

# Ovarian Tumors: Pattern of Histomorphological Types- A 10 Years Study in a Tertiary Referral Center and Review of Literature

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## Citation

Ghosh A, Ghartimagar D, Thapa S, Sathian B, Narasimhan R, Talwar OP. Ovarian Tumors: Pattern of Histomorphological Types-10 Years Study in a Tertiary Referral Center and Review of Literature. *Kathmandu Univ Med J* 2016;54(2):153-8.

## ABSTRACT

### Background

Ovarian cancer accounts for 6% of all cancers in females. Among cancers of female genital tract, the incidence of ovarian cancers ranks below only carcinoma of the cervix and the endometrium.

### Objective

To find the frequency of different types of histomorphological types and their association with age, side and size distribution.

### Method

This study is a hospital based retrospective study carried out in the Department of Pathology, Manipal Teaching Hospital over a time period from Jan. 2006 to Sep. 2015. Specimens were received from the Manipal Teaching Hospital and other hospitals within the Himalayan valley of Pokhara. All the clinical and histopathological data were retrieved from the departmental data bank and were analyzed.

### Result

A total of 409 cases of ovarian tumors have been reported in the same period. Among them, 215 cases were of surface epithelial origin including 172 benign, 07 borderline and 36 malignant cases. Among the surface epithelial tumors, the commonest was serous cystadenoma (119 cases) followed by mucinous cyst adenoma (40 cases). There were 176 cases of tumors with germ cell origin which included 170 cases of teratoma, four dysgerminoma and one each case of choriocarcinoma and yolk sac tumor. Among seven metastatic tumors, one case was of Krukenberg tumor. Age range was 12 to 90 years and the size range from 3 to 36 cm.

### Conclusion

In our study, we analyzed all the spectrum of ovarian tumors diagnosed on morphological bases and most of the findings were similar to other national & international studies. However, we have reported increased percentage of mucinous tumors and less sex cord stromal tumors.

## KEY WORDS

*Germ cell tumor, metastatic, mucinous, ovarian tumor, serous*

## INTRODUCTION

Ovarian cancers are common among females comprising 6% of all cancers and 30% of cancers of female genital tracts. Among cancers of female genital tract, the incidence of ovarian cancers rank below carcinoma of cervix and endometrium.<sup>1,2</sup> It is the commonest cause of death due to cancer of female genital tract and the fifth leading cause of cancer related deaths in females.<sup>3</sup> The age adjusted incidence rate vary from 2-15 per 100000 women. Its incidence is least in the developing countries of South East Asia and Africa and highest in the industrialized developed countries of Europe and North America.<sup>1,4</sup> The classification of ovarian tumors is based mainly on histomorphology. Most ovarian tumors are benign.<sup>1</sup> In the present study, we have analyzed the spectrum of ovarian tumors. This study was carried out to find the frequency of different types of histomorphological types and their correlation with age, side and size distribution.

## METHODS

This study was a hospital based retrospective study carried out in the Department of Pathology , Manipal Teaching Hospital over a time period from Jan. 2006 to Sep. 2015. All the specimens diagnosed with ovarian tumors, which were received from Manipal Teaching Hospital and other hospitals within the Pokhara valley, were included in this study. All the histopathological data were collected from the departmental data bank and were analyzed. The tissues were routinely fixed with 10% formalin and the slides were stained with H & E stain and also with special stains (e.g., PAS, Mucicarmine, Reticulin) wherever

required. Ethical approval was taken prior to the study. The data were analyzed with SPSS 16 software using descriptive and inferential statistics. P value <0.05 was considered as statistically significant.

## RESULTS

A total of 409 cases of ovarian tumors have been reported in the same period. Age range was from 12 to 90 years and the tumor size ranged from 3 to 36 cm. Among all cases, 215 cases were of surface epithelial origin including 172 benign, 7 borderline and 36 malignant cases. Table 1 shows the frequency, age distribution, side affected and size distribution of all surface epithelial tumors. Among the benign surface epithelial tumors, the commonest was serous cystadenoma (119 cases) followed by mucinous cystadenoma (40 cases) and benign Brenner (eight cases). Among the malignant group, the commonest was of serous type (22 cases) followed by mucinous type (11 cases) and malignant Brenner (one case). Among all surface epithelial tumors left side (51.5%, CI 44.8,58.2) is slightly more affected than right side (48.5%, CI 41.8, 55.2). 115 cases (53.49%, CI 47.9, 61.2) were above 40 years of age. Number of cases with tumor size more than 10 cm (103 cases, 45.37%, CI 38.8,52.7) and cases with tumor size 5-10 cm (101 cases, 44.49% CI 38.3,51.7) were almost similar and much more than cases with less than 5 cm tumor size (23 cases, 10.13% CI 6.5,14.8). Association between tumor types and age distribution, and size distribution were statistically significant (p = 0.0001, p=0.0001) while side distribution was not statistically significant (p=0.9841). The microscopic features of all cases of serous adenocarcinoma have been summarized in Table 2. Necrosis and increased

