The Study of the Correlation Between Doppler Indices of Intratumoral Blood Flow and CD-31 in Malignant Ovarian Tumors of Epithelial Origin

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The correlation among quantitative indices (VI-vascular index, PI-pulsatility index, RI- resistive index, VFI-vascular flow indices) of dopplerometry with CD-31 in malignant ovarian tumors was studied. ROC examination of quantitative indices of doplerometry was also performed in malignant ovarian tumors. As a result of the research a positive correlation relationship between dopplerometric indices of blood flow and CD-31 was esdtablished. It was found that increases in dopplerometric indices occur in accordance with CD-31 depending on the degree of malignancy.

Keywords: Ovarian cancer, CD-31, dopplerography, neongiogenesis

INTRODUCTION

The growth and metastasis of cancer cells is based on angiogenesis - forming and growth of new blood vessels. The formation of microvascular net is important for providing tumor metabolism (Morgan et al., 2007). Creation of new microveins occurs through vasculogenesis, intussuseptive angiogenesis and neangiogenesis. The last mechanism plays a crucial role in this process.

Migration of perisits from basal membranes of capillaries, degradation of extracellular matrix around capillaries, migration of endothelial cells, formation of tube-like structures and at last formation of anastomoses with neighboring veins occur during neangiogenesis (Carmeliet, 2005; Emoto et. al., 2006). Thus, neangiogenesis provides growth and metastasis of tumor.

The study of angiogenesis in practical oncomorphology allowed getting information on the relapses, formation of metastasis, and course of the oncological disease depending on the degree of the development of vessels (Folkman and Klagsburn, 2007). For this purpose CD-31 prognostic factor, which does not depend on the other characteristic features of tumor, is determined in the histological preparation.

Color dopplerographic imaging is considered to be a promising opportunity of ultrasonic examination in the differential diagnostics of the malignant and benign ovarian tumors. Dopplerography allows visualizing tumor blood vessels, including capillaries. High opportunities of the method allow visualizing and identifying even the tiniest blood vessels of the microcirculatory system, which cannot be detected when scanning in the regime B. Twisted, abnormally shaped vessels more characteristic for malignant tumors can be identified by dopplerography (Ivashina et al., 2012; Fedorova and Lipman, 2012).

Recently, ROC (Receiver Operating Characteristic) analysis has been used for checking the efficiency of the laboratory examination. ROC is considered as a common denominator between the sensitivity and specificity of the examination. ROC allows objectively assessing the diagnostic significance of laboratory tests.

This method can be used for evaluating the tests diagnosing various diseases. ROC allows defining individual criteria for interpreters used in the evaluation of the tests. We can assess the quality of the test according to the deviation of test criterion line from the average line. If the curve of the examined criterion is higher than the average line, then an increase of this parmeter has a diagnostic importance and if the curve is lower then a decrease of this parameter has a diagnostic importance.

MATERIALS AND METHODS

Data of the examination of 123 patients diagnozed with malignant ovarian tumors and treated at the Oncological Clinic of the Azerbaijan Medical University during 2008-2015 years have been used in the presented research. The final diagnosis was verified at the laboratory of Patomorphology of Oncological Clinic of AMU. The researches were performed after cytological and histological verification, patients were systematized, the clinical picture of the disease was clarified, and the clinical phases of the process were determined after the summariza-

tion of the results of laboratory instrumental analyses of the patients. According to the research plan all the patients were subjected to ultrasound examination. The examination was carried out through transabdominal and transvaginal sensors at 3.5-5 MHz using the Ultrasound Scanner ALOKA SSD-4000. DAKO ((France) CD 31, Endothelial Cell, clone JC 70A, isotype: Lg GI, kappa 0.2/1ml) reagents were used for histological examinations. Cryostat sections prepared from a material frozen in liquid nitrogen and fixed in acetone and paraffin blocks fixed in a 10% formalin solution were used for the immunohistochemical examination. The results were analyzed using modern statistic methods.

RESULTS AND DISCUSSION

We have revealed that an increase in CD-31 concentration in epithelial ovarian tumors indicates the malignancy. Color doppler examination showed that, the systolic velocity of the blood circulation was higher in malignant tumors compared to the benign tumors and the resistance of the intratumor blood circulation was lower. Low peripheral vascular resistance in malignant tumors is associated with a sharp increase in the diameter of the arterial vessels. Malignant ovarian tumors are also synthesized by angiogenic factors, which cause the formation of new vessels and further progression of tumors. Histological structure and density of blood vessels are different in diseased and healthy ovary, and this influences on the type of tumor blood circulation.

