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Current Status of the Treatment for Sacral Chordomas and its Future Trends

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Abstract: Chordomas are rare slow-growing, low to intermediate-grade malignant neoplasms (less than 5% of all primary bone neoplasms); however they sometimes metastasise to distant organs. The 10-year overall survival rate is relatively low. The sacrococcygeal region is one of the most common sites. Intensive surgery is the first line for the treatment, since chordomas are resistant to chemotherapy. In turn, radiotherapy presents marginal effect. It has been reported that surgical margins govern local recurrence and survival. However, sacral chordomas represent a therapeutic challenge as a large number of sacral chordomas are often very large at the time of diagnosis and may comprise adjacent vital organs. Sacrectomy includes four surgical approaches; *i.e.*, a combined sequential anterior and posterior approach, a combined simultaneous anterior and posterior approach, a posterior approach alone and combined extended ilioinguinal and posterior approaches. Because of its large invasion, various postoperative complications were considered. Bladder, bowel and sexual dysfunction and wound complications were major and important complications. The efficacy of adjuvant therapy for the treatment of sacral chordoma is under debate. Chemotherapy has not significant benefit to local control as well as overall survival in patients with chordomas. Standard dose of radiotherapy is not effective for chordomas, either. Some authors described that Hadron-based therapy has several advantages compared with conventional photon-based therapy. Recently some authors described efficacy of new molecular-targeting agents. The infrequency of this disease has prevented to establish the optimal treatment. In this review, we summarized accumulating knowledge of the treatment for sacral chordomas and discuss future trends.

Keywords: Bladder and bowel function, chordoma, molecular-targeting agents, radiation, sacrum, surgical resection, wound complication.

INTRODUCTION

Chordomas are rare slow-growing, low to intermediate-grade malignant neoplasms, which are thought to arise from cellular remnants of the notochord [1]. Chordomas represent less than 5% of all primary bone tumors. They can arise from bone in the skull base and anywhere along the spine; however the most common site is the sacrococcygeal region (40%-50%) and the base of the skull (35%-40%) followed by the vertebral bodies (15%-20%) [2, 3].

Despite low to intermediate-grade tumor, chordomas metastasize to distant organs such as the lungs, bone, soft tissues, lymph nodes, liver and skin in up to 43% of patients [4, 5]. The 10-year overall survival rate ranges from 30% to 65% [6-12].

Intensive surgery remains the first line for the treatment, since chordomas are resistant to chemotherapy. In turn, radiotherapy shows marginal effect [6, 7, 9, 13, 14]. It has been reported that surgical margins govern both local recurrence and survival [7, 8]. Indeed, recent literatures reported that the rate of local recurrence ranging between 0% and 60% for wide margins, between 31% and 71% for marginal margins, and between 67% and 100% for intralesional resection margins [11, 15-20].

Sacral chordomas represent a therapeutic challenge as a large number of sacral chordomas are often very large at the time of diagnosis (Fig. **1**) and may comprise adjacent vital organs. The large sizes, anatomical complexity of the pelvis, intimate relation with neurovascular structures, make it extremely difficult to extirpate the lesion with adequate margins [8].

In this review, we summarized accumulating knowledge of the treatment for sacral chordomas.

SURGICAL RESECTION

In the 1970s, the concept of wide *en block* surgical resection for the treatment of sacral tumors was advocated by Stener and Gunterberg [21]. Since then, *en block* excision, *i.e.*, sacrectomy has remained a first line in the surgical management of sacral chordoma. Owing to the development of more vigorous surgery which enables wider surgical margins, local control of the lesions has significantly improved

