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Aggressive Local Control With Multisite Stereotactic Body Radiation in Metastatic Ewing Sarcoma: A Literature Review and Case Report

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Abstract. *Ewing sarcoma (ES) is an undifferentiated small round blue cell tumor most commonly originating in the bone of adolescents 10-20 years of age, although 30% are diagnosed in adults. The most important prognostic factor is the presence of metastatic disease. Results of the EURO-EWING 99 trial of ES patients showed that local treatment of not only the primary, but also of the sites of metastatic disease should be considered to improve event-free survival. The use of stereotactic body radiotherapy (SBRT) has been extensively reported for tumors of lung, liver, pancreas, and spine. The use of SBRT in these sites is well-accepted. Here, we report a detailed case of SBRT to multisite metastatic ES. We demonstrate the feasibility, safety, and efficacy of aggressive local control with multisite SBRT for the treatment of metastatic ES.*

Ewing sarcoma (ES) is an undifferentiated small round blue cell tumor most commonly originating in the bone of adolescents 10-20 years of age, although 30% are diagnosed in adults. The most important prognostic factor is the presence of metastatic disease, and even patients who present with locally confined disease at diagnosis have high risk of metastatic disease with only local therapy (1). Patients with metastatic disease require multi-agent chemotherapy as the backbone of their treatment, and may benefit from targeted agents based on molecular profile. The EURO-EWING 99 trial of ES patients with multiple extra-pulmonary metastases consisted of high dose multi-agent chemotherapy followed by consideration of local treatment to the primary site as well as to all sites of metastatic disease. Three year event-free survival was significantly improved at 39% for patients who received local treatment to the primary and metastatic disease compared with 17% for those who received local treatment to the primary or metastatic disease and 14% for patients received no local therapy ($p<0.001$) (2). Given this evidence, local treatment of not only the primary, but also the sites of metastatic disease should be considered in an effort to improve event free survival when deemed safe. Although most patients treated on EURO-EWING 99 received conventional radiation therapy, stereotactic body radiation therapy (SBRT) provides several advantages including enhanced biologic effective dose, fewer treatments resulting in decreased chemotherapy disruption and less impact on everyday life, and decreased radiation exposure of the bone marrow and immune system (3). We present the outcomes of an adult with metastatic ES treated with SBRT to multiple sites with concurrent chemotherapy.

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Case Report

The patient, then a 42-year old male, was found to have a mass at the T12-L1 vertebral bodies with paraspinal soft tissue extension after a several-month history of lumbar back pain with associated radiculopathy and progressive bilateral lower extremity weakness. Initial biopsy noted poorly-differentiated carcinoma and he subsequently developed

Table I. *Description of metastases treated with SBRT.*

Lesion(s)	Concurrent therapy	Local control	Duration of local control	Toxicity
T5-T6	TMZ & IRINO	Controlled	28 months	-
L5	TMZ & IRINO	Controlled	28 months	-
T10	TMZ & IRINO	Controlled	25 months	-
Occipital skull	TMZ, IRINO, Vigil vaccine	Controlled	19 months	Grade 2 alopecia
T1-T2	VCR & DOXIL	Controlled	6 months	Grade 1 pneumonitis
Left 2nd rib	VCR & DOXIL	Controlled	6 months	
Left sacrum/iliac crest	VCR & DOXIL	Controlled	6 months	-
C2-C3	VCR, DOXIL, pazopanib	N/A	N/A	-
Right clavicle	VCR, DOXIL, pazopanib	N/A	N/A	-

SBRT done at outside hospital (OSH); TMZ: temozolomide; IRINO: irinotecan; VCR: vincristine; DOXIL: doxorubicin liposomes.

Table II. *Technical details of SBRT. Radiation was given on consecutive days.*

Lesion (s)	Dose (Gy)	Fraction #	Mean dose (Gy)	Max dose (Gy)	Margin detail	Immobilization	Image fusion
T5-T6*	35	5	*	*	*	*	*
L5*	35	5	*	*	*	*	*
T10*	35	5	*	*	*	*	*
Occipital skull	30	4	35.8	42.7	GTV + 2.5 mm=CTV + 3 mm=PTV	3-point mask	MRI
T1-T2	35	5	36.3	39.2	CTV^=PTV	5-point mask	MRI
Left 2nd rib	27.5	5	32.2	38.5	GTV + 7 mm=ITV/PTV	5-point mask	PET
Left sacrum	35	5	37.7	42.0	GTV+ 1 cm and regional bone=CTV=PTV	BodyFIX®	PET
C2-C3	35	5	39.5	46.6	CTV^= PTV	5-point mask	MRI
Right clavicle	35	5	38.0	44.7	GTV+ 1 cm and regional bone= CTV + 3 mm=PTV	5-point mask	PET

