



CLINICOPATHOLOGICAL, IMMUNOHISTOCHEMICAL, AND MOLECULAR SPECTRUM OF SYNOVIAL SARCOMA IN A TERTIARY CARE ONCOLOGY CENTRE: A TWO-YEAR STUDY

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ABSTRACT Synovial sarcoma is a molecularly defined soft tissue sarcoma characterised by the SS18::SSX fusion oncogene. This prospective observational study evaluated 88 cases diagnosed over two years at a tertiary care oncology centre, to define their clinicopathological features, immunohistochemical profile, molecular findings and outcome. Immunohistochemistry was performed in all cases and FISH for SS18::SSX in selected cases. Tumours were graded by the FNCLCC system, and associations with vital status were tested using Fisher's exact test. Median age was 34 years with a slight male predominance, and the lower limb was the commonest site (46.5%). Monophasic histology predominated (86.4%). TLE1 was positive in all cases, followed by CD99 (98.0%), BCL2 (91.8%), EMA (85.5%) and CK (83.6%). FISH was positive in 14 of 20 tested cases. Most tumours were FNCLCC grade 2 (97.7%), and both grade 3 tumours resulted in death. Of 67 patients with known vital status, 43 were alive and 24 had died. No clinicopathological variable was significantly associated with mortality. TLE1 immunohistochemistry is indispensable for diagnosis, FISH aids confirmation in difficult cases, and wide excision remains the mainstay of treatment. This 88-case series is among the larger single-institution Indian cohorts of synovial sarcoma. Tumours mainly affected young adults and arose most often in the deep soft tissues of the lower limb. Ten patients presented with metastasis, all from lower-limb primaries. Diagnosis rested on morphology and TLE1, with FISH reserved for equivocal cases because SS18-SSX fusion immunohistochemistry was unavailable at the centre. FNCLCC grading was almost uniformly grade 2, since differentiation is fixed at the maximum score in this tumour. The lack of significant prognostic associations most likely reflects small subgroups and missing time-to-event data rather than a true absence of effect. Follow-up was less complete than in recent Indian series, so larger studies with full follow-up are needed.

KEYWORDS : Synovial Sarcoma; TLE1; SS18::SSX Fusion; Immunohistochemistry

INTRODUCTION

Synovial sarcoma is a rare, molecularly defined mesenchymal neoplasm accounting for approximately 5–10% of soft tissue sarcomas, with an estimated incidence of 1–3 cases per million per year [1,2]. It is characterised by the recurrent translocation t(X;18)(p11.2;q11.2), producing the SS18::SSX1, SS18::SSX2 or, rarely, SS18::SSX4 fusion oncogene in over 90% of cases [1,2]. Despite its name, it does not arise from synovial tissue; the WHO Classification of Soft Tissue and Bone Tumours, 5th edition (2020), retains it among tumours of uncertain differentiation [3].

The tumour typically affects adolescents and young adults, most often in the deep soft tissues of the extremities [4]. It is classified histologically into monophasic, biphasic and poorly differentiated subtypes. Monophasic and poorly differentiated variants mimic other spindle and round cell sarcomas, including malignant peripheral nerve sheath tumour, Ewing sarcoma and BCOR-rearranged sarcoma, so extensive immunohistochemical and molecular evaluation is often needed [5].

TLE1, cytokeratin, EMA, BCL2 and CD99 aid diagnosis, though TLE1's high sensitivity is offset by imperfect specificity [6]. FISH or RT-PCR for SS18::SSX rearrangement is valuable in difficult cases [7]. A fusion-specific antibody against the SS18-SSX chimeric protein (clone E9X9V) has recently been validated, with 95–100% sensitivity and near-100% specificity, as a possible surrogate where molecular testing is limited [8,9,10]. Wide excision with negative margins is the standard of care; tumour size, margin status and histologic grade — rather than fusion transcript type — are the best-validated prognostic factors [11,12,13,14]. This study evaluates the clinicopathological

spectrum, immunohistochemical profile, molecular findings and short-term outcome of synovial sarcoma at a tertiary care oncology centre, in the context of recent Indian and international series.

