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PHASE II STUDY OF HIGH DOSE PHOTON/PROTON RADIOTHERAPY IN THE MANAGEMENT OF SPINE SARCOMAS

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Abstract

Purpose—Radiotherapy (XRT) for spine sarcomas is constrained by spinal cord, nerve, and viscera tolerance. Negative surgical margins are uncommon; hence, doses of ≥ 66 Gy are recommended. A Phase II clinical trial evaluated high dose photon/proton XRT for spine sarcomas.

Materials/Methods—Eligible patients had non-metastatic, thoracic, lumbar, and/or sacral spine/paraspinal sarcomas. Treatment included pre- and/or post-op photon/proton XRT +/- radical resection; patients with osteosarcoma and Ewing's sarcoma received chemotherapy. Shrinking fields delivered 50.4 cobalt Gray equivalent (GyRBE) to subclinical disease, 70.2 GyRBE to microscopic disease in the tumor bed, and 77.4 GyRBE to gross disease at 1.8 GyRBE q.d. Doses were reduced for radiosensitive histologies, concurrent chemoradiation, or when diabetes or autoimmune disease present. Spinal cord dose was limited to 63/54 GyRBE to surface/center. Intra-operative boost doses of 7.5-10 Gy could be given by dural plaque.

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CONFLICT OF INTEREST NOTIFICATION Dr. DeLaney has received honoraria from IBA Proton Therapy for speaking at Industry Sponsored Symposia on Proton Beam Radiotherapy.

Results—50 patients (29 chordoma, 14 chondrosarcoma, 7 other) underwent gross total (n=25) or subtotal (n=12) resection or biopsy (n=13). With 48 month median follow-up, five-year actuarial local control, recurrence-free survival, and overall survival are: 78%, 63%, and 87% respectively. Two of 36 (5.6%) patients treated for primary versus 7/14 (50%) for recurrent tumor developed local recurrence, $p<0.001$. Five patients developed late radiation-associated complications; no myelopathy developed but three sacral neuropathies appeared following 77.12-77.4 GyRBE.

Conclusions—Local control with this treatment is high in patients radiated at the time of primary presentation. Spinal cord dose constraints appear to be safe. Sacral nerves receiving 77.12-77.4 GyRBE are at risk for late toxicity.

Keywords

Spine; sarcoma; chordoma; proton radiotherapy

INTRODUCTION

Tumors of the spine and paraspinal tissues present treatment challenges. Complete resection with negative resection margins is rarely possible. Management is complex because of the critical importance of the normal function of the spinal cord and (at some levels) nerve roots, the important weight bearing function of the spine and sacrum, and the frequent need for protracted rehabilitation/physical medicine intervention following aggressive surgery.

The limited radiation tolerance of the spinal cord and cauda equina can also present significant challenges for delivery of an effective dose to the defined target. The commonly employed spinal cord dose limits of 45-50 Gy given to the full cross section of the cord (1) are well below what is necessary to reliably control most sarcomas, which require substantially higher doses (2-5). Hence, innovative strategies are necessary to safely irradiate these tumors to curative doses.

Investigators report poor local control (LC) of spinal/sacral chordomas with radical surgery and conventional radiation at doses below 60 Gy, *viz*., 0-50% (6-8). All 21 chordoma patients recurred locally in a Washington University series (9). The time to failure was greater with combined surgery and radiation than surgery alone. Local failure(LF) rates ≥75% were reported by the Mayo Clinic (8) and the Memorial Hospital. (10) While LF predominates, distant metastasis constitutes a real but less frequent cause of failure.

LC of spine chondrosarcomas by surgery alone may also be quite low, particularly if treatment consists of curettage or local excision (11,12). Bergh et al. reported LF in 3 of 7 sacral chondrosarcomas and 5 of 12 mobile spine tumors (13); marginal or intralesional procedures were associated with higher LF rates. Talac et al. reported 3 LF in 9 spine chondrosarcomas; control was higher with en bloc resections (14).

The Massachusetts General Hospital(MGH) pioneered the clinical use of protons, initially in collaboration with the Harvard Cyclotron Laboratory(HCL) and since 2001 at a dedicated hospital-based Francis H. Burr Proton Therapy Center (FHBPTC). Because the biological effectiveness of protons is the near equivalent of high energy x-rays, *viz* the RBE is 1.1, the interest in protons is based exclusively on the physical properties that provide superior dose distributions to deliver less dose to uninvolved normal tissue for any specified dose to the target (15). Details of the planning process and various treatment techniques have been published previously (15-18).

A pilot study of patients with axial skeleton tumors treated with combined high dose proton/photon radiation from MGH demonstrated promising rates of LC (18). For chordomas and

chondrosarcomas, LC was achieved in 9/14 (64%) and 6/6 patients respectively with a mean target dose of 73.9 GyRBE. A trend for improved LC was noted for primary vs. recurrent tumors, target doses > 77 GyRBE, and gross total resection.

The current, prospective Phase II study was built upon the results of the pilot study. Aggressive surgery was recommended and standardized radiation doses according to histology and extent of residual disease were specified in the protocol. Eligibility was extended to include thoracic and upper lumbar lesions that could not be included in the prior protocol because of technical limitations of the HCL, as well as paraspinal soft tissue sarcomas.

