

Chordoma

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ETIOPATHOLOGY

- extradural 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!
 - exiting 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, *CHONDROSARCOMA*.

Echordosis physaliphora (Virchow term in 1857) - small, well-circumscribed, gelatinous masses adherent to brainstem.

- although composed of notochordal remnants, seldom (if ever) progresses into *CHORDOMA*.
- found in $\approx 2\%$ 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!

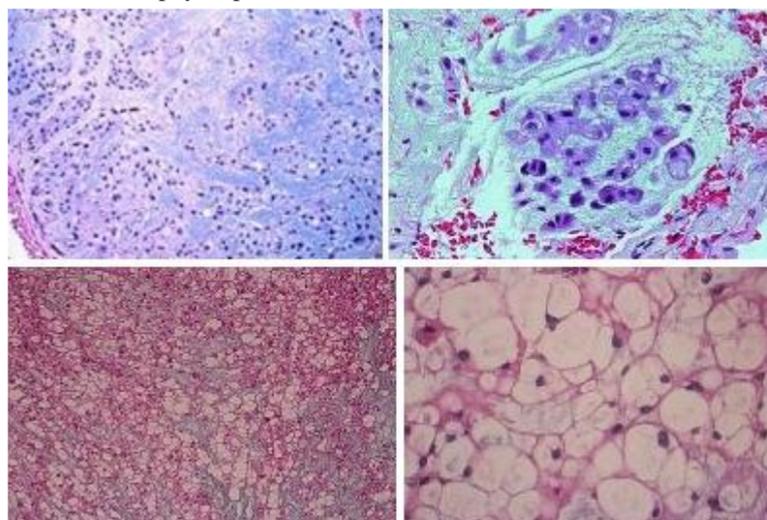
in embryo, notochord extends from tip of dorsum sellae to coccyx;
in adult, remnants of notochord are present as nucleus pulposus (disappear as disc becomes avascular);
areas where small masses of notochord may persist throughout life - region of clivus and sacrococcygeal area

HISTOLOGY

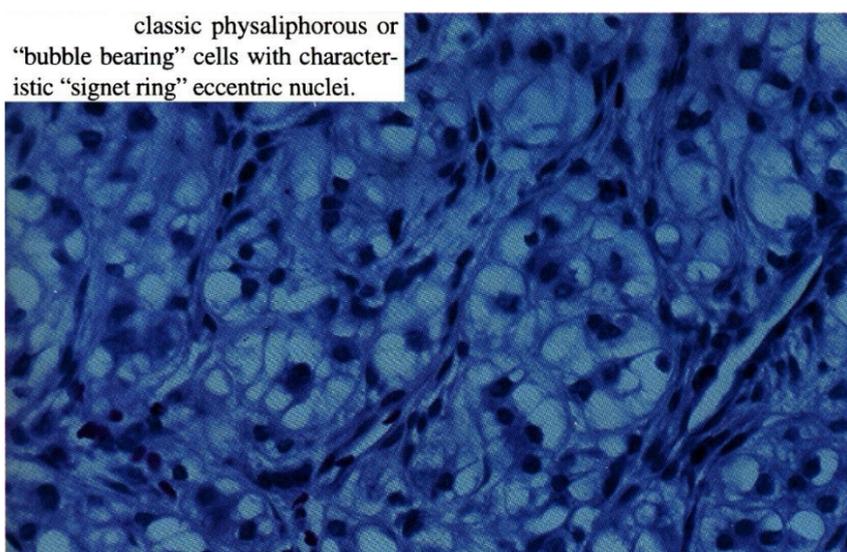
HALLMARK - uniform large **physaliphorous cells** - **numerous, variably sized VACUOLES in cytoplasm** [Gr. *physaliphorous* – having bubbles]; vacuoles contain chondroitin-type mucopolysaccharide;

- PAS positive.
- small oval or round eccentric nuclei and dense chromatin.
- immunohistochemically positive for: **cytokeratins**, **epithelial membrane antigen (EMA)** (vs. chondrosarcoma - cytokeratins and EMA negative), **S-100** (vs. most carcinomas are S-100 negative!)
- cells are arranged in various patterns – diffuse, lobular, clustered in islands in sheetlike pattern.
- 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:



classic physaliphorous or "bubble bearing" cells with characteristic "signet ring" eccentric nuclei.



