Research Article

Endoglin Expression (CD105) in Ephithelial Ovarian Cancer

Ekspresi Endoglin (CD105) pada Kanker Ovarium Tipe Epitelial

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Abstract

Objective: To address the endoglin expression (CD105) in the primary tumour and metastases tumour (omentum) and their relation with clinicopathological factors: stadium, differentiation level, and histological epithelial ovarian cancer.

Methods: The research was performed at Public Service Hall of Dr. Wahidin Sudirohusodo Hospital and educational networking hospital of Obstetrics and Gynecology Department of Faculty of Medicine Universitas Hasanuddin. The research design is cross-sectional with 55 samples consisting of 55 samples of primary tumours and 55 metastatic tumours. Imunohistochemistry examination was performed on all samples.

Results: The results show a significant relation between endoglin (CD105) at omentum metastases tumour and stadium and cell differentiation level of epithelial ovarian cancer. There is no significant relation between endoglin (CD105) expression at primary tumour of ovarian cancer and stadium and differentiation and type of histopathological cell. In addition, there is no significant relation between endoglin expression (CD105) in omentum metastases tumour and type of histopathological cell of ovarian cancer. There is a significant correlation (strong category) between endoglin expression at omentum metastases tumour and endoglin expression at primary tumour of epithelial ovarian cancer.

Conclusion: Endoglin expression in ovarian cancer metastatic tumour to omentum is correlated with clinical stage and differentiation level of ovarian cancer. And endoglin is one of the proangiogenic and prometastatic factors.

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Keywords: CD105, endoglin expression, epithelial ovarian cancer, immunohistochemistry

Abstrak

***Tujuan**: Mengetahui ekspresi endoglin (CD105) pada tumor primer dan tumor metastases (omentum) serta hubungannya dengan faktor klinikopatologik: stadium, derajat diferensiasi, dan jenis histopatologi kanker ovarium tipe epitel.*

***Metode**: Penelitian ini menggunakan rancangan potong lintang. Penelitian dilaksanakan di BLU RS Dr. Wahidin Sudirohusodo dan RS jejaring pendidikan Departemen Obstetri dan Ginekologi Fakultas Kedokteran Universitas Hasanuddin Makassar. Sampel penelitian sebanyak 55 orang dengan rincian masing-masing 55 sampel untuk kelompok tumor primer dan 55 kelompok tumor metastases omentum. Pemeriksaan imunohistokimia dilakukan terhadap semua sampel.*

***Hasil**: Hasil penelitian menunjukkan terdapat hubungan bermakna antara ekspresi endoglin (CD105) pada tumor metastases omentum dengan stadium dan derajat diferensiasi sel kanker ovarium epitelial. Tidak didapatkan hubungan bermakna antara ekspresi endoglin (CD105) pada tumor primer kanker ovarium dengan stadium, derajat diferensiasi dan jenis histopatologi sel. Juga tidak didapatkan hubungan bermakna antara ekspresi endogin (CD105) pada tumor metastases omentum dengan tipe histopatologi sel kanker ovarium. Terdapat korelasi yang signifikan (kategori kuat) antara ekspresi endoglin pada tumor metastases omentum dan ekspresi endoglin pada tumor primer kanker ovarium tipe epitelial.*

***Kesimpulan**: Ekspresi endoglin pada tumor metastases omentum kanker ovarium berhubungan dengan stadium klinis dan derajat diferensiasi sel pada kasus kanker ovarium. Selain itu, endoglin juga merupakan faktor proangiogenik dan prometastases.*

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***Kata kunci**: CD105, ekspresi endoglin, imunohistokimia, kanker ovarium epitelial*

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INTRODUCTION

Ovarian cancer is the fifth leading cause of death worldwide and is the most deadly cancer among all gynecology cancer. Annually, there are 204.000 women diagnosed with ovarian cancer, and 125.000 women died of the disease worldwide.[1]

The risk of ovarian cancer occurrence in women is 1 : 70, and is related to the age of the patients, which is approximately 61 years old. Eighty-five to ninety percent of diagnosed ovarian cancer is known as the epithelial type of ovarian cancer. Hereditary factor is the major risk factor for the disease, especially the presence of ovarian cancer history in the family. Approximately 5-10% of ovarian cancer cases were suspected inherited, while the remaining 90-95% are related to continuous ovulation cycle.[1]

Ovarian cancer is a very challenging clinical situation because initially, the disease does not provoke any symptom. Thus, more than two-third

of the cases are diagnosed in its late stage, where cancer has been spread outside the ovary or even widely metastasized.[2] Although nowadays, the aetiology of the disease is better understood, the presence of aggressive cytoreductive surgery and more combined modern chemotherapy, there is no significant statistical mortality rate decrease in the last 30 years.

