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Bone Cancer

Multidisciplinary Management of Primary Tumors of the Vertebral Column

*Wesley Hsu, MD**
Thomas A. Kosztowski, BS
Hasan A. Zaidi, BS
Michael Dorsi, MD
Ziya L. Gokaslan, MD
Jean-Paul Wolinsky, MD

Address
**Department of Neurosurgery, The Johns Hopkins University School of Medicine, Johns Hopkins Medical Institutions, Meyer Bldg. 8-161, 600 N. Wolfe St., Baltimore, MD 21287, USA.*
E-mail: weshsu@jhmi.edu

Opinion statement

Primary spinal neoplasms are rare tumors that can lead to significant morbidity secondary to local bone destruction and invasion into adjacent neurological and vascular structures. These tumors represent a clinical challenge to even the most experienced physicians and require a multidisciplinary approach to ensure optimal patient outcomes. This review will discuss the most common primary bone tumors and focus on recent surgical, medical, and radiation treatment advances.

Introduction

Primary spinal neoplasms make up less than 10% of all the tumors seen in the spinal column. These rare tumors can lead to significant morbidity secondary to local bone destruction and invasion into adjacent neurological and vascular structures. These tumors represent a clinical challenge to even the most experienced physicians and require a multidisciplinary approach to ensure optimal patient outcomes. This review will discuss the most common primary bone tumors and focus on recent surgical, medical, and radiation treatment advances.

Plasmacytoma/multiple myeloma

- Multiple myeloma (MM) is a B-cell lymphoid malignancy characterized by clonal proliferation of plasma cells in the hematopoietic bone marrow [1]. In the United States, 65% of patients with MM are above the age of 65 [2], with patients typically presenting with osteolytic lesions, osteoporosis, or spinal compression fractures. This is a result of either erosion of bone due to direct infiltration of plasma cells [3]

or secretory factors released by plasma cells resulting in an imbalance in bone metabolism, whereby erosive osteoclasts are preferentially activated and restorative osteoblasts are inhibited [4–7].

- The extent of disease is an important factor in directing future treatments. Early in the disease, patients with plasma cell malignancies may present only with localized solitary plasmacytoma of bone or extramedullary plasmacytoma that contains a risk of progressing to generalized disease (MM) [8]. These tumors are exquisitely radiosensitive, and radiotherapy typically achieves a local control rate of 96% [9•–12].
- The standard of care for MM patients less than 65 years old involves high dose chemotherapy followed by autologous stem cell transplantation (ASCT) rescue. Induction therapy traditionally includes a regimen of vincristine, adriamycin, and dexamethasone (VAD), but there has been increasing evidence to suggest that agents such as thalidomide, lenalidomide, or bortezomib combined with dexamethasone (TD, BD, RD) followed by the mustard agent melphalan significantly increases response rates to treatment. Thalidomide and lenalidomide are sedatives known to not only kill myeloma cells directly [13] but also downregulate cell surface markers (i.e., CXCR4) involved in homing and migration of myeloma cells. Bortezomib is a novel protease inhibitor [14]. For patients who are not candidates for transplant therapy (i.e., those with a number of medical co-morbidities or the elderly), the standard of care is considered to be either a combination of melphalan, prednisone, and thalidomide (MPT) or melphalan, prednisone, and bortezomib (MPB).
- A number of medical drugs are recommended to treat skeletal complications of MM. Bisphosphonates such as pamidronate and zoledronic act to inhibit osteoclasts and serve solely to prevent further bone degradation. However, these drugs do not help to redeposit new bone and have significant side effects themselves, such as renal insufficiency and osteonecrosis of jaw. Recently, it has been discovered that bortezomib has many important qualities beyond its established role as an induction agent. Much similar to the bisphosphonates, this drug has the ability to inhibit osteoclast differentiation, thereby preventing further bone destruction [15].
- Because of the radio- and chemosensitivity of plasmacytoma/multiple myeloma, the role for surgery is generally limited. Even rare cases of plasmacytoma/MM with epidural extension causing spinal cord compression can be treated emergently with radiosurgery producing excellent clinical results. Surgical intervention is generally reserved for patients who develop mechanical instability. Tumor-induced osteolysis may lead to symptomatic compression/burst fractures and progressive kyphotic deformity, which may require surgical intervention. In such instances, many centers are utilizing vertebroplasty/kyphoplasty to stabilize compression fractures and improve pain control [16].

Aneurysmal bone cysts

- According to the World Health Organization, aneurysmal bone cysts (ABCs) are defined as "an expanding lesion with blood filled cavities separated by septa of trabecular bone or fibrous tissue containing osteoclast giant cells." The pathophysiology of ABCs remains unclear, and there is much debate as to whether these lesions are neoplastic. Approximately 80% of cases occur in the first two decades of life

[17, 18]. The natural history of these lesions is variable and difficult to predict for a given lesion. Although some lesions may resolve spontaneously in time, the majority of these lesions exhibit variable growth rates over time. There is much debate over the best treatment for spinal ABCs. Among the treatment modalities for ABCs, complete surgical excision of the lesion remains the most effective with the lowest rate of recurrence [19, 20]. Boriani and colleagues recommended the use of en bloc resection especially when ABCs involved the posterior elements, whereas complete curettage (preferably preceded by embolization) is preferred for anterior lesions [21]. However, kyphoscoliosis, compression of the spinal cord and nerve roots, and functional impairment may complicate complete surgical excision. Thus, lesions are often treated by curettage and bone grafting. The disadvantage to this technique is that it is often associated with greater blood loss and with high recurrence rates ranging from 20% to 60% in different studies [22, 23]. Several less-invasive methods have been studied for the treatment of ABCs including multiple injections of calcitonin with methylprednisolone into the cyst [24–26], particulate embolization [27], intralesional injection of alcoholic zein [28], radiotherapy alone [29], and radiotherapy combined with surgery [18, 30]. Recently, radionuclide ablation with ^{32}P chromic phosphate colloid injected into the cyst proved to be an effective treatment modality with resultant stabilization and progressive ossification within the lesion [31].

- There have been several case reports that have examined the treatment of ABCs with injections of calcitonin combined with methylprednisolone into the cyst [24–26]. In Szendroi *et al.*, percutaneous injection of calcitonin into the lesion three times per week for five weeks resulted in growth arrest of the ABC and progressive ossification of the cyst in six out of the seven patients [26]. Under this treatment, it is necessary to monitor the patients for hypocalcemia and hypophosphatemia. Although this modality has proven to have potential, larger studies are necessary to convincingly demonstrate its effectiveness.
- Selective embolization of ABCs has been shown to avoid excessive bleeding when used with surgery and has also proven to be an effective sole treatment in cases that were difficult to treat surgically [19, 20, 32, 33]. In Boriani *et al.*, they recommended that selective arterial embolization be performed if the diagnosis of ABC was certain and stability was not a concern [21]. However, this treatment has the risk of embolization of the blood supply of unintended areas such as the spinal cord or brain stem.
- Intralesional injection of a sclerosing agent, such as alcoholic solution of zein, has shown efficacy in the treatment of ABCs [28, 34, 35]. However, Topouchian and colleagues reported a high rate (33%) of complications with this treatment modality including pulmonary embolization, fistulization, and local abscess [36]. In Peraud *et al.*, injection of an alcoholic solution of zein in the ABC at the C2 level resulted in inadvertent embolization of the vertebrobasilar system and subsequent death of a child [37].
- Radiotherapy can be used as an alternative or adjunct to surgery when ABCs are located in sites where an adequate resection cannot be done without resulting in significant morbidity or poor cosmetic results. Feigenberg and colleagues demonstrated that megavoltage radiotherapy with doses of 26–30 Gy effectively treated ABCs that were recurrent or inoperable [38]. Local control rates after radiotherapy have been reported to be 75–92% [39–43]. Historically,

radiation therapy fell out of favor because of the concern about increased risk of radiation-induced cancers including sarcomatous degeneration of the lesions [22, 41, 44]. On a review of the literature, it was discovered that all the cases of radiation-induced malignancies occurred in patients who were treated suboptimally, because of using orthovoltage equipment and employing techniques that are considered obsolete today [38]. Megavoltage therapy allows for the delivery of low doses of radiation while penetrating deeper into the tissue to reach the actual lesion, thus reducing the incidence of radiation-induced cancer [38].

