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Article

SOX-11 and Epithelial-Mesenchymal Transition in Metastatic Serous Ovarian Cancer

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Abstract: Background: Ovarian cancer is the leading cause of death from gynecological malignancies with serous carcinoma being the most common histopathologic subtype. Epithelial-Mesenchymal Transition (EMT) correlates with an increased metastatic potential, whereas the transcription factor SOX11 is overexpressed in diverse malignancies. Methods: In the present study, we aim to evaluate the potential role of the immunohistochemical expression of SOX11 in 30 serous ovarian carcinomas in association with E-cadherin and Vimentin expression as well as with patients' clinicopathological data. Results: Most of the examined cases showed concurrent expression of E-cadherin and Vimentin, whereas SOX11 was expressed in a minority of the cases (26,7%). Interestingly, the positive cases had more frequently a metastatic disease at the time of diagnosis compared to the negative cases ($p=0.09$), an association, however, of marginal significance. Moreover, there was a negative correlation between E-Cadherin and SOX11 expression ($p=0.0077$) and a positive correlation between Vimentin and SOX11 expression ($p=0.0130$). Conclusions: The present work, for the first time, provides preliminary evidence SOX11 overexpression alongside E-cadherin loss in the promotion of EMT in serous ovarian cancer, thereby endorsing tumor metastasis.

Keywords: SOX11; epithelial-mesenchymal; transition; E-cadherin; vimentin; ovarian; cancer; metastasis; survival

Introduction

The fifth most frequent tumor-related cause of death for women in the United States is ovarian cancer, which is the most common cause of death from malignancies of the female genital tract[1]. The American Cancer Society predicts that in the United States in 2023, there will be about 19,710 new cases of ovarian cancer diagnosed and about 13,270 women will pass away from ovarian cancer[1]. Ovarian cancer comes in a variety of histological forms. The majority of ovarian cancers are epithelial carcinomas, with high-grade serous ovarian cancer being the most prevalent morphological subtype[2]. Given the lack of specific symptoms in the early stages of the disease, ovarian cancer is typically discovered when the tumor is at an advanced stage and after metastasis has taken place[3,4]. When a distant metastasis is present, the 5-year survival rate for women with invasive epithelial ovarian cancer falls to 31%[5]. A histologic examination of the tumor mass is necessary for a conclusive diagnosis; this is typically done after the tumor has been surgically removed[6].

The Epithelial-Mesenchymal Transition (EMT) is a biological process that enables a polarized epithelial cell to undergo numerous biochemical changes that allow it to assume a mesenchymal cell phenotype, which includes enhanced migratory capacity, invasiveness, elevated resistance to apoptosis, and significantly increased production of extracellular matrix components[7]. Normally,

this cell interacts with the basement membrane via its basal surface. The breakdown of the underlying basement membrane and the development of a cell with a mesenchymal phenotype that can move away from the epithelial layer in which it originated are signs that an EMT has occurred[8]. EMT requires a number of various molecular processes to be activated. These consist of the induction of ECM-degrading enzymes, the activation of transcription factors, the expression of particular microRNAs, changes in the expression of specific cell-surface proteins, and reorganization and expression of cytoskeletal proteins. These contributing factors are frequently used as biomarkers to show that a cell has undergone EMT[8]. α -Smooth muscle actin (α -SMA), Fibroblast-Specific Protein 1 (FSP1), vimentin, and desmin are examples of mesenchymal markers that carcinoma cells can express[9]. These cells are frequently present at the invasive front of primary tumors and are thought to be those that eventually progress through the subsequent stages of the invasion-metastasis cascade, including intravasation, transport through the circulation, extravasation, the formation of micrometastases, and finally the development of small colonies into macroscopic metastases[10–12].

