Diagnosis and Treatment of Ovarian Cancer

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KEYWORDS

• Ovarian cancer • Neoadjuvant • HIPEC • Intraperitoneal • Dose-dense
• Chemotherapy

KEY POINTS

- Epithelial ovarian cancer is the most deadly gynecologic malignancy with most women diagnosed at an advanced stage; the authors review the initial presentation, diagnosis, and treatment.
- Management of ovarian cancer involves a combination approach with surgery and platinum/taxane chemotherapy; the authors discuss the surgical paradigm of optimal cytoreductive intervention coupled with the available chemotherapy options.
- An expanded discussion for the potential clinical scenarios is presented for intraperitoneal, dose-dense, heated intraperitoneal chemotherapy, neoadjuvant, and maintenance chemotherapy.

The diagnosis and treatment planning for newly diagnosed ovarian adenocarcinomas are unique among solid cancers. Ovarian cancer is insidious in presentation with few sentinel symptoms and lacks effective screening test strategies. This article focuses on the care of the patient with newly diagnosed ovarian cancer.

EPIDEMIOLOGY AND CLINICAL PRESENTATION

Epithelial ovarian cancer is the fifth most common cancer in women with 22,400 cases last year but has the highest mortality with greater than 14,000 deaths.[1–6] The median age of onset is 62. The incidence of ovarian cancer appears to have slightly decreased over the last 10 years.[1]

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Clinical Presentation

The clinical presentation of ovarian cancer can be difficult to differentiate from other causes of carcinomatosis, such as gastrointestinal or metastatic breast cancer. However, there are several elements that may lead to earlier recognition of the condition. Understanding the history and physical findings and having a low threshold for diagnostic imaging in higher-risk patients currently represent the only approach for ovarian cancer detection for patients without familial risk factors.

The hallmark of ovarian cancer biology is peritoneal dissemination. Once the primary tumor extends to the ovarian/fallopian tube surface, tumor cells are shed into the intraperitoneal (IP) fluid, which continuously circulates through the abdomen and transports the deposits of malignant tumor cells in a diffuse peritoneal distribution. Common sites of implantation are the pelvis, right hemidiaphragm, liver, paracolic gutters, bowel, and omentum.[7] Transdiaphragmatic spread to the pleura is common in patients with ovarian cancer. However, early stage disease may present with a dominant mass alone in about 30% of ovarian cancer cases.[8–15] Metastatic cancer from other sites, such as gastrointestinal or breast, may mimic ovarian cancer with ovarian masses and omental caking or ascites, so the workup of this presentation may require multiple imaging and laboratory testing.[16,17]

Ovarian, fallopian tube, and primary peritoneal adenocarcinoma all present similarly and tend to be approached as a single disease and are collectively referred to as epithelial ovarian cancer. Prodromal symptoms tend to be vague and include distension, constipation, and vague pelvic pressure. Pain is minimal, and the progression to advanced disease is insidious.[18,19] Without sentinel symptoms of early disease, patients frequently present with symptoms at distant sites to the ovary.

Physical Examination Findings

Generally, patients present with dominant pelvic mass and findings of carcinomatosis with ascites and marked abdominal distension. Comprehensive outpatient physical examination findings that are possible findings associated with ovarian cancer include the following:

- Abdomen: distended nontender abdomen, palpable mass, carcinomatosis, apparent ascites
- Cardiovascular: tachycardia, deep vein thrombosis, lower extremity edema
- Pulmonary: decreased breath sounds in lung bases (pleural effusions, right more common than left)
- Pelvic: adnexal mass, limited/fixed mobility of uterus, rectovaginal examination with cul-de-sac nodularity
- Nodal: palpably enlarged inguinal or cervical nodes infrequently encountered.

The remainder of comprehensive examination is typically normal and consistent with the expectation for the patient's age and medical comorbidities.

Imaging and Diagnostic Evaluation

Frequently, women with undiagnosed ovarian cancer undergo workup of pleural effusion, ascites, change in bowel/bladder habits, or weight loss. Diagnosis is suspected only after radiographic imaging demonstrates intra-abdominal masses, ascites, pleural effusions, and/or carcinomatosis.

The imaging for ovarian cancer usually involves computed tomography (CT) or magnetic resonance (MR) of the chest, abdomen, and pelvis if cancer is suspected to define the extent of peritoneal disease and to evaluate for distant spread. PET imaging is

infrequently used at initial diagnosis. PET imaging has limitations to detect small-volume and diffuse miliary peritoneal disease due to individual lesion size and background PET activity of bowel/bladder. PET is typically reserved for indeterminate lesions on CT/MR that would preclude primary surgery or in the recurrent setting. Some data suggest improved detection of occult nodal metastasis, but further studies are needed to address the potential benefit of PET imaging in the pretreatment setting.[20]

Concurrent tumor marker testing aids to narrow the differential diagnosis during evaluation and when cytology alone is used to define the primary. Common panels to assess are CA-125, CEA, and CA 19-9.[16,17,19]

