Austin Journal of Trauma and Treatment

Open Access

Austin Publishing Group

Research Article

Primary Osseous Spine Tumors in Adults: A Review and Update on Diagnosis and Treatment

Emerson BD[1]*, Ameri BJ[1], Downing MA[2] and Temple HT[3]

[1]Broward Health Medical Center, Fort Lauderdale, Florida

[2]Nova Southeastern University, Davie, Florida

[3]Mercy Hospital, Miami, Florida

***Corresponding author:** Blaze D Emerson, Broward Health Medical Center, 1600 S Andrews Ave, Fort Lauderdale, Florida

Received: April 23, 2021; **Accepted:** May 17, 2021; **Published:** May 24, 2021

Abstract

Objective: This article aims to provide a convenient and comprehensive review describing unique features of the most common primary osseous spine tumors, as well as current diagnostic and therapeutic modalities for each tumor.

Background: Primary osseous spine tumors are a rare and diverse group of neoplasms with varying biologic behavior. Clinical, radiographic, and pathologic correlation is critical in making a correct diagnosis. Prompt treatment is necessary to optimize clinical outcomes, and is based on tumor type, location, and disease stage. Most patients with spinal tumors present with a history of pain often similar in quality and intensity as non-tumoral etiologies of back pain. Spinal neoplasms, especially malignant tumors, require a multidisciplinary approach and are best treated in dedicated cancer centers to mitigate incorrect diagnoses and inappropriate treatment.

Methods: A literature review was conducted using PubMed and EBSCO. Multiple search queries for relevant articles between 2014 to present were included. Preference was given to recent articles with clinical evidence, current treatment, diagnostic modalities and/or future potential therapies and diagnostic strategies.

Results: Numerous modalities including surgery, chemotherapy, evolving immunologic and targeted therapies as well as stereotactic external beam radiation therapy are utilized to optimize care. Still, current therapeutic strategies result in significant morbidity and mortality and local disease recurrence and systemic relapse are common despite chemotherapy and advanced surgical techniques.

Conclusion: Because primary spinal tumors are uncommon, level I and II data are scarce though novel treatment strategies are emerging. Medical and orthopaedic oncologists and spine surgeons therefore should have a fundamental knowledge of the current state of literature pertaining to this topic.

Keywords: Spine; Tumor; Orthopaedics; Surgery; Chordoma; Chondrosarcoma; Multiple Myeloma; Giant Cell Tumor; Osteosarcoma; Orthopaedic Oncology; Hemangioma

Introduction

Primary osseous spine tumors are rare and represent a diverse group of neoplasms with varying biologic behavior. Clinical, radiographic, and pathologic correlation is critical in making a correct diagnosis. The tumor type can often be predicted knowing the patient's age, tumor location, and radiographic characteristics. Treatment is individualized and based on: tumor type, location, and disease stage. Most patients with spinal tumors present with a history of pain often similar in quality and intensity as non-tumor causes of back pain. Spinal neoplasms, especially malignant tumors, require a multidisciplinary approach and are best treated in dedicated cancer centers to mitigate incorrect diagnoses and inappropriate treatment [1]. Accurate diagnosis and prompt treatment are necessary to optimize clinical outcomes.

In this article, we describe the unique features of the most common primary osseous spine tumors in adults regarding: epidemiology, diagnosis, current treatment modalities and potential future therapies. Because primary spinal tumors are uncommon, level I and II data is scarce though novel treatment strategies are emerging. Medical and orthopaedic oncologists and spine surgeons therefore should have a fundamental knowledge of the current state of literature pertaining to this topic.

Materials and Methods

A literature review was conducted using PubMed and EBSCO. Multiple search queries for relevant articles between 2014 to present were included. Preference was given to recent articles with clinical evidence, current treatment, diagnostic modalities and/or future potential therapies and diagnostic strategies.

Benign tumors

Hemangioma: Hemangiomas are hamartomas, normal tissue in an abnormal location, composed of blood vessels, either capillary or cavernous. Neurologic deficits may occur without vertebral collapse, due to expansion and impingement on the neural elements. Vertebral

Citation: Emerson BD, Ameri BJ, Downing MA and Temple HT. Primary Osseous Spine Tumors in Adults: A Review and Update on Diagnosis and Treatment. Austin J Trauma Treat. 2021; 6(1): 1015.

Table 1: Spinal tumor type and its associated demographics.