MATERIALS AND METHODS

This prospective observational study was conducted over two years at the Kidwai Memorial Institute of Oncology, Bengaluru. Cases referred from the Departments of Surgical, Paediatric and Medical Oncology to the Department of Pathology for routine diagnosis were included. The procedures followed were in accordance with the ethical standards of the Institutional Ethics Committee, which approved the study, and with the Helsinki Declaration of 1975, as revised in 2013.

A total of 88 cases were analysed; the minimum sample size, calculated as 80 using finite population correction on the previous year's case load, was met. Primary and metastatic synovial sarcomas diagnosed on biopsy or resection specimens in all age groups were included; recurrent cases were excluded.

Specimens were fixed in 10% neutral buffered formalin and routinely processed. Haematoxylin and eosin-stained sections were classified as monophasic, biphasic or poorly differentiated. Mitotic count (per 10 high-power fields) and necrosis were recorded to derive FNCLCC grade. As synovial sarcoma is assigned the maximum differentiation score (3), grade depended only on mitotic count (1–3) and necrosis (0–2), so grade 1 was not achievable.

Immunohistochemistry was performed in all cases using CK, EMA, SMA, desmin, S100, CD34, CD99, BCL2 and TLE1, with additional markers (including SOX10, STAT6, DOG1, BCOR, NKX2.2,

myogenin, ERG and p40) applied selectively to exclude site-specific mimics, using appropriate positive controls. FISH for SS18::SSX rearrangement was performed in selected cases with overlapping histological and immunohistochemical features. SS18-SSX fusion-specific immunohistochemistry was not available during the study period. Clinical, treatment and follow-up details were retrieved from medical records, and no patient-identifying information is included.

Data were summarised as frequencies, percentages, and medians with ranges. Vital status at last contact was known for 67 of 88 patients (76.1%); the rest were excluded from outcome analysis. Time-to-event data were not captured, so Kaplan-Meier analysis was not performed. Associations between vital status and tumour size (cut-off 5 cm), margin status, adjuvant treatment, site (lower limb versus other) and FNCLCC grade were tested with Fisher's exact test; a two-tailed $p < 0.05$ was considered significant. These are cross-sectional associations with observed mortality, not survival estimates.

RESULTS

Age ranged from 2 months to 86 years (median 34 years; mean 36.4 ± 18.1 years); the commonest age group was 31–40 years ($n=22$). There were 46 males and 42 females (M:F = 1.10:1). The commonest presentation was a painless, slowly growing swelling.

The lower limb deep soft tissues were the commonest site (41 cases, 46.5%), followed by chest and thorax (16, 18.1%), upper limb (14, 15.9%), head and neck (6, 6.8%) and abdomen (6, 6.8%); uncommon sites (5, 5.6%) included breast, kidney, sciatic nerve, urethra and paravertebral region. Monophasic tumours predominated (76 cases, 86.4%), followed by biphasic (8, 9.1%) and poorly differentiated (4, 4.5%) (Table 1).

Table 1: Anatomical Site and Histological Subtype of Synovial Sarcoma (n=88).

Characteristic	Frequency	Percentage
Anatomical site		
Lower limb (deep soft tissue)	41	46.5
Chest and thorax	16	18.1
Upper limb	14	15.9
Head and neck	6	6.8
Abdomen	6	6.8
Uncommon sites*	5	5.6
Histological subtype		
Monophasic	76	86.4
Biphasic	8	9.1
Poorly differentiated	4	4.5
Total	88	100

*Breast, kidney, sciatic nerve, urethra, paravertebral region.

