Role of Genetics in Sarcoma for the Practicing General Surgeon

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KEYWORDS

• Sarcoma • Genetics • Hereditary sarcoma syndromes

KEY POINTS

- Most sarcomas occur sporadically.
- Germline mutations cause a small minority of sarcomas.
- Multidisciplinary care of patients with sarcoma is paramount.
- Aside from inherited syndromes, prior irradiation for other cancers can increase the risk of developing secondary sarcoma.
- Management of all hereditary sarcoma syndromes requires lifelong surveillance and multidisciplinary care to minimize death from cancer.

INTRODUCTION

Soft tissue sarcomas (STS) comprise a heterogeneous group of rare mesenchymal tumors exhibiting diverse primary site locations and clinical behavior.[1] With over 100 distinct histologic subtypes, accurate diagnosis and subtype-specific management are crucial for optimal patient outcomes.[2] The rarity and heterogeneity of these tumors frequently complicate diagnosis and treatment, often leading to delayed intervention and suboptimal therapeutic strategies.[3] The multidisciplinary management of soft tissue sarcomas in specialized sarcoma centers is highly recommended, as highlighted by consensus conference recommendations.[4] The most common soft tissue sarcoma subtypes are liposarcomas, leiomyosarcomas, pleomorphic sarcomas, and synovial sarcomas, which predominantly manifest in the extremities and trunk.[5] These mesenchymal neoplasms arise from various connective tissues including fat, muscle, nerves, and blood vessels, with retroperitoneal or intra-abdominal involvement occurring in a significant minority of cases.[6–8] A comprehensive understanding of these varied presentations, alongside the molecular and genetic underpinnings of each subtype, is essential for guiding targeted therapeutic interventions.[9]

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Abbreviations	
NF1	neurofibromatosis type 1
STS	soft tissue sarcomas

GENETICS

Most sarcomas occur sporadically but approximately 10% to 20% are associated with inherited genetic predisposition syndromes. Key genetic syndromes increasing sarcoma risk include Li-Fraumeni syndrome, neurofibromatosis type 1, and retinoblastoma. While rare, genetic testing can identify these inherited risks to guide surveillance when appropriate.

Inherited (Germline) Mutations:

Li-Fraumeni Syndrome: a mutation in the TP53 gene, often causing soft tissue sarcomas and other cancer.

Neurofibromatosis Type 1 (NF1): Linked to malignant peripheral nerve sheath tumors.

Retinoblastoma: Inherited eye cancer linked to higher sarcoma risk.

Other Syndromes: Gardner syndrome, Werner syndrome and familial adenomatous polyposis.

Genetic changes in tumors (somatic mutations):

Most sarcomas develop due to acquired gene mutations after birth, often involving complex genomic changes or specific chromosomal translocations that create fusion genes, such as the SS18-SSX fusion in synovial sarcoma. This will be discussed later in this article.

RISK FACTORS

Aside from inherited syndromes, prior radiation therapy for other cancers can increase the likelihood of developing a secondary sarcoma.

DIAGNOSIS

The diagnostic landscape for soft tissue sarcomas has progressively shifted from reliance on histopathological morphology alone to an integrative approach incorporating molecular analyses, which are increasingly crucial for accurate classification and treatment planning.[10] Despite the complexities, advances in diagnostic imaging, pathologic classification, and molecular profiling have significantly refined the diagnostic approach, facilitating more precise staging and treatment planning.[11] For instance, the European Society of Musculoskeletal Radiology has established guidelines to standardize imaging techniques, which are critical for early and accurate diagnosis given the considerable variability in clinical practice across regions.[12] The integration of pathologic, immunohistochemical, and molecular features is increasingly emphasized to guide histology-specific therapeutic approaches, especially given the more than 70 recognized histologic subtypes.[13,14]

