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Factors Associated With Recurrence Of Epithelial Ovarian Cancer In RSUP Dr. Kariadi Semarang

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ABSTRACT

Background: Epithelial ovarian cancer accounts for 90% of all ovarian malignancies. More than 70% of patients will experience a relapse even after receiving operative therapy and chemotherapy. There are several prognostic factors that influence the recurrence of ovarian cancer. In Indonesia, especially at Dr. Kariadi Hospital, Semarang, the data as mentioned above is still very limited
Objective: Knowing the disease-free survival rate, optimizing surgery and factors related to the incidence of recurrence in epithelial ovarian cancer patients at Dr. Kariadi Hospital Semarang
Methods: This study is a retrospective cohort study with survival analysis. Data were collected through medical records, with the study population are patients with a diagnosis of epithelial ovarian cancer who were treated at Dr. Kariadi Hospital Semarang in period January 2018-December 2019. Furthermore, patients who had been remission were observed for signs of disease recurrence for 2 years period.
Results: There were 361 patients with epithelial ovarian cancer who underwent primary treatment at Dr. Kariadi Hospital, Semarang in 2018-2019. Furthermore, there were observations of recurrence in 148 patients who achieved remission. Of these 76 patients (51.4%) experienced recurrence, while 72 patients not relapse. From 148 epithelial ovarian cancer patients who underwent cytoreduction surgery at Dr. Kariadi Hospital, Semarang, 113 patients (76.4%) achieved optimal operation with a residu less than 2 cm, while 35 patients (23.6%) were not optimal with a residu more than 2 cm. FIGO stage (HR 2.44) and tumor residu (HR 2.15) were shown to be significant factors associated with the recurrence of epithelial ovarian cancer
Conclusion: Overall disease-free survival in epithelial ovarian cancer at Dr. Kariadi Semarang were 74.8% (6 months), 57.1% (1 year), 42.5% (18 months), and 37.4% (2 years). Tumor residual factors and FIGO stage were shown to be significant prognostic factors influencing the recurrence of epithelial ovarian cance

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1. Introduction

Ovarian cancer is the eighth most common cancer in women worldwide and the third most common gynecological malignancy in the world, and accounts for about 160,000 deaths each year. In the world, ovarian cancer affects more than 200,000 women every year or about 3.4% of all malignancies in women, but accounts for 4.9% of cancer deaths in women, this is due to the low survival rate due to most cases diagnosed in women. advanced stage.1.2

Epithelial ovarian cancer accounts for 90% of all ovarian malignancies. More than 70% of patients will experience a relapse even after receiving operative therapy and chemotherapy. This recurrence event can occur at different time intervals, which are further classified based on the platinum-free interval.3-5 The success of epithelial ovarian cancer therapy can be assessed by monitoring the occurrence of recurrence by measuring the disease free interval or disease-free survival, i.e. the length of time that occurs. calculated from the time after primary cancer treatment is completed until the patient can survive without signs or symptoms of cancer.6

There are several papers on prognostic factors in patients with ovarian cancer and many investigators emphasize the importance of these factors This is for treatment planning and final results. Factors such as stage, tumor residue, age, histologic type and degree of differentiation, preoperative serum CA-125 (Cancer Antigen 125), ascites, patient performance status, and postoperative adjuvant therapy were reported as factors influencing recurrence.7-10

In Indonesia, especially at the general hospital dr. Kariadi Semarang, the data as mentioned above is still very limited. What is the actual survival rate of ovarian cancer, how many recurrences occur in ovarian cancer, and what are the factors that influence it.

2. Methods

This study is a retrospective cohort study with a survival analysis technique. Data retrieval through medical records, with the study population in the form of patients with a diagnosis of epithelial ovarian cancer who were treated at the RSUP dr. Kariadi Semarang in the period January 2018- December 2019. Inclusion criteria were patients with a diagnosis of epithelial ovarian cancer with complete medical record data, and have received primary therapy (surgery with or without adjuvant chemotherapy). Meanwhile, the criteria for exclusion were patients with two primary malignancies (double primary), borderline tumors, or non-epithelial types. Patients who have completed primary therapy and are declared in remission will then be observed for signs of disease recurrence during 2 years period (2020-2021).

