



National Comprehensive  
Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

# Ovarian Cancer

## Including Fallopian Tube Cancer and Primary Peritoneal Cancer

Version 1.2020 — March 11, 2020

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**\*Deborah K. Armstrong, MD/Chair Ω †**  
The Sidney Kimmel Comprehensive  
Cancer Center at Johns Hopkins

**\*Ronald D. Alvarez, MD/Vice Chair Ω**  
Vanderbilt-Ingram Cancer Center

**Jamie N. Bakkum-Gamez, MD Ω**  
Mayo Clinic Cancer Center

**Lisa Barroilhet, MD Ω**  
University of Wisconsin  
Carbone Cancer Center

**Kian Behbakht, MD Ω**  
University of Colorado Cancer Center

**Andrew Berchuck, MD Ω**  
Duke Cancer Institute

**Jonathan S. Berek, MD, MMS Ω**  
Stanford Cancer Institute

**Lee-may Chen, MD Ω**  
UCSF Helen Diller Family  
Comprehensive Cancer Center

**Mihaela Cristea, MD †**  
City of Hope  
National Medical Center

**Maria DeRosa, RN ¥**

**Eric L. Eisenhauer, MD Ω**  
Massachusetts General Hospital  
Cancer Center

**Adam C. EINaggar, MD Ω**  
St. Jude Children's Research Hospital/  
University of Tennessee  
Health Science Center

**David M. Gershenson, MD Ω**  
The University of Texas  
MD Anderson Cancer Center

**Heidi J. Gray, MD Ω**  
Fred Hutchinson Cancer Research Center/  
Seattle Cancer Care Alliance

**Ardeshir Hakam, MD ≠**  
Moffitt Cancer Center

**Angela Jain, MD †**  
Fox Chase Cancer Center

**Charles A. Leath III, MD Ω**  
O'Neal Comprehensive  
Cancer Center at UAB

**Joyce Liu, MD, MPH † ‡**  
Dana-Farber/Brigham and  
Women's Cancer Center

**Haider Mahdi, MD, MPH Ω**  
Case Comprehensive Cancer Center/  
University Hospitals Seidman Cancer  
Center and Cleveland Clinic Taussig  
Cancer Institute

**Lainie Martin, MD †**  
Abramson Cancer Center at the  
University of Pennsylvania

**Daniela Matei, MD Ω † ‡**  
Robert H. Lurie Comprehensive Cancer Center  
of Northwestern University

**Michael McHale, MD Ω**  
UC San Diego Moores Cancer Center

**Karen McLean, MD, PhD Ω**  
University of Michigan  
Rogel Cancer Center

**David M. O'Malley, MD Ω**  
The Ohio State University Comprehensive  
Cancer Center - James Cancer Hospital  
and Solove Research Institute

**Sanja Percac-Lima, MD, PhD † ‡**  
Massachusetts General Hospital  
Cancer Center

**Elena Ratner, MD Ω**  
Yale Cancer Center/Smilow Cancer Hospital

**Steven W. Remmenga, MD Ω**  
Fred & Pamela Buffett Cancer Center

**Paul Sabbatini, MD † ‡**  
Memorial Sloan Kettering Cancer Center

**Theresa L. Werner, MD † ‡**  
Huntsman Cancer Institute  
at the University of Utah

**Emese Zsiros, MD, PhD Ω**  
Roswell Park Comprehensive Cancer Center

**NCCN**  
**Jennifer Burns**  
**Anita Engh, PhD**

Ω Gynecology oncology  
‡ Hematology/Hematology oncology  
‡ Internal medicine  
† Medical oncology  
≠ Pathology  
¥ Patient advocacy  
\* Discussion writing committee member

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### [NCCN Ovarian Cancer Panel Members](#) [Summary of the Guidelines Updates](#)

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[Principles of Surgery \(OV-A\)](#)  
[Principles of Pathology \(OV-B\)](#)  
[Principles of Systemic Therapy \(OV-C\)](#)  
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[WHO Histologic Classification \(OV-E\)](#)  
[Staging \(ST-1\)](#)

**Clinical Trials:** NCCN believes that the best management for any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

To find clinical trials online at NCCN Member Institutions, [click here: nccn.org/clinical\\_trials/member\\_institutions.aspx](#).

**NCCN Categories of Evidence and Consensus:** All recommendations are category 2A unless otherwise indicated.

See [NCCN Categories of Evidence and Consensus](#).

**NCCN Categories of Preference:** All recommendations are considered appropriate.

See [NCCN Categories of Preference](#).

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Updates in Version 1.2020 of the NCCN Guidelines for Ovarian Cancer from Version 3.2019 include:

### General

- Changed "Less Common Ovarian Histopathologies (LCOH)" to "Less Common Ovarian Cancers (LCOC)."

### OV-1

- Changed "total abdominal hysterectomy (TAH)" to "hysterectomy." (Also on OV-2)
- Recommendations for genetic risk evaluation have been modified: Patients...should have genetic risk evaluation and *BRCA1/2* germline and somatic testing (if not previously done). (Also on OV-2)
  - ▶ Footnote e modified: ~~Primary treatment should not be delayed for a genetic counseling referral.~~ Germline and/or somatic *BRCA1/2* status may inform maintenance therapy. (Also on OV-2 and OV-3)
  - ▶ Footnote f added: In the absence of a *BRCA1/2* mutation, homologous recombination deficiency (HRD) status may provide information on the magnitude of benefit of PARP inhibitor therapy (category 2B). (Also on OV-2, OV-3, and OV-5)

### OV-2

- Changed "comprehensive surgical staging" to "cytoreduction."

### OV-3

- This page has been significantly revised to clarify recommendations for patients referred with newly diagnosed ovarian cancer after a recent surgical procedure.
- Findings: Links added to LCOC-10 and LCOC-11 for malignant germ cell/sex cord-stromal tumors.

### OV-4

- Modified: Stage IC (*High-grade serous or grade 4 2/3 endometrioid*).
- Stage IA or IB, grade 2 endometrioid: removed "3-6 cycles" from platinum-based therapy. Recommended number of cycles is included on OV-C, 6 of 9.

### OV-5

- This page has been significantly revised.
- Niraparib has been added to the maintenance therapy options for those with complete or partial remission (CR/PR), if:
  - ▶ *BRCA1/2* wild-type or unknown, and no bevacizumab used during primary therapy.
  - ▶ Germline or somatic *BRCA1/2* mutation (category 1 if no bevacizumab used during primary therapy, category 2A if bevacizumab was used during primary therapy).
- Category of evidence has been modified for olaparib for patients with a germline or somatic *BRCA1/2* mutation who did not receive bevacizumab during primary therapy: (category 1 for germline mutations; category 2A for somatic mutations)
- Bevacizumab + olaparib has been added as an option for patients with CR/PR, if bevacizumab was used as part of primary therapy. This is a category 2A option.
- Olaparib has been added as an option for patients with a CR/PR and germline or somatic *BRCA1/2* mutation, if bevacizumab was used as part of primary therapy. This is a category 2A option.
- Postremission bevacizumab is no longer an option for patients with stable disease after primary therapy with a bevacizumab-containing regimen.
- Indications modified for postremission bevacizumab: It is an option for those with CR/PR after treatment with a bevacizumab-containing regimen, if *BRCA1/2* wildtype or unknown; it is not recommended for patients with a *BRCA1/2* mutation.
- Footnote u has been modified: *After first-line therapy with bevacizumab, data are limited on the addition of maintenance therapy with a single-agent PARP inhibitor (olaparib or niraparib) for patients with a germline or somatic BRCA1/2 mutation. However, based on the magnitude of benefit of PARP inhibitor maintenance therapy for other subgroups, single-agent PARP inhibitors can be considered. Combination bevacizumab and olaparib maintenance therapy is not recommended at this time.*
- Footnote v has been added: Data are limited for maintenance therapy with a PARP inhibitor for patients with stage II disease.

[Continued](#)

**UPDATES**



Updates in Version 1.2020 of the NCCN Guidelines for Ovarian Cancer from Version 3.2019 include:

### **OV-7**

- Footnote hh has been modified: For patients with platinum-sensitive disease who have completed two or more lines of platinum-based therapy (*preferred for those with a BRCA mutation*). There are limited data on the use of a maintenance PARP inhibitor *in patients who previously received a PARP inhibitor or after recurrence therapy with bevacizumab*. Combination bevacizumab/PARP inhibitor is not recommended at this time for maintenance *after recurrence therapy*.

### **Less Common Ovarian Cancers**

#### **LCOC-1**

- Footnote b has been modified: Due to emerging therapeutics for **specific histologies less common ovarian cancers**, there is value in identifying potential pathways for rare **histologies cancers** and it may be useful for clinical trial recruitment. *Tumor molecular testing can be considered, if not previously done, as it may help guide treatment*. There are limited data in these cancers given...

#### **LCOC-2**

- Modified: ~~Complete~~ *Consider surgical staging, if not previously done*
- Adjuvant treatment options have been modified. IV paclitaxel 175/ carboplatin is preferred; and links have been added to OV-C for the other systemic therapy options.

#### **LCOC-3**

- Stage II-IV, modified adjuvant therapy: *Systemic therapy (see OV-C, 5 of 10) Chemotherapy as per epithelial ovarian cancer (see primary chemotherapy/primary adjuvant therapy on OV-4)*
- Pathway for borderline has been removed. (Also on LCOC-5/6)
- Footnote g has been modified: Refer to ~~OV-3~~ *for complete surgical staging: Consider surgical staging (if not previously done) if considering observation*. See Principles of Surgery (OV-A).

#### **LCOC-4**

- CA 19-9 added to additional workup, if not previously done.
- Adjuvant treatment options have been modified.
- A link has been added to OV-C (4 of 10) for systemic therapy options for stage IC disease, and to OV-C (5 of 10) for stage II-IV disease. (Also on LCOC-5 and LCOC-6)
- Replaced surgical staging in algorithm with footnote g: *Consider surgical staging (if not previously done) if considering observation*. See Principles of Surgery (OV-A).

#### **LCOC-5**

- Footnote g has been added: *Consider surgical staging (if not previously done) if considering observation*. See Principles of Surgery (OV-A). (Also on LCOC-6)

#### **LCOC-7**

- Pathways modified for those with invasive implants following complete surgical staging. Options to see LCOC-6 for low-grade serous carcinoma, or see OV-4 for high-grade serous carcinoma.

#### **LCOC-8**

- This page has been significantly revised.

#### **LCOC-9**

- The following recommendation has been moved from "monitoring/ follow-up" to LCOC-8 (see footnote l): After completion of childbearing in patients who underwent USO, consider completion surgery (category 2B)

#### **LCOC-10**

- Changed "stage IA/IC" to "disease clinically confined to the ovary, fertility desired."
- Footnote r has been modified: Acceptable options include paclitaxel/carboplatin (*preferred*) (~~category 2B~~), EP (*etoposide, cisplatin*), or BEP (bleomycin, etoposide, cisplatin) (category 2B).

#### **LCOC-11**

- Incompletely staged, dysgerminoma or grade 1 immature teratoma with negative imaging and positive tumor markers, management option modified: Consider observation (category 2B) *with close monitoring of tumor markers until normalization (See LCOC-13)*.
- Footnote v has been added: Repeat imaging if tumor markers plateau at significant abnormal level or rise. If imaging positive, follow pathway above for positive imaging and positive tumor markers.

#### **LCOC-12**

- Where high-dose chemotherapy is recommended, clarified "+ stem cell transplant (SCT)."
- Footnote t added: Palliative localized RT can be considered.

[Continued](#)

**UPDATES**



Updates in Version 1.2020 of the NCCN Guidelines for Ovarian Cancer from Version 3.2019 include:

#### [OV-A \(3 of 4\)](#)

- First bullet modified: IDS, including completion TAH *hysterectomy* and BSO with staging, should be performed after 4 3–4 cycles of neoadjuvant chemotherapy...

#### [OV-A \(4 of 4\)](#)

- Mucinous tumors, modified: Thus, the upper and lower GI tract should be carefully evaluated to rule out an occult GI primary with ovarian metastases, and an ~~appendectomy should be performed at primary surgery in patients with a suspected or confirmed mucinous ovarian neoplasm~~: *an appendectomy need only be performed in patients with a suspected or confirmed mucinous ovarian neoplasm if it appears to be abnormal. A normal appendix does not require surgical resection in this setting.*

#### [OV-B \(1 of 3\)](#)

- Modified bullets under "Elements from CAP protocol":
  - ▶ Tumor site(s) (eg, ovary, fallopian tube, ~~or primary peritoneum~~ pelvic/abdominal peritoneum, uterus, cervix, omentum)
  - ▶ Added: Other tissue/organ involvement

#### [OV-C](#)

- Principles of Systemic Therapy have been reorganized.
- Bullet added: Consider scalp cooling to reduce incidence of alopecia for patients receiving chemotherapy with high rates of alopecia.

#### [OV-C \(2 of 10\)](#)

- Added to last bullet: Patients with stable disease who are tolerating therapy may continue past 6 cycles.

#### [OV-C \(4 of 10\)](#)

- NCCN Categories of Preference have been included for the primary systemic therapy regimens. (Also on OV-C, 5 of 10)
- Footnote d added, with modified bullet from prior version: Elderly patients...Based on clinical judgment and expected tolerance to therapies, ~~the following IV regimens alternate dosing~~ may be appropriate for elderly patients with ~~stage I–IV~~ epithelial ovarian cancer (including carcinosarcoma, clear cell, mucinous, and low-grade serous). (See OV-C, 6 of 10) (Also on OV-C, 5 of 10)

#### [OV-C \(6 of 10\)](#)

- Dosing information for primary systemic therapy regimens updated and reformatted.
- Infusion time has been removed from all regimens.
- Footnote h has been modified: For stage I disease: 6 cycles is recommended for high-grade serous; 3–6 cycles for all other ~~histologies ovarian cancer types~~. For stage II–IV disease: 6 cycles is recommended.

#### [OV-C \(7 of 10\)](#)

- Olaparib, footnote p has been modified: For patients with deleterious germline *BRCA*-mutated (as detected by an FDA-approved test or other validated test performed in a CLIA-approved facility) advanced ovarian cancer who have been treated with three two or more lines of chemotherapy. (Also on OV-C, 8 of 10)
- Footnote o modified: "...whose cancer is associated with HRD ~~positive status~~ defined by either..." (Also on OV-C, 8 of 10)

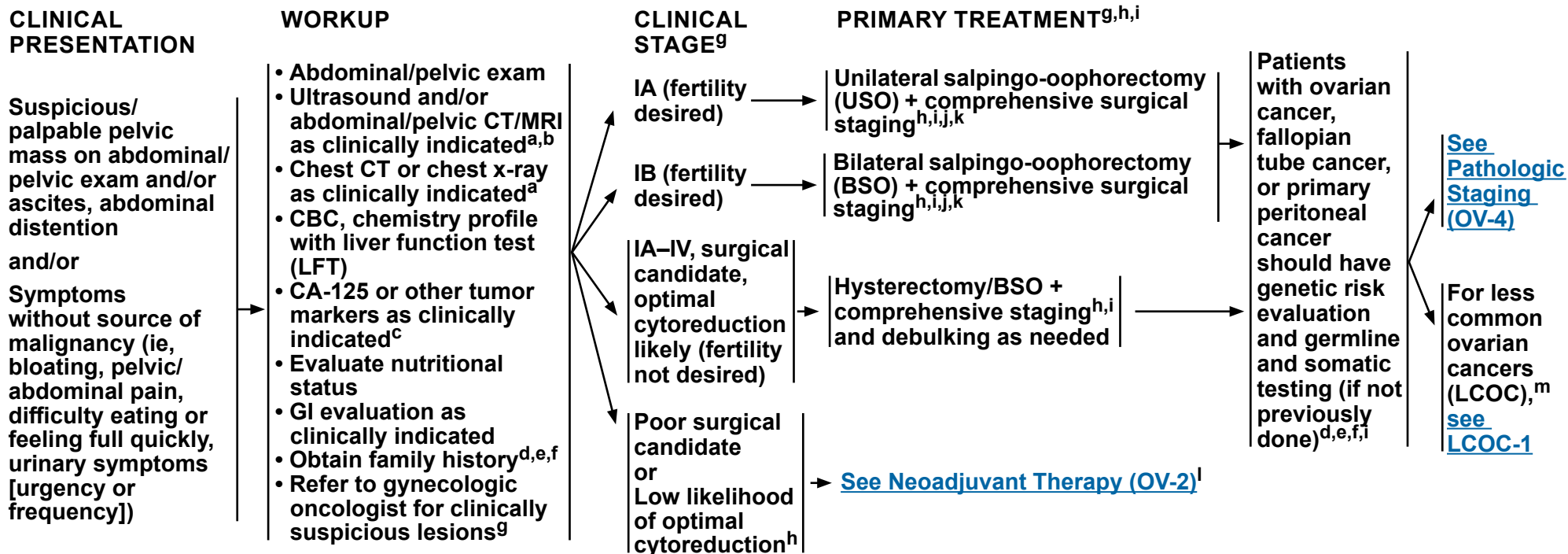
#### [OV-C \(9 of 10\)](#)

- NCCN Categories of Preference included for primary and recurrence systemic therapy regimens for malignant germ cell/sex cord-stromal tumors.
- Malignant sex cord-stromal tumors
  - ▶ Paclitaxel/carboplatin has been changed from a category 2B to a category 2A preferred primary therapy option.
  - ▶ Etoposide/cisplatin (EP) has been added as a category 2A, other recommended primary and recurrence therapy option.
  - ▶ BEP has been added as a category 2B, useful in certain circumstances recurrence therapy option.



# NCCN Guidelines Version 1.2020

## Epithelial Ovarian Cancer/Fallopian Tube Cancer/ Primary Peritoneal Cancer



<sup>a</sup> Imaging performed with contrast unless contraindicated.

<sup>b</sup> PET/CT or MRI may be indicated for indeterminate lesions if results will alter management.

<sup>c</sup> Other tumor markers may include inhibin, beta-human chorionic gonadotropin (β-hCG), alpha-fetoprotein, lactate dehydrogenase (LDH), carcinoembryonic antigen (CEA), and CA 19-9. See [Discussion](#) for usefulness of diagnostic tests.

<sup>d</sup> See [NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic](#) and [NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal](#).

<sup>e</sup> Germline and/or somatic *BRCA1/2* status informs maintenance therapy.

<sup>f</sup> In the absence of a *BRCA1/2* mutation, homologous recombination deficiency (HRD) status may provide information on the magnitude of benefit of PARP inhibitor therapy (category 2B).

<sup>g</sup> Evaluation by a gynecologic oncologist is recommended for:

- All patients with suspected ovarian malignancies; published data demonstrate that primary assessment and debulking by a gynecologic oncologist results in a survival advantage.
- Patients being evaluated for neoadjuvant therapy prior to being considered a poor surgical candidate.
- Management of occult serous tubal intraepithelial carcinomas.
- Consideration of laparoscopic evaluation to determine feasibility of debulking surgery in select patients.

<sup>h</sup> See [Principles of Surgery \(OV-A\)](#).

<sup>i</sup> See [Principles of Pathology \(OV-B\)](#).

<sup>j</sup> May be an option for select patients with stage IC based on histology.

<sup>k</sup> Uterine preservation for potential future assisted reproductive approaches.

<sup>l</sup> See [Principles of Systemic Therapy \(OV-C\)](#) and [Management of Drug Reactions \(OV-D\)](#).

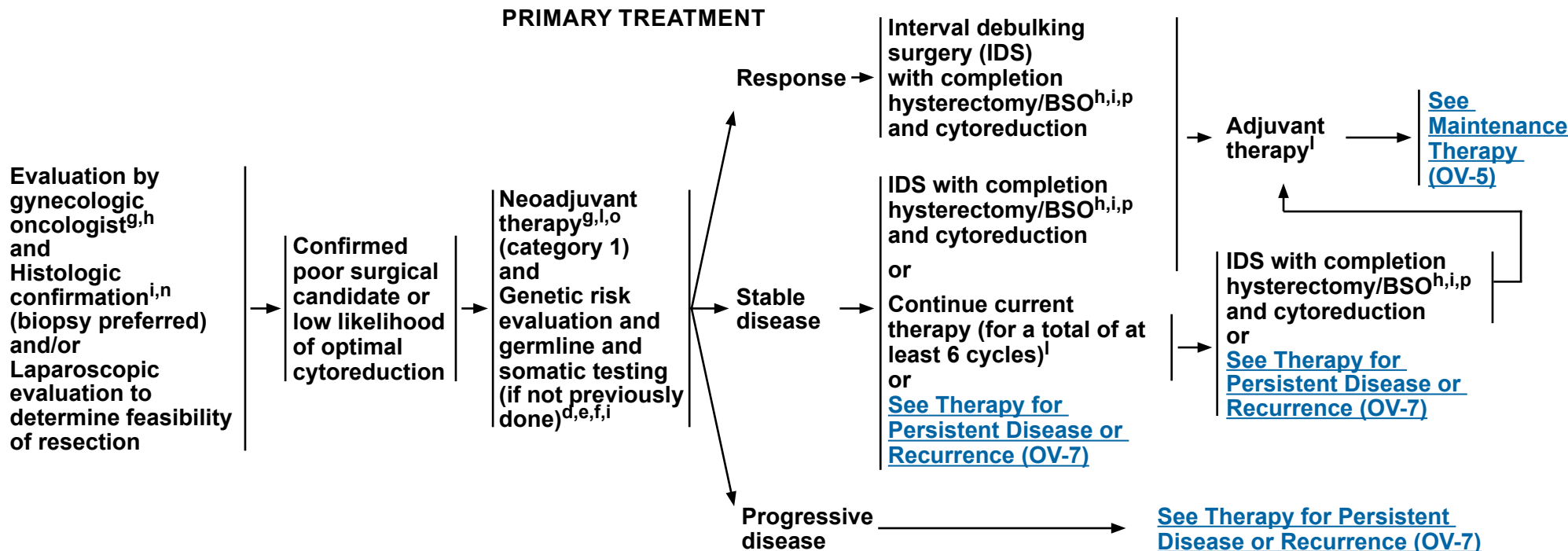
<sup>m</sup> Carcinosarcoma, clear cell, mucinous, low-grade serous, grade 1 endometrioid, borderline epithelial, malignant sex cord-stromal tumors, and germ cell tumors.

**Note:** All recommendations are category 2A unless otherwise indicated.

**Clinical Trials:** NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

# NCCN Guidelines Version 1.2020 Epithelial Ovarian Cancer/Fallopian Tube Cancer/ Primary Peritoneal Cancer

## POOR SURGICAL CANDIDATE OR LOW LIKELIHOOD OF OPTIMAL CYTOREDUCTION NEOADJUVANT THERAPY



<sup>d</sup> See [NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic](#) and [NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal](#).

<sup>e</sup> Germline and/or somatic *BRCA1/2* status informs maintenance therapy.

<sup>f</sup> In the absence of a *BRCA1/2* mutation, HRD status may provide information on the magnitude of benefit of PARP inhibitor therapy (category 2B).

<sup>g</sup> Evaluation by a gynecologic oncologist is recommended for:

- All patients with suspected ovarian malignancies; published data demonstrate that primary assessment and debulking by a gynecologic oncologist results in a survival advantage.
- Patients being evaluated for neoadjuvant therapy prior to being considered a poor surgical candidate.
- Management of occult serous tubal intraepithelial carcinomas.
- Consideration of laparoscopic evaluation to determine feasibility of debulking surgery in select patients.

<sup>h</sup> See [Principles of Surgery \(OV-A\)](#).

<sup>i</sup> See [Principles of Pathology \(OV-B\)](#).

<sup>l</sup> See [Principles of Systemic Therapy \(OV-C\)](#) and [Management of Drug Reactions \(OV-D\)](#).

<sup>n</sup> If biopsy is not feasible, cytopathology from ascites or pleural effusion combined with CA-125:CEA ratio of >25 can be used.

<sup>o</sup> Completion surgery after 3–4 cycles is preferred; however, surgery may be performed after 4–6 cycles based on the clinical judgment of the gynecologic oncologist.

<sup>p</sup> Hyperthermic intraperitoneal chemotherapy (HIPEC) with cisplatin (100 mg/m<sup>2</sup>) can be considered at the time of IDS for stage III disease.

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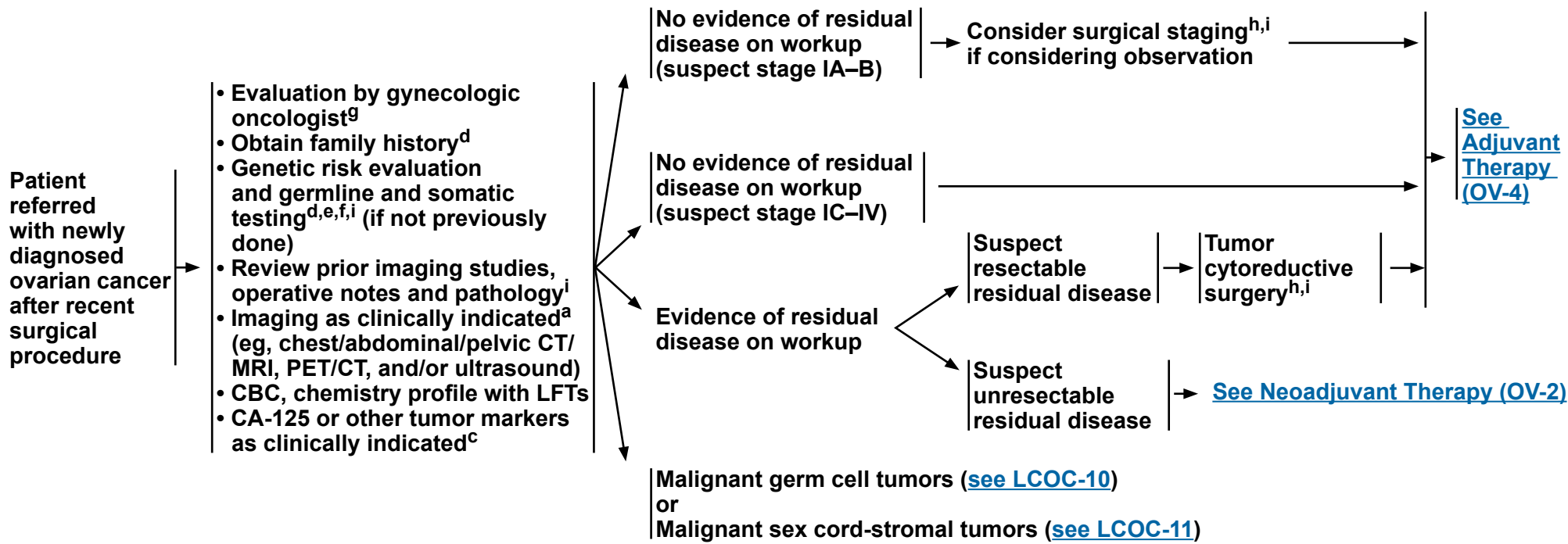


# NCCN Guidelines Version 1.2020 Epithelial Ovarian Cancer/Fallopian Tube Cancer/ Primary Peritoneal Cancer

## DIAGNOSIS BY PREVIOUS SURGERY

## FINDINGS

## PRIMARY TREATMENT



<sup>a</sup> Imaging performed with contrast unless contraindicated.  
<sup>c</sup> Other tumor markers may include inhibin, β-hCG, alpha-fetoprotein, LDH, CEA, and CA 19-9. See [Discussion](#) for usefulness of diagnostic tests.  
<sup>d</sup> See [NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic](#) and [NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal](#).  
<sup>e</sup> Germline and/or somatic *BRCA1/2* status informs maintenance therapy.  
<sup>f</sup> In the absence of a *BRCA1/2* mutation, HRD status may provide information on the magnitude of benefit of PARP inhibitor therapy (category 2B).

<sup>g</sup> Evaluation by a gynecologic oncologist is recommended for:

- All patients with suspected ovarian malignancies; published data demonstrate that primary assessment and debulking by a gynecologic oncologist results in a survival advantage.
- Patients being evaluated for neoadjuvant therapy prior to being considered a poor surgical candidate.
- Management of occult serous tubal intraepithelial carcinomas.
- Consideration of laparoscopic evaluation to determine feasibility of debulking surgery in select patients.

<sup>h</sup> See [Principles of Surgery \(OV-A\)](#).  
<sup>i</sup> See [Principles of Pathology \(OV-B\)](#).

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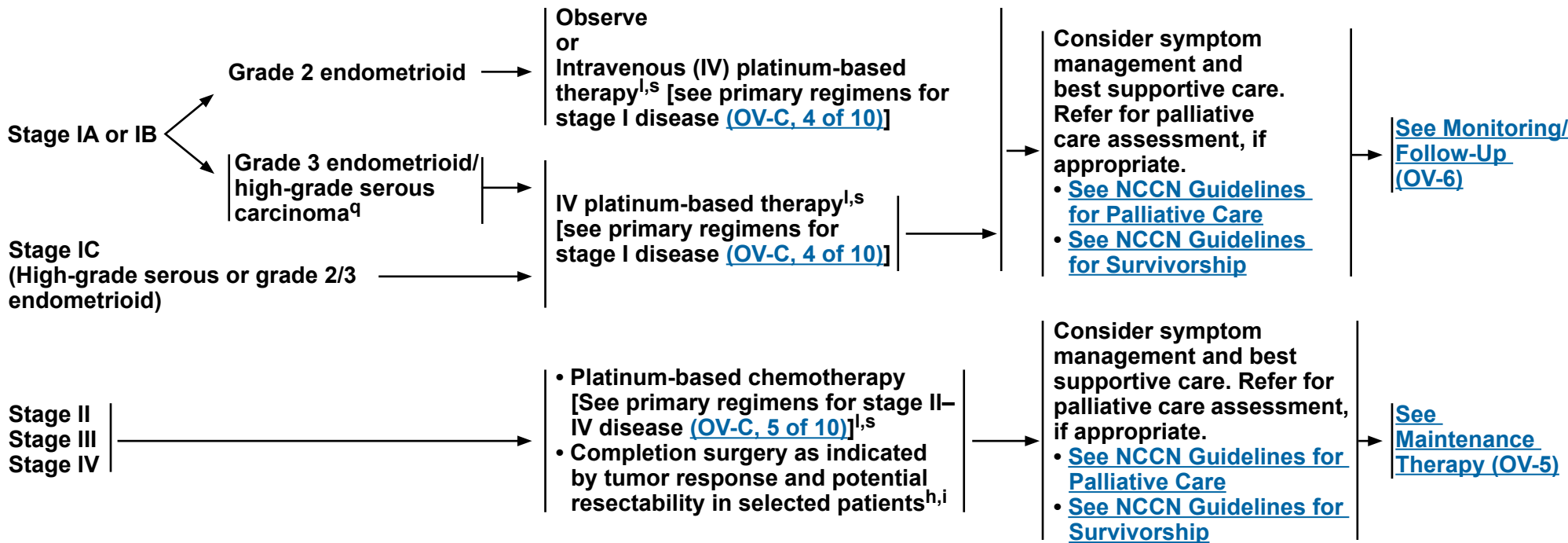
## Epithelial Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer

### **PATHOLOGIC STAGING<sup>q,r</sup>**

### **PRIMARY CHEMOTHERAPY/PRIMARY ADJUVANT THERAPY<sup>s</sup>**

Less Common Ovarian Cancers (LCOC), any stage<sup>m,r</sup>

[See LCOC-1](#)



<sup>h</sup> See Principles of Surgery (OV-A).

<sup>i</sup> See Principles of Pathology (OV-B).

<sup>l</sup> See Principles of Systemic Therapy (OV-C) and Management of Drug Reactions (OV-D).

<sup>m</sup> Carcinosarcoma, clear cell, mucinous, low-grade serous, grade 1 endometrioid, borderline epithelial, malignant sex cord-stromal tumors, and germ cell tumors.

<sup>q</sup> Pathologists recommend categorizing serous ovarian cancer as either low-grade or high-grade. Grade 2 serous is considered high-grade.

<sup>r</sup> Consider expert pathologic review to confirm histologic diagnosis. See WHO Histologic Classification (OV-E).

<sup>s</sup>Patients receiving primary chemotherapy will be monitored as follows:

1. Every 1–3 cycles: Physical exam and consider pelvic exam
2. Interim CBC with platelets as indicated
3. Chemistry profiles if indicated
4. CA-125 levels or other tumor markers as clinically indicated prior to each cycle of chemotherapy
5. Chest/abdominal/pelvic CT or MRI with contrast, PET/CT (skull base to mid-thigh), or PET as indicated

**Note:** All recommendations are category 2A unless otherwise indicated.

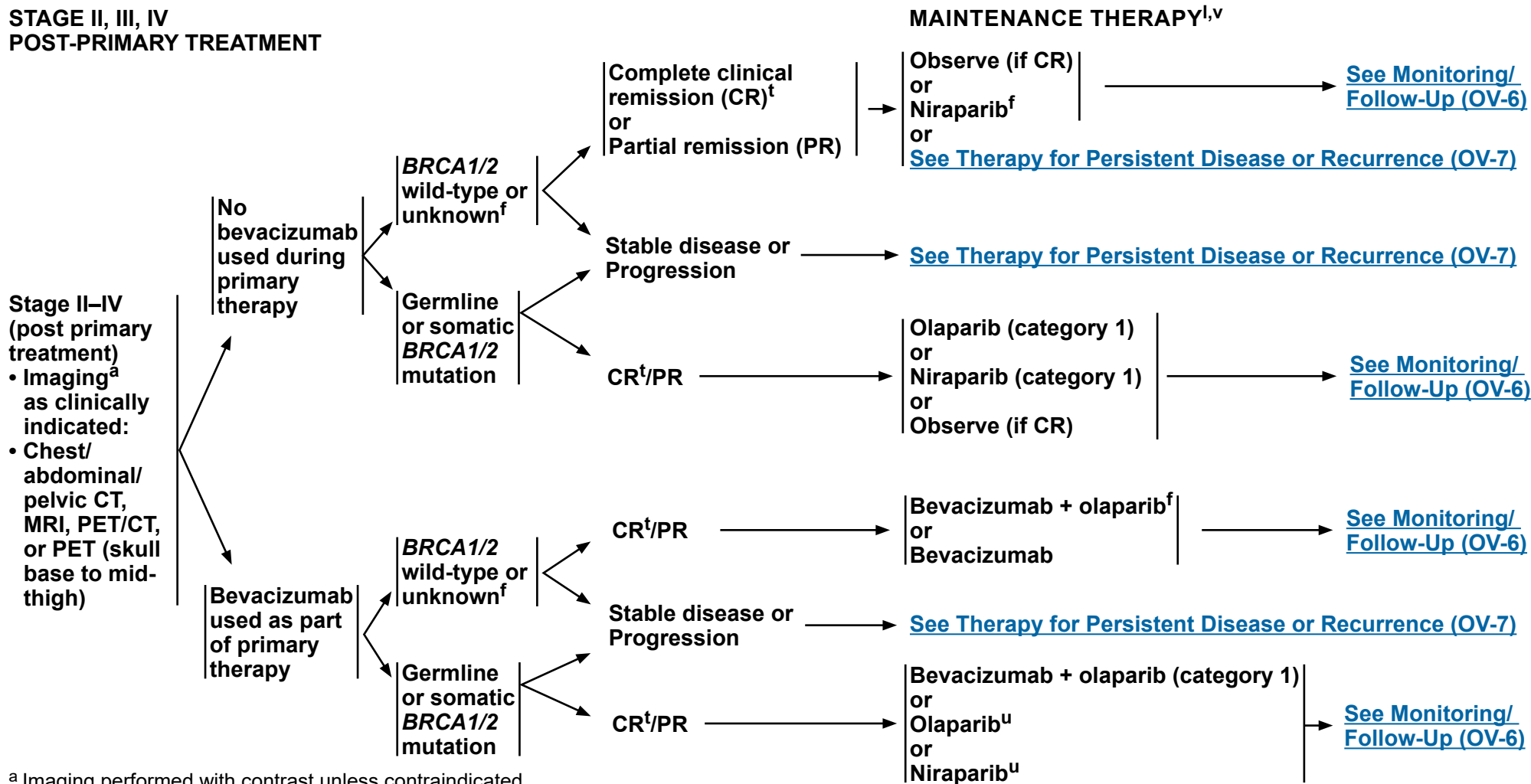
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# NCCN Guidelines Version 1.2020

## Epithelial Ovarian Cancer/Fallopian Tube Cancer/ Primary Peritoneal Cancer

### STAGE II, III, IV POST-PRIMARY TREATMENT



<sup>a</sup> Imaging performed with contrast unless contraindicated.

<sup>f</sup> In the absence of a *BRCA1/2* mutation, HRD status may provide information on the magnitude of benefit of PARP inhibitor therapy (category 2B).

<sup>l</sup> [See Principles of Systemic Therapy \(OV-C\)](#) and [Management of Drug Reactions \(OV-D\)](#).

<sup>t</sup> No definitive evidence of disease.

<sup>u</sup> After first-line therapy with bevacizumab, data are limited on maintenance therapy with a single-agent PARP inhibitor (olaparib or niraparib) for patients with a germline or somatic *BRCA1/2* mutation. However, based on the magnitude of benefit of PARP inhibitor maintenance therapy for other subgroups, single-agent PARP inhibitors can be considered.

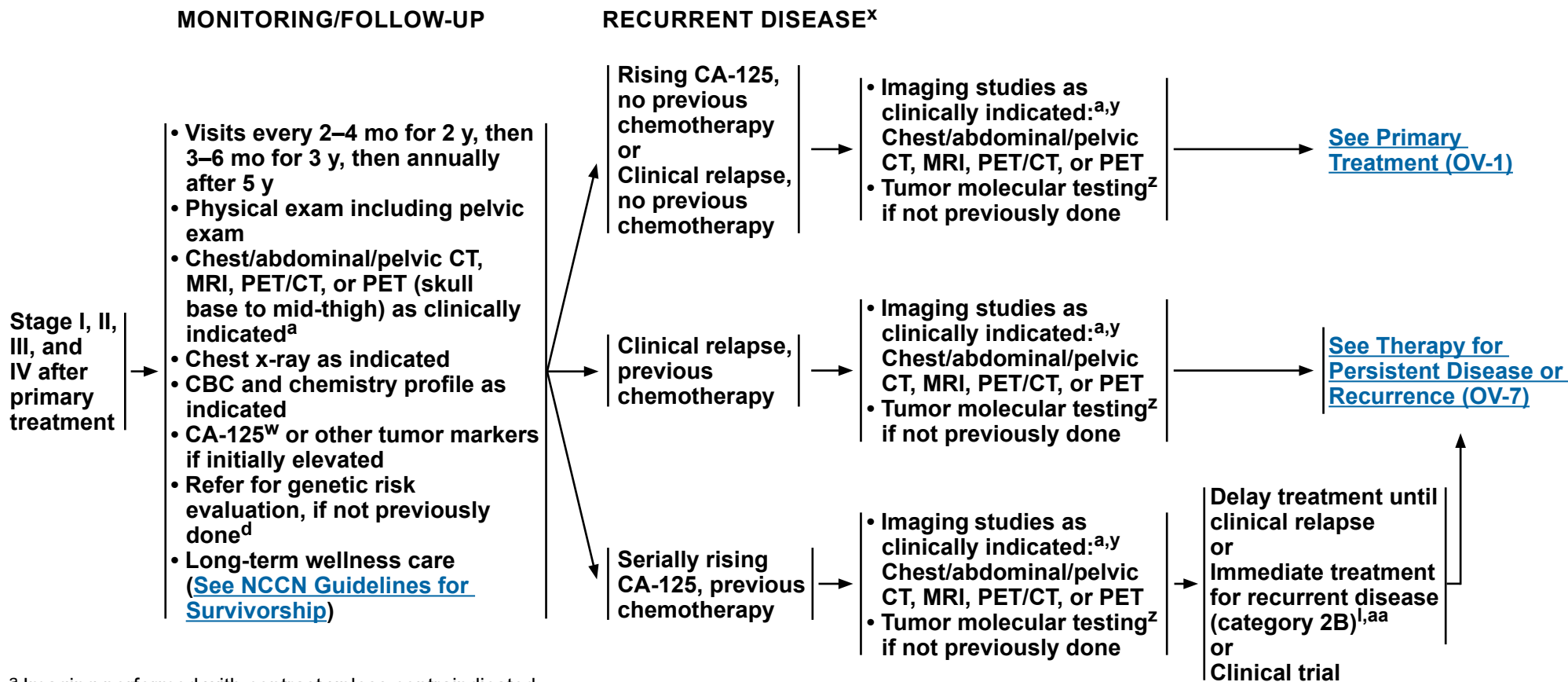
<sup>v</sup> Data are limited for maintenance therapy with a PARP inhibitor for patients with stage II disease.

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# NCCN Guidelines Version 1.2020 Epithelial Ovarian Cancer/Fallopian Tube Cancer/ Primary Peritoneal Cancer



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<sup>d</sup> [See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic](#) and [NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal](#).

<sup>l</sup> [See Principles of Systemic Therapy \(OV-C\)](#) and [Management of Drug Reactions \(OV-D\)](#).

<sup>w</sup> There are data regarding the utility of CA-125 for monitoring of ovarian cancer after completion of primary therapy. See [The Society of Gynecologic Oncology \(SGO\) position statement](#) and [Discussion](#).

<sup>x</sup> Consider symptom management and best supportive care. See [NCCN Guidelines for Palliative Care](#). Refer for palliative care assessment, if appropriate.

<sup>y</sup> Surveillance imaging may be indicated when tumor markers are considered unreliable, the physical exam is unreliable, and/or there is a high risk of recurrence.

<sup>z</sup> Validated molecular testing should be performed in a CLIA-approved facility using the most recent available tumor tissue. Testing recommended to include at least: *BRCA1/2*, and microsatellite instability or DNA mismatch repair if not previously done. Evaluation of homologous recombination deficiency can be considered. Additional somatic tumor testing can be considered at the physician's discretion to identify genetic alterations for which FDA-approved tumor-specific or tumor-agnostic targeted therapy options exist.

<sup>aa</sup> [See Acceptable Recurrence Therapies \(OV-C, 7 of 10\)](#).

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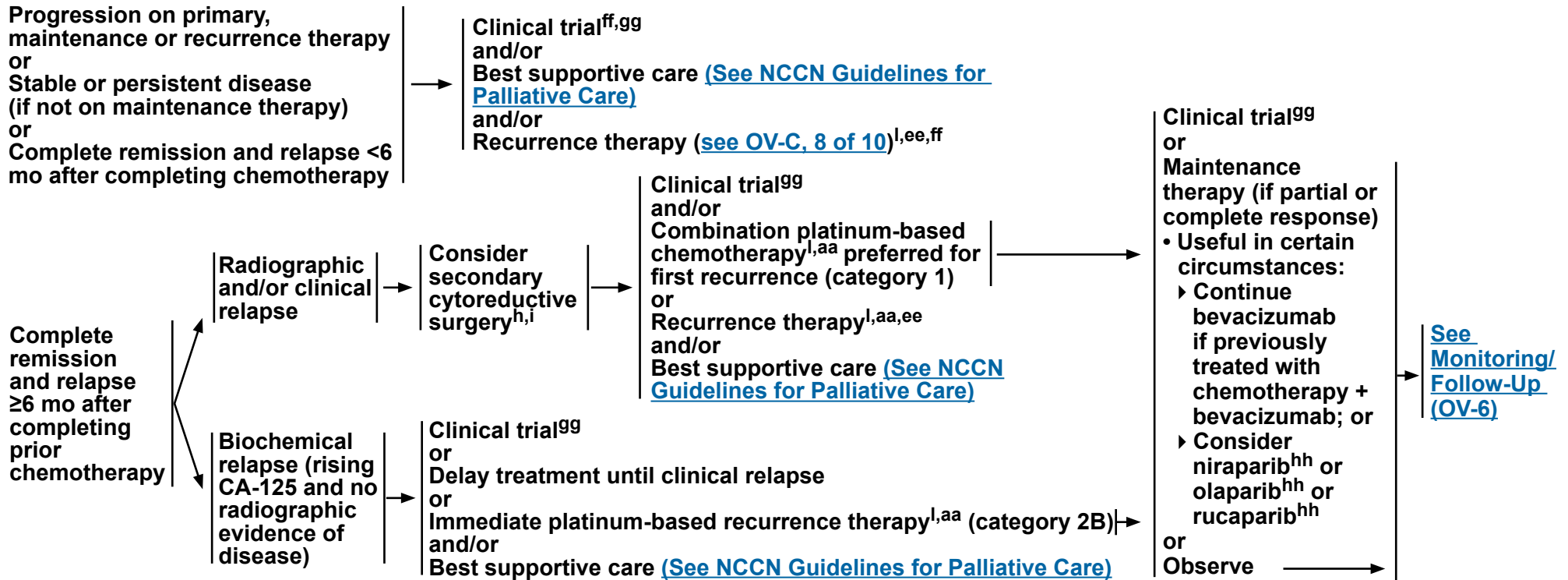
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# NCCN Guidelines Version 1.2020

## Epithelial Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer

**DISEASE STATUS<sup>d,z,bb</sup>**

**THERAPY FOR PERSISTENT DISEASE OR RECURRENCE<sup>l,aa,cc,dd</sup>**



<sup>d</sup> See [NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic](#) and [NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal](#).

<sup>h</sup> See [Principles of Surgery \(OV-A\)](#).

<sup>i</sup> See [Principles of Pathology \(OV-B\)](#).

<sup>l</sup> See [Principles of Systemic Therapy \(OV-C\)](#) and [Management of Drug Reactions \(OV-D\)](#).

<sup>z</sup> Validated molecular testing should be performed in a CLIA-approved facility using the most recent available tumor tissue. Testing recommended to include at least: BRCA1/2, and microsatellite instability or DNA mismatch repair if not previously done. Evaluation of homologous recombination deficiency can be considered. Additional somatic tumor testing can be considered at the physician's discretion to identify genetic alterations for which FDA-approved tumor-specific or tumor-agnostic targeted therapy options exist.

<sup>aa</sup> See [Acceptable Recurrence Therapies \(OV-C, 7 of 10\)](#).

<sup>bb</sup> Tumor molecular testing prior to initiation of therapy for persistent/recurrent disease, if not previously done.

<sup>cc</sup> During and after treatment for recurrence, patients should be evaluated as indicated with tumor markers and repeat imaging (with modalities previously used) to document response and/or disease status.

<sup>dd</sup> See [Ancillary Palliative Surgical Procedures \(OV-A 4 of 4\)](#).

<sup>ee</sup> Palliative localized RT can be considered.

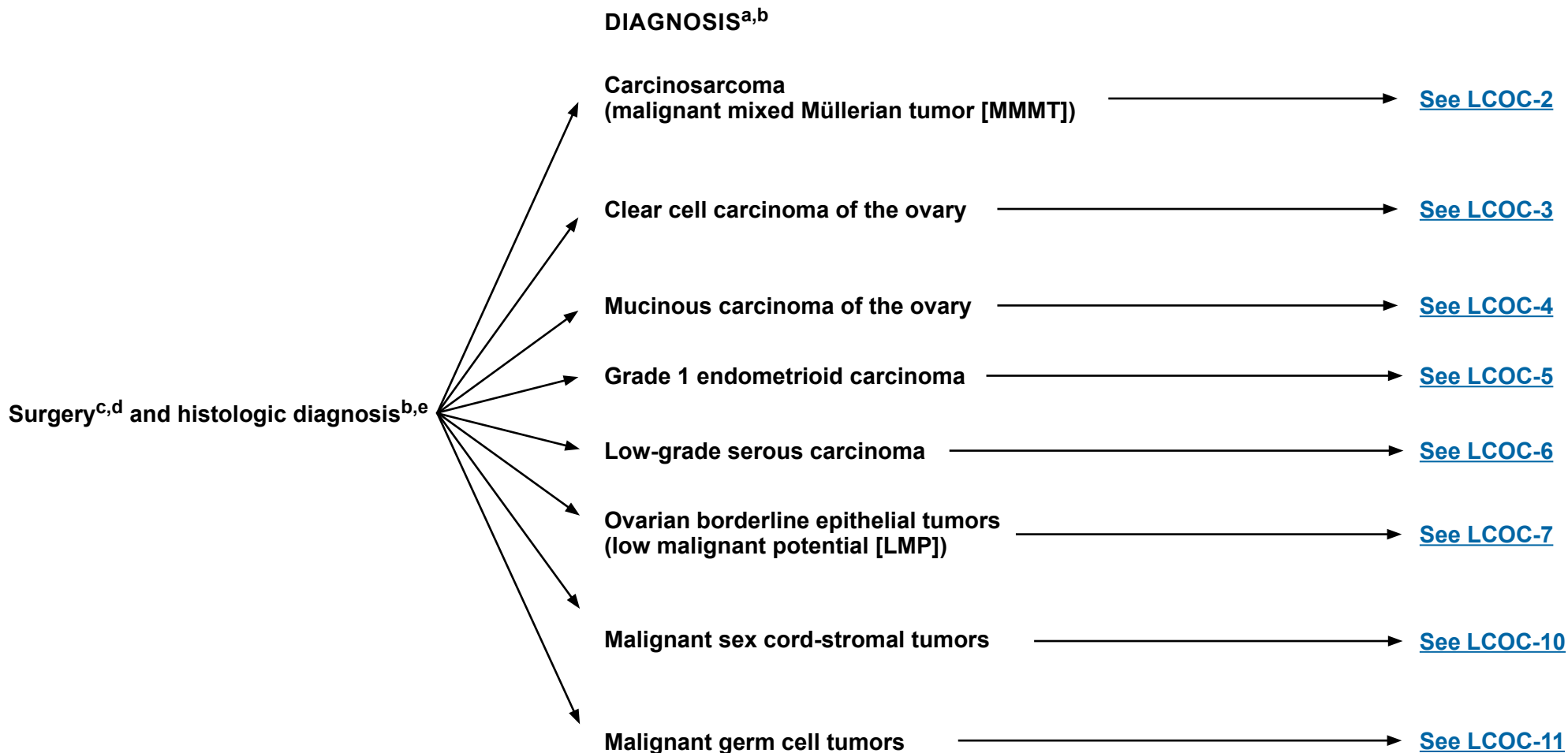
<sup>ff</sup> Patients who progress on 2 consecutive therapy regimens without evidence of clinical benefits have diminished likelihood of benefitting from additional therapy. Decisions to offer clinical trials, supportive care only, or additional therapy should be made on a highly individual basis.

<sup>gg</sup> Clinical trials with newer agents should be strongly considered.

<sup>hh</sup> For patients with platinum-sensitive disease who have completed two or more lines of platinum-based therapy (preferred for those with a BRCA mutation). There are limited data on the use of a maintenance PARP inhibitor in patients who previously received a PARP inhibitor or after recurrence therapy with bevacizumab. Combination bevacizumab/PARP inhibitor is not recommended at this time for maintenance after recurrence therapy.

**Note:** All recommendations are category 2A unless otherwise indicated.

**Clinical Trials:** NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



<sup>a</sup> [See WHO Histologic Classification \(OV-E\).](#)

<sup>b</sup> Due to emerging therapeutics for less common ovarian cancers, there is value in identifying potential pathways for rare cancers and it may be useful for clinical trial recruitment. Tumor molecular testing can be considered, if not previously done, as it may help guide treatment. There are limited data in these cancers given their infrequency and it will be difficult to acquire prospective data. Individualized treatment may be the best treatment for these rare tumors. [Committee on the State of the Science in Ovarian Cancer, et al. Ovarian Cancers: Evolving Paradigms in Research and Care. Washington (DC): National Academies Press (US) Copyright 2016 by the National Academy of Sciences. All rights reserved; 2016.]

<sup>c</sup> [See Principles of Surgery \(OV-A\).](#)

<sup>d</sup> [See Principles of Pathology \(OV-B\).](#)

<sup>e</sup> Less common ovarian cancers are typically diagnosed after surgery. [See Workup \(OV-1\).](#)

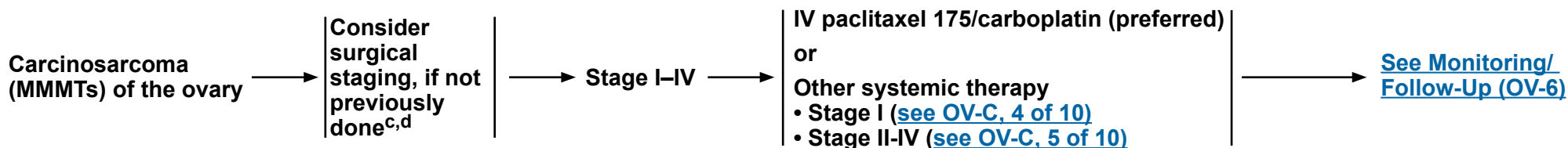
**Note:** All recommendations are category 2A unless otherwise indicated.

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### PATHOLOGIC DIAGNOSIS<sup>a</sup>

### ADJUVANT TREATMENT<sup>f</sup>

### MONITORING/ FOLLOW-UP



<sup>a</sup> See [WHO Histologic Classification \(OV-E\)](#).

<sup>c</sup> See [Principles of Surgery \(OV-A\)](#).

<sup>d</sup> [Principles of Pathology \(OV-B\)](#).

<sup>f</sup> See [Principles of Systemic Therapy \(OV-C\)](#) and [Management of Drug Reactions \(OV-D\)](#).

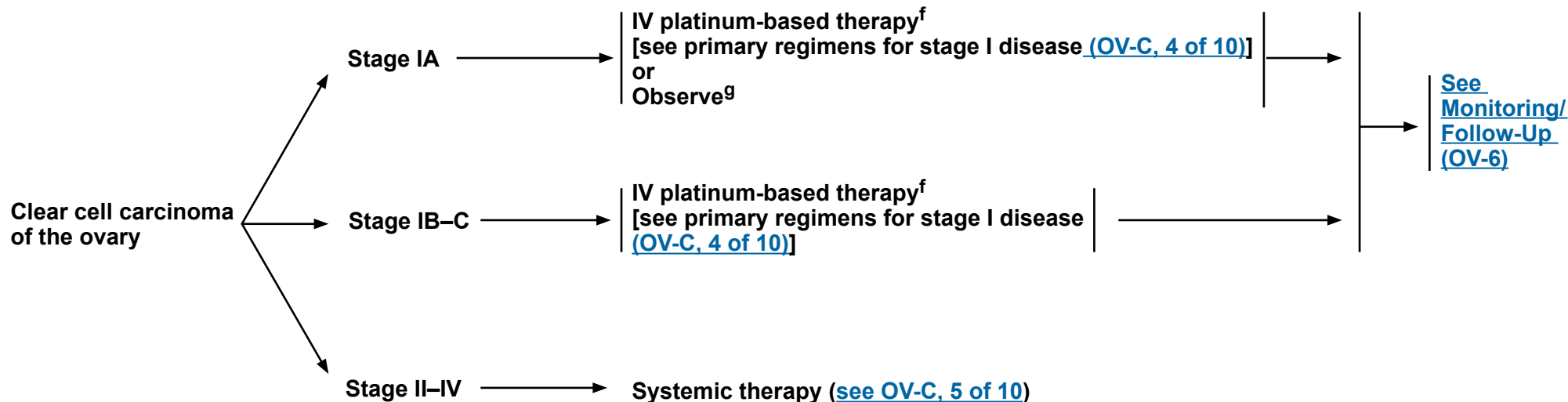
**Note:** All recommendations are category 2A unless otherwise indicated.

