Radiation for local control.

Is Proton Therapy the panacea?

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What is Proton Therapy?

What is it good for?
What is Bragg Peak?

Depth Distribution of Energy

- **PHOTONS**
- **PROTONS**

Delivered radiation dose to tissues outside of the tumour during conventional radiation.

Bragg peak

- **Tumour**

Bethe-Bloch formula:

\[
\frac{\Delta E}{\Delta x} \sim -\frac{\rho}{v^2}
\]

Energy loss (\(\Delta E\)) per unit length (\(\Delta x\)):

- **Density**
- **Velocity**

Reduction of proton fluence: 1.2% /cm

Dose, including losses

Dose from nuclear reactions

Interaction with **electrons**

- **Ionization**
  - "no" deflection, small \(\Delta E\)
  - \(< \text{keV}\)
What is Bragg Peak?
What do we do currently?
Comparison of plans IMRT vs Proton

• Low dose that matters !!
What is Proton indicated for?

- Uveal melanoma
- Paediatrics cancer
- Ewings sarcoma
- Chondrosarcoma
- Base of skull tumors
The Promises and the Peril

The Promises:
- Lower upstream dose
- No downstream dose

The Peril:
- Finite Range !!!

Graph showing dose vs. depth for different types of beams:
- Photons 10MV
- Protons: Spread-out Bragg Peak
- Protons: Pristine Bragg Peak

Increased density indicated by a shaded area.
The rationale for proton radiation therapy for extra-carnial lesions

- High target doses of ~ 70 Gy(RBE)
- Targets close to or surrounded by radiation-sensitive structures
e.g. lung tissue
  heart, vessels
  kidneys, liver, intestines
  spinal cord
  peripheral nerves
  pediatric organs and tissues,
  entire growing and maturing body
- Large volumes, ⇒ need to reduce integral dose to compartments
- Irregularly shaped targets, making 3-D conformation challenging

Dose, Site, Size and Shape matter for the decision to use protons
Para-spinal / para-vertebral tumors

**rare lesions** (e.g. plasmocytoma, chondrosarcoma, chordoma, osteosarcoma, Ewing’s sarcoma in pediatric patients)

**demanding treatment concepts**

- surgical resection (often anatomic / functional restrictions for en bloc resection)
- chemo-resistance of some histologies
- need for high-dose radiotherapy to relatively large volumes, inherently situated very closely to sensitive structures
- outcome data after conventional radiotherapy often unsatisfactory due to dose limitations given by normal tissues
- particles and novel RT-technologies offer improved dose distributions
Para-spinal / para-vertebral tumors –
Extra-cranial chordomas treated with spot-scanning technology at PSI

The situation

- all targets adjacent to / surrounding spinal cord and/or nerves
- target doses >70 Gy(RBE)
- ~ 50% patients with substantial gross residual disease after surgery
- ~ 50% after surgical stabilization of the spine with Titanium implants

- consecutive difficulties:
  definition of targets & OARs
  precision of tissue densities
  calculation of beam range & dose distribution
Spot-scanning-based proton therapy for extracranial chordoma

• n = 40 (1999 – 2006)

• Median Follow-up: 43 months (24 – 91 months)

• Median total dose: 72 Gy (RBE) (59.4 – 75.2 Gy(RBE))

• 48% (19/40) gross residual disease

• 53% (21/40) surgical stabilization with Titanium implants
Spot-scanning-based proton therapy for extracranial chordoma

Complex Titanium implants

Dose distribution, spot scanning

Titanium implants, effects on CT

IMPT, dose reduction in nerve roots & cauda

SFUD
Spot-scanning-based proton therapy for extracranial chordoma

T-spine chordoma with extensive metal implants

Spot-scanning-based proton therapy for extra-cranial chordoma

Entire cohort (n=40):
- 62% OALC
- 80% OAS
- 57% QADSF
- 2 Grade III toxicities: 1 osteonecrosis, 1 soft tissue necrosis both after extensive surgeries
Proton therapy for extra-cranial sarcomas / chordomas –
Experiences at other institutions

