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Mechanisms of Lymphatic Metastasis and Immune Microenvironment Regulation in Ovarian Cancer: From Molecular Mechanisms to Precision Lympho-Immune Surgery

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ABSTRACT

Ovarian cancer is a highly prevalent and lethal malignancy in women, with lymphatic metastasis representing one of the key determinants of patient prognosis. In recent years, advances in molecular biology and immunology have gradually unveiled the multifaceted mechanisms underlying lymphatic dissemination in ovarian cancer, including tumor cell invasiveness, lymphangiogenesis, and the dynamic regulation by immune cells within the tumor microenvironment (TME). The complex interplay among various immune cells not only influences metastatic potential but also provides potential therapeutic targets. Meanwhile, the rise of precision lympho-immune surgery has provided novel strategies for the accurate identification and resection of sentinel or metastasized lymph nodes, offering hope for improved clinical outcomes. This review systematically summarizes the molecular mechanisms of ovarian cancer lymphatic metastasis and its association with the immune microenvironment, with a special focus on advances in precision lympho-immune surgical practice, aiming to provide theoretical and technical support for the development of individualized therapeutic strategies in ovarian cancer.

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1. Introduction

Ovarian cancer is one of the most common and lethal malignancies in women, particularly high-grade serous ovarian cancer (HGSOC), whose pronounced invasiveness and metastatic potential make it a major challenge in clinical management [1, 2]. Traditionally, ovarian cancer was thought to metastasize primarily through peritoneal dissemination; however, recent studies on lymphatic spread have revealed that the lymphatic system plays an important role in tumor progression and metastasis [2, 3]. The mechanisms of lymphatic dissemination in ovarian cancer are complex, involving multiple molecular and cellular processes such as the interactions between tumor cells and lymphatic endothelial cells (LECs), tumor-associated macrophage (TAM)-mediated immune regulation, and lymphangiogenesis [3, 4].

Within the tumor immune microenvironment, the composition and functional state of immune cells directly influence tumor initiation, progression, and dissemination. TAMs, as major immune cells in the tumor microenvironment, display considerable heterogeneity, and their polarization state determines whether they exert tumor-promoting or tumor-suppressive effects [4]. Evidence shows that, in ovarian cancer, TAMs not only support tumor cell growth and invasion but also regulate lymphangiogenesis and enhance immunosuppression, thereby facilitating tumor cell spread through the lymphatic system [3, 5]. Moreover, interactions between lymphatic ves-

sels and TAMs may give rise to "macphatics", a macrophage subset expressing lymphatic markers, which may play a potentially important role in lymphatic metastasis and tumor microenvironment remodeling [6].

Notably, recent insights into ovarian cancer origins suggest that most HGSOCs arise from epithelial cells at the distal fallopian tube. This discovery provides a new perspective for understanding early tumorigenesis and metastasis, with profound implications for prevention and early diagnosis strategies [7, 8]. At the same time, genetic mutations, particularly inactivation of breast cancer gene 1/2 (BRCA1/2), play critical roles in regulating DNA repair, shaping the immune microenvironment, and enhancing metastatic capacity, thereby becoming essential targets for precision therapy [9, 10].

In summary, lymphatic metastasis in ovarian cancer is not only a key step in tumor progression but also an important determinant of prognosis. The tumor immune microenvironment, especially the complex interactions between TAMs and the lymphatic system, profoundly affects tumor dissemination and immune evasion. Elucidating these molecular mechanisms and immune regulatory networks will help develop more effective precision lympho-immune therapeutic strategies and improve clinical outcomes for patients with ovarian cancer [2-4].

2. Main Body

2.1 Mechanisms of Lymphatic Metastasis in Ovarian Cancer

2.1.1 Structure and Function of Lymphatic Vessels

Lymphatic vessels are key structures of the lymphatic system, responsible for tissue fluid recovery, antigen transport, and the maintenance of immune homeostasis. In ovarian tissue, the structural features of lymphatic vessels and their roles in tumor dissemination are of particular significance. Lymphatic vessels are divided into initial lymphatics and collecting lymphatics. The former possesses "button-like" endothelial junctions with high permeability, allowing interstitial fluid, cells, and macromolecules to enter; the latter have "zipper-like" endothelial junctions, characterized by low permeability and valves that prevent lymphatic reflux, thereby ensuring unidirectional lymph flow.

Within the tumor microenvironment (TME), lymphatic vessels not only serve as conduits for tumor cell dissemination but also regulate the migration and activation of immune cells, thereby influencing local immune responses. Tumor-associated lymphatics frequently undergo structural remodeling, such as vessel dilation, endothelial cell proliferation, and altered expression of junctional molecules, which facilitate the entry of tumor cells into the lymphatic circulation. Furthermore, inflammatory cytokines and growth factors within the TME, especially vascular endothelial growth factor C (VEGF-C) and vascular endothelial growth factor D (VEGF-D), acting through the vascular endothelial growth factor receptor 3 (VEGFR-3) signaling pathway, induce lymphangiogenesis and functional changes, further promoting lymphatic metastasis [11-13].

The structural integrity and function of lymphatic vessels are essential for immune cell trafficking. Lymphoendothelial cells (LECs) not only provide a physical barrier but also secrete chemokines, such as C-C motif chemokine ligand 21 (CCL21), to guide dendritic cells and lymphocytes, facilitating antigen delivery to draining lymph nodes and initiating adaptive immune responses. In the TME, lymphatic dysfunction, manifested as endothelial apoptosis, senescence, and aberrant junctional molecule expression, results in impaired lymphatic drainage and exacerbated local inflammation, thereby creating an immunosuppressive milieu that favors tumor immune escape [13-15].

Modern imaging technologies, such as multiphoton microscopy and near-infrared (NIR) lymphography, have provided powerful tools for observing lymphatic structure and function. These approaches allow real-time, in vivo visualization of dynamic changes in lymphatic vessels, including contraction rhythms, valve activity, and lymph flow direction, thereby enhancing our understanding of the roles of lymphatics in tumor metastasis and immune regulation [16, 17].

In addition, the mechanical properties of lymphatic vessels, such as shear stress, exert profound effects on the biological functions of LECs. Mechanical signals regulate vessel expansion and contraction through molecular mechanisms, maintaining lymphatic fluid homeostasis. In the TME, altered mechanical forces may impair lymphatic function and thereby facilitate tumor lymphatic dissemination [18].

