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Epidemiological, functional and oncologic outcome analysis of spinal sarcomas treated surgically at a single institution over ten years

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Abstract:

Background/Context: Spinal sarcomas are aggressive tumors that originate from cells of mesechymal origin, specifically fat, cartilage, bone and muscle. They are high-grade lesions, and treatment of spinal sarcomas can involve chemotherapy, radiation therapy, and surgery. In the appendicular skeleton, sarcomas are often treated with amputation, however in the spinal column, surgical resection poses a unique set of challenges.

Purpose: Large-scale studies of spinal sarcoma are needed to better understand optimal treatment regimens and the impact of en bloc or intralesional resection on patient outcome.

Study design/setting: A cohort of 25 sarcoma patients treated at a single medical institution between 2002 and 2012 was reviewed.

Patient Sample and Outcome measures: Patients were classified by tumor type for subgroup analysis, including chondrosarcoma, osteosarcoma, and other malignant spinal sarcoma. Demographic data for review included patient age, tumor type, tumor location, surgery type, exposure to chemotherapy and radiation therapy.

Methods: Survival statistics and Kaplan-Meier curves were calculated using GraphPad Prism 5.0. The threshold for statistical significance was set at $p < 0.05$. Unpaired, two-tailed, equal variance t-tests were performed for statistical analyses in Microsoft Excel 2010. Portions of this work were supported by the AOSpine Primary Tumor Knowledge Forum. The authors report no potential conflicts of interest related to this manuscript.

Results: Twenty-five patients with spinal sarcomas were treated over the ten-year period. Diagnosis included chondrosarcoma (n=9), osteosarcoma (n=4) and other sarcoma (n=12). Mean age at the time of diagnosis was 42 years. Pain was present at the time of diagnosis in 92% of patients. Median survival after surgery was 59.5 months for chondrosarcoma, undefined for other sarcomas and 16.8 months for osteosarcoma. Median survival following en bloc resection was undefined. Median survival following intralesional resection was 17.8 months**.** The difference in median survival between en bloc and intralesional resection was statistically significant (p=0.049).

Conclusion: The authors report the largest cohort of patients with spinal sarcoma. Median survival in this cohort was longest for patients with sarcomas of varying pathology. Median survival was longer for chondrosarcoma. En bloc resection demonstrated a survival advantage over intralesional resection. Long term follow-up is needed for patients with spinal sarcoma to establish definitive survival data.

Key Words: Sarcoma; Osteosarcoma; Chondrosarcoma; Outcome

Introduction:

Spinal sarcomas are a rare group of spinal malignancies that are associated with high rates of morbidity and mortality. Epidemiological studies of spinal sarcomas, such as from the Surveillance Epidemiology and End Results (SEER) database cancer statistics review from 1975-2009, demonstrate that sarcomas represent less than 5% of all osseous neoplasms and less than 0.2% of all new cancers. [1, 2] Sarcomas can occur in a variety of osseous regions throughout the body. However, sarcomas of the spine and surrounding structures often elicit debilitating consequences due to severe focal pain and neurological morbidity.

Chondrosarcoma represents 25% of sarcomatous tumors and increases in likelihood in patients over the age of 50.[3, 4, 5, 6] Chondrosarcomas are part of a family of malignant tumors where the cells differentiate uncontrollably into cartilaginous tissue. It is further classified as central, peripheral, or periosteal, with mesenchymal and clear cell variants.[7] Osteosarcoma tends to be more common, representing 35% of all sarcaoms and 3 to 15% of all primary spine tumors. There exist a variety of subtypes including conventional osteosarcomas, telangiectatic, small-cell, giant-cell, epithelioid, and osteoblastoma-like osteosarcomas [8, 9]

Whereas previous studies have been confined by limited patient data or the size of their patient population, this database of spinal sarcomas is comprised of 25 spinal sarcoma patients who underwent surgical resection at a single institution from 2002 to 2012. We investigate the impact of en bloc resection on patient outcome through analyzing a single institutions surgical management of spinal sarcomas over the last decade. While the SEER database provided invaluable epidemiological data of 1378 sarcoma patients, it did not stratify outcomes based on surgical approach from each surgical institution separately. Thus, by looking only at patients from a single institution during a single decade, this study allows for a controlled standard of

care, which we hope may then be used by neurosurgical and orthopedic spinal surgeons to determine functional and oncologic survival data for a variety of surgical techniques and treatments.

