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PREDICTIVE ASSESSMENT OF MALIGNANCY RISK IN OVARIAN CYSTIC LESIONS BASED ON MORPHOLOGICAL AND MOLECULAR MARKERS

Yakubbekova S.S.
Department of Oncology, Andijan State Medical Institute
Andijan, Uzbekistan
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Abstract: Ovarian cystic lesions represent a heterogeneous group of pathological conditions ranging from benign functional and neoplastic processes to borderline tumors and invasive ovarian carcinomas. Differential diagnosis and assessment of malignant potential remain important challenges in gynecologic oncology. Conventional imaging, serum tumor markers, and histopathological examination provide essential diagnostic information; however, individual parameters may have insufficient specificity for accurate risk stratification. The integration of morphological, immunohistochemical, and molecular characteristics may improve the identification of ovarian lesions with increased malignant potential. Particular attention is currently focused on morphological indicators of epithelial proliferation and invasion, proliferative activity assessed by Ki-67, abnormal p53 expression, and molecular alterations involving TP53, BRCA1/2, KRAS, BRAF, PIK3CA, PTEN, and ARID1A. An integrated multiparametric approach may improve differential diagnosis, prognostic assessment, and individualized clinical decision-making.

Keywords: ovarian cystic lesions, ovarian cancer, malignant transformation, malignancy risk, morphology, immunohistochemistry, molecular biomarkers, p53, Ki-67, BRCA1/2.

Introduction

Ovarian cystic lesions are frequently detected in women of different age groups and include a broad spectrum of functional, benign neoplastic, borderline, and malignant processes. The majority of ovarian cystic lesions are benign; nevertheless, early identification of tumors with malignant potential is one of the most important tasks in gynecologic oncology.

The clinical significance of this problem is determined by several factors. First, ovarian malignant tumors may remain asymptomatic or present with nonspecific manifestations during the early stages of disease. Second, benign, borderline, and malignant ovarian lesions may demonstrate overlapping clinical and imaging characteristics. Third, the therapeutic approach differs considerably according to the biological nature of the lesion. While conservative management or organ-preserving surgery may be appropriate for selected benign and borderline tumors, invasive ovarian carcinoma requires oncologically appropriate staging, cytoreductive surgery, and, in many cases, systemic anticancer therapy.

Ultrasonography is the primary imaging method for the evaluation of adnexal masses. Morphological characteristics such as irregular walls, thick septa, papillary projections, solid components, vascularization, and ascites may increase suspicion of malignancy. Serum biomarkers, particularly CA-125 and HE4, may provide additional information. However, neither imaging findings nor serum biomarkers can independently provide definitive discrimination between all benign, borderline, and malignant lesions.

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Histopathological examination remains the cornerstone of definitive diagnosis. Nevertheless, contemporary concepts of ovarian carcinogenesis indicate that morphological assessment can be strengthened by immunohistochemical and molecular analysis. Different histological types of ovarian carcinoma demonstrate distinct molecular pathways, patterns of biomarker expression, biological behavior, prognosis, and therapeutic sensitivity.

Therefore, the development of an integrated system combining morphological and molecular parameters represents a promising direction for improving the prediction of malignant potential in ovarian cystic lesions.

Aim

The aim of this study was to analyze the principal morphological, immunohistochemical, and molecular characteristics associated with malignant potential of ovarian cystic lesions and to evaluate their possible application in an integrated predictive model for oncological practice.

Materials and Methods

An analytical assessment of contemporary data concerning the morphological and molecular characteristics of ovarian cystic lesions was performed.

The analyzed lesions were considered within three principal categories: benign ovarian cystic tumors, borderline ovarian tumors, and invasive malignant epithelial ovarian tumors.

Morphological assessment included the following parameters: epithelial proliferation and stratification, architectural complexity, papillary formations, solid components, nuclear atypia and pleomorphism, mitotic activity, necrotic changes, stromal reaction, and the presence or absence of destructive stromal invasion.

Particular attention was paid to immunohistochemical markers reflecting proliferative activity, tumor-suppressor pathway abnormalities, and tumor differentiation. The principal markers analyzed included **Ki-67, p53, WT1, PAX8, p16, estrogen receptor (ER), and progesterone receptor (PR).**

Molecular characteristics included alterations involving **TP53, BRCA1, BRCA2, KRAS, BRAF, PIK3CA, PTEN, and ARID1A**, as well as abnormalities of homologous recombination and mismatch-repair pathways.

The potential diagnostic and predictive value of these parameters was considered in relation to tumor morphology, histological subtype, and biological behavior.

