



Characteristics of Ovarian Tumor Clinicopathology: 3 Years Experience

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ABSTRACT

Ovarian tumors account for 30% of all malignancies in the female genital organs and can be benign, borderline, and malignant tumors. According to World Health Organization (WHO) based on the origin of tumor cells are divided into three groups, namely epithelial tumors, cord-stromal sex, and germ cells where the most types are epithelial types. This study aims to determine the clinicopathological characteristics of ovarian tumors carried out in a descriptive observational manner. Samples using secondary data of ovarian tumor patients who came to the Anatomical Pathology Section of Dr. Mohammad Hoesin Hospital Palembang for the 2018-2020 period who met the inclusion criteria using the total sampling technique obtained 325 secondary data all included as research samples. The results of the study found proportional morbidity rate of ovarian tumors based on the type of histopathology most epithelial tumors obtained by 55%. The highest ovarian tumor patients in the age group of 20-34 years are 91 people, the most common type of tumor histopathology is epithelial tumors as many as 179 cases where mucinous tumor most occur at the age of 20-34 years as many as 23 people, the most growth patterns are cystic 140 cases, the most ovarian tumor behavior is malignant tumors as many as 143 cases. Malignant ovarian tumors are most common in the age group of 20-34 and 45-54 years, which is 37 people each. The cystic growth pattern is most prevalent in benign ovarian tumors, which are as many as 87 cases. It can be concluded that the most common ovarian tumors are epithelial tumors. Based on age and growth patterns, most ovarian tumors occur at the age of 20-34 years with cystic growth patterns. The behavior of most ovarian tumors is malignant tumors.

1. Introduction

Based on the growth pattern, ovarian neoplasms are divided into tumors with solid, cystic, and mixed growth patterns.¹ In histopathology, these neoplasms can be found ranging from the benign, borderline, and malignant spectrum. According to the World Health Organization (WHO), based on its origin, ovarian neoplasms are divided into tumors of epithelial, cord-stromal sex, germ cell and mixed cell origin. But among this group, the most common type is ovarian neoplasms of the epithelial type.¹

Some risk factors that play a role in ovarian neoplasms include old age, nullipara, primigravida more than 30 years of age, menarche less than 12 years, use of hormone replacement therapy, obesity, oral contraceptives and a family history of ovarian/breast/endometrial/colon cancer.

Similarly, there is no data available describing ovarian neoplasms, especially at Dr. Mohammad Hoesin General Hospital Palembang, which is a national referral hospital for the southern Sumatra region. So that this research is carried out with the aim of describing the characteristics of ovarian

neoplasms based on clinico-histopathology and so that it can be used as a reference and basic data for future research.

2. Methods

This study is a descriptive study using secondary data of ovarian tumor patients in the Anatomical Department of Dr. Mohammad Hoesin General Hospital Palembang for the 2018-2020 period. A total-sampling techniques used according to inclusion and exclusion criteria. Three hundred and twenty-five selected samples were carried out univariate and bivariate analysis to determine the distribution of ovarian neoplasms based on clinico-histopathological characteristics such as age, histopathological type, growth pattern, tumor behavior and proportional morbidity rate calculation.

3. Results

Based on age, ovarian neoplasms are found in the age range of 1 to 99 years with the highest frequency

in the young adult group of 20-34 years (28%). The most common ovarian neoplasms were epithelial neoplasms, which accounted for 55% of samples, followed by neoplasms of germ cell origin and neoplasms of cord-stromal sex origin as much as 32.7% and 12.3% of samples, respectively. Histopathologically, the most epithelial neoplasms in this study were mucinous-type neoplasms as much as 52.5% of all epithelial neoplasms. While neoplasia from cord-stromal sex is the most type of adult granulose cell tumor (57.5%) and neoplasia from germ cells is mostly at mature (67.9%). Based on growth patterns, the most ovarian neoplasia was with cystic growth patterns, which was 43.1% of samples. Based on tumor behavior, epithelial neoplasia has the most malignant behavior (48.6%) compared to benign or borderline behavior as well as neoplasia from the most cord-stromal sex have malignant/malignant behavior (60%). As for germ cell type neoplasia, the most common is benign neoplasia, which is as much as 69.8% of all neoplasia of germ cell origin.