With advanced disease, above the diaphragm percutaneous core biopsy is acceptable, but with disease limited to the abdominal cavity, laparoscopic assessment is often necessary to assess stage of the disease and whether primary resection is possible.[21,22] Identification of extra-abdominal nodal involvement, bone, or parenchymal liver metastasis is uncommon. Such a presentation may reflect a uterine or other primary cancer.[15,23–25] However, clear cell ovarian cancer has faster hematogenous/lymphatic spread and can present with parenchymal liver/lung disease.[26] For patients with atypical presentations, image-guided biopsy is the standard of care usually targeting the most easily accessed mass. Core biopsy is preferred, but for patients who are debilitated or biopsy is not feasible, cytology from pelvic mass or ascites aspiration may be used, as aspiration cytology of masses is 75% sensitive when compared with a standard biopsy.[24]

For the common presentation of stage IIIC/IV disease, the evaluation and management decision involve understanding of the disease process and timing of surgical and chemotherapy. The miliary distribution of peritoneal metastasis limits the ability to define unresectable disease clinically before surgery. Retrospective studies and subanalysis of prospective trials have found associations with likelihood of optimal resection, but have not found a consistent predictor for feasibility of resection outside of apparent stage IV disease.[27,28] Laparoscopic assessment can enhance CT and laboratory evaluation, and most experts and current active trials incorporate laparoscopic assessment of resection for patients who appear to have likely resectable disease.[29–31] Given the limitations of evaluation and inherent controversy concerning determination of primary surgical intervention versus neoadjuvant chemotherapy (NACT) candidacy, the American Society of Clinical Oncology (ASCO) and Society of Gynecologic Oncology (SGO) collaboratively developed clinical practice guidelines for newly diagnosed patients with advanced ovarian cancer in 2016.[32] The key recommendations are listed below.

- All patients with stage III/IV ovarian cancer should be evaluated by gynecologic oncologist prior to initiation of therapy whether they are candidates for primary cytoreductive surgery.
- For women with high perioperative risk or a low likelihood of achieving cytoreduction to <1cm (ideally no visible disease) should receive neoadjuvant chemotherapy.
- Women who are fit for primary surgery with potentially resectable disease, either NACT or primary cytoreductive surgery may be offered. Neoadjuvant is associated with less peri- and post-operative morbidity and mortality and shorter hospitalizations, but primary cytoreductive surgery may offer superior survival in selected patients.
- For women with high likelihood for achieving cytoreduction to <1cm (ideally no visible disease) with acceptable morbidity, primary cytoreductive surgery is recommended over NACT.

- For women who are fit for primary cytoreductive surgery but are deemed to unlikely to have cytoreduction to <1cm (ideally no visible disease) by a gynecologic oncologist, NACT is recommended over primary cytoreductive surgery.
- Interval cytoreductive surgery should be performed after four or fewer cycles of NACT for women who respond to chemotherapy or with stable disease. Alternative timing of surgery has not been prospectively evaluated but may be considered based on patient-centered factors.
- Patients with progressive disease on NACT have a poor prognosis. Options include alternative chemotherapy regimens, clinical trials, and/or discontinuation of active cancer therapy and initiation of end-of-life care. In general, there is little role for surgery and it is not typically advised, unless for palliation, eg, relief of a bowel obstruction.

SURGICAL STAGING OF OVARIAN CANCER

Women with an isolated pelvic mass are often completely asymptomatic until the mass itself produces distension or pelvic pressure. Complete surgical staging will "upstage" a patient with an isolated ovarian mass in up to 30% of patients due to occult disease.[33] An assessment of preoperative risk features by ultrasound or CT should define solid components, high blood flow, and associated ascites fluid. High quality imaging is important to have pre-operatively to confirm that the required surgical expertise to complete all staging requirements can be available.

Traditional Open Surgery in Advanced Cancer

Once ovarian cancer is histologically confirmed, the patient should be evaluated by a gynecologic oncologist for surgical debulking feasibility. Staging is performed via laparotomy with complete hysterectomy, bilateral salpingo-oophorectomy, and comprehensive surgical evaluation of the peritoneal cavity with maximal cytoreductive surgery of all visible peritoneal disease. In these cases, a complete clinical and surgical assessment of the peritoneal surfaces, including the diaphragm, paracolic gutters, and bowel mesentery along with pelvic and para-aortic node assessment, pelvis washings, and complete omentectomy, should be addressed to completely assign stage of disease (**Table 1**).[15,34]

Use of Laparoscopy

Laparoscopic surgical staging of ovarian cancer offers several clearly defined benefits when compared with laparotomy. In endometrial cancer, there is both randomized and retrospective literature that suggests that laparoscopic staging offers lower estimated blood loss, shorter hospital stay, and fewer postoperative complications with an improved quality of life and faster return of normal functioning.[22] In ovarian cancer, because of the frequent presentation of advanced disease, there are only retrospective series that are limited to presumed early stage disease.[35,36] In cases where the surgical resection versus NACT is in question, the use of laparoscopic evaluation is advocated, and validated scoring systems have been created to aid in the intraoperative decision of ability to predict optimal resection.[29–31,37,38] Complete surgical staging of ovarian masses or restaging of unexpected ovarian cancer may be performed laparoscopically with minimal morbidity in select patients.[21,22,39]

SURGICAL STAGING AND TREATMENT DECISIONS

Current therapy recommendations depend on several prognostic factors, including the patient's age at presentation, performance status, and stage at presentation.

