Review Paper:

Assessing the Effect of Chemotherapy on Treatment of Ovarian Cancer

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Abstract
Ovarian cancer, a gynecologic disease caused by ovarian epithelium mutations, is the most common and deadly cancer due to its advanced nature. Frequently known as "the Silent Killer," it often presents with nonspecific symptoms, leading to delayed diagnosis. Most patients have a 10%-30% survival rate. Treatment involves tumor-debunking surgery and six cycles of chemotherapy. While 70% of patients respond, over 50% will have recurrence within two years. In addition to ascites and small bowel obstruction, ovarian tumors can spread to the liver and lungs.

Keywords: Silent Killer, BRCA1 and BRCA2 mutations, Obesity endometriosis, Pleural effusion, Pelvic examinations.

Introduction

Ovarian cancer is a gynecologic malignancy arising primarily from mutations or disruptions in the epithelium of the ovary. It holds the highest mortality rate among gynecologic cancers, largely due to its late-stage diagnosis in most cases. Often called the "Silent Killer," its vague symptoms often make it difficult to identify. The rate of 5-year survival for the small percentage of patients with localized illness is higher than 90%[1-3].

On the other hand, advanced-stage cases have a far worse prognosis with survival rates between 10% and 30%. The main course of treatment consists of six rounds of taxane-platinum chemotherapy after tumor-debulking surgery. Despite initial responses in 70% of patients, over half experience recurrence within two years of diagnosis. Ovarian cancer metastasizes primarily through lymphatic and hematogenous routes to the liver and lungs. Advanced disease often leads to complications such as ascites and small bowel obstruction.

The term "ovarian cancer" describes the unregulated growth and division of cells that are abnormal that start in the peritoneum, fallopian tube, or ovary. A tumor created by this growth has the potential to spread to other parts of the body if left untreated.

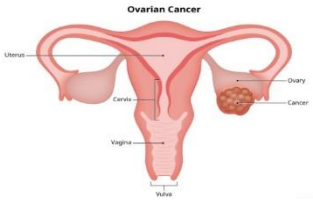


Fig. 1: A visual representation of ovarian cancer

Epidemiology

In India, ovarian cancer is the third most frequent disease among women; an expected 47,333 new cases and 32,978 deaths were recorded in 2022[4-6]. It accounts for 6.6% of all cancers affecting women in the country, making its late-stage diagnosis a significant public health challenge. Globally, ovarian cancer ranks third among gynecologic cancers after cervical and uterine cancer, However, it has the highest death rate and the worst prognosis. Projections indicate that by 2035, the annual incidence of ovarian cancer will rise by 55% to approximately 371,000 cases, with a corresponding 67% increase in deaths (254,000 annually). The upward trend is attributed to population growth, increasing cancer risk factors, decreased fertility rates, shorter lactation periods and reduced tubal ligation. Ovarian cancer is categorized by prognosis, therapeutic options, risk factors, pathological grade and cell origin.

Etiology[7-10]: Ovarian cancer can occur due to a number of reasons such as:

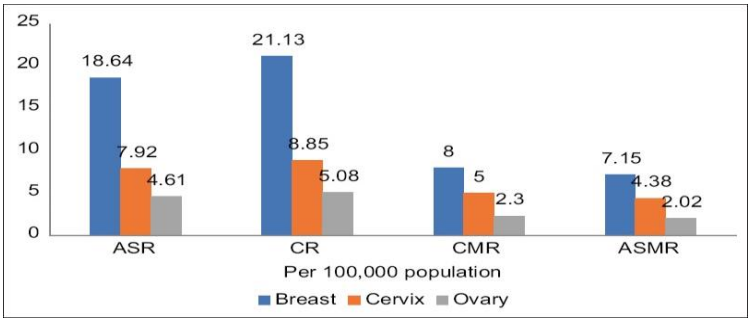


Fig. 2: Statistical data of Ovarian cancer

Genetic susceptibility:

- The syndrome of ovarian and breast cancer that runs in families, dramatically raises the risk of ovarian cancer and is brought on by germline mutations in the BRCA1 and BRCA2 genes.
- **Lynch syndrome:** A familial condition linked to germline mutations in DNA mismatch repair enzymes, accounting for as many as 12 percent of cases of hereditary ovarian cancer.

