General Considerations

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Sacral tumors are rare. To diagnose a sacral tumor is challenging because of the lack of specific clinical symptoms, so sacral tumors are often diagnosed in advanced stages with extensively involving the sacral nerves, iliac vessels, and other surrounding structures. The management could be quite challenging for orthopedic surgeons because of the complicated anatomy. For most cases, only aggressive procedure with adequate surgical margin (en bloc resection) could guarantee satisfied local control, but in the meantime, sacrectomy also brings several problems such as bowel, bladder, and sexual dysfunction; wound infection; and major blood loss during the surgery or postoperatively which might jeopardize the safety of the surgery, the postoperational function [1], and prognosis of the patients.

Primary benign and malignant tumors of the sacrum are 2–4% of all primary bone neoplasms and 1–7% of all primary spinal tumors [2]. Sacral tumors can be classified into four main categories: congenital, metastatic, primary osseous, and primary neurogenic. Congenital lesions of the sacrum include dermoid cysts, anterior and intrasacral meningoceles, perineural cysts, teratomas, hamartomas, and chordomas. Of these neoplasms, chordomas are the most common primary sacral tumors that account for 40% of all primary sacral neoplasms in the USA [3]. According to a research from Peking University People's Hospital, chordomas account for 24.4% of all primary sacral tumor cases; they are also the most common primary sacral neoplasms in the Chinese population [4]. Chondrosarcoma is the second most frequent primary malignant bone tumor of the sacrum in the USA, though its sacral location is less than 7% of all cases [5]. Giant cell tumor (GCT) is the most common benign sacral neoplasm and accounts for 8–18% of all primary sacral tumors [3]. Neurogenic tumors (benign or malignant) are also frequently seen in the sacral tumor cases which represent up to 16.6% of all primary cases [4]. Rarer tumor types such as multiple myeloma, teratoma, Ewing sarcoma, osteosarcoma, lymphoma, hemangioma, and angiosarcoma could also be seen in the sacrum.

More than half of all sacral tumors are metastatic tumors. These lesions are most often disseminated from a solid organ. Lung, breast, prostate, thyroid, renal, and rectal cancers are the most common origins of sacral metastases [6]. Aggressive rectal carcinomas can directly invade the sacrum, increasing the complexity of surgical resection.

As it is mentioned above, the surgical treatment of these tumors is challenging because of the complex regional anatomy and the advanced stage of cancer at the time of diagnosis. Surgeons must not only be familiar with local anatomy from a neurologic, colorectal, urologic, gynecological, orthopedic, and plastic standpoint but also sometimes have to face the dilemma between functional preservation and cure of the tumor. The operating strategy requires precise preoperative planning to locate the exact extent of tissue involvement to decide the level of the osteotomy and the muscle, the nerve, and vessels that will require resection; to plan reconstruction method; and to determine if adjuvant treatments as preoperative embolization and radiation (preoperative or intraoperative) are needed. However, this chapter focuses only on the general information of sacral tumors, as the anatomy, surgical approaches to the sacrum, and some other information are discussed more extensively elsewhere in this textbook.

20.1 Clinical Presentation

Sacral tumors are very rare and usually grow insidiously with nonspecific symptoms such as lower back, buttock, sacrococcygeal, or referred leg pain [7]. Routine X-ray, CT, and MRI studies often fail to detect the sacrum neoplasm especially that of the lower sacrum. Unfortunately, many patients are misdiagnosed with lumbar disc disease for which they receive subsequent treatment. Norstrom et al. reported the mean delay from symptom onset to diagnosis is 2 years

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[8]. This delay often allows the tumors to grow larger and cause neurological dysfunction and/or mechanical instability.

The first presentation may be a painless sacral mass; sometimes the giant mass could even be palpable on abdominal examination. Some patients may only present with minor neurologic symptoms, with or without pain. The large presacral mass often causes constipation because of rectal compression, as well as impedes bladder function.