Osteoid osteoma and osteoblastoma

- Osteoid osteomas and osteoblastoma are bone-producing lesions, which often occur in long bones but may also be found in the spine (20% of osteoid osteomas and 40% of osteoblastomas) with a predilection for posterior elements of the vertebrae [45–47]. These lesions are similar histologically to one another, containing osteoblasts that produce osteoid and woven bone. Osteoid osteomas are small, self-limited, and benign, whereas osteoblastomas are often larger, more aggressive, and can become malignant.
- Osteoid osteomas and osteoblastomas are common causes of painful scoliosis in children and adolescents. The most common presenting symptom is neck or back pain that often responds to aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs). Scoliosis secondary to muscle spasms, which result from the inflammatory process around the tumor, occurs in 63–70% of affected adolescents [48]. Pain from osteoid osteomas is often initially managed with NSAIDs or aspirin, especially for nocturnal pain [49•]. Chemotherapy has played a minimal role in the treatment of these lesions and has only been used in selected patients with recurrent aggressive lesions or in patients with surgically inaccessible lesions [50, 51]. Surgery becomes the primary treatment for osteoid osteoma and osteoblastoma, as the pain becomes more severe and less responsive to medication [49•]. Complete resection is often curative for these lesions, and modern surgical techniques allow for complete resections in over 90% of cases [52, 53]. Incomplete resections occur more frequently in osteoblastomas than in osteoid osteomas because the lesions are greater in size and more frequently involve extraosseous tissue. Osteoblastomas recur in 10–15% of cases [46, 54–57], whereas the recurrence rate of osteoid osteomas is 4.5% [46].
- New technologies are making surgical resection more effective for osteoid osteomas and osteoblastomas. Rajasekaran and colleagues reported the complete excision of a spinal osteoid osteoma without causing spinal instability or necessitating fusion using iso-C 3D computer navigation [58]. Barend and colleagues demonstrated that computer-assisted surgery combined with γ-probe-guided high-speed drill excision of osteoid osteoma of the spine assured complete resection of the nidus in all the five patients, thus avoiding en bloc resection of the tumor and subsequent stabilization with posterior fusion of the spine [59]. Moreover, histological confirmation of the lesions was possible with this technique. Since osteoid osteomas and osteoblastomas are often very vascular, several studies have advocated preoperative embolization [60, 61]. In Denaro *et al.*, all the nine cases that were treated with preoperative embolization had no signs of recurrence at an average follow up of 39 months [61].

- There are several treatments under CT guidance now available allowing for less-invasive approaches. These treatments include drill resection accompanied by ethanol injection [62], trephine resection [63, 64], and thermal destruction using radiofrequency ablation [65, 66] or laser thermocoagulation [67, 68]. CT-guided percutaneous resection using a drill inside a trocar has been studied in the treatment of osteoid osteomas of the extremities and spine as a less-invasive treatment modality [69, 70]. As reported in Sierre *et al.*, percutaneous resection of osteoid osteomas was achieved successfully in all the 18 patients with primary and secondary success rates of 100% and 94.5%, respectively, and with no complications reported [71].
- CT-guided laser thermocoagulation has many advantages. The optic fiber is so small that it can be introduced through an 18-gauge spinal needle. This results in a minimally invasive procedure so that patients are only hospitalized one night and are able to bear weight and resume activities immediately after hospitalization [72]. As reported in Aschero *et al.*, laser thermocoagulation was initially effective in 96% of the treated children with osteoid osteoma and had a positive long-term effect in 92% of the patients [72]. In another, larger study, Gangi *et al.* reported a primary clinical success rate of 99% and a secondary clinical success rate of 93.8% (with six recurrences) with the same technique [67]. Similar to percutaneous resection and radiofrequency ablation, a major disadvantage of laser thermocoagulation is that it does not allow for histological confirmation of the lesion.
- CT-guided radiofrequency ablation is another treatment modality that causes thermal destruction of the lesion. Radiofrequency ablation has been shown to be effective in the treatment of osteoid osteoma of the hip and limbs [65, 73, 74] as well as the cervical spine [75]. This treatment modality can substitute for posterior approaches for osteoid osteoma involving the posterior arch and joint pillars of the cervical spine, thus decreasing the need for subsequent spinal reconstruction after the lesion has been treated [75]. Samaha and colleagues reported that radiofrequency ablation was effective and safe in the treatment of lesions adjacent to neural structures [76]. However, osteoid osteomas of the cervical spine are frequently localized in the vicinity of the vertebral artery, spinal cord, or nerve roots, thus rendering heat-generating treatment difficult and risky. In order to ensure the success of radiofrequency ablation, proper patient selection is necessary. Ideal candidates are patients in whom the cortex of the vertebrae can be preserved, and there is no contact of the lesion with neural structures [76].

Hemangiomas

- Spinal hemangiomas (Fig. 1) are benign lesions that are found incidentally in the spinal column in approximately 11% of autopsy specimens [77]. The lesions are aggregates of thin-walled vessels with qualities that are more hamartomatous than neoplastic [78]. Hemangiomas are usually asymptomatic, but they may occasionally cause symptoms of local pain, tenderness, or neurologic deficit secondary to nerve root or spinal cord compression. They have a very distinctive radiographic appearance and seldom require any intervention.
- Clinical management of painful lesions usually begins with medical management involving oral analgesics. Other options include transarterial embolization [79], vertebroplasty [80], radiotherapy [81],

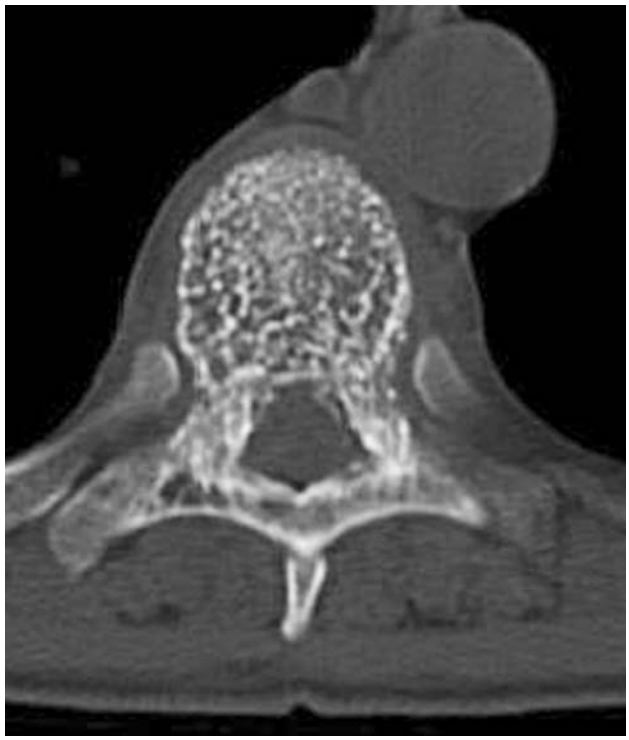

Figure 1. Axial CT of a thoracic vertebral body hemangioma

and ethanol injection [82]. Recently, balloon kyphoplasty has been reported to be effective in a patient with a cervical vertebral hemangioma [83]. All of these therapies have been reported to provide long-term relief for painful hemangiomas. Patients with persistent pain despite these therapies may benefit from definitive surgical resection.

- For hemangiomas that cause neurologic deficit and/or have extraosseous tumor extension, surgical management is typically the first line of therapy. Decompressive laminectomy combined with transarterial embolization has been proposed by some authors to treat hemangiomas limited to the vertebral body and/or posterior elements [79]. Primary resection of the hemangioma with 360-degree reconstruction may also be an option, particularly with tumors with extraosseous extension. Alternatively, radiotherapy has also been shown to reverse neurologic deficit in patients with vertebral hemangiomas [81, 84].

Giant cell tumor

- Giant cell tumors (GCTs) of the spinal column have a predilection for the thoracolumbar and sacral regions (Fig. 2). It is the second most common primary sacral tumor after chordoma [85]. Patients with spinal involvement usually present in the third and forth decades of life [86]. The GCTs are believed to arise from mononuclear cells of macrophage origin. Histologically, GCTs are multinucleated giant cells and macrophages that may contain areas resembling aneurismal bone cysts, and care should be made when interpreting bone biopsy samples to avoid an errant diagnosis. Although they are histologically benign, approximately 5–10% of giant cell tumors may undergo malignant degeneration and assume a more aggressive course [87].

