

Extraskeletal Mesenchymal Chondrosarcoma

Komal Arora, MD; Nicole D. Riddle, MD

• **Extraskeletal mesenchymal chondrosarcoma is a rare soft tissue sarcoma arising from soft tissues, mainly of the lower extremities, meninges, and orbits. It usually presents during the second to third decades of life, and has a slight predominance in females. Histologically, it has a typical biphasic pattern comprising small cells and islands of hyaline cartilage. It can pose a diagnostic challenge in small biopsy specimens where 1 of the 2 components can be absent. The prognosis is extremely variable; survival varies depending on the location of the tumor.**

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Extraskeletal mesenchymal chondrosarcoma (EMCS) is a rare malignant soft tissue tumor of chondroprogenitor cell origin. Mesenchymal chondrosarcoma (MCS) was first described by Lichtenstein and Bernstein¹ in 1959. Two years after its original description, Dahlin and Henderson² reported 9 cases from the files of the Mayo Clinic. Originally, it was considered restricted to bone, but that is no longer the case. More recent literature^{3,4} reports that 20% to 33% of these tumors occur at extraskeletal sites. The first case of MCS occurring at an extraskeletal site was described⁵ in 1964. Extraskeletal MCS represents about 1% of all chondrosarcomas. It is a high-grade malignancy with strong tendency for distant metastasis. The tumor has a characteristic biphasic histology comprising sheets of primitive mesenchymal cells with interspersed islands of well-differentiated hyaline cartilage. The tumor is diagnosed primarily on the basis of morphology because of a nonspecific immunoprofile and a general lack of availability of molecular diagnostics.

CLINICAL FEATURES

Most frequently, the tumor occurs in young adults during the second or third decades of life, with a slight preponderance in females. The tumor is found more commonly in the head and neck regions, including the

orbit, brain, meninges, and soft tissues of the face, and the lower extremities.^{4,6} Based on the tumor location, 2 separate categories of EMCS have been previously described: one occurring in skeletal muscle and soft tissue and the other in the central nervous system and spinal cord.⁷

PATHOGENESIS

Both the undifferentiated round or spindled cells and the differentiated cartilage are thought to originate from cartilage forming primitive mesenchyme. Studies⁸ performed on rat embryos demonstrated that the histologic architecture and the growth pattern of EMCS resemble the centripetal growth pattern of fetal cartilage. Subsequent immunohistochemical study by Wehrli et al⁹ confirmed that MCS had phenotypic features corresponding to the early condensational phase of cartilaginous differentiation. Their study showed Sox9, a master regulator of chondrogenesis, to be expressed immunohistochemically in both components of the tumor in 95.5% of cases.

RADIOLOGIC FINDINGS

The tumor appears as a well-circumscribed soft tissue mass with areas of granular, ring-and-arc, or irregularly shaped calcifications upon examination by computerized tomography. The noncalcified areas of the tumor are hypodense as compared with the surrounding soft tissue. These findings are not specific to EMCS, and can be seen in other benign cartilaginous tumors. When examined by magnetic resonance imaging, the calcified areas exhibit low intensity in both T1- and T2-weighted images, and the noncalcified areas show low intensity on T1- and high intensity on T2-weighted images. However, the magnetic resonance imaging findings may vary according to the patterns formed by the calcified and noncalcified areas. Focal low-intensity areas surrounded by high-intensity areas on T2-weighted imaging have been suggested to be characteristic of this tumor.^{6,10}

PATHOLOGIC FEATURES

Gross Examination

The tumors can range from 5 to 12 cm. Externally, they are often well circumscribed and covered with a thin fibrous capsule. The cut surface of the tumor is tan-white and soft to rubbery, with a glistening, lobulated appearance. Focal areas of hemorrhage and coarse calcifications are often seen.

Histologic Findings

A characteristic biphasic pattern, comprising sheets of undifferentiated round or spindled mesenchymal cells interspersed with islands of well-differentiated hyaline

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From the Department of Pathology, University of Texas Health Science Center, San Antonio. Dr Arora is now with the Department of Pathology and Genomic Medicine, Houston Methodist Hospital, Houston, Texas. Dr Riddle is now with the Department of Pathology, Cunningham Pathology, Birmingham, Alabama.

