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Ovarian Carcinoma: An Overview of Current Status

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Abstract - *One of the most common causes of illness and death among female cancers is ovarian carcinoma. It is the seventh most deadly cancer in women globally and is a leading cause of mortality from gynecological carcinoma. It is made up of a diverse range of neoplasms. Variations in the severity and patterns of ovarian cancer are specific to various regions of the world, and the disease's situation is always evolving. As a result, the current research on ovarian cancer has to be updated and reviewed. From PubMed and Google Scholar, reviews of ovarian cancer from 2000 to 2015 were retrieved, and a few chosen seminal studies that used historical data were also included. Consolidating a current worldwide perspective on epithelial ovarian carcinoma, the most common kind of ovarian cancer, is the main goal of this work. The epidemiology, types, diagnosis, prognosis, and therapy of epithelial ovarian cancer are all covered in this article.*

Key Words: diagnostic, prognosis, treatment, epidemiology, and ovarian cancer.

1.INTRODUCTION

The seventh most deadly cancer in the world for women (and the eighteenth most prevalent type of carcinoma overall), ovarian carcinoma is a diverse group of neoplasms that contribute significantly to gynecological carcinoma-related deaths in the western world. The ovarian surface epithelium or postovulatory inclusion cysts, which develop following follicular rupture and healing, had previously been proposed as the source of the majority of ovarian carcinomas. Numerous theories exist regarding the incidence of ovarian cancer in females. Every ovulation causes a wound, which leads to greater cell proliferation to heal the epithelial cells, according to the "incessant ovulation" theory. This could lead to a higher risk of malignant mutation and DNA damage. According to a different theory involving gonadotropin-based stimulation, higher gonadotropin levels during menopause are associated with an increased incidence rate of ovarian cancer. Ovulation is strongly linked to ovarian cancer, and the inflammation hypothesis suggests that inflammation may play a role in this process. However, progesterone stimulation has shown a protective effect and lowers the risk of ovarian carcinoma. The hormonal theory, on the other hand, suggests that excess androgen stimulates the ovarian surface epithelium, increasing the risk of ovarian carcinoma. About 75% of women who have the illness are found to have it in a more advanced stage. According to histology, ovarian carcinoma can be divided into three main categories based on the ovarian tissues that cause it: sex cord-stromal cell tumor (which produces hormones) and germ cell tumor (which is made up of cells that develop into ova and its subtypes include dysgerminoma immature teratoma and yolk sac tumor), as well as epithelial ovarian tumor (which covers the ovary and its subtypes that include serous, mucinous, endometrioid, and clear cell). The epithelial cells are where ovarian cancer occurs most frequently (around 85%). Serous tubal intraepithelial carcinoma is the precursor lesion in high-grade serous ovarian carcinoma and is a relatively new discovery in the understanding of ovarian carcinoma development.

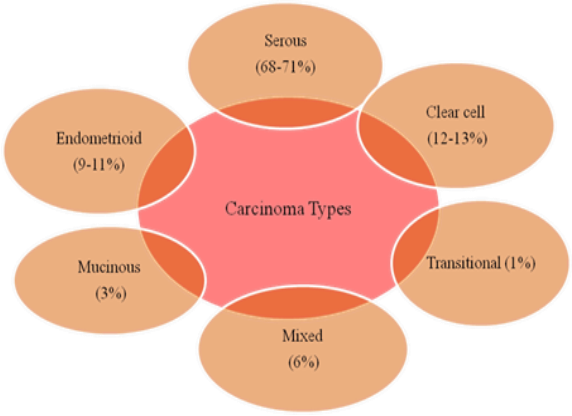

Fig-1: Relative frequencies of ovarian carcinoma sub-types.

