

A Systemic Review of Primary Malignant Long Bone Tumors in Children and Adolescents

Systematický přehled primárních maligních nádorů dlouhých kostí u dětí a dospívajících

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ABSTRACT

PURPOSE OF THE STUDY

Managing bone tumours is complex, relying on limited evidence, expert opinions, and retrospective reviews. Multidisciplinary approaches and early diagnosis are crucial for better outcomes, especially in young patients with growing skeletons.

The aim of this systemic review and meta-analysis is to give a comprehensive review of common malignant tumors affecting long bones in children and adolescents.

MATERIAL AND METHODS

A PubMed/Medline search for “primary malignant long bone tumours in children” initially retrieved 1120 papers, which were subsequently narrowed down to 110 articles based on inclusion and exclusion criteria. These articles were reviewed, focusing on clinical presentation, diagnostic workup, treatment options, surgical planning, and variations in presentation, including rare tumours. The two most commonly reported tumours were osteosarcoma and Ewing sarcoma, leading to the division of studies into five groups. The inclusion criteria encompassed malignancies in patients aged 2–25 years, work-up, imaging, surgical treatment, rare tumour case reports, and surgical management principles, resulting in a heterogeneous group of articles. To enhance categorisation, it was clarified that studies with 10 or more cases were considered retrospective reviews.

RESULTS

Reviewing of results thus demonstrate that the two likely tumours in children under consideration were osteosarcoma and Ewing sarcoma. Their presentation findings and clinical features were discussed in detail in the review. It is worth noting here that in case of differential diagnosis this should be the first on the list.

DISCUSSION AND CONCLUSIONS

Although focus of literature is more on the two most common tumours. However, rare tumours should be considered as they can mimic these common tumors.

Key words: primary, malignant, bone tumors, children, adolescent.

INTRODUCTION

Management of bone tumors is a complex subject where there is variation in presentation along with numerous factors that can define the outcome as well as choice of treatment. Considering the relatively rare nature of this disease, evidence available in the literature is largely based on expert opinions, retrospective reviews, cases series and single centre studies across the world.

However, as the knowledge regarding tumor biology as well as factor defining the long- and short-term response to intervention along with disease free survival period is evolving the concept of multi-model team approach has taken a center stage in the management of these cases where different health professionals work as a team to find the best possible solution with the aim of reducing morbidity and mortality.

In terms of dealing with tumors involving young adults and children problems associated with growing skeleton in terms of limb salvage surgery psychological and emotion turmoil associated with amputation is an added factor that comes up as an extra challenge to the treating physicians.

Despite of variable reports regarding factors that can affect overall survival, limb early diagnosis and referral to specialized tumor centre has been considered as an important factor that can help in achieving the better outcome for these clinically challenging cases. Based on this background we have conducted this systemic review to help clinicians and surgeons in diagnosing these cases by summarizing the presentation, investigation, surgical management, variation in clinical picture along with brief review of rare tumors and their presentation.

Aims and objectives

The aim of this systemic review and meta-analysis is to give a comprehensive review of common malignant tumors affecting long bones in children and adolescents. As per our search of literature there is not a single study that has been published with this narrative.

This study will help readers to have a better understanding of common findings of these malignant bone tumors and available surgical options. It can give surgeons a rough framework with a better thought process based on clinical features and radiological findings before referring to a local tumor unit. This study is more focused on surgical aspect of treatment as part of MDT approach.

MATERIAL AND METHODS

A Pubmed / Medline search with the phrase ‘primary malignant long bone tumors in children’ was conducted which revealed (Fig. 1) 1120 papers. On initial screening the search was narrowed down to 110 articles based on the exclusion and inclusion criteria. Each study was reviewed in terms of:

- Clinical presentation of disease for common pediatric and adolescent tumor.
- Diagnostic work up.
- Treatment options and what to consider in terms of planning for treatment from a surgical point of view.
- Variation in terms of presentation and rare tumors that can present and mimic common pathologies.

Further screening of articles led to exclusion 60 articles that were not able to meet the criteria mentioned below:

Based on these tumors, the 2 most common types of reported tumors were osteosarcoma and Ewing sarcoma. Studies were divided into 5 broad groups.

1. Those covering osteosarcoma and its presentation. (Osteosarcoma group).
2. Ewing sarcoma presentation and surgical treatment. (Ewing sarcoma group).
3. Rare form of tumors of long bones that can mimic these common malignancies. (Rare tumor group).
4. Primary lymphoma of bone. (Lymphoma group).
5. Papers discussing common tumors, imaging, or principles of intervention in general were discussed in the discussion section of the article. (General principles group).

Based on the above following sub-division of articles was made see Table 1.

Inclusion criteria for the study:

1. Presentation of primary malignancy in patients between the age of 2–25 years.
2. Malignant disease work-up and imaging modality that is being used.
3. Surgical treatment that can be considered for primary tumor.