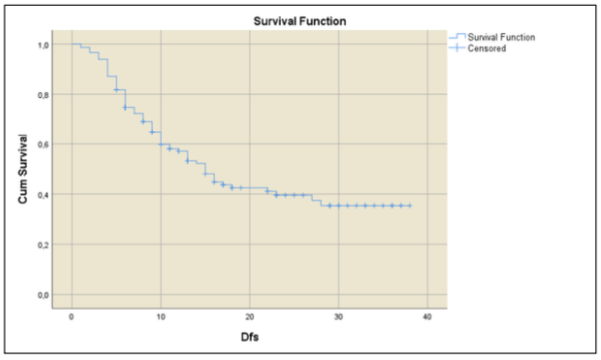

Figure 1. Disease free survival curve from epithelial ovarian cancer

Variable	Ovarian Cancer Recurrence	
	Relapsed (%)	**Not relapse (%)**
Tumor Residue		
2 cm	31 (88.6)	4 (11,4)
< 2 cm	45 (39.8)	68 (60.2)
Age		
60 years	13 (61.9)	8 (38.1)
< 60 years old	63 (49.6)	64 (50.4)
BMI		
Obesity	5 (33.3)	10 (66.7)
Not obese	71 (53.4)	62 (46.6)
Stadium		
Stage I	14 (24.6)	43 (75.4)
Stage II	13 (54.2)	11 (45.8)
Stage III	46 (71.9)	18 (28.1)
Stage IV	3 (100)	0 (0)
Histology		
HGSOC	28 (70)	12 (30)
LGSOC	2 (22.2)	7 (77.8)
Endometrioid	22 (64.7)	12 (35.3)
clear cell	10 (40)	15 (60)
Mucinosum	14 (35)	26 (65)
Operation history		
Yes	12 (52.2)	11 (47.8)
No	64 (51.2)	61 (48.8)
Neoadjuvant		
Chemotherapy	5 (50)	5 (50)
Yes	71 (51.4)	67 (48.6)
No		

Table 1. Characteristics of research data

3. Results

A. Characteristics of Research Data

In observation, from 361 epithelial ovarian cancer patients who underwent primary treatment, 78 patients developed progressive disease during the treatment period, 195 patients were declared in remission after completing primary treatment, while 88 patients did not complete their treatment. Furthermore, observation of disease recurrence for 2 years (2020-2021) was carried out in 195 patients who had been declared in remission. After being declared in remission, 47 patients were not in control. Then over a 2 year period, 76 patients (51.4%) had a relapse, whereas 72 patients did not

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Table 2. Epithelial ovarian cancer-free survival based on various variables

Variable	Recurrence		p♥	PH Assumption
	Relapsed	Sensor		
Tumor residue				
2 cm	31 (88.6%)	4 (11.4%)	<0.001*	Fulfilled
< 2 cm	45 (39.8%)	68 (60.2%)		
Age				
60 years	13 (61.9%)	8 (38.1%)	0.502	Not
< 60 years old	63 (49.6%)	64 (50.4%)		
BMI				
Obesity	5 (33.3%)	10 (66.7%)	0.211	Not
Not obese	71 (53.4%)	62 (46.6%)		
Stadium				
Early	23 (30.3%)	53 (69.7%)	<0.001*	Fulfilled
Advanced	53 (73.6%)	19 (26.4%)		
Histology				
Type 1	48 (44.4%)	60 (55.6%)	0.008*	Fulfilled
Type 2	28 (70%)	12 (30%)		
Operation history				
Yes	12 (52.2%)	11 (47.8%)	0.807	Not
No	64 (51.2%)	61 (48.8%)		
Nac				
Yes	5 (50%)	5 (50%)	0.876	Not
No	71 (51.4%)	67 (48.6%)		

B. Epithelial Type Ovarian Cancer Recurrence Rate

From the study, it was found that the recurrence incidence of epithelial ovarian cancer at Dr. Kariadi Hospital Semarang in the 2020-2021 period was 51.4%, which was calculated from the time the patient was declared in remission until signs of disease recurrence were found. Furthermore, for the overall disease-free survival rate for epithelial ovarian cancer at Dr. Kariadi Semarang were 74.8% (6 months), 57.1% (1 year), 42.5% (18 months), and 37.4% (2 years).

