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Neoadjuvant Chemotherapy for Newly Diagnosed, Advanced Ovarian Cancer: Society of Gynecologic Oncology and American Society of Clinical Oncology Clinical Practice Guideline

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Abstract

Purpose—To provide guidance to clinicians regarding the use of neoadjuvant chemotherapy and interval cytoreduction among women with stage IIIC or IV epithelial ovarian cancer.

Methods—The Society of Gynecologic Oncology and the American Society of Clinical Oncology convened an Expert Panel and conducted a systematic review of the literature.

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Results—Four phase III clinical trials form the primary evidence base for the recommendations. The published studies suggest that for selected women with stage IIIC or IV epithelial ovarian cancer, neoadjuvant chemotherapy and interval cytoreduction are noninferior to primary cytoreduction and adjuvant chemotherapy with respect to overall and progression-free survival and are associated with less perioperative morbidity and mortality.

Recommendations—All women with suspected stage IIIC or IV invasive epithelial ovarian cancer should be evaluated by a gynecologic oncologist prior to initiation of therapy. The primary clinical evaluation should include a CT of the abdomen and pelvis, and chest imaging (CT preferred). Women with a high perioperative risk profile or a low likelihood of achieving cytoreduction to < 1 cm of residual disease (ideally to no visible disease) should receive neoadjuvant chemotherapy. Women who are fit for primary cytoreductive surgery, and with potentially resectable disease, may receive either neoadjuvant chemotherapy or primary cytoreductive surgery. However, primary cytoreductive surgery is preferred if there is a high likelihood of achieving cytoreduction to < 1 cm(ideally to no visible disease) with acceptable morbidity. Before neoadjuvant chemotherapy is delivered, all patients should have confirmation of an invasive ovarian, fallopian tube, or peritoneal cancer. Additional information is available at www.asco.org/NACT-ovarian-guideline and www.asco.org/guidelineswiki.

INTRODUCTION

Nearly 75% of women with ovarian cancer are diagnosed with advanced stage disease (International Federation of Gynecology and Obstetrics [FIGO] IIIC or IV) at presentation. Treatment with primary cytoreductive surgery (PCS) followed by chemotherapy has been the standard of care for these women. Recently, however, two randomized clinical trials (RCTs) compared PCS and chemotherapy to neoadjuvant chemotherapy (NACT) followed by interval cytoreductive surgery (ICS) and adjuvant chemotherapy for women with advanced ovarian cancer.[1,2] These trials demonstrated that NACT was noninferior to PCS with respect to progression-free and overall survival and resulted in a lower incidence of treatment-related morbidity and mortality. However, both trials have been criticized because the median overall survival, mean operative time, and rates of optimal cytoreduction were lower than expected.[3] The choice between PCS and NACT remains controversial. The purpose of this guideline is to provide clinicians with information regarding the use of NACT and interval cytoreduction versus primary cytoreduction and chemotherapy among women with stage IIIC or IV epithelial ovarian cancer.

GUIDELINE QUESTIONS

This clinical practice guideline addresses the following clinical questions: (1) What clinical evaluations should be performed in all women with suspected or newly diagnosed stage IIIC or IV epithelial ovarian cancer? (2) Which patient and disease factors should be used as criteria for identifying patients who are not suitable for PCS? (3) How do NACT and PCS compare with respect to progression-free survival, overall survival, and perioperative morbidity and mortality in women with newly diagnosed stage IIIC or IV epithelial cancer who are fit for primary cytoreduction and have potentially resectable disease, and how should this information be used to select initial treatment? (4) What additional clinical

evaluations should be performed in all women with suspected or newly diagnosed stage IIIC or IV epithelial ovarian cancer before NACT is delivered? (5)What is the preferred chemotherapy regimen for women with stage IIIC or IV epithelial ovarian cancer who will receive NACT? (6) Among women treated with NACT, does the timing of interval cytoreduction or the number of chemotherapy cycles after interval cytoreduction affect the safety or efficacy of treatment? (7)What are the treatment options for patients with progressive disease on NACT?

METHODS

Guideline Development Process

The Expert Panel met four times. The authors were asked to consider the available evidence, contribute to the development of the guideline, provide critical review, and finalize the guideline recommendations. Members of the Expert Panel (Appendix Table A1, online only) were responsible for reviewing and approving the penultimate version of guideline, which was then circulated for external review and submitted to *Gynecologic Oncology* and the *Journal of Clinical Oncology* (*JCO*) for editorial review and consideration for publication. The guideline was also reviewed and approved by the ASCO Clinical Practice Guidelines Committee, SGO Publications, and the SGO Clinical Practice Committees prior to publication.

The recommendations were developed by an Expert Panel with multidisciplinary representation. Panelists were drawn from both community and academic settings, and they included gynecologic oncologists, medical oncologists, and a patient/advocacy representative. Panelists considered evidence from a systematic review of phase III RCTs, meta-analyses, and multicenter cohort studies published between March 20, 2005, and March 20, 2015. A list of search terms is provided in the Data Supplement. Meeting abstracts were included if they provided results from still-unpublished RCTs and were presented at meetings of ASCO, SGO, or the European Society for Medical Oncology (ESMO) from 2010 to 2015.

Articles were selected for inclusion in the systematic review of the evidence based on the following criteria:

- Population: Women with newly diagnosed stage III or stage IV epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer.
- Study type: Evidence regarding the outcomes of NACT was drawn from published or presented 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.

Additional information, including a Data Supplement with additional evidence tables, a Methodology Supplement, slide sets, clinical tools and resources, and links to patient information at www.cancer.net, is available at www.asco.org/NACT-ovarian-guideline and www.asco.org/guidelineswiki.

Articles were excluded from the systematic review if they were editorials, commentaries, letters, news articles, case reports, narrative reviews, or published in a non-English language.

Ratings for the type and strength of the recommendation and the quality of the evidence are provided with each recommendation. The basis for these ratings is described in the Methodology Supplement (www.asco.org/NACT-ovarian-guideline), which also provides details regarding the literature search, data extraction processes, and other aspects of the guideline development. Guideline staff will work with the Expert Panel cochairs to keep abreast of the need for any substantive updates to the guideline. Based on formal review of the emerging literature and input from the Panel, SGO and ASCO will determine the need to update the guideline.

Guideline Disclaimer

The Clinical Practice Guidelines and other guidance published herein are provided by the American Society of Clinical Oncology, Inc. (ASCO) to assist providers 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 provider, as the information does not account for individual variation among patients. Recommendations reflect high, moderate, or low 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 provider in the context of treating the individual patient. Use of the information is voluntary. 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.

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/rwc). All members of the 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 Panel did not disclose any relationships constituting a conflict under the Policy.

