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Vascular Endothelial Growth Factor and Intratumoral Microvessel Density as Prognostic Factors in Endometrial Cancer

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A B S T R A C T

The aim of this research was to determine the VEGF A expression in tumor cells and the intratumoral microvessel density and their prognostic significance in the survival of the subjects. 87 subjects were monitored retrospectively for a period of 60 to 132 months. The subjects were treated at the Department of Obstetrics and Gynecology of Osijek University Hospital Center, Croatia. We analysed standard clinical, pathohistological and therapeutical prognostic factors, intratumoral microvessel density and expression of VEGF A. Five-year survival was calculated by the life chart method and presented graphically by Kaplan-Meier curves. Reaching conclusions on statistical hypotheses in this paper was done with a reliability level $p<0.05$. Of the analyzed clinical prognostic factors, those which proved to be statistically significant and independent prognostic factors were age and clinical stage of the disease, and of pathohistologic ones it was the depth of myometrial invasion and VEGF expression. An elevated VEGF expression is associated with deep myometrial invasion, poorly differentiated tumors, histologic type and intratumoral microvessel density to a statistically significant degree. Elevated VEGF expression, age, FIGO stage and depth of myometrial invasion play a significant prognostic role in patients with endometrial cancer. VEGF receptors could be a target for adjuvant therapy in VEGF positive endometrial cancer.

Key words: *angiogenesis, endometrial cancer, prognostic significance, VEGF*

Introduction

In the human endometrium angiogenesis occurs periodically as a part of the cyclic growth during the menstrual cycle[1]. The angiognenesis initiation phase is a result of the activation of vascular cells and the activation of growth factors which accelerate angiogenesis, including the basic fibroblast growth factor (bFGF), the vascular endothelial growth factor (VEGF), the platelet-derived endothelial cell growth factor (PDECGF) and the tumor necrosis factor alpha (TNFα)[2]. These citokyne and other angiogenic molecules can be released by inflammatory cells, mastocytes, macrophagi and various tumor cells[3]. Once activated, the endothelial cells start proliferating and migrating, which results in tube formation and blood flow[4]. Tumors larger than 1–2 mm^3 require adequate blood support for their growth[5]. Progressive tumor growth is angiogenesis-dependent. Many human tumors can persist in an *in situ* form for a long period of time (months and years) in an avascular quiet state. In this state the tumor may have up to several million cells. When a part of the cells changes angiogenic phenotype, a change of balance occurs between the positive and the negative angiogenesis regulators, the tumor begins to grow rapidly and it becomes clinically detectable. Stimulated by angiogenic molecules, endothelial cells produce proteins as growth and survival factors for the tumor cells[6]. Findings showing a VEGF which is pronounced, spread and specific to vascular endothelial cells lead to a hypothesis that these molecules can play a unique role in

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regulating physiological and pathological blood vessel growth[7]. VEGF-A transcription is emphasized as a response to hypoxia and activated oncogenes[8]. A correlation between the VEGF expression and microvascular density in primary breast and gastric cancer preparations was noticed[9,10]. Intratumoral microvessel density (IMD) is the measure of the overall effect of the angiogenesis factor[11]. Many studies have shown the association of IMD with the VEGF expression in the early stage of breast cancer[12], where a multivariation analysis showed IMD an independent prognostic factor in recurrence-free survival time. The work of Kirschner and his associates has showed that angiogenic factors correlate with survival when it comes to endometrial cancer. Patients with low intratumoral microvessel density had an average survival time of 123 months, whereas patients with a high microvessel density had 75 months[13]. In a study on cervical carcinoma it was demonstrated that the cellular type also plays a role in the level of secretion of angiogenic molecules[14]. Most authors agree that angiogenetic factors, primarilly VEGF and intratumoral microvessel density as an expression of overall angiogenetic activity, play a significant role in evaluating the course of disease, the malignant potential of the tumor and the prognosis in patients suffering from endometrial cancer and other malignoma.