Table 1. Distribution of ovarium tumors based on age, histopathology type, pattern of growth, and tumor behavior.

Clinicopathological characteristics				Total (n)	Percentage (%)
Age (years)					
				30	9,2
				91	28
				70	21,5
				70	21,5
				44	13,5
				16	4,9
				3	0,9
				1	0,3
Histopathology type					
Adult granulose cell tumor				23	7,1
Sex cord tumor with annular tubules				1	0,3
Mixed sex cord-stromal tumor				3	0,9
Mixed epithelial and sex cord-stromal tumor				1	0,3
Germinal cell tumors				106	32,7
Mature teratoma				72	22,2
Immature teratoma				11	3,4
Dysgerminoma				8	2,5
Yolk sac tumor				10	3,1
Mixed germ cell tumor				2	0,6
Struma ovarii				3	0,9
Growth pattern					
Mixture				67	20,6
Cystic				140	43,1
Dense				118	36,3
Tumor behavior					
	Benign	Borderline	Malignant		
Epithelial type	53	39	87	179	55
Cord-stromal sex type	8	8	24	40	12,3
Types of germ cells	74	-	32	106	32,7

It was found that the most common ovarian neoplasms in the sample were mucinous type neoplasms (28.9%) followed by teratomas and serous type neoplasms. On the other hand, thecoma, Brenner tumor and stromal sex cord tumor are rare neoplasms. Ovarian serous tumors are most commonly found in the age group of 45-54 years, which is about 25.45% of all serous neoplasm samples, while mucinous neoplasms most occur in the age group of 20-34 years, which is around 13.8%. Endometrioid neoplasms were only found in 3 samples, namely in the age group of 45-54 years and clear cell tumor were most commonly found in the age group of 35-44 years, which was 39.1% of the total neoplasms of this type.

In the group of neoplasms derived from stromal cells and ovarian sex cord such as fibroma, these neoplasms are most commonly found in the age group of 35-44 years (37.5%). Thecoma and sclerosing tumor were only found in 1 sample each in the age group of 20-34 years. Similarly, the type of mixed epithelial and sex cord-stromal tumor only 1 sample was studied and was in the age group of 55-64. Signet ring stromal tumor only found 2 cases in the age group of 35-44 years as well as neoplasms type sex cord tumor with annular tubules which only found 1 sample in the age group of <20 years. While the type of mixed sex cord-stromal tumor was found in 3 cases in the age range of 20-64 years. Among the other types in this group, adult granulosa cell tumor is the most common type with the most samples in the age group of 45-54 years (47.8%) (Table 2). In the group of neoplasms of germ cell origin, such as mature teratoma, immature, dysgerminoma, yolk sac and mixed are most found in the age group of 20-34 years (41.6%, 54.54%, 62.5%), 100% and 66.6%) (Table 2).

From Table 3, it can be seen that benign and malignant epithelial ovarian neoplasms are most prevalent in the age group of 45-54 years, namely 3.6% and 8% respectively, while borderline ovarian neoplasms most occur in the age group of 35-44

years (3.0%). Of the 53 samples of benign neoplasms, 54.7% of samples had cystic growth but on the contrary, from 87 samples of malignant neoplasm, the most frequent growth pattern was the solid pattern growth (49.4%).

In the stromal and sex-cord cell origin group, the age range of samples was found between <20-74 years, with the highest age frequency in the age group of 45-54 years (72%). Of the 48 samples of neoplasia from stromal cells and sex cord, benign and borderline tumor behavior were each present in 14.5% of samples while malignant/malignant behavior was found in 50% of samples. The most common growth pattern in benign and malignant neoplasia in this group of neoplasia is solid growth pattern compared to cystic and mixed growth (Table 3).

