

Prognostic Impact of Fascin-1 (FSCN1) in Epithelial Ovarian Cancer

LARS C. HANKER¹, THOMAS KARN¹, UWE HOLTRICH¹, MONIKA GRAESER², SVEN BECKER¹, JOSCHA REINHARD¹, EUGEN RUCKHÄBERLE¹, HEIDRUN GEVENSLEBEN^{3*} and ACHIM RODY^{4*}

¹Department of Obstetrics and Gynecology, Goethe University, Frankfurt, Germany;

²Department of Gynecology and Gynecologic Oncology, University Medical Center, Hamburg, Germany;

³The Breakthrough Breast Cancer Research Centre, Institute of Cancer Research, London, U.K.;

⁴Department of Obstetrics and Gynecology, University Hospital Schleswig-Holstein, Lübeck, Germany

Abstract. *Background:* Fascin-1 (FSCN1) plays an important role in cancer development and is associated with invasion and metastasis. Therefore, we explored the expression and localization of FSCN1 in epithelial ovarian cancer (EOC). *Materials and Methods:* Expression analysis was performed by immunohistochemistry of paraffin-embedded tumor samples from 89 patients with EOC. Staining intensity and the percentage of positively stained tumor cells were used to calculate an immunoreactive score of 0-12 (IRS). These results were correlated to clinical and pathological characteristics as well as to patient survival. *Results:* Negative (IRS=0), weak (IRS=0-2) and strong (IRS>2) expression of FSCN1 in EOC was found in 5 (5.6%), 30 (33.7%) and 54 (60.7%) tumor samples, respectively. There was a strong correlation of residual postoperative tumor of >1 cm with higher immunoreactivity of FSCN1 ($p=0.04$). Lower FSCN1 expression was associated with significantly poorer overall survival ($p=0.02$). *Conclusion:* FSCN1 is frequently expressed in primary EOC. Its prognostic impact and function remains inconclusive and should be further examined in larger trials.

Epithelial ovarian cancer (EOC) is one of the most frequent types of cancers in women. According to the latest report of the American Cancer Society, it represents the sixth most common type of cancer in women in the US (1). Since the

introduction of platinum-based therapies in the 1980s, treatment and prognosis has slightly improved over the years (2). New developments, both in surgical and systemic therapy, have contributed to a moderate improvement of ovarian cancer-specific survival (3). Nevertheless, the prognosis remains poor, because of the lack of effective screening measures (4). Most cases of ovarian cancer are diagnosed at an advanced stage when the tumor has metastatically spread to the abdominal cavity (5, 6). These patients eventually experience relapse in about 80% of cases, even after optimal surgical debulking and systemic treatment (7). The identification of new molecular markers associated with metastatic spread to the peritoneum could help to define new subgroups and therapeutic approaches in order to improve clinical outcome.

A crucial step in the progression to metastatic disease is the alteration of intercellular adhesion between tumor cells. Ovarian cancer cells undergo an epithelial-to-mesenchymal transition which loosens the cell-cell adhesions and cell-extracellular matrix interactions (8). Several adhesion glycoproteins, such as intercellular adhesion molecules (ICAMs) and cadherins, are responsible for the stability of intercellular adhesions. Other molecules such as integrins contribute to the regulation of normal tissue organization and homeostasis. One of the critical factors for the cohesion of neighboring cells is E-cadherin. This protein connects actin microfilaments with the cytoplasm by generating α - and β -catenin junctions (9, 10). Hence, the epithelial cells are fixed firmly to each other. A loss of E-cadherin expression in ovarian cancer leads to a more metastatic phenotype (11). Changes in the actin cytoskeleton are another important precondition for the enhancement of tumor cell motility that can allow for detachment of malignant cells from the primary tumor and their spread to the peritoneal cavity. Under normal conditions, cell motility is modulated by several intracellular and extracellular factors that change actin expression and activity. One of these factors is fascin-1 (FSCN1), which

*These Authors contributed equally to this study.

