Section 10: Neurological Malignancies

54 Chordomas

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Introduction

Chordomas are rare, histologically benign, but clinically aggressive tumors of the axial skeleton first described in 1856 by both Virchow and Luschka.[1,2] The tumor discovered by Virchow was found within the clivus during a routine autopsy, prompting the theory that the tumor had arisen from cartilage. In 1858, Muller was the first to suggest that chordomas may originate from embryonic rests of the primitive notochord, the "chorda dorsalis."[3] The first description of a symptomatic chordoma was made in 1864 by Klebs, in a patient with a tumor of the sphenooccipital region.[4] In 1894, Ribbert was the first to use the term "chordoma" and further characterized Muller's theory by producing experimental chordomas after releasing tissue of notochordal origin from the nucleus pulposus of rabbits.[5,6] The tumors produced in these experiments were histologically similar to *de novo* chordomas. The experiments of Ribbert were replicated by Congdon in 1952 using a similar rabbit model.[7]

The modern theory of the origin of chordomas proposes that the tumors derive from embryonic rests of the primitive notochord that persist within the axial skeleton.[8–11] The notochord forms from ectodermal cells during the third or fourth week of development and is believed to act as an embryonic organizer.[12] During the fourth to sixth week of development, mesenchymal cells from adjacent sclerotomes envelop the notochord as they merge to form the spinal vertebral bodies.[8,12] The notochord degenerates during this process and by the seventh week remains only between the vertebral bodies as the nucleus pulposus of the intervertebral disks. Pathological studies of tissue using both light and electron microscopic techniques have demonstrated similarities between chordoma and human intervertebral disk.[8,12] It is postulated that incomplete degeneration of residual notochord may occur within the vertebral body at the junction of the adjacent sclerotomal regions. These incompletely degenerated rests can potentially undergo malignant transformation and develop into a chordoma. Investigations of the persistence and regression of the human notochord in fetuses of 4–18 weeks' gestation suggest that there is great variation in this process and that the presence of aberrant notochordal tissue is not uncommon.[13] Furthermore, the topographical distribution of these heterotopic notochordal rests corresponds closely to the common sites of chordoma in the adult (i.e. sacrococcygeal, clivus).[12,14] Autopsy studies reveal rests of presumed notochordal tissue anterior to the clivus and around the sacrum in up to 2% of cases.[10,11]

Finally, a shared immunophenotype is noted between notochordal and chordoma cells, with both types of cells containing S-100 protein, cytokeratins, and human epithelial polymorphic mucin.[14]

Tumor epidemiology

Chordomas are rare neoplasms, representing only 0.1–0.2% of all intracranial tumors, 6.15% of all primitive skull base tumors, and 1–4% of primary malignant bone tumors.[8–11,15] They can arise anywhere within the midline axial skeleton where the notochord existed (i.e. clivus, sellar and parasellar region, nasopharynx, foramen magnum, vertebrae, and sacrococcygeal region), but have a predilection for the sacrum and clivus. In adults, approximately 50% of chordomas arise in the sacrum, 35–40% within the base of skull and clivus, and 10–15% throughout the true vertebrae.[8–11,15–17] When chordomas affect the vertebral column, more than half will occur in the lumbar region, 25–30% in the cervical vertebrae, and 10–15% in the thoracic spine.[16] In children, chordomas most often involve the skull base.[18,19] On rare occasions, chordomas can arise in extraosseous or off-the-midline sites such as the transverse process of a vertebra, skin, paranasal sinuses, sella turcica, hypothalamus, or foramen magnum.[8–11,15,20–23]

Chordomas can occur at any age but are most common between the fourth and sixth decades of life.[8–11,15] Although these tumors can arise in children, less than 5% of all cases develop before 20 years of age.[18,19] There is a male predominance in some series, especially for tumors of the sacrum, with

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a ratio ranging from 2:1 to 3:1.[8–11,15] In other series, especially chordomas of the skull base, the male to female frequency is equal.[8]

Pathology

Chordomas are generally slow-growing, unencapsulated neoplasms that are locally invasive within bone and soft tissues.[8–11,24–26] A pseudocapsule may be noted around tumors that grow into soft tissues or the dura mater. As the tumors enlarge, they often stretch cranial nerves and displace structures such as blood vessels and the brainstem. Grossly, the tumors are usually reddish or purple in color, with a nodular appearance to the surface. Internally, the mass is frequently gelatinous and soft; regions that contain cartilage or calcium are firmer. Foci of hemorrhage may be present and can be small or extensive. The size of the lesion can be quite variable, with sacral tumors often becoming very large. In one series of cranial base chordomas, average tumor volume was 58 cm.[3,8]

On microscopic examination, chordomas can be grouped into several different histological categories, including a typical pattern, a chondroid pattern, and tumors with features of malignant degeneration.[8–11,24–30] The typical or classic pattern of chordoma (65–80% of all cases) is distinguished by a lobular arrangement, with the neoplastic cells disposed in solid sheets or irregular intersecting cords (Fig. 54.1). The sheets and cords of cells are set in a stroma that contains an abundant mucinous matrix. The individual cells are large, often with vacuolated eosinophilic cytoplasm, and contain variable amounts of mucin. The cell type considered diagnostic for chordomas is called physaliphorous (i.e. bubble-bearing). These cells are distinctively large and vacuolated, with eccentric nuclei (see Fig. 54.1). Nuclei tend to be hyperchromatic, with prominent nucleoli, and rarely demonstrate atypia. Potentially aggressive features such as mitoses, necrosis, hypervascularity, and spindle cells (i.e. sarcomatous degeneration) are typically absent or rare.[24–31] DNA ploidy analysis of typical chordomas demonstrates aneuploidy in 15–40% of cases.[8–11,25] There is a trend for tumors with aneuploid DNA content to behave more aggressively and for patients with these tumors to have shorter survival.[25] Other authors have not found a correlation between DNA ploidy status and tumor behavior, in terms of overall survival and tendency for local recurrence or distant metastases.[32]

Many authors contend that the chondroid pattern (15–30% of all cases) is a separate histological variant of chordoma, although this is controversial.[8–11,24–31,33] The chondroid pattern has been associated with a more favorable prognosis, as originally described by Heffelfinger and colleagues.[31] However, other authors contend that chondroid chordomas are a subgroup of low-grade chondrosarcoma and are not related to chordomas.[34,35] By definition, chondroid chordomas contain regions of typical chordoma with physaliphorous cells, against a background of areas characterized by cartilaginous matrix that have stellate tumor cells occupying lacunar spaces (resembling chondrocytes; Fig. 54.2).[31,33] As in typical chordoma, anaplastic or aggressive features such as mitoses, necrosis, hypervascularity, and spindle cells are typically absent or rare.[24–31,33] Electron microscopic studies support the dual nature (i.e. epithelial–mesenchymal) of these neoplasms by identifying cells with epithelial features and other cells consistent with chondrocytes.[36]

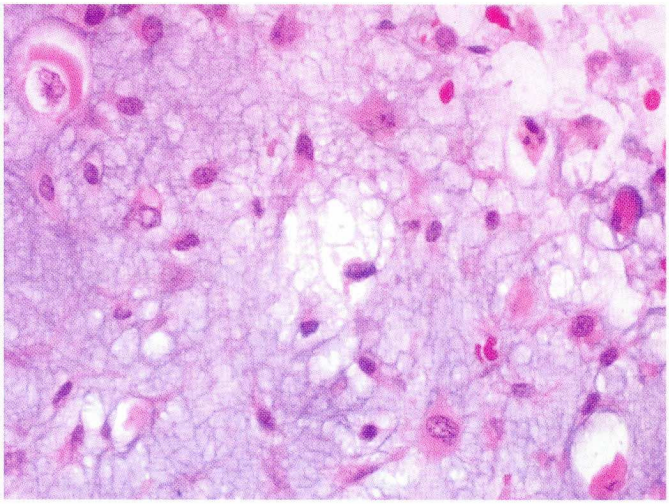


Figure 54.1 High-power view (600×) of classic or typical chordoma, demonstrating physaliphorous (bubble-bearing) cells. Note the large size, vacuolization, and eccentric nuclei. Several cells have hyperchromatic nuclei and prominent nucleoli. Mitoses, spindle cells, and regions of necrosis are absent.

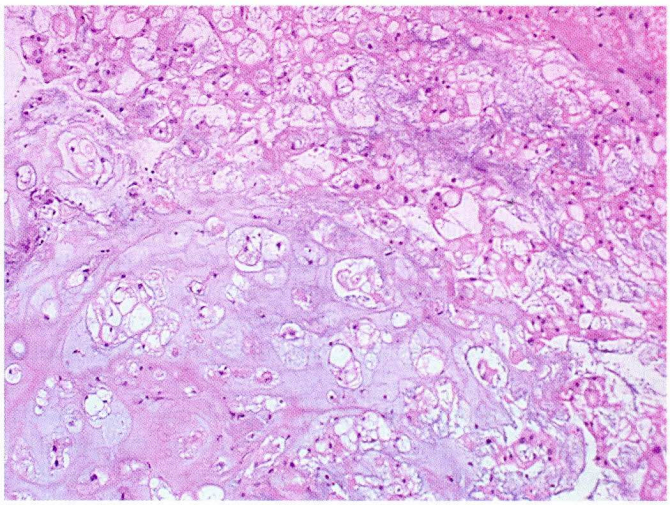


Figure 54.2 Low-power view (100×) of chondroid chordoma, demonstrating an area of classic chordoma with physaliphorous cells in the upper portion of the field, with a chondroid region that demonstrates cartilaginous metaplasia in the lower portions of the field. No anaplastic or malignant features are present.

