Clinical Trials In Particle Therapy

Hak Choy, MD
UT Southwestern
Dallas, Texas
"Proton Therapy is Superior to the Conventional Radiation Therapy (Photon)."
"Proton Therapy is *Superior* to the Conventional Radiation Therapy (Photon)."

*Los Angeles Times* | Business

Blue Shield of California to curb coverage of pricey cancer therapy

Blue Shield says the high cost of some proton beam therapies for cancer treatment compared with conventional radiation isn't justified. The decision comes as hospitals build high-tech facilities.

By Chad Terhune

August 28, 2013 | 6:16 p.m.
"Proton/Carbon (Hadron) Radiotherapy is Superior to Intensity Modulated Radiotherapy (IMRT)."
"Proton/Carbon (Hadron) Radiotherapy is Superior to Intensity Modulated Radiotherapy (IMRT)."
In Comparing Proton Beam Therapy with Other Modalities
“Is PBT better than IMRT?”
1. “It has not, as of yet, sufficiently answered the question on the minds of patients, care providers, and policy makers across the country.”
2. “Given the clear limitations in the available data and the lack of consensus regarding the comparative effectiveness of PBT and photon-based radiotherapy, a more rigorous and definitive study in needed.”
2D vs. 3D vs. IMRT vs. Proton

Superior?

Grand Unification of Sciences
"Proton/Carbon (Hadron) Radiotherapy is Superior to Intensity Modulated Radiotherapy (IMRT)."

Superior?  How many phase III Trials Completed Comparing IMRT Vs Proton Therapy?

"0"
Dose Distribution Advantage

Relative dose deposited in the tissue

- X rays 8 MV
- Protons 230 MeV
- Electrons 20 MeV
- Cobalt photons 60

Depth of the tissue

0 = Skin level

0 - 32 cm
The Proton plan delivers less scatter radiation dose to the pelvis compared to IMRT plan (axial view). Protons IMRT

**RED** is high dose, **GREEN** is intermediate dose, **BLUE** is lower dose

**Protons**

**RED**: PTV $\rightarrow$ related to TUMOR Control $\rightarrow$ LC and OS

**GREEN**: Surrounding critical Normal Tissue $\rightarrow$ Toxicity, QOL

**BLUE**: V5 $\rightarrow$ possible 2$^{nd}$ malignancy
The Proton plan delivers less scatter radiation dose to the pelvis compared to IMRT plan (axial view) Protons IMRT

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**RED** : PTV $\rightarrow$ related to TUMOR Control $\rightarrow$ LC and OS

**GREEN**; Surrounding critical Normal Tissue $\rightarrow$ Toxicity, QOL

**BLUE** : V5 $\rightarrow$ possible 2$^{nd}$ malignancy
How can **WE** prove the Proton Radiotherapy is Superior to Intensity Modulated Radiotherapy (IMRT)?

1. Understanding the impact on biologically-effective proton dose distributions delivered to the patient
2. Linear energy transfer (LET) guided plan optimization with intensity modulated proton therapy (IMPT)
3. Minimize the uncertainties: dose distribution, range uncertainty, intra-fractional motion, inter-fractional anatomic changes
4. Randomized Phase III trials in certain Tumor
# RTOG 1308

**Phase III Randomized Trial Comparing Overall Survival after Photon versus Proton Radiochemotherapy for Inoperable Stage II-IIIIB NSCLC**

## SCHEMA

**Arm 1:** Photon

- **Stage:**
  1. II
  2. IIIA
  3. IIIB

- **GTV Volume:**
  1. $\leq 130$ cc
  2. $> 130$ cc

- **Histology:**
  1. Squamous
  2. Non-Squamous

- **Neoadjuvant Chemo:**
  1. No
  2. Yes

- **Randomized:**
  - photon dose—Higher achievable dose between 60-70 Gy, once daily plus platinum-based doublet chemotherapy*

**Arm 2:** Proton

- **Stage:**
  1. II
  2. IIIA
  3. IIIB

- **GTV Volume:**
  1. $\leq 130$ cc
  2. $> 130$ cc

- **Histology:**
  1. Squamous
  2. Non-Squamous

- **Neoadjuvant Chemo:**
  1. No
  2. Yes

- **Randomized:**
  - proton dose—Higher achievable dose between 60-70 Gy (RBE), once daily plus platinum-based doublet chemotherapy*  