The pain caused by sacral tumors is the most common symptom. The location of pain usually indicates the origin of the tumors. For example, chordomas from lower sacrum could cause continuous rectal-anal pain [9]. Invasion of bone such as the sacroiliac joints can cause pain when sitting or walking and could be alleviated by lying supine. This usually suggests the instability of the joint and need to be reconstructed in the operation.

When the tumor invades the neurological structures, patients may present with radiated pain, numbness, paresthesias, or muscle weakness. On neurologic examination, the patients might have decreased reflexes, anal sphincter dysfunction, and lower extremity weakness. Bowel and bladder dysfunction can also occur in such scenarios. Some patients could present with cauda equina syndrome when the cauda equina is compressed by tumor, and these cases often need immediate intervention. General signs of cancer such as weight loss, anemia, or weakness are signs of metastatic cancer rather than primary sacral tumors.

20.2 General Information of Common Primary Sacral Tumor Types

20.2.1 Giant Cell Tumor

Giant cell tumors are the most common benign primary tumors of the sacrum and usually occur with a peak incidence in the third decade of life, with a female predilection [3]. GCTs are typically eccentric, expansile, osteolytic lesions without sclerotic margin or calcification. The lesions usually arise in the upper sacrum and often invade sacroiliac joints and intervertebral disks [10, 11], which is rare for other benign sacral tumors. Giant cell tumors (GCTs) are locally invasive and highly vascularized [12]; curettage surgery with no intraoperative hemorrhage control usually leads to local failure and major blood loss during the surgery. Because of the high recurrence rate, some scholars suggest the optimal treatment is wide resection [12]. However, total resection often associates with sacral nerve dysfunction and higher morbidity. So we preferred conservative surgery such as intralesional curettage and/or partial excision with effective intraoperative bleeding control (embolization and/or aortic balloon) in patients with sacral GCTs. During 2000 to 2013, 135 cases underwent such conservative surgery in our department with a mean blood loss of 3223 ml, and only 25 (25/135, 18.9%) cases had local recurrence [4].

There is some adjuvant therapy for GCTs such as argon beam coagulation, cryotherapy, serial embolization, and application of bisphosphonates, interferon alpha-2b, and denosumab. FDA had approved denosumab for the treatment of GCTs. Denosumab is a monoclonal antibody that targets receptor of activator nuclear factor kappa-B ligand (RANKL), thereby downregulating osteoclast activity. Denosumab has been shown to induce significant radiographic responses and to alleviate pain in extremity and spinal GCTs [13]. Chawla et al. [14] showed that denosumab had a 96% response rate in surgically unresectable GCTs in a 63-sacral GCT patient cohort. Thomas et al. treated 37 GCT cases with denosumab; 24 of them had recurrent disease. A positive response was seen in 86% of the patients [15]. Rutkowski et al. reported a 222 case series with denosumab; 86% of all patients experienced surgical downstaging. Only 15% of all the patients who underwent surgery had a local recurrence [16]. The current evidence shows that denosumab can control GCTs and sometimes shrink the tumor which facilitates subsequent surgery. However, there is no defined duration for the use of denosumab preoperatively as "overcalcification" of the tumor may make curettage during the surgery difficult. Moreover, we have no consensus on the endpoint for the use of this medicine as stand-alone treatment.

In conclusion, together with preoperative arterial embolization and/or aortic balloon, complete resection with perioperative denosumab might be the optimal treatment. However, because en bloc resection of these tumors is often very morbid, conservative resection could be a good choice. Denosumab, serial embolization [17], or radiotherapy might be considered for the patients who have an unresectable tumor or when it is too risky for surgery. Nevertheless, the role of radiotherapy remains unclear, as it has been implicated in the sarcomatous transformation [18].

