JAMA | Review

Ovarian Cancer
A Review

Giuseppe Caruso, MD; S. John Weroha, MD, PhD; William Cliby, MD

IMPORTANCE Ovarian cancer is the eighth most common cause of cancer and cancer death in women worldwide. In 2022, ovarian cancer was diagnosed in approximately 324 398 individuals, and 206 839 died of ovarian cancer worldwide. In 2025, it is estimated that 20 890 US women will be diagnosed with ovarian cancer and 12 730 patients will die of ovarian cancer.

OBSERVATIONS Approximately 90% of ovarian cancers are epithelial malignancies, of which 70% to 80% are high-grade serous ovarian cancers. Less common epithelial subtypes include endometrioid, clear cell, low-grade serous, mucinous, and carcinosarcoma. The median age at diagnosis of ovarian cancer is 63 years. Risk factors include older age, family history of breast or ovarian cancer, endometriosis, and nulliparity. Hereditary factors are associated with 25% of cases, predominantly linked to *BRCA1/2* gene variants. At diagnosis, approximately 95% of patients experience nonspecific symptoms, such as abdominal pain, bloating, and urinary urgency and frequency, and about 80% have advanced-stage disease (stage III-IV), including extrapelvic disease, ascites, and abdominal masses. Diagnostic and staging evaluation includes pelvic ultrasound; computed tomography of the chest, abdomen, and pelvis; and serum tumor markers such as carbohydrate antigen 125, carbohydrate antigen 19-9, and carcinoembryonic antigen. First-line treatment for early-stage ovarian cancer, defined as limited to the ovary or fallopian tube (stage I) or confined to the pelvis (stage II), is surgery (hysterectomy, bilateral salpingo-oophorectomy, omentectomy, and lymphadenectomy), followed by adjuvant chemotherapy (carboplatin and paclitaxel). With treatment, early-stage ovarian cancer has a 5-year overall survival of 70% to 95%. Advanced-stage ovarian cancer may be treated with primary cytoreductive surgery (removal of all visible cancer in the abdominal cavity) and adjuvant chemotherapy (carboplatin and paclitaxel) or with neoadjuvant chemotherapy followed by cytoreductive surgery and adjuvant chemotherapy. Most patients with advanced-stage ovarian cancer receive maintenance therapy with bevacizumab (a monoclonal antibody that blocks angiogenesis) and/or poly–adenosine diphosphate ribose polymerase (PARP) inhibitors. With treatment, the 5-year overall survival rate for advanced-stage ovarian cancer is 10% to 40%. However, individuals with *BRCA*-related gene variants have a 5-year overall survival rate of approximately 70% with PARP inhibitor treatment. Despite an initial remission rate of 80%, approximately 75% of patients with advanced-stage disease have ovarian cancer relapse within 2 years.

CONCLUSIONS AND RELEVANCE Approximately 21 000 women are diagnosed with ovarian cancer annually in the US, and approximately 80% have advanced-stage ovarian cancer at diagnosis. First-line treatment of early-stage ovarian cancer is surgery and adjuvant platinum-based chemotherapy. Treatment of advanced-stage ovarian cancer includes cytoreductive surgery, platinum-based chemotherapy, and targeted maintenance therapies such as bevacizumab and/or PARP inhibitors.

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Author Affiliations: Department of Obstetrics and Gynecology, Division of Gynecologic Oncology, Mayo Clinic, Rochester, Minnesota (Caruso, Cliby); Division of Gynecologic Oncology, European Institute of Oncology (IEO), IRCCS, Milan, Italy (Caruso); Department of Experimental Medicine, Sapienza University of Rome, Rome, Italy (Caruso); Department of Oncology, Mayo Clinic, Rochester, Minnesota (Weroha).

Corresponding Author: William Cliby, MD, Department of Obstetrics and Gynecology, Division of Gynecologic Surgery, Mayo Clinic, 200 First St SW, Rochester, MN 55905 (cliby.william@mayo.edu).

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Among US women, the lifetime risk of developing ovarian cancer is 1 in 91, and death due to ovarian cancer occurs 1 in 143 women.[1] Approximately 80% of ovarian cancers are at an advanced stage at diagnosis.[2-4] Earlier detection is difficult because there are no effective screening methods, and 95% of patients have nonspecific initial symptoms, such as abdominal pain, bloating, and urinary urgency or frequency.

Epithelial malignancies comprise 90% of ovarian cancers, with 70% to 80% being high-grade serous ovarian cancers.[5] Early-stage ovarian cancer includes stage I (confined to the ovary or fallopian tube) and stage II (involving the uterus or other pelvic organs) (**Figure 1**). With surgery and adjuvant platinum-based chemotherapy, the 5-year overall survival of patients with early-stage ovarian cancer is 70% to 95%.[2,4] Advanced-stage ovarian cancer, which comprises stage III (involving pelvic and para-aortic lymph nodes or extrapelvic peritoneum) and stage IV (metastases to the liver or spleen or outside the abdominal cavity), may be treated with a combination of cytoreductive surgery, platinum-based chemotherapy, and targeted therapies such as the antiangiogenic drug bevacizumab and/or poly–adenosine diphosphate ribose polymerase (PARP) inhibitors. Initial remission rates of advanced-stage ovarian cancer are 80%, but approximately 75% of patients with advanced-stage ovarian cancer relapse within 2 years, and 5-year overall survival is 10% to 40%.[2,4] Approximately 50% of patients with advanced-stage ovarian cancer have heritable (germline) or tumor-acquired (somatic) *BRCA1/2* or other *BRCA*-related gene variants, and when treated with PARP inhibitors, have 5-year overall survival rates approaching 70%.[6] This Review focuses on diagnosis and management of high-grade serous ovarian cancer. **Box 1** provides some common questions and answers about ovarian cancer.