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Corresponding author: Komal Arora, MD, Department of Pathology and Genomic Medicine, Houston Methodist Hospital, 6565 Fannin St, Houston, TX 77030 (email: mreskxa2@houstonmethodist.org).

cartilage, is observed at low magnification (Figure 1). The undifferentiated mesenchymal cells have oval to elongated hyperchromatic nuclei and a scant amount of cytoplasm. These cells may be arranged in small clusters or around blood vessels in a hemangiopericytomatous pattern (Figure 2). The cartilaginous foci are usually well circumscribed with a well-defined interface with undifferentiated cells, or can rarely have poorly defined borders that gradually merge with the undifferentiated tumor cells. In addition, foci of osteoid formation and calcification can be seen. Other less common patterns include a predominant spindle cell component with variably prominent collagen formation (Figure 3).

Cytologic Findings

The diagnosis of EMCS can be challenging on cytology smears because of the rarity of this tumor. The smears are usually highly cellular and show clusters and scattered small, round blue cells with perivascular arrangement (Figure 4). These cells have a high nuclear to cytoplasmic ratio and round to oval hyperchromatic nuclei, with irregular nuclear membrane, fine to coarsely clumped chromatin, single to multiple nucleoli, and a small amount of pale cytoplasm. The background shows a fibrillary matrix infiltrated by tumor cells (Figure 5). A second population of larger tumor cells with abundant foamy cytoplasm containing multiple clear vacuoles embedded in abundant basophilic myxoid matrix can also be seen. Marked nuclear atypia and multiple irregular large nucleoli are common.¹¹

ANCILLARY STUDIES

Immunohistochemistry

Similar to other chondrosarcomas, the cartilaginous component is strongly positive for S100 protein. The undifferentiated cells show scant patchy positivity for S100 protein. As with other round cell tumors, the undifferentiated cells are positive for CD99 (strong membranous), neuron-specific enolase, and Leu-7, a fact limiting use of the previous immunostains. Sox9 is a recently described marker that shows nuclear positivity in both undifferentiated mesenchymal cells and cartilaginous component (Figure 6).^{9,12} Other markers, including cytokeratin, epithelial membrane antigen, and muscle markers, are usually negative. However, rare cases showing scattered tumor cells with desmin, myogenin, and myoD1 positivity have also been described in tumors with areas of rhabdomyosarcomatous differentiation.^{13,14} Type II collagen stains the extracellular matrix of the small cell regions in EMCS, and has been shown to be useful in distinguishing EMCS from other round cell sarcomas in a small series of limited tumor types.¹⁵ However, it cannot be used as a sensitive and specific marker for this tumor. In general, there is no single best stain for this tumor, and hence a panel of stains should be used to arrive at an accurate diagnosis. The tumor is also negative for FLI-1, which can be helpful in excluding MCS and identifying Ewing sarcoma when only small, round blue cells are present in the biopsy specimen.¹⁶ The tumor cells retain expression of INI-1 immunostain, and hence it can be used to distinguish EMCS in the central nervous system from atypical teratoid rhabdoid tumor.¹³ INI-1 expression can also be useful in distinguishing EMCS from other soft tissue tumors with loss of INI-1, such as epithelioid

sarcoma, myoepithelial carcinoma, and extraskelatal myxoid chondrosarcoma.¹⁷

Cytogenetics and Molecular Diagnostics

Most of the EMCSs studied in the past were found to have complex cytogenetic alterations. A 13;21 Robertsonian translocation has been described in 2 cases, 1 each of skeletal MCS and EMCS.¹⁸ Others have reported isolated cases with trisomy 8 as well as reciprocal translocation (11;22)(q24;q12).^{19,20} Shakked et al⁶ previously reported a complete list of the published cytogenetic findings. Most of the published cytogenetic studies revealed diverse karyotypic findings, until recently Wang et al²¹ identified a novel, recurrent *HEY1-NCOA2* (8;8)(q21;q13) fusion in MCS. However the t(8;8) fusion can be cryptic and may not be seen in all the karyograms. According to the current World Health Organization classification of soft tissue tumors, the consistent molecular detection of the *HEY1-NCOA2* fusion in EMCS establishes it as a marker of potential clinical utility.²² Later, Nyquist et al²³ reported another novel fusion between the *IRF2BP2* gene and the transcription factor *CDX1* gene arising from the translocation through fluorescent in situ hybridization and whole-transcriptome sequencing analysis. Unlike the central and periosteal chondrosarcomas, *IDH1* and *IDH2* mutations are not detected in EMCS.²⁴ If a diagnosis of EMCS is considered, the tumor can be sent to centers performing gene sequencing whenever the local testing for gene fusion is unavailable.

DIFFERENTIAL DIAGNOSIS

Mesenchymal chondrosarcoma can be very difficult to diagnose with certainty if no overt cartilaginous differentiation is visible in the tissue specimen, especially in small biopsy specimens. The differential diagnosis for EMCS includes synovial sarcoma, malignant solitary fibrous tumor, Ewing sarcoma, and other small, round blue cell tumors, particularly in biopsy specimens.

