Spinal Osteosarcoma

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Abstract: Although osteosarcoma represents the second most common primary bone tumor, spinal involvement is rare, accounting for 3%-5% of all osteosarcomas. The most frequent symptom of osteosarcoma is pain, which appears in almost all patients, whereas more than 70% exhibit neurologic deficit. At a molecular level, it is a tumor of great genetic complexity and several genetic disorders have been associated with its appearance. Early diagnosis and careful surgical staging are the most important factors in accomplishing sufficient management. Even though overall prognosis remains poor, en-block tumor removal combined with adjuvant radiotherapy and chemotherapy is currently the treatment of choice. This paper outlines histopathological classification, epidemiology, diagnostic procedures, and current concepts of management of spinal osteosarcoma.

Keywords: spine, primary tumors, osteosarcoma, imaging/diagnosis

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Introduction

Osteosarcomas are primary malignant bone tumors characterized by the production of osteoid or immature bone from malignant cells.\(^1\)\(^-\)\(^3\) Although osteosarcoma is considered to be the most common primary bone tumor, it represents only 3%–5% of all spinal malignancies.\(^4\)\(^-\)\(^9\) Age of onset follows a bimodal distribution, being more common in adolescents and young adults, with a second peak in the elderly population.\(^10\) The sacral area followed by the lumbar and thoracic spine segments, are the most common locations.\(^11\)\(^,\)\(^12\)

Clinically, osteosarcomas present almost always with pain—often with insidious onset and becoming progressively intolerable, even during sleep—and neurological deficiency. As the tumor is frequently seen within the spinal canal, two thirds of patients show some neurologic impairment.\(^11\)\(^,\)\(^12\) Histologically osteosarcoma in its classic form contains tumor cells varying in shape, from spindled to polyhedral, with pleomorphic and hyperchromatic nuclei producing bone or osteoid.\(^16\) Plain radiographs usually show a blastic lesion, occasionally appearing as an “ivory body”.

The low incidence of spinal osteosarcoma, its anatomical location, and its proximity to vital structures make the treatment of osteosarcoma challenging; this applies particularly to neo-adjuvant chemotherapy with subsequent en bloc excision and postoperative chemotherapy. When full resection of the tumor is doubtful, radiation therapy can be used.\(^13\)\(^-\)\(^15\)

Despite advances in diagnostic and treatment regimens, the long term outcome in patients with spinal osteosarcoma remains poor. According to literature the local recurrence is 20% after en bloc excision and 60% after intraregional excision.\(^17\)\(^-\)\(^19\)

The aim of this study is to present a review in the literature regarding epidemiology, imaging presentation, staging, diagnostic workup, and current concepts of management of spinal osteosarcoma.

Epidemiology and Risk Factors

The incidence of osteosarcoma varies by race and sex based on the age at onset. For individuals over the age of sixty, it is higher in white population; for patients between the age of 25 and 29, the incidence is greater in African Americans.\(^20\)

Generally, it has been reported that primary osteosarcomas affect males more frequently than females, although for those under 15 years of age females have slightly higher rates.\(^21\)\(^-\)\(^27\) However, according to one of the largest in scale, multi-institutional studies, a slightly increased incidence of spinal osteosarcoma in females has been noted.\(^14\)

Age of onset of spinal osteosarcoma follows a bimodal distribution and as a primary malignancy it is more common in adolescents and young adults; there is a tendency to occur in older age groups compared to osteosarcoma of the extremities,\(^5\) with a mean age of 38.\(^14\) The incidence of spinal osteosarcoma in the elderly appears in the seventh decade of life.\(^10\)

Osteogenic sarcoma of the spine represents 3.6%–14.5% of primary spinal tumors and 0.85%–3% of all osteosarcomas.\(^14\) Osteosarcoma is located in the sacrum in 30% of cases, lumbar and thoracic spine in 25%, and cervical spine in 25%.

The majority of patients affected by osteosarcoma show no risk factors and the number of proven risk factors associated with osteosarcoma is limited.\(^28\) Paget’s disease is a known risk factor. In different series it has been estimated that about 1% of patients with Paget’s disease will develop osteosarcoma.\(^29\)

Osteosarcoma can also occur after therapeutic radiation for different cancer types; these commonly includeg Li-Fraumeni syndrome,\(^30\)\(^,\)\(^31\) Retinoblastoma,\(^32\) Rothmund Thomas Syndrome,\(^33\) Werner syndrome,\(^34\)\(^,\)\(^35\) Diamond Blackfan Anemia,\(^36\) and Bloom syndrome.\(^37\)

Histology/Molecular Biology

The conducted studies concerning the molecular biology and histology of spinal osteosarcoma are extremely limited due to the rarity of the disease; however, such studies could be useful assets in finding promising therapeutic strategies.

