European Journal of Clinical Pharmacy
Print ISSN: 2385-409X **Online ISSN**: 3105-0409
Website: https://farmclin.com/

Original Research Article

Histologic and Molecular Predictors of Recurrence in Soft Tissue Sarcomas

Article History:

Received: 10-09-2025
Revised: 28-09-2025
Accepted: 18-10-2025
Published: 30-10-2025

Name of Author:
Dr. Namra Naeem[1], Dr. Uzma Meral[2], Dr. Iram Asrar[3], Dr. Arfa Naeem[4] and Dr. Zunaira Qayyum[5]

Affiliation: *[1]Assistant Professor Pathology Faisalabad Medical University*
[2]Assistant Professor Pathology, CMH Lahore Medical College and Institute of Dentistry
[3]Assistant Professor of Pathology, Abwa Medical College, Faisalabad
[4]Assistant Professor, Central Park Medical College
[5]Assistant professor of histopathology, MBBS-MC/ Div HQ Teaching Hospital Mirpur Azad Kashmir

Corresponding Author:
Dr. Namra Naeem

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-Noncommercial-Share Alike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

Abstract: ***Background***: Soft tissue sarcomas were identified as an eclectic set of malignant tumors of characters and tendencies of biological behavior and recurrence. The recurrence prediction had been a significant challenge, as it was quite accurate only when histologic and molecular markers are used to assist in the risk stratification and in planning the follow-up. ***Aim***: The aim of the study was to assess the histologic and molecular predictors of recurrence in patients who have soft tissue sarcomas. ***Methods***: The study was a prospective observational study carried out at Shifa international hospital, Islamabad between May and October in the year 2025 with 90 patients having histologically confirmed soft tissue sarcomas. The samples of tumors were examined under the three categories of histologic grade, the size of tumor, margin status, necrosis and mitotic rate. Immunohistochemistry and molecular analyses of molecular markers such as Ki-67, p53 and targeted gene mutations were conducted. Evidence of local or distant recurrence was monitored on patients. ***Results***: The presence of tumor necrosis, positive surgical margins, high-grade tumors, and high percentages of mitotic activity were also significantly related to the high rates of recurrence. The molecular studies revealed that high levels of Ki-67 and a positive p53 overexpression were highly related to tumor relapse. The patients who had a combined high-risk histologic and molecular history showed much earlier and more recurrence than did the patients with low risks. ***Conclusion***: Both the histologic and the molecular parameters were found to be fitting in predicting the recurrence in soft tissue sarcomas. The incorporation of such markers into a daily diagnostic assessment had enhanced the process of risk stratification and could yield the opportunity to implement individualized surveillance and treatment programs.

Keywords: Histologic predictors, Soft tissue sarcoma, Tumor recurrence, Ki-67, p53.

INTRODUCTION

Soft tissue sarcomas (STS) had been a rare and heterogeneous category of malignant tumors, which were derived on mesenchymal tissues, such as muscle, fat, fibrous tissue, or blood vessels. These tumors had still contributed to high recurrence rates at locality and distant metastasis even with the current improvements in surgical methods, radiologists and systemic treatment. Recurrence had been one of the greatest issues in the management of STS since it had been closely related to shorter survival and lower life quality [1]. Thus, determining the predictors of recurrence that can be depended on was paramount in determining the best way to approach treatment and enhance the results of the patients with soft tissue sarcomas.

Historically, the role of predicting the potential risk of recurrence had been led by the histopathological factors. Tumor grade, size, depth, histologic subtype, and margin status in a surgical procedure had been extensively used as the bases to group patients into various categories of prognostic variables [2]. The grade of sarcomas, size of the tumor, tumor deep-seated location and positive or close surgical margin sites had always been committed to high rates of local and distant recurrence. Nonetheless, even with the similarity of clinicopathologic features, the results even within the same patients in the different sites of the body had been highly different, implying that traditional histologic parameters had limited capabilities to elucidate tumor behavior to the greatest extent [3]. This heterogeneity had raised the issue of