RESULTS

Four RCTs met eligibility criteria and form the primary evidence base for the guideline recommendations.[1,2,4,5] At the time that the recommendations were being formulated, two of these trials had been published[1,2] and two were available only as oral presentations from national meetings.[4,5] All four trials enrolled women with stage IIIC or IV epithelial ovarian cancer, but two studies also included women with substage IIIA and IIIb disease,[2,5] and the specific requirements regarding biopsy, imaging, serum, or staging laparoscopy findings varied by study (Table 1). The two published trials provided results for overall and progression-free survival as well as perioperative morbidity and mortality. Secondary analyses of the European Organisation for Research and Treatment of Cancer (EORTC) trial explored survival by patient subset, and evaluated quality of life. Results from the unpublished trials focused on perioperative outcomes.

Elements of study quality were assessed for the two published RCTs with detailed results provided in Data Supplement 1. Factors such as randomization, intention to treat, funding sources, etc. generally indicated a low to intermediate potential risk of bias in each trial. Refer to Methodology Supplement for definitions of quality ratings.

Key results from each RCT are presented in Table 1. In the two published RCTs, NACT was noninferior to PCS with respect to overall and progression-free survival.[1,2] A secondary analysis of the EORTC 55971 trial suggested that outcomes by treatment arm varied by stage of disease and tumor size.[6] Specifically, patients with stage IIIC cancer and less extensive metastatic tumors (≤ 45 mm) had higher survival with PCS than with NACT, and patients with stage IV disease and larger metastatic tumors (> 45 mm) had better survival with NACT than with PCS.[6] In all four RCTs, perioperative morbidity was lower with NACT than with PCS.

Information about prognostic and predictive factors in ovarian cancer was collected from nine multicenter or population-based cohort studies,[7–15] three single-center cohort studies,[16–18] and one meta-analysis.[19] These studies evaluated predictors of optimal cytoreduction, predictors of perioperative morbidity and mortality, and prognostic factors in advanced ovarian cancer with detailed results provided in Data Supplement 2.

RECOMMENDATIONS

An algorithm for the clinical evaluation and treatment of women with suspected stage IIIC or IV epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer is displayed in Figure 1.

CLINICAL QUESTION 1

What clinical evaluations should be performed in all women with suspected or newly diagnosed stage IIIC or IV epithelial ovarian cancer?

Recommendation 1.1—All women with suspected stage IIIC or IV invasive epithelial ovarian cancer should be evaluated by a gynecologic oncologist prior to initiation of therapy to determine whether they are candidates for PCS. (Type: evidence based; benefits outweigh harms; evidence quality: intermediate; strength of recommendation: strong.)

Recommendation 1.2—A primary clinical evaluation should include a CT of the abdomen and pelvis with oral and intravenous contrast and chest imaging (CT preferred) to evaluate the extent of disease and the feasibility of surgical resection. The use of other tools to refine this assessment may include laparoscopic evaluation or additional radiographic imaging (eg, FDG-PET scan or diffusion-weighted MRI). (Type: informal consensus; benefits outweigh harms; evidence quality: intermediate; strength of recommendation: moderate.)

Literature review and analysis: Three multicenter cohort studies[8,10,11] and one meta-analysis[19] evaluated CT findings and/or serum CA-125 predictors of suboptimal cytoreduction (residual disease > 1 cm). The use of CT of the abdomen and pelvis and serum CA-125 as predictors of suboptimal cytoreduction was evaluated among 350 women with stage III or IV ovarian cancer diagnosed from 2001 to 2012.[11] Clinical factors that were associated with suboptimal cytoreduction were age ≥ 60 years, CA-125 ≥ 500 U/mL, and an American Society of Anesthesiologists (ASA) Physical Status classification of 3 or 4 (https://www.asahq.org/resources/clinical-information/asa-physical-status-classification-system). Radiologic predictors of suboptimal cytoreduction were retroperitoneal lymph nodes above the renal hilum (including supradiaphragmatic) > 1 cm, diffuse small bowel adhesions or thickening, small bowel mesentery lesions > 1 cm, root of the superior mesenteric artery lesions > 1 cm, perisplenic lesions > 1 cm, and lesser sac lesions > 1 cm.

CT and clinical predictors of suboptimal cytoreduction were also evaluated among 115 women diagnosed with stage III or IV ovarian cancer diagnosed between 2005 and 2008.[10] Factors that were associated with suboptimal cytoreduction were elevated preoperative blood platelet count (though this result was not statistically significant); diffuse peritoneal thickening, and ascites on at least two-thirds of CT scan slices.

A meta-analysis of 14 studies and 154 additional patients evaluated pretreatment CA-125 as a predictor of suboptimal cytoreduction.[19] High CA-125 (> 500 U/mL) increased the risk of suboptimal cytoreduction (odds ratio, 3.69; 95% CI, 2.02 to 6.73) but had low sensitivity (68.9%) and specificity (63.2%) as a predictor of suboptimal cytoreduction.

Cross-validation of CT predictors of cytoreduction was performed using three cohorts of women with stage III or IV ovarian cancer treated at different institutions.[8] Predictors of suboptimal cytoreduction in the first cohort were diaphragm disease and large bowel mesentery implants. The accuracy of these predictors was 77% in the first cohort but was lower in the other two cohorts (34% and 64%, respectively). The researchers concluded that

the high accuracy rates of CT predictors of suboptimal cytoreduction could not be confirmed in cross validation.

While FDG-PET has the potential to inform operability, there are limited data to inform its use on a routine basis. In one prospective evaluation, compared with CT alone, FDG-PET was significantly better at the detection of carcinomatosis involving the subdiaphragmatic and small bowel peritoneal surfaces but ultimately did not correlate with the extent of surgery required.[17] Whole-body MRI with diffusion-weighted sequence (WB-DWI/MRI) has also been studied in a small group of patients with suspected ovarian cancer for assessing surgical resection. Compared with CT and FDG-PET/CT, WB-DWI/MRI had higher accuracy in detecting peritoneal staging as well as high accuracy in detecting distant metastases.[18]

The safety and findings of staging laparoscopy have been evaluated in both a single-institution study and a multicenter study of women with advanced ovarian cancer.[9,16] Both studies demonstrated that staging laparoscopy is both feasible and safe, and provides a reliable assessment of the extent of the disease burden.

Clinical interpretation: The initial evaluation of a woman with presumed stage IIIC/IV ovarian carcinoma should focus on whether she is a candidate to undergo PCS with acceptable risks and associated morbidity. A gynecologic oncologist has specialized in the surgical and medical management of gynecologic malignancies and is trained to perform the surgery needed to manage women with ovarian cancer and to understand the risks and complications associated with such therapeutic procedures. Studies have shown that women with ovarian cancer who are treated by a gynecologic oncologist are more likely to undergo proper staging, cytoreductive surgery, and receive adjuvant chemotherapy, compared with gynecologists and general surgeons, and have superior survival.[20–22] The complex surgery needed to achieve resection of all visible disease completely or at least to < 1 cm is more likely to occur when the surgery is performed at hospitals with specialists who perform these procedures frequently.[23–26] Given that residual tumor still serves as the most important predictor of overall survival, the initial decision about surgery requires the input of a gynecologic oncologist.

