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Radiation for Primary Spine Tumors

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Primary spine tumors represent a difficult treatment paradigm because of the complexities of tumor resection and significant resistance to chemotherapy and radiation therapy. The most common primary malignant bone tumors reported in the literature are chordoma, chondrosarcoma, and osteogenic sarcoma. Great interest has been generated in the techniques of en bloc resection to achieve wide or marginal margins with the intention of achieving a surgical cure [1–4]. Unfortunately, many tumors are not amenable to en bloc resection because of the presence of significant epidural disease, large paraspinal masses, or circumferential bone disease [4,5]. Additionally, most of the literature regarding en bloc resection has been applied to low-grade tumors, but many tumors are high- or intermediate-grade sarcomas, decreasing the chance of a purely surgical cure [5]. Chemotherapy has a role in improving local and systemic tumor control, particularly for osteogenic sarcoma and possibly for chordoma. Novel uses and improvements in advanced radiation techniques may improve local control for these primary bone tumors traditionally considered to be radioresistant to conventional radiation therapy, however. These developments include charged particle radiation (ie, proton beam), brachytherapy (eg, ^{90}Yttrium), and high-dose conformal photon therapy (eg, image-guided intensity-modulated radiation therapy [IGRT], Cyberknife, tomotherapy).

Chemotherapy

Chemotherapy plays a major role in the treatment of osteogenic sarcoma and may have some impact on the treatment of chordoma. Patients who have osteogenic sarcoma often respond to neoadjuvant chemotherapy, improving the chances of achieving a complete resection. A recent prospective randomized trial compared the addition of ifosfamide or muramyl tetrapeptide (MTP) to the standard regimen of cisplatin, doxorubicin, and high-dose methotrexate in 677 patients [6]. All patients underwent definitive surgical resection. Patients treated with standard chemotherapy showed a 71% 3-year event-free survival. Those receiving the addition of ifosfamide and MTP showed a 78% 3-year event-free survival. Additionally, 265 patients (45%) showed grade 3 or 4 necrosis of the tumor at resection.

Chordoma has traditionally been considered chemoresistant, but these tumors have shown responses to tyrosine kinase inhibitors. A small series recently reported excellent results in six patients treated for chordoma using imatinib mesylate (Gleevec) [7]. Imatinib mesylate is a tyrosine kinase inhibitor that targets platelet-derived growth factor receptor-β (PDGFRβ), BCR-ABL, and KIT, and all patients in this series were positive for PDGFRβ. Each tumor showed liquefaction on imaging, indicating a 100%

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response rate. The authors have treated several patients at recurrence without being able to duplicate this response. Sunitinib (Sutent), a multitarget receptor tyrosine kinase inhibitor, is currently being explored as a candidate drug to treat chordoma in a prospective multi-institutional trial.

Radiation therapy

Radiation has long been used as adjuvant, neoadjuvant, and primary therapy for primary malignant bone tumors. From the experience in extremity sarcomas, high-dose radiation can potentially provide local control to these highly radioresistant tumors. Patient with close surgical margins are offered radiation at a dose greater than 60 Gy, and those who have gross residual disease are given radiation at a dose greater than 70 Gy at a conventional 200 cGy per fraction [8]. These doses are greater than spinal cord tolerance, which is considered to be 50 Gy at 120 to 200 cGy per fraction [9]. Hence, because of the dose restrictions imposed by the spinal cord, the results of conventional radiotherapy for primary spine tumors have been, on the whole, disappointing. Several strategies have been developed to increase the dose of radiation to spine tumors while sparing toxic doses to the spinal cord and other surrounding structures, such as the esophagus, bowel, and kidney. These strategies include proton beam radiation, brachytherapy, and high-dose conformal photon therapy (eg, IGRT, Cyberknife, tomotherapy).