MATERIALS/METHODS

This prospective, IRB-approved Phase II clinical trial was open to patients ≥ 16 years of age with spine and paraspinal sarcomas; for spine lesions, extra-ossseous tumor extension was required. Pathologic review was required by pathologists with subspecialty sarcoma expertise. Tumors could be primary or locally recurrent after prior surgery. Patients with incompletely resected primary tumors were eligible; they were considered for additional surgery at our institution if the surgeons judged that complete resection was possible with acceptable morbidity. Patients with lesions not thought to be resectable with acceptable morbidity or patients who declined aggressive surgical procedures were also accepted for radiation alone. Selected patients with high-grade tumors also received chemotherapy; Adriamycin was not given concurrent with radiation. Patients were ineligible if the affected spinal level had received prior radiation or if metastases were present. Karnofsky Performance Status had to be ≥ 70, excluding loss of function secondary to the local tumor growth.

Study workup included history and physical examination with documentation of tumorrelated neurologic including bowel, bladder, and erectile dysfunction; laboratory tests including complete blood counts, electrolytes, blood urea nitrogen, serum creatinine, liver function tests, and lactate dehydrogenase; and imaging with spine CT and MRI (with gadolinium) scans, and chest imaging.

Surgery

The intent of radical surgery was removal of all gross tumor and, if feasible, negative margins. For patients with neurologic compromise, at least a posterior decompression was to be performed before the start of radiation treatments. If possible, the patients were given 19.8 - 50.4 Gy prior to definitive resection. Maximal resection was followed by spine reconstruction with allografts or cages where appropriate, minimizing the use of metallic rods(19). If metallic hardware was required, titanium constructs were used. Cross-links between rods were to be placed at levels above and/or below the affected spine level(s). Post-operative radiation commenced when the wound was sufficiently healed. Patients who underwent biopsy, rather than definitive resection, were patients declining radical surgery, patients with high (S1-S2) sacral tumors for whom resection entailed loss of limb or sexual function or bowel/bladder control, and patients with locally recurrent tumor after prior surgery where a gross total resection was not deemed technically possible without major morbidity.

Radiation

Patients were treated with a combination of photons and 3D conformal, passively scattered protons. Photon treatments were only 3D conformal for the first 12 patients treated from 12/97-1/02; thereafter, intensity modulated photons were also employed. Patients could receive up to 50.4 Gy with photons, although most patients received 19.8-30.6 Gy with photons. For photons, portal imaging was done at least weekly. For protons, kilovoltage orthogonal and

individual field port imaging was performed daily with any requisite table adjustments and re-imaging where necessary to verify accuracy prior to each fraction.

The RBE for proton radiation was set at 1.1. Thus, the dose unit, GyRBE, was the physical dose in Gy × 1.1.

Radiation Timing—As noted above, except where immediate posterior decompression was undertaken for relief of spinal cord or cauda compression, it was recommended to give some pre-operative irradiation to reduce the risk of tumor seeding at surgery. This allowed a substantially smaller CTV than exclusive post-op XRT, because the CTV would not include surgical scars, uninvolved vertebrae instrumented with stabilization hardware, drain sites, etc. For sacral tumors, the pre-op CTV received only 19.8 GyRBE at 1.8 GyRBE daily to reduce wound-healing delay at this site (where wound healing can be difficult following surgery alone). For thoracolumbar lesions, the pre-operative dose was 45-50.4 GyRBE at 1.8 GyRBE daily. For patients referred after biopsy or decompression at another institution, pre-operative irradiation was given prior to definitive surgery performed at our institution. For patients undergoing radical surgery at another institution, irradiation was post-operative.

Immobilization and Treatment Planning—Customized body immobilization was used for the planning CT scan and radiation treatment. From 1999-2001, supine position was used for photons and lateral decubitus position for protons because of the fixed horizontal proton beam used then. Thereafter, the patients were prone with their face on a Duncan Head Rest (Red-Care Products, Sunnyvale, CA, USA) mounted on a frame with arm handles +/- additional body casting for all treatments as 360°-rotational proton gantries were available and this position minimized the air gap between treatment snout and target to minimize beam penumbra. The single prone position facilitated integration of photon, proton, pre- and post-operative radiation doses.

Intravenous contrast was employed for the planning CT unless contrast allergy contravened. For patients with lesions above the level of the conus, patients underwent instillation of myelographic contrast for their radiation planning CT scan to determine the position of the spinal cord. In selected patients, the diagnostic MRI scan was fused with the planning CT scan to enhance target definition.

Target volumes and organs at risk (OAR) were contoured on the planning CT sections and radiation dose constraints were defined for the OAR. Radiation planning was performed using CMS XIO (CMS Inc., St. Louis, MO, USA) treatment planning system for 3D conformal photons and protons. Photon IMRT was incorporated into treatment beginning in February 2002, initially on Helios (Varian Medical Sytems Inc., Palo Alto, CA), later on Corvus (Bestnomos, Pittsburgh PA), and finally in 2004 using CMS XIO for both photon IMRT and protons.

