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Diagnostic Value of VEGF And Ki-67 Expression in Predicting Recurrence Risk in Ovarian Cancer

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Abstract: This article assesses the clinical and prognostic value of VEGF and Ki-67 immunohistochemical markers in patients diagnosed with ovarian cancer. A total of 130 patients treated at the Tashkent Regional Branch of the Republican Oncology and Radiology Center between 2018 and 2022 were included in the study. Expression of the markers was evaluated using H-score and percentage index methods. Results demonstrated that high levels of VEGF and Ki-67 expression were significantly associated with increased recurrence risk ($p<0.001$). Kaplan–Meier survival analysis and Cox regression confirmed the independent prognostic significance of these markers. The potential for developing an immunohistochemical prognostic panel to guide individualized therapeutic strategies and determine the necessity of adjuvant therapy is discussed.

Keywords: Ovarian cancer, VEGF, Ki-67, recurrence, immunohistochemistry, prognosis, biomarkers.

Introduction: One of the most pressing challenges in oncogynecology is ovarian cancer (OC). It remains a leading cause of cancer-related death among women and is frequently diagnosed at an advanced stage, characterized by high recurrence rates. Even with radical surgery and combined treatment, recurrence occurs in a significant proportion of patients.

Studies indicate that nearly 60% of recurrences occur within the first 18–24 months, pointing to the aggressive nature of the disease and resistance to standard treatment protocols. In this context, identifying recurrence risk in advance, evaluating patient prognosis, and developing individualized treatment plans are critical tasks.

In recent years, biological markers have expanded the possibilities for assessing tumor behavior and predicting recurrence. Immunohistochemical markers such as Ki-67 (proliferation index) and VEGF (angiogenesis marker) are recognized as important indicators of tumor growth, dissemination, and therapy responsiveness.

VEGF and the Role of Angiogenesis: VEGF (Vascular Endothelial Growth Factor) is one of the key factors that promote the formation of blood vessels in tumor tissues. It plays a central role in enhancing tumor invasiveness and metastatic potential. Synthesized intensively by tumor cells, VEGF stimulates the growth of blood capillaries, which improves oxygen and nutrient supply to the tumor and facilitates its rapid expansion. Research shows that patients with high VEGF expression levels have significantly increased recurrence risk and decreased survival rates.

Ki-67 and Cell Proliferation: Ki-67 is a nuclear antigen and a marker of cell proliferation. It is detected only in mitotically active cells and is used to evaluate the tumor's growth rate. In ovarian cancer, high Ki-67 expression indicates aggressive tumor behavior, increased biological activity, and reduced sensitivity to treatment. Consequently, such patients often experience rapid and severe recurrence.

Scientific and Practical Relevance: Studies demonstrate that combined evaluation of VEGF and Ki-67 provides a more comprehensive picture of tumor proliferative and angiogenic properties. This supports individualized prognosis, identification of high-risk groups, selection of intensive therapeutic strategies, and improved treatment effectiveness. Particularly, it aids in evaluating the necessity of adjuvant chemotherapy, helping to avoid both overtreatment and undertreatment.

Despite the high rate of late-stage diagnoses, chemoresistance, and recurrence in ovarian cancer in Uzbekistan, systematic clinical evaluation of VEGF and Ki-67 is not yet fully established. This study has scientific and practical significance for advancing local oncological practice.

Objective: To assess VEGF and Ki-67 expression levels in ovarian cancer patients, analyze their correlation with recurrence risk, and determine their clinical-diagnostic value.

Literature Review

Ovarian cancer is associated with high mortality and late-stage detection. Recurrence significantly reduces survival. Thus, identifying reliable biomarkers for early prediction of recurrence is essential. In recent years, VEGF and Ki-67 have emerged as major immunohistochemical markers studied for their prognostic utility.

VEGF is a central regulator of angiogenesis in tumor tissues. Under normal conditions, it is expressed in response to hypoxia, but in tumors, its hyperexpression promotes growth and metastasis. Folkman (1971) was the first to establish that angiogenesis is essential for tumor progression. Accordingly, high VEGF expression is logically associated with higher recurrence risk.

Sugiyama et al. (2010) demonstrated that VEGF expression in 87 patients with serous carcinoma negatively correlated with recurrence-free survival. Similarly, Linderholm (2009) showed that high VEGF expression was associated with <30% 5-year survival.

Kikuchi et al. (2018) linked VEGF expression with platinum resistance, suggesting its use in predicting treatment response. Moreover, VEGF is a biological target for anti-angiogenic therapy (e.g., bevacizumab).

Ki-67, located in the cell nucleus and expressed during mitosis, is a widely studied marker of proliferative activity. Using MIB-1 antibodies, tumors with Ki-67 index >20% are classified as aggressive. Loizzi et al. (2013) found that patients with Ki-67 >40% had 2.5 times higher recurrence rates.