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**PATHOLOGIC  
DIAGNOSIS<sup>a</sup>**

**ADJUVANT TREATMENT**

**MONITORING/  
FOLLOW-UP**



<sup>a</sup>See [WHO Histologic Classification \(OV-E\)](#).

<sup>f</sup>See [Principles of Systemic Therapy \(OV-C\)](#) and [Management of Drug Reactions \(OV-D\)](#).

<sup>g</sup>Consider surgical staging (if not previously done) if considering observation. See [Principles of Surgery \(OV-A\)](#).

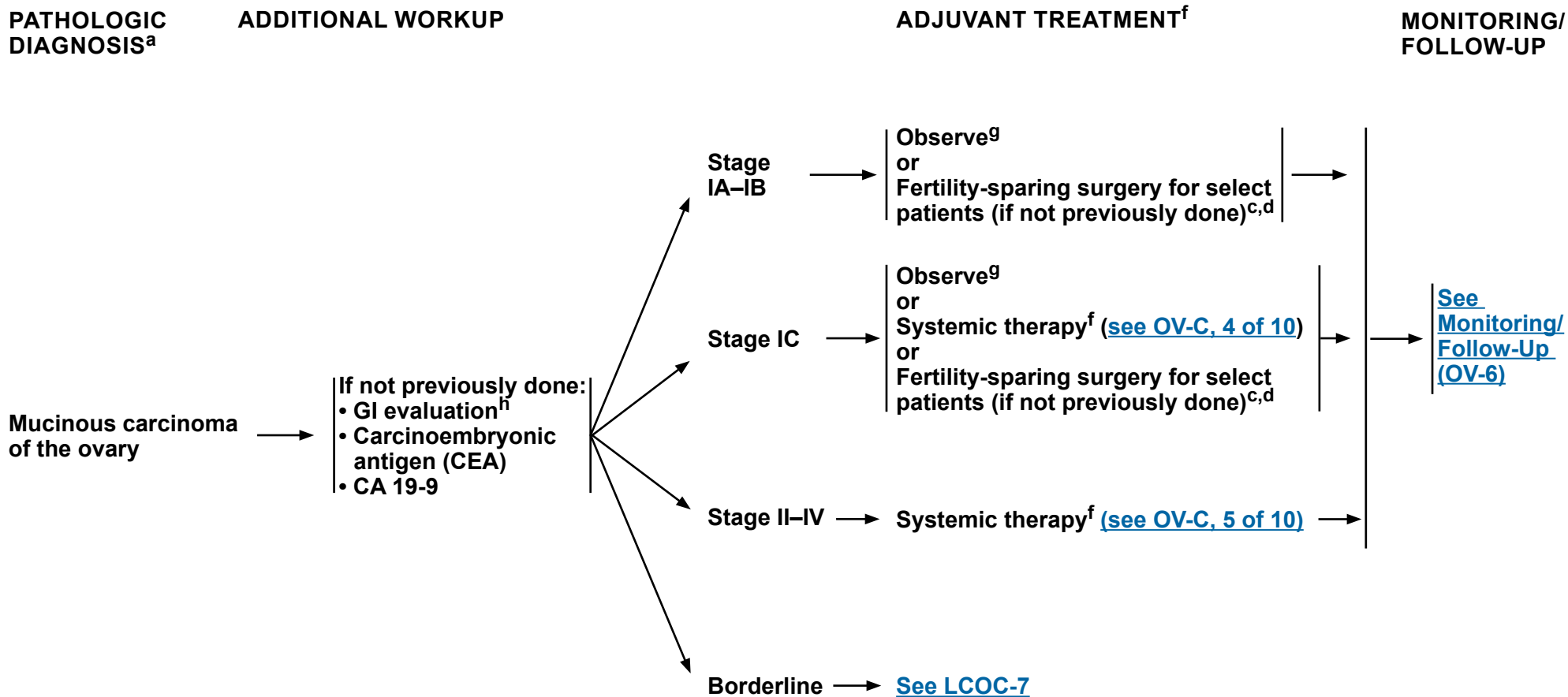
**Note: All recommendations are category 2A unless otherwise indicated.**  
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# NCCN Guidelines Version 1.2020

## Mucinous Carcinoma of the Ovary



<sup>a</sup> [See WHO Histologic Classification \(OV-E\).](#)

<sup>c</sup> [See Principles of Surgery \(OV-A\).](#)

<sup>d</sup> [Principles of Pathology \(OV-B\).](#)

<sup>f</sup> [See Principles of Systemic Therapy \(OV-C\)](#) and [Management of Drug Reactions \(OV-D\).](#)

<sup>g</sup> Consider surgical staging (if not previously done) if considering observation. [See Principles of Surgery \(OV-A\).](#)

<sup>h</sup> Consider additional testing, including but not limited to upper and lower endoscopic evaluation, to aid in the identification of metastatic GI malignancies versus primary mucinous ovarian cancer.

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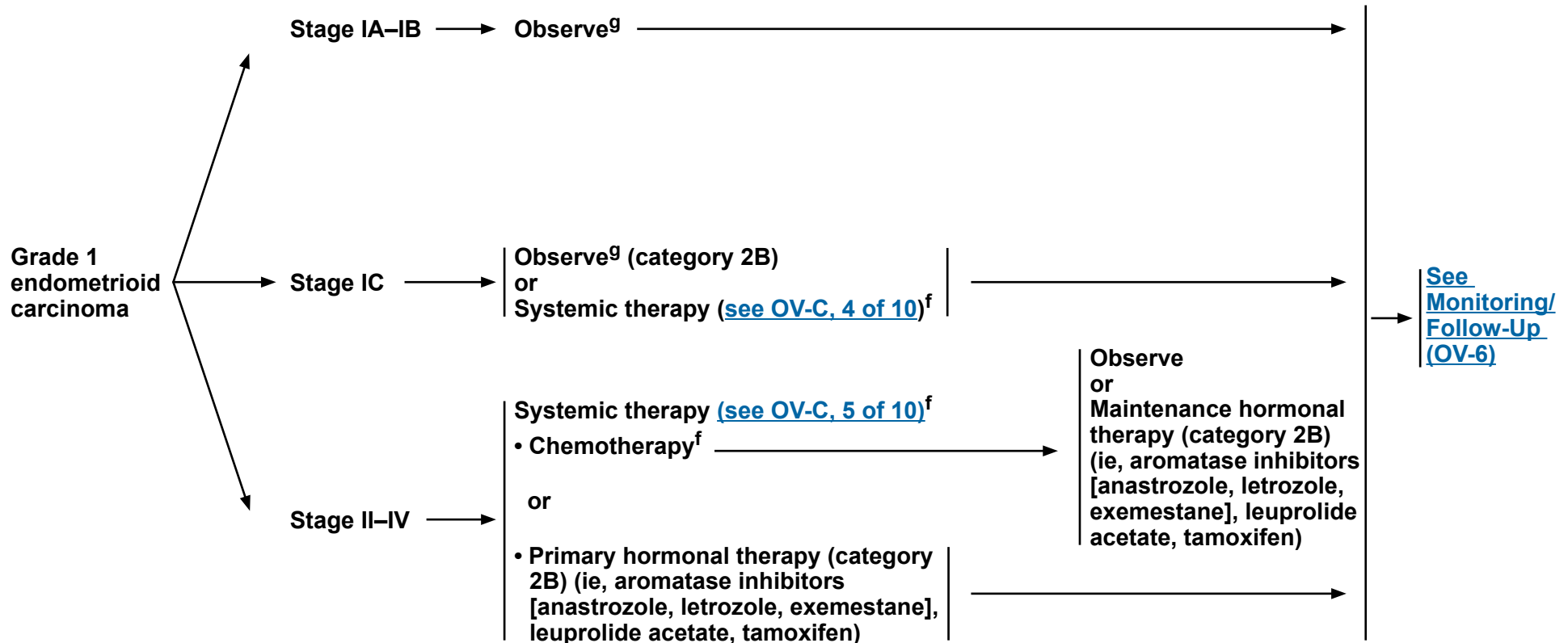
# NCCN Guidelines Version 1.2020

## Grade 1 Endometrioid Epithelial Carcinoma

**PATHOLOGIC  
DIAGNOSIS<sup>a</sup>**

**ADJUVANT TREATMENT**

**MONITORING/  
FOLLOW-UP**



<sup>a</sup>See [WHO Histologic Classification \(OV-E\)](#).

<sup>f</sup>See [Principles of Systemic Therapy \(OV-C\)](#) and [Management of Drug Reactions \(OV-D\)](#).

<sup>g</sup>Consider surgical staging (if not previously done) if considering observation. See [Principles of Surgery \(OV-A\)](#).

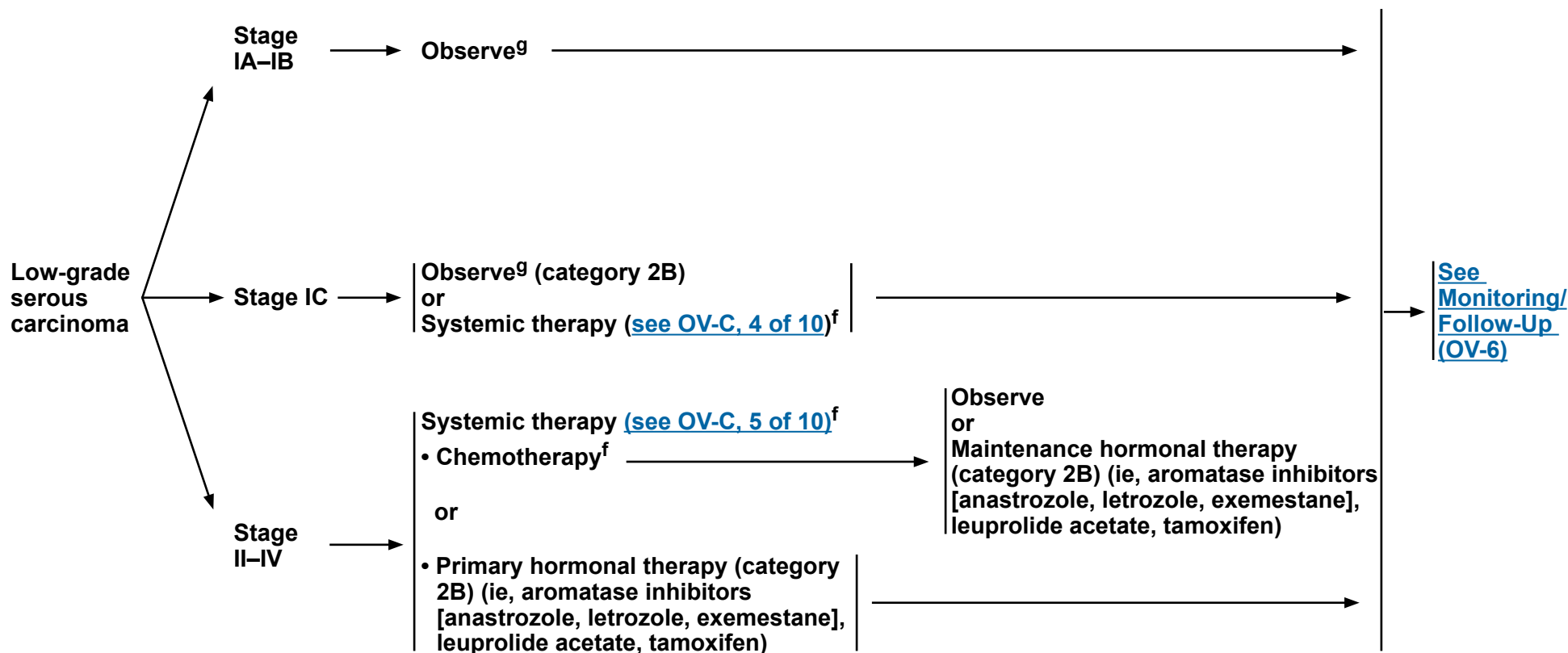
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**PATHOLOGIC DIAGNOSIS<sup>a</sup>**

**ADJUVANT TREATMENT**

**MONITORING/ FOLLOW-UP**



<sup>a</sup> See [WHO Histologic Classification \(OV-E\)](#).

<sup>f</sup> See [Principles of Systemic Therapy \(OV-C\)](#) and [Management of Drug Reactions \(OV-D\)](#).

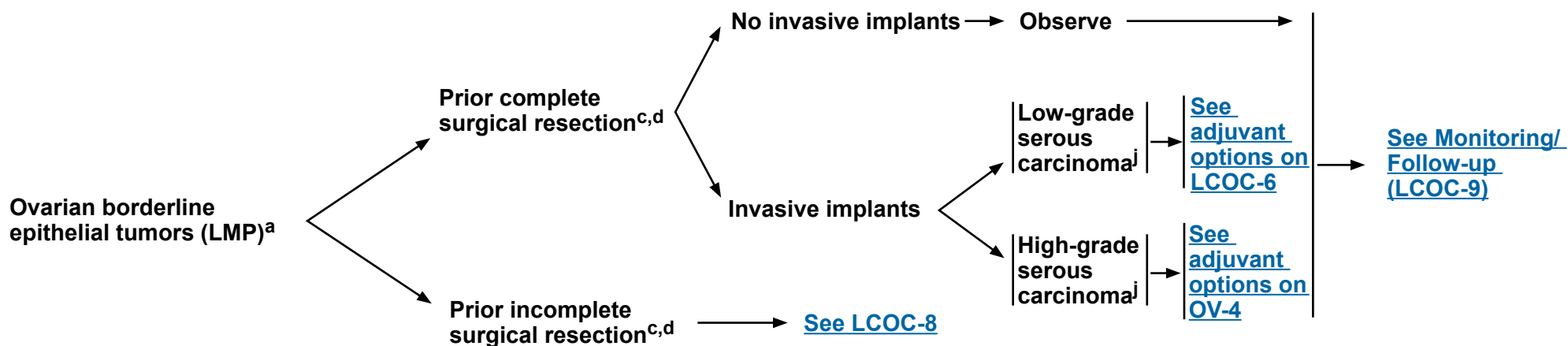
<sup>g</sup> Consider surgical staging (if not previously done) if considering observation. See [Principles of Surgery \(OV-A\)](#).

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**Clinical Trials:** NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

**PATHOLOGIC DIAGNOSIS<sup>a</sup>**

**ADJUVANT TREATMENT<sup>i</sup>**



<sup>a</sup>See WHO Histologic Classification (OV-E).

<sup>c</sup>See Principles of Surgery (OV-A).

<sup>d</sup>Principles of Pathology (OV-B).

<sup>i</sup>Standard recommendation includes a patient evaluation by a gynecologic oncologist.

<sup>j</sup>Chemotherapy (IV or IP) has not been shown to be beneficial in ovarian borderline epithelial tumors (LMP).

**Note:** All recommendations are category 2A unless otherwise indicated.

**Clinical Trials:** NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

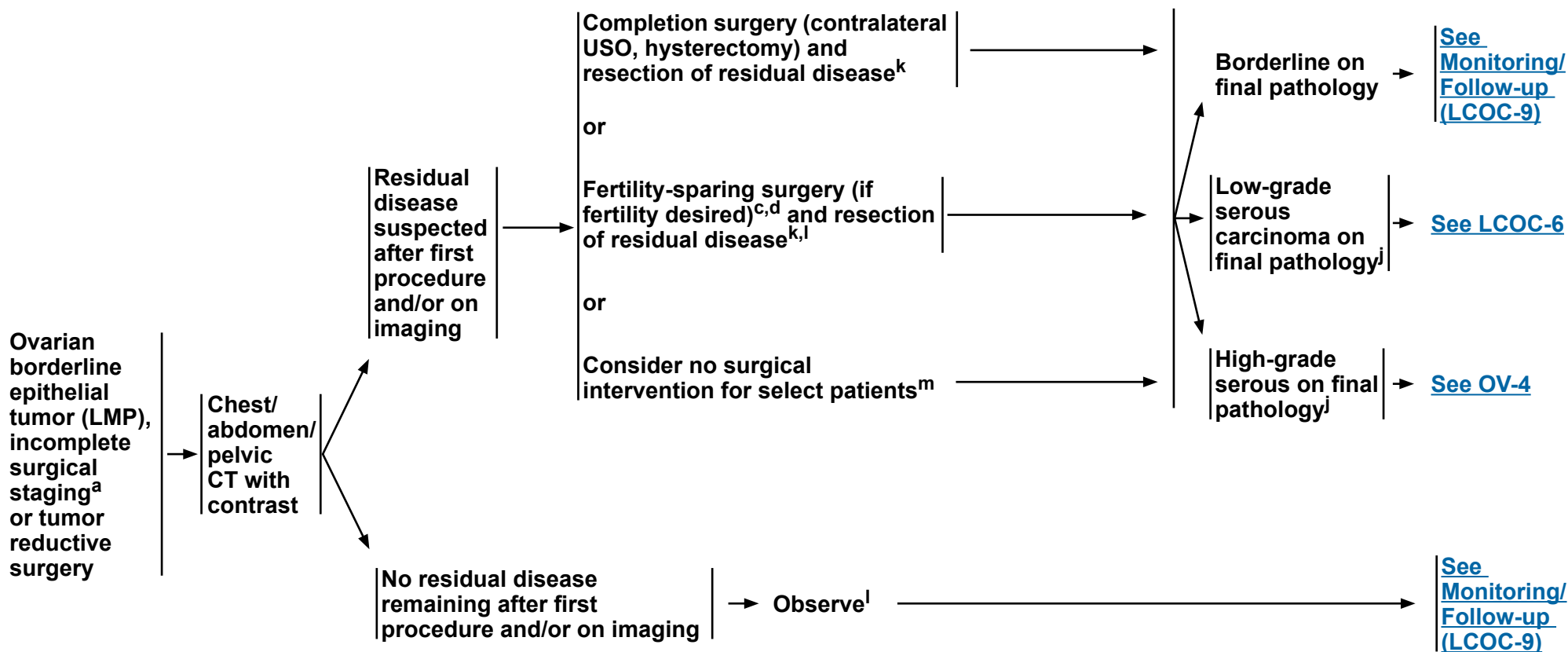


# NCCN Guidelines Version 1.2020

## Ovarian Borderline Epithelial Tumors (Low Malignant Potential)

### PATHOLOGIC DIAGNOSIS<sup>a</sup>

### ADJUVANT TREATMENT<sup>i</sup>



<sup>a</sup> See [WHO Histologic Classification \(OV-E\)](#).

<sup>c</sup> See [Principles of Surgery \(OV-A\)](#).

<sup>d</sup> [Principles of Pathology \(OV-B\)](#).

<sup>i</sup> Standard recommendation includes a patient evaluation by a gynecologic oncologist.

<sup>j</sup> Chemotherapy (IV or IP) has not been shown to be beneficial in ovarian borderline epithelial tumors (LMP).

<sup>k</sup> For pathologically proven ovarian borderline epithelial tumors, lymph node evaluation may be considered on a case-by-case basis.

<sup>l</sup> In patients who underwent USO, consider completion surgery (eg, contralateral USO, hysterectomy) after completion of childbearing (category 2B).

<sup>m</sup> If patient is medically unfit, or for those with unresectable residual disease.

**Note:** All recommendations are category 2A unless otherwise indicated.

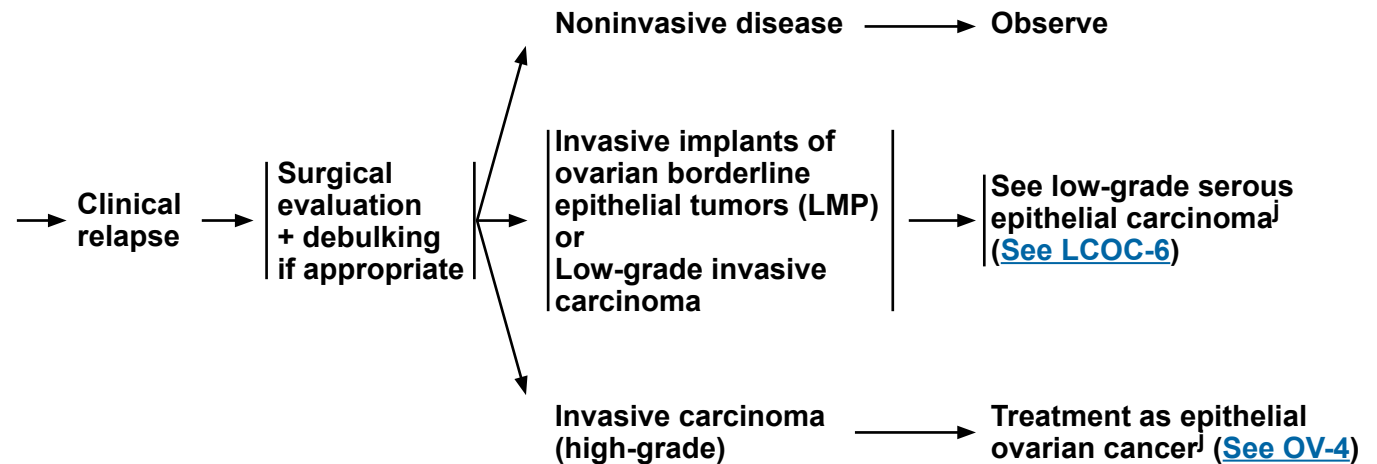
**Clinical Trials:** NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

**MONITORING/FOLLOW-UP**

**RECURRENT DISEASE**

**RECURRENCE THERAPY**

- Visits every 3–6 mo for up to 5 y, then annually
- Physical exam including pelvic exam
- CA-125<sup>n</sup> or other tumor markers every visit if initially elevated
- CBC, chemistry profile as indicated
- Imaging<sup>o</sup> as clinically indicated: Chest/abdominal/pelvic CT, MRI, PET/CT, or PET (skull base to mid-thigh)
- Ultrasound as indicated for patients with fertility-sparing surgery



<sup>j</sup> Chemotherapy (IV or IP) has not been shown to be beneficial in ovarian borderline epithelial tumors (LMP).

<sup>n</sup> There are data regarding the utility of CA-125 for monitoring of ovarian cancer after completion of primary therapy. See [The Society of Gynecologic Oncology \(SGO\) position statement](#) and [Discussion](#).

<sup>o</sup> Imaging performed with contrast unless contraindicated.

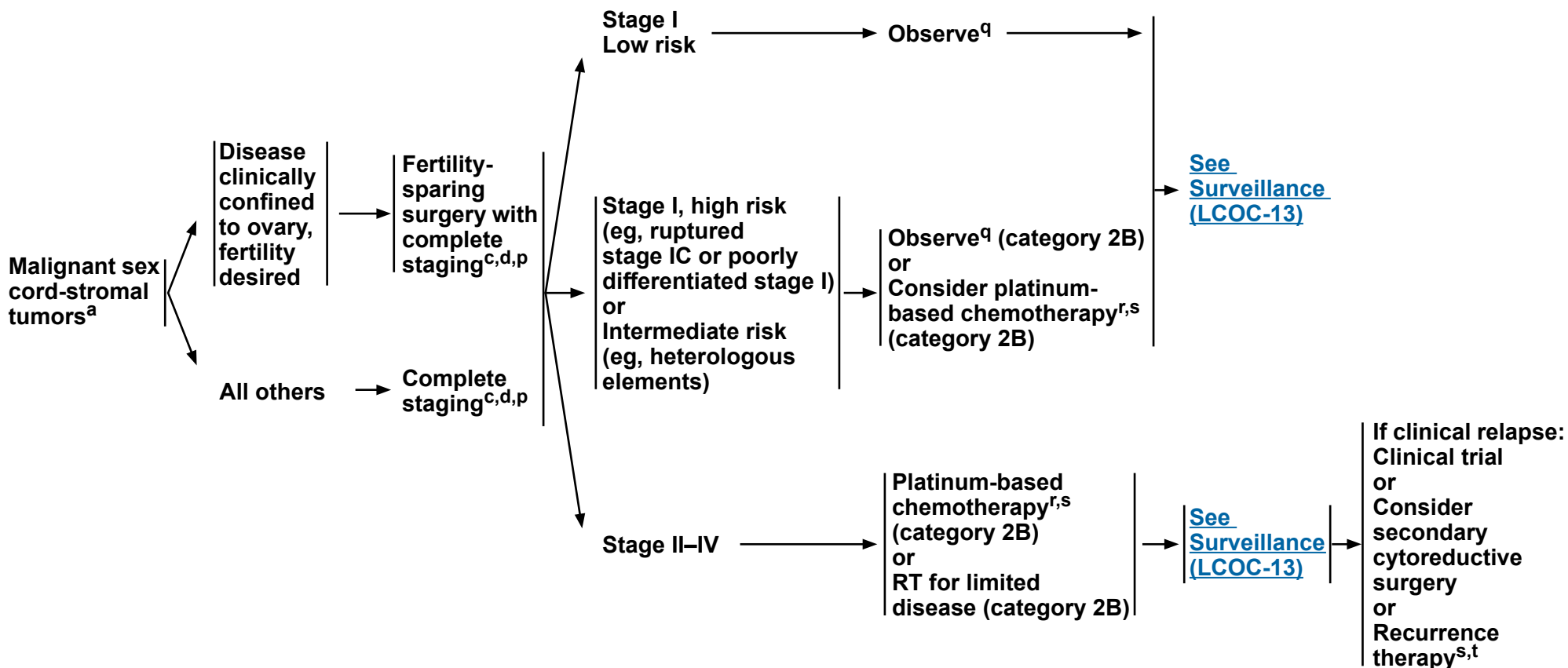
**Note:** All recommendations are category 2A unless otherwise indicated.

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**CLINICAL PRESENTATION/  
DIAGNOSIS**

**ADJUVANT  
TREATMENT**

**RECURRENCE  
THERAPY**



<sup>a</sup>See WHO Histologic Classification (OV-E).

<sup>c</sup>See Principles of Surgery (OV-A).

<sup>d</sup>Principles of Pathology (OV-B).

<sup>p</sup>Lymphadenectomy may be omitted.

<sup>q</sup>Inhibin levels can be followed if initially elevated for granulosa cell tumors (category 2B).

<sup>r</sup>Acceptable options include paclitaxel/carboplatin (preferred), EP (etoposide, cisplatin), or BEP (bleomycin, etoposide, cisplatin) (category 2B).

<sup>s</sup>See Principles of Systemic Therapy (OV-C) and see Systemic Therapy Regimens for Malignant Germ Cell/Sex Cord-Stromal Tumors (OV-C, 9 of 10).

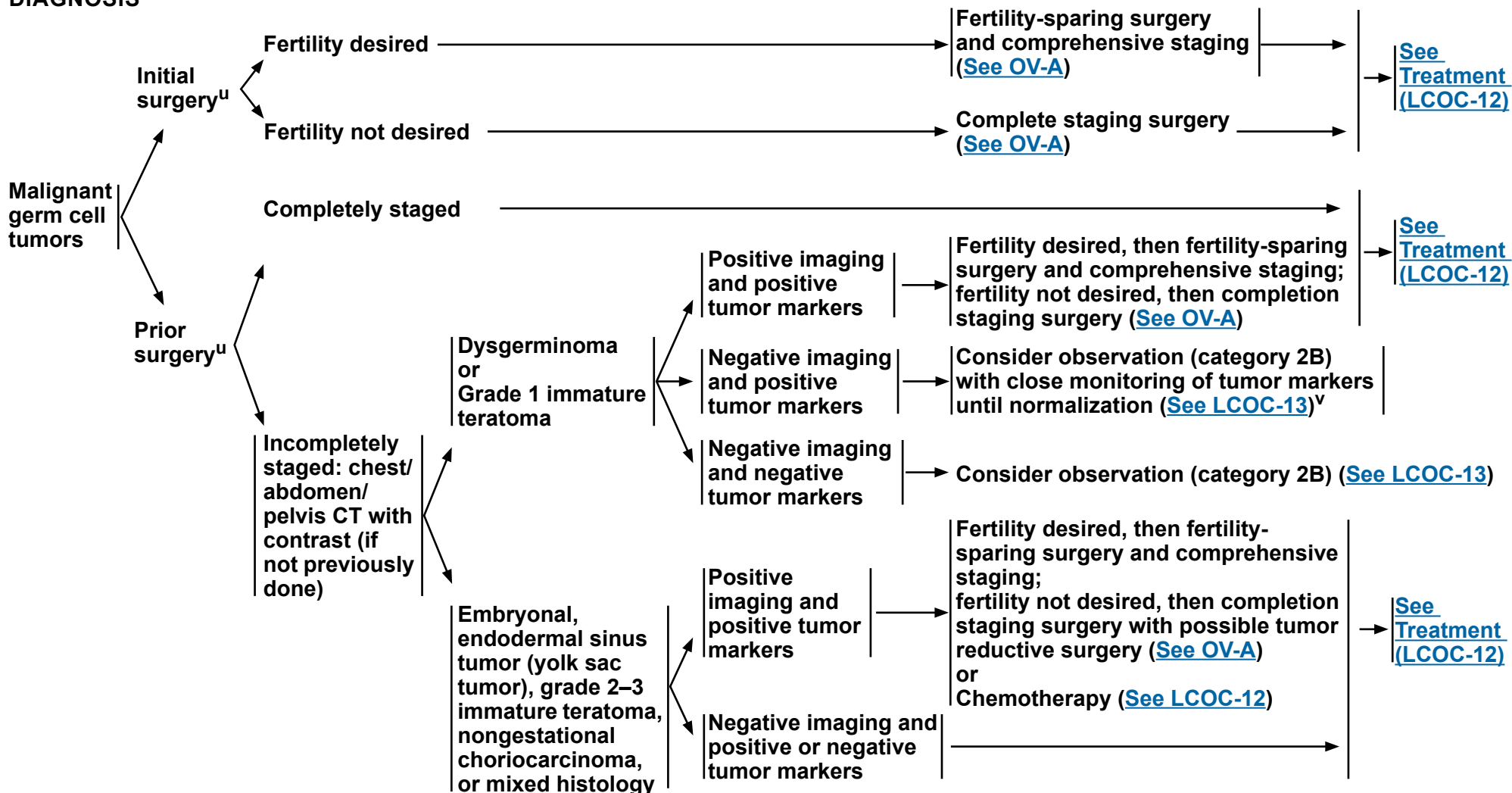
<sup>t</sup>Palliative localized RT can be considered.

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### CLINICAL PRESENTATION/ DIAGNOSIS

### TREATMENT<sup>i</sup>



<sup>i</sup> Standard recommendation includes a patient evaluation by a gynecologic oncologist.

<sup>u</sup> Surgical principles for pediatric/young adult patients may differ from those for adult patients. [See Principles of Surgery \(OV-A\)](#).

<sup>v</sup> Repeat imaging if tumor markers plateau at significant abnormal level or rise. If imaging positive, follow pathway above for positive imaging and positive tumor markers.

**Note:** All recommendations are category 2A unless otherwise indicated.

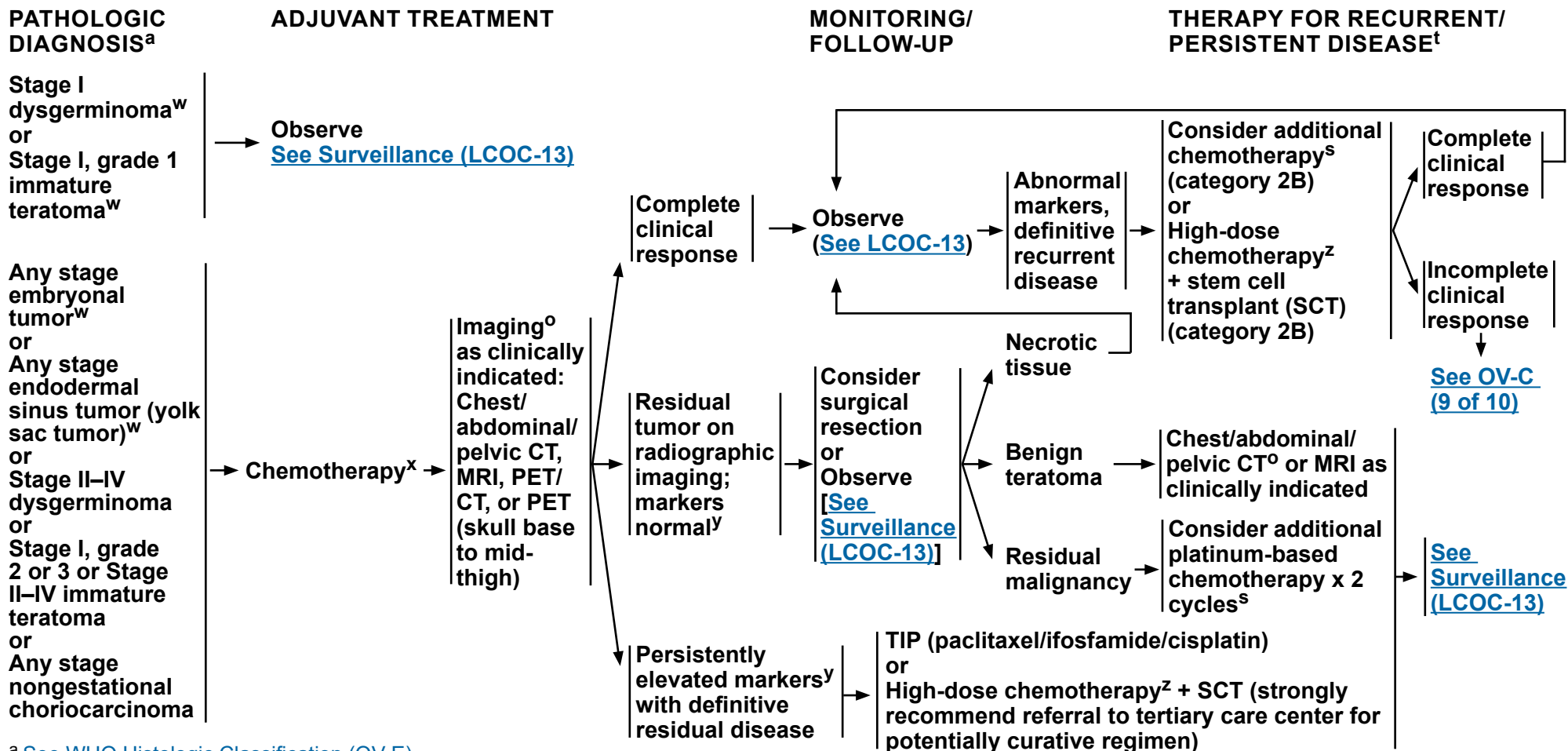
**Clinical Trials:** NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.





# NCCN Guidelines Version 1.2020

## Malignant Germ Cell Tumors



<sup>a</sup> See [WHO Histologic Classification \(OV-E\)](#).

<sup>o</sup> Imaging performed with contrast unless contraindicated.

<sup>s</sup> See [Principles of Systemic Therapy \(OV-C\)](#) and [See Systemic Therapy Regimens for Malignant Germ Cell/Sex Cord-Stromal Tumors \(OV-C, 9 of 10\)](#).

<sup>t</sup> Palliative localized RT can be considered.

<sup>w</sup> Pediatric/adolescent patients with the following clinical presentations may consider observation or chemotherapy as treatment options: stage IA, IB dysgerminoma; stage IA, grade 1 immature teratoma; stage IA embryonal tumors; or stage IA yolk sac tumors.

<sup>x</sup> See [Primary Systemic Therapy Regimens for Malignant Germ Cell Tumors \(OV-C, 9 of 10\)](#).

<sup>y</sup> See [OV-1](#) for markers.

<sup>z</sup> High-dose chemotherapy regimens vary among institutions. Some patients are potentially curable with stem cell transplantation. Patients with potentially curable recurrent germ cell disease should be referred to a tertiary care institution for stem-cell transplant consultation and potentially curative therapy.

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# NCCN Guidelines Version 1.2020

## Malignant Germ Cell and Sex Cord-Stromal Tumors

### SURVEILLANCE FOR MALIGNANT GERM CELL AND SEX CORD-STROMAL TUMORS

| Malignant Germ Cell Tumors                         |   |   |                                     |                                     |                         |
|--|---|---|-------------------------------------|-------------------------------------|-------------------------|
|  | Year 1  | Year 2  | Year 3                              | Years 4–5                           | After 5 Years           |
| <b>Dysgerminoma</b>                                | Every 2–3 mo  | Every 3–4 mo  | Every 6 mo                          | Every 6 mo                          | Annually                |
| Physical exam and serum tumor markers <sup>y</sup> |   |   |                                     |                                     |                         |
| Radiographic imaging <sup>aa</sup>                 | Abdominal/pelvic CT (every 3–4 mo)  | Abdominal/pelvic CT (every 6 mo)                                      | Abdominal/pelvic CT (annually)      | Abdominal/pelvic CT (annually)      | As clinically indicated |
| <b>Non-dysgerminoma</b>                            | Every 2 mo  | Every 2 mo  | Every 4–6 mo                        | Every 6 mo                          | Annually                |
| Physical exam and serum tumor markers <sup>y</sup> |   |   |                                     |                                     |                         |
| Radiographic imaging                               | Posteroanterior (PA) and lateral chest x-ray and abdominal/pelvic CT (every 3–4 mo) | PA and lateral chest x-ray and abdominal/pelvic CT (every 4–6 months) | Abdominal/pelvic CT (every 6–12 mo) | Abdominal/pelvic CT (every 6–12 mo) | As clinically indicated |

| Malignant Sex Cord-Stromal Tumors <sup>bb</sup> |   |   |
|---|---|---|
|   | 0–2 Years   | After 2 Years   |
| <b>Physical exam</b>                            | As clinically indicated based on stage (ie, 6–12 mo if early-stage, low-risk disease; 4–6 mo if high-risk disease)  | As clinically indicated based on stage (ie, 6–12 mo if early-stage, low-risk disease; 4–6 mo if high-risk disease)  |
| <b>Serum tumor markers<sup>y</sup></b>          | <ul style="list-style-type: none"> <li>• Testing as clinically indicated, if applicable</li> <li>• If done, frequency based on stage (ie, 6–12 mo if early-stage, low-risk disease; 4–6 mo if high-risk disease)</li> </ul> | <ul style="list-style-type: none"> <li>• Testing as clinically indicated, if applicable</li> <li>• If done, frequency based on stage (ie, 6–12 mo if early-stage, low-risk disease; 4–6 mo if high-risk disease)</li> </ul> |
| <b>Radiographic imaging<sup>aa</sup></b>        | Reserved for patients with symptoms, elevated biomarkers, or suspicious findings on physical exam   | Reserved for patients with symptoms, elevated biomarkers, or suspicious findings on physical exam   |

<sup>y</sup>See [OV-1](#) for markers.<sup>aa</sup> Chest x-ray, chest/abdominal/pelvic CT, MRI, PET/CT, or PET; with contrast unless contraindicated.<sup>bb</sup> Salani R, Khanna N, Frimer M, et al. An update on post-treatment surveillance and diagnosis of recurrence in women with gynecologic malignancies: Society of Gynecologic Oncology (SGO) recommendations. *Gynecol Oncol* 2017;146(1):3-10.**Note:** All recommendations are category 2A unless otherwise indicated.**Clinical Trials:** NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



### PRINCIPLES OF SURGERY<sup>1</sup>

#### General Considerations

- It is recommended that a gynecologic oncologist perform the appropriate surgery.
- An open laparotomy including a vertical midline abdominal incision should be used in most patients with a suspected malignant ovarian/fallopian tube/primary peritoneal neoplasm in whom a surgical staging procedure, a primary debulking procedure, an interval debulking procedure, or secondary cytoreduction is planned.
  - ▶ For select patients, a minimally invasive surgical approach may be employed by an experienced surgeon to manage early-stage disease. Laparoscopy may be useful to evaluate whether optimal cytoreduction can be achieved in patients with newly diagnosed advanced stage or recurrent disease.
  - ▶ Minimally invasive techniques can be used for select patients for interval debulking procedures. Patients who are unable to be optimally debulked using minimally invasive techniques should be converted to an open procedure.
- Intraoperative pathologic evaluation with frozen sections may assist in management.
- Prior to surgery for ovarian cancer, counsel patients about port placement if intraperitoneal (IP) chemotherapy is being considered.

#### Operative Reports

- Surgeons should describe the following in the operative report:
  - ▶ Extent of initial disease before debulking pelvis, mid-abdomen, or upper abdomen (cutoffs: pelvic brim to lower ribs).
  - ▶ Amount of residual disease in the same areas after debulking.
  - ▶ Complete or incomplete resection; if incomplete, indicate the size of the major lesion and total number of lesions. Indicate if miliary or small lesions.

<sup>1</sup>Fleming GF, Seidman J, Yemelyanova A, and Lengyl E: Epithelial Ovarian Cancer. In Chi DS, Berchuck A, Dizon D, et al. (eds): Principles and Practice of Gynecologic Oncology, 7th ed, Philadelphia, Lippincott Williams & Wilkins, 2017:611-705.

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[Continued](#)



# NCCN Guidelines Version 1.2020

## Ovarian Cancer/Fallopian Tube Cancer/ Primary Peritoneal Cancer

### PRINCIPLES OF SURGERY<sup>1</sup>

#### Newly Diagnosed Invasive Epithelial Ovarian Cancer Apparently Confined to an Ovary or to the Pelvis

In general, every effort should be made during a primary cytoreduction procedure to achieve maximum cytoreduction of all pelvic disease and to evaluate for occult disease in the upper abdomen or retroperitoneum.

- On entering the abdomen, aspiration of ascites or peritoneal lavage should be performed for peritoneal cytologic examinations.
- All peritoneal surfaces should be visualized, and any peritoneal surface or adhesion suspicious for harboring metastasis should be selectively excised or biopsied. In the absence of any suspicious areas, random peritoneal biopsies should be taken from the pelvis, paracolic gutters, and undersurfaces of the diaphragm (diaphragm scraping for Papanicolaou stain is an acceptable alternative).
- BSO and hysterectomy should be performed with every effort to keep an encapsulated mass intact during removal.
- For selected patients desiring to preserve fertility, USO or BSO with uterine preservation may be considered. Uterine preservation allows for potential future assisted reproductive approaches.
- Omentectomy should be performed.
- Para-aortic lymph node dissection should be performed by stripping the nodal tissue from the vena cava and the aorta bilaterally to at least the level of the inferior mesenteric artery and preferably to the level of the renal vessels.
- The preferred method of dissecting pelvic lymph nodes is bilateral removal of lymph nodes overlying and anterolateral to the common iliac vessel, overlying and medial to the external iliac vessel, overlying and medial to the hypogastric vessels, and from the obturator fossa at a minimum anterior to the obturator nerve.<sup>2</sup>

#### Newly Diagnosed Invasive Epithelial Ovarian Cancer Involving the Pelvis and Upper Abdomen

In general, every effort should be made during a primary cytoreduction procedure to achieve maximum cytoreduction of all abdominal, pelvic, and retroperitoneal disease. Residual disease <1 cm defines optimal cytoreduction; however, maximal effort should be made to remove all gross disease since this offers superior survival outcomes.<sup>3</sup>

- Aspiration of ascites (if present) should be performed for peritoneal cytologic examinations. All involved omentum should be removed.
- Suspicious and/or enlarged nodes should be resected, if possible. Resection of clinically negative nodes is not required.
- Those patients with tumor nodules outside the pelvis  $\leq 2$  cm (presumed stage IIIB) should have bilateral pelvic and para-aortic lymph node dissection as previously described.
- Procedures that may be considered for optimal surgical cytoreduction (in all stages) include bowel resection and/or appendectomy, stripping of the diaphragm or other peritoneal surfaces, splenectomy, partial cystectomy and/or ureteroneocystostomy, partial hepatectomy, partial gastrectomy, cholecystectomy, and/or distal pancreatectomy.
- Select patients with low-volume residual disease after surgical cytoreduction for invasive epithelial ovarian or peritoneal cancer are potential candidates for IP therapy. In these patients, consideration should be given to placement of IP catheter with initial surgery.

<sup>1</sup> Fleming GF, Seidman J, Yemelyanova A, and Lengyl E: Epithelial Ovarian Cancer. In Chi DS, Berchuck A, Dizon D, et al. (eds): Principles and Practice of Gynecologic Oncology, 7th ed, Philadelphia, Lippincott Williams & Wilkins, 2017:611-705.

<sup>2</sup> Whitney CW, Spirtos N. Gynecologic Oncology Group Surgical Procedures Manual. Philadelphia: Gynecologic Oncology Group; 2010.

<sup>3</sup> Chi DS, Eisenhauer EL, Zivanovic O, et al. Improved progression-free and overall survival in advanced ovarian cancer as a result of a change in surgical paradigm. Gynecol Oncol 2009;114:26-31.

[Continued](#)

**Note:** All recommendations are category 2A unless otherwise indicated.

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# NCCN Guidelines Version 1.2020

## Ovarian Cancer/Fallopian Tube Cancer/ Primary Peritoneal Cancer

### PRINCIPLES OF SURGERY<sup>1</sup>

#### Interval Debulking Surgery After Neoadjuvant Chemotherapy of Invasive Epithelial Ovarian Cancer

As with a primary debulking procedure, every effort should be made to achieve maximum cytoreduction during an interval debulking procedure. Maximal effort should be made to remove all gross disease in the abdomen, pelvis, and retroperitoneum. Consultation with a gynecologic oncologist is recommended.

- IDS, including completion hysterectomy and BSO with staging, should be performed after 3–4 cycles of neoadjuvant chemotherapy 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 individual patient-centered factors.
- Hyperthermic intraperitoneal chemotherapy (HIPEC) with cisplatin (100 mg/m<sup>2</sup>) can be considered at the time of IDS for stage III disease.
- All peritoneal surfaces should be visualized, and any peritoneal surface or adhesion suspicious for harboring metastasis should be selectively excised or biopsied.
- An omentectomy should be performed.
- Suspicious and/or enlarged nodes should be resected, if possible. Removal of lymph nodes noted to have potential metastasis at the time of initial diagnosis should be considered, even if not currently suspicious or enlarged.
- Procedures that may be considered for optimal surgical debulking include bowel resection and/or appendectomy, stripping of the diaphragm or other peritoneal surfaces, splenectomy, partial cystectomy and/or ureteroneocystostomy, partial hepatectomy, partial gastrectomy, cholecystectomy, and/or distal pancreatectomy.

#### Risk-Reducing Salpingo-Oophorectomy (RRSO) Protocol

- For information on when RRSO is indicated, [see NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic](#).
- Perform minimally invasive laparoscopic surgery.
- Survey upper abdomen, bowel surfaces, omentum, appendix (if present), and pelvic organs.
- Biopsy any abnormal peritoneal findings.
- Obtain pelvic washing for cytology (50 cc normal saline instilled and aspirated immediately).
- Perform total BSO, removing 2 cm of proximal ovarian vasculature/IP ligament, all tube up to the cornua, and all peritoneum surrounding the ovaries and tubes, especially peritoneum underlying areas of adhesion between tube and/or ovary and the pelvic sidewall.<sup>4</sup>
- Engage in minimal instrument handling of the tubes and ovaries to avoid traumatic exfoliation of cells.<sup>4</sup>
- Both ovaries and tubes should be placed in an endobag for retrieval from the pelvis.
- Both ovaries and tubes should be processed according to SEE-FIM protocol.<sup>5</sup>
- If occult malignancy or serous tubal intraepithelial carcinoma (STIC) is identified, provide referral to gynecologic oncologist.
- The prevention benefits of salpingectomy alone are not yet proven. If considered, the fallopian tube from the fimbria to its insertion into the uterus should be removed. In addition, the fallopian tube should be processed and assessed as described above. The concern for risk-reducing salpingectomy alone is that women are still at risk for developing ovarian cancer. In addition, in premenopausal women, oophorectomy reduces the risk of developing breast cancer but the magnitude is uncertain. [See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic](#).

<sup>1</sup> Fleming GF, Seidman J, Yemelyanova A, and Lengyl E: Epithelial Ovarian Cancer. In Chi DS, Berchuck A, Dizon D, et al. (eds): Principles and Practice of Gynecologic Oncology, 7th ed, Philadelphia, Lippincott Williams & Wilkins, 2017:611-705.

<sup>4</sup> Powell CB, Chen LM, McLennan J, et al. Risk-reducing salpingo-oophorectomy (RRSO) in BRCA mutation carriers: experience with a consecutive series of 111 patients using a standardized surgical-pathological protocol. Int J Gynecol Cancer 2011;21:846-851.

<sup>5</sup> Mingels MJ, van Ham MA, de Kievit IM, et al. Müllerian precursor lesions in serous ovarian cancer patients: using the SEE-Fim and SEE-End protocol. Mod Pathol 2014;27:1002-1013.

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[Continued](#)



# NCCN Guidelines Version 1.2020

## Ovarian Cancer/Fallopian Tube Cancer/ Primary Peritoneal Cancer

### PRINCIPLES OF SURGERY<sup>1</sup>

#### Special Circumstances

##### • Fertility-sparing surgery:

▶ Fertility-sparing surgery with USO (preserving the uterus and contralateral ovary) or BSO (preserving the uterus) can be considered for patients with apparent early-stage disease and/or low-risk tumors (early-stage invasive epithelial tumors, LMP lesions, malignant germ cell tumors, mucinous, or malignant sex cord-stromal tumors) who wish to preserve fertility. Refer to reproductive endocrinologist for evaluation and consultation as clinically indicated. Comprehensive surgical staging should still be performed to rule out occult higher stage disease but may be omitted in pediatric/adolescent patients with clinically apparent early-stage malignant germ cell tumors based on the pediatric surgical literature.<sup>6</sup>

• Mucinous tumors: Primary invasive mucinous tumors of the ovary are uncommon. Thus, the upper and lower GI tract should be carefully evaluated to rule out an occult GI primary with ovarian metastases, and an appendectomy need only be performed in patients with a suspected or confirmed mucinous ovarian neoplasm if it appears to be abnormal. A normal appendix does not require surgical resection in this setting.

• Ovarian borderline epithelial (LMP) tumors: Although data show upstaging with lymphadenectomy, other data show that lymphadenectomy does not affect overall survival. However, omentectomy and multiple biopsies of peritoneum (the most common sites of peritoneal implants) may upstage patients in approximately 30% of cases and may affect prognosis.

• Secondary cytoreduction: A secondary cytoreduction procedure can be considered in patients with recurrent ovarian cancer who recur more than 6–12 months since completion of initial chemotherapy, have an isolated focus (or limited foci) of disease amenable to complete resection, and do not have ascites.

#### Ancillary Palliative Surgical Procedures<sup>7</sup>

These procedures may be appropriate in select patients:

- Paracentesis/indwelling peritoneal catheter
- Thoracentesis/pleurodesis/video-assisted thoracoscopy/indwelling pleural catheter
- Ureteral stents/nephrostomy
- Gastrostomy tube/intestinal stents/surgical relief of intestinal obstruction

<sup>1</sup> Fleming GF, Seidman J, Yemelyanova A, and Lengyl E: Epithelial Ovarian Cancer. In Chi DS, Berchuck A, Dizon D, et al. (eds): Principles and Practice of Gynecologic Oncology, 7th ed, Philadelphia, Lippincott Williams & Wilkins, 2017:611-705.

<sup>6</sup> Billmire D, Vinocur C, Rescorla F, et al. Outcome and staging evaluation in malignant germ cell tumors of the ovary in children and adolescents: an intergroup study. J Pediatr Surg 2004;39:424-429.

<sup>7</sup> Decisions on the use of ancillary procedures should be made in conjunction with a gynecologic oncology surgeon or a practitioner familiar with ovarian cancer patterns of recurrence.

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# NCCN Guidelines Version 1.2020

## Ovarian Cancer/Fallopian Tube Cancer/ Primary Peritoneal Cancer

### PRINCIPLES OF PATHOLOGY

#### General

- The complete histologic classification from the WHO is included in the NCCN Guidelines ([see WHO Histologic Classification on OV-E](#)).<sup>1</sup> The WHO pathology manual is also a useful resource.<sup>1,2</sup>
- Most ovarian cancers, including the LCOC, are diagnosed after pathologic analysis of a biopsy or surgical specimen. Fine-needle aspiration (FNA) should be avoided for diagnosis of ovarian cancer in patients with presumed early-stage disease to prevent rupturing the cyst and spilling malignant cells into the peritoneal cavity. However, FNA may be necessary in patients with bulky disease who are not candidates for primary debulking.<sup>3,4</sup>
- Both primary peritoneal and fallopian tube cancers are usually diagnosed postoperatively (if there is no major involvement of the ovary) or preoperatively (if there is a biopsy and the patient has already had a bilateral oophorectomy). Primary peritoneal and fallopian tube cancers are treated in the same manner as epithelial ovarian cancer.
- The CAP protocol is a useful tool for pathology reports.<sup>5,6,7</sup> Pathologic assessment should include:
  - ▶ Elements from CAP protocol:<sup>5,6,7</sup>
    - ◇ Tumor site(s) (eg, ovary, fallopian tube, or primary peritoneum)
    - ◇ Tumor size(s)
    - ◇ Other tissue/organ involvement
    - ◇ Ovarian/fallopian tumors: surface involvement (present/absent/cannot determine), specimen integrity (capsule/serosa intact/fractured/fragmented)
    - ◇ Histologic type and grade
    - ◇ Extension and/or implants (if sampled/identified)
    - ◇ Cytology: peritoneal or ascitic fluid or washings/pleural fluid
    - ◇ Lymph nodes: number and location of nodes examined, size of largest metastatic deposits
    - ◇ Serous tubal intraepithelial carcinoma (STIC), endometriosis (particularly if in continuity with endometrioid or clear cell carcinoma), endosalpingiosis
  - ▶ Tumor molecular analyses as clinically indicated:
    - ◇ Next-generation sequencing (NGS) for *BRCA1/2* somatic mutations
    - ◇ Immunohistochemistry (IHC) for DNA mismatch repair (MMR) proteins (MLH1, MSH2, MSH6, and PMS2) or microsatellite instability (MSI) testing via polymerase chain reaction (PCR)
    - ◇ Consider evaluation of homologous recombination deficiency
    - ◇ Additional somatic tumor testing can be considered at the physician's discretion to identify genetic alterations for which FDA-approved tumor-specific or tumor-agnostic targeted therapy options exist.

