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A Comprehensive Review, Epithelial Ovarian Cancer: A Journey Through Molecular Mechanisms, Clinical Management, And Future Perspectives

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ABSTRACT

About 6000 new cases of epithelial ovarian cancer are detected in the UK yearly, making it the most fatal gynecological cancer among women internationally. Although most women respond well to treatment in the beginning, most recur after presenting with severe disease. The 5-year survival rate is 47% generally, while for women with severe illness, it lowers to approximately 29%. In current randomized trials, CA125,transvaginal sonography, and the tumor indicator are being studied for screening reasons.The management of ovarian cancer comprises a multidisciplinary team and is contingent upon the clinical stage of the disease.Adjuvant chemotherapy, as well as pelvic clearance, are required for the majority of patients.The National Institute of Clinical Excellence (NICE) has updated its instructions,stating that paclitaxel or a platinum-based regimen should be a part of first-line chemotherapy.Although ovarian cancer, which has relapsed,is fatal,treatment can extend survival and enhance the standard of life.Recent clinical research examines gene therapy,immunotherapy,and signal transduction blockers as potential treatments for ovarian cancer.Studies have shown that as people age, their ovaries' cells experience metabolic changes, diminished DNA repair,mitochondrial failure,and epigenetic modifications.With almost 90% of cases, high-grade serous carcinoma (HGSOC) is the most prevalent kind of epithelial ovarian cancer. Ineffective wound healing or fallopian tube cancers may be part of its etiology.Malignant ascites indicate a terrible prognosis.Tumor metastasis, chemoresistance, and tumor formation are all encouraged by the disease's microenvironment, which includes immune cells and tumor-associated fibroblasts.This work analyzes research on pathophysiology, epidemiology, clinical characteristics, and available ovarian epithelial cancer treatments.

KEYWORDS:*Ovarian cancer,Gynecological cancer, Cytoreduction, Adjuvant therapy,Targeted therapy, Survival, Treatment, Carcinoma.*

INTRODUCTION

Epithelialovariancarcinoma(EOC)is considered the most deadly type of gynecological cancer.Globally,ovariantumors cause about200,000 fatalities annually,resulting from their diverse range of malignancies.Tubo-ovarian carcinomas(OC),which are often detected at a severe stage and have a high risk of relapse and death, account for the great majority of cases [1].Early signs of OC may appear generic and can go unnoticed.The most typical is bloating in the abdomen;other typical symptoms in women include constant pelvic or abdominal pain,trouble eating or feeling full swiftly, and urgency or frequency of urination [2].With more than two-thirds of women appearing with advanced stages of ovarian cancer, the 5-year survival rate is expected to be anywhere from 20 to 40 percent. On the other hand, almost 90% of patients who receive a diagnosis at earlier stages (like a stage 1 illness) survive for five years [3].Excellent interdisciplinary care is necessary for treatment.Molecular genomics is currently used to inform

novel methods for early detection and prevention, as population-based screening appears unhelpful in this regard [4]. Similar to lung and colon cancer, the therapy landscape for ovarian cancer has also started to see innovation in the discovery of biomarkers [5.] High-grade serous carcinoma (HGSOC) is the most prevalent presentation of epithelial ovarian cancer (EOC),which accounts for more than 90% of cases of the disease.Fallopian tube tumors or ineffective wound healing during ovulation may be the root cause of the complex and multidimensional pathogenesisof HGSOC.Malignantascites,a form of inflammatory fluid comprising cancer cells, DNA,signaling compounds,and extracellular matrix (ECM) proteins, are symptomatic of a poor prognosis. The microenvironment of the disease performs a critical role in its advancement.Through their interactions with cancer cells, tumor-associated fibroblasts (CAFs) as well as immune cells, including T-cells and tumor-associated macrophages (TAMs), generate a pro-tumoral milieu that promotes metastasis, chemoresistance, and tumor development via a variety of signaling pathways, most notably those including TGF-β [6]. As there are no prominent symptoms in the beginning stages of OC,studies have been centered on discovering beneficial biomarkers for diagnosis.The fundamental goal of these investigations is to discover unique proteins and chemicals closely associated with the onset of OC.The readily available and less invasive blood serum and plasma samples include these diagnostic biomarkers.Among the serum indicators, it is essential to highlight VEGF, transthyretin (TTR),prostasin (PSN),HE4, Kallikreins, CA-125,and transferring.In terms of plasma markers, osteopontin (OPN) and apolipoprotein A-I (apoA-I) are frequently tested in clinics [7].Prognostic biomarkers are another category of biomarkers that can predict which clinical events,for instance,disease relapse or mortality,will happen in the future or following a specific course of treatment.These biomarkers may be applied to choose a combination of more severe treatments, including CA-125, OPN, and VEGF [8].

METHODS

EPIDEMOLOGY

EOC is the deadliest kind of gynecological cancer.One of the leading causes of the high death- to-incidence rate is the severe stage of the disease at the time of detection;75% of patients receive the diagnosis at a later stage due to the silent development of EOC,and up to 15% of affected women have a genetic predisposition to the disease[9].Women possess a 47.3% probability of surviving for five years.13.7% of ovarian cancer cases are found locally, and 52% of cases are identified when the cancer has expanded,at which point the five-year survival rate drops to 29.7% from 91.8% if the cancer was found earlier before it spread locally.90% of ovarian cancers are epithelial,with the serous subtype being the most prevalent.According to the statistical methods of assessment,the rate of fresh cases of ovarian cancer adjusted for age is becoming less common [10].