Proton beam radiation

Proton beam radiation is one of the first modalities developed that could deliver effective high-dose radiation to primary spine tumors. Protons are able to deliver a high dose to the target using the Bragg peak effect with a steep gradient fall-off past the target. The two limitations of the proton beam technique are the inability to deliver single-fraction therapy and the limited availability of proton facilities. Currently, several new facilities are being built in the United States. Carbon ion beam radiation, which exhibits a higher linear energy transfer (LET) than proton beams but maintains the Bragg peak effect, is also being developed at select international centers and may prove useful in the treatment of spinal tumors.

Two large series have reported on the treatment of primary neuraxis tumors with proton beam radiation. Hug [10] reported the results of 47 patients who received between 61.8 and 73.9 cobalt gray equivalents (CGE) to the prescribed tumor volume. Most patients had gross residual disease. Five-year control rates were approximately 50% for chordoma and osteogenic sarcoma and 100% for chondrosarcoma. Failure analysis in six cases showed that five failures occurred in field recurrences. Austin and colleagues [11] similarly reported on 141 patients treated for chordoma and chondrosarcoma of the skull base and cervical spine at a median of 69 CGE. Of the 26 failures, 77% were in field recurrences. Both of these series suggest that the failures were the result of a dosing issue as opposed to a targeting issue (ie, out-of-field recurrence). The tumors received less than the prescribed tumoral dose to spare normal tissue tolerance, such as the spinal cord.