#### [References](#)

#### [Continued](#)

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**PRINCIPLES OF PATHOLOGY****Less Common Ovarian Cancers (LCOC)**

- A borderline tumor is a primary epithelial lesion with cytologic characteristics suggesting malignancy but without frank invasion. The terms for borderline epithelial tumors (also known as LMP tumors or atypical proliferative tumors) have changed over the years.<sup>8</sup> The 2016 and 2017 CAP cancer protocols for ovarian cancer use borderline and do not use LMP.<sup>5,6</sup> Borderline epithelial tumors are typically serous or mucinous; other histologic subtypes can also occur ([see WHO Histologic Classification on OV-E](#)).<sup>1,9</sup> The characteristic pathologic hallmark of typical epithelial ovarian cancer is the identification of peritoneal implants, which microscopically and/or macroscopically invade the peritoneum. A borderline epithelial tumor may grossly resemble an invasive cancer. However, microscopic evaluation fails to reveal evidence of frank invasion by the tumor nodules, although rarely invasive implants (which continue to be consistent with the diagnosis of borderline epithelial lesions) can be identified microscopically by the pathologist.
- Clear cell carcinomas are high-grade tumors that may arise in endometriosis. Most clear cell carcinomas express Napsin A and are negative for WT1 and estrogen receptors.<sup>8</sup>
- It is difficult to distinguish based on histology between primary mucinous ovarian carcinomas and gastrointestinal metastases.<sup>10,11,12</sup> PAX8 immunostaining is typical of primary ovarian tumors, although the absence of PAX8 does not rule out ovary as the primary site,<sup>13</sup> while SATB2 is consistent with colonic origin.<sup>14</sup> Metastatic colorectal adenocarcinomas also usually are positive for CK20 and CEA.
- Endometrioid carcinomas may be associated with endometriosis.<sup>13,15</sup> Endometrioid adenocarcinomas are usually positive for cytokeratin 7 (CK7), PAX8, CA-125, and estrogen receptors. Endometrioid tumors are also very similar in appearance to sex cord stromal tumors.<sup>8</sup>
- Most pathologists now consider MMTs to be a variant of poorly differentiated epithelial ovarian cancer (metaplastic carcinoma).<sup>16</sup>

**Special Circumstances**

- Other cancers<sup>17,18</sup> that can commonly involve the adnexa include:
  - ▶ Uterine
  - ▶ Cervical
  - ▶ Gastrointestinal (small and large bowel, pancreatic)
  - ▶ Lymphoma
- For risk-reducing surgery, pathologic assessment should include:
  - ▶ Fallopian tubes should be processed by sectioning and extensively examining the fimbriated end (SEE-FIM) of the tubes and then assessed to determine whether any evidence of cancer is present.<sup>19,20</sup>
  - ▶ The ovaries should also be carefully sectioned, processed, and assessed.<sup>20</sup> The 2016 and 2017 CAP protocols describe the process for sectioning the fallopian tubes and ovaries.<sup>5,6,21</sup>
- Patients who have equivocal pathologic findings or who are referred to NCCN Member Institutions after having a previous diagnosis of ovarian cancer should have their pathology reviewed by pathologists at NCCN Member Institutions.

**References**

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**PRINCIPLES OF PATHOLOGY  
REFERENCES**

- 1 Kurman RJ, Carcangiu ML, Harrington CS, et al. WHO Classification of Tumours of Female Reproductive Organs, 4th Edition. WHO/IARC Classification of Tumours. Vol. 6. Lyon: IARC Publications; 2014.
- 2 Meinhold Heerlein I, Fotopoulou C, Harter P, et al. The new WHO classification of ovarian, fallopian tube, and primary peritoneal cancer and its clinical implications. *Arch Gynecol Obstet* 2016;293:695-700.
- 3 Cannistra SA, Gershenson DM, Recht A. Ovarian cancer, fallopian tube carcinoma, and peritoneal carcinoma. In: DeVita Jr. VT, Lawrence TS, Rosenberg SA, eds. *DeVita, Hellman, and Rosenberg's Cancer: Principles & Practice of Oncology (Cancer Principles and Practice of Oncology)*, 10th ed Philadelphia: Lippincott Williams & Wilkins; 2014:1075-1099.
- 4 Vergote I, De Brabanter J, Fyles A, et al. Prognostic importance of degree of differentiation and cyst rupture in stage I invasive epithelial ovarian carcinoma. *Lancet* 2001;357:176-182.
- 5 Gilks B, Movahedi Lankarani S, Baker PM, et al. Protocol for the examination of specimens from patients with carcinoma of the ovary or Fallopian tube: Based on AJCC/UICC TNM, 7th edition: College of American Pathologists; 2016.
- 6 Movahedi Lankarani S, Krishnamurti U, Bell DA, et al. Protocol for the examination of specimens from patients with primary tumors of the ovary, fallopian tube, or peritoneum. Based on AJCC/8th edition/2015 FIGO: Protocol web posting date: June 2017: College of American Pathologists; 2017.
- 7 Movahedi Lankarani S, Baker PM, Gilks B, Soslow RA. Protocol for the examination of specimens from patients with carcinoma of the ovary: Based on AJCC/UICC TNM, 7th edition: Protocol web posting date: October 2013: College of American Pathologists; 2013.
- 8 McCluggage WG, Judge MJ, Clarke BA, et al. Data set for reporting of ovary, fallopian tube and primary peritoneal carcinoma: recommendations from the International Collaboration on Cancer Reporting (ICCR). *Mod Pathol* 2015;28:1101-1122.
- 9 Fischerova D, Zikan M, Dundr P, Cibula D. Diagnosis, treatment, and follow-up of borderline ovarian tumors. *Oncologist* 2012;17:1515-1533.
- 10 Bruls J, Simons M, Overbeek LI, et al. A national population based study provides insight in the origin of malignancies metastatic to the ovary. *Virchows Arch* 2015;467:79-86.
- 11 McCluggage WG, Wilkinson N. Metastatic neoplasms involving the ovary: a review with an emphasis on morphological and immunohistochemical features. *Histopathology* 2005;47:231-247.
- 12 de Waal YR, Thomas CM, Oei AL, et al. Secondary ovarian malignancies: frequency, origin, and characteristics. *Int J Gynecol Cancer* 2009;19:1160-1165.
- 13 Madore J, Ren F, Filali Mouhim A, et al. Characterization of the molecular differences between ovarian endometrioid carcinoma and ovarian serous carcinoma. *J Pathol* 2010;220:392-400.
- 14 Strickland S, Wasserman JK, Giassi A, et al. Immunohistochemistry in the diagnosis of mucinous neoplasms involving the ovary: the added value of SATB2 and biomarker discovery through protein expression database mining. *Int J Gynecol Pathol* 2016;35:191-208.
- 15 Mackay HJ, Brady MF, Oza AM, et al. Prognostic relevance of uncommon ovarian histology in women with stage III/IV epithelial ovarian cancer. *Int J Gynecol Cancer* 2010;20:945-952.
- 16 Berton Rigaud D, Devouassoux Shisheboran M, Ledermann JA, et al. Gynecologic Cancer InterGroup (GCIG) consensus review for uterine and ovarian carcinosarcoma. *Int J Gynecol Cancer* 2014;24:S55-60.
- 17 Young RH. From Krukenberg to today: the ever present problems posed by metastatic tumors in the ovary. Part II. *Adv Anat Pathol* 2007;14:149-177.
- 18 Lee KR, Young RH. The distinction between primary and metastatic mucinous carcinomas of the ovary: gross and histologic findings in 50 cases. *Am J Surg Pathol* 2003;27:281-292. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12604884>.
- 19 Medeiros F, Muto MG, Lee Y, et al. The tubal fimbria is a preferred site for early adenocarcinoma in women with familial ovarian cancer syndrome. *Am J Surg Pathol* 2006;30:230-236.
- 20 Mingels MJ, van Ham MA, de Kievit IM, et al. Mullerian precursor lesions in serous ovarian cancer patients: using the SEE Fim and SEE End protocol. *Mod Pathol* 2014;27:1002-1013.
- 21 Clarke BA, Crum CP, Nucci MR, et al. Protocol for the examination of specimens from patients with carcinoma of the fallopian tube: Based on AJCC/UICC TNM, 7th edition, and FIGO 2006 Annual Report: Protocol web posting date: October 2013: College of American Pathologists; 2013.

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### PRINCIPLES OF SYSTEMIC THERAPY

#### General

- Patients with ovarian, fallopian tube, or peritoneal cancer should be encouraged to participate in clinical trials during all aspects of their diagnosis and treatment.
- Prior to recommending chemotherapy, requirements for adequate organ function and performance status should be met.
- Prior to the initiation of any therapy:
  - ▶ 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).
  - ▶ Patients of child-bearing potential who desire fertility-sparing procedures should be referred to an appropriate fertility specialist. ([See NCCN Guidelines for Adolescent and Young Adult Oncology](#))
  - ▶ Goals of systemic therapy should be discussed.
- Consider scalp cooling to reduce incidence of alopecia for patients receiving chemotherapy with high rates of alopecia.
- Patients should be observed closely and treated for any complications during chemotherapy. Appropriate blood chemistry tests should be monitored. Appropriate dose reductions and modifications of chemotherapy should be performed depending on toxicities experienced and goals of therapy.
- After completion of chemotherapy, patients should be assessed for response during and following treatment and monitored for any long-term complications.
- Chemosensitivity/resistance and/or other biomarker assays are being used at some NCCN Member Institutions for decisions related to future chemotherapy in situations where there are multiple equivalent chemotherapy options available. The current level of evidence is not sufficient to supplant standard-of-care chemotherapy (category 3).

#### Definitions Used in the NCCN Guidelines for Ovarian Cancer

- Adjuvant therapy: Drugs, radiation, or other forms of supplemental treatment following cancer surgery intended to decrease the risk of disease recurrence or to primarily treat residual disease, whether gross or microscopic, following surgical cytoreduction.
- Neo-adjuvant therapy: Drugs, radiation, or other forms of treatment given prior to cancer surgery intended to reduce tumor burden in preparation for surgery.
- Recurrence therapy: Drugs, radiation, or other forms of treatment used to treat recurrent cancer, control symptoms, or increase length and/or quality of life at the time of clinical, biochemical, or radiographic evidence of recurrent cancer following the initial treatment.

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[Continued](#)

**PRINCIPLES OF SYSTEMIC THERAPY****For Patients with Newly Diagnosed Ovarian, Fallopian Tube, or Primary Peritoneal Cancer:**

- If they are eligible for chemotherapy, patients should be informed about the different options that are available—that is, IV chemotherapy, a combination of IP and IV chemotherapy, or a clinical trial—so they can decide which is the most appropriate option. For stage I disease, [see OV-C 4 of 10](#); for stage II-IV disease [see OV-C, 5 of 10](#).
- Prior to the administration of the combined IP and IV regimen, patients must be apprised of the increased toxicities with the combined regimen when compared to using IV chemotherapy alone (increased myelosuppression, renal toxicities, abdominal pain, neuropathy, GI toxicities, metabolic toxicities, and hepatic toxicities).
- Patients considered for the IP cisplatin and IP/IV paclitaxel regimen should have normal renal function prior to starting, a medically appropriate performance status based on the future toxicities of the IP/IV regimen, and no prior evidence of medical problems that could significantly worsen during chemotherapy (eg, pre-existing neuropathy).
- Prior to receiving and after receiving each cycle of IP cisplatin, adequate amounts of IV fluids need to be administered in order to prevent renal toxicity. After each cycle has been completed, patients need to be monitored carefully for myelosuppression, dehydration, electrolyte loss, end-organ toxicities (such as renal and hepatic damage), and all other toxicities. Patients often require IV fluids postchemotherapy in the outpatient setting to prevent or help treat dehydration.
- Refer to the original references ([See Discussion](#)) for full toxicity data, doses, schedule, and dose modifications.

**Neoadjuvant Therapy**

- Consider the histology of the primary tumor and the potential response to primary chemotherapy when evaluating for neoadjuvant chemotherapy.
- Any of the primary IV regimens for stage II–IV high-grade serous carcinoma can be used as neoadjuvant therapy before IDS. [See OV-C \(5 of 10\)](#).
- Bevacizumab-containing regimens should be used with caution before IDS due to potential interference with postoperative healing. If bevacizumab is being used as part of a neoadjuvant regimen, bevacizumab should be withheld from therapy for at least 6 weeks prior to IDS.
- After neoadjuvant therapy and IDS any of the adjuvant therapy options for high-grade serous carcinoma (IV or IP/IV) can be considered. [See OV-C \(5 of 10\)](#).
- There are limited data for the use of IP chemotherapy regimens after neoadjuvant therapy and IDS. The following is an additional IP option after IDS: Paclitaxel 135 mg/m<sup>2</sup> IV on Day 1, carboplatin AUC 6 IP Day 1, paclitaxel 60 mg/m<sup>2</sup> IP Day 8.<sup>a</sup>
- A minimum of 6 cycles of treatment is recommended, including at least 3 cycles of adjuvant therapy after IDS. Patients with stable disease who are tolerating therapy may continue past 6 cycles.

<sup>a</sup>Provencher DM, Gallagher CJ, Parulekar WR, et al. OV21/PETROC: A randomized Gynecologic Cancer Intergroup phase II study of intraperitoneal versus intravenous chemotherapy following neoadjuvant chemotherapy and optimal debulking surgery in epithelial ovarian cancer. *Ann Oncol* 2018;29:431-438.

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**Continued**



# NCCN Guidelines Version 1.2020

## Ovarian Cancer/Fallopian Tube Cancer/ Primary Peritoneal Cancer

### PRINCIPLES OF SYSTEMIC THERAPY

#### Recurrent Ovarian, Fallopian Tube, or Primary Peritoneal Cancer:

- Refer to the original references ([See Discussion](#)) for full toxicity data, doses, schedule, and dose modifications.
- Patients should be informed about the following:
  - 1) Availability of clinical trials, including the risks and benefits of various treatments, which will depend on the number of prior lines of chemotherapy the patient has received, and
  - 2) Performance status, end-organ status, and pre-existing toxicities from prior regimens. If appropriate, palliative care should also be discussed as a possible treatment choice. [See NCCN Guidelines for Palliative Care.](#)
- Tumor molecular testing is recommended prior to initiation of therapy for persistent/recurrent disease. Validated molecular testing should be performed in a CLIA-approved facility using the most recent available tumor tissue. Testing recommended to include at least: *BRCA1/2*, and MSI or dMMR if not previously done. Evaluation of homologous recombination deficiency can be considered. Additional somatic tumor testing can be considered at the physician's discretion to identify genetic alterations for which FDA-approved tumor-specific or tumor-agnostic targeted therapy options exist.
- Because of prior platinum exposure, myelosuppression occurs more frequently with any myelotoxic agent given in the recurrent setting.
- With repeat use of either carboplatin and/or cisplatin, patients are at an increased risk of developing a hypersensitivity reaction (also called an allergic reaction) that could be life-threatening. Thus, patients should be counseled about the risk that a hypersensitivity reaction may occur, educated about the signs and symptoms of hypersensitivity reactions, treated by medical staff who know how to manage hypersensitivity reactions, and treated in a medical setting where appropriate medical equipment is available in case of an allergic reaction. [See Management of Drug Reactions \(OV-C\).](#)
- Before any chemotherapy drug is given in the recurrent setting, the clinician should be familiar with the drug's metabolism (ie, renal, hepatic) and should make certain that the patient is an appropriate candidate for the drug (eg, that the patient has adequate renal or hepatic function).
- Clinicians should be familiar with toxicity management and appropriate dose reduction.
- The schedule, toxicity, and potential benefits of any treatment should be thoroughly discussed with the patient and caregivers. Patient education should also include a discussion of precautions and measures to reduce the severity and duration of complications.

[See Acceptable Recurrence Therapies for Platinum-Sensitive Disease \(OV-C, 7 of 10\)](#)

[See Acceptable Recurrence Therapies for Platinum-Sensitive Disease \(OV-C, 8 of 10\)](#)

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[Continued](#)



# NCCN Guidelines Version 1.2020

## Ovarian Cancer/Fallopian Tube Cancer/ Primary Peritoneal Cancer

### PRINCIPLES OF SYSTEMIC THERAPY

#### Primary Systemic Therapy Regimens<sup>a</sup> - Epithelial Ovarian/Fallopian Tube/Primary Peritoneal

#### STAGE I DISEASE

|   |  |   |  |
|---|--|---|--|
| <ul style="list-style-type: none"> <li>• High-grade serous</li> <li>• Endometrioid (Grade 2/3)</li> <li>• Clear cell carcinoma<sup>b</sup></li> <li>• Carcinosarcoma<sup>b</sup></li> </ul> | <p><b>Preferred Regimens</b></p> <ul style="list-style-type: none"> <li>• Paclitaxel 175/carboplatin<sup>d</sup></li> </ul>  | <p><b>Other Recommended Regimens</b></p> <ul style="list-style-type: none"> <li>• Carboplatin/liposomal doxorubicin</li> <li>• Docetaxel/carboplatin</li> </ul>   | <p><b>Useful in Certain Circumstances</b></p> <ul style="list-style-type: none"> <li>• Carboplatin (if elderly [age &gt;70] and/or for those with comorbidities)</li> </ul> <p>For carcinosarcoma:</p> <ul style="list-style-type: none"> <li>• Carboplatin/ifosfamide</li> <li>• Cisplatin/ifosfamide</li> <li>• Paclitaxel/ifosfamide (category 2B)</li> </ul> |
| <p><b>Mucinous Carcinoma (stage IC)<sup>b</sup></b></p>   | <p><b>Preferred Regimens</b></p> <ul style="list-style-type: none"> <li>• Paclitaxel 175/carboplatin<sup>d</sup></li> <li>• 5-FU/leucovorin/oxaliplatin</li> <li>• Capecitabine/oxaliplatin</li> </ul> | <p><b>Other Recommended Regimens</b></p> <ul style="list-style-type: none"> <li>• Carboplatin/liposomal doxorubicin</li> <li>• Docetaxel/carboplatin</li> </ul>   | <p><b>Useful in Certain Circumstances</b></p> <ul style="list-style-type: none"> <li>• Carboplatin (if elderly [age &gt;70] and/or for those with comorbidities)</li> </ul>  |
| <p><b>Low-Grade Serous (stage IC)/Grade I Endometrioid (stage IC)<sup>b,c</sup></b></p>   | <p><b>Preferred Regimens</b></p> <ul style="list-style-type: none"> <li>• Paclitaxel 175/carboplatin<sup>d</sup></li> </ul>  | <p><b>Other Recommended Regimens</b></p> <ul style="list-style-type: none"> <li>• Carboplatin/liposomal doxorubicin</li> <li>• Docetaxel/carboplatin</li> <li>• Hormone therapy (aromatase inhibitors [anastrozole, letrozole, exemestane], leuprolide acetate, tamoxifen) (category 2B)</li> </ul> | <p><b>Useful in Certain Circumstances</b></p> <ul style="list-style-type: none"> <li>• Carboplatin (if elderly [age &gt;70] and/or for those with comorbidities)</li> </ul>  |

[Stage II–IV \(See OV-C, 5 of 10\)](#)

[Primary Systemic Therapy Dosing \(See OV-C, 6 of 10\)](#)

<sup>a</sup> See [Discussion](#) for references.

<sup>b</sup> There are limited data on the primary systemic therapy regimens for these LCOC.

<sup>c</sup> Borderline disease with invasive implants may be treated as low-grade serous disease. [See LCOC-6](#) and [LCOC-7](#).

<sup>d</sup> Elderly patients and those with comorbidities may be intolerant to the combination chemotherapy regimens recommended in these NCCN Guidelines. Based on clinical judgment and expected tolerance to therapies, alternate dosing ([see OV-C, 6 of 10](#)) may be appropriate for elderly patients with epithelial ovarian cancer (including carcinosarcoma, clear cell, mucinous, and low-grade serous). Algorithms have been developed for predicting chemotherapy toxicity. [See the NCCN Guidelines for Older Adult Oncology](#).

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[Continued](#)



# NCCN Guidelines Version 1.2020

## Ovarian Cancer/Fallopian Tube Cancer/ Primary Peritoneal Cancer

### PRINCIPLES OF SYSTEMIC THERAPY

#### Primary Systemic Therapy Regimens<sup>a</sup> - Epithelial Ovarian/Fallopian Tube/Primary Peritoneal

#### STAGE II–IV DISEASE

|   |   |  |   |
|---|---|--|---|
| <ul style="list-style-type: none"> <li>• High-grade serous</li> <li>• Endometrioid (Grade 2/3)</li> <li>• Clear cell carcinoma<sup>b</sup></li> <li>• Carcinosarcoma<sup>b</sup></li> </ul> | <p><b>Preferred Regimens</b></p> <ul style="list-style-type: none"> <li>• Paclitaxel 175/carboplatin<sup>d</sup></li> <li>• Paclitaxel/carboplatin/bevacizumab + maintenance bevacizumab<sup>e</sup> (ICON-7 &amp; GOG-218)</li> </ul>  | <p><b>Other Recommended Regimens</b></p> <ul style="list-style-type: none"> <li>• Paclitaxel weekly/carboplatin weekly<sup>d,f</sup></li> <li>• Docetaxel/carboplatin</li> <li>• Carboplatin/liposomal doxorubicin</li> <li>• Paclitaxel weekly/carboplatin q3weeks</li> </ul>   | <p><b>Useful in Certain Circumstances</b></p> <ul style="list-style-type: none"> <li>• IP/IV paclitaxel/cisplatin (for optimally debulked stage II–III disease)</li> <li>• For carcinosarcoma:                             <ul style="list-style-type: none"> <li>▶ Carboplatin/ifosfamide</li> <li>▶ Cisplatin/ifosfamide</li> <li>▶ Paclitaxel/ifosfamide (category 2B)</li> </ul> </li> <li>• Carboplatin (if elderly [age &gt;70] and/or for those with comorbidities)</li> </ul> |
| <p><b>Mucinous Carcinoma<sup>b</sup></b></p>  | <p><b>Preferred Regimens</b></p> <ul style="list-style-type: none"> <li>• Paclitaxel 175/carboplatin<sup>d</sup></li> <li>• Paclitaxel/carboplatin/bevacizumab + maintenance bevacizumab<sup>e</sup> (ICON-7 &amp; GOG-218)</li> <li>• 5-FU/leucovorin/oxaliplatin ± bevacizumab<sup>e</sup> (category 2B for bevacizumab)</li> <li>• Capecitabine/oxaliplatin ± bevacizumab<sup>e</sup> (category 2B for bevacizumab)</li> </ul> | <p><b>Other Recommended Regimens</b></p> <ul style="list-style-type: none"> <li>• Paclitaxel weekly/carboplatin weekly<sup>d,f</sup></li> <li>• Docetaxel/carboplatin</li> <li>• Carboplatin/liposomal doxorubicin</li> <li>• Paclitaxel weekly/carboplatin q3weeks</li> </ul>   | <p><b>Useful in Certain Circumstances</b></p> <ul style="list-style-type: none"> <li>• Carboplatin (if elderly [age &gt;70] and/or for those with comorbidities)</li> </ul>   |
| <p><b>Low-Grade Serous/Grade I Endometrioid<sup>b,c</sup></b></p>   | <p><b>Preferred Regimens</b></p> <ul style="list-style-type: none"> <li>• Paclitaxel 175/carboplatin<sup>d</sup></li> <li>• Paclitaxel/carboplatin/bevacizumab + maintenance bevacizumab<sup>e</sup> (ICON-7 &amp; GOG-218)</li> </ul>  | <p><b>Other Recommended Regimens</b></p> <ul style="list-style-type: none"> <li>• Paclitaxel weekly/carboplatin weekly<sup>d,f</sup></li> <li>• Docetaxel/carboplatin</li> <li>• Carboplatin/liposomal doxorubicin</li> <li>• Paclitaxel weekly/carboplatin q3weeks</li> <li>• Hormone therapy (aromatase inhibitors [anastrozole, letrozole, exemestane], leuprolide acetate, tamoxifen) (category 2B)</li> </ul> | <p><b>Useful in Certain Circumstances</b></p> <ul style="list-style-type: none"> <li>• Carboplatin (if elderly [age &gt;70] and/or for those with comorbidities)</li> </ul>   |

#### [Primary Systemic Therapy Dosing \(See OV-C, 6 of 10\)](#)

<sup>a</sup> See [Discussion](#) for references.

<sup>b</sup> There are limited data on the primary systemic therapy regimens for these LCOC.

<sup>c</sup> Borderline disease with invasive implants may be treated as low-grade serous disease. [See LCOC-6](#) and [LCOC-7](#).

<sup>d</sup> Elderly patients and those with comorbidities may be intolerant to the combination chemotherapy regimens recommended in these NCCN Guidelines. Based on clinical judgment and expected tolerance to therapies, alternate dosing ([see OV-C, 6 of 10](#)) may be appropriate for elderly patients with epithelial ovarian cancer (including carcinosarcoma, clear cell, mucinous, and low-grade serous). Algorithms have been developed for predicting chemotherapy toxicity. [See the NCCN Guidelines for Older Adult Oncology](#).

<sup>e</sup> An FDA-approved biosimilar is an appropriate substitute for bevacizumab.

<sup>f</sup> Regimen may be considered for those with poor performance status.

**Note:** All recommendations are category 2A unless otherwise indicated.

**Clinical Trials:** NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

[Continued](#)

**PRINCIPLES OF SYSTEMIC THERAPY****Primary Systemic Therapy Regimens<sup>a</sup> - Epithelial Ovarian (including LCOG)/Fallopian Tube/Primary Peritoneal****Primary Systemic Therapy Recommended Dosing****IV/IP Paclitaxel/cisplatin**

- Paclitaxel 135 mg/m<sup>2</sup> IV continuous infusion<sup>g</sup> Day 1; Cisplatin 75–100 mg/m<sup>2</sup> IP Day 2 after IV paclitaxel; Paclitaxel 60 mg/m<sup>2</sup> IP Day 8
- Repeat every 21 days x 6 cycles

**Paclitaxel 175/carboplatin<sup>h</sup>**

- Paclitaxel 175 mg/m<sup>2</sup> IV followed by carboplatin<sup>i</sup> AUC 5–6 IV Day 1
- Repeat every 21 days x 3–6 cycles<sup>h</sup>

**Paclitaxel weekly/carboplatin q3weeks**

- Dose-dense paclitaxel 80 mg/m<sup>2</sup> IV Days 1, 8, and 15 followed by carboplatin<sup>i</sup> AUC 5–6 IV Day 1
- Repeat every 21 days x 6 cycles

**Paclitaxel weekly/carboplatin weekly**

- Paclitaxel 60 mg/m<sup>2</sup> IV followed by carboplatin AUC 2 IV
- Days 1, 8, and 15; repeat every 21 days x 6 cycles (18 weeks)<sup>f</sup>

**Docetaxel/carboplatin<sup>h</sup>**

- Docetaxel 60–75 mg/m<sup>2</sup> IV followed by carboplatin<sup>c</sup> AUC 5–6 IV Day 1
- Repeat every 21 days x 3–6 cycles<sup>h</sup>

**Carboplatin/liposomal doxorubicin<sup>h</sup>**

- Carboplatin AUC 5 IV + pegylated liposomal doxorubicin 30 mg/m<sup>2</sup> IV
- Repeat every 28 days for 3–6 cycles<sup>h</sup>

**Paclitaxel/carboplatin/bevacizumab + maintenance bevacizumab<sup>e</sup> (ICON-7)**

- Paclitaxel 175 mg/m<sup>2</sup> IV followed by carboplatin<sup>i</sup> AUC 5–6 IV, and bevacizumab 7.5 mg/kg IV Day 1
- Repeat every 21 days x 5–6 cycles
- Continue bevacizumab for up to 12 additional cycles

**Paclitaxel/carboplatin/bevacizumab + maintenance bevacizumab<sup>e</sup> (GOG-218)**

- Paclitaxel 175 mg/m<sup>2</sup> IV followed by carboplatin<sup>i</sup> AUC 6 IV Day 1. Repeat every 21 days x 6 cycles
- Starting Day 1 of cycle 2, give bevacizumab 15 mg/kg IV every 21 days for up to 22 cycles

**Elderly Patients (age >70 years) and/or those with comorbidities****Paclitaxel 135/carboplatin<sup>1</sup>**

- Paclitaxel 135 mg/m<sup>2</sup> IV + carboplatin AUC 5 IV given every 21 days x 3–6 cycles<sup>h</sup>

**Paclitaxel weekly/carboplatin weekly**

- Paclitaxel 60 mg/m<sup>2</sup> IV over 1 hour followed by carboplatin AUC 2 IV over 30 minutes
- Days 1, 8, and 15; repeat every 21 days x 6 cycles (18 weeks)

**Carboplatin<sup>1</sup>**

- Carboplatin AUC 5 IV given every 21 days

<sup>a</sup> See [Discussion](#) for references.<sup>e</sup> An FDA-approved biosimilar is an appropriate substitute for bevacizumab.<sup>f</sup> Regimen may be considered for those with poor performance status.<sup>g</sup> The published randomized trial regimen used IV continuous infusion paclitaxel over 24 hours.<sup>h</sup> For stage I disease: 6 cycles is recommended for high-grade serous; 3–6 cycles for all other ovarian cancer types. For stage II–IV disease: 6 cycles is recommended.<sup>i</sup> Due to changes in creatinine methodology, changes regarding carboplatin dosing can be considered. For carboplatin dosing guidelines, see <https://www.mskcc.org/clinical-updates/new-guidelines-carboplatin-dosing>.**Note: All recommendations are category 2A unless otherwise indicated.****Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.****Continued****OV-C  
6 OF 10**



# NCCN Guidelines Version 1.2020

## Ovarian Cancer/Fallopian Tube Cancer/ Primary Peritoneal Cancer

### PRINCIPLES OF SYSTEMIC THERAPY

#### Acceptable Recurrence Therapies for Epithelial Ovarian (including LCOC)<sup>j</sup>/Fallopian Tube/Primary Peritoneal Cancer<sup>k</sup>

##### Recurrence Therapy for Platinum-Sensitive Disease<sup>l</sup> (alphabetical order)

| Preferred Regimens   | Other Recommended Regimens <sup>r</sup>  | Useful in Certain Circumstances  |
|--|--|--|
| Carboplatin/gemcitabine <sup>2</sup> ± bevacizumab <sup>e,m,n,3</sup><br>Carboplatin/liposomal doxorubicin <sup>4</sup> ± bevacizumab <sup>e,5</sup><br>Carboplatin/paclitaxel <sup>6</sup> ± bevacizumab <sup>e,m,n,7</sup><br>Cisplatin/gemcitabine <sup>8</sup><br><u>Targeted Therapy (single agents)</u><br>Bevacizumab <sup>e,m,9,10</sup><br>Niraparib <sup>o,11</sup><br>Olaparib <sup>p,12</sup><br>Rucaparib <sup>q,13</sup> | Carboplatin/docetaxel <sup>14,15</sup><br>Carboplatin/paclitaxel (weekly) <sup>16</sup><br>Capecitabine<br>Carboplatin <sup>s,2</sup><br>Cisplatin <sup>6</sup><br>Cyclophosphamide<br>Doxorubicin<br><br><u>Targeted Therapy</u><br>Niraparib/bevacizumab <sup>e,17</sup><br>Pazopanib (category 2B) <sup>18</sup><br><br><u>Hormone Therapy</u><br>Aromatase inhibitors (anastrozole, exemestane, letrozole)<br>Leuprolide acetate<br>Megestrol acetate<br>Tamoxifen | Ifosfamide<br>Irinotecan<br>Melphalan<br>Oxaliplatin<br>Paclitaxel<br>Paclitaxel, albumin bound<br>Pemetrexed<br>Vinorelbine<br><br>For mucinous carcinoma:<br>• 5-FU/leucovorin/oxaliplatin ± bevacizumab (category 2B for bevacizumab) <sup>e,m</sup><br>• Capecitabine/oxaliplatin ± bevacizumab (category 2B for bevacizumab) <sup>e,m</sup><br>Carboplatin/paclitaxel, albumin bound (for confirmed taxane hypersensitivity)<br>Carboplatin/paclitaxel <sup>s</sup> (for age >70)<br>Irinotecan/cisplatin (for clear cell carcinoma) <sup>19</sup><br><br><u>Targeted Therapy (single agents)</u><br>Entrectinib or larotrectinib (for <i>NTRK</i> gene fusion-positive tumors) <sup>t</sup><br>Trametinib (for low-grade serous carcinoma) <sup>20</sup><br><br><u>Hormone Therapy</u><br>Fulvestrant (for low-grade serous carcinoma)<br><br><u>Immunotherapy</u><br>Pembrolizumab (for microsatellite instability-high [MSI-H] or mismatch repair-deficient [dMMR] solid tumors) <sup>t,21</sup> |

<sup>e</sup>An FDA-approved biosimilar is an appropriate substitute for bevacizumab.

<sup>j</sup>Chemotherapy has not been shown to be beneficial in ovarian borderline epithelial tumors (LMP).

<sup>k</sup>Patients who progress on two consecutive regimens without evidence of clinical benefits have diminished likelihood of benefitting from additional therapy. (Griffiths RW, et al. *Int J Gyn Ca* 2011;21:58-65.) Decisions to offer clinical trials, supportive care, or additional therapy should be made on a highly individual basis.

<sup>l</sup>In general, the panel would recommend combination, platinum-based regimens for platinum-sensitive recurrent disease based on randomized trial data, especially in first relapses.

<sup>m</sup>Contraindicated for patients at increased risk of GI perforation.

<sup>n</sup>If response after chemotherapy, bevacizumab can be continued as maintenance therapy until disease progression or unacceptable toxicity. Discontinue bevacizumab before initiating maintenance therapy with a PARP inhibitor.

<sup>o</sup>For patients treated with three or more prior chemotherapy regimens and whose cancer is associated with HRD defined by either: 1) a deleterious or suspected deleterious *BRCA* mutation; or 2) genomic instability and progression >6 months after response to the last platinum-based chemotherapy.

#### [Platinum-Resistant Disease, see OV-C, 8 of 10](#)

<sup>p</sup>For patients with deleterious germline *BRCA*-mutated (as detected by an FDA-approved test or other validated test performed in a CLIA-approved facility) advanced ovarian cancer who have been treated with two or more lines of chemotherapy.

<sup>q</sup>For patients with deleterious germline and/or somatic *BRCA* mutated (as detected by an FDA-approved test or other validated test performed in a CLIA-approved facility) advanced ovarian cancer who have been treated with two or more lines of chemotherapy.

<sup>r</sup>Many of these single-agent cytotoxic therapy options have not been tested in patients who have been treated with modern chemotherapy regimens.

<sup>s</sup>[For recommended dosing for elderly patients, see OV-C, 6 of 10.](#)

<sup>t</sup>Validated molecular testing should be performed in a CLIA-approved facility using the most recent available tumor tissue. Testing recommended to include at least: *BRCA1/2*, and microsatellite instability or DNA mismatch repair if not previously done. Evaluation of homologous recombination deficiency can be considered. Additional somatic tumor testing can be considered at the physician's discretion to identify genetic alterations for which FDA-approved tumor-specific or tumor-agnostic targeted therapy options exist.

**Note: All recommendations are category 2A unless otherwise indicated.**

**Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.**

[Continued](#)





### PRINCIPLES OF SYSTEMIC THERAPY

#### Acceptable Recurrence Therapies for Epithelial Ovarian (including LCOC)<sup>j</sup>/Fallopian Tube/Primary Peritoneal Cancer<sup>k</sup>

##### Recurrence Therapy for Platinum-Resistant Disease (alphabetical order)

| Preferred Regimens   | Other Recommended Regimens  | Useful in Certain Circumstances  |
|--|---|--|
| <p><u>Cytotoxic Therapy</u></p> <p>Cyclophosphamide (oral)/bevacizumab<sup>e,22</sup><br/>Docetaxel<sup>23</sup><br/>Etoposide, oral<sup>24</sup><br/>Gemcitabine<sup>25,26</sup><br/>Liposomal doxorubicin<sup>25,26</sup><br/>Liposomal doxorubicin/bevacizumab<sup>e,m,27</sup><br/>Paclitaxel (weekly)<sup>28</sup><br/>Paclitaxel (weekly)/bevacizumab<sup>e,m,27</sup><br/>Topotecan<sup>29,30</sup><br/>Topotecan/bevacizumab<sup>e,m,27</sup></p> <p><u>Targeted Therapy (single agents)</u></p> <p>Bevacizumab<sup>e,m,9,10</sup><br/>Niraparib<sup>o,11</sup><br/>Olaparib<sup>p,12</sup><br/>Rucaparib<sup>q,13</sup></p> | <p><u>Cytotoxic Therapy<sup>f</sup></u></p> <p>Capecitabine<br/>Cyclophosphamide<br/>Doxorubicin<br/>Ifosfamide<br/>Irinotecan<br/>Melphalan</p> <p>Oxaliplatin<br/>Paclitaxel<br/>Paclitaxel, albumin bound<br/>Pemetrexed<br/>Sorafenib/topotecan<sup>31</sup><br/>Vinorelbine</p> <p><u>Targeted Therapy (single agents)</u></p> <p>Pazopanib (category 2B)<sup>18</sup></p> <p><u>Hormone Therapy</u></p> <p>Aromatase inhibitors (anastrozole, exemestane, letrozole)<br/>Leuprolide acetate<br/>Megestrol acetate<br/>Tamoxifen</p> | <p><u>Immunotherapy</u></p> <p>Pembrolizumab (for MSI-H or dMMR solid tumors)<sup>t,21</sup></p> <p><u>Hormone Therapy</u></p> <p>Fulvestrant (for low-grade serous carcinoma)</p> <p><u>Targeted Therapy (single agents)</u></p> <p>Entrectinib or larotrectinib (for <i>NTRK</i> gene fusion-positive tumors)<sup>t</sup><br/>Trametinib (for low-grade serous carcinoma)<sup>20</sup></p> |

<sup>e</sup>An FDA-approved biosimilar is an appropriate substitute for bevacizumab.

<sup>j</sup>Chemotherapy has not been shown to be beneficial in ovarian borderline epithelial tumors (LMP).

<sup>k</sup>Patients who progress on two consecutive regimens without evidence of clinical benefits have diminished likelihood of benefitting from additional therapy. (Griffiths RW, et al. Outcomes after multiple lines of chemotherapy for platinum-resistant epithelial cancers of the ovary, peritoneum, and fallopian tube. *Int J Gyn Ca* 2011;21:58-65.) Decisions to offer clinical trials, supportive care, or additional therapy should be made on a highly individual basis.

<sup>m</sup>Contraindicated for patients at increased risk of GI perforation.

<sup>o</sup>For patients treated with three or more prior chemotherapy regimens and whose cancer is associated with HRD defined by either: 1) a deleterious or suspected deleterious *BRCA* mutation; or 2) genomic instability and progression >6 months after response to the last platinum-based chemotherapy.

<sup>p</sup>For patients with deleterious germline *BRCA*-mutated (as detected by an FDA-approved test or other validated test performed in a CLIA-approved facility) advanced ovarian cancer who have been treated with two or more lines of chemotherapy.

#### [Platinum-Sensitive Disease, see OV-C, 7 of 10](#)

<sup>q</sup>For patients with deleterious germline and/or somatic *BRCA* mutated (as detected by an FDA-approved test or other validated test performed in a CLIA-approved facility) advanced ovarian cancer who have been treated with two or more lines of chemotherapy.

<sup>r</sup>Many of these single-agent cytotoxic therapy options have not been tested in patients who have been treated with modern chemotherapy regimens.

<sup>t</sup>Validated molecular testing should be performed in a CLIA-approved facility using the most recent available tumor tissue. Testing recommended to include at least: *BRCA1/2*, and microsatellite instability or DNA mismatch repair if not previously done. Evaluation of homologous recombination deficiency can be considered. Additional somatic tumor testing can be considered at the physician's discretion to identify genetic alterations for which FDA-approved tumor-specific or tumor-agnostic targeted therapy options exist.

**Note: All recommendations are category 2A unless otherwise indicated.**

**Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.**

[Continued](#)



# NCCN Guidelines Version 1.2020

## Ovarian Cancer/Fallopian Tube Cancer/ Primary Peritoneal Cancer

### PRINCIPLES OF SYSTEMIC THERAPY

#### Systemic Therapy Regimens<sup>a</sup> - Malignant Germ Cell/Sex Cord-Stromal Tumors

#### MALIGNANT GERM CELL TUMORS<sup>a,u,v</sup>

|                    | <b>Preferred Regimens</b>   | <b>Other Recommended Regimens</b>  | <b>Useful in Certain Circumstances</b>  |
|--------------------|---|--|---|
| Primary Therapy    | <ul style="list-style-type: none"> <li>• BEP (bleomycin, etoposide, cisplatin)<sup>w</sup> <ul style="list-style-type: none"> <li>▶ Bleomycin 30 units IV per week plus etoposide 100 mg/m<sup>2</sup> IV daily on days 1–5 plus cisplatin 20 mg/m<sup>2</sup> IV daily on days 1–5; repeat every 21 days for 3 cycles for good risk (category 2B), or 4 cycles for poor risk.</li> </ul> </li> </ul> | <ul style="list-style-type: none"> <li>• None</li> </ul>   | <ul style="list-style-type: none"> <li>• Etoposide/carboplatin<sup>a</sup> (for select patients with stage IB–III resected dysgerminoma for whom minimizing toxicity is critical)                             <ul style="list-style-type: none"> <li>▶ Carboplatin 400 mg/m<sup>2</sup> IV on day 1 plus etoposide 120 mg/m<sup>2</sup> IV on days 1, 2, and 3 every 28 days for 3 cycles.</li> </ul> </li> </ul> |
| Recurrence Therapy | <p><b>Preferred Regimens</b><br/>(Potentially Curative)</p> <ul style="list-style-type: none"> <li>• High-dose chemotherapy<sup>u</sup></li> <li>• TIP (paclitaxel, ifosfamide, cisplatin)</li> </ul>   | <p><b>Other Recommended Regimens</b><br/>(Palliative Only)</p> <ul style="list-style-type: none"> <li>• Cisplatin/etoposide</li> <li>• Docetaxel</li> <li>• Docetaxel/carboplatin</li> <li>• Etoposide/ifosfamide/cisplatin (VIP)</li> <li>• Paclitaxel</li> <li>• Paclitaxel/carboplatin</li> <li>• Paclitaxel/gemcitabine</li> </ul> | <ul style="list-style-type: none"> <li>• Paclitaxel/ifosfamide</li> <li>• VeIP (vinblastine, ifosfamide, cisplatin)</li> <li>• VAC (vincristine, dactinomycin, cyclophosphamide)</li> <li>• TIP</li> <li>• Supportive care (<a href="#">See NCCN Supportive Care Guidelines</a>)</li> </ul>   |

#### MALIGNANT SEX CORD-STROMAL TUMORS<sup>a,v</sup>

|                    | <b>Preferred Regimens</b>   | <b>Other Recommended Regimens</b>  | <b>Useful in Certain Circumstances</b>  |
|--------------------|---|--|---|
| Primary Therapy    | <ul style="list-style-type: none"> <li>• Paclitaxel/carboplatin</li> </ul>                                  | <ul style="list-style-type: none"> <li>• Etoposide/cisplatin (EP)</li> </ul>   | <ul style="list-style-type: none"> <li>• BEP (category 2B)<sup>b,w</sup></li> </ul>   |
| Recurrence Therapy | <p><b>Preferred Regimens</b></p> <ul style="list-style-type: none"> <li>• Paclitaxel/carboplatin</li> </ul> | <p><b>Other Recommended Regimens</b></p> <ul style="list-style-type: none"> <li>• EP</li> <li>• Paclitaxel/ifosfamide</li> <li>• Docetaxel</li> <li>• Paclitaxel</li> <li>• VAC</li> </ul> | <p><b>Useful in Certain Circumstances</b></p> <ul style="list-style-type: none"> <li>• Aromatase inhibitors (ie, anastrozole, exemestane, letrozole)</li> <li>• Leuprolide acetate (for granulosa cell tumors)</li> <li>• Tamoxifen</li> <li>• BEP (category 2B)<sup>w</sup></li> </ul> |

<sup>a</sup>See [Discussion](#) for references.

<sup>b</sup>There are limited data on the primary systemic therapy regimens for these LCOC.

<sup>e</sup>An FDA-approved biosimilar is an appropriate substitute for bevacizumab.

<sup>u</sup>High-dose chemotherapy regimens vary among institutions. Some patients are potentially curable with stem cell transplantation. Patients with potentially curable recurrent germ cell disease should be referred to a tertiary care institution for stem-cell transplant consultation and potentially curative therapy.

<sup>v</sup>[See WHO Histologic Classification \(OV-E\)](#).

<sup>w</sup>Recommend pulmonary function test if considering bleomycin.

**Note:** All recommendations are category 2A unless otherwise indicated.

**Clinical Trials:** NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

[Continued](#)

**PRINCIPLES OF SYSTEMIC THERAPY**  
**REFERENCES**

- 1 von Gruenigen VE, Huang HQ, Beumer JH, et al. Chemotherapy completion in elderly women with ovarian, primary peritoneal or fallopian tube cancer - An NRG oncology/Gynecologic Oncology Group study. *Gynecol Oncol* 2017;144(3):459-467.
- 2 Pfisterer J, Plante M, Vergote I, et al. Gemcitabine plus carboplatin compared with carboplatin in patients with platinum-sensitive recurrent ovarian cancer: an intergroup trial of the AGO-OVAR, the NCIC CTG, and the EORTC GCG. *J Clin Oncol* 2006;24:4699-4707.
- 3 Aghajanian C, Blank SV, Goff BA, et al. OCEANS: A randomized, double-blind, placebo-controlled phase III trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer. *J Clin Oncol* 2012;30:2039-2045.
- 4 Pujade-Lauraine E, Wagner U, Aavall-Lundqvist E, et al. Pegylated liposomal doxorubicin and carboplatin compared with paclitaxel and carboplatin for patients with platinum-sensitive ovarian cancer in late relapse. *J Clin Oncol* 2010;28:3323-3329.
- 5 Pfisterer J, Dean AP, Baumann K, et al. Carboplatin/pegylated liposomal doxorubicin/bevacizumab (CD-BEV) vs. carboplatin/gemcitabine/bevacizumab (CG-BEV) in patients with recurrent ovarian cancer. A prospective randomized phase III ENGOT/GCIG-Intergroup study (AGO Study Group, AGO-Austria, ANZGOG, GINECO, SGCTG). Presented at: 2018 ESMO Congress; October 19-23, 2018; Munich, Germany. Abstract 9330.
- 6 Parmar MK, Ledermann JA, Colombo N, et al. Paclitaxel plus platinum-based chemotherapy versus conventional platinum-based chemotherapy in women with relapsed ovarian cancer: the ICON4/AGO-OVAR-2.2 trial. *Lancet* 2003;361:2099-2106.
- 7 Coleman RL, Brady MF, Herzog TJ, et al. Bevacizumab and paclitaxel-carboplatin chemotherapy and secondary cytoreduction in recurrent, platinum-sensitive ovarian cancer (NRG Oncology/Gynecologic Oncology Group study GOG-0213): a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol* 2017;18:779-791.
- 8 Rose PG. Gemcitabine reverses platinum resistance in platinum-resistant ovarian and peritoneal carcinoma. *Int J Gynecol Cancer* 2005;15:18-22.
- 9 Burger RA, Sill MW, Monk BJ, et al. Phase II trial of bevacizumab in persistent or recurrent epithelial ovarian cancer or primary peritoneal cancer: a Gynecologic Oncology Group Study. *J Clin Oncol* 2007;25:5165-5171.
- 10 Cannistra SA, Matulonis UA, Penson RT, et al. Phase II study of bevacizumab in patients with platinum-resistant ovarian cancer or peritoneal serous cancer. *J Clin Oncol* 2007;25:5180-5186.
- 11 Moore KN, Secord AA, Geller MA, et al. Niraparib monotherapy for late-line treatment of ovarian cancer (QUADRA): a multicentre, open-label, single-arm, phase 2 trial. *Lancet Oncol* 2019;20:636-648.
- 12 Kaufman B, Shapira-Frommer R, Schmutzler RK, et al. Olaparib monotherapy in patients with advanced cancer and a germline BRCA1/2 mutation. *J Clin Oncol* 2015;33:244-250.
- 13 Swisher EM, Lin KK, Oza AM, et al. Rucaparib in relapsed, platinum-sensitive high-grade ovarian carcinoma (ARIEL2 Part 1): an international, multicentre, open-label, phase 2 trial. *Lancet Oncol* 2017;18:75-78.
- 14 Strauss HG, Henze A, Teichmann A, et al. Phase II trial of docetaxel and carboplatin in recurrent platinum-sensitive ovarian, peritoneal and tubal cancer. *Gynecol Oncol* 2007;104:612-616.
- 15 Kushner DM, Connor JP, Sanchez F, et al. Weekly docetaxel and carboplatin for recurrent ovarian and peritoneal cancer: a phase II trial. *Gynecol Oncol* 2007;105:358-364.
- 16 Katsumata N, Yasuda M, Takahashi F, et al. Dose-dense paclitaxel once a week in combination with carboplatin every 3 weeks for advanced ovarian cancer: a phase 3, open-label, randomised controlled trial. *Lancet* 2009;374:1331-1338.
- 17 Mirza MR, Avall Lundqvist E, Birrer MJ, et al. Niraparib plus bevacizumab versus niraparib alone for platinum-sensitive recurrent ovarian cancer (NSGO-AVANOVA2/ENGOT-ov24): a randomised, phase 2, superiority trial. *Lancet Oncol* 2019;20:1409-1419.
- 18 Friedlander M, Hancock KC, Rischin D, et al. A Phase II, open-label study evaluating pazopanib in patients with recurrent ovarian cancer. *Gynecol Oncol* 2010;119:32-37.
- 19 Sugiyama T, Okamoto A, Enomoto T, et al. Randomized Phase III Trial of Irinotecan Plus Cisplatin Compared With Paclitaxel Plus Carboplatin As First-Line Chemotherapy for Ovarian Clear Cell Carcinoma: JGOG3017/GCIG Trial. *J Clin Oncol* 2016;34:2881-2887.
- 20 Gershenson DM, Miller A, Brady W, et al. A randomized phase II/III study to assess the efficacy of trametinib in patients with recurrent or progressive low-grade serous ovarian or peritoneal cancer [abstract]. *Ann Oncol* 2019;30(Suppl. 5):abstr LBA61.
- 21 Le DT, Durham JN, Smith KN, et al. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. *Science* 2017;357:409-413.
- 22 Barber EL, Zsiros E, Lurain JR, et al. The combination of intravenous bevacizumab and metronomic oral cyclophosphamide is an effective regimen for platinum-resistant recurrent ovarian cancer. *J Gynecol Oncol* 2013;24:258-264.
- 23 Rose PG, Blessing JA, Ball HG, et al. A phase II study of docetaxel in paclitaxel-resistant ovarian and peritoneal carcinoma: a Gynecologic Oncology Group study. *Gynecol Oncol* 2003;88:130-135.
- 24 Rose PG, Blessing JA, Mayer AR, Homesley HD. Prolonged oral etoposide as second-line therapy for platinum-resistant and platinum-sensitive ovarian carcinoma: a Gynecologic Oncology Group study. *J Clin Oncol* 1998;16:405-410.
- 25 Mutch DG, Orlando M, Goss T, et al. Randomized phase III trial of gemcitabine compared with pegylated liposomal doxorubicin in patients with platinum-resistant ovarian cancer. *J Clin Oncol* 2007;25:2811-2818.
- 26 Ferrandina G, Ludovisi M, Lorusso D, et al. Phase III trial of gemcitabine compared with pegylated liposomal doxorubicin in progressive or recurrent ovarian cancer. *J Clin Oncol* 2008;26:890-896.
- 27 Pujade-Lauraine E, Hilpert F, Weber B, et al. Bevacizumab combined with chemotherapy for platinum-resistant recurrent ovarian cancer: The AURELIA open-label randomized phase III trial. *J Clin Oncol* 2014;32:1302-1308.
- 28 Markman M, Blessing J, Rubin SC, et al. Phase II trial of weekly paclitaxel (80 mg/m<sup>2</sup>) in platinum and paclitaxel-resistant ovarian and primary peritoneal cancers: a Gynecologic Oncology Group study. *Gynecol Oncol* 2006;101:436-440.
- 29 Gordon AN, Tonda M, Sun S, Rackoff W. Long-term survival advantage for women treated with pegylated liposomal doxorubicin compared with topotecan in a phase 3 randomized study of recurrent and refractory epithelial ovarian cancer. *Gynecol Oncol* 2004;95:1-8.
- 30 Sehouli J, Stengel D, Harter P, et al. Topotecan weekly versus conventional 5-day schedule in patients with platinum-resistant ovarian cancer: A randomized multicenter phase II trial of the North-Eastern German Society of Gynecological Oncology Ovarian Cancer Study Group. *J Clin Oncol* 2011;29:242-248.
- 31 Chekerov R, Hilpert F, Mahner S, et al. Sorafenib plus topotecan versus placebo plus topotecan for platinum-resistant ovarian cancer (TRIAS): a multicentre, randomised, double-blind, placebo-controlled, phase 2 trial. *Lancet Oncol* 2018; 19:1247-1258.

