**EMERGING TRENDS IN THE TREATMENT OF OVARIAN CANCER**

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**INTRODUCTION:**

Ovarian cancer (OC) is recognized as one of the most aggressive forms of cancer, often diagnosed at advanced stages, which significantly impacts prognosis and complicates end-of-life care1. It is the leading cause of cancer-related deaths among women and ranks fourth overall in cancer mortality. In 2019, there were approximately 22,240 new diagnoses and an estimated 14,170 deaths due to ovarian cancer2. The disease primarily manifests in three histological types, with epithelial ovarian cancer (EOC) being the most prevalent. The 5-year survival rate for EOC is around 45.6%, though early detection can improve this figure to approximately 70%. Regrettably, only about 20% of cases are diagnosed early, leading to a much lower survival rate of around 35% for those diagnosed at later stages. Managing recurrent EOC remains particularly challenging, with no definitive cure available at present3. The progression of ovarian cancer is influenced by a complex combination of genetic and epigenetic factors. Notably, BRCA1 and BRCA2 gene mutations account for 10-15% of familial ovarian cancer cases4. Additionally, mutations and functional losses in the TP53 gene are present in 60-80% of both familial and sporadic cases. These genetic changes activate various oncogenic signaling pathways, contributing to the cancer’s aggressive growth. Furthermore, ovarian cancer is associated with abnormal activation of coagulation pathways, which can increase the risk of thrombosis and complicate patient outcomes5,6.

This article will explore the latest trends and innovations in ovarian cancer management, focusing on how emerging therapies, genetic insights, and novel treatment approaches are transforming care strategies. By highlighting these advancements, we aim to offer a thorough overview of how they could potentially enhance survival rates and the quality of life for those affected by this challenging disease.

**CAUSES AND ORIGINS OF THE DISEASE:**

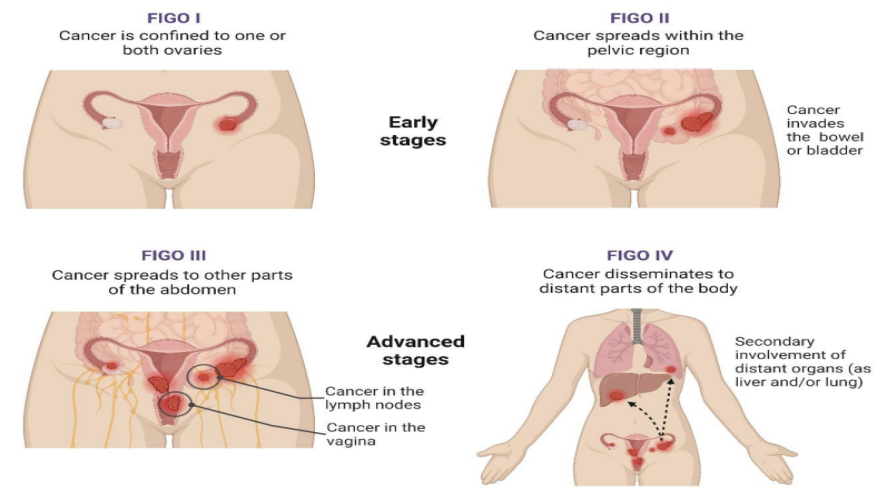
Ovarian tumourigenesis is influenced by a range of aetiological determinants, varying with tumour histology. Key factors include advanced age, genetic predisposition, and family history of cancer, which are associated with continuous ovulation, hormonal shifts, cumulative genetic damage, and chronic inflammation7-9. Ovarian cancer (OC) is rare in women under 30 but significantly more common after age 50, with peak diagnoses between 50 and 70 years. The genetic component is notable, as OC is highly heritable, particularly linked to mutations in BRCA1 and BRCA2, as well as MLH1, MSH2, MSH6, and PMS2 in hereditary non-polyposis colorectal cancer syndrome10,11. Women with BRCA mutations have a 20-40% and 10-20% lifetime risk of OC, respectively, compared to <2% in the general population12. Reproductive factors such as early menarche, late menopause, long-term hormone replacement therapy, and nulliparity are associated with increased risk, while pregnancy, breastfeeding, and oral contraceptive use are considered protective13-17.