In the last few years, the understanding of molecular biology, especially regarding angiogenesis in ovarian cancer, is improving, leading to the finding of some new therapeutic target and molecular prognostic factor. Hence, this triggers the development of some more radical therapy of ovarian cancer. Some factors that involve in angiogenesis are keys to better understand the mechanism and management of ovarian cancer. One of the factors is Endoglin (CD105).

Endoglin (CD105) is the glycoprotein membrane which is included in zona pellucida protein group. Endoglin is expressed strongly in proliferated vascular endothelial cells and has been identified as an accessory receptor for transforming growth factor-β (TGF-β). The endoglin gene in human is located on chromosome 9q34ter.[3]

The main role of endoglin is regulating the TGF-β-dependent vascular remodelling and angiogenesis. The signal produced by the TGF-β might induce various process, including proliferation, migration, and adhesion. TGF-β is expressed in endothelial cells of the embryo, infected tissue, healing tissue, inflamed arthritis synovial, and solid tumour. Currently, endoglin is suggested as the marker of neovascularization in solid tumours.[4]

In the studies of fertility, endocrinology, and reproduction, especially endometriosis, the role of endoglin has been improved, compared with its role in the cases of ovarian malignancies. The serum endoglin level was identified as a predictor factor of endometriosis, with the threshold of ≥ 11 ng/ml for endometriosis cases and <11 ng/ml for non-endometriosis cases.[5]

The role of endoglin in the spreading process of cancer has been discussed in several previous studies. In the study of gastric cancer, found a correlation of increased VEGF with endoglin expression in tumours metastasized to the lymph node, and suggested it as an important prognostic indicator. Similar result was found by, indicated a correlation of VEGF and endoglin expression in the cases of prostate cancer, and suggested that the increase of both VEGF and endoglin expression is associated with the low survival rate. In breast cancer, endoglin assessment has a higher specificity to assess the neovascularization compared with other pan-endothelial markers, such as CD31, CD34, and Von Willebrand Factor (vWF).[6,7]

The suppression of endoglin regulation may trigger apoptosis, induce significant DNA destruction by modulating some DNA restoration gene, increase the sensitivity of platinum, both in vivo and in vitro, and become a specific therapeutic target in epithelial ovarian cancer.[8]

Endoglin expression is frequently found in ovarian cancer effusion, both in the tumour cells and the reactive mesothelial cells. The extent of endoglin expression is correlated to the chemotherapy state, and endoglin expression is found higher in solid metastatic tumour than that in effusion.[9]

The role of endoglin in ovarian cancer has not been reported in a considerable number compared with that in other malignancies, such as gastric cancer, prostate cancer, and breast cancer. Therefore, the investigators sensed the need to conduct the study, which aims to understand the expression of endoglin (CD105) in primary and metastatic tumours (omentum) as well as its correlation with tumour clinicopathologic factors: staging, differentiation level, and histopathology of epithelial ovarian cancer.

METHOD

Study Location and Period

The study was conducted in several educational networking hospitals of Obstetrics and Gynecology Department of the faculty of medicine of Universitas Hasanuddin: RS Dr. Wahidin Sudirohusodo, RS Pendidikan UNHAS, RS Pelamonia, RSU Labuang Baji, RSI Faisal, RS Bhayangkara, RS Ibnu Sina, and RSUD Syekh Yusuf Gowa; as well as Pathology Laboratory of Pathology Anatomy Department of the faculty of medicine of Universitas Hasanuddin and Pathology Laboratory of RS Dr. Wahidin Sudirohusodo Makassar. The study was conducted after been approved by the local authorities and the patients in regard to the sampling process. The study was conducted from December 2015 until the period of the sample completion.

Study Design and Variables

The study used cross-sectional study design. The variables of the study consisted of: independent variable (endoglin expression), dependent variable (staging, differentiation level, histopathology of epithelial ovarian cancer), intervening variable (apoptosis inhibition, vasopermeability increase, proliferation, migration, and invasion), and confounding variable (hereditary factor, hormonal factor, radiation, and carcinogenic agents).