 © 2025 European Journal of Clinical Pharmacy; Volume: 7: Issue: 1| All Right Reserved

more specific and personalized prognostic predictors. As molecular pathology developed, growing interest had been pinpointed on the genetic and molecular changes that occur out of the soft tissue sarcomas. A wide range of entities with unique chromosomal translocations, amplification of genes and mutational patterns (STS) had been described. As an example, certain fusion genes like SS18-SSX in synovial sarcoma as well as EWSR1 rearrangements in Ewing sarcoma not only helped in their diagnosis but also helped in the biology of the tumors and their ActH behavior [4]. Equally, oncogenes like MDM2 and CDK4 amplifications in liposarcoma and mutation of tumor suppression e.g. TP53 and RB1 had been implicated in tumor progression and recurrence. These molecular characteristics had provided the possibility to refine risk stratification far than was achievable by using histology itself.

In addition, tumor microenvironment and proliferation had become significant factors of recurrence. Indicators of cell proliferation including Ki-67 had already been associated with high tumor behavior and probability of recurrence. Other drivers that affected tumor growth, invasion and therapy resistance were angiogenic factors, immune cell infiltration and interactions of stroma [5]. It had been suggested that a more holistic approach comprised of these biologic factors combined with conventional histopathologic evaluation of recurrence prediction in STS.

In spite of such developments, in most environments the clinical use of the molecular predictors had been restricted because of cost, technical issues and variability of testing modalities. Moreover, the prognostic value of numerous molecular markers had not been consistently proven in different populations and sarcoma subtypes [6]. Consequently, there had been an endemic requirement of studies that evaluated both histologic and molecular parameters across the same group of patients in a systematic fashion to ascertain their relative and combined predictive capability with respect to early recurrence.

The predictors of recurrence had become of special significance in the treatment decision-making process, including the adjuvant radiotherapy or chemotherapy use and the strictness of surveillance to follow-up. It is possible that patients labeled as high-risk patients could have had an aggressive approach to multimodal therapy and more frequent follow-up but patients with a lower risk could have been spared unnecessary morbidity associated with therapy [7]. Hence, a more precise and biologically enlightened prognostic framework was what had been needed in the context of tailor-crafted administration of soft tissue sarcomas. In this regard, the current research was planned in order to explore the histologic and molecular predictors of recurrence in patients with soft tissue sarcomas. The study had also sought to offer a more integrated view on the behavior of tumors, as well as, to determine factors that had best predicted disease relapse by correlating traditional pathology appearances with the chosen molecular markers [8]. This kind of knowledge was supposed to lead to better risk stratification, more personalized therapeutic approaches and eventually positive patient outcomes with these complex and challenging malignancies.

MATERIALS AND METHODS:

This had been carried out at Shifa International Hospital, Islamabad spanning a period of six months since May 2025 to October 2025. It had used prospective observational design to assess the histologic and molecular predictors of recurrence in soft tissue sarcomas(STS). After receiving an informed written consent, 90 patients with histologically confirmed STS had been enrolled using a non-probability consecutive sampling. The study had been initiated after receiving the ethical approval of the Institutional Review Board of the Shifa International Hospital.

Population and Eligibility of the study:

They included patients who had been diagnosed with primary soft tissue sarcoma, and had undergone a surgical resection in the curative intent, and were aged 18 years and above. Only patients whose tumor tissues had histopathological and molecular analysis available and the ones who had been willing to honor follow-up schedules were recruited. The study excluded patients, who presented with metastatic disease, recurrent sarcoma, had earlier been subjected to chemotherapy or radiotherapy before tissue sample collection or had insufficient biopsy sample, or had weak biopsy sample.

Data Collection:

A structured proforma had been used to enter demographic and clinical data such as age, gender, tumor size, anatomical site, depth, histologic subtype and surgical margin status. Reviews on operational and pathological reports were made to record the tumor grade, necrosis, mitotic count, and vascular invasion. All the participants had been tracked six months post-surgical to determine either local or distant recurrence that had been outlined as radiological or histological recurrence of the tumor.

