Definitive High Dose Radiotherapy for Unresected Chordomas

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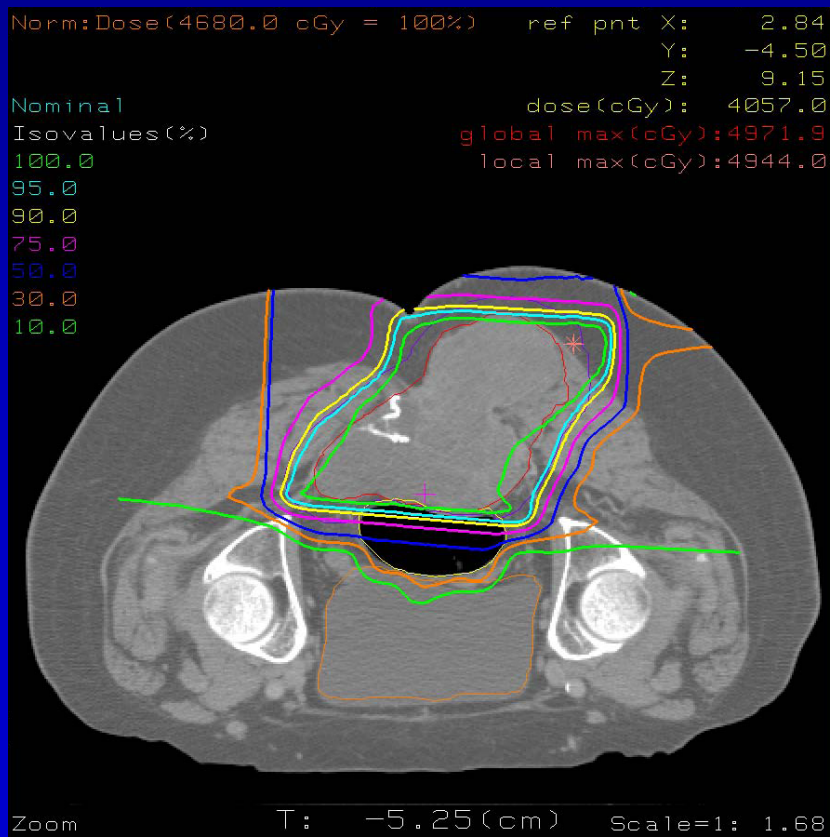

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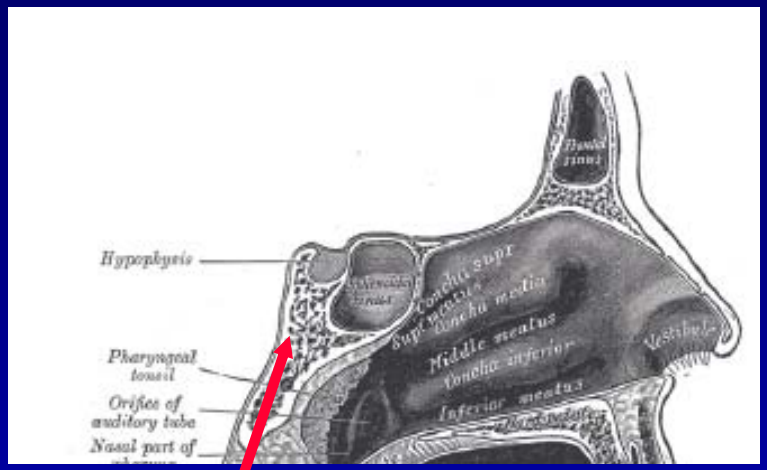
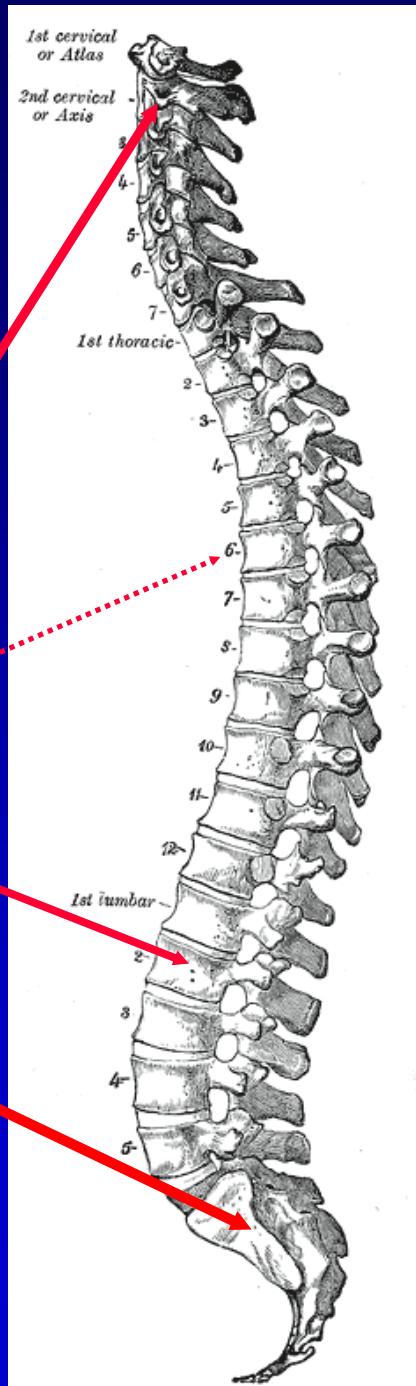
Chordomas



