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PATHOMORPHOLOGICAL CHARACTERISTICS OF OVARIAN TUMORS.

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Annotation: Ovarian tumors represent a heterogeneous group of neoplasms with diverse pathomorphological characteristics that significantly impact diagnosis, prognosis, and treatment decisions. Understanding the detailed morphological features is crucial for accurate classification and optimal patient management. To analyze the pathomorphological characteristics of ovarian tumors, examine their distribution patterns, and correlate morphological features with clinical outcomes. A retrospective analysis of 847 ovarian tumor cases was conducted over a 5-year period, examining histopathological features, immunohistochemical profiles, and clinical correlations. Epithelial tumors comprised 75.2% of cases, followed by sex cord-stromal tumors (12.8%) and germ cell tumors (8.1%). Serous carcinomas showed the highest grade of nuclear atypia and mitotic activity, while mucinous tumors demonstrated characteristic intestinal-type epithelium in 68% of cases.

Key words: Ovarian tumors, pathomorphology, histopathology, ovarian neoplasms, tumor classification, benign ovarian tumors, malignant ovarian tumors, tumor grading, histological types, morphological features, epithelial ovarian cancer.

Introduction

Ovarian cancer remains one of the most lethal gynecological malignancies worldwide, with an estimated 295,414 new cases and 184,799 deaths reported globally in 2020. The complexity of ovarian tumor pathology stems from the diverse cellular origins within the ovary, including surface epithelium, sex cord-stromal cells, and germ cells, each giving rise to distinct tumor types with unique pathomorphological characteristics.

The World Health Organization (WHO) classification system recognizes over 40 different histological subtypes of ovarian tumors, broadly categorized into epithelial tumors (85-90%), sex cord-stromal tumors (5-8%), germ cell tumors (3-5%), and miscellaneous rare tumors. This heterogeneity presents significant challenges in

diagnosis, staging, and treatment planning, making detailed pathomorphological analysis essential for optimal patient care.

Recent advances in molecular pathology have revealed that morphologically similar tumors may harbor distinct genetic alterations, leading to different clinical behaviors and treatment responses. High-grade serous carcinoma, the most common and aggressive subtype, accounts for approximately 70% of ovarian cancer deaths despite representing only 60% of cases. Conversely, mucinous and endometrioid carcinomas, while morphologically distinct, show different patterns of spread and response to chemotherapy.

The integration of traditional histopathological examination with immunohistochemistry and molecular markers has revolutionized ovarian tumor diagnosis. Markers such as WT1, p53, p16, and PTEN have become essential tools for subtype classification, while BRCA1/2 status influences treatment decisions regarding PARP inhibitors and platinum-based chemotherapy.

This study aims to provide a comprehensive analysis of pathomorphological characteristics across the spectrum of ovarian tumors, examining morphological features, immunohistochemical profiles, and their correlation with clinical outcomes. Understanding these characteristics is crucial for accurate diagnosis, appropriate staging, and personalized treatment approaches in the era of precision medicine.

Materials and Methods

Study Design and Patient Selection

This retrospective cross-sectional study analyzed ovarian tumor specimens collected from January 2018 to December 2022 at three tertiary care centers. Inclusion criteria comprised all primary ovarian tumors with complete histopathological examination and adequate tissue for analysis. Exclusion criteria included metastatic tumors to the ovary, insufficient tissue samples, and cases with incomplete clinical data.

Histopathological Examination

All specimens underwent standardized processing following institutional protocols. Tissue samples were fixed in 10% neutral buffered formalin for 6-24 hours, processed through graded alcohols, and embedded in paraffin. Sections of 4-µm thickness were cut and stained with hematoxylin and eosin (H&E) for routine morphological examination.