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**MANAGEMENT OF DRUG REACTIONS****Overview**

- Virtually all drugs used in oncology have the potential to cause adverse drug reactions while being infused, which can be classified as either infusion or allergic reactions.<sup>1</sup>
  - ▶ Infusion reactions are often characterized by milder symptoms (eg, hot flushing, rash).
  - ▶ Hypersensitivity (allergic) reactions are often characterized by more severe symptoms (eg, shortness of breath, generalized hives/itching, changes in blood pressure).
- Most adverse drug reactions that occur are mild reactions, but more severe reactions can occur.<sup>2,3</sup>
  - ▶ Anaphylaxis is a rare type of very severe allergic reaction that can occur with the platinum and taxane agents (and others less commonly), can cause cardiovascular collapse, and can be life-threatening.<sup>4-6</sup>
  - ▶ Drug reactions can occur either during the infusion or following completion of the infusion (and can even occur days later).
- In gynecologic oncology treatment, drugs that more commonly cause adverse reactions include carboplatin, cisplatin, docetaxel, liposomal doxorubicin, oxaliplatin, and paclitaxel.<sup>1</sup>
  - ▶ Adverse reactions associated with taxane drugs (ie, docetaxel, paclitaxel) and biotherapeutic agents tend to be infusion-related often attributed to cremophor in paclitaxel and tend to occur during the first few cycles of treatment (although they can be seen during any infusion regardless of how many previous cycles were administered).
  - ▶ Adverse reactions associated with platinum drugs (ie, carboplatin, cisplatin), a true allergy, tend to occur following re-exposure to the inciting drug or less commonly at the completion of initial chemotherapy (ie, cycle 6 of a planned 6 treatments).<sup>3</sup>
- Preparation for a possible drug reaction
  - ▶ Patients and their families should be counseled about the possibility of a drug reaction and the signs and symptoms of one. Patients should be told to report any signs and symptoms of a drug reaction, especially after they have left the clinic (ie, delayed rash).
  - ▶ Clinicians and nursing staff should be prepared for the possibility of a drug reaction every time a patient is infused with a drug. Standing orders should be written for immediate intervention in case a severe drug reaction occurs and the treatment area should have appropriate medical equipment in case of a life-threatening reaction.<sup>5</sup>
  - ▶ Epinephrine (intramuscular 0.3 mL of 1 mg/mL solution/Epipen) should be used for any patient experiencing hypotension (systolic BP of <90 mm Hg) with or without other symptoms of an allergic/hypersensitivity reaction during or shortly after any chemotherapy drug treatment. In the setting of acute cardiopulmonary arrest, standard resuscitation (ACLS) procedures should be followed.
- Desensitization refers to a process of rendering the patient less likely to react in response to an allergen and can be considered an option for patients who have had drug reactions.<sup>1,7-9</sup>
- If a patient has previously had a very severe life-threatening reaction, the implicated drug should not be used again unless under guidance of an allergist or specialist with desensitization experience.

[Continued on OV-D, 2 of 7](#)[References on OV-D, 3 of 7](#)**Note:** All recommendations are category 2A unless otherwise indicated.**Clinical Trials:** NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

**MANAGEMENT OF DRUG REACTIONS****Infusion Reactions**

- **Symptoms include:** hot flushing, rash, fever, chest tightness, mild blood pressure changes, back pain, and chills.
- **Symptoms usually can be treated by decreasing the infusion rate and resolve quickly after stopping the infusion. However, patients who have had mild reactions to carboplatin, cisplatin, or oxaliplatin may develop more serious reactions even when the platinum drug is slowly infused; therefore, consider consultation with an allergist.<sup>10</sup>**
- **Infusion reactions are more common with paclitaxel (27% of patients); however, mild reactions can occur with liposomal doxorubicin.<sup>10</sup>**
- **If an infusion reaction has previously occurred in response to a taxane:**
  - ▶ **For mild infusion reactions (eg, flushing, rash, chills), patients may be rechallenged with the taxane if:**
    - 1) the patient, physician, and nursing staff are all comfortable with this plan;
    - 2) the patient has been counseled appropriately; and
    - 3) emergency equipment is available in the clinic area.
  - ▶ **Typically the taxane infusion can be re-started at a much slower rate, and the rate can be slowly increased as tolerated as per the treating clinician's judgment.<sup>7,11</sup> Note that this slow infusion is different from desensitization.**
  - ▶ **Many institutions have nursing policies that stipulate how to reinfuse the drug if the patient has had a prior infusion reaction.**

**Allergic Reactions (ie, True Drug Allergies)**

- **Symptoms include:** rash, edema, shortness of breath (bronchospasm), syncope or pre-syncope, chest pain, tachycardia, hives/itching, changes in blood pressure, nausea, vomiting, chills, changes in bowel function, and occasionally feeling of impending doom.
- **Symptoms may continue to persist after stopping infusion and/or after treatment interventions.**
- **Allergic reactions are more common with platinum drugs such as carboplatin (16% of patients), cisplatin, and oxaliplatin.<sup>11</sup> Mild reactions can occur with platinum agents.<sup>11</sup>**
- **Patients who are at higher risk of developing a hypersensitivity (allergic) reaction include those in the following settings:**
  - ▶ **Re-introduction of the drug after a period of no exposure and following multiple cycles of the drug during the first and subsequent exposures**
  - ▶ **IV administration of the drug rather than oral or IP administration**
  - ▶ **With allergies to other drugs**
  - ▶ **Those who have previously had a reaction**
- **If an allergic reaction has previously occurred:**
  - ▶ **Consider consultation with an allergist (or qualified medical or gynecologic oncologist) and skin testing for patients who have experienced a platinum reaction (eg, carboplatin-hypersensitivity reaction).<sup>11-13</sup>**
  - ▶ **Patients who have had mild reactions may develop more serious reactions even when the platinum drug is slowly infused.<sup>11</sup>**
  - ▶ **For more severe or life-threatening reactions—such as those involving blood pressure changes, dyspnea, tachycardia, widespread urticaria, anaphylaxis, or hypoxia—the implicated drug should not be used again unless under guidance of a specialist with desensitization experience.**
  - ▶ **If it is appropriate to give the drug again, patients should be desensitized prior to resuming chemotherapy even if the symptoms have resolved. Patients must be desensitized with each infusion if they previously had a drug reaction.<sup>7-9</sup>**

**[References on OV-D, 3 of 7](#)**

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### MANAGEMENT OF DRUG REACTIONS REFERENCES

- <sup>1</sup>Castells MC, Tennant NM, Sloane DE, et al. Hypersensitivity reactions to chemotherapy: Outcomes and safety of rapid desensitization in 413 cases. *J Allergy Clin Immunol* 2008;122:574-580.
- <sup>2</sup>Dizon DS, Sabbatini PJ, Aghajanian C, et al. Analysis of patients with epithelial ovarian cancer or fallopian tube carcinoma retreated with cisplatin after the development of a carboplatin allergy. *Gynecol Oncol* 2002;84:378-382.
- <sup>3</sup>Markman M, Kennedy A, Webster K, et al. Clinical features of hypersensitivity reactions to carboplatin. *J Clin Oncol* 1999;17:1141-1145.
- <sup>4</sup>Manivannan V, Decker WW, Stead LG, et al. Visual representation of National Institute of Allergy and Infectious Disease and Food Allergy and Anaphylaxis Network criteria for anaphylaxis. *Int J Emerg Med* 2009;2:3-5.
- <sup>5</sup>Oswalt ML, Kemp SF. Anaphylaxis: office management and prevention. *Immunol Allergy Clin North Am* 2007;27:177-191.
- <sup>6</sup>Sampson HA, Muñoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: summary report--second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *Ann Emerg Med* 2006;47:373-380.
- <sup>7</sup>Lee CW, Matulonis UA, Castells MC. Rapid inpatient/outpatient desensitization for chemotherapy hypersensitivity: standard protocol effective in 57 patients for 255 courses. *Gynecol Oncol* 2005;99:393-397.
- <sup>8</sup>Lee CW, Matulonis UA, Castells MC. Carboplatin hypersensitivity: A 6-hour 12 step protocol effective in 35 desensitizations in patients with gynecological malignancies and mast cell/IgE-mediated reactions. *Gynecol Oncol* 2004;95:370-376.
- <sup>9</sup>Markman M, Hsieh F, Zanutti K, et al. Initial experience with a novel desensitization strategy for carboplatin-associated hypersensitivity reactions. *J Cancer Research Clin Oncol* 2004;130:25-28.
- <sup>10</sup>Gabizon AA. Pegylated liposomal doxorubicin: metamorphosis of an old drug into a new form of chemotherapy. *Cancer Invest* 2001;19:424-436.
- <sup>11</sup>Lenz HJ. Management and preparedness for infusion and hypersensitivity reactions. *Oncologist* 2007;12:601-609.
- <sup>12</sup>Markman M, Zanutti K, Peterson G, et al. Expanded experience with an intradermal skin test to predict for the presence or absence of carboplatin hypersensitivity. *J Clin Oncol* 2003;21:4611-4614.
- <sup>13</sup>Zanutti KM, Rybicki LA, Kennedy AW, et al. Carboplatin skin testing: A skin-testing protocol for predicting hypersensitivity to carboplatin chemotherapy. *J Clin Oncol* 2001;19:3126-3129.

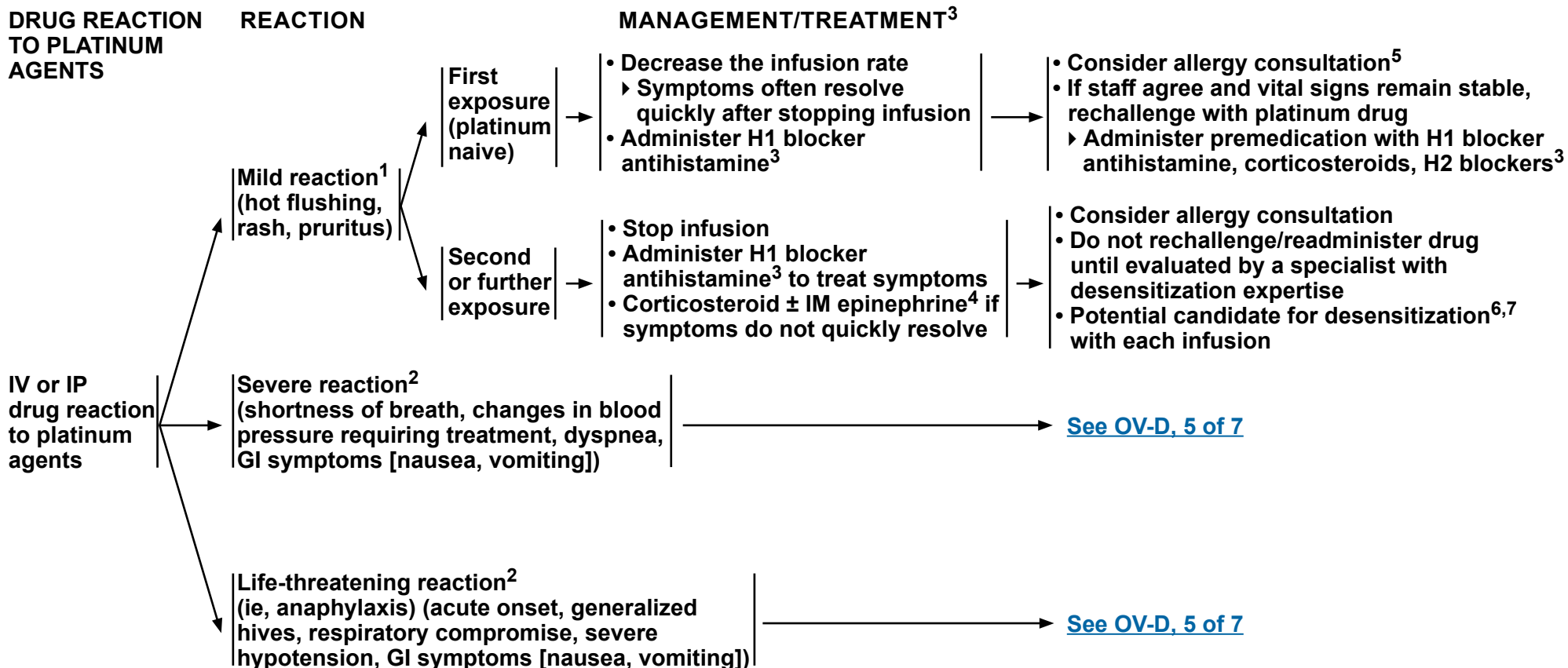
[See Drug Reaction to Platinum Agents on OV-D, 4 of 7](#)

[See Drug Reaction to Taxane, Liposomal Doxorubicin, or Biotherapeutic Agents on OV-D, 6 of 7](#)

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### MANAGEMENT OF DRUG REACTIONS



[See Drug Reaction to Taxane, Liposomal Doxorubicin, or Biotherapeutic Agents on OV-D, 6 of 7](#)

<sup>1</sup>Most mild reactions are infusion reactions and more commonly are caused by taxanes (ie, docetaxel, paclitaxel), but can also occur with platinum agents (ie, carboplatin, cisplatin).

<sup>2</sup>Most severe reactions are allergic reactions and more commonly are caused by platinum agents.

<sup>3</sup>H1 blocker antihistamine (eg, diphenhydramine or hydroxyzine); H2 blockers (eg, cimetidine, famotidine); corticosteroids (eg, methylprednisolone, hydrocortisone, dexamethasone).

<sup>4</sup>In the setting of acute cardiopulmonary arrest, standard resuscitation (ACLS) procedures should be followed.

<sup>5</sup>Mild reactions can progress to severe reactions by re-exposure. An allergy consultation may provide skin testing and evaluate sensitization and the risk for further, more severe reactions.

<sup>6</sup>Referral to academic center with expertise in desensitization is preferred.

<sup>7</sup>Castells MC, Tennant NM, Sloane DE, et al. Hypersensitivity reactions to chemotherapy: Outcomes and safety of rapid desensitization in 413 cases. J Allergy Clin Immunol 2008;122:574-580.

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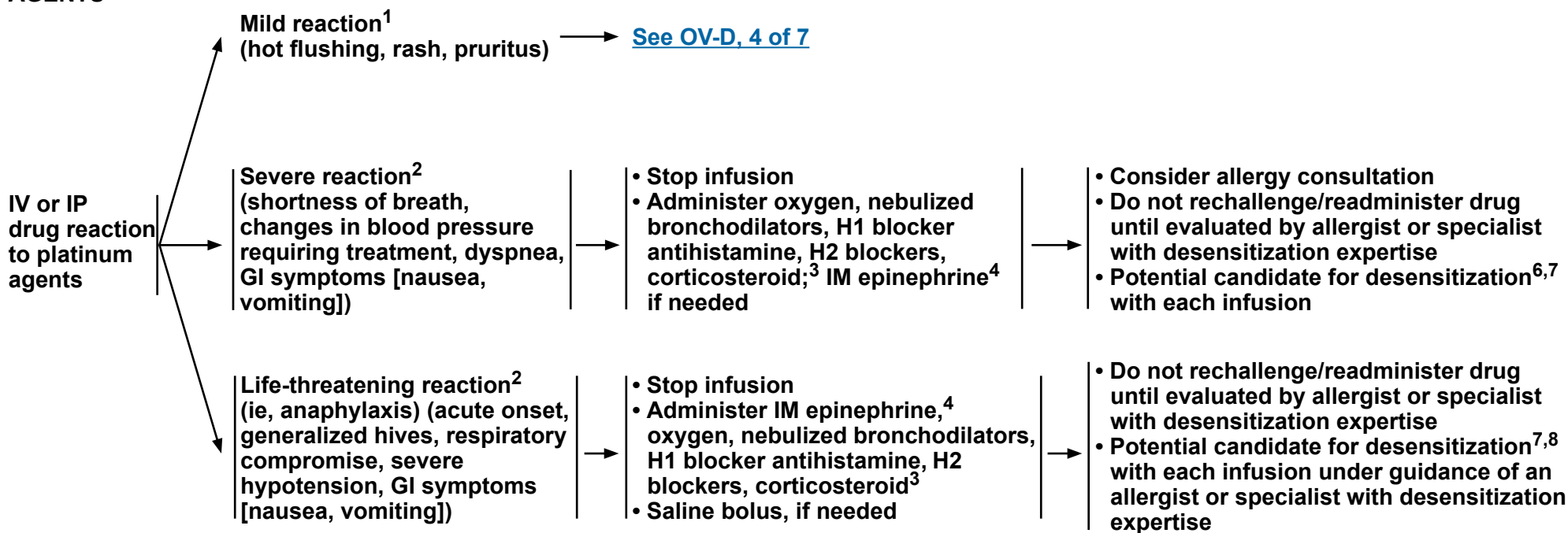
## Ovarian Cancer/Fallopian Tube Cancer/ Primary Peritoneal Cancer

### MANAGEMENT OF DRUG REACTIONS

#### DRUG REACTION TO PLATINUM AGENTS

#### REACTION

#### MANAGEMENT/TREATMENT<sup>3</sup>



[See Drug Reaction to Taxane, Liposomal Doxorubicin, or Biotherapeutic Agents on OV-D, 6 of 7](#)

<sup>1</sup>Most mild reactions are infusion reactions and more commonly are caused by taxanes (ie, docetaxel, paclitaxel), but can also occur with platinum agents (ie, carboplatin, cisplatin).

<sup>2</sup>Most severe reactions are allergic reactions and more commonly are caused by platinum agents.

<sup>3</sup>H1 blocker antihistamine (eg, diphenhydramine or hydroxyzine); H2 blockers (eg, cimetidine, famotidine); corticosteroids (eg, methylprednisolone, hydrocortisone, dexamethasone).

<sup>4</sup>In the setting of acute cardiopulmonary arrest, standard resuscitation (ACLS) procedures should be followed.

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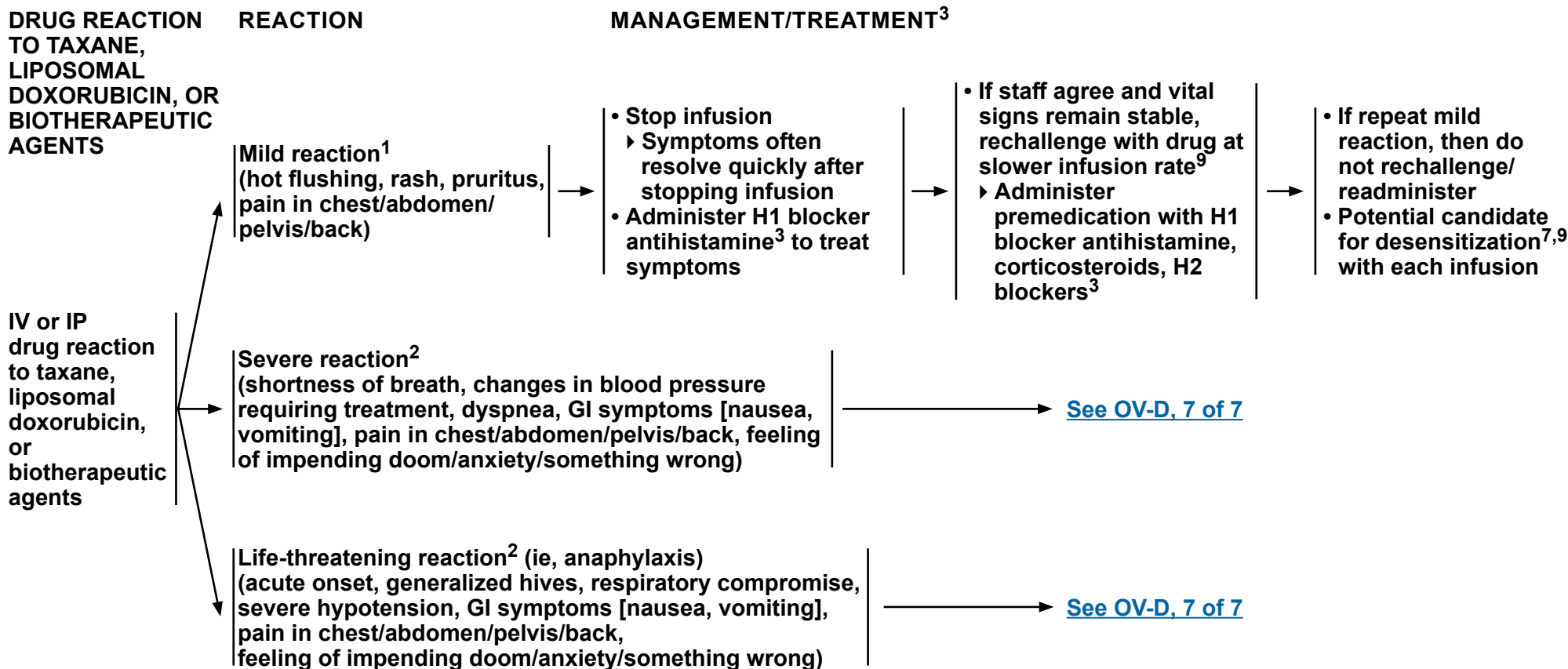
<sup>8</sup>For both taxanes and platinum analogues, it is preferred that anyone with a life-threatening reaction be evaluated and referred to an academic center if the drug is still considered first line.

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### MANAGEMENT OF DRUG REACTIONS



[See Drug Reaction to Platinum Agents on OV-D, 4 of 7](#)

<sup>1</sup>Most mild reactions are infusion reactions and more commonly are caused by taxanes (ie, docetaxel, paclitaxel), but can also occur with platinum agents (ie, carboplatin, cisplatin).

<sup>2</sup>Most severe reactions are allergic reactions and more commonly are caused by platinum agents.

<sup>3</sup>H1 blocker antihistamine (eg, diphenhydramine or hydroxyzine); H2 blockers (eg, cimetidine, famotidine); corticosteroids (eg, methylprednisolone, hydrocortisone, dexamethasone).

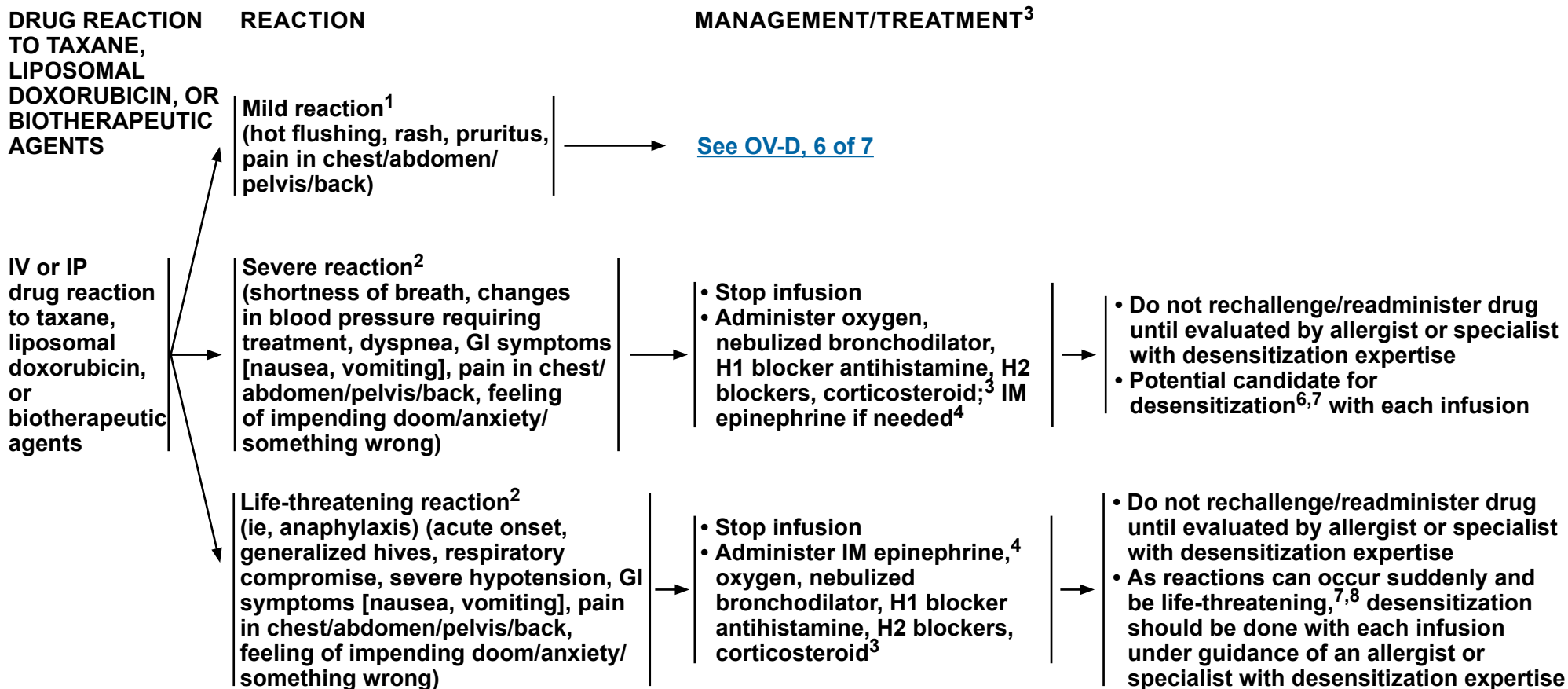
<sup>7</sup>Castells MC, Tennant NM, Sloane DE, et al. Hypersensitivity reactions to chemotherapy: Outcomes and safety of rapid desensitization in 413 cases. *J Allergy Clin Immunol* 2008;122:574-580.

<sup>9</sup>Consider switching to paclitaxel (albumin-bound) due to medical necessity (ie, hypersensitivity reaction), or consider switching to docetaxel; however, there are no data to support switching taxanes. Cross reactions have occurred and have been life-threatening. Some reactions to paclitaxel may occur because of the diluent.

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### MANAGEMENT OF DRUG REACTIONS



[See Drug Reaction to Platinum Agents on OV-D, 4 of 7](#)

<sup>1</sup>Most mild reactions are infusion reactions and more commonly are caused by taxanes (ie, docetaxel, paclitaxel), but can also occur with platinum agents (ie, carboplatin, cisplatin).

<sup>2</sup>Most severe reactions are allergic reactions and more commonly are caused by platinum agents.

<sup>3</sup>H1 blocker antihistamine (eg, diphenhydramine or hydroxyzine); H2 blockers (eg, cimetidine, famotidine); corticosteroids (eg, methylprednisolone, hydrocortisone, dexamethasone).

<sup>4</sup>In the setting of acute cardiopulmonary arrest, standard resuscitation (ACLS) procedures should be followed.

<sup>6</sup>Referral to academic center with expertise in desensitization is preferred.

<sup>7</sup>Castells MC, Tennant NM, Sloane DE, et al. Hypersensitivity reactions to chemotherapy: Outcomes and safety of rapid desensitization in 413 cases. J Allergy Clin Immunol 2008;122:574-580.

<sup>8</sup>For both taxanes and platinum analogues, it is preferred that anyone with a life-threatening reaction be evaluated and referred to an academic center if the drug is still considered first line.

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### WHO HISTOLOGIC CLASSIFICATION<sup>1,2</sup>

|   |  |
|---|--|
| <p><b>Serous Tumors</b></p> <ul style="list-style-type: none"> <li>• Serous cystadenoma</li> <li>• Serous adenofibroma</li> <li>• Serous surface papilloma</li> <li>• Serous borderline tumor/atypical proliferative serous tumor</li> <li>• Serous borderline tumor-micropapillary variant/non-invasive low-grade serous carcinoma</li> <li>• Low-grade serous</li> <li>• High-grade serous</li> </ul> | <p>Benign<br/>Benign<br/>Benign<br/>Borderline</p> <p>Carcinoma in-situ/<br/>grade III intraepithelial<br/>neoplasia<br/>Malignant<br/>Malignant</p> |
| <p><b>Mucinous Tumors</b></p> <ul style="list-style-type: none"> <li>• Mucinous cystadenoma</li> <li>• Mucinous adenofibroma</li> <li>• Mucinous borderline tumor/atypical proliferative mucinous tumor</li> <li>• Mucinous carcinoma</li> </ul>  | <p>Benign<br/>Benign<br/>Borderline</p> <p>Malignant</p>   |
| <p><b>Endometrioid Tumors</b></p> <ul style="list-style-type: none"> <li>• Endometriotic cyst</li> <li>• Endometriotic cystadenoma</li> <li>• Endometriotic adenofibroma</li> <li>• Endometrioid borderline tumor/atypical proliferative endometrioid tumor</li> <li>• Endometrioid carcinoma</li> </ul>  | <p>Benign<br/>Benign<br/>Benign<br/>Borderline</p> <p>Malignant</p>  |
| <p><b>Clear Cell Tumors</b></p> <ul style="list-style-type: none"> <li>• Clear cell cystadenoma</li> <li>• Clear cell adenofibroma</li> <li>• Clear cell borderline tumor/atypical proliferative clear cell tumor</li> <li>• Clear cell carcinoma</li> </ul>  | <p>Benign<br/>Benign<br/>Borderline</p> <p>Malignant</p>   |

|  |  |
|--|--|
| <p><b>Brenner Tumors</b></p> <ul style="list-style-type: none"> <li>• Brenner tumor</li> <li>• Borderline Brenner tumor/atypical proliferative Brenner tumor</li> <li>• Malignant Brenner tumor</li> </ul>   | <p>Benign<br/>Borderline</p> <p>Malignant</p>            |
| <p><b>Seromucinous Tumors</b></p> <ul style="list-style-type: none"> <li>• Seromucinous cystadenoma</li> <li>• Seromucinous adenofibroma</li> <li>• Seromucinous borderline tumor/atypical proliferative seromucinous tumor</li> <li>• Seromucinous carcinoma</li> </ul> | <p>Benign<br/>Benign<br/>Borderline</p> <p>Malignant</p> |
| <p>Undifferentiated carcinoma</p>  | <p>Malignant</p>   |
| <p><b>Mesenchymal Tumors</b></p> <ul style="list-style-type: none"> <li>• Low-grade endometrioid stromal sarcoma</li> <li>• High-grade endometrioid stromal sarcoma</li> </ul>   | <p>Malignant<br/>Malignant</p>                           |
| <p><b>Mixed Epithelial &amp; Mesenchymal Tumors</b></p> <ul style="list-style-type: none"> <li>• Adenosarcoma</li> <li>• Carcinosarcoma</li> </ul>   | <p>Malignant<br/>Malignant</p>                           |

[Continued](#)

<sup>1</sup>Reproduced with permission from Kurman RJ, Carcangiu ML, Herrington CS, Young RH. World Health Organization Classification of Tumours of the Female Reproductive Organs. IARC, Lyon, 2014.

<sup>2</sup>Borderline = Unspecified, borderline, or uncertain behavior.

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### WHO HISTOLOGIC CLASSIFICATION<sup>1,2</sup>

|   |   |  |   |  |   |
|---|---|--|---|--|---|
| <p><b>Sex Cord-Stromal Tumors:</b><br/><b>Pure Stromal Tumors</b></p> <ul style="list-style-type: none"> <li>• Fibroma</li> <li>• Cellular fibroma</li> <li>• Thecoma</li> <li>• Luteinized thecoma associated with sclerosing peritonitis</li> <li>• Fibrosarcoma</li> <li>• Sclerosing stromal tumor</li> <li>• Signet-ring stromal tumor</li> <li>• Microcystic stromal tumor</li> <li>• Leydig cell tumor</li> <li>• Steroid cell tumor</li> <li>• Steroid cell tumor, malignant</li> </ul>   | <p>Benign<br/>Borderline<br/>Benign<br/>Benign</p> <p>Malignant<br/>Benign<br/>Benign<br/>Benign<br/>Benign<br/>Malignant</p> | <p><b>Germ Cell Tumors</b></p> <ul style="list-style-type: none"> <li>• Dysgerminoma</li> <li>• Yolk sac tumor</li> <li>• Embryonal carcinoma</li> <li>• Non-gestational choriocarcinoma</li> <li>• Mature teratoma</li> <li>• Immature teratoma</li> <li>• Mixed germ cell tumor</li> </ul>   | <p>Malignant<br/>Malignant<br/>Malignant<br/>Malignant<br/>Benign<br/>Malignant<br/>Malignant</p>                   | <p><b>Miscellaneous Tumors</b></p> <ul style="list-style-type: none"> <li>• Adenoma of rete ovarii</li> <li>• Adenocarcinoma of rete ovarii</li> <li>• Wolffian tumor</li> <li>• Small cell carcinoma, hypercalcaemic type</li> <li>• Small cell carcinoma, pulmonary type</li> <li>• Wilms tumor</li> <li>• Paraganglioma</li> <li>• Solid pseudopapillary neoplasm</li> </ul>  | <p>Benign<br/>Malignant<br/>Borderline<br/>Malignant</p> <p>Malignant<br/>Borderline<br/>Borderline</p> |
| <p><b>Sex Cord-Stromal Tumors:</b><br/><b>Pure Sex Cord Tumors</b></p> <ul style="list-style-type: none"> <li>• Adult granulosa cell tumor</li> <li>• Juvenile granulosa cell tumor</li> <li>• Sertoli cell tumor</li> <li>• Sex cord tumor with annular tubules</li> </ul>   | <p>Malignant<br/>Borderline<br/>Borderline<br/>Borderline</p>   | <p><b>Monodermal Teratoma &amp; Somatic-type Tumors from Dermoid Cyst</b></p> <ul style="list-style-type: none"> <li>• Struma ovarii, benign</li> <li>• Struma ovarii, malignant</li> <li>• Carcinoid                             <ul style="list-style-type: none"> <li>▸ Strumal carcinoid</li> <li>▸ Mucinous carcinoid</li> </ul> </li> <li>• Neuroectodermal-type tumors</li> <li>• Sebaceous tumors                             <ul style="list-style-type: none"> <li>▸ Sebaceous adenoma</li> <li>▸ Sebaceous carcinoma</li> </ul> </li> <li>• Other rare monodermal teratomas</li> <li>• Carcinomas                             <ul style="list-style-type: none"> <li>▸ Squamous cell carcinoma</li> <li>▸ Others</li> </ul> </li> </ul> | <p>Benign<br/>Malignant<br/>Malignant<br/>Borderline<br/>Malignant</p> <p>Benign<br/>Malignant</p> <p>Malignant</p> | <p><b>Mesothelial Tumors</b></p> <ul style="list-style-type: none"> <li>• Adenomatoid tumor</li> <li>• Mesothelioma</li> </ul>   | <p>Benign<br/>Malignant</p>   |
| <p><b>Mixed Sex Cord-Stromal Tumors</b></p> <ul style="list-style-type: none"> <li>• Sertoli-Leydig cell tumors                             <ul style="list-style-type: none"> <li>▸ Well differentiated</li> <li>▸ Moderately differentiated                                     <ul style="list-style-type: none"> <li>◊ With heterologous elements</li> </ul> </li> <li>▸ Poorly differentiated                                     <ul style="list-style-type: none"> <li>◊ With heterologous elements</li> </ul> </li> <li>▸ Retiform                                     <ul style="list-style-type: none"> <li>◊ With heterologous elements</li> </ul> </li> </ul> </li> <li>• Sex cord-stromal tumors, NOS</li> </ul> | <p>Benign<br/>Borderline<br/>Borderline<br/>Malignant<br/>Malignant<br/>Borderline<br/>Borderline<br/>Borderline</p>          | <p><b>Germ Cell- Sex Cord-Stromal Tumors</b></p> <ul style="list-style-type: none"> <li>• Gonadoblastoma, including gonadoblastoma with malignant germ cell tumor</li> <li>• Mixed germ cell- sex cord-stromal tumor, unclassified</li> </ul>  | <p>Borderline<br/>Borderline</p>  | <p><b>Soft Tissue Tumors</b></p> <ul style="list-style-type: none"> <li>• Myxoma</li> <li>• Others</li> </ul>  | <p>Benign</p>   |
|   |   |  |   | <p><b>Tumor-like Lesions</b></p> <ul style="list-style-type: none"> <li>• Follicle cyst</li> <li>• Corpus luteum cyst</li> <li>• Large solitary luteinized follicle cyst</li> <li>• Hyperreactio luteinalis</li> <li>• Pregnancy luteoma</li> <li>• Stromal hyperplasia</li> <li>• Stromal hyperthecosis</li> <li>• Fibromatosis</li> <li>• Massive oedema</li> <li>• Leydig cell hyperplasia</li> <li>• Others</li> </ul> |   |
|   |   |  |   | <p><b>Lymphoid and Myeloid Tumors</b></p> <ul style="list-style-type: none"> <li>• Lymphomas</li> <li>• Plasmacytoma</li> <li>• Myeloid neoplasms</li> </ul>   | <p>Malignant</p>  |

<sup>1</sup>Reproduced with permission from Kurman RJ, Carcangiu ML, Herrington CS, Young RH. World Health Organization Classification of Tumours of the Female Reproductive Organs. IARC, Lyon, 2014.

<sup>2</sup>Borderline = Unspecified, borderline, or uncertain behavior.

**Note:** All recommendations are category 2A unless otherwise indicated.

**Clinical Trials:** NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



## Staging

**Table 1**  
**American Joint Committee on Cancer (AJCC)**  
**TNM and FIGO Staging System for Ovarian, Fallopian Tube, and Primary Peritoneal Cancer (8th ed., 2017)**

### Primary Tumor (T)

| TNM       | FIGO       |  | TNM       | FIGO         |   |
|-----------|------------|--|-----------|--------------|---|
| <b>TX</b> |            | Primary tumor cannot be assessed   | <b>T2</b> | <b>II</b>    | Tumor involves one or both ovaries or fallopian tubes with pelvic extension below pelvic brim or primary peritoneal cancer  |
| <b>T0</b> |            | No evidence of primary tumor   |           |              |   |
| <b>T1</b> | <b>I</b>   | Tumor limited to ovaries (one or both) or fallopian tube(s)  | T2a       | <b>IIA</b>   | Extension and/or implants on the uterus and/or fallopian tube(s) and/or ovaries   |
| T1a       | <b>IA</b>  | Tumor limited to one ovary (capsule intact) or fallopian tube, no tumor on ovarian or fallopian tube surface; no malignant cells in ascites or peritoneal washings       | T2b       | <b>IIB</b>   | Extension to and/or implants on other pelvic tissues  |
| T1b       | <b>IB</b>  | Tumor limited to both ovaries; (capsules intact) or fallopian tubes; no tumor on ovarian or fallopian tube surface; no malignant cells in ascites or peritoneal washings | <b>T3</b> | <b>III</b>   | Tumor involves one or both ovaries or fallopian tubes, or primary peritoneal cancer, with microscopically confirmed peritoneal metastasis outside the pelvis and/or metastasis to the retroperitoneal (pelvic and/or para-aortic) lymph nodes                       |
| T1c       | <b>IC</b>  | Tumor limited to one or both ovaries or fallopian tubes, with any of the following:  | T3a       | <b>IIIA2</b> | Microscopic extrapelvic (above the pelvic brim) peritoneal involvement with or without positive retroperitoneal lymph nodes   |
| T1c1      | <b>IC1</b> | Surgical spill   | T3b       | <b>IIIB</b>  | Macroscopic peritoneal metastasis beyond pelvis 2 cm or less in greatest dimension with or without metastasis to the retroperitoneal lymph nodes  |
| T1c2      | <b>IC2</b> | Capsule ruptured before surgery or tumor on ovarian or fallopian tube surface  | T3c       | <b>IIIC</b>  | Macroscopic peritoneal metastasis beyond the pelvis more than 2 cm in greatest dimension with or without metastasis to the retroperitoneal lymph nodes (includes extension of tumor to capsule of liver and spleen without parenchymal involvement of either organ) |
| T1c3      | <b>IC3</b> | Malignant cells in ascites or peritoneal washings  |           |              |   |

[Continued](#)

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## Staging

### Table 1 (Continued)

#### American Joint Committee on Cancer (AJCC)

#### TNM and FIGO Staging System for Ovarian, Fallopian Tube, and Primary Peritoneal Cancer (8th ed., 2017)

##### Regional Lymph Nodes (N)

| TNM       | FIGO           | Description   |
|-----------|----------------|---|
| <b>NX</b> |                | Regional lymph nodes cannot be assessed                               |
| <b>N0</b> |                | No regional lymph node metastasis                                     |
| N0(i+)    |                | Isolated tumor cells in regional lymph node(s) no greater than 0.2 mm |
| <b>N1</b> | <b>IIIA1</b>   | Positive retroperitoneal lymph nodes only (histologically confirmed)  |
| N1a       | <b>IIIAii</b>  | Metastasis up to and including 10 mm in greatest dimension            |
| N1b       | <b>IIIAiii</b> | Metastasis more than 10 mm in greatest dimension                      |

##### Distant Metastasis (M)

| TNM       | FIGO       | Description   |
|-----------|------------|---|
| <b>M0</b> |            | No distant metastasis   |
| <b>M1</b> | <b>IV</b>  | Distant metastasis, including pleural effusion with positive cytology; liver or splenic parenchymal metastasis; metastasis to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside the abdominal cavity); and transmural involvement of intestine |
| M1a       | <b>IVA</b> | Pleural effusion with positive cytology   |
| M1b       | <b>IVB</b> | Liver or splenic parenchymal metastases; metastases to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside the abdominal cavity); transmural involvement of intestine  |

[Continued](#)

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## Staging

**Table 2. AJCC Prognostic Groups**

**TNM and FIGO Staging System for Ovarian, Fallopian Tube, and Primary Peritoneal Cancer (8th ed., 2017)**

|                    | <b>T</b> | <b>N</b> | <b>M</b> |
|--------------------|----------|----------|----------|
| <b>Stage I</b>     | T1       | N0       | M0       |
| <b>Stage IA</b>    | T1a      | N0       | M0       |
| <b>Stage IB</b>    | T1b      | N0       | M0       |
| <b>Stage IC</b>    | T1c      | N0       | M0       |
| <b>Stage II</b>    | T2       | N0       | M0       |
| <b>Stage IIA</b>   | T2a      | N0       | M0       |
| <b>Stage IIB</b>   | T2b      | N0       | M0       |
| <b>Stage IIIA1</b> | T1/T2    | N1       | M0       |
| <b>Stage IIIA2</b> | T3a      | NX/N0/N1 | M0       |
| <b>Stage IIIB</b>  | T3b      | NX/N0/N1 | M0       |
| <b>Stage IIIC</b>  | T3c      | NX/N0/N1 | M0       |
| <b>Stage IV</b>    | Any T    | Any N    | M1       |
| <b>Stage IVA</b>   | Any T    | Any N    | M1a      |
| <b>Stage IVB</b>   | Any T    | Any N    | M1b      |

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**NCCN Categories of Evidence and Consensus**

|                    |  |
|--------------------|--|
| <b>Category 1</b>  | Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.    |
| <b>Category 2A</b> | Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.   |
| <b>Category 2B</b> | Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.           |
| <b>Category 3</b>  | Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate. |

All recommendations are category 2A unless otherwise indicated.

**NCCN Categories of Preference**

|  |   |
|--|---|
| <b>Preferred intervention</b>          | Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability.  |
| <b>Other recommended intervention</b>  | Other interventions that may be somewhat less efficacious, more toxic, or based on less mature data; or significantly less affordable for similar outcomes. |
| <b>Useful in certain circumstances</b> | Other interventions that may be used for selected patient populations (defined with recommendation).  |

All recommendations are considered appropriate.





# NCCN Guidelines Version 1.2020 Ovarian Cancer

## Discussion

This discussion corresponds to the NCCN Guidelines for Ovarian Cancer. Update is in progress. Last updated 11/09/2017.

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## Ovarian Cancer

### Overview

Ovarian neoplasms consist of several histopathologic entities; treatment depends on the specific tumor type.<sup>1</sup> Epithelial ovarian cancer comprises the majority of malignant ovarian neoplasms (about 90%);<sup>2-4</sup> other less common pathologic subtypes may occur such as malignant germ cell and sex-cord stromal cell tumors. The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines<sup>®</sup>) for Ovarian Cancer were originally published in 1996 and have been subsequently updated at least once every year.<sup>5</sup> These NCCN Guidelines<sup>®</sup> discuss epithelial ovarian cancer and less common ovarian histopathologies (LCOH), including carcinosarcomas (malignant mixed Müllerian tumors [MMMTs] of the ovary), clear cell carcinomas, mucinous carcinomas, low-grade (also known as grade 1) serous carcinomas/endometrioid epithelial carcinomas, borderline epithelial tumors (also known as low malignant potential tumors), malignant sex cord-stromal tumors, and malignant germ cell tumors. The NCCN Guidelines also discuss Fallopian tube cancer and primary peritoneal cancer, which are less common neoplasms that are managed in a similar manner to epithelial ovarian cancer. The LCOH may be managed differently.

These NCCN Guidelines also include sections on *Principles of Surgery*, *Principles of Systemic Therapy*, *Management of Drug Reactions*, and *WHO Histologic Classification*. The Summary of the Guidelines Updates section in the algorithm briefly describes the new changes for 2017 (see the NCCN Guidelines for Ovarian Cancer). Some of the new additions for 2017 include: 1) carboplatin/liposomal doxorubicin for first-line therapy; 2) niraparib and olaparib for maintenance therapy; and 3) rucaparib, carboplatin/albumin-bound paclitaxel, and carboplatin/paclitaxel/bevacizumab for recurrence therapy. It is important to note that all recommendations are category 2A in the NCCN Guidelines unless otherwise indicated. Category 2A recommendations are based on lower level evidence (such as phase 2 trials) and uniform NCCN

consensus (at least 85% of panel members) that the intervention is appropriate.

Epithelial ovarian cancer is the leading cause of death from gynecologic cancer in the United States and is the country's fifth most common cause of cancer mortality in women. In 2018, it is estimated that 22,240 new diagnoses and 14,070 deaths from this neoplasm will occur in the United States; less than 40% of women with ovarian cancer are cured.<sup>6</sup> Five-year survival is about 46.5%, although survival is longer for select patients with some of the LCOH.<sup>7</sup> The incidence of ovarian cancer increases with age and is most prevalent in the sixth and seventh decades of life.<sup>4</sup> The median age at the time of diagnosis is 63 years, and more than 70% of patients present with advanced disease.<sup>6,7</sup>

Epidemiologic studies have identified risk factors in the etiology of ovarian cancer.<sup>4,8,9</sup> A 30% to 60% decreased risk for cancer is associated with younger age at first pregnancy and first birth ( $\leq 25$  years), the use of oral contraceptives, and/or breastfeeding.<sup>10</sup> Conversely, nulliparity or older age ( $>35$  years) at first pregnancy and first birth confers an increased risk for ovarian cancer. Data suggest that postmenopausal hormone therapy and pelvic inflammatory disease may increase the risk for ovarian cancer.<sup>11-13</sup> The risk for borderline epithelial tumors (also known as low malignant potential tumors) may be increased after ovarian stimulation for in vitro fertilization.<sup>14,15</sup> Smoking is associated with an increased risk for mucinous carcinomas but a decreased risk for clear cell carcinomas.<sup>8</sup> Obesity does not appear to be associated with the most aggressive types of ovarian cancer.<sup>16</sup> Environmental factors have been investigated, but so far they have not been conclusively associated with the development of this neoplasm.

Family history (primarily patients having 2 or more first-degree relatives with ovarian cancer)—including linkage with *BRCA1* and *BRCA2* genotypes (hereditary breast and ovarian cancer [HBOC] syndrome) or



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## Ovarian Cancer

families affected by Lynch syndrome (hereditary nonpolyposis colorectal cancer [HNPCC] syndrome)—is associated with early-onset disease.<sup>17-29</sup> These patients account for only 15% of all women who have ovarian cancer.<sup>10,25,30,31</sup> In women at high risk (with either *BRCA1* or *BRCA2* mutations), risk-reducing bilateral salpingo-oophorectomy (BSO) is associated with a reduced risk for breast, ovarian, Fallopian tube, and primary peritoneal cancers (see *Risk-Reducing Salpingo-Oophorectomy [RRSO] Protocol [BRCA/HBOC syndrome]* in the NCCN Guidelines for Ovarian Cancer, *Cytoreductive Surgery* in this Discussion, and *Risk Reduction Surgery* in the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian, available at [www.NCCN.org](http://www.NCCN.org)).<sup>31-36</sup> There is a residual risk for primary peritoneal cancer after risk-reducing BSO in these women at high risk for cancer. Occult ovarian cancer is sometimes found after RRSO, thus emphasizing the need for careful pathologic review of the ovaries and tubes (see *Risk-Reducing Salpingo-Oophorectomy [RRSO] Protocol [BRCA/HBOC syndrome]* in the NCCN Guidelines for Ovarian Cancer).<sup>37-40</sup> The risks of surgery include injury to the bowel, bladder, ureter, and vessels.<sup>41</sup>

It is now generally accepted that the Fallopian tube is the origin of many serous ovarian and primary peritoneal cancers, including serous intraepithelial carcinoma of the Fallopian tube (also known as serous tubal intraepithelial carcinoma [STIC]).<sup>1,42,43</sup> STIC is a precursor of high-grade serous ovarian cancer. A referral to a gynecologic oncologist/comprehensive cancer center is recommended for management of occult STIC.<sup>44-46</sup> It is not clear whether surgical staging and/or adjuvant chemotherapy is beneficial for women with STIC.

### Screening

Because of the location of the ovaries and the biology of most epithelial cancers, it has been difficult to diagnose ovarian cancer at an earlier, more curable stage. Evaluations of patients with newly diagnosed ovarian

cancer have resulted in consensus guidelines for ovarian cancer symptoms, which may enable earlier identification of patients who may be at an increased risk of having developed early-stage ovarian cancer.<sup>47,48</sup> Symptoms suggestive of ovarian cancer include: bloating, pelvic or abdominal pain, difficulty eating or feeling full quickly, and urinary symptoms (urgency or frequency), especially if these symptoms are new and frequent (>12 d/mo).<sup>47</sup> Physicians evaluating women with this constellation of symptoms must be cognizant of the possibility that ovarian pathology may be causing these symptoms.<sup>49</sup> Some evidence suggests that the screening test using these symptoms is not as sensitive or specific as necessary, especially in those with early-stage disease.<sup>41,50-52</sup>

The literature does not support routine screening for ovarian cancer in the general population, and routine screening is not currently recommended by any professional society.<sup>41,49,53-61</sup> Some physicians follow women with high-risk factors (eg, those with *BRCA* mutations, those with a family history) using cancer antigen 125 (CA-125) monitoring and endovaginal ultrasound,<sup>54</sup> however, prospective validation of these tests remains elusive. An intriguing study suggests that ovarian cancer is associated with unique odors that can be detected.<sup>62-65</sup>

A UK trial assessed screening for ovarian cancer (UK Collaborative Trial of Ovarian Cancer Screening [UKCTOCS]) using multimodality screening with ultrasound and CA-125 versus either ultrasound alone or no screening.<sup>66,67</sup> Preliminary results suggested that multimodality screening was more effective at detecting early-stage cancer; however, after a median of 11 years of follow-up, a significant mortality reduction was not observed.<sup>68,69</sup> Some feel that this UKCTOCS screening approach may be useful for women at high risk such as those with *BRCA* mutations.<sup>39</sup> A large randomized trial in more than 78,000 women (the Prostate, Lung, Colorectal, and Ovarian [PLCO] Cancer Screening Trial) in the United States found that screening with transvaginal ultrasonography and CA-125



did not decrease mortality from ovarian cancer.<sup>56,70,71</sup> In addition, false-positive results led to serious complications in some women (n = 163) in the PLCO trial. Another study—comparing 1) CA-125 alone; 2) ultrasound with CA-125; or 3) ultrasound alone—found that CA-125 did not increase the detection of cancer over ultrasound alone and that ultrasound was superior to CA-125 alone.<sup>72</sup>

The Society of Gynecologic Oncology (SGO), the FDA, and the Mayo Clinic have stated that the OVA1 test should not be used as a screening tool to detect ovarian cancer. The OVA1 test uses 5 markers (including transthyretin, apolipoprotein A1, transferrin, beta-2 microglobulin, and CA-125) to assess who should undergo surgery by an experienced gynecologic oncologist and who can have surgery in the community. The Simple Rules algorithm attempts to preoperatively classify adnexal masses as benign or malignant and suggests that patients can be assessed for who should undergo surgery by an experienced gynecologic oncologist and who can have surgery in the community.<sup>73</sup> Based on data documenting an increased survival, NCCN Guidelines Panel Members recommend that all patients should undergo surgery by an experienced gynecologic oncologist (category 1).<sup>49,74-77</sup> The NCCN Panel believes that the OvaSure screening test should not be used to detect ovarian cancer.<sup>78-81</sup> The OvaSure test uses 6 biomarkers, including leptin, prolactin, osteopontin, insulin-like growth factor II, macrophage inhibitory factor, and CA-125.<sup>82</sup> Data show that several markers (including CA-125, HE4, mesothelin, B7-H4, decoy receptor 3 [DcR3], and spondin-2) do not increase early enough to be useful in detecting early-stage ovarian cancer.<sup>83-85</sup>

### **Staging**

The NCCN Guidelines for Ovarian Cancer reflect the importance of stage and grade of disease on prognosis and treatment recommendations. Ovarian cancer is classified primarily as stages I to IV using the FIGO

(International Federation of Gynecology and Obstetrics) and AJCC staging systems (see Table 1 and other staging tables in the NCCN Guidelines for Ovarian Cancer).<sup>86</sup> Most patients present with stage 3 disease.<sup>87</sup> Serous ovarian cancer is now often referred to as either low grade (most grade 1 serous tumors) or high grade (most grade 2 or 3 serous tumors).<sup>87-92</sup> Pathologists may use histologic grades 1, 2, or 3 for endometrioid carcinomas, mucinous carcinomas, and stage IC tumors.<sup>88</sup> Primary peritoneal adenocarcinoma and LCOH are also staged using the ovarian cancer staging system (see Table 1 in the NCCN Guidelines for Ovarian Cancer).<sup>86</sup> Until January 1, 2018, Fallopian tube carcinomas will be staged using a separate FIGO and AJCC staging system (see Table 2 in the NCCN Guidelines for Ovarian Cancer and see next paragraph).<sup>86</sup> The new AJCC/FIGO staging guidelines (8<sup>th</sup> edition) will combine staging for Fallopian tube carcinoma and ovarian cancer, and will be effective on January 1, 2018 (see *Staging* in the NCCN Guidelines for Ovarian Cancer).<sup>93</sup> Except for select women with stage I, grade 1 tumors (in whom survival is greater than 95% after comprehensive laparotomy), patients in all other stages of ovarian cancer should be encouraged to enter clinical trials for both primary and recurrence therapy.

FIGO recently updated the staging for ovarian, Fallopian tube, and peritoneal cancer; their new staging system has been approved by the AJCC (see *Staging* in the NCCN Guidelines for Ovarian Cancer).<sup>87,89</sup> For example, in the new staging guidelines, old stages IC, IIIA, and IV are now subdivided; the old stage IIC has been eliminated. These changes are included in the 8th edition of the AJCC Cancer Staging Manual, which was published in late 2016 and will be effective for all cancer cases recorded on or after January 1, 2018.<sup>93</sup> A pathology and staging cancer protocol is available from the College of American Pathologists (CAP) for Fallopian tube carcinoma and ovarian cancer that is based on the 8th edition of the AJCC; earlier editions are also available.<sup>94</sup> By definition, the NCCN Guidelines cannot incorporate all possible clinical variations and are not



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## Ovarian Cancer

intended to replace good clinical judgment or individualization of treatments. Exceptions to the rule were discussed among panel members during the process of developing these guidelines. A 5% rule (omitting clinical scenarios that comprise less than 5% of all cases) was used to eliminate uncommon clinical occurrences or conditions from these guidelines.

