

Distribution of Age and Location of Chordoma in 39 Cases and Review of Treatment Options

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ABSTRACT

Introduction: Skull base chordomas are rare neoplasms arising from the notochord. Although histologically benign, these tumors are locally aggressive and present significant management challenges. There are some studies on chordoma cases but there was no study about Iranian cases. In this study we evaluated the location, age and gender of the patients with Chordoma in two referral centers in Tehran.

Methods: A database of patients with chordoma tumors referred to two centers (Shariati and Imam Hospitals, Tehran) from 2001 to 2011 was retrospectively reviewed.

Results: In our subjects tumors affect men nearly twice as frequently as women, and they are most commonly diagnosed in middle-aged (mean age was 50.6). Tumors typically occur in the axial skeleton and have a tendency for the spheno-occipital region of the skull base and sacral region. In adults 33.3% of chordomas involve the sacrococcygeal region, 53% occurred at the base of the skull near the spheno-occipital area, and near 14% were found in the vertebral column. The cranial nerves mostly affected were abducens, oculomotor and trochlear, with some overlaps. All patients were treated with surgery and some cases referred for gamma-knife radiosurgery (GKS).

Discussion: Findings of this study showed more involvement of males compare to females; that is different from other studies, however, few studies reported more male to female ratio. Despite the progress in current surgical techniques and some encouraging results with the use of targeted therapy, disease control and long-term prognosis of patients are still poor.

Key Words:

Chordoma,
Skull Base Tumor,
Sacral Tumor.

1. Introduction

Virchow, for the first time described the small nodules along the clivus fissure in 1846, and named them "ecchondrosis physaliphora" in 1857, because he hypothesized that they are of cartilaginous origin (Chugh et al., 2007). In 1909, Harvey Cushing reported successful

removal of a chordoma in a 35-year-old man, although the patient died during reoperation some 6 months later.

Chordomas are a rare neoplasm, arising from vestigial or ectopic remnants of the notochord in the axial skeleton with an incidence rate of 0.1 per 100,000 per year. It accounts for 1%–4% of all primary malignant bone tumors. Microscopic foci remain in the vertebral bod-

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ies at the cranial and caudal ends of the embryo (Wu et al., 2010). The peak incidence has been reported to occur in the eighth decade of life, and development of chordomas is quite rare before the age of 40 (Chugh et al., 2007). Some investigators reported that mean age ranges from 35 - 53 respectively (Cetas, Hughes, & Delashaw, 2011; Pamir & Ozduman, 2008).

Malignant transformation typically occurs in the third to fourth decades of life for sphenoid-occipital lesions and in the fifth to sixth decades for the sacro-coccygeal type. They are mostly located in the clivus or sacrum.

Pathologically benign, chordomas are slow growing but locally aggressive. They rarely metastasize, but they can lead to significant morbidity and mortality related to mass effect and invasion of surrounding tissue (Dassoulas, Schlesinger, Yen, & Sheehan, 2009). Presenting symptoms may include hydrocephalus, headache, visual disturbances and cranial nerve dysfunction, most commonly involving the third and sixth cranial nerves (Dassoulas et al., 2009). The overall median survival time with chordoma has been anticipated to be approximately 6 years, with a survival rate of 70% at 5 years, falling to 40% at 10 years (Dassoulas et al., 2009). Regarding the rare occurrence and poor prognosis of chordoma, the aim of this study was to investigate the distribution pattern of sex, age and location of this tumor in Iranian patients.

2. Methods

The database of patients with chordoma tumors referred to two centers in Tehran (Shariati and Imam Hospitals) from 2001 to 2011 was retrospectively reviewed. In this study we evaluated the location, age and gender of the patients with diagnosis of chordoma.

All patients undertook surgery and some of them had referred for gamma-knife radiosurgery (GKS). Some patients had returned with local recurrence of tumor and had reoperated in addition to adjuvant therapy (chemotherapy, radiotherapy). Here we also reviewed the literature of suggested treatments.

3. Results

3.1. Age and Location of Tumor

Our study involved 39 patients, 25 males and 14 females, with a mean age of 50.6 (range: 21-83 years old). The clivus was the site mostly affected by the tumor (n=21), followed by the sacral, cervical and lumbar regions (n=13, n=4, n=1, respectively).

3.2. Clinical Presentations of Cases

The cranial nerves mostly affected were abducens, oculomotor and trochlear nerves with some overlaps. Trigeminal symptoms and visual defects relating to optic pathway involvement were also reported in clivus location. Sacral pain is reported to be the most common presenting symptom, especially with a gradual and insidious onset. Chordomas often invade the spinal canal, and they may cause compression on the spinal cord, cauda equina, or nerve roots. This is reflected in a wide range of presenting neurologic symptoms, including weakness, sensory deficits, bowel and bladder incontinence, and sexual dysfunction.

4. Discussion

The findings of this study showed that the common site of chordoma in these cases was clivus followed by sacral, cervical and lumbar regions. Results of other studies such as Sciubba et al. have reported the anatomic loci were approximately 50% sacro-coccygeal and 35% sphenoid-occipital, and 15% occurring at the mobile spine (Brindza, Chaloupka, & Grosman, 2009). Another study reported the site of origin of chordoma in sacrum in 11 patients, spine in 13 (10 localized in the lumbar spine, 2 in cervical and 1 in thoracic spine), and the skull base in 1 patient (Sciubba et al., 2009). Chugh et al, studied the chordoma in adults, and reported 50% of chordomas in sacro-coccygeal region, 35% in base of skull near the sphenoid-occipital area, and 15% in the vertebral column (table 1 and 2).

