# Chordoma

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### ETIOPATHOLOGY

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**- extramural malignant tumor of ectopic notochordal remnants** (i.e. embryonal tumor).
- soft, gelatinous, smooth or lobulated.
- appears to be encapsulated when in soft tissue (but not when in bone).
- on cut section - homogeneous in color and consistency; calcification is usually present (occasionally, hemorrhages are present).
- continuously slow-growing and locally very aggressive (local bone destruction and infiltration into adjacent soft tissue; dural invasion occurs late in course) - patients die from regional tumor spread!
- existing nerves may become entrapped in tumor.

**Benign-histology neoplasm that displays malignant behavior**

**- metastases are recognized (esp. in spinal/sacral tumors) but are uncommon.**
- may degenerate to more malignant histological appearance, CHONDROID CHORDOMA.

**Ecchordosis physaliphora** (Vichow term in 1857) - small, well-circumscribed, gelatinous masses adherent to brainstem:
- although composed of notochordal remnants, seldom if ever progresses into chordomes.
- found in 2% autopsies!
- check for clival abnormalities!

### LOCATION

- midline along axial skeleton at developmentally active sites *(ends of neuraxis and vertebral bodies)* - in descending order of frequency:
  1. sacrum (49-50%)
  2. sphenoccipital synchondrosis of clivus (30-35%)
  3. vertebral (15%): lumbar > cervical > thoracic.

**N.B. chordomas do not arise from intervertebral discs!**

**in adults, remnants of notochord are present as nuclear palpozus (disappear as disc becomes avascular); area where small masses of notochord may persist throughout life - region of clivus and sphenoccipital area**

### HISTOLOGY

**Hallmark -** uniform large physaliphorous cells - numerous, variably sized VACUOLES in cytoplasm (Gr. physaliphorous – having bubbles); vacuoles contain chondroitin-type mucopolysaccharide;
- PAS positive.
- small oval or round eccentric nuclei and dense chromatin.
- immunohistochemically positive for: cytokeratin, epithelial membrane antigen (EMA) (vs. chondrosarcoma - cytokeratins and EMA negative).
- 3:100 (vs. most carcinomas are S-100 negative!)

**- cells are arranged in various patterns – diffuse, lobular, clustered in islands in sheetlike fashion.**
- between cells or clusters – abundant mucinous matrix (basophilic-to-metachromatic; stains diffusely with mucicarmine and Alcian blue; negative with Sudan black).
- fibrous tissue surrounds neoplasm (pseudocapsule) and extends projections into tumor.

**Histologic types:**
1. CONVENTIONAL CHORDOMA
2. CHONDROID CHORDOMA - contains more cartilage and is less aggressive.
3. MALIGNANT CHORDOMA - distinguished by spindle cells and mitotic cells; metastasizes in 25% cases.

**Characteristic physaliphorous cells and mucinous matrix.**
GENETICS

N.B. sacral chordomas are not the same genetically as clival chordomas

- Brachyury gene, T-protein - early mutational event in chordoma evolution
  - discriminates chordoma from chondrosarcoma
  - gives poor prognosis – progression-free survival 5 mos (vs. 13 mos in absence of Brachyury mutation).
  - yeast-Brachyury vaccine is in phase II trial (NCT02383498).

- EGFR, PDGF, CDKN2A - targetable alteration in chordoma genomics.

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- EPIDEMIOLOGY

  - 0.2% of intracranial tumors (2-4% of all primary bone neoplasms).
  - male-to-female ratio = 2:1
  - average age at diagnosis - 56 years (range 27-80 years).
  - peak incidence varies by site:
    - intracranial chordomas - 48 years (clival region produces earlier symptomatology)
    - chordomas along vertebrae - 46 years
    - sacrococcygeal chordomas - 56-63 years