**Table 1. Showing frequency and spectrum of surface epithelial tumors (n=215 )**

Histopathological diagnosis	N	%	95% Confidence Interval		Age (years)				Side affected			Size (cm) (Including bilateral tumors)					
					<40	>40	Mean	SD	R	L	Bilat- etral	<5	5-10	>10	Mean	SD	
<b>Benign n=172</b>	Serous	119	55.3	46.10	59.50	62	57	42.6333	14.0897	57	61	1	19	62	39	9.1	4.1453
	Mucinous	40	18.6	13.30	23.70	25	15	44.878	14.4364	20	19	1	1	6	34	12.439	3.2097
	Brenners	8	3.7	1.50	6.80	-	8	56.625	5.7056	3	5	-	-	8	0	7.5	1.1952
	Combined Serous + benign Brenner	3	1.39	0.30	3.80	1	2	46.3333	7.3711	2	1	-	-	-	3	15	1
	Combi ed Serous + Mucinous	1	0.46	0.00	2.40	1	-	32	-	-	-	1	-	2	-	7	-
	Serous cystad- enofibroma	1	0.46	0.00	2.40	1	-	36	-	-	1	-	-	-	1	14	-
<b>Borderline n=7</b>	Mucinous ( pure )	4	1.86	0.50	4.50	-	4	49.5	3.5119	2	2	-	-	-	4	13.75	1.5
	Serous	3	1.39	0.30	3.80	2	1	40.3333	6.8069	2	1	-	-	2	1	10	4.3589
<b>Malignant n=36</b>	Serous	22	10.23	9.10	18.30	2	20	64.9333	13.4496	6	8	8	2	12	16	10.633	3.634
	Mucinous	11	5.11	2.80	9.10	6	5	43.5	16.0991	5	5	1	1	8	3	8.75	3.137
	Serous+mucinous	2	0.93	0.10	3.10	-	1	65	4.2426	1	1	-	-	1	1	11	4.2426
	Brenner	1	0.46	0.00	2.40	-	1	59	-	1	-	-	-	-	1	13	-
<b>Total</b>		215	100			100	115			99	104	12	23	101	103		

**Table 2. Showing gross and microscopic features of serous cyst adenocarcinoma tumors (total number of tumors = 30 including 22 patients with 8 bilateral cases)**

Microscopic features		N	%
Pattern	Papillae	30	100
	Solid sheets	30	100
	Cribriform area	03	10
Necrosis (gross/microscopy)		30	100
Increased atypical mitosis		30	100
Peritoneal implant		12	40
Emboli (vascular/lymphatic)		09	30
Psammoma body		07	23.3
Comedo pattern necrosis		05	16.7
Metastasis to other sites		3(FT2*, U1†)	10
Focal mucin production		01	3.3
Other cell type (<10% of tumor)		01	3.3

\*FT= Fallopian tube, †U= Uterus body

atypical mitoses were noted in all cases and among different histopathological patterns, papillae formation and solid sheets of tumor cells were seen in all cases. Psammoma bodies were seen in 23.3% cases. Three cases had metastases to other sites including 2 cases to fallopian tube and one case to uterine body.

