Fascin-1 expression as stratification marker in borderline epithelial tumours of the ovary

Ahmed El-Balat,[1] Ruza Arsenic,[2] Nicole Sänger,[1] Thomas Karn,[1] Sven Becker,[1] Uwe Holtrich,[1] Knut Engels[3]

▶ Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/jclinpath-2015-203224).

[1]Department of Obstetrics and Gynecology, University Hospital Frankfurt, Frankfurt, Germany
[2]Institute of Pathology, Charité University Hospital, Berlin, Germany
[3]Center for Pathology, Cytology and Molecular Pathology, Neuss, Germany

Correspondence to
Dr Thomas Karn, Department of Obstetrics and Gynecology, Goethe University Frankfurt, Theodor-Stern-Kai 7, Frankfurt 60590, Germany; t.karn@em.uni-frankfurt.de

AE-B and RA contributed equally.

Received 25 June 2015
Accepted 29 July 2015
Published Online First 11 September 2015

ABSTRACT

Aims To evaluate the actin-bundling protein fascin-1 (FSCN1) as marker for borderline ovarian tumours (BOTs).

Methods We analysed a retrospective cohort of 140 BOTs with validated diagnosis by an independent pathologist. Immunohistochemical detection of FSCN1 was quantified as combined immunoreactive score (CIS) blinded to clinical patient data. Analyses were first performed for FSCN1 positive versus negative, and then verified using three categories derived from the observed distribution (negative, weak, strong; CIS 0, 1–2, 3–9).

Results We detected FSCN1 positivity in 51.4%, and strong expression (CIS 3–9) in 14.3% of the samples. FSCN1 positivity was associated with serous subtype ($p<0.001$) and micropapillary pattern ($p<0.001$). Correlation with micropapillary pattern remained significant within the serous BOT (SBOT) subgroup ($p=0.022$). Strong FSCN1 expression (CIS 3–9) was associated both with the presence of implants ($p=0.022$), and a higher International Federation of Gynecology and Obstetrics (FIGO) stage ($p=0.020$).

Conclusions Our analysis links FSCN1 with SBOT with micropapillary pattern. Strong expression is associated with higher FIGO stage and the presence of implants, both related to elevated risk of recurrence. Hence, FSCN1 is an interesting marker worth further analyses of its prognostic value in BOTs.

INTRODUCTION

Borderline ovarian tumours (BOTs) have been extensively investigated since this category was created 40 years ago.[1] About 9%–15% of all serous neoplasms are of borderline type and an incidence of 2.5 per 100 000 women-years has been reported for the USA.[1 2] These tumours are puzzling neoplasms that do not fall neatly into benign or malignant categories, their behaviour is enigmatic, their pathogenesis unclear and their clinical management controversial, especially for serous BOTs (SBOTs), the most common of the five histological subtypes.[3] Patients with a BOT tend to be younger than those with invasive ovarian cancer and prognosis is excellent for limited tumour extent and surprisingly good even for those with extensive peritoneal disease.[4] Still some patients relapse or succumb to disease.[1 5] Since high-risk BOTs have not been defined by consensus, identification of risk factors for invasive recurrence or disease-related death is pivotal.[1 6 7] Much of the confusion and controversy concerning these tumours is due to a lack of understanding of their pathogenesis and the absence of a model for the development of ovarian carcinoma.[3] To this end a unifying theory for origin and pathogenesis of epithelial ovarian cancer (EOC) has been proposed which distinguishes two distinct groups (type I and type II) of tumours including both borderline and invasive forms of the disease.[8] Kurman *et al*[9] divided serous tumours into five categories, consisting of adenoma or benign disease, SBOTs devoid of micropapillary patterns (now designated atypical proliferative serous tumours), non-invasive micropapillary low-grade serous carcinoma, invasive low-grade serous carcinoma (invasive micropapillary serous carcinoma) and high-grade serous carcinoma.[1] The main issue was if patients with SBOTs with micropapillary patterns should be included in a high-risk group and their disease regarded as low-grade carcinoma.[1] Molecular data seem to confirm the view that invasive low-grade serous carcinoma develops in a stepwise fashion from benign cystadenofibroma to classic invasive low-grade serous carcinoma via transformations to SBOT (or, atypical proliferative serous tumours) and serous lesions with micropapillary pattern.[9–12] Several studies indicate that SBOTs with micropapillary patterns have a worse prognosis than lesions without this histological feature[13–18] but debate still exists.[19] Indeed, SBOTs with micropapillary patterns without implants (stage I) or with non-invasive implants (stage II–III) have the same prognosis as do SBOTs without micropapillary patterns (or, atypical proliferative serous tumours).[9]

A crucial step in the progression of ovarian tumours relates to the alteration of intercellular adhesion and cell motility.[20] These processes are modulated by many factors but one key regulator is the actin-bundling protein fascin-1 (FSCN1), which has been associated with invasion and metastasis in different cancers.[21–26] In previous work we demonstrated that invasive EOC is associated with increased expression of FSCN1.[25] Moreover, higher expression of FSCN1 was found in the serous subtype of EOC. In the present study, we have analysed the expression of FSCN1 in a cohort of 140 BOTs. We found expression of FSCN1 to be associated with SBOTs with micropapillary pattern. However, not all SBOTs with a micropapillary differentiation show FSCN1 expression. Therefore, FSCN1 could be a valuable marker to differentiate micropapillary cases with differing prognosis.