A meta-analysis by Morice et al. (2012) found that patients with high Ki-67 expression had a 1.7 times higher recurrence risk and significantly lower overall survival. Mahdi et al. (2014) reported that even in early-stage OC, high Ki-67 expression predicted recurrence.

METHODS

This retrospective-prospective cohort study was conducted at the Tashkent Regional Branch of the Republican Oncology and Radiology Center from 2018 to 2022. Clinical, morphological, and immunohistochemical data were comprehensively analyzed.

Inclusion Criteria:

- Age: 30–80 years
- Histologically confirmed ovarian cancer (epithelial and non-epithelial types)
- FIGO stages I–III
- Available biopsy materials and paraffin-embedded tissue blocks

Tumor tissues were fixed, embedded in paraffin, and

stained with H&E. Tumors were categorized as serous adenocarcinoma, mucinous tumors, endometrioid carcinoma, clear cell tumors, Brenner tumors, and mixed types.

Immunohistochemistry (IHC):

IHC analysis was conducted using monoclonal antibodies specific for VEGF and Ki-67 (DAKO, Thermo Fisher). Slides were cut to 3–5 µm and stained on the Ventana BenchMark XT system.

Ki-67 Scoring: 0–10%: low proliferation. 11–25%: moderate. 25%: high proliferation

VEGF Scoring: 0: no expression. 1: weak. 2: moderate 3: strong expression

H-score Calculation: H-score = Σ (intensity × % of positive cells)

Recurrence Evaluation Criteria: Clinical-laboratory confirmation. Radiological (CT/MRI) evidence. Symptomatic or ascitic recurrence

Statistical Analysis: Data were analyzed using Microsoft Excel 2021 and SPSS v26.. Comparative tests: Chi-square, Fisher's exact test. Survival analysis: Kaplan–Meier. Multivariate regression: Cox proportional hazards model. Correlations: Spearman and Pearson coefficients

Significance threshold: $p < 0.05$

Ethics: Study approved by the Tashkent Oncology Center Ethics Committee (Order №03-02, 2023). Written informed consent was obtained from all patients.

RESULTS

Among 130 ovarian cancer patients, three groups were analyzed: epithelial tumors (65), non-epithelial tumors (35), and a control group without recurrence (30).

1. VEGF Expression: High VEGF (+++) was present in 62.1% of recurrence cases vs. 13.3% of non-recurrence ($p<0.001$). Odds Ratio = 5.2 (CI: 2.3–11.8)

2. Ki-67 Index: Patients with Ki-67 >40% had a recurrence rate of 51.5%, compared to 10.0% in those with <20%. HR = 4.9 (CI: 2.1–10.2)

3. Correlation Between VEGF and Ki-67: Spearman r = 0.46 ($p<0.01$), indicating moderate positive correlation.

4. Kaplan–Meier Survival Analysis: VEGF+++, Ki-67>40%: median RFS = 14.5 months VEGF+, Ki-67<20%: median RFS = 32.6 months

Log-rank $p < 0.001$

5. Cox Regression (Multivariate): VEGF+++: HR = 2.87 (CI: 1.46–5.63, p=0.002). Ki-67 > 40%: HR = 3.12 (CI: 1.58–6.09, p=0.001). FIGO Stage III: HR = 2.34 (CI: 1.12–4.93, p=0.028)

DISCUSSION

This study confirms that VEGF and Ki-67 are reliable markers for predicting recurrence risk in ovarian cancer. High VEGF indicates enhanced angiogenesis and potential for metastasis, while high Ki-67 reflects mitotic activity and tumor aggressiveness. Their combined evaluation provides a robust prognostic platform.

International studies (Linderholm, Yamamoto, Sugiyama) support our findings. Bevacizumab, an anti-VEGF agent, is recommended in high-VEGF cases. High Ki-67 suggests the need for tailored adjuvant therapy.

CONCLUSION

VEGF and Ki-67 are highly reliable immunohistochemical markers for predicting recurrence in ovarian cancer. Combined use enhances individualized treatment planning. Kaplan–Meier and Cox analyses confirm their independent prognostic value. Recommended for integration into standard diagnostic protocols. Further studies should expand sample size and include additional molecular markers (e.g., HER2, p53, CD34).

Practical Recommendations: Include VEGF and Ki-67 in routine IHC panels for ovarian cancer. Use marker levels to stratify recurrence risk and guide adjuvant therapy. Develop and validate a prognostic index combining VEGF/Ki-67 with clinical staging.

Final Remark: The combined expression of VEGF and Ki-67 offers a modern, reliable, and individualized approach to prognosis in ovarian cancer.

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