**PATHOPHYSIOLOGY:**

Ovarian carcinoma is a complex and varied disease that undergoes numerous molecular alterations. Tumours often develop from the surface epithelium and manifest in several histological forms: serous ovarian carcinoma (SOC) is most common in older women, while endometrioid carcinoma, which is frequently linked with endometriosis, tends to affect younger women. Mucinous and clear cell carcinomas are also seen more often in younger patients. Other ovarian cancers can arise from germ cells or stroma. The tumour microenvironment, influenced by both genetic and epigenetic changes, plays a vital role in diagnosis and treatment. Tumour markers, which are affected by abnormal expression of homeobox genes such as HOXA9, HOXA10, and HOXA11, are important for targeted therapy development. While platinum- and taxane-based chemotherapies work well for serous and endometrioid cancers, they are less effective for clear-cell and mucinous carcinomas18.

**OVARIAN CANCER DIAGNOSIS AND PROGNOSIS ASSESSMENT:**

Recent advancements in diagnosing ovarian cancer have greatly improved through the integration of biomarkers and sophisticated imaging techniques. The use of mucin 16 (CA-125) in conjunction with pelvic ultrasound has increased the specificity of cancer detection, while the combination of human epididymis protein 4 (HE4) with transvaginal sonography has further enhanced screening capabilities19. These technological and methodological improvements have significantly advanced both diagnostic and treatment approaches. Emerging biomarkers, such as various proteins, nucleic acids, and genetic alterations, are being investigated to refine prediction and diagnostic accuracy. Current diagnostic practices involve a thorough medical history review, gynecological examination, serum CA-125 measurement, and a range of imaging tests—including transvaginal ultrasound, CT scans, MRI, and PET scans. Definitive diagnosis and staging often require histopathological analysis from biopsies or surgical specimens. For diagnosing mucinous carcinoma, the European Society for Medical Oncology (ESMO) 2023 guidelines recommend assessing tumour markers like CEA and CA 19-920,21.



Prognosis in ovarian cancer is traditionally assessed using factors such as the FIGO stage, histologic subtype, tumor grade, baseline serum CA-125 levels, extent of debulking surgery, and chemotherapy regimens22. Generally, earlier disease stages, type I tumors, and lower CA-125 levels are associated with better survival outcomes 23. Recent research, however, has highlighted the importance of molecular biomarkers in predicting treatment response and prognosis. For example, high-grade serous carcinoma (HGSC), the most common and deadly subtype, has been further classified into subtypes based on genomic signatures: C1 (high stromal response), C2 (high immune response), C4 (low stromal response), and C5 (mesenchymal). The classic dualist model, distinguishing type I from type II tumors, and later findings from the Cancer Genome Atlas (TCGA) identified four HGSC subtypes: mesenchymal, proliferative, differentiated, and immunoreactive. These subtypes correlate with prognosis, with the mesenchymal subtype showing the lowest five-year overall survival rate at 18%, while the immunoreactive subtype has the highest at 45%. The ongoing integration of these molecular signatures is expected to enhance personalized treatment strategies for ovarian cancer24.

**CURRENT TREND IN TREATMENT OF OVARIAN CANCER:**

1. **Advances in Targeted Therapies:**

The body maintains balance through apoptosis, a process of eliminating unnecessary cells. In ovarian cancer (OC), certain genes disrupt this process, allowing cancer cells to survive. Bcl-2 family proteins and Tyrosine-protein kinases are involved in the intrinsic and extrinsic pathways of apoptosis, with Bcl-2 being notably anti-apoptotic and prevalent in OC. This protein, along with Bcl-X and Mcl-1, contributes to chemotherapy resistance and decreased survival. Conversely, proteins like Bid, Bad, and Bax promote apoptosis and improve survival rates. Clinical trials with Bcl-2 inhibitors have shown improved responses to cisplatin in OC. Additionally, IAP proteins like Survivin, which inhibit apoptosis, play a role in tumor growth and chemotherapy resistance. Studies have shown that targeting Surviving can suppress tumors and enhance chemotherapy sensitivity. Upregulation of the Tyrosine-protein kinase Met (c-Met) in OC is linked to poor treatment outcomes, affecting cell proliferation and survival. Inhibiting c-Met has led to reduced cell growth and increased apoptosis in experimental settings. Specific transcription factors regulate VEGF expression, impacting tumor growth and metastasis25.