MATERIALS AND METHODS

Patients and samples

All analyses were performed according to the 'REporting recommendations for tumour MARKer prognostic studies' (REMARK).[27] A corresponding REMARK diagram is given in online

To cite: El-Balat A, Arsenic R, Sänger N, *et al*. *J Clin Pathol* 2016;**69**:142–148.

supplementary figure S1. We retrospectively assembled a cohort of 156 BOTs undergoing surgical resection between January 1997 and September 2013 at the Goethe University Hospital in Frankfurt/Main, Germany. Formalin-fixed paraffin-embedded tissue samples were obtained from the Senckenberg Institute of Pathology, University of Frankfurt, and were re-evaluated by a second pathologist at the Institute of Pathology at the Charité Universitätsmedizin Berlin, Germany. For 140 of the samples with validated diagnosis sufficient archival material for immunohistochemical analysis was available. Pathological characteristics of this cohort are listed in table 1. The Local Research Ethics Committees approved studies of human tissue and samples were processed anonymously.

Histopathological evaluation and immunohistochemistry

Routine histopathology sections stained with H&E were used for primary diagnosis (KE) and second reviewing (RA) by two experienced pathologists. Diagnosis and classification was performed according to the current criteria of WHO.[28] After mounting on Superfrost Plus slides, paraffin sections (2 µm) were dewaxed 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-FSCN1 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 haematoxylin. FSCN1 were scored semiquantitatively (RA) based on the product of staining intensity (SI) and percentage of positively stained cells (PP) as a combined immunoreactive score (CIS): CIS=SI×PP. SI was assigned as 0, negative; 1, weak; 2, moderate or 3, intense. PP was defined as 0, none; 1, <25%; 2, 25%–50%; 3, 51%–75% or 4, >80% positive stained cells. All assessments were made blinded with respect to clinical patient data. For samples consisting of invasive carcinoma with an underlying borderline tumour in the histology only the borderline tumour was scored.

Statistical analysis

χ^2 and Fisher's exact tests were used to determine the significance of categorical variables, Mann–Whitney U test for the analysis of continuous variables. All p values are two sided and 0.05 was applied as the significance level. Subjects with missing values were excluded from the analyses. For the first analysis a dichotomic classification between no expression of FSCN1 (CIS=0) and any expression (CIS>0) was used. Subsequently, based on the distribution of the CIS a further separation in the three categories was also applied. All analyses were performed using SPSS Statistics V.22 (IBM).

RESULTS

Cohort

We retrospectively identified 156 cases of BOT from pathology records. For 142 samples sufficient archival material was present for standard H&E staining and immunohistochemistry using a monoclonal antifascin antibody. However, on re-evaluation one of the 142 samples was recharacterised as adenoma of the ovary and for one BOT only material from implants was available, leaving a total of 140 BOT samples for analysis.

Sample characteristics of the cohort

We finally studied a cohort of 140 BOTs with validated diagnosis by a second pathologist and sufficient archival material for immunohistochemical analysis. Median age of patients was 49.5 years (IQR 36.0–64.3). Additional sample characteristics are given in table 1. The majority of the samples were either of serous (60.0%, SBOT) or mucinous subtype (32.1%, MBOT). The high frequency of mucinous histology in BOT as compared with EOC has also been described by others.[29] The FIGO stage for most of the patients was either IA (30.0%) or IC (37.9%). Micropapillary pattern was observed for 22.9% (17.9% partially) and implants were detected among 9.3% of the patients (table 1).

To analyse consistency of subtype classification we also compared results of the second pathology in the present study with the original subtype classification from primary diagnosis available for 136 samples and found an overall agreement of 89.0% (serous 98.8%, mucinous 86.7%, mixed 11.0%). For a subset of 22 samples the BOT diagnosis was also verified at the time of primary diagnosis by an additional reference pathology. For this subset of samples agreement with subtype classification from the present study reached 100%.

FSCN1 expression in borderline tumours of the ovary

We next studied FSCN1 expression by immunohistochemical analysis of tissue samples from all 140 borderline tumours from

Table 1 Sample characteristics

Characteristic according to second pathology	n	Per cent
Subtype		
Serous	84	60.0
Mucinous	45	32.1
Endometroid	2	1.4
Mixed	9	6.4
FIGO stage		
IA	42	30.0
IB	8	5.7
IC	53	37.9
II	7	5.0
III	7	5.0
IV	1	0.7
n.a.	22	15.7
Implants		
No	127	90.7
Yes	13	9.3
Micropapillary pattern		
No	108	77.1
Partially	25	17.9
Yes	7	5.0
Presence of in situ carcinoma*		
No	121	90.7
Yes	13	9.3
Macroinvasion†		
No	126	92.6
Yes	10	7.4
Microinvasion		
No	137	97.9
Yes	3	2.1

*According to WHO criteria: Cribriform glands measuring 5 mm in one dimension and nuclear atypia greater than that allowed in serous borderline ovarian tumour.[28]
†Macroinvasion refers to invasive carcinoma with underlying borderline tumour in the histology.
FIGO, International Federation of Gynecology and Obstetrics; NA, not available.