Hormonal and reproductive history:

- Increased lifetime ovulation, associated with factors such as nulliparity, late menopause and early menarche increase the risk of epithelial ovarian cancer. The incessant ovulation hypothesis suggests that repeated ovarian epithelium repair increases the likelihood of mutations over time.
- Prolonged estrogen exposure further contributes to risk.

Environmental and Dietary influences:

- While a diet rich in vegetables may have protective effects, a diet high in galactose, animal fats, or red meat may increase risk.
- Controversial associations exist between ovarian cancer and exogenous exposures, such as talcum powder use and asbestos.

Cellular mechanisms:

- Resistance of ovarian cancer cells to cytotoxic agents is often linked to mechanisms that induce DNA damage.
- Understanding these diverse etiological factors can guide prevention, early detection and personalized treatment strategies for ovarian cancer.

Classification of Ovarian Cancer

Ovarian Cancer and its types

1. Epithelial Ovarian Cancer: This is the most common type of ovarian cancer, originating from cells covering to ovaries. Key subtypes include:

- **Serous**:
  - **High-level serous ovarian cancer**: More aggressive and common.
  - **Low-level serous ovarian cancer**: Less aggressive and rarer.
- **Endometriosis**:
  - Second most common subtype.
  - Often linked to endometriosis.
  - Typically, low grade and diagnosed early.
  - Can co-exist with uterine (endometrial) cancer.
- **Clear Cell**:
  - Rare and linked to endometriosis.
  - Responds less effectively to chemotherapy compared to other epithelial subtypes.
- **Mucinous**:
  - Rare and challenging to diagnose.
  - Requires tests to confirm whether it originated in the ovary or spread from another organ (e.g. the digestive system).
  - May be benign, borderline, or malignant.
- **Undifferentiated or Unclassifiable**:
  - Cells are underdeveloped, making it impossible to identify their origin.

2. Germ Cell Ovarian Tumours

Arising from ovarian cells that develop into eggs, these tumors may be cancerous or benign.

- **Tumors of benign germ cells:**
  - Most common type: Mature teratomas, also called ovarian dermoid cysts.
  - Frequently seen in women aged teens to forties.
- **Malignant Germ Cell Tumours**:
  - Types include:
    - Immature teratomas
    - Dysgerminoma
    - Yolk sac tumours
    - Non-gestational choriocarcinoma
    - Embryonal carcinoma

3. Sex Cord Stromal Tumours (SCSTs)

These tumours originate from the ovaries' connective tissue cells and can be either benign or cancerous.

- **Main Groups**:
  - **Pure Stromal Tumours**: Include fibromas and thecomas, often benign.
  - **Pure Sex Cord Tumours**: Include adult and juvenile granulosa cell tumours.
  - **Mixed Tumours**: Include Sertoli-Leydig cell tumours.
- **Granulosa Cell Tumours**:
  - **Adult Granulosa Cell Tumours**: Common in middle-aged and older women.
  - **Juvenile Granulosa Cell Tumours**: Rare, typically before puberty.
  - May produce oestrogen (functioning tumours) or remain non-functional.

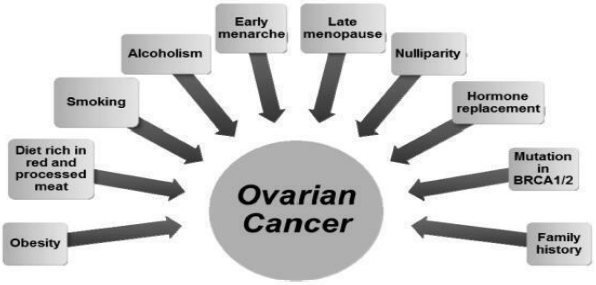


Fig. 3: Etiological factors for ovarian cancer

4. Borderline Ovarian Tumours

These are abnormal, non-cancerous cells that develop on the ovary's surface and are typically curable with surgery.

- **Types**:
  - Serous (50%)
  - Mucinous (45%)
  - Rare types: Endometrioid, clear cell, seromucinous and Brenner tumours.

5. Stages of Ovarian Cancer[11-13]

Cancer staging helps to determine the extent of spread, prognosis and treatment.

