Particle Radiation Therapy: Current Status – Indications - Results

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Particle Radiation Therapy:

Selection of the optimum particle:

- **increased biologic effectiveness (selectively higher in tumor compared to normal, surrounding tissues)**
- and / or
- **Improved dose conformity compared to photons**
Heavy ion therapy – A summary

Biological effectivity

Dose conformation

Co-60
X-rays 10MV.
X-rays IMRT
P konv.
P IMRT
n konv.
Pions
Ar
Si
Ne
C-12
Present Clinical Reality:

- > 55 000 patients have been treated with particles
- > 50 000 patients with protons
- > 4500 with Carbon Ions (< 10%) (> 90% at one facility (NIRS))

->> proton facilities built world wide

• „Carbon Ion“ facilities permit use of multiple particles
Why Protons?

Protons stop ...........X-rays keep going*

* Herman Suit, Michael Goitein
Why Protons?

Comparison of single-beam proton and photons treatments for retinoblastoma

Protons  Photons

Gy
49
48
46
40
30
20
Why Protons?

Comparison of single-beam proton and photons treatments for retinoblastoma.
The Ultimate Goals of any Cancer Therapy

Complication-free Tumor Control
The 2 legs of Proton Radiotherapy

High-Dose Target coverage

Reduction of low-moderate dose volume
HISTORIC MILESTONES OF CLINICAL PROTON-RADIOThERAPY
1946 - Robert D. Wilson publishes the concept of **PROTON-BASED** therapy

**Start of Proton Therapy:**
- 1954 - Lawrence Berkeley Laboratory, USA
- 1957 - Gustav Werner Institute, Uppsala, Schweden, *(first treatment of a cancer patient)*
- 1961 - Harvard Cyclotron Laboratory, USA
Early clinical Phase: Proof of Safety and Efficacy

1974 — Modern era of fractionated, „large field“ Proton Therapy Collaboration between Massachusetts General Hospital und Harvard Cyclotron, Boston und Cambridge, USA
Early Clinical Phase: Proof of Safety and Efficacy

Choice of clinical Indications and tumor entities =
tumor models with highest chance to proof superiority of protons

Emphasis: increasing tumor dose in tumors with unsatisfactory cure rates by combining protons with 3D-treatment planning
Proton-Radiotherapy: Eye tumors

Start 1976 USA (MGH)
Start 1984 Europa (PSI)
> 15 000 patients treated world wide

> 98% diagnosis: melanoma of the retina
Proton-Radiotherapy:  
Eye tumors

Local Tumor Control (at actuarial 10 years and depending in size and site)

- 96% (PSI, > 5000 patients)
- 95.7% (MGH/MEEI)

Retention of the eye: depending on tumor size and location, about 70-97% (PSI)
Primary skull base tumors:
- Chordoma, Chondrosarcoma

Secondary infiltration from intracranial tumors:
- Meningioma

Secondary infiltration from primary H&N tumors:
- Nasopharynx CA,
- Paranasale Sinus CA,
- Adenoid-cystic CA
- A.o.
Proton-Radiotherapy for skull base tumors:

Paul Scherrer Institute (> 120 pts.):  Mass. General Hospital (> 500 pts.)
Local control 5 years Local control 5 years
Chordoma 81 % Chordoma 73 %
Chondrosarcoma 94 % Chondrosarcoma 98 %

Severe Late Toxicities: 5 – 7 %
Chordomas of the Base of Skull

5-year Local Control rates (%)

Dose [Gy (RBE)]

- Photons
  - Romero 1993
  - Zorlu 2000
  - SRT – Heidelb. 2000

- Protons
  - MGH 1999
  - PSI 2007
  - LLUMC 1999

- C-ions
  - GSI
Chordomas of the Base of Skull

5-year Local Control rates (%)

Dose [Gy (RBE)]

SMALL CHORDOMAS CHONDROSAR COMAS SOME CARBON IONS

Photons
- Romero 1993
- Zorlu 2000
- SRT – Heidelb. 2000

Protons
- MGH 1999
- PSI 2007
- LLUMC 1999

C-ions
- GSI
Primary tumor: tongue

Recurrence at 6 yrs.: skull base

Proton-Radiotherapy for skull base tumors: Adenoid Cystic Carcinoma of the H&N
Adenoid-cystic Carcinoma of the Lacrimal gland
(treated at Massachusetts General Hospital)

“Sculpting” of the dose distribution by protons
Adenoid-cystic Carcinomas with infiltration of the skull base

Photons:
- Chen (UCSF, 2006)
- Historic data

5-year Local Control (%) vs. Dose [Gy (RBE)]
Adenoid-cystic Carcinomas with infiltration of the skull base

- Neutrons:
  - Lawrence (1993)
Adenoid-cystic Carcinomas with infiltration of the skull base

C-ions:
Schulz-Ertner et al.
GSI – U Heidelberg
Adenoid-cystic Carcinomas with infiltration of the skull base

5-year Local Control (%) vs. Dose [Gy (RBE)]

Protons:
Pommier et al.
MGH, 2006
Proton Radiotherapy:

High-dose and/or hypofractionated therapy concepts increased tumor control compared to conventional photon RT by approximately 10–50%.