Synovial sarcoma usually lacks the cartilaginous component and is positive for keratin, epithelial membrane antigen, and transducin-like enhancer of split 1 by immunohistochemistry. Synovial sarcoma also shows the characteristic t(X;18) translocation, which is not seen in EMCS. Although Ewing sarcoma shows CD99 positivity, similar to EMCS, it lacks the cartilaginous component and can have either *EWSR1*- or *FUS*- gene fusions. A number of fusions have been reported, with the most common being *EWSR1-FLI1*. Malignant solitary fibrous tumor is usually patternless, lacks cartilaginous component, and is positive for CD34. However, the tumor is not always patternless and may be negative for CD34. Positivity for Stat6 immunohistochemical stain is helpful in diagnosing such cases of solitary fibrous tumor.²⁵ *NAB2-STAT6* fusion is characteristic of solitary fibrous tumor and can be of diagnostic utility.²⁶

TREATMENT AND OUTCOME

Surgery involving wide resection followed by adjuvant chemotherapy is the mainstay of treatment. The role of adjuvant radiation therapy is not well defined. Addition of chemotherapy has been reported to improve survival.^{6,27} In general, EMCS is an aggressive tumor with a propensity to metastasize. A recent retrospective review²⁸ in children and young adults reported 68.2% 5-year disease-free survival