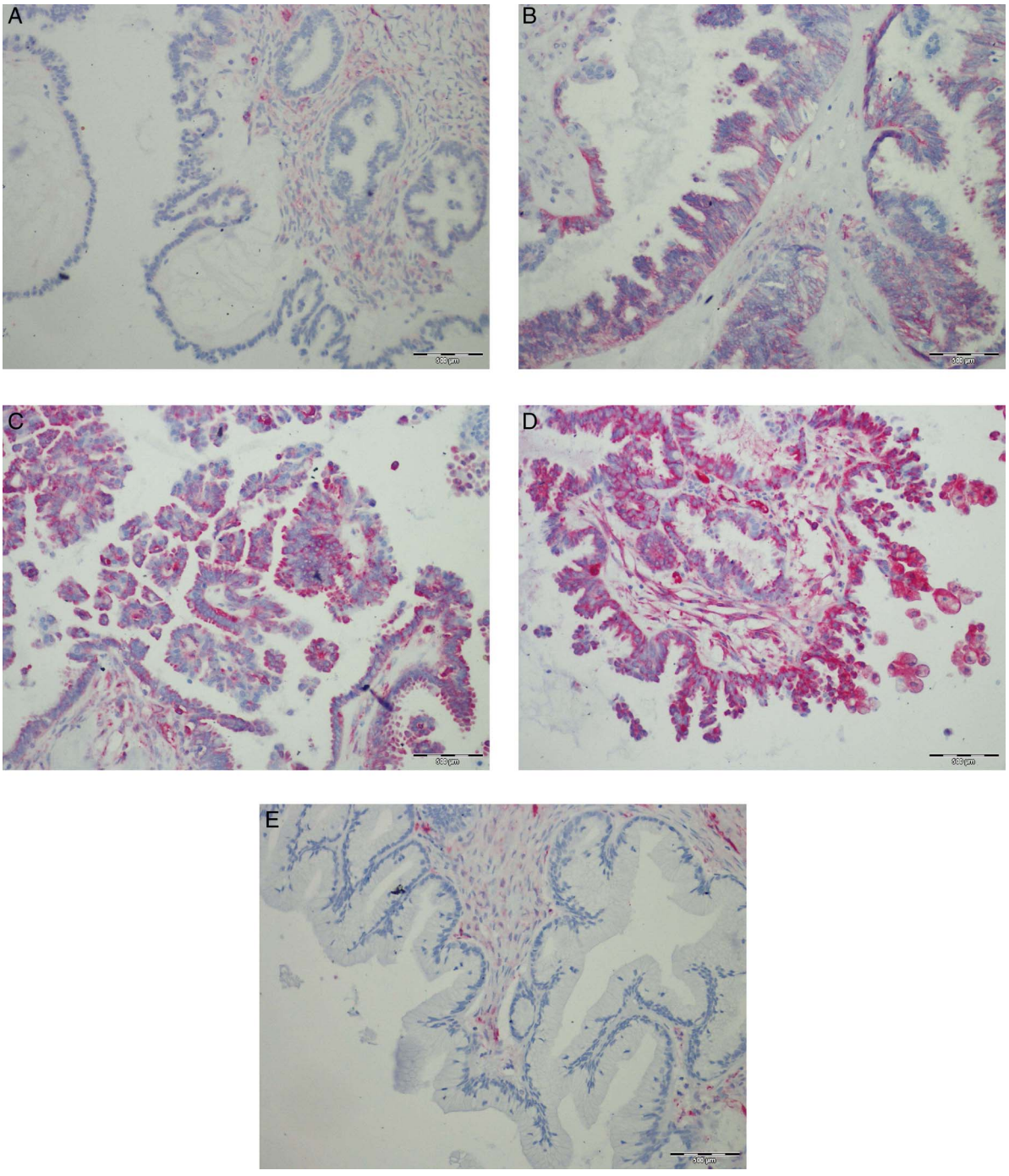

Figure 1 Immunohistochemical detection of fascin-1 (FSCN1) expression in borderline tumours of the ovary. Immunohistochemical staining of formalin-fixed paraffin-embedded borderline tumour tissues using FSCN1 antibody. Examples of tissue sections with different staining intensities are shown: Serous borderline ovarian tumours (BOTs) with negative (A), weak (B), moderate (C) and intense (D) FSCN1 staining. An example of a negative mucinous BOT is shown in (E). ×300, scale bar 500 μm.