Chordomas with malignant degeneration (less than 5% of all nonirradiated cases) typically demonstrate sarcomatous features (i.e. spindle cells).[8–11,37–40] These tumors will contain areas of classic chordoma admixed with regions characterized by the presence of atypical spindle cells. The spindle cell component demonstrates high cellularity, marked nuclear pleomorphism, and a high mitotic rate. Within the malignant spindle cell zones, regions of cartilaginous or osseous differentiation may be noted. In many tumors, a transitional

zone may be present between the regions of typical chordoma and regions containing the malignant spindle cells. This transitional zone may contain an intermediate, stellate type of cell. DNA ploidy analysis of chordomas with sarcomatous degeneration usually demonstrates aneuploid cell populations with a high proliferating fraction.[37,40] The mean proliferating fraction (%S+G2M) of a series of spindle cell chordomas was 34.1%.[37] In comparison to the mean proliferating fraction of a series of typical chordomas (20.2%), the growth fraction of spindle cell chordomas was significantly larger ($p < 0.01$).

In addition to the diagnostic information obtained from the histological evaluation of chordomas, immunohistochemical analysis may also be helpful in clarifying the pathological differential diagnosis.[8,11,28,33,34,37,40–45] Other tumor types to be considered are ependymoma, schwannoma, neurofibroma, metastasis (e.g. clear cell type), chondrosarcoma, and fibrous histiocytoma. The immunohistochemical profile of typical chordomas illustrates the dual epithelial–mesenchymal nature of these tumors and consists of frequent positivity to cytokeratin and epithelial membrane antigen (EMA) and less consistent staining for S-100 protein and vimentin.[8,12,33,37,42] Variable staining has also been noted with α1-antichymotrypsin and tissue polypeptide antigen.[41,42] Chondroid chordomas with a small cartilaginous component may have variable staining of S-100, with preserved positivity to cytokeratin and EMA.[33] When the cartilaginous component is more robust (20–50%), the staining within the chondroid regions for cytokeratin and EMA may become variable, with persistent positivity for S-100.[33] Chondrosarcomas stain consistently negative for cytokeratin and EMA since there is no epithelial component to these tumors. Chordomas with sarcomatous degeneration have an alteration of the immunohistochemical profile in the malignant regions containing spindle cells.[37,38,40] The staining for vimentin becomes more prominent, while staining for cytokeratin and EMA is markedly decreased. In some tumors, staining for S-100 may also be reduced.[40]

Other immunohistochemical studies of chordomas have evaluated the expression of cell adhesion molecules (CAMs), including E-, P-, and N-cadherin, CD44, β-catenin, intercellular CAM, neural CAM, and vascular CAM.[46,47] Overall, chordomas were shown to frequently demonstrate expression of N-CAM, VCAM-1, CD44, N-cadherin, and E-cadherin. The expression of E-cadherin, in particular, was very prominent and ubiquitous, and was noted in all histological variants of chordoma.

Preliminary data from studies using cytogenetic and molecular techniques are beginning to elucidate the mechanisms of transformation of chordomas.[48–57] No specific or characteristic chromosomal abnormalities have been described thus far. Many of the cases have shown hypodiploidy or near-diploidy, which is in contrast to the DNA flow cytometry data. Several tumors have shown structural anomalies of chromosomes 1 and 21, while others have alterations (usually elongation) of the telomere.[52,53] A loss of heterozygosity (LOH) analysis by Riva *et al.* suggests that the 1p36.13 region is abnormal in up to 85% of chordomas.[55] Candidate tumor suppressor genes in this region with a potential role in oncogenesis include *CASP9*, *EPH2A*, and *DVL1*. LOH at 1p36.13 appeared to be an early event in the transformation process, since it was present in tumors of all grades and locations.

Using immunohistochemical techniques, Matsuno *et al.* found that p53 protein was present in chordomas that had a high proliferative index (as determined by MIB-1 staining) and in recurrent tumors.[56] Furthermore, a significant correlation was noted between cyclin D1 staining and MIB-1 proliferative index or tumor recurrence. Interestingly, none of the tumors evaluated for bcl-2 were immunopositive, suggesting that apoptosis may not contribute to the recurrence of chordomas.

Eisenberg *et al.* studied seven skull base chordomas and found that, in two very aggressive cases, there was LOH for the *Rb* tumor suppressor gene on chromosome 13, suggesting that alterations or loss of *Rb* may play a role in the transformation of chordomas.[57] A study of skull base chordomas evaluated the expression of growth factors and structural proteins in good prognosis versus poor prognosis patient cohorts.[58] The mean expression of transforming growth factor-α and basic fibroblast growth factor was elevated in the patients with a poor prognosis and more rapid tumor progression. A similar, but not as pronounced, difference was noted for fibronectin.

Several authors have attempted to correlate pathological features of chordomas with prognosis.[24,28,29] In a series of 48 mixed chordomas, Rich *et al.* were unable to detect a correlation between cellular pleomorphism, mitotic figures, or hyperchromatic nuclei with survival.[24] The only histological variable to correlate with survival was the presence of chondroid elements. Chondroid chordomas had a more indolent course, longer duration of symptoms, and increased survival. Forsyth *et al.* evaluated 51 intracranial chordomas and were unable to detect a correlation between mitosis, chondroid elements, and survival.[28] In a series of 62 skull base chordomas, O'Connell *et al.* found that tumors with greater than 10% necrosis were associated with shorter patient survival.[29] The presence of chondroid elements, mitoses, pleomorphism, nucleolar prominence, and vascular invasion was not correlated with overall survival.

A molecular evaluation of a similar series of skull base tumors revealed that the expression of human telomerase reverse transcriptase (*hTERT*) messenger RNA was frequently associated with faster rates of tumor growth and an increased risk of recurrence.[59] The expression of *hTERT* was also associated with the presence of mutated p53 protein and an increased doubling time for residual tumor following surgical resection. Naka *et al.* performed a clinicopathological comparison of skull base and nonskull base chordomas in a series of 122 patients.[60] Skull base tumors were noted to have a higher MIB-1 labeling index than nonskull base tumors. The higher MIB-1 labeling index was often associated with older age, greater risk of recurrence, and nuclear pleomorphism. In contrast, for patients with nonskull base chordomas, only nuclear pleomorphism was noted to be a significant negative prognostic factor. A similar study by Horbinski *et al.* evaluated the prognostic value of Ki-67, p53, epidermal growth factor receptor (EGFR), and various chromosomal deletions in a series of 28 patients with skull base chordomas.[61] Tumors with a Ki-67 labeling index of 5% or higher (69.2 months versus 159.3 months; $p = 0.005$) and deletion at 9p21 (71.7 months

versus 146.2 months; $p=0.03$) were noted to have a more aggressive course and shorter overall survival. Expression of EGFR, accumulation of p53, and loss of chromosomes 1p36, 10q23, and 17p13 did not correlate with survival.

Another molecular target under consideration is c-Met, a receptor tyrosine kinase that binds hepatocyte growth factor/scatter factor (HGF), is localized to chromosome 7, and is known to function as an oncogene in other solid tumors.[62–64] In a series of 22 chordoma samples, Walter and colleagues evaluated for changes in copy number of chromosome 7 and correlated it with EGFR and C-Met protein expression.[62] Aneusomy of chromosome 7 was noted in 73% of all samples, including 100% of the recurrent tumors. In addition, there was a significant correlation between chromosome 7 aneusomy and C-Met expression ($p=0.001$). In a human sacral chordoma cell line, it has also been shown that C-Met and HGF are often coexpressed in the same cells, and that aberrations of chromosome 7 may be involved in altered tyrosine kinase signaling.[63] Using micro-RNA (miRNA) microarray techniques, Duan *et al.* evaluated the miRNA expression profiles of a series of chordoma cell lines and tissue samples.[64] They noted that the expression of miRNA-1 and miRNA-206 was markedly reduced in chordoma cell lines and samples. When miRNA-1 was transfected back into chordoma cell lines, the expression of C-Met was downregulated. These results suggest that the reduced level of miRNA-1 in chordoma tissue may be related to the frequent finding of overexpression of C-Met, and could be a contributing factor to the transformation process in these tumors.

Clinical features and presentation

Approximately 50% of chordomas arise in the sacrum, 35–40% within the skull base and clivus, and 10–15% throughout the vertebral column.[8–11,15–17] In general, chordomas are relatively slow growing and often have a prolonged duration of symptoms before diagnosis. The specific symptoms and neurological findings noted at presentation will vary according to the location of the tumor. Although these tumors are often benign histologically, systemic metastases have been noted in 10–40% of cases.[8–11,65,66] The most frequent sites for metastases are the lungs, regional lymph nodes, liver, bone, and skin.

Chordomas of the sacrum

Chordomas represent the most common primary neoplasm of the sacrum.[10,11,67–70] They often reach substantial size prior to diagnosis because of the ample room for tumor growth before critical structures are disturbed. The median age of patients in the majority of series is approximately 60 years; males are affected more often than females. The most common symptom (60–70% of patients) consists of persistent low back pain, which is slowly progressive and is often present for 12–18 months before diagnosis (Table 54.1).[10,11,67–70] Patients occasionally complain of more specific locations of the pain, such as the coccygeal, buttock, or anal regions. The pain may have a radicular component to it, with radiation down one of the legs. This presentation often leads to the erroneous diagnosis of nonspecific "sciatica," delaying discovery of the tumor by many months. Rectal dysfunction consisting of alteration of bowel habits (i.e. constipation), tenesmus, or bleeding is common (approximately 40% of patients).

