



Mmp-9 and Fascin-1 Expression in Endometrioid-Type Endometrial Carcinoma and Their Prognostic Value

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Abstract

Backgrounds Matrix metalloproteinases (MMP) and fascin-1 play roles in epithelial–mesenchymal transition and tumour invasion.

Aims This study was performed to investigate the relationships of fascin-1 and MMP-9 expression with prognostic parameters in endometrioid-type endometrial carcinoma (EEC).

Methods A total of 100 cases of EEC were included in the study. Tissues were stained with antibodies against fascin-1 and MMP-9. The relationships between the immunohistochemical findings and clinicopathological prognostic parameters of EEC were examined.

Results Tumour diameter was significantly related to lymphovascular invasion, FIGO stage and FIGO grade ($p < 0.05$). A tumour size > 2 cm was associated with a poor prognosis. The staining score for fascin-1 was ≤ 5 in 81 cases and > 5 in 19 cases ($p > 0.05$), and that for MMP-9 was ≤ 5 in 39 cases and > 5 in 61 cases ($p > 0.05$). Neither fascin-1 nor MMP-9 expression was significantly related to any of the clinicopathological parameters examined.

Conclusion There were no significant relationships of fascin-1 and MMP-9 expression with the clinicopathological parameters of EEC. The results of this study suggested that these molecules do not contribute to the clinical behaviour of EECs. A tumour size > 2 cm is associated with a poor prognosis in EEC patients. To verify these results, more studies are needed with larger patient groups.

Keywords Endometrial carcinoma · Endometrium · Fascin-1 · MMP-9 · Prognosis

Introduction

Endometrial carcinoma (EC) is the fifth most common cancer in women worldwide and ranks second in incidence among gynaecological cancers after cervical uterine cancer [1]. EC is the fourth most prevalent cancer and the first most prevalent gynaecologic cancer among women in Turkey according to the 2014 cancer statistics [2].

ECs are divided into two groups according to their clinical, endocrine and morphological features. The first group develops due to exposure to unopposed oestrogen, and the precursor lesion is endometrial hyperplasia. The prototype of this group is endometrioid-type EC (EEC). The other group is associated with p53 mutation, and its prototype is serous carcinoma.

The endometrioid type accounts for 80% of endometrial cancers. Most are well to moderately differentiated and have a good prognosis. The 5-year survival rate of patients with International Federation of Gynecology and Obstetrics (FIGO) stage I EEC is 87% [3].

The mechanism of cancer invasion is an area of active research. Determining the aggressiveness of cancer in early-stage disease is very important in terms of predicting the clinical course of the disease and developing targeted therapies.

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Epithelial cells in carcinoma tissue invade stromal tissues by gaining mesenchymal features via epithelial–mesenchymal transition (EMT) [4, 5]. Studies that examined the mechanism of invasion have identified complex pathways involving many mediators, including the gelatinase subtype of matrix metalloproteinases (MMP-2 to MMP-9), involved in local invasion [6], and fascin-1, which was demonstrated *in vitro* to play an important role in EMT [7].

Understanding the invasive potential of cancer is very important because of the high prevalence rate and poor prognosis of some types of EEC. This study was performed to evaluate the relationships of fascin-1 and MMP-9 expression with prognostic parameters, as well as invasive potential, in patients with EEC.

Materials and Methods

The archive of İnönü University Turgut Özal Medical Center Medical Pathology Laboratory was scanned, and 106 cases diagnosed with EEC between 2011 and 2017 were retrospectively included in this study. All patients underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy. Bilateral pelvic and para-aortic lymph node dissection was also performed in 88 of these cases. Six cases without myometrial invasion were excluded from the study.

The clinicopathological prognostic parameters, FIGO grade and stage, myometrial invasion depth, lymphovascular invasion, cervical invasion, lymph node involvement and positive peritoneal cytology were evaluated. In addition, data regarding age, tumour size and distant organ metastases were obtained from the medical files of the patients (Table 1).