Methods:

Study population

Demographic, treatment and outcome data was collected retrospectively from the electronic medical record following protocols dictated by the Institutional Review Board (IRB application NA_00066200). 25 consecutive patients with histology-confirmed spinal sarcomas treated at a single institution from 2002-2012 were reviewed. Patient medical records, including clinic notes, primary radiographs, computed tomography (CT) scans and magnetic resonance imaging (MRI) were reviewed. Pathology reports were also reviewed.

Study criteria

All patients included in this study presented with histologically confirmed sarcoma of the spine. Covariates identified were epidemiological data such as age, gender, length of hospitalization, location of sarcoma, number of spinal levels involved, surgical approach, tumor volume, pathology of sarcoma, extent of resection, pain at diagnosis, Frankel score, presence of myelopathy and caudaequina, adjunctive treatment, local recurrence, and overall survival. The diagnosis of other sarcoma included epithelioid sarcoma (n=3), pleomorphic undifferentiated sarcoma (n=2), spindle cell sarcoma (n=2), alveolar soft part sarcoma (n=1), unusual low grade sarcoma (n=1), postradiation sarcoma (n=1), fibromyxoid sarcoma (n=1) and Ewing sarcoma (n=1).

Surgical approach was recorded from operative notes. Pain at diagnosis was self-reported by patients at any pre-operative clinic visit within 3 months of surgery. The number of spinal levels involved and the presence or absence of a pathologic fracture was determined from the radiology reports of preoperative CT and MRI scans.

Vital statistics were recorded from the Social Security Death Master File accessed online. All vital statistics reflect the status of patients as of July 31, 2012. Survival data for non-US citizens was recorded as unknown. Recurrence data is recorded for all patients at the last clinical follow up. Recurrence was determined from post-operative neurosurgery clinic notes reporting the neurosurgeon's interpretation of radiographic recurrence at the time of last follow up.

Tumor size and volume was recorded from primary review of preoperative MRI or CT scans. Volume was calculated via the formula for the volume of an ellipsoid ($(4\pi/3)r^1r^2r^3$). Radii were taken as one-half the cranial-caudal, anterior-posterior and lateral measurements of the tumor. Measured values were corroborated with radiology reports.

Following surgery, patients were seen at one month then at three, six, nine and twelve months. Patients were followed every six months in the second year, then yearly, or as clinical progression dictated their plan of care. MRI with and without contrast was used to evaluate tumor recurrence at the time of clinical follow-up. Early complications, defined as occurring within thirty days postoperatively, and late complications, defined as occurring after thirty days postoperatively were recorded.

Statistical Analysis

Survival statistics and Kaplan-Meier curves were calculated using GraphPad Prism 5.0 (GraphPad, La Jolla, CA). The threshold for statistical significance was set at $p < 0.05$. Unpaired,

two-tailed, equal variance t-tests were performed for statistical analyses in Microsoft Excel 2010. 95% confidence intervals were determined using the Confidence Interval Calculator for Proportions (Online, McCallum-Layton; 2010).

Results:

Patient Population

Twenty-five patients with spinal sarcomas were treated over the ten-year period. Mean age at the time of diagnosis was 42 years (range 17-75 years) and the disease was found predominantly in women (56%). The mean age at presentation differed by tumor type. Chondrosarcoma (46.7 years ±10.4 years) and osteosarcoma (48.8 years ± 23.5 years) presented at an older mean age than other sarcomas (36.2 years ±18.0 years). Median length of stay after surgery was 16 days (range 4 – 52 days). Median follow up time was 11.8 months (range 0.1 – 71.6 months).

Clinical Presentation

Pain was present at the time of diagnosis of a majority of patients (92%). Pathological fractures were typically not present at the time of diagnosis (12%). Myelopathy was present in a majority of patients (68%), more so in cases involving chondrosarcoma (67%) and osteosarcoma (100%) than other sarcomas (58%). Cauda equina was absent in a majority of patients (16%). Ten patients (40 %) had undergone a previous spinal tumor resection. Pre-operative Frankel scores of the sarcoma patients were C (28%), D (36%), and E (36%).

