THE BIOLOGY AND NATURAL HISTORY OF CHORDOMAS

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Chordoma is an uncommon neoplasm that is believed to be derived from areas of primitive notochordal tissue. Although this tumor may arise anywhere along the vertebral axis, it is most often found at the ends of the spinal column. Chordomas originate at the skull base in about 30-40% of cases, and in the sacrococcygeum in about 50% of cases. There is little difference in the basic biological behaviour of intracranial and vertebral chordomas. This review will focus on intracranial chordomas for obvious reasons, but mention will also be made of the significantly different aspects of the biology of the vertebral chordomas.

Chordomas are histologically benign, slow-growing tumors that occur most frequently at the cranial and sacral ends of the axial skeleton. Approximately 30-40% of all chordomas are localized to the cranium; of these, the vast majority extensively involve the skull base, resulting in neurological symptoms and a slow, inexorable course that is nearly always fatal.

The similarities in histological appearance between the typical chordoma and the fetal notochord were discovered by pathologists more than a century ago. Thought to be derived initially from the epithelium, the notochord is the initial axial structure in human embryogenesis. Except for its contribution to the nucleus pulposus, the notochord almost completely disappears by the sixth week of gestation. However, ecchordoses, or small nests of ectopic notochordal tissue that persist into adult life, can be found incidentally in approximately 2% of autopsies. It has been thought, but not proven, that chordomas may arise from these aberrant notochordal nodules.

Chordomas at the skull base account for approximately 1% of all intracranial malignancies. They are found predominantly in adults and usually occur at about 40 years of age, approximately 10 years earlier than the sacral chordomas. The results of several large series suggest that intracranial chordomas affect males twice as often as females. There does not appear to be a genetic predisposition to the development of chordoma.

Intracranial chordomas are preferentially located over an extensive area of the skull base, including the sellar and parasellar regions, the lateral middle cranial fossa, the cerebellopontine angle, and occasionally extending as far anteriorly as the olfactory groove. Chordomas are generally expansile lesions that erode bone and often form a soft tissue mass. Tumors arising from the rostral clivus have been classified as basisphenoidal chordomas, while those arising from the caudal clival margin, at or below the spheno-occipital synchondrosis, have been classified as basi-occipital. By virtue of their proximity to the pons and diencephalon, basisphenoidal chordomas tend to cause upper cranial nerve palsies and endocrine disturbances. Basi-occipital chordomas generally produce lower cranial nerve palsies and long tract signs. Lateral extension of the tumor usually gives rise to unilateral signs. In approximately one-third of cases, basisphenoidal and basi-occipital chordomas extend ventrally into the nasal cavities, the paranasal sinuses, and the pharynx. Rarely, craniocervical chordomas will present extracranially as exophthalmos in patients with orbital invasion or as a mass in the parotid region in patients with extensive ventral tumor spread from the clivus.

The biological behavior of cranial chordomas is reflected in their x-ray appearance.

Erosion of bone at the base of the skull is seen in 75-95% of cases, intratumoral calcification in 30-50%, a soft tissue tumor mass in the sphenoid sinus in 40%, and evidence of bilateral destruction of bone in approximately 60%. Sclerosis of bone is rare.

The cut pathological surfaces of the typical chordoma are soft, with a lobulated pattern of greyish areas frequently showing focal hemorrhage. Microscopically, chordomas are composed of compact masses of elongated cords of clear cells known as physaliferous cells. The lobulated appearance is often supported by thick strands of fibrous connective tissue. Within the lobules, tumor cells may be PAS- and mucicarmine-positive. Mitotic activity is rarely encountered. Immunohistochemical studies have recently demonstrated keratin-, epithelial membrane antigen-, and S-100-positivity in most classic chordomas. By electron microscopy, epithelial-like cell:cell junctions such as desmosomes are often found. The presence of keratin-positive tumor cells and desmosomes within the classic chordomas argues strongly for their origin from the epithelium. In addition, studies on human fetal notochord have similarly demonstrated keratin-positive cells and desmosomes by electron microscopy, further supporting the notion that chordomas derive from the primitive notochord.

Although patients with cranial chordoma survive longer than those with nasopharyngeal carcinoma or chondrosarcoma of the skull base, there are probably no real cures in patients with chordoma in the sense that their survival rate becomes equal to that of the general popultion. There appears to be little success in delaying the progression of the disease, and most patients die of uncontrolled, recurrent local tumor growth. The 5-year survival rate for the classic chordoma is 30-50%.

The chondroid variant of chordoma has an unusual biological behavior. Its histological appearance is similar to that of the classic chordoma, except for the conspicuous presence of cartilaginous foci intertwined with tumor cells. Unlike the typical chordoma, the chondroid chordoma appears in younger patients (average age: 35 years), is equally common among men and women, has a preference for the basi-occiput, and is associated with a far better 5-year survival rate; many patients live for two to three decades after diagnosis.

The metastatic potential for cranial chordomas is about 10%. Blood-borne metastases have been found in the lung, liver, lymph, bone, skin, and peritoneum. As the duration of patient survival increases, so does the metastatic potential. It has been suggested that the malignant and metastatic potentials of chordomas are lower when cartilaginous foci are present. Some evidence also suggests that the more anaplastic the chordoma, the more likely it is to metastasize. In later stages of growth, chordomas can invade and transgress the dura and leptomeninges, which may explain the rare dissemination of chordomatous nodules in the subarachnoid space.