Osteosarcoma is a malignant tumor of connective tissue (mesodermal) origin, within which the tumor cells produce osteoid. Osteosarcoma may produce various kinds of extracellular matrix and present different degrees of differentiation. Histologically the following subtypes of spinal osteosarcoma have been asserted:\(^14\) chondroblastic and osteoblastic (the most common); small cell tumor; teleangiectatic; and fibroblastic tumor (most rare). Many tumors have mixed histological patterns, varying significantly from case to case and from area to area in the same case.
Histologic grading in osteosarcomas is important in oncologic staging of the tumor and for determining adjuvant treatment following surgery. Using the Society of Musculoskeletal Oncology staging schema, staging depends on whether the tumor is high or low graded. Almost all conventional osteosarcomas are high-grade tumors and almost all surface osteosarcomas are low-grade tumors.

According to the World Health Organization bone osteosarcoma is currently classified as follows: conventional, telangiectatic, small cell, low-grade central, secondary, parosteal, periosteal, and high-grade surface.

Surface osteosarcomas, whose epicenters are outside the cortex of the bone, are about 20 times less frequent than their medullary counterparts. Most surface osteosarcomas are of low grade, with a limited distal metastasis capacity, whereas the majority of medullary osteosarcomas are of high grade.

Conventional osteosarcoma is the classic form of osteosarcoma. It is a high grade malignant primary central osteogenic tumor. Traditionally, according to the predominant type of extracellular matrix produced, it is further divided into osteoblastic, chondroblastic, and fibroblastic subtypes. The tumor cells are often highly anaplastic, with pleomorphic and hyperchromatic nuclei, and are spindle shaped. The metaphyseal medullary parts of the long bones (usually distal femur, proximal tibia, proximal humerus) are often affected by this tumor.

Parosteal osteosarcoma is the most common form of surface osteosarcoma. It accounts for fewer than 5% of all osteosarcoma cases. The tumor usually occurs in the metaphyses of long bones; in 75% of cases it arises from the distal posterior femur. Parosteal osteosarcoma originates from the outer fibrous layer of the periosteum and it is usually low grade, with minimal fibroblastic stromal atypia and extensive bone matrix production. Dedifferentiation of low-grade parosteal osteosarcoma to high-grade parosteal osteosarcoma has been reported in 16%–43% of cases. Histologically these tumors consist of a mixture of a low grade parosteal osteosarcoma and a high grade component. Prognosis is determined by the least differentiated part of the tumor.

High-Grade surface osteosarcoma is the least common form of surface osteosarcoma and it is completely high grade histologically. High-grade surface osteosarcoma is believed to have the same prognosis as conventional osteosarcoma; however, recent studies have demonstrated an improved prognosis.

Telangiectatic Osteosarcoma mimics aneurysmal bone cyst. The 5-year survival rate has increased from 17% to 67%, approaching that of conventional osteosarcoma. At higher power, the presence of nuclear pleomorphism and a high mitotic rate are usually obvious.

Small Cell Osteosarcoma patients have a slightly less favorable prognosis than those with conventional osteosarcoma. Histologically, small cell osteosarcoma exhibits features combining those of osteosarcoma and Ewing sarcoma. Small cell osteosarcomas may be mistaken for Ewing sarcomas due to their positivity to membrane staining for CD99 (a marker typically found in Ewing sarcoma). Furthermore the EWS-ETS chromosome 22 translocation, commonly found in Ewing sarcoma, can also be found occasionally in small cell osteosarcoma tumors.

Histologically, low grade central osteosarcoma presents similarities to fibrous dysplasia or low grade parosteal osteosarcoma. It carries a better prognosis than conventional osteosarcoma, although at times a secondary dedifferentiated high grade osteosarcoma could be developed within the original low grade tumor.

At the molecular level, osteosarcoma is a tumor of great genetic complexity. Numerous studies have demonstrated various molecular pathways and genetic alterations associated with osteosarcoma development and metastasis. Recently, it has been shown using micro-array analysis that new genes (eg, pleiotrophin, FGFR2, TGFβ1) are expressed differently in various subtypes of osteosarcoma. These genes, whose down-regulation or up-regulation is important to the biological behavior of the subtypes of osteosarcoma, may be targeted in the future for novel therapeutic methods.

