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Neoadjuvant Chemotherapy for Newly Diagnosed, Advanced Ovarian Cancer: ASCO Guideline Update

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Neoadjuvant Chemotherapy for Newly Diagnosed, Advanced Ovarian Cancer: ASCO Guideline Update

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Abstract

ASCO Guidelines provide recommendations with comprehensive review and analyses of the relevant literature for each recommendation, following the guideline development process as outlined in the ASCO Guidelines Methodology Manual. ASCO Guidelines follow the ASCO Conflict of Interest Policy for Clinical Practice Guidelines.

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PURPOSE—To provide updated guidance regarding neoadjuvant chemotherapy (NACT) and primary cytoreductive surgery (PCS) among patients with stage III-IV epithelial ovarian, fallopian tube, or primary peritoneal cancer (epithelial ovarian cancer [EOC]).

METHODS—A multidisciplinary Expert Panel convened and updated the systematic review.

RESULTS—Sixty-one studies form the evidence base.

RECOMMENDATIONS—Patients with suspected stage III-IV EOC should be evaluated by a gynecologic oncologist, with cancer antigen 125, computed tomography of the abdomen and pelvis, and chest imaging included. All patients with EOC should be offered germline genetic and somatic testing at diagnosis. For patients with newly diagnosed advanced EOC who are fit for surgery and have a high likelihood of achieving complete cytoreduction, PCS is recommended. For patients fit for PCS but deemed unlikely to have complete cytoreduction, NACT is recommended. Patients with newly diagnosed advanced EOC and a high perioperative risk profile should receive NACT. Before NACT, patients should have histologic confirmation of invasive ovarian cancer. For NACT, a platinum-taxane doublet is recommended. Interval cytoreductive surgery (ICS) should be performed after ≤four cycles of NACT for patients with a response to chemotherapy or stable disease. For patients with stage III disease, good performance status, and adequate renal function treated with NACT, hyperthermic intraperitoneal chemotherapy may be offered during ICS. After ICS, chemotherapy should continue to complete a six-cycle treatment plan with the optional addition of bevacizumab. Patients with EOC should be offered US Food and Drug Administration–approved maintenance treatments. Patients with progressive disease on NACT should have diagnosis reconfirmed via tissue biopsy. Patients without previous comprehensive genetic or molecular profiling should be offered testing. Treatment options include alternative chemotherapy regimens, clinical trials, and/or initiation of end-of-life care.

Additional information is available at www.asco.org/gynecologic-cancer-guidelines.

This guideline has been endorsed by the Society of Gynecologic Oncology.

INTRODUCTION

The identification and treatment of patients with ovarian cancer remains a critical challenge within gynecologic oncology because of a lack of effective screening tools and diagnosis at advanced stages. Patients with advanced ovarian cancer, classified as International Federation of Gynecology and Obstetrics (FIGO) stage III or IV, require a sophisticated, multimodal treatment strategy to improve patient outcomes. Historically, primary cytoreductive surgery (PCS) has been the cornerstone of treatment, aiming for maximal tumor debulking followed by chemotherapy. However, the emergence of neoadjuvant chemotherapy (NACT) offers an alternative approach, potentially optimizing surgical outcomes and reducing perioperative morbidity.

PCS involves extensive surgical effort to achieve optimal debulking, defined as no residual tumor or minimal residual disease. This approach has been associated with improved survival rates when complete cytoreduction is achieved.¹ However, PCS can be associated with substantial surgical morbidity such as pleural effusion, anastomotic leakage, wound opening, and intra-abdominal abscess, especially in patients with high tumor burden or poor performance status, and this may lead to delays or omission of postoperative chemotherapy.²

NACT aims to reduce tumor volume and enhance the feasibility of achieving optimal cytoreduction during subsequent surgery. This approach can decrease surgical complexity and morbidity, potentially improving overall patient outcomes. Several randomized controlled trials (RCTs) and meta-analyses have demonstrated the noninferiority of NACT followed by interval cytoreductive surgery (ICS) compared with PCS in terms of survival outcomes and a reduction in perioperative complications.^{3–7} In the years since these trials were first published, there has been a major shift in the upfront treatment practices in the United States, with a substantial decline in PCS and significant rise in NACT and ICS.⁸ NACT followed by ICS has now become the most common upfront treatment approach for advanced epithelial ovarian cancer (EOC).⁸

The decision between NACT and PCS must be individualized, considering factors such as tumor biology, patient performance status, comorbidities, and the potential for achieving optimal cytoreduction. This underscores the importance of a multidisciplinary approach, involving surgical gynecologic oncologists, medical oncologists, radiologists, and pathologists, to tailor the treatment plan to the patient's specific clinical context.

This guideline provides updated evidence-based recommendations on the use of NACT and interval cytoreduction versus primary cytoreduction and chemotherapy among patients with stage III or IV epithelial ovarian, fallopian tube, or primary peritoneal cancer (hereafter referred to as ovarian cancer). ASCO previously published a prior guideline in 2016 in collaboration with the Society of Gynecologic Oncology (SGO).⁹ New evidence published since the last iteration includes initial assessment to guide treatment, selection criteria for NACT versus PCS, preferred chemotherapy regimens, timing of surgical intervention, role of hyperthermic intraperitoneal chemotherapy (HIPEC), role of maintenance therapy after completion of primary chemotherapy, and management for patients who do not have a clinical response to NACT. This update has been endorsed by the SGO.

GUIDELINE QUESTIONS

This clinical practice guideline addresses 10 overarching clinical questions: (1) In patients with newly diagnosed pelvic masses and/or upper abdominal or peritoneal disease, what initial assessment should be performed to guide treatment? (2) In which patients with newly diagnosed advanced EOC is PCS recommended? (3) In which patients with newly diagnosed advanced EOC is NACT recommended? (4) For patients with newly diagnosed stage III or IV EOC who will receive NACT, what tests or procedures should be performed before NACT is delivered, in order to ensure accurate diagnosis? (5) What is the preferred chemotherapy regimen for patients with stage III or IV EOC who will receive NACT? (6) Among patients treated with NACT, does the timing of ICS, the number of chemotherapy cycles before ICS, or timing in between chemotherapy and ICS affect the safety or efficacy of treatment? (7) Is there a role for HIPEC at ICS? (8) Among patients treated with NACT, what is the recommended number of chemotherapy cycles after ICS? (9) Is there a role for maintenance therapy after completion of primary chemotherapy? (10) What is the management approach for patients who do not have a clinical response to NACT?

METHODS

Guideline Development Process

This systematic review-based guideline product was developed by a multidisciplinary Expert Panel of ASCO members, an SGO representative, a patient representative, and an ASCO guidelines staff member with health research methodology expertise (Appendix Table A1, online only).

The recommendations were developed by using a systematic review of evidence identified through online searches of PubMed from March 20, 2015, through April 5, 2023, of phase III RCTs, meta-analyses, and cohort studies. The literature searches were rerun on September 27, 2024, to identify articles published since April 5, 2023. A list of search terms is provided in the Data Supplement (online only). Articles were selected for inclusion in the systematic review based on the following criteria:

- Population: Patients with newly diagnosed stage III or stage IV EOC, fallopian tube cancer, or primary peritoneal cancer.
- Interventions and comparisons: Tests and procedures including biopsy, cytology, surgery (open, laparoscopy), imaging, serum tumor markers; characteristics of surgeon or treatment facility; oncologic interventions including NACT, ICS, and HIPEC.
- Outcomes: Accurate pretreatment diagnosis, optimal cytoreduction, perioperative morbidity and mortality, progression-free survival (PFS) and overall survival (OS), toxicity, and quality of life.
- Study type: Evidence regarding the outcomes of NACT was drawn from published phase III RCTs. Evidence regarding predictive and prognostic factors in advanced ovarian cancer was drawn from RCTs, multicenter cohort studies,

meta-analyses, and population-based observational data. Inclusion of influential single-center cohort studies was made at the discretion of the panel.

Articles were excluded from the systematic review if they were (1) meeting abstracts not subsequently published in peer-reviewed journals; (2) editorials, commentaries, letters, news articles, case reports, and narrative reviews; and (3) published in a non-English language.

Three full panel meetings were held, and members were asked to provide ongoing input on the quality and assessment of the evidence, generation of recommendations, draft content, as well as review and approve drafts during the entire development of the guideline. ASCO staff met routinely with the Expert Panel co-chairs and corresponded with the panel via e-mail to coordinate the process to completion. Ratings for strength of the recommendation and evidence quality are provided with each recommendation. The quality of the evidence for each outcome was assessed using the Cochrane Risk of Bias tool and elements of the GRADE quality assessment and recommendations development process.^{10,11} GRADE quality assessment labels (ie, high, moderate, low, and very low) were assigned for each outcome by the project methodologist in collaboration with the Expert Panel co-chairs and reviewed by the full Expert Panel. All funding for the administration of the project was provided by ASCO.

Guideline Review and Approval

The draft recommendations were released to the public for open comment from July 19 through August 2, 2024. Response categories of “Agree as written,” “Agree with suggested modifications” and “Disagree. See comments” were captured for every proposed recommendation with 20 written comments received. All eight respondents either agreed or agreed with slight modifications to the recommendations. Expert Panel members reviewed comments from all sources and determined whether to maintain original draft recommendations, revise with minor language changes, or consider major recommendation revisions.

All changes were incorporated into the final manuscript prior to ASCO Evidence Based Medicine Committee (EBMC) review and approval. All ASCO guidelines are ultimately reviewed and approved by the Expert Panel and the ASCO EBMC before submission to the *Journal of Clinical Oncology* for editorial review and consideration for publication.

Guideline Updating

The ASCO Expert Panel and guidelines staff will work with co-chairs to keep abreast of any substantive updates to the guideline. Based on formal review of the emerging literature, ASCO will determine the need to update. The ASCO Guidelines Methodology Manual (available at www.asco.org/guideline-methodology) provides additional information about the guideline update process. This is the most recent information as of the publication date.

RESULTS

Characteristics of Studies Identified in the Updated Literature Search

A total of 1,063 studies were identified in the initial updated literature search. The literature refresh search identified an additional 180 studies. After applying the eligibility criteria, 61 studies remained. Two clinical practice guidelines,^{12,13} three systematic reviews,^{14–16} nine RCTs (published in 14 papers),^{3–6,17–25} one analysis of RCT data,²⁶ and 46 observational studies^{27–40,41–60,61–73} form the evidentiary basis for the new and/or updated guideline recommendations.

The identified studies were published between March 2015 and February 2024. Characteristics of the studies' participants and key outcomes of interest and adverse events (AEs) are reported in Tables 1–4.

Evidence Quality Assessment

The quality of evidence was assessed for each included study, and factors such as study design, consistency of results, directness of evidence, precision, and magnitude of effect were also assessed by one reviewer. Systematic reviews and meta-analyses were evaluated using the Assessment of Multiple Systematic Reviews (AMSTAR) rating.⁷⁴ To evaluate RCTs, research design characteristics including random assignment, blinding of outcome assessment(s), selective reporting, complete outcome data, and conflicts of interest were evaluated. Observational studies and studies investigating prognostic and predictive factors were assessed by the Prediction model Risk Of Bias ASsessment Tool (PROBAST).⁷⁵ Each element in the RCT and observational study assessment was rated as having low, uncertain, or high risk of bias. Refer to Appendix Table A2 for definitions for the quality of the evidence, and the ASCO Methodology Manual for more information.

For systematic reviews and meta-analyses, AMSTAR scores ranged from 6 to 11 out of a possible 11 points (higher scores indicate higher quality; Data Supplement, Table S1). For RCTs comparing NACT to primary surgery, overall risk of bias was judged to be low for one trial⁶ and low-moderate for three trials.^{3–5} All three HIPEC trials were assessed as being at low risk of bias.^{21–23} Two phase II open-label multicenter studies considering NACT chemotherapy regimens^{24,25} were assessed to be at a low-moderate risk of bias (Data Supplement, Table S2).^{24,25} The quality of evidence of 46 observational studies was assessed to be low,^{28,30–34,37–39,41–43,45–53,55–57,59–62,64,66–68,70–72} low-to-moderate,^{29,35,36,40,44,58,63,65} and moderate^{27,54} (Data Supplement, Table S3). According to GRADE criteria,¹¹ the results from the neoadjuvant trials were considered direct, and with no serious concerns regarding consistency or imprecision.

RECOMMENDATIONS

All recommendations are available in Table 5 and presented as an algorithm in Figure 1.

