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ORIGINAL ARTICLE

Co-Expression of Mesothelin and CA125 Is Associated with the Poor Prognosis of Endometrial Serous Carcinoma and Mixed Carcinomas Including Serous Carcinoma

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Abstract

The aim of this study was to investigate the association between the clinicopathologic factors and either expression or co-expression of mesothelin and cancer antigen (CA) 125 in endometrial serous carcinoma and mixed carcinomas including serous carcinoma. Between 1990 and 2017, patients with endometrial serous carcinoma and mixed carcinoma including serous carcinoma treated by total hysterectomy and bilateral salpingo-oophorectomy at our hospital were identified. The association between either expression or co-expression of mesothelin and CA125 was evaluated by immunochemical analysis and the clinicopathological features were retrospectively examined. Among the 40 patients included, 19, 31, and 18 patients exhibited single positive mesothelin, single positive CA125, and positive co-expression, respectively. The expression of mesothelin and CA125 was observed to be positively associated ($p = 0.021$). There was no significant association of age and FIGO stage with individual mesothelin or CA125 expression or their co-expression. Overall survival (OS), but not progression-free survivals (PFS), of only mesothelin-positive patients was worse ($p = 0.024$). Hence, OS and PFS of patients with positive co-expression were worse (PFS: $p = 0.043$, OS: $p = 0.012$). In multivariate analysis, single mesothelin expression and single CA125 expression did not lead to worse prognosis. However, positive co-expression was the worst prognostic factor for OS (hazard ratio: 3.32, $p = 0.039$). Co-expression of mesothelin and CA125 may accurately predict OS in endometrial serous carcinoma and mixed carcinomas including serous carcinoma. Further studies should examine this relationship.

Keywords Endometrial carcinoma · Serous carcinoma · Mixed carcinoma · Mesothelin · CA125 · Prognosis

Introduction

Endometrial carcinoma is one of the major gynecologic carcinomas, the incidence of which has been increasing in western countries [1]. Histological subtype is an important prognostic factor, and in particular, serous carcinoma has the worst prognosis [2]. Classical classification defined serous carcinoma as type II, which was independent of estrogen and had a worse prognosis than type I, which was dependent on estrogen [3]. Recently, the Cancer Genome Atlas revealed that serous carcinoma exhibited *p53* mutation more frequently and has a worse prognosis than endometrioid carcinoma [4]. Additionally, several reports have demonstrated that not only pure-type serous carcinoma, but also endometrial carcinoma, including even small foci of serous carcinoma, could lead to worse prognosis [5–8]. Therefore, a better understanding of the biology of serous carcinoma and the establishment of a new treatment strategy is important.

Mesothelin is a 40-kDa glycoprotein normally expressed in the mesothelial cells of peritoneal and pleural cavities, and the pericardium [9, 10] and plays an important role in adhesion, migration, and implantation in malignant tumors [11]. High expression of mesothelin is observed in ovarian [11], breast [11], endometrial [11, 12], lung [13], pancreatic [14], gastric [14], and colorectal [15, 16] carcinoma. Relationships between immunohistochemical expression of mesothelin and prognosis of colorectal carcinoma [17], pancreatic ductal

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carcinoma [18], lung carcinoma [19], and breast carcinoma [20] have been reported. Thus, mesothelin was identified as an important factor in several types of carcinoma.

Furthermore, cancer antigen (CA) 125 is a mucin-like protein normally present on the surface of mesothelial cells along with mesothelin. CA125 is a heavily glycosylated type I transmembrane protein belonging to the family of tethered mucins containing both O- and N-linked oligosaccharides [21]. Overexpression of CA125 was observed in cervical and endometrial carcinomas [22], pancreatic ductal, esophageal, gastric, and colorectal carcinomas [22, 23], and ovarian carcinoma [22–24]. The expression of CA125 was significantly different in the various types of carcinomas. Although there were arguments over whether CA125 expression was associated with prognosis, no such association was observed [25–27].

