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Extraskeletal osteosarcomas: current update

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Extraskeletal osteosarcoma is a very infrequently diagnosed soft-tissue sarcoma subtype which has identical histological features to bone osteosarcoma. However, its demographics, presentation, radiology and treatment strategy differ from those of osteosarcoma. Its diagnosis can be at times challenging due to radiological and pathological mimics which have more common incidence. A multimodality approach is essential for optimizing the outcomes in extraskeletal osteosarcoma. Although there are certain caveats on inclusion of adjuvant therapies (radiotherapy and chemotherapy), in all cases surgical resection with wide local margins is considered the gold standard for adequate local control. The outcome in advanced disease remains dismal and there is a huge unmet need for prospective studies addressing the optimal treatment strategy. In this article, we review the evidence available for the management of extraskeletal osteosarcoma.

Lay abstract: Extraskeletal osteosarcomas are cancerous outgrowths (tumors) arising from the soft tissues of the human body, outside the skeletal framework. They closely resemble their counterparts arising from the bone, known as osteosarcomas (osteo: bone; sarcoma: a type of cancer affecting soft tissues) with the exception that they have no bony connections. These tumors are rare, arising most commonly from the extremities (upper and lower limbs). They present with slowly enlarging masses that may be associated with pain. Treatment involves surgery (removal of the tumor alone or the affected limb), use of chemotherapeutic drugs (drugs acting on cancerous cells) and radiotherapy. The outcome of these tumors is poor, with most patients succumbing to disease during follow-up.

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Keywords: amputation • bone • chemotherapy • extraskeletal • limb salvage • metastases • osteosarcoma • radiotherapy • surgery

Osteosarcomas occurring outside the skeletal framework are referred to as extraskeletal osteosarcoma (ESOS). These tumors are defined as malignant mesenchymal neoplasms, producing neoplastic osteoid or cartilage-like material, localized to soft tissues with no obvious bony or periosteal attachment [1]. Criteria for defining these tumors are that they should:

- Possess a uniform sarcomatous pattern, thereby removing the possibility of a mixed malignant mesenchymal tumor;
- Produce neoplastic osteoid (with or without cartilaginous matrix);
- Have a fibroblastic component without any other differentiation;
- Not include an epithelial component;
- Not have an osseous source as the cause (this must be excluded clinicoradiologically) [2].

ESOS was first described by Wilson in 1941 [3,4]. In 1956 Fine and Stout [5] showed that these tumors behave similarly to skeletal osteosarcomas. These rare cancers constitute approximately 1% of all soft-tissue sarcomas and less than 5% of all osteosarcomas [1,2]. The ratio of skeletal to extraskeletal osteosarcomas is around 25:1.