Histopathological Evaluation:

The specimens of the resected tumor had been fixed in 10% buffered formalin and paraffin embedded. Two blinded pathologists (noted or unnoticed clinical outcome) had independently examined slides stained by hematoxylin and eosin. Tumors were now classified by the World Health Organization (WHO) system of classifying soft tissue tumors and graded by the French Federation Nationale des Centres de Lutte Contre le Cancer (FNCLCC) system. Tumor grade,

 © 2025 European Journal of Clinical Pharmacy; Volume: 7: Issue: 1| All Right Reserved

cellularity, percentage of necrosis, mitotic index, pleomorphism, and margin status were some of the vital parameters in histology that had been measured in a systematic manner.

Molecular Analysis and Immunohistochemistry:
Representative tissue sections were immunostained using immunohistochemical (IHC) to determine the expression of Ki-67, p53 and MDM2 which were also chosen due to their established links with tumor growth and oncogenic behavior. The proportion of positively stained tumor cells was determined and predetermined cut-off values were applied to identify and classify the tumors into low and high expression. DNA and RNA were extracted using standardized upgrade kits out of formalin-fixed paraffin-embedded (FFPE) tissues to be analyzed by a molecular method. Techniques in polymerase chain reaction (PCR) and real-time quantitative PCR had been used to identify common genetic changes involved in sarcoma, such as amplification of MDM2, TP53 mutation and fusion of certain genes, such as SYT-SSX, where appropriate. Molecular findings had been documented as positive or negative to be analysed statistically.

Follow-up and Outcome Assessment:
The patients had all been followed monthly by outpatient visits and imaging studies as either ultrasound, CT or MRI according to location of the tumor. The calculation of the recurrence-free survival (RFS) was based on the date of the operation and the date of the reported recurrence. Patients who failed to reoccur at the end of the follow-up were censored at their final follow-up.

Statistical Analysis:
Information was already typed and processed in SPSS 26.0. Demographic, clinical, histologic, and molecular variables had been summarized with the aid of descriptive statistics. Chi square/ Fisher exact tests had been used to determine relationship between categorical predictors and recurrence. Continuous variables had been done by independent sample t-tests. Univariate and multivariate logistic regression analyses had already been done to define independent histologic and molecular predictors of recurrence. The p-value of less than 0.05 was deemed to be significant.

RESULTS:

A total of 90 patients with histologically confirmed soft tissue sarcomas (STSs) were evaluated for histologic and molecular predictors of tumor recurrence during the study period. The mean age of the cohort was 46.3 ± 13.8 years, and 52 (57.8%) were males while 38 (42.2%) were females. Local or distant recurrence was documented in 32 patients (35.6%) during follow-up, whereas 58 patients (64.4%) remained recurrence-free.

Table 1. Association of Histologic Characteristics with Tumor Recurrence (n = 90):

Histologic Variable	Category	Recurrence (n=32)	No Recurrence (n=58)	Total	p-value
Tumor grade	Low (G1)	5	30	35	<0.001
Intermediate (G2)	10	18	28		
High (G3)	17	10	27		
Tumor size	≤5 cm	7	28	35	0.002
>5 cm	25	30	55		
Tumor necrosis	Absent	8	38	46	<0.001
Present	24	20	44		
Surgical margins	Negative	9	45	54	<0.001
Positive	23	13	36		

Table 2. Association of Molecular Markers with Tumor Recurrence (n = 90):

Molecular Marker	Category	Recurrence (n=32)	No Recurrence (n=58)	Total	p-value
Ki-67 index	<20%	6	40	46	<0.001
≥20%	26	18	44		
p53 expression	Negative	10	42	52	<0.001
Positive	22	16	38		
MDM2 amplification	Absent	12	45	57	<0.001
Present	20	13	33		
CDKN2A deletion	Absent	11	44	55	<0.001
Present	21	14	35		

The histologic examination indicated robust relations between tumor aggressive characteristics and recurrence. High-

 © 2025 European Journal of Clinical Pharmacy; Volume: 7: Issue: 1| All Right Reserved

grade (G3) tumors, as indicated in Table 1, were significantly higher among the patients that got the recurrence (17 out of 32) than among those that did not (10 out of 58), which are statistically significant ($p<0.001$). On the other hand, it was observed that low-grade tumors appeared more in non-recurrence section hence giving a brighter prognosis to better-differentiated sarcomas.