The diagnosis of vertebral chordoma should be entertained in patients with longstanding symptoms such as pain in the low back or coccygeal region, radicular pain, rectal dysfunction, and sensory disturbances. Vertebral chordomas often involve two or more vertebrae, producing destructive lesions which often have a sclerotic rim. The intervertebral discs are commonly affected. A paraspinal soft tissue mass, half the time containing calcification, is often present and more extensive than the osseous involvement. Sacral lesions are often characterized by a midline destructive lesion, occasionally associated with expansion, with or without osteosclerosis. A firm, fixed, extrarectal, presacral mass which may contain calcification or fragments of bone is almost always present. The pathology and metastatic potential of vertebral chordoma are the same as for the intracranial chordoma, and there have been several series which have reported similar survival rates for patients with vertebral and intracranial chordoma.

Table 1. Characteristics of skull base tumors

Tumor	Frequency	M:F ratio	Genetics	Age at Onset (years)	X-ray appearance	Survival	Metastases	Radiosensitivity	Other
Meningioma	8% of all intracranial tumors	1:3	Von Recklinghausens	20–60	hyperostosis	less than normal population at 15 years	rare	probably radiosensitive	sex steroid hormones
Chordoma	1% of all intracranial tumors	2:1	--	40	erosion of bone tumor Ca^{++} sphenoid mass	30–50% 5-year	10%	unknown	chondroid chordoma variant
Nasopharyngeal Carcinoma	25% of NPCs affect skull base	3:1	HLA A2, BW46, D, DR	45	destruction of bone	20–40% 5-year	55%	radioresistant except lympho-epithelioma	Chinese, EBV
Chondro-sarcoma	6% of all skull base tumors	1:1	--	30–40	erosion of bone tumor Ca^{++}	40–60% 5-year	rare	radioresistant	--
Esthesioneuro-blastoma	3% of all nasal tumors	2:1	--	bimodal: 20–30; 50–60	erosion of cribiform plate	40% 5-year	20–40%	radiosensitive	long survival with RT
Glomus jugulare	1% of all intracranial tumors	1:6	familial clustering	55	destruction of bone	93% 10-year	rare	local control frequent	--

EBV = Epstein-Barr virus; NPC = nasopharyngeal carcinoma; Ca^{++} = calcification; RT = radiation therapy.

Biochemical studies have shown that the mucinous, metachromatically staining matrix of the chordoma contains a concentration of glycosaminoglycan that is more similar to the fetal notochord than to mature, adult intervertebral discs. Since cartilaginous matrix is primarily composed of glycosaminoglycans and has been found to modulate the growth and proliferation of tumor cells, further biochemical studies may help to delineate more fully the biology of chordoma.

The biological characteristics of chordomas and other skull base tumors are summarized in Table I.

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SURGICAL APPROACHES TO INTRACRANIAL CHORDOMAS

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Location is the predominant factor which determines the choice of a surgical approach. The most common tumors arise from the upper clivus involving the cerebellopontine angles bilaterally, the midbrain, posterior hypothalamus, pituitary, and cavernous sinuses. Cranial nerves II through VIII are at risk. The second common location is the lower half of the clivus from the cerebellopontine angle down to the foramen magnum. Cranial nerves VII through XII are commonly involved and brainstem compression is pontine and medullary rather than midbrain. The basilar artery and its branches are commonly distorted by either of these tumors, but since they are largely extradural, it is uncommon for the arteries to be incorporated into the tumor capsule. A third (unusual) location is the lateral clivus. These tumors are usually small, eccentrically placed, and diagnosed only when they arise in the immediate vicinity of a cranial nerve which they compress causing isolated symptoms which lead to early diagnosis. In our series, these small isolated tumors have always been high at the junction of clivus and sphenoid bone.

Goals of Treatment

The outcome of treatment for chordoma is dismal. While long-term survivors are possible, cures are rare and recurrence the rule. The date no combination of therapy has produced satisfactory results. The least useful technique is limited surgery. To date the best results have been obtained through radical resection followed by local irradiation. The goal of surgery should be a radical removal with excision of bone well back from the margins of the tumor. These tumors are relatively well-encapsulated and are excluded by the dura most of the time. A dissection of the capsule from surrounding structures followed by excision of tumor-bearing bone holds the possibility of surgical cure, and this should always be the goal. The nature of these tumors is such that they frequently grow to enormous size before they are detected and this kind of total removal cannot be obtained. Nevertheless, this should be the goal, and the choice of the surgical procedure is predicated upon the desire of the surgeon to obtain a total removal with tumor-free margins rather than biopsy and decompression. Of course, sometimes the decompression is the only possibility and then adjuncts of therapy are necessary.

Surgical Approaches for Intracranial Chordomas

Subfrontal or Subtemporal Craniotomy

Approaching chordomas by traditional subfrontal or subtemporal craniotomy is of little value. These are extradural tumors and most commonly the surgeon is confronted with a large smooth expansion of the dura which distorts the brain, but is not truly intracranial. Whilea significant amount of tumor can be removed by this route, it is more common that a biopsy is obtained and inadequate decompression done and the patient has been benefited little except for the diagnosis. The newer extracranial approaches offer much more in terms of the possibility of prolonged palliation or cure and from the standpoint of decompression.