Tumor	Age/Gender	% of Primary Spinal Tumors	Location	Unique imaging features
Hemangioma	4th-6th decade [7] Female (slight preference) [7]	30% of primary spinal tumors7 Observed in 11% of post mortems7	No preference Vertebral bodies	"Jail bar" Striations "Honeycombed" Multiple lesions
Giant Cell Tumor	2nd-4th decades peak incidence is 3rd decade [12] Female predilection [12]	5% of primary spinal tumors [7,8]	Thoracic and lumbosacral Vertebral bodies 2nd most common tumor of sacrum 4.9% of GCT's occur in sacrum [12,71]	Aneurysmal features Heterogeneous MRI hypointense on T1 and T2 pulse weighted sequences due to hemosiderin
Chordoma	4th-6th decades Male (2:1)	2-4 % of primary spinal tumors Rare: 0.51-0.8 patients per 100,000141,142	50% sacrum and coccyx [7] 35% skull base 15% mobile spine [7] Youth: spheno-occipital predilection [39,64] Vertebral bodies Most common primary sacral Tumor [64]	Subtle on radiography best seen on lateral radiograph Midline location Anterior soft tissue extension Hyperintense on T2 and STIR images and hypointense on T1
Multiple Myeloma/ Plasmacytoma	5th-6th decade Male (2:1)	20-30 % of primary spinal tumors	Thoracic [7,73] Vertebral bodies	Diffuse osteopenia "punched out or moth eaten appearance" Soft tissue extension
Chondrosarcoma	3rd-4th decade Male (2:1)	Most common primary malignant spinal tumor [7,74] 7-12% of primary spinal tumors 10% of CS occur in axial spine [143]	Thoracic	Matrix producing (arcs and rings) Expansile soft tissue extension Lobular appearance on MR
Osteosarcoma	3rd-6th decades Male (slight) Spinal OS more common in older patients [93,120]	<5% of primary spinal tumors Rare in spine (0.3-3.2 % of all OS) [93,119]	Lumbosacral predilection [120] Vertebral bodies; primary involvement of posterior elements seen in 10-17% of cases [144]	Matrix producing "cloud like" Destructive with soft tissue extension Venous involvement common in sacroiliac region

GCT: Giant cell tumor; CS: Chondrosarcoma; OS: Osteosarcoma.

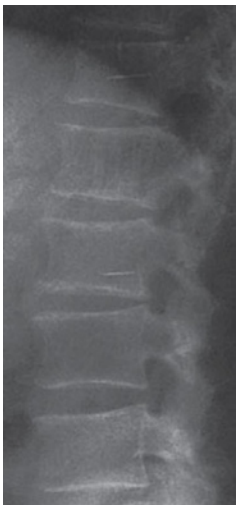

Figure 1: Radiographically VHs may demonstrate a coarsened or "jail bar" trabecular appearance.

Hemangiomas (VH) are located in the vertebral body and may extend into the pedicles and neural arches (Table 1). Radiographically, the lesion is less radio dense than the surrounding bone conferring a coarsened or "jail bar" trabecular appearance (Figure 1) while on axial CT it is described as "honeycombed" (Figure 2). Bone enlargement and cortical thinning may be observed. Technetium99 pyrophosphate bone scintigraphy (99mTC) usually reveals mildly increased uptake, unless pathologic fracture supervenes in which case uptake is intense. The characteristic MR appearance is mottled and unlike other osseous tumors, is hyperintense on T1 and T2 pulse weighted sequences [2]. They enhance diffusely with gadolinium administration.

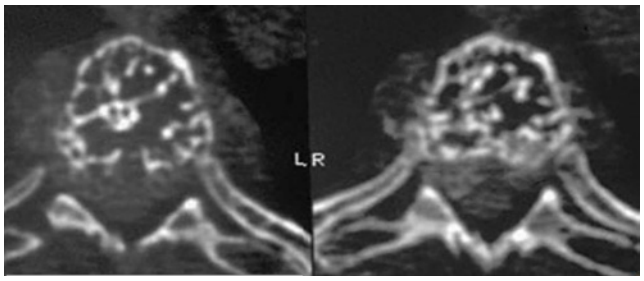

Figure 2: VH. Axial CT demonstrating "honeycombed" appearance of vertebral body.

Most VH are asymptomatic and treated non-operatively [3]. VH that cause pain, neurologic deficits, or pathologic fracture were traditionally treated by excision following embolization [3,4] (Table 2). In a multicentric study reviewing intralesional resection for symptomatic VH, Goldstein et al. demonstrated tumor recurrence in 2.9% at a mean follow-up of 3.9 years. These results were confounded by treatment variability with 35% receiving preoperative embolization, 10% adjuvant radiation, and 81% undergoing posterior alone surgery [5]. Radiation Therapy (RT) has been advocated for patients with mild pain and minimal bone destruction [4]. When used alone for patients with neurologic symptoms, 82% had complete recovery of their motor and sensory function [6]. In a recent meta-analysis of 197 VH cases, Piper et al. advocated both (RT) and surgery demonstrating a decrease in tumor recurrence [4].

