The Clinics of Hadron Therapy

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A short introduction
Improvement in Technology

Improvement in Dose Distribution
Radiotherapy worldwide and in Europe

- 7,500 operating centers
- 11,500 treatment rooms
- ≈2 M/patients/y
- ≈ 50% of all cancers

Global Cancer Observatory – GLOBOCAN 2020; Lievens Y, Borras JM, Grau C. Mol Oncol 2020
In operation

Under construction

*12 with Carbon Ions

**5 under construction

104* operating centers
180 treatment rooms
38** under construction
28 in planning (*)

P ≈ 250,000
C ≈ 40,000

ratio P+/C_12 6.4 : 1

Patients treated with Protons and C-ions worldwide

PTCOG Website 2022
Hadron Therapy: from lighter to heavier ions
First patients treated in 1975 at Bevalac, Berkeley (CA) even ion properties were well know since the beginning of years ‘50

2000 patients treated with helium ions and 500 with neon ions in 20 years

In 1994 the first patient treated with carbon ions in Japan
First hospital-based Carbon Ion Radiotherapy center
Some numbers
Carbon Ions Centers worldwide

China
- 2 in operation
- 1 under construction
- 1 in planning

South Korea
- 2 under construction

Japan
- 6 in operation
- 1 under construction

Taiwan
- 1 under construction

South Korea
- 2 under construction

Japan
- 6 in operation
- 1 under construction

Taiwan
- 1 under construction

CNAO, Pavia

ARCHADE Caen

HIT Heidelberg
- MIT Marburg

MED-AUSTRON
- MIT Marburg
- Wiener Neustadt

PTCOG Website, April 2022
Number of eligible patients for CIRT in USA

Estimated percentage and number of patients likely benefiting using inclusion criteria from clinical trials and retrospective studies

- **Glioblastoma**: 1,000 patients
- **Hepatocellular Carcinoma**: 3,734 patients
- **Cholangiocarcinoma**: 415 patients
- **Pancreas**: 574 patients
- **Sarcoma**: 484 patients
- **Head and Neck**: 3,714 patients

8922 patients estimated (10% of those eligible based on inclusion criteria)

Applying the adaption correction rate, and excluding prostate and lung cancers, this number is expected to increase by 25% in 2025

Malouff TD et Al. Int J Particle Ther 2020
Patients selection methods

- Clinical decision-making tools
  - Informed decision-making
  - Diagnosis/clinical indications list
  - Multi-disciplinary team consensus
  - Cost-effectiveness

- Dose comparative methods
  - Comparative planning/dosimetry
  - NTCP (between plans)
  - Knowledge-based DVH prediction
  - Influence diagram
  - Different prediction softwares
  - Radiobiologic Markov model
  - Risk analysis/long-term outcomes

- Hybrid techniques
  - PRODECIS (computer generated model that selects modality based on dosimetry, toxicity levels and cost-effectiveness)

The rules in Italy

- Chordoma & Chondrosarcoma skull base/spine
- Meningiomas (skull base)
- Brain tumors (high/low grade, trunk)
- Adenoid Cystic Carcinoma (ACC) salivary glands
- Orbit tumors including Eye Melanoma
- Sinonasal carcinoma
- Soft Tissue & Bone sarcomas (every sites)
- Recurrent tumors (re-treatments)
- Patients with immunological syndromes
- Paediatric solid tumors

Reimbursed by NHS

About 7,000 new cases per year

About 7,000 new cases per year

Patients selection methods

- Clinical decision-making tools
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- Hybrid techniques
  - PRODECIS (computer generated model that selects modality based on dosimetry, toxicity levels and cost-effectiveness)
The lack of a gold standard

Paediatric patients/tumors

Adults patients/tumors

The Dutch Model-Based (NTCP)

