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Clinical Profile and Treatment Outcome of Chordoma: A Tertiary Care Experience in North India

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Abstract

Chordoma is a slow growing cancer of tissue found inside the spine. Chordoma can happen anywhere along the spine. It is most often found near the tailbone (called a sacral tumor) or where the spine meets the skull (called a clival tumor). Chordoma is also called notochordal sarcoma. The main objective of this study was to determine the clinical profile and treatment outcome of chordoma patients. All the patients were diagnosed using radiological imaging and biopsy. The site of origin of chordoma was the sacrum in seventeen (71%) patients, the spine in six (25%) patients, and the skull base in one (4%) patient. 21 (88%) of the twenty-four patients received primary surgery. These 21 patients then received adjuvant radiation therapy using the intensity modulated radiation therapy (IMRT) strategy, with radiation dose ranging from 70Gy to 74Gy. Three patients (12%) did not undergo surgery; two had low performance status and received only radiotherapy; the third with the disease at the base of the skull was unresectable; this patient received radiotherapy first, then imatinib. Compared to individuals who get radiation alone, the addition of adjuvant radiation therapy to surgery in chordoma patients enhances overall survival.

Keywords: *chordoma, radiotherapy, targeted therapy.*

INTRODUCTION

Chordoma is a rare, low-grade, primary malignant bone tumor arising from primitive notochord remnants of the axial skeleton. It accounts for 1-4% of all primary skeletal tumors and its incidence rate is inferior to 0.1 per 100,000 inhabitants per year (Jemal, *et al.*, 2007, Chugh, *et al*., 2007). It is a low to intermediate grade tumor and accounts for 1 to 4% of all primary malignant bone tumors (Mirra, *et al.*, 2002, Fechner, *et al*., 1993). In almost all cases, it occurs in the midline of the axial skeleton and affects men much more often than women with the

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male to female ratio of 2:1 (Inwards, *et al*., 2010, Unni, *et al*., 2000). Most patients are in their fifth to seventh decades of life (Fechner, *et al.*, 1993). About 60% of the cases occur in the sacral region, 25% in the spheno-occipital/nasal, and 15% in the cervico-thoraco-lumbar spine (Fechner, *et al*., 1993). Chordomas grow slowly (Rosai, *et al.*, 1994) but their treatment is difficult. Prognosis has improved with the modern surgical techniques of resection, especially with tumors of the sacrum and the spine (Mirra, *et al*., 2002). Its natural history is characterized by repeated episodes of local recurrences and an often-fatal outcome (Rosai, *et al.*, 1994). Metastasis occurs to the lungs, bone, soft tissue, lymph nodes, and skin (Mirra, *et al*., 2002). Patients surviving for a long time have significant morbidity due to the neurological deficit (Unni, *et al*., 2000).

Adequate wide surgery still remains the cornerstone of chordoma treatment even though safe margins are often hard to obtain because of its anatomical sites of origin. The achievement of negative surgical margins favorably correlates with the rate of local relapse and survival (Boriani, *et al*., 2006, Tzortzidis, *et al*., 2006, Baratti, *et al*., 2003). Conventional radiotherapy with high-energy photons is poorly active and needs, moreover, to be delivered in doses as high as 60-65 Gy (Schulz-Ertner, *et al*., 2004). It may offer some temporary benefit in disease control in patients with inadequate surgery (*i.e*., close or positive margins) or, as exclusive treatment, in patients with unresectable/inoperable disease. Proton radiotherapy may succeed in offering better tumor control and fewer side effects even if it is still not readily available in comparison to external-beam radiotherapy (Weber, *et al*., 2005). Sensitivity to chemotherapy is very low and generally reported in the small subgroup of patients with high grade dedifferentiated chordomas with agents active in high-grade sarcomas (Fleming, *et al*., 1993). Chordoma overexpresses platelet-derived growth factor receptor (PDGFR)-b and its phosphorylated form, denoting constitutive activation (Tamborini, *et al*., 2006). The purpose of this study was to evaluate the clinical profile and advantages of postoperative adjuvant radiation in terms of locol control and survival benefit in chordoma patients.