Clivus 30-35%

Vertebrae: 15-30%

Sacrococcygeal: 30-50%



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Surgical Resection

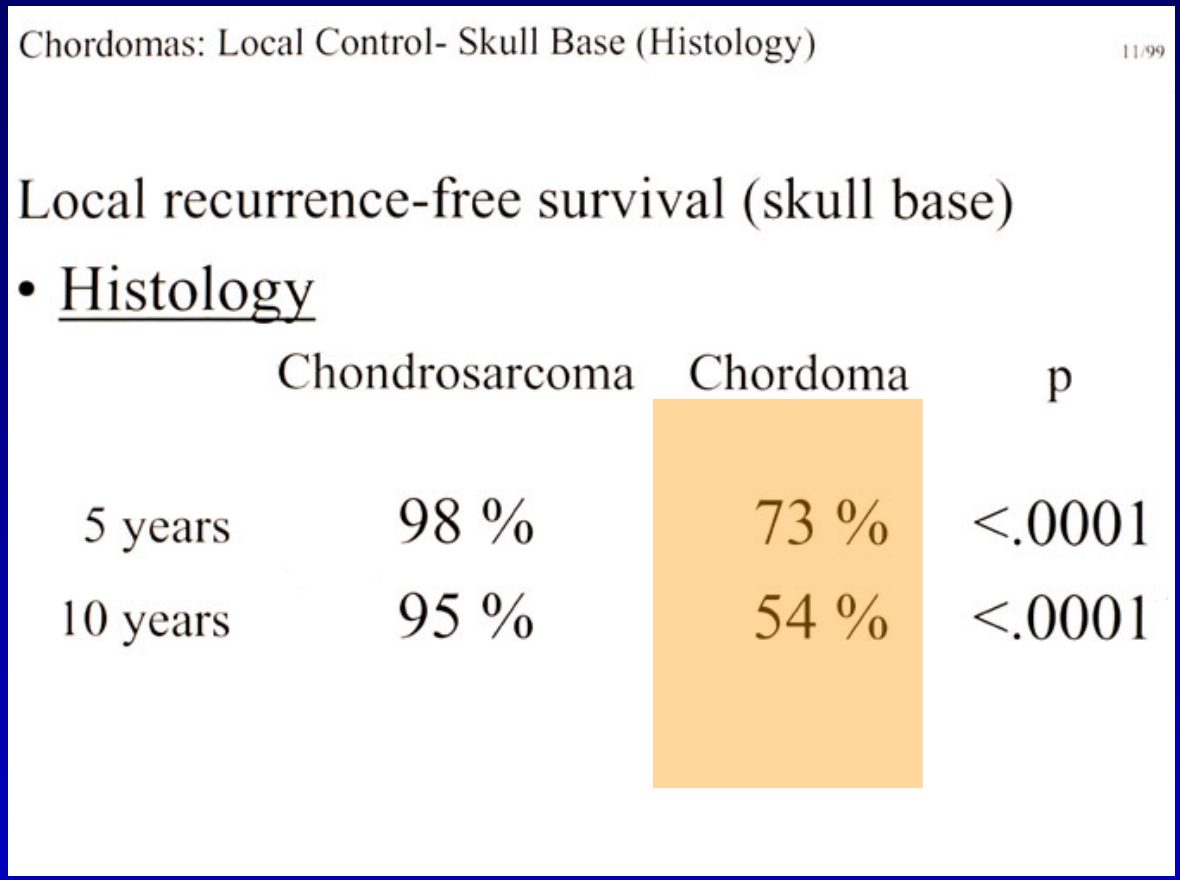
- Skull base : ~ 50% likelihood of complete or “near complete” resection, always “piecemeal”, non-oncologic surgery (Sekhar et al, Neurosurg Focus, 2001)
  - Hence most MDs recommend post op XRT
- Sacrum/mobile spine:
  - Outcome better with radical than subtotal resection
  - Adjuvant radiation only effective at high dose
  - Many series report local recurrences of 65-70%
    - York et al, Neurosurgery 1999; Sundaresan, Arch Surg, 1987

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



Courtesy: John Munzenrider, MGH/HCL

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

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 — Chordoma (n=3/29)
  - 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
p= 0.084 (1-sided)
p=0.221 (2 sided)
R0-2 vs. Bx. p=0.76