While histopathological findings remain the gold standard, an integrated diagnostic approach incorporating morphology, immunohistochemistry, and advanced molecular techniques is increasingly essential for achieving diagnostic precision and refining classification, particularly given the inherent intertumoral and intratumoral heterogeneity of soft tissue sarcomas.[15–17] This detailed diagnostic workup is paramount, as misdiagnosis or inadequate initial excisions outside specialized sarcoma centers can lead to increased morbidity and mortality.[4] The challenges associated with

incorrect or late diagnosis, coupled with a lack of clinical expertise, underscore the critical need for advanced diagnostic methodologies in STS.[3,18]

The initial diagnostic process for soft tissue sarcomas chiefly involves imaging and pathologic analysis.[19] Biopsy-based tumor characterization, which remains the standard of care, presents limitations such as tumor heterogeneity and procedural risks.[20] These limitations frequently result in diagnostic inconsistencies and suboptimal patient management, particularly in settings outside specialized sarcoma centers, where a lack of adherence to established diagnostic protocols often occurs.[19] The diagnostic accuracy of biopsy in soft tissue sarcoma is further complicated by interobserver variability among pathologists, leading to discrepancies in histologic grading and subtyping.[15] To mitigate these issues, expert pathology review, often augmented by molecular diagnostics, significantly enhances diagnostic precision and informs clinical management decisions.[21] This highlights the indispensable role of a multidisciplinary team approach in improving the accuracy of both diagnosis and treatment of bone and soft tissue sarcomas.[22]

The integration of radiomics, artificial intelligence, and molecular signatures further promises to bridge imaging-molecular divides, establishing a roadmap for clinically translatable, multimodal diagnostic systems in musculoskeletal oncology.[23] Case in point, extended molecular profiling, using massive parallel sequencing or next-generation sequencing technologies, has substantially advanced the diagnostic and therapeutic landscape for bone and soft tissue sarcomas, enabling a more granular understanding of their complex genetic alterations.[24] The ongoing evolution of molecular diagnostics, including integrated histomolecular approaches and specific molecular panels, is increasingly critical for tumor classification and therapeutic planning in soft tissue and bone tumors.[17]

The 5th edition of the World Health Organization (WHO) classification of soft tissue and bone sarcomas, updated in 2020, underscores the significant role of genetic mutations in diagnosis and classification, especially for sarcomas with complex karyotypes that are challenging to identify with conventional methods.[25,26] This genomic profiling, although often not directly targetable, provides critical insights for refining diagnosis, patient stratification, and treatment strategies, despite the variability in testing access and data interpretation.[24] However, next-generation sequencing offers significant advancements; its limitations in detecting complex structural variations and copy number alterations are addressed by emerging technologies such as optical genome mapping, which provides high-resolution genome-wide analysis for improved diagnostic and prognostic assessment in sarcoma.[27] Despite these advanced diagnostic tools, diagnostic errors in sarcoma remain a significant concern, often attributable to the disease's complexity and variations in access to specialized pathology or advanced reagents globally.[28] For instance, optical genome mapping has demonstrated success in analyzing sarcoma samples, identifying diagnostic-defining alterations in a substantial percentage of cases, thereby refining diagnoses and uncovering novel oncogenic and tumor suppressor gene alterations.[27] In light of these advancements, the integration of artificial intelligence and digital health platforms holds significant promise for synthesizing such vast and complex datasets, moving beyond isolated impacts toward a cohesive, data-driven strategy for personalized sarcoma care.[28] This convergence of artificial intelligence (AI) with precision medicine offers a breakthrough in biomarker research and disease diagnosis, addressing the inherent molecular heterogeneity of sarcomas where *one-size-fits-all* molecular targets are often ineffective.[28,29]

Therefore, comprehensive genomic profiling, including next-generation sequencing, is crucial for uncovering resistance mechanisms and guiding alternative

treatment strategies in sarcoma patients.[25] Next-generation sequencing provides a comprehensive genomic profile, allowing for the identification of actionable genetic alterations that can inform personalized treatment strategies.[30] However, the clinical utility of next-generation sequencing in sarcoma remains contentious due to the low mutational burden and scarcity of recurrent targetable alterations across most histologic subtypes.[31]