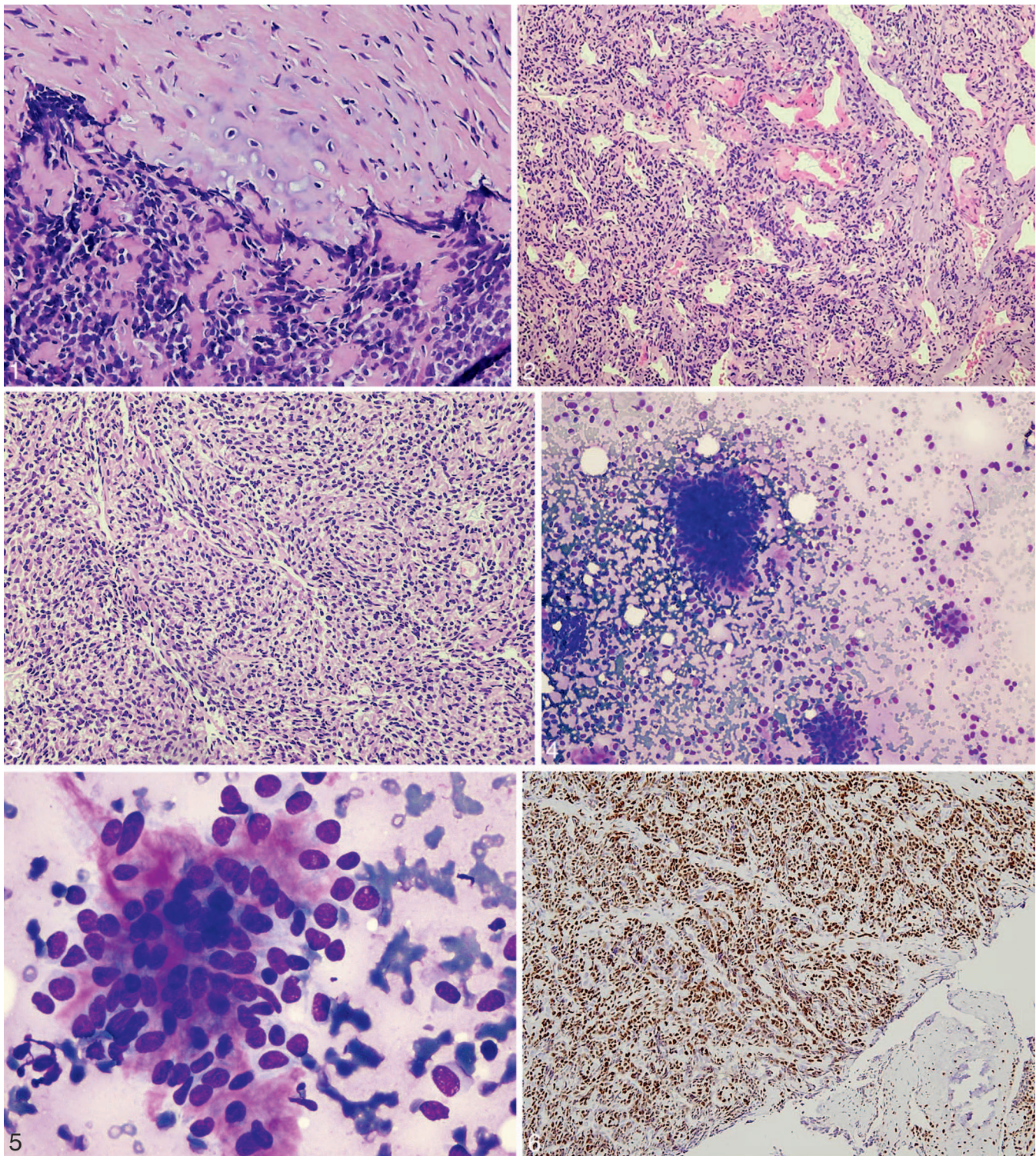


Figure 1. Photomicrograph showing the biphasic component of mesenchymal chondrosarcoma. In the upper half of the image there is well-differentiated hyaline cartilage, and in the lower half the undifferentiated small cell component is seen (hematoxylin-eosin, original magnification $\times 120$).

Figure 2. Photomicrograph showing hemangiopericytoma-like pattern of tumor cells around blood vessels (hematoxylin-eosin, original magnification $\times 100$).

Figure 3. Photomicrograph showing the spindle cell component of mesenchymal chondrosarcoma (hematoxylin-eosin, original magnification $\times 100$).

Figure 4. Photomicrograph showing highly cellular cytology smears (Diff-Quik, original magnification $\times 100$).

Figure 5. Photomicrograph showing round tumor cells having high nuclear to cytoplasmic ratio infiltrating a fibrillary matrix (Diff-Quik, original magnification $\times 400$).

Figure 6. Photomicrograph of immunohistochemical staining of tumor cells with SOX9 (original magnification $\times 120$).

and 88.9% overall survival at a median follow-up of 4.8 years. Another recent study²⁹ found that the overall survival was worse for tumors in axial locations compared with appendicular and cranial locations. In this study, the presence of metastatic disease and tumor size were found to be the main predictors of poor outcome.