CLINICAL QUESTION 2

Which patient and disease factors should be used as criteria for identifying patients who are not suitable for PCS?

Recommendation 2.1—Women who have a high perioperative risk profile or a low likelihood of achieving cytoreduction to < 1 cm (ideally to no visible disease) should receive NACT. (Type: evidence based; benefits outweigh harms; evidence quality: intermediate; strength of recommendation: moderate.)

Recommendation 2.2—Decisions that women are not eligible for medical or surgical cancer treatment should be made after a consultation with a gynecologic oncologist and/or a medical oncologist with gynecologic expertise. (Type: informal consensus; benefits outweigh harms; evidence quality: intermediate; strength of recommendation: moderate.)

Literature review and analysis: Population-based or multicenter cohort studies evaluated risk factors for high perioperative morbidity and mortality or for poor overall survival after primary cytoreduction. Using SEER-Medicare data, Thrall et al[12] analyzed data from more than 5,000 women age 65 years or older who had undergone cytoreductive surgery for advanced ovarian cancer. Overall 30-day mortality was 8%. Among women with elective admissions and no NACT, 30-day mortality varied by age, cancer stage, and comorbidity. Older women (age ≥ 75 years) who had stage III disease and a modified Charlson comorbidity score of ≥ 1 or stage IV disease had higher 30-day mortality. These patients accounted for 26% of patients and roughly half of the deaths, with a 30-day mortality of 13%. A low-risk group consisted of younger patients (age 65 to 74 years) with either stage III or stage IV disease and a comorbidity score of ≤ 1. These patients accounted for 49% of the patient population and had a 30-day mortality of 4%. The authors noted that these results require confirmation from prospective investigation.

Wright et al[14] examined perioperative morbidity and mortality among more than 28,000 women diagnosed with ovarian cancer who underwent surgery between 1998 and 2007 using the Nationwide Inpatient Sample. Overall, perioperative morbidity was 17% among women under the age of 50 years, but it rose to 30% among women age 70 to 79 years and 32% among women age 80 years or older. In multivariable models, rates of surgical site complications, medical complications, infectious complications, and death increased with age, the number of radical procedures, and the Charlson comorbidity index.

Patient and tumor factors also contributed to 30-day morbidity in another study, which examined 564 women who underwent surgery for stage III or stage IV cancer from 1994 to 2003.[7] In a multivariate analysis, factors that were associated with an increased risk of 30-day morbidity included: increasing age, an ASA score of 3 or 4, low albumin (< 3.5 g/dL), a higher surgical complexity score, and stage IV disease. Older age and an ASA score of 3 or 4 were also associated with higher 3-month mortality.

General prognostic factors in advanced ovarian cancer were evaluated in a study of 1,895 women with stage III ovarian cancer treated with primary cytoreduction and chemotherapy.[13] Independent predictors of mortality were older age, worse Gynecologic Oncology Group (GOG) performance status, residual disease, and histology (compared with serous tumors, mortality was lower with endometrioid tumors and higher with clear cell and mucinous tumors).

Clinical interpretation: Factors that have been studied and shown to increase the risk of morbidity associated with cytoreductive surgery include advanced age or frailty, multiple chronic conditions, poor nutritional status, low albumin, and newly diagnosed venous thromboembolism (Table 2). Recent studies have focused on using tools to assess the patient's functional age and frailty status, which can better predict the risk of morbidity.[27,28] Additionally a surgical risk calculator based on the American College of Surgeons NSQIP database has been developed to predict surgical complications (http://www.riskcalculator.facs.org/). However, a recent study in a gynecologic oncology population demonstrated that the calculator was able to predict the risk of death and cardiac complications, but was not accurate for other surgical complications.[29] The SGO/ASCO

Panel looks forward to reviewing validated and tested, user-friendly risk prediction tools when they are available, but at present, none can be fully recommended.

After assessing the patient's status to undergo cytoreductive surgery, an assessment of resectability of the cancer to < 1 cm (ideally to no visible disease) must be performed. Baseline imaging with a CT scan of the abdomen and pelvis and chest imaging (CT preferred) serves as the standard initial assessment of disease distribution and the initial evaluation of feasibility of resection. Women who have evidence of disease that has spread to the lungs or mediastinum, unresectable parenchymal liver metastasis, bulky periportal lymph nodes, mesenteric retraction, or nonresectable extra abdominal lymph nodes are best treated with initial NACT. While the goal for primary surgery should be resection to no visible disease, maximal cytoreduction to < 1 cm still provides benefit,[30] including the option of receiving intraperitoneal and intravenous (IP/IV) chemotherapy, which has a demonstrated survival benefit compared with intravenous (IV) chemotherapy.[31] Women with a low likelihood of achieving cytoreduction to < 1 cm (ideally to no visible disease), due to disease distribution, should receive NACT.

At present there are no prospectively validated nonoperative tools to predict the likelihood of maximal cytoreduction to < 1 cm or no visible disease. CT imaging may underestimate the distribution of disease, and therefore may have limitations for predicting which women can achieve surgical cytoreduction to < 1 cm (ideally to no visible disease). Alternative imaging modalities including WB-DWI/MRI and/or positron emission tomography have also been suggested to be useful in evaluating the extent of disease, but they require further evaluation before being recommended. More recently, the use of diagnostic laparoscopy has been suggested as a modality to better assess tumor distribution and predict surgical resection to a goal of no visible postoperative tumor or residuum. Some centers have demonstrated external validity using laparoscopic evaluation of tumor distribution for this purpose. In a randomized trial from the Netherlands, Buist et al[32] reported that laparoscopy was of additive value to predict the outcome of PCS and to prevent futile laparotomies. However, at present, the role of laparoscopy is still undefined as there are insufficient published data to suggest that it is more accurate than clinical or radiologic studies. A Cochrane review of multiple trials did not show a decrease in the rates of women undergoing a suboptimal debulking surgery when laparoscopy was used in the triage of a patient with ovarian cancer; however, the authors noted that no women (who might achieve maximal cytoreduction to < 1 cm or no visible disease) were excluded from having cytoreductive surgery.[33]

CLINICAL QUESTION 3

How do NACT and PCS compare with respect to progression-free survival, overall survival, and perioperative morbidity and mortality in women with newly diagnosed stage IIIC or IV epithelial ovarian cancer who are fit for primary cytoreduction and have potentially resectable disease, and how should this information be used to select initial treatment?

Recommendation 3.1—For women who are fit for PCS, with potentially resectable disease, either NACT or PCS may be offered based on data from phase III RCTs that demonstrate that NACT is noninferior to PCS with respect to progression-free and overall

survival. NACT is associated with less peri- and postoperative morbidity and mortality and shorter hospitalizations, but PCS may offer superior survival in selected patients. (Type: evidence based; benefits outweigh harms; evidence quality: intermediate; strength of recommendation: moderate.)