The estimate of 313,959 new ovarian cancer cases globally in 2022 is based on data from the GLOBOCAN 2022 database,managed by the International Agency for Research on Cancer (IARC).The ASR incidence and mortality of ASR (World) per 100,000 people are shown in Figure 1.Geographically, ovarian cancer incidence and mortality rates differ significantly;more excellent rates are generally seen in more developed locations like Europe and North America, whereas lower rates are found in South-Central Asia and Africa.The high mortality rate associated with ovarian cancer is primarily due to its often late diagnosis,which underscores the need for improved early detection methods and more effective treatment options.[11]

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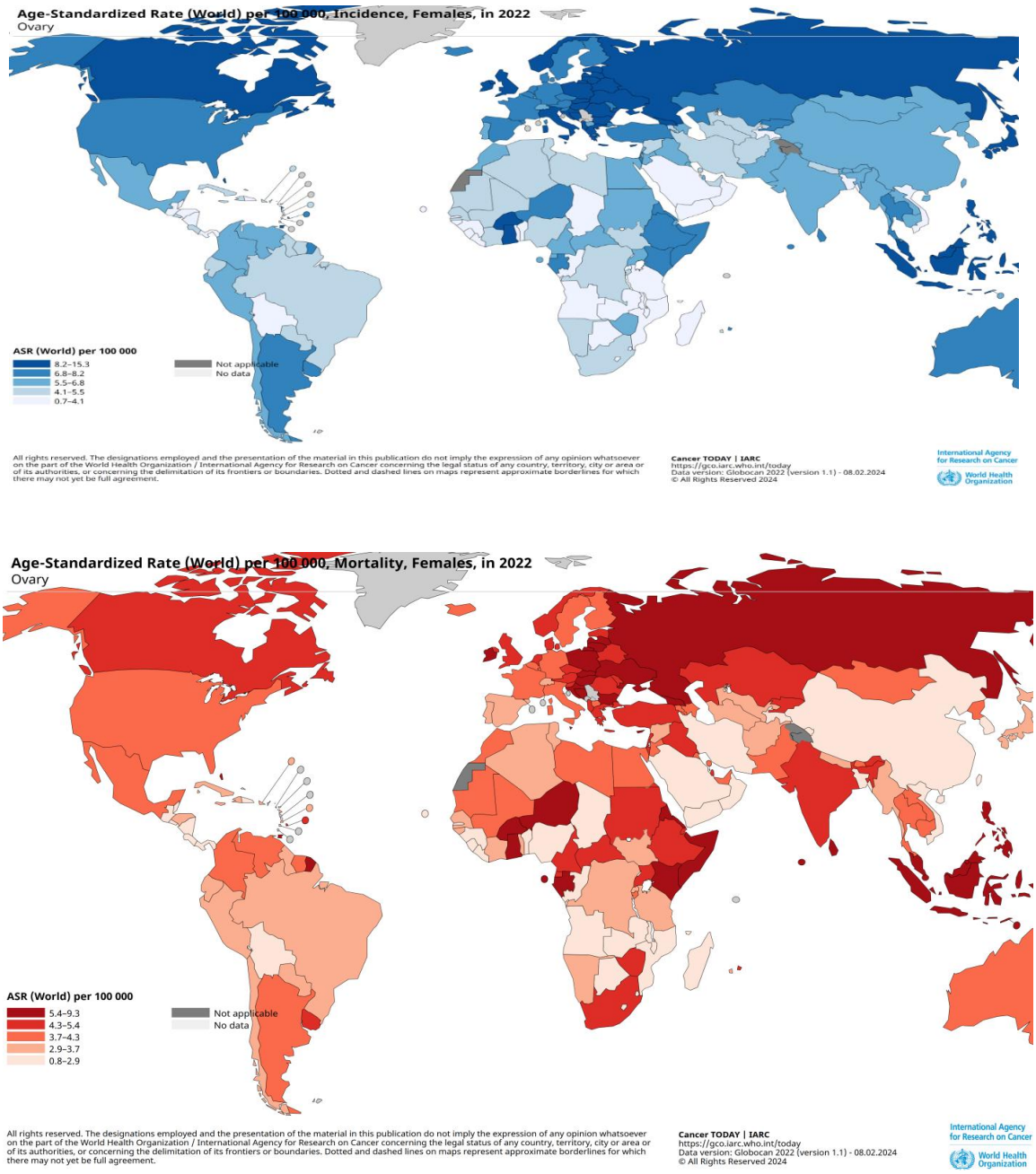

Figure1.Global incidence and mortality of ovarian cancer, all ages, in 2022; Data source: https://gco.iarc.who.int/today

RISK FACTORS

Women having a family record of ovarian cancer are considered to have a greater chance of developing the disease. The risk is approximately three times greater for women who possess a first-degree afflicted relative than for those without any, and it is substantially more significant for those whose relative has been diagnosed under 50 years old.

BRCA (BReast CAncer) gene mutations cause many hereditary malignancies,yet these mutations are also frequently observed in ovarian cancer patients who lack a family history of the disease [12]. While the

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lifetime risk for acquiring EOC is 1.3%, for women harboring a BRCA1 mutation, it may vary from 40-45%, and for those having a BRCA2 mutation,it can reach 15-20%.Increasingage,infertility,endometriosis,polycysticovariansyndrome,and usage of cigarettes (for mucous carcinomas) are the common risk factors for endometriosis and polycystic ovarian syndrome.A germline mutation is linked to an estimated 18% of EOC cases.The two crucial additional risk variables are hormonal and reproductive. It seems that ovulation plays an integral part in the development of ovarian cancer as a more significant lifetime number of menstrual cycles corresponds to an increased risk of EOC. Pregnancy, breastfeeding, and the oral contraceptive pill are examples of factors that delay ovulation;nulliparity is linked to increased risk.Elevated height,weight,and body mass index are all connected with a slight but long-lasting risk, as is hormone replacement treatment (HRT).Alcohol and diet fail to strongly correlate [13].