- **Standard indication**
  - Skull base or spinal chordoma and chondrosarcoma
  - Other intracranial, spinal, and paraspinal tumors, including meningioma
  - Pediatric tumors, including bone tumors, soft-tissue sarcoma, low-grade glioma, meningioma, medulloblastoma, ependymoma, and neuroblastoma
- **Potential indications** (cases for which protons may be specifically utilized to improve local control)
  - Re-irradiation (malignant brain tumors, head and neck cancer)
  - Paranasal sinus tumors, nasopharyngeal carcinoma, prostate, NSCLC, retroperitoneal sarcoma
  - Model based indication (cases where proton will be utilized to reduce side effect)
    - Re-irradiation (meningioma, head and neck cancer)
    - Head and neck cancers, prostate
    - Reduction of secondary cancer
    - Breast cancer
    - Lymphoma
    - Testis

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**National Protocol for Model-Based Selection for Proton Therapy in Head and Neck Cancer**

- **VMAT (protons)**
- **IMPT (protons)**

**HNC patients**
- **(n=227)**
- **Non-protocol tumor location**
  - (n=38, 12%)
- **Unsuitable for protons**
  - (n=27, 12%)
- **Preselection Tool**
- **Plan comparison**
- **Photons**
  - (n=147, 65%)
- **Protons**
  - (n=80, 35%)

**Expected (NTCP) all patients**
- **Observed rate should be S expected**

**NTCP=VMAT (Photons)**
- **Predefined NTCP criteria met?**
  - **YES**
    - Treatment with IMPT (protons)
  - **NO**
    - Treatment with VMAT (photons)

**NTCP=IMPT (Protons)**
- **Predefined NTCP criteria met?**
  - **YES**
    - Treatment with IMPT (protons)
  - **NO**
    - Treatment with VMAT (photons)

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Lagendijk JA et Al. Sem Radiat Oncol 2018 & Int J Particle Ther 2021; Tambas M et Al. Radiother Oncol 2020
A new trend in selecting patients

From rare tumors ...

... to more frequent tumors

- Head & Neck (pharynx, paranasal sinuses)
- Lung (including advanced stage)
- Breast (left)
- Esophagus
- Liver
- Pancreas
- Rectum
- Uterus
- Lymphomas

- ..... ....
Favourable outcomes in radioresistant H&N tumours, such as MMM and ACC.

In sacral chordoma, a 5-year LC and OS rates of 88% and 86%. Good LC reported also in skull-base tumours.

About 1000 patients with prostate cancer treated with hypo-fractionation with very good outcomes.

5-year LC of 81% in HCC with a negligible hepatic impairment. Since 2003, 2 fractions/3 days, with minor toxicity.

In locally recurrent rectal cancer, high LC, DFS and OS (93%, 51% and 45%).

In pancreatic cancer CIRT combined with gemcitabine: 2-year LC and OS of 58% and 54%. Median survival 2 times longer than the best standard option.

Results of CIRT on ACC

CIRT alone
289 patients in Japan
2-y OS, PFS, and LC: 94%, 68%, and 88%
15% G≥3 toxicity, 2 death
Nasopharynx (2-y LC: 88%), paranasal sinuses (3-y LC: 79%, 5-y LC: 51%), tongue (5-y LC: 92%), parotid (5-y LC: 74.5%), lacrimal gland (5-y LC: 62%)

CIRT as a boost
3-year LC of 62% at HIT
59 NP patients in Japan
2-y LC, dPFS, and OS: 83%, 81%, and 87%
Acute G3 in 7 patients, late G3 in 4 patients

CIRT in adjuvant setting
Sinonasal patients 3-y LC 82%
Acute toxicity 41.6%

Loap P et Al. Front Oncol 2021
CNAO Clinical experience on ACC

- 128 patients
- CIRT 68.8 Gy(RBE)/16 fx/4 fx/wk
- PFS 12/24 months: 81%/67%
- DMFS 12/24 months: 86%/81%
- OS 12/24 months: 95%/85%
- Median Survival 24 months

Late toxicity

- G4: one bleeding requiring surgery
- one epidural abscess

14 relapses close to OARs
9 pts close to the spared Optic Nerve
Results of CIRT on recurrent ACC

Reirradiation of salivary gland tumors with carbon ion radiotherapy at CNAO


rcT4a (51%) and rcT4b (37%). MD prior RT 60 Gy. MD CIRT 60 Gy [RBE], 3 Gy/fraction