The Extradural Subfrontal Approach (The Derome Procedure)

Tumors which involve the upper one-third to one-half of the clivus without invasion of

the cavernous sinuses may be approached by a subfrontal extradural route. Derome has described this approach in detail and defined its limitations. Before undertaking this procedure, it is important to be certain of the size of the tumor and its extensions. It is not possible to go far laterally, and if the cavernous sinus is involved in one or both sides, there are simpler ways to achieve palliation. When it appears that total removal will be possible, this approach provides excellent orientation to the optic chiasm, structures of the cavernous sinus and upper brain stem which is more traditional and therefore more familiar most neurosurgeons. The operation begins with a bifrontal bone flap. The flap should be turned as low as possible and the frontal sinus entered if necessary to keep the lower margin of the flap on the supraorbital ridge. The attachment of the dura to the crista galli must be divided and then the frontal lobes elevated leaving the dura intact. When the planum is completely exposed, self-retaining retractors are put in place and the sphenoid sinus opened by totally opening the planum. If the ethmoids are involved, they may be included in the resection. However, since the operation is more useful for tumors which involve only the upper clivus and posterior portion of the sphenoid, it is rarely necessary to include the ethmoids in the resection. The sphenoid sinus is opened exposing the tumor. The resection of tumor then depends upon its extent. The pituitary can be exposed and reflected upward and an extensive removal of the posterior wall of the sphenoid sinus and upper clivus achieved. The ultrasonic dissector or laser are useful adjuncts which greatly expedite removal of these tumors, which usually are gelatinous but may sometimes be quite cartilaginous in nature. The disadvantages of this approach are the extensive nature of the brain retraction, sacrifice of olfaction and the lateral limitations imposed by the structures of the cavernous sinus. The principal advantage is the excellent exposure in an orientation familiar to neurosurgeons.

Midfacial Degloving

This operation is the most useful of the various approaches to the upper clivus and can be utilized with tumors which have extensively invaded sphenoid maxillary and ethmoid sinuses. The patient is positioned in the supine position with the head and torso angled up about 30°. An oral tube is used. The incision is sublabial and extends as far laterally as possible. The soft tissues of the face are then lifted off the skull to expose both maxillary sinuses. The front walls of the maxillary sinuses are removed providing access to the sphenoid through both maxillary sinuses. Tumor involving the maxillary sinuses is removed. If tumor is in the ethmoid, then the ethmoidal resection can take place at this point. The sphenoid sinus is opened from both sides and the combination of the exposure of maxillary sinuses and sphenoid sinus provides extensive exposure of the upper clivus and entire skull base. The angle is somewhat difficult. The anatomy is unusual for the neurosurgeon not used to this approach, but probably does not present difficulties for the skilled pituitary surgeon. The cavernous sinuses are not nearly so limiting and this exposure will allow removal of large subtemporal extensions and provides access far down the clivus. Exiting cranial nerves can be visualized and seen. This is the best of current approaches to the large tumors which involve the anterior skull base. The advantages of the approach are the ability to remove extensions of tumor from all the paranasal sinuses, the broad exposure of the anterior skull base, and the excellent view it affords of the brain stem. The principal disadvantage is the lack of a way to stop a CSF leak reliably. If the tumor has an extensive intradural component or the dura has been shredded so that CSF will leak after tumor removal, it is extremely difficult to stop that leak. The whole area is packed with fat, but there is nothing really to hold it in place. Our current approach in such a situation is to immediately place a spinal drain, pack the area as well as possible, and maintain the drain until the wound appears to be sealed. This extensive operation is amazingly well tolerated by patients. Most are awake, alert, and eating within a few hours of surgery. The risk to

the brain is minimal. This is the best of the approaches to the upper clivus currently available.

The Transoral Approach

The clivus may be approached by splitting the midline structures. The operation most familiar to neurosurgeons involves a transoral procedure in which the posterior pharyngeal wall and soft palate are divided to expose the clivus. This is adequate for biopsy and for very small tumors, but the overall area exposed is quite small and radical tumor removal is not possible. In order to remove anything but the smallest kind of tumor, it is necessary to carry out a much more extensive procedure. The patient is placed in the supine position and nasal intubation employed. A midline skin incision over the mandible is made and the mandible is divided. It is important to remember adequate occlusion; so, a preoperative guide can be fashioned to prevent any abnormalities of inaccurate approximation of the mandibular halves. The tongue and floor of the mouth is then split and these structures retracted laterally so that a broad exposure of the skull base is possible. This operation allows adequate exposure of the entire clivus. It is best for lesions of the lower third, but will expose virtually all tumors. Radical tumor resection with good visualization of lateral margins is possible. This exposure is the principal advantage. The second advantage is that a tight posterior closure can be obtained if the CSF space in front of the brain stem is entered. The principal disadvantage is the extensive nature of the procedure with the need for division of the mandible and tongue. It is then important to approximate the tongue and mandible so that their function is not impaired and so that occlusion is restored to normal.

The Transpalantinotemporal Approach (The Holliday Procedure)

This operation is most useful for tumors more laterally placed at the junction of clivus with sphenoid. The patient is either placed in the park-bench position or is supine with one shoulder elevated on a roll. The head should be parallel to the floor. The incision is made in the hairline behind the orbit, down in front of the ear, and then carried down in a convenient skin fold behind the angle of the mandible into the neck if an extensive exposure of neck vessels is required. There are many variations possible, but the usual chordoma requires that the zygoma be removed and then replaced on closure, the jaw dislocation anteriorly, in some more radical descriptions the ramus of the mandible is actually divided and then replaced, but this is not necessary. The high speed drill is then used to remove the lower portion of the temporal bone and the sphenoid bone to the skull base until the clivus is reached. The carotid artery can be skeletonized, the gasserian ganglion exposed, sphenoid bone can be removed to the optic canal and the posterior two-thirds of the orbit can be exposed laterally by this approach. The 7th nerve may need to be rerouted. In spite of this extensive exposure, the operation is well tolerated by patients, since the brain is virtually not exposed. Temporary 7th nerve palsy may occur from the rerouting, but if the mandible and zygoma are appropriately replaced, the morbidity is otherwise small. The advantages of the operation are the small incision, the small brain exposure and the minimal morbidity. The principal disadvantage is the limited exposure of the tumor which does not allow a completely extracapsular dissection. Since such a dissection is rarely possible anyway. This is not a major disadvantage.

