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Genetic Aspects of Soft Tissue Sarcomas

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Abstract

Introduction. Soft tissue sarcomas are a rare and heterogeneous group of mesenchymal malignancies arising from connective tissues, including fat, muscle, nerves, and vascular structures. They account for a small proportion of adult malignancies but demonstrate significant biological diversity and clinical complexity. Advances in molecular biology have significantly improved the understanding of their pathogenesis, particularly through the identification of specific genetic alterations such as chromosomal translocations and gene fusions.

Materials and methods. This work is based on a narrative review of recent literature focusing on histopathological, molecular, and clinical aspects of soft tissue sarcomas. Data were obtained from peer-reviewed articles indexed in PubMed and other scientific databases. Emphasis was placed on studies describing genetic alterations, diagnostic approaches, and treatment strategies published in recent years.

Results. Soft tissue sarcomas are classified into two main molecular groups: tumors with specific chromosomal translocations and tumors with complex genomic alterations. The first group includes entities such as Ewing sarcoma, synovial sarcoma, and myxoid liposarcoma, characterized by fusion genes like EWSR1–FLI1, SS18–SSX, and FUS–DDIT3. The second group comprises leiomyosarcoma, undifferentiated pleomorphic sarcoma, and pleomorphic liposarcoma, which exhibit genomic instability and mutations in tumor suppressor genes such as TP53 and RB1. Histologically, these tumors range from well-differentiated lesions resembling normal tissue to poorly differentiated, highly aggressive neoplasms with marked atypia and necrosis. Tumor grading systems such as FNCLCC are essential for prognostic evaluation.

The management of soft tissue sarcomas requires a multidisciplinary approach. Surgical resection with negative margins remains the cornerstone of treatment, while radiotherapy and chemotherapy are used as adjunctive modalities depending on tumor subtype and stage. Targeted therapies are increasingly applied in cases with identifiable molecular alterations, supporting a shift toward personalized medicine. Prognosis is influenced by tumor size, depth, histological grade, presence of metastasis, and surgical margin status. Lung metastasis represents the most common and significant adverse prognostic factor.

Recent advances in molecular diagnostics have improved classification accuracy and therapeutic decision-making.
Conclusion. Soft tissue sarcomas represent a biologically and genetically diverse group of tumors requiring integrated diagnostic and therapeutic approaches. Molecular characterization, combined with histopathological assessment, plays a crucial role in accurate classification and individualized treatment planning. Despite advances in management, these tumors remain clinically challenging due to their heterogeneity and aggressive potential.
Keywords: soft tissue sarcoma, sarcoma, molecular genetics, chromosomal translocation, gene fusion, histopathology, FNCLCC grading system, immunohistochemistry, targeted therapy, surgical margins

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Генетические аспекты сарком мягких тканей

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Резюме

Введение. Саркомы мягких тканей представляют собой редкую и гетерогенную группу злокачественных мезенхимальных опухолей, возникающих из соединительных тканей, включая жировую, мышечную, нервную и сосудистую. Они составляют небольшую долю злокачественных новообразований у взрослых, однако характеризуются значительным биологическим разнообразием и клинической сложностью. Достижения молекулярной биологии существенно расширили понимание патогенеза данных опухолей, особенно благодаря выявлению специфических генетических изменений, таких как хромосомные транслокации и генные слияния.
Материалы и методы. Данная работа основана на нарративном обзоре современной литературы, посвященной гистопатологическим, молекулярным и клиническим аспектам сарком мягких тканей. Использованы данные рецензируемых статей, индексируемых в базе PubMed и других научных базах данных. Основное внимание уделялось исследованиям, описывающим генетические изменения, диагностические подходы и современные стратегии лечения, опубликованным в последние годы.
Результаты. Саркомы мягких тканей подразделяются на две основные молекулярные группы: опухоли со специфическими хромосомными транслокациями и опухоли со сложными геномными изменениями. К первой группе относятся такие