Correspondence to: Lars Hanker, MD, Department of Obstetrics and Gynecology, J.W. Goethe University, Theodor-Stern-Kai 7, 60590 Frankfurt, Germany. Tel: +49 6963017024, Fax: +49 69630183469, e-mail: hanker@med.uni-frankfurt.de

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bundles actin filaments into tertiary structures. It represents a key molecule in diverse forms of actin-based cell motility (12, 13). FSCN1 is predominantly expressed only in a few types of human tissues, such as brain and spleen (14). Some authors point out that this gene is abundantly overexpressed in normal highly differentiated cells such as neuronal cells, endothelial cells, fibroblasts, and antigen-presenting dendritic cells (15-18). In contrast to this restricted transcription of the *FSCN1* gene in normal tissues, several author showed a marked expression of FSCN1 in human breast (19), gastrointestinal (20-22) pulmonary (23) and ovarian cancer (24). In various malignant tumors, such as breast cancer, FSCN1 expression correlates with a more aggressive biological behavior (19). In ovarian carcinoma cell cultures, FSCN1 expression was significantly associated with intraperitoneal cell growth (24), indicating the growth advantage of FSCN1-positive cells in this microenvironment. However, the exact function of FSCN1 and its interaction with other genes is poorly understood and needs further elucidation. In the present study, we analyzed the expression of FSCN1 in tumors from 89 patients with ovarian cancer. To evaluate the clinical and prognostic role of FSCN1, only primary epithelial ovarian carcinomas were included in the study.

Materials and Methods

Patients and treatment. The study included patients with primary EOC treated between 1995 and 2008 at the Department of Obstetrics and Gynecology at the University of Frankfurt. For a total of 89 patients, formalin-fixed, paraffin-embedded (FFPE) tissue samples were obtained and analyzed retrospectively. Patients' characteristics are listed in Table I. Clinical and pathological factors were evaluated by reviewing medical charts and pathology records. The Local Research Ethics Committees approved studies of human tissue and samples were processed anonymously. Clinical outcome was followed-up from the date of surgery to the date of death, or censored at the end of 2009. Only patients with histologically confirmed EOC were included. The majority of patients had advanced disease stages (FIGO III-IV) and had undergone primary surgery followed by a platinum- and taxane-based chemotherapy.

Tissue samples and immunohistochemistry. Routine histopathology sections stained with hematoxylin-eosin (HE) were used for primary diagnosis and second reviewing (HG). Diagnosis and grading was performed according to current criteria of the World Health Organization (WHO) (25). After mounting on Superfrost Plus slides, paraffin sections (2 μ m) were de-waxed in xylene and rehydrated to water by a series of graduated ethanol. For antigen retrieval, sections were incubated for 20 min in a microwave oven (800 W) using EDTA buffer (10 mmol/l; pH 8.0). Monoclonal anti-fascin antibody (Cat.-no. M356701-08, Clone55K-2; Dako, Glostrup, Denmark) was used at a 1:100 dilution. Incubation with the antibody for 1 h at room temperature was performed. For negative controls, the primary antibody was omitted. For secondary antibody incubation, the Dako REAL Detection System Alkaline Phosphatase/RED (Dako) was applied, following the instructions of the vendor. Sections were

counterstained with hematoxylin. Expression levels for cytoplasmic FSCN1 were scored semiquantitatively based on the product of staining intensity (SI) and the percentage of positively stained cells (PP) using the immunoreactive score (IRS) (26): $IRS = SI \times PP$. SI was assigned as 0, negative; 1, weak; 2, moderate; or 3, strong. PP was defined as 0, none; 1, <10%; 2, 11-50%; 3, 51-80%; or 4, >80% positive-stained cells. All assessments were performed blinded with respect to patient clinical data.

Statistical analysis. For statistical analysis, a cutoff value was defined according to the IRS, *i.e.* score 0-2 (negative and low) was combined as the low score and a score >2 was defined as a high FSCN1 expression score. The Chi-square test, Fisher's exact test and Mann-Whitney test were used to test for associations between FSCN1 expression of tumors and clinicopathological parameters. For patients with available follow-up data, Kaplan-Meier curves were constructed and the log-rank test used to determine the univariate significance of the variables. Cox regression analysis was performed to determine hazard ratios. All reported *p*-values are two-sided and *p*-values of less or equal than 0.05 were considered to indicate a significant result. All analyses were performed using the SPSS software package (SPSS, Chicago, IL, USA) version 18.0.

Results

A total of 89 patients were included in this study. All patients underwent radical surgery at the time of primary diagnosis, including hysterectomy, bilateral salpingo-oophorectomy, appendectomy, omentectomy and systematic pelvic and paraaortic lymphadenectomy, with the aim of resection of all visible tumors. In the majority of patients ($n=62$, 69.7%), optimal debulking, *i.e.* reaching at least a so-called optimal postoperative residual tumor to maximum of 1 cm, was achieved. Most patients received platinum-based first-line chemotherapy, predominantly in combination with a taxane.