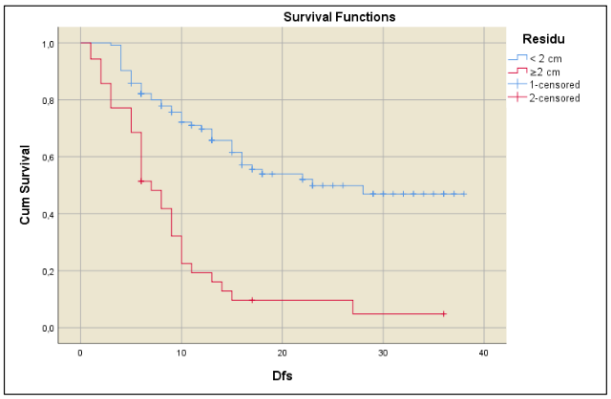

Figure 2. Disease free survival curve from epithelial ovarian cancer based on tumor residu

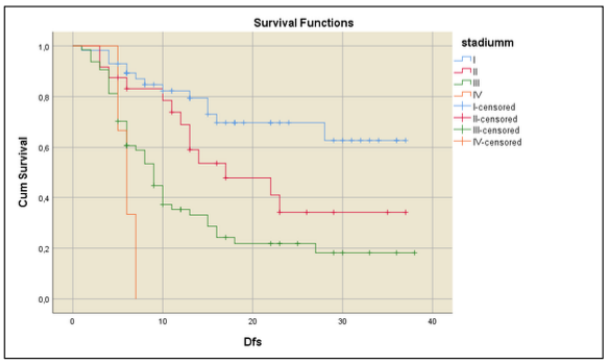

Figure 3. Epithelial ovarian cancer-free survival curve by stage

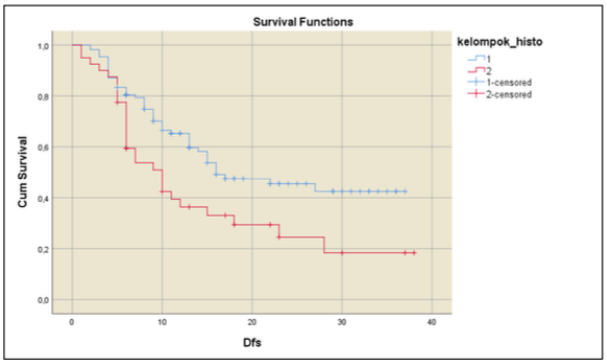

Figure 4. Epithelial-type ovarian cancer-free survival curve by histologic type

C. Operation Optimization

Of the 148 epithelial ovarian cancer patients who underwent cytoreduction surgery at Dr. Kariadi Hospital, Semarang in the 2018-2019 period, 113 patients (76.4%) achieved surgery optimization with a residue of less than 2 cm, while 35 patients (23.6 %) is not optimal with a residue of more than 2 cm. Furthermore, from 148 patients who underwent surgery at RSUP Dr. Kariadi Semarang, as many as 23 patients had previously undergone obstetrical surgery at a level two health facility with PA results in the form of malignancy before undergoing cytoreduction surgery at Dr. Kariadi Hospital Semarang. Of these 10 patients received neoadjuvant chemotherapy before continuing with cytoreduction surgery. Of these 10 patients, all achieved optimal debulking (residual < 2 cm).

D. Disease Free Survival

Kaplan Meier curve was used to determine the characteristics of DFS patients with epithelial ovarian cancer based on the factors thought to influence it. The status variable observed in this study was disease recurrence, while the censored data were patients who did not experience recurrence during the observation period or patients who disappeared from observation. Person time in this study was calculated in units of months, which was calculated from the beginning of the observation of recurrence, namely after the patient was declared in remission. In Figure 35 it can be seen that the group of patients with a tumor residue of less than 2 cm had a longer disease-free survival rate than the group with a residue of more than 2 cm. And in the Log rank test, the p value <0,