Immunohistochemical staining using antibodies against fascin-1 and MMP-9 was performed using a fully automated immunohistochemical staining device (BenchMark ULTRA; Ventana Medical Systems, Tucson, AZ, USA).

Table 1 Clinicopathological prognostic parameters

- | |
|----------------------------------|
| (1) FIGO grade |
| (2) FIGO stage |
| (a) Myometrial invasion depth |
| (b) Lymph node involvement |
| (c) Cervical invasion |
| (d) Metastasis |
| (e) Positive peritoneal cytology |
| (3) Lymphovascular invasion |
| (4) Tumour size |
| (5) Age |

Table 2 lists information such as the clone numbers, dilutions and production site of the antibodies used in the study.

The prevalence and level of fascin-1 and MMP-9 cytoplasmic staining were evaluated. The average percentage of cells showing positive staining for both fascin-1 and MMP-9 in five areas at 100 × magnification was calculated. Staining was scored semi-quantitatively: 0, negative; 1, focal positivity (< 25%); 2, moderate positivity (26–50%); 3, diffuse positivity (> 50%).

The intensity of staining was scored as follows: 1, mild; 2, medium; 3, strong. The two staining scores were multiplied, and the total staining score was between 0 and 9. In the statistical analysis, cases were divided into two groups according to a total staining score ≤ 5 or > 5. This grouping was preferred in order to include the cases with the least score 2 in the staining extent and intensity scores to be in the highly stained group.

Statistical analyses were performed using SPSS for Windows (SPSS Inc., Chicago, IL, USA). Quantitative variables are presented as the arithmetic mean ± standard deviation, and qualitative variables are presented as numbers (*n*) and percentages (%). The Shapiro–Wilk normality test showed that the quantitative data did not have a normal distribution ($p < 0.05$). Quantitative variables were analysed using the unpaired *t* test, Mann–Whitney *U* test and Kruskal–Wallis variance analysis. Qualitative variables were analysed using Pearson’s Chi-square test, Monte Carlo simulation of Pearson’s Chi-square test and Fisher’s exact test. In all analyses, $p < 0.05$ was taken to indicate statistical significance.

Results

The 100 patients included in the study had a mean age of 59.81 years (range 37–87 years). The mean tumour diameter was 3.80 cm (range 0.5–11.5 cm).

According to the FIGO grading system, 34 cases were classified as grade 1, 56 as grade 2 and 10 as grade 3; 67 were classified as stage IA, 18 as stage IB, 3 as stage II, 10 as stage III, and two as stage IV. There were statistically significant relationships of the FIGO grade with both FIGO stage and tumour diameter ($p < 0.05$) (Table 3).

A statistically significant relationship was found between lymphovascular invasion and tumour size ($p < 0.05$). However, tumours were larger in patients with myometrial invasion, cervical invasion, adnexal involvement, pelvic and/or para-aortic lymph node metastasis, distant metastasis and positive peritoneal cytology, but the relationships were not statistically significant ($p > 0.05$) (Table 4).

Table 2 Fascin-1 and MMP9 antibody information

Antibody	Clone number	Concentration	Company	Production
Fascin-1	FCN01	1:100	Thermo Fisher Scientific	Fremont, CA
MMP-9	Polyclonal	1:50	Thermo Fisher Scientific	Fremont, CA

Table 3 FIGO degrees and stages and tumour size

FIGO	Tumour size n (%)		p
	< 2 cm	≥ 2 cm	
<i>Grade</i>			
1	10 (29.4)	24 (70.6)	0.032
2	5 (8.9)	51 (91.1)	
3	1 (10)	9 (90)	
<i>Stage</i>			
pT1a	14 (20.9)	53 (79.1)	0.041
pT1b	2 (11.1)	16 (88.9)	
pT2	0 (0)	3 (100)	
pT3 and pT4	0 (0)	12 (100)	
Total	16 (16)	84 (84)	