20.2.2 Chordoma

Chordomas are slow-growing, low-grade malignant tumors that arise from vestigial notochordal remnants with a predilection for the ends of the spine. Chordomas often occur in the sacrococcygeal region and involve the fourth and fifth sacral segments [3, 19]. Chordomas are the most common primary malignant sacral tumor, with a peak incidence in the sixth decade and a male predominance [3, 18]. Chordomas are relatively resistant to conventional radiotherapy [20, 21] and chemotherapy [22], so surgical excision is the mainstay of treatment. It is reported that 5–40% of patients had local recurrence or distant metastases [22, 23]. The overall 5- and

10-year survival rates after sacrectomy are 45–77% and 28–50%, respectively [22–25].

The imaging of a chordoma often shows a large, lytic, destructive midline lesion with or without peripheral amorphous calcification centered in the vertebral body with adjacent presacral and/or sacral canal mass. Chordoma could extend across the sacroiliac joint and the intervertebral disk [3] and invade the surrounding muscles along with the piriformis and gluteus maximus muscle.

Stener and Gunterberg [26] first reported the idea of wide en bloc surgical resection for the treatment of sacral tumors. Since then, en bloc resection has been a goal in the surgical management of sacral chordomas. Fuchs et al. showed a significant difference in local control rate between patients who underwent wide resection and those who had a subtotal resection of sacral chordomas [27]; the time from surgery to local recurrence was 2.27 years and 8 months, respectively. Several other research also support that aggressive surgical resection could bring optimal local control in chordomas of the sacrum [27]. Moreover, some researcher advocate that total resection combined with advanced radiotherapy could substantially improve the local control rate of chordomas of the sacrum in recent years [22, 27].

20.2.3 Neurogenic Tumors

Benign sacral neurogenic tumors include peripheral schwannoma and neurofibroma. Malignant peripheral neurogenic tumors include malignant schwannoma (malignant peripheral nerve sheath tumor) and neurofibrosarcoma [28]. Neurogenic tumors arising from the sacrum are rare, with only about 7% of intraspinal neurogenic tumors involving the sacrum. The tumors often originate in the spinal canal or in close relation to the sacral nerve roots or their coverings, and grow out of the spinal canal through the neural foramina from the sacral canal and have a dumbbell shape. Inward growth of the tumors is generally limited due to the defined space of the sacral canal. However, for outward-growing tumors, a huge mass is often seen anterior to the sacrum. Initially, clinical symptoms are not evident in patients with sacral neurogenic tumors, especially for benign tumors, and symptoms such as lower back pain and sciatica occur only when the tumors become very large. Many patients visit the hospital because of an abdominal palpable painless mass or because a mass is discovered in the lower abdomen during a physical examination. The tumors often occur in females between 20 and 50 years old [28, 29].

Radiograph examination usually shows enlargement of the sacral neural foramen in benign cases, although the feature is not obvious in malignant neurogenic tumors. Most of the benign neurogenic tumors are shown as homogeneous lesions on an MRI, with about 6% showing a cystic degeneration change; however, most malignant neurogenic tumors show a heterogeneous signal change in the MRI, with about 75% showing cystic change. Therefore, an inhomogeneous signal and cystic change in huge neurogenic tumors indicates the possibility of malignancy [30, 31].

In a 790 consecutive primary sacral tumor case series from Peking University [4], there were 150 neurogenic tumors, with 131 benign neurogenic tumors (83 neurofibromas and 48 schwannomas) and 19 malignant schwannomas, which accounted for 19% of all primary sacral tumors. Among 131 benign neurogenic tumors, there were 62 males and 69 females with an average age of 42.3 years (17–67 years). All cases experienced marginal excision, and postoperative recurrence occurred in 17 (12.9%). According to our experience, surgical approach depends on the location and size of the tumors. Intraspinal tumors should be excised from a posterior approach. For giant neurogenic tumors that arise from the sacrum and involve the sacral canal, excision should be done by a combined anterior-posterior approach. Giant presacral neurogenic tumors located below the S1 level could be removed by a posterior approach. The anterior surgical approach should be applied for giant presacral neurogenic tumors that are located above S1 and do not involve the spinal canal [28].