Materials and Methods

Subject

The examination included 87 subjects treated with primary surgery as a result of endometrial cancer at the Department of Obstetrics and Gynecology of the Osijek University Hospital Centre, Croatia. Depending on their clinical stage, some of the subjects underwent adjuvant radiation therapy, chemotherapy or hormonal treatment. The subjects were monitored for a period of 60 to 132 months, and the monitoring ceased as a result of death by primary or other desease or as a result of the end of research.

Methods

We showed the clinical-pathologic prognostic indicators and method of treatment in all patients.

I. *Clinical indicators*

1. age
2. menopausal status
3. clinical stage.

The clinical stage was defined by surgico-pathological criteria, but is necessary to mention that at the time of our patients treatment lymphadenectomy was not being applied. Therefore, this indicator is not listed in the analysis, nor in the surgico-pathological staging.

II. *Pathohistologic and cytological indicators*

1. histologic type
2. histologic grade
3. depth of myometrial invasion
4. limphovascular space involvement
5. presence of atypical endometrial hyperplasia
6. presence of malignant cells in peritoneal washing
7. intratumoral microvessel density
8. VEGF A expression in tumor cells.

Measuring pathohistologic indicators

For a presentation of pathohistologic indicators an analysis of archival pathohistologic material was done by routine methods, according to the criteria accepted by World Healt organization (WHO), International Society of Gynecological Pathologists (ISGYP) and International Federation of Gynecology and Obstetrics (FIGO)[15–18]. By analysis of the significance of histologic type for prognosis we simply divided the tumors in two groups; those with a favourable prognosis, where we grouped the endometrioid, viloglandular, secretory, adenoacanthoma and mucinous tumor type, and those with a unfavourable prognosis, where we grouped the adenosquamous, clear cell and mixed tumor type.

Determining the density of intratumoral microvessels was done by applying the immunohistochemical method. Tumor tissue fixed by standard techniques and embedded in parafin was used. The primary antibody was the mouse monoclonal antibody M 3527 for CD-105 (endoglin) (DAKO, Kopenhagen**,** Denmark) in a dilution of 1:50. The location of binding of the primary antibody was visualized by the LSAB (labelled streptavidin-biotin) technique (DAKO, Kopenhagen, Denmark). Quantitative measuring of intratumoral microvessel density was done by determining the vascular hot spots. The vascular hot spots were localized at low magnification (10 X). That was followed by counting blood vessels on a high power field (200 X) and expressed as a median of the number of blood vessels in five high power fields (HPF). The analysis was done according to the international concensus of quantification of angiogenesis in solid human tumors[11]. Resuslts were analysed on the basis of our own cut-off value for the number of microvessels. This cut-off value divides tumors into two groups: the ones with favourable and the ones with unfavourable prognosis.

Determining VEGF A expression in tumor cells was done by application of the immunohistochemical method. The primary antibody was a commercial rabbit polyclonal anti-VEGF antibody (sc-152, Santa Cruz Biotechnology, USA), intended for the detection of 165, 189 and 121 amino acid isoform of VEGF A, in a dilution of 1:100. 2 μg were applied *per* preparation. Immunohistochemical staining was performed by biotinisated secondary antibodies, a procedure of streptavidin marked by horseradish peroxidase (HRP), followed by AEC (aminoethil-carbasol) chromogene (DAKO, Kopenhagen, Denmark), which gives a red-brow coloration. The intensity of the red-brown coloration development in the tumoral cell, as a measure of VEGF expression is proportional to the amount of the antibody bound to the antigenes. The intensity of coloration is determined in two levels: 1-negative – when the intensity of the color is either weaker or equal in comparison with the nearby non-neoplastic en-

dometrial gland of the same pathohistologic preparation, 2-positive – when the intensity of the color is stronger in comparison with the »healthy gland«. All preparations were evaluated by two independent investigators,and disagreements were solved with a consensus.

III. *Method of postoperative treatment*

1. adjuvant radiotherapy
   a) pelvic radiation
   b) brachytherapy
   c) combination of pelvic radiation and brachytherapy
2. chemotherapy
3. hormonal therapy.

