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REVIEW ARTICLE

Review of current treatment of sacral chordoma

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Chordoma is a relatively rare, locally aggressive tumor which is known to arise from embryonic remnants of the notochord and to occur exclusively along the spinal axis, with a predilection for the sacrum. Although chordoma typically presents as a single lesion, a few cases of metastasis have been reported and the prognosis of such patients may be poor. Chordomas are slowly growing tumors with insidious onset of symptoms, making early diagnosis difficult. Recent improvements in imaging have provided valuable information for early diagnosis. The optimal treatment for sacral chordoma is en bloc sacral resection with wide surgical margins. Improvement in surgical techniques has widened the opportunities to provide effective treatment. However, the effects of adjuvant treatment options are still both unclear and controversial. Substantial progress has been made in the study of molecular-targeted therapy. The authors review the current surgical and adjuvant treatment modalities, including molecular-targeted therapy, available for management of sacral chordoma.

Key words: Chordoma; Orthopaedic procedures; Sacrum

Introduction

Chordoma is a rare, low to intermediate-grade malignant bone tumor known to arise from embryonic remnants of the notochord[1–3]. However recent studies suggest that chordomas arise from a precursory benign notochordal lesion[4]. Chordoma accounts for 4% of malignant bone tumors[2]. The majority of chordomas develop in the sacrococcygeal region (40% to 50%) or the base of the skull (35% to 40%), and only a small proportion are found in the vertebral bodies (15% to 20%)[5–7]. The tumor occurs predominantly in the fifth to seventh decade of life, although it has been reported in infants and older people. It has a higher incidence in male than in female patients with a ratio of 1.8 : 1[8], although a younger mean age in female patients has been reported[1,9].

Chordomas generally grow slowly with insidious symptoms. Local pain, which at times radiates to the buttocks, is the chief presenting symptom in most patients. Bowel or urinary disturbances are frequently observed. Early diagnosis is difficult, but is important if patients are to receive adequate and effective treatment. The excellent capabilities of magnetic resonance (MR) and computed tomography (CT) imaging allow precise delineation of tumors in terms of volume and anatomic characteristics, and aid in diagnosis (Fig. 1A–D)[8]. They are required for preoperative evaluation, and often are complemented with immunohistochemistry, electron microscopy, DNA cytometry, and cytogenetics. Fine-needle aspiration biopsy (FNAB) of conventional chordomas has been described, with special attention given to the differential diagnosis[10].

Proximity to rectum, bladder, and neurologic structures limits en bloc resection of sacral tumors[2,7]. Although recent advances in surgical techniques have widened the opportunities for better management, problems such as control of blood loss during surgery, sphincteric and sexual dysfunction secondary to sacrifice of sacral nerve roots, and reconstruction of lumbo-pelvic stability still pose a significant challenge.

The purpose of this article is to review the current surgical and adjuvant treatment techniques, including molecular-targeted therapy, available for the management of sacral chordoma.

Treatment

Complete excision of sacral chordoma is necessary at initial surgery because of its poor sensitivity to radiotherapy and chemotherapy. Surgical removal is a very effective treatment for sacral chordomas. With advances in imaging technology, preoperative evaluation can now provide more detailed characterization of the lesion and