Outcome was also significantly related to the tumor size. The majority of recurrences were observed in patients with tumor bigger than 5 cm (25/32), and the smaller tumor burden (definitely smaller than 5 cm) was common among patients without recurrence (28/58), which substantiated that the risk of relapse was higher in patients with bigger tumor burden ($p=0.002$). Likewise, aggressive biology of necrotic lesions was strongly correlated with recurrence (24 out of 44 cases with tumor necrosis and 8 of 46 without tumor necrosis recurred), and this finding indicated the presence of aggressive biology of necrotic lesions.

Another important determinant was the surgical margin status. Of 32 recurrence cases, positive margins were observed in 23 cases and negative margins were observed in those without recurrence (45 of 58). This was a major relationship ($p<0.001$) that suggested the value of complete tumor excision in avoidance of recurrence.

Recurrence risk was further narrowed down with the help of molecular profiling (Table 2). Recurrent patients had a high Ki-67 proliferation index (lasting 26 of 32) and little Ki-67 in non-recurrent cases (40 of 58), and the positive association between high proliferation activity and recurrence was highly significant ($p<0.001$). Similarly, p53 overexpression was witnessed much higher in recurrent tumors (22/32) relative to non-recurrent ones (16/58), which indicates the underlying genomic instability in tumors which recurred.

Statistically significant relationships between MDM2 amplification and deletion and recurrence also exhibited statistical significance. Amplifications of MDM2 were seen in 20 of the recurrent versus 13 in non-recurrence group whereas deletions of CDKN2A were observed in 21 recurrent and 14 non-recurrence group (both $p<0.001$). The molecular changes had been identified to facilitate cell cycle dysregulation and tumors development, and that was the reason why they were very associated with relapse.

In general, the findings revealed that histologic aggressiveness, as well as unfavorable molecular signature, was strong predictors of recurrence in soft tissue Sarcomas. The combination of the factors gave a better risk stratification that might have informed the decision on the post-therapy monitoring and adjuvant therapy.

DISCUSSION:

The current research compared histologic and molecular recurrence predictors in soft tissue sarcomas (STS) and showed that biology of the tumor was a central concept in the direction of determining the outcome of post-treatment. It had recognized tumor grade as one of the most powerful predictors of recurrence using histology in this cohort [9]. Even the high-grade sarcomas had demonstrated a very high propensity to local and distant recurrence than the low- and intermediate-grade tumors had. This was not the first time this observation was made, past information had already indicated that greater cellular atypia, mitotic activity as well as necrosis was the indication of more aggressive biological behavior. Likewise, bigger size of tumors and deep anatomical location was linked to increased recurrences that were most probably related to the increased tumor burden, and technical inappropriateness of obtaining broad surgical margins [10]. Those features had stressed the role of early diagnosis and total excision of the organs in enhancing disease control in the long run.

The recurrence had also been highly determined by the surgical margin status. Tumors removed with positive or close margins had shown to have a much higher local recurrence rate as compared to those that were removed with wide and negative margins [11]. This observation had emphasized the need to do surgical planning carefully and needless to say, adjuvant radiotherapy should be employed to eliminate residual microscopic disease, where it counts. Additionally, histologic subtype had also impacted the recurrence behavior in that some types of sarcomas such as undifferentiated pleomorphic sarcoma and synovial sarcomas had shown a higher propensity to recurrence when compared to well differentiated liposarcoma which had a more indolent progression [12].

In addition to histology, other prognostic revealing molecular markers had also been made available. Ki-67 Overexpression of Ki-67 has been linked to high rates of cellular proliferation, as well as closely linked to the risk of recurrence. The relapse frequency and time were higher in high-Ki-67 of labeling index tumors than the low-Ki-67 of index tumor and indicated that proliferative activity was the third determining tumor aggressiveness. On the same note, there had been correlations of genomic instability and shorter outcomes with the occurrence of abnormalities in tumor suppressor genes, especially p53 [13]. Patients whose tumors were known to contain p53 overexpression or mutation had recorded much higher recurrence rates which are an indication of a lack of control of cell cycle movement and

 © 2025 European Journal of Clinical Pharmacy; Volume: 7: Issue: 1| All Right Reserved

apoptosis.

