PROTON RADIATION THERAPY FOR BONE AND SOFT TISSUE SARCOMAS

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Management of Sarcomas

- Specialized expertise
  - These tumors are relatively uncommon and present in a variety of anatomic sites
    - Hence, most clinicians see them infrequently
  - Because successful treatment with good functional outcome often requires appropriate multidisciplinary expertise, referral to centers with experienced sarcoma teams is the most appropriate management strategy

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.

- **Bone sarcomas**
  - Spine, pelvis
  - Chordomas, chondrosarcomas
  - Osteosarcomas
- **Retroperitoneal sarcoma**

Primary Bone Sarcomas of the Mobile Spine, Sacrum, and Pelvis

- Surgical margins are often positive because of proximity of organs at risk
- Radiotherapy doses need to be ≥ 66 Gy (> 70 Gy for chordoma)
  - Difficult to deliver with spinal cord dose constraint
  - Other dose limiting structures
    - C spine: pharynx, larynx, parotids
    - T spine: lungs, heart, esophagus, stomach, liver
    - L spine: kidneys, small bowel, colon
    - Sacrum and pelvis: rectum, bladder, ovaries

Primary Bone Sarcomas of the Mobile Spine, Sacrum, and Pelvis

- Low rates of control with standard therapy
- Chordoma (Spine/Sacrum)
  - 44%(en bloc surgery) - 100%(intralesional) local failure rate
- Chondrosarcoma (Spine/Sacrum)
  - 42% crude local failure rate (Göteborg, Sweden)
- Osteosarcoma
  - Spine: 15/22 (68%) local failure (Ozaki, 2002)
  - Pelvis: Local failure 70% (Ozaki, 2003)
    - Resected 62%; Unresected 94%
  - Contrast with extremity where local failures < 10%

Radiation Dose- Bone Sarcomas

- Chondrosarcomas and Osteosarcomas
  - Microscopic residual disease 68 Gy
  - Gross residual disease 72 Gy

- Chordomas
  - Microscopic residual disease ~ 70 Gy
  - Gross residual disease 77.4 Gy

- Ewing's Sarcoma
  - Microscopic residual disease ~ 50.4 Gy
  - Gross residual disease 55.8 Gy in children;
  - Adults 59.4 Gy

Long-Term Follow-Up on Prospective Phase II Clinical Trial of High-Dose Photon/ Proton XRT For Spine Sarcomas

Thomas F. DeLaney, Norbert J. Liebsch, Francis X. Pedlow, Judith Adams , Elizabeth Weyman, Beow Y. Yeap, G. Petur Nielsen , David C. Harmon, Sam S. Yoon, Yen-Lin Chen, Joseph H. Schwab, Francis J. Hornicek

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DeLaney et al, J Surg Oncol, 2014

Spine/Paraspinal Sarcoma Clinical Trial

- Eligibility : patients with primary or locally recurrent thoracic, lumbar, sacral sarcomas; no prior radiation
- Surgery: Maximal resection/spine stabilization
  - Biopsy only allowed for unresected tumors (i.e. upper sacrum)
- IORT: ^{90}Y dural plaque: 10 Gy for lesions abutting spinal cord, if surgery done at MGH
- Study published in 2009 with median f/u 4 years
  - DeLaney et al, Int. J. Radiat Oncol Biol. Phys. 2009; 74(3): 732–739.
- Updated now with median follow-up of 7.3 years and 32 patients still alive

Clinical Trial: Spine Sarcomas

- Photon/Proton Radiotherapy
  - 70.2 GyRBE (Microscopic residual)
    - 50.4 GyRBE/28 fx CTV1 (tumor bed + subclinical disease)
      - Preop RT preferred (sacral tumors 19.8 Gy to reduce wound healing complications
    - 19.8 GyRBE/11 fx CTV2 (tumor bed)
  - 77.4 GyRBE (Gross residual disease)*

* Concurrent chemotherapy, diabetes : 70.2-72 GyRBE

- Giant cell tumor, Ewing's Sarcoma: 61.2 GyRBE

DeLaney et al. Int J Radiat Oncol Biol 2009

Spine and Paraspinal Sarcoma

- Accrual: 50 Patients 12/1997-3/2005
- HISTOLOGY
  - Chordoma 29
  - Liposarcomas 1
  - Ewing's Sarcoma 1
  - MPNST 1
  - Spindle + round cell 1
  - Chondrosarcoma 14
  - Angiosarcoma 1
  - Giant cell tumor 1
  - Osteosarcoma 1
- Thoracic 11 Lumbar 13 Sacrum 26
- Primary 36 Locally recurrent 14

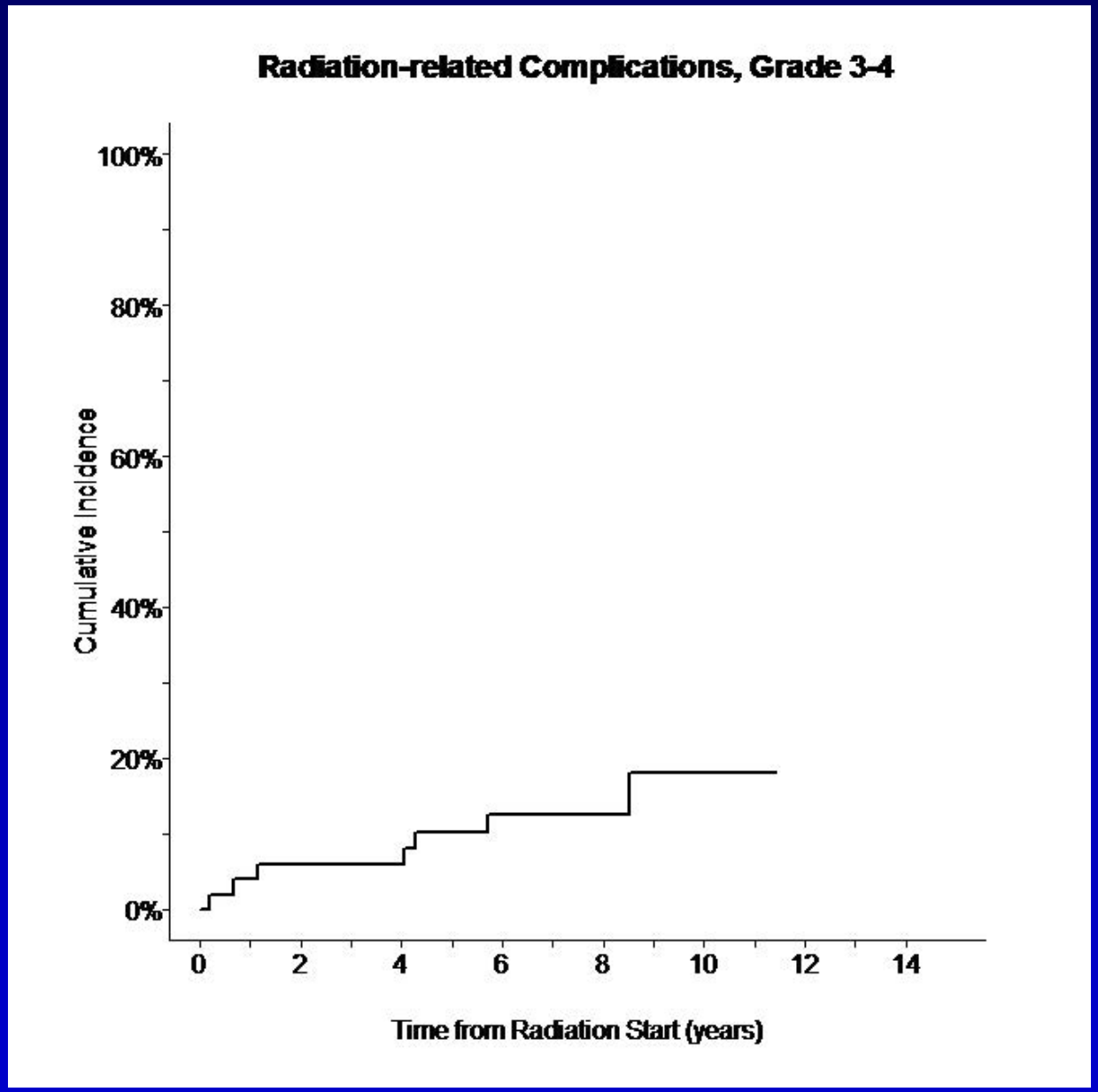
Spine and Paraspinal Sarcoma

5-year	8-year	
94%	84%	Local Control, Primary tumors
53%	53%	Local Control, Recurrent tumors
81%	74%	Local Control, All tumors
76%	69%	Locoregional Control
84%	65%	Overall Survival
64%	52%	Relapse-Free Survival
10%	13%	Grade 3-4 RT complications
16%	19%	Risk of RT complication(any)

Spine and Paraspinal Sarcoma

- Local Failure — All Patients (n=11/50)
  - R0 0/8 — R0 vs. R1,R2: p= 0.111
  - R1 4/17
  - R2 5/12
  - Biopsy only 2/13

- Local Failure — Chordoma (n=4/29)
  - R0 0/7
  - R1 1/10
  - R2 2/3 — R2 vs. bx only: p=0.827
  - Biopsy only 2/9
    - 1/23 1º Chordomas vs. 3/6 chordomas recurrent after prior surgery, p=0.005


Radiation-related Complications, Grade 3-4
100%
80%
60%
40%
20%
0%
Cumulative Incidence
0
2
4
6
8
10
12
14
Time from Radiation Start (years)

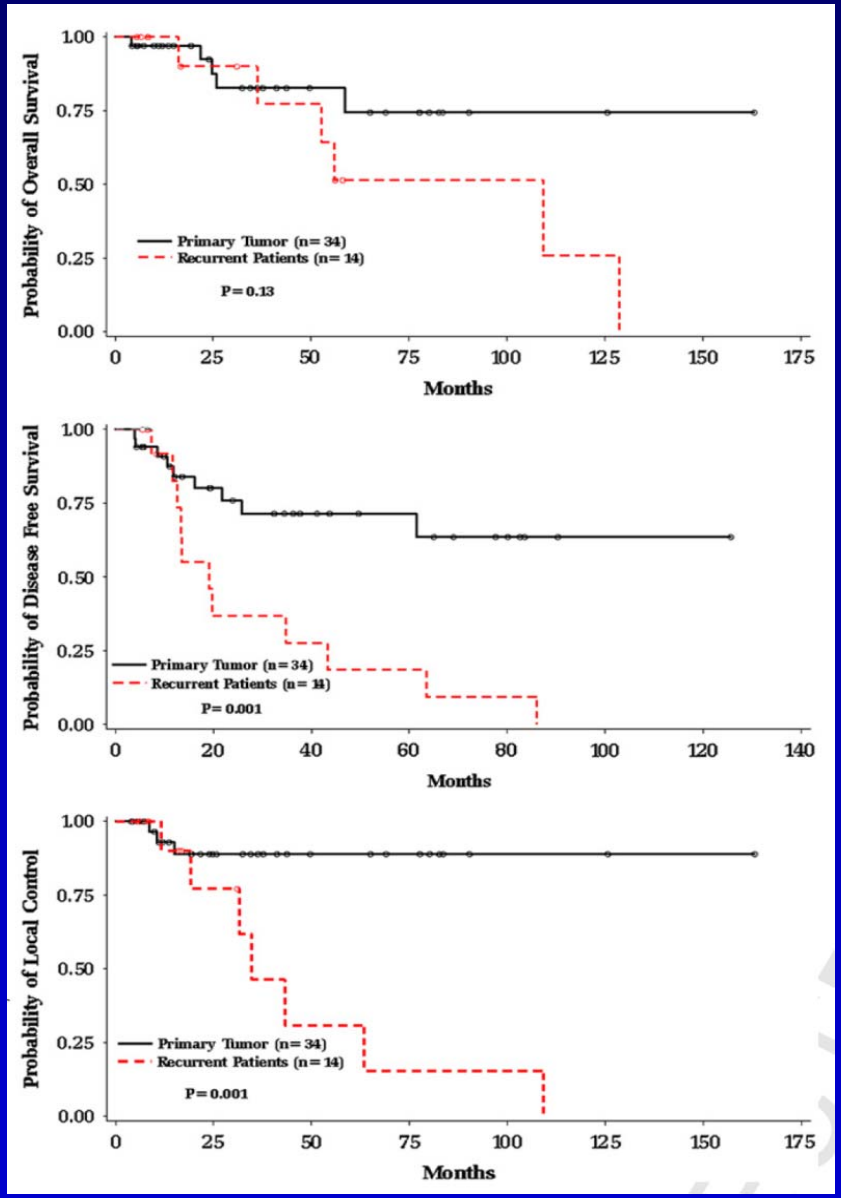
Spine and Paraspinal Sarcoma

- Conclusions
  - High dose photon/proton XRT can be delivered
  - Morbidity to date appears acceptable.
  - Encouraged by the treatment results with these challenging tumors
    - Results appear durable with occasional late recurrences
    - Prefer to radiate these high risk patients at time of initial presentation, as successful Rx of recurrences after surgery alone is much more difficult
  - Late sacral nerve toxicity in patients receiving 77.4 GyRBE has been seen but is uncommon

Low Dose Preop RT for Bone Sarcomas

Wagner et al IJROBP 2007

- Median of 20 Gy low dose preop + resection + postop boost
- Results:
  - Primary spine sarcoma LC 74% (compared to historical 30-40% range)
  - Reduces tumor seeding/implant, surgical bed failure
  - However patients who failed after prior surgery do not do well



High-dose Proton-based Radiation Therapy with or without Surgery in the Management of Primary and Recurrent Spine Chordomas

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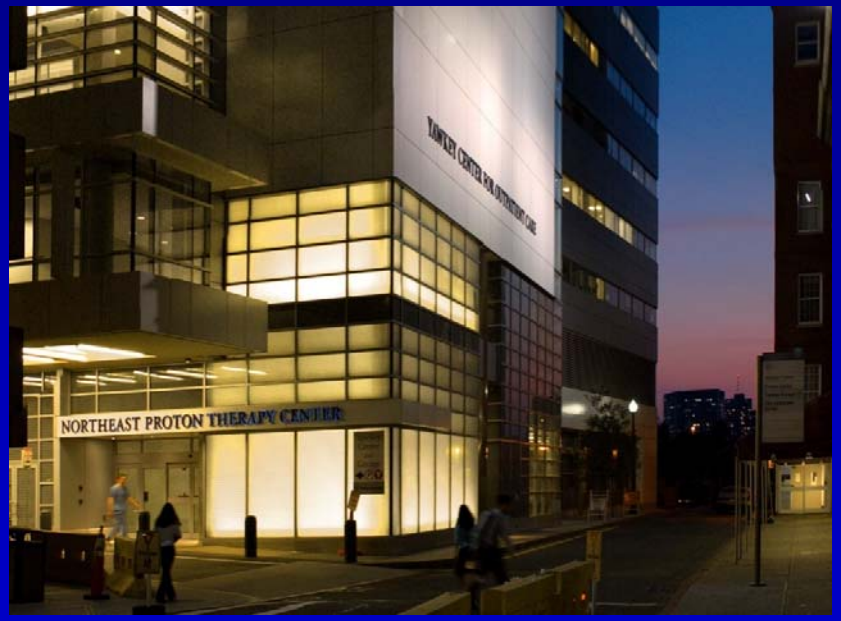

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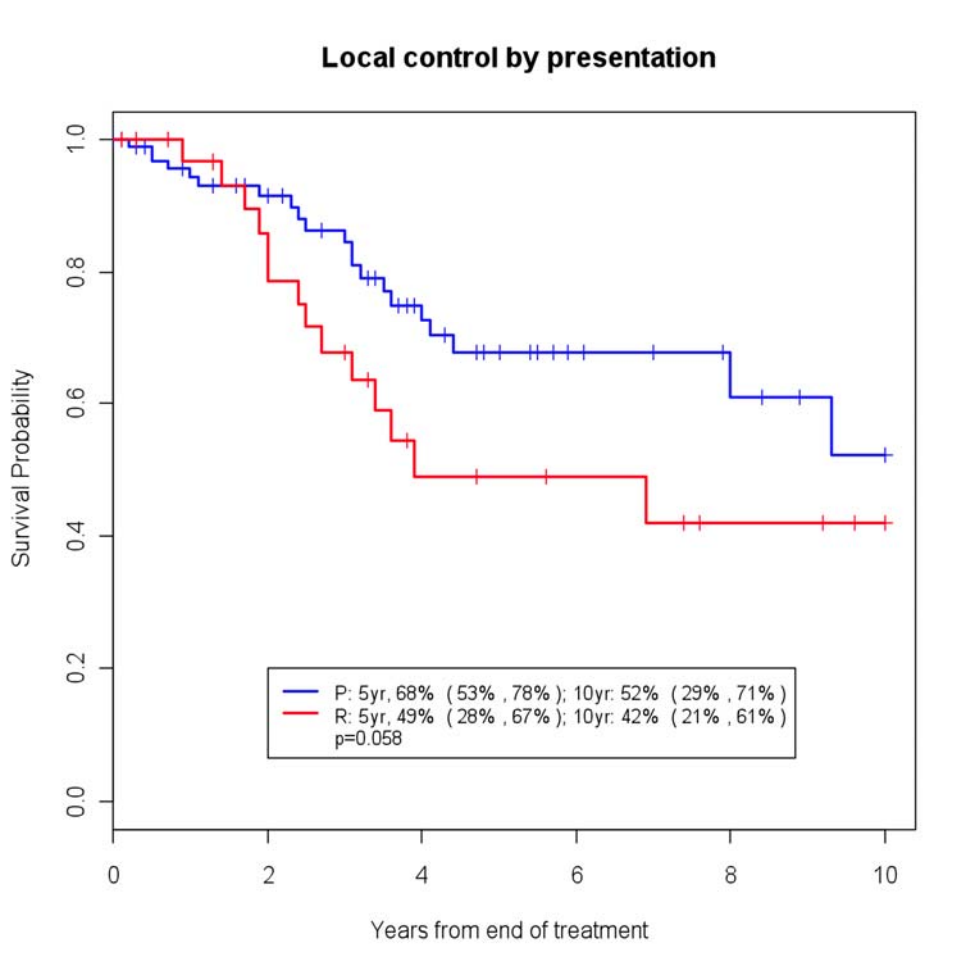
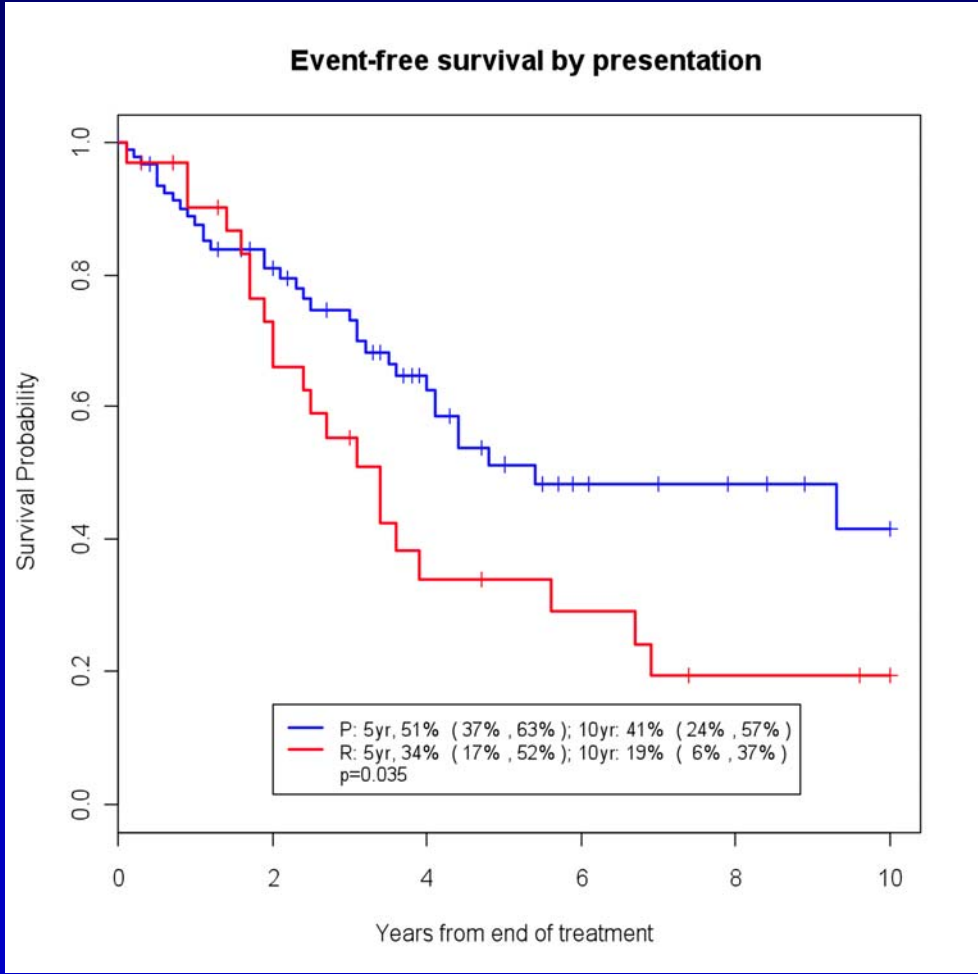
J Neurosurgery Spine, 2015