Table 54.1 Symptoms and signs in patients with chordoma of the sacral region.

Symptoms and signs	Percentage of patients
General low back pain	60–70
Rectal dysfunction	40–45
Constipation	30–35
Sciatica	25–30
Coccygeal pain	20
Sacral pain	15
Urinary incontinence	10–15
Buttock pain	5–7
Anal pain	5–7
Perianal numbness	5
Impotence	5
Fecal incontinence	5

Data compiled from Sundaresan,[10] Healey and Lane,[11] Bethke *et al.*,[67] Lybeert and Meerwaldt,[68] Schoenthaler *et al.*[69]

As the tumor continues to enlarge, it usually grows ventrally and may encroach on the sacral foramina and nerve roots, causing neurological dysfunction. Symptoms from sacral nerve root compression are variable and include perianal numbness, urinary hesitancy or retention, urinary incontinence, impotence, and rectal incontinence. The general physical examination is typically benign, except for the rectal examination, which often demonstrates a presacral mass.[10,67] The neurological examination may be normal or show evidence of sacral root dysfunction (e.g. perianal numbness, loss of anal sphincter tone).

Chordomas of the skull base, clivus, and intracranial cavity

Chordomas comprise 6.15% of all skull base tumors and 0.1–0.2% of all intracranial tumors.[8–11,15] They occur most often in the clivus but can arise in other areas such as the sphenoid sinus, cavernous sinus, occipital condyle, and sella.[8–11,18,22,28,29,71–74] Depending on the primary site of tumor involvement and direction of growth (e.g. anterior, lateral, posterior), symptoms and signs may vary considerably. The mean age of patients with skull base chordomas is in the range of 38–45 years.[68,69,71] In the majority of series, the most common symptoms are either diplopia or headache (Table 54.2).[8,9,24,28,71–74] Diplopia is the initial symptom in 50–90% of patients. The diplopia is usually horizontal and exacerbated by attempts at lateral gaze. Headache is noted at presentation in 25–60% of patients. In many patients, headache and diplopia develop simultaneously. Symptoms such as facial pain, vertigo, tinnitus, dysphagia, hoarseness, alterations of vision, and gait disturbance are present in 12–15% of patients.[71–74] Infrequent complaints include hearing loss, dizziness, unilateral weakness, facial dysesthesias, and neck pain.

On neurological examination, the most common findings are cranial nerve palsies (see Table 54.2).[8,9,24,28,71–74] The VIth

Table 54.2 Symptoms and signs in patients with chordoma of the skull base, clivus, and intracranial cavity.

Symptoms and signs	Percentage of patients
Diplopia	50–90
Cranial nerve VI palsy	45–75
Headache	25–60
Cranial nerve IX, X, XI, XII palsy	25–40
Cranial nerve II, III, IV, V_1, VII palsy	15–25
Diplopia and headache	15–20
Pyramidal tract dysfunction	15–20
Facial pain	12–15
Vertigo/tinnitus	12–15
Dysphagia/hoarseness	12–15
Alterations of vision	12–15
Gait disturbance	12–15

Data compiled from Gay *et al.*,[8] Miller,[9] Rich *et al.*,[24] Forsyth *et al.*,[28] Yoneoka *et al.*,[71] Al-Mefty and Borba,[72] Volpe *et al.*[73]

cranial nerve is involved most frequently, with abnormal function noted in 45–75% of patients. The deficit is usually unilateral but can be bilateral in some cases. Abducens palsy can be associated with dysfunction of cranial nerves II, III, IV, V^1, and VII in 15–25% of patients.[28,73,74] Although uncommon, isolated palsy of cranial nerves II, III, or IV is seen in some patients. Abnormalities of the lower cranial nerves (i.e. IX, X, XI, XII) are noted in 25–40% of patients.[28,71–74] Similar to abducens palsy, the deficits are usually unilateral but can be bilateral in some cases. Cranial nerves of the cerebellopontine angle (i.e. VII, VIII) are rarely affected on examination at presentation, but can develop in patients with large tumors. Pyramidal tract dysfunction is present in 15–20% of patients and develops from tumors that compress the ventral surface of the brainstem.[8,9,28] The findings may be unilateral or bilateral and in some cases are associated with ataxia. Furthermore, patients with brainstem compression by tumor may manifest inappropriate laughing or crying. The emotional lability is thought to occur from disturbance of ventral pontine tegmental pathways.[9]

Chordomas of the true vertebrae

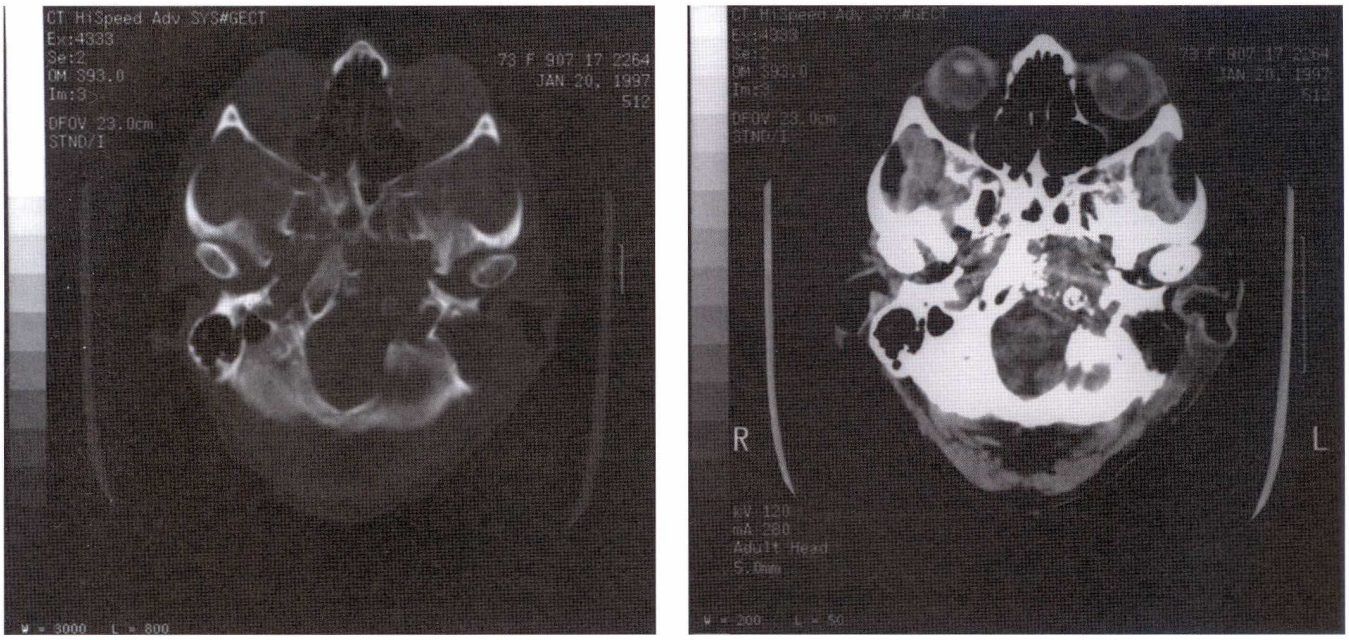
Chordomas are uncommon tumors of the vertebral column (usually the vertebral body), representing less than 5% of all tumors in this region.[16,17] Approximately 60% of vertebral chordomas arise in the lumbar region, 10–15% develop in the thoracic area, and 25–30% in the cervical spine. Ventral tumor growth will cause bone destruction and infiltration into paraspinal soft tissues, while dorsal expansion may cause nerve root displacement or spinal cord compression. The mean age of patients with spinal chordomas ranges from 45 to 50 years. Patients with these tumors often have a shorter duration of symptoms before diagnosis than patients with tumors of the sacrum, due to the smaller volume of bone in proximity to sensitive neural structures.[70] In one series, the mean duration of symptoms prior to diagnosis was 7 months.[16] In the majority of cases (>90%), the initial symptom is localized pain in and around the involved vertebral body. There may be a radicular component to the pain from displacement or compression of nerve roots, with lancinating pain in a limb or anteriorly around the thorax. Other alterations of sensation, such as dysesthesias or sensory deficits, may occur. Cervical chordomas that grow ventrally and compress the esophagus may cause dysphagia.[17] Occasionally, tumors can cause myelopathic weakness, gait ataxia, or sphincter dysfunction.

