NON EPITHELIAL TUMORS OF OVARY

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ABSTRACT: BACKGROUND: Non epithelial tumors of ovary are uncommon tumors and may generate difficulty in establishing a diagnosis. Small cell carcinoma (SCC) of the female genital tract and primary lymphoma of ovary is even rarer, constituting less than 1% of all gynecologic malignancies. These tumors have poor prognosis. In the present study an effort was made to review these tumors in our Institute. AIMS: To know the prevalence, age distribution, clinical presentation and morphological appearance of these tumors. MATERIALS AND METHODS: Analyzed 34 cases of non-epithelial tumors of ovary received in the department of pathology during a period of three years. Specimens were grossed, routinely processed under standardized conditions for paraffin embedding and stained with hematoxylin and eosin using standard procedures. Special stains and Immunohistochemistry was done where ever necessary. RESULTS: A total of ovarian tumors received during this period were 136. Non epithelial tumors of ovary constituted 34/136 (25%), of the ovarian neoplasms. Germ cell tumors constituted 23/34(67.64%) followed by sexcord stromal tumors 7/34 (20.58%). Among the rare tumors we encountered a case of small cell carcinoma, primary lymphoma of ovary and 2 cases of Krukenberg tumors of ovary 2/34 (5.88%). CONCLUSION: Small cell carcinoma and primary lymphoma are morphologically similar to sex cord stromal tumors and germ cell tumors, may pose significant problems in establishing the correct diagnosis. Immunohistochemistry is a must to diagnose these lesions as they have grave prognosis.

KEYWORDS: Non epithelial tumors of ovary, Rare.

INTRODUCTION: Non epithelial tumors of ovary are uncommon ovarian tumors and may generate difficulty in establishing a diagnosis. They are carcinosarcomas of the ovary, sex cord stromal tumours, germ cell tumours, small cell tumours, squamous carcinoma arising within a dermoid, struma ovarii malignum and lymphomas. Sex cord stromal tumors are uncommon and account for 5% of ovarian neoplasms and 7% of malignant ovarian tumors. Clinically they often present with no distinguishing features, but some are functional and may cause virilization or symptoms from excess estrogen secretion, such as endometrial hyperplasia and postmenopausal bleeding. Small cell carcinoma and primary lymphoma are rare and account for 1% of ovarian cancers. Germ cell tumors account for only 5% of ovarian tumors but >75% of tumors in younger patients [1].In the present study these tumors are reviewed for rarity.

MATERIAL AND METHODS: This is a prospective study at a tertiary care center for a period of three years. A total of 136 ovarian neoplasms were received in the department of pathology. Non epithelial ovarian neoplasms constituted 34 in number, all were fixed in 10% buffered formalin and allowed to stand overnight. Specimens were grossed and adequate representative sections were taken with special emphasis given in case of large specimens to solid foci, areas adjacent to the ovarian surface. The specimens were routinely processed under standardized conditions for paraffin embedding.

Sections were cut and stained with hematoxylin and eosin using standard procedures. Special stains and Immunohistochemistry was done where ever necessary.

RESULTS: A total of ovarian tumors received during this period were 136. Non epithelial tumors of ovary constituted 34/136 (25%), of the ovarian neoplasms. Germ cell tumors constituted 23/34(67.64%) followed by sexcord stromal tumors 7/34 (20.58%). Among the rare tumors we encountered a case of small cell carcinoma, primary lymphoma of ovary (Fig. 5, 6) and 2 cases of Krukenberg tumors of ovary 2/34 (5.88%). (Table1).Benign cystic teratoma (Fig. 1) was the commonest germ cell tumor (17/23, 73.91%), followed by dysgerminoma (Fig 2) (5/23, 21.73%). Granulosa cell tumor (Fig 3) was the commonest sex cord - stromal tumor (4/7, 57.14%). (Table 2).

Tumors common beyond the age of 50 years were granulosa cell tumor, small cell carcinoma (Fig. 4) and fibrothecoma. Tumors common between 11-30 years were benign cystic teratoma, fibrothecoma and dysgerminoma. Metastatic tumors (Fig 7, 8) were common between 41-50 years. (Table 3). Sex cord-stromal tumors presented as mass per abdomen (6/7, 85.71%) and one case with menstrual irregularity. Benign cystic teratoma mainly presented as pain abdomen. The tumors which presented with ascites were dysgerminoma and small cell carcinoma. Metastatic tumors presented with gastrointestinal disturbances. (Table 4).Small cell carcinoma microscopically resembled granulosa cell tumor but was inhibin negative. Primary lymphoma was positive with Leucocyte common antigen and signet ring cells in Krukenberg's tumor were positive with PAS stain.

