# Fascin-1 is associated with recurrence in solitary fibrous tumor/hemangiopericytoma

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**Abstract.** Fascin-1, an actin-bundling protein, is associated with poor prognosis in patients with various types of human carcinoma. However, research is limited on the role of fascin-1 in sarcoma. Solitary fibrous tumor (SFT) and hemangiopericytoma (HPC) are rare sarcomas derived from the mesenchyme. Although the prognosis of SFT/HPC is generally favorable, fatalities are possible with repeated recurrence and distant metastasis. The current study included a total of 20 Japanese patients, who were diagnosed with SFT/HPC and underwent surgery at Kochi University Hospital from January 2000 to December 2019. The statistical relationship between recurrence and the following variables were examined: Sex, age of onset, tumor origin, tumor size, necrosis, mitosis ≥1/10 high power field (HPF; magnification, x400), Ki-67 >5% and Fascin-1. A significant association was determined between recurrence and necrosis, mitosis ≥1/10 HPF (magnification, x400), Ki-67 >5%, and Fascin-1 ≥'strongly positive' ($P<0.05$). The results demonstrated that Fascin-1 immunostaining may be a highly effective and useful evaluation factor for predicting poor prognosis in patients with SFT/HPC, a fatal sarcoma of humans.

## Introduction

Solitary fibrous tumor (SFT) and hemangiopericytoma (HPC) are rare tumors that derive from mesenchyme. SFT and HPC were formerly considered to be different diseases, however closely related due to similarities observed in immunohistochemical positive staining in CD34, CD99, vimentin, BCL2, and epithelial membrane antigen (1-5). This lack of specificity in SFT/HPC occasionally caused problems in differentiating them from other tumors that are immunohistologically alike them. In 2013, three groups reported that SFT and HPC have a common gene fusion between NGFI-A-binding protein 2 (NAB2) and signal transducer and activator of transcription 6 (STAT6) (1,6,7). Thereafter, STAT6, which has dual functions as a signal transducer and as transcription activator in SFT and HPC, was recognized as the highly sensitive and specific immunohistochemical marker for SFT/HPC (2-5,8-11).

Clinical progression of SFT/HPC is different in each case. For example, we reported one case where it was diagnosed accidentally and treated completely by a successful surgery, whereas in other cases relapse occurred with local recurrence and/or multiple metastases after many years of surgical treatment followed by radiotherapy and/or intensive chemotherapy (1,3,9,10,12-18). Regardless of the many attempts that have been made to classify NAB2-STAT6 fusion variants to prognose clinical characteristics of SFT/HPC, any absolute fusion variant related to malignancy has not yet been detected (11,19,20). However, recently classical grading of SFT/HPC with histopathological backgrounds, such as mitosis and necrosis, have been reevaluated to detect factors that may be associated with a malignant prognosis (15,16,21). Furthermore, several groups reported that Ki-67, a protein widely known to associate with a poor prognosis in various cancers (2,22-25), is related to recurrence in SFT/HPC derived from the pleura and central nervous system (2,14,15). We also detected a significant relationship to recurrence between necrosis, mitosis ≥1/10 HPF (magnification, x400), and Ki-67 >5% in SFT/HPC regardless of its origin (26).

In this study, we added evaluation of Fascin-1 immunostaining as a potential factor that may predict recurrence of SFT/HPC. Fascin-1, an actin-bundling protein, plays an important role in the regulation of cell adhesion, migration and invasion (27,28). It is known that Fascin-1 has a strong upregulation in various human carcinomas. However, regarding sarcomas, there are only a few earlier reports (29). Our study showed that Fascin-1 was strongly associated with recurrence of SFT/SFT and it suggested that Fascin-1 could be used as a predictive factor for malignancy of SFT/HPC.