Several authors have attempted to correlate various clinical parameters with overall survival and prognosis.[28,29] Patients less than 40 years appear to have improved survival and a better prognosis. Forsyth *et al.* noted a significant difference in survival (5-year survival of 75% versus 30%) for patients less than 40 years ($p < 0.0001$).[28] The presence of diplopia was also suggestive of a better prognosis and improved survival, especially when correlated with patient age.[28] Female sex was associated with improved survival (median 158 months versus 86 months; $p < 0.004$) and a better prognosis in both univariate and multivariate analyses by O'Connell *et al.*[29] For patients with sacral and spinal chordomas, negative prognostic factors included larger tumor size, inadequate surgical margins, the presence of necrosis, a labeling index of greater than 5%, and local recurrence.[70]

Radiological diagnosis

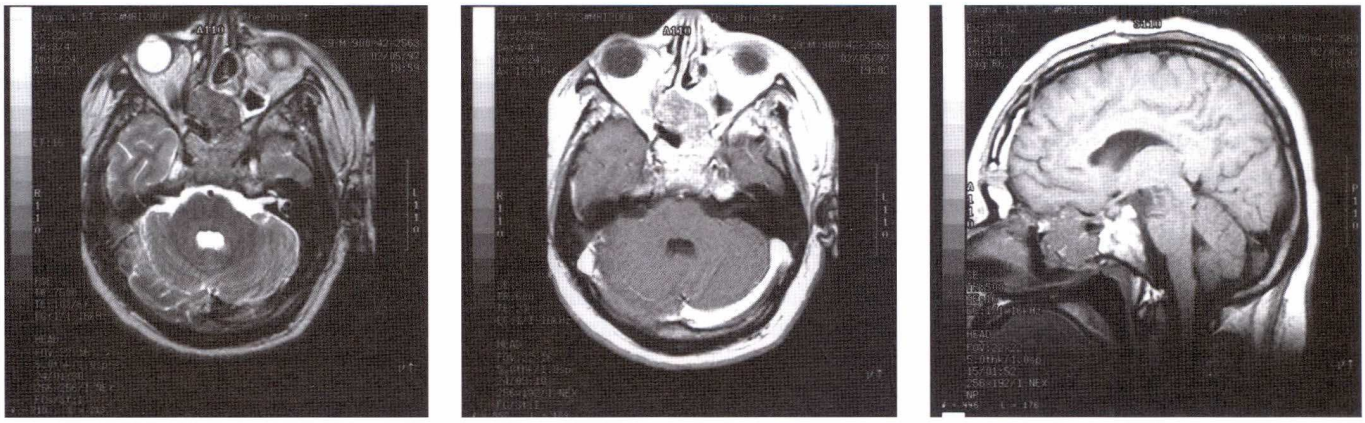
Patients with a history and neurological examination suspicious for a chordoma of the skull base, vertebral column, or sacrum require a radiological evaluation with either computed tomography (CT) or magnetic resonance imaging (MRI).[8,75–84] CT and MRI are equivalent in their ability to delineate the presence of a tumor. Both modalities clearly demonstrate the mass within bone, bone erosion or destruction, and extension into soft tissues.[75–78,82–84] Rarely, MRI may have trouble detecting small tumors confined within the margins of the clivus.[76] On noncontrast CT, the tumor usually appears as a soft tissue mass, isodense or hyperdense with neural tissues, causing destruction of the adjacent bone (Fig. 54.3). Bone-windowed CT scans demonstrate the precise amount of bone destruction caused by the tumor, with sharp margins (see Fig. 54.3). Calcification is noted in 40–70% of chordomas (especially clival) with CT imaging. Small regions of sequestered bone can also be noted in approximately 15–20% of cases. MRI is inferior to CT in its ability to delineate the exact margins of bone destruction or the presence of calcification.[75,76] With the administration of contrast, chordomas always demonstrate contrast enhancement. The amount of enhancement may vary but is often quite dense and homogeneous. Sagittal and coronal reconstruction of CT images is sometimes helpful to better delineate the extent of skull base and sacral tumors. However, the ability of CT to evaluate tumors in the sagittal and coronal planes is inferior to MRI.

In general, MRI with sagittal, coronal, and axial sections clearly defines the margins of chordomas of the skull base, vertebral column, and sacrum.[8,75–84] On T1-weighted images, 75% of tumors appear isointense, while 25% appear hypointense, compared to surrounding neural tissues (Fig. 54.4).[8,76,84] With administration of gadolinium, chordomas usually enhance. As with CT, the degree of enhancement is variable; in most



(a) (b)

Figure 54.3 (a) Bone-windowed CT of the skull base demonstrating a large, eccentric chordoma of the clivus on the left side, which is causing severe erosion and destruction of surrounding bone. (b) Noncontrast CT of the skull base at the same level as Fig. 54.3(a), demonstrating the clival chordoma as a mass with soft tissue density within the region of eroded bone.



(a) (b) (c)

Figure 54.4 (a) Noncontrast MRI (TR 7500, TE 102) of the brain, at the level of the upper clivus and orbits, demonstrating an isointense chordoma within the clivus that extends into the sphenoid sinus region and tracks along both optic nerves. (b) Gadolinium-enhanced MRI (TR 600, TE 23) of the brain, at the same level as Fig. 54.4(a), demonstrating heterogeneous enhancement of the chordoma within the clivus and sphenoid sinus. (c) Midsagittal, noncontrast MRI (TR 500, TE 16) of the brain, demonstrating the chordoma anterior to the brainstem within the clivus and extending into the sphenoid sinus region. The signal intensity of the mass is heterogeneous: hyperintense within the bone of the clivus and more isointense in the sinus.

tumors, the pattern is heterogeneous. On T2-weighted images, chordomas are always hyperintense to all surrounding structures. The pattern of hyperintensity is homogeneous in 20% of cases and heterogeneous in the remaining 80% (mild in 30%, marked in 50%).[76–78] Tumor calcification, exact margins of eroded bone, and the presence of sequestered bone are noted in some tumors, but these are not demonstrated as well as with CT. However, the multiplanar capability of MRI allows for better visualization of the extent of tumor margins and infiltration into soft tissues than is possible on CT.

Sagittal MRI clearly shows the anterior–posterior margins of tumor involvement. For chordomas of the skull base, MRI is helpful for determining the anterior extension of tumor into the sinuses or nasopharynx and posterior extension toward the brainstem.[77,78] The posterior fossa is affected by tumor (e.g. brainstem compression, cranial nerve displacement) in approximately 80% of skull base tumors.[78] Sagittal MRI is essential for tumors of the sacrum to determine the extent of the lesion anteriorly into the rectum and other soft tissues.[82] Coronal MRI images are useful for assessing lateral extension of skull base

tumors toward the cavernous sinuses. The cavernous sinuses are infiltrated by tumor in approximately 65% of skull base chordomas.[78] Furthermore, with sacral chordomas, coronal MRI can determine involvement of sacral nerve roots within the neural foramina.

Magnetic resonance imaging is far superior to CT in demonstrating the relationship of tumor to cranial nerves and vascular structures.[75–78,84] The carotid and basilar arteries are delineated clearly on T2-weighted images because of the contrast between the flow void inside the vessels and surrounding high signal tumor. Meyer *et al.* noted displacement of the carotid or basilar arteries in 57% of skull base chordomas.[78] Furthermore, in 36% of their cohort, vascular encasement was present. Encasement of vessels by chordomas has also been reported by other authors.[75–78,84] Universally, the lumen of encased vessels is not compromised by tumor and they continue to have normal blood flow.

Most authors do not report any MRI signal characteristics that can be used to differentiate between typical chordomas and those with chondroid regions.[78] However, Sze *et al.* noted that chondroid chordomas were less intense on T2-weighted images than were conventional chordomas.[76] Assessment of mean quantitative T1 and T2 relaxation values (msec) has shown that chondroid tumors often have shorter times than conventional chordomas. The use of MR angiography can further delineate the presence of arterial vascular encasement and luminal narrowing.[84] In addition, MR venography can also clearly demonstrate any venous involvement by tumor (e.g. narrowing, occlusion).

Treatment

The treatment of many chordomas is limited by the invasive and infiltrative nature of these tumors. The tumor is often too extensive at diagnosis for a complete, curative resection.[8,69,72] Even when the lesion is small and radical surgery is attempted, local recurrence rates remain high (i.e. 50–100%). Therefore, the therapeutic approach for chordomas is primarily to maintain local control and minimize regional damage to neural structures.[8,69,72] Despite the emphasis on local disease, systemic metastases can occur and are noted in 10–30% of patients.[8,66,67] The most common sites for metastases are the lungs, regional lymph nodes, liver, bone, and skin. Infrequent sites include cardiac muscle, brain, adrenal glands, pancreas, pituitary gland, and eyelid.[66,67] In the majority of patients, recurrence at the local site is most likely to affect morbidity and survival.

Surgical resection

Most authors agree that surgical resection is an important aspect of the initial treatment of patients with chordoma.[8,10,11,28,67,72,74,84–88] The most aggressive resection possible should be attempted after initial diagnosis, depending on the location (e.g. clivus, vertebral body, sacrum) and the extent of the tumor. It appears that the aggressiveness of resection has a critical impact on local control rates and may correlate with overall survival.[8,28,72,74] In a review of 51 patients with intracranial chordomas, Forsyth *et al.* found that the extent of resection affected survival.[28] In a univariate analysis, the extent of resection was significantly ($p=0.02$) associated with survival. For patients receiving only biopsy, the 5- and 10-year survival rates were 36% and 0%, respectively. In the cohort of patients undergoing subtotal resections, the 5- and 10-year survival rates were 55% and 45%, respectively. This effect of resection on survival was most apparent in younger patients.

Chordomas of the skull base and clivus can be grouped according to their size and extension into contiguous areas.[72] Type I tumors are small and restricted to one compartment of the skull base (e.g. clivus or sphenoid sinus). Type II tumors are larger and extend to two or more contiguous areas of the skull base. Type III lesions are very extensive and involve several contiguous compartments of the skull base (e.g. clivus, sphenoid sinus, and middle fossa). In most series type I chordomas are rare and usually amenable to radical resection using a single skull base approach.[8,72] Type II tumors are most common (50–65%) and in many cases can also be radically resected using a single skull base procedure.[72] The type III chordomas develop in 10–20% of patients and require two or more surgical procedures to attempt radical removal.