Treatment plans were designed to deliver the prescription dose to the target volumes with consideration of normal tissue constraints (see below). A planning target volume (PTV) expansion of 5 mm was employed for the photon portion of the treatment to CTV1. For protons, apertures were designed to allow for 3 mm of lateral target expansion secondary to intrafraction motion based on our published studies(20). No target expansion is required for protons along the beam axis, as the proton range will not be affected by this degree of intrafraction motion along the axis of the beam. Any potential proton dosimetric error related to misregistration secondary to intrafraction motion between the patient and the range compensators was addressed with compensator “smearing” as described by Urie et al.(21).

Target Volumes and Dose Prescriptions—Radiation was delivered by shrinking fields. The initial clinical target volume (CTV1) received 50.4 GyRBE in 28 fractions given by photons or protons. Radiation doses were modified per protocol guidelines in Table 1 for radiation-sensitive histologies, patients receiving chemoradiation, and medical conditions where dose was reduced to decrease the risk of normal tissue injury. The initial CTV1 included the gross tumor volume plus tissues suspected of subclinical tumor invasion. For patients undergoing pre-operative radiation, this included the gross tumor with ≥1 cm of soft tissue margin on extraosseous tumor, as well as grossly involved vertebrae plus one vertebra above and below. Where this CTV1 would extend beyond a fascial barrier i.e., pleura or peritoneum, the volume was reduced to encompass but not extend beyond the fascia. Biopsy sites were included in CTV1. For sacral chordomas, with a local failure pattern that includes infiltration into the glutei and piriformis musculature, more generous margins of ≥ 1.5 cm on areas of extraosseous tumor were employed. For patients undergoing only post-operative irradiation, CTV 1 was to include surgically manipulated tissues including scars, drain sites, and stabilization hardware, although certain surgical approaches (such as flank approach to lumbar chordoma) made inclusion of all surgical scars not feasible.

For thoracolumbar tumors irradiated pre-operatively, CTV1 received 50.4 GyRBE and resection followed 4-5 weeks later. For pre-operatively radiated sacral lesions, 19.8 GyRBE was delivered, followed by immediate resection, with radiation resuming upon recovery from surgery to complete irradiation to CTV1 for an additional 30.6 GyRBE without any attempt to include surgically manipulated tissues or stabilization hardware.

After 50.4 GyRBE to CTV1, treatment was directed at CTV2 which encompassed the radiographically evident tumor on imaging studies at the time of presentation. CTV2 received 19.8 GyRBE in 11 proton fractions (to a total dose of 70.2 GyRBE) when all gross disease was resected; no dose differential was used for negative or positive margins, because margins were close even when negative. For unresected patients, CTV2 received another 7.2 GyRBE in 4 proton fractions to a total dose of 77.4 Gy RBE. For grossly incomplete resections, gross residual disease (CTV3) was boosted with another 7.2 GyRBE in 4 proton fractions with protons to a total dose of 77.4 GyRBE. Doses were reduced in selected patients per Table 1.

Normal Tissue Radiation Dose Constraints—Spinal cord center dose was limited to 54 GyRBE and cord surface dose to 63 GyRBE over a length ≤ 5 cm. The cauda equina was constrained to 70.2 GyRBE, except areas in direct contact with tumor where the dose limit was 77.4 GyRBE. No specific sacral nerve constraints were used, other than trying to spare contralateral sacral nerves for lateralized lesions. Small bowel dose was ≤ 50.4 GyRBE. No specific constraint was placed on the rectal dose (as the posterior rectal wall abutted the anterior surface of sacral lesions), but every effort was made to spare the lateral and anterior rectal walls. Where possible, omentum was placed posterior to the rectum at surgery to limit rectal dose. Recommended posterior skin doses were ≤ 66 GyRBE.

Dural plaque—Given the challenges of protocol dose delivery to target volumes near the spinal cord, we developed intraoperative dural plaque brachytherapy applicators(22) to boost the dural surface during surgery performed at our institution. Patients could receive 7.5 Gy with ^{192}Ir or 10 Gy with the ^{90}Y applicator. ^{90}Y was preferred, allowing higher dural dose because of more favorable dosimetry; estimated spinal cord surface with ^{90}Y was only 9% (assuming 4 mm of cerebrospinal fluid between dura and cord) and no dose to cord center (22).

Chemotherapy

Ewing's sarcoma and osteosarcoma patients underwent induction chemotherapy followed by ifosfamide/etoposide chemoradiation +/- surgery starting around week 12. Adriamycin was not given concurrent with the radiation. Although adjuvant chemotherapy was permitted for intermediate/high grade paravertebral soft tissue sarcomas, none was actually given.

Follow-Up

Per protocol, patients underwent history, examination, and spine MRI or CT scan 6 weeks after treatment. Thereafter, patients were seen every 6 months for 4 years and then yearly with history, examination, spine MRI or CT, and chest imaging. Radiation toxicity was graded according to NCI Common Toxicity Criteria for Adverse Events[, June 10, 2003, 2003] (CTCAE) version 3.0 with attention to spinal cord and lumbosacral nerve function and bone necrosis or fracture.