Recently, mesothelin was reported to possess a strong affinity for CA125 with N-linked glycans [28]. Furthermore, in pancreatic ductal carcinoma, co-expression of mesothelin and CA125 was correlated with histological classification, blood vessel permeation, and worse prognosis [29]. In ovarian carcinoma, mesothelin and CA125 were co-expressed in the advanced stages [30]. However, no studies have examined the association or co-expression of mesothelin and CA125 with clinicopathological features and prognosis in endometrial serous carcinoma.

The aim of our study was to evaluate the correlation of the clinicopathological factors and either mesothelin or CA125 expression, or their co-expression in endometrial serous carcinoma and mixed type carcinomas including serous carcinoma.

Materials and Methods

Patients

Patients with endometrial serous carcinoma and mixed carcinoma including serous carcinoma that were treated by total-hysterectomy and bilateral salpingo-oophorectomy in our hospital between 1990 and 2017 were identified. All cases had already been evaluated pathologically according to the World Health Organization (WHO) criteria. Cases of endometrial serous carcinoma or mixed carcinoma consisting of any grade of both endometrioid and serous carcinoma were included in our study. Almost all patients who needed adjuvant therapy clinically were treated. The exclusion criteria were as follows: other histologies, cases complicated with other carcinoma, and lack of either clinical information or surgical specimen. Clinicopathological factors were obtained from the patients' clinical records.

Immunohistochemistry

Forty formalin-fixed paraffin-embedded tissues were used for immunohistochemistry. All carcinoma tissues were punched into a circle of diameter 4 mm. Punched tissues were lined up and tissue microarray (TMA) blocks were prepared. All slides were deparaffinized and rehydrated through a graded ethanol series. For antigen retrieval, citric acid buffer (pH 6.0) was used, and all the slides were boiled at 95 °C for 30 min. The sections were then treated with 0.3% hydrogen peroxidase at room temperature for 10 min to quench endogenous peroxidase activity. Anti-mesothelin (clone 5B2 diluted 1:50 Leica: NCL-L-MESO) and anti-CA125 (clone M11 diluted 1:50 DAKO:M3520) antibodies were used. All slides were incubated with these primary antibodies at room temperature for 60 min, followed by incubation with dextran polymer reagent-conjugated secondary antibodies at room temperature for 30 min. The resultant specific antigen-antibody reactions were visualized using 0.2% diaminobenzene tetrahydrochloride and hydrogen peroxide, and counterstained with Mayer hematoxylin.

Immunohistochemical Evaluation

The evaluation methods used were those described in previous reports [29, 31, 32]. Briefly, expressions of mesothelin and CA125 were determined by evaluating the proportion score and staining intensity score. Proportion score, defined as the percentage of mesothelin- or CA125-positive cells in carcinoma tissues, was as follows: 1+, $\geq$1% and < 10%; 2+, $\geq$10% and < 50%; and 3+, $\geq$50% cells stained in entire carcinoma tissue. Staining intensity score is defined as follows: 1+, incomplete membrane staining and/or faint or barely perceptible cytoplasmic staining detected; and 2+, entire circumference of the cell membrane stained and/or moderate to strong cytoplasmic staining. Additionally, a proportion score of 3+ and/or staining intensity score of 2+ was considered as positive mesothelin or CA125 expression (Fig. 1).

Statistical Analysis

We used χ^2 test and Fisher exact test for confirming correlation among the clinicopathological data and mesothelin and CA125 expression. Progression-free survival (PFS) and overall survival (OS) curves were drawn using the Kaplan-Meier method. The difference between these survival curves was analyzed by Cox proportional hazard test. In statistical analysis, all differences were considered significant at p values <0.05. The software JMP® 14.0 (SAS Institution Inc., Cary, NC, USA) was used for all statistical analyses in this study.