Collectively, the lymphatic vasculature of the ovary exhibits layered specificity and high dynamism. Acting both as conduits for cell migration and hubs of immune regulation, lymphatic vessels play a critical role in tumor metastasis. Their structural remodeling, functional abnormalities, and interactions with immune cells constitute the molecular and cellular basis of lymphatic metastasis, providing essential theoretical support for precision lympho-immune surgery.

2.1.2 Molecular Mechanisms

The molecular mechanisms of lymphatic metastasis in ovarian cancer involve multiple key signaling pathways and regulatory molecules (Figure 1). These mechanisms not only promote tumor cell migration and invasion but also reshape the tumor microenvironment, thereby accelerating the formation of lymphatic dissemination. Based on recent literature, this section focuses on molecular signaling pathways closely associated with lymphatic metastasis, such as lymphatic vessel endothelial hyaluronan receptor 1 (LYVE-1) and VEGF-C, as well as the interactions between tumor cells and lymphatic endothelial cells.

Lymphangiogenesis is a prerequisite for lymphatic metastasis. VEGF-C, a pivotal regulator of lymphangiogenesis, is markedly upregulated in ovarian cancer. By binding to its receptor VEGFR-3, VEGF-C promotes the proliferation and migration of LECs, leading to the formation of new lymphatic networks that provide conduits for tumor cells to enter the lymphatic system. Clinical studies have revealed that high VEGF-C expression is closely associated with lymph node metastasis in ovarian cancer patients and is predictive of poor prognosis [3]. In addition, angiopoietin-2 (Ang-2), another lymphangiogenic factor, plays a role in lymphatic activation. Ang-2 expression in ovarian tumor tissue is significantly correlated with retroperitoneal metastasis, and patients with high expression respond more favorably to anti-angiogenic therapy with bevacizumab, suggesting its potential as a molecular biomarker for lymphatic metastasis [19].

Interactions between LECs and tumor cells are critical for lymphatic dissemination. Tumor cells secrete various factors, such as matrix metalloproteinases (MMPs) and transforming growth factor-β (TGF-β), which activate LECs and increase vessel permeability, thereby facilitating transendothelial migration. Activated stroma, particularly cancer-associated fibroblasts (CAFs), further supports lymphatic metastasis. Analyses of TCGA datasets have identified a set of lymphovascular space invasion (LVSI)-related gene signatures, including POSTN and FAP1, reflecting stromal activation that promotes lymphovascular dissemination [20]. Furthermore, epithelial-to-mesenchymal transition (EMT) enhances tumor cell motility and invasiveness by downregulating adhesion molecules such as E-cadherin and upregulating vimentin. The protein PARD6A regulates EMT *via* the integrin β1-ILK-SNAIL1 signaling axis, thereby enhancing ovarian cancer cell migration and lymphatic dissemination [21].

Cancer stem cells (CSCs) and circulating tumor cells (CTCs) also play critical roles in lymphatic spread. The presence of CTCs confirms the potential for long-distance dissemination through the blood and lymphatic systems. These cells often display high invasiveness and self-renewal capacity, acting as "seed" cells for metastasis [22]. Genetic mutations further contribute to this process. For instance, NOTCH1 mutations (e.g., NOTCH1-p.C702fs) significantly enhance ovarian cancer cell migration and invasion, promoting lymph node metastasis. Importantly, this effect can be suppressed by NOTCH inhibitors, indicating that the NOTCH signaling pathway represents a promising therapeutic target [23].

At the epigenetic level, aberrant methylation of specific long noncoding RNAs (lncRNAs) is closely linked to lymphatic metastasis in ovarian cancer. For example, hypermethylation of sHAND2-AS1 is strongly associated with lymph node metastasis. These lncRNAs promote EMT and stromal remodeling, thereby facilitating lymphatic spread [24]. Similarly, MEOX1 is highly expressed in ovarian cancer tissues, where it regulates lymphangiogenesis, EMT, and extracellular matrix degradation. Its overexpression is associated with poor clinical prognosis [25].

In summary, lymphatic metastasis in ovarian cancer results from multilayered and synergistic molecular mechanisms. Factors such as VEGF-C and Ang-2 drive lymphangiogenesis and vessel activation; tumor cell–LEC and stromal interactions enhance lymphatic invasion; EMT and specific genetic and epigenetic regulators further potentiate tumor dissemination. In-depth investigation of these key molecules and pathways is expected to provide novel strategies for precise diagnosis and targeted therapy of lymphatic metastasis in ovarian cancer.