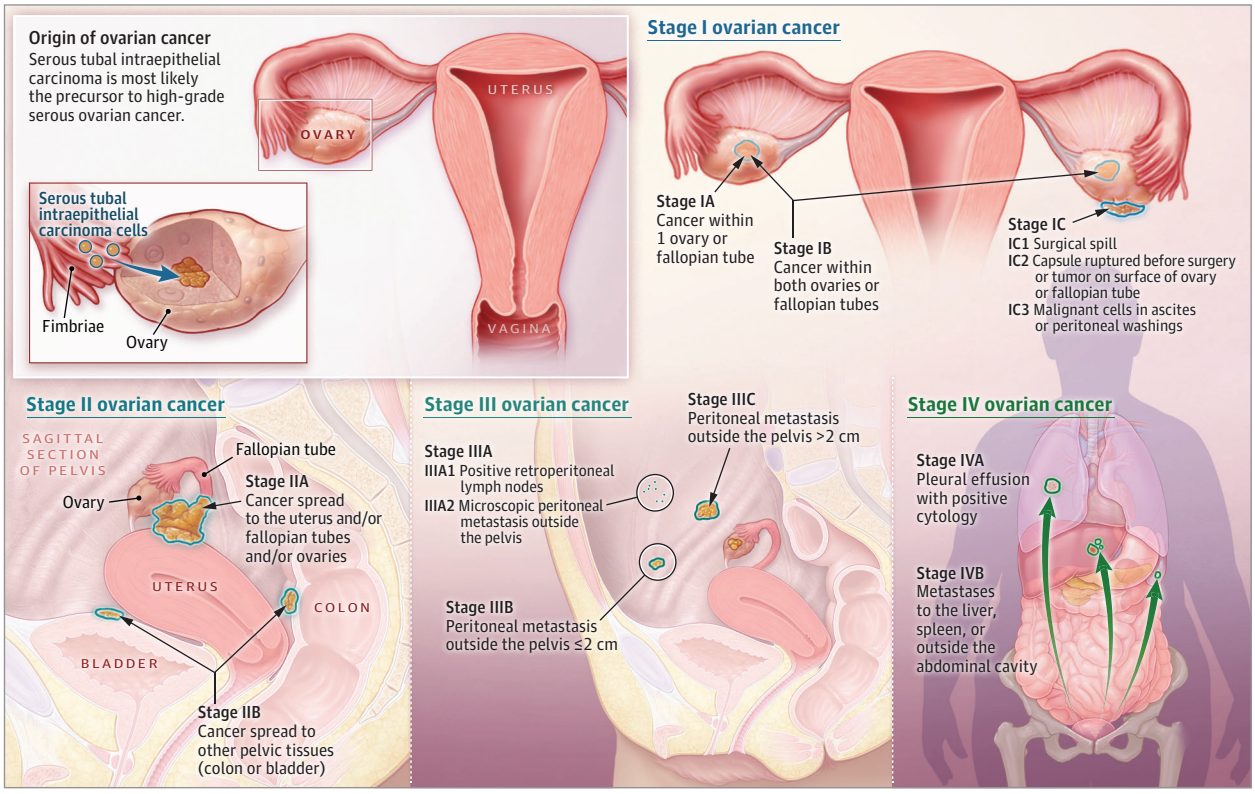
Methods

A PubMed search of English-language articles describing randomized clinical trials (RCTs), meta-analyses, systematic reviews, and practice guidelines published between January 1, 1995, and May 3, 2025, identified 1733 RCTs, 1457 meta-analyses, 1770 systematic reviews, and 295 guidelines. Priority was given to the selection of high-quality RCTs and meta-analyses. A total of 123 articles were included, comprising 65 RCTs, 9 meta-analyses, 5 systematic reviews, 16 guidelines, 6 narrative reviews, 12 prospective observational studies, and 10 retrospective observational studies.

Epidemiology and Risk Factors

Ovarian cancer is the eighth most common cause of cancer and cancer death in women worldwide.[7] Globally, in 2022, there were an estimated 324 398 new cases of ovarian cancer and 206 839 deaths, with incidence and mortality rates of 6.6 and 4.2 per 100 000 women-years, respectively.[7] In the US, ovarian cancer incidence and mortality rates have declined by approximately 3% annually since 2004 due to increased use of oral contraceptives (preventing repetitive ovulation-related ovarian injury), prophylactic salpingo-oophorectomy in women with high-risk genetic variants such as

Figure 1. Origin and Stages of Ovarian Cancer



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BRCA1/2 (hereditary breast and ovarian cancer syndrome), and improved treatment options.[1] Globally, ovarian cancer incidence has decreased in other higher-income countries such as the UK, Austria, the Netherlands, and Norway but has increased in some lower-income regions such as Africa and some parts of Asia.[7,8]

Ovarian cancer is predominantly of epithelial origin (90%). The World Health Organization in 2020 recognized 6 principal epithelial subtypes: high-grade serous (70%-80%), endometrioid (10%-20%), clear cell (5%-10%), low-grade serous (5%-10%), mucinous (3%-5%), and carcinosarcoma (1%-3%).[5] Less commonly, ovarian cancer involves germ cell tumors (3%-5%) and sex cord stromal tumors (2%-5%).[5]

The median age at diagnosis of ovarian cancer is 63 years, although it is 10 years earlier in patients with germline *BRCA* gene variants.[9] Approximately 25% of ovarian cancers are hereditary due to germline pathogenic variants in DNA damage repair genes: 90% in the *BRCA1* and *BRCA2* genes[10] and 10% attributable to other gene variants, including the DNA mismatch repair genes (Lynch syndrome) and genes involved in the DNA double-strand breaks repair system, such as *CHEK2*, *RAD51*, *BRIP1*, and *PALB2*.[11] The estimated lifetime risk of developing ovarian cancer in patients with a *BRCA* gene variant is 20% to 70% and is 10% to 18% with a mismatch repair gene variant.[12,13]

Endocrine and reproductive risk factors for ovarian cancer include endometriosis (hazard ratio, 4.20; 95% CI, 3.59-4.91),[14] infertility (standardized incidence ratio, 2.0; 95% CI, 1.8-4.0), and postmenopausal estrogen therapy (relative risk, 1.31; 95% CI, 1.21-1.41).[15] Possible protective factors are multiparity (odds ratio for each additional birth, 0.81; 95% CI, 0.75-0.85), breastfeeding (odds ratio, 0.72; 95% CI, 0.68-0.76), and oral contraceptive use (odds ratio, 0.66; 95% CI, 0.52-0.83).[15]

Box 1. Commonly Asked Questions About Ovarian Cancer

What Are Common Presenting Signs and Symptoms of Ovarian Cancer?

Up to 95% of women with ovarian cancer initially experience nonspecific symptoms, such as abdominal pain, bloating, and urinary urgency. Signs and symptoms of advanced-stage ovarian cancer may include ascites, palpable abdominal masses, and/or dyspnea (caused by abdominal distension or pleural effusions).

Are There Effective Methods to Decrease Risk of Ovarian Cancer?

The US Preventive Services Task Force in 2018 recommended against ovarian cancer screening with transvaginal ultrasound and/or carbohydrate antigen 125 in both asymptomatic individuals without a high-risk hereditary cancer syndrome and high-risk individuals (eg, *BRCA1/2* gene variant carriers). Women with a family history of a *BRCA* gene variant or with a first-degree relative with ovarian cancer at any age or early-onset breast cancer (age <40 years) should undergo genetic testing. Bilateral salpingo-oophorectomy is recommended between ages 35 and 40 years for *BRCA1* carriers who have completed childbearing, between ages 40 and 45 years for *BRCA2* carriers, and between ages 45 and 50 years for women with Lynch syndrome.

What Is the Initial Treatment and Prognosis for Patients With Ovarian Cancer?

First-line treatment for early-stage ovarian cancer (stages I-II) is surgery followed by platinum-based chemotherapy, which is associated with 5-year overall survival rates of 70% to 95%. Advanced-stage ovarian cancer (stages III-IV) is treated with a combination of cytoreductive surgery, platinum-based chemotherapy, and targeted therapies (bevacizumab and/or PARP inhibitors) and has a 5-year survival rate of 10% to 40%. However, with PARP inhibitor treatment, patients with advanced-stage ovarian cancer and *BRCA*-related gene variants have a 5-year survival rate of approximately 70%.