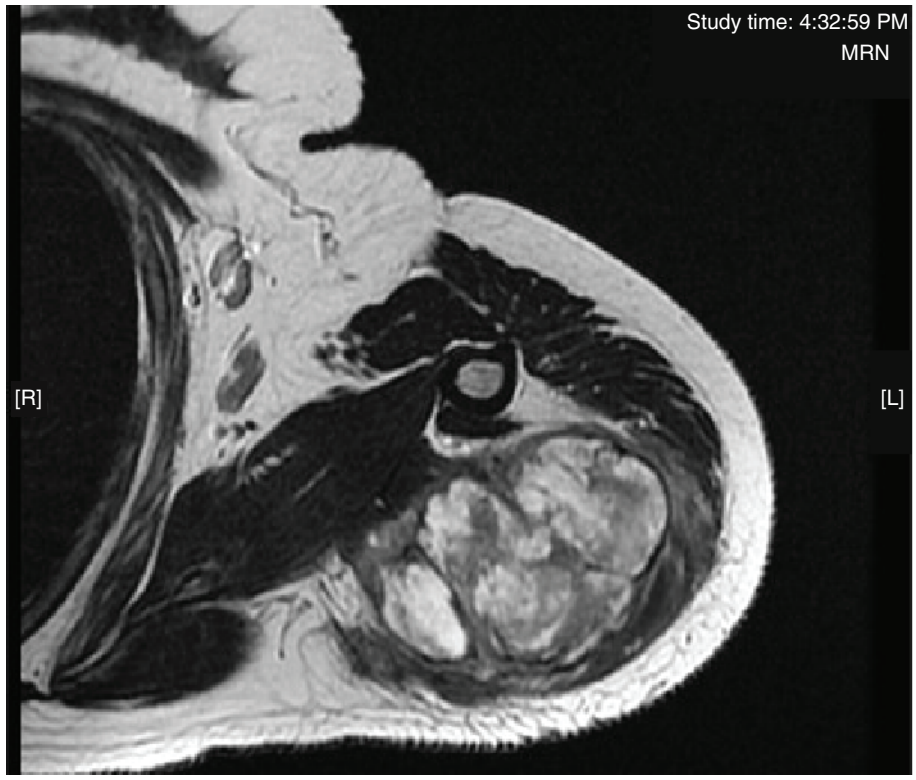

Figure 1. Axial contrast magnetic resonance image showing heterogeneously enhancing tumor occupying the posterior compartment of the left arm with areas of necrosis and soft tissue involvement.

Epidemiology

Unlike its skeletal counterparts, ESOS is predominantly seen in adults in the sixth and eighth decades of life [1,2,6]. Although some studies have shown no gender predilection [2], others have shown either a male [7,8] or female preponderance [6,9]. The pathogenesis of these tumors is not completely understood. Various theories have been postulated:

- Metaplasia theory: Huggins [10] states that metaplasia of connective tissue to bone can occur in soft tissues due to unknown cause;
- Theory of anoxia: Binkley and Stewart [11] postulate that tissue anoxia secondary to telangiectatic vessels is responsible for deposition of dense hyaline tissues within muscle or soft tissues;
- Theory of embryonic rests: propounds that during embryogenesis, bone-forming cells get misplaced into soft tissues and remain dormant for many years, ultimately producing bone under certain physiological conditions;
- Osteoblast migration theory: states that the bloodstream deposits osteoblasts at unusual locations, where they can produce osteoid.

A history of prior radiation exposure or trauma has often been implicated. A past history of irradiation can be elicited in 4–10% of patients [9]. In a study by Laskin *et al.*, ESOS accounted for 13% of all radiation-associated sarcomas [12]. In another study, four cases out of 14 radiation-associated sarcomas were ESOS, with a latency of around 4 years [13]. However, a prior history of trauma can only be elicited in about 12–30% cases. This history is important for many reasons: trauma can lead to the development of myositis ossificans which is one of the important differential diagnoses for ESOS (see below). Furthermore, osteosarcomas developing in pre-existing myositis have also been reported in the literature [14].

The most common locations for ESOS (in descending order of frequency) include lower limbs (75%, with the thigh being the commonest site, constituting 42–45% of cases) [1,3,7], upper limbs, retroperitoneum, trunk and head/neck regions [15].

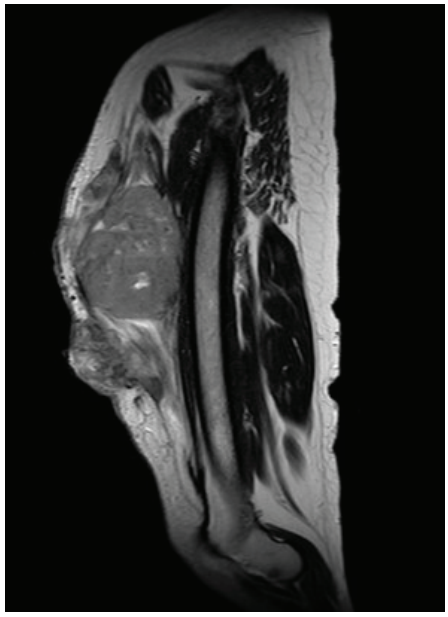

Figure 2. Sagittal contrast magnetic resonance image showing multilobulated tumor in the anterior compartment of the thigh with skin and extensive soft tissue involvement. Underlying bone is free.