HISTOPATHOLOGY

Epithelial ovarian cancer (EOC) accounts for 90% of all ovarian cancers (OCs) and is one of the most thoroughly studied forms of the disease.EOCs are believed to originate from the epithelium, the ovary's outer layer.This type of cancer is age-related, primarily affecting postmenopausal women[14].The diagram Figure 2 shows

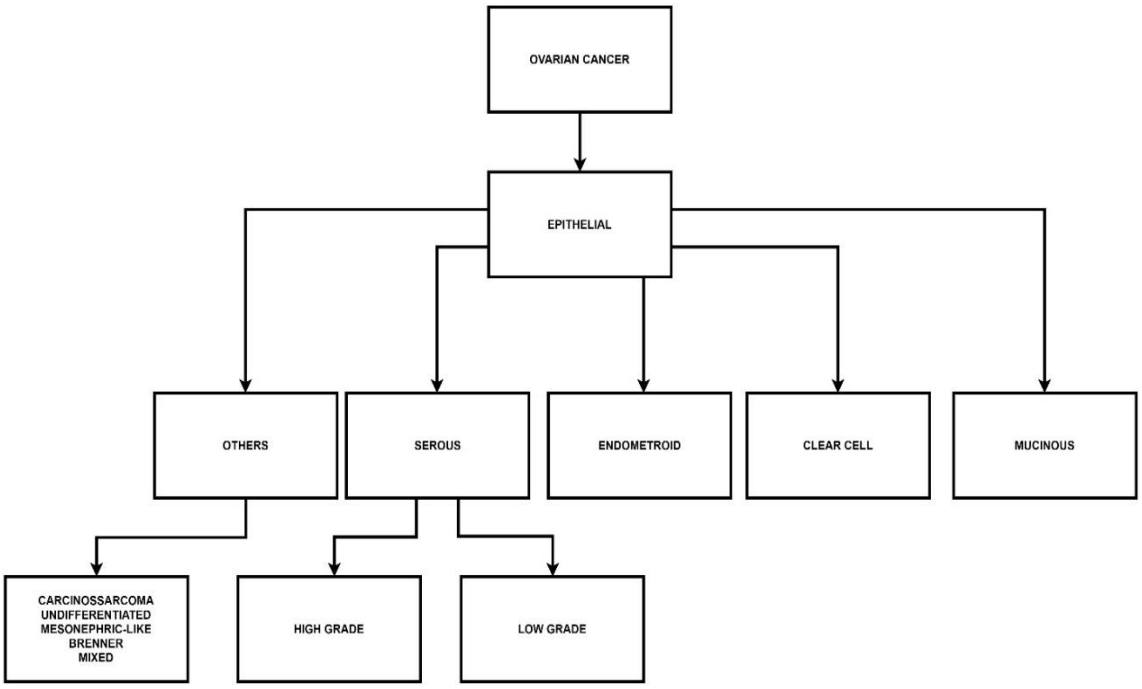

Figure 2: Classification of ovarian cancer subtypes, focusing on epithelial ovarian cancers and their salient features..

The hierarchical organization of epithelial ovarian cancers,which include the significant subtypes:serous,endometrioid,clear cell, mucinous, and others.Serous carcinomas are further divided into high-grade (HGOSC) and low-grade (LGOSC) categories.The "Others" category encompasses rare types such as carcinosarcoma, undifferentiated, mesonephric-like, Brenner, and mixed tumors.Based on the morphology of the tumor cells,EOCs are further classified into high-grade serous ovarian carcinoma

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(HGSOC),low-grade serous ovarian carcinoma (LGSOC),mucinous ovarian carcinoma (MOC),endometrioid carcinoma (EC),and clear-cell carcinoma (CCC),in Figure3.

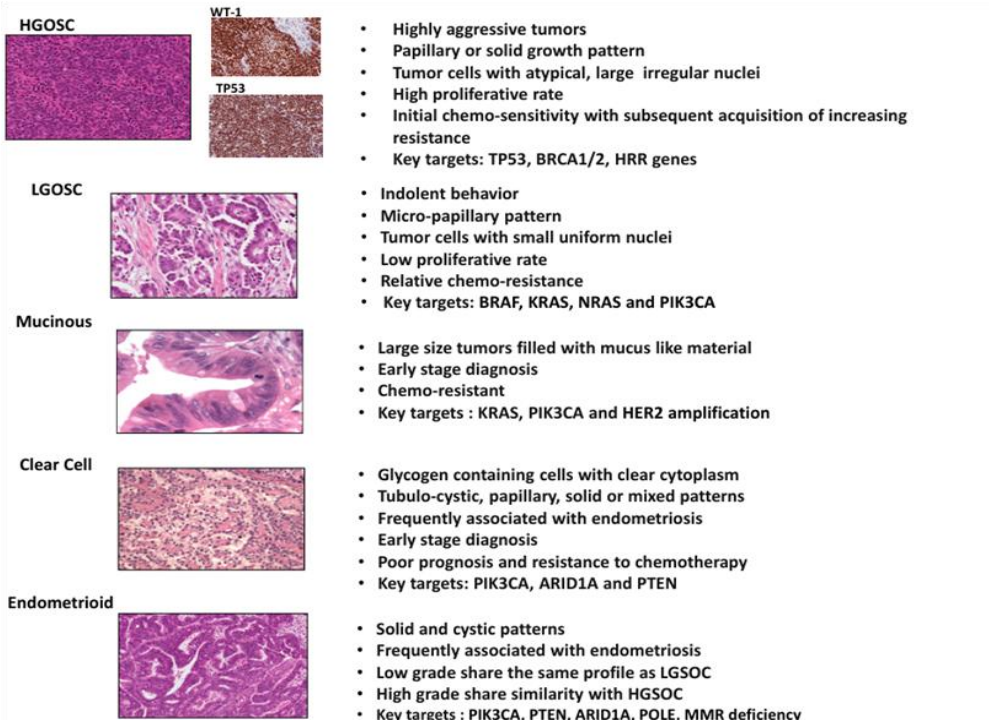

Figure 3:Different histological subtypes of epithelial ovarian cancer

It provides an overview of the histological characteristics,epidemiology,molecular alterations,and pathways associated with each EOC subtype.Since ovarian cancer can present as various histology subtypes with differing treatment approaches,pathologic diagnosis of tumor tissue is crucial. In the past ten years, it has become evident that EOC is a group of diseases with different precursor lesions,tissues of origin, molecular biology,clinical presentation,chemosensitivity, and patient outcome[15]

