# Chordoma and chondrosarcoma of the skull base

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**INTRODUCTION** — The anatomic junction of the neural and facial viscerocranium is termed the skull base (figure 1A-B). This area is critically important because it supports the brain and allows all the neurovascular structures to either enter or exit the skull.

Neoplasms may originate within the skull base or involve it by growth from either the dura or extracranial structures. Skull base tumors include a number of different histologic cell types.

Chordoma and chondrosarcoma arising in the skull base will be reviewed here. Topics discussed elsewhere include:

- Chordomas arising in the sacrum or elsewhere along the spinal cord (see "Spinal cord tumors").
- Chondrosarcomas at sites other than the skull base (see "Chondrosarcoma").
- Other histologic tumor types involving the skull base (see appropriate topic reviews).

## CLINICAL PRESENTATION

**Signs and symptoms** — The clinical presentation of a skull base tumor depends in part upon the site of origin of the tumor and its direction of growth.

Most patients with a skull base tumor complain of headache and intermittent diplopia. Gradually, headache worsens with upper clivus tumors and neck pain develops with lower clivus tumors. Invasion of the cavernous sinus can produce diplopia and facial numbness. Lower clivus tumors initially compress the lower cranial nerves; brainstem compression may follow. The diagnosis of a clival chordoma is often delayed because symptoms are vague.

The clinical features of chordoma and chondrosarcoma are similar [1,2]. In one series of 48 patients with chordoma and 49 with low-grade chondrosarcoma, headache and diplopia from abducens nerve palsy was common in both groups [1]. Normal neurologic examinations were more common in patients with chordoma, while visual loss, facial numbness, and multiple cranial neuropathies were more common in patients with chondrosarcoma. These differences probably reflect the tendency of chordomas to originate from the clivus and chondrosarcomas from the petroclival fissure (junction of clivus and temporal bone).

**Imaging studies** — Magnetic resonance imaging (MRI) is the best technique to assess the soft tissue extent of tumor and visualize its dural extension [3]. Chordomas and chondrosarcomas are typically heterogeneously bright on T2-weighted images, which can aid with diagnosis. CT scan is more effective for demonstrating bone lesions (image 1). Calcification is not uncommon with chondrosarcoma. The characteristic ring-forming calcifications seen on CT scans can be correlated with the histologic pattern of calcification [4]. CT MRI image fusion may provide additional anatomic information regarding the tumor and surrounding tissues [5].

Chondrosarcomas typically originate laterally at the petroclival junction, but there are no pathognomonic imaging findings that distinguish chordoma from chondrosarcoma. Although imaging studies may result in a working diagnosis, biopsy and histologic studies are necessary to confirm the diagnosis. Both chordomas and chondrosarcomas can be staged according to the TNM system for primary malignant tumors of bone (table 1), but this has limited prognostic value in the skull base region.

## PATHOLOGY

**Chordomas** — Chordomas are rare, slow growing, locally aggressive neoplasms of bone that arise from embryonic remnants of the notochord. These tumors typically occur in the axial skeleton and are most common in the sphenooccipital region of the skull base and in the sacral regions [6-11]. In adults, 50 percent of chordomas involve the sacrococcygeal region, 35 percent occur at the base of the skull, and 15 percent are found elsewhere in the vertebral column [6]. Craniocervical chordomas most often involve the dorsum sella, clivus, and nasopharynx. (See "Spinal cord tumors", section on 'Chordomas'.)

Chordomas are divided into three subgroups:

- Conventional chordomas are the most common. They are characterized by the absence of cartilaginous or other mesenchymal components.
- Chondroid chordoma is a distinct entity that contains both chordomatous and chondromatous features and has a predilection for the sphenooccipital region of the skull base [6,12-14]. This variant accounts for 5 to 15 percent of all chordomas and up to 33 percent of cranial chordomas. Chondroid and conventional chordomas appear to have a similar prognosis [15].
- Dedifferentiation or sarcomatous transformation occurs in 2 to 8 percent of chordomas. This can be present at diagnosis or occur later [16,17]. Histologically, the sarcomatous component, which may be a malignant fibrous histiocytoma, fibrosarcoma, osteosarcoma, or chondrosarcoma, is interspersed with areas of conventional chordoma. Most of these aggressive chordomas are aneuploid on DNA analysis (compared to only one-fourth of conventional chordomas) and survival tends to be shorter. In one series of 15 patients with interpretable DNA histograms, 3 of 12 conventional chordomas and all four dedifferentiated chordomas were aneuploid [17]. Four of the seven patients with aneuploid tumors died of disease within two to four years, while only one of eight patients with diploid tumors died of disease at six years.