MATERIALS AND METHODS

Study Design

This was an observational study performed in our hospital. All necessary clinical and epidemiological details of the 24 cases diagnosed with chordoma from January 2011 to December 2020 were retrieved. Clinical and radiological features, histopathological findings, treatment, and follow-up data were analyzed. The patients who were followed up at our center were planned to undergo an MRI/CT scan of the primary site every 3 months for the first 2 years, every 6 months for the following 3 years, and then every year from then onwards. The primary aim of this study was to assess the survival rate in patients who had received radiotherapy (postoperative or sole treatment) in our institute. Overall survival was calculated from the date of diagnosis to the event (death).

Sample Selection Method

Sample size were calculated by using Gpower Software v 3.1.9.4 have Alpha 0.05, effect size 0.5 and power of study were 80% and sample size of our study were 27 of them 3 were drop-outs, so desired sample size of our study were 24 subjects.

Statistical Analysis

Statistical analysis was done using IBM SPSS Statistics for Windows from IBM Corp. (released 2020, Version 27.0. Armonk, NY, USA). Categorical variables were shown in the form of frequencies and percentages. Survival was calculated using the Kaplan-Meier method, and the groups were compared using the Log-rank test.

RESULTS

In the current study, a total of 24 patients were analyzed. The mean age of patients was 52 years, ranging from 27 to 82 years. Fifteen (62%) patients were males, and nine (38%) were females. The site of origin of chordoma was the sacrum in seventeen (71%) patients, the spine in six (25%) patients, and the skull base in one (4%) patient. Patients with involvement of the sacral region had symptoms ranging from severe back pain with radiation to the lower limbs along with its weakness to constipation and difficulty in defecation, and those with involvement of the spine had lower limb weakness. Patients with involvement of the base of the skull had symptoms due to raised intracranial pressure, including headache, vomiting, and dizziness.

Out of the twenty-four patients, twenty-one (88%) underwent primary surgery. Following that, these twenty-one patients had adjuvant radiation therapy utilizing the intensity modulated radiation therapy (IMRT) approach, with radiation dose ranging from 70Gy to 74Gy @ 2Gy per fraction with five fractions per week. Three patients (12%) were not operated on; two had low performance status and were treated only with radiotherapy; the third had a condition at the base of the skull that was surgically incurable and was treated with radiotherapy followed by imatinib 400 mg once daily for two years before the medication was stopped because the patient had severe bleeding problems and lower limb edema (Table 1).

From the date of diagnosis until the last follow-up, the 5- and 10-year overall survival rates were computed. Using the Kaplan-Meir method,

Table 1. Profile of Chordoma (n=24)

Variables	Category	Frequency	%
Age	<=35	3	12.50
	36-45	4	16.67
	46-55	9	37.50
	56-65	4	16.67
	66+	4	16.67
Gender	Male	15	62.50
	Female	9	37.50
Primary Site	Sacral	17	70.83
	Spine	6	25.00
	Base of Skull	1	4.17
Surgery	Yes	21	87.50
	No	3	12.50
Radiation/Dose(Gy)	70Gy/35#	17	70.83
	72Gy/36#	4	16.67
	74Gy/37#	3	12.50
Targeted therapy	Imatinib	1	4.17
	No	23	95.83

the 5-year and 10-year overall survival rates in our sample were 58% and 37%, respectively (Figure 1). In this study, we discovered that patients who obtained adjuvant radiotherapy after surgical resection fared better than those who only received radiotherapy.