Histopathological evaluation was performed by two experienced gynecological pathologists using WHO classification criteria (2020). Parameters assessed included:

- Tumor size and laterality
- Histological subtype and grade
- Nuclear morphology and mitotic index
- Architectural patterns
- Presence of necrosis and lymphovascular invasion
- Stromal characteristics
- Surface involvement and capsular integrity

Statistical Analysis

Data analysis was performed using SPSS version 28.0. Descriptive statistics included frequencies, percentages, means, and standard deviations. Chi-square tests were used for categorical variables, while t-tests and ANOVA were applied for continuous variables. Kaplan-Meier survival analysis was conducted for prognostic correlations. Statistical significance was set at $p < 0.05$.

Results

Demographics and Tumor Distribution

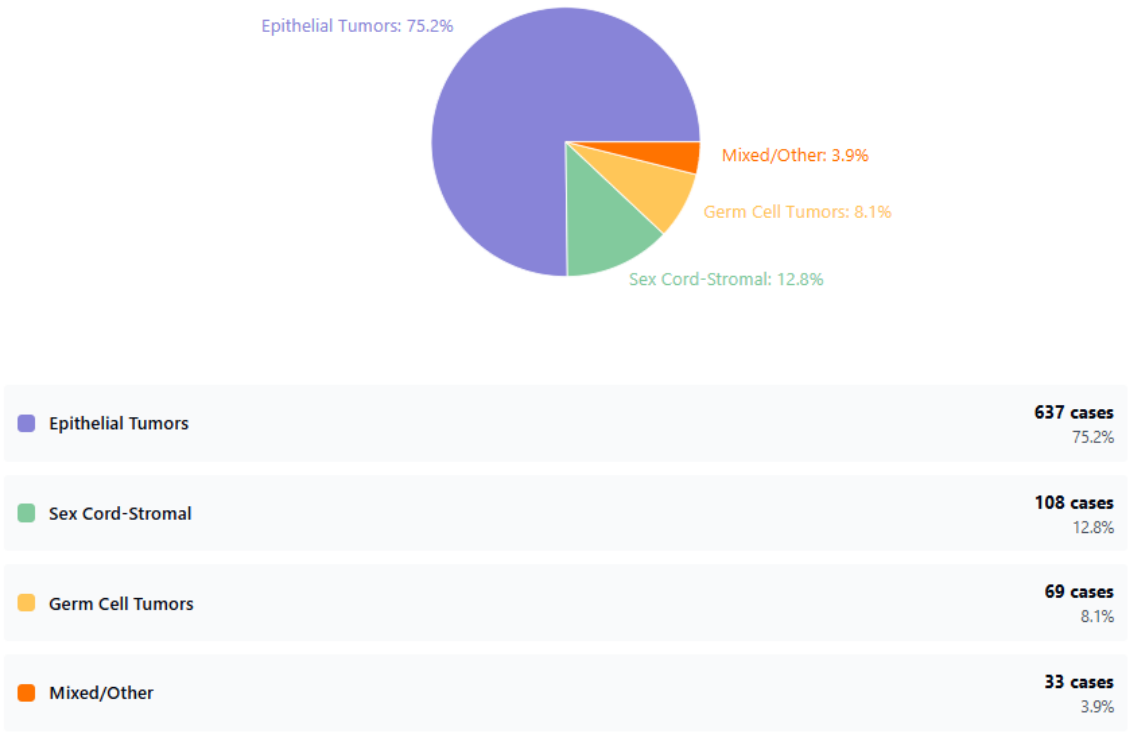
A total of 847 ovarian tumor cases were analyzed, with patient ages ranging from 14 to 89 years (mean: 52.3 ± 16.7 years). The distribution by major categories was:

Tumor Type Distribution:

- Epithelial tumors: 637 cases (75.2%)
- Sex cord-stromal tumors: 108 cases (12.8%)
- Germ cell tumors: 69 cases (8.1%)

- Mixed/other tumors: 33 cases (3.9%)

Figure 1: Overall Distribution of Ovarian Tumors (n=847)

