Hadrontherapy and Clinical Trials

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The 2 legs
of Particle Radiotherapy

High-Dose Target effectiveness

Reduction of low-moderate dose volume
Particle Radiotherapy:
The ultimate Goals

*Increasing Local Control (dose escalation, higher biologic effectiveness)*

- Residual disease or unresectable disease
- Disease at high risk for failure

*Decreasing Late Adverse Events by reduction of Integral dose:*

- Improving functional outcome and QoL by reducing normal tissue dose
- Reducing risks of Secondary malignancy
Evidence-Based Medicine:

Levels of Evidence

= Study design

Plus Endpoints
NCI guidelines*: „Levels of Evidence for Human Studies of Cancer Complementary and Alternative Medicine (PDQ®)“

„Strength of Study Design“

• **Level 1:** Randomized controlled clinical trials  
  – i: double-blinded  
  – ii: non-blinded  
• **Level 2:** Non-randomized controlled clinical trials  
• **Level 3:** Case series  
  – i: Population-based consecutive case series  
  – ii: Consecutive case series  
  – iii: Non-consecutive case series  
• **Level 4:** Best case series

NCI guidelines*: „Levels of Evidence for Human Studies of Cancer Complementary and Alternative Medicine (PDQ®)“

„Strength of Endpoints Measured“

• **A:** Total mortality
• **B:** Cause-specific mortality
• **C:** Carefully assessed quality of life
• **D:** Indirect surrogates
  – i: Disease-free survival
  – ii: Progression-free survival
  – iii: Tumor response rate

http://www.cancer.gov/cancertopics/pdq/levels-evidence-cam/HealthProfessional/page3
NCI: Indices of clinical relevance

Strength of endpoint

Overall mortality
Cause-specific mortality
Quality of life
Indirect surrogates

Levels of evidence

Randomized
Non-randomized
Case series
Best case series

Caveat:
„Local Tumor Control“ only a „low-strength“ endpoint
The Clinical Status of Hadrontherapy:

Carbon Ions and Protons
Particle-RT:
Status of Clinical Evidence reporting

- Retrospective single-institution reports
- Prospective data accumulation
- Phase I and Phase II studies: Skull Base, Lung, Liver, H&N, Prostate, Sarcomas a.o.

Clinical relevance

<table>
<thead>
<tr>
<th>Strength of endpoint</th>
<th>Levels of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>IV, III, II, I</td>
</tr>
<tr>
<td>B</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td></td>
</tr>
<tr>
<td>D</td>
<td></td>
</tr>
</tbody>
</table>

Levels of evidence: Low, Moderate, High.
Randomized trial photons versus protons:

- Has not been done, EXCEPT:
  - MGH/HCL Prostate trial: 67.2 Gy photons vs. 75.6 Gy protons/photons, T3 and T4

Randomized Trials: protons versus protons

- PROG 9509: Prostate CA, mixed photon/proton versus mixed photon/proton dose escalation:
- MGH + LBL+ LLUMC Chordoma and Chondrosarcoma – Skull Base and C-spine randomized protocol (PROG)
- MGH/MEEI/HCL: Uveal Melanoma, dose de-escalation trial 70 vs. 53 Gy(RBE)
Proton Therapy for Prostate CA: Single-institution Phase III Trial at MGH/HCL by W. Shipley et al.

- Clinical Stages T3 and T4.
- Trial design in the early 80’s
- Randomization:
  67.2 Gy Photons only (4-field box)
  versus
  75.6 CGE mixed photons (50.4Gy) and perineal proton boost (25.2 CGE)
Proton Therapy for Prostate CA: Single-institution Phase III Trial at MGH/HCL by W. Shipley et al.

- MGH Phase III results:
  - Decreased local failure in all patients treated with PT to higher dose level. Reached statistical significance in Gleason 8-10 tumors only.
  - Increased low-grade rectal bleeding (primarily Gr. 1) in high-dose group (34% versus 16%).
  - No difference in survival.