Examples: Skull Base Chordomas, Chondrosarcomas and adenoid cystic Carcinomas, Uveal Melanomas, Unresectable Sarcomas (paraspinal, sacral)
Clinical Phase of the 90’s: Start of hospital-based Proton Radiotherapy
Introduction of Gantry

Choice of clinical Indications = Exploring high-frequency diseases: Prostate, lung
Prostate Cancer-80 Gy

IMRT

PROTONS
Prostate Ca
> 12 000 Patients  (annually approx. 50% of all PT)

- Loma Linda University Medical Center (Drs. Rossi, Slater)
- 1255 patients treated between 10/91 and 12/97
- Patients had no prior surgery or hormonal therapy
- 74-75 CGE at 1.8 – 2.0 CGE per fraction
- Follow-up mean 63 mos., median 62 mos. (range 1-132)

<table>
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<tr>
<th>Stage</th>
<th>Patients</th>
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<tr>
<td>1A/1B</td>
<td>35</td>
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<tr>
<td>1C</td>
<td>314</td>
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## Treatment Morbidity
### RTOG Scale

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<tr>
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<th>Grade 2</th>
<th>Grade 3 &amp; 4</th>
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<tbody>
<tr>
<td>GI</td>
<td>3.5%</td>
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<tr>
<td>GU</td>
<td>5.4%</td>
<td>0.3%</td>
</tr>
<tr>
<td>Total</td>
<td>9%</td>
<td>0.3%</td>
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</tbody>
</table>
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 28.8GyE

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.
Proton-Radiotherapy for early Stage Lung Cancer

Hypofractionated Proton Radiotherapy for Stage I Lung Cancer.
Bush et al. Chest 126(4), 2004

• Proton radiotherapy only
• 68 patients,
• T1 (29 patients) and T2 (39 patients), NO, MO
• medically inoperable Non-small-cell Lung CA
• Dose: 51 cobalt Gray equivalent (CGE) in 10 fractions over 2 weeks. Subsequently 60 CGE in 10 fractions.
• Median follow-up time 30 months
Hypofractionated Proton Beam Radiotherapy for Stage I Lung Cancer.
Bush et al. Chest 126(4), 2004

- No symptomatic pneumonitis or late esophageal or cardiac toxicity
- 3-year local control: 74%; 3-year disease-specific survival: 72%
- Local tumor control T1 vs T2 tumors = 87% vs 49%
- Trend toward improved survival.
Status of Proton-Radiotherapy for Carcinoma of Prostate and inoperable Lung-CA:

- Thus far a conservative approach
- Similar dose levels and fractionation regimen compared to modern photon RT (IMRT, SBRT etc.)
- Similar rates of tumor control – as had to be expected
- Indications of decreasing rates of severe side effects for protons.

**URGENTLY NEEDED: IDENTIFY SUBGROUPS OF PATIENTS THAT WILL LIKELY BENEFIT MOST FROM PROTONS. DOSE-ESCALATION STUDIES.**
Carbon Ion Therapy for Lung Cancer: The NIRS experience
Clinical Study on Carbon Beam Therapy for Stage I Non-Small Cell Lung Cancer

Dose-escalation

- 59.4 GyE
- 64.8
- 72.0
- 79.2
- 86.4
- 90.0
- 95.4

Dose recommended
- 90 GyE
- 72 GyE

Total 129 pats

For stage IA
- 60.0 GyE

For stage IB
- 52.8 GyE

From: Dr. Tsujii – ESTRO Teaching course 2009
Four beam irradiation

From: Dr. Tsujii – ESTRO Teaching course 2009
Local Control vs. Carbon Ion Dose for Different Fractionations in NSCLC

Local Control (%)

GyE:
- 9 Fr.
- 18 Fr.
- 4 Fr.
- 1 Fr.

Patients’ data
- 30 GyE (TCP=0.95)

From: Dr. Tsujii – ESTRO Teaching course 2009
Radiation Therapy for Malignancies of the Childhood

- The Issue:
  - Cure
  - Quality of Life for
  - the Surviving Cancer Patient
Orbitales Rhabdomyosarkom: Protonen versus Photonen

Hein, Hug et al.
IJROBP 62, 2005

Hug, et al. IJROBP,
47, 2000
Orbitales Rhabdomyosarkom: Protonen versus Photonen

Hein, Hug et al. IJROBP 62, 2005

Hug, et al. IJROBP, 47, 2000
Proton-Radiotherapy for children and young adults:

REDUCTION OF THE „IRRADIATED VOLUME“

= REDUCTION OF LATE EFFECTS

= REDUCTION OF RISK FOR INDUCTION OF SECOND MALIGNANCY (SCANNING TECHNOLOGY)
Proton Therapy at PSI for children and infants:

Collaboration: PSI, University Hospital and Childrens’ Hospital Zürich
Proton Radiation Therapy for pediatric indications:

- Established and accepted modality
- permitted in multi-institutional studies of Children’s Oncology Group (USA)
- growing acceptance in European studies
- At PSI: continuously 5 children under treatment, 3-4 with general anesthesia
- Main focus at PSI: brain tumors, sarcomas
Proton RT

• after >35 years and > 50 000 patients treated no single disease entity ever treated with protons was later found unsuitable

• no publication has raised the issue of unexpected acute or late toxicity. Any incidence of late toxicity is related to high dose escalation rather than use of protons.