4. Case report of rare tumor mimicking common malignancy.
5. Principles of surgical management
6. Hybrid studies covering pediatrics and adolescent tumors.

Exclusion criteria:

1. Paper involving the primary malignancy of sites other than long bones.
2. Metastatic disease / recurrence of disease.
3. Molecular pathology of tumor / histopathology / complications following primary treatment / regenerative cell base therapy.
4. Paper discussing survival long term follow up following intervention.
5. Chemotherapeutic agents’ use and toxicity as a primary objective of study.
6. Papers discussing reconstruction options as primary objective of study.
7. Articles not in English.
8. Soft tissue tumors of children.
9. Ultrasound guided / radiofrequency ablation / cryosurgery of primary tumor.
10. Chapters of books.
11. Primary bone tumor because of underlying genetic syndrome / chromosomal abnormality.

A heterogenous group of articles were identified covering different aspects of bone tumor. In terms of design of study, the following subdivision was made for the 50 articles that were being considered. In terms of “rare tumor group” we have also discussed rare presentation of common tumors that can help readers in keeping a high index of suspicion and proceed with the work up. The case series design of study was highest for rare tumors where reported outcome of small number of patients was being considered along with presentation and differential diagnosis for the tumor. However, differentiation between the case series and retrospective review was difficult at times. It was agreed among authors for clarification purposes that any study with 10 or more cases will be considered as retrospective review rather than a case series. The idea behind that was to classify the available literature in a more precise way for readers to understand and gauge the level of evidence on a more scientific basis.

Table 1. Subdivision of articles included in the systematic review

Group subtype:	Paper count:
Osteosarcoma	23
Ewing sarcoma	06
Rare tumors	11
Lymphoma	02
General principles	9
Total number of articles	50

