ACCELERATING INNOVATION ... IN MEDICINE

CERN, Geneva
20th November 2014

Particles that fight cancer:
The use of protons and carbon ions in cancer therapy

Roberto Orecchia
Chair of Radiation Oncology at the University of Milan
Scientific Director at European Institute of Oncology in Milan and at The National Centre of Oncological Hadrontherapy in Pavia
12.7 million new cases per year worldwide

7.6 million deaths

63% of deaths in developing countries
Numbers of RT Treatments

30 years ago: less than 40% of patients with cancer

15 years ago: more than 50%

Today: about 65%

RT contributes towards 40% of curative treatment

Only 5% of the total cost of cancer care
The Future of Radiation Therapy......,

JCO 2010

Expected Patients from 2010 to 2020 (+ 22%)

Prostate + 35%

Liver + 26%

Lung + 25%

Stomach + 27%

Pancreas + 25%

Breast + 15%
Improvement in Technology

Improvement in Dose Distribution
Baclesse: daily doses of 200R (1.8 Gy) given over 10 minutes using regimens of up to 4 months

Coutard: daily fractions lasting 2-3 hours on regimen lasting 4-6 weeks

The Early 1920s

Once more reliable equipment became available, single fraction treatments were tried, with German speakers more in favour of massive single dose, “Terapia Magna Sterilans” and Francophones delivering ”Fractionated treatment”
As a result of his influence and teaching there is a belief amongst radiation oncologists in the USA that to treat using fewer than 30 fractions is inherently dangerous.
Since '60
Evolution in Radiation Therapy
High Tecnology & IGRT/IMRT/SRT
High Tecnology
& BRT
Our goal ...
Dose Distribution?

Is not a clinical issue

but

It's the condition necessary to improve clinical outcomes
Adaptive treatment planning

Scifoni et al, GS Rep. 2010
Santiago A. ULICE Rep 2011
Improved Dose Distribution

Technology

- Smaller volume
- Higher dose

\[ \text{Inverse Square Law} \]

\[ \Rightarrow \text{LC & Survival} \]

\[ \leq \text{Toxicity} \]

\[ \Rightarrow \text{Shorter treatment} \]
Hadrons. A new dimension ......
Physical Selectivity

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

A-PROTONS

B-PHOTONS
Protons in pediatric tumors
Radiobiology of particles

Graph showing RBE (Relative Biological Effectiveness) vs LET (Linear Energy Transfer) with peaks labeled p, C, and Ne.
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
- High angiogenic potential

**Radioresistant for proliferation status**
- Up-regulated defense system
- High content of quiescent cell clones
- Slow proliferation activity
122,499 treated patients
- 105,743 with p+, mainly in USA, 53,532
  Loma Linda 17,829, Boston (NPTC) 7,345
- 13,119 with C-12, mainly in Japan, 10,993
  Nirs (Chiba) 8,073, HIT (Heidelberg) 1,368
+ 46,000 in the past 5 years
≈ 10,000 patients per year

www.ptcog.psi.ch
Some numbers …..

42 centres with protons
(USA 14, Europe 12, Japan 8, .....)

6 centres with carbon ions
(Japan 3, Europe 2, China 1)
of these, 3 dual centres (p+ C-12)

27 new centres planned
Worldwide Access to Hadrons
The ULICE project is co-funded by the European Commission under FP7 Grant Agreement Number 228436.

Map of Europe with symbols indicating sites under construction, in operation, and in planning stage.

- **Under construction**
- **In operation**
- **In planning stage**
Literature survey
In-silico studies
Cancer Registry

Standard Indications

Improved Local Control

Reduced Side Effects

Reduced Second Tumors

Recommends to treat

Recommends to investigate
Standard Indications
1% of RT
Eye, Pediatrics, Base of skull

Improved LC
3% of RT
Intracranial, H&N, Urologic, Lung, Sarcoma, Reirradiation

Reduced Side Effects
12% of RT
Intracranial, H&N, Urologic, Lung, Breast, GI, Lymphoma, Sarcoma, Gynecological