Despite the *quieter* genomes in some sarcoma subtypes, structural variations are more common than previously recognized, with next-generation sequencing technologies proving highly impactful for characterizing these events and copy number variations clinically.[32] In these instances, *hot spot* or exome sequencing lacks the ability to discriminate structural genomic alterations.[33] Whole genome sequencing further expands upon this by detecting diagnostic and actionable genomic characteristics, as well as underlying hereditary conditions, thereby optimizing clinical care for sarcoma patients.[34] Whole genome sequencing has been shown to revise cancer diagnoses in a significant proportion of patients, leading to crucial changes in treatment plans.[34] This comprehensive genomic approach, encompassing whole genome sequencing, facilitates the identification of precise therapeutic targets and enhances prognostic accuracy, especially within the diverse landscape of soft tissue and bone sarcomas.

NF1 mutations are prevalent in soft tissue sarcomas and have implications for treatment response and prognosis. The NF1 gene can be altered in somatic fashion or through a germline hereditary cancer syndrome, such as NF1. The observed rates of actionable mutations in genomic profiling studies are high, particulalry with respect to NF1 mutations and RAS signaling.[25,35] MPNSTs, in particular, harbor NF1 mutationsin nearly 80% of cases, making this gene a critical focus for targeted therapeutic development and genetic counseling. Therapy resistance in MPNSTs is common, frequently attributed to mechanisms such as loss of CDKN2A and activation of receptor tyrosine kinase pathways, underscoring the necessity for combinatorial therapeutic strategies to overcome these intrinsic resistance mechanisms.[36,37]

Other mutations are also present in soft tissue sarcomas. For example, gastrointestinal stromal tumors commonly exhibit mutations in KIT or PDGFRA, with less frequent inactivation of the SDH or NF1 genes.[38] However, a broader analysis of various sarcoma subtypes reveals a diverse landscape of genomic alterations beyond these commonly recognized mutations, including alterations in cell cycle control genes, receptor tyrosine kinases/PI3K/RAS pathway components, and epigenetic regulators.[39] This genetic heterogeneity underscores the importance of comprehensive genomic profiling to identify subtype-specific alterations that may guide personalized therapeutic strategies. A table of relevant soft tissue sarcoma mutations is referenced as follows (**Table 1**).

Despite these advances, the clinical impact of genomic profiling in STS has not been prospectively investigated, and data regarding the efficacy of targeted treatments based on identified mutations remain scarce, particularly given the challenges in translating genomic findings into effective therapeutic strategies for many sarcoma subtypes. Consequently, despite the detailed reports on diverse gene mutations, fusions, or amplifications detected through various next generation sequencing (NGS) technologies, robust evidence supporting the clinical utility and efficacy of targeted treatments remains limited.[21] For instance, a multicenter, randomized phase III trial is currently underway to evaluate the feasibility of using molecular profiling by NGS-exome in clinical practice for advanced STS patients and to assess the efficacy of NGS-guided targeted therapies.[40] Such trials are essential to establish the prospective clinical utility of NGS in STS, given that, while genomic profiling can identify potential actionable alterations in up to 50% of advanced STS patients, the routine,

Table 1
Examples of chromosomal translocations and associated gene fusions most frequently detected in soft tissue sarcomas and mesenchymal tumors