Materials & Methods

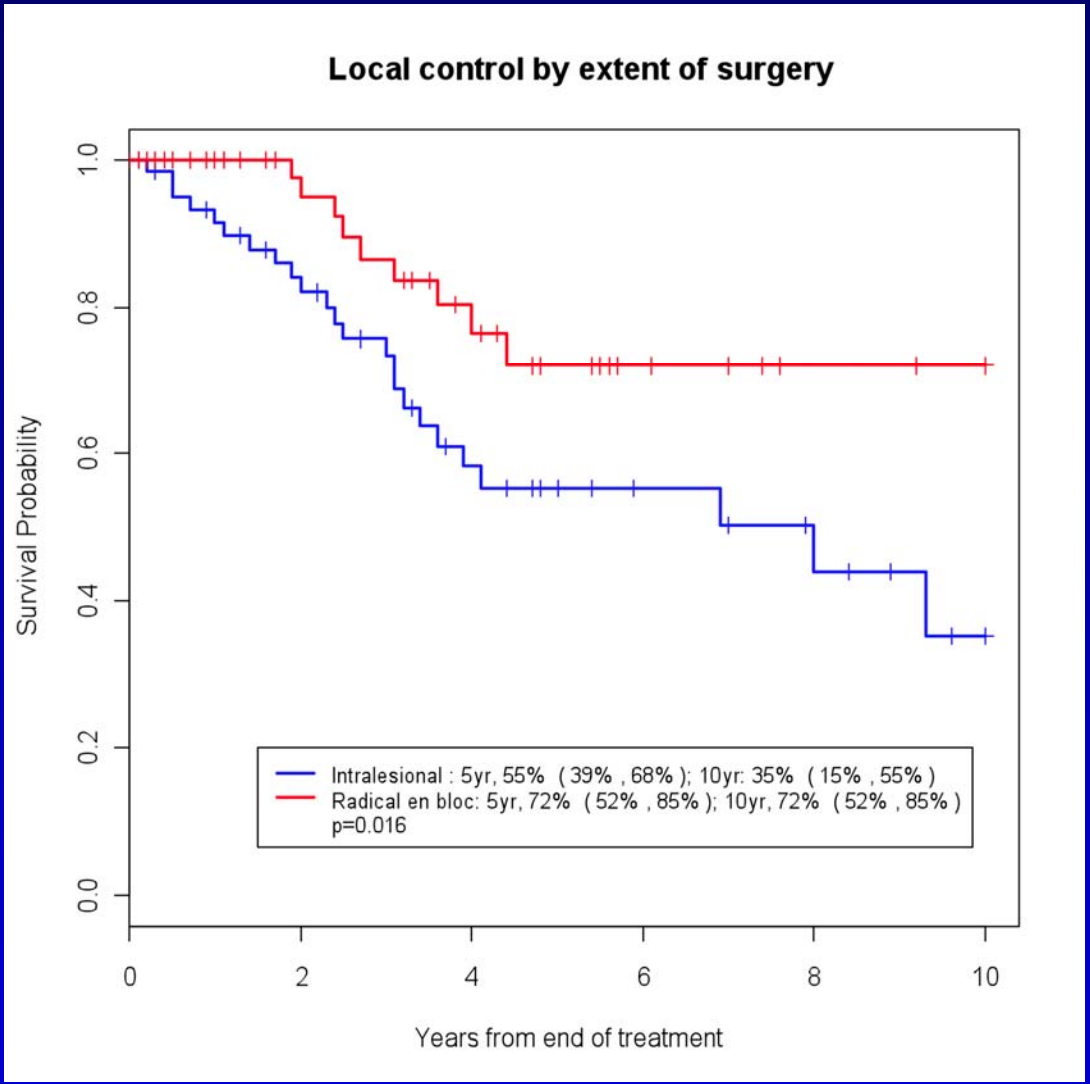
- Retrospective review
  - Study Period: Nov 1982 - Jan 2011
  - 126 pts (127 lesions) with localized, histologically-confirmed diagnosis of chordoma
  - Thoracic, lumbar, and sacrococcygeal spine
  - High-dose proton-based RT with or without surgery
    - Harvard Cyclotron Laboratory
    - Massachusetts General Hospital

Primary vs. Recurrent





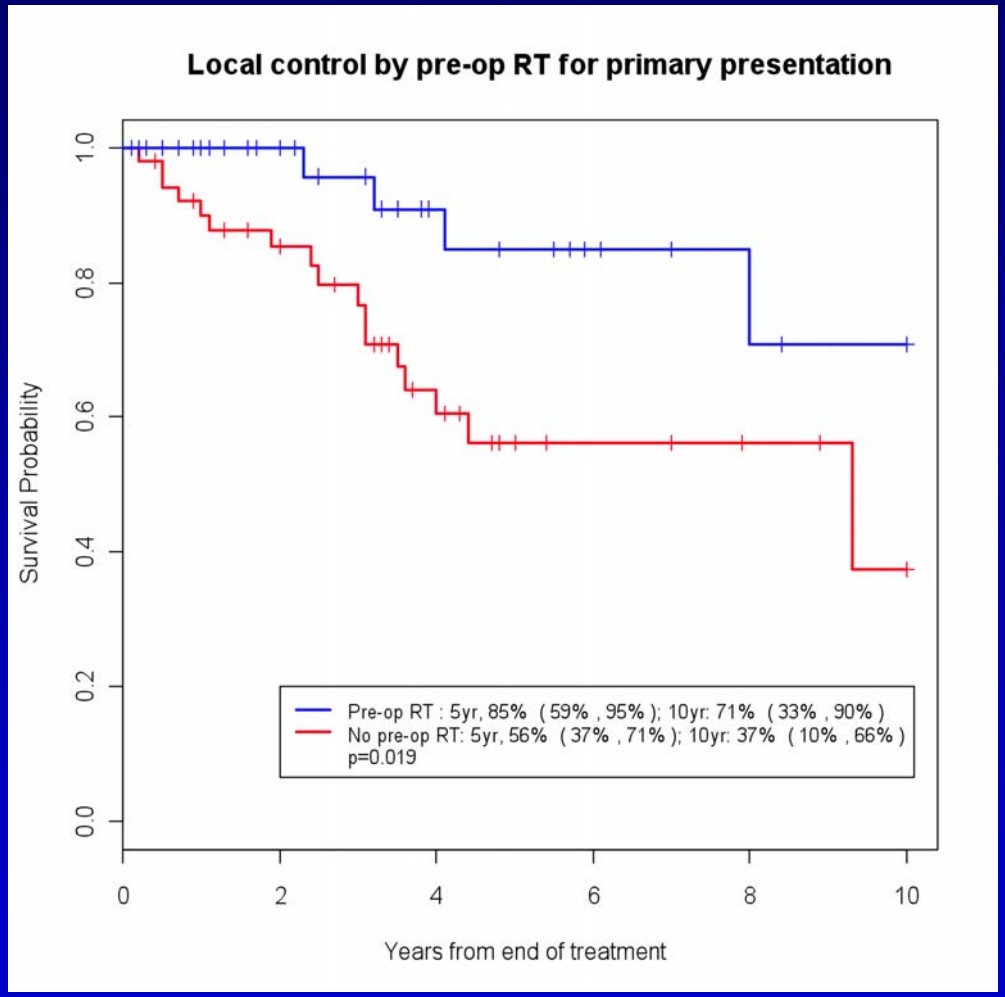
en bloc vs. Intralesional Resection

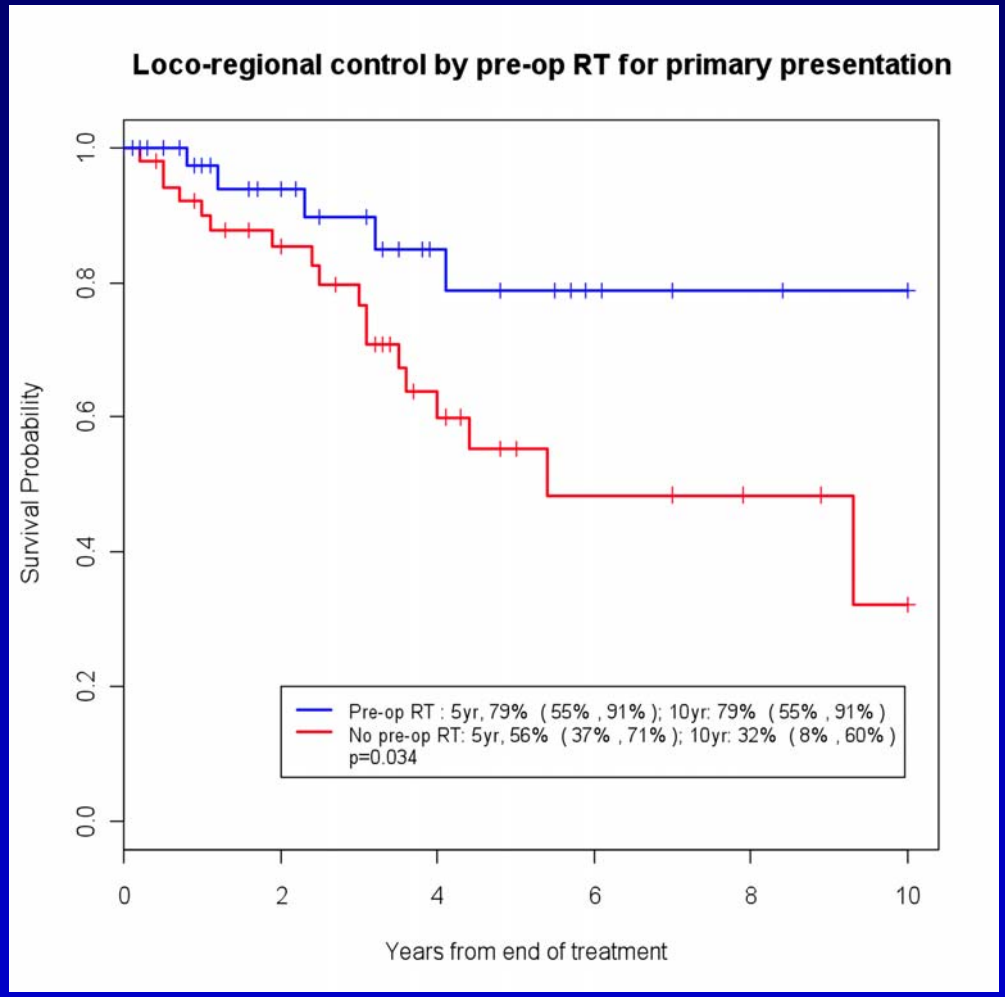


Number of Prior Surgical Interventions before Definitive Surgical Procedure

LC HR & 95% CI	LC P value	RC HR & 95% CI	RC P value	EFS HR & 95% CI	EFS P value
1.44 (1.03, 2.02)	0.034	1.99 (1.01, 3.90)	0.046	1.28 (0.98, 1.69)	0.071

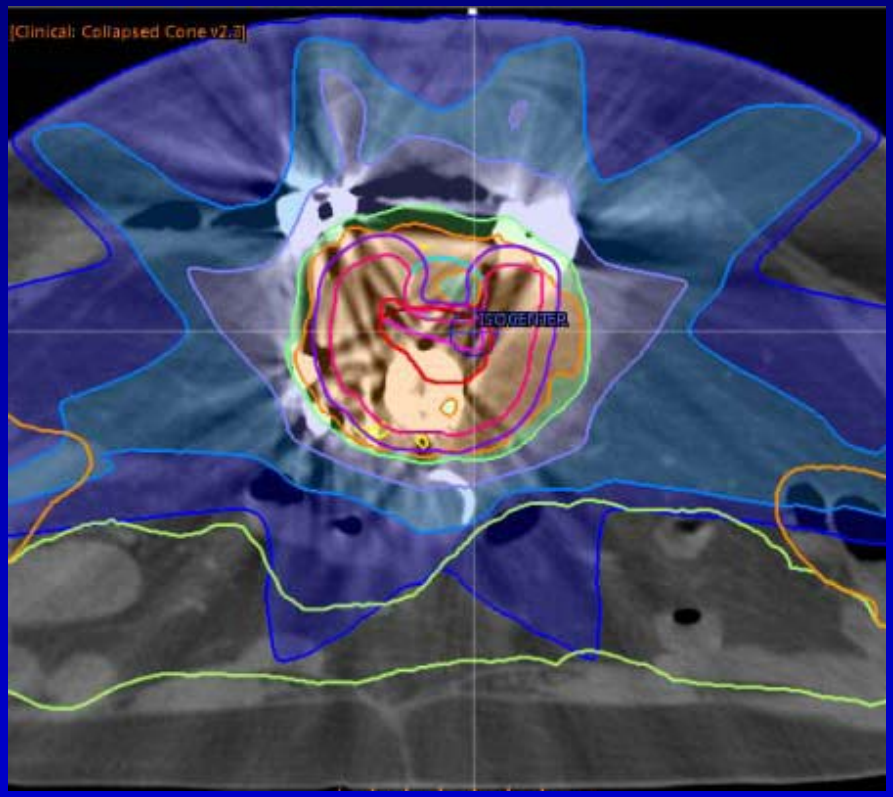
Pre-op RT for Primary Presentation

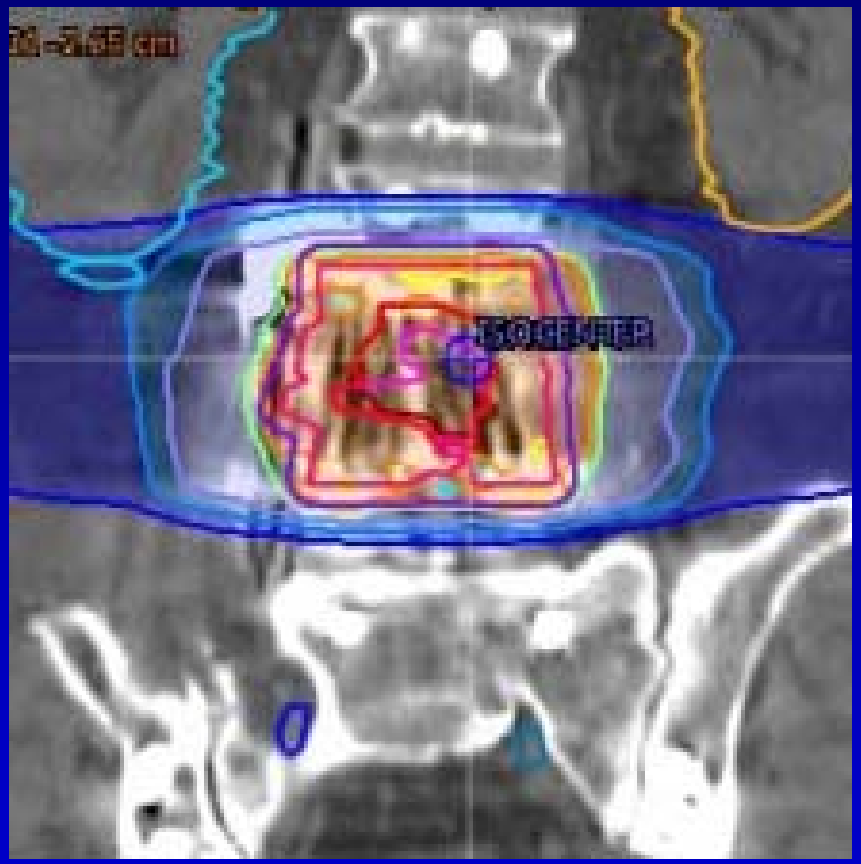




No LF in 28 1º pts who had core bx, preop RT, en bloc rxn→reduced total dose in pts with (-) margins from 70.2 to 68.4 GyRBE with no LR at 3 yrs, and protocol now allows reduction in total dose to 64.8 GyRBE

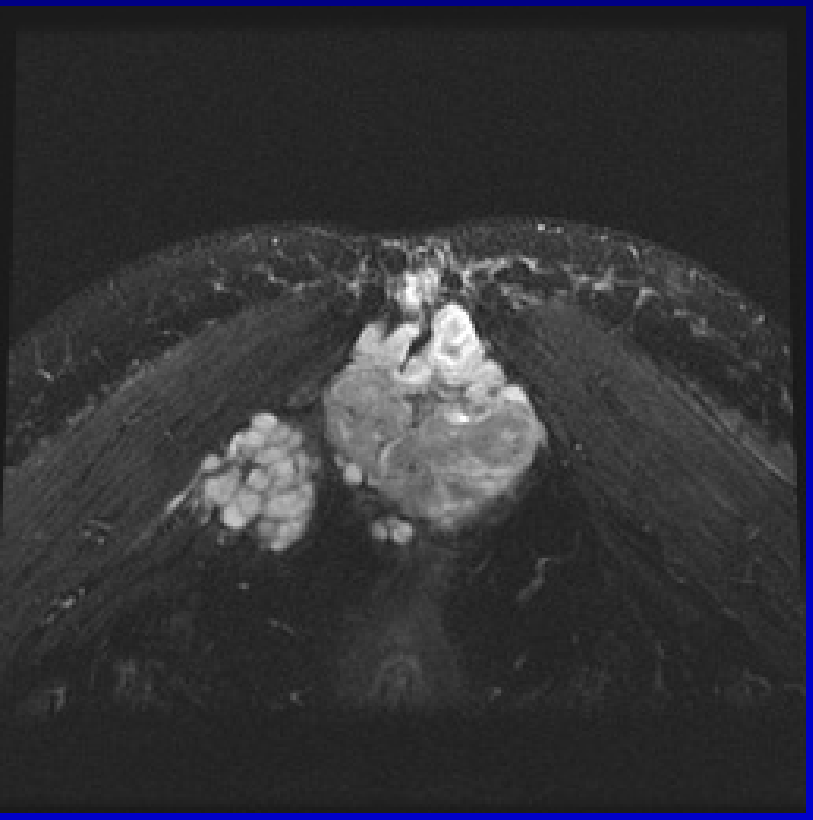
Lumbar Chordoma: Postop Boost with IMRT 2° to Hardware

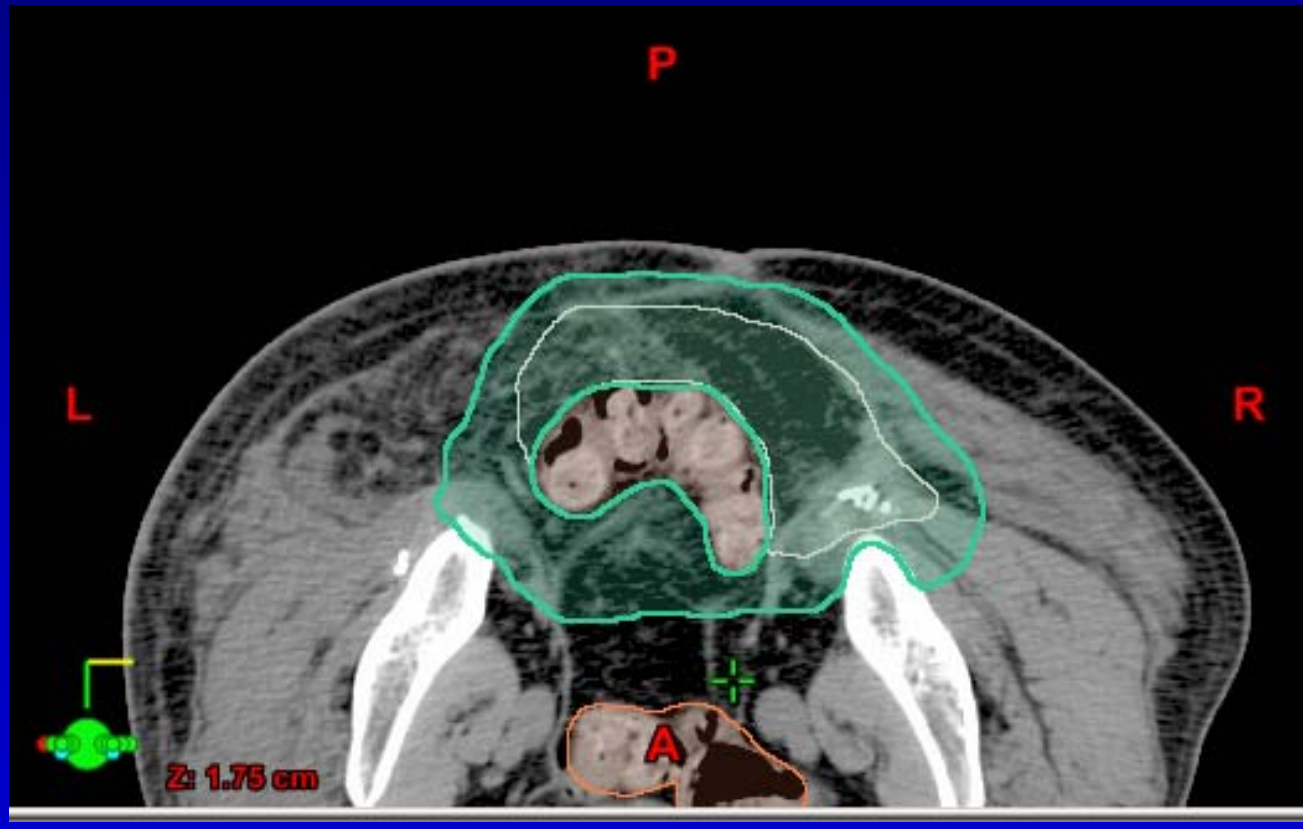




50.4 GyRBE/28 fx to elective CTV1 preop(19.8 Gy IMRT/30.6 GyRBE p+)
21.6 Gy IMRT to tumor bed CTV2 postop (+ margin, prior tumor violation)

Postoperative Radiation for Sacral Chordoma:
Bowel herniates into the postop radiation field→
Provides good rationale for a component of preoperative radiation.
Surgeon should try to displace bowel with omentum, rectus flap





Definitive High Dose Proton Based Radiotherapy for Unresected Chordomas

Yen-Lin Chen MD, Norbert Liebsch MD PhD, Wendy Kobyashi, Francis Hornicek MD PhD, Joseph Schwab MD, Andrew Rosenberg MD, G. P. Nielsen MD, Daniel Rosenthal MD, David Kirsch MD PhD, Herman Suit MD, Thomas DeLaney MD

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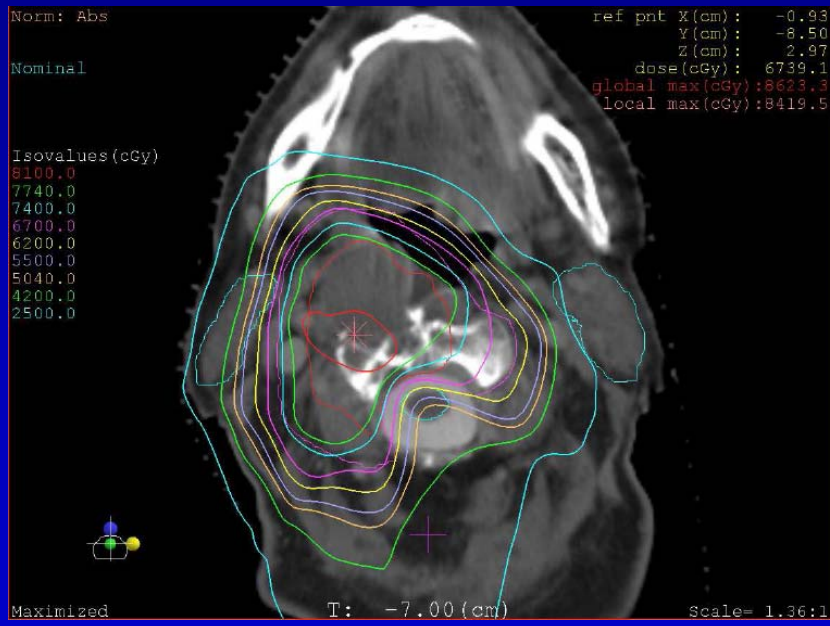

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Chen et al, Spine 2013;38(15): E930-6.

