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Research Article

Coexpression of Survivin+/VEGF+ Indicates Poor Prognosis of Endometrial Cancer

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Abstract

Objective: To explore the coexpression of Survivin and VEGF in endometrial cancer (EC) and to explore their correlation with the clinicopathological parameters and prognosis of EC.

Materials and Methods: From Mar, 2005 to Oct, 2019, 126 cases of paraffin-embedded EC tissues that had been pathologically confirmed at the First People's Hospital of Chenzhou and Integrated Hospital of Traditional Chinese Medicine, Southern Medical Universtiy were included in this study. Survivin and VEGF expression were detected with immunohistochemistry with antibody specific for Survivin and VEGF, respectively.

Results: Co-overexpression of Survivin and VEGF was associated with recurrence free progression and overall survival of EC patients; and co-overexpression was associated with International Federation of Gynecology and Obstetrics stage, deep myometrial invasion, lymph node metastasis, survival status. Moreover, in a multivariate model co-overexpression was an indeed independent predictor of poor survival in EC.

Conclusion: Co-overexpression of Survivin and VEGF is a useful independent prognostic marker in EC, which provides important clinical value of EC in future.

Keywords: Endometrial cancer; Survivin; VEGF; Prognosis

Introduction

Endometrial Cancer (EC) is the most common malignant tumor of the female reproductive tract in the developed countries [1,2]. Its incidence is increasing [3]. Patients are usually diagnosed when the disease is still limited to the uterus, which often results in a good prognosis [4]. Thus, the 5years survival is very high in early stage of EC. However, the prognosis of recurrent or metastatic patient is poor [4]. Recently more and more prognostic predictor was reported [5,6], but these biomarkers are neither extremely sensitive nor specific. Therefore, to search new prognostic biomarkers and to provide novel targeted therapy are very crucial, which will provide more biologically informative data from EC and assist in planning the optimal treatment methods for the patients.

Survivin gene is a gene located on chromosome 17q25, and is a member of the inhibitor of apoptosis protein family [7]. Survivin inhibits apoptosis and controls the checkpoint in G2/M phase of the cell cycle [8-10]. It has been reported to be overexpressed in many cancer cell lines [11,12], including endometial, ovarian, prostate, breast, brain, colon, cervical and lung cancers. Survivin has been associated with the increase in tumor growth and the decrease in patient survival [13,14].

Vascular Endothelial Growth Factor (VEGF) is an over-expressed vascular endothelial growth factor in many human tumors, which can promote angiogenesis of tumor tissue [15-20]. In recent years, VEGF has been shown to directly stimulate

endothelial cell division and proliferation, and to be a highly specifific mitogen for vascular endothelial cells [10]. The current studied showed that VEGF plays a critical role during the angiogenesis process [15], and the activation of VEGFR signaling induces the activation of intracellular signal transduction proteins and then leads to cell proliferation, migration, and survival. Thus, VEGF is considered to be a candidate attractive target for tumor therapy [10].

The coexpression of Survivin and VEGF has been reported in various cancers yet. In breast cancer, Survivin expression is significantly correlated VEGF expression [21], and the coexpression of survivin and VEGF-C is more statistically significant to assess lymphatic metastasis in breast cancer [22]. Moreover, over-expression of Survivin and VEGF in small cell lung cancer may predict the poorer prognosis [23]. However, the coexpression and relationship between Survivin and VEGF in EC have not been reported.

Therefore, in this research we aimed to explore the expression of Survivin and VEGF and coexpression of Survivin/VEGF in EC tissues, and to study their clinicopathological parameters and prognostic value in EC.