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, PDGFR, CDKN2A - targetable alterations implicated in chordoma genomics.

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 palsies**; 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.

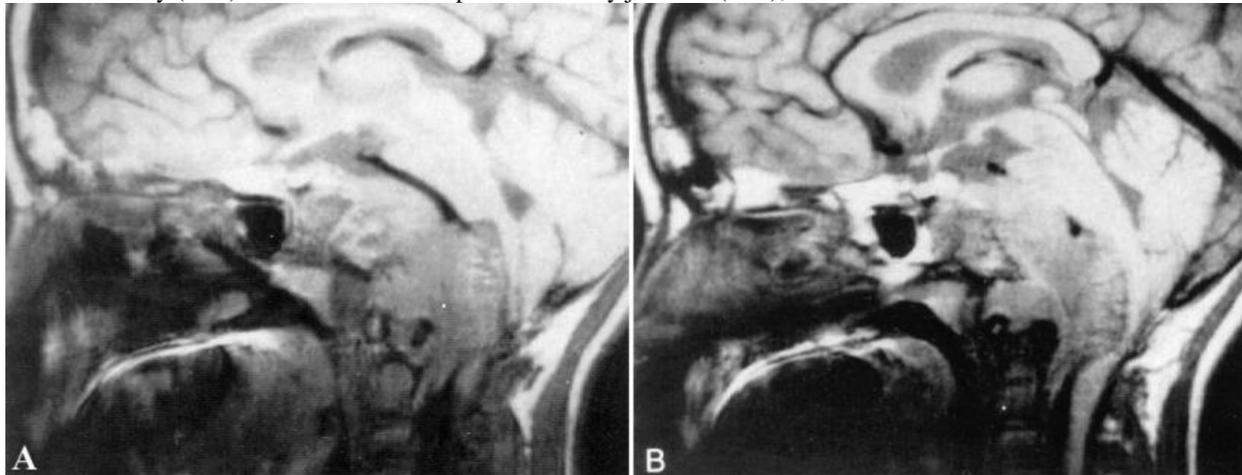
- **calcification** (87%) - amorphous and predominates in periphery of lesion.
- variable enhancement.
- *intervertebral discs* above or below chordoma may be involved and narrowed in manner that simulates infection; tumor can make its way through intervertebral disc to infiltrate adjacent level (11-14% cases).
- **CHONDROID CHORDOMA** has focal regions of hyperdensity.

MRI – hypointense on T1, hyperintense on T2.

