Definitive High Dose Radiotherapy for Unresected Chordomas


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Chordomas

- Clivus 30-35%
- Vertebrae: 15-30%
- Sacrococcygeal: 30-50%
Surgical Resection

- Skull base: ~ 50% likelihood of complete or “near complete” resection, always “piecemeal”, non-oncologic surgery (Sekhar et al, Neurosurg Focus, 2001)
  - Hence most MDs recommend post op XRT

- Sacrum/mobile spine:
  - Outcome better with radical than subtotal resection
  - Adjuvant radiation only effective at high dose
  - Many series report local recurrences of 65-70%
Conventional Radiation Therapy

• Prior to 3D radiation planning and highly conformal radiation techniques such as protons and IMRT, attempts to deliver tumoricidal radiation doses to skull base tumors limited by critical normal tissue tolerance.

• In that era, photon radiation doses ranged between 50 and 60 Gy and tumors recurred locally in 70% to 100% of the patients.
Traditional Radiation Therapy

- Hacettepe University (Ankara, Turkey)
  - 18 patients with clival chordomas
  - Modern imaging and radiation treatment techniques but at conventional doses of 50-64 Gy
  - 5-year progression-free survival rate: 23%
  - 5-year overall survival rate: 35%
  - Confirms the poor outcome with these doses and emphasize the importance of high target doses.

Historic Photon 2D Radiotherapy data: 5-year Local Control 30-50% with doses ~60 Gy...and falling

**Chordomas: Local Control- Skull Base (Histology)**

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<tr>
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<th>Chondrosarcoma</th>
<th>Chordoma</th>
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<tbody>
<tr>
<td>5 years</td>
<td>98 %</td>
<td>73 %</td>
<td>&lt;.0001</td>
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<td>10 years</td>
<td>95 %</td>
<td>54 %</td>
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*Courtesy: John Munzenrider, MGH/HCL*
Clinical Trial

- Phase II Clinical Trial for Spine/Paraspinal Sarcoma (PI T. DeLaney MD)
  - Surgery + IORT (Dura Plaque) + Photon/Proton
    - Surgery: Maximal debulking/spine stabilization
    - IORT: $^{90}$Y dural plaque: 10 Gy
    - Photon/Proton Radiotherapy
      - 70.2 GyE (Microscopic residual)
      - 77.4 GyE (Gross residual disease)*
        - * Concurrent chemotherapy, diabetes: 70.2-72 GyE
        - *Giant cell tumor, Ewing’s Sarcoma: 61.2 GyE
Thoracolumbosacral Chordomas

- **Local Failure**
  
  - **ALL LOCAL RECURRENCES WERE IN PATIENTS WHO HAD FAILED AFTER PRIOR SURGERY**
    
    - Local failure: 0/23 at initial presentation vs. 3/6 at recurrence!

- R0
  - 0/7

- R1
  - 1/10

- R2
  - 1/3

- Biopsy only
  - 1/9

- R0-2
  - 2/10

R0 vs. R1,2 vs. Bx

- R0 vs. Bx. p=0.084 (1-sided)

- p=0.221 (2 sided)

- R0-2 vs. Bx. p=0.76
Objective

• Because of high rate of local control in prior prospective study with high dose photon/proton radiation after biopsy alone, elected to assess all patients treated without resection

• RATIONALE
  – High risk of neurologic injury with surgical resection at selected sites such as S1 and S2
  – Interest in avoiding surgery in selected elderly patients or those with medical co-morbidities
  – Some patients decline surgery
74 year old Female

C2 Chordoma

Declined surgery
C2 Chordoma

77.4 Gy RBE

19.8 Gy IMRT +
57.6 Gy RBE 3-D protons
Materials and Methods

• Retrospective study
• Identified all patient managed by definitive high dose photon/proton XRT with curative intent at initial presentation following biopsy only
  – MGH Dept. of Radiation Oncology Sarcoma and Proton Databases
  – Separate query of MGH hospital information system
• Radiation Oncology treatment charts and hospital records were then reviewed to assess local control, disease status, survival, morbidity
Results

• Identified 19 patients treated 1997-2008
  – Male 10    Female  9
• Age at diagnosis: median 62 years
• Sites
  – Cervical  2
  – Thoracic  1
  – Lumbar    2
  – Sacral    15
    • Involving S1,S2  12
    • S3 or below   2
• Size: median 8.7 cm
Results

• Radiation dose
  – GTV: median 77.4 GyRBE
  – CTV: median 50.4 GyRBE

Photons: 34.0 Gy (median) 17 fractions
Protons: 45 GyRBE (median) 22 fractions

60 days (median)
Results

• Follow-up: 9-114.8 months (mean 29.5 months)
  – Follow-up > 3 years: 7 patients
  – Follow-up > 5 years: 3 patients