Material and Methods

Tissue Sections

From Mar, 2005 to Oct, 2019, a total of 126 paraffin-embedded endometrial cancer tissues that had been operated and pathologically diagnosed at the First People's Hospital of Chenzhou and Integrated Hospital of Traditional Chinese Medicine, Southern Medical Universtiy were collected in this study. Survival date was calculated from the operation date until October 31, 2019 (at last follow-up). This investigation was obtained approval from the First People's Hospital of Chenzhou and Integrated Hospital of Traditional Chinese Medicine, Southern Medical Universtiy Ethics Committee. All of patients signed the informed consent before operation.

Immunohistochemistry (IHC)

The Survivin and VEGF expression in endometrial cancer paraffin-embedded tissues were detected by immunohistochemical staining (see the following flow diagram Figure 1). Briefly, 4 μm-thick paraffin-embedded sections were baked at 65 ^{0}C for more than 2 h, deparaffinized with xylene, rehydrated, high tension was used for antigen retrieval, and the specimens were treated with 3% hydrogen peroxide in methanol, and then followed by incubation with 1% bovine serum albumin to block nonspecific binding, and incubation with anti-rabbit Survivin monoclonal antibodies (1:100; CST; Cat: 2808) and anti-rabbit VEGF polyclonal antibodies (1:50; Proteintech; Cat: 19003-1-AP) at 4 ^{0}C overnight, respectively. The next day the tissue sections were treated with the secondary antibody (Sigma), and then incubated with streptavidin horseradish peroxidase complex (Sigma), immersed in 3-amino-9-ethyl carbazole. The sections were then counterstained with 10% Mayer's hematoxylin, dehydrated, and mounted in Crystal Mount. Two pathologists evaluated the score of immunostaining of each section. The score was due to both the proportion and the intensity of positively stained cancer cells. The percentage was scored as follows: <10% positive cancer cells were scored as 0; 10-50% were scored as 1; 50-75% were scored as 2; and >75% were scored as 3. Meanwhile, the tissues were sorted into four grades based on staining intensity: 0 indicated no staining; 1 indicated weak staining; 2 moderate staining; and 3 strong staining. The staining index (0-9) was calculated as the product of the proportion of positive cells multiplied by the staining intensity score. The best cut-off value was defined as follows: a staining score of ≥6 was considered to have high Survivin or VEGF expression (also called Survivin+ or VEGF+), and a staining score of ≤5 indicated low Survivin or VEGF expression (also called Survivin- or VEGF-) [24-26].

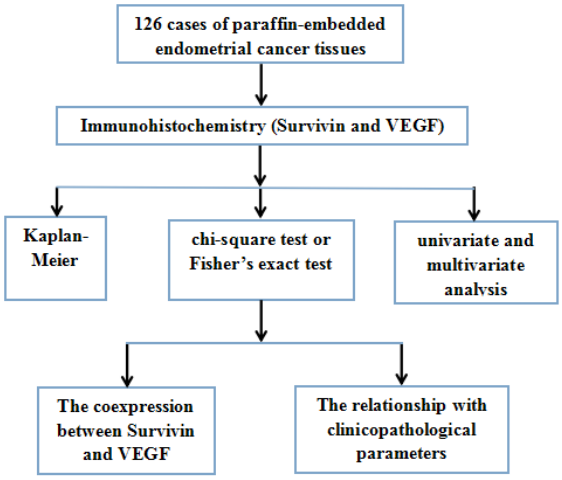

Figure 1: The patients' flow diagram.

Statistical analysis

All data were analyzed with the statistical software SPSS 21.0. The chi-square test or Fisher's exact test were used to analyze the relationship between Survivin/VEGF expression and clinicopathological parameters. Moreover, Patients Recurrence free survival (also called RFS) and overall survival (also called OS) were analyzed by a Kaplan–Meier survival analysis, and the differences were counted by the log-rank test. Cox's proportional hazards regression model was used to the univariate and multivariate analysis. All of p value of < 0.05 were considered statistically significant.