From 325 samples, there were 106 (32.61%) ovarian neoplasm derived from germ cells with an age range between <20-84 years. However, in general, the sample with the most frequent age is in the age group of 20-34 years (46.2%). Among them, neoplasia was found with benign tumor behavior as much as 30.1% and malignant 16.03% of samples. Based on the growth pattern, neoplasms of benign germ cell origin generally have cystic growth patterns (77.02%) while neoplasms with germ cell origin with malignant behavior are generally with a solid growth pattern (68.75%) (Table 3).

Proportional morbidity rate or ovarian neoplasm incidence rate based on histopathology type showed that epithelial, germinal and stromal sex cord tumor had PMR of 55%, 32.6% and 12.3% respectively.

4. Discussion

Clinicopathological characteristics of ovarian tumors

Due to age and repeated ovulation processes, the ovary surface epithelium will experience continued irritation that cause genetic changes lead to neoplastic lesion.⁵ The wide age range of ovarian

neoplasm patients can be caused by the presence of certain types of neoplastic lesion associated with certain ages, such as neoplasms of germinal cell's which is indeed found at one and second decade of age. Similarly, neoplasms of malignant germ cell origin are commonly found at the age of 20 to 30 years.⁶ This finding is in line with the results of Gupta et al's study in 2019 in which 212 cases of ovarian tumors were found to occur most in the age group of 10 to 30 years.⁷

Most cases of ovarian malignancy are diagnosed at an advanced stage (stage 3 and 4) when cancer cells have begun to spread to other surrounding tissues or organs. Based on data from the American Cancer Society, only about 20% of ovarian malignancy cases are diagnosed at an early stage. Women with symptoms and a high risk of ovarian cancer are recommended to have ovarian cancer screening tests such as transvaginal ultrasound examination (TVUS) and CA-125. High levels of CA-125 in endometriosis patients are closely associated with ovarian cancer.⁸ Research by Puspasari et al found that the age of endometriosis and epithelial type ovarian tumors is most common in the 30-34 years. This suggests a link between endometriosis and epithelial-ovarian tumors.^{9,10}

In accordance with Pratama G et al at Riau Regional General Hospital and Arnila et al at Mohammad Hoesin Hospital, epithelial tumors are the most often tumor found after germ cell and stromal sex cord tumor.^{3,6} Similarly, Gupta's study conducted at Tertiary Care Hospital in India found that epithelial ovarian tumors as the most common tumor (71.7%) followed by tumors of germinal and stromal sex cord origin.⁷ Epithelial ovarian neoplasms generally originate from germinativum cells on the outer surface of the ovary that are inclusions into the ovarian cortex.¹¹ Risk factors such as endometriosis that are commonly found in women of reproductive age could be risk of high rates of PMR ovarian neoplasms.^{9,10}

Musinus type ovarian neoplasms are the most common neoplasms among other epithelial neoplasms such as serous, endometrioid, clear cell, brenner and mixed type. Based on the progression and response of chemotherapy, ovarian tumors are divided into two types. The first type tends to be slow growth, causes few symptoms, and has a good response to chemotherapy. Included in this type are low-grade serous carcinoma (LGSC), clear cell carcinoma, mucinous carcinoma, and endometrioid carcinoma. The second type of ovarian tumor tend to be more progressive and have a better response to chemotherapy. Included in this type is a high grade serous carcinoma (HGSC).¹²

Cord-stromal sex tumor are a rare ovarian tumor that account for about 1% of all types of ovarian tumors and among them granulosa cell tumors are the most common type, which is about 90%. More than half of stromal sex cord tumors are found in women over 50 years. The most common symptom is abnormal vaginal bleeding. Malignant ovarian tumors of stromal sex cord cell origin such as granulosa cell type and sertoli-leydig cell tumors are usually considered as a low-grade cancer which have a good prognosis compared to malignant epithelial tumors.^{11,13}

