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Review Article

An Update on the Diagnosis, Treatment and Prognosis in Osteosarcoma

Rajeshwar Nath Srivastava[1]*, Priyanka Sharma[2], Saloni Raj[1], Lavini Raj[3], Mukesh Dwivedi[1], Dharmendra Kumar[1] and Wahid Ali[2]

[1]Department of Orthopaedic Surgery, King George's Medical University, Lucknow, Uttar Pradesh, India

[2]Department of Pathology, King George's Medical University, Lucknow, Uttar Pradesh, India

[3]Hult International Business School, USA

***Corresponding Author:** Rajeshwar Nath Srivastava, Professor, Department of Orthopaedic Surgery, King George's Medical University, Lucknow, Uttar Pradesh, India.

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Abstract

The most common primary bone cancer is Osteosarcoma, a neoplasm thought to arise from bone-forming mesenchymal stem cells. Musculoskeletal radiologists, pathologists and clinicians are needed to interpret imaging findings and tissue samples to make a definitive diagnosis and establish a prognosis for the better enhancement towards good results with more prolonged disease-free survival, including imagery and histological profile, to make an accurate diagnosis and decide the best course of treatment, it's essential to compare gross, radiographic, and microscopic findings. If the results and quality of life are to be improved, an interprofessional team approach is needed.

Keywords: Osteosarcoma; National Comprehensive Cancer Network-2021; American Joint Committee on Cancer (AJCC); Malignant Musculoskeletal Tumors; Nuclear Imaging; Magnetic Resonance Imaging; Body Mass Index

Abbreviations

DOAJ: Directory of Open Access Journals; OS: Osteosarcoma; ALP: Alkaline Phosphates; LDH: Lactate Dehydrogenase; MRI: Magnetic Resonance Imaging; CT: Computed Tomography; PET: Positron Emission Tomography; Tc99 MDP: Scan-Tc99 Methylenediphosphonate; AJCC: American Joint Committee on Cancer; BMI: Body Mass Index; CI: Confidence Interval

Introduction

Osteosarcoma (OS) is a high-grade skeletal malignancy characterized by the accumulation of immature osteoid matrix by mesenchymal spindle cells [1,2]. It is a primary malignant bone tumour of 3.4 per million people per annum worldwide [3]. Classic OS had a five-year survival rate of 20% in the twentieth century, while using adjuvant chemotherapy in the treatment of OS improved survival rates to 50% in 1970 [4-6]. Amputation was the surgical treatment for high-grade OS in the mid-1970s. By 1990, high-grade operating systems had shifted their emphasis to chemotherapy and limb salvage, resulting in a current survival rate of more than 65% [7]. The occurrence of OS is bimodally distributed through generation. Although long extremity bones remain the most common site for OS after the age of 60 years, they are no longer accountable for most cases due to increased primary tumour site diversity. Craniofacial and axial tumours become more prevalent as people get older, ac-

counting for 40% of all OS cases after 60 years of age, up from less than 12% before the age of twenty-four.

Background

Osteosarcoma is a form of bone cancer that most commonly affects children and teenagers. The tumour is considered secondary when it appears in older people, typically due to Paget disease or irradiated bone. However, as these tumours arise for the first time later in life, there is a second incidence peak of primary osteosarcoma. The clinical, features, imaging techniques and treatment of primary osteosarcoma are described in this article, including demographic data, diagnosis, and prognosis of the osteosarcoma.

Summary

This comprehensive review aims to find the past, present and future of diagnosis, prognosis and treatment of Osteosarcoma.

Osteosarcoma epidemiology and demographics

Global perspective

The initial height, referring to the pubertal growth spurt, is in the 10 to 14 year age range [8]. In the 0 to 14 years age group, the prevalence rate of Osteosarcoma is 4 cases per million people per year of all races and ethnicities (3.5 to 4.6, CI of 95%). Between the ages of 0 and 19 years, the number increases to 5 cases per million people annually (4.6 to 5.6, 95% CI). Osteosarcoma is the eighth most common malignancy in children, accounting for around 2.4% of all cancers in children. The incidence of Osteosarcoma in adults over 65 years is more likely to signify secondary cancer due to malignant Paget disease degeneration, bone infarction sites, and other factors. The subject's age were related to survival; older subjects have the lowest survival rate. Osteosarcoma death rates have been steadily declining at about 1.3% per year. Regardless of gender, the overall 5-year survival rate is about 68% [8].

Site incidence of osteosarcoma

Osteosarcoma frequently occurs close to the metaphysis of the appendicular skeleton's long bones. The femur (42%; 75% of tumours in the bone's distal portion), tibia (19%; 80% of tumours in the bone's proximal portion), and humerus (40%; 75% of tumours in the bone's proximal portion) are the most common positions (10%; 90% of tumours in the bone's proximal portion). The skull or jaw (8%), as well as the pelvis, are other potential locations (8%) [8]:

- Primary tumours typically occur in the long bone metaphysis and have a pronounced knee predilection, where approximately 60% occur at this spot. The vast majority of those affected by this disease comprise children and adolescents [8].
- Secondary tumours are spread much more broadly, indicating the varying complexity of their underlying predisposing state however adults are almost always affected. They are more common in flat bones, particularly the pelvis (a common site for Paget's disease) [8].

Osteosarcoma clinical presentation

Subjects may experience osteosarcoma symptoms for weeks or months before seeking treatment. Bone pain is the most commonly reported symptom, particularly when moving. Parents are also concerned about their child's sprain, arthritis, or increasing discomfort. Known history of traumatic musculoskeletal injury may or may not exist [9]. Except for the osteosarcoma telangiectatic type which may be associated with pathological fractures, pathological fractures, this is not a typical pillar of Osteosarcoma, the resulting pain will show up as limp. Depending on the tumour's size and position, a swelling or lump might or may not be identified. Fever, night sweats, and other symptoms associated with lymphoma are irregular [9]. While respiratory symptoms are uncommon, when they do occur, they signify lung diseases. Additional signs are rare due to the rarity of metastases to other organs [9].

Physical test evidence is usually based on the primary tumour's position and can include the following [9]:

- A smooth, moist mass with or without overlying pulsation that can be felt or noise, a red, hot, angry appearance of the tumour, angular veins, but not limited to these symptoms
- Joint participation with reduced range of motion
- Lymphadenopathy in the local or metropolitan area (unusual)
- Respiratory Findings in Metastasis

Diagnostic assessment of osteosarcoma

Guidelines for Initial Evaluation of Osteosarcoma published by the National Comprehensive Cancer Network in 2021 (Version 1.2021).

Physical assessment and medical history

At the time of maintaining a record, We may collect a rich data at the patient's training and social background, and to a lesser extent,

there might be bodily symptoms and symptoms to select out up. Examination wishes to be as targeted as history. The initial part of any physical assessment is to observe. Examination of the cardiovascular or respiration device does now no longer begin with the stethoscope. You can also additionally get precious records from the skin colouration, gait, handshake and private hygiene (reflective of physical, mental and social background).

Lactate dehydrogenase and alkaline phosphatase levels measurement

Biochemical indicators, including serum alkaline phosphatase (ALP) and lactate dehydrogenases (LDH), are checked during the preliminary investigation since they have proof of diagnosis as well as prognosis. Because of the elevated osteoblastic activity correlated with Osteosarcoma, ALP concentrations should be elevated. Ultrahigh levels have been related to an aggressive tumour load and are considered a poor prognostic indicator. Later in the treatment cycle, biomarker levels must be assessed because levels may drop as treatment progresses or rise as disease or occurrence persists [10].

Imaging of primary tumour site for diagnostic purposes

Even though an MRI is a preferred method for diagnosing Osteosarcoma, radiographs are often the first test requested when a suspicious bone mass is found during a medical assessment [10]. A typical radiograph of Osteosarcoma will reveal:

- The deterioration of medullary and cortical bones
- Moths have eaten cortex that is porous or that
- "Sunburst" structure (combative periostitis)
- "Codman's triangle" structure (due to advancement of the periosteum away from the bone)
- Ill-defined "fluffy" or "cloud-like" osseous lesion
- Mass of soft tissues
- The osteoid matrix formed by the tumour is calcified [10].

Magnetic resonance imaging

MRI could be appropriate for further analysis after detecting a suspected lesion on an X-ray. The MRI is a valuable tool for determining a tumour's size both inside and outside the bone. To avoid missing "skip" lesions, the whole bone involved, as well as one joint above and one joint below the tumour, should be examined. MRI will precisely and reliably delineate

- Tumor grade in neighbouring soft tissue
- Participation of all joints
- If the tumour reaches the physis or not
- Proximity to the nearest neurovascular bundle.

MRI can be used to evaluate nearly every aspect of treatment, from preoperative limb-sparing resection to the degree of response to chemotherapy in the form of tumour necrosis, shrinkage, and enhanced capsulation [10]. The following are examples of typical Osteosarcoma MRI sequences.

T1 weighted images

- Non-ossified tender tissue portion: medium signal intensity
- Osteoid components: insufficient signal intensity
- Peritumoral edema: medium signal intensity
- Scattered foci of haemorrhage: flexible signal intensity based on chronicity.

T2 weighted images

- Non-ossified soft tissue component: high signal intensity
- Osteoid components: low signal intensity
- Peritumoral edema: high signal intensity.

Computer tomography

The primary purpose of a CT scan is to help with biopsy preparation and disease staging. After radiography and MRI, CT cannot significantly contribute to direct assessment of the tumour if the osseous lesion in question is predominantly lytic. In lytic lesions, small quantities of mineralized material may be impossible to detect on transparent film and MRI.

Nuclear imaging

Positron emission tomography (PET)

PET (positron emission tomography) is a form of nuclear medicine imaging that detects highly metabolic lesions. It is a helpful method for determining the tumour's degree and looking for hidden lesions after initial diagnostic imaging reveals a suspicious mass. PET scans can be used to detect recurrence later in the healing process.

Radionuclide bone

Scan-Tc99 methylenediphosphonate (Tc99 MDP) is an important and widely available screening test for detecting bony metastases. PET imaging is a less expensive but less accurate option [10].

Following up on metastasis sites found on PET or bone scan with MRI or CT (both with contrast)

Among the numerous imaging modalities presently to be had for imaging skeletal metastasis, hybrid strategies which fuse morphological and purposeful information are the maximum touchy and specific, and positron emission tomography (PET)/computed tomography and PET/magnetic resonance imaging will nearly surely maintain to adapt and emerge as an increasing number of vital on this regard.

A fertility consultation might be something to consider (chemotherapy and radiation therapy may affect fertility).

Through biopsy of osteosarcoma

A biopsy is required after a medical assessment, laboratory review, and diagnostic imaging reveal the existence of an osteosarcoma-like lesion. To avoid cancer cells from seeding the biopsy tract and causing reoccurrence, the final surgical procedure will involve resectioning the biopsy tract, which should be inscribed for easy identification. The biopsy should ideally be performed by the same surgeon who conducts the resection because they are familiar with the biopsy's route and scope. Due to high precision levels, previously, it was thought that taking an inclusive approach to biopsy was the top pick. Nonetheless, recent research has discovered that a versatile approach is associated with an intensified risk of complications such as infection, slow wound healing, and tumour cell seeding of the site, as previously mentioned. As a result, core biopsy has largely replaced the conventional open method, owing to the lower risk of tumour cell contamination of the surgical bed and lower costs and shorter recovery times. It is essential for subjects who have a good chance of limb-sparing surgery to preserve local tissue safely. A single deep stab with a "Jamshidi needle" through a trocar traverses a single tissue plane at a spot to be used in the definitive resection to achieve a core needle biopsy. A considerable proportion of cores from the mass's representative regions, soft tissue at the lesion's periphery are required. The central necrotic region will yield only reactive bone, while the "Codman's triangle" region will yield no viable tissue. Importantly, recent research has shown that aspiration with fine needles is ineffective as a biopsy technique because it does not provide enough tissue for accurate diagnosis. Following Pathologists will analyze fresh or frozen tissue samples for a conclusive diagnosis, grading, and histological subtyping during the biopsy, both of which will affect the medical and surgical treatment technique [11].

Differential diagnosis

The biopsy confirms the diagnosis and depicts the tumour grade. The most widely used is the Enneking method for staging malignant musculoskeletal tumours and the "American Joint Committee on Cancer (AJCC)" staging methods for extremity sarcomas.

Figure 1 represents the differential diagnostic categories for Osteosarcoma.

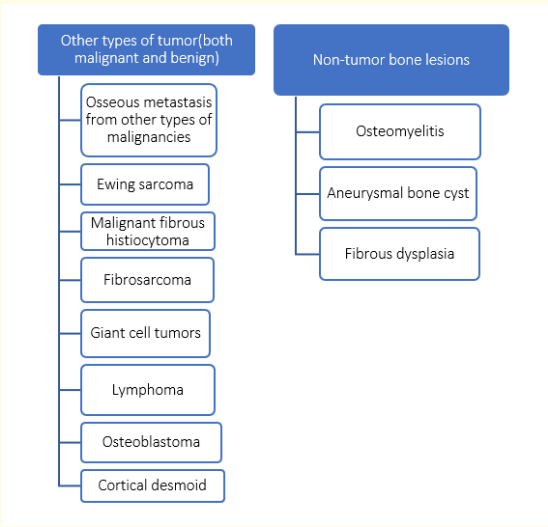

Figure 1: Differential Diagnosis of Osteosarcoma.

Staging of intraosseous extent of osteosarcoma

Presently, only two standard bone tumour staging systems existing. Orthopaedic clinicians mostly use the Musculoskeletal Tumor Society's Enneking procedure due to considering the tumour's anatomical position: intra-compartmental (wholly enclosed inside the bone) vs extra-compartmental (outside the bone) (extension beyond the bone). The different approach identified by the "American Joint Committee on Cancer" does not take an anatomical position into account. However, it compensates for tumour size, which

has been shown in studies to be a significant prognostic factor in predicting treatment response and overall survival. Massive lesions are more likely to metastasize, allowing subjects to advantage from chemotherapeutic action, which has made the AJCC system more common among oncologists [12]. Figure 2 is explaining the Musculoskeletal Tumor Society/ "Enneking system for staging" of malignant musculoskeletal tumours and the "American Joint Committee on Cancer (AJCC) system for staging" of primary bone sarcomas (8th edition).

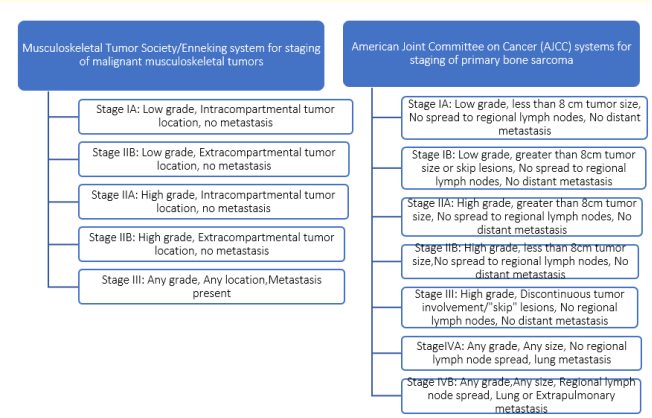

Figure 2: The "Musculoskeletal Tumor Society/Enneking system for staging of malignant musculoskeletal tumours and American Joint Committee on Cancer (AJCC) system for staging" of primary bone sarcomas (8th edition).

Treatment/management strategies

Osteosarcoma treatment typically involves surgery and chemotherapy. This table 1 represents the "National Comprehensive Cancer Network's" 2021 Guidelines for Management of Osteosarcoma (Version 1.2021).

Prognosis for subjects who have osteosarcoma

Age

Middle-aged subjects (over forty years old) have significantly lower survival rates than younger adults, particularly after secondary causes of osteosarcoma have been removed. Several studies have shown that subjects over the age of forty are more likely to present with axial skeleton involvement and metastatic lesions, all of which are associated with worse outcomes (as described below). Subjects over 60 years of age are more severely affected than chemotherapy resistance and advanced surgery [13].

Gender

Men seem to have a worse response to chemotherapy, a fourfold increase in morbidity, and a higher incidence. On the other hand, women were linked to a higher percentage of chemo-related tumour necrosis and prolonged overall survival [13]. Furthermore, serum alkaline phosphatase levels may be present in nearly half of subjects at the time of diagnosis, especially in tumours with minimal osteoid deposition [11]. LDH (lactate dehydrogenase) is another helpful biomarker. Compared to subjects with local disease alone, subjects with metastasis on initial presentation had significantly higher serum LDH levels [14].

OSTEO-1 (Low-grade osteosarcoma, no metastasis)	If postsurgical pathology demonstrates low-grade features	No adjuvant chemotherapy
Intramedullary and surface	If postsurgical pathology demonstrates high-grade features,	Adjuvant chemotherapy should be considered.
Wide excision alone (no neo-adjuvant chemotherapy)	If postsurgical pathology demonstrates is consistent with biopsy (low grade features only)	No adjuvant chemotherapy
Periosteal		Adjuvant chemotherapy should be considered.
Neoadjuvant chemotherapy then perform a wide excision	If postsurgical pathology demonstrates high-grade features	

OSTEO-2 (High-grade intramedullary or surface osteosarcoma, no metastasis) Neoadjuvant chemotherapy then restage the lesion Positive margins Negative margins	[If restaging suggests the lesion is resectable, then perform a wide excision] If there was an excellent response to preoperative neoadjuvant chemotherapy (less than10% viable tumour on postsurgical pathology) If there was an inadequate response to preoperative neoadjuvant chemotherapy (greater than 10% viable tumour on postsurgical pathology) If there was a good response to preoperative neoadjuvant chemotherapy (less than 10% viable tumour on postsurgical pathology) If there was an inadequate response to preoperative neoadjuvant chemotherapy (greater than 10% viable tumour on postsurgical pathology) [If restaging suggests the lesion is unresectable, then continue chemotherapy and consider radiation therapy]	Continue the same neoadjuvant chemotherapy regimen and consider additional surgical resection +/- radiation therapy. Continue the same neoadjuvant Chemotherapy regimen or consider a new regimen and consider additional surgical resection +/- radiation therapy Continue the same neoadjuvant chemotherapy regimen. No further resection is required. Continue neoadjuvant chemotherapy regimen or consider a new regimen. No further resection is required.
OSTEO-3 (Any grade with metastasis at presentation)	If metastases are resectable (pulmonary, visceral or skeletal) If metastases are unresectable	Perform metastasectomy and follow OSTEO-2 guidelines. Consider chemotherapy and radiation therapy, after which the primary site requires reassessment for local control.
OSTEO-4 (Follow-up and surveillance) Surveillance schedule Surveillance visit should include Consider PET/CT or Bone scan. If a relapse is detected, the following are the guidelines to follow. Response to these treatments should have an evaluation via: Good response to treatment: Poor response/progression of the disease:	Every three months for post-op years 1 and 2 Every four months in post-op year 3 Every six months in post-op years 4 and 5 Yearly for post-op years six and beyond Physical exam with assessment of function Imaging of post-op site and chest CBC +/- additional laboratory tests as clinically indicated (e.g., alkaline phosphatase levels) Chemotherapy +/- resection (if possible) Radiographs of the original tumour site CT or MRI (both with contrast) of the site of relapse CT of the chest to assess for pulmonary lesions Surveillance (restart OSTEO-4 guidelines) Resection (if possible) Clinical Trial Palliative Radiation Best supportive care	NA
Extraskeletal Osteosarcoma	We Follow the National Comprehensive Cancer Network's guidelines for the treatment of soft tissue sarcoma.	NA

Table 1: "National Comprehensive Cancer Network's 2021 Guidelines" for Management of Osteosarcoma (Version 1.2021).

Location of tumours

Subjects with axial skeleton tumours have a poorer prognosis than subjects with appendicular skeleton tumours. There is a 10-year gap in survival between races. On the other hand, subjects with femoral tumours frequently do worse than those with distal tibia lesions [13].

Tumour burden

Larger/bulky tumours bear worse prognoses than smaller lesions, as one would expect. One research showed that the risk of morbidity in greater masses (over 15 cm) is 3.4 times higher. Subjects are considerably less likely to have effective limb salvage when the tumour volume exceeds 200 mL; they also show a more inadequate response to chemotherapy and a higher probability of recurrence. It is not unusual that the risk of death in subjects with evidence of metastasis on presentation is substantially higher [13].

Histology

Histology plays a minor role in determining the outcome of chemotherapy and survival. For fibroblastic differentiation, histology is generally considered acceptable. This histological profile is linked to less tumour necrosis due to chemotherapy and a lower risk of death than other histological subtypes. The most common histology of chondroid tumours is linked to a poor prognosis.

Preoperative chemotherapy response

Survival outcome depends on many factors, but the degree of tumour necrosis caused by chemotherapy is the most significant predictor of success; necrosis of ninety per cent or more of the tumour is correlated with an excellent prognosis [13].

Pathological fracture

If a pathological fracture is present at the time of diagnosis, subjects with Osteosarcoma have a greater risk of local recurrence and a lower survival rate. Subjects who have pathological fractures due to preoperative chemotherapy have a lower survival rate than those who do not have a pathological fracture due to therapy [15].

Body mass index

A high BMI is linked to a lower overall survival rate [16].

Complications

Tumour-specific complications

It Include pathological fractures within the tumour itself. These may happen during the presentation or before surgery. As previously mentioned, subjects in both cases have worse outcomes than those who do not have pathological fractures [15].

Biopsy-related complications

When putting together a biopsy strategy for a lesion associated with Osteosarcoma (or any sarcoma, for that matter), careful biopsy preparation is needed to minimize the chance of tumour cells seeding the biopsy tract and surrounding tissues. A biopsy tract that spans multiple chambers can require a larger resection region, increasing the risk of treatment complications [17].

Treatment-related complications

Several chemotherapies, severe common side effects such as nausea, malaise, alopecia, anaemia, and anorexia, but usually go away quickly. However, prolonged side effects such as cardiotoxicity, pulmonary toxicity, and progressive hearing loss have been recorded [18].

Radiation side effects

Radiation is known to cause side effects that are only visible such as skin dryness, burning, peeling, and, on rare occasions, burns. Menstrual changes, erectile dysfunction, and infertility are the most commonly recorded side effects of pelvic radiation. Diarrhoea, incontinence, rectal bleeding, nausea, vomiting, dry mouth, dysphagia, pneumonitis, and fibrosis are potential side effects of radiation therapy on the chest and abdomen [19].

Periprosthetic infection

Long surgical times, repeated surgeries at the exact location, and secondary chemotherapy immunosuppression is all factors that contribute to prosthesis-related infections (which account for around 10% of limb salvage surgery). One or more debridement procedures involving local and systemic antibiotic therapy are the most popular first treatment for periprosthetic infections (systemic and local cement beads). If these steps fail, the implant can need to be removed, debrided, and washed out. Until cement is inserted, a cement spacer impregnated with an antibiotic is usually placed [19].

Implant failure

The mechanical breakdown of the mega prosthesis is the most common cause of failure in reconstruction. Mechanical malfunction necessitates prosthetic replacement. The most common site of mechanical failure is the tibia [19].

Fracture/non-union of allograft/autograft

Allograft/autograft replacement fracture/non-union is a relatively rare complication, but it does occur. Chemotherapy, radiation, and extracorporeal autograft bone treatment have all been related to a higher risk of these side effects. Metallic implants may be placed, or amputation may be required in refractory cases [19].

Rationale for multidisciplinary treatment approach

Following consultation with the multidisciplinary Osteosarcoma team, surgeons must be familiar with all surgical procedures and use the best for each patient.

Materials and Methods

Databases MEDLINE, PubMed, and DOAJ were scanned for eligible articles published in the English language. The search technique ["osteosarcoma"/"osteogenic sarcoma"] was applied ["prognosis"/"treatment"/"survival"] to find publications that mainly addressed survival factors in Osteosarcoma subjects. We also included or reviewed the literature with keywords like "meta-analysis," "study", and "case report" to increase the search performance. The publication period was from 1 January 1973 to 1 March 2021. We also manually scanned the reference list of publications we had received:

- **Inclusion criteria:** Only those articles which focused on the treatment, prognostic factors and/or survival were included.
- **Exclusion criteria:** (1) Repetitive published literature; (2) no relevant information was given in the literature; (3) the research lacked a control group.

Conclusion

Ideally, Osteosarcoma subjects should be treated by an interprofessional team comprising "radiology, pathology, medical/surgical oncology, and orthopaedics" specialists. An orthopaedician radiologists and pathologists must interpret imaging findings and tissue samples to make a decisive diagnosis and establish a prognosis. Oncologists are valuable team partners because they can administer neoadjuvant and adjuvant chemotherapy and assist in long-term monitoring for local or distinct regression. The pain is usually managed with the aid of a pain specialist. A board-certified oncology pharmacist can collaborate with the oncologist to decide agent selection and dosing and provide pain management and treatment options to the patient. A mental health nurse should be involved inpatient and family therapy because depression and anxiety are common. The oncology nurse will provide information about treatment choices, pain management, and support services to the patient and family and assist with care and follow-up coordination. If cancer has spread, a team of palliative care specialists will be brought in early to help. Orthopaedic oncologists plan and carry out a tumour resection approach that includes adequate reconstruction. Since Osteosarcoma can present itself in various ways, including imagery and histological profile, to make an accurate diagnosis and decide on the best treatment regimen, it's necessary to evaluate gross, radiographic, microscopic results. Subjects must be monitored for a long time after treatment because tumour recurrence and extra-osseous metastases are possible. If the results and quality of life are to be improved, an interprofessional team approach is needed.

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Conflict of Interest

No potential conflicts.

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