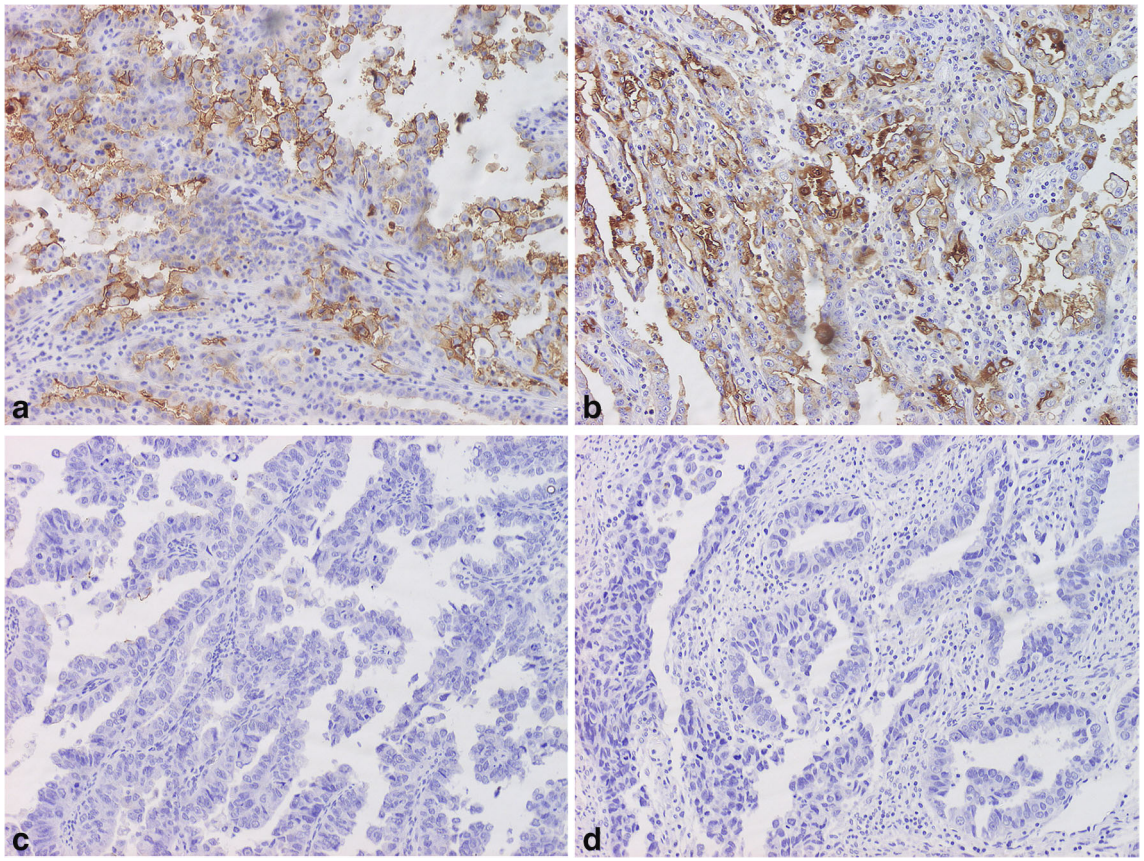

Fig. 1 The expression variation of mesothelin and cancer antigen (CA) 125. **a** Mesothelin-positive cells. The percentage of mesothelin-positive cells is ≥50% (proportion score 3+) and the entire circumference of the cancer cell membrane is stained (intensity score 2+). **b** CA125-positive cells. The percentage of CA125-positive cells is ≥50% (proportion score 3+) and the cytoplasm of cancer cell is highly stained (intensity score 2+). **c** Mesothelin negative. Cells There is no staining of the cancer cell's membrane. **d** CA125 negative cells. There is no staining of the cancer cell's membrane. Magnification for all slides: ×100. *HE, hematoxylin-eosin

Results

Among the 40 cases, positive expression of mesothelin and CA125 was observed in 19 (47.5%) and 31 (77.5%) patients, respectively, and their co-expression was seen in 18 patients (45%) (Table 1). The expression levels of mesothelin and CA125 were seen to be positively associated ($p = 0.021$).