The incidence of osteosarcoma is increased in several genetic disorders associated with genetic mutations of tumor suppressor genes. In patients with hereditary retinoblastoma (RB1 gene), Li-Fraumeni syndrome (p53 gene), Rothmund-Thomson syndrome (RecQL4 gene) and Werner Syndrome (WRN gene), secondary malignancies—among them osteosarcoma—are common. Osteosarcoma has great chromosomal complexity, with numerous chromosome and gene alterations resulting in various
molecular pathway changes. Some of these molecular alterations contribute to the biological behavior of metastatic cells. Several pathways are shown to affect tumor angiogenesis and cell proliferation (EGFR, PDGF-R, VEGF, IGF-1R, PTH/PTHr, TGF-β, IL-8 and MMPs), 47–51 cell adhesion and migration (integrins, Ezrin, src, CD44, Wnt, Notch), 51,52 and apoptosis resistance (src, NF-kB, Wnt). 51

Our understanding of the molecular basis of osteosarcoma has made great advances over the last few years. New knowledge of the pathogenesis of osteosarcoma contributes significantly to the discovery of novel therapeutic targets for osteosarcoma treatment. Current therapeutic strategies are effective mostly in patients with localized disease rather than patients with metastatic disease. Various preclinical and clinical studies have shown that monoclonal antibodies (eg, monoclonal antibodies against IGF-1R, ezrin, and src) 50 targeting molecules could be a promising future therapeutic strategy because their altered expression plays a critical role in tumor cell behavior and therefore affects the progression of the disease.

Imaging of Spinal Osteosarcomas
Imaging plays an important role both in the depiction and treatment planning of spinal osteosarcomas (Fig. 1–3). Radiologic findings on X-rays show the majority of cases either osteoblastic appearance of the vertebrae (sclerosing osteoblastic osteosarcoma) or osteolysis occurs. A purely lytic pattern is also seen in various subtypes, eg, telangiectatic osteosarcoma with predominant cystic architecture simulating ABC. In 20% of cases a mixed pattern may be found, whereas in 5% no abnormalities can be found. 14 Computed tomography (CT) is superior to plain radiographs in depicting the mineralization pattern of lytic lesions. It has been shown that in 80% of osteolytic cases, CT demonstrates matrix mineralization; CT is superior to both plain radiographs and MR imaging in depicting cortical destruction.

MR imaging signal intensity characteristics are usually nonspecific (Fig. 2). Dense mineralization is demonstrated with low signal on all pulse sequences. 53 Fluid-fluid levels have been described in association with telangiectatic osteosarcoma (Fig. 3). 53–55 As opposed to ABCs, telangiectatic osteosarcomas with prominent fluid filled hemorrhagic spaces are characterized by thick, solid tissue with nodular pattern surrounding the cystic spaces, matrix mineralization, and a more aggressive growth pattern. 55

In addition, expansile remodeling, periosteal reaction with aggressive characteristics, cortical destruction, associated soft tissue mass, and pathologic fractures may be seen (Fig. 3). 55

Staging
When radiologic findings are highly suggestive of sarcoma, tumor extension and metastasis presentation should be investigated. Bone sarcoma’s primary site of metastasis is the lung. 56

According to Enneking staging system, lesions are classified as follows: histologically low-grade intracompartmental (IA); histologically high-grade intracompartmental (IIA); histologically low-grade extracompartmental (IB); and histologically high-grade extracompartmental (IIB). 9,37,38

Grade
In the Enneking system, bone tumors are graded as follows: (i) G0 = benign lesion; (ii) G1 = low-grade malignant lesion; (iii) G2 = high-grade malignant lesion.

The third column of Table 1 is explained below.

Site
In the Enneking system, the site and local extent of bone tumors are classified as follows: (i) T0 = a benign tumor that is confined within a true capsule and the lesion’s anatomic compartment of origin (ie, a benign intracapsular, intracompartmental lesion); (ii) T1 = intracompartmental lesion; (iii) T2 = extracompartmental lesion.

The fourth column of Table 1 is explained; metastatic classification in the Enneking system is as follows: (i) M0 = no regional or distant metastasis and (ii) M1 = regional or distant metastasis.

Staging
Under the Enneking system, malignant tumors are classified into stages I–III, with further subdivisions into A and B. Grade 1 and grade 2 tumors are stage I and stage II, respectively. T1 and T2 tumors are stage A and stage B, respectively. Tumors with distant metastasis are stage III.

Furthermore, the extent of the lesions has been classified according to the surgical staging system for spinal tumors (Weinstein-Boriani-Biagini (WBB)),

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with data from radiographs, CT and MRI scans, as well as surgical reports. The vertebral body is topographically divided in twelve zones similar to the clock hours; five layers beginning from the paravertebral bony compartment until the meningeal layer and the site of the tumor is recorded.

Finally, Tomita staging is as follows: lesion within the vertebral body (I); the lesion extends to the pedicle (II); lesion extends to the whole vertebra (III); extension to epidural space (IV); extension to paravertebral space (V); extension to paravertebral space and neighboring vertebral levels (VI); and extension to multiple levels (VII).57–59

Surgical Treatment

Like osteosarcoma of the extremities, the most effective surgical intervention in the spine is the wide, en-block resection; this surgery is defined as removal of the tumor in a single piece, surrounded by healthy tissue outside the pseudocapsule.60,61 In studies comparing wide surgical resection combined with chemotherapy and radiation, long-term survival rates were higher for these approaches than for conservative treatment alone.14,15,62–66

Although wide en-block resection is the surgery of best results, the optimal resection depends on the location and the extension of the tumor in the spine column. Wide en-block excision should be considered when the tumor does not affect at least one pedicle and there is no evidence of metastatic disease. Tumors, which involve both pedicles, are extended into the vertebral artery foramen or into the lamina, or located into the tip of the odontoid, making en-block excision practically impossible. In such cases intrallesional surgical resection should be considered.11,12,60

During preoperative planning provided by an experienced oncological multi-disciplinary team, potentially scarifying nerve roots, potential motor or sensory deficiencies, and other potential complications such as blood loss, wound problems, implant failure, or local regression, should be taken into serious account and the patient should be informed.11,12,67–69

When the tumor invades the cervical region, the cervical roots (and the Th1) at this area are functionally important; in contrast, for osteosarcoma in the thoracic and thoracolumbar regions damage to these

Figure 1. A 32-year-old female with a proven osteoblastic osteosarcoma arising from the transverse process of the 2nd thoracic vertebra and the left ipsilateral rib. The CT with axial (A), coronal (B) and parasagittal (C) reformations, show the lesion with osteoblastic matrix (arrows).

Figure 2. A 46-year-old male with a proven osteosarcoma arising from the spinous process of the 6th cervical vertebra. The patient presented with acute myelopathy resulting from compression of the lesion. (A) The sagittal T1-w MR image, shows a moderate signal intensity lesion invading the spinous process (open arrows). The lesion displaces anteriorly the cord (thin arrow). The sagittal (B) and transverse (C) T2-w gradient echo MR images show the high intensity lesion (open arrows) and the low signal intensity small matrix calcifications (thin arrows). The contrast enhanced sagittal T1-w (D) and axial fat suppressed T1-w (E) MR images, show the intense and inhomogeneous enhancement of the lesion (open arrows). The lesions abuts the anteriorly displaced spinal cord (thin arrows).
nerves causes less significant neurologic impairment and a solely posterior approach may be enough for en-block resection of the tumor. Tumors located in the lumbar region are more difficult to remove by only the posterior approach below the S2 region. Although challenging, surgical treatment is usually successful.11,12

Non-Surgical Treatment

In general, osteosarcomas represent a rare group of tumors that pose many management challenges. In comparison to primary extremity osteosarcomas, spinal osteosarcoma lesions are harder to treat since local control with surgery and chemotherapy is neither always adequate nor favorable. Survival rates for patients with osteosarcoma are much lower in the spinal affliction in comparison to limb-non-metastatic patients, with 5 year overall survival reaching 30%–40%.14

Non-surgical management strategies of osteosarcoma consist of radiation therapy and chemotherapy.14,61 Due to the proximity to the spinal cord, radiation as a treatment of both sarcomas of the spine and of paraspinal soft tissues is significantly constrained by the radiation tolerance of the spinal cord, which is generally quoted at 45 Gy.64,70 However, this is well below the dose that is required to reliably control most osteosarcomas in the setting of subclinical microscopic disease or with microscopically positive margins or gross residual disease.61,70,71

Radiation for the treatment of osteosarcomas can be employed as neoadjuvant (preoperative), adjuvant (postoperative or intraoperative), or primary local therapy, depending on the resectability of the tumor and the efficacy of chemotherapy. The same classification applies to chemotherapy.71

Table 1.

| Stage | Grade | Site | Metastasis |
|-------|-------|------|------------|
| IA    | G1    | T1   | M0         |
| IB    | G1    | T2   | M0         |
| IIA   | G2    | T1   | M0         |
| IIB   | G2    | T2   | M0         |
| III   | G1 or G2 | T1 or T2 | M1         |

Notes: The Enneking surgical staging system for the staging of malignant bone and soft tissue lesions; it is based on a combination of histologic grade (G), anatomic site (T), and presence or absence of distant metastasis (M). G0 = benign; G1 = low grade malignant; G2 = high grade malignant; T0 = intracapsular; T1 = extracapsular, intracomartmental; T2 = extracapsular, extracomartmental; M0 = no metastasis; M1 = distant metastasis. Stages IA = low grade malignant, intracomartmental (G1, T1, M0); IB = low grade malignant, extracomartmental (G1, T2, M0); IIA = high grade malignant, intracomartmental (G2, T1, M0); IIB = high grade malignant, extracomartmental (G2, T2, M0); III = with metastases (G1 or 2, T1 or 2, M1).
Neoadjuvant radiotherapy can be delivered prior to the resection of osteosarcomas of the spine. In some situations, neoadjuvant radiation may be applied with the hopes of downsizing the tumor; this is done in order to facilitate surgical resection, making it safer and more feasible. Adjuvant radiation can be applied after surgical resection, for patients with osteosarcomas with positive or inadequate margins. Postoperative radiation improves survival for some patients with osteosarcoma of the spine. Radiation therapy as primary local therapy without surgery should be restricted to medically inoperable patients and can be useful in securing local control of the disease. However, unresected and unresectable sarcomas require higher doses of radiation therapy in order to achieve the best chances of local control, thereby increasing the possibility of significant normal tissue toxicity. New approaches and high technology techniques aim to minimize acute as well as late toxicity of the normal tissue after radiotherapy and may represent a promising alternative when surgery is not applicable.

Intensity-modulated photon radiation therapy (IMRT) is increasingly being employed for the treatment of challenging osteosarcomas of the axial skeleton because of its ability to adjust dosage and spare normal tissues from high-dose radiation, producing encouraging clinical results. The application of higher radiation doses to spinal tumors, even in close proximity to the spinal cord, in combination with lower radiation doses to the spinal cord, which do not exceed the radiation tolerance, is now possible with the use of IMRT.

Proton beams can also be subjected to intensity modulation (IMPT), granting the potential to further optimize dose distribution. With the ability to spare the spinal cord and adjacent tissues, such as the kidney, lung, heart, esophagus, and bowel, proton radiation therapy offers advantages for the treatment of spinal osteosarcomas. Sarcomas of the cervical spine were among the first tumors to be treated with protons systematically; spinal tumors comprise one of the anatomic sites at which excellent clinical results have been achieved. Combination of high-dose photon/proton radiation therapy can also be applied to inoperative osteosarcomas involving the spine and paraspinal tissues.

Heavy charged particles have also been thought to be advantageous, since there appears to be an increased energy deposition in the abnormal tissue; they have thus been used for the treatment of sarcomas, with promising results. Current interest in heavy charged particles is focused on carbon ions; carbon ion beams possess unique physical and biological properties. They have a large energy release on targets, as well as insignificant scatter in tissues, resulting in an excellent physical dose deposition. Therefore, carbon ion radiotherapy provides good local control and a survival advantage; the morbidity rate has so far been quite acceptable. It seems to be safe and efficacious as a valid local treatment for osteosarcomas of the spine, which are not eligible for surgical resection. Targeted internal radiotherapy with high-dose 153Samarium-ethylenediaminetetramethylene-phosphonate (153Sm-EDTMP, Quadramet) may also offer an alternative for some patients with inoperable osteosarcomas.

There are only a few reports focused on long-term spinal osteosarcoma survivors who have after receiving chemotherapy with or without radiation therapy. Survival rate can be increased by a combination of complete tumor resection, chemotherapy, and radiation. Neoadjuvant chemotherapy and radiotherapy, in combined use, have also been investigated to determine whether they improve resectability.

Compared to solely surgical treatment or solely post-operative chemotherapy, neoadjuvant chemotherapy for 8–12 weeks prior to surgery offers patients higher response, higher survival rates, and more time until metastases occur. Long-term survival of 16% was seen with uniquely local treatment. Despite the amelioration of survival in osteosarcoma patients, no consensus on a standard chemotherapy approach has been formed. The usual medication includes adriamycin (doxorubin), cisplatin, and high-dose methotrexate and/or ifosfamide. Meta-analysis of single agent phase II studies has shown high response rates for adriamycin (43%), ifosfamide (33%), methotrexate (32%), and cisplatin (26%), but only 4% for etoposide. It is to be emphasized that intensifying the dosage beyond a certain level does not improve outcome. The importance of doxorubin in doses of 390–450 mg/m² has been highlighted. High dose methotrexate appears to be an unnecessary hardship but more studies are needed. In a recent meta-analysis study to determine the most effective chemotherapy regimen for localized high-grade osteosarcoma, protocols of 3 active substances were found to be the answer. The 5-year
event free survival was calculated to 48% for 2-drug regimens and 58% for 3-drug regimens; the 5-year overall survival rates were 62% and 70%, respectively. It was shown that regimens with methotrexate plus adriamycin plus cisplatin (plus ifosfamide) had significantly better outcome. Unfortunately, changing drugs or intensifying treatment postoperatively has been shown to be ineffective for the treatment of poor responders. The molecular profile of this ailment is incomplete. At the moment, there are few molecular elements that serve as effective therapeutic targets or as accurate prognosis for the outcome of chemotherapy. It is known that overexpression of alkaline phosphatase, lactate dehydrogenase, and human epidermal growth factor receptor 2 can predict poor outcome. Further research is required in order to produce efficacious targeted therapies. The latest introductions to the chemotherapeutical arsenal that raise hope for the future are interferon and immunomodulators such as liposomal muramyl tripeptide phosphatidylethanolamine (Mifamurtide—MTP), which has been approved by the European Medicines Agency.

Despite the small number of studies concerned specifically with spinal osteosarcoma, it is clear that survival rates are much lower in comparison to limb-non-metastatic patients. This is most likely the outcome of poor respectability and poor response to non-surgical treatment, with 5-year over-all survival reaching 30%–40%. From a radiotherapeutic perspective, the main focus of current research is to improve targeting of therapy in order to achieve a higher percentage of tumor control for a given level of normal tissue toxicity or a similar percentage of tumor control with less normal tissue toxicity. From a systemic therapy perspective, current chemotherapy continues to result in high toxicity. There are an increasing number of new technologies and treatment options used for the treatment of osteosarcomas; experience on the matter continues to grow. However, the long-term safety of these approaches for patients with osteosarcomas of the spine needs to be monitored. The evaluation and management of patients with sarcoma in a multi-disciplinary study is crucial in order to optimize treatment options. In light of this, the EURAMOS-1 trial is eagerly expected as part of the required international collaboration.

Conclusion
In conclusion, osteosarcoma of the spine, as a primary malignancy, is more common in adolescents and young adults. Osteosarcoma of the spine tends to occur in older age groups than osteosarcoma of the extremities (mean age of 38); however, after-complication, incidences are higher in the elderly population, particularly in the seventh decade of life. A slightly increased incidence of spinal osteosarcoma in females has also been noted, unlike primary osteosarcomas in general. Osteogenic sarcoma of the spine represents 3.6%–14.5% of primary spinal tumors and 0.85%–3% of all osteosarcomas.

Histologically, the subtypes of spinal osteosarcoma that have been asserted are chondroblastic and osteoblastic (the most common), small cell tumor, telangiectatic, and fibroblastic tumor (the most rare). CT is superior to plain radiographs and MR imaging in depicting cortical destruction. Survival rates of patients with osteosarcoma are much lower in the spinal affliction in comparison to limb-non-metastatic patients, with 5 year overall survival reaching 30%–40%. Treatment options must be chemotherapy/radiotherapy and most importantly en-block resection or at least marginal surgery, the latter only when the tumor is operable. Postoperative radiotherapy may be beneficial to some patients. Combination therapies, including surgery, radiation and chemotherapy, achieve adequate short-term survival rates. However, the overall prognosis remains poor for this particular subset of sarcomas.

Author Contributions
Analyzed the data: GD, AK, AK, SL, SL. Wrote the first draft of the manuscript: GD, AK, AK, SL, SL. Contributed to the writing of the manuscript: PK, EP, KA. Agree with manuscript results and conclusions: GD, AK, AK, SL, SL PK, EP, KA. Jointly developed the structure and arguments for the paper: GD, AK, AK, SL, SL PK, EP, KA. Made critical revisions and approved final version: PK, EP, AK, KA. All authors reviewed and approved of the final manuscript.

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References

1. McKenna RJ, Swinn CP, Soong KY, Higinbotham NL. Sarcomata of the osteo-sarcomatous series (osteosarcoma, fibrosarcoma, chondrosarcoma, parosteal osteosarcoma and sarcoma arising in abnormal bone). An analysis of 552 cases. J Bone Joint Surg. 1966;48(1):1–26.
2. Sissons HA. The WHO classification of bone tumors. Recent Results Cancer Res. 1976;54:104–8.
3. Huvos AG. Bone Tumors: Diagnosis, Treatment, and Prognosis; Saunders; 1991.
4. Barwick KW, Huvos AG, Smith J. Primary osteogenic sarcoma of the vertebral column: a clinicopathologic correlation of ten patients. Cancer. 1980;46(3):595–604.
5. Shives TC, Dahlín DC, Sim FH, Pritchard DJ, Earle JD. Osteosarcoma of the spine. J Bone Joint Surg Am. 1986;68(5):660–8.
6. Weinstein JN, McLain RF. Primary tumors of the spine. Spine (Phila Pa 1976). 1987;12(9):843–51.
7. Sundaresan N, Rosen G, Huvos AG, Krol G. Combined treatment of osteosarcoma of the spine. Neurosurgery. 1988;23(6):714–9.
8. Drehorn CR, Newman RJ, Hardy GJ, Dickson RA. Primary tumors of the axial skeleton. Experience of the Leeds Regional Bone Tumor Registry. Spine (Phila Pa 1976). 1990;15(2):137–40.
9. Kelley SP, Ashford RU, Rao AS, Dickson RA. Primary bone tumours of the spine: a 42-year survey from the Leeds Regional Bone Tumour Registry. Eur Spine J. 2007;16(3):405–9.
10. Cade S. Osteosarcoma; a study based on 133 patients. J R Coll Surg Edinb. 1955;10(2):79–111.
11. Fischgrund J, Jeffrey, editors. Orthopaedic Knowledge Update 9 (v. 9). Amer Academy of Orthopaedic; 2008.
12. Fischgrund J. Orthopaedic Knowledge Update 9. American Academy of Orthopaedic Surgeons; 2008:635.
13. Bielack SS, Wulff B, Delling G, et al. Osteosarcoma of the trunk treated by multimodal therapy: experience of the Cooperative Osteosarcoma study group (COSS). Med Pediatr Oncol. 1995;24(1):6–12.
14. Orkú T, Fiege S, Liljencivist U, et al. Osteosarcoma of the spine: experience of the Cooperative Osteosarcoma Study Group. Cancer. 2002;94(4):1069–77.
15. DeLaney TF, Park L, Goldberg SI, et al. Radiotherapy for local control of osteosarcoma. Int J Radiat Oncol Biol Phys. 2005;61(2):492–8.
16. Klein MJ, Siegal GP. Osteosarcoma: anatomic and histologic variants. Am J Clin Pathol. 2006;125(4):555–81.
17. Huang TL, Cohen NJ, Sahgal S, Tseng CH. Osteosarcoma complicating Paget’s disease of the spine with neurologic complications. Clin Orthop Relat Res. 1979;141:260–5.
18. Sharma H, Mehdi SA, MacDuff E, Reece AT, Jane MJ, Reid R. Paget’s sarcoma of the spine: Scottish Bone Tumor Registry experience. Spine (Phila Pa 1976). 2006;31(12):1344–50.
19. Sofka CM, Ciavarra G, Saboico G, Gielman B. Paget’s disease of the spine and secondary osteosarcoma. Hss J. 2006;2(2):188–90.
20. Mirabello L, Troisi RJ, Savage SA. Osteosarcoma incidence and survival rates from 1973 to 2004: data from the Surveillance, Epidemiology, and End Results Program. Cancer. 2009;115(7):1531–43.
21. Price CH. Osteogenic sarcoma; an analysis of the age and sex incidence. Br J Cancer. 1955;9(4):558–74.
22. Glass AG, Fraumeni JF Jr. Epidemiology of bone cancer in children. J Natl Cancer Inst. 1970;44(1):187–99.
23. Larsson SE, Lorentzon R. The incidence of malignant primary bone tumours in relation to age, sex and site. A study of osteogenic sarcoma, chondrosarcoma and Ewing’s sarcoma diagnosed in Sweden from 1958 to 1968. J Bone Joint Surg Br. 1974;56B(3):534–40.
24. Guney YG, Severson RK, Davis S, Robison LL. Incidence of cancer in children in the United States. Sex-, race-, and 1-year-age-specific rates by histologic type. Cancer. 1995;75(8):2186–95.
25. Stillier CA, Bielack SS, Sundt G, Stelianova-Fouchier E. Bone tumours in European children and adolescents, 1978–97. Report from the automated childhood cancer information system project. Eur J Cancer. 2006;42(13):2124–35.
26. Mirabello L, Troisi RJ, Savage SA. International osteosarcoma incidence patterns in children and adolescents, middle ages and elderly persons. Int J Cancer. 2009;125(1):229–34.
27. Eyre R, Felthower RG, James PW, et al. The epidemiology of bone cancer in 0–39 year olds in northern England, 1981–2002. BMC Cancer. 2010;10:357.
28. Savage SA, Mirabello L. Using epidemiology and genomics to understand osteosarcoma etiology. Sarcoma. 2011:2011:548151.
29. Hansen MF, Seton M, Merchant A. Osteosarcoma in Paget’s disease of bone. J Bone Miner Res. 2006;21 Suppl 2:S58–63.
30. Li FP, Fraumeni JF Jr. Soft-tissue sarcomas, breast cancer, and other neoplasms. A familial syndrome? Am Intern Med. 1969;71(4):747–52.
31. Schneider K, Garber J. Li-Fraumeni Syndrome. 1993. In: Pagon RA, Bird TD, Dolan CR, Stephens K, Adam MP, editors. Source Gene Reviews™ [Internet]. Seattle (WA): University of Washington, Seattle; 1993–9.
32. Kleinerman RA, Tucker MA, Abramson DH, Seddon JM, Tarone RE, Fraumeni JF Jr. Risk of soft tissue sarcomas by individual subtype in survivors of hereditary retinoblastoma. J Natl Cancer Inst. 2007;99(1):24–31.
33. Wang LL, Levy ML, Lewis RA, et al. Clinical manifestations in a cohort of 41 Rothmund-Thomson syndrome patients. Am J Med Genet. 2001;102(1):11–7.
34. Goto M, Miller RW, Ishikawa Y, Sugano H. Excess of rare cancers in Werner syndrome (adult progeria). Cancer Epidemiol Biomarkers Prev. 1996;5(4):239–46.
35. Ishikawa Y, Miller RW, Machinami R, Sugano H, Goto M. Atypical osteosarcomas in Werner Syndrome (adult progeria). Jpn J Cancer Res. 2000;91(12):1345–9.
36. Clinton C, Gazda HT, Diamond-Blackfan Anemia. 1993. In: Pagon RA, Bird TD, Dolan CR, Stephens K, Adam MP, editors. Source Gene Reviews™ [Internet]. Seattle (WA): University of Washington, Seattle; 1993–2009.
37. Sanz MM, German J. Bloom’s Syndrome. 1993. In: Pagon RA, Bird TD, Dolan CR, et al. editors. GeneReviews™[Internet]. Seattle (WA): University of Washington, Seattle; 1993–
38. Fletcher CDM, Unni KK, Mertens F, World Health O, International Academy of P. Pathology and Genetics of Tumours of Soft Tissue and Bone: IARC Press; 2002.
39. Campanacci M, Picci P, Gherlinzoni F, Guerra A, Bertoni F, Neff JR. Parosteal osteosarcoma. J Bone Joint Surg Br. 1984;66(3):313–21.
40. Sheh DS, Yasko AW, Raymond AK, et al. Conventional and dedifferentiated parosteal osteosarcoma. Diagnosis, treatment, and outcome. Cancer. 1996;78(9):1592–9.
41. Sheth DS, Yasko AW, Raymond AK, et al. Conventional and dedifferentiated parosteal osteosarcoma. Diagnosis, treatment, and outcome. Cancer. 2002;94(4):1069–77.
42. Weiss A, Khoury JD, Hoffer FA, et al. Telangiectatic osteosarcoma: the Spinal osteosarcoma