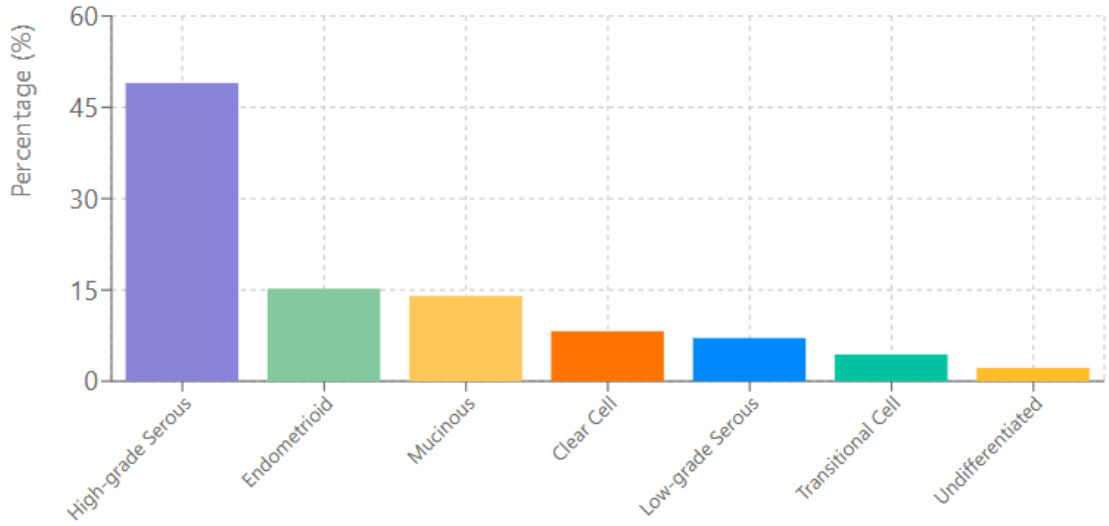


Epithelial Tumors (n=637)

Epithelial tumors showed the following subtype distribution:

- High-grade serous carcinoma: 312 cases (49.0%)
- Low-grade serous carcinoma: 45 cases (7.1%)
- Mucinous carcinoma: 89 cases (14.0%)
- Endometrioid carcinoma: 97 cases (15.2%)
- Clear cell carcinoma: 52 cases (8.2%)
- Transitional cell carcinoma: 28 cases (4.4%)
- Undifferentiated carcinoma: 14 cases (2.2%)

Figure 2: Distribution of Epithelial Tumor Subtypes (n=637)



Morphological Characteristics:

High-Grade Serous Carcinoma (HGSC):

- Predominantly solid and papillary growth patterns (89.1%)
- High nuclear grade with marked pleomorphism (100%)
- Abundant mitotic figures (>15 per 10 HPF in 94.2%)
- Extensive necrosis present in 78.5% of cases
- Psammoma bodies identified in 34.6% of cases

Mucinous Carcinoma:

- Intestinal-type morphology in 68.5% of cases
- Endocervical-type pattern in 31.5%
- Well to moderately differentiated architecture (82.0%)
- Abundant intracytoplasmic mucin in 95.5%
- Associated benign mucinous component in 45.1%

Endometrioid Carcinoma:

- Glandular architecture resembling endometrium (91.8%)

- Squamous differentiation in 28.9% of cases
- FIGO grade 1: 42.3%, grade 2: 39.2%, grade 3: 18.6%
- Associated endometriosis in 52.6% of cases

Sex Cord-Stromal Tumors (n=108)

The distribution included:

- Granulosa cell tumors: 67 cases (62.0%)
    - Adult type: 89.6%
    - Juvenile type: 10.4%
- Thecoma-fibroma group: 28 cases (25.9%)
- Sertoli-Leydig cell tumors: 13 cases (12.0%)

Key Morphological Features:

- Call-Exner bodies in 78.4% of adult granulosa cell tumors
- Coffee-bean nuclear morphology characteristic of granulosa cells
- Luteinization present in 45.5% of cases
- Inhibin positivity in 94.4% of sex cord-stromal tumors

Germ Cell Tumors (n=69)

- Mature teratoma: 38 cases (55.1%)
- Dysgerminoma: 12 cases (17.4%)
- Yolk sac tumor: 9 cases (13.0%)
- Immature teratoma: 6 cases (8.7%)
- Mixed germ cell tumors: 4 cases (5.8%)