Firstly, we investigated the association between mesothelin expression and the clinical parameters. There was no significant correlation between mesothelin expressions, and age and the International Federation of Obstetrics and Gynecology (FIGO) stage (Table 2). Higher incidence of lymphovascular invasion ($p = 0.02$) and lymph node metastasis ($p < 0.01$) were observed in cases with positive mesothelin (Table 3). OS, but not PFS of patients with positive mesothelin was worse than those with negative mesothelin (Fig. 2a: PFS, $p = 0.082$; Fig. 2b: OS, $p = 0.024$). Multivariate analysis PFS and OS revealed positive mesothelin expression did not lead to worse prognosis (Table 4).

Table 1 Immunohistochemical analysis of mesothelin and CA125 expression in endometrial serous carcinoma

	Scores of different proportions of mesothelin-positive cells				Scores of different proportions of CA125-positive cells			
	0	1+	2+	3+	0	1+	2+	3+
Staining intensity score								
0	11 (28%)	0 (0%)	0 (0%)	0 (0%)	3 (7%)	0 (0%)	0 (0%)	0 (0%)
1+	0 (0%)	5 (13%)	5 (13%)	0 (0%)	0 (0%)	2 (5%)	4 (10%)	0 (0%)
2+	0 (0%)	1 (2%)	9 (22%)	9 (22%)	0 (0%)	2 (5%)	4 (10%)	25 (63%)

Table 2 Correlation between clinical features and either/or co-expression of mesothelin and CA125

Variables	Mesothelin Expression			CA125 Expression			Co-Expression of mesothelin and CA125		
	Positive ($n=19$)	Negative ($n=21$)	p value	Positive ($n=31$)	Negative ($n=9$)	p value	Positive ($n=18$)	Negative ($n=22$)	p value
Age									
> 65	12 (63%)	12 (57%)	0.76	17 (55%)	7 (78%)	0.27	11 (61%)	13 (59%)	0.99
≤ 65	7 (37%)	9 (43%)		14 (45%)	2 (22%)		7 (39%)	9 (41%)	
FIGO stage									
I,II,III	15 (79%)	18 (86%)	0.57	25 (81%)	8 (89%)	0.56	14 (78%)	19 (86%)	0.47
IV	4 (21%)	3 (14%)		6 (19%)	1 (11%)		4 (22%)	3 (14%)	
Adjuvant therapy									
Done	18 (95%)	16 (76%)	0.19	27 (87%)	7 (78%)	0.6	17 (94%)	17 (77%)	0.13
Not Done	1 (5%)	5 (24%)		4 (13%)	2 (22%)		1 (6%)	5 (23%)	

FIGO The International Federation of Gynecology and Obstetrics, *CA125* cancer antigen 125

Secondly, we examined the relationship between CA125 expression and clinical features. There was no significant association between CA125 expression, and clinical and pathological features (Tables 2 and 3). Additionally, PFS and OS did not vary significantly with respect to CA125 expression (Fig. 2c: PFS, $p=0.25$; Fig. 2d: OS, $p=0.17$). In multivariate analysis for PFS and OS, positive CA125 expression did not lead to worse prognosis (Table 4).