DISCUSSION

Chordomas account for less than 5% of all bone tumor and their histological assessment is often delayed due to non-typical signs and symptoms of disease with a frequent clinical diagnosis of pelvic or vertebral and irradiated pain due to discogenic or a specific pathology. The slow modality of biological growth, associated with a relatively low incidence of metastatic spread makes surgery the primary treatment of this rare bone tumor. Although potentially curative, a margin-free "en bloc" resection is often very hard to obtain due to the anatomical sites of origin of the chordoma, *i.e.*, skull base, spine, and sacrum. The extension of margins is, in fact, a very important prognostic factor correlated with the incidence of local relapses and overall survival.

The pathogenesis of chordoma is unclear but tumor cells are characterized by a notochordal differentiation. Three subtypes have been described as pathological. The classical form and chondroid form are generally low grade and locally aggressive tumors, but the dedifferentiated form shows aggressive behavior (Fletcher, *et al*., 2013). Stacchiotti and Sommer published the first guidelines for the diagnosis and treatment of chordoma in 2015 (Stacchiotti, *et al*., 2015). Complete surgical resection with a negative surgical margin in localized disease is the mainstay of care. Standard adjuvant radiotherapy is recommended for cervical spine and skull base chordoma. Definitive radiotherapy is the option in cases where resection is not suitable. Radiotherapy is recommended after R1 resected sacral chordomas. A study showed that local progression-free time is longer with the addition of radiotherapy (Moojen, *et al*., 2011). Ten-year local progression-free survival (PFS) was 35-50% in patients with sacral chordoma who were treated by adjuvant radiotherapy (Stacchiotti, *et al*., 2015). Twenty-nine patients with chordomas of the mobile spine and sacrum who were treated by surgery and high-dose proton−/photon irradiation were evaluated in a phase II trial (DeLaney, *et al*., 2009). In this trial, no significant difference between R0 and R1/R2/biopsy could be shown regarding local control (DeLaney, *et al.*, 2009). Retrospective data of 17 patients compared surgery only with carbon ion therapy. The local recurrence-free survival rate at 5 years was 62.5% for the surgery group and 100% for the carbon ion radiotherapy group, and

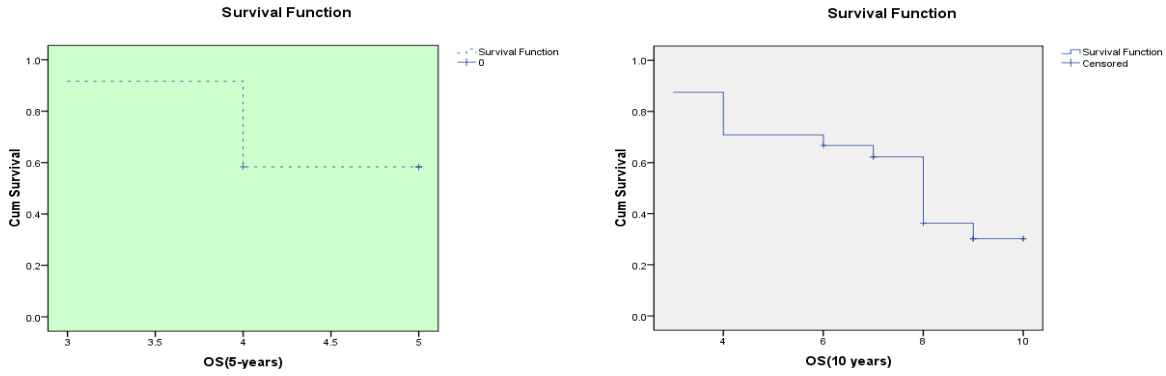

Figure 1. 5-year and 10-year Overall Survival (OS) by using Kalpan Meir plot. The 5-year and 10-year overall survival rates in our sample were 58% and 37%, respectively.

the disease-specific survival rate at 5 years was 85.7% and 53.3%, respectively (Nishida, *et al.*, 2011). Metastases can occur in 30–40% of the patients and that usually occurs after local relapse and at a later stage of the disease (Radelli, *et al*., 2016).