This classification is essential for understanding the distinct biological behaviors, prognosis, and therapeutic responses associated with each subtype.Approximately 90 percent of ovarian tumors are of epithelial origin,while the remaining 10 percent consist of tumors arising from stromal or germ cells [16].The most common types of ovarian carcinoma, based on their histological features, include endometrioid, mucinous, serous, and clear-cell carcinomas, all of which are derived from epithelial cells.These carcinomas are further divided into subtypes based on their biological characteristics and responses to treatment, with Brenner and seromucous carcinomas being rarer forms. Ovarian cancer is categorized into two primary subtypes:Type 1 and Type 2 tumors.Type 2 tumors are more lethal and are often linked to prolonged ovulatory cycles, which can lead to inflammation and conditions such as endometriosis.In contrast,Type 1 tumors,which are less aggressive,encompass low-grade serous,endometrioid,clear-cell,and mucinous carcinomas,along with the uncommon seromucous and Brenner tumors.It is believed that Type 1 cancers may develop from borderline (atypical proliferative) tumors.Type 2 tumors generally originate from tubal intra-epithelial carcinoma, specifically of the serous type, and include various forms such as carcinoma, carcinosarcoma, and high-grade serous carcinoma. These tumors are typically poorly differentiated and lack distinct features. On the other hand, Type 1 tumors are often low-grade, tend to appear in the early stages of cancer, and include clear-cell tumors, although clear-cell tumors themselves are considered high-grade. Type 1 tumors grow slowly, leading to a better prognosis and higher likelihood of early diagnosis. In contrast,Type2 tumors are classified as

high-grade and are usually identified at more advanced stages of the disease. A significant level of chromosomal instability characterizes them,and they grow rapidly and aggressively.This starkly contrasts Type1 tumors, where p53 mutations are commonly observed.The aggressive nature of Type2 tumors,coupled with their advanced stage at diagnosis, contributes to their poorer prognosis compared to Type1 tumors [17].

SCREENING

Upon comparing annual transvaginal ultrasound screening with no screening, the risk for ovarian cancer algorithm (ROCA) failed to demonstrate a substantial decline in death rates, according to the UKCTOCS trial (NCT00058032), a randomized controlled study involving over 200,000 women evaluating annual multimodal screening with serum cancer antigen (CA125).A considerable phase shift in women diagnosed with invasive ovarian, tubal, or peritoneal cancer with multimodal screening relative to no screening has prompted additional follow-up to evaluate the late benefit (7–14 years after an index screening event) in postmenopausal women.CA125 has been utilized to assess other biomarker combinations, including human epididymis protein 4,a glycoprotein released by the female reproductive tract's Mullerian epithelia.Implementing transvaginal ultrasound and ROCA, a study12 tested 4348 women who had a lifetime risk of 10% or greater for ovarian or fallopian tube cancer. The outcomes demonstrated a stage shift, with 53% of diagnoses made during the trial being early-stage cancers, compared to just 6% of early-stage cancers identified over a year after the trial screening oncluded. A longer time frame of observation will reveal how this tactic impacts survival. In healthy individuals with a high hereditary risk of ovarian cancer, risk-reducing salpingo-oophorectomy at a genetically predetermined age is advised. In addition, efforts are being made to enhance the genomic screening approach [18].

CLINICAL PRESENTATION

Since the initial Phase of the disease can often be asymptomatic, more severe forms of ovarian cancer are usually diagnosed.Abdominal distension,altered bowel habits,vaginal bleeding,or pain constitute common symptoms.Constipation or frequent urination are instances of pressure symptoms which can result from a big pelvic tumour. A stable uneven pelvic mass, easily felt by vaginal examination,serves as one of the most significant clinical indicators of ovarian cancer. Ascites, palpable neck nodes, and pleural effusions are possible additional clinical signs [19].

DIAGNOSIS

Abdominal bloating,early satiety,nausea,abdominal distension,alteration in bowel function, urinary symptoms,back pain,exhaustion,and weight loss are among the non-specific symptoms of EOC that usually appear months before a diagnosis [20].Determining CA125 concentrations and pelvic ultrasonography are two of the first investigations.Additional imaging should include a pelvic MRI, if necessary, and CT scans of the abdomen, pelvis, and chest for staging to precisely determine EOC extension.Surgical procedures that comprise total abdominal hysterectomy, bilateral salpingo-oophorectomy,omentectomy,peritoneal surface examination with biopsy or excision of any suspect areas,and dissection of the para-aortic and pelvic lymph nodes are all considered optimal staging.A skilled gynecological oncology surgeon should perform the surgery to leave no residual illness.The International Federation of Gynecology and Obstetrics staging of ovarian cancer (FIGO stage) or AJCC-TNM classifications will be used in the staging technique to determine the surgical stage [21].Prospective investigations have assessed the diagnostic and staging capabilities of different imaging modalities for ovarian cancer,including computed tomography, magnetic resonance imaging (MRI),and FDG-PET [22].The preferred pre-operative imaging test is still ultrasound; computed to mography is most helpful in tracking the spread of metastatic disease,while magnetic

resonance imaging (MRI) aids in differentiating between benign and malignant cystic masses[23].Many people use repeated CA125 measurements to track their condition during treatment.

STAGING

The disease ovarian cancer can be surgically staged.The majority of ovarian malignancies are treated surgically except if there is a severe medical reason why the procedure cannot be performed. The table1 represents the FIGO staging classification for cancer of the ovary[24.]

FIGO Stage	Description of OC
Stage I	Tumor limited to the ovaries (one or both)
Stage IA	Tumors are limited to one ovary; the capsule is intact, and there is no tumor on the ovarian surface. No malignant cells in ascites or peritoneal washings*
Stage IB	Tumor limited to both ovaries; capsule intact, no tumor on the ovarian surface. No malignant cells in ascites or peritoneal washings
Stage IC	Tumor limited to one or both ovaries with any of the following: capsule ruptured, tumor on ovarian surface, malignant cells in ascites or peritoneal washings
Stage II	Tumor involves one or both ovaries with pelvic extension.
Stage IIA	Extension and/or implants on uterus and/or tube(s). No malignant cells in ascites or peritoneal washing.
Stage IIB	Extension to other pelvic tissue. No malignant cells in ascites or peritoneal washings
Stage IIC	Pelvic extension (2a or 2b) with malignant cells in ascites or peritoneal washings
Stage III	Tumor involves one or both ovaries with microscopically confirmed peritoneal metastasis outside the pelvis and/or regional lymph node metastasis.
Stage IIIA	Microscopic peritoneal metastasis beyond the pelvic
Stage IIIB	Macroscopic peritoneal metastasis beyond pelvic 2 cm or less in great dimension
Stage IIIC	Peritoneal metastasis beyond pelvic more than 2 cm in most significant dimension and/or regional lymph node metastasis.
Stage IV	Distant metastasis (excludes peritoneal metastasis)

Table 1:The different stages of Ovarian cancer progression and its hallmark features.