Problem of the Study: Due to long accrual time, low-dose level outdated at time of reporting and high dose arm accepted routine in many photon centers

Positive effect of study: contributed to awareness of partial rectal wall tolerance (Hartford, IJROBP 36:721, 1996; Benk IJROBP 26:551, 1993)
Comparison of Conventional-Dose vs High-Dose Conformal Radiation Therapy in Clinically Localized Adenocarcinoma of the Prostate: A randomized controlled trial
Zietman AL et al. JAMA 2005; 294:1233-1239

• 1996 - 1999
• 393 patients enrolled
• 2 US academic institutions (LLUMC and HCL/MGH)
• Stage T1b through T2b prostate cancer
• Prostate-specific antigen (PSA) levels less than 15 ng/mL. Median PSA level was 6.3 ng/ml

• Median follow-up was 5.5 (range, 1.2-8.2) years.
Randomized Trials:
protons versus protons
PROG 9509

T1b-2b prostate cancer
PSA <15ng/ml

Randomization
ACR/RTOG

Proton boost
19.8 GyE

3-D conformal photons
50.4 Gy

Total prostate dose
70.2 GyE

Proton boost
28.8 GyE

3-D conformal photons
50.4 Gy

Total prostate dose
79.2 GyE
Freedom From Biochemical Failure (ASTRO Definition) Following Either Conventional-Dose (70.2 GyE) or High-Dose (79.2 GyE) Conformal Proton / Photon Radiation Therapy
Authors’ conclusions: Men with clinically localized prostate cancer have a lower risk of biochemical failure if they receive high-dose rather than conventional-dose conformal radiation. This advantage was achieved without any associated increase in RTOG grade 3 acute or late urinary or rectal morbidity.
JAMA 2008: Correction

Authors discovered incorrect coding in data base:

**Intended**: biochem. failure = 3 successive PSA increases (ASTRO Def.)

**Coded**: biochem. Failure = *any* 3 failures

Result: higher # of pts. incorrectly coded as failures

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Corrected 2008

![Graph showing corrected data]

Incorrect 2005

![Graph showing corrected data]
A Phase III Trial Employing Conformal Photons with Proton Boost in Early-stage Prostate Cancer: Conventional Dose (70.2 GyE) Compared to High-dose Irradiation (79.2 GyE): Long-term Update analysis of Proton Radiation Oncology Group (PROG)/American College of Radiology (ACR) 95-09

• Median follow-up: 8.9 years.
Freedom From Biochemical Failure (ASTRO Definition – with backdating)
Following Either Conventional-Dose (70.2 GyE) or High-Dose (79.2 GyE)
Conformal Proton / Photon Radiation Therapy

• 70.2 vs. 79.2 GyE: 10-year BF rates (ASTRO) 35.3% vs. 16.3 % (p=0.0001)
• Low –risk: 29% vs. 6.1% (p=0.0001)
• Intermed. Risk: 44.6 vs. 28.6% (p=0.06)
• No diff. in OS: 83.4 vs. 78.4% (p=0.45)
• No diff. in high Grade, late toxicity (> Gr. 3): overall 2.1%
• Higher toxicity, if Grade 2 included: (> Gr. 2): 29.4 vs. 39.4% (p=0.045)

Authors’ conclusions: This RCT shows a long-term advantage in terms of freedom from biochemical failure for men with low and intermediate risk prostate cancer receiving high-dose vs. conventional dose conformal radiation delivered with mixed proton and photon beams. This advantage was achieved without any associated increase in Grade ≥3 late urinary or rectal morbidity.
Chordoma and Chondrosacoma of Skull Base and C-Spine (PROG-protocol MGH +LBL+LLUMC)

Stratification

„High Risk“ Groups

„Low Risk“ Group

Randomization

75.6 vs 82.9 Gy (RBE)
65.6 vs 75.6 Gy (RBE)

High Risk = Female: Chordomas, Skull Base
All C-Spine Chordomas and Chondrosarcomas