Population and Sample

The population of this study included all patients with epithelial ovarian cancer who were treated and underwent the surgery in RS Dr. Wahidin Sudirohusodo Makassar and several educational networking hospitals of Obstetrics and Gynecology Department of the faculty of medicine of Universitas Hasanuddin Makassar. Sample is the part of population. The sample of this study included all patients with epithelial ovarian cancer who were treated and underwent the surgery in RS Dr. Wahidin Sudirohusodo Makassar and several educational networking hospitals of Obstetrics and Gynecology Department of the faculty of medicine of Universitas Hasanuddin Makassar.

Data Collection Method

Patients who consented to participate in the study should sign the informed consent form then complete the questionnaire, consisted of history taking, physical examination, and another workup. The data were subsequently analyzed.

Data Analysis Technique

The data were categorised based on the purpose and type of the data, with appropriate statistic method, then processed with SPSS programme for Windows version 16.

RESULT

The study was an observational study with a cross-sectional design. This study aims to address endoglin (CD105) expression in primary tumour and metastatic tumour (omentum) of epithelial ovarian cancer and its correlation with some clinicopathology factors, such as clinical stage, differentiation level, and histopathology type. This study was conducted in several educational hospitals of obstetrics and gynecology department of faculty of medicine, Universitas Hasanuddin, Makassar, from December 2015 until the period of the sample completion.

There were 55 patients enrolled in the study (20-76 years old) where most cases, as much as 27 (49.1%), were younger than 45 years old. As many as 42 patients (76.4%) were unemployed. The highest parity was 1-3 parities, which was found in 23 patients (41.9%). Of all patients, 18 patients (32.7%) suffered from early-stage ovarian cancer, and 37 patients (67.3%) suffered from late-stage ovarian cancer. Serous type of ovarian cancer was found in 29 patients (52.7%), and mucinous type was found in 26 patients (47.3%). Poorly differentiated cell was found in 39 patients (70.9%), and well differentiated cell was found in 16 patients (29.1%) (Table 1).

Table 1. Characteristic of Sample

Characteristic	Total	
	n = 55	%
Age (year)		
<45	27	49.1
45-50	20	36.4
>50	8	14.5
Parity		
0	19	34.5
1-3	23	41.9
>3	13	23.6
Educational level		
Uneducated	6	10.9
≤ 9 years of education	32	58.2
> 9 years of education	17	30.9
Employment		
Unemployment	42	76.4
Employment	13	23.6
Clinical stage		
Early stage (I and II)	18	32.7
Late stage (III and IV)	37	67.3
Endoglin Expression (Primary)		
Negative	10	18.2
Positive	45	81.8
Endoglin Expression (Omentum)		
Negative	18	32.7
Positive	37	67.3

The distribution of endoglin expression based on the clinical stage in epithelial ovarian cancer tissue (primary tumor) showed that both negative endoglin expression and positive endoglin expression (the weak and the strong one) were found higher in late stage ovarian cancer, as much as 60.0% and 68.9%, respectively. The distribution of endoglin expression based on cell differentiation of epithelial ovarian cancer (primary tumour) showed that both negative and positive endoglin expression in the primary tumour of ovarian cancer was found higher in poorly differentiated cell, as much as 70% and 71.1%, respectively. The distribution of endoglin expression based on histopathology type of epithelial ovarian cancer (primary tumour) showed that both negative and positive endoglin expression in the primary tumour of ovarian cancer was found higher in serous type, as much as 60.0% and 51.1%, respectively. (Table 2).

The distribution of endoglin expression based on the clinical stage of epithelial ovarian cancer (omentum metastatic tumour) showed that negative endoglin expression was found higher in early-stage ovarian cancer (61.1%), while positive endoglin expression was found higher in late stage ovarian cancer (81.1%). The distribution of endoglin expression based on cell differentiation of epithelial ovarian cancer (omentum metastatic tumour) showed that negative endoglin expression was found higher in the well differentiated cell (61.1%), while positive endoglin expression was found higher in the poorly differentiated cell (86.5%). The distribution of endoglin expression based on histopathology type of epithelial ovarian cancer (omentum metastatic tumour) showed that negative endoglin expression was found higher in serous type (61.1%), while positive endoglin expression was found higher in mucinous type (51.4%). (Table 3).