table 1. Representative examples of FSCN1 staining results are shown in figure 1A–E. As previously reported, FSCN1 was localised to cell membrane and cytoplasm in all tumours with positive staining results. Fibroblasts, endothelial cells and dendritic cells of surrounding lymphoid tissue stained positive for FSCN1 and served as internal positive controls. No expression was seen in non-neoplastic epithelium. Intensity of staining and percentage of stained cells were scored separately and amalgamated as a combined immunoreactive score (CIS, see Materials and Methods section). For the first analysis we applied a dichotomic classification between no expression of FSCN1 (CIS=0) and any expression (CIS>0) resulting in 68 (48.6%) negative cases and 72 (51.4%) positive cases, respectively. We then compared this classification with sample characteristics as presented in table 2. We found no strong differences regarding patients' age, FIGO stage, presence of in situ carcinoma, macroinvasion or microinvasion and the presence of implants between samples positive and negative for FSCN1, respectively (table 2). In contrast, FSCN1 positivity was highly correlated to serous subtype of BOTs with 75.0% of samples with serous histology showing

Table 2 FSCN1 expression in borderline tumours of the ovary

Sample characteristic	FSCN1 negative (CIS=0)	Per cent	FSCN1 positive (CIS>0)	Per cent	p Value
Frequency	68	48.6	72	52.1	
Median age					
(95% CI)	53.0	(48.5 to 57.4)	47.8	(43.9 to 51.8)	0.086
FIGO stage					
IA	19	45.2	23	54.8	0.173
IB	3	37.5	5	62.5	
IC	26	49.1	27	50.9	
II	1	14.3	6	85.7	
III	3	42.9	4	57.1	
IV	0	0	1	100	
n.a.	22				
Subtype					
Serous	21	25.0	63	75.0	**<0.001**
Mucinous	40	88.9	5	11.1	
Endometroid	1	50.0	1	50.0	
Mixed	6	66.7	3	33.3	
Presence of in situ carcinoma*					
No	66	47.2	67	52.8	0.39
Yes	8	61.5	5	38.5	
Micropapillary pattern					
No	64	59.3	44	40.7	**<0.001**
Partially	3	12.0	22	88.0	
Yes	1	14.3	6	85.7	
Macroinvasion†					
No	63	50.0	63	50.0	0.75
Yes	4	40.0	6	60.0	
Microinvasion					
No	68	49.6	69	50.4	0.25
Yes	0	0	3	4.2	
Implants					
No	65	51.2	62	48.8	P=0.079
Yes	3	23.1	10	76.9	

*According to WHO criteria: Cribriform glands measuring 5 mm in one dimension and nuclear atypia greater than that allowed in serous borderline ovarian tumour.[28]
†Macroinvasion refers to invasive carcinoma with underlying borderline tumour in the histology.
Significant p Values are given in bold face.
CIS, combined immunoreactive score; FIGO, International Federation of Gynecology and Obstetrics; FSCN1, fascin-1; NA, not available.

FSCN1 expression compared with only 16.1% among other subtypes (p<0.001; table 2). Moreover, we also detected a high frequency of FSCN1 positivity in those BOTs displaying a micropapillary pattern. About 85.7% and 88.0% of samples with micropapillary pattern and partially micropapillary pattern, respectively, were positive for FSCN1, in contrast to only 40.7% of those with no micropapillary pattern (p<0.001; table 2). To verify that this observation is independent from the association of both FSCN1 expression and micropapillary pattern with the serous subtype, we also repeated the analysis within the subgroup of SBOT. As presented in table 3 we validated the significant association of micropapillary pattern with FSCN1 expression even within this subgroup (p=0.044; table 3).

Table 3 FSCN1 expression and micropapillary pattern in SBOT

Sample characteristic	FSCN1 negative	Per cent	FSCN1 positive	Per cent	p Value
Micropapillary pattern					
No	18	34.0	35	66.0	**0.044**
Partially	2	8.3	22	91.7	
Yes	1	14.3	6	85.7	

Significant p Values are given in bold face.
FSCN1, fascin-1; SBOT, serous borderline ovarian tumours.

We also analysed the CIS using additional categories. Figure 2A shows the distribution of the observed CIS among the 140 BOT samples. Based on the observed bimodal distribution we stratified samples into three categories with either no FSCN1 expression (CIS 0), weak FSCN1 expression (CIS 1–2) or strong FSCN1 expression (CIS 3–9). Figure 2B demonstrates that expression of FSCN1 was mainly found in the subtype of SBOTs independently of the applied cut-off (weak or strong, p<0.001). Figure 2C demonstrates that the same holds true for the association of micropapillary pattern with FSCN1 expression. However, since in SBOTs micropapillary pattern is recognised as an important pathological feature, we also repeated this analysis within the serous subgroup. Still we observed a trend for an association of FSCN1 expression and micropapillary pattern within this group (p=0.079; figure 2D). Finally, we analysed the association of strong FSCN1 expression (CIS 3–9) with pathohistological parameters in our cohort. As shown in