Stable Disease 41.2%, Tumor Progression 58.8%

Acute and late G3 toxicities 3.9% and 17.5%

Vischioni B et Al, Radiother Oncol 2020; Loap P et Al. Front Oncol 2021
Chordoma the second ...
<table>
<thead>
<tr>
<th>Study</th>
<th>Tumor Type</th>
<th>Radiation Type</th>
<th>Carbon Dose</th>
<th>5-y Local Control</th>
<th>10-y Local Control</th>
<th>5-y Overall Survival</th>
<th>10-y Overall Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mizoe et al, 2009</td>
<td>Chordoma</td>
<td>Carbon</td>
<td>60.8 GyEq</td>
<td>LC 85% (5y)</td>
<td>LC 64% (10y)</td>
<td>OS 88% (5y)</td>
<td>OS 67% (10y)</td>
</tr>
<tr>
<td>Uhl et al, 2014</td>
<td>Chondrosarcoma</td>
<td>Carbon ion</td>
<td>5 GyEq</td>
<td>LC 72% (5y)</td>
<td>LC 54% (10y)</td>
<td>OS 85% (5y)</td>
<td>OS 75% (10y)</td>
</tr>
<tr>
<td>Uhl et al, 2014</td>
<td>Chondrosarcoma</td>
<td>Carbon</td>
<td>60 GyEq</td>
<td>LC 88% (5y)</td>
<td>LC 88% (10y)</td>
<td>OS 96% (5y)</td>
<td>OS 79% (10y)</td>
</tr>
</tbody>
</table>
High Control Rates of Proton- and Carbon-Ion-Beam Treatment With Intensity-Modulated Active Raster Scanning in 101 Patients With Skull Base Chondrosarcoma at the Heidelberg Ion Beam Therapy Center

**HIT Studies**

a) *Randomised trial proton vs carbon ion in chordoma of the skull base* (BMC Cancer, 2010)

b) *Randomised trial proton vs carbon ion in low and intermediate chondrosarcoma of the skull base* (BMC Cancer, 2010)

Mattke M et al, Cancer 2018
Skull-Base Chordoma: a customized approach

This prospective study evaluates PT outcomes in view of personalized medicine. For the first time the choice of particle (P+ and C-12) was based on multiple features regarding tumor characteristics, toxicity risk, and post-surgery outcomes.

Proton and carbon ion radiotherapy in skull base chordomas: a prospective study based on a dual particle and a patient-customized treatment strategy

Alberto Iannalfi, Emma D'Ippolito, Giulia Riva, Silvia Molinelli, Sara Gandini, Gisela Viselner, Maria Rosaria Fiore, Barbara Vischioni, Viviana Vitolo, Maria Bonora, Sara Ronchi, Rachele Petrucci, Amelia Barcellini, Alfredo Miranda, Stefania Russo, Alessandro Vai, Edoardo Mastella, Giuseppe Magro, Davide Maestri, Mario Ciocca, Lorenzo Preda, Francesca Valvo, and Roberto Orecchia

Local Control
PT: 84%
CIRT: 71%

GTV median
PT: 3.5 cm³
CIRT: 13 cm³

Overall Survival
PT: 83%
CIRT: 82%

On multivariate analysis, GTV, optic pathways, and/or brainstem compression and dose coverage are independent prognostic factors.

Toxicity G ≥3 in 11% of patients.

Iannalfi A et Al. Neuro Oncol 2020
Skull-Base Chordoma: attempt for predictive models

To derive personalized TCP models, using (DW-) MRI for defining initial tumor cellular density. The inclusion of the cellular density derived from ADC into TCP\textsubscript{ADC} yielded slightly higher dose values at which TCP = 0.5 \[D_{50} = 38.91 \text{ Gy (RBE)}\] with respect to TCP\textsubscript{LIT} \[D_{50} = 34.16 \text{ Gy (RBE)}\].
These analyses predicting the risk of adverse LC were implemented integrating MRI, CT, dose maps, and clinical features. Promising results in terms of performance and generalization abilities are observed. Validation is needed before these models can be applied in the clinical practice.
Head & Neck cancers: MedAustron protocols

