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Morphological Analysis of Solid Ovarian Tumors with Special Emphasis on Rare Variants: An Institutional Experience

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Abstract

Background: Ovarian lesions exhibit a wide range of heterogeneity in their morphological patterns. Majority of ovarian lesions are benign (90%). Malignant ovarian lesions are complex and predominantly present as solid/ solid- cystic lesion with higher case fatality rate. Ovarian carcinomas are one of the lethal gynecological cancers commonly presenting in the advanced stage of the disease. **Objective:** This study was performed to assess the histomorphological patterns and age distribution of solid ovarian lesions with adjunct of immunohistochemistry in selected cases. **Material and methods:** A total of 38 solid ovarian tumors were included in the study. Clinical and histomorphological features were studied and correlated. **Results:** Of the 38 cases studied, 36.84% cases were benign, 2.63% cases were borderline and 60.53% cases were malignant. 5.26% cases were bilateral. Majority of the lesions were in the age group of 51-60 years. Among the histopathological subtypes, surface epithelial tumors comprised 47.37% followed by sex cord stromal tumors (18.42%) and germ cell tumors(15.97%). Serous adenocarcinoma was the most common malignant tumor. High grade B cell lymphoma, Metastatic ovarian tumor and Mixed epithelial carcinoma were the rarest. **Conclusion:** Solid ovarian lesions mostly are of malignant origin. Surface epithelial tumors is the most common histopathological subtype. Histomorphological examination remains the mainstay in the diagnosis of ovarian carcinomas and is supplemented by immunohistochemistry in problematic cases. Recent advances in elucidation of molecular events play a vital role in predicting the biological behavior of ovarian carcinomas.

Keywords: High grade B cell lymphoma, Metastatic ovarian tumor, Mixed epithelial carcinoma, Serous adenocarcinoma, Surface epithelial tumor

INTRODUCTION

Solid ovarian lesions are commonly encountered in gynecological practice and divert the attention for surgical excision in majority of the cases. Both neoplastic and non- neoplastic pathological conditions lead to solid enlargement of ovary. The estimated risk of ovarian cancer is 1 in every 70 women in her life time.[1] It represents 2.5% of all the female cancers and 21% malignancies of female genital tract.[2] Most of malignant lesions are commonly encountered as solid/ solid- cystic ovarian tumor with gradual increase in the pain and size of the abdomen. They remain indolent and present in the advanced stage of the disease with poor 5-year survival rate of 45%.[3,4, 5] This reflects the wide variation in the tumor, epidemiological factors, genetic risk factors, molecular alterations and its biological behaviour.[2]

A significant number of solid tumor-like lesions massive edema of ovary, pregnancy luteoma, stromal hyperplasia and hyperthecosis, leydig cell hyperplasia also lead to excision of ovarian masses. Definitive histopathological categorization with molecular testing of malignant ovarian tumors helps in proper institution of chemotherapy and prognosticate the disease process.[1, 6] Thus in this study, we spotlight the prevalence of diverse histopathological patterns of solid ovarian lesions in correlation with epidemiological data and categorized rare subtypes of solid ovarian lesions with adjunct of immunohistochemistry in selected cases.

Material and methods:

A total of 38 cases of solid ovarian lesions were analyzed prospectively during a period of 7.5 years from January 2014 to May 2021 in the Department of Pathology, BGS Global institute of Medical Sciences (BGS GIMS), Bengaluru. The samples were received from Department of Gynecology, BGS GIMS and directly from referral hospitals. Relevant case details and information were noted from request forms and the biopsy records.

The surgical specimens were examined grossly and sectioned using the standard protocol after overnight fixation in formalin. For all solid malignant tumors, one section for every centimeter of tumor's largest dimension was taken. Modification in the protocol is based on tumor heterogeneity and suspicious areas especially in cases of mucinous tumors, solid teratomas and malignant germ cell tumors.[7] Tissue sections were routinely processed and stained by hematoxylin and eosin. Special stains were included wherever necessary. Histopathological patterns of ovarian lesions were analyzed according to the WHO classification of ovarian tumors 2020. The cases were studied in detail with the special emphasis on categorization of rare selected lesions with the help of immunohistochemistry. Inclusion criteria included all solid ovarian lesions and solid tumors with focal cystic components in the age group of 1-80 years. Exclusion criteria included all cystic ovarian lesions and partial oophorectomy specimens.