Benign aggressive tumors

Giant cell tumor: Giant Cell Tumors (GCT) are benign albeit aggressive lesions composed of bland stromal cells and multinucleated giant cells [7,8]. Patients present with pain and 50% have neurologic

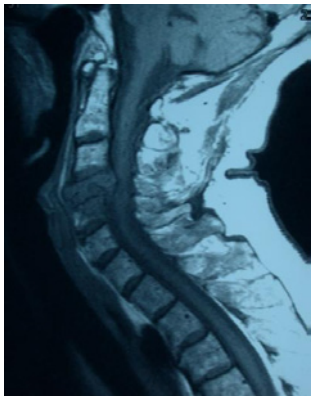

Figure 3: GCT. Sagittal view of the cervical spine, T1 weighted imaging demonstrating hypointense signal, soft tissue mass, and extension into adjacent vertebrae.

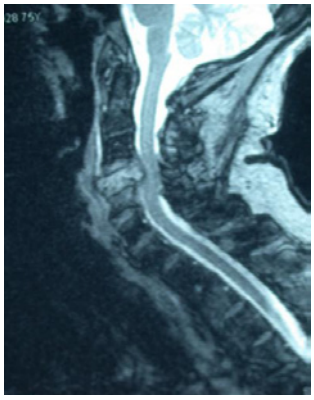

Figure 4: GCT. Sagittal view of the cervical spine, T2 weighted imaging demonstrating hypointense signal, soft tissue mass, and extension into adjacent vertebrae.

symptoms [9]. Radiographically, GCT has a variable appearance. Geographic lysis and expansile growth with cortical thinning may be seen along with a soft tissue mass. Pathologic fracture may occur with extension into adjacent discs and vertebrae [10] (Figure 3 and 4). Pseudotrabeculations may be observed; mineralization is generally absent. In the sacrum, direct extension across the sacroiliac joint into the ilium has been described [11]. Scintigraphically, uptake is heterogeneous, but is generally increased. Aneurysmal changes are relatively common in GCT [12]. MR appearance is variable demonstrating hypointense signal on T1 and T2 pulse-weighted sequences in the solid components due to hemosiderin deposits [12]. Cystic areas are hyperintense on T2 imaging; fluid-fluid levels may be observed [12].

Biopsy and staging are required as up to 14% of patients with GCT may develop pulmonary metastasis [13,14]. Traditionally, en bloc resection with decompression and stabilization was the preferred treatment resulting in lower recurrence rates and increased survival [8,13,15] (Table 2). Boriani et al stratified surgical resection for GCT of the mobile spine based on Enneking stage. For stage 2 GCTs, intralesional curettage resulted in local recurrence of 6% at 5 years while stage 3 lesions recurred in 61%. Stage 3 lesions treated with en bloc resection recurred in 10% of patients [14]. The treatment of sacral GCTs is complex though traditionally resection with tumor free margins was the goal, with recurrence rates as high as 47% with intralesional resection [16].

Tumor free margins are often not possible due to tumor extent and the risk of permanent neurologic injury. Radiotherapy has been used in select cases where residual macroscopic disease is present or tumor resection is not possible. There is conflicting data on its efficacy and the risk of sarcomatous transformation is reported to be as high as 11% [8,9,11,16-19] Selective Arterial Embolization (SAE) has can reduce intra-operative blood loss, decrease the rate of tumor progression, provide significant pain relief, and alleviate neurologic symptoms [8]. Serial Arterial Embolization (SAE) is used as primary treatment in inoperable lesions. In a review by He et al. SAE of pelvic and sacral GCTs resulted in local disease control and overall survival in 75% and 81.8% of patients respectively [20]. Domovitov et al. compared intralesional resection of sacral GCTs with and without adjuvant XRT and/or SAE. They found significantly fewer local recurrences in patients who underwent neoadjuvant XRT or SAE compared to resection alone [21].

Adjuvant therapy combined with en bloc and subtotal resection may reduce the risk of recurrence. Xu et al. combined surgery with bisphosphonate therapy in treating sacral GCTs observing recurrence in 10.53% of patients in the bisphosphonate group and 47.75% in the control group [22]. In studies involving the mobile spine several authors found increased Recurrence Free Survival (RFS) with adjuvant bisphosphonate therapy and resection [23,24]. Denosumab has been shown to improve neurological symptoms and pain control, and restore bone as single therapy for inoperable GCTs [8,25-27]. Neoadjuvant treatment with denosumab decreases tumor size, blood loss, and defines tumor borders facilitating complete excision [25,26,28]. Lim et al. studied intralesional resection of GCTs and demonstrated 95% recurrence-free survival with adjuvant denosumab *vs.* 70.3% without [28].