Although the exact origin of ovarian carcinoma is uncertain, epidemiologic studies have shown that the biggest risk factor is a positive family history of both breast and ovarian cancer. Patients with ovarian carcinoma have a poor prognosis due to a number of factors, including the cancer's localization within the peritoneal cavity, the lack of early symptoms, the difficulty of surgically eradicating the cancer completely, and patient resistance to chemotherapy, which results in a 45% five-year survival rate. The disease is treated with antibody therapy, immune checkpoint inhibitors, vaccination methods, adoptive cell therapy, and combinatorial immunotherapy. The genesis and progression of ovarian cancer, its kinds and subtypes, diagnosis, prognosis, and treatment are all covered in a large number of review publications. As a result, current knowledge about ovarian cancer has to be reviewed and updated. Since epithelial ovarian carcinoma (EOC) is one of the most common gynecological carcinomas, the goal of this study is to provide the most recent worldwide perspective on this condition.

The epidemiology, diagnosis, prognosis, and therapy of epithelial ovarian cancer are all covered in this review.

2. LITERATURE

An ovarian cancer literature survey would normally entail compiling and summarizing important research papers, reviews, clinical trials, and other pertinent literature on a range of topics related to the pathophysiology, diagnosis, therapy, and prognosis of ovarian cancer. An example of how to organize your literature review is as follows:

- Introduction to Ovarian Cancer: A succinct summary of the disease's types (e.g., stromal, germ cell, and epithelial), prevalence, risk factors, and importance to women's health.
- The molecular pathways and pathogenesis: An outline of the molecular and cellular processes linked to the onset and spread of ovarian cancer, such as interactions between the tumor microenvironment and genetic abnormalities (TP53, PTEN), aberrant signal pathways (PI3K/AKT, MAPK), and others.
- Diagnostic Approaches: An overview of the current approaches to ovarian cancer diagnosis, including imaging tools (MRI, ultrasound), tumor markers (CA-125, HE4), and newer procedures including molecular profiling and liquid biopsies.
- Treatment Modalities: Examining the conventional approaches to treating ovarian cancer, such as hormone therapy, immunotherapy, targeted medicines (such as angiogenesis inhibitors and PARP inhibitors), chemotherapy (such as platinum-based regimens), and surgery. clinical studies, new developments, and customized medical strategies.

3. SUMMARY OF LITERATURE SURVEY

The diverse character of ovarian cancer and patient outcomes are highlighted in this summary, which offers a comprehensive review of the main conclusions and topics of interest within the literature survey. Survival variables and prognostic factors Results: Numerous factors, including tumor stage, subtype, genetic profile, and response to treatment, influence prognosis; research is continuously being conducted to improve prognostic markers.

Issues and Prospects: Research is being directed towards new therapeutic targets, biomarkers, and personalized medicine strategies in response to issues with ovarian cancer management, such as late diagnosis, treatment resistance, and recurrence.

4. EPIDEMIOLOGY

Compared to middle- and low-income countries, high-income countries have a higher incidence of ovarian cancer. About 239,000 instances were reported in 2012, representing over 4% of all new cases of carcinoma in women (2% total). Globally, the incidence rate of ovarian cancer is 4.1 per 100,000 in China, 5 per 100,000 in Africa, 11.7 per 100,000 in the United States, 5.2 per 100,000 in Brazil, and 11 per 100,000 in Central and Eastern Europe. An estimated 65,697 new cases and 41,448 fatalities occur year in Europe. According to the US Center for Disease Control and Prevention, around 20,000 women receive an ovarian cancer diagnosis each year, and 14,500 of them pass away as a result of the condition. With an overall five-year survival rate of 44.2%, the mortality rate for ovarian carcinoma has remained constant over the past 50 years, despite a decline in the mortality rate for many solid tumors. A woman has a 1 in 75 chance of getting invasive ovarian cancer in her lifetime, and she has a 1 in 102 chance of dying from it. Every year, some 9,600 women in Germany get malignant ovarian tumors, and 5,500 of them pass away from ovarian carcinoma. Because of the late state of the disease at diagnosis, the cure rate for epithelial ovarian carcinoma (EOC), which accounts for 14,030 of the 22,240 cases identified in the United States, is less than 40%. The information above clearly shows that ovarian carcinoma is one of the most deadly gynecologic cancers, accounting for the greatest number of deaths. Ovarian cancer has various morphological subtypes, each of which has a unique pathogenesis, natural history, prognosis, and molecular changes. According to various population-based cancer registries, the incidence of ovarian cancer in India (age- adjusted rate per 100,000) ranged from 1.7 to 15.2 over the2012–2014 period. In India, 45,231 and 59,276 incidences of this cancer are anticipated in 2015 and 2020, respectively.