Germ cell tumors of ovary is originated from primitive germ cells with an indent of about 30% of all ovarian tumors, mainly affecting children and young adults. About 3% of these tumors are usually malignant.^{14,15} The etiology and pathogenesis of these tumors are uncertain, but some studies suggest that the incidence of germ cell tumors is related to genetic etiology.¹⁴ Based on Surveillance, Epidemiology, and End Results (SEER) data, most ovarian tumors of germ cell origin have a better prognosis and high cure rate while epithelial cell tumors are the type of cancer with the worst prognosis. Data from 2010-2016 found that the highest life expectancy of ovarian cancer patients was ovarian tumor patients of germ cell origin (93%), followed by stromal tumors (88%),

and the lowest was invasive epithelial ovarian cancer (48%).¹⁶

Based on growth patterns, this study shows that the most growth patterns were cystic. In benign tumors, the dominant growth pattern is cystic, while in malignant tumors, the dominant growth pattern is solid.⁷ Research conducted at the Department of Pathology MR Medical College, Basaveshwara Teaching and General Hospital Kalaburgi in 2021 found that the most ovarian tumor growth pattern was cystic growth pattern of 85.71% followed by solid growth pattern of 8.93% and the lowest was mixed growth pattern of 5.36%.¹⁷ Research conducted at the Department of Pathology Chalmeda Anand Rao Institute of Medical Sciences, Karimnagar in 2020 stated the same thing where the most growth patterns obtained was cystic, which was 66.7%, followed by solid-cystic or mixed at 26.6% and solid at 6.7%.¹⁸ Growth patterns tend to be cystic, especially if the precursors of epithelial ovarian tumors are endometriosis and inclusion cysts.

Based on tumor behavior, the most ovarian tumors found in this study were malignant tumors. Research conducted by Vs and Bu in 2020 also stated the same thing where of 53 cases, the most ovarian tumors were malignant tumors, which were 71.7%, followed by benign tumors at 22.64% and the lowest was borderline tumors at 5.66%.¹⁹

Malignant ovarian tumors account for about 30% of all malignancies in the female genital system and are highest mortality among gynecologic tumors.²⁰ Based on Globocan 2020 data, the incidence of ovarian cancer was 313,959 and 207,252 of them died or this disease. In this study, the most epithelial type malignant tumors were high-grade serous carcinoma, the most stromal type malignant tumors were adult granulosa cell tumors, and the most germinal type malignant tumors were yolk sac tumor. The theory states that 90% of ovarian cancers originate from epithelial cells, of which the most common is serous carcinoma.²¹ According to the

American Cancer Society, ovarian epithelial cancer is the leading cause of death of any other type of female reproductive system cancer in the United States, as most cases of ovarian malignancy are high-grade serous ovarian cancer (HGSC).¹² Epithelial tumors are closely associated with endometriosis and other cystic lesions such as simplex cysts and follicular cysts.

Distribution of histopathological types of ovarium tumors by age

Serous tumors are most common in the age group of 45-54 years, while musinus tumors are most common in the age group of 20-34 years. Benign serous tumors are usually found in reproductive age woman, borderline serous tumors average age 50 years, and malignant serous tumors are in the fifth and sixth decades, while benign musinus tumors occur at an average age of 50 years, borderline musinus tumors average age 45 years, and malignant sinus tumors average age 55 years. Research conducted by Sharma M et al in 2017 found that serous tumors and musinus tumors most occur at the age of >50 years, namely 26 cases and 13 cases, respectively.²²

In this study, endometrioid carcinoma occurred in the age group of 45-54 years in accordance with the theory that the average age of endometrioid carcinoma patients is around the age of 55 years.¹¹

Clear cell tumors are also one of the rare tumors, especially for benign and borderline types. Clear cell carcinoma is generally found on average at the age of 55-56 years, according to Arianto et al's research in 2021 where this type of carcinoma was found to occur most at the age of >40 years.²³

Brenner's tumors account for about 5% of benign epithelial ovarian tumors and the majority occur in the fifth to seventh decades of life.¹¹ This is in accordance with the results in this study, namely the age of 65-74 years.