Phase II Study of High-Dose Photon/Proton RT of Spine Sarcomas
DeLaney et al. MGH, IJROBP 2009; 74:372-9

n = 50 primary & recurrent TUs
(29 chordomas, 14 chondrosarcs.,
7 other)
GRD = 50%
med. F/U = 48 m
tot. dose = 77.4 Gy(RBE) to GD
= 70.2 to micr. dis (TU-bed)
= 50.4 to subclin.dis.;
some Y^{90} dural plaques
LF = 31% (5/16) with metal implant
= 12% (4/34) without (p=0.103)
toxicities = 3 sacral nerve injuries >Grade 2

5-y LC = 78%
RFS = 63%
OAS = 87%
Sacral chordomas: High-dose p+X-RT +/- surgery for primary vs. recurr. TU

\[ n \] = 27 (16 primaries, 11 recurrent TUs)

Time period = 1982 - 2002

Min. F/U = 3 ys

Surg. + RT = 78% (21/27: 21/14 prim.; 1/7 recurr.)
RT only = 23% (6/27)

Tot. dose = 71 Gy(RBE) mean (prim.)
= 77 Gy(RBE) mean (recurr.)

Surg. + RT = LC 85.7% (12/14 prim.); 14% (1/7 recurr.)
RT alone = LC 91% (10/11 marg.+ prim), 0/5 marg.+ rec.

RT alone = LC 3/4 (≥ 73 Gy(RBE))
Proton therapy for extra-cranial sarcomas / chordomas –
Experiences at other institutions

Proton-based Radiotherapy for unresectable or incompletely resected osteosarcoma

n = 55 (33 = 60% extra-carnial)
Time period = 1983 – 2009
Med. F/U = 27 m (0 – 196)
p+ + X-RT = 58.2% protons as part of total radiation (11 – 100%)
+ surg. + CTX = 78% surgery; 91% CTX
Tot. dose = 68.4 Gy(RBE) mean

Outcome
3ys = LC 82%, DF=26%
5ys = LC 72%, DF=26%, DFS=65%, OAS=67%
Risk factors = ≥ Grade 2 histology, total treatment time
Toxicities = 30.1% Grade 3-4 late toxicity
Proton therapy for extra-cranial sarcomas / chordomas –
Experiences at other institutions

The role of radiotherapy in osteosarcoma
Schwarz R et al., Med. Center HH-Eppendorf; Cancer Treat Res. 2009;152:147-64

n = 100 (66 prim., 11 recurr., 23 mets.)
Med. F/U = 17.4 m (2.1 – 47.3)
TTT = all CTX – important for response to RT;
  98 X-RT, 2 p+, 2 IORT, 2 NT
  +/-biopsy / surgery
Dose = 55.8 Gy med. (30 – 120)
5-y LC = 30% all
  = 48% surgery + RT
  = 22% RT alone
  = 40% primary TU
  = 17% recurrence
5-y OAS = 41% biopsy
  = 36% whole group RT
  = 55% primary TU
  = 15% recurrence
Retroperitoneal sarcomas

The situation

- **Rare** tumors, 15% of all STS, incidence ~1600/y in U.S.
- **Primary therapy**: surgical resection, as complete as possible (en bloc ...)
- Controversial attitudes towards optimal treatment concepts and the role of RT
- **Targets** adjacent to, surrounding and/or surrounded by radiation-sensitive structures (kidney, liver, intestines, spinal cord)
- Adequate target doses (>70 Gy(RBE)) are often judged to be not applicable (in many cases and centers)
- **Local recurrence rates after surgery alone >40%**
- modern RT technologies and the use of particle beams offer new treatment options
Retroperitoneal sarcomas

Radiotherapy and extent of surgical resection in retroperitoneal soft-tissue sarcoma: multi-institutional analysis of 261 patients
Sampath S et al., Univ. of Utah, J Surg Oncol. 2010 Apr 1;101(5):345-50

n = 261
TTT = surgery +/- positive margins
71 (27%) plus RT
Dose med. = 50.2 Gy mostly post-op
F/U med. = 59 m
5-y CSS = 73% (Grade, histol., surg.margin predictive p<0.05)
5-y LFFS = 66%
= 79% with RT
= 64% without RT
Retroperitoneal sarcomas