Criteria for adjuvant therapy were astablished according to surgico-pathological staging, with no insight in lymphonodi status. Hormonal therapy and chemotherapy were often applied as an opportunistic systemic treatment in infaust patients with an advanced clinical stage of the disease.

Statistical methods

Five-year survival is calculated by the life chart method and graphically presented by Kaplan-Meier curves. Statistical indicators of the survival analysis are based on a log normal distribution of data. Univariate analysis was performed by means of a t-test. A simultaneuous effect of all indicators on the survival prognosis was analyzed by the multivariation regression method on incomplete data, the so called Cox regression test. An χ^2-test was used to determine the association of VEGF expression and intratumoral microvessel density with histologic chracteristics. The cut off for the number of blood vessels *per* unit and for age, which best differentiate the life expectancy, were found as the value of the maximum χ^2-test, by means of the proportional risk regression method. Reaching conclusions on statistical hypotheses in this paper was done with a significance level $p<0.05$ for all the tests applied.

Results

In the monitored period 24 subjects out of 87 (27.6%) died. The overall survival rate in endometrial cancer was 72.4%. Most of the patients die within two years of diagnosing.

Clinical indicators

The clinical indicators analyzed were age, menopausal status and clinical stage (Table 1). The average age of patients included in the study was 64 (range 36–82 years of age). The cut off age which best differentiates life expectancy was 65. In the univariate and multivariate analysis age and clinical stage are statistically significant factors, and menopausal status is not.

Pathohistologic indicators

Histologic grade, deep of myometrial invasion, positive peritoneal cytology and the expression of VEGF are statistically significant patohistological prognostic factors in univariate analysis, and in multivariate analysis deep od myometrial invasion and VEGF expression (Table 2).

Intratumoral microvessel density (IMD)

The average number of intratumoral blood vessels was 22.4 (range of 9.8 to 42.6). The average number of blood vessels in a tumor-unaffected (healthy) endometrium was 13.8 (range 4.0 to 32.0). Our own cut off value was 31 microvessels. According to that criterium 86.2% of tumors were poorly vascularisated and 13.8% was well vascularisated. Tumors with a higher microvessel density had a worse prognosis and their five-year survival rate was less than 60%, and in the group with lower microvessel density it was about 75%. This difference in survival is not statistically significant.

VEGF expression in tumor cells

In the immunohistochemical analysis 50.5% of the tumors were VEGF positive, and 49.5% VEGF negative. The median survival time in the group of VEGF positive

TABLE 1
CLINICAL PROGNOSTIC FACTORS

Clinical prognostic factors	Subjects		Five-year survival rate (%)	p-value	
	Number (n)	%		Univ.	Multiv.
Age				0.005	0.026
<65	46	52.8	84.8		
≥65	41	47.2	58.5		
Menopausal status				NS	NS
premonepausal	9	10.3	77.8		
postmenopausal	78	89.7	71.8		
Clinical stage				<0.00001	0.052
I stage	73	83.9	80.8		
other stage	14	16.1	28.6		

TABLE 2
PATOHISTOLOGICAL PROGNOSTIC FACTORS

Pathohistological prognostic factors	Subjects		Five-year survival rate (%)	p-value	
	Number (n)	%		Univ.	Multiv.
Histologic type					
type 1	74	85.1	71.6	NS	NS
type 2	13	14.9	76.9		
Grade					
G1	26	29.9	76.9	0.014	NS
G2	45	51.8	77.8		
G3	16	18.3	50.0		
Depth of myometrial invasion					
none invasion	3	3.4	100.0	<0.0001	0.017
≤1/2	54	62.1	85.2		
>1/2	30	34.5	46.7		
LVS involvement					
none	75	86.2	70.7	NS	NS
with	12	13.8	83.3		
Peritoneal cytology					
positive	7	8.0	28.6	0.0006	NS
negative	54	62.1	79.7		
not done	26	29.9	69.2		
IMD					
<31	75	86.2	74.7	NS	NS
≥31	12	13.8	58.3		
VEGF					
positive	44	50.5	63.4	0.015	0.049
negative	43	49.5	83.7		

NS – not significant

tumors was 82 months, and in the VEGF negative group it was 118 months. VEGF positive tumors expresed a statistically significant unfavourable survival rate (Figure 1). There was an additional analysis of the association between VEGF expression and other unfavourable pathohistologic prognostic factors. On the multivariate analysis VEGF expression proved to be an independent prognostic factor in endometrial cancer.