The SOX family is a group of transcription factors that play significant roles in determining cell fate, which includes the transcription factor SOX11, mapping to chromosome 2p25.3[13]. SOX11 has the N- and C-terminal transactivation domains as its functional domains[14]. It has been discovered that SOX11 functions downstream of proneural basic helix-loop-helix (bHLH) proteins, which commit progenitor cells to a neurogenic program to create a neuronal phenotype. Its functional relevance to neurogenesis was further confirmed by the discovery of SOX11 expression in medulloblastoma[15]. Moreover, SOX11 shows normal expression in the developing central nervous system of the embryo, keratinocytes, and several other epithelial tissues[16]. Interestingly, SOX11 has been shown to be expressed in a number of malignancies, such as mantle cell lymphomas, pancreatic solid pseudo-papillary tumors, brain tumors and breast carcinomas[17–20]. Recently, SOX11 was also implicated to play a significant role in mesenchymal state and embryonic cellular phenotypes in breast cancer[21].

In view of these considerations, the present study aims to investigate the potential role of SOX11 in metastatic serous ovarian cancer as a marker of EMT, as well as its influence on patients' clinico-pathological characteristics including survival.

Materials and Methods

Patient Collective

This is a study of archival histopathological material from 30 patients with a serous ovarian carcinoma diagnosed during 2017–2018 at the Department of Pathology, in Klinikum Nuremberg, Germany, for whom medical records were available. All patients underwent a surgical resection and none of them had received any kind of neoadjuvant radio- or chemotherapy prior to surgery. Our cohort was based on the random selection of 15 patients with the presence of metastasis and 15 patients with no evidence of metastasis at the time of diagnosis. Other histological subtypes, borderline tumors as well as mixed carcinomas were excluded from our analysis. Patients were assigned a clinical stage according to the International Federation of Obstetrics and Gynecology (FIGO) standards[22]. Surgical and pathological findings and postoperative abdominopelvic computerized tomography scans were used to determine the FIGO stage for the ovarian adenocarcinomas and the residual disease after initial surgery. The study was conducted in accordance with the Declaration of Helsinki and was approved by the Bioethics Committee of the Paracelsus University, Nuremberg, Germany. Due to the retrospective nature of the studies, as well as the lack of impact on the treatment of patients, it was not necessary to obtain informed consent.

Immunohistochemical analysis

Immunohistochemistry (IHC) for E-cadherin, Vimentin and SOX11 was performed on formalin-fixed, paraffin-embedded tissue sections using the following antibodies: mouse monoclonal anti-SOX11 (clone MR-58, Firma Cell Marque), mouse monoclonal anti-E-cadherin (NCH-38, Dako) and mouse monoclonal Vimentin (clone V9, DAKO). Envision Flex+ Mouse (K8021,

DAKO) was used as a detection system. For each antibody, suitable negative and positive controls were used as appropriate. IHC evaluation was performed by counting by an experienced pathologist, blinded to clinical information.

Statistical analysis

Statistical analysis was performed by a MSc biostatistician. The association between the IHC expression of E-cadherin, Vimentin, and SOX11, and clinicopathological characteristics was examined using non-parametric tests with correction for multiple comparisons, as appropriate. Survival analysis was performed using Kaplan–Meier survival curves and the differences between the curves were compared with log-rank test. A p-value of <0.05 was considered statistically significant. A p-value of > 0.05 but lower of < 0.10 was considered of marginal significance. The analysis was performed with the statistical package STATA 11.0/SE for Windows.

Results

Patients' characteristics

The patients' characteristics are shown in Table 1. The median age was 61,5 (range 46-79 years). Tumor stage according to FIGO was as follows: 23% has a FIGO-stage I, 10% a FIGO-stage II, 67% a FIGO-stage III and 30% a FIGO-stage IV. Five patients had a low grade (LG) and 25 a high grade (HG) carcinoma. Follow-up information was available in 21 patients, six of whom died of their disease within a period of 3,4-35 months. From the 15 patients with metastatic disease at diagnosis 6 of them had a lymph node metastasis, 3 a lymph node and a liver metastasis, 4 a pleura metastasis, one a liver metastasis and one a skin metastasis.

Table 1. Patients' characteristics.