Surgical Approach

Chondrosarcoma and osteosarcoma were found predominantly in the cervical, thoracic, or lumbar spine, while other sarcomas are more common in the sacral spine. The median number of vertebral levels involved was three (range 1-7). A posterior approach was used most commonly (56%) followed by surgeries involving both an anterior and posterior approach (40%). The most common procedure was a laminectomy or hemilaminectomy, which was performed in 15 cases (60%). The most common type of reconstruction used was an allograft (48%), followed by the use of a titanium cage (32%). Often times, chondrosarcoma patients underwent no form of reconstruction (60%).

Adjuvant Treatment

Adjuvant treatment was used in 15 cases (60%). Six patients received preoperative chemotherapy (24%), four received postoperative chemotherapy (16%), seven underwent pre-op radiation (28%), and ten underwent post-op radiation (40%). Local recurrence occurred in six cases (24%).

Complications

Complications noted earlier than thirty days postoperatively (early complications) and later than thirty days (late complications) were stratified by either en bloc resection or intralesional resection. In the En bloc resection group, five patients (33.3%) required reoperation secondary to wound dehiscence, and three patients (20%) developed deep venous thrombosis less than thirty days postoperatively. Greater than thirty days postoperatively, four patients (26.7%) required reoperation for three cases of wound dehiscence and one case of

instrumentation failure that resulted in loss of correction of deformity. The other two cases of instrument failure did not have any loss of deformity correction and no operative intervention was pursued. In the Intralesional resection group, two patients 230.0%) required reoperation secondary to wound dehiscence and postoperative hematoma, and one patient (10%) developed deep venous thrombosis less than thirty days postoperatively. Greater than thirty days postop, there was one complication of esophageal erosion requiring revision surgery to remove the cervical plate in the intralesional group. **(Table 1)**

Patient Survival

Median survival following surgery for chondrosarcoma was 59.5 months (range 0.2-70.6 months), undefined for other sarcomas (range 0.2-26.5 months) and 16.8 months for osteosarcoma (range 0.5-28.5 months). (**Figure 1)** The difference in survival was not statistically significant on Mantel-Cox testing. (p=0.27) Median survival following en bloc resection was undefined. Median survival following intralesional resection was 17.8 months. (**Figure 2**) Survival following en bloc resection was significantly different than survival after intralesional resection on Gehan-Breslow-Wilcoxon test (p = 0.049). The survival difference was not statistically significant on Mantel-Cox testing (p=0.07).

Discussion:

This subset of malignant spinal tumors encompasses chondrosarcomas, osteosarcomas, as well as a variety of other sarcomatous tumors including Ewings sarcoma. Although previous studies have examined the broad epidemiologic outcomes of patients at multiple institutions, these studies did not investigate outcomes relative to the specifics of treatment.[10, 11, 12] Our

review highlights the important aspects of surgical management, namely the benefit of en bloc resection for spinal sarcoma.

Surgical management of sarcomas is diverse, and is dependent on location of tumor burden. For example, the orthopedic literature recommends wide excision or amputation of extremity sarcoma when feasible, with use of adjuvant treatments such as phenol, radiation, and chemotherapy as needed [13]. En bloc strategies available to patients include corpectomy, sacral amputations, and finally hemipelvectomy [14]. However, surgical resection of spinal sarcomas cannot extend this concept of amputation at mobile spine levels due to the necessity of adjacent anatomical structures. The results of this study suggest that en bloc resection, when feasible, should be offered to patients with diverse sarcomatous pathologies in the spinal column in order to optimize patient survival.

Chondrosarcoma patients have shown to have a 5-year survival rate close to 70% and a median survival ranging from 70 to 160 months.[15, 16, 17] Our data showed a median survival of 60 months. This variation can be accounted for in part by our small patient pool (10 chondrosarcoma patients) and with not all patients reaching five years of follow up (median follow up 11.8 months, range 0.1 – 71.6). Osteosarcoma patients are shown to have a median survival ranging from 7 to 23 months. [18, 19] Our data demonstrates that the osteosarcoma patients had a median survival of almost 17 months. This is in accordance with previously published data from Schwab et al. who noted increased survival of 60 months in their cohort of 17 patients over 2 decades [20].