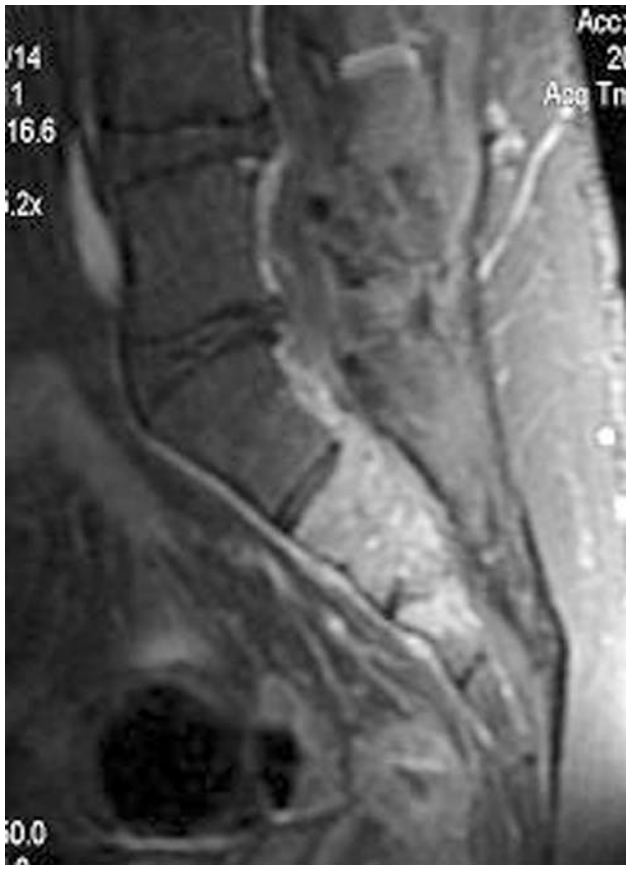

Figure 2. Sagittal MRI of a sacral giant cell tumor

- Clinical management of GCTs is difficult given their high propensity for recurrence. En bloc resection of GCTs with wide margins is the gold standard for treating these lesions. Unfortunately, these tumors often grow to a large size before initial diagnosis, and extension of the tumor into the spinal canal and adjacent soft tissues is not uncommon. Therefore, subtotal resection in concert with adjuvant chemotherapy, arterial embolization, and/or radiosurgery is the typical treatment algorithm when en bloc resection is not feasible.
- The literature suggests that successful en bloc resection of GCTs can minimize the risk of tumor recurrence. In a literature review of 159 patients with GCT of the sacrum, Leggon and colleagues reported that no patients demonstrated tumor recurrence after en bloc resection. Patients who were treated with radiotherapy alone or with incomplete surgical resection with or without radiation therapy had a 48% risk of tumor recurrence [88]. Some other authors also report isolated cases of complete cure after en bloc resection in the cervical spine [89–91].
- Arterial embolization of GCTs is a critical adjuvant therapy that may increase the safety of surgery as well as improve progression-free survival. Preoperative embolization is a useful tool that minimizes intraoperative blood loss during the resection of these highly vascularized tumors. Embolization may be especially useful to limit bleeding during intralesional resections. Interestingly, arterial embolization may also be useful as a primary treatment modality for GCTs. Hosalkar and colleagues recently reported the use of serial embolization of GCTs in a small series of nine patients. These patients received serial embolization of arterial vessels feeding the tumor every

six weeks until no new vessels were noted, followed by repeat embolizations at 6 and 18 months following tumor stabilization. Seven patients demonstrated no evidence of tumor progression (median followup of 7.8 years) without the need for surgery or radiation therapy [92]. This promising technique may be useful in patients who cannot tolerate surgery or may be used as a postoperative adjuvant treatment after incomplete tumor resection.

- Traditional photon beam radiation has been used as a primary treatment for GCT as well as postoperative adjuvant therapy. When used as a primary therapy, the risk of tumor recurrence approaches 50% [88, 93]. In addition to the high rate of tumor recurrence, there is a significant risk of developing secondary sarcomas (most commonly osteosarcoma) [94] after traditional radiation therapy techniques. Several retrospective reviews document this risk at approximately 10% [88, 93, 95]. Recently, stereotactic radiosurgery has been utilized to treat patients with primary spine tumors [96]. Although stereotactic radiosurgery allows clinicians to deliver higher radiation doses to the tumor while sparing adjacent structures, it is unclear at this time whether such techniques will lead to improvements in clinical outcome and risk of secondary sarcoma compared to traditional radiotherapy.

Chordoma

- Chordoma (Fig. 3) is the most common primary malignant bone tumor of the spine with an overall incidence of less than 1 in 1,000,000 people [97]. It is most commonly found in the sacrococcygeal spine. The median age at diagnosis is 58.5 years, although it can occur even in young children [98]. Chordomas are slow-growing tumors that are thought to be derived from remnants of the notochord and are characterized by physaliphorous cells. Clinical morbidity from chordoma is secondary to local bone destruction and compression of spinal elements. Extension of the tumor into the surrounding soft tissue is typical and accounts for the difficulty in surgical resection of these lesions. Approximately 30% of patients with sacrococcygeal chordoma eventually develop metastatic disease [99]. A recent literature suggests that five-year survival is ranging from 50% to 68% [98, 100, 101].
- En bloc resection of spinal chordoma is the most critical factor in promoting tumor-free survival [99]. However, this is a difficult endeavor for a number of reasons. First, chordomas often grow to large sizes before the initial diagnosis is made. Furthermore, although chordomas often have a grossly distinct capsule, chordoma cells interdigitate with surrounding tissue on a microscopic level. It is therefore critical to include a wide margin of normal tissue along with the surgical specimen when resecting these tumors en bloc [102]. Adequate margins can be obtained in approximately half of sacral chordomas [99, 103–105], and even less success has been reported with other locations in the mobile spine [106]. The center of chordomas, particularly large tumors, is often liquefied, and care must be made to avoid violating the tumor capsule during surgical resection. Spillage of tumor into surrounding tissue may place the patient at higher risk of recurrence. Unfortunately, even with an apparent en bloc resection, approximately 50% of patients experience a recurrence

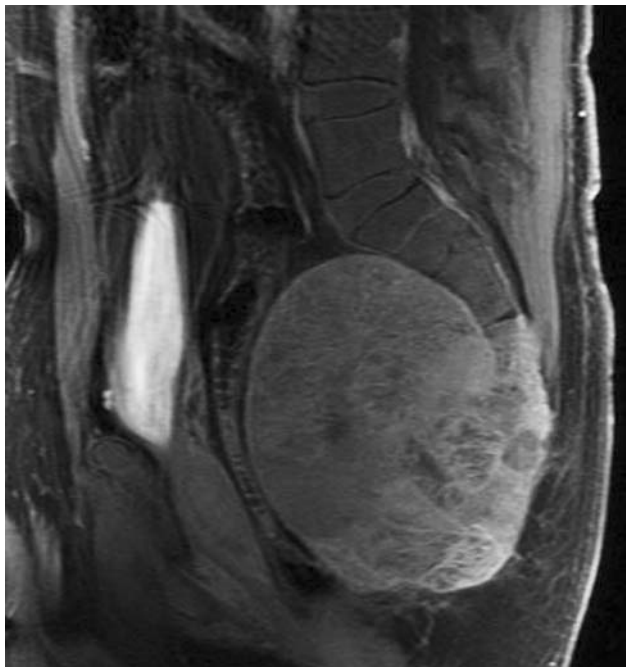

Figure 3. Sagittal MRI of a large sacral chordoma

[107•]. Those without recurrence may still be left with significant weakness, numbness, or bowel/bladder dysfunction as a result of surgery.

- In cases where adequate margins are unable to be obtained, radiation therapy is currently used as an adjuvant modality. Radiation therapy is complicated by the fact that the curative dose for chordomas, a radioresistant tumor, is higher than the tolerance dose for the spinal cord, rectum, and other adjacent structures. The current literature is mixed with respect to the efficacy of conventional or hyperfractionated photon beam radiation with respect to extending disease-free survival. Some data suggest that radiotherapy after subtotal resection increases disease-free survival compared to subtotal resection alone [99]. Other studies suggest that the addition of radiation therapy after surgery does not lead to significant benefit [108–110].
- Recent innovations in radiosurgical techniques may increase the efficacy of radiosurgery for chordomas. Intensity-modulated radiotherapy (IMRT) is a technique that increases conformal delivery of radiation. This allows for the delivery of higher doses of radiation while minimizing exposure to adjacent critical structures. The use of hadrons (high-dose proton or charged particles such as helium, neon, or carbon), as opposed to conventional photon, radiation has also been utilized to improve conformal delivery of radiation to the target lesion while sparing adjacent structures. The ballistic properties of hadrons cause a progressive increase in the quantity of energy deposited along its trajectory until it stops suddenly in the form of a "Bragg peak" [111]. This allows for clinicians to use the "Bragg peak" to deliver high doses of radiation to tumor but spare surrounding structures. Proton beams have been used successfully in chordomas of the skull base and upper cervical spine [111], and this modality may eventually play a role in sacrococcygeal chordomas as well as other primary spine tumors.

- There is a growing interest in utilizing radiosensitizing agents to augment the efficacy of radiation therapy in the treatment of chordoma. Rhomberg and colleagues reviewed a series of five patients with chordoma who received oral razoxane before radiation therapy. They report that all the five patients were alive at five years with locally controlled tumor [112]. The potential for radiosensitizing agents in patients with chordoma continues to be investigated.
- As of now, chemotherapy is not typically employed in the treatment of "classic" chordomas (dedifferentiated chordomas, a particularly rare subgroup of chordoma, may respond to chemotherapeutic regimens employed for high-grade sarcomas). However, several preliminary studies suggest that a number of chemotherapeutic agents may have efficacy against chordoma. The most promising agent to date is imatinib mesylate (Gleevec©, Novartis), a tyrosine kinase inhibitor that targets platelet-derived growth factor receptor-β. In their initial series of six cases followed by a larger institutional series of 18 patients, Casali and colleagues report that imatinib mesylate has antitumor activity against advanced chordoma [113•, 114]. Further clinical studies with imatinib mesylate are currently in progress.
- It has been demonstrated that chordomas demonstrate increased expression of epidermal growth factor, c-Met, and HER2/neu compared to other malignancies [115]. Interestingly, Hof and colleagues report the use of a combination of cetuximab/gefitinib for the treatment of a patient with EGF receptor positive sacral chordoma and pulmonary metastasis [116]. Other investigators are investigating the possible role of antiangiogenic agents in the treatment of chordomas [117].