Table 4 Clinicopathological prognostic factors and tumour size

Prognostic factors	Tumour size n (%)		p
	< 2 cm	≥ 2 cm	
<i>Myometrial invasion</i>			
< ½	14 (19.7)	57 (80.3)	0.113
≥ ½	2 (6.9)	27 (93.1)	
<i>Cervical invasion</i>			
Negative	16 (16.8)	79 (83.2)	0.317
Positive	0 (0)	5 (100)	
<i>Adnexal involvement</i>			
Negative	16 (17)	78 (83)	0.270
Positive	0 (0)	6 (84)	
<i>Lymphovascular invasion</i>			
Negative	16 (20.8)	61 (79.2)	0.017
Positive	0 (0)	23 (100)	
<i>Lymph node metastasis</i>			
Negative	13 (16.5)	66 (83.5)	0.187
Positive	0 (0)	9 (100)	
<i>Metastasis</i>			
Negative	16 (16.3)	82 (83.7)	0.533
Positive	0 (0)	2 (100)	
<i>Peritoneal cytology</i>			
Negative	9 (23.7)	29 (76.3)	0.221
Positive	0 (0)	5 (100)	

Distant organ metastasis was detected in 2 of 100 patients (2%). The lung hilar region lymph nodes were involved in both cases.

There were no significant correlations of the fascin-1 and MMP-9 staining scores with FIGO grade or stage ($p > 0.05$) (Table 5) (Figs. 1, 2).

There were no statistically significant relationships of fascin-1 and MMP-9 expression scores with myometrial invasion, cervical invasion, adnexal involvement, lymphovascular invasion, regional lymph node involvement, distant metastasis or positive peritoneal cytology ($p > 0.05$) (Table 6).

Discussion

The incidence of EC is second among gynaecological cancers worldwide and the first in developed countries [1]. According to the 2014 cancer statistics, the incidence of EC in Turkey was 9.8/100,000 [2].

EEC generally has a better prognosis than other uterine neoplasms. Some subgroups, however, have a rather poor prognosis. The 5-year survival rate of patients with FIGO stage I disease is 87%. However, high FIGO stage, deep myometrial invasion and lymph node metastasis are associated with a poor prognosis and survival.

Distant metastasis is an important cause of death in EEC patients. Understanding the pathophysiology of the mechanism of metastasis will be useful in guiding treatment and determining prognosis.

Metastatic cancer cells are characterised by increased invasion and migration. Cell invasion in tumour progression is largely related to EMT. In the EMT process, epithelial cells lose their basal apical polarity, adopt the form of spindle cells and gain mobility. In addition, transformed cells acquire new markers, such as smooth muscle actin, fibronectin and vimentin and show increased activities of MMPs (MMP-2, MMP-3 and MMP-9) [8].

MMP-9 is a zinc-dependent endopeptidase that regulates extracellular matrix protein metabolism. Tumour invasion is associated with angiogenesis and metastasis, and MMP-9 may be associated with invasion and tumour progression in many organ cancers [9]. Expression of MMPs in carcinomatous tumour cells may be an indicator of tumour aggressiveness [8].

Planaguma et al. [10] reported that MMP-9 is expressed on the invasive surface of endometrial and ovarian cancers

Table 5 FIGO grade and stage, fascin-1 and MMP9 expressions

FIGO grades and stages	FASCIN-1 <i>n</i> (%)		<i>p</i>	MMP9 <i>n</i> (%)		<i>p</i>
	Score ≤ 5	Score > 5		Score ≤ 5	Score > 5	
<i>FIGO grade</i>						
1	29 (85,3)	5 (14,7)	0.730	12 (35,3)	22 (64,7)	0.702
2	44 (78,6)	12 (21,4)		22 (39,3)	34 (60,7)	
3	8 (80)	2 (20)		5 (50)	5 (50)	
<i>FIGO stage</i>						
IA	52 (77,6)	15 (22,4)	0.308	25 (37,3)	42 (62,7)	0.237
IB	17 (94,4)	1 (5,6)		10 (55,6)	8 (44,4)	
II	3 (100)	0 (0)		0 (0)	3 (100)	
III + IV	9 (75)	3 (25)		4 (33,3)	8 (66,7)	
Total	81	19		39	61	