Definitive High Dose PRT for Unresected Chordomas

24 patients treated at the Harvard Cyclotron or Francis H. Burr Proton Therapy Center 1997-2010

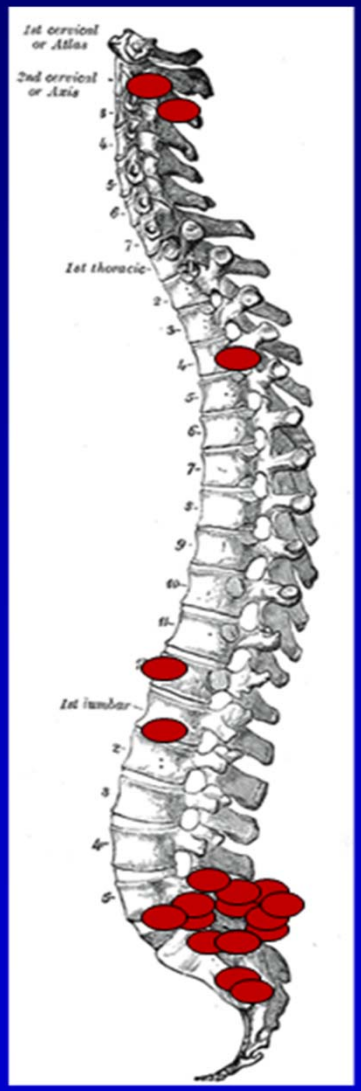
Male 13 Female 11

Conventional chordomas	23
Chondroid chordoma	1

Age at diagnosis: median 69.5 years

Median diameter: 6.6 cm (1.4-25.5 cm)

Median tumor volume was 198.3 cc (4.65-2061)
Median follow up: 56 months (24 to 168 mo)



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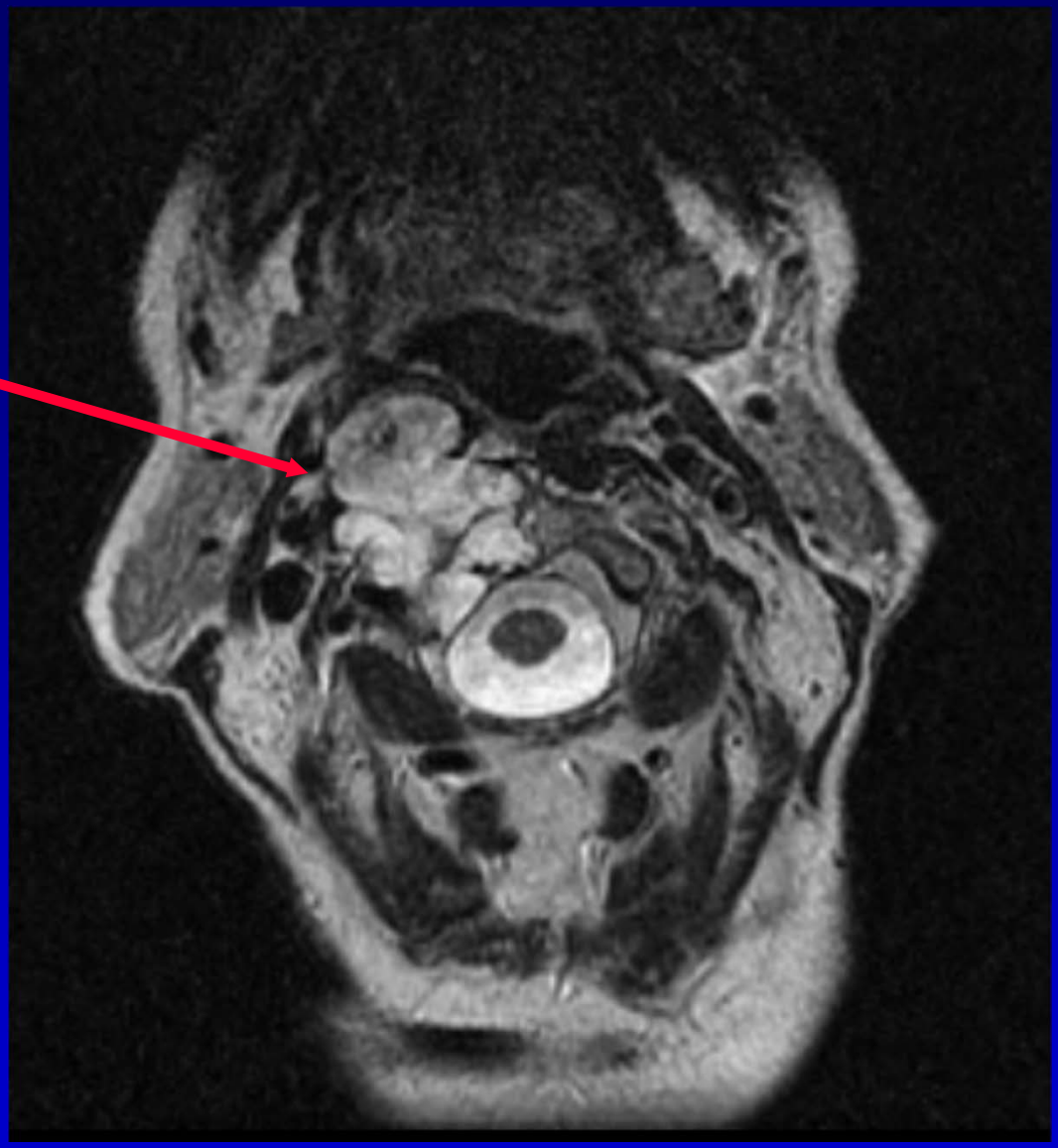
74 year old
Female

C2 Chordoma

Declined surgery



Definitive High Dose PRT for Unresected Chordomas

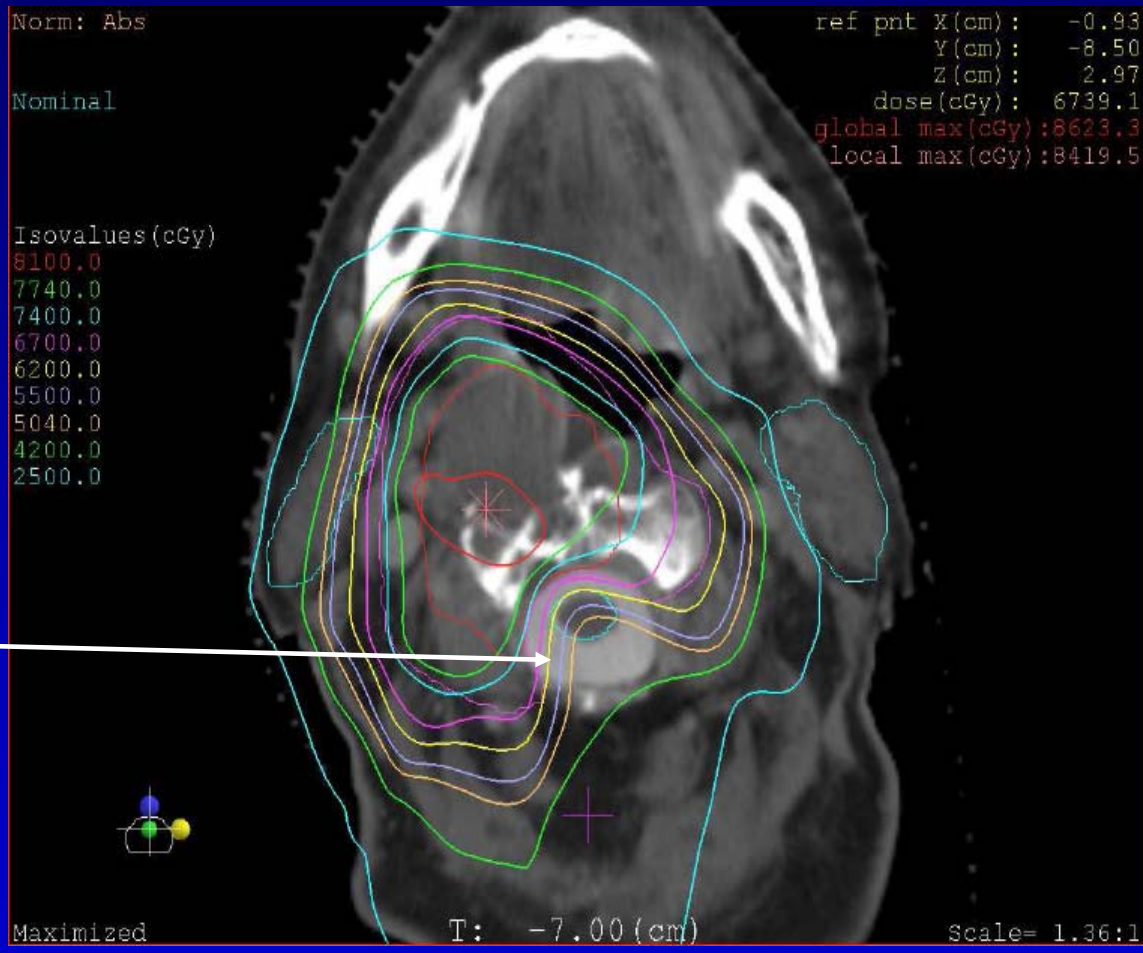
Radiation doses:

GTV: median 77.4 GyRBE
CTV: median 50.4 GyRBE

Photons: 34.0 Gy/17 fx (median)

Protons: 45 GyRBE /22fx (median)

Note intrathecal contrast



C2 Chordoma: Disease free 6.5 years
77.4 GyE (19.8 Gy IMRT + 57.6 GyE protons)

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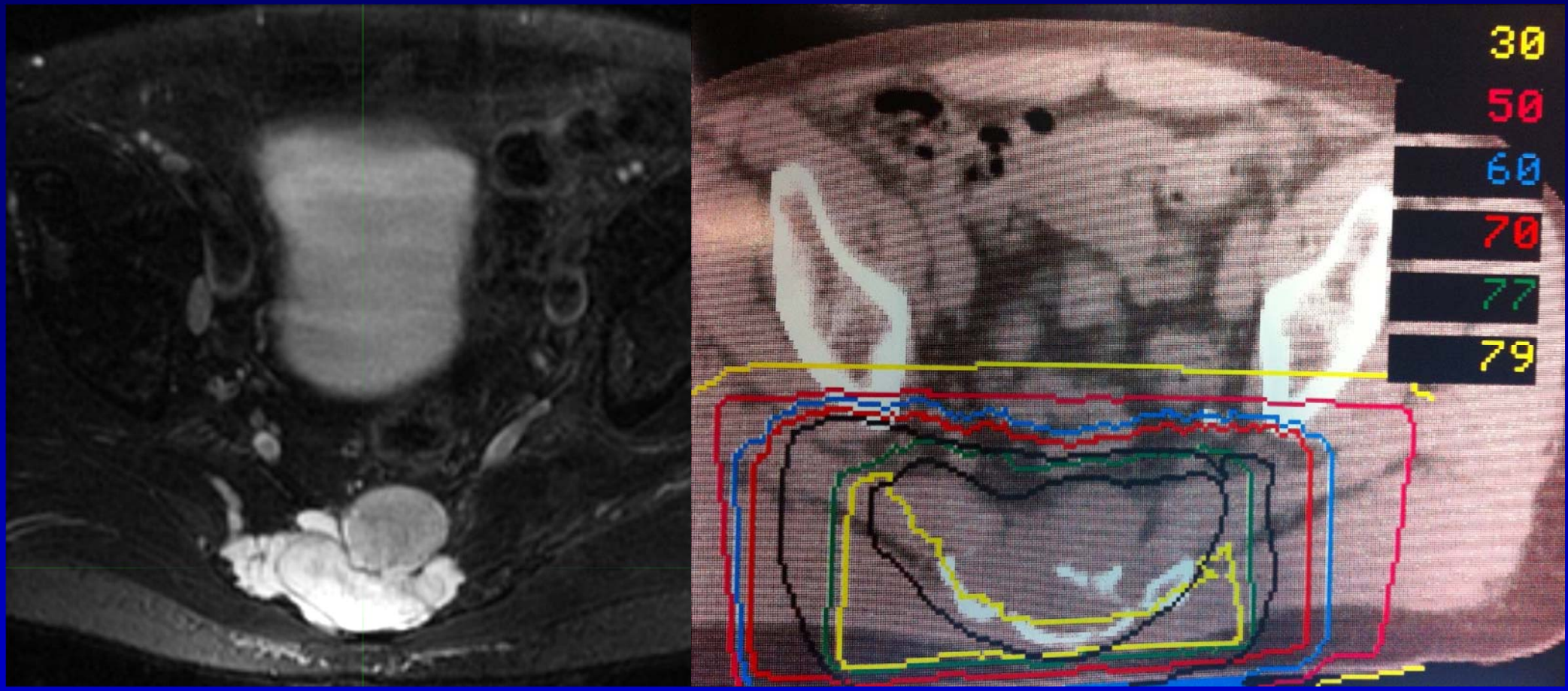
Definitive High Dose PRT for Unresected Chordomas

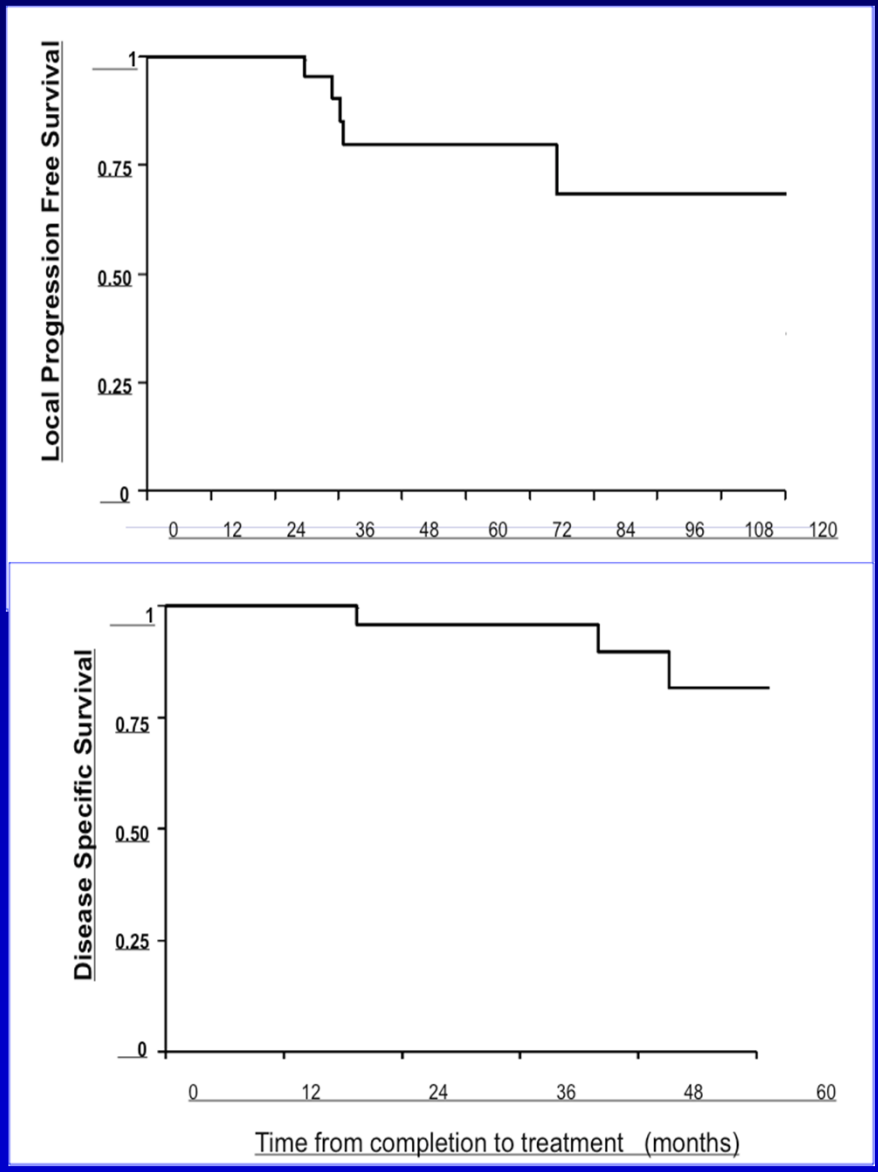


Sacral chordoma NED at 14 years
77.4 GyE
19.8 Gy 3D photons + 57.6 GyRBE protons

Definitive High Dose PRT for Unresected Chordomas

- OS3: 91.7% OS5: 78.1%
- DFS3 95.7% DFS5: 81.5%
- LPFS3: 90.5% LPFS5: 79.8%
- Tumor volume >500 cc correlated
- with worse DFS

• Spinal cord injury	0
• Neuropathy Grade 3	1 (4%)
– CN	0
– Lumbosacral weakness in foot	1 (4%) S1
• New erectile dysfunction	1 (4%)
• Soft tissue fibrosis	3 (12.5%)
• Rectal bleeding	4 (16%)
• Sacral insufficiency fx	8 (33%)



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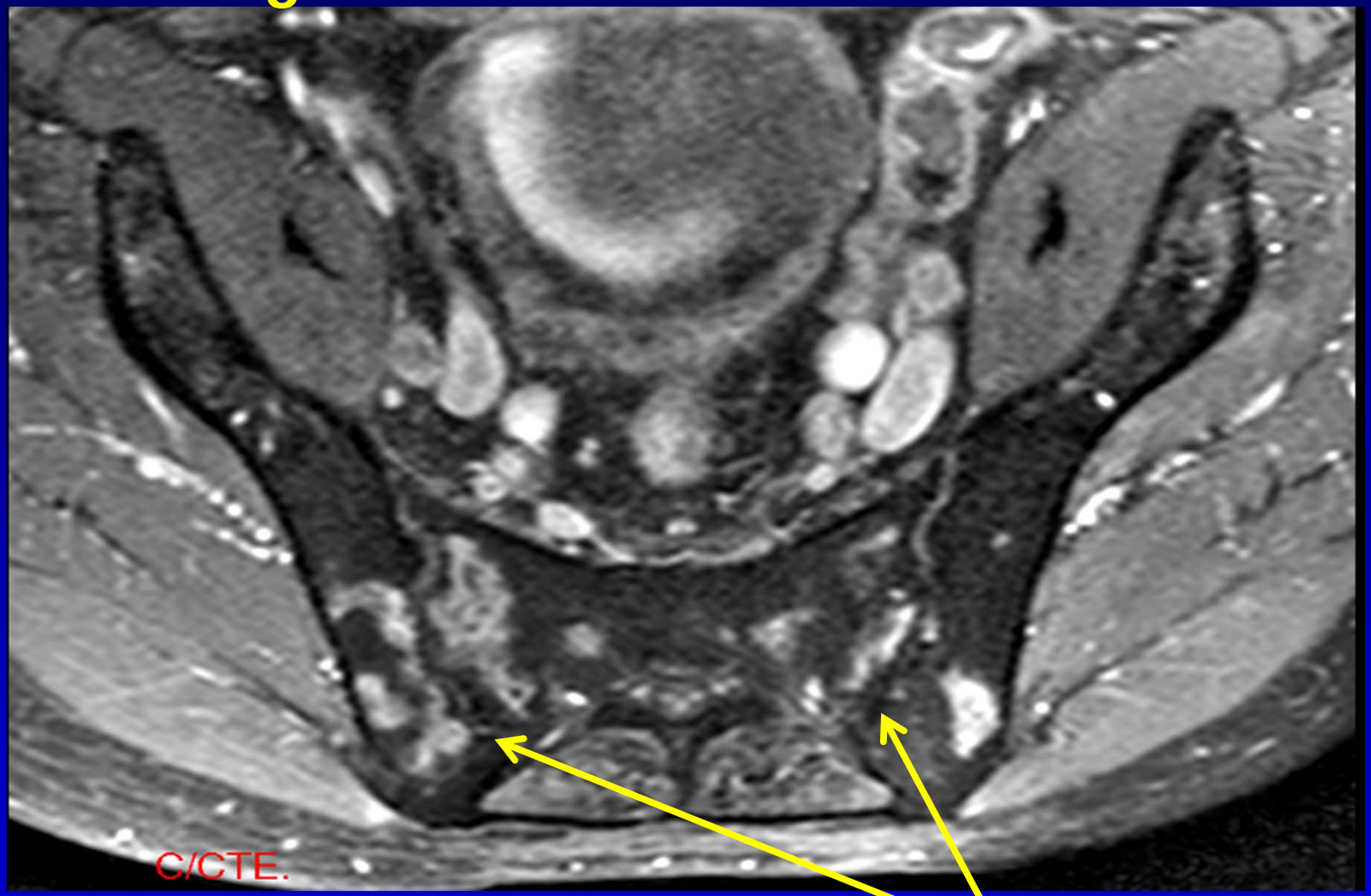
Definitive High Dose PRT for Unresected Chordomas



Sacral insufficiency fractures

Carbon Ion Therapy

- Less lateral diffusion and sharper Bragg peak
- Higher radiobiological equivalence (~3) that may be even higher in tumor vs. normal tissue
- Lower oxygen enhancement ratio (OER)
  - Possibly more effective than photons against hypoxic tumor
- ↓ capacity for sublethal/potentially lethal damage repair
  - Possibly more effective against slowly proliferating tumors
- Cost is substantially higher than protons
  - Hyogo (2001: 28 B ¥/ $ 230 million) vs. ~ $100 million proton
  - Will be important to define indications for carbon ions
- Dose schedules for carbon different
  - Hard to compare: is effect just very high dose versus different biology?

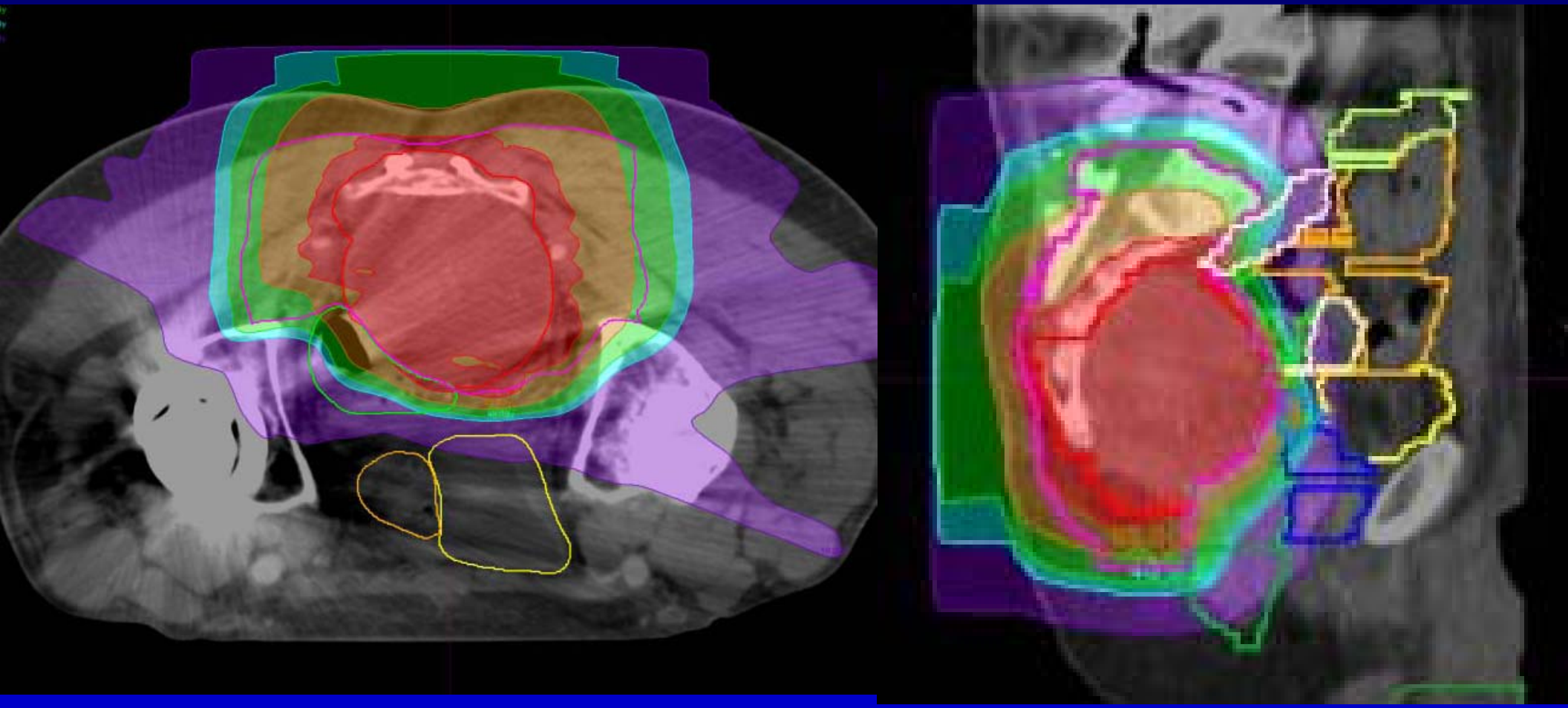
Carbon Ion Therapy

- Imai *et al.* (NIRS, Chiba, Japan)
  - 95 patients with unresectable sacral chordomas
    - 84 primary 11 local recurrent after resection
      - **Clinical target volume 370 cm^3**
    - 52.8-73.6 GyE (median 70.4) in 16 fx over 4 weeks
  - Local control rate at 5 years: 88%
  - Overall survival at 5 years: 86%
  - Two skin/soft tissue necrosis requiring skin grafts.
  - 15 patients had severe sciatic nerve complications
  - No other treatment-related surgical interventions, including colostomy or urinary diversion required post carbon ion.
  - 91% of patients have remained ambulatory
    - Imai et al, Br J Radiol 2011;84 (S1): 48-54.