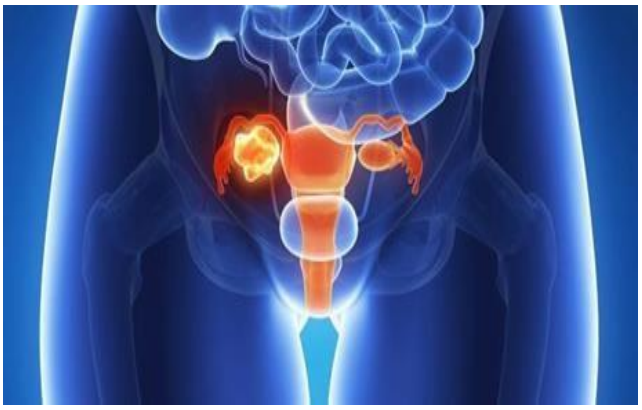

Fig-2: Female uterus with tumor

5. RISK FACTORS

The prevalence of ovarian carcinoma is influenced by a number of factors, and epidemiologic studies have shown that a positive family history of breast and ovarian carcinomas is one of the highest risk factors. The chance of contracting the disease may also be influenced by environmental variables and age. However, there is currently no conclusive evidence linking therapeutic radiation or industrial exposure to carcinogens to ovarian cancer. On the other hand, a lower incidence of ovarian cancer is associated with a number of reproductive characteristics, including hysterectomy, breastfeeding, tubal ligation, oral contraceptive use, and (multi) parity. Women up to the age of 70 have a 30% lifetime chance of getting ovarian cancer due to germ line mutations in the BRCA1 and BRCA2 genes, which appear to be a part of the family's phenotype. The length of time and duration of usage determine the overall advantages and disadvantages of oral contraceptives. The gene expression profile includes overexpression of genes (HNF-1 beta, HER2/neu, AKT, HLA-G, APO-E), microsatellite instability linked to type I and type II ovarian cancers, and genetic instability with mutations of genes (PTEN, AR1D1A, CTNNB1, KRAS, BRAF, ERBB2, TP53).

Because of the elevated levels of follicle stimulating hormone (FSH) and luteinizing hormone (LH), women undergoing infertility treatment are at a significantly higher risk of developing ovarian cancer.

5.1 Types of epithelial ovarian carcinoma:

Type I and type II are the two classes into which EOC is divided according to the dualistic paradigm. New histopathological, molecular, and genetic investigations have been based on an improved model of the two main kinds of ovarian carcinogenesis, namely type I and type II. Type I tumors are indolent, slow-growing neoplasms that develop from atypical hyperplasia, a well-defined precursor. These tumors do not exhibit TP53 mutations within a stable genome and are limited to the ovary at the time of diagnosis. On the other hand, somatic mutations are often linked to specific genes in the case of type I tumor. Endometrioid adenocarcinoma, mucinous carcinoma, clear cell carcinoma, and low-grade serous carcinoma are all classified as type I tumors. Most type II tumors have TP53 mutations, are discovered at an advanced stage, are high-grade clinically with more aggressive neoplasms, and are genetically extremely unstable. Previous investigations have revealed that the ovarian surface epithelium and/or the epithelium of the fimbrial part of the fallopian tube may be the origin of type II cancers, including high-grade serous carcinoma.