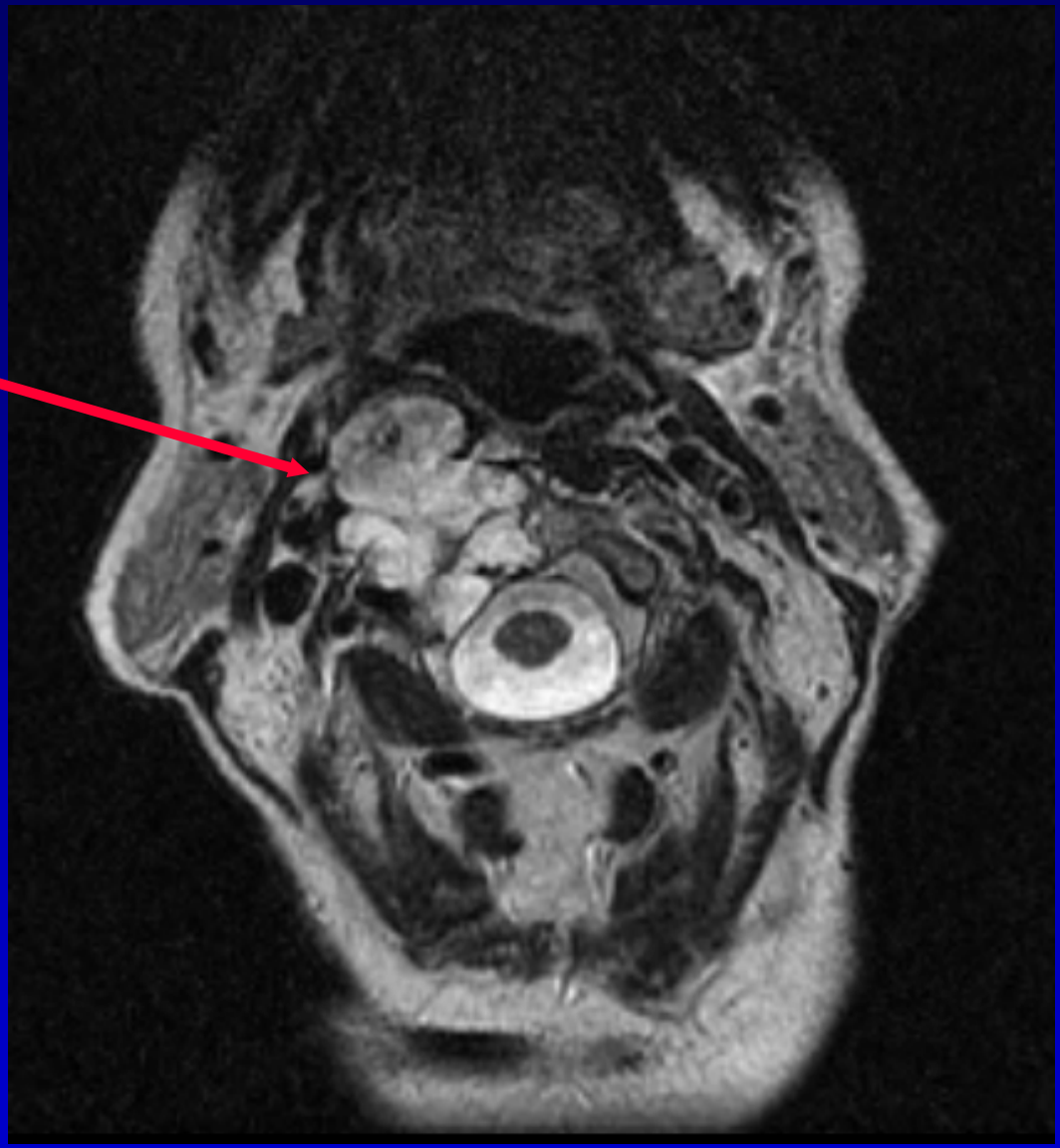
Objective

- 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

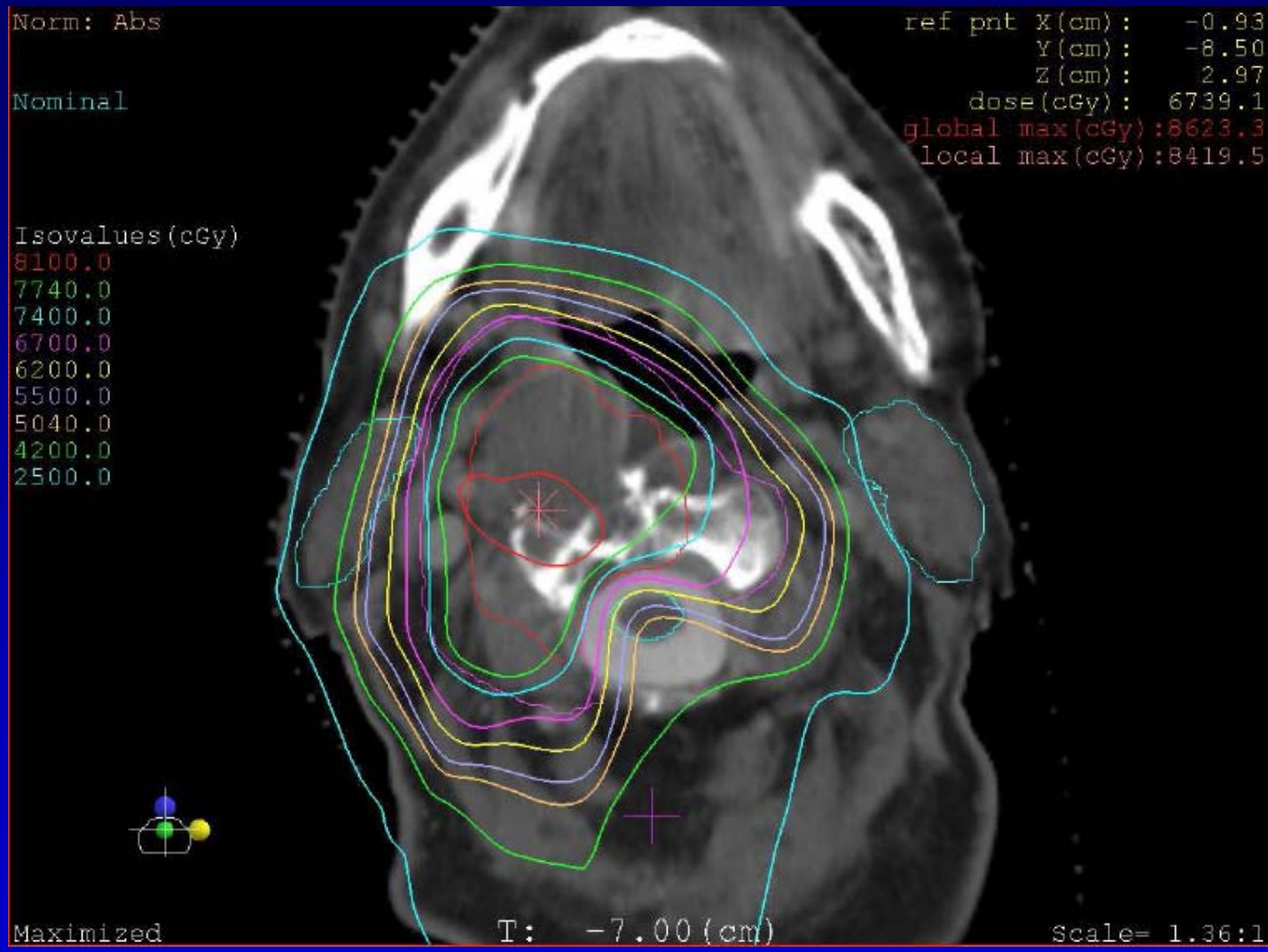
Declined surgery