Clinical Trials and Proton Therapy

- Randomized Carbon Ion Studies (Heidelberg)
  - Skull base chordoma RCT
    - Carbon 45 GyRBE/15 fx CTV1 + 18 GyRBE/6 fx CTV2
    - Proton 50 GyRBE/25 fx CTV1 + 22 GyRBE/11 fx CTV2
  - Sacrococcygeal chordoma RCT-Phase II
    - Carbon 64 GyRBE/16 fx of 4 GyRBE
    - Proton 64 GyRBE/16 fx of 4 GyRBE
    - Endpoints: Primary: Toxicity/Safety/feasibility
      Secondary: Local control, Survival

Unresected Sacral Chordoma: Definitive RT



50.4 GyRBE/28 fx to elective CTV1 (19.8 Gy IMRT/30.6 GyRBE scanned p+)
+ 27 GyRBE/15 fx to GTV = 77.4 GyRBE

Normal Tissue Constraints Spine, Skull Base

Structure	Surface	Center (GyRBE)
Brainstem	67	55
Cervical cord	67	55
Thoracic/Lumbar cord	63	54
(Cord constraints reduced 8% if chemoRx used)		
Brachial plexus	68.4	68.4
Cauda Equina	77.4	70.2
Sacral Nerves	77.4	77.4
Small bowel	V57.6<50% circumference, <10 cm,	
Skin (if possible)	66	

High Dose Proton Beam Boosted Radiation Therapy (PBT) in Management of Extracranial Chondrosarcomas

Thomas F. DeLaney MD, Aashish D. Bhatt MD, Alex Jacobson BS, Richard Y. Lee MD, PhD, Christine Giraud BS, Joseph H. Schwab MD, MS, Francis J. Hornicek MD, PhD, Petur Nielsen MD, Edwin Choy MD, PhD, David Harmon MD and Yen-Lin E. Chen MD

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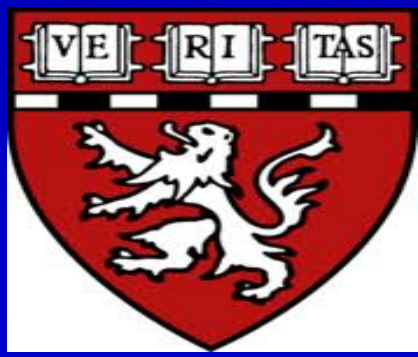

Connective Tissue Oncology Society
2014, Berlin, Germany

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Patient Population

- **Median age** - **45.5 yrs** (4-83) Male 45%: Female 55%
- **Site: Spine/Sacrum 80%** Pelvis 14% Other 3%
- Median tumor **size** was **13 cms** (range: 1-27)
- **Tumor Grade** - I (27%), **II (59%)** and III (14%)

Patient Population

- **Primary** tumor: **73%** Recurrent after prior surgery: 27%
- Surgery: resection status
  - Gross total 50% Subtotal 41% Bx only 9%
- Margin status
  - R0: 25%
  - R1: 14%
  - **R2: 50%** Unknown: 11%
- Median follow-up was **29.1 months** (range: 3-96.8)

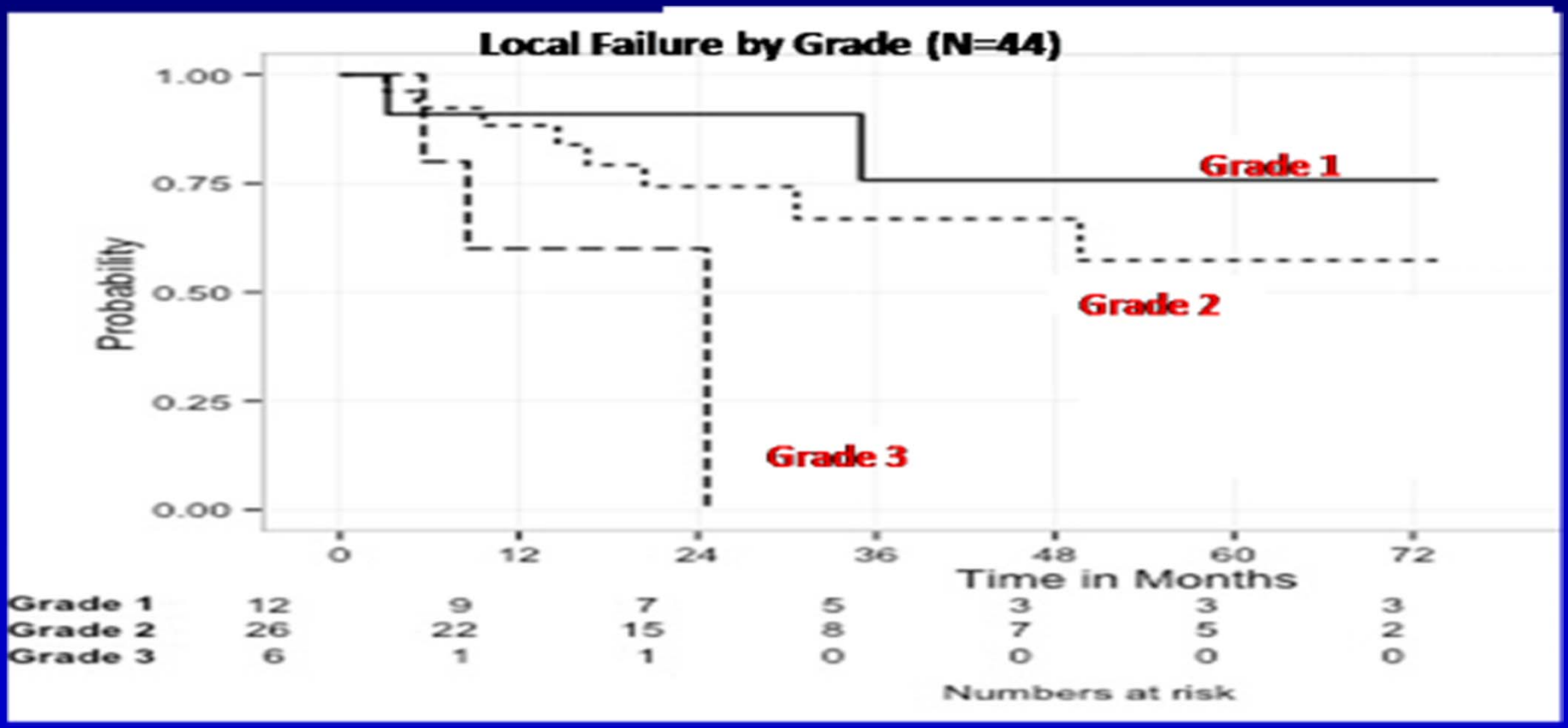
Radiation Therapy

- **RT Schedule**
  - Pre-op +/- postop boost : 50%
  - Post-operative: 41%
  - Definitive, non-surgical Rx 9%
- **Median RT dose:** 70.2 GyRBE at 1.80 Gy per fraction
  - **Maximum RT dose:** 77.4 GyRBE
- **Photon RT + Proton :** 77% **Proton only:** 23%
- **Intra-operative RT (IORT)** was used in **5** patients

Chondrosarcoma Results

- **Local control** **Overall Survival**
  - **2 year: 76%**
    - **2 year: 90%**
  - **5 year: 57%**
    - **5 year: 68%**
- **Toxicity:**
  - **Acute wound complication 16%**
  - **Neuropathy (G2 sciatic, G3 sacral) 5% (74, 77.4 GyRBE)**
    - **No myelopathies**
  - **Sacral fracture 5%**
  - **Chronic pain 5%**
  - **Hypothyroidism 2%**

Local Failure By Grade



Local Control– Multivariate Analysis

Variable		Hazard Ratio (HR)	95% Confidence Interval (C.I.)	p-value
Sex	Female (ref.)	1.00	-	-
	Male	0.34	(0.06-2.01)	0.233
Tumor Grade	I (ref.)	1.00	-	-
	II	2.29	(0.23-22.48)	0.476
	III	26.46	(1.73-405.27)	0.019
Primary /Recurrent	Primary (ref.)	1.00	-	-
	Recurrence	1.92	(0.43-8.46)	0.391
Site of Tumor	Non-Spine (ref.)	1.00	-	-
	Spine	1.45	(0.11-18.48)	0.777
Resection Margin	R0 (ref.)	1.00	-	-
	R1	0.88	(0.05-16.07)	0.928
	R2	1.69	(0.22-12.91)	0.611
	Not Reported	0.25	(0.01-6.47)	0.405

Grade III tumors were associated with decreased local control, (p=0.019).

Conclusions

- Our series is the largest report on the use of proton radiation in the management of non-skull base chondrosarcomas
- Protons, in combination with surgery in most pts in this series, resulted in LC in 57% despite high risk factors (i.e. 50% R2, spine sites)
- Protons allowed high RT doses in spinal/sacral tumors
  - No myelopathy but 5% risk of neuropathy, sacral fracture, chronic pain
  - 16% risk of acute wound healing problems
    - Use only 19.8 Gy preop for sacral lesions unless subcutaneous sparing possible as well as flaps (i.e. rectus) in conjunction with plastic surgery
- **Female gender** was predictive for **decreased survival** while **grade III** tumors predicted for **decreased local control and survival**

Osteosarcomas

- Osteosarcomas of skull, face, spine, pelvis
  - Satisfactory resections difficult
  - Local failure more common
  - Meta-analysis: Head and neck lesions
    - Local failure ~50%
      - As you move from mandible to sinuses to skull base, local control in increasingly difficult

Osteosarcomas

- Osteosarcomas of spine, pelvis
  - 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 biopsy

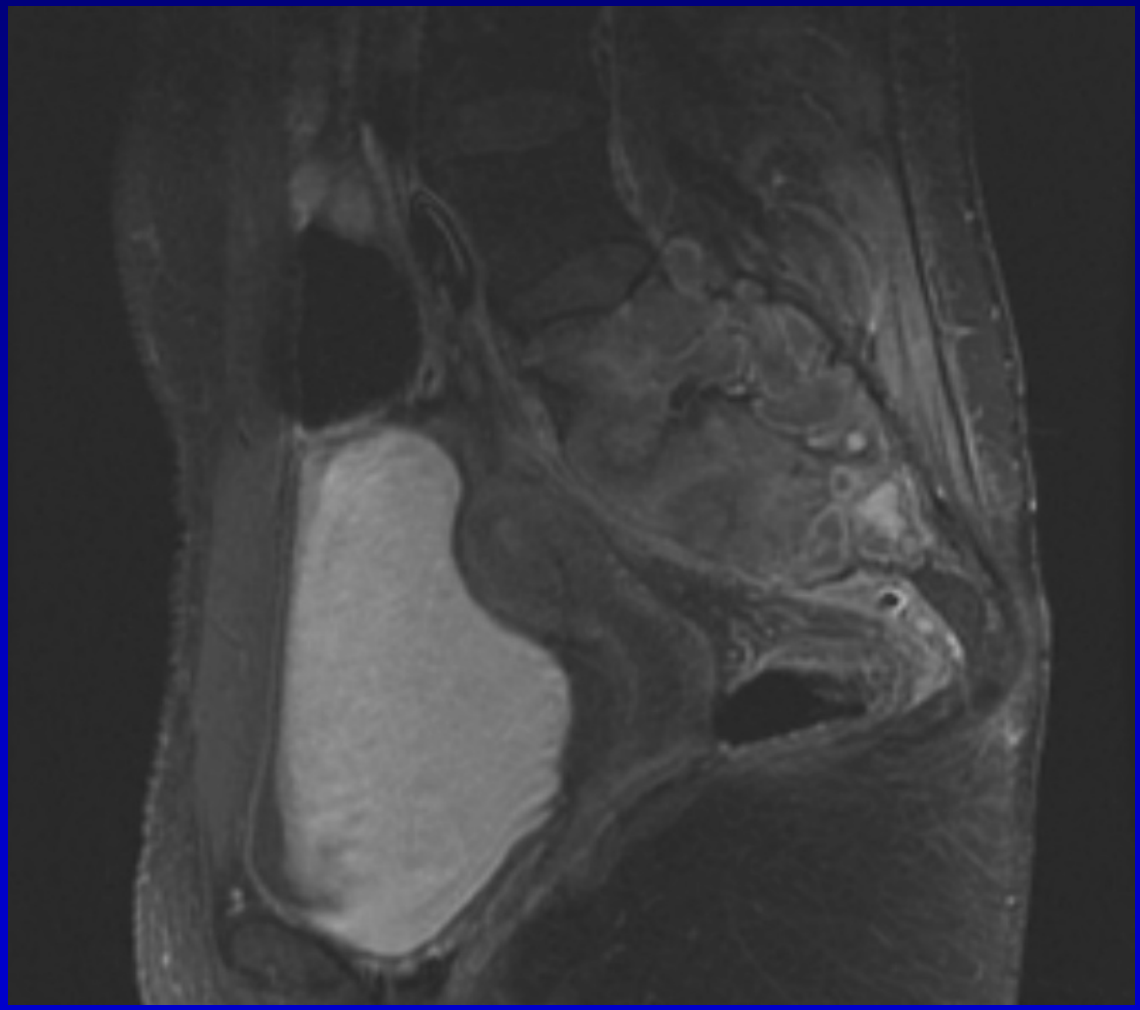
Unresectable Sacral Osteosarcoma

18 year old with sacral osteosarcoma

Neoadjuvant chemotherapy with doxorubicin/platinum alternating with methotrexate

Concurrent chemoradiation with ifosfamide/etoposide

45 GyRBE to elective CTV1
72 GyRBE to gross tumor (GTV)



Unresectable Sacral Osteosarcoma

18 year old with sacral osteosarcoma

Neoadjuvant chemotherapy with doxorubicin/platinum alternating with methotrexate

Concurrent chemoXRT with ifosfamide/etoposide→Disease-Free 6 years after treatment

45 GyRBE to elective CTV1
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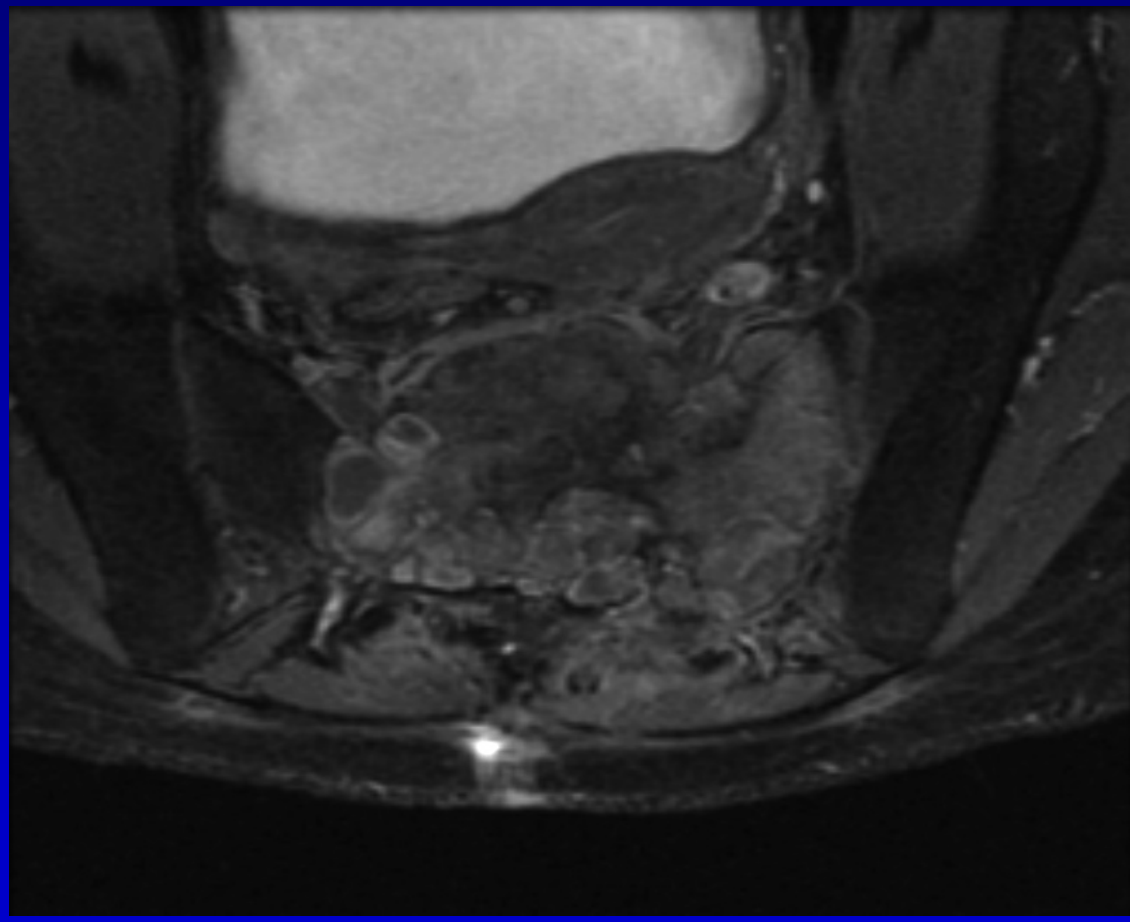
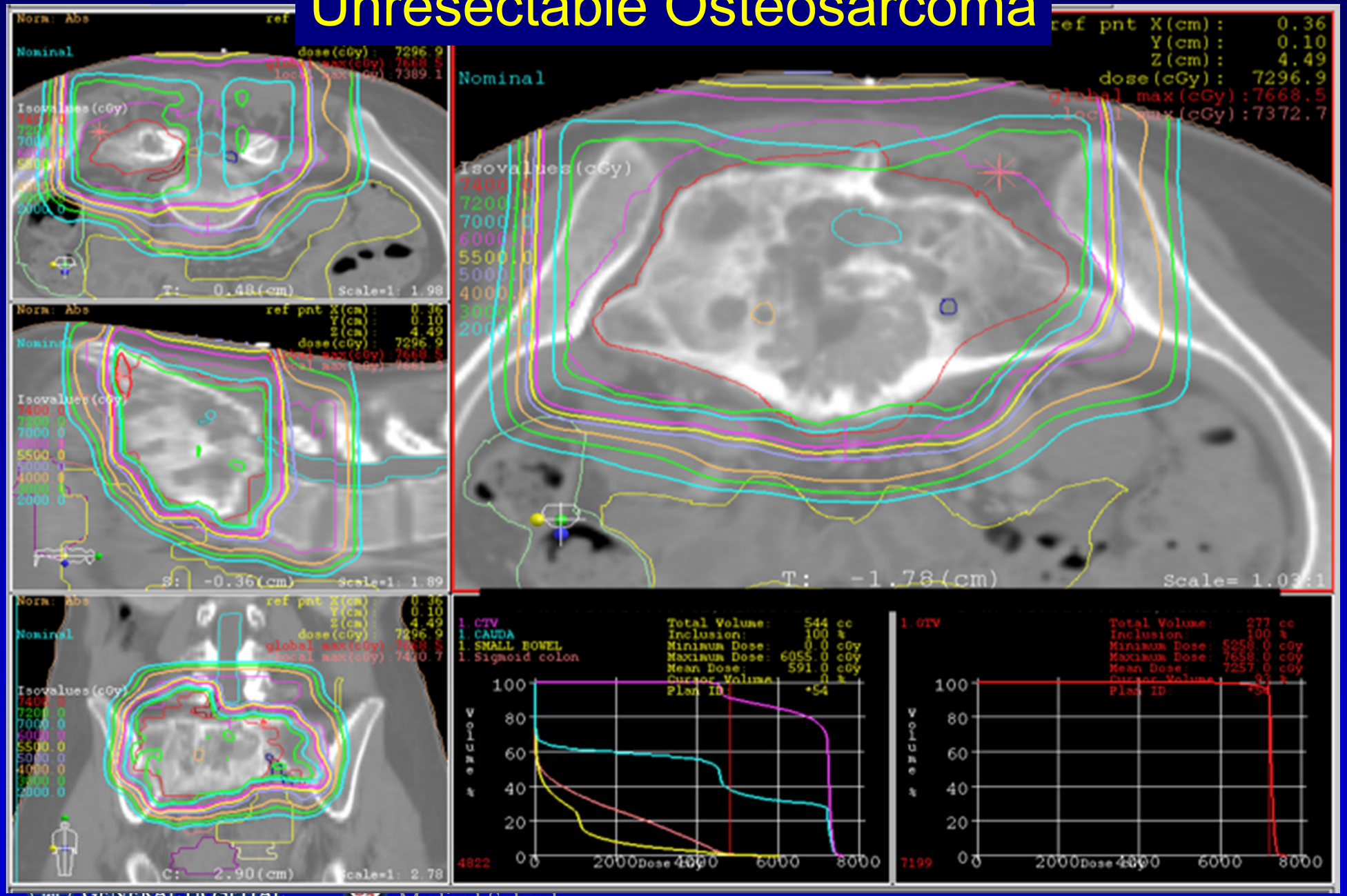