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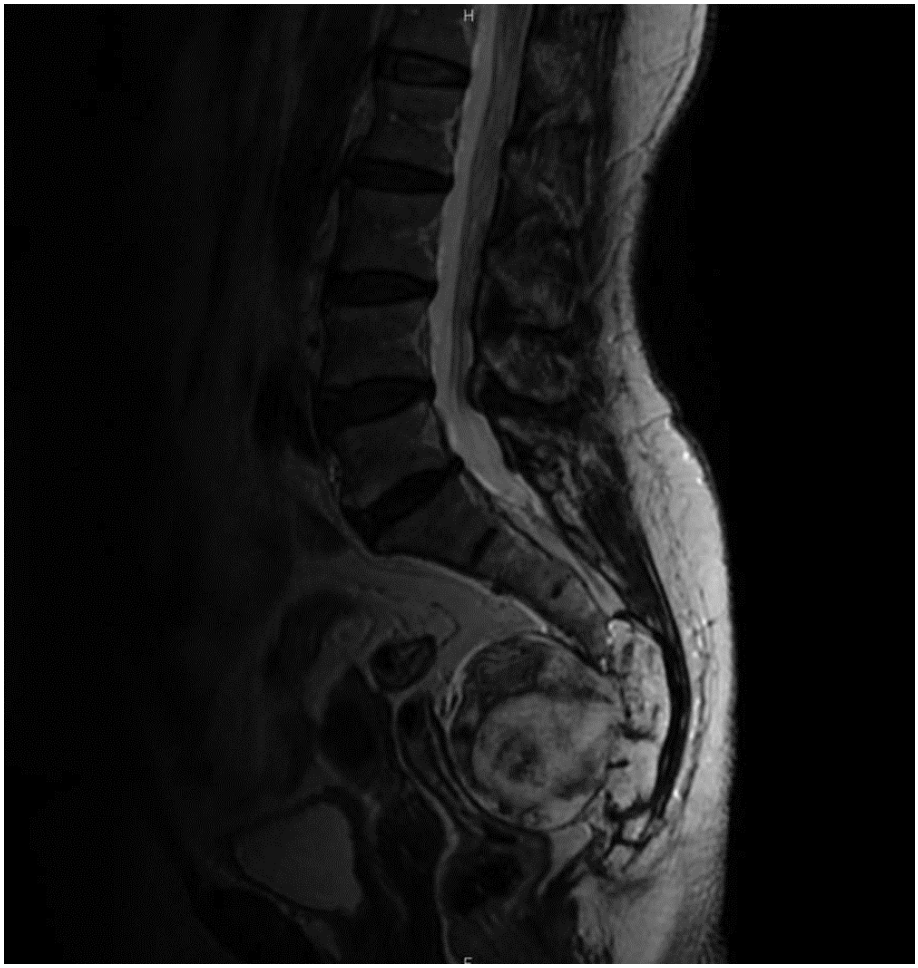

Fig. (1). Magnetic resonance imaging of 66 years old female patient with sacral chordoma at the time of diagnosis revealed a large soft tissue mass emanating from the sacrum.

in chordomas [22]. Sacrectomy includes four surgical approaches; *i.e.*, a combined sequential anterior and posterior approach, a combined simultaneous anterior and posterior approach, a posterior approach alone and combined extended ilioinguinal and posterior approaches [23-25].

A less invasive, posterior alone approach may be enough for the resection of smaller, distal lesions [18, 24, 26, 27]. Contrary, for proximal chordomas and/or for chordomas infiltrating the mesorectum, a combined approach allows us to confirm the proximal end of the lesion in the pelvis and facilitates *en bloc* removal of the ano-rectum with the sacral lesion. Accordingly, some authors considered that the extension of the lesion above S3 needs a combined approach [7, 15, 18].

Some authors suggested that the extension of the lesions into adjacent soft tissue was a significant risk factor for inadequate surgical margins [13, 15]. The surgical strategies are needed to discuss carefully at a multidisciplinary sarcoma tumor team to achieve adequate surgical margins at the initial surgery.

The efficacy of adjuvant therapy for the treatment of sacral chordoma is under debate. Chemotherapy (cyclophosphamide, doxorubicin, dacarbazine, vincristine, cisplatin, methotrexate) does not have significant benefit to local control as well as overall survival in patients with chordomas. Radiotherapy is another option of adjuvant therapy in other malignant tumors; however standard dose of radiotherapy ($\leq$ 60 Gy) is not effective for chordomas [4, 28, 29]. However, recent advances in radiation technology and treatment show possible favorable effect of radiotherapy (see Radiotherapy section).

Schwab *et al.*, reported the capability of cryosurgery for the treatment of chordomas in adjuvant setting [17]. Cryosurgery was first indicated to both benign and malignant tumors by Cahan [30, 31]. Marcove promoted the indication of its use in bone tumors [32]. Subsequently, several authors used cryosurgery for the treatment of sacral tumors including chordomas in adjuvant setting [33, 34]. Schwab *et al.*, reported that the patients who had wide contaminated margins treated with cryosurgery in adjuvant setting did not show a higher recurrence rate or lower survival rate compared to those who received wide resection [17]. Further studies are needed to confirm the capability of cryosurgery as a local adjuvant therapy for the treatment of chordomas.

POSTOPERATIVE COMPLICATIONS

Bladder, bowel and sexual dysfunction, motor deficits, lymphatic complications, pelvic hematomas, cerebrospinal

Table 1. Association of most cranial preserved root level and bowel and bladder function [6, 24, 35, 38, 39].