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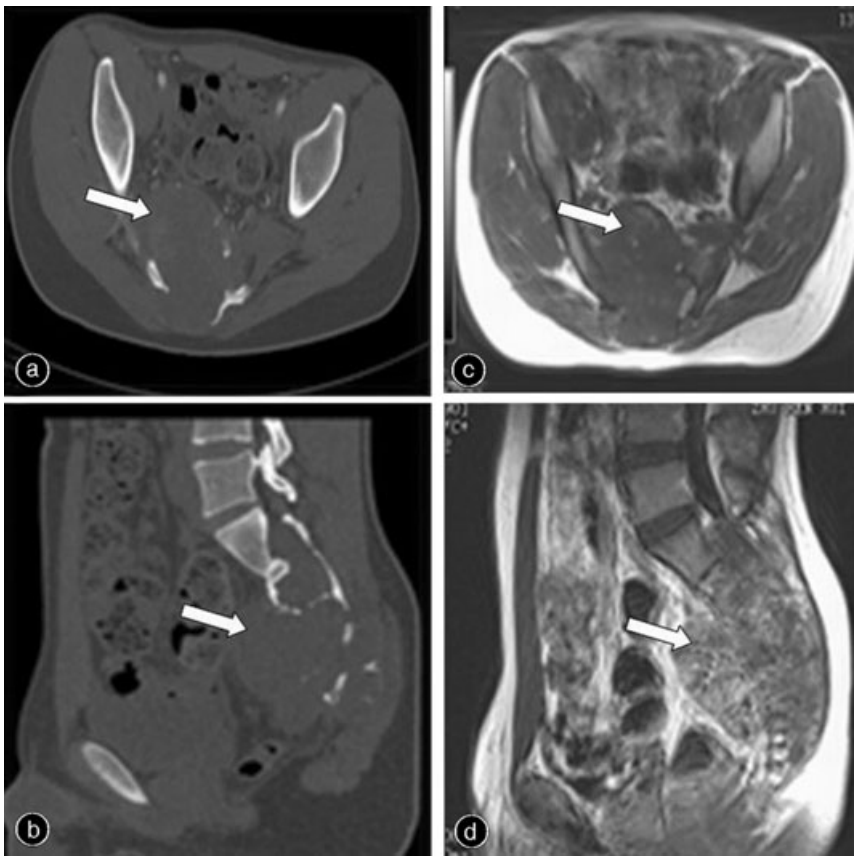

Figure 1 (a) and (b): Preoperative CT image of a 54-year-old man shows a sacral chordoma, with lytic bone destruction of the osseous pelvis. (c) and (d): Preoperative T_1-weighted MR image shows the tumor affecting the entire sacrum with a soft tissue mass covered anteriorly by the presacral fascia.

aid in choosing the optimal surgical approach. In addition, new and aggressive surgical techniques allow radical total resection with minimal complications.

Surgery

Operative technique

The surgical techniques for resection of sacral chordoma include intralesional, marginal, wide and radical excision such as total sacrectomy. We believe that wide resection is the best treatment for sacral chordomas. However various factors, including anatomic characteristics, size of tumor, extent of intraoperative blood loss, and a desire to preserve nerve roots often result in intralesional excision being employed, resulting in a high incidence of local recurrence for which curative resection in a second procedure is more difficult to achieve[6,11,12]. Complete removal of the tumor at the time of initial surgery is important for good prognosis because recurrence after the complete removal is almost impossible[13].

Surgical approaches

Several surgical approaches can be adopted to remove a sacral chordoma, and it is unclear which of these increase the probability of obtaining a wide margin. Most surgeons agree that a posterior approach is satisfactory for lesions at the third sacral segment or below, but for lesions that are farther cephalad a combination of anterior and posterior exposure is advised. In a study by Wuisman *et al.*, several approaches are described for high-level sacral tumors, including a midline posterior, an ilioinguinal and posterior, and a combined anterior transperitoneal or retroperitoneal and posterior approach[11]. The anterior retroperitoneal approach offered the advantages of good exposure of the iliac veins, arteries and their branches; iliolumbar nerve roots; upper part of the sacrum from the ventral aspect and adjacent iliac wings. The midline posterior approach offers better exposure of the sacrum, dorsal parts of both iliac wings, surrounding soft tissues and lumbar vertebrae if necessary. For lesions above S3, Fuchs *et al.* have described a combination anteroposterior approach[6]. They found that the anterior approach allowed exposure of the entire sacrum with mobilization of the rectum, ureter, iliac veins and arteries, and that ligation of the internal iliac arteries might reduce blood loss during mobilization of the tumor. They state that an anterior approach is more popular and allows harvesting of a pedicled rectus abdominis flap to facilitate final wound closure. Simpson *et al.* accept the feasibility of wide resection of a primary malignant sacral tumor through a

combination of anterior and posterior approaches and their study demonstrates that a combined extended ilioinguinal and posterior approach is both possible and effective for wide resection of a tumor in the cephalad part of the sacrum[14]. Localio *et al.* have suggested that the posterior approach is associated with a high recurrence rate due to poor exposure of the sacrum and difficulty in removal of the tumor en bloc without spillage of tumor tissue[15]. However, the posterior approach offers the advantages of a single operation, shorter operative time, and less morbidity[1,6]. Therefore, it would be better to use a posterior approach for lesions at S3 and below, and a combined anteroposterior approach for lesions above S3.