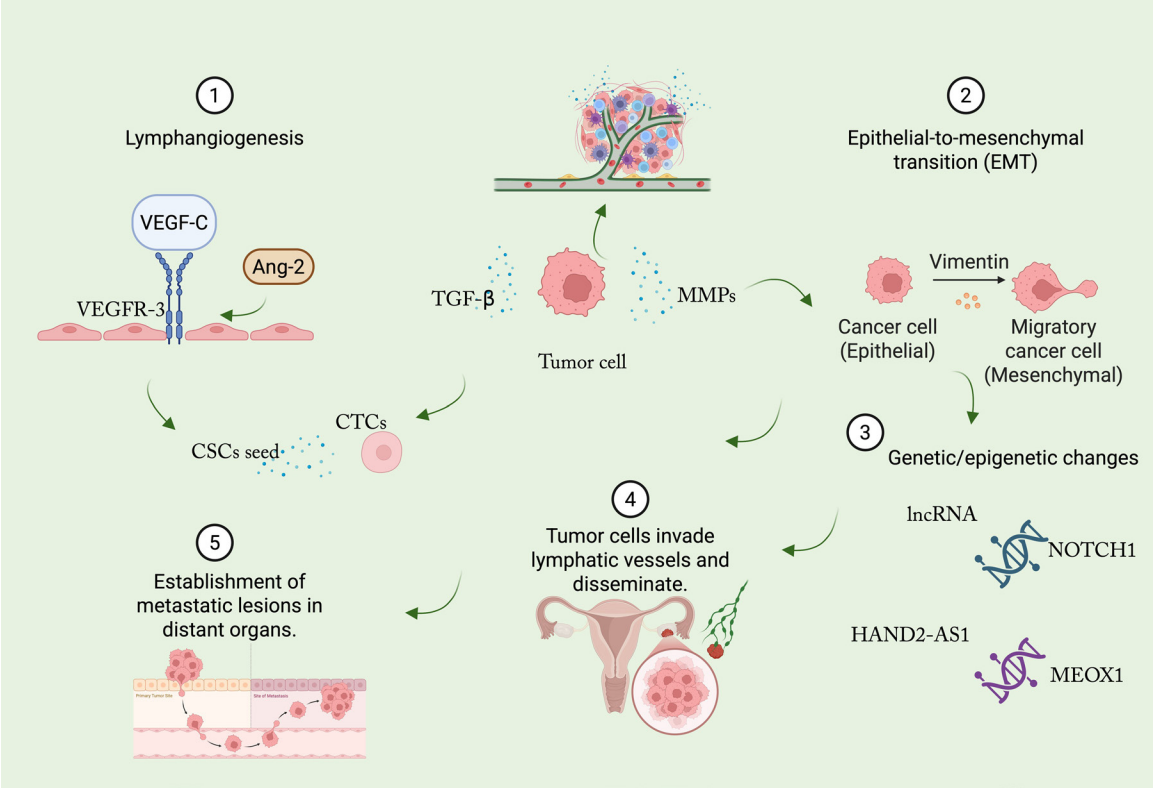

Figure 1. Molecular mechanisms of lymphatic metastasis in ovarian cancer.

2.1.3 Immune Microenvironment Changes

The composition and function of immune cells within the tumor microenvironment (TME) play a pivotal role in the initiation, progression, and lymphatic metastasis of ovarian cancer. Among these, the polarization status and functional alterations of tumor-associated macrophages (TAMs) represent one of the key determinants of the balance between immune suppression and immune activation. TAMs are highly heterogeneous, comprising both tissue-resident macrophages and newly recruited monocytes, and can be polarized toward either a pro-inflammatory M1 phenotype or an immunosuppressive M2 phenotype. Most studies indicate that TAMs in ovarian cancer are predominantly M2-polarized, thereby promoting tumor growth, invasion, and immune escape, and serving as major contributors to the immunosuppressive microenvironment. For example, studies have demonstrated that the absence of transglutaminase 2 (TG2) in the TME reduces the frequency of immunosuppressive M2 TAMs while increasing the proportions of T cells, NK cells, and B cells, suggesting that TG2-regulated TAM polarization is closely related to immune evasion [26]. In addition, ovarian cancer cells secrete high levels of HE4 protein, which enhances the recruitment and polarization of M2 macrophages, strengthens immunosuppression, and upregulates PD-L1 expression, thereby inhibiting cytotoxic T cell activity and further exacerbating local immunosuppression [27]. The remodeling of TAMs not only affects tumor immune escape but also indirectly facilitates the establishment and progression of lymphatic metastasis.

Among immunosuppressive factors, B7-H4 plays a critical role as an immune checkpoint molecule in ovarian cancer lymphatic metastasis. Elevated levels of soluble B7-H4 (sB7-H4) in patient plasma are closely associated with advanced disease, poor surgical outcomes, lymphatic metastasis, and platinum resistance. Furthermore, when combined with traditional biomarkers CA125 and HE4, sB7-H4 significantly improves the diagnostic accuracy of ovarian cancer [28]. Mechanistically, B7-H4 inhibits T-cell activation and promotes immune escape, providing a key molecular basis for immunosuppression within the TME. The complexity of this microenvironment also manifests through the synergistic action of multiple immune checkpoint molecules. For example, PD-L1, IDO, CTLA-4, LAG-3, and TIGIT are all upregulated in recurrent ovarian cancer, reflecting enhanced adaptive immune tolerance [29].

During recurrence, the ovarian cancer immune

microenvironment undergoes significant remodeling, with notable increases in $CD8^+$ T cells and PD-L1 expression. These dynamic changes in immune status suggest potential therapeutic targets for immunotherapy [30, 31]. Moreover, metabolic reprogramming, particularly lipid metabolism, within the TME further affects immune cell functions, creating an immunosuppressive state that promotes tumor proliferation and metastasis [32]. Tumor-derived exosomes also contribute to immune suppression by inducing M2 polarization of macrophages and promoting the expansion and activity of regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs), thereby enabling tumor cells to evade immune surveillance [33].

Collectively, the immune microenvironment during ovarian cancer lymphatic metastasis is characterized by immune cell remodeling, particularly enhanced M2 polarization and functional reprogramming of TAMs, together with the elevated expression and activity of immunosuppressive factors such as B7-H4. This immunosuppressive niche not only suppresses cytotoxic immune responses but also facilitates tumor invasion and dissemination, providing fertile "soil" for lymphatic metastasis. Targeting TAM polarization and immunosuppressive molecules such as B7-H4 may represent promising strategies to improve the efficacy of immunotherapy and control lymphatic metastasis in ovarian cancer.

2.2 The Impact of the Immune Microenvironment on Ovarian Cancer Metastasis

2.2.1 Roles of Immune Cells

Immune cells play critical roles in regulating lymphatic metastasis and shaping the tumor microenvironment (TME) in ovarian cancer. Different immune cell types, including T cells, B cells, and macrophages, exert distinct functions and mechanisms of action, collectively contributing to the processes of tumor immune surveillance and immune evasion.

T cells, particularly $CD8^+$ cytotoxic T lymphocytes (CTLs), are central effectors of anti-tumor immunity. In high-grade serous ovarian cancer (HGSOC), the spatial distribution of $CD8^+$ T cells and their interactions with tumor cells have been found to be closely associated with patient prognosis. In HGSOC patients harboring BRCA1/2 mutations, both $CD8^+$ and $CD4^+$ T cells exhibit enhanced immunosurveillance and stronger anti-tumor immune responses, underscoring the critical role of T cells in this subtype [34, 35]. However, the ovarian cancer TME often induces T-cell dysfunction and exhaustion. The upregulation of immune checkpoint molecules such as programmed cell death protein 1 (PD-1) and CTLA-4 reduces T-cell activity, thereby facilitating tumor progression [36, 37]. Moreover, regulatory T cells (Tregs) suppress effector T-cell function and promote immune escape. Studies have shown that T cell immunoreceptor with Ig and ITIM domains $(TIGIT)^+/CD4^+$/Tregs enhance PD-1 expression on $CD8^+$ T cells, thereby supporting tumor growth. Therapeutic strategies targeting TIGIT may help alleviate this immunosuppressive state [38, 39].