- **Stage 1**:
  - **1A**: Confined to one ovary or fallopian tube.
  - **1B**: Involves both ovaries and tubes.
  - **1C**: May spread to the ovary or tube surface or abdominal fluid.
- **Stage 2**:
  - **2A**: Spreads to the uterus or other fallopian tube.
  - **2B**: Involves other pelvic tissues.
- **Stage 3**:
  - **3A**: Reached lymph nodes or abdominal lining.
  - **3B**: Tumours in the abdominal lining are ≤2 cm.
  - **3C**: Tumours in the abdominal lining are >2 cm.
- **Stage 4**:
  - **4A**: Spreads to the lung's fluid.
  - **4B**: Reached distant organs, such as the liver or spleen.

Pathophysiology

1. Tumour Suppressor Gene Mutations

- BRCA1 (chromosome 17q12–21) and BRCA2 (chromosome 13q12–13) mutations are critical in ovarian cancer development:
  - BRCA1 is implicated in 90% of inherited cases and 10% of sporadic cases.
  - Linked to younger patients, aggressive serous tumours and advanced-stage cancers.

2. Gene Mutations

- P53 Mutation: Found in 50% of cases, especially in high-grade serous cancers.
- Other Mutations:
  - B-raf, K-ras and PTEN: Common in endometrioid, mucinous and low-grade tumours.
  - HER2/neu Amplification: Occurs in ~8% of cases and indicates a poor prognosis.

Ovarian Cancer: Clinical Presentation, Risk Factors, Complications, Diagnosis and Screening.

I. Clinical Presentation

Ovarian cancer symptoms are often vague, leading to delayed diagnoses. It is commonly referred to as the "Silent Killer" due to its vague symptoms.

Common Symptoms

- **Abdominal and Pelvic Discomfort**:
  - Pain, distension, or ascites.
  - Persistent bloating or a feeling of fullness.
- **Digestive Disturbances**:
  - Nausea, dyspepsia, flatulence and early satiety.
  - Weight changes or changes in bowel habits (diarrhea or constipation).
- **Urinary Symptoms**:
  - Increased frequency or urgency.