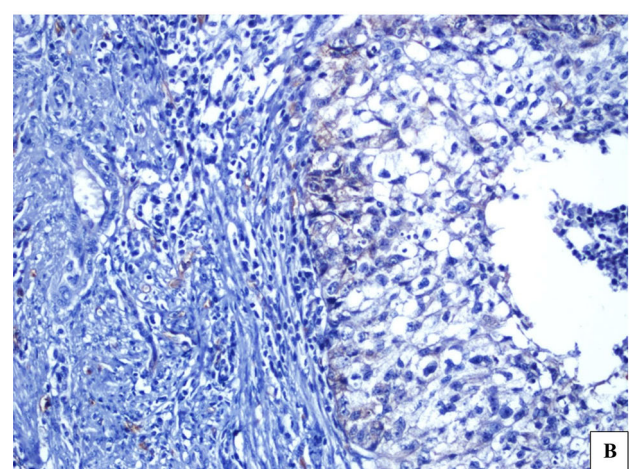
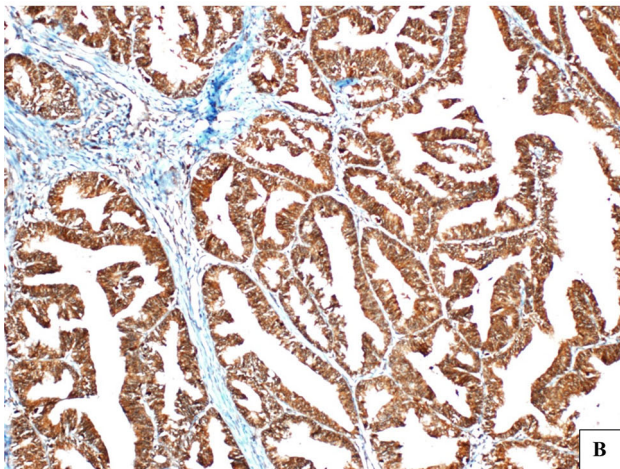
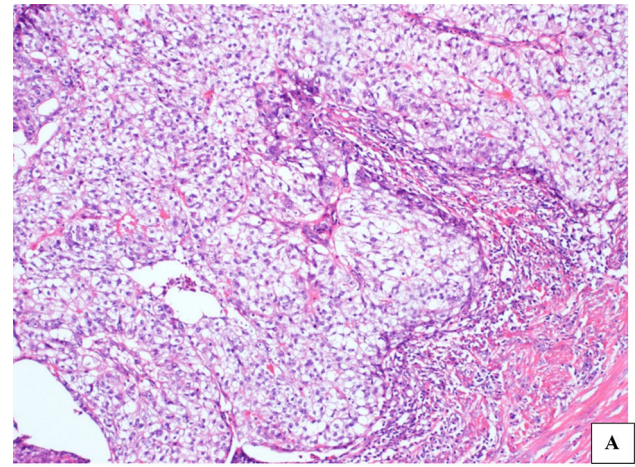
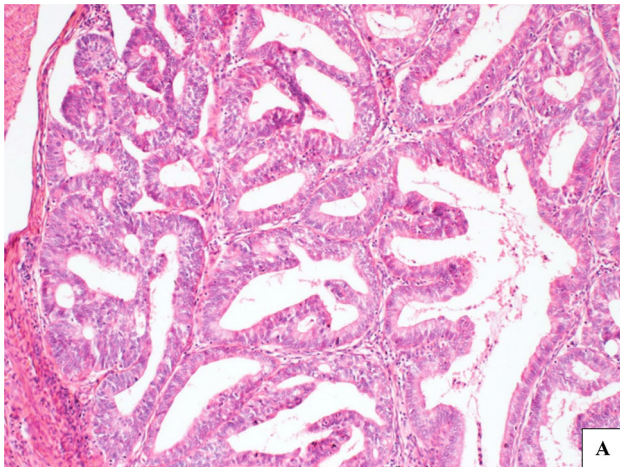