It displays the different stages of ovarian cancer progression and their key characteristics,and then four stages of ovarian cancer,showing the extent of cancer spread at each stage.Stage 1 is when the cancer is confined to one or both ovaries,with tumors localized only in the ovaries.Stage 2 is when the cancer has spread within the pelvic region,affecting nearby organs such as the bowel or bladder.Stage 3 is when the cancer has spread to other parts of the abdomen, including the lymph nodes and vagina.Stage 4 is when the cancer grows beyond the abdomen and spreads to distant organs, including the lungs and liver.This progression highlights the increasing severity and spread of cancer as it advances through the four stages.[25]

PROGNOSIS

Numerous clinical and biological variables are connected with the prognosis of ovarian cancer. The best indicators of prognosis are the tumor stage, grade, and extent of metastatic disease following resection.Tumor grade is correlated with prognosis in patients with low-stage disease (i.e., patients with stage I high-grade lesions had a shorter survival than those with low grade [26]. After surgery,the extent of the remaining disease in individuals with advanced stages of the disease most strongly corresponds with survival.Additionally correlated with survival is the rate at which the illness regresses throughout chemotherapy.More than a dozen studies have found a correlation between increased survival and the serum tumor marker CA 125's short apparent half-life.After the third round of treatment,normalization of CA 125 has been linked to a good prognosis [27].Several biological variables have been linked to the prognosis of ovarian epithelial carcinoma. Friedlander and colleagues have demonstrated through the use of flow cytometry that ovarian malignancies are typically aneuploid and that there is a relationship between ploidy and FIGO stage (high-stage tumors likely to be aneuploid, while low-stage cancers tend to be diploid).The median survival time for patients with diploid tumors is five years, compared to 1 year for those with aneuploid tumors [28].Ploidy is one of the most important predictors of survival and an independent prognostic variable, as multivariate analyses have shown.The cell cycle is another topic covered by flow cytometric analysis,and some research has found a correlation between prognosis and the proliferation fraction (S phase) ascertained using this method.

TREATMENT OF EARLY-STAGE OVARIAN CANCER

Individualized care is required for patients with early-stage epithelial ovarian cancer.It is recommended that all patients with early-stage illness have comprehensive surgical investigation and staging.It is reasonable for women who are most at risk of recurrence to have adjuvant treatment,such as chemotherapy or radiotherapy [29].

SURGERY

Early disease that is appropriately staged can be treated conservatively.For invasive stage I epithelial ovarian cancer,surgery—complete abdominal hysterectomy,bilateral salpingo-oophorectomy,and surgical staging—is the main course of treatment [30].

RADIOTHERAPY

External beam radiation therapy has been the subject of two randomized studies in stage I EOC. Both examined pelvic irradiation in the absence of any postoperativecare.Although the peritoneal cavity was the site of relapses,these trials indicated that pelvic irradiation decreased the incidence of pelvic relapses;nonetheless,this was not a therapeutic advantage.While not examined in a PhaseIII trial,abdominal-pelvic radiotherapy was contrasted with pelvic radiotherapy,and no treatment was performed in Stage I.In grade1,where the total risk of recurrence was less than 5%, no benefit was observed.There was a nonsignificant drop in the risk of recurrence in grades2 and3.Patients with highly adherent tumors showed

a considerable reduction in relapse probability;however,these patients are more accurately diagnosed in stage II [31].

CHEMOTHERAPY

Chemotherapy for women with early-stage cancer has been questioned by some researchers, who contend that there is insufficient data to support a long-term benefit to survival. Furthermore, unless there is a clear benefit, adjuvant therapy should not be administered due to the risks of leukemia associated with cisplatin and alkylating drugs [32].

MANAGEMENT OF EARLY-STAGE BORDERLINE TUMORS

The primary tumor is surgically removed as the main course of treatment for ovarian tumors that are borderline.There is no proof that receiving radiation or chemotherapy later on increases survival.Unilateral salpingo-oophorectomy is one conservative procedure that may be used to preserve ovarian function in premenopausal females who wish to maintain it after a frozen section is performed.The histology is found to be borderline.Fertility and hormone function can thus be preserved.There is no need for further surgery in patients who have had an ovarian cystectomy and a borderline tumor identified in the permanent pathology [33].

MANAGEMENT OF INVASIVE EARLY STAGE LOW RISK DISEASE (STAGE IA AND IB, LOW GRADE)

An abdominal hysterectomy and bilateral salpingo-oophorectomy are suitable treatments for patients who have had a thorough staging laparotomy and show no signs of the cancer spreading outside of the ovary.In women who prefer to maintain their fertility yet have stage IA diploid lesions, the uterus and contralateral ovary can be retained.Follow-up care for these women should include regular pelvic exams and CA125 titers.When childbearing is finished, the other ovary and uterus are typically removed.

MANAGEMENT OF INVASIVE EARLY-STAGE HIGH-RISK DISEASE (STAGE IA AND IB, HIGH GRADE, STAGE IC, AND STAGE II)

Further therapy is appropriate for patients with poorly differentiated illnesses or malignant cells in their peritoneal washings or ascitic fluid. Postoperative treatment is necessary for patients with grade2 and grade3 tumors,densely adherent tumors, large-volume ascites,and positive peritoneal cytology, as these patients have a 20% to 45% chance of relapse.Unfortunately,it seems that complete staging with negative results—including random lymph node sampling and peritoneal biopsies—does not seem to completely remove the possibility of relapse in patients who exhibit these traits [34].Treatment options for these patients include abdominopelvic radiation therapy or platinum-based chemotherapy, although the best course of action is unknown. Patients with high-risk, early-stage epithelial ovarian cancer may receive three to six cycles of chemotherapy consisting of either carboplatin alone or in combination with a taxane.Despite being simple to administer,melphalan is not advised because of its leukemogenic qualities,long-term marrow reserve compromise,and unpredictable oral absorption [35].