Precursor lesions of epithelial ovarian tumors are generally benign cystic lesions such as endometriosis and inclusion cysts so that they take longer time to become malignant lesions, while germ cell type ovarian tumors do not have precursor lesions so this type of tumor is often found at a younger age.⁶

Fibroma can occur at any age, but most often appears in middle age and rarely occurs before age 30.¹¹ Adult granulosa cell tumor is the most prevalent tumor in the age group of 45-54 years. This is in accordance with the research of Solanki et al in 2021, where in the study it was found that this tumor occurred in the age group of 40-59 years or postmenopausal women with a peak age of 50-55 years.¹¹

Mature teratoma is the most common germ cell ovarian tumor found in the age group of 20-34 years. This study is consistent with the theory that mature teratomas often occur in reproductive age.¹¹ Solanki et al in 2021 in their research also stated that mature teratomas most occur in the age group of 20-39 years.²⁴

Immature teratoma, dysgerminoma, and yolk sac tumor were most commonly found within the first three decades of life, but dysgerminomas often occur in children and young women. In this study, the youngest patients diagnosed with dysgerminoma was 1 year old, and yolk sac tumor was most common in the second and third decades of life.¹¹ Sharma M et al in 2017, where it was found that yolk sac tumor occurred in the age group of 20-40 years.²²

Age distribution and growth patterns based on tumor behavior

Benign ovarian tumors and malignant ovarian tumor most often occur in the age group of 20-34 years and 45-54 years, respectively. Research conducted by Vs and Bu in 2020 also stated the same thing, namely most benign tumors occur in younger age groups and malignant tumors are more common in older age groups.¹⁹ It can be concluded that the

behavior of ovarian tumors will increase with age. Unlike the case with malignant germ cell ovarian tumors, the theory states that two-thirds of cases of these tumors are found around the age of 20 years and are rarely found in the thirties.⁶ Carcinogenesis takes longer in epithelial ovarian tumors while germ cell type ovarian tumors can directly become malignant lesions so that this type of tumor is often found at a younger age.⁶

The mixed and solid growth patterns were most prevalent in malignant ovarian tumors while cystic growth patterns were most prevalent in benign ovarian tumors. According to research conducted at the Department of Pathology MR Medical College, Basaveshwara Teaching and General Hospital Kalaburgi in 2021, mixed and solid growth patterns were most prevalent in malignant ovarian tumors and cystic growth patterns were most prevalent in benign ovarian tumors.¹⁷ Several previous research studies stated that the majority of cystic growth patterns occur in benign tumors while solid growth patterns are most prevalent in malignant tumors, borderline ovarian tumors that lead to malignancy then the growth pattern is also dense. In accordance with precursor lesions where epithelial tumor precursor lesions are endometriosis, simplex cysts, and follicular cysts, benign tumors are often found cystic growth patterns and when they change towards malignancy, the tumor will become solid.^{7,12}

Proportional morbidity rate

The highest proportional morbidity rate of ovarian tumors based on histopathological type was epithelial tumors. The dualistic model of ovarian epithelial carcinoma divides the pathogenesis pathway into type 1 and type 2 tumor. The precursor lesion of type 1 tumor undergoes morphological changes to malignancy after going beyond the borderline phase. The most common genetic changes in this type are KRAS and BRAF mutations that can activate the MAPK oncogenic pathway. Type 2 is thought to form

de novo or originate from unrecognized precursor lesions, develop very quickly and often metastasize. The most common genetic mutations in this type are TP53 and BRCA 1/2 gene mutations.^{12,25}

Recent studies state that genomic events and genetic locks contribute to the pathogenesis of sex cord stromal cell tumors. These tumors can be found in hereditary syndromes such as Peutz-Jeghers syndrome, Ollier's disease, Maffucci's syndrome, and DICER1 syndrome. About 30% of juvenile granulose

cell tumors contain GNAS mutations, while another 60% have active mutations in the AKT gene. While in the case of adult granulose cell tumors, most have FOXL2 C134W mutations (>95%).^{13,26}

Ovarian tumors of dysgerminoma type germ cells and yolk sac tumor have the majority of changes in chromosome 12p (KRAS), which are around 80 and 60%, respectively, while those with KIT mutations are around 30-50 and 55%, respectively.²⁶

Table 2. Distribution of histopathological types of ovarium tumor by age.