Monophasic tumours showed uniform spindle cells in sheets and fascicles with scant cytoplasm, ovoid hyperchromatic nuclei, and focal myxoid change, calcification and staghorn-shaped vessels. Biphasic tumours showed glandular epithelial components admixed with spindle cells. Poorly differentiated tumours showed sheets of round to epithelioid cells mimicking Ewing sarcoma, rhabdomyosarcoma or malignant peripheral nerve sheath tumour (Figure 1).

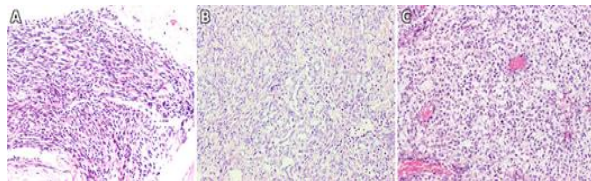


Figure 1: Histological Subtypes (H&E). (A) Monophasic: Uniform Spindle Cells with Staghorn Vasculature (x10). (B) Biphasic: Glandular and Spindle Components (x40). (C) Poorly Differentiated: Round-to-epithelioid Cells Mimicking Ewing Sarcoma (x40).

TLE1 showed diffuse strong nuclear positivity in all 88 cases (100%), followed by CD99 (98.0%), BCL2 (91.8%), EMA (85.5%) and CK (83.6%); SMA (5.7%), desmin (5.7%) and CD34 (4.0%) were only focally positive, and S100 was positive in 21.0% (Table 2). In biphasic tumours, TLE1 and cytokeratin stained both the epithelial and spindle components (Figure 2).

Table 2: Immunohistochemical Marker Positivity (n=88).

Marker	Positivity (%)	Marker	Positivity (%)
TLE1	100.0	S100	21.0
CD99	98.0	SMA	5.7
BCL2	91.8	Desmin	5.7
EMA	85.5	CD34	4.0
CK	83.6		

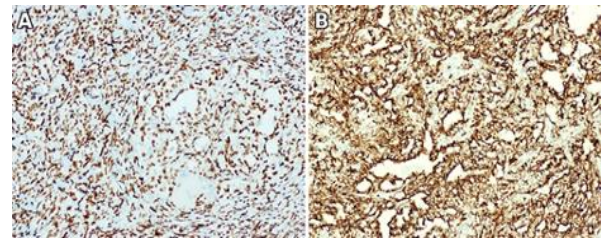


Figure 2: Biphasic Synovial Sarcoma. (A) TLE1: Diffuse Nuclear Positivity in Both Glandular and Spindle Components (x40). (B) Pancytokeratin: Positivity in Both Components (x40).

Mitotic count ranged from 1 to 12 per 10 high-power fields (median 3); necrosis was present in 8 cases (9.1%). FNCLCC grading classified 86 cases (97.7%) as grade 2 and 2 (2.3%) as grade 3; no case was grade 1, as expected from the fixed differentiation score [12,14]. FISH for SS18::SSX rearrangement was performed in 20 diagnostically challenging cases, of which 14 (70%) were positive (Figure 3); four were indeterminate due to suboptimal fixation and two were equivocal.