Fig. 1 **a** FIGO grade 2 endometrioid-type endometrial carcinoma (hematoxylin and eosin, $\times 200$), **b** widespread and strong cytoplasmic staining with MMP9 (MMP-9, $\times 100$)

Fig. 2 **a** Solid areas in high-grade endometrioid-type endometrial carcinoma (hematoxylin and eosin, $\times 100$), **b** poor staining with fascin-1 on the invasive surface of the tumour (fascin-1, $\times 200$)

and plays an important role in the progression of carcinogenesis.

The role of MMP-9 in the benign-to-malignant differentiation of endometrial lesions has been evaluated, and

MMP-9 expression has been detected in almost all EECs but at varying frequencies [17]. MMP-9 expression was positive in all cases in the present study, which was

Table 6 Fascin-1 and MMP9 expressions with prognostic parameters

Prognostic parameters	Fascin1 n (%)		p	MMP9 n (%)		p
	Score ≤ 5	Score > 5		Score ≤ 5	Score > 5	
<i>Myometrial invasion</i>						
< ½	56 (78,9)	15 (21,1)	0.386	26 (36,6)	45 (63,4)	0.445
≥ ½	25 (86,2)	4 (13,8)		13 (44,8)	16 (55,2)	
<i>Cervical invasion</i>						
Negative	76 (80)	19 (20)	0.267	38 (40)	57 (60)	0.371
Positive	5 (100)	0 (0)		1 (20)	4 (80)	
<i>Adnexal involvement</i>						
Negative	77 (81,9)	17 (18,1)	0.356	38 (40,4)	56 (59,6)	0.247
Positive	4 (66,7)	2 (33,3)		1 (16,7)	5 (83,3)	
<i>Lymphovascular invasion</i>						
Negative	61 (79,2)	16 (20,8)	0.407	31 (40,3)	46 (59,7)	0.637
Positive	20 (87)	3 (13)		8 (34,8)	15 (65,2)	
<i>Lymph node metastasis</i>						
Negative	64 (81)	15 (19)	0.312	28 (35,4)	51 (64,6)	0.595
Positive	6 (66,7)	3 (33,3)		4 (44,4)	5 (55,6)	
<i>Metastasis</i>						
Negative	79 (80,6)	19 (19,4)	0.489	39 (39,8)	59 (60,2)	0.253
Positive	2 (100)	0 (0)		0 (0)	2 (100)	
<i>Peritoneal cytology</i>						
Negative	29 (76,3)	9 (23,7)	0.855	12 (31,6)	26 (68,4)	0.596
Positive	4 (80)	1 (20)		1 (20)	4 (80)	

consistent with the high MMP-9 expression in EEC reported previously [10].

Some previous immunohistochemical studies of EECs using anti-MMP-9 antibodies indicated statistically significant relationships between some clinicopathological prognostic parameters and MMP-9 expression [11–15] (Table 7). However, other studies did not detect significant relationships between MMP-9 expression and clinicopathological prognostic parameters [11–17] (Table 7). In the present study, MMP-9 expression showed no statistically significant relationships with any clinicopathological parameter examined ($p > 0.05$).

Fascin-1 is a 55-kDa actin-bundling protein that plays a key role in the stability and regulation of cell protrusions and other actin-based structures involved in cell motility, migration and invasion. Its expression has been reported to be associated with increased invasion and metastatic potential in mouse xenograft tumour models and increased migratory capacity in carcinoma cells in culture [6].

A relationship between increased fascin-1 expression and aggressive clinical course has been reported in many organ cancers. Fascin-1 may be an early marker of metastatic potential in aggressive carcinomas. Fascin-1 expression has been suggested to increase the risk of mortality by 2.5 fold in breast, colorectal and oesophageal

carcinomas [18]. It has also been shown to be associated with an increased risk of metastasis in colorectal and gastric carcinomas [18].

