Proton Radiotherapy for Skull Base and Para-spinal Tumors

Carmen Ares
Tumors of the Skull Base

• Primary tumors
  - Chordomas, Chondrosarcomas

• Secondary infiltration or involvement by intracranial tumors
  - Meningiomas

• Secondary infiltration by primary H&N tumors
  - Adenoid Cystic Ca
  - Nasopharynx Ca
  - Paranasal Sinus Ca
Skull Base Primary Tumors:

Chordomas and Chondrosarcomas
Primary tumors: Chordomas

- rare primary bone tumor
  
  # incidence rate <0.1 per 100,000 per year

  # accounts for 1 - 4% of all primary malignant bone tumors

- arise from embryonic remnants of notochord

- show a dual epithelial-mesenchymal differentiation
Primary tumors: Chordomas

- microscopic foci of notochord remain in the vertebral bodies of the embryo

- **malignant transformation** typically occurs in:
  
  # 3rd - 4th decades of life for spheno-occipital lesions

  # 5th - 6th decades for the sacro-coccygeal type
Primary tumors: Chordomas

- as have ectodermal origin are technically not sarcomas

- however traditionally classified and approached as sarcomas on the basis of being a primary bone tumor
Primary tumors: Chordomas

- Usually relatively slow-growing, low grade malignancies

- Localization
  - Sacrum 50% - 60%
  - Skull base region 25% - 35%
  - Cervical spine 10%
  - Thoraco-lumbar spine 5%
Primary tumors: Chordomas

- Have **low metastatic potential**

- **Control of primary disease remains the major therapeutic challenge**

- Metastasis usually occur after the local failure of the disease (to lung, bone, soft tissue, lymph node, liver, and skin)
Primary tumors: Chondrosarcomas

- Develop in any bone performed by cartilage
- Primary chondrosarcomas of the cranial base arise from the chondrocranium
- Association with
  # Ollier’s disease (enchondromatosis)
  # Maffucci’s syndrome (enchondromatosis + hemangiomatosis)
Primary tumors: Chondrosarcomas

Primary chondrosarcomas of the cranial base arise from the chondrocranium

**Chondrocranium**
Part of the skull base that undergoes enchondral ossification during fetal life
Primary tumors: Chondrosarcomas

Histology

Conventional chondrosarcoma of the skull base can resemble chordoma, and indeed it is misdiagnosed frequently as such.
**IMMUNOHISTOCHEMISTRY:**

Chondrosarcoma (ChSa) vs. Chordoma (Ch)

<table>
<thead>
<tr>
<th>Marker</th>
<th>ChSa</th>
<th>Ch</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epithelial Markers</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>(cytokeratin, EMA)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>S-100</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

Carmen Ares, Center for Proton Therapy, Winter School, January 10-13, 2010
In 37% of the 200 patients treated with PT for low-grade ChSa, the referral diagnosis was Ch and changed to ChSa upon review of the tumor material at MGH utilizing:

- H & E Stains
- Immunohistochemistry

Primary Skull Base Tumors

**Chordomas:**
Midline, soft, gelatinous

**Chondrosarcomas:**
Midline or lateral, can be calcified, hard
Primary Skull Base Tumors

- **Chordomas and chondrosarcomas** located in the skull base are uncommon tumors and **challenging to manage**

- The ability to obtain a **complete surgical resection remains elusive for many patients**

- Collaboration between surgeon and radiation oncologist **critical**
  - Surgical goal: **accomplish maximally safe tumor reduction**
  - **Improve geometry for Proton RT** (decompression of brainstem, optic chiasm etc.)
Primary Tumors of the Skull base

Results
Primary skull base tumors: Surgery series

- Tzortzidis et al (1) in 74 patients with chordomas who underwent surgery aimed at performing complete resection, accomplished gross total removal in 53 patients (71.6%)

- The 10-year recurrence-free survival was 31% indicating that even after a gross total removal the likelihood of tumor control is low with surgery alone

1 Neurosurgery 2006;59:230-7
Primary skull base tumors: Photon RT series

• Local control rates after total doses <60 Gy is disappointing and most patients died of locally progressive disease

• Recurrences rates as high as 70 to 100% even for small lesions have been reported after conventional RT