DISCUSSION: Sexcord Stromal Tumors: Sex cord-stromal tumors are ovarian tumors that are believed to originate in theca cells, other stromal cells, granulosa cells and their testicular sex cord counterparts, the Sertoli and Leydig cells. These tumors often are associated with endocrine manifestations. They account for approximately 8% of all ovarian tumors and approximately 7% of all malignant ovarian tumors. They are sub type of ovarian neoplasm that is relatively infrequent. Sex-cord stromal tumors are mainly low grade and present generally in young age patients than ovarian epithelial malignancies.[2] They encompass a heterogenous group of neoplasms containing variety of cells which are derived from gonadal sex cords or stromal cells. [3] Because of the smaller size, low grade of malignancy and rarity of these tumors, they are often diagnosed by pathology following surgery. The morphology of these tumors varies and these can simulate epithelial ovarian neoplasms or mesenchymal tumors histologically to an extent of misdiagnosis. [4] IHC staining may be useful for establishing the diagnosis in problematic cases due to varied appearance and rarity. Steroidenic factor 1(SF 1) and FOXL 2, although not available in our set up are useful marker studied in recent times and is positive in lesions of sex cord stromal differentiation. Although some of these tumors are cytokeratin (CK), AE1/ AE3 positive, epithelial membrane antigen negativity may be useful for the differential diagnosis with epithelial ovarian tumours. These tumors can show somewhat fascinating behavior profile with the fluctuating clinical presentations of precocious puberty to menorrhagia to post-menopausal bleeding.^[5,6]

Granulosa cell tumors are rare sex cord ovarian tumors that are formed by cells believed to be derived from those that surround the germinal cells in the ovarian follicles. Two major forms of granulosa cell tumors are recognized: the adult form, which primarily occurs in middle-aged and older women, and the juvenile form, which typically occurs in children and younger women. Most adult granulosa cell tumors are partially cystic, with multiple fluid-filled or blood-filled loci and solid

areas. They represent approximately 95% of all granulosa cell tumors. These tumors, the majority of which are unilateral, most often occur in postmenopausal women. Adult granulosa cell tumors are the ovarian tumor type most commonly associated with manifestations that are caused by the overproduction of female sex hormones (estrogenic manifestations). These manifestations include endometrial hyperplasia and endometrial cancer, which are present in 5–25% of cases. Adult granulosa cell tumors are considered to be tumors of low grade or low malignant potential. Ninety percent are Stage I at diagnosis, with a reported 10-year survival rate of 86–96%; the corresponding reported survival rate for patients with tumors found at more advanced stages is 26–49%. Treatment is primarily surgical. Rupture of the tumor during surgery adversely affects prognosis. Recurrences can occur 30 years or more after removal.

Juvenile granulosa cell tumors are grossly similar to those of the adult subtype. They account for only 5% of all granulosa cell tumors. Most are unilateral, and approximately half occur before puberty. Because of their estrogenic hormone production, many of these tumors result in precocious sexual development. Most juvenile granulosa cell tumors are limited to the ovary at the time of diagnosis. Surgical excision is curative in most cases. Recurrences are rare and typically occur within three years.

In the study by WHO analyzed sexcord stromal tumors for 20 years, constituted 70% of nonepithelial tumors, on which granulosa cell tumor(GCT) composed 43.5%, all were solid cystic on gross examination, with age of presentation of adult GCT being more than 50 years. In their study juvenile GCT constituted 10% of GCT. A total of 47 cases of fibrothecoma were analyzed, out of which one was associated with endometrial hyperplasia and one was with carcinoma cervix. Median age range was 50 years. Right side was more commonly involved, two cases were bilateral, follow up of these patients were healthy.[7] In the present study, among 7 sex cord stromal tumors encountered, 4 were diagnosed as adult granulosa cell tumors. All the cases presented with mass per abdomen, while one patient gave history of post-menopausal bleeding, these tumors were bilateral while one granulosa cell tumor was unilateral. On cut section two were completely solid and remaining two were both solid and cystic in nature filled with brown colored fluid, microscopy of all 4 cases showed microfollicular pattern, along with trabecular pattern in 2 cases. Tumors were composed of small to oval cells having round to angulated nucleus with nuclear grooving resulting in a coffee bean appearance and occasional call exner bodies. Nuclear pleomorphism and mitoses were seen in some of them. All of these were grade 1 tumors. Three cases of fibrothecoma presented with pain and mass per abdomen. Cut section of the tumor was grey white to yellow with 2 cases seen in 27 years and one case at age of 55 years. Histology showed spindle cells arranged in interlacing bundles interspersed with focal plump cells with luteinisation. The prevalence of sexcord stromal was comparable with other studies. [8,9,10,11,12] (Table 5).