Low Risk = Male: Chordoma, All Skull Base Chondrosarcomas
Chordoma and Chondrosacoma of Skull Base and C-Spine (PROG-protocol MGH +LBL+LLUMC)

- Accrual since 1993
- 400 patients enrolled (over >12 years?)
- „an interim report is expected soon“ (statement since 2005)
- OAR dose tolerance increased by 5%
  - At least interim toxicity analysis would be / would have been very helpful to the proton-community
The MGH / MEEI Phase III randomized trial: Proton Therapy for Ocular Melanomas – a dose de-escalation study

- Study Question: Improved visual outcome and reduced enucleation rate by dose reduction – considering > 95% Local Tumor control?
- 70 CGE versus 50 CGE in 5 fractions
- Small to medium-sized tumors (> 15 mm base, >5 mm height)
- Near optic disc or macula (< 4 disc diameters distance to either)
- Accrual: 188 patients

• RESULTS:
  • Similar visual acuity retention (55% at 5 years 20/200 or better)
  • Similar rate of maculopathy and papillopathy
  • Similar Local Control (2 LF at 50 CGE, 3 LF at 70 CGE)
  • Similar Rate of Metastasis
  • Only signif. Difference: Less Visual Field Loss in 50 CGE group
“Level 1” evidence to support proton therapy:?
Essentially: NO

Higher doses lead to better results and can be given safely with protons“ according to PROG 9509 - that is not to say that this can not be done with photons also.
**Carbon-Ion** Hypofractionation trials since 1994 at HIMAC / NIRS

Optimal dose-fractionations determined in dose escalation studies for carbon ion radiotherapy at NIRS

<table>
<thead>
<tr>
<th>Tumor Sites</th>
<th>Dose-Fractionation (GyE/fr/week)</th>
<th>Gy/fr</th>
<th>BED (α/β =10)</th>
<th>BED (α/β =2.5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skull Base</td>
<td>60.8 / 16 / 4</td>
<td>3.8</td>
<td>83.9</td>
<td>153.2</td>
</tr>
<tr>
<td>H &amp; N: ACC/MM etc</td>
<td>57.6 / 16 / 4</td>
<td>3.6</td>
<td>78.3</td>
<td>140.5</td>
</tr>
<tr>
<td>H &amp; N: Sarcoma</td>
<td>64.0 / 16 / 4</td>
<td>4.0</td>
<td>89.6</td>
<td>166.4</td>
</tr>
<tr>
<td>NSCLC: Peripheral type</td>
<td>70.4 / 16 / 4</td>
<td>4.4</td>
<td>101.4</td>
<td>194.3</td>
</tr>
<tr>
<td>NSCLC: (Stage I)</td>
<td>90.0 / 18 / 5</td>
<td>5.0</td>
<td>135.0</td>
<td>270.0</td>
</tr>
<tr>
<td>NSCLC: Peripheral type</td>
<td>72.0 / 9 / 3</td>
<td>8.0</td>
<td>129.6</td>
<td>302.4</td>
</tr>
<tr>
<td>NSCLC: Peripheral type</td>
<td>52.8 / 4 / 1 (T1)</td>
<td>13.2</td>
<td>122.5</td>
<td>331.6</td>
</tr>
<tr>
<td>NSCLC: Peripheral type</td>
<td>60.0 / 4 / 1 (T2)</td>
<td>15.0</td>
<td>150.0</td>
<td>420.0</td>
</tr>
<tr>
<td>Hilar type</td>
<td>44.0 or 46.0 / 1 / 1/day</td>
<td>44.0 or 46.0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Liver: HCC</td>
<td>68.4 / 12 / 3</td>
<td>5.7</td>
<td>107.4</td>
<td>224.4</td>
</tr>
<tr>
<td>Liver: HCC</td>
<td>79.5 / 15 / 5</td>
<td>5.3</td>
<td>121.6</td>
<td>248.0</td>
</tr>
<tr>
<td>Liver: HCC</td>
<td>69.6 / 12 / 3</td>
<td>5.8</td>
<td>110.0</td>
<td>231.1</td>
</tr>
<tr>
<td>Liver: HCC</td>
<td>58.0 / 8 / 2</td>
<td>7.2</td>
<td>100.1</td>
<td>226.2</td>
</tr>
<tr>
<td>Liver: HCC</td>
<td>52.8 / 4 / 2</td>
<td>13.2</td>
<td>122.5</td>
<td>331.6</td>
</tr>
<tr>
<td>Liver: HCC</td>
<td>38.8 / 2 / 2 days</td>
<td>19.4</td>
<td>114.1</td>
<td>339.9</td>
</tr>
<tr>
<td>Prostate</td>
<td>66.0 / 20 / 5</td>
<td>3.3</td>
<td>87.8</td>
<td>153.1</td>
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<tr>
<td>Prostate</td>
<td>63.0 / 20 / 5</td>
<td>3.2</td>
<td>82.8</td>
<td>142.4</td>
</tr>
<tr>
<td>Prostate</td>
<td>57.6 / 16 / 4</td>
<td>3.6</td>
<td>78.3</td>
<td>140.5</td>
</tr>
<tr>
<td>Bone / Soft tissue</td>
<td>70.4 / 16 / 4 (Pelvis)</td>
<td>4.4</td>
<td>101.4</td>
<td>194.3</td>
</tr>
<tr>
<td>Bone / Soft tissue</td>
<td>64.0 / 16 / 4 (paraspinal)</td>
<td>4.0</td>
<td>89.6</td>
<td>166.4</td>
</tr>
<tr>
<td>Rectum (Post-one recurrence)</td>
<td>29.5 / 9 / 2</td>
<td>4.6</td>
<td>107.5</td>
<td>209.0</td>
</tr>
<tr>
<td>Uterine Cervix (Adenocarcinoma)</td>
<td>74.4 / 20 / 5</td>
<td>3.7</td>
<td>102.1</td>
<td>185.1</td>
</tr>
</tbody>
</table>
**Carbon-Ion** Hypofractionation trials since 1994 at HIMAC / NIRS

