Chordoma 101
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What is chordoma

• Malignant tumor arising from the bone of the skull base and spine
• It is a cancer and has a tendency to be locally invasive and a tendency to spread (metastasize)
• Its origin is traced to remnants of primitive embryonal cells called the “notochord”
Incidence

- Approx 2380 cases of bone malignancies diagnosed annually
- 5% of these are located in the spine
- 8% of the spinal tumors are Chordomas

Association of surgical resection and survival in patients with malignant primary osseous spinal neoplasms from the Surveillance, Epidemiology, and End Results (SEER) database

Eur Spine J
Published online: 21 December 2012

NCI database 1973 to 2003
Incidence

Facts:

• Affects people of all ages, most diagnosed in 50’s for sacral and 40’s for other types.

• Most frequent in skull base and lower spine

• More frequent in men than women (2:1) for sacral chordoma; 1:1 for clival and spinal.

• Incidence: 1 new case per million people per year
  • ~300 new cases per year in US
Where does it grow?

- Skull base (clivus) ~35%
- Sacrum/coccyx ~50%
- Other spinal ~15%
Phylum chordata: subphylum vertebrata

• 550 million years ago Chordates emerged from the common ancestor
• Presence of the **notochord** is the most prominent feature of the Phylum Chordata
• Notochord is ectodermal and guides development of mesenchymal spine
• We are vertebrates: the notochord is replaced by vertebrae
<table>
<thead>
<tr>
<th>Phylum</th>
<th>Classes</th>
<th>Orders</th>
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<tbody>
<tr>
<td>a. Porifera</td>
<td>Caicarea</td>
<td>Demospongia</td>
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<tr>
<td>b. Placozoa</td>
<td>Tricoplacia</td>
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<td>c. Ctenophora</td>
<td>Tentaculata</td>
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<td>d. Cnidaria</td>
<td>Anthozoa</td>
<td>Scleratinia</td>
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<td>Scyphozoa</td>
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<td>Hydrozoa</td>
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<td>e. Chordata</td>
<td>Subphyla:</td>
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<tr>
<td></td>
<td>Cephalochordata</td>
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<td></td>
<td>Urochordata (class Ascidiacea)</td>
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<td>Vertebrata</td>
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<tr>
<td>f. Echinodermata</td>
<td>Echinoidea</td>
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<td>g. Acanthocephala</td>
<td>Palaeacanthocephala</td>
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<td>h. Platyhelminthes</td>
<td>Trematoda</td>
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<td>Monogenea</td>
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<td>Cestoda</td>
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<td>i. Arthropoda</td>
<td>Insecta</td>
<td>Coleoptera</td>
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<td>Lepidoptera</td>
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<td>Diptera</td>
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<td>Odonata</td>
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<td>Malacostraca</td>
<td>Decapoda</td>
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<td>Pycnogonida</td>
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<td>Arachnida</td>
<td>Araneae</td>
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<td>j. Nematoda</td>
<td>Secernentea</td>
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The Notochord and neural tissue formation

17th day
The notochord
Fate of the notochord

- Essential for neural tube formation and embryonal organization
- Not normally found in the vertebral bodies after 10 weeks of gestation
- The last vestiges of the notochord disappear by age 10 years
- Notochordal cells in the nucleus pulposus also disappear
- This regression may get arrested leading to persistence of notochordal remnants
- Remnants are known as ecchordosis physaliphora
T-box gene: Brachyury

- T box family of transcription factors involved in tissue organization in the embryo
- Expressed in undifferentiated notochord
- Essential for development
- Absence is lethal
Notochord and brachyury

• Brachyury is over expressed in chordomas and many epithelial cancers
• Brachyury causes epithelial cells to grow uncontrollably and become more invasive and mobile
• These strongly suggest that brachyury may transform the notochordal remnants to become tumors
• Overexpressed in chordomas but not in other bone and cartilage tumors
• Duplication of brachyury gene has been observed in familial chordomas
• Inhibition of brachyury in chordoma cell cultures leads to decreased proliferation
The clivus
The Spine

Vertebral Column

- Cervical vertebrae
- Thoracic vertebrae
- Lumbar vertebrae
- Sacrum
- Coccygeal vertebrae

Cervical curve
Thoracic curve
Lumbar curve
Sacral curve
Clivus chordoma
Cervical spine chordoma
Sacral chordoma
Ecchordosis physaliforma

Absence of bone destruction
Benign notochordal cell tumor (BNCT)

H & E

cytokeratin
Benign notochordal cell tumor

- Asymptomatic lesions within the axial skeleton that are larger than a normal notochordal remnant
- They are confined within the bone
- Imaging signal characteristics are like a chordoma
- Histologically, physaliphorous cells; but lacks myxoid matrix, trabecular destruction, nuclear anomalies, mitosis, necrosis
- Some reports indicate these as precursors of chordomas
- Treatment of this entity is debated
Current treatment

• Radical removal either piecemeal or en bloc depending on location
• Followed by stabilization of the spine
• Radiation therapy (high dose)
  – Proton beam
  – Carbon ion
  – Intensity modulated radiation therapy
  – Stereotactastic radiosurgery (gamma knife, cyberknife)
Implications