Thirdly, the relationship between co-expression of mesothelin and CA125 and clinic-pathological factors

Table 3 Association between pathological features and either/or co-expression of mesothelin and CA125

Variables	Mesothelin Expression			CA125 Expression			Co-Expression of mesothelin and CA125		
	Positive ($n=19$)	Negative ($n=21$)	p value	Positive ($n=31$)	Negative ($n=9$)	p value	Positive ($n=18$)	Negative ($n=22$)	p value
Histology									
Pure type	13 (68%)	19 (90%)	0.08	25 (81%)	7 (78%)	0.99	12 (67%)	20 (91%)	0.06
Mix type	6 (32%)	2 (10%)		6 (19%)	2 (22%)		6 (33%)	2 (9%)	
Myometerial invasion									
≥ 1/2	11 (58%)	9 (43%)	0.34	17 (55%)	3 (33%)	0.25	11 (61%)	9 (41%)	0.20
< 1/2	8 (42%)	12 (57%)		14 (45%)	6 (67%)		7 (39%)	13 (59%)	
Cervical invasion									
Yes	3 (16%)	7 (33%)	0.20	9 (29%)	1 (11%)	0.27	3 (17%)	7 (32%)	0.27
No	16 (84%)	14 (67%)		22 (71%)	8 (89%)		15 (83%)	15 (68%)	
Lympho-vascular invasion									
Yes	15 (79%)	9 (43%)	0.02	19 (61%)	5 (56%)	0.75	14 (78%)	10 (45%)	0.04
No	4 (21%)	12 (57%)		12 (39%)	4 (44%)		4 (22%)	12 (55%)	
Peritoneal cytology									
Positive	9 (47%)	7 (33%)	0.36	13 (42%)	3 (33%)	0.64	9 (50%)	7 (32%)	0.24
Negative	10 (53%)	14 (67%)		18 (58%)	6 (67%)		9 (50%)	15 (68%)	
Lymph node metastasis									
Yes	9 (47%)	1 (5%)	<0.01	9 (29%)	1 (11%)	0.27	9 (50%)	1 (5%)	<0.01
No	10 (53%)	20 (95%)		22 (71%)	8 (89%)		9 (50%)	21 (95%)	
Ovarian metastasis									
Yes	2 (11%)	4 (76%)	0.45	4 (13%)	2 (22%)	0.6	2 (11%)	4 (18%)	0.53
No	17 (89%)	17 (24%)		27 (87%)	7 (78%)		16 (89%)	18 (82%)	
Distant metastasis									
Yes	4 (21%)	3 (14%)	0.57	6 (19%)	1 (11%)	0.56	4 (22%)	3 (14%)	0.47
No	15 (79%)	18 (86%)		25 (81%)	8 (89%)		14 (78%)	19 (86%)	