- CLINICAL FEATURES

  - Intracranial – headache, multiple lower cranial nerve palsy; occasionally invades nasopharynx (pharyngeal bleeding).
  - Cervical vertebrae – neck pain, palpable prevertebral / retropharyngeal soft tissue mass, hoarseness, dysphagia, torticollis.
  - Lower vertebrae – pain, bladder dysfunction, lower extremity weakness.
  - Sacrum – cauda equina or conus medullaris disruption:
    1) back and/or lower extremity pain
    2) numbness, motor weakness
    3) palpable presacral / pelvic mass (50%)
    4) constipation (uniform finding!), urinary incontinence (50%)

- DIAGNOSIS

  - Plain X-ray – well-demarcated destructive mass with bone destruction and sclerotic bone reaction.
  - CT – extra-axial hypodense area with significant erosion (of clivus, vertebrae, or sacrum) displacing brain stem or other structures; fingers of low density radiate throughout mass into adjacent tissues.
    - calcification (87%) - amorphous and predominates in periphery of lesion
    - variable enhancement.
    - intervertebral discs above or below chordoma may be involved and narrowed in manner that simulates infection; tumor can make its way through intervertebral disc to infiltrate adjacent level (11-14% cases).
  - MRI - has focal regions of hyperintensity.
  - MRI – hypointense on T1, hyperintense on T2.

- Biopsy – only when other bone lesions remain in differential diagnosis after imaging studies are performed.

  - Fine needle aspiration (FNA) is preferred method (lower local recurrence rates when compared with open biopsy).
  - diagnostic criteria in FNA – large mucin-containing physaliphorous cells in abundant myxoid ground substance.

- CAUTION

  - Clival chordoma (T1-MRI) – exophytic lesion involving clivus with extraxial mass effect, posterior displacement of basilar artery (in A) and of brain stem at pons (in B); mass effect on 4th ventricle.
**TREATMENT**

**Surgical resection** - primary mode of treatment!
Complete excision is difficult at best

**Approach:**
- a. upper clivus tumor – transseptal, transsphenoidal approach.
- b. lateralized upper clival tumor or lateralized midclival tumor - approach through sphenoethmoidectomy (± maxillectomy).
- c. midline midclival tumor or lower clivus tumor – transoral approach.

- Combined approaches: medio lateral (transcranial + endonasal), superoinferior (endonasal + transoral)
- Every attempt must be made to keep dura intact (CSF leakage → meningitis); impossible in ≈ 50% cases (H: patch leak with fat and muscle graft → lumbar drain)

*Incomplete resection* → high-dose adjuvant radiotherapy with charged-particle* irradiation.
* with proton beams - higher doses (65-70 Gy) can be achieved (vs. conventional photon irradiation like SRS) because protons lose charge very quickly and there is no exiting beam that could damage nearby structures (like brainstem) – Bragg’s peak

**CHORDOMA** is relatively radioresistant - rarely destroyed by radiation alone (using standard megavoltage beams) at tolerable doses.

Chordoma, also previously thought to be chemoresistant, has been shown to be sensitive to chemotherapy with tyrosine kinase inhibitors:
- IMATINIB MESYLATE (Gleevec) has shown promise in early clinical trials - in initial studies, imaging revealed extensive tumor necrosis in six out of six patients treated with imatinib mesylate.
- SUNITINIB (Sutent) is currently being tested in clinical trials.

**PROGNOSIS**

- **local extent and degree of resection** are most important for prognosis.
- 5-year survival – 40-67%; 10-year survival – 35-40%.
- **high rate of multiple local recurrences**, average interval to recurrence
  - radically resected tumors - 3.8 years
  - subtotal resection with radiotherapy - 2.1 years
  - subtotal resection without radiotherapy - 8 months.

**CEVICAL CHORDOMA**

Cervical chordomas are rare (5% of all chordomas)

**CLINICAL FEATURES**

1) progressive pain in the neck (aggravated pain at nighttime)
2) radicular pain in upper limbs
3) cord compression
4) dysphagia (retropharyngeal soft tissue mass)
IMAGING

CT - bone destruction and sclerotic bone reaction up to collapsed vertebrae and subluxation.
  - tumor can make its way through intervertebral disc to infiltrate adjacent level
MRI
  - T1- isointense or hypointense
  - T2- hyperintense.