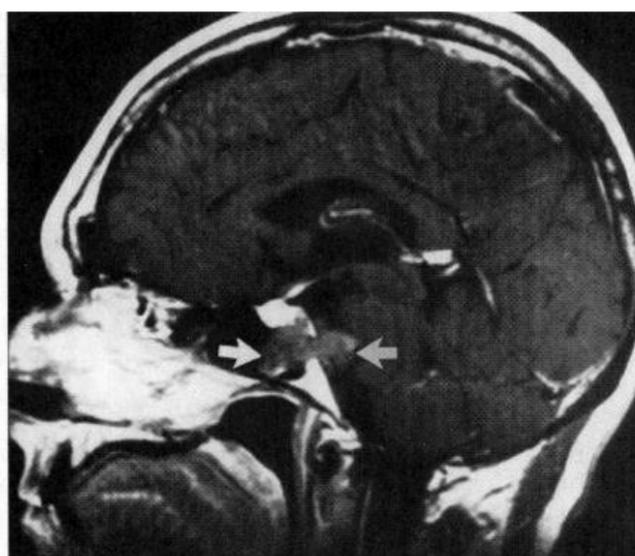
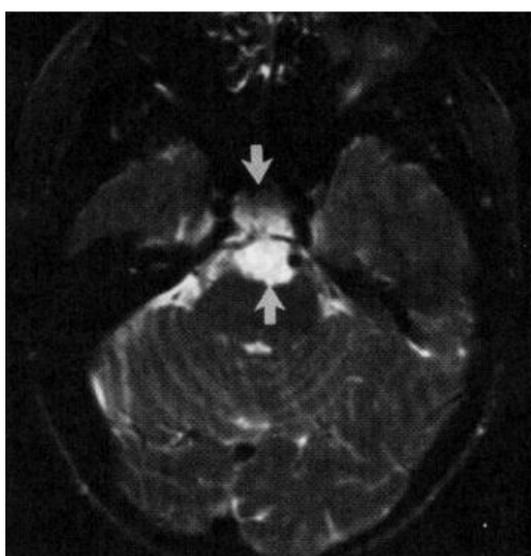
Biopsy – only when other bone lesions remain in differential diagnosis after imaging studies are performed.

- many experts mandate biopsy all suspected chordomas (→ preop proton beam)
- **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.

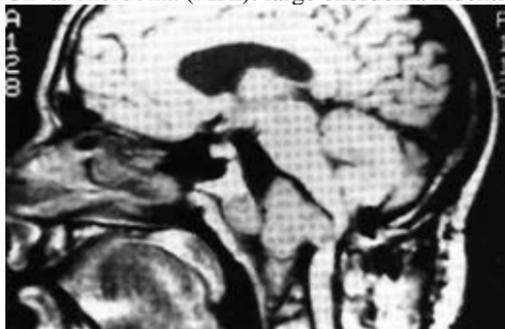
Clival chordoma (T1-MRI) - exophytic lesion involving clivus with extraaxial mass effect, posterior displacement of basilar artery (in A) and of brain stem at pontomedullary junction (in B); mass effect on 4th ventricle:



Clival chordoma:
 A. T2-MRI - chordoma of clivus (*arrows*).
 B. Contrast MRI - tumor extension anteriorly into sphenoid sinus, and posteriorly to compress pons (*arrows*).



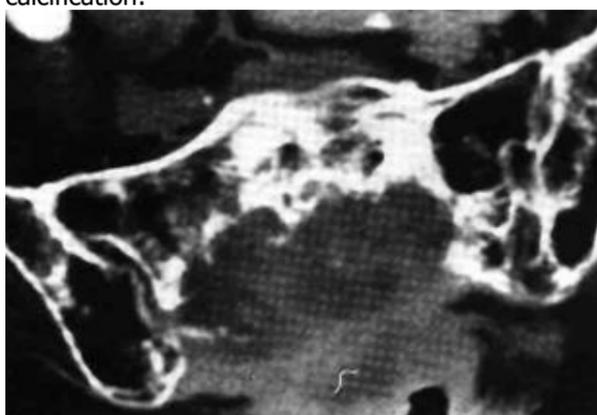
Clival chordoma (MRI): large chordoma indenting pons and cervicomedullary junction:



Sacral chordoma (MRI) - large presacral mass eroding bone:



Sacral chordoma (axial CT bone window) - large mass with extensive bone destruction and focal sites of calcification:



TREATMENT

Surgical resection - primary mode of treatment!

N.B. treatment approaches vary from center to center

Complete excision is difficult at best

Approach:

- upper clivus** tumor - *transseptal*, *transsphenoidal* approach.
 - lateralized upper clival** tumor or **lateralized midclival** tumor - approach through *sphenoethmoidectomy* (\pm maxillectomy).
 - 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 \rightarrow meningitis); impossible in \approx 50% cases (H: patch leak with fat and muscle graft \rightarrow lumbar drain)
 - some centers (e.g. MGH) use **neoadjuvant*** **proton beams**, then surgery (en bloc wide-margin resection) weeks later.