Chordomas of the Lower Third of the Clivus

The midline approaches which have already been described are the best for radical removal of chordomas of the lower third of the clivus. Surgery is not different than those used for higher tumors. However, there are some technical details that are of great importance. It is not uncommon for the lower cranial nerves, 9 through 12, to be involved

bilaterally. 9th and 10th nerve injury deficits are well known and certainly appreciated, but bilateral 12th nerve palsies are virtually as bad. The location of these cranial nerves and their preservation is an important part of these operations.

The Posterior Transtemporal Approach

Another operation which is useful for excentrically placed chordoma is the transpetrous approach similar to that utilized for tumors of the jugular bulb. The patient is placed in the park-bench position and a curved retroauricular incision planned. This should extend far enough back to allow exposure of the lateral third of the occipital bone so the surgeon can gain control of the sigmoid sinus if necessary. The incision has been curved down into the neck, along the anterior border of the sternoclidal mastoid muscle. Radical removal of the petrous bone with a high speed drill is then done. The structures of the jugular bulb can be identified and skeletonized. The carotid artery can be followed and exposed. For those tumors which extend into the upper cervical canal, it is possible to swing the incision slightly further back and then expose the lateral aspect of C-1 and C-2. The vertebral artery can be unroofed in its bony canal at C-1 and C-2 and then mobilized out of the way to allow access to the region of the odontoid and the anterior or posterior portions of C-1 and C-2. Most commonly, tumors in this location involve the odontoid and the anterior arch of C-1, so this is the area of access. The disadvantage of the procedure is the limited access to the midline that it provides. The principal advantage is the fact that the lateral structures and the space anterior to the upper cervical cord can be reached more directly than with the midline approach.

SUMMARY

Chordomas of the clivus, whether midline or laterally placed, represent a major challenge for which no good solution is yet available. The principal goal of surgery is total tumor removal with preservation of all adjacent neural and vascular structures. This is possible with small circumscribed lesions and hopefully the better imaging techniques now available will provide early diagnosis for more of these small tumors. Because these tumors are so often silent for a long period, they frequently grow to enormous size before they are detected. Most of these tumors cannot be cured by surgery, but a gross total removal with preservation of surrounding neural and vascular structures should still be the surgical goal for maximum palliation. The radical midface degloving provides the best access for tumors of the upper clivus spreading into the paranasal sinuses and beneath the temporal lobes. Midline approaches are best for tumors of the lower clivus. The lateral techniques are superior for tumors which are excentrically placed and involve the temporal and sphenoid bones as well as the clivus.

These are all difficult and unusual approaches. The surgical exposure and the exposed anatomy are not familiar to most neurosurgeons. These are not operations for the uninitiated. Anyone planning to utilize them needs experience either gained in the operating room or in the dissecting room. Since both the exposures and the techniques involved cross a specialty line, a team approach has many advantages. Our surgical team involves neurosurgery, neuro-ophthalmology, and neuro-otology/head and neck surgery. The operations are both time consuming and difficult. The team approach brings not only different skills, but also fresh surgeons at critical points throughout the operation.

There are no series large enough to make meaningful comparisons between success rates involving different operations and it is probable that no such series can be collected. Rather, the operation must be chosen according to the configuration of the tumor to produce the greatest likelihood of surgical cure or maximum palliation.

Radical surgery of the skull base is a new challenge in Neurosurgery. Chordomas are but one of many tumors which involve this region. The techniques applicable to chordomas are useful in all forms of skull base tumor surgery and these unusual operations desire emphasis by neurosurgeons and a place in the armamentarium of all devoted to the treatment of skull base tumors.

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SPINAL CHORDOMAS

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INTRODUCTION

Chordomas are primary malignant tumors of the axial skeleton that are traditionally considered slowly growing, locally invasive neoplasms. These tumors account for between 1-4% of primary malignant bone tumors. Approximately 50% originate in the sacrum, 35% at the base of the skull, and 15% in the true vertebra; there are also occasional reports of chordomas arising from ectopic sites such as the maxilla and paranasal sinuses, larynx, and other soft tissues. Although more than 1000 cases have been reported to date, most institutions treat between two to three cases a year. As a result, carefully designed prospective studies regarding the efficacy of treatment modalities other than complete surgical resection are difficult to design, and current recommendations regarding the value of treatment modalities such as radiation therapy (RT) difficult to evaluate. Using the staging system of the Musculo-Skeletal Society, these tumors are classified as "low grade aggressive neoplasms"; however, their clinical behaviour may be more capricious, with widespread metastases that portend a rapidly fatal outcome.

CLINICAL, RADIOLOGICAL & PATHOLOGICAL FEATURES

Although these tumors have been reported in all age groups, they are predominantly tumors of the fifth through seventh decades of life. In contrast to sacral tumors, tumors arising from the true vertebra tend to occur in a younger age group, and generally have a more aggressive clinical behaviour. The male to female ratio shows a two-to-one preponderance favouring males. Although rare, this tumor represents the most important diagnostic consideration whenever a primary neoplasm of the axial skeleton is encountered in the older patient.

