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Original Article

Histomorphological Spectrum of Surface Epithelial Tumors of Ovary and Role of Ki67 in Serous Ovarian Tumors

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ABSTRACT

Background: Surface epithelial tumors of the ovary represent the most prevalent type of ovarian tumors and are characterized by great histogenetic diversity. Accurate histopathological classification is crucial for patient management and prognosis. **Objectives**: This study aimed to analyze the histomorphological spectrum among benign, borderline, and malignant categories of ovarian surface epithelial tumors, and to investigate the role of Ki-67 as a proliferative indicator in serous ovarian tumors. **Methodology**: An 18-month prospective study was conducted from October 2019 to March 2021 with a total of 156 surface epithelial ovarian tumor specimens. Relevant clinical information was extracted from hospital records. H&E stained slides were analyzed and histological diagnosis was made according to WHO classification. Ki-67 antigen immunoreactivity was studied on 30 selected serous ovarian tumors (15 benign and 15 malignant) and expressed as Ki-67 labeling index (Ki-67 LI). **Results**: The mean age at diagnosis was 43 years. Eighty-four percent of tumors were unilateral, while 13% were bilateral. Among the 156 cases, 75% were benign (118 cases), 17% were malignant (26 cases), and 8% were borderline (12 cases). Serous tumors were the most common histological type (92 cases, 59%). Ki-67 LI was significantly higher in malignant serous tumors (34.66±28.3%) compared to benign serous tumors (1.81±1.16%), with p=0.001. High Ki-67 LI was observed in high-grade serous carcinomas and advanced FIGO stages. **Conclusion**: Precise histopathological classification is critical for elective treatment of surface epithelial ovarian tumors. Ki-67 immunohistochemical expression, when combined with histological grade and FIGO stage, aids in understanding tumor biological behavior and can serve as a prognostic marker. Ki-67 LI demonstrates significant discriminatory power between benign and malignant serous ovarian tumors.

Keywords: *Surface epithelial ovarian tumors, histomorphological spectrum, serous tumors, Ki-67 labeling index*

INTRODUCTION

Ovarian cancer accounts for approximately 6% of all female cancers with diverse clinical, morphological, and histological characteristics [1]. It predominantly affects older age groups, typically by age 65, with 70% of women presenting with advanced disease due to inadequate screening techniques [2]. The age-standardized incidence rate of ovarian cancer in India has been steadily increasing, ranging from 0.26% to 2.4% annually [3]. Surface epithelial ovarian tumors represent the most prevalent type of ovarian neoplasm and constitute the fifth leading cause of cancer-related death in women.

Accurate histopathological diagnosis and classification are essential for determining appropriate treatment strategies, predicting prognosis, and assessing the need for adjuvant chemotherapy. The combination of histological grade and FIGO stage in the histopathology report, when coupled with molecular markers such as Ki-67, provides crucial prognostic information. Ovarian cancer proliferative activity is a useful predictor of tumor aggressiveness [4]. The Ki-67 monoclonal antibody reacts with a nuclear antigen expressed exclusively by proliferating cells, making it an excellent growth fraction indicator.

Objectives of the Study

1. To study the histomorphological spectrum of surface epithelial tumors of the ovary

2. To evaluate Ki-67 immunohistochemical expression in serous ovarian tumors
3. To correlate Ki-67 expression with tumor grade and FIGO stage

METHODOLOGY

Study Design and Source of Data

This was an observational, prospective study conducted in the Department of Pathology, Father Muller Medical College (FMMC), Mangalore. All surface epithelial ovarian tumor (SEOT) specimens received as oophorectomy specimens or as part of total hysterectomy specimens between October 2019 and March 2021 were included in the study.

Study Duration: The study period was 18 months, from October 2019 to March 2021.

Inclusion Criteria

All surface epithelial tumors of the ovary diagnosed in the Department of Pathology, FMMC were included for histomorphological analysis. From the total cases of surface epithelial tumors, 30 serous ovarian tumors (15 benign and 15 malignant) were selected for Ki-67 immunohistochemistry evaluation.

Exclusion Criteria

- Previously treated (post chemotherapy/radiotherapy) cases of ovarian neoplasms
- Serous ovarian tumors that did not fall within the first 15 benign or 15 malignant cases were excluded from Ki-67 IHC evaluation

Data Collection and Processing: Clinical information and demographic data were extracted from hospital records. Tumor specimens were fixed in 10% neutral buffered formalin and underwent routine gross examination. Macroscopic findings including outer surface appearance, presence of deposits, capsule integrity, cut surface appearance, content, areas of necrosis, and papillary excrescences were documented.