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*Key words:* Fascin-1, solitary fibrous tumor, hemangiopericytoma, NGFI-A-binding protein 2-signal transducer, activator of transcription 6, Ki-67, mitosis

Table I. Clinical background of patients.

| Case | Sex | Age of onset (years) | Tumor location | Tumor size (cm) | STAT6 | Ki-67 >5% | Mitosis ≥1/10 HPF | Necrosis | Fascin-1 | Recurrence | Recurrence free months |
|---|---|---|---|---|---|---|---|---|---|---|---|
| I | F | 80-89 | Bone and soft tissue | 3.5 | + | - | - | - | + | - | 205 |
| II | F | 50-59 | Bone and soft tissue | 10.5 | + | - | - | - | - | - | 198 |
| III | M | 50-59 | Bone and soft tissue | 12.5 | + | + | + | - | Strongly positive | + | 89 |
| IV | M | 70-79 | Bone and soft tissue | 10.0 | + | + | + | + | Strongly positive | + | 0 |
| V | M | 60-69 | Bone and soft tissue | 15.0 | + | - | - | - | + | - | 97 |
| VI | M | 30-39 | Bone and soft tissue | 11.0 | + | - | - | - | - | - | 91 |
| VII | F | 70-79 | Bone and soft tissue | 10.0 | + | + | + | + | Strongly positive | + | 4 |
| VIII | F | 50-59 | Bone and soft tissue | 12.5 | + | - | - | - | + | - | 60 |
| IX | F | 60-69 | Bone and soft tissue | 9.0 | + | - | - | - | + | - | 6 |
| X | F | 50-59 | Head and neck | 1.7 | + | + | - | - | + | - | 175 |
| XI | F | 60-69 | Lung | 4.0 | + | - | - | - | - | - | 170 |
| XII | M | 70-79 | Lung | 6.0 | + | + | + | + | - | + | 2 |
| XIII | M | 30-39 | Lung | 14.0 | + | - | - | - | + | - | 114 |
| XIV | F | 50-59 | Lung | 8.0 | + | - | - | - | - | - | 111 |
| XV | F | 30-39 | CNS | 1.0 | + | - | + | - | Strongly positive | + | 136 |
| XVI | M | 60-69 | CNS | 5.0 | + | - | - | - | - | - | 195 |
| XVII | F | 50-59 | CNS | 2.0 | + | - | - | - | - | - | 188 |
| XVIII | F | 60-69 | CNS | 1.0 | + | + | + | - | - | + | 2 |
| XIX | F | 30-39 | CNS | 5.5 | + | + | + | - | Strongly positive | + | 49 |
| XX | F | 60-69 | CNS | 1.5 | + | - | + | - | - | - | 49 |

STAT6, signal transducer and activator of transcription 6; F, female; M, male; CNS, central nervous system; +, positive; -, negative; HPF, high power field (magnification, x400).

Table II. Examination of Fascin-1 staining cut off points.

| Cut-off point for Fascin-1 staining | Sensitivity | False positive rate | Concordance rate |
|---|---|---|---|
| 'negative'-'positive','strongly positive' | 0.71 | 0.46 | 0.60 |
| 'negative','positive'-'strongly positive' | 0.71 | 0.00 | 0.90 |

The most effective cut-off point for Fascin-1 staining for the judgement of recurrence (+) was between 'positive' and 'strongly positive', where sensitivity, false positive rate and concordance were 0.71, 0.00 and 0.90, respectively.

## Materials and methods

*Materials*. A total of 20 Japanese patients, previously diagnosed with SFT/HPC at Kochi University Hospital from January 2000 to December 2019, were included in this study. Table I shows the backgrounds of these patients. All patients underwent one or more tumor resection surgery. Tissues obtained during surgery were embedded in paraffin blocks after formalin fixation and preserved. All patients were observed at Kochi University Hospital following surgery. Seven cases had one or more recurrence and two patients (cases III and VII) died due to the disease.

*Immunohistochemical examination and evaluation*. For the present study, formalin-fixed paraffin-embedded tissue samples were freshly cut into 4 $\mu$m thick slices and heat-treated with ULTRA cell conditioning 1 retrieval solution (CC1; Ventana Automated Systems). Immunohistochemical examination was performed using a Ventana automated system with the following antibodies: STAT6 (D-1, sc-374021, dilution 1:50; Santa Cruz Biotechnology, Inc.), Ki-67 (MIB-1, dilution 1:50; Dako; Agilent Technologies, Inc.), and anti-Fascin-1 mouse monoclonal antibody (55k-2, dilution 1:50; Dako; Agilent Technologies, Inc.). Immunohistochemical expression of STAT6, Ki-67, and Fascin-1 was evaluated in the density of the nuclear staining and graded as 'negative', 'weak', 'moderate', or 'strong'. Grades 'moderate' and 'strong', were then defined as 'positive' in terms of diagnosis. To investigate the proportion of positive Ki-67, a total of 100 tumor cells were counted at five different hot spots. Then, the mean value of positive cells was calculated and input as a percentage for statistical analysis. As for the evaluation for Fascin-1, the intensity and extent of staining were examined (28,29). The intensity of staining was scored as 0 (negative), 1 (weak), 2 (moderate), or 3 (strong). The extent of staining was scored as 0 (0%), 1 (1-20%), 2 (21-70%), and 3 (71-100%). When the sum of staining intensity and extent scores was 2-4 and 5-6, it was defined as 'positive' and 'strongly positive', respectively. Independent evaluation of immunostaining was performed by two different expert pathologists who were blinded to the clinical data.

