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Original Research Paper

Histopathology

CORRELATION OF HISTOPATHOLOGICAL TYPE OF OVARIAN TUMOURS WITH CA-125 LEVELS

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ABSTRACT

Introduction: Ovarian tumors are the sixth most common in women, accounting for 3% of female cancers. They're often asymptomatic until advanced stages, leading to high mortality. Serum tumor markers like CA-125 aid in screening and monitoring. However, CA-125 alone isn't sensitive enough for early detection. Levels increase with disease progression, detected in 50% and 92% of early and late-stage ovarian cancers respectively. Combining CA125 with transvaginal ultrasonography improves early detection. **Methods:** A descriptive cross-sectional study was done at a tertiary health care center for 18 months. 56 patients with clinically and ultrasonography-diagnosed ovarian tumors were studied. Preoperative serum CA-125 levels were measured using chemiluminescent immunoassay and correlated with tumor histopathology. **Results:** Abdominal pain was the primary symptom, with surface epithelial tumors being most prevalent (69.64%). CA-125 levels reliably differentiated between benign (<35 IU/ml) and malignant tumors (>35 IU/ml) with 90.48% sensitivity and 100% specificity. **Conclusion:** Elevated CA-125 levels indicate malignant surface epithelial ovarian tumors, making CA-125 measurement an effective screening tool for early detection. Coupled with ultrasonography, particularly in high-risk cases, it significantly improves early detection rates and boosts survival outcomes in ovarian tumor patients.

KEYWORDS : Surface Epithelial Tumors, CA-125, Ovarian Tumors

INTRODUCTION

Ovarian cancer ranks sixth globally among women's cancers and seventh in terms of cancerrelated fatalities. [1] In India, it stands as the third leading cancer type in women, trailing only cervical and breast cancers, as reported by major populationbased cancer registries. The incidence of ovarian cancer varies, with age-adjusted rates between 5.4 and 8.0 per 100,000 across different regions of the country. [2] Unfortunately, late-stage diagnosis contributes to its poor prognosis, yielding a five-year survival rate of 45%. [3]

The disease presents in three primary types: epithelial (90% of cases), germ cell (3%), and sex cord-stromal (2%). [4] Among these, epithelial tumors further diversify based on molecular pathways, risk factors, and treatments. Serous (52%), endometrioid (10%), mucinous (6%), and clear cell (6%) tumors make up the subtypes. These tumors often display aggressive behavior and are commonly diagnosed at an advanced stage, particularly high-grade serous carcinomas originating from microscopic fallopian tube lesions. [5-8] Germ cell and sex cord-stromal tumors contribute a minor 5% to ovarian cancer cases. Germ cell tumors arise in adolescents and young women from ovarian germ (egg) cells. Sex cord-stromal tumors, involving supportive ovarian tissue, manifest across age groups and often secrete sex hormones. While these tumors are rare, hormone exposure and genetic mutations elevate their risk. [4-9] Several factors influence ovarian cancer risk, including reproductive history and genetics. Nulliparity, older age at first birth, pelvic inflammatory disease, and hormone replacement therapy increases the risk, whereas early pregnancy, oral contraceptive use, and breastfeeding decrease it. Family history of ovarian cancer and certain genetic mutations also contribute to susceptibility. Furthermore, hormone exposure, obesity, and weight gain also heighten the risk. [10-15] Diagnosing ovarian cancer early proves pivotal for favorable outcomes, as the disease typically remains asymptomatic in its initial stages. Symptoms, when they manifest, tend to be nonspecific, often including abdominal discomfort, bloating, and urinary symptoms. Clinical remission is common, but relapse often occurs, leading to disease progression and eventual death. Efforts to identify effective screening methods and early symptoms are ongoing to improve early diagnosis and treatment outcomes. Notable tumor markers include CA125, with elevated levels observed in ovarian cancers. Nonetheless, a comprehensive diagnostic approach remains essential, considering the complexities of ovarian cancer manifestations.

MATERIAL AND METHODS

This 18-month research endeavor enrolled 56 patients diagnosed with ovarian tumors via rigorous clinical assessments and ultrasonography at a tertiary health center's Department of Pathology. These patients were meticulously selected based on predefined inclusion criteria, ensuring comprehensive representation across all age groups. Prior to tumor removal surgery, preoperative CA-125 assays were conducted, adhering strictly to institutional and international guidelines.

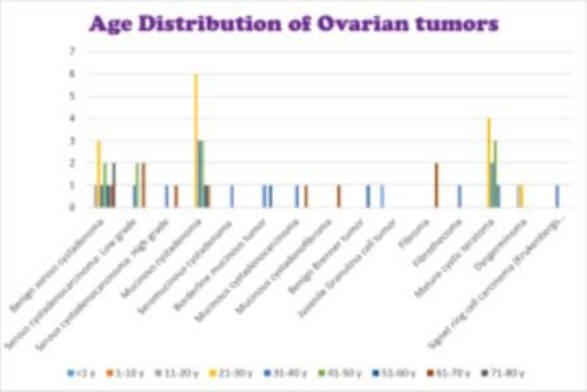
Exclusion criteria were meticulously defined, excluding individuals with non-neoplastic ovarian lesions or experiencing tumor recurrence. The study protocol was developed in accordance with the highest ethical standards and guidelines, including those set forth by institutional ethics committees and international regulatory bodies like the International Conference on Harmonisation/Good Clinical Practice Guidelines. Data collection involved detailed compilation of demographic information and comprehensive histopathological analysis of tissue specimens.

Throughout this study, a multidimensional approach was employed, integrating clinical observations with rigorous histopathological examinations. Notably, CA-125 levels were analyzed using chemiluminescent immunoassay, providing valuable insights into the diagnostic landscape of ovarian neoplasms. The findings from this study contribute significantly to the ongoing efforts aimed at enhancing our understanding of ovarian cancer detection and management strategies, underscoring the importance of interdisciplinary collaboration in advancing clinical practice and patient care.

RESULTS

In this 18-month study, we analyzed 56 cases of ovarian

tumors, comprising 42 benign, 2 borderline, and 12 malignant instances. The age range varied from 4 months to 80 years, with a mean age of 41.97±17.26 years. Notably, surface epithelial tumors were prevalent in the third to seventh decades, while germ cell tumors predominantly occurred in the second and third decades.



In our study, abdominal pain was the predominant presentation in 55.36% of patients, followed by abdominal distension in 23.21%. Additional symptoms included an abdominal mass, irregular menstruation, appetite loss, vomiting, and infertility. These findings highlight the diverse clinical manifestations of ovarian tumors.

We examined the parity distribution among participants, revealing that 62.5% were multiparous, 14.29% nulliparous, and 16.07% biparous. (Table 1)

Table 1: Relationship Between Ovarian Tumor and Parity

Sr. No	Parity of the patient	Benign 42 (75%)	Borderline 2 (3.57%)	Malignant 12 (21.42%)	Total	Percentage (%)
1	Nulliparous	4	0	4	8	14.29
2	Single parous	3	0	1	4	7.143
3	Biparous	8	0	1	9	16.07
4	Multiparous	27	2	6	35	62.5

Unilateral ovarian tumors were predominant, representing 91.07% (51 cases), while bilateral tumors constituted only 8.93% (5 cases). Laterality analysis revealed 26 cases on the right side and 25 on the left. Notable instances included serous cystadenocarcinoma, benign serous cystadenoma, mature cystic teratoma, and signet ring cell carcinoma (Krukenberg's tumor), enriching the rare bilateral presentation observed in our study.

In our study of surface epithelial tumors, 35.71% measured between 11 to 20 cm, while 28.57% fell within 1 to 10 cm. Sex cord stromal tumors spanned 1 to 20 cm, and germ cell tumors mostly ranged from 1 to 10 cm. Benign tumors were predominantly under 10 cm (24 cases), contrasting with malignant tumors where 9 out of 12 instances exceeded this threshold, illustrating the sizebehavior relationship.

In the study, cystic tumors are prominent, representing 48.21% of cases, with a notable predominance of uniloculated cysts over multiloculated ones. Conversely, malignant tumors exhibit primarily solid or amalgamated textures. These observations emphasize the varied morphological profiles of the tumors investigated, highlighting the need for nuanced consideration regarding their clinical significance. (Table 2)

Table 2: Gross Features of Ovarian Tumors

Sr.No	Gross appearance	Total number	Percentage
1.	Cystic	27	48.21%
2.	Cystic-Solid (Mixed)	24	42.85%
3.	Solid	5	8.92%
	Total	56	100%

Surface epithelial tumors comprised 69.64% of cases, with mucinous cystadenoma and benign serous cystadenoma being the most prevalent at 25% and 21.42% respectively. Other surface epithelial tumors included serous cystadenocarcinoma (10.71%), borderline mucinous tumor (3.57%), mucinous cystadenocarcinoma (3.57%), seromucinous cystadenoma (1.78%), mucinous cystadenofibroma (1.78%), and benign Brenner tumor (1.78%) (Table 3). 4 (7.14%) of the cases were sex cord stromal tumors. Among sex cord tumors, 2 cases were fibroma (3.57%), and one case each of granulosa cell tumor and fibrothecoma (Table 4). In present study we found 12 (21.42%) cases of germ cell tumors.

Among germ cell tumors 10 cases were mature cystic teratoma (17.85%) and 2 cases were dysgerminoma (3.57%).

Table 3: Types of Surface Epithelial Tumors

Types of Surface epithelial tumors	Total numbers	Percentage
Benign serous cystadenoma	12	21.42%
Serous cystadenocarcinoma	6	10.71%
Mucinous cystadenoma	14	25%
Borderline mucinous tumor	2	3.57%
Mucinous cystadenocarcinoma	2	3.57%
Seromucinous cystadenoma	1	1.78%
Mucinous cystadenofibroma	1	1.78%
Benign Brenner tumor	1	1.78%
Total	39	69.64%

Table 4: Types of Sex Cord Stromal Tumours

Types of Sex cord stromal tumors	Total numbers	Percentage
Granulosa cell tumor	1	1.78%
Fibroma	2	3.57%
Fibrothecoma	1	1.78%
Total	4	7.14%

Table 5: Germ Cell Tumors

Types of Germ Cell Tumors	Total Numbers	Percentage
Mature cystic teratoma	10	17.85%
Dysgerminoma	2	3.57%
Total	12	21.42%

Table 6: Secondary Tumors

Types of Secondary tumors	Total number	Percentage
Signet ring cell carcinoma (Krukenbergs tumour)	1	1.78%

(H&E, 40X)

In our study, cystectomy was the most common surgery (32.14%), exclusively for benign tumors. Total abdominal hysterectomy (TAH) + bilateral salpingo-oophorectomy (BSO) followed, performed in 21.42% of cases, including benign, borderline, and malignant tumors. Oophorectomy was conducted in 14.29% of patients, with procedures like hysterectomy (8.92%), unilateral salpingooophorectomy (7.14%), and cystectomy during lower segment caesarean section (LSCS) also observed. Malignant ovarian tumors underwent various extensive procedures for treatment, including TAH, BSO, and omentectomy (3.57%), TAH, BSO, lymph node dissection, and omentectomy (1.78%), and ovarian cystectomy with sigmoid colon resection for metastasis (1.78%). Notably, in the study, 69.64% of patients had CA-125 levels below 35 IU/ml, mostly with benign tumors, while 30.36% had levels above this cutoff, predominantly in malignant cases. Fisher's exact test showed a highly significant difference ($p < 0.0001$) in CA-125 levels between benign and malignant tumors, highlighting its utility as a biomarker for differentiation.

Table 7: Distribution of Cases Based on Serum CA-125 and Tumor Type

Seru m CA-125 levels	Benign	Borderline	Malignant	Total	Percentage

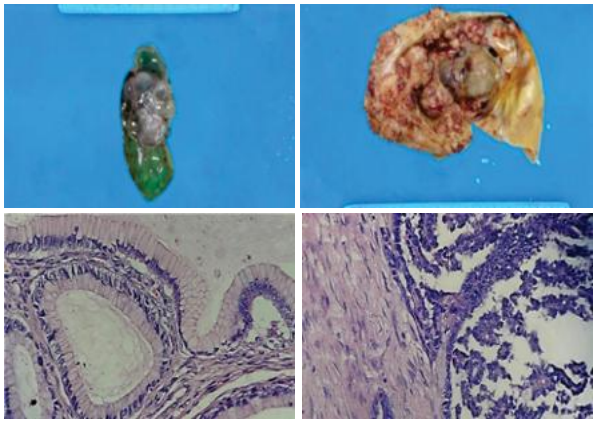
≤35	38	1	-	39	64.28
>35 and <65	4	1	2	7	10.71
>65 and <100	0	-	2	2	3.57
≥100	0	-	8	8	21.42
Total	42	2	12	56	100

Table 8: Fisher Exact Test for CA 125 in Benign and Malignant Tumors

Sr. No	Parameter	Benign	Malignant	Total	Fisher exact test P value
1	CA 125level≤35	38	0	38	< 0.0001
2	CA 125level≥35	4	12	16	
	Total	42	12	54	

Table 9: Sensitivity and Specificity of CA 125 in Benign and Malignant Tumors

1	Sensitivity	90.48%
2	95% confidence interval	77 to 97
3	Specificity	100%
4	95% confidence interval	73 to 100
5	Positive predictive value	100
6	Negative predictive value	75



(In Clockwise Direction, Starting from Upper Left) - Figure1: Gross of mucinous cystadenoma of ovary showing multiloculated cysts filled with mucinous fluid. Figure 2: Microscopy of Benign Mucinous Cystadenoma, showing lining of tall columnar epithelial cells with apical mucin. (H&E, 40X) Figure 3: Gross of serous cystadenocarcinoma ovary showing solid and cystic tumor with papillary excrescences. Figure 4: Microscopy of Serous Cystadeno-carcinoma - The cells lining the micro papillae are round with high N:C ratio and nuclear atypia.

DISCUSSION

The present study was conducted on 56 cases of ovarian tumors received in the Department of Pathology over a period of 18 months. The histopathology of the tumor was studied in relation to clinical parameters and CA-125 levels and classified according to WHO classification (2014). The age group for ovarian tumors in our study ranged from 4 months to 80 years. In present study mean age of patients was 41.97years. We found highest number of cases in 20-40 years of life, constituting for 27 (48.21%) of the total cases. Majority of the surface epithelial tumors were seen in 3rd to 7th decade of life.

Benign serous and mucinous cystadenoma were commonly seen in 20- 40 years of life. Granulosa cell tumor was seen in a 4month child. Malignant tumors were seen in 2nd to 7th decade of life. Dysgerminoma was present in patients with age between 11 to 30 years and one patient with secondary tumor presented at age of 39 years. Incidence of ovarian cancer increases with age. [16] In study done by Pilli et al [17], 58% of the cases occurred in 20-39 years of life followed by 30% cases occuring in 40-59 years. In present study we found 48.21% cases in 20-39 years of life followed by 26.78% cases seen in 40-59 years. Findings of current study are in accordance with the results of study done by Pilli et al [17]. In present study highest number of patients had cystic tumors and were uniloculated. Malignant tumors had solid or mixed consistency. These findings are in accordance with the findings of Thakkar et al [18] and Cuoto F et al [19] studies.

In surface epithelial tumors, 20 (35.71%) cases had size between 11-20 cm and 16 (28.57%) cases had size range 1-10 cm. In sex cord stromal tumors, size ranged between 1- 20 cm. In germ cell tumors majority of the cases had size between 1-10 cm and secondary tumor size ranges between 11 cm to 20 cm. Malignant ovarian tumors had size more than 10 cm. Our findings are in accordance with the study done by Okugawa et al. [20] In the present study we found majority of the cases were benign ovarian tumors. 42 (75%) cases were benign in nature. Two cases were borderline tumors which formed (3.57%) of the cases. Malignant tumors were 12 (21.42%) of the total cases. In all previously done studies the benign tumors were more common than borderline and malignant ovarian tumors. [17,18,21, 22-26]

In a study of Uma Devi et al most common mode of presentation was mass per abdomen.[21] Among 120 patients, 81 presented with mass per abdomen. The next common symptom being vague abdominal pain seen in 21 patients. In a study of Nivedha A et al common presenting complain was abdominal pain seen in 70.2% patients.[27] High parity is associated with a reduced risk of developing ovarian cancer and nulliparity is associated with higher incidence of malignant ovarian tumor.[28] Currently CA-125 is the most widely used tumor marker for ovarian epithelial tumors. The test is usually positive in high borderline and malignant tumors and some localized disease.[29] In a study of Ben Van Calsteret al, CA-125 serum levels differed depending on histology.[30] CA-125 serum levels were 30 IU/mL or higher in 183 of the 242 women with malignant tumors. In a study of Begum Ret al, among the 100 cases of malignant tumors, it was seen that serum CA- 125 level was found to be above 35 U/ml in all (100%) of the cases.[31] In 97% cases the level was above 65 U/ml, of which 88% cases had level above 200U/ml. Among the sex cord stromal tumor, Granulosa cell tumor showed a level between 35 to 65 U/ml. When the cut-off was taken as 35 IU/ml, CA-125 tumor marker had a sensitivity of 90.48%, specificity of 100% and diagnostic accuracy of 92.5%. This is similar to observations made by O'Connell GJ et al.[32]

CONCLUSION

In our investigation at a tertiary care center, we scrutinized 56 ovarian tumors, encompassing a spectrum of 42 benign, 2 borderline, and 12 malignant cases. Noteworthy was the average patient age of 41.97 ± 17.26 years, with primary symptoms of abdominal pain and distension. Our surgical approach, predominantly cystectomy for benign tumors, was guided by the WHO 2014 classification. Crucially, serum CA-125 levels emerged as a highly sensitive and specific diagnostic tool, particularly effective in distinguishing between benign and malignant tumors. Ultimately, our findings underscore the significance of surface epithelial tumors, especially those exhibiting elevated CA-125 levels, in the landscape of ovarian pathology.

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