**Table 3. Showing frequency and spectrum of germ cell tumors (with and without other components ) (n=176)**

Histopathological diagnosis	N	%	95% Confidence Interval		Age (years)		Side affected			Size (cm) (Including bilateral tumors)							
			<40	>40	Mean	SD	R	L	Bilateral	<5	5-10	>10	Mean	SD			
Mature cystic	149	84.7	78	89	108	41	29.28	9.5598	81	59	9	39	64	55	9.5253	6.2778	
Struma ovarii	7	3.9	1.9	8.2	4	3	35.5	10.184	1	5	1	1	1	6	11.5	4.2426	
Immature teratoma	4	2.3	0.6	5.4	4	-	23.75	4.113	1	3	-	-	1	3	13.75	4.1932	
With Mucinous cystadenoma	3	1.7	0.3	4.6	-	3	42.33	1.5275	2	1	-	-	-	3	16.6667	2.0817	
<b>Teratoma (n=170)</b>	With Serous cystadenoma	2	1.1	0.1	3.8	2	-	27	7.0711	1	1	-	-	1	1	13	7.0711
	With benign Brenner	2	1.1	0.6	5.4	-	2	46	1.1547	-	-	2	-	1	3	13.25	4.113
	With Sq Cell CA	1	0.6	0.0	2.9	-	1	48	-	-	1	-	-	-	1	17	-
	With Sq Cell CA and Mucinous borderline	1	0.6	0.0	2.9	-	1	45	-	-	1	-	-	-	1	14	-
	With undiff CA	1	0.6	0.0	2.9	-	1	52	-	1	-	-	-	-	1	16	-
Dysgerminoma	4	2.4	0.6	5.4	3	1	29.75	8.3417	2	2	-	-	1	3	14	3.559	
Choriocarcinoma	1	0.6	0.0	2.9	1	-	26	-	1	-	-	-	1	-	9	-	
Yolk sac	1	0.6	0.0	2.9	1	-	16	-	-	1	-	-	-	1	15	-	
<b>Total</b>	<b>170</b>	<b>100</b>			<b>123</b>	<b>53</b>				<b>90</b>	<b>74</b>	<b>12</b>	<b>40</b>	<b>70</b>	<b>78</b>		

## DISCUSSION

The classification of ovarian tumor is primarily morphologic - reflecting the concept of embryogenesis and histogenesis of ovary.<sup>3</sup> On the basis of four major types of tissues,

One hundred seventy six cases were reported to be of germ cell origin which included 170 teratoma, four dysgerminoma and one each of choriocarcinoma and yolk sac tumor. (Table 3) Among 176 cases of germ cell tumors, commonest subtype was mature cystic teratoma, comprising 149 cases (84.7%, CI 78,89), followed by four cases of dysgerminoma and one case each of choriocarcinoma and yolk sac tumor. Most of the cases (69.9%, CI 65.4, 78.6) were below 40 years of age. Among all the germ cell tumors, right side was more commonly affected (54.3%, CI 46.8, 61.5) compared to left side (45.7%, CI 38.5, 53.2). Majority were more than 10 cm in size (41%, CI 33.9, 48.3) followed by 5-10 cm group (37.8%, CI 30.8, 45.1) and less than 5 cm group (21.3%, CI 15.7, 27.8). Correlation of age group distribution with tumor types is statistically significant (p=0.0006) while side and size distributions are statistically not significant (p= 0.5207 and p= 2618 respectively).

Table 4 shows the age distribution, side affected and size of sex cord stromal and other tumors which included were granulosa cell tumor (6 cases), fibrothecoma (2 cases) mixed Mullerian (1 case), atypical leiomyoma (1 case), undifferentiated carcinoma (1 case) and metastatic carcinoma (7 cases). Due to less number of cases in this group, statistical significance was not relevant.

primary ovarian neoplasms can be broadly classified as surface epithelial-stromal tumors, germ cell tumors and sex cord-stromal tumors. For the diagnosis of ovarian tumors, clinical data, gross features and detail microscopic examination are required. One of the most important

**Table 4.** Showing frequency and spectrum of Sex cord-stromal and other tumors (n= 18)

Histopathological diagnosis	N	%	95% Confidence Interval		Age (years)				Side affected			Size (cm) (Including bilateral tumors)				
					<40	>40	Mean	SD	R	L	Bilat- etral	<5	5-10	>10	Mean	SD
Metastatic tumor	7	38.9	19.1	63.9	2	5	56.125	12.1354	3	3	1	2	4	2	7.625	3.2043
Granulosa cell tumor	6	33.4	11.9	54.3	1	5	44.00	4.7329	-	6	-	2	3	1	7.3333	3.3862
Fibrothecoma	2	11.1	1.2	31.7	-	2	47.5	2.12	2	-	-	-	1	1	10.50	2.1213
Mixed Mullerian with serous cystadenoma	1	5.6	0.1	24.9	-	1	51	-	-	-	1	-	1	1	11.0	4.2426
Undifferentiated carcinoma	1	5.6	0.1	24.9	-	1	52	-	1	-	-	-	1	-	7.0	-
Leiomyoma	1	5.6	0.1	24.9	-	1	46	-	1	-	-	-	-	1	15.0	-
<b>Total</b>	<b>18</b>	<b>100</b>			<b>3</b>	<b>15</b>			<b>7</b>	<b>9</b>	<b>2</b>	<b>4</b>	<b>10</b>	<b>6</b>		

clinical features is the age of the patient. Ovarian tumors are common in women of all age groups. About 80% of ovarian tumors are benign and occur in age between 20-45 years, the remaining 20% are malignant and are more common in older women between 45-65 years.<sup>1</sup> Among females of reproductive age group, 8% cases are asymptomatic.<sup>5</sup> Mature cystic teratoma, the most common ovarian tumor occurs at all ages similarly like the sex cord stromal tumors. Other ovarian neoplasms are mostly restricted to certain age groups.<sup>4</sup>