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

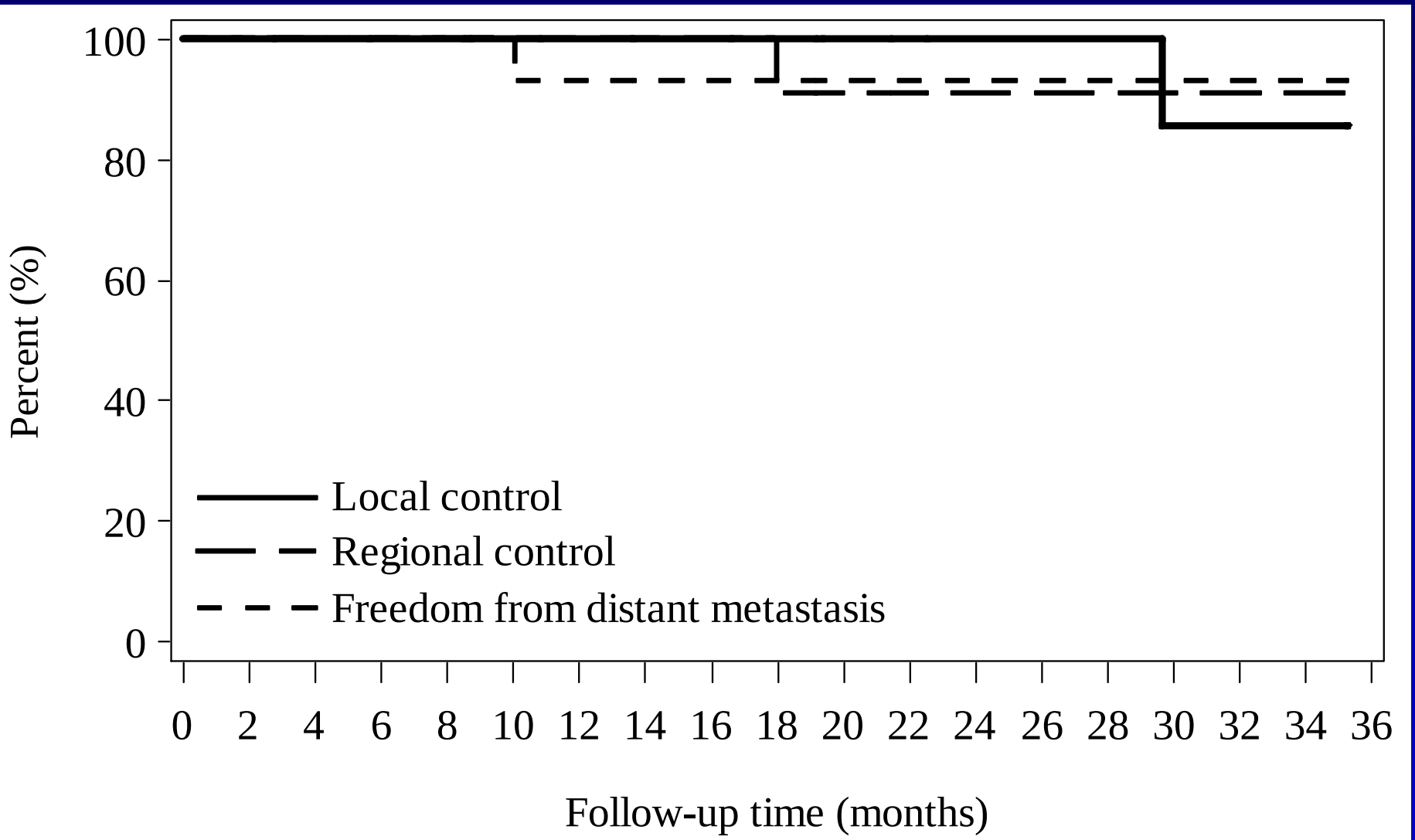
Photons: 34.0 Gy (median) 17 fractions
Protons: 45 GyRBE (median) 22 fractions

60 days (median)