Results and Discussion

Morphological Characteristics and Malignant Potential

Morphological assessment remains fundamental for determining the biological nature of ovarian cystic tumors.

Benign lesions are generally characterized by relatively simple architecture, preservation of epithelial polarity, minimal nuclear atypia, low mitotic activity, and absence of stromal invasion. Serous and mucinous cystadenomas usually demonstrate well-organized epithelial lining without significant cellular atypia.

Borderline ovarian tumors occupy an intermediate position between benign and invasive malignant neoplasms. Morphologically, these tumors demonstrate increased epithelial proliferation, stratification, papillary complexity, nuclear atypia, and increased mitotic activity. The critical feature separating a borderline tumor from invasive carcinoma is the absence of destructive stromal invasion.

Malignant ovarian tumors demonstrate progressive loss of normal tissue architecture and cellular organization. Important morphological characteristics include pronounced nuclear atypia,

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pleomorphism, loss of polarity, increased and atypical mitoses, complex papillary or cribriform architecture, solid components, necrosis, and invasive stromal growth.

Therefore, destructive stromal invasion remains one of the most important morphological indicators of malignancy.

Ki-67 and Proliferative Activity

Ki-67 is a nuclear marker expressed during active phases of the cell cycle and is widely used to estimate proliferative activity.

Benign ovarian lesions generally demonstrate low Ki-67 expression. Borderline tumors may show an intermediate or heterogeneous proliferation index, reflecting increased epithelial proliferation.

In malignant ovarian tumors, particularly high-grade carcinomas, Ki-67 expression may be substantially increased. High proliferative activity can reflect aggressive biological behavior, although Ki-67 values should always be interpreted according to histological subtype and in combination with morphological findings.

Thus, Ki-67 is potentially useful as one component of a multiparametric assessment of malignant potential rather than as an independent diagnostic criterion.

p53 and TP53 Alterations

The p53 pathway plays a central role in the development of high-grade serous carcinoma.

Abnormal p53 immunohistochemical patterns are highly characteristic of TP53-altered high-grade serous carcinoma. These patterns may include diffuse strong nuclear overexpression or a complete absence of tumor-cell staining.

In contrast, a heterogeneous wild-type pattern is more commonly observed in tumors without TP53-driven pathogenesis.

The combination of marked cellular atypia, high proliferative activity, and abnormal p53 expression is particularly informative in the diagnosis of high-grade serous carcinoma.

However, p53 should not be interpreted as a universal marker of malignancy because different histological types of ovarian cancer develop through different molecular mechanisms.

WT1, PAX8 and Tumor Differentiation

WT1 and PAX8 are important markers in the immunohistochemical evaluation of ovarian epithelial tumors.

WT1 is particularly useful for supporting serous differentiation and is commonly expressed in serous ovarian carcinomas. PAX8 is a nuclear transcription factor associated with Müllerian differentiation and is expressed in many primary ovarian epithelial malignancies.

The combined use of morphology, WT1, PAX8, and p53 may contribute to more accurate classification of ovarian carcinomas and help distinguish primary Müllerian tumors from selected metastatic lesions involving the ovary.

BRCA1/2 and Homologous Recombination Deficiency

BRCA1 and BRCA2 are essential components of homologous recombination DNA repair. Pathogenic alterations in these genes contribute to genomic instability and are particularly important in the pathogenesis of a subset of high-grade serous carcinomas.

Identification of BRCA1/2 alterations has significance beyond tumor classification. It may identify hereditary cancer susceptibility and provide clinically relevant information for genetic counseling.

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Furthermore, BRCA1/2 abnormalities and homologous recombination deficiency may predict sensitivity to specific targeted treatment strategies, including PARP inhibitors in appropriate clinical settings.

Consequently, molecular characterization contributes to both risk assessment and personalized treatment selection.

Other Molecular Pathways

The molecular profile of ovarian tumors varies substantially according to histological subtype.

Low-grade serous tumors are biologically distinct from high-grade serous carcinoma and may demonstrate alterations involving the MAPK pathway, particularly **KRAS and BRAF**.

Endometrioid and clear-cell ovarian tumors may demonstrate abnormalities involving **ARID1A, PIK3CA, and PTEN**. These alterations are of particular interest because a proportion of these tumors are associated with endometriosis.

Mismatch-repair deficiency may also occur in selected ovarian tumors, particularly endometrioid carcinomas. Identification of mismatch-repair abnormalities may have implications for hereditary cancer evaluation and therapeutic decision-making.