Prior studies have shown that an en bloc resection of spinal sarcomas with adequate margins decreases recurrence rates.[21, 22, 23] However, a number of other studies have shown the dangers of an en bloc resection in the spine, including the increased morbidity of the procedure

and the varying difficulty in different locations of the spine.[24, 25, 26] Through our database, we have shown that en bloc resection of spinal sarcomas does increase patient survival as compared to purely intralesional resection ($p = 0.049$).

The authors acknowledge the limitations of this study. This study was limited by its small cohort size, which resulted in some of the trends observed not reaching statistical significance. Our findings add to the growing amount of sarcoma literature, with a focus on cancer varieties and surgical approaches. In the future, these studies can be utilized to provide a better quality of care to patients affected by the disease.

Conclusion:

Sarcomas of the spine are a unique group of highly aggressive and malignant spinal tumors that represent a surgical and management challenge for the surgeon and the entire health care team. Reports continue to demonstrate a high morbidity and mortality in this population. However, the results of this study suggest that en bloc resection of these tumors, when possible, may increase patient survival. Continued improvement in surgical and adjuvant treatment will undoubtedly continue to further alter the survival curve for this population of spinal tumors.

Figure Legends

Figure 1. Survival by pathology. Median survival following surgery for chondrosarcoma was 59.5 months (range 0.2-70.6 months), undefined for other sarcomas (range 0.2-26.5 months) and 16.8 months for osteosarcoma (range 0.5-28.5 months). The difference in survival was not statistically significant on Mantel-Cox testing. (p=0.27).

Figure 2. Survival by Resection. Median survival following en bloc resection was undefined. Median survival following intralesional resection was 17.8 months. Survival following en bloc resection was significantly different than survival after intralesional resection on Gehan-Breslow-Wilcoxon test (p = 0.049). The survival difference was not statistically significant on Mantel-Cox testing (p=0.07).

Tables

Table 1. Complications of En bloc vs Intralesional resection.

References

1. Caudell JJ, Ballo MT, Zagars GK, Lewis VO, Weber KL, Lin PP, et al: Radiotherapy in the management of giant cell tumor of bone. Int J Radiat Oncol Biol Phys 57:158-165, 2003

2. Imai R, Kamada T, Tsuji H, Yanagi T, Baba M, Miyamoto T, et al: Carbon ion radiotherapy for unresectable sacral chordomas. Clin Cancer Res 10:5741-5746, 2004

3. Hsieh PC, Xu R, Sciubba DM, McGirt MJ, Nelson C, Witham TF, et al: Long-term clinical outcomes following en bloc resections for sacral chordomas and chondrosarcomas: A series of twenty consecutive patients. Spine (Phila Pa 1976) 34:2233-2239, 2009

4. Strike SA, McCarthy EF: Chondrosarcoma of the spine: A series of 16 cases and a review of the literature. Iowa Orthop J 31:154-159, 2011

5. Mukherjee D, Chaichana KL, Adogwa O, Gokaslan Z, Aaronson O, Cheng JS, et al: Association of extent of local tumor invasion and survival in patients with malignant primary osseous spinal neoplasms from the surveillance, epidemiology, and end results (SEER) database. World Neurosurg 76:580-585, 2011

6. Mukherjee D, Chaichana KL, Gokaslan ZL, Aaronson O, Cheng JS, McGirt MJ: Survival of patients with malignant primary osseous spinal neoplasms: Results from the surveillance, epidemiology, and end results (SEER) database from 1973 to 2003. J Neurosurg Spine 14:143-150, 2011

7. Samson IR, Springfield DS, Suit HD, Mankin HJ: Operative treatment of sacrococcygeal chordoma. A review of twenty-one cases. J Bone Joint Surg Am 75:1476-1484, 1993

8. Amendola BE, Amendola MA, Oliver E, McClatchey KD: Chordoma: Role of radiation therapy. Radiology 158:839-843, 1986

9. Thilmann C, Schulz-Ertner D, Zabel A, Herfarth KK, Wannenmacher M, Debus J: Intensity-modulated radiotherapy of sacral chordoma--a case report and a comparison with stereotactic conformal radiotherapy. Acta Oncol 41:395-399, 2002