Chondroma/chondrosarcoma

- Chondromas are cartilaginous tumors found primarily in the small bones of the hands and feet. These tumors are rarely found in the spine. They can be divided into enchondromas (originating from the medullary cavity) or periosteal chondromas (originating from the cortex). These lesions commonly present with local tenderness and/or a palpable mass when the tumor expands into surrounding tissue [118].
- Complete surgical resection with negative margins is the primary treatment for chondromas. Less than 10% of patients experience tumor recurrence after complete resection [119]. If incomplete resection is performed, residual tumor is at risk for sarcomatous degeneration [120]. As chondromas are radioresistant lesions, radiosurgery at present does not have a significant role in the treatment of these tumors.
- Chondrosarcomas are extremely rare tumors with a predilection towards the thoracic spine. These slow-growing tumors commonly present with focal pain or neurologic deficits [121]. Although chondrosarcomas can be divided into multiple pathologic subgroups, the most important characteristic with respect to clinical outcome is the World Health Organization (WHO) grade. Grade I chondrosarcomas have a 90% 10-year survival rate from 30% to 40% compared with high grade lesions [122].
- Regardless of WHO-specified tumor grade, the gold standard for treating chondrosarcomas is gross total resection with negative margins. The literature suggests that en bloc resection is associated with long-term recurrence-free survival [123–125]. En bloc resection may

result in recurrence rates of 20% or less [126]. In cases of tumor recurrence, repeat resection may lead to improved survival [127].

- The role for radiation therapy in chondrosarcomas, a relatively radioresistant tumor, is unclear. Typically, radiation therapy is utilized after incomplete surgical resection or in nonoperable lesions. A recent study by Normand and colleagues reports that in a small series of 13 patients with unresectable and symptomatic chondrosarcoma, six patients exhibited an improvement in clinical symptoms after radiation [128]. However, there are no studies existing now demonstrating that radiation therapy increases long-term survival.
- There is no clear role for the use of chemotherapy for patients with chondrosarcoma. These slow-growing tumors are poorly vascularized and have a large amount of extracellular matrix, thus limiting the access of antitumor agents [129]. Chondrosarcomas also express the multidrug-resistance-1 and p-glycoprotein, which may also play a role in chemoresistance [130]. Various subtypes of chondrosarcomas may have different responses to chemotherapy. For mesenchymal chondrosarcoma, small studies suggest that there may be a role for chemotherapy [131, 132]. In contrast, the role of chemotherapy for dedifferentiated chondrosarcoma is less clear. Staals and colleagues reported that in a small series of patients with dedifferentiated chondrosarcomas arising from pre-existing osteochondromas, adjuvant chemotherapy after surgical resection improved overall survival compared to surgical resection alone. The majority of patients received a combination of adriamycin (doxorubicin), cisplatin, methotrexate, and ifosfamide [133]. Nooij and colleagues reported that two patients with dedifferentiated chondrosarcoma receiving a combination of doxorubicin and cisplatin preoperatively demonstrated no significant response to chemotherapy [132]. The phase II trials investigating the use of gemcitabine/docetaxel, ifosfamide, and tyrosine kinase inhibitors such as imatinib, sunitinib, and dasatinib are currently being investigated [134].

Ewing's sarcoma

- Ewing's sarcoma is a primary bone tumor rarely found in the spine. Ewing's sarcoma of the spine typically occurs at a young age, and the sacrum is the most common location in the spinal axis. The etiology of this tumor is unclear, although there is recent evidence that mesenchymal stem cell progenitors may play a role [135]. Pain is the usual presenting symptom, and neurologic deficit is common.
- The current treatment regimen for Ewing's sarcoma involves surgery, chemotherapy, and radiation therapy. Patients with localized disease have been reported to have five-year relapse-free or event-free survival rates of 59–76% [136–138]. Chemotherapy plays a central role in the treatment of Ewing's sarcoma. Current protocols typically use a combination of vincristine, cyclophosphamide, and doxorubicin [139]. The addition of ifosfamide and etoposide to this four-drug regimen has shown improved outcomes and is considered the standard of care in the United States [137]. Recent studies have investigated other chemotherapeutic agents for Ewing's sarcoma. Paulussen and colleagues recently published the results of the EICESS-92 study, which showed that the addition of etoposide to vincristine, dactinomycin, ifosfamide, and doxorubicin (VAIA) therapy approached, but did not reach, statistical significance with respect to improving survival. In a separate arm in this study, cyclophosphamide was used in place of ifosfamide to determine whether toxicity could be reduced

without decreasing overall survival. The study suggests that replacing ifosfamide with cyclophosphamide in a standard VAIA therapy had no effect on event-free and overall survival but may actually increase toxicity [140•]. Camptothecan derivatives have shown some success in preliminary studies. Irinotecan has been used in combination with temozolamide with some success in advanced relapsed Ewing's Sarcoma [141]. A recent phase II trial using the mammalian target of rapamycin (mTOR), a critical protein kinase involved in the regulation of cell proliferation and growth, showed drug activity in patients with advanced sarcoma, including patients with Ewing's sarcoma [142]. Inhibitors to the insulin growth factor-1 receptor (IGF-1R) have shown promise in reducing proliferation of Ewing's sarcoma in vitro and in vivo [143]. The use of a monoclonal antibody against IGF-1R in a patient with refractory Ewing's sarcoma led to a complete response [144].

- The addition of surgical resection and/or radiation to chemotherapy may improve outcomes for patients with Ewing's sarcoma. There is some evidence that en bloc resection leads to improved local control. In a review of 244 patients with Ewing's sarcoma in a variety of locations, including the spine, Ozaki and colleagues found that patients with radical or wide surgical margins had improved local control compared to marginal or intralesional resections [145]. Bacci and colleagues also showed that adequate surgical margins improve both local control and event-free survival [146].
- Radiation therapy plays an important role in the treatment of Ewing's sarcoma, a relatively radiosensitive tumor compared to other sarcomas. In a retrospective study by Schuck and colleagues, patients who have received radiation therapy as the lone primary treatment had a 22.6% local recurrence rate [147]. Radiation therapy is utilized after chemotherapy or in conjunction with chemotherapy and surgical resection, particularly in cases where residual tumor remains after surgery. Radiation therapy may be of particular benefit in patients who are poor responders to chemotherapy [148]. In addition to traditional radiation therapy, stereotactic radiosurgery is playing an emerging role in Ewing's sarcoma [149].

Osteosarcoma

- Osteosarcoma (Fig. 4), the most common primary spine sarcoma, represents from 3% to 15% of all primary spine tumors [150–152]. It is most commonly found in the posterior elements of the sacral and thoracic spine [151]. Paget's disease is a known risk factor for osteosarcoma, but less than 1% of patients with Paget's disease will develop malignant transformation [153]. There are multiple histological subtypes of osteosarcomas. High grade lesions include conventional osteosarcomas, the most common subtype, as well as telangiectatic, small-cell, giant-cell, epithelioid, and osteoblastoma-like osteosarcomas. Surface osteosarcomas are generally lower grade lesions but are rare in the spine [154].
- The prognosis of patients with spinal osteosarcomas continues to be poor. The difficulty in obtaining adequate surgical margins when resecting these tumors likely explains why the outcomes of these patients are much worse compared with patients presenting with osteosarcomas of the extremities. Furthermore, the radiation dose delivered by traditional methods of radiotherapy is limited by the proximity of the tumor to critical neural structures.

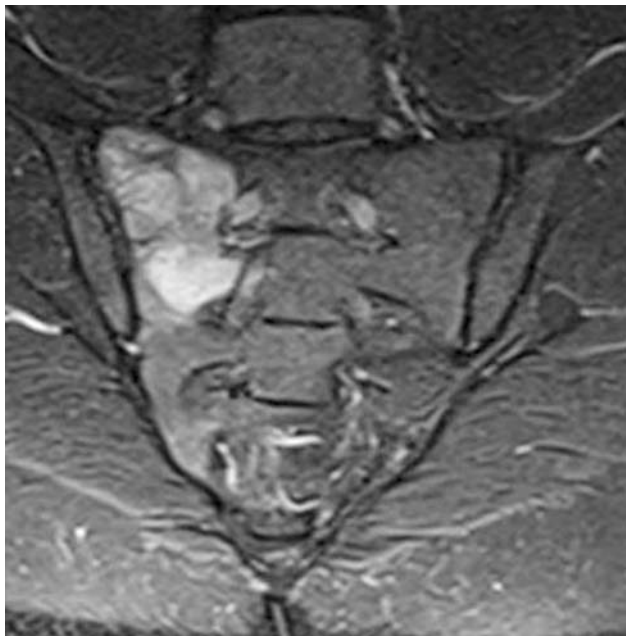

Figure 4. Coronal MRI of a sacral osteosarcoma

- Advances in surgical techniques have improved our ability to perform en bloc resections of osteosarcomas while preserving spinal stability. Because of the rarity of these lesions and the relative novelty of the surgical techniques, there are no large case series evaluating the efficacy of en bloc resection of osteosarcomas with respect to long-term outcomes. Rao and colleagues recently published their series of 80 patients with primary or metastatic sarcoma of various histologies, including osteosarcoma. Twelve patients with en bloc resections had a median survival of 26.2 months compared to 18.6 months for patients with intralesional resection [155]. Although the difference in survival was not statistically significant, this result may be secondary to the small number of patients in the en bloc resection group. However, it is our opinion that en bloc resection should be pursued when possible to offer patients with the greatest chance of long-term survival.
- Despite surgical advances, en bloc resection of these lesions will not always be feasible. Osteosarcomas are generally radioresistant lesions, and traditional radiotherapy has limited benefit in the treatment of this pathology [156]. There is no evidence showing that traditional means of radiotherapy offers improvement in clinical outcome [157]. In contrast, adjuvant chemotherapy currently plays a role in the treatment of patients with spinal osteosarcoma. Current protocols use a combination of methotrexate, cisplatin, ifosfamide, and doxorubicin. There has been evidence of recent interest in the use of the immunostimulant muramyl tripeptide-phosphatidylethanolamine (MTP-PE). In combination with traditional agents, the addition of MTP-PE led to marginal improvements in event-free survival [158].
- The combination of gemcitabine and docetaxel has been investigated for the use in patients with osseous sarcomas. Gemcitabine is a difluorinated deoxycytidine analog that is activated by deoxycytidine kinase after cellular uptake. In activated dihposphate and triphosphate forms, gemcitabine depletes deoxynucleotide stores and interferes with DNA elongation [159]. In phase I and II trials with gemcitabine

