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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

Introduction

The purpose of this guideline is to provide clinicians with information regarding the use of neoadjuvant chemotherapy and interval cytoreduction versus primary cytoreduction and chemotherapy among women with stage IIIC or IV epithelial ovarian cancer.



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www.asco.org/NACT-ovarian-guideline

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SGO/ASCO Guideline Development Methodology

The guideline process includes:

- a systematic literature review
- an expert panel provides critical review and evidence interpretation to inform guideline recommendations
- final guideline approval by ASCO Clinical Practice Guidelines, SGO Publications, and the SGO Clinical Practice Committees

The full Guideline methodology supplement can be found at:

www.asco.org/NACT-ovarian-guideline



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Clinical 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 utilized 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?



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Clinical Questions

- (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?



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Target Population and Audience

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.



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Summary of Recommendations

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 (e.g., FDG-PET scan or diffusion-weighted MRI). (Type: informal consensus; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate)



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Summary of Recommendations

CLINICAL QUESTION 2

Which patient and disease factors should be utilized 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)



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Summary of Recommendations

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 non-inferior 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)



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Summary of Recommendations

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 post-operative morbidity and mortality and shorter hospitalizations. (Type: evidence based; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate)



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Summary of Recommendations

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 CA125 to 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)



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Summary of Recommendations

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)



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Summary of Recommendations

CLINICAL QUESTION 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?

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)



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Summary of Recommendations

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 (e.g., relief of a bowel obstruction). (Type: evidence based; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: strong)



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Patient and Clinician Communication

- 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's 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.



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Health Disparities

- Awareness of 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 of older patients from therapy.



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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.
- To date, researchers have not included quality-adjusted life-years (QALY) 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.



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Future Directions

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

- Development and validation of a pre-operative 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 (e.g., perfusion CT, dynamic MRI, PET-CT) in risk-stratifying patients for PCS vs. 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.



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Future Directions

- Exploration of novel agents in the NACT setting (e.g., 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 vs every-three-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 vs. 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.



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Additional Resources

More information, including a Data Supplement, a Methodology Supplement, slide sets, and clinical tools and resources, is available at

www.asco.org/NACT-ovarian-guideline

Patient information is available at www.cancer.net



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