The symptoms and signs of the tumor are related to location and size of the tumor along the spinal axis, and are relatively nonspecific. A history of trauma to the involved region may be present in 40% of patients. Low lying tumors may be asymptomatic for long periods of time i.e. more than a year before the diagnosis is entertained. Pain in the low back or coccygeal region represented the most frequent symptom (72%) in the author's series. Rectal dysfunction (altered bowel habits, obstipation, tenesmus, or bleeding) occurred in 42%. A mass was noted in 17% of patients. Most patients carried the diagnosis of degenerative disc disease or coccydynia, or were being treated for associated or incidental hemorrhoids for many months. Rectal examination invariably disclosed a palpable pre-sacral mass that did not involve the mucosa, but this examination was generally not performed. Vertebral chordomas are generally diagnosed within a year of onset of symptoms, because cord compression is an early presenting feature; the majority of patients may present with back pain and associated radicular deficit, while on occasion, the prevertebral componant may be so large (in cervical lesions) that patients present with dysphagia or a lateral neck mass. Exceptionally, lumbar tumors may grow laterally with very little intra-osseous involvement, and mimic other retroperitoneal tumors.

The conventional radiographic findings of spinal chordomas have been well described in several reviews; sacral tumors are characterized by the destruction of several sacral segments by an expansile ballooning mass; the presence of a presacral mass and calcification may be difficult to appreciate because of overlying gas shadows. Lesions involving the true

vertebra are characterized by focal destructive changes with a surrounding area of reactive sclerosis; adjacent vertebral bodies may be involved with sparing of the disc spaces. Angiography is useful in selected cases for demonstrating encasement or displacement of important vascular structures, such as the carotid and vertebral arteries in the neck. Although chordomas are characteristically avascular tumors, hypertrophic tumor vessels and a tumor blush may be seen on subtraction films. Myelography is essential to rule out epidural extension; virtually every patient with lesions above the sacrum will have varying degrees of epidural extension of tumor at initial presentation.

Computed tomography (CT) scans and magnetic resonance imaging (MRI) are the radiographic examinations of choice for evaluating this tumor. The presence of soft tissue involvement, associated with varying degrees of calcification, along with osseous destruction, and epidural extension is demonstrated with a single examination. Calcification is more evident in sacral lesions and is often amorphous and located at the periphery. The incidence of tumor calcification may vary from 40-80%. Extension of tumor into the epidural space may be suspected whenever obliteration of epidural fat is noted, or if there is a soft tissue density posterior to the vertebral body. Soft tissue extensions often have the same density as adjacent muscle and do not enhance with contrast. Routine use of contrast-enhanced scans is recommended only to detect intracranial extension for those tumors located at the skull base. Although soft-tissue extensions have the same density as muscle, they are often clearly demarcated from adjacent structures, because a well defined pseudocapsule is present. Although these tumors grow strictly in the midline, diagnostic confusion may result when these tumors grow eccentrically and present as pelvic or intra-abdominal masses with minimal or no apparent osseous involvement. In our more recent series, 50% of sacral tumors involved the third through fifth sacral segments, three vertebral tumors were almost entirely intra-osseous with minimal epidural extension. Pathologically, these tumors are well-demarcated, lobulated lesions that vary considerably in size. A well-formed pseudocapsule is noted in the soft tissues, but this capsule is not present within bone. In the bone itself, the boundary between tumor and destroyed bone is indistinct. The consistency varies considerably; the tumor may be soft and jelly-like in most areas, and be firm and cartilaginous in others. Recurrent tumors, especially those that have been treated by radiation, often infiltrate muscle and soft tissues with associated satellite tumor nodule formation. Areas of hemorrhage and necrosis may be present, giving the tumor a frank sarcomatous appearance. Microscopically, the tumors are characterized by the "physaliferous" cell, with its ample vacuolated cytoplasm. The cells are arranged in sheets, cords, or lobules. Dense fibrous septae are sometimes seen; these septae are usually infiltrated by tumor cells or lymphocytes. Occasional giant cells may be observed, but mitotic figures are rare. The distinction between chordomas and chondrosarcomas may pose a diagnostic problem, especially at the skull base. Chondrosarcomas generally stain positively with the phosphotungstic acid-hemotoxylin stain (PTAH) and are readily impregnated with silver reticulin. In limited biopsy specimens, the histologic diagnosis may be confused with mucin-producing adenocarcinoma, myxosarcoma, reticulum cell sarcoma, or chondrosarcoma. In recurrent or radiated tumors, many more anaplastic features, including transformation into spindle cell sarcoma (malignant fibrous histiocytoma) may be seen. Areas of cartilage are occasionally present in true chordomas, resulting in a histologic variant called "chondroid" chordoma. Tumors resembling chordomas are also encountered at ectopic sites, especially adjacent to tendons and bone; these tumors, termed "chordoid sarcoma" may resemble chordomas at the light microscopic level but are probably related to chondrosarcomas on electron microscopy.

Although the propensity of chordomas to recur locally is well known, their metastatic potential is less well appreciated. Early reports indicated that less than 10% of patients with chordomas developed distant metastases. In our series, 40% of patients with spinal

chordomas developed distant metastases, which occurred uniformly throughout the course of the disease. Eleven of 18 vertebral lesions and 10 of 36 sacrococcygeal lesions developed distant metastases, predominantly to lungs, bones, soft tissues, and liver. Chambers and Schwinn found an incidence of 30% in 27 cases, but curiously, the locations of metastases in their study were predominantly skin and bone. In two of three patients with dermal metastases, the lesions in the skin were diagnosed prior to the primary tumor. While the presence of a locally aggressive tumor and the use of radiation therapy are positively correlated with the presence of metastases, the histologic appearance often is not. Metastatic lesions in chordomas have little impact on overall survival, because death usually results from the complications of local treatment failure i.e. paraplegia.