Complications

Blood loss

The blood supply of the sacrum is from the internal iliac and median sacral arteries, and many anastomotic branches and accompanying veins form the presacral venous plexus. The close proximity of sacral tumors to the main vessels means that massive blood loss can occur during surgery. Using a sequential combined anterior and posterior approach, Hulen *et al.* reported a mean intraoperative blood loss of 5000 ml (range, 1500–8000 ml) in 16 patients[12]. Yonemoto *et al.* reported an average intraoperative blood loss of 5170 ml (range, 1000–24 200 ml) in 13 patients with sacrococcygeal chordoma[13]. Simpson *et al.*used a combined anterior and posterior approach for the resection of large tumors of the cephalad part of the sacrum in 12 patients[14]. Although the internal iliac vessels were ligated, the average blood loss was 7000 ml (range, 2000–20 000 ml). Yang *et al.* reported using a posterior approach in 29 sacral chordoma patients 1–2 days after transcatheter arterial embolization[16]. Intraoperative blood loss was significantly reduced, the average blood loss being 1360 ml (range, 400–3000 ml). We also think that preoperative arterial embolization is effective in decreasing intraoperative blood loss and can lead to good results. Other methods to control blood loss include manipulative hypotensive anesthesia, low temperature and low pressure anesthesia, embolization of the internal arterial vessels, ligation of the internal vein and artery, and interdiction of the abdominal aorta. The importance of proximal control of the common iliac vessels during a sacral osteotomy must be emphasized.

Functional considerations

Sphincteric and sexual dysfunctions are important problems which impact the patients' quality of life postoperatively. The key factor in averting such problems is preservation of sacral nerves during surgery. Todd *et al.* described 53 patients in total[17]. In their study, patients who underwent unilateral sacrectomy with preservation of contralateral sacral nerves retained normal bowel (87%) and bladder function (89%), while all patients whose S2–S5 nerve roots were destroyed bilaterally had abnormal bowel and bladder function. In patients who had bilateral S3–S5 resection, normal bowel and bladder function was retained in 40% and 25%, respectively. In patients who had bilateral S4-S5 resection with preservation of the S3 nerves bilaterally, normal bowel and bladder function was retained in 100% and 69%, respectively. In patients who had asymmetric sacral resections, with preservation of the S3 nerve root on at least one side, normal bowel and bladder function was retained in 67% and 60%, respectively. These results show that unilateral resection of sacral roots, or preservation of at least one S3 root in bilateral resection, preserves bowel and bladder function in the majority of patients. Nakai *et al.* evaluated bowel and bladder function by clinical symptoms, physiologic tests, and intravesical pressure measurement with cytometry[18]. They concluded that unilateral destruction of sacral nerves results in little bladder or anorectal dysfunction. No matter which level is resected, damage to the lumbosacral trunks or sciatic nerves may cause serious postoperative motor and sensory deficits.

Reconstruction

The advantages of reconstruction after total sacrectomy remain debatable. Gunterberg *et al.* evaluated pelvic strength after major amputations of the sacrum[19]. They stated that the pelvic ring was weakened by approximately 30% after resection of one third of the sacroiliac joints and associated ligamentous structures. They concluded that the pelvic ring remains stable as long as half of the S1 segment is left intact. Although the pelvis is weakened by approximately 50%, the residual strength is sufficient for normal weight bearing in the standing position. The findings of Simpson *et al.*[14], who reported that reconstruction of the massive defect after a total sacrectomy may facilitate walking, are consistent with the view of Gunterberg *et al.*[19]. However, because of the high risk of a major wound complication, they did not attempt to implant hardware or bone grafts after total sacrectomy.