Chordoma

Chordoma arises from notochord remnants. Microscopically, multi-vacuolated physaliferous cells are seen in a bluish myxoid background (Figure 4). Dedifferention is reported and portends a worse prognosis [29]. Patients present with constipation and difficulty sitting though diagnosis is often delayed [30,31]. Metastases occur late in the disease in 10-43 % of patients, principally lungs and liver, although other locations are described [32-35]. Metastatic disease was most common in the youngest patients (P=0.07), and was 2.5 times more frequent for patients with local recurrence (26.3%) compared to those without (10.8%) (P=0.003) [36].

Radiographs are difficult to interpret although lateral radiographs may show a large soft tissue component that is better appreciated on CT or MR. In the mobile spine, chordoma can be expansile and sclerotic, "ivory vertebra" [37]. CT better demonstrates osseous destruction and soft tissue disease extension that often displaces the rectum anteriorly; the fat plane between the mass and the rectum is often preserved although in neglected or recurrent cases, direct rectal involvement may occur (Figures 5 and 6). Inappropriate biopsy through the rectum can also obliterate this important soft tissue plane. Amorphous calcifications have been noted on CT32 along with tumor extension into the spinal canal in 60% of cases [35]. The mass

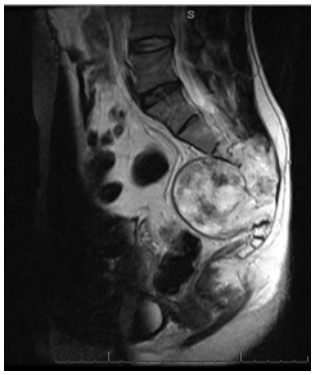

Figure 5: Chordoma. Axial view T2 weighted image with marked hyperintensity involving and surrounding the sacrum. The fat plane between the mass and the rectum is preserved.

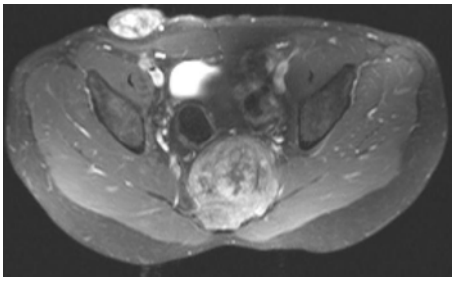

Figure 6: Chordoma. Sagittal T1 weighted image with low to intermediate signal. The bony architecture of the sacrum has been disrupted however, the fat plane between the tumor and the rectum is intact.

appears uniformly hyperintense on T2 pulse weighted sequences on MR. It has a low to intermediate signal intensity on corresponding T1 images [12].

Treatment is surgical and despite wide margins on gross and microscopic examination, local recurrence is common [38,39]. Intralesional or marginal excisions are associated with high rates of local recurrence [31,33,40] and these patients may have a worse prognosis [39]. Meticulous planning should be undertaken prior to tumor resection and should carefully assess bone and soft tissue extension with particular attention to the level of sacral involvement [38]. Preoperative embolization can reduce surgical blood loss and may be a treatment option in unresectable cases [38,41]. For tumors below the level of S2, a posterior approach is preferred [38]. Tumors above S2 require a combined anterior and posterior approach to mobilize the iliac vessels and omentum and to perform a colostomy [38]. The omentum decreases the dead space along with an acellular dermis or synthetic mesh to prevent rectal prolapse. Gluteal flaps or mobilization of a musculofasciocutaneous rectus abdominis flap may be necessary for wound closure [42,43]. There is a delicate balance between preserving nerve roots and removing adequate tissue to achieve local disease control [39]. Neurological function is highly variable amongst patients treated with sacrectomy [38]. If the S3 nerve roots can be preserved bilaterally, normal bowel and bladder function can be expected although this varies [31,44-46]. Reconstruction following sacrectomy may require spinopelvic fixation, posterior pelvic ring stabilization, and anterior column support due to gross instability [38,47,48].

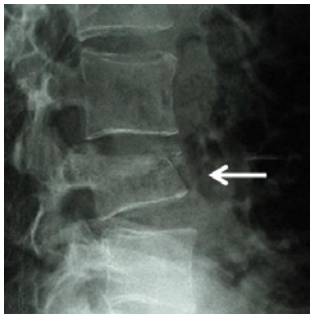

Figure 7: Multiple myeloma. Radiographically MM may demonstrate punched out lesions or in the spine compression fractures and vertebra planae.

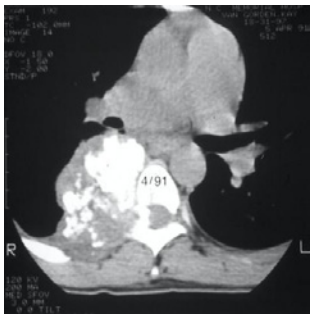

Figure 8: Chondrosarcoma. Axial CT demonstrates cortical destruction and calcific matrix production.