INITIAL ASSESSMENT TO GUIDE THERAPY

In patients with newly diagnosed pelvic masses and/or upper abdominal or peritoneal disease, what initial assessment should be performed to guide treatment?

Literature Review Update and Analysis

Role of Surgeon—The updated literature search identified five studies investigating the role of surgeon and/or institutional factors on the outcomes of patients with advanced EOC.^{66–70}

Patients undergoing extended surgical cytoreduction (ECR) were more likely treated at high-volume hospitals (37% *v* 31%, $P < .001$), with higher odds of ECR at high-volume centers (odds ratio [OR], 1.25; $P < .001$).⁷⁰ High-volume hospitals also had higher rates of complete gross resection (43.3%) compared to low- (41.0%) and intermediate- (41.6%) volume centers and, after adjustments, patients in low- and intermediate-volume centers had lower odds of complete resection (OR, 0.85 [95% CI, 0.74 to 0.97] and OR, 0.90 [95% CI, 0.82 to 0.99], respectively).⁶⁷ Worse survival outcomes were observed for patients treated by low-volume clinicians (median OS, 32.8 months) compared to medium- (41.9 months) and high-volume clinicians (42.1 months; $P < .01$), with low-volume clinicians associated with higher mortality rates (adjusted hazard ratio [HR], 1.25 [95% CI, 1.08 to 1.43]) and lower chemotherapy compliance (64.5% *v* 72.2% and 71.7%, $P = .02$).⁶⁶ Furthermore, patients in rural areas were less likely to receive surgery from gynecologic oncologists than patients in urban areas (adjusted OR, 0.48 [95% CI, 0.30 to 0.78]).⁶⁹ Gynecologic oncologist–provided surgery conferred a 3-year cause-specific survival advantage among patients in rural areas (adjusted HR, 0.57 [95% CI, 0.33 to 0.97]).⁶⁹

Primary Clinical Evaluation—Two systematic reviews^{14,15} and 39 cohort studies^{27–65} assessing the prediction of resectability based on preoperative imaging methods, biomarkers, laparoscopy, and laparotomy were identified in the updated literature review. Detailed results from observational studies are provided in the Data Supplement (Table S4).

Several studies underscore the value of laparoscopy in assessing resectability. Study authors report finding that diagnostic laparoscopy can reduce the rate of suboptimal cytoreduction and unnecessary laparotomies, offering better predictive accuracy than computed tomography (CT).^{51,60} A lower suboptimal cytoreduction rate in the laparoscopy group (2.0%) versus in the CT group (11.1%) has been reported,⁵¹ and laparoscopy had a higher AUC (0.955) compared to CT (0.755) in predicting optimal cytoreduction.⁶⁰

Two systematic reviews^{14,15} further reinforce laparoscopy's accuracy in predicting surgical outcomes, with one systematic review showing an overall accuracy rate of 90% in assessing optimal cytoreduction.¹⁴ Additionally, evidence suggests that reclassification of FIGO stage IV into stages IVA or IVB provided prognostic and predictive information for NACT, with patients with stage IVB benefiting more.⁵⁹ Two studies^{48,61} supported laparoscopy as an accurate method for predicting inoperability⁶¹ and cytoreduction to no macroscopic residual disease (R0).⁴⁸ Other studies^{42,65} further emphasized the role of laparoscopy in assessing peritoneal carcinomatosis and selecting patients for cytoreductive surgery. Peritoneal cancer index (PCI) has been reported to be the best method for classifying patients for primary

treatment, with high reliability in predicting complete or optimal surgery (tumor residue <1 cm).⁴⁵

Studies on preoperative predictors for ovarian cancer surgery reveal the varying effectiveness of imaging modalities and biomarkers. Ultrasound, when conducted by expert sonographers, can be a reliable alternative to CT and whole-body diffusion-weighted imaging (WB-DWI)/magnetic resonance imaging (MRI) for predicting nonresectability, with a high specificity of 98% and an accuracy of 90%.³¹ Biomarkers such as human epididymis protein 4 (HE4) and composite models including the Ovarian Malignancy Risk Algorithm (ROMA) index and Suidan score provide valuable insights into surgical outcomes, with HE4 demonstrating strong predictive capabilities.^{29,34,54} Combining cancer antigen 125 (CA-125) with other markers may enhance prediction accuracy for suboptimal cytoreduction,⁴⁰ but insufficient data limit current clinical use. CT imaging also plays a significant role, with studies showing that high CT scores of disease burden and mesenchymal tumor subtypes are linked to greater residual disease likelihood.³⁵

Studies demonstrate that WB-DWI/MRI is highly accurate in predicting nonresectability and incomplete resection in patients suspected of ovarian cancer, with superior performance compared to CT in specific sites such as the mesentery and lumbo-aortic lymph nodes.^{37,56} High sensitivity (94%) and specificity (98%) for predicting nonresectability have been reported,³⁷ as has an overall accuracy of 88% for WB-DWI/MRI.⁵⁶ Other studies support the accuracy of WB-DWI/MRI in predicting surgical outcomes, although sensitivity can vary, while specificity remained high (98%).^{31,46}

The diagnostic value of fluorodeoxyglucose-18 (FDG)–positron emission tomography (PET)–CT has been investigated, with high sensitivity, specificity, and AUC for both FDG-PET/CT and FDG-PET/MRI reported.^{41,62} High sensitivity and specificity (both 100%) were also found in characterizing ovarian masses, indicating FDG-PET-CT's potential role in selecting patients for PCS.⁴³

Laparotomy combined with predictive models has been studied for its role in forecasting surgical outcomes in ovarian cancer. A systematic scoring system based on operative findings and MRI has been reported to effectively predict nonoptimal cytoreduction.⁵⁰ Additionally, specific regions within the PCI have proven more predictive of complete resection and survival than the entire PCI, suggesting that early intraoperative examination of these regions could help determine resectability.⁵⁷ The importance of laparoscopy in cases with a high risk of suboptimal cytoreduction has also been highlighted.⁴² Study authors have reported preoperative PET-CT imaging to reflect tumor burden and predict the likelihood of complete cytoreduction.³³ A PCI cutoff of 24 has been proposed for predicting incomplete resection, with the recommendation to consider NACT if the PCI exceeds this threshold.⁴⁹ A validated four-step integrated prediction model algorithm has been introduced for clinicians to triage patients to PCS or NACT, demonstrating high sensitivity and specificity for predicting optimal cytoreduction.⁵⁵ The use of a predictive score for complete cytoreduction has been further supported.⁴⁷

Overall, these studies highlight the strengths and specific applications of WB-DWI/MRI, FDG-PET-CT, and staging laparoscopy in the preoperative assessment of ovarian cancer, each providing valuable, complementary information for surgical planning and patient management.

Genomic Testing—The role of genomic testing in ovarian cancer is covered in detail in the *Germline and Somatic Tumor Testing in Epithelial Ovarian Cancer: ASCO Guideline*.¹² Briefly, existing evidence and guidance from ASCO and other national and international medical societies^{76–78} consistently recommend routine testing for germline pathogenic variants in *BRCA1* and *BRCA2* and other ovarian cancer susceptibility genes in all patients diagnosed with EOC. The presence of a germline pathogenic variant can guide treatment decisions, such as eligibility for maintenance therapy with poly(ADP-ribose) polymerase inhibitors (PARPi) and inform discussions with family members about their potential cancer risks and reproductive options. Guidelines also advocate for consideration of tumor testing for somatic *BRCA1/2* pathogenic variants and measure(s) of homologous recombination to guide medical decisions. Sequencing germline DNA is the most sensitive method for detecting these variants, and if no variant is found, tumor DNA should be tested, as up to 5% of women may have somatic *BRCA* pathogenic variants.¹² Understanding the underlying molecular alterations in ovarian cancer can enable clinicians (or health care systems) to provide more personalized diagnostic, predictive, prognostic, and therapeutic strategies to patients, while also having important clinical implications for her family members.

Clinical Interpretation—Gynecologic oncologists provide specialized surgical and medical management of gynecologic malignancies and are trained to perform the surgery needed for patients with ovarian cancer and to understand the risks and complications associated with such therapeutic procedures. The original ASCO NACT guidelines emphasized the importance of an evaluation by a gynecologic oncologist in determining whether a patient is a candidate to undergo PCS with acceptable risks and associated morbidity. The updated data support this recommendation and continue to show that patients benefit from having surgery with high-volume clinicians and at high-volume centers. One of the most important predictors of OS in this patient population is volume of residual tumor after surgical cytoreduction, with the goal of no gross residual disease. Patients treated at high-volume centers and by gynecologic oncologists are more likely to undergo extensive surgical cytoreduction, including complete resection, receive postoperative chemotherapy, and have better OS outcomes.

The evaluation to determine the extent of disease and the feasibility of surgical resection should, at a minimum, include CA-125 and a CT of the abdomen and pelvis with oral, intravenous, and if appropriate rectal contrast and chest imaging (CT preferred). In cases where the feasibility of optimal cytoreduction is unclear, further evaluation with laparoscopy or additional imaging methods (such as MRI, FDG-PET, or ultrasound) may be beneficial. Laparoscopic evaluation is highly reliable in predicting feasibility of complete resection. Given the potential for patients with endometrial cancer to present with similar signs and symptoms as patients with ovarian cancer and the diverging treatment options for patients

with these diseases, the panel recommended consideration of an endometrial biopsy when warranted.

Recognizing the importance of identifying patients with pathogenic variants in germline *BRCA1* and *BRCA2* and other ovarian cancer susceptibility genes early because of their treatment implications, impact on other cancer risk, and determination of risk in other family members, the panel added Recommendation 1.3 recommending that testing should occur at the time of diagnosis or as soon as feasibly possible. Genetic counseling is recognized as an important component to testing and is recommended to be offered to all patients with an identified heritable alteration in ovarian cancer susceptibility genes, those with variants of uncertain significance, and those with a concerning family history.

PRIMARY CYTOREDUCTIVE SURGERY

In Which Patients With Newly Diagnosed Advanced EOC Is PCS Recommended?

Literature Review Update and Analysis—Staging laparotomy with PCS followed by platinum-based chemotherapy has been the standard treatment of advanced ovarian cancer (FIGO stage III-IV) for decades. The updated literature search focused on trials that compared this standard to NACT. As reported in the original guideline,⁹ four RCTs—EORTC 55971,³ CHORUS,⁴ SCORPION,⁵ and JCOG0602⁶—compared NACT followed by interval cytoreduction with PCS followed by chemotherapy in patients with advanced-stage EOC.

In EORTC 55971,³ 94% of women in the PCS arm underwent surgery, surgeons achieved residual tumor of 1 cm or less in 42% of cases, with no difference in OS or PFS noted between patients who underwent NACT and upfront cytoreductive surgery (CRS) (HR, 0.98 [90% CI, 0.84 to 1.13]; HR, 1.01 [90% CI, 0.89 to 1.15], respectively). The CHORUS trial⁴ showed that 91% of women in the PCS arm received surgery, with 41% surgeons achieving optimal cytoreduction (<1 cm residual disease), and no difference between the arms were found for OS (HR, 0.87 [95% CI, 0.72 to 1.05]) or PFS (HR, 0.91 [95% CI, 0.76 to 1.09]). In the SCORPION trial,⁵ PCS resulted in complete cytoreduction in 46% of patients, with no difference in OS (HR, 1.12 [95% CI, 0.76 to 1.65]) or PFS (HR, 1.12 [95% CI, 0.76 to 1.65]). Similarly, in the JCOG0602 trial,⁶ OS (HR, 1.05 [95% CI, 0.84 to 1.33]) and PFS (HR, 0.96 [95% CI, 0.75 to 1.23]) did not differ between the arms. A meta-analysis of these four studies pooled data from the 1,692 participants and demonstrated little or no difference in OS or PFS between PCS and NACT for initial treatment in advanced ovarian cancer (HR, 0.96 [95% CI, 0.86 to 1.08]; HR, 0.98 [95% CI, 0.88 to 1.08], respectively).⁷

Clinical Interpretation—In the 2016 guidelines, the panel identified three clinical situations: (1) patients who are fit for PCS, with potentially resectable disease, for whom either NACT or PCS could be offered; (2) patients with a high likelihood of achieving a cytoreduction with no gross residual disease with acceptable morbidity, for whom PCS was recommended over NACT; and (3) women who are fit for PCS but are deemed unlikely to have cytoreduction to no gross residual disease by a gynecologic oncologist, for whom NACT was recommended over PCS. These recommendations were based on four randomized clinical trials—EORTC 55971, CHORUS, JCOG0602, and SCORPION

—which compared NACT and interval cytoreduction with primary cytoreduction and chemotherapy among women with stage III or IV EOC. EORTC and CHORUS, both designed as noninferiority studies, enrolled patients with suspected stage III or IV ovarian cancer. JCOG0602, also a noninferiority study, required imaging confirmation of stage III or IV disease prior to enrollment. SCORPION was designed as a superiority study and required a two-step enrollment including a staging laparoscopic procedure to determine the predictive index of tumor burden. Patients with a high tumor burden identified at laparoscopic staging (predictive index ≥ 8 or ≤ 12), but whose disease was still deemed capable of being maximally cytoreduced, were enrolled. At the time of publication of the guideline, survival data were available in published form only for the EORTC and CHORUS studies, while JCOG0602 had been presented at ASCO 2016. The perioperative and postoperative complications in the SCORPION trial had been published but survival data were unavailable. The last guideline addressed some of the concerns regarding the shorter than expected median OS and lower rates of upper abdominal surgeries observed in the EORTC and CHORUS studies, and factors including patient population and surgical effort have been proposed as potential explanations. While EORTC, CHORUS, and JCOG0602 allowed all-comers with stage III or IV disease, participants were older, and had a higher tumor burden and poorer performance status than participants on other studies. JCOG0602 did not confirm the noninferiority of NACT compared to PCS, a difference that may be due to higher rates of ICS after incomplete PCS in the study and small sample size. In SCORPION, the NACT arm was not superior to PCS, supporting PCS as the standard of care in patients with maximally cytoreducible disease.