		Percentage of Patients who have Minimal or no Problem of Bowel and Bladder Function	
Most Cranial Preserved Root		**Bowel Function**	**Bladder Function**
Bil S3		75-100	69-100
Bil S2		25-77.8	20-77.8
Bil S1		0-20	0-5.3
Uni S3		62.5-67	60*
Uni S2		25*	50*

Bil: bilateral Uni: unilateral *Only one author described.

fluid fistulae, deep-vein thrombosis and wound complications were previously reported common postoperative complications sacral chordomas in the literature [7, 17, 22, 35-37].

Wound complications are one of the major complications, which are found around half of the patients [8, 17, 36, 37]. The majorities of them were managed with local control care as an outpatient setting, however some patients were required operative management such as operative debridement and musculocutaneous flaps [17]. Several authors advocated to use omental flap [8], transverse rectus abdominis musculocutaneous flap [7, 17]. Chen *et al.* [37] found that low albumin (<3.0 g/dL), longer operating times (>6 hours) and previous surgery were statistically significant risk factors for wound infection after sacral tumor surgeries.

Bladder and bowel dysfunction is another major concern. Percentage of patients who had minimal or no problem of bowel and bladder function after sacrifice of sacral nerve roots was summarized according to the previous reports [6, 24, 35, 38, 39]. If bilateral S3 nerve roots were preserved (bilateral S4 nerve roots were sacrificed), many patients have almost normal bowel and bladder function (75-100% patient: bowel function, 69-100% patient: bladder function). When bilateral S2 nerve roots were intact (bilateral S3 nerve roots were sacrificed), bowel function of 25-77.8% patient was maintained and bladder function of 20-77.8% patient was maintained. If bilateral S2 nerve roots were sacrificed (bilateral S1 nerve roots were preserved), many patients have bowel and bladder problem (0-20% patients' bowel function was maintained and 0-5.3% patients' bladder function was maintained). If unilateral S3 nerve root was spared, 62.5-67% patients have normal bowel function, and 60% patients have normal bladder function. If unilateral S2 nerve root was preserved, 25% patients' bowel function was maintained, and 50% patients' bladder function was maintained (Table **1**). Intriguingly, Schwab *et al.*, sound an alarm concerning the pudendal nerves. Larger sacral tumors can comprise or approximate the pudendal nerve. Sacrifices of bilateral pudendal nerves lose any bowel, bladder or sexual function even if all the sacral roots are preserved [17].

RADIOTHERAPY

The use of radiation therapy as a primary or adjuvant treatment for chordomas is controversial, because effective dose to eradicate chordomas is much higher than the tolerance dose of the spinal cord and rectum. Treatment with conventional radiotherapy at dose of 40-60 Gy has yielded only 10-40% 5-year local control [4, 28, 29]. Recent developments of radiation technology and treatment have allowed more planned targeting of neoplasms with higher doses of radiation.

High-dose protons or charged particles, *i.e.*, carbon ions, helium, or neon can deliver higher dose of radiation to the target, which improve radiobiological effect with minimum side effect to the adjacent normal tissues [40-42]. Hadron-based therapy has several advantages compared with conventional photon-based therapy. Accumulating results suggested its efficacy for the treatment of chordoma. Indeed, hadron therapy in skull base, cervical spine and sacrococcygeal chordomas achieved 50-60% 5-year local control [43, 44].

SUMMARY AND FUTURE TRENDS

Despite vigorous, careful surgical management and strict surveillance protocols, a considerable percentage of the patients will develop local recurrence and late onset metastasis [45]. Recent advance of molecular researches open the door for the treatment of chordomas. Overexpression of platelet-derived growth factor receptor (PDGFR) A, PDGFRB and KIT receptors has confirmed in chordomas. These findings can contribute to develop new molecular-targeting agents [46]. Indeed, preliminary reports have shown favorable effect of imatinib, a tyrosine-kinase inhibitor with specificity for the kinase domain of PDGFR and KIT receptors in both symptomatic and radiological levels in patients with advanced disease [47, 48].

Clinical trials targeting other agents, *i.e.*, epidermal growth factor receptor (EGFR) (cetuximab, gefitinib and erlotinib) [49, 50] and signal transducer and activation of transcription 3 (STAT3) [51, 52] in the treatment of chordomas were ongoing, we are looking forward to their results.

The infrequency of this disease has prevented to establish the optimal treatment. We believe that accumulated experiences in the treatment of sacral chordomas might well contribute to establish its optimal treatment.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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