TREATMENT OF ADVANCED-STAGE EPITHELIAL OVARIAN CANCER

CYTOREDUCTIVE SURGERY IN OVARIAN CANCER

Patients with advanced-stage epithelial ovarian cancer are advised to undergo cytoreductive surgery to remove as much of the tumor and its metastases as feasible and increase the efficacy of later therapy [36].Complete omentectomy,bilateral salpingo-oophorectomy,a total abdominal hysterectomy, and removal of metastatic lesions from the intestines or peritoneal surfaces are among the standard procedures performed during the procedure.Three theoretical reasons underpin the justification for cytoreductive surgery:better

immunologic competence, improved tumor perfusion and increased growth fraction, and potential physiologic benefits from tumor removal [37].Cytoreductive surgery aims to remove all of the original malignancy as well as any metastases if feasible.The objective is to decrease the tumor burden by resecting each tumor to an ideal state if resection of all metastases is impractical.However, the existence of drug-resistant cells and the size, extent, and location of metastases before cytoreduction limit cytoreductive surgery's efficacy [38].

CHEMOTHERAPY FOR ADVANCED-STAGE EPITHELIAL OVARIAN CANCER

Systemic chemotherapy is the standard treatment for metastatic epithelial ovarian cancer. Eventually, combination chemotherapy based on platinum took the place of the first-ever single alkylating medications like melphalan.It was found that the combination of doxorubicin, cyclophosphamide, and cisplatin was effective yet less harmful. Paclitaxel was introduced in the 1990s. To eliminate drug-resistant cancer cells, clinical research focuses on the optimal dosage, compound selection and timing, and addition of additional compounds [39].

PLATINUM COMPOUNDS

For the past 20 years,platinum compounds have been the most effective treatment for ovarian cancer.Cisplatin was discovered to be more effective than cyclophosphamide,both alone and in combination with other medications.Platinum-based chemotherapy was found to be superior in a meta-analysis comparing regimens comprising cisplatin with regimens without containing platinum [40].Nonetheless,there was no discernible variation in survival across the therapy groups.US regimens for epithelial ovarian cancer have not included doxorubicin in doxorubicin-containing regimens. Introduced in the 1980s,the second-generation platinum analog carboplatin showed decreased nephrotoxicity, ototoxicity, peripheral neurotoxicity, and emetogenic potential but more myelotoxicity.According to a meta-analysis,the efficacy of carboplatin and cisplatin against epithelial ovarian cancer is similar,as are their response and survival rates [41].

PACLITAXEL

Paclitaxel is a highly active agent against ovarian cancer, with an overall response rate of 36% in previously treated patients. Three large randomized trials compared paclitaxel and a platinum compound to platinum-containing regimens that did not comprise paclitaxel [42]. The Gynecologic Oncology Group randomized 410 women with suboptimally cytoreduced stage III-IV ovarian cancer to six cycles of chemotherapy with a combination of cisplatin (75 mg/M2) and paclitaxel (135 mg/M2 over 24 hr) or with cisplatin (75 mg/M2) and cyclophosphamide (GOG-111) (Vasey et al., 2002). Patients who received the paclitaxel combination had a greater overall response rate (73% vs 60%), clinical complete response rate (51% vs 31%), prolongation of disease-free survival (18 months vs. 14 months), and prolongation of overall survival (36 months vs. 24 months) [43]. The superiority of paclitaxel-cisplatinum was confirmed in a trial (OV-10) conducted jointly by the European Organization for the Research and Treatment of Cancer (EORTC), the Nordic Ovarian Cancer Study Group (NOCOVA), and the National Cancer Institute of Canada (NCIC). In this study, the paclitaxel-containing arm produced a significant improvement in the median progression-free interval (15.5 vs. 11.5 months) and overall median survival (35.6 vs. 25.8 months) that extended to both optimal and suboptimal groups [44].Two randomized,prospective clinical studies have compared the combination of paclitaxel and carboplatin to that of paclitaxel and cisplatin.Both studies have similar response rates and survival duration, but the carboplatin-containing regimens have more acceptable toxicity.Thus, the best-established regimen in patients with advanced-stage disease is a combination of carboplatin and paclitaxel over 3 hours [45].

DOCETAXEL

Docetaxel is a semi-synthetic second-generation taxane with distinct properties, unlike paclitaxel.Regarding encouraging microtubule assembly and stabilization,paclitaxel is less successful than docetaxel.Docetaxel is more effectively taken up,bound,and maintained by cancer cells than paclitaxel.Dacatetracetal has produced

an overall response rate of 23% to 28% with platinum-resistant ovarian cancer.Docetaxel plus cisplatin or carboplatin has demonstrated an overall response rate of 66% to 81% in Phase II trials.Thus, in the SCOTROC trial, docetaxel (75 mg/M2 over one hour) and carboplatin (AUC 5) were compared with paclitaxel (175 mg/M2) and carboplatin (AUC 5).Although similar efficacy was shown, docetaxel-carboplatin was associated with notably less neurotoxicity [46].

OTHER DOUBLETS AND TRIPLETS

Patients with advanced ovarian cancer are living longer thanks to platinum compounds and taxanes;however,medication resistance frequently occurs.Topotecan, gemcitabine,and liposomal doxorubicin have all effectively treated recurring illnesses.The selection of appropriate combinations for the Phase III trial has prompted the start of Phase I pilot research.Eight cycles of chemotherapy are currently being given to individuals with newly diagnosed stage III/IV ovarian cancer as part of a five-arm study.Triplets, sequential doublets,and sequential doublets are all included in the study [47].

DOSE INTENSIFICATION WITH INTRAVENOUS CHEMOTHERAPY

The efficacy of more significant or frequent chemotherapy doses for poor ovarian cancer was investigated in a prospective trial conducted by the GOG.The same overall survival rate and no variation in response rates were found in the results.According to a Scottish study,patients' median survival was longer when they received 750 mg/M2 of cyclophosphamide and 100 mg/M2 of cisplatin.Nevertheless,cisplatin dose doubling did not increase long-term survival[48].