Meta-analyses of these four studies similarly showed little or no difference in survival outcomes between PCS and NACT for initial treatment in advanced ovarian cancer.^{79–81} However, other meta-analyses, which included observational studies,^{82,83} showed that NACT was associated with more surgical completeness and reduced risk of postsurgical death and infections; however, PCS was associated with improved OS. Recognizing that delays in the initiation of adjuvant therapy after PCS can lead to detrimental outcomes,^{84,85} it is important to weight the risk of surgical complexity and morbidity during PCS, especially in patients with bulky disease, that may lead to delays in start of adjuvant therapy. While there may be bias, especially in the observational studies, the concern for early development of chemoresistance in patients treated with NACT has been raised^{86–88} and this question remains unanswered. The panel acknowledges that the four randomized clinical trials did not evaluate NACT in patients who are fit for surgery and have a high likelihood of achieving complete cytoreduction with acceptable morbidity and strongly recommends PCS be the standard of care for this patient population. The use of NACT increased significantly during the recent COVID-19 pandemic,⁸⁹ and while the reasons for this are understandable under these extraordinary circumstances, the panel cautions against the routine use of NACT-ICS for medically fit patients who have resectable disease at diagnosis.

Two RCTs, TRUST (ENGOT ov33/AGO-OVAR OP7)⁹⁰ and Shanghai Gynecologic Oncology Group SUNNY (SOC-2),⁹¹ comparing ICS after three cycles of NACT with chemotherapy after PCS are currently underway. These trials have the primary objective of evaluating whether quality-assured PCS followed by chemotherapy improves survival

compared with interval debulking surgery (IDS) following NACT in patients with advanced EOC. The TRUST trial allows maintenance therapy with bevacizumab and PARPi. The results of these RCTs are expected to clarify the role of NACT followed by ICS under the latest chemotherapy protocols.

NEOADJUVANT CHEMOTHERAPY

In Which Patients With Newly Diagnosed Advanced EOC Is NACT Recommended?

Literature Review Update and Analysis—The systematic review identified updates to the four RCTs comparing NACT and interval cytoreduction with primary cytoreduction and chemotherapy among patients with stage III-IV EOC included in the original guideline⁹ (Table 1).

The chemotherapy regimens used in the studies typically involved either carboplatin or cisplatin combined with paclitaxel. These were given at least six cycles following PCS or three to four cycles before and after ICS. Among the four trials (EORTC 55971, CHORUS, JCOG0602, and SCORPION), three employed a noninferiority design^{3,4,6} while one was a superiority trial.⁵ In two out of the three noninferiority trials,^{3,4} NACT was found to be at least as effective as primary surgery regarding OS, with median follow-ups of 4.7 and 4.4 years, respectively. In contrast, the third trial did not validate this result after a median follow-up of 6 years.⁶ The SCORPION trial did not show superiority of NACT over PCS in terms of PFS (14.0 months *v* 15.0 months; HR, 1.05 [95% CI, 0.77 to 1.44], *P* = .73).⁵

NACT was linked to a reduced rate of postoperative deaths within 28 days of surgery (0.6% compared to 2.6%, *P* = .0439) and lower occurrences of severe nausea (0.5% *v* 4.8%, *P* = .0057) and vomiting (0.5% *v* 4.8%, *P* = .0057). However, it was associated with a higher rate of severe leukopenia (4.6% *v* 0%, *P* = .0086). The SCORPION trial found no advantage of NACT over primary surgery in terms of toxicity after a median follow-up of 59 months (about 5 years).

Quality-of-life assessments varied among the trials. In EORTC 55971, no significant differences were observed between patients in treatment arms on any functioning scales. The CHORUS trial reported slightly higher quality-of-life scores at 6 months post-treatment for patients receiving NACT compared to patients receiving PCS (mean difference, -7.6 [95% CI, -13.3 to -1.9], *P* = .0438). The SCORPION trial found that quality-of-life scores were more favorable for patients receiving NACT for greater emotional functioning (*P* = .02), cognitive functioning (*P* = .008), nausea and vomiting (*P* = .047), dyspnea (*P* = .013), insomnia (*P* = .024), and less hair loss (*P* = .013). Lower global health scores for those undergoing PCS than for those receiving NACT (difference in mean score, 6.27 [95% CI, 0.440 to 12.11], *P* = .035) were observed over a 12-month period, but the difference was deemed not clinically relevant.⁹² No clinical or statistically significant difference between treatment groups in any of the quality-of-life functioning scales was observed at 12 months.⁹² Each of the four studies aimed to determine if specific subgroups of patients, classified by FIGO stage, residual disease volume, and histologic type, would benefit more from one treatment over another. None of these subgroups showed a clear advantage for any particular treatment. Nevertheless, a combined analysis of long-term data from the EORTC

55971 (median follow-up of 7.6 years) and CHORUS (median follow-up of 5.9 years) trials revealed that women with stage IV disease had improved OS (24.3 months *v* 21.2 months; HR, 0.76 [95% CI, 0.58 to 1.00], *P* = .048) and PFS (10.6 months *v* 9.7 months; HR, 0.77 [95% CI, 0.59 to 1.00], *P* = .049) with NACT compared to primary surgery.

Factors that have been studied and shown to increase the risk of morbidity associated with CRS include advanced age or frailty, multiple chronic conditions, poor nutritional status, low albumin, and newly diagnosed venous thromboembolism (Data Supplement, Table S5). A recent meta-analysis confirmed these findings.⁹³ Patients with the following preoperative status were at higher risk for having postoperative complications, defined as any AE within 30 days after surgery: age ≥ 60 years (OR, 1.93 [95% CI, 1.35 to 2.76]; *P* < .001), Eastern Cooperative Oncology Group score > 0 (OR, 1.95 [95% CI, 1.29 to 2.94]; *P* = .001), comorbidities (OR, 2.06 [95% CI, 1.09 to 3.90]; *P* = .026), and presence of ascites on preoperative images (OR, 2.746 [95% CI, 1.48 to 5.11]; *P* = .001).⁹³ Surgical procedures including peritonectomy (*P* = .012), splenectomy (*P* < .001), and colon surgery (*P* < .001) were also significant predictors for postoperative complications. Patients who received NACT followed by ICS had a lower risk of developing severe complications compared to those who underwent PCS (*P* < .001).⁹³

Clinical Interpretation—The guideline recommends NACT for patients who are fit for surgery but deemed unlikely to have complete cytoreduction and for patients who have a high perioperative risk profile (Data Supplement, Table S5). The Expert Panel strongly recommends gynecologic oncologists, who are specially trained in assessing feasibility of complete cytoreduction and perioperative risk, evaluate patients in this population.

The data from the four randomized clinical trials and meta-analyses have consistently shown improved perioperative complications and a reduced rate of postoperative deaths with NACT-ICS without adverse impact on quality of life. NACT has the potential to improve patients' disease-related symptoms, allow clinicians time to address comorbidities that may increase surgical risk, and reduce patients' disease burden allowing for shorter surgical times, fewer surgical complications, and increased maximal cytoreduction. Several analyses of the randomized NACT versus PCS studies report a survival advantage for NACT in patients with stage IV disease, although inconsistencies between studies were noted.^{7,94,95}

TESTS BEFORE NACT

For Patients With Newly Diagnosed Stage III or IV EOC Who Will Receive NACT (ie, not suitable candidates for complex cytoreduction surgery), What Tests or Procedures Should be Performed Before NACT Is Delivered, in Order to Ensure Accurate Diagnosis?

Literature Review Update and Analysis—One analysis of RCT data²⁶ and three cohort studies were identified by the updated systematic review.^{64,71,72}

In both the EORTC and CHORUS trials, the occurrence of nonovarian cancers among participants was assessed. In the EORTC trial, eligible patients were required to have biopsy-proven stage IIIC or IV invasive epithelial ovarian, primary peritoneal, or fallopian tube cancer, with specific criteria to exclude other primary tumors. Despite these

precautions, 3% of the 670 randomly assigned patients were later found to have a different diagnosis after CRS. Similarly, the CHORUS trial included participants with advanced ovarian, fallopian tube, or primary peritoneal cancer, verified by clinical or radiographic evidence and a CA-125 to carcinoembryonic antigen ratio >25. For those undergoing NACT, the diagnosis was confirmed through laparoscopy, biopsy, or cytology. In this trial, 3% of the 474 patients who had surgery were also found to have nonovarian cancer.

Considering whether CT staging can be the surrogate for surgicopathologic FIGO staging in advanced ovarian cancer, Onda et al²⁶ analyzed data from the JCOG0602 trial. While CT staging had a high positive predictive value (PPV) and sensitivity for surgical stage III ovarian cancer, it was less effective at detecting small extrapelvic peritoneal disease, indicating reliability of diagnosis of stage IIIB disease by CT alone is inadequate.²⁶

A comparative analysis of 23 patients who underwent laparoscopy and 27 who underwent exploratory laparotomy before initiating NACT revealed several key differences.⁷¹ The laparoscopy group experienced significantly less blood loss (5 mL *v* 320 mL, *P* < .05) and had a shorter time to start NACT (12 days *v* 16 days, *P* < .05). However, OS was comparable between the two groups, with median survival times of 25.4 months and 24.7 months, respectively (*P* = .53). These findings support the use of laparoscopic tumor biopsy as a safe and effective method for early initiation of NACT.

In a study involving 551 patients age 51 years and older, cytology for ovarian cancer diagnosis showed a sensitivity of 80.6%, a specificity of 100%, a PPV of 100%, and a negative predictive value of 16.7%.⁷² Additionally, immunohistochemistry performed on cell blocks from 79 cases confirmed ovarian origin in 94.9% of cases.

Furthermore, an assessment of 52 patients who underwent transvaginal sonography (TVS)–guided core biopsies demonstrated a high histologic concordance rate with surgical specimens (diagnostic accuracy of 93.6%) and no biopsy-related complications.⁶⁴ TVS-guided core biopsy proves to be a feasible and effective procedure for diagnosing adnexal masses, especially in patients with advanced ovarian malignancies who are candidates for NACT.

Clinical Interpretation—Imaging is not sufficient to diagnose patients with ovarian cancer, as adnexal masses may be benign and other cancers can involve the adnexa including uterine, cervical, and GI cancers and less commonly breast cancer and lymphoma. Therefore, histologic confirmation of the diagnosis of ovarian, fallopian tube, or primary peritoneal cancer is essential before administering of NACT to ensure accurate diagnosis and appropriate treatment planning, including avoidance of unnecessary surgeries. Core tissue biopsies, rather than fine-needle aspirates, are preferred to provide adequate sampling. Cytology alone may be insufficient to distinguish between borderline and invasive cancer cells, and core biopsies will ensure adequate material for genetic and somatic tumor testing. While imaging-guided biopsies are preferred as a less invasive approach, laparoscopic tumor biopsies can be performed in combination with laparoscopic assessment of potential for maximal cytoreduction at PCS. Given diverging treatment paradigms for endometrial cancer, which can mimic advanced EOC, endometrial sampling, through endometrial biopsy or

dilation and curettage, should be considered when appropriate. Diagnosis by fine-needle aspirate and biomarker (CA-125:CEA ratio >25) should be reserved for extraordinary situations where biopsies cannot be performed.