Pathophysiology and Molecular Biology

The pathogenesis of epithelial ovarian cancers is not clear, but gene expression profiling suggests that most high-grade serous ovarian cancers likely arise from precursors in the tubal fimbria and metastasize to the ovary and peritoneal cavity (Figure 1).[16] About 50% of high-grade serous ovarian cancers have genetic variants (25% heritable/germline and 25% tumor-acquired/somatic) in homologous recombination repair genes resulting in an inability to repair DNA double-strand breaks, known as homologous recombination deficiency (HRD). *BRCA1* and *BRCA2* gene variants account for approximately half of HRD cases, found in 25% of all high-grade serous ovarian cancers.[17] The remaining half of HRD cases are caused by other genes involved in the homologous recombination repair pathway, including *CHEK2*, *RAD51*, *BRIP1*, and *PALB2*.

Prevention

High-Risk Individuals

Individuals at high risk of ovarian cancer include those with germline *BRCA1/2* gene variants and those with a family history of ovarian cancer at any age or early-onset breast cancer (age <40 years). The National Comprehensive Cancer Network (NCCN) guidelines recommend genetic testing for ovarian cancer susceptibility genes (*ATM*, *BRCA1*, *BRCA2*, *BRIP1*, *MLH1*, *MSH2*, *MSH6*, *EPCAM*, *PALB2*, *RAD51C*, and *RAD51D*) in individuals with a first- or second-degree relative with epithelial ovarian cancer at any age or with a personal or family cancer history suggestive of hereditary breast and ovarian cancer syndrome based on genetic counseling.[10]

For patients with known ovarian cancer susceptibility genes, prophylactic bilateral salpingo-oophorectomy is the most effective preventive measure for ovarian cancer.[18] A meta-analysis of 3 prospective studies including 9192 women with *BRCA1/2* variants reported that bilateral salpingo-oophorectomy reduced the risk of ovarian cancer by 81% over 4 years (hazard ratio, 0.19; 95% CI, 0.13-0.27).[19] The NCCN guidelines recommend bilateral salpingo-oophorectomy at age 35 to 40 years for *BRCA1* gene variant carriers who have completed childbearing, age 40 to 45 years for *BRCA2* carriers, and age 45 to 50 years for women with other pathogenic gene variants, such as for Lynch syndrome.[10] Prior to prophylactic surgery, clinicians should discuss the potential effects of early menopause (eg, increased risk of vasomotor symptoms, osteoporosis, cardiovascular disease, cognitive decline, adverse effects on sexual function), and hormone therapy should be considered for premenopausal women with no personal breast cancer history.[10]

Oral contraceptives reduce ovarian cancer risk for high-risk younger individuals (eg, *BRCA* variant carriers) who do not undergo bilateral salpingo-oophorectomy. A meta-analysis of women with

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BRCA1/2 variants using oral contraceptives reported a hazard ratio of 0.62 (95% CI, 0.52-0.74) for ovarian cancer based on 2 studies of 10 981 women and an odds ratio of 0.49 (95% CI, 0.38-0.63) from 8 studies including 10 390 women.[20] Similarly, another meta-analysis of 5 observational studies including 1503 participants with *BRCA1*/2 pathogenic variants reported that oral contraceptive use was associated with a decreased risk of ovarian cancer (summary relative risk, 0.50; 95% CI, 0.33-0.75), and each additional 10 years of use was associated with a 36% reduced risk (summary relative risk, 0.64; 95% CI, 0.53-0.78).[21]

General Population

The American College of Obstetricians and Gynecologists and International Federation of Gynecology and Obstetrics guidelines recommend considering surgical and hormonal preventive approaches for the general population to reduce ovarian cancer risk.[22,23] For postmenopausal women undergoing pelvic surgery for benign conditions (eg, hysterectomy for uterine fibroids or pelvic surgery for colon disease), bilateral salpingo-oophorectomy may be considered. For premenopausal women not interested in childbearing who are undergoing pelvic surgery, bilateral salpingectomy (removal of the fallopian tubes) while preserving the ovaries can avoid early menopause and its potential adverse effects on health.[22,23]

A meta-analysis of 24 case-control and cohort studies reported a reduced incidence of ovarian cancer in oral contraceptive ever users compared with never users (odds ratio, 0.73; 95% CI, 0.66-0.81). Oral contraceptive use for more than 10 years was associated with lower risk (odds ratio, 0.43; 95% CI, 0.37-0.51).[24] Lifetime ovarian cancer reduction attributable to oral contraceptive use was estimated at 0.54% (number needed to treat, 185 for 5 years of oral contraceptive use).[24]

Screening

The US Preventive Services Task Force in 2018 recommended against ovarian cancer screening in asymptomatic women without high-risk hereditary syndromes based on 2 large RCTs (PLCO and UKCTOCS; N = 271 103) that found no significant mortality reduction with use of annual transvaginal ultrasound and/or carbohydrate antigen 125 (CA125) testing vs no screening among average-risk, asymptomatic women (PLCO: relative risk, 1.18; 95% CI, 0.82-1.71; UKCTOCS: hazard ratio, 0.91; 95% CI, 0.76-1.09).[25] Similarly, large prospective studies of high-risk individuals (eg, those with *BRCA* gene variants) have shown that screening with transvaginal ultrasound and CA125 has a low positive predictive value (4.6%-10.8%) and does not reduce ovarian cancer mortality.[26-29] Thus, screening for ovarian cancer is not recommended, even in high-risk individuals.

Clinical Presentation

Prior to ovarian cancer diagnosis, 95% of women report a gradual onset of nonspecific symptoms, such as abdominal pain, bloating, and urinary urgency or frequency.[30] A prospective case-control study of symptoms in women with a pelvic mass (84 benign and 44 ovarian cancer) compared with women visiting 2 primary care clinics (n = 1709) found that patients with ovarian cancer reported more frequent bloating (70% vs 38%; $P < .001$), increased abdominal size (64% vs 19%; $P < .001$), urinary urgency/frequency (55% vs 32%; $P = .002$), abdominal pain (50% vs 30%; $P = .006$), and pelvic pain (41% vs 26%; $P = .02$).[31] The combination of bloating, increased abdominal size, and urinary urgency/frequency was observed in 43% of patients with ovarian cancer vs 8% in patients without ovarian cancer (odds ratio, 9.4; 95% CI, 5.0-17.7).[31] In a survey of 1725 US and Canadian women with ovarian cancer, 89% of patients with early-stage disease and 97% of patients with advanced-stage disease reported symptoms before diagnosis, with no significant difference in symptom type based on stage.[30] Persistent abdominal pain or bloating, ascites, a palpable abdominal or pelvic mass, weight loss, and dyspnea (caused by abdominal distension or pleural effusions) may indicate advanced-stage ovarian cancer. Rarely (<1% of patients), ovarian cancer presents with extra-abdominal symptoms caused by distant metastases (bone pain, seizures) or paraneoplastic syndromes (cerebellar degeneration, peripheral polyneuropathy).[32]