Table 3. Bivariate and Multivariate Analysis

Variable	Bivariate Analysis		Multivariate Analysis	
	Hazard ratio	p value	Hazard ratio	p value
Residue 2 cm	3,772 (2.36-6.02)	0.001	2,150 (1.24-3.71)	0.006
Advanced Stadium	3,567 (2.17-5.84)	0.001	2.44 (1.38-4.33)	0.002
Histological type 2	1,833 (1.14-2.92)	0.011	1.320 (0.81-2.14)	0.261

In addition to tumor residues, the investigators also assessed disease-free survival based on the stage and histological type of the tumor. The 2-year survival of epithelial ovarian cancer at stage I was 62.8.%, stage II 34.1%, stage III 18.2%, while for stage IV all had recurrence within 7 months of observation. Based on the histological type, 2-year disease-free survival was found to be higher in patients with histologic type 1 (42.5%) compared to histological type 2 (18.4%).

E. Bivariate and Multivariate Analysis

From the multivariate analysis, it was found that tumor residue and stage had a significant relationship with the incidence of recurrence. Where patients with tumor residues of more than 2 cm had HR of 2.15 compared to patients with residues of less than 2 cm, meaning that at any time the group of patients with residual tumors of more than 2 cm was 2.15 times faster to experience recurrence than the group of residues of less than 2 cm.

Likewise, patients with advanced stages have HR of 2.44 compared to early-stage patients, which means that the group of patients with advanced stage epithelial ovarian cancer is 2.44 times faster for recurrence than the group of early-stage epithelial ovarian cancer.

4. Discussions

This study is a retrospective cohort study with survival analysis techniques to determine the factors that influence the recurrence of epithelial ovarian cancer patients at Dr. Kariadi Semarang.

The overall disease-free survival rate for epithelial ovarian cancer at Dr. Kariadi Semarang were 74.8% (6 months), 57.1% (1 year), 42.5% (18 months), and 37.4% (2 years). Another study conducted by khonsa showed the overall survival of epithelial ovarian cancer in Dr. Ciptomangunkusumo Jakarta was 89.3% (1 year), and 76.3% (2 years). However, it should be noted that the study conducted by Khonsa calculated overall survival rates, while in this study, disease-free survival or the length of time before disease recurrence was assessed.[9]

There are several factors that influence the recurrence of epithelial ovarian cancer. One of the factors that are often associated with ovarian

cancer recurrence is tumor residue factors and optimization of primary cytoreduction surgery. The standard treatment for advanced ovarian cancer is primary cytoreduction surgery followed by combination platinum-based chemotherapy. In accordance with the Gompertzian model, a large reduction in the initial tumor burden during surgery would increase the 5-year survival rate in conjunction with adjuvant chemotherapy. This understanding is based on the concept that the fraction of tumor growth decreases with time, so chemotherapy will destroy tumor cells based on their growth curve. The smaller the volume of the tumor will be more easily destroyed than the larger volume.

Optimization of surgery is one of the factors that play a role in determining the prognostication of ovarian cancer patients, especially advanced stage ovarian cancer. The results of this study are in accordance with the research of Hoskin et al in 1994 which showed that survival was better in the group with complete resection. The overall survival rate increased gradually as the size of the tumor residue decreased from 2 cm to no residue macroscopically. In addition, in multivariate analysis, it was also found that patients with tumor residues of more than 2 cm had a HR of 3.772 (CI 2.36-6.02), which means that at any time patients with residuals of more than 2 cm were 3.77 times faster to experience recurrence than with a group of patients with a residue of less than 2 cm.[11,12]

The success of cytoreduction surgery as reflected by the size of the tumor residue has been consistently shown to be one of the most influential factors in disease-free and patient survival rates. Age factor is also associated with epithelial ovarian cancer recurrence. Previous research conducted by Mallen et al[13] showed that the risk of death from ovarian cancer in elderly patients was 1.8 times higher than in patients under 70 years of age. Several studies have shown the relationship between cellular and humoral immunity with the prognosis of epithelial ovarian cancer. Aging induces several changes in cellular immunity and a broad immune response. There is no definite evidence of a relationship between the two.[11-13]