On gross examination, chordomas are gelatinous, pink or gray masses with solid and cystic areas. Chondroid chordomas demonstrate both chordomatous and variable degrees of benign or malignant cartilaginous components.

Chordomas are composed of lobules that contain epithelioid cells arranged in cords or clusters and separated by fibrous strands in a mucinous matrix. The tumor cells have vesicular nuclei and abundant vacuolated, soap bubble-like cytoplasm (physaliphorous cells) that contains glycogen (PAS positive) or mucin (picture 1). Nuclear pleomorphism and mitoses are uncommon. Ultrastructurally, chordomas exhibit epithelial features with prominent desmosomes.

Tumor cells in almost all chordomas are diffusely and strongly positive for cytokeratin. Staining for epithelial membrane antigen (EMA) is present in more than 80 percent of cases, although it is typically more focal and less strongly positive than other antigen stains [12-14,18]. Expression of brachyury, a key transcription factor in notochord development, appears to be a sensitive and specific biomarker of chordoma, and immunohistochemical staining for brachyury is routinely performed to help distinguish chordoma from cartilaginous tumors [19].

Other immunostains are variable depending upon the type of chordoma. In one study, all 16 classic chordomas stained for keratin, while only 32 percent of 25 chondroid chordomas did [12]. In the same study, 44 percent of the classic and 85 percent of the chondroid chordomas were positive for S-100 protein [12].

**Chondrosarcomas** — Chondrosarcomas are rare malignant cartilaginous tumors that make up 11 percent of primary malignant bone neoplasms and account for about 6 percent of all skull base tumors [4,20,21]. Most skull base chondrosarcomas arise in the middle fossa, followed by the posterior or anterior fossae.

Grossly, chondrosarcomas are smooth, lobulated, hard tumors, and often are more than 2 cm in diameter (picture 2). Microscopically, they are lobulated and, depending upon their degree of differentiation, show increased cellularity, with hyperchromatic and pleomorphic tumor cells, prominent nucleoli, and binucleated or multinucleated chondrocytes.

Microscopic grading has prognostic value in chondrosarcomas.

- Well-differentiated (grade 1) lesions were reclassified as "atypical cartilaginous tumors" (ACT/CS1) in the World Health Organization (WHO) 2013 classification system [22]. They consist of chondrocytes with small, round nuclei and occasional binucleated cells. Mitoses are absent.

- Moderately differentiated (grade 2) chondrosarcomas have more cellularity and less matrix than grade I tumors, and mitoses are widely scattered in the tumor. The nuclei of chondrocytes are enlarged, vesicular or hyperchromatic, and often show more than one cell in a lacuna.

- Poorly differentiated (grade 3) tumors display even more cellularity and nuclear pleomorphism than grade 2 tumors. Cords or clumps of chondrocytes have irregular, vesicular or spindle shaped nuclei, less matrix, and easily found mitoses.

The majority of skull base chondrosarcomas are conventional chondrosarcomas that are ACT/CS1, and less commonly, moderately differentiated (grade 2) tumors (picture 3) [23]. Osteoid metaplasia may be present within a chondrosarcoma and is distinguished from the chondroblastic variant of osteosarcoma by the absence of osteoid that is lined by cytologically atypical osteoblasts.

Other rare types of chondrosarcoma that may present at the skull base include high grade mesenchymal chondrosarcoma, and the so-called extraskeletal myxoid chondrosarcoma. (See "Chondrosarcoma", section on 'Classification, histology, and clinical features'.)