Table 1
International Federation of Gynecology and Obstetrics staging of ovarian cancers

Stage	Definition
I	Tumor confined to ovaries and fallopian tube(s)
IA	Tumor limited to one ovary (capsule intact) or fallopian tube; no tumor on ovarian or fallopian tube surface; no malignant cells in the ascites or peritoneal washings
IB	Tumor limited to both ovaries (capsules intact) or fallopian tubes; no tumor on ovarian or fallopian tube surface; no malignant cells in the ascites or peritoneal washings
IC	Tumor limited to one or both ovaries or tubes with any of the following:
IC1	Surgical spill intraoperatively
IC2	Capsule ruptured before surgery or tumor on ovarian or fallopian tube surface
IC3	Malignant cells present in the ascites or peritoneal washings
II	Tumor involves one or both ovaries or fallopian tube with pelvic extension (below pelvic brim) or primary peritoneal cancer
IIA	Extension and/or implants on the uterus and/or fallopian tubes and/or ovaries
IIB	Extension to other pelvic IP tissues
III	Histology-confirmed spread to the peritoneum outside of the pelvis and/or metastasis to the retroperitoneal lymph nodes
IIIA	Metastasis to the retroperitoneal lymph nodes with or without microscopic peritoneal involvement beyond the pelvic
IIIA(i)	Positive retroperitoneal nodes only (cytologically or histologically proven)
IIIA(ii)	Metastases >10 mm in dimension
IIIA2	Microscopic peritoneal involvement with or without nodes
IIIB	Macroscopic peritoneal <2 cm above the pelvic brim
IIIC	Macroscopic involvement >2 cm above the pelvic brim
IV	Distant metastasis excluding peritoneal metastases
IVA	Pleural effusion with positive cytology
IVB	Metastases to extra-abdominal organs, inguinal nodes, and lymph nodes outside abdominal cavity

Adapted from Mutch DG, Prat J. 2014 FIGO staging for ovarian, fallopian tube and peritoneal cancer. Gynecol Oncol 2014;133(3):402; with permission.

Critical in the clinical assessment is surgical resectability and the need for additional chemotherapy. For patients with stage I disease, the resection is the primary therapy with the need for adjuvant therapy dictated by the tumor grade, histology, and adherence to adjacent structures. Clinically significant ascites with stage I disease is considered a significant predictor of relapse.[40] With high-grade adherent stage I cancer, the risk of death from the disease can approach 30%.[41–44] Histologies that portend a worse prognosis include clear cell or undifferentiated cancers, whereas better prognosis is associated with mucinous or transitional cell cancer.[45,46] Cancers matched for stage and grade that associated with BRCA 1 or 2 tend to respond better to chemotherapy and may have prolonged survival as compared with non-BRCA-mutated cancer.[24,47] This improved response and survival for BRCA positive patients is seen in platinum and nonplatinum regimens.

Treatment of Early Stage Ovarian Cancer

Surgical staging for stage I disease may involve incidental finding postoperatively or via intraoperative frozen pathologic confirmation after intact mass excision. If

the lesion is determined intraoperatively, comprehensive staging is recommended via laparotomy, with peritoneal washings, complete hysterectomy, bilateral salpingo-oophorectomy, pelvic and para-aortic lymph node dissection, omentectomy, and examination/sampling of peritoneal surfaces of the diaphragm, paracolic gutters, and pelvis.[48] Post-operative discovery should involve a gynecologic oncology consultation and decision tree involving histology, grade, potential of residual disease, and fertility potential. Conservative surgery for younger patients with low-grade disease is certainly indicated, including preservation of the remaining normal ovary and the uterus, but absolute ascertainment of the grade of disease should be determined if possible. High-grade tumors in younger patients usually require complete surgical staging and adjuvant therapy, but must be considered in context with the patient's circumstances and risk assessment.[24,49,50] Treatment with chemotherapy will depend on the presence of complete surgical staging and the grade of disease (**Table 2**). Generally, correctly surgically staged patients with well-differentiated disease can be observed without chemotherapy adjuvant treatment, whereas grade II and grade III patients generally receive additional adjuvant platinum/taxane-based therapy for 3 to 6 cycles. Randomized trials support platinum and taxane combination with improved survival in early stage presentation of high-grade lesions.[49–56] Bell and colleagues[56] reported data from the Gynecologic Oncology Group (GOG) 157 that no significant difference in stage I recurrence or overall survival (OS) was seen with 3 versus 6 cycles of paclitaxel/carboplatin overall, but post hoc analysis revealed a benefit of 6 cycles in the serous subtype with improved 5-year recurrence-free survival (83% vs 60%, $P = .007$).[57]