The surface epithelial tumors comprise of 58% of all ovarian neoplasms and about 90% of malignant ovarian tumors occurring in the Western world however their frequency is less in the East.<sup>4,6,7</sup> The epithelial tumors arise mostly from the inclusion glands leading to its cystic nature.<sup>4</sup> Inclusion glands are unusual in reproductive age and rare before puberty explaining the occurrence of this type of tumor in older age group. The classification of ovarian epithelial tumors currently used by pathologists is based entirely on tumor cell morphology.<sup>8</sup> The cell type may be serous, mucinous, endometrioid, Brenner/transitional, clear cell and undifferentiated. More than one cell type is often seen. If the secondary cells type involve less than 10% of the tumor, it is classified according to the predominant cell type, while if it is more than 10%, it is classified as mixed epithelial tumor.<sup>4</sup>

In serous tumors, approximately 75% are benign, 5-10% are borderline and 20-25% are malignant in current literature.<sup>1,4</sup> Our study showed 80% of benign, 3.2% borderline tumors and 16.8% malignant tumors. Benign serous tumors occur mostly in 5<sup>th</sup> to 6<sup>th</sup> decade and account for 16% of all ovarian epithelial neoplasms.<sup>1,4</sup> In the present study, benign serous tumors comprised of 119(55.3%) cases of all epithelial tumors. Grossly benign serous tumors are usually 1-10 cm but may be up to 30 cm or more in size.<sup>1</sup> In our study, 81(68%) cases of benign serous tumors were less than 10 cm and 39(32.7%) cases were more than 10 cm.

Mucinous tumors account for 15% of ovarian tumor in the West but occur more in the East.<sup>4</sup> In the current study,

55(25.6%) cases of all epithelial tumors were of mucinous type of which 40, 4 and 11 cases were benign, borderline and malignant tumors respectively. In literature, 75% of mucinous tumors are benign, 20% borderline and 5% malignant.<sup>3,4</sup> So, compared to international data, we had more benign subtype in serous tumors and more malignant ones in mucinous tumors. They are associated with dermoid cysts in up to 5%.<sup>7</sup> Our study showed three cases combined with mature cystic teratoma. We also had one case of bilateral mixed epithelial tumor with both serous and mucinous components. Brenner tumors comprise less than 5% of all benign epithelial tumors.<sup>1</sup> Most of them are found incidentally and are less than 2 cm in size.<sup>4,9</sup> In our study, we had 8 pure Brenner tumors and three cases with serous component and two cases with mature cystic teratoma (Table 1 and 2). All eight cases of pure Brenner were less than 10 cm in size. Among a total of 7 borderline epithelial tumors, we reported three and four cases of serous and mucinous borderline tumors respectively. All four mucinous borderline cases were found in females more than 40 years of age, were unilateral and of size more than 10 cms (Table 4). Mucinous borderline tumors are further subdivided into endocervical and intestinal type.

Approximately 90% of primary malignant ovarian tumors arise from the ovarian surface epithelium.<sup>8</sup> Serous cyst adenocarcinoma comprises 80% to 84% of all ovarian carcinoma in Western world. Seidman JD et al. in their study of 220 ovarian carcinomas found that 70% were of serous origin.<sup>10</sup> We had 22 cases of serous carcinoma comprising 61% of all 36 surface epithelial carcinomas. The morphologic and genetic heterogeneity suggests that serous carcinomas may represent transformation or progressions from other tumor types.<sup>11</sup> 2/3<sup>rd</sup> of these tumors are bilateral. Similarly, we had 8(36.4%) cases out of 22 cases of serous cystadenocarcinoma with bilateral involvement. All the microscopic features of 22 cases have been summarized in Table 5. Papillae and solid sheets of malignant cells, increased mitosis, necrosis were seen in all cases. Approximately 30% of this type are known to show psammoma bodies, we found it in only 7(31.8%) cases.<sup>3</sup>

Mucinous adenocarcinomas are uncommon and composed 2.4% of primary surface epithelial carcinomas in the studies done by Seidman JD et al.<sup>10,12</sup> However, in this study, there were 11(30.5%)cases of mucinous carcinoma out of 36 malignant surface epithelial carcinomas (Table 2) which is higher than other series. The malignant area may be quite small and hence a generous sampling of all mucinous tumors is advised.<sup>1</sup> If frank stromal invasion (more than 10 mm<sup>2</sup> area) is not seen, papillary areas or back to back malignant glands with even little stroma may be assumed as invasion.<sup>1</sup> The main differential diagnoses include endometrioid carcinoma, serous carcinoma with intraluminal mucin and metastatic adenocarcinoma. Coexisting mucinous borderline tumor, absence of endometriosis and squamous metaplasia favor a mucinous neoplasm instead of an endometrioid tumor.<sup>11</sup>