There are numerous surgical approaches and techniques available for resection of skull base and clivus chordomas.[8,72,74,85,86,89–98] The approach will depend on the location of the tumor and the degree of extension from the primary site. Most often, tumors are centered within the lower, middle, or upper clivus and extend into the cavernous sinus or petrous apex.[72,85,86] The four most common approaches allow for an extensive resection of tumor either extradurally or intradurally. The subtemporal, transcavernous, transpetrous apex approach is used most often (30–35%) and provides access to the clivus, cavernous sinus, sella turcica, and petrous apex.[8,72,94] The extended frontal approach is used in 25–30% of patients and is advantageous for tumors with extension into the orbits, ethmoid sinus, and anterior skull base.[8,85] The subtemporal–infratemporal approach is utilized in approximately 20% of patients and offers excellent exposure of the middle fossa, clivus, and lateral skull base.[8,85] For chordomas of the lower clivus, temporal bone, and occiput, the extreme lateral transcondyle and transjugular approach is used (approximately 15% of patients).[8,85]

Uncommon surgical approaches include the transoral, transmaxillary, transcervical–transclival, anterior cervical, and transsphenoidal procedures.[8,74,86,89–95,97] Recent reports suggest that the transsphenoidal approach can even be used in combination with endoscopy for removal of clival chordomas in selected cases.[98] In general, most authors would agree that the choice of surgical approach is less important than the expertise of the surgical team and its ability to perform an extensive resection of the tumor.[74]

Studies using the most advanced skull base approaches for removal of chordomas report various results. Radical or total resection of tumor is achieved in 43.5–55% of patients, near-total or subtotal resection is noted in 40–47%, and partial resection is attained in 8–10%.[8,72,74,85,86] In a series of patients with chordomas and chondrosarcomas involving the skull base and cavernous sinus, after a median follow-up of 24 months, Lanzino *et al.* noted three recurrences in 14 patients with

subtotal or partial removal of tumor.[85] No recurrences were observed in the group of patients that had undergone radical resections. In a study of skull base chordomas by Gay *et al.*, there was a statistically significant difference ($p < 0.05$) between the risk of recurrence in patients with radical or near-total resections and patients with subtotal or partial resections.[86] The overall recurrence-free survival estimates were 80% at 3 years and 76% at 5 years. In contrast, the survival estimates for patients who had recurrence of disease were 52% at 2 years and 26% at 3 years. Previous surgery or radiation therapy was associated with an increased risk of recurrence and surgical complications. Similar survival rates are described by Crockard *et al.* in a series of 42 patients with skull base chordomas, with 5- and 10-year rates of 77% and 69%, respectively.[74] Overall, an aggressive surgical resection at the time of tumor diagnosis, regardless of the approach and technique used, has the most impact on subsequent local tumor control and survival.

Sacral chordomas are often very large at diagnosis but most authors advise radical resection whenever possible.[10,11,67,88,99] Similar to the experience with skull base tumors, recurrence-free survival is improved after radical or near-total resection. For tumors of the lower sacrum and coccygeal region, many authors recommend a posterior approach.[11,88] Other investigators argue that a combined anterior–posterior approach is preferable.[67] Tumors of the upper sacrum are resected most efficiently with a staged, combined anterior–posterior approach.[10,11,67,88,99] Regardless of the approach used to resect the tumor, it is important to attempt preservation of the upper sacral nerve roots and the pudendal nerve. If the bilateral S2 nerve roots are sectioned during surgery, urogenital and rectal function will be lost or impaired. If both S2 nerve roots are preserved, 50% of patients will retain at least partial bladder and bowel control.[87,95] To maintain normal bowel continence, preservation of at least one set of ipsilateral S1, S2, and S3 nerve roots is recommended. The local recurrence rates are approximately 25–30% for tumors removed *en bloc* by radical resection.[10,11,67] If the tumor is removed by subtotal or partial resection, local recurrence rates increase to approximately 60–65%.

It is also recommended that chordomas of the true vertebrae be radically resected whenever feasible.[11,17,87] For tumors of the cervical vertebrae, most authors recommend an anterior approach to perform a corporectomy, followed by bone grafting, if necessary.[16] Thoracic tumors are best approached by thoracotomy or a staged procedure that combines a laminectomy and thoracotomy.[11] Lumbar chordomas will usually require an anterior approach; on occasion, a posterolateral approach may be necessary.[11]

Radiation therapy

Although radical resection is considered in each patient with a chordoma of the skull base, vertebrae, or sacrum, it is often impossible due to the invasive nature of these tumors. Therefore, radiation therapy to eradicate residual or recurrent disease is an important therapeutic consideration in many patients.[8,10,11,28,69] Unfortunately, chordomas have proved to be relatively radioresistant tumors. The clinical results in most radiation therapy trials of chordomas have demonstrated only modest improvements in local control, recurrence-free survival, and overall survival.[8,10,11,28,69,100–106] Early reports in the radiation oncology literature using photon-based megavoltage therapy suggested a dose–response relationship for chordoma.[105,106] It was recommended that patients received at least 6000–7000 cGy to the tumor bed for optimal response. However, more recent studies have been unable to document a consistent dose–response relationship for chordoma using conventional photon techniques.[8,106–108] In the reports by Cummings *et al.* and Saxton, doses of 2500–7000 cGy were used for patients with chordomas of various sites after surgical resection.[107,108] Palliation of symptoms and improvement of relapse-free survival were as likely to occur with doses of 4000–5500 cGy as with higher doses.

In an extensive review of reported dose–response data for photon techniques in treatment of cranial chordoma, Tai *et al.* concluded that no dose–response relationship was evident.[106] Administration of doses in the range of 4500–5500 cGy were as effective as higher doses. In addition, the authors state that surgical resection in combination with irradiation significantly prolongs survival when compared to either modality used alone. In a study of 21 patients with chordomas of various sites, Keisch *et al.* concluded that irradiation prolonged the time to first relapse for tumors of the lower spine and sacrum, but not for tumors of the skull base.[103] The overall 5- and 10-year actuarial survival rates were 74% and 46%, respectively. Forsyth *et al.* evaluated the results of 51 patients with intracranial chordomas and determined that conventional irradiation did not affect the overall survival of the cohort, but did prolong disease-free survival, especially in younger patients.[28] The 5- and 10-year disease-free survival rates in irradiated patients were 39% and 31%, respectively. A similar improvement of progression-free survival, without a change in overall survival, has been reported by Thieblemont *et al.* in 26 patients with chordomas of various sites.[105]

Newer radiation therapy techniques currently being applied to patients with chordomas include intensity-modulated radiation therapy (IMRT) and conformal techniques. Several case studies have reported using IMRT for chordomas of the sacrum and spine.[109,110] IMRT was well tolerated and appeared to offer a more homogeneous radiation distribution pattern within the planning target volume. Conformal radiotherapy approaches have also been reported and have similar radiation distribution patterns to IMRT.[111]

Irradiation of chordomas with charged particles (i.e. protons, carbon, helium, neon) has shown promise as a more efficacious therapeutic option.[8,69,100–102,106,112–116] There are several radiobiological advantages of charged particles over photons. The high linear energy transfer (LET) of charged particles allows for a more defined and superior dose distribution (i.e. steeper fall-off in dose). Higher doses can be prescribed to the tumor volume with minimal risk of augmented toxicity to surrounding normal structures. Austin-Seymour *et al.* have used fractionated proton irradiation for skull base chordomas and chondrosarcomas, administering a mean total dose of 69 GyE (gray equivalent).[101,102,106] The 5- and 10-year local

control rates were 82% and 58% respectively, while the 5- and 10-year disease-free survival rates were 76% and 53%, respectively. The median time to local failure was 53 months. In their opinion, these results represent a significant improvement over the results of conventional radiation techniques. A similar study in a series of 34 patients with skull base chordomas used a combination of high-energy photons and protons, in a two-thirds to one-third ratio of the total dose, respectively.[117] The 3-year local control rate was 83.1%, with a 3-year overall survival rate of 91%.

The superiority of proton therapy in comparison to photon irradiation techniques has been corroborated by a recent metaanalysis of more than 200 studies and a total of 416 patients with skull base chordoma.[113] In a study using helium and neon particles, Berson *et al.* treated 25 patients with chordomas of the skull base and cervical spine and reported a 5-year local control rate of 55%.[100,106] Recent experience with carbon ion radiotherapy after surgical resection from Takahashi *et al.* suggests improved efficacy over photon irradiation or untreated follow-up, with a 3-year recurrence-free survival rate of 70% versus 57.1% and 7.1% ($p=0.001$), respectively.[114] In a review of 14 patients with sacral chordomas treated with charged helium and neon particles, Schoenthaler *et al.* reported a 5-year local control rate of 55%.[69] The 5- and 10-year survival rates were 85% and 22%, respectively, with an overall median survival of 77 months.