**Both Arms:**

- Consolidation chemotherapy x 2 is allowed*
PCORI: Patient-Centered Outcomes Research Institute

Pragmatic Randomized Trial of Proton vs. Photon Therapy for Patients with Stage II or III Breast Cancer

Principal Investigator Justin Bekelman, MD
Pragmatic Randomized Trial of Proton vs. Photon Therapy for Patients with Stage II or III Breast Cancer

The primary outcomes: major cardiovascular events, such as heart attacks, chest pain, and other heart problems
Number of pts need to be randomized: 1716
Project Budget: $11,830,530
Phase III: Proton Beam or Intensity-Modulated Radiation Therapy in Treating Patients with Low or Low-Intermediate Risk Prostate Cancer

Jason Alexander Efstathiou, Principal Investigator

PRIMARY OBJECTIVES:

I. Compare the reduction in mean Expanded Prostate Cancer Index Composite (EPIC) bowel scores for men with low or intermediate risk prostate cancer (PCa) treated with PBT versus IMRT at 24 months following radiation (where higher scores represent better outcomes).

SECONDARY OBJECTIVES:

I. Assess the effectiveness of PBT versus IMRT for men with low or intermediate risk PCa in terms of disease-specific quality of life as measured by patient-reported outcomes, perceptions of care and adverse events.

II. Assess the cost-effectiveness of PBT versus IMRT under current conditions and model future cost-effectiveness for alternative treatment delivery and cost scenarios.
Clinical Trials: IMPT vs. IMRT

| 1) Brain Tumors                  | RANDOMIZATION |
| 2) H/N Cancer                   | IMRT          |
| 3) Breast Cancer                |               |
| 4) Lung Cancer                  | IMPT          |
| 5) HCC                          |               |
| 6) Prostate Cancer              |               |
How about the Carbon Therapy?
What is Heavy Ion therapy?

It is a radiation therapy with accelerated nuclei of He-4, Li-6, Be-8, B-10, C-12 …
1) Heavy Ions Stop In Tumor
2) Heavy Ions exhibit low entrance dose
3) Heavy Ions – have very sharp edges

- Sharp Carbon
- Proton or X-ray
4) Heavy Ions – Are Magnetically Controlled to Very High Precision
5) Heavy Ions – Offer Unique Verification of Energy Deposition
The biological responses seen after heavy charged particle exposure is mostly driven by the unique pattern of energy deposition

- Energy deposition patterns become more discrete

X-rays $\ll 1$ keV/um
Protons @ 200 MeV, 20 keV/um
Carbon @ 390 MeV, 112 keV/um
Oxygen @ 468 MeV, 175 keV/um
Discrete patterns of energy deposition result in clustered DNA damage and greater cell killing.
Enhanced cell killing described by Relative Biological Effectiveness

- Common RBE values:
  - X-ray (reference) 1.0
  - Protons 1.0 - 1.2
  - Carbon 2 - 4
Heavy charged particles can overcome radioresistance due to hypoxia

- Hypoxia limits the efficacy of radiotherapy
Decreased repair between dose fractions with heavy charged particles

- Conventional radiotherapy delivers dose in daily fractions
  - Daily schedule based on potential for
  - Tumor reoxygenation
  - Normal tissue sparing (1920s)
Advantages with heavy charged particles: Physics and BIOLOGY!

- Enhanced cell killing for the same amount of dose
  - Opportunities to treat radioresistant tumors

- Potential to enhance tumor response in hypoxic settings

- Limited tumor sparing with dose fractionation
  - Precise placement of dose limits normal tissue exposure