Statistics

The actuarial rates of local tumor control (LC), recurrence-free (RFS) and overall survival(OS), and complications were estimated by the Kaplan-Meyer method. Follow-up was measured from start of radiation until LF, distant metastasis(DM) or death; failure time was censored at last follow-up for patients who had not reached the event of interest. The logrank test was used to compare local recurrence rates between patient subgroups; exact two-sided p-values were computed using StatXact 6 (Cytel; Cambridge, MA).

RESULTS

Patient Accrual and Treatment

Fifty patients entered the study from 12/1997-3/2005. Patient characteristics are shown in Table 2. One patient received 19.8 Gy prior to sacral chordoma resection without treatment toxicity; he declined post-operative radiation for social reasons. Otherwise, radiation was given per protocol within 3% of specified dose. Three patients received dural brachytherapy plaque boosts with ^{125}I(1 patient, 7.5 Gy) or ^{90}Y (2 patients, 10 Gy). One patient with an unresected sacral osteosarcoma and another with an unresected lumbar spine Ewing's sarcoma underwent induction chemotherapy followed by concurrent chemoradiation.

Treatment Outcome

Median follow-up radiation start was 48 months among the 42 patients alive at the time of April 2008 data analysis. Actuarial LC, RFS, and OS figures at 1, 3, and 5 years are shown in Table 3 and Figures 1-3. Nine patients have had LF (6 chondrosarcomas [1 sacrum, 1 lumbar, 4 thoracic] and 3 chordomas [2 sacrum, 1 lumbar]), four of whom also developed DM [sacral and lumbar chondrosarcomas, lumbar and sacral chordoma]. LF occurred 8-43 months after radiotherapy. Seven of 14 patients treated for locally recurrent tumor developed LF, versus 2/36 patients treated for primary tumors ($p< 0.001$). Among 23 primary chordomas, none recurred locally versus 3 of 6 treated for locally recurrent chordoma after prior surgery ($p=0.003$). Table 4 shows LF according to extent of surgery during protocol treatment. The relationship between extent of surgery in resected patients and LF was of borderline significance relationship; there were no LF in 8 patients who had R0 resections compared to 8 of 29 patients who had R1 or R2 resections ($p=0.110$). Five of 16 patients (31%) with spine stabilization hardware suffered local recurrences versus 4 of 34 (12%) patients without ($p=0.103$).

Five patients suffered isolated DM [lumbosacral malignant peripheral nerve sheath tumor (MPNST), lumbar Ewing's sarcoma, sacral chondrosarcoma, sacral and lumbar chordomas].

Five patients died of tumor (2 sacral and 1 lumbar chondrosarcoma, 1 lumbosacral MPNST, 1 sacral chordoma), two died of a second primary cancer and one suffered cardiac death. Three patients were lost to follow-up at 0, 49 months, and 76 months after the end of treatment.

The sites of first distant failures among the 9 patients who developed distant failure according to histology were: chondrosarcoma (3): liver, lung, and pelvic musculature; chordoma (4): bone, liver and lung, para-aortic and mediastinal nodes, and lung; MPNST (1): lung; and Ewing's sarcoma(1): lung.

Complications

Radiation complications ≥ grade 3 are listed in Table 5. The actuarial grade 1-3 complication risk at 6 years for grade 1-3 complications was 31% (n=8), grade 2 or 3 complications (n=7) was 30%, and grade 3 complications was 28% (2 neuropathies, 1 erectile dysfunction, 1 rectal bleed, and two sacral insufficiency fractures). No spinal cord injuries were seen. The grade 3 sacral neuropathies and erectile dysfunction occurred at doses of 77.12-77.4 GyRBE to central sacral chordomas where spinal canal/sacral nerve sparing was not possible because of tumor location. . While we would not want to minimize the clinical significance of these sacral nerve injuries, they must be considered in the context of the near certainty of immediate sacral nerve injury in these patients with resection or local tumor recurrence.

DISCUSSION

High dose photon/proton radiation with resection or following only biopsy (generally reserved for high sacral tumors where resection would entail immediate anorectal/bladder dysfunction) controls a high proportion of spine/paraspinal tumors. These results are consistent with our prior pilot experience (18). The 78% five-year actuarial LC figure is better than that achievable with lower radiation doses delivered with conventional photon techniques. Of particular interest is the extremely high LC in 34/36 (94%) primary tumors and 23/23 (100%) primary chordomas. This underscores the importance of appropriately selecting patients for aggressive, combined modality treatment at the time of initial presentation.

Rutz et al. recently reported the experience from the Paul Scherrer Institute in Switzerland with surgery and spot-scanned protons (median dose 72.0 GyRBE) for treatment of 26 cervical, thoracic, lumbar, and sacral chordomas(23). Their 3-year LC rate of 86% was identical to that noted in our series. They had also reported a higher rate of local recurrence in patients with metallic, spine stabilizing implants, 5/13 vs. 0/13, (p=0.032); their proposed explanation included artifacts in CT and MRI datasets, with difficulties to plan and deliver radiation treatment, including target definition and dose inhomogeneities. This may also just be related to the involved anatomic level; 15/16 of the patients in our series who had metallic implants had tumors at the thoracic or lumbar level where the proximity of the spinal cord and cauda might make wide resection and radiation delivery more challenging than in the sacrum.