Beyond histologic confirmation of the disease, obtaining adequate tissue samples is important for molecular diagnostic and somatic variant testing, especially for *BRCA1* and *BRCA2* pathogenic variants and measure(s) of homologous recombination. As therapeutic advancement continues, the panel expects that tumor-based genomic and molecular testing will become increasingly important in determining appropriate treatment plans. Since tumor cells from ICS may be too necrotic, after exposure to chemotherapy, to adequately identify histology or perform additional diagnostic testing, obtaining adequate tissue at the outset will be vital to patient care.

CHEMOTHERAPY REGIMENS

What Is the Preferred Chemotherapy Regimen for Patients With Stage III or IV EOC Who Will Receive NACT?

Literature Review Update and Analysis—The four key phase III trials examined were EORTC 55971, CHORUS, JCOG0602, and SCORPION. The chemotherapy regimens evaluated in the studies included carboplatin or cisplatin combined with paclitaxel (Table 2). In the neoadjuvant arms, the platinum-taxane regimen was administered for three to four cycles before and after ICS.

In terms of OS, two of the noninferiority trials (EORTC 55971 and CHORUS) found NACT to be noninferior to primary surgery. However, the third noninferiority trial (JCOG0602) did not confirm these findings. The SCORPION trial did not show superiority of NACT followed by IDS over primary surgery with similar PFS outcomes achieved (14.0 months *v* 15.0 months; HR, 1.05 [95% CI, 0.77 to 1.44], *P* = .73).

Two trials investigated the impact of adding bevacizumab to NACT on complete macroscopic resection rate (CRR).^{24,25} The ANTHALYA trial²⁴ was a multicenter, open-label, phase II study. Ninety-five patients underwent four cycles of NACT with or without three concomitant cycles of bevacizumab, followed by IDS. The study concluded that adding bevacizumab to NACT achieved an encouraging CRR with IDS in patients with initially unresectable advanced ovarian cancer. The addition of bevacizumab did not increase the rate of AEs or serious AEs after NACT compared with chemotherapy alone. The GEICO1205 trial²⁵ recruited 68 patients with newly diagnosed advanced ovarian cancers. Patients were randomly assigned to receive four cycles of NACT with or without ≥three cycles of bevacizumab. The results of the trial revealed that in patients with initially unresectable ovarian cancer, the rate of complete macroscopic response with an IDS was <10% in both treatment arms. Therefore, the study authors concluded that adding bevacizumab to NACT did not improve the complete macroscopic response rate. However, the surgical operability was improved. AEs greater than grade 3 were significantly less common in the bevacizumab-containing arm than in the chemotherapy alone arm during neoadjuvant therapy (29% *v* 61%, respectively).

Clinical Interpretation—Platinum-taxane doublet therapy has been the accepted standard of care for the adjuvant treatment after PCS of advanced EOC, especially of high-grade serous or endometrioid histology, since the late 1990s. All of the NACT studies have used platinum and taxane regimens although there has been some variability between the agents and doses used among the studies. While EORTC 55971 and CHORUS allowed choice of platinum-based therapy, in both studies, most patients who underwent NACT-ICS received platinum and taxane (88% in EORTC 55971 and 77% in CHORUS). All patients were required to receive platinum and taxane in the JCOG0602 and SCORPION trials. In SCORPION, an amendment allowed the addition of bevacizumab to chemotherapy and as maintenance therapy after its approval by the Italian medical agency, and 38% of patients received bevacizumab as part of their regimen.

Notably, of the patients receiving NACT, 23% in CHORUS and 6% in EORTC 55971 received single-agent carboplatin. A GINECO/GCIG randomized clinical trial⁹⁶ evaluated single-agent carboplatin (AUC 5–6 mg/mL/min once every 3 weeks) versus standard carboplatin-paclitaxel (carboplatin AUC 5 mg/mL/min plus paclitaxel 175 mg/m once every 3 weeks) versus once weekly carboplatin-paclitaxel (carboplatin AUC 2 mg/mL/min plus paclitaxel 60 mg/m² on days 1, 8, and 15 of each 28-day cycle) after PCS for vulnerable older adult patients with ovarian cancer. The study showed that single-agent carboplatin was less active and yielded significantly worse survival outcomes in a vulnerable patient population. Treatment-related AEs were less common with carboplatin-paclitaxel once every 3 weeks than with once weekly carboplatin-paclitaxel or single-agent carboplatin, solidifying the recommendation for combined therapy once every 3 weeks even in a vulnerable patient population.⁹⁷ Given these findings, the panel strongly recommends a platinum-taxane doublet be used as NACT in patients with high-grade serous or endometrioid ovarian cancer to avoid the risk of undertreating patients. When treating older adults, one should monitor closely for neuropathy and consider using geriatric assessment tools as outlined in the ASCO Practical Assessment and Management of Vulnerabilities in Older Patients Receiving Systemic Cancer Therapy Guidelines.⁹⁸ In GOG273, functional dependency as measured by IADLs (instrumental activities of daily living) was predictive of survival and tolerance to platinum-based chemotherapy in older adults with ovarian cancer.^{99,100} However, while a platinum-taxane doublet is preferred, the Expert Panel recognizes the need for personalized treatment plans based on individual patient characteristics, risk tolerance, and disease factors.

While the NACT studies predominantly enrolled patients with high-grade serous and endometrioid histology, response data for NACT therapy with a platinum-taxane in other histologic subtypes are limited. PCS may be preferred for histologies where response rates to chemotherapy are especially low, such as in low-grade serous ovarian cancer and clear cell carcinoma. Alternative chemotherapy regimens, such as fluorouracil-based regimens for mucinous histology, can also be considered. Thus, individualized patient-specific factors should be considered when determining whether NACT is appropriate in these clinical situations, and clinical trial participation, when available, is strongly encouraged.

NACT AND ICS

Among Patients Treated With NACT, Does the Timing of ICS, the Number of Chemotherapy Cycles Before ICS, or Timing in Between Chemotherapy and ICS Affect the Safety or Efficacy of Treatment?

Literature Review Update and Analysis—RCTs have not yet explored whether the timing of ICS or the number of chemotherapy cycles following ICS affects treatment outcomes. In studies such as EORTC, CHORUS, and SCORPION, patients received three cycles of NACT before and three cycles after ICS, while JCOG0602 followed four cycles of carboplatin and paclitaxel before ICS. A recent systematic review and meta-analysis¹⁶ examined the optimal number of NACT cycles for ovarian cancer management prior to IDS. This analysis, encompassing 22 studies and 7,005 patients, revealed no significant difference in PFS between those receiving three or fewer cycles versus four or more cycles (HR, 1.13; $P = .07$). However, OS was better in patients receiving fewer NACT cycles (HR, 1.31; $P = .006$). Additionally, patients who received fewer than five cycles showed significantly better PFS and OS compared to those receiving five or more cycles, indicating a potential decline in survival outcomes with an increased number of NACT cycles.

Supplementary studies offer additional insights into the impact of NACT cycles on patient outcomes. Several studies found no significant differences in OS, PFS, or disease-free survival when comparing 3–4 NACT cycles with six cycles or more,¹⁰¹ three versus four NACT cycles,¹⁰² and three cycles versus more.¹⁰³ However, evidence suggests that 6 NACT cycles before surgery can improve optimal cytoreduction and reduce surgical morbidity compared to three cycles.¹⁰⁴ Initiating IDS within 4 weeks of NACT has been shown to significantly improve PFS and OS.¹⁰⁵ Achieving complete cytoreduction remains a key factor for better outcomes, regardless of the number of NACT cycles,¹⁰⁶ and favorable outcomes have been observed even after five or more cycles when complete resection is achieved.¹⁰⁷ Additionally, modifications in NACT dosing and scheduling, when necessary, did not significantly impact patient outcomes, indicating a level of flexibility in treatment approaches.¹⁰⁸

Ongoing clinical trials are currently investigating the optimal number of NACT cycles for advanced EOC. The CHRONO trial ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT03579394) identifier: [NCT03579394](https://clinicaltrials.gov/ct2/show/study/NCT03579394)) is evaluating PFS when ICS is performed after three versus six cycles in patients with stage IIIB-IV disease who are initially inoperable but deemed eligible for ICS after three cycles. Similarly, the GOG-01 trial ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02125513) identifier: [NCT02125513](https://clinicaltrials.gov/ct2/show/study/NCT02125513)) is examining the rate of complete cytoreduction when ICS is conducted after three versus six cycles in the same patient group. An important consideration is that performing standard ICS earlier rather than delaying it could enable earlier initiation of maintenance therapy, such as bevacizumab with or without PARPi.¹⁰⁹

Clinical Interpretation—Response to NACT is essential to determine the role and timing of ICS. Close clinical assessments and CA-125 measurements with each cycle (every 3 weeks) should be performed. The CA-125 ELIMination Rate Constant K (KELIM) is a marker of chemosensitivity in ovarian cancer and can provide additional prognostic and predictive information.^{110,111} KELIM score can be calculated easily from an available

online tool.¹¹² Lastly, radiographic imaging should be performed early, preferably after three cycles of NACT, and compared to the baseline study. If there is a clinical response to NACT and the surgical assessment has a high likelihood to achieve complete cytoreduction, ICS should be performed ideally after no more than four cycles of NACT. Medical optimization and the logistical scheduling of surgery may influence those who receive three or 4 NACT cycles; however, there have been no significant differences in outcomes if surgery is performed before cycle 5.

HYPERTHERMIC INTRAPERITONEAL CHEMOTHERAPY

Is There a Role for HIPEC at ICS?

Literature Review Update and Analysis—Several trials have evaluated the efficacy of HIPEC in combination with NACT and ICS for patients with stage III or IV invasive EOC (Table 3). In the OVHIPEC-1 trial,¹⁵ updated in 2023,²⁰ patients receiving HIPEC (one time perfusion with cisplatin 100 mg/m²) showed a median OS of 44.9 months compared to 33.3 months in the control group, with a HR of 0.70 (95% CI, 0.53 to 0.92). Disease-free survival (DFS) also improved with HIPEC (14.3 months *v* 10.7 months, HR, 0.63 [95% CI, 0.48 to 0.83]). Similar benefits have been reported in another trial, with a median OS of 61.8 months for the HIPEC group versus 48.2 months for the control group (HR, 0.53 [95% CI, 0.29 to 0.97]) and a median DFS of 17.4 months versus 15.4 months (HR, 0.60 [95% CI, 0.37 to 0.97]).²² Another HIPEC trial²³ found an OS of 52 months in the HIPEC group compared to 45 months in the control group (HR, 0.05 [95% CI, 0.00 to 0.80]) and a DFS of 18 months versus 12 months (HR, 0.12 [95% CI, 0.02 to 0.72]).

Pooled data from these studies (Table 4) show that HIPEC, when added to NACT and CRS, significantly improves OS (HR, 0.57 [95% CI, 0.33 to 0.99], *P* = .04; Fig 2) and DFS (HR, 0.59 [95% CI, 0.43 to 0.82], *P* = .002; Fig 3) with moderate heterogeneity. These results indicate that incorporating HIPEC into the treatment regimen for qualifying patients with advanced ovarian cancer may lead to better survival outcomes and support the recommendation for its use in clinical practice.

Clinical Interpretation—The use of HIPEC during ICS has shown significant improvement in OS across several studies, although this evidence predates the introduction of PARPi in the maintenance setting. If HIPEC is given, patients should be carefully informed and consent to the reported risks and benefits of HIPEC in context of future maintenance options. Given high-dose cisplatin (100 mg/m²) is used, significant renal dysfunction would exclude HIPEC administration (Creatinine Clearance <30 or serum Creatinine <1.5). In addition, careful consideration should be given to patients with diabetes, neuropathy, hearing loss, or advanced age.

Due to the resource intensity required to administer HIPEC, availability is limited to centers that have adequately trained staff and dedicated resources. In preparation for HIPEC administration, multidisciplinary coordination with pharmacy, nursing, anesthesia, and surgery is vital to guarantee safe delivery of intraoperative chemotherapy. Proper training in HIPEC administration and supportive medication is essential. Surgeons should minimize nephrotoxins (ie, contrast scans, anti-inflammatories) perioperatively and postoperatively.