Surgical and Chemotherapy Decisions for Advanced Stage Disease

Treatment options for stages II–IV of epithelial ovarian cancer consist of initial complete surgical resection, if possible, followed by platinum-based chemotherapy or the use of NACT, interval cytoreductive surgery, and then followed by additional platinum/taxane chemotherapy. Currently, there are 5 treatment options considered standard and acceptable for advanced stage ovarian cancer:

1. Cytoreductive surgery followed by IV platinum/taxane-based chemotherapy
2. Cytoreductive surgery followed by IP/IV chemotherapy
3. Cytoreductive surgery followed by IV platinum/taxane-based chemotherapy combined with bevacizumab, with bevacizumab maintenance
4. NACT with interval cytoreductive surgery between courses 3 and 6, followed by chemotherapy with consideration of intra-abdominally directed regional therapy for optimally debulked patients (heated intraperitoneal chemotherapy [HIPEC] at time of surgery or IP after surgery)
5. Chemotherapy for patients who cannot undergo surgery or progress through NACT

Surgical resection is central to the management of advanced ovarian cancer, and extent of residual disease is one of the most important determinants of long-term

Table 2
Treatment options for early stage

Stage I, grade 1/2, surgically staged	Observe
Stage I B/C, grade 1/2, not staged	Laparoscopic stage or platinum/taxane X3 cycles
Stage I, grade 3	Platinum/taxane X3-6 cycles
Stage II, grade 1-3	Platinum/taxane X6 cycles

survival.[58–62] For the last 30 years, clinical trials have been typically designed or stratified by cytoreduction status with the goal of complete surgical cytoreduction, but anywhere from 30% to 60% of presenting patients may not be candidates for cytoreduction to less than 1 cm of disease.[15,34,63–65] Incomplete surgery with failure to resect disease to less than 1 cm may lead to delays in chemotherapy and increased morbidity and mortality.[66] Meta-analyses have confirmed this with a median OS of 39 months for optimal cytoreduction as compared with 17 months for suboptimal cytoreductive attempt.[48] Optimally resected patients defined as patients with residual disease less than 1 cm in largest dimension may be treated with different regimens, but the most profound increase in OS in phase 3 cooperative group trials has been produced with the combination of optimal cytoreduction followed by the GOG 172 regimen of combination IV taxane followed by IP cisplatin and IP taxane, achieving an overall median survival of 66 months, resulting in an National Cancer Institute Clinical Advisory notice in 2006.[61]

Treatment selection after cytoreductive surgery

Standard approach for first-line chemotherapy involves platinum and taxane combination therapy. **Table 3** lists selected trials that led to the standard 6 cycles platinum/taxane doublet (carboplatin, area under the curve [AUC] 6; paclitaxel, 175 mg/m^2 every 21 days).

Timing of chemotherapy initiation after surgery is recommended to begin as soon as possible, typically between 2 and 4 weeks; greater delays are associated with worse outcomes.[82,83] For patients with optimally resected disease (<1 cm residual disease), they are candidates for combination IV/IP chemotherapy or IV chemotherapy alone based on GOG 172.

Patients who are not candidates for IV/IP therapy or who had suboptimal resection should receive IV chemotherapy. Delivery of chemotherapy in a weekly dose-dense regimen seen in JGOG 3016 study showed an advantage of 10.5 months for PFS and 37.8 months for OS compared with a conventional 21-day cycle.[75] GOG 262 and ICON 8 did not show the same benefit in PFS that was seen in the Japanese population.[81,84] In the JGOG 3016 trial, the patients who appeared to have the most benefit were the suboptimal (>1-cm residual disease) resected patients with an 18-month improvement in OS compared with no advantage in the optimal cohort.[75] For this reason, some experts will use dose-dense therapy for >1 cm residual patients over the standard every 21-day regimen, but the decision needs to be individualized to the patients potential for side effects and ability to adhere to weekly treatment.

Front-line trials over the last 10 years have often included the addition of bevacizumab with consistent 3- to 4-month progression-free survival (PFS); no OS benefits have been observed. The inclusion of bevacizumab has often made several of the resulting trials difficult to interpret.

Retrospective analysis of ICON7 identified subgroup of patients with suboptimally cytoreduced ovarian cancer did show an OS benefit.[77,85]

Intraperitoneal chemotherapy

The direct application of cytotoxic chemotherapy to diffuse peritoneal carcinomatosis was first established in the 1970s. The pharmacologic concentration gradient was cited as the rationale, and most of the studies were performed in a series of phase 2 studies with cisplatin-based regimens and were limited to small volume disease at second-look surgery after primary therapy or platinum-sensitive recurrent disease. A series of randomized GOG front-line trials were then performed

Table 3
Selected phase 3 studies of intravenous adjuvant therapy for advanced ovarian cancer after initial surgery