Patients' characteristics	Median value	Value range
Age (in years)	61,5	46-92
FIGO stadium	Number of patients	Percentage
I	7	23%
II	3	10%
III	11	37%
IV	9	30%
Tumor grade	Number of patients	Percentage
Low grade	5	17%
High grade	25	83%
Metastasis	Number of patients	Percentage
Metastatic cancer	15	50%
Non-metastatic cancer	15	50%
Residual disease		
None/minimal	25	83%
>2cm	5	17%
Event	Number of patients	Percentage
Death of disease	6/21 (follow-up: 3,4-35 months)	28%
Censored	15/21 (follow-up: 5-68 months)	71%

Immunohistochemical expression of E-Cadherin in ovarian serous carcinoma

E-cadherin expression was observed in 29/30 ovarian serous carcinomas with a median value of 92,5% (range 0-100%, Figure 1 A, D). There was no variety in the staining intensity, which was considered moderate to high. The LG ovarian serous carcinomas showed an increased expression of E-cadherin when compared to the HG carcinomas, but this association was of marginal significance (Mann Whitney U Test, p=0,06). Moreover, the carcinomas with metastasis at the time of diagnosis

showed a lower E-cadherin expression compared to the ones without a metastatic disease (Mann Whitney U Test, $p=0,0063$) (Figure 1). There was no significant association with the FIGO-stage (Kruskal Wallis ANOVA, $p>0,10$) or the patients' survival (log rank test, $p>0,10$).

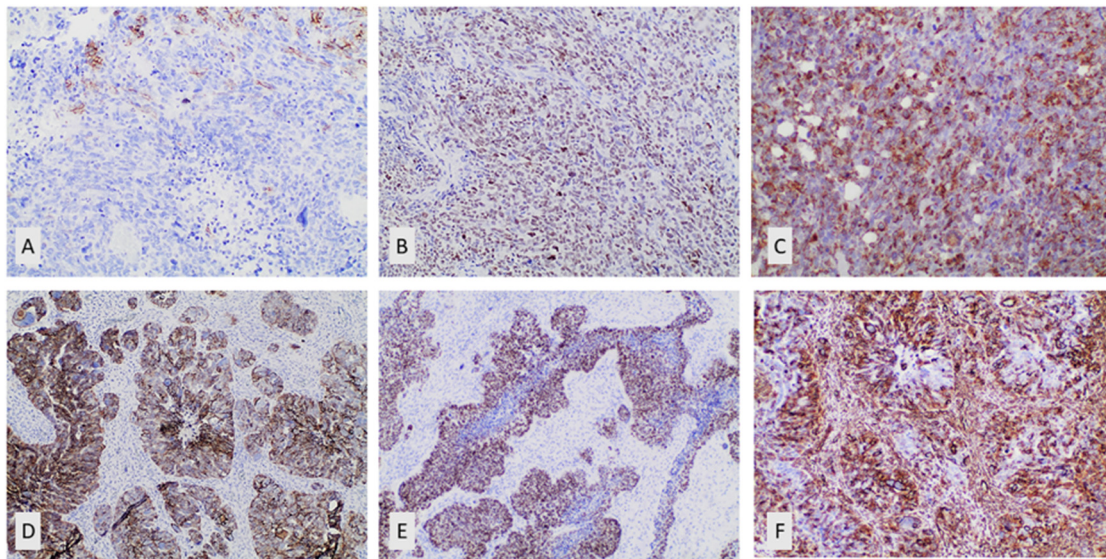


Figure 1. E-Cadherin, SOX11 and Vimentin expression in ovarian serous carcinomas. (A, B, C) A high grade serous carcinoma with loss of E-Cadherin (A, x400) and increased expression of SOX11 (B, x400) and Vimentin (C, x400), (D-F) A high grade serous carcinoma with expression of E-Cadherin (D, x200), SOX11 (E, x200) and Vimentin (F, 400).