The median follow-up time was 34.9 months. The median progression-free survival (PFS) and overall survival (OS) for the whole group were 16.9 [95% confidence interval (CI)=14.23-19.57] and 52.2 [95% CI=47.09-57.31] months. The corresponding 5-year PFS and OS rates were 17.6% and 37.2%, respectively. Patient characteristics for the whole cohort are displayed in Table I.

Expression of FSCN1. Of the 89 ovarian cancer cases analyzed, negative staining (IRS=0) was observed in five cases (5.6%). A low FSCN1 expression (IRS=1-2) was detected in 30 tumor samples (33.7%) and 54 cases (60.7%) displayed strong immunoreactivity for FSCN1 (IRS>2). Representative images of FSCN1 immunostaining are shown in Figure 1. In all tumors with positive staining results, FSCN1 was localized to the cell membrane and cytoplasm. As previously reported, fibroblasts, endothelial cells and dendritic cells of surrounding lymphoid tissue stained positively for FSCN1 and served as internal positive controls. No expression was seen in normal epithelium.

Table I. Patients' characteristics

| | |
|----------------------------------|-------------|
| No. of patients (%) | 89 (100) |
| Residual tumour after surgery | |
| 0 mm | 42(47.2) |
| 1-10 mm | 20 (22.5) |
| >10 mm | 27 (30.3) |
| Grading | |
| 1 | 3 (3.4) |
| 2 | 27 (30.3) |
| 3 | 59 (66.3) |
| Age (years) | |
| Median | 59.2 |
| Mean | 58.8 |
| Range | 31-83 |
| FIGO stage | |
| I | 16 (18.0) |
| II | 8 (9.0) |
| III | 50 (56.2) |
| IV | 15 (16.9) |
| Histological subtype | |
| Serous | 68 (76.4) |
| Mucinous | 5 (5.6) |
| Endometrioid | 7 (7.9) |
| Clear cell | 6 (6.7) |
| Transitional cell | 1 (1.1) |
| Other | 2 (2.2) |
| Survival (months) | |
| Progression-free survival (n=88) | |
| Median | 16.9 |
| Range | 14.23-19.57 |
| Overall survival (n=89) | |
| Median | 52.2 |
| Range | 47.09-57.31 |
| Platinum sensitivity | |
| Resistant | 29 (33.7) |
| Sensitive | 55 (64.0) |
| Not applicable/unknown | 2 (2.3) |

The mean IRS of FSCN1 expression for all histological subtypes of EOC overall, was 4.25 (SEM±2.93) (moderate 57.5%, strong 8.0%). When comparing samples of the serous subtype of EOC *vs.* the pooled group of all less frequent histological subtypes, a strong trend for a higher expression in serous EOC (median IRS=4) than non-serous subtypes (median IRS=2) was revealed (Figure 2; $p=0.056$). FSCN1 was expressed at higher levels in serous EOC in comparison to several histological subtypes (Figure 3 and Table II).

Correlation of FSCN1 expression with clinicopathological parameters. The clinical characteristics of the patients stratified according to high FSCN1 expression (IRS >2) *vs.* low expression (IRS 0-2) are shown in Table III. We detected no association of FSCN1 expression and FIGO stage, histological grading, age or platinum sensitivity in the cohort of 89 patients. Nevertheless, a significant correlation

Table II. Immunostaining score for fascin-1 (FSCN1) in different histological subtypes of ovarian cancer.

| Histological Subtype | Mean IRS | SEM |
|----------------------|----------|------|
| Serous | 4.46 | 0.33 |
| Mucinous | 3.20 | 1.36 |
| Endometrioid | 5.29 | 1.97 |
| Clear cell | 2.00 | 0.58 |
| Non-serous | 4.25 | 0.33 |

IRS, Immunoreactive score; SEM, standard error of the mean.

of high FSCN1 expression and the occurrence of residual postoperative tumor >1 cm was revealed ($p=0.04$). In addition, the serous subtype of carcinoma was associated with high FSCN1 expression ($p=0.05$).

