ORIGINAL ARTICLE

Prognostic Factors of Non-epithelial Ovarian Cancer in a Tertiary Hospital in Indonesia

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ABSTRACT

Introduction: Non-epithelial is a rare type of ovarian cancer but the most common ovarian neoplasm in reproductive age. This study analyzed the correlation of clinical characteristics to disease-free survival (DFS) and 3-year survival in non-epithelial ovarian cancer. **Methods:** A cohort analysis of medical records of 30 patients with non-epithelial ovarian cancer from 2016 to 2017 at Dr. Soetomo General Academic Hospital. Survival analysis was performed using Kaplan–Meier test, log-rank test, and Cox regression to determine the correlation of characteristics including age, stage, tumor size, tumor residue, histopathology type and chemotherapy status as prognostic factors for recurrence and mortality. **Results:** DFS was significantly affected by stage (p=0.049), tumor residue (p<0.0001), and chemotherapy (p=0.005). Stage I, no residual disease, and adequate chemotherapy had the highest DFS and mean DFS rates (94.1% and 35.6 months; 95.5% and 35.7 months; 75% and 31.94 months, respectively). Highest recurrence rates were found in patients with unstaged disease (hazard ratio [HR]=10.08), residue >0 cm (HR=23.13), and inadequate chemotherapy (HR=6.55). Three-year survival was significantly affected by stage (p=0.001), tumor residue (p<0.0001), and chemotherapy (p<0.0001). Stage I, no residual disease, and adequate chemotherapy had the highest 3-year survival rate and mean survival time (94.1% and 35.47 months; 95.5% and 35.7 months; 87.5% and 33 months). The highest mortality were found in patients with unstaged disease (HR=19.99), residue >0 cm (HR=11.33), and inadequate chemotherapy (HR=11.71). **Conclusion:** Stage, tumor residue, and chemotherapy status in patients with non-epithelial ovarian cancer are significant prognostic factors for DFS and 3-year survival.
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Keywords: Ovarian neoplasms, Prognostic factors, Disease free survival

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INTRODUCTION

Ovarian cancer is the second most common gynecological cancer after cervical cancer. Ovarian cancer is also termed "silent killer" because there is no screening method for early detection, and mostly symptomatic until the advanced stage. There were 313,959 new cases of ovarian cancer recorded in 2020, with 207,252 mortality cases (1). In Indonesia, 14,896 new cases of ovarian cancer have been recorded, with 9,581 mortality cases (2). Based on their origin, ovarian cancer is divided into epithelial and non-epithelial cancers.

Non-epithelial cells are found in up to 10% of all ovarian cancers (3). The two most frequently diagnosed tumors are malignant ovarian germ cell tumors (MOGCTs) and sex cord-stromal tumors (SCSTs), with several histological subtypes for each type. The yearly adjusted incidence rate is approximately 4 per 1,000,000 and 2 per 1,000,000 women with MOGCTs and SCSTs, respectively (4).

MOGCTs are commonly diagnosed in patients in their first three decades of life; in contrast, SCSTs occurs in all ages but is most common in patients in their 40s and 50s (5). MOGCTs are highly malignant and grow rapidly but are very chemo-sensitive (6). SCSTs is a 95% unilateral and slowly growing tumor with late recurrence (7). The main treatment in MOGCT is adequate surgery (surgical staging or debulking), followed by chemotherapy, except for immature teratoma stage IA grade I and dysgerminoma stage IA. The first line chemotherapy regimen is bleomycin, etoposide and cisplatin (BEP). The main treatment in SCST is also adequate surgery, but some cases with residue can be followed by BEP chemotherapy (8).

This study evaluated the effects of characteristics, such as age, stage, tumor size, tumor residue, histopathology type, and chemotherapy status on disease-free survival (DFS) and 3-year survival. The results of this study will serve as a guideline for improving the quality of health services in patients with ovarian cancer in our developing country.