**Differential diagnosis** — Distinguishing chordoma from chondrosarcoma can be difficult histologically but is important because of the significantly better prognosis associated with chondrosarcomas. As an example, in one series of 200 patients with chondrosarcoma, 37 percent initially were referred with a diagnosis of chordoma [23].

The differential diagnosis of chordoma and chondrosarcoma also includes mucinous adenocarcinoma and myxopapillary ependymoma (table 2).

Immunohistochemistry is an important tool in establishing the diagnosis:

- Chondrosarcomas do not express cytokeratin, while S-100 protein expression is present in both chondrosarcomas and chordomas [23,24].
- Tumor cells in chondrosarcoma and myxopapillary ependymoma are negative for cytokeratin and EMA, unlike chordomas [13,14,18]. In addition, they do not have desmosomes on ultrastructural examination.
- Only myxopapillary ependymoma is positive for glial fibrillary acidic protein (GFAP), while chordomas and chondrosarcomas are negative for this marker. In one series, immunoreactivity was present for vimentin and GFAP in all cases and for S-100 protein in 50 percent of myxopapillary ependymomas [14].
- The differentiation of adenocarcinoma from chordoma may be difficult because both neoplasms are cytokeratin and EMA positive. Although positivity for vimentin and S-100 protein supports the diagnosis of chordoma over adenocarcinoma, this finding should be interpreted with caution, as rare adenocarcinomas may be positive for S-100 protein.

**TREATMENT** — There are no randomized clinical trials and no large prospective series that define the optimal treatment for either chordomas or chondrosarcomas.

Literature reviews of small retrospective series support a combined modality approach using maximal surgical resection and radiation therapy (RT).

**Surgery** — Surgery is performed both to obtain tissue for diagnosis and to reduce the tumor burden [25]. Complete resection is desirable for both chordomas and chondrosarcomas of the skull base. However, a complete resection is often not feasible because of anatomic constraints to surgical access and proximity to critical normal structures. Both open (transcranial and transfacial) and endoscopic endonasal surgical approaches are successfully used for these tumors. There is evidence from observational studies that gross total resection of chordomas is better facilitated with a midline endoscopic endonasal approach [26].

Although these tumors are slow growing, they are locally invasive tumors and there is a high incidence of local recurrence that can result in death due to uncontrolled local disease. For patients with chondrosarcoma, metastases occur in about 10 percent of cases. For patients with chordoma, dedifferentiation or sarcomatous transformation occurs in 2 to 8 percent of chordomas [16,17].

**Radiation therapy** — Tumors involving the skull base are difficult to manage as a result of their proximity to critical neural structures. Maximal surgical resection is the mainstay of therapy, but complete resections are difficult to achieve.

Adjuvant RT is commonly employed, although it has been difficult to administer adequately high doses of radiation with older techniques. For patients with chordoma, adjuvant RT is generally advocated because of the poor prognosis in those who recur. For patients with chondrosarcoma, salvage therapy has been successful in some cases, and it is unclear whether immediate adjuvant radiation therapy is better than salvage surgery and/or salvage RT.

Conventional two- or three-dimensional RT techniques using photons have a significant risk of damaging the brainstem and cranial nerves, and the lower doses historically used with these techniques have been associated with a high rate of local recurrence and treatment failure. The limitations of photon therapy in the treatment of chordomas are illustrated by a series of 48 patients (20 with skull base lesions), 44 of whom had macroscopic disease following surgery [27]. The local control rate with conventional photon radiation was only 27 percent, although 85 percent of patients achieved useful and prolonged palliation of pain. The median survival was 62 months.

High-dose focused radiation delivery techniques with particles (primarily protons) or photons (stereotactic radiosurgery [SRS], stereotactic radiation therapy [SRT], and intensity modulated radiation therapy [IMRT]) have allowed for higher doses of RT to be delivered to the tumor while sparing surrounding structures. The most extensive data comes from proton beam therapy, but there are no randomized trials comparing these different contemporary techniques, and the advantages of proton beam therapy are primarily theoretical and anecdotal.