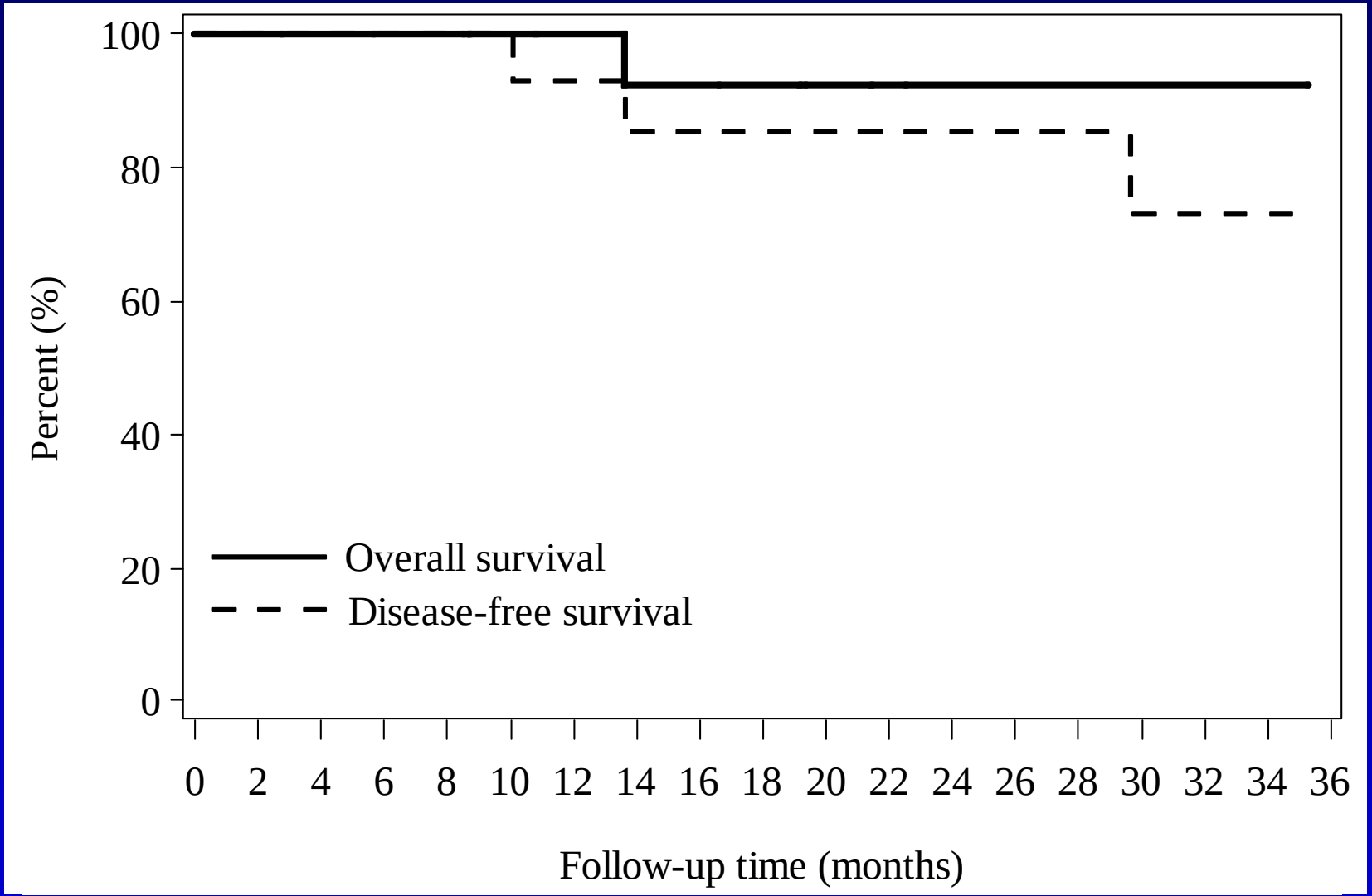
Results

- 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


100
80
60
40
20
0
Percent (%)
Local control
Regional control
Freedom from distant metastasis
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36
Follow-up time (months)

Results


100
80
60
40
20
0
Percent (%)
Overall survival
Disease-free survival
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36
Follow-up time (months)

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

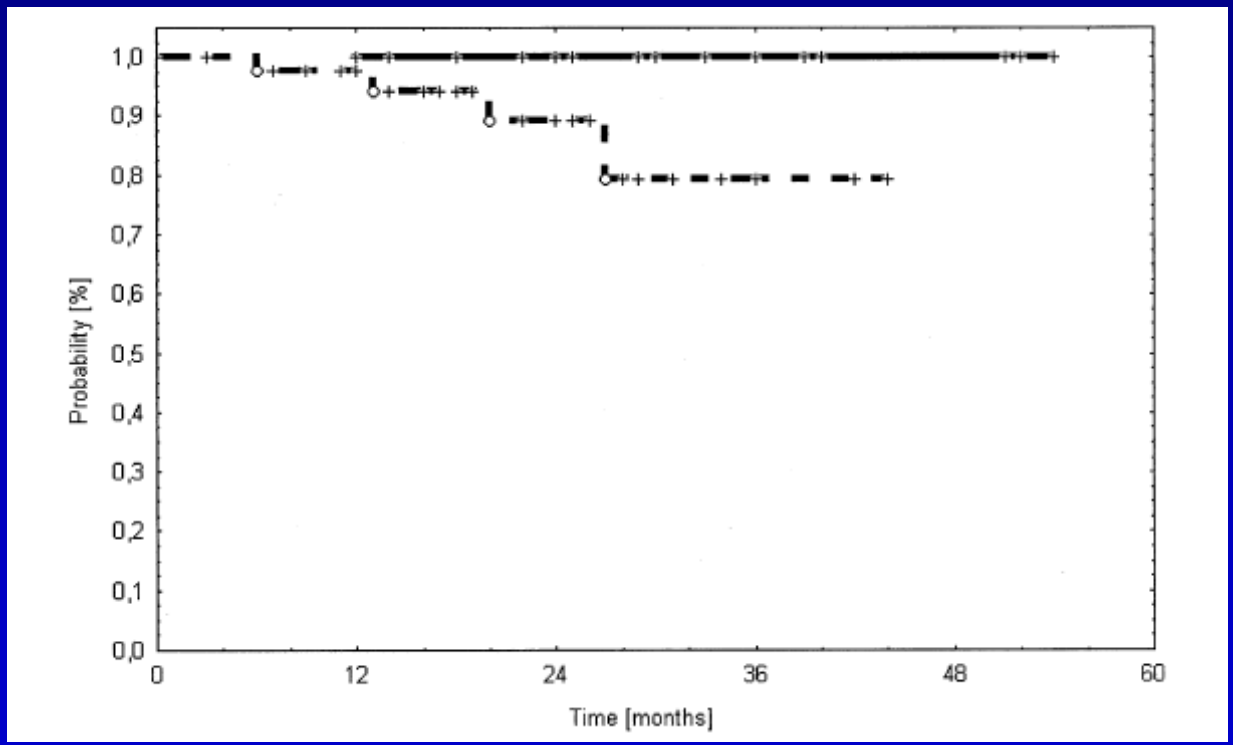
- **Low LET(linear energy transfer) radiation**
  - Ionization with similar biologic effect to photons
  - Relative Biologic Effect (RBE) is ~1.1 vs. ^{60}Co
  - Proton doses: cobalt gray equivalents (CGE)
    - CGE= physical dose in Gray x 1.1 (RBE correction)
  - Protons have been successfully combined with photons in reasonably straight forward 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

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Schulz-Ertner D , Debus et al. IJROBP 2004