Recommendation 3.2—For women with a high likelihood of achieving a cytoreduction to < 1 cm (ideally to no visible disease) with acceptable morbidity, PCS is recommended over NACT. (Type: evidence based; benefits outweigh harms; evidence quality: intermediate; strength of recommendation: moderate.)

Recommendation 3.3—For women who are fit for PCS but are deemed unlikely to have cytoreduction to < 1 cm (ideally to no visible disease) by a gynecologic oncologist, NACT is recommended over PCS. NACT is associated with less peri- and postoperative morbidity and mortality and shorter hospitalizations. (Type: evidence based; benefits outweigh harms; evidence quality: intermediate; strength of recommendation: moderate.)

Literature review and analysis: Four randomized clinical trials—EORTC 55971, CHORUS, JCOG0602, and SCORPION—have compared NACT and interval cytoreduction with primary cytoreduction and chemotherapy among women with stage IIIC or IV epithelial ovarian cancer (CHORUS and JCOG0602 also included women with stage IIIA and stage IIIB disease).

In EORTC 55971,[1] 670 women were randomly assigned to either PCS followed by at least six cycles of platinum-based chemotherapy or to three cycles of neoadjuvant platinum-based chemotherapy, followed by interval cytoreduction in those who had a response to chemotherapy or stable disease, followed by at least three cycles of platinum-based chemotherapy. Among women in the primary cytoreduction arm, 94% underwent primary cytoreduction and 88% started chemotherapy. Among women in the NACT arm, 98% started NACT and 88% underwent interval cytoreduction. Residual tumor of 1 cm or less was achieved in 42% of patients in the primary cytoreduction arm and in 81% of patients in the NACT arm. In the intent-to-treat analysis, the NACT arm was noninferior to the PCS arm with respect to the primary outcome of overall survival (Table 1). Perioperative morbidity and mortality were numerically lower in the NACT arm. In a subset analysis, patients with stage IIIC cancer and less extensive metastatic tumors (≤ 45 mm) had higher survival with PCS than with NACT, and patients with stage IV disease and larger metastatic tumors (> 45 mm) had better survival with NACT than with PCS.[6] Patients outside of these two subgroups had similar survival with either NACT or PCS.

In the CHORUS trial,[2] 550 women were randomly assigned to either PCS followed by six cycles of platinum-based chemotherapy or to three cycles of NACT, followed by interval cytoreduction, followed by three courses of platinum-based chemotherapy. Of the 276 women in the PCS arm, 91% underwent surgery and 77% started postoperative chemotherapy. Of the 274 women in the NACT arm, 92% received NACT and 79% underwent interval cytoreduction. Cytoreduction to < 1 cm residual disease was achieved in 41% of patients in the PCS arm and 73% of patients in the NACT arm ($P = 0.0001$). The NACT arm was noninferior to the PCS arm with respect to the primary outcome of overall

survival (Table 1). Postoperative mortality and serious (grade 3 or 4) postoperative adverse events were less common in the NACT arm than in the PCS arm. The frequency of serious chemotherapy-related adverse events was not statistically significantly different in the two study arms.

The SCORPION trial examined perioperative outcomes for 55 women assigned to PCS and 52 women assigned to NACT, all of whom had a significant upper abdominal disease burden.[34] Complete cytoreduction was achieved in 58% of women in the NACT arm and 46% of women in the primary cytoreduction arm, with a shorter median operative time in the neoadjuvant arm (Table 1). The frequency of upper abdominal procedures and major postoperative complications was lower in the neoadjuvant arm, as was the length of hospital stays.

Data from JCOG0602 were presented at the 2014 ASCO Annual Meeting.[5] Three hundred and one women were randomly assigned to either PCS followed by eight cycles of carboplatin and paclitaxel or to NACT with four cycles of carboplatin and paclitaxel followed by interval cytoreduction, followed by four more cycles of paclitaxel and carboplatin. Operative time during surgery was longer in the NACT arm than in the PCS arm, but patients in the NACT arm experienced less blood loss and ascites during or after surgery, and were less likely to experience a grade 3 or grade 4 nonhematologic adverse events after surgery (Table 1).

One significant limitation of NACT, compared with PCS, is that there are insufficient data to support the use of IP/IV chemotherapy as adjuvant treatment after NACT. Several RCTs have demonstrated that IP/IV chemotherapy improves survival in optimally resected, stage III ovarian cancer, compared with IV chemotherapy alone.[31,35,36] In GOG 172, women who received IP/IV chemotherapy had a 16-month improvement in median overall survival, compared with women treated with IV chemotherapy alone.[31]

Clinical interpretation: To date, the EORTC and CHORUS studies are the only published randomized phase III trials to compare NACT and PCS. In both studies the median progression-free and overall survival were similar among women who received NACT followed by ICS and those who underwent PCS followed by chemotherapy. However, critics of these trials have noted that both had a shorter median overall survival than what has been reported in previous studies. Prior phase III clinical trials have reported median overall survival times of 45 to 66 months in women who undergo PCS with < 1 cm of residual disease, while the median overall survival was only 32 months and 44 months in patients with < 1 cm residual and no residual disease, respectively, after PCS in the EORTC study. Additionally, some have argued that the “surgical effort” in both EORTC and CHORUS may be lower than the standard of care since the median operative times and rates of upper abdominal surgeries were lower than expected in clinical practice and much lower than what was reported in the SCORPION and JCOG0602 trials.

Alternatively, the lower median overall survival reported in the EORTC and CHORUS trials may reflect the population of patients who were willing to be randomly assigned to a trial comparing PCS and NACT and who had clear evidence of advanced-stage disease based on

imaging only. The short survival results may reflect the trial participants, rather than differences in treatment, which included a population of patients who were older, with a poorer performance status, and had higher stage tumors compared with other trials. Observational studies examining women > 65 years of age in the SEER-Medicare database had median survivals that were similar to the EORTC and CHORUS trial participants.[37,38] In addition, nearly 25% of the patients enrolled in the CHORUS trial received single-agent carboplatin instead of a platinum-based doublet in both the PCS and neoadjuvant arms. Together, these results suggest that PCS and NACT have similar results in this patient population, but it remains to be seen whether these results apply to populations of patients who are younger, have better performance statuses, or have less bulky disease in light of the data from an exploratory subset analysis of EORTC, which showed that patients with less extensive tumors (≤ 45 mm) had better survival with PCS compared with NACT.[6]

The extent of residual disease after PCS is a significant prognostic predictor in ovarian cancer reviews.[30,39] A recent meta-analysis of studies evaluating survival among patients undergoing PCS for advanced ovarian cancer demonstrated a significant survival advantage associated with patients who had no gross visible disease after surgery; each 10% increase in cytoreduction to no visible disease was associated with a 2.3 month increase in median survival.[39] It is unclear whether the extent of residual disease reflects tumor biology, surgical aggressiveness, or both, but PCS to < 1 cm (ideally no visible disease) remains one of the most significant predictors of survival. Therefore, PCS is recommended for those patients with a high likelihood of achieving a cytoreduction to < 1 cm (ideally no visible disease) with acceptable morbidity.