**Charged particle RT** — Charged particle irradiation offers several theoretical advantages over conventional photon RT to minimize incidental irradiation to adjuvant normal structures. (See "Radiation therapy techniques in cancer treatment", section on 'Particle therapy'.)

Proton beam RT is the most widely used charged ion technique. This approach appears to be more effective than earlier use of conventional photon RT with lower doses of radiation:

- Chordomas - A systematic review of the literature in patients with chordomas analyzed seven retrospective studies that included a total of 416 patients who were treated either with protons or with a combination of protons plus photons [28]. The radiation doses and schedules varied within and between series, but generally the total radiation dose was 70 Gy equivalents or higher. Clinical outcomes were available for all patients with a minimum follow-up of two years. At a median follow-up of 46 months, the five-year local control and overall survival rates were 69 and 80 percent, respectively.

- Chondrosarcomas - In patients with chondrosarcoma, the largest series comprised 200 patients treated at a single institution [23]. The median total dose of radiation in that series was 72 Gy equivalents. The 10-year local control and survival rates were 98 and 99 percent, respectively. A subsequent review of the literature included that series plus 54 patients with chondrosarcoma identified in three other studies; the results in those series were similar [29].

Other charged particles, especially carbon ions, have been used in addition to protons in patients with skull base chordoma and chondrosarcoma [28,30-33]. Although these approaches appear to have

similar efficacy to proton therapy, there are no comparative studies and these techniques are not widely available.

**Photon techniques** — Several other techniques have been used to deliver higher doses of photon radiation to central nervous system targets, while minimizing incidental exposure to normal critical structures. There are no randomized trials that compare SRS, SRT, or IMRT to proton beam or older photon techniques.

- Experience with SRS has been reported in several retrospective series [34,35]. A review of the literature identified 148 patients with chordomas treated in four series [34]. The five-year survival rate ranged from 69 to 84 percent, at a median follow-up of 28 to 60 months. SRS is limited to tumors with a relatively small tumor volume.

- SRT can be used for larger lesions than SRS. In one series of 37 chordoma patients treated with SRT, the five-year survival rate was 82 percent, although the mean follow-up was only 27 months.

- Favorable local control rates and survival have also been reported in small studies using IMRT for skull base chordomas and chondrosarcomas [36].

**Advanced disease**

**Chondrosarcoma** — Historically, chondrosarcomas have been considered resistant to chemotherapy. Although the majority of patients with recurrent or metastatic sarcoma do not respond to the usual chemotherapy regimens for advanced sarcoma, there have been isolated reports of successful treatment with ifosfamide plus doxorubicin or single agent methotrexate.

Chemotherapy for advanced chondrosarcomas is discussed in detail elsewhere. (See "Chondrosarcoma", section on 'Systemic treatment'.)

**Chordoma** — Studies reporting the use of chemotherapy and molecularly targeted agents in patients with advanced chordoma primarily include patients with tumors arising in the sacral region or spine, as well as the base of skull. Results of these trials are discussed separately. (See "Spinal cord tumors", section on 'Chordomas'.)

**INFORMATION FOR PATIENTS** — UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topic (see "Patient education: Chondrosarcoma (The Basics)")

**SUMMARY AND RECOMMENDATIONS** — Both chordomas and chondrosarcomas are rare tumors that can arise in the skull base. Because of their anatomic location and proximity to critical structures, complete resection is difficult and local recurrences are frequent.

- For patients with a primary tumor of the skull base, initial surgical resection can provide a tissue diagnosis. A complete or near complete resection may be associated with a prolonged disease-free period and may enhance the effectiveness of subsequent radiation therapy. (See 'Surgery' above.)
- For patients with a chordoma, we suggest adjuvant radiation therapy following surgery rather than observation (**Grade 2C**). This approach appears to be associated with a longer disease-free period, and salvage therapy has generally not been successful in patients with chordomas. Many patients with recurrent disease are candidates for additional surgery. (See 'Radiation therapy' above.)
- For patients with a chondrosarcoma, we suggest adjuvant radiation therapy following maximal surgical resection (**Grade 2C**). For patients with a low grade tumor who have undergone a gross total resection, deferring radiation therapy is an alternative, and patients who recur should be retreated aggressively with surgery and/or radiation therapy. (See 'Radiation therapy' above.)
- When radiation therapy is indicated, achieving an adequate tumor dose while minimizing damage to critical neurologic structures is critical. Radiation should be delivered using high-dose focused proton or photon radiation delivery technology. Options include proton beam radiation and contemporary photon-based techniques, such as stereotactic radiation surgery, stereotactic radiation therapy, or intensity-modulated radiation therapy. Of these, we suggest proton beam radiation therapy when this modality is available (**Grade 2C**).