Results

The protein expression of Survivin and VEGF in EC

To determine the protein expression of Survivin and VEGF in EC, we stained 126 cases of EC with both Survivin and VEGF

antibodies, respectively. The results showed that 40/126 (31.75%) had weak/absent staining and 86/126 (68.25%) had moderate/strong staining of Survivin in EC, and 38/126 (30.16%) had weak/absent staining and 88/126 (69.84%) had moderate/strong staining of VEGF in EC, respectively. Moreover, we found that both Survivin and VEGF protein expression staining located at cytoplasmic (Figure 2).

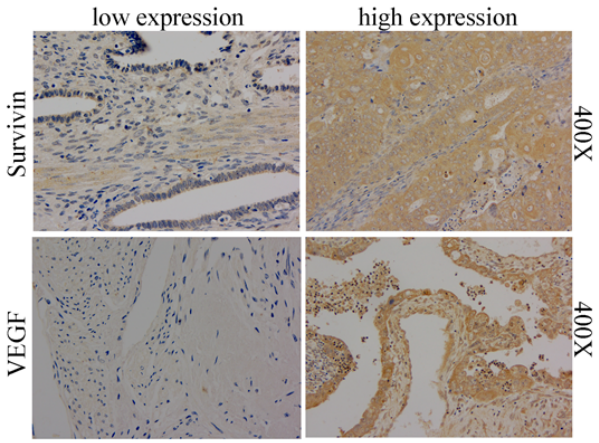

Figure 2: Both Survivin and VEGF expression in EC tissues with immunohistochemically staining (400X, scale bar: 25μm).

Survivin, VEGF and coexpression of Survivin/VEGF were associated with RFS and OS of EC patients

In the present study, patients with Survivin+ exhibited a median overall survial of only 63 months (median RFS 49 months), while patients with Survivin- exhibited a median overall survial of 90.5 months (median RFS 78.5 months). Moreover, patients with VEGF+ exhibited a median overall survial of only 65.5 months (median RFS 52.5 months), while patients with VEGF- exhibited a median overall survial of 91 months (median RFS 74.5 months). In addition, patients with Survivin+/VEGF+ exhibited a median overall survial of only 60.5 months (median RFS 47.5 months), while patients with others coexpression (including Survivin+/VEGF-, Survivin-/VEGF+, Survivin-/VEGF-, and so on) exhibited a median overall survial of 84 months (median RFS 72 months). Kaplan-Meier survival analysis demonstrated that there were statistically significant on RFS and OS between Survivin- and Survivin+(P=0.0037 and P=0.0050, respectively), and there were also statistically significant on RFS and OS between VEGF- and VEGF+(P=0.0089 and P=0.0029, respectively). Moreover, there were also statistically significant on RFS and OS between Survivin+/VEGF+ coexpression and others coexpression (P=0.0217 and P=0.0136, respectively) (Figure 3). A survival analysis showed that the cumulative OS and RFS rates of EC patients increased with increasing in Survivin+/VEGF+ coexpression (Figure 3).