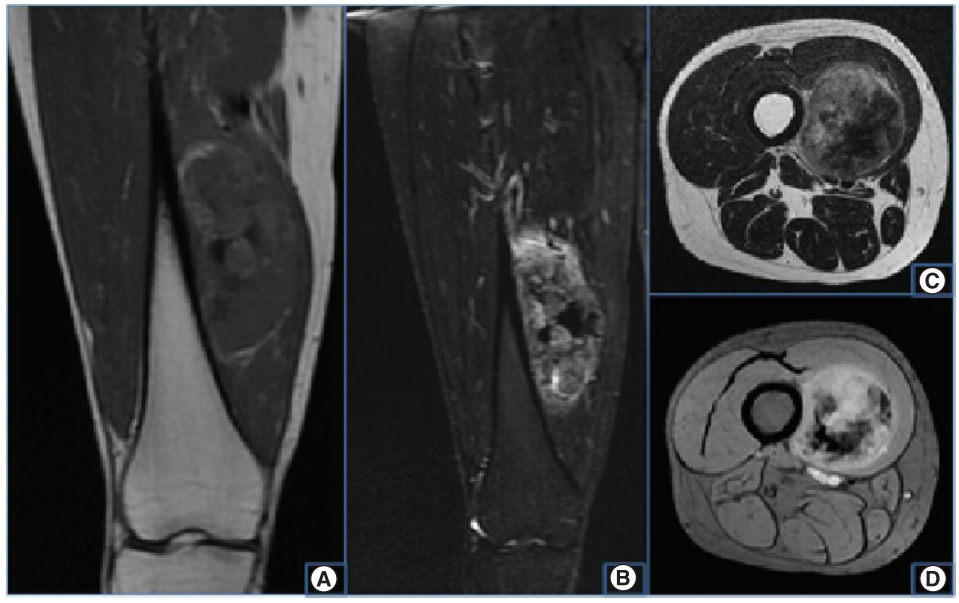

Figure 3. Contrast magnetic resonance image showing a well-defined spindle-shaped soft tissue mass measuring 5.3 × 4.7 × 11.5 cm in the medial aspect of the thigh. The mass appears hypointense on T1W, heterogeneously hyperintense on T2W and short tau inversion recovery sequences. Few hypointense areas are seen on both T1W and T2W sequences, suggestive of calcification/ ossification. The mass involves the vastus medialis and adductor magnus muscles, with associated edema. The mass abuts the femoral cortex; however, there is no evidence of cortical erosion. The femoral artery is compressed.

Pathology

ESOS are high-grade spindle cell tumors. Most of them are deep-seated and measure >5 cm. In a study by Lidang-Jenson *et al.* [15], out of the 25 cases of ESOS reported, 18 (72%) were intramuscular (i.e., deep). Though these tumors grossly appear well circumscribed, microscopically they often show an infiltrative pattern with satellite nodules. They often possess a thick fibrous capsule which can be adherent to adjacent and subjacent tissues [6]. Rarely, they may lie in contact with periosteum. They may often show central cystic areas admixed with areas of hemorrhage and necrosis [6].

Histologically, they are divided into six types or variants which are similar to their skeletal counterparts: osteoblastic, chondroblastic, fibroblastic, telangectatic, small-cell and giant-cell-rich types. The most common type is the osteoblastic variant. A 'reverse zoning' phenomenon (i.e., central zone of osteoid formation with a peripheral zone of atypical spindle cells) has been described. Angioinvasion has been observed in a few cases.

A very rare subtype of ESOS, the 'well-differentiated extraskeletal osteosarcoma', has been reported. First described by Umiker and Jafee [16] in 1953, about six cases have been published thus far [17]. Pathologically, these tumors show compact bone in the center with immature, neoplastic bone and spindle cells at the periphery, with cells showing mild to moderate atypia. This sub-type is known for its long latent period and late recurrences (heralding dedifferentiation) manifesting as sudden increase in size of the swelling, development of high-grade histology or the appearance of new tumor nodules [18].