- Novel tissue effects
  - Dose thresholds achieved at lower dose
  - Enhanced immunologic response
  - Reduction in metastatic potential
## Chemoradiotherapy for Locally Advanced Pancreatic Cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Treatment</th>
<th>Radiation Dose (Gy)</th>
<th>Local Control (%)</th>
<th>Survival Rate (%)</th>
<th>1-yr</th>
<th>1.5-yr</th>
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<tbody>
<tr>
<td>ECOG (1985)</td>
<td>47</td>
<td>5FU + RT</td>
<td>40</td>
<td>68</td>
<td>32</td>
<td>11</td>
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<tr>
<td></td>
<td>44</td>
<td>5FU alone</td>
<td>-</td>
<td>68</td>
<td>26</td>
<td>21</td>
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<td>Crane (2002)</td>
<td>61</td>
<td>5FU + RT</td>
<td>30</td>
<td>46</td>
<td>28</td>
<td>7</td>
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<tr>
<td></td>
<td>34</td>
<td>GEM + RT</td>
<td>30</td>
<td>45</td>
<td>42</td>
<td>12</td>
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<tr>
<td>Okusaka</td>
<td>42</td>
<td>GEM + RT</td>
<td>50.4</td>
<td>94</td>
<td>28</td>
<td>25</td>
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<tr>
<td>Murphy (2007)</td>
<td>74</td>
<td>GEM + RT</td>
<td>20-42</td>
<td>74</td>
<td>46</td>
<td>24</td>
<td></td>
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<tr>
<td>NIRS (2012)</td>
<td>46</td>
<td>Carbon ion</td>
<td>45.6-52.8</td>
<td>87</td>
<td>47</td>
<td>26</td>
<td></td>
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<tr>
<td>NIRS (2013)</td>
<td>47</td>
<td>GEM + Carbon</td>
<td>45.6-55.2</td>
<td>-</td>
<td>74</td>
<td></td>
<td>54 (2yr)</td>
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</tbody>
</table>

GEM: Gemcitabine

More than Doubled Survival Rate!
Local Control and Survival Rates with Different Modalities for Mucosal Malignant Melanoma

<table>
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<tr>
<th>Authors</th>
<th>N</th>
<th>Modality</th>
<th>5-yr OS (%)</th>
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<tbody>
<tr>
<td>Gilligan</td>
<td>28</td>
<td>Radiotherapy (+/- Surgery)</td>
<td>18</td>
</tr>
<tr>
<td>Shibuya</td>
<td>28</td>
<td>Radiotherapy (+/- Surgery)</td>
<td>25</td>
</tr>
<tr>
<td>Chang</td>
<td>163</td>
<td>Surgery (+/- RT, +/- Chemotherapy)</td>
<td>32</td>
</tr>
<tr>
<td>Patel</td>
<td>59</td>
<td>Surgery (+/- RT, +/- Chemotherapy)</td>
<td>35</td>
</tr>
<tr>
<td>Lund</td>
<td>58</td>
<td>Surgery (+/- RT, +/- Chemotherapy)</td>
<td>28</td>
</tr>
<tr>
<td>NIRS (2011)</td>
<td>102</td>
<td>Carbon ion alone</td>
<td>35</td>
</tr>
<tr>
<td>NIRS (2011)</td>
<td>100</td>
<td>Carbon ion + Chemotherapy</td>
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Slide Courtesy of Dr. Azusa Hasegawa (NIRS)
Local Control and Survival Rates with Different Modalities for Mucosal Malignant Melanoma

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<td>Carbon ion + Chemotherapy</td>
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Why Heavy Ion Therapy over conventional photon or proton Therapy?

What Is the Best Radiotherapy?

- Photons (x-rays)
  Neither precise nor potent
- Protons
  Precise, but not potent
- Heavy Ions
  The MOST precise and MOST potent
World Wide Heavy Ion Therapy Centers

Operational (8)
- China: Fudan Univ CC, Shanghai
- China: IMP-CAS, Lanzhou
- Germany: HIT, Heidelberg
- Italy: CNAO, Pavia
- Japan: HIMAC, Chiba
- Japan: HIBMC, Hyogo
- Japan: GHMC, Gunma
- Japan: SAGA-HIMAT, Tosu

Under Construction (6)
- China: HITFiL, Lanzhou
- China: Another Center, Lanzhou
- Germany: MIT, Marburg
- Austria: MedAustron, Wiener Neustadt
- Japan: i-ROCK, Kanagawa
- Japan: South Korea KHIMA, Busan

Advanced Planning (4)
- France: ETOILE, Lyon
- Japan: Okinawa
- Japan: Yamagata
- Japan: Osaka

Total: 18
ALL CARBON CENTERS BUILT WITH GOVERNMENTAL SUPPORT

- USA pioneered the heavy ion therapy
  - Clinical trials ran at Lawrence Berkeley National Lab
    - First proton patient in the world 1954 at LBL
    - First heavier ion patient in the world 1975 at LBL
  - A huge therapy experience was gained with governmental support
  - Lack of funding closed the program in 1993

- Japan and Germany obtained the USA experience and data
  - their governments supported every single installation
  - they dominate the clinical and research landscape
  - Carbon therapy is approve by the Govt/Private Ins.
Number of patients treated with Protons and C-ions in the world

