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The relationship between clinicopathology factors and omental metastasis in epithelial ovarian cancer

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Summary. *Background*: Aside from being a major metastatic site in epithelial type ovarian cancer, omentum has an immunological role. Omentum has the ability to colonize the spread of cancer cells by forming omental caking. This study aims to determine the relationship between clinicopathology factors with metastasis in omentum in epithelial type ovarian cancer. *Methods:* The study used cross-sectional study design. Subjects were patients diagnosed with epithelial type ovarian cancer who underwent surgery at Cipto Mangunkusumo Hospital between January 2010 and December 2017. *Results*: There were association between serous as well as mucinous type, omental nodules, and between CA 125 and metastasis in omentum (OR 1.7, CI 95% 24.1-47.7; p=0.002, OR 14.5, CI 95% 2.5-82.2; p=0.002, OR 61, CI 95% 11.4-324.8; p<0.01, and OR 3.5, CI 95% 1.2-9.7; p=0.013). Multivariate analysis demonstrated a significant association between mucinous types with metastases in the omentum (aOR 9.71, CI 95% 1.11-84.89; p=0.04) and between the omental nodules and metastases in the omentum (aOR 40.92, CI 95% 6.64-251.96 ; p <0.01). *Conclusions:* The incidence of omental metastasis in epithelial ovarian cancer is higher in mucinous histological types of and omental nodules only.

Key words: clinicopathology factors, epithelial ovarian cancer, omentum, omental metastasis

Introduction

According to the National Cancer Institute, the incidence of ovarian cancer in America in 2015 was 11.6 per 100,000 women (1). In Indonesia, Indonesian Society of Gynecology Oncology (INASGO) reported that new cases of epithelial type ovarian cancer from 2015, 2016 and 2017 were 463 cases, 379 cases and 280 cases, respectively (2). Particularly, in Cipto Mangunkusumo Hospital, Jakarta, Indonesia, there were 397 epithelial ovarian cases during the period of 2010 to 2017, with serous type cancer as the most common type (3).

Several factors are associated with the prognosis of omental metastasis and occult metastasis. The most histological type in which omental metastasis occurs is the serous type, and the most degree of differentiation which metastasis to the omentum is the third-degree (4-6). Almost all omental nodules are positive for microscopic metastasis. However, there are a few cases of hidden metastases in the omentum (5, 7). The size of the tumor is also related to the prognosis of ovarian cancer: those with early stages of ovarian cancer have a tumor size greater than in the late stages of ovarian cancer (8). Ascites is also a clinical prognostic factor that distinguishes between benign and malignant adnexal masses before surgery (9). The presence of ascites and CA 125 levels increases the incidence of hidden metastases in early-stage ovarian cancer (4, 6).

Omentum is a major site for intraperitoneal metastases in epithelial type ovarian cancer (7, 10, 11). Several studies have suggested that of patients with early-stage ovarian cancer, who are macroscopically confined to the ovary and then undergoing surgical staging, 29% -36% of them turned out to have an elevated stage due to metastasis in the omentum,

peritoneum, and retroperitoneal lymph nodes (4, 12). Omentectomy is one of the procedures for surgical staging according to FIGO (7, 13). Despite being a common site for metastasis, omentum also has a protective function; it has an immunological role in the presence of milky spot structures. Omentum contains macrophages, T cells and B cells in the omentum stroma (11, 14). In addition, milky spots and adipose tissue cause colonization of cancer metastases cell in the omentum in the form of omental caking, which can localize the metastatic process (15, 16). Due to the role of omentum, studies are required to determine the relationship between clinicopathological factors associated with metastasis in omentum in epithelial type ovarian cancer. Therefore, we could determine whether omentectomy is needed in cases of epithelial ovarian cancer.

Methods

We used a cross-sectional study design by evaluating medical records of patients diagnosed with epithelial type ovarian cancer who underwent surgery at Cipto Mangunkusumo Hospital, Jakarta, Indonesia during the period between January 2010 and December 2017. Those with epithelial ovarian cancer from anatomical pathology report and performed omentectomy based on the surgery report were included in the present study. Those who had received chemotherapy therapy or had previously been operated at an outside hospital were excluded. Data were taken non-randomly, from the cancer registry of Cipto Mangunkusumo Hospital in 2010-2017. Data that meets the inclusion criteria, were reviewed based on data from the results of anatomical pathology examination, operating reports and laboratory examination results.