CLINICAL QUESTION 4

What additional clinical evaluations should be performed in all women with suspected or newly diagnosed stage IIIC or IV epithelial ovarian cancer before NACT is delivered?

Recommendation 4—Before NACT is delivered, all patients should have histologic confirmation (core biopsy 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 carcinoembryonic antigen (CEA) ratio > 25 is acceptable to confirm the primary diagnosis and exclude cancers that are not ovarian, fallopian tube, or primary peritoneal carcinomas (Type: informal consensus; benefits outweigh harms; evidence quality: intermediate; strength of recommendation: moderate.)

Literature review and analysis: The frequency of other nonovarian cancers was described in both the EORTC and CHORUS trials. In the EORTC trial, eligible patients had to have either biopsy-proven stage IIIC or IV invasive epithelial ovarian cancer, primary peritoneal cancer, or fallopian tube cancer, or fine-needle aspirate showing adenocarcinoma in a patient with a pelvic mass, metastases outside the pelvis of at least 2 cm in diameter, regional lymph node metastasis, or proof of stage IV disease, and a CA-125 to CEA ratio of > 25.[1] If the CA-125 to CEA ratio was 25 or lower, patients had to have a barium enema or colonoscopy, gastroscopy or radiologic examination of the stomach, and mammography to exclude presence of an alternate primary tumor. Using these criteria, the incidence of other

malignancies was 3%, with 18 of 670 randomized patients having a change in diagnosis after cytoreductive surgery.

In the CHORUS trial, participants had clinical or radiographic evidence of a pelvic mass with extrapelvic disease compatible with FIGO 1988 stage III or IV ovarian, fallopian tube, or primary peritoneal cancer, and a CA-125 to CEA ratio > 25.[2] If the CA-125 to CEA ratio was < 25, a gastrointestinal carcinoma had to be excluded. For women assigned to NACT, the diagnosis was confirmed by laparoscopy, biopsy, or cytology. Among the 474 study participants who had surgery, 3% were found to have a nonovarian cancer.

Clinical interpretation: A central tenet of oncology is that pathology should be obtained before treatment is initiated to confirm that a malignancy is present, to identify the site of origin, and to plan optimal treatment since malignancies are treated differently based upon their site of origin. Thus, all patients must have a histologic or cytologic evaluation (core biopsy preferred) to confirm the primary diagnosis of an invasive ovarian, fallopian tube, or primary peritoneal cancer and exclude other primaries before receiving chemotherapy. In addition, data on inherited mutations (eg, germline *BRCA*), cell surface proteins (eg, PD-L1), and the tumor microenvironment are beginning to be used for treatment selection and clinical trial enrollment [eg, poly (ADP-ribose) polymerase (PARP) inhibitors, immunotherapy]. The panel expects that this information will become increasingly important with time, and thus recommends obtaining a core biopsy prior to treatment to perform immunohistochemistry to verify the diagnosis and site of origin since cytology may be insufficient to distinguish between borderline and invasive cancer cells, and tumor cells may be too necrotic to identify after exposure to chemotherapy.

CLINICAL QUESTION 5

What is the preferred chemotherapy regimen for women with stage IIIC or IV epithelial ovarian cancer who will receive NACT?

Recommendation 5—For NACT, a platinum/taxane doublet is recommended. However, alternate regimens, containing a platinum agent, may be selected based on individual patient factors. (Type: evidence based; benefits outweigh harms; evidence quality: intermediate; strength of recommendation: moderate.)

Literature review and analysis: Since the publication of GOG 111, GOG 158, and AGO-OVAR3,[40–42] the standard of care for first-line treatment of advanced ovarian cancer has been six cycles of carboplatin and paclitaxel. In the EORTC trial, 83% of patients received treatment with a combination of carboplatin and paclitaxel delivered every 3 weeks. However, only 76% of CHORUS participants received both carboplatin and paclitaxel; nearly 24% were treated with single-agent carboplatin. Alternate regimens were used rarely in both trials: 6.3% of participants in EORTC and 1% in CHORUS received another chemotherapy combination. Information on the use of specific chemotherapy regimens in the JCOG0602 or SCORPION trials is limited.

Clinical interpretation: Treatment of advanced ovarian cancer has evolved over the past decade. Several large phase III studies have demonstrated improved survival with alternate

treatment strategies, including IP/IV chemotherapy,[31] dose-dense paclitaxel,[43] and the addition of bevacizumab for patients with inoperable or sub-optimally cytoreduced disease.[44] To date, randomized trials of NACT have tested an every-3-week regimen of IV carboplatin and paclitaxel. At some institutions, clinicians have replaced the 3-week administration of paclitaxel with the "dose-dense" weekly approach in light of the superior survival demonstrated in JGOG 3016.[43] Similarly, in GOG 262, which compared carboplatin and weekly paclitaxel to carboplatin and paclitaxel every 3 weeks (with administration of bevacizumab at the discretion of the treating physician, but delivered to 84% of patients), patients who received weekly paclitaxel had a similar progression-free survival to those who received carboplatin and paclitaxel with bevacizumab every 3 weeks in the intent-to-treat analysis.[45] In the 112-patient cohort in whom bevacizumab was not used, patients receiving weekly paclitaxel (n = 55) had a significantly longer median PFS (14.2 *v* 10.3 months; HR, 0.62; 95% CI, 0.40 to 0.95). In the MITO-7 trial, however, weekly administration of lower doses of carboplatin and paclitaxel was not superior to administration of carboplatin and paclitaxel every 3 weeks.[46] Thus, the use of weekly paclitaxel for NACT should be formally tested in future clinical trials.

At many institutions, patients who receive NACT are not treated with IP/IV chemotherapy after ICS. At present, data on the use of IP/IV chemotherapy after NACT and ICS is limited. A phase II Southwest Oncology Group Study examined the use of IP/IV chemotherapy after NACT and ICS in a group of patients with bulky stage III/IV (pleural effusion only) ovarian cancer for whom optimal cytoreduction was thought to be unlikely on radiographic imaging. Among 58 eligible patients, only 26 patients received NACT, ICS, and postoperative IP/IV chemotherapy; in this group, the median progression free and overall survival were 29 and 34 months, respectively.[47] Another ongoing multinational randomized phase II study, PETROC/OV21, is comparing IP/IV carboplatin and paclitaxel versus continued treatment with IV carboplatin and paclitaxel among women who received NACT and optimal ICS.[48] This trial was originally designed as a phase II/III clinical trial, but was later modified to a randomized phase II trial due to poor accrual. Nevertheless, in an interim analysis, reported in abstract form, IP/IV chemotherapy was found to be both feasible and safe to use after NACT.[49] A comparison of the rates of progression-free survival at 9 months (the new primary end point of the trial) showed 42.2% of women randomized to receive IV chemotherapy had progressive disease, compared with 23.3% of those who received IP/IV chemotherapy. While these studies suggest that it is feasible and safe to use IP/IV chemotherapy after optimal ICS, there are insufficient data about the efficacy of this approach to make a formal recommendation either for or against the use of IP/IV chemotherapy after NACT at this time.