In our cases chordoma affected men nearly twice as frequently as women and they were diagnosed in middle-aged and onset of elderly. However, other studies had reported nearly equal involvement of females and males or even more F/M ratio (Hug et al., 1999; Rosenberg et al., 1999), but other studies reported more M/F ratio (Forsyth et al., 1993). Hug et al, reported 25 cases with median age 43.7 (range 19-70) and M/F ratio of 9/16 (Hug et al., 1999). Rosenberg et al, reported 200 patients with median age 39 (range 10-79) and M/F ratio of 87/113 (Rosenberg et al., 1999).

Treatment

All patient are treated with surgery and some cases refer for gamma-knife radiosurgery (GKS). Surgery continues to be the first option in the management of chordomas. Rates of local recurrence, as well as survival, appear to depend on the achievement of negative surgical margins, with recurrence rates on the order of

70% in cases where negative margins are not achieved. The surgical techniques for margin-free en-bloc tumor resection have been proven to be effective in terms of local recurrence and long-term prognosis of chordomas. Surgical outcomes are dependent on local control and tumor size at diagnosis (Wu et al., 2010).

Patients with cranial base chordoma can benefit from favorable outcome with surgery followed by IR and /or SRS, as well as surgery followed by proton beam or heavy particle therapy such as carbon ion radiotherapy (Ferraresi et al., 2010). Most chordomas recurred after surgical resection and some kind of adjuvant therapy is almost always needed. Radiation therapy is therefore used in an attempt to gain local control. Early studies showed that conventional radiotherapy after subtotal resection of chordomas was associated with a high rate of treatment failure and recurrence. Progression free survival rates in these studies ranged from 17 to 39% at 5 years (Stacchiotti & Casali, 2011).

Gamma-Knife radiosurgery is potentially useful in the treatment of small sized residual chordomas (less than 30 cm), but it is not so effective in treatment of recurrence. However, the definitive role needs to be addressed in larger studies with adequate follow-up durations (Stacchiotti & Casali, 2011). Gamma Knife radiosurgery affords a reasonable rate of local tumor control in patients with recurrent or residual chordomas. Patients warrant long term follow-up to detect any late tumor progression (Dassoulas et al., 2009).

For patients with chordoma, surgical resection, proton beam radiation, and stereotactic radiosurgery with photons appear to play valuable role. The low incidence of these tumors, the variation in tumor behavior, disparate clinical presentation of patients, and differences in treatment algorithms at leading neurosurgical centers make comparisons of existing published series difficult.

Medical Treatments

Medical treatment of advanced chordomas is challenging. In fact, cytotoxic chemotherapy is known to be almost ineffective in the treatment of disease. The mechanism underlying inherent resistance to chemotherapy is not clear, even if it has been hypothesized that it is associated with the overexpression of some multidrug resistance-related genes, such as the multidrug resistance-associated protein 1 (MRP1), and to hypoxia-inducible factor-1 α (HIF-1 α). Among receptor tyrosine kinases (RTK), in almost all cases chordomas express activated platelet-derived growth factor receptor- β (PDGFRB). PDGFRB play an important role in the cell proliferation, differentiation, and growth. One of its main roles being angiogenesis stimulation (Yoneoka et al., 2008). About 70% of chordomas express epidermal growth factor receptor (EGFR), and, to a lesser extent, epidermal growth factor receptor 2 and 4 (EGF2 and EGF4). EGFRs and its family members are known to play a key role in tumorigenesis and growth of a variety of cancers (Yoneoka et al., 2008). Overexpression of MET and its ligand, the hepatocyte growth factor (HGF), was confirmed in most chordomas and was found to be related to their aggressiveness (Yoneoka et al., 2008).

Inhibition of PDGFRB and use of small molecules to inhibit several tyrosin kinases such as Imatinib Mesylate in combination with mTOR Inhibitors like rapamycin (sirolimus) or its analogues have shown beneficial effects in treatment of chordoma. Combination of Imatinib with Cisplatin in aim to more efficacy in chordoma is not clear yet (Yoneoka et al., 2008).

Table 1. Location of chordoma in some studies

Reference	Sacral	Skull base	Cervical	Other sites of the spine
Ferraresi et al.	11(50%)	1	2	8
Rashimi Chugh et al.	50%	35%	-	15%
Our study	13 (33.3%)	21 (53.8%)	4 (10.2%)	1 (2.5%)

Table 2. Studies and patient characteristics in series of chordoma

Reference	Patients	Median age in years (range)	Gender
Hug et al. 1999 (3)	25	43.7 (19–70)	M: 9; F: 16
Rosenberg et al. 1999 (3)	200	39 (10–79)	M: 87; F: 113
Noël et al. 2003 (3)	18	42 (17–68)	M: 9; F: 9
Weber et al. 2005 (3)	11	40 (15–77)	M: 38% ;F: 62%
OUR STUDY	39	51(21-83)	M :25; F:14

NEURSCIENCE

In Conclusions, despite the progress of current surgical techniques and some encouraging results with the use of targeted therapy, disease control and long-term prognosis are still poor and chordoma results, generally, in a long-lasting life-affecting disease. Nevertheless, specific experience of the multi-disciplinary teams (surgeons, medical oncologists, radiotherapists, pathologists, radiologists) is a very important pre-requisite in succeeding to improve patients' quality of life and, hopefully outcome.

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