Multiple representative sections were taken for histomorphological examination and subjected to routine processing. Paraffin-embedded sections were prepared, sectioned, and stained with H&E stain. Histopathological diagnosis was made based on morphological features and categorized according to WHO classification of ovarian tumors.

Immunohistochemical Staining: Ki-67 antigen immunoreactivity was studied on selected serous ovarian tumors. Distribution of Ki-67 immunoreactivity was expressed as Ki-67 labeling index (Ki-67 LI). Ki- 67 expression was considered positive when tumor cells exhibited brown granular nuclear staining. Ki-67 LI was calculated as percentage of positively stained cells using high power objective of microscope (×400) in 500 cells, with an average of 3 counts taken. Ki-67 immunoexpression was considered negative when Ki-67 LI <1% and positive when Ki-67 LI ≥1%. Positive staining was scored as: 1+ (Ki-67: 1-30%), 2+ (Ki-67: 30-50%), and 3+ (Ki-67: >50%).

Sample Size Estimation: Sample size was calculated using standard formulas. For surface epithelial tumors, the minimum sample size was calculated as 137 cases (with 7% error and 77.5% prevalence). During the stipulated time period, 156 samples were collected and analyzed. Ki-67 IHC marker study was performed on 30 serous ovarian tumors (15 benign and 15 malignant).

Data Analysis: Collected data were analyzed as frequency and percentage. Different histomorphological variables were cross-tabulated under benign, borderline, and malignant categories and Pearson Chi-square test was performed to determine significance. A p-value <0.05 was considered statistically significant. Ki-67 LI among benign and malignant tumors, tumor grade groups, and FIGO stages were expressed as mean ± standard deviation with comparison performed using independent t-test.

RESULTS

A total of 156 surface epithelial ovarian tumors were included in the study.

Age Distribution

Age of patients ranged from 14 to 85 years with mean age of 43 years. Maximum patients were in the 41-50 years age group (33.3%), with minimum in the 81-90 years age group (0.6%) as given in the table.

Age Group (Years)	No. of Cases	Percentage
11-20	15	9.6
21-30	19	12.2
31-40	27	17.3
41-50	52	33.3
51-60	25	16.0
61-70	12	7.7
71-80	5	3.2
81-90	1	0.6

Nature and Size of Specimens
The majority of specimens were received as part of hysterectomy (89 cases, 57.1%), with the remainder as oophorectomies including cystectomies (67 cases, 42.9%). Size of specimens ranged from 2-37 cm in greatest dimension with mean size of 12.2 cm.

Laterality of Tumors
Of 156 cases, majority were unilateral (130 cases, 83.3%) [Fig 1]. Left laterality was more common (44%) followed by right laterality (40%), with bilateral involvement in 13% of cases.

Distribution of Surface Epithelial Ovarian Tumors
Out of 156 SEOTs analyzed, majority were benign tumors (118 cases, 75%), followed by malignant tumors (26 cases, 17%) and borderline tumors (12 cases, 8%).

Macroscopic Findings
Among benign SEOTs (n=118), majority had smooth outer surface (98.3%), intact capsule (75.4%), predominantly cystic cut surface (98.3%), and papillary excrescences were absent in 92.4% cases [Fig 2]. Among borderline SEOTs (n=12), majority had smooth outer surface (75%), intact capsule (83.3%), and cystic cut surface (66.7%), with papillary excrescences present in 66.7% cases. Among malignant SEOTs (n=26), majority had nodular outer surface (53.8%), solid more than cystic cut surface (34.6%), and papillary excrescences (69.2%), with capsular breach in 50% cases. These findings were statistically significant ($p<0.001$) [Fig 3-4].

Fig 1: Unilateral serous cystadenoma of the right ovary in hysterectomy specimen. Fig 2: A)Smooth outer surface of Mucinous cystadenoma. B) Multiloculated cystic cut surface of the same tumor with mucoid content. Fig 3: Outer surface (A) and cut-surface (B) of a case of serous carcinoma. Outer surface is nodular with capsular breach and cut surface of the tumor is solid > cystic with areas of hemorrhage and necrosis. Fig 4: A) Smooth outer surface of mucinous carcinoma of the ovary. B) Mucinous friable tumor content seen in the cut surface.