alone, 4 out of 13 patients with osteosarcoma demonstrated disease stabilization. No patients demonstrated objective responses [160, 161]. Docetaxel is a cytotoxic agent that stabilizes microtubules against depolymerization and results in cell cycle arrest. The use of docetaxel as a single agent has demonstrated modest responses in patients with osteosarcoma [162–164]. Navid and colleagues retrospectively reviewed their institutional experience using a combination of gemcitabine and docetaxel in the treatment of patients with pediatric sarcoma. Out of 10 patients with recurrent or progressive osteosarcoma, three patients demonstrated a partial response, while one patient had no disease progression [159].

Conclusion

- Primary tumors of the spine encompass a wide variety of pathologies, each with their own unique clinical algorithms. Multi-disciplinary management of these lesions is critical to maximize clinical outcomes. Although the ability to surgically resect primary spine tumors continues to be refined, it is likely that advances in chemotherapy and radiation therapy will be much more critical in significantly improving patient outcomes in the future.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- • Of major importance

1. Malpas JS, Caroll JJ.: **Myeloma: clinical presentation and diagnosis**. In *Myeloma: Biology and Management.* Edited by Malpas JS, Bergsagel DE, Kyle RA. New York, NY: Oxford University Press; 1995:169–190.
2. Ries LAG, Eiser MP, Kosary CL, *et al.*: *SEER Cancer Statistics Review, 1975–2000*. National Cancer Institute. http://seer.cancer.gov//csf/1975_2001. Accessed on 7 September 2004.
3. Kyle RA: **Multiple myeloma: review of 869 cases.** *Mayo Clin Proc* 1975, **50:**29–40.
4. Wu S, Dahut WL, Gulley JL: **The use of bisphosphonates in cancer patients.** *Acta Oncol* 2007, **46:**581–591.
5. Sezer O, Heider U, Zavski I, *et al.*: **RANK ligand and osteoprotegerin in myeloma bone disease.** *Blood* 2003, **101:**2094.
6. Simonet WS, Lacey DL, Dunstan CR, *et al.*: **Osteoprotegerin: a novel secreted protein involved in the regulation of bone density.** *Cell* 1997, **89:**309–319.
7. Nakagawa N, Kinosaki M, Yaaguchi K, *et al.*: **Rank is the essential signaling receptor for osteoclast differentiation factor in osteoclastogenesis.** *Biochem Biophys Res Commun* 1998, **252:**395–400.
8. Moulopoulos LA, Dimopoulos MA, Weber D, *et al.*: **Magnetic resonance imaging in the staging of solitary plasmacytoma of bone.** *J Clin Oncol* 1993, **11:**1311–1315.
9. • Soutar R, Lucraft H, Reece A, *et al.*: **Guidelines on the diagnosis and management of solitary plasmacytoma of bone and solitary extramedullary plasmacytoma.** *Clin Oncol* 2004, **16:**405–413.
10. Liebross RH, Ha CS, Cox JD, *et al.*: **Solitary bone plasmacytoma: outcome and prognostic factors following radiotherapy.** *Int J Radiat Oncol Biol Phys* 1988, **41:**1063–1067.
11. Chak LY, Cox RS, Bostwick DG, Hoppe RT: **Solitary plasmacytoma of bone: treatment, progression, and survival.** *J Clin Oncol* 1987, **5:**1911–1915.
12. Bolek TW, Marcus RB, Mendenhall NP: **Solitary plasmacytoma of bone and soft tissue.** *Int J Radiat Oncol Biol Phys* 1996, **36:**329–333.
13. Singhal S, Mehta J, Desikan R, *et al.*: **Antitumor activity of thalidomide in refractory multiple Myeloma.** *NEJM* 1999, **341:**1565–1571.
14. Palumbo A, Rajkumar SV: **Treatment of newly diagnosed myeloma.** *Leukemia* 2009, **23**:449–456.
15. Von Metzler I, Krebbel H, Hecht M, *et al.*: **Bortezomib inhibits human osteoclastogenesis.** *Leukemia* 2007, **21:**2025–2034.
16. Hentschel SJ, Burton AW, Fourney DR, *et al.*: **Percutaneous vertebroplasty and kyphoplasty performed at a cancer center: refuting proposed contraindications.** *J Neurosurg Spine* 2005, **2:**436–440.
17. Campanacci M, Capanna R, Picci P: **Unicameral and aneurysmal bone cysts.** *Clin Orthop Relat Res* 1986, **204**:25–36.
18. Vergel De Dios AM, Bond JR, Shives TC, *et al.*: **Aneurysmal bone cyst. A clinicopathologic study of 238 cases.** *Cancer* 1992, **69:**2921–2931.
19. Cottalorda J, Bourelle S: **Modern concepts of primary aneurysmal bone cyst.** *Arch Orthop Trauma Surg* 2007, **127:**105–114.