Trial (Year Published), Patient Population	Treatment Regimens	Patients Enrolled	PFS (mo)	OS (mo)
GOG-111[67] (1996), suboptimal stage III-IV	Cyclophosphamide (750 mg/m^2) Cisplatin (75 mg/m^2)	202	13	24
	Paclitaxel (135 mg/m^2, 24 h) Cisplatin (75 mg/m^2)	184	18 (P<.001)	38 (P = .001)
EORTC-55931[68] (2000), stage IIB-IV	Cyclophosphamide (750 mg/m^2) Cisplatin (75 mg/m^2)	161	11.5	25.8
	Paclitaxel (175 mg/m^2, 3 h) Cisplatin (75 mg/m^2)	162	15.5 (P<.001)	35.6 (P = .001)
GOG-132[69] (2000), suboptimal stage III-IV	Paclitaxel (200 mg/m^2, 24 h) Cisplatin (100 mg/m^2)	213	11.2	26
		200	16.4	30.2
	Paclitaxel (135 mg/m^2, 24 h) Cisplatin (75 mg/m^2) Every 3 wk ×6	201	14.2	26.6 (NS; less toxic)
MRC-ICON3[70] (2002) (carboplatin vs carboplatin/paclitaxel and CAP vs carboplatin/ paclitaxel), stage I-IV	Carboplatin (AUC, 6) Every 3 wk ×6	943	16.1	35.4
	Paclitaxel (175 mg/m^2, 3 h) Carboplatin (AUC, 6) Every 3 wk ×6	478	17.3	36.1 (NS)
	Cyclophosphamide (500 mg/m^2) Doxorubicin (50 mg/m^2) Cisplatin (50 mg/m^2) (CAP) Every 3 wk ×6	421	17	40
	Paclitaxel (175 mg/m^2, 3 h) Carboplatin (AUC, 6) Every 3 wk ×6	232	17	40 (NS)
GOG-158[71] (2003), optimal stage III <1 cm	Paclitaxel (135 mg/m^2, 24 h) Cisplatin (75 mg/m^2) Every 3 wk ×6	425	14.5	48
	Paclitaxel (175 mg/m^2, 3 h) Carboplatin (AUC, 6) Every 3 wk ×6	415	15.5 (NS)	52 (NS; less toxic)
OVAR-3[72] (2003), stage IIB-IV	Paclitaxel (185 mg/m^2, 24 h) Cisplatin (75 mg/m^2) Every 3 wk ×6	386	19.2	44.1
	Paclitaxel (185 mg/m^2, 24 h) Carboplatin (AUC 6) Every 3 wk ×6	397	17.2	43.3 (NS; less toxic)

SOCTROC[73] (2004), stage IC-IV	Paclitaxel (175 mg/m^2, 3 h) Carboplatin (AUC, 5) Every 3 wk ×6	538	14.8	2-y OS 68.9%
	Docetaxel (75 mg/m^2) Carboplatin (AUC 5) Every 3 wk ×6	539	15 (NS; less neuropathy)	2-y OS 64.2%
GOG-182/ICON-5[74] (2009), stage III-IV	Paclitaxel (175 mg/m^2, 3 h) Carboplatin (AUC, 6) Every 3 wk cycle ×8 (C 1–8)	864	16	NR
	Paclitaxel (175 mg/m^2, 3 h) C 1–8 Carboplatin (AUC, 5) C 1–8 Gemcitabine (800 mg/m^2) D1/D8, C1-8	864	PFS ranged from 15.4 to 16.4 (NS)	NR
	Paclitaxel (175 mg/m^2, 3 h) C 1–8 Carboplatin (AUC, 5) C 1–8 PLD (30 mg/m^2) D1, C1-8	862		NR
	Paclitaxel (175 mg/m^2, 3 h) C 1–8 Carboplatin (AUC, 5) D3, C 1–4 Carboplatin (AUC, 6) D1, C 5–8 Topotecan (1.25 mg/m^2) D1, 2, 3 ×1-8	861		NR
	Paclitaxel (175 mg/m^2, 3 h) C 1–8 Carboplatin (AUC, 6) D8, C 1–4 Carboplatin (AUC, 6) D1, C 5–8 Gemcitabine (800 mg/m^2) D1/D8 C1-4	861		NR
JGOG 3016[75] (2009), stage II-IV	Paclitaxel (180 mg/m^2) Carboplatin (AUC 6) Every 3 wk ×6	319	17.5	62.2
	Paclitaxel (80 mg/m^2) weekly Carboplatin (AUC 6) every 3 wk ×6 cycles	312	28.5 (P = .037)	100.5 (P = .039)
MITO-2[76] (2011), stage IC-IV	Paclitaxel (175 mg/m^2) Carboplatin (AUC 5) Every 3 wk ×6	410	16.8	NR
	Carboplatin (AUC 5) PLD (30 mg/m^2) Every 3 wk ×6	410	19 (NS)	NR

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Table 3
(continued)