Germ Cell Tumors of Ovary: Germ cell tumors are ovarian tumors formed by cells that are believed to be derived from primordial germ cells. These tumors make up approximately one-fourth of all ovarian tumors but only 3–7% of malignant ovarian tumors. In parts of Asia and Africa where the prevalence of surface epithelial-stromal tumors is relatively low, germ cell tumors constitute a larger proportion of all ovarian neoplasms. More than half of the ovarian neoplasms that develop in children and adolescents are of germ cell origin, with one-third of these being malignant. Conversely, in adults,

germ cell tumors are relatively infrequent, and the great majority of them are benign, with most being mature cystic teratomas (dermoid cysts).

The prototypical germ cell tumors are the dysgerminomas. Embryonal carcinomas are germ cell tumors composed of poorly differentiated, multipotential germ cells. Germ cell tumors with differentiation in an embryonal or somatic direction result in teratomas. Those that differentiate in an extraembryonic (placental or trophoblastic) direction result in yolk sac tumors or choriocarcinomas. Mixed subtypes of germ cell tumors also occur frequently.

Teratomas are germ cell tumors that are formed by cells derived from more than one of the three primitive embryonic layers (ectoderm, mesoderm, and endoderm). Teratomas can be mature (benign) or immature (benign or malignant). Teratomas formed predominantly by endodermal or ectodermal elements are referred to as monodermal or specialized.

Mature teratomas can be solid or cystic. Mature solid teratomas are rare, as most solid teratomas are at least partially immature. Mature teratomas occur mostly in children and young adults. These tumors, most of which are unilateral, grow slowly and usually are large at the time of diagnosis. Surgical excision is curative.

Mature cystic teratomas are the most common kind of ovarian germ cell tumor. In most studies, they are reported to represent at least 10% of all ovarian tumors. In most mature cystic teratomas, the ectodermal elements predominate; when this is the case, these teratomas are designated as dermoid cysts. Mature cystic teratomas commonly have a single cyst cavity filled with sebaceous material, and they often have a focal internal protuberance that may contain hair, teeth, bone, and/or cartilage. Mature cystic teratomas most commonly occur during the reproductive years. In most cases, surgical excision is curative. Rupture of the tumor may result in peritoneal implants.

In rare cases, mature cystic teratomas may undergo malignant transformation, most often in postmenopausal patients, that most commonly results in squamous cell carcinoma. Other malignant tumor types, including carcinoid, thyroid carcinoma, basal cell carcinoma, intestinal adenocarcinoma, melanoma, leiomyosarcoma, and chondrosarcoma, may arise. Prognosis is generally unfavorable; reported 5-year survival rate are only 15–31%. Better prognosis is observed if the malignant component is squamous cell carcinoma and if the tumor is confined to the ovary.

Dysgerminomas are tumors composed of cells that are similar to primordial germ cells. They display a striking similarity to their testicular counterpart, the seminoma. Dysgerminomas are solid, white or grayish-white tumors. Unilateral tumors are more common in the right ovary, and 10--20% of dysgerminomas are bilateral. Most cases occur in the second and third decades of life. Dysgerminomas account for $\leq 2\%$ of all ovarian tumors and only 3–5% of all malignant ovarian tumors; nevertheless, they represent the most common type of malignant ovarian germ cell neoplasm. High prevalence has been reported in Japan and India. Dysgerminomas are among the most common malignant neoplasms during adolescence and early adulthood. A high level of serum lactic dehydrogenase is associated with dysgerminoma and can be used as a tumor marker. Dysgerminomas spread late and do so primarily through the lymphatic system. These tumors respond very well to radiation therapy. The overall prognosis for patients with dysgerminomas is excellent; the 5-year survival rate approaches 100% for patients with Stage I disease and is 75--90% for patients with other stages of malignancy. Poor prognosis is associated with large tumor size, bilateralism, age < 20 years or > 40 years, and the presence of other neoplastic germ cell elements.