Histopathology type	Age (years)								n	%
	<20	20-34	35-44	45-54	55-64	65-74	75-84	>84		
Serous tumor	2	10	13	14	10	4	2	-	55	16,9
Mucinous tumor	7	23	19	20	18	6	-	1	94	28,9
Endometrioid tumor	-	-	-	3	-	-	-	-	3	0,9
Clear cell tumor	-	1	9	7	5	1	-	-	23	7,1
Brenner tumor	-	-	-	-	-	1	-	-	1	0,3
Other carcinomas	-	-	-	1	-	-	-	-	1	0,3
Mixed epithelial tumor	-	-	-	2	-	-	-	-	2	0,6
Fibroma	-	-	3	2	2	1	-	-	8	2,5
Thecoma	-	1	-	-	-	-	-	-	1	0,3
Sclerosing stromal tumor	-	1	-	-	-	-	-	-	1	0,3
Signet-ring stromal tumor	-	-	2	-	-	-	-	-	2	0,6
Adult granulose cell tumor	-	5	3	11	3	1	-	-	23	7,1
Sex cord tumor with annular tubules	1	-	-	-	-	-	-	-	1	0,3
Mixed sex cord-stromal	-	1	1	-	1	-	-	-	3	0,9
Mixed epithelial and sex cord-stromal tumor	-	-	-	-	1	-	-	-	1	0,3
Mature teratoma	9	30	17	10	3	2	1	-	72	22,2
Immature teratoma	5	6	-	-	-	-	-	-	11	3,4
Dysgerminoma	3	5	-	-	-	-	-	-	8	2,5
Yolk sac tumor	3	4	2	-	1	-	-	-	10	3,1
Mixed germ cell tumor	-	2	-	-	-	-	-	-	2	0,6
Struma ovarii	-	2	1	-	-	-	-	-	3	0,9
Total	30	91	70	70	44	16	3	1	325	100

Table 3. Age distribution and growth patterns based on tumor behavior.

	Tumor behavior			Total (n)	Percentage (%)
	Tame	Borderline	Ferocious		
Epithelial type					
Age					5
<20	7	1	1	9	19
20-34	10	9	15	34	22,9
35-44	9	10	22	41	26,3
45-54	12	9	26	47	18,4
55-64	8	7	18	33	6,7
65-74	7	2	3	12	1,1
75-84	-	-	2	2	6
>84	-	1	-	1	
Growth patterns					
Mixture	10	12	19	41	22,9
Cystic	29	19	25	73	40,8
Dense	14	8	43	65	36,3
Cord-Stromal sex type					
Age					
<20	-	1	-	1	2,5
20-34	2	1	5	8	20
35-44	3	3	3	9	22,5
45-54	1	1	11	13	32,5
55-64	1	2	4	7	17,5
65-74	1	-	1	2	5
75-84	-	-	-	-	-
>84	-	-	-	-	-
Growth patterns					
Mixture	2	2	9	13	32,5
Cystic	1	1	7	9	22,5
Dense	5	5	8	18	45
Germinal cell type					
Age					
<20	9	-	11	20	18,9
20-34	32	-	17	49	46,2
35-44	17	-	3	20	18,9
45-54	10	-	-	10	9,4
55-64	3	-	1	4	3,8
65-74	2	-	-	2	1,9
75-84	1	-	-	1	0,9
>84	-	-	-	-	-
Growth patterns					12,3
Mixture	4	-	9	13	54,7
Cystic	57	-	1	58	33
Dense	13	-	22	35	

5. Conclusion

Ovarian tumors often occur are malignant tumors, in reproductive age where tumors of epithelial origin are mainly mucinous, cystic and malignant types. Solid and mixed growth patterns are most prevalent in malignant ovarian tumors while cystic growth patterns are most prevalent in benign ovarian tumors.

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