Trial (Year Published), Patient Population	Treatment Regimens	Patients Enrolled	PFS (mo)	OS (mo)
GOG-218[77] (2011), incompletely resected stage III-IV	Paclitaxel (175 mg/m^2) Carboplatin (AUC 6) × 6 cycles Placebo cycles 2–22	625	10.3	39.3
	Paclitaxel (175 mg/m^2) Carboplatin (AUC 6) × 6 cycles Bevacizumab cycles 2–6 Placebo cycles 7–22	625	11.2	38.7
	Paclitaxel (175 mg/m^2) Carboplatin (AUC, 6) × 6 cycles Bevacizumab cycles 2–22	623	14.1 (P<.001)	29.7 (NS)
ICON-7[78] (2011), stage I-IIA, grade 3 stage IIB-IV	Paclitaxel (175 mg/m^2, 3 h) Carboplatin (AUC, 6)	764	22.4	44.6
	Paclitaxel (175 mg/m^2) Carboplatin (AUC 5 or 6) Bevacizumab 7.5 mg/kg × 6 cycles Bevacizumab alone cycles 7–18	764	24.1 (P = .04)	45.5 (NS)
MITO-7[79] (2014), stage IC-IV	Paclitaxel (175 mg/m^2) Carboplatin (AUC, 6) Every 3 wk ×6	404	17.3	NR
	Paclitaxel (60 mg/m^2) weekly Carboplatin (AUC 2) weekly × 6 cycles	406	18.3 (NS; less toxic)	NR
AGO-OVAR16[80] (2014), stage II-IV	Platinum/taxane therapy, at least ×5 21-d cycles Placebo daily × 24 mo or PD	468	12.3	NS
	Platinum/taxane therapy, at least ×5 21-d cycles Pazopanib 800 mg PO daily × 24 mo or PD	472	17.9 (P = .002)	NS
GOG-262[81] (2016), incompletely resected stage III-IV	Paclitaxel (175 mg/m^2) every 3 wk Carboplatin (AUC 6) every 3 wk plus optional Bevacizumab cycles 2–6, and every 3 wk until progression	346	14.0	NR
	Paclitaxel (80 mg/m^2) weekly Carboplatin (AUC 6) every 3 wk Plus optional bevacizumab cycles 2–6, and every 3 wk until progression	346	14.7 (NS)	NR

Abbreviations: EORTC, European Organization for Research and Treatment of Cancer; ICON, International Collaboration on Ovarian Neoplasms; JGOG, Japanese Gynecologic Oncology Group; MITO, Multicentre Italian Trials in Ovarian cancer; MRC, Medical Research Council; NR, not reported; NS, not significant; PD, progressive disease; PLD, methoxypolyethylene glycosylated liposomal doxorubicin; PO, per os (oral).

with increasingly complex trial designs (**Table 4**). The initial trial reported by Alberts and colleagues[86] GOG 104 (SWOG-8501) most definitively demonstrates the locoregional dose intensity with randomization of the same dose of cisplatin (100 mg/m^2) to either IV or IP delivery as the single variable produced improved OS with fewer systemic toxicities. Subsequent GOG 114 and 172 study results confirmed the survival advantage of the IP approach, but added systemic toxicity.[61,87] GOG 172 reported by Armstrong and colleagues[61] had significant dose intensity differences aside from the IV versus IP question with resulting more toxicity and a much lower percentage of the patients completing the prescribed 6 cycles (42% vs 83%) and yielded the highest OS ever reported in a

Table 4
Intraperitoneal trials

Trial (Year Published), Patient Population	Treatment Regimen	Patients Enrolled	PFS (mo)	OS (mo)
GOG 104[86] (1996), optimal stage III <2 cm	Cisplatin (100 mg/m^2) IV Cyclophosphamide (600 mg/m^2) IV Every 3 wk × 6	279	NR	41
	Cisplatin (100 mg/m^2) IP Cyclophosphamide (600 mg/m^2) IV Every 3 wk × 6	267	NR	49 (P = .02)
GOG 114[87] (2001), optimal stage III <1 cm	Cisplatin (75 mg/m^2) IV Paclitaxel (135 mg/m^2 24 h) IV, every 3 wk × 6	227	22.2	51.4
	Carboplatin (AUC 9) IV every 28 d × 2 Cisplatin (100 mg/m^2) IP Paclitaxel (135 mg/m^2 24 h) IV Every 3 wk × 6	235	27.9	61.8 (P = .05)
GOG 172[61] (2006), optimal stage III <1 cm	Cisplatin (75 mg/m^2) IV Paclitaxel (135 mg/m^2 24 h) IV Every 3 wk × 6	210	18	49.7
	Paclitaxel (135 mg/m^2 24 h) IV Cisplatin (100 mg/m^2) IP Paclitaxel (60 mg/m^2) IP on day 8 Every 3 wk × 6	235	24	65.6 (P = .03)
GOG 252[92] (2016), optimal stage III <1 cm	Paclitaxel (80 mg/m^2) IV, day 1, 8, 15 Carboplatin (AUC 6) IV, day 1 Bevacizumab (15 mg/kg) IV day 1 Followed by maintenance Bevacizumab (15 mg/kg) IV for cycles 7–22	461	26.8 (Ref)	NR
	Paclitaxel (80 mg/m^2) IV, day 1, 8, 15 Carboplatin (AUC 6) IP, day 1 Bevacizumab (15 mg/kg) IV day 1 Followed by maintenance Bevacizumab (15 mg/kg) IV for cycles 7–22	464	28.7 (NS)	NR
	Paclitaxel (135 mg/m^2 3 h) IV, day 1 Cisplatin (75 mg/m^2) IP, day 2 Paclitaxel (60 mg/m^2) IP on day 8 Bevacizumab (15 mg/kg) IV day 1 Every 3 wk ×6 Followed by maintenance Bevacizumab (15 mg/kg) IV for cycles 7–22	456	27.8 (NS)	NR