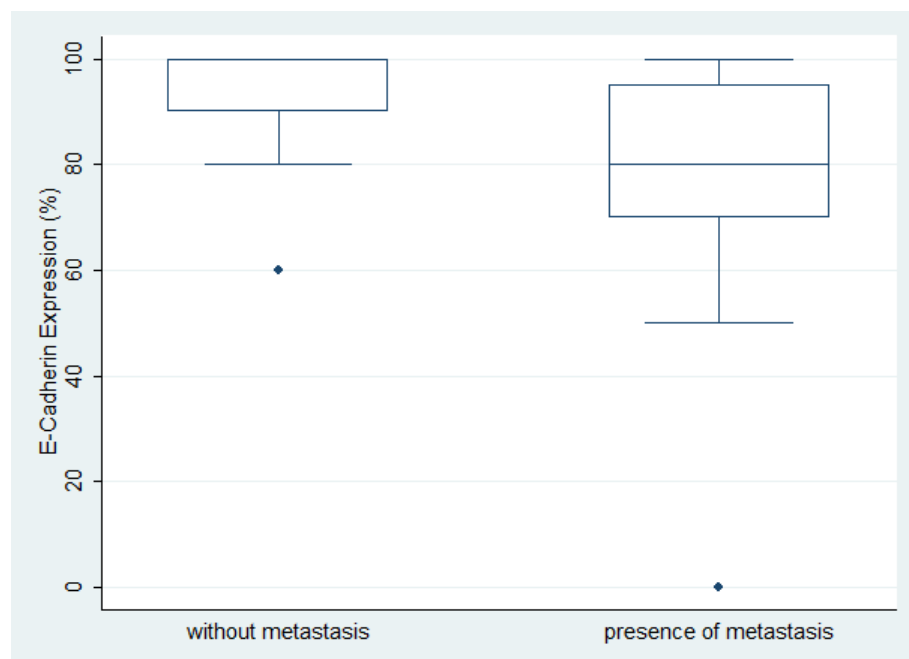


Figure 2. Schematic representation of the association between E-cadherin expression and presence of metastasis.

Immunohistochemical expression of Vimentin in ovarian serous carcinoma

Vimentin expression was observed in 22/30 cases, showing a median value of 15% (range 0-90%, Figure 1C, F). There was no variety in the staining intensity, which was considered moderate to high.

No significant association was detected in terms of FIGO-stage, tumor grade, presence of metastasis or patients' survival (Kruskal Wallis ANOVA, Mann Whitney U Test, and log-rank test, $p>0,10$).

Immunohistochemical expression of SOX11 in ovarian serous carcinoma

SOX11 was negative in the majority of the cases and was observed only in 8/30 cases (26,7%, median value 0, range 0-90%, Figure 1 B, E). These eight positive cases had more frequently a metastatic disease at the time of diagnosis compared to the negative cases (75% versus 41%, Chi-square Test, $p=0.09$, Figure 3). This association was, however, of marginal significance. There was no significant correlation with FIGO-stage, tumor grade, or patients' survival (Kruskal Wallis ANOVA, Mann Whitney U Test, and log-rank test, $p>0,10$).