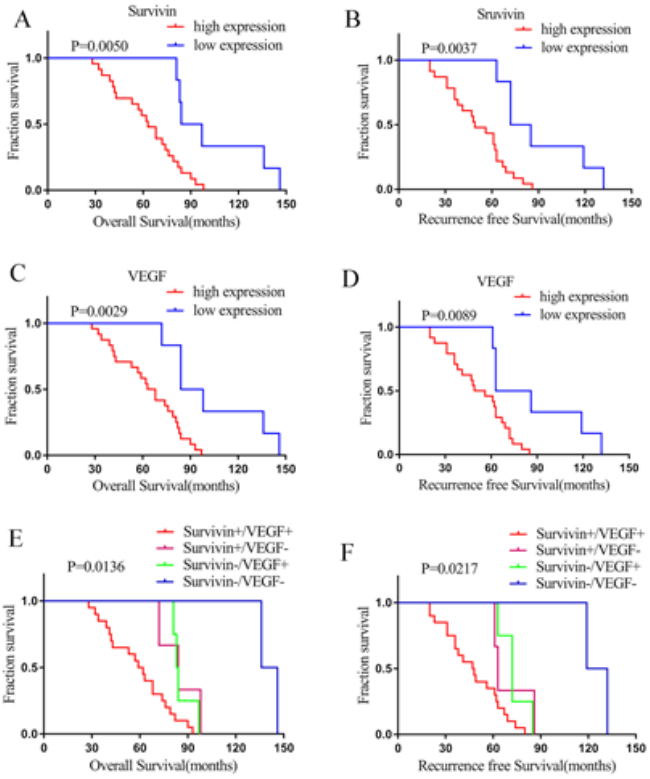

Figure 3: Kaplan-Meier survival of Overall Survival (OS) and Recurrence Free Survival (RFS) among Survivin, VEGF and coexpression of Survivin/VEGF of dead EC patients: A. Kaplan-Meier survival of OS of Survivin in dead EC patients. B. Kaplan-Meier survival of RFS of Survivin in dead EC patients. C. Kaplan-Meier survival of OS of VEGF in dead EC patients. D. Kaplan-Meier survival of RFS of VEGF in dead EC patients. E. Kaplan-Meier survival of OS of Survivin/VEGF in dead EC patients. F. Kaplan-Meier survival of RFS of Survivin/VEGF in dead EC patients.

Survivin, VEGF and Survivin/VEGF coexpression were associated with the clinicopathological parameters of EC

Subsequently, we explored their association with the clinicopathological parameters of EC patients. The results showed in Table 1. Further, $\chi 2$ or Fisher's Exact test showed that there were significant relationships between Survivin expression and parameters of EC, such as the following factors: FIGO stage, Depth of myometrial invasion, and so on (Table 1). Moreover, using $\chi 2$ or Fisher's Exact test showed that there were significant relationships between VEGF expression and clinicopathological parameters of EC, such as the following factors: FIGO stage, Lymph node metastasis, Recurrence, Depth of myometrial invasion, and so on (Table 1). More importantly, we used $\chi 2$ or Fisher's Exact test to

explore the relationship between Survivin/VEGF coexpression and clinicopathological parameters of EC, and we found that there were significant differences in the following factors, such as: FIGO stage, Lymph node metastasis, Recurrence, Depth of myometrial invasion, vital status (at last follow-up), and so on (Table 1).

parameters		Total	*Survivin*			*VEGF*			Coexpression of *Survivin/VEGF*		
			low	high	P-value(χ2 or Fisher's Exact test)	low	high	P-value(χ2 or Fisher's Exact test)	Survivin+/ VEGF+	others	P-value(χ2 or Fisher's Exact test)
Age (years)	≤50	62	19	43	0.5	20	42	1	31	31	0.4
	>50	64	16	48		19	45		37	27	
FIGO stage	I	36	15	21	**0**	17	19	**0**	11	25	**0**
	II	43	12	31		14	29		23	20	
	III	47	8	39		8	39		34	13	
Lymph node metastasis	No	82	23	59	0.6	33	49	**0**	39	43	**0**
	Yes	21	4	17		1	20		16	5	
Vital status	Alive	82	28	54	0.2	30	52	0	38	44	**0**
	Dead	29	6	23		5	24		20	9	
Menopausal Status	No	57	20	37	0.1	15	42	0	29	28	0.5
	Yes	69	15	54		24	45		39	30	
Recurrence	No	78	25	53	0.2	30	48	**0**	35	43	**0**
	Yes	48	10	38		9	39		33	15	
Depth of myometrial invasion	≤1/2	61	26	35	**0**	27	34	**0**	21	40	**<0.001**
	>1/2	65	9	56		12	53		47	18	