^Vertebral body spine stereotactic radiosurgery (SRS) consensus guidelines (13); SBRT done at outside hospital; GTV: gross tumor volume; CTV: clinical target volume; PTV: planning target volume.

cauda equina syndrome, requiring urgent T12-L1 laminectomy with epidural and paraspinal tumor resection. The final pathology was again poorly differentiated carcinoma and systemic staging was negative. The patient was treated with post-operative radiation, 54 Gy in 27 fractions, to the resection bed and surrounding region. After completing radiation further pathologic testing revealed the malignant cells were positive for CD99 and the EWSR gene rearrangement was detected; establishing the diagnosis of ES. The patient went on to receive adjuvant chemotherapy with VAC-IE (vincristine, doxorubicin, cyclophosphamide, ifosfamide, and etoposide).

Fourteen months into follow up, surveillance MRI of the spine demonstrated new masses involving vertebral bodies T2, T5, T6, T10, and L5, consistent with the first occurrence of ES metastases. Positron emission tomography/computed tomography (PET/CT) demonstrated F-18 fluorodeoxyglucose (FDG) avidity of the spine lesions, additional extra-axial bone metastases, and a right lung nodule, all compatible with metastatic ES. Given his excellent performance status, young age, and risk of morbidity with progression of T5-6 and L5, these sites were treated with SBRT. Technical details of SBRT are provided in Tables I and II. First salvage chemotherapy with temozolomide and irinotecan was started at that time.

On follow up PET/CT and MRI of the spine, two months into salvage, there was overall improvement but progression of the T10 and right lung metastases. The lung metastasis was used as an indicator lesion for follow up and the T10 was treated with SBRT. After an additional two month follow up the right lung nodule progressed and was removed via lobectomy. Following recovery from lobectomy the Vigil vaccine was added to temozolomide and irinotecan.

Three months after lobectomy, an occipital mass became symptomatic with interval growth and biopsy was consistent with ES. Brain MRI demonstrated a posterior midline calvarial mass measuring 6.1 cm × 5.9 cm × 5.9 cm with subgaleal and intracranial components (Figure 1) and the decision was made to proceed with SBRT. Following calvarial SBRT the patient remained on temozolomide, irinotecan, and the Vigil vaccine for an additional six

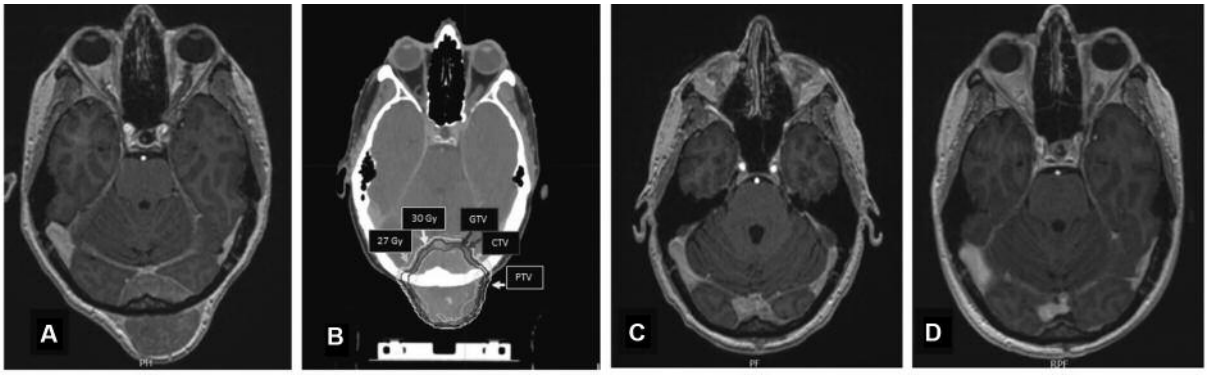

Figure 1. *SBRT for a calvarial metastasis from Ewing Sarcoma. A) Occipital mass demonstrated on T1 contrast enhanced axial MRI. B) axial treatment planning CT demonstrating target volumes and treatment isodose lines. C) axial T1 contrast enhanced MRI demonstrating reduction in tumor size 2 months post SBRT. D) axial T1 contrast enhanced MRI demonstrating reduction in tumor size 11 months post SBRT.*

