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<p>The 2020 WHO Classification of Soft Tissue and Bone Tumors features revisions based on recent advances in the histopathologic and molecular diagnostic workup of soft tissue tumors. We herein highlight select new entities in the categories of adipocytic tumors, fibroblastic and myofibroblastic tumors, smooth muscle tumors, vascular tumors, and tumors of uncertain differentiation, a novel category for undifferentiated round cell sarcomas of bone and soft tissue, and revisions to nomenclature, grading, and risk stratification. This article provides an overview on revised diagnostic criteria, state-of-the-art genetic and immunohistochemical markers, and prognostication with an impact on clinical management. In addition, we discuss challenging aspects in the diagnosis and/or prognostication of select well-established entities that will be discussed in more detail in other articles of this book.</p>	
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<p>Sarcoma and locally aggressive connective tissue tumors are a complex group of diseases with a growing number of histotypes in the most recent WHO classification. Most of these tumors are rare (incidence $<6/10^5/y$) or ultrarare ($<1/10^6/y$). Despite their rarity, sarcomas are often good models for the development of personalized medicine, and a large number of new clinical trials in select histotypes and molecular subsets were reported</p>	

during the past 5 years, leading to a faster rate of new drug approvals. We analyzed the published literature and the abstracts reported in major congresses dedicated to sarcoma and connective tissue tumor management in the last 5 years. Several targeted therapies, cytotoxic treatments, and immunotherapies have demonstrated activity in dedicated histologic and molecular subtypes of sarcomas. The majority of the studies for ultrarare entities are uncontrolled studies, as a consequence of the rarity of histotypes, but randomized controlled trials were available in the less rare histotypes. Most successful trials were based on biomarker selection, which were often driver molecular alterations, while a large number of ongoing research programs aim to identify biomarkers in parallel to new drug development. Availability of the new agents varies across countries. This article describes the new drugs that made it through to the finish line and new agents with promising activity that are in later stages of investigation in the large family of malignant connective tissue tumors.

Immunotherapy in Sarcoma: Where Do Things Stand?

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Cristiam Moreno Tellez, Yan Leyfman, Sandra P. D'Angelo, Breelyn A. Wilky, and Armelle Dufresne

Early experiences with modern immunotherapy have been disappointing in trials of unselected sarcoma subtypes. However, remarkable efficacy has been observed with immune checkpoint inhibitors (ICIs) in a subset of patients, with the most promising outcomes to date in alveolar soft part sarcoma, cutaneous angiosarcoma, undifferentiated pleomorphic sarcoma (UPS), and dedifferentiated liposarcoma (dLPS). Adoptive cellular therapies targeting cancer testis antigens have shown promising activity, but only synovial sarcoma (SS) and myxoid/round cell liposarcomas reliably express these targets. The majority of sarcomas are immunologically "cold" with sparse immune infiltration, which may explain the poor response to immunotherapy. Current immunotherapy trials for sarcomas explore combination therapies with checkpoint inhibitors to overcome immune evasion and novel targets in adoptive cellular therapies. The role of tertiary lymphoid structures, PD-L1 expression, tumor mutational burden, microsatellite instability, and tumor lymphocytes as biomarkers for response are areas of active investigation. In this review, we highlight prior and ongoing clinical efforts to improve outcomes with immunotherapy and discuss the current state of understanding for biomarkers to select patients most likely to benefit from this approach.

Retroperitoneal and Mesenteric Liposarcomas

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Caroline C.H. Siew, Sameer S. Apte, Marco Baia, David E. Gyorki, Samuel Ford, and Winan J. van Houdt

Retroperitoneal liposarcomas are a rare entity and are comprised mostly of the well-differentiated and dedifferentiated subtypes. Eight-year survival ranges from 30% to 80% depending on histologic subtype and grade. Surgery is the cornerstone of treatment and compartment resection is the current standard. Mesenteric liposarcomas are extremely rare and comprise more high-grade lesions, with poorer prognosis of 50% 5-year overall survival. They are managed with a similar aggressive surgical approach. This review presents the current management of retroperitoneal and mesenteric liposarcomas.

Management of Myxofibrosarcoma and Undifferentiated Pleomorphic Sarcoma 419

Aimee M. Crago, Kenneth Cardona, Hanna Koseła-Paterczyk, and Piotr Rutkowski

Undifferentiated pleomorphic sarcoma (UPS) and myxofibrosarcoma (MFS) are genomically complex tumors commonly diagnosed in the extremities or trunk of elderly patients. They likely represent a spectrum of disease differentiated by myxoid stroma and curvilinear vessels observed in MFS but not in UPS. Limb-sparing surgery is the standard of care although the infiltrative nature of MFS mandates wider resection margins than are necessary for UPS. UPS are conversely associated with high risks of distal recurrence, often prompting recommendations for adjuvant chemotherapy. In both histologies, anthracycline-based therapies or gemcitabine and docetaxel are used to manage advanced disease; immunotherapy may be of benefit in a subset of patients.

Gastrointestinal Stromal Tumor: New Insights for a Multimodal Approach 431

Ashwyn K. Sharma, Teresa S. Kim, Sebastian Bauer, and Jason K. Sicklick

Over the past 20 years, gastrointestinal stromal tumor (GIST) has evolved into an increasingly complex clinical entity with ever more challenges. While surgical resection is the gold standard, advancements in genetic testing, therapeutic options, immunotherapy, and management of metastatic disease necessitate a comprehensive, multimodal approach for these tumors. This chapter highlights the importance of genomic testing of GIST, the use of neoadjuvant and adjuvant therapy for localized disease, surgical principles for GIST, as well as current and new approaches for addressing metastatic disease.