*Statistical analysis*. Statistical relationship was examined between recurrence and the following variables: Sex, onset age, tumor origin, tumor size, mitosis ≥1/10 HPF (magnification, x400), necrosis, Ki-67>5% and Fascin-1. Pearson's correlation coefficient analysis was applied to detect relationship between recurrence and sex, tumor origin, mitosis ≥1/10 HPF (magnification, x400), necrosis, or Ki-67>5%. Logistic regression analysis and Wilcoxon rank test were applied to compare recurrence with tumor size and onset age, respectively. Regarding Fascin-1, after the determination of its cut-off point for recurrence as between 'positive' and 'strongly positive', Wilcoxon rank test was applied to detect the relationship between recurrence and Fascin ≥'strongly positive'. Kaplan-Meier analysis was conducted to analyze the recurrence-free survival distributions between patients with Fascin-1 'strongly positive' or not.

Table III. Analyses of the relationship between recurrence and each variable.

| Variables | P-value |
|---|---|
| Male vs. female | NS |
| Onset age | NS |
| Tumor origin | NS |
| Tumor size (cm) | NS |
| Necrosis | <0.05 |
| Ki-67 >5% | <0.01 |
| Mitosis >1/10 HPF | <0.01 |
| Fascin-1 ≥strongly positive | <0.01 |

Pearson's correlation coefficient analysis was applied to detect the relationship between recurrence and sex, tumor origin, necrosis, mitosis ≥1-10 HPF (magnification, x400), or Ki-67>5%. Logistic regression analysis was applied to compare recurrence with tumor size. Wilcoxon rank test was applied to compare recurrence with onset age and Fascin-1 ≥'strongly positive'.

This study was reviewed and approved by the Ethics Committee for Clinical Research of the School of Medicine, Kochi University (ERB-105384). All procedures were carried out with the adequate understanding and written consent of each patient.

## Results

*Clinical background of patients*. Table I includes the results of histopathological and immunochemical evaluation of all cases.

*Fascin-1 staining*. Table II shows sensitivity, false positive rate, and concordance rate in two proposed groups with different cut-off points of Fascin-1 immunostaining. When the cut-off

