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Case Report

Characteristics of granulosa cell tumor at Dr. Soetomo general hospital from 2014 to 2019

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ABSTRACT

Objectives: The aim of the present study was to investigate tumor characteristics, treatment, recurrence, and prognosis in both Granulosa Cell Tumor types.

Materials and Methods: A retrospective review study of 38 patients in a single institute; We identified patients with GCTs diagnosed between 2014 and 2019 in the Regional General Dr. Soetomo Hospital. Surgical outcome, pathological findings and follow-up data were analyzed. Statistical analyses were conducted using Fisher exact test and Kaplan-Meier survival curves and compared with the log-rank test.

Results: The prevalence of AGCT subtypes as the most common type occurring in 97% of cases. The median age at diagnosis among patients with AGCT is 47.5 years (range 41-59), and most women are premenopausal and multiparous. In our literature review Stage 1 disease is 76% with Overall Survival (OS) for 5 years is 89.7%. FIGO stage and adjuvant therapy was not shown a positive correlation with recurrency ($p > 0.05$). Rate of recurrence in AGCT is reported to be as high as 5.26%.

Conclusions: GCT is a rare low malignant tumor, majority of patients present with early-stage disease and generally have a favorable prognosis. Stage is not considered as the most important prognostic factor. The role of adjuvant chemotherapy treatment is debatable as it was not shown to reduce recurrence rates. Long-term surveillance including routine clinical follow-up and tumor markers serial evaluation is mandatory to evaluate recurrency.

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1. Introduction

Granulosa cell tumor (GCT) is a rare type of tumor and only accounts for 2-8% of all ovarian malignancies.¹⁻⁸ Estimated incidence is estimated at 0.99/100,000 in the United States, whereas incidence for other developed countries ranges from 0.4 to 1.7/100,000.^{2,4-7,9,10} GCT is characterized by slow growth in a sluggish course, and recurrence is possible even after more than a decade. For this reason, prolonged follow-up is required. Although the prognosis is often favorable, tumors that recur or are in an advanced stage at diagnosis may have a poor prognosis.

The case of granulosa cell tumor which was treated at RSUD Dr. Soetomo for the period 2014 – 2019 was an average of 6 patients per year. Researchers will specifically review how the characteristics of granulosa cell tumors in RSUD Soetomo especially in terms of management, recurrence rate and survival rate. At the end of this review, readers can understand how to diagnose and how to properly treat this rare ovarian malignancy.

2. Materials and Methods

The researcher used a retrospective analytic review study. We identified GCT patients diagnosed between 2014 and 2019 at the Dr. Soetomo. Complete patient data used were secondary data obtained from the medical record

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and Electronic Medical Record (EMR) database of the oncology department. Surgical results, pathological findings and follow-up data were analyzed. Statistical analysis was performed using Fisher exact test and Kaplan-Meier survival curves with log-rank test as comparison. The results of statistical processing presented in this investigation are in the form of Frequency and Percentage Distribution Tabulations and graphs.

3. Results

The results of the study were 38 cases of granulosa cell tumors in the oncology division of the Department of Obstetrics and Gynecology dr. Soetomo, Surabaya is presented in the following table:

Of 38 patients with malignant granulosa cell tumors who underwent surgery, the youngest patient was 13 years old and the oldest was 72 years old. The most granulosa cell tumors were in the 41-60 year age group, namely 22 patients (57.9%), followed by the 21-40 year age group as many as 13 patients (34.2%), the 61-80 year age group as many as 2 patients (5.3%) and at least 1 patient (2.6%). Patients with granulosa cell tumors who underwent surgery at Dr. Hospital. Soetomo in 2014 to 2019 were mostly referrals from outside the city of Surabaya, but still covered the East Java area, namely 32 patients (85%), from within Surabaya as many as 11 patients (34%) and there were also referrals from outside East Java. As many as 1 patient (3%). Based on parity, granulosa cell tumor patients who underwent surgery were mostly primi/multiparous as many as 31 patients (82%) and the rest were nulliparous as many as 7 patients (18%). Based on menopausal status, most of the patients were not menopausal as many as 27 patients (71%) and the remaining 11 patients (29%) had menopause.

