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Recurrence In Non-Epithelial Ovarian Cancer Patients at RSUP Dr. Kariadi Semarang

Gabriele Emi Badia[1]*, Teuku Mirza Iskandar[2], Suhartono[3]

[1]Resident of Obstetrics and Gynecology, Faculty of Medicine, Diponegoro University, Semarang, Indonesia
[2]Department of Obstetrics and Gynecology, Faculty of Medicine, Diponegoro University, Semarang, Indonesia
[3]Department of Environmental Health, Faculty of Medicine, Diponegoro University, Semarang, Indonesia

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*) Correspondence to:
gabrieleemibadia@gmail.com

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ABSTRACT

Background: Non-epithelial ovarian cancer is a scarce type, accounting for less than 10% of ovarian cancers. This type of cancer originates from germ cells or stromal-sex cord cells. Disease-free survival (DFS) in cancer is the length of time after primary treatment for cancer ends so that patients survive without signs or symptoms of cancer. Recurrence is the return of cancer declared in remission, usually after a certain period in which cancer cannot be detected. Cancer can return to the same place (primary) or other parts of the body. Ovarian cancer is a disease with a high probability of recurrence after achieving a complete response to chemotherapy, >70%. Assessment of the recurrence rate is one way to assess the effectiveness of therapy.
Objective: Knowing the incidence of recurrence in patients with non-epithelial ovarian cancer who have received operative therapy with or without adjuvant chemotherapy.
Methods: Descriptive study with a case series research design and analytical works. The research sample was 50 non-epithelial ovarian cancer patients treated at RSUP Dr Karadi Semarang from 2018-2019 who met the inclusion criteria and did not have exclusion criteria, 22 patients lost follow-up during observation. The data collection technique used is total sampling. Data analysis was performed using the Chi-Square test with a significance level of $p<0.05$.
Results: The most reported types of non-epithelial ovarian cancer were granulosa (39.3%), dysgerminoma (21.4%), yolk sac (17.9%), and mixed germ cell (17.9%). Most of the cancer cases are progressive (60.7%). Three recurrence incidents happened during the observation period: two patients with granulosa cell tumour in the>50 years age group and one patient with Yolk Sac cell tumour in the 20-50 age group. Higher survival rates were found for tumour residues <2cm compared to >2cm at six months (54.5% vs 45.5%), 12 months (54.5% vs 36.4%), 18 months (45.5% vs 36.4%), and 24th month (45.5% vs 36.4%).
Conclusion: Surgery optimization depends on the type of non-epithelial ovarian cancer cells, age, and the stage when the diagnosis was first established to be a factor in the incidence of recurrence.

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1. Introduction

The ovaries are paired gonadal structures between the pelvic wall and the uterus. Average ovary sizes vary, up to 5x3x3 cm, formed by 3 (three) types of cells, namely epithelial cells, germ cells, and stromal-sex cord cells, where each cell type gives rise to various types of tumours. Ovarian cancer originating from non-epithelial cells, consisting of germ cells and stromal-sex cord cells, and a scarce type of ovarian cancer, is the cause of less than 10% of ovarian cancers.[1-3]

The incidence of non-epithelial ovarian cancer often occurs at a young age, and most cases are unilateral, so an accurate diagnosis is needed to decide on the type of treatment and consider fertility-sparing if necessary. The management of ovarian cancer is non-epithelial removal, which is a conservative operation by leaving the contralateral ovary suggested in patients with granulosa cell type (due to the nature of cells that are sensitive to chemotherapy). Stage I stromal-sex cord, whereas in postmenopausal women and advanced stages or involvement of both Ovarian stromal-sex cord cell types suggest abdominal hysterectomy and bilateral salpingo-oophorectomy with surgical staging. The staging system for non-epithelial ovarian cancer is generally adopted from epithelial ovarian cancer as defined by the International Federation of Obstetrics and Gynecology.[4,5]

The incidence of non-epithelial ovarian cancer is less than that of epithelial ovarian cancer, and there are fewer studies on this type of cancer. At Dr. Kariadi General Hospital (RSUP), several studies were carried out, which included the incidence of non-epithelial ovarian cancer at

Dr. Kariadi General Hospital. Research in 1980-1986 recorded the incidence of non-epithelial ovarian cancer in as many as 13 germ cells and 11 stromal-sex cord cells.[4]

Ovarian cancer is a disease with a high probability of recurrence. After achieving a complete response to chemotherapy, >70% of patients relapse within two years. There are essential prognostic factors influencing recurrence. The incidence of recurrence and chemoresistance in ovarian cancer is associated with intratumor heterogeneity, microenvironment interactions, and the presence of dynamic cancer stem cell subpopulations. Three main models that explain the heterogeneity of intra-tumour cell populations are clonal evolution theory (stochastic model), stem cell theory (hierarchical model), and tumour niche theory (plasticity model).[6-8]