B cells and their associated markers, such as marginal zone B and B1 cell-specific protein (MZB1), also play important roles in the ovarian cancer immune microenvironment. High MZB1 expression correlates with increased immune cell infiltration, reduced proliferation and migration of ovarian cancer cells, and favorable clinical outcomes, indicating its potential as a regulator of anti-tumor immunity [40]. Conversely, B-cell dysfunction may impair immune responses, making B cells a potential therapeutic target in future immunotherapy.

Macrophages, particularly tumor-associated macrophages (TAMs), represent one of the most abundant immune cell populations within the TME and exhibit high phenotypic and functional heterogeneity. TAMs can be reprogrammed by the TME toward an immunosuppressive M2 phenotype, thereby supporting tumor growth, invasion, and lymphatic metastasis [4, 41]. For instance, ALKBH5 has been shown to promote M2 polarization, contributing to an immunosuppressive TME, with high ALKBH5 expression correlating with poor prognosis [41]. Additionally, infiltration of leukocyte immunoglobulin-like receptor subfamily B member 1 $(LILRB1)^+$ immune cells has been strongly associated with M2 macrophages, implicating their role in immune tolerance and $CD8^+$ T-cell dysfunction [42]. The spatial distribution and polarization state of TAMs significantly influence tumor progression and treatment response, making them an important target for immunomodulatory strategies.

Dysfunction of immune cells is another major factor contributing to ovarian cancer progression. Aberrant expression of microRNAs (miRNAs) regulates immune cell function and crosstalk within the TME, leading to immunosuppression and tumor immune evasion [43]. Moreover, tumor-secreted factors such as PDZD11 and pituitary tumor-transforming

gene 1 interacting protein (PTTG1IP), also known as pituitary tumor-transforming gene-binding factor (PBF), have been shown to influence immune infiltration, immune checkpoint expression, and immune cell activity, serving as potential diagnostic and prognostic biomarkers [37, 44]. Cancer stem cells (CSCs) further modulate immune responses by suppressing effector immune cells, thereby enhancing tumor heterogeneity, immune evasion, and therapeutic resistance [45, 46].

In summary, the diversity and functional state of immune cells directly influence ovarian cancer progression and metastasis. Through complex signaling networks, T cells, B cells, and macrophages interact within the TME to regulate tumor immunity. Dysfunction of these immune cells promotes tumor immune evasion and lymphatic dissemination. A deeper understanding of the molecular mechanisms governing immune cell regulation will provide a theoretical foundation and practical guidance for designing precision immunotherapies and improving the prognosis of patients with ovarian cancer [2, 4, 47].

2.2.2 Immunosuppressive Mechanisms

Immunosuppressive mechanisms within the tumor microenvironment (TME) are key factors influencing the efficacy of immunotherapy in ovarian cancer. Tumor-associated macrophages (TAMs) play a complex and dual role in tumor immune regulation. On the one hand, TAMs promote immunosuppression in the TME, impair effector immune cell functions, and facilitate tumor progression; on the other hand, under certain conditions, TAMs may also support anti-tumor immunity. In ovarian cancer, M2-polarized TAMs are the primary executors of immunosuppression. They secrete inhibitory cytokines, modulate immune checkpoint expression, and influence the recruitment and function of other immune cells, thereby creating an immunosuppressive milieu that fosters tumor growth and metastasis [48, 49].

Specifically, the immunosuppressive effects of TAMs manifest in several ways. First, cytokines such as interleukin-10 (IL-10) and transforming growth factor beta (TGF-β) secreted by TAMs inhibit the activity of $CD8^+$ T cells and natural killer (NK) cells, reducing their cytotoxic capacity against tumor cells [50]. Second, TAMs express checkpoint ligands such as PD-L1 and CD155, which directly suppress T-cell effector functions and promote immune escape [51]. Additionally, tumor cells and cancer-associated fibroblasts (CAFs) secrete molecules such as Activin A and prostacyclin (PGI2), which promote TAM polarization toward the M2 phenotype, further enhancing their immunosuppressive activity [52, 53].

The TME also profoundly regulates immune cell recruitment and function. In ovarian cancer, tumor and stromal cells secrete chemokines such as C-C motif chemokine ligand 2 (CCL2) and C-C motif chemokine ligand 22 (CCL22), which recruit monocytes and regulatory T cells (Tregs) into the tumor region, thereby forming an immunosuppressive network [54, 55]. Furthermore, metabolic reprogramming within the TME, such as lactate accumulation resulting from enhanced glycolysis, alters immune cell metabolism and suppresses anti-tumor activity [56, 57]. Elevated lactate concentrations further promote immunosuppression by inducing programmed death-ligand 1 (PD-L1) expression and modulating macrophage polarization [58].

With respect to immune cell functionality, tumor-infiltrating lymphocytes (TILs) are often present but functionally impaired. Studies have shown that T cells at metastatic ovarian cancer sites exhibit diminished effector activity, and checkpoint blockade alone cannot fully restore their function [48]. Myeloid-derived suppressor cells (MDSCs), which are abundant in the ovarian cancer TME, further inhibit T-cell activity through metabolic pathways (e.g., glutamine metabolism) and cytokine signaling [59].

Tumors also exploit specific signaling pathways to achieve immune escape. For example, activation of the NLR family pyrin domain-containing 3 (NLRP3) inflammasome upregulates PD-L1 expression, thereby promoting immunosuppression [60]. RAD21 gene amplification suppresses interferon signaling by forming transcriptional repressor complexes, reducing immune activation [61]. TAM-specific molecules, such as high retinoblastoma (Rb) protein expression in M2 TAMs, are associated with poor prognosis in ovarian cancer. Mechanistically, Rb promotes immune suppression by inducing stress response and cell-death pathways in the TME [62, 63].