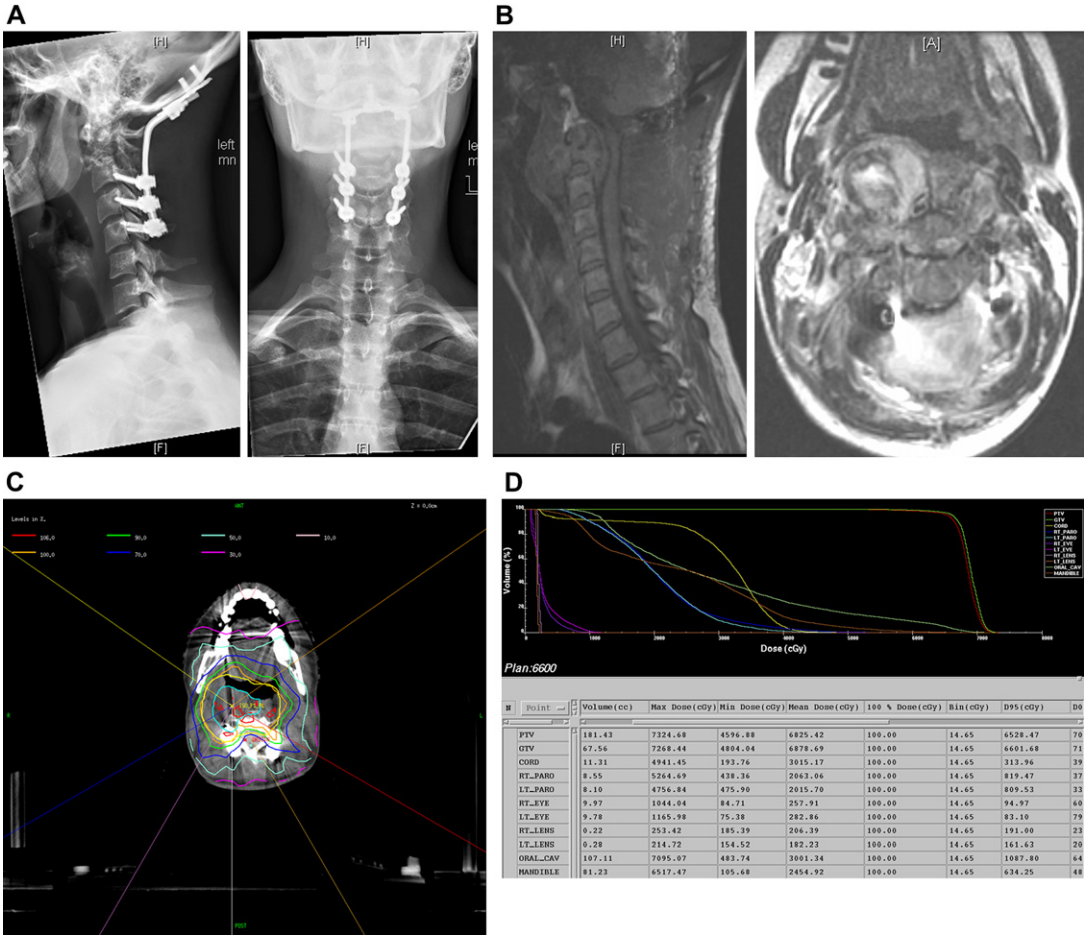
Brachytherapy

The proton beam experience suggests that treating the dural margin is problematic because of spinal cord tolerance. One solution is the use of brachytherapy to treat the dural margin. ^{125}Iodine has been used in the past [12,13], but it is difficult to achieve proper dosimetry adjacent to the spinal cord. Perhaps more interesting is the application of ^{90}Yttrium. This is a pure β-emitting isotope that delivers extremely high-dose radiation with limited penetrance, making it ideal for intraoperative treatment after epidural tumor resection. DeLaney and colleagues [14] reported on eight cases using ^{90}Yttrium plaques, seven of which were sarcomas. Six tumors were controlled for a median of 24 months. The utility of ^{90}Yttrium may be as an adjuvant to high-dose external beam radiation by improving the coverage at the spinal cord margin. ^{90}Yttrium recently received US Food and Drug Administration (FDA) approval for intraoperative application and is commercially available.

High-dose conformal photon therapy

Experience with high-dose image-guided photon therapy is relatively limited because of the novelty of this technology. IGRT-capable platforms are able to deliver high precision radiotherapy in standard fractions (120–200 cGy per fraction), hypofractionated (eg, 500–600 cGy per fraction), or as single-fraction therapy (eg, 24 Gy). Before the development of IGRT technologies, the conformal delivery of photon therapy that could deliver a cytotoxic dose to the tumor while

sparing spinal cord tolerance was impossible without significant risks for radiation-induced myelopathy. The development of inverse treatment planning, noninvasive immobilization strategies, and targeted radiation delivery systems has made it possible to deliver standard fraction radiation in doses similar to or higher than proton beam radiation.



	Volume(cc)	Max Dose(cGy)	Min Dose(cGy)	Mean Dose(cGy)	100 % Dose(cGy)	Bin(cGy)	D95(cGy)	D0
PTV	181.43	7324.68	4596.88	6825.42	100.00	14.65	6528.47	70
GTV	67.56	7268.44	4804.04	6878.69	100.00	14.65	6601.68	71
CORD	11.31	4941.45	193.76	3015.17	100.00	14.65	313.96	39
RT_PARO	8.55	5264.69	438.36	2063.06	100.00	14.65	819.47	37
LT_PARO	8.10	4756.84	475.90	2015.70	100.00	14.65	809.53	33
RT_EYE	9.97	1044.04	84.71	257.91	100.00	14.65	94.97	60
LT_EYE	9.78	1165.98	75.38	282.86	100.00	14.65	83.10	79
RT_LENS	0.22	253.42	185.39	206.39	100.00	14.65	191.00	23
LT_LENS	0.28	214.72	154.52	182.23	100.00	14.65	161.63	20
ORAL_CAV	107.11	7095.07	483.74	3001.34	100.00	14.65	1087.80	64
MANDIBLE	81.23	6517.47	105.68	2454.92	100.00	14.65	634.25	48