Based on the type of complaint, the most with complaints of abdominal pain as many as 14 patients (37%), enlarged abdomen in 10 patients (27%), palpable masses in 8 patients (21%) and the least bleeding in 6 patients (16%). There were no asymptomatic patients (0%). Based on CA-125 results, most patients had CA-125 values > 35 as many as 20 patients (53%) and the rest had CA-125 values < 35 as many as 19 patients (47%). Based on the type of granulosa cell tumor, the most common types were adults with 97 patients (97%) and adolescents with 1 patient (3%). Based on the type of surgery performed on the patient, the most TAH-BSO type surgery was performed, namely 29 patients (74%), followed by USO as many as 6 patients (16%), and the least type of surgery was debulking of tumor mass/biopsy as many as 3 patients. (8%). The histopathological results showed that the tumor size which was more than or equal to 10cm was 34 specimens (89%), while the tumor size smaller than 10cm was 4 specimens (11%). Based on the classification of the condition of the tumor during surgery, whether it was ruptured or not, 7 patients were found to have ruptured tumors, namely (18%),

while those that did not rupture or were compressed before the tumor was removed from the abdominal cavity were 31 patients (82%). Based on the presence or absence of residual tumor after surgery, 7 patients (18%) had residual tumors of various sizes (cm) and 31 patients (82%) had no residual tumor.

From the results of the post-op parade, the most common staging of granulosa cell tumor patients was stage I, which was 29 patients (76%), followed by stage III with 5 patients (13%), advanced as many as 3 patients (8%) and at least stage II that is 1 patient (3%). The data showed that from 38 patients who underwent surgery, there were 8 patients (21%) who received post-op adjuvant chemotherapy and as many as 30 patients (79%). Of 38 patients with granulosa cell tumors who were operated on for the first time until a recurrence appeared in the form of a residif mass during patient follow-up, there were 2 patients (5%) relapsed and the remaining 36 patients (95%) did not show recurrence. Based on the last condition of the patients we followed up, from 38 granulosa cell tumor patients, 10 patients (26%) died, the remaining 28 patients (74%) were alive and well without any complaints.

Until October 2020, from a total of 38 patients who were followed up, the Overall Survival (OS) for 5 years was 73.7% with an average patient survival of 29 months. Successively the survival rate for Stage I is 89.7%. Stage II is 100%, Stage III is 20% and from the advanced stage we did not get 1 patient (0%) who managed to survive.

The results showed that most adjuvant chemotherapy was given on the basis of stage and presence of tumor residues. Patients diagnosed with stage 1 (86.7%) did not receive adjuvant therapy, while patients with stage II and above were 62.5% (p 0.010) receiving adjuvant therapy. Post-op patients with residual tumor who received adjuvant therapy were 62.5% (p 0.002)

The results showed that none of these factors had significant significance (p value > 0.05) on the incidence of recurrence of granulosa cell tumors.

4. Discussion

Based on secondary data obtained in 2014-2019 from medical records, this tumor can be present at any age, 80% of the more common forms of Adult GCT appear in women older than 40 years, most often in perimenopausal or postmenopausal women between 50 years and 54 years.^{2,4-7,9-13} Half of Juvenile GCTs are diagnosed in girls younger than 10 years, with studies showing a median age at diagnosis of 8 to 13 years.^{14,15} Some case report also describe juvenile GCT found in infants.¹⁶ However, during the period 2014 to 2019, we did not find any cases of granulosa cells in infants. Patients with granulosa cell tumors who underwent surgery at Dr. Hospital. Soetomo in 2014 to 2019 were mostly referrals from outside the city of Surabaya. The same thing was found in the study of Wei K,

Table 1: Frequency distribution of patient characteristics of Granulose cell tumor operated on at Dr. Soetomo 2014 to 2019