Results:

A total of 38 cases of solid ovarian lesions were studied during a 7.5-year study period from January 2014 to May 2021. Out of which 14 cases were benign (36.84%), 1 (2.63%) case was borderline and 23 (60.53%) cases were malignant (Table-1). Bilaterality of the lesions were noted in 5.26% cases. Lesions were more commonly seen in the age group of 51-60 years followed by 31-40 years (Table-2). Majority of the malignant tumors were seen in 51-60 years and non-neoplastic lesions were frequent in the age group of 31-40 years.

Surface epithelial tumors were the commonest tumors (47.37%) followed by sex cord stromal tumors (18.42%), germ cell tumors (15.79%) and tumor-like lesions (13.16%). Metastatic lesions and lymphoid lesions accounted for 2.63% each respectively (Table-3). The distribution of solid ovarian lesions is depicted in the Figure-1.

Figure1: Distribution of solid ovarian lesions (n=38).

Serous adenofibroma	1
Endometrioid adenofibroma	1
Brenner Tumor	2
Serous Borderline Tumor with Microinvasion.	1
Low grade Serous Carcinoma	4
High Grade Serous Carcinoma	2
Bilateral High Grade Serous Carcinoma	1
Mixed Epithelial Carcinoma	1
Mucinous adenocarcinoma	2
Clear Cell Adenocarcinoma	1
Endometrioid Adenocarcinoma	1
Malignant Brenner Tumor	1
Dysgerminoma	2
Struma Ovarii	1
Yolk Sac Tumor	1
immature teratoma	1
Mixed germ cell tumor	1
Granulosa Cell Tumor With Sex Cord Elements	4
Cellular Fibroma	1
Fibrothecoma Ovary	1
Steroid cell Tumor	1
High grade B- Cell lymphoma	1
Metastases to the ovary (Krukenberg Tumor)	1
Pregnancy Luteoma	1
Stromal Hyperthecosis	1
Leydig cell hyperplasia	1
Massive ovarian edema	1
Xanthogranulomatous oophoritis	1

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Among the benign solid surface epithelial tumors, Brenner tumor was the commonest solid tumor reported in a 33 year and 68 year old respectively. Histopathological examination showed nests of transitional epithelium in a dense fibromatous stroma. We reported a rare case of serous adenofibroma and endometrioid adenofibroma (Figure 2a, 2b & 2c). In the borderline category, a case of serous borderline tumor (SBT) (11.9%) showed solid with focal cystic component and microinvasion of 4mm.

Among the malignant surface epithelial tumors (30.9%), we reported 4 cases of low-grade serous carcinoma (LGSC) and 3 cases of high-grade serous carcinoma (HGSC) (Figure 2d & 2e). Two cases of mucinous carcinoma were reported along with a case of clear cell carcinoma, malignant endometrioid tumor and malignant Brenner (Figure 2f). A rare case of bilateral ovarian tumor was diagnosed with mixed epithelial carcinoma (serous, endometrioid, undifferentiated and Brenner tumor components) on one side and high-grade serous morphology on contralateral ovary.