In addition, tumor regulation of immune cell recruitment alters not only their abundance but also their functional states. For instance, mucin 16 (MUC16) interacts with the sialic acid-binding immunoglobulin-like lectin 9 (Siglec-9) receptor on neutrophils, inducing an inflammatory and immunosuppressive phenotype, which results in the secretion of inflammatory mediators and inhibition of NK-cell cytotoxicity [64]. Tumor-secreted pigment epithelium-derived factor (PEDF) promotes infil-

tration of IL-10–producing $CD206^+$ macrophages, thereby establishing an immunosuppressive environment conducive to tumor dissemination [50]. Similarly, tumor-derived ubiquitin protein ligase E3 component n-recognin 5 (UBR5) facilitates macrophage recruitment and activation, further supporting the establishment of an immunosuppressive TME [65].

Collectively, immunosuppressive mechanisms in the ovarian cancer TME are primarily mediated through M2 polarization of TAMs, checkpoint molecule expression, secretion of immunosuppressive cytokines, and metabolic reprogramming. The TME not only dictates the abundance and diversity of immune cells but also modulates their functional states, forming a complex immunosuppressive network that impedes effective anti-tumor responses. These findings provide a theoretical foundation for developing precision surgical and immunomodulatory strategies targeting TAMs and associated pathways. In the future, precise regulation of TAMs and the immune microenvironment may enhance the efficacy of immunotherapy and improve clinical outcomes in ovarian cancer [48, 49, 52].

2.3 Recent Advances

2.3.1 Emerging Biomarkers

In the diagnosis and prognostic evaluation of ovarian cancer, identification of biomarkers with high sensitivity and specificity is critical for improving early detection rates and guiding therapeutic strategies. In recent years, with the rapid development of high-throughput omics technologies, multiple emerging biomarkers have been identified, showing promising clinical applicability.

First, the immune checkpoint molecule soluble B7 homolog 4 (sB7-H4) has demonstrated significant value in the diagnosis and prognosis of epithelial ovarian cancer (EOC). Elevated plasma levels of sB7-H4 have been shown to be strongly associated with advanced disease stage, poor surgical outcomes, lymphatic metastasis, and platinum resistance. When combined with conventional markers such as CA125 and HE4, sB7-H4 significantly improves the diagnostic accuracy of EOC and provides new insights into disease progression and therapeutic response [28]. These findings underscore the role of sB7-H4 in immune evasion and highlight its potential as a therapeutic target.

In addition, molecules carried by circulating exosomes, such as circular RNA forkhead box P1 (circFoxp1), confer cisplatin resistance to ovarian cancer cells by regulating microRNA-22 (miR-22) and microRNA-150-3p (miR-150-3p), which in turn modulate the expression of CCAAT enhancer-binding protein γ (CEBPG) and formin-like protein 3 (FMNL3). Elevated levels of exosomal circFoxp1 in the blood not only correlate with disease progression but also represent potential diagnostic biomarkers and therapeutic targets [66]. This mechanism illustrates the role of noncoding RNAs in drug resistance and expands the scope of biomarker research.

Among protein biomarkers, NaPi2b, a sodium-dependent phosphate transporter highly expressed on the surface of ovarian cancer cells, has been identified as a promising marker. Antibody-drug conjugates (ADCs) targeting NaPi2b have demonstrated encouraging responses in early-phase clinical trials, suggesting that NaPi2b serves not only as a diagnostic marker but also as a therapeutic target with substantial potential [67]. Moreover, serum glycoproteins such as α1-antitrypsin (A1AT), α1-antichymotrypsin (AACT), and complement component 9 (CO9) have been identified as potential early diagnostic markers for high-grade serous ovarian cancer [68].

In the noncoding RNA domain, circulating miRNAs and long non-coding RNA (lncRNAs) provide powerful non-invasive tools for diagnosis. For example, OCaMIR, a diagnostic signature comprising multiple miRNAs, has been validated across cohorts, demonstrating high accuracy for early ovarian cancer detection and outperforming the conventional marker CA125 [69]. Likewise, lncRNA MYU promotes ovarian cancer cell proliferation by sponging miR-6827-5p to upregulate high mobility group AT-hook 1 (HMGA1) expression, indicating its potential role as both a prognostic biomarker and a therapeutic target [70].

Metabolomic studies have also identified novel biomarkers. Lipid metabolites, such as palmitoylcarnitine, are significantly elevated in pelvic fluid of ovarian cancer patients and are positively correlated with clinical stage, lymph node metastasis, and recurrence. Palmitoylcarnitine exhibits strong diagnostic performance, with an area under the curve (AUC) of 0.942 [71]. Additionally, metabolomic analyses have revealed widespread alterations in metabolic pathways, providing new perspectives on tumor immunology and treatment response [72].

Integrated multi-omics analyses have demonstrated that prognostic models based on glycolysis-related genes can effectively predict survival in ovarian cancer patients and correlate with immune cell infiltration in the TME, suggesting an important interplay between metabolism and immune regulation in disease progression [73].

Key immune-related molecules within the TME, such as programmed death zone protein 11 (PDZD11), pituitary tumor-transforming gene 1 interacting protein (PTTG1IP/PBF), and C-X3-C motif chemokine receptor 1 (CX3CR1), have also been linked to immune infiltration and prognosis in ovarian cancer, showing potential diagnostic and therapeutic value. For example, PDZD11 overexpression correlates with advanced tumor stage and co-expression of checkpoint molecules, suggesting its potential utility as an auxiliary biomarker in immunotherapy [44]. Similarly, high PTTG1IP expression is associated with immune infiltration and poor prognosis [37], while CX3CR1 expression positively correlates with immune cell infiltration and predicts unfavorable survival outcomes [74].

In summary, emerging biomarkers encompass a broad spectrum, including proteins, noncoding RNAs, exosomal components, metabolites, and immune-related molecules. These biomarkers not only enrich the diagnostic and prognostic toolkit for ovarian cancer but also provide molecular insights into lymphatic metastasis and immune regulation, thereby laying a strong biological foundation for precision lympho-immune surgical practice. Looking forward, the integration of multi-omics data and machine learning techniques is expected to uncover more efficient and specific biomarkers, driving progress in early detection and personalized treatment of ovarian cancer [25, 75].