VEGF and the depth of myometrial invasion

Prognosis of the tumor with the depth of invasion of more than half the myometrial depth depends on VEGF expression to a statistically significant degree (Table 3). If the VEGF is positive, five year survival rate is less than 30%, unlike in those with deep invasion, but without an elevated VEGF expression, in which the ten year

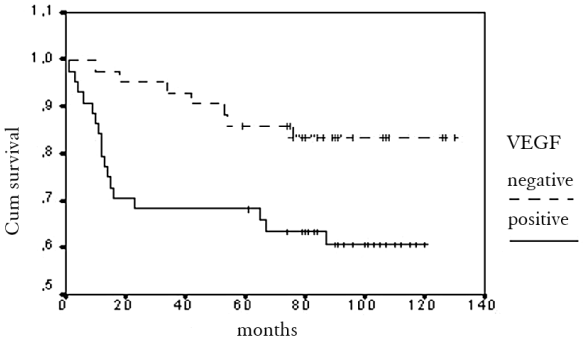

Fig. 1. Kaplan-Meier curves for overall survival according to VEGF expression.

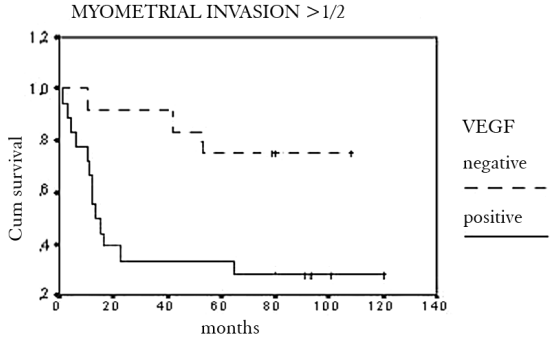

Fig. 2. Kaplan-Meier curves for overall survival according to VEGF expression when myometrial invasion is >½.

TABLE 3
DEPTH OF MYOMETRIAL INVASION, HISTOLOGIC GRADE, LYMPHVASCULAR SPACE INVOLVEMENT, INTRATUMORAL MICROVESSEL DENSITY AND VEGF EXPRESSION RELATION

Prognostic factor	VEGF negative		VEGF positive		p-value
	n (%)	Five-year survival rate (%)	n (%)	Five-year survival rate (%)	
Myometrial invasion					
none	1 (1.1%)	100.0	2 (2.2%)	100.0	NS
≤1/2	30 (34.6%)	86.7	24 (27.6%)	83.3	NS
>1/2	12 (13.8%)	75.0	18 (20.7%)	27.8	0.008
Histologic grade					
G 1	13 (14.9%)	92.3	13 (14.9%)	61.5	NS
G 2	23 (26.5%)	78.2	22 (25.3%)	77.2	NS
G 3	7 (8.0%)	85.7	9 (10.3%)	22.2	0.007
LVS involvement					
no	37 (42.5%)	81.1	38 (43.7%)	60.5	0.039
yes	6 (6.9%)	100.0	6 (6.9%)	66.7	NS
IMD					
<31	37 (42.5%)	85.6	38 (43.7%)	67.5	NS
≥31	5 (5.8%)	83.3	7 (8.0%)	28.6	0.033

NS – not significant

survival rate is 75%. This difference is statistically significant (Figure 2).

VEGF and the histologic grade

Poorly differentiated tumors with an elevated VEGF expression have an extremely negative prognosis and the five-year survival rate is 22.2 % (Table 3). If a poorly differentiated tumor does not have an elevated VEGF expression, the five-year survival rate is 85%. This difference in survival is statistically significant (Figure 3).