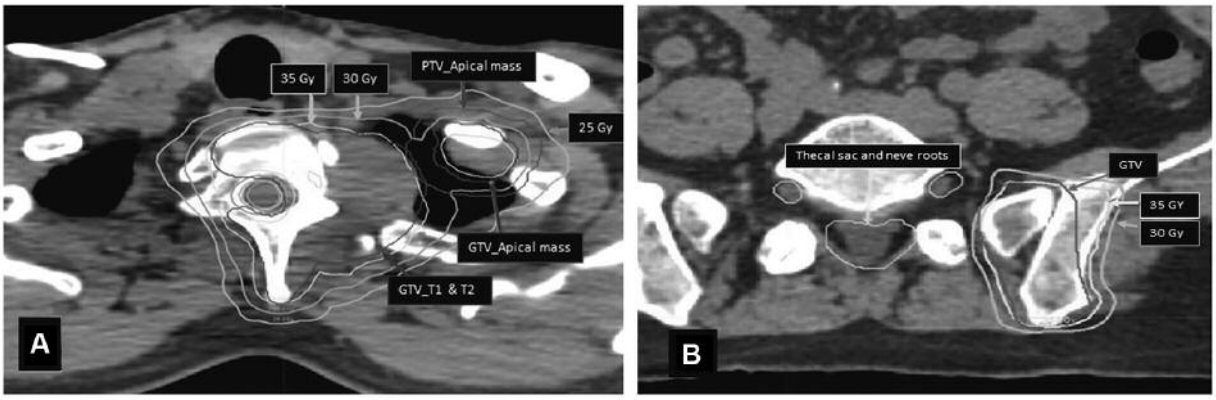

Figure 2. *Example of simultaneous multi-site SBRT for Ewing's metastases. A) axial treatment planning CT demonstrating target volumes for T1, T2 and apical mass and treatment isodose lines as detailed, of note the planning target volume (PTV) for the apical mass also includes an internal target volume (ITV) determined from a 4D CT at time of simulation. B) axial treatment planning CT demonstrating target volumes and treatment isodose lines as detailed as well as contoured normal structures.*

months. The patient was deemed to have no evidence of disease on follow up imaging and was switched to pazopanib, which he only tolerated for six weeks. Pazopanib was chosen based on high sensitivity demonstrated during *in vitro* testing.

After stopping pazopanib the patient was off all therapy for five months. He then developed neuropathic symptoms of the left upper extremity. CT and MRI demonstrated small bilateral pulmonary nodules, left second rib metastasis, and T1-2 vertebral metastases with paravertebral and epidural extension resulting in mild to moderate canal compromise without cord edema. Restaging PET/CT demonstrated additional metastases of the left sacrum/iliac crest and right iliac crest.

At this time systemic therapy was restarted with vincristine and doxorubicin liposomes (Doxil). SBRT was utilized to treat the T1-2 and the left second rib in a single volume as well as the left sacrum/iliac crest in an additional volume (Figure 2). The T1-2 epidural disease was deemed to have adequate separation from the spinal cord, permitting delivery of SBRT without surgical resection. All sites were treated simultaneously and chemotherapy was delivered two weeks prior to and two weeks following SBRT. An additional site of disease in the right iliac was treated with cryotherapy following biopsy for tissue acquisition.

Four months after SBRT to T1-2 and left sacrum/iliac crest routine staging demonstrated a known stable metastasis at C2, but new lesions at C3 and right medial clavicle. SBRT to C2-3 was performed without incident and low dose pazopanib was re-attempted with vincristine and doxorubicin liposomes. There was no toxicity related to SBRT, but the patient continued to have significant fatigue related to pazopanib. Dosing of pazopanib was changed to one week on and one week off, which he tolerated.

Table III. *Spine SBRT sarcoma series.*

Study	Patients	Treated lesions	Tumor histology	Prescription median (range)	Local control	Toxicity
Kim *et al.* (4)	24	NR	ES (25%) CS (25%) OS (21%) other (29%)	30 Gy (8-40) in 5 fx (1-10)	96% (6 months)	Grade ≥3: none
Chang *et al.* (5)	27	32	OS (50%) other (50%)	21.8 Gy (16-45) in 1 fx (1-3)	76.9% (2 years)	NR
Elibe *et al.* (6)	23	53	LMS (39%) ES (13%) OS (9%) other (39%)	18 Gy (10-20) in 1 fx	66% (14 months)	2 VCF
Miller *et al.* (7)	18	40	LMS (32%) CS (17%) SC (17%)	16 Gy (10-25) in 1 fx (1-5)	51% (12 months)	3 VCF 4 pain flare
Levine *et al.* (8)	24	30	LMS (29%) CS (21%) other (50%)	30 Gy (20-30) in 3 fx	75% (Response)	2 transient radiculopathy 1 rectal fistula
Spratt *et al.* (9)	9	12	LMS (50%) Myxoid FS (17%) HP (17%)	24 Gy (24-30) in 1 fx (1-3)	88.8% (10 months)	NR
Bishop *et al.* (10)	48	66	LMS (42%) Epithelioid (14%) MFH (12%) CS (9%) other (23%)	Reported in BED in 1 fx (47%)	73% for single fx (3 years)	Grade ≥3: none
Folkert *et al.* (11)	88	120	LMS (30%) HP (16%) LS (14%) FS (9%) other (31%)	24 Gy (18-24) in 1 fx 28.5 Gy (24-36) in 3 fx (3-5)	77.4% (2 years)	Grade 3: 4.5% Grade 4: none