The genetic basis of these tumors is largely unknown. Recently, four cases with complex clonal chromosomal aberrations and amplifications of chromosome 12q have been reported; this karyotypic abnormality has been associated with favorable prognosis [19].

Radiology

Several types of radiological investigations may be performed [20,21]:

- Plain radiographs: these show large soft-tissue tumors with spotty or massive calcification, although in about 50% cases calcification may be absent. The involvement of adjacent bone is rare;
- Magnetic resonance imaging: this is the investigation of choice for local staging and planning for the resection. On T1 weighted images, these tumors appear hypo- to iso-intense compared with muscle; on T2 weighted images, they appear hyper-intense enhancing with gadolinium, with a heterogeneous enhancement depending on the degree of necrosis within the tumor. Relationship to adjacent neurovascular bundle, joint and skip metastasis are best evaluated (Figure 1, Figure 2 & Figure 3);
- Computerized tomography: this is not used very frequently for evaluation. It identifies mineralization and necrosis within the tumor. However, despite being nonspecific, it is quite helpful in recognizing the adjacent bone involvement (Figure 4);
- Bone scintigraphy: this demonstrates increased uptake at both the primary and metastatic sites and is a useful modality in staging these tumors;
- Positron emission tomography: demonstrates uptake by the tumor with intense peripheral enhancement and relative central photopenia. The tracer uptake depends on the degree of hemorrhage and necrosis within the tumor.

Clinical features

Patients commonly present with a slowly growing soft tissue mass, most commonly in the thigh [1,3,7]. It may or may not be painful, although pain can be present in up to 50% of cases. In the Mayo Clinic study [8], 93% of patients presented with an enlarging soft tissue swelling. The median duration of symptoms is around 4–6 months. Most tumors are often deep to deep fascia and fixed to adjacent soft tissues. The incidence of lymph node involvement is variable and ranges from 4–5% upwards to around 25–30%, although nodal involvement is higher as compared with skeletal osteosarcomas.

Differential diagnosis

There are a number of pathological and radiological differential diagnoses for ESOS. Pathologically differential diagnoses include: myositis ossificans, synovial sarcoma, extraskeletal chondrosarcoma and ossifying fibromyxoid tumor of soft parts.

The radiological differential diagnoses include: myositis ossificans, osteoma of soft parts, synovial sarcoma, epithelioid sarcoma, liposarcoma, undifferentiated pleomorphic sarcoma, chondrosarcoma of soft parts and calcified hematoma. Other rare differentials include calcified lymph nodes, tumor calcinosis, pilomatrixoma, calcified tophi, calcified dermoid and fibroids (in females). The differential diagnoses of well-differentiated ESOS include parosteal osteosarcoma, ossifying fibromyxoid tumor and osteoma of soft parts.