VEGF and intratumoral microvessel density

According to microvessel density the tumors are divided on the basis of the cut-off value criterion. From Table 3 it is visible that tumors with an elevated VEGF expression have a worse survival rate, regardless of the intratumoral microvessel density, however it is particularly expressed in the group of subjects with microvessel density ≥31 and it amounts to merely 28.6%. If a well vascularised tumor does not have an elevated VEGF expression, the overall survival is 83.3% (Figure 4). This difference in survival is statistically significant, and this group of subjects represents a high-risk group for a negative outcome.

Method of postoperative treatment

In 93.1% of subjects one or more adjuvant therapeutic procedures were carried out. Subjects with whom brachytherapy was carried out had the most favourable five-year survival (88.0%). Subjects with whom no radiaion therapy was carried out at all had the most unfaourable five-year survival (40.0%). In univariation analysis chemotherapy and hormonal therapy were not statistically significant. Adjuvant therapy in the multivariate analysis was not a significant prognostic factor.

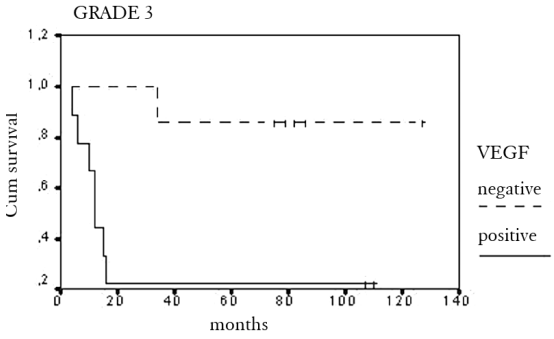

Fig. 3. Kaplan-Meier curves for overall survival according to VEGF expression with poorly differentiated tumors (G3).

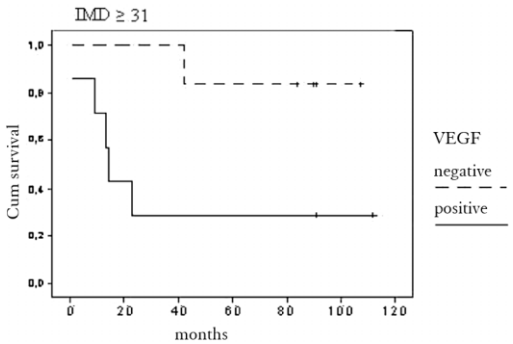

Fig. 4. Kaplan-Meier curves for overall survival with well vascularisated tumors according to VEGF expression.

Discussion

Endometrial adenocarcinoma is the most common malignant tumor of the female reproductive system in Croatia. Generally speaking, given its relatively early diagnosing, this tumor can be categorized as a gynecologic tumor with a positive prognosis. However, about 35% patients who die of this deasease belong to the group of patients diagnosed in the first stage. Therefore it is important to determine the key risk factors based on which the patients can be categorized as high-risk or low-risk group, and modify the therapy approach, the treatment and monitoring extensity accordingly**.**

It was to be expected that the intratumoral microvessel density was associated with the outcome and the survival. Angiogenic molecules of the tumor tissue activated the creation of a higher number of blood vessels in comparison to a healthy endometrium (22.4:13.8). According to the cut off number of microvessels (31) 86.2% of the tumor was poorly, and 13.8% was well vascularisated. Subjects who had tumor with a microvessel density of 31 and higher had a 20% worse five-year survival, however this difference showed no statistical significance. A similar result was reached by a number of other authors[13,19]. This kind of result can in part be attributed to insufficient objectivity and imperfection of the model of solid tumor angiogenesis quantification. Nevertheless, most authors agree that intratumoral microvessel density has prognostic significance, and in some cases it is an independent prognostic factor, also[20].