Differentiation grade	G1	30	10	20	0.2	12	18	0	13	17	0.1
	G2	55	18	37		18	37		28	27	
	G3	41	7	34		9	32		27	14	
Pathological type	Adenocarcinoma	98	24	74	0.1	27	71	0	57	41	0.1
	others	28	11	17		12	16		11	17	
CA125 (U/mL)	≤35	16	6	10	0.4	5	11	1	7	9	0.4
	>35	108	29	79		33	75		60	48	
HE4 (pmol/L)	≤140	25	8	17	0.6	8	17	>0.9999	14	11	0.9
	>140	50	13	37		16	34		29	21	

Table 1: Survivin, VEGF and coexpression in association with standard clinicopathological variables using the χ2 or Fisher's Exact test in EC patients.

Correlation between Survivin and VEGF expression

To explore the relationship between Survivin and VEGF, Spearman correlation and χ2 test were used to analyze, and the results showed that there was a statistical significance between them (P=0.0262) (Table 2).

Survivin	VEGF		Spearman's R	**χ2**	*P*
	high	low			
high	68	23	0.198	4.941	0.0262
low	19	16			

Table 2: Correlation between Survivin and VEGF expression.

Coexpression of Survivin+/VEGF+ was a useful indeed independent prognostic predictor of EC

Further, we evaluated the prognostic value of Survivin, VEGF, and Survivin/VEGF coexpression in EC patients. In a univariate Cox analysis, Survivin+, VEGF+, Survivin+/VEGF+ coexpression, and were significant prognostic factors (Table 3). Moreover, in a multivariate Cox regression model we found that Survivin+/VEGF+ coexpression and serum CA153 were indeed independent prognostic factors of EC (Table 3), but Survivin+, VEGF+ and were no longer significant.

Variable	**Univariate Analysis**			**Multivariate Analysis**	
	Number of Patients	***p***	**Regression Coefficient (SE)**	***p***	**95% Confidence Interval**
Survivin		0.010	0.558	0.386	-
Low expression	35				
High expression	91				

Variable	Univariate Analysis			Multivariate Analysis	
	Number of Patients	*p*	Regression Coefficient (SE)	*p*	95% Confidence Interval
VEGF		0.011	0.755	0.557	-
Low expression	39				
High expression	87				
Coexpression of Survivin/VEGF		0.001	0.519	0.049	0.014-0.993
Survivin+/VEGF+	68				
others	58				
FIGO stage		0.000	0.386	0.759	-
I	36				
II	43				
III	47				
Lymph node metastasis		0.007	1.109	0.026	1.351-105.355
No	82				
Yes	21				
Depth of myometrial invasion		0.037	0.404	0.953	-
≤1/2	61				
>1/2	65				

Table 3: Cox regression univariate and multivariate analyses of prognostic factors in EC.

Discussion

Survivin can be detected in many human tumors, and overexpression of surviving is closely related to poor prognosis of cervical cancer [7,27]. Brunner, et al. [28] reported that in endometrial cancer, survivin were overexpressed and were associated with type II and high-grade tumours, and increasing expression levels of survivin were associated with adverse prognostic factors. In the present study, our results showed that 86/126 (68.25%) had moderate/strong staining of Survivin compared with 40/126 (31.75%) of weak/absent staining in EC, respectively. and the survival duration (RFS or OS) of patients with Survivin+ was much shorter than Survivin-. Thus our study was consistent with previous reports [28]. Moreover, Survivin expression was associated with FIGO stage and Depth of myometrial invasion, which indicates that Survivin may correlate with the development and progression of disease. And these results support earlier reports that Survivin was associated with the increase in tumor growth and the decrease in patient survival [13,14].