MATERIALS AND METHODS

Data Collection

This study was a retrospective cohort study with a total sampling of medical records all patients with non-epithelial ovarian cancer treated between January 2016 and December 2017 in our tertiary hospital (Dr. Soetomo General Academic Hospital). Patients were excluded if their medical records were missing or if their mortality was not related to the malignancy.

Subject Characteristics

Data on patient demographics, subject characteristics, treatment received, and prognostic factors were collected, including age, cancer stage, tumor size, tumor residue, histopathology type, and chemotherapy status. Survival was calculated from the moment of histopathological diagnosis until reccurence (disease free survival, DFS) or death within 3 years observation. DFS defined as interval time of free of disease after treatment until recurrence happened. Recurrence defined as recurrent mass on clinical examination and imaging within follow-up time after completion of first line treatment. Three-year survival is defined as proportion of patients who were alive since they got treatment until 3-years after.

Adequate surgery as primary treatment includes mass resection (unilateral salpingo-oophorectomy/ total abdominal hysterectomy and bilateral salpingo-oophorectomy), peritoneal washing, omental biopsy, peritoneal biopsy, and lymphadenectomy. Stage was defined during surgery with classification of FIGO 2014 (3) by an experienced oncologist. Tumor size was the biggest diameter of mass and tumor residue data was obtained from surgery report or pelvic CT-scan. Subtype of cancer was defined by histopathology examination according to classification of WHO 2014 (8). Adequate chemotherapy consisted of Bleomycin (30 mg/m2) on day 4th, 11th and 18th, Etoposide (100 mg/m2) and Cisplatin (20 mg/m2) on day 1st till 5th. They were given one week after surgery for minimal three cycles, repeated every 21 days.

Statistical Analysis

IBM SPSS Statistics version 20.0 (IBM Corp., Armonk, NY, USA) was used for statistical analyses. Descriptive statistics were calculated for all subjects. Chi-square or Kruskal–Wallis tests were used for the univariate analysis. DFS and 3-year survival were analyzed using Kaplan–Meier and log-rank tests to determine differences in survival curves. Hazard ratios were calculated using Cox regression analysis. Statistical significance was set at p-value <0.05.

Ethical Clearance

This study was approved by Research Ethics Committee of Dr. Soetomo General Academic Hospital No. 0530/ LOE/301.4.2/VII/2021 on July 28th 2021.

RESULTS

Subject Characteristics

We recorded 30 cases of non-epithelial ovarian cancer based on their histopathology results. They consisted of 15 women with SCSTs and 15 women with MOGCTs. SCSTs consisted of 14 patients with adult granulosa cell tumors and one juvenile granulosa cell tumor. MOGCT consisted of nine patients with dysgerminoma, two patients with immature teratomas, and four patients with yolk sac tumors. Most patients (80%) were referred from outside the hospital. The average age was 33 years, the youngest age in MOGCTs and SCSTs group were 13 years and 24 years, the oldest were 57 years and 55 years old. The average body mass index was 24.14 kg/m2, and 16.67% of them (5 of 30) were obese. Nulliparity was identified in 12/30 patients. Most patients experienced menarche at 12 years, and 28/30 of them were pre-menopausal. Tumor markers including alpha fetoprotein (AFP), human chorionic gonadotropin (hCG), lactate dehydrogenase (LDH), and cancer antigen-125 (Ca-125) were completely examined in patients aged < 35 years with suspected non-epithelial ovarian cancer (Table I).

Surgery in our hospital was performed on 14/30 patients as their first surgery, including conservative surgical staging, which was conducted on 6/14 patients. Secondary surgery was performed on patients who underwent inadequate first surgery outside our hospital in 9/16 of the patients.