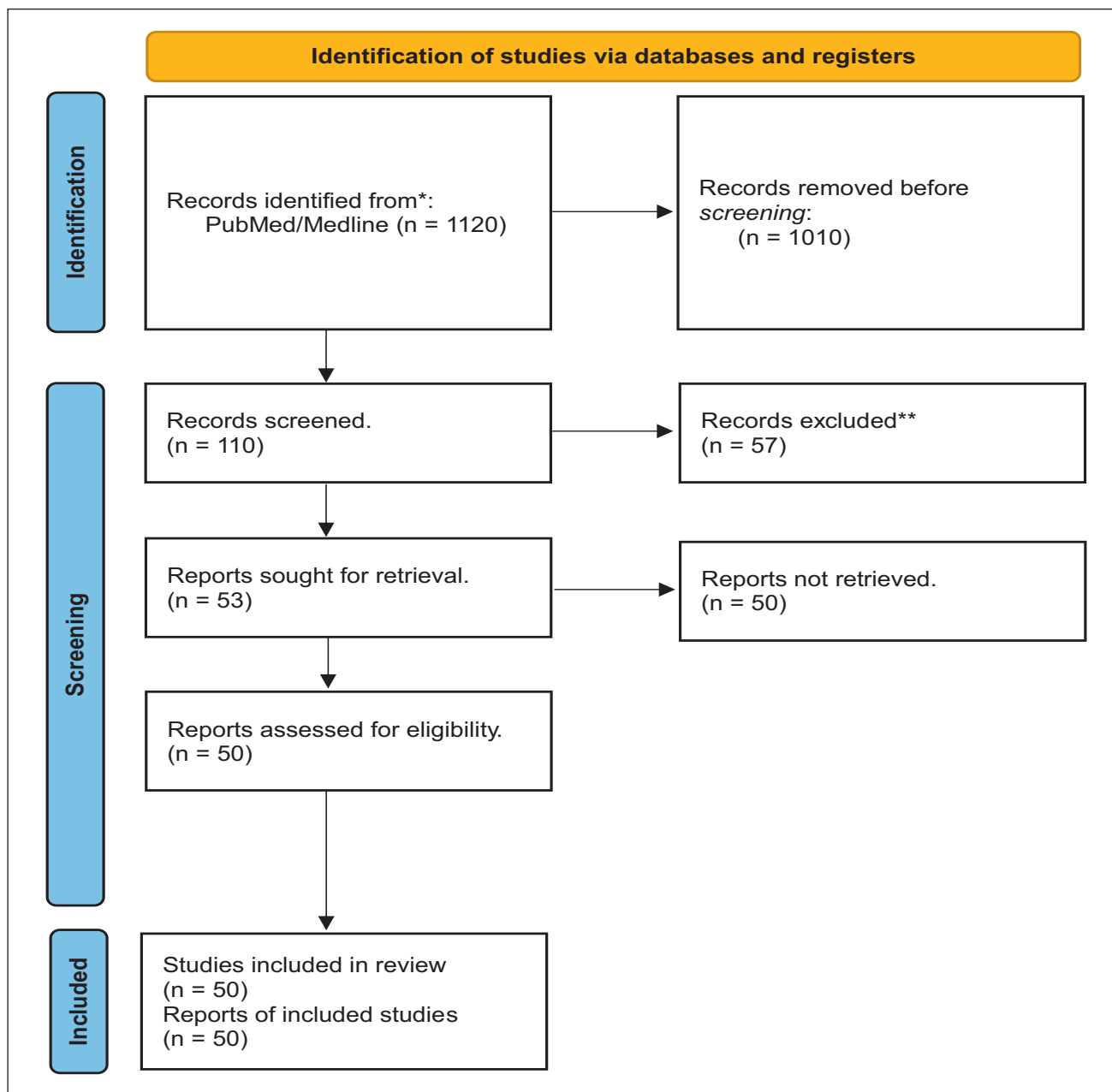


Fig. 1. PRISMA chart showing the inclusion and exclusion of studies.

LITERATURE REVIEW

Osteosarcoma

Osteogenic sarcoma or osteosarcoma (OS) is the primary malignant bone tumor. Classification of this tumor is particularly based on the predominant histological type of the tumor. In terms of definition of this tumor as per WHO “primary malignant bone tumor characterizes by direct formation of bone or osteoid tissue by tumor cell, and this should be the dominant feature of tumor though histological pattern may vary in terms of amount of tumor bone or osteoid tissue (13). Table 1 and 2 explains the different types of studies being considered for the review.

Incidence:

OS predominantly demonstrates a bimodal pattern of distribution in terms of incidence with slight male predominance 1.3:1 with peak incidence around 24 years of age. However, the precise subtypes can vary based on the age of the patient. The most common site is knee and proximal humerus (8). There are various subtypes of OS. See Fig. 2 for details (50).

Surface osteosarcoma arises from juxtacortical region of tubular bone with paraosteal type 65% and periosteal type 25%. The former occurs in female in 3rd or 4th decade with involvement of posterior aspect of distal femur / proximal tibia. Ganathic type incidence is 6–9% which usually occurs in older children. However, Mul-

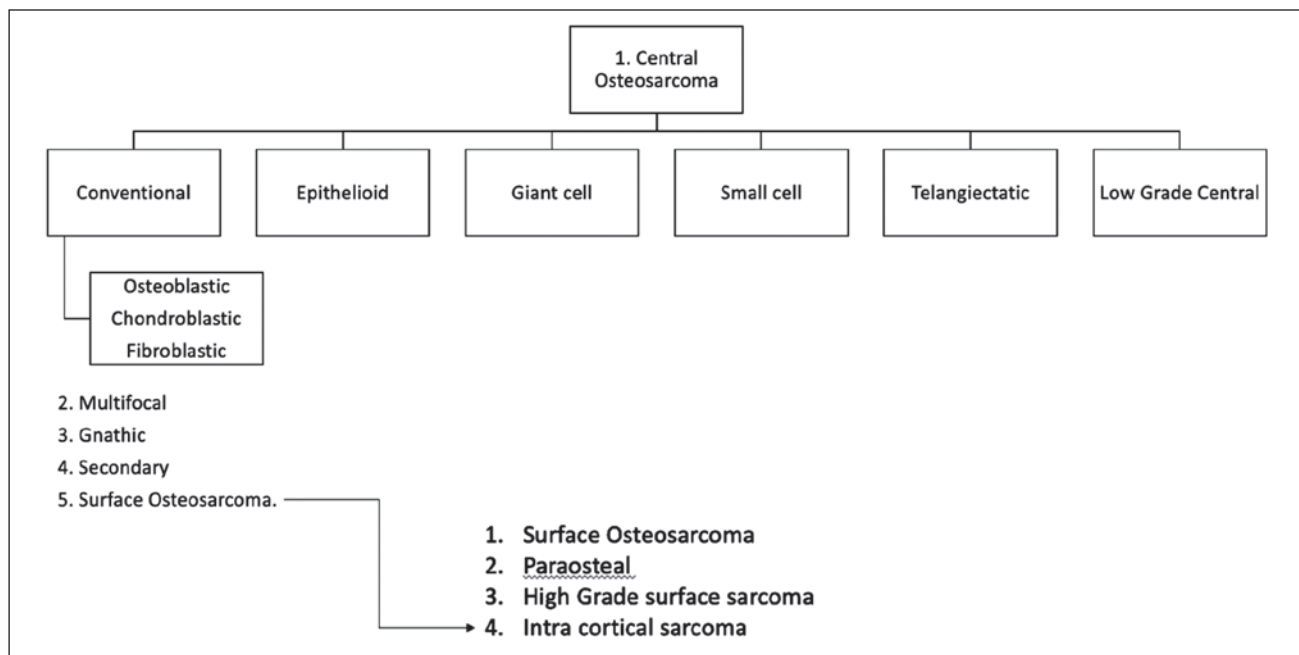


Fig. 2. Subtypes of osteosarcoma.

ticentric osteosarcoma has incidence of 3–4% with predominance in mature skeleton.