Fig. 1. A 33-year-old woman, 27 weeks pregnant, with no precedent history tripped on an airplane tarmac. She had the acute onset of central cord syndrome with plegia of the upper extremities. MRI showed a tumor replacing the C2 body with high-grade spinal cord compression and a large parapharyngeal mass. (*A*) Patient was taken urgently to surgery for posterolateral decompression of the tumor and posterior occipital-to-C5 fixation. The patient had immediate return of neurologic function, with the exception of persistent paresthesias in the hands. Pathologic findings were consistent with leiomyosarcoma, estrogen receptor- and progesterone receptor-positive, and suspected uterine origin. (*B*) Postoperative sagittal and axial MRI scans show sufficient epidural decompression to provide a safety margin for IGRT. Myelography/CT for IGRT planning confirmed the absence of spinal cord compression. The baby was delivered at 33 weeks of gestation without incident. Systemic workup after delivery showed lytic pelvic lesions and small lung metastases. A transmandibular approach was contemplated, but the decision was made to irradiate with high-dose conformal photons using standard fraction radiotherapy (66 Gy in 37 fractions). (*C*) Dose distribution through the isocenter of a large leiomyosarcoma (67.5 cc) involved C2 to C5 with a significant paraspinal component. A total of seven beams of 6-MV photons were used around a single isocenter to deliver the prescribed dose of 66 Gy given to the 100% isodose line. The combination of intensity-modulated radiotherapy and near-real-time image-guided techniques allowed a relatively high dose of radiation to the tumor while maintaining less than 50 Gy to the spinal cord. (*D*) Dose volume histogram of the treatment. Excellent coverage of the gross tumor volume (GTV; *blue outline*) and planning target volume (PTV; *yellow outline*) was achieved while sparing nearby surrounding dose-sensitive structures, such as the spinal cord (maximum dose of 49.4 Gy) and parotid glands (mean dose <21 Gy).

At Memorial Sloan-Kettering Cancer Center, seven chordomas and five chondrosarcomas have been treated with standard fraction radiation at a median dose of 66 Gy (Fig. 1) [15]. At a median follow-up of 18 months, one failure occurred in each of the histologic groups. The histology of the chondrosarcoma failure was high grade. No patient experienced radiculopathy or myelopathy. Although follow-up is short, the dose delivery and results seem to be similar to those reported in the proton beam literature.

Recently, radiation oncologists and spine surgeons have begun to explore the role of stereotactic radiation for primary spine tumors. In theory, single-fraction therapy may improve local control by increasing the biologic effective dose (BED). Tumors, such as sarcomas, which typically have low α/β ratios, are more likely to respond favorably to higher doses per fraction. Theoretically, doses greater than 15 Gy per fraction induce cellular apoptosis by stimulating the sphingomyelinase pathway [16]. Additional microvascular changes contribute to cell death. A high radiation dose per fraction increases the BED; thus, higher doses per fraction are a method of dose escalation. A patient who receives 76 Gy at 2 Gy per fraction by means of proton beam radiation or IGRT would have a calculated BED of 152 Gy. Conversely, 24 Gy delivered in a single fraction provides a BED of approximately double that achieved in the fractionated schedule. Image-guided treatment technologies have allowed the safe delivery of high BED treatment to tumors with relative sparing of surrounding and nearby normal structures.

Currently, the authors are using stereotactic radiosurgery (SRS) only as neoadjuvant therapy before resection of chordomas. Recent review of a case, which underwent neoadjuvant radiation at a dose of 24 Gy, showed significant tumor necrosis with minimal residual islands of tumor. Particularly in cases in which gross total resection is feasible, neoadjuvant radiation may add a measure of control that allows intralesional resection for neurologic preservation and reduces the morbidity of surgery. The combination of neoadjuvant SRS, intraoperative brachytherapy using ^{90}Yttrium, and postoperative standard fraction therapy may ultimately improve local tumor control for these difficult primary tumors.

Summary

Malignant primary tumors of the spine present difficult management problems because of the complexities of en bloc resection and their chemoresistance and radioresistance. En bloc resection to achieve a marginal or wide resection is feasible in a limited number of malignant primary tumors. The utility of chemotherapy has been limited with the exception of osteogenic sarcoma, in which neoadjuvant chemotherapy and resection have had a major impact on cure. Tyrosine kinase inhibitors may hold some promise in the treatment of chordomas.

