(International Print/Online Journal)

SJIF IMPACT FACTOR: 5.565
PUBMED-National Library of Medicine ID-101739732

ISSN (Print): 2209-2870
ISSN (Online): 2209-2862

International Journal of Medical Science and Current Research (IJMSCR)
Available online at: www.ijmscr.com
Volume 7, Issue 3 , Page No: 478-490
May-June 2024

IJMSCR

Prospective Histopathological Study Of Ovarian Tumors And Immunohistochemical Correlation Wherever Indicated

[1]Juhi Shishodia*, [2]Sudhamani S.
[1]Department of Pathology, Senior Resident, D.Y Patil University, Nerul, Navi Mumbai
[2]Department of Pathology, Professor, D.Y Patil University, Nerul, Navi Mumbai

***Corresponding Author:**
Juhi Shishodia
Department of Pathology, Senior Resident, D.Y Patil University, Nerul, Navi Mumbai

Type of Publication: Original Research Paper
Conflicts of Interest: Nil

Abstract

Ovarian tumors are a common cause for morbidity and mortality, with ovarian cancer accounting for 3% of all cancers in women and 30% of all cancers of the female genital tract. Among cancers of the female genital tract, the incidence of ovarian cancer ranks below only carcinoma of the cervix and the endometrium. [1] Specific diagnosis needs careful gross and histopathological examination to categorise tumors into benign, borderline and malignant. [1] Although standard morphological examination using routine Hematoxylin and eosin stained sections can lead to categorisation of majority of ovarian neoplasms, significant problems may arise in diagnosis due to neoplasms of similar or even diverse histogenic origins mimicking each other to a greater or lesser extent. Immunohistochemistry (IHC) plays a significant role in the classification of these tumors. [1] IHC can act as an adjunct to arrive at a correct diagnosis and to differentiate between primary and metastatic tumors, especially in the absence of a known primary. [1]

Keywords: Ovarian tumors, Histopathology, Immunohistochemistry

Introduction

Ovarian tumors possess a wide gamut of histology, with an almost bewildering array of morphological features, which is more than that seen in any other organ.[1] It is extremely essential to understand the origin of ovarian cancer and the specific histological types to aid diagnosis as well as to offer specific treatment. [2] World Health Organization (WHO) classifies ovarian tumors according to their cell of origin and histo-morphologic features.[3] More than 90% of ovarian tumors are epithelial in origin. [4] Survival of women with epithelial ovarian cancer, which is the most common type of malignancy, has not changed much even when survival rates for solid cancers have improved drastically. [5] Immunohistochemistry (IHC) can act as an adjunct to arrive at a correct diagnosis and to differentiate between primary and metastatic tumors, especially in the absence of a known primary. [1] Use of immunostaining significantly improves both diagnostic accuracy and agreement between pathologists. All the main categories of ovarian tumors have distinctive IHC features and different stains can be used to suggest or confirm a diagnosis. Immunohistochemistry, when indicated, is also helpful in the identification of underlying genetic events, characterizing various tumors as well as precancerous lesions. [5] Study of different IHC markers in correlation with histopathological diagnosis will help in determining the therapeutic approach and prognosis for the patients. The present study included 83 cases of ovarian tumors received over a period of 2 years. The study was undertaken to assess the varied morphological aspects of ovarian tumors in detail and to stratify them into benign, borderline, and malignant tumors, so as to indicate effective management, and so that the prognosis of the

patient could be decided. We also aimed to correlate the histopathological findings with immunohistochemical markers, wherever indicated; and to compare our findings with other similar studies to look for any changing trend or any new emerging trend in this important field of gynaecological pathology.

Materials And Methods:

Setting: Study was done at the Department of Pathology in D.Y. Patil School of Medicine, Hospital and Research Centre, histopathology section.

Study Design: Prospective Study.

Study Site: Department of Pathology.

Duration Of Study: 2 years after getting clearance from IEC.

Sample Size: 83.

Study Participants: All women diagnosed with ovarian tumors who were operated for diagnostic and therapeutic purposes.

Sampling Procedure: Simple Random sampling. (All cases during study period were included in the study.)

Method:

1. All the operated ovarian malignancies received in histopathology department were immediately studied for gross features and clinical details were noted simultaneously.
2. Tissue was fixed using 10% buffered formalin solution and processed with standard tissue processing techniques.
3. 5 micrometer sections of paraffin-embedded sections were cut.
4. Hematoxylin and Eosin (H&E) stained slides were reviewed in each tumor and all tumors were classified according to theWorld Health Organization criteria.
5. The ovarian tumors which needed IHC were decided based on histopathological features. IHC was done for diagnostic and prognostic purposes. IHC was performed using standard technique.
6. Slides were counter stained using H&E stain.
7. Intensity of staining was scored as follows: 0 (No staining), 1 (Weak), 2 (Moderate),and 3 (Strong).
8. Appropriate controls were included.

Parameters: The findings of histopathology and IHC (when available) were noted as per the study proforma and correlated and entered on a master chart.

Inclusion Criteria:

1. All benign, borderline, and malignant primary tumors of the ovary operated for diagnostic and therapeutic purposes.
2. Those tumors for which IHC had been done for diagnosis were included.
3. Metastatic tumors to ovary were also included.

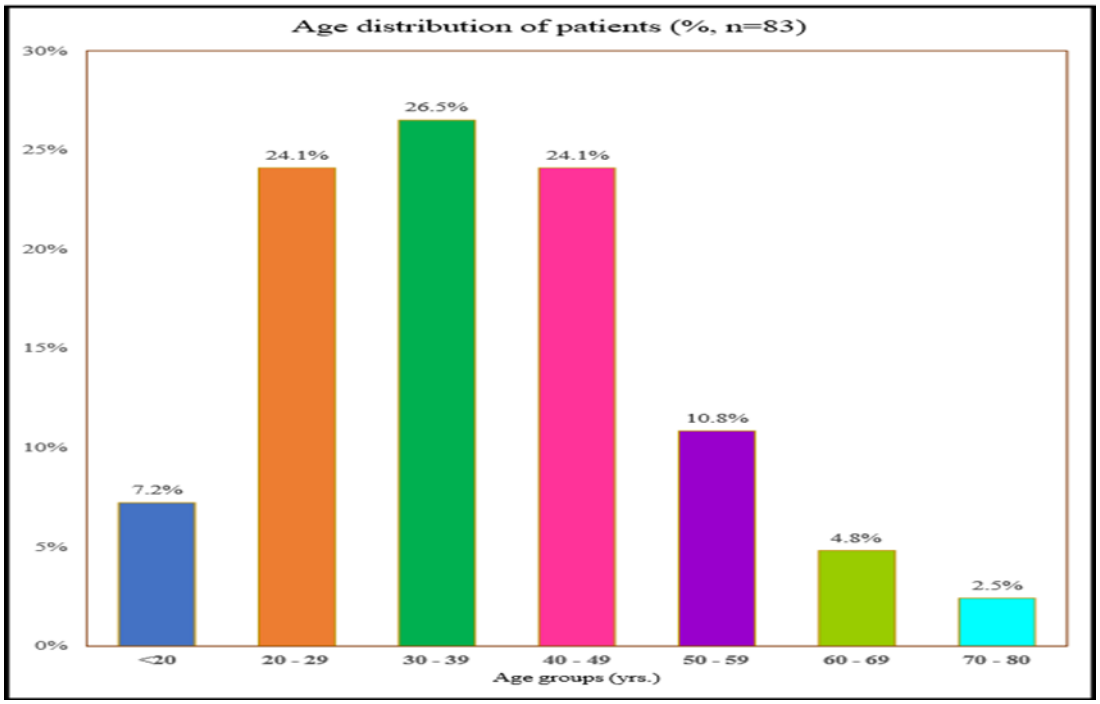
Exclusion Criteria:

1. Inadequate/ necrotic/autolyzed samples.
2. Adherent tumors from surrounding structures were excluded.

Results:

Volume 7, Issue 3; May-June 2024; Page No 478-490

Chart 1: Age distribution of patients included in the study (%, n = 83)



The age range of patients included in the study varied from 8 to 76 years, with the maximum number of patients (n=22,26.5%) in the age group of 30-39years.

Table 1: Laterality of specimens in correlation with nature of neoplastic lesions (%, n = 83)

	Histopathological diagnosis				
Laterality	**Benign**		**Malignant**		**N**
	No.	***%***	***No.***	***%***	
Right	40	85.11%	7	14.89%	47
Left	25	83.33%	5	16.67%	30
Bilateral	1	16.8%	5	83.3%	6
Total	66	79.52%	17	20.48%	83

Most of the lesions included in the study were right-sided (47 cases, 56.6%) followed by 30 (36.1%) left-sided lesions. 6 lesions (7.3%) were bilateral. Out of the 47 right-sided lesions, 40(85.11%) were benign and7 (14.89%) were malignant. Out of 30 left-sided lesions, 25 (83.33%) were benign and 5 (16.67%) were malignant. There were 6 bilateral lesions in the study, out of which 1 (16.8%) was benign and 5 (83.3%) were malignant.

Table 2: Correlation of consistency of tumors (on gross) and histopathological diagnosis (%, n=83)

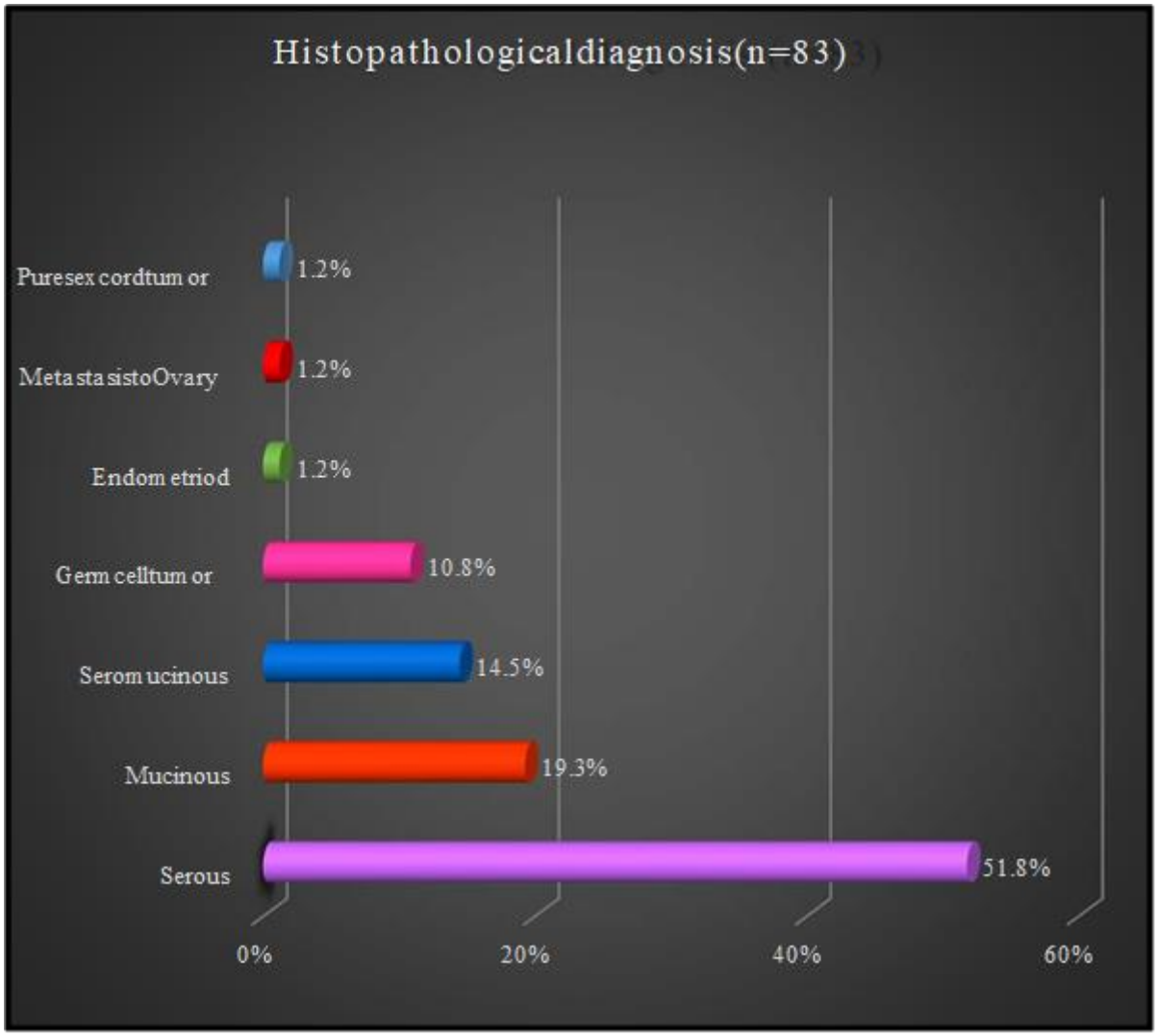
Consistency of tumors on gross	**Histopathological diagnosis**		**Total**
	Benign	**Malignant**	

Volume 7, Issue 3; May-June 2024; Page No 478-490

Cystic	65(78.31%)	4(4.81%)	69(83.1%)
Solid	0(0.0%)	9(10.84%)	9(10.84%)
Solid + Cystic	1(1.20%)	4(4.81%)	5(6.02%)
Total	**66(79.5%)**	**17(20.48%)**	**83**

Out of the 69 cystic lesions on cut surface, 65 were benign and 4 malignant after histopathological evaluation. All 9 solid lesions turned out to be malignant histopathologically. Amongst the 5 solid and cystic lesions, 1 was benign and 4 were malignant after histopathological examination.

Chart 2: Major histopathological subtypes of tumors included in the study (%, n=83)



The spectrum of lesions studied included a maximum of serous tumors (N=43,51.8%), out of which 26 were cystadenomas followed by 10 cystadenofibromas, 6 high-grade serous carcinomas and a single low-grade serous carcinoma. This was followed by 16 cases (19.3%) of mucinous tumors which included 11 cystadenomas, 2 borderline tumors and 3 adenocarcinomas. Out of the 12 cases (14.5%) of seromucinous tumors, 11 were cystadenomas and a single case was cystadenofibroma. There were 9 germ cell tumors (10.8%) with 7 teratomas, and a single yolk sac tumor and mixed germ cell tumor each.

Volume 7, Issue 3; May-June 2024; Page No 478-490

The study included a single case each of pure sex-cord stromal tumor (adult granulosa cell tumor), endometrioid adenocarcinoma and metastases to the ovary.

Table 3: Clinico-histopathological correlation (%, n=83)

Clinical diagnosis	Histopathological diagnosis		
	Benign	**Malignant**	**Total**
Benign	55 (66.26%)	4 (4.81%)	59 (71.08%)
Malignant	4 (4.81%)	9 (10.8%)	13 (15.66%)
Non-neoplastic	7 (8.43%)	4 (4.81%)	11 (13.25%)
Total	**66 (79.51%)**	**17 (20.48%)**	**83**

Malignancy predictor model based on our study

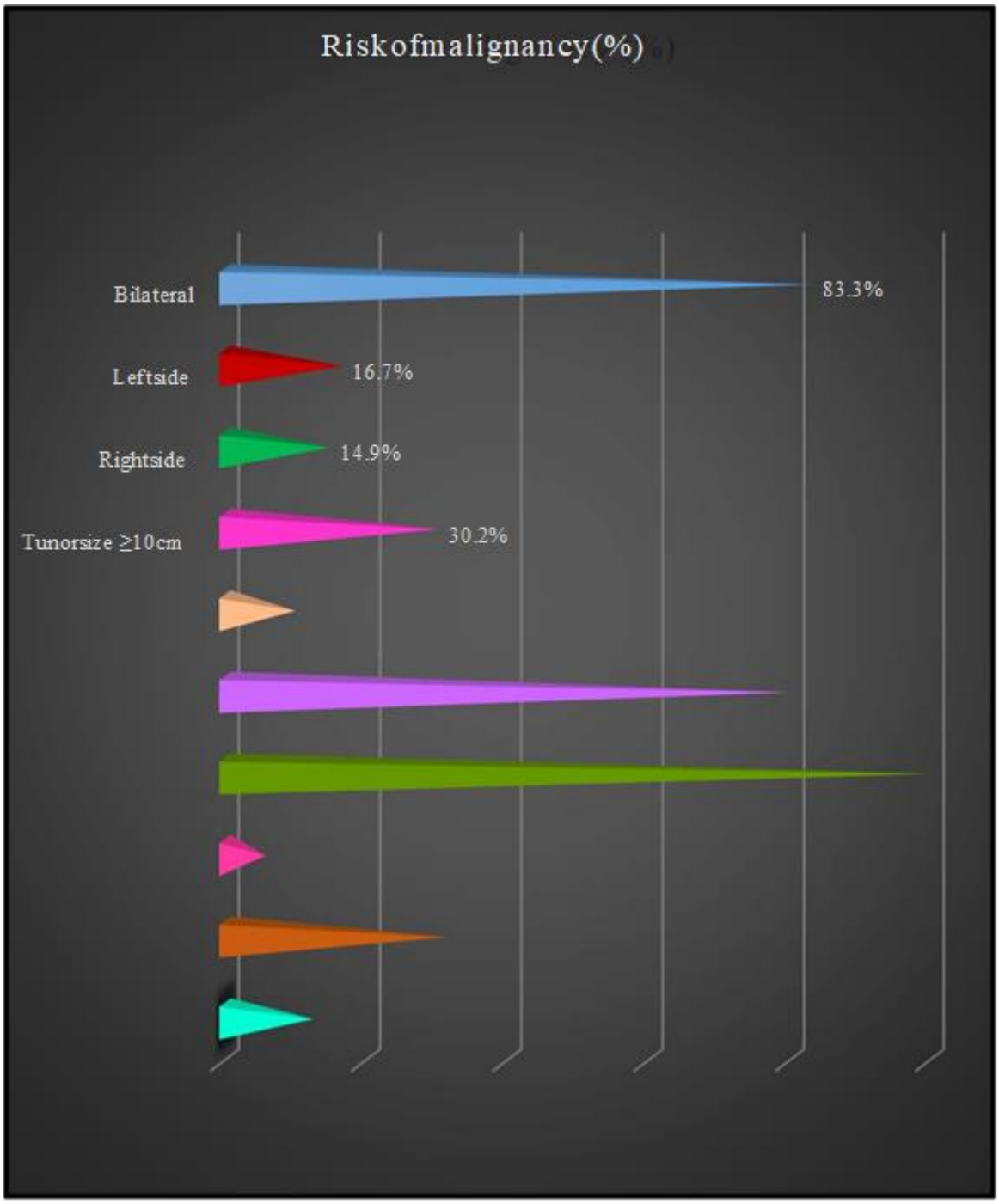
Table 4: Variables related to the risk of malignancy

Variables	N	Malignant (No.)	%	'p' value
Age				

Volume 7, Issue 3; May-June 2024; Page No 478-490

• <40yrs.	48	6	12.5%	0.0360
• ≥40yrs.	35	11	31.4%	
Tumor morphology				
• Cystic	69	4	5.8%	<0.0001
• Solid	9	9	100.0%	
• Solid + cystic	5	4	80.0%	
Tumor size				
• <10cm	40	4	10.0%	0.013
• ≥10cm	43	13	30.2%	
Laterality				
• Right	47	7	14.89%	0.0004
• Left	30	5	16.6%	
• Bilateral	6	5	83.3%	

Volume 7, Issue 3; May-June 2024; Page No 478-490



Based on this model, advancing age, solid nature of lesions, increasing size and bilateral lesions are associated with a higher risk of malignancy.

Immunohistochemical Staining Results Of Tumors

Immunohistochemical staining (IHC) staining was employed for the confirmation of diagnosis in 3 cases included in the study, and in case of metastatic adenocarcinoma to detect the source of primary tumor. The use of IHC was very limited in the study as the patients were non-affording in this study conducted in a charitable hospital.

WT1 staining was employed in 3 cases of serous carcinomas in the study. In the positive controls, known case of ovarian carcinoma cells showed nuclear positivity with WT1. It also showed strong nuclear positivity in the tumor

Volume 7, Issue 3; May-June 2024; Page No 478-490

cells of high-grade serous carcinoma and low-grade serous carcinoma, thereby confirming the diagnosis. Results of staining are summarized in the table below:

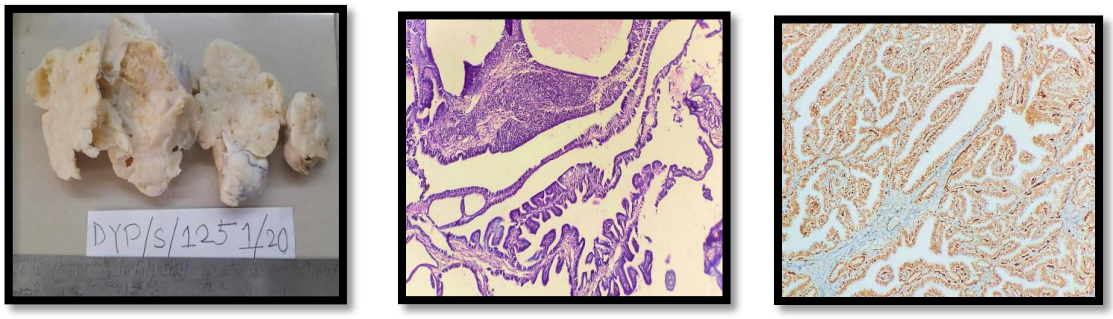
Table 5: WT1 staining of tumors in the study

Tumor type	Control (Known case of carcinoma of ovary)	Number of positive cases	Ratio (%)
High-grade serous carcinoma (HGSC)	Positive	1/6	16.6%
Low-grade serous carcinoma (LGSC)	Positive	1/1	100%

Immunohistochemical staining was employed in a single case of mucinous carcinoma with mural nodule of carcinosarcoma, to categorize the mural nodules. The IHCs performed were Pan-Cytokeratin (Pan-CK), Vimentin and Epithelial Membrane Antigen (EMA). The carcinomatous component in the tumor showed diffuse and strong positivity for Pan-CK and EMA but was negative for vimentin. On the other hand, the sarcomatous element of the tumor showed diffuse and strong positivity for vimentin, and was also negative for Pan-CK and EMA. Therefore, the mutually exclusive expression of Pan-CK/EMA and vimentin in the carcinomatous and sarcomatous components respectively, paved the way for the diagnosis of mural nodule of carcinosarcoma in a case of mucinous ovarian carcinoma.

Immunohistochemical staining was employed in a single case of metastatic adenocarcinoma to confirm the primary source of the metastatic tumor. The markers used were PAX8 and CDX2 based upon the suspicion after histopathological evaluation. PAX8 showed negative staining, thereby ruling out primary nature of the tumor, while CDX2 showed positive nuclear staining in the tumor cells, indicating metastases of gastro-intestinal origin in the ovary. The morphology of tumor cells in conjunction with IHC staining pattern was consistent with metastatic signet ring cell adenocarcinoma of gastric origin.

Figure 1: LOW-GRADE SEROUS CARCINOMA



A: Ovary displaying a heterogeneous yellow and friable mass. A unilocular cyst also identified.

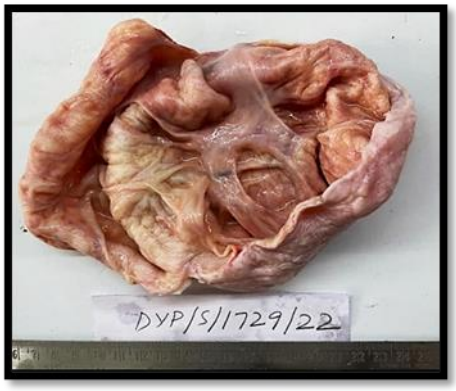
B:H&E(10x): Tumor displaying micropapillary architecture.

C.10x: WT1 IHC showing positivity in tumor cells in the same case.

Volume 7, Issue 3; May-June 2024; Page No 478-490

Figure 2: MUCINOUSCYSTADENOMA

A: Smooth, translucent and multi-loculated cyst wall



B:H&E(40x): Cyst lined by single layer of bland mucinous epithelium.

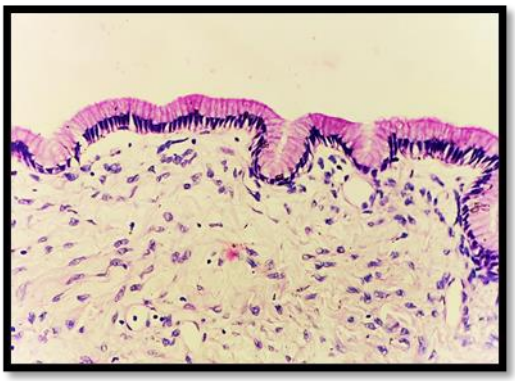


Figure 3: MATURE CYSTIC TERATOMA

A: Excised cyst filled with yellow pultaceous material and surrounded by tuft of hair.

B:H&E(10x): Squamous epithelium with underlying sebaceous glands seen in ovarian stroma.

Volume 7, Issue 3; May-June 2024; Page No 478-490

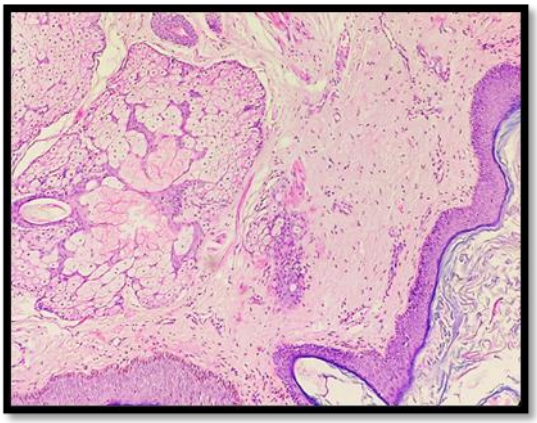
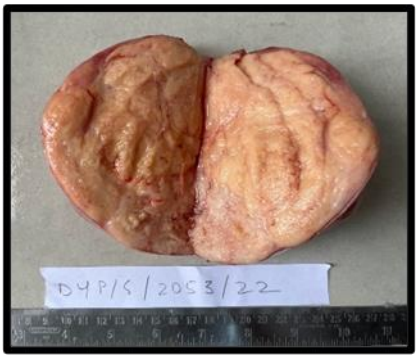
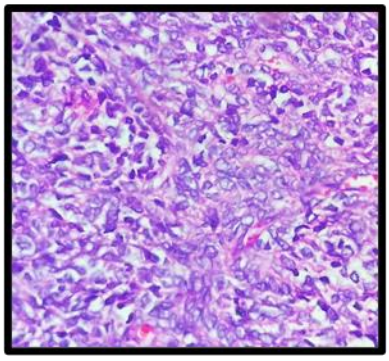


Figure 4: ADULT GRANULOSA CELL TUMOR

A: Shiny, smooth, bosselated external surface with intact capsule.



B:H&E(40x): Individual tumor cells displaying grooving.



Discussion

1. AGE OF PRESENTATION: Our study was in concordance with the studies conducted by Pilli et al [6], R Jha [7] and discordant with Mondal et al [8].
2. PRESENTING COMPLAINTS: The results comply well with a study carried out by Rashid et al [9]. The study was discordant with a retrospective analysis by Jamal et al [10].
3. CA-125 LEVELS: The present study was in concordance with a study conducted by W.H. Gotlieb et al [11], wherein CA-125 levels were elevated in 75% of patients with serous tumors of borderline malignancy before surgery (mean,156 IU/mL) compared with 30% of mucinous tumors.

Volume 7, Issue 3; May-June 2024; Page No 478-490

4. LATERALITY: Our study was concordant with various other studies, like Swamy GG [12] et al, Jha R [7] et al.
5. Comparative analysis of behaviour of bilateral tumors: The studies conducted by R Jha [7] et al and Swamy GG [12] et al were in concordance with the present study indicating that malignant tumors usually tend to present bilaterally. Comparative analysis of behaviour of unilateral tumors: The incidence of benign tumors amongst unilateral lesions in our study was concordant with the study of Pilli et al [6], with 98.4% incidence in the present study compared to 92.2% in the study conducted by Pilli et al [6].
6. TYPES OF SPECIMENS RECEIVED: The present study is discordant with the study conducted by Jain R et al [13] and Sharma P et al [14].
7. MAXIMUM GROSS SIZE OF SPECIMENS: The present study is concordant with study by Pilli et al [6].
8. CONSISTENCY OF TUMORS ON GROSS: The present study is concordant with a study conducted by Jain R et al [13].
9. NATURE OF NEOPLASTIC LESIONS ON HISTOPATHOLOGY: Our study was in concordance with various other studies done by Pilli et al [6], Sharma P et al [14] and R Jha et al [7]. However, in a study conducted by Divya K et al [1], 42% of lesions were benign and 48% were malignant.
10. IMMUNOHISTOCHEMICAL STAINING IN TUMORS: Our study was concordant with study conducted by Geza Acs et al [15] and M Al-Hussaini [16].

Summary

1. We conducted a prospective histopathological study at Dr. D. Y. Patil School of Medicine, Nerul, Navi Mumbai over a period of 2 years.
2. A total of 83 cases of ovarian neoplastic lesions were studied during this period.
3. The most common age group of patients presenting with ovarian tumors was 30-39 years (26.5%).
4. The most common presenting complaint was pain in the abdomen (59%).
5. Majority of the lesions included in the study were found to be unilateral (92.7%) with right-sided tumors (56.6%) being more common than left-sided tumors (36.1%).
6. 85.11% of right-sided tumors were benign and14.89% were malignant.
7. 83.33% of left-sided tumors were benign and16.67% were malignant.
8. Majority of the bilateral tumors in the study turned out to be malignant (83.3%).
9. The specimens were received most commonly in the form of ovarian cysts (67.5%).
10. The tumors ranged in size from 0.9 to 27 cm, with most of them in the size range of 10-19 cm (39.8%).
11. Majority of the tumors had a cystic appearance on cut surface (90.2%), out of which 49.4% were uniloculated and 39.8%were multi-loculated.
12. All of the tumors with solid cut surface were diagnosed as malignant on histopathological evaluation (100%).
13. Of the total 83 cases, the incidence of benign tumors (79.5%) was found to be much higher than that of malignant (18.1%) and borderline (2.4%) tumors.
14. The most common histopathological subtype was serous tumors (51.8%), out of which serous cystadenomas (31.3%) formed the majority of the cases.
15. The most common malignant tumor was high-grade serous carcinoma (7.2%).
16. One of the cases of high-grade serous carcinomas, the most common malignant tumor encountered in our study, showed metastases to the omentum; and another case showed para-aortic lymph nodes and peritoneal metastases with bilateral fallopian tubes showing features of serous tubal intra-epithelial carcinoma.
17. There was a good correlation between radiological and histopathological diagnosis.
18. Increased incidence of malignancy was noted with advancing age (≥40 years, 31.4%), solid nature of lesions (100%), increasing size (≥10 cm, 20.2%), and bilateral nature (83.3%) of lesions.
19. Immunohistochemical evaluation was limited in the study due to the non-affordability of the patients included in the study. It was done for only 4 cases included in the study and showed

Volume 7, Issue 3; May-June 2024; Page No 478-490

a good correlation with histopathological diagnosis in those 4 cases.

20. Our study showed good agreement with various other studies in the literature with regard to the different parameters examined.

Conclusion

Of all gynecological malignancies, ovarian cancer is responsible for the second-highest number of deaths worldwide, accounting for over 151,000 deaths annually. Presenting symptoms are often quite vague. Therefore, most women present with advanced-stage disease. Due to the wide variation in histological appearance, accurate diagnosis requires careful examination of gross and histological characteristics so as to categorize tumors into benign, borderline, and malignant. It is also quintessential for early diagnosis and management to establish clinical, radiological, biochemical, and histopathological correlation. The present study indicates that non-specific abdominal symptoms like pain in the abdomen should be given significance as they may be the only clue to diagnosing the underlying malignancy. Our study also reflects close proximity in the mean age of malignancy with the mean age of benign ovarian tumors, emphasizing the need for ruling out malignancy in all the age groups. We also found that most of the ovarian tumors presented unilaterally and most bilateral tumors were malignant. There was a 100% correlation between solid nature of tumors and malignancy, indicating the significance of thorough gross examination of tumors. Nearly 33.33% of high-grade serous tumors presented with metastases at the time of initial surgery, emphasizing that these tumors are likely to present at an advanced stage at the time of the first presentation.

As stated earlier, there exists a wide morphological variation within and between various ovarian neoplasms which can lead to diagnostic difficulties, with tumors in one group mimicking those in another. Immunohistochemistry (IHC) evaluation can aid with such diagnostic difficulties and can be used to arrive at a correct diagnosis, and also for patient stratification for therapy. Additionally, it can also be utilized to differentiate between primary and metastatic tumors. IHC and histopathological diagnosis showed a 100% correlation in the present study.

References:

1. Divya Kriplani and Mandakini M. Patel. Immunohistochemistry: A diagnostic aid in differentiating primary epithelial ovarian tumours and tumours metastatic to the ovary. South Asian J Cancer. 2013 Oct-Dec;2(4):254-258
2. Sharadha S, Sridevi TA, Renudevaki TK, Gowri R, Binayak D, Indra V. Ovarian masses: changing clinic histopathological trends. J Obstet Gynaecol India. 2015 Feb;65(1):34-8. Doi: 10.1007/s13224-014-0575-7.Epub 2014 Jun 6.PMID: 25737620; PMCID: PMC4342375
3. Gilks Blake. Ovary. John R. Goldblum, laura W. Lamps, Jesse K. McKenney, Jeffrey L. Myers (Ed.) (2018), Rosai and Ackerman's Surgical Pathology. Philadelphia, Elsevier.
4. Kurman RJ,Carcangiu ML, Herrington CS, Young RH. WHO Classification of Tumors of Female Reproductive Organs. 5th ed. Lyon: International Agency for Research on Cancer; 2014.
5. Hatice Ozer, Goncalmir Yenicesu, sema Arici, Meral Cetin, Ersin Tuncer & Ali Cetin. Immunohistochemistry with apoptotic-antiapoptotic proteins (p53, p21, bax, bcl-2), c-kit, telomerase, and metallothionein as a diagnostic aid in benign, borderline, and malignant serous and mucinous ovarian tumors. Diagnostic Pathology 7, Article Number: 124 (2012).
6. Ganga S Pilli, K.P.Sunitha, A.V.Dhaded, V V.Yenni. Ovarian tumors a study of 282 cases. J Indian Med Associ 2002; 100(7): 420-424
7. R Jha and S Karki. Histological pattern of ovarian tumors and their age distribution. Nepal Med Coll J 2008; 10(2):81-85.
8. Mondal SK, Banyopadhayay R, Nag DR, et al. Histologic pattern, bilaterality and clinical evaluation of 957 ovarian neoplasms: a 10 year study in a tertiary hospital of eastern India. J Cancer Res Ther.2011;7(4):433-437. Doi: 10.4103/0973-1482.92011. [PubMed] [CrossRef] [Google Scholar].
9. Rashid S, Sarwar G, Ali A. A clinicopathological study of ovarian cancer. Departments of Radiotherapy and oncology Sir Ganga Ram Hospital and Mayo Hospital Lahore. J Pak Med Assoc 1998;36;117-25.

Volume 7, Issue 3; May-June 2024; Page No 478-490

10. Jamal S, Quddusi H, Mehmood A. A clinic Histopathological analysis of 110 ovarian tumors. Pak J Med Sci 1997;14:19-23.
11. Gotleib WH, Soriano D, Achiron R, Zalel Y, Davidson B, Kopolovic J, Novikov I, Ben-Baruch G. CA 125 measurement and ultrasonography in borderline tumors of the ovary. Am J Obstet Gynecol. 2000 Sep;183(3):541-6. Doi: 10.1067/mob.2000.105940. PMID: 10992171.)
12. Swamy GG, Satyanarayana N. Clinicopathological analysis of ovarian tumors—a study on five years samples. Nepal Med Coll J.2010 Dec;12(4):22-1. PMID: 21744762.
13. Jain, Runjhun & Patel, pooja & Goyal, Sharda. Clinico-pathological study of ovarian tumors at tertiary care hospital, Udaipur. International Journal of Reproduction, Contraception, Obsteterics and Gynecology. 2021;10. 555. 10.18203/2320-1770.ijrcog20210301.
14. Sharma P, Rao P S, Mogra N, talreja K. Histopathological study of ovarian tumors in a tertiary care hospital of southern Rajasthan. Indian Journal of Pathology and Oncology.2020;7(4):561-566.
15. Acs G, Pasha T, Zhang PJ. WT1 is differentially expressed in serous, endometrioid, clear cell, and mucinous carcinomas of the peritoneum, fallopian tube, ovary and endometrium. Int J Gynecol Pathol. 2004 Apr;23(2):110-8. Doi: 10.1097/00004347-200404000-00004. PMID: 15084838.
16. Al-Hussaini M, Stockman A, Foster H, McCluggage WG. WT-1 assists in distinguishing ovarian from uterine serous carcinoma and in distinguishing between serous and endometrioid ovarian carcinoma. Histopathology. 2004 Feb;44(2):109-15. Doi: 10.1111/j.1365-2559.2004.01787. PMID: 14764054103.

Volume 7, Issue 3; May-June 2024; Page No 478-490