References

1. Lichtenstein L, Bernstein D. Unusual benign and malignant chondroid tumors of bone: a survey of some mesenchymal cartilage tumors and malignant chondroblastic tumors, including a few multicentric ones, as well as many atypical benign chondroblastomas and chondromyxoid fibromas. *Cancer*. 1959;12(6):1142–1157.
2. Dahlin DC, Henderson ED. Mesenchymal chondrosarcoma: further observations on a new entity. *Cancer*. 1962;15(2):410–417.
3. Dobin SM, Donner LR, Speights VO Jr. Mesenchymal chondrosarcoma: a cytogenetic, immunohistochemical and ultrastructural study. *Cancer Genet Cytogenet*. 1995;83(1):56–60.
4. Nakashima Y, Unni KK, Shives TC, Sweet RG, Dahlin DC. Mesenchymal chondrosarcoma of bone and soft tissue: a review of 111 cases. *Cancer*. 1986;57(12):2444–2453.
5. Dowling EA. Mesenchymal chondrosarcoma. *J Bone Joint Surg Am*. 1964;46(4):747–754.
6. Shakked RJ, Geller DS, Gorlick R, Dorfman HD. Mesenchymal chondrosarcoma: clinicopathologic study of 20 cases. *Arch Pathol Lab Med*. 2012;136(1):61–75.
7. Chetty R. Extraskelletal mesenchymal chondrosarcoma of the mediastinum. *Histopathology*. 1990;17(3):261–263.
8. Vilanova JR, Simon-Marin R, Burgos-Bretones J, Ramirez MM, Rivera-Pomar JM. Non-conventional chondrosarcomas and chondrogenesis. *Histopathology*. 1985;9(7):719–728.
9. Wehrli BM, Huang W, De Crombrughe B, Ayala AG, Czerniak B. Sox9, a master regulator of chondrogenesis, distinguishes mesenchymal chondrosarcoma from other small blue round cell tumors. *Hum Pathol*. 2003;34(3):263–269.
10. Shapeero LG, Vanel D, Couanet D, Contesso G, Ackerman LV. Extraskelletal mesenchymal chondrosarcoma. *Radiology*. 1993;186(3):819–826.
11. Vij M, Krishnani N, Agrawal V, et al. Cytomorphology of intraparenchymal mesenchymal chondrosarcoma in frontal lobe: report of a case. *Diagn Cytopathol*. 2011;39(11):837–842.
12. Fanburg-Smith JC, Auerbach A, Marwaha JS, Wang Z, Rushing EJ. Reappraisal of mesenchymal chondrosarcoma: novel morphologic observations of the hyaline cartilage and endochondral ossification and beta-catenin, Sox9, and osteocalcin immunostaining of 22 cases. *Hum Pathol*. 2010;41(5):653–662.
13. Fanburg-Smith JC, Auerbach A, Marwaha JS, et al. Immunoprofile of mesenchymal chondrosarcoma: aberrant desmin and EMA expression, retention of INI1, and negative estrogen receptor in 22 female-predominant central nervous system and musculoskeletal cases. *Ann Diagn Pathol*. 2010;14(1):8–14.
14. Salvati M, Caroli E., Frati A. et al. Central nervous system mesenchymal chondrosarcoma. *J Exp Clin Cancer Res*, 2005;24(2):317–324.
15. Müller S, Söder S, Oliveira AM, Inwards CY, Aigner T. Type II collagen as specific marker for mesenchymal chondrosarcomas compared to other small cell sarcomas of the skeleton. *Mod Pathol*. 2005;18(8):1088–1094.
16. Lee AF, Hayes MM, LeBrun D, et al. FLI-1 distinguishes Ewing sarcoma from small cell osteosarcoma and mesenchymal chondrosarcoma. *Appl Immunohistochem Mol Morphol*. 2011;19(3):233–238.
17. Hollmann TJ, Hornick JL. INI1-deficient tumors: diagnostic features and molecular genetics. *Am J Surg Pathol*. 2011;35(10):e47–e63.
18. Naumann S, Krallman PA, Unni KK, Fidler ME, Neff JR, Bridge JA. Translocation der(13;21)(q10;q10) in skeletal and extraskelletal mesenchymal chondrosarcoma. *Mod Pathol*. 2002;15(5):572–576.
19. Gatter KM, Olson S, Lawce H, Rader AE. Trisomy 8 as the sole cytogenetic abnormality in a case of extraskelletal mesenchymal chondrosarcoma. *Cancer Genet Cytogenet*. 2005;159(2):151–154.
20. Sainati L, Scapinello A, Montaldi A, et al. A mesenchymal chondrosarcoma of a child with the reciprocal translocation (11;22)(q24;q12). *Cancer Genet Cytogenet*. 1993;71(2):144–147.
21. Wang L, Motoi T, Khanin R, et al. Identification of a novel, recurrent HEY1-NCOA2 fusion in mesenchymal chondrosarcoma based on a genome-wide screen of exon-level expression data. *Genes Chromosomes Cancer*. 2012;51(2):127–139.
22. Nakashima Y, de Pinieux G, Ladanyi M. Mesenchymal chondrosarcoma. In: Fletcher CDM, Bridge JA, Hogendoorn PCW, Mertens F, eds. *Pathology and Genetics of Tumours of Soft Tissue and Bone*. Lyon, France: IARC Press; 2013: 271–272. *World Health Organization Classification of Tumours*; vol 5.
23. Nyquist KB, Panagopoulos I, Thorsen J, et al. Whole-transcriptome sequencing identifies novel IRF2BP2-CDX1 fusion gene brought about by translocation t(1;5)(q42;q32) in mesenchymal chondrosarcoma. *PLoS One*. 2012;7(11):e49705.
24. Amary MF, Bacsi K, Maggiani F, et al. IDH1 and IDH2 mutations are frequent events in central chondrosarcoma and central and periosteal chondromas but not in other mesenchymal tumours. *J Pathol*. 2011;224(3):334–343.
25. Vogels RJ, Vletterie M, Versleijen-Jonkers YM, et al. Solitary fibrous tumor—clinicopathologic, immunohistochemical and molecular analysis of 28 cases. *Diagn Pathol*. 2014;29(11):9:224.
26. Mohajeri A, Tayebwa J, Collin A, et al. Comprehensive genetic analysis identifies a pathognomonic NAB2/STAT6 fusion gene, nonrandom secondary genomic imbalances, and a characteristic gene expression profile in solitary fibrous tumor. *Genes Chromosomes Cancer*. 2013;52(10):873–886.
27. Cesari M, Bertoni F, Bacchini P, Mercuri M, Palmerini E, Ferrari S. Mesenchymal chondrosarcoma: an analysis of patients treated at a single institution. *Tumori*. 2007;93(5):423–427.
28. Bishop MW, Somerville JM, Bahrami A, et al. Mesenchymal chondrosarcoma in children and young adults: a single institution retrospective review. *Sarcoma*. 2015;2015:608279. doi: 10.1155/2015/608279.
29. Schneiderman BA, Kliethermes SA, Nystrom LM. Survival in mesenchymal chondrosarcoma varies based on age and tumor location: a survival analysis of the SEER database. *Clin Orthop Relat Res*. 2017;475(3):799–805.