Out of the total number of immunohistochemically treated tumors, 50.5% of them exhibited an elevated VEGF expression. The average five-year survival rate in the group of subjects with an elevated VEGF expression amounted to 60%, wheareas in the group with negative expression it was about 85%, which means that subjects with VEGF positive tumors have statistically significant unfavourable five-year survival. In the univariate analysis VEGF proved to be a significant prognostic factor. Results similar to these were published by some other authors as well[20]. Some of the authors found no association between elevated VEGF expression and a negative outcome[21,22] or found no elevated VEGF expression in the tumor compared to healthy tissue[23]. In tumors which invade more than half of the myometrium there is a statistically significant difference in survival if there is an elevated VEGF expression present. The five-year survival rate in this group is below 30%. Results of this kind are reported by some other authors as well[24]. By comparing the role of tumor differentiation and VEGF expression, we found, like other authors[25], that an extremely negative prognosis results from poorly differentiated tumors (G3) if they have a positive VEGF expression. Of all the combinations analyzed this one represents the worst when it comes to survival. Statistically significant is also the difference in survival between the predictably histologically more favourable tumor types with poor and elevated VEGF expression. The former group has a standard survival rate of 85%, and the latter below 60%. When we analyzed the association between the VEGF expression and intratumoral microvessel density, we found that the VEGF expression changes the prognosis in well vascularisated tumors with microvessel density ≥31 to a statistically significant degree. This group of subjects represents a group with a high-risk of a negative outcome, because more than half the patients with a combination of these two risk factors die within two years of diagnosing.

Generally speaking, we can point out that VEGF expression is a significant prognostic factor in a univariate analysis, and that in a multivariate analysis it is an independent prognostic factor in endometrial cancer. It is significantly associated to deep myometrial invasion, poorly differentiated tumors, histologic tumor type and higher intratumoral microvessel density. In correlation with all the prognostic factors, elevated VEGF expression can bring a negative prognosis. Special notice can be made to a group of well vascularisated (≥31 microvessels) and poorly differentiated tumors, and of those with a deep myometrial invasion, with an elevated VEGF expression. The prognosis in these tumors is extremely poor and requires special attention upon determining the extensity of the treatment. This leads us to the conclusion that the use of VEGF receptor inhibitors in these high-risk groups would be justified as a new form of ajduvant therapy.

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VASKULARNI ENDOTELNI ČIMBENIK RASTA I GUSTOĆA TUMORSKIH KAPILARA KAO PROGNOSTIČKI ČIMBENICI U ENDOMETRIJSKOM RAKU

S A Ž E T A K

Cilj ovog istraživanja bio je odrediti genski izražaj VEGF A u tumorskim stanicama i vrijednosti tumorske gustoće kapilara i njihov prognostički značaj za preživljenje ispitanica. Retrospektivno je kroz period od 60 do 132 mjeseca praćeno 87 ispitanica, liječenih u Odjelu za ginekologiju i porodništvo Kliničke bolnice Osijek, Hrvatska. Analizirali smo standardne kliničke, patohistološke i terapijske prognostičke čimbenike, gustoću tumorskih kapilara i izražaj VEGF A. Vjerojatnost preživljenja računali smo metodom životnih tablica i prikazali je grafički Kaplan-Meierovim krivuljama. Zaključivanje o statističkim hipotezama u ovom je radu provedeno uz razinu sigurnosti $p<0,05$. Od analiziranih kliničkih prognostičkih čimbenika statistički značajnim i neovisnim prognostičkim čimbenicima pokazali su se dob i klinički stadij bolesti, a od patohistoloških, dubina miometrijske invazije i izražaj VEGF-a. Povišen izražaj VEGF-a statistički je značajno povezan s dubokom miometrijskom invazijom, slabo diferenciranim tumorima, histološkim tipom tumora i gustoćom tumorskih kapilara. Povećan genski izražaj VEGF-a, dob, FIGO stadij i dubina miometrijske invazije imaju značajnu prognostičku ulogu u bolesnica s endometrijskim rakom. VEGF receptori bi mogli biti meta adjuvantne terapije u VEGF pozitivnim karcinomima endometrija.