Particle Radiation Therapy in the Treatment of Bone and Soft Tissue Sarcoma



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Management of Sarcomas

- Multidisciplinary approach
 - Contemporary management of sarcomas requires a multidisciplinary approach, often using a combination of surgery, radiation, and chemotherapy specific for tumor type, histologic grade, and stage of disease.
 - Rare tumors: ~1% of adult malignancies
 - Care optimized in centers with experience





Local Recurrence of Soft Tissue Sarcomas after Surgery

- Related to infiltration of tumor cells into peritumoral tissue beyond the gross tumor
 - Invade locally along anatomic planes (muscle fibers, neurovascular bundles, fascial planes)
 - LN involvement uncommon (5% overall)
 - Exceptions: <u>Synovial</u>, <u>Clear cell</u>, <u>Angiosarcoma</u> <u>R</u>habdoyosarcoma, <u>E</u>pithelioid





Wide Surgery Alone for Extremity and Truncal Sarcoma

- Appropriate for
 - Superficial low grade lesions < 5 cm that can be widely excised
 - Selected larger low grade lesions
 - Selected superficial intermediate and high grade lesions < 5 cm
- Most intermediate and high grade lesions > 5 cm will be considered for adjuvant radiotherapy





Fig 2. Local recurrence-free survival in patients with high-grade, locally resectable extremity soft tissue sarcomas randomized to treatment with surgery and adjuvant chemotherapy versus surgery, adjuvant chemotherapy, and postoperative XRT. LR occurred only in the absence of XRT.

Impact of Local Recurrence

- Pisters et al (Memorial Sloan Kettering)
 - Analysis of prognostic factors showed that presentation with local recurrence was adverse factor for distant recurrence and disease-specific survival
 - J Clin Oncol 1996; 14:1679.
- Eilber et al (UCLA)
 - Patients with high grade STS who suffer a local recurrence are ~ 3 x higher risk of sarcoma death vs. patients with local control
 - Ann Surg 2003;237:218.





Bone Sarcomas

- Surgery
 - Treatment of the primary lesion for most patients
 - Acceptable margins difficult to achieve in the axial skeleton including skull, spine, sacrum, and pelvis
 - These are sites where radiation can be important component of local control





- Integration of Radiation Therapy
 - Radiotherapy can be employed as neoadjuvant (pre-operative), adjuvant (post-operative), or primary local therapy depending upon the site and type of tumor, the availability and acceptability of the surgical option, and the efficacy of the chemotherapy





- Neoadjuvant (pre-op) Radiation Therapy
 - Frequently employed for large, deep soft tissue sarcomas
 - Can also be delivered prior to resection of spine or pelvic sarcomas.
 - Can be advantageous to facilitate resection, reduce risk of wound seeding, and minimize radiated volume



- Adjuvant (post-op) Radiation Therapy
 - Following resection of <u>soft-tissue sarcoma</u> if tumor or surgically contaminated tissues in patients with incomplete excision, can not be excised with ≥ 1 cm margin or an intact fascial plane.





- Adjuvant (post-op) Radiation Therapy
 - Bone sarcomas with (+) or inadequate margins
 - Presentation with a pathologic fracture
 - Close margin and poor histologic response to chemoRx
 - Intralesional excision of or intramedullary rod placement through a radiographically or cytologically benign-appearing lesion later found to be sarcoma





- Definitive (Primary) Radiation Therapy after Biopsy or Subtotal Resection
 - Medically inoperable patients
 - Axial or extremity Ewing sarcomas where surgery would compromise function
 - Primary bone tumors involving upper sacrum, portions of the pelvis, the base of skull, and ethmoid/sphenoid sinus.





- External beam
 - 3D
 - IMRT
 - Charged particles
- Brachytherapy
- Intraoperative radiation therapy
 - Retroperitioneal
 - Extremity





Radiation Dose- Sarcomas

- Soft Tissue Sarcomas
 - The radiation sensitivity of soft tissue sarcomas similar to breast and other epithelial tissues.
 - Pre-operative adjuvant radiation doses of 50 Gy or post-operative radiation therapy doses of 60 Gy are associated with local tumor control rates ≥ 90% in patients with extremity lesions resected with negative margins





Radiation Dose- Sarcomas

Soft Tissue Sarcomas

- Radiation therapy provides local control of ~ 75% of patients with soft tissue sarcomas resected with positive margins
- Doses of 66-68 Gy are recommended
- Doses of ≥ 65 Gy are associated with higher rates of local control and reported to be as high as 85% in MGH data (DeLaney et al, IJROBP 2007;67:1460)





Unresected Soft Tissue Sarcomas

- Massachusetts General Hospital
 - 112 patients with unresected sarcomas 1971-2001

LOCAL CONTROL

| | < 63 Gy | <u>>63 Gy</u> |
|-------------------------|------------|------------------|
| <u><</u> 5 cm | 22% | 72% |
| >5 cm <u><</u> 10 cm | 49% | 42% |
| >10 cm | 0% | 25% |
| | p=0.08 | p< 0.05 |

Kepka et al, IJROBP 2005; 63:852.