Wuisman *et al.* deemed that a decision to reconstruct the surgically created defect depends on the extent of resection of the iliac wing and of the underlying disease[11]. They established several resection levels through the iliac bone in which both left and right sides were taken into account. The first level, resection through both sacroiliac joints, saves the dorsal bony part of the ilium and the attachments of iliolumbar muscles and ligaments.

Because these muscles and ligaments, along with scar tissue, may function as a biologic sling, stabilization is not needed. The second level, resection lateral to both sacroiliac joints but perpendicular to the frontal plane, includes the sacrum and the posterior parts of the ilium. The attachments of the iliolumbar muscles and ligaments are partially dissected. The biologic sling may function and again stabilization is not needed. The third level, resection through the ilium and ventral part of the sacroiliac joint perpendicular to the sacroiliac joint, includes the sacrum and the posterior quarter to third of the ilium. At this level, thinning of the iliac wing is apparent, and the gap between the ilium and the lumbar spine is of vital importance. Technically, it may be difficult to use horizontal bars for fixation and to approximate the iliac wings. Bone bridging between the lumbar spine and the remaining ilia may be difficult. The fourth level, resection more ventrally of the sacroiliac joint through the iliac wing including the posterior third to half of the iliac wing, disrupts almost all iliolumbar muscles and ligaments, leading to spinopelvic instability. Fixation with horizontal bars in combination with a spinal screw and rod system is technically impossible. Therefore, total sacrectomy including iliac resection at levels three and four are best reconstructed with individually designed prostheses.

Traditionally, reconstructions include various combinations of rods, bolts, screws, and grafts. Gokaslan *et al.* used the Galveston L-rod technique for establishment of a bilateral liaison between the lumbar spine and ilia (Fig. 2A–D), and the pelvic ring was then reestablished by means of a threaded rod connecting left and right ilia[20]. Reconstruction facilitated postoperative rehabilitation. However, there were no significant differences in functional outcome between patients with reconstruction and those without[11].

Adjuvant radiation therapy and chemotherapy

Traditional radiation and chemotherapy are controversial because chordomas are not sensitive to them[1,2,21,22]. Previous studies regarding the effect of early radiotherapy when the surgical margin is positive have demonstrated mixed results[1,2,6,13]. Indications for radiation therapy may include surgically inaccessible lesions, contaminated surgical margins, or incomplete surgical excision of the tumor[6]. Samson *et al.* concluded that preoperative radiotherapy to a maximum dose of fifty grays is recommended if contamination during the operation is likely, as in patients who have a large tumor, or for whom a cephalic sacral resection is planned[1]. If contamination by tumor occurs during surgery, radiotherapy of sixteen grays can be administered postoperatively. They also suggest that the use of preoperative or postoperative irradiation might permit the surgeon to perform a marginal resection in the case of high-level sacral tumors, allowing preservation of