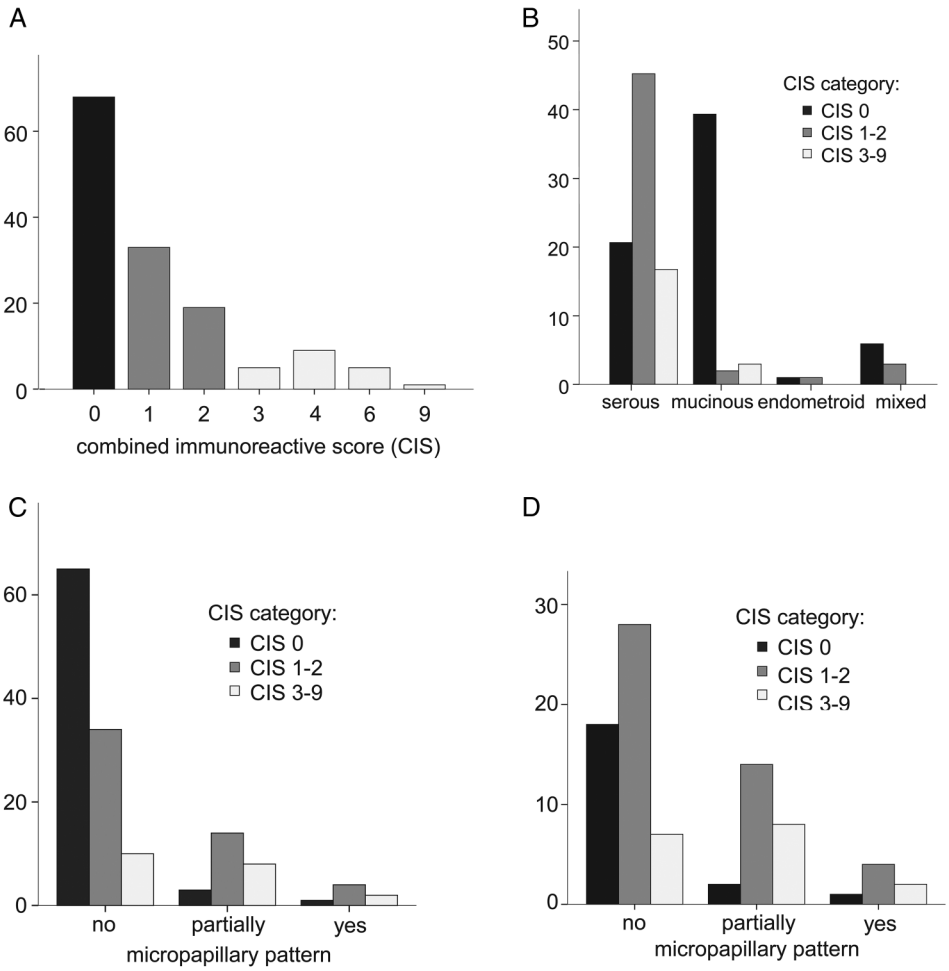

Figure 2 Stratification of borderline ovarian tumour (BOT) according to three categories of combined immunoreactive score (CIS) of fascin-1 (FSCN1) expression. (A) Based on the observed distribution of CIS three categories (CIS 0, CIS 1–2 and CIS 3–9) were chosen for stratification. (B) Distribution of CIS categories of FSCN1 expression in histological subtypes of BOTs. (C) Distribution of CIS categories of FSCN1 expression according to micropapillary pattern. (D) Distribution of CIS categories of FSCN1 expression according to micropapillary pattern within the subgroup of serous BOTs.

table 4 we observed a significant positive association of strong FSCN1 expression with the presence of implants (p=0.022). Moreover, strong FSCN1 expression was associated with a higher FIGO stage (FIGO II and above, p=0.088; FIGO IC and above, p=0.020).

DISCUSSION

In the present study, we analysed the expression of the actin-bundling protein FSCN1 in a cohort of 140 BOTs. To our knowledge, this represents the largest analysis of FSCN1 in BOT up to date. The overall composition of our cohort with respect to high prominence of SBOT and MBOT subtypes (64.5% and 31.9%, respectively) resembled that of large meta-analyses.[29] In our analysis we found a highly significant association of FSCN1 positivity both with serous histology (SBOT) and with micropapillary patterns (p<0.001 for both). Importantly, even within the subgroup of SBOT the correlation of FSCN1 with micropapillary pattern is still significant (p=0.044). Strong FSCN1 expression (CIS 3–9) was also associated with the presence of implants (p=0.022) and a higher FIGO stage. The comparison of FIGO I with FIGO II and above only showed a trend (p=0.088, table 4) to significance, presumably due to the small number of samples (n=8). However, a significant difference was found for samples of FIGO IC and above (p=0.020, table 4). Cases of FIGO IC are characterised by capsule rupture and/or the release of malignant cells in the peritoneal cavity. Unfortunately, not enough data were available to distinguish cases with surgical tumour spill (FIGO 1C1) from those with capsule ruptured before surgery (FIGO 1C2). However, it seems unlikely that the surgical tumour spill would be associated with FSCN1 expression.

The strength of our study is the large sample size, the use of a central pathology as well as the blinded re-evaluation by a second pathologist. Limitations, however, include the retrospective design of the analysis and most importantly the missing follow-up of the patients.