Immunotherapy leverages the immune system to combat cancer, a concept dating back to 2600 BC. One method involves adoptive cell transfer, where T cells from a patient’s blood or tumor are cultured and expanded ex vivo before being reintroduced to the patient with recombinant interleukin 2. Cancer vaccines are another method, aiming to activate the immune system by stimulating antigen-presenting cells26.

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| **DRUG NAME** | **IMMUNE CHECKPOINT TARGET** | **CURRENT APPROVAL AS OF JUNE, 2019** |
| Ipilimumab | CTLA‐4 | Melanoma, renal cell carcinoma (combined with nivolumab), colorectal cancer |
| Pembrolizumab | PD‐1 | Non-small cell lung cancer (NSCLC),squamous cell carcinoma of head and neck (SCCHN), classic Hodgkin's lymphoma, large B‐cell lymphoma, urothelial cancer, micro‐satellite instability‐ high (MSI\_H)or mismatch repair deficient (dMMR) cancers, gastric or GEJ adenocarcinoma and cervical cancer |
| Nivolumab | PD‐1 | NSCLC, melanoma, RCC, classic HL, squamous cell carcinoma of head and neck (SCCHN), urothelial cancer (UC), MSI‐H or dMMR colorectal cancer, hepatocellular cancer |
| Avelumab | PD‐L1 | Merkel cell carcinoma (MCC), UC |
| Durvalumab | PD‐L1 | UC, NSCLC |
| Atezolizumab | PD‐L1 | UC, NSCLC |
| Tremelimumab | CTLA‐4 | Awaiting approval |

Abbreviations: CTLA‐4, cytotoxic T lymphocyte‐associated antigen 4; PD‐1: programmed cell death 1; PD‐L1: programmed cell death ligand 1.

1. **New Chemotherapeutic Agents:**
2. **Postoperative chemotherapy:**

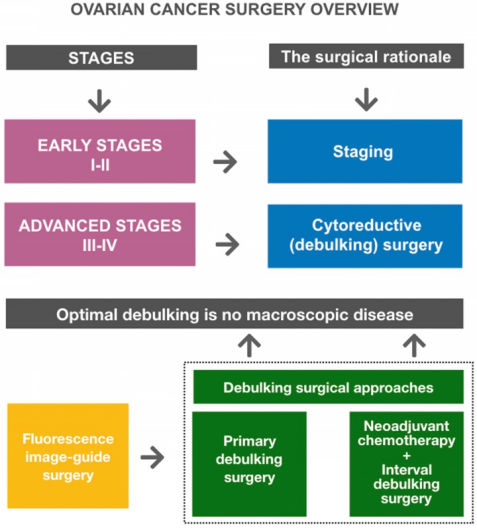
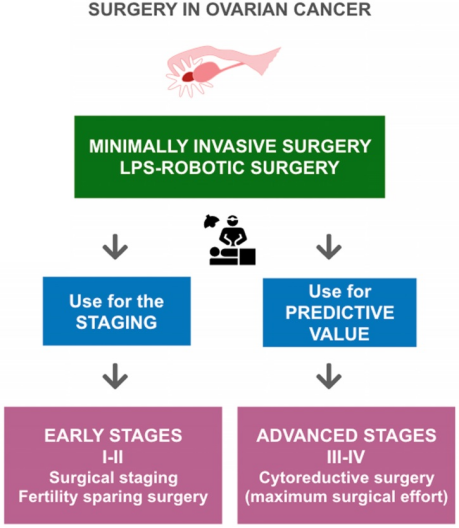
Postoperative chemotherapy is typically required for both early high-risk and advanced ovarian cancer. Surgical staging is crucial for determining appropriate treatment. Adjuvant therapy depends on the cancer's stage, grade, and type, focusing on controlling micro-metastatic disease and managing side effects. Standard treatment combines a platinum compound (cisplatin or carboplatin) with a taxane (paclitaxel or docetaxel). Early ovarian cancer is often treated with surgery, but due to a significant risk of recurrence, many patients also receive adjuvant chemotherapy. For advanced cases, surgery is usually followed by chemotherapy, though 70-80% of patients experience relapse within two years, necessitating additional treatment. Research continues to enhance the effectiveness of first-line chemotherapy27,28.