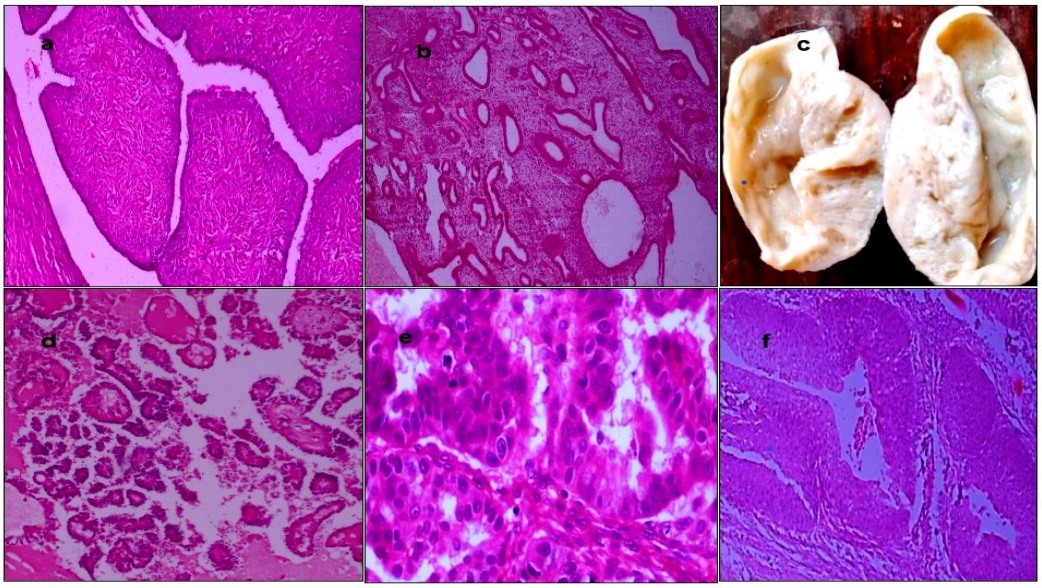

Figure 2:(a) **Serous adenofibroma** with slit like small glands in a dense fibromatous stroma, H&E, 10X. (b,c) **Endometrioid adenofibroma** with widely spaced benign endometrial glands in a fibromatous stroma H&E, 10X and gross specimen with grey tan appearence. (d) **Low grade serous carcinoma** composed of small papillae with mild to moderate nuclear atypia H&E, 10X (e) **High grade serous carcinoma** of papillary architecture with marked nuclear atypia H&E, 40X. (f) **Malignant brenner tumor** with solid and pseudoglandular structures separated by fibrous stroma H&E, 10X.

An unusual presentation of a case of primary mucinous adenocarcinoma was encountered in a 20-year pregnant lady. Ovary was excised during her caesarean section with normal CA-125 levels of 5.5U/ml. Her follow up ultrasound scans showed gradual enlargement of right ovary**.** Grossly, ovary showed a solid nodularity in the cyst wall**.** Her immediate postoperative tumor markers CA-125, CEA, AFP, Beta-HCG, CA19.9 levels were all within normal limits. Immunostains showed diffuse positivity for CK7 and patchy positivity to CK20 and focal CDX2 positivity and negative for ER, PAX8 and SATB2 (Figure 3). The follow up status showed no lesion in the contralateral ovary. Further, colonoscopy, oral gastroduodenoscopy and appendicectomy showed no significant pathology, thereby ruling out metastatic mucinous carcinoma. Another case of mucinous adenocarcinoma was reported in a 59-year lady.