Management of Desmoid Tumors 447

Gaya Spolverato, Giulia Capelli, Bernd Kasper, and Mrinal Gounder

The management of desmoid tumors (DT) is shifting toward conservative and patient-tailored strategies. Active surveillance is currently considered the first line of treatment for most DT patients, according to international guidelines. When active treatment is required, several systemic and local treatments are considered. The choice of the first-line systemic therapy and the management of recurrence still represent a therapeutic challenge, for which well-defined and shared guidelines are lacking. Such issues represent the next challenge for The Desmoid Tumor Working Group.

Toward Better Understanding and Management of Solitary Fibrous Tumor 459

Karineh Kazazian, Elizabeth G. Demicco, Marc de Perrot, Dirk Strauss, and Carol J. Swallow

Solitary fibrous tumor (SFT) comprises a histologic spectrum of soft tissue neoplasms that are characterized by the unique NAB2-STAT6 gene fusion. Changes in diagnostic terminology and site-specific classification over the past few decades have resulted in a disjointed literature. Complete surgical excision with preservation of function remains the mainstay of treatment. New risk stratification systems including risk factors such as mitotic rate, age, tumor size, and presence of necrosis, among others, can be used to predict risk of recurrence or metastasis. Long-term

follow-up after surgical resection is recommended. The clinical manifestations, diagnosis, management, and prognosis of SFT are reviewed here.

Management of Vascular Sarcoma

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Aparna Subramaniam, Claudia Giani, Andrea Napolitano, Vinod Ravi, Anna Maria Frezza, and Robin L. Jones

Vascular sarcomas encompass 3 well-defined sarcoma types: heman-gioendothelioma, Kaposi sarcoma, and angiosarcoma. These distinct types are exceedingly rare and very different in terms of clinical behavior, biological features, and treatment approach. Because of this rarity and heterogeneity, it is crucial that vascular sarcomas are treated in sarcoma reference centers or networks, in order to ensure optimal management. The diversity of vascular sarcomas also needs to be taken into account in the design of clinical trials, in order to produce meaningful results that can be consistently translated into everyday clinical practice.

Management of Skin Sarcomas

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Valentina Messina, Brandon Cope, Emily Z. Keung, and Marco Fiore

Skin sarcomas are tumors that are superficial and small in size in comparison with other sarcomas arising in intramuscular or intrabdominal sites. Skin sarcomas are often underrecognized and misdiagnosed. A high level of suspicion is needed, as early recognition and appropriate management including initial surgery is important for oncologic outcomes. Here, the epidemiology, clinical presentation, management, and surveillance of 4 common cutaneous sarcomas are reviewed.

Leiomyosarcoma: Current Clinical Management and Future Horizons

527

Nicolas Devaud, Olga Vornicova, Albiruni R. Abdul Razak, Korosh Khalili, Elizabeth G. Demicco, Cristina Mitric, Marcus Q. Bernardini, and Rebecca A. Gladdy

Leiomyosarcomas are soft tissue tumors that are derived from smooth muscle mainly in the pelvis and retroperitoneum. Percutaneous biopsy is paramount to confirm diagnosis. Imaging is necessary to complete clinical staging. Multimodal treatment should be directed by expert sarcoma multidisciplinary teams that see a critical volume of these rare tumors. Surgery is the mainstay of curative intent treatment; however due to its high metastatic progression, there may be a benefit for neoadjuvant systemic treatment. Adjuvant systemic treatment has no proven disease-free survival, and its main role is in the palliative setting to potentially prolong overall survival.

Management of Synovial Sarcoma and Myxoid Liposarcoma

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Nadia Hindi and Rick L. Haas

Synovial sarcoma and myxoid liposarcoma are translocation-related sarcomas, with a high risk of developing distant metastasis, which often affect young patients and which are sensitive to chemo and radiotherapy. Surgery is the mainstay of therapy in localized disease. In these entities, peri-operative radiotherapy is frequently administered, and chemotherapy is evaluated in patients with high-risk limb/trunk wall tumors in which an

advantage in overall survival has been shown in the latest clinical trials. In the advanced setting, new strategies, such as cellular therapy are being developed in these histologic types, with promising, although still preliminary, results.

The Cancer Genome Atlas: Impact and Future Directions in Sarcoma

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Jessica Burns, Jeffrey M. Brown, Kevin B. Jones, and Paul H. Huang

Sarcomas are rare and heterogeneous malignancies. Owing to their low prevalence and limited capacity to conduct large-scale clinical trials, understanding the molecular mechanisms of sarcomagenesis has become important in determining appropriate treatment. The Cancer Genome Atlas soft tissue sarcoma (STS) project (TCGA-SARC) was the largest and most comprehensive attempt to profile the genomics of multiple STS subtypes. TCGA-SARC made huge contributions to disease understanding. Since the publication of TCGA-SARC, numerous studies have used molecular profiling to assess STS biology. Herein molecular profiling studies in STS are reviewed and future directions with regard to omics profiling in STS research are discussed.