Adjuvant radiotherapy combined with surgery or alone for palliative care is useful [49,50-52]. Park et al demonstrated that localized radiation after en bloc resection yielded five and ten-year survivorship of 93% and 91%, respectively [38,53]. Radiation seems to confer longer continuous disease-free survival than patients who do not have adjuvant radiotherapy. For those unfit for surgery, radiation therapy can be used as sole therapy [38]. Chen et al demonstrated a 78% five-year survival rate with high dose radiation alone [38,54].

Chordoma is chemotherapy resistant however new biologic pathways are being explored and improved systemic treatments may be available in the future, particularly for advanced disease [55]. There are several new and emerging treatments for patients with chordoma, that are summarized in (Table 2) [38,55-64]. Presently, wide local excision with or without radiation is the preferred treatment while systemic agents are reserved for clinical trials, inoperable or recurrent and metastatic cases.

Multiple Myeloma/Plasmacytoma

Multiple Myeloma (MM) is a clonal proliferation of plasma cells in bone marrow that may be associated with end organ damage. More than 80% of MM patients will develop clinically detectable bone disease; 60% will develop a pathological fracture during the course of the disease [65,66]. Pain, deformity, and neurological deficits are common [67,68].

Radiographs demonstrate well defined lytic "punched-out" lesions usually involving multiple spinal levels (Figure 7). Compression fractures and diffuse osteopenia are due to the upregulation of osteoclast activity through various ligands in the MM microenvironment ie. RANK Ligand (RANKL) [68]. Osteoblast

Table 2: Spinal tumor type and its prospective treatment(s).

Tumor	Prospective Therapy	Outcomes
Hemangioma	Surgery Embolization Radiation therapy	Surgical resection for symptomatic VH showed tumor recurrence of just 2.9% at 3.9-year follow-up (n=68). 35% of these cases received pre-operative embolization, 10% received adjuvant radiotherapy [5]. Radiation therapy and pre-operative embolization demonstrated reduced recurrence rates and symptomatic improvement in a meta-analysis analyzing 197 VH cases [4].
Giant Cell Tumor	Surgery	Intralesional curettage of stage 2 and 3 tumors resulted in a 6% and 61% recurrence respectively at 5 years. Stage 3 lesions treated with enbloc resection demonstrated recurrence of 10% [14].
	Embolization	In inoperable lesions pelvic and sacral SAE resulted in local disease control in 75% [20]. Pre-operative SAE resulted in decreased intraoperative blood loss [8]. Neoadjuvant SAE combined with intralesional excision resulted in less recurrence than intralesional excision alone [21].
	External beam radiation therapy	Conflicting results of the effects of EBRT alone on GCT. Domovitv et al. demonstrated decreased recurrence with preoperative EBRT combined with intralesional resection [21].
	Bisphosphonates	Patients who received neoadjuvant and adjuvant bisphosphonate therapy showed significantly improved 2- and 5-year RFS, as well as overall RFS ($p<0.01$ for all) when compared to those who did not [22].
	Denosumab	Denosumab as single therapy in unresectable cases demonstrates resolution of neurological symptoms, improved pain control, and restoration of bone morphology [8,25-27]. As neoadjuvant treatment denosumab decreases tumor size, blood loss, and defines tumor borders facilitating complete excision [25,26,28]. Combined with intralesional resection demonstrated a 95% RFS [28].
Chordoma	Tyrosine Kinase Inhibitors	Imatinib showed therapeutic benefit in 64% of patients and an average 9-month progression-free period in non-surgical or salvage cases [38,62]. Review of approximately 300 patients with advanced chordoma treated with conventional chemotherapy and TKI, less than 10% showed partial response [61].
	EGFR Inhibitors (afatinib)	Promoted degradation of EGFR and brachyury in xenograft derived chordoma cell lines [59].
	Brachyury targeted therapies and vaccine	Vaccine shows pre-clinical and clinical evidence of potential use in targeting Brachyury protein [57].
	CDK-Inhibitors	CDK-Inhibitors tested in mice with human chordoma cell line demonstrated down-regulation of Brachyury [63]. In one small series resulted in a favorable radiologic tumor response [60,61].
	PD-1 monoclonal antibodies (pembrolizumab and nivolumab)	
Multiple Myeloma	Proteasome inhibitors (bortezomib, carfilzomib and ixazomib)	Bone anabolic effects promoting osteoblast differentiation demonstrated with increased levels of alkaline phosphatase. In murine MM models, induced an increase in bone formation and mineral density. Bortezomib decreases DKK-1 levels in bone cells and in MM patients and inhibits osteoclast function [75-82].
	Immunomodulatory drugs (thalidomide, lenalidomide)	IMiDs reduce osteoclastic resorption by inhibiting factors such as PU.1 and BAFF and decreasing the interactions between MM cells and other cells in the MM microenvironment [83-85]. IMiDs decrease bone turnover markers, DKK-1 levels and RANKL/OPG ratios. IMiDs were shown to negatively affect osteoblast differentiation *in vitro* [86,87].
	Dickopf-1 (DKK-1) neutralizing antibodies (BHQ880, DKN-01)	Increased osteoblast numbers and trabecular bone as well as inhibition of MM cell growth in murine MM models [88].
	Anti-sclerostin antibodies (Romosozumab)	Early clinical trials show an increase in bone formation after pathologic bone loss. Inhibition of sclerostin reversed MM bone disease in a murine xenograft MM model [89,90].
	Soluble Activin-A Receptors (Sotatercept)	Preclinical trials suggest prevention of bone disease in MM-mice. Phase II clinical trials show partial repair of bone lesions in MM patients with increased bone mineral density and alkaline phosphatase in patients off bisphosphonate therapy [91].