### Local Control and Morbidity of Carbon Ion RT in Hepatocellular Carcinoma

<table>
<thead>
<tr>
<th>Fractionation</th>
<th>Local Control</th>
<th>Morbidity (3~12 mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TD / Fx / Wk</td>
<td>3-yr LC No.</td>
<td>Grade (CTC modified)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0 1 2 3 4</td>
</tr>
<tr>
<td>49.5~79.5/15fx /5wk</td>
<td>24 81%</td>
<td>20 10 4 5 1(5%) 0</td>
</tr>
<tr>
<td>54.0~69.6/12fx /3wk</td>
<td>34 86%</td>
<td>24 16 2 6 0(0%) 0</td>
</tr>
<tr>
<td>48.0~58.0 / 8fx /2wk</td>
<td>24 86%</td>
<td>16 10 5 0 1(6%) 0</td>
</tr>
<tr>
<td>48.0~52.8 / 4fx /1wk</td>
<td>75 90%</td>
<td>54 40 6 6 2(4%) 0</td>
</tr>
<tr>
<td>32.0~38.8 / 2fx /2day</td>
<td>36 90%</td>
<td>13 9 2 2 0(0%) 0</td>
</tr>
<tr>
<td>Total</td>
<td>181 -</td>
<td>127 85 19 19 4(3%)* 0</td>
</tr>
</tbody>
</table>

*All recovered to pre-treatment function.*

“Level 1” evidence to support particle therapy:?
Essentially: NO
CLINICAL TRIALS ARE ESSENTIAL TO ADVANCE THE FIELD OF RADIATION ONCOLOGY
DO WE NEED PHASE III TRIAL EVIDENCE TO JUSTIFY THE CLINICAL USE OF NEW TECHNOLOGY, SPECIFICALLY PARTICLE THERAPY?
Level-1 Evidence to support IMRT in 2006:

Wilfried De Neve,
Ghent University Hospital
PTCOG 2006

IMRT in nasopharyngeal cancer
Kam et al., Univ. Hong Kong
ASCO proceedings (2005) abstract
Very small trial: 52 patients
Endpoints: Xerostomia and QoL

Pow et al., Univ. Hong Kong
IJROBP, 66(4):981, 2006

Clinical relevance

Conclusion: De facto no Level-1 Evidence at a time when >80% of institutions had already purchased and implemented IMRT
The *Confusing* World of Precision- RT
The *Confusing* World of Precision- RT

- Clinical trial required
- Clinical trial required
- Clinical trial required
The *Confusing* World of Precision- RT

Clinical trial required

Clinical trial required

Clinical trial required
The Case for prospective, randomized Phase III trials

Clear evidence for LC increase, or side effect decrease

Phase II suggests some LC increase or some side effect decrease

No LC increase, Moderate / minor late effect decrease

weak (ethics) → strong

weak (practicality, logistics)
The Case for prospective, randomized Phase III trials

Clear evidence for LC increase, or Critically important Integral dose reduction

Phase II with some LC increase or adverse effect reduction

No LC increase, Moderate / minor late effect decrease

weak

strong

protons

photons

weak
The Case for prospective, randomized Phase III trials

Clear evidence for LC increase, or Critically important Integral dose reduction

Phase II with some LC increase or adverse effect reduction

No or minor LC increase, Moderate / minor late effect decrease
The „Ethics“ of a Phase III Trial of Protons versus Photons

- Clear evidence for LC increase, or side effect decrease
- Phase II suggests some LC increase or some side effect decrease
- No LC increase, Moderate / minor late effect decrease
- weak (ethics)
- strong
- weak (practicality, logistics)
M GOITEIN, H SUIT, J COX *:

- Phase III trial „Protons versus Photons“ is unethical

- Proton dose distribution is invariably better due to inherent reduction of Integral Dose, i.e. the reduction of the „Irradiated Normal Tissue Volume“

- Violates the principle of „equipoise“, i.e. the mandate of risk-balanced tx-arms of a Phase III trial

- JCO, 2008 and Radiother Oncol, 2008
- Radiother Oncol 2010
„Reduction of Integral Dose“

= Dose Reduction in the low-moderate dose range:
  5-10-20-30 Gy volume

*Does it matter in the adult patient?*
„The Story of 20 Gy“

Assume, that…….

I) Tomo vs. Protons

II) „Tomo delivers a dose of 20 Gy to the entire facial circumference – protons do not“

III) „Protons are approx. 5000 Euros more expensive.“

L. WIDESOTT, M. SCHWARZ. IJROBP, 2008
I will give you 5000 Euros for 20 Gy RT to your head

– surely, you would take the money – wouldn‘t you ?

After all – 20 Gy don‘t matter.

(Otherwise, how can you ask your patient to accept photons…… ? )

* Paraphrasing M. Goitein
**However.. not only one factor, but...**

Multiple factors influence the „**equipoise**“ of a particle trial.

Are risks balanced:

- dose escalation to target
- Acute and late high grade toxicity
- Low grade late toxicity
- normal tissue: High-dose conformity
- normal tissue: Integral Dose
- radiobiology
- The „unexpected“
Discussion: The side-effect profiles of thalidomide are well known. There was no data on how the duration or intensity of an exposure to thalidomide might affect patients receiving whole-brain irradiation. Thalidomide was less well tolerated in this cohort of patients. Somnolence was a major limiting side effect.

Conclusion: Thalidomide provided no survival benefit for patients with metastases. Nearly half the patients discontinued thalidomide due to side effects.

Discussion: The side-effect profiles of thalidomide are well known. There was no data on how the duration or intensity of an exposure to thalidomide might affect patients receiving whole-brain irradiation. Thalidomide was less well tolerated in this cohort of patients. Somnolence was a major limiting side effect.