TREATMENT

The two major treatment modalities in the management of the tumor are surgery and radiation therapy. To date, chemotherapy has not proved even marginally effective. Curative surgical resection is precluded in many patients by the extent of tumor at time of initial presentation; therefore, previous data have shown that the disease-free survival is less than 10% despite a median survival of 5 years. In this review, only surgical approaches to sacral tumors will be considered.

For sacral lesions, preoperative evaluation should include sigmoidoscopic evaluation, as well as CT scans and myelography. In the majority of patients, the periosteum of the sacrum and presacral fascia form an unbroken barrier; thus the rectum and other viscera in the pelvis are not infiltrated by tumor till late. Trans-rectal biopsies are to be condemmed, since this transgresses the anterior fibrous barrier and necessitates inclusion of the sacrum if curative surgery is performed. Posteriorly, the tumor may exit through the sacral hiatus, and the posterior resection should therefore include the overlying soft tissues, as well as the biopsy site and tract. A major surgical principle for the surgical management of these tumors is to section continuously through healthy tissue without tumor being entered into at any point (wide local excision). For the sacrum, the osteotomy must be through uninvolved vertebra, and for large tumors may necessitate osteotomies through the canals of the S-1 nerve roots, or above it. Stener has shown that it is possible to section all sacral nerve roots on one side without loss of bladder or bowel function. Furthermore, amputation of the sacrum through the first sacral segment does not impair the pelvic girdle's ability to resist a vertical load without breaking. All radical resections in which complete resection of the tumor was accomplished have yielded long-term disease-free survivors. For smaller tumors, the combined trans-perineal and posterior approach may suffice. If the palpating finger in the rectum can reach the upper margin of the tumor, we advocate this approach.

For tumors involving the true vertebra, previous efforts have largely been limited to laminectomy with limited tumor removal. Since the main mass of the tumor is antero-lateral to the spine, an antero-lateral approach to the spine is indicated. For upper cervical lesions (C1-C3), the trans-mandibular approach provides the best access to the tumor, while true clival lesions are best approached by cranio-facial approaches and resection of the palate. The the thoracic region, thoracotomy is required, while a thoraco-abdominal or retroperitoneal flank approach is used for tumors involving the lower spinal segments. Following tumor resection, stability of the spine should be ensured by the use of methyl-methacrylate or bone grafts. This operative approach is termed "subtotal spondylectomy", and long-term disease-free survival is feasible without additional treatment. If posterior elements are involved, a second stage complete spondylectomy may be required.

Although this tumor is radio-resistant, RT has been advocated for symptomatic palliation of recurrent lesions and inoperable tumors. Doses in excess of 5000 rads are

recommended for "curative" treatment, and lesser doses of 4000-4500 rads are given for palliation. A major limitation in this regard has been the radiation tolerance of the spinal cord; a variety of recently developed techniques to minimize this complication are therefore in evolution. Wedge filter techniques, rotational beam therapy, and the use of brachytherapy to increase the total dose delivered while sparing normal tissues are useful alternatives to conventional RT. In our recent experience, conventional RT has not proved useful in delaying clinical "time to tumor recurrence" following incompletely resected tumors. However, Suit and Saunders have shown that particle beam therapy may allow high doses (up to 7600 cobalt Gray equivalents) to be delivered to inaccessible small tumors with excellent local control. The long-term effectiveness of these sophisticated techniques remains to be established, since local control can also be achieved by spondylectomy alone.

In our recent series of 34 patients, the median survival was 5 years, and a third of the patients are disease-free survivors. All disease-free survivors underwent initial curative surgery, and no patient with recurrent disease was considered cured. These data can be improved upon further, since most patients with spinal chordomas are being diagnosed earlier. The role of RT in the management of patients with microscopic residual disease should be the focus of future prospective studies.

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RADIATION THERAPY OF CHORDOMAS

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Chordomas occur along the craniospinal axis in close association with normal structures of the central nervous system. They occur most commonly in the sacrococcygeal region (50%), while other sites of origin include the base of the skull (35%) and the spine (15%). These tumors are locally aggressive; metastases are uncommon except for massive lesions of the sacrum[1]. The anatomic location of these tumors presents challenges for both the neurosurgeon[2] and the radiation oncologist[3]. Complete surgical resection of these tumors is uncommon[4]. Most patients receive post-operative radiation treatments in an attempt to control the often bulky residual disease. The tumors are located next to normal structures which can be affected by radiation. For base of skull tumors, these structures include the brainstem, the pituitary gland, the optic nerves and chiasm, and the brain. Sacrococcygeal tumors are adjacent to the large and small bowel and spinal chordomas are usually closely associated with the spinal cord. With conventional radiation techniques these tumors can often be given only a moderate dose of radiation, and most tumors recur locally[3,5]. Recently, proton and helium ion radiation treatments have been used for these tumors with promising initial results[6,7].

In order to better understand the results of conventional radiation techniques, a review of the literature is useful. Because the majority of the work with protons and helium ions has been in the base of the skull and cervical spine regions, this literature review will include only these two sites of origin of chordoma. In this review, patients with low-grade chondrosarcomas (Grade I-II) of the base of the skull or the cervical spine have also been included because chordomas and chondrosarcomas in this area can simulate each other pathologically[1]. Most series in the literature each contain only a small number of patients. Forty-five patients with base of skull tumors and nine patients with cervical spine tumors were reported in a total of thirteen publications. All of these patients were initially managed with both surgery and radiation. Only patients treated with radiation beam energies greater than 1 MeV or patients treated since 1960 were included. This group of patients is heterogeneous and many factors such as the extent of the surgical removal and the definition of the radiation target volume are not known for all patients.