Microscopic Findings
The most common epithelium identified was simple columnar to cuboidal type (76 cases, 48.7%) followed by mucinous epithelium (40 cases, 25.6%). Cystic pattern was most common in benign SEOTs (96.6%), while papillary pattern was most common in borderline (33.3%) and malignant (57.7%) tumors. Capsular breach was confirmed microscopically in 13 malignant tumors (50%). Necrosis was identified in 88.5% of malignant and 8.3% of borderline SEOTs. Desmoplastic stroma was observed only in malignant tumors (73.1%).

Cellular Features
Benign tumor cells showed normal N/C ratio (100%), absent nuclear pleomorphism (97.5%), ne chromatin (97.5%), and moderate cytoplasm (61.9%). As tumor category progressed from benign to borderline to malignant, cellular features shifted to high-grade characteristics ($p<0.001$).

Histological Types
Major histological types identified were serous tumors (92 cases, 59%), mucinous tumors (50 cases, 32%), and endometrioid tumors (7 cases, 4.5%). Serous cystadenoma was the most common benign tumor (59 cases, 37.8%), while serous carcinoma was most common among malignant tumors (13 cases, 8.3%) [Fig 5-8].

Ki-67 Immunoexpression in Serous Ovarian Tumors
Thirty serous ovarian tumors (15 benign and 15 malignant) were evaluated for Ki-67 immunoreactivity. In benign tumors, six cases showed negative Ki-67 staining (Ki-67 LI <1%), with remaining cases showing focal nuclear staining. Mean Ki-67 LI in benign serous tumors was 1.81±1.16%.

In malignant serous tumors, Ki-67 LI was calculated with corresponding FIGO stages and tumor grades. Mean Ki-67 LI in malignant serous tumors was 34.66±28.3%. Borderline tumors demonstrated low Ki-67 expression (score 1+, highest 14%), while malignant tumors exhibited high Ki-67 expression (score 3+, >50%).

Ki-67 LI and FIGO Stages & tumor grade

Comparison of Ki-67 LI with FIGO stages showed mean values of Stage IV (63.25), Stage III (46.4), Stage I (18.8), and Stage II (10.5). This difference was not statistically significant (p=0.087) [Fig 9A]. Among 12 serous carcinomas, 8 were high-grade and 4 were low-grade. Mean Ki-67 LI was higher in high-grade tumors (51.05±25.37%) compared to low-grade tumors (20.5±25.02%), but this difference was not statistically significant (p=0.077) [Fig 9B].

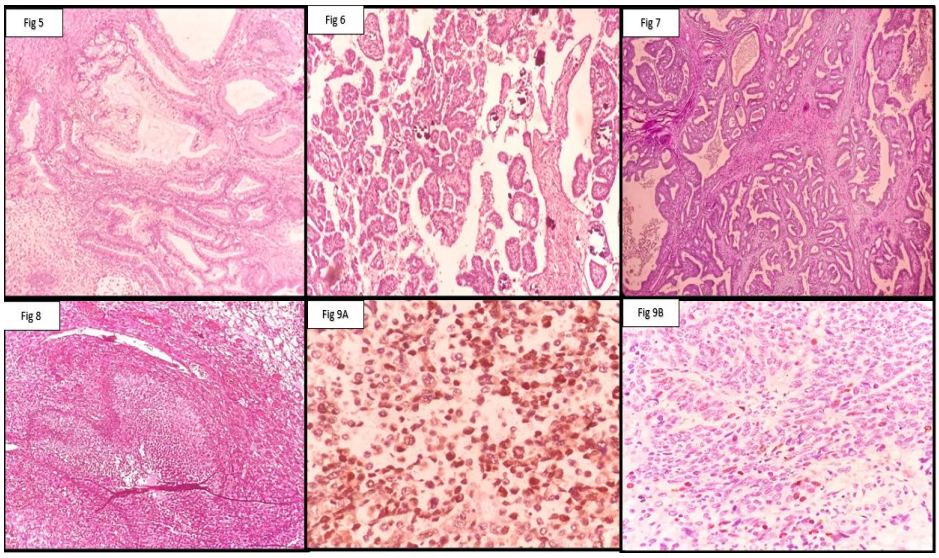

Fig 5: Photomicrograph of mucinous borderline tumor (H & E stain -10x). Fig6: Photomicrograph of serous carcinoma showing tumor cells arranged predominantly in papillary architecture with psammoma bodies (H & E stain low 40x). Fig 7: Photomicrograph of Endometrioid carcinoma (H & E stain-10x). Fig 8: Photomicrograph of Benign Brenner tumor (H & E stain-40x). Fig 9: A)Photomicrograph of FIGO stage IV serous carcinoma with high Ki-67 LI.Tumour cells show diffuse intense brown granular nuclear staining. B)Photomicrograph of low grade serous carcinoma with low Ki-67 LI.