Sarcoma Subtype	Translocation	Genes	Oncogenic Mechanism
Ewing sarcoma	t(11;22)(q24;q12); t(21;22)(q22;q12); t(16;21)(p11;q22)	EWSR1, FLI1; EWSR1, ERG; FUS, ERG	Transcription factor
DSRCT	t(11;22)(p13;q12)	EWSR1, WT1	Transcription factor
Alveolar rhabdomyosarcoma	t(2;13)(q35;q14); t(1;13)(p36;q14)	PAX3, FOXO1; PAX7, FOXO1	Transcription factor
Clear cell sarcoma	t(12;22)(q13;q12)	EWSR1, ATF1	Transcription factor
Extraskeletal myxoid chondrosarcoma	t(9;22)(q22;q12)	EWSR1, NR4A3	Transcription factor
Myxoid liposarcoma	t(12;16)(q13;p11)	FUS, CHOP	Transcription factor
Alveolar soft part sarcoma	t(X;17)(p11;q25)	ASPL, TFE3	Transcription factor
Low-grade fibromyxoid sarcoma	t(7;16)(q33;p11)	FUS, CREB3L2	Transcription factor
Sclerosing epithelioid fibrosarcoma	t(11;22)(p11;q11)	EWSR1, CREB3L1	Transcription factor
Low grade endometrial stromal tumor	t(7;17)(p15;q21)	JAZF1, SUZ12	Transcription factor
Synovial sarcoma	t(X;18)(p11;q11)	SYT, SSX1, SSX2, SSX4	Chromatin remodeling
Congenital fibrosarcoma	t(12;15)(p13;q25)	ETV6, NTRK3	Tyrosine kinase
Inflammatory myofibroblastic tumor	t(2;2)(p23;p13); t(1;2)(q22;p23)	TPM3, ALK; TPM4, ALK	Tyrosine kinase
Dermatofibrosarcoma protuberans	t(17;22)(q22;q13)	COL1A1, PDGFB	Growth factor
PVNS/TGCT	t(1;2)(p13;q37)	COL6A3, CSF1	Growth factor

Adapted from Vibert and Watson Cancers 2022.

nonselective use of NGS in sarcoma patients still lacks robust evidence. Moreover, the retrospective nature, small cohort sizes, and difficulties in capturing long-term treatment outcomes in many genomic studies on sarcomas present additional limitations to firmly establish the widespread clinical utility of NGS in guiding therapeutic decisions.

These limitations highlight the importance of multidisciplinary sarcoma-expert institutions in interpreting NGS results and guiding treatment recommendations, as evidenced by guidelines emphasizing expert review for complex genomic panels.[41] Further complicating the widespread implementation of NGS, barriers such as variable testing access, prolonged turnaround times, suboptimal specimen quality, and substantial costs impede its routine adoption. However, ongoing efforts to standardize

protocols, reduce costs, and improve data interpretation through AI-driven analytics are critical for integrating these sophisticated diagnostic modalities into routine sarcoma management.[25] Overcoming these challenges is paramount for maximizing the impact of genomic insights on patient outcomes, particularly for advanced or refractory soft-tissue sarcomas where traditional treatment modalities like doxorubicin have reached their therapeutic ceiling.[42] This requires the exploration of alternative therapeutic strategies, including immunotherapy and targeted agents, particularly for patients with limited options.[43] Given the heterogeneity of STS and the modest improvements in overall survival with conventional chemotherapy, there is a pressing need to explore novel treatment avenues that capitalize on the unique molecular landscapes of individual tumors. This necessitates a paradigm shift toward personalized medicine, where treatment decisions are increasingly guided by comprehensive genomic profiling and a deeper understanding of tumor biology.

IMAGING

Imaging options for soft tissue sarcoma continue to evolve. Definitive characterization of a soft tissue sarcoma often requires advanced imaging modalities, such as MRI, which provides superior soft tissue contrast and detailed anatomic information for precise tumor delineation and local staging. Given that soft tissue sarcomas often present as large, painless masses with increasing volume, initial diagnostic evaluations can involve ultrasonography, which offers a cost-effective method with a high negative predictive value for ruling out soft tissue masses.[14] Multiparametric ultrasound, incorporating B-mode, Doppler, elastography, and contrast enhancement, has also emerged as a promising, noninvasive adjunct to MRI, offering comprehensive morphologic, vascular, and biomechanical insights to aid in differential diagnosis and potentially reduce unnecessary biopsies.[44] Other modalities, such as multiparametric magnetic resonance imaging (MRI) and positron emission tomography/computed tomography (PET/CT) with novel tracers, are crucial for improved tumor delineation, assessment of treatment response, and detection of subtle metastatic disease. Other imaging advances in soft tissue sarcoma include artificial intelligence-driven methodologies for enhanced diagnostic accuracy and prognostic stratification, moving toward noninvasive quantitative biomarkers for treatment monitoring.