- Catton, R&O 1996 5 y LC 20%
- Rich, Cancer 1985 5 y LC 28%
- Zorlu, Neurol Sci 2000 5 y LC 23%
<table>
<thead>
<tr>
<th>Author</th>
<th>Institution</th>
<th>Year</th>
<th>Journal</th>
<th>Volume</th>
<th>Pages</th>
</tr>
</thead>
</table>
## Primary skull base tumors: Stereotactic RT series


<table>
<thead>
<tr>
<th></th>
<th>Chordomas</th>
<th>Chondrosarcomas</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>37</td>
<td>8</td>
</tr>
<tr>
<td>Median dose</td>
<td>66.6 Gy</td>
<td>64.9 Gy</td>
</tr>
<tr>
<td>mean follow-up</td>
<td>27 months</td>
<td>19 months</td>
</tr>
<tr>
<td>5-y LC</td>
<td>50 %</td>
<td>100 %</td>
</tr>
</tbody>
</table>
## Primary skull base tumors: Radiosurgery series

<table>
<thead>
<tr>
<th></th>
<th>Chordomas</th>
<th>Chondrosarcomas</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>5-y LC</td>
</tr>
<tr>
<td><strong>Krishan, 05</strong>*</td>
<td>25</td>
<td>32 %</td>
</tr>
<tr>
<td><strong>Martin, 07</strong>*</td>
<td>18</td>
<td>53 %</td>
</tr>
<tr>
<td><strong>Hasegawa, 07</strong></td>
<td>30</td>
<td></td>
</tr>
<tr>
<td><strong>Liu, 08</strong></td>
<td>28</td>
<td>21 %</td>
</tr>
<tr>
<td><strong>Dassoulas, 09</strong></td>
<td>15</td>
<td>50%</td>
</tr>
</tbody>
</table>

* 19 patients external RT previously or in conjunction with RS (median dose 50.4 Gy)
# 22 patients external RT previously
Primary skull base tumors:

Stereotactic RT and RS series

• Stereotactic RT and Radiosurgery can be a good option for the treatment of selected patients with small chondrosarcomas of the skull base

• Local control of selected patients with small chordomas of the skull base is inferior to proton series
PSI experience

Skull base chordomas and chondrosarcomas

Experience 1998 - 2005
Fractioned Proton Therapy at *Paul Scherrer Institute*

**Fraction Dose:** 2.0 Gy (RBE), 5 frcts. per week

\[ CTV = 54 \text{ Gy (RBE)} \quad \text{GTV} = 74 \text{ Gy (RBE)} \]

**OAR constraints:** OPTIC Chiasm and Nerves: 60 Gy(RBE); Brainstem surface 64 Gy(RBE); BS-Center: 53 Gy(RBE), BS max. volume: 60 Gy(RBE) < 1.0 cc.

Carmen Ares, Center for Proton Therapy, Winter School, January 10-13, 2010
Primary skull base tumors: PSI experience

Material & Methods

- N = 64 patients (Oct-98 Nov-05)
  - Chordoma 42 (65%)
    (3/42 chondroid features)
  - Chondrosarcoma 22 (34%)
    (low grade → 5 G2, 17 G1)

- Mean age 44.5 years
- Minimum follow-up 14 months
- Mean follow-up 38 months (14 - 92 months)
Primary skull base tumors: PSI experience

Material and Methods

• Prescription dose (mean) (at 2 Gy(RBE) per frct., 4 fractions per week)
  – Chordoma (Ch) 74 Gy(RBE) (range 67 - 74)
  – Chondrosarcoma (ChSa) 68 Gy(RBE) (range 63 - 74)

• GTV volume (mean) 25.8 cc (1.5 - 100 cc)
  – Ch 27 cc
  – ChSa 23 cc
Skull base tumors: PSI experience

Local control definition

Local control defined as radiological control by MRI ± CT
<table>
<thead>
<tr>
<th></th>
<th>Chordoma (n = 42)</th>
<th>Chondrosarcoma (n = 22)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Local failure</strong></td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>male</td>
<td>1*</td>
<td>0</td>
</tr>
<tr>
<td>female</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td><strong>Deaths</strong></td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>local progression</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>NED</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td><strong>Brainstem compression vs. local failures</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1*</td>
<td>0</td>
</tr>
<tr>
<td>Yes</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Abutment</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