Association between age and survival

There was no significant difference in recurrence rate between <40 years and >40 years groups (p=0.62), but recurrence was most frequent in patients aged <40 years (21.1%). The patient's age had no statistically significant effect on DFS in non-epithelial ovarian cancer (p=0.436) (table II). There was no significant difference in the mortality rate between the two groups (p=0.452). Age

Table I: Descriptive analysis of tumor marker levels in each non-epithelial type ovarian cancer

Tumor Marker	Germ Cell Tumor Median (min-max)	Sex Cord-Stromal Tumor Median (min-max)
hCG	2.0 (2.0–40.25)	2.0 (2.0–3.42)
AFP	7.7 (0.8–5119)	3.0 (1.30–8.10)
LDH	1036 (222–6927)	214 (138–299)
Ca-125	128 (5.0–600)	11 (3.90–600)

hCG, human chorionic gonadotropin; AFP, alpha fetoprotein; LDH, lactate dehydrogenase; Ca-125, cancer antigen-125.

Table II: Analytic of prognostic factors on recurrence, disease free survival, and hazard ratio

Prognostic Factors	Total n	Recurrence n (%)	p-value (univariate analysis)	DFS (%)	Mean DFS (months) (95% CI)	p-value (Log rank)	Hazard Ratio (95% CI)	p-value (Cox-regression)
Age			0.62			0.436		
≤40 years old	19	4 (21.1%)		78.9%	27.89 (20.40–35.37)		1	0.448
>40 years old	11	2 (18.2%)		81.8%	30.96 (24.64–37.27)		0.51 (0.09–2.83)	
Stage			0.037*			0.049*		
I	17	1 (5.9%)		94.1%	35.6 (35.07–36.26)		1	
II	1	1 (100%)		0 %	17 (17.0–17.0)		15.47 (0.94–253.64	0.05
III	5	1 (20%)		80%	20.5 (0.00–41.98)		9.75 (0.60–158.25)	0.19
Unstaged	7	3 (42.9%)		57.1%	19.2 (7.14–31.26)		10.08 (1.03–98.26)	0.047
Tumor size			0.40			0.447		
≤10 cm	9	1 (11.1%)		88.9%	32.2 (25.53–38.86)		1	0.46
>10 cm	21	5 (23.8%)		76.2%	28.19 (21.86–34.51)		2.23 (0.26–19.16)	
Tumor Residue			0.002*			<0.0001*		
Residue 0 cm	22	1 (4.5%)		95.5%	35.7 (35.3–36.2)		1	0.005
Residue>0 cm	8	5 (62.5%)		37.5%	16 (5.9–26.0)		23.13 (2.62–203.79)	
Histopathology type			0.55			0.659		
Germ Cell Tumor								
Dysgerminoma	9	3 (33.3%)		66.7%	-		1	
Immature Teratoma	2	0 (0%)		100%	-		0.00 (0.00)	0.982
Yolk Sac Tumor	4	0 (0%)		100%	-		0.00 (0.00)	0.986
Sex-Cord Stromal Tumor								
Adult Granulosa Cell Tumor	14	3 (21.4%)		78.6%	-		0.468 (0.093–2.341)	0.355
Juvenile Granulosa Cell Tumor	1	0 (0%)		100%	-		0.00 (0.00)	0.995
Chemotherapy status			0.12			0.005*		
Adequate	8	2 (25%)		75%	31.94 (25.27–38.60)		1	
Inadequate	11	4 (27.3%)		63.6%	13.67 (7.56–19.77)		6.55 (0.72–59.30)	0.24
Not indicated chemotherapy	11	0 (0%)		100%	-		0.00 (0.00)	0.95

*p<0.05
CI, confidence interval

had no effect on the 3-year survival (p=0.455) and was not a prognostic factor for recurrence (p=0.448) and mortality (p=0.46) in patients with non-epithelial ovarian cancer but mortality was highest in patients aged <40 years (36.8%) (table III).