20.2.4 High-Grade Osseous Tumors

High-grade osseous tumors including chondrosarcoma, osteosarcoma, and Ewing sarcoma often are very aggressive. Because these tumors respond poorly to chemotherapy and irradiation as for the advanced stage and axial location, they require a wide excision in the absence of systemic disease [27, 32]. Most osteosarcomas are primary, but sometimes they are the consequence of a malignant transformation of a giant cell tumor or of Paget disease. Sacral osteosarcoma is very rare, with only 2% of osteosarcomas involving the sacrum [31]. Peak incidence occurs in the third to fourth decade [33]. Osteosarcoma typically shows an aggressive, osteolytic, permeative pattern of bone destruction with cortical breakthrough and soft tissue mass [33]. Matrix mineralization of the soft tissue mass is more easily detected on CT.

Chondrosarcoma tends to be less aggressive except for the dedifferentiation type. Less than 7% of all chondrosarcomas arise in the sacrum [5]. Patients most commonly present in the fourth to sixth decades [31]. The typical imaging characteristic of chondrosarcoma is an osteolytic lesion with soft tissue mass and characteristic “rings and arcs” chondroid matrix mineralization. Unmineralized chondroid matrix often shows intermediate signal on T1-weighted and high signal on T2-weighted images. Mineralized region displays low signal intensity on all MRI sequences. Sometimes it is hard to distinguish between chondrosarcoma and chondroid

chordoma because both of the tumors had chondroid matrix mineralization, though chordomas often affect the fourth and fifth sacral segments and centered in the vertebral body, while chondrosarcomas tend to originate from the upper sacrum in an eccentric pattern.

Ewing sarcoma is a small, round blue cell malignancy usually seen in the second decade of life with a male predominance [34]. More than half of spinal Ewing sarcomas occur in the sacrum, and more than two thirds occur in the sacral ala [34]. On radiographs, the tumors may show permeative osteolysis. CT often reveals a permeative pattern of bone destruction. Sometimes, lesions may show a mixed pattern of osteolysis and sclerosis, but there is no matrix mineralization in the soft tissue mass [34]. Soft tissue mass and spinal canal involvement are frequently seen and best defined on MRI. Ewing sarcoma has one of the highest mortality rates among all malignant bone tumors. It is regarded as a surgical condition only when encountered in the sacrum because of its propensity to metastasize early and because of its favorable response to both irradiation and chemotherapy [32].

From 2000 to 2013, 26 osteosarcomas, 49 chondrosarcomas, and 28 Ewing sarcomas/PNETs out of all 790 primary sacral tumors underwent surgeries in our department [4]. Ewing sarcomas/PNETs accounted for 3.5% of all primary sacral tumors. Twenty-one cases accepted neoadjuvant chemotherapy, while 27 cases received postoperative chemotherapy and radiotherapy. Fourteen cases underwent en bloc resection or total sacrectomy, while 14 cases underwent piecemeal resection. Fifteen cases (53.6%) were noted postoperative recurrence. Three-year overall survival rate was 39.1%, and the 5-year overall survival rate was 19.6%. A total of 49 sacral chondrosarcomas accounted for 6.2% of all cases. There were 26 males and 23 females with an average age of 42.5 years (17–69 years). Among these 49 patients, 29 cases underwent en bloc resection or total sacrectomy, while piecemeal resection was performed on the others. Twenty-two cases (44.9%) were noted postoperative recurrence. The overall survival rate at 2 years and 5 years was 58.7% and 47.0%, respectively. The disease-free survival rate at 2 years and 5 years was 42.3% and 31.8%, respectively. A total of 26 sacral osteosarcomas were enrolled [35], which accounted for 3.3% of the whole series. There were 15 males and 11 females with a median age of 28 years (range, 12–68 years). Adequate and inadequate surgical margins were obtained in 16 and 10 cases, respectively. Distal metastasis occurred in 13 patients (50%), and local recurrence occurred in 10 patients (38.5%, including six patients with additional distal metastasis). The 1-year and 5-year survival rates were 92.3% and 38.7%, respectively. The result of this research reveals that adequate margins can significantly improve the recurrence rate and event-free survival rate compared to inadequate margins. There are very limited reports about the prognosis after integrated therapy such as chemotherapy and radiation of high-grade osseous sacrum tumors because of the rarity. So it is hard to draw a sound conclusion of the optimal treatment strategy for these cases yet. Current evidence support that surgical excision with adequate margin is still the golden standard for high-grade primary sacral tumors. The prognosis remains dismal, and more collaborative clinical trials are needed to improve the survival.