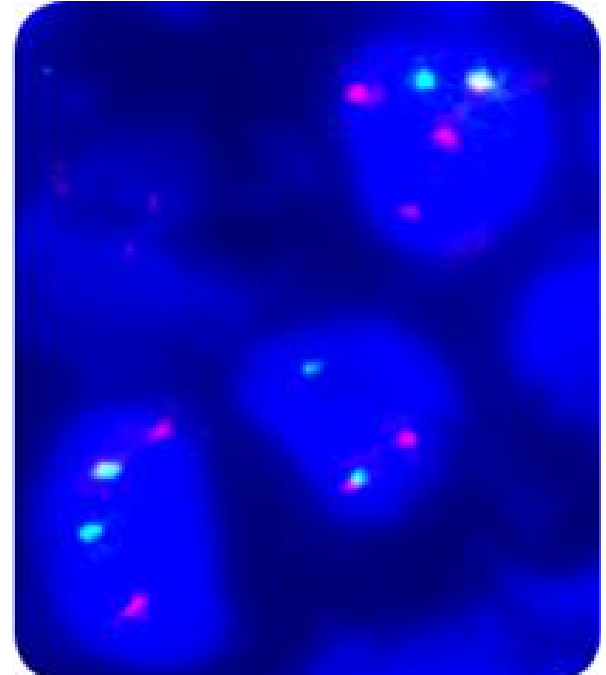


Figure 3: SS18 Break-apart FISH Showing One Fused and One Separated Red/Green Signal Per Nucleus, Indicating SS18 Rearrangement.

Ten cases (11.4%) presented with metastasis (lung in 9, pharyngeal wall in 1), all from lower-limb primaries. Tumour size ranged from 3 to 13.5 cm (median 6.55 cm). Neoadjuvant chemotherapy was given in 11 cases (12.5%); of 8 resected, 6 (75%) had residual viable tumour. Of 41 cases with recorded margins, 38 (92.7%) were negative. Adjuvant treatment data were available for 41 patients, of whom 33 (80.5%) received chemotherapy and/or radiotherapy. Of 67 patients with known vital status, 43 (64.2%) were alive and 24 (35.8%) had died. Tumour size > 5 cm ($p=0.60$), margin status ($p=0.53$), adjuvant treatment ($p=0.36$) and lower-limb site ($p=0.13$) were not significantly associated with mortality; the 2 grade 3 tumours were too few to test, but both patients died (Table 3).

Table 3: Vital Status and its Association with Clinicopathological Factors (n=67 with Known Vital Status).

Variable	n	p-value	Interpretation
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Alive at last contact	43 (64.2%)	—	—
Deceased	24 (35.8%)	—	—
Tumour size >5 cm vs ≤5 cm	67	0.60	Not significant
Positive vs negative margin	34	0.53	Not significant
Adjuvant treatment vs none	34	0.36	Not significant
Lower limb vs other site	67	0.13	Not significant
FNCLCC grade 3 vs grade 2	67	0.13	n=2; both died

Fisher's exact test. Outcome unknown in 21 patients (23.9%). Associations are exploratory given small subgroups and absent time-to-event data.

DISCUSSION

Synovial sarcoma is diagnostically challenging owing to its variable morphology, wide anatomical distribution and overlap with other spindle and round cell malignancies. At 88 cases, this is among the larger single-institution series from India.

The predilection for young adults is consistent with earlier series [4,15], although the wide age range shows the tumour must be considered at any age. The lower-extremity predominance concurs with the literature [1,4], and all metastatic cases arose from lower-limb primaries, supporting a higher metastatic propensity of deep extremity tumours [11,16]. The lung was the commonest metastatic site (9 of 10 cases), in keeping with the usual haematogenous spread of synovial sarcoma and supporting chest imaging at staging and follow-up. Monophasic tumours formed the majority, as in a recent 108-case Indian cohort (72.2%) [5,17,18]. Biphasic tumours are easier to diagnose, whereas monophasic and poorly differentiated variants overlap with other sarcomas, including BCOR-rearranged sarcoma. Poorly differentiated tumours, although few here, were disproportionately seen in older patients, as also reported previously, possibly reflecting more aggressive biology [12,13].

Our findings are broadly comparable with recent Indian data. A 2025 series of 108 cases reported a similar median age (30.5 years) and site pattern, TLE1 positivity of 96.2% and molecular confirmation in 10 of 15 tested cases (67%), against 70% here [18]. The male predominance in our cohort (M:F 1.10:1) was less marked than in that series (1.30:1) and in a 157-patient extremity series (1.53:1) [18,19]. Residual viable tumour in 6 of 8 resected cases after neoadjuvant chemotherapy suggests limited response in a subset, but the numbers are too small for conclusions and chemosensitivity in synovial sarcoma remains incompletely defined [11].