The distinction between BOT and cystadenoma is based on the presence of cellular atypia. BOTs are delineated from serous low-grade and high-grade ovarian carcinomas by the presence of destructive stromal invasion.[30] Cystadenoma can progress to BOT and finally becomes an ovarian carcinoma.[30] However, presently no final consensus on the definition of high-risk SBOTs exists.[1 6 7] Several factors have been associated with the prognosis of BOT. Surgical pathological stage and classification of extraovarian disease into invasive and non-invasive implants are the most important prognostic indicators for SBOTs.[31] On the other hand, the presence of a micropapillary architecture in the primary SBOT is a strong predictor of invasive implants.[31 32] Since we found in our analysis that SBOT micropapillary architecture is associated with FSCN1 expression, it may be of interest to correlate expression of this marker with relapse-free survival. The loss of cell–cell adhesion and increased cell motility of epithelial precancerous or cancer cells is a fundamental process in the progression to malignant disease. FSCN1 bundles actin filaments thereby forming motility-associated cell structures and membrane protrusions resulting in a central role in regulation of cell adhesion, migration and invasion.[21 22] Much of the controversy on SBOTs is due to the lack of understanding

Table 4 Strong FSCN1 expression in borderline tumours of the ovary

Sample characteristic	FSCN1 negative or weak (CIS 0–2)	Per cent	FSCN1 strong (CIS 3–9)	Per cent	p Value
Frequency	120	85.7	20	14.3	0.088
Median age					
(95% CI)	51.0	(47.7 to 54.2)	46.6	(39.3 to 53.8)	0.27
FIGO stage I versus II–IV					
I	90	87.4	13	12.6	0.088
II–IV	5	62.5	3	37.5	
FIGO stage IAB versus IC–IV					
IA–IB	47	94.0	3	6.0	**0.020**
IC–IV	53	77.9	15	22.1	
Subtype					
Serous	67	79.8	17	20.2	0.094
Mucinous	42	93.3	3	6.7	
Endometroid	2	100	0	0	
Mixed	9	100	0	0	
Presence of in situ carcinoma*					
No	109	85.8	18	14.2	1.0
Yes	11	84.6	2	15.4	
Macroinvasion†					
No	110	87.3	16	12.7	0.15
Yes	7	70.0	3	30.0	
Microinvasion					
No	118	86.1	19	13.9	0.37
Yes	2	66.7	1	33.3	
Implants					
No	112	88.2	15	11.8	**0.022**
Yes	8	61.5	5	38.5	

*According to WHO criteria: Cribriform glands measuring 5 mm in one dimension and nuclear atypia greater than that allowed in serous borderline ovarian tumour.[28]
†Macroinvasion refers to invasive carcinoma with underlying borderline tumour in the histology.
Significant p Values are given in bold face.
CIS, combined immunoreactive score; FIGO, International Federation of Gynecology and Obstetrics; FSCN1, fascin-1.

of their pathogenesis.[3] Analyses of SBOT on the molecular level have shown that these tumours are frequently associated with KRAS and BRAF mutations.[33] Interestingly, in colorectal adenocarcinoma positivity for FSCN1 correlates with the presence of KRAS mutations.[34] On the other hand, Vignjevic *et al*[35] have recently shown that β-catenin-signalling is involved in regulating FSCN1 expression in human colon cancer cells. Since mutated KRAS activates CDK8 to stimulate epithelial mesenchymal transition (EMT) via the β-catenin pathway,[36] KRAS is also involved in FSCN1 regulation. These data are in line with the observation that activating EMT in SBOT promoted both cell migration and invasion.[37]

Similar to the results obtained in BOTs we previously also observed higher FSCN1 expression in the serous subtype of EOC[25] in line with results of other groups.[38] Moreover, in a smaller study restricted to serous histology a steady increase in the frequency of FSCN1-positive samples comparing benign serous cystadenoma (0%), SBOT (65%) and EOC (84%) was seen, suggesting that upregulation of FSCN1 plays a role in increasing aggressiveness of serous ovarian tumours.[39] Similar results of an increase in FSCN1 expression comparing benign ovarian tissue with BOT and EOC have also been reported by others.[40–43]

Taken together, our analysis links FSCN1 expression to SBOT with micropapillary pattern. In addition, strong expression of FSCN1 is associated with higher FIGO stages and the presence of implants, both of which are related to an elevated rate of recurrence. Hence, FSCN1 is an interesting marker and may be worth further analyses of its prognostic value in BOTs.

Take home messages

- Risk factors for invasive recurrence of borderline ovarian tumours (BOTs) are needed.
- Strong fascin-1 (FSCN1) expression was found in 14.3% of BOTs linked to features related to elevated risk of recurrence such as serous subtype, higher FIGO and the presence of implants.
- FSCN1 could be a valuable marker worth further analyses of its prognostic value in BOTs.

Handling editor Runjan Chetty

Acknowledgements We thank Katerina Brinkmann and Samira Adel for expert technical assistance. Furthermore, the authors thank Professor Dr M-L Hansmann, Senckenberg Institute of Pathology, University of Frankfurt, for providing formalin-fixed paraffin-embedded tissue samples.

