

# Correlation of Serum CA-125 Marker with Histopathological Findings in Ovarian Tumors

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## Abstract

**Objective:** To evaluate the correlation between serum CA-125 levels and histopathological findings in ovarian tumors. **Design:** Prospective descriptive study. **Subjects/Patients:** A total of 59 patients with radiologically diagnosed ovarian tumors, presenting between May 2023 and October 2024, were included. **Methods:** Serum CA-125 levels were measured pre-operatively, and histopathological examination was performed post-surgery. Data were analyzed to assess the association between CA-125 levels and tumor type. **Results:** Of the 59 cases, 42 (71.18%) were benign, 15 (25.42%) malignant, and 2 (3.38%) borderline. Mean CA-125 levels were significantly higher in malignant tumors ( $406.38 \pm 372.43$  U/mL) compared to benign ( $28.79 \pm 22.16$  U/mL). Malignancy was more common in postmenopausal women. CA-125 levels were highest in high-grade serous carcinoma ( $888.96 \pm 92.93$  U/mL). Elevated CA-125 ( $>35$  U/mL) showed a sensitivity of 93.33%, specificity of 76.19%, and accuracy of 80.70% for malignancy prediction. **Conclusion:** Serum CA-125 is a valuable biomarker in distinguishing malignant from benign ovarian tumors, especially in postmenopausal women and surface epithelial tumors.

**Keywords:** CA-125 Antigen, Ovarian Neoplasms, Ovary, Tumor Markers.

## Introduction

Ovarian cancer ranks as the third most prevalent cancer among women in India, following breast and cervical cancers. It is also the third leading cause of cancer-related mortality among Indian women. In 2020, India reported around 38,200 new cases of ovarian cancer, with approximately 25,400 deaths attributed to the disease<sup>[1,2]</sup>.

Globally, ovarian cancer is the eighth most common cancer in women and the seventh leading cause of cancer-related deaths among women. In 2020, an estimated 313,959 new cases and 207,252 deaths were recorded worldwide due to ovarian cancer<sup>[1,2]</sup>.

Because most ovarian cancers are diagnosed after they have spread beyond the ovary, they contribute to a disproportionately high number of deaths from cancers of the female genital tract<sup>[3]</sup>.

CA125 is a glycoprotein encoded by the MUC16 gene at locus 19p13, produced by malignant cells with epithelial differentiation. Its serum level is associated with the biological potential of tumors, making it the gold standard for detecting and prognosticating epithelial ovarian cancers<sup>[4]</sup>.

The measurement of CA125 levels is performed using a chemiluminescence immunoassay analyzer. This method relies on

detecting light emitted from a chemical reaction between the glycoprotein antigen and a chemiluminescent substrate, with the intensity of the emitted light being proportional to the reagent under investigation. CA125 levels above 35 U/ml are considered abnormal. Serum CA125 levels measured before any treatment or surgery are regarded as a reliable predictor of patient survival in cases of epithelial ovarian cancer<sup>[5]</sup>.

Ovarian tumors present a significant challenge in gynecological oncology due to their varied histopathological features and often asymptomatic progression, which complicates early detection and diagnosis. Among the various biomarkers available, Cancer Antigen 125 (CA-125) has been widely studied for its potential in aiding the diagnosis of ovarian tumors. CA-125 is a glycoprotein that is elevated in a range of conditions, but its role in differentiating between benign and malignant ovarian tumors remains a key focus of research.

Histopathological examination of ovarian tumors is the gold standard for diagnosis, providing crucial information on tumor type and grade. However, the integration of serum CA-125 levels with histopathological findings could enhance diagnostic accuracy, potentially leading to improved patient outcomes. This study aims to investigate the correlation between serum CA-125 levels and the

histopathological findings in ovarian tumors, with the goal of assessing the utility of CA-125 as a reliable biomarker in the differentiation of ovarian tumor types.

## Material and Methods

### Study Design

This was a descriptive observational study.

### Study Setting

The study was conducted in the Department of Pathology at Surat Municipal Institute of Medical Education and Research (SMIMER), a tertiary care center located in Surat, Gujarat.

### Study Duration

The study was carried out over 18 months, from May 2023 to October 2024.

### Sample Size

A total of 59 ovarian specimens meeting the inclusion criteria were analyzed.

### Study Population and Procedure

All consenting patients with radiologically diagnosed ovarian tumors who had preoperative serum CA-125 levels measured were included. Ethical approval was obtained from the Institutional Human Research Ethics Committee prior to commencement. Following specimen receipt in the histopathology department, serum CA-125 levels were correlated with the final histopathological diagnosis (**Figure 1**).

### Inclusion Criteria

- Patients of all ages with radiologically confirmed ovarian tumors.
- Patients with serum CA-125 levels measured prior to any chemotherapy or surgical intervention.

### Exclusion Criteria

- Patients without preoperative serum CA-125 measurements.
- Patients whose CA-125 levels were measured after chemotherapy or surgery.
- Autolyzed specimens.

### Ethical Considerations

Ethical clearance was obtained from the Human Research Ethics Committee of the medical college and affiliated hospital.

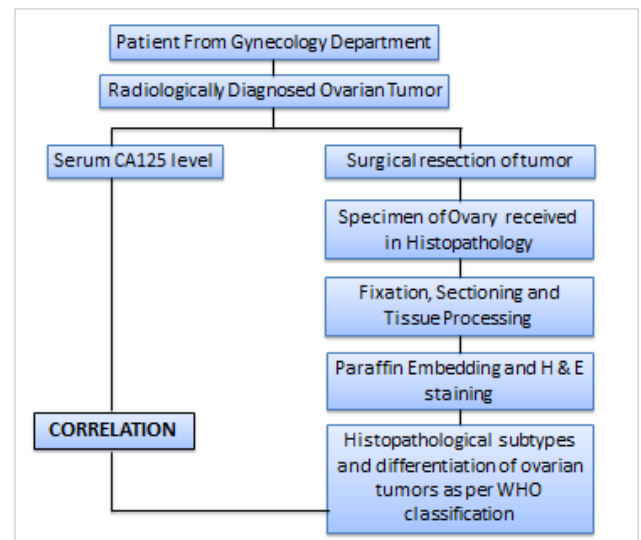
### Data Analysis

Histopathological diagnosis of the tumors were taken as the 'gold standard' and all data was entered in excel sheet and master chart was prepared.

Qualitative data will be presented as frequency table using number of percentages.

Quantitative data will be represented by mean, standard deviation.

To know the association between CA125 and histopathological classification Chi Square test, ANOVA was applied.



**Figure1: Methodology for Correlation of Serum CA125 Levels with Histopathological Classification of Ovarian Tumors**

## Results

The present study, titled “Correlation of Serum CA-125 Marker with Histopathological Findings in Ovarian Tumors,” was conducted in the Department of Pathology at a tertiary care hospital from May 2023 to October 2024. This prospective analysis included 59 cases. Detailed clinical history was recorded, serum CA-125 levels were measured, and histopathological examination of all specimens was performed for correlation.

Among the 59 cases, 42 (71.18%) were benign with a mean CA-125 level of  $28.79 \pm 22.16$  U/mL, 15 (25.42%) were malignant with a mean CA-125 of  $406.38 \pm 372.43$  U/mL, and 2 (3.38%) were borderline with a mean CA-125 of  $22.30 \pm 15.70$  U/mL (**Figure 2**). Additionally, 3 cases of torsion and 6 cases of endometriosis were noted, all showing elevated CA-125 levels.

Benign tumors were more common among younger women of reproductive age (mean age:  $32.45 \pm 10.81$  years), while malignant tumors were more prevalent in older, postmenopausal women (mean age:  $48.27 \pm 15.40$  years), indicating increasing malignancy risk with age.

Tumors  $\leq 10$  cm were most frequently observed in both benign (50.88%) and malignant (10.53%) categories, while malignant tumors were more commonly found in the 11-20 cm range (14.04%).

In terms of consistency, benign tumors were predominantly cystic (39.0%), whereas malignant tumors were most often of mixed consistency (11.9%). Cystic tumors were the most common overall (45.8%), while solid tumors were least frequent.

Malignant tumors were more frequently seen in parous women with lower gravidity (G1 and G2: 14 cases), while benign tumors were common in women with higher gravidity (G3 and G>4: 33 cases). Only one borderline tumor occurred in each group.

Pain was the most frequent presenting symptom (59.32%), followed by abdominal mass (18.64%) and irregular menstruation or postmenopausal bleeding (8.47%) (**Figure 3**).

The right ovary was affected in 47.5% of cases and showed a higher proportion of malignancy (16.9%), while the left ovary was involved in 40.7% of cases, mostly benign (33.9%). Bilateral and borderline involvements were rare (**Figure 4**).

CA-125 levels were significantly higher in Surface Epithelial Tumors ( $123.58 \pm 248.06$  U/mL) compared to Germ Cell Tumors ( $22.58 \pm 10.90$  U/mL) and Sex Cord-Stromal Tumors (33.69

$\pm 22.50$  U/mL), supporting CA-125's role as a diagnostic biomarker. Serous Cystadenoma and Serous Carcinoma were the most common epithelial tumors. Mature Cystic Teratoma was the most frequent germ cell tumor, while Fibroma and Granulosa Cell Tumor were predominant among sex cord-stromal tumors (**Table 1**).

Serous Cystadenoma was the most common benign lesion (22.03%), followed by Mature Cystic Teratoma (15.25%) and Mucinous Cystadenofibroma (10.17%). High-Grade Serous Carcinoma was the most common malignant tumor (8.47%) and exhibited the highest CA-125 levels ( $888.96 \pm 92.93$  U/mL),

markedly higher than other tumors, including Fibroma ( $78.85 \pm 5.44$  U/mL) and Brenner Tumor ( $52.5 \pm 17.67$  U/mL) (**Table 2**).

Among cases with serum CA-125  $>35$  U/mL, 23.7% were malignant and 18.6% benign. In contrast, only 1.6% of cases with CA-125  $\leq 35$  U/mL were malignant, while 52.5% were benign. This marked difference demonstrates the significant association between elevated CA-125 levels and malignancy.

CA-125 showed a sensitivity of 93.33%, specificity of 76.19%, negative predictive value of 96.97%, and an overall accuracy of 80.70%, confirming its utility in differentiating between benign and malignant ovarian tumors.

Figure 2: Frequency of Ovarian Tumors

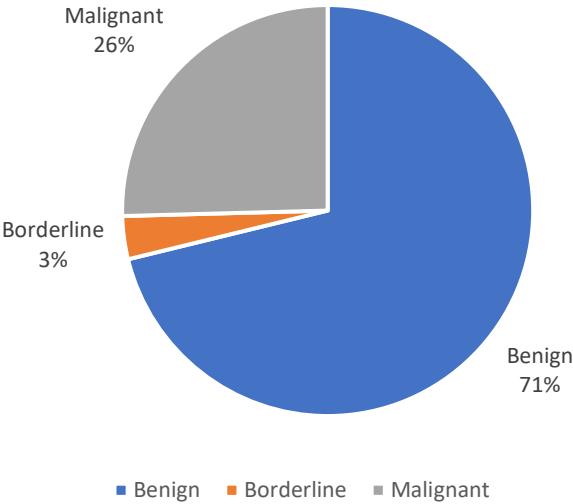


Figure 2: Frequency of Ovarian Tumors

Figure 3: Clinical Presentation of Patients

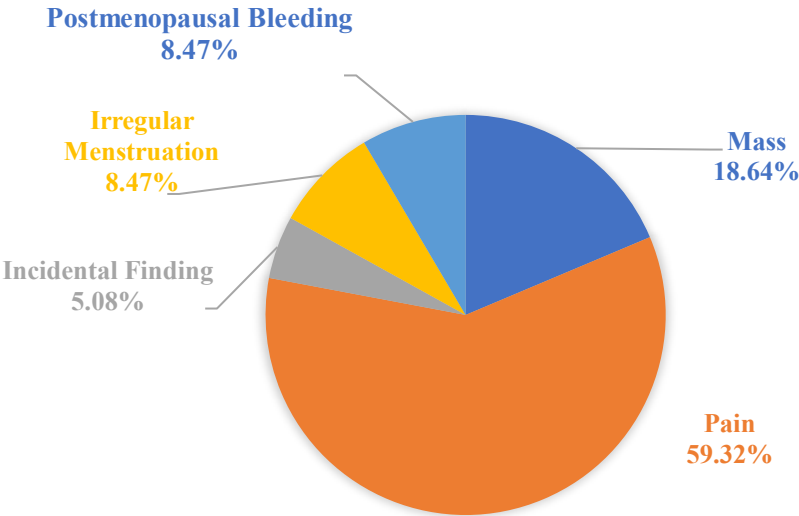


Figure 3: Clinical Presentation of Patients

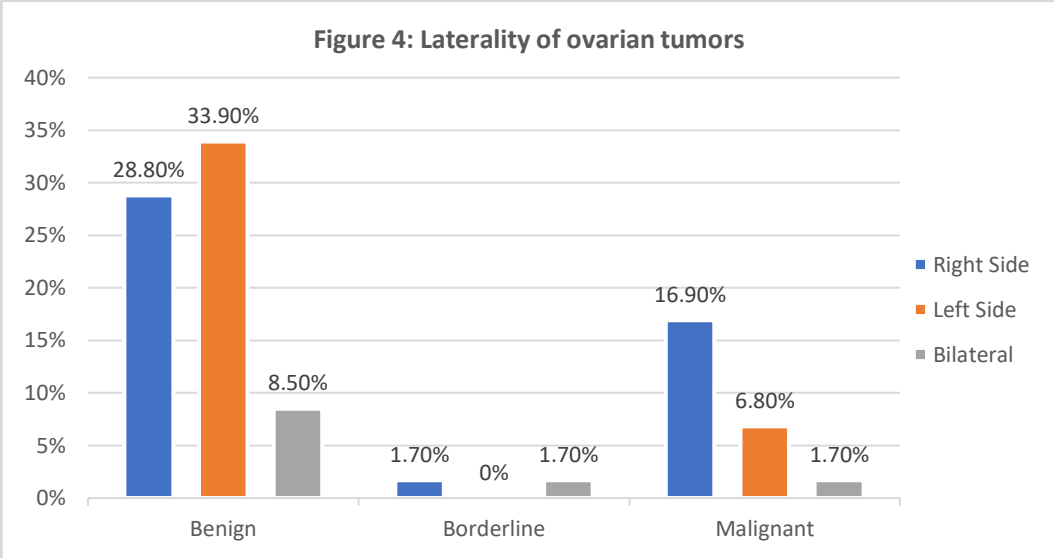


Figure 4: Laterality of ovarian tumors

Table 1: Distribution of Ovarian Tumor Types and Associated CA125 Levels

Tumor Type	N	Percentage (%)	Mean ± SD of Ca125	P value
Surface Epithelial Tumor	41	69.49%	123.58 ± 248.06	<0.0001
Germ Cell Tumor	12	20.34%	22.58 ± 10.90	
Sex Cord Stromal Tumor	6	10.17%	33.69 ± 22.50	

Table 2: Number of cases and values of CA125 in different types of ovarian tumors

Histopathological-Microscopic findings		Frequency		Mean ±Standard Deviation of CA125 (U/ml)
		No of cases	Percentage	
Benign	Serous Cystadenoma	13	22.03%	23.47 ± 14.09
	Serous Cystadenofibroma	5	8.47%	39.16 ± 39.85
	Seromucinous Cystadenoma	1	1.69%	23.300
	Mucinous Cystadenofibroma	6	10.17%	25.16 ± 18.2
	Benign Brenner Tumor	2	3.39%	52.5 ± 17.67
	Steroid Cell Tumor	1	1.69%	10.100
	Fibroma	2	3.39%	78.85 ± 5.44
	Dermoid Cyst	3	5.08%	13.83 ± 7.58
	Mature Cystic Teratoma	9	15.25%	25 ± 12.44
Borderline	Mucinous Borderline Tumor	1	1.69%	33.400
	Serous Borderline Tumor	1	1.69%	11.200
Malignant	Mucinous Cystadenocarcinoma	4	6.78%	145.42 ± 36.31
	Serous Carcinoma- High Grade	5	8.47%	888.96 ± 92.93
	Serous Carcinoma- Low Grade	3	5.08%	291.3 ± 196.41
	Granulosa Cell Tumor	3	5.08%	57.83 ± 22.13

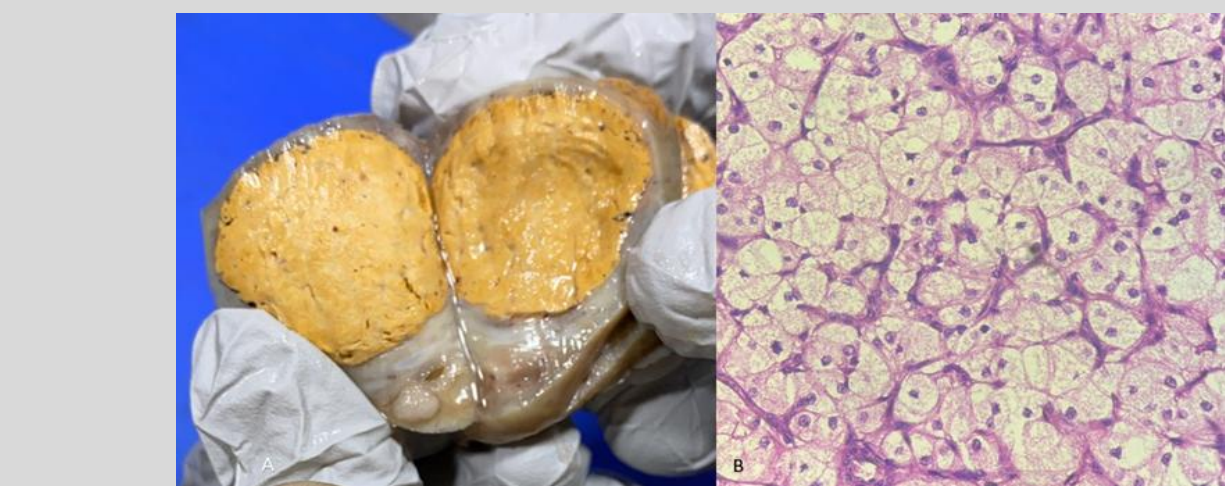
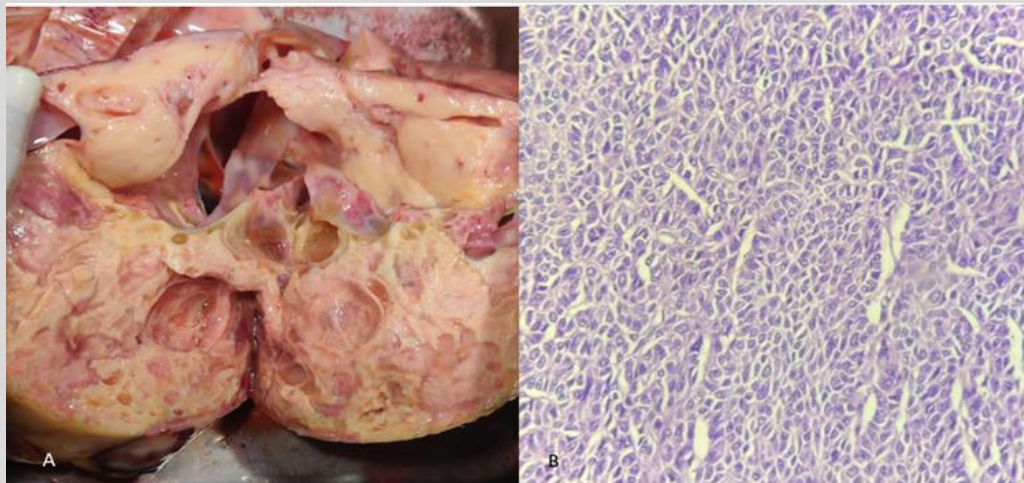
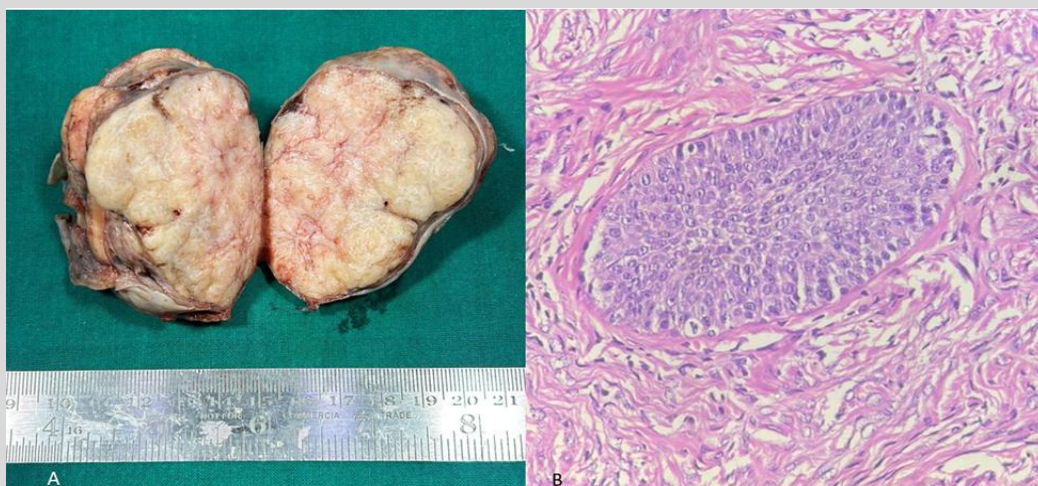


Figure 5: A) Cut section of Steroid Cell Tumor showing bright yellow well circumscribed area. B) Microscopy shows tumour cells arranged in nests separated by thin fibrous septas. Malignant cells are Polygonal in shape with clear to eosinophilic vacuolated cytoplasm with centrally placed nucleus and prominent nucleoli. (H&E, 40X)

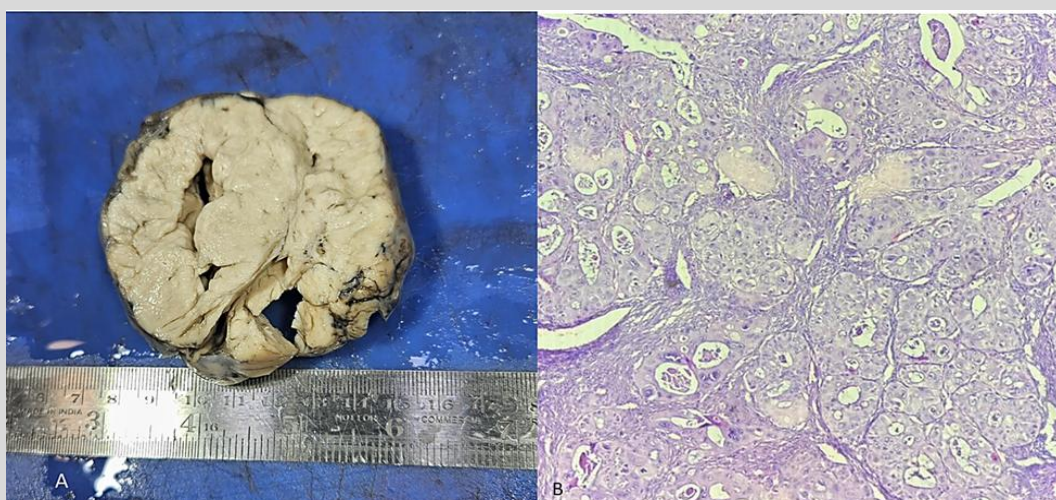




**Figure 6:** A) Cut section of Granulosa cell tumor showing yellowish tan mass with solid cystic areas. B) Microscopy shows polygonal to round cells with high N:C ratio, grooved nuclei, irregular nuclear membrane with scant amount of pale cytoplasm. (H&E, 40X)



**Figure 7:** A) Cut section of Benign Brenner tumor showing homogenous tan-yellow lobulated areas. B) Microscopy shows benign transitional cells arranged in nests within abundant fibromatous stroma. Transitional cells are having uniform oval nuclei. (H&E, 40X)



**Figure 8:** A) Cut section of Serous Carcinoma- High grade showing firm, grayish white lobulated area. B) Microscopy shows malignant cells having marked nuclear pleomorphism arranged in glandular pattern with inspissated material. (H&E, 10X)

## Discussion

Ovarian neoplasms exhibit a wide spectrum of histogenesis, clinical behavior, and malignant potential. The lifetime risk for a female of developing an ovarian tumor is approximately 6%-7%, with a 1.5% risk of developing ovarian cancer and a 1% risk of mortality from the disease [6]. Despite advances in diagnostic modalities such as

ultrasonography (USG), peritoneal fluid cytology, and various immunological tests, accurate preoperative diagnosis remains challenging through clinical examination alone. The generally poor prognosis of ovarian cancer is attributed to its asymptomatic nature in early stages, with 60%-70% of cases presenting at an advanced stage [6]. Consequently, detailed histopathological examination is essential for definitive diagnosis and appropriate management.

In our study, 59 ovarian tumors were evaluated and classified according to the WHO 2020 Histological Classification of Ovarian Tumors. The most common age group for benign tumors was the third decade, while malignant tumors were most prevalent in the fourth decade. Similar trends have been documented by Patel *et al.*<sup>[7]</sup>, Rao *et al.*<sup>[8]</sup>, Bhagat *et al.*<sup>[9]</sup>, Agarwal *et al.*<sup>[10]</sup> and Shintre *et al.*<sup>[12]</sup>, indicating a higher incidence during reproductive years and a peak in malignancies near menopause.

Tumors measuring  $\leq 10$  cm were the most frequently encountered in both benign (50.88%) and malignant (10.53%) categories. These findings are consistent with Bhagat *et al.*<sup>[9]</sup> and Marachapu<sup>[13]</sup>, who also reported a predominance of smaller tumors overall, though medium-sized tumors were more often malignant.

Benign tumors were predominantly cystic in nature (39.0%), whereas malignant tumors frequently exhibited mixed consistency (11.9%). This pattern aligns with findings by Patel *et al.*<sup>[7]</sup>, Pant *et al.*<sup>[11]</sup>, Marachapu<sup>[13]</sup>, Arpitha K *et al.*<sup>[14]</sup>, and Bhagat *et al.*<sup>[9]</sup>, supporting the notion that cystic morphology is typically associated with benign lesions, while mixed and solid tumors are more indicative of malignancy.

In terms of parity, malignant tumors were more prevalent in women with lower gravidity (G1 and G2, with 14 cases), while benign tumors were more common in those with higher parity (G3 and G>4, with 33 cases). This finding supports the hypothesis of a protective effect of pregnancy against ovarian malignancy, as similarly noted in the studies by Patel *et al.*<sup>[7]</sup> and Marachapu<sup>[13]</sup>.

Abdominal pain was the most frequently reported symptom (59.32%), followed by an abdominal mass (18.64%). This is consistent with observations by Pant *et al.*<sup>[11]</sup>, Marachapu *et al.*<sup>[13]</sup>, and Shintre *et al.*<sup>[12]</sup>, though the prevalence of abdominal mass varied in other studies, such as those by Patel *et al.*<sup>[7]</sup> and Arpitha K *et al.*<sup>[14]</sup>. Pain remains a common and early symptom and should prompt further evaluation.

Right ovarian involvement was more common (47.5%), particularly in malignant tumors, whereas the left ovary was affected in 40.7% of cases, predominantly benign. This distribution pattern corresponds with findings from Marachapu *et al.*<sup>[13]</sup> and Patil *et al.*<sup>[6]</sup>, although Patel *et al.*<sup>[7]</sup> reported a higher incidence of left-sided involvement (78.75%). Despite some variability, right-sided ovarian involvement appears more frequently associated with malignancy.

A statistically significant association ( $P < 0.001$ ) was observed between elevated CA125 levels ( $>35$  U/mL) and malignant ovarian tumors. In contrast, benign and borderline tumors were generally associated with lower CA125 levels. These findings are consistent with the results reported by Pant *et al.*<sup>[11]</sup>, Shintre *et al.*<sup>[12]</sup>,

Bhagat *et al.*<sup>[9]</sup>, and Habib *et al.*<sup>[15]</sup>. Collectively, these studies underscore CA125's utility as a biomarker for distinguishing malignant from benign ovarian tumors and highlight its relevance in clinical practice.

Our study demonstrated the high diagnostic performance of CA-125, with a sensitivity of 93.33%, specificity of 76.19%, NPV of 96.97%, and overall accuracy of 80.70%. These findings are consistent with Pant *et al.*<sup>[11]</sup> and Shintre *et al.*<sup>[12]</sup>, who reported similar sensitivities and NPVs, underscoring CA-125's strength in ruling out malignancy. Verma *et al.*<sup>[16]</sup> also supported its diagnostic value, though with slightly lower sensitivity and specificity, while Shintre *et al.*<sup>[12]</sup> noted a lower PPV, reflecting the marker's limitations in confirming malignancy (**Table 3**).

Despite its widespread use, CA125 is not entirely specific to ovarian malignancy. Elevated levels may also be observed in other cancers (e.g., uterine, colorectal, lung, pancreatic) and benign conditions such as pregnancy, menstruation, endometriosis, uterine fibroids, liver disease, kidney disease, and heart failure<sup>[17]</sup>. In our study, elevated CA125 levels were noted in three cases of torsion and six cases of endometriosis. Therefore, elevated CA125 levels, particularly in reproductive-aged women, should be interpreted cautiously to avoid unnecessary interventions and associated anxiety. However, in postmenopausal women, CA125 may offer greater specificity in detecting malignancy.

Surface epithelial tumors account for approximately 90% of all ovarian malignancies. In contrast, although germ cell and sex cord-stromal tumors comprise 20%-30% of all ovarian neoplasms, they constitute less than 10% of malignant cases<sup>[3]</sup>. Our findings mirrored this distribution, corroborating prior reports by Rao *et al.*<sup>[8]</sup>, Kayastha *et al.*<sup>[18]</sup>, Patil *et al.*<sup>[6]</sup>, Arpitha K *et al.*<sup>[14]</sup>, Bhagat *et al.*<sup>[9]</sup>, Verma *et al.*<sup>[16]</sup>, and Patel *et al.*<sup>[7]</sup>, who also reported a predominance of surface epithelial tumors (**Table 4**).

CA125 levels were highest in surface epithelial tumors in our study, particularly in serous carcinomas, corroborating data from Habib *et al.*<sup>[15]</sup> and Pant *et al.*<sup>[11]</sup>. Among benign tumors, fibromas showed the highest CA125 levels. These observations reinforce the diagnostic utility of CA125 in identifying surface epithelial tumors while highlighting its limited relevance in sex cord-stromal and germ cell tumors. The observed variation in tumor type prevalence across different studies may reflect population differences, diagnostic approaches, or regional variations. These findings also highlight the need for more specific biomarkers in diagnosing sex cord-stromal tumors, as CA125 offers limited diagnostic value in such cases.

**Table 3: Comparison of Sensitivity and Specificity of CA125 in Predicting Malignant Ovarian Tumors**

Study	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
<b>Our Study</b>	93.33%	76.19%	58.33%	96.97%
Pant <i>et al.</i> <sup>[11]</sup>	94.44%	81.82%	87.18%	64.29%
Shintre <i>et al.</i> <sup>[12]</sup>	93.30%	87.70%	70.00%	97.70%
Verma <i>et al.</i> <sup>[16]</sup>	85.00%	75.00%	-	-

**Table 4: Comparison of Ovarian Tumor Frequency in Various Studies Based on WHO Classification**

Study	Surface Epithelial Tumors (%)	Germ Cell Tumors (%)	Sex Cord Stromal Tumors (%)
<b>Our Study</b>	69.49%	20.34%	10.17%
Rao <i>et al.</i> <sup>[8]</sup>	76.92%	18.46%	3.07%
Kayastha <i>et al.</i> <sup>[18]</sup>	73.00%	27.00%	0%
Patil <i>et al.</i> <sup>[6]</sup>	72.20%	19.90%	6.60%
Arpitha K <i>et al.</i> <sup>[14]</sup>	73.21%	16.96%	11.00%
Bhagat <i>et al.</i> <sup>[9]</sup>	78.70%	14.80%	6.60%
Verma <i>et al.</i> <sup>[16]</sup>	69.80%	23.90%	6.30%
Patel <i>et al.</i> <sup>[7]</sup>	67.91%	22.29%	4.38%



## Conclusion

Our study provides valuable insight into the diverse presentation and histological spectrum of ovarian tumors. Histopathological examination remains the most definitive and reliable method for accurate diagnosis. The majority of ovarian tumors encountered were benign, with serous cystadenoma being the most common. Malignant tumors were most frequently diagnosed in women with a mean age of 48 years, with serous carcinoma being the predominant malignancy.

Clinical features such as patient age, tumor location, size, consistency, and histological type are important factors in predicting prognosis and guiding management. Elevated CA125 levels were strongly associated with surface epithelial malignancies, particularly in postmenopausal women, supporting its role as a useful preoperative marker. However, its limited specificity, especially in younger women and in cases of sex cord-stromal tumors, necessitates cautious interpretation and further diagnostic correlation.

The WHO 2020 histological classification enhances our understanding of ovarian tumor subtypes, aiding early diagnosis and informed treatment decisions. Despite advancements in imaging and serological testing, histopathology remains the gold standard for diagnosing primary ovarian tumors.

Measurement of serum CA125 levels should be part of the preoperative evaluation for ovarian tumors, especially in older women. However, elevated CA125 alone is not diagnostic of malignancy, particularly in reproductive-aged women. Our study demonstrated that a CA125 level >35 U/mL had a significant association with malignancy and an overall diagnostic accuracy of 80.70%.

## Limitations

This study had several limitations. The relatively small sample size and short study duration may affect the generalizability and long-term applicability of the findings. Only cases with pre-operative CA-125 data and surgeries performed at our institute were included, introducing potential selection bias. Additionally, important variables such as hormonal contraceptive use, BMI, socioeconomic status, age at first conception, and familial cancer risk were not considered. As a descriptive study, it also lacked long-term follow-up, limiting insights into prognosis and the risk of malignancy over time.

## Declarations

## Conflict of interest

None

## Funding/ financial support

None

## Ethical Clearance

Obtained from the Institutional Ethics Committee prior to the commencement of the study.

## Trial details

Not applicable

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