Table 1 contains a summary of the 45 patients with base of skull tumors. Forty-one of these patients had chordomas and four had chondrosarcomas. The median dose was 55 Gray (Gy) and the median follow-up time was 3.4 years. Sixteen patients did not have tumor recurrence (36%). Twenty-nine patients had local recurrence, and two of these patients also developed distant metastases. When these results are analyzed using a life table method, the actuarial disease-free survival was 39% at five years and 18% at ten years. In the twenty-nine patients who had local tumor recurrence, the median time to local recurrence or death from disease was 2 years. This review suggests that higher doses of radiation may result in higher local control rates. Seventeen of the 22 patients who received less than 55 Gy (the median dose for the whole group) experienced tumor recurrence, while there were 12 recurrences in the 22 patients who received more than 55 Gy.

Table 2 summarizes the reported results for nine patients with cervical spine tumors. All of these are chordomas. Three have had no tumor recurrence, while six patients have experienced local tumor regrowth. One patient with a local failure also developed distant metastases.

Protons and helium ions have a finite range in tissue. They can provide a better concentration of radiation dose in the tumor than conventional x-rays when the tumor is very close to a radiosensitive normal structure. Protons and helium ions can deliver a dose of radiation to a base of skull chordoma which is higher than the threshold dose for radiation damage to the spinal cord or brainstem. This is possible because of the physical characteristics of these particles and the methods employed in planning and delivering these treatments.

Fractioned radiation therapy with protons has been given since 1974 to patients with chordomas or low grade chondrosarcomas of the base of skull or cervical spine under a collaborative program by the Radiation Medicine Service at Massachusetts General Hospital and the Harvard Cyclotron Laboratory. At HCL, protons are accelerated to 160 MeV and have a 15.9 cm range in soft tissue. The dose decreases very rapidly at the end of the beam range: the dose drops from 80% to 20% in 4 mms.

Protons are only slightly different biologically than conventional x-rays. The biological effectiveness of protons is 1.1 times than of Cobat 60 radiation. Dose is expressed in the units of Cobalt Gray Equipvalent (CGE) and is obtained by multiplying the physical dose in Gy by 1.1.

The initial evaluation of patients with chordomas or low grade chondrosarcomas of the base of skull or cervical spine is a multidisciplinary effort. One important component is the radiographic evaluation of the extent of disease. All patients have high resolution CT scans with intravenous contrast. Recently magnetic resonance images (MRI) have proven to be useful in evaluating the location of the tumor and the relationships between the tumor and normal structures such as the brainstem and optic chiasm. CT scans with intrathecal contrast have also been necessary in some patients to determine the position of the brainstem or spinal cord. A neurosurgical opinion is obtained to evaluate whether additional tumor could be removed prior to beginning proton treatments. In some patients a second surgical procedure has been performed in order to reduce the volume of tumor.

Proton treatments are formulated using a computerized multi-dimensional treatment planning system. The first step is immobilization of the patient. A lightweight face mask and a mold for the neck and shoulders is constructed with the patient supine or seated. In these positions, the mean patient movements are less than 1 mm[19]. A CT scan is then done in the treatment position with the immobilization device in place. This scan is done with a special CT scanner which has been modified to scan patients in either a supine or seated position. The fixed horizontal beam necessitates treatment in the seated position in some cases. The slice thickness is 3 mm through the region of the tumor.

The tumor volumes and the relevant normal structures are then outlined on each slice of the treatment planning scan using an interactive computerized treatment planning system[20]. This is a difficult task which requires the synthesis of all available information including the findings at the time of surgery and the radiographic evaluation.

Treatment fields for the tumor are designed which minimize the radiation dose to adjacent critical normal tissues, such as the brainstem, spinal cord, optic structures and temporal lobes[21]. Distributions of dose using all treatment fields are computed on each CT slice. Before each treatment the position of the tumor relative to the beam aperature is verified radiographically using an iterative process. The field placement accuracy is within 2 mm.

Sixty-three patients have received post-operative fractionated proton radiation

treatments for tumor of the base of skull (50) or the cervical spine (13) with a minimum follow-up time of 16 months. These tumors were either chordomas (39) or grade I-II chondrosarcomas (24). There were 30 females and 33 males. The median age was 39 years. The median tumor dose was 69 CGE with a range from 56.9 CGE to 76.2 CGE. This is 25% higher than the median dose for cases reported in the literature using conventional treatment modalities. The treatments were given over approximately eight weeks with a daily dose of 1.8 to 2.0 CGE. Follow-up has been by clinical examination and CT scan. The median follow-up time is 34 months with range from 16 to 149 months.

For the 50 patients with tumors of the base of skull, the five year actuarial results are 78% for local control and 76% for disease-free survival. Six patients have developed new neurologic symptoms with an increase in tumor size on CT at 8 to 83 months. Four of these patients are stable 1 to 38 months after further surgery for recurrent disease. Four of the six had chordomas. One patient with a chordoma recurred anterior to the original lesion 16 months after treatment. One patient with chondrosarcoma developed a supraclavicular lymph node metastasis 27 months after treatment.