Our results showed that 5 and 10-year overall survival was (58 and 37%) which is similar to a study done by Forsyth, *et al*., in which 51 patients with intracranial chordomas were treated with surgery and 39 patients received postoperative irradiation. Overall 5 and 10-year survival rates were 51 and 35%, respectively. Patients with postoperative radiotherapy had longer disease-free survival times (Forsyth, *et al*., 1993). In another study by Keisch, *et al*., 21 patients (five clival, two nasopharyngeal, and one lumbar) were treated with surgery, and 8 had a subtotal resection and postoperative RT, and 4 received RT after biopsy. Five- and 10-year actuarial survival was better in patients treated with surgery alone or surgery and irradiation than RT alone 52%, 32%, 0% (Keisch, *et al*., 1991) which are comparable to our 5 and 10-year overall survival (58 and 37%).

Tamborini, *et al*. showed that beta-type platelet-derived growth factor receptor (PDGFRB) was highly expressed and phosphorylated, but platelet-derived growth factor receptor alpha (PDGFRA) and KIT were less expressed in chordomas (Tamborini, *et al*.,2006). Likewise, Weinberger, *et al*. found epidermal growth factor receptor (EGFR) expression in a series of 12 patients with chordoma (Weinberger, *et al*., 2005). Therefore, in the last decade, molecular targeted therapy has been investigated for systemic therapy. Imatinib, a platelet-derived growth factor receptor (PDGFR) TKI has shown positive results in a phase 2 study in advanced chordoma. This trial included 56 patients. One patient (2%) achieved a partial response and 11 patients had a minor response. Thirty-five patients had stable disease (62.5%) and clinical benefits were reported for 64% of patients. Median PFS and overall survivals were 9 months and 35 months, respectively (Stacchiotti, *et al*., 2012). Another retrospective trial confirmed imatinib activity with 34 (74%) patients having stable disease (Hindi, *et al*., 2015). Lapatinib in EGFR-positive chordomas has been investigated in a prospective phase 2 trial. The overall response rate was 33.3% with a median PFS of 8 months (Stacchiotti, *et al*., 2013). Sorafenib was given to 27 patients with chordoma in a phase 2 study (Bompas, *et al*., 2015). Results showed 9 months PFS rate of 73% and a 1-year overall survival rate of 86.5%. The activity of sunitinib was assessed in a basket trial in advanced sarcoma. Nine patients with advanced chordoma were treated. No objective responses were seen and four stable diseases were detected. Median PFS was 12 months (George, *et al.*, 2009). There was a retrospective study by the French Sarcoma Group of 80 patients with advanced chordoma who were treated with first-line molecular targeted therapies (Lebellec, *et al.*, 2017). Patients were treated with imatinib (77.5%), sorafenib (13.7%), erlotinib (6.3%), sunitinib (1.2%), and temsirolimus (1.2%). Five patients had a partial response (three patients treated with imatinib, one with sorafenib, and one with erlotinib), and 58 patients had stable disease (72.5%). Median progression-free and overall survivals were 9.4 months and 52.8 months (Lebellec, *et al*., 2017). A retrospective case series of five patients with advanced chordoma was published. Four patients were treated with pazopanib and one patient was treated with sunitinib. Median PFS was 8.5 months in the pazopanib subgroup, and 27 months in the sunitinib subgroup (Lipplaa, *et al*., 2016).

CONCLUSION

Compared to individuals who get radiation alone, the addition of adjuvant radiation therapy to surgery in chordoma patients enhances overall survival. Despite the progress of current surgical techniques and some encouraging results with the use of radiotherapy and targeted therapy, disease control, and long-term patients' prognosis

are still poor and chordoma results, generally, in a long-lasting life-affecting disease. Therefore, still, new treatment strategies are needed for this rare disease.

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CONFLICT OF INTEREST & FUNDING

There is no conflict of interested in this study.

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