Fascin-1 has been investigated most extensively in ovarian tumours among gynaecological cancers and has been reported to be associated with high tumour grade and stage, drug resistance in serous carcinoma and poor survival and prognosis [19]. On the other hand, there have been very few studies of fascin-1 in EEC.

Stewart et al. [20] found fascin-1 expression in all cases of EEC examined. Gün et al. [21] reported that fascin-1 expression in EEC was significantly related to both tumour grade and neural invasion (Table 8). However, no significant relationships of its expression with tumour size, myometrial depth of invasion, lymphovascular invasion and tumour stage have been reported. In the present study, there were no statistically significant relationships between fascin-1 expression and clinicopathological prognostic factors.

When the relationship between MMP9 expression and survival was investigated, Mihalj et al. [15] indicated these two parameters significantly related. The relationship between MMP9 expression and survival was not found to be significant in the study conducted by Yu et al. [13] and

Table 7 Relationship between MMP9 expression and clinicopathological parameters in the literature

Clinicopathological prognostic parameters	Significant relationship with MMP9	No significant relationship with MMP9
FIGO grade	Di Nezza et al. [11] Aglund et al. [12] Yu et al. [13]	Inoue et al. [14]
FIGO stage	Aglund et al. [12]	Grybos et al. [16] Mihalj et al. [15] Graesslin et al. [17]
Myometrial invasion	Yu et al. [13]	Di Nezza et al. [11] Aglund et al. [12] Inoue et al. [14] Mihalj et al. [15] Graesslin et al. [17]
Lymphovascular invasion	Di Nezza et al. [11] Inoue et al. [14]	Mihalj et al. [15] Graesslin et al. [17]
Lymph node metastasis	Yu et al. [13]	Inoue et al. [14] Mihalj et al. [15] Graesslin et al. [17]
Survival	Mihalj et al. [15]	Yu et al. [13] Graesslin et al. [17]
Age	–	Aglund et al. [13] Mihalj et al. [15]

Table 8 Relationship between fascin-1 expression and clinicopathological parameters in the literature

Clinicopathological prognostic parameters	Significant relationship with fascin-1	No significant relationship with fascin-1
FIGO grade	Gün et al. [21]	Stewart et al. [20]
Neural invasion	Gün et al. [21]	Stewart et al. [20]

Graesslin et al. [17]. However, there is no survival research with fascin-1.

There have been many studies regarding MMP-9 and fascin-1 expression in EC [10–21]. Expression of MMP-9 and fascin-1 only in EEC cases was not examined before. Therefore, it would not be appropriate to compare these previous studies with the present study. We identified no relationship of MMP-9 or fascin-1 expression with prognostic factors of EEC.

The numbers of cases in studies reported in the literature range from 20 to 128 [10–21]. In most of those studies, the number of cases was insufficient to draw definitive conclusions regarding prognosis. The number of cases included in the present study was greater than those of most previous studies reported to date.

Öz et al. [22] did not find a statistically significant relationship between tumour diameter and lymph node metastasis. However, in the present study, statistically significant relationships were detected between tumour diameter and FIGO grade, FIGO stage and lymphovascular invasion ($p < 0.05$).

Therefore, MMP-9 and fascin-1 appear to play roles in cancer invasion. However, as tumour invasion is the result of complex interactions among many molecules, the expression of proteins such as MMP-9 or fascin-1 alone may not be sufficient to detect the invasive capacity of cancer cells.

The significant relationships between tumour diameter and many clinicopathological parameters detected in the present study suggest that patients with tumours > 2 cm in diameter have a poorer prognosis.

Conclusion

There were no significant relationships of fascin-1 and MMP-9 expression with the clinicopathological parameters of EEC. This study's results suggest that MMP9 and fascin-1 do not contribute to the clinical behaviour of EECs. A tumour size > 2 cm is associated with a poor prognosis in EEC patients. Although the number of patients in this study is higher than the previous studies, these results should be verified by studies with invitro and invivo methods on larger patient groups.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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