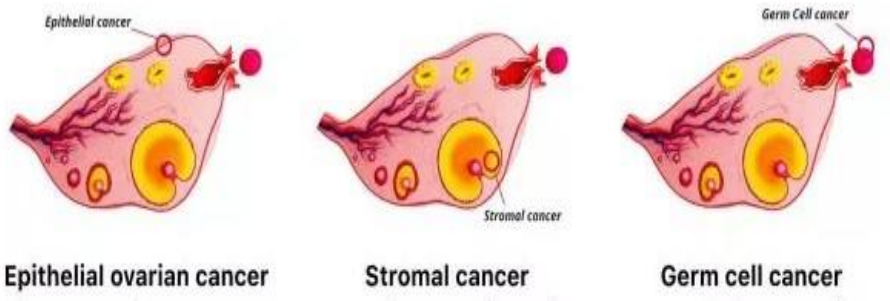


Fig. 4: Classification of Ovarian Cancer

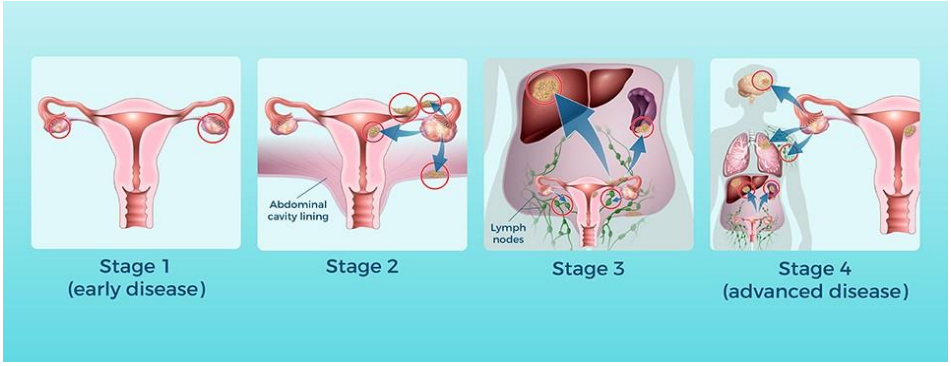
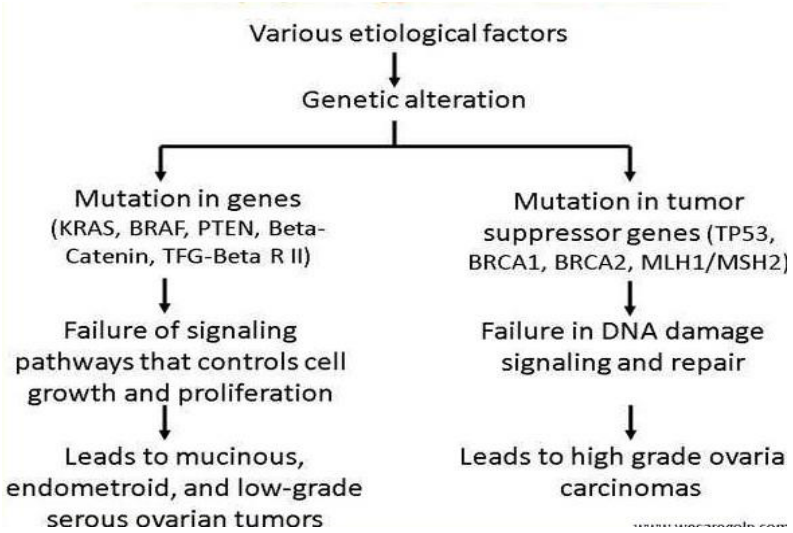


Fig. 5: Stages of Ovarian Cancer



Signs

- **Palpable Abdominal or Pelvic Mass**:
  - Masses may be solid, irregular, or nodular.
- **Lymphadenopathy**: Enlarged lymph nodes.
- **Ascites**:
  - Abdominal distension resembling a "pregnant abdomen," with shifting dullness to percussion.
- **Irregular Vaginal Bleeding**.

Laboratory Findings

- **Liver Function Abnormalities**: Suggest hepatic involvement.
- **Renal Function Abnormalities**: May indicate compression of the renal system by the tumour.

II. Risk Factors[14-16]

Key factors increasing the risk of ovarian cancer include:

- **Age**: Higher risk post-menopause.
- **Family History**: Ovarian cancer in close relatives increases risk.
- **Genetic Mutations**: Mutations in BRCA1/BRCA2 or Lynch syndrome genes.
- **Hormone Therapy**: Prolonged use of hormone replacement therapy (HRT).
- **Lifestyle and Medical Conditions**:
  - Obesity, diabetes and smoking.
  - Endometriosis or previous cancers (breast, uterine, or colorectal).
- **Reproductive History**:
  - Early menstruation, difficulty conceiving, or never giving birth.
- **Ethnicity**: Higher risk among Ashkenazi Jewish and Eastern European women.

III. Complications

Ovarian cancer and its treatments can lead to various complications, classified as:

Short-Term Complications

- **Fatigue**: Especially during chemotherapy or radiotherapy.
- **Gastrointestinal Issues**: Nausea, vomiting, diarrhea, constipation, or bowel obstruction.
- **Peripheral Neuropathy**: Tingling or numbness in extremities.
- **Fluid Build-Up**: Ascites, pleural effusion (fluid in the lungs), or lymphedema (fluid in limbs).

Long-Term Complications

- **Chronic Ascites and Pleural Effusion**.
- **Anemia and Lymphedema**.

Surgical Complications

- **Blood Clots**: Risk of embolism.
- **Wound Infections**: May require antibiotics or additional surgery.

IV. Diagnosis

Timely and accurate diagnosis is crucial.

Initial Workup:

- **Physical Examination**: Includes pelvic and rectovaginal exams.
  - A pelvic tumor that is permanent, solid, or irregular may indicate ovarian cancer.
- **Family History**: Evaluate cancer patterns among first-degree relatives.

Laboratory Tests:

- **Tumour Markers**:
- **CA-125**: Elevated in epithelial ovarian carcinoma (>35 units/mL).
  - Correlates with tumour burden but may be nonspecific.
  - Elevated levels can also occur in endometriosis, diverticulitis and other conditions.
- **Carcinoembryonic Antigen (CEA)** and **CA19-9**: Rule out gastrointestinal cancers.
- **Blood Tests**: Includes CBC and liver/renal function tests.