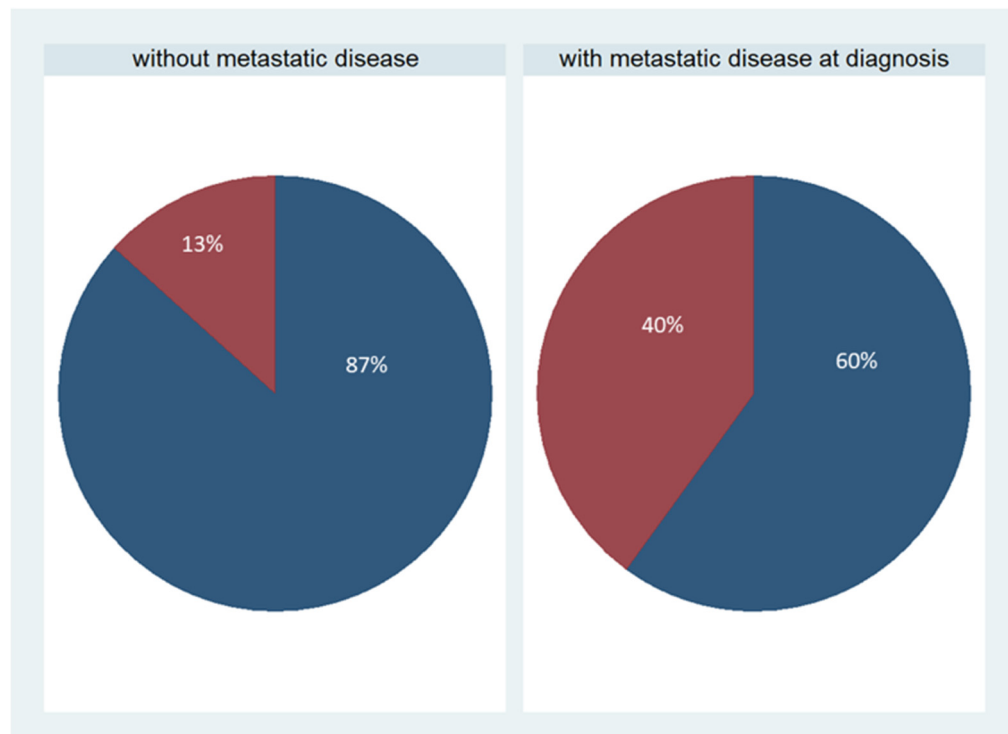


Figure 3. Schematic representation of the association between SOX11 positivity and the presence of metastasis.

Associations between the examined molecules

There was a negative correlation between E-Cadherin and SOX11 expression (Spearman correlation coefficient $R = -0,4773$, $p = 0,0077$) and a positive correlation between Vimentin and SOX11 expression (Spearman correlation coefficient $R = 0,4480$, $p = 0,0130$). In particular, the one case in our cohort which was negative for E-cadherin displayed an increased expression of SOX11, calculated as 70%.

Discussion

Given its high prevalence and mortality, ovarian cancer has long attracted the interest of diverse international study groups with a view to identifying and determining trustworthy biomarkers in the context of tumor metastasis and patient survival. Despite the therapeutic advancements over the past 20 years, which have undoubtedly revolutionized the anti-ovarian-cancer therapy, 5-year relative survival rates amount to only 31% for invasive epithelial ovarian cancer in a distant Surveillance, Epidemiology, and End Results (SEER) stage[5]. Recently, Huh et al. tried to uncover novel diagnostic biomarkers for HG serous ovarian cancer by data-independent acquisition mass spectrometry and succeeded in identifying a total of four potential biomarkers (Fibrinogen-A, von-Willebrand factor, Rho GDP dissociation inhibitor beta and Serpin family F member) that might play

a significant role in HG serous ovarian cancer cell proliferation and migration[23]. Similarly, Atallah et al. proved that both bikunin and creatine kinase b represent useful biomarkers concerning ovarian cancer survival and prognosis, while osteopontin seems to correlate with ovarian cancer progression and metastasis[24].

In general, the decrease of E-cadherin as a marker of the epithelial phenotype has been suggested to indicate the progression of EMT[25]. Evidence has also shown the correlation between loss of E-cadherin expression by tumor cells and the progression of EMT in the cell[8]. However, the complete conduction of EMT and the subsequent acquisition of a pure mesenchymal phenotype is not always necessary for metastasis[26], which is in alignment with the results of this project. Of the total 30 cases, there was only one case with complete loss of E-cadherin expression and high vimentin expression, implicating a loss of the epithelial phenotype. All the other cases possessed either a hybrid phenotype, co-expressing both E-cadherin and Vimentin or an epithelial phenotype, expressing only E-cadherin. Interestingly, 21 of 30 cases displayed concurrent E-cadherin and vimentin expression. This high proportion of cases positive for both E-cadherin and vimentin is also reported in the literature in the serous subtype of ovarian carcinomas[27].

As far as SOX11 is concerned, only four study groups have to date examined the role of SOX11 as an epithelial ovarian cancer biomarker in terms of tumor metastasis and patient survival. In 2009, Brennan et al. were the first to describe SOX11 as a prognostic factor for enhanced recurrence-free survival in epithelial ovarian cancer after controlling for tumor stage and grade, with the loss of SOX11 correlating with a diminished recurrence-free survival as well as a more aggressive phenotype[28]. Two years later, Sernbo et al. reported that SOX11 expression accounts for an improved survival of patients with high grade epithelial ovarian cancer, depending on cancer stage[29]. Davidson et al. could not, however, identify SOX11 as a marker of longer survival in serous ovarian cancer effusions[30]. Last but not least, Fang et al. suggested that ovarian cancer cell proliferation and invasion were inhibited by SOX11 overexpression, indicating that miR-223-3p controls ovarian cancer cell growth and invasion by specifically targeting SOX11 expression[31].