20.3 Management Consideration

20.3.1 Biopsy

With the age, gender, symptom, location, and imaging characteristics, experienced doctors should make a preliminary diagnosis. However, the preoperative biopsy is still critical especially for the patients whose pathologic diagnosis would influence the decision to operate or the type of surgery. Although open biopsies and transrectal biopsies were common in the past years, almost all biopsies are now performed percutaneously with the assistance of image guidance. The biopsy tract should be included within the boundaries of the subsequent surgery. As for the spine tumors, the accuracy of percutaneous vertebral biopsy varies from 66% to 96% [36–38]. The highest diagnostic precision is generally achieved in metastatic cases, with a diagnostic accuracy rate of 79–96% [36–38]. Accuracy and diagnostic value are lower in cases of primary bone tumors, estimated at 60–80% [36–38]. Taking into account that the sacrococcygeal region is easily accessible for surgical sampling, an open biopsy would be considered if the percutaneous biopsy failed to obtain an adequate sample.

20.3.2 Primary Sacral Tumors

The goal of the treatment of primary sacral tumors is to be curative. Surgical excision is still the optimal way to achieve local control. The surgical intervention will be discussed profoundly in other chapters. Because of the advanced disease and critical anatomy location, surgery with adequate margin is not always feasible for all cases. Conventional therapeutic methods, such as radiotherapy and chemotherapy, could be used as the neoadjuvant or adjuvant treatment in certain histologic types or even the only treatment for the unresectable tumors.

20.3.3 Radiotherapy

Radiotherapy is a feasible adjuvant option especially for subtotally resected tumors, local recurrences, and unresect-

able tumors. Carbon ion radiotherapy and proton/photon therapy were shown to have better results compared to conventional radiotherapy because of increased effective doses and the lower complication rate [39]. Reiko et al. reported [40] patients with unresectable sacral chordomas received carbon ion radiotherapy with the dose of 52.8–73.6 Gray equivalents. The 5-year overall survival rate was 86%, and the 5-year local control rate was 89%. Thomas et al. [41] reported a total of 50 patients (29 chordomas, 14 chondrosarcomas, 7 others) underwent gross total [29] or subtotal [14] resection or biopsy [15]. With 48-month median follow-up, 5-year local control rate, recurrence-free survival, and overall survival are 78%, 63%, and 87%, respectively. Moreover, modern intensity-modulated radiation therapy and stereotactic radiosurgery (SRS) also allow high-dose hypofractionation and minimized complications [42, 43]. Radiotherapy is a crucial treatment for sacral sarcomas. Osteosarcomas are considered to be radiation resistant, but advanced techniques can also improve the local control rate for the cases undergoing piecemeal or subtotal resection [44]. For sacral Ewing sarcomas, radiotherapy might be the best way for local control when en bloc resection is not feasible or patient could not tolerate the postoperative nerve dysfunction [45].