Association between stage and survival

Most patients were identified in stage I (56.67%). There was a significant difference in recurrence between each of the stages of cancer (p=0.037). The highest recurrence within 3 years occurred in patients with unstaged disease (42.9%; three patients), and the lowest recurrence occurred in those with stage I (5.9%; one patient). Only one patient found in stage II had a recurrence to which she succumbed, so the DFS and 3-years survival were 0%. The stage was significantly correlated with DFS (p=0.049). The highest DFS rate was identified in stage I (94.1%), with the longest mean DFS time of 35.6 months (fig. 1). The lowest DFS in patients with unstaged disease was 57.1% with a mean DFS time of 19.2 months. Hazard ratio of of stage I = 1, HR of stage II =15.47 (95% CI, 0.94-253.64), HR of stage III =9.75 (95% CI, 0.60-158.25) and HR of unstaged disease =10.08 (95% CI, 1.03-98.26).

There was significant difference in mortality between all stages (p=0.001). The highest mortality was identified in patients with unstaged disease (71.5%), and the lowest mortality was found in stage I (5.9%). The stage had significant effect on 3-year survival (p=0.001). Stage I had 3-year survival rate of 94.1%, with mean survival time of 35.47 months (fig. 2). Patients with unstaged disease had 28.6% of 3-years survival rate with mean survival time of 15.57 months. Hazard ratio of mortality in stage I =1, HR of stage II =20.66 (95% CI, 1.26-338.60), HR of stage III =19.48 (95% CI, 2.01-189.10), and HR of unstaged disease =19.99 (95% CI, 2.28-174.82) (table III).

Association between tumor size and survival

The average tumor size in the present study was 15 cm, the smallest was 5 cm, and the largest was 30 cm. There was no significant difference in recurrence between tumor size <10 cm and >10 cm (p=0.40), however recurrence was more common in patients with tumor size >10 cm (23.8% vs. 11.1%). Tumor size was not correlated with DFS (p=0.447) and was not a significant prognostic factor for recurrence (p=0.46) (table II). Mortality in each group was not significantly different (p=0.344), but patients with tumor size >10 cm had a higher mortality rate (38.1% vs. 22.2%). Tumor size was not correlated with 3-year survival and also not a significant prognostic factor of mortality (p=0.42) (table III).

Association between residual tumor and survival

There was a significant difference of recurrence rate between residual tumor 0 cm and >0 cm groups

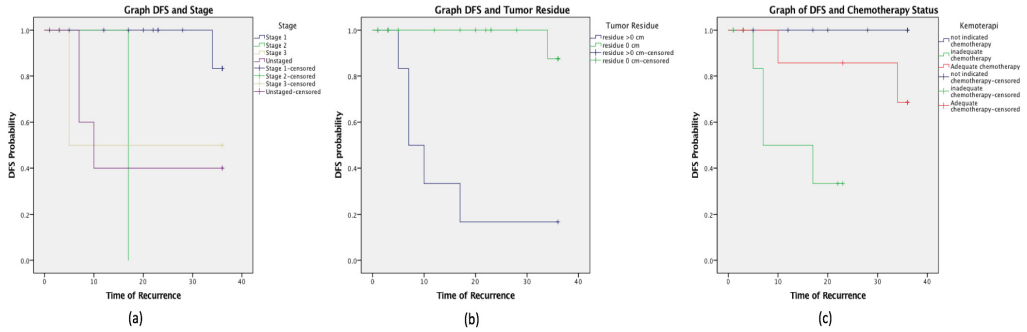

Fig. 1: Graph of disease free survival and significant prognostic factors using Kaplan-Meier (a) based on stage of cancer, (b) based on tumor residue, (c) based on chemotherapy status.