	Number of patients (N)	Percentage (%)
Age		
≤40	14	37
>40	24	63
Menopausal status		
Pre-menopause	27	71
Post-menopause	11	29
Parity		
Nullipara	7	18
Primi/multipara	31	82
Referral from		
Surabaya	11	29
Outside Surabaya	26	68
Outside East Java	1	3
Stage		
I	29	76
II	1	3
III	5	13
Advanced	3	8
GCT's type		
Adult	37	97
Juvenile	1	3
Symptoms		
No symptoms	0	0
Bleeding	6	16
Abdominal pain	14	37
Abdominal distention	10	26
Palpable mass	8	21
CA-125		
<35	18	47
≥35 U/mL	20	53
Surgery		
TAH-BSO	29	76
USO	6	16
Debulking/Biopsy	3	8
Tumor size		
<10 cm	4	11
≥10cm	34	89
Tumor rupture		
Yes	7	18
No	31	82
Residual tumor		
Yes	7	18
No	31	82

Table 2: Overall Survival (OS) 5 years for patients with granulosa cell tumors who underwent surgery at Soetomo Hospital in 2014 to 2019

Stage	Total N	N of Events	N	Percentage (%)
Advanced	3	3	0	0.0%
Stage I	29	3	26	89.7%
Stage II	1	0	1	100.0%
Stage III	5	4	1	20.0%
Overall	38	10	28	73.7%

Table 3: Distribution of clinical pathology in patients receiving adjuvant chemotherapy versus no treatment

Number of patients (n = 38)	Adjuvant therapy ^b		p value ^a
	No n (%) (n = 30)	Yes n (%) (n = 8)	
Age			
≤40	13(43,3)	1(12,5)	0.114
>40	17(56,7)	7(87,5)	
Stage			
I	26(86,7)	26(86,7)	0.010
II - advanced	4(13,3)	5(62,5)	
Surgery			
Complete	25(83,3)	7(87,5)	0.628
Fertility preserves	5(16,7)	1(12,5)	
Tumor size			
<10 cm	2(6,66)	2(25)	0.189
≥10 cm	28(93,4)	6(75)	
Tumor rupture			
Yes	4(13,3)	3(37,5)	0.146
No	26(86,7)	5(62,5)	
Residual tumor			
Yes	2(6,66)	5(62,5)	0.002
No	28(93,4)	3(37,5)	

^aCalculated by Fisher's exact test for proportion.^bCalculated on the data available**Table 4:** Distribution of clinico-pathological parameters as prognostic factors for recurrence

Number of patients (n = 38)	Recurrence ^b		p value ^a
	No n (%) (n = 36)	Yes n (%) (n = 2)	
Age			
≤40	13(36,1)	1(50)	0,607
>40	23(63,8)	1(50)	
Stage			
I	28(77,8)	1(50)	0,422
II - advanced	8(22,2)	1(50)	
Tumor size			
<10 cm	4(11,1)	0	0,618
≥10 cm	32(88,9)	2(100)	
Tumor rupture			
Yes	6(16,7)	1(50)	0,339
No	30(83,3)	1(50)	
Residual tumor			
Yes	6(16,7)	1(50)	0,339
No	30(83,3)	1(50)	
Adjuvant			
Yes	7(19,4)	1(50)	0,833
No	29 (80,6)	1(50)	
Surgery			
Complete	31(86,1)	1(50)	0,294
Fertility preserves	5(13,9)	1(50)	

^aCalculated by Fisher's exact test for proportion.^bCalculated on the data available

Table 5: Clinical characteristics of the 2 cases of GCT recurrence

	Mrs. J	Mrs. C
Age	37 years old	45 years old
Referral	Outside of Surabaya (Situbondo)	Outside of Surabaya (Bangil)
Chief complaint	Abdominal distended	Abdominal pain
Ca-125 U/mL	243,6	3,9
Primary surgery	SOS + PFC (3/2014)	Debulk Sin + Omentectomy (3/2017)
FIGO Stage	IC3	IIIB
Histopathology	AGCT PFC atypical cell (malignant)	AGCT; tumor confined inside capsule; No tumor found in omentum
Tumor size	≥10cm (21x20x5)	>10cm (13x9x8)
Tumor rupture	Yes	No
Residual tumor	-	Yes (4x4cm)
Chemotherapy	BEP 3series (2014)	-
Recurrent	Residif mass 4,7x2,9x5,4 (2/2016)	Residif mass 7,5 x5 x 5 (9/2017)
DFS	23 months	6 months
Recurrent therapy	Loss of ff up	Optimalization surgery TAH + Salpingectomy bilat + debulking mass tumor Sin (9/2017) BEP (-) Lost of follow up
Last follow up	3/2016	8/2018
Death	6/2016	9/2018

et al. that the incidence and mortality of ovarian cancer was higher in urban areas than in rural areas.