Contributors RA and KE performed histopathology and diagnosis and data assembly. UH conceived the study performed immunohistochemical analyses of the samples and coordinated the study conduct. RA evaluated and scored stained tissue slides and helped finalising the manuscript. TK carried out the statistical analyses. AE-B, NS, SB provided clinical samples and participated in study conduct. KE, UH, TK drafted and finalised the manuscript. All authors approved the final manuscript.

Funding This work was supported by grants from the Margarete Bonifer-Stiftung, Bad Soden, the H.W. & J. Hector-Stiftung, Mannheim (grant number: M67) and the BANSS-Stiftung, Biedenkopf.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement Data are available on request from the corresponding author.

REFERENCES

1 Morice P, Uzan C, Fauvet R, *et al*. Borderline ovarian tumour: pathological diagnostic dilemma and risk factors for invasive or lethal recurrence. *Lancet Oncology* 2012;13:e103–15.
2 Mink PJ, Sherman ME, Devesa SS. Incidence patterns of invasive and borderline ovarian tumors among white women and black women in the United States. Results from the SEER Program, 1978–1998. *Cancer* 2002;95:2380–9.
3 Shih I, Kurman RJ. Molecular pathogenesis of ovarian borderline tumors: new insights and old challenges. *Clin Cancer Res* 2005;11:7273–9.
4 Hart WR. Borderline epithelial tumors of the ovary. *Mod Pathol* 2005;18(Suppl 2): S33–50.
5 Trillsch F, Mahner S, Woelber L, *et al*. Age-dependent differences in borderline ovarian tumours (BOT) regarding clinical characteristics and outcome: results from a sub-analysis of the Arbeitsgemeinschaft Gynaekologische Onkologie (AGO) ROBOT study. *Ann Oncol* 2014;25:1320–7.
6 Harter P, Gershenson D, Lhomme C, *et al*. Gynecologic Cancer InterGroup (GCIG) consensus review for ovarian tumors of low malignant potential (borderline ovarian tumors). *Int J Gynecol Cancer* 2014;24(9 Suppl 3):S5–8.
7 du Bois A, Ewald-Riegler N, de Gregorio N, *et al*. Borderline tumours of the ovary: a cohort study of the Arbeitsgmeinschaft Gynäkologische Onkologie (AGO) Study Group. *Eur J Cancer* 2013;49:1905–14.
8 Kurman RJ, Shih I. The origin and pathogenesis of epithelial ovarian cancer: a proposed unifying theory. *Am J Surg Pathol* 2010;34:433–43.
9 Kurman RJ, Seidman JD, Shih I. Serous borderline tumours of the ovary. *Histopathology* 2005;47:310–15.
10 May T, Virtanen C, Sharma M, *et al*. Low malignant potential tumors with micropapillary features are molecularly similar to low-grade serous carcinoma of the ovary. *Gynecol Oncol* 2010;117:9–17.
11 Shih I. Ovarian serous low malignant potential (borderline) tumor—does "micropapillary" matter? *Gynecol Oncol* 2010;117:1–3.
12 Meinhold-Heerlein I, Bauerschlag D, Hilpert F, *et al*. Molecular and prognostic distinction between serous ovarian carcinomas of varying grade and malignant potential. *Oncogene* 2005;24:1053–65.
13 Deavers MT, Gershenson DM, Tortolero-Luna G, *et al*. Micropapillary and cribriform patterns in ovarian serous tumors of low malignant potential: a study of 99 advanced stage cases. *Am J Surg Pathol* 2002;26:1129–41.
14 Longacre TA, McKenney JK, Tazelaar HD, *et al*. Ovarian serous tumors of low malignant potential (borderline tumors): outcome-based study of 276 patients with long-term (or=5-year) follow-up. *Am J Surg Pathol* 2005;29:707–23.
15 Bristow RE, Gossett DR, Shook DR, *et al*. Recurrent micropapillary serous ovarian carcinoma. *Cancer* 2002;95:791–800.
16 Prat J, De Nictolis M. Serous borderline tumors of the ovary: a long-term follow-up study of 137 cases, including 18 with a micropapillary pattern and 20 with microinvasion. *Am J Surg Pathol* 2002;26:1111–28.
17 Slomovitz BM, Caputo TA, Gretz HF, *et al*. A comparative analysis of 57 serous borderline tumors with and without a noninvasive micropapillary component. *Am J Surg Pathol* 2002;26:592–600.
18 Shih KK, Zhou Q, Huh J, *et al*. Risk factors for recurrence of ovarian borderline tumors. *Gynecol Oncol* 2011;120:480–4.
19 Prat J. Serous tumors of the ovary (borderline tumors and carcinomas) with and without micropapillary features. *Int J Gynecol Pathol* 2003;22:25–8.
20 Lengyel E. Ovarian cancer development and metastasis. *Am J Pathol* 2010;177:1053–64.
21 Jayo A, Parsons M. Fascin: a key regulator of cytoskeletal dynamics. *Int J Biochem Cell Biol* 2010;42:1614–17.