Radiation Dose- Sarcomas

Ewing's Sarcoma

- Surgery preferred at sites with acceptable morbidity
 - Microscopic residual disease is usually treated to 50.4 Gy.
- Radiation sensitive: James Ewing
- Gross disease
 - 55.8 Gy in association with chemotherapy
 - Consideration of higher doses for high risk bulky axial tumors i.e. pelvis is reasonable
 - Vertebral lesions traditionally treated to only 45 Gy





Radiation Dose- Sarcomas

Chondrosarcomas and Osteosarcomas

 Microscopic residual disease ~ 66 Gy
 Gross residual disease > 70 Gy

- Chordomas
 - Microscopic residual disease ~ 70 Gy
 Gross residual disease > 75 Gy





Protons: Physical Dose Advantage

- Protons: more conformal than 2-D or 3-D RT
 - Physical rather than biologic advantage
 - Allow higher doses to tumor target
 - Improved local control
 - Improved survival
 - Reduce dose to normal tissue
 - Except slightly higher entrance dose with passively scattered protons
 - Reduced acute morbidity and better integration with systemic Rx
 - Fewer interruptions in radiation, chemotherapy
 - Improved local control, survival
 - Reduction in late morbidity





Protons: Physical Dose Advantage

- Intensity modulated radiotherapy (IMRT)
 - Target dose distributions similar to protons
 - Integral dose is ALWAYS higher
 - Although selected normal tissues can be spared, cost is
 INCREASED DOSE TO OTHER NORMAL TISSUES
 - No patient benefit by irradiation of normal tissue
 - Clinical toxicity of IMRT low-moderate dose bath?
- Proton cost ~ 2.4 fold higher than IMRT photons
 - Future efficiency gains might decrease this to 1.7
 - Important to define appropriate indications
- INTENSITY MODULATION IS APPLICABLE TO PROTONS





L1 Angiosarcoma



Proton





IMRT



Paravertebral Epithelioid Sarcoma Intensity Modulated Protons (IMPT) vs. Intensity Modulated Photons (IMRT) (7 field)



Protons: Radiation Biology

- Low LET(linear energy transfer) radiation
 - Ionization with similar biologic effect to photons
 - Relative Biologic Effect (RBE) is ~1.1 vs. ⁶⁰Co
 - 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 straight forward manner
 - Many reported results are combined photon-proton results





The Harvard Cyclotron Laboratory







Radiation Therapy for Skull Base and Cervical Spine Chordomas and Chondrosarcomas



The Clivus







Local recurrence-free survival (skull base)

<u>Histology</u>

| | Chondrosarcoma | Chordoma | р |
|----------|----------------|----------|--------|
| 5 years | 98 % | 73 % | <.0001 |
| 10 years | 95 % | 54 % | <.0001 |
| | | | |
| | | | |

Courtesy: John Munzenrider, MGH/HCL

11/99

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





Conventional 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.
 - Zorlu F et al. Conventional external radiotherapy in the management of clivus chordomas with overt residual disease. Neurol Sci. 2000;21:203-207.





Other Radiation Modalities

Stereotactic Photons

- Debus et al., Heidelberg
 - Fractionated, stereotactic 3D photons 66.6 Gy (median)
 - Local control for chordomas 50% at 5 years
 - Int J Radiat Oncol Biol Phys 2000:47:591.
- Krishnan, Foote et al, Mayo Clinic
 - Gamma Knife Radiosurgery
 Median size 14.4 cc
 - Median margin dose 15 Gy (10-20 Gy range)
 - Median maximum dose 30 Gy (20-40 Gy range)
 - 19/29 patients also had external beam, median 54 Gy
 - Local control 32% at 5 years Complications 34%





Proton Treatment Delivery Intensity Modulated Proton Therapy: The simultaneous optimisation of all Bragg peaks from all incident beams.