Results

Of 394 cases of epithelial ovarian cancer in Cipto Mangunkusumo Hospital from 2010-2017, 123 medical cases were not obtained, 190 exclusion cases, and 81 inclusion cases. The clinicopathological factors that had a relationship with metastasis in the omentum were serous and mucous histology, omentum nodules, and CA 125 levels. Serous type had an association with metastasis in the omentum with clear cells as a reference (OR 10.7 CI 95% 24.1-47.7; p=0.002). The mucinous type also had a significant relationship with metastasis in the omentum with clear cells as a reference (OR 14.5, CI 95% 2.5-82.2; p=0.002). We also found significant association between omental nodules and omental metastasis (OR 61, CI 95% 11.4-324.8; p<0.01). After merging cells, with categories of CA 125> 500 U / ml and CA125≤500 U / ml levels, bivariate analysis was performed with chi-square test, the results met the requirements and obtained a significant relationship (OR 3.5, CI 95% 1.2-9.7; p=0.013).

Multivariate analysis demonstrated significant association between omental nodules with metastases in omentum (aOR 40.9, CI 95% 6.6-251.9; p<0.01) and histological types of mucinous is associated with the presence of omental metastases (aOR 9.71, CI 95% 1.11-84.89; p=0.04).

Table 1. Characteristic Data.

	Frequency (n)	Percent (%)	Median (cm)
Tumor Size			20 (4,5-40)
<10 cm	9	11.1	
≥10 cm	72	88.9	
Ascites			
Yes	27	33.3	
No	54	66.7	
Omental Nodule			
Yes	11	13.6	
No	64	79	
Omental cake	6	7.4	
Histology type			
Serous	19	23.5	
Mucinous	10	12.3	
Endometrioid	20	24.7	
Clear cell	23	39.5	
Differentiation degree			
Degree 1	23	24.8	
Degree 2	22	27.2	
Degree 3	36	44.4	
Omentum metastasis			
Positive	22	27.2	
Negative	59	72.8	
Ca-125 level			245.5 (15,8-172.540)
>500U/ml	12	44.4	
35-500U/ml	9	18.8	
≤35 U/ml	1	16.7	

Table 2. Bivariate analysis of the relationship between clinicopathology factors with metastasis in omentum.

	Omental Metastasis				
	Positive	Negative	p	OR	CI 95%
Histology Type					
Serous	10 (52.6%)	9(47.4%)	0.002**	10.7	24.1-47.7
Mucinous	6 (60%)	4(40%)	0.002**	14.5	2.5-82.2
Endometrioid	3 (15%)	17(85%)	0.66**	1.7	0.3-9.4
Clear cell	3 (9.4%)	29(90.6%)	Reference	Reference	Reference
Differentiation degree					
Degree 3	12 (33.3%)	24(66.7%)	0.44*	-	-
Degree 2	4 (18.2%)	18(81.8%)			
Degree 1	6 (26.1%)	17(73.9%)			
Tumor size					
≥10 cm	18 (24.7%)	55(75.3%)	0.203**	0.32	0.07-1.44
< 10 cm	4 (50.0%)	4 (50.0%)			
Omental nodule					
Yes	15 (88.2%)	2(11.8%)	0.00**	61.0	11.4-324.8
No	7 (10.9%)	57 (89.1%)			
Ascites					
Yes	11 (40.7%)	16(59.3%)	0.052*	2.6	0.9-7.40
No	11 (20.4%)	43 (79.6%)			
CA 125 level					
>500 U/ml	12 (44.4%)	15(55.6%)	0.013*	3.5	1.2-9.7
≤500 U/ml	10 (18.5%)	44(81.5%)			

*Chi-square test
**Fisher's exact test

Table 3. Bivariate analysis of the relationship between clinicopathology factors with metastasis in omentum.