Prognostic effect of FSCN1. We detected no significant prognostic value of FSCN1 for PFS ($p=0.39$). A slight trend towards a better OS was observed for patients with tumors displaying high expression of FSCN1 ($p=0.35$, Figure 4). Median OS in the low expression group was 50.7 (95% CI=24.3-77.0) months *vs.* 58.7 (95% CI=48.3-69.1) months in the high expression group. In univariate Cox regression analysis, residual postoperative tumor ($p<0.001$) and FIGO stage ($p<0.001$) had a significant prognostic impact on OS. For PFS serous histology ($p=0.033$), residual postoperative tumor ($p<0.001$), and FIGO stage ($p<0.001$) were significant for prognosis. In a subgroup analysis of 43 serous high-grade (G2 and G3) FIGO stage III carcinomas, FSCN1 expression had a significant prognostic impact on OS ($p=0.02$) but not on PFS. Median OS in this analysis was 23.8 (95% CI=8.1-39.4) months in the low-expression group *vs.* 53.2 (95% CI=35.6-70.7) months in the high-expression group (Figure 5).

Discussion

In the present study, we investigated the expression and prognostic significance of the actin-bundling protein FSCN1 in primary EOC by immunohistochemistry in a clinically well-described cohort of 89 patients.

In EOC the course of the disease is often associated with an early metastatic spread in the abdominal cavity (5, 6). This peritoneal dissemination is characteristic of ovarian cancer and differs from other tumor entities. One feature of this type of metastatic expansion is the loss of cell-cell adhesion and increased cell motility of epithelial cancer cells (8). For maintaining the epithelial cell line structure, homeostasis of the factors stabilizing the cytoskeleton and cell junctions is essential. FSCN1 bundles the actin filaments and thereby forms motility-associated cell structures and membrane protrusions (13). Furthermore, a proven co-localization of FSCN1 and β -