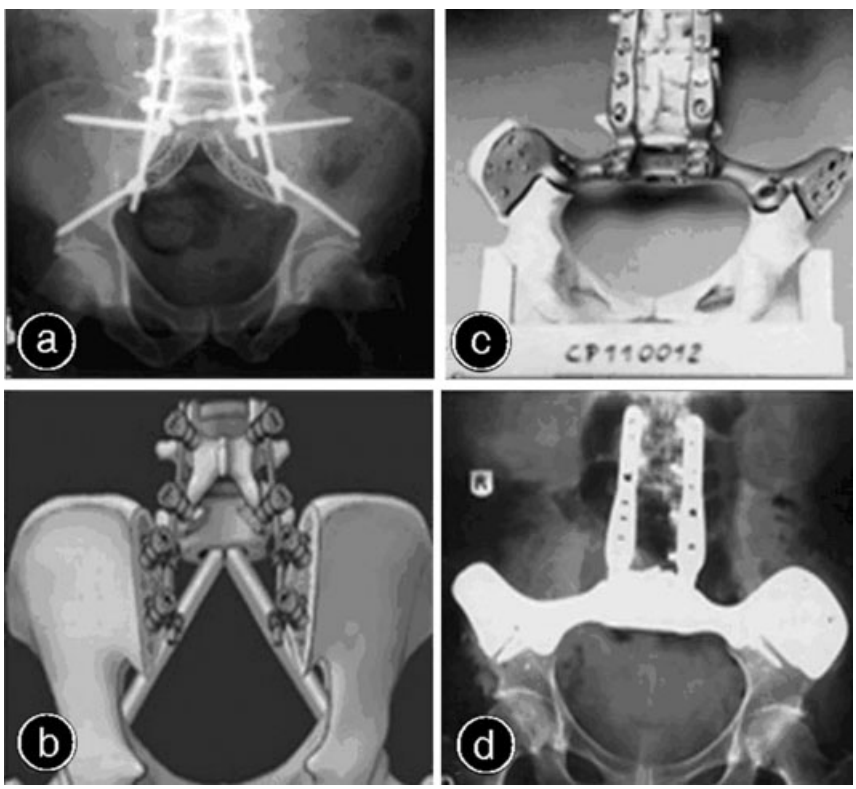

Figure 2 (a): Anteroposterior radiographs and (b) three-dimensional model obtained after implantation of the improved Galveston L-rod. (c): Three-dimensional model of patient's pelvis with the special prosthesis, and (d) postoperative radiograph showing well-incorporated grafts at the pelvic sites and unchanged stable position of the prosthesis.

nerve roots. We strongly believe that the surgeon should preserve sacral nerve roots at the time of surgery, except when their destruction is necessary to obtain negative margins. In the latter case inadequate clearance of tumor would otherwise result in continued tumor growth or local recurrence, leading to even more severe neurological dysfunction than when the nerve roots are surgically destroyed.

For almost all patients with chordoma, Catton *et al.* found that external beam photon therapy does not improve local control and survival, and provides only effective palliation of pain[21]. With respect to both the degree and duration of symptoms, and progression-free survival, they found no difference between conventional and hyperfractionated radiotherapy regimens for chordoma. They also found no advantage for doses greater than 50 grays[7,21]. Fuchs *et al.* suggested that radiation therapy can also be used after removal of the primary tumor or when there is a local recurrence, but their results did not demonstrate a significant improvement in survival rate[6]. Cheng *et al.* reported that when the surgical margin was positive, use of radiation earlier, rather than later was associated with a better continuous disease-free survival and local recurrence-free survival[23]. York *et al.* demonstrated that conventional radiation therapy lengthened the disease-free interval for patients treated with subtotal excision (2.12 years vs. 8 months)[22]. The authors of a recent promising report found carbon-ion radiotherapy to be an effective treatment for chordomas[6,24].

Chemotherapy has little value in the management of chordoma. York *et al.* reported that chemotherapy was not used frequently[22]. However when it was used, it was late in the course of the disease. Therefore, no meaningful results were obtained regarding the effect of chemotherapy on control of recurrence or survival rate. Anis *et al.* reported good results and low morbidity of chemotherapy in the palliative treatment of two patients[25].

Molecular-targeted therapy

Over the past few years, molecular-targeted therapy based on the discovery of new tumor therapeutic targets and understanding of the pathways which accommodate cell proliferation and metastasis has been developed. It provides a new treatment for low to intermediate grade malignant bone tumor which is insensitive to chemotherapy. Recently, there have been many studies about the inhibitor of protein tyrosine kinase. Regarding chordoma, Casali *et al.* reported that they treated six chordoma patients with imatinib mesylate at a dose of 800 mg daily[26]. They found that imatinib mesylate had anti-tumor activity and that platelet-derived growth factor receptor (PDGFR) B expressed positively in all patients. Tamborini *et al.* found the clinical benefit observed in chordoma patient treated with imatinib seems to be attributable to the switching off of PDGFRB, PDGFRA and Kit[27]. An antiangiogenic therapy has been reported anecdotally to have been active in one patient[28] and this therapy may be used in clinics exploring new molecular-targeted drugs. At the same time, a strong expression of epidermal growth factor receptor and c-Met has been described in a series of 12 chordomas[29], and a single case responding to a combination of cetuximab and gefitinib has been reported[30]. Molecular-targeted therapy combined with traditional surgical treatment may become a useful method for treating chordoma, and improve its cure rate.