Using Spirmen's correlation analysis we detected correlation relationship between dopplerometric indices of intratumoral blood flow and CD-31 (Table 1). Thus, high expression of CD-31 corresponds to high values of FI. In this case correlation index $r=0.463$, and $p<0.001$ (Figure 1). A strong correlation relationship was observed between VI and CD-31. Correlation coefficient $\rho=0.658$ ($p<0.01$) (Figure 2).
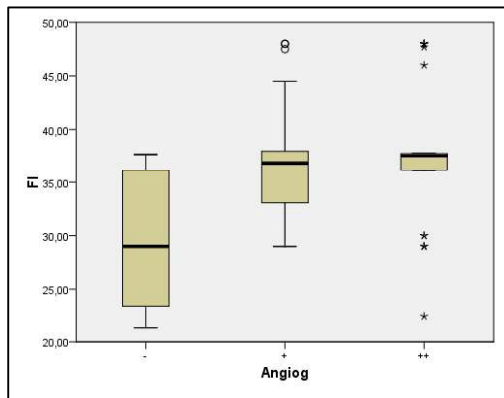
There is also a strong correlation relationship between VFI and CD-31. In this case $\rho=0.463$ ($p<0.01$) (Figure 3).

No relationship was found between PI index and CD 31: $\rho=0.006$ ($p=0.938$) (Figure 4).

Table 1. Correlational relationship between dopplerometric indices of intratumoral blood flow and CD-31 indices

			FI	VFI	RI	PI	CD-31
ρ-Spearman test	VI	*P*	0.874**	0.758**	-0.193*	0.121	0.658**
		P	0.000	0.000	0.045	0.210	0.000
	FI	*P*	1.000	0.861**	-.0273**	0.100	0.463**
		P	.	0.000	0.004	0.300	0.000
	VFI	*P*	0.861**	1.000	-0.302**	0.157	0.385**
		P	0.000	.	0.001	0.103	0.001
	RI	*P*	-.273**	-0.302**	1.000	-0.019	-0.051
		P	0.004	0.001	.	0.844	0.675
	PI	*P*	0.100	0.157	-0.019	1.000	0.006
		P	0.300	0.103	0.844	.	0.958
	CD-31	*P*	0.463**	0.385**	-0.051	0.006	1.000
		P	0.000	0.001	0.675	0.958	.

Note: statistical confidence of ρ-correlation coefficient using bivariate criterion; * – p < 0.05; ** – p < 0.01
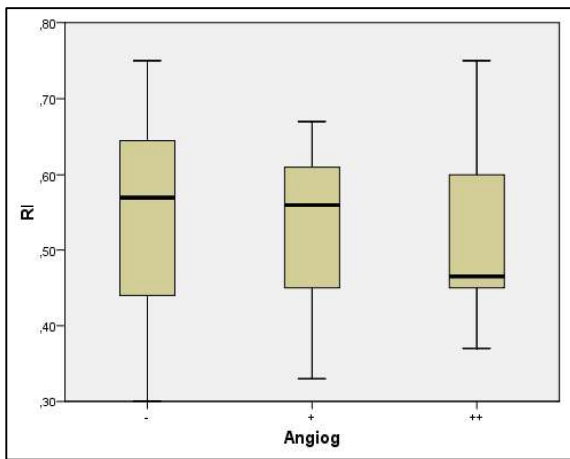

Figure 1. Correlation relationship between FI index and CD-31.
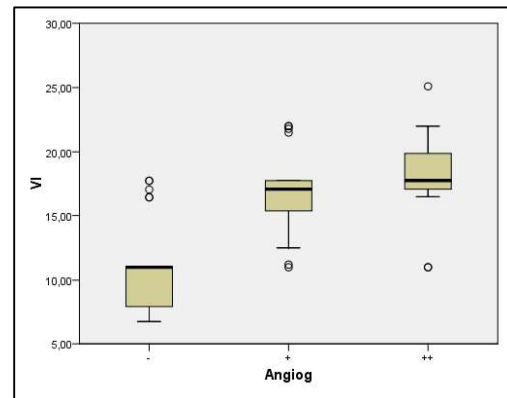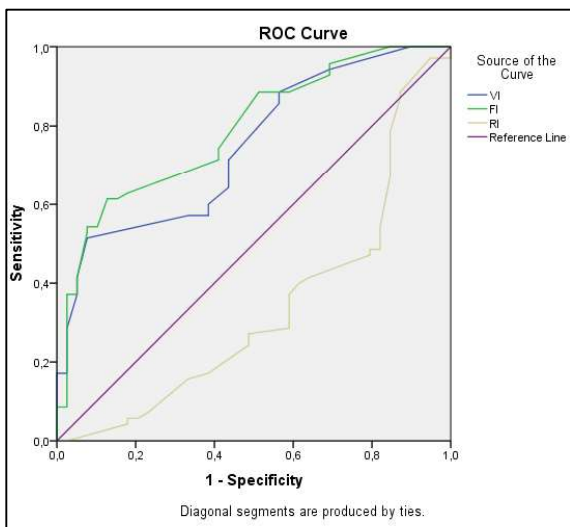