Imaging:

- **Transvaginal or Abdominal Ultrasound**:
  - Assesses ovarian mass size, shape and vascularity.

- **CT, MRI, or PET Scans**: to assess the severity of the illness.
- **Chest Radiography**: Detects pleural effusion or metastases.

Specialized Procedures:
- GI Series, Cystoscopy, or Proctoscopy: Confirm diagnosis and rule out metastasis.

V. Screening and Prevention[17-19]
Detecting ovarian cancer early remains challenging due to the lack of effective screening tools.
General Screening Challenges:
- **Pelvic Exams**: Effective for detecting large tumours but limited for early disease.
- **Transvaginal Ultrasound (TVUS)**:
  - Identifies masses but lacks specificity.
  - Difficult to identify cancer in ovaries of normal size or peritoneal carcinoma.
- **CA-125 Testing**:
  - Useful for monitoring tumour progression but unreliable for routine screening due to non-specificity.

Genetic Screening:
- Suggested for females who have a substantial family history of ovarian cancer.
- Tests for BRCA1, BRCA2 and other associated genes (e.g. Lynch syndrome).
- **Genetic Counseling**: Essential before and after testing to address health and psychosocial concerns

Pharmacological treatment[20-22]**:**
Surgical Treatment: Surgery is the cornerstone of ovarian cancer management, particularly in early-stage disease (Stage IA). Key goals include accurate staging and optimal debunking to improve chemotherapy efficacy and overall survival.

Primary Surgical Procedures:
- The uterus, ovaries and fallopian tubes are removed during a total abdominal hysterectomy combined with a bilateral salpingo-oophorectomy.
- **Omentectomy**: Resection of the omentum.
- **Lymph Node Dissection**: Assessment of nodal involvement.

Surgical Goals:
- Debulk tumor to achieve residual disease <1 cm.
- Accurate staging using FIGO guidelines to avoid tumor seeding.
- Comprehensive exploratory laparotomy for diagnosis and staging.

Additional Surgical Interventions:
- **Second-Look Surgery**: Performed in select patients achieving clinical complete response post-chemotherapy to assess residual disease. The utility remains controversial.

Radiation Therapy: Radiation have a limited role in ovarian cancer treatment and it is primarily used for symptom management in recurrent or advanced cases.

Indications:
- Palliation of symptoms such as small bowel obstructions.
- Alleviation of pelvic disease-related discomfort.

Types and Dosage:
- **External Beam Whole-Abdominal Irradiation**: 35-45 Gy, based on patient tolerance.
- **Intraperitoneal Isotopes**: Use of isotopes like 32P for symptom management.

Chemotherapy: Chemotherapy is integral to ovarian cancer management, especially in advanced stages or as an adjunct to surgery.

First-Line Systemic Therapy:
A taxane-platinum regimen is the standard of care post-surgery.
Stage-Based Protocols**:**
- Stage I: Chemotherapy is optional for stages IA/IB (grade 1) but recommended for grades 2/3 or Stage IC.
  - Regimen:
    - Paclitaxel: 175 mg/m² IV over 3 hours/day
    - Carboplatin: AUC 5-6 IV over 1 hour/day (21-day cycles).
- Stages II-III:
  - Combination therapies such as:
    - Paclitaxel (IV 175 mg/m²) + Carboplatin (IV AUC 5-6) every 21 days.
    - Intraperitoneal regimens with Paclitaxel and Cisplatin for optimally debulked patients.
- Stage IV: Similar protocols to Stage III, with strong consideration for clinical trial enrollment.

Neoadjuvant Chemotherapy: Administered pre-surgery in advanced disease to reduce tumor burden. Common regimens include:

- Paclitaxel (175 mg/m² IV) + Carboplatin (AUC 5-6 IV) every 21 days.
- Dose-dense schedules for improved outcomes in select patients.

Advanced Treatment Approaches:
Hyperthermic Intraperitoneal Chemotherapy (HIPEC):
A promising approach combining heated chemotherapy with surgery, improving drug penetration and efficacy.

- Common regimens:
  - Paclitaxel (IV 175 mg/m²) + Carboplatin (IV AUC 5).