Prognosis

Local recurrence is the most important predictor of mortality in patients with chordoma. There is general agreement that complete surgical resection with wide, tumor-free margins is the treatment of choice for chordoma. The oncologic outcomes reported in similar published studies are as follows (Table 1). Bergh *et al.* reported a follow-up study of 39 patients with chordoma[5]. The estimated survival rates at 5-, 10-, 15-, and 20-years were 84%, 64%, 52% and 52%, respectively. Local recurrence was significantly associated with an increased risk of metastasis and tumor-related death. Samson *et al.* reported that local recurrence occurred principally in the first three years, but that metastasis might appear nine years or more after the initial surgery[1]. York *et al.* reported

Table 1 Comparison of oncologic outcomes for sacral chordomas

Authors	Patients	Follow-up (years)	Local recurrence	Metastasis	Tumor-related death
Samson *et al.*[1]	21	4.5	4 (19.0%)	4 (19.0%)	3 (14.3%)
Bergh *et al.*[5]	39	8.1 (0.2–23)	17 (43.6%)	11(28.2%)	10 (25.6%)
Fuchs *et al.*[6]	52	7.8 (2.1–23)	23 (44.2%)	16 (30.8%)	19 (36.5%)
Hulen *et al.*[12]	16	5.5 (1.25–14.5)	12 (75.0%)	6 (37.5%)	6 (37.5%)
Yonemoto *et al.*[13]	13	6.3 (0.5–13.7)	6 (46.2%)	6 (46.2%)	7 (53.8%)
York *et al.*[22]	27	3.6 (0.3–34)	18 (66.7%)	7(25.9%)	15 (55.6%)

a retrospective study of 27 sacral chordoma patients and the overall survival time for the group was 7.38 years (range, 0.33–34 years)[22]. Fuchs *et al.* reported that 52 patients who underwent surgical treatment for sacrococcygeal chordoma had an average survival time of 7.8 years (range, 2.1–23 years)[16]. The overall survival rates were 74%, 52%, and 47% after 5, 10 and 15 years, respectively.

Yonemoto *et al.* examined the sites of local recurrence in six patients, revealing a high proportion of local recurrences in the gluteal muscles attached to the sacrum (gluteus maximus and piriformis muscles)[13]. Therefore, for the prevention of local recurrence, precise preoperative assessment by MR imaging of any tumor infiltration into the gluteal muscles must be emphasized. Cheng *et al.* reported that the proximal extent of tumor location is the most valuable prognostic indicator[23]. Berth *et al.* reported that larger tumor size, performance of an invasive morphologic diagnostic procedure outside of the tumor center, inadequate surgical margins, microscopic tumor necrosis, Ki-67 > 5%, and local recurrence were all found to be adverse prognostic factors[5]. Kaiser *et al.* reported a 28% recurrence rate in patients with en bloc resection, but a 64% rate in patients in whom the tumor capsule was breached during surgery[31]. York *et al.* reported a disease-free interval of 2.27 years in patients with radical resection and only 8 months in patients with subtotal excision[22]. They concluded that surgical type and surgical margins are intimately correlated with local recurrence, and that the initial resection margin appears to be the critical factor in the final outcome.

Summary

CT and MR imaging are valuable for early diagnosis. En bloc sacral resection with a wide surgical margin is very important for survival and local control of sacrococcygeal chordoma. Chordoma is insensitive to radiation therapy and chemotherapy, making standard adjuvant treatment a controversial issue. Functional reconstruction is also important, and should be evaluated preoperatively.

Sacral chordoma is rare but usually lethal, and current treatment measures needs to be improved. It is concluded that early diagnosis, complete surgical resection with tumor-free margins, and probably molecular-targeted therapy can not be over emphasized for local control and good results.

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