1. **Intraperitoneal chemotherapy:**

Intraperitoneal (IP) chemotherapy was developed to improve the efficacy of first-line treatments by targeting ovarian cancer cells directly in the abdominal cavity, where the disease often remains localized. It is particularly useful for addressing microscopic disease and has shown potential benefits for advanced cases with peritoneal metastases29. Recent findings from the Gynecologic Oncology Group (GOG) studies indicate that IP therapy can significantly improve 10-year overall survival compared to standard treatments, despite its limited use due to side effects. In contrast, the GOG 252 study did not find IP chemotherapy to be more effective than intravenous (IV) therapy, showing similar outcomes in terms of efficacy and toxicity. Additionally, hyperthermic intraperitoneal chemotherapy (HIPEC), which involves using heated chemotherapy agents, may enhance treatment by improving drug penetration and sensitivity after surgery. However, assessing its overall impact on survival remains challenging30-35.

1. **Emerging Surgical Techniques:**
2. **Fluorescence image-guided surgery:** New contrast agents are crucial for improving intra-operative imaging in ovarian cancer surgery. Several fluorescent nanoparticles (NPs) are being developed to enhance fluorescence image-guided surgery:
3. **CF800 Liposomes:** These liposomes integrate a CT contrast agent and a near-infrared (NIR) dye for dual imaging, aiding in better surgical guidance36.
4. **HER-2-Targeted Magnetic Iron Oxide Nanoparticles (IONPs):**  These NPs offer both optical and MR imaging capabilities, with HER-2 targeting and a unique NIR dye for enhanced imaging37.
5. **Silicon Naphthalocyanine (SiNc) Nanoparticles:**  Encapsulated in biodegradable materials, these NPs remain non-fluorescent until they accumulate in tumors, where they activate NIR fluorescence37.
6. **Porphyrin Lipoprotein-Mimicking Nanoparticles (PLPs):** These ultra-small particles combine PET, NIR fluorescence, and photodynamic therapy (PDT) for multifunctional imaging and treatment38.
7. **ACPP-Conjugated Dendrimers (ACPPDs):** Coated with cell-penetrating peptides and labeled with Cy5 and gadolinium, these dendrimers target specific enzymes in vivo40.
8. **Fluorescent Gold Nanoparticles (AS1411-DA-AuNPs):** These nanoparticles combine CT contrast with an aptamer targeting nucleolin, providing both CT and fluorescent imaging41.
9. **Fluorescent HA-Derived NIRF NPs:** Derived from hyaluronic acid, these NPs use entrapped ICG or conjugated Cy7.5 for NIR fluorescence imaging**.** Among these, CF800 liposomes have shown promise in preclinical models for enhancing tumor localization and detection. Silicon naphthalocyanine-based nanoparticles also offer effective tumor resection and phototherapy in animal models. Additionally, ultrasound-responsive nanoparticles may improve various image-guided cancer therapies, including radiotherapy and drug delivery, paving the way for more precise treatments41.
10. **Ultra sound-responsive nanoparticles :**

Ultrasound-responsive nanoparticles (NPs) represent an advanced class of multifunctional carriers that integrate both imaging and therapeutic capabilities. These NPs are designed to release their drug payloads specifically at target tissues when exposed to ultrasound. The ultrasound can induce localized and controlled drug release through thermal or mechanical effects, enhancing tumor-targeted therapy. This approach leverages ultrasound's advantages as a non-invasive, safe, and cost-effective imaging modality. It allows for precise energy delivery to tumor areas with millimeter accuracy, and ultrasound-guided procedures can reach deep-seated tumors through laparoscopic or percutaneous techniques. Recent applications include the development of alginate-shelled nano droplets for delivering doxorubicin and curcumin, targeting multidrug-resistant ovarian cancer. These NPs have demonstrated significant tumor growth reduction when combined with ultrasound irradiation in both laboratory and animal studies42-44.