Germ cell tumors are a heterogenous group, majority originating at different stages of development from germ cells.<sup>1</sup> They account for nearly 30% of all ovarian tumors and 95% of germ cell tumors are mature cystic teratoma while the remaining 5% are malignant.<sup>1,13</sup> The median age of germ cell tumors is 18 years.<sup>14</sup> Malignant germ cell tumors are common in children and adolescent females.<sup>1</sup> They are usually encapsulated and unilateral in 90% of cases. Bilateral involvement of the tumor is seen in 10% of cases.<sup>1,7</sup> In our study, 12(6.8%) cases showed bilateral germ cell tumors comprising of nine cases of pure mature cystic teratoma, two cases of combined mature cystic teratoma with benign Brenner component and one case of struma ovarii.

Mature cystic teratoma is the most common ovarian neoplasm comprising upto 25% or more in different studies.<sup>9,15,16</sup> In our study, we reported 170 cases of mature cystic teratoma comprising 41.6% of all tumors and 96.6% of germ cell tumors. A majority of patients were found to be less than 50 years as in other study. We had seven cases with thyroid element comprising more than 50% of the tumor and was reported as Struma ovarii which is the most common type of monodermal teratoma.<sup>1</sup> We had three cases of mature cystic teratoma with malignant component. Immature teratoma is one of the most common malignant germ cell tumors representing 3% of teratomas, 1% of all ovarian cancers and 20-30% of malignant ovarian germ cell tumors.<sup>17,18</sup> They occur in young age group and are typically unilateral, and average 18 cm in size as we found in all three cases in our study.<sup>7</sup> In our study, we had only four cases of immature teratoma and all cases were below 20 years of age. There were three cases reported as grade two and one case as grade 1. Studies show that 1-3% of mature teratoma may undergo malignant transformation.<sup>7</sup> We had only three cases with malignant transformation including

two cases with squamous cell carcinoma and one case with undifferentiated carcinoma. Dysgerminoma is the most common malignant germ cell tumor of the ovary.<sup>9,15,16</sup> 80% of tumors develop in women younger than 30 yrs of age with mean age 21 years. They are extremely rare above 50 years.<sup>13</sup> Out of four cases in our study, one case was of 55 years. Pure primary ovarian choriocarcinoma of germ cell origin is extremely rare comprising less than 1% of all ovarian germ cell neoplasms and we had only one case.<sup>1,7</sup> Yolk sac tumors are morphologically heterogenous and may show many epithelial patterns.<sup>19</sup> The only case we had was of 16 yrs and showed reticular pattern and Schiller Duval bodies.

Granulosa cell tumors are the most common sex cord stromal tumor comprising less than 2% of all ovarian neoplasms and 6% of ovarian cancers.<sup>13</sup> The average age for this tumor is 50-55 yrs. We had six cases, out of which five cases were above 60 years and one case was of 37 yrs. All the cases were of adult type. Jamal S et al. in their study in Pakistan found 13% of ovarian tumor has sex cord stromal origin.<sup>20</sup> In their study, sex cord stromal tumors and germ cell tumors were more common than in Western studies. The authors mentioned that their findings are similar to other Pakistani, Indian and African studies. Unlike their studies, we found only 6(1.5%) cases of sex cord stromal origin.

The ovary is a common site of involvement for metastasis. Approximately 7% of ovarian tumors are of metastatic origin and over 50% of them are bilateral.<sup>3</sup> Among seven metastatic tumors, five cases were of metastatic adenocarcinoma, one case of metastatic cervical squamous cell carcinoma and one case of metastatic retroperitoneal leiomyosarcoma. Among five metastatic adenocarcinoma, four cases were from gastrointestinal tract and one case from breast. The only bilateral case was reported as Krukenberg tumor with presence of mucin positive signet ring cells.

## CONCLUSION

In the current study, we presented the variety of different types of ovarian tumors according to the old albeit existing classification based on morphology. However, the importance of the gene expression patterns of ovarian tumors are being studied and a new classification system of ovarian tumors based mainly on molecular findings has been proposed.<sup>8</sup> In our study, most of the clinical and pathological data corroborate with international literature. We however reported increased percentage of mucinous tumors and less sex cord stromal tumors than other studies.

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