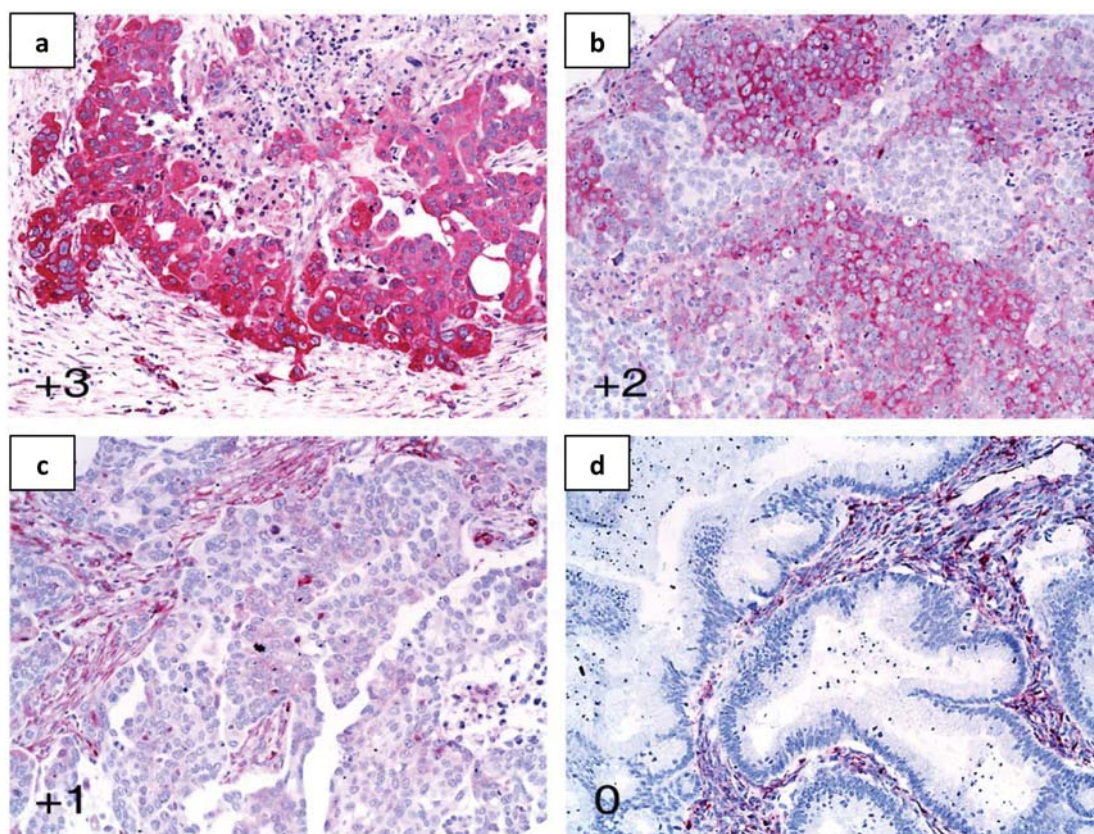


Figure 1. Immunohistochemical expression of fascin-1 (FSCN1) showing strong (a), moderate (b), weak (c) and negative (d) immunoreactivity. Note the positive staining of endothelial cells and adjacent connective tissue.

Table III. Clinical characteristics of ovarian cancer according to fascin-1 (FSCN1) expression.

| | | FSCN1-negative (IRS 0-2), n (%) | FSCN1-positive (IRS >2), n (%) | p-Value | Total n=89 |
|----------------|-----------|------------------------------------|-----------------------------------|---------|---------------|
| Residual tumor | 0 cm | 21 (50.0%) | 21 (50.0 %) | 0.04 | 42 |
| | >0 cm | 14 (29.8%) | 33 (70.2 %) | | 47 |
| Grading | 1, 2 | 13 (44.8%) | 16 (55.2%) | 0.31 | 29 |
| | 3 | 22 (36.7%) | 38 (63.3%) | | 60 |
| Age | ≤50 years | 9 (50.0%) | 9 (50.0%) | 0.22 | 18 |
| | >50 years | 26 (36.6 %) | 45 (63.4%) | | 71 |
| FIGO stage | I, II | 13(54.2%) | 11 (45.8%) | 0.06 | 24 |
| | III, IV | 22(33.8%) | 43 (66.2%) | | 65 |
| Histology | Serous | 23 (33.8 %) | 45 (66.2 %) | 0.05 | 68 |
| | Other | 12 (57.1%) | 99 (42.9%) | | 21 |

catenin to cell–cell borders in immunofluorescence analyses indicates an interaction in modulating motility and adhesion (27). Alteration of E-cadherin and catenin has been shown to promote and trigger invasiveness and development of metastatic phenotype of ovarian cancer (8). Despite the relevance of cell motility for metastatic spread in EOC, the

expression of FSCN1 has not been previously evaluated thoroughly in EOC, in a comprehensive patient cohort. Hue *et al.* highlighted a quantifiable expression of FSCN1 in 9/18 cultured cell lines of EOC. The authors described both a focal and a diffuse expression pattern in primary and metastatic cell lines. Furthermore, the authors reported on a significant

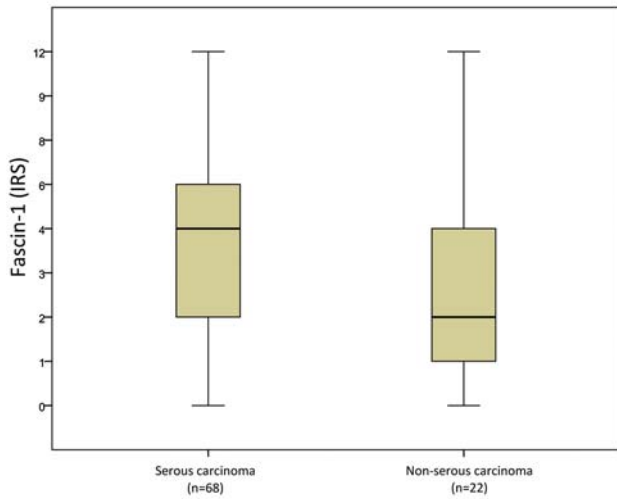


Figure 2. Comparison of fascin-1 (*FSCN1*) expression in serous and non-serous epithelial ovarian cancer. Two box plots are given for *FSCN1* median immune reactive score (IRS). The bottom and top of the box represent the 25th and 75th percentile, the band within the box the median, and the whiskers the highest and lowest values.