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нозологические формы, как саркома Юинга, синовиальная саркома и миксоидная липосаркома, характеризующиеся наличием генов слияния, таких как EWSR1–FLI1, SS18–SSX и FUS–DDIT3. Вторая группа включает лейомиосаркому, недифференцированную плеоморфную саркому и плеоморфную липосаркому, которые характеризуются геномной нестабильностью и мутациями генов-супрессоров опухолевого роста, таких как TP53 и RB1. С гистологической точки зрения эти опухоли варьируют от хорошо дифференцированных образований, напоминающих нормальные ткани, до низкодифференцированных высокоагрессивных новообразований с выраженной атипией и некрозом. Системы градации опухолей, такие как FNCLCC, играют ключевую роль в прогностической оценке. Лечение сарком мягких тканей требует мультидисциплинарного подхода. Хирургическое удаление с отрицательными краями резекции остается основным методом лечения, тогда как лучевая терапия и химиотерапия применяются в качестве дополнительных методов в зависимости от подтипа опухоли и стадии заболевания. Таргетная терапия все чаще используется при наличии идентифицированных молекулярных изменений, что отражает переход к персонализированной медицине. Прогноз зависит от размера опухоли, глубины инвазии, гистологической степени злокачественности, наличия метастазов и состояния хирургических краев резекции. Метастазы в легкие являются наиболее частым и неблагоприятным прогностическим фактором. Современные достижения молекулярной диагностики повысили точность классификации и эффективность выбора терапии.

Заключение. Саркомы мягких тканей представляют собой биологически и генетически разнообразную группу опухолей, требующих комплексного диагностического и лечебного подхода. Молекулярная характеристика в сочетании с гистопатологическим анализом играет ключевую роль в точной классификации и индивидуализированном выборе лечения. Несмотря на достижения современной медицины, данные опухоли остаются клинически сложными из-за их гетерогенности и агрессивного течения.

Ключевые слова: саркома мягких тканей, саркома, молекулярная генетика, хромосомные транслокации, генные слияния, гистопатология, система градации FNCLCC, иммуногистохимия, таргетная терапия, хирургические края

■ INTRODUCTION

From a molecular standpoint, soft tissue sarcomas can broadly be divided into two categories based on their genomic characteristics [1, 2, 4]. This molecular classification provides an important framework for understanding tumor pathogenesis, biological behavior, and diagnostic approaches. It also plays a crucial role in guiding modern personalized therapeutic strategies in sarcoma management.

■ MATERIALS AND METHODS

This work is based on a narrative review of recent literature focusing on histopathological, molecular, and clinical aspects of soft tissue sarcomas. Data were obtained from peer-reviewed articles indexed in PubMed and other scientific databases. Emphasis was placed on studies describing genetic alterations, diagnostic approaches, and treatment strategies published in recent years.

Sarcomas with Specific Chromosomal Translocations

These tumors are characterized by relatively simple karyotypes and recurrent, tumor-specific chromosomal translocations that lead to the formation of fusion genes. The resulting fusion proteins often act as abnormal transcription factors that drive tumor development and progression [4, 5].

- Ewing sarcoma is typically associated with the t (11;22) (q24; q12) translocation, which produces the EWSR1–FLI1 fusion gene.
- Synovial sarcoma is defined by the t(X;18) (p11; q11) translocation, resulting in the SS18–SSX fusion gene [6].
- Alveolar rhabdomyosarcoma commonly shows either t (2;13) or t (1;13) translocations, leading to the formation of PAX3–FOXO1 or PAX7–FOXO1 fusion genes.
- Myxoid liposarcoma is associated with the t (12;16) translocation, which produces the FUS–DDIT3 fusion gene.
- Liposarcoma.

  Associated with t (12;16), generating the FUS–DDIT3 fusion gene.

These sarcomas tend to occur in younger individuals and are often highly sensitive to specific molecular diagnostic techniques such as FISH and RT-PCR.