20. Liu JK, Brockmeyer DL, Dailey AT, Schmidt MH: **Surgical management of aneurysmal bone cysts of the spine.** *Neurosurg Focus* 2003, **15:**E4.
21. Boriani S, De Iure F, Campanacci L, *et al.*: **Aneurysmal bone cyst of the mobile spine: report on 41 cases.** *Spine* 2001, **26:**27–35.
22. Marcove RC, Sheth DS, Takemoto S, Healey JH: **The treatment of aneurysmal bone cyst.** *Clin Orthop Relat Res* 1995, **311**:157–163.
23. Szendroi M, Cser I, Konya A, *et al.*: **Aneurysmal bone cyst. A review of 52 primary and 16 secondary cases.** *Arch Orthop Trauma Surg* 1992, **111:**318–322.
24. Gladden ML Jr, Gillingham BL, Hennrikus W, Vaughan LM: **Aneurysmal bone cyst of the first cervical vertebrae in a child treated with percutaneous intralesional injection of calcitonin and methylprednisolone. A case report.** *Spine* 2000, **25:**527–530.
25. Ohashi M, Ito T, Hirano T, Endo N: **Percutaneous intralesional injection of calcitonin and methylprednisolone for treatment of an aneurysmal bone cyst at C-2.** *J Neurosurg Pediatrics* 2008, **2:**365–369.
26. Szendroi M, Antal I, Liszka G, *et al.*: **Calcitonin therapy of aneurysmal bone cysts.** *J Cancer Res Clin Oncol* 1992, **119:**61–65.
27. Koci TM, Mehringer CM, Yamagata N, Chiang F: **Aneurysmal bone cyst of the thoracic spine: evolution after particulate embolization.** *AJNR Am J Neuroradiol* 1995, **16:**857–860.
28. Guibaud L, Herbreteau D, Dubois J, *et al.*: **Aneurysmal bone cysts: percutaneous embolization with an alcoholic solution of zein—series of 18 cases.** *Radiology* 1998, **208:**369–373.
29. Nobler MP, Higinbotham NL, Phillips RF: **The cure of aneurysmal bone cyst. Irradiation superior to surgery in an analysis of 33 cases.** *Radiology* 1968, **90:**1185–1192.
30. Papagelopoulos PJ, Currier BL, Shaughnessy WJ, *et al.*: **Aneurysmal bone cyst of the spine. Management and outcome.** *Spine* 1998, **23:**621–628.
31. Bush CH, Drane WE: **Treatment of an aneurysmal bone cyst of the spine by radionuclide ablation.** *AJNR Am J Neuroradiol* 2000, **21:**592–594.
32. De Cristofaro R, Biagini R, Boriani S, *et al.*: **Selective arterial embolization in the treatment of aneurysmal bone cyst and angioma of bone.** *Skeletal Radiol* 1992, **21:**523–527.
33. Meyer S, Reinhard H, Graf N, *et al.*: **Arterial embolization of a secondary aneurysmal bone cyst of the thoracic spine prior to surgical excision in a 15-year-old girl.** *Eur J Radiol* 2002, **43:**79–81.
34. de Gauzy JS, Abid A, Accadbled F, *et al.*: **Percutaneous Ethibloc injection in the treatment of primary aneurysmal bone cysts.** *J Pediatr Orthop* 2005, **14:**367–370.
35. Dubois J, Chigot V, Grimard G, *et al.*: **Sclerotherapy in aneurysmal bone cysts in children: a review of 17 cases.** *Pediatr Radiol* 2003, **33:**365–372.
36. Topouchian V, Mazda K, Hamze B, *et al.*: **Aneurysmal bone cysts in children: complications of fibrosing agent injection.** *Radiology* 2004, **232:** 522–526.
37. Peraud A, Drake JM, Armstrong D, *et al.*: **Fatal ethibloc embolization of vertebrobasilar system following percutaneous injection into aneurysmal bone cyst of the second cervical vertebra.** *AJNR Am J Neuroradiol* 2004, **25:**1116–1120.
38. Feigenberg SJ, Marcus RB Jr, Zlotecki RA, *et al.*: **Megavoltage radiotherapy for aneurysmal bone cysts.** *Int J Radiat Oncol Biol Phys* 2001, **49:**1243–1247.
39. Biesecker JL, Marcove RC, Huvos AG, Mike V.: **Aneurysmal bone cysts. A clinicopathologic study of 66 cases.** *Cancer* 1970, **26:**615–625.
40. Cruz M, Coley BL: **Aneurysmal bone cyst.** *Surg Gynecol Obstet* 1956, **103:**67–77.
41. Dabska M, Buraczewski J: **Aneurysmal bone cyst. Pathology, clinical course and radiologic appearances.** *Cancer* 1969, **23:**371–389.
42. Enneking WF.: *Musculoskeletal Tumor Surgery*. New York: Churchill Livingstone, 1983, 1–741.
43. Tillman BP, Dahlin DC, Lipscomb PR, Stewart JR: **Aneurysmal bone cyst: an analysis of ninety-five cases.** *Mayo Clin Proc* 1968, **43:**478–495.
44. Kyriakos M, Hardy D: **Malignant transformation of aneurysmal bone cyst, with an analysis of the literature.** *Cancer* 1991, **68:**1770–1780.
45. Fountain EM, Burge CH: **Osteoid osteoma of the cervical spine. A review and case report.** *J Neurosurg* 1961, **18:**380–383.
46. Jackson RP, Reckling FW, Mants FA: **Osteoid osteoma and osteoblastoma. Similar histologic lesions with different natural histories.** *Clin Orthop Relat Res* 1977, **128:**303–313.
47. Marsh BW, Bonfiglio M, Brady LP, Enneking WF: **Benign osteoblastoma: range of manifestations.** *J Bone Joint Surg Am* 1975, **57:**1–9.
48. Lundeen MA, Herring JA: **Osteoid-osteoma of the spine: sclerosis in two levels. A case report.** *J Bone Joint Surg Am* 1980, **62:**476–478.
49.• Kan P, Schmidt MH: **Osteoid osteoma and osteoblastoma of the spine.** *Neurosurg Clin N Am* 2008, **19:**65–70.
50. Berberoglu S, Oguz A, Aribal E, Ataoglu O: **Osteoblastoma response to radiotherapy and chemotherapy.** *Med Pediatr Oncol* 1997, **28:**305–309.
51. Camitta B, Wells R, Segura A, *et al.*: **Osteoblastoma response to chemotherapy.** *Cancer* 1991, **68:**999–1003.
52. Ozaki T, Liljenqvist U, Hillmann A, *et al.*: **Osteoid osteoma and osteoblastoma of the spine: experiences with 22 patients.** *Clin Orthop Relat Res* 2002, **397:**394–402.
53. Zileli M, Cagli S, Basdemir G, Ersahin Y: **Osteoid osteomas and osteoblastomas of the spine.** *Neurosurg Focus* 2003, **15:**E5.
54. Bloem JL, Kroon HM: **Osseous lesions.** *Radiol Clin North Am* 1993, **31:**261–278.
55. Cerase A, Priolo F.: **Skeletal benign bone-forming lesions.** *Eur J Radiol* 1998, **27(Suppl 1):**S91–S97.
56. Lucas DR, Unni KK, McLeod RA, *et al.*: **Osteoblastoma: clinicopathologic study of 306 cases.** *Hum Pathol* 1994, **25:**117–134.
57. Mitchell ML, Ackerman LV: **Metastatic and pseudomalignant osteoblastoma: a report of two unusual cases.** *Skeletal Radiol* 1986, **15:**213–218.

58. Rajasekaran S, Kamath V, Shetty AP: **Intraoperative Iso-C three-dimensional navigation in excision of spinal osteoid osteomas.** *Spine* 2008, **33:**25–29.
59. Van Royen BJ, Baayen JC, Pijpers R, *et al.*: **Osteoid osteoma of the spine: a novel technique using combined computer-assisted and gamma probe-guided high-speed intralesional drill excision.** *Spine* 2005, **30:**369–373.
60. Silva ML, Brunelle F: **Embolisation of vascular lesions of the spinal column in childhood: a report of three cases.** *Neuroradiology* 1996, **38:**809–811.
61. Denaro V, Denaro L, Papalia R, *et al.*: **Surgical management of cervical spine osteoblastomas.** *Clin Orthop Relat Res* 2007, **455:**190–195.
62. Adam G, Neuerburg J, Vorwerk D, *et al.*: **Percutaneous treatment of osteoid osteomas: combination of drill biopsy and subsequent ethanol injection.** *Semin Musculoskelet Radiol* 1997, **1:**281–284.
63. Assoun J, Railhac JJ, Bonnevialle P, *et al.*: **Osteoid osteoma: percutaneous resection with CT guidance.** *Radiology* 1993, **188:**541–547.
64. Sans N, Galy-Fourcade D, Assoun J, *et al.*: **Osteoid osteoma: CT-guided percutaneous resection and follow-up in 38 patients.** *Radiology* 1999, **212:**687–692.
65. Barei DP, Moreau G, Scarborough MT, Neel MD: **Percutaneous radiofrequency ablation of osteoid osteoma.** *Clin Orthop Relat Res* 2000, **373:**115–124.
66. Osti OL, Sebben R: **High-frequency radio-wave ablation of osteoid osteoma in the lumbar spine.** *Eur Spine J* 1998, **7:**422–425.
67. Gangi A, Alizadeh H, Wong L, *et al.*: **Osteoid osteoma: percutaneous laser ablation and follow-up in 114 patients.** *Radiology* 2007, **242:**293–301.
68. Gangi A, Dietemann JL, Guth S, *et al.*: **Percutaneous laser photocoagulation of spinal osteoid osteomas under CT guidance.** *AJNR Am J Neuroradiol* 1998, **19:**1955–1958.
69. Cove JA, Taminiau AH, Obermann WR, Vanderschueren GM: **Osteoid osteoma of the spine treated with percutaneous computed tomography-guided thermocoagulation.** *Spine* 2000, **25:**1283–1286.
70. Hadjipavlou AG, Lander PH, Marchesi D, *et al.*: **Minimally invasive surgery for ablation of osteoid osteoma of the spine.** *Spine* 2003, **28:**E472–E477.
71. Sierre S, Innocenti S, Lipsich J, *et al.*: **Percutaneous treatment of osteoid osteoma by CT-guided drilling resection in pediatric patients.** *Pediatr Radiol* 2006, **36:**115–118.
72. Aschero A, Gorincour G, Glard Y, *et al.*: **Percutaneous treatment of osteoid osteoma by laser thermocoagulation under computed tomography guidance in pediatric patients.** *Eur Radiol* 2009, **19**:679–686.
73. Ghanem I, Collet LM, Kharrat K, *et al.*: **Percutaneous radiofrequency coagulation of osteoid osteoma in children and adolescents.** *J Pediatr Orthop B* 2003, **12:**244–252.
74. Pinto CH, Taminiau AH, Vanderschueren GM, *et al.*: **Technical considerations in CT-guided radiofrequency thermal ablation of osteoid osteoma: tricks of the trade.** *AJR Am J Roentgenol* 2002, **179:**1633–1642.
75. Laus M, Albisinni U, Alfonso C, Zappoli FA: **Osteoid osteoma of the cervical spine: surgical treatment or percutaneous radiofrequency coagulation?** *Eur Spine J* 2007, **16:**2078–2082.
76. Samaha EI, Ghanem IB, Moussa RF, *et al.*: **Percutaneous radiofrequency coagulation of osteoid osteoma of the "Neural Spinal Ring".** *Eur Spine J* 2005, **14:**702–705.
77. Doppman JL, Oldfield EH, Heiss JD: **Symptomatic vertebral hemangiomas: treatment by means of direct intralesional injection of ethanol.** *Radiology* 2000, **214:**341–348.
78. Burger P, Scheithauer B, Vogel F: *Surgical Pathology of the Nervous System and its Coverings*. Philadelphia: Churchill Livingstone, , 2002.
79. Acosta FL, Sanai N, Chi JH, *et al.*: **Comprehensive management of symptomatic and aggressive vertebral hemangiomas.** *Neurosurg Clin N Am* 2008, **19:**17–29.
80. Peh WC, Gilula LA: **Percutaneous vertebroplasty: indications, contraindications, and technique.** *Br J Radiol* 2003, **76:**69–75.
81. Faria SL, Schlupp WR, Chiminazzo H Jr: **Radiotherapy in the treatment of vertebral hemangiomas.** *Int J Radiat Oncol Biol Phys* 1985, **11:**387–390.
82. Munk PL, Marotta TR: **Intralesional injection of absolute alcohol into vertebral hemangiomas: a new treatment option?.** *AJNR Am J Neuroradiol* 1999, **20:**959–960.
83. Zapalowicz K, Skora P, Myslinski R, *et al.*: **Balloon kyphoplasty for painful C-7 vertebral hemangioma.** *J Neurosurg Spine* 2008, **9:**458–461.
84. Yang ZY, Zhang LJ, Chen ZX, *et al.*: **Hemangioma of the vertebral column. A report on twenty-three patients with special reference to functional recovery after radiation therapy.** *Acta Radiol Oncol* 1985, **24:**129–132.
85. Diel J, Ortiz O, Losada RA, *et al.*: **The sacrum: pathologic spectrum, multimodality imaging, and subspecialty approach.** *Radiographics* 2001, **21:**83–104.
86. Boriani S, Weinstein J:**Differential diagnosis and surgical treatment of primary benign and malignant neoplasms**. In *The Adult Spine: Principles and Practice*. Edited by Frymoyer J. Philadelphia: Lippincott-Raven; 1997:951–987.
87. Bell GR: **Surgical treatment of spinal tumors.** *Clin Orthop Relat Res* 1997, **97:**54–63.
88. Leggon RE, Zlotecki R, Reith J, *et al.*: **Giant cell tumor of the pelvis and sacrum.** *Clin Orthop Relat Res* 2004, **423:**196–207.
89. Gille O, Soderlund C, Berge J, *et al.*: **Triple total cervical vertebrectomy for giant cell tumor: case report.** *Spine* 2005, **30:**E272–E275.
90. Abdelwahab IF, Camins MB, Hermann G, *et al.*: **Giant cell tumour of the seventh cervical vertebra.** *Can Assoc Radiol J* 1995, **46:**454–457.
91. Shirakuni T, Tamaki N, Matsumoto S, *et al.*: **Giant cell tumor in cervical spine.** *Surg Neurol* 1985, **23:**148–152.
92. Hosalkar HS, Jones KJ, King JJ, *et al.*: **Serial arterial embolization for large sacral giant-cell tumors.** *Spine* 2007, **32:**1107–1115.
93. Sanjay BK, Sim FH, Unni KK, *et al.*: **Giant-cell tumours of the spine.** *J Bone Joint Surg Br* 1993, **75:**148–154.