Several authors have reported their experience with carbon ion radiotherapy in chordomas.[116,118,119] Schulz-Ertner *et al.* evaluated a series of 24 patients with skull base chordoma, using a median tumor dose of 60 GyE.[118] With a mean follow-up of 13 months, the 2-year local control and progression-free survival rates were 83% and 83%, respectively. A similar study in 30 patients with unresectable sacral chordomas used carbon ion radiotherapy at a median dose of 70.4 GyE.[119] At a median follow-up of 30 months, the 5-year local control and overall survival rates were 96% and 52%, respectively. A recent summary of phase 1/2 and phase 2 trials of carbon ion radiotherapy in 38 patients with inoperable sacral chordoma demonstrated a 5-year overall survival rate of 86% and a 5-year local control rate of 89%.[116]

Other methods of irradiation of chordoma include brachytherapy with radioactive seeds (e.g. iodine-125) and radiosurgery.[8,101,120–124] It is difficult to evaluate the efficacy of these modalities because of the small number of patients that have been treated and the limited follow-up intervals reported.[8,101,120–124] There may be a role for brachytherapy and radiosurgery in the palliation of residual and recurrent disease in carefully selected patients. One recent approach that has been applied to a small group of patients with skull base chordomas involves the combination of maximal tumor resection and gamma-knife radiosurgery, with a mean treatment dose of 17 Gy.[122] Although follow-up was limited, the local tumor control rate of 93.3% and mean tumor-free survival of 17 months were encouraging. In a similar and more recent study of 19 patients with clival chordomas, Ito and co-workers noted 2- and 5-year progression-free survival rates of 77.9% and 47.9%, respectively.[123] Another group has reported the use of the CyberKnife for adjuvant therapy in a series of 18 patients with chordomas of the cranium, mobile spine, and sacrum.[124] Treatment was administered over five sessions, with a median dose of 35 Gy (range 24.0–40.0 Gy). The overall survival rate at 65 months was 74.3%, with a local control rate of 88.9%.

Chemotherapy

The role of chemotherapy in the treatment of chordomas remains limited.[8,11,87,105,125,126] The main indication for chemotherapy has been in patients with recurrent or widespread disease not amenable to further surgery or radiation therapy. In most cases, the regimens have been designed to resemble protocols used for soft tissue sarcomas. Unfortunately, very few patients have responded to this approach. Chemotherapeutic agents that have been used (as single agents or in combination) without success include methotrexate, vincristine, cisplatin, doxorubicin, etoposide, actinomycin-D, and cyclophosphamide.[11,87,105,125]

Fleming *et al.* report two patients with malignant sacral chordomas and lung metastases in whom chemotherapy produced objective responses.[125] One patient responded to a multiagent regimen consisting of etoposide, cisplatin, vincristine, dacarbazine, cyclophosphamide, and doxorubicin administered intravenously over 3 days every 4–5 weeks. The second patient responded to this multiagent regimen for five cycles and then progressed. A second regimen of single-agent continuous infusion ifosfamide was initiated, which produced dramatic shrinkage of the lung lesion.

In recent years, many investigators have been attempting to treat chordomas with molecular treatment approaches, as the molecular biology of these tumors has been elucidated.[126,127] One report evaluated the efficacy of imatinib mesylate, a tyrosine kinase inhibitor with activity against c-KIT, BCR-ABL, and platelet-derived growth factor receptors (PDGFR) that has been previously utilized for gastrointestinal stromal tumors (GIST) and high-grade gliomas.[128] Six patients with advanced chordoma (five sacral, one skull base) were treated with imatinib mesylate (800 mg/day). Pathologically, all the tumors were noted to be positive for expression of PDGFR. Several of the patients had evidence of liquefaction on CT and MRI scans, as well as reduced glucose uptake on positron emission tomography scans. Four of five symptomatic patients also reported subjective improvement, usually early in the course of treatment. A phase 2 trial with a larger cohort of patients has been initiated and remains open to further accrual.

A case report by Singhal *et al.* demonstrated tumor shrinkage in a patient with a progressive sacral chordoma after treatment with erlotinib, a tyrosine kinase inhibitor with specificity for EGFR.[129] The tumor was positive for EGFR and responded to erlotinib (150 mg/day) after 3 months of treatment, with a partial reponse and improvement of symptoms. Stacchiotti *et al.* treated a series of 10 patients with advanced and progressive chordoma using a combination molecular therapeutic approach of imatinib and sirolimus.[130] Sirolimus (rapamycin) is an inhibitor of the mammalian target of rapamycin (mTOR), which is often upregulated in solid tumors.[131] Treatment consisted of imatinib (400 mg/day) and sirolimus (2 mg/day), with a mean treatment duration of 9 months.

On follow-up imaging, there was one partial response and seven tumors with stable disease. Molecular therapy directed at inhibiting the PI3Kinase/mTOR signaling pathway has also been supported by *in vitro* studies from Schwab *et al.*[132] Activation of the PI3K/mTOR pathway was first verified in 13 chordoma tumor resection specimens. Then they used a dual kinase inhibitor, PI-103, to treat a chordoma cell line (UCH-1), and noted reduced activation of the Akt and mTOR pathways. In addition, cell proliferation of the cultures was inhibited and apoptosis was induced in over 50% of cells.

Conclusion

Chordomas are rare, locally invasive tumors that arise from embryonic rests of the primitive notochord, with the potential to develop anywhere along the midline of the axial skeleton. Patients with chordomas of the skull base, true vertebrae, or sacrum in whom a gross total resection has been performed can be followed closely with serial contrast-enhanced MR imaging, without further treatment. For the more typical patient, with significant residual disease after surgery, some form of irradiation should be considered. The most effective radiotherapy techniques use charged particles (e.g. protons, carbon), which allow for higher doses to the tumor bed in a more well-defined dose distribution. However, access to facilities which can offer charged particle radiotherapy remains somewhat limited. If charged particle radiation therapy is not available, aggressive photon-based irradiation is still strongly recommended. Chemotherapy has a limited role in the treatment of chordoma, but should be considered for patients with recurrent or progressive disease that is refractory to further surgical intervention or irradiation.

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References

1. Virchow R. *Untersuchungen Uber die Entwickelung des Schadelgrundes*. Berlin: George Reimer, 1857.
2. Luschka H. Die altersveranderungen der zwischen-wirbelknorpel. Virchows Arch Pathol Anat Physiol Klin Med 1864; 31: 396–9.
3. Muller H. Ueber das vorkommen von resten der chorda dorsalis bei menschen nach der geburt und uber ihr verhaltnis zu den gallertgeschwulsten am clivus. Ztschr Rat Med 1858; 2: 202.
4. Klebs E. Ein fall von ecchondrosis spheno-occipitalis amylacea. Virchows Arch Pathol Anat 1864; 31: 396.
5. Ribbert H. Ueber die echondrosis physalifora spheno-occipitalis. Centralbl Allg Pathol Pathol Anat 1894; 5: 457.
6. Ribbert H. Ueber die experimentelle erzeugung einer ecchondrosis physalifora. Verh Dtsch Kong Inn Med 1895; 13: 455.
7. Congdon CC. Proliferative lesions resembling chordoma following puncture of nucleus pulposus in rabbits. J Natl Cancer Inst 1952; 12: 893.
8. Gay E, Sekhar LN, Wright DC. Chordomas and chondrosarcomas of the cranial base. In: Kaye H, Laws ER (eds) *Brain Tumors. An Encyclopedic Approach*. New York: Churchill Livingstone, 1995. pp. 777–94.
9. Miller NR. Secondary tumors of the central nervous system. In: Miller NR (eds) *Walsh and Hoyt's Clinical Neuro-Ophthalmology*, 4th edn. Baltimore, MD: Williams and Wilkins, 1988. pp. 1662–709.
10. Sundaresan N. Chordomas. Clin Orthop Relat Res 1986; 204: 135–42.
11. Healey JH, Lane JM. Chordoma: a critical review of diagnosis and treatment. Orthop Clin North Am 1989; 20: 417–26.
12. Salisbury JR. The pathology of the human notochord. J Pathol 1993; 171: 253–5.
13. Horwitz T. Chordal ectopia and its possible relation to chordoma. Arch Pathol 1941; 31: 354–62.
14. Salisbury JR, *et al.* Three-dimensional reconstruction of human embryonic notochords: clue to the pathogenesis of chordoma. J Pathol 1993; 171: 59–62.
15. McMaster ML, *et al.* Chordoma: incidence and survival patterns in the United States, 1973–1995. Cancer Causes Control 2001; 12: 1–11.
16. Klekamp J, Samii M. Spinal chordomas – results of treatment over a 17-year period. Acta Neurochir 1996; 138: 514–19.
17. D'Haen B, *et al.* Chordoma of the lower cervical spine. Clin Neurol Neurosurg 1995; 97: 245–8.
18. Yadav YR, *et al.* Cranial chordoma in the first decade. Clin Neurol Neurosurg 1992; 94: 241–6.
19. Coffin CM, *et al.* Chordoma in childhood and adolescence. A clinicopathologic analysis of 12 cases. Arch Pathol Lab Med 1993; 117: 927–33.
20. Katayama Y, *et al.* Intradural extraosseous chordoma of the foramen magnum region. Case report. J Neurosurg 1991; 75: 976–9.
21. Commins D, *et al.* Hypothalamic chordoma. Case report. J Neurosurg 1994; 81: 130–2.
22. Elias Z, Powers LK. Intrasellar chordoma and hyperprolactinemia. Surg Neurol 1985; 23: 173–6.
23. Kakuno Y, *et al.* Chordoma in the sella turcica. Neurol Med Chir 2002; 42: 305–8.
24. Rich TA, *et al.* Clinical and pathologic review of 48 cases of chordoma. Cancer 1985; 56: 182–7.
25. Schoedel KE, *et al.* Chordomas: pathological features; ploidy and silver nucleolar organizing region analysis. A study of 36 cases. Acta Neuropathol 1995; 89: 139–43.
26. Crapanzano JP, *et al.* Chordoma. A cytologic study with histologic and radiologic correlation. Cancer 2001; 93: 40–51.
27. Chetty R, Levin CV, Kalan MR. Chordoma: a 20-year clinicopathologic review of the experience at Groote Schuur Hospital, Cape Town. J Surg Oncol 1991; 46: 261–4.
28. Forsyth PA, *et al.* Intracranial chordomas: a clinicopathological and prognostic study of 51 cases. J Neurosurg 1993; 78: 741–7.
29. O'Connell JX, *et al.* Base of skull chordoma. A correlative study of histologic and clinical features of 62 cases. Cancer 1994; 74: 2261–7.
30. Kay PA, *et al.* Chordoma. Cytomorphologic findings in 14 cases diagnosed by fine needle aspiration. Acta Cytol 2003; 47: 202–20.
31. Heffelfinger MJ, *et al.* Chordomas and cartilaginous tumours at the skull base. Cancer 1973; 32: 410–20.
32. Berven S, *et al.* Clinical outcome in chordoma. Utility of flow cytometry in DNA determination. Spine 2002; 27: 374–9.
33. Ishida T, Dorfman HD. Chondroid chordoma versus low-grade chondrosarcoma of the base of the skull: can immunohistochemistry resolve the controversy? J Neurooncol 1994; 18: 199–206.
34. Bottles K, Beckstead JH. Enzyme histochemical characterization of chordomas. Am J Surg Pathol 1984; 8: 443–7.
35. Brooks JJ, LiVolsi VA, Trojanowski JQ. Does chondroid chordoma exist? Acta Neuropathol 1987; 72: 229–35.
36. Valderrama E, *et al.* Chondroid chordoma: electron-microscopic study of two cases. Am J Surg Pathol 1983; 7: 625–32.
37. Hruban RH, *et al.* Chordomas with malignant spindle cell components. A DNA flow cytometric and immunohistochemical study with histogenetic implications. Am J Pathol 1990; 137: 435–47.