Presentation:

Localized pain, swelling and occasional joint dysfunction. 10–20% are affected by metastasis at the time of diagnosis (50). The pain following OS can be explained based on stretching of periosteum. The other rationale for pain can be attributed to microfracture that can inflict pain.

At times, patients can present with limp. Out of the broad spectrum of diagnosis that should be considered for the limping child, OS should be thought off as well lower down the line. As mentioned in the introduction, early diagnosis thus affects the prognosis and thus contributes to a better outcome. Any complaint of pain especially at rest or presence of mass should warrant further investigation and evaluation to rule out any bone pathology.

INVESTIGATIONS

a) Localized staging:

X-rays:

1. Size and extent of tumor.
2. Degree of bone destruction.
3. Periosteal reaction referred to as Codman triangle, paint brush, hair on end appearance and sun burst appearance. All of this demonstrates the aggressive nature of tumor^(3,4).
4. Extra osseous soft tissue will be present 80–90% and 90% cases will contain clouds of mineralized osteoid.
5. Pathological fracture can be appreciated in 15–20% of cases.

However, the downside of this modality is lack of ability to pick up tiny bone damage or accurate description of soft tissue masses (50).

CT scan: The 3D modality helps in assessment of involvement of bone as well as identification of micro mineralize bone like tumor. CT sensitivity for picking up metastatic disease in the lungs is 75% and specificity of 100% for lung metastasis. However, not all nodules are metastatic especially when size is <5 mm (50).

MRI scan: MRI is superior to CT in detection of skip metastasis. Presence or absence of skip lesions and jump metastasis. However, specificity of MRI in terms of identification of Codman triangle and periosteal reaction is not high so ideally a combination of MRI and CT scan should be considered (50).

b) Distant staging:

PET CT scan: Children oncology group 2008 recommended PET with whole body CT or MRI scan. If the above is not available, then isotope scan can be used (8).

PET CT scan helps in identification of metastatic spread and skip lesions. However, there is no role in diagnosis and local staging. It helps in differentiation of post op changes from presence of residual tumor.

F-18 FDG PET /CT could be used to detect sub-centimeter lesion even in lung nodule. Accuracy in detecting bone lesion is 95%. CT detects 67% and MRI detects 86% (49).

Telangiectatic osteosarcoma

Incidence: In this case the male to female ratio has been reported to be 2:1. This type of OS usually occurs in patients with age from 15 to 20 years of age with a median age of 17.5 years (42).

Table 2. Details of studies under consideration. Serial No. is the same as reference number at the end of article

Serial No.	Type of study	Authors	Main consideration
1	Review article	Abed et al.	Surgical management of OS
3	Review article	Ando et al.	Current strategies in OS
8	Review article	Bierd et al.	management and features of OS
13	Review article	Copeland et al.	management and features of OS
24	Case series	Kaste et al.	Surface osteosarcoma
25	Review article	Kim et al.	Paediatric OS
27	Case series	Kunze et al.	Multifocal OS
31	Review article	Meyers et al.	management and features of OS
32	Retrospective review	Morris et al.	Extent of surgical resection
33	Case series	Muscolo et al.	Epiphyseal origin of OS and Ewing sarcoma
34	Case series	Niimi et al.	Limb salvage for Lower limb OS
39	Review article	Picci et al.	Osteosarcoma (Osteogenic sarcoma)
40	Retrospective review	Puri et al.	Surgical management of OS
41	Case series	Samardziski et al.	Diagnostic and treatment of paraosteal OS
42	Review article	Sangle et al.	Telangiectatic Osteosarcoma
43	Review article	Schajowicz et al.	Juxtacortical OS
44	Retrospective review	Schneiderbauer et al.	Fibular Osteosarcoma
45	Review article	Stitzlein et al.	Management of OS
47	Review article	Wang et al.	Diaphyseal OS imaging features
48	Review article	Yasko et al.	Surgical management of OS
49	Review article	Zhang et al.	PET / CT diagnosis and management of OS
50	Review article	Zhao et al.	management and features of OS

Presentation:

It usually presents with recent onset of localized pain, soft tissue mass or both. Pathological fracture was identified in 29% of cases either at time of initial diagnosis or during treatment. An important differential diagnosis here is to rule out ABC (aneurysm bone cyst) which can sometimes mimic the presentation. (42)

Imaging: X-ray shows purely lytic lesion with destruction along with intralesional sclerosis. CT and MRI characteristically demonstrate a Doughnut sign (42).

Diaphyseal osteosarcoma

It accounts for 10% of all OS. It is commonly seen in young adults.

