Spinal Chordomas: Current Medical and Surgical Management

Alp Yurter, Daniel M. Sciubba, Ziya L. Gokaslan and Paul E. Kaloostian*
Johns Hopkins University Medical Center, USA

EDITORIAL

Chordomas are rare, benign tumors that account for 1-4% of bony lesions and most frequently occur in the skull base, mobile spine, and sacrum. Historically, they have been most effectively managed with en bloc surgical resection, as they are resistant to conventional radiotherapy and chemotherapy. Currently, the gold standard treatment for spinal chordomas is en bloc excision with negative margins followed by postoperative external-beam radiation therapy. However, with recent technological advances in radiation delivery and the discovery of potential targeting sites, the role of both radiation therapy and chemotherapy is gaining prominence [1].

SURGICAL MANAGEMENT

En bloc total and high sacrectomies have been traditionally performed using a combined anterior-posterior approach. Unfortunately, the anterior part of the operation requires a separate procedure, abdominal incision, and access surgeon. Further, devascularizing surrounding tissue by tying off the iliac vessels increases the risk of wound complications. To circumvent these issues, Clarke et al. recently described the largest series of sacral chordoma patients from Johns Hopkins treated with the posterior-only approach and biomechanical reconstruction, which included high and total procedures. Out of the 36 total patients, 30 chordoma patients were treated, 20% of which developed recurrence or distant metastases at a median time of 23.3 months post-operatively. The overall complication rate was 36%, and amputation was maintained in 95% of patients. The authors concluded that a posterior-only approach can be safely performed in those that do not have tumors extending beyond the lumbosacral junction or invade the bowel, which would require bowel resection and diversion. Because no significant morbidity was encountered with this technique, further investigation was suggested [2].

Osaka et al. recently reported the long-term outcomes of 16 sacral chordoma patients treated with primary wide excision (15 patients) and intralesional excision using ethanol for local control and radiation therapy (1 patient). Both anterior-posterior and posterior-only approaches were employed and the modified thread-wire (MT) saw was used for resection. Those with wide surgical margins had a 5-year survival rate of 81% and a 10-year survival rate of 62%, results which are superior to those reported in previous studies investigating radical sacrectomy using the MT saw. Of these patients, 69% were alive 5-28 years postoperatively. Local recurrence and major complications occurred in 4 out of 11 patients with tumor ≥10cm, but none in the 5 patients with tumors <10cm. Long-term local recurrence rate and metastases rate were 29% and 21%, respectively. Notably, patients who did not develop local recurrence within 10 years post-op were extremely unlikely to develop it in the future, and experienced long-term survival. The authors suggested an anterior-posterior approach for large tumors (≥10cm). Wide excisions were especially recommended for younger patients [3].

RADIATION THERAPY

Radiotherapy alone has long been recognized as ineffective means to treat chordomas; however, recent technological advances that allow for large radiation doses are beginning to change this sentiment [1]. Namely, radiation treatment via hadrons, high-dose protons or other charged particles (e.g. carbon ions, helium, or neon), has allowed for the local delivery of high doses while sparing nearby delicate neural structures. Relative to photon therapy, hadron therapy has demonstrated higher biological effectiveness and a smaller oxygen-enhancement ratio in the tumor area [1]. Moreover, carbon ion beams are superior to proton beams, as they are able to deliver a greater energy per unit length of their trajectory to the targeted tissues [4].

In 2006, Park et al. [5] reported a high rate of control for the primary sacral tumor cohort treated with en bloc surgery followed by photon and/or proton-beam therapy, relative to the local recurrence cohort. Dosage ranged from 59.4-77.4 GyE. In the former group, 5-year and 10-year local control, progression free survival, and overall survival rates were reported to be 91%, 91%, and 93%. On the other hand, in the recurrent group, the 5-year local control, progression free survival, and overall survival rates were reported to be 57%, 43%, and 68%; the 10-year rates were 19%, 14%, and 44%, respectively. More recently, Chen et al. [6] treated 24 inoperable patients with sacral or mobile spine chordomas using only definitive high-dose photon/proton-beam
therapy. Cumulative median radiation dose was 77.4 GyRBE. Five-year post-op overall survival, local control, and metastases-free rates were 78%, 80%, and 76%, respectively. Notably, local control rates compared favorably to other radiation and surgical series, especially in light of the limited late sequelae.