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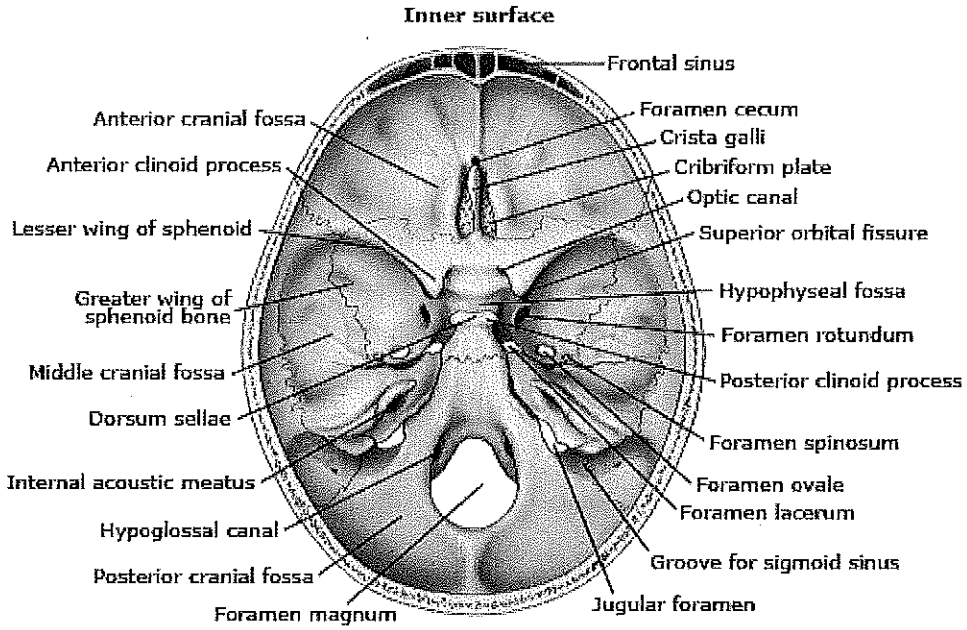
## GRAPHICS

### Base of skull anatomy



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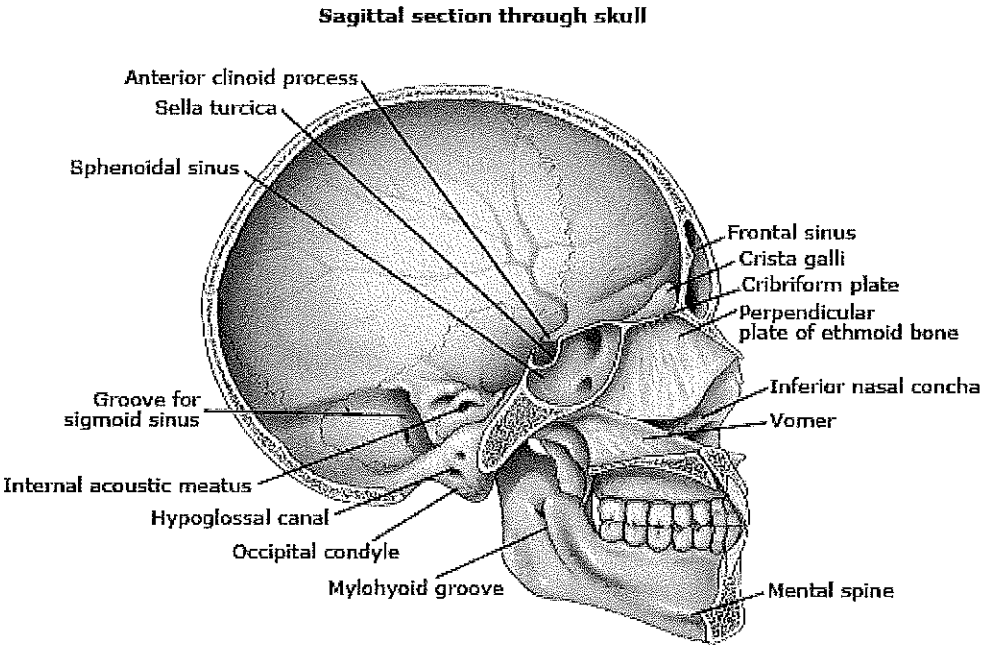
## Skull sagittal section



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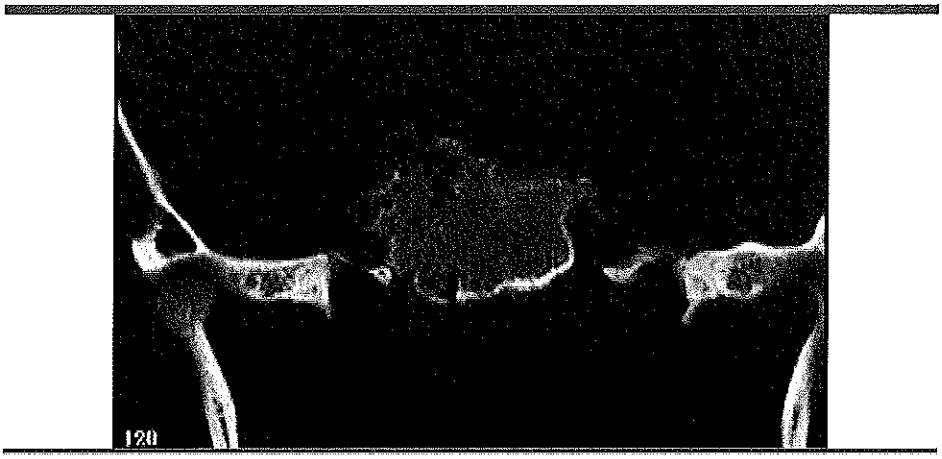
**Chondrosarcoma**




Bone window of a coronal CT scan shows a chondrosarcoma of the right clivus.

CT: computed tomography.

*Courtesy of Silloo B Kapadia, MD.*

Graphic 79863 Version 3.0

## Definition of TNM for bone tumors other than lymphoma and myeloma

| Primary tumor (T) | |
|---|---|
| TX | Primary tumor cannot be assessed |
| T0 | No evidence of primary tumor |
| T1 | Tumor 8 cm or less in greatest dimension |
| T2 | Tumor more than 8 cm in greatest dimension |
| T3 | Discontinuous tumors in the primary bone site |
| **Regional lymph nodes (N)*** | |
| NX | Regional lymph nodes cannot be assessed |
| N0 | No regional lymph node metastasis |
| N1 | Regional lymph node metastasis |
| **Distant metastasis (M)** | |
| M0 | No distant metastasis |
| M1 | Distant metastasis |
| M1a | Lung |
| M1b | Other distant sites |
| **Histologic grade (G)¶** | |
| Grade is reported in registry systems by the grade value. A two-grade, three-grade, or four-grade system may be used. If a grading system is not specified, generally the following system is used: | |
| GX | Grade cannot be assessed |
| G1 | Well differentiated - low grade |
| G2 | Moderately differentiated - low grade |
| G3 | Poorly differentiated - high grade |
| G4 | Undifferentiated - high grade |

| Anatomic stage/prognostic groups | | | | |
|---|---|---|---|---|
| Stage IA | T1 | N0 | M0 | G1, 2 Low grade, GX |
| Stage IB | T2 | N0 | M0 | G1, 2 Low grade, GX |
| | T3 | N0 | M0 | G1, 2 Low grade, GX |
| Stage IIA | T1 | N0 | M0 | G3, 4 High grade |
| Stage IIB | T2 | N0 | M0 | G3, 4 High grade |
| Stage III | T3 | N0 | M0 | G3, 4 High grade |
| Stage IVA | Any T | N0 | M1a | Any G |
| Stage IVB | Any T | N1 | Any M | Any G |
| | Any T | Any N | M1b | Any G |

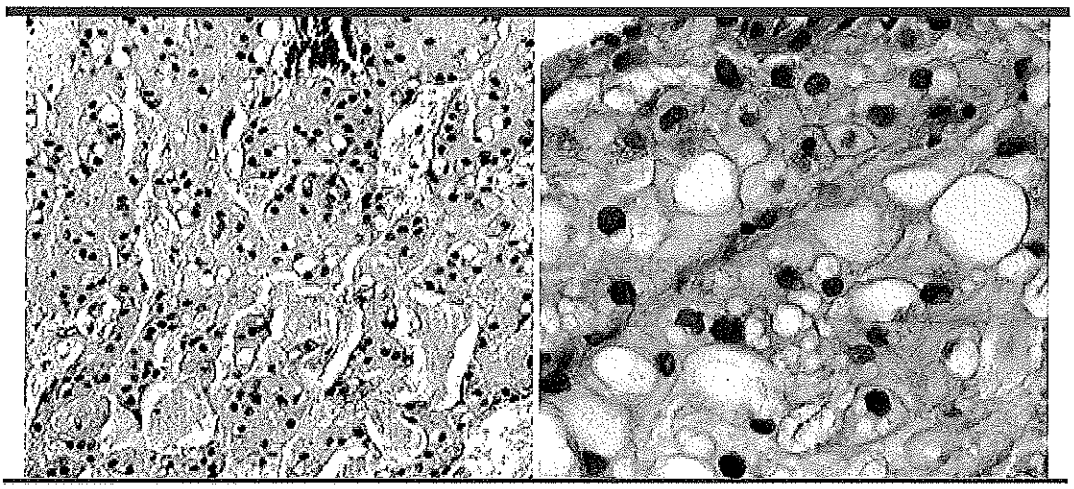
NOTE: cTNM is the clinical classification, pTNM is the pathologic classification.

* Because of the rarity of lymph node involvement in bone sarcomas, the designation NX may not be appropriate and cases should be considered N0 unless clinical node involvement is clearly evident.
¶ Ewing's sarcoma is classified as G4.



Graphic 62124 Version 14.0

**Chordoma**

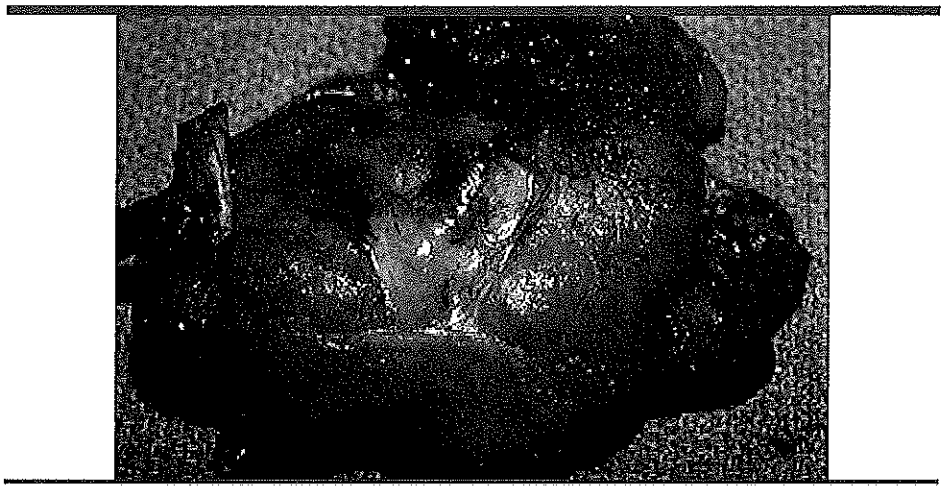


Low and high power light micrographs of a skull base chordoma. The tumor cells have vesicular nuclei and abundant vacuolated, soap bubble-like cytoplasm (physaliphorous cells) that contains glycogen (PAS positive) or mucin.