phase 3 cooperative group trial at 66 months versus 50 months for receiving IV cytotoxic therapy only. Note that the systemic IV cisplatin arm received cisplatin 75 mg/m^2, whereas the IP arm received 100 mg/m^2 of cisplatin, a confounding variable in determining the impact of the IP infusion route and the toxicities that have been incorrectly attributed to IP infusion rather than dose intensity. However, in the GOG 172 longer-term follow-up report (>10 years), the median survival for IP cisplatin was 61.8 months compared with 51.4 months for the IV arm, with younger patients being more likely to complete the IP regimen, and IP therapy being associated with a 23% reduced risk of death.[88] There have additionally been Cochrane meta-analysis and other systemic reviews that favor IP regimens over IV.[89,90] Despite the survival advantage of IP therapy, utilization of IP chemotherapy has not been universally implemented likely due to excessive toxicity, inpatient infusion of paclitaxel, and IP port complications. As few as 50% of eligible patients were receiving IP/IV chemotherapy, which led to the development of modified GOG 172 and outpatient regimens with similar retrospective outcomes.[91]

GOG 252 intended to address the dose-dense and IP question with 3 upfront regimens, IV carboplatin with weekly IV paclitaxel, IP carboplatin with weekly IV paclitaxel, and IV/IP cisplatin/paclitaxel, all containing bevacizumab and bevacizumab maintenance (see **Table 4**). PFS was the primary endpoint of this study, and there were no PFS differences between the 3 groups; OS results have not been reported yet.[92] Interpretation of preliminary GOG 252 data is confounded by the inclusion of many variables between the 3 arms comparing IP cisplatin to IP carboplatin, weekly dose dense paclitaxel to every 3 week traditional schedules, the addition of bevacizumab, and lack of a control arm.[92] Several factors may have influenced the results, including the reduction in IP cisplatin dose to 75 mg/m^2 as compared with the 100 mg/m^2 in GOG 172, crossover rate, and bevacizumab interactions and recommended no change in treatment patterns until survival data are mature.

Neoadjuvant chemotherapy

NACT is the administration of chemotherapy before definitive surgery. NACT utilization in ovarian cancer has steadily increased over the past decade.[93,94] NACT has demonstrated reduction in operative morbidity and comparable OS with upfront cytoreductive surgery in 4 trials (**Table 5**).[95–97] As mentioned above, the decision for which to pursue primary resection versus NACT was inherently challenging, which led to the ASCO/SGO practice guidelines in 2016. Despite the potential benefits of NACT, the current literature has shown that survival is not improved with NACT compared with primary debulking.[96–98] CHORUS and EORTC 55971 were able to show noninferiority OS of NACT to primary surgery.[96,97] Criticism of these trials include inferior survival outcomes compared with previous trials, low optimal cytoreduction rates, and lack of standardization of chemotherapy given. Additional considerations for NACT are that approximately 10% will progress during NACT and not undergo cytoreductive surgery and 3% will have a change in histologic diagnosis at time of surgery.[96] JCOG 0602 presented survival data at the 2018 ASCO meeting, which revealed that NACT was unable to meet the noninferior threshold and that NACT should not be a substitute for primary surgery, but considered in carefully selected unresectable patients or in higher risk of morbidity.[99]

With improvement in morbidity and optimal debulking rates with NACT, there has been growing interest in using peritoneal chemotherapy after NACT. Results from a phase 2 trial have shown promising results of NACT followed by IP chemotherapy.

Table 5
Neoadjuvant chemotherapy trials

Trial (Year Published)	Treatment Regimen	Patients Enrolled	No Residual Disease	G3-4 Postoperative Complication	PFS (mo)	OS (mo)
EORTC 55971[96] (2010), stage III-IV	PDS: ×6 cycles of platinum-based chemotherapy	336	19%	18%	12	29
	NACT: platinum-based ×3, interval surgery, then ×3 platinum-based	334	51%	6%	12	30 (NI)
CHORUS[97] (2015)	PCS: ×6 cycles of platinum-based chemotherapy	274	17%	24%	10.7	22.6
	NACT: platinum-based ×3, interval surgery, then ×3 platinum-based	276	39% (P<.001)	14% (P = .007)	12	24.1 (NI)
SCORPION[95] (2016)	PDS: ×6 cycles Paclitaxel (175 mg/m^2) Carboplatin (AUC, 5)[a]	54	46%	6%	NR	NR
	NACT: ×3-4 cycles Paclitaxel (175 mg/m^2) Carboplatin (AUC, 5) interval surgery, then 2–3 more cycles (total of 6)[a]	55	58% (NS)	53% (P<.001)	NR	NR
JCOG 0602[99,100] (2016, OS data 2018 ASCO abstract)	PDS: ×8 cycles Paclitaxel (175 mg/m^2) Carboplatin (AUC, 6)	149	30%	15%	15.1	49
	NACT: ×4 cycles Paclitaxel (175 mg/m^2) Carboplatin (AUC, 6) interval surgery, then ×4 cycles	152	63%	5% (P = .005)	16.4	44.3 (NI-NC)

Abbreviations: NI, noninferior; NI-NC, noninferior not confirmed; PDS, primary debulking surgery.
[a] Allowed bevacizumab with standard regimen and maintenance in 2014.