Research on the recurrence of non-epithelial ovarian cancer, which is related to many factors, has never been done at Dr. Kariadi, so we intend to conduct a study on the recurrence of non-epithelial ovarian cancer in this hospital and assess the factors that influence its occurrence

2. Methods

A descriptive study with a case series research design and analytical works to find out the recurrence rate of non-epithelial type ovarian cancer and how to describe factors that influence recurrence cases which include FIGO stage, histological type of cancer, adjuvant chemotherapy, patient age, disease-free survival (DFS). In non-epithelial ovarian cancer. This research took place at the medical record installation at Dr. Kariadi General Hospital, Semarang. The study took secondary data from medical records of patients diagnosed with non-epithelial ovarian cancer in 2018-2019 as many as 50 patients met the inclusion criteria and did not have exclusion criteria, and 22 patients lost follow-up during observation. Sample selection according to inclusion criteria was patients with non-epithelial ovarian cancer who have received operative therapy with or without chemotherapy and routine control at the RSDK obstetric polyclinic. Exclusion criteria were 1) ovarian cancer patients with incomplete medical record data and histopathological examination results, 2) patients with two primary malignancies (double primary), and 3) ovarian cancer patients who did not undergo surgery or chemotherapy.

3. Result

In this study, we observed the incidence of non-epithelial ovarian cancer and the factors that influence cases of recurrence, namely patient age, surgery optimization, cell histology type, adjuvant chemotherapy, FIGO stadium, and diabetes mellitus. The incidence of diabetes mellitus during observation only occurred in 1 patient who experienced progression during treatment.

Table 1. Distribution of data based on survival

Variable	Survival			p
	Not recurred (%) n=8	Recurred (%) n=3	Progressive (%) n=17	
Age				
≤ 20 years	3 (37,5%)	0 (0%)	5 (62,5%)	0,561¥
21 – 50 years	3 (25%)	1 (8,3%)	8 (66,7%)	
> 50 years	2 (25%)	2 (25%)	4 (50%)	
Operation optimization				
Optimal	4 (33,3%)	2 (16,7%)	6 (50%)	0,533¥
Suboptimal	4 (25%)	1 (6,3%)	11 (68,7%)	
PA results				
Dysgerminoma	4 (66,7%)	0 (0%)	2 (33,3%)	0,302¥
Mix Germ cells	0 (0%)	0 (0%)	5 (100%)	
Teratoma	0 (0%)	0 (0%)	1 (100%)	
Yolk Sac	1 (20%)	1 (20%)	3 (60%)	
Granulosa	3 (27,3%)	2 (18,2%)	6 (54,5%)	
Chemotherapy				
Yes	6 (28,6%)	3 (14,3%)	12 (57,1%)	0,555¥
No	2 (28,6%)	0 (0%)	5 (71,4%)	
Stadium				
I	4 (80%)	1 (30%)	0 (0%)	**0,002¥***
II	0 (0%)	1 (100%)	0 (0%)	
III	2 (13,3%)	0 (0%)	13 (86,7%)	
IV	0 (0%)	1 (33,3%)	2 (66,7%)	
Inadequate	2 (50%)	0 (0%)	2 (50%)	
DM				
Yes	0 (0%)	0 (0%)	1 (100%)	0,715¥
No	8 (29,6%)	3 (11,1%)	16 (59,3%)	
Metastases				
Yes	0 (0%)	2 (28,6%)	5 (71,4%)	0,060¥
No	8 (38,1%)	1 (4,8%)	12 (57,1%)	

¥Chi-square; *significant p<0.05

Patients who develop progressively are generally patients with advanced stages (stages III and IV) and who have complications during surgery, such as a mass that is tightly attached to the intestine, so surgery is needed along with digestive surgery.

Table 2. Details of the recurrence of non-epithelial ovarian cancer patients

Patient	Age	Stage	PA	Operation Optimization	Adj Chemo	DM	Metastase	DFS	Recurrence sign
1	21	IIB	Yolk sac	Optimal	Yes	No	Hepar	12	Abdominal ultrasound: - Hepar metastase - Peritoneal carcinomatosis - Ascites
2	55	I	Granulosa	Optimal	Yes	No	No	24	Abdominal MSCT with contrast: - 3 solid lesions with cystic sections in the umbilical region, inframbilical region and right adnexa region (attached and difficult to separate from the surrounding bowel - suspected residual ovarian neoplasm - Multiple lymphadenopathy - Nodules accompanied by infiltrates in the right lung, suspected metastases
3	63	IVA	Granulosa	Suboptimal	Yes	No	Hepar, pulmo	1	Abdominal MSCT with contrast: - Lobulated cystic mass with solid portions and septa - likely to be ovarian neoplasm - Solid cystic nodule with internal calcification in liver, multiple small cystic lesions in hepatic segments - likely to metastasize - Peritoneal carcinomatosis - Ascites

Table 3. Percentage of 2-year disease-free survival (survival rate) of non-epithelial type ovarian cancer based on tumour residue