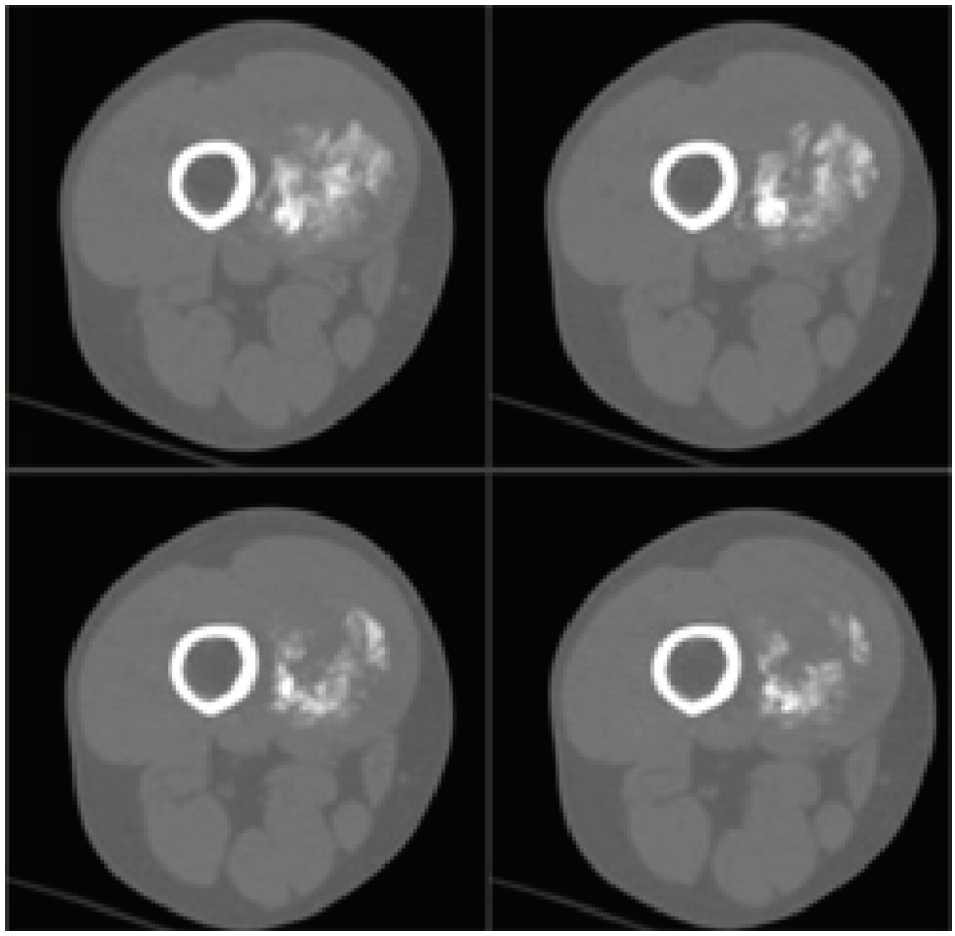

Figure 4. Axial computerized tomography scan image (in the bony window sequence) shows an ill-defined mass in the soft tissue adjacent to the bone with calcification. However, the bony cortex is uninvolved.

Treatment

Multimodal treatment is the cornerstone of success in the management of ESOS [22,23]. All three modalities – surgery, chemotherapy and radiation therapy – may be required to achieve optimum oncological outcomes, although the available data are retrospective and not conclusive. The studies of adjuvant therapy published thus far are divided regarding the benefit of adjuvant therapy.

Wide surgical excision with limb salvage surgery is a commonly performed procedure. In some cases, amputation may be required (large tumors with encasement of neurovascular bundle) to achieve negative surgical margins. Although there are no head-to-head comparisons for limb salvage versus amputation in extraskeletal osteosarcomas, criteria for limb salvage similar to those in conventional osteosarcomas apply. Lungs are the most common site of distant metastasis and are treated with resection if the metastatic tumor burden is limited.

Surgical treatment is usually followed by adjuvant chemotherapy and radiation. Some studies have demonstrated a survival benefit with the use of adjuvant treatment after standard resection [1,24,25]. A Japanese study showed an overall survival (OS) of 66% at 5 years in patients treated with chemotherapy and concluded some benefit based upon historical controls [24]. Similarly, Goldstein *et al.,* who conducted a retrospective study of 17 patients pooled from 17 different centers, reported an OS of 77% and event-free survival of 56% at 3 years. All patients but one were treated on conventional osteosarcoma protocols. Pertinent drawbacks of this study were limited patient numbers, the retrospective design, inadequate margin descriptions and short follow-up period [25]. In a recent published study by Liao *et al.*, there was no difference in outcome, progression-free survival (PFS) or OS in patients who received or did not receive chemotherapy [26]. In a nutshell, there is still a controversy because most of the data are retrospective, with small patient numbers spanning across decades. Research in sarcomas is plagued with issues related to limited number of patients and differing treatment at various treating centers. These issues hinder the possibility of

Table 1. Published literature on extraskeletal osteosarcomas.