Diagnosis

Diagnostic workup includes eliciting a personal and family history of cancer to determine if patients have a known genetic variant associated with ovarian cancer, such as *BRCA1/2*, and a physical examination, including pelvic and abdominal evaluations for palpable masses or ascites (**Box 2**). Pelvic ultrasound is highly sensitive (70%-93%) and specific (80%-98%) for identification of malignant adnexal masses.[33,34] Computed tomography (CT) of the abdomen/pelvis is less sensitive (60%-90%) and specific (85%-94%) for diagnosis but has a sensitivity of 94% for detecting peritoneal disease and omental thickening, which are important findings for staging and planning.[34,35] A detailed staging system for ovarian cancer is outlined in eTable 1 in the Supplement.[36] Compared with CT, abdominal magnetic resonance imaging (MRI) is more sensitive (92%-94%) and specific (85%-98%) for evaluating peritoneal carcinomatosis and mesenteric or bowel serosal involvement.[34,35,37] If uncertainty remains about cancer resectability after CT or MRI imaging, diagnostic laparoscopy may be performed prior to laparotomy to determine resectability.[38] Total-body positron emission tomography has higher sensitivity (73%-75%) than CT (43%-55%) for detection of extra-abdominal lesions, such as distant lymph nodes (eg, mediastinal, inguinal, supraclavicular) and pulmonary metastases, potentially altering management to systemic therapy instead of abdominal debulking.[39,40]

Serum Tumor Markers

Serum tumor markers, such as CA125, human epididymis protein 4, carbohydrate antigen 19-9 (CA19-9), and carcinoembryonic antigen (CEA), are not diagnostic of epithelial ovarian cancer but can help monitor treatment response and posttreatment surveillance. Carbohydrate antigen 125 is the most commonly elevated serum tumor marker,[41] and based on 17 studies that included 2374 women with ovarian tumors, CA125 (≥35 U/mL) was elevated at diagnosis in approximately 50% of patients with early-stage ovarian cancer and in 75% to 92% with advanced-stage ovarian cancer.[42] Human epididymis protein 4 is another serum tumor marker that can be useful for early epithelial ovarian cancer detection (sensitivity, 65%-83%; specificity, 78%-99%).[43] Elevated levels of CA19-9 and

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CEA, associated with mucinous gastrointestinal cancers, may be detected in patients with mucinous ovarian tumors. Primary ovarian mucinous cancers are rare, so upper and lower endoscopy should be performed to evaluate for primary gastrointestinal tumor metastatic to the ovary. A CA125/CEA ratio greater than 25 is suggestive of a primary mucinous ovarian tumor instead of gastrointestinal metastasis to the ovary.[2,4,41]

Biopsy

Preoperative biopsy (eg, fine-needle aspiration) is contraindicated in patients with presumed early-stage ovarian cancer because it may lead to tumor rupture and spillage of malignant cells into the peritoneal cavity. Intraoperative frozen section of a surgical specimen is usually performed to make the pathological diagnosis of ovarian cancer.[4,44] For patients with advanced-stage disease not suitable for primary surgery, core biopsy (preferred) or fine-needle aspiration preoperative tissue analysis is required to confirm the diagnosis of ovarian cancer and guide chemotherapy selection. For patients with advanced-stage disease who are eligible for initial surgery without preoperative chemotherapy, diagnostic intraoperative biopsy suffices. For patients with ascites or pleural effusion, paracentesis or thoracentesis can provide cytological diagnosis and symptom relief.[2,4]

Genetic and Molecular Testing

The NCCN and the American Society of Clinical Oncology guidelines recommend germline blood testing for all patients with epithelial ovarian cancer to screen for inherited *BRCA1/2* variants.[10,13,45] Negative germline test findings should prompt surgical specimen evaluation for tumor-specific acquired (somatic) *BRCA1/2* variants. Germline and somatic testing inform treatment and counseling of patients and at-risk relatives (Box 2).[10,13,45] Testing for HRD in advanced-stage, high-grade serous or endometrioid ovarian cancer also guides treatment,[46] with HRD positivity associated with a higher response to platinum-based chemotherapy and treatment with DNA repair inhibitors such as PARP inhibitors.[42] Mismatch repair tumor testing is recommended by NCCN guidelines for endometrioid, clear cell, or mucinous subtypes to screen for Lynch syndrome.[4,13]

Box 2. Diagnostic Workup for Epithelial Ovarian Cancer

- Cancer history (personal and family)
  - Hereditary disorders: hereditary breast and ovarian cancer syndrome (*BRCA* gene variants), Lynch syndrome
  - Breast, ovarian, endometrial, colon, or pancreatic cancer in first- or second-degree relatives
- Clinical examination (including pelvic examination)
- Serum tumor markers
  - CA125
  - CA19-9 and CEA (for suspected [based on imaging findings] or confirmed mucinous histology)
- Imaging
  - Pelvic ultrasound by expert examiner (to characterize adnexal masses, especially in early-stage disease)
  - Computed tomography of the chest, abdomen, and pelvis with oral and intravenous contrast (for clinical staging and surgical planning)
  - Additional tools in selected cases
    - Abdominal diffusion-weighted magnetic resonance imaging, laparoscopy, or mini laparotomy (to assess extent of peritoneal carcinomatosis and resectability)
    - Total-body 18F-fluorodeoxyglucose–positron emission tomography (to characterize suspicious distant lymph nodes and extra-abdominal sites)
- Endoscopy (esophagogastroduodenoscopy and colonoscopy) if suspected (based on elevated CA19-9, elevated CEA, CA125/CEA ratio ≤25, and/or imaging findings) or confirmed mucinous histology, to exclude primary gastrointestinal tumors
- Pathological examination of adequate tumor sample from diagnostic core biopsy or surgical specimen[a]
- Cytological assessment of ascites or pleural effusion, if present
- Genetic and molecular testing
  - Germline testing for *BRCA1/2* and other ovarian cancer susceptibility genes for all patients with epithelial ovarian cancer (to screen for hereditary breast and ovarian cancer syndrome and inform treatment decisions). In patients without a germline pathogenic *BRCA1/2* variant, somatic tumor testing for *BRCA1/2* should be performed to guide treatment decisions.
  - Tumor testing for homologous recombination deficiency for advanced high-grade serous or endometrioid ovarian cancers (to inform treatment decisions)
  - Tumor mismatch repair system testing—specifically, immunohistochemistry and microsatellite instability testing—for patients with endometrioid, clear cell, or mucinous subtypes (to screen for Lynch syndrome)

Abbreviations: CA125, carbohydrate antigen 125; CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen.

[a] Preoperative biopsy should be avoided in presumed early-stage disease to prevent spilling malignant cells into the peritoneal cavity.