### Carbon Ion Dose Constraints in the Head and Neck and Skull Base: Review of MedAustron Institutional Protocols

<table>
<thead>
<tr>
<th>Disease</th>
<th>Total dose, Gy RBE (LEM)</th>
<th>Dose/fraction, Gy RBE (LEM)</th>
<th>Total No. of fractions</th>
<th>Fractions/wk</th>
<th>Comment, schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microsomal melanoma</td>
<td>65 RBE–69 RBE</td>
<td>4.1–4.3</td>
<td>16</td>
<td>4</td>
<td>Japanese</td>
</tr>
<tr>
<td>Salivary glands (no ENI)</td>
<td>65.6–66.8</td>
<td>4.1–4.3</td>
<td>16</td>
<td>4</td>
<td>Japanese</td>
</tr>
<tr>
<td>Paranasal sinuses (no ENI)</td>
<td>65.6–68.8</td>
<td>4.1–4.3</td>
<td>16</td>
<td>4</td>
<td>Japanese</td>
</tr>
<tr>
<td>Sarcoma, except skull base chordoma</td>
<td>76.8</td>
<td>4.8</td>
<td>16</td>
<td>4</td>
<td>Japanese</td>
</tr>
<tr>
<td>Skull base chordoma</td>
<td>66</td>
<td>3</td>
<td>22</td>
<td>5</td>
<td>German</td>
</tr>
<tr>
<td>Salivary gland with ENI (low-LET photon RT up to 50 Gy, then CIRT boost)</td>
<td>24</td>
<td>3</td>
<td>8</td>
<td>5</td>
<td>German</td>
</tr>
<tr>
<td>Paranasal sinuses with ENI (low-LET photon RT up to 50 Gy, then CIRT boost)</td>
<td>24</td>
<td>3</td>
<td>8</td>
<td>5</td>
<td>German</td>
</tr>
</tbody>
</table>

**Fractionation Safe constraint, Gy RBE (LEM)**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Low-to-medium risk, Gy RBE (LEM)</th>
<th>Medium-to-high risk, Gy RBE (LEM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Japanese</td>
<td>$D_{15} \leq 50$</td>
<td>$D_{15} \leq 54$</td>
</tr>
<tr>
<td></td>
<td>$D_{2500} \leq 40$</td>
<td>$D_{2500} \leq 40$</td>
</tr>
<tr>
<td>German</td>
<td>$D_{15} \leq 54$</td>
<td>$D_{15} \leq 57$</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Disease</th>
<th>Low-to-medium risk, Gy RBE (LEM)</th>
<th>Medium-to-high risk, Gy RBE (LEM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Japanese</td>
<td>$D_{2500} \leq 30$</td>
<td>$D_{2500} \leq 40$</td>
</tr>
<tr>
<td></td>
<td>$D_{2500} &lt; 40$ and $D_{1000} &lt; 30$</td>
<td>NA</td>
</tr>
<tr>
<td>German</td>
<td>$D_{2500} &lt; 8$</td>
<td>$D_{mean} &lt; 40$</td>
</tr>
<tr>
<td></td>
<td>$D_{mean} &lt; 30$</td>
<td>$D_{mean} &lt; 40$</td>
</tr>
<tr>
<td></td>
<td>$D_{2500} &lt; 40$</td>
<td>$D_{2500} &lt; 45$</td>
</tr>
<tr>
<td></td>
<td>$D_{2500} &lt; 40$</td>
<td>$D_{2500} &lt; 45$</td>
</tr>
</tbody>
</table>

**Normal constraint, Gy RBE (LEM)**

| Japanese and German                    | $D_{mean} < 30$                 | $D_{mean} < 43$                  |
|                                        | $D_{mean} < 26$                 | $D_{mean} < 20$                  |