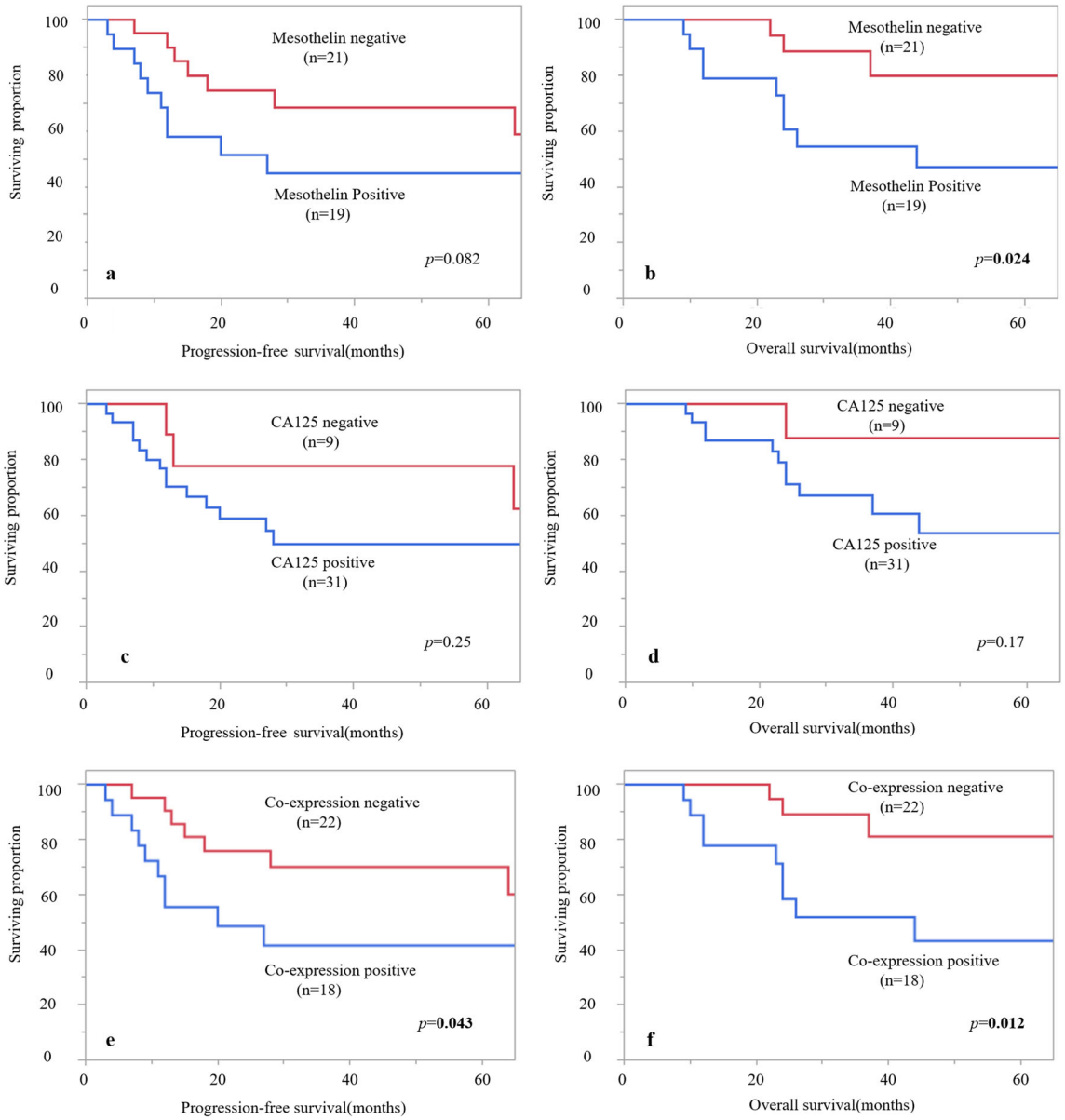

Fig. 2 Progression-free and overall survival of patients according to their differences in expression of mesothelin and CA125, and in the co-expression of both mesothelin and CA125

was examined. We determined no significant correlation of clinic-pathological features stage and co-expression of mesothelin and CA125 (Table 2). Additionally, we observed a higher incidence of lympho-vascular invasion ($p = 0.04$) and lymph node metastasis ($p < 0.01$) in cases with positive mesothelin (Table 3). PFS and OS of patients with co-expression were worse compared to those without co-expression (Fig. 2d: PFS, $p = 0.043$; Fig. 2e: OS, $p = 0.012$). Multivariate analyses for PFS and OS demonstrated co-expression was the independent worst prognostic factor for OS (HR 3.32, 95%CI: 1.05–12.4, $p = 0.039$), but not for PFS (HR 1.60, 95%CI: 0.59–4.38, $p = 0.34$) (Table 4).

Discussion

In this study, with a higher incidence of lympho-vascular invasion and lymph node metastasis in positive co-expression of mesothelin and CA125 was observed. Individual expression of mesothelin or CA125 was not a predictive factor for OS and PFS. However, co-expression of mesothelin and CA125 was a major prognostic factor for OS.