CLINICAL QUESTION 6

Among women treated with NACT, does the timing of ICS or the number of chemotherapy cycles after ICS affect the safety or efficacy of treatment?

Recommendation 6—RCTs tested surgery following three or four cycles of chemotherapy in women who had a response to NACT or stable disease. ICS should be performed after ≤ 4 cycles of NACT for women with a response to chemotherapy or stable

disease. Alternate timing of surgery has not been prospectively evaluated but may be considered based on patient-centered factors. (Type: informal consensus; benefits outweigh harms; evidence quality: insufficient; strength of recommendation: weak.)

Literature review and analysis: RCTs have not addressed whether the timing of ICS or the number of chemotherapy cycles after ICS affect the safety or efficacy of treatment. In both the EORTC 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, but survival data from this trial are not expected until 2017.

Rates of cytoreduction to < 1 cm (and no visible disease) are higher among patients treated with NACT, compared with PCS, but have less prognostic significance.[1] Böhm et al[15] have developed and validated the three-tier Chemotherapy Response Score as a simple, prognostically significant, and reproducible system for grading the response to NACT using ICS specimens. This three-tier scoring system, which uses pathologists' ratings of the most viable residual disease present in the omentum at ICS (where lower scores indicate poor response to NACT and higher scores indicate good response), predicted PFS and sensitivity to first-line platinum in analyses that adjusted for age, stage, and debulking status.

Clinical interpretation: Patients' responses to NACT should be regularly monitored with clinical assessments and routine measurement of CA-125 each cycle and radiographic imaging should be performed early (preferentially after three cycles of chemotherapy) to assess clinical response. To date, phase III studies have only tested surgery after ≤ 4 cycles of chemotherapy, and alternate timing has not been prospectively evaluated. Future studies should validate the Chemotherapy Response Score in prospective RCTs, and explore whether it can be used to risk-stratify patients for additional treatment.

CLINICAL QUESTION 7

What are the treatment options for patients with progressive disease on NACT?

Recommendation 7—Patients with progressive disease on NACT have a poor prognosis. Options include alternative chemotherapy regimens, clinical trials, and/or discontinuation of active cancer therapy and initiation of end-of-life care. In general, there is little role for surgery and it is not typically advised, unless for palliation (eg, relief of a bowel obstruction). (Type: evidence based; benefits outweigh harms; evidence quality: intermediate; strength of recommendation: strong.)

Literature review and analysis: Women who develop progressive disease during first-line treatment with chemotherapy (ie, platinum-refractory disease) have a poor prognosis with a median overall survival of < 1 year, and often shorter.[50] RCTs have not compared treatment options for women who develop progressive disease during NACT. However, if treatment with further chemotherapy is appropriate, then use of agents that do not have cross-resistance to carboplatin or paclitaxel (eg, gemcitabine, pegylated liposomal doxorubicin, or bevacizumab) would be recommended.

Clinical interpretation: Patients who develop progressive disease during neoadjuvant chemotherapy 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, palliative chemotherapy with alternate agents, and/or discontinuation of active cancer therapy and initiation of end-of-life care.

PATIENT AND CLINICIAN COMMUNICATION

For women with advanced ovarian cancer, decision-making regarding first-line treatment should be a process that is shared between clinicians and their patients.[51] 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. 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.

For patients faced with a decision between PCS and NACT, it is essential that providers first explain the diagnosis, including the extent of disease identified, stage, and prognostic implications of what is known. Only by ensuring a common starting point can each discuss and ultimately decide on a treatment plan. For women in whom the choice is between NACT and PCS, 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.

HEALTH DISPARITIES

Although ASCO and SGO clinical practice guidelines represent expert recommendations on the best practices in disease management to provide the highest level of cancer care, it is important to note that many patients have limited access to medical care. Racial and ethnic disparities in health care contribute significantly to this problem in the United States. Patients with cancer who are members of racial/ethnic minorities suffer disproportionately from comorbidities, experience more substantial obstacles to receiving care, are more likely to be uninsured, and are at greater risk of receiving care of poor quality than other Americans. Many other patients lack access to care because of their geographic location and distance from appropriate treatment facilities. Awareness of these disparities in access to care should be considered in the context of this clinical practice guideline, and health care providers should strive to deliver the highest level of cancer care to these vulnerable populations.

Older women with ovarian cancer also receive less surgery and chemotherapy than younger women, suffer worse toxicity, and have worse overall survival. Performance status alone has been shown to be an inadequate tool to predict toxicity in older patients from therapy. Use of formal geriatric assessment tools is a promising direction for risk-stratifying older patients on trials.[52] The GOG elderly group recently completed two important trials: (1) the first prospective trial of first-line chemotherapy in an older patient population in the United

States (comparing dose-modified carboplatin, carboplatin/paclitaxel, and carboplatin/weekly paclitaxel), and (2) a geriatric preoperative assessment tool to predict surgical morbidity. Both studies included patients who received NACT. Once published, these results will further guide clinicians in the treatment of older women with ovarian cancer.

MULTIPLE CHRONIC CONDITIONS

Creating evidence-based recommendations to inform treatment of patients with additional chronic conditions, a situation in which the patient may have two or more such conditions—referred to as multiple chronic conditions (MCC)—is challenging. Patients with MCC are a complex and heterogeneous population, making it difficult to account for all of the possible permutations to develop specific recommendations for care. In addition, the best available evidence for treating index conditions, such as cancer, is often from clinical trials whose study selection criteria may exclude these patients to avoid potential interaction effects or confounding of results associated with MCC. As a result, the reliability of outcome data from these studies may be limited, thereby creating constraints for expert groups to make recommendations for care in this heterogeneous patient population.

As many patients for whom guideline recommendations apply present with MCC, any treatment plan needs to take into account the complexity and uncertainty created by the presence of MCC and highlights the importance of shared decision making regarding guideline use and implementation. Therefore, in consideration of recommended care for the target index condition, clinicians should review all other chronic conditions present in the patient and take those conditions into account when formulating the treatment and follow up plan.

COST IMPLICATIONS

Decisions between PCS and NACT should be driven by the expected clinical risks and benefits rather than by cost. Nevertheless, cost may warrant consideration when the two treatment options appear similarly beneficial, or when cost is an important concern for the patient. The comparative cost of PCS and NACT has been evaluated using observational data from SEER-Medicare. Among 4,506 older women with advanced ovarian cancer, the costs associated with PCS and NACT were similar for women with stage IIIC disease, but PCS was associated with higher costs in women with stage IV disease.[53] The cost of care among older women (age ≥ 65 years) with advanced ovarian cancer has also been evaluated using a 5-year Markov model, which assumed similar overall survival with PCS and NACT based upon the results of EORTC 55971.[54] In this study, NACT was associated with a cost savings of $5,616 compared with PCS, when costs included surgery, chemotherapy, and hospital stays. To date, researchers have not included quality-adjusted life-years in comparisons of the costs between PCS and NACT. Given the limitations of current data, the relative costs of the two treatment approaches remain uncertain.