<table>
<thead>
<tr>
<th>Proton</th>
<th>Carbon</th>
<th>Total</th>
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<tbody>
<tr>
<td>95,424 (88.2%)</td>
<td>12,778 (11.8%)</td>
<td>108,202 (100%)</td>
</tr>
</tbody>
</table>

Proton
Carbon
Total

UK
France
Germany
Italy
Sweden
Swiss
Czech
Poland
Russia
S. Africa
Japan
China
Korea
Canada
USA
ALL CARBON CENTERS BUILT WITH GOVERNMENTAL SUPPORT

1. Office of Science and Technology Policy (OSTP) at the White House
2. National Cancer Institute (NCI)
3. Dep’t of Energy (DOE)

“They all understand the need of Heavy Ion Therapy Center for patient Care and Research” in US

- Italians, Austrians, Chinese built Heavy Ion Therapy Facility

- Almost 40 years after the first heavy ion patient, there is still no heavy ion therapy center in the USA
Planning for a National Center for Particle Beam Radiation Therapy Research (P20)

**Key Dates**

<table>
<thead>
<tr>
<th>Description</th>
<th>Dates</th>
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<tr>
<td>Posted Date</td>
<td>January 28, 2013</td>
</tr>
<tr>
<td>Letter of Intent Due Date(s)</td>
<td>April 21, 2013; December 21, 2013</td>
</tr>
<tr>
<td>Application Due Date(s)</td>
<td>May 21, 2013; January 21, 2014</td>
</tr>
<tr>
<td>AIDS Application Due Date(s)</td>
<td>Not Applicable</td>
</tr>
<tr>
<td>Scientific Merit Review</td>
<td>October 2013; June, 2014</td>
</tr>
<tr>
<td>Advisory Council Review</td>
<td>January 2014; October 2014</td>
</tr>
<tr>
<td>Earliest Start Date</td>
<td>April 2014; December 2014</td>
</tr>
<tr>
<td>Expiration Date</td>
<td>January 22, 2014</td>
</tr>
<tr>
<td>Due Dates for E.O. 12372</td>
<td>Not Applicable</td>
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</table>
Targeting Tumors with Particle Beams

Today, the National Cancer Institute (NCI), part of the National Institutes of Health, and the Department of Energy (DOE) are each announcing the selection of several new research awards to advance particle beam therapies for the treatment of cancer. Particle beam approaches use directed protons—or heavier ions, such as carbon ions—to target and kill cancerous tissue. Because the delivered particles interact strongly with tissue at a certain distance within the body that depends on the energy of the beam, the damage to surrounding healthy tissue can be minimized, offering an important possible alternative or supplement to more conventional radiotherapy (using x-rays or gamma rays), chemotherapy, and surgery. At present, there are 14 proton therapy centers in the United States; there are only a few carbon ion therapy facilities worldwide, but none are in the United States. The NCI awards announced today support planning for the establishment of a Center for Particle Beam Radiation Therapy as a national research resource, and the DOE awards address development of improved hardware that could shrink the size, increase the maneuverability, and considerably reduce the steep costs of particle beam therapy equipment.

The Planning Grant awards for the national research center are being made by NCI. The planned center would serve as a research adjunct to an independently created and funded, sustainable clinical facility for particle beam radiation therapy. Ultimately, the proposed center is expected to perform clinically relevant research using ion beams. The planning grants include pilot projects that will enable a research agenda in particle beam delivery systems, dosimetry, radiation biology, and/or translational pre-clinical studies. NCI encourages other researchers to collaborate with the awardees in advancing the capabilities for particle beam therapies.

The DOE awards are being made under the Accelerator Stewardship Program. The machinery needed to produce and control particle beams, such as synchrotrons, cyclotrons, and related beam delivery systems, is expensive and complex. This machinery, however, can be used in a variety of fields, ranging from high-energy physics to materials science to medical treatment. The DOE program has the responsibility for long-term, fundamental research and development of such instrumentation. The new efforts will support improvements in the generation of the accelerated particles and in the powerful magnets that direct the charged particle beams, aiming to make these key components smaller, lighter, more versatile, and potentially less expensive.