* patient with surgical pathway failure

P = 0.0077
Primary skull base tumors: PSI experience

Local control

Actuarial Local Control

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>3 years</th>
<th>5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chordomas</td>
<td>87 %</td>
<td>81 %</td>
</tr>
<tr>
<td>Chondrosarcomas</td>
<td>94 %</td>
<td>94 %</td>
</tr>
</tbody>
</table>

P = 0.25
Primary skull base tumors: PSI experience

Disease Specific Survival

<table>
<thead>
<tr>
<th></th>
<th>3 years</th>
<th>5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chordomas</td>
<td>90%</td>
<td>81%</td>
</tr>
<tr>
<td>Chondrosarcomas</td>
<td>100 %</td>
<td>100 %</td>
</tr>
</tbody>
</table>
Primary skull base tumors: PSI experience

Example of chondrosarcoma with subsequent local relapse

Pre-Proton-RT

GTV

V95 → 48%

Brainstem compression
Primary skull base tumors: PSI experience

Prognostic factors for LC in chordoma:

• Brainstem compression
  yes / no  p= 0.0077

• Residual tumor volume
  ≤ / > 25 cc  p= 0.03

• Gender  n.s.

• Age  n.s.

• PT for
  primary / recurrence  n.s.

• GTV V95  n.s.

• GTV max, mean or min dose  n.s.
Primary skull base tumors: PSI experience

Radiation induced late toxicity (CTCAE v3.0)

• Asymptomatic MRI white matter changes: 5 patients
  (= G1 neurologic toxicity)

• High grade late toxicity (all Ch): 4 patients
  – optic pathway G 4 → 1 patient (unilateral blindness)
    G 3 → 1 patient (unilateral visual deficit, steroid dependent)
  – neurologic        G 3 → 2 patients (symptomatic brain necrosis)

• Any patient presented brainstem toxicity
Skull base tumors: PSI experience

Radiation induced toxicity (CTCAE v3.0)

Actuarial 5-year freedom for high grade late toxicity

94%

Due to the small number of events no risk factors predictive of high grade toxicity were identified.
## Skull Base Chordomas: Comparison of Literature

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Radiation</th>
<th>Mean dose</th>
<th>LC 3-yr</th>
<th>LC 5-yr</th>
<th>LC 10-yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Munzenrider, 1999</td>
<td>169</td>
<td>PT, RT</td>
<td>76</td>
<td>73</td>
<td>54</td>
<td></td>
</tr>
<tr>
<td>Terahara, 1999</td>
<td>115</td>
<td>PT, RT</td>
<td>69</td>
<td>59</td>
<td>44</td>
<td></td>
</tr>
<tr>
<td>Hug, 1999</td>
<td>33</td>
<td>PT, RT</td>
<td>71</td>
<td>67</td>
<td>59</td>
<td></td>
</tr>
<tr>
<td>Noel, 2005</td>
<td>100</td>
<td>PT, RT</td>
<td>67</td>
<td>86 @2y</td>
<td>53 @4y</td>
<td></td>
</tr>
<tr>
<td>Igaki, 2004</td>
<td>13</td>
<td>PT, RT</td>
<td>72</td>
<td>67</td>
<td>46</td>
<td></td>
</tr>
<tr>
<td>Schulz-Ertner, 2007</td>
<td>96</td>
<td>Carbon, RT</td>
<td>60 *</td>
<td>81</td>
<td>70</td>
<td></td>
</tr>
<tr>
<td>Mizoe, 2009**</td>
<td>33</td>
<td>Carbon</td>
<td>57 *</td>
<td>85</td>
<td>64</td>
<td></td>
</tr>
<tr>
<td>Ares, (PSI) 2009</td>
<td>42</td>
<td>PT</td>
<td>74</td>
<td>87</td>
<td>81</td>
<td></td>
</tr>
</tbody>
</table>