Recent studies also show that these fusion proteins not only act as transcription factors but also remodel chromatin structure and epigenetic regulation, contributing to lineage reprogramming of mesenchymal cells into malignant phenotypes [7].

Sarcomas with Complex Genomic Alterations

This group is characterized by complex karyotypes, multiple chromosomal gains and losses, and widespread genomic instability.

Leiomyosarcoma, Undifferentiated pleomorphic sarcoma, and Pleomorphic liposarcoma are examples of soft tissue sarcomas that typically show complex genetic alterations rather than single defining translocations.

Common genetic abnormalities in these tumors include mutations in key tumor suppressor genes such as TP53 and RB1, which contribute to genomic instability, uncontrolled cell proliferation, and tumor progression [3, 8].

Amplification of oncogenes like MDM2 (notably in well-differentiated and dedifferentiated liposarcomas).

Unlike translocation-associated sarcomas, these tumors typically occur in older adults and exhibit more aggressive biological behavior.

Additional Molecular Note

Next-generation sequencing (NGS) studies have further revealed additional recurrent alterations in genes involved in cell cycle regulation, PI3K/AKT/mTOR signaling pathway, and DNA damage response mechanisms, highlighting the molecular heterogeneity of this group [9, 10].

Clinicopathological Features

Soft tissue sarcomas usually present as painless, progressively enlarging masses. Soft tissue sarcomas most commonly arise in the extremities, particularly in the thigh, although they can develop in any anatomical location, including the retroperitoneum.

Clinically, they are typically characterized by a gradual increase in size and often remain painless in the early stages. Pain usually appears later, mainly due to compression of adjacent structures.

These tumors also have the potential for local invasion and can spread to distant sites, with the lungs being the most common location for metastasis.

Early diagnosis significantly improves prognosis, and imaging modalities such as MRI combined with biopsy remain the gold standard for evaluation. Increasing evidence supports the integration of molecular profiling into routine diagnostic workup for personalized therapy selection [11, 12].

Histopathological Characteristics

Histologically, soft tissue sarcomas display a wide spectrum of differentiation.

Well-differentiated tumors resemble normal mesenchymal tissue and generally have a better prognosis. These tumors often maintain some degree of tissue architecture similar to their tissue of origin, which reflects a lower level of biological aggressiveness. However, even well-differentiated lesions may undergo dedifferentiation over time, resulting in more aggressive behavior.

Poorly differentiated or anaplastic tumors exhibit marked cellular atypia, high mitotic activity, and areas of necrosis, all of which indicate aggressive biological behavior and a poorer prognosis. These tumors frequently show loss of normal tissue architecture, increased nuclear pleomorphism, and abnormal mitotic figures, which are key indicators of high-grade malignancy.

Major histological subtypes of soft tissue sarcomas include liposarcoma, rhabdomyosarcoma, angiosarcoma, and fibrosarcoma, each arising from different types of mesenchymal tissue and showing distinct pathological features. In addition to these, entities such as malignant peripheral nerve sheath tumors (MPNST) and synovial sarcoma also represent important diagnostic categories with specific morphological and immunohistochemical profiles.

Tumor grading is an essential component in evaluating these neoplasms, as it helps determine their level of aggressiveness and guides clinical management, most commonly using systems such as the FNCLCC grading system [13].

Histological grading is a critical prognostic factor. The most widely used system is the FNCLCC grading system, which is widely used to assess the aggressiveness of soft tissue sarcomas. It evaluates three main parameters: tumor differentiation, mitotic count, and the extent of tumor necrosis [14, 15].

Based on these criteria, tumors are classified into low, intermediate, or high grade, which helps predict clinical behavior and guide treatment decisions.

Recent immunohistochemical and molecular pathology studies have significantly improved the diagnostic accuracy of soft tissue sarcomas. Markers such as Ki-67 (proliferation index), MDM2 (liposarcoma), desmin (muscle differentiation), and CD34 (vascular tumors) are now routinely used to support histological diagnosis and refine tumor classification [16, 17].