Author (year)	n	Age (median), year	Site	Stage	Protocol of treatment	F/U (months)	LR	DM	5 year OS	D+D	Ref.
Chung (1987)	88	59	Ex: 67% RP: 17% Tr: 11.4%	NA	Sx alone: 51.1% Sx + CT: 6.8% Sx + RT: 3.4%	20.4	43%	63%	12.3% (DSS)	55.4%	[30]
Bane (1990)	26	54	Ex: 73% RP: 11.5%	NA	Sx alone: 34.6% Sx + CT: 38.5% Sx + RT: 15.4% Sx + RT + CT: 7.7%	140	50%	61.5%	28%	61.5%	[7]
Lee (1995)	40	50.7†	Ex: 76% Tr: 22.5%	L: 92.5% IV: 7.5%	Sx: 82.5% RT: 27.5% CT: 5%	71	45%	65%	38%	73%	[8]
Lidang-Jensen (1998)	25	67	Ex: 52%	NA	NA	NA	36%	60%	25% (DSS)	NA	[15]
McCarter (2000)	15	61	Ex: 100%	L: 100%	Sx + CT: 20% Sx + RT: 13.3% Sx + CT + RT: 20%	35	6.7%	40%	50% (DSS)	46.7%	[23]
Ahmed (2002)	60	55†	Ex: 52%	II: 25% III: 43% IV: 28%	Sx: 58.3% RT: 10% CT: 40%	NA	20%	40%	46%	54%	[27]
Goldstein-Jackson (2005)	17	44	Ex: 58.8% Tr: 41.2%	L: 88.2% IV: 11.8%	Sx + CT: 94% Sx + RT: 6%	38.4	23.5%	17.6%	77%	17.6%	[25]
Torigoe (2007)	20	50†	Ex: 65% Tr: 20%	II: 25% III: 65% IV: 10%	Sx: 95% Sx + CT: 75%	45†	15%	45%	66%	30%	[24]
Fabbri (2010)	36/48	53.6†	Ex: 69% Tr: 30.6%	L: 63.9% IV: 36%	Sx: 94.4% CT: 52.8% Sx + RT:16.7%	69.6†	64%	NA	41%	23/36	[31]
Choi (2014)	53	64	Ex: 88.7% Tr: 11.3%	L: 79.2% IV: 3.8%	Sx alone: 45.2% Sx + RT: 23.8% Sx + CT: 12% Sx + CT + RT: 19%	33	19%	38%	61% (3 year DSS)	50%	[9]

† Represents the mean value.

CT: Chemotherapy; D+D: Death due to disease; DM: Distant metastases; DSS: Disease-specific survival; Ex: Extremity; F/U: Follow-up; HR: Hazard ratio; II: Stage II disease; III: Stage III disease; IV: Stage IV disease; L: Localized disease; LR: Local recurrence; mo.: Months; NA: Not available; OS: Overall survival; RP: Retroperitoneum; RT: Radiotherapy; Sx: Surgery; Tr: Trunk.

Table 1. Published literature on extraskeletal osteosarcomas (cont.).