In the present study of the 23 germ cell tumors 17 cases were diagnosed as benign cystic teratomas, 16 of these were unilateral and one case was bilateral. Peak age incidence of 14 cases was noted between 20-40 years, 2 cases between 41-50 years and one case in the age above 50 years. Cut section of benign cystic teratoma showed presence of hair, fat and sebaceous material. In one case focal hard whitish nodule, Rokitansky's protuberance was noticed containing teeth protruding into the cyst lumen. Microscopically they showed heterologous elements derived from different germ layers. All of them exhibited predominant ectodermal differentiation in the form of stratified squamous epithelium and dermal appendages like hair shafts and lobules of sebaceous glands. All the 5 dysgerminomas encountered were unilateral. Patients came with the complaints of pain and mass per abdomen. The tumors were grey white with nodular external surface and intact capsule. Cut section was homogenously grey white in color with necrotic material. Microscopy showed tumor cells arranged in sheets, cords and nests separated by variable amounts of fibrous septa infiltrated by lymphocytes. Tumor cells were polyhedral in shape with abundant eosinophilic granular to clear cytoplasm and centrally placed vesicular nuclei with prominent nucleoli. Tumour cells showed increased abnormal mitoses. A single case of mixed germ cell tumor presented as unilateral mass at 16 yrs old girl. External surface was nodular and cut section was solid grey white with central areas of necrosis and honey comb appearance. Histologically tumor was predominantly composed of dysgerminoma component and to a lesser extent by yolk sac component by presence of typical schiller – duval bodies with areas of necrosis and hemorrhage. In the study by Dr. Benjamin Piura et al analyzed 20 patients with malignant ovarian germ cell tumors 35% had dysgerminomas and 20% as mixed germ cell tumor. The prevalence of germ cell tumors in the present study was comparable with other studies. [8,9,10,11,12] (Table -5)

Small cell carcinoma of ovary: Small cell cancers were only recognized as a separate entity in 1979. Three main variants of small cell carcinoma are seen: small cell carcinoma of hypercalcaemic type (SCCOHT), small cell carcinoma of pulmonary type (SCCOPT) and large cell variant of small cell carcinoma or non-small cell small cell carcinoma (NSCSCC). There are differences in age at presentation and clinical syndromes. Ovarian small cell carcinoma is a biologically aggressive neoplasm of uncertain histogenesis that occurs predominantly in young women.

Felix Distelmaier et al $^{[13]}$ has reported small cell carcinoma in patients ranging between 13 to 55 yrs of age with average patients age of 24 yrs. The clinical presentation was non-specific symptoms as abdominal distension, abdominal or pelvic pain, nausea or vomiting and abdominal mass. About $2/3^{rd}$ of patients have hypercalcemia. SCC is usually unilateral, solid, nodular, grey or tan tumor that ranges from 6 to 27 cm with average diameter of 15 cm. On cut section small cysts, areas of hemorrhage and necrosis were present in some of the tumors. Histologically SCC is characterized by sheets of closely packed, small cells with scanty cytoplasm, forming scattered follicle like structures and morphologic similar to sex cord stromal tumors and germ cell tumor may pose significant problems in establishing the correct diagnosis. The largest series reported to date included 150 patients. These tumors are negative for inhibin and co-expression of EMA and Wilms tumor 1 (WT -1) gene may be of diagnostic value. Finally the immuno histochemical demonstration of parathyroid hormone – related peptide confirms the diagnosis.

In the present study one case of SCC was noted which was large and solid macroscopically. On cut section there were areas of necrosis and hemorrhage. The diagnosis was made on microscopic findings. The tumor was negative for inhibin.