Furthermore, digital pathology and AI-assisted histopathology are emerging tools that may enhance tumor grading reproducibility and reduce inter-observer variability in sarcoma diagnosis [18].

Diagnostic Approaches

Accurate diagnosis of soft tissue sarcomas requires a multidisciplinary approach:

- Biopsy (core needle or excisional) is the gold standard [19].
- Immunohistochemistry (IHC) helps identify lineage-specific markers [20].
- Molecular genetic testing (FISH, PCR, next-generation sequencing) detects characteristic genetic alterations [21].

Imaging studies such as MRI and CT scans assess tumor extent and metastasis [22]. The management of soft tissue sarcomas depends on several factors, including tumor type, grade, location, and stage. Surgical resection with negative margins remains the cornerstone of treatment, as complete removal of the tumor significantly reduces the risk of local recurrence [23].

Radiotherapy is frequently used as an adjunct to surgery to improve local control, particularly in high-grade or large tumors where the risk of recurrence is higher [24].

Chemotherapy is effective in certain subtypes, especially in tumors such as Alveolar rhabdomyosarcoma and Ewing sarcoma, where it plays an important role in both localized and metastatic disease [25].

Targeted therapy is increasingly being incorporated into treatment strategies, particularly for tumors with identifiable molecular alterations, offering a more personalized approach and improved therapeutic outcomes [26].

Several factors influence patient outcomes in soft tissue sarcomas. Larger tumors, especially those deeper than the fascia, are associated with a poorer prognosis because they have a higher risk of recurrence and metastasis.

The histological subtype and grade of the tumor also play a crucial role. High-grade tumors, as determined by systems such as the FNCLCC grading system, tend to behave more aggressively and are linked to worse survival outcomes; for example, tumors like Undifferentiated pleomorphic sarcoma often show rapid progression [27].

The presence of metastases, particularly in the lungs, is one of the most important negative prognostic indicators and significantly reduces overall survival [23, 27].

Surgical margin status is another critical factor, as complete tumor removal with negative margins lowers the risk of local recurrence, while positive margins are associated with poorer outcomes [24].

Finally, specific genetic alterations, including characteristic fusion genes seen in tumors such as Synovial sarcoma, can influence tumor behavior, response to treatment, and overall prognosis [27, 28].

■ CONCLUSION

Soft tissue sarcomas are a biologically diverse group of malignancies that require integration of genetic and clinicopathological data for optimal management. Advances in molecular biology have significantly improved diagnostic accuracy and opened new avenues for targeted therapies. Continued research into the genetic underpinnings of these tumors is expected to further enhance personalized treatment strategies and patient outcomes.