PARP Inhibitors:

Approved for maintenance therapy in patients with BRCA mutations or homologous recombination deficiency (HRD):

- **Olaparib**: 300 mg PO BID.
- **Rucaparib**: 600 mg PO BID.
- **Niraparib**: 300 mg PO daily.
- Often combined with Bevacizumab in HRD-positive cases.

Targeted Therapy (Bevacizumab):
- Combined with chemotherapy (e.g. Paclitaxel and Carboplatin) for advanced stages.
- Maintenance dose: 7.5-15 mg/kg IV every 21 days for up to 15 months.

Hormonal Therapy:
Used in asymptomatic recurrence or for patients intolerant to chemotherapy:
- **Tamoxifen**: 20 mg PO twice daily.
- **Letrozole**: 2.5 mg PO daily.

Elderly or Comorbid Patients:
Dose modifications and close monitoring are necessary.
- Weekly low-dose Paclitaxel + Carboplatin.
- Adjusted regimens to minimize toxicity.

Patient-Centered Care:
- Treatment decisions should consider performance status, comorbidities and patient preferences.
- Enrollment in clinical trials is strongly encouraged when available.

Non- pharmacological treatment
Physical Activity:
- **Exercise therapy:** Moderate-intensity aerobic exercise, resistance training, or tailored exercise programs can help manage fatigue, improve mood and maintain physical function.
- **Yoga and Tai Chi:** These practices can aid in flexibility, balance and stress reduction.

Nutritional Support:
- **Balanced diet:** Emphasize foods high in nutrients to boost immunity and fight malnutrition, which is frequently linked to cancer therapy.
- **Dietary counseling:** Consult a registered dietitian to address specific nutritional needs based on treatment side effects.

Psychological Support:
- **Counseling and therapy:** Individual or group therapy can help manage emotional distress, anxiety, depression and coping mechanisms related to diagnosis and treatment.
- **Support groups:** Making connections with patients going through comparable situations can offer both practical knowledge sharing and emotional assistance.

Pain Management:
- **Massage therapy:** Can help alleviate pain and discomfort associated with treatment side effects.
- **Relaxation techniques:** Pain and anxiety can be controlled by progressive muscle relaxation, deep breathing techniques and guided imagery.

Complementary and Alternative Medicine (CAM):
- **Acupuncture:** May be used to manage pain, nausea and other symptoms, though evidence is still emerging.
- **Aromatherapy:** Using essential oils for relaxation and symptom management, but should be used cautiously and with professional guidance.

Treatment
- Stage the cancer: Determine how far the cancer has spread
- Remove as much cancer as possible: Reduce the size of the tumor and remove as much cancer as possible
- Improve the chances of a cure: Treat the cancer to stop or slow its growth, or lessen the chance it will return
- Tailor treatment to the patient's needs: Use evidence-based treatments to improve quality of life

Treatment methods
- Surgery: Remove the uterus, ovaries, fallopian tubes and other organs that have cancer
- Chemotherapy: Use drugs to stop or slow the growth of maeloma cells
- Targeted site therapy: Use of drugs for identify and combat cancer cells
- Hormone therapy: Block hormones to slow or stop the growth of cancer

Staging
- Accurate staging is important because it helps determine the best treatment
- Ovarian cancers are staged using the International Federation of Gynecology and Obstetrics (FIGO) staging standard. Other things to think about
- The type of surgery, whether it is laparoscopy or laparotomy, depends on the extent of the cancer
- Chemotherapy can be given before or after surgery
- Patients can also take steps to reduce stress and fatigue, such as eating well, relaxing and getting enough rest

Conclusion

One of the biggest problems in gynecologic oncology is still ovarian cancer. Patient education and knowledge of the symptoms and indicators of ovarian cancer are important factors in improving the outcome. The prognosis and overall survival are significantly improved with an earlier diagnosis. Even though there has been some significant advancement in the last few decades in terms of improving overall and progression-free survival, many questions remain. More research is required to identify the best agents for IP chemotherapy, the value of maintenance chemotherapy and

how these factors affect overall survival for oncologic disorders. In order to treat advanced primary, recurrent and refractory ovarian cancer, research must find and create novel strategies for preventing recurrence as well as novel molecular targets, agents to modify or overcome drug resistance and chemotherapy regimen optimization.

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