CLINICAL TRIALS

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NATIONAL CANCER INSTITUTE
TOMORROW
CARBON-ION RIF IN A HUMAN FIBROBLAST NUCLEUS
10 hits per position, 7 microns apart

[Heiss M, Rad Res 165: 231-9, 2006]
ARGON-ION RIF, 3 MICRONS APART
The debate is not about the money.

We do not know if patients treated by protons live longer or better than those treated without protons.

*Without comparative trials we do not know that they will even do as well as those treated without protons!*
LEVEL 1 EVIDENCE OF SUPERIORITY OVER 3D-CRT

<table>
<thead>
<tr>
<th></th>
<th>LESS</th>
<th>TOXIC</th>
<th>BETTER</th>
<th>SURVIVAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROTONS</td>
<td>C-IONS</td>
<td></td>
<td>PROTONS</td>
<td>C-IONS</td>
</tr>
<tr>
<td>Brain</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>H&amp;N</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
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<td>Breast</td>
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<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Lung</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Colorectal</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Prostate**</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Cervix</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
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</tbody>
</table>
CA PROSTATE: SUMMARY OF THREE RANDOMIZED TRIALS

• Patients treated with protons suffered worse toxicity than those treated without protons.
• Patients receiving high dose RT (>75 Gy by photons, protons or both) suffered worse toxicity than those receiving a standard dose (~70 Gy).
• Patients treated with protons or high doses did not live any longer, even after 8-25 years follow-up.
MGH Ca Prostate trial: Photons +/- Protons

Shipley W, IJROBP 32:3-12, 1995
**MGH CaP trial: 3DCRT +/- Protons**

*Shipley W, IJROBP 32:3-12, 1995*

<table>
<thead>
<tr>
<th></th>
<th>Urethral Strictures</th>
<th>Rectal Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CRT</strong></td>
<td>8%</td>
<td>12%</td>
</tr>
<tr>
<td><em>N=99</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CRT+PRT</strong></td>
<td>19% (p=0.07)</td>
<td>32% (p=0.002)</td>
</tr>
<tr>
<td><em>N=103</em></td>
<td></td>
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</table>
MGH trial – GU toxicity

MDACC CaP TRIAL: 1993-98

Kuban DA. IJROBP 70:67-74, 2008

![Graph showing freedom from grade >= 2 GI toxicity over years after end of RT for different doses of radiation (70 Gy vs 78 Gy). The graph indicates a statistically significant difference (P = 0.001).]
MDACC CaP TRIAL: 1993-98
Kuban DA. IJROBP 70:67-74, 2008
# STANDARD VS HIGH DOSE PROTON RT


<table>
<thead>
<tr>
<th>Dose</th>
<th>70 GyE</th>
<th>79 GyE</th>
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</thead>
<tbody>
<tr>
<td>Survival</td>
<td>97%</td>
<td>96%</td>
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<tr>
<td><em>(n.s.)</em></td>
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<tr>
<td>GI Toxicity</td>
<td>41%</td>
<td>57%</td>
</tr>
<tr>
<td><em>(p=0.004)</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GU Toxicity</td>
<td>8%</td>
<td>17%</td>
</tr>
<tr>
<td><em>(p=0.005)</em></td>
<td></td>
<td></td>
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</tbody>
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IMPLICATIONS

1. PSA as an end-point.
HOW OFTEN HAS THE “PERCEPTION” BY ACADEMIC CLINICIANS THAT AN EXPERIMENTAL CANCER TREATMENT IS SUPERIOR TO STANDARD TREATMENT BEEN PROVEN CORRECT?

• So infrequently as to make us all humble !!

(Bill Shipley, MGH)
Summary of RCT Outcomes

RTOG: In 71% of the RCTs the standard treatment was favored.

COG: In 53% of the RCTs the standard treatment was favored.

“The value of new experimental treatments can NOT be confidently predicted in advance.”
Hypothesis: Patients treated by high-dose protons (or IMRT) without androgen-deprivation live as long as patients treated with AD plus 3D-CRT.
BEFORE ROUTINELY EMPLOYING A NEW TECHNOLOGY

- Head to head trials are needed to show that it helps patients live longer or better.
- If those trials were not part of pre-marketing testing, they must be conducted ASAP after the technology is licensed by the FDA.
- At present, however, the FDA does not demand such trials!
• The manufacturers can not be relied upon to sponsor those trials voluntarily, because they frequently serve no commercial purpose.
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• So, *who should twist their arms?*
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• So, who should twist their arms?

• *Who has the financial leverage?*
• **Physicians** must demand that the manufacturer provides evidence from controlled clinical trials that a new technology didn’t just produce pretty pictures but actually helped patients live longer or better!!

• **Physicians** must participate in clinical trials that generate the evidence.
STEPS IN EVALUATING A NEW TECHNOLOGY

1. Demonstrate that the dose distribution *in-silico* looks promising.

2. Ensure consistency in planning, optimization and execution by
   • Establishing a credentialing mechanism.
   • Conducting feasibility studies.