PRIMARY NHL OF OVARY: Lymphoma is a rare tumor of the ovary and its presence most commonly represents involvement in overt systemic disease, almost always of the Non-Hodgkin's type.^[14] The diffuse large B cell lymphoma appears to be the most common type of primary ovarian Non-Hodgkin's lymphoma. There has been debate has to whether lymphoma can arise denovo in the ovary; lymphoid aggregates do exist is normal ovarian tissue, which could give rise to such lesions.^[15] The majority of primary ovarian lymphomas present with pelvic complaints. Some cases present with ascites and elevated serum CA -125.^[16] The bilateral ovarian involvement, peritoneal implants and omental involvement at the time of surgery, my argue against a primary ovarian disease.^[17] Patients with disease localized to one ovary usually due well with surgical resection and systemic chemotherapy. The presence of positive staining for leukocyte common antigen (LCA) in the histological specimen distinguishes malignant lymphoma from non-lymphoid neoplasm. Diffuse, large B-cell lymphomas were positive for CD20 and BCL-6 and or CD-10 and or BCL-2.^[18, 19]

In the present study one case of primary NHL of ovary presented in 26 yrs of age. The clinical presentation was pain with mass per abdomen. The tumor was bosselated with grey white appearance on cut section. Microscopy showed uniform round small to medium sized nuclei with coarse chromatin and 1-3 nucleoli. Mytoic figures were frequent. The cytoplasm was scanty and basophilic. The cells were punctuated by spaces that contain phagocytic histiocytes, producing the starry sky appearance typical of Burkit's lymphoma. The diagnosis was made on microscopic features and positivity with Leucocyte common antigen.

METASTATIC TUMOR OF OVARY: Ovarian metastasis comprises 5-10 % of all malignant ovarian tumors.^[20] Based on the pathology of the involved ovaries and on clinical and operative findings, lymphatic and trans- peritoneal spread account for most ovarian metastases particularly from primary sites within the abdomen. Adenocarcinoma of breast, large intestine, endometrium and stomach are the most common primary sites. Clinically usually they present as pelvic or abdominal pain, gastro-intestinal or urinary disturbances, abdominal distension or abnormal uterine bleeding.

In the present study two cases of Krukenberg tumor had primary carcinoma in the stomach and presented with gastro-intestinal disturbances. Grossly these tumors were solid bilateral and had bosselated external surface. On cut section they showed multiple, solid areas with foci of necrosis and hemorrhages. Histopathological sections revealed sheets of signet ring cells, having abundant an amount of vacuolated to clear cytoplasm with eccentric hyperchromatic nuclei with PAS positivity. These signet ring cells were separated by fibrous stroma.

CONCLUSION: Sex cord stromal tumors, germ cell tumors and krukenberg tumors can be easily diagnosed on morphological basis. Immunohistochemistry is very much essential in differentiating sex cord and germ cell tumors from small cell carcinoma of ovary. Small cell carcinoma are negative for inhibin. Primary lymphoma of ovary needs confirmation by IHC which is positive for leucocyte common antigen and CD20.

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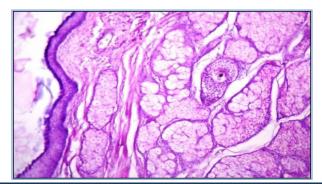


Fig. 1: Benign cystic teratoma with skin and pilosebaceous units. (H&E, 400X)

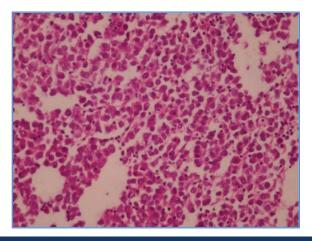


Fig. 2: Dysgerminoma with polygonal cells with prominent nucleoli and lymphocytes in the septa. (H&E, 400X)

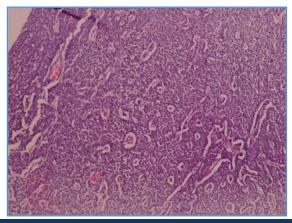


Fig. 3: Granulosa cell tumor shows round cells with Call Exner bodies. (H&E, 400X)

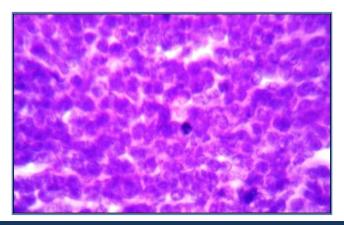


Fig. 4: Small cell carcinoma shows sheets of closely packed, small cells with scanty cytoplasm