Unresectable Osteosarcoma



Proton Radiotherapy for Osteosarcoma
Ciernik et al., Cancer 2011

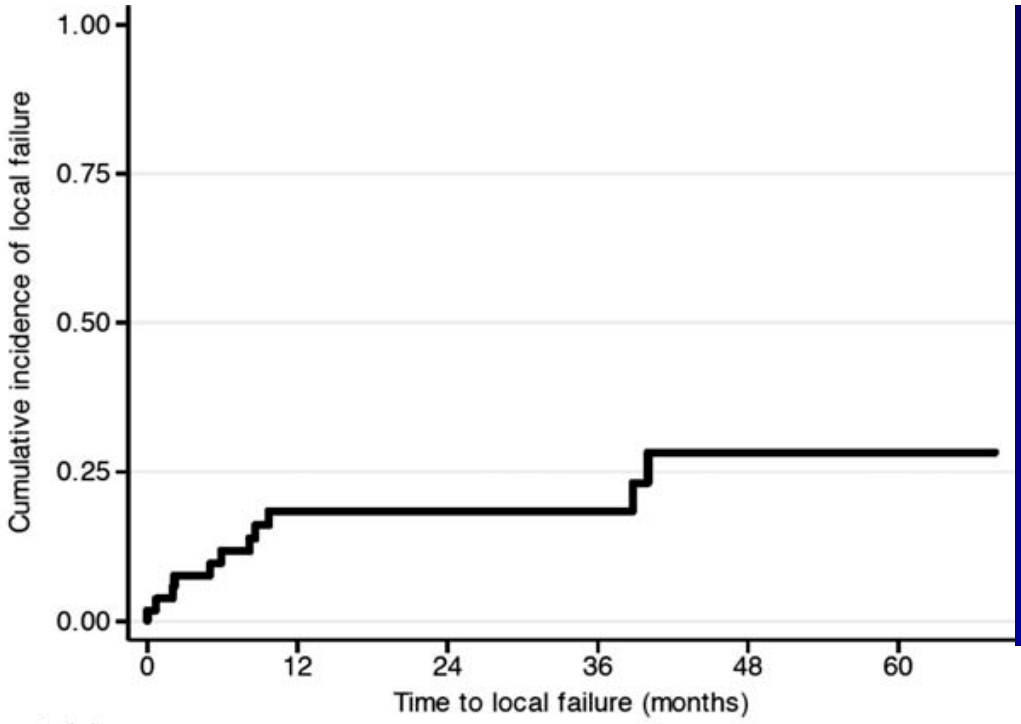
- 55 patients: 1983-2009
- Patient age
  - Range 2-76 years
  - Median 26.9 years

  - Primary tumor 35 (64%)
  - Local recurrence 17 (31%)
  - Metastatic site 3 (5%)

SITE	Number	%
Craniofacial	22	40%
C-spine	5	9%
T-spine	8	15%
L-spine	4	7%
Pelvis/sacrum	13	24%
Femur/hip	2	4%
Rib/chest wall	1	2%

Proton Radiotherapy for Osteosarcoma
Ciernik et al. Cancer 2011

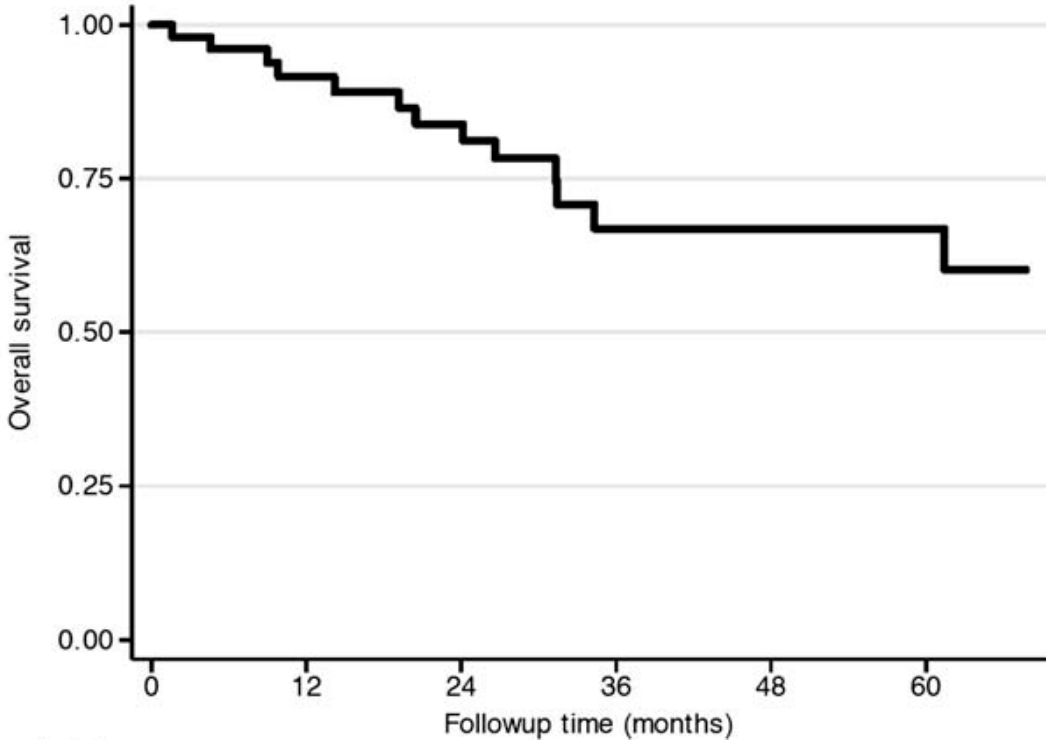
- Surgery
  - Biopsy only 22%
  - R1 (margins +) 43%
  - R2 (Subtotal) 35%
- RT
  - Median dose 68.4 Gy (54-80)
  - Proton radiation therapy
    - 58% of total dose
- Local control
  - 3 years: 82%
  - 5 years: 72%
- Disease-Free Survival
  - 5 years: 65%
- Overall Survival
  - 5 years: 67%



Osteosarcoma Protons

Overall Survival 67%

Local Failure 28%



MASSACHUSETTS GENERAL HOSPITAL

Harvard Medical School

- **Bone sarcoma**
- **Retroperitoneal sarcoma**

Background

- Approximately 15% of soft tissue sarcomas occur in the retroperitoneum
- The only proven treatment modality for RPS is surgery
  - Local tumor control however only ~50% at 5 years with surgery
- Many believe pre-operative RT may improve local control but this has not been proven

Defining the Role of Pre-op RT

ACOSOG Z9031 RCT:

- Surgery Alone *vs* Pre-op RT 50.4 Gy → Surgery
- Closed due to poor accrual

EORTC 62092-22092 RCT

- Surgery Alone *vs* Pre-op 50.4 Gy RT → Surgery
- Ongoing
- Accrual to date ~150 of planned 300
- Results are eagerly awaited

Radiation Dose-Escalation

- Dose escalation using intraoperative electrons or brachytherapy combined with external beam radiotherapy have been reported to improve local control.
  - BrachyRx associated with toxicity in the upper abdomen
  - IORT: neural/ureteral toxicity; anatomic limits
- Preoperative IMRT of 45 Gy (1.8 Gy/fx) to the tumor PTV with a simultaneous integrated boost to 57.5 Gy (2.3 Gy/fx) to high-risk margin in 25 fx was well tolerated in 16 patients (Tzeng et al., Cancer 2006)
  - Nevertheless, local failure rate was still 20% at 2 years.

Hypotheses

- *Higher radiation dose to the high risk RPS margin will improve local tumor control*
- *Radiation dose may be escalated with less normal tissue toxicity with IMPT than IMRT.*
  - *Separate IMPT and IMRT cohorts*

Schema

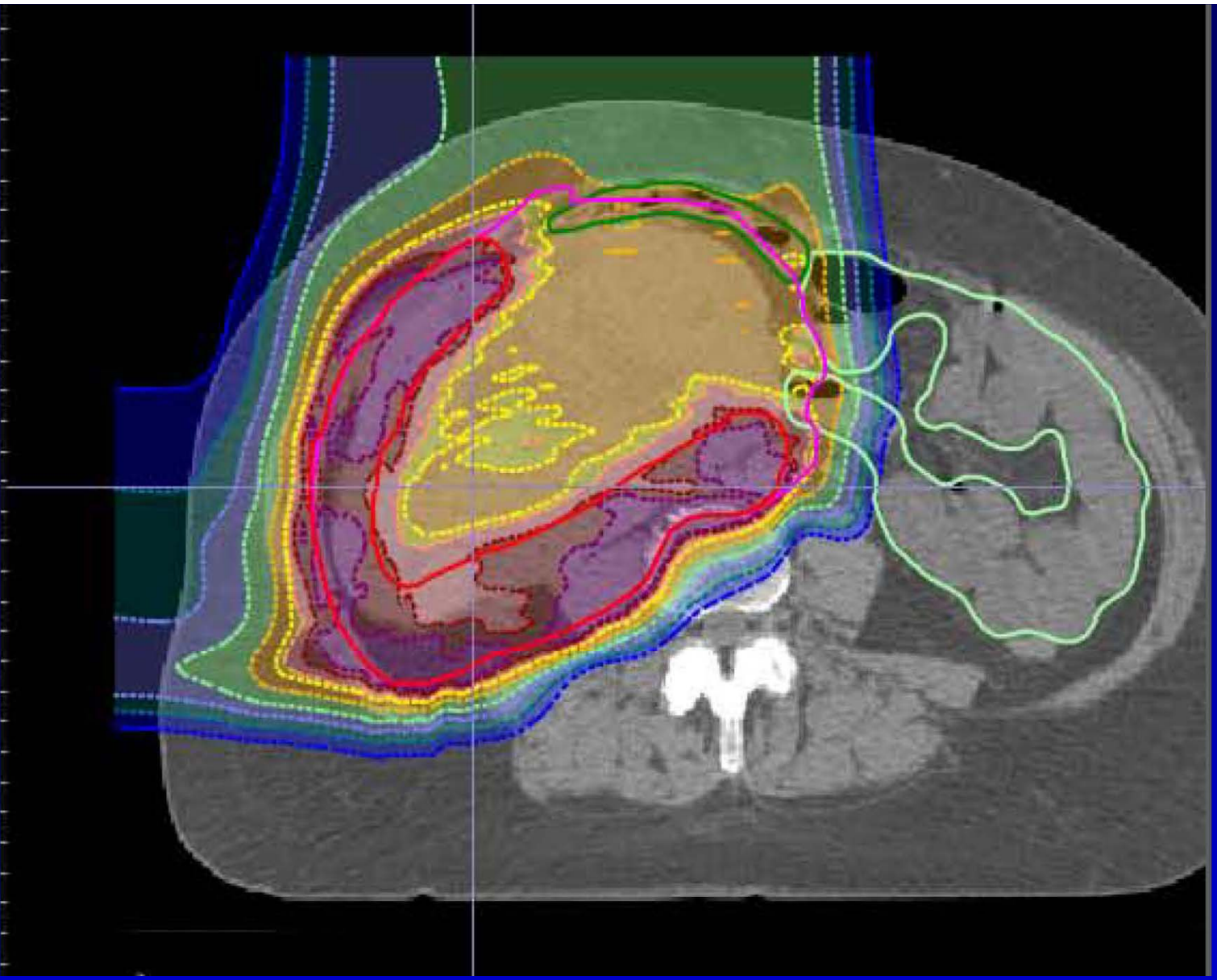
Phase I/II Preop Intensity Modulated Photons (IMRT)

Phase I/II Preop Intensity Modulated Protons (IMPT)

for Retroperitoneal Sarcoma:

Patients with retroperitoneal sarcoma → IMRT/IMPT 50.4 Gy/ 28 fx to Lower Risk CTV1 → Resection 4-12 weeks after IMRT/IMPT

SIB 60.2/61.6/63 Gy/ 28 fx to the high risk CTV2 margin predicted for recurrence



PREOP IMPT/IMRT
PROTOCOL
PHASE I/II
CTV1 50.4 GyRBE
High Risk CTV2 SIB
60.2→61.6→63 GyRBE

58 yo female with Grade 2/3 retroperitoneal leiomyosarcoma- Pre-op IMPT

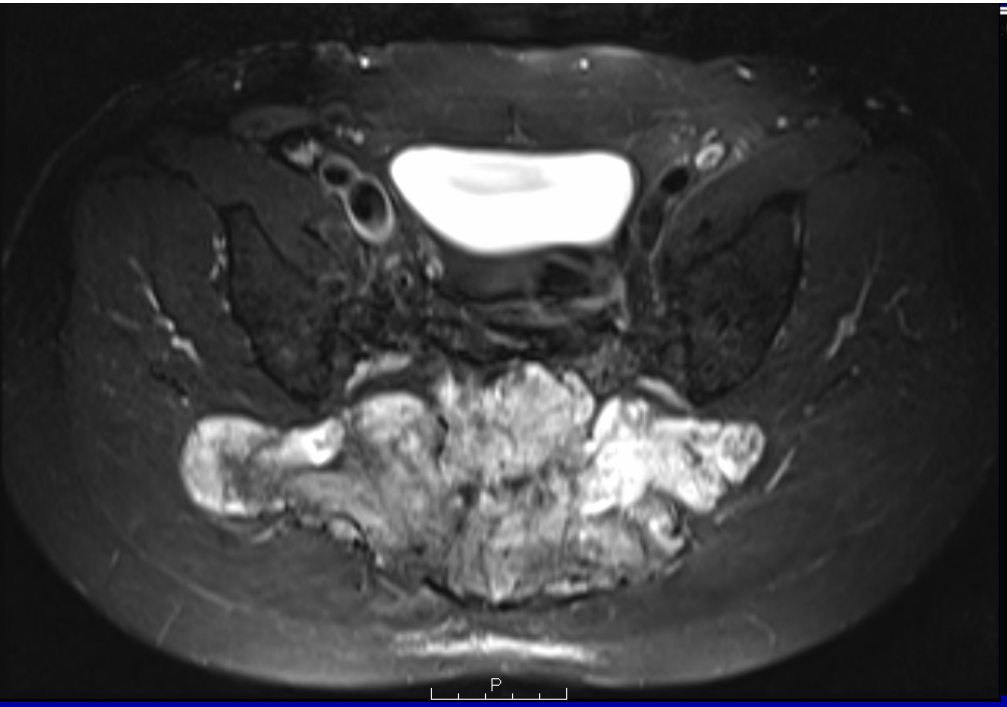
CTV 1: 50.4 Gy and CTV2 60.2 Gy/28 fx with IMPT

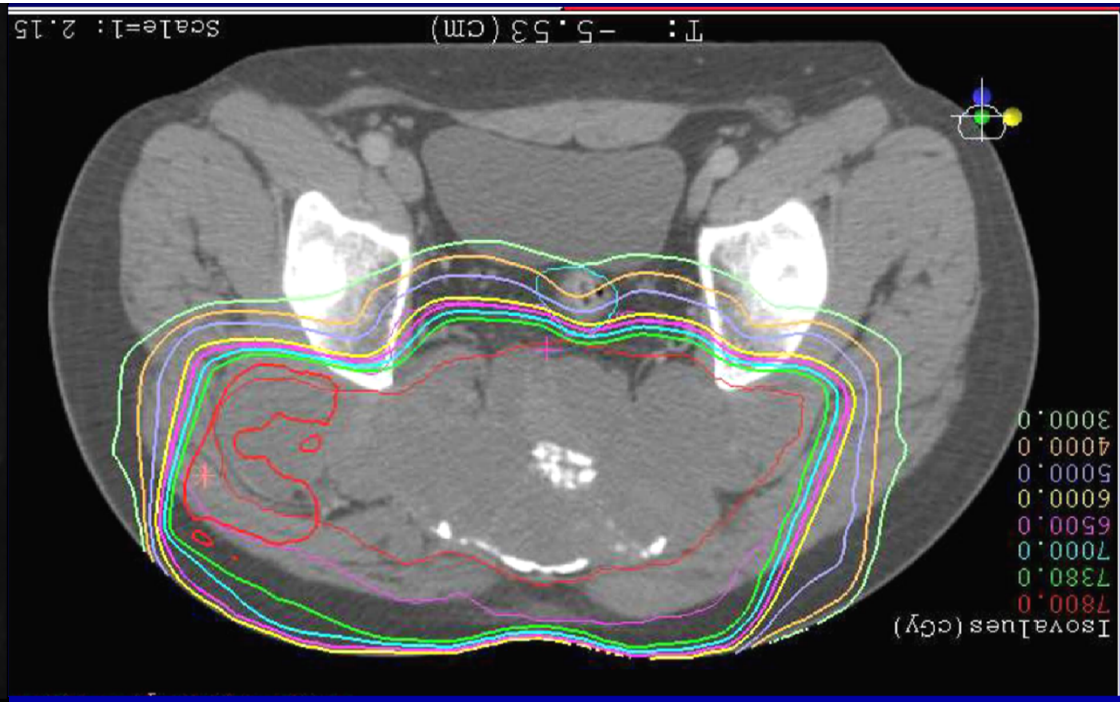
Proton Clinical Trials: Sarcoma

- Phase II Study of High Dose IMPT +/- Surgical Resection of Sarcomas of the Spine, Sacrum, and Base of Skull (T. DeLaney, MD)*
  - Beam scanning; with MD Anderson

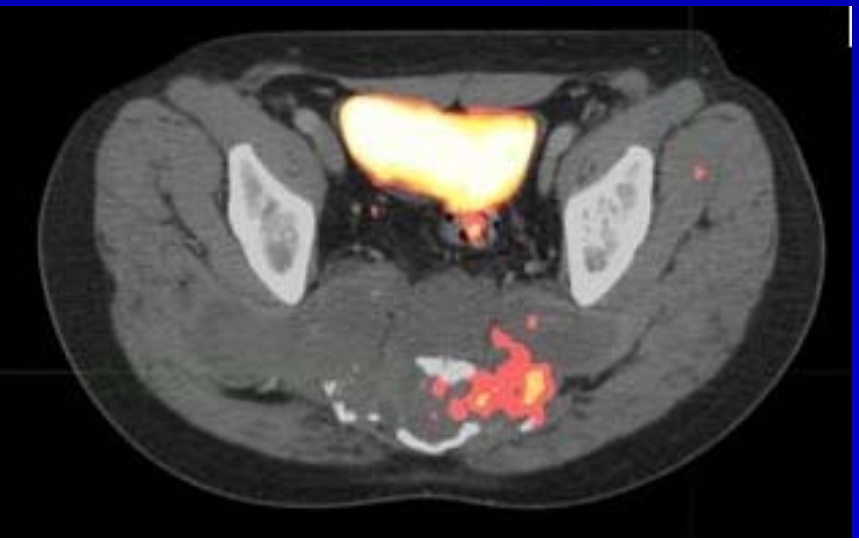
- Phase I/II Study of Pre-Op Dose-Painted IMPT/IMRT for Retroperitoneal Sarcoma (T. DeLaney, MD)*
  - IMPT beam scanning: with University of Pennsylvania
  - IMRT: DFCI, Rush, Roswell Park, Mayo Clinic

*Multi-center study





Hypoxia: F-18 Misonidazole PET/CT



Sacral Chordoma 77.4 Gy RBE + Nilotinib (IMRT 30.6 Gy, Protons 46.8 GyRBE) Locally controlled at 2.5 years with slight increase in R toe numbness at 2.5 years

←--Cheney et al, Int J Radiat Oncol Biol Phys, 2014

Educational Session :
Sarcoma- Bone and soft tissue
19 May, 2015

Carbon Ion Radiotherapy of Bone & Soft Tissue Sarcomas

Tadashi KAMADA, MD, PhD

Research Center for Charged Particle Therapy

National Institute of Radiological Sciences

Chiba, JAPAN

Clinical Trials for Unresectable Bone and Soft Tissue Sarcomas

Phase I/II Dose Escalation Study
June 1996 – Feb 2000 n=59

J Clin oncol(20) 4466-4471.2002

- Efficacy depended on total irradiated dose.(52.8GyE/-73.6GyE/16Fr)
- G3 acute skin reactions were observed with the total dose of 73.6GyE/16Fr

Phase II Fixed Dose Study
April 2000 – Aug 2013 n=584

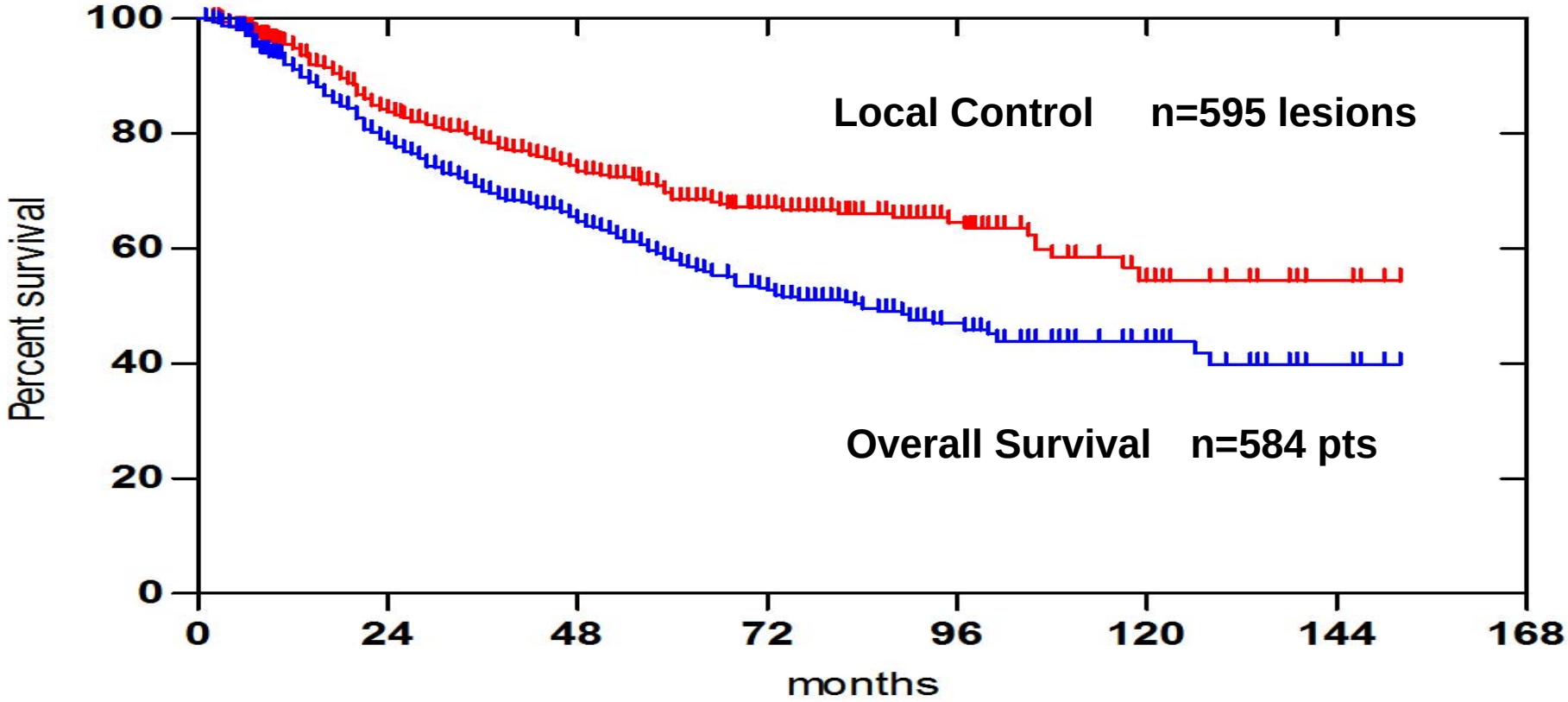
- 70.4GyE/16Fr was basic workable dose.
- Better beam delivery to avoid severe skin reaction

J Clin oncol(26)562s.2008

Palliative cases
April 2005-Aug 2013 n=336

Short course regimen of 1,2, and 3 weeks

Bone and Soft Tissue Sarcomas
Result of CIRT: Phase II Study n=584 patients



	2-year(%)	5-year (%)
Local Control	84	69
Overall Survival	78	58

Bone and Soft Tissue Sarcomas
Late Morbidities after CIRT: Phase II Study

		Grade					
	Number	0	1	2	3	4	5
Skin/soft tissue	596	6	542	39	7	2	0
GI tract	494	488	2	0	0	3	0
Spinal cord	54	49	1	2	2	0	0
Edema	24	17	5	2	0	0	0

Impairment ADL (peripheral nerve dysfunction) : 27
Femoral neck fracture : 4 (all ilioacetabular sarcoma)

Late Soft Tissue/Skin Reaction in B & STSs

	No of Pts	Gr3-4 (%)
2000~2001	25	7 (28)
2002~2005 (Modified group)	151	2

Risk factor

Total Dose : 73.6
Two direction
Skin margin

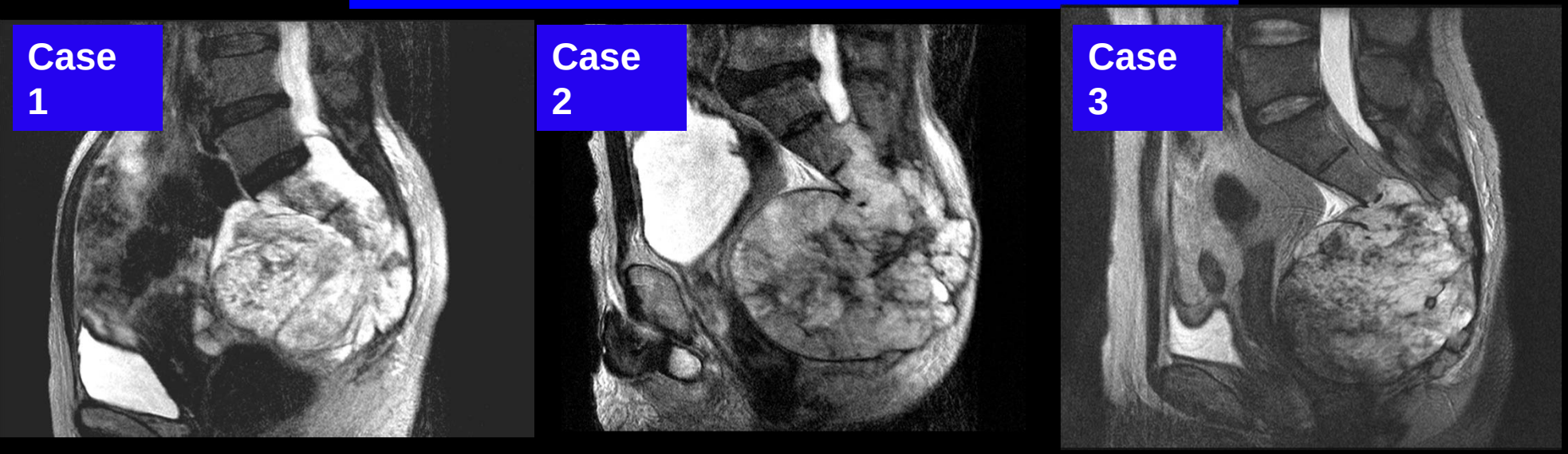
→

Modifications

70.4 or less
Three direction or more
Reduced skin margin

Yanagi et al.Radiotherapy and Oncology. 2010;95:60-65

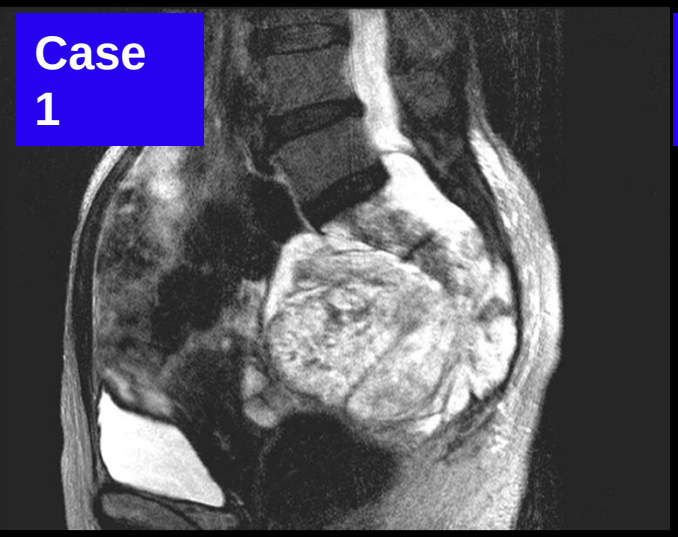
Chordoma (of the sacrum)

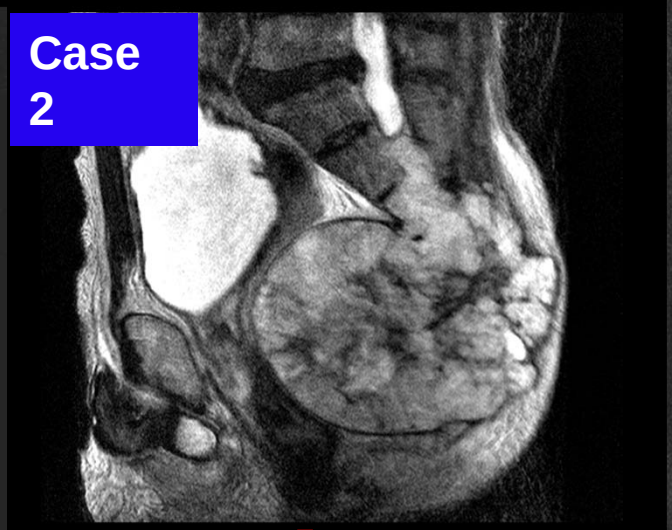


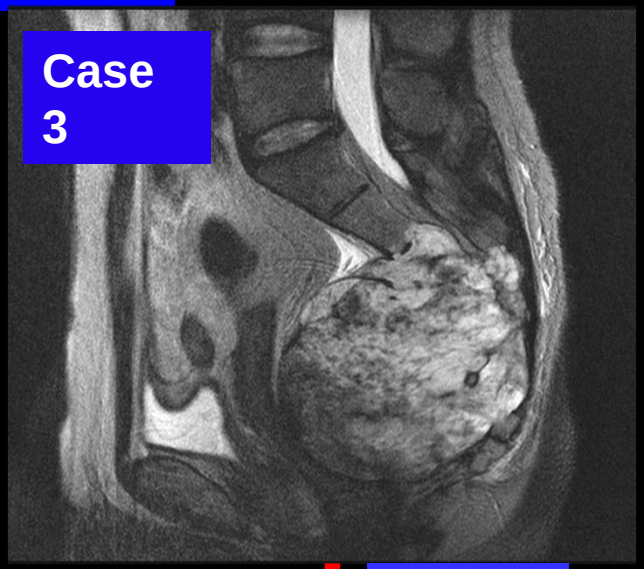
- 3% of all primary bone sarcoma (50% from sacrum bone)
- Radio-chemo-resistant, and surgery is treatment of choice
- However, surgery is extremely difficult in many cases
- Slow growing, sometimes presenting huge tumor size

Imai R, Kamada T, Tsuji H, et al. Carbon Ion Radiotherapy for Unresectable Sacral Chordomas. Clinical Cancer Research. 2004;10:5741-5746.

Chordoma of the sacrum



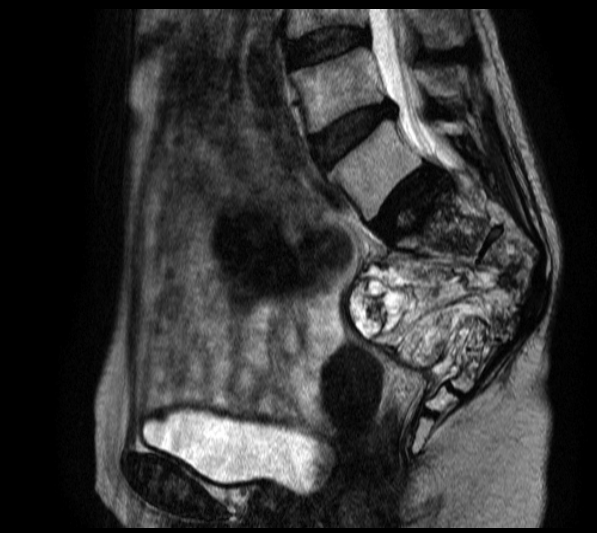


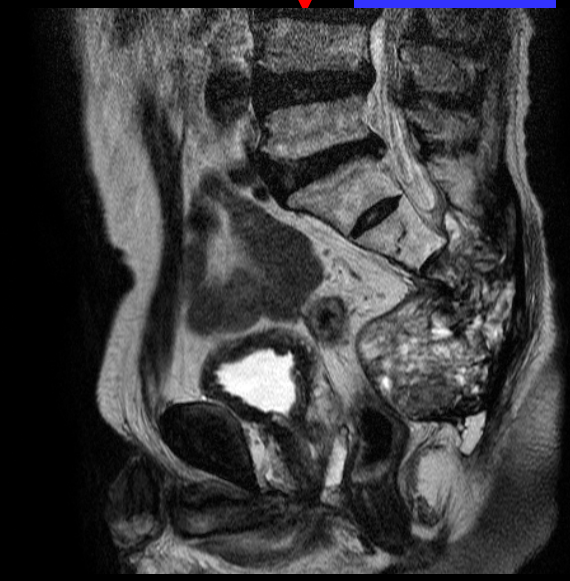


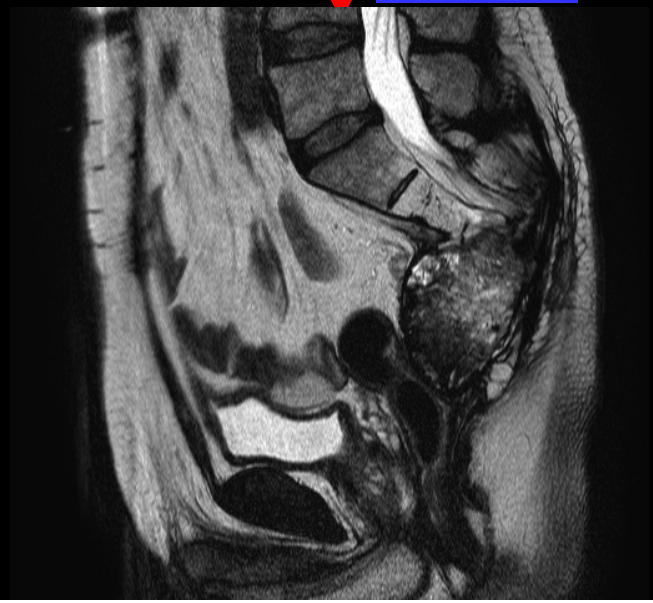
6 years

5 years

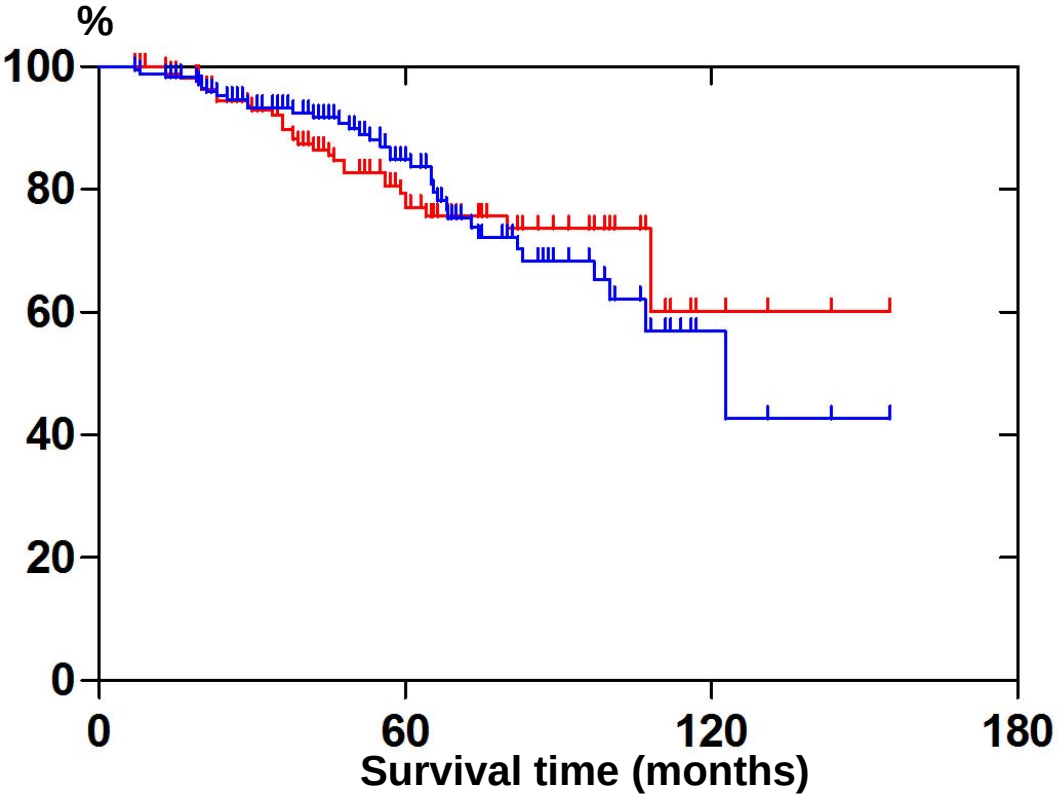
6 years







Chordoma of the Mobile Spine and Sacrum
1996.6-2011.2 n=183 pts (phase I/II and II study)



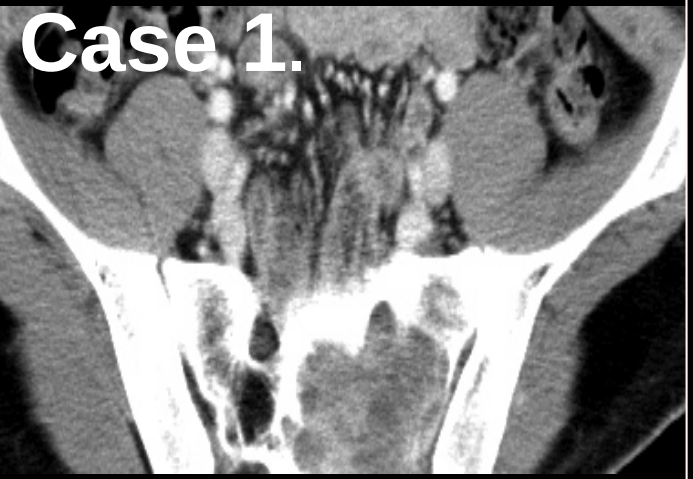
Median Follow-up : 68 months (7-155)
Median Age : 66 yo (26-87)
Median CTV : 330 cm^3
(Sacral chordoma : Median 636 cm^3)
Prescribed dose 64~73.4GyE/16Fx
Mobile spine :64GyE
Sacrum :67.2GyE
Patients remain ambulatory : 97%
Sciatic nerve dysfunction: 15pts

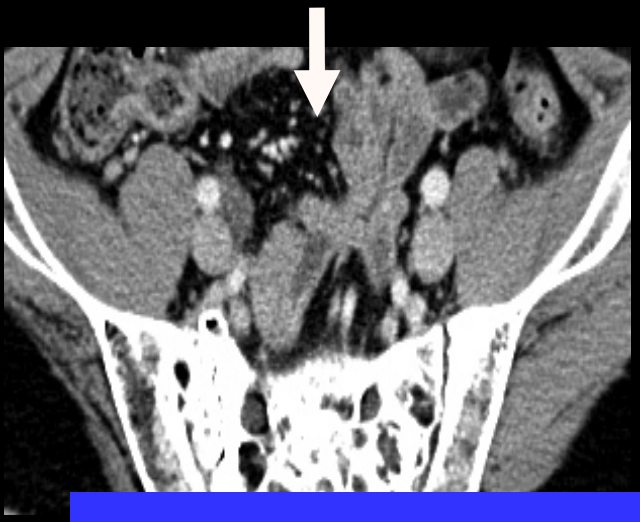
	5-year(%)
Local Control	77
Overall Survival	85

Osteosarcoma

Matsunobu A, Imai R, Kamada T, et al.
Impact of Carbon Ion Radiotherapy for Unresectable Osteosarcoma of the Trunk.
Cancer 2012;118:4555-4563.

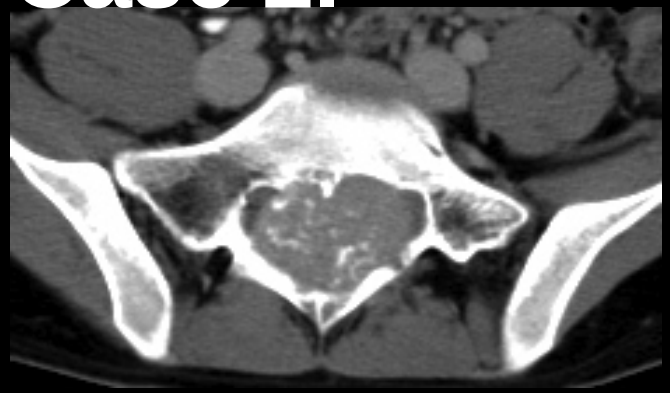
Case 1.

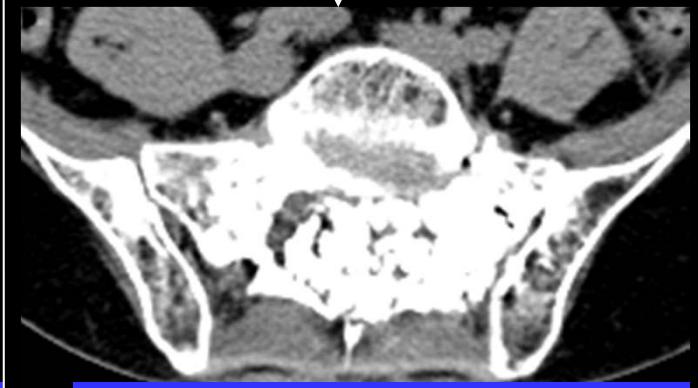




At 13 years

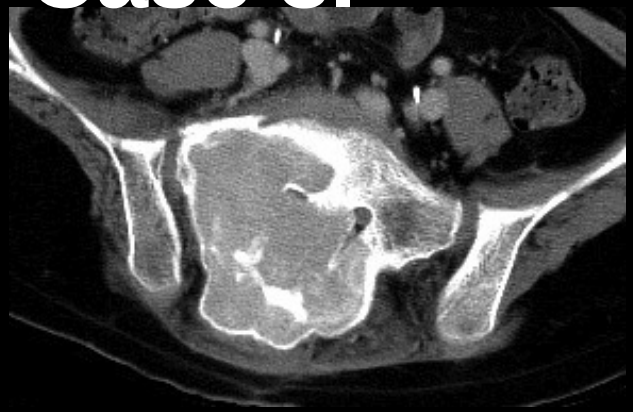
Case 2.

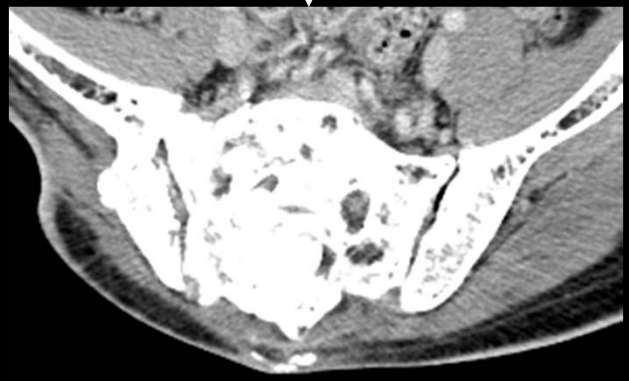




At 9 years

Case 3.

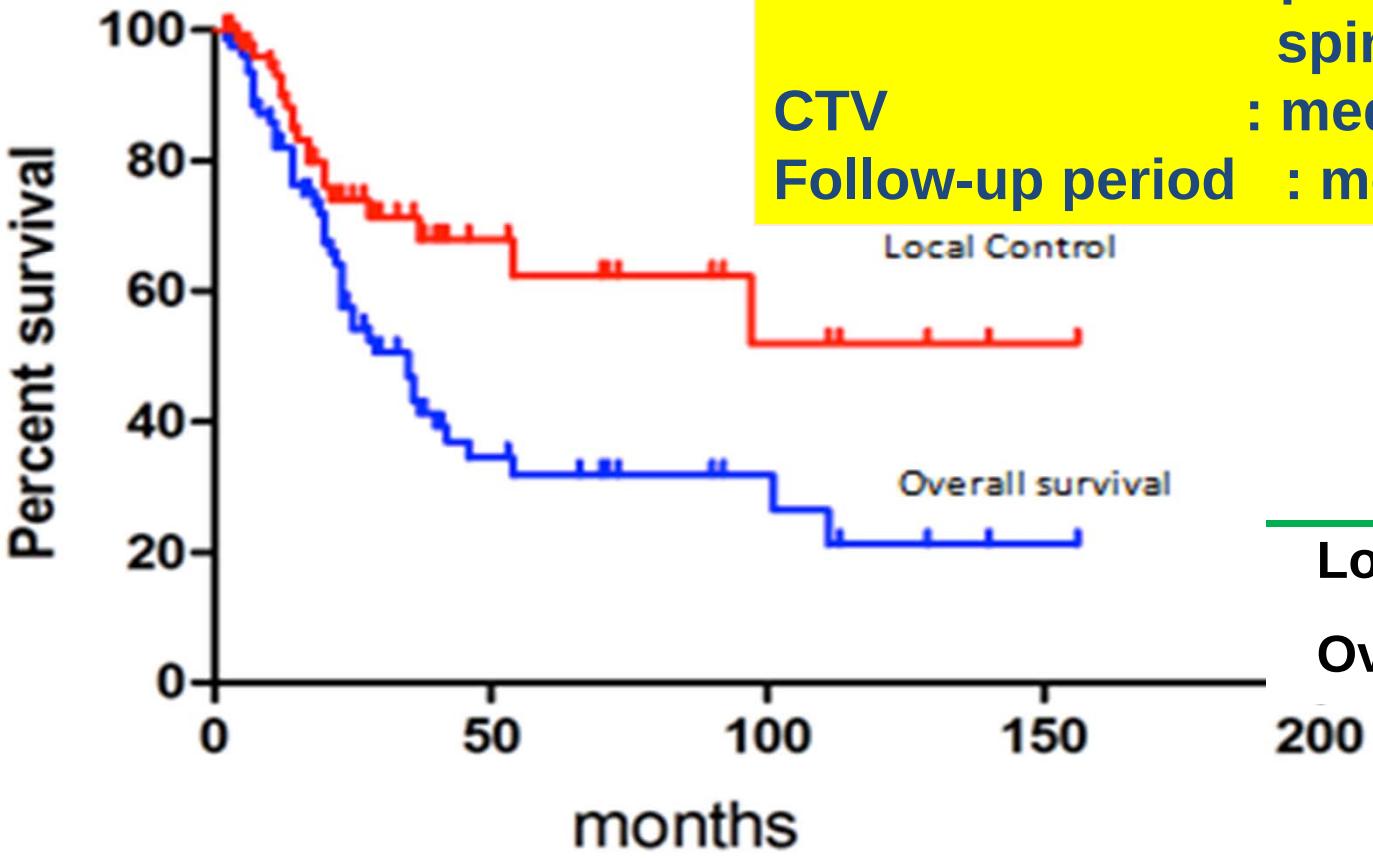




At 7 years

Osteosarcoma of the Trunk
1996.6-2009.6 n=78 pts

Age	:Median 42 yo (11-83)
Tumor site	: pelvis 61, spine/paraspine 15, others 2
CTV	: median 510cc (60-2290)
Follow-up period	: median 70 months

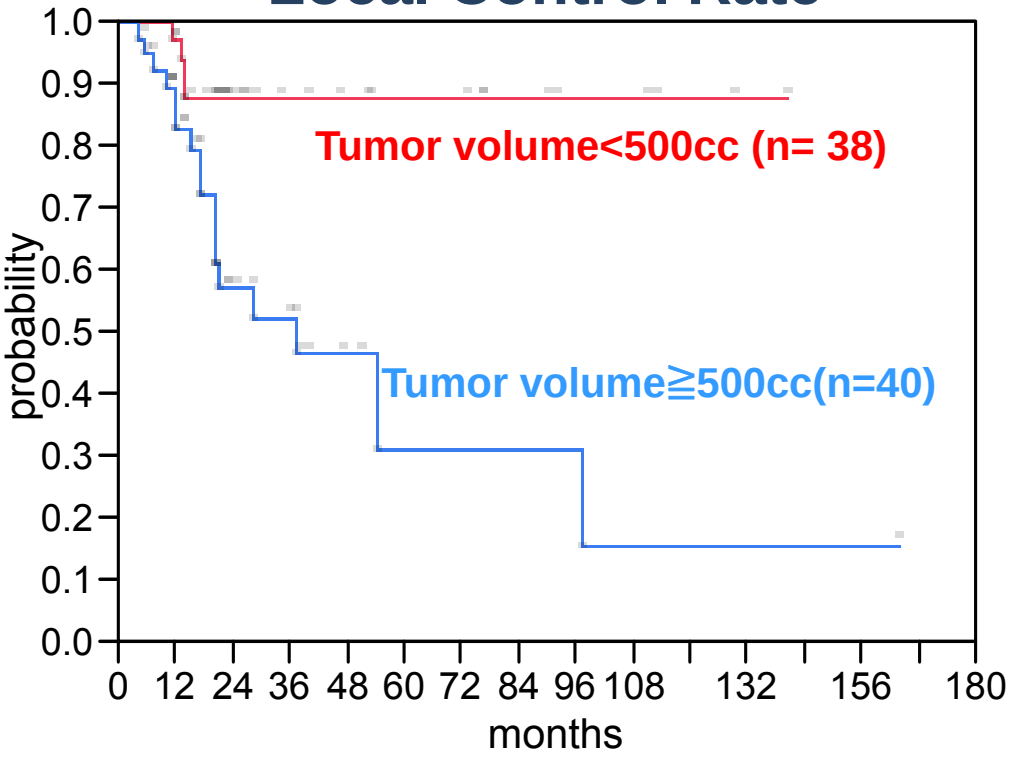


	2y	5y
Local Control	73%	61%
Overall Survival	57%	32%

Osteosarcoma of the Trunk
Result By Tumor Volume

A smaller tumor volume provides a better result.

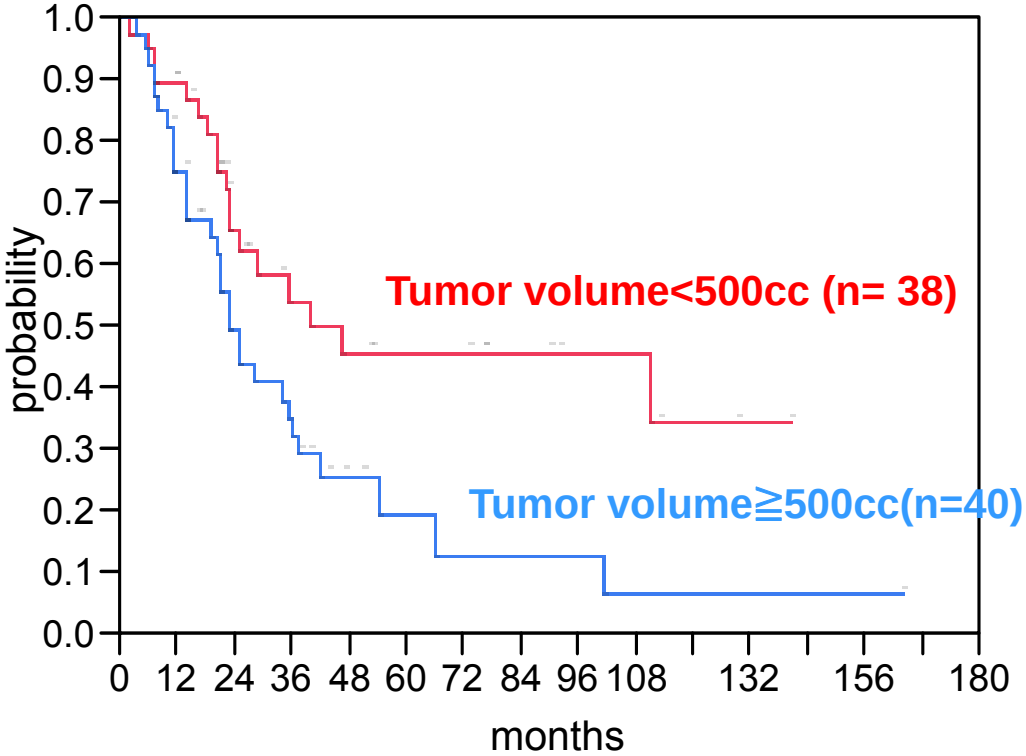
Local Control Rate



	2y	5y
＜500cc	87%	87%
≧ 500cc	57%	31%

Logrank p=0.0006

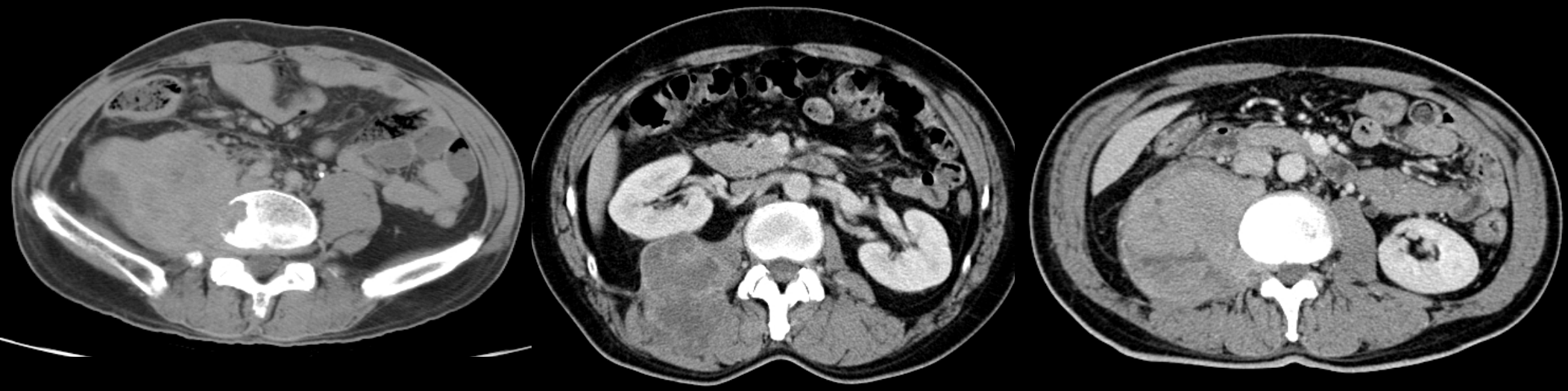
Overall Survival Rate



	2y	5y
＜ 500cc	65%	46%
≧ 500cc	50%	19%

Logrank p=0.015

Retroperitoneal sarcomas

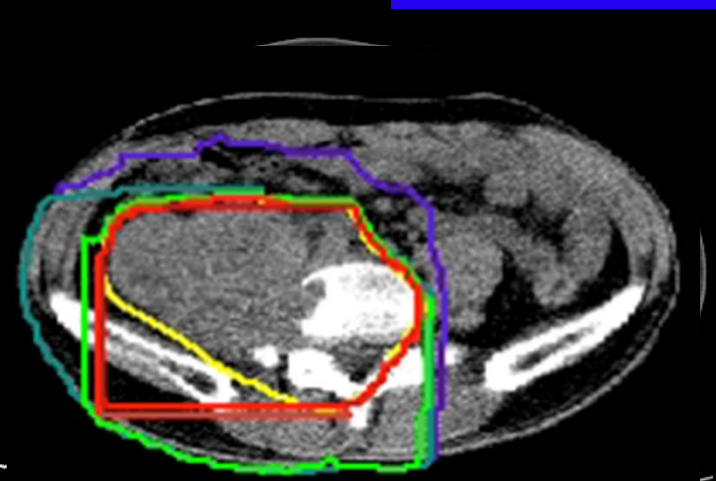


Rhabdomyosarcoma	MFH	Ewing tumor

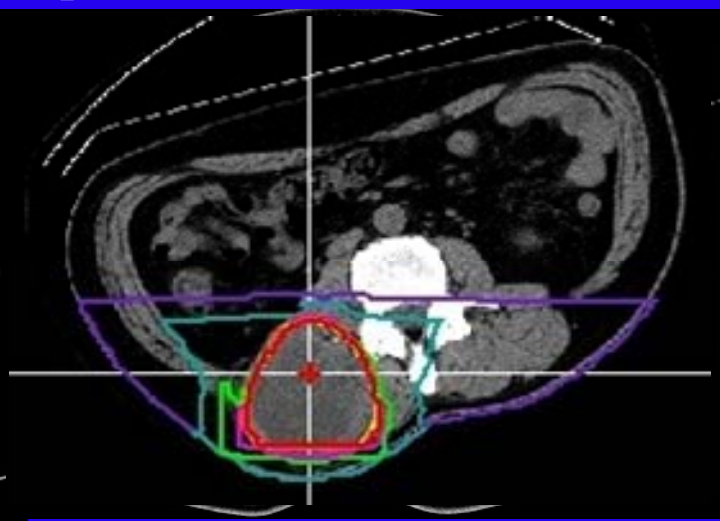
- 15 % of all STS (STS:1% of all cancer in US)
- More than 50 histological diagnoses
- Difficulty in surgery due to its location and size
- Poor outcomes

Serizawa I, Kagei K, Kamada T, et al. Carbon Ion Radiotherapy for Unresectable Retroperitoneal Sarcomas. Int J Radiat Oncol Biol Phys. 2009;75(4):1105-10.

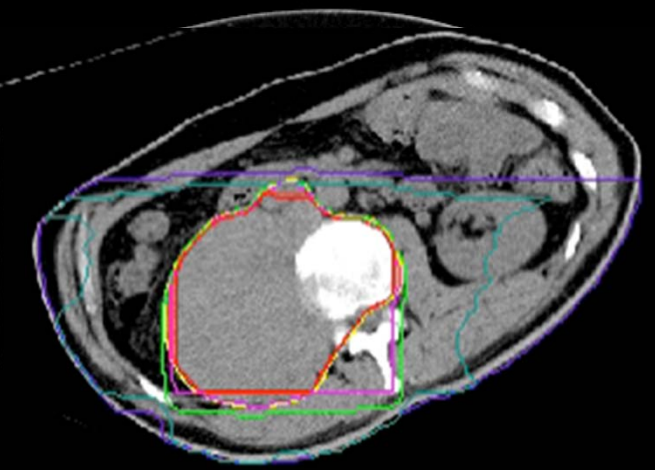
Retroperitoneal sarcomas



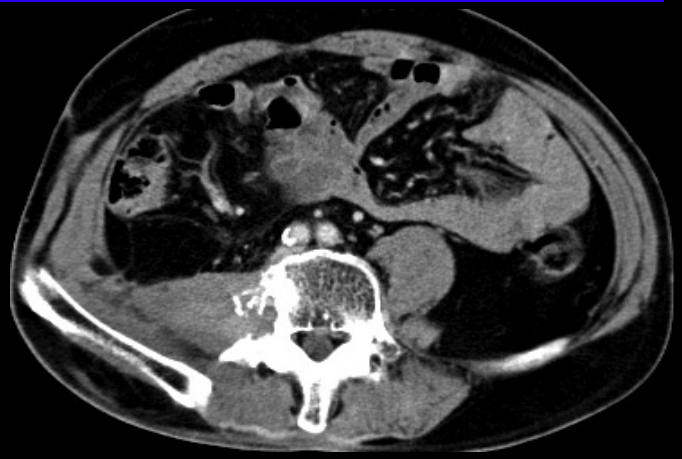
Rhabdomyosarcoma



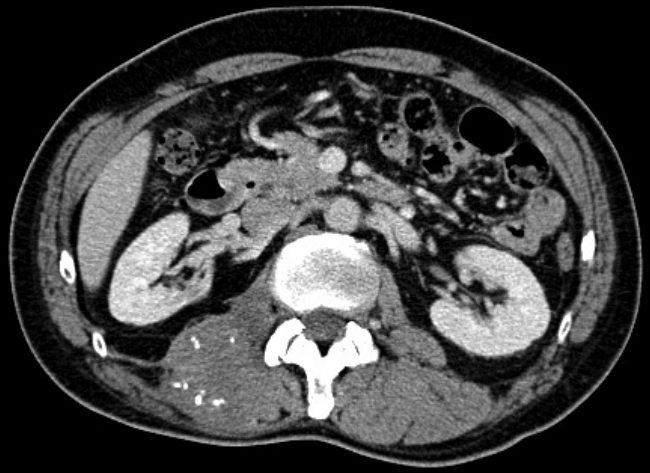
Malignant fibrous Histiocytoma



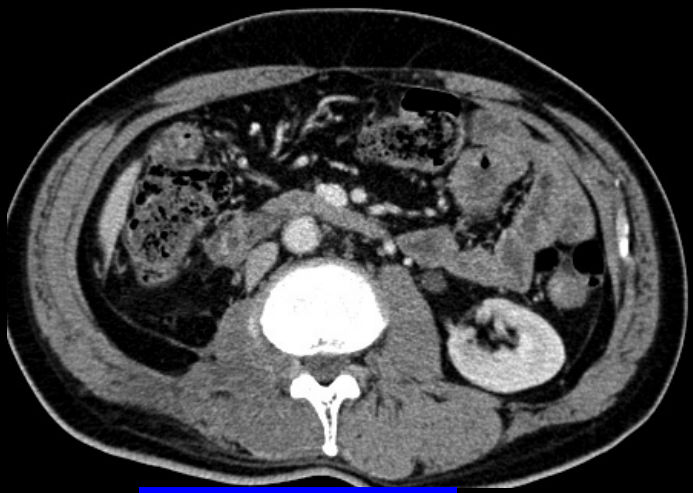
Ewing tumor



5 years after

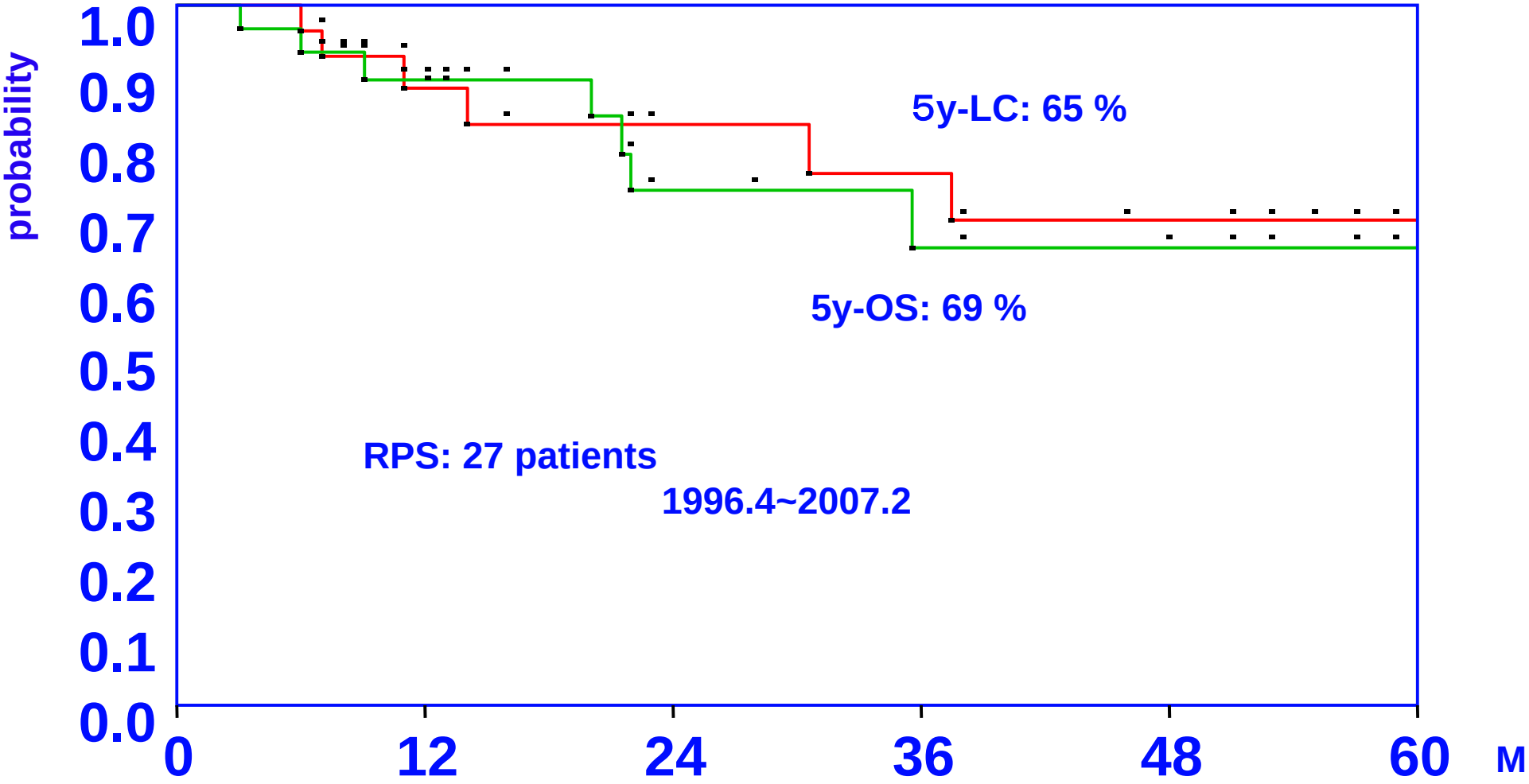


10 years after



2 years after

RPS: Overall Survival and Local Control



Serizawa I, Kagei K, Kamada T, et al. Carbon Ion Radiotherapy for Unresectable Retroperitoneal Sarcomas. Int J Radiat Oncol Biol Phys. 2009;75(4):1105-10.

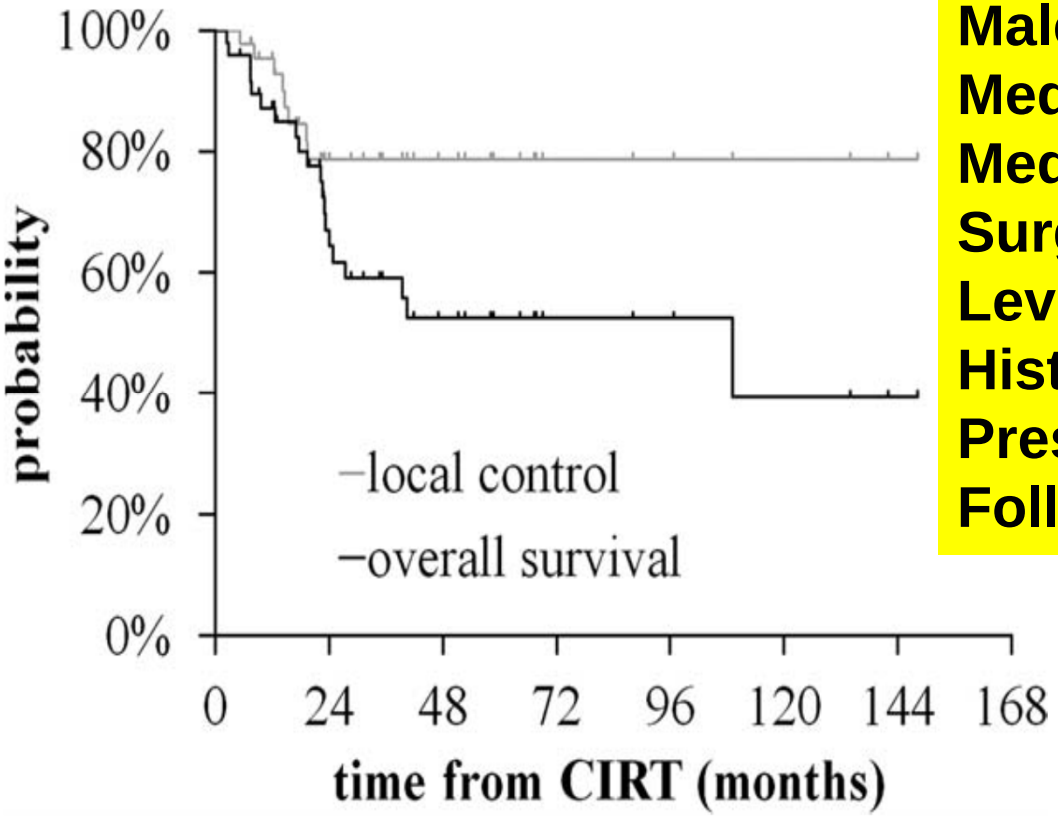
RPS : Reported Treatment Results

Reference	Years Studied	No. of Patients	Complete resection (%)	5-yr OS(%)	5-yr LC(%)
Catton	1975-1988	104	52	36	28
Lewis	1982-1997	231	67	54[a]	29[a]
Van Dalen	1989-1994	114	-	ND	32[b]
Stoeckle	1980-1994	94	-	46	43[c]
Gilbeau	1990-2000	45	96	60	40
Hassan	1983-1995	63	-	51[d]	44[d]
Gronchi	1982-2001	167	88	53	54[e]
Krepien	1991-2004	67	82	58	40
NIRS - C ion*	1996-2007	27	-	69	65

- Abbreviations: OS = overall survival; LC = local control; ND = no data available
- [a] Outcomes for 231 patients who underwent resection; the survival rate is cause specific.
- [b] Outcomes for 114 patients who underwent complete resection; the local control rate is crude percentage.
- [c] Outcomes for 94 patients who underwent complete resection.
- [d] Outcomes for 63 patients who underwent complete resection.
- [e] The control rate is the 5-year crude cumulative local recurrence rate.

*IJROBP 2009

Primary Spinal Sarcomas
1996.6-2012.2 n=48 pts (phase I/II and II study)



Male/Female : 24/24
Median Age : 54 yo (12-82)
Median CTV : 190cm^3 (25~1295)
Surgery Y/N : 13/35
Level C/T/L : 10/22/16
Histology Os/Cs/Cdm/Oths :13/13/9/7/6
Prescribed dose : 70.4GyE(52.8~70.4)
Follow-up period : 25 mths (2-162)

	5-year(%)
Local Control	79
Overall Survival	52

Matsumoto K, Imai R, Kamada T, et al.
Impact of Carbon Ion Radiotherapy for Primary Spinal Sarcoma. Cancer 2013;119:3496-3503

Local Control Rate According to the Tumor Size in Primary Spinal Sarcomas Receiving Carbon Therapy

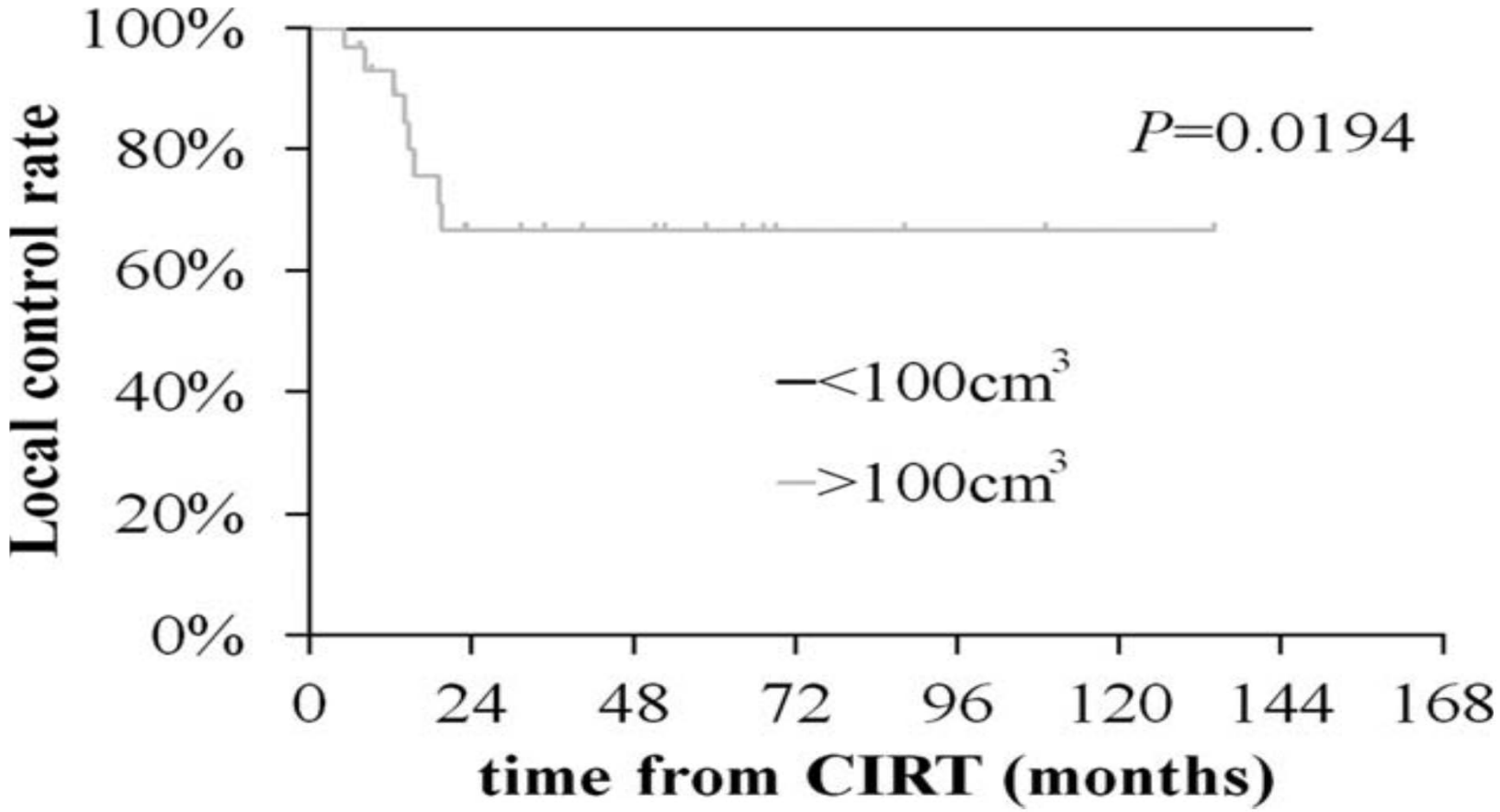


Figure 2. Local control rates are illustrated according to tumor size. The 5-year local control rates were 100% in the group with tumors $\leq$100 cm^3 and 67% in the group with tumors >100 cm^3.

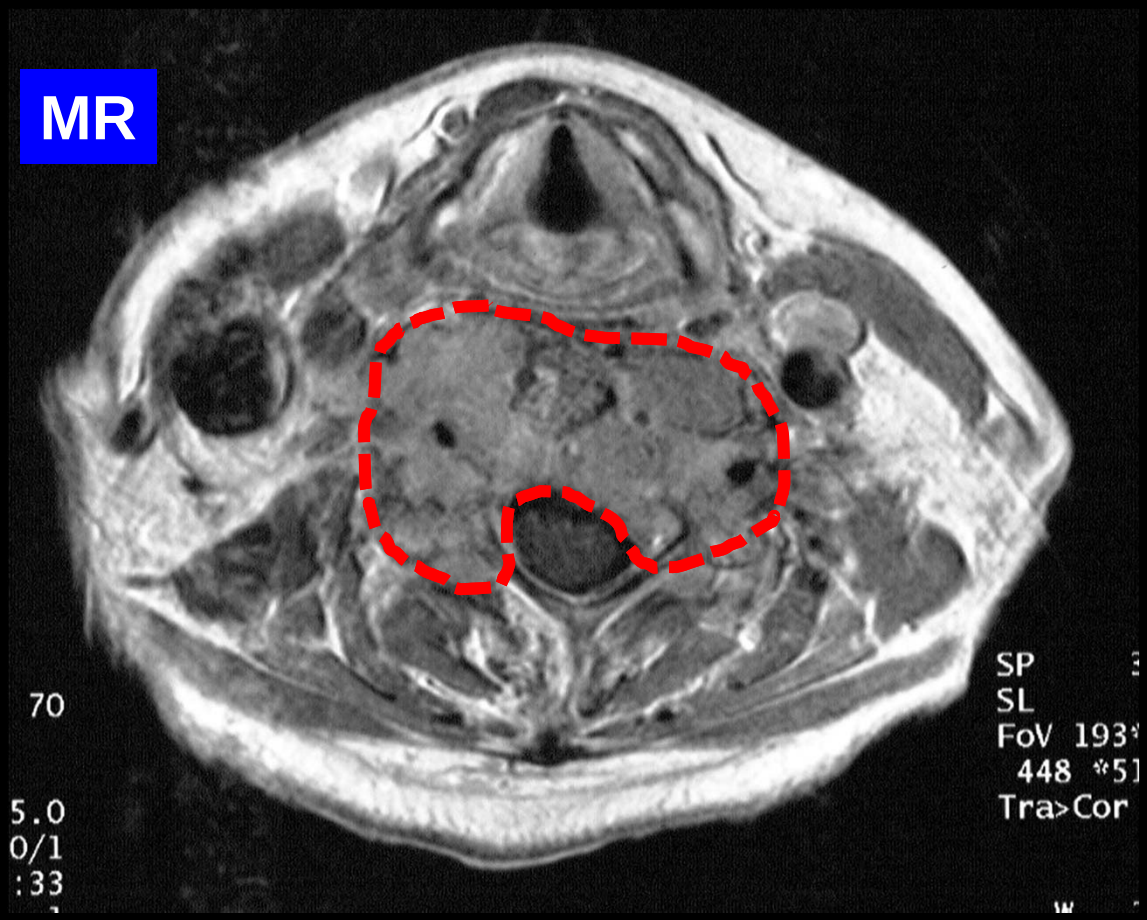
Particle Therapy for Primary Spinal Sarcomas

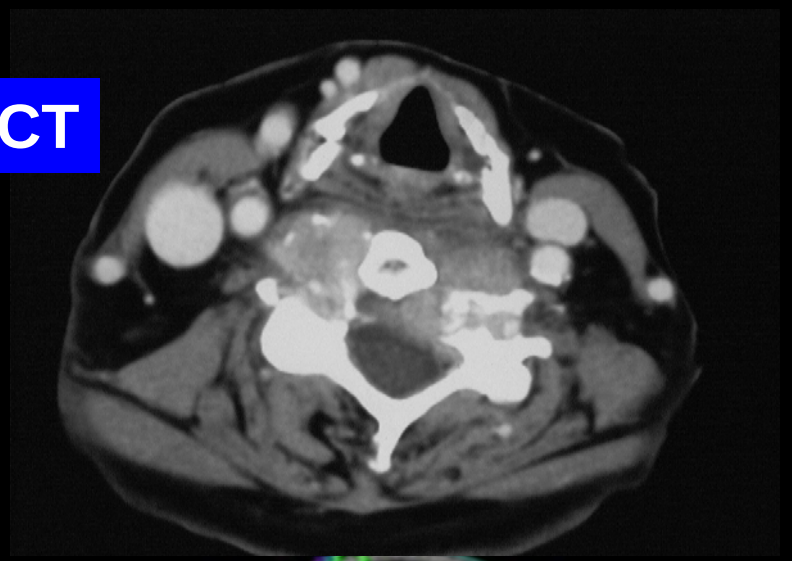
Facility	No. of Patients	Treatment	5 y Local Control(%)	5 y Overall Survival(%)
MGH1)	50	Surgery +Proton	78	87
LBL2)	36	He, Ne	73	61(3y)
NIRS3)	48	Carbon*	79	52

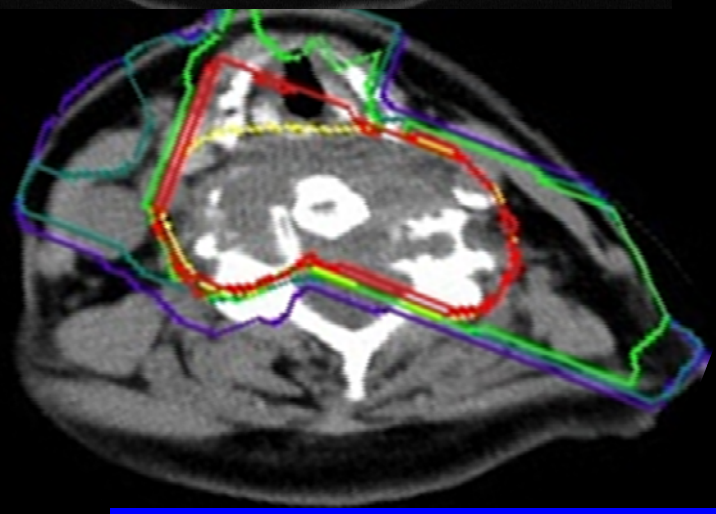
*unresectable or post op recurrence

1) Int J Radiat Oncol Biol Phys. 2009;74:732-739.
2) Int J Radiat Oncol Biol Phys. 1991;22:295-303.
3) Cancer. 2013;119:3496-503.

Neck Bone Cancer(osteosarcoma) 82yo F







Neck bone was destructed by cancer, un-resectable due to location and age.

64GyE/4weeks
Using patch tech

Osteosarcoma of the 5th Cervical Spine
Mucosal Reaction after C-ion
(64GyE/16Fx/4wks)

Max reaction

2 weeks later

Osteosarcoma of the 5th Cervical Spine
Skin Reaction after C-ion
(64GyE/16Fx/4wks) after 60 months

Neck Bone Cancer(osteosarcoma) 82yo F

Before therapy

CT images after 8 years

51M　osteosarcoma of rt. rib

Before CIRT

70.4GyE/16Fr

8 years after NED

Red line　95%dose
Green line 50%dose

Continue his job(management of construction company)

Osteoblastoma L4 14 F

June 2008, just after her third operation

Osteoblastoma L4 14 F

June 2008, just after her third operation

Osteoblastoma L4 14 F

64GyE/16fractions/4 weeks, four box fields

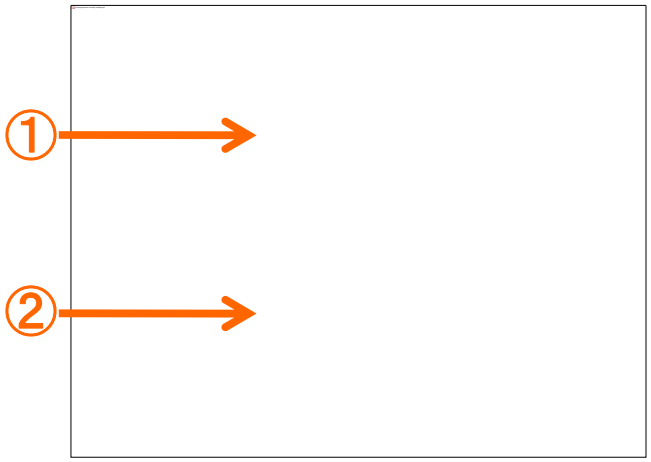
Osteoblastoma L4 14 F

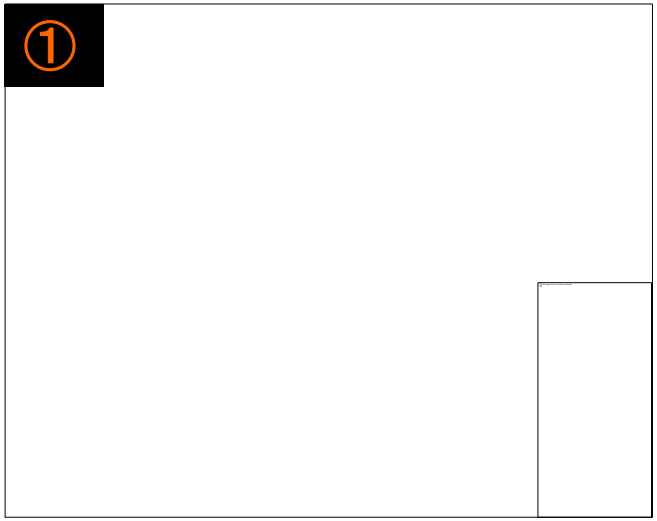
Before treatment
(ALP 3731 IU/L)

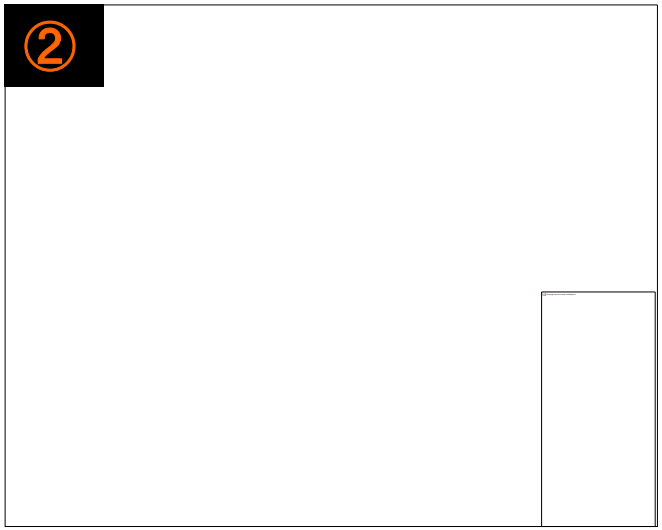
6 years after 64GyE/16fx
(ALP 162 IU/L)
Alive NED at age 20, working as a saleswoman

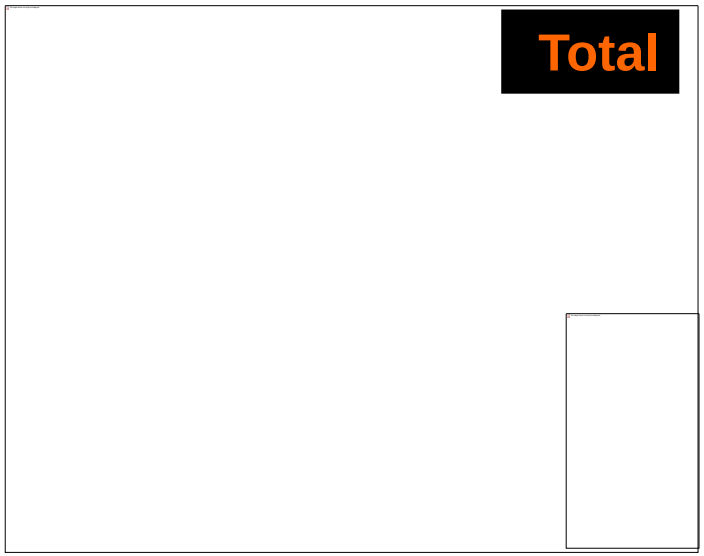
Patch-technique for Large Field by Scanning

Patch-field by Scanning







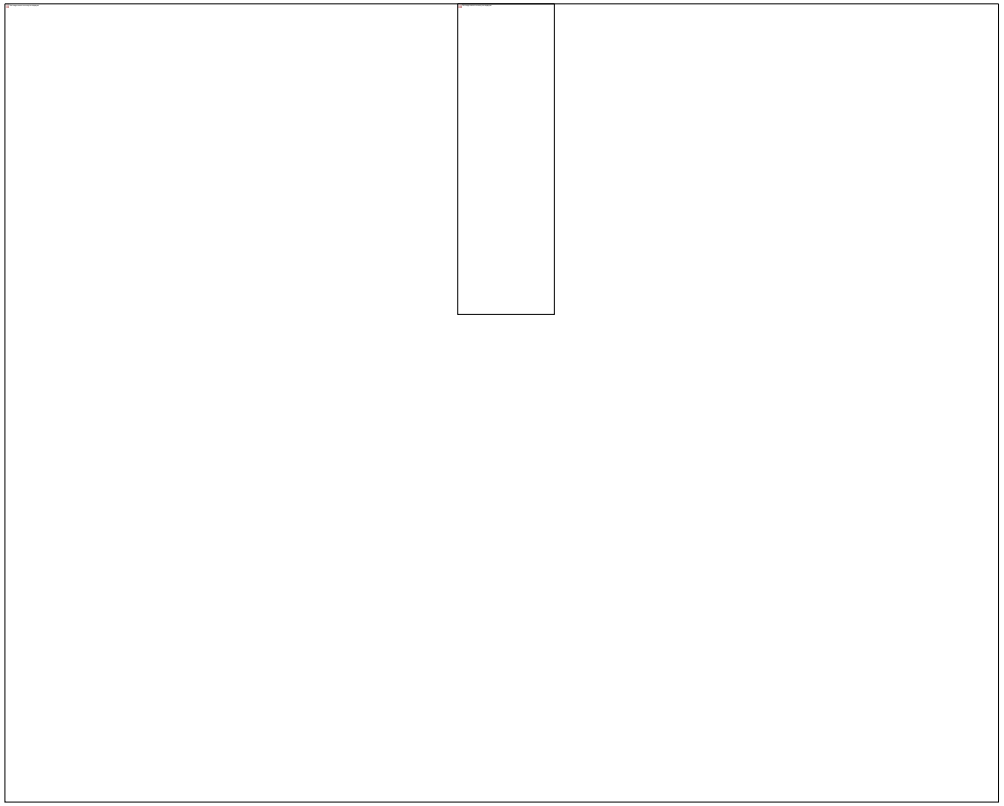


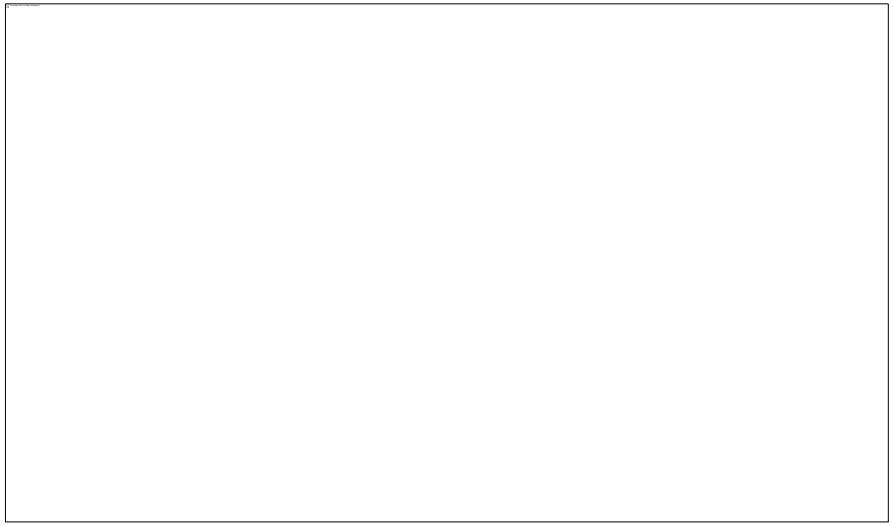
- **Patch line**
  → Unnecessary to define

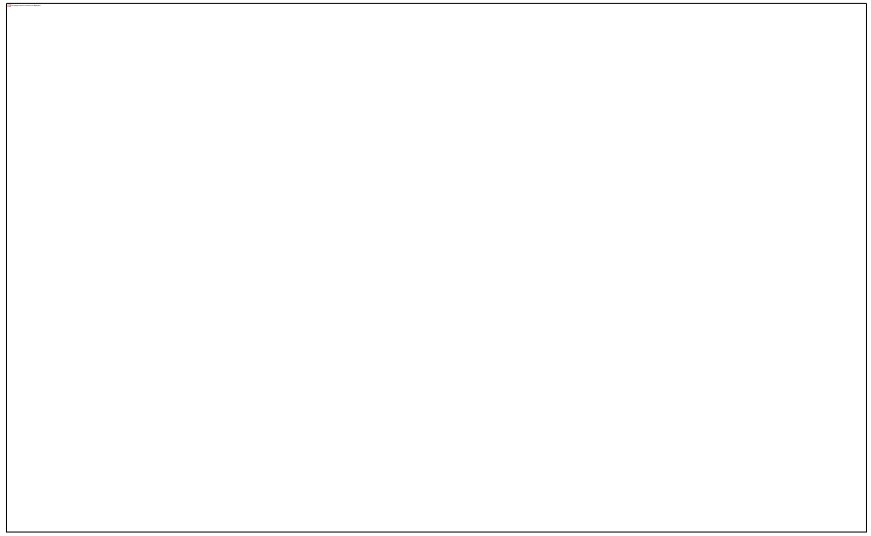
- **Calculation Time**
  → Comparable to conventional 2-fields plan

“Easy” & “Safe”

UPS 85yo M (27cmx18cmx15cm)







Dose distribution wth patch scan

Before (T1Gd)

After 6 months (T1Gd))

Summary 1) Bone & Soft Tissue Sarcoma Treated with CIRT

- Carbon therapy was administered to the more than 900 patients with inoperable sarcoma during the period from 1996 until 2014.
- Irradiation of a total dose of 64~73.6GyE in 16 fractions over 4 weeks resulted in a local control rate at around 70% with acceptable morbidity.

Summary 2) Bone & Soft Tissue Sarcoma Treated with CIRT

- **It is imperative to continue with the long-term follow-up observation and carry out further analyses to assess local control, toxicities, survival and QOL.**
- **Systematic analyses will be essential to determine the optimum dose, fractionation and irradiation field setting of CIRT in accordance with the patients histological type and tumor location.**

“Conclusion”

Carbon therapy is a safe and effective local treatment for inoperable bone and soft tissue sarcomas with acceptable morbidity