Tumor type -1: Serous carcinoma of low grade. In the United Kingdom, serous carcinoma is now classified as low-grade and high-grade. The MD Anderson Group (Houston, Texas, USA) first developed this two-tiered grading system, which is currently used by many gynecological pathologists. From a benign serous cystadenoma to a serous borderline tumor to an invasive low-grade serous carcinoma, low-grade serous carcinoma is believed to develop in a well-defined adenoma-carcinoma sequence in a stepwise manner. This kind of tumor has less than or equal to 12 mitoses per 10 high power fields, mild atypia, and neither necrosis nor multinucleation. With glands and papillae encircled by intracytoplasmic mucin and clefts or non-epithelial lined spaces, psammoma bodies are quite prevalent. Although TP53 mutations are not linked to low-grade serous carcinoma, KRAS or BRAF mutations—which are mutually exclusive—are linked to two-thirds of its cases. Some doctors do not use adjuvant chemotherapy because low-grade serous carcinomas do not react well to conventional chemotherapeutic drugs.

Mucinous carcinoma: It affects people of several ages, including occasionally children and teenagers, and is quite rare. It has been determined that smoking is a significant risk factor for mucinous, benign, and borderline carcinoma. Small and bilateral tumors, ovarian involvement in the form of nodules, destructive stromal invasion, single cell infiltration with signet ring cells, cells floating in mucin, extraovarian spread, and significant lymphovascular space invasion are common characteristics of ovarian mucinous carcinoma that favor metastasis. Although goblet cells and occasionally paneth or neuroendocrine cells are present in many ovarian mucinous carcinomas, the majority are of the intestinal type. KRAS mutations are frequently seen in ovarian mucous carcinoma, just like in low-grade serous carcinoma. However, ovarian mucous carcinoma does not have a BRAF mutation, in contrast to low-grade serous carcinoma.

Clear cell carcinoma: Approximately as common as endometrioid adenocarcinoma, clear cell carcinoma is mostly made up of cells with a robust cell membrane and an abundance of clear cytoplasm. While clear cell carcinoma is often either positive or negative for the p16 gene, it is typically triple negative for the p53, Wilms tumor (WT1), and estrogen receptor (ER) genes. Most of these cancers originate in the endometrium and are identified early on (stage I or II). A stage I disease has a comparatively excellent prognosis, despite the fact that such cancer has a rather bad prognosis. These tumors have a low proliferation index and are not responsive to the transitional chemotherapy drugs used to treat ovarian cancer. Previously, there were no known molecular events associated with clear cell carcinoma; however, it has subsequently been discovered that the ARID1A mutation plays a role in these cases.

Endometrioid adenocarcinoma: Usually unilateral, with 10% being bilateral, endometrioid adenocarcinomas are low-grade tumors with a low staging (stage I); however, some of these tumors may be high-grade. They typically develop from an underlying borderline adenofibroma or from the implantation of endometrial tissue, particularly an endometriosis cyst. Mutations in the phosphatase and tensin homolog (PTEN), which are removed from the

chromosome 10 tumor suppressor, are commonly observed in ovarian endometrioid carcinomas. Similar molecular events, including as PTEN, β-catenin, KRAS, and PIK3CA mutations with microsatellite instability, are seen in ovarian endometrioid adenocarcinoma and uterine endometrioid adenocarcinoma.

Tumor Type-2: High-grade serous carcinoma. Compared to low-grade serous carcinoma, high-grade serous carcinoma is more prevalent. This kind of tumor is high-grade from the beginning, develops swiftly, and is usually discovered at an advanced stage. Numerous high-grade ovarian serous carcinomas have been shown in the literature to arise from the distal fimbrial part of the fallopian tube's epithelium. With more than 12 mitoses per 10 high power fields, high-grade serous carcinoma exhibits mild to considerable nuclear atypia, necrosis, and multinucleate cells. TP53 mutation or p53 malfunction is frequently implicated in such situations, and it seems to happen during the early stages of neoplastic growth. Patients with low-grade neoplasms who received chemotherapy have a substantially higher survival rate than those with high-grade tumors.