- High rate of recurrence and numerous high risk surgeries
- Significant morbidity - patients often live for years with disease and disability
- No effective chemotherapy
- **20-30%** cure rate
Association of surgical resection and survival in patients with malignant primary osseous spinal neoplasms from the Surveillance, Epidemiology, and End Results (SEER) database
Clival chordomas: clinical management, results, and complications in 71 patients

Clinical article

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Department of Neurosurgery, St. Lukes-Roosevelt Hospital Center, New York, New York; and the Department of Community and Preventive Medicine, The Mount Sinai School of Medicine, New York, New York
Survival: Prior surgery v/s Initial surgery

Sen C, Shrivastava R, Triana A, Berglind N, Godbold J: Clival Chordomas
Current comprehensive management of cranial base chordomas: 10-year meta-analysis of observational studies

Clinical article

Salvatore Di Maio, M.D.C.M., F.R.C.S.C., Nancy Temkin, Ph.D.,
Dinesh Ramanathan, M.D., and Laligam N. Sekhar, M.D.

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Seattle, Washington
Fig. 3. Kaplan-Meier PFS (upper) and OS (lower) compared using log-rank analysis by extent of resection in 199 patients. The dashed line represents complete resection and the solid line incomplete resection. The vertical line indicates the 60-month time point. The 5-year PFS was 87% with complete resection versus 50% with incomplete resection (p < 0.0001). The 5-year OS was 95% with complete resection versus 71% without (p = 0.001).
Posterior-Only Approach for En Bloc Sacrectomy: Clinical Outcomes in 36 Consecutive Patients

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Ali Bydon, MD$,
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BACKGROUND: En bloc resection of primary sacral tumors has a demonstrated survival benefit. Total and high sacral amputations are traditionally performed by using a staged anterior and subsequent posterior approach. However, we have found that en bloc resection and biomechanical reconstruction of the spinal column is possible from a posterior-only approach in many cases.

OBJECTIVE: To assess our series of posterior-only sacrectomies, emphasizing post-operative complications and overall surgical and oncologic outcome.

METHODS: Sixty-nine consecutive patients underwent sacral resections for tumor at our institution between 2004 and 2009. Medical records of all patients were reviewed, and patients were excluded if they had an intentional intralesional resection, hemipelvectomy, or a previous operation. The records of the resulting 36 consecutive patients who underwent primary posterior-only en bloc sacral resections were retrospectively reviewed.

RESULTS: Of the posterior-only patients, all underwent midline posterior approaches for en bloc sacral resection. Sacral amputation was defined by the by sacral root preservation: total (2 cases), high (8 cases), middle (9 cases), low (12 cases), and distal (5 cases). Chordoma was the most common tumor type (30 cases), and surgical margins were marginal in 34 cases and contaminated in 2. Overall, there were 13 complications, including 9 wound infections/revisions. The extent of sacrectomy, and thus the extent of roots sacrificed, correlated with functional outcome.

CONCLUSION: It may be possible to perform a posterior-only approach to en bloc sacral resections/reconstructions in patients with tumors that do not extend beyond the lumbosacral junction or invade the bowel requiring bowel resection and diversion.

KEY WORDS: Chordoma, En bloc resection, Posterior-only approach, Sacrectomy

Sacral chordomas

**FIGURE.** Kaplan-Meier time to recurrence in en bloc resection sacral chordomas.
Survival

- Median: 6.29 years
- 5 years: 67.6%
- 10 years: 39.9%
- 20 years: 13.1%

Other prognostic factors
Prognostic factors

- Proliferation index
- Expression of cell cycle markers
Histological Classification

- Classical
- Chondroid
- Dedifferentiated
Chordoma v. Chondrosarcoma

- Misdiagnosis on routine histology
- Epithelial v. Mesenchymal origin
- Immunohistochemistry
  - Cytokeratin
  - Brachyury
- Survival
  - Much better for chondrosarcoma (gr 1)
what happens to the cells
Acquired capabilities of cancer

(Hanahan & Weinberg)

Hanahan and Weinberg. Cell (100):57-70, Jan 2000
The cell cycle

Figure 14.1 Phases of the cell cycle
The division cycle of most eukaryotic cells is divided into four discrete phases: M, G1, S, and G2. M phase (mitosis) is usually followed by cytokinesis. S phase is the period during which DNA replication occurs. The cell grows throughout interphase, which includes G1, S, and G2. The relative lengths of the cell cycle phases shown here are typical of rapidly replicating mammalian cells.
Cell architecture

<table>
<thead>
<tr>
<th>Normal</th>
<th>Cancer</th>
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</thead>
<tbody>
<tr>
<td>• Tight adhesion to each other</td>
<td>• Disruption of adhesion</td>
</tr>
<tr>
<td>• Adhesion to basement membrane</td>
<td>• Motility of cells</td>
</tr>
<tr>
<td>• Cell-cell signaling</td>
<td>• Disruption of signaling</td>
</tr>
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</table>
Research tools

• Study of the tumor specimen

• Cell lines

• Animal models
Drug therapy
Cell cycle control

Fig. 1 The cell cycle. This figure depicts critical molecules and relationships in the control of the cell cycle. Sites of therapeutic inhibitor development are highlighted.
The effects of chemotherapeutic agents on differentiated chordoma cells

Laboratory investigation

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Our mission is to rapidly develop effective treatments, and ultimately a cure for chordoma, while improving the diagnosis, treatment and quality of life for chordoma patients.