*Courtesy of Silloo B Kapadia, MD.*

Graphic 76084 Version 1.0

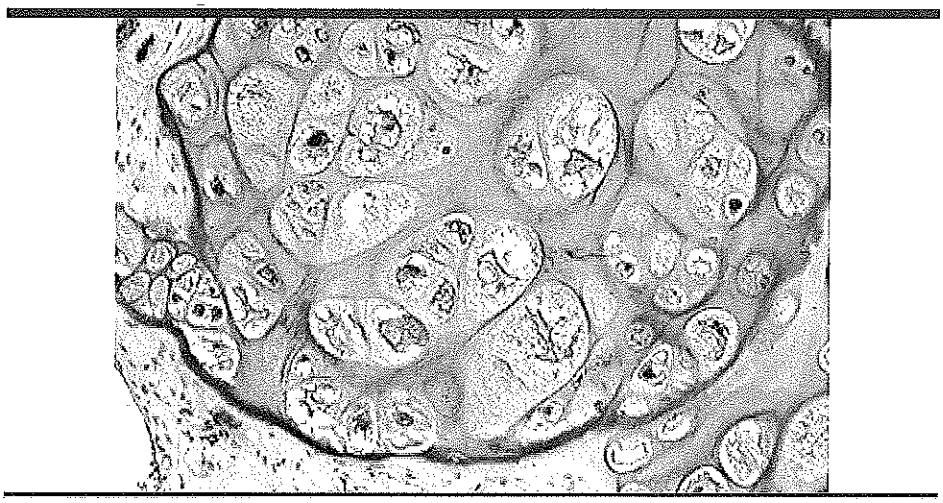
**Chondrosarcoma**



Gross appearance of a chondro-sarcoma.

Graphic 60109 Version 1.0

**Chondrosarcoma**



Light micrograph of a moderately well differentiated chondrosarcoma.

*Courtesy of Silloo B Kapadia, MD.*

Graphic 70909 Version 1.0

**Differential diagnosis of tumors at the base of the skull**

| Site of lesion | Associated tumors | Clinical findings |
|---|---|---|
| Anterior parts | Carcinoma invasive from frontal and ethmoid sinuses; meningiomas | Unilateral anosmia, frontal lobe syndrome, seizures |
| Superior orbital fissure | Meningiomas, carcinoma of nasopharynx | III, IV, V, VI cranial nerve lesions with ophthalmoplegia. Pain and hypesthesia in distribution of V. |
| Cavernous sinus | Chordomas, meningiomas, sellar, and parasellar tumors | III, IV, VI, and sometimes V nerve involvement with ophthalmoplegia |
| Apex of the petrous temporal bone | Cholesteatoma, chordoma, meningioma, neurinoma, sarcoma | V and VI nerve involvement with sensory and motor findings and diplopia |
| Sphenoid and petrous bone | Meningioma, chordoma, nasopharyngeal carcinoma, metastasis | III, IV, VI nerve lesions result in ophthalmoplegia; V may be associated with trigeminal neuralgia syndrome |
| Jugular foramen | Glomus jugulare tumors, neurinomas, chordomas, cholesteatoma, meningiomas, nasopharyngeal carcinoma | IX, X, XI nerves producing difficulty with swallowing, speaking, and weakness of strap muscles of neck |
| Cerebellopontine angle | Neurinoma, meningioma, cholesteatoma, metastasis cerebellar tumors | VII nerve lesions causing loss of hearing, vertigo, and nystagmus; cerebellar lesions producing ataxia of limbs and gait; V, VII, and occasionally IX and XII nerve lesions; brainstem symptoms and signs of increased intracranial pressure |

*Adapted from Bingas, B. Tumors of the base of the skull. In: Vinken, PJ, Bruyn, GW (Eds), Handbook of Clinical Neurology: Tumors of the Brain and Skull, vol 17. Amsterdam, North Holland, 1974:136.*

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## Contributor Disclosures

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