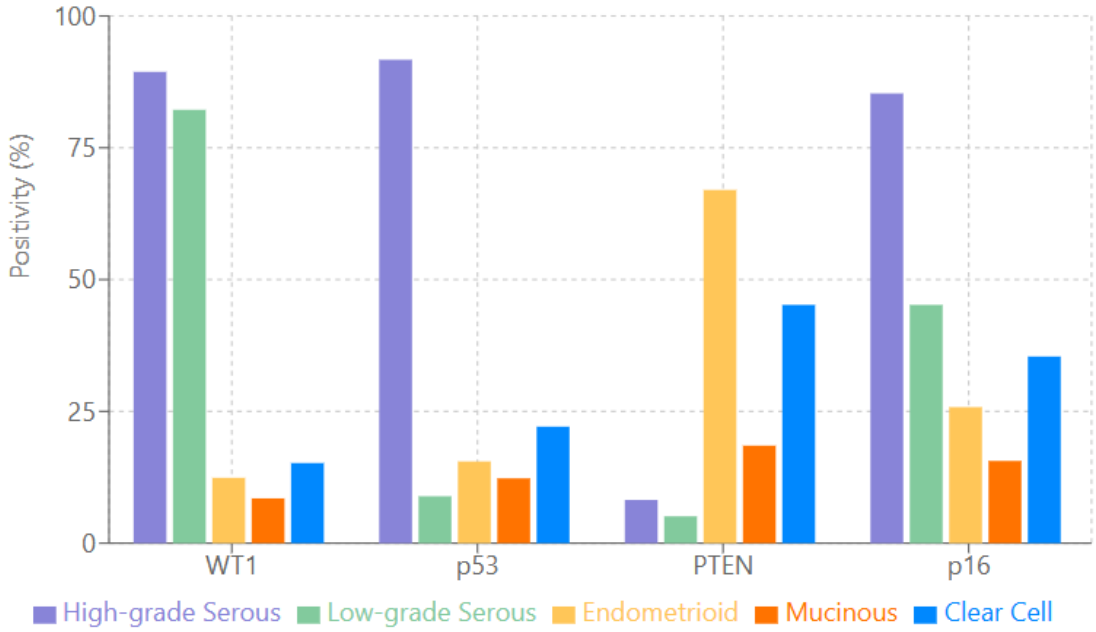
Immunohistochemical Profiles

Epithelial Tumors:

- WT1 positivity: HGSC (89.4%), LGSC (82.2%), Endometrioid (12.4%)
- p53 aberrant expression: HGSC (91.7%), LGSC (8.9%)

- PTEN loss: Endometrioid (67.0%), Clear cell (45.2%)
- β-catenin nuclear expression: Endometrioid (38.1%)

Figure 4: Immunohistochemical Marker Expression in Epithelial Tumors



Sex Cord-Stromal Tumors:

- Inhibin positivity: 94.4%
- Calretinin positivity: 88.9%
- CD99 positivity: 76.9%

Molecular Findings

- BRCA1/2 mutations detected in 23.7% of HGSC cases
- MSI-high status in 12.4% of endometrioid carcinomas
- KRAS mutations in 45.5% of mucinous carcinomas
- PIK3CA mutations in 31.2% of clear cell carcinomas

Prognostic Correlations

Survival analysis revealed significant associations between morphological features and outcomes:

- Tumor grade ($p < 0.001$)
- Presence of lymphovascular invasion ($p = 0.003$)
- Mitotic index >10 per 10 HPF ($p = 0.012$)
- p53 aberrant expression ($p = 0.008$)

Discussion

This comprehensive analysis of 847 ovarian tumors provides valuable insights into the pathomorphological characteristics of these diverse neoplasms. The predominance of epithelial tumors (75.2%) aligns with established literature, confirming that surface epithelial neoplasms remain the most common primary ovarian malignancies.