In the present study, we were able to show that SOX11 seems to positively correlate with a metastatic disease at the time of diagnosis, but not with FIGO-stage, tumor grade, or patients' survival. Moreover, a negative correlation was noted between E-Cadherin and SOX11 expression, and a positive correlation between Vimentin and SOX11 expression. In this regard, the results of our study for the first time highlight the fact that SOX11 overexpression could play a role in the promotion of EMT in serous ovarian cancer, hence stimulating tumor metastasis. A similar observation has been reportedly made in breast cancer, in which SOX11 seems to promote epithelial/mesenchymal hybrid state and alter tropism of invasive breast cancer cells, also enhancing tamoxifen resistance[21,32]. The hybrid EMT state gives tumor cells the advantage of acquiring the mesenchymal characteristics without the complete loss of epithelial characteristics. Thus, the tumor cells can attach to the ECM with increased connectivity[33], which is why cells in partial EMT states exhibit greater metastatic competence than cells that have an epithelial or mesenchymal phenotype. This relationship was also observed in this project with the association between low expression of E-cadherin and positive expression of SOX11 with the presence of metastasis. There is evidence that the hybrid states of EMT may be triggered by calcium signaling[34]. In addition, tumor cells in the partial EMT state are thought to not only enhance the invasive properties of the cell, but also generate circulating tumor cells and cancer stem cells, as well as promote anticancer drug resistance. The phenotypic changes that allow cells to adopt a hybrid EMT state are regulated by extracellular matrix components, exosomes, and soluble factors. These in turn regulate multiple EMT transcription factors[33]. These previous assumptions and findings about EMT highlight the complexity of the topic.

Notably, our observations are contradictory to the aforementioned results of the previous studies in ovarian cancer[28–31]. Brennan et al. used an *in silico* transcriptomic screen and evaluated SOX11 expression using IHC and automated algorithms in 76 epithelial ovarian cancer cases, hence concluding that SOX11 loss correlates with a decreased recurrence-free survival and a more aggressive phenotype[28]. Sernbo et al. compared SOX11 expression and clinicopathological data in

a cohort of 154 primary invasive epithelial ovarian cancer cases of several histological types, including mucinous and endometrial carcinoma, and suggested that SOX11 expression was associated with an improved survival of patients with high grade epithelial ovarian cancer, depending on cancer stage[29]. Furthermore, Davidson et al. assessed the expression of E-cadherin, vimentin and SOX11 in 100 advanced-stage serous ovarian carcinoma effusions using IHC and reported that only vimentin expression was significantly related to poor chemotherapy response at diagnosis[30]. Last but not least, Fang et al. highlighted that the SOX11 mRNA expression is significantly lower in the ovarian cancer cell lines SKOV3, OVCAR3, A2780, and ES2, compared to the HOSE normal ovarian cell line, and that the SOX11 mRNA expression is also significantly downregulated in ovarian cancer than in normal tissues[31]. This discrepancy might be attributed to the different study populations (cell lines vs. patients, size of patient collectives, absence of control group, histopathological ovarian cancer subtype), the employed study methods (IHC vs. Western Blot) and/or the preferred statistical testing methods.

The results of our study are only preliminary and, by no means, allow for generalized conclusions on the role of SOX11 as a biomarker for serous ovarian carcinoma. Given the small patient number, our findings undoubtedly represent an interesting observation concerning the role of SOX11 as a potential biomarker for metastatic serous ovarian cancer, but still need to be studied in larger study populations in order to be further verified and avoid statistical errors due to study sample size.

In summary, we report, for the first time, the potential role of E-cadherin and SOX11 as biomarkers for serous ovarian cancer with a special focus on EMT and distant metastasis. Our findings may, hence, pave the way for the identification of novel biomarkers in the context of advanced (serous) ovarian cancer diagnosis and treatment.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and it was approved by the Bioethics Committee of the Paracelsus medical University (April 2022).

Informed Consent Statement: Not applicable. Due to the retrospective nature of the studies and the lack of impact on the treatment of patients, it was not necessary to obtain informed consent.

Data Availability Statement: The data presented in this study are available on request from the corresponding author.

Conflicts of Interest: The authors declare no conflict of interest.

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