94. Bertoni F, Bacchini P, Stalls EL: **Malignancy in giant cell tumor of bone.** *Cancer* 2003, **97:**2520–2529.
95. Caudell JJ, Ballo MT, Zagars GK, *et al.*: **Radiotherapy in the management of giant cell tumor of bone.** *Int J Radiat Oncol Biol Phys* 2003, **57:**158–165.
96. Rock J, Kole M, Yin FF, *et al.*: **Radiosurgical treatment for Ewing's sarcoma of the lumbar spine: case report.** *Spine* 2002, **27:**E471–E475.
97. McMaster ML, Goldstein AM, Bromley CM, *et al.*: **Chordoma: incidence and survival patterns in the United States, 1973–1995.** *Cancer Causes Control* 2001, **12:**1–11.
98. McMaster ML, Boriani S, Chevalley F, Weinstein JN, *et al.*: **Chordoma of the spine above the sacrum. Treatment and outcome in 21 cases.** *Spine* 1996, **21:**1569–1577.
99. York JE, Kaczaraj A, Abi-Said D, *et al.*: **Sacral chordoma: 40-year experience at a major cancer center.** *Neurosurgery* 1999, **44:**74–79.
100. Cummings BJ, Hodson DI, Bush RS: **Chordoma: the results of megavoltage radiation therapy.** *Int J Radiat Oncol Biol Phys* 1983, **9:**633–642.
101. Bjornsson J, Wold LE, Ebersold MJ, *et al.*: **Chordoma of the mobile spine. A clinicopathologic analysis of 40 patients.** *Cancer* 1993, **71:**735–740.
102. Yonemoto T, Tatezaki S, Takenouchi T, *et al.*: **The surgical management of sacrococcygeal chordoma.** *Cancer* 1999, **85:**878–883.
103. Baratti D, Gronchi A, Pennacchioli E, *et al.*: **Chordoma: natural history and results in 28 patients treated at a single institution.** *Ann Surg Oncol* 2003, **10:**291–296.
104. Fuchs B, Dickey ID, Yaszemski MJ, *et al.*: **Operative management of sacral chordoma.** *J Bone Joint Surg* 2005, **87:**2211–2216.
105. Osaka S, Kodoh O, Sugita H, *et al.*: **Clinical significance of a wide excision policy for sacrococcygeal chordoma.** *J Cancer Res Clin Oncol* 2006, **132:**213–218.
106. Boriani S, Bandiera S, Biagini R, *et al.*: **Chordoma of the mobile spine: fifty years of experience.** *Spine* 2006, **31:**493–503.
107.• Fourney DR, Rhines LD, Hentschel SJ, *et al.*: **En bloc resection of primary sacral tumors: classification of surgical approaches and outcome.** *J Neurosurg Spine* 2005, **3:**111–122.
108. Sundaresan N, Huvos AG, Krol G, *et al.*: **Surgical treatment of spinal chordomas.** *Arch Surg* 1987, **122:**1479–1482.
109. Fuller DB, Bloom JG: **Radiotherapy for chordoma.** *Int J Radiat Oncol Biol Phys* 1988, **15:**331–339.
110. Catton C, O'Sullivan B, Bell R, *et al.*: **Chordoma: long-term follow-up after radical photon irradiation.** *Radiother Oncol* 1996, **41:**67–72.
111. Noel G, Feuvret L, Calugaru V, *et al.*: **Chordomas of the base of the skull and upper cervical spine. One hundred patients irradiated by a 3D conformal technique combining photon and proton beams.** *Acta Oncol* 2005, **44:**700–708.
112. Rhomberg W, Eiter H, Bohler F, *et al.*: **Combined radiotherapy and razoxane in the treatment of chordosarcomas and chordomas.** *Anticancer Res* 2006, **26:**2407–2411.
113.• Casali PG, Messina A, Stachiotti S, *et al.*: **Imatinib mesylate in chordoma.** *Cancer* 2004, **101:**2086–2097.
114. Casali PG, Stacchiotti S, Messina A, *et al.*: **Imatinib mesylate in 18 advanced chondroma patients [abstract].** *J Clin Oncol* 2005, **23:**9012.
115. Weinberger PM, Yu Z, Kowalski D, *et al.*: **Differential expression of epidermal growth factor receptor, c-Met, and HER2/neu in chordoma compared with 17 other malignancies.** *Arch Otolaryngol Head Neck Surg* 2005, **131:**707–711.
116. Hof H, Elzel T, Debus J: **Effectiveness of cetuximab/gefitinib in the therapy of a sacral chordoma.** *Onkologie* 2006, **29:**572–574.
117. Schonegger K, Gelpi E, Prayer D, *et al.*: **Recurrent and metastatic clivus chordoma: systemic palliative therapy retards disease progression.** *Anticancer Drugs* 2005, **16:**1139–1143.
118. Palaoglu S, Akkas O, Sav A: **Chondroma of the cervical spine.** *Clin Neurolo Neurosurg* 1988, **90:**253–255.
119. Mordard M, DeTribolet N, Janzer R: **Chondromas of the spine: report of two cases and review of the literature.** *Br J Neurosurg* 1993, **7:**551–556.
120. Schajowicz F, Gallardo H.: **Chondromyxoid fibroma (fibromyxoid chondroma) of bone. A clinicopathological study of 33 cases.** *J Bone Joint Surg* 1971, **53:**198–216.
121. York J, Berk R, Fuller G, *et al.*: **Chondrosarcoma of the spine: 1954–1997.** *J Neurosurg* 1999, **90:**73–78.
122. Chow W: **Update on chodrosarcomas.** *Curr Opin Oncol* 2007, **19:**371–376.
123. Marmor E, Mandelli C, Bernucci C, *et al.*: **Chondrosarcoma of the thoracic spine: total en bloc sagittal resection. Case report.** *J Neurosurg Sci* 2001, **45:**114–119.
124. Hasegawa K, Homma T, Hirano T, *et al.*: **Margin-free spondylectomy for extended malignant spine tumors: surgical technique and outcome of 13 cases.** *Spine* 2007, **31:**142.
125. Tomita K, Kawahara N, Baba H, *et al.*: **Total en bloc spondylectomy. A new surgical technique for primary malignant vertebral tumors.** *Spine* 1997, **22:**324–333.
126. Jacobs W, Fehlings M: **Primary vertebral column tumors**. In *Spinal Cord and Spinal Column Tumors: Principles and Practice.* Edited by Dickman C, Fehlings M, Gokaslan Z. New York: Thieme; 2006:369–386.
127. Weber K, Pring M, Sim FH: **Treatment and outcome of recurrent pelvic chondrosarcoma.** *Clin Orthop Relat Res* 2002, **397:**19–28.
128. Normand AN, Ballo MT, Yasko AW: **Palliative radiation therapy for advanced chondrosarcoma.** *Proc Conn Tiss Oncol Soc* 2006, **12:**745a.
129. Gelderblom H, Hogendoorn PCW, Dijkstra SD, *et al.*: **The clinical approach towards chondrosarcoma.** *The Oncologist* 2008, **13:**320–329.
130. Wyman JJ, Hornstein AM, Meitner PA, *et al.*: **Multidrug resistance-1 and p-glycoprotein in human chondrosarcoma cell lines: Expression correlates with decreased intracellular doxorubicin and in vitro chemoresistance.** *J Orthop Res* 1999, **17:**935–940.