Chondrosarcoma	Chemotherapeutic regimes for unresectable CS based on histologic subtype	Conventional CS: hormonal therapy (aromatase and estrogen inhibitors) had the highest average of PFS of 6.7-months. This could not be reproduced *in-vitro* [108-110]. Dedifferentiated CS: Doxorubicin monotherapy group had 5.5-month average PFS *vs* doxorubicin + cis-platin with or without MTX group 2.9-months (p=0.275) [107]. Mesenchymal CS: Cisplatin with doxorubicin had the longest average PFS of 7.7-months. Average PFS for all regimes was 6.7-months [107]. Clear Cell CS: Sunitinib or Pazopanib + Denosumab had PFS of 9.7-months [107].
	Isocitrate Dehydrogenase Inhibitors	IDH pathway may no longer be essential once the benign precursor enchondroma progresses to CS, thus IDH Inhibitors may not be of benefit [111,112.
	Hedgehog Pathway Inhibitors	Primary human CS tissue xenotransplanted in mice showed downregulation of HH pathway and inhibition of tumor growth with treatment of HHI IPI-296 [113]. CS xenografts treated with HHI triparanol showed a 60% decrease in tumor volume [114]. HHI Saridegib showed no improvement in PFS *vs* placebo in patients with inoperable CS [107]. Median PFS for CS treated with Dasatinib (inhibits SRC pathway) = 2.2months [107].
	Tyrosine Kinase Inhibitors	Combo therapy with doxorubicin shows synergistic inhibition of CS cell line, suggesting use in chemo resistant CS [115,116]. Phase II study of dasatinib in incurable CS subtypes showed median PFS of 5.5-months [145].
Osteosarcoma	Bone seeking radioisotopes	[153] Sm-EDP mainly utilized for pain control; inadequate evaluation of this treatment method [125].
	Immunomodulators (Mifamurtide)	Activity against OS, but clinical activity is not yet known [126,127].
	PD-1 Inhibitor (Pembrolizumab)	25% of OS display PD-L1 [128]; Pembrolizumab displayed 8-week PFS in 24% of patients. The best outcome was partial response, seen in 1/22 patients [129].
	Tyrosine Kinase Inhibitors	Sorafenib + everolimus achieved 6-month PFS in 45% of patients in phase 2 trials [130]. Apatinib shows high objective response (43.24%) in phase-II clinical trials for advanced OS [131]. Double-blind study with Regorafenib has shown promise in clinical trials PFS 3.6-months *vs* 1.7-month placebo [132].
	Targeted gene therapies	MYC is the most commonly amplified gene in OS; MYC-inhibitors show tumor shrinkage [133]. Nanocarriers with MYC-siRNA showed tumor inhibition in mouse models [134,135]. Palbociclib targeting CDK4 decrease OS cell proliferation, growth, and migration [136]. Pazopanib & Sorafenib (VEGF Inhibitors) demonstrate antitumor activity in clinical trials [130,137]. MK2206 (pan-AKT inhibitor) and Rapamycin (mTOR inhibitor) arrest OS tumor growth in patient derived OS xenografts [133]. Ridaforolimus (mTOR inhibitor) shows partial response in OS patients [138]. Insulin-like Growth Factor inhibitors have displayed partial or complete responses [139,140].

SAE: Serial Arterial Embolization; GCT: Giant Cell Tumor; EBRT: External Beam Radiation Therapy; RFS: Recurrence Free Survival; TKI: Tyrosine Kinase Inhibitors; EGFR: Epidermal Growth Factor; CDK: Cyclin Dependent Kinase; PD-1: Programmed Death-1; MM: Multiple Myeloma; DKK-1: Dickopf-1 Neutralizing Antibodies; IMiDs: Immunomodulatory Drugs; RANKL: Receptor Activator of Nuclear Factor Kappa-B Ligand; OPG: Osteoprotegerin; CS: Chondrosarcoma; PFS: Progression-Free Survival; IDH: Isocitrate Dehydrogenase; HHI: Hedgehog pathway Inhibitors; OS: Osteosarcoma; VEGF: Vascular Endothelial Growth Factor; mTOR: Mammalian Target of Rapamycin.