Feasibility study of volumetric modulated arc therapy for the treatment of retroperitoneal sarcomas.
Llacer-Moscardo C et al., Montpellier, Radiat Oncol 2010 Sep 20;5:83

Dosimetric study
- 6 preoperative (A)
- 4 postoperative (B)
Prescribed dose
- 45 Gy for group A
- 50 Gy for group B
PTV=CTV+5 mm
CTV=GTV+10 mm or
the tumoral bed
RapidArc Eclipse
Normalization:
coverage of 99% of the
PTV by 95% of the dose
Retroperitoneal sarcomas

Proton-beam, intensity-modulated, and/or intraoperative electron radiation therapy combined with aggressive anterior surgical resection for retroperitoneal sarcomas


<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All patients</th>
<th>Patients with primary tumors</th>
<th>Patients with local recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>28</td>
<td>20</td>
<td>8</td>
</tr>
<tr>
<td>External-beam radiation median dose, Gy (range)</td>
<td>50.0 (37.5–66.6)</td>
<td>50.0 (45–66.6)</td>
<td>50.2 (37.5–54)</td>
</tr>
<tr>
<td>Type of external-beam radiation, n (%)</td>
<td>10 (35.7%)</td>
<td>6 (30.0%)</td>
<td>4 (50.0%)</td>
</tr>
<tr>
<td>Proton beam</td>
<td>11 (39.3%)</td>
<td>8 (40%)</td>
<td>3 (37.5%)</td>
</tr>
<tr>
<td>Intensity modulated</td>
<td>7 (25%)</td>
<td>6 (30.0%)</td>
<td>1 (12.5%)</td>
</tr>
<tr>
<td>Both proton beam and intensity modulated</td>
<td>7 (25%)</td>
<td>6 (30.0%)</td>
<td>1 (12.5%)</td>
</tr>
<tr>
<td>Timing of external-beam radiation, n (%)</td>
<td>20 (71.4%)</td>
<td>14 (70%)</td>
<td>6 (75%)</td>
</tr>
<tr>
<td>Preoperative</td>
<td>6 (21.4%)</td>
<td>5 (25%)</td>
<td>1 (12.5%)</td>
</tr>
<tr>
<td>Postoperative</td>
<td>2 (7.1%)</td>
<td>1 (5.0%)</td>
<td>1 (12.5%)</td>
</tr>
<tr>
<td>Intraoperative radiation</td>
<td>12 (42.9%)</td>
<td>8 (40%)</td>
<td>5 (62.5%)</td>
</tr>
<tr>
<td>Patients, n (%)</td>
<td>11 (6–15)</td>
<td>11.75 (7.5–15)</td>
<td>10 (6–12.5)</td>
</tr>
</tbody>
</table>
Retroperitoneal sarcomas

Proton-beam, intensity-modulated, and/or intraoperative electron radiation therapy combined with aggressive anterior surgical resection for retroperitoneal sarcomas


DVHs for IMRT & proton beams
- Liver
- Small bowel
- Stomach
- Left kidney
- Colon
- Spinal cord
Retroperitoneal sarcomas

Proton-beam, intensity-modulated, and/or intraoperative electron radiation therapy combined with aggressive anterior surgical resection for retroperitoneal sarcomas

F/U med. = 33 months
3-y LRFS = 90% (primaries), 30% (recurrent TUs)
Proton therapy for extra-cranial tumors – summary

- The oncological concept must be defined

- Oncological concepts are mainly determined by biological factors (e.g. histology, grade, local & systemic aggressiveness, surgical margins, primary vs. recurrence, ....)

- Expectations must be clear

- WHY Protons? – a serious medical question to a physical method

- Protons give geometrically superior dose distributions (in most cases)

- „Geometry“ needs to be translated into „biology“ (effect of dose to tissues)

- Significant improvements in LC, reduced toxicity and survival are hard to show

- Learning curves have to be considered and analyzed