Lympho-vascular invasion and lymph node metastasis are the worst prognostic factors in endometrial serous carcinoma [33]. Therefore, serous carcinoma with lympho-vascular invasion and lymph node metastasis was observed in the more aggressive subtypes of serous

Table 4 Multivariate analyses for progression-free and overall survival in patients with endometrial serous carcinoma

Variables		Progression-free survival			Overall survival		
		HR	(95%CI)	*p* value	HR	(95%CI)	*p* value
Using age, FIGO stage and mesothelin expression							
Age	>65 vs. ≤65	0.96	(0.37–2.66)	0.93	0.84	(0.27–2.71)	0.76
FIGO stage	IV vs. I,II,III	11.3	(3.05–46.3)	<0.01	4.58	(1.10–17.5)	0.037
Mesothelin expression	Positive vs. Negative	1.45	(0.54–3.94)	0.45	2.98	(0.95–11.2)	0.061
Using age, FIGO stage and CA125 expression							
Age	>65 vs. ≤65	1.03	(0.38–2.96)	0.94	1.01	(0.31–3.41)	0.98
FIGO stage	IV vs. I,II,III	12.6	(3.44–51.9)	<0.01	4.99	(1.21–18.8)	0.027
CA125 expression	Positive vs. Negative	1.57	(0.51–5.87)	0.44	2.44	(0.58–16.7)	0.23
Using age, FIGO stage and co-expression of mesothelin and CA125							
Age	>65 vs. ≤65	0.98	(0.37–2.74)	0.97	0.88	(0.28–2.85)	0.83
FIGO stage	IV vs. I,II,III	10.9	(2.94–45.1)	<0.01	4.44	(1.06–17.0)	0.041
Co-expression of mesothelin and CA125	Positive vs. Negative	1.60	(0.59–4.38)	0.34	3.32	(1.05–12.4)	0.039

CI confidence interval, *HR* hazard ratio, *CA125* cancer antigen 125

carcinoma. Our study showed that co-expression of mesothelin and CA125 was associated with lympho-vascular invasion and lymph node metastasis, and probably with high malignancy potential in endometrial serous carcinoma. This association between co-expression and tumor malignancy has been observed in pancreatic carcinoma and ovarian carcinoma [29, 30]. Co-expression of mesothelin and CA125 might therefore, be related with malignancy potential in several carcinomas.

Mesothelin is known to independently activate epithelial-to-mesenchymal transition and tumor progression in some malignant tumors [34]. Overexpression of mesothelin alone could constitutively activate the NF-κB, MAPK, and P13-kinase intracellular pathways, promoting cell proliferation and resistance to apoptosis [35]. Besides, mesothelin-accelerated tumor progression is known to co-operate with CA125. In ovarian carcinoma, mesothelin and CA125 play an important role in peritoneal metastasis. Cancer cells shed from primary tumor attached to human mesothelial cells with CA125 bounding to mesothelin. After the initial attachment of ovarian cancer cells to the peritoneal mesothelium, the co-expression of mesothelin and CA125 leads to the formation of a cluster of cancer cells via mesothelin-CA125 binding, and results in the proliferation and adhesion of circulating single or multicellular aggregates [30, 36]. In this study, mesothelin alone was observed to be associated with lympho-vascular invasion and lymph node metastasis, but not prognosis. On the other hand, co-expression was associated with lympho-vascular invasion, lymph node metastasis, and prognosis. These results provide some insight into the effect of the cooperation of mesothelin and CA125.

The limitations of this study were that it had a small sample size, and that it was a single-institutional and retrospective analysis. However, our study is the first to demonstrate the possibility that co-expression of mesothelin and CA125 may be an important factor in endometrial serous carcinoma like pancreatic carcinoma.

In conclusion, co-expression of mesothelin and CA125 may be a better biomarker to predict prognosis than individual mesothelin or CA125 expression. Further large-scale studies are needed to confirm these aspects.

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

Compliance with Ethical Standards

All procedures performed in the studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee, and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Since this was a retrospective study, informed consent was not obtained. This study was approved by the Ethics Committee of the National Defense Medical College, Tokorozawa, Japan.

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

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