* at 3.0 Gy (RBE) per fraction

** 5y LC = 100% for 19 patients to 60.8 GyE
## Skull Base Chondrosarcomas: Comparison of Literature

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Radiation</th>
<th>Mean dose</th>
<th>LC 3 -yr</th>
<th>LC 5 -yr</th>
<th>LC 10 -yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Munzenrider, 1999</td>
<td>229</td>
<td>PT, RT</td>
<td>72</td>
<td>98</td>
<td>94</td>
<td></td>
</tr>
<tr>
<td>Hug, 1999</td>
<td>25</td>
<td>PT, RT</td>
<td>71</td>
<td>94</td>
<td>75</td>
<td></td>
</tr>
<tr>
<td>Johson, 2002</td>
<td>58</td>
<td>PT, RT</td>
<td>71</td>
<td></td>
<td>91</td>
<td></td>
</tr>
<tr>
<td>Noel, 2003</td>
<td>26</td>
<td>PT, RT</td>
<td></td>
<td>94</td>
<td>75@4y</td>
<td></td>
</tr>
<tr>
<td>Schulz-Ertner, 2007</td>
<td>54</td>
<td>Carbon, RT</td>
<td>60*</td>
<td>96</td>
<td>89@4y</td>
<td></td>
</tr>
<tr>
<td>Ares, (PSI) 2009**</td>
<td>22</td>
<td>PT</td>
<td>68</td>
<td>94</td>
<td>94</td>
<td></td>
</tr>
</tbody>
</table>

* at 3.0 CGE per fraction
** IJROBP
Chordomas of the Base of Skull

5-year Local Control rates (%)

Chordomas of the Base of Skull

Small Chordomas
Chondrosarcomas

Dose [Gy (RBE)]

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

Protons
- MGH 1999
- PSI 2009
- LLUMC 1999

C-ions
- GSI

Carmen Ares, Center for Proton Therapy, Winter School, January 10-13, 2010
Chordoma and Chondrosarcoma of Skull Base and C-Spine (Phase I/II-protocol: selective result reporting)

- **ASTRO 2009, J. Munzenrider** *(IJROBP 72(1), suppl.)*

- 105 patients with skull base or cervical spine Chondrosarcoma or Chordoma
- From 1987 to 1993, either “70.2 (LD) vs. 76 CGE (HD)”

- **F/U: median 16.7 y (4.5-20 y)**

- **Results**

<table>
<thead>
<tr>
<th></th>
<th>5-yr</th>
<th>10-yr</th>
<th>15-yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS all pts. (LD - HD)</td>
<td>81 vs. 81 %</td>
<td>61 vs. 55 %</td>
<td>57 vs. 45 %</td>
</tr>
<tr>
<td>LC for CSA (LD - HD)</td>
<td>94 vs. 85 %</td>
<td>89 vs. 67 %</td>
<td>89 vs. 58 % (p=0.045)</td>
</tr>
</tbody>
</table>

Median time to failure: 11.9 y
No statement on complications in abstract
Chordoma and Chondrosacoma of Skull Base and C-Spine (Phase I/II-protocol: selective result reporting)

- ASTRO 2009, J. Munzenrider *(IJROBP 72(1), suppl.)*

**Results:**

- Late failures occur (MEDIAN time 11 y) – long term f/u essential

- High dose arm with inferior local control – difficult to explain and not consistent with other reported data

- Long term LC for Chondrosarcomas at MGH lower than previously reported. At 10 years likely 80%-90 % compared to >95% ? – conflicting data from the same institution

- Further results of PROG trial needed
Prognostic Factors:

Influence of (residual) tumor size on the ability to achieve local control:

Improved LC for “smaller” size

- < 70 ml vs. > 70 ml (MGH)
- < 20cc vs. 20 - 35cc vs. > 35 cc (LBL) (80% vs. 33%)
- < 25 ml vs. > 25 ml (LLUMC) (100% vs. 56%)

Loma Linda UMC Analysis

RT for Skull Base Chordomas

Prognostic Factors:
Influence of ability to deliver dose vs. limitations of dose delivery 2nd to normal structure constraints:


Factors predicting Local Control:
- 95% GTV encompassed by 95% Isodose (p=0.01)
- Minimal dose < 56 Gy to GTV (p=0.04)
## Prognostic factors

- \((+++\))  
  **Skull base: Chondrosarcomas versus Chordomas**
- \((+++\))  
  **Tumor Size**
- \((++\))  
  **Skull Base versus Spine**
- \((+\))  
  **Primary versus recurrent disease**
- \((+\))  
  **Chondroid versus Non-Chondroid Pathology**
- \((++\))  
  **Gender**
- \((+\))  
  **Age**
- \((+\))  
  **Pediatric versus Adult**
- \((+++\))  
  **Ability versus Inability to deliver dose: Optimal / suboptimal dose distribution by involvement or abutment of critical structures**
- \((+++\))  
  **Radiation Dose**
- \((+++\))  
  **Protons versus Photons**
Future directions for primary skull base tumors
RT for Skull Base Chordomas