The Kaplan Meier curve and log rank test showed that there was no significant difference in disease-free survival between the group of patients aged more than 60 years and the group of patients aged less than 60 years. This is not in accordance with previous studies which showed that ovarian cancer patients aged more than 60 years had a higher risk of recurrence than those aged less than 60 years. This of course can be influenced by several factors such as differences in performance status and the presence or absence of comorbidities in each patient.[14]

Another factor, obesity is also associated with ovarian cancer recurrence. Obesity is a generator of chronic inflammation, because adipose tissue not only acts as an energy reservoir but also causes infiltration and activation of immune cells and excessive production of pro-inflammatory cytokines. In addition, obesity is also associated with high comorbidities, where obesity is a risk factor for several diseases.[14]

In this study, there was no statistically significant difference in disease recurrence in obese and non-obese ovarian cancer patients. As previously explained obesity is associated with chemoresistance which affects the prognosis. While the data analysis in this study was limited only to the group of patients who were said to be in remission, the group of patients who progressed during treatment was not included in the analysis. It is still necessary to conduct further studies regarding the relationship of obesity with epithelial ovarian cancer recurrence.

Histological type of tumor is also said to be an important prognostic factor in epithelial ovarian cancer. However, in multivariate analysis, it was found that histological type 2 had a HR of 1.320 (CI 0.81-2.14) with a p value of 0.261. This shows that the histological type variable cumulatively has no effect as a recurrence factor for epithelial ovarian cancer. Differences in survival patterns based on tumor histology type are thought to be caused by differences in tumor biology and effectiveness of therapy. The heterogeneity of epithelial ovarian cancer causes different sensitivity to chemotherapy regimens. Meanwhile, nutritional status, age, history of previous surgery and neoadjuvant chemotherapy were not shown to be

significant factors associated with epithelial ovarian cancer recurrence.

This study is in accordance with research conducted by Khonsa et al[9] who also showed that the FIGO stage is the main determinant of prognosis and is very influential in determining the good or bad survival of ovarian cancer compared to other variables. The higher the stage of the disease, the worse the survival. Chance of risk compared to stage I, to die up to almost 70 times in stage IV. This concludes that the stage of the disease is very good for survival if it is still at an early stage.[9]

This study has several limitations, where this study is a retrospective cohort, has limitations in terms of data collection through medical records, where some incomplete medical records were obtained, there were a number of patients who were not controlled after treatment (loss follow-up) and there were some obstacles in the implementation of primary therapy for ovarian cancer such as chemotherapy schedules or delayed surgery schedules, as well as a number of patients who are not controlled on time, which of course can affect the assessment of the success of therapy.

5. Conclusion

The incidence of epithelial ovarian cancer recurrence at Dr. Kariadi Hospital Semarang in the 2020-2021 time period is 51.4%. Overall disease-free survival in epithelial ovarian cancer at Dr. Kariadi Semarang were 74.8% (6 months), 57.1% (1 year), 42.5% (18 months), and 37.4% (2 years).

The FIGO stage factor was also proven to be significant as a prognostic factor influencing the recurrence of epithelial ovarian cancer, where the 2-year disease-free survival at stage I was 62.8.%, stage II 34.1%, stage III 18.2%, while for stage I was 18.2%. IV all had recurrence within 7 months of observation

Factors of age, nutritional status, histological type and neoadjuvant chemotherapy, surgery history were not proven to be significant prognostic factors influencing the recurrence of epithelial ovarian cancer in Dr. Kariadi Semarang

Ethical Approval

All procedures have been approved by the issuance of ethical clearance

Conflicts of Interest

The authors declare that there was no conflict of interest.

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Author Contributions

All of the authors developed the plan and design of the study together. Conceptualization, IMK, EA, TMI, HT, JD, AAM, YT; methodology,IMK, EA, TMI, HT, JD, AAM, YT; software, validation, formal analysis, investigation, IMK, EA, TMI, HT, JD, AAM, YT; resources, EIMK, EA, TMI, HT, JD, AAM, YT; writing—original draft preparation, ES; writing—review and editing, IMK, EA, TMI, HT, JD, AAM, YT; visualization,; supervision, JD; project administration; funding acquisition IMK, EA, TMI, HT, JD, AAM, YT.

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