	Omental Metastasis		
	Positive	Negative	P
Tumor size (cm)	18.5(4.5-35)	20 (6-40)	0.23***
CA 125 (U/ml)	465.5 (43-6656)	212.1 (15.8-172540)	0.013***

***Mann whitney test

Discussion

In this study, the most histological types in which omental metastases occurred were mucinous types (N=6, 60%), followed with serous (N=10, 52.6%), endometrioid (N=3, 15%), and clear cell types (N=3, 9.4%). This is different from some previous studies on early-stage epithelial-type ovarian cancer which found that the histological type with the most occult metastasis was serous type (37.7%-40%); whereas the most histological type of metastasis to the omentum was serous type (20%-37.5%) (4, 6). Doig et al found that from the 318 cases of malignant tumours, the most histological type was serous, which was 144 cases, of which 120 cases (83%) had omental metastasis (17). This difference can be caused by the number of mucinous type samples is only 10 cases out of a total of 81 inclusion cases. While the number of other types of samples is more, the difference in this number is that fewer types of mucinous can cause the mucinous type to be impressed as a histological type that has a greater proportion of metastasis to the omentum.

Epithelial ovarian cancer originates from the ovarian surface epithelium, which is embryologically derived from the coelomic mesothelium (mesodermal epithelium); whereas, the uterus, cervix, and fallopian tubes develop from the Müllerian duct (ductus paramesonefros) (18-20). Coelomic mesothelium undergoes metaplasia which causes the development of cell differentiation into serous (similar to tubal epithelium), endometrioid (similar to endometrial epithe-

Table 4. Multivariate analysis of the relationship between clinicopathology factors with metastasis in the omentum.

		Wald	P	aOR	CI 95%	
					Lower	Upper
Histology type	Serous	1.67	0.19	3.99	0.49	32.42
	Mucinous	4.22	0.04	9.71	1.11	84.89
	Endometrioid	0.15	0.69	1.52	0.19	11.98
	Clear cell			Reference		
Omental nodule		16.02	0.00	40.92	6.64	251.96
Ca 125		0.02	0.96	1.04	0.18	5.86
Ascites		0.46	0.49	1.69	0.37	7.77

Regression logistic test

lium), clear cells (similar to endometrial epithelium), and mucinous (similar to the cervical epithelium and intestinal epithelium) (20, 21).

One hypothesis regarding the formation of epithelial ovarian tumours is in the transition region between mesothelial fallopian tubes and ovary fimbriae, which is an epithelial transition area that is susceptible to changes in malignancy, where the transition part is a source of carcinogenetic processes (18, 22). The mesothelium lining of the ovary consists of epithelium (keratin) and mesenchyme (vimentin). This structure also lines the fallopian tubes, uterus and peritoneal, pleural, and pericardium cavities (18, 19).

As previously known, the ovary is hung on the mesovarium and the tuba is hung on mesosalpinx. Mesovarium and mesosalpinx are part of the peritoneum. Tubes and ovaries are adjacent organs. Omentum is a continuation of the visceral peritoneum which starts from the major curvature of the stomach and the proximal part of the duodenum then extends downward, above the anterior surface of the intestine. Ovarian, tubes, omentum, and peritoneum are covered by mesothelium (23, 24). This can explain the reason why in the previous study, the histology type which had the most metastasis to the omentum was the serous type. The serous type resembles the tubal epithelium, where the ovary, tuba, and omentum are covered with mesothelium. Anatomically, there is a potential source of high-grade serous ovarian carcinoma, which is epithelial surface, fallopian tube epithelium, and mesothelium lining the peritoneal cavity (18).

In this study, omental metastasis was found in the highest number of third-degree epithelial ovarian cancers as much as 33.3%. This is consistent with previous studies which found that the most prevalent causes of occult metastases as well as the most numerous degrees of metastasis to the omentum were the third degree (52.6%-56% and 24%-37.5%, respectively) (4, 6). Theoretically, there is a figure of the growth of solid parts and atypical structures and cytology that are more common in the third-degree compared to the first- and second-degree (25). The insignificant association between the degree of differentiation and omental metastasis are not in line with previous findings. Several studies found that occult metastasis was associated with an increased degree differentiation of the tumour (4-6). This difference might be due to the proportion of positive metastatic omentum at each degree was not significantly different, resulting in insignificant relationship between the degree differentiation and omental metastasis. Previous studies described occult metastasis in all organs, not only in the omentum but also the peritoneum, lymph nodes, uterus and fallopian tubes, and the adhesion section; whereas, this study only described omental metastasis.