10. Gibbs IC, Chang SD: Radiosurgery and radiotherapy for sacral tumors. Neurosurg Focus 15:E8, 2003

11. Ikeda H, Honjo J, Sakurai H, Mitsuhashi N, Fukuda T, Niibe H: Dedifferentiated chordoma arising in irradiated sacral chordoma. Radiat Med 15:109-111, 1997

12. Gerszten PC, Ozhasoglu C, Burton SA, Welch WC, Vogel WJ, Atkins BA, et al: CyberKnife frameless single-fraction stereotactic radiosurgery for tumors of the sacrum. **Neurosurg Focus 15:**E7, 2003

13. Sundaresan N, Galicich JH, Chu FC, Huvos AG: Spinal chordomas. **J Neurosurg 50:**312-319, 1979

14. Ashenhurst EM, Quartey GR, Starreveld A: Lumbo-sacral radiculopathy induced by radiation. **Can J Neurol Sci 4:**259-263, 1977

15. Breteau N, Demasure M, Favre A, Leloup R, Lescrainier J, Sabattier R: Fast neutron therapy for inoperable or recurrent sacrococcygeal chordomas. **Bull Cancer Radiother 83 Suppl:**142s-5s, 1996

16. Schulz-Ertner D, Nikoghosyan A, Thilmann C, Haberer T, Jakel O, Karger C, et al: Results of carbon ion radiotherapy in 152 patients. **Int J Radiat Oncol Biol Phys 58:**631-640, 2004

17. Turcotte RE, Sim FH, Unni KK: Giant cell tumor of the sacrum. **Clin Orthop Relat Res (291):**215-221, 1993

18. Catton C, O'Sullivan B, Bell R, Laperriere N, Cummings B, Fornasier V, et al: Chordoma: Long-term follow-up after radical photon irradiation. **Radiother Oncol 41:**67-72, 1996

19. Cheng EY, Ozerdemoglu RA, Transfeldt EE, Thompson RC,Jr: Lumbosacral chordoma. prognostic factors and treatment. **Spine (Phila Pa 1976) 24:**1639-1645, 1999

20. Kim RY, Salter MM, Brascho DJ: High-energy irradiation in the management of chondrosarcoma. **South Med J 76:**729-31, 735, 1983

21. Leggon RE, Zlotecki R, Reith J, Scarborough MT: Giant cell tumor of the pelvis and sacrum: 17 cases and analysis of the literature. **Clin Orthop Relat Res (423):**196-207, 2004

22. Fuchs B, Dickey ID, Yaszemski MJ, Inwards CY, Sim FH: Operative management of sacral chordoma. **J Bone Joint Surg Am 87:**2211-2216, 2005

23. Schoenthaler R, Castro JR, Petti PL, Baken-Brown K, Phillips TL: Charged particle irradiation of sacral chordomas. **Int J Radiat Oncol Biol Phys 26:**291-298, 1993

24. Kollender Y, Meller I, Bickels J, Flusser G, Issakov J, Merimsky O, et al: Role of adjuvant cryosurgery in intralesional treatment of sacral tumors. **Cancer 97:**2830-2838, 2003

25. Rajkumar A, Basu R, Datta NR, Dhingra S, Gupta RK: Radiation therapy for sacral osteoblastoma. **Clin Oncol (R Coll Radiol) 15:**85-86, 2003

26. Kanamori M, Ohmori K: Curettage and radiotherapy of giant cell tumour of the sacrum: A case report with a 10-year follow-up. **J Orthop Surg (Hong Kong) 13:**171-173, 2005

Complications of En bloc vs Intralesional resection				
	En Bloc (n=15)	%	Intralesional (n=10)	%
Early Complications				
Reoperation	5	33.3%	2	20.0%
Wound dehiscence	5	33.3%	1	10.0%
DVT	3	20.0%	1	10.0%
Hematoma	0	0.0%	1	10.0%
Late Complications				
Reoperation	4	26.7%	1	10.0%
Instrument Failure	3	20.0%	0	0.0%
Wound dehiscence	3	20.0%	0	0.0%
Esophageal Erosion	0	0.0%	1	10.0%