### **Literature Search Criteria and Guidelines Update Methodology**

An electronic search of the PubMed database was performed to obtain key literature in ovarian cancer using the following search term: ovarian cancer. The PubMed database was chosen because it remains the most widely used resource for medical literature and indexes only peer-reviewed biomedical literature.<sup>95</sup> The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: Clinical Trial, Phase 3; Clinical Trial, Phase IV; Guideline; Randomized Controlled Trial; Meta-Analysis; Systematic Reviews; and Validation Studies.

The PubMed search resulted in 151 citations and their potential relevance was examined. The data from key PubMed articles, as well as articles from additional sources deemed as relevant to these Guidelines and discussed by the panel, have been included in this version of the Discussion section (eg, e-publications ahead of print, meeting abstracts). Recommendations for which high-level evidence is lacking are based on the panel's review of lower-level evidence and expert opinion. The complete details of the Development and Update of the NCCN Guidelines are available on the NCCN webpage ([www.NCCN.org](http://www.NCCN.org)).

## **Epithelial Ovarian Cancer**

### **Recommended Workup**

The NCCN Guidelines for Epithelial Ovarian Cancer begin with the management of an undiagnosed pelvic mass or a prior diagnosis of a

malignant epithelial ovarian tumor. Many patients with this diagnosis come to NCCN Member Institutions after having had previous surgery. The NCCN Guidelines recommend symptom management and best supportive care for all patients; women should be referred for palliative care assessment if appropriate (see the NCCN Guidelines for Palliative Care, available at [www.NCCN.org](http://www.NCCN.org)).<sup>53,96</sup>

### ***Undiagnosed Pelvic Mass***

The primary workup should include an abdominal/pelvic ultrasound and/or abdominal/pelvic CT/MRI scan (after an abdominal/pelvic examination) and appropriate laboratory studies for a patient with a suspicious pelvic mass (detected on abdominal/pelvic exam) and/or ascites, abdominal distention, and/or symptoms (ie, bloating, pelvic or abdominal pain, difficulty eating or feeling full quickly, urinary symptoms) without other obvious sources of malignancy (see *Workup* in the NCCN Guidelines for Epithelial Ovarian Cancer).<sup>47,97-104</sup> Tumor markers (including CA-125, inhibin, alpha-fetoprotein [AFP], and beta-human chorionic gonadotropin [beta-hCG]) can be measured if clinically indicated to assess for LCOH and pregnancy (see *Less Common Ovarian Histopathologies* in this Discussion and the NCCN Guidelines for Ovarian Cancer).<sup>105-107</sup> For example, clinicians should consider measuring AFP levels to assess for germ cell tumors in women younger than 35 years with a pelvic mass.<sup>105-107</sup> Ultrasound is typically used for initial evaluation; abdominal/pelvic CT is useful to assess for metastases.<sup>99</sup> Abdominal/pelvic MRI may be useful for determining malignant potential if ultrasound is not reliable.<sup>103,104</sup> CT/MRI imaging should be performed with contrast unless contraindicated. FDG-PET/CT scan or MRI may be useful for indeterminate lesions.<sup>108-110</sup>

Most ovarian cancers, including the LCOH, are diagnosed after pathologic analysis of a biopsy or surgical specimen, which may occur preoperatively, intraoperatively, or postoperatively. Both primary peritoneal and Fallopian



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tube cancers are usually diagnosed postoperatively (if there is no major involvement of the ovary) or preoperatively (if there is a biopsy and the patient has already had a bilateral oophorectomy). Primary peritoneal and Fallopian tube cancers are treated in the same manner as epithelial ovarian cancer. If possible, fine-needle aspiration (FNA) should be avoided for diagnosis of ovarian cancer in patients with presumed early-stage disease to prevent rupturing the cyst and spilling malignant cells into the peritoneal cavity; however, FNA may be necessary in patients with bulky disease who are not surgical candidates.<sup>111,112</sup> Other cancers that should be ruled out include bowel, uterine, and pancreatic cancers or lymphoma;<sup>113,114</sup> benign ovarian and non-ovarian conditions also need to be ruled out (eg, serous cystadenoma).<sup>115</sup> In addition, metastases to the ovaries need to be ruled out (see *Mucinous Carcinomas* in this Discussion).

It has been suggested that specific biomarkers (serum HE4 and CA-125) along with an algorithm (Risk of Ovarian Malignancy Algorithm [ROMA]) may be useful for determining whether a pelvic mass is malignant or benign.<sup>116,117</sup> The FDA has approved the use of HE4 and CA-125 for estimating the risk for ovarian cancer in women with a pelvic mass. Currently, the NCCN Panel does not recommend the use of these biomarkers for determining the status of an undiagnosed pelvic mass.<sup>118-121</sup> Although there is no direct evidence that chest x-ray or chest CT is necessary, panel members felt that it should be part of the overall evaluation of a patient before surgical staging if clinically indicated. Gastrointestinal tract evaluation should be done for mucinous histology to determine whether patients have metastases to the ovary or primary mucinous carcinoma of the ovary (see *Mucinous Carcinomas* in this Discussion).<sup>122</sup>

### **Prior Diagnosis of Malignancy**

Patients are often referred to NCCN Member Institutions after having a previous diagnosis of ovarian cancer by surgery or tissue biopsy (cytopathology). Often they have had cytoreductive surgery and comprehensive staging procedures (ie, having met the standards for surgical staging of the Gynecologic Oncology Group [GOG]). In some instances, referral occurs after incomplete surgery and/or staging (eg, uterus and/or adnexa intact, omentum not removed, incomplete lymph node dissection, residual disease that is potentially resectable, surgical stage not completely documented). The components of surgical staging are listed in the algorithm (see *Principles of Surgery* in the NCCN Guidelines for Epithelial Ovarian Cancer). Identical workup procedures are recommended for patients having undiagnosed or diagnosed pelvic masses at the time of referral. Tissue diagnosis of metastatic sites can be considered.

### **Histologic Subtypes**

Epithelial ovarian cancer has 4 main histologic subtypes, including serous, endometrioid, mucinous, and clear cell; most patients (about 70%) have serous histology.<sup>3,86,90,123,124</sup> Primary treatment recommendations for the LCOH subtypes—mucinous, clear cell, and low-grade (grade 1) serous/endometrioid—may be different from the treatment recommendations for the high-grade serous/endometrioid subtypes (see the NCCN Guidelines for Epithelial Ovarian Cancer and the NCCN Guidelines for Less Common Ovarian Histopathologies).<sup>90</sup> Molecular characterization of clear cell, mucinous, or low-grade (grade 1) serous tumors suggests that mutations in these histologies are different from those in higher grade tumors.<sup>125-127</sup> Ovarian cancer can be divided into Types 1 and 2 based on these molecular alterations. Data suggest that serous tumors can be categorized as either low grade (most grade 1 serous tumors) or high grade (most grade 2 or 3 serous tumors).<sup>87,89-92,128,129</sup> High-grade endometrioid tumors are difficult to



distinguish from high-grade serous tumors.<sup>90</sup> Low-grade (grade 1) serous tumors are relatively resistant to standard chemotherapy regimens.<sup>90,130</sup> Pathology review at NCCN Member Institutions is recommended for all patients. The CAP protocol is a useful tool for pathology reports; it was revised for 2016 and 2017.<sup>88,94,131</sup> The complete histologic classification from the WHO is included in the NCCN Guidelines (see *WHO Histologic Classification* in the NCCN Guidelines for Ovarian Cancer Histopathologies).<sup>1</sup> The WHO pathology manual is also a useful resource.<sup>1,132</sup>

### **Risk-Reducing Surgery**

The RRSO protocol is recommended for patients at risk for HBOC and is described in detail in the algorithm (see the *Principles of Surgery* in the NCCN Guidelines for Epithelial Ovarian Cancer, the *Overview* in this Discussion, and the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian, available at [www.NCCN.org](http://www.NCCN.org)).<sup>39</sup> This protocol recommends that the Fallopian tubes should be processed by sectioning and extensively examining the fimbriated end (SEE-Fim) of the tubes and then assessed to determine whether any evidence of cancer is present.<sup>37,133</sup> The ovaries should also be carefully sectioned, processed, and assessed.<sup>134</sup> The 2016 and 2017 CAP protocols describe the process for sectioning the Fallopian tubes and ovaries.<sup>88,94,134</sup> Note that it is controversial whether a hysterectomy should also be done.<sup>30</sup> The prevention benefits of salpingectomy alone are not yet proven.<sup>135-140</sup> If salpingectomy alone is considered, the Fallopian tube from the fimbria to its insertion into the uterus should be removed; the Fallopian tubes should also be carefully processed and assessed as previously described.<sup>135</sup>

### **Primary Treatment**

Primary treatment for presumed ovarian cancer consists of appropriate surgical staging and debulking surgery, followed in most (but not all) patients by systemic chemotherapy.<sup>74,141-143</sup> The surgeon should describe

the following in the operative report: 1) the extent of initial disease; 2) the amount of residual disease; and 3) whether a complete or incomplete resection (including a description of the lesions) was achieved (see *Principles of Surgery: Operative Reports* in the NCCN Guidelines for Epithelial Ovarian Cancer).<sup>144</sup> For most patients, initial surgery should include a total abdominal hysterectomy (TAH) and BSO with comprehensive staging and debulking as indicated (see the *Principles of Surgery* in the NCCN Guidelines for Ovarian Cancer).<sup>10,145,146</sup> Based on published improved outcomes, it is recommended (category 1) that a gynecologic oncologist perform the primary surgery.<sup>75-77</sup> For a young patient who wishes to maintain fertility, a unilateral salpingo-oophorectomy (USO) (preserving the uterus and contralateral ovary) and comprehensive surgical staging may be adequate for select unilateral stage I tumors (stage 1A and 1C, but not stage 1B) and/or low-risk ovarian tumors (ie, early-stage, grade 1 tumors; borderline tumors).<sup>147-152</sup> For those with stage IB tumors who wish to maintain fertility, a BSO (preserving the uterus) and comprehensive surgical staging are needed.

Comprehensive surgical staging should still be performed to rule out occult higher-stage disease, because data show that approximately 30% of patients undergoing complete staging surgery are upstaged.<sup>153</sup> In select patients, minimally invasive procedures may be used for surgical staging.<sup>145,154-157</sup> In early-stage disease, minimally invasive techniques to achieve the surgical goals may be considered in selected patients if performed by an experienced gynecologic oncologist.<sup>104,145,158,159</sup> Surgeons tend to use an open laparotomy for patients with more widespread disease.<sup>159,160</sup> Minimally invasive techniques may be considered for risk-reducing salpingo-oophorectomy. For some of the LCOH, comprehensive staging may not be necessary for select patients, such as patients with borderline epithelial tumors (see the NCCN Guidelines for Less Common Ovarian Histopathologies).

### Debulking Surgery

Debulking surgery is the initial treatment recommendation for patients with clinical stage II, III, or IV disease (see *Primary Treatment* in the NCCN Guidelines for Epithelial Ovarian Cancer and the NCCN Guidelines for Less Common Ovarian Histopathologies).<sup>74,77,143,149,153,161-163</sup> Although debulking surgery is the standard of care, this recommendation is based on retrospective data (and thus is not a category 1 recommendation).<sup>164</sup> In general, the procedures outlined in the next paragraph should be part of the surgical management of patients with ovarian, Fallopian tube, or primary peritoneal cancer in an effort to fully stage patients and to achieve maximal debulking to less than 1-cm residual disease or resection of all visible disease in appropriate circumstances.<sup>165-167</sup> These procedures also apply to many of the LCOH. Surgical debulking is optimal if the residual tumor nodules are less than 1 cm in maximum diameter or thickness;<sup>146,149,164,168,169</sup> the goal is resection to R0. Extensive resection of upper abdominal metastases is recommended for patients who can tolerate this surgery.<sup>162,170</sup>

In select patients, minimally invasive procedures may be used to assess whether debulking surgery is feasible.<sup>145,158,159,171-173</sup> A recent trial assessed whether laparoscopy can be used to determine if debulking surgery will be futile (because patients actually have disease that cannot be optimally debulked to less than 1 cm). Of patients in the laparoscopy group, 10% (10/102) had futile laparotomy versus 39% (39/99) in the primary surgery group (relative risk, 0.25; 95% CI, 0.13– 0.47;  $P < .001$ ).

A maximal effort should be made to remove all gross disease, because the more complete the debulking the better the outcomes.<sup>161</sup> On entering the abdomen, aspiration of ascites or peritoneal lavage should be performed for cytologic examinations. For obvious disease beyond the ovaries, cytologic assessment of ascites and/or lavage specimens will not alter stage or management. Hysterectomy and BSO should be performed.

Although total hysterectomy is recommended for most patients, a supracervical hysterectomy is appropriate in some circumstances. An encapsulated mass should be removed intact, if possible.<sup>112,155</sup> All involved omentum should be removed. Suspicious and/or enlarged nodes should be resected, if possible.<sup>174,175</sup> Bilateral pelvic and para-aortic lymph node dissection is recommended for those patients with tumor nodules, outside the pelvis, of 2 cm or less (presumed stage IIIB) (see *Principles of Surgery* in the NCCN Guidelines for Epithelial Ovarian Cancer). For young patients who will abruptly enter menopause after surgery, various supportive care measures may be used to help decrease hot flashes and other symptoms.<sup>176-179</sup>

Most patients have a hysterectomy with BSO, omentectomy, and lymphadenectomy of suspicious/enlarged nodes (see *Principles of Surgery* in the NCCN Guidelines for Epithelial Ovarian Cancer). Some surgeons classify debulking based on the number of procedures. In patients with advanced ovarian cancer who have had complete debulking, data indicate that overall survival is increased in those who receive systematic lymphadenectomy.<sup>180</sup> Patients with low-volume residual disease after surgical debulking for stage II or III invasive epithelial ovarian or peritoneal cancer are candidates for intraperitoneal (IP) therapy.<sup>181,182</sup> In these patients, consideration should be given to placement of an IP catheter with initial surgery.<sup>145</sup> Procedures that may be considered for optimal surgical debulking include: radical pelvic dissection, bowel resection and/or appendectomy, lymphadenectomy, diaphragm or other peritoneal surface stripping, splenectomy, partial hepatectomy, partial gastrectomy, or partial cystectomy and/or ureteroneocystostomy, cholecystectomy, and/or distal pancreatectomy.<sup>162,170,183</sup>

The surgical guidelines emphasize that an open laparotomy should be used for patients with suspected malignant ovarian cancer if the treatment plan involves surgical staging, primary debulking, interval debulking, or





secondary debulking surgery (see *Principles of Surgery* in the NCCN Guidelines for Epithelial Ovarian Cancer). The surgical guidelines also state that if patients cannot be optimally debulked using minimally invasive techniques, they should be converted to an open procedure. Neoadjuvant therapy can be considered if maximal debulking cannot be achieved (see *Neoadjuvant Chemotherapy* in this Discussion).<sup>184,185</sup> For patients with incomplete previous surgery and/or staging, treatment recommendations are outlined in the algorithm (see *Diagnosis by Previous Surgery* in the NCCN Guidelines for Epithelial Ovarian Cancer).

### Neoadjuvant Chemotherapy

The therapeutic benefit of neoadjuvant chemotherapy followed by interval cytoreduction remains controversial (see third paragraph).<sup>164,184,186-193</sup> The best outcomes are consistently seen for patients who have complete resection of all visible disease (ie, R0) who subsequently receive IV/IP therapy.<sup>194</sup> Those who do not have an attempt at complete cytoreduction may miss this opportunity. Neoadjuvant chemotherapy may be considered (category 1) for patients with bulky stage III to IV disease who are assessed by a gynecologic oncologist and deemed unlikely to be completely cytoreduced to R0, or for patients who are poor surgical candidates; a gynecologic oncologist should make this assessment before neoadjuvant chemotherapy is administered.<sup>184,195-201</sup> Neoadjuvant chemotherapy is not appropriate for patients with disease apparently confined to the ovary. Standard intravenous regimens described in the algorithm may be used for neoadjuvant chemotherapy (see *Principles of Systemic Therapy: Primary Chemotherapy/Primary Adjuvant Therapy Regimens* in the NCCN Guidelines for Ovarian Cancer). Before initiation of neoadjuvant chemotherapy, histologic confirmation of ovarian cancer should be obtained (by FNA, biopsy, or paracentesis) in this group of patients; a core biopsy is preferred. Minimally invasive techniques may be used to obtain the biopsy. Obtaining a CA-125:CEA ratio is also useful.

*Neoadjuvant therapy* refers to treatment (eg, drugs, radiation, other treatment) that is given to reduce the tumor burden before cancer surgery (see *Principles of Systemic Therapy: Primary Chemotherapy/Primary Adjuvant Therapy Regimens* in the NCCN Guidelines for Epithelial Ovarian Cancer). Intravenous taxane/carboplatin and liposomal doxorubicin/carboplatin regimens are recommended for neoadjuvant chemotherapy and adjuvant therapy after interval debulking surgery.

The standard IP/IV regimen (paclitaxel/cisplatin) may be used after intravenous neoadjuvant chemotherapy and interval debulking surgery.<sup>202</sup> Preliminary data from a phase 2 trial suggest that an IV/IP paclitaxel/carboplatin regimen may be used after neoadjuvant chemotherapy and interval debulking surgery.<sup>202</sup> A phase 2 randomized trial assessed a neoadjuvant regimen with bevacizumab/carboplatin/paclitaxel versus chemotherapy alone in patients (n=71) with unresectable stage III to IV ovarian cancer.<sup>203</sup> Surgical feasibility was improved in the bevacizumab arm when compared with chemotherapy alone (88.6% vs. 66.7%,  $P = .029$ ). At interval debulking surgery, the number of patients deemed unresectable was similar (0 vs. 2). The median PFS was similar in both arms (20.36 vs. 20.13 mo; HR: 1.14 [IC 95%, 0.656–1.994]).

A randomized phase 3 international trial assessed neoadjuvant chemotherapy with interval debulking surgery versus upfront primary debulking surgery in patients with extensive-stage IIIC/IV ovarian, primary peritoneal, and Fallopian tube carcinoma (sponsored by the EORTC-GCG and the NCIC-CTG).<sup>196</sup> Median overall survival was equivalent in these patients (29 vs. 30 months), but patients receiving neoadjuvant chemotherapy with interval debulking surgery had fewer complications. A major criticism of this international trial is that reported progression-free survival (PFS) and overall survival were inferior to those reported in randomized studies in the United States of patients undergoing primary

debulking surgery followed by postoperative intravenous chemotherapy for advanced ovarian cancer (overall survival averages about 50 months in the United States).<sup>182,201</sup> Although the median overall survival in the international trial is 20 months lower than that reported in U.S. trials using the customary sequence of therapeutic interventions (ie, primary debulking surgery followed by chemotherapy), this difference may have been a result of selection of patients at higher risk to the international trial (which did not include patients with stage IIIB or earlier-stage cancer). Also, primary or interval debulking surgery in the international trial may have been suboptimal (ie, patients may have had >1 cm of residual disease).<sup>164</sup>

A retrospective analysis of the EORTC-NCIC trial reported that patients with stage IV disease with bulky tumors had longer survival with neoadjuvant therapy, whereas those with stage IIIC disease and less bulky tumors had longer survival with upfront surgery.<sup>185</sup> In the opinion of the subcommittee for the NCCN Guidelines for Ovarian Cancer, more data will be necessary prior to recommending neoadjuvant chemotherapy in patients with potentially resectable ovarian cancer, and upfront debulking surgery remains the treatment of choice in the United States.<sup>145,204</sup> A large (586 patients) single-institution study in the United States reported that patients with advanced ovarian cancer who had standard debulking surgery had improved median overall survival (71.7 months [CI, 59.8–not reached]) when compared with those who had neoadjuvant chemotherapy (42.9 months [CI, 37.1–56.3]).<sup>205</sup> A report of more than 14,000 patients reported that median survival is improved by almost 2 years in those receiving upfront debulking surgery when compared with those receiving neoadjuvant chemotherapy (69 vs. 45 months).<sup>206</sup> A recent retrospective Italian study in women in complete response after primary treatment reported better outcomes with upfront surgery (n = 322) when compared with neoadjuvant therapy followed by surgery (n = 62); overall survival at 2 years, 5 years, and 7 years was 96.4%, 69.3%, and 50.4% for upfront

surgery versus 87.1%, 41.8%, and 32.6% for neoadjuvant therapy ( $P = .001$ ).<sup>186</sup>

### **Interval Debulking Surgery**

Patients should be evaluated for potential interval debulking surgery, including completion TAH and BSO with staging, before the fourth cycle of neoadjuvant chemotherapy (see *Primary Treatment* in the NCCN Guidelines for Epithelial Ovarian Cancer). A minimum of 6 cycles of treatment is recommended including at least 3 cycles of adjuvant therapy after interval debulking surgery. The surgical guidelines describe the procedures for interval debulking in patients with invasive epithelial ovarian cancer who respond to or have stable disease after neoadjuvant chemotherapy (see *Principles of Surgery* in the NCCN Guidelines for Ovarian Cancer). These surgical procedures are similar to those recommended for a primary debulking procedure. For example, every effort should be made to achieve maximal cytoreduction during an interval debulking procedure. Any peritoneal surface or adhesion suspicious for harboring metastasis should be selectively excised or biopsied. Removal of lymph nodes noted to have potential metastasis at the time of initial diagnosis should be considered, even if the nodes are not currently suspicious or enlarged.

### **Incomplete Surgery and/or Staging**

For patients with incomplete previous surgery and/or staging, treatment recommendations are outlined in the algorithm (see *Diagnosis by Previous Surgery* in the NCCN Guidelines for Epithelial Ovarian Cancer). For patients with stage II to IV disease who have residual disease that is considered unresectable, an evaluation for interval debulking surgery is recommended before the fourth cycle of chemotherapy. Interval debulking surgery after 3 cycles of chemotherapy is preferred; surgery may be performed after 4 to 6 cycles based on the clinical judgment of the gynecologic oncologist. Depending on the surgical results, postoperative



chemotherapy may be recommended. Tumor reductive surgery is recommended for all patients with stage II to IV disease with suspected residual disease that is potentially resectable.

### Postoperative Chemotherapy

Most patients with epithelial ovarian cancer receive postoperative systemic chemotherapy (see *Principles of Systemic Therapy* in the NCCN Guidelines for Epithelial Ovarian Cancer). Observation is recommended for patients with surgically staged IA or IB, grade 1 endometrioid carcinomas and other histologies, because survival is greater than 90% for this group with surgical treatment alone.<sup>207-209</sup> If observation is considered for stage IA or IB grade 1 or 2 tumors, a surgical staging procedure is recommended for all patients. Recommendations regarding initial primary chemotherapy/primary adjuvant therapy include intravenous with [or without] IP options (see *Primary Chemotherapy/Primary Adjuvant Therapy Regimens* in the NCCN Guidelines for Epithelial Ovarian Cancer).<sup>210</sup> All of the regimens (including the combined intravenous/IP chemotherapy) may be used for epithelial ovarian, primary peritoneal, and Fallopian tube cancers; some of these regimens are recommended for some of the LCOH.

The intravenous/IP chemotherapy regimen (IP chemotherapy) is recommended for patients with stage III cancer with optimally debulked (<1 cm residual) disease based on randomized controlled trials (category 1).<sup>181,182,211,212</sup> The best outcomes are consistently seen for patients who have complete resection of all visible disease (ie, R0) who subsequently receive IV/IP therapy.<sup>194</sup> Women with optimally debulked stage II disease may also receive IP chemotherapy, although no randomized evidence for stage II has been published; therefore, this is a category 2A recommendation. IP chemotherapy is not recommended for stage I or IV disease. In women with stage III cancer, survival was increased by 16 months after IP therapy using cisplatin/paclitaxel when compared with

standard intravenous therapy (65.6 vs. 49.7 months,  $P=.03$ ) in the GOG 172 trial. For patients who are not candidates for IP therapy (eg, those with poor performance status [PS]), other regimens may be recommended (see *Primary Chemotherapy/Primary Adjuvant Therapy Regimens* in the NCCN Guidelines for Epithelial Ovarian Cancer).<sup>75,213</sup> Intravenous docetaxel plus carboplatin (category 1)<sup>214</sup> or paclitaxel plus carboplatin (category 1) are options for alternative regimens.<sup>215,216</sup> The docetaxel/carboplatin or liposomal doxorubicin/carboplatin regimens may be considered for patients who are at high risk for neuropathy (eg, patients with diabetes).<sup>217</sup>

Recommendations for the number of cycles of treatment vary with the stage of the disease. Panel members had an extensive discussion about the number of cycles of chemotherapy that should be recommended for patients with advanced-stage disease. There is no evidence confirming that more than 6 cycles of combination chemotherapy are required for initial chemotherapy.<sup>218</sup> For patients with advanced-stage disease (stages II–IV), a total of 6 cycles of intravenous chemotherapy are recommended, whereas 3 to 6 cycles are recommended for earlier-stage disease (see *Primary Treatment* in the NCCN Guidelines for Epithelial Ovarian Cancer).<sup>191,215,219</sup> Data suggest there is a potential survival advantage for 6 cycles of chemotherapy in select patients with serous cytology.<sup>220</sup>

The recommended intravenous regimens accepted by a consensus of the NCCN Panel include: 1) paclitaxel, 175 mg/m<sup>2</sup> over 3-hour intravenous infusion, followed by carboplatin, dosed at an area under the curve (AUC) of 5 to 6 intravenous over 1 hour on day 1, given every 3 weeks for 6 cycles (category 1);<sup>213,215</sup> 2) dose-dense paclitaxel, 80 mg/m<sup>2</sup> intravenous over 1 hour on days 1, 8, and 15 plus carboplatin AUC 5 to 6 intravenous over 1 hour on day 1, every 3 weeks for 6 cycles (category 1);<sup>221</sup> 3) paclitaxel 60 mg/m<sup>2</sup> over 1 hour followed by carboplatin AUC 2 intravenous over 30 minutes, weekly for 18 weeks (category 1);<sup>222</sup> 4)



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docetaxel, 60 to 75 mg/m<sup>2</sup> 1-hour intravenous infusion followed by carboplatin, dosed at AUC of 5 to 6 intravenous over 1 hour on day 1, every 3 weeks for 6 cycles (category 1);<sup>214</sup> and 5) carboplatin AUC 5 plus pegylated liposomal doxorubicin 30 mg/m<sup>2</sup> every 4 weeks for 6 cycles (category 2A).<sup>215</sup> For the 2017 update, the NCCN Panel added the fifth regimen (see last paragraph in this section). These intravenous regimens may also be used for neoadjuvant chemotherapy (see *Principles of Systemic Therapy* in the NCCN Guidelines for Ovarian Cancer). The weekly carboplatin/paclitaxel regimen may be considered for elderly patients or those with poor PS based on the phase 3 MITO-7 trial.<sup>222</sup> Note that carboplatin dosing may be revised based on changes in serum creatinine methodology (see FDA carboplatin dosing statement). The AUC of 5 to 6 for carboplatin reflects contemporary treatment.

The recommended IP chemotherapy regimen is paclitaxel, 135 mg/m<sup>2</sup> continuous intravenous infusion over 3 or 24 hours on day 1; cisplatin, 75 to 100 mg/m<sup>2</sup> IP on day 2 after intravenous paclitaxel; paclitaxel, 60 mg/m<sup>2</sup> IP on day 8; repeat every 3 weeks for 6 cycles (category 1).<sup>182</sup> The randomized phase 3 trial for this IP/intravenous regimen used intravenous continuous infusion of paclitaxel over 24 hours. A 3-hour infusion of paclitaxel has not been proven to be equivalent to a 24-hour infusion, although a 3-hour infusion has been reported to be more convenient, easier to tolerate, and less toxic.<sup>223</sup> Note that these IP regimens include intravenous regimens so that systemic disease can also be treated. All of these regimens have different toxicity profiles. The docetaxel/carboplatin regimen is associated with increased risk for neutropenia; the intravenous paclitaxel/carboplatin regimen is associated with sensory peripheral neuropathy; and dose-dense paclitaxel is associated with increased anemia and decreased quality of life.<sup>214,215,221,224</sup> Note that there are no agents to prevent chemotherapy-induced peripheral neuropathy.<sup>225</sup>

The IP paclitaxel/cisplatin regimen is associated with leukopenia, infection, fatigue, renal toxicity, abdominal discomfort, and neurotoxicity.<sup>226-228</sup> In the initial studies, only 42% of women were able to complete all 6 treatment cycles of the IP regimen because of toxicity; with more experience, this percentage has improved in the major cancer centers.<sup>229</sup> Although it has been suggested that a lower IP cisplatin dose of 75 mg/m<sup>2</sup> may help to decrease toxicity, preliminary data from GOG 252 suggest that the reduced-dose IP regimen should not be used.<sup>223,229-231</sup> Patients who are candidates for the IP cisplatin and IP/intravenous paclitaxel regimen should have normal renal function before starting, a medically appropriate PS based on the future toxicities of the IP/intravenous regimen, and no previous evidence of medical problems that could significantly worsen during chemotherapy, such as preexisting neuropathy (see *Principles of Systemic Therapy* in the NCCN Guidelines for Epithelial Ovarian Cancer). Reasons for discontinuing the IP regimen included catheter complications, nausea/vomiting/dehydration, and abdominal pain.<sup>232</sup> Women unable to complete IP therapy should receive intravenous therapy. Techniques to decrease catheter complications include catheter choice and timing of insertion.<sup>211,233</sup> Expert nursing care may help to decrease complications.<sup>210</sup> Giving intravenous hydration before and after IP chemotherapy is a useful strategy to prevent renal toxicity.<sup>229</sup> After chemotherapy, patients often require intravenous fluids (5–7 days) in the outpatient setting to prevent or help treat dehydration. Whether to use IP or intravenous chemotherapy remains controversial.<sup>232,234-237</sup>

Patients with poor PS, comorbidities, stage IV disease, or advanced age (>65 years) may not tolerate the IP regimen or the other combination intravenous regimens described in the NCCN Guidelines. Single-agent platinum agents, such as cisplatin or carboplatin, may be more appropriate for these patients. A phase 3 randomized trial (MITO-7) assessed carboplatin/paclitaxel every week compared with standard therapy given every 3 weeks (ie, intravenous carboplatin/paclitaxel) in women with



advanced epithelial ovarian cancer.<sup>222</sup> Median PFS was similar between the 2 regimens. The weekly carboplatin/paclitaxel regimen was associated with fewer side effects and yielded a better quality of life. For example, fewer patients receiving the weekly regimen had grade 3 to 4 neutropenia (167 [42%] of 399 patients vs. 200 [50%] of 400 patients). Therefore, this weekly carboplatin/paclitaxel regimen may be considered for elderly patients or those with poor PS based on the phase 3 MITO-7 trial.<sup>222</sup> Algorithms are available for predicting chemotherapy toxicity (see the NCCN Guidelines for Senior Adult Oncology, available at [www.NCCN.org](http://www.NCCN.org)).

The IP regimen published by Armstrong et al reported a median survival of 65.6 months in women with optimally debulked stage III cancer.<sup>182,194</sup> A study reported overall survival of 110 months in patients with stage III ovarian cancer and no residual disease who received the IP regimen.<sup>194</sup> Another study showed that survival improves with each cycle of IP chemotherapy.<sup>238</sup> Patients with optimally debulked stage II or III primary peritoneal cancer, Fallopian tube cancer, or MMTT can also be considered for IP chemotherapy.<sup>212,233</sup> If the NCCN Guidelines state that treatment as per epithelial ovarian cancer is an option, then IP chemotherapy can be considered an option for other LCOH including clear cell carcinoma, mucinous carcinoma, low-grade serous carcinoma, endometrioid carcinoma, and borderline epithelial tumors with invasive implants (see the NCCN Guidelines for Less Common Ovarian Histopathologies). All women should be counseled about the clinical benefit associated with combined intravenous and IP chemotherapy administration before undergoing surgery for epithelial ovarian cancer, Fallopian tube cancer, primary peritoneal cancer, or MMTT.<sup>181,239</sup> A study reported that women with aberrant *BRCA1* expression had increased survival when treated with IP cisplatin/paclitaxel.<sup>240</sup> A recent study reported that young women with some residual disease (1–10 mm)

remaining after debulking still benefited from IP chemotherapy, although removing all gross disease yielded the longest survival.<sup>241</sup>

Dose-dense weekly paclitaxel with carboplatin has been shown to increase both PFS (28 vs. 17 months,  $P = .0037$ ) and overall survival when compared with standard therapy given every 3 weeks (ie, intravenous carboplatin/paclitaxel) in women with advanced epithelial ovarian cancer (JGOG 3016).<sup>221,242,243</sup> In the dose-dense group, median overall survival was 100.5 months (95% CI, 65.2–∞) versus 62.2 months (95% CI, 52.1–82.6) in the conventional treatment group (hazard ratio [HR], 0.79; 95% CI, 0.63–0.99;  $P = .039$ ).<sup>243</sup> The dose-dense regimen is more toxic, and patients discontinued dose-dense paclitaxel therapy more often than did those receiving standard therapy. A study reported that dose-dense weekly paclitaxel did not prolong PFS.<sup>244</sup>

For the 2017 update, the NCCN Panel added carboplatin/liposomal doxorubicin as another first-line postoperative intravenous option for patients with stages II to IV ovarian cancer; this regimen has a category 2A recommendation. The regimen was added based on a phase 3 randomized trial in 820 patients with stages III and IV ovarian cancer comparing carboplatin/liposomal doxorubicin versus carboplatin/paclitaxel.<sup>215</sup> There was no significant difference in the median overall survival with carboplatin/liposomal doxorubicin versus carboplatin/paclitaxel (61.6 and 53.2 months, respectively; HR, 0.89; 95% CI, 0.72–1.12;  $P = .32$ ). Toxicity was different in the 2 groups. More hematologic adverse effects but less neurotoxicity and alopecia occurred with carboplatin/liposomal doxorubicin; therefore, this regimen may be useful in select patients at high risk for neurotoxicity or those who would like to avoid alopecia.

### **Anti-Angiogenesis Agents**

A phase 3 randomized trial (GOG 0218) assessed bevacizumab combined with carboplatin/paclitaxel in the upfront setting compared to



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carboplatin/paclitaxel alone. The median PFS was significantly increased (14.1 vs. 10.3 months,  $P < .001$ ) in patients receiving prolonged bevacizumab (upfront and as maintenance therapy) when compared with chemotherapy alone.<sup>245,246</sup> PFS was not significantly increased in patients who did not receive maintenance bevacizumab (upfront with placebo maintenance) versus chemotherapy alone (ie, bevacizumab/carboplatin/paclitaxel vs. carboplatin/paclitaxel). Quality of life was not improved in GOG 0218.<sup>247</sup> An analysis of the data from GOG 0218 suggests that upfront therapy with carboplatin/paclitaxel/bevacizumab may be beneficial in patients with ascites.<sup>248</sup> Women with ascites who received the bevacizumab regimen had significantly improved PFS (adjusted hazard ratio [AHR] 0.71; 95% CI, 0.62–0.81;  $P < .001$ ) and overall survival (AHR 0.82; 95% CI, 0.70–0.96;  $P = .014$ ) when compared with those only receiving chemotherapy.

Another phase 3 randomized trial (ICON7) also assessed bevacizumab/carboplatin/paclitaxel in the upfront setting. The trial design of ICON7 differs from GOG 0218 (see next paragraph).<sup>249</sup> Although the PFS data from ICON7 confirm the findings of GOG 0218, the benefits appear to be modest (2.4-month increase in PFS).<sup>247</sup> Data for ICON7 suggest that overall survival was increased in the subset of patients with a poor prognosis, although overall survival was not increased in the whole study population.<sup>250</sup> In women with a poor prognosis who received bevacizumab plus chemotherapy, overall survival was increased when compared with those receiving chemotherapy alone (restricted mean survival time 39.3 months [37.0–41.7] with bevacizumab vs. 34.5 months [95% CI, 32.0–37.0] with chemotherapy alone;  $P = .03$ ).

The addition of bevacizumab to upfront chemotherapy with carboplatin/paclitaxel followed by bevacizumab as maintenance therapy is a category 2B recommendation (see *Primary Chemotherapy/Primary Adjuvant Therapy Regimens: Ovarian, Fallopian Tube, and Primary*

*Peritoneal Cancer* in the NCCN Guidelines for Epithelial Ovarian Cancer).<sup>250,251</sup> Some panel members believe that bevacizumab should not be added to upfront chemotherapy in patients with ovarian cancer, because data from these 2 phase 3 randomized trials (ie, GOG 0218, ICON7) have not shown a statistically significant increase in overall survival in the whole study population and/or improved quality of life.<sup>246,247,249,251-254</sup> Note that a category 2B recommendation indicates that many but not all ( $\geq 50\%$  and  $< 85\%$ ) panel members agree that the intervention is appropriate.

The NCCN Panel recommends (category 2B) that if bevacizumab is used with upfront chemotherapy followed by maintenance therapy, then either the GOG 0218 or ICON7 regimens should be used (see *Primary Chemotherapy/Primary Adjuvant Therapy Regimens: Ovarian, Fallopian Tube, and Primary Peritoneal Cancer* in the NCCN Guidelines for Epithelial Ovarian Cancer).<sup>246,249</sup> The only GOG 0218 regimen that is recommended (category 2B) is the prolonged bevacizumab regimen (upfront with carboplatin/paclitaxel followed by maintenance bevacizumab).<sup>246</sup> The NCCN Panel encourages participation in ongoing clinical trials that are further investigating the role of anti-angiogenesis agents in the treatment of ovarian cancer, both in the upfront and recurrence settings.<sup>255</sup>

### **Postremission Therapy**

Paclitaxel (category 2B) is a postremission therapy option for patients with stages II to IV epithelial ovarian cancer, Fallopian tube cancer, or primary peritoneal cancer who have had complete clinical remission after first-line therapy. Maintenance (or postremission) therapy is an option based on the results from GOG 178. This trial randomly assigned patients to 3 versus 12 months of further paclitaxel (135–175 mg/m<sup>2</sup> every 4 weeks for 12 cycles) after initial chemotherapy.<sup>256</sup> The published study treated patients at 175 mg/m<sup>2</sup>; the plan was to decrease the dose to 135 mg/m<sup>2</sup>, but the



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protocol closed before any patients were treated at the lower dose. The results of this trial suggest that patients receiving 12 months of therapy sustained a PFS advantage (28 vs. 21 months). Postremission paclitaxel chemotherapy is a category 2B recommendation, because it is associated with peripheral neuropathy and because it only increased PFS but not overall survival.<sup>257</sup> Another study suggests that postremission paclitaxel is not beneficial.<sup>258</sup>

Pazopanib (category 2B) is a postremission therapy option for patients with stages II to IV epithelial ovarian cancer, Fallopian tube cancer, or primary peritoneal cancer who have had complete clinical remission after first-line therapy. This recommendation is based on a phase 3 randomized trial showing an increase in PFS (17.9 vs. 12.3 months) in patients treated with pazopanib compared with placebo.<sup>259</sup> Pazopanib is a category 2B recommendation for postremission therapy because the FDA has not approved this indication, there was no increase in overall survival, and patients had increased toxicity with pazopanib such as grade 3 or 4 hypertension. A subset analysis suggests that postremission pazopanib may be less effective in east Asian women with ovarian cancer; however, overall survival data were not obtained because of the limited number of patients.<sup>260</sup>

Bevacizumab may be continued after primary systemic therapy if an upfront chemotherapy/bevacizumab regimen was used, but there are no data to support introducing bevacizumab as maintenance therapy if other initial primary regimens were used.

### Drug Reactions

Virtually all drugs have the potential to cause adverse reactions (infusion reactions or allergies), either during or after the infusion.<sup>261-265</sup> Drugs used in gynecologic oncology treatment that more commonly cause adverse reactions include carboplatin, cisplatin, docetaxel, liposomal doxorubicin, oxaliplatin, and paclitaxel. Drug reactions can occur with either

intravenous or IP administration of these drugs.<sup>266</sup> Most of these drug reactions are mild infusion reactions (ie, skin reactions, cardiovascular reactions, respiratory or throat tightness), but more severe allergic reactions (ie, life-threatening anaphylaxis) can occur.<sup>267,268</sup> Infusion reactions are more common with paclitaxel,<sup>269</sup> but mild reactions can also occur with liposomal doxorubicin.<sup>270</sup> Allergic reactions (ie, true drug allergies) are more common with platinum agents (ie, carboplatin, cisplatin, oxaliplatin).<sup>269,271</sup>

Algorithms are provided for management of mild, severe, and life-threatening reactions (see *Management of Drug Reactions* in the NCCN Guidelines for Ovarian Cancer).<sup>272</sup> These drug reaction algorithms are also useful for patients with other gynecologic cancers (eg, cervical, vulvar, and uterine cancers) who are receiving carboplatin, cisplatin, docetaxel, liposomal doxorubicin, oxaliplatin, or paclitaxel. Typically, the infusion should be stopped for patients having a reaction; further management is provided in the algorithms. Standard resuscitation procedures (ie, Advanced Cardiovascular Life Support [ACLS]) should be followed for patients with acute cardiopulmonary arrest.<sup>273-276</sup>

For patients with allergic reactions, various desensitization protocols have been published.<sup>262,265,277,278</sup> To maximize safety, patients may be desensitized in the intensive care unit.<sup>265,278</sup> Almost all patients can be desensitized (about 90%).<sup>265</sup> For severe life-threatening reactions, the implicated agent should not be used again unless under the supervision and guidance of an allergist or specialist with expertise in desensitization. If a mild allergic reaction is suspected, and it is appropriate to administer the drug again, a desensitization regimen should be used even if the symptoms have resolved.<sup>263</sup> Patients must be desensitized with each infusion if they previously had a drug reaction.<sup>279-281</sup> Data suggest that an extended infusion schedule and use of premedication may decrease the



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number of hypersensitivity reactions to carboplatin.<sup>282,283</sup> Skin testing is associated with false-negative results.<sup>284,285</sup>

### **Radiation Therapy**

Whole abdominal radiation therapy is rarely used for epithelial ovarian, primary peritoneal, and Fallopian tube cancers in NCCN Member Institutions. It is not included as a treatment recommendation in the NCCN Guidelines for Ovarian Cancer. Palliative localized RT is an option for symptom control in patients with recurrent disease (see *Principles of Systemic Therapy: Acceptable Recurrence Therapies (Ovarian, Fallopian Tube, and Primary Peritoneal Cancer)* in the NCCN Guidelines for Epithelial Ovarian Cancer).<sup>286-290</sup> Patients who receive radiation are prone to vaginal stenosis, which can impair sexual function.<sup>291</sup> Women can use vaginal dilators to prevent or treat vaginal stenosis. Dilator use can start 2 to 4 weeks after RT is completed and can be done indefinitely.<sup>292</sup>

### **Recommendations After Primary Treatment**

After initial treatment (eg, surgery followed by chemotherapy), patients should undergo a clinical re-evaluation. Observation with follow-up is recommended for patients who have no evidence of progression of cancer (ie, complete clinical remission) after initial treatment (see *Follow-Up Recommendations* in this Discussion) (also see *Monitoring/Follow-up* in the NCCN Guidelines for Epithelial Ovarian Cancer); other options are discussed below. Patients with progression, persistent disease, or stable disease during initial treatment should be treated with second-line approaches (see *Recurrent Disease* in this Discussion) (see *Therapy for Persistent Disease or Recurrence* in the NCCN Guidelines for Epithelial Ovarian Cancer).<sup>293,294</sup> The NCCN Guidelines recommend symptom management, best supportive care, and long-term wellness care for all patients; patients should be referred for palliative care assessment if appropriate (see the NCCN Guidelines for Palliative Care and the NCCN Guidelines for Survivorship, available at [www.NCCN.org](http://www.NCCN.org)). The NCCN

Guidelines also recommend that all patients with ovarian cancer, Fallopian tube cancer, or primary peritoneal cancer be referred for genetic risk evaluation (see the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian and the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal, available at [www.NCCN.org](http://www.NCCN.org)).<sup>295,296</sup> Primary treatment should not be delayed for genetic counseling.

Options for the management of patients with advanced-stage (stages II–IV) disease who are in complete clinical remission after their initial therapeutic regimen include observation alone, a clinical trial, or postremission systemic therapy (category 2B)<sup>256</sup> (see the NCCN Guidelines for Epithelial Ovarian Cancer). The NCCN Panel recommends postremission paclitaxel or pazopanib (category 2B) for management of stage II to IV disease (see *Postremission Therapy* in this Discussion).<sup>259</sup> As previously described, postremission paclitaxel or pazopanib prolong PFS when administered following initial chemotherapy. If used, the recommended paclitaxel regimen is 135 to 175 mg/m<sup>2</sup> every 4 weeks for 12 cycles.<sup>256</sup> Note that complete clinical remission is defined as no definitive evidence of disease.<sup>293,294</sup>

Use of maintenance bevacizumab (category 2B) is discussed in an earlier section and has been shown to modestly increase PFS when administered following initial chemotherapy that included bevacizumab (see *Anti-Angiogenesis Agents* in this Discussion). Maintenance bevacizumab is not recommended for patients who did not receive a primary treatment regimen containing bevacizumab.

### **Follow-up Recommendations**

Recurrent disease may be identified clinically (eg, pelvic pain, weight loss), biochemically (ie, elevated CA-125 levels), and/or with imaging. After the completion of primary surgery and chemotherapy in patients with





all stages of ovarian cancer (or Fallopian tube cancer or primary peritoneal cancer) who have had a complete response, the standard recommendation is observation with follow-up to monitor for recurrent disease. Recommendations for monitoring are described in the algorithm and also apply to some of the LCOH (see *Monitoring/Follow-up* in the NCCN Guidelines for Epithelial Ovarian Cancer). Chest/abdominal/pelvic CT, MRI, FDG-PET/CT, FDG-PET scans (skull base to mid-thigh), and chest x-ray may be ordered if clinically indicated; imaging is done with contrast unless contraindicated.<sup>297-300</sup> Patients should be educated about the signs and symptoms suggestive of recurrence (eg, pelvic pain, bloating, early satiety, obstruction, weight loss, fatigue). Patients who have had fertility-sparing surgery should be monitored by ultrasound examinations of the abdomen and pelvis if indicated; completion surgery should be considered (category 2B) after they finish childbearing. For the 2017 update (Version 1), the NCCN Panel added a recommendation for long-term wellness care (see the NCCN Guidelines for Survivorship, available at [www.NCCN.org](http://www.NCCN.org)).

If the CA-125 level was initially elevated, then measurement of a CA-125 level or other tumor markers is recommended. A multi-institutional European trial assessed the use of CA-125 for monitoring for ovarian cancer recurrence after primary therapy.<sup>301,302</sup> The data suggest that treating recurrences early (based on detectable CA-125 levels in patients who are asymptomatic) is not associated with an increase in survival and is associated with a decrease in quality of life.<sup>303</sup> Recommendations from the SGO state that use of CA-125 levels for surveillance is optional.<sup>299</sup> The NCCN Panel feels that the European trial has limitations and patients should discuss the pros and cons of CA-125 monitoring with their physicians. In addition, patients seem reluctant to give up monitoring.<sup>304</sup> Others have discussed this study in greater detail.<sup>305-307</sup>

### **Management of an Increasing CA-125 Level**

The management of patients in a clinical complete remission is somewhat controversial; this includes patients who are found to have an increasing CA-125 level (during routine monitoring and follow-up) but no signs or symptoms of recurrent disease (eg, pelvic pain, bloating, obstruction), following an evaluation including a negative pelvic examination and negative chest/abdominal/pelvic CT scans.<sup>308</sup> Patients who have never received chemotherapy (ie, naïve to chemotherapy) should be managed using recommendations for newly diagnosed patients, should undergo clinically appropriate imaging studies and surgical debulking, and should be treated as previously described (see *Primary Treatment* in the NCCN Guidelines for Epithelial Ovarian Cancer).

Recurrence therapy refers to drugs, radiation, or other treatment that is given to decrease tumor burden, control symptoms, or increase length and/or quality of life for patients with recurrent disease. After the documentation of an increased CA-125 level (ie, biochemical relapse), the median time for a clinical relapse is 2 to 6 months. Data suggest that immediate treatment for biochemical relapse is not beneficial; therefore, immediate treatment is a category 2B recommendation in the NCCN Guidelines.<sup>301</sup> After biochemical relapse, recommended options include enrollment in a clinical trial, delaying treatment (ie, observation) until clinical symptoms arise, or immediate treatment (category 2B) (see *Recurrent Disease* in the NCCN Guidelines for Epithelial Ovarian Cancer). Because tamoxifen and other hormonally active agents have a defined response rate for patients with recurrent disease who have progressed after platinum-based chemotherapy,<sup>309</sup> these agents are frequently administered to patients who have only a rising CA-125 level<sup>310</sup> as evidence of tumor progression.<sup>311</sup> Tamoxifen, other hormonal agents, or other recurrence therapy are acceptable recommendations for this clinical situation (category 2B for all).

### Recurrent Disease

The prognosis is poor either 1) for patients who progress after 2 consecutive chemotherapy regimens without ever sustaining a clinical benefit (refractory),<sup>312</sup> or 2) for those whose disease recurs in less than 6 months (platinum resistant). Note that progression is typically defined using RECIST (Response Evaluation Criteria in Solid Tumor) criteria.<sup>293,294</sup> Panel members emphasized the importance of clinical trials to identify agents active in this group of patients.<sup>313,314</sup> Because their disease was resistant to the primary induction regimen, retreatment with a platinum compound or paclitaxel is not generally recommended. Although panel members do not recommend retreatment with platinum agents, they recognize that altering the schedule of paclitaxel may produce secondary responses.<sup>315,316</sup> Before any drug is given in the recurrent setting, the clinician should be familiar with the drug's metabolism and should make certain that the patient is an appropriate candidate for the drug (eg, that the patient has adequate renal or hepatic function). Clinical judgment must be used when selecting postoperative chemotherapy.

Options for patients with platinum-resistant disease or for those with stages II to IV disease who have a partial response include clinical trial, recurrence therapy (see *Acceptable Recurrence Therapies* in the NCCN Guidelines for Epithelial Ovarian Cancer),<sup>317</sup> and/or best supportive care (see NCCN Guidelines for Palliative Care, available at [www.NCCN.org](http://www.NCCN.org)). Although palliative care is appropriate at many stages during the disease course, an assessment for palliative care is especially appropriate for women with platinum-resistant disease who may be receiving continuous systemic therapy. Patients who relapse 6 months or more after initial chemotherapy are termed *platinum sensitive*.<sup>318,319</sup> Combination platinum-based chemotherapy for a total of 6 cycles is preferred for first recurrence (category 1) in patients with platinum-sensitive disease (see *Therapy for Persistent Disease or Recurrence* in the NCCN Guidelines for Epithelial Ovarian Cancer); other recurrence therapies are also an

option.<sup>319,320</sup> Possible regimens are discussed in the following section (see *Acceptable Recurrence Modalities* in this Discussion).

Patients with ovarian cancer will often be retreated with multiple courses of recurrence therapy. Caution should be used in patients who receive multiple sequential courses of chemotherapy, because they may experience excessive toxicity and may not be able to tolerate doses used for first-line recurrence therapy; thus, clinical judgment should be used when selecting doses (see *Principles of Systemic Therapy* in the NCCN Guidelines for Epithelial Ovarian Cancer). Potential ancillary palliative, surgical, and/or supportive care procedures for selected patients are summarized in the algorithm (see *Principles of Surgery* in the NCCN Guidelines for Epithelial Ovarian Cancer).<sup>321-326</sup> Secondary cytoreductive surgery can be considered for patients who recur (ie, radiographic and/or clinical relapse) after a long disease-free interval (6 months or more).<sup>164,327-332</sup> A meta-analysis suggests that survival increases for patients with recurrent disease who have complete debulking.<sup>165</sup> The duration of the disease-free interval has not been established, although panel members agreed that it should be at least 6 months before surgery is considered.<sup>145,333</sup>

Although chemotherapy/resistance assays and/or other biomarker assays are being used in some NCCN Member Institutions to aid in selecting chemotherapy in situations where multiple equivalent chemotherapy options are available; the current level of evidence (category 3) is not sufficient to supplant standard-of-care chemotherapy.<sup>334,335</sup> The NCCN Panel feels that in vitro chemosensitivity testing to choose a chemotherapy regimen for recurrent disease situations should not be recommended (category 3), owing to the lack of demonstrable efficacy for such an approach. ASCO also does not recommend use of chemotherapy sensitivity and resistance assays, unless in a clinical trial setting.<sup>336</sup> Note that a category 3 recommendation reflects strong disagreement about the



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intervention. At least 3 different NCCN Member Institutions must agree to include the category 3 intervention in the guideline, otherwise it is deleted.

Regardless of which regimen is selected initially, reevaluation should follow after 2 to 4 cycles of chemotherapy (depending on the agent) to determine if patients benefited from chemotherapy. Patients who primarily progress on 2 consecutive chemotherapy regimens without evidence of clinical benefit may not benefit from additional therapy.<sup>312</sup> Decisions to offer supportive care, additional therapy, or clinical trials should be made on a highly individual basis. Localized RT can also provide effective palliation when radiation ports are tailored to specific symptomatic disease sites.<sup>286,287</sup>

### Acceptable Recurrence Modalities

The NCCN Panel feels that no single therapeutic agent should be currently recommended as the treatment of choice for recurrent ovarian carcinoma. Some regimens and agents are preferred based on expert opinion primarily for reasons of decreased toxicity and/or marginally increased effectiveness (see *Principles of Systemic Therapy: Acceptable Recurrence Therapies* in the NCCN Guidelines for Epithelial Ovarian Cancer).<sup>210</sup> A meta-analysis of chemotherapy for recurrent ovarian cancer was published in 2007.<sup>318</sup> Recurrence therapy refers to therapy (eg, drugs, radiation, or other treatment) that is given for recurrent cancer to control symptoms and increase length or quality of life for clinical, biochemical, or radiographic evidence of recurrent cancer following initial treatment.