Phase III trials uncover unexpected events.
The „Ethics“ of a Phase III Trial of Protons versus Photons

Clear evidence for LC increase, or side effect decrease

Phase II suggests some LC increase or some side effect decrease

No LC increase, moderate / minor late effect decrease

Weak (ethics)

Strong

Plenty of examples that ethically justify conduct of a Phase III trial
**Trial-Concepts** for applying Proton RT in relation to Photon-RT

**Concept 1**

- Enrollment in established cooperative group photon trials, i.e. replace photons with protons
- dose and volume regimen identical to photon concepts

**Advantage:** Proton-RT embedded in multi-institutional concepts. Increases proton acceptance. Matched-case comparability of late effects data with photons.

**Disadvantage:** no increase in tumor control probability from protons by applying Tx-prescriptions similar to photons. Requires extensive long-term data collection and/or QoL component.
Trial-Concepts for applying Particle RT in relation to Photon-RT

Concept 2

Disease-specific Phase II trials

dose and volume regimen adjusted to particle concepts.

Advantage: Establish Particle-RT efficacy. Explore opportunities and new treatment concepts (dose escalation, hypofractionation etc.) for Particle RT to increase LC and decrease side effects.

Disadvantage: No comparison with photons.
Challenges of a treatment modality-oriented Phase III Trial comparing photons with particle therapy:

*Hadron-therapy is still an evolving technology*

Phase III Trial

<table>
<thead>
<tr>
<th>Design</th>
<th>Pat. Accrual /Tx</th>
<th>F/U</th>
<th>Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 ½ yrs.</td>
<td>3 years</td>
<td>1 year</td>
<td>½ yr.</td>
</tr>
</tbody>
</table>

- Design in 2010 based on 2005 technology
- Data in 2017 based on 12 year old technology
- Acceptance of outcome results in 2017 likely be challenged by „looser“ on grounds of changed technology concepts.
The question: What is the best RT-modality = the Holy Grail

Is a Phase III trial the answer?

Has a Phase III trial the chance of providing the answer?

Time spent on discussing treatment modalities versus time spent on their best use for the patient?
**RT-modality oriented Trial Design: Phase III**

RT modality comparison

- **Arm I** (IMRT, Tomo, SBRT)
- **Arm II** (Particles)

Both arms with identical Tx-concepts

RT-Modality Analysis

- Limited additional information about disease management
- Patient has no clear benefit – no better chance of cure either way
- Patient Accrual ?
**RT-modality oriented Trial Design: Phase III**

RT modality comparison

- **Arm I** (IMRT, Tomo, SBRT)
- **Arm II** (Particles)

No new information about disease management
Patient has no clear benefit – no better chance of tumor control, likely better chance of reduction of side effects
Patient Accrual?

ORIENTED TOWARDS TECHNOLOGY, NOT THE PATIENT
Disease- and Patient-oriented Trial
Design: Phase III

Treatment concept comparison

Arm I (conventional Tx)

Established RT Modality

Clinical Endpoints. RT-Modality Analysis

Arm II (high-dose Tx)

Stratify according to RT-Modality (SBRT, Tomo, IMRT, Particles)
Disease- and Patient-oriented Trial Design: Phase II

Innovative Treatment concept

Example: high-dose, hypofractionated RT

Stratify according to RT-Modality (SBRT, Tomo, IMRT, Particles)*

Clinical Endpoints. RT-Modality Analysis

* RT modality according to Institution. Requires matched-pair Analysis
Summary:

- The importance of prospective clinical studies to provide medical evidence of effectiveness and safety of Hadron Therapy is undisputed
- Multiinstitutional efforts would be preferable
- There is currently no common society or co-operative group that would unequivocally offer/support hadron-trial conduct.
- New hadron centers in major academic institutions will facilitate a new era of hadron studies – many trials are already accruing or are in final phase of initiation
- Phase III studies remain problematic
- The socio-economic impact and overall acceptance of Hadron therapy will realistically and likely not be dependent on Phase III trials
Thank you