Reduced Second Tumors
2% of RT
Breast, Lymphoma, Testis
Chordoma: Base of Skull

- Base of skull chordomas account for ~1/3 of chordomas
<table>
<thead>
<tr>
<th>Reference</th>
<th>Institution</th>
<th>Pts</th>
<th>Histo-logy</th>
<th>RT</th>
<th>GTV</th>
<th>Dose , mean (CGE)</th>
<th>% LC</th>
<th>F-up (Months)</th>
</tr>
</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%): 0 to ≤15 mL (12%): &gt;15 to ≤25 mL (79%): &gt;25 mL</td>
<td>71.9 (66.6-79.2)</td>
<td>3 yrs: 67 (C)</td>
<td>3 yrs: 67 (C)</td>
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<td></td>
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<td>CS (25)</td>
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<td>5 yrs: 59</td>
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<td>33 (7-75)</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>
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<td>5 yrs: 73</td>
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<td>41 (1-254)</td>
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<td>Igaki et al, 2004</td>
<td>Tsukuba</td>
<td>13</td>
<td>C</td>
<td></td>
<td></td>
<td>Median 72.0 (63.0 -95.0)</td>
<td>3 yrs: 67.1 (C)</td>
<td>5 yrs: 46.0</td>
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<td>69.3 (14.6-123. 4)</td>
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<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 (60.0-71.0)</td>
<td>2 yrs: 86 (C)</td>
<td>3 yrs: 91 (CS)</td>
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<td>4 yrs: 53</td>
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<td>31 (0-87)</td>
</tr>
<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></td>
<td>3 yrs: 91</td>
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<td>34 (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>p</td>
<td>≤25 mL n=24 (C) , n= 15 (CS) &gt; 25 mL n=18 (C) , n= 7 (CS)</td>
<td>73.5 for C (67-74)</td>
<td>3 yrs: 87 (C)</td>
<td>3 yrs: 94 (CS)</td>
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<td>CS (22)</td>
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<td>5 yrs: 81</td>
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<td>38 (14-92)</td>
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</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
**PROGETTO DI SPERIMENTAZIONE CLINICA**

A CURA DI:
- Erminio Borioni – Presidente
- Roberto Oracchia – Direttore Scientifico
- Sandro Rossi – Segretario Generale e Direttore Tecnico

**IL CENTRO NAZIONALE DI ADROTERAPIA ONCOLOGICA**
Strada Privata Campeggi – 27100 Pavia

Presented to:
- Italian Ministry of Health
- Lombardy Region

**Main Tasks:**
- Dosimetric characterization
- Radiobiological characterization
- 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

(16 energies)
Cell Survival vs Depth
Dose uniformity

Carbon Ion Radiobiology
Set-up

Horizontal beam, direction ventral - dorsal

3 animals per field
Comparison of RBE results (CNAO vs GSI \ NIRS)
Experimental Activity

Between January 2012 and December 2013

147 patients have been treated in the framework of 23 clinical prospective phase II protocols.

With the aim to prove safety and effectiveness of CNAO Beam

CE label -> CNAO Sinchrotron

Patients in routine clinical practice since January 2014
2014 Clinical Activity: Total number of patients >350

- Skull base chordoma and chondrosarcoma
- Spinal and sacral chordoma and chondrosarcoma
- Intracranial Meningioma
- Boost for locally advanced head and neck cancer
- Salivary gland tumors
- Spine and H&N bone and soft tissue sarcoma
- Mucosal melanoma
- Recurrent pleomorphic adenoma
- Reirradiation of head and neck tumors
- Orbital tumor
- High risk prostate cancer
- Locally advanced pancreatic cancer
- Reirradiation of local recurrence rectal cancer
- Hepatocarcinoma
<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Number</th>
</tr>
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<tbody>
<tr>
<td>Salivary gland tumors</td>
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</tr>
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<tr>
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</tr>
<tr>
<td>Sarcoma</td>
<td>32</td>
</tr>
<tr>
<td>Retreatment local recurrence rectal cancer</td>
<td>1</td>
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<tr>
<td>HCC</td>
<td>1</td>
</tr>
<tr>
<td>Local advanced pancreatic cancer</td>
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</tr>
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</table>
## Adenoid Cystic Carcinoma 34 patients