### Preferred Therapies

The consensus of the NCCN Panel for the treatment of recurrent disease is summarized in the algorithm (see *Principles of Systemic Therapy: Acceptable Recurrence Therapies* in the NCCN Guidelines for Epithelial Ovarian Cancer). Platinum-based combination chemotherapy is recommended (category 1) for a total of 6 cycles for platinum-sensitive recurrence (see *Therapy for Persistent Disease or Recurrence* in the

NCCN Guidelines for Epithelial Ovarian Cancer).<sup>318,319</sup> For patients with platinum-sensitive disease who cannot tolerate combination therapy, the preferred single agent is carboplatin or cisplatin.<sup>319,337,338</sup> Preferred combinations for platinum-sensitive recurrent disease include carboplatin/paclitaxel (category 1),<sup>319</sup> carboplatin/liposomal doxorubicin (category 1),<sup>339-341</sup> carboplatin/weekly paclitaxel,<sup>221</sup> carboplatin/albumin-bound paclitaxel (for taxane hypersensitivity), carboplatin/docetaxel,<sup>342,343</sup> carboplatin/gemcitabine (which has been shown to improve PFS),<sup>319,337,338</sup> cisplatin/gemcitabine, or carboplatin/gemcitabine/bevacizumab.<sup>337</sup>

The category 1 recommendation for carboplatin/liposomal doxorubicin is based on recent data and uniform consensus from the panel.<sup>339,340,344-347</sup> Carboplatin/liposomal doxorubicin is equivalent to carboplatin/paclitaxel but has a different toxicity profile. Carboplatin/liposomal doxorubicin is easier to tolerate; women tend to discontinue therapy with carboplatin/paclitaxel more often than they do with carboplatin/liposomal doxorubicin. Other combination regimens, including those with bevacizumab, are discussed in the following paragraphs. For the 2017 update (Version 1), the NCCN Panel added a recommendation (category 2A) for carboplatin/albumin-bound paclitaxel as recurrence therapy for women with platinum-sensitive disease and confirmed taxane hypersensitivity. Preliminary data from a phase 2 study of carboplatin/nab-paclitaxel in platinum-sensitive patients indicated that the overall response rate was 79%; 39% (15/38) of patients had a complete response rate.<sup>348</sup> A recent study of carboplatin/albumin-bound paclitaxel in patients with gynecologic tumors included 22 patients with ovarian cancer; the regimen was well tolerated and no patients had hypersensitivity reactions.<sup>349</sup>

For platinum-resistant disease, non-platinum-based agents or regimens are preferred (ie, docetaxel, oral etoposide, gemcitabine, weekly paclitaxel

with or without pazopanib, liposomal doxorubicin with or without bevacizumab, weekly paclitaxel/bevacizumab, topotecan with or without bevacizumab); sequential therapy using single agents is typically used.<sup>350,351</sup> A phase 2 trial (MITO-11) assessed weekly paclitaxel with (or without) pazopanib in patients with platinum-resistant or refractory advanced ovarian cancer.<sup>350</sup> The data show that PFS was increased in the paclitaxel/pazopanib arm when compared with paclitaxel alone (median 6.35 months [95% CI, 5.36–11.02] vs. 3.49 months [2.01–5.66]; HR, 0.42 [95% CI, 0.25–0.69];  $P = .0002$ ). Combination regimens with bevacizumab (AURELIA trial) are described later in this section (see *Bevacizumab* in this Discussion). Combination therapy is not preferred over single-agent therapy for platinum-resistant disease. For the 2017 update (Version 2), the NCCN Panel clarified this point by adding a footnote stating that the panel recommends combination, platinum-based regimens for platinum-sensitive recurrent disease, especially first relapses.

The response rate of the following agents appears to be similar: topotecan, 20%;<sup>352</sup> gemcitabine, 19%;<sup>353,354</sup> liposomal doxorubicin, 26%;<sup>353-355</sup> and oral etoposide, 27%.<sup>356</sup> In patients with platinum-resistant disease, the response rate for docetaxel is 22% and for weekly paclitaxel is 21%.<sup>315,357,358</sup> Reports suggest that weekly topotecan is less toxic than the daily regimen.<sup>359,360</sup> Palliative chemotherapy has been shown to reduce symptoms in patients with platinum-resistant disease.<sup>361</sup>

### Other Potentially Active Agents

Other potentially active agents include altretamine, capecitabine, cyclophosphamide, doxorubicin, ifosfamide, irinotecan, melphalan, oxaliplatin, paclitaxel, nanoparticle albumin-bound paclitaxel (nab-paclitaxel), pemetrexed, and vinorelbine (see *Principles of Systemic Therapy: Acceptable Recurrence Therapies* in the NCCN Guidelines for Epithelial Ovarian Cancer).<sup>358,362-366</sup> Nab-paclitaxel has an overall response rate of 64%.<sup>367</sup> Vinorelbine has a response rate of 20%.<sup>368,369</sup> Altretamine

has a 14% response rate<sup>370</sup> and ifosfamide has a 12% response rate,<sup>371</sup> although less information is available regarding their use in patients with paclitaxel-refractory disease. In women with platinum-resistant disease, the response rate for pemetrexed is 21%.<sup>315,357,358</sup> Single-agent paclitaxel, nab-paclitaxel, and oxaliplatin can be used in appropriate patients.<sup>256,319,357,372</sup> Capecitabine has activity if disease was resistant to platinum and taxanes.<sup>373</sup> Other alkylating agents, including cyclophosphamide and melphalan, can also be used.<sup>216,374</sup> In addition, hormonal therapy with tamoxifen or other agents including aromatase inhibitors (such as anastrozole and letrozole), leuprolide acetate, or megestrol acetate continues to be a viable therapeutic option for patients who cannot tolerate or have not responded to cytotoxic regimens.<sup>375-381</sup> Studies are ongoing for new agents to treat platinum-resistant disease.<sup>382</sup> The NCCN Panel also recommends (category 2B) single-agent pazopanib as a potentially active targeted recurrence therapy in patients who had a complete response to initial therapy.<sup>383</sup> In a phase 2 trial in 36 patients, the overall response rate was 18% with grade 3 elevations in ALT and AST in a few patients (8%).

### Bevacizumab

Based on phase 2 trials, panel members feel that single-agent bevacizumab is a preferred option in patients who have recurrent disease (especially those with ascites), which is reflected in the category 2A recommendation for bevacizumab alone for women with either platinum-sensitive or platinum-resistant disease.<sup>111,351,384,385</sup> The response rate for single-agent bevacizumab is about 20%;<sup>111,247,384,386-388</sup> it may cause hypertension, arterial thrombosis, or intestinal perforation. Bevacizumab combination regimens, or single-agent bevacizumab, are contraindicated in patients at increased risk of gastrointestinal perforation.<sup>389,390</sup> For the 2017 update (Version 2), the NCCN Panel added a footnote that there are limited data about the efficacy of bevacizumab as recurrence therapy (either single-agent or combination therapy) for



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patients previously treated with bevacizumab. The NCCN Panel added another footnote to clarify that bevacizumab can be continued as single-agent maintenance therapy until disease progression or unacceptable toxicity if patients respond to the initial recurrence chemotherapy/bevacizumab regimens described in the following paragraphs (see *Principles of Systemic Therapy: Acceptable Recurrence Therapies* in the NCCN Guidelines for Epithelial Ovarian Cancer).

Several phase 3 randomized trials have assessed combination therapy with bevacizumab for recurrent ovarian cancer (ie, AURELIA, OCEANS).<sup>389,391</sup> The AURELIA trial assessed bevacizumab combined with chemotherapy—either liposomal doxorubicin, weekly paclitaxel, or topotecan—versus chemotherapy alone in patients with advanced platinum-resistant ovarian cancer. For patients receiving bevacizumab/chemotherapy, the primary endpoint of PFS was 6.7 months versus 3.4 months with chemotherapy alone. The median overall survival was 16.6 months for the bevacizumab/chemotherapy arm versus 13.3 months for chemotherapy alone; the overall survival HR was 0.85 (95% CI, 0.66–1.08;  $P < .174$ ). Hypertension and proteinuria ( $\geq$  grade 2) were more common with bevacizumab. Gastrointestinal perforation occurred in 2.2% of patients on the bevacizumab arm. Based on the results of the AURELIA trial, the NCCN Panel recommends the following combination regimens for patients with platinum-resistant recurrent ovarian cancer: weekly paclitaxel/bevacizumab, liposomal doxorubicin/bevacizumab, and topotecan/bevacizumab.<sup>389,392</sup>

A phase 3 randomized trial (OCEANS) assessed carboplatin/gemcitabine with and without bevacizumab in patients with platinum-sensitive recurrent ovarian cancer who had not previously received bevacizumab. In the OCEANS trial, PFS was increased in patients receiving the chemotherapy/bevacizumab arm when compared with chemotherapy alone (12.4 vs. 8.4 months,  $P < .0001$ ).<sup>391</sup> The final survival analysis did

not show an increase in overall survival with the chemotherapy/bevacizumab arm when compared with chemotherapy alone (bevacizumab/chemotherapy: 33.6 months; chemotherapy alone: 32.9 months; HR, 0.95;  $P = .65$ ).<sup>393</sup> Gastrointestinal perforation occurred in 2 patients in the chemotherapy/bevacizumab arm. One patient died from intracranial hemorrhage in the chemotherapy/bevacizumab arm. For the 2017 update, the NCCN Panel revised the recommendation for carboplatin/gemcitabine/bevacizumab to category 2A (from category 2B) based on clinical experience. However, category 1 combination regimens are recommended over this bevacizumab regimen. The carboplatin/gemcitabine/bevacizumab regimen is not recommended in patients who are at risk for gastrointestinal perforation.

A recent phase 3 randomized trial (GOG-0213) assessed recurrence combination therapy with carboplatin/paclitaxel/bevacizumab in patients with platinum-sensitive recurrent ovarian cancer.<sup>394</sup> Women receiving chemotherapy/bevacizumab had slightly increased median overall survival when compared with chemotherapy alone (42.2 months [95% CI, 37.7–46.2] versus 37.3 months (32.6–39.7) (HR, 0.829; 95% CI, 0.683–1.005;  $P = .056$ ). Most patients in both arms had at least one grade 3 or worse adverse event; 96% (317/325) of patients in the chemotherapy/bevacizumab group versus 86% (282/332) with chemotherapy alone; the most common of these adverse events were hypertension, fatigue, and proteinuria. Nine (3%) treatment-related deaths occurred in the bevacizumab arm versus 2 (1%) deaths in the chemotherapy alone arm. For the 2017 update, the NCCN panel added carboplatin/paclitaxel/bevacizumab as a potentially active regimen based on this trial.

### PARP Inhibitors

#### *Olaparib*

Data suggest that olaparib (AZD2281), which is a PARP (poly ADP-ribose polymerase) inhibitor, is active in select patients (those with *BRCA1* and *BRCA2* mutations have higher response rates than those who are *BRCA* negative), especially those with platinum-sensitive disease.<sup>351,395-399</sup> If disease is resistant or refractory to platinum, then a lower response rate to olaparib is observed.<sup>396,398</sup> A trial assessed olaparib in women with recurrent advanced ovarian cancer; the overall response rate was 34% (complete response, 2%; and partial response, 32%).<sup>400,401</sup> The FDA approved olaparib for patients with advanced ovarian cancer who have received treatment with 3 or more lines of chemotherapy and who have a germline *BRCA* mutation.<sup>401,402</sup> The NCCN Panel recommends single-agent olaparib as recurrence therapy for patients with advanced ovarian cancer (platinum sensitive or resistant) who have received 3 or more lines of chemotherapy and who have a germline *BRCA* mutation (detected using an FDA-approved test or other validated test performed in a CLIA-approved facility) based on this trial and the FDA approval.<sup>403</sup>

A recent phase 3 randomized trial (SOLO2/ENGOT-Ov21) assessed olaparib (tablets) as maintenance therapy for women (n=295) with platinum-sensitive high-grade serous ovarian cancer and *BRCA* mutations who had received 2 or more lines of chemotherapy; the trial also included patients with high-grade endometrioid cancer, primary peritoneal, or fallopian tube cancer.<sup>404</sup> Data show that the median PFS was significantly longer in women receiving olaparib (19.1 months [95% CI, 16.3–25.7]) than in those receiving placebo (5.5 months [5.2–5.8]; HR, 0.30 [95% CI, 0.22–0.41],  $P < .0001$ ). More patients receiving olaparib maintenance therapy had serious adverse events (18% [35/195]) compared with placebo (8% [8/99]). The most common serious (grade 3 or worse) adverse events included anemia (19% [38/195] in the olaparib group vs.

2% [2/99] in the placebo group), fatigue or asthenia (4% [8/195] vs. 2% [2/99]), and neutropenia (5% [10/195] vs. 4% [4/99]). In the olaparib group, one (1%) patient died from a treatment-related adverse event (acute myeloid leukemia). The FDA recently approved olaparib (tablets) as maintenance therapy for women with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who have had complete or partial responses to platinum-based chemotherapy.

For the 2017 update (Version 3), the NCCN Panel recommends that olaparib (tablets) be considered as maintenance therapy for women with ovarian cancer who have received 2 or more lines of chemotherapy based on this trial (SOLO2/ENGOT-Ov21) and the FDA approval.<sup>404</sup> Note that olaparib is transitioning from capsules (original FDA approval) to tablets for the maintenance and recurrence therapy indications. Olaparib tablets (100 mg and 150 mg) should not be substituted with olaparib capsules (50 mg) because of differences in the dosing and bioavailability of each formulation.

#### *Rucaparib*

Rucaparib is also an oral PARP inhibitor.<sup>405</sup> A recent phase 2 trial (ARIEL2) assessed rucaparib as recurrence therapy for patients with platinum-sensitive ovarian cancer.<sup>406</sup> PFS was increased in patients (n=40) with *BRCA* mutations (12.8 months [95% CI, 9.0–14.7]) when compared with wild type (n = 70) (5.2 months [95% CI, 3.6–5.5]) (HR, 0.27; 95% CI, 0.16–0.44,  $P < .0001$ ). For women taking rucaparib, serious adverse events were small intestinal obstruction (10 [5%] of 204 patients), malignant neoplasm progression (10 [5%]), and anemia (9 [4%]). During the trial, 3 patients died (2 with disease progression; one with sepsis and disease progression); deaths were not reported as related to treatment. Based on this trial and the FDA approval, the NCCN Panel recommends single-agent rucaparib as recurrence therapy for patients with platinum-sensitive or platinum-resistant ovarian cancer who have been

treated with 2 or more lines of chemotherapy and have BRCA mutations (detected as previously described).<sup>406,407</sup> The NCCN Panel feels that rucaparib is preferred for patients with platinum-resistant disease, because there are fewer good options for this setting. In a pooled analysis, the overall response rate with rucaparib was reported as 66% (52/79; 95% CI, 54–76) for platinum-sensitive disease and 25% (5/20; 95% CI [9–49]) for platinum-resistant disease.<sup>405</sup> A recent phase 1 to 2 study reported a response rate of 59.5% in patients with platinum-sensitive disease and BRCA mutations who had received 2 to 4 courses of therapy.<sup>405</sup>

### *Niraparib*

Niraparib is another oral PARP 1/2 inhibitor.<sup>408</sup> A phase 3 trial (NOVA) assessed niraparib as maintenance therapy for patients with platinum-sensitive ovarian cancer who responded to recurrence therapy.<sup>408</sup> For the 2017 update (Version 1), the NCCN Panel added a recommendation to repeat the prior imaging to assess response. Data showed that niraparib increased PFS regardless of whether patients had a BRCA mutation when compared with placebo. Patients receiving niraparib without a germline BRCA mutation had increased PFS (12.9 months vs. 3.8 months). Women with a germline BRCA mutation had a much greater increase in PFS (21.0 vs. 5.5 months) (HR, 0.27; 95% CI, 0.17–0.41). For those taking niraparib, grade 3 or 4 adverse events that were commonly reported included thrombocytopenia (33.8%), anemia (25.3%), and neutropenia (19.6%). For the 2017 update (Version 1), the NCCN Panel recommends niraparib as maintenance therapy for patients with platinum-sensitive disease who have had 2 or more lines of platinum-based therapy and a complete or partial response to the most recent line of recurrence therapy based on this trial and the FDA approval.<sup>408,409</sup>

### Less Common Ovarian Histopathologies

The LCOH include carcinosarcomas (MMMTs), clear cell carcinoma, mucinous carcinoma, low-grade (grade 1) serous/endometrioid epithelial carcinoma, borderline epithelial tumors, malignant sex cord-stromal tumors, and malignant germ cell tumors (see the NCCN Guidelines for Less Common Ovarian Histopathologies).<sup>43</sup> The complete histologic classification for ovarian cancer from the WHO describes the different types of LCOH (see *WHO Histologic Classification* in the NCCN Guidelines for Ovarian Cancer Histopathologies).<sup>1</sup> The AJCC/FIGO staging system for ovarian cancer is also used to stage the LCOH (see Table 1 and other staging tables in the NCCN Guidelines for Ovarian Cancer). Panel members believe there is value in identifying pathways that may serve as therapeutic targets for the LCOH because of the promise of new and novel approaches to treatment.<sup>43</sup> However, there are limited data for these rare histologies because of their infrequency and it will be difficult to acquire prospective data. Clinical trials for eligible patients and individualized treatment plans, for those who are ineligible for trials, may be the most suitable approaches to treatment in these patients at this time. The different IV and IV/IP chemotherapy regimens used for high-grade serous ovarian cancer may also be recommended for patients with LCOH; however, the recommendations are only category 2A for LCOH because of the limited data.

### Recommended Workup

Patients may obtain consultation at an NCCN Member Institution for recommendations and treatment of an undiagnosed pelvic mass, or for management of a previously biopsied malignant ovarian tumor. Many such patients come to NCCN Member Institutions after having had previous surgery at other institutions. Patients having a histologically undiagnosed pelvic mass should undergo evaluation and staging as described in the algorithm (see *Workup* in the NCCN Guidelines for Epithelial Ovarian Cancer). The diagnosis of LCOH is often not made until after surgery for a

suspicious pelvic mass (see *Primary Treatment* in the NCCN Guidelines for Epithelial Ovarian Cancer). Therefore, the workup for LCOH is the same as for other types of ovarian cancer except that tumor markers are measured and other testing is done to determine the specific histopathology (see *Workup* in the NCCN Guidelines for Epithelial Ovarian Cancer). Tumor markers may include CA-125, inhibin, beta-hCG, alfa-fetoprotein, and carcinoembryonic antigen (CEA). Women younger than 35 years with a pelvic mass should have AFP levels measured to assess for germ cell tumors and to rule out pregnancy.<sup>105-107</sup> A gastrointestinal tract evaluation is recommended for mucinous histology to determine whether an occult gastrointestinal primary has metastasized to the ovaries.<sup>122</sup> An intraoperative frozen section evaluation is recommended for women who would like to maintain their fertility (see next section).

### Surgery

In contrast to high-grade serous epithelial ovarian cancer or MMMTs, many patients with other LCOH present at an early stage. Some of the tumors may be confined to one ovary. Thus, some of these patients are candidates for fertility-sparing surgery, which may be done laparoscopically (see *Principles of Surgery* in the NCCN Guidelines for Epithelial Ovarian Cancer).<sup>148,149,152,410-414</sup> Fertility-sparing surgery may be performed (if technically feasible) if the intraoperative frozen section results are positive for apparent early-stage tumors and/or low-risk tumors (ie, malignant germ cell tumors, borderline epithelial tumors, clinical stage I epithelial ovarian tumors, clinical stage I mucinous tumors, or clinical stage I sex cord-stromal tumors).<sup>148,149,152,411-414</sup> Patients who do not desire fertility preservation; those who have a clinical stage II, III, or IV epithelial ovarian cancer; those with a clinical stage II, III, or IV sex cord-stromal tumor; or those with MMMT should undergo comprehensive surgical staging as per the ovarian cancer guidelines (see *Principles of Surgery* in the NCCN Guidelines for Ovarian Cancer).

Patients may have been referred to an NCCN Member Institution after receiving a diagnosis of an LCOH tumor. The recommended initial surgical recommendation depends on the specific histologic diagnosis. Often, patients have been comprehensively staged (having met the standards for surgical staging of the GOG) and have undergone cytoreductive surgery. In some instances, they are referred after having had *incomplete* staging (ie, uterus and/or adnexa intact, omentum not removed, surgical stage not documented).

### Clear Cell Carcinoma

Clear cell carcinomas are considered high-grade tumors; they are more common than the other LCOH.<sup>415</sup> Most clear cell carcinomas are negative for WT1 and estrogen receptors.<sup>415</sup> The NCCN Guidelines provide an algorithm for clear cell carcinomas (see the NCCN Guidelines for Clear Cell Carcinoma and the *WHO Histologic Classification* in the NCCN Guidelines for Ovarian Cancer Histopathologies).<sup>1</sup> Because patients are typically diagnosed with clear cell carcinoma after pathologic analysis of a surgical specimen, the workup for suspicious or palpable pelvic masses is done before surgery as described in the algorithm (see *Workup* in the NCCN Guidelines for Epithelial Ovarian Cancer).

Primary treatment for these patients includes completion surgery with comprehensive staging followed by postoperative therapy (see the NCCN Guidelines for Clear Cell Carcinoma).<sup>416</sup> Fertility-sparing surgery is not recommended for stage IA to C clear cell carcinomas. Lymphadenectomy has been shown to improve survival.<sup>417</sup> The staging system for high-grade serous ovarian and primary peritoneal cancer is also used for clear cell carcinomas (see Table 1 in the NCCN Guidelines for Ovarian Cancer).<sup>93</sup> Lynch syndrome is associated with risk for endometrioid carcinomas, clear cell carcinomas, and papillary serous carcinomas.<sup>17-19</sup> For patients with stage IA to IC disease, recommended postoperative treatment is the standard intravenous taxane-carboplatin regimens (with paclitaxel or



docetaxel) used for high-grade serous ovarian cancer.<sup>417</sup> Fertility-sparing surgery and/or observation/monitoring are an option for patients with unilateral clear cell borderline tumors (see the NCCN Guidelines for Borderline Epithelial Tumors [Low Malignant Potential]). For patients with stage II to IV clear cell carcinoma, postoperative treatment is standard regimens used for epithelial ovarian cancer (eg, intravenous carboplatin with paclitaxel, docetaxel, or liposomal doxorubicin). Patients with advanced clear cell carcinoma have a poor prognosis.<sup>416,417</sup> Data suggest that 6 or 3 cycles of postoperative chemotherapy are equivalent for patients with clear cell carcinoma.<sup>220,418</sup>

### **Mucinous Carcinomas**

Mucinous tumors are unusual because they may be very large cystic masses that may fill the abdomen and pelvis; this presentation often suggests mucinous histology. Patients with mucinous carcinoma of the ovary are often diagnosed with early-stage disease and have a good prognosis; the 5-year disease-free survival is about 80% to 90%.<sup>122,419</sup> Women with mucinous tumors typically present at a younger age (20–40 years) than those with high-grade serous ovarian cancer. The NCCN Guidelines provide an algorithm for mucinous carcinoma (see the NCCN Guidelines for Mucinous Carcinoma and the *WHO Histologic Classification* in the NCCN Guidelines for Ovarian Cancer Histopathologies).<sup>1</sup> For the 2017 update (Version 1), the NCCN Panel added a recommendation for fertility-sparing surgery, if not previously done, for select patients with stage IA to C disease.

Patients are typically diagnosed with mucinous carcinoma after surgery for a suspicious pelvic mass (see *Primary Treatment* in the NCCN Guidelines for Epithelial Ovarian Cancer). Therefore, the initial workup is the same as for other types of ovarian cancer (see *Workup* in the NCCN Guidelines for Epithelial Ovarian Cancer). Primary treatment for these patients includes completion surgery with comprehensive staging followed by postoperative

therapy or observation (see the NCCN Guidelines for Mucinous Carcinoma).<sup>122</sup> An appendectomy is also recommended at primary surgery in patients with suspected or confirmed mucinous ovarian tumors. Fertility-sparing surgery is an option for select patients with stage I mucinous tumors (see the NCCN Guidelines for Borderline Epithelial Tumors [Low Malignant Potential]). The staging system for high-grade serous epithelial ovarian cancer and primary peritoneal cancer is also used for mucinous carcinomas (see Table 1 in the NCCN Guidelines for Ovarian Cancer).<sup>93</sup>

The additional workup includes a gastrointestinal tract evaluation and CEA level for patients with mucinous histology to determine whether patients have either occult gastrointestinal primary that has metastasized to the ovaries or primary mucinous carcinoma of the ovaries (see *Workup* in the NCCN Guidelines for Epithelial Ovarian Cancer).<sup>122</sup> Metastases to the ovaries are more common, and primary mucinous tumors of the ovaries are uncommon; it is difficult to distinguish between metastatic adenocarcinomas to the ovaries and primary mucinous carcinomas.<sup>420-422</sup> PAX8 immunostaining may be useful.<sup>420</sup>

Postoperative observation and monitoring are recommended for patients with stage IA or IB mucinous tumors because most of these tumors are benign or borderline.<sup>122,415</sup> For patients with stage IC mucinous carcinomas, postoperative options include: 1) observation; 2) intravenous carboplatin with either paclitaxel or docetaxel; 3) 5-FU/leucovorin/oxaliplatin (gastrointestinal regimen); or 4) capecitabine/oxaliplatin (gastrointestinal regimen).<sup>122</sup> Some clinicians feel the gastrointestinal regimens are appropriate because mucinous carcinomas of the ovary are similar to gastrointestinal tumors.<sup>423</sup> For patients with stages II to IV mucinous carcinomas, postoperative options include: 1) chemotherapy using the regimens for epithelial ovarian cancer (eg, intravenous carboplatin with paclitaxel, docetaxel, or liposomal



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doxorubicin); 2) 5-FU/leucovorin/oxaliplatin (gastrointestinal regimen); or 3) capecitabine/oxaliplatin (gastrointestinal regimen). For the 2017 update (Version 1), the NCCN Panel added recommendations for recurrence therapy for mucinous carcinomas: 1) 5-FU/leucovorin/oxaliplatin with or without bevacizumab (category 2B for bevacizumab); or 2) capecitabine/oxaliplatin.

### **Low-Grade (Grade 1) Serous/Endometrioid Epithelial Carcinomas**

The NCCN Guidelines provide an algorithm for grade 1 (low-grade) serous carcinomas/endometrioid epithelial carcinomas (see the NCCN Guidelines for Grade 1 (Low-Grade) Serous Carcinomas/Endometrioid Epithelial Carcinomas and the *WHO Histologic Classification* in the NCCN Guidelines for Ovarian Cancer Histopathologies).<sup>1</sup> Endometrioid carcinomas may be associated with endometriosis.<sup>424,425</sup> Endometrioid adenocarcinomas are usually positive for cytokeratin 7 (CK7), PAX8, CA-125, and estrogen receptors; metastatic colorectal adenocarcinomas are usually positive for CK20, CEA, and CDX2.<sup>415</sup> Endometrioid tumors are also very similar in appearance to sex cord-stromal tumors.<sup>415</sup> Lynch syndrome is associated with risk for endometrioid carcinomas, clear cell carcinomas, and serous carcinomas.<sup>17-19</sup>

Patients with low-grade (grade 1) serous carcinomas often have more indolent disease and present at a younger age than those with high-grade serous carcinomas; however, they may also present with more advanced disease.<sup>130,426</sup> Low-grade serous carcinomas do not typically progress to high-grade serous carcinomas; the 2 types of tumors are quite different.<sup>43</sup> Serous carcinomas are usually positive for WT1 and estrogen receptors.<sup>415</sup>

Primary treatment for these patients includes completion surgery with comprehensive staging followed by postoperative therapy or observation; patients are typically diagnosed after surgery (see the NCCN Guidelines

for Low-Grade (Grade 1) Serous Carcinomas/Endometrioid Epithelial Carcinomas).<sup>130</sup> The staging system for high-grade serous ovarian and primary peritoneal cancer is also used for low-grade (grade 1) serous/endometrioid carcinomas (see Table 1 in the NCCN Guidelines for Ovarian Cancer).<sup>93</sup> Fertility-sparing surgery is an option for patients with serous and endometrioid borderline tumors (see the NCCN Guidelines for Borderline Epithelial Tumors [Low Malignant Potential] and the *WHO Histologic Classification* in the NCCN Guidelines for Ovarian Cancer Histopathologies).<sup>1</sup> Some clinicians feel that neoadjuvant therapy should not be recommended for patients with low-grade (grade 1) serous carcinomas, because they often respond poorly to chemotherapy.<sup>130</sup>

Postoperative observation and monitoring are recommended for patients with stage IA or IB disease. For patients with stage IC to II disease, postoperative options include: 1) intravenous carboplatin with either paclitaxel or docetaxel; 2) observation (category 2B); or 3) hormone therapy including anastrozole, letrozole, leuprolide, or tamoxifen (category 2B for all hormone therapy). Postoperative options for patients with stage III to IV disease include: 1) first-line chemotherapy regimens used for epithelial ovarian cancer (eg, intravenous carboplatin with paclitaxel, docetaxel, or liposomal doxorubicin); or 2) hormone therapy (category 2B) as previously described (see *Principles of Systemic Therapy: Primary Chemotherapy/Primary Adjuvant Therapy Regimens* in the NCCN Guidelines for Epithelial Ovarian Cancer).<sup>130,427-429</sup> A recent study suggested that hormone maintenance therapy may be useful for women with stage II to IV low-grade serous ovarian carcinomas after surgery and platinum-based chemotherapy, although overall survival was not significantly improved when compared with observation (102.7 vs. 115.7 months, respectively).<sup>130,430</sup>



### **Malignant Germ Cell Tumors**

These malignant tumors include dysgerminomas, immature teratomas, embryonal tumors, and endodermal sinus (yolk sac) tumors (see the NCCN Guidelines for Malignant Germ Cell Tumors and the *WHO Histologic Classification* in the NCCN Guidelines for Ovarian Cancer Histopathologies).<sup>1</sup> They mainly occur in girls, adolescents, and younger women who are often diagnosed with stage I disease; the median age at diagnosis is 16 to 20 years.<sup>431,432</sup> Germ cell tumors are the predominant ovarian tumor in this age group.<sup>433</sup> The recommended workup may include pulmonary function studies if bleomycin is being considered (see *Recommended Workup* in the NCCN Guidelines for Epithelial Ovarian Cancer).<sup>105,434</sup> In young women (<35 years) with a pelvic mass, AFP levels can indicate the presence of germ cell tumors.<sup>105-107</sup> However, pregnancy should also be ruled out. Gonadal dysgenesis is a risk factor for germ cell tumors.<sup>433</sup> Malignant germ cell tumors have an excellent prognosis.<sup>435</sup> After appropriate treatment, 5-year survival is more than 85%.<sup>431,436,437</sup>

### **Treatment**

Fertility-sparing surgery is recommended for those desiring fertility preservation, regardless of stage (see the NCCN Guidelines for Malignant Germ Cell Tumors).<sup>152,432,437-440</sup> Surgery for children or adolescents may differ from that for adult women (see *Principles of Surgery* in the NCCN Guidelines for Ovarian Cancer). In children or adolescents with early-stage germ cell tumors, comprehensive staging may be omitted.<sup>441,442</sup> Completion surgery with comprehensive staging is recommended as initial surgery for patients who do not desire fertility preservation (see the NCCN Guidelines for Malignant Germ Cell Tumors).<sup>433</sup> The staging system for high-grade serous ovarian and primary peritoneal cancer is also used for malignant germ cell tumors (see Table 1 in the NCCN Guidelines for Epithelial Ovarian Cancer).<sup>93</sup> After comprehensive surgical staging, observation with monitoring is recommended for patients with stage I dysgerminoma or stage I, grade 1 immature teratoma.<sup>443</sup> If patients have

had incomplete surgical staging, recommended options depend on the type of tumor, the results of imaging and tumor marker testing (eg, AFP, beta-HCG), the age of the patient, and whether the patient desires fertility preservation (see the NCCN Guidelines for Malignant Germ Cell Tumors). Patients who chose fertility-sparing surgery should be monitored by ultrasound examinations if necessary; completion surgery (category 2B) should be considered after finishing childbearing.

After surgery, observation with surveillance is the recommended option for patients with stage I dysgerminoma or stage I, grade I immature teratoma based on European and pediatric reports.<sup>444-447</sup> Observation or chemotherapy may be considered for children or adolescents with select stage IA or IB tumors (see the NCCN Guidelines for Malignant Germ Cell Tumors).<sup>432,444,446,448-450</sup> For patients with stage II to IV malignant dysgerminomas or immature teratomas, postoperative chemotherapy is recommended (see Principles of Systemic Therapy: *Malignant Germ Cell Tumors* in the NCCN Guidelines for Epithelial Ovarian Cancer and the Less Common Ovarian Histopathologies).

Postoperative chemotherapy for 3 to 4 cycles with bleomycin/etoposide/cisplatin (BEP) (category 2B for 3 vs. 4 cycles) is recommended for: 1) any stage embryonal tumors or endodermal sinus tumors; 2) stages II to V dysgerminoma; or 3) stage I, grade 2 to 3, or stage II to IV immature teratoma (see the *Principles of Systemic Therapy: Malignant Germ Cell Tumors* in the NCCN Guidelines for Epithelial Ovarian Cancer and the Less Common Ovarian Histopathologies).<sup>434,451-453</sup> If considering the use of bleomycin, pulmonary function tests are recommended.<sup>434,436</sup> The 4-cycle BEP regimen is recommended (category 2A) as the standard regimen. Although most clinicians avoid a 3-week BEP regimen, some feel that a 3-week BEP regimen (3 cycles) may be useful in patients with low-risk or stage 1 disease, although this is a category 2B recommendation; the Memorial Sloan Kettering Cancer



Center criteria can be used to identify tumors that are low risk.<sup>444,454-461</sup> In select patients with stage IB to III dysgerminoma for whom minimizing toxicity is critical, 3 courses of etoposide/carboplatin can be used (carboplatin 400 mg/m<sup>2</sup> [AUC =~5–6] on day 1 plus etoposide 120 mg/m<sup>2</sup> on days 1–3 every 4 weeks for 3 courses).<sup>462</sup> Dose reductions or delays are not recommended even in the setting of neutropenia.

Surveillance recommendations for germ cell tumors are described in the algorithm (see *Surveillance for Malignant Germ Cell and Sex Cord-Stromal Tumors* in the NCCN Guidelines for Malignant Germ Cell and Sex Cord-Stromal Tumors).<sup>299</sup> Patients achieving a complete clinical response after chemotherapy should be observed clinically every 2 to 4 months with AFP and beta-HCG levels (if initially elevated) for 2 years. For those with abnormal markers and definitive recurrent disease, options (category 2B) include: 1) high-dose chemotherapy;<sup>463</sup> or 2) consider additional chemotherapy (see *Principles of Systemic Therapy: Acceptable Recurrence Therapies* in the NCCN Guidelines for Epithelial Ovarian Cancer). Referral of these patients to a tertiary care center for stem-cell transplant consultation and potentially curative therapy is strongly recommended. Several case reports suggest that patients who have received chemotherapy for germ cell tumors may later present with growing teratoma syndrome.<sup>464-467</sup>

### ***Residual or Recurrent Disease***

For patients having radiographic evidence of residual tumor (after surgery and chemotherapy) but with normal AFP and beta-HCG, consider surgical resection of the tumor; observation with monitoring is also an option. Clinical judgment should be used regarding the frequency of imaging.<sup>468</sup> Further options depend on which findings are present: residual malignancy, benign teratoma, or necrotic tissue (see *Recurrent/Persistent Disease for Malignant Germ Cell Tumors* in the NCCN Guidelines for Less Common Ovarian Histopathologies). For patients with definitive residual

disease and with persistently elevated AFP and/or beta-HCG after first-line chemotherapy, recommendations include TIP (paclitaxel, ifosfamide, cisplatin)<sup>469</sup> or high-dose chemotherapy. Referral to a tertiary care center for potentially curative treatment is strongly recommended.<sup>470</sup> There are small series but no major trials in adult patients.

Patients with recurrent or residual malignancy after multiple chemotherapeutic regimens may be treated with a recurrence modality (see *Principles of Systemic Therapy: Acceptable Recurrence Therapies for Malignant Germ Cell/Sex Cord-Stromal Tumors* in the NCCN Guidelines for Epithelial Ovarian Cancer), including potentially curative high-dose chemotherapy or TIP. Other regimens include VAC (vincristine, dactinomycin, cyclophosphamide), VeIP (vinblastine, ifosfamide, cisplatin), VIP (etoposide, ifosfamide, cisplatin), cisplatin/etoposide, docetaxel/carboplatin, paclitaxel/carboplatin, paclitaxel/gemcitabine, paclitaxel/ifosfamide, docetaxel, paclitaxel, RT, or supportive care only.<sup>457,470-474</sup> These recurrence regimens (see *Principles of Systemic Therapy: Acceptable Recurrence Therapies for Malignant Germ Cell/Sex Cord-Stromal Tumors* in the NCCN Guidelines for Epithelial Ovarian Cancer) are not generalizable for all of the uncommon histology tumors; therefore, patients should be referred to tertiary care institutions for treatment.

### **Malignant Sex Cord-Stromal Tumors**

Malignant sex cord-stromal tumors are rare and include granulosa cell tumors (most common) and Sertoli-Leydig cell tumors; they are typically associated with a good prognosis.<sup>475,476</sup> Most patients with granulosa tumors present with early-stage disease; the disease is typically indolent.<sup>477</sup> The complete histologic classification for ovarian cancer from the WHO includes the different types of sex cord-stromal tumors; it is important to determine whether the sex cord-stromal tumor is benign or malignant (see *WHO Histologic Classification: Sex Cord-Stromal Tumors*



in the NCCN Guidelines for Ovarian Cancer Histopathologies).<sup>1</sup> The staging system for high-grade serous ovarian and primary peritoneal cancer is also used for sex cord-stromal tumors (see Table 1 in the NCCN Guidelines for Ovarian Cancer).<sup>93</sup>

Patients with stage IA or IC sex cord-stromal tumors desiring to preserve their fertility should be treated with fertility-sparing surgery (see the NCCN Guidelines for Malignant Sex Cord-Stromal Tumors).<sup>477-480</sup> Although complete staging is recommended for all other patients, lymphadenectomy may be omitted for tumors grossly confined to the ovary.<sup>481</sup> For patients who choose fertility-sparing surgery, completion surgery (category 2B) should be considered after childbearing is finished. Postoperative options in the NCCN Guidelines have category 2B recommendations (see the NCCN Guidelines for Malignant Sex Cord-Stromal Tumors).<sup>478</sup> For patients with high-risk stage I tumors (tumor rupture, stage 1C, poorly differentiated tumor, and tumor size >10–15 cm<sup>482</sup>), postoperative recommendations (all are category 2B) include observation or consideration of platinum-based chemotherapy.<sup>483</sup> Observation is recommended for those with surgical findings of low-risk stage I tumor (ie, without high-risk features) (see *Surveillance for Malignant Germ Cell and Sex Cord-Stromal Tumors* in the NCCN Guidelines for Less Common Ovarian Histopathologies). For patients with granulosa cell tumors who are being observed, inhibin levels can be followed if they were initially elevated (category 2B). For patients with stage II to IV tumors, recommended options (all are category 2B) include RT for limited disease or platinum-based chemotherapy (BEP or paclitaxel/carboplatin regimens are preferred).<sup>484-487</sup>

Surveillance recommendations for malignant sex cord-stromal tumors are provided in the algorithm, which are based on the SGO recommendations (see *Surveillance for Malignant Germ Cell and Sex Cord-Stromal Tumors* in the NCCN Guidelines for Less Common Ovarian Histopathologies).<sup>299</sup>

Prolonged surveillance is recommended for granulosa cell tumors, because they can recur years later (eg, 30 years).<sup>439,475,476,488</sup> For patients with stage II to IV tumors who subsequently have a clinical relapse, options include a clinical trial or recurrence therapy (see *Principles of Systemic Therapy: Acceptable Recurrence Therapies for Malignant Germ Cell/Sex Cord-Stromal Tumors* in the NCCN Guidelines for Epithelial Ovarian Cancer).<sup>476,488-491</sup> Cytotoxic recurrence therapy includes: docetaxel, paclitaxel, paclitaxel/ifosfamide, paclitaxel/carboplatin, and VAC. Hormone recurrence therapy includes: aromatase inhibitors, leuprolide, and tamoxifen. Note that single-agent bevacizumab or leuprolide is an option for patients with recurrent granulosa cell tumors.<sup>491,492</sup> Secondary cytoreductive surgery may also be considered. Palliative localized RT may also be useful.

### **Carcinosarcomas (Malignant Mixed Müllerian Tumors)**

MMMTs are rare tumors with a poor prognosis; they are the most aggressive tumors in the algorithm (see the NCCN Guidelines for Less Common Ovarian Histopathologies).<sup>493-496</sup> Most pathologists now consider MMTs to be a variant of poorly differentiated epithelial ovarian cancer (metaplastic carcinoma).<sup>497</sup> Patients with MMTs are not candidates for fertility-sparing surgery regardless of age or stage. The staging system for ovarian and primary peritoneal cancer is also used for MMTs (see Table 1 in the NCCN Guidelines for Ovarian Cancer).<sup>93,495</sup>

Optimal surgical debulking is recommended for patients with MMTs (see *Principles of Surgery* in the NCCN Guidelines for Ovarian Cancer).<sup>495,498-500</sup> After complete surgical staging, several postoperative chemotherapy regimens are recommended for patients with stage I to IV MMT. Patients with stage I to IV MMT or recurrence may be treated using the same primary chemotherapy regimens that are recommended for epithelial ovarian cancer; for the 2017 update (Version 1), the panel decided these chemotherapy regimens are preferred options (see *Primary*



*Chemotherapy/Primary Adjuvant Therapy* in the NCCN Guidelines for Ovarian Cancer).<sup>497,501-506</sup> For example, intravenous carboplatin with either paclitaxel, docetaxel, or liposomal doxorubicin are recommended for patients with stage I-IV MMT. The IP chemotherapy regimen described for ovarian cancer can be used for select patients with MMT. Other recommended postoperative chemotherapy options include cisplatin/ifosfamide (category 2A), carboplatin/ifosfamide (category 2A), and ifosfamide/paclitaxel (category 2B).<sup>493,497,501,507</sup> After treatment, the surveillance and follow-up recommendations for epithelial ovarian cancer are also used for MMTs.

### **Borderline Epithelial Tumors (Low Malignant Potential)**

#### ***Diagnosis***

Borderline epithelial tumors are rare tumors and are managed differently than high-grade carcinomas (see the NCCN Guidelines for Borderline Epithelial Tumors [Low Malignant Potential]).<sup>410,508</sup> Five-year survival exceeds 80%.<sup>509</sup> In contrast to patients with frankly invasive ovarian carcinoma, women with borderline epithelial tumors tend to be younger, are often diagnosed with stage I disease, and are candidates for fertility-sparing surgery.<sup>510,511</sup> A borderline tumor is a primary epithelial lesion with cytologic characteristics suggesting malignancy but without frank invasion and with a clinically indolent course and good prognosis.<sup>512,513</sup>

The terms for borderline epithelial tumors (also known as low malignant potential tumors or atypical proliferative tumors) have changed over the years.<sup>415</sup> The 2016 and 2017 CAP cancer protocols for ovarian cancer use borderline and do not use low malignant potential.<sup>88,94</sup> Borderline epithelial tumors are typically serous or mucinous; other histologic subtypes can also occur (see *WHO Histologic Classification* in the NCCN Guidelines for Ovarian Cancer Histopathologies).<sup>1,410</sup>

The characteristic pathologic hallmark of typical epithelial ovarian cancer is the identification of peritoneal implants, which microscopically and/or macroscopically invade the peritoneum. A borderline epithelial tumor may grossly resemble an invasive cancer. However, microscopic evaluation fails to reveal evidence of frank invasion by the tumor nodules, although rarely invasive implants (which continue to be consistent with the diagnosis of borderline epithelial lesions) can be identified microscopically by the pathologist.

#### ***Treatment***

Surgery is the primary treatment for borderline epithelial tumors, including standard ovarian cancer debulking surgery or fertility-sparing surgery depending on the surgical evaluation and other factors (see the NCCN Guidelines for Borderline Epithelial Tumors [Low Malignant Potential]).<sup>514</sup> Treatment guidelines for borderline epithelial tumors depend on the histologic and clinical characteristics, the age of the patient,<sup>511</sup> and whether invasive implants are present. Patients should be evaluated by a gynecologic oncologist. At NCCN Member Institutions, patients may be initially evaluated with an undiagnosed pelvic mass or with an established diagnosis of borderline epithelial tumor. NCCN Panel Members are less likely to recommend aggressive treatment after surgery; observation is one of several possible approaches.<sup>410,515</sup> Although the staging system for epithelial ovarian cancer is used for borderline epithelial tumors, the NCCN Guidelines use the presence or absence of invasive implants to determine the need for postoperative therapy (see the NCCN Guidelines for Borderline Epithelial Tumors [Low Malignant Potential]).

Patients with a borderline epithelial tumor who desire to maintain their fertility may undergo surgery limited to a USO (preserving the uterus, contralateral ovary, and contralateral Fallopian tube) with resection of residual disease.<sup>148,149,516</sup> BSO and preserving the uterus is an option for select patients. If the patient does not desire fertility-sparing surgery,

standard ovarian cancer surgery (TAH, BSO, and debulking as needed) and resection of residual disease are recommended. Data do not show increased survival with lymphadenectomy and omentectomy for borderline epithelial tumor, although upstaging does occur.<sup>517,518</sup> Lymph node evaluation may be considered on a case-by-case basis.

For patients with known borderline epithelial tumors who had incomplete previous surgery and/or were incompletely staged at the time of their initial laparotomy, recommendations depend on whether invasive implants are present and whether fertility preservation is desired (see *Primary Treatment for Incomplete Previous Surgery* in the NCCN Guidelines for Borderline Epithelial Tumors [Low Malignant Potential]). Patients who want to preserve their fertility should have fertility-sparing surgery and resection of residual disease. Some clinicians feel that the appearance of invasive implants on the peritoneal surfaces in patients with borderline epithelial tumors portends a less favorable prognosis; therefore, postoperative chemotherapy with the same regimens used for low-grade (grade 1) serous epithelial ovarian cancer can be considered for these patients (see *Primary Treatment* in the NCCN Guidelines for Borderline Epithelial Tumors [Low Malignant Potential]).<sup>510,511,519</sup> Postoperative intravenous carboplatin with either docetaxel or paclitaxel is recommended. The benefit of chemotherapy, either IP or intravenous, is controversial in patients with borderline epithelial tumors. The significance of invasive implants remains under investigation.<sup>410,520</sup> The benefit of postoperative chemotherapy has not been demonstrated for patients who have no microscopically demonstrable invasive implants.<sup>521</sup> Although observation is an option for all patients, it is a category 3 recommendation for patients with invasive implants and a category 2B recommendation for patients without invasive implants (see *Primary Treatment* for Borderline Epithelial Tumors [Low Malignant Potential]).

### Follow-up

Treatment recommendations after surgery depend on the presence or absence of invasive implants. The initial therapeutic approach for patients having invasive implants may include treatment with the same chemotherapeutic regimens used for low-grade (grade 1) serous epithelial ovarian cancer or observation (category 3) (see *Primary Treatment* in the NCCN Guidelines for Borderline Epithelial Tumors [Low Malignant Potential]).<sup>520</sup> Patients with no invasive implants may be observed (category 2B) and monitored (see *Monitoring/Follow-Up* in the NCCN Guidelines for Borderline Epithelial Tumors [Low Malignant Potential]).<sup>510,522</sup> Patients who chose fertility-sparing surgery should be monitored by ultrasound examinations if necessary. After childbearing is completed, completion surgery should be considered (category 2B).<sup>410</sup>

### Relapse

At the time of clinical relapse, surgical evaluation and debulking are recommended if appropriate. Patients who have low-grade invasive carcinoma or invasive implants from borderline epithelial tumors may be treated using the same recommendations as for low-grade (grade 1) serous epithelial ovarian cancer; those with high-grade invasive implants may be treated using the same recommendations as for epithelial ovarian cancer (see *Primary Chemotherapy/Primary Adjuvant Therapy* in the NCCN Guidelines for Borderline Epithelial Tumors [Low Malignant Potential]). Observation is recommended for those with noninvasive disease.

### Summary

Epithelial ovarian cancer is the leading cause of death from gynecologic cancer in the United States and is the country's fifth most common cause of cancer mortality in women. More than 70% of patients present with advanced disease. The literature does not support routine screening for ovarian cancer in the general population, and routine screening is not



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currently recommended by any professional society. These NCCN Guidelines discuss epithelial ovarian cancer and LCOH, including carcinosarcomas (MMMTs of the ovary), clear cell carcinomas, mucinous carcinomas, low-grade serous carcinomas/endometrioid epithelial carcinomas, borderline epithelial tumors (also known as low malignant potential tumors), malignant sex cord-stromal tumors, and malignant germ cell tumors. Primary peritoneal and Fallopian tube cancers are treated in the same manner as epithelial ovarian cancer.

The complete histologic classification for ovarian cancer from the WHO describes the different types of LCOH. Panel members believe there is value in identifying pathways that may serve as therapeutic targets for the LCOH because of the promise of new and novel approaches to treatment. However, there are limited data for these rare histologies because of their infrequency and it will be difficult to acquire prospective data. Clinical trials for eligible patients, and individualized treatment plans for those who are not eligible for trials, may be the most suitable approaches to treatment in these patients at this time.

Most ovarian cancers, including the LCOH, are diagnosed after pathologic analysis of a biopsy or surgical specimen. Based on published improved outcomes, it is recommended (category 1) that a gynecologic oncologist perform the primary surgery. Primary treatment for presumed ovarian cancer consists of appropriate surgical staging and debulking surgery, followed in most (but not all) patients by systemic chemotherapy. Debulking surgery is the initial treatment recommendation for patients with clinical stage II, III, or IV disease. For most patients, initial surgery should include hysterectomy, BSO, and debulking as needed. Procedures that may be considered for optimal surgical debulking include: radical pelvic dissection, bowel resection and/or appendectomy, lymphadenectomy, diaphragm or other peritoneal surface stripping, splenectomy, partial hepatectomy, partial gastrectomy, or partial cystectomy and/or

ureteroneocystostomy, cholecystectomy, and/or distal pancreatectomy. Most patients have a hysterectomy with BSO, omentectomy, and lymphadenectomy of suspicious/enlarged nodes. Patients with low-volume residual disease after surgical debulking for stage II or III invasive epithelial ovarian or peritoneal cancer are candidates for IP therapy. In these patients, consideration should be given to placement of an IP catheter with initial surgery. In women with optimally debulked stage III cancer, the IP regimen has yielded median survival of 65.6 months. In women receiving a dose-dense weekly paclitaxel/carboplatin regimen, median overall survival was 100.5 months.

For a young patient who wishes to maintain fertility, a USO (preserving the uterus and contralateral ovary) and comprehensive surgical staging may be adequate for select unilateral stage I tumors (stage 1A and 1C, but not stage 1B) and/or low-risk ovarian tumors (ie, early-stage, grade 1 tumors; borderline tumors). For those with stage IB tumors who wish to maintain fertility, a BSO (preserving the uterus) and comprehensive surgical staging are recommended.

Most patients with epithelial ovarian cancer receive postoperative systemic chemotherapy. Consideration of palliative care interventions is appropriate at several stages during the disease course. Recommendations regarding initial primary systemic therapy include intravenous with [or without] IP options. All of the regimens (including the combined intravenous/IP chemotherapy) may be used for epithelial ovarian, primary peritoneal, and Fallopian tube cancers; some of these regimens are recommended for some of the LCOH. Neoadjuvant chemotherapy may be considered (category 1) for patients with bulky stage III to IV disease or high-risk surgical candidates; a gynecologic oncologist should make this assessment before neoadjuvant chemotherapy is administered.

For all patients, the NCCN Guidelines recommend symptom management, best supportive care, and long-term wellness care; patients should be





referred for palliative care assessment if appropriate. Patients should be educated about signs and symptoms suggestive of recurrence such as pelvic pain, bloating, early satiety, obstruction, weight loss, and fatigue. Recurrent disease may be identified clinically (eg, pelvic pain, weight loss), biochemically (ie, elevated CA-125 levels), and/or with imaging. The NCCN Guidelines recommend a number of different regimens and agents for recurrence therapy; some of them are designated as preferred regimens. Patients with ovarian cancer will often be retreated with multiple courses of recurrence therapy. Patients who relapse 6 months or more after initial chemotherapy are termed *platinum sensitive*. Those who relapse after less than 6 months are termed *platinum resistant*. Platinum-based combination chemotherapy is preferred in patients with platinum-sensitive disease, especially for first recurrence. For platinum-resistant disease, non-platinum-based agents or regimens are preferred. Some of the new additions for 2017 include: 1) carboplatin/liposomal doxorubicin for first-line therapy; 2) niraparib and olaparib for maintenance therapy; and 3) rucaparib, carboplatin/albumin-bound paclitaxel, and carboplatin/paclitaxel/bevacizumab for recurrence therapy.

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### Recommended Readings

Alberts DS, Green S, Hannigan EV, et al. Improved therapeutic index of carboplatin plus cyclophosphamide versus cisplatin plus cyclophosphamide: final report by the Southwest Oncology Group of a phase III randomized trial in stages III and IV ovarian cancer. *J Clin Oncol* 1992;10:706-717. &

Armstrong D, Bundy B, Wenzel L, et al. Intraperitoneal cisplatin and paclitaxel in ovarian cancer. *N Engl J Med* 2006;354:34-43. &

Bell J, Brady MF, Young RC, et al. Randomized phase III trial of three versus six cycles of adjuvant carboplatin and paclitaxel in early stage epithelial ovarian carcinoma: A Gynecologic Oncology Group study. *Gynecol Oncol* 2006;102:432-439.

Berton-Rigaud D, Devouassoux-Shisheboran M, Ledermann JA, et al. Gynecologic Cancer InterGroup (GCIg) consensus review for uterine and ovarian carcinosarcoma. *Int J Gynecol Cancer* 2014;24(9 Suppl 3):S55-60.

Brown J, Friedlander M, Backes FJ, et al. Gynecologic Cancer InterGroup (GCIg) consensus review for ovarian germ cell tumors. *Int J Gynecol Cancer* 2014;24(9 Suppl 3):S48-54.

Cristea M, Han E, Salmon L, Morgan RJ. Practical considerations in ovarian cancer chemotherapy. *Ther Adv Med Oncol* 2010;2:175-187.

Committee on the State of the Science in Ovarian Cancer. *Ovarian Cancers: Evolving Paradigms in Research and Care*, Washington (DC): National Academies Press (US) Copyright 2016 by the National Academy of Sciences. All rights reserved; 2016.

Eisenhauer EL, Abu-Rustum NR, Sonoda Y, et al. The addition of extensive upper abdominal surgery to achieve optimal cytoreduction improves survival in patients with stages IIIC-IV epithelial ovarian cancer. *Gynecol Oncol* 2006;103:1083-1090.