3. Demonstrate by controlled clinical trials that patients live longer and/or better.
• Advanced techniques are less tolerant of poor implementation than ‘standard’ techniques.
• Misadministrations are harder to detect and may lead to worse outcomes for patients.
• In-vivo dosimetry is not possible at present. There is, therefore, no substitute for analysis of both tumor control and adverse effects.
• That is best done by participating in clinical trials.
LESSON LEARNED SO FAR

• IMRT, SRT, Protons, etc. pose a greater risk of missing the target than ‘traditional’ techniques of radiation therapy.
Halperin’s Rule

• Most tumors are radioresistant if you miss them!
  – Protons may offer many new and expensive ways of missing the tumor.
‘MISADMINISTRATIONS’ WITH ADVANCED TECHNOLOGIES

- Discrepancies between prescribed dose and planned dose.
- Discrepancies between planned dose and dose delivered ‘to an ideal patient’.
- Discrepancies between planned dose and dose delivered to an actual patient.
• Discrepancies between prescribed dose and planned dose.
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• Discrepancies between planned dose and dose delivered to an actual patient.
• Studied 803 patients at five institutions.
• Treatment plans were done by experienced physicists (>50 IMRT cases each).
RESULTS:

- In 46% of patients the plan delivered to the CTV a maximum dose more than 10% higher than prescribed by the MD (worst case: 40% higher).
- In 63% of patients the plan delivered to the CTV a minimum dose more than 10% lower than prescribed (worst case: 100% lower = zero).
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THE IDEAL PATIENT

• We know the CTV precisely.
• There is absolutely no voluntary or involuntary movement.
• There is absolutely no change in the position, size or shape of the CTV or the OAR.
RPC Phantoms

prostate RTOG 0126 (IMRT)

H&N IMRT
RTOG 0225, 0126;
COG ACNS0331

thorax RTOG 0236 (SBRT)

liver RTOG 0438
128 RTOG member institutions imaged a phantom, developed a treatment plan, then treated the phantom.

**Goal:** Deliver to the CTV a dose within 7% of the planned dose.

**Results:** One-third of the institutions failed the test (*the dose delivered differed from the planned dose by up to 22%; the high dose region was off by up to 15 mm*).
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• Discrepancies between planned dose and dose delivered ‘to an ideal patient’.
• *Discrepancies between planned dose and dose delivered to an actual patient.*
Very tight margins (PTV approximates the CTV) make it critical to:

• **Know the correct position, size and shape of the CTV and OAR**

• **Constantly account for (between and within fractions):**
  
  – *changes in position*
  – *changes in size*
  – *changes in shape (deformation)*
WHAT IS THE TARGET?

- Current imaging tools are often inadequate for determining the ‘correct’ CTV.
- The current state of imaging QA leaves much to be desired.
- The ‘correct’ CTV can vary greatly even among experts.
TOP TEN PRIORITIES FOR RADIATION ONCOLOGY
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1. Better imaging
2. Better imaging
3. Better imaging
4. Better imaging
5. Better imaging
6. Better imaging
7. Better imaging
8. Better imaging
9. Better imaging
10. Better targeting
• We have made enormous progress in our ability to hit the target

BUT

• What is the correct target?
• Overlap between GTVs drawn by 8 ‘experts’ averaged only 50% (in the worst case: 0%).
• **Bad News:** Overlap between CTVs (axilla) drawn by 8 ‘experts’ averaged only 45% (in the worst case: 15%).

  – **Good News:** Overlap between hearts drawn by 8 ‘experts’ averaged 95% (in the worst case: 45% !!).
• **Patient 1**: CTVs (iliac nodes) drawn by 11 ‘experts’ ranged from 82 – 877 cc. All of them agreed upon only 30 cc.

• **Patient 2**: CTVs (iliac nodes) ranged from 60 – 630 cc. All agreed upon only 17 cc.
• Atlases (created by experts’ consensus) in effect propose a hypothesis regarding the ‘correct’ CTV, that must then be proven or disproven by clinical trials.
TOP TEN PRIORITIES FOR RADIATION ONCOLOGY

1. Better imaging
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7. Better imaging
8. Better imaging
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10. Better targeting
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CREDENTIALING MECHANISM


• Any institution putting a patient on a protocol must be credentialed.

• At present, no such credentialing is required by the FDA or the payers!
• Particle therapy has great potential for helping some patients live longer or better.

• The best way forward is by prospective clinical trials, *underpinned by robust quality assurance*, due to the very demanding QA and the possibility of harm to the patients.
Institutions participating in NCI-sponsored clinical trials are credentialed for the new technology and must participate in ongoing QA.

No such safeguards exist for patients not participating in those trials. There are, at present, no minimum standards mandated by the FDA or the payers.
• That could delay the fulfillment of the promise of this exciting new technology and even give it a bad name unless the profession itself steps up to the plate.
A ‘GOOD’ CLINICAL TRIAL

• Hypothesis.
• Sample size calculation.
• Roles of retrospective analyses.