**Carbon ion protocols by treatment volume for head and neck and skull base**

<table>
<thead>
<tr>
<th>Treatment volume</th>
<th>Japanese</th>
<th>German</th>
</tr>
</thead>
<tbody>
<tr>
<td>$D_{0.1cm^3}$</td>
<td>$&lt; 46$</td>
<td>$&lt; 38$</td>
</tr>
<tr>
<td>$D_{0.7cm^3}$</td>
<td>$&lt; 46$</td>
<td>$&lt; 38$</td>
</tr>
<tr>
<td>$D_{2cm^3}$</td>
<td>$&lt; 50$</td>
<td>$&lt; 50$</td>
</tr>
<tr>
<td>$D_{max}$</td>
<td>$&lt; 54$</td>
<td>$&lt; 54$</td>
</tr>
</tbody>
</table>

Fossati P et Al. Int J Particle Ther 2021
Lung cancer: Particle Therapy versus SBRT

3y LC
PBT 87.4%
SBRT 86.1%

3y OS: PBT 69.5%, SBRT 58.8%
p<0.05

5y OS: CIRT 60.0%, SBRT 41.3%
p<0.05

3y LC: PBT 93.3%, SBRT 70.7%
p<0.05

3y PFS: PBT 63.5%, SBRT 50.7%
p<0.05

5y PFS: PBT 57.2%, SBRT 37.7%
p<0.05

Comparison of Oncologic Outcomes between Carbon Ion Radiotherapy and Stereotactic Body Radiotherapy for Early-Stage Non-Small Cell Lung Cancer

Propensity score matching/adjusted analysis
CIRT: 52.8-60 Gy / 4 fr
SBRT: 48 Gy / 4 fr

3y OS: CIRT 93.3%, SBRT 55.0%
5y OS: CIRT 71.8%, SBRT 34.4%

3y LC: CIRT 92.3%, SBRT 70.7%
3y LC: CIRT 92.3%, SBRT 42.4%

Meta-analysis
PBT: 9 studies
SBRT: 72 studies

Meta-analysis
PBT 9 studies
SBRT 72 studies
CIRT in patients with coexisting Interstitial Lung Disease

The first study to compare safety and efficacy of CIRT in this groups

In stage I NSCLC, CIRT is safe in the ILD as in the non-ILD group
In the ILD group increased risk after SBRT

Coexisting ILD remains a poor prognostic factor for OS

Okano N et Al. Cancers 2021

### Radiation pneumonitis G≥2 with or without ILD

<table>
<thead>
<tr>
<th>Authors</th>
<th>Treatment Modality</th>
<th>Number of Patients (ILD+)/(ILD−)</th>
<th>Dose and Fractionation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yoshitake T et al. [38]</td>
<td>SBRT</td>
<td>18/242</td>
<td>48 Gy/4 fr</td>
</tr>
<tr>
<td>Nakamura M et al. [39]</td>
<td>SBRT</td>
<td>7/49</td>
<td>48−56 Gy/4 fr</td>
</tr>
<tr>
<td>Okubo M et al. [40]</td>
<td>SBRT</td>
<td>11/60</td>
<td>40−60 Gy/5−10 fr</td>
</tr>
<tr>
<td>Tsurugai Y et al. [41]</td>
<td>SBRT</td>
<td>42/466</td>
<td>40 or 50 Gy/5 fr</td>
</tr>
<tr>
<td>Glick D et al. [21]</td>
<td>SBRT</td>
<td>39/498</td>
<td>60 Gy/8 fr</td>
</tr>
<tr>
<td>Ikemig H et al. [22]</td>
<td>SBRT</td>
<td>30/474</td>
<td>54−60 Gy/3 fr</td>
</tr>
<tr>
<td>Present study</td>
<td>CIRT</td>
<td>26/98</td>
<td>52.8 or 60.0 Gy (RBF)/4 fr</td>
</tr>
</tbody>
</table>

#### OS and LC with or without ILD

<table>
<thead>
<tr>
<th>Authors</th>
<th>Treatment Modality</th>
<th>Number of Patients (ILD+)/(ILD−)</th>
<th>ILD(+)</th>
<th>ILD(−)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present study</td>
<td>CIRT</td>
<td>26/98</td>
<td></td>
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The first study to compare safety and efficacy of CIRT in this groups

In stage I NSCLC, CIRT is safe in the ILD as in the non-ILD group
In the ILD group increased risk after SBRT