http://m.whitehouse.gov/blog/2015/02/10/targeting-tumors-particle-beams

Posted by Tof Carim on February 10, 2015 at 11:15 AM EST
A Prospective Randomized Phase 3 Trial of Carbon Ion versus Conventional Radiation Therapy for Locally Advanced, Unresectable Pancreatic Cancer
Solicitation Number: HHS-NIH-NCI-ETSB-51007-51
Agency: Department of Health and Human Services
Office: National Institutes of Health
Location: National Cancer Institute, Office of Acquisitions
CIPHER: CIPHER PC
Carbon Ion versus PHoton thERapy for Pancreatic Cancer
Lead Institution – University of Texas Southwestern Medical Center Dallas, Texas
Jeffrey Meyer, M.D.
Hak Choy, M.D, Robert Timmerman, M.D.
Jeffrey Meyer, M.D., Steve Jiang, Ph.D.
Arnold Pompos, Ph.D., Michael Story, Ph.D.

National Institute of Radiological Science (NIRS)
Chiba, Japan
Hirohiko Tsujii, MD, PhD.
Tadashi Kamada, MD, PhD.
Shigeru Yamada MD., Ph.D.
Koji Noda, Ph.D.
Yoshiya Furusawa, Ph.D.

Heidelberg Ion Therapy (HIT)
Heidelberg, Germany
Jürgen Debus, MD. Ph.D.
Oliver Jäkel, Ph.D.
Peter Peschke, Ph.D.
Kristian Karger, Ph.D.
Amir Abdollahi, Ph.D.

National Centre of Oncological Hadrontherapy (CNAO)
Pavia, Italy
Roberto Orrechia, MD., Ph.D.
Piero Fossati, MD., PhD.
Silvia Molinelli MS.
Marco Durante, Ph.D.

Gunma University Heavy-ion Radiotherapy Maebashi, Japan
Takashi Nakano, MD.Ph.D
Tatsuaki Kanai, Ph.D.
Akihisa Takahashi, Ph.D.
Tatsuya Ohno MD, PhD
Randomization

**Carbon Ion Arm**
- Induction chemotherapy
- 55.2 GyE in 12 fractions (3 weeks)
- Weekly concurrent gemcitabine (1000mg/m²)
- Continued chemotherapy

**Photon Arm**
- Induction chemotherapy
- 50.4 Gy in 28 fractions + concurrent capecitabine
- Continued chemotherapy

**Eligibility Criteria:**
1) Adenocarcinoma histology
2) Age >18 yo
3) Locally advanced tumor presentation
4) Tumors not in direct contact with the duodenum or stomach (NIRS experience, 5mm gap)
The 2nd ISIT: International Symposium on Ion Therapy schedule: Oct 22-23
Dallas, Texas
http://www.isit-sw.org
Conclusion

1. It appears that proton beam is more precise than photon
Conclusion

1. It appears that proton beam is more precise than photon
2. It appears that caron beam is more precise and potent than photon
Conclusion

1. It appears that proton beam is more precise than photon.
2. It appears that carbon beam is more precise and potent than photon.
3. The physics of proton/Carbon may indeed be precise and predictable, however the actual delivery of proton/Carbon therapy comes with many uncertainties: dose distribution, range uncertainty, intra-fractional motion, inter-fractional anatomic changes.
Conclusion

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4. The higher biological dose of carbon therapy can potentially cause higher normal tissue toxicity when the distal margin of the tumor is uncertain.
Conclusion

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5. The real benefit of Proton/Carbon treatment must be proven by accumulating evidences before they become new standard of care.
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4. The higher biological dose of carbon therapy can potentially cause higher normal tissue toxicity when the distal margin of the tumor is uncertain.
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6. Evidence must be based on science that's hypothesis-based, empirical, reproducible, and the randomized clinical trials are the best way to provide such evidence.
Conclusion

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4. The higher biological dose of carbon therapy can potentially cause higher normal tissue toxicity when the distal margin of the tumor is uncertain.
5. The real benefit of Proton/Carbon treatment must be proven by accumulating evidences before they become new standard of care.
6. Evidence must be based on science that's hypothesis-based, empirical, reproducible, and the randomized clinical trials are the best way to provide such evidence.
7. Our treatment decision must be based on evidence-based medicine.
Thank you!
Which answer indicates correctly the advantages for each type of radiation the

| 7% | 4% | 85% | 1% | 4% |
Which answer indicates correctly the advantages for each type of radiation the

1. Photons – precise, not potent
2. Photons – not precise, potent
3. Carbon ions – precise, potent
4. Protons – not precise, potent
5. Protons – not precise, not potent

Answer: 3– Carbon ions – precise, potent