*thus, biopsy first all suspected chordomas!

Incomplete resection \rightarrow 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 with very steep falloff, i.e. 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.

Brachyury vaccine - in research for recurrences.

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** (even in wide-margin resections – tumor cells are found 2 cm from tumor edge)
average interval to recurrence:
 - radically resected tumors - 3.8 years
 - subtotal resection with radiotherapy - 2.1 years
 - subtotal resection without radiotherapy - 8 months.

CERVICAL 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

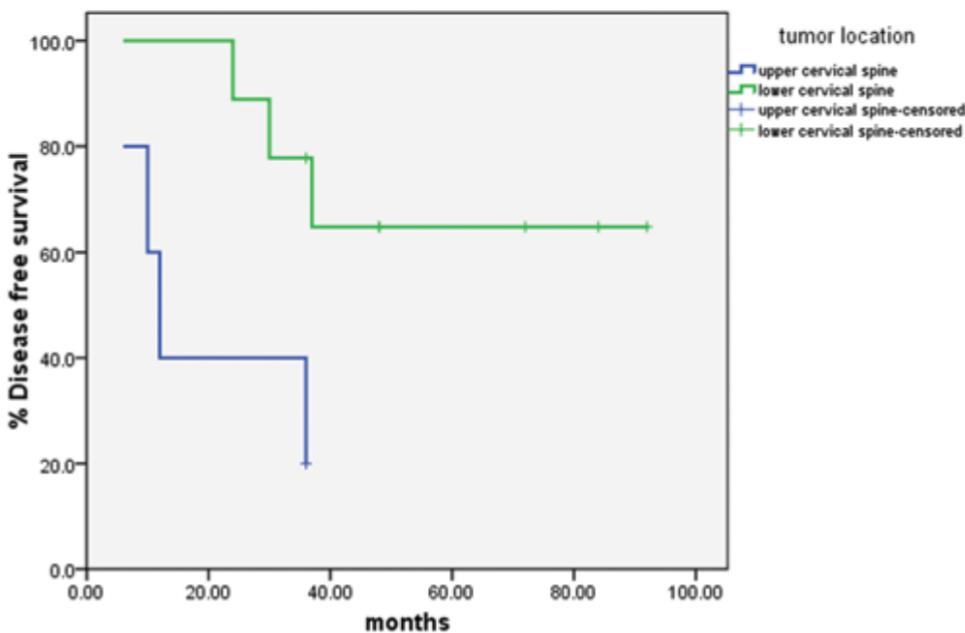
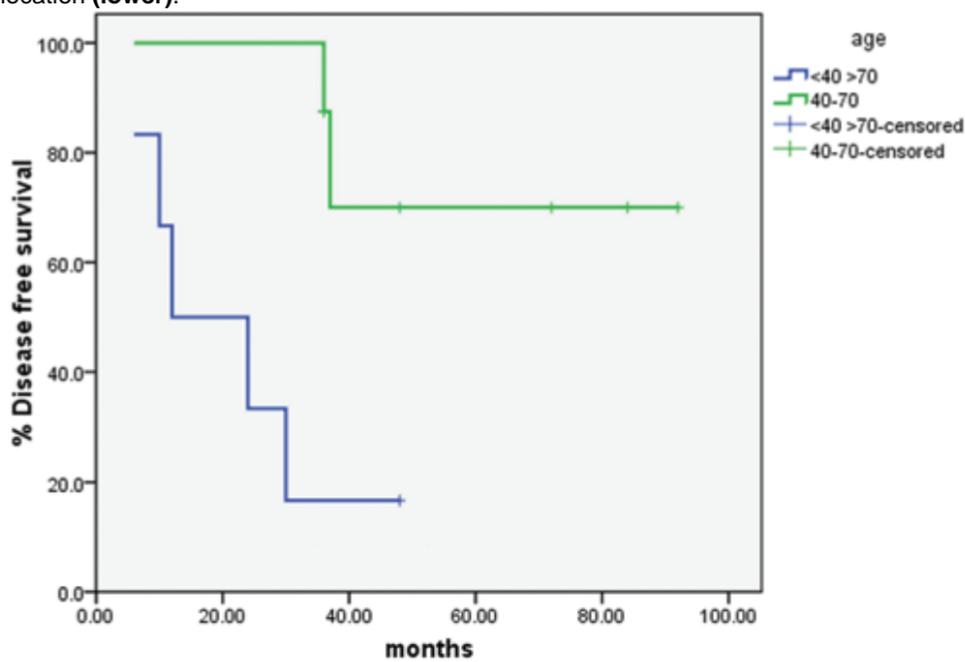
5-year **disease-free survival rate** - 50%
 5-year **survival rates** - 85.7%.