Author (year)	n	Age (median), year	Site	Stage	Protocol of treatment	F/U (months)	LR	DM	5 year OS	D+D	Ref.
Thampi (2014)	256	60.7†	Tr: 61% Ex: 40%	IV:18.6%	RT: 25.3%	NA	NA	NA	37%	HR: 0.75	[32]
Berner (2015)	37	68	Ex: 24% Tr: >60%	L: 78.4% IV: 21.6%	Sx: 78.3% Sx + CT: 13.5% Sx + RT + CT: 13.5%	NA	28%	52%	16% (DSS)	NA	[33]
Fan (2015)	36/40	59†	Ex: 80% Tr: 17%	II: 30.6% III: 69.4%	Sx: 100% CT: 36% RT: 44%	51	50%	NA	53% (DSS)	52.8%	[34]
Nystrom (2016)	12	60†	Ex: 83.3% Tr: 16.7%	IV: 33%	Sx alone: 25% Sx + CT: 58.3% Sx + RT: 33.3% Sx + CT + RT: 16.7%	29.3	16.7%	41.7%	11.7%	75%	[35]
Sio (2016)	37	55	Ex: 43% Tr: 43%	II: 14% III: 76% IV: 11%	Sx + CT: 39% Sx + CT + RT: 48%	45	16%	30%	43%	35%	[36]
Paludo (2018)	43	55	Ex: 60% Tr: 40%	L: 86% IV: 14%	Sx alone: 5% Sx + CT: 25% Sx + RT: 23% Sx + CT + RT: 45%	126	13%	44%	45%	NA	[28]
Wang (2018)	41	60	Ex: 63% Tr: 37%	II: 37% III: 42% IV: 17%	Sx alone: 39% CT: 53.7% RT: 56.1%	29.6	12.2%	17.1%	41%	NA	[37]
Longhi (2019)	266	57	Ex: 83% Tr: 16.9%	L: 80.8% IV: 18.7%	Sx alone: 21.8% Sx + CT: 39.3% Sx + RT: 20.3% Sx + RT + CT: 17.5%	22.5	52	88 + 36	47%	85.5%	[29]
Liao (2019)	22	55.5	Ex: 68% Tr: 32%	IIA: 23% IIB: 64% IV: 14%	Sx alone: 9% Sx + CT: 82% Sx + RT: 9%	48.5	45.5%	47.3%	58%	40.9%	[26]
Heng (2020)	451	58	Ex: 87% Tr: 11.4%	L: 84% IV: 16%	Sx alone: 33% Sx + CT: 26% Sx + RT: 19% Sx + CT + RT: 22%	NA	9%	38%	56%	43%	[38]

†Represents the mean value.

CT: Chemotherapy; D+D: Death due to disease; DM: Distant metastases; DSS: Disease-specific survival; Ex: Extremity; F/U: Follow-up; HR: Hazard ratio; II: Stage II disease; III: Stage III disease; IV: Stage IV disease; L: Localized disease; LR: Local recurrence; mo.: Months; NA: Not available; OS: Overall survival; RP: Retroperitoneum; RT: Radiotherapy; Sx: Surgery; Tr: Trunk.

generating level 1 evidence. This highlights the need for a common platform for multicenter collaboration at national and international level. The concept of neoadjuvant chemotherapy is controversial in ESOS. Neoadjuvant chemotherapy is generally reserved for a selected patient population – for example, those who present with upfront metastatic disease or large tumors at presentation – in view of the variable response rates.

Single or combination chemotherapy is commonly employed, with a wide armamentarium of agents (e.g., doxorubicin, ifosfamide, etoposide, platinum agents and/or methotrexate) to choose from. Chemotherapy schedules can include conventional osteosarcoma (platinum-based) or soft-tissue sarcoma (doxorubicin with or without ifosfamide) regimens. Response rates are variable, ranging from 19–45%; these are generally lower than for their skeletal counterparts. One study by Ahmed *et al.* [27] demonstrated a response rate of 19 versus 13% in favor of doxorubicin-based chemotherapy over platinum, highlighting the overall poor chemoresponsiveness. However, others who have included platinum in their chemotherapeutic schedules have reported better outcomes [1,25,28]. The Mayo Clinic study [28] depicted both OS and PFS advantages by adding cisplatin into the treatment arm. In short, the optimal chemotherapeutic regimen for ESOS still remains to be defined.

The role of radiotherapy is controversial, as these tumors are relatively radioresistant. Radiotherapy is more commonly used in centers that treat ESOS as soft-tissue sarcomas [29]. According to Sordillo *et al.* [1], radiotherapy increases survival and often delays time to recurrence. A large pooled analysis from Europe has suggested that radiotherapy seems to be beneficial in patients with tumors >5 cm and those undergoing complete surgical excision (R0). On the contrary, there is little or no benefit in R1 or R2 resections [29]. Table 1 depicts the various published studies on ESOS.

Clinical course & prognostic factors

The most common site of metastasis of these tumors is the lung (80%) [1,3,7]; however, in <25% cases, metastases occur in the bone (8–19%), lymph nodes (4–29%), liver (8–17%), adrenals (<5%), peritoneum, subcutaneous tissues and skin [39]. These metastatic deposits resemble the primary tumor in most cases, although they may or may not show calcifications or osteoid formation.