GOAL

• Develop a risk-classification

low - intermediate - high

to correlate with recommendations for adjuvant Tx

observation - aggressive Tx - palliative Tx

• Rather than stating “all skull base chordoma patients should / should not undergo adjuvant Tx”

the question should be

“WHICH patient will likely benefit from adjuvant Tx”
Futute directions

• Dose escalation
  → Biological GTV definition
    – PET uptake
    – functional MRI [measure of angiogenesis]
  → Simultaneous Integrated Boost

→ Hypofractionation

→ With Gantry 2 possibility of dose escalation with:
  - smaller pencil beam
  - collimators: dose escalation using inhomogeneous coverage of the GTV

• Concomitant use of biologic agents for high-risk patients not suited for dose escalation
Secondary infiltration from intracranial tumors:

Meningiomas
Secondary infiltration from intracranial tumors: Meningiomas

- extra-axial, slow-growing tumors that arise from the arachnoid cap cells of the central nervous system
- 13 to 26% of primary intracranial tumors
- most common non-glial brain tumors
- The majority are benign (WHO Grade I)
- atypical (WHO Grade II) or anaplastic (malignant, WHO Grade III) are uncommon, accounting for 4.7–7.2% and 1.0–2.8% of all resected meningiomas
- If the tumor is resectable, complete surgical excision is the standard therapy and results in excellent (68–92%) long term tumor control for benign meningiomas
**Secondary infiltration from intracranial tumors:**

**Meningiomas**

**Indications for RT**

- **Subtotal excision**
  
  Local recurrence rates can be decreased from 50 - 60% to 12 - 23% at 8 - 10 years

- **Not resectable tumor** or **contraindication to surgery**
  
  5-y local tumor control rates of 80–86%

- **Atypical and malignant meningiomas** ➔ at high risk for local failure after surgery
  
  RT is recommended to decrease the probability of local recurrence
Secondary infiltration from intracranial tumors:
Meningiomas

Adjuvant treatment or Radical treatment by:

• conventional external beam photon radiotherapy
• 3D conformal radiation therapy
• radiosurgery
• stereotactic fractionated radiotherapy
• intensity modulated radiotherapy (IGRT-IMRT)
• tomotherapy
• etc.etc.
Intracranial Meningiomas – PSI series

- N = 16
- 1997 - 2002
- median follow-up 34.1 months

PT indications
- 8 as adjuvant therapy for incomplete resection
- 5 for recurrence
- 3 radical PT after presumptive diagnosis based on imaging

median prescribed dose was 56 Gy(RBE) (range, 52.2–64)
All atypical meningioma patients received 64 Gy(RBE)

Intracranial Meningiomas – PSI series

- 3-year local control 91.7%
- 3-year progression-free survival 91.7%
- 3-year overall survival were 92.7%
- No patient died from recurrent meningioma
- Cumulative 3-year toxicity free survival was 76.2%.
  - One patient with radiation induced optic neuropathy (SOMA Grade 3)
  - One patient with retinopathy (SOMA Grade 2)
  - One patient developed a symptomatic brain necrosis (CTCAE Grade 4)


Carmen Ares, Center for Proton Therapy, Winter School, January 10-13, 2010
Intracranial Meningiomas

Proton – RT indications at PSI

• Complex benign meningiomas
• Anaplastic meningiomas
• Malignant meningiomas
Secondary infiltration by primary H&N tumors

Adenoid Cystic Ca
Adenoid Cystic Carcinoma of the H&N

Patient A

Primary site: tongue

Skull base recurrence at 6 y.

Patient B

Carmen Ares, Center for Proton Therapy, Winter School, January 10-13, 2010
Adenoid Cystic Carcinoma of the Lacrimal gland
(treated at Massachusetts General Hospital)

“Sculpting” of the dose distribution by protons

Carmen Ares, Center for Proton Therapy, Winter School, January 10-13, 2010
Adenoid Cystic Carcinomas with infiltration of the skull base

![Graph showing 5-year local control (%) vs. dose (Gy (RBE)) with markers for different sources.]