- **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:

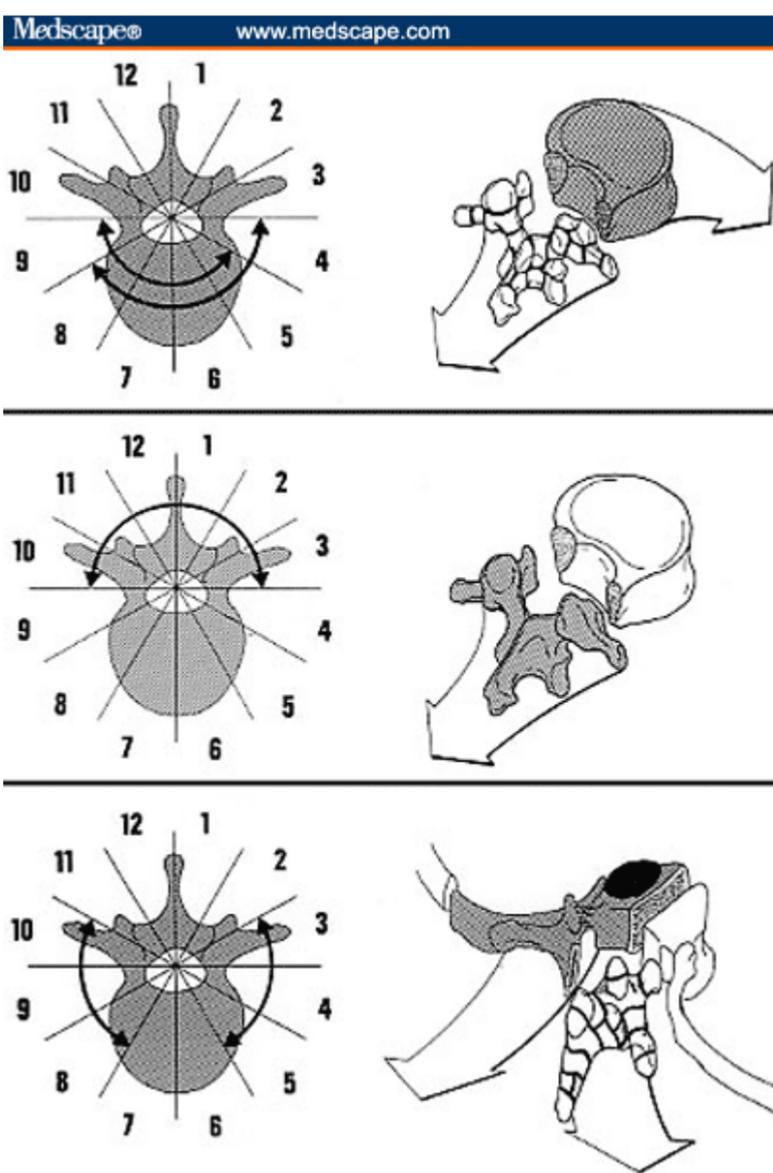
- 1) age less than 40 years or greater than 70 years
- 2) upper cervical tumor location

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: Neurosurg Focus © 2003 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**.