TREATMENT STRATEGY

All patients - radical surgery.
Adjuvant radiotherapy 44-80 Gy - all patients.
Chemotherapy - not effective.

RESULTS

3-year disease-free survival rate - 50%
5-year survival rates - 85.7%.

- Local tumor recurrence - 57.1%; most recurrence events appear within 3 years of initial surgeries (but one patient had recurrence in the 7th year after the initial surgery - long-term follow-up is necessary)
- reported metastatic rate of chordomas ranges from 10% to 48% (usually sacrococcygeal chordomas); no metastasis (distant or neuraxis) were demonstrated in cervical chordomas.

Variables significantly associated with a high rate of tumor recurrence:
1) age less than 40 years or greater than 70 years
2) upper cervical tumor location

Graphs of log-rank test results demonstrating the disease-free survival curve based on age (upper) and tumor location (lower).

STAGING

Weinstein-Boriani-Biagini system – based on layers and zones of tumor involvement:

Source: Neurosurgery Focus © 2001 American Association of Neurological Surgeons.
Upper: Ideal distribution of tumor in the VB for cutting of both pedicles and REMOVAL OF THE ENTIRE VERTEBRA.
Center: Ideal distribution of tumor in the posterior elements for cutting of both pedicles and REMOVAL OF THE POSTERIOR ELEMENTS only in an en bloc fashion.
Lower: Asymmetrical distribution of tumor in the VB and posterior elements that is amenable to en bloc removal via SAGITTAL SPLIT OSTEOTOMY.

**TREATMENT**

Treatment challenges:
1) often are quite large by the time of diagnosis
2) highly risky anatomical region.

Surgical planning is based on tumor extension (according to the Weinstein-Boriani-Biagini system) and a patient's general health status:
- both the anterior and the posterior elements involved → combined anterior-posterior approach; total spondylectomy was performed in 5 cases
- anterior column involvement → anterior approach (some patients also requiring a posterior approach for reconstruction) total spondylectomy is unnecessary for tumors limited to a single column
- transoral approach was employed in 1 and the extraoral approach (retropharyngeal approach) in 4 patients
- all surgeries were completed in 1 stage.

Resection:
- it has been proven that **EN BLOC RESECTION** is the most effective procedure for improving survival, this may not be the case for cervical chordomas because of the risky anatomy (local vertebral arteries and nerve roots have to be sacrificed for tumor resection) - no patients in this series underwent en bloc tumor resection, i.e. **RADICAL PIECMEAL RESECTION** was done
  - mean blood loss and the operative duration in our series were 1042.9 ml and 4.25 hours, respectively, while they were 2900 ml and 11 hours, respectively, in en bloc cases in patients reported by Cloyd et al.
  - in our series, the 5-year disease-free survival rate in patients with primary cervical chordomas was 50% (in contrast, it was 58.3% in the en bloc resection group reported by Molina et al)
  - en bloc tumor resection should only be undertaken in patients with cervical chordoma that are limited within the vertebral body
- chordomas are tumors with less vasculature, despite the fact that we often encounter heavy bleeding intraoperatively, which is probably due to the aggressive extension of the neoplasm encausning the surrounding abundant vasculatures.
- **fluidity** feature of cervical chordomas makes them capable of seeding in the surgical field, which may explain high rate of tumor recurrence
  - To minimize tumor seeding, we usually irrigate the surgical field copiously with cisplatin-containing deionized water and try to complete the combined anterior-posterior procedure in a single stage.

Reconstruction:
- **anterior reconstruction**: titanium mesh cage* and titanium locking plate
  - Considering high local recurrence rates, we prefer bone cement to autobone for filling cages; cement provides immediate local stability + kills potentially remaining tumor cells through heat release
- **posterior reconstruction**: pedicle screw system.

Huge primary chordoma of C-3: total spondylectomy → titanium plate and a titanium mesh cage filled with bone cement were used for anterior reconstruction, and pedicle screws and rods were applied for posterior reconstruction.

Huge primary chordoma of C-4 encasing the vertebral artery bilaterally: