

Osteosarcoma: Current treatment trends and outcome

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Abstract: Osteosarcoma is more common in pediatric patients and in males. In the US there is ethnic variation more common in individuals of black than white. Frequent causes include: familial cases, bone dysplasia, Fraumeni syndrome, and Rothmund Thomson syndrome. The role of water fluoridation is unclear. Diagnosis begins with X-ray, CT scan, PET scan, and bone scan, MRI, and biopsy. The biopsy of suspected osteosarcoma outside the facial region should be performed by an orthopedic oncologist. Conventional therapy is a combination of limb-salvage orthopedic surgery when possible (or amputation in some cases) and combination of high dose methotrexate with other drugs added. In stage three osteosarcoma with lung metastases depends on the resectability of the primary tumor and lung nodules, degree of necrosis of the primary tumor, and number of metastases. Overall prognosis is about 30%. Osteosarcoma is the common bone tumor in dogs especially in aged large breed dogs.

CT guided radiofrequency ablation and thermal ablation techniques are frequently used in bone tumor. Sarcomas are quite rare in the US, and are usually treated surgically, radiotherapy and chemotherapy. The US and the UK July is the sarcoma awareness month

Keywords: Osteosarcoma, Bone cancer, Sarcoma, Therapy, Prognosis.

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I. Introduction

Osteosarcoma (OS) or osteogenic sarcoma (OGS) is a cancerous tumor in a bone, specifically, it is an aggressive malignant neoplasm that arises from primitive transformed cells of mesenchymal origin (and thus a sarcoma) and that exhibits osteoblastic differentiation and produces malignant osteoid [1]. Osteosarcoma is the most common histological form of primary bone cancer [2]. It is most prevalent in teenagers and young adults [3]. Osteosarcoma is the eighth most common form of childhood cancer, comprising 2.4% of all malignancies in pediatric patients, and about 20% of all primary bone cancers [2]. Incidence rates for osteosarcoma in U.S. patients under 20 years of age are estimated at 5.0 per million per year in the general population, with slight variation between individuals of black, Hispanic, and white ethnicities (6.8, 6.5, and 4.6 per million per year respectively). It is slightly more common in males (5.4% per million per year) than in females (4.0 per million per year) [2]. Around 300 to 900 people diagnosed in the United States will die each year. A second peak in incidence occurs in the elderly. Usually associated with an underlying bone pathology such as Paget's disease of bone [2]. It originates more frequently in the metaphyseal region of tubular long bones, 40% occurring in the femur, 19% in tibia, and 10% in humerus. About 8% of all cases occur in the skull and jaw, and another 8% in pelvis [2]. Surgery en bloc resection of the cancer, is the treatment of choice [4]. Prognosis is divided into three groups, stage I, stage II, and stage III, [5, 6]. Long term survival have improved and approximated 68% in 2009 [2]. The paper reviews the current notions, causes, diagnosis and therapy of Osteosarcoma.

II. Predisposing factor

Several research groups are investigating cancer stem cells and their potential to cause tumors along with genes and proteins causative in different phenotypes [7]. Radiotherapy for unrelated conditions may be a rare cause [8]. Frequent contributory factor includes:

2.1. Familial cases where the deletion of chromosome 13q14 inactivates the retinoblastoma gene is associated with high risk of osteosarcoma development.

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2.2. Bone dysplasia, including Paget's disease of bone, fibrous dysplasia, enchondromatosis, and hereditary multiple exostoses, increase the risk of osteosarcoma.

2.3. Li-Fraumeni syndrome (germline TP53 mutation) is a predisposing factor for osteosarcoma development.

2.4. Rothmund-Thomson syndrome (i.e. autosomal recessive association of congenital bone defects, hair and skin dysplasias, hypogonadism, and cataracts), is associated with increased risk of this disease.

2.5. Large doses of Sr-90 emission from nuclear reactor, nicknamed bone seeker increases the risk of bone cancer and leukemia in animals, and is presumed to do so in people [9].

2.6. Association with fluoridation. Despite persistent rumors otherwise, there is no clear association between water fluoridation and cancer or deaths due to cancer, both for cancer in general and also specifically for bone cancer and osteosarcoma [10]. Series of research concluded that concentrations of fluoride in water doesn't associate with osteosarcoma. The beliefs regarding association of fluoride association exposure and osteosarcoma stem from a study of US National Toxicology program in 1990, which showed uncertain evidence of association of fluoride and osteosarcoma in male rats. But there is no solid evidence of cancer-causing tendency of fluoride in mice [11]. Fluoridation of water is practiced around the world to improve citizen's dental health. It is also deemed as major health success [12]. Fluoride concentration levels in water supplies are regulated, such United States Environmental Protection Agency regulates fluoride levels to not be greater than a 4 milligrams per liter [13]. Actually, water supplies already have natural occurring fluoride, but many communities chose to add more to reduce tooth decay [14]. Fluoride also known for its ability to cause new bone formation [15]. Yet, further research shows no osteosarcoma risks from fluoridated water in humans [16]. Most of the research involved counting number of osteosarcoma patients cases in particular areas which has difference concentrations of fluoride in drinking water [17]. The statistical analysis of the data shows no significant difference in occurrences of osteosarcoma cases in different fluoridated regions [18]. Another important research involved collecting bone samples from osteosarcoma patients to measure fluoride concentration and compare them to bone samples of newly diagnosed malignant bone tumors. The result is that the median fluoride concentrations in bone samples of osteosarcoma patients and tumor control are not significantly different [19]. Not only fluoride concentration in bones, fluoride exposure of osteosarcoma patients also proven to be not significantly different from healthy people [20].

III. Disease progression

Osteosarcoma tends to occur at the site of bone growth, presumably because the proliferation makes osteoblastic cells in this region prone to acquire mutations that could lead to transformation of cells (the RB gene and p53 gene are commonly involved). Due to this tendency, high incidence of osteosarcoma is seen in some large breed dogs (St. Bernards and Great Danes). The tumor may be localized at the end of long bone (commonly in the metaphysis). Most often it affects the proximal end of tibia or humerus, or distal end of femur. Osteosarcoma tends to affect regions around the knee in 60% of cases, 15% around in hip, 10% at the shoulder, and 8% in the jaw. The tumor is solid, hard, irregular ("fir-tree" "moth-eaten" or "sun-burst" appearance on x-ray examination) due to the tumor spicules of calcified bone radiating in right angles. These right angles form what is known as a Codman triangle, which is characteristic but not diagnostic of osteosarcoma. Surrounding tissues are infiltrated.

Microscopically: The characteristic features of osteosarcoma are presence of osteoid (bone formation) within the tumor. Tumor cells are very pleomorphic (anaplastic), some are giant, numerous atypical mitoses. These cells produce osteoid describing irregular trabeculae (amorphous, eosinophilic/pink) with or without central calcification (hematoxylinophilic/blue, granular)-tumor bone. Tumor cells are included in the osteoid matrix. Depending on the features of the tumor cells present (whether they resemble bone cells), the tumor can be sub-classified. Osteosarcoma may exhibit multinucleated osteoclast-like giant cells [21].

IV. Diagnosis

Family physician and orthopedists rarely see a malignant bone tumor (most bone tumors are benign). The route to osteosarcoma diagnosis usually begins with X-ray, continue with a combination of scans (CT scan, PET scan, bone scan, RI) and ends with a surgical biopsy. A characteristic often seen in an X-ray is Codman's triangle, which is basically a sub-periosteal lesion, formed when the periosteum is raised due to the tumor. Films are suggested are suggested, but bone biopsy is the only method to determine whether a tumor is malignant or benign. Most times, the early signs of osteosarcoma are caught on X-rays taken during routine dental check-up. Osteosarcoma frequently develops in the mandible (lower jaw); accordingly. Dentists are trained to look for signs that may suggest osteosarcoma. Even though radiographer findings for cancer vary

greatly, one usually sees a symmetrical widening of the periodontal ligament space. If the dentist has reason to suspects osteosarcoma or another underlying disorder, he or she would refer the patient to an Oral & Maxillofacial surgeon for biopsy. **Abiopsy** of suspected osteosarcoma outside of the facial region should be performed by **an** orthopedic oncologist. The American Society states: "Probably in no other cancer is it as important to perform this procedure properly. An improperly performed biopsy may make it difficult to save the affected limb from amputation". It may also metastasise to lungs, mainly appearing on the chest X-ray as solid or multiple round nodules most common at lower regions.

Various types of osteosarcoma (OS):

- i).Conventional osteoblastic,chondroblastic,fibroblastic OS
- ii).Telagiectatic OS,
- iii).Small cell OS
- .iv).Lower grade central OS.
- v)Periosteal OS.
- vi)Paraosteal OS.
- vii).Secondary OS
- viii).High grade surface OS
- xi).Extra -skeletal OS.[21].

V. Therapy and Prognosis

A complete radical,enbloresection of the cancer, is the treatment of choice in osteosarcoma[2].Although 90% of the patients are able to have limb-salvage surgery,complications,particularlyinfection, prosthetic loosening and non-union,or local tumor recurrence may cause the need for further surgery or amputation.Mifmurtide is used after a patient has had surgery to remove tumor and together with chemotherapy to kill remaining cancer cells to reduce the risk of cancer recurrence. Also, option to have rotationplasty after the tumor is taken out exists [4].Patients with osteosarcoma are best managed by a medical oncologist and an orthopedic oncologist experienced in managing sarcomas. Current standard treatment is to use neoadjuvant chemotherapy (chemotherapy given before surgery) followed by surgical resection. The percentage of tumor cell necrosis (cell death) **seen** in the tumor after surgery given an idea of the prognosis and also lets oncologist know if the chemotherapy regimen should be altered after surgery. Standard therapy is a combination of limb-salvage orthopedic surgery when possible(or amputation in some cases) and a combination of high dose methotrexatewithlenocovrinresue,intra-arterial cisplatin,adriamycinh,ifosfamide with mesna.BCD(bleomycin,cyclophosphamide,dactinomycin),etoposide,andmuramyltripeptide.Rotationplasty may be used.Ifosfamide can be used as an adjuvant treatment if the necrosis rate is low. Despite the success of chemotherapy for osteosarcoma, it has one of the lowest survival rates for pediatric cancer. The best reported 10-year survival rate is 92%,the protocol used is an aggressive intra-arterial regimen that individualizes therapy based on arteriography response[22].

Three years event free survival ranges from 50% to 75%,and five year survival ranges from 60% to 85% in some studies.Overall,65-70% patients treated five years ago will be alive[23].These survival rates are overall averages and vary greatly depending on the individual necrosis rates.Filgrastim or pegfilgrastin**help** with white blood cell counts and neutrophil counts. **Blood transfusion** andepoetin alfa help with anemia. **Computational analysis** on a panel of Osteosarcoma cell lines identified new shared and specific **therapeutic targets** (proteomic and genetic) in Osteosarcoma,while phenotypes showed an increased role of tumor microenvironments [24].

Prognosis

Prognosis of osteosarcoma is divided into three groups:

a).Stage one, osteosarcoma is rare and includes parosteal osteosarcoma or low grade central osteosarcoma.It has an excellent prognosis(>90%) with wide section.

b). Stage two the prognosis depends on the site of the tumor (proximal tibia,femur,pelvis,etc), size of tumor mass, and the degree of necrosis from **neoadjuvant chemotherapy**. Other pathological factors such as the degree ofp-glycoprotein,whether the the tumor is cxcr4-positive[5] or Her2-positive are also important, as these are associated with distant metastases to the lung. The prognosis for patients with metastatic osteosarcoma improves with longer times to metastases (more than 12 months to 4 months),a smaller number of metastases, and their resectability. It is better to have fewer metastases than longer time to metastases, Those with a longer length of time(more than 24 months) and fewer nodules(two or fewer)have the best prognosis, with two year survival

after metastases of 50%, five year of 40% and 10 year of 20%. If metastases are both local and regional, the prognosis is worse.

c). Stage three. In initial stage of stage three osteosarcoma with lung metastases depends on the resectability of the primary tumor and lung nodules, degree of necrosis of the primary tumor, and maybe the number of metastases. Overall survival prognosis is about 30% [6].