Lomax, Phys. Med. Biol. 44:185-205, 1999





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
- • Lapacity 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 Schulz-Ertner D, Debus et al. IJROBP 2004

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





Challenges in Managing Spine Sarcomas

- Surgical
 - Oncologic ideal of achieving a resection with negative margins through an approach that does not violate tumor or pseudocapsule rarely possible
 - Extraosseous extension frequent
 - Involvement of adjacent mediastinal/retroperitoneal structures, as well dura and spinal cord
 - Tumor cell often in direct contact with dura, thereby invading it on microscopic basis
 - Resection/disruption of dura can seed tumor into CSF





Sarcomas of the Spine

- Low rates of control with standard therapy – Osteosarcoma
 - 15/22 (68%) local failure (Ozaki, 2002)
 - Contrast with extremity where local control > 90%
 - Chondrosarcomas
 - 3/14 (21%) local failure after en bloc excision but 10/10 (100%) local recurrence after piecemeal excision (Boriani et al, Bologna)
 - Chordoma
 - 75% Local failure (Mayo Clinic)





Challenges in Managing Spine Sarcomas

- Radiation therapy
 - Effective adjuvant therapy for sarcomas
 - Proximity of spinal cord make dose delivery difficult with conventional 3D radiation therapy
 - IMRT and imaged guided techniques have facilitated delivery of higher doses





Phase II Study of Proton Radiation Therapy for Spine and Paraspinal Sarcomas

TF DeLaney, NJ Liebsch, IJ Spiro, PL McManus, JA Adams, S Dean, FJ Hornicek, FX Pedlow, AL Rosenberg, GP Nielsen, DC Harmon, SS Yoon, KA Raskin, HD Suit







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: ⁹⁰Y dural plaque: 10 Gy
 - Photon/Proton Radiotherapy
 - 70.2 GyE (Microscopic residual)
 - 77.4 GyE (Gross residual disease)*
 - * Concurrent chemotherapy, diabetes : *Giant cell tumor, Ewing's Sarcoma:

70.2-72 GyE 61.2 GyE





Spine/Paraspinal Sarcoma: CT myelogram for Radiation Planning

T6 spine/paraspinal Chondrosarcoma

CT myelogram for lesions above the conus to outline spinal cord

Spinal cord limits Surface: 63 GyRBE Center: 54 GyRBE







Sacral Chordoma

Treatment plan

S2-5 chordoma

Biopsy only

77.4 GyE (photons 30.6 Gy protons 46.8 GyE)

No evidence of progressive disease 32 months after start of proton treatment







⁹⁰Y Plaque Irradiation







• Accrual: 50 Patients

12/1997-3/2005

HISTOLOGY

- Chordoma
- Liposarcomas
- Ewing's Sarcoma
- MPNST
- Spindle + round cell

| Chondrosarcoma | 14 |
|------------------|----|
| Angiosarcoma | 1 |
| Giant cell tumor | 1 |
| Osteosarcoma | 1 |

Thoracic 11 Lumbar 13 Sacrum 26

29

1

1

• Primary 36 Locally recurrent 14





- Extent of surgery
 - Grossly resected 25 Margins (+) 17 (-)8

13

- Subtotally excised 12
- Biopsy only
 - Size 7 cm median (Range 3-20 cm)
- XRT Median Dose 76.6 GyE (Range 59.4-77.4 GyE)
 - All but 1 patient completed Rx (social reasons)
 - Dose delivery within 3% of protocol target in all patients
 - Spinal cord dose constraint
 - Dural Plaques
 3 patients





- Results
 - Median follow-up: 48 months
 - Local Recurrence: 9 pts at 8-43 months after start of XRT
 - 5 Isolated 4 also with distant metastases
 - 7/14 locally recurrent tumor vs. 2/36 for primary tumor, p<0.001
 - 3/29 Chordomas 6/14 chondrosarcomas* p=0.014
 - * Three patients presented with recurrences (two with 4-5 prior) and another had a dedifferentiated chondrosarcoma with tumor cut-through.





Local Failure All Patients (n=9/50)

| | | 5 Yea |
|---------------------------------|------|-------|
| – R0 | 0/8 | 0% |
| – R1 | 4/17 | 30% |
| – R2 | 4/12 | 40% |
| Biopsy only | 1/13 | 8% |

R0 vs. R1,2 vs Bx p=0.110 (2 sided)

Local Failure Chordoma (n=3/29)

| – R0 | 0/7 | 0% |
|---------------------------------|------|-----|
| – R1 | 1/10 | 13% |
| – R2 | 1/3 | 13% |
| Biopsy only | 1/9 | 13% |

Harvard

Medical School

R0 vs. R1,2 vs Bx p=0.258 (2 sided)