Time (Month)	Percentage of *disease-free survival* (%)	
	Residue < 2 cm (n=6) (%)	Residue ≥ 2 cm (n=5) (%)
6	6 (54,5%)	5 (45,5%)
12	6 (54,5%)	4 (36,4%)
18	5 (45,5%)	4 (36,4%)
24	5 (45,5%)	4 (36,4%)

The observation results showed that the disease-free survival rate was higher in the group of patients with a residue of less than 2 cm than in the group with more than 2 cm residue. In the first six months, the disease-free survival rate in the group of patients with a residue of less than 2 cm was 54.5%, and in the group with a residue of more than 2 cm, it was 45.5%, and the percentage decreased in the first 12 months, after which it stayed until the 24th month. However, the results of this observation still have to consider the factors of different types of cells (germinal and sex cord-stromal), which have different types of treatment and different degrees of sensitivity to chemotherapy.

4. Discussion

Three recurrence incidents happened during the observation period, one patient with Yolk Sac cell tumour stage IIB in the 20-50 age group. The risk factor of recurrence in the patient with Yolk Sac was the type of cell and advanced stage; as we know, Yolk Sac is a very malignant cancer, which invades local structures and metastasizes quickly; survival in stages II-IV Yolk Sac patients decreases to 64%.[8] Two patients with granulosa cell tumours in the>50 age group, stage I and IVA, respectively. Granulosa patient with stage IVA was operated on sub-optimally. Risk factors of recurrence in the patients with Granulosa cells were stage and age when first diagnosed and operation optimization; as we know, patients with granulosa cell type at advanced stages II-IV have an initial 5-year survival of just 30%. The incidence of recurrence and prognosis in patients with the granulosa cell type include optimization of surgery and age at first diagnosis.[3, 6, 12]

The patient's age with non-epithelial ovarian cancer depends on the cell type. More than 95% of granulosa cells are of the adult type, occurring in middle-aged and postmenopausal women, with a median age at diagnosis of 50-55 years in which 13 of 14 patients with granulosa cell ovarian cancer were middle-aged women and postmenopausal aged 40-63 years.

Germ cell ovarian cancer usually occurs in the teens or early 20s, generally has a low incidence in childhood, increases at the age of 8-9 years, and the highest incidence is at the age of 18 years[10-12], seen in children, adolescents, and 20s ovarian cancer patients with dysgerminoma cell type in this study. Immature teratomas, the second most common germ cell cancer, are most common in adolescents and young adults of reproductive age. It is said that 50% occurs in women aged 10-20 years, with a peak incidence occurring between 18-19 years.[1] In the age profile of patients with teratoma malignancy at Dr. Kariadi General Hospital, 7 out of 9 patients were over 20 years old, with the oldest being 54 years old. Likewise, Yolk Sac type ovarian cancer often occurs in women in the second and third decades of life, with an average age of 16-18 years, and as many as 1/3 of sufferers are pre-menarche at the time of diagnosis[1], compared with the description of the age of patients with the Yolk Sac cell type at Dr. Kariadi General Hospital, three patients were under 20 years old, four patients were between 21-50 years old, and one patient was 59 years old.

Management of ovarian cancer is surgery and can be continued with chemotherapy according to the stage of the disease. Non-epithelial ovarian cancer that originates from germ cells usually occurs in the young, the teens, or the early 20s[13], so surgery to maintain fertility can still be considered. Even if the patient is diagnosed with an advanced stage, there is room for maintaining fertility in patients who still desire offspring at any stage.[4] However, in stages above stage IA and advanced stages, it is desirable to continue postoperative adjuvant chemotherapy and re-operate for complete surgical staging after the patient has offspring[13] In Yolk Sac type germinal patients, the presence of residual tumour (suboptimal surgery) increases the incidence of recurrence.

In non-epithelial ovarian cancer originating from stroma-sex cord cells, it is recommended to perform optimal surgery/complete surgical staging at any stage. However, in stage I patients who wish to maintain fertility, surgery to maintain fertility function can still be considered, but after the patient's childbearing, completion surgery should be performed. Thorough resection of the tumour mass (optimum operation) at the initial operation is an essential factor because it has been proven that in patients who underwent cytoreduction surgery and had tumour residues, all of them experienced recurrence. 2 In patients with high-risk stage I (ruptured mass, stage 1C, differentiated nasty, mass size >10-15 cm), and stage II-IV, it is recommended to give adjuvant chemotherapy[4].

5. Conclusion

Surgery optimization depends on the type of non-epithelial ovarian cancer cells, age, and the stage when the diagnosis was first established to be a factor in the incidence of recurrence.

Ethical Approval

The research was approved by the Health Research Ethics Committee, Faculty of Medicine, Diponegoro University – Dr. Kariadi and carried out following the principles of the Declaration of Helsinki.

Conflicts of Interest

The authors certify that they have no competing financial interests or personal relationships that could influence the work reported in this paper

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Author Contributions

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