formation is inhibited by MM cell-derived factors, (DKK-1) protein, that inhibits the Wnt pathway resulting in lytic lesions that do not remodel [68,69]. Vertebral lesions may not be apparent radiographically until substantial bone loss has occurred, thus, whole-body low-dose CT is preferred due to its increased sensitivity to detect both osseous and extraosseous lesions.69 MRI is sensitive for detecting intraosseous tumor extent and soft tissue extension [70]. 18F-FDG PET/CT is as sensitive as MRI in identifying solitary plasmacytoma and tumor infiltrated bone marrow [70]. PET/CT is useful for Myeloma (MM) staging and tumor surveillance. Up to 40% of patients initially diagnosed with solitary plasmacytoma have additional lesions diagnosed on PET/CT [70].

MM is best managed by a multidisciplinary approach involving systemic regimens and possibly bone marrow transplantation that is beyond the scope of this review. Disease extent dictates therapy. For example, patients with solitary plasmacytoma are treated with radiation therapy alone achieving local disease control in 96% of cases [71]. Bisphosphonates are the mainstay of MM bone disease therapy and should be initiated in patients with or without osteolytic lesions and in MM precursor diseases with associated osteoporosis

[68]. Intravenous pamidronate and zoledronic acid have been shown to increase overall survival, alleviate bone pain, and decrease Skeletal Related Events (SREs) [68]. Recombinant Osteoprotegerin (OPG) modulates the RANK/RANK-L differentiation of osteoclasts and decreases the number of SREs with efficacy similar to pamidronate (body). Raje et al. demonstrated that denosumab was not inferior to zoledronic acid in decreasing time to the first skeletal related event in newly diagnosed MM patients [72]. Diffuse osteoporosis and pathologic fractures are associated with significant pain, deformity and overall debility. To mitigate these effects, The International Myeloma Working Group recommends early cement augmentation (vertebroplasty) in MM patients with symptomatic vertebral compression fractures.. Prospective treatments for MM can be found in Table 2 [73-91].

Chondrosarcoma

Chondrosarcoma (CS) is a slow-growing, heterogenous group of primary malignant bone tumors characterized by hyaline cartilage formation [92]. Histopathologically, CS can be low, intermediate, or high grade depending on the degree of cellularity, atypia, necrosis and presence of mitoses. There are several disease subcategories including: dedifferentiated, mesenchymal and clear cell variants. CS can arise from benign antecedent tumors such as osteochondromas and enchondromas or, rarely, pagetoid lesions and bone exposed to prior radiation. In general, CS invades locally and the higher the tumor grade, the more likely distant metastases occur, most commonly to the lungs. The most common presenting symptom is pain however neurologic symptoms have been reported in nearly half of patients [93]. Approximately 10% of CS arise in the mobile spine and may be prodigious before causing symptoms (Table 1) [94].

Radiographs show osseous destruction and cartilage matrix reminiscent of arcs and rings, flocculations or stippled calcifications. Bone scintigraphy reveals increased radiotracer uptake. The uptake pattern is more often heterogeneous in malignant cartilage tumors and homogeneous in benign lesions [95]. CT delineates the degree of cortical destruction and matrix production (Figure 8). MR demonstrates a lobular growth pattern that is hyperintense on T2 pulse weighted and STIR images and hypointense on corresponding T1 images. Septal or diffuse enhancement may be observed with gadolinium administration.

These tumors are resistant to both radiotherapy and chemotherapy [92,96]. Radiation remains a potential option for incomplete resections, high grade lesions, or palliative care [97]. For this reason, wide local excision alone is the most effective treatment for this disease [94,98-104]. Chen et al performed a retrospective study that stratified and matched primary spinal CS patients by tumor grade and compared outcomes treating CS with surgery alone versus surgery and radiation [105]. Their data demonstrated that patients with low grade tumors treated with surgery alone had better outcomes although those with high grade lesions seemed to benefit from radiation as well [105]. Shamesh et al. demonstrated acceptable results treating low grade chondrosarcoma with intralesional resection [106].

Although systemic therapies have been ineffective for patients with CS, many new potential treatment pathways have emerged. Studies regarding novel targeting microRNA, glucose-metabolism, cyclin-dependent kinase, matrix metalloproteinase, integrins, herbal compounds, adipokines, growth factors and many other molecules are in pre-clinical or early clinical phase trials [92,97]. There are inherent challenges in treating CS with chemotherapy, including the so-called "two-hit" scenario which suggests that more than one pathway is responsible for malignant transformation [97]. Chemotherapy may be used in select cases for example, unresectable tumors that have an estimated five year survival of only 2% [97,107]. A review of new and emerging chemotherapy strategies and pathways are summarized in Table 2 [107-116]. IDH inhibitors have recently been touted as a treatment strategy for CS due to the presence of driver mutations in this pathway and promising results with other tumors bearing similar mutations including leukemia and glioma [107,111,117]. Unfortunately, once malignant progression has occurred in CS, the IDH pathway is no longer thought to be essential for replication [107,111,112]. For this reason IDH targeting therapies may not be as useful in treating CS as once thought [107].