ES: Ewing sarcoma; CS: chondrosarcoma; OS: osteosarcoma; LMS: leiomyosarcoma; SC: spindle cell; FS: fibrosarcoma; MFH: malignant fibrous histiocytoma; HP: hemangiopericytoma; LS: liposarcoma; NR: not reported; fx: fraction; VCF: vertebral compression fracture.

Follow-up PET/CT three months later demonstrated continued local control of all sites treated with SBRT, no new areas of disease, but persistent FDG uptake in the right medial clavicle. SBRT was performed to this last site of active disease and the patient remains on systemic therapy with vincristine, doxorubicin liposomes, and low dose pazopanib.

Summary. This is a case of a 46-year old male diagnosed with localized ES of the spine. His initial treatment consisted of surgical resection, post-operative radiation, and systemic therapy with VAC-IE. He developed metastatic disease 14 months after completing initial chemotherapy and 26 months after diagnosis. He received multiple lines of systemic therapy including temozolomide/irinotecan, pazopanib, and vincristine/doxorubicin liposomes while receiving SBRT as his primary modality of local treatment for metastatic sites of disease. The patient received SBRT to nine anatomical sites over two and a half years. He tolerated all SBRT extremely well with only grade 1 lung pneumonitis and grade 2 localized alopecia with no pain flares and no radiation related delays in chemotherapy. Local control of his sites is up to 28 months from the time of submission. He continues to work full time and has an excellent performance status.

Discussion

In this case report we demonstrate the feasibility, safety, and efficacy of aggressive local control with multisite SBRT for the treatment of metastatic ES. The importance of local therapy for patients with metastatic ES disease has been described (2). Local control of spine SBRT for sarcoma patients ranges from 66-96% when greater than or equal to 18 Gy in a single fraction is used (4-11) (Table III). Data on outcomes for non-spine bone SBRT for metastatic sarcoma are limited.

Our patient was mostly asymptomatic from his bone metastases and did not experience any pain flares post SBRT.

It is important to note that in addition to durable local control, retrospective data has demonstrated that sarcoma SBRT has good pain relief, neurologic and radiographic tumor response, with limited toxicity (6, 7). There are three ongoing trials exploring the efficacy of SBRT to treat osseous metastasis in sarcomas (NCT01763970, NCT02306161, and NCT02567435) and these will provide useful data to guide the use of SBRT for metastatic sarcoma.

Our patient has been maintained on vincristine and doxorubicin liposomes concurrently during the last five SBRT treatments. This regimen was chosen not only for efficacy, but to reduce anthracycline-associated cardiotoxicity and maintain an excellent quality of life. We have not seen any evidence of radiation recall, skin reactions, cardiotoxicity, or significant myelosuppression. A recent publication has indicated that the incidence of cardiotoxicity after doxorubicin liposomes is very low (12). Therefore, if SBRT is "sandwiched" between monthly doxorubicin liposome cycles, this may be an effective chemoradiation regimen for oligometastatic Ewing sarcoma.

The combination of systemic therapy and SBRT is an evolving paradigm, and it is important to consider drug-radiation interactions, toxicity, and goals of care. Safety is the number one priority and expert multidisciplinary care is imperative as we investigate novel approaches for the treatment of oligometastatic Ewing sarcoma.

Conflicts of Interest

None of the Authors have any conflicts of interest to declare.

Authors' Contributions

Conception and design: Ahmad M Karimi, Shauna R Campbell, Shireen Parsai, Erin Murphy; Data collection: Ahmad M Karimi, Shauna R Campbell, Shireen Parsai, Erin Murphy; Data analysis and interpretation: Ahmad M Karimi, Shauna R Campbell, Shireen Parsai, Erin Murphy; Manuscript writing: Ahmad M Karimi, Shauna R Campbell, Shireen Parsai, Lilyana Angelov, Jacob Scott, Peng Qi, Peter Anderson, Samuel T Chao, Erin S Murphy; Final approval of manuscript: Ahmad M Karimi, Shauna R Campbell, Shireen Parsai, Lilyana Angelov, Jacob Scott, Peng Qi, Peter Anderson, Samuel T Chao, Erin S Murphy.

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