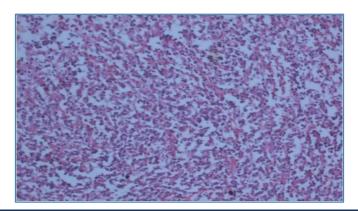


Fig. 5: Primary NHL of ovary shows small mononuclear cells and large cells with septa (H&E, 200X)

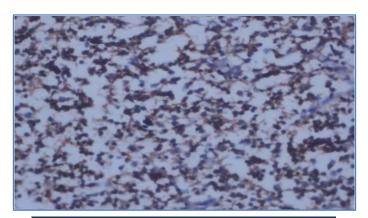


Fig. 6: Primary NHL of ovary positive with Leucocyte common antigen (IHC, 200X)

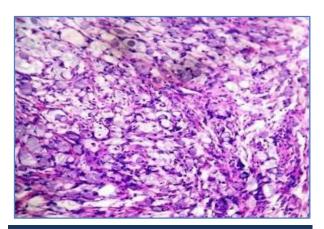


Fig. 7: Krukenberg tumor of ovary showing signet ring cells. (H&E, 400X)

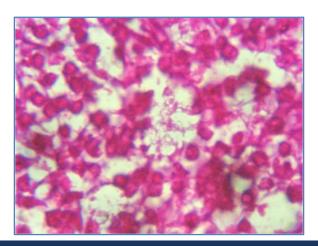


Fig. 8: Krukenberg tumor of ovary signet ring cells positive with PAS stain. (PAS, 400X)

Tumor type	No. of cases	Percentage	
Germ cell tumors	23	67.64	
Sexcord stromal tumors	07	20.58	
Small cell carcinoma	01	2.94	
Non-Hodgkin's lymphoma of ovary(NHL)	01	2.94	
Metastatic tumor	02	5.88	
Total	34		

Table 1:Prevalence of Nonepithelial Tumours of Ovary-34

Tumor type	No. of cases	Percentage	
Germ cell tumors	23	67.64	
Benign cystic teratoma	17	50	
Dysgerminoma	5	14.7	
Mixed germ cell tumor	1	2.9	
Sexcord stromal tumors	7	20.58	
Granulosa cell tumor	4	11.76	
Fibrothecoma	3	8.82	
Small cell carcinoma	1	2.94	
Primary NHL of ovary	1	2.94	
Metastatic tumors (Krukenberg tumor)	2	5.88	

Table 2: Histological subtypes of nonepithelial tumours of ovary-34.

Type of tumor	No. of	0 - 10	11 -20	21-30	31-40	41-50	51-60
Type of tuillor	cases	years	years	years	years	years	years
Germ cell tumors							
Benign cystic teratoma	17	-	-	06	08	02	01
Dysgerminoma	05	-	02	03	-	-	-
Mixed germ cell tumor	01	-	01	-	-	-	-
Sex cord stromal tumors							
Granulosa cell tumor	04	-	-	-	-	-	04
Fibrothecoma	03			02			01
Small cell carcinoma	01						01
NHL of ovary	01			01			
Metastatic tumors	02					02	
(Krukenberg tumor)	02					02	
Total	34	-	3	12	8	4	7

Table 3: Age Distribution of Non Epithelial Tumors of Ovary-34

Type of tumor	No. of cases	Pain abdomen	Mass per abdomen	Menstrual irregularities	Ascites	G I disturbances
Germ cell tumors	23	17	3	2	1	-
Sex cord stromal tumors	07	-	6	1	-	-
Small cell carcinoma	01	-	-	-	1	-
NHL of ovary	01		1			
Metastatic tumors	02	-	-	-	-	2
Total	34	17	10	3	2	2

Table 4: Clinical Presentation of Non Epithelial Tumours of Ovary

Type of tumor	Gupta et al ^[8]	Prabhakar and Maingi ^[9]	Pilli et al ^[10]	Couto et al[11]	Shah PK et al ^[12]	Present study
Germ cell tumors	31.18%	27.20%	21.2%	20.41%	-	25%
Sex cord stromal tumors	7.06%	8%	6.7%	4.08%	-	5.14%
Granulosa cell tumors	-	-	-	4%	6%	2.94%
Benign Teratoma	25.88%	22.30%	17.02%	16.03%	-	12.50%

Table 5: Comparison of Prevalence of Non Epithelial Tumors with other Studies

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