1. **Combination Therapy in strategies for Advanced Ovarian Cancer:**
2. **Chemotherapy + PARP Inhibitor + Anti-PD-1/PD-L1 Antibody + VEGFR Inhibitor:**

Various phase III trials are testing combinations of standard platinum/taxane chemotherapy with PD-1/PD-L1 inhibitors, potentially followed by maintenance therapy with PARP inhibitors and/or anti-PD-1/PD-L1 antibodies. For instance, the JAVELIN ovarian PARP 100 trial was halted due to insufficient benefit from avelumab. Similarly, the IMagyn050/GOG 3015/ENGOT-ov39 trial found no significant improvement in median progression-free survival (mPFS) with atezolizumab addition, though a trend towards better outcomes was noted in patients with high PD-L1 expression45-48.

1. **PARP Inhibitor + VEGFR Inhibitor Combinations:**

Combining VEGFR inhibitors with PARP inhibitors is being explored due to VEGFR's role in reducing homologous recombination DNA repair, which may enhance PARP inhibitor effectiveness. Cediranib, a VEGFR inhibitor, has shown promising results when combined with olaparib, improving mPFS and overall survival in platinum-sensitive ovarian cancer. Similarly, bevacizumab plus niraparib has demonstrated significant mPFS improvements. Ongoing phase III trials are investigating these combinations further49-52.

1. **PARP Inhibitor + Anti-PD-1/PD-L1 Antibody ± VEGFR Inhibitor Combinations:**

Clinical trials are exploring combinations of PARP inhibitors with anti-PD-1/PD-L1 antibodies, and in some cases, VEGFR inhibitors. Trials such as those involving niraparib with pembrolizumab and talazoparib with avelumab are underway. The TOPACIO/Keynote-162 study found that niraparib combined with pembrolizumab yielded an 18% overall response rate (ORR) in patients with recurrent ovarian cancer, with no new safety concerns noted. This ORR is notably higher compared to historical data for similar treatments53-55.

**6.Development of Novel Theranostic Approaches for Ovarian Cancer:**

**I. MUC16 and MSLN Targeting:**

MUC16 and MSLN are emerging as key theranostic targets for ovarian cancer. MUC16, highly expressed in 99% of serous ovarian carcinomas, interacts with MSLN, activating survival pathways that promote cancer progression. A monoclonal anti-MSLN antibody has shown promise in reducing tumor growth in murine models. Recent strategies include engineered T-cells with receptors targeting MSLN and MUC16, enhancing anti-tumor responses. This approach utilizes a chimeric antigen receptor (CAR-T) to target MUC16, potentially improving therapeutic efficacy56,57.

**II . FOLR1 Targeting:**

FOLR1 is a validated theranostic target for ovarian cancer. The FDA-approved antibody-drug conjugate (ADC) MIRV targets FOLR1, and the VENTANA FOLR1 assay helps identify suitable patients for FOLR1-targeted therapy. CAR-CIK cells, engineered to recognize FOLR1, have shown superior tumor-killing capabilities compared to CAR-T cells. Additionally, TNB-928B, a novel T-cell engager targeting FOLR1, enhances T-cell activation and selectively targets FOLR1-expressing tumors. Targeting immune checkpoints like CD24 and Siglec-10 also holds promise by boosting immune response and reducing tumor growth58-61.

1. **Experimental Biomarkers and Novel Targets:**

**Bispecific Antibodies:**

Antibodies such as Catumaxomab, MT110, and M701, targeting EPCAM and CD3, stimulate T-cell responses against ovarian cancer. The CD73xEPCAM antibody binds to EPCAM on cancer cells, indirectly activating T-cells by inhibiting CD73, which prevents immune suppression. WNT Signaling: DKK1, a WNT pathway regulator, might influence anti-tumor immunity and is a potential therapeutic target, especially when combined with immune-modulatory treatments. These approaches aim to personalize therapy based on ovarian cancer’s unique molecular characteristics62-65.

**CONCLUSION :**

Ovarian cancer treatment is evolving through the integration of conventional methods with novel strategies. Targeted therapies, including PARP inhibitors and immune checkpoint inhibitors, are pushing the boundaries of personalized medicine. Emerging theranostic agents and nanoparticles are enhancing precision in treatment, while clinical trials are exploring effective combinations to address resistance. Advanced techniques like fluorescence-guided surgery and hyperthermic intraperitoneal chemotherapy are improving surgical outcomes. These developments reflect a trend towards more individualized, effective, and minimally invasive treatments, aiming to enhance patient survival and quality of life.

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