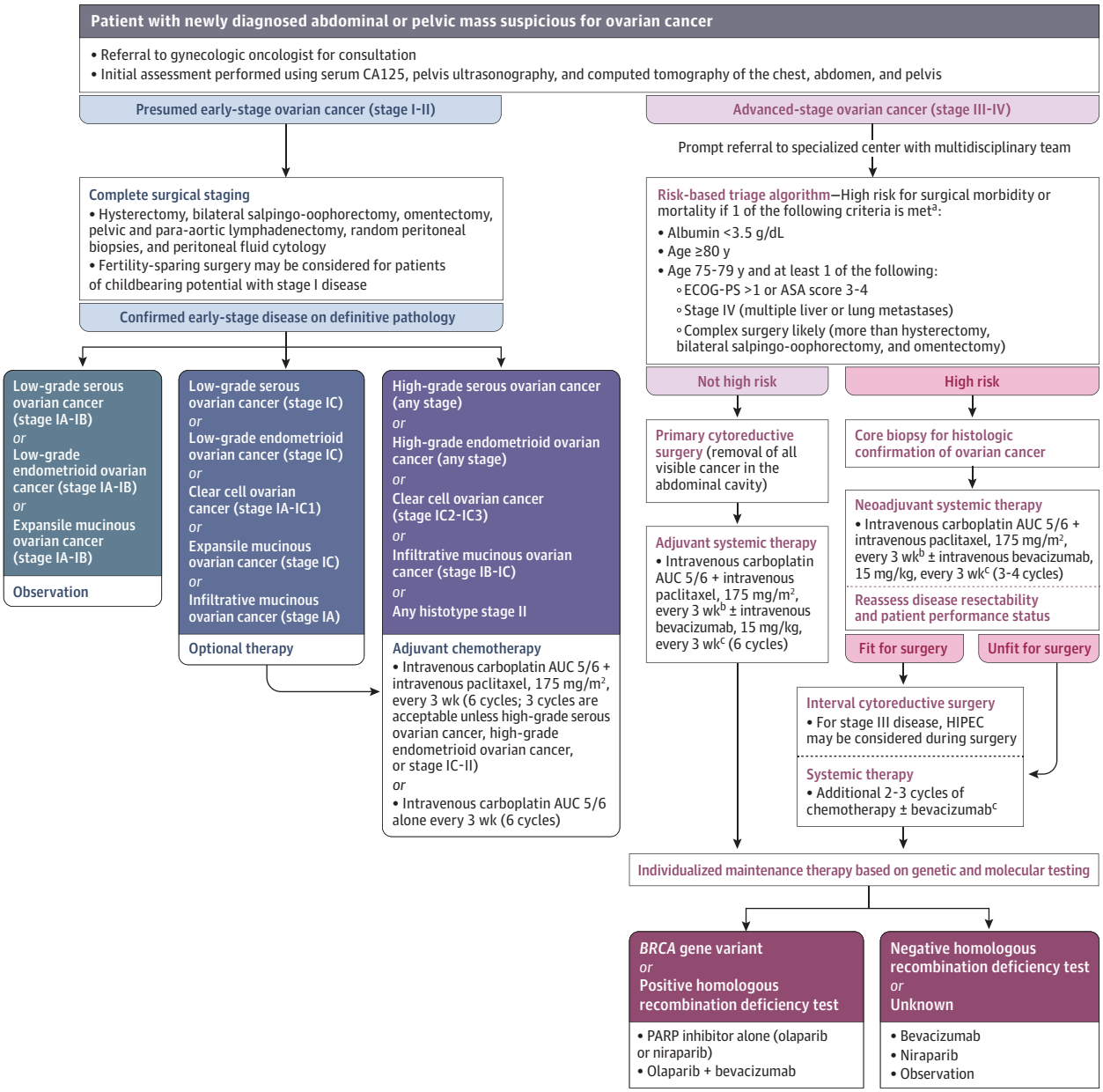
Treatment of Early-Stage Ovarian Cancer

First-line therapy for presumed early-stage ovarian cancer is surgery to resect and stage the tumor, followed by adjuvant platinum-based chemotherapy (**Figure 2**). Surgery for most patients with early-stage ovarian cancer includes (1) en bloc resection of the involved ovary and fallopian tube to avoid spillage of cancer cells into the peritoneum during surgery; (2) hysterectomy and salpingo-oophorectomy of the contralateral ovary and fallopian tube; (3) retroperitoneal (pelvic and paraaortic) lymphadenectomy; (4) omentectomy; (5) random peritoneal biopsies; and (6) peritoneal fluid cytology. Appendectomy may also be performed for some patients with mucinous ovarian cancer.[4,47] Intraoperative staging is important because approximately 30% of patients with presumed early-stage ovarian cancer by imaging have occult metastatic disease on definitive pathological examination of retroperitoneal lymph nodes, omentum, and peritoneal surface biopsies.[4,47]

Patients with stage I disease who are considering having children in the future may undergo fertility-sparing surgery, consisting of unilateral salpingo-oophorectomy (preserving the uterus and contralateral ovary/fallopian tube without ovarian cancer).[2,4] Cryopreservation of oocytes before bilateral salpingo-oophorectomy may allow future assisted reproductive approaches, such as in vitro fertilization and uterine embryo transfer. Consultation with an oncofertility specialist preoperatively is recommended. In a multiinstitutional retrospective study of 211 women undergoing

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Figure 2. Primary Treatment for Early-Stage and Advanced-Stage Ovarian Cancer



ASA indicates American Society of Anesthesiologists; AUC, area under the curve; CA125, carbohydrate antigen 125; ECOG-PS, Eastern Cooperative Oncology Group performance status; HIPEC, hyperthermic intraperitoneal chemotherapy; and PARP, poly–adenosine diphosphate ribose polymerase.

[a]Consider neoadjuvant chemotherapy also if recent (<6 months) venous thromboembolism, myocardial infarction, stent, or laparotomy.

[b]An alternative weekly chemotherapy regimen of carboplatin AUC 2 and paclitaxel, 60 mg/m², is a reasonable option for frail patients who cannot tolerate the every-3-week schedule.

[c]Bevacizumab should be stopped 6 to 8 weeks before surgery and reinitiated 4 to 8 weeks after surgery due to wound-healing issues.

fertility-sparing surgery for unilateral epithelial ovarian cancer (stage IA, n = 126; stage IC, n = 85), 5-year overall and recurrence-free survival varied by subtype, with the highest rates (100% and 97.8%) for stage IA grade 1 to 2 disease and lower rates (66.7% and 66.0%) for stage IC grade 3 disease.[48]

The benefit of adjuvant chemotherapy in early-stage ovarian cancer depends on stage, histotype, and tumor grade, and decisions about adjuvant chemotherapy should involve considerations of age, comorbidities, performance status, and possible adverse events (**Table**; eTable 2 in the Supplement).[49-54,65,67,68] A Cochrane meta-analysis of 5 RCTs including 1277 women with early-stage ovarian cancer found that adjuvant platinum-based chemotherapy improved 10-year overall survival compared with no chemotherapy (hazard ratio, 0.72; 95% CI, 0.57-0.92; absolute data not available).[97] Among patients with high-risk disease (stage IA grade 3, stage IB-IC grade 2-3, stage II, or any clear cell ovarian cancer), those who

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Table. Summary of Evidence on Standard Treatment Strategies for Ovarian Cancer