2.3.2 Clinical Trials and Novel Therapeutics

In recent years, significant progress has been made in clinical trials and therapeutic strategies targeting lymphatic metastasis in ovarian cancer, with major advances focused on overcoming platinum resistance, applying immunotherapy in combination regimens, and developing novel targeted agents. Platinum-based chemotherapy has remained the standard of care for more than three decades; however, the emergence of platinum resistance poses a major challenge for patients with recurrent ovarian cancer, who typically experience poor outcomes. Thus, there is an urgent need for new treatment strategies. Although biological targeted agents represented by bevacizumab and poly (ADP-ribose) polymerase (PARP) inhibitors were initially approved in platinum-resistant settings, they are now primarily used in first-line or platinum-sensitive patients to extend platinum-free intervals and delay non-platinum treatment. Recent clinical trials have shown that, in platinum-resistant ovarian cancer, single-agent targeted therapy has not significantly improved progression-free survival (PFS) or overall survival (OS), but biomarker-driven individualized treatment strategies offer hope for future therapeutic approaches [76].

With respect to immunotherapy, immune checkpoint inhibitors (ICIs) have demonstrated efficacy in multiple solid tumors, achieving breakthroughs particularly in endometrial and cervical cancers, but their efficacy as monotherapy in ovarian cancer has been limited. Current clinical research is focusing on combining ICIs with conventional chemotherapy, PARP inhibitors, or anti-angiogenic drugs to enhance immune responses and overcome resistance. For instance, PARP inhibitors not only directly inhibit tumor DNA repair but also induce DNA damage, thereby increasing tumor antigen release and immune activation, making them ideal candidates for combination with ICIs [77]. In addition, the combination of anti-angiogenic therapy, such as bevacizumab, with PARP inhibitors has shown significant PFS benefit and favorable safety in newly diagnosed advanced ovarian cancer, providing a new frontline treatment option [78].

Emerging therapeutic approaches such as ADCs have also demonstrated promise in ovarian cancer. Mirvetuximab soravtansine, an ADC targeting folate receptor-α–positive platinum-resistant ovarian cancer, has received regulatory approval and shown favorable efficacy and tolerability in clinical trials. The rapid development of ADCs and the discovery of new targets suggest that future therapies will become more precise and diverse [79]. In addition, CAR-T cell therapy, a novel immunotherapeutic strategy, is still in its early stages in ovarian cancer, but clinical trials targeting tumor-associated antigens such as mesothelin, MUC16, and folate receptor alpha (FOLR1) are ongoing, with encouraging potential efficacy [80].

Histology-specific therapeutic strategies are also being actively explored. For example, low-grade serous ovarian carcinoma, which is relatively resistant to platinum and characterized by longer survival, is under investigation in clinical trials evaluating mitogen-activated protein kinase (MAPK) pathway in-

hibitors and cyclin-dependent kinase 4/6 (CDK4/6) inhibitors in combination with endocrine therapy to overcome chemotherapy resistance and prolong survival [81]. Furthermore, trials targeting rare histological subtypes, such as clear cell carcinoma, are evaluating new targeted agents such as phosphatidylinositol 3-kinase (PI3K) pathway inhibitors to improve outcomes [82].

Overall, clinical trials addressing lymphatic metastasis in ovarian cancer are shifting toward multi-target combination therapies and precision immunomodulation, emphasizing individualized treatment design based on patients' molecular profiles. With growing understanding of the TME, immune regulation, and resistance mechanisms, new therapies are expected to emerge that will further improve clinical outcomes. Clinical trial design is increasingly prioritizing biomarker integration and patient stratification to enhance therapeutic precision and efficacy [76, 77, 83].

The combination of immunotherapy with conventional treatments holds broad prospects. Although ICIs as monotherapy have limited efficacy, their combination with PARP inhibitors, anti-angiogenic drugs, and chemotherapy can enhance activation of the tumor immune microenvironment and strengthen anti-tumor immune responses. For example, defects in DNA damage repair increase tumor antigen load and enhance tumor immunogenicity, thereby potentiating the effects of immunotherapy [77]. Furthermore, novel immunotherapy modalities such as ADCs and chimeric antigen receptor T (CAR-T) cells, when combined with conventional therapies, may help overcome drug resistance and immunosuppression, ultimately increasing clinical benefit [79, 80]. Future studies should continue to focus on the safety of these combination strategies and the development of predictive biomarkers, thereby paving the way toward true precision lympho-immune surgical practice.

2.4 Applications in Precision Surgery

2.4.1 Preoperative Assessment and Individualized Therapy

In the clinical management of ovarian cancer, preoperative evaluation of lymphatic metastasis is crucial, as it directly affects surgical planning and patient prognosis (Figure 2). Because ovarian cancer often presents with occult symptoms at early stages, it is commonly diagnosed at an advanced stage with extensive dissemination, particularly involving lymph nodes. Accurate preoperative assessment facilitates tumor staging, determination of metastatic spread, and feasibility of surgical resection, thereby providing a scientific basis for individualized therapy.

Imaging evaluation represents the cornerstone of preoperative assessment. Techniques such as computed tomography (CT) and positron emission tomography/computed tomography (PET/CT) have shown high specificity and sensitivity in the evaluation of nodal status. A meta-analysis reported that PET/CT achieved a specificity of 0.96 and a sensitivity of 0.81 in detecting lymph node metastasis in ovarian cancer, outperforming CT, which demonstrated a specificity of 0.99 but a sensitivity of only 0.47. These findings suggest that PET/CT should serve as a standard auxiliary tool in assessing nodal metastasis, especially in advanced-stage patients [84]. In addition, fusion imaging technologies combining real-time ultrasound and CT can enhance diagnostic accuracy for peritoneal and nodal lesions, improve concordance with intraoperative findings, and provide surgeons with more precise lesion localization and resection strategies [85]. Ultrasound, as a preliminary tool for assessing tumor dissemination, has also been shown, when performed by experienced operators, to reliably predict resectability and assist in surgical planning [86].