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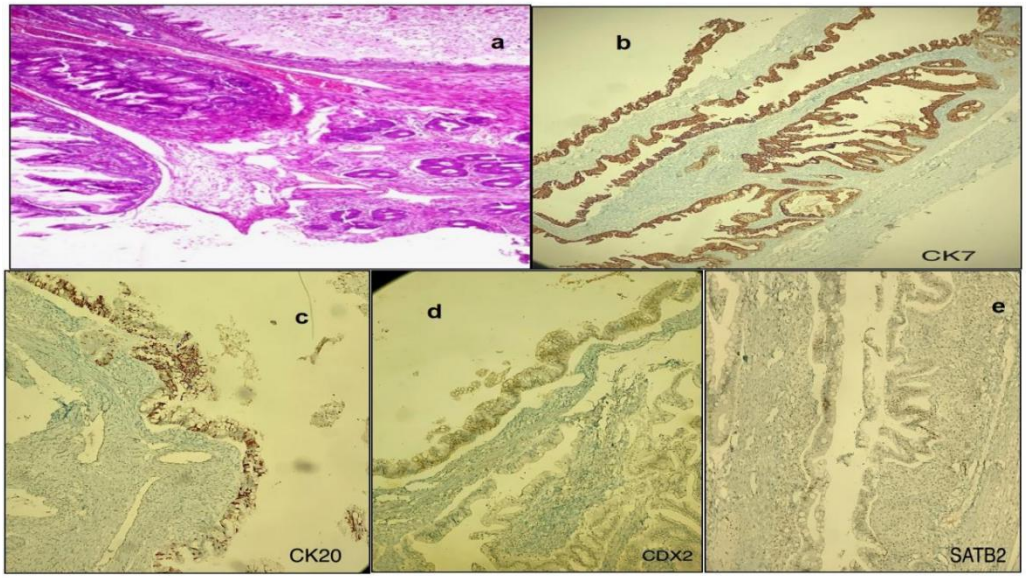

F**igure 3: Mucinous adenocarcinoma** (a). Expansile growth of the tumor with architectural and cytological atypia, H&E 4X. **Immunomarkers:** (b) Positive for CK7, (c) Patchy positivity for CK20, (d) Focal positivity for CDX2, (e) Negative for SATB2.

Among the benign stromal tumors, one each case of cellular fibroma, fibrothecoma and steroid cell tumor were reported. Four cases of granulosa cell tumors (10.52%), malignant sex cord tumors were noted in our study. One case of granulosa cell tumor had a minor sex cord element along with the tumor (Figure 4).

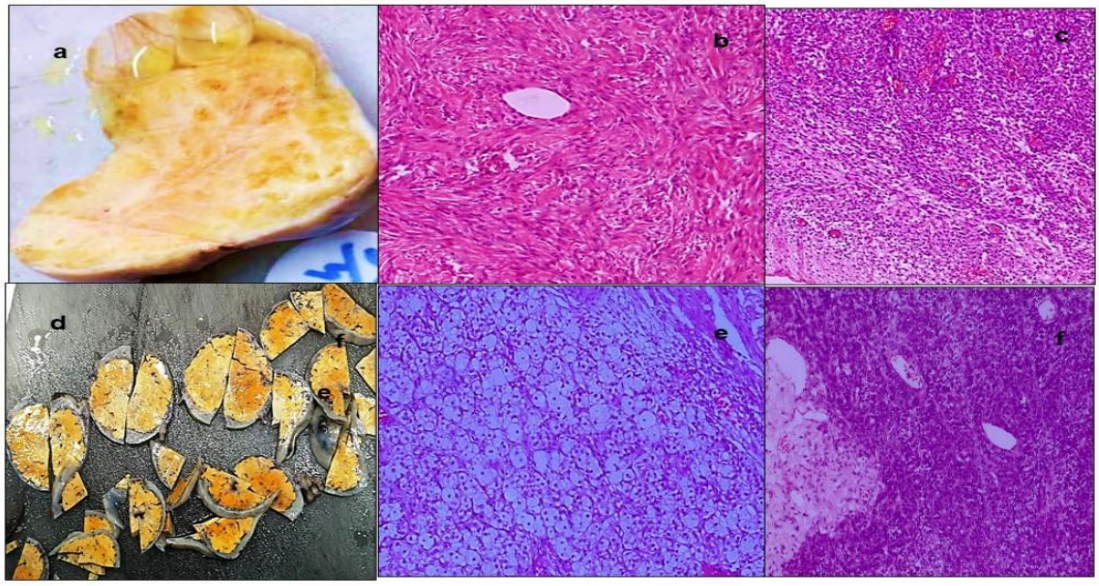

Figure 4 (a, b): Cellular fibroma with yellowish-white surface and fascicles of bland spindle cells admixed with collagen H&E, 10X. **(c) Fibrothecoma** with fibrous and thecal components H&E, 10X. **(d, e) Steroid cell tumor** with golden yellow capsulated lesion composed of polygonal tumor cells with abundant cytoplasm H&E, 40X. (f) **Granulosa cell tumor** with diffuse sheets and trabecular pattern H&E, 10X.