Setting of therapy	Selected phase 3 randomized clinical trials	No. of randomized patients	Survival data[a]	Common serious adverse events[a,b]	Conclusions
Early-stage ovarian cancer					
Adjuvant systemic chemotherapy after surgery	ACTION,[49,50] ICON1,[51,52] GOG-157,[53] ICON3[54]	1765	10-Year overall survival: 73%-82% for adjuvant platinum-based chemotherapy vs 64%-76% for observation	Neutropenia (86%), thrombocytopenia (21%), anemia (7%), neurotoxicity (grade ≥2: 18%-29%), nausea/vomiting (9%-10%), allergy (3%), alopecia (grade 2: 64%-80%)	Adjuvant platinum-based chemotherapy (carboplatin and paclitaxel) is well tolerated and improves long-term overall survival
Advanced-stage ovarian cancer					
Cytoreductive surgery	EORTC 55971,[55] CHORUS,[56] JCOG0602,[57] SCORPION[58]	1654	Median overall survival: 24-44 months for interval cytoreductive surgery vs 23-49 months for primary cytoreductive surgery	28-Day mortality (<1% vs 1%-6%), hemorrhage (4%-6% vs 3%-7%), venous thrombosis (0%-3% vs 2%-5%), infection (1%-3% vs 1%-8%), gastrointestinal fistula (<1% vs 1%-3%)	Survival with neoadjuvant chemotherapy followed by interval cytoreductive surgery is not inferior to primary cytoreductive surgery, which, however, carries a higher risk of perioperative complications
First-line systemic chemotherapy	ICON3,[54] GOG-158,[59] AGO-OVAR-3,[60] SCOTROC1,[61] JGOG3016,[62,63] MITO-2,[64] MITO-7,[65] GOG-262,[66] ICON8[67,68]	8847	Median overall survival: 36-57 months for carboplatin-paclitaxel vs 35-49 months for other platinum-based regimens	Neutropenia (11%-88% vs 3%-94%), thrombocytopenia (2%-39% vs 1%-16%), anemia (1%-44% vs 1%-11%), neurotoxicity (3%-30% vs 1%-13%), nausea/vomiting (3%-10% vs 10%-23%), allergy (2%-3% vs 3%), alopecia (grade 2: 60%-80% vs 5%-76%)	Given the favorable toxicity profile and efficacy, carboplatin-paclitaxel is the standard first-line chemotherapy
Bevacizumab concurrent with chemotherapy and as maintenance therapy	ICON7,[69,70] GOG-0218[71,72]	3401	Median PFS: 14-24 months for chemotherapy plus bevacizumab vs 10-22 months for chemotherapy alone	Hypertension (18%-23% vs 2%-7%), proteinuria (1%-2% vs <1%), gastrointestinal perforation (1% vs <1%), bleeding (1%-2% vs <1%), venous thromboembolism (7% vs 6%), wound dehiscence (1%-3% vs <1%-3%)	Addition of bevacizumab to platinum-based chemotherapy followed by bevacizumab maintenance therapy prolongs PFS by 2-4 months
PARP inhibitor (olaparib or niraparib) maintenance therapy after response to platinum-based chemotherapy	SOLO1,[73,74] PAOLA-1,[75,76] PRIMA[77,78]	1930	• *BRCA* variants: 7-year overall survival: 67% for olaparib vs 47% for placebo • HRD positive: median overall survival: 75 months for olaparib plus bevacizumab vs 57 months for bevacizumab • HRD negative: median PFS: 8.4 months for niraparib vs 5.4 months for placebo	Neutropenia (6%-15%), anemia (17%-31%), thrombocytopenia (1%-29%), fatigue (2%-5%), vomiting (1%), diarrhea (2%-3%), abdominal pain (1%-2%), hypertension (7%)	• Olaparib improves long-term overall survival in patients with *BRCA* variants • Olaparib plus bevacizumab improves overall survival in patients with HRD-positive ovarian cancer • Niraparib improves PFS regardless of *BRCA* or HRD status
Platinum-sensitive recurrent ovarian cancer					
Secondary cytoreductive surgery	GOG-213,[79] DESKTOP III,[80] SOC-1[81,82]	1249	Median overall survival: 51-58 months for secondary cytoreductive surgery followed by chemotherapy vs 46-65 months for platinum-based chemotherapy	Surgical morbidity at 30 days was 5%-9%; patient-reported quality of life did not differ between the 2 groups	Secondary cytoreductive surgery before platinum-based chemotherapy may be considered if complete resection of macroscopic disease is achievable
Second-line systemic chemotherapy	ICON4,[83] Pfisterer et al,[84] CALYPSO,[85,86] OCEANS,[87,88] GOG-213,[89] AGO-OVAR-2.21[90]	3974	Median overall survival: 18-42 months for platinum-based doublets (carboplatin plus paclitaxel, gemcitabine, or pegylated liposomal doxorubicin) with or without bevacizumab	Neutropenia (70%), anemia (27%), thrombocytopenia (35%), fatigue (2%), vomiting (3%), neurotoxicity (grade ≥2: 20%)	Platinum-based doublet chemotherapy with or without bevacizumab is the standard treatment for platinum-sensitive recurrent ovarian cancer
PARP inhibitor (olaparib, niraparib, or rucaparib) maintenance therapy	SOLO2,[91,92] NOVA,[93] ARIEL-3[94]	1412	*BRCA* variants: median overall survival: 41-52 months for PARP inhibitor vs 38-39 months for placebo	Neutropenia (5%-20%), anemia (19%-25%), thrombocytopenia (1%-34%), hypertension (8%), fatigue (4%-8%), vomiting (2%-4%), diarrhea (1%), abdominal pain (1%-3%)	Second-line PARP inhibitor maintenance therapy improves overall survival in patients with *BRCA* variants who did not previously receive a PARP inhibitor

(continued)

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Table. Summary of Evidence on Standard Treatment Strategies for Ovarian Cancer (continued)

Setting of therapy	Selected phase 3 randomized clinical trials	No. of randomized patients	Survival data[a]	Common serious adverse events[a,b]	Conclusions
Platinum-resistant recurrent ovarian cancer					
Second-line systemic chemotherapy	AURELIA[95]	361	Median PFS: 6.7 months for single-agent chemotherapy (pegylated liposomal doxorubicin, weekly paclitaxel, or topotecan) plus bevacizumab vs 3.4 months for chemotherapy alone	Hypertension (grade ≥2: 20% vs 7%), proteinuria (2% vs 0%), gastrointestinal perforation (2% vs 0%), fistula/abscess (2% vs 0%), thromboembolism (5% vs 4%)	Non-platinum-based single-agent chemotherapy plus bevacizumab is the traditional standard treatment for platinum-resistant recurrent ovarian cancer
Mirvetuximab soravtansine (anti-folate receptor α antibody-drug conjugate)	MIRASOL[96]	453	Median overall survival: 16.5 months for mirvetuximab vs 12.7 months for single-agent chemotherapy	Blurred vision (7.8% vs 0%), keratopathy (9.2% vs 0%), dry eye (3.2% vs 0%), neutropenia (0.9% vs 17.4%), anemia (0.9% vs 10.1%), abdominal pain (2.8% vs 1.4%)	Mirvetuximab is the new standard treatment for patients with platinum-resistant recurrent ovarian cancer with high folate receptor α expression

Abbreviations: HRD, homologous recombination deficiency; PARP, poly-adenosine diphosphate ribose polymerase; PFS, progression-free survival.

[a] Survival data rates and adverse event rates across randomized clinical trials are reported as ranges.