Beyond imaging, the integration of biomarkers and immune microenvironment features offers new perspectives for individualized treatment. Serum tumor markers such as carbohydrate antigen 125 (CA125) and human epididymis protein 4 (HE4), along with inflammation-related indices like the lymphocyte-to-monocyte ratio (LMR), are closely associated with lymphatic metastasis and prognosis. Studies have shown that an LMR $\leq$ 3.8 and CA125 $>$ 34 U/mL are significantly correlated with shorter progression-free survival (PFS) and overall survival (OS). A combined index, COLC, integrating these parameters, demonstrated greater specificity in predicting mortality risk, suggesting its potential as a useful preoperative prognostic tool [87]. Moreover, radiomics-based multiparametric models incorporating clinical indices have been developed to efficiently predict the likelihood of complete cytoreduction (R0 resection) and nodal involvement in high-grade serous ovarian cancer (HGSOC), thereby supporting surgical decision-making and promoting individualized therapy [88].

Nutritional status assessment should also not be overlooked. Malnutrition is common among ovari-

an cancer patients and adversely impacts postoperative recovery and overall prognosis. A comparative study of body mass index (BMI), the Nutritional Risk Screening 2002 (NRS 2002), and the Prognostic Nutritional Index (PNI) revealed that PNI performed best in predicting 1-year mortality and recurrence, underscoring the importance of incorporating nutritional support into the preoperative evaluation system to optimize patient condition [89].

The immune microenvironment also provides valuable guidance for treatment responses. Preoperative immunohistochemistry (IHC) and proteomic profiling can identify the distribution of tumor-infiltrating lymphocytes (TILs), such as $CD8^+$ T cells and regulatory T cells, as well as macrophages. These immune signatures can be integrated into prognostic models to predict immunotherapy response and support the development of precision immuno-surgical approaches [90, 91]. In addition, immune risk models constructed using machine learning algorithms can more accurately reflect the TME, stratify patients by prognostic risk, and guide individualized immunotherapy regimens [92].

Taken together, individualized treatment planning should comprehensively incorporate tumor imaging features, biomarker profiles, immune microenvironment characteristics, and overall patient condition. For patients with radiological evidence of nodal involvement and abnormal biomarker levels, neoadjuvant chemotherapy may be considered to reduce tumor burden and improve resectability. Conversely, patients with an active immune microenvironment may benefit from immunotherapy. The integration of fusion imaging and multi-omics data in preoperative assessments will further advance the precise diagnosis and treatment of lymphatic metastasis, supporting the development of precision lympho-immune surgery [84, 86, 88].

Collectively, preoperative evaluation is not only essential for determining nodal metastasis and tumor distribution but also forms the foundation of individualized treatment planning. Future approaches that integrate advanced imaging techniques, biomarker assessment, immune microenvironment profiling, and artificial intelligence algorithms will enable more precise risk stratification and therapeutic decision-making, ultimately improving postoperative survival and quality of life in ovarian cancer patients.

2.4.2 Innovations in Surgical Techniques

In recent years, significant progress has been made in surgical approaches for ovarian cancer, offering new possibilities for improving the prognosis of patients with lymphatic metastasis (Figure 2). Traditionally, ovarian cancer surgery involves pelvic and para-aortic lymphadenectomy to accurately determine nodal involvement; however, this procedure is often associated with adverse effects such as substantial blood loss, prolonged operative time, and extended hospitalization. Thus, optimizing nodal assessment while minimizing the extent of lymphadenectomy has become a focus of current research. Sentinel lymph node (SLN) mapping, which has been validated and applied in cervical, vulvar, and endometrial cancers, is now being investigated in ovarian cancer. Studies using ovarian ligaments as injection sites for radiotracers (e.g., 99mTc) or fluorescent dyes (e.g., indocyanine green) have reported detection rates of up to 84.5% across both open and laparoscopic procedures. SLN mapping may reduce unnecessary extensive lymphadenectomy, lower surgical risks, and improve quality of life, though larger prospective trials are still needed to confirm its clinical utility [93].

For peritoneal metastases and complex peritoneal disease, novel techniques such as the Sarta-Bat procedure (bat-shaped en-bloc total peritonectomy) and the TROMP surgery (total retroperitoneal en bloc resection of multivisceral–peritoneal packet) have been developed. The Sarta-Bat approach achieves complete cytoreduction by en bloc removal of the peritoneum and reproductive organs, including the rectosigmoid colon, while maintaining manageable complication rates, demonstrating both safety and feasibility [94]. The TROMP procedure, using a "no-touch" isolation technique, significantly improves complete resection rates (87.9% vs. 61.3% with conventional methods) without increasing intraoperative blood loss or complications, and even shortens operative time, particularly benefiting patients with advanced disease [95]. These approaches enhance the thoroughness of cytoreduction, which is directly associated with improved survival outcomes.

Minimally invasive techniques are also gaining prominence. Vaginal natural orifice transluminal endoscopic surgery (vNOTES) has been applied in staging surgery for borderline and early-stage ovarian cancer. Studies indicate that vNOTES can accomplish comprehensive staging procedures, including peritoneal washing, unilateral or bilateral adnexectomy, peritoneal biopsies, hysterectomy when required, and thorough abdominal inspection, while reducing blood loss, surgical complications, operative time,