22 Li A, Dawson JC, Forero-Vargas M, *et al*. The actin-bundling protein fascin stabilizes actin in invadopodia and potentiates protrusive invasion. *Curr Biol* 2010;20:339–45.
23 Yoder BJ, Tso E, Skacel M, *et al*. The expression of fascin, an actin-bundling motility protein, correlates with hormone receptor-negative breast cancer and a more aggressive clinical course. *Clin Cancer Res* 2005;11:186–92.
24 Hu W, McCrea PD, Deavers M, *et al*. Increased expression of fascin, motility associated protein, in cell cultures derived from ovarian cancer and in borderline and carcinomatous ovarian tumors. *Clin Exp Metastasis* 2000;18:83–8.
25 Hanker LC, Karn T, Holtrich U, *et al*. Prognostic impact of fascin-1 (FSCN1) in epithelial ovarian cancer. *Anticancer Res* 2013;33:371–7.
26 Daponte A, Kostopoulou E, Papandreou CN, *et al*. Prognostic significance of fascin expression in advanced poorly differentiated serous ovarian cancer. *Anticancer Res* 2008;28:1905–10.
27 McShane LM, Altman DG, Sauerbrei W, *et al*. Reporting recommendations for tumor marker prognostic studies (REMARK). *J Natl Cancer Inst* 2005;97:1180–4.
28 Kurman RJ. *WHO classification of tumours of female reproductive organs*. 4th edn. Lyon: International Agency for Research on Cancer, 2014. (World Health Organization classification of tumours).
29 Du Bois A, Ewald-Riegler N, Du Bois O, *et al*. Borderline-Tumoren des Ovars—eine systematische Übersicht. *Geburtsh Frauenheilk* 2009;69:807–33.
30 Amortegui AJ, Trucco G, Sukumvanich P. Ovarian Tumors of Low Malignant Potential (Borderline Ovarian Tumors). *Glob libr women's med* 2013. doi:10.3843/GLOWM.10247
31 Seidman JD, Kurman RJ. Ovarian serous borderline tumors: a critical review of the literature with emphasis on prognostic indicators. *Hum Pathol* 2000;31:539–57.
32 Park J, Kim D, Kim J, *et al*. Micropapillary pattern in serous borderline ovarian tumors: does it matter? *Gynecol Oncol* 2011;123:511–16.
33 Ardighieri L, Zeppernick F, Hannibal CG, *et al*. Mutational analysis of BRAF and KRAS in ovarian serous borderline (atypical proliferative) tumours and associated peritoneal implants. *J Pathol* 2014;232:16–22.
34 Koçer NE, Kayaselçuk F. Is availability of anti-EGFR therapy for the colorectal adenocarcinomas showing fascin expression limited? *Target Oncol* 2014;9:171–5.
35 Vignjevic D, Schoumacher M, Gavert N, *et al*. Fascin, a novel target of beta-catenin-TCF signaling, is expressed at the invasive front of human colon cancer. *Cancer Res* 2007;67:6844–53.
36 Xu W, Wang Z, Zhang W, *et al*. Mutated K-ras activates CDK8 to stimulate the epithelial-to-mesenchymal transition in pancreatic cancer in part via the Wnt/β-catenin signaling pathway. *Cancer Lett* 2015;356(2 Pt B):613–27.
37 Cheng J, Auersperg N, Leung, *et al*. EGF-induced EMT and invasiveness in serous borderline ovarian tumor cells: a possible step in the transition to low-grade serous carcinoma cells? *PLoS One* 2012;7:e34071.
38 Lin C, Chao T, Yu C, *et al*. The expression of six biomarkers in the four most common ovarian cancers: correlation with clinicopathological parameters. *APMIS* 2009;117:162–75.
39 Wen YH, Yee H, Goswami S, *et al*. Fascin expression in serous tumors of ovary correlates with aggressiveness of malignancy. *Int J Gynecol Pathol* 2009;28:187–92.
40 Kabukcuoglu S, Ozalp SS, Oner U, *et al*. Actin bundling protein fascin expression in ovarian neoplasms: comparison of histopathologic features of tumors obtained by the first and secondary cytoreduction surgeries. *Eur J Gynaecol Oncol* 2006;27:123–8.
41 Kabukcuoglu S, Oner U, Ozalp SS, *et al*. The role of actin bundling protein fascin in the progression of ovarian neoplasms. *Eur J Gynaecol Oncol* 2006;27:171–6.
42 Alici O, Kefeli M, Yildiz L, *et al*. Fascin and EMMPRIN expression in primary mucinous tumors of ovary: a tissue microarray study. *Pathol Res Pract* 2014;210:934–8.
43 Kostopoulou E, Daponte A, Terzis A, *et al*. Fascin in ovarian epithelial tumors. *Histol Histopathol* 2008;23:935–44.

Fascin-1 expression as stratification marker in borderline epithelial tumours of the ovary

Ahmed El-Balat, Ruza Arsenic, Nicole Sänger, Thomas Karn, Sven Becker, Uwe Holtrich and Knut Engels

J Clin Pathol 2016 69: 142-148 originally published online September 11, 2015
doi: 10.1136/jclinpath-2015-203224