Coexisting ILD remains a poor prognostic factor for OS

Okano N et Al. Cancers 2021
CIRT in hepatocellular carcinoma: an overview

- Surgical resection, thermal ablation, and liver transplant remain the gold standard treatment, with favourable clinical outcome

- Physical and biological properties of CIRT allow hypofractionation and dose-escalation

- Less risk for RILD (Radiation Induced Liver Disease)
  - CIRT used in special scenarios:
    - Older patients (over 80)
    - Larger tumours (> 10 cm)
    - Proximity to the porta hepatis (<2 cm)
    - Liver cirrhosis/Child-Pugh B and C
    - Recurrent or remnant lesions after other local therapies

- Liver-related minimal toxicity
Liver cancer: the Japanese and Italian experiences

CIRT in Gumna
11 patients, median dose 60 Gy/4 fr or 60 Gy/12 fr
Low toxicity

PT in Trento
The first clinical experience in Europe
18 patients, median dose 58.05 Gy

One-year OS 63%
Significant correlation between OS and performance status, vascular invasion, T-stage
One-year LC 90%
Low toxicity
No RILD

Shiba et al. Radiat Oncol 2020; Dionisi F et al. Tumori J 2021
Pancreatic cancer: the Japanese experience

Multi-institutional Study of Carbon-ion Radiotherapy for Locally Advanced Pancreatic Cancer: Japan Carbon-ion Radiation Oncology Study Group (J-CROS) Study 1403 Pancreas

J-CROS institutions prospective clinical trial is under way

Kawashiro S et Al. Int J Radiat Oncol Biol Phys 2018
Pancreatic cancer: the German experience

Differences with the Japanese study

- **Dose concept**
  48 Gy (RBE) versus 55.2 Gy (RBE) but doses cannot be compared (LEM I-based approach at HIT)

- **Volume concept**
  ENI and neuro-plexus region in the Japanese CTV
  Volume as small is possible and without ENI in Germany

- **Concomitant CT**
  In Japan 1.000 mg/m² GEM
  In Germany only 14% with CT

- **Selection bias**
  67% of patients pre-treated with CT

Liermann J et Al. Front Oncol 2021
Mixed-beam approach for HR-Pca: an Italian protocol

AIRC IG-14300
Phase II, prospective, multicentric study

Adenocarcinoma of the prostate, high risk (cT3a, and/or PSA>20 ng/ml, and/or GS 8-10)

Anticipated PTV C-12 boost 16.6 gy (RBE)
4 fractions/1 week (EqD2Gy 24Gy)
Pelvic IMRT 45-50.4 Gy in conventional fractionation

<table>
<thead>
<tr>
<th>Tissue</th>
<th>CI + IMRT (%)</th>
<th>IMRT-only (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RECTUM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D0.03 cm³ (%)</td>
<td>98.9%</td>
<td>100.0%</td>
</tr>
<tr>
<td>V20 Gy (%)</td>
<td>0.8%</td>
<td>2.4%</td>
</tr>
<tr>
<td>V40 Gy (%)</td>
<td>3.4%</td>
<td>5.9%</td>
</tr>
<tr>
<td>V60 Gy (%)</td>
<td>40.0%</td>
<td>80.0%</td>
</tr>
<tr>
<td>URINARY BLADDER</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D0.03 cm³ (%)</td>
<td>98.8%</td>
<td>101.9%</td>
</tr>
<tr>
<td>V20 Gy (%)</td>
<td>1.8%</td>
<td>6.0%</td>
</tr>
<tr>
<td>V40 Gy (%)</td>
<td>36.9%</td>
<td>70.0%</td>
</tr>
<tr>
<td>FEMORAL HEADS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>V60 Gy (%)</td>
<td>1.8%</td>
<td>0.9%</td>
</tr>
<tr>
<td>ANUS CAVITY</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dmax (Gy)</td>
<td>17.6</td>
<td>25.9</td>
</tr>
<tr>
<td>PENILE BULB</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D0.03 cm³ (Gy)</td>
<td>48.9</td>
<td>55.4</td>
</tr>
<tr>
<td>Dmax (Gy)</td>
<td>11.3</td>
<td>15.2</td>
</tr>
</tbody>
</table>

Marvaso G et Al. Tumori J 2017; Gugliandolo SG et Al. Phys Med 2020; Russo S et Al. Front Oncol 2021
AIRC-IG-14300. HR Pca: preliminary results

Only acute toxicity events

As of today, no biochemical recurrence

Patient- and physician-reported outcomes were overall satisfactory

The only exception was represented by the erectile function, worsening at the end of RT and at 12 months (cumulative side effects of ADT and RT?)