Radiology: X-ray shows bone destruction, lamellar, periosteal reaction with or without Codman triangle, soft tissue mass or calcification. Thickening / destruction of diaphyseal cortex with neoplastic bone and periosteal reaction. CT scan shows high rate of detecting periosteal reaction, neoplastic bone. X-ray can show osteolytic, blastic or mixed type but predominantly lytic. MRI is more helpful in detection of soft tissue mass. However, its ability to detect periosteal reaction is rare (47). It is worth mentioning here that the extent of diaphyseal OS is more than the metaphyseal variant. This

has clinical implication as extensive involvement might preclude the idea of limb salvage surgery (1, 25).

Parosteal osteosarcoma

It is a rare form of OS. It occurs between the 2nd and 7th decade of life. It is usually present in the distal dorsal femur. This diagnosis should be considered especially at this site unless proven otherwise. The positive aspect regarding this tumor is the chances of skip lesion and satellite nodule is not a feature. The differential diagnosis of this tumor is osteochondroma or heterotopic ossification (HO) (41). The ossification pattern originates from bone to soft tissue which is vice versa for HO.

SURGICAL MANAGEMENT PRINCIPLES**Management guidelines:**

It should be managed as part of MDT (multidisciplinary team) approach with at least following members being kept on board:

- Pediatrician.
- Medical oncologist.
- Surgeon.
- Pathologist.
- Specialized nurse (8).

Biopsy:

- Diagnosis involves pathological evaluation of tumor which can be done using a core needle or open biopsy. FNA is not recommended due to lack of sufficient histological content and thus difficulty is to assess the tumor grade (8).
- Biopsy should be performed by surgeon who is able to perform the limb salvage procedure as the biopsy tract needs to be extracted during the limb salvage procedure. Closed biopsy can be performed with the needle. However, multiple passes will be required to obtain tissue for assessment of tumor.
- Practically the advantage of core needle biopsy is that it does not require hemostasis. The accuracy can be improved using image guided intervention. This can help in identification of necrotic area of tumor thus increasing the yield of procedure.

Surgical management principles:

The broad management principles can be considered as limb salvage versus amputation. Limb salvage along with neoadjuvant chemotherapy achieve 80% 5-year survival. However, in the case of incomplete resection can lead to high recurrence of 25% (50). It is worth mentioning here that the primary goal for surgery is to extend the disease-free survival and secondary objective is salvage surgery for the limb (31).

Proximal humerus:

In case of OS involving the proximal humerus Tikhoff Lindberg procedure can be used which has the advantage of good functional outcome in terms of movement of elbow as well use of hand. The procedure involves:

- En bloc resection of tumor.
- Resection of distal clavicle.
- Removal of portion of scapula (31).

Rotationplasty:

After excision of distal femur, the lower leg is brought up to femoral stem after rotating to 180 degrees. Thus, ankle behaves like knee and patient is fitted with below knee prosthesis (47).

Decision about type of surgery will depend on:

1. Nature of tumor.
 2. Extent of tumor.
 3. Response to chemotherapy.
 4. Expertise available, cosmetic, and functional outcome following limb salvage.
 5. In terms of local recurrence is directly related to margin of excision, tumor necrosis following chemotherapy.
 6. Close margins of excision and <90% tumor necrosis following chemotherapy can lead to local recurrence as high as 30% (1).
- Adequate margin of surgical excision is roughly around 5–7 cm based on pre-op investigation of MRI or bone scan (25).

Limb salvage:

In terms of consideration of limb salvage the following should be considered:

- Type of tumor.
 - Size of tumor.
 - Location.
 - Status of proximal neurovascular bundle.
 - Response to chemotherapy.
- This is considered as an important factor when limb salvage is being considered and this has implications for long-term disease-free survival as well (25).
- Assessment of cosmetic and functional outcome.

In terms of growing skeleton, it will involve excision of growth plate as well. If anticipated leg length is >30 mm then allowance must be made in reconstruction for future growth (1).

Distal leg OS:

Although the classical approach in this case historically has been amputation. However, there is some evidence regarding limb salvage procedure with the following options:

- Arthrodesis with combination of autograft and intra-operative and intra op autoclaved tumor bone.
- Ankle joint preservation using irradiated tumor bone graft (34).

DISCUSSION

In terms of imaging of choice for primary malignant bone tumors all available imaging modalities have their limitation with some advantages and disadvantages. For example, a plan X-ray film is easily available, gives information regarding the bony component of tumor but unable to give information regarding extent of soft tissue involvement.

MRI with contrast helps to identify accurate extent of marrow edema along with degree of necrosis following chemotherapy and presence of skip lesions. Skip lesions are separated from the main tumor but are still in the same bone that is affected by primary tumor (45).

For OS 80–85% can undergo reconstruction. However, the principles of reconstruction should be considered and kept in mind as mentioned above in the surgical management portion of this article. This also applies to low grade sarcomas like paraosteal sarcoma (24, 48).