Baseline laboratory studies, specifically renal function and blood counts, should be within the week prior to ICS or HIPEC. Since cisplatin has high emetic potential, standard preventive antiemetic treatment should be provided such as intravenous palonosetron, aprepitant, and dexamethasone.¹¹³ Perioperative, goal-directed fluid therapy approaches should be implemented to maintain optimal hemodynamic indices, maximize tissue oxygenation, and avoid volume overload, which can delay postoperative recovery and increase postoperative complications.¹¹⁴ Sodium thiosulfate (bolus at start of HIPEC followed by continuous infusion) should be administered to prevent nephrotoxicity. In the postoperative period, careful assessment for cisplatin side effects is warranted as well as an antiemetic regimen (dexamethasone, ondansetron, and/or olanzapine) and close monitoring of kidney function, electrolytes, glucose, and blood pressure, particularly in patients with higher risk (eg, those with older age, diabetes, hypertension).

CHEMOTHERAPY AFTER ICS

Among Patients Treated With NACT, What Is the Recommended Number of Chemotherapy Cycles After ICS?

Literature Review Update and Analysis—The recommended number of chemotherapy cycles after ICS is informed by findings from the key clinical trials, each offering slightly different approaches. In the EORTC 55971 trial, patients who underwent NACT followed by ICS received at least three cycles of chemotherapy post-surgery, totaling at least six cycles. The CHORUS and SCORPION trials followed a similar protocol, also administering three cycles of chemotherapy after ICS. In contrast, the JCOG0602 trial administered four cycles of chemotherapy after ICS as part of a treatment plan that included eight cycles in total. Collectively, these trials indicate that administering an additional two to three cycles of chemotherapy after ICS, for a total of six-plus cycles in the overall treatment regimen, is an effective approach.

Clinical Interpretation—In patients who obtained complete gross resection at ICS, the completion of at least six cycles of a platinum-taxane doublet in total is recommended. In the EORTC, SCORPION, and CHORUS studies, patients received three cycles of NACT before ICS and three cycles thereafter. In the JCOG0602 study, ICS followed four cycles of carboplatin and paclitaxel. The total number of postoperative chemotherapy cycles should be determined by tolerability and clinical benefit. Dose modification or discontinuation of a component of the regimen may be required for cumulative neuropathy or other toxicities. At most institutions in North America, patients who undergo NACT-ICS are not treated with postoperative intraperitoneal (IP) chemotherapy, although one small trial reported improvement in 9-month progression disease rate with IP carboplatin plus IV and IP paclitaxel.¹¹⁵ Lastly, in high-risk patients (ie, stage IV, suboptimal ICS), the inclusion of IV bevacizumab may be considered, although evidence is based on patients who underwent PCS.^{116,117} If bevacizumab is added, IV bevacizumab is started at postoperative cycle 2 to allow adequate healing from surgery.

In each of the NACT phase III studies, postoperative chemotherapy was started ≤ 6 weeks after surgery. No studies have specifically evaluated the timing of chemotherapy after

NACT + ICS; however, based on studies identifying detrimental outcomes with delays in the initiation of adjuvant therapy after PCS,^{84,85} it is recommended to start postoperative chemotherapy within 4–6 weeks after surgery if feasible.

At chemotherapy completion (total six to eight cycles), CA-125 measurement and imaging is used to determine response and finalize decision for next steps. Options clinicians may discuss with patients include a treatment break or maintenance therapy if response is observed, or conversely if disease progression occurs, a discussion on goals of care and next options (clinical trials, second-line treatment, or redirection in goals of care).

MAINTENANCE THERAPY

Is There a Role for Maintenance Therapy After Completion of Primary Chemotherapy?

Literature Review Update and Analysis—In the frontline maintenance setting for patients with newly diagnosed advanced ovarian cancer, three trials investigated the efficacy of PARPi and are covered in detail in the ASCO guideline by Tew et al.¹³ Briefly, the SOLO1 trial demonstrated that olaparib significantly improved PFS compared to placebo in patients with *BRCA*-pathogenic variant associated ovarian cancer (HR, 0.30 [95% CI, 0.23 to 0.41]). The PRIMA trial showed that niraparib extended PFS in patients with high-risk advanced ovarian cancer regardless of homologous recombination deficiency (HRD) status, with significant benefits in both HRD-positive (HR, 0.51 [95% CI, 0.40 to 0.66]) and proficient (HR, 0.67 [95% CI, 0.50 to 0.89]) subgroups. The PAOLA-1 trial combined olaparib with bevacizumab, revealing substantial PFS improvement in patients with *BRCA* pathogenic variants and positive HRD status, although no benefit was observed in patients with HRD-negative tumors.

Clinical Interpretation—In patients with response to platinum-based therapy, options after adjuvant chemotherapy include observation as well as maintenance treatments, and the decision on which option to choose is based on individual patient factors, such as *BRCA* status, HRD test results, stage, extent of response to platinum-based therapy, and patient preference. If bevacizumab was started with chemotherapy, the continuation of bevacizumab for up to 12 months or progression is reasonable. In patients with a germline/somatic *BRCA* pathogenic variants or whose cancer is HRD score positive, PARPi (olaparib and niraparib) are strongly recommended. Tumor testing for somatic pathogenic variants and HRD score should be prioritized with ICS pathology specimen, if not obtained on initial diagnostic core biopsy.

PROGRESSION ON NACT

What Is the Management Approach for Patients Who Do Not Have a Clinical Response to NACT?

Literature Review Update and Analysis—Patients with progressive disease during first-line chemotherapy (platinum-refractory disease) typically have a poor prognosis, with a median OS of less than 1 year. Although no RCTs have compared treatment options for patients whose disease progresses during NACT, chemotherapy with agents that do not exhibit cross-resistance to carboplatin or paclitaxel, such as gemcitabine,

pegylated liposomal doxorubicin, or bevacizumab, may be appropriate.⁹ Results from studies investigating novel approaches have not been promising. A phase III trial (JAVELIN Ovarian 200) demonstrated that neither avelumab monotherapy nor its combination with chemotherapy improved PFS or OS in patients with platinum-resistant or platinum-refractory ovarian cancer.¹¹⁸ While the combination of sorafenib with topotecan significantly extended PFS compared to placebo in the randomized, phase II TRIAS trial,¹¹⁹ its significant toxicity and limited clinical efficacy warrant further study.

Clinical Interpretation—In the prospective NACT randomized trials, most patients who received NACT underwent ICS (88% in EORTC, 79% in CHORUS). However, outside of randomized controlled clinical trials, the reported rates of ICS are much lower (53%-72%).^{100,102,120} Patients who do not undergo ICS were chronologically older, non-White, more frail, and require more dose reduction-modification with NACT. Reported reasons for not undergoing ICS include progressive disease or death on NACT, high-burden stage IV disease, comorbidities, and patient preference. For patients with progressive disease, a repeat core tissue biopsy is warranted to confirm correct diagnosis and to perform further tumor testing (ie, molecular profile, folate receptor). In addition, it is important to confirm that germline *BRCA* testing has been performed. Although guidelines recommend *BRCA* testing in all women diagnosed with ovarian cancer, Liu reported that patients who did not undergo ICS were less likely to have genetic testing (52%) compared with patients who had ICS (81%).

Patients who develop progressive disease during NACT should avoid ICS unless they have a demonstrated response to an alternate chemotherapy. It is very unlikely that an optimal surgical cytoreduction can be achieved in patients with primary platinum-refractory disease, and the survival benefit of a potentially morbid surgery is uncertain in this context. Instead, patients should be offered opportunities to participate in clinical trials or start palliative chemotherapy with alternate agents, and/or discontinuation of active cancer therapy and initiation of end-of-life care. Early engagement of palliative care should be considered for those with high symptom burden.¹²¹

Patients with progressive disease on NACT (ie, platinum refractory disease) should not be offered surgery unless for palliation (ie, ostomy for bowel obstruction). Goals of care and prognosis should be emphasized with a focus on palliation of symptoms and improvements in quality of life, as outlined in the ASCO Guideline for Palliative Care for Patients with Cancer.¹²¹

LIMITATION OF THE RESEARCH AND FUTURE RESEARCH

The evidence base has several limitations. First, the heterogeneity of clinical trials and retrospective studies poses challenges in generalizing findings across diverse patient populations. Variation in surgical expertise, chemotherapy regimens, and patient selection criteria can introduce bias, making it difficult to apply results universally. Additionally, most trials comparing NACT to PCS are limited by relatively short follow-up periods, which can obscure long-term survival outcomes and recurrence patterns. Finally, differences in how

treatment outcomes, such as optimal debulking and quality of life, are measured across studies further complicate direct comparisons between the two approaches.

It is important to acknowledge that the studies, meta-analyses, and systematic reviews that comprise the panel's evidence base for clinical practice recommendations are limited by a lack of racial and/or ethnic diversity in cancer clinical trials and workforce teams. Less diverse trials impede the generalizability of trial results and inhibit our understanding of safety and efficacy across populations.

Future research that focuses on stratification of patients based on molecular and genetic markers, as well as tumor biology and histology, could offer a more personalized approach to treatment. This would help to identify which subgroups may benefit more from NACT versus PCS, thereby optimizing individual patient outcomes. Additionally, further studies investigating quality of life, cost-effectiveness, and long-term functional outcomes after treatment are needed to guide clinical decision making and enhance patient-centered care. Researchers should also aim to standardize surgical and chemotherapy protocols across trials to minimize variability and increase the comparability of results.

PATIENT AND CLINICIAN COMMUNICATION

For patients with advanced ovarian cancer, decision making about first-line treatment should be shared between clinicians and patients. Clinicians must communicate evidence-based options for treatment, inclusive of their benefits and risks, and patients must be allowed to express their goals and preferences. Given the complexity of the decision and the potential for high emotional and psychological impact, it is crucial for clinicians and other members of the care team to create a supportive environment where patients feel comfortable asking questions and discussing their fears or uncertainties. It is important to recognize that patients are no longer reliant solely upon their medical team for information, and often access other sources online, in print, or through social media and support groups and via family members and caregivers. It is important to address any misinformation and guide patients toward reliable resources. Clinicians should emphasize the importance of a collaborative and transparent decision-making process.

For patients faced with a decision between PCS and NACT, it is essential that clinicians first explain the diagnosis, including the extent of disease identified, stage, and prognostic implications of what is known. Sharing data about comparative morbidity, survival, and quality-of-life outcomes in plain language can help to ensure understanding and help patients make more informed decisions. Encouraging patients to involve their family members or caregivers in discussions can also be beneficial, as these individuals often play a critical role in the patient's support system and decision-making process. Only by ensuring a common starting point can each discuss and ultimately decide on the best treatment plan.