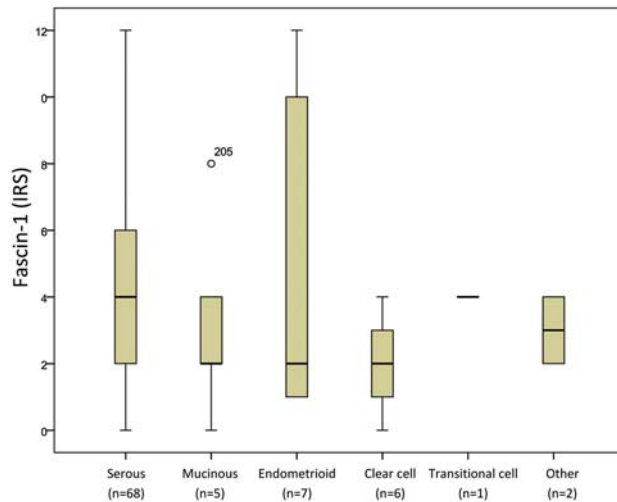


Figure 3. Comparison of fascin-1 (*FSCN1*) expression between histological subtypes in epithelial ovarian cancer. Box plots are given for *FSCN1* median immunoreactive score (IRS). The bottom and top of the box represent the 25th and 75th percentile, the band within the box the median, and the whiskers the highest and lowest values.

association ($p=0.05$) of expression of *FSCN1* and the ability of these established cell lines to grow intraperitoneally (24). Our results are in line with these findings. We revealed an overexpression (IRS >3) of *FSCN1* in 60.7% (54/89) of primary ovarian cancer biopsies, exhibiting a cytoplasmatic and membranous expression pattern.

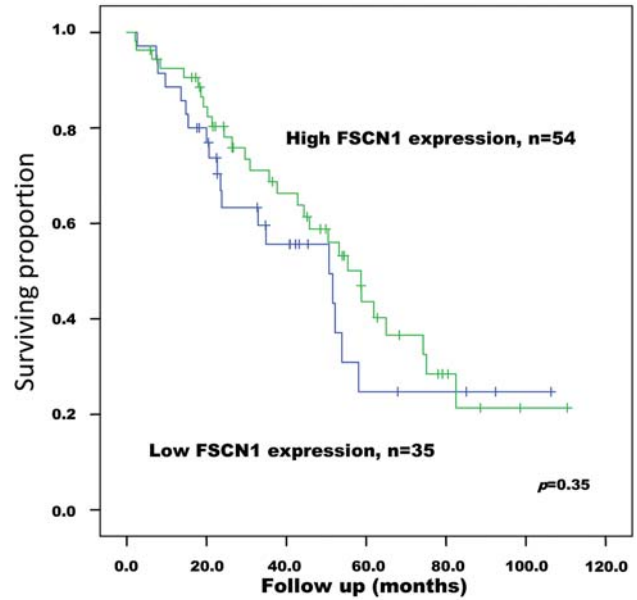


Figure 4. Kaplan–Meier analyses of overall survival was performed for 89 patients with epithelial ovarian cancer according to fascin-1 (*FSCN1*) expression.

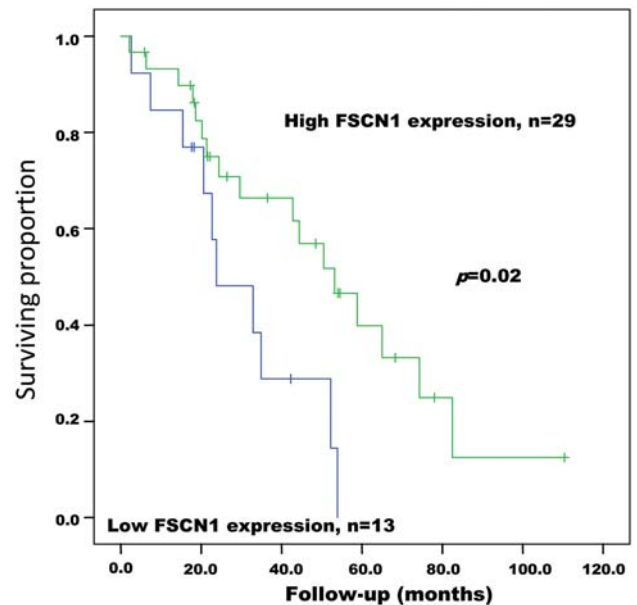


Figure 5. Kaplan–Meier analyses of overall survival was performed for the subgroup of 43 patients with serous high grade (G2 and G3) stage FIGO III epithelial ovarian cancer, according to fascin-1 (*FSCN1*) expression.