Radiation therapy at conventional doses has shown limited success in controlling malignant primary tumors. The primary limitation to delivering cytotoxic doses has been spinal cord and other adjacent structure tolerance. Advanced radiation techniques, such as proton beam radiation, brachytherapy, and high-dose conformal photon therapy, have provided the means of treating cytotoxic doses of the tumor. Conformal photon therapy has the advantage of being able to deliver SRS, which may provide a treatment advantage over conventional dose radiation by increasing the BED. A combination of these radiation techniques and advances in systemic therapy may ultimately provide improved local tumor control and cure for these treatment-resistant tumors.

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References

[1] Boriani S, Bandiera S, Biagini R, et al. Chordoma of the mobile spine: fifty years of experience. Spine 2006;31(4):493–503.

[2] Tomita K, Kawahara N, Baba H, et al. Total en bloc spondylectomy. A new surgical technique for primary malignant vertebral tumors. Spine 1997; 22(3):324–33.

[3] Yao KC, Boriani S, Gokaslan ZL, et al. En bloc spondylectomy for spinal metastases: a review of techniques. Neurosurg Focus 2003;15(5):E6.

[4] Boriani S, Weinstein JN, Biagini R. Primary bone tumors of the spine. Terminology and surgical staging. Spine 1997;22(9):1036–44.

[5] Bilsky MH, Boland PJ, Panageas KS, et al. Intralesional resection of primary and metastatic sarcoma involving the spine: outcome analysis of 59 patients. Neurosurgery 2001;49(6):1277–86 [discussion: 1286–7].

[6] Meyers PA, Schwartz CL, Krailo M, et al. Osteosarcoma: a randomized, prospective trial of the

addition of ifosfamide and/or muramyl tripeptide to cisplatin, doxorubicin, and high-dose methotrexate. J Clin Oncol 2005;23(9):2004–11.

[7] Casali PG, Messina A, Stacchiotti S, et al. Imatinib mesylate in chordoma. Cancer 2004;101(9):2086–97.

[8] Pisters PW, Leung DH, Woodruff J, et al. Analysis of prognostic factors in 1,041 patients with localized soft tissue sarcomas of the extremities. J Clin Oncol 1996;14(5):1679–89.

[9] Tanabe KK, Pollock RE, Ellis LM, et al. Influence of surgical margins on outcome in patients with preoperatively irradiated extremity soft tissue sarcomas. Cancer 1994;73(6):1652–9.

[10] Hug EB. Review of skull base chordomas: prognostic factors and long-term results of proton-beam radiotherapy. Neurosurg Focus 2001;10(3):E11.

[11] Austin JP, Urie MM, Cardenosa G, et al. Probable causes of recurrence in patients with chordoma and chondrosarcoma of the base of skull and cervical spine. Int J Radiat Oncol Biol Phys 1993;25(3): 439–44.

[12] Cheng EY, Ozerdemoglu RA, Transfeldt EE, et al. Lumbosacral chordoma. Prognostic factors and treatment. Spine 1999;24(16):1639–45.

[13] Rogers CL, Theodore N, Dickman CA, et al. Surgery and permanent 125I seed paraspinal brachytherapy for malignant tumors with spinal cord compression. Int J Radiat Oncol Biol Phys 2002; 54(2):505–13.

[14] DeLaney TF, Chen GT, Mauceri TC, et al. Intraoperative dural irradiation by customized 192iridium and 90yttrium brachytherapy plaques. Int J Radiat Oncol Biol Phys 2003;57(1):239–45.

[15] Yamada Y, Lovelock DM, Yenice KM, et al. Multifractionated image-guided and stereotactic intensity-modulated radiotherapy of paraspinal tumors: a preliminary report. Int J Radiat Oncol Biol Phys 2005;62(1):53–61.

[16] Garcia-Barros M, Paris F, Cordon-Cardo C, et al. Tumor response to radiotherapy regulated by endothelial cell apoptosis. Science 2003;300(5622): 1155–9.