In 2010, Imai et al. [4] reported the results of phase I-II and phase II clinical trials investigating carbon ion radiotherapy for unresectable sacral chordomas in 38 patients. A median dose 70.4 GyE over 16 fractions was applied. The 5-year overall survival, local control, and progression-free survival rates were 86, 89%, and 54%, respectively. Moreover, 27 of 30 patients with primary chordoma maintained ambulation with or without assistance.

In 2013, Mima et al. [7] investigated the use of proton or carbon ion radiotherapy (70.4 GyE) in 23 patients with primary sacral chordoma. The follow-up period was limited; at 3-years post-op, overall survival, local control, and progression-free survival was 83%, 94%, and 68%. Of note, the authors determined that the 32-fraction protocol was associated with reduced severe toxicities in both the acute and late phases compared to the 16-fraction protocol.

Stereotactic radiosurgery (SRS) is another mode of radiotherapy that has been adapted for chordoma treatment. Recently, Yamada et al. [8] applied high-dose single-fraction SRS (median dose: 24Gy) to 24 patients (21 primary, 3 metastatic) of the sacrum and mobile spine; in 7 patients, SRS was delivered as planned adjuvant therapy, and in 13 patients, SRS was administered as neoadjuvant therapy. At a median follow-up of 24 months, 95% demonstrated stable or reduced tumor burden, though 6 of 13 patients who underwent neoadjuvant SRS opted for surgery based on lack of radiographic progression. Extended follow-up is necessary to determine long-term recurrence risk; however, this SRS treatment achieved good control with low therapy-related morbidity.

CHEMOTHERAPY

Chemotherapy is another treatment modality in which advances have been made within the past decade. The effectiveness of chemotherapy has been largely been reported using aneodical responses to anthracyclines, cisplatin, and alkylating agents, as well as targeted therapies including as cetuximab, gefitinib, thalidomide, erlotinib [1,9,10]. However, recent phase II studies for imatinib, sunitinib, campothecin, cetuximab, gefitinib, thalidomide, erlotinib [1,9,10]. However, the importance of the NF-kB pathway in the growth of chordomas is involved in notochord development. In fact, 90% of confirmed chordomas positively express the Brachyury gene, making it a promising target [9]. Subsequently, Hsu et al. [11] silenced the Brachyury gene using short hairpin RNA in a xenograft model growing the JHC7 cell line. Notably, the authors found that the morphology of chordoma cells changed to a more differentiated-like state and exhibited complete growth arrest and senescence.

In 2013, Chen et al. [12] identified a 70% prevalence of Survivin positivity in 30 patients with sacral chordoma. Survivin, a protein that inhibits apoptosis and promotes tumor angiogenesis was thus suggested to be a potential biotarget for chordoma therapies. In the same year, Trucco et al. [13] highlighted the importance of the NF-kB pathway in the growth of chordomas after observing tumor growth-inhibiting effects of hertzomibin in a xenograft model.

FUTURE DIRECTIONS

Chordoma treatment will likely evolve to be increasingly multidisciplinary and aggressive, especially as radiotherapies and chemotherapies advance. Postoperative outcomes of chordoma excision followed by proton-beam therapy have already been investigated, with promising 5-year progression free and overall survival rates [14]. However, while hadron-based radiotherapies offer a less invasive alternative to surgery, and are particularly suited for unresectable chordomas, the technology is currently too costly to be widely used [1]. In the future, the roles of hadron therapy and SRS will become more apparent. Additionally, more effective chemotherapies will be identified, especially as a result of the recent establishment of chordoma cell lines, such as U-CH1, U-CH2, BCH8, CCL-3, CH22, MUG-Chor1, and JHC7 [9,11,13]. These cell lines will also elucidate the effects of the numerous chromosomal mutations that have been linked to chordoma development [9,15]. Pharmaceuticals that act on highly prevalent targets, such as the Brachyury gene, will most likely yield the most promising results.

CONFLICT OF INTEREST

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