Using similar spinal cord constraints (63 Gy surface and 54 Gy center), the PSI group also reported no cases of spinal cord injuries. They also did not constrain the dose to the nerves below L5; they did not see any grade 3 sacral neuropathies but their median dose was lower (72.0 Gy RBE vs. 76.6 RBE) and their median follow-up was shorter (35 months). While the patient populations are somewhat different, both of these reported experiences underscore a marked improvement in outcome in these challenging tumors with higher radiation doses. Indeed, we have a number of patients managed nonsurgically with high dose radiation alone who have been locally controlled for ≥ 5 years. The first patient entered onto our study was treated with 77.4 GyRBE following biopsy of 8.5 cm sacral chordoma and remains free of local progression over 10 years later. He did develop erectile dysfunction 4 years after XRT, however, and we suspect that the dose response for nerve injury becomes steeper between 70.2

and 77.4 GyRBE. No patient in the current series developed neural injury at ≤ 70.2 GyRBE, which is consistent with prior work by Pieters et al. evaluating cauda equina tolerance(24).

Higher radiation doses to spine tumors can also now be delivered with the combination of intensity-modulated photon RT (IMRT), improved spine immobilization with body frames and/or spine tumor localization by in-treatment room image guidance. Yamada et al. reported 14 patients with primary spine/paraspinal sarcomas treated with multifractionated stereotactic and image-guided IMRT coupled with noninvasive body frames(25).In previously unirradiated patients, the median prescribed dose was 70 Gy (59.4 to 70 Gy) with a median planning target volume receiving the prescribed dose of 90%. The median dose maximum to the cord was 68% of the prescribed dose for previously unirradiated patients. Eighty-one percent of the primary lesions exhibited local control with 2 to 30 months of follow-up. No cases of radiation-induced myelopathy were encountered. Although preliminary, these clinical results are also encouraging. Treatment planning studies, however, show a very marked advantage for protons over IMRT for normal tissue sparing anterior to the spine(26).

There is also substantial interest in the use of heavier charged particles, in particular carbon ions, because of their excellent physical dose distribution and higher RBE. Kamada et al (27) reported results of a phase I/II study of carbon-ion RT in 57 patients with 64 sites of unresected bone and soft tissue sarcomas including 19 patients with spine or paraspinous tumors. The total dose was 52.8 to 73.6 carbon gray equivalent(GyE) in 16 fixed fractions over 4 weeks (3.3 to 4.6 CGE/fraction). Seven of 17 patients treated with the highest total dose of 73.6 CGE had RTOG grade 3 acute skin reactions. Dose escalation was then halted at this level. No other severe acute reactions (grade ≥3) were observed in this series. The local control rates were 88% at 1 year and 73% at 3 years. The 1- and 3-year overall survival rates were 82% and 46%, respectively. A more recent report describes the successful treatment of a patient with a cervical osteosarcoma using carbon ions(28).

Imai et al(29) reported a retrospective analysis of 30 patients with unresectable sacral chordomas treated with carbon-ion RT at similar doses with local control rate of 96%. Two patients experienced severe 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 RT. These results suggest that carbon-ion RT can be effective, safe treatment for patients with unresectable sacral chordomas and offers a promising alternative to surgery.

In summary, very promising results are now being achieved, particularly in patients with primary spine tumors, with modern surgical and a variety of sophisticated radiation techniques. In this study, high dose photon/proton radiation with surgical resection or following biopsy alone in selected patients appears to be effective in achieving local control in a high proportion of patients with challenging spine/paraspinal tumors. Local control is substantially better in patients treated at the time of primary presentation. The spinal cord dose constraints as employed in this study appear safe. Late morbidity to date appears to be acceptable, although doses of 77.4 Gy can be associated with late sacral nerve toxicity in some patents.