- a) both the anterior and the posterior elements involved → combined anterior-posterior approach; total spondylectomy was performed in 5 cases
 - b) 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
 - c) transoral approach was employed in 1 and the extraoral approach (retropharyngeal approach) in 4 patients
- all surgeries were completed in 1 stage.

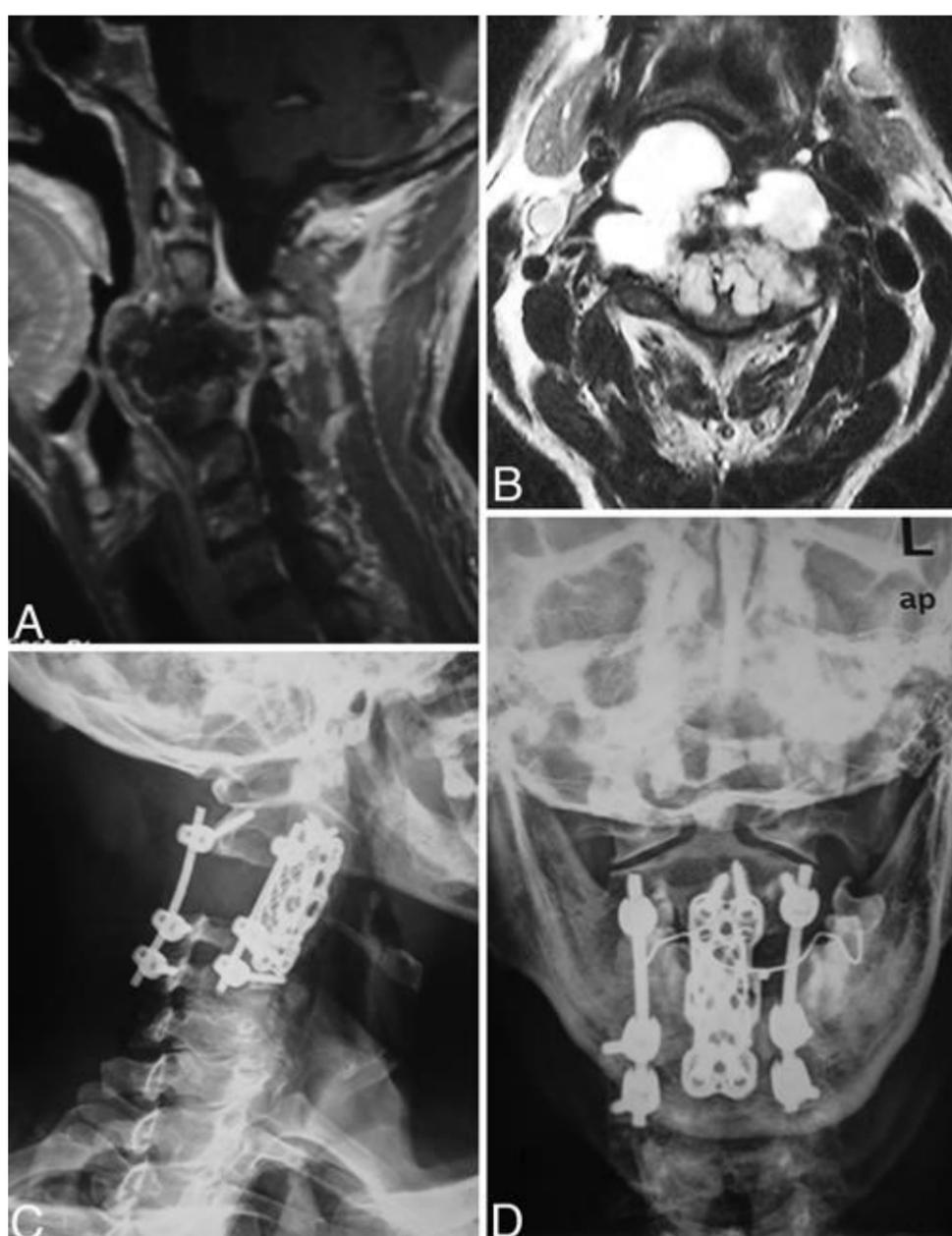
Resection:

- 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 PIECEMEAL 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 encasing 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.