MRI remains the gold standard for local staging due to its superior spatial resolution and tissue characterization capabilities,[45] enabling comprehensive assessment of tumor extent, involvement of adjacent structures, and neurovascular relationships.[46] The diagnostic utility of MRI extends beyond initial staging, playing a crucial role in detecting local recurrences posttreatment, often enhanced by contrast agents and sometimes integrated with PET imaging for improved specificity.[47] However, despite the advancements in MRI technology, a significant challenge remains in differentiating between benign and malignant lesions, particularly lipomas and well-differentiated liposarcomas, where radiomics—the extraction and analysis of high-throughput quantitative features from medical images—shows promise in augmenting diagnostic accuracy and improving differential diagnosis.[48] Moreover, the integration of multimodality imaging with clinical data and advanced computational techniques, such as radiomics and artificial intelligence, may further enhance the interpretability of imaging changes in patients undergoing neoadjuvant therapies.[49]

Beyond initial diagnosis, MRI is invaluable for monitoring treatment response and detecting disease recurrence, although ultrasonography is also a viable alternative in certain contexts. However, while ultrasound is highly accurate for identifying specific superficial lesions with typical features, it lacks specificity compared to MRI for

diagnosing recurrence.[50] Despite these advantages, the choice between MRI and ultrasonography (USG) for surveillance depends on the clinical context, as USG offers benefits such as lower cost, portability, and shorter scan times, making it suitable for frequent follow-up and evaluation of regional lymph nodes. Conversely, PET/CT studies, while limited by small patient numbers and retrospective designs, offer metabolic information that complements anatomic imaging, with PET/MRI demonstrating improved accuracy for local recurrence detection compared to MRI alone.[15] The integration of advanced imaging techniques, particularly contrast-enhanced computed tomography, provides critical information regarding tumor location, stage, and post-treatment follow-up, offering enhanced delineation of nodular septa and differential enhancement patterns useful in distinguishing malignant from benign lesions.[51]

TREATMENT ADVANCES

Surgical resection, when possible, remains the cornerstone of sarcoma therapy. Complete tumor eradication, while preserving function, is paramount whenever possible. Unfortunately, curative surgical resection may be difficult to achieve in many patients. However, there have been several treatment breakthroughs in soft tissue sarcoma over the last decade. For instance, while progress in the overall treatment of bone and soft tissue sarcomas has been slow, molecular subgrouping through multigene next-generation sequencing is improving understanding of their genetic landscape leading to more informed precision medicine approaches.[52] Genomic approaches are confirming known genomic markers, such as the SYT::SSX fusion in synovial sarcoma, and providing deeper insights into the variability around known markers, as well as complex karyotypes that distinguish dedifferentiation from lower-grade lesions.[10] Such molecular insights are pivotal not only for refined diagnostic accuracy but also for identifying novel therapeutic targets and predicting treatment responses in a personalized medicine framework. Despite these advances, the rarity and heterogeneity of sarcomas continue to pose significant challenges to the development and regulatory approval of effective new therapies.[53]

Immunotherapy treatment options are emerging for soft tissue sarcoma. Specifically, immune checkpoint inhibitors, such as nivolumab in combination with ipilimumab, have demonstrated therapeutic activity in advanced STS subtypes like undifferentiated pleomorphic sarcoma, dedifferentiated liposarcoma, and synovial sarcoma, leading to their regulatory approval.[54] Beyond checkpoint blockade, other immunotherapeutic strategies are under investigation, including adoptive cell therapies like afami-cel for synovial sarcoma and tumor-agnostic therapies such as NTRK inhibitors for tumors with NTRK fusions.[55] The growing interest in immunotherapy for soft tissue sarcoma stems from its potential to offer new therapeutic avenues for this heterogeneous group of malignancies.[56] However, despite encouraging advancements, the response rates to anti-PD-1 monotherapies in STS remain modest, averaging approximately 15%, with notable variability across histotypes.[57] This underscores the critical need for identifying predictive biomarkers and developing combination strategies to enhance therapeutic efficacy and overcome primary or acquired resistance mechanisms within the diverse STS molecular landscape.[58]