Deaths due to malignant neoplasms of the bones and joints accounts for an unknown number of childhood cancer deaths. Mortality rates due to osteosarcoma have been declining at about 1.3% per year. Long term survival probabilities for osteosarcoma have improved dramatically during the late 20th century and approximated 68% in 2009 [2].

VI. Osteosarcoma in Animals

Osteosarcoma is the most common bone tumor in dogs and typically afflicts middle aged large giant breed dogs such as Irish Wolfhounds, German Shepherd, Rottweiler, mountain breeds (Great Pyrenees, St. Bernard, Leonberger, Newfoundland), Doberman Pinschers and Great Danes. It has a 10 fold greater incidence in dogs than humans [25]. A hereditary base has been shown in St. Bernard dogs [26]. Spayed/neutered dogs have twice the risk of intact ones to develop osteosarcoma [27]. Infestation with the parasite *Spirocercalupi* can cause osteosarcoma of the esophagus [28].

6.1. Signs and symptoms: The most commonly affected bones are the proximal humerus, the distal radius, the distal femur, and the tibia [29,], following the basic premise “far from the elbow, close to knee”. Other sites include the ribs, the mandible, the spine, and the pelvis. Rarely osteosarcoma may arise from soft tissue (extraskelatal osteosarcoma). Metastases of tumors involving the limb bones is very common, usually to the lungs. The tumor causes a great deal of pain, and can even lead to fracture of the affected bones. As with human osteosarcoma; bone biopsy is the definitive method to reach a final diagnosis. Osteosarcoma should be differentiated from other bone tumors and a range of other lesions, such as osteomyelitis. Differential diagnosis of osteosarcoma of the skull in particular includes, among others, chondrosarcoma and the multilobular of bone [30,31].

Osteosarcoma is also the most common bone tumor in cats, although not as frequently encountered and most typically affects the rear legs. The cancer is generally less aggressive in cats than in dogs, so amputation can lead to a significant survival time in many affected cats, though post amputation chemotherapy is recommended when high grade is confirmed on histologically [29].

6.2. Therapy and outcome: Amputation is the initial treatment, although this alone will not prevent metastases. Chemotherapy combined with amputation improves the survival time, but dogs still die within a year. Surgical techniques designed to save the leg (limb sparing procedures) do not improve prognosis [29].

VII. Bone tumor and Sarcoma

7.1. Bone tumor: Bone tumor is a neoplastic growth of tissue in bone. Abnormal growths found in the bone can be benign (non-cancerous) or malignant (cancerous). Average five-year survival in the United States after being diagnosed with bone and joint cancer is 67% [32]. Primary tumors of bone can be divided into benign tumors and cancers. Common benign tumors may be neoplastic, developmental, traumatic, infections, or inflammatory in etiology. Some benign tumors are not true neoplastic, but rather represent hamartomas, namely the osteochondroma. The most common locations for primary tumors, both benign and malignant include the distal femur and proximal tibia (around the knee joint). Examples of benign bone tumors include osteoma, osteoid osteoma, osteochondroma, osteoblastoma, enchondroma, giant cell tumor of bone, aneurysmal bone cyst, and fibrous dysplasia of bone. Malignant primary bone tumors include osteosarcoma, chondrosarcoma, Ewing's sarcoma, fibrosarcoma and other types. While malignant fibrous histiocytoma (MFH) - now generally called “pleomorphic undifferentiated sarcoma” - primary in bone is known to occasionally, current paradigms tend to consider MFH a “wastebasket” diagnosis, and the current trend is toward using specialized studies (i.e. genetic and immunocytochemical tests) to classify these undifferentiated tumors into other classes [33].

7.2. Clinical manifestation: The most common symptom of bone tumors is pain, which will gradually increase over time. A person may go weeks, months, and sometimes years before seeking help, pain increases with the growth of the tumor. Additional symptoms may include, fatigue, weight loss, anemia, and/or unexplained bone fractures. Many patients may not experience any symptoms, except for a painless mass. Some bone tumors may weaken the structure of the bone, causing pathologic fractures [34].

7.3. Therapy: Chemotherapy and radiotherapy are effective in some tumors (such as Ewing's sarcoma) but less so in others (such as chondrosarcoma) [35]. There is a variety of chemotherapy treatment protocols for bone tumors. The protocol with best reported survival in children and adults is an intra-arterial protocol where tumor response is tracked by serial arteriogram. When tumor response has reached >90% surgical intervention is planned [36,37]. Over the past two decades, CT guided **radiofrequency ablation** has emerged as less invasive alternative to surgical resection in the care of benign tumors, most notably osteoid osteoma [38]. It has been shown in numerous studies to be less invasive and expensive, to result in less bone destruction and to have equivalent safety and efficacy to surgical, with 66% to 96% of patients reporting freedom from symptoms [39-41]. While initial success rates with RF are high, symptom recurrence after RFA treatment has been reported with some studies demonstrating a recurrence rate similar to surgical treatment [42]. Thermal ablation techniques are also increasingly being used in the palliative treatment of painful metastatic bone disease [43].

7.4. Drug therapy: One of the main concern is bone density and bone loss. On-hormonal bisphosphonates increases bone strength and are available as once-week prescription pills. Metastron also known as strontium-89 chloride is an intravenous medication given to help with the pain and can be given in three month intervals. Generic Strontium chloride Sr-89 Injection UPS manufactured by BiO-Nucleonics Inc., it is the generic version of Metastron [44].

7.5. Sarcoma: A sarcoma is a cancer that arises from transformed cells of mesenchymal origin. The term is from the Greek, Sarx meaning "flesh" [45]. Sarcomas are quite rare with only 15,000 new cases per year in the United States [46]. Sarcomas therefore represent about one percent of the 1.5 million new cancer diagnoses in that country each year [47]. Sarcomas affect people of all ages. Approximately 50% of bone sarcomas and 20% of soft tissue sarcoma are diagnosed in people under age of 35 [48]. The malignant tumors made of cancellous bone, cartilage, fat, muscle, vascular, or hematopoietic tissues are by definition, considered sarcomas. This in contrast to a malignant tumor originating from epithelial cells, which are termed carcinoma. Human sarcomas are quite rare. Common malignancies, such as breast, colon and lung cancer, are always carcinoma [45].

7.5.1. Diagnosis: Sarcomas are given a number of names based on the type of tissue that most closely resemble. For example, osteosarcoma resemble bone, chondrosarcoma resemble cartilage, lip sarcoma resemble fat, and leiomyosarcoma resemble smooth muscle. In addition to being named based on the tissue of origin, sarcomas are also assigned a grade (low, intermediate, or high) based on the presence and frequency of certain cellular and subcellular characteristics associated with malignant biological behavior. Low sarcomas are usually treated surgically, although sometimes radiation therapy or chemotherapy are used. Intermediate and high grade sarcomas are more frequently treated with a combination of surgery, chemotherapy and/or radiation therapy [49]. Since higher grade tumors are more likely to undergo metastasis (invasion and spread to loco-regional and distant sites), they are treated more aggressively. The recognition that many sarcomas are sensitive to chemotherapy has dramatically improved the survival of patients. For example, the era before chemotherapy, long term survival for patients with localized osteosarcoma was only approximately 20 %, but now has risen to 60-70% [50]. In the US, July is widely recognized as Sarcoma Awareness Month [51]. The UK has a Sarcoma Awareness Week July led Sarcoma UK: the bone and soft tissue cancer charity [52].

VIII. Conclusions

Osteosarcoma is a malignant growth in a bone. In US disease is more common in patients under 20 years of age. Surgery-resection of the cancer is the treatment of choice. Better prognosis in stage one with long term survival than in stage three.

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