131. Huvos AG, Rosen G, Dabska M, *et al.*: **Mesenchymal chondrosarcoma. A clinicopathologic analysis of 35 patients with emphasis on treatment.** *Cancer* 1983, **51**:1230–1237.
132. Nooij MA, Whelan J, Bramwell VH, *et al.*: **Doxorubicin and cisplatin chemotherapy in high-grade spindle cell sarcomas of the bone, other than osteosarcoma or malignant fibrous histiocytoma: a European Osteosarcoma Intergroup Study.** *Eur J Cancer* 2005, **41**:225–230.
133. Staals EL, Bacchini P, Mercuri M, *et al.*: **Dedifferentiated chondrosarcomas arising in preexisting osteochondromas.** *J Bone Joint Surg Am* 2007, **89**:987–993.
134. http://www.clinicaltrials.gov/ct/results?term=chondrosarcoma, searched December 10, 2008.
135. Tirode F, Laud-Duval K, Prieur A, *et al.*: **Mesenchymal stem cell features of Ewing tumors.** *Cancer Cell* 2007, **11**:421–429.
136. Granowetter L, Womer R, Devidas M, *et al.*: **Comparison of dose intensified and standard dose chemotherapy for the treatment of non-metastatic Ewing's sarcoma (ES) and primitive neuroectodermal tumor (PNET) of bone and soft tissue: a Paediatric Oncology Group Children's Cancer Group Phase II trial [abstract].** *Med Pediatr Oncol* 2001, **37**:172.
137. Grier HE, Krailo MD, Tarbell NJ, *et al.*: **Addition of ifosfamide and etoposide to standard chemotherapy for Ewing's sarcoma and primitive neuroectodermal tumor of bone.** *N Engl J Med* 2003, **348**:694–701.
138. Paulussen M, Ahrens S, Braun-Munzinger G, *et al.*: **EICESS 92 (European Intergroup Cooperative Ewing's Sarcoma Study): preliminary results.** *Klin Padiatr* 1999, **211**:276–283.
139. Bernstein M, Kovar H, Paulussen M, *et al.*: **Ewing's sarcoma family of tumors: current management.** *Oncologist* 2006, **11**:503–519.
140.• Paulussen M, Craft AW, Lewis A, *et al.*: **Results of the EICESS-92 study: two randomized trials of Ewing's sarcoma treatment-cylophosphamide compared with ifosfamide in standard-risk patients and assessment of benefit of etoposide added to standard treatment in high-risk patients.** *J Clin Oncol* 2008, **26**:4385–4393.
141. Wagner LM, McAllister N, Goldsby RE, *et al.*: **Temozolomide and intravenous irinotecan for treatment of advanced Ewing sarcoma.** *Pediatr Blood Cancer* 2007, **48**:132–139.
142. Chawla SP, Tolcher AW, Staddon AP, *et al.*: **Survival results with AP23573, a novel mTOR inhibitor, in patients (pts) with advanced soft tissue or bone sarcomas: update of phase II trial [abstract].** *Proc Am Soc Clin Oncol* 2007, **25**:10076.
143. Scotlandi K, Benini S, Nanni P, *et al.*: **Blockage of insulin-like growth factor-I receptor inhibits the growth of Ewing's sarcoma in athymic mice.** *Cancer Res* 1998, **58**:4127–4131.
144. Tolcher AW, Rothenberg ML, Rodon J, *et al.*: **A phase I pharmacokinetic and pharmacodynamic study of AMG 479, a fully human monoclonal antibody against insulin-like growth factor type I receptor (IGF-1R), in advanced solid tumors [abstract].** *Proc Am Soc Clin Oncol* 2007, **25**:3002.
145. Ozaki T, Hillmann A, Hoffmann C, *et al.*: **Significance of surgical margin on the prognosis of patients with Ewing's sarcoma. A report from the Cooperative Ewing's Sarcoma Study.** *Cancer* 1996, **78**:892–900.
146. Bacci G, Longhi A, Briccoli A, *et al.*: **The role of surgical margins in treatment of Ewing's sarcoma family tumors: experience of a single institution with 512 patients treated with adjuvant and neoadjuvant chemotherapy.** *Int J Radiat Oncol Biol Phys* 2006, **65**:766–772.
147. Schuck A, Ahrens S, von Schorlemer I, *et al.*: **Radiotherapy in Ewing tumors of the vertebrae: treatment results and local relapse analysis of the CESS 81/86 and EICESS 92 trials.** *Int J Radiat Oncol Biol Phys* 2005, **63**:1562–1567.
148. Schuck A, Aherens S, Paulussen M, *et al.*: **Local therapy in localized Ewing tumors: results of 1058 patients treated in the CESS 81, CESS 86, and EICESS 92 trials.** *Int J Radiat Oncol Biol Phys* 2003, **55**:168–177.
149. Rock JP, Ryu S, Shukairy MS, *et al.*: **Postoperative radiosurgery for malignant spinal tumors.** *Neurosurgery* 2006, **58**:891–898.
150. Kelley SP, Ashford RU, Rao AS, *et al.*: **Primary bone tumours of the spine: a 42-year survey from the Leeds Regional Bone Tumour Registry.** *Eur Spine J* 2007, **16**:405–409.
151. Ozaki T, Flege S, Liljenqvist U, *et al.*: **Osteosarcoma of the spine: experience of the Cooperative Osteosarcoma Study Group.** *Cancer* 2002, **94**:1069–1077.
152. Tasdemiroglu E, Bagatur E, Ayan I, *et al.*: **Primary spinal column sarcomas.** *Acta Neurochir (Wien)* 1996, **138**:1261–1266.
153. Sharma H, Mehdi SA, MacDuff E, *et al.*: **Paget sarcoma of the spine: Scottish Bone Tumor Registry experience.** *Spine* 2006, **31**:1344–1350.
154. Klein MJ, Siegal GP: **Osteosarcoma: anatomic and histologic variants.** *Am J Clin Pathol* 2006, **125**:555–581.
155. Rao G, Suki D, Chakrabarti I: **Surgical management of primary and metastatic sarcoma of the mobile spine.** *J Neurosurg Spine* 2008, **9**:120–128.
156. Marina N, Gebhardt M, Teot L, *et al.*: **Biology and therapeutic advances for pediatric osteosarcoma.** *Oncologist* 2004, **9**:422–441.
157. Ozaki T, DeLaney TF, Park L, *et al.*: **Radiotherapy for local control of osteosarcoma.** *Int J Radiat Oncol Biol Phys* 2005, **61**:492–498.
158. Meyers PA, Schwartz CL, Krailo M, *et al.*: **Osteosarcoma: a randomized, prospective trial of the addition of ifosfamide and/or muramyl tripeptide to cisplatin, doxorubicin, and high-dose methotrexate.** *J Clin Oncol* 2005, **23**:2004–2011.
159. Navid F, Willert JR, McCarville MB, *et al.*: **Combination of gemcitabine and docetaxel in the treatment of children and young adults with refractory bone sarcoma.** *Cancer* 2008, **113**:419–425.
160. Reid JM, Qu W, Safgren SL, *et al.*: **Phase I trial and pharmacokinetics of gemcitabine in children with**

advanced solid tumors. *J Clin Oncol* 2004, **22:**2445–2451.

161. Wagner-Bohn A, Henze G, von Stackelberg A, Boos J: **Phase II study of gemcitabine in children with relapsed leukemia.** *Pediatr Blood Cancer* 2006, **46:**262.
162. Blaney SM, Seibel NL, O'Brien M, *et al.*: **Phase I trial of docetaxel administered as a 1-hour infusion in children with refractory solid tumors: a collaborative pediatric branch, National Cancer Institute and Children's Cancer Group trial.** *J Clin Oncol* 1997, **15:**1538–1543.
163. Seibel NL, Blaney SM, O'Brien M, *et al.*: **Phase I trial of docetaxel with filgrastim support in pediatric patients with refractory solid tumors: a collaborative Pediatric Oncology Branch, National Cancer Institute and Children's Cancer Group trial.** *Clin Cancer Res* 1999, **5:**733–737.
164. Zwerdling T, Krailo M, Monteleone P, *et al.*: **Phase II investigation of docetaxel in pediatric patients with recurrent solid tumors: a report from the Children's Oncology Group.** *Cancer* 2006, **106:**1821–1828.