Refinements in Sarcoma Classification in the Current 2013 World Health Organization *Classification of Tumours of Soft Tissue and Bone*

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KEYWORDS

• Sarcoma • Soft tissue • Bone • Tumor • Classification • Histology
• World Health Organization

KEY POINTS

- The 2013 World Health Organization *Classification of Tumours of Soft Tissue and Bone* provides updated and reproducible diagnostic criteria based on morphologic, immunohistochemical, and genetic/molecular data.
- Most soft tissue and bone tumors can be classified according to differentiation as determined by morphologic, immunohistochemical, and genetic features.
- The numerous advances in the genetic/molecular features of soft tissue and bone tumors has facilitated more accurate classification and the development of useful diagnostic tools.

INTRODUCTION

The fourth edition of the World Health Organization (WHO) *Classification of Tumours of Soft Tissue and Bone*[1] was published in 2013, and represents an updated consensus text assembled by an expert working group. The WHO classification propagates reproducible diagnostic criteria and is organized by tumor type as determined by morphologic, immunohistochemical, and genetic features. The classification of soft tissue and bone tumors has evolved considerably in the 11 years since the third volume,[2] primarily because of genetic insights that have led to the development of useful diagnostic markers, reclassification of certain entities, and recognition of novel distinct

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tumor types. For soft tissue and bone neoplasms, this consensus work is important given the diagnostic challenges caused by the rarity of sarcomas, diversity of tumor types, and rapid rate of immunohistochemical and genetic/molecular advances. The WHO classification stratifies soft tissue and bone tumors into 4 categories based on clinical behavior: (1) benign; (2) intermediate, locally aggressive; (3) intermediate, rarely metastasizing; and (4) malignant (ie, sarcoma). Accurate pathologic diagnosis is critical for appropriate prognostication and management, and requires correlation with clinical and radiologic data. This article reviews updates in the 2013 WHO classification (as well as new findings since its publication), outlining changes from the 2002 volume; although the focus of this article is sarcoma classification, selected benign tumors are also reviewed.

TUMORS OF SOFT TISSUE

Adipocytic Tumors

No major changes in the category of adipocytic tumors were effected, with the exception of the removal of the terms round cell liposarcoma and mixed-type liposarcoma. Myxoid liposarcoma is graded based on cellularity using a 3-tier system (low, intermediate, and high); transition between different grades is often seen within a tumor. Histologic grade is prognostic and high-grade tumors show greater risk for recurrence, metastasis, and tumor-related death, thus tumors are classified according to the highest grade present. Although some high-grade myxoid liposarcomas show a predominance of round cell morphology (hence previously classified as round cell liposarcoma), the hypercellular high-grade areas more commonly show a spindle cell morphology. All myxoid liposarcomas, regardless of grade, harbor *FUS-DDIT3* gene fusion,[3] or rarely an alternate *EWSR1-DDIT3* fusion.[4]

Most tumors previously classified as mixed-type liposarcoma are now considered to represent unusual examples of dedifferentiated liposarcoma, based on currently available immunohistochemical and molecular studies that confirm the presence of amplification of chromosome 12q13-15. Amplification of 12q13-15 (via supernumerary ring or giant marker chromosomes) results in overexpression of the encoded gene products, MDM2 and CDK4. Since 2002, MDM2 and CDK4 immunohistochemistry and/or fluorescence in situ hybridization for *MDM2* gene amplification have come into widespread use for the diagnosis of atypical lipomatous tumor (ALT)/well-differentiated liposarcoma (WDLPS) and dedifferentiated liposarcoma (DDLPS).[5] In addition to enabling accurate reclassification of mixed-type liposarcoma, these immunohistochemical and molecular studies also facilitate the diagnosis of retroperitoneal lipoma and exclude the more likely possibility of WDLPS at this anatomic site; the former follows a benign clinical course,[6,7] unlike WDLPS, which requires surgical resection given its risk for recurrence and dedifferentiation.

Note that although the 2013 WHO classification lists the term ALT as the section heading, it is pointed out that the retention of WDLPS in practice is still appropriate for tumors in sites at which complete resection is often not feasible, such as the mediastinum and retroperitoneum, and there is associated significant morbidity by locally aggressive growth, recurrence, and extensive surgical resections that often requires removal of multiple organs.

DDLPS, previously defined as a nonlipogenic sarcoma, is now known to occasionally show homologous lipoblastic differentiation by having morphologic features indistinguishable from pleomorphic liposarcoma.[8] Since publication of the 2013 WHO classification, a subset of such lipogenic DDLPS have been reported to show low nuclear grade.[9] It has also recently been suggested that the histologic grade of DDLPS is