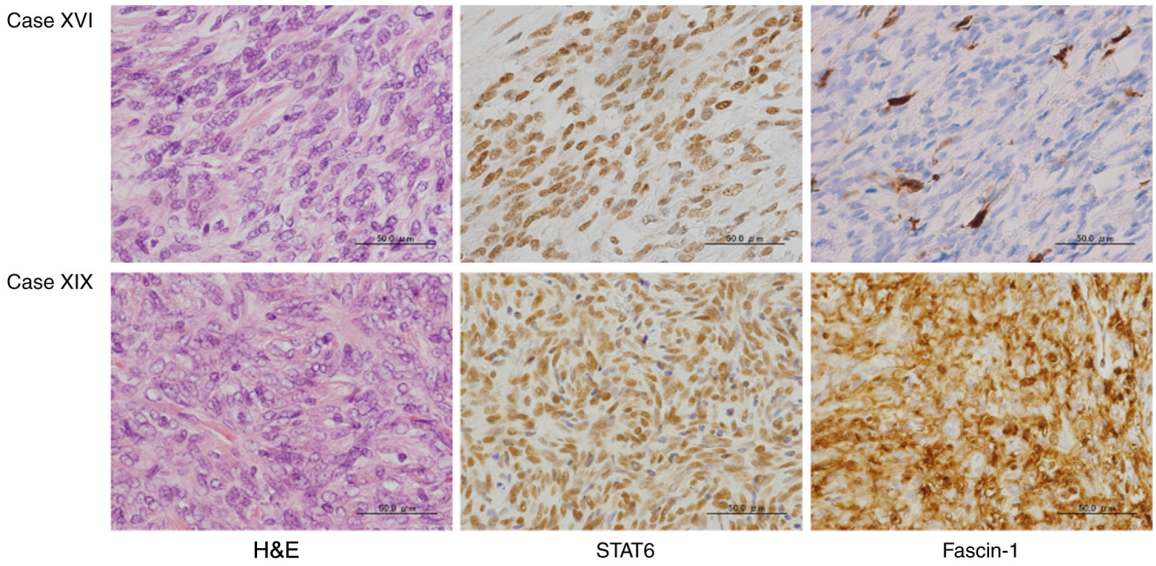


Figure 1. Immunohistochemical images of H&E, STAT6 and Fascin-1 staining in cases XVI and XIX. STAT6 was positive in each case and Fascin-1 was strongly positive in case XIX but negative in case XVI, of which staining was localized to the endothelium cells of the vessel. Scale bars, 50 $\mu$m. H&E, hematoxylin and eosin; STAT6, signal transducer and activator of transcription 6.

point was set between 'positive' and 'strongly positive', the sensitivity, false positive rate, and concordance were 0.71, 0.00, and 0.90, respectively. On the other hand, when the cut-off point was set between 'negative' and 'positive', its sensitivity, false positive rate and concordance were 0.71, 0.46 and 0.6, respectively. By these findings, the most effective cut-off point of Fascin-1 was determined to be between 'positive' and 'strongly positive'.

*Statistical analyses*. Table III shows the results of relationship between recurrence and each variable. A significant relationship to reference was detected with necrosis ($P<0.05$), mitosis ≥1/10 HPF (magnification, x400) ($P<0.01$), Ki-67 >5% ($P<0.01$), and Fascin-1 ≥'strongly positive' ($P<0.01$). Sex, onset age, tumor size, or tumor origin did not relate to recurrence. Fig. 1 shows representative images of the microscopic and immunohistochemical findings, specifically from Case XVI and Case XIX, where Fascin-1 was 'negative' in Case XVI and was 'strongly positive' in Case XIX. Fig. 2 shows Kaplan-Meier curve of patients with Fascin-1 'strongly positive' or not.

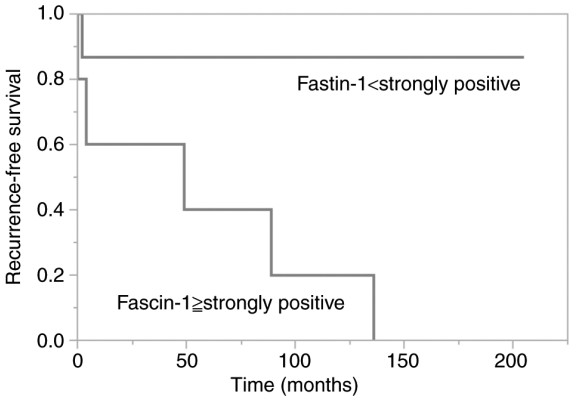


Figure 2. Kaplan-Meier curve of patients that were or were not 'strongly positive' for Fascin-1. The average observation period of patients without recurrence was 127.6 months.

## Discussion

SFT and HPC had long been regarded as different tumors since 1931, when Klemperer and Coleman first reported on primary mesenchymal tumors of the pleura (29). However, after the year 2000, controversial discussions about the classification of SFT/HPC prompted a unification of these tumors into a single disease entity. As a result, the 2013 WHO Classification of Tumors of Soft Tissue and Bone removed the term 'hemangiopericytoma' as a synonym for SFT, joining these tumors together as SFT under the category of fibroblastic/myofibroblastic tumors (5,8,30-32). In the same year, the common gene fusion between NAB2 and STAT6 was discovered in SFT/HPC. The 2016 WHO Classification of Tumors of the Central Nervous System designated these tumors, characterized by the NAB2-STAT6 gene fusion, as SFT/HPC in mesenchymal/non-mesenchymal tumors (2,9,33,34).