38. Hruban RH, *et al.* Lumbo-sacral chordoma with high-grade malignant cartilaginous and spindle cell components. Am J Surg Pathol 1990; 14: 384–9.
39. Fukuda T, *et al.* Sacrococcygeal chordoma with a malignant spindle cell component. A report of two autopsy cases with a review of the literature. Acta Pathol Jpn 1992; 42: 448–53.
40. Tomlinson FH, *et al.* Sarcomatous transformation in cranial chordoma. Neurosurgery 1992; 31: 13–18.
41. Burger PC, Makek M, Kleihues P. Tissue polypeptide antigen staining of the chordoma and notochordal remnants. Acta Neuropathol 1986; 70: 269–72.
42. Meis JM, Giraldo AA. Chordoma. An immunohistochemical study of 20 cases. Arch Pathol Lab Med 1988; 112: 553–6.
43. Bouropoulou V, *et al.* Immunohistochemical investigation of chordomas: histogenetic and differential diagnostic aspects. Curr Top Pathol 1989; 80: 183–203.
44. Maiorano E, *et al.* Expression of intermediate filaments in chordomas. An immunocytochemical study of five cases. Pathol Res Pract 1992; 188: 901–7.
45. Plate KH, Bittenger A. Value of immunocytochemistry in aspiration cytology of sacrococcygeal chordoma. A report of two cases. Acta Cytol 1992; 36: 87–90.
46. Mori K, *et al.* Expression of E-cadherin in chordomas: diagnostic marker and possible role in tumor cell affinity. Virchows Arch 2002; 440: 123–7.
47. Hiroguchi H, *et al.* Expression of cell adhesion molecules in chordomas: an immunohistochemical study of 16 cases. Acta Neuropathol 2004; 107: 91–6.
48. Persons DL, Bridge JA, Neff JR. Cytogenetic analysis of two sacral chordomas. Cancer Genet Cytogenet 1991; 56: 197–201.
49. Gibas Z, Miettinen M, Sandberg AA. Chromosomal abnormalities in two chordomas. Cancer Genet Cytogenet 1992; 58: 169–73.
50. DeBoer JM, Neff JR, Bridge JA. Cytogenetics of sacral chordoma. Cancer Genet Cytogenet 1992; 64: 95–6.
51. Mertens F, *et al.* Clonal chromosome aberrations in three sacral chordomas. Cancer Genet Cytogenet 1994; 73: 147–51.
52. Bridge JA, Pickering D, Neff JR. Cytogenetic and molecular cytogenetic analysis of sacral chordoma. Cancer Genet Cytogenet 1994; 75: 23–5.
53. Butler MG, *et al.* Cytogenetic, telomere, and telomerase studies in five surgically managed lumbosacral chordomas. Cancer Genet Cytogenet 1995; 85: 51–7.
54. Gil Z, *et al.* Cytogenetic analysis of three variants of clival chordoma. Cancer Genet Cytogenet 2004; 154: 124–30.
55. Riva P, *et al.* Mapping of candidate region for chordoma development to 1p36.13 by LOH analysis. Int J Cancer 2003; 107: 493–7.
56. Matsuno A, *et al.* Immunohistochemical examination of proliferative potentials and the expression of cell cycle-related proteins of intracranial chordomas. Hum Pathol 1997; 28: 714–19.
57. Eisenberg MB, *et al.* Loss of heterozygosity in the retinoblastoma tumor suppressor gene in skull base chordomas and chondrosarcomas. Surg Neurol 1997; 47: 156–61.
58. Deniz ML, *et al.* Expression of growth factors and structural proteins in chordomas: basic fibroblast growth factor, transforming growth factor α, and fibronectin are correlated with recurrence. Neurosurgery 2002; 51: 753–60.
59. Pallini R, *et al.* Chordoma of the skull base: predictors of tumor recurrence. J Neurosurg 2003; 98: 812–22.
60. Naka T, *et al.* Skull base and nonskull base chordomas. Clinicopathologic and immunohistochemical study with special reference to nuclear pleomorphism and proliferative activity. Cancer 2003; 98: 1934–41.
61. Horbinski C, *et al.* The prognostic value of Ki-67, p53, epidermal growth factor receptor, 1p36, 9p21, 10q23, and 17p13 in skull base chordomas. Arch Pathol Lab Med 2010; 134: 1170–6.
62. Walter BA, Begnami M, Valera VA, Santi M, Rushing EJ, Quezado M. Gain of chromosome 7 by chromogenic in situ hybridization (CISH) in chordomas is correlated to c-MET expression. J Neurooncol 2011; 101: 199–206.
63. Ostroumov E, Hunter CJ. Identifying mechanisms for therapeutic intervention in chordoma: c-Met oncoprotein. Spine 2008; 33: 2774–80.
64. Duan Z, *et al.* Differential expression of microRNA (miRNA) in chordoma reveals a role for miRNA-1 in Met expression. J Orthop Res 2010; 28: 746–52.
65. Ogi H, *et al.* Cutaneous metastasis of CNS chordoma. Am J Dermatol 1995; 17: 599–602.
66. Hall WA, Clark HB. Sacrococcygeal chordoma metastatic to the brain with review of the literature. J Neurooncol 1995; 25: 155–9.
67. Bethke KP, Neifeld JP, Lawrence W. Diagnosis and management of sacrococcygeal chordoma. J Surg Oncol 1991; 48: 232–8.
68. Lybeert MLM, Meerwaldt JH. Chordoma. Report on treatment results in eighteen cases. Acta Radiol Oncol 1986; 25: 41–3.
69. Schoenthaler R, *et al.* Charged particle irradiation of sacral chordomas. Int J Radiat Oncol Biol Phys 1993; 26: 291–8.
70. Bergh P, *et al.* Prognostic factors in chordoma of the sacrum and mobile spine. A study of 39 patients. Cancer 2000; 88: 2122–34.
71. Yoneoka Y, *et al.* Cranial base chordoma – long term outcome and review of the literature. Acta Neurochir (Wien) 2008; 150: 773–8.
72. Al-Mefty O, Borba LAB. Skull base chordomas: a management challenge. J Neurosurg 1997; 86: 182–289.
73. Volpe NJ, *et al.* Neuro-ophthalmologic findings in chordoma and chondrosarcoma of the skull base. Am J Ophthalmol 1993; 115: 97–104.
74. Crockard HA, *et al.* A multidisciplinary team approach to skull base chordomas. J Neurosurg 2001; 95: 175–83.
75. Oot RF, *et al.* The role of MR and CT in evaluating clival chordomas and chondrosarcomas. Am J Roentgenol 1988; 151: 567–75.
76. Sze G, *et al.* Chordomas: MR imaging. Radiology 1988; 166: 187–91.
77. Larson TC, Houser OW, Laws ER. Imaging of cranial chordomas. Mayo Clin Proc 1987; 62: 886–93.
78. Meyer SP, *et al.* Chordomas of the skull base: MR features. Am J Neuroradiol 1992; 13: 1627–36.
79. Leproux F, *et al.* MRI of cranial chordomas: the value of gadolinium. Neuroradiology 1993; 35: 543–5.
80. Kumar AJ, *et al.* Imaging features of skull base tumors. Neuroimag Clin North Am 1993; 3: 715–34.
81. Ikushima I, *et al.* Chordomas of the skull base: dynamic MRI. J Comp Ass Tomogr 1996; 20: 547–50.
82. Rosenthal DI, *et al.* Sacrococcygeal chordoma: magnetic resonance imaging and computed tomography. Am J Roentgenol 1985; 145: 143–7.
83. De Bruïne FT, Kroon HM. Spinal chordoma: radiologic features in 14 cases. Am J Roentgenol 1988; 150: 861–3.
84. Erdem E, *et al.* Comprehensive review of intracranial chordoma. Radiographica 2003; 23: 995–1009.
85. Lanzino G, *et al.* Chordomas and chondrosarcomas involving the cavernous sinus: review of surgical treatment and outcome in 31 patients. Surg Neurol 1993; 40: 359–71.
86. Gay E, *et al.* Chordomas and chondrosarcomas of the cranial base: results and follow-up of 60 patients. Neurosurgery 1995; 36: 887–97.
87. Sciubba DM, Chi JH, Rhines LD, Gokaslan ZL. Chordoma of the spinal column. Neurosurg Clin North Am 2008; 19: 5–15.
88. Ozaki T, Hillmann A, Winkelmann W. Surgical treatment of sacrococcygeal chordoma. J Surg Oncol 1997; 64: 274–9.
89. Arnold H, Herrmann HD. Skull base chordoma with cavernous sinus involvement. Partial or radical tumour-removal? Acta Neurochir 1986; 83: 31–7.
90. Crumley RL, Gutin PH. Surgical access for clivus chordoma. The University of California, San Francisco, experience. Arch Otolaryngol Head Neck Surg 1989; 115: 295–300.
91. Sen CN, *et al.* Chordoma and chondrosarcoma of the cranial base: an 8-year experience. Neurosurgery 1989; 25: 931–41.
92. Goel A. Middle fossa sub-gasserian ganglion approach to clivus chordomas. Acta Neurochir 1995; 136: 212–16.
93. Maira G, *et al.* Surgical treatment of clival chordomas: the transsphenoidal approach revisited. J Neurosurg 1996; 85: 784–92.
94. Megerian CA, *et al.* The subtemporal-transpetrous approach for excision of petroclival tumors. Am J Otol 1996; 17: 773–9.