REFERENCES

1. Fletcher CDM, Bridge JA, Hogendoorn PCW, Mertens F. *WHO Classification of Tumours of Soft Tissue and Bone*. 5th ed. Lyon: IARC; 2020.
2. Sbaraglia M, Bellan E, Dei Tos AP. The 2020 WHO Classification of Soft Tissue Tumours: news and perspectives. *Pathologica.* 2021;113(2):70–84.
3. Vibert J, Watson S. The molecular biology of soft tissue sarcomas: current knowledge and future perspectives. *Cancers (Basel).* 2022;14:2548. doi: 10.3390/cancers14102548
4. Mertens F, Antonescu CR, Mitelman F. Gene fusions in soft tissue tumors: recurrent and overlapping pathogenetic themes. *Genes Chromosomes Cancer*. 2016;55(4):291–310.
5. Machado I, Llombart-Bosch A, Charville GW, et al. Sarcomas with EWSR1::Non-ETS fusion. *Surg Pathol Clin.* 2024;17(1):31–55. doi: 10.1016/j.path.2023.07.001
6. Thway K, Fisher C. Synovial sarcoma: defining features and diagnostic evolution. *Ann Diagn Pathol.* 2014;18(6):369–380.
7. Jo VY. EWSR1 fusions: Ewing sarcoma and beyond. *Cancer Cytopathol.* 2020;128(4):229–231. doi: 10.1002/cncy.22239
8. Popovich JR, Kashyap S, Gasalberti DP, et al. Sarcoma. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2026.
9. Durer S, Gasalberti DP, Shaikh H. Ewing sarcoma. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2026.
10. Gündoğdu Y, Şenocak Taşçı E, Özer L, et al. Next-generation sequencing-based genomic profiling of sarcomas. *Front Oncol.* 2025;15:1627452. doi: 10.3389/fonc.2025.1627452
11. Smith SM, Coleman J, Bridge JA, Iwenofu OH. Molecular diagnostics in soft tissue sarcomas. *J Surg Oncol.* 2015;111(5):520–531. doi: 10.1002/jso.23882
12. Frazzette N, Jour G. Novel molecular methods in soft tissue sarcomas. *Cancers (Basel).* 2025;17:1215. doi: 10.3390/cancers17071215
13. Neuville A, Chibon F, Coindre JM. Grading of soft tissue sarcomas. *Pathology*. 2014;46(2):113–120.
14. Casali PG, Abecassis N, Aro HT, et al. Soft tissue and visceral sarcomas: ESMO guidelines. *Ann Oncol.* 2018;29(Suppl 4):iv51–iv67.
15. Gronchi A, Miah AB, Dei Tos AP, et al. Soft tissue sarcoma: ESMO–EURACAN guidelines. *Ann Oncol*. 2021;32(11):1348–1365.
16. Miettinen M. Immunohistochemistry of soft tissue tumours. *Histopathology.* 2014;64(1):101–118.
17. Anderson WJ, Jo VY. Diagnostic immunohistochemistry of soft tissue tumors. *Diagnostics (Basel).* 2021;11(4):690. doi: 10.3390/diagnostics11040690
18. Crombé A, Roulleau-Dugage M, Italiano A. Sarcoma diagnosis and treatment in the era of AI and immunotherapy. *Cancer Commun (Lond).* 2022;42(12):1288–1313.
19. Kiefer J, Mutschler M, Kurz P, et al. Accuracy of core needle biopsy for sarcoma diagnosis. *Sci Rep.* 2022;12:1886. doi: 10.1038/s41598-022-05752-4
20. Wei S, Henderson-Jackson E, Qian X, Bui MM. Immunohistochemistry update in soft tissue tumors. *Arch Pathol Lab Med.* 2017;141(8):1072–1091.
21. Groisberg R, Roszik J, Conley A, et al. Role of NGS in sarcomas. *Curr Oncol Rep.* 2017;19:78. doi: 10.1007/s11912-017-0641-2
22. Vibhakar AM, Cassels JA, Botchu R, et al. Imaging update on soft tissue sarcoma. *J Clin Orthop Trauma.* 2021;22:101568. doi: 10.1016/j.jcot.2021.101568
23. Gonzalez MR, Mendez-Guerra C, Goh MH, Pretell-Mazzini J. Surgical treatment of soft tissue sarcomas. *Cancers (Basel).* 2025;17:401. doi: 10.3390/cancers17030401
24. Larrier NA, Czito BG, Kirsch DG. Radiation therapy for soft tissue sarcoma. *Surg Oncol Clin N Am.* 2016;25(4):841–860.
25. Mata Fernández C, Sebio A, Orcajo Rincón J, et al. Ewing sarcoma clinical guidelines. *Clin Transl Oncol.* 2025;27(3):824–836.
26. Fuchs JW, Schulte BC, Fuchs JR, Agulnik M. Targeted therapies in soft tissue sarcoma. *Front Oncol.* 2023;13:1122508.
27. Mahyudin F, Edward M, Basuki MH, et al. Prognostic factors in soft tissue sarcoma. *Ann Med Surg (Lond).* 2020;57:257–263.
28. Lesovaya E, Fetisov TI, Bokhyan BY, et al. Genetic and molecular heterogeneity of synovial sarcoma. *Cells*. 2024;13:1695. doi: 10.3390/cells13201695