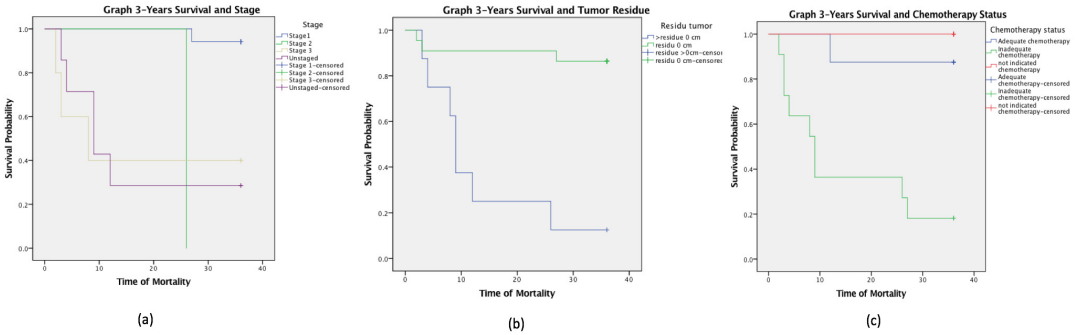

Fig. 2: Graph of 3-years survival and significant prognostic factors using Kaplan-Meier (a) based on stage of cancer, (b) based on tumor residue, (c) based on chemotherapy status.

Table III: Analytic of prognostic factors on mortality, 3-years survival, and hazard ratio

Prognostic factors	Total n	Mortality n (%)	p-value (univariate analysis)	3-Year Survival (%)	Mean Survival (months) (95% CI)	p-value (Log rank)	Hazard Ratio (95% CI)	p-value (Cox-Regression)
Age			0.452			0.455		
≤40 years old	19	7 (36.8%)		63.2%	24.89 (18.28–31.50)		1	0.46
>40 years old	11	3 (27.3%)		72.7%	31.81 (27.04–36.59)		0.60 (0.15–2.33)	
Stage			0.001*			0.001*		
I	17	1 (5.9%)		94.1%	35.47 (34.46–36.47)		1	
II	1	1 (100%)		0%	26.0(26.0–26.0)		20.66 (1.26–338.60)	0.03
III	5	3 (60%)		40%	17.0 (3.28–30.71)		19.48 (2.01–189.10)	0.01
Unstaged	7	5 (71.4%)		28.6%	15.57 (5.76–25.37)		19.99 (2.28–174.82)	0.007
Tumor size			0.344			0.409		
≤10 cm	9	2 (22.2%)		77.8%	31.22 (24.39–38.05)		1	0.42
>10 cm	21	8 (38.1%)		61.9%	25.81 (19.91–31.70)		1.89 (0.40–8.92)	
Tumor residue			<0.0001*			<0.0001*		
Residue=0 cm	22	3 (13.6%)		86.4%	32.54 (28.49–36.59)		1	0.001
Residue >0 cm	8	7 (87.5%)		12.5%	13.37 (5.88–20.87)		11.33 (2.73–46.99)	
Histopathology type			0.981			0.708		
Germ Cell Tumor	9							
Dysgerminoma	2	3 (33.3%)		66.7%	-		1	
Immature Teratoma	4	0 (0%)		100%	-		0.00 (0.00)	0.991
Yolk Sac Tumor		2 (50%)		50%	-		1.84 (0.30–11.11)	0.503
Sex-Cord Stromal Tumor	14							
Adult Granulosa Cell Tumor	1	5 (35.7%)		64.3%	-		0.95 (0.23–3.99)	0.948
Juvenile Granulosa Cell Tumor		0 (0%)		100%	-		0.00 (0.00)	0.994
Chemotherapy status			<0.0001*			<0.0001*		
Adequate	8	1 (12.5%)		87.5%	33.0 (27.50-38.50)		1	
Inadequate	11	9 (81.8%)		18.2%	14.81 (7.16-22.47)		11.71 (1.46–93.80)	0.06
Not indicated chemotherapy	11	0 (0%)		100%	-		0.00 (0.00)	0.96

