Editorial Commentary

Treatment of chordoma—where is it going?

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Chordomas are rare, slow-growing primary malignant tumors of the bone in which the cell of origin is derived from primitive notochordal tissues. The incidence of chordomas is estimated to be approximately 1 per 1,000,000 people (1), and they predominantly occur at the ends of the vertebral column, with approximately half of the cases occurring in the sacral region and 10% presenting in vertebral bodies. Sacral chordomas are often diagnosed late because they present with neither any significant early symptoms nor external findings. Therefore, at initial presentation, they are often detected to be quite large and at an advanced stage. In addition, chordomas are prone to recurrence and are associated with a poor prognosis.

Generally, chordomas are very soft tumors. If the tumor is cut or violated during resection, the surgical field is contaminated by the tumor, and thus, recurrence frequently occurs. Conventionally, chordomas are considered tumors with low radiation sensitivity; therefore, some surgeons prefer to not administer local radiation before or after surgery. According to Baratti *et al.* (2), the 5- and 10-year survival rates of chordoma patients are 87.8% and 48.9%, respectively. Moreover, 17 of 28 cases in this study experienced relapse. The disease-free survival rates were 60.0% and 24.2% at 5 and 10 years, respectively. These results suggest that following diagnosis and treatment, long-term follow-up is necessary for chordomas.

Sacral chordomas are one of the commonest sarcomas that are examined by orthopedic tumor surgeons. Many articles describing the treatment of chordomas have been reviewed to better understand and improve treatment outcomes for this tumor type (3-7). However, because of the structural complexity of the sacrum and its surrounding anatomy, it is often impossible to achieve an adequate resection of the tumor margin. Therefore, a multidisciplinary team comprising other subspecialty surgeons is usually required to provide comprehensive treatment. Extensive soft tissue resection accompanied by posterior muscle resection often causes problems with wound healing and postoperative infections. High-level sacral amputation with root sacrifice may result in impaired urination and defecation and significantly affects a patient's quality of life.

This unique and invaluable study assessed treatment outcomes of 101 sacral chordoma patients at a single referral center who were treated by orthopedic tumor surgeons over a 35-year period. The results of this study offered the reader an opportunity to evaluate and assess treatment strategies at a referral center where surgical resection was performed by experienced orthopedic tumor surgeons and subspecialists in addition to administering adjuvant radiotherapy. Of particular importance was the comparison of treatment results at a single referral center (before and after January 2000) between a tumor group that was surgically treated and received a conventional radiation dose (mean 50 Gy) and a group that was surgically treated and received a higher radiation dose (mean 70 Gy). In that study, the authors compared their clinical results and concluded that the "*Combination of surgical resection and adjuvant radiotherapy allowed us to obtain good overall survival (OS), local relapse-free survival, and distant relapse-free survival*

in patients presenting with either a primary tumor or an initial local recurrence. The use of adjuvant radiotherapy appears to have a positive effect on OS and distant metastases and should be considered as an adjuvant treatment".

The above conclusion, however, should be carefully analyzed and interpreted. The authors reported that regarding the clinical results of primary tumors treated at this single referral center, "*Multivariate analysis confirmed the above results of tumor size being the only independent predictor for worse OS*", "*Multivariate analysis confirmed that not receiving radiation was an independent predictor for worse L-RFS*", and "*Multivariate analysis confirmed the above results of tumor size being the only independent predictor for worse D-RFS*". The authors also reported that "*On bivariate analysis, there were no significant differences according to age, tumor size, time period of treatment, surgical margin, and use of radiation in OS*"; "*There were no significant differences according to patient age, time period of treatment, surgical margin, and the use of radiation in L-RFS*"; and "*On bivariate analysis, there were no significant differences according to age, tumor size, time period of treatment, surgical margin, and use of radiation in D-RFS and in the clinical results of recurrent tumors treated at a single referral center*". Additionally, the authors concluded that a high-dose radiation was meaningful only to improve the local control rate at the time of the first surgery compared to overall surgical outcomes with a traditional radiation dose (mean 50 Gy) and surgical outcomes with a high radiation dose (mean 70 Gy). These results can be summarized as follows: (I) treatment of chordomas at a specialized center has a favorable effect on prognosis, (II) treatment at a specialized center and adjuvant local high-dose radiation do not alter a patient's prognosis, and (III) adjuvant radiotherapy is only effective for reducing the local recurrence rate at the time of the first surgery.

In this paper, the authors reported complications in the high-dose radiation group treated after 2000. They also report that of the complications in the group with recurrent tumors, "*50% had deep infection, of whom 90% needed a surgical intervention. In the bivariate analysis, the use of neo- and/or adjuvant radiotherapy was predictive of a higher chance of infection*". This finding is likely reflective of a significant side effect of high-dose radiation performed at the time of the first surgery.

The authors also mentioned that "*In theory, all recurrent tumors left tumor cells behind at the initial surgery, even if the initial pathology report stated that negative margins were obtained. For example, in this study, three primary tumors were resected, and negative margins were obtained and did eventually recur. This raises a question about the value of negative margins as reported by the pathologist and undermines the idea of using adjuvant radiotherapy only when tumor margins are positive*". Thus, this finding may imply the necessity of using radiation in all cases. However, because of the high rate of infection in cases of recurrent tumors, it may be better to carefully reconsider using radiation, especially in cases where surgical reconstruction using implants and/or hardware has been performed in high-level sacral amputations with negative margins.

As the authors mentioned, during this 35-year period, surgical, radiation, and imaging modalities and techniques have advanced, and treatment philosophies have dramatically evolved. A recent study of unresectable sacral chordomas using only carbon-ion radiotherapy revealed promising results (5-year local control and OS of 77.2% and 81.1%, respectively) (8). In Japan, after the approval of the insurance application of carbon-ion radiotherapy for unresectable chordomas, the number of surgeries for sacral chordomas declined.

Thus far, defining and describing "unresectable chordomas" have been very difficult possibly because of the surgical culture in each country, concept of "quality of life", changing social values and expectations, and evolving definition over time as treatment modalities/techniques advance. It is certainly crucial for orthopedic tumor surgeons to provide current and standard treatment that considers the patient's preferences and quality of life and satisfies their expectations.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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