Based on parity, the majority of granulosa cell tumor patients who underwent surgery at RSUD Soetomo were primi/multiparous, based on several case studies that have been reviewed previously explained that parity does not seem to affect the risk of GCT.^{1,2} 71% of granulosa cell tumor patients who had not yet menopause and 29% who had menopause were found. This is not in accordance with the results of previous studies which stated that almost 60% of adult GCT occurred after menopause.^{17–20} Menopause does not cause granulosa cell tumors, but the risk of granulosa cell tumors increases with age. When a woman has gone through menopause, the risk of granulosa cell tumors increases due to old age. Based on several case studies that have been reviewed previously explained that menopausal status does not seem to affect the risk of GCT.^{1,2}

The patients we treated at the Soetomo General Hospital had symptoms that were often non-specific as in common ovarian cancer. None of the patients we treated were asymptomatic. All patients were symptomatic and came with the most complaints of abdominal pain (37%), after which successively followed by complaints of enlarged abdomen, palpable mass and abnormal vaginal bleeding only (16%). This complaint of abdominal pain is a symptom related to the fact that GCTs are often large (10 to 15 cm) and hemorrhagic.^{6,10,21,22} We did not find any patients with acute onset of pelvic pain due to torsion of the tumor mass or cases of spontaneous hemorrhagic rupture (hemoperitoneum). Bleeding in the granulosa cell tumor patients that we treated were not dominant and not

in accordance with the developed theory, because there were only 6 patients who came with bleeding complaints. Abnormal uterine bleeding in 3 premenopausal patients and 3 postmenopausal patients.

All patients who underwent TAH-BSO, only 1 patient (3.5%) had nonatypical hyperplasia, this is not in accordance with the previous case study which stated that as many as 25% to 50% of the adult form of GCT is associated with the development of endometrial hyperplasia.^{2–4,9,23} In our patients USO (mean age 31 years) for fertility preservation was not routine for endometrial biopsy because the study results showed endometrial carcinoma/atypical hyperplasia was common in GCT patients >40 years; Based on this study, priority endometrial sampling was performed in symptomatic women with a minimum age of 40 years. In asymptomatic women < 40 years, endometrial sampling is not preferred.²⁴ We did not find precocious pseudopuberty, because in one case of juvenile GCT our 13-year-old patient was a postmenarchal adolescent.

Preoperative CA-125 levels are routinely checked in all cases with suspected ovarian cancer, only to differentiate the case diagnosis that these 38 cases are not epithelial ovarian cancer, until proven yes. The ideal tumor marker examined in cases of granulosa cell tumors is inhibin, several other studies have confirmed this observation (Boggess JF et. al, 1997). However, the obstacle and this is the limitation of our study is the unavailability of this Inhibin tumor marker in Indonesia. Our patient diagnosed with this granulosa cell tumor had almost 53% CA-125 levels above 35 U/mL. And this does not conclude that granulosa cell tumor patients have high CA-125 levels, but it could be caused by other conditions. Because high levels of CA-125 can be caused by

Endometriosis, PID, fibroids, impaired liver function, and others.

We found 97% of cases were adult type and 3% were juvenile type. From a total of 38 patients, we found one 13-year-old juvenile type patient. This is in accordance with the results of previous studies which stated that these granulosa cell tumors were of adult type (95%) and juvenile type (<20 years) (5%) based on histological findings. The mean size of the tumor as a result of histopathological measurements was 89% with a diameter of 10cm. This is in accordance with the results of studies that have been reviewed previously, namely that the average diameter size is 10-15cm.^{17,19,25} We found 18% of tumor ruptures, and the incidence of tumor rupture in 7 of our patients was caused by the evacuation process during surgery because the tumor was large, fragile with great adhesion. Based on tumor residuals, there were 18% of patients with post-op tumor residual. Residual tumors are caused by the attachment of the tumor mass to the peritoneal cavity organs such as the rectum or abdominal wall that is difficult to free.