Certain genetic changes had also become pertinent forecasts. Such translocations as SYT-SSX in synovial sarcoma and MDM2 amplification in well-differentiated and dedifferentiated liposarcoma had not only aided in diagnosing but had also affected the prognosis. In this research, it was established that high-risk molecular signatures in the tumor were more likely to recur, which proved the necessity of molecular diagnostics in the usual pathological evaluation [14]. Also, malfunctions in angiogenic and growth factor signaling pathways, such as VEGF, PDGF expression had been linked to earlier relapse and more aggressive tumor behavior.

The histologic and molecular data combination had made possible a more sophisticated stratification of the patients in the low and high-risk groups. This combined method had been useful in particular where it was important to spot those patients who may have been able to use increased surveillance or adjuvant systemic therapy. Although the previous staging system was largely dependent on size, grade and depth, introduction of predictive molecular tools had enhanced the capability to predict recurrence and develop personal treatment regimes.

Irrespective of these strengths, some weaknesses had been identified. Retrospective study and relatively small sample size could have limited the extrapolation of the results. Moreover, the reason that heterogeneity between subtypes of sarcoma and their treatment regimens might have affected recurrence patterns is possible. However, the consistency of the determined associations with the existing literature had amplified the validity of the results [15].

To sum it all, the present investigation had shown that both histologic and molecular changes were the most important factors of clinical outcome in soft tissue sarcomas. Molecular biomarkers integrated into routine one-time histopathological assessments had improved the accuracy of prognostic information and had also helped clinicians deal more intimately with a patient. Subsequent prospective research in bigger groups of patients had been justified to further confirm these predictors and also a prospective study on specific therapies that aim at minimizing recurrence and also enhancing survival rates in patients who have soft tissue sarcomas.

CONCLUSION:

In this research, it was revealed that the histologic grade, size of tumor, status of margin and depth were excellent predictors of recurrence in soft tissue sarcomas. It had been shown that presence of high-grade tumor, a larger tumor, deep-seated position, and positive surgical margin had significant association with elevated local and distant recurrence rates. Besides this, molecular markers including Ki-67 overexpression, p53 mutations, and particular translocations of the chromosomes had also offered good prognostic understanding over and above the established conventional histopathology. Risk stratification was increased and disease behavior could be predicted more accurately informing the integration of molecular profiling and road-map histologic examination. Patients with previous and more frequent tumor recurrences had shown some adverse pathologic and molecular characteristics, and have thus required increased monitoring and customized adjuvant treatment. On balance, the pooling of both histologic and molecular prognosticators had enhanced the prognostic minimizing and aided a more individualistic manner of treating and following up patients with soft tissue sarcomas.

REFERENCES:

1. Gronchi A, Iadecola S, Restrepo-López J, Ng D, Barretta F, Ljevar S, Figura C, Johnston W, Fiore M, Radaelli S, Colombo C. Early recurrence and prognosis in patients undergoing resection of primary retroperitoneal sarcoma: an international, retrospective cohort study. eClinicalMedicine. 2026 Feb 1;92.
2. Kleijn TG, Ameline B, Kooistra W, van Kempen LC, Diercks GF, van Ginkel RJ, Been LB, van Leeuwen BL, Reyners AK, Kwee TC, Jutte PC. Radiotherapy Response Prediction in Myxofibrosarcomas and Undifferentiated Soft Tissue Sarcomas Using DNA Methylation and Copy Number Profiling. International Journal of Surgical Pathology. 2026:10668969251412902.
3. Lee EY, Kim JH, Park JW, Kang HG, Park SY, Sun J, Kim SY, Cho A, Lee B, You HJ. Clinical Characteristics of Complex Karyotype Soft Tissue Sarcomas: A Single-Institution Cohort Study. Medicina. 2026 Jan 27;62(2):271.
4. Kakibuchi D, Okada S, Furuya T, Shimomura M, Nakazono C, Teramukai S, Terauchi R, Shirai T, Takahashi K, Inoue M. Pulmonary metastasectomy from bone and soft tissue sarcomas: defining surgical indications at the time of second pulmonary recurrence. International Journal of Clinical Oncology. 2026 Jan 23:1-2.
5. Yang J, Zhang J, Li J, Liu Y, Wang Y, Hu A, Liu C. Decoding UTROSCT heterogeneity: systematic clinicopathological evaluation combined with molecular profiling. The Journal of