R0-2 vs Bx. p=0.76











- Acute Complications
 - <u>></u> Grade 3
 - 1 sacral insufficiency stress fracture after fall following surgery and 27 Gy without late sequelae.
- Late Complications
 - <u>></u> Grade 3
 - 2 sacral neuropathies: Sacral chordomas (77.4 GyE)

arvard

- L leg weakness, stress urinary incontinence, \downarrow rectal tone (5.5 y)
- L leg weakness at 4 yrs (also 18 Gy IMRT/27 Gy p+ Ca Cervix)
- 1 sacral insuff Fx after fall after S + 77.4 GyE \rightarrow nail ; chronic pain
- 1 Rectal bleeding: Resected sacral chordoma+70.2 GyE at 2 years
- 1 erectile dysfunction (77.4 Gy, age 66, 8.5 cm sacral chordoma)



Conclusions

- High dose photon/proton XRT can be delivered
- Morbidity to date appears acceptable.
- Encouraged to date by the treatment results with these challenging tumors
 - Await further follow-up, especially for the chordomas
 - Prefer to radiate at time of initial presentation
- Potential concern about late sacral nerve toxicity in patients receiving 77.4 Gy





Multiply recurrent G2 chondrosarcoma T4







Same case with IMPT









3D conformal proton plan (3DCP) vs. IMPT

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Axial Osteosarcomas

- Osteosarcomas of spine, pelvis, skull
 - Satisfactory resections difficult
 - Local failure more common
 - Cooperative Osteosarcoma Study Group
 - Pelvic lesions: Local failure 70%
 - Resected 62%; Unresected 94%
 - 5 Yr EFS: 14% ; OS 28.9%
 - Spine lesions: Local failure 68%
 - 3/22 (13.6%) Disease Free at 6 years
 - OS better with XRT after intralesional Surgery or Bx
 - Meta-analysis: Head and neck lesions

Local failure ~50%



Chemoradiation Therapy for the Treatment of Osteosarcoma

- Machak et al (Moscow)
 - 31 extremity sarcoma pts
 - Refused amputation after chemotherapy
 - Actuarial local control at 5 years: 56%
 - 11 patients had good imaging/biochemical response
 - Local control 100%Survival 90%





Unresectable Sacral Osteosarcoma

- Coronal T1 post-gadolinium MRI 19 year old with S1 Osteosarcoma
- Initial progression after cisplatin/ adriamycin and MTX
- Responded to ifosfamide/ etoposide
- Concurrent chemoradiation with ifosfamide/etoposide starting week 16

70.2 CGE (photons 18 Gy protons 52.2 CGE)









Unresectable Sacral Osteosarcoma

- Treatment Plan (Axial)
- 19 year old with S1 Osteosarcoma
- After 12 weeks of chemotherapy
- Concurrent chemoradiation starting week 16
- 70.2 CGE (photons 18 Gy protons 52.2 CGE)







Unresectable Sacral Osteosarcoma

Axial CT scan 19 year old with S1 Osteosarcoma

16 months after treatment

Chemotherapy + 70.2 CGE (photons 18 Gy protons 52.2 CGE)

No evidence of progressive disease at 5 years after treatment





Harvard Medical School





24 year old who is now 5 years out from chemoradiation with protons/photons free of tumor; some pelvic pain related to sigmoid colon prolapse





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 60 months







Sacral chordoma treated with carbon ion 70.4 GyE/16 Fx







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 cm³
 - 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)







Protons: Soft Tissue Sarcomas

- SITES WITH POTENTIAL BENEFIT
- Retroperitoneum
 - Reduce dose to bowel, other viscera
- Trunk
 - Reduce dose to lungs, heart, viscera
- Extremities

- Reduce dose to joints, bone, gonads, anus





A COMPARISON OF 3D CONFORMAL PROTON THERAPY, IMPT, AND IMRT FOR RETROPERITONEAL SARCOMA

Chung CS, Trofimov A, Adams J, Kung J, Kirsch DG, Yoon S, Doppke K, Bortfeld T, Delaney TF

ASTRO 2006





24 year old with Liposarcoma

3D Proton



IMXT





Retroperitoneal Sarcoma Boost







59 year old female with high grade posterior, proximal thigh sarcoma. IMRT used to spare vulva and femur. Note dose "bath".







Protons: Trunk/Extremity Sarcomas



38 year with G2/3T1bN0M0 alveolar soft part sarcoma of the right shoulder.





Protons: Extremity



39 year old with high grade STS of thigh undergoing pre-op chemotherapy and XRT





SUMMARY

- Charged particles have important role for skull base, spine, and pelvic sarcomas
- Because of the large size of many sarcomas and location near sensitive structures, role may be expanded to treat more retroperitoneal, truncal, and selected extremity lesions, particularly if treatment facilities can accommodate them
- Role for heavier charged particles such as carbon ideally defined in controlled studies