INTRAPERITONEAL CHEMOTHERAPY

In patients with ovarian cancer less than 2 cm in diameter, intraperitoneal treatment (IP) cisplatin was compared to intravenous chemotherapy (IV cisplatin) in a randomized prospective trial conducted by the Southwest Oncology Group (SWOG) and the GOG.The intraperitoneal cisplatin arm had a notably longer overall median survival than the intravenous arm. In a GOG follow-up trial, a dose-intense regimen that generated marginally higher progression-free median survival but no meaningful difference in overall survival was compared to a conventional regimen of IV cisplatin and IV paclitaxel [49].

NEOADJUVANT CHEMOTHERAPY

Individuals with bad stage III and stage IV sickness may receive chemotherapy in place of cytoreductive surgery. In a series of studies at Yale, Schwartz and colleagues found that patients treated with "neoadjuvant" or cytoreductive chemotherapy fared similarly to those who had undergone cytoreductive surgery at the same facility and then conventional chemotherapy [50]. As prior authors have shown the benefits of debulking patients before chemotherapy, a prospective clinical trial would be required to address the issue.On the other hand, before cytoreductive surgery, patients with significant pleural effusions or severe ascites might benefit from two or three cycles of chemotherapy. Chemotherapy may eliminate the effusions, improve the patient's performance status, and lessen postoperative morbidity, particularly in the chest.

RADIOTHERAPY IN ADVANCED INVASIVE DISEASE

Patients with advanced ovarian cancer have achieved success with whole abdominal radiation therapy (WAR). According to six studies, 38% to 62% of patients with residual illness less than 2 cm in diameter were cured after WAR.These studies also showed long-term survival or relapse-free rates.Stage II illness,with radiation doses much higher than the upper abdomen, was present in the majority of long-term survivors.However,there is little chance of recovery for more prominent remaining lesions.These investigations offer compelling proof of WAR's therapeutic advantages,yet uncertainties persist regarding how to apply WAR to contemporary surgical methods and chemotherapy regimens[51].

SURVEILLANCE

After initial therapy,the SGO recommends post-treatment surveillance for patients in complete clinical remission.Patients should have close follow-ups every three to four months,including symptom management, medical examinations,and long-term wellness care.They ought to be informed about signs of

recurrence and assessment of hereditary risk.Tumor marker testing is advised if the initial CA-125 concentration is raised. Early intervention,however, might not boost survival or enhance quality of life.A randomized experiment concluded that routine testing of CA-125 is not necessary for disease surveillance [52].Imaging tests,such as computed tomography scans,should be performed when a recurrence is suspected.Other imaging modalities like positron emission tomography or magnetic resonance imaging might be considered. Individuals undergoing fertility-sparing surgery may find ultrasonography especially helpful.

RECURRENT OVARIAN CANCER

PLATINUM SENSITIVITY

Platinum sensitivity is the term used to describe the situation where the next round of platinum-based chemotherapy starts more than six months after the previous round. Platinum retreatment is anticipated to benefit 60–70% of patients with a platinum-free interval (PFI) greater than 24 months. The OVA301 research clarifies practical challenges and treatment differences for patients with a predominantly platinum-sensitive recurrence. Post hoc analysis showed that the combination of trabectedin and pegylated liposomal doxorubicin (PLD) enhanced the prognosis and reduced the probability of death by 41%. Furthermore, the combination was postponed by 2.5 months after platinum treatment[53].

SURGERY FOR RECURRENT OVARIAN CANCER

Prospective randomized trials have investigated the role of subsequent cytoreductive surgery in ovarian cancer (EOC) that is platinum-sensitive and recurring. A phase III open-label experiment called GOG213 included 485 EOC patients whose condition was deemed treatable after they had received one prior medication. According to the study, chemotherapy alone did not lead to a longer overall survival than secondary surgical cytoreduction followed by chemotherapy.This clinical question is being assessed by two Phase III randomized clinical trials:the Netherlands SOCceR experiment and the AGO trial.The most significant distinctions between GOG213 and DESKTOP III relate to patient selection criteria and adjuvant therapy, precisely the maintenance rate of bevacizumab.The primary endpoint of overall survival is still in the infancy[54].

EMERGING AND NOVEL THERAPIES

IMMUNOTHERAPY

Since immunological checkpoints control the immune system, immunotherapy is a possible treatment for recurrent Eocystectomy-associated lymphoma (EOC). Research has demonstrated that immune-based treatments increase survival rates in several diseases, such as lung cancer, renal cell carcinoma, and metastatic melanoma.Nevertheless,preliminary studies on the effectiveness of these modalities have produced contradictory findings [55].The use of bevacizumab, PARP inhibitors,and checkpoint inhibitors together has not been extensively studied. Research has demonstrated that PARP inhibitors can complement PD-1 or CTLA-4 inhibition by stimulating interferon signaling.Pembrolizumab and niraparib together have demonstrated effectiveness in platinum-sensitive malignancies, with a mean progression-free survival (PFS) of 12.1 months and an overall response rate (ORR) of 40% [56].

GENE THERAPY

About half of ovarian malignancies and many solid tumors have mutations in the tumor suppressor gene p53.To restore the function of p53 in mutant tumor cells,adenoviruses are used as vectors in the current gene therapy techniques for ovarian cancer.However,despite encouraging Phase I results, a sizable randomized Phase II/III trial had to be discontinued after the first interim analysis revealed that adding intraperitoneal p53 gene therapy to first-line chemotherapy did not increase treatment morbidity but instead did not improve treatment efficacy in patients with optimally debulked advanced ovarian cancer [57].Using an attenuated virus that would specifically propagate and kill tumor cells with a mutant p53 gene is an alternate strategy.Phase I trials have evaluated this idea by administering the viral ONYX-015 intraperitoneally.Additionally,ganciclovir and the herpes simplex virus's Thymidine Kinase (TK) gene have

been employed to specifically destroy ovarian cancer cells.By delivering an enzyme-encoding gene to ovarian cancer cells, ganciclovir is selectively activated, leading to the death of cancer cells.This method's effectiveness is increased by a "bystander" cytotoxic effect on nearby non-transfected cells [58].