• Local control (absence of local progression): 18/19
  – One patient with > 9.5 cm tumor had regression to 3 x 3.5 cm tumor but then had isolated local progression after 2 years
  – Other patients remain locally controlled

• One patient with 17 cm buttock chordoma developed metastatic disease at 1 year and died at 15 months but was locally controlled
Results

- **Local control**
- **Regional control**
- **Freedom from distant metastasis**

Follow-up time (months)
Results

Overall survival

Disease-free survival

Follow-up time (months)

Percent (%)
### Results

- **Spinal cord injury**: 0
- **Neuropathy Grade 3**: 1 (5%)
  - Cranial: 0
  - Sacral: 1 (leg weakness)
- **Erectile dysfunction**: 1 (5%)
- **Soft tissue fibrosis**: 3 (16%)
- **Rectal bleeding**: 3 (16%)
- **Sacral insufficiency fx**: 1 (5%)
Protons: Radiation Biology

- **Low LET (linear energy transfer) radiation**
  - Ionization with similar biologic effect to photons
  - Relative Biologic Effect (RBE) is ~1.1 vs. \(^{60}\text{Co}\)
  - Proton doses: cobalt gray equivalents (CGE)
    - CGE = physical dose in Gray x 1.1 (RBE correction)
  - Protons have been successfully combined with photons in reasonably straightforward manner
    - Many reported results are combined photon-proton results
Carbon Ion Therapy

• Carbon ions are under study in Japan and Germany
• Less lateral diffusion and sharper Bragg peak
• Higher RBE (~3) that may be even higher in tumor vs. normal tissue because of
  • Lower oxygen enhancement ratio (OER)
    – ? Relatively more effective vs photons against hypoxic tumor
  • ↓ capacity for sublethal/potentially lethal damage repair
    – ? More effective against slowly proliferating tumors
• Cost is higher than protons
  – Hyogo (2001: 28 B ¥/ $ 230 million) vs. ~ $100 million proton
  – Will be important to define indications for carbon ions
Carbon-Ion Therapy for Skull Base Chondrosarcomas and Chordomas

87 patients, 1997-2002, F/U: 3-54 months, median 20 months, Median dose 60 CGE (60-70 CGE) in 20 fractions

Chordoma LC: 81% at 3 years

Schulz-Ertner D, Debus et al. IJROBP 2004
Sacral Chordoma

T1 post-gadolinium sagittal MRI

Pre-treatment

S3-4 chordoma

77.4 GyE (photons 30.6 Gy protons 46.8 GyE)
Sacral Chordoma

Treatment Plan

S3-4 chordoma

Biopsy only

77.4 GyE (photons 30.6 Gy protons 46.8 GyE)
Sacral Chordoma

T1 post-gadolinium sagittal MRI

S3-4 chordoma

Biopsy only

77.4 GyE (photons 30.6 Gy  
protons 46.8 GyE)

No evidence of progressive disease  
at 36 months
Sacral Chordoma

T1 sagittal MRI

S1-S4 chordoma

Biopsy only

77.4 GyE (photons 50.4 Gy, protons 27.0 GyRBE)

Regression of 9.5 cm tumor but local re-growth at 32 months
Sacral Chordoma

T1 sagittal MRI

S1-S4 chordoma

Biopsy only

77.4 GyE (photons 50.4 Gy
protons 27.0 GyRBE)

Regression of tumor but local regrowth at 32 months

Follow-Up MRI 14 months after start of XRT
Sacral chordoma treated with carbon ion 70.4 GyE/16 Fx

Pre-Rx

3 years
Post-Rx

Courtesy of Tadashi Kamada, M.D., Ph.D.
Chordomas of the Sacrum

• Imai et al. (NIRS, Chiba, Japan)
  – 30 patients with unresectable sacral chordomas
    • 23 primary    7 local recurrent after resection
      – Clinical target volume 546 cm$^3$
    • 52.8-73.6 GyE (median 70.4) in 16 fx over 4 weeks
  – Local control rate at 5 years: 96%
    • 26 patients alive
    • 24 disease-free at median f/u of 30 months (range, 9-87 mos)
  – Two skin/soft tissue complications requiring skin grafts.
  – No other treatment-related surgical interventions, including colostomy or urinary diversion, were carried out.
  – All patients have remained ambulatory and able to stay at home after carbon ion radiotherapy
Chordomas of the Sacrum

- Imai et al. (NIRS, Chiba, Japan)
Summary

• Encouraging preliminary results with high dose photon/proton radiation in patients with chordomas treated with definitive XRT after biopsy
• Await further follow-up
• Have an open protocol with NIRS to compare outcomes in patients for bone/soft tissue sarcomas treated with photon/protons versus those with carbon ions
  – May have sufficient patients to begin comparison if we can identify matched patients for appropriate comparison