Targeted therapy options are also emerging for soft tissue sarcoma. These therapies often focus on specific molecular aberrations identified through genomic profiling, such as inhibitors of IDH1, ATR, DNMT, HDACs, and BET, which are currently being investigated in early-phase trials.[59] Furthermore, drugs targeting BRAF, ALK, NTRK, ROS1, EZH1/2, RET, and KIT mutations in specific rare sarcoma subtypes have demonstrated relatively high response rates. While NTRK fusions are

infrequent in sarcomas, they are nearly pathognomonic in certain pediatric tumors like infantile fibrosarcoma, highlighting the importance of comprehensive genomic profiling in identifying actionable alterations.[60] Similarly, RET fusions have also emerged as tissue-agnostic targets, with selective RET inhibitors showing promise in sarcomas harboring these fusions.[61] Moreover, several novel agents have recently gained regulatory approval, including tyrosine kinase inhibitors such as avapritinib and ripretinib for gastrointestinal stromal tumors, and the immune checkpoint inhibitor atezolizumab for alveolar soft part sarcomas. These advancements underscore the growing repertoire of targeted treatments, moving beyond conventional chemotherapy to more precise interventions based on individual tumor characteristics.

Combination therapy options are also emerging for soft tissue sarcoma. These regimens often combine immune checkpoint inhibitors with other therapeutic agents, such as nivolumab with gemcitabine/doxorubicin/docetaxel, or retifanlimab with gemcitabine/docetaxel, aiming to synergistically enhance antitumor responses.[58] Beyond chemotherapy combinations, other multi-modal strategies include the integration of immune checkpoint inhibitors with targeted therapies like cabozantinib[40] or radiation therapy to potentially overcome resistance mechanisms and improve clinical outcomes. The ongoing exploration of these multifaceted combination approaches, including those integrating oncolytic viruses or novel drug delivery systems, signifies a pivotal shift toward optimizing therapeutic regimens for the heterogeneous landscape of soft tissue sarcomas. The continuous evolution of therapeutic strategies underscores the critical role of robust preclinical models and comprehensive clinical trial designs to effectively evaluate the efficacy and safety of these complex regimens. However, despite these advancements, the inherent heterogeneity and rarity of sarcomas continue to present substantial challenges to the development and regulatory approval of broadly effective therapies.[53]

Sarcoma radiation therapy is also evolving with preclinical studies demonstrating the equivalent efficacy of photon and proton irradiation in sarcoma mouse models, offering promising avenues for optimizing radiation protocols.[62] Furthermore, innovative approaches combining radiotherapy with immunotherapeutic agents, such as pembrolizumab in neoadjuvant and adjuvant settings, have demonstrated transformative potential in high-grade sarcomas such as undifferentiated pleomorphic sarcoma and liposarcoma of the extremity.[63] Such combined modalities, particularly neoadjuvant immunotherapy, have shown encouraging preliminary results in phase 2 trials, with significant pathologic responses observed in specific STS subtypes.[64] Ongoing trials are further exploring the integration of immunotherapy with radiation therapy by investigating habitat-escalated adaptive therapy, which tailors RT doses to radioresistant intratumoral habitats based on genomic and radiomic profiles.[65,66]

GENETIC COUNSELING

Evaluation is recommended for individuals with a family history of sarcoma or related cancers, as genetic testing can aid in personalized cancer management and surveillance.

SUMMARY

Soft tissue sarcomas have been rigorously characterized from a genomics and transcriptomics standpoint. Precision medicine trials are emerging, focused on immune therapies and selected targeted therapies, which appear to hold promise. Therapy resistance remains a significant issue, particularly for metastatic disease.

CLINICS CARE POINTS

- The clinical management of sarcoma should be done in a center with dedicated, multispecialty sarcoma expertise.
- The diagnosis of sarcoma is becoming increasingly sophisticated. Molecular diagnostics are essential for accurate and timely treatment.
- It is important to stay abreast of rapidly changing diagnostic and therapeutic technologies in the care of sarcoma patients.

DISCLOSURE

None.

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