Table 2. Distribution of Endoglin Expression based on Clinical Stage, Cell Differentiation, and Histopathology Type in Epithelial Ovarian Cancer Tissue (Primary Tumour)

Endoglin Expression	Clinical Stage							Cell Differentiation							Histopathology Type						
	Early		Late		Total		p	Well		Poor		Total		p	Mucinous		Serous		Total		p
	n	%	n	%	n	%		n	%	n	%	n	%		n	%	n	%	n	%	
Negative	4	40.0	6	60.0	10	100.0		3	30.0	7	70.0	10	100.0		4	40.0	6	60.0	10	100.0	
Positive	14	31.1	31	68.9	45	100.0	0.588	13	28.9	32	71.1	45	100.0	0.944	22	48.9	23	51.1	45	100.0	0.611
Total	18	32.7	37	67.3	55	100.0		16	29.1	39	70.9	55	100.0		26	47.3	29	52.7	55	100.0	

Table 3. Distribution of Endoglin Expression based on Clinical Stage, Cell Differentiation, and Histopathology Type in Epithelial Ovarian Cancer Tissue (Omentum Metastatic Tumour)

Endoglin Expression	Clinical Stage							Cell Differentiation							Histopathology Type						
	Early		Late		Total		p	Well		Poor		Total		p	Mucinous		Serous		Total		p
	n	%	n	%	n	%		n	%	n	%	n	%		n	%	n	%	n	%	
Negative	11	61.1	7	38.9	18	100.0		11	61.1	7	38.9	18	100.0		7	38.9	11	61.1	18	100.0	
Positive	7	18.9	30	81.1	37	100.0	0.002	5	13.5	32	86.5	37	100.0	0.000	19	51.4	18	48.6	37	100.0	0.385
Total	18	32.1	37	67.9	45	100.0		16	29.1	39	70.9	55	100.0		26	47.3	29	52.7	55	100.0	

There is a significant correlation of endoglin expression in primary tumour and endoglin expression in omentum metastatic tumour of ovarian cancer ($p<0.05$). The coefficient value of 0.771 indicated a strong correlation of endoglin expression in omentum metastatic tumour and endoglin expression in primary tumour of ovarian cancer (Table 4).

Table 4. Correlation of Endoglin Expression in Primary Tumor and Endoglin Expression in Omentum Metastatic Tumor of Epithelial Ovarian Cancer

Primary Endoglin	
Endoglin Omentum	rs = 0.771
	p = 0.000

DISCUSSION

The study showed a significant correlation (strong category) of endoglin expression in omentum metastatic tumour and endoglin expression in the primary tumour of epithelial ovarian cancer.

Statistically, this result showed no significant correlation between endoglin expression and clinical stage of epithelial ovarian cancer. Similar result was reported by Zhai (2011) and Satya *et al.* (2016), as well as Annika *et al.* (2011), concluded that regardless the cell type, endoglin expression was not correlated to tumour stage, FIGO classification, or volume of the remaining disease after surgery. Annika *et al.* (2011) observed endoglin expression in serous ovarian cancer by assessing the efusion fluid and the primary tumour. They found a stronger endoglin expression in patients with recurrent disease, both in the efusion fluid and in the primary tumour.[9-11]

Although there was no statistical correlation of endoglin expression and clinical stage, the data showed a linear tendency indicating that positive endoglin expression was found dominant in the late stage. Of 37 cases of late-stage ovarian cancer, 31 expressed positive endoglin.

Endoglin expression in primary tumour of ovarian cancer is not statistically significant at various level of cells differentiation. The result is in accordance with the result of Zhai (2011), Nikiteas *et al.* (2007), and Satya *et al.* (2016), which found that there was no correlation of endoglin expression and the differentiation level. Previous study showed that endoglin involved more in tumour progressivity, proven by its presence as cell differentiation marker in ovarian cancer. Previous studies did not specifically state cell differentiation type. Endoglin (CD105) is a part of Transforming Growth Factor (TGF)-β complex receptor, a pleiotropic cytokine which involved in cellular proliferation, differentiation, and migration.[6,10,11]

In this study, we did not find any significant statistical difference of endoglin expression and the histopathology of epithelial ovarian cancer. Similar result was found by Nikiteas *et al.* (2007), which showed no correlation between endoglin expression and the histopathology type of cancer. Data showed that positive endoglin expression was higher in serous type (52.7%) than in mucinous type (48.9%).[6]

From the statistical test, this study indicated a significant correlation of endoglin expression in omentum metastatic tumour and the clinical stage of epithelial ovarian cancer. Endoglin is suggested as a progressivity marker of various solid tumours and their metastases by many researchers. This is different with the study result of Annika *et al.* (2011), which concluded that, regardless of the cell type, endoglin expression is not correlated to the staging of the tumour, FIGO classification, or the volume of the remaining disease after surgery.

