Conclusion and Future Perspectives

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University of Liverpool / Cockcroft Institute
Look into the future

- Workshop at Archamps, June 2018
- [indico.cern.ch/event/682210](indico.cern.ch/event/682210)

- Where do we want to go next?
What is the main obstacle to proton therapy replacing X-rays?

- Cost/benefit ratio: 35
- Range uncertainties: 33
- Protons will never replace X-rays: 19

Slides courtesy M. Durante, GSI
Protons stop...
Treating moving targets

- **Motion**: Geometric miss of target
- **Range changes**: Position of Bragg Peak under motion
- **Interplay**: Interference between scanning and tumor motion
- **Current solution**: ITV, rescanning
- **Future**: 4DTP, online tracking

Courtesy of Christian Graeff, GSI, Germany
In situ control with PET

Before collision
Projectile $^{12}\text{C}$
Atomic nuclei of tissue $^{16}\text{O}$

After collision
Projectile fragment $^{11}\text{C}$ Neutrons Target fragment $^{15}\text{O}$

dose plan
measured

Courtesy of Wolfgang Enghardt, HZDR, Dresden
Future: imaging with RIB

<table>
<thead>
<tr>
<th>Positron-emitting accelerated ion</th>
<th>Half-life (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{10}$C</td>
<td>0.32</td>
</tr>
<tr>
<td>$^{11}$C</td>
<td>20.3</td>
</tr>
<tr>
<td>$^{15}$O</td>
<td>2.04</td>
</tr>
</tbody>
</table>

Reducing costs: accelerators

1954 | Now | Mañana

- Cyclotron
- Synchrotron
- Small synchrocyclotron
- Linac
- FFAG
- Lasers

Quality vs. Current Useability

Courtesy of Marco Schippers, PSI
This is happening today in the market

IBA/SHI – 250 Ton Isochronous Cyclotron

Varian – 90 Ton Isochronous Cyclotron

IBA – 60 Ton Synchrocyclotron

MEVION – 15 Ton Synchrocyclotron
Plan of Miniaturizing Machine

1st Model: HIMAC
2nd Model: GHMC
3rd Model
4th Model: Next Generation
5th Model: Future Type

Courtesy of Dr. Kojii Noda
Table 1 | Ongoing randomized clinical trials comparing different radiation modalities for the same disease

<table>
<thead>
<tr>
<th>Study</th>
<th>Institution</th>
<th>Phase</th>
<th>Condition</th>
<th>Radiation arm 1</th>
<th>Radiation arm 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>R03CA188162: IMPT vs IMRT</td>
<td>MDACC</td>
<td>III</td>
<td>Oropharyngeal cancer (head and neck cancer)</td>
<td>Protons*</td>
<td>X-rays*</td>
</tr>
<tr>
<td>PARTIQoL (NCT01617161): proton therapy vs IMRT</td>
<td>MGH</td>
<td>III</td>
<td>Low-risk or intermediate-risk prostate cancer</td>
<td>Protons</td>
<td>X-rays</td>
</tr>
<tr>
<td>NCT01512589: proton-beam therapy vs IMRT</td>
<td>MDACC</td>
<td>III</td>
<td>Oesophageal cancer</td>
<td>Protons*</td>
<td>X-rays*</td>
</tr>
<tr>
<td>RADCORE (NCT02603341): pragmatic randomized trial of proton vs photon therapy</td>
<td>PTCORI</td>
<td>III</td>
<td>Post-mastectomy stage II or III breast cancer</td>
<td>Protons</td>
<td>X-rays</td>
</tr>
<tr>
<td>NRG BN001: dose-escalated IMRT or IMPT vs conventional photon radiation</td>
<td>NRG Oncology</td>
<td>II</td>
<td>Newly diagnosed glioblastoma</td>
<td>Protons*</td>
<td>X-rays*</td>
</tr>
<tr>
<td>NRG 1542: proton radiation vs conventional photon radiation</td>
<td>NRG Oncology</td>
<td>III</td>
<td>Hepatocellular carcinoma</td>
<td>Protons</td>
<td>X-rays</td>
</tr>
<tr>
<td>NCT01182753: proton radiation vs carbon-ion radiation therapy</td>
<td>Heidelberg University, Germany</td>
<td>III</td>
<td>Low-grade and intermediate-grade chondrosarcoma of the skull base</td>
<td>Protons</td>
<td>Carbon ions</td>
</tr>
<tr>
<td>NCT01182779: proton radiation vs carbon-ion radiation therapy</td>
<td>Heidelberg University, Germany</td>
<td>III</td>
<td>Chordoma of the skull base</td>
<td>Protons</td>
<td>Carbon ions</td>
</tr>
<tr>
<td>CLEOPATRA (NCT01165671): proton radiation vs carbon-ion radiotherapy</td>
<td>Heidelberg University, Germany</td>
<td>II</td>
<td>Primary glioblastoma</td>
<td>Protons*</td>
<td>Carbon ions*</td>
</tr>
<tr>
<td>IPI (NCT01641185): proton radiation vs carbon-ion radiotherapy</td>
<td>Heidelberg University, Germany</td>
<td>II</td>
<td>Prostate cancer</td>
<td>Protons</td>
<td>Carbon ions</td>
</tr>
<tr>
<td>ISAC (NCT01811394): proton radiation vs carbon-ion radiation therapy</td>
<td>Heidelberg University, Germany</td>
<td>II</td>
<td>Sacrococcygeal chordoma</td>
<td>Protons</td>
<td>Carbon ions</td>
</tr>
<tr>
<td>ETOILE (NCT02838602): carbon-ion radiotherapy vs IMRT</td>
<td>Lyon University Hospital, France</td>
<td>III</td>
<td>Radioresistant adenoid cystic carcinoma and sarcomas</td>
<td>Carbon ions</td>
<td>IMRT</td>
</tr>
<tr>
<td>BAA-N01CM51007-51: prospective trial of carbon-ion therapy vs IMRT</td>
<td>NCI</td>
<td>I/III</td>
<td>Locally advanced pancreatic cancer</td>
<td>Carbon ions*</td>
<td>X-rays*</td>
</tr>
<tr>
<td>CIPHER: prospective multicentre randomized trial of carbon-ion radiotherapy vs conventional radiotherapy</td>
<td>UTSW</td>
<td>III</td>
<td>Locally advanced pancreatic cancer</td>
<td>Carbon ions*</td>
<td>X-rays*</td>
</tr>
</tbody>
</table>