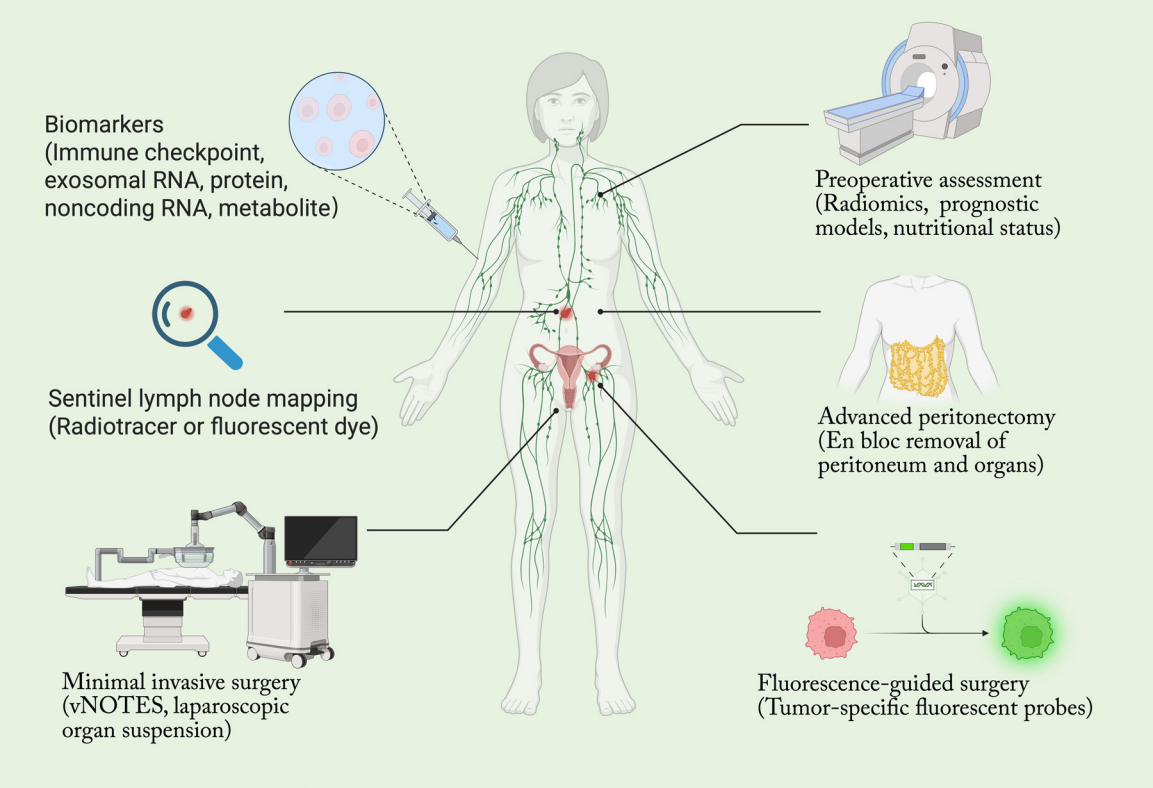

Figure 2. Individualized Therapy and Innovations in Surgical Techniques

and hospital stay, with favorable postoperative recovery, highlighting its strong clinical potential [96]. Other supportive techniques, such as laparoscopic organ suspension (sec. Angioni), provide a simple, safe, and cost-effective method to improve surgical visualization and working space, thereby enhancing efficiency, reducing bleeding, and shortening hospitalization, further expanding the role of minimally invasive approaches in gynecologic oncology [97].

Intraoperative diagnostic assistance has also advanced through fluorescence-guided surgery and real-time microscopic imaging. Novel ovarian cancer-specific fluorescent antibody probes, such as COC183B2-800, enable highly specific labeling of tumor tissue intraoperatively, improving resection accuracy and minimizing residual disease [98]. Similarly, probe-based confocal laser endomicroscopy (pCLE) provides high-resolution, real-time imaging to distinguish malignant from normal tissue, thereby assisting surgeons in defining resection margins and enhancing radicality [99]. These technologies hold promise for the precise identification and removal of lymphatic and peritoneal metastases.

The future of precision surgery emphasizes multidisciplinary integration and individualized treatment. Stratification of patients based on molecular biomarkers and immune microenvironment features may guide both the extent of surgical resection and adjuvant therapy strategies. For example, molecules such as ALOX5AP, implicated in shaping the immunosuppressive microenvironment, suggest that combined approaches integrating immune regulation with surgery may become an important research focus [100]. Furthermore, the incorporation of nanotechnology and targeted drug delivery systems is expected to improve the precision and efficacy of postoperative adjuvant therapies, reducing recurrence rates [101]. The integration of advanced immunotherapeutic strategies, such as CAR-T cell therapy, with surgical intervention also offers new hope for patients with refractory ovarian cancer, necessitating deep integration between surgical innovation and immunotherapy [102].

In summary, surgical techniques for ovarian cancer patients with lymphatic metastasis are evolving toward greater precision, minimal invasiveness, and personalization. Through innovations in SLN mapping, advanced peritonectomy approaches, minimally invasive procedures, and real-time intraoperative imaging, surgery has become safer and more effective, with improved cytoreduction rates. Looking forward, precision surgery, integrated with molecular

biology, immunology, and advanced technologies, will continue to move toward greater intelligence and accuracy, ultimately advancing individualized treatment and improving patient outcomes.

3. Conclusion and Perspectives

Ovarian cancer, one of the most lethal gynecologic malignancies, is profoundly influenced by the complexity of lymphatic metastasis, which remains a critical barrier to improving therapeutic outcomes. As reviewed herein, lymphatic dissemination in ovarian cancer is not merely a simple process of tumor cell migration but rather a dynamic system involving multifaceted interactions between tumor cells, the lymphatic microenvironment, immune cells, and diverse signaling molecules. These multilayered and multidimensional interactions provide new perspectives for understanding metastasis and point toward diversified therapeutic strategies.

From a professional perspective, elucidating the regulatory mechanisms of the ovarian cancer immune microenvironment, particularly the functional alterations of tumor-associated immune cells and their crosstalk with tumor cells, has emerged as both a research hotspot and a major challenge. Although different studies highlight distinct molecular pathways and key regulators, the overall trend underscores immune evasion and the establishment of an immunosuppressive microenvironment as pivotal drivers of lymphatic metastasis. Integrating and balancing these diverse findings to construct a comprehensive and dynamic immune regulatory network model will lay a robust foundation for precision therapy.

Meanwhile, advances in precision surgical techniques are progressively translating the concept of individualized treatment into clinical practice. Tailoring the extent of surgical resection and adjuvant therapies based on patients' molecular profiles and immune status not only maximizes tumor clearance but also reduces postoperative complications and recurrence risk. This "precision + personalization" paradigm heralds a new era in ovarian cancer management, with the potential to significantly improve both survival outcomes and quality of life.

In conclusion, future research and treatment of ovarian cancer must bridge the gap between mechanistic insights and clinical application. Multidisciplinary collaboration integrating advances in molecular biology, immunology, and surgical oncology will be essential to deepen our understanding of immune microenvironment regulation and to foster innovative applications of precision surgical techniques. Confronted with the complex and evolving mechanisms of lymphatic metastasis, only through continuous mechanistic exploration and refinement of therapeutic strategies can we achieve truly precise management and deliver long-term benefit to patients with ovarian cancer.

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