Fader AN, Rose PG. Role of surgery in ovarian carcinoma. *J Clin Oncol* 2007;25:2873-2883. &

Goff BA, Mandel LS, Drescher CW, et al. Development of an ovarian cancer symptom index: possibilities for earlier detection. *Cancer* 2007;109:221-227.

Gourley C, Farley J, Provencher DM, et al. Gynecologic Cancer InterGroup (GCIg) consensus review for ovarian and primary peritoneal low-grade serous carcinomas. *Int J Gynecol Cancer* 2014;24(9 Suppl 3):S9-13.

Harter P, Gershenson D, Lhomme C, et al. Gynecologic Cancer InterGroup (GCIg) consensus review for ovarian tumors of low malignant potential (borderline ovarian tumors). *Int J Gynecol Cancer* 2014;24(9 Suppl 3):S5-8.

Katsumata N, Yasuda M, Takahashi F, et al. Dose-dense paclitaxel once a week in combination with carboplatin every 3 weeks for advanced ovarian cancer: a phase 3, open-label, randomised controlled trial. *Lancet* 2009;374:1331-1338.

Kurman RJ, Carcangiu ML, Harrington CS, et al. *WHO Classification of Tumours of Female Reproductive Organs*, 4th Edition. WHO/IARC Classification of Tumours. Vol. 6. Lyon: IARC Publications; 2014.

Ledermann JA, Luvero D, Shafer A, et al. Gynecologic Cancer InterGroup (GCIg) consensus review for mucinous ovarian carcinoma. *Int J Gynecol Cancer* 2014;24(9 Suppl 3):S14-9.



Morice P, Denschlag D, Rodolakis A, et al. Recommendations of the Fertility Task Force of the European Society of Gynecologic Oncology about the conservative management of ovarian malignant tumors. *Int J Gynecol Cancer* 2011;21:951-963.

Okamoto A, Glasspool RM, Mabuchi S, et al. Gynecologic Cancer InterGroup (GCIG) consensus review for clear cell carcinoma of the ovary. *Int J Gynecol Cancer* 2014;24(9 Suppl 3):S20-5.

Ozols RF, Bundy BN, Greer BE, et al. Phase III trial of carboplatin and paclitaxel compared with cisplatin and paclitaxel in patients with optimally resected stage III ovarian cancer: Gynecologic Oncology Group study. *J Clin Oncol* 2003;21:3194-3200. &

Ray-Coquard I, Brown J, Harter P, et al. Gynecologic Cancer InterGroup (GCIG) consensus review for ovarian sex cord stromal tumors. *Int J Gynecol Cancer* 2014;24(9 Suppl 3):S42-7.

Swenerton K, Jeffrey J, Stuart G, et al. Cisplatin-cyclophosphamide versus carboplatin-cyclophosphamide in advanced ovarian cancer: a randomized phase III study of the National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol* 1992;10:718-726. &

Trimbos JB, Parmar M, Vergote I, et al. International Collaborative Ovarian Neoplasm trial 1 and Adjuvant Chemotherapy In Ovarian Neoplasm trial: two parallel randomized phase III trials of adjuvant chemotherapy in patients with early-stage ovarian carcinoma. *J Natl Cancer Inst* 2003;95:105-112.

Walker JL, Armstrong DK, Huang HQ, et al. Intraperitoneal catheter outcomes in a phase III trial of intravenous versus intraperitoneal chemotherapy in optimal stage III ovarian and primary peritoneal cancer: a Gynecologic Oncology Group Study. *Gynecol Oncol* 2006;100:27-32. &

Young RC, Walton LA, Ellenberg SS, et al. Adjuvant therapy in stage I and stage II epithelial ovarian cancer. *N Engl J Med* 1990;322:1021-1027. &

**References marked with the symbol “&” provide the basis for the algorithms.**

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### References

1. Kurman RJ, Carcangiu ML, Harrington CS, et al. WHO Classification of Tumours of Female Reproductive Organs, 4th Edition. WHO/IARC Classification of Tumours. Vol. 6. Lyon: IARC Publications; 2014. Available at: <https://www.iarc.fr/news-events/iarc-publications-who-classification-of-tumours-of-female-reproductive-organs-fourth-edition/>
2. Chan JK, Cheung MK, Husain A, et al. Patterns and progress in ovarian cancer over 14 years. *Obstet Gynecol* 2006;108:521-528. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16946210>.
3. Prat J. New insights into ovarian cancer pathology. *Ann Oncol* 2012;23 Suppl 10:x111-117. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22987944>.
4. Jelovac D, Armstrong DK. Recent progress in the diagnosis and treatment of ovarian cancer. *CA Cancer J Clin* 2011;61:183-203. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21521830>.
5. Morgan RJ, Jr., Copeland L, Gershenson D, et al. NCCN Ovarian Cancer Practice Guidelines. The National Comprehensive Cancer Network. *Oncology (Williston Park)* 1996;10:293-310. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/8953610>.
6. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. *CA Cancer J Clin* 2018;68:7-30. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29313949>.
7. Howlader N, Noone A, Krapcho M, et al. SEER Cancer Statistics Review, 1975-2014, based on November 2016 SEER data submission, posted to the SEER web site, April 2017. Bethesda, MD: National Cancer Institute; 2017. Available at: [https://seer.cancer.gov/csr/1975\\_2014/](https://seer.cancer.gov/csr/1975_2014/).
8. Wentzensen N, Poole EM, Trabert B, et al. Ovarian cancer risk factors by histologic subtype: an analysis from the Ovarian Cancer Cohort Consortium. *J Clin Oncol* 2016;34:2888-2898. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27325851>.
9. Holschneider CH, Berek JS. Ovarian cancer: epidemiology, biology, and prognostic factors. *Semin Surg Oncol* 2000;19:3-10. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10883018>.
10. Fleming GF, Seidman J, Lengyel E. Epithelial ovarian cancer. In: Barakat RR, Markman M, Randall ME, eds. *Principles and Practice of Gynecologic Oncology*, 6th ed. Philadelphia: Lippincott Williams & Wilkins; 2013:757-847.
11. Morch LS, Lokkegaard E, Andreassen AH, et al. Hormone therapy and ovarian cancer. *JAMA* 2009;302:298-305. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19602689>.
12. Morch LS, Lokkegaard E, Andreassen AH, et al. Hormone therapy and different ovarian cancers: a national cohort study. *Am J Epidemiol* 2012;175:1234-1242. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22517811>.
13. Lin HW, Tu YY, Lin SY, et al. Risk of ovarian cancer in women with pelvic inflammatory disease: a population-based study. *Lancet Oncol* 2011;12:900-904. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21835693>.
14. van Leeuwen FE, Klip H, Mooij TM, et al. Risk of borderline and invasive ovarian tumours after ovarian stimulation for in vitro fertilization in a large Dutch cohort. *Hum Reprod* 2011;26:3456-3465. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22031719>.
15. Pearce CL, Templeman C, Rossing MA, et al. Association between endometriosis and risk of histological subtypes of ovarian cancer: a pooled analysis of case-control studies. *Lancet Oncol* 2012;13:385-394. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22361336>.
16. Olsen CM, Nagle CM, Whiteman DC, et al. Obesity and risk of ovarian cancer subtypes: evidence from the Ovarian Cancer Association Consortium. *Endocr Relat Cancer* 2013;20:251-262. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23404857>.



17. Nakonechny QB, Gilks CB. Ovarian Cancer in Hereditary Cancer Susceptibility Syndromes. *Surg Pathol Clin* 2016;9:189-199. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/27241103>.

18. Chui MH, Ryan P, Radigan J, et al. The histomorphology of Lynch syndrome-associated ovarian carcinomas: toward a subtype-specific screening strategy. *Am J Surg Pathol* 2014;38:1173-1181. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25025451>.

19. Lu KH, Daniels M. Endometrial and ovarian cancer in women with Lynch syndrome: update in screening and prevention. *Fam Cancer* 2013;12:273-277. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23765559>.

20. Lancaster JM, Powell CB, Chen LM, et al. Society of Gynecologic Oncology statement on risk assessment for inherited gynecologic cancer predispositions. *Gynecol Oncol* 2015;136:3-7. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25238946>.

21. Rebbeck TR, Mitra N, Wan F, et al. Association of type and location of BRCA1 and BRCA2 mutations with risk of breast and ovarian cancer. *JAMA* 2015;313:1347-1361. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25849179>.

22. Daly MB, Axilbund JE, Buys S, et al. Genetic/familial high-risk assessment: breast and ovarian. *J Natl Compr Canc Netw* 2010;8:562-594. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20495085>.

23. Walsh CS, Blum A, Walts A, et al. Lynch syndrome among gynecologic oncology patients meeting Bethesda guidelines for screening. *Gynecol Oncol* 2010;116:516-521. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20034658>.

24. Lancaster JM, Powell CB, Kauff ND, et al. Society of Gynecologic Oncologists Education Committee statement on risk assessment for inherited gynecologic cancer predispositions. *Gynecol Oncol* 2007;107:159-162. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17950381>.

25. Shulman LP. Hereditary breast and ovarian cancer (HBOC): clinical features and counseling for BRCA1 and BRCA2, Lynch syndrome, Cowden syndrome, and Li-Fraumeni syndrome. *Obstet Gynecol Clin North Am* 2010;37:109-133. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20494261>.

26. Bulletins ACoP. Hereditary breast and ovarian cancer syndrome. *Gynecol Oncol* 2009;113:6-11. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19309638>.

27. The American Congress of Obstetricians and Gynecologists. ACOG Practice Bulletin No. 103: Hereditary breast and ovarian cancer syndrome. *Obstet Gynecol* 2009;113:957-966. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19305347>.

28. Zhang S, Royer R, Li S, et al. Frequencies of BRCA1 and BRCA2 mutations among 1,342 unselected patients with invasive ovarian cancer. *Gynecol Oncol* 2011;121:353-357. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21324516>.

29. Liu G, Yang D, Sun Y, et al. Differing clinical impact of BRCA1 and BRCA2 mutations in serous ovarian cancer. *Pharmacogenomics* 2012;13:1523-1535. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23057551>.

30. Stan DL, Shuster LT, Wick MJ, et al. Challenging and complex decisions in the management of the BRCA mutation carrier. *J Womens Health (Larchmt)* 2013;22:825-834. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23987739>.

31. Finch A, Beiner M, Lubinski J, et al. Salpingo-oophorectomy and the risk of ovarian, fallopian tube, and peritoneal cancers in women with a BRCA1 or BRCA2 Mutation. *JAMA* 2006;296:185-192. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16835424>.

32. Marchetti C, De Felice F, Palaia I, et al. Risk-reducing salpingo-oophorectomy: a meta-analysis on impact on ovarian cancer risk and all cause mortality in BRCA 1 and BRCA 2 mutation carriers. *BMC Womens Health* 2014;14:150. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25494812>.
33. Reitsma W, de Bock GH, Oosterwijk JC, et al. Support of the 'fallopian tube hypothesis' in a prospective series of risk-reducing salpingo-oophorectomy specimens. *Eur J Cancer* 2013;49:132-141. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22921157>.
34. Domchek SM, Friebel TM, Singer CF, et al. Association of risk-reducing surgery in BRCA1 or BRCA2 mutation carriers with cancer risk and mortality. *JAMA* 2010;304:967-975. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20810374>.
35. Rebbeck TR, Kauff ND, Domchek SM. Meta-analysis of risk reduction estimates associated with risk-reducing salpingo-oophorectomy in BRCA1 or BRCA2 mutation carriers. *J Natl Cancer Inst* 2009;101:80-87. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19141781>.
36. Powell CB, Chen LM, McLennan J, et al. Risk-reducing salpingo-oophorectomy (RRSO) in BRCA mutation carriers: experience with a consecutive series of 111 patients using a standardized surgical-pathological protocol. *Int J Gynecol Cancer* 2011;21:846-851. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21670699>.
37. Mingels MJ, van Ham MA, de Kievit IM, et al. Mullerian precursor lesions in serous ovarian cancer patients: using the SEE-Fim and SEE-End protocol. *Mod Pathol* 2014;27:1002-1013. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24309326>.
38. Callahan MJ, Crum CP, Medeiros F, et al. Primary fallopian tube malignancies in BRCA-positive women undergoing surgery for ovarian cancer risk reduction. *J Clin Oncol* 2007;25:3985-3990. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17761984>.
39. Sherman ME, Piedmonte M, Mai PL, et al. Pathologic findings at risk-reducing salpingo-oophorectomy: primary results from Gynecologic Oncology Group Trial GOG-0199. *J Clin Oncol* 2014;32:3275-3283. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25199754>.
40. Domchek SM, Friebel TM, Garber JE, et al. Occult ovarian cancers identified at risk-reducing salpingo-oophorectomy in a prospective cohort of BRCA1/2 mutation carriers. *Breast Cancer Res Treat* 2010;124:195-203. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20180014>.
41. Clarke-Pearson DL. Clinical practice. Screening for ovarian cancer. *N Engl J Med* 2009;361:170-177. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19587342>.
42. Kuhn E, Kurman RJ, Shih IM. Ovarian cancer is an imported disease: fact or fiction? *Curr Obstet Gynecol Rep* 2012;1:1-9. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22506137>.
43. Ovarian Cancers: Evolving Paradigms in Research and Care; Committee on the State of the Science in Ovarian Cancer Research; National Academies of Sciences, Engineering, and Medicine. Washington, DC: The National Academies Press; 2016.
44. Vaughan MH, Modesitt SC, Mo Y, Trowbridge ER. Serous tubal intraepithelial carcinoma: an incidental finding at the time of prophylactic bilateral salpingo-oophorectomy. *Case Rep Obstet Gynecol* 2015;2015:760429. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25802782>.
45. Patrono MG, Iniesta MD, Malpica A, et al. Clinical outcomes in patients with isolated serous tubal intraepithelial carcinoma (STIC): A comprehensive review. *Gynecol Oncol* 2015;139:568-572. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26407480>.
46. Wethington SL, Park KJ, Soslow RA, et al. Clinical outcome of isolated serous tubal intraepithelial carcinomas (STIC). *Int J Gynecol Cancer* 2013;23:1603-1611. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24172097>.



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47. Goff BA, Mandel LS, Drescher CW, et al. Development of an ovarian cancer symptom index: possibilities for earlier detection. *Cancer* 2007;109:221-227. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17154394>.
48. Andersen MR, Goff BA, Lowe KA, et al. Combining a symptoms index with CA 125 to improve detection of ovarian cancer. *Cancer* 2008;113:484-489. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18615684>.
49. The American Congress of Obstetricians and Gynecologists. Committee Opinion No. 477: the role of the obstetrician-gynecologist in the early detection of epithelial ovarian cancer. *Obstet Gynecol* 2011;117:742-746. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21343791>.
50. Lim AW, Mesher D, Gentry-Maharaj A, et al. Predictive value of symptoms for ovarian cancer: comparison of symptoms reported by questionnaire, interview, and general practitioner notes. *J Natl Cancer Inst* 2012;104:114-124. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22247022>.
51. Rossing MA, Wicklund KG, Cushing-Haugen KL, Weiss NS. Predictive value of symptoms for early detection of ovarian cancer. *J Natl Cancer Inst* 2010;102:222-229. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20110551>.
52. Gilbert L, Basso O, Sampalis J, et al. Assessment of symptomatic women for early diagnosis of ovarian cancer: results from the prospective DOvE pilot project. *Lancet Oncol* 2012;13:285-291. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22257524>.
53. Rimel BJ, Burke WM, Higgins RV, et al. Improving quality and decreasing cost in gynecologic oncology care. Society of gynecologic oncology recommendations for clinical practice. *Gynecol Oncol* 2015;137:280-284. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25735256>.
54. Smith RA, Manassaram-Baptiste D, Brooks D, et al. Cancer screening in the United States, 2015: a review of current American cancer society guidelines and current issues in cancer screening. *CA Cancer J Clin* 2015;65:30-54. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25581023>.
55. Nolen BM, Lokshin AE. Protein biomarkers of ovarian cancer: the forest and the trees. *Future Oncol* 2012;8:55-71. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22149035>.
56. Buys SS, Partridge E, Black A, et al. Effect of screening on ovarian cancer mortality: the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Randomized Controlled Trial. *JAMA* 2011;305:2295-2303. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21642681>.
57. Hartge P. Designing early detection programs for ovarian cancer. *J Natl Cancer Inst* 2010;102:3-4. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20042718>.
58. Moyer VA, Force USPST. Screening for ovarian cancer: U.S. Preventive Services Task Force reaffirmation recommendation statement. *Ann Intern Med* 2012;157:900-904. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22964825>.
59. Gentry-Maharaj A, Menon U. Screening for ovarian cancer in the general population. *Best Pract Res Clin Obstet Gynaecol* 2012;26:243-256. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22182415>.
60. Schorge JO, Modesitt SC, Coleman RL, et al. SGO White Paper on ovarian cancer: etiology, screening and surveillance. *Gynecol Oncol* 2010;119:7-17. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20692025>.
61. Brown DL, Andreotti RF, Lee SI, et al. ACR appropriateness criteria(c) ovarian cancer screening. *Ultrasound Q* 2010;26:219-223. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21084936>.



62. Elliker KR, Sommerville BA, Broom DM, et al. Key considerations for the experimental training and evaluation of cancer odour detection dogs: lessons learnt from a double-blind, controlled trial of prostate cancer detection. *BMC Urol* 2014;14:22. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24575737>.
63. Horvath G, Andersson H, Nemes S. Cancer odor in the blood of ovarian cancer patients: a retrospective study of detection by dogs during treatment, 3 and 6 months afterward. *BMC Cancer* 2013;13:396. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23978091>.
64. Horvath G, Jarverud GA, Jarverud S, Horvath I. Human ovarian carcinomas detected by specific odor. *Integr Cancer Ther* 2008;7:76-80. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18505901>.
65. Horvath G, Chilo J, Lindblad T. Different volatile signals emitted by human ovarian carcinoma and healthy tissue. *Future Oncol* 2010;6:1043-1049. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20528240>.
66. Menon U, Griffin M, Gentry-Maharaj A. Ovarian cancer screening--current status, future directions. *Gynecol Oncol* 2014;132:490-495. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24316306>.
67. Sharma A, Apostolidou S, Burnell M, et al. Risk of epithelial ovarian cancer in asymptomatic women with ultrasound-detected ovarian masses: a prospective cohort study within the UK collaborative trial of ovarian cancer screening (UKCTOCS). *Ultrasound Obstet Gynecol* 2012;40:338-344. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22911637>.
68. Jacobs IJ, Menon U, Ryan A, et al. Ovarian cancer screening and mortality in the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS): a randomised controlled trial. *Lancet* 2016;387:945-956. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26707054>.
69. Menon U, Gentry-Maharaj A, Hallett R, et al. Sensitivity and specificity of multimodal and ultrasound screening for ovarian cancer, and stage distribution of detected cancers: results of the prevalence screen of the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS). *Lancet Oncol* 2009;10:327-340. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19282241>.
70. Partridge E, Kreimer AR, Greenlee RT, et al. Results from four rounds of ovarian cancer screening in a randomized trial. *Obstet Gynecol* 2009;113:775-782. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19305319>.
71. Pinsky PF, Zhu C, Skates SJ, et al. Potential effect of the risk of ovarian cancer algorithm (ROCA) on the mortality outcome of the Prostate, Lung, Colorectal and Ovarian (PLCO) trial. *Int J Cancer* 2013;132:2127-2133. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23065684>.
72. Valentin L, Jurkovic D, Van Calster B, et al. Adding a single CA 125 measurement to ultrasound imaging performed by an experienced examiner does not improve preoperative discrimination between benign and malignant adnexal masses. *Ultrasound Obstet Gynecol* 2009;34:345-354. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19585547>.
73. Timmerman D, Van Calster B, Testa A, et al. Predicting the risk of malignancy in adnexal masses based on the Simple Rules from the International Ovarian Tumor Analysis group. *Am J Obstet Gynecol* 2016;214:424-437. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26800772>.
74. Bristow RE, Chang J, Ziogas A, Anton-Culver H. Adherence to treatment guidelines for ovarian cancer as a measure of quality care. *Obstet Gynecol* 2013;121:1226-1234. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23812456>.





75. Giede KC, Kieser K, Dodge J, Rosen B. Who should operate on patients with ovarian cancer? An evidence-based review. *Gynecol Oncol* 2005;99:447-461. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16126262>.

76. Earle CC, Schrag D, Neville BA, et al. Effect of surgeon specialty on processes of care and outcomes for ovarian cancer patients. *J Natl Cancer Inst* 2006;98:172-180. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16449677>.

77. du Bois A, Quinn M, Thigpen T, et al. 2004 consensus statements on the management of ovarian cancer: final document of the 3rd International Gynecologic Cancer Intergroup Ovarian Cancer Consensus Conference (GCIG OCCC 2004). *Ann Oncol* 2005;16 Suppl 8:viii7-viii12. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16239238>.

78. Coates RJ, Kolor K, Stewart SL, Richardson LC. Diagnostic markers for ovarian cancer screening: not ready for routine clinical use. *Clin Cancer Res* 2008;14:7575-7576; author reply 7577-7579. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18948387>.

79. McIntosh M, Anderson G, Drescher C, et al. Ovarian cancer early detection claims are biased. *Clin Cancer Res* 2008;14:7574; author reply 7577-7579. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18948385>.

80. Greene MH, Feng Z, Gail MH. The importance of test positive predictive value in ovarian cancer screening. *Clin Cancer Res* 2008;14:7574; author reply 7577-7579. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18948386>.

81. Buchen L. Cancer: Missing the mark. *Nature* 2011;471:428-432. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21430749>.

82. Visintin I, Feng Z, Longton G, et al. Diagnostic markers for early detection of ovarian cancer. *Clin Cancer Res* 2008;14:1065-1072. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18258665>.

83. Cramer DW, Bast RC, Jr., Berg CD, et al. Ovarian cancer biomarker performance in prostate, lung, colorectal, and ovarian cancer screening trial specimens. *Cancer Prev Res (Phila)* 2011;4:365-374. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21372036>.

84. Anderson GL, McIntosh M, Wu L, et al. Assessing lead time of selected ovarian cancer biomarkers: a nested case-control study. *J Natl Cancer Inst* 2010;102:26-38. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20042715>.

85. Mai PL, Wentzensen N, Greene MH. Challenges related to developing serum-based biomarkers for early ovarian cancer detection. *Cancer Prev Res (Phila)* 2011;4:303-306. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21372029>.

86. Edge SB, Byrd DR, Compton CC, et al. *AJCC Cancer Staging Manual*, 7th ed. New York: Springer; 2010.

87. Prat J. Staging classification for cancer of the ovary, fallopian tube, and peritoneum. *Int J Gynaecol Obstet* 2014;124:1-5. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24219974>.

88. Gilks B, Movahedi-Lankarani S, Baker PM, et al. Protocol for the examination of specimens from patients with carcinoma of the ovary or Fallopian tube: Based on AJCC/UICC TNM, 7th edition: College of American Pathologists; 2016. Available at:

89. Zeppernick F, Meinhold-Heerlein I. The new FIGO staging system for ovarian, fallopian tube, and primary peritoneal cancer. *Arch Gynecol Obstet* 2014;290:839-842. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25082067>.

90. McCluggage WG. Morphological subtypes of ovarian carcinoma: a review with emphasis on new developments and pathogenesis. *Pathology* 2011;43:420-432. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21716157>.



91. Malpica A, Deavers MT, Tornos C, et al. Interobserver and intraobserver variability of a two-tier system for grading ovarian serous carcinoma. *Am J Surg Pathol* 2007;31:1168-1174. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17667538>.
92. Malpica A, Deavers MT, Lu K, et al. Grading ovarian serous carcinoma using a two-tier system. *Am J Surg Pathol* 2004;28:496-504. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15087669>.
93. Amin M, Greene F, Edge S. *AJCC Staging Manual*, 8th edition: Springer International Publishing; 2017:1-1024.
94. Movahedi-Lankarani S, Krishnamurti U, Bell DA, et al. Protocol for the examination of specimens from patients with primary tumors of the ovary, fallopian tube, or peritoneum. Based on AJCC/8th edition/2015 FIGO: Protocol web posting date: June 2017: College of American Pathologists; 2017. Available at: <https://documents.cap.org/protocols/cp-ovary-fallopian-tube-peritoneum-2017-v1001.pdf>
95. U.S. National Library of Medicine-Key MEDLINE® Indicators. Available at: [http://www.nlm.nih.gov/bsd/bsd\\_key.html](http://www.nlm.nih.gov/bsd/bsd_key.html). Accessed
96. Ferrell BR, Temel JS, Temin S, et al. Integration of palliative care into standard oncology care: American Society of Clinical Oncology Clinical Practice Guideline Update. *J Clin Oncol* 2017;35:96-112. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28034065>.
97. Mitchell DG, Javitt MC, Glanc P, et al. ACR appropriateness criteria staging and follow-up of ovarian cancer. *J Am Coll Radiol* 2013;10:822-827. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24183551>.
98. Im SS, Gordon AN, Buttin BM, et al. Validation of referral guidelines for women with pelvic masses. *Obstet Gynecol* 2005;105:35-41. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15625139>.
99. The American Congress of Obstetricians and Gynecologists. ACOG Practice Bulletin. Management of adnexal masses. *Obstet Gynecol* 2007;110:201-214. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17601923>.
100. Dearing AC, Aletti GD, McGree ME, et al. How relevant are ACOG and SGO guidelines for referral of adnexal mass? *Obstet Gynecol* 2007;110:841-848. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17906018>.
101. Timmerman D, Testa AC, Bourne T, et al. Simple ultrasound-based rules for the diagnosis of ovarian cancer. *Ultrasound Obstet Gynecol* 2008;31:681-690. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18504770>.
102. Iyer VR, Lee SI. MRI, CT, and PET/CT for ovarian cancer detection and adnexal lesion characterization. *AJR Am J Roentgenol* 2010;194:311-321. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20093590>.
103. Harris RD, Javitt MC, Glanc P, et al. ACR Appropriateness Criteria(R) clinically suspected adnexal mass. *Ultrasound Q* 2013;29:79-86. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23358212>.
104. Dodge JE, Covens AL, Lacchetti C, et al. Management of a suspicious adnexal mass: a clinical practice guideline. *Curr Oncol* 2012;19:e244-257. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22876153>.
105. Gregory JJ, Jr., Finlay JL. Alpha-fetoprotein and beta-human chorionic gonadotropin: their clinical significance as tumour markers. *Drugs* 1999;57:463-467. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10235686>.
106. Schneider DT, Calaminus G, Reinhard H, et al. Primary mediastinal germ cell tumors in children and adolescents: results of the German cooperative protocols MAKEI 83/86, 89, and 96. *J Clin Oncol* 2000;18:832-839. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10673525>.



107. Kawai M, Furuhashi Y, Kano T, et al. Alpha-fetoprotein in malignant germ cell tumors of the ovary. *Gynecol Oncol* 1990;39:160-166. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/1699854>.

108. Yamamoto Y, Oguri H, Yamada R, et al. Preoperative evaluation of pelvic masses with combined 18F-fluorodeoxyglucose positron emission tomography and computed tomography. *Int J Gynaecol Obstet* 2008;102:124-127. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18423470>.

109. Castellucci P, Perrone AM, Picchio M, et al. Diagnostic accuracy of 18F-FDG PET/CT in characterizing ovarian lesions and staging ovarian cancer: correlation with transvaginal ultrasonography, computed tomography, and histology. *Nucl Med Commun* 2007;28:589-595. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17625380>.

110. Risum S, Hogdall C, Loft A, et al. The diagnostic value of PET/CT for primary ovarian cancer--a prospective study. *Gynecol Oncol* 2007;105:145-149. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17229460>.

111. Cannistra SA, Gershenson DM, Recht A. Ovarian cancer, fallopian tube carcinoma, and peritoneal carcinoma. In: DeVita Jr. VT, Lawrence TS, Rosenberg SA, eds. *DeVita, Hellman, and Rosenberg's Cancer: Principles & Practice of Oncology (Cancer Principles and Practice of Oncology)*, 10th ed Philadelphia: Lippincott Williams & Wilkins; 2014:1075-1099.

112. Vergote I, De Brabanter J, Fyles A, et al. Prognostic importance of degree of differentiation and cyst rupture in stage I invasive epithelial ovarian carcinoma. *Lancet* 2001;357:176-182. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11213094>.

113. Young RH. From Krukenberg to today: the ever present problems posed by metastatic tumors in the ovary. Part II. *Adv Anat Pathol* 2007;14:149-177. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17452813>.

114. Lee KR, Young RH. The distinction between primary and metastatic mucinous carcinomas of the ovary: gross and histologic findings in 50 cases. *Am J Surg Pathol* 2003;27:281-292. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12604884>.

115. Kim KA, Park CM, Lee JH, et al. Benign ovarian tumors with solid and cystic components that mimic malignancy. *AJR Am J Roentgenol* 2004;182:1259-1265. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15100129>.

116. Romagnolo C, Leon AE, Fabricio AS, et al. HE4, CA125 and risk of ovarian malignancy algorithm (ROMA) as diagnostic tools for ovarian cancer in patients with a pelvic mass: An Italian multicenter study. *Gynecol Oncol* 2016;141:303-311. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26801941>.

117. Moore RG, Miller MC, Disilvestro P, et al. Evaluation of the diagnostic accuracy of the risk of ovarian malignancy algorithm in women with a pelvic mass. *Obstet Gynecol* 2011;118:280-288. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21775843>.

118. Yoshida A, Derchain SF, Pitta DR, et al. Comparing the Copenhagen Index (CPH-I) and Risk of Ovarian Malignancy Algorithm (ROMA): Two equivalent ways to differentiate malignant from benign ovarian tumors before surgery? *Gynecol Oncol* 2016;140:481-485. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26825617>.

119. Jacob F, Meier M, Caduff R, et al. No benefit from combining HE4 and CA125 as ovarian tumor markers in a clinical setting. *Gynecol Oncol* 2011;121:487-491. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21420727>.

120. Molina R, Escudero JM, Auge JM, et al. HE4 a novel tumour marker for ovarian cancer: comparison with CA 125 and ROMA algorithm in patients with gynaecological diseases. *Tumour Biol* 2011;32:1087-1095. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21863264>.





135. The American Congress of Obstetricians and Gynecologists. Committee opinion no. 620: Salpingectomy for ovarian cancer prevention. *Obstet Gynecol* 2015;125:279-281. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25560145>.

136. Oliver Perez MR, Magrina J, Garcia AT, Jimenez Lopez JS. Prophylactic salpingectomy and prophylactic salpingoophorectomy for adnexal high-grade serous epithelial carcinoma: A reappraisal. *Surg Oncol* 2015;24:335-344. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26690823>.

137. Falconer H, Yin L, Gronberg H, Altman D. Ovarian cancer risk after salpingectomy: a nationwide population-based study. *J Natl Cancer Inst* 2015;107. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25628372>.

138. Gaitskell K, Green J, Pirie K, et al. Tubal ligation and ovarian cancer risk in a large cohort: Substantial variation by histological type. *Int J Cancer* 2016;138:1076-1084. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26378908>.

139. Hartmann LC, Lindor NM. The role of risk-reducing surgery in hereditary breast and ovarian cancer. *N Engl J Med* 2016;374:454-468. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26840135>.

140. Polcher M, Hauptmann S, Fotopoulou C, et al. Opportunistic salpingectomies for the prevention of a high-grade serous carcinoma: a statement by the Kommission Ovar of the AGO. *Arch Gynecol Obstet* 2015;292:231-234. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25914073>.

141. Erickson BK, Martin JY, Shah MM, et al. Reasons for failure to deliver National Comprehensive Cancer Network (NCCN)-adherent care in the treatment of epithelial ovarian cancer at an NCCN cancer center. *Gynecol Oncol* 2014;133:142-146. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24517876>.

142. Bristow RE, Chang J, Zogas A, et al. Impact of National Cancer Institute Comprehensive Cancer Centers on ovarian cancer treatment and survival. *J Am Coll Surg* 2015;220:940-950. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25840536>.

143. Ledermann JA, Raja FA, Fotopoulou C, et al. Newly diagnosed and relapsed epithelial ovarian carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2013;24 Suppl 6:vi24-32. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24078660>.

144. Cliby WA, Powell MA, Al-Hammadi N, et al. Ovarian cancer in the United States: contemporary patterns of care associated with improved survival. *Gynecol Oncol* 2015;136:11-17. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25449311>.

145. Schorge JO, Eisenhauer EE, Chi DS. Current surgical management of ovarian cancer. *Hematol Oncol Clin North Am* 2012;26:93-109. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22244664>.

146. Whitney CW, Spirtos N. *Gynecologic Oncology Group Surgical Procedures Manual*. Philadelphia: Gynecologic Oncology Group; 2009.

147. Schlaerth AC, Chi DS, Poynor EA, et al. Long-term survival after fertility-sparing surgery for epithelial ovarian cancer. *Int J Gynecol Cancer* 2009;19:1199-1204. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19823055>.

148. Schilder JM, Thompson AM, DePriest PD, et al. Outcome of reproductive age women with stage IA or IC invasive epithelial ovarian cancer treated with fertility-sparing therapy. *Gynecol Oncol* 2002;87:1-7. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12468335>.

149. Fader AN, Rose PG. Role of surgery in ovarian carcinoma. *J Clin Oncol* 2007;25:2873-2883. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17617518>.

150. Wright JD, Shah M, Mathew L, et al. Fertility preservation in young women with epithelial ovarian cancer. *Cancer* 2009;115:4118-4126. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19670446>.



151. Satoh T, Hatae M, Watanabe Y, et al. Outcomes of fertility-sparing surgery for stage I epithelial ovarian cancer: a proposal for patient selection. *J Clin Oncol* 2010;28:1727-1732. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20194858>.

152. Gershenson DM. Treatment of ovarian cancer in young women. *Clin Obstet Gynecol* 2012;55:65-74. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22343230>.

153. Stier EA, Barakat RR, Curtin JP, et al. Laparotomy to complete staging of presumed early ovarian cancer. *Obstet Gynecol* 1996;87:737-740. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/8677077>.

154. Chi DS, Abu-Rustum NR, Sonoda Y, et al. The safety and efficacy of laparoscopic surgical staging of apparent stage I ovarian and fallopian tube cancers. *Am J Obstet Gynecol* 2005;192:1614-1619. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15902166>.

155. Covens AL, Dodge JE, Lacchetti C, et al. Surgical management of a suspicious adnexal mass: a systematic review. *Gynecol Oncol* 2012;126:149-156. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22522189>.

156. Fagotti A, Vizzielli G, Fanfani F, et al. Introduction of staging laparoscopy in the management of advanced epithelial ovarian, tubal and peritoneal cancer: impact on prognosis in a single institution experience. *Gynecol Oncol* 2013;131:341-346. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23938372>.

157. Park JY, Kim DY, Suh DS, et al. Comparison of laparoscopy and laparotomy in surgical staging of early-stage ovarian and fallopian tubal cancer. *Ann Surg Oncol* 2008;15:2012-2019. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18437497>.

158. Liu CS, Nagarsheth NP, Nezhat FR. Laparoscopy and ovarian cancer: a paradigm change in the management of ovarian cancer? *J Minim Invasive Gynecol* 2009;16:250-262. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19321390>.

159. Mori KM, Neubauer NL. Minimally invasive surgery in gynecologic oncology. *ISRN Obstet Gynecol* 2013;2013:312982. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23997959>.

160. Brockbank EC, Harry V, Kolomainen D, et al. Laparoscopic staging for apparent early stage ovarian or fallopian tube cancer. First case series from a UK cancer centre and systematic literature review. *Eur J Surg Oncol* 2013;39:912-917. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23721765>.

161. Bristow RE, Tomacruz RS, Armstrong DK, et al. Survival effect of maximal cytoreductive surgery for advanced ovarian carcinoma during the platinum era: a meta-analysis. *J Clin Oncol* 2002;20:1248-1259. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11870167>.

162. Eisenhauer EL, Abu-Rustum NR, Sonoda Y, et al. The addition of extensive upper abdominal surgery to achieve optimal cytoreduction improves survival in patients with stages IIIC-IV epithelial ovarian cancer. *Gynecol Oncol* 2006;103:1083-1090. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16890277>.

163. du Bois A, Reuss A, Pujade-Lauraine E, et al. Role of surgical outcome as prognostic factor in advanced epithelial ovarian cancer: a combined exploratory analysis of 3 prospectively randomized phase 3 multicenter trials: by the Arbeitsgemeinschaft Gynaekologische Onkologie Studiengruppe Ovarialkarzinom (AGO-OVAR) and the Groupe d'Investigateurs Nationaux Pour les Etudes des Cancers de l'Ovaire (GINECO). *Cancer* 2009;115:1234-1244. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19189349>.

164. Schorge JO, Garrett LA, Goodman A. Cytoreductive surgery for advanced ovarian cancer: quo vadis? *Oncology (Williston Park)* 2011;25:928-934. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22010391>.

165. Bristow RE, Puri I, Chi DS. Cytoreductive surgery for recurrent ovarian cancer: a meta-analysis. *Gynecol Oncol* 2009;112:265-274. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18937969>.



166. Aletti GD, Dowdy SC, Gostout BS, et al. Aggressive surgical effort and improved survival in advanced-stage ovarian cancer. *Obstet Gynecol* 2006;107:77-85. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/16394043>.

167. Eisenhauer EL, Abu-Rustum NR, Sonoda Y, et al. The effect of maximal surgical cytoreduction on sensitivity to platinum-taxane chemotherapy and subsequent survival in patients with advanced ovarian cancer. *Gynecol Oncol* 2008;108:276-281. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/18063020>.

168. Chang SJ, Bristow RE. Evolution of surgical treatment paradigms for advanced-stage ovarian cancer: redefining 'optimal' residual disease.

*Gynecol Oncol* 2012;125:483-492. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/22366151>.

169. Elattar A, Bryant A, Winter-Roach BA, et al. Optimal primary surgical treatment for advanced epithelial ovarian cancer. *Cochrane Database Syst Rev* 2011;CD007565. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/21833960>.

170. Chi DS, Eisenhauer EL, Zivanovic O, et al. Improved progression-free and overall survival in advanced ovarian cancer as a result of a change in surgical paradigm. *Gynecol Oncol* 2009;114:26-31.

Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19395008>.

171. Rutten MJ, van Meurs HS, van de Vrie R, et al. Laparoscopy to predict the result of primary cytoreductive surgery in patients with advanced ovarian cancer: a randomized controlled trial. *J Clin Oncol* 2017;35:613-621. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/28029317>.

172. Fagotti A, Vizzielli G, De Iaco P, et al. A multicentric trial (Olympia-MITO 13) on the accuracy of laparoscopy to assess peritoneal spread in ovarian cancer. *Am J Obstet Gynecol* 2013;209:462 e461-462 e411. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/23891632>.

173. Magrina JF, Zanagnolo V, Noble BN, et al. Robotic approach for ovarian cancer: perioperative and survival results and comparison with laparoscopy and laparotomy. *Gynecol Oncol* 2011;121:100-105. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/21194736>.

174. Panici PB, Maggioni A, Hacker N, et al. Systematic aortic and pelvic lymphadenectomy versus resection of bulky nodes only in optimally debulked advanced ovarian cancer: a randomized clinical trial. *J Natl Cancer Inst* 2005;97:560-566. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/15840878>.

175. Aletti GD, Powless C, Bakkum-Gamez J, et al. Pattern of retroperitoneal dissemination of primary peritoneum cancer: basis for rational use of lymphadenectomy. *Gynecol Oncol* 2009;114:32-36.

Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19361840>.

176. Eeles RA, Morden JP, Gore M, et al. Adjuvant hormone therapy may improve survival in epithelial ovarian cancer: results of the AHT randomized trial. *J Clin Oncol* 2015;33:4138-4144. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/26417001>.

177. The American Congress of Obstetricians and Gynecologists. ACOG Practice Bulletin No. 126: Management of gynecologic issues in women with breast cancer. *Obstet Gynecol* 2012;119:666-682. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/22353976>.

178. Barton DL, Loprinzi C, Gostout B. Current management of menopausal symptoms in cancer patients. *Oncology (Williston Park)* 2002;16:67-72, 74; discussion 75-66, 79-80. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/11831612>.

179. Jenkins MR, Sikin AL. Update on nonhormonal approaches to menopausal management. *Cleve Clin J Med* 2008;75 Suppl 4:S17-24.

Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18697262>.



180. du Bois A, Reuss A, Harter P, et al. Potential role of lymphadenectomy in advanced ovarian cancer: a combined exploratory analysis of three prospectively randomized phase III multicenter trials. *J Clin Oncol* 2010;28:1733-1739. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20194855>.

181. Gourley C, Walker JL, Mackay HJ. Update on intraperitoneal chemotherapy for the treatment of epithelial ovarian cancer. *Am Soc Clin Oncol Educ Book* 2016;35:143-151. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/27249695>.

182. Armstrong DK, Bundy B, Wenzel L, et al. Intraperitoneal cisplatin and paclitaxel in ovarian cancer. *N Engl J Med* 2006;354:34-43. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16394300>.

183. Wimberger P, Lehmann N, Kimmig R, et al. Prognostic factors for complete debulking in advanced ovarian cancer and its impact on survival. An exploratory analysis of a prospectively randomized phase III study of the Arbeitsgemeinschaft Gynaekologische Onkologie Ovarian Cancer Study Group (AGO-OVAR). *Gynecol Oncol* 2007;106:69-74. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17397910>.

184. Wright AA, Bohlke K, Armstrong DK, et al. Neoadjuvant chemotherapy for newly diagnosed, advanced ovarian cancer: Society of Gynecologic Oncology and American Society of Clinical Oncology Clinical Practice Guideline. *Gynecol Oncol* 2016;143:3-15. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27650684>.

185. van Meurs HS, Taji P, Hof MH, et al. Which patients benefit most from primary surgery or neoadjuvant chemotherapy in stage IIIc or IV ovarian cancer? An exploratory analysis of the European Organisation for Research and Treatment of Cancer 55971 randomised trial. *Eur J Cancer* 2013;49:3191-3201. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23850170>.

186. Gadducci A, Cosio S, Zizioli V, et al. Patterns of recurrence and clinical outcome of patients with stage IIIc to stage IV epithelial ovarian cancer in complete response after primary debulking surgery plus chemotherapy or neoadjuvant chemotherapy followed by interval debulking surgery: an Italian Multicenter Retrospective Study. *Int J Gynecol Cancer* 2017;27:28-36. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27870700>.

187. Leary A, Cowan R, Chi D, et al. Primary surgery or neoadjuvant chemotherapy in advanced ovarian cancer: the debate continues. *Am Soc Clin Oncol Educ Book* 2016;35:153-162. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/27249696>.

188. Chi DS, Bristow RE, Armstrong DK, Karlan BY. Is the easier way ever the better way? *J Clin Oncol* 2011;29:4073-4075. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21931018>.

189. Vergote I, Trope CG, Amant F, et al. Neoadjuvant chemotherapy is the better treatment option in some patients with stage IIIc to IV ovarian cancer. *J Clin Oncol* 2011;29:4076-4078. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21931032>.

190. Rose PG, Nerenstone S, Brady MF, et al. Secondary surgical cytoreduction for advanced ovarian carcinoma. *N Engl J Med* 2004;351:2489-2497. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15590951>.

191. van der Burg ME, van Lent M, Buyse M, et al. The effect of debulking surgery after induction chemotherapy on the prognosis in advanced epithelial ovarian cancer. Gynecological Cancer Cooperative Group of the European Organization for Research and Treatment of Cancer. *N Engl J Med* 1995;332:629-634. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/7845426>.

192. Colombo PE, Mourregot A, Fabbro M, et al. Aggressive surgical strategies in advanced ovarian cancer: a monocentric study of 203 stage IIIc and IV patients. *Eur J Surg Oncol* 2009;35:135-143. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18289825>.





193. Rauh-Hain JA, Rodriguez N, Growdon WB, et al. Primary debulking surgery versus neoadjuvant chemotherapy in stage IV ovarian cancer.

Ann Surg Oncol 2012;19:959-965. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/21994038>.

194. Landrum LM, Java J, Mathews CA, et al. Prognostic factors for stage III epithelial ovarian cancer treated with intraperitoneal chemotherapy: A Gynecologic Oncology Group study. Gynecol Oncol 2013;130:12-18.

Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23578540>.

195. Morrison J, Haldar K, Kehoe S, Lawrie TA. Chemotherapy versus surgery for initial treatment in advanced ovarian epithelial cancer.

Cochrane Database Syst Rev 2012;8:CD005343. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/22895947>.

196. Vergote I, Trope CG, Amant F, et al. Neoadjuvant chemotherapy or primary surgery in stage IIIC or IV ovarian cancer. N Engl J Med 2010;363:943-953. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/20818904>.

197. Steed H, Oza AM, Murphy J, et al. A retrospective analysis of neoadjuvant platinum-based chemotherapy versus up-front surgery in advanced ovarian cancer. Int J Gynecol Cancer 2006;16 Suppl 1:47-53.

Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16515567>.

198. Tangjitgamol S, Manusirivithaya S, Laopaiboon M, Lumbiganon P. Interval debulking surgery for advanced epithelial ovarian cancer.

Cochrane Database Syst Rev 2009:CD006014. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/19160263>.

199. Tiersten AD, Liu PY, Smith HO, et al. Phase II evaluation of neoadjuvant chemotherapy and debulking followed by intraperitoneal chemotherapy in women with stage III and IV epithelial ovarian, fallopian tube or primary peritoneal cancer: Southwest Oncology Group Study S0009. Gynecol Oncol 2009;112:444-449. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/19138791>.

200. Vandenput I, Van Calster B, Capoen A, et al. Neoadjuvant chemotherapy followed by interval debulking surgery in patients with serous endometrial cancer with transperitoneal spread (stage IV): a new preferred treatment? Br J Cancer 2009;101:244-249. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/19568245>.

201. Chi DS, Musa F, Dao F, et al. An analysis of patients with bulky advanced stage ovarian, tubal, and peritoneal carcinoma treated with primary debulking surgery (PDS) during an identical time period as the randomized EORTC-NCIC trial of PDS vs neoadjuvant chemotherapy (NACT). Gynecol Oncol 2012;124:10-14. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/21917306>.

202. Mackay H, Gallagher CJ, Parulekar WR. OV21/PETROC: A randomized Gynecologic Cancer Intergroup (GCIG) phase II study of intraperitoneal (IP) versus intravenous (IV) chemotherapy following neoadjuvant chemotherapy and optimal debulking surgery in epithelial ovarian cancer (EOC) [abstract]. J Clin Oncol 2016;34:Abstract LBA5503. Available at:

203. Garcia YG, Juan AD, Mendiola C, et al. Phase II randomized trial of neoadjuvant (NA) chemotherapy (CT) with or without bevacizumab (Bev) in advanced epithelial ovarian cancer (EOC) (GEICO 1205/NOVA TRIAL) [abstract]. J Clin Oncol 2017;35:Abstract 5508-5508. Available at: [http://ascopubs.org/doi/abs/10.1200/JCO.2017.35.15\\_suppl.5508](http://ascopubs.org/doi/abs/10.1200/JCO.2017.35.15_suppl.5508).

204. Dewdney SB, Rimel BJ, Reinhart AJ, et al. The role of neoadjuvant chemotherapy in the management of patients with advanced stage ovarian cancer: survey results from members of the Society of Gynecologic Oncologists. Gynecol Oncol 2010;119:18-21. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/20673970>.

205. Mueller JJ, Zhou QC, Iasonos A, et al. Neoadjuvant chemotherapy and primary debulking surgery utilization for advanced-stage ovarian cancer at a comprehensive cancer center. Gynecol Oncol 2016;140:436-442. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/26777991>.



206. Chiva L, Lapuente F, Castellanos T, et al. What should we expect after a complete cytoreduction at the time of interval or primary debulking surgery in advanced ovarian cancer? *Ann Surg Oncol* 2016;23:1666-1673. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26714955>.

207. Young RC, Walton LA, Ellenberg SS, et al. Adjuvant therapy in stage I and stage II epithelial ovarian cancer. Results of two prospective randomized trials. *N Engl J Med* 1990;322:1021-1027. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/2181310>.

208. Winter-Roach BA, Kitchener HC, Dickinson HO. Adjuvant (post-surgery) chemotherapy for early stage epithelial ovarian cancer. *Cochrane Database Syst Rev* 2009:CD004706. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19588360>.

209. Hogberg T, Glimelius B, Nygren P, Care SB-gSCoTAiH. A systematic overview of chemotherapy effects in ovarian cancer. *Acta Oncol* 2001;40:340-360. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11441940>.

210. Cristea M, Han E, Salmon L, Morgan RJ. Practical considerations in ovarian cancer chemotherapy. *Ther Adv Med Oncol* 2010;2:175-187. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21789133>.

211. Markman M, Walker JL. Intraperitoneal chemotherapy of ovarian cancer: a review, with a focus on practical aspects of treatment. *J Clin Oncol* 2006;24:988-994. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16461779>.

212. Marth C, Walker JL, Barakat RR, et al. Results of the 2006 Innsbruck International Consensus Conference on intraperitoneal chemotherapy in patients with ovarian cancer. *Cancer* 2007;109:645-649. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17238177>.

213. Ozols RF, Bundy BN, Greer BE, et al. Phase III trial of carboplatin and paclitaxel compared with cisplatin and paclitaxel in patients with optimally resected stage III ovarian cancer: a Gynecologic Oncology Group study. *J Clin Oncol* 2003;21:3194-3200. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12860964>.

214. Vasey PA, Jayson GC, Gordon A, et al. Phase III randomized trial of docetaxel-carboplatin versus paclitaxel-carboplatin as first-line chemotherapy for ovarian carcinoma. *J Natl Cancer Inst* 2004;96:1682-1691. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15547181>.

215. Pignata S, Scambia G, Ferrandina G, et al. Carboplatin plus paclitaxel versus carboplatin plus pegylated liposomal doxorubicin as first-line treatment for patients with ovarian cancer: the MITO-2 randomized phase III trial. *J Clin Oncol* 2011;29:3628-3635. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21844495>.

216. McGuire WP, Hoskins WJ, Brady MF, et al. Cyclophosphamide and cisplatin compared with paclitaxel and cisplatin in patients with stage III and stage IV ovarian cancer. *N Engl J Med* 1996;334:1-6. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/7494563>.

217. Hershman DL, Till C, Wright JD, et al. Comorbidities and risk of chemotherapy-induced peripheral neuropathy among participants 65 years or older in Southwest Oncology Group Clinical Trials. *J Clin Oncol* 2016;34:3014-3022. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27325863>.

218. Bookman MA, Brady MF, McGuire WP, et al. Evaluation of new platinum-based treatment regimens in advanced-stage ovarian cancer: a Phase III Trial of the Gynecologic Cancer Intergroup. *J Clin Oncol* 2009;27:1419-1425. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19224846>.

219. Bell J, Brady MF, Young RC, et al. Randomized phase III trial of three versus six cycles of adjuvant carboplatin and paclitaxel in early stage epithelial ovarian carcinoma: a Gynecologic Oncology Group study. *Gynecol Oncol* 2006;102:432-439. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16860852>.





233. Walker JL, Armstrong DK, Huang HQ, et al. Intraperitoneal catheter outcomes in a phase III trial of intravenous versus intraperitoneal chemotherapy in optimal stage III ovarian and primary peritoneal cancer: a Gynecologic Oncology Group Study. *Gynecol Oncol* 2006;100:27-32. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16368440>.
234. Rowan K. Intraperitoneal therapy for ovarian cancer: why has it not become standard? *J Natl Cancer Inst* 2009;101:775-777. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19470952>.
235. Gore M, du Bois A, Vergote I. Intraperitoneal chemotherapy in ovarian cancer remains experimental. *J Clin Oncol* 2006;24:4528-4530. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17008689>.
236. Armstrong DK, Brady MF. Intraperitoneal therapy for ovarian cancer: a treatment ready for prime time. *J Clin Oncol* 2006;24:4531-4533. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17008690>.
237. Ozols RF, Bookman MA, du Bois A, et al. Intraperitoneal cisplatin therapy in ovarian cancer: comparison with standard intravenous carboplatin and paclitaxel. *Gynecol Oncol* 2006;103:1-6. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16904166>.
238. Tewari D, Java JJ, Salani R, et al. Long-term survival advantage and prognostic factors associated with intraperitoneal chemotherapy treatment in advanced ovarian cancer: a gynecologic oncology group study. *J Clin Oncol* 2015;33:1460-1466. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25800756>.
239. Gotimer KF, Bondoc C, Chalas E, Vilella JA. Self reported quality of life among patients who have undergone outpatient IP chemotherapy for ovarian cancer. *Obstet Gynecol* 2016;127 Suppl 1:4S. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/27176164>.
240. Lesnock JL, Darcy KM, Tian C, et al. BRCA1 expression and improved survival in ovarian cancer patients treated with intraperitoneal cisplatin and paclitaxel: a Gynecologic Oncology Group Study. *Br J Cancer* 2013;108:1231-1237. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23462720>.
241. Sioulas VD, Schiavone MB, Kadouri D, et al. Optimal primary management of bulky stage IIIC ovarian, fallopian tube and peritoneal carcinoma: Are the only options complete gross resection at primary debulking surgery or neoadjuvant chemotherapy? *Gynecol Oncol* 2017;145:15-20. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28238354>.
242. Boere IA, van der Burg ME. Review of dose-intense platinum and/or paclitaxel containing chemotherapy in advanced and recurrent epithelial ovarian cancer. *Curr Pharm Des* 2012;18:3741-3753. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22591417>.
243. Katsumata N, Yasuda M, Isonishi S, et al. Long-term results of dose-dense paclitaxel and carboplatin versus conventional paclitaxel and carboplatin for treatment of advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer (JGOG 3016): a randomised, controlled, open-label trial. *Lancet Oncol* 2013;14:1020-1026. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23948349>.
244. Chan JK, Brady MF, Penson RT, et al. Weekly vs. every-3-week paclitaxel and carboplatin for ovarian cancer. *N Engl J Med* 2016;374:738-748. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26933849>.
245. Burger RA, Brady MF, Rhee J, et al. Independent radiologic review of the Gynecologic Oncology Group Study 0218, a phase III trial of bevacizumab in the primary treatment of advanced epithelial ovarian, primary peritoneal, or fallopian tube cancer. *Gynecol Oncol* 2013;131:21-26. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23906656>.
246. Burger RA, Brady MF, Bookman MA, et al. Incorporation of bevacizumab in the primary treatment of ovarian cancer. *N Engl J Med* 2011;365:2473-2483. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22204724>.
247. Hall M, Gourley C, McNeish I, et al. Targeted anti-vascular therapies for ovarian cancer: current evidence. *Br J Cancer* 2013;108:250-258. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23385789>.