20.3.4 Chemotherapy

Most sacral tumors are benign lesions or low-grade malignancies. Thus, chemotherapy is not necessary for such cases. However, for the chemo-resistant tumors such as chordomas and GCTs, the targeted therapeutic agents are used in recent years. Casali et al. [46] first published the result of imatinib therapy in chordoma patients. A multicenter phase II study also supports the positive effect of imatinib on progression-free survival. Hof et al. [47] used cetuximab and gefitinib with a good response in a chordoma patient with local recurrence and lung metastases. Chawla et al. [14] showed that denosumab had a 96% response rate in surgically unresectable GCTs in a 63-sacral GCT patient cohort. Thomas et al. treated 37 GCT cases with denosumab; 24 of them had recurrent disease. A positive response was seen in 86% of the patients [15]. Rutkowski et al. reported a 222 case series with denosumab; 86% of the patients experienced surgical downstaging. Only 15% of all the patients who underwent surgery had a local recurrence [16].

Similar to the treatment strategy for sarcomas of other sites, chemotherapy is crucial for high-grade primary malignant sacral tumors (Ewing and osteosarcoma). Recurrence-free and overall survival is increased significantly with combined adjuvant chemotherapy in the osteosarcomas and Ewing sarcomas [48–50]. Hoffman et al. reported the histologic response to chemotherapy was analyzed in the surgical specimen and had a significant influence on survival [51]. Unfortunately, there is no optimal chemotherapy protocol for chondrosarcomas yet. Italiano et al. reported 180 patients treated with chemotherapy in 15 institutions in Europe and the USA; the response rate is 31% for mesenchymal chondrosarcoma, 20.5% for dedifferentiated chondrosarcoma, only 11.5% for conventional chondrosarcoma, and 0% for clear cell chondrosarcoma [52]. But with the development of immunology and in-depth study of the mechanism of cancer initiation, there are high hopes for new therapeutic agents.

20.4 Metastatic Tumors

Metastatic tumors are the most common malignancies in the sacrum. Breast, lung, renal, thyroid, and prostate cancers are the predominant primary origins; less common primary lesions include lymphoma, melanoma, and tumors of unknown origin [53, 54]. Hematogenous metastasis is the main way of spreading cancer, although direct invasion from pelvic tumors is also commonly seen [55, 56].

The treatment decision of sacral metastasis is based on individualized evaluation such as the health status of the patient, the location of the lesion, the biology, and the response to chemotherapy of the tumors. The mainstay of management for sacral metastatic tumors is palliative therapy. Radiotherapy is the major treatment for the cases without spinal instability. Good pain relief and neurological improvement are attainable after radiation [57, 58]. Minimal invasive procedures such as sacroplasties could also provide immediate pain relief and improvement with ambulation [59]. Only when the bone destruction jeopardizes the spinal stability and conservative therapy fails to improve neurological status, an aggressive surgery including tumor resection and lumbosacral reconstruction should be considered [60, 61], as radiosurgery has demonstrated promising results with local disease control [62].

20.5 Summary

Sacral tumors are rare in incidence. The most common tumors are metastatic neoplasms. Chordomas, giant cell tumors, neurogenic tumors, and chondrosarcomas are the most frequently seen primary pathologic types. The rarity and insidiously growing pattern lead to a delay in diagnosis and intervention. The surgical treatment of sacral tumors could be very challenging because of the advanced disease and complicated anatomy. The multidisciplinary team including neurologic, colorectal, urologic, gynecological, and plastic surgeons, as well as sophisticated ICU doctors and anesthetists, are often needed. Surgical resection with

adequate margin (en bloc resection) is still vital for local control, but only quite limited centers have enough such experiences. Radiotherapy and chemotherapy are proved to be effective for certain tumors. However, the prognosis of sacral sarcomas and metastatic cancer is still unencouraging. In the later chapters, we will discuss the topics including the anatomy of the sacrum, diagnostic imaging method, pathology, surgical treatment strategy, and its results of the sacral tumors. Some special experience from Peking University such as hemorrhage control, neurologic complications and wound care, and rehabilitation protocols are also to be introduced.

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