Among the benign category of germ cell tumors, a case of struma ovarii comprised predominantly of thyroid tissue was reported. In the malignant category, 2 cases of dysgerminoma(10.52%) and a case of yolk sac tumor and immature teratoma (Grade-2) was diagnosed. All the malignant germ cell tumors were below the age of 12-35 years. A case of mixed germ cell tumor (2.4%) was reported in an 18-year female which showed components of dysgerminoma and yolk sac tumor (Figure 5).

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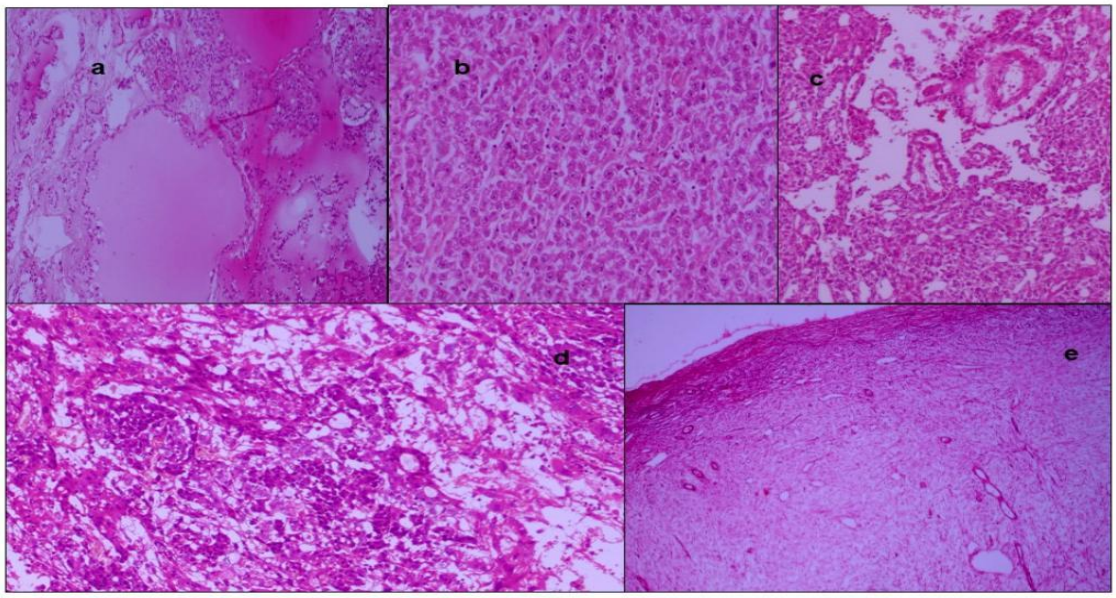

Figure 5: (a) **Struma Ovarii** showing normal thyroid tissue in the ovary H&E, 10X. (b) **Dysgerminoma** with sheets of tumor cells and interspersed lymphocytes H&E, 40X. (c) **Yolk sac tumor** with solid-hepatoid-reticular pattern and schiller dual bodies H&E, 40X. (d) **Mixed germ cell tumor** with components of dysgerminoma and yolk sac tumor H&E,40X. (e) **Massive ovarian edema** with markedly edematous stroma H&E, 10X.

We ought to highlight a rare case of primary ovarian lymphoma (2.63%) in a 28-year lady who presented with Meig's syndrome. A diagnosis of malignant ovarian tumor was rendered on frozen section. A preliminary diagnosis of primary large B-cell lymphoma of ovary was offered after a thorough clinical and histopathological examination with no extra ovarian involvement. With positivity for LCA and negative for Pan CK immunostains, further evaluation at quaternary oncocentre showed positivity for CD45, CD20, BCL6 and CD10 immunostains. Ki-67 was 90%. Pan CK, CD99, Chromogranin, BCL 2, CD 3, Tdt, MUM1 were negative. C-MYC gene rearrangement on FISH was negative and hence a final diagnosis of High-grade B cell lymphoma, NOS was made (Figure 6a-f).