Marvaso G et Al. Front Oncol 2021
More Evidence-Based
CIRT clinical trials. Status

63 clinical trials, 84% no randomized
Median intended enrollment 47 patients (from 6 to 689)
Most trials in Japan: 38 (60%), Germany: 16 (25%), China: 7 (11%), and Italy: 1 (2%)
One trial (2%) on radioresistant H&N tumors in France

Lazar AA et Al. Cancer 2018
Primary endpoint for the majority of clinical trials (32 of 63; 51%) was adverse events (13) or toxicity and/or dose response (19). LC only in 15 (24%), PFS in 9 (14%), and OS in 7 (11%). Of the 10 R trials, only 1 phase II trial included OS as the primary endpoint, (2 PFS).

Recommendations to accelerate progress in the field

1) increase number of multinational randomized clinical trials
2) leverage existing CIRT facilities to launch larger multinational trials directed at common cancers with high-level quality assurance
3) develop more compact and less expensive next-generation treatment systems integrated with radiobiologic research and preclinical testing

Lazar AA et Al. Cancer 2018
Early clinical prospective and retrospective studies suggested safety and efficacy of Ions for a variety of cancer sites.

To-date, based on comparative data, the clinical outcomes of Ions are NEVER inferior (SOMETIMES superior …)

On the contrary, OFTEN an increase in local control rate is observed in many tumours (complex sites, different histologies, hypoxic mass, …)

In some sites (H&N, as example) less toxicities are reported, with very positive impact on the QoL of the patients.

Ions in combination with new and advanced treatment modalities is not sufficiently investigated.
The need for cooperation

- **ENLIGHT (2002 -....)**, to coordinate European efforts in PT (hadrontherapy), with focus primarily on basic and translational research issue within ion beam therapy

- **ULICE (2009 - 2014)**, to respond to the need for greater access to hadron therapy facilities for PT research. Funded by EU grant (8.4 M€), with 20 leading European research organizations, including 2 industrial partners

- **INSPIRE (2019 -....)**, funded by EU, complements for collaborative networking, transnational access and joint research activities
Further integrate the activities of ENLIGHT and EPTN, in the first place by having back-to-back annual meetings.

EPTN will also actively collaborate with PTCOG, founded in 1985 with the mission of promote science, technology and clinical application of PT for cancer care.

In 2013, PTCOG North America was additionally created a non-profit professional society to foster collaboration between US centers and to develop education and training.

The key difference is that EPTN will interact with health care politics, the various European health care systems and professional societies as an integrated part of RO, utilizing the interdisciplinary structure of ESTRO.
About 400 clinical studies on PT are ongoing, and new data will come from www.clinicaltrials.gov, PTCOG Website.

Most patients don’t accept the results of a flip of a coin.
Prospective data registration and clinical trials for particle therapy in Europe

Johannes A. Langendijk, Roberto Orecchia, Karin Haustermans, Daniel Zips, Jacques Balosso, Denis Lacombe, Yolande Lievens, Damien C. Weber, Cai Graul, Esther G.C. Troost

The European Particle Therapy Network
ESTRO & EORTC Vision

E²-RADIatE Steering Committee

OligoCare
ParticleCare
Cohort X

Core E²-RADIatE Data Items
Specific data items

Langendijk JA et Al. Radiother Oncol 2018
A new project started in Europe...
The world’s first superconducting gantry at HIMAC

