Metastatic disease from spinal chordoma: a 10-year experience

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Object. Metastastic lesions have been reported in 5 to 40% of patients with spinal and sacrococcygeal chordoma, but few contemporary series of chordoma metastatic disease exist in the literature. Additionally, the outcome in patients with chordoma-induced metastatic neoplasms remains unclear. The authors performed a retrospective review of the neurosurgery database at the University of Texas M. D. Anderson Cancer Center in Houston to determine the incidence of metastatic disease in a contemporary series of spinal and sacrococcygeal chordoma as well as to determine the outcomes.

Methods. Thirty-seven patients underwent surgery for spinal and sacrococcygeal chordoma between June 1, 1993, and March 31, 2004. All records were reviewed, and appropriate statistical analyses were used to compare patient data for preoperative characteristics, treatments, and outcomes.

The authors identified seven patients (19%) in whom metastatic disease developed; in three the disease had metastasized to the lungs only, in two to the lungs and liver, and in two to distant locations in the spine. There were no significant differences in age, sex, tumor location, or history of radiation treatments between patients with and those without metastases. In cases with local recurrent tumors, metastatic disease was more likely to develop than in those without recurrence (28 compared with 0%, respectively; p = 0.07). In two (12%) of 17 patients who underwent en bloc resection, metastatic disease developed, whereas it developed in five (25%) of 20 patients treated by curettage (p = 0.42). The median time from first surgery to the appearance of metastatic disease, as calculated using the Kaplan–Meier method, was 143.4 months (95% confidence interval [CI] 66.8–219.9). The median survival duration of patients with metastatic disease after the first surgery was 106 months (95% CI 55.7–155.7), and this did not differ significantly from that in patients in whom no metastases developed (p = 0.93).

Conclusions. Spinal chordoma metastasized to other locations in 19% of the patients in this series. In patients with local disease recurrence, metastatic lesions are more likely to develop. Metastatic lesions were shown to be aggressive in some cases. Surgery and chemotherapy can play a role in controlling metastatic disease.

KEY WORDS • chordoma • metastasis • spine tumor • en bloc resection • vertebrectomy

Chordomas are uncommon, slow-growing but locally aggressive and malignant neoplasms that account for 1 to 4% of all malignant bone tumors. Because of the neoplasm’s origin in the embryonic notochord, most chordomas occur in the midline of the body, involving the clivus (50%), the sacrum (35%), and the remainder of the spine (15%). Although the chordoma is a relatively slow-growing tumor, it is associated with a high incidence of local recurrence and with a poor long-term prognosis. Thus, treatment recommendations for chordoma typically involve radical resection and subsequent radiotherapy. Despite the provision of radical treatment, local recurrences ultimately develop in most patients and require additional treatment.

In general, chordoma has been considered primarily a local disease, although the authors of previously published reports have noted that the incidence of metastasis has ranged from 5 to 40%. Chordoma-induced metastatic lesions have been noted in the liver, lungs, lymph nodes, peritoneum, skin, heart, brain, and distant regions of the spine. Importantly, the largest series involving metastatic chordoma were all published prior to the advent of magnetic resonance imaging, and the diagnoses in many were based on postmortem examination. Additionally, in many of the cases involving metastatic lesions documented in the literature, asymptomatic lesions or lesions that were found only on postmortem examination were also present, leading the investigators to conclude that metastatic lesions from chordoma could be considered indolent in the majority of cases.

To improve the understanding of metastatic chordoma
as a disease entity, we reviewed the incidence of metastatic lesions in a contemporary series of patients with chordomas who were treated at a major cancer center, and we investigated which factors played a role in the development of metastatic lesions. We also sought to determine the clinical outcomes of patients in whom metastatic neoplasms developed. In the present study, we detail our 10-year experience in the surgical treatment of 37 patients with spinal and sacrococcygeal chordomas and focus our attention on cases in which metastatic disease developed.