A rare entity like bilateral metastatic tumor (Krukenberg tumor) of the ovary (2.63%) was diagnosed in a 45-year lady. Intraoperative frozen diagnosis of signet ring stromal tumor in the ovary with the suspicion of metastatic lesion was alerted to the surgeon. Histopathology proved it to be a metastatic deposit in the ovary. On further evaluation, endoscopic biopsy showed signet ring cell carcinoma in the antrum of the stomach. The other ovary also showed similar metastatic deposits (Figure 6g& 6h).

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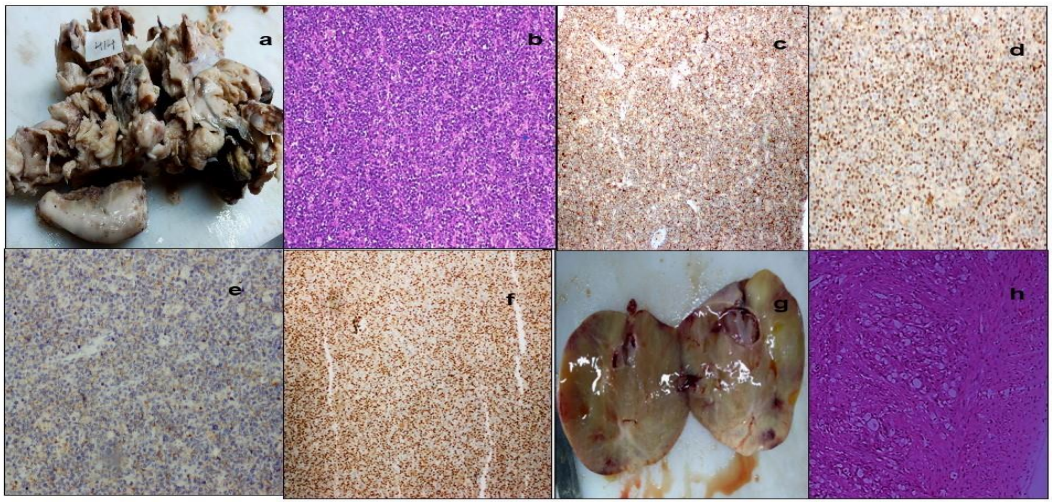

Figure 6: High grade B cell lymphoma: (a) Solid, grey white, fleshy and homogenous surface. (b) Monotonous population of large lymphoid cells with interspersed macrophages H&E, 10X. **Immunomarkers: (**c, d,e,f) Positive for CD45, BCL6, CD10, Ki67(90%), 10X. **Krukenberg tumor:** (g) Gelatinous grey- tan uniform surface. (h) Infiltrating tumor nests of signet ring cells in the cortical surface of ovary H&E, 40X.

Among the tumor-like conditions (15.79%), a case of massive ovarian edema (Figure 5e) was reported with enlargement of ovary and slimy surface on gross appearance. Histopathology showed markedly edematous stroma with congested blood vessels. We had one case of pregnancy luteoma and one case of xanthogranulomatous oophoritis. An incidental case of Leydig cell hyperplasia was reported in the hilar region of ovary in a 46-year lady. Additionally, a case of stromal hyperthecosis with nodules of luteinised stromal cells was reported in a 55-year lady.