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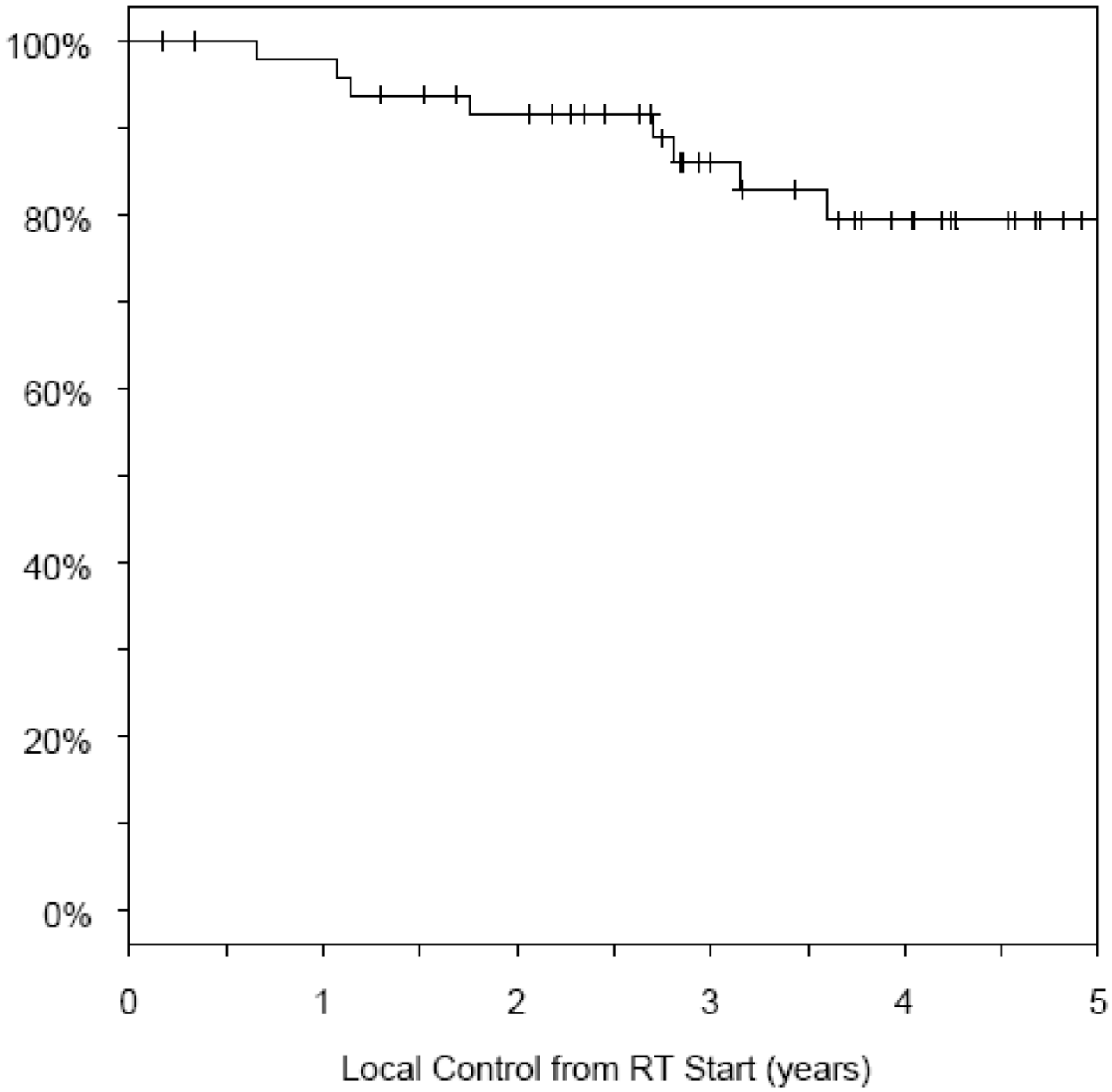