Clinical Material and Methods

The prospectively collected database of the Department of Neurosurgery at the University of Texas M. D. Anderson Cancer Center was reviewed, and all patients who underwent surgical treatment of spinal and sacrococcygeal chordomas between June 1, 1993, and March 31, 2004, were included. Patient characteristics were recorded, and charts and imaging studies were then reviewed to identify cases in which there was evidence of metastatic disease. Treatments for metastatic disease were then recorded. Follow-up data including any imaging studies were reviewed and documented.

Frequencies and descriptive statistics were obtained. The chi-square or Fisher exact test was used, as appropriate, with categorical variables. The Kaplan–Meier survival and Cox proportional hazards analyses with time-dependent covariates were performed.

This study was approved by the institutional review board of the University of Texas M. D. Anderson Cancer Center, and we followed the practices and recommendations of the Health Insurance Portability and Accountability Act.

Results

Patient Population

During the period of study, 37 patients with spinal or sacrococcygeal chordomas underwent surgical treatment at the M. D. Anderson Cancer Center. There were 24 men and 13 women whose median age was 59 years (range 24–86 years). The majority of primary tumors were located in the sacrum (23 [62%] of 37); thereafter, they were documented in the cervical spine (nine [24%] of 37) and in the lumbar region (five [14%] of 37).

Surgical Treatment and Radiotherapy

All patients initially underwent resection; en bloc resection was performed in 17 patients (46%), whereas intraleisional resection was undertaken in 20 (54%). Local tumor recurrence developed in 25 patients (68%). In the majority of cases (15 [60%] of 25), the local recurrent tumors were extirpated and the tumor bed was thereafter irradiated. In the remaining cases (six [24%] of 25) the patients underwent surgery alone, radiotherapy alone (two [8%] of 25), or no additional treatment (two [8%] of 25). In total, 21 patients (57%) required additional surgical procedures for local recurrent tumors.

Overall 17 patients (46%) received radiotherapy, either as adjuvant postoperative treatment or as treatment for local recurrent tumor; in two of these patients, this involved the administration of proton-beam radiotherapy. Two patients also underwent a second course of radiation therapy after local recurrent disease was noted.

Patients With Metastatic Lesions

Overall, metastatic lesions developed in seven (19%) of 37 patients (Table 1): in the lung in three (42%), lung and liver in two (29%), and distant spine in two (29%). The characteristics in the group of patients with metastatic disease did not differ significantly from those in the group without metastatic disease in terms of age, sex, location of primary tumor, or history of radiation treatment. In patients with local recurrent tumor, metastatic disease was more likely to develop (28% of patients) than in those without local tumor recurrence (0%), although this did not reach statistical significance (p = 0.07). Additionally in patients who initially underwent intraleisonal resection, metastatic disease was more likely to develop than in those treated initially with en bloc resection (25 and 12%, respectively), although the difference was not statistically significant either (p = 0.42).

Distant metastatic neoplasms occurred late in the disease course (median time from first surgery to metastatic disease 143.4 months [95% CI 66.8–219.9, Kaplan–Meier

<table>
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<th>Case No.</th>
<th>Age (yrs), Sex</th>
<th>Spinal Location</th>
<th>Treatment</th>
<th>Local Recurrence</th>
<th>Since 1st Op (mos)</th>
<th>Location</th>
<th>Treatment</th>
<th>Current Status</th>
<th>Survival (mos)†</th>
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*EBR = en bloc resection; PBRT = proton-beam radiotherapy; RT = radiotherapy.
†Duration since initial surgery.
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method]) and occurred following, but not preceding, local recurrence in all cases. In patients with metastatic disease, the median survival time after first surgery was 106 months (95% CI 55.7–155.7), and this did not differ significantly from the survival in patients without metastatic disease \( (p = 0.93) \). The Kaplan–Meier estimate of median survival duration from the time of diagnosis of metastases was 7.6 months (95% CI 0.01–30.4).