[b] Grade 3 or higher according to Common Terminology Criteria for Adverse Events version 5.0 unless otherwise specified.

received adjuvant chemotherapy had improved 10-year overall survival compared with those not treated with adjuvant chemotherapy (hazard ratio, 0.52; 95% CI, 0.33-0.81; absolute data not available).[97]

Treatment of Advanced-Stage Ovarian Cancer

Treatment of advanced-stage epithelial ovarian cancer typically involves a combination of cytoreductive surgery, systemic chemotherapy, and individualized maintenance therapy (Figure 2).[2,4] For patients at low risk of perioperative complications and resectable advanced-stage ovarian cancer based on imaging, primary cytoreductive surgery (hysterectomy with bilateral salpingo-oophorectomy and omentectomy) is recommended before adjuvant platinum-based chemotherapy.[98-100] Patients with ovarian cancer involving other organs may require resection of enlarged retroperitoneal pelvic and para-aortic lymph nodes, spleen, bowel, and diaphragm.[98-101]

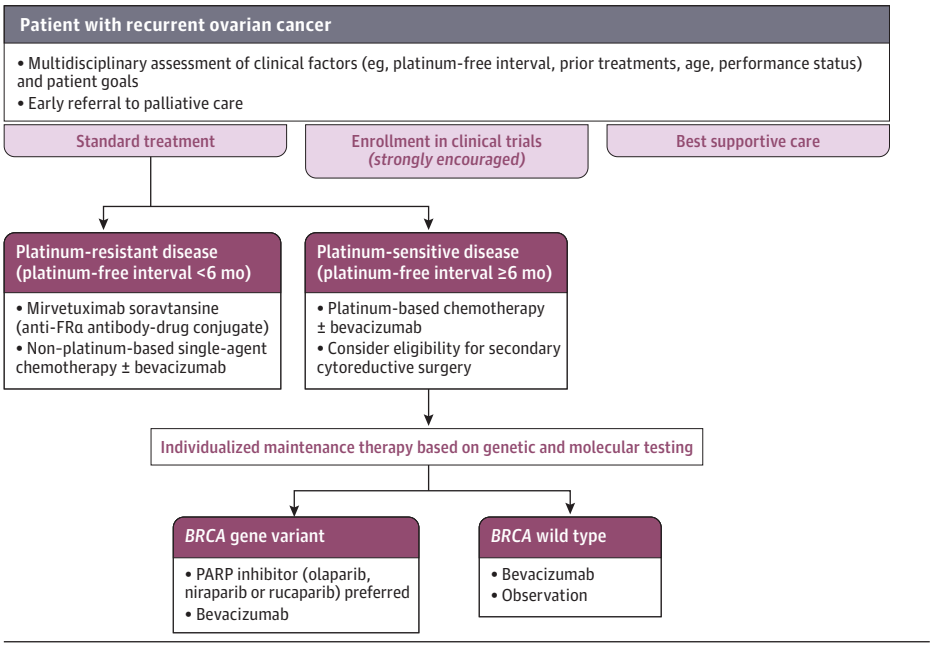
Patients with advanced-stage ovarian cancer at high risk of perioperative complications or unlikely to achieve complete cytoreduction at primary surgery should receive neoadjuvant chemotherapy followed by interval cytoreductive surgery and adjuvant systemic chemotherapy (Table; eTable 2 in the Supplement).[55-58,102] A meta-analysis of 4 phase 3 RCTs including 1692 patients with advanced-stage ovarian cancer found that those who underwent interval cytoreductive surgery (n = 847) had similar overall survival (hazard ratio, 0.96; 95% CI, 0.86-1.08) and lower rates of postoperative complications (relative risk, 0.22; 95% CI, 0.13-0.38)[103] compared with those who underwent primary cytoreductive surgery (n = 845).[103] For patients with stage III ovarian cancer, hyperthermic intraperitoneal chemotherapy, which involves delivery of heated platinum-based chemotherapy into the abdominal cavity during surgery, may be offered during interval cytoreductive surgery (eTable 2 in the Supplement).[102,104-107]

First-line systemic chemotherapy for advanced-stage ovarian cancer consists of carboplatin plus paclitaxel every 3 weeks for 6 cycles (Table; eTable 2 in the Supplement).[4,59-68,108,109] Patients undergoing primary cytoreductive surgery receive 6 cycles of chemotherapy, starting within 6 weeks after surgery. Patients undergoing interval cytoreductive surgery typically receive 3 to 4 chemotherapy cycles prior to surgery and 2 to 3 after surgery.[102] A weekly regimen of carboplatin and paclitaxel delivering the same cumulative dose as the every-3-week schedule is a reasonable alternative for patients who are unable to tolerate the standard schedule.[65,67,68] Two large phase 3 RCTs (GOG-0218 and ICON7) demonstrated that adding bevacizumab to chemotherapy followed by bevacizumab maintenance therapy for up to 22 cycles (15 months) in patients with advanced-stage ovarian cancer prolonged mean progression-free survival (PFS) by 2 to 4 months vs chemotherapy alone (GOG-0218, 14.1 months vs 10.3 months; median follow-up, 17 months; ICON7, 24.1 months vs 22.4 months; median follow up, 28 months) (Table; eTable 2 in the Supplement).[69,71] When these 2 trials were combined in a meta-analysis of 3401 patients, the bevacizumab group had improved PFS (hazard ratio, 0.72; 95% CI, 0.65-0.81; absolute data not available) compared with chemotherapy alone, although with no overall survival improvement.[110] An exploratory analysis of a predefined subgroup of 502 high-risk patients (stage IV,

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Figure 3. Treatment Algorithm for Recurrent Ovarian Cancer



FRα indicates folate receptor α; PARP, poly–adenosine diphosphate ribose polymerase.

inoperable stage III, or >1-cm residual disease after surgery for stage III ovarian cancer) in ICON7 showed improvement in mean overall survival in the bevacizumab group compared with chemotherapy alone (39.3 months vs 34.5 months; hazard ratio, 0.78; 95% CI, 0.63-0.97).[70]

Bevacizumab and/or PARP inhibitor (olaparib or niraparib) maintenance therapy after primary treatment may be considered for patients with advanced-stage ovarian cancer depending on their response to chemotherapy, histology, *BRCA*/HRD status, and comorbidities (Table; eTable 2 in the Supplement).[69-78,111-113] PARP inhibitors are guideline recommended for maintenance therapy in patients with high-grade serous or endometrioid ovarian cancer who respond to platinum-based chemotherapy, especially in *BRCA* variant or HRD-positive tumors.[2,4] PARP inhibitors are administered orally, with olaparib dosed at 300 mg twice daily for 2 years and niraparib dosed at 200 mg to 300 mg once daily for 3 years.[6] Olaparib provided a 7-year overall survival benefit compared with placebo (67.0% vs 46.5%; median overall survival, not reached vs 75.2 months; hazard ratio, 0.55; 95% CI, 0.40-0.76) in a phase 3 RCT of 391 patients with *BRCA* variant high-grade advanced-stage ovarian cancer (eTable 2 in the Supplement).[73,74] In another phase 3 trial of 806 patients with advanced-stage ovarian cancer responding to platinum-based chemotherapy and bevacizumab, addition of olaparib to bevacizumab improved 5-year overall survival in patients with HRD-positive tumors (including *BRCA* variants) compared with placebo plus bevacizumab (65.5% vs 48.4%; median overall survival, 75.2 months vs 57.3 months; hazard ratio, 0.62; 95% CI, 0.45-0.85). Five-year overall survival rates were 73.2% vs 53.8% (median overall survival, 75.2 months vs 66.9 months; hazard ratio, 0.60; 95% CI, 0.39-0.93) for those with *BRCA* variants and 54.7% vs 44.2% (median overall survival, not reached vs 52.0 months; hazard ratio, 0.71; 95% CI, 0.45-1.13) for those without *BRCA* variants (eTable 2 in the Supplement).[75,76] Three other trials investigating PARP inhibitor maintenance therapy found that PFS was highest among patients with *BRCA* variant tumors followed by HRD-positive tumors and lowest for those with HRD-negative tumors (eTable 2 in the Supplement).[77,111,112]