**Convincing the non-believers: phase-III clinical trials**

The big question: shall we need radiotherapy at all in the future?
Metastatic Melanoma Response to Ipilimumab

Before Ipilimumab
04/22/11

After Ipilimumab
08/05/11

Courtesy of Dr. Paolo Ascierto, Istituto Pascale, Naples, Italy
A new cancer immunotherapy suffers a setback

An exciting drug failed in a large trial, triggering a retreat and raising questions about the field’s frantic pace

By Ken Garber

The surprising failure last month of a large clinical trial of a promising cancer immunotherapy drug from the biotech company Incyte has quickly reverberated across the pharmaceutical industry. Three companies have canceled, suspended, or downsized 12 other phase III trials of the compound, epacadostat, or two similar drugs, together slated to enroll more than 5,000 patients with a variety of advanced cancers.

The companies say they aren’t dropping the potential drugs, designed to unleash the immune system on cancer cells by blocking an enzyme called indoleamine (2,3)-dioxygenase (IDO). But the retrenching suggests that the frenzy to combine novel drugs with the wildly successful immunotherapies known as checkpoint inhibitors is outpacing the science (Science, 23 March, p. 1546).

The IDO strategy, says neurooncologist Michael Platten of the University of Heidelberg in Germany, “has been moved to many different strategies.”

The results from smaller, phase II trials don’t always predict how a cancer drug will do in a randomized phase III trial. But the epacadostat data “were pretty compelling,” says Yale University immuno-oncologist Mario Sznol, who expected to see some benefit to patients. (Sznol was not involved in treated? “You could go through the whole list of reasons,” Sznol says.

The field still generally agrees that IDO makes sense to target, in combination with checkpoint inhibitors. Those drugs release a molecular brake on tumor-killing immune T cells. But the unleashed cells then stimulate the production of IDO, which, in a negative feedback loop, shuts them down again. IDO does this mainly by indirectly activating a protein inside immune cells called the aryl hydrocarbon receptor (AHR). Suppressing IDO should therefore make checkpoint inhibitors work better.

But much about IDO remains unknown, Platten says. Exactly how IDO stifles the immune system is unresolved, nor is it clear which immune cells are most involved, he says. Even the idea that IDO blunts the antitumor effects of checkpoint inhibitors is suspect. “The evidence that this is really happening in the clinical situation ... is very slim,” Platten says.

The drug, not the target, might be the problem. Some IDO inhibitors bind the AHR and thus could suppress the immune system, the opposite of the drug’s intent. NewLink Genetics reports that its drug does activate the AHR, but in a way that it still believes promotes a strong immune response against tumors. Both Incyte and Eli Lilly and Company say their drugs do not affect the AHR.

Levi Garraway, Eli Lilly’s senior vice president of oncology global development and medical affairs in Indianapolis, says that going forward the company will try to select patients who are most likely to respond to IDO inhibitors, using unspecified biomarkers. At a recent cancer meeting, immuno-oncologist Tom Gajewski of the University of Chicago in Illinois noted that biomarker analysis in the IDO trials has been “lagging.” The epacadostat trial failure, he added, is “a good wake-up call to make sure all the boxes are checked” for new combination therapies. But companies may still be tempted to press ahead with limited data. “There can be a sense of, ‘I’d better act now,’”
Proton therapy facilities

- Existing/planned proton facilities in Europe

Source: CERN
Proton therapy facilities

- Number of proton facilities in Europe

![Graph showing the number of proton therapy centers in Europe over time from 2000 to 2025. The number of centers increases significantly over time.](image)
New therapy centres

Basic concepts for a
SOUTH-EAST EUROPE
INTERNATIONAL INSTITUTE FOR
SUSTAINABLE TECHNOLOGIES
(SEEIIST)

January 15, 2018
Funding opportunities

- Medical R&D
- Technology transfer developments
  - ATTRACT
  - EIC
  - MSCA individual Fellows
  - ERC
  - Etc

- Brexit?
OMA Events

- International Schools on medical accelerators and Monte Carlo simulations;
- Topical Workshops on focused research topics – all material available online;
- Symposium and Final Conference this year to engage wider community and general public.
28 June 2019 in Liverpool, UK

indico.cern.ch/event/798052/

Talks via live-stream
Join in! Participate via social media
Conferences

- International conference on particle therapy
- Seville, Spain
- 4-6 September 2019
- [indico.cern.ch/event/803528/](indico.cern.ch/event/803528/)
- Contributed talks, poster session, proceedings
URL: (http://www.)oma-project.eu
Summary

- Future of particle therapy will depend on solution of technical issues (e.g., online imaging, range uncertainty) and decreasing cost/benefit ratio.

- While industry is progressing in reducing size and costs, no major breakthroughs in past 20 years.

- Good time to establish R&D programs – huge expertise in OMA – this School highlighted many of the needs.

- Opportunities everywhere: national funding, KT, EIC, H2020 Design studies, etc.

Exciting field – still a LOT to be done.

I look forward to seeing you at next OMA events.