A study published from India which was a single centre retrospective review demonstrated poor survival in their patient following chemotherapy and surgical resection. In this group the authors were of the view that the outcome was poor due to delay in presentation along with variable response to chemotherapy. In this study 100% necrosis can lead to superior outcome. However, authors have very wisely critiqued the idea of necrosis assessment being subjective with considerable interobserver variability (7).

It is also worth discussing here that the type of resection that is being documented by surgeons is again variable. The differentiation between wide local excision and

Table 3. Ewing sarcoma included studies. Serial number is same as reference number at the end of article

Serial No.	Type of study	Authors	Main consideration
4	Cases Series	Arkader et al.	Ewing sarcoma in fibrous dysplasia
16	Case report	Esmaili et al.	Epiphyseal tumour Ewing sarcoma
21	Review article	Iwamoto et al.	Diagnosis and treatment of Ewing sarcoma
23	Review article	Karosas et al.	Management of Ewing sarcoma
26	Review article	Kuleta-Bosak et al.	Imaging Modality of Ewing sarcoma
30	Review article	Meyers et al.	Management of Ewing sarcoma
46	Review article	Wagner et al.	Fracture in Ewing sarcoma

radical excision as per referred study was not clear all the time and there was discordance of 43% (32).

Although this study was a retrospective review and thus has its limitations, but it is providing an important message to surgeons that accuracy of information and awareness regarding the terminology is of paramount importance to access for long term outcome of patient who undergo surgical intervention. Based on our assessment of literature, most of the studies are retrospective reviews so these findings can affect review of treatment options to ascertain what is considered best for patient in long run.

Current therapy for OS is based on MDT approach where different allied health professional work towards a common goal of achieving the best possible solution for patients. Critically reviewing the literature, the recent publication has stressed the need of multidisciplinary approach and limb salvage surgery has been considered as a gold standard in terms of choice of surgical treatment for these patients (3). However, relatively older papers are more inclined to offer amputation to patients with no mention of MDT approach.

RARE TUMORS

Synchronous multifocal OS

Is a rare form of OS which presents multifocal OS in the bone which again affects young individuals. It is worth mentioning here that although it is considered locally aggressive, it is unlikely to cause lung metastasis (27).

OS of fibula

It is a rare form of OS comprising 3–5% of all OS. However, there has been a report regarding inadequate margins of excision was reported highest for this tumor. However, as per this study incomplete resection was not associated with poor outcome. However, high grade tumor, below knee amputation as primary treatment and presence of metastasis were associated with poor outcome (44).

Epiphyseal origin of OS and ES (Ewing sarcoma)

This is a rare occurrence where the said tumors originate from epiphysis rather than from the metaph-

ysis / diaphysis with extension into the epiphysis. Although origin of these tumors from this area is rare and thus can lead to delay in presentation and difficulty in treatment with a likely chance of locally advanced disease (33).

Juxtacortical chondrosarcoma

It has been renamed in WHO classification as periosteal chondrosarcoma. It appears as a small tumor adjacent to cortex with spotty calcification with radiation of bone specks along with presence of Codman triangle (43).

EWING SARCOMA

It is the second most common malignancy in patients younger than 20 years with peak incidence around 20 years and accounts for approximately 3% of all malignancy in pediatric patients. It is infrequently diagnosed after the 3rd decade of life. In terms of frequency of occurrence (most to least likely) femur, humerus, tibia, and fibula. It is associated with a high degree of metastasis in lungs and bone marrow. In case the tumor arises from soft tissue it is labelled as extraosseous Ewing sarcoma. It is technically a small round cell tumor typically arising in bone. It has most unfavorable prognosis of all musculoskeletal tumor with slight predilection to male sex. It is usually a disease of long bones but can occur anywhere along the bone. Table 3 demonstrates the type of studies that were considered for this study. Diagnosis is confirmed by biopsy and assessment of histology. Differential diagnosis in this case is:

- Small cell sarcoma.
- Non-Hodgkin lymphoma
- Neuroblastoma can be ruled out using urinary catecholamine (21, 23, 30).

Presentation:

1. Patients can usually present with mild pain at the site of tumor which increases as the tumor mass increases in size leading to regular use of pain killers (23).
2. 10–20% will present with weight loss, anemia, fever, malaise due to high level of circulating cytokines (23).
3. In the case of Ewing sarcoma involving the femur there is a high risk of fracture. However, this does not affect the long-term survival of these patients (46).