The discovery of the NAB2-STAT6 gene fusion, has resulted in both quicker and more accurate diagnosis of SFT/HPC. Cases difficult to diagnose with classical immunostainings, such as CD34, CD99, and vimentin, can easily be definitively diagnosed as SFT/HPC through the evaluation of STAT6 immunostaining. The prognosis of SFT/HPC is generally favorable, however, fatalities are possible with repeated recurrence and distant metastasis. In this study, seven of 20 cases had recurrence and two patients passed away due to the disease. The advancement of diagnostic techniques for SFT/HPC by STAT6 immunostaining may result in more cases being properly diagnosed in the future. Therefore, it is crucial for clinicians to identify patients with high risk of recurrence to adequately carry out their follow-ups.

Previously, we reported that recurrence of SFT/HPC was significantly related to necrosis, mitosis ≥1/10 HPF (magnification, x400), and Ki-67 >5% (26). Here, an

additional factor potentially related to recurrence has been added, specifically, Fascin-1 immunostaining. Fascin-1, an actin-bundling protein, plays an important role in the regulation of cell adhesion, migration, and invasion (27-29,35). Fascin-1 widely exists in different tissues of the human body, such as mesenchyme and nervous tissue, however it is not present in most normal epithelia. Fascin-1 has been commonly observed to be highly upregulated in various human carcinomas (27,28). Furthermore, the overexpression of Fascin-1 is positively correlated with poor prognosis of carcinomas, because it increases the chance of metastasis. Regarding sarcomas, few reports had been made about any relationship with Fascin-1. However, after 2019, Arlt *et al* reported Fascin-1 expression also correlates with progression and metastasis in osteosarcoma and chondrosarcoma (29). Additionally, Richmond *et al* reported that Fascin-1 is a mediator of invasion in uterine carcinosarcoma as a component of epithelial-mesenchymal transition (35).

Since 2012, pazopanib hydrochloride, a broad-spectrum tyrosine kinase inhibitor, has been approved for the treatment of soft tissue sarcoma in Japan, and its effectiveness has been reported in several papers (36,37). In this study, three patients (Case VII, XV and XI) had been treated with pazopanib hydrochloride, however, Case VII patient passed away within six months following its administration. The development of new medicines that may directly target the NAB2-STAT6 gene fusion is desired for patients with SFT/HPC. Furthermore, additional therapeutics that may target and inhibit Fascin-1 will also greatly benefit patients with malignant tumors.

We attempted to detect the relationship between Fascin-1 immunostaining and recurrence of SFT/HPC. Presently, classical histological findings, such as mitosis and necrosis, are generally accepted to be useful to prognose its recurrence. As shown in Table I, sensitivity of mitosis was excellent, but there was a false-positive case. As for necrosis, its specificity was excellent, but there were four false-negative cases, which implied necrosis was not a clinically favorable factor to predict its recurrence. Regarding Fascin-1, as shown in Tables I and II, sensitivity was 0.71 and two cases had false-negative, although, its false-positive rate was 0.0 and it was negative in Case XX, where mitosis had a false-positive. By using two factors, Fascin-1 and mitosis, recurrence in SFT/HPC could be prognosed more accurately. To confirm the benefit of Fascin-1 as a factor to predict recurrence in SFT/HPC, further studies with more cases should be performed in the future. However, in this study, we observed Fascin-1 immunostaining to be one of the most effective and useful evaluation factors to predict poor prognosis in patients with SFT/HPC. Through a meticulous histological and immunochemical observation of these factors after the initial surgery, clinicians should be better informed during follow-ups with patients most at risk for recurrence and subsequently able to treat them at early stages of recurrence.

The evaluation of Fascin-1 immunostaining is useful for recurrence prediction of SFT/HPC. These data indicate that Fascin-1 may play an important role in the recurrence of SFT/HPC, one of sarcomas.

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## Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

## Authors' contributions

YY and YH conceived the current study. YY and YH performed the histological examination. YY and HS performed statistical analysis. YY and IM made substantial contributions to study conception and design. IM critically revised the manuscript and gave final approval for the manuscript to be published. All authors read and approved the final manuscript. YY and YH confirmed the authenticity of all the raw data.

## Ethics approval and consent to participate

The current study was reviewed and approved by the Ethics Committee for Clinical Research of the School of Medicine, Kochi University (approval no. ERB-105384). All procedures were carried out with adequate understanding and the written consent of each patient.

## Patient consent for publication

Not applicable.

## Competing interests

The authors declare that they have no competing interests.

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