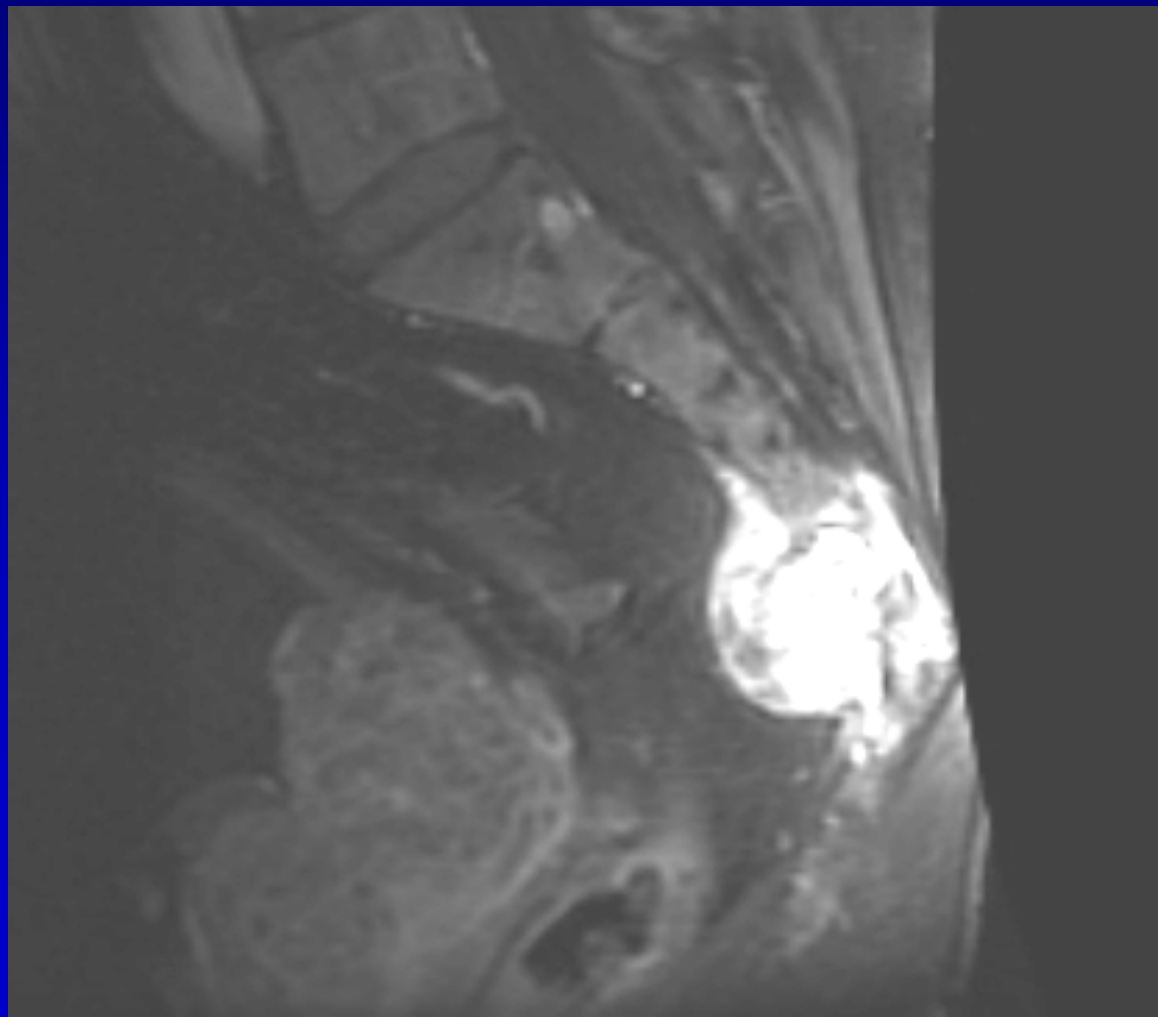
Sacral Chordoma

T1 post-gadolinium sagittal MRI

Pre-treatment

S3-4 chordoma

77.4 GyE (photons 30.6 Gy
protons 46.8 GyE)



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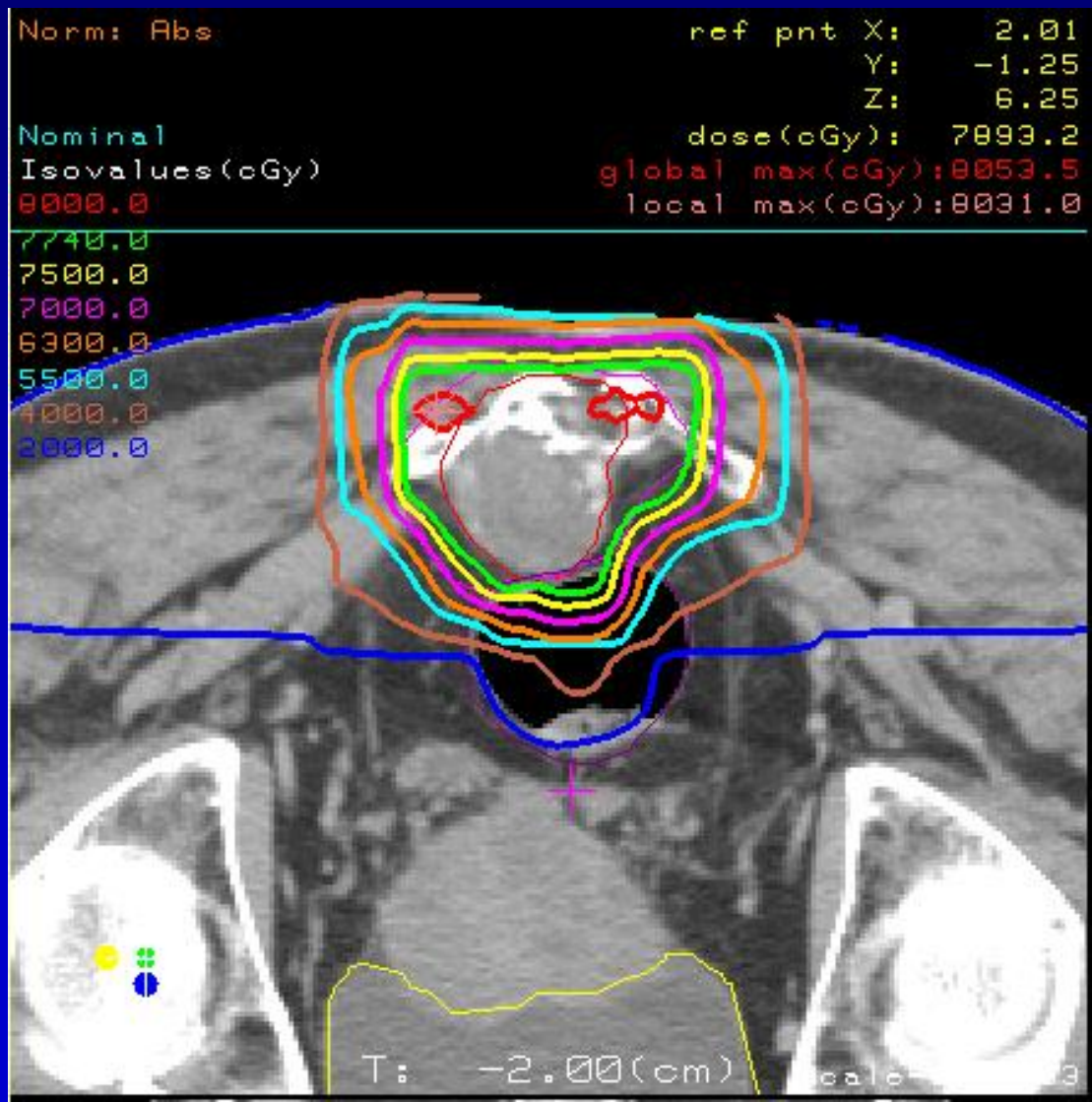
Sacral Chordoma