These observations confirm that ovarian carcinoma represents a heterogeneous group of molecularly distinct diseases rather than a single biological entity.

Development of an Integrated Predictive Model

The major limitation of using isolated biomarkers is the biological heterogeneity of ovarian tumors. No single serum, morphological, immunohistochemical, or molecular marker provides sufficient diagnostic accuracy for all ovarian cystic lesions.

For this reason, a predictive approach should integrate several categories of information.

The first level should include clinical characteristics such as age, menopausal status, hereditary history, and symptoms.

The second level should incorporate imaging characteristics, including lesion size, multilocularity, wall irregularity, septations, papillary projections, solid components, vascularization, and associated ascites.

The third level may include serum biomarkers such as CA-125 and HE4 when clinically appropriate.

The fourth level should incorporate histomorphological characteristics, particularly epithelial proliferation, nuclear atypia, mitotic activity, architectural complexity, and stromal invasion.

Finally, immunohistochemical and molecular findings may provide additional biological characterization.

A conceptual predictive pathway may therefore be represented as:

Clinical characteristics → Imaging features → Serum biomarkers → Morphological criteria → Immunohistochemical profile → Molecular alterations → Integrated malignancy-risk assessment.

Such an approach could potentially stratify patients into low-, intermediate-, and high-risk categories and support individualized clinical decision-making.

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Significance for Oncological Practice

An integrated predictive assessment of ovarian cystic lesions may have several practical advantages.

Improved identification of low-risk lesions may reduce unnecessary radical surgery, particularly in young women with reproductive plans.

More accurate recognition of borderline tumors may facilitate appropriate fertility-preserving treatment in carefully selected patients.

Early identification of lesions with a high probability of malignancy may ensure timely referral to specialized gynecologic oncology centers and appropriate surgical planning.

Molecular characterization may additionally identify hereditary cancer syndromes and clinically actionable tumor characteristics.

Therefore, integration of conventional morphology with immunohistochemical and molecular parameters represents an important step toward precision medicine in gynecologic oncology.

Conclusion

Ovarian cystic lesions represent a heterogeneous group of diseases with substantially different biological behavior and malignant potential. Their accurate differentiation remains an important diagnostic problem.

Morphological features associated with increasing malignant potential include epithelial proliferation, architectural complexity, nuclear atypia, increased mitotic activity, solid growth, necrosis, and particularly destructive stromal invasion.

Immunohistochemical assessment of **p53, Ki-67, WT1, PAX8, p16, ER, and PR** provides additional information concerning proliferative activity, tumor differentiation, and molecular abnormalities. Molecular alterations involving **TP53, BRCA1/2, KRAS, BRAF, PIK3CA, PTEN, and ARID1A** further demonstrate the biological heterogeneity of ovarian neoplasms.

The combination of clinical, imaging, morphological, immunohistochemical, and molecular parameters appears more informative than the use of individual markers. Development and validation of an integrated predictive model may improve early detection of malignant transformation, optimize surgical strategy, facilitate personalized treatment, and improve risk stratification of patients with ovarian cystic lesions.

References

1. WHO Classification of Tumours Editorial Board. *Female Genital Tumours*. 5th ed. Lyon: International Agency for Research on Cancer; 2020.
2. Kurman RJ, Shih IM. The dualistic model of ovarian carcinogenesis: revisited, revised, and expanded. *Am J Pathol.* 2016;186(4):733–747.
3. Cancer Genome Atlas Research Network. Integrated genomic analyses of ovarian carcinoma. *Nature.* 2011;474:609–615.
4. Prat J, D'Angelo E, Espinosa I. Ovarian carcinomas: at least five different diseases with distinct histological features and molecular genetics. *Hum Pathol.* 2018;80:11–27.

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5. Bowtell DD, Böhm S, Ahmed AA, et al. Rethinking ovarian cancer II: reducing mortality from high-grade serous ovarian cancer. *Nat Rev Cancer.* 2015;15(11):668–679.
6. Lheureux S, Gourley C, Vergote I, Oza AM. Epithelial ovarian cancer. *Lancet.* 2019;393(10177):1240–1253.
7. Matulonis UA, Sood AK, Fallowfield L, Howitt BE, Sehouli J, Karlan BY. Ovarian cancer. *Nat Rev Dis Primers.* 2016;2:16061.
8. Lisio MA, Fu L, Goyeneche A, Gao ZH, Telleria C. High-grade serous ovarian cancer: basic sciences, clinical and therapeutic standpoints. *Int J Mol Sci.* 2019;20(4):952.