EXTERNAL REVIEW

The draft was submitted to two external reviewers with content expertise in medical and gynecologic oncology. Revisions made in response to the external reviews were reviewed and approved by the Expert Panel.

GUIDELINE IMPLEMENTATION

ASCO guidelines are developed for implementation across health settings. Barriers to implementation include the need to increase awareness of the guideline recommendations among front-line practitioners and survivors of cancer and caregivers, and to provide adequate services in the face of limited resources. The guideline Bottom Line Box was designed to facilitate implementation of recommendations. This guideline will be distributed widely through the ASCO Practice Guideline Implementation Network. ASCO guidelines are posted on the ASCO Web site and most often published in the *Journal of Clinical Oncology* and the *Journal of Oncology Practice*.

FUTURE DIRECTIONS

There are several areas that the panel agreed required future study, including:

- Development and validation of a preoperative risk prediction model to identify patients who are at high risk of morbidity from PCS
- Optimized selection criteria to determine whether an R0 resection is feasible with PCS based upon radiographic imaging and/or laparoscopic findings
- Examination of the value of functional imaging (eg, perfusion CT, dynamic MRI, PET-CT) in risk-stratifying patients for PCS versus NACT
- Prospective validation of the Chemotherapy Response Score in RCTs, and an exploration of whether it can be used to risk-stratify patients for future therapies after completion of adjuvant chemotherapy
- Determination of benchmarks for clinical complete remission rate, pathologic complete remission rate, and progression-free survival in patients treated with NACT to facilitate the design of clinical trials in this population
- Exploration of novel agents in the NACT setting (eg, targeted therapies, immunotherapy, vaccines, and cancer stem-cell–directed treatments) with or without chemotherapy
- Determination of whether there is a role for IP/IV chemotherapy in the setting of NACT
- Prospective study of weekly dose-dense paclitaxel versus every-3-week paclitaxel in the setting of NACT
- Prospective study to determine the ideal timing of ICS and the number of cycles of chemotherapy delivered before and after surgery

- Performance of a large, pragmatic, randomized clinical trial of PCS versus NACT in the United States since the median overall survival, mean operative time, and rates of optimal cytoreduction in existing trials were lower than expected
- Development of an ASCO Value in Cancer Care Framework for NACT.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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THE BOTTOM LINE

Guideline Question

To provide guidance to clinicians and patients regarding the use of neoadjuvant chemotherapy (NACT) and interval cytoreduction among women with advanced epithelial ovarian cancer.

Target Population

Women with newly diagnosed or suspected stage IIIC or IV epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer.

Target Audience

Gynecologic and medical oncologists and women with advanced ovarian cancer.

Methods

An Expert Panel was convened to develop clinical practice guideline recommendations based on a systematic review of the medical literature.

Key Points

Recommendation 1.1. All women with suspected stage IIIC or IV invasive epithelial ovarian cancer should be evaluated by a gynecologic oncologist prior to initiation of therapy to determine whether they are candidates for primary cytoreductive surgery (PCS). (Type: evidence based; benefits outweigh harms; evidence quality: intermediate; strength of recommendation: strong.)

Recommendation 1.2. A primary clinical evaluation should include a computed tomography (CT) scan of the abdomen and pelvis with oral and intravenous contrast and chest imaging (CT preferred) to evaluate the extent of disease and the feasibility of surgical resection. The use of other tools to refine this assessment may include laparoscopic evaluation or additional radiographic imaging (eg, [^{18}F]fluorodeoxyglucose positron-emission tomography [FDG-PET] scan or diffusion-weighted magnetic resonance imaging [MRI]). (Type: informal consensus; benefits outweigh harms; evidence quality: intermediate; strength of recommendation: moderate.)

Recommendation 2.1. Women who have a high perioperative risk profile or a low likelihood of achieving cytoreduction to < 1 cm (ideally to no visible disease) should receive NACT. (Type: evidence based; benefits outweigh harms; evidence quality: intermediate; strength of recommendation: moderate.)

Recommendation 2.2. Decisions that women are not eligible for medical or surgical cancer treatment should be made after a consultation with a gynecologic oncologist and/or a medical oncologist with gynecologic expertise. (Type: informal consensus; benefits outweigh harms; evidence quality: intermediate; strength of recommendation: moderate.)

Recommendation 3.1. For women who are fit for PCS, with potentially resectable disease, either NACT or PCS may be offered based on data from phase III RCTs that demonstrate that NACT is noninferior to PCS with respect to progression-free and overall survival. NACT is associated with less peri- and postoperative morbidity and mortality and shorter hospitalizations, but PCS may offer superior survival in selected patients. (Type: evidence based; benefits outweigh harms; Evidence quality: intermediate, Strength of recommendation: moderate)

Recommendation 3.2. For women with a high likelihood of achieving cytoreduction to < 1 cm (ideally to no visible disease disease) with acceptable morbidity, PCS is recommended over NACT. (Type: evidence based; benefits outweigh harms; evidence quality: intermediate; strength of recommendation: moderate.)

Recommendation 3.3. For women who are fit for PCS but are deemed unlikely to have cytoreduction to < 1 cm (ideally to no visible disease) by a gynecologic oncologist, NACT is recommended over PCS. NACT is associated with less peri- and postoperative morbidity and mortality and shorter hospitalizations. (Type: evidence based; benefits outweigh harms; evidence quality: intermediate; strength of recommendation: moderate.)

Recommendation 4. Before NACT is delivered, all patients should have histologic confirmation (core biopsy 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 carcinoembryonic antigen (CEA) ratio > 25 is acceptable to confirm the primary diagnosis and exclude a nongynecologic cancer. (Type: informal consensus; benefits outweigh harms; evidence quality: intermediate; strength of recommendation: moderate.)

Recommendation 5. For NACT, a platinum/taxane doublet is recommended. However, alternate regimens, containing a platinum agent, may be selected based on individual patient factors. (Type: evidence-based, benefits outweigh harms; evidence quality: intermediate; strength of recommendation: moderate.)

Recommendation 6. RCTs tested surgery following three or four cycles of chemotherapy in women who had a response to NACT or stable disease. Interval cytoreductive surgery should be performed after ≤ 4 cycles of NACT for women with a response to chemotherapy or stable disease. Alternate timing of surgery has not been prospectively evaluated but may be considered based on patient-centered factors. (Type: informal consensus; benefits outweigh harms; evidence quality: insufficient; strength of recommendation: weak.)