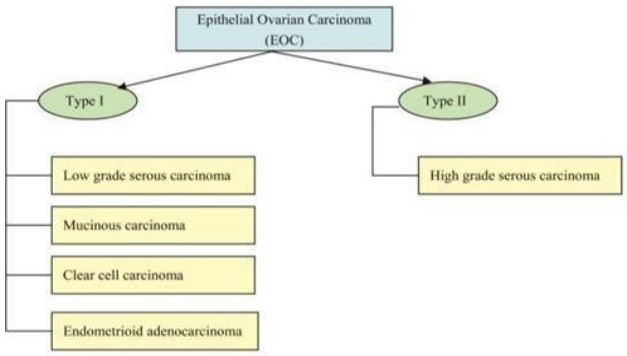

Fig-3: Different types and subtypes of epithelial ovarian carcinoma

6. Screening and diagnosis

The lack of certain symptoms in patients makes it extremely difficult to diagnose ovarian carcinoma at an early stage, which lowers the patient's chance of survival. According to the International Federation of Gynecologists and Obstetricians (FIGO) committee, imaging is a crucial factor in determining the location and degree of ovarian cancer dissemination as well as the best course of treatment. Magnetic resonance imaging (MRI), computed tomography (CT) scans, and ultrasound are frequently utilized imaging techniques. Exploratory laparotomy is done to confirm the etiology of ovarian cysts, and physical examination and transvaginal ultrasonography are utilized to diagnose tumors. Combining the Symptom Index (SI) with a blood HE4 or CA125 test can enhance the screening process for ovarian cancer. A statistical technique called the risk of ovarian cancer algorithm (ROCA) is used to screen for EOC by estimating the likelihood of a change-point based on a woman's age and CA125 profile.

6.1 Different stages and grades

Following diagnosis, the International Federation of Gynecologists and Obstetricians (FIGO) developed a stage system for ovarian carcinoma that is primarily based on whether the cancer is confined to the ovary or has progressed to other parts of the body. Stage IIC was eliminated from the previous staging system when it was changed in 2014, and new sub-stages of IC (IC1, IC2, and IC3), IIIA (IIIA1 and IIIA2), and IV (IVA and IVB) were added. Figure 4 illustrates the various stages. Bloating, edema, and overall abdominal discomfort are possible early symptoms.

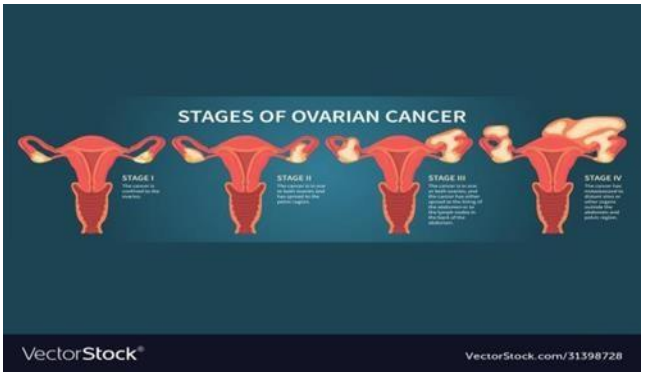

Fig-4: Different stages of ovarian cancer

6.2 Prognosis

Seven microarray research have been carried out to predict the gene profiles in ovarian carcinoma cells, and microarray studies have been utilized to analyze gene expressions in carcinoma cells. Numerous parameters, including the patient's age, performance status, tumor stage and ascites, tumor grade, histopathologic subtype, obesity, surgical de-bulking, gene expression (CYP4B1, CEPT1, CHMP4A), and immunological factors, were found to be connected with the prognosis of EOC in a recent study.

6.3 Treatment

Surgery alone, without adjuvant chemotherapy, can cure the cancer in the majority of low-risk cases that are identified early. However, patients with a high-grade disease staging (FIGO IC) have been observed to benefit from adjuvant treatment. Currently, the stage and grade of the tumor—rather than its type—determine the adjuvant therapy. Chemotherapy can, however, have certain adverse effects, including infertility, menopause, rashes on the hands and feet, mouth sores, hair loss, nausea, and vomiting. Chemotherapy occasionally causes bone marrow destruction as well, which raises the risk of infection. As a result, patients who exhibit these adverse effects cannot benefit from chemotherapy; instead, they require other forms of treatment. Women with advanced ovarian carcinoma (stage III–IV) who undergo surgical cytoreduction (complete abdominal hysterectomy, bilateral salpingo-oophorectomy, removal of pelvic and para-aortic lymph nodes, and