The analysis of correlations of clinicopathological factors with *FSCN1* expression showed no correlation to most standard parameters. Only for histological subtype ($p=0.05$) and postoperative tumor mass ($p=0.042$) was an association

detected. Serous EOC demonstrated a higher expression of FSCN1 when compared to other histological subtypes, suggesting an impact on the distinct biological behavior of serous carcinoma. These results are partially in line with Lin *et al.* These authors also showed a higher FSCN1 expression in serous EOC in comparison to mucinous and clear cell, but not to endometrioid EOC (28). In addition we observed a significant correlation of high FSCN1 expression and the occurrence of residual postoperative tumor of >1 cm ($p=0.042$). One might suggest that higher invasiveness, triggered by FSCN1 expression, could result in profound metastatic peritoneal distribution of the carcinoma cells and thus more frequently in residual tumor mass. These results support the findings of Hue *et al.* of a correlation of intraperitoneal growth and increasing FSCN1 expression in ovarian cancer cell lines (24). Other expression analyses in ovarian cancer contribute to these findings by suggesting that up-regulation of *FSCN1* in tumor tissues may promote invasiveness of EOC (29, 30). However, in our survival analysis, the negative prognostic impact of FSCN1 found in these pre-clinical studies was not confirmed.

Previous studies evaluating the prognostic impact of FSCN1 in EOC are inconsistent and very limited. Lin *et al.* reported on a poorer survival rate in the subgroup of patients with mucinous EOC (30), overexpressing FSCN1. However, only a small group of 47 patients was included in that study and no other histological subtypes were evaluated. Daponte *et al.* demonstrated a prognostic value of FSCN1 in serous EOC (31). A higher immunostaining score was significantly associated with shortened PFS and OS. The study, however, included a highly selected group of 56 patients with FIGO stage III G3 serous carcinomas. In our present study we were not able to confirm this impact of FSCN1 in the entire group of patients with EOC. In our full cohort of 89 women we detected neither a significant effect on PFS nor on OS. Even in the subgroup of patients with serous carcinoma, FSCN1 did not have any significant impact on survival ($p=0.5$). In contrast to the study of Daponte *et al.*, including only patients with very advanced stage disease, our cohort encompassed both patients with early-stage, *i.e.* FIGO stage I-IIA, and late-stage, *i.e.* FIGO stage IIB-IV, disease. Thus these data may suggest an impact of FSCN1 on prognosis only in late-stage disease. Therefore, we also performed a subgroup analysis of different FIGO stages, *i.e.* early-stage (FIGO I/II) and late-stage disease (FIGO III/IV), including only high-grade (G2/G3) serous carcinomas. Only in the subgroup of stage III disease was a significant prognostic impact on OS ($p=0.02$) detected. But quite in contrast to Daponte *et al.*, those patients with lower expression of FSCN1 had poorer OS. Moreover, it is pertinent to consider that there was no effect on PFS. However, one might suggest that this subgroup analysis is limited due to the low number of patients. A difference in postoperative tumor

mass could contribute to explaining these inconclusive results between the present study and the one of Daponte *et al.* The high rate of optimally debulked patients (>70%) in our cohort might dilute an effect on PFS. FSCN1 overexpression might promote further metastatic progress and could be more evident in patients with a higher postoperative tumor burden. The assumed negative prognostic effect of FSCN1 overexpression could be overcome by optimal tumor debulking, *i.e.* no postoperative tumor mass. This thesis is endorsed by the lack of prognostic impact of FSCN1 expression in the multivariate analysis in the trial of Daponte *et al.* However, the possible negative impact of FSCN1 overexpression on survival is distinctively supported by the significant impact on PFS and OS in patients with FIGO stage III, *i.e.* a disease stage characterized by more or less extended peritoneal metastasis, in the trial of Daponte *et al.* These results indicate that the prognostic impact of FSCN1 is most evident in the state of wide metastatic dissemination in the abdominal cavity, reflecting the relevance FSCN1 in initiating peritoneal seeding of EOC cells.

Our study is limited by its retrospective monocentric nature and the fact that tumor tissue was not strictly gathered in consecutive patients. This might cause a possible selection bias. Nevertheless, the high number of patients in a well-characterized, comprehensive cohort, and the established technique of immunohistochemistry are strengths of this study. However, the impact of FSCN1 should be further examined in larger trials and the underlying molecular mechanism should be assessed.

Conflicts of Interest

None.

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The work was approved by the appropriate local Ethical Committee.

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