FOLATE RECEPTOR ANTIBODY-DRUG CONJUGATES

Patients with platinum-resistant and recurrent ovarian cancer have a supplementary therapy option in the form of pharmaceutical conjugates that target the folate receptor,such as mirvetuximab soravtansine.This was examined in 66 participants taking bevacizumab and mirvetuximab as part of a phase IB trial.This doublet combination showed noteworthy utilization promise in an extensively pretreated recurrent population,with an objective response rate of 39% and a mean progression-free survival of 6.8 months.It takes proactive mitigation methods,such as lubricating and steroid eye drops,to manage ocular adversative effects like keratopathy and reduced vision.Additionally,patients must be closely observed for any long-term eye consequences [59].

IN OVARIAN CANCERS MISMATCH REPAIR AND MICROSATELLITE INSTABILITY

Determining the peril of developing inherited cancer syndromes—which is raised by testing for microsatellite instability and mismatch repair deficiencies—necessitates identifying point mutations in ovarian cancer.These defects are crucial for developing novel treatments and genetic testing.Recent studies have advised that mismatch repair deficit and microsatellite instability-H malignancies could be markers of a tumor's susceptibility to anti-PDL-1 immunotherapy medications [60].

CHIMERIC ANTIGEN RECEPTOR THERAPY

CAR-T is one possible state-of-the-art treatment for metastatic ovarian cancer in EOC.The complex and expensive CAR-T process has shown potential in eradicating cancer cells from various disease sites.The procedure involves eliminating host T cells and using gene editing to induce the expression of chimeric antibodies on the cell surface of these cells.These antibodies, when reinstated, adhere to host cancer cells.Though solid tumors like ovarian cancer may probably benefit greatly from this form of treatment,blood malignancies have revealed the most promise for it.This is because ovarian cancer cells overexpress MUC 16,which permits them to evade immune surveillance by host defense systems [61].

POTENTIAL DRUGS FOR TARGETED THERAPIES IN OVARIAN CANCER

Epithelial ovarian cancer (EOC) is often diagnosed at an advanced stage and has a high mortality rate despite current treatments.Research is focused on understanding molecular characteristics and platinum resistance to develop new drugs.Treating platinum-resistant disease remains challenging,and various targeted therapies are being tested in clinical trials.Additionally, nanoparticles are being explored to improve drug delivery and enhance treatment effectiveness.[62] The different therapeutic agents being investigated for treating epithelial ovarian cancer (EOC) are listed in Table 2.

Therapy	**Drug Name**
Chemotherapy agents	Toptoecan, Gemcitabine, Paciltaxel
PARP inhibitors	Olaparib,Rucaparib,Niraparib
Angiogenesis Inhibitors	Bevacizumaab
Aromatase Inhibitors	Letrozole,Anastrozole
Anti neurotrophins	Entrectinib,Larotrectinib,Seritrectinib
Immune checkpoint inhibitors	Niraparib,Pembrolizumab,Varlilumab Nivolumab
Repurposing drugs	Chloroquine,Ivermectin Statins, Disulfiram Arsenic trioxide, Metformin NSAIDs
Antifolate receptors	Mirvetuximab Soravtansine
Tyrosine Kinase Inhibitors	Pazopanib, Cediranib

Table 2: Drugs for target therapies in OC

The Current and emerging targeted therapies for ovarian cancer (OC).Bevacizumab,an anti-angiogenic agent, and olaparib,a PARP inhibitor,are highlighted as drugs approved for first-line maintenance therapy in advanced OC, particularly in BRCA-mutated cases[63].The FDA recently approved a combination of bevacizumab and olaparib for HRD-positive advanced OCs.Additionally,receptor tyrosine kinase (RTK) inhibitors,immune checkpoint inhibitors like Pembrolizumab, and epigenetic modulators such as HDAC inhibitors are being investigated for their potential to treat various types of OC[64].

QUALITY OF LIFE AND PALLIATIVE CARE

Recognizing that cancer care is a lifetime journey that exposes many patients to numerous relapses and treatment-related adverse events that may have a detrimental impact on quality of life is essential to providing comprehensive cancer care.Guidelines from the NCCN can assist oncology practitioners in optimizing symptom management early in the course of the disease and conversing with patients' families and other caregivers about treatment goals that align with their values,beliefs, and cultures Regardless of the cancer stage or the requirement for additional medicines, palliative care aims to predict, prevent,and reduce suffering and provide the best possible quality of life [65].When palliative care is executed early on, particularly for patients with advanced cancer, it has been shown to dramatically improve quality of life and reduce the harshness of symptoms.Over the past 20 years,palliative care has advanced into a vital part of general healthcare,aiming to refine quality of life by early intervention that may also increase survival chances. Prominently, robust research efforts are keeping pace with this advancement in clinical care,with ongoing fforts being made to integrate patient-centered outcomes into the designs of clinical trials [66]. While palliative care should begin early in the course of an illness to maximize the quality of life,we also recognize that when disease-directed,life-prolonging medicines are no longer wanted or effective,palliative care takes center stage in patient care.When choosing the best course of therapy,patients and oncologists must work together to make decisions to ensure a shared goal,an acceptable safety profile,and a balance between the benefits and dangers of the symptoms.

CONCLUSIONS

Globally, the most deadly gynecological cancer to affect women is epithelial ovarian carcinoma. The majority of women arrive with advanced cancer,and even if the first surgery and treatment had outstanding results,the 5-year survival rate is still relatively low.Because there is a clear relationship between the amount of postsurgical tumor residue and both progression-free and overall survival,surgical cytoreduction is an influential prognostic factor.Individuals with advanced-stage EOC often receive PCS followed by platinum-based chemotherapy;however, pre-operative chemotherapy may be taken into consideration for individuals who are not likely to achieve adequate cytoreduction or who are not good candidates for surgery.The optimization of traditional chemotherapy with platinum/taxane doublet (e.g., dose intensity,dose density, and incorporation of different agents, as well as intraperitoneal drug administration) and extended maintenance with cytotoxic chemotherapy during remission have been the main areas of research on first-line treatment. Despite these developments, the majority of patients with advanced-stage cancer relapse, and the platinum-free interval has a significant impact on the patient's propensity to respond to successive courses of platinum-based chemotherapy.As a first-line treatment, the focus of current clinical trials is on adding new medications in combination or consecutively.In the future,immunotherapy and biological agents may be used in addition to cytotoxics for treatment; however,these treatments are still in the early phases of development.

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Conflict Of Interests

Declared none.

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