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Original Research Article

Biomarker Intelligence: Decoding Tumor Marker Roles in Ovarian Cancer Workup

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Abstract

Introduction: Ovarian cancer is a leading cause of gynecological cancer mortality, often diagnosed at advanced stages due to nonspecific symptoms. Tumor markers such as CA125, CA19.9, CEA, LDH, AFP, and βhCG are widely used as adjuncts in diagnosis and monitoring, though their utility varies across histological subtypes.

Aim: To evaluate the diagnostic role of tumor markers in ovarian tumors and correlate their elevation patterns with histopathological subtypes and tumor aggressiveness.

Methods: A prospective observational study was conducted on 60 patients with ovarian masses at BKL Walawalkar Rural Medical College, Ratnagiri. Histopathological examination was performed using hematoxylin and eosin staining, and preoperative serum levels of CA125, CA19.9, CEA, LDH, AFP, and βhCG were measured using immunoassay techniques. Data were analyzed for age distribution, histopathological spectrum, and marker elevation.

Results: The majority of patients were aged 45–70 years (63.5%). High-grade serous adenocarcinoma was the most common subtype (30%), followed by serous cystadenoma (17%) and mucinous cystadenocarcinoma (12%). CA125 was the most frequently elevated marker (13.3%), predominantly in high-grade serous adenocarcinoma (33.3%). CA19.9 and CEA were elevated in mucinous carcinomas (14.3% each). LDH showed minor elevation (5.6%), while AFP and βhCG were not elevated in germ cell tumors. Overall marker positivity was lower compared to tertiary-center studies, possibly due to early-stage detection, smaller tumor volumes, and rural referral bias.

Conclusion: CA125 remains the most reliable marker for serous carcinomas, while CA19.9 and CEA are useful in mucinous tumors. Germ cell tumors require AFP and βhCG evaluation, though marker negativity may occur in early disease. Integration of histopathology with biomarker profiling enhances diagnostic accuracy and prognostic assessment in ovarian cancer.

Keywords: Tumor markers, Histopathology.

Introduction

Ovarian cancer is among the most lethal gynecological malignancies worldwide, largely due to its asymptomatic onset and late clinical presentation. Despite advances in surgery and chemotherapy, the overall 5-year survival rate remains poor, averaging around 40% [1]. Tumor markers are measurable substances produced either by tumor cells or by the host in response to tumor growth. They are widely used as adjuncts in diagnosis, therapeutic monitoring, and prognostic assessment of ovarian cancer [2]. Among these, CA125 is the most extensively studied marker, particularly in epithelial ovarian cancers, where its elevation correlates with tumor burden and disease progression [3]. However, CA125 lacks specificity, as it may also be elevated in benign gynecological

conditions such as endometriosis and pelvic inflammatory disease [4]. Other markers, including CA19.9 and CEA, have demonstrated utility in mucinous ovarian carcinomas, reflecting their distinct biological behavior [5]. Similarly, LDH, AFP, and βhCG are more relevant in germ cell tumors, where they provide insights into tumor aggressiveness and metabolic activity [6]. Granulosa cell tumors, on the other hand, are better tracked using hormonal markers such as inhibin and estradiol, highlighting the heterogeneity of ovarian neoplasms [7]. The integration of histopathological diagnosis with tumor marker profiling offers a more comprehensive understanding of ovarian cancer biology. Such correlation not only aids in differentiating malignant from benign lesions but also provides prognostic insights into disease aggressiveness and recurrence potential [8]. This study aims to decode the role of tumor markers in ovarian cancer workup, correlating their elevation patterns with histological subtypes and clinical aggressiveness, thereby contributing to improved patient stratification and management.

Aims and Objectives

1. To study the age distribution and histopathological spectrum of ovarian tumors in the cohort.
2. To evaluate the diagnostic role of tumor markers (CA125, CA19.9, CEA, LDH, AFP, βhCG).
3. To correlate marker elevation with specific histological subtypes and tumor aggressiveness.
4. To generate clinically relevant interpretations linking biomarker status with disease progression and recurrence risk.

Material and Methods

This was a prospective observational study conducted in the Department of Pathology at BKL Walawalkar Rural Medical College, Ratnagiri, Maharashtra, India, over a defined study period. A total of 60 patients presenting with ovarian masses were included.

Inclusion Criteria

1. Patients with clinically suspected ovarian tumors undergoing surgical excision.
2. Availability of complete clinical records, histopathological diagnosis, and tumor marker data.

Exclusion Criteria

1. Incomplete clinical or laboratory records.
2. Patients with non-ovarian pelvic masses.

Sample Collection and Processing: All specimens were received in the pathology department following surgical excision. Standard gross examination was performed, and representative tissue sections were processed for histopathological evaluation using hematoxylin and eosin staining [9].

Tumor Marker Analysis: Preoperative serum samples were analyzed for CA125, CA19.9, CEA, LDH, AFP, and βhCG using standard immunoassay techniques [10]. Marker positivity was defined according to established reference ranges:

- CA125 > 35 U/mL
- CA19.9 > 37 U/mL
- CEA > 5 ng/mL
- LDH > 250 U/L
- AFP > 10 ng/mL
- βhCG > 5 mIU/mL

Data Compilation

Clinical details, age distribution, histopathological diagnosis, and tumor marker status were recorded in structured case record forms. Data were tabulated and analyzed to determine:

1. Age distribution of ovarian tumors.
2. Histopathological spectrum.
3. Frequency of tumor marker elevation across subtypes.
4. Correlation between marker positivity and tumor aggressiveness.

Statistical Analysis: Descriptive statistics were applied to calculate frequencies and percentages.

Correlation between histopathological diagnosis and tumor marker elevation was interpreted qualitatively and quantitatively.

Observation and Result

Table 1: Age Distribution

Sr No	Age Group	Number of Patients	Percentage (%)
1	**< 18 years**	1	1.5 %
2	**18–45 years**	21	35 %
3	**45–70 years**	38	63.5 %
Total		**60**	100 %

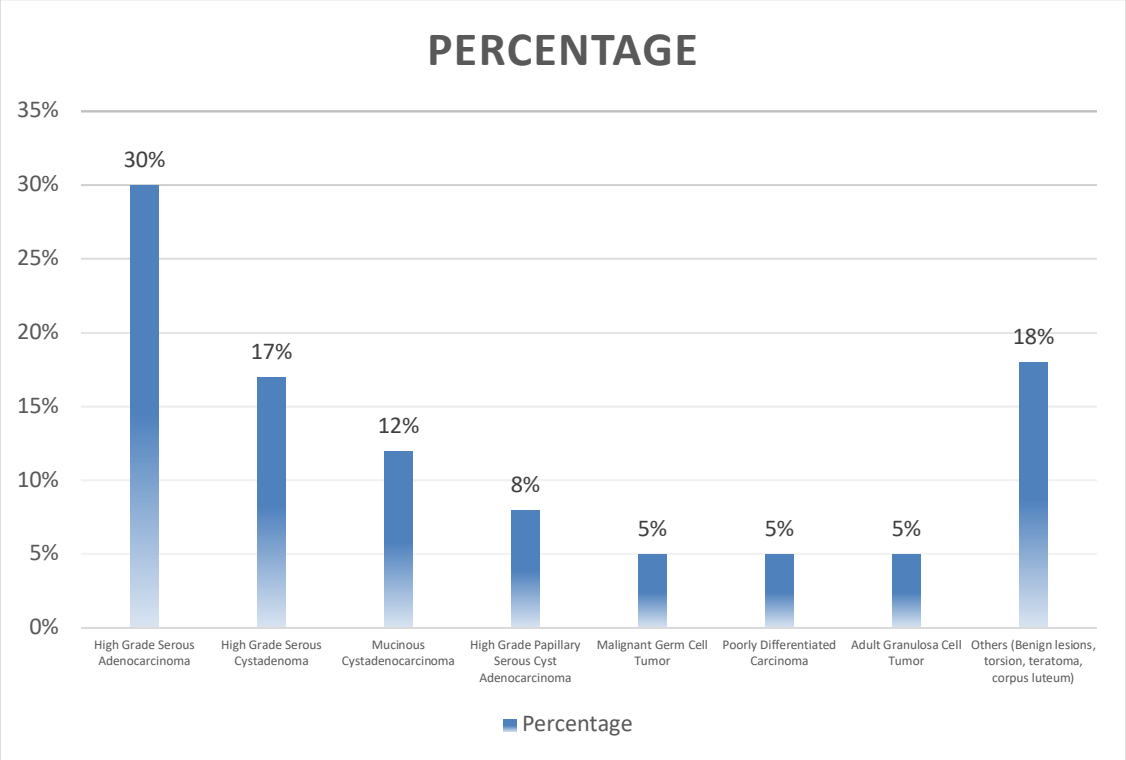
The majority of ovarian cancer patients in this cohort were between 45–70 years of age, accounting for nearly two-thirds (63.5%) of the study population. Women in the reproductive age group (18–45 years) represented 35% of cases, while only a single patient (1.5%) was younger than 18 years. This age distribution highlights the predominance of ovarian malignancies in peri- and

post-menopausal women, consistent with global epidemiological trends.

Table 2: Histopathological Spectrum

Sr No	Histopathological Diagnosis	No. of Patients	Percentage (%)
1	High Grade Serous Adenocarcinoma	18	30 %
2	High Grade Serous Cystadenoma	10	17 %
3	Mucinous Cystadenocarcinoma	07	12 %
4	High Grade Papillary Serous Cyst Adenocarcinoma	05	8 %
5	Malignant Germ Cell Tumor	03	5 %
6	Poorly Differentiated Carcinoma	03	5 %
7	Adult Granulosa Cell Tumor	03	5 %
8	Benign Matured Teratoma	04	7.5 %
9	Low Grade Papillary Serous Cyst Adenocarcinoma	02	3 %
10	Benign Paraovarian Cyst	02	3 %
11	Primary Ovarian Moderate Differentiated Adenocarcinoma	01	1.5 %
12	Ovarian Torsion	01	1.5 %
13	Haemorrhagic Corpus Luteum	01	1.5 %
Total		60	100 %

High-grade serous adenocarcinoma was the most common histological subtype, observed in 30% of patients. Other frequent diagnoses included high-grade serous cystadenoma (17%) and mucinous cystadenocarcinoma (12%). Less common but clinically significant entities were high-grade papillary serous cystadenocarcinoma (8%), malignant germ cell tumors (5%), poorly differentiated carcinoma (5%), and adult granulosa cell tumors (5%). Benign lesions such as mature teratomas (7.5%), paraovarian cysts (3%), ovarian torsion (1.5%), and hemorrhagic corpus luteum (1.5%) were also encountered. This distribution underscores the heterogeneity of ovarian pathology, with epithelial tumors forming the bulk of malignant cases.



Graph1: Histopathological Spectrum

Table 3: Tumor Marker Elevation

Sr No	Histopathological Diagnosis	CA-125 ↑	CA-19.9 ↑	CEA ↑	LDH ↑	AFP ↑	β-HCG ↑
1	High Grade Serous Adenocarcinoma	6 (33.3%)	2 (11.1%)	0 (0%)	1 (5.6%)	0 (0%)	0 (0%)
2	High Grade Serous Cystadenoma	1 (10.0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
3	Mucinous Cystadenocarcinoma	0 (0%)	1 (14.3%)	1 (14.3%)	0 (0%)	0 (0%)	0 (0%)
4	High Grade Papillary Serous Cyst Adenocarcinoma	1 (20.0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
5	Malignant Germ Cell Tumor	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
6	Poorly Differentiated Carcinoma	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
7	Adult Granulosa Cell Tumor	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
8	Others (Benign lesions, torsion, teratoma, corpus luteum)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Total		**8 (13.3%)**	**3 (5.0%)**	**1 (1.7%)**	**1 (1.7%)**	**0 (0%)**	**0 (0%)**

Among the 60 patients, CA125 was the most frequently elevated marker, detected in 13.3% of cases overall. Its rise was most notable in high-grade serous adenocarcinoma (33.3%) and, to a lesser extent, in papillary serous cystadenocarcinoma (20%) and serous cystadenoma (10%). CA19.9 elevation was seen in 5% of patients, particularly in mucinous cystadenocarcinoma (14.3%) and a subset of serous adenocarcinomas (11.1%). CEA was elevated in 1.7% of cases, exclusively in mucinous carcinomas. LDH showed a minor increase (1.7%), again in serous adenocarcinoma. Interestingly, none of the germ cell tumors in this cohort demonstrated AFP or βhCG elevation, although these markers are typically associated with advanced disease. Overall, marker positivity was relatively low, reflecting either early disease detection or histological subtypes less reliant on classical markers.

Table 4: Marker–Aggressiveness Correlation

Sr No	Histopathological Diagnosis	Key Marker(s) Elevated	Interpretation
1	High Grade Serous Adenocarcinoma	CA-125 ↑ (33.3%), CA-19.9 ↑ (11.1%), LDH ↑ (5.6%)	CA-125 elevation reflects tumor burden and progression; LDH rise indicates metabolic activity.
2	High Grade Serous Cystadenoma	CA-125 ↑ (10%)	Mild CA-125 rise suggests limited malignant potential.
3	Mucinous Cystadenocarcinoma	CA-19.9 ↑ (14.3%), CEA ↑ (14.3%)	CA-19.9 and CEA elevations correlate with mucinous biology
4	High Grade Papillary Serous Cyst Adenocarcinoma	CA-125 ↑ (20%)	CA-125 elevation tracks disease activity and relapse risk.
5	Malignant Germ Cell Tumor	None elevated	markers usually elevated in advanced disease
6	Poorly Differentiated Carcinoma	None elevated	Marker negativity does not reduce aggressiveness, progression tracked clinically.
7	Adult Granulosa Cell Tumor	None elevated	Aggressiveness better tracked by inhibin/estradiol rather than classical markers.
8	Others (Benign lesions, torsion, teratoma, corpus luteum)	None elevated	Absence of marker elevation consistent with benign biology.

CA125 elevation correlated strongly with aggressive epithelial subtypes, particularly

high-grade serous adenocarcinoma and papillary serous variants, where it reflected tumor burden and progression risk.

CA19.9 and CEA were linked to mucinous carcinomas, aligning with their biology and metastatic potential. LDH elevation, though infrequent, suggested enhanced metabolic activity in aggressive tumors. Germ cell tumors, despite their known association with LDH, AFP, and βhCG, showed no marker elevation in this dataset, possibly due to limited sample size or early stage presentation. Poorly differentiated carcinomas remained highly aggressive despite marker negativity, emphasizing the need for clinical vigilance. Granulosa cell tumors similarly lacked classical marker elevation, with aggressiveness better tracked by hormonal markers such as inhibin and estradiol. Benign lesions consistently showed marker negativity, reinforcing their non-aggressive nature.

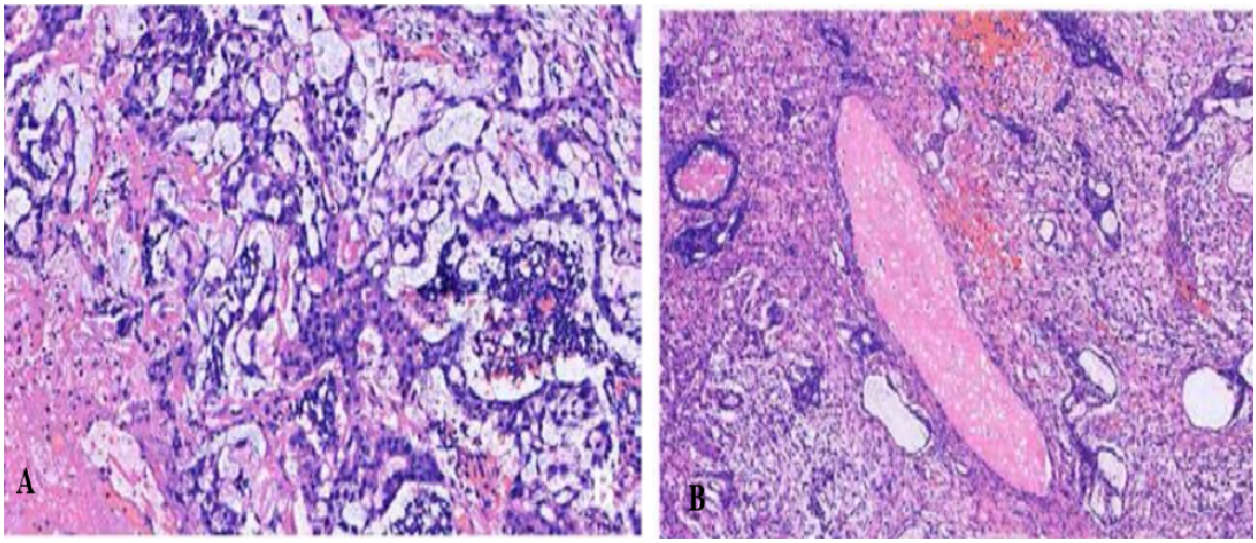


Figure 1: Histological image of (magnification: ×400) A) mixed germ cell tumour B) mature teratoma

Discussion

In the present study, high-grade serous adenocarcinoma emerged as the most common histological subtype (30%), followed by serous cystadenoma and mucinous cystadenocarcinoma. This predominance of serous carcinoma is consistent with global literature, where serous epithelial tumors account for nearly half of ovarian malignancies [11]. A clinicopathological study from Chennai similarly reported serous carcinoma as the leading subtype, though with slightly higher CA125 positivity rates compared to our cohort [12]. The lower marker positivity in our dataset may reflect earlier stage detection or smaller tumor burden at presentation.Age distribution in our cohort showed that 63.5% of patients were between 45–70 years, aligning with studies from India and abroad that highlight peri- and post-menopausal women as the most affected group [13]. However, unlike some reports where germ cell tumors are more frequent in younger women, our study identified only 5% germ cell tumors, none of which showed AFP or βhCG elevation. This discrepancy may be due to the limited sample size and the rural referral pattern, where advanced germ cell tumors may have been managed at tertiary centers. Tumor marker analysis revealed CA125 elevation in 13.3% overall, most notably in high-grade serous adenocarcinoma (33.3%). In contrast, Bagde et al. reported CA125 elevation in over 70% of malignant ovarian tumors, particularly serous carcinomas [14]. The comparatively lower rate in our study could be attributed to inclusion of borderline and benign lesions, as well as possible early stage disease at diagnosis. Additionally, rural patient populations may present with smaller tumor volumes due to earlier surgical intervention.CA19.9 and CEA were elevated in mucinous carcinomas in our cohort, consistent with findings from Matsas et al., who emphasized their diagnostic utility in mucinous ovarian tumors11. However, the frequency of elevation was lower (14.3%) compared to other series reporting 30–40% [15]. This may be explained by histological heterogeneity within mucinous tumors and limited sample size. Interestingly, LDH elevation was rare in our study (5.6% in serous carcinoma), whereas other studies have reported LDH as a more consistent marker in germ cell tumors and aggressive epithelial variants [14].

The absence of AFP and βhCG elevation in germ cell tumors here contrasts with established evidence, where these markers are typically elevated in advanced disease [15]. A plausible explanation is that the germ cell tumors in our cohort were either early stage or biologically less aggressive, leading to marker negativity. Poorly differentiated carcinomas and granulosa cell tumors

showed no marker elevation, consistent with prior reports that emphasize the limited role of classical markers in these subtypes [16]. Instead, inhibin and estradiol remain more reliable for granulosa cell tumors. The consistent marker negativity in benign lesions such as teratomas and paraovarian cysts reinforces their non-aggressive biology, in agreement with other studies [12]. Overall, the present study demonstrates lower overall marker positivity compared to larger tertiary-center studies. Possible causes include smaller sample size, rural referral bias, early-stage detection, and histological heterogeneity. Despite these differences, the correlation between marker elevation and histological subtype remains consistent with global evidence, underscoring the importance of integrating histopathology with biomarker profiling for accurate diagnosis and prognostication.

Conclusion

Present study demonstrates that ovarian tumors are heterogeneous, with high-grade serous adenocarcinoma being the most common subtype. CA125 was the most useful marker, correlating with tumor burden in serous carcinomas, while CA19.9 and CEA were informative in mucinous tumors. Germ cell tumors showed no AFP or βhCG elevation, likely due to early-stage disease or small sample size. Marker negativity in poorly differentiated carcinomas and granulosa cell tumors highlights the need for alternative markers such as inhibin and estradiol.

Compared with larger tertiary-center studies, overall marker positivity was lower, possibly due to early detection, smaller tumor volumes, and rural referral bias. Despite this, the correlation between histopathology and biomarker elevation remained consistent with global evidence, reinforcing the importance of combining histopathology with biomarker profiling for accurate diagnosis and prognostication.

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