Three of the patients with metastatic disease remained alive at the last review. All three patients had systemic metastatic lesions: two had lung metastases and one had liver and lung metastases. Two of the patients underwent chemotherapy: gemcitabine-based chemotherapy and regresion of metastatic disease in one, and Gleevec-based che-rnotherapy and stabilization of metastatic disease in the other. The third surviving patient underwent resection of a lung metastatic lesion and has stable disease since that treatment.

The remaining four patients are dead. In two patients the cause of death was progression of systemic metastatic disease. The lesion had metastasized to the lung in one of these patients and to the lungs and liver in the other patient. In both of these patients the disease was considered too extensive for systemic treatment. In the other two patients the lesions had metastasized to distant regions of the spine and were treated with resection. Both patients were lost to follow up and the cause of death in each was unclear.

Discussion

This is the most modern series to date in which the issue of metastatic spinal chordoma has been examined. It represents a relatively large number of patients with spinal and sacral chordomas—37 cases accrued during a 10-year period at a major cancer center. The majority of series involving patients with metastatic disease from spinal chordoma were published before the introduction of magnetic resonance imaging.\(^5\)^\(^8\)\(^–\)\(^10\)\(^12\) Additionally, many of the diagnoses in the past have been established based on autopsy-derived data. In this contemporary series, the incidence of metastatic disease was 19%. This finding was consistent with the range of incidences of metastatic disease reported in prior studies\(^5\)\(^8\)\(^–\)\(^10\)\(^12\) and is also consistent with the findings of one recent study in which the authors examined the natural history of 28 patients with chordomas treated at a single institution during a 23-year period; the authors reported finding distant metastatic lesions in six patients (21%).\(^2\) The authors of previous reports have also shown metastatic neoplasms from chordomas to develop in multiple locations, including the liver, lungs, lymph nodes, peritoneum, skin, heart, brain, and distant regions of the spine.\(^2\)\(^5\)\(^6\)\(^8\)\(^–\)\(^10\)\(^12\) In the present study, metastatic lesions were also found systemically in the lungs and liver, as well as in distant regions of the spine.

Data in the two groups of patients, those with metastatic disease and those without, were first compared to determine if any historical characteristics—such as age, sex, location of primary tumor, type of resection (that is, en bloc resection or intralesional resection), or use of adjuvant radiotherapy—was predictive of the development of metastatic disease. Statistical analysis revealed no differences between these two groups in terms of age, sex, and location of primary tumor. Additionally, the use of adjuvant radiotherapy to treat the patient’s primary tumor played no significant role in preventing metastatic disease. Local tumor recurrence was the only factor that approached statistical significance in predicting the development of metastatic disease. In none of the patients with stable local disease did metastatic disease develop, whereas in 28% of those with local recurrence metastatic disease occurred. This difference approached but did not reach statistical significance, likely because of the small sample size.

Control of local disease in cases of spinal chordoma has been best accomplished using radical resection.\(^4\)\(^15\) In a series of 21 spinal chordomas above the sacrum, en bloc excision produced better results in terms of disease-free interval than intralesional resection.\(^4\) In a study of sacral chordomas in which the patients were treated at M. D. Anderson during a 40-year period, patients in whom a radical resection was performed had a disease-free interval of 2.27 years compared with 8 months in patients who underwent subtotal excision.\(^3\) In the present series, the risk of developing metastatic disease was 12% in patients who underwent en bloc resection of the chordoma whereas the same risk was 25% in patients treated initially with intralesional resection; thus, the risk was increased twofold in cases in which intralesional excision was performed. Of note, this finding could not be supported by statistical analysis, although again this is likely due to small sample power. The absence of statistical support could also relate to the time of follow up in that en bloc resection is a more contemporary treatment strategy, and therefore the follow-up duration may not have been long enough to account for the development of metastases in this group. In comparing the follow-up durations between the two groups of patients with metastases, however, there was no significant difference in duration (intralesional group, 83.3 months; en bloc group, 77.9 months; \( p = 0.86 \)). Therefore, we believe that two findings underscore the superiority of initial radical resection in reducing the risk of metastatic disease: 1) the reduced risk of developing metastatic lesions in patients who underwent en bloc resection of the primary chordoma; and 2) the aforementioned association between the development of metastatic disease and local recurrent lesions.