In this study, the median tumour size was 20 (4.5-40) cm. The median size of a tumour in cancer early stage was greater compared to the advanced stage (20 [6-40] vs 17 [4.5-35] cm, respectively). However, the differences are not statistically significant. This is in accordance with Horvart et al. who found that patients with early-stage ovarian cancer had a larger tumour size than those found in advanced ovarian cancer. In early stages, the average tumour size was 10.7 cm, and at an advanced stage of 4.8 cm (8). In this study, there was no association between the size of the tumour

with metastasis in the omentum. This is in accordance with Ahyan et al. which found that the size of tumours did not have a significant relationship with the occurrence of an increasing stage (p=0.9) (6). In this study, the differences of the median size of the tumour with omental metastasis positive and negative were not significant, 18 cm and 20 cm. In addition, the tumour size range in both positive and negative omental metastases was not significant, 4.5-35 cm and 6-40 cm.

In this study, there were 15 cases (88.2%) with omental nodules and positive omental metastases; whereas there were 57 cases (89.1%) with negative omental nodules and negative omental metastases. It is concluded that a macroscopic impression according to the microscopic impression. This is in line with a study by Usubutun et al. which found that the macroscopic impression was in accordance with the microscopic impression of 97.3% (5, 26). Doig et al. found that the impression of macroscopic is in accordance with the microscopic impression in 97.1% of cases, with PPV of 98.4% and NPV of 88% (17).

In this study, there was no correlation between ascites and omental metastasis. This is in contrast with several studies that found a correlation between the presence of ascites and more advanced stage as well as occult metastasis in early-stage ovarian cancer (4, 6). One of the metastatic pathways in ovarian cancer, is intraperitoneal metastasis (21). The ovary contacts with the peritoneum through the mesovarium, where the mesovarium is part of the mesentery. The mesentery and the omentum are parts of the peritoneum (24). Ascites, which found in the peritoneal cavity, is a medium where cancer cells will be present in the ascitic fluid. Because the capsules of ovarian tumours are disrupted, malignant cells spread to the peritoneal cavity, cells that survive can be single cells or multicellular aggregates which free-floating, called spheroids. This spheroid attaches to the extracellular mesothelial matrix, which allows it to attach as a secondary lesion to other pelvic organs, including the omentum (18, 27). In this study there was no association between ascites in the presence of metastasis in the omentum because the proportion of ascites with metastasis in the omentum was 40.7%.

According to previous studies by Ahyan et al., there was a relationship between CA 125 levels with more advanced stage in early-stage ovarian cancer (p<0.001) (6) CA125 is expressed by coelomic epithelium and tissue in adults originating from coelomic (mesothelial pleural, pericardial and peritoneal cells) and Mullerian epithelium (tube, endometrium, and endocervix) (28). CA125 is expressed as a membrane-bound protein on the surface of a cell that undergoes metaplastic differentiation into a müllerian type epithelium, or released in the form of a solution in body fluid (29). CA 125 also plays a role in cancer cell migration, and serum levels can predict metastasis (30).

After adjusting for clinicopathological factors by multivariate analysis, we found that the mucinous type had a relationship with metastasis in the omentum (aOR 9.71, 95% CI 95% 1.11-84.89; p=0.04) and the omental nodule had a relationship with omental metastasis (aOR 40.92, CI 95% 6.64-251.96; p<0.01). Whereas for the CA 125 level, there was no meaningful relationship. Soto et al. also stated that there was no relationship between CA 125 levels and occult metastases (4).

This is the first study that investigates the relationship between clinicopathologic factors with metastasis in omentum in epithelial type ovarian cancer. Several previous studies have assessed the relationship between several clinicopathological factors with occult metastases; however, they only used epithelial type ovarian cancer populations at an early stage. This study can be used as a preliminary study to provide descriptive characteristics of epithelial type ovarian cancer at Cipto Mangunkusumo Hospital. This study is limited by the small number of the subjects, as ovarian cancer cases referred to Cipto Mangunkusumo Hospital are often cases with advanced stages; therefore, many of these patients have undergone neoadjuvant chemotherapy before surgery, or they already underwent surgery in other hospitals. Thus, intraoperative data were often difficult to obtain.

Conclusions

We found that the incidence of omental metastasis in epithelial ovarian cancer is higher in mucinous histological types of and omental nodules only. Further prospective studies with larger samples are required to evaluate this relationship better. In addition, the co-

hort design can determine the causal relationship between clinicopathological factors with metastasis in omentum in epithelial type ovarian cancer.

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