The results from OV21/PETROC, which included 275 women randomized to IV carboplatin and IV paclitaxel or IP carboplatin and IP paclitaxel plus IV paclitaxel, showed that 9-month progression rate was lower in the IP carboplatin arm compared with the IV carboplatin arm: 24.5% versus 38.6% ($P = .065$). The IP carboplatin regimen was well tolerated with no reduction in quality of life or increase in toxicity.[101] These data further establish feasibility as well as demonstrate improvement in progression. Nonetheless, additional data are needed to establish whether IP chemotherapy in this setting offers a survival advantage, as was demonstrated with primary adjuvant therapy.

Heated intraperitoneal chemotherapy

HIPEC refers to the intraoperative instillation of chemotherapy at the completion of cytoreductive surgery. Drug penetration is enhanced by heating the perfusate and has demonstrated efficacy in other peritoneal malignancies.[102–105] HIPEC has historically has been a speculative addition to the multimodality therapy for ovarian cancer given the pattern of spread, with encouraging early phase and retrospective results, but was reserved for institutions with capability and expertise.[106–111] In a recent phase 3 randomized trial of 245 women with phase 3C who were deemed unresectable at initial presentation, patients underwent NACT of 3 cycles of carboplatin/paclitaxel and at time of interval surgery they were randomized to either receive HIPEC (cisplatin 100 mg/m^2) or surgery alone with both arms then completing 3 additional cycles of carboplatin/paclitaxel. The HIPEC arm had longer PFS (14.2 vs 10.7 months) and median OS (45.7 vs 33.9 months; $P = .02$) with similar toxicity profiles.[112] The 12-month survival improvement is impressive in an otherwise unresectable primary presentation that historically had survival in the 24- to 30-month range in the available clinical trials.[96,97] The implementation in institutions will depend on surgical technical expertise, and perioperative infrastructure development is required. There are additionally ongoing trials evaluating HIPEC in the primary debulking patient population.

Maintenance The available data are limited to support the routine use of maintenance therapy following completion of first-line therapy with no clear benefit for use of platinum, doxorubicin, paclitaxel, or erlotinib.[113,114] As mentioned above and highlighted in **Table 3**, there are several trials investigating antiangiogenesis maintenance with improvement in PFS, but not OS.[77,80,85] The 3.8-month PFS seen in GOG 218 prompted Food and Drug Administration orphan product designation approval in 2018 of bevacizumab in combination with carboplatin and paclitaxel followed by maintenance up to 10 months. Subsequent SGO Clinical Practice Committee release states this approval does not negate previous results of other landmark trials, including IV/IP and dose-dense trials and recommends carefully selected candidates for bevacizumab with the following considerations[115]:

- Patients with poor prognostic factors (and no contraindications) are most likely to benefit
- Patients with ascites may have additional benefit with inclusion of bevacizumab
- Bevacizumab should not be given in combination with IV/IP due to toxicities
- Caution should be used when given in neoadjuvant setting to toxicities related to upcoming surgery
- Decision to use bevacizumab should be a shared decision with the patient's goals and priorities because the PFS is approximately 4 months with additional 11 months of treatment

There are also active and in-development phase 3 trials investigating maintenance therapy after primary treatment of PARP inhibitors, checkpoint blockade, and other biologic agents that are highly anticipated:

- SOLO-1 (NCT01844986): maintenance olaparib after primary platinum/taxane standard therapy for BRCA-mutated patients. Investigators have issued a press release that the plan is to report statistically significant and clinically meaningful improvement in PFS compared with placebo
- GOG-3012 (NCT02655016): maintenance niraparib versus placebo after primary platinum-based therapy
- GOG-3015 (NCT03038100): carboplatin/paclitaxel/bevacizumab/atezolizumab followed by maintenance bevacizumab and atezolizumab (vs placebo for atezolizumab)
- PAOLA-1 trial (NCT02477644): combination platinum/taxane/bevacizumab, maintenance bevacizumab ± olaparib
- MEOC-1 (NCT01081262): carboplatin/paclitaxel versus oxaliplatin/capecitabine versus carboplatin/paclitaxel/bevacizumab, maintenance bevacizumab, versus oxaliplatin/capecitabine/bevacizumab, maintenance bevacizumab
- BOOST (NCT01462890): carboplatin/paclitaxel/bevacizumab and then 16 cycles versus 38 cycles of bevacizumab
- ATHENA (NCT03522246): maintenance rucaparib and nivolumab (rucaparib + placebo vs nivolumab + placebo vs rucaparib + nivolumab vs placebo + placebo) after primary platinum based therapy

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