For recommendations and strategies to optimize patient-clinician communication, see Patient-Clinician Communication: ASCO Consensus Guideline.¹²²

HEALTH EQUITY CONSIDERATIONS

Social determinants of health, defined by the WHO as the conditions in which an individual is born, grows, lives, works, and ages, can undermine ASCO's expert recommendations on best practices for prevention, screening, palliative and supportive care, and disease management for many patients with cancer.^{123,124} It is important to acknowledge that many people in the United States and elsewhere do not receive the highest level of cancer care due to the long-term impact of structural racism and the consequential unequal distribution of wealth among racial groups.¹²⁵

In the United States, many patients remain unable to reap the benefits of innovative prevention and early detection programs, biomarker testing, and new cancer therapies due to structural barriers including lack of transportation, stable housing, and adequate insurance coverage as well as food insecurity, health literacy, proximity to a dedicated cancer center, and cost of treatment and other services.¹²⁶ Additionally, sexual and gender minority people may experience stigma along with barriers to cancer screening, prevention, and treatment that contribute to these cancer disparities.¹²⁷ Disparities widen in those who are also from a racial or ethnic minority, underscoring the influence of intersectionality in cancer health disparities.¹²⁸

When treating advanced ovarian cancer, health equity is a key factor influencing outcomes, particularly across different racial, ethnic, and socioeconomic groups. Disparities in access to testing, treatment, survival rates, and adherence to clinical guidelines are well documented in ovarian cancer care, highlighting the need for a more equitable approach to treatment. Analysis of germline genetic testing for *BRCA1/2* trends indicate that, compared with non-Hispanic White patients, rates of testing were lower among Asian, Black, and Hispanic patients.^{129,130}

Studies demonstrate the survival disparity in women who are Black with ovarian cancer compared with their White counterparts. In the African American Cancer Epidemiology Study, which selected study sites based on geographic regions with high Black population density in the United States, women who are Black with EOC had a significantly lower 5-year OS rate (49%) compared with women who are White (60%) in the SEER registry.¹³¹ Contributing factors included lower levels of income, education, and insurance coverage among women who are Black, which were associated with reduced access to optimal treatment, including both NACT and cytoreductive surgery. Additionally, women who are Black were less likely to undergo optimal debulking surgery, a critical factor in improving survival outcomes.¹³¹ Other studies support the finding that women who are Black and Asian women more likely to receive NACT plus IDS relative to PCS plus adjuvant chemotherapy than women who are non-Hispanic White women (OR, 1.12 [95% CI, 1.02 to 1.22] and OR, 1.12 [95% CI, 0.99 to 1.28], respectively) and had increased hazard of all-cause mortality (HR, 1.14 [95% CI, 1.09 to 1.20]) compared with women who are White.¹³² Compared with women who are White, better survival outcomes have been reported in women who are Asian with ovarian cancer, although EOC diagnosis, treatment, survival, and trends differed across Asian American ethnic subgroups.^{132–134} While these differences were partly attributed to younger age at diagnosis, better performance status,

and earlier stage of disease, race remained a significant prognostic factor even after adjusting for these variables. This suggests that genetic or other racial differences may influence treatment responses and outcomes, which should be considered in clinical practice. Nonetheless, adherence to treatment of advanced ovarian cancer guidelines significantly improves survival across all racial, ethnic, and socioeconomic groups.¹³⁵

Additionally, structural equation modeling revealed that health care access domains—affordability, availability, and accessibility—mediate racial disparities in ovarian cancer treatment quality.¹³⁶ Non-White patients, including Black and Hispanic patients, had lower levels of affordability and availability of care, which were shown to directly impact their likelihood of receiving gynecologic oncology consultations and less likely to receive the standard of care—combining surgery and chemotherapy—resulting in poorer OS rates.^{120,136}

Socioeconomic status and insurance type also play a significant role in determining access to surgery and NACT. Goldberg et al¹³⁷ reported that patients treated at facilities serving lower-income populations or those with nonprivate insurance were significantly less likely to receive cytoreductive surgery. Similarly, Black patients were 38% less likely to undergo CRS for ovarian cancer compared with non-Black patients. These disparities highlight the importance of ensuring equitable access to both surgical and chemotherapeutic interventions, regardless of income or insurance status.

Geographical region also influences access to treatment and outcomes for patients with advanced ovarian cancer. A European study found significant variation in the use of primary CRS or NACT and in the likelihood of achieving complete cytoreduction between different geographical regions, even after adjusting for case-mix factors.¹³⁸ Furthermore, geographic disparities can affect the quality of care patients receive. For instance, patients who live in rural areas of the United States are more likely to have worse survivorship outcomes and experience higher mortality rates compared with patients who live in nonrural areas. This can be attributed, in part, to a lower density of specialists and dedicated cancer centers, as only 21% of nonmetropolitan counties in the United States have one or more practicing oncologists.¹³⁹

Addressing these disparities requires a multifaceted approach that includes improving health care access, ensuring guideline adherence, and eliminating barriers to quality care.

GUIDELINE IMPLEMENTATION

ASCO guidelines are developed for implementation across health settings. Each ASCO guideline includes a community oncologist member on the panel. The additional role of this community oncologist member on the guideline panel is to assess the suitability of the recommendations to implementation in the community setting, but also to identify any other barrier to implementation a reader should be aware of. Barriers to implementation include the need to increase awareness of the guideline recommendations among frontline practitioners and survivors of cancer and caregivers, and also to provide adequate services in the face of limited resources. The guideline recommendations table and accompanying

tools (available at www.asco.org/gynecologic-cancer-guidelines) were designed to facilitate implementation of recommendations. This guideline will be distributed widely. ASCO guidelines are posted on the ASCO website and most often published in the *Journal of Clinical Oncology*.

ASCO believes that cancer clinical trials are vital to inform medical decisions and improve cancer care, and that all patients should have the opportunity to participate.

ADDITIONAL RESOURCES

For current information, including selected updates, supplements, slide sets, and clinical tools and resources, visit www.asco.org/gynecologic-cancer-guidelines. The Data Supplement for this guideline includes quality assessments, additional evidence tables, search strategy and the PRISMA diagram. Guideline recommendations and algorithms are also available in the free ASCO Guidelines app (available for download in the Apple App Store and Google Play Store). Listen to key recommendations and insights from panel members on the ASCO Guidelines podcast. The Methodology Manual (available at www.asco.org/guideline-methodology) provides additional information about the methods used to develop this guideline. Patient information is available at www.cancer.org.

ASCO welcomes your comments on this guideline, including implementation challenges, new evidence, and how this guideline impacts you. To provide feedback, contact us at guidelines@asco.org. Comments may be incorporated into a future guideline update. To submit new evidence or suggest a topic for guideline development, complete the form available at www.asco.org/guidelines.

GENDER-INCLUSIVE LANGUAGE

ASCO is committed to promoting the health and well-being of individuals regardless of sexual orientation or gender identity.¹⁴⁰ Transgender and nonbinary people, in particular, may face multiple barriers to oncology care including stigmatization, invisibility, and exclusiveness. One way exclusiveness or lack of accessibility may be communicated is through gendered language that makes presumptive links between gender and anatomy.^{141–144} With the acknowledgment that ASCO guidelines may impact the language used in clinical and research settings, ASCO is committed to creating gender-inclusive guidelines. For this reason, guideline authors use gender-inclusive language whenever possible throughout the guidelines. In instances in which the guideline draws upon data based on gendered research (eg, studies regarding women with ovarian cancer), the guideline authors describe the characteristics and results of the research as reported.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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APPENDIX 1.: GUIDELINE DISCLAIMER

The Clinical Practice Guidelines and other guidance published herein are provided by ASCO Inc to assist clinicians in clinical decision making. The information herein should not be relied upon as being complete or accurate, nor should it be considered as inclusive of all proper treatments or methods of care or as a statement of the standard of care. With the rapid development of scientific knowledge, new evidence may emerge between the time information is developed and when it is published or read. The information is not continually updated and may not reflect the most recent evidence. The information addresses only the topics specifically identified therein and is not applicable to other interventions, diseases, or stages of diseases. This information does not mandate any particular course of medical care. Further, the information is not intended to substitute for the independent professional judgment of the treating clinician, as the information does not account for individual variation among patients. Recommendations specify the level of confidence that the recommendation reflects the net effect of a given course of action. The use of words like “must,” “must not,” “should,” and “should not” indicates that a course of action is recommended or not recommended for either most or many patients, but there is latitude for the treating physician to select other courses of action in individual cases. In all cases, the selected course of action should be considered by the treating clinician in the context of treating the individual patient. Use of the information is voluntary. ASCO does not endorse third party drugs, devices, services, or therapies used to diagnose, treat, monitor, manage, or alleviate health conditions. Any use of a brand or trade name is for identification purposes only. ASCO provides this information on an “as is” basis and makes no warranty, express or implied, regarding the information. ASCO specifically disclaims any warranties of merchantability or fitness for a particular use or purpose. ASCO assumes no responsibility for any injury or damage to persons or property arising out of or related to any use of this information, or for any errors or omissions.

APPENDIX 2.: GUIDELINE AND CONFLICTS OF INTEREST

The Expert Panel was assembled in accordance with ASCO’s Conflict of Interest Policy Implementation for Clinical Practice Guidelines (“Policy,” found at <http://www.asco.org/guideline-methodology>). All members of the Expert Panel completed ASCO’s disclosure form, which requires disclosure of financial and other interests, including relationships with commercial entities that are reasonably likely to experience direct regulatory or commercial impact as a result of promulgation of the guideline. Categories for disclosure include employment; leadership; stock or other ownership; honoraria, consulting or advisory role; speaker’s bureau; research funding; patents, royalties, other intellectual property; expert testimony; travel, accommodations, expenses; and other relationships. In accordance with the Policy, the majority of the members of the Expert Panel did not disclose any relationships constituting a conflict under the Policy.

TABLE A1.

NACT for Newly Diagnosed, Advanced Ovarian Cancer Guideline Update Expert Panel Membership

Name	Affiliation/Institution	Area of Expertise
William P. Tew, MD (co-chair)	Memorial Sloan Kettering Cancer Center, New York, NY	Medical Oncology
Stephanie Gaillard, MD, PhD (co-chair)	Johns Hopkins University, Baltimore, MD	Medical Oncology
Deborah K. Armstrong, MD	Johns Hopkins University, Baltimore, MD	Medical Oncology
William A. Cliby, MD	Mayo Clinic, Rochester, MN	Gynecologic Oncology
Mitchell I. Edelson, MD, MBA	Jefferson Health-Abington, Willow Grove, PA	Gynecologic Oncology
Agustin A. Garcia, MD	LSU School of Medicine, New Orleans, LA	Medical Oncology
RahelG. Ghebrey, MD, MPH	University of Minnesota Medical School & St Paul's Hospital Millennium Medical School, Minneapolis, MN	Gynecologic Oncology
Gregory M. Gressel, MD, MS	Corewell Health Cancer Center and Michigan State University, Grand Rapids, MI	Gynecologic Oncology
Joseph J. Kash, MD	Edward Cancer Center, Naperville, IL	PGIN representative
Jamie L. Lesnock, MD	University of Pittsburgh Medical Center, Pittsburgh, PA	Gynecologic Oncology
Larissa A. Meyer, MD, MPH	University of Texas MD Anderson Cancer Center, Houston, TX	Gynecologic Oncology
Kathleen N. Moore, MD, MS	University of Oklahoma, Oklahoma City, OK	Gynecologic Oncology
Roisin E. O'Cearbhaill, MD	Society of Gynecologic Oncology representative, Memorial Sloan Kettering Cancer Center, New York, NY	Medical Oncology
Alexander B. Olawaiye, MD	University of Pittsburgh Medical Center, Pittsburgh, PA	Gynecologic Oncology
Ritu Salani, MD, MBA	University of California Los Angeles, Los Angeles, CA	Gynecologic Oncology
Dee Sparacio, MS	Hightstown, NJ	Patient representative
Willemien J. van Driel, MD, PhD	Netherlands Cancer Institute, Amsterdam, the Netherlands	Gynecologic Oncology
Christina Lacchetti	ASCO, Alexandria, VA	ASCO Practice Guideline Staff (Health Research Methods)

TABLE A2.

Recommendation Rating Definitions

Term	Definition
Quality of evidence	
High	We are very confident that the true effect lies close to that of the estimate of the effect
Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Term	Definition
Very low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect
Strength of recommendation	
Strong	In recommendations for an intervention, the desirable effects of an intervention outweigh its undesirable effects In recommendations against an intervention, the undesirable effects of an intervention outweigh its desirable effects All or almost all informed people would make the recommended choice for or against an intervention
Conditional/weak	In recommendations for an intervention, the desirable effects probably outweigh the undesirable effects, but appreciable uncertainty exists In recommendations against an intervention, the undesirable effects probably outweigh the desirable effects, but appreciable uncertainty exists Most informed people would choose the recommended course of action, but a substantial number would not

NOTE. GRADE Handbook, Schünemann et al.¹⁴⁵

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TARGET POPULATION AND AUDIENCE**Target Population**

Patients with newly diagnosed stage III or stage IV epithelial ovarian, fallopian tube, or primary peritoneal cancer (EOC).

Target Audience

Gynecologic and medical oncologists, and others involved in gynecologic cancer care, patients with advanced ovarian cancer and caregivers.