Prognosis and Surveillance

Overall 5-year survival rates are 70% to 95% for patients treated for early-stage ovarian cancer and 10% to 40% for those with advanced-stage disease.[114] More than 80% of patients with advanced-stage ovarian cancer have initial complete remission (no disease on post-treatment imaging). PARP inhibitor maintenance therapy after platinum-based chemotherapy improves 5-year overall survival rates to approximately 70% in patients with *BRCA* variant or HRD-positive advanced-stage ovarian cancer.[74,76]

There are currently no evidence-based treatment follow-up protocols, so surveillance should be individualized based on stage of disease, histology, genetic variants, and radiological and serum tumor marker response to primary treatment. Patients with complete remission after primary treatment should receive clinical reevaluation and CA125 testing (if initially elevated) every 2 to 4 months for the first 2 years, every 3 to 6 months during years 3 to 5, and then annually. Computed tomographic imaging should be individualized based on recurrence risk or clinical suspicion of recurrence (eg, abdominal pain, bloating, weight loss, increasing CA125 level).[2,4]

Ovarian Cancer Relapse

Approximately 75% of patients with advanced-stage ovarian cancer and 10% to 30% of patients with early-stage ovarian cancer relapse within 2 years.[2,4] Decisions about additional therapy, enrolling in clinical trials, or initiating palliative care should be made on an individual basis (**Figure 3**). Recurrent disease treatment depends on

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the platinum-free interval—the time from the last dose of platinum-based chemotherapy to recurrence—which predicts response to subsequent platinum therapy. At first relapse, approximately 80% of patients have platinum-sensitive disease (platinum-free interval ≥6 months) and 20% have platinum-resistant disease (platinum-free interval <6 months).[115] With each remission and recurrence, platinum-free intervals shorten, and about 60% to 75% of patients with recurrent disease develop platinum resistance.[115] Patients with recurrent ovarian cancer should undergo tumor testing for folate receptor α (FRα [*FOLR1*]) and *ERBB2* (previously *HER2/neu*) to identify potential targets for therapy.

Platinum-Sensitive Ovarian Cancer

For patients with platinum-sensitive recurrent ovarian cancer, platinum-based chemotherapy (carboplatin plus pegylated liposomal doxorubicin, gemcitabine, or paclitaxel) with or without bevacizumab is recommended (Table; eTable 2 in the Supplement).[83-90] The median PFS with this treatment is 8 to 13 months.[115] Secondary cytoreductive surgery prior to chemotherapy may be considered for platinum-sensitive disease if imaging and performance status indicate potentially resectable disease (Table; eTable 2 in the Supplement).[79-82]

Clinical trial data support use of maintenance therapy with a PARP inhibitor (olaparib, niraparib, or rucaparib) for recurrent disease in PARP inhibitor–naive patients with *BRCA1/2* gene variants who responded to platinum-based chemotherapy (Table).[91-94,116,117] A phase 3 RCT including 295 patients with *BRCA* gene variants and platinum-sensitive recurrent ovarian cancer showed that olaparib maintenance provided a median overall survival benefit of 12.9 months compared with placebo (51.7 months vs 38.8 months; hazard ratio, 0.74; 95% CI, 0.54-1.00).[91,92] Niraparib and rucaparib have similar results (eTable 2 in the Supplement).[93,94,116,117]

For patients with recurrent ovarian cancer without a *BRCA* variant or who received PARP inhibitor as first-line treatment, bevacizumab maintenance can be considered.[118] A phase 3 RCT including 484 patients with first platinum-sensitive recurrence reported that adding bevacizumab to platinum-based chemotherapy followed by bevacizumab maintenance improved median PFS (12.4 months vs 8.4 months; hazard ratio, 0.48; 95% CI, 0.38-0.61) compared with chemotherapy alone (eTable 2 in the Supplement).[87,88]

Platinum-Resistant Ovarian Cancer

Platinum-resistant recurrent ovarian cancer may be treated with single-agent non–platinum-based chemotherapy (pegylated liposomal doxorubicin, gemcitabine, weekly paclitaxel, or topotecan), associated with a median PFS of 3 to 9 months.[95,115] Combining bevacizumab with chemotherapy improved PFS compared with chemotherapy alone in a phase 3 RCT of 361 patients with platinum-resistant recurrent ovarian cancer (6.7 months vs 3.4 months; hazard ratio, 0.48; 95% CI, 0.38-0.61) (Table; eTable 2 in the Supplement).[95]

For the 30% to 35% of patients with platinum-resistant ovarian cancers exhibiting high FRα expression who have received 1 to 3 rounds of any type of anticancer therapy, the US Food and Drug Administration (FDA) has approved an antibody-drug conjugate targeting FRα, mirvetuximab soravtansine.[96,119] In a phase 3 RCT of 453 patients, mirvetuximab provided a median overall survival benefit compared with conventional chemotherapy (16.5 months vs 12.7 months; hazard ratio, 0.67; 95% CI, 0.50-0.89) (Table; eTable 2 in the Supplement).[96] Another recently FDA-approved antibody-drug conjugate is trastuzumab deruxtecan, which targets *ERBB2* and provides a treatment option for patients with *ERBB2*-expressing ovarian cancer (eTable 2 in the Supplement).[120]

Palliative Care

The NCCN guidelines recommend providing supportive care for all patients with ovarian cancer, including referral for palliative care assessment for those with advanced-stage or recurrent disease.[4] Palliative care clinicians provide comprehensive multimodal symptom management, addressing pain, mental health, sexual health, and menopausal symptoms, and can facilitate transition to hospice care.[121] Use of palliative care optimizes quality of life and may improve survival.[121,122] Although not specific to ovarian cancer, outpatient palliative care for advanced-stage cancers has been shown to increase 1-year survival by 14% (56% vs 42%; $P < .001$) and median overall survival by 4.6 months (14.6 months vs 10.0 months) compared with usual care.[123]

Limitations

This Review has several limitations. First, it is not a systematic review, and the quality of included studies was not formally evaluated. Second, this Review did not include less common epithelial and nonepithelial ovarian cancers. Third, treatments, outcomes, and prognostic estimates were derived from trials conducted primarily in North America and Europe and may not be generalizable to lower-income countries.

Conclusions

Approximately 21 000 women are diagnosed with ovarian cancer annually in the US, and approximately 80% have advanced-stage ovarian cancer at diagnosis. First-line treatment of early-stage ovarian cancer is surgery and adjuvant platinum-based chemotherapy. Treatment of advanced-stage ovarian cancer includes cytoreductive surgery, platinum-based chemotherapy, and targeted maintenance therapies such as bevacizumab and/or PARP inhibitors.

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