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# IMMUNE AND ANGIOGENIC COMPONENTS OF THE TUMOR MICROENVIRONMENT IN DISSEMINATED OVARIAN CANCER: PROGNOSTIC AND THERAPEUTIC IMPLICATIONS

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**Abstract**

**Background** The tumor microenvironment (TME) plays a decisive role in the progression of epithelial ovarian cancer (EOC). Immunosuppressive cells and pro-angiogenic factors such as tumor-associated macrophages (TAMs), VEGF, and PD-L1 contribute to metastasis, chemoresistance, and poor prognosis. A better understanding of these interactions is essential for developing targeted therapies. **Aim.** To assess the role of immune cells ($CD4^+$, $CD8^+$, $CD68^+$) and angiogenesis regulators (VEGF, CD31, HIF-1α) in the TME of advanced-stage ovarian cancer and their impact on disease progression and survival. **Methods.** A cohort of 135 women with stage IIIA–IV EOC treated between 2020–2025 was analyzed. Tumor and metastatic lesions were examined via immunohistochemistry for CD4, CD8, CD68, VEGF, CD31, HIF-1α, and PD-L1. Quantitative assessment of immune infiltration and angiogenesis markers was performed, followed by correlation with hypoxia and clinical outcomes using Kaplan–Meier and Cox proportional hazards models. **Results.** $CD4^+$ and $CD8^+$ T-cells were significantly reduced in hypoxic tumor zones (HIF-1α↑), particularly in high-grade tumors. $CD68^+$ TAM density was elevated in necrotic, VEGF-rich regions, correlating with aggressive tumor behavior. High PD-L1 expression was associated with T-cell exhaustion and reduced overall survival ($p < 0.05$). Combined high VEGF + PD-L1 expression independently predicted poor survival (median OS: 12 months vs. 28 months, $p < 0.01$).

**Conclusions.** The co-existence of angiogenesis and immunosuppression within the TME defines an aggressive phenotype in ovarian cancer. Immuno-angiogenic

profiling offers predictive value and therapeutic guidance, supporting the integration of anti-VEGF and immune checkpoint inhibitors in clinical practice.

**Keywords:** Ovarian cancer, tumor microenvironment, angiogenesis, immune escape, VEGF, PD-L1, $CD8^+$ T-cells, macrophages.

## Introduction

Epithelial ovarian cancer (EOC) remains one of the most lethal gynecologic malignancies, largely due to late diagnosis, peritoneal dissemination, and resistance to platinum-based chemotherapy. Despite advances in cytoreductive surgery and systemic therapy, the five-year survival rate for patients with advanced disease remains below 30%. In recent years, attention has shifted toward the tumor microenvironment (TME), which is increasingly recognized as a decisive factor in tumor progression. The TME consists of immune cells, stromal cells, endothelial cells, cytokines, and extracellular matrix components. Interactions within this ecosystem strongly influence angiogenesis, immune evasion, and therapy resistance. Key players include: Tumor-associated macrophages (TAMs, $CD68^+$) – often polarized toward an immunosuppressive, pro-angiogenic M2 phenotype. VEGF and CD31 – critical regulators of neovascularization. HIF-1α – a marker of hypoxia driving angiogenesis and metabolic adaptation. PD-L1 – an immune checkpoint molecule that induces T-cell exhaustion and limits antitumor immunity. Understanding the balance between immune infiltration and angiogenesis in EOC may identify prognostic markers and open new therapeutic opportunities, particularly for combined immunotherapy and anti-angiogenic treatment.

**Materials and Methods** This retrospective-prospective study included 135 women aged 38–74 years with stage IIIA–IV epithelial ovarian cancer treated at the Samarkand Branch of the Republican Specialized Scientific and Practical Medical Center of Oncology and Radiology between 2020–2025. All patients underwent primary cytoreductive surgery followed by platinum-based chemotherapy. Tissue Collection and Processing Tumor tissue and metastatic lesions (omentum, peritoneum, lymph nodes) were formalin-fixed and paraffin-embedded. Sections

were stained by immunohistochemistry (IHC) for: CD4, CD8 (T-cell subsets), CD68 (macrophages), VEGF, CD31 (angiogenesis markers), HIF-1α (hypoxia), PD-L1 (immune checkpoint). IHC staining intensity and percentage of positive cells were semi-quantitatively scored. Tumor-infiltrating lymphocytes (TILs) and TAMs were counted per high-power field. VEGF and CD31 expression were quantified by microvessel density (MVD).

**Statistical Analysis**

Correlations between markers were assessed using Spearman's rank test. Survival outcomes were analyzed with Kaplan–Meier curves and log-rank tests. Cox regression identified independent prognostic factors. $p < 0.05$ was considered statistically significant.

**Results Immune Infiltration:** $CD4^+$ and $CD8^+$ T-cells were markedly reduced in hypoxic tumor zones (HIF-1α high areas), especially in high-grade serous carcinomas. $CD8^+/CD4^+$ ratio was significantly lower in patients with poor outcomes ($p < 0.01$). Tumor-Associated Macrophages $CD68^+$ TAM density was significantly elevated in necrotic and VEGF-rich tumor areas.TAM infiltration correlated with advanced FIGO stage, high ascites volume, and shorter progression-free survival. Angiogenesis and Hypoxia VEGF and CD31 expression were upregulated in high-grade tumors and peritoneal implants. Hypoxia marker HIF-1α strongly correlated with VEGF expression ($r = 0.62$, $p < 0.001$).Immune Checkpoint Expression PD-L1 positivity (>5% tumor cells) was observed in 46% of cases. PD-L1 expression was associated with reduced $CD8^+$ T-cell infiltration and evidence of T-cell exhaustion.

**Survival Analysis** Patients with high VEGF + PD-L1 expression had a median overall survival (OS) of 12 months, compared with 28 months in patients with low expression ($p < 0.01$). Multivariate Cox analysis confirmed VEGF, PD-L1, and $CD8^+$ TIL density as independent prognostic markers.

**Discussion**

This study highlights the dual role of the TME in advanced ovarian cancer:

1. **Angiogenesis** – Hypoxia-driven VEGF overexpression promotes neovascularization but creates abnormal, leaky vasculature that facilitates peritoneal spread and chemotherapy resistance.
2. **Immune suppression** – TAM accumulation and PD-L1–mediated T-cell exhaustion prevent effective immune clearance of tumor cells.

The simultaneous presence of these mechanisms defines an "immuno-angiogenic phenotype" associated with aggressive disease biology. Importantly, our data support the rationale for combined anti-angiogenic and immune checkpoint blockade therapies. Clinical trials with bevacizumab (anti-VEGF) plus PD-1/PD-L1 inhibitors (e.g., nivolumab, atezolizumab) are ongoing and could provide significant benefit in this subgroup of patients.

**Conclusions**

Disseminated ovarian cancer is characterized by a synergistic interplay of angiogenesis and immune evasion. High VEGF + PD-L1 expression is an independent predictor of poor survival. $CD8^+$ T-cell density remains a favorable prognostic factor, but its effect is diminished in hypoxic, immunosuppressive microenvironments. Immuno-angiogenic profiling should be integrated into patient stratification and may guide personalized therapy. Combined approaches targeting VEGF and immune checkpoints hold promise for improving outcomes in advanced ovarian cancer.

**Clinical Implications** Routine testing of PD-L1, VEGF, and $CD8^+$ TILs in ovarian cancer biopsies can enhance risk stratification. Bevacizumab + immune checkpoint inhibitors may be particularly effective in patients with immuno-angiogenic phenotype.Further clinical trials are justified to validate these findings and optimize treatment sequencing.