- **Photons:**
  - Chen (UCSF, 2005)
  - Historic data
Adenoid Cystic Carcinomas with infiltration of the skull base

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

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

- C-ions:
  - Schulz-Ertner et al.
  - GSI – U Heidelberg
  - 4-yr LC 78%
Adenoid Cystic Carcinomas with infiltration of the skull base

Pommier et al.
MGH,
Median F/U > 5 yrs
93% 5-yr LC

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

Protons:
Secondary infiltration by primary H&N tumors

Nasopharynx Ca
Paranasal Sinus Ca
Proton Therapy for Re-irradiation of recurrent Nasopharynx Ca.

*Lin R et al for LLUMC, Radiology1999;213:489*

- Patients: 16
- Dx: recurrent Ca of Nasopharynx after full course photon RT
- Re-treatment: Protons to 59.4 – 70.2 CGE at 1.8-2.0 CGE per day
- F/U: mean 23.7 months (range 4 – 47 months)

**Optimal DVH**

≥90 % of Prescription Dose to 
≥90% of GTV (8 patients)

**Suboptimal DVH**

(8 patients)
Local Control probability is dependent on ability to deliver intended dose

Optimal DVH

P = 0.05

Increased LC translates into increased Overall Survival rates: p=0.006
PT for primary sphenoid sinus malignancies

Truong MT et al. MGH. Head & Neck 2009

- 20 patients
  (10 SCC, 7 ACC, 2 Neuroendocrine tumor, 1 AdenoCa)
- 1991 – 2005
- PT – median dose 76 Gy (RBE)

- Median follow-up 27 months
- 2 year
  - LC 86%
  - Regional control 86%
  - Freedom from metastasis 50%
PT for primary sphenoid sinus malignancies

Truong MT et al. MGH. Head & Neck 2009

- 2 years DFS 31%
- 2 years OS 53%

Negative predictive factors
  - Oropharyngeal involvement (p=0.005)
  - Anterior cranial fossa invasion (p=0.02)
  - Brain invasion (p=0.05)
Conclusions

- Referral Centers for rare diseases
- Accumulation of large series of patients treated homogeneously
- Add to understanding of natural history of disease
- Foster multidisciplinary approach
- Accomplishes previously unknown CURE in some patients/tumors
- Understand Prognostic Factors for others
- Develop new treatment algorithms
Spot Scanning Proton Radiation Therapy

for Para-spinal Tumors
Para-spinal Tumors: Introduction

- Primary malignant tumors of the vertebral column are relatively rare with prevalence of 2.5 to 8.5 cases per 100,000 persons per year.

- In adults:
  - Plasmocytoma: 30%
  - Chondrosarcoma: 10%
  - Chordoma: < 5%
  - Osteosarcoma: < 5%

- In children:
  - Ewing’s sarcoma: 4 – 10%
Para-vertebral Tumors: Treatment generalities

- Difficult treatment paradigm because of the complexities of tumor resection (en-bloc resection) and significant resistance to chemotherapy and radiotherapy of some of these tumors

- Novel uses and improvements in advanced radiation techniques improve local control
Para-vertebral Tumors: Treatment generalities

- High-dose RT can provide local control to these “radioresistant” tumors
  - Doses > 70 Gy have demonstrated the benefit
  - These doses are greater than OAR tolerance (i.e. spinal cord)
    - Due to the dose restrictions for the spinal cord and other surrounding structures (esophagus, bowel, kidney) the results of conventional RT have been disappointing
Extracranial Chordomas of the Axial Skeleton treated with Spot Scanning Proton Therapy at PSI
Extracranial Chordomas of the Axial Skeleton treated with Spot Scanning Proton Therapy at PSI

- Update of the initial publication (Rutz HP et al. IJROBP 2007:67(2):512) Updated manuscript in progress.