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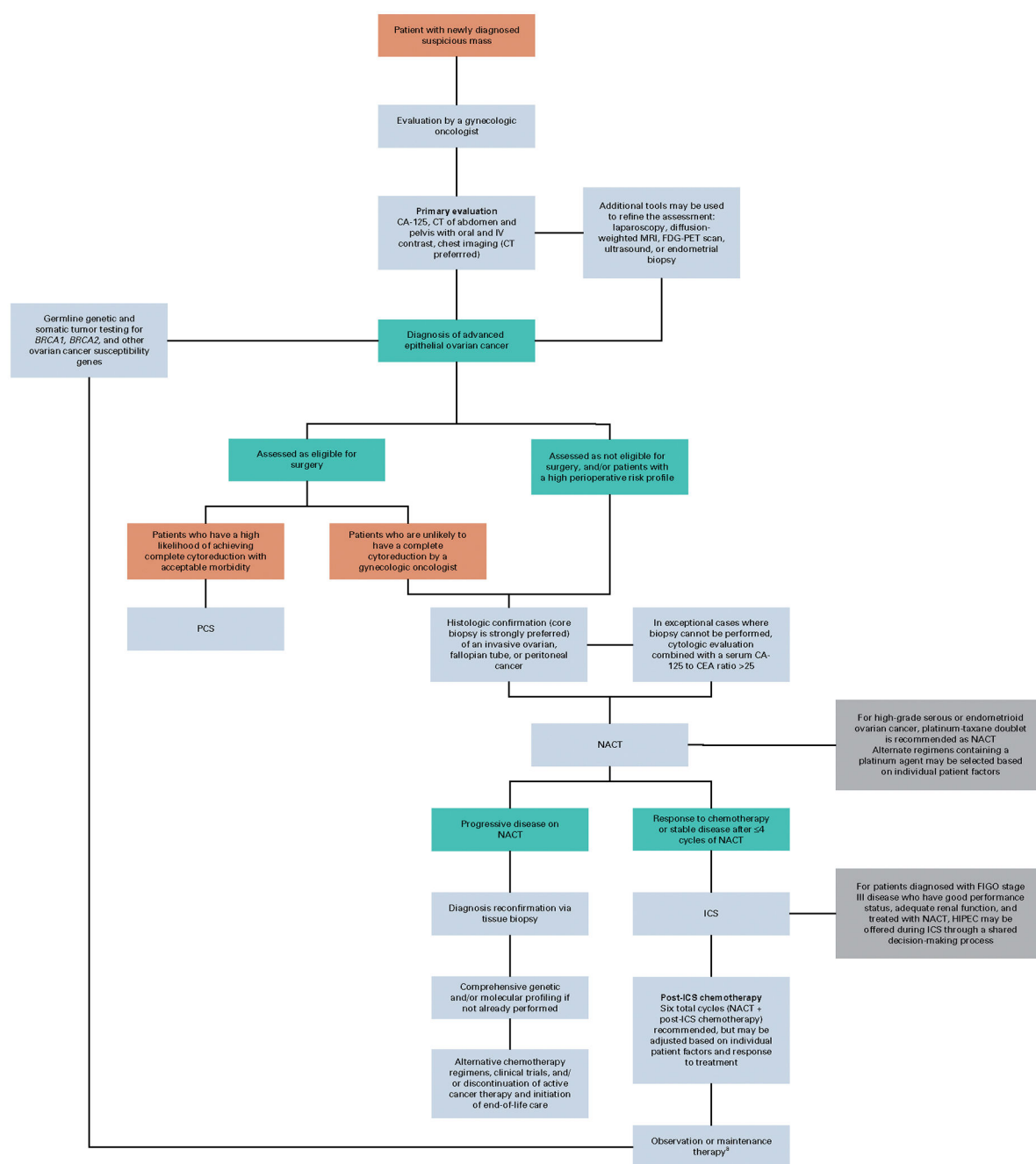
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RELATED ASCO GUIDELINES

- Germline and Somatic Tumor Testing in Epithelial Ovarian Cancer¹² (<https://ascopubs.org/doi/10.1200/JCO.19.02960>)
- Poly(ADP-Ribose) Polymerase Inhibitors in the Management of Ovarian Cancer¹³ (<https://ascopubs.org/doi/10.1200/JCO.22.01934>)
- Palliative Care for Patients With Cancer¹²¹ (<http://ascopubs.org/doi/10.1200/JCO.24.00542>)
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- Antiemetics¹¹³ (<https://ascopubs.org/doi/10.1200/JCO.20.01296>)
- Practical Assessment and Management of Vulnerabilities in Older Patients Receiving Systemic Cancer Therapy⁹⁸ (<https://ascopubs.org/doi/10.1200/JCO.23.00933>)

**FIG 1.**

Algorithm. ^aOptions include bevacizumab, PARPi, and bevacizumab + PARPi depending on clinical scenario. Refer to Tew et al.¹³ CA-125, cancer antigen 124; CEA, carcinoembryonic antigen; CT, computed tomography; FDG, fluorodeoxyglucose-18; FIGO, International Federation of Gynecology and Obstetrics; HIPEC, hyperthermic intraperitoneal chemotherapy; ICS, interval cytoreductive surgery; IV, intravenous; MRI, magnetic resonance imaging; NACT, neoadjuvant chemotherapy; PARPi, poly(ADP-ribose) polymerase inhibitors; PCS, primary cytoreductive surgery.

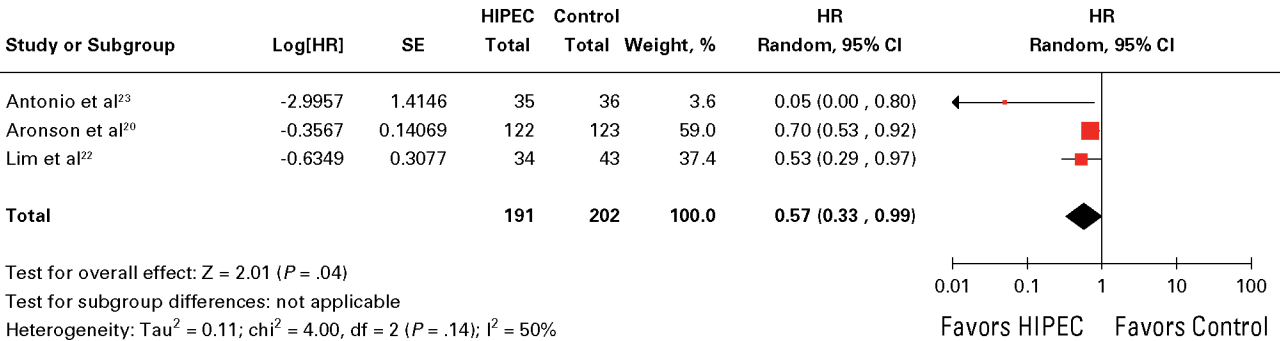


FIG 2.
Overall survival. HIPEC, hyperthermic intraperitoneal chemotherapy; HR, hazard ratio.

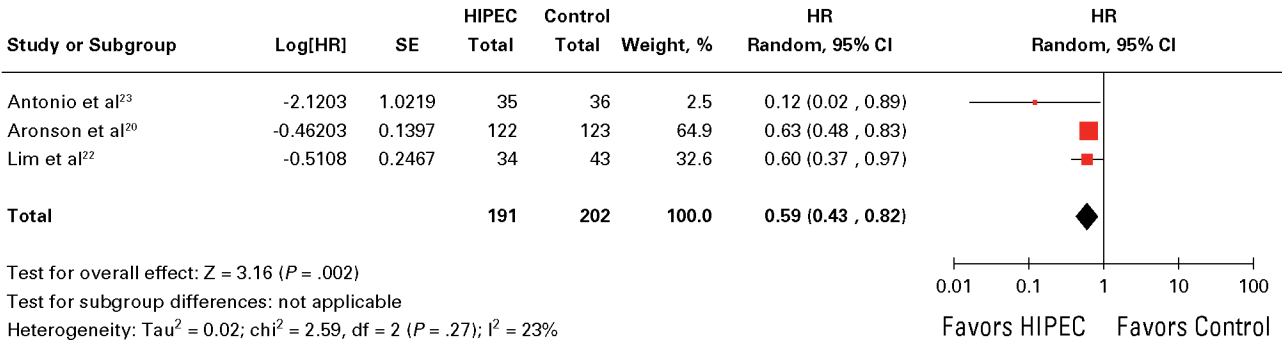


FIG 3.
Disease-free survival. HIPEC, hyperthermic intraperitoneal chemotherapy; HR, hazard ratio.

TABLE 1.
Results of Phase III Randomized Controlled Trials of NACT in Stage III or IV Epithelial Ovarian Cancer

Author, Year(s) Study	Enrollment Criteria	Primary End Point	Study Arm	No. of Patients	Age, Years	Stage IV	Operative Time, Minutes	No Residual Disease	Grade 3–4 Postoperative Complications	PFS, Months, HR (CI)	OS, Months, HR (CI)
Kehoe et al, ⁴ 2015 CHORUS	Stage III or IV ovarian cancer based upon imaging or clinical evidence of pelvic mass with extrapelvic disease; CA-125 to CEA ratio > 25; if less, had to exclude gastrointestinal carcinoma	OS	NACT PCS	274 276	65 66	25% 25%	120 120	39% 17% $P = .0001$	14% 24% $P = .007$	12.0 10.7 HR, 0.91 (95% CI, 0.76 to 1.09) $P = NS$	24.1 22.6 HR, 0.87 (95% CI, 0.72 to 1.05) upper bound of one-sided 90% CI, 0.98; excludes noninferiority boundary of 1.18
Fagotti et al, 2016, ⁵ 2020 ¹⁷ SCORPION	Pathologically proven ovarian cancer, stage IIIC–IV. Intraoperative high tumor load (Fagotti's score of 8–12) assessed by staging laparoscopy	PFS and postoperative complications ^a	NACT PCS	87 84	56 55	9% 15%	253 461 $P < .0001$	77% 48%	32.6% 67.8% ^b	14.0 15.0 HR, 1.05 (95% CI, 0.77 to 1.44) $P = .73$	43.0 41.0 HR, 1.12 (95% CI, 0.76 to 1.65) $P = .56$
Onda et al, 2016, ⁹ 2020 ¹⁸ JCOG0602	Stage III or IV based on CT, MRI, and cytologic tests. CA-125 > 200 U/mL and CEA < 20 ng/mL	OS	NACT PCS	152 149	61 59	30% 32%	302 240 $P < .001$	64% 31% (includes ICS results in PCS arm)	5% 15% $P = .005$ (nonhematologic adverse events)	16.4 15.1 HR, 0.96 (95% CI, 0.75 to 1.23) $P = NS$	44.3 49.0 HR, 1.05 (95% CI, 0.84 to 1.33) A HR of 0.953 was the boundary to reject the null hypothesis that NACT is inferior to PCS
Vergote et al, 2010 ³ ; Greimelet al, 2013 ¹⁹ EORTC 55971	Biopsy-proven stage IIIC or IV. If no biopsy specimen, fine-needle aspirate showing adenocarcinoma was allowed under certain circumstances	OS	NACT PCS	334 336	63 62	24% 23%	180 165	51% 19%	Hemorrhage NACT: 4% PCS: 7% Infections NACT: 2% PCS: 8% Venous NACT: 0 PCS: 3%	12 12 HR, 1.01 (90% CI, 0.89 to 1.15) $P = NS$	30 29 HR, 0.98 (90% CI, 0.84 to 1.13) $P = .01$ for noninferiority

Abbreviations: CA-125, cancer antigen 125; CEA, carcinoembryonic antigen; CT, computed tomography; HR, hazard ratio; ICS, interval cytoreductive surgery; ITT, intention-to-treat; min, minutes; MRI, magnetic resonance imaging; NACT, neoadjuvant chemotherapy; NS, not significant; OS, overall survival; PCS, primary cytoreductive surgery; PFS, progression-free survival.

^a A second primary end point was added: superiority of NACT followed (or not) by interval debulking surgery versus primary debulking surgery in terms of PFS, and the sample size was enlarged accordingly.