Recommendation 7. Patients with progressive disease on NACT have a poor prognosis. Options include alternative chemotherapy regimens, clinical trials, and/or discontinuation of active cancer therapy and initiation of end-of-life care. In general, there is little role for surgery and it is not typically advised, unless for palliation (eg, relief of a bowel obstruction). (Type: evidence-based; benefits

outweigh harms; evidence quality: intermediate; strength of recommendation: strong.)

Additional Resources

More information, including a Data Supplement with additional evidence tables, a Methodology Supplement with information about evidence quality and strength of recommendations, slide sets, and clinical tools and resources, is available at www.asco.org/NACT-ovarian-guideline and www.asco.org/guidelineswiki. Patient information is available at www.cancer.net.

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

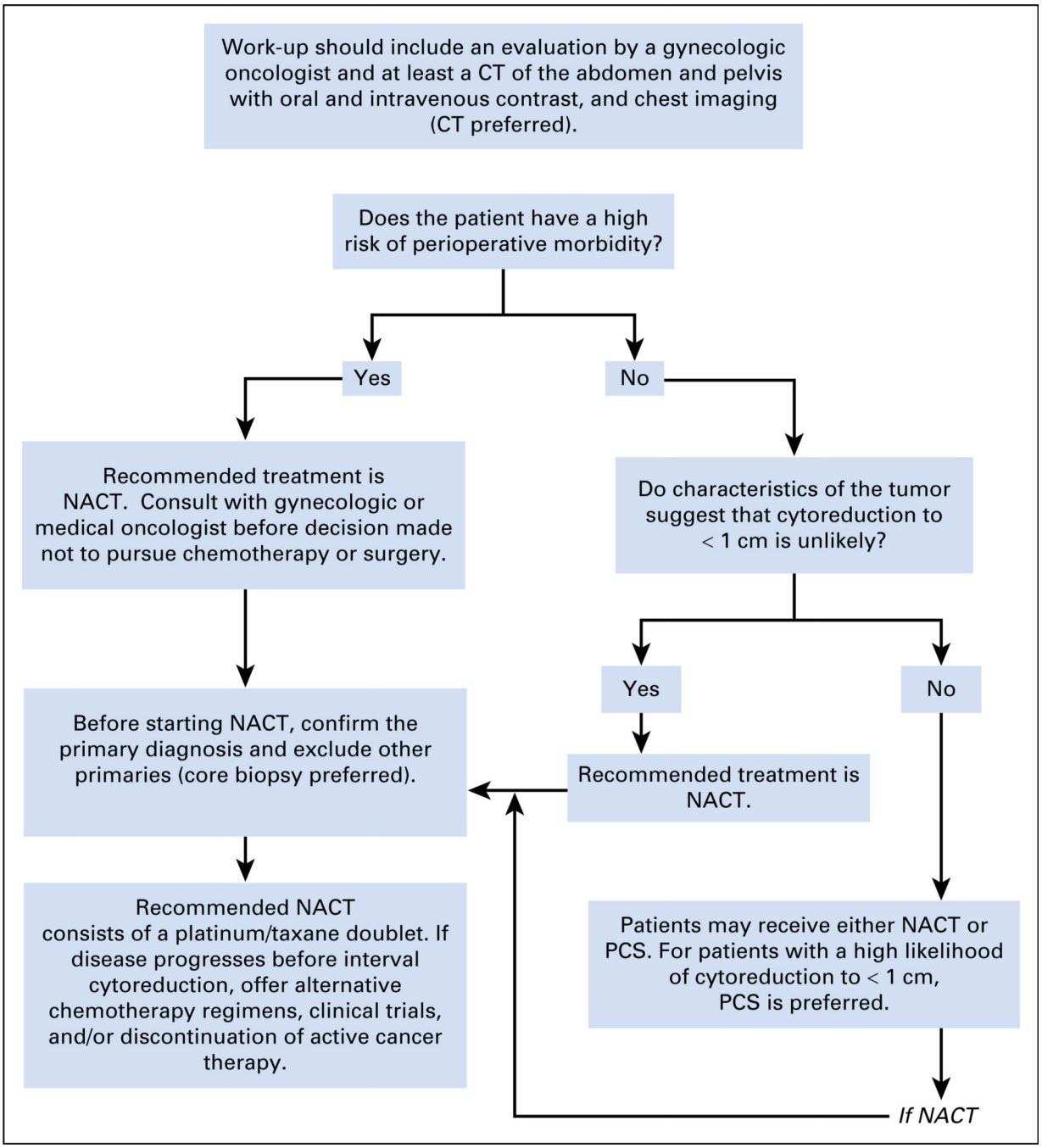

Fig 1.

Algorithm for the clinical evaluation and treatment of women with suspected stage IIIC or IV epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer. CT, computed tomography; NACT, neoadjuvant chemotherapy; PCS, primary cytoreductive surgery.

Table 1

Phase III RCTs of Neoadjuvant Chemotherapy in Stage III or IV Epithelial Ovarian Cancer

Author, Year, and Study	Enrollment Criteria	Primary End Point	Study Arm	No. of Patients	Age (years)	Stage IV	Operative Time (min)	No Residual Disease	Grade 3 to 4 Postoperative Complications	PFS (months)	OS (months)
Fagotti et al, 2016[34] SCORPION	Pathologically proven ovarian cancer, stage IIIC-IV. Intraoperative high tumor load (Fagotti's score of 8 to 12) assessed by staging laparoscopy.	Surgical complications	NACT PCS	55 55	55 54	7% 15%	275 451 $P = 0.0001$	58% 46% $P = 0.16$	6% 53%* $P = 0.0001$	Not yet reported	Not yet reported
Kehoe et al, 2015[2] CHORUS	Stages 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% $P = 0.0001$	14% 24% $P = 0.007$	12.0 10.7 ITT analysis: HR, 0.91; 95% CI, 0.76 to 1.09	24.1 22.6 ITT analysis: 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
Onda et al, 2014[5] JCOG0602 Meeting abstract	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 $P < 0.001$	63% 30% (includes ICS results in PCS arm)	5% 15% $P = 0.005$ (Nonhematologic adverse events)	Not yet reported	Not yet reported
Vergote et al, 2010[1] 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 ITT analysis: HR, 1.01; 90% CI, 0.89 to 1.15	30 29 ITT analysis: HR, 0.98; 90% CI, 0.84 to 1.13 $P = 0.01$ for noninferiority

Abbreviations: CA-125, cancer antigen 125; CEA, carcinoembryonic antigen; HR, hazard ratio; ICS, interval cytoreductive surgery; ITT, intent-to-treat; NACT, neoadjuvant chemotherapy; OS, overall survival; PCS, primary cytoreductive surgery; PFS, progression-free survivial; RCT, randomized clinical trial.

*Two patients in the PCS group had grade 5 complications.

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Table 2

Risk Factors for Perioperative Morbidity or Mortality[7,12,14,55]

Advanced age or frailty
Multiple chronic conditions
Poor nutritional status or low albumin
Ascites
Newly diagnosed venous thromboembolism
Body mass index
Stage
Performance status