VEGF is the strongest pro-angiogenic factor that regulates the proliferation and directional migration of tumor cells. VEGF can promote the formation of new vessels in tumor tissue to facilitate tumor growth, and is an important indicator of tumor Prognosis [15-20]. Xu, et al. [29] reported that in endometrial carcinoma, the positive expression of NGAL and VEGF was related to FIGO staging, differentiation grade and myometrial invasion depth. And the higher expression of NGAL and VEGF was correlated with the tumor stage and the depth of invasion, but was not associated with age, pathological type and tumor size. So they concluded that the abnormal high expression of NGAL and VEGF in EC may be an important biomarker for early tumor diagnosis or as a novel target for therapeutic

intervention. In the present study, the results showed that 88/126 (69.84%) had moderate/strong staining of VEGF compared with 38/126 (30.16%) of weak/absent staining in EC, respectively, and the survival duration (RFS or OS) of patients with VEGF+ was much shorter than VEGF-. Moreover, VEGF expression was associated with FIGO stage, Lymph node metastasis, Recurrence, Depth of myometrial invasion, and so on. All of these results indicates that VEGF may correlate with the progression and recurrence of disease, which support earlier reports that VEGF facilitates tumor growth, and is an important indicator of tumor prognosis.

Further, we explored the coexpression of Survivin/VEGF in EC. The results showed that Survivin was positively correlated with VEGF expression, and patients with Survivin+/VEGF+ exhibited a shorter OS or RFS than others coexpression (including Survivin+/VEGF-, Survivin-/VEGF+, Survivin-/VEGF-), and Survivin/VEGF coexpression was associated with FIGO stage, Lymph node metastasis, Recurrence, Depth of myometrial invasion and vital status. And the survival analysis showed that the cumulative OS and RFS rates of EC patients decreased with increasing in Survivin+/VEGF+ coexpression. Moreover, in a multivariate Cox regression analysis we found that Survivin+/VEGF+ coexpression and Lymph node metastasis were indeed independent prognostic predictors of EC, which showed that combination of Survivin and VEGF predicting EC prognosis was more accurate and feasible than Survivin or VEGF alone. Thus, all of these results showed that coexpression of Survivin/VEGF was closely correlated with EC development, metastasis and recurrence, and Survivin/VEGF combinating detection should be taken into our IHC evaluation, which could be very helpful to clinical diagnose, treatment and supervision, and it may help to improve the EC prognosis.

Taken together, our study was the first to investigate the coexpression of Survivin/VEGF in EC. All of these results show that coexpression of Survivin+/VEGF+ was associated with FIGO stage, Lymph node metastasis, Recurrence, Depth of myometrial invasion and vital status. Additionally, coexpression of Survivin+/VEGF+ is an indeed independent prognostic predictor, and Survivin+/VEGF+ coexpression predicts poor prognosis of EC patients, and it can be recommended as a meaningful EC biomarke. Thus this study may provide important value in EC diagnosis, treatment, and supervision. In future, we need more in vivo and in vitro studies to demonstrate its role and molecular mechanism in initiation, progression, metastasis and prognosis of EC.

Clinical Significance

The present study was the first to investigate the coexpression of Survivin/VEGF in EC tissues. And our results show that coexpression of Survivin+/VEGF+ is an indeed independent prognostic predictor, and Survivin+/VEGF+ coexpression predicts poor prognosis of EC patients, and it can be recommended as a meaningful EC biomarke. Thus this study may provide important value in EC diagnosis, treatment, and supervision.

Conclusion

Survivin+/VEGF+ coexpression can predict poor prognosis of EC patients, and it can be recommended as a meaningful EC biomarke.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' Contributions

HW and CH conceived and designed the experiments; YY and LL performed the experiments; LL analyzed the data; ZX and LL contributed the paraffin-embedded EC tissues; LL wrote the paper. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The Ethics Committee of the First People's Hospital of Chenzhou and Integrated Hospital of Traditional Chinese Medicine, Southern Medical Universtiy authorized the experimental and research protocols of this study. All procedures performed in this study 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. All controls and patients (or relatives of patients who already died) provided written informed consent.

Patient consent for publication

Not applicable

Conflicts of Interest

The authors declare no conflict of interest.

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