Radiological investigation:

1. CT scan is used to access metastatic disease in lungs which is likely in this tumor considering the systemic nature of this tumor (30).
2. X-ray: In terms of radiological findings periosteal reaction is very common and can present as onion skin / onion peel appearance, sun burst or spicule pattern in perpendicular reaction or presence of Codman triangle. However, sun burst appearance is less common compared to OS. Sometimes intramedullary destruction can present as moth eating appearance (21).
3. MRI in this case is particularly important as X-ray will not be able to delineate the extent of tumor. It is also of vital significance to radiologically access response to chemotherapy (21).
4. On rare occasions Ewing sarcoma can affect the epiphysis. It is worth nothing here that the lesion of epiphysis is usually considered as benign (chondroblastoma). However, in case of involvement of metaphyseal-diaphyseal junction, periosteal reaction, and cortical thinning along with involvement of epiphysis Ewing sarcoma should be considered (4, 16, 26).
5. MRI will demonstrate inhomogeneous structure and blurred borders. The sequence that can be useful in this case are fat saturation (STIR sequence) and T2 and T1 weighted images following IV contrast (26).

Surgical management

Surgical management principles described under OS do hold true in this case as well. In this section only important differential steps or considerations will be discussed based on tumor biology. MDT approach hold a lot of significance in this case for two key reasons:

1. Firstly, those patients that are initially deemed unsuitable for limb salvage due to extent of tumor can be deemed suitable candidates following neo-adjuvant chemotherapy.
2. Secondly surgery alone will always lead to metastatic disease so systemic therapy in this case is of paramount significance. Advances in chemotherapy led to improved survival in this case rather than surgical intervention itself (30).

3. In terms of explaining the terminologies for resection:

- Intralesional excision means excision involving the tumor / within the tumor.
- Debulking means leaving gross tumor behind, which does not help in local control of tumor.
- Marginal excision where plane of dissection goes through the pseudo capsule, and it is not ideal as capsule will involve microscopic metastatic disease.
- Radical excision involves all compartments involving the tumor are removed en-bloc (21).

RARE TUMORS

In this portion of review, we will be discussing rare tumors presentation. The goal of this component of review is to provide a summary regarding reported presentation of relatively rare tumors and any discussion regarding change in surgical planning for these rare tumors. Again, details regarding the type of studies along with the type of tumor can be considered in Table 4.

Kaposiform hemangioendothelioma

In the referred study two patients were discussed with age 5- and 9-year-old presenting with lytic lesion involving femur and humerus respectively without cutaneous lesion. Radiological diagnosis demonstrates lytic lesion without periosteal reaction resembling chondroblastoma and fibrous dysplasia. Treatment in the said case was complete surgical resection with high chances of recurrence in case of incomplete excision (29).

Primary leiomyosarcoma of bone

In this retrospective review involving 16 cases. In this study 13 patients had a tumor originating from the knee. Patients were presented with a lytic lesion and presented with pathological fracture. The clinical behavior is considered highly malignant with ability to demonstrate cutaneous metastasis as well (9).

Table 4. Rare tumors included in our systematic review. Serial number is same as reference number at the end of article

Serial No.	Authors	Type of study	Type of tumour
2	Ajabnoor et al.	Case report	Histiocytic sarcoma
9	Berlin et al.	Case series	Leiomyosarcoma of bone
10	Bjornsson et al.	Retrospective review	Chondrosarcoma
12	Chow et al.	Case report	Primary osteochondromyosarcoma
14	Dantonello et al.	Retrospective review	Chondrosarcoma
18	Ghandur-Mnaymneh et al.	Case Series	Malignant fibrous histiocytoma
28	Little et al.	Case series	Malignant fibrous histiocytoma
29	Ma et al.	Case series	Kaposiform haemangioendothelioma
35	Nishida et al.	Retrospective review	Malignant fibrous histiocytoma
36	Odintsov et al.	Case series	Clear cell carcinoma

Malignant mesenchynoma (MMC)

It is defined in the literature as 2 or more unrelated differential tissue elements other than a fibrosarcoma component. It is a primary soft tissue tumor that can rarely occur in bone. In the referred paper a 10-year-old child presented with tumor involving the proximal fibula. In case of localized disease, it has a good prognosis. However, metastatic disease can lead to death in a years' time. The likely site of metastasis is lungs like OS. Radiological findings demonstrate osteolytic lesion in the metaphyseal region of proximal fibula. This tumor responds poorly to chemotherapy and thus the only curative option in this case is wide local excision (12).

Malignant fibrous histiocytoma (MFH)

High grade primary bone sarcoma with a bimodal distribution. Like conventional OS this also occurs around the knee or end of long bones. The principle of adequate surgical excision leads to good outcomes. In terms of MFH the 5-year survival rate has been documented to be 36.5%. There is a high chance of metastatic disease associated with this tumor along with poor survival. Again, this tumor can affect patients with age ranging from 6–81 years. Like OS this tumor should also be delt with complete excision with adequate surgical margins. However, in contrast to OS it might respond to certain degree. X-ray shows signs of bone destruction with lesion that can be lytic, mixed, or sclerotic (2, 18, 28). Again, this paper stresses the need for a high index of suspicion and confirmation of diagnosis with a biopsy before proceeding with definitive excision. Intralesional excision leads to a high recurrence rate.