Seven patients in the PCS group had grade 5 complications.
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TABLE 2.
NACT Regimens Tested in Randomized Prospective Trials Comparing NACT and PCS

Trial	NACT Regimen Offered (each once every 3 weeks)	Route	Cycle Length, Weeks	NACT Arm Cycles, No.		PCS Arm Cycles, No.	
				Before PCS	After PCS	Before PCS	After PCS
Kehoe 2015 ⁴ CHORUS Randomized Phase III open-label multicenter study	Carboplatin AUC 5–6 + paclitaxel 175 mg/m ²	IV	3	3	3		6
	Carboplatin AUC 5–6	IV	3	3	3		6
Fagotti 2020, ¹⁷ 2016 ⁵ SCORPION Randomized Phase III open-label multicenter study	Carboplatin AUC 5 + paclitaxel 175 mg/m ² ± bevacizumab	IV	3	3	3		6
Onda 2020, ¹⁸ 2016 ⁶ JCOG0602 Randomized Phase III open-label multicenter study	Paclitaxel 175 mg/m ² + carboplatin AUC 6	IV	3	4	4		8
Vergote 2010 ³ EORTC 55971 Randomized Phase III open-label multicenter study	Platinum-taxane, recommended options: • Paclitaxel 135 mg/m ² + cisplatin 75 mg/m ² • Paclitaxel 175 mg/m ² + cisplatin 75 mg/m ² • Paclitaxel 175 mg/m ² + carboplatin AUC 5	IV	3	3	≥3		≥6
	Platinum only: • Cisplatin ≥75 mg/m ² • Carboplatin AUC ≥5	IV	3	3	≥3		≥6
Rouzier 2017 ²⁴ ANTHALYA Randomized Phase II open-label multicenter study	Carboplatin AUC 5 + paclitaxel 175 mg/m ²	IV	3	4	4		NA
García García 2019 ²⁵ GEICO1205 Randomized Phase II open-label multicenter study	Carboplatin AUC 5 + paclitaxel 175 mg/m ² + bevacizumab ^a 15 mg/kg; then bevacizumab monotherapy after PCS	IV	3	4	4		NA
	Carboplatin AUC 6 + paclitaxel 175 mg/m ² before PCS Carboplatin AUC 6 + paclitaxel 175 mg/m ² + bevacizumab 15 mg/kg; then bevacizumab monotherapy after PCS	IV	3	4	Three cycles of postoperative chemotherapy 15 months of bevacizumab		NA
	Carboplatin AUC 6 + paclitaxel 175 mg/m ² + bevacizumab 15 mg/kg	IV	3	4 NACT ± ≥three cycles of bevacizumab	Three cycles of postoperative chemotherapy 15 months of bevacizumab		NA
	Carboplatin AUC 6 + paclitaxel 175 mg/m ² + bevacizumab 15 mg/kg; then bevacizumab monotherapy after PCS	IV	3				

Abbreviations: IP, intraperitoneal; IV, intravenous; NA, not applicable; NACT, neoadjuvant chemotherapy; PCS, primary cytoreductive surgery.

^a Bevacizumab was held for the final cycle of chemotherapy before ICS and the first cycle of chemotherapy after ICS.

TABLE 3.

Results of HIPEC Trials

Author Year of Publication	HIPEC Arm	Control Arm	HIPEC				Median Follow-Up, Months	Median OS, Months, HR (95% CI)	Median DFS, Months, HR (95% CI)
			HIPEC Scheme	Duration, Minutes	Temperature, °C	NACT Scheme			
Aronson 2023 ²⁰ Van Driel 2018 ²¹ OVHIPEC-1 Final Long-Term Analysis	NACT + CRS + HIPEC + ASC n = 122	NACT + CRS + ASC n = 123	Cisplatin (100 mg/m ²)	90	40–42	Carboplatin (AUC 5–6 mg/mL/min) + paclitaxel (175 mg/m ² BSA)	10.4 years in HIPEC 10.1 years in surgery-alone	HIPEC: 44.9 Control: 33.3 HR, 0.70 (0.53 to 0.92)	PFS HIPEC: 14.3 Control: 10.7 HR, 0.63 (0.48 to 0.83)
Lim 2022 ²²	NACT + CRS + HIPEC + ASC n = 34	NACT + CRS + ASC n = 43	Cisplatin (75 mg/m ²)	90	41.5	Carboplatin (AUC 5 mg/mL/min) + paclitaxel (175 mg/m ² BSA)	69.4	HIPEC: 61.8 Control: 48.2 HR, 0.53 (0.29 to 0.96)	PFS HIPEC: 17.4 Control: 15.4 HR, 0.60 (0.37 to 0.99)
Antonio 2022 ²³	NACT + CRS + HIPEC + ASC n = 35	NACT + CRS + ASC n = 36	Cisplatin (75 mg/m ²)	60	42–43	Carboplatin (AUC 5) + paclitaxel (175 mg/m ²)	32	HIPEC: 52 Control: 45 HR, 0.05 (0.00 to 0.80)	HIPEC: 18 Control: 12 HR, 0.12 (0.02 to 0.72)

Abbreviations: ASC, adjuvant systemic chemotherapy; BSA, body-surface area; HIPEC, hyperthermic intraperitoneal chemotherapy; CRS, cytoreductive surgery; DFS, disease-free survival; HR, hazard ratio; NACT, neoadjuvant chemotherapy; OS, overall survival; PFS, progression-free survival.

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TABLE 4.

Pooled Hyperthermic Intraperitoneal Chemotherapy Data

OS			DFS		
HR (95% CI)	P	Heterogeneity	HR (95% CI)	P	Heterogeneity
0.57 (0.33 to 0.99)	.04	50%	0.59 (0.43 to 0.82)	.002	23%

Abbreviations: DFS, disease-free survival; HR, hazard ratio; NACT, neoadjuvant chemotherapy; OS, overall survival; PFS, progression-free survival.

TABLE 5.

Summary of All Recommendations

Clinical Question	Recommendation
<i>General Note.</i> The following recommendations (strong or conditional) and terminology (Data Supplement) represent reasonable options for patients depending on clinical circumstances and in the context of individual patient preferences. Recommended care should be accessible to patients whenever possible.	
1. In patients with newly diagnosed pelvic masses and/or upper abdominal or peritoneal disease, what initial assessment should be performed to guide treatment?	1.1. All patients with suspected stage III or IV EOC should be evaluated by a gynecologic oncologist prior to initiation of therapy to determine whether they are candidates for PCS. (Evidence quality: Moderate; Strength of recommendation: Strong) 1.2. A primary clinical evaluation should include CA-125 and a CT of the abdomen and pelvis with oral and intravenous contrast (if not contraindicated) and chest imaging (CT preferred) to evaluate the extent of disease and the feasibility of surgical resection. (Evidence quality: Moderate; Strength of recommendation: Strong). The use of other tools to refine this assessment may include: • Laparoscopy (Evidence quality: Moderate; Strength of recommendation: Conditional) • Diffusion-weighted MRI (Evidence quality: Moderate; Strength of recommendation: Conditional) • FDG-PET scan (Evidence quality: Moderate; Strength of recommendation: Conditional) • Ultrasound (Evidence quality: Moderate; Strength of recommendation: Conditional) • Endometrial biopsy to exclude an advanced endometrial cancer as the etiology (Evidence quality: moderate; Strength of recommendation: Conditional)
2. In which patients with newly diagnosed advanced EOC is PCS recommended?	1.3. All patients with EOC should be offered germline and somatic testing for <i>BRCA1</i> and <i>BRCA2</i>. Germline testing for other ovarian cancer susceptibility genes is recommended. Somatic tumor testing should include measure(s) of homologous recombination. Testing should occur at the time of diagnosis or as soon as feasibly possible. (Evidence quality: High; Strength of recommendation: Strong) 2.1. For patients with newly diagnosed advanced EOC who are fit for surgery and who have a high likelihood of achieving complete cytoreduction with acceptable morbidity, PCS is recommended over neoadjuvant therapy (NACT). (Evidence quality: Moderate; Strength of recommendation: Conditional) Note: Evaluation for surgery suitability should include both patient performance characteristics, such as fitness, ECOG PS, age, degree of frailty and nutritional status, and disease characteristics such as complexity of surgery required
3. In which patients with newly diagnosed advanced EOC is NACT recommended?	3.1. For patients who are fit for PCS but are deemed unlikely to have complete cytoreduction by a gynecologic oncologist, NACT is recommended over PCS. (Evidence quality: High; Strength of recommendation: Strong) 3.2. Patients with newly diagnosed advanced EOC who have a high perioperative risk profile should receive NACT. (Evidence quality: High; Strength of recommendation: Strong) 3.3. Decisions that patients are not eligible for primary cytoreductive surgery should be made after a consultation with a gynecologic oncologist. (Evidence quality: High; Strength of recommendation: Strong) Note: Prospective studies have predominantly included patients with high-grade serous ovarian cancer, with a limited representation of other histologic subtypes
4. For patients with newly diagnosed stage III or IV EOC who will receive NACT (ie, not suitable candidates for complex cytoreduction surgery), what tests or procedures should be performed before NACT is delivered, in order to ensure accurate diagnosis?	4.1. Before NACT is delivered, all patients should have histologic confirmation (core biopsy is strongly preferred) of an invasive ovarian, fallopian tube, or peritoneal cancer. In exceptional cases, when a biopsy cannot be performed, cytologic evaluation combined with a serum CA-125 to CEA ratio >25 is acceptable to confirm the primary diagnosis and exclude a nongynecologic cancer. (Evidence quality: Moderate; Strength of recommendation: Conditional)
5. What is the preferred chemotherapy regimen for patients with stage III or IV EOC who will receive NACT?	5.1. For NACT, a platinum-taxane doublet is recommended, especially for patients with high-grade serous or endometrioid ovarian cancer. (Evidence quality: High; Strength of recommendation: Strong) 5.2. Alternate regimens containing a platinum agent may be selected based on individual patient factors, such as advanced age or frailty, or disease factors, such as stage or rare histology. (Evidence quality: Moderate; Strength of recommendation: Conditional)

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Clinical Question	Recommendation
6. Among patients treated with NACT, does the timing of ICS, the number of chemotherapy cycles before ICS, or timing in between chemotherapy and ICS affect the safety or efficacy of treatment?	6.1. ICS should be performed after ≤4 cycles of NACT for patients with a response to chemotherapy or stable disease. Alternative timing of surgery has not been prospectively evaluated but may be suggested based on patient-centered factors. (Evidence quality: Low; Strength of recommendation: Conditional)
7. Is there a role for HIPEC at ICS?	7.1. For patients diagnosed with FIGO stage III disease who have good PS, adequate renal function, and treated with NACT, HIPEC may be offered during ICS through a shared decision-making process that considers patient preferences, quality of life, and availability. Participation in HIPEC clinical trials is encouraged. (Evidence quality: Moderate; Strength of recommendation: Conditional)
8. Among patients treated with NACT, what is the recommended number of chemotherapy cycles after ICS?	8.1. For patients treated with NACT, post-ICS chemotherapy (preferably with a platinum-taxane doublet) is recommended. While a total of six cycles of treatment is recommended (NACT plus post-ICS), the exact number of post-ICS chemotherapy cycles may be adjusted based on individual patient factors and response to treatment. The addition of bevacizumab to chemotherapy after sufficient post-surgical healing may be an option. (Evidence quality: High; Strength of recommendation: Strong)
9. Is there a role for maintenance therapy after completion of primary chemotherapy?	9.1. Patients diagnosed with EOC should be offered maintenance treatments that are US FDA-approved under their labeled indication, such as bevacizumab or PARPi, or observation weighing potential for benefit, patient preferences, potential adverse effects, and quality of life. (Evidence quality: Moderate; Strength of recommendation: Strong)
10. What is the management approach for patients who do not have a clinical response to NACT?	10.1. Patients with progressive disease on NACT should have their diagnosis reconfirmed via tissue biopsy, if appropriate. Patients who have not had comprehensive genetic or molecular profiling at the time of diagnosis should be offered testing as soon as possible. (Evidence quality: Moderate; Strength of recommendation: Conditional) 10.2. Treatment options include alternative chemotherapy regimens, clinical trials, and/or discontinuation of active cancer therapy and initiation of end-of-lifecare. In general, there is little role for surgery, and it is not typically advised, unless for palliation (eg, relief of a bowelobstruction). (Evidence quality: Moderate; Strength of recommendation: Strong)

NOTE. The strength of the recommendation is defined as follows. Strong: In recommendations for an intervention, the desirable effects of an intervention outweigh its undesirable effects. In recommendations against an intervention, the undesirable effects of an intervention outweigh its desirable effects. All or almost all informed people would make the recommended choice for or against an intervention. Conditional/weak: In recommendations for an intervention, the desirable effects probably outweigh the undesirable effects, but appreciable uncertainty exists. In recommendations against an intervention, the undesirable effects probably outweigh the desirable effects, but appreciable uncertainty exists. Most informed people would choose the recommended course of action, but a substantial number would not.

Abbreviations: CA-125, cancer antigen 125; CEA, carcinoembryonic antigen; CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; EOC, epithelial ovarian cancer; FDA, US Food and Drug Administration; FDG, fluorodeoxyglucose-18; FIGO, International Federation of Gynecology and Obstetrics; HIPEC, hyperthermic intraperitoneal chemotherapy; ICS, interval cytoreductive surgery; MRI, magnetic resonance imaging; NACT, neoadjuvant chemotherapy; PARPi, poly(ADP-ribose) polymerase inhibitors; PCS, primary cytoreductive surgery; PET, positron emission tomography; PS, performance status.