Figure 2. Correlation relationship between VI index and CD-31.
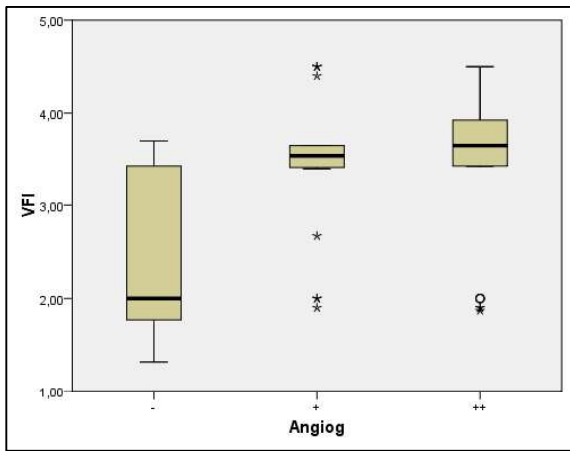
Figure 3. Correlation relationship between VFI index and CD-31.

Figure 4. There is no correlation relationship between RI index and CD-31.

Figure 5. Results of ROS analysis

Test Result Variable(s)	Area	Std. Error	Asymptotic Sig. (p)	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
Septa thickness	0.748	0.054	0.000	0.642	0.853
VI	0.761	0.056	0.000	0.651	0.872
FI	0.798	0.054	0.000	0.693	0.903
VFI	0.736	0.069	0.001	0.601	0.872
RI	0.374	0.076	0.070	0.225	0.522
PI	0.460	0.076	0.566	0.311	0.609
PSVcm³	0.641	0.076	0.043	0.492	0.790

Figure 5 shows ROS curves of dopplerometric indices of intratumoral blood flow in malignant ovarian tumors of epithelial origin

ROC curves of dopplerometric indices in malignant epithelial ovarian tumors indicate that dopplerography is of great importance in diagnosis of this disease.

Thus, we have established a positive correlation relationship between dopplerometric indices of blood flow and CD-31. It has been found that increases in dopplerometric indices occur in accordance with CD-31 depending on the degree of malignancy. Thus, high dopplerometric indices of blood flow determine the malignancy of the tumor mass.

Because of the positive correlation between CD-31 and dopplerographic indices, it is possible to determine the characteristics of tumor vasculization using non-invasive method. Thus, the characteristics of tumor can be determined prior to surgery. This is particularly important for the correct selection of treatment tactics and surgery volume. Moreover, based on the doppler examination of malignant ovarian tumors and dopplerometric indices of the blood, the necessity of the administration of antiangiogenic preparations to the patients can be elucidated.

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Bədxassəli Epitel Mənşəli Yumurtalıq Şişlərində Şişdaxili Qan Axınının Doplerometrik Göstəriciləri ilə CD-31 Arasında Korrelyasiyanın Öyrənilməsi

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Bəd xassəli yumurtalıq şişində CD-31 ilə doplerometriyanın kəmiyyət göstəriciləri (VI - vaskulyar index, PI – pulsasion indeks, RI – rezistentlik indeksi, VFI – vaskulyar axın indeksi) arasında korrelyasiya öyrənilmişdir. Həmçinin bədxassəli yumurtalıq şişlərində doplerometriyanın kəmiyyət göstəricilərinin ROC müayinəsi aparılmışdır. Beləliklə, tədqiqat işinin nəticəsində qanaxınının dopplerometrik göstəriciləri ilə CD-31 arasında müsbət korrelyasiya əlaqəsi olduğu müəyyən edilmişdir. Məlum olmuşdur ki, şişin bədləşmə dərəcəsindən asılı olaraq CD-31-ə müvafiq olaraq doplerometrik göstəricilərdə də artma baş verir.

Açar sözlər: Yumurtalıq xərçəngi, CD-31, doppleroqrafiya, neoangiogenez

Изучение Корреляции Между Допплеровыми Индексами Внутриутробного Кровотока и CD-31 При Злокачественных Опухолях Яичников Эпителиального Происхождения

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Изучена корреляция между количественными показателями (индекс сосудистой системы, индекс пульсативности, индекс резистентности, индексы сосудистого потока) допплерометрии и CD-31 при злокачественных опухолях яичников. Также проводилось ROC исследование количественных показателей доплерометрии при злокачественных опухолях яичников. В результате исследования была установлена положительная корреляционная связь между допплерометрическими показателями кровотока и CD-31. Было обнаружено, что увеличение допплерометрических показателей происходит в соответствии с CD-31 в зависимости от степени злокачественности.

Ключевые слова: Рак яичников, CD-31, допплерография, неангиогенез