<table>
<thead>
<tr>
<th>Specification</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment rooms</td>
<td>Rooms E and F; H and V beams in each</td>
</tr>
<tr>
<td></td>
<td>Room G: Rotating gantry (26 possible angles)</td>
</tr>
<tr>
<td>Accelerated energies</td>
<td>140–430 MeV/u</td>
</tr>
<tr>
<td>Range</td>
<td>Up to 30 cm</td>
</tr>
<tr>
<td>Field size</td>
<td>22 × 22 cm in rooms E and F</td>
</tr>
<tr>
<td></td>
<td>20 × 20 cm in room G (compared to 15 × 15 cm in the HIMAC)</td>
</tr>
<tr>
<td>Dose rate</td>
<td>Up to 5 GyE/min</td>
</tr>
<tr>
<td>Irradiation method</td>
<td>3D fast rescanning with gating for moving targets</td>
</tr>
<tr>
<td>Scanning technology</td>
<td>Multiple-energy operation with extended flattops with &gt;200 energy steps</td>
</tr>
</tbody>
</table>
A new model of gantry in planning at CNAO

R&D: carbon ions gantry
Collaboration CNAO-INFN-CERN-MedAustron under discussion: start 2021, 4 years project

The success with the use of superconducting magnet technologies opens the field to the design and construction of smaller and cheaper synchrotrons.

SIGRUM
Superconducting Ion Gantry with Riboni’s Unconventional Mechanics
Treatment monitoring by in-beam PET

Monte Carlo simulation tool for online treatment monitoring in hadrontherapy with in-beam PET: A patient study

INSIDE in-beam PET scanner

Pearson’s Correlation Coefficient analysis in time

Evolution of the beam-induced activity in time

Fiorina E et Al. Phys Med 2018
Auto-activation positron emission tomography (AAPET)

Use of a Si/CdTe Compton Camera for *In vivo* Real-Time Monitoring of Annihilation Gamma Rays Generated by Carbon Ion Beam Irradiation


Shiba S et Al. *Front Oncol* 2020; Shiba S et Al. *In vivo* 2021
RBE, a complex quantity

Considerable uncertainty with dosimetric planning, with 3 different model for calculating RBE each yielding a different dose and fractionation scheme

- Mixed-beam model (passive scanning in Japan)
- Microdosimetric kinetic model (MKM) (active scanning in Japan)
- Local effect model (LEM) (for raster scan, in Europe)

- To retrospectively compare results of different facilities nominal reported RBE weighted doses are not sufficient
- In prospective multicentric trials prescription doses and dose constraints should not be set at nominal identical values but on adapted values minimizing the difference of the delivered treatments

Inaniwa T et Al. Phys Med Biol 2015; Fossati P et Al. Med Phys 2018
Future directions
CICR (Combined Ion-beam with Constant RBE) Biologically robust treatment is feasible combining heavy and light ions in a single field yielding uniform effective dose within the CTV Multi-Ions (P+, He, C-12) improve target conformality and reduce dose and LET_d in normal tissue

Kopp B et Al. Int J Radiat Oncol Biol Phys 2020; Ebner DK et Al. Front Oncol 2021
INSPirit. A new source at CNAO

Supports and quadripoles in the synchrotron room

CNAO-INFN-HiFuture collaboration

Superconducting magnet

Diagnostics of the beam

End of 2022
C-ions and targeted therapy combination

Konings K et Al. Front Oncol 2020; Tinganelli W & Durante M. Cancers 2020
PT has the potential to inflict higher immunogenicity than X-rays, especially CIRT, due to more unrepaired DNA damage and genomic mutations or instability.
Research, Research, and Research

Ultra HDR
MICROBEAM

Research, Research, and Research
Ultra High Dose Rate

Comparative toxicity of synchrotron and conventional radiation therapy based on total and partial body irradiation in a murine model

Smyth LML et Al, Sci Report/Nature 2018

Ultra high dose rate Synchrotron Microbeam Radiation Therapy. Preclinical evidence in view of a clinical transfer

Eling L et Al, Radiother Oncol 2019

Imaging and Medical Beamline (IMBL), Australian Synchrotron, Clayton

Biomedical Beamline (ID17) of the European synchrotron ESRF, Grenoble

Laser-plasma accelerated beams PHASER project, Stanford University, USA