Discussion:

Most of the solid ovarian lesions are malignant. The commonly diagnosed ovarian carcinomas include: high grade serous (70%), endometrioid (10%), clear cell (10%), mucinous (3%), and low grade serous carcinomas (<5%).[2] The diagnosis of ovarian lesions is based on findings of imaging modalities, tumor markers and histomorphological evaluation of resected surgical specimens.[5,8] A thorough histopathological examination with the findings of imaging tests will help the clinician in proper staging of ovarian tumors.[5, 8, 9] Histopathological examination provides a baseline access to the identification of different molecular genetic alterations. A few high-grade serous carcinoma are thought to originate from fimbriated end of the fallopian tube and hence the SEE-FIM protocol of completely embedding the fallopian tube.[2] Recent studies have emphasized genetic counselling and testing of BRCA mutations in cases with strong family history of ovarian cancer.[2,10] This will help them to plan for prophylactic oophorectomy in such individuals.[2,4]

The study conducted by Matt A, Morgan et al, Tyagi et al, reported overall 23.4% prevalence of solid ovarian tumors. Similarly, Sudhakar et al, Pradhan et al, Kancherla observed the prevalence of 24%, 13.2%, and 16% respectively.[11] In our study, the prevalence of solid ovarian lesions was 3.43% among all the ovarian lesions studied. Present study reported maximum number of solid ovarian lesions in the age group of 51-60 years. Other studies by Tyagi SP et al reported average age range of 42-45 years.[12] However, Sudhakar G et al reported 41-50 years as the most common age group of solid ovarian tumors in their study.[11] All the germ cell tumors were reported in the early age group of 12-35 years. Sudhakar G et al reported 2 cases (8.6%) of germ cell tumors within 10 years of age. Bilateral solid ovaries were 17.4% and 23.2% as reported by Sudhakar G and Tyagi SP et al respectively.[11, 12] Present study showed 5.26% of bilaterality which showed concordance with Tejaswini et al (5.4%).[8]

The study conducted by Sudhakar G and Tyagi SP et al showed that 47.8% and 16.2% of benign solid ovarian tumors respectively.[11, 12] Our study showed 34.21% of benign solid ovarian tumors. Similarly, their study reported a prevalence of 52.2% and 83.8% of malignant solid ovarian tumors.[11, 12] However, our study showed a prevalence of 65.78% cases which was in concordance with Sudhakar G et al. Chandanwale SS et al in a study of 50 ovarian malignancies reported

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42% of malignant ovarian lesions to be solid in nature.[5]

Study of solid tumor of ovary by Tyagi SP et al reported 28.2% of surface epithelial tumors, 22.2% germ cell tumors, 21.4% sex cord stromal tumors, 19.7% metastatic tumors and the rest nonspecific tumors.[12] Similar study of solid ovarian tumors by Sudhakar G et al reported 39.1% germ cell tumors, 26.03% of sex cord stromal tumors and 13.07% each of surface epithelial and metastatic tumors.[11] Our study showed prevalence of 47.37% surface epithelial tumors,18.42% of sex cord stromal tumors, 15.79% of germ cell tumors, 13.16% of tumor –like lesions, and 2.63% cases each of lymphoma and metastatic tumors. Chandanwale et al reported 6% of metastatic tumors in their study.[5]

In our study, 4 cases of low grade and 3 cases high-grade serous carcinoma was reported. A case of high-grade serous carcinoma was bilateral. Psammoma bodies were seen in two of the cases of LGSC. Chandanwale et al reported psammoma bodies in 40% of tumors.[5] In evaluating the surface epithelial ovarian tumors one must be careful in extensive sampling of tumor specimens with one section in every 1-2 cm of tumor diameter especially in suspicious areas.[13] The clinical implications of borderline lesion are staging surgery and follow up protocol when reported next to benign lesions. Likewise, in Mucinous borderline tumor, appendix, omentum is removed as a part of staging surgery. In malignant tumors with equivocal degrees of nuclear pleomorphism, mitotic figures of more than 12/10 HPF are helpful diagnostic clues in making a diagnosis of high-grade serous carcinoma.[2,6,14]