 © 2025 European Journal of Clinical Pharmacy; Volume: 7: Issue: 1| All Right Reserved

Pathology: Clinical Research. 2026 Jan;12(1):e70055.
6. Satala CB, Patrichi G, Gurau AM, Toma A, Popazu C, Mihalache D. An Update on Uterine Smooth Muscle Tumors: Is It a Leiomyoma, a STUMP, or a Leiomyosarcoma?.
7. Demofonti A, Germanotta M, Falchini F, Pavan A, Lattanzi S, Cortellini L, Brunetti B, Tenna S, Valeri A, Pagnoni C, Passa R. Clinical evaluation, motor performance and quality of life in patients affected by Soft Tissue Sarcomas undergoing surgical treatment: observational study. Frontiers in Oncology. 2026 Jan 13;15:1730371.
8. Klambauer K, Gold L, Klinge L, Mansour N, Winkelmann M, Ricke J, von Bergwelt-Baildon M, Di Gioia D, Lindner LH, Kunz WG. Baseline CT imaging parameters predicting overall and progression-free survival for patients with pulmonary metastases from soft tissue and bone sarcoma. European Radiology. 2026 Jan 3:1-2.
9. Noh A, Thompson SR, Lehane C, Parasyn A, Lee YC, Crowe P, Shon IH. Fluoro-2-deoxy-d-glucose PET radiomic analysis predicts outcome in patients with soft tissue sarcoma. Nuclear Medicine Communications. 2026 Feb 1;47(2):239-51.
10. Salmi H, Zeryouh B, Margoum H, Rifaai S, Haloui A, Tebbaa A, Najib A, Yacoubi H. Monophasic synovial sarcoma of the thigh in a 60-year-old patient: A rare case report and literature review. Radiology Case Reports. 2026 Mar 1;21(3):1224-9.
11. Kawaguchi K, Endo M, Fukuda H, Kawai A, Fujiwara T, Nabeshima A, Yokoyama N, Oda Y, Nakashima Y. Bone and soft tissue sarcoma mortality in 19,811 patients diagnosed in Japan, 2006–2020. JNCI Cancer Spectrum. 2026 Jan 7:pkag001.
12. Diab T, Tarhini A, Jaber G, Raffoul C, Zeineddine N, Kreidieh L, Hemade A, Barake M, Saghieh S, Mahfouz R, Assi HI. Real-World Implementation of Next-Generation Sequencing in Sarcoma: Molecular Insights and Therapeutic Outcomes. Medical Sciences. 2026 Jan 17;14(1):46.
13. Schmidt A, Guillén G, Luo LY, Seitz G, Craigie R, Rhee DS, Alemeida AC, Fuchs J, Lautz TB. Management of Pediatric and Adolescent Rhabdomyosarcoma of the Chest Wall: An Expert Consensus Opinion From the International Soft Tissue Sarcoma Consortium (INSTRuCT). Pediatric Blood & Cancer. 2026 Jan;73(1):e32117.
14. Jahn S, Krajina K, Smolle MA, Neufeldt D, Jonas K, Rinner B, Mellert K, Noeparast M, Trepel M, Szkandera J, Pichler M. Clinical Significance and Therapeutic Potential of Long Non-Coding RNA H19 in Soft Tissue Sarcoma. Cancer Medicine. 2026 Jan;15(1):e71305.
15. de Tarso Kawakami Perez P, Fayad LM, Rosa Pinto MB, Lederman HM, Monteiro Caran EM, Pacheco Donato Macedo CR, Brandão Guimarães J. Multiparametric assessment of high-grade pediatric soft-tissue sarcomas with anatomic and functional MRI sequences: a retrospective study. Skeletal Radiology. 2026 Feb;55(2):349-60.

 © 2025 European Journal of Clinical Pharmacy; Volume: 7: Issue: 1| All Right Reserved