cell lines: HSG (human salivary gland tumour), T98G (human glioblastoma), V79 (Chinese hamster lung fibroblast)

Field 10x10 cm², 33x33 spots, scanning step 3 mm
**Carbon ions**

**Animals**

**Group Leader:**
Yoshiya Furusawa, NIRS, Chiba

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**X-ray Patient Verification System (PVS)**
- 2 X-ray tubes (deployable) + 2 flat panels (deployable)
- Supporting structure rotation: ±180°
- Rotation and deployment accuracy: ±0.15mm, ±0.1°

**Patient Positioning System (PPS)**
- Automatic couch or chair docking
- Absolute accuracy: ±0.3 mm

**3D Real-time IR Optical Tracking (OTS)**
- Real time reconstruction of spherical markers and surfaces
- Sub-millimeter accuracy: peak 3D errors <0.5 mm
- 3D data flow at 70 Hz

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22 September 2011
Chondrosarcoma G2

Contouring with image fusion TC/RM
T1 post gadolinium

sequences in T2
Dose distribution
RBE value 1.1

Optical & X-ray tracking systems for set-up verification
CNAO Protocol P/01:
closed 13th February 2013

30 patients enrolled
14 males/16 females
53 ys median age (range 15-75)
26 chordomas/4 chondrosarcomas:
7 radical surgery
23 subtotal surgery/biopsy

No Interruption of treatment
No Grade 3-4 toxicity
No Progression of disease (SD)

Changes in size (volume cc)

3 Months after and every 3 months
### Prescription doses (GyE)
(16 fractions, 4 fractions per week)

<table>
<thead>
<tr>
<th>Indication</th>
<th>NIRS dose (GyE)</th>
<th>CNAO dose (GyE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opposed ports</td>
<td>q.e.</td>
<td>q.e.</td>
</tr>
<tr>
<td>Cube s Spheres Cubes Spheres Cubes Spheres Cubes Spheres</td>
<td>3.6 4.2 4.15 4.2 4.15 4.2 4.15 4.19</td>
<td>3.8 4.35 4.3 4.35 4.3 4.35 4.3 4.33</td>
</tr>
<tr>
<td>Skull base chordoma and chondrosarcoma</td>
<td>4.4 4.8 4.7 4.8 4.7 4.8 4.7 4.75</td>
<td>4.4 4.8 4.75 4.8 4.75 4.8 4.75 4.78</td>
</tr>
<tr>
<td>Spinal chordoma and chondrosarcoma</td>
<td>4.4 4.8 4.75 4.8 4.75 4.8 4.75 4.78</td>
<td></td>
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</tbody>
</table>


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**13 November 2012**

Local recurrence of adenoideocistic carcinoma involving pterigopalatina fossae, orbital apex, right cavernous sinus and medium skull, already treated with surgery and RT (60 Gy) in 1995
- Carbon ion
- 12 fractions of 4.1 GyE each, 4 frs x week, 49.2 GyE total
- Boost with 4 additional fractions, same fractionation
- 3 fixed fields by IMPT

Dose distribution
What in the next future?

2012: 60 patients
2013: 300 patients (3 rooms)
2014: 700 patients (moving target)
2015: 1200 patients (time 8:00am-9:00pm)

20% with protons
80% with carbon ions
Different endpoints, not only in LC & S, but in QoL and other surrogate markers

Multicentric/Multidisciplinary ESTRO, EORTC, PTCOG, National Societies

Altered Fractionation Hypofractionation

“Difficult” tumors, not only for dose distribution, but for biology

High Tech RT vs Proton vs Carbon & Mixed beam

Molecular Imaging & Biology driven

Thank you very much for your attention !!!