### Pre-treatment Imaging
- CT
- MRI with contrast
- PET with C11 metionina

### Prescription doses
- PTV1 Dose (low risk volume)
  - 38.7 Gy RBE /9 fractions
- PTV2 Dose (High risk volume)
  - 30.1 Gy RBE /7 fractions
- Total dose: 68.8 Gy RBE/16 fractions
Clinical case

Pre- CIRT

62 year old female

ACC left Meckel cave

21/05/2013 temporal craniotomy and biopsy
CIRT: \[68.8 \text{ Gy}(\text{RBE}) \ (4.3 \text{ Gy}(\text{RBE})/\text{fraction}, \ 16 \text{ fractions, 4 fractions/weekly}\]
May 2014 (9 months)
Radiological control of disease confirmed by MRI.
Late Tox G0
Clinical case

53 year old male

ACC in parafaringeal region with extension on clivus and petrous bone

07/2013 Nasopharynx biopsy: El adenoide cistic carcinoma

15/10/2013 -- 07/11/2013 CIRT 68.8 Gy [RBE]
Toxicity at the end of CIRT: erythema G1, mucositis G1
Partial Remission and Acute Toxicity G0 after 3 months

PET metionine: significant decrease in MET uptake after 3 months

PET metionine at 6 months: negative

PET pre CIRT

PET after 6 months
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</table>
Recurrent ACC already treated by 60 Gy conventional RT and surgery in 1995

Clinical case
CIRT:  60 Gy E ; 15 fr;  4 Gy E /fr
Skin toxicity

End of treatment

4 months after
Before treatment

4 months after
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<td>1</td>
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</table>
Clinical case

75 year old men

March 2013: endoscopic surgery R2

No CT for age and coomorbidity

CIRT: 68.8 Gy [RBE] / 16 fractions
FOLLOW-UP 9 AND 12 Months
tox G1 - CR
During CIRT

End of CIRT

Mucositis

Erytema

6 months
<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Count</th>
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## Toxicity

<table>
<thead>
<tr>
<th></th>
<th>Max during treat</th>
<th>End of treat</th>
<th>3 months</th>
<th>6 months</th>
<th>9 months</th>
<th>12 months</th>
<th>15 months</th>
<th>18 months</th>
<th>21 months</th>
<th>24 months</th>
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<tr>
<td>Pz</td>
<td>142</td>
<td>142</td>
<td>115</td>
<td>97</td>
<td>72</td>
<td>60</td>
<td>39</td>
<td>35</td>
<td>18</td>
<td>11</td>
</tr>
<tr>
<td>G0</td>
<td>38</td>
<td>48</td>
<td>69</td>
<td>56</td>
<td>40</td>
<td>36</td>
<td>22</td>
<td>17</td>
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<tr>
<td>G1</td>
<td>56</td>
<td>56</td>
<td>28</td>
<td>29</td>
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<td>9</td>
<td>10</td>
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<td>G2</td>
<td>46</td>
<td>37</td>
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<td>G3</td>
<td>2*</td>
<td>1*</td>
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<td>1**</td>
<td>4***</td>
<td>3***</td>
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<td>1++</td>
</tr>
</tbody>
</table>

* Mucositis and Reactivation of herpes zoster infection responsive to antiviral drugs
** Hearing impairment with acoustic device
*** 2 hearing impairment 1 stroke 1 partial blindness
**** 1 blindness ++ 1 intestinal perforation
G1 Skin toxicity
G2 Skin toxicity
G2 Skin toxicity
G2 Skin toxicity
CLINICAL CASE
SKULL BASE CHORDOMA: Proton therapy

10 months F-up
Sacral chordoma, male, 69 years old
After one year hypoesthesia at the left foot: G1 toxicity, marked improvement in urinary and rectal continence, and pain, patient can sit and can walk for 15-20 minutes.
<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Cases</th>
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Yes, but how much does it cost?

High Tech
An Evidence-Based review of the role of Particle Therapy in the treatment of prostate cancer
Improvement in Technology

Improvement in Dose Distribution
The gray scale of appropriateness
Patient Treatment Plan Comparison
Photons vs Hadrons

NTCP
Small or absent

Randomized Clinical Trial

NTCP
Moderate or questionable

NTCP
Major in favour of P+

Photons

Hadrons
Technology Transfer in Clinics

Thanks for your attention !!!!!!!