Osteosarcoma

Osteosarcoma is a malignant tumor of bone that produces osteoid [118]. It may be secondary to other conditions such as Paget disease or areas of the spine previously irradiated. Although Paget disease commonly involves the spine, secondary osteosarcoma in this location is very rare [118]. Osteosarcoma of the spine is associated with significant morbidity, early metastases and death [119,120]. Patients with osteosarcomatosis (metachronous or synchronous disease) or patients with relapsed disease may have spinal involvement at multiple levels. As with most spine tumors, pain is the hallmark symptom often accompanied by neurologic deficits [93]. Generally speaking, OS survivorship has plateaued over the past few decades with minimal advances in chemotherapy. Survival is much lower in the axial skeleton [118,121].

Radiographically, tumors are primarily blastic and may appear as an ivory vertebra but may also be predominantly lytic or mixed (blastic and lytic). The tumor begins in the vertebral body and usually has an extraosseous component at the time of diagnosis that is best seen on MR. Dural compression is frequently observed in patients with neurologic deficits. Microscopically, there are many subtypes: osteoblastic (conventional), fibroblastic, chondroblastic, telangiectatic, and small cell. Despite the histologic heterogeneity, the common thread between histologic subtypes is the presence of malignant cells making osteoid. The cells are large and spindled with hyperchromatic nuclei, varying degrees of mitotic activity and cellular and nuclear pleomorphism. Vascular invasion is a prominent feature of pelvic osteosarcoma.

Generally, patients at the extremes of age do poorly. Often older patients, due to comorbidities, cannot tolerate chemotherapy and in those than can, it is difficult to predict tumor response [55]. Patients with axial tumors in general, especially the spine, have a worse prognosis than patients with appendicular lesions. In one study only one patient in twenty-seven was alive at the latest follow-up [93]. The mean survival was 14 months; six patients were paraplegic and three were quadriplegic at the time of death. Dekutoski et al. recently pooled data from twelve spine referral centers studying 58 patients with primary spine osteosarcoma with a mean age of 36 years [122]. An improvement in survival was observed with en bloc resection with

a mean survival of 6.8 years compared to those with intralesional resection with a mean survival of 3.7 years [122]. Although 30% of the cohort had local recurrence and 41% were dead at latest follow up, these results were better than those in previous studies [122]. These results were ascribed to improved resection techniques and more aggressive chemotherapy [122]. In their study, age, previous surgery, biopsy method, tumor size, spine level, and chemotherapy timing did not significantly affect recurrence or survival [122]. Previous studies cited local recurrence, secondary osteosarcomas (related to previous radiation or Paget's disease) and possibly pathologic fractures as negative risk factors for survival [122]. There is a careful balance between preserving function and obtaining an optimal oncologic result [122].

Patients receiving radiation therapy have worse outcomes likely due to patient selection bias, nevertheless, radiation is generally reserved for unresectable tumors and palliative care [55]. Patients with spinal OS are more likely to receive radiation due to the nature of the disease, especially when symptomatic cord compression is present [120]. External beam or proton beam radiation therapy is recommended for patients with gross or residual microscopic disease following resection [55]. The most important survival indicator however is tumor response to neo-adjuvant chemotherapy as measured by tumor necrosis [123,124]. Patients with greater than 90% tumor necrosis after chemotherapy are statistically more likely to survive than those with less tumor necrosis [123,124]. The current chemotherapy OS regimen includes: cisplatin, doxorubicin, and methotrexate [55]. Methotrexate is generally not used in older patients due to its toxicity profile [55,118]. There are several new or emerging treatments and pathways that have garnered interest in osteosarcoma treatment which are summarized in Table 2 [125-140].

Discussion

Primary spine bone tumors in adults are challenging to diagnose and treat for surgeons and oncologists. Resection and preservation of function is the goal and worse outcomes compared to patients with appendicular tumors are expected. Clinical, radiographic and pathologic correlation in a multidisciplinary setting is critical to properly diagnose and treat these conditions. Appropriate workup and treatment is optimized in tertiary spine and tumor referral centers. Surgery, chemotherapy, evolving immunologic and targeted therapies as well as stereotactic EBRT and proton therapy are utilized to optimize care. Still current therapeutic strategies result in significant morbidity and mortality and local disease recurrence and systemic relapse are common despite chemotherapy and advanced surgical techniques.

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