The recent proposal of expansile type of growth in mucinous carcinoma referred to as the intraglandular pattern has a more favorable prognosis when compared to infiltrative growth which was reported in one of our case. Similarly evaluating primary vs secondary mucinous carcinoma in the ovary is of paramount importance which was revealed in the same case. Jingjing Hu et al used distinctive gross features of unilaterality, size more than 13 cm and absence of surface nodules to support the diagnosis of primary mucinous tumor over metastatic ovarian tumors.[15] Immunohistochemistry such as CK7 is strongly positive in primary mucinous carcinomas in 80% cases. However, Metastatic mucinous tumors are positive for CK20, CDX2 and negative for CK7 and plays a pivotal role in such a diagnostic scenario of evaluating mucinous tumors of primary vs secondary origin.[13,14,15,16]

Gilks B et al described those mixed epithelial carcinomas are better classified as HGSC based on the molecular studies in which histological components showed a distinct unequivocal recognizable growth pattern on histomorphology.[10,14] The role of tumor markers in malignant surface epithelial tumors and germ cell tumors are a valuable tool in diagnosis, surveillance and follow up of the cases.[5]

In general, sex cord stromal tumors represent nearly 7% of all ovarian tumors. Our study had 3 benign stromal tumors with typical histomorphological features. An unusual morphological presentation with elevated CA-125 levels was reported by Arya et al.[17] Obeidat et al also reported a rare unusual aggressive behavior of a case of fibrothecoma with multiple recurrences in their studies.[18]

F.Vazquez Rueda et al reported 65% germ cell tumors followed by 22% surface epithelial tumors in their study of solid ovarian tumors in Spanish pediatric population.[9] However, in our study all the germ cell tumors were reported in the age group of 12-35 years with a prevalence of 15.79%.

Primary lymphoma in ovary is extremely rare accounting for 0.5% of all Non-Hodgkin's Lymphoma and 1.5% of all ovarian neoplasms.[19] Histomorphological evaluation with the help of imaging modalities helps to arrive at a diagnosis of primary lymphoma in the ovary. We reported a unique case of High-grade lymphoma, a morphological mimicker of Burkitt lymphoma with a similar clinical presentation as reported by Kagawa H et al.[19] Molecular studies and immunohistochemistry helps in subtyping the lesion. [16, 20]

In our study, we reported a case (2.63%) of metastatic gastric adenocarcinoma with a Krukenberg tumor. Verma & Bhatia reported a higher incidence of 6.5% and Tejaswini et al reported 1.08%.[8] While the prevalence of metastatic tumors was 19.6% and 13.07% respectively by Tyagi and Sudhakar G et al in their studies.[11,12] Careful evaluation with the help of clinical features, histomorphological and immunohistochemical studies to report the primary

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origin plays a significant role in diagnostic evaluation of metastatic ovarian tumors.[16]

Conclusion:

Analysis of this study has provided an understanding into various non- neoplastic, neoplastic primary and secondary solid ovarian lesions depicting its wide spectrum of histogenesis. Accurate histopathological diagnosis provides a baseline access to molecular testing which helps in subtype- specific treatment of malignant ovarian tumors. Advanced research studies on prognostic and predictive markers have immense role in management of solid ovarian tumors.

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Categories	**No of cases (%)**
Benign	14 (36.84)
Borderline	1 (2.63)
Malignant	23 (60.53)
Total	38 (100)

Table1: Nature of solid ovarian tumors (n=38).

Age group (years)	**No of cases.**
1-10	-
11-20	3
21-30	5
31-40	9
41-50	8
51-60	11
>60	2

T**able 2: Age distribution of ovarian lesions(n=38).**

	Benign	**Borderline**	**Malignant**	**Total (%)**
Surface epithelial tumors	4	1	13	18 (47.37%)
Sex cord stromal tumors	3	-	4	7 (18.42%)
Germ cell tumors	1	-	5	6 (15.79%)
Lymphoid tumors	-	-	1	1 (2.63%)
Metastatic tumors	-	-	1	1 (2.63%)
Tumor-like lesions	5	-	-	5 (13.16%)

Table 3: Histopathological patterns of solid ovarian tumors(n=38).

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