248. Ferriss JS, Java JJ, Bookman MA, et al. Ascites predicts treatment benefit of bevacizumab in front-line therapy of advanced epithelial ovarian, fallopian tube and peritoneal cancers: an NRG Oncology/GOG study. *Gynecol Oncol* 2015;139:17-22. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26216729>.

249. Perren TJ, Swart AM, Pfisterer J, et al. A phase 3 trial of bevacizumab in ovarian cancer. *N Engl J Med* 2011;365:2484-2496. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22204725>.

250. Oza AM, Cook AD, Pfisterer J, et al. Standard chemotherapy with or without bevacizumab for women with newly diagnosed ovarian cancer (ICON7): overall survival results of a phase 3 randomised trial. *Lancet Oncol* 2015;16:928-936. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26115797>.

251. Morgan RJ, Jr., Alvarez RD, Armstrong DK, et al. Ovarian cancer, version 3.2012. *J Natl Compr Canc Netw* 2012;10:1339-1349. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23138163>.

252. Stark D, Nankivell M, Pujade-Lauraine E, et al. Standard chemotherapy with or without bevacizumab in advanced ovarian cancer: quality-of-life outcomes from the International Collaboration on Ovarian Neoplasms (ICON7) phase 3 randomised trial. *Lancet Oncol* 2013;14:236-243. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23333117>.

253. Monk BJ, Huang HQ, Burger RA, et al. Patient reported outcomes of a randomized, placebo-controlled trial of bevacizumab in the front-line treatment of ovarian cancer: a Gynecologic Oncology Group Study. *Gynecol Oncol* 2013;128:573-578. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23219660>.

254. Friedlander ML, Stockler MR, Butow P, et al. Clinical trials of palliative chemotherapy in platinum-resistant or -refractory ovarian cancer: time to think differently? *J Clin Oncol* 2013;31:2362. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23669225>.

255. Ledermann JA, Hackshaw A, Kaye S, et al. Randomized phase II placebo-controlled trial of maintenance therapy using the oral triple angiokinase inhibitor BIBF 1120 after chemotherapy for relapsed ovarian cancer. *J Clin Oncol* 2011;29:3798-3804. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21859991>.

256. Markman M, Liu PY, Wilczynski S, et al. Phase III randomized trial of 12 versus 3 months of maintenance paclitaxel in patients with advanced ovarian cancer after complete response to platinum and paclitaxel-based chemotherapy: a Southwest Oncology Group and Gynecologic Oncology Group trial. *J Clin Oncol* 2003;21:2460-2465. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12829663>.

257. Bookman MA. Should studies of maintenance therapy be maintained in women with ovarian cancer? *J Gynecol Oncol* 2013;24:105-107. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23653825>.

258. Pecorelli S, Favalli G, Gadducci A, et al. Phase III trial of observation versus six courses of paclitaxel in patients with advanced epithelial ovarian cancer in complete response after six courses of paclitaxel/platinum-based chemotherapy: final results of the After-6 protocol 1. *J Clin Oncol* 2009;27:4642-4648. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19704064>.

259. du Bois A, Floquet A, Kim JW, et al. Incorporation of pazopanib in maintenance therapy of ovarian cancer. *J Clin Oncol* 2014;32:3374-3382. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25225436>.

260. Kim JW, Mahner S, Wu LY, et al. Pazopanib maintenance therapy in East Asian women with advanced epithelial ovarian cancer: results from AGO-OVAR16 and an East Asian study. *Int J Gynecol Cancer* 2015. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26588236>.

261. Brennan PJ, Rodriguez Bouza T, Hsu FI, et al. Hypersensitivity reactions to mAbs: 105 desensitizations in 23 patients, from evaluation to treatment. *J Allergy Clin Immunol* 2009;124:1259-1266. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19910036>.



262. Boulanger J, Boursiquot JN, Cournoyer G, et al. Management of hypersensitivity to platinum- and taxane-based chemotherapy: cepto review and clinical recommendations. *Curr Oncol* 2014;21:e630-641. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25089112>.

263. Cernadas JR, Brockow K, Romano A, et al. General considerations on rapid desensitization for drug hypersensitivity - a consensus statement. *Allergy* 2010;65:1357-1366. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20716314>.

264. Romano A, Torres MJ, Castells M, et al. Diagnosis and management of drug hypersensitivity reactions. *J Allergy Clin Immunol* 2011;127:S67-73. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21354502>.

265. Castells MC, Tennant NM, Sloane DE, et al. Hypersensitivity reactions to chemotherapy: outcomes and safety of rapid desensitization in 413 cases. *J Allergy Clin Immunol* 2008;122:574-580. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18502492>.

266. Dizon DS, Sabbatini PJ, Aghajanian C, et al. Analysis of patients with epithelial ovarian cancer or fallopian tube carcinoma retreated with cisplatin after the development of a carboplatin allergy. *Gynecol Oncol* 2002;84:378-382. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11855873>.

267. Sampson HA, Munoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: summary report--second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *Ann Emerg Med* 2006;47:373-380. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16546624>.

268. Manivannan V, Decker WW, Stead LG, et al. Visual representation of National Institute of Allergy and Infectious Disease and Food Allergy and Anaphylaxis Network criteria for anaphylaxis. *Int J Emerg Med* 2009;2:3-5. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19390910>.

269. Lenz HJ. Management and preparedness for infusion and hypersensitivity reactions. *Oncologist* 2007;12:601-609. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17522249>.

270. Gabizon AA. Pegylated liposomal doxorubicin: metamorphosis of an old drug into a new form of chemotherapy. *Cancer Invest* 2001;19:424-436. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11405181>.

271. Navo M, Kunthur A, Badell ML, et al. Evaluation of the incidence of carboplatin hypersensitivity reactions in cancer patients. *Gynecol Oncol* 2006;103:608-613. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16797060>.

272. Markman M, Zanotti K, Peterson G, et al. Expanded experience with an intradermal skin test to predict for the presence or absence of carboplatin hypersensitivity. *J Clin Oncol* 2003;21:4611-4614. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/14673050>.

273. Link MS, Berkow LC, Kudenchuk PJ, et al. Part 7: Adult Advanced Cardiovascular Life Support: 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation* 2015;132:S444-464. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26472995>.

274. Neumar RW, Shuster M, Callaway CW, et al. Part 1: Executive Summary: 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation* 2015;132:S315-367. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26472989>.

275. Simons FE, Arduzzo LR, Bilo MB, et al. 2012 Update: World Allergy Organization Guidelines for the assessment and management of anaphylaxis. *Curr Opin Allergy Clin Immunol* 2012;12:389-399. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22744267>.



276. Simons FE, Arduso LR, Bilo MB, et al. World allergy organization guidelines for the assessment and management of anaphylaxis. *World Allergy Organ J* 2011;4:13-37. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23268454>.

277. Banerji A, Lax T, Guyer A, et al. Management of hypersensitivity reactions to Carboplatin and Paclitaxel in an outpatient oncology infusion center: a 5-year review. *J Allergy Clin Immunol Pract* 2014;2:428-433. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25017531>.

278. Li Q, Cohn D, Waller A, et al. Outpatient rapid 4-step desensitization for gynecologic oncology patients with mild to low-risk, moderate hypersensitivity reactions to carboplatin/cisplatin. *Gynecol Oncol* 2014;135:90-94. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25110329>.

279. Lee CW, Matulonis UA, Castells MC. Rapid inpatient/outpatient desensitization for chemotherapy hypersensitivity: standard protocol effective in 57 patients for 255 courses. *Gynecol Oncol* 2005;99:393-399. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16054201>.

280. Lee CW, Matulonis UA, Castells MC. Carboplatin hypersensitivity: a 6-h 12-step protocol effective in 35 desensitizations in patients with gynecological malignancies and mast cell/IgE-mediated reactions. *Gynecol Oncol* 2004;95:370-376. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15491759>.

281. Markman M, Hsieh F, Zanotti K, et al. Initial experience with a novel desensitization strategy for carboplatin-associated hypersensitivity reactions: carboplatin-hypersensitivity reactions. *J Cancer Res Clin Oncol* 2004;130:25-28. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/14564516>.

282. Jerzak KJ, Deghan Manshadi S, Ng P, et al. Prevention of carboplatin-induced hypersensitivity reactions in women with ovarian cancer. *J Oncol Pharm Pract* 2016. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27856924>.

283. O'Cearbhaill R, Zhou Q, Iasonos A, et al. The prophylactic conversion to an extended infusion schedule and use of premedication to prevent hypersensitivity reactions in ovarian cancer patients during carboplatin retreatment. *Gynecol Oncol* 2010;116:326-331. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19944454>.

284. Gomez R, Harter P, Luck HJ, et al. Carboplatin hypersensitivity: does introduction of skin test and desensitization reliably predict and avoid the problem? A prospective single-center study. *Int J Gynecol Cancer* 2009;19:1284-1287. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19823066>.

285. Patil SU, Long AA, Ling M, et al. A protocol for risk stratification of patients with carboplatin-induced hypersensitivity reactions. *J Allergy Clin Immunol* 2012;129:443-447. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22099941>.

286. Corn BW, Lanciano RM, Boente M, et al. Recurrent ovarian cancer. Effective radiotherapeutic palliation after chemotherapy failure. *Cancer* 1994;74:2979-2983. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/7525039>.

287. Tinger A, Waldron T, Peluso N, et al. Effective palliative radiation therapy in advanced and recurrent ovarian carcinoma. *Int J Radiat Oncol Biol Phys* 2001;51:1256-1263. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11728685>.

288. Smith SC, Koh WJ. Palliative radiation therapy for gynaecological malignancies. *Best Pract Res Clin Obstet Gynaecol* 2001;15:265-278. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11358401>.

289. Yan J, Milosevic M, Fyles A, et al. A hypofractionated radiotherapy regimen (0-7-21) for advanced gynaecological cancer patients. *Clin Oncol (R Coll Radiol)* 2011;23:476-481. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21482082>.



290. Teckie S, Makker V, Tabar V, et al. Radiation therapy for epithelial ovarian cancer brain metastases: clinical outcomes and predictors of survival. *Radiat Oncol* 2013;8:36. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23414446>.

291. Huffman LB, Hartenbach EM, Carter J, et al. Maintaining sexual health throughout gynecologic cancer survivorship: A comprehensive review and clinical guide. *Gynecol Oncol* 2016;140:359-368. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26556768>.

292. Brand AH, Do V, Stenlake A. Can an educational intervention improve compliance with vaginal dilator use in patients treated with radiation for a gynecological malignancy? *Int J Gynecol Cancer* 2012;22:897-904. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22552831>.

293. Nishino M, Jagannathan JP, Ramaiya NH, Van den Abbeele AD. Revised RECIST guideline version 1.1: What oncologists want to know and what radiologists need to know. *AJR Am J Roentgenol* 2010;195:281-289. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20651182>.

294. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009;45:228-247. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19097774>.

295. Lu KH, Wood ME, Daniels M, et al. American Society of Clinical Oncology Expert Statement: collection and use of a cancer family history for oncology providers. *J Clin Oncol* 2014;32:833-840. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24493721>.

296. Moyer VA, Force USPST. Risk assessment, genetic counseling, and genetic testing for BRCA-related cancer in women: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med* 2014;160:271-281. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24366376>.

297. Fulham MJ, Carter J, Baldey A, et al. The impact of PET-CT in suspected recurrent ovarian cancer: A prospective multi-centre study as part of the Australian PET Data Collection Project. *Gynecol Oncol* 2009;112:462-468. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19150121>.

298. Risum S, Hogdall C, Markova E, et al. Influence of 2-(18F) fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography on recurrent ovarian cancer diagnosis and on selection of patients for secondary cytoreductive surgery. *Int J Gynecol Cancer* 2009;19:600-604. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19509556>.

299. Salani R, Backes FJ, Fung MF, et al. Posttreatment surveillance and diagnosis of recurrence in women with gynecologic malignancies: Society of Gynecologic Oncologists recommendations. *Am J Obstet Gynecol* 2011;204:466-478. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21752752>.

300. Bhosale P, Peungjesada S, Wei W, et al. Clinical utility of positron emission tomography/computed tomography in the evaluation of suspected recurrent ovarian cancer in the setting of normal CA-125 levels. *Int J Gynecol Cancer* 2010;20:936-944. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20683399>.

301. Rustin GJ, van der Burg ME, Griffin CL, et al. Early versus delayed treatment of relapsed ovarian cancer (MRC OV05/EORTC 55955): a randomised trial. *Lancet* 2010;376:1155-1163. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20888993>.

302. Rustin G, van der Burg M, Griffin C, et al. Early versus delayed treatment of relapsed ovarian cancer. *Lancet* 2011;377:380-381. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21277438>.

303. Miller RE, Rustin GJ. How to follow-up patients with epithelial ovarian cancer. *Curr Opin Oncol* 2010;22:498-502. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20498597>.





304. Markman M, Petersen J, Belland A, Burg K. CA-125 monitoring in ovarian cancer: patient survey responses to the results of the MRC/EORTC CA-125 Surveillance Trial. *Oncology* 2010;78:1-2. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20215782>.

305. Morris RT, Monk BJ. Ovarian cancer: relevant therapy, not timing, is paramount. *Lancet* 2010;376:1120-1122. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20888975>.

306. Karam AK, Karlan BY. Ovarian cancer: the duplicity of CA125 measurement. *Nat Rev Clin Oncol* 2010;7:335-339. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20368726>.

307. Bast RC, Jr. CA 125 and the detection of recurrent ovarian cancer: a reasonably accurate biomarker for a difficult disease. *Cancer* 2010;116:2850-2853. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20564390>.

308. Lindemann K, Kristensen G, Mirza MR, et al. Poor concordance between CA-125 and RECIST at the time of disease progression in patients with platinum-resistant ovarian cancer: analysis of the AURELIA trial. *Ann Oncol* 2016;27:1505-1510. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27407100>.

309. Hatch KD, Beecham JB, Blessing JA, Creasman WT. Responsiveness of patients with advanced ovarian carcinoma to tamoxifen. A Gynecologic Oncology Group study of second-line therapy in 105 patients. *Cancer* 1991;68:269-271. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/2070324>.

310. Van Der Velden J, Gitsch G, Wain GV, et al. Tamoxifen in patients with advanced epithelial ovarian cancer. *Int J Gynecol Cancer* 1995;5:301-305. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11578494>.

311. Markman M, Webster K, Zanotti K, et al. Use of tamoxifen in asymptomatic patients with recurrent small-volume ovarian cancer. *Gynecol Oncol* 2004;93:390-393. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15099951>.

312. Griffiths RW, Zee YK, Evans S, et al. Outcomes after multiple lines of chemotherapy for platinum-resistant epithelial cancers of the ovary, peritoneum, and fallopian tube. *Int J Gynecol Cancer* 2011;21:58-65. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21178570>.

313. Rodriguez-Freixinos V, Mackay HJ, Karakasis K, Oza AM. Current and emerging treatment options in the management of advanced ovarian cancer. *Expert Opin Pharmacother* 2016;17:1063-1076. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26918413>.

314. An MW, Han Y, Meyers JP, et al. Clinical utility of metrics based on tumor measurements in phase II trials to predict overall survival outcomes in phase III trials by using resampling methods. *J Clin Oncol* 2015;33:4048-4057. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26503199>.

315. Markman M, Blessing J, Rubin SC, et al. Phase II trial of weekly paclitaxel (80 mg/m<sup>2</sup>) in platinum and paclitaxel-resistant ovarian and primary peritoneal cancers: a Gynecologic Oncology Group study. *Gynecol Oncol* 2006;101:436-440. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16325893>.

316. Sharma R, Graham J, Mitchell H, et al. Extended weekly dose-dense paclitaxel/carboplatin is feasible and active in heavily pre-treated platinum-resistant recurrent ovarian cancer. *Br J Cancer* 2009;100:707-712. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19223898>.

317. Markman M, Rothman R, Hakes T, et al. Second-line platinum therapy in patients with ovarian cancer previously treated with cisplatin. *J Clin Oncol* 1991;9:389-393. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/1999708>.

318. Fung-Kee-Fung M, Oliver T, Elit L, et al. Optimal chemotherapy treatment for women with recurrent ovarian cancer. *Curr Oncol* 2007;14:195-208. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17938703>.



319. Parmar MK, Ledermann JA, Colombo N, et al. Paclitaxel plus platinum-based chemotherapy versus conventional platinum-based chemotherapy in women with relapsed ovarian cancer: the ICON4/AGO-OVAR-2.2 trial. *Lancet* 2003;361:2099-2106. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12826431>.

320. Raja FA, Counsell N, Colombo N, et al. Platinum versus platinum-combination chemotherapy in platinum-sensitive recurrent ovarian cancer: a meta-analysis using individual patient data. *Ann Oncol* 2013;24:3028-3034. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24190964>.

321. Courtney A, Nemcek AA, Jr., Rosenberg S, et al. Prospective evaluation of the PleurX catheter when used to treat recurrent ascites associated with malignancy. *J Vasc Interv Radiol* 2008;19:1723-1731. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18951041>.

322. Iyengar TD, Herzog TJ. Management of symptomatic ascites in recurrent ovarian cancer patients using an intra-abdominal semi-permanent catheter. *Am J Hosp Palliat Care* 2002;19:35-38. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12171424>.

323. Brooks RA, Herzog TJ. Long-term semi-permanent catheter use for the palliation of malignant ascites. *Gynecol Oncol* 2006;101:360-362. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16499957>.

324. White J, Carolan-Rees G. PleurX peritoneal catheter drainage system for vacuum-assisted drainage of treatment-resistant, recurrent malignant ascites: a NICE Medical Technology Guidance. *Appl Health Econ Health Policy* 2012;10:299-308. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22779402>.

325. Roeland E, von Gunten CF. Current concepts in malignant bowel obstruction management. *Curr Oncol Rep* 2009;11:298-303. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19508835>.

326. Baron TH. Interventional palliative strategies for malignant bowel obstruction. *Curr Oncol Rep* 2009;11:293-297. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19508834>.

327. Salani R, Santillan A, Zahurak ML, et al. Secondary cytoreductive surgery for localized, recurrent epithelial ovarian cancer: analysis of prognostic factors and survival outcome. *Cancer* 2007;109:685-691. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17219441>.

328. Harter P, Heitz F, Mahner S, et al. Surgical intervention in relapsed ovarian cancer is beneficial: pro. *Ann Oncol* 2013;24 Suppl 10:x33-34. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24265400>.

329. Schorge JO, Wingo SN, Bhore R, et al. Secondary cytoreductive surgery for recurrent platinum-sensitive ovarian cancer. *Int J Gynaecol Obstet* 2010;108:123-127. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19892337>.

330. Shih KK, Chi DS. Maximal cytoreductive effort in epithelial ovarian cancer surgery. *J Gynecol Oncol* 2010;21:75-80. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20613895>.

331. Eisenkop SM, Friedman RL, Spirtos NM. The role of secondary cytoreductive surgery in the treatment of patients with recurrent epithelial ovarian carcinoma. *Cancer* 2000;88:144-153. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10618617>.

332. Onda T, Yoshikawa H, Yasugi T, et al. Secondary cytoreductive surgery for recurrent epithelial ovarian carcinoma: proposal for patients selection. *Br J Cancer* 2005;92:1026-1032. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15770211>.

333. Chi DS, McCaughty K, Diaz JP, et al. Guidelines and selection criteria for secondary cytoreductive surgery in patients with recurrent, platinum-sensitive epithelial ovarian carcinoma. *Cancer* 2006;106:1933-1939. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16572412>.

334. Matsuo K, Eno ML, Im DD, et al. Clinical relevance of extent of extreme drug resistance in epithelial ovarian carcinoma. *Gynecol Oncol* 2010;116:61-65. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19840886>.



335. Karam AK, Chiang JW, Fung E, et al. Extreme drug resistance assay results do not influence survival in women with epithelial ovarian cancer. *Gynecol Oncol* 2009;114:246-252. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19500821>.

336. Burstein HJ, Mangu PB, Somerfield MR, et al. American Society of Clinical Oncology clinical practice guideline update on the use of chemotherapy sensitivity and resistance assays. *J Clin Oncol* 2011;29:3328-3330. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21788567>.

337. Rose PG. Gemcitabine reverses platinum resistance in platinum-resistant ovarian and peritoneal carcinoma. *Int J Gynecol Cancer* 2005;15 Suppl 1:18-22. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15839954>.

338. Pfisterer J, Plante M, Vergote I, et al. Gemcitabine plus carboplatin compared with carboplatin in patients with platinum-sensitive recurrent ovarian cancer: an intergroup trial of the AGO-OVAR, the NCIC CTG, and the EORTC GCG. *J Clin Oncol* 2006;24:4699-4707. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16966687>.

339. Lawrie TA, Bryant A, Cameron A, et al. Pegylated liposomal doxorubicin for relapsed epithelial ovarian cancer. *Cochrane Database Syst Rev* 2013;7:CD006910. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23835762>.

340. Wagner U, Marth C, Largillier R, et al. Final overall survival results of phase III GCIG CALYPSO trial of pegylated liposomal doxorubicin and carboplatin vs paclitaxel and carboplatin in platinum-sensitive ovarian cancer patients. *Br J Cancer* 2012;107:588-591. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22836511>.

341. Pujade-Lauraine E, Wagner U, Aavall-Lundqvist E, et al. Pegylated liposomal doxorubicin and carboplatin compared with paclitaxel and carboplatin for patients with platinum-sensitive ovarian cancer in late relapse. *J Clin Oncol* 2010;28:3323-3329. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20498395>.

342. Strauss HG, Henze A, Teichmann A, et al. Phase II trial of docetaxel and carboplatin in recurrent platinum-sensitive ovarian, peritoneal and tubal cancer. *Gynecol Oncol* 2007;104:612-616. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17069876>.

343. Kushner DM, Connor JP, Sanchez F, et al. Weekly docetaxel and carboplatin for recurrent ovarian and peritoneal cancer: a phase II trial. *Gynecol Oncol* 2007;105:358-364. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17258800>.

344. Gladieff L, Ferrero A, De Rauglaudre G, et al. Carboplatin and pegylated liposomal doxorubicin versus carboplatin and paclitaxel in partially platinum-sensitive ovarian cancer patients: results from a subset analysis of the CALYPSO phase III trial. *Ann Oncol* 2012;23:1185-1189. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21976386>.

345. Gibson JM, Alzghari S, Ahn C, et al. The role of pegylated liposomal doxorubicin in ovarian cancer: a meta-analysis of randomized clinical trials. *Oncologist* 2013;18:1022-1031. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23881990>.

346. Staropoli N, Ciliberto D, Botta C, et al. Pegylated liposomal doxorubicin in the management of ovarian cancer: a systematic review and metaanalysis of randomized trials. *Cancer Biol Ther* 2014;15:707-720. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24658024>.

347. Mahner S, Meier W, du Bois A, et al. Carboplatin and pegylated liposomal doxorubicin versus carboplatin and paclitaxel in very platinum-sensitive ovarian cancer patients: results from a subset analysis of the CALYPSO phase III trial. *Eur J Cancer* 2015;51:352-358. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25534295>.

348. Benigno BB, Burrell MO, Daugherty P, Hernandez P. A phase II nonrandomized study of nab-paclitaxel plus carboplatin in patients with recurrent platinum-sensitive ovarian or primary peritoneal cancer [abstract]. *J Clin Oncol* 2010;28:Abstract 5011. Available at: [http://ascopubs.org/doi/abs/10.1200/jco.2010.28.15\\_suppl.5011](http://ascopubs.org/doi/abs/10.1200/jco.2010.28.15_suppl.5011).



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## Ovarian Cancer

349. Maurer K, Michener C, Mahdi H, Rose PG. Universal tolerance of nab-paclitaxel for gynecologic malignancies in patients with prior taxane hypersensitivity reactions. *J Gynecol Oncol* 2017;28:e38. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28541630>.

350. Pignata S, Lorusso D, Scambia G, et al. Pazopanib plus weekly paclitaxel versus weekly paclitaxel alone for platinum-resistant or platinum-refractory advanced ovarian cancer (MITO 11): a randomised, open-label, phase 2 trial. *Lancet Oncol* 2015;16:561-568. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25882986>.

351. Elit L, Hirte H. Palliative systemic therapy for women with recurrent epithelial ovarian cancer: current options. *Onco Targets Ther* 2013;6:107-118. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23459506>.

352. Gordon AN, Tonda M, Sun S, Rackoff W. Long-term survival advantage for women treated with pegylated liposomal doxorubicin compared with topotecan in a phase 3 randomized study of recurrent and refractory epithelial ovarian cancer. *Gynecol Oncol* 2004;95:1-8. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15385103>.

353. Ferrandina G, Ludovisi M, Lorusso D, et al. Phase III trial of gemcitabine compared with pegylated liposomal doxorubicin in progressive or recurrent ovarian cancer. *J Clin Oncol* 2008;26:890-896. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18281662>.

354. Mutch DG, Orlando M, Goss T, et al. Randomized phase III trial of gemcitabine compared with pegylated liposomal doxorubicin in patients with platinum-resistant ovarian cancer. *J Clin Oncol* 2007;25:2811-2818. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17602086>.

355. Markman M. Pegylated liposomal doxorubicin: appraisal of its current role in the management of epithelial ovarian cancer. *Cancer Manag Res* 2011;3:219-225. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21792330>.

356. Rose PG, Blessing JA, Mayer AR, Homesley HD. Prolonged oral etoposide as second-line therapy for platinum-resistant and platinum-sensitive ovarian carcinoma: a Gynecologic Oncology Group study. *J Clin Oncol* 1998;16:405-410. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9469322>.

357. Rose PG, Blessing JA, Ball HG, et al. A phase II study of docetaxel in paclitaxel-resistant ovarian and peritoneal carcinoma: a Gynecologic Oncology Group study. *Gynecol Oncol* 2003;88:130-135. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12586591>.

358. Miller DS, Blessing JA, Krasner CN, et al. Phase II evaluation of pemetrexed in the treatment of recurrent or persistent platinum-resistant ovarian or primary peritoneal carcinoma: a study of the Gynecologic Oncology Group. *J Clin Oncol* 2009;27:2686-2691. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19332726>.

359. Sehouli J, Stengel D, Harter P, et al. Topotecan weekly versus conventional 5-day schedule in patients with platinum-resistant ovarian cancer: a randomized multicenter phase II trial of the North-Eastern German Society of Gynecological Oncology Ovarian Cancer Study Group. *J Clin Oncol* 2011;29:242-248. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21115872>.

360. Herzog TJ, Sill MW, Walker JL, et al. A phase II study of two topotecan regimens evaluated in recurrent platinum-sensitive ovarian, fallopian tube or primary peritoneal cancer: a Gynecologic Oncology Group Study (GOG 146Q). *Gynecol Oncol* 2011;120:454-458. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21168198>.

361. Friedlander ML, Stockler M, O'Connell R, et al. Symptom burden and outcomes of patients with platinum resistant/refractory recurrent ovarian cancer: a reality check: results of stage 1 of the gynecologic cancer intergroup symptom benefit study. *Int J Gynecol Cancer* 2014;24:857-864. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24844219>.



362. Matsumoto K, Katsumata N, Yamanaka Y, et al. The safety and efficacy of the weekly dosing of irinotecan for platinum- and taxanes-resistant epithelial ovarian cancer. *Gynecol Oncol* 2006;100:412-416. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16298422>.

363. Bolis G, D'Incalci M, Gramellini F, Mangioni C. Adriamycin in ovarian cancer patients resistant to cyclophosphamide. *Eur J Cancer* 1978;14:1401-1402. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/738344>.

364. de Palo GM, de Lena M, Di Re F, et al. Melphalan versus adriamycin in the treatment of advanced carcinoma of the ovary. *Surg Gynecol Obstet* 1975;141:899-902. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/1103333>.

365. Dieras V, Bougnoux P, Petit T, et al. Multicentre phase II study of oxaliplatin as a single-agent in cisplatin/carboplatin +/- taxane-pretreated ovarian cancer patients. *Ann Oncol* 2002;13:258-266. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11886003>.

366. Hubbard SM, Barkes P, Young RC. Adriamycin therapy for advanced ovarian carcinoma recurrent after chemotherapy. *Cancer Treat Rep* 1978;62:1375-1377. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/688281>.

367. Teneriello MG, Tseng PC, Crozier M, et al. Phase II evaluation of nanoparticle albumin-bound paclitaxel in platinum-sensitive patients with recurrent ovarian, peritoneal, or fallopian tube cancer. *J Clin Oncol* 2009;27:1426-1431. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19224848>.

368. Rothenberg ML, Liu PY, Wilczynski S, et al. Phase II trial of vinorelbine for relapsed ovarian cancer: a Southwest Oncology Group study. *Gynecol Oncol* 2004;95:506-512. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15581954>.

369. Bajetta E, Di Leo A, Biganzoli L, et al. Phase II study of vinorelbine in patients with pretreated advanced ovarian cancer: activity in platinum-resistant disease. *J Clin Oncol* 1996;14:2546-2551. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/8823334>.

370. Alberts DS, Jiang C, Liu PY, et al. Long-term follow-up of a phase II trial of oral altretamine for consolidation of clinical complete remission in women with stage III epithelial ovarian cancer in the Southwest Oncology Group. *Int J Gynecol Cancer* 2004;14:224-228. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15086720>.

371. Markman M, Hakes T, Reichman B, et al. Ifosfamide and mesna in previously treated advanced epithelial ovarian cancer: activity in platinum-resistant disease. *J Clin Oncol* 1992;10:243-248. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/1732425>.

372. Ferrandina G, Ludovisi M, De Vincenzo R, et al. Docetaxel and oxaliplatin in the second-line treatment of platinum-sensitive recurrent ovarian cancer: a phase II study. *Ann Oncol* 2007;18:1348-1353. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17470449>.

373. Wolf JK, Bodurka DC, Verschraegen C, et al. A phase II trial of oral capecitabine in patients with platinum--and taxane--refractory ovarian, fallopian tube, or peritoneal cancer. *Gynecol Oncol* 2006;102:468-474. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16516276>.

374. Wadler S, Yeap B, Vogl S, Carbone P. Randomized trial of initial therapy with melphalan versus cisplatin-based combination chemotherapy in patients with advanced ovarian carcinoma: initial and long term results--Eastern Cooperative Oncology Group Study E2878. *Cancer* 1996;77:733-742. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/8616766>.

375. Yokoyama Y, Mizunuma H. Recurrent epithelial ovarian cancer and hormone therapy. *World J Clin Cases* 2013;1:187-190. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24303498>.



376. Markman M, Iseminger KA, Hatch KD, et al. Tamoxifen in platinum-refractory ovarian cancer: a Gynecologic Oncology Group Ancillary Report. *Gynecol Oncol* 1996;62:4-6. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/8690289>.

377. Rao GG, Miller DS. Hormonal therapy in epithelial ovarian cancer. *Expert Rev Anticancer Ther* 2006;6:43-47. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16375643>.

378. Papadimitriou CA, Markaki S, Siapkarakas J, et al. Hormonal therapy with letrozole for relapsed epithelial ovarian cancer. Long-term results of a phase II study. *Oncology* 2004;66:112-117. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15138362>.

379. Bowman A, Gabra H, Langdon SP, et al. CA125 response is associated with estrogen receptor expression in a phase II trial of letrozole in ovarian cancer: identification of an endocrine-sensitive subgroup. *Clin Cancer Res* 2002;8:2233-2239. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12114425>.

380. del Carmen MG, Fuller AF, Matulonis U, et al. Phase II trial of anastrozole in women with asymptomatic mullerian cancer. *Gynecol Oncol* 2003;91:596-602. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/14675683>.

381. Ramirez PT, Schmeler KM, Milam MR, et al. Efficacy of letrozole in the treatment of recurrent platinum- and taxane-resistant high-grade cancer of the ovary or peritoneum. *Gynecol Oncol* 2008;110:56-59. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18457865>.

382. Hamanishi J, Mandai M, Ikeda T, et al. Safety and antitumor activity of anti-PD-1 antibody, nivolumab, in patients with platinum-resistant ovarian cancer. *J Clin Oncol* 2015;33:4015-4022. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26351349>.

383. Friedlander M, Hancock KC, Rischin D, et al. A phase II, open-label study evaluating pazopanib in patients with recurrent ovarian cancer. *Gynecol Oncol* 2010;119:32-37. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20584542>.

384. Burger RA, Sill MW, Monk BJ, et al. Phase II trial of bevacizumab in persistent or recurrent epithelial ovarian cancer or primary peritoneal cancer: a Gynecologic Oncology Group Study. *J Clin Oncol* 2007;25:5165-5171. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18024863>.

385. Emile G, Chauvenet L, Tigaud JM, et al. A clinical experience of single agent bevacizumab in relapsing ovarian cancer. *Gynecol Oncol* 2013;129:459-462. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23474345>.

386. Bidus MA, Webb JC, Seidman JD, et al. Sustained response to bevacizumab in refractory well-differentiated ovarian neoplasms. *Gynecol Oncol* 2006;102:5-7. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16697451>.

387. Wright JD, Hagemann A, Rader JS, et al. Bevacizumab combination therapy in recurrent, platinum-refractory, epithelial ovarian carcinoma: A retrospective analysis. *Cancer* 2006;107:83-89. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16736514>.

388. Simpkins F, Belinson JL, Rose PG. Avoiding bevacizumab related gastrointestinal toxicity for recurrent ovarian cancer by careful patient screening. *Gynecol Oncol* 2007;107:118-123. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17658587>.

389. Pujade-Lauraine E, Hilpert F, Weber B, et al. Bevacizumab combined with chemotherapy for platinum-resistant recurrent ovarian cancer: The AURELIA open-label randomized phase III trial. *J Clin Oncol* 2014;32:1302-1308. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24637997>.

390. Burger RA, Brady MF, Bookman MA, et al. Risk factors for GI adverse events in a phase III randomized trial of bevacizumab in first-line therapy of advanced ovarian cancer: A Gynecologic Oncology Group Study. *J Clin Oncol* 2014;32:1210-1217. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24637999>.



391. Aghajanian C, Blank SV, Goff BA, et al. OCEANS: a randomized, double-blind, placebo-controlled phase III trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer. *J Clin Oncol* 2012;30:2039-2045. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22529265>.

392. Stockler MR, Hilpert F, Friedlander M, et al. Patient-reported outcome results from the open-label phase III AURELIA trial evaluating bevacizumab-containing therapy for platinum-resistant ovarian cancer. *J Clin Oncol* 2014;32:1309-1316. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24687829>.

393. Aghajanian C, Goff B, Nycum LR, et al. Final overall survival and safety analysis of OCEANS, a phase 3 trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent ovarian cancer. *Gynecol Oncol* 2015;139:10-16. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26271155>.

394. Coleman RL, Brady MF, Herzog TJ, et al. Bevacizumab and paclitaxel-carboplatin chemotherapy and secondary cytoreduction in recurrent, platinum-sensitive ovarian cancer (NRG Oncology/Gynecologic Oncology Group study GOG-0213): a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol* 2017;18:779-791. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28438473>.

395. Suh DH, Lee KH, Kim K, et al. Major clinical research advances in gynecologic cancer in 2014. *J Gynecol Oncol* 2015;26:156-167. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25872896>.

396. Gelmon KA, Tischkowitz M, Mackay H, et al. Olaparib in patients with recurrent high-grade serous or poorly differentiated ovarian carcinoma or triple-negative breast cancer: a phase 2, multicentre, open-label, non-randomised study. *Lancet Oncol* 2011;12:852-861. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21862407>.

397. Audeh MW, Carmichael J, Penson RT, et al. Oral poly(ADP-ribose) polymerase inhibitor olaparib in patients with BRCA1 or BRCA2 mutations and recurrent ovarian cancer: a proof-of-concept trial. *Lancet* 2010;376:245-251. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20609468>.

398. Fong PC, Yap TA, Boss DS, et al. Poly(ADP)-ribose polymerase inhibition: frequent durable responses in BRCA carrier ovarian cancer correlating with platinum-free interval. *J Clin Oncol* 2010;28:2512-2519. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20406929>.

399. Ledermann J, Harter P, Gourley C, et al. Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer. *N Engl J Med* 2012;366:1382-1392. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22452356>.

400. Kaufman B, Shapira-Frommer R, Schmutzler RK, et al. Olaparib monotherapy in patients with advanced cancer and a germline BRCA1/2 mutation. *J Clin Oncol* 2015;33:244-250. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25366685>.

401. Butler T, Maravent S, Boisselle J, et al. A review of 2014 cancer drug approvals, with a look at 2015 and beyond. *P T* 2015;40:191-205. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25798040>.

402. Deeks ED. Olaparib: first global approval. *Drugs* 2015;75:231-240. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25616434>.

403. Kim G, Ison G, McKee AE, et al. FDA approval summary: olaparib monotherapy in patients with deleterious germline BRCA-mutated advanced ovarian cancer treated with three or more lines of chemotherapy. *Clin Cancer Res* 2015;21:4257-4261. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26187614>.



404. Pujade-Lauraine E, Ledermann JA, Selle F, et al. Olaparib tablets as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a BRCA1/2 mutation (SOLO2/ENGOT-Ov21): a double-blind, randomised, placebo-controlled, phase 3 trial. *Lancet Oncol* 2017;18:1274-1284. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28754483>.

405. Kristeleit R, Shapiro GI, Burris HA, et al. A phase I-II study of the oral PARP inhibitor rucaparib in patients with germline BRCA1/2-mutated ovarian carcinoma or other solid tumors. *Clin Cancer Res* 2017;23:4095-4106. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28264872>.

406. Swisher EM, Lin KK, Oza AM, et al. Rucaparib in relapsed, platinum-sensitive high-grade ovarian carcinoma (ARIEL2 Part 1): an international, multicentre, open-label, phase 2 trial. *Lancet Oncol* 2017;18:75-87. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27908594>.

407. Balasubramaniam S, Beaver JA, Horton S, et al. FDA Approval Summary: Rucaparib for the treatment of patients with deleterious BRCA mutation-associated advanced ovarian cancer. *Clin Cancer Res* 2017. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28751443>.

408. Mirza MR, Monk BJ, Herrstedt J, et al. Niraparib maintenance therapy in platinum-sensitive, recurrent ovarian cancer. *N Engl J Med* 2016;375:2154-2164. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27717299>.

409. Scott LJ. Niraparib: first global approval. *Drugs* 2017;77:1029-1034. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28474297>.

410. Fischerova D, Zikan M, Dunder P, Cibula D. Diagnosis, treatment, and follow-up of borderline ovarian tumors. *Oncologist* 2012;17:1515-1533. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23024155>.

411. Ayhan A, Celik H, Taskiran C, et al. Oncologic and reproductive outcome after fertility-saving surgery in ovarian cancer. *Eur J Gynaecol Oncol* 2003;24:223-232. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12807228>.

412. Zanetta G, Bonazzi C, Cantu M, et al. Survival and reproductive function after treatment of malignant germ cell ovarian tumors. *J Clin Oncol* 2001;19:1015-1020. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11181664>.

413. Lee SJ, Schover LR, Partridge AH, et al. American Society of Clinical Oncology recommendations on fertility preservation in cancer patients. *J Clin Oncol* 2006;24:2917-2931. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16651642>.

414. Lai CH, Chang TC, Hsueh S, et al. Outcome and prognostic factors in ovarian germ cell malignancies. *Gynecol Oncol* 2005;96:784-791. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15721426>.

415. McCluggage WG, Judge MJ, Clarke BA, et al. Data set for reporting of ovary, fallopian tube and primary peritoneal carcinoma: recommendations from the International Collaboration on Cancer Reporting (ICCR). *Mod Pathol* 2015;28:1101-1122. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26089092>.

416. Okamoto A, Glasspool RM, Mabuchi S, et al. Gynecologic Cancer InterGroup (GCIG) consensus review for clear cell carcinoma of the ovary. *Int J Gynecol Cancer* 2014;24:S20-25. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25341576>.

417. Magazzino F, Katsaros D, Ottaiano A, et al. Surgical and medical treatment of clear cell ovarian cancer: results from the multicenter Italian Trials in Ovarian Cancer (MITO) 9 retrospective study. *Int J Gynecol Cancer* 2011;21:1063-1070. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21633300>.





418. Prendergast EN, Holzapfel M, Mueller JJ, et al. Three versus six cycles of adjuvant platinum-based chemotherapy in early stage clear cell ovarian carcinoma - A multi-institutional cohort. *Gynecol Oncol* 2017;144:274-278. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27979319>.

419. Massad LS, Gao F, Hagemann I, Powell M. Clinical outcomes among women with mucinous adenocarcinoma of the ovary. *Gynecol Obstet Invest* 2016;81:411-415. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26583769>.

420. Bruls J, Simons M, Overbeek LI, et al. A national population-based study provides insight in the origin of malignancies metastatic to the ovary. *Virchows Arch* 2015;467:79-86. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25894432>.

421. McCluggage WG, Wilkinson N. Metastatic neoplasms involving the ovary: a review with an emphasis on morphological and immunohistochemical features. *Histopathology* 2005;47:231-247. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16115224>.

422. de Waal YR, Thomas CM, Oei AL, et al. Secondary ovarian malignancies: frequency, origin, and characteristics. *Int J Gynecol Cancer* 2009;19:1160-1165. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19823050>.

423. Sato S, Itamochi H, Kigawa J, et al. Combination chemotherapy of oxaliplatin and 5-fluorouracil may be an effective regimen for mucinous adenocarcinoma of the ovary: a potential treatment strategy. *Cancer Sci* 2009;100:546-551. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19154404>.

424. Madore J, Ren F, Filali-Mouhim A, et al. Characterization of the molecular differences between ovarian endometrioid carcinoma and ovarian serous carcinoma. *J Pathol* 2010;220:392-400. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19967725>.

425. Mackay HJ, Brady MF, Oza AM, et al. Prognostic relevance of uncommon ovarian histology in women with stage III/IV epithelial ovarian cancer. *Int J Gynecol Cancer* 2010;20:945-952. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20683400>.

426. Bodurka DC, Deavers MT, Tian C, et al. Reclassification of serous ovarian carcinoma by a 2-tier system: a Gynecologic Oncology Group Study. *Cancer* 2012;118:3087-3094. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22072418>.

427. Gershenson DM, Sun CC, Iyer RB, et al. Hormonal therapy for recurrent low-grade serous carcinoma of the ovary or peritoneum. *Gynecol Oncol* 2012;125:661-666. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22406638>.

428. Gershenson DM, Bodurka DC, Coleman RL, et al. Hormonal maintenance therapy for women with low grade serous carcinoma of the ovary or peritoneum [abstract]. *J Clin Oncol* 2016;34:Abstract 5502. Available at: <http://meetinglibrary.asco.org/content/164517-176>.

429. Piccart MJ, Bertelsen K, James K, et al. Randomized intergroup trial of cisplatin-paclitaxel versus cisplatin-cyclophosphamide in women with advanced epithelial ovarian cancer: three-year results. *J Natl Cancer Inst* 2000;92:699-708. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10793106>.

430. Gershenson DM, Bodurka DC, Coleman RL, et al. Hormonal maintenance therapy for women with low-grade serous cancer of the ovary or peritoneum. *J Clin Oncol* 2017;35:1103-1111. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28221866>.

431. Mangili G, Sigismondi C, Gadducci A, et al. Outcome and risk factors for recurrence in malignant ovarian germ cell tumors: a MITO-9 retrospective study. *Int J Gynecol Cancer* 2011;21:1414-1421. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21795985>.

432. Gershenson DM. Management of ovarian germ cell tumors. *J Clin Oncol* 2007;25:2938-2943. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17617525>.



433. Brown J, Friedlander M, Backes FJ, et al. Gynecologic Cancer Intergroup (GCIg) consensus review for ovarian germ cell tumors. *Int J Gynecol Cancer* 2014;24:S48-54. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25341580>.

434. Gershenson DM, Morris M, Cangir A, et al. Treatment of malignant germ cell tumors of the ovary with bleomycin, etoposide, and cisplatin. *J Clin Oncol* 1990;8:715-720. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/1690272>.

435. Gershenson DM, Frazier AL. Conundrums in the management of malignant ovarian germ cell tumors: Toward lessening acute morbidity and late effects of treatment. *Gynecol Oncol* 2016;143:428-432. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27569583>.

436. Zanagnolo V, Sartori E, Galleri G, et al. Clinical review of 55 cases of malignant ovarian germ cell tumors. *Eur J Gynaecol Oncol* 2004;25:315-320. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15171308>.

437. Low JJ, Perrin LC, Crandon AJ, Hacker NF. Conservative surgery to preserve ovarian function in patients with malignant ovarian germ cell tumors. A review of 74 cases. *Cancer* 2000;89:391-398. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10918171>.

438. Vazquez I, Rustin GJ. Current controversies in the management of germ cell ovarian tumours. *Curr Opin Oncol* 2013;25:539-545. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23942298>.

439. Pectasides D, Pectasides E, Kassanos D. Germ cell tumors of the ovary. *Cancer Treat Rev* 2008;34:427-441. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18378402>.

440. Tangir J, Zelterman D, Ma W, Schwartz PE. Reproductive function after conservative surgery and chemotherapy for malignant germ cell tumors of the ovary. *Obstet Gynecol* 2003;101:251-257. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12576247>.

441. Billmire D, Vinocur C, Rescorla F, et al. Outcome and staging evaluation in malignant germ cell tumors of the ovary in children and adolescents: an intergroup study. *J Pediatr Surg* 2004;39:424-429; discussion 424-429. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15017564>.

442. Mahdi H, Swensen RE, Hanna R, et al. Prognostic impact of lymphadenectomy in clinically early stage malignant germ cell tumour of the ovary. *Br J Cancer* 2011;105:493-497. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21772335>.

443. Mangili G, Scarfone G, Gadducci A, et al. Is adjuvant chemotherapy indicated in stage I pure immature ovarian teratoma (IT)? A multicentre Italian trial in ovarian cancer (MITO-9). *Gynecol Oncol* 2010;119:48-52. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20599258>.

444. Billmire DF, Cullen JW, Rescorla FJ, et al. Surveillance after initial surgery for pediatric and adolescent girls with stage I ovarian germ cell tumors: report from the Children's Oncology Group. *J Clin Oncol* 2014;32:465-470. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24395845>.

445. Cushing B, Giller R, Ablin A, et al. Surgical resection alone is effective treatment for ovarian immature teratoma in children and adolescents: a report of the pediatric oncology group and the children's cancer group. *Am J Obstet Gynecol* 1999;181:353-358. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10454682>.

446. Patterson DM, Murugaesu N, Holden L, et al. A review of the close surveillance policy for stage I female germ cell tumors of the ovary and other sites. *Int J Gynecol Cancer* 2008;18:43-50. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17466047>.

447. Marina NM, Cushing B, Giller R, et al. Complete surgical excision is effective treatment for children with immature teratomas with or without malignant elements: A Pediatric Oncology Group/Children's Cancer Group Intergroup Study. *J Clin Oncol* 1999;17:2137-2143. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10561269>.



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448. Billmire DF, Krailo M, Rodriguez-Galindo C, Frazier AL. Reply to G. Mangili et al and C. Lhomme et al. *J Clin Oncol* 2014;32:2816-2817.

Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25071123>.

449. Lhomme C, Leary A, Uzan C, et al. Adjuvant chemotherapy in stage I ovarian germ cell tumors: should indications and treatment modalities be different in young girls and adults? *J Clin Oncol* 2014;32:2815-2816.

Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25071130>.

450. Mangili G, Sigismondi C, Lorusso D, Pignata S. Surveillance policy for stage IA malignant ovarian germ cell tumors in children and young adults. *J Clin Oncol* 2014;32:2814-2815. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/25071128>.

451. Brown J, Shvartsman HS, Deavers MT, et al. The activity of taxanes compared with bleomycin, etoposide, and cisplatin in the treatment of sex cord-stromal ovarian tumors. *Gynecol Oncol* 2005;97:489-496. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/15863149>.

452. Williams S, Blessing JA, Liao SY, et al. Adjuvant therapy of ovarian germ cell tumors with cisplatin, etoposide, and bleomycin: a trial of the Gynecologic Oncology Group. *J Clin Oncol* 1994;12:701-706. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/7512129>.

453. Kang H, Kim TJ, Kim WY, et al. Outcome and reproductive function after cumulative high-dose combination chemotherapy with bleomycin, etoposide and cisplatin (BEP) for patients with ovarian endodermal sinus tumor. *Gynecol Oncol* 2008;111:106-110. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/18656249>.

454. Saxman SB, Finch D, Gonin R, Einhorn LH. Long-term follow-up of a phase III study of three versus four cycles of bleomycin, etoposide, and cisplatin in favorable-prognosis germ-cell tumors: the Indian University experience. *J Clin Oncol* 1998;16:702-706. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/9469360>.

455. Xiao H, Mazumdar M, Bajorin DF, et al. Long-term follow-up of patients with good-risk germ cell tumors treated with etoposide and cisplatin. *J Clin Oncol* 1997;15:2553-2558. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/9215824>.

456. Nichols CR, Catalano PJ, Crawford ED, et al. Randomized comparison of cisplatin and etoposide and either bleomycin or ifosfamide in treatment of advanced disseminated germ cell tumors: an Eastern Cooperative Oncology Group, Southwest Oncology Group, and Cancer and Leukemia Group B Study. *J Clin Oncol* 1998;16:1287-1293. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/9552027>.

457. Hinton S, Catalano PJ, Einhorn LH, et al. Cisplatin, etoposide and either bleomycin or ifosfamide in the treatment of disseminated germ cell tumors: final analysis of an intergroup trial. *Cancer* 2003;97:1869-1875. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/12673712>.

458. Horwich A, Sleijfer DT, Fossa SD, et al. Randomized trial of bleomycin, etoposide, and cisplatin compared with bleomycin, etoposide, and carboplatin in good-prognosis metastatic nonseminomatous germ cell cancer: a Multiinstitutional Medical Research Council/European Organization for Research and Treatment of Cancer Trial. *J Clin Oncol* 1997;15:1844-1852. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/9164194>.

459. Toner GC, Stockler MR, Boyer MJ, et al. Comparison of two standard chemotherapy regimens for good-prognosis germ-cell tumours: a randomised trial. Australian and New Zealand Germ Cell Trial Group. *Lancet* 2001;357:739-745. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/11253966>.

460. Bamias A, Aravantinos G, Kastriotis I, et al. Report of the long-term efficacy of two cycles of adjuvant bleomycin/etoposide/cisplatin in patients with stage I testicular nonseminomatous germ-cell tumors (NSGCT): a risk adapted protocol of the Hellenic Cooperative Oncology Group. *Urol Oncol* 2011;29:189-193. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/19362863>.



461. Dimopoulos MA, Papadimitriou C, Hamilos G, et al. Treatment of ovarian germ cell tumors with a 3-day bleomycin, etoposide, and cisplatin regimen: a prospective multicenter study. *Gynecol Oncol* 2004;95:695-700. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15581984>.

462. Williams SD, Kauderer J, Burnett AF, et al. Adjuvant therapy of completely resected dysgerminoma with carboplatin and etoposide: a trial of the Gynecologic Oncology Group. *Gynecol Oncol* 2004;95:496-499. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15581952>.

463. Reddy Ammakannavar N, Matei D, Abonour R, Einhorn LH. High-dose chemotherapy for recurrent ovarian germ cell tumors. *J Clin Oncol* 2015;33:226-227. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25452440>.

464. Shibata K, Kajiyama H, Kikkawa F. Growing teratoma syndrome of the ovary showing three patterns of metastasis: a case report. *Case Rep Oncol* 2013;6:544-549. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24348391>.

465. Matsushita H, Arai K, Fukase M, et al. Growing teratoma syndrome of the ovary after fertility-sparing surgery and successful pregnancy. *Gynecol Obstet Invest* 2010;69:221-223. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20068327>.

466. Amsalem H, Nadjari M, Prus D, et al. Growing teratoma syndrome vs chemotherapeutic retroconversion: case report and review of the literature. *Gynecol Oncol* 2004;92:357-360. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/14751185>.

467. Djordjevic B, Euscher ED, Malpica A. Growing teratoma syndrome of the ovary: review of literature and first report of a carcinoid tumor arising in a growing teratoma of the ovary. *Am J Surg Pathol* 2007;31:1913-1918. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18043048>.

468. Brenner DJ, Hall EJ. Computed tomography--an increasing source of radiation exposure. *N Engl J Med* 2007;357:2277-2284. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18046031>.

469. Kondagunta GV, Bacik J, Donadio A, et al. Combination of paclitaxel, ifosfamide, and cisplatin is an effective second-line therapy for patients with relapsed testicular germ cell tumors. *J Clin Oncol* 2005;23:6549-6555. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16170162>.

470. Einhorn LH, Williams SD, Chamness A, et al. High-dose chemotherapy and stem-cell rescue for metastatic germ-cell tumors. *N Engl J Med* 2007;357:340-348. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17652649>.

471. Loehrer PJ, Sr., Gonin R, Nichols CR, et al. Vinblastine plus ifosfamide plus cisplatin as initial salvage therapy in recurrent germ cell tumor. *J Clin Oncol* 1998;16:2500-2504. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9667270>.

472. Hinton S, Catalano P, Einhorn LH, et al. Phase II study of paclitaxel plus gemcitabine in refractory germ cell tumors (E9897): a trial of the Eastern Cooperative Oncology Group. *J Clin Oncol* 2002;20:1859-1863. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11919245>.

473. Nichols CR, Roth BJ, Loehrer PJ, et al. Salvage chemotherapy for recurrent germ cell cancer. *Semin Oncol* 1994;21:102-108. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/7992061>.

474. Slayton RE, Park RC, Silverberg SG, et al. Vincristine, dactinomycin, and cyclophosphamide in the treatment of malignant germ cell tumors of the ovary. A Gynecologic Oncology Group Study (a final report). *Cancer* 1985;56:243-248. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/2988740>.

475. Mangili G, Ottolina J, Gadducci A, et al. Long-term follow-up is crucial after treatment for granulosa cell tumours of the ovary. *Br J Cancer* 2013;109:29-34. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23756859>.

476. Colombo N, Parma G, Zanagnolo V, Insinga A. Management of ovarian stromal cell tumors. *J Clin Oncol* 2007;25:2944-2951. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17617526>.



477. Lee IH, Choi CH, Hong DG, et al. Clinicopathologic characteristics of granulosa cell tumors of the ovary: a multicenter retrospective study. *J Gynecol Oncol* 2011;22:188-195