Universal TLE1 positivity confirms its high sensitivity and closely mirrors the 108-case Indian series (96.2%) [6,18,20]. However, TLE1 is also expressed in malignant peripheral nerve sheath tumour and solitary fibrous tumour, so it must be interpreted with other markers [20]. In practice, TLE1 should be paired with cytokeratin, EMA, BCL2 and CD99 and, where doubt persists in monophasic spindle cell tumours, with molecular confirmation. Frequent BCL2 and CD99 expression supports their adjunct role, while focal S100 and muscle marker expression is a diagnostic pitfall.

FISH resolved equivocal cases, consistent with prior work [7,21], and indeterminate results underscore the importance of optimal fixation. SS18-SSX fusion-specific immunohistochemistry (clone E9X9V) was not available at this centre. Since its validation in 400 tumours (95% sensitivity, 100% specificity), it has been replicated in independent cohorts and in pulmonary metastases [8,9,10]; a 108-case Indian series reported the same access constraint, performing the stain in only 5 cases [18]. Adopting this antibody is a clear direction for future work, offering near-molecular confirmation where FISH or RT-PCR is costly or slow.

FNCLCC grade was almost uniformly 2 (97.7%). Because the differentiation score is fixed at 3 in synovial sarcoma, grade is driven by mitotic count and necrosis alone, both low in most cases [12,14]. Both grade 3 patients died, consistent with the adverse prognosis of high mitotic activity and necrosis in larger grading studies [12,14], although the numbers preclude inference. Molecular status carried no prognostic information here, in keeping with grade rather than fusion type determining outcome [12,14].

Mortality among patients with known vital status was substantial (24 of 67, 35.8%), broadly in line with the historical 5-year survival of 50–60% [3,11,13], though not directly comparable without time-to-event data. Tumour size, margin status, adjuvant treatment and site

were not significantly associated with mortality, mirroring a 57-case Hyderabad series and a 108-case Indian series [18,22]. Larger Western series consistently identify size and margin status as prognostic [11,13,23]; the discrepancy most likely reflects small subgroups here (as few as 34 patients for margin and adjuvant comparisons) rather than absence of effect. The 108-case series reported 4-year overall survival of 93.6% with closer follow-up [18], while a 157-patient series of localised extremity synovial sarcoma reported 5-year overall survival of 53.4% [19]; the latter was restricted to extremity tumours, whereas ours included all sites.

Accurate subtyping, immunophenotyping and grading have practical consequences: they separate synovial sarcoma from mimics that are managed differently, and they identify the few tumours with high-grade features that may warrant closer surveillance. Reporting protocols that record mitotic count, necrosis and margin status in every case would make future multi-institutional comparisons possible.

This study has limitations. It is single-centre, and although vital status was known for 76.1% of patients, the absence of time-to-event data precluded Kaplan-Meier analysis, so the findings are cross-sectional and hypothesis-generating. Margin and adjuvant analyses were underpowered. FISH was not done in all cases for technical and resource reasons; because it was reserved for diagnostically difficult cases, the 70% positivity rate should not be read as the true fusion prevalence in the cohort. Fusion-specific immunohistochemistry was unavailable. Complete follow-up, full margin and treatment documentation, and larger samples are priorities for future work.

CONCLUSION

Synovial sarcoma is a morphologically diverse sarcoma of young adults with wide anatomical distribution and significant diagnostic challenges. TLE1 immunohistochemistry is pivotal in diagnosis, and FISH aids confirmation in difficult cases. FNCLCC grading showed a near-uniform intermediate-grade distribution, with both grade 3 tumours resulting in death. The absence of significant associations with size, margins, adjuvant treatment or site most plausibly reflects small subgroups. Complete excision with negative margins remains the cornerstone of treatment; fusion-specific immunohistochemistry, complete follow-up and larger samples would strengthen future work.

Conflicts of Interest

None declared.

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None.

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