95. Jho HD, *et al.* Endoscopic transsphenoidal resection of a large chordoma in the posterior fossa. Acta Neurochir 1997; 139: 343–8.
96. Samii A, *et al.* Chordomas of the skull base: surgical management and outcome. J Neurosurg 2007; 107: 319–24.
97. Al-Mefty O, Kadri PAS, Hasan DM, Isolan GR, Pravdendova S. Anterior clivectomy: surgical technique and clinical applications. J Neurosurg 2008; 109: 783–93.
98. Dehdashti AR, Karabatsou K, Ganna A, Witterick I, Gentili F. Expanded endoscopic endonasal approach for treatment of clival chordomas: early results in 12 patients. Neurosurgery 2008; 63: 299–309.
99. Samson IR, *et al.* Operative treatment of sacrococcygeal chordoma. A review of twenty-one cases. J Bone Joint Surg 1993; 75: 1476–84.
100. Berson AM, *et al.* Charged particle irradiation of chordoma and chondrosarcoma of the base of skull and cervical spine: the Lawrence Berkeley laboratory experience. Int J Radiat Oncol Biol Phys 1988; 15: 559–65.
101. Austin-Seymour M, *et al.* Fractionated proton radiation therapy of chordoma and low-grade chondrosarcoma of the base of skull. J Neurosurg 1989; 70: 13–17.
102. Austin-Seymour M, *et al.* Fractionated proton radiation therapy of cranial and intracranial tumors. Am J Clin Oncol 1990; 13: 327–30.
103. Keisch ME, Garcia DM, Shibuya RB. Retrospective long-term follow-up analysis in 21 patients with chordomas of various sites treated at a single institution. J Neurosurg 1991; 75: 374–7.
104. Austin JP, *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: 439–44.
105. Thieblemont C, *et al.* Prognostic factors in chordoma: role of postoperative radiotherapy. Eur J Cancer 1995; 31: 2255–9.
106. Tai PTH, Craighead P, Bagdon F. Optimization of radiotherapy for patients with cranial chordoma. A review of dose-response ratios for photon techniques. Cancer 1995; 75: 749–56.
107. Saxton JP. Chordoma. Int J Radiat Oncol Biol Phys 1981; 7: 913–15.
108. Cummings BJ, Hodson DI, Bush RS. Chordoma: the results of megavoltage radiation therapy. Int J Radiat Oncol Biol Phys 1983; 9: 633–42.
109. Thilmann C, *et al.* Intensity-modulated radiotherapy of sacral chordoma. A case report and a comparison with stereotactic conformal radiotherapy. Acta Oncol 2002; 41: 395–9.
110. Gabriele P, *et al.* Feasibility of intensity-modulated radiation therapy in the treatment of advanced cervical chordoma. Tumori 2003; 89: 298–304.
111. Jena R, *et al.* Conformal rotation therapy with central axis beam block is a feasible alternative to intensity-modulated radiotherapy for chordomas of the cervical spine. Clin Oncol 2004; 16: 449–56.
112. Taylor RE, *et al.* Proton therapy for base of skull chordoma: a report of the Royal College of Radiologists. The proton therapy working party. Clin Oncol 2000; 12: 75–9.
113. Amichetti M, Cianchetti M, Amelio D, Enrici RM, Minniti G. Proton therapy in chordoma of the base of the skull: a systematic review. Neurosurg Rev 2009; 32: 403–16.
114. Takahashi S, Kawase T, Yoshida K, Hasegawa A, Mizoe J. Skull base chordomas: efficacy of surgery followed by carbon ion radiotherapy. Acta Neurochir 2009; 151: 759–69.
115. DeLaney TF, Liebsch NJ, Pedlow FX, *et al.* Phase II study of high-dose photon/proton radiotherapy in the management of spine sarcomas. Int J Rad Oncol Biol Phys 2009; 74: 732–9.
116. Imai R, *et al.* Effect of carbon ion radiotherapy for sacral chordoma: results of phase I-II and phase II clinical trials. Int J Rad Oncol Biol Phys 2010; 77: 1470–6.
117. Noël G, *et al.* Combination of photon and proton radiation therapy for chordomas and chondrosarcomas of the skull base: the Centre de Protontherapie D'Orsay experience. Int J Rad Oncol Biol Phys 2001; 51: 392–8.
118. Schulz-Ertner D, *et al.* Radiotherapy for chordomas and low-grade chondrosarcomas of the skull base with carbon ions. Int J Rad Oncol Biol Phys 2002; 53: 36–42.
119. Imai R, *et al.* Carbon ion radiotherapy for unresectable sacral chordomas. Clin Cancer Res 2004; 10: 5741–6.
120. Kumar PP, *et al.* Local control of recurrent clival and sacral chordoma after interstitial irradiation with iodine-125: new techniques for treatment of recurrent or unresectable chordomas. Neurosurgery 1988; 22: 479–83.
121. Kondziolka D, Lunsford LD, Flickinger JC. The role of radiosurgery in the management of chordoma and chondrosarcoma of the cranial base. Neurosurgery 1991; 29: 38–46.
122. Feigl GC, Bundschuh O, Gharabachi A. *et al.* Evaluation of a new concept for the management of skull base chordomas and chondrosarcomas. J Neurosurg 2005; 102: 165–70.
123. Ito E, Saito K, Okada T, Nagatani T, Nagasaka T. Long-term control of clival chordoma with initial aggressive surgical resection and gamma knife radiosurgery for recurrence. Acta Neurochir (Wien) 2010; 152: 57–67.
124. Henderson FC, McCool K, Seigle J, Walter J, Harter W, Gagnon GJ. Treatment of chordomas with cyberknife: Georgetown University experience and treatment recommendations. Neurosurgery 2009; 64: A44–A53.
125. Fleming GF, *et al.* Dedifferentiated chordoma. Response to aggressive chemotherapy in two cases. Cancer 1993; 72: 714–18.
126. Newton HB. Molecular neuro-oncology and the development of "targeted" therapeutic strategies for brain tumors. Part 1 – growth factor and ras signaling pathways. Expert Rev Anticancer Ther 2003; 3: 595–614.
127. Barry JJ, *et al.* The next step: innovative molecular targeted therapies for treatment of intracranial chordoma patients. Neurosurgery 2011; 68: 231–40.
128. Casali PG, *et al.* Imatinib mesylate in chordoma. Cancer 2004; 101: 2086–97.
129. Singhal N, Kotasek D, Parnis FX. Response to erlotinib in a patient with treatment refractory chordoma. Anti-Cancer Drugs 2009; 20: 953–5.
130. Stacchiotti S, Marrari A, Tamborini E, *et al.* Response to imatinib plus sieolimus in advanced chordoma. Ann Oncol 2009; 20: 1886–94.
131. Newton HB. Molecular neuro-oncology and the development of "targeted" therapeutic strategies for brain tumors. Part 2 – PI3K/Akt/PTEN, mTOR, SHH/PTCH, and angiogenesis. Expert Rev Anticancer Ther 2004; 4: 105–28.
132. Schwab J, *et al.* Combination of PI3K/mTOR inhibition demonstrates efficacy in human chordoma. Anticancer Res 2009; 29: 1867–72.