The authors of previous studies involving chordoma-related metastatic disease have found that many of the lesions were asymptomatic or found during postmortem examination and thus suggested that metastases from chordoma could be considered indolent in the majority of cases.\(^3\)\(^9\) In at least two of the patients in the present series, however, this was not the case. Two patients presented with extensive disease metastatic from chordoma and ultimately died of their disease. Because of their initial disease burden, in both cases the treating oncologist recommended no systemic treatment. This suggests that in some cases an aggressive disease pattern exists for spinal chordoma–induced metastatic disease. In contrast, three other patients presented with limited metastatic disease to the lungs and liver, and their disease was controlled, either by surgical or chemotherapeutic intervention. The number of cases in this series is too small to determine whether these patients would have had stable disease even in the absence of treatment, but it does suggest that in some patients with
metastatic disease from spinal and sacrococcygeal chordomas, aggressive treatment of metastatic lesions can play a role in stabilizing the disease.

Histologically, there have been few reliable features by which to predict the local aggressiveness of chordoma. Mitoses and anaplasia can be present in chordomas without adversely affecting the duration of a patient’s survival. Heffelfinger and colleagues first described the “chondroid chordoma” variant as a group of tumors in which there were foci of chordoma amid a large cartilaginous matrix. This variant has been reported to exhibit less malignant potential and to be associated with better patient survival. In our study, histopathological analysis showed that one (14%) of the seven patients in whom metastatic disease developed had a chondroid chordoma and that four (13%) of 30 patients without metastatic disease had the chondroid chordoma variant. Therefore, in this study the presence of a chondroid chordoma variant did not suggest a more benign prognosis in terms of the potential for developing metastatic disease. Additionally, dedifferentiation was documented in tumor specimens obtained in three patients, in none of whom did metastatic disease later develop. Analysis with the monoclonal antibody MIB-1 was not conducted in the majority of cases. Furthermore, the results of pathological analyses of the metastatic tumors did not show any changes from the primary tumors. Therefore, no correlation can be made in this series between histopathological findings of chordoma and the risk of developing a subsequent metastasis.

As seen in this study, the biological behavior of chordoma, both at local and distant sites, differs from patient to patient; some patients, for example, harbor tumors capable of aggressive behavior both locally and distantly and others have tumors that behave more indolently. Whether histologically or epidemiologically, there remains no good method to predict the behavior of individual chordomas, and we must rely on aggressive surgical and local adjuvant therapies in all cases to prevent the development of recurrent lesions and metastatic neoplasms. Future laboratory investigation into the nature of the biology of chordoma could help to identify markers to predict which tumors will behave more aggressively and even help to direct therapies toward discovering those tumors that are more aggressive.

Conclusions

In a contemporary series of 37 patients with spinal and sacral chordomas treated during a 10-year period at a major cancer center, the incidence of metastatic disease was 19%. The single factor predictive of metastatic disease was a local recurrence, which occurred prior to the development of metastatic disease in all patients. As demonstrated in prior studies, radical resection is the best means of controlling local disease, and in this study radical resection was also shown to be beneficial by decreasing the incidence of metastatic disease by 50%—a clinically, although not statistically, significant finding. The results obtained in this series also demonstrated that chordoma-related metastatic lesions can be aggressive and that surgery and chemotherapy can play a role in controlling them.

As patients with spinal and sacral chordomas live longer as a result of more aggressive surgical and adjuvant treatments, the problem of metastatic disease will become one that neurosurgeons and oncologists will have to face with increasing frequency. The problem of metastatic disease from chordoma should not be ignored or forgotten, and patients should be monitored and treated appropriately with either surgery or chemotherapy.

References


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