omentectomy) and platinum-based chemotherapy have shown a survival rate of 10%–30%. Another study found that having a bilateral oophorectomy at the same time as a hysterectomy increased the risk of lung cancer, coronary heart disease, both fatal and nonfatal, and all-cause mortality. Patients who were given combinational chemotherapy had a significantly higher survival rate than those who received single chemotherapy, according to a study done on platinum-sensitive patients with ovarian carcinoma to compare the effectiveness of single chemotherapy (platinum alone) versus combinational chemotherapy (platinum plus paclitaxel). One weekly dose of paclitaxel is less harmful than three weekly doses, according to a recent study. Although the use of biomarkers to select ovarian cancer cells has been promoted, finding these markers has proven difficult. As of right now, two indicators have been found: the overexpression of folate receptor-α in this form of cancer and the mutation in the BRCA gene, which indicates a lack of DNA repair via the homologous recombination pathway. A novel approach to treating ovarian cancer includes dose-dense chemotherapy, intraperitoneal chemotherapy, molecular targeted therapy, and optimum cytoreductive therapy. Investigating immunological checkpoints—the process by which cancer cells disable the immune system—represents a promising treatment option for ovarian cancer in recent years. Lipkowitz and Kohn have reported using hormone replacement therapy to treat cancer. Another promising and secure method for treating ovarian cancer is fertility sparing surgery (FSS). Recently, early-stage epithelial ovarian cancer and borderline ovarian cancers have been successfully treated with FSS therapy. In addition to being used in logical pathway-targeted therapeutic combinations, such as co-targeting PI3-kinase signaling, and dosing strategies to prevent or delay drug resistance and achieve long-term survival benefit, BRAF inhibitors (vemurafenib and dabrafenib) and MEK inhibitors (trametinib) provide ovarian carcinoma patients with a more promising option. The US Food and Drug Administration (FDA) has licensed poly(ADP-ribose) polymerase (PARP) inhibitors as a monotherapy for patients who have received chemotherapy in the past. Because of oxygenation changes, the inhibitors have also demonstrated synergistic activity with anti-angiogenic medicines. For patients with BRCA-deficient ovarian cancer in the US and Europe, the use of these inhibitors has created an entirely new therapeutic option. medications that damage DNA, such as doxorubicin and bleomycin, have been demonstrated to inhibit the expression of PTTG1 (pituitary tumor transforming gene) and activate p53. These medications cause cell cycle arrest in order to repair the damaged DNA. Additionally, through controlling cellular transcription, p53 facilitates programmed cell death. Following vaccination, patients with advanced refractory gastrointestinal malignancies showed improved T-cell identification of p53 in the first human trial of the p53-targeting modified vaccinia Ankara (p53MVA) vaccine. Nivolumab, an anti-PD-1 immunotherapy medication, was found to be beneficial in a prior research including patients with advanced platinum-resistant ovarian cancer.

Fig-5: Different treatments for ovarian cancer

7. COMPARISION

characteristics	Epithelial tumours	Cell tumours germs
Prevalence	Much more common	Less common
Age group	Mainly adult women	Mainly female child and young women
Affected race	More common in white women	More common in black and Asian women
Laterality	Malignant serous and mucinous tumour cells	bilateral
Tumour markers	Cancer-125	a-fetoprotein
Endocrine Manifestations	No	Resulting from hormone production.

8. CONCLUSION

With a high incidence rate of up to 15 per 100,000, ovarian cancer is the most deadly cancer in women and the leading cause of death. Of the several forms of ovarian cancer, EOC is the most common. Based on the genes implicated in carcinogenesis, the stage, and the risk factors involved, EOC is classified as either Type I or Type II. The most widely used methods for ovarian cancer screening and diagnosis include ultrasound, CT, and MRI. Meanwhile, the treatment is either chemotherapy, surgery, or a mix of the two. The condition can now be treated with a variety of more recent medicines. Research is under underway with the goal of creating new, efficient screening techniques to identify the illness early.

9. ACKNOWLEDGEMENT

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