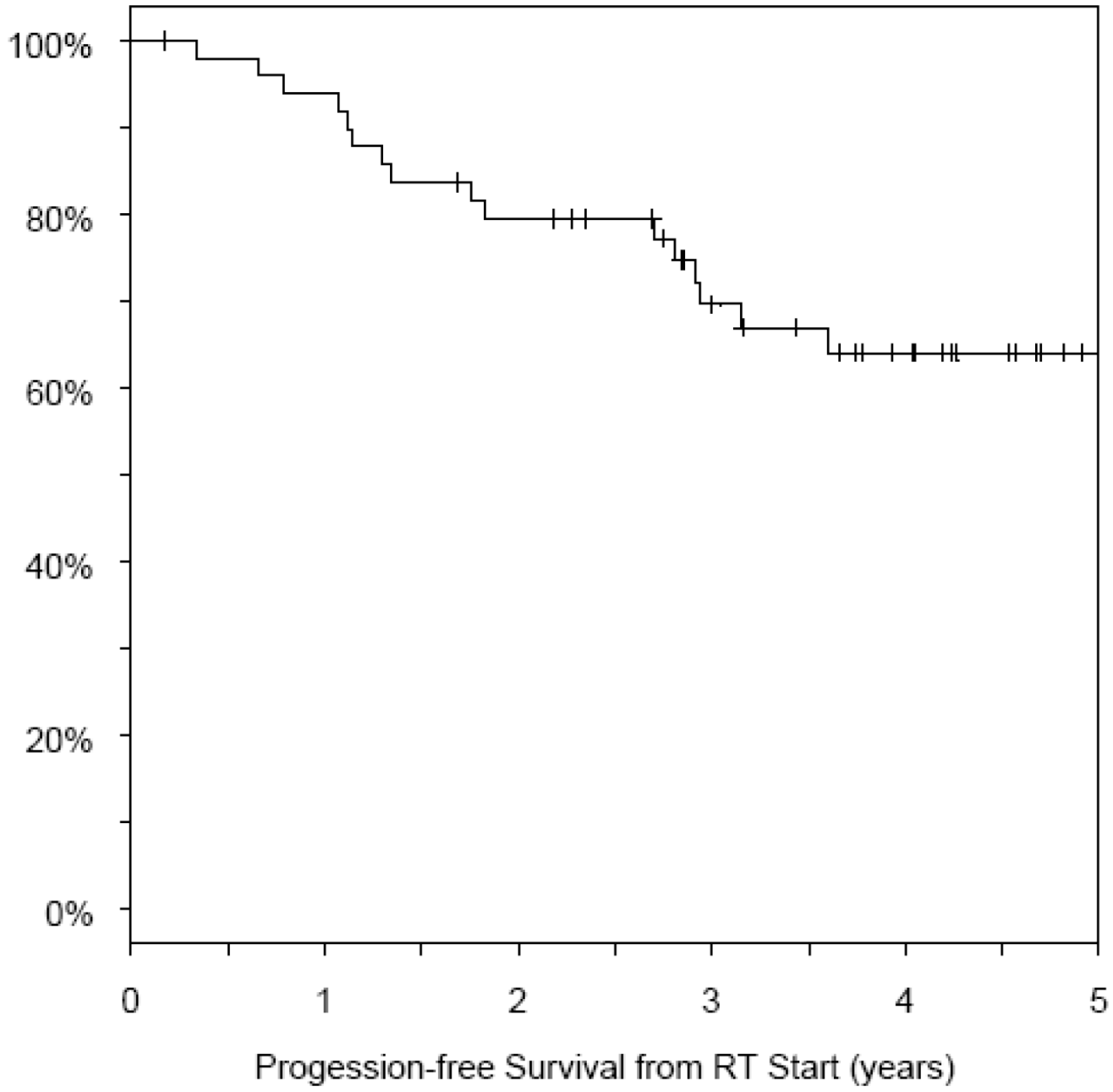
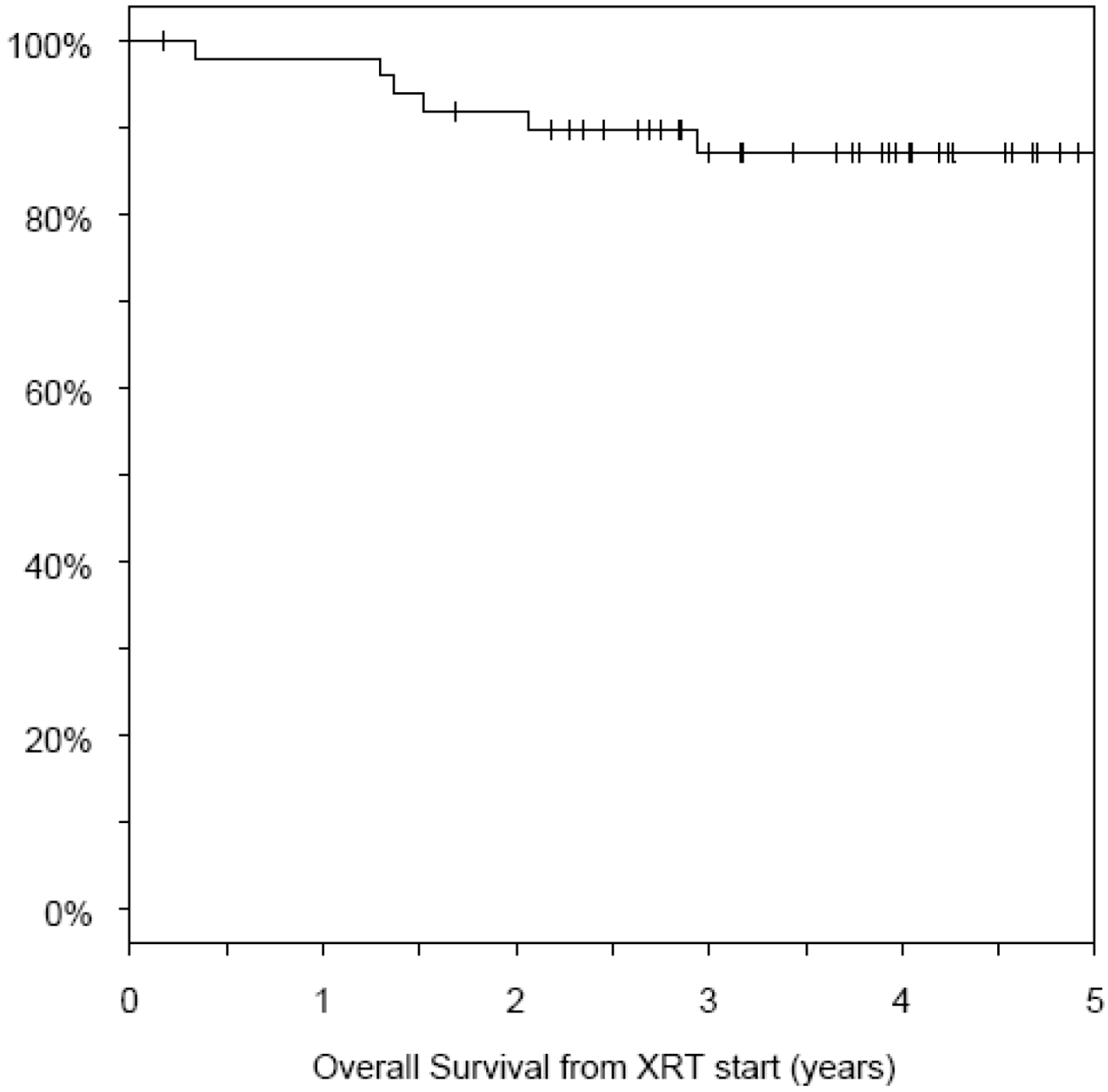