*p<0.05
CI, confidence interval

(p=0.002). The recurrence occurred more often in patients with residual tumor than in those without (62.5% vs. 4.5%). Residual tumor had significant effect on DFS (p=<0.0001). Higher DFS rate was found in patients without residual tumor (95.5% vs. 37.5%) with longer mean DFS time (35.7 months vs. 16 months) (fig. 1). Residual tumor is a significant prognostic factor of recurrence (HR = 23.13; 95% CI, 2.62-203.79). The highest mortality was found in patients with residual tumor (87.5% vs. 13.6%). Residual tumor had significant effect on survival (p<0.0001). Patients without residual tumor had longer mean survival time (32.54 months vs. 13.37 months) (fig. 2). Residual tumor is significant prognostic factor of mortality (HR of residual tumor = 11.33; 95% CI, 2.73-46.99).

Association between histopathology type of cancer and survival

There was no significant difference in recurrence between histopathological types (p=0.55). Recurrence occurred in patients with dysgerminoma (33.3%) and adult granulosa cell tumors (21.4%). Histopathological type of non-epithelial ovarian cancer had no effect on DFS and was not a prognostic factor of recurrence (p=0.659) (table II). Mortality was found in 33.3% of patients with dysgerminoma, 50% with yolk sac tumor, and 35.7% with adult granulosa cell tumors. There was no correlation between histopathological type and mortality (p=0.981). Histopathological type also had no significant effect on 3-years survival (p=0.708) (table III).

Association between chemotherapy status and survival

Recurrence occurred in four patients (27.3%) with inadequate chemotherapy, and in two patients (25%) with adequate chemotherapy. Patients with adequate chemotherapy experienced recurrence of dysgerminoma IC and unstaged adult granulosa cell tumors. One of five patients (20%) with advanced stage (stage II-IV) who were administered chemotherapy adequately had recurrence, whereas recurrence was higher in patients with inadequate chemotherapy, as noted in four of eight patients (50%). DFS in patients with adequate chemotherapy was better than those with inadequate chemotherapy (75% vs. 63.3%) (table II) and a longer mean DFS time (31.94 months vs. 13.67 months) (fig. 1). Inadequate chemotherapy is a significant prognostic factor of recurrence (HR=6.55; 95% CI, 0.72-59.30).

Death occurred more commonly (81.8%) in patients who received inadequate chemotherapy (p<0.0001). Chemotherapy status had a significant effect on the survival rate (p<0.0001). Three-year survival rate was higher in patients who received adequate chemotherapy than inadequate chemotherapy (87.5% vs. 18.2%) (table III), with longer mean survival time (33 months vs. 14.81 months) (fig. 2). Chemotherapy status was a significant prognostic factor for mortality (p=0.02). Patients with inadequate chemotherapy had higher risk of mortality (HR= 11.71).

DISCUSSION

Stage, residual tumor, and chemotherapy significantly affected DFS and 3-year survival of patients with non-epithelial ovarian cancer. Better prognosis with a lower rate of recurrence and mortality was found in patients with stage I, without postoperative residual tumor, and adequate chemotherapy.

The best prognosis found in patients with stage I (17/30). Reccurence and mortality only found in 1/17 patients. Patients with unstaged disease have a risk of recurrence 10 times higher and risk of mortality 20 times higher than those with stage I. These results are consistent with the clinical perspective that optimal debulking surgery is more difficult to perform in higher disease stages. This study result is consistent with previous studies stating that the advanced stage is a significant independent prognostic factor for survival and low DFS in granulosa cell tumors (9). A study reported a recurrence of 5% in stage I of SCSTs and approximately 33% in an advanced stage (10).

In this study all patients underwent operation and 22/30 with complete resection. The highest recurrence and mortality occurred in patients with residual tumors >0 cm. Patients with a residual tumor >0 cm have 23 times higher risk of recurrence and 11 times higher of mortality. This result is consistent with a study of epithelial ovarian cancer which showed that residual tumor significantly increased the risk of mortality by 2.47 times (11). A previous study of MOGCTs also showed that stage I patients who underwent adequate surgery had a higher DFS than those who did not (12). Overall survival of MOGCTs patients with residual tumor was lower than patients without residual tumor (65.7% vs. 91.5%) (13).