The overall prognosis is poor, with 80–90% of patients developing either local (45–50%) or distant (>60%) recurrences. In a study by Lee *et al.* [8], recurrences occurred in more than half of cases. Reports of recurrences as late as 10 years after diagnosis have also been documented. 60–70% of patients who develop recurrence eventually succumb to the disease. Spontaneous regression of tumors or the metastases is not uncommon [40].

The 5 year overall survival (OS) rate averages 25–37% with surgery alone. With the addition of adjuvant treatment, this figure has improved to upwards of 50% or more. In a study by Paludo *et al.* [28], the median OS was 50 months and median progression free survival (PFS) was 21 months. The survival was higher in those who had received chemotherapy. In contrast, Nystrom *et al.* [35] found no significant difference in outcomes between those who received chemotherapy and those who did not; the median survival was 17 months. Thampi *et al.* [32] reported higher (estimated 5 year) OS rates in skeletal osteosarcomas (50.8 vs 37%) compared with their extraskeletal counterparts. For localized disease, the OS figures were 63 and 47%, respectively; for metastatic disease, they were 19 and 10%, respectively.

Tumor size is an important prognostic factor. In a study by Bane *et al.* [7], tumors <5 cm in size were associated with better long-term survival compared with those >5 cm. Similarly, Sio *et al.* [36] showed that tumor size >10 cm was an important prognostic factor which significantly affected OS as well as disease-free survival (DFS) on multivariate analysis. In contrast, a study by Lee *et al.* [8] showed no difference in prognosis based on tumor size. Prognosis is better in those undergoing wide/radical resections compared with marginal resections [25]. There is no relationship between histological subtype and OS [1,6,7,15], though some have reported better prognosis with chondroblastic [8] and fibroblastic types [18]. Other poor prognostic factors include elevated LDH and ALP levels [1,3], older age [36,41] and metastatic disease at presentation. Factors such as tumor location [1], depth or quantity of osseous tissue or the degree of mitosis [6] do not alter the prognosis.

Conclusion

ESOS are rare and an important subset of soft-tissue tumors with distinct tumor biology, clinical course and management options. Multimodality treatment forms the mainstay of treatment. Complete surgical resection is the optimal modality for management of localized disease. Local and systemic recurrences are not uncommon and are the main cause of mortality in these tumors. The pathogenesis and genetic make-up of these tumors is yet to be fully elucidated.

Future perspective

With improvements in diagnostic radiology and pathology, we expect to find more and more patients being diagnosed with ESOS. Standardization of surgical as well as adjuvant chemotherapy regimens will see improvement in both disease-free survival and OS in the years to come. This may translate to achieving outcomes similar to those of conventional osteosarcomas. Multidisciplinary care of these patients would be the way forward.

Executive summary

Epidemiology
- Extraskeletal osteosarcomas are exceedingly rare cancers predominantly affecting older adults.
- Common sites of affliction are extremities, trunk and retroperitoneum.
- Etiopathogenesis remains poorly understood.

Pathology
- High-grade, deep-seated tumors with infiltrative pattern of spread demonstrating areas of hemorrhage and necrosis.

Clinical features
- Slow-growing soft-tissue masses, occasionally painful at presentation. Lymph nodes may be involved.

Radiology
- Conventional radiographs and CT scans demonstrate soft tissue calcification and cortical involvement. MRI is useful for local tumor staging and assessing neurovascular involvement.
- A number of radiological differentials should be excluded.

Treatment
- Wide local excision with limb salvage surgery is the preferred modality, although amputation might be needed in advanced tumors.
- There is a lack of prospective trials evaluating adjuvant radiation and chemotherapy. Published retrospective data thus far show conflicting results of oncological benefit.
- Platinum- and doxorubicin-based chemotherapy schedules are commonly employed.

Clinical course & prognostic factors
- Lung is the most common site of metastasis, and metastatic disease has an extremely poor prognosis.
- Survival rates have shown increasing trend over the years.
- Tumor size, histology, age, LDH levels and stage of disease are plausible prognostic factors influencing outcomes.

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The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

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