- N = 40

- 1999 – 2005

- Location:
Extracranial *Chordomas of the Axial Skeleton* treated with Spot Scanning Proton Therapy at PSI

- 19/40 patient (48%): gross residual disease prior to PT (GTV range: 13 - 495 ml)
- 21/40 patients (53%): surgical stabilization (SS) of the axial skeleton
Extracranial Chordomas of the Axial Skeleton treated with Spot Scanning Proton Therapy at PSI

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

- Follow-up period:
  - Median 43 months (range 24 – 91 months)
Chordomas of the Axial Skeleton at PSI: 5-year outcome data

Local control probability
13 / 40 patients with local failure

5-year LC: 62%
Chordomas of the Axial Skeleton at PSI: 5-year outcome data

Prognostic factors analyzed for LC / OS:

- surgical stabilization (SS)
- residual disease
No SS-R:
- only 1 LF in 19 pts
- resulting in actuarial LC rate at 5 years of 100%

With SS-R:
- 12 LF in 21 pts.
- yielding a 5 year LC rate of 30% (p=0.0003)
Local Control Probability (LC): residual disease

The overall LC-rate: Significantly reduced in patients with residual disease

5-year LC rate: 66%

Chordomas of the Axial Skeleton at PSI: 5-year outcomes data
• **Clinical factors:**
  – Negative selection of patients with more advanced tumor – i.e. larger and more complex tumor presentation requiring more extensive surgery?

• **Treatment planning issues:**
  – (Difficulties defining Targets?)
  – Difficulties in dose calculation?
  – Difficulties in range calculations?

Similar experience for passive scattering technique?
Chordomas of the Axial Skeleton at PSI: 5-year outcomes data

Late Toxicity (CTCAE)

- Neurotoxicity: none
- GI or GU-toxicity: none
- 2 Grade III toxicities: 1 soft tissue necrosis and 1 osteonecrosis in patients following extensive surgeries and reconstruction
Conclusion:

- Proton Therapy resulted in excellent Local Control for Chordomas of the axial skeleton

- Despite target doses > 70 Gy(RBE) in vicinity to the spinal cord, no high grade neurotoxicity was observed

- Decreased local control was observed in patients with surgical stabilization and with macroscopic residual disease

- The causes of this result are still under investigation
Mixed photon/proton RT for Sacral Chordomas: long-term MGH experience

Park, Delaney et al. MGH, IJROBP, 65:1514, 2006

- 27 patients
- Tx: 1982-2002
- S+RT 21 pts, RT alone 6 pts
- 16 primary, 11 recurrent Chordomas
- Mean dose 71 Gy(RBE) primary, 77 Gy (RBE) recurrent Chordoma
- Minimum F/U 3 years
- Factors:
  - Primary vs. rec.
  - Positive vs. negative margins
  - S+RT vs. RT only

Local Control (27 pts.):
- 72% at 5 years
- 57% at 10 years
Phase II Study of high-dose Photon/Proton RT of Spine Sarcomas

*DeLaney et al. MGH, IJROBP 2009;74:732-9*

- n = 50
- 29 Chordomas, 14 ChSa, 7 other
- 50 % gross disease
- 77.4 Gy(RBE) gross disease
- 70.2 microsc., 1.8 Gy/fract.
- Some patients dural plaque (Y\(^90\))
- Median F/U 48 months
- Factors: Primary vs. Recurrence (p=signif.)
- Spine stabilization:
  - 5/16 (31%) LF versus 4/34 (12%) without (p=0.103)
- No myelopathy, 3 sacral nerve injuries at 77 Gy

Local Control (50 pts.):
78% at 5 years
IGRT-IMRT Photons for Paraspinal Chordomas and Sarcomas

Terekakis, Bilsky et al. MSKCC, IJROBP, 69:1502-08, 2007

27 patients
Subtotal resection or unresect. disease
5/27 pts. prior RT
Standard fractionated XRT
Median prescr. Dose: 66 Gy (54-71 Gy)
Median F/U 17 months (2.1-47.3)

act. 2-year Local Control: 65%
Carbon ions for sacral chordoma


  - 30 no previous treatment
  - 8 recurrence after previous resection
- Carbon ion median dose 70.4 GyE (52.8 – 73.6) in 16 fractions in 4 weeks
- Median follow-up 80 months

- 5-y OS 86%
- 5-y LC 89%

- 27/30 with primary tumor remained ambulatory with or without supportive devices
- 2 patients G3 skin reaction
- 2 patients G4 skin reaction
- 1 patient sacral fracture
- No G3 or G4 urinary or rectal toxicity
- 3 severe and permanent neurological impairment
Proton Radiotherapy for Skull Base and Para-spinal Tumors

Increasing dose levels with protons
(long-term data: eyes, skull base, paraspinal tumors, unresectable sarcomas)

= 

Increasing tumor control
Thank you for your attention!