• The initial concept of physical dose distribution and effectiveness has not been called into question by clinical results

• HOWEVER: NO Phase III trials available comparing protons and photons. All data based on Phase I/II trials or retrospective reviews. Limited multi-institutional collaboration.
Types (Modalities) of EXTERNAL beam Radiation Therapy (RT)

Single Fraction RT  
(photons = x-rays)  

- **Radiosurgery (RS)**
  - Gammaknife, Cyberknife, Tomotherapy, Rapid Arc

Multiple Fraction RT  
(photons = x-rays)  

- 2D-standard RT
- 3D-standard RT
- Stereotactic RT
- Intensity Modulated RT (IMRT), IGRT, adaptive RT

**Particles**
- Electrons
- Neutrons
- Carbon Ions
- Protons
Planning-Comparison:

Tomotherapy versus IMPT

for high-risk Prostate CA –

RT to prostate, seminal vesicles and pelvic LN‘s

Lamberto Widesott, Claudio Fiorino, Ralf Schneider, Tony Lomax
Tomotherapy

IMPT
Tomotherapy

IMPT

78 Gy

15 Gy
Tomotherapy vs IMPT 3 fields

Dose [Gy]

Bladder_Tomo
Rectum_Tomo
Bulb_Tomo
Bladder_Proton
Rectum_Proton
Bulb_Proton

OARs
Combined rectal dose–volume curves for proton therapy and intensity-modulated radiotherapy (IMRT) ($n = 20$ plans)

Volume Comparison of Proton Therapy and Intensity-Modulated Radiotherapy for Prostate Cancer
Vargas et al, IJROBP 2008, 70(3):744
Volume Comparison of Proton Therapy and Intensity-Modulated Radiotherapy for Prostate Cancer

Vargas et al, IJROBP 2008, 70(3):744
Conventional Wisdom *:

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<th>„low“ dose range</th>
<th>„moderate“ dose range</th>
<th>„high“ dose range</th>
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<tr>
<td>1 Gy ---- 10/15 Gy</td>
<td>15/20 ---35/45 Gy</td>
<td>60/65 Gy and up</td>
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<tr>
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<td>50/55 Gy and up</td>
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<tr>
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<td>„therapeutic“ dose range</td>
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<tr>
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<td>(most solid tumors)</td>
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{Official definition of “low dose”}
ICRU: < 5% isodose (report in progress)
BEIR IV Committee: < 0.1 Gy}

* = for use in radiooncology, not general public
Conventional Wisdom (i.e. my personal interpretation as clinician)*:

- "low" dose range: 1 Gy ---- 10/15 Gy
- "moderate" dose range: 15/20 --- 35/45 Gy
- "therapeutic" dose range (most solid tumors): 50/55 Gy and up
- "high" dose range: 60/65 Gy and up

{Official definition of "low dose"
ICRU: < 5% isodose (report in progress)
BEIR IV Committee: < 0.1 Gy}

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The Paradigm Shift
in proton therapy
equipment and facility
design
Paradigm of 80’s and 90’s:

*From research institute to hospital based large-scale facilities serving large geographic regions*
**Proton-Radiotherapy facilities: the paradigm shift**

*Paradigm since 2000:*

*From large scale facilities to smaller facilities with few rooms or even single-room units serving populations of a mid-size Cancer Center*

Prerequisite: Reduction of production costs, stable reimbursement system, established and accepted indications
The Future of Particle Therapy

„Particles for everybody“

Proton accelerator and delivery technology are the furthest advanced amongst particles and will likely continue its success.

Wide-spread availability of protons is imminent.
"Cure without complications" will become a major paradigm for curable patients.

Protons (and other particles?) will become the "RT modality of choice" for

- pediatric malignancies,
- in young adults,
- patients with tumor-unrelated co-morbidities
- for selected indications
Carbon Ion Therapy:

Clinical results limited in number and institutions

- „Safety and Efficacy“ phase successfully passed
- Majority of clinical outcomes data similar to protons.
- Hypothetical superiority to protons for „radioresistant“ tumors not generally demonstrated
- Promising data for large, unresectable tumors
- Exciting data on single/few fraction treatments of lung and liver CA
- Need more data before conclusions can be drawn
- Versatility to study different particles, combining particles etc. very promising
What we clinicians need from particle researchers and developers:

• More compact (Carbon ions, Gantries)
• More precise, i.e. a „sharper“ beam (lateral penumbra)
• Faster (scanning of mobile tumors)
• Cheaper (particle therapy is the logical evolutionary next step of radiotherapy. The ONLY argument against particles are high costs)
• Continuation of creative solutions
Continue the search and quest for the „Holy Grail“ of particle therapy:

The illusive „ideal particle“ has yet to be found
THANK YOU !