Histiocytic sarcoma

Two patients with a rare tumor have been reported in this study. One involving the femur and other a young child with involvement of radius. It presents a highly destructive soft lesion with soft tissue extension. As per this paper this tumor, although can affect patients involving a wider age group (35).

Clear cell carcinoma

It is sometimes difficult to get distinguished between melanomas. In this case clear cell carcinoma arising from the bone is being considered. All tumors arise from femur, humerus, and fibula. Radiological features demonstrate expansile lytic lesion with poorly defined margins and cortical disruption. MRI demonstrates high signal in T2 along with soft tissue component associated with the tumor and cortical breakthrough. It is an aggressive form of primary bone tumor with reported death of 3 patients as per this study (14).

Chondrosarcoma

Is usually tumor of adults as per referred paper, the mean age of presentation was 46 years with age ranging from 5–82 years. In the case of young children osteochondroma can develop into chondrosarcoma. This tu-

mor usually involves diaphysis. The radiological feature of this tumor on X-ray involves cartilaginous calcification with lytic zone, cortical destruction, and periosteal reaction. It is a slow growing malignant tumor with 5-year survival of 77% (10).

Primary bone lymphoma (PBL)

Two papers were identified, both of which were retrospective reviews discussing primary bone lymphoma. PBL is rare in children / adolescents. It comprises of 5% of all Non-Hodgkins lymphoma and 3% of all malignancy. It is usually reported in adults around 5th and 6th decade of life. It is usually more common in males; early presentation of disease is a feature with presenting complaint of pain at the site of involvement. Sometimes patients are present with fractures of the affected bone as well. However, the age range that was included in the study was from (11–83 years). Differential diagnosis of tumor involve:

- Small round cell tumor diagnosed on histopathology.
- Infection.
- Ewing sarcoma.
- Disseminated lymphoma.
- Multiple myeloma.

In terms of treatment offered, 57% of patients were treated with combined therapy, 14% with radiotherapy and 30% with chemotherapy alone. Combined modality leads to better outcomes compared to use of isolated modality (7, 11).

DISCUSSION AND CONCLUSIONS

MMC 10-year survival is less than 50%. It is worth comparing it with classic chondrosarcoma (CCS) which is an important differential diagnosis.

- MMC is rare compared to CSS.
- MMC present at a younger age compared to CSS which is usually >50 years of age.
- MMC is considered to be a high-grade malignancy with poor 10-year survival.
- 1/3rd of MMC occur in soft tissue compared to less than 1 percent for CCS (36).

Osteosarcoma (OS) is associated with Li Fraumeni syndrome (p53 Oncogene Mutation), retinoblastoma (Rb oncogene), Rothmund Thomas Syndrome, history of radiation therapy and previous history of orthopedic surgery. In terms of Ewing sarcoma, it is associated with chromosomal translocation of chromosomes 11 and 22 in 95% of cases. Translocation of 21 and 22 are present in 5–10% of cases.

There can be variation in tumor pattern in different regions, one paper from Nigeria suggested lack of bimodal distribution of for osteosarcoma considering rare incidence of Paget disease in Nigeria. In terms of age of presentation OS usually present in patient younger than 20 years followed by Ewing sarcoma. Both Ewing sarcoma and OS account for 6% of all childhood tumors. The incidence of Ewing sarcoma is infrequent after the age of 20. In terms of children / adolescent the 3 most

frequent tumors along with their mean age of presentation are:

1. Osteosarcoma (10–29 years of age)
2. Ewing sarcoma (female 10–14 years of age and for male 15–19 years of age)
3. Rhabdomyosarcoma.

In terms of utility of MRI scan as part of work up for intramedullary tumor median gross specimen (112 mm range 45–300 mm) was longer than that by MRI (108 mm range 45–304 mm). Under estimation of tumor length on MRI was seen 24 patients. However, it will only affect resection if it is 3–5 cm of tumor free bone. However, the largest under estimation was 18 mm. Thus, even under estimation will not lead to compromise in surgical resection (5, 6, 15, 17, 19, 20, 22, 38).

In terms of chondrosarcoma, it is resistant to chemotherapy as cartilage cells has a poor blood supply. Like Ewing sarcoma radiation therapy can be used in cases where surgical resection is not possible. It was the most frequently diagnosed bone tumor in population older than 50 years (19).

Although focus of literature is more on the two most common tumours. However, rare tumours should be considered as they can mimic these common tumors.

Limitations of study

1. Bone tumors is a complex and evolving topic. The behavior of tumor cannot be predicted all the time. Although authors have tried to cover objectives as mentioned in the aims of the study, it is likely that few aspects of disease will still be missed.
2. Another important consideration especially in terms of rare tumors is the tumors have been documented both in elderly as well as young children, so these papers were included in the review. However, being critical of the choice, this does not exactly fit with the study protocol. However, to avoid missing them and give readers a thorough review we have included them in our review.

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