Of the total 38 patients we treated, all of them received surgical treatment, either primary surgery, optimizing surgery due to recurrence, or optimizing surgery due to incomplete surgery from another referral hospital. The type of surgery that was performed the most was TAH-BSO 76% on the basis of the consideration that most of our patients did not want to maintain their fertility anymore. Our patients 82% were primi/multiparous with at least one live child. Meanwhile, 6 patients (18%) underwent USO (Unilateral Salpingo Oophorectomy without contralateral ovarian biopsy because the incidence of bilaterality was about 2–8%. This is consistent with previous studies, because in our patient who had both ovaries removed, we found 1 Bilateral tumor incidence (2.6%). Biopsies of the contralateral ovary are controversial and should be performed with caution to preserve fertility.⁴ In 3 cases (8%) we performed only suboptimal debulking or tumor mass biopsy only with death. The tumor residue on the basis of Durante Op's considerations, the tumor mass is so large with great adhesions that it is difficult to free it with profuse bleeding during the operation.

Adjuvant chemotherapy is an additional postoperative therapy that is considered for patients who have a high risk of recurrence, such as stage IC and above, tumor rupture, large tumor size, and residual tumor. The main considerations in the patients we treated were the patient's stage (p 0.010) and the presence of residual tumor (p 0.002). Until now the recommended adjuvant chemotherapy is BEP (Bleomycin / Etoposide / Cisplatin) because it is well tolerated by Bjorkholm and Silfversward,⁹ reported that patients with clinical stage I disease whose tumor ruptured should be treated with BEP 3 series. Post-operative adjuvant chemotherapy was given to 8 patients (21%) namely in patients with stage IC to advanced stage who had a ruptured tumor/spillage durante op or with residual tumor. However,

from the 8 patients there were 2 patients who received Pacli Carbo adjuvant therapy, 1 patient because they could not afford Etoposide (Etoposide was not covered by BPJS). Paclitaxel has been used in repeated GCT with dramatic response.²⁶ The potential activity of paclitaxel has been confirmed by the study of Brown et al.²⁷ Patients outside of stage IC to advanced patients were only followed up after surgery, this was because most of the stages we got were stage IA and did not require adjuvant therapy.^{3,6,9,10,12}

From a total of 38 patients we treated, there were 2 adult GCT patients who had relapsed (5%), and we tried to relate it to various factors such as age, stage, tumor size, tumor rupture, residual tumor, adjuvant therapy and type of surgery. Of all the factors we tested, none of them gave any significance to the degree of recurrence (p > 0.05). Two relapsed patients were from the IC3 group of patients who received adjuvant and IIIB who did not receive adjuvant since primary surgery. And both patients died after experiencing a relapse.

From a total of 38 patients treated at RSUD Soetomo, the 5-year survival rate was 73.7% of all diagnosed stages. The 5-year survival rate of high granulosa cell tumors was caused by as many as 76% of patients being diagnosed as stage I. The 5-year survival rate of Stage I itself was 89.7%. This is in accordance with the survival rate according to tumor stage according to FIGO, where the 5-year survival rate Stage I is 90 to 100%.

Tumor stage is the most important prognostic factor.^{3,5,6,9,10,12,28} Tumor stage is closely related to the patient's survival rate. The relationship between survival rate and staging has been tested by researchers and is in accordance with the 5-year FIGO survival rate. The results of the linkage test can be concluded that the patients treated at RSUD Dr. Soetomo is diagnosed mostly at an early stage, and this provides a better prognostic and 5-year survival rate.

5. Conclusion

GCT is a rare low-grade malignant tumor, most patients are diagnosed at an early stage and generally have a good prognosis. Stage is not considered the most important prognostic factor. The role of adjuvant chemotherapy treatment is still debated because it has not been shown to reduce recurrence rates. Long-term surveillance including routine clinical follow-up and serial evaluation of tumor markers is mandatory to evaluate recurrence.

6. Source of Funding

None.

7. Conflict of Interest

The authors declare no conflict of interest.

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