Chemotherapy was administered to 19/30 patients and 8/19 patients had adequate chemotherapy who had higher DFS and 3-years survival (75% and 87.5%). Inadequate chemotherapy has 7 times higher risk of recurrence and 12 times higher risk of mortality. This result was consistent with previous studies. Chemotherapy administered to patients with epithelial ovarian cancer had significant effect on overall survival (14) and also for MOGCT, surgery followed by adequate chemotherapy lead to a longer survival time (15). In this study, chemotherapy was also administered to 4/7 patients with unstaged disease, and only 1/4 of them with inadequate chemotherapy experienced recurrence and mortality. Three surgical unstaged disease did not receive chemotherapy because of the suspicion of stage 1A, based on evaluation of clinical examination, description of operative report and the postoperative radiological modalities. Higher reccurence (1/3) and mortality (3/3) found in patients with unstaged disease who didn't receive chemotherapy. In fact, in this group of highly chemo-sensitive patients, only less than half of them received adequate chemotherapy because lack

of patient's adherence to treatment. It is important to do more intense counseling and communication with patients regarding chemotherapy schedule.

In this study result, patient's age, tumor size, and histopathological type were not a prognostic factor. On the other hand, some previous studies have shown correlation. A retrospective study in Italy reported that age was a predictor of recurrence in MOGCT (16). Women aged <40 years with SCST had better survival than those aged >40 years (93% vs. 84%) (13). In theory, increasing age increases comorbidity and decreases immunological status. The aged >40 years group in this study was dominated by patients with SCST with good prognosis because based on literature, 95% of SCST occur unilaterally, 78–91% are identified in stage I, and there is slow growth with late recurrence (17). Previous studies defined that larger tumor size in epithelial ovarian cancer is associated with worse prognosis (18-19). A large mass can be presume to result form rapid growth and crowding effect which can lead to complications and adhesions with surrounding organs and tissues that worsen the prognosis. In addition, patients with SCSTs who have a tumor size <10 cm have better survival (20). The difference between our results and previous studies in epithelial type might be caused by the small sample size for each group. Also the tumor size group >10 cm consisted of 11 patients (52.4%) with stage IA, which had isolated cancer mass and had a better prognosis. This study was in concordance with a previous study on 42 patients with MOGCTs and SCSTs which reported that tumor size of cancer was not significantly associated with patient survival (21). This study was slightly different from previous study on MOGCTs that showed the highest recurrence occurred in immature teratoma and the lowest in dysgerminoma (13). However, this study result was consistent with another study which stated that yolk sac tumor had the worst prognosis and highest mortality in patients with MOGCT (22). Yolk sac tumors are highly malignant, it grows rapidly, spreads hematogenously and intra-abdominally (23).

Based on this study, 17/30 cases were found at early stage and 7/30 patients with unstaged disease. Unstaged disease had worst prognosis. Adequate surgical staging is very important treatment of non-epithelial ovarian cancer especially for early stage. Patients who underwent inadequate operation outside our hospital, should be considered carefully to have re-surgery. Adequate surgical staging defines stage accurately which is important to determine next treatment and monitoring. Complete resection should be done for advanced stage so that no residual tumor is left. It also help enhance the response to chemotherapy. Adequate dose and cycles of chemotherapy should be administered with close follow-up. Best prognosis is dictated by early stage, complete surgery and adequate chemotherapy. At suspicion of a malignant ovarian tumor it is better to refer to a tertiary hospital with specialized oncologists and adequate facilities for cancer treatment.

CONCLUSION

Early stage, no residual tumor, and adequate chemotherapy associated with higher DFS and 3-year survival rate and were significant prognostic factors affecting recurrence and mortality in patients with non-epithelial ovarian cancer.

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