Treatment Plan

S3-4 chordoma

Biopsy only

77.4 GyE (photons 30.6 Gy
protons 46.8 GyE)



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Sacral Chordoma

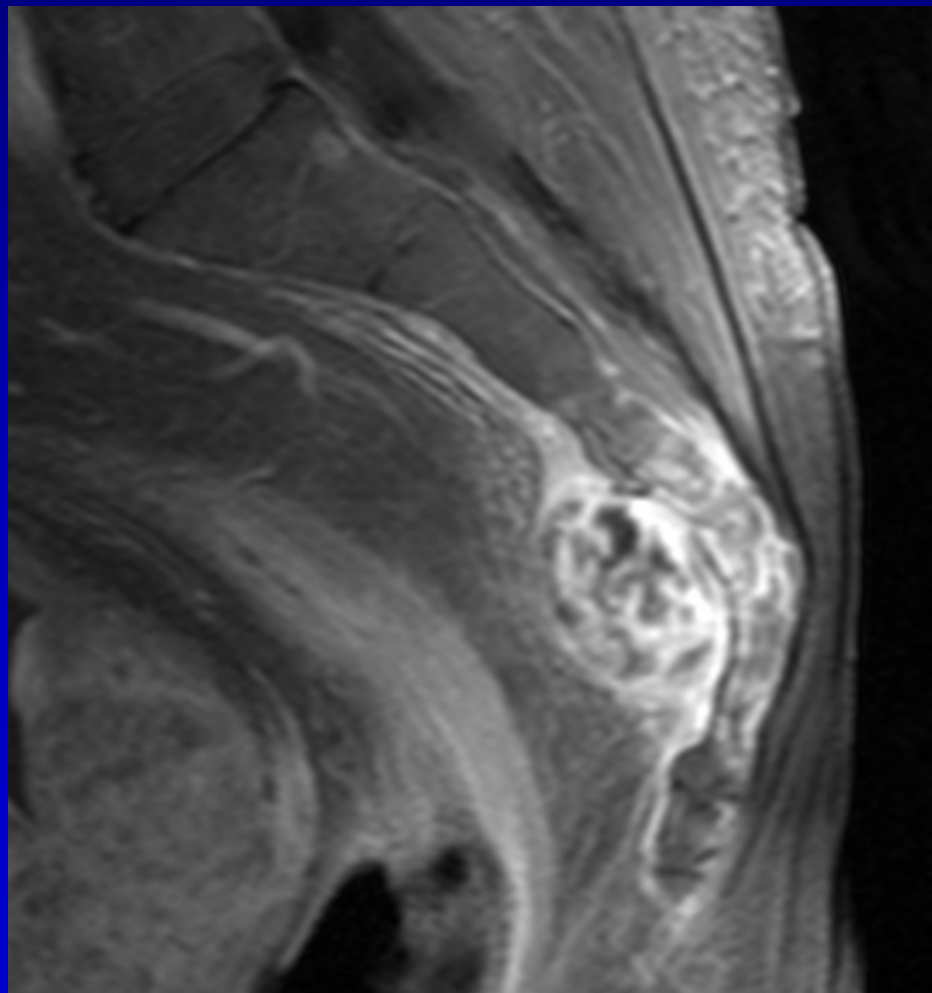
T1 post-gadolinium sagittal MRI

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

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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 re-growth at 32 months