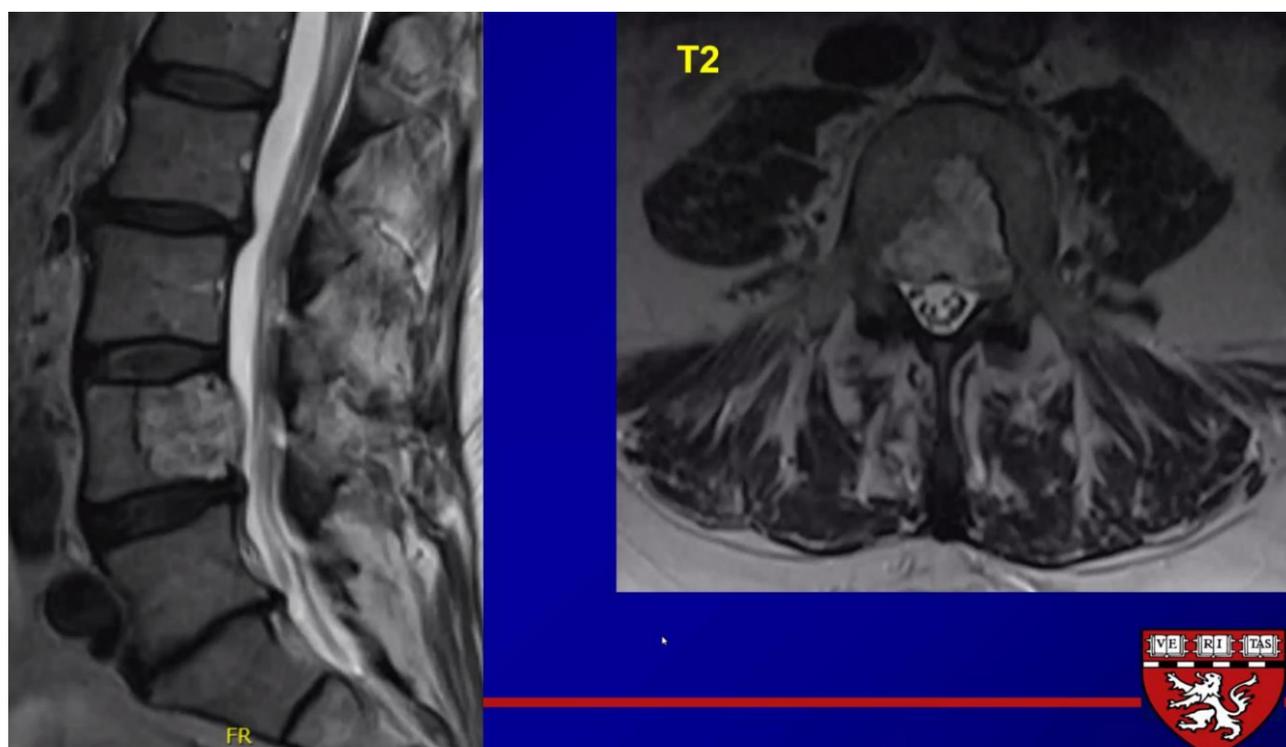
Huge primary chordoma of C-3: total spondylectomy → titanium plate and a titanium mesh cage filled with bone cement were used for anterior reconstruction, and pedicle screws and rods were applied for posterior reconstruction:

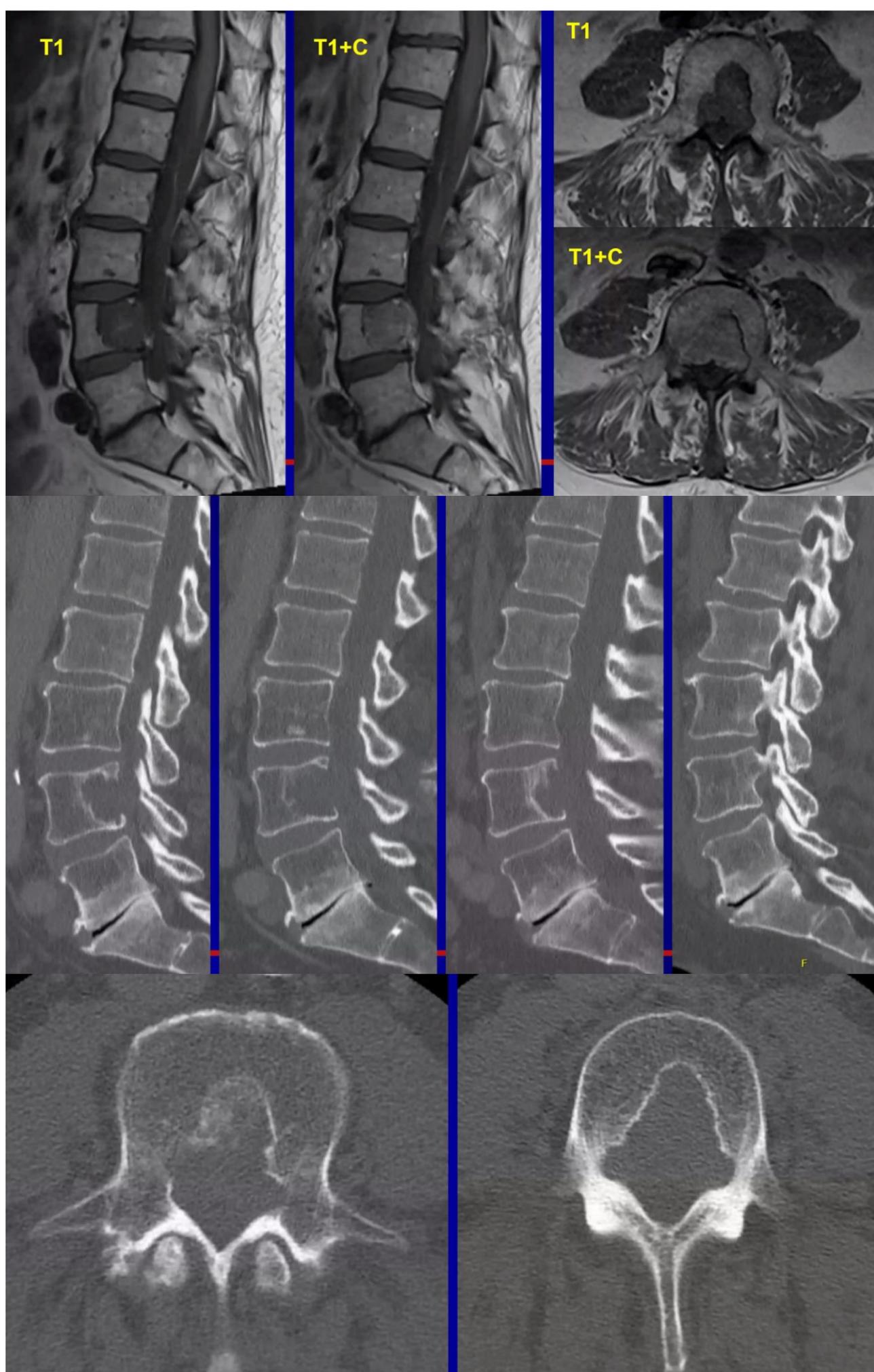


Huge primary chordoma of C-4 encasing the vertebral artery bilaterally:



LUMBAR CHORDOMA





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