Comparison of Ki-67 LI Between Benign and Malignant Tumors

The comparison of Ki-67 LI between benign (1.81±1.16%) and malignant (34.66±28.3%) serous ovarian tumors was statistically significant (t=4.492, p=0.001).

DISCUSSION

Ovarian tumors represent one of the most serious gynecological cancers, particularly in older women. Despite numerous improvements in diagnosis and therapy, survival rates have not improved significantly over the past 30 years, with these tumors often termed "silent killers" due to late-stage presentation. Age, clinical stage, tumor grade and type are known prognostic factors, but additional parameters are needed to accurately predict biological behavior and patient outcomes.

Age and Presentation: In this study, peak incidence occurred in the 41-50 years age group, consistent with multiple previous reports. The mean age of 43 years aligns with findings from comparable studies. Age remains an independent prognostic factor, with incidence and malignancy risk increasing exponentially with age.

Laterality: The present study revealed that 83.3% of tumors were unilateral with 13.5% bilateral, consistent with other published studies reporting 89.5-95.5% unilateral and 4.5-10.5% bilateral involvement.

Distribution of Tumor Categories: In this cohort, 75% were benign, 17% malignant, and 8% borderline tumors, consistent with literature reporting benign tumors as the most prevalent category. The higher proportion of borderline tumors in this series may reflect the comprehensive nature of the analysis.

Histological Types and Subtypes: Serous tumors were most common (58.9%), followed by mucinous (31.4%) and endometrioid (4.5%) tumors. Serous cystadenoma was the most frequent benign subtype while serous carcinoma was most common among malignant tumors. These findings align with literature showing serous and mucinous tumors as predominant types in surface epithelial neoplasms.

Macroscopic and Microscopic Correlations: Histomorphological evaluation integrating both gross and microscopic findings proved essential for accurate diagnosis. Benign tumors characteristically showed smooth outer surface, intact capsule, and cystic consistency. Malignant tumors demonstrated nodular surface, capsular breach, and solid components. These gross features provided important clues regarding microscopic architecture and final diagnosis.

Papillary architectural pattern showed strong association with borderline and malignant tumors, while cystic pattern was characteristic of benign lesions. Cellular features including N/C ratio, nuclear pleomorphism, chromatin pattern, and presence of necrosis showed statistically significant differences between benign, borderline, and malignant categories ($p<0.001$).

Role of Ki-67 as Proliferative Marker: Cell proliferation significantly impacts clinical behavior and aggressiveness of ovarian cancers. Ki-67 as a nuclear proliferation marker has become widely used for determining tumor proliferative potential. In this study, Ki-67 LI showed significantly higher expression in malignant tumors compared to benign tumors ($p=0.001$), confirming its utility as a discriminatory marker between these categories.

Mean Ki-67 LI was higher in high-grade serous carcinomas and advanced FIGO stages, though the differences were not statistically significant, likely due to small sample size. Borderline tumors exhibited intermediate Ki-67 expression, aligning with patient age, clinical presentation, tumor laterality, distribution of tumor categories, histological types and subtypes, as well as macroscopic and microscopic features, reflecting their intermediate biological behavior. These findings support the use of Ki-67 as an additional prognostic parameter alongside traditional histopathological variables.

Recent literature increasingly emphasizes the value of proliferative markers in ovarian cancer prognostication. Combined assessment of histological grade, FIGO stage, and Ki-67 LI provides comprehensive information regarding tumor biological behavior and can guide treatment decisions and follow-up strategies.

CONCLUSION

Among 156 examined surface epithelial ovarian tumors, accurate diagnosis could be achieved through comprehensive correlation of clinical presentation, gross morphology, and microscopic features. Serous tumors were the most common histological type, with serous cystadenoma being most frequent benign subtype and serous carcinoma the most common malignant variant.

Precise histopathological classification remains the gold standard for diagnosing surface epithelial ovarian tumors. When combined with Ki-67 immunohistochemical expression as a proliferative indicator, along with histological grade and FIGO stage, comprehensive prognostic assessment becomes possible. Nuclear Ki-67 immunoexpression was significantly more prominent in malignant tumors compared to benign and borderline lesions, underscoring the importance of this marker in tumor development and behavior prediction.

Ki-67 expression assessment, when incorporated into standard histopathology reports, aids in forecasting tumor biological behavior, determining aggressiveness, and identifying patients who may benefit from aggressive adjuvant therapy. This additional biomarker information complements traditional morphological assessment and provides valuable prognostic data for improved patient management and outcome prediction.

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