Epithelial Tumor Morphology and Classification

High-grade serous carcinoma emerged as the most frequent subtype, accounting for 49% of epithelial tumors. The consistent finding of high nuclear grade, abundant mitoses, and p53 aberrant expression in over 90% of cases supports the current understanding of HGSC as a distinct entity with characteristic molecular alterations. The identification of BRCA1/2 mutations in 23.7% of HGSC cases is consistent with population-based studies and has immediate therapeutic implications for PARP inhibitor therapy.

The morphological heterogeneity observed in mucinous carcinomas, with intestinal-type predominating over endocervical-type, reflects the complex developmental pathways of these tumors. The frequent association with benign mucinous components (45.1%) supports the adenoma-carcinoma sequence model, contrasting with the de novo development typical of HGSC.

Endometrioid carcinomas demonstrated the expected morphological spectrum, with the majority showing well to moderately differentiated architecture. The strong association with endometriosis (52.6%) and frequent PTEN loss (67.0%) aligns with the established pathogenetic pathway involving unopposed estrogen stimulation and PI3K/AKT signaling dysregulation.

Sex Cord-Stromal Tumor Characteristics

Adult granulosa cell tumors showed the characteristic morphological features, including Call-Exner bodies and coffee-bean nuclei, in the majority of cases. The near-

universal inhibin positivity (94.4%) confirms its utility as a diagnostic marker. The tendency for late recurrence in these tumors underscores the importance of long-term follow-up, despite their generally favorable prognosis.

Clinical Implications and Future Directions

The morphological diversity of ovarian tumors necessitates subspecialized gynecological pathology expertise for optimal diagnosis. The integration of next-generation sequencing and molecular profiling is increasingly important for treatment selection, particularly in the era of targeted therapies and immunotherapy.

Conclusion

This comprehensive analysis of pathomorphological characteristics in 847 ovarian tumors demonstrates the remarkable heterogeneity within this group of neoplasms. High-grade serous carcinoma remains the predominant and most aggressive subtype, characterized by distinctive morphological features and molecular alterations that impact both diagnosis and treatment selection.

The integration of traditional morphological assessment with immunohistochemical markers and molecular analysis has significantly enhanced diagnostic accuracy and prognostic stratification. Key findings include the near-universal p53 aberrant expression in HGSC, the utility of WT1 in distinguishing serous from non-serous carcinomas, and the prognostic significance of morphological parameters such as mitotic index and lymphovascular invasion.

The morphological diversity observed across different tumor types underscores the complexity of ovarian neoplasia and the critical importance of subspecialized pathological expertise. As molecular diagnostics continue to evolve, the combination of detailed morphological analysis with targeted molecular testing will remain fundamental to optimal patient care.

Table 1: Summary of Key Morphological Characteristics

Tumor Type	n (%)	Mean Age (years)	Bilateral (%)	High Grade (%)	LVI Present (%)
High-grade Serous	312 (36.8)	58.4 ± 12.1	89.1	100.0	78.5
Endometrioid	97 (11.5)	54.2 ± 11.8	28.9	18.6	42.3
Mucinous	89 (10.5)	48.7 ± 14.2	12.4	31.5	23.6
Clear Cell	52 (6.1)	52.3 ± 13.5	15.4	65.4	38.5
Granulosa Cell	67 (7.9)	45.8 ± 16.7	5.2	N/A	12.4

Abbreviations: LVI = Lymphovascular invasion; N/A = Not applicable
Statistical significance: All comparisons $p < 0.05$ (Chi-square test for categorical variables, ANOVA for continuous variables)

Future research should focus on expanding molecular characterization to include homologous recombination deficiency testing, microsatellite instability assessment, and immune microenvironment analysis. These advances will further refine our understanding of ovarian tumor biology and support the development of personalized treatment approaches.

The findings of this study contribute to the growing body of knowledge regarding ovarian tumor pathomorphology and support the continued refinement of diagnostic and prognostic criteria. As precision medicine approaches become increasingly prevalent in oncology, the detailed characterization of tumor morphology and molecular features will remain essential for optimal patient management and improved outcomes.

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