According to Annika *et al.* (2011), endoglin expression in solid metastases is higher than that in efusion. Similarly, a non-significant tendency indicated that there is a higher expression in a primary tumour than in efusion. There is no significant difference in endoglin staining of the solid metastatic tumour and primary tumour. The latter is consistent with our finding which indicated that there is no significant difference in endoglin staining of the solid metastatic tumour and primary tumour. However, we can not confirm the previous statement since we did not assess endoglin expression in the efusion fluid of ovarian cancer.[9]

In this study, we did not find a significant statistical correlation of endoglin expression and histopathology type of epithelial ovarian cancer. The data showed that positive endoglin expression was the slightly higher mucinous type (51.4%) compared to serous type (48.6%). Theoretically, serous type of epithelial ovarian cancer was found more frequently. The study of McCluggage (2011) found that serous adenocarcinoma is the most

frequent type of epithelial ovarian cancer, and most serous type epithelial ovarian cancer was found in late stage (III & IV). This finding is consistent with the result of our study, where we found 29 (51.8%) cases of serous type epithelial ovarian cancer, and most cases are late-stage ovarian cancer (67.8%).[12]

This study showed no significant correlation between endoglin expression increase and the clinical stage, differentiation level, and histopathology type of epithelial ovarian cancer primary tumour. However, there was a significant correlation of endoglin expression increase of omentum metastatic tumour and the clinical stage as well as differentiation level of epithelial ovarian cancer, but there was no significant correlation of endoglin expression increase of omentum metastatic tumour and histopathology type of epithelial ovarian cancer.

One of some possibilities that may appear is the presence of angiogenic factor molecular heterogeneity of ovarian cancer. That might be caused by the mutation of ALK-1 and ALK-5 proteins which then suppress/influence endoglin expression, both in protein level and mRNA level.[3]

ALK-1 or activin receptor-like kinase 1 is an enzyme that is encoded by ACVRL1 gene which is a receptor in TGF-β signaling pathway. While ALK-5 is a specific receptor enzyme for TGF-β1. Mutation and deletion of ALK-1 and ALK-5 are frequently found in various cancers of human.

There was a significant correlation between endoglin expression in primary tumours and endoglin expression in omentum metastatic tumour of ovarian cancer. The correlation of endoglin expression in omentum metastatic tumour and endoglin expression in primary tumours was considered as a strong correlation.

The increase of endoglin (CD105) expression might be detected in microvascular endothelial cells and in vascular endothelial cells of tissues with active ongoing angiogenesis, such as tissues that are in their regeneration process as well as tumour and its metastases or inflammation. The result of endoglin (CD105) staining showed more evident stain in the area with active angiogenesis, including tumour borders, metastases tumour, while less evident stain was seen in the central area of the tumour, and no stain was seen in normal tissues around a tumour.

This result is consistent with the results of previous studies which stated that measuring endoglin expression by assessing microvascular density is a proper prognostic indicator; the study found that the density of endoglin-positive vascular is associated with metastases of various solid tumours.[3]

High level of endoglin expression was associated with ovarian cancer growth and metastatic tumour. In tumour pathogenesis, endoglin plays some big roles, such as inducing tumour proliferation, invasion, and metastases. Metastases includes some gradual steps of malignant cells that spread from the primary tumour to other distant organs. The recruitment of endothelial cells and neovascularization play an important role in tumour progression and metastases. Important events of metastases including the ability of tumour to survive in circulation and to invade other tissues, initiate and maintain the growth, and form a proangiogenic micrometastases in the tissue, then eventually form a vascularization for the macrometastases tumour.

CONCLUSION AND RECOMMENDATION

The investigators concluded that endoglin expression in ovarian cancer primary tumour is not correlated to clinical stage, differentiation level, and histopathology of epithelial ovarian cancer. Endoglin expression in ovarian cancer metastatic tumour to omentum is correlated with clinical stage and differentiation level of ovarian cancer. Endoglin expression in ovarian cancer metastatic tumour to omentum is not correlated to histopathological of epithelial ovarian cancer. There is a strong correlation between endoglin expression in omentum metastatic tumour and endoglin expression in primary tumor of ovarian cancer. And endoglin is one of the pro angiogenic and pro metastases factors. Further studies are needed, considering the role of endoglin in therapeutic target of ovarian cancer has not been reported considerably. However, endoglin expression is a proper prognostic marker and a promising therapeutic target of antiangiogenesis process and anti-tumor; thus, further studies are needed. Deeper analyses are needed to explain the molecular mechanism of other angiogenic factors in ovarian cancer progressivity.

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