For the 13 patients with cervical spine tumors, seven have had no recurrence of disease. Three patients have had regrowth of tumor in the original area of disease at 22 to 41 months. Three have failed just beyond the margin of the treatment field at 3 to 54 months. Two of these six patients with recurrent tumor have also developed pulmonary metastases.

Five patients have had complications productive of functional impairment. One patient developed unilateral blindness and seizures associated with an enhancing area in the temporal lobe on CT scan nine months after receiving 69 CGE for a parasellar chondrosarcoma. Another patient experienced bilateral visual loss 34 months after receiving 67 CGE for a base of skull chordoma. The optic chiasm had received 60 CGE. This patient also had longstanding diabetes mellitus. An additional patient developed a sudden onset of unilateral blindness 11 months after receiving 70 CGE for a parasellar chondrosarcoma. Two other patients have experienced chronic and severe headaches after treatment of clival tumors.

In our experience proton radiotherapy appears to be an effective treatment modality for chordomas and low-grade chondrosarcomas of the base of the skull and the cervical spine. The five year actuarial local control of 78% for the base of skull tumors compares favorably with the local control rate of 36% achieved with conventional radiation techniques. The initial results of proton treatment for cervical tumors (7 or 13 patients without disease) appear to be somewhat better than the results reported in the literature with a limited number of cases. Further follow-up will be necessary to judge the long-term efficacy of these treatments. A course of proton radiation treatments requires considerable effort. On the average, each daily set-up and treatment takes one hour. The planning for each patient requires approximately forty hours at the computer.

Helium ion radiation has also been used in the treatment of sacral chordomas. This has been possible because the helium ion beam has a 26 cm range in tissue. In 1986, Saunders et al.[22] reported the experience with the initial eight patients. Local control was achieved in seven of eight patients. Prior to the radiation treatments, three patients had gross total tumor removal, two had partial tumor resections, and three had biopsies only. The doses ranged from 70 to 80.5 CGE with a daily fraction size of 2.0 CGE and average follow-up was 33 months.

Twenty-three patients with chordomas and low-grade chondrosarcomas of the base of

skull and cervical spine have received helium ion treatment. The mean dose was 68 CGE and the mean follow-up time was 24 months. Local control has been achieved in sixteen patients. Three patients have developed distant metastases. One patient developed blindness eight months after receiving 72 CGE for a large chordoma of the clivus.

Chordomas are challenging tumors for both the neurosurgeon and the radiation oncologist. The initial results of post-operative fractionated proton and helium ion radiation treatments appear encouraging. Further follow-up will be required to judge the long-term effectiveness of this approach.

Table 1
Base of Skull Chordoma and Chondrosarcoma

Publication	Patient No.*	Histology	Dose (Gy)	Status+	Follow-time (Yrs)
Reddy, et al.	3	chordoma	58	DOD	9
	4	chordoma	50	NED	15
Cummings, et al.	16	chordoma	60	DOD	2.9
	17	chordoma	60	DID	7.2
	18	chordoma	60	DID	3.4
	20	chordoma	52.5	NED	10
	15	chordoma	50	DOD	2.2
	19	chordoma	50	DOD	7.4
	22	chordoma	46	AWD	6
	14	chordoma	45	DOD	1.2
	21	chordoma	25	AWD	8
Saxton		chordoma	65	DOD	10
		chordoma	60	DOD	11
		chordoma	48	DOD	1.5
		chordoma	55	NED	3
		chordoma	35	DOD	7
Pearlman and	5	chordoma	80	AWD	5
Friedman	10	chordoma	70	AWD	1
	11	chordoma	42.8	DOD	2
	12	chordoma	78	DOD	1.5
Perzin and	2	chordoma	50	DOD	1.3
Pushparij	4	chordoma	60	DOD	1.5
	5	chordoma	60	DOD	1.8
	7	chordoma	52	AWD	6.3
	8	chordoma	60	DOD	0.5
	9	chordoma	60	NED	0.8
	13	chordoma	45	AWD	8
Fu and Perzin	9	chondrosarcoma	50	DOD	1.1
	8	chondrosarcoma	50	DOD	4.3
Rich, et al		chordoma	61	NED	3.5
Richter, et al.	2	chordoma	66.3	NED	10.7
	4	chordoma	60	DOD	1
Harwick and	6	chordoma	60	NED	0.6
Miller	7	chordoma	60	NED	0.5
Phillips and	1	chordoma	56	NED	2.3
Newman	2	chordoma	54	NED	5.5
	3	chordoma	50	DOD	1.9
	4	chordoma	60	NED	2.1
	5	chordoma	54	DOD	1.2
	6	chordoma	60	NED	10.5
	10	chordoma	60	DOD	3.5
Krayenbuhl and	4	chordoma	45	AWD	13
Yasargil	8	chordoma	30	NED	1.5
Harwood, et al.	2	chondrosarcoma	50	NED	5
	8	chondrosarcoma	36	AWD	8

* Patient number in original reference
\+ NED = no evidence of disease
DOD = dead of disease
AWD = alive with disease
DID = dead of intercurrent disease

Table 2

CERVICAL SPINE CHORDOMA

Publication	Patient No.*	Dose(Gy)	Status+	Follow-up Time (Yrs)
Cummings, et al.	11	35	NED	15
Pearlman and Friedman	15	70	DOD	1
Harwick and Miller	3	40	AWD	6.5
	5	60	AWD	3.5
Murali, et al.	2	60	DOD	2
	3	45	NED	3
	6	60	AWD	0.3
	7	60	NED	1
Phillips and Newman	11	64	DOD	2

*Patient number in original reference
+NED = no evidence of disease
DOD = dead of disease
AWD = alive with disease

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