Follow-Up MRI 14 months after start of XRT

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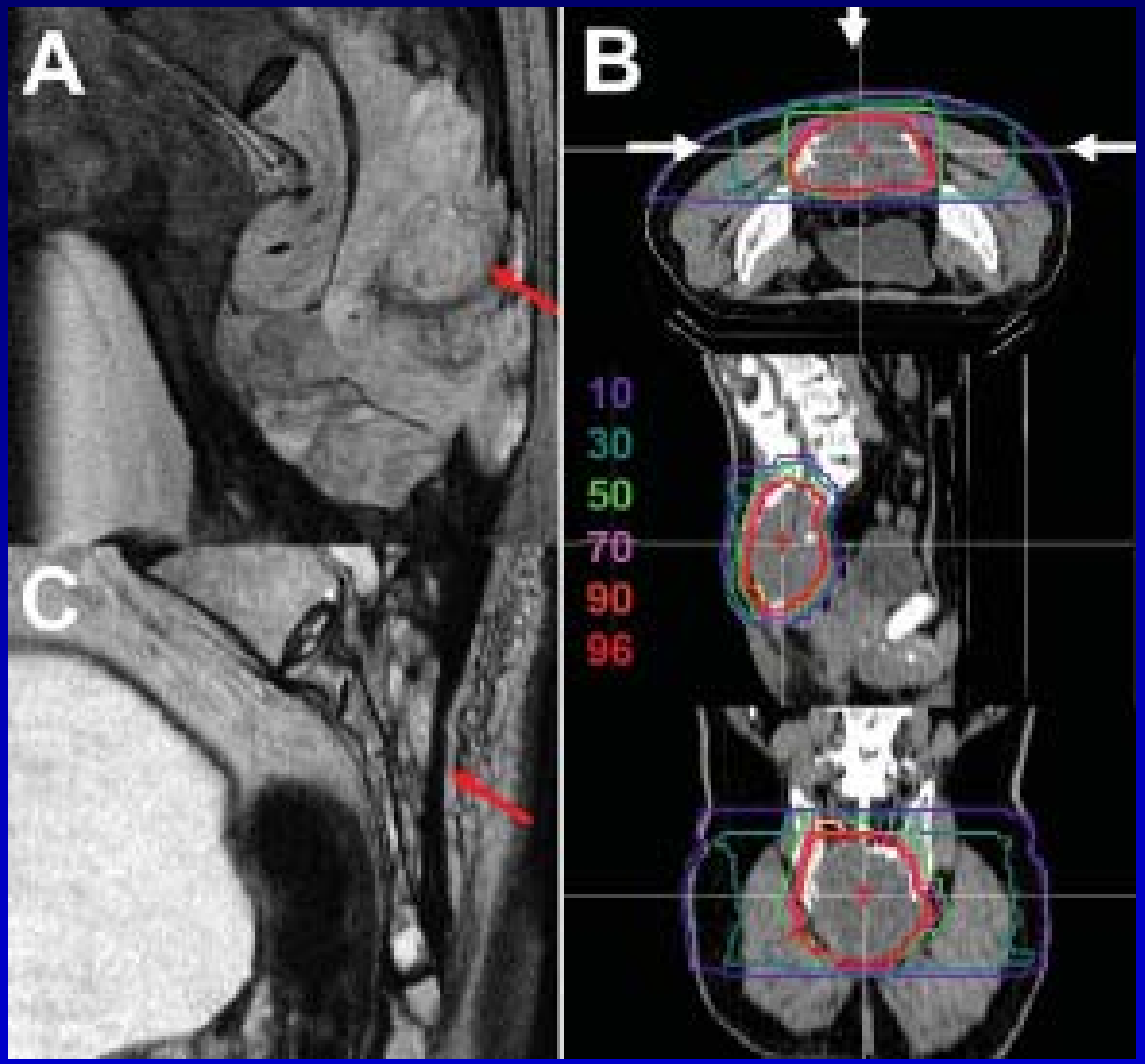
Sacral chordoma treated with carbon ion 70.4 GyE/16 Fx

Pre-Rx

3 years
Post-Rx



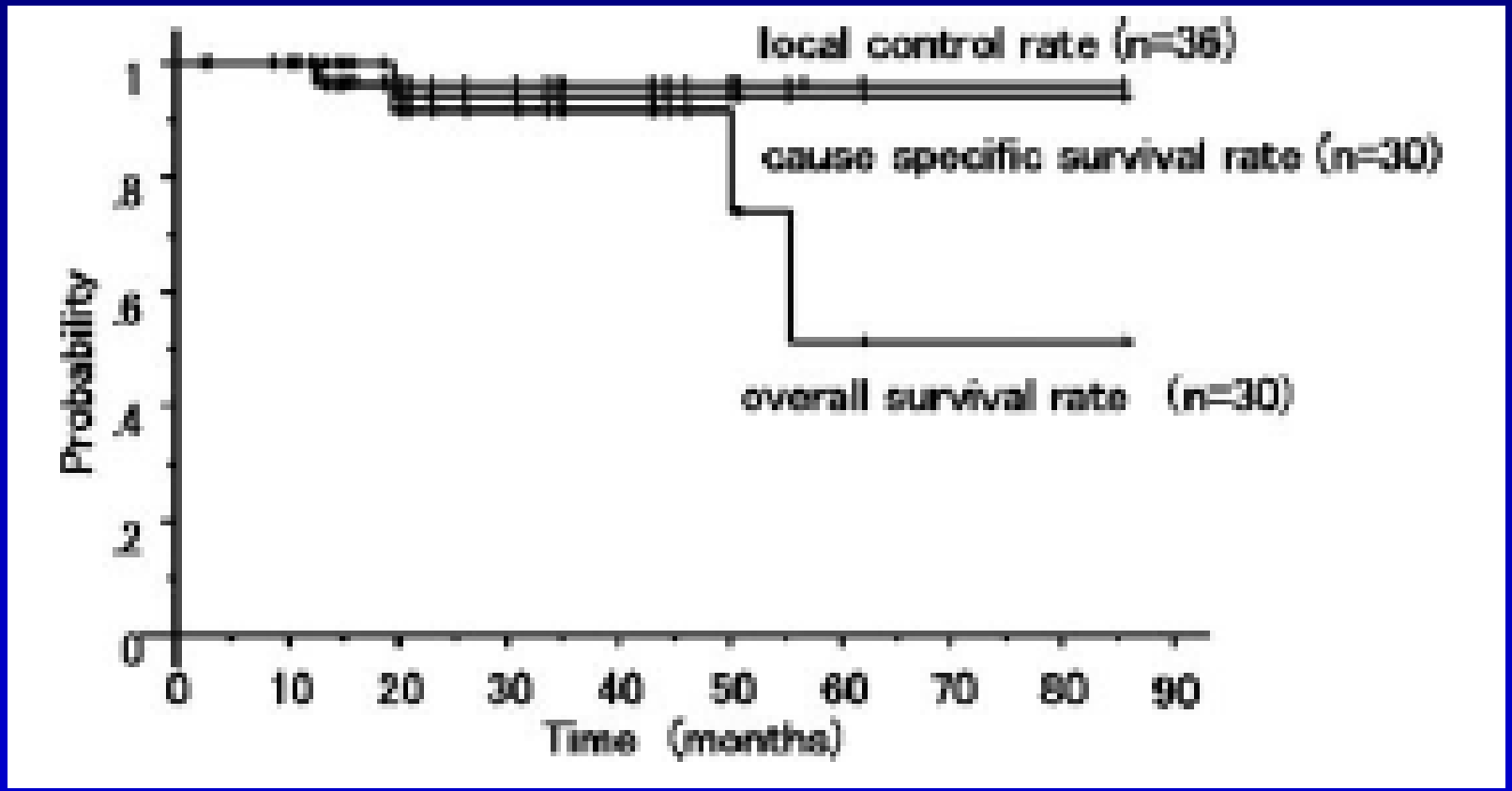
Courtesy of Tadashi Kamada, M.D., Ph.D.

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