1.
Actuarial local control in the 50 patients treated in the study.



2.
Progression-free survival in the study patients.



3.
Overall survival in the patients in the study.

TABLE 1

Protocol target volume doses. The target volumes are described in the text. For patients who did not undergo resection, the volumes CTV2 and CTV3 were the same and were carried to the dose listed for CTV3.

	Total Radiation Dose GyRBE		
Histology	**CTV1**	**CTV2**	**CTV3**
Sarcoma NOS	50.4	70.2	77.4
Sarcoma NOS (IDDM or CTD)	46.8	64.8	72.0
Osteosarcoma	45.0	64.8	72.0
Giant Cell Tumor	50.4	54.0	61.2
Ewing's Sarcoma	45.0	50.4	59.4

NOS: not otherwise specified, IDDM: insulin dependent diabetes mellitus, CTD: autoimmune connective tissue disease.

TABLE 2

Patient characteristics

	N
Number of patients	50
Follow-Up (42 patients alive)	
Median	48 months
Range	37-124 months
Histology	
Chordoma	29 (58%)
Chondrosarcoma	14 (28%)
Osteosarcoma	1
Ewing's sarcoma	1
Giant cell tumor of bone	1
Angiosarcoma	1
Spindle and round cell sarcoma	1
Liposarcoma (myxoid)†	1
MPNST†	1
Site of origin	
Spine	48 (96%
Paraspinal Soft Tissue	2 (4%)
Location	
Thoracic	11(22%)
Lumbar	13 (26%)
Sacrum	26 (52%)
Presentation	
Primary	36 (72%)
Locally recurrent	14 (28%)
Surgery	
Microscopic negative margin	8 (16%)
Microscopic positive margin	17 (34%)
Gross residual disease	12 (24%)
Biopsy only	13 (26%)
Spine Stabilization Hardware	
Absent	34 (68%)
Present	16 (32%)
Radiation Dose(CGE)	
Median (range)*	76.6 (59.4-77.41)

MPNST: malignant peripheral nerve sheath tumor

*excluding 19.8 CGE due to patient refusal.

†Paraspinal soft tissue.

TABLE 3

Actuarial survival, relapse-free survival, and local control.

	Events	1-year	3-year	5-year
Overall Survival	8 deaths (5 progressive tumor, 2 second primary tumors, 1 cardiac)	98%	87%	87%
RFS	17 failures (5 local only, 4 local + distant, 5 distant only, 3 non-sarcoma deaths [2 2nd primary tumor, 1 cardiac])	94%	68%	63%
Local Control	9 local recurrences	98%	84%	78%

RFS: Recurrence-free survival

TABLE 4

Local recurrences by presentation and extent of surgery.

	Local Recurrence	5-year actuarial rate	2-sided p-value
Primary tumor	2/36	6%	
Locally recurrent	7/14	69%	<0.001
R0 resection	0/8	0%	0.110 (R0 vs. R1,R2)
R1 resection	4/17	30%	
R2 resection	4/12	40%	
Biopsy only	1/13	8%	
CHORDOMAS			
Primary chordoma	0/23	0%	
Locally recurrent chordoma	3/6	56%	0.003
R0 resection	0/7	0%	0.258 (R0 vs. R1,R2)
R1 resection	1/10	13%	
R2 resection	1/3	33%	
Biopsy only	1/9	13%	

Table 5

Radiation-related treatment complications ≥ Grade 3.

TYPE	GRADE	TREATMENT	TIME COURSE	COMMENT
ACUTE				
Insufficiency fracture, contralateral sacrum	3	R0 surgery, 70.2 GyRBE for sacral chordoma	1 month after surgery and 19.8 Gy preop XRT	Patient fell and fractured uninvolved sacrum. Resolved without surgery or late sequelae
LATE				
Sacral neuropathy	3	Bx, 77.4 GyRBE for 5.5 cm sacral chordoma	5.5 years after XRT	Unilateral leg weakness, stress urinary incontinence, poor rectal tone
Sacral neuropathy	3	R2 resection, 77.4 GyRBE for 10.5 cm sacral chordoma	4 years after XRT	Unilateral leg weakness; also received 18Gy IMRT + 27 GyRBE protons after simple hysterectomy for cervix cancer 2.5 years after protocol Rx
Erectile dysfunction	3	Bx, 77.4 GyRBE for 8.4 cm sacral chordoma	3 years after XRT	Patient age 66 at time of XRT. Not responsive to sildenafil
Contralateral sacral insufficiency fracture	3	R2 resection, 77.4 GyRBE for 6.2 cm sacral chondrosarcoma	4 months after treatment	Patient fell and fractured uninvolved sacrum. Managed by screw fixation.
Rectal bleed	3	R0 resection and 70.2 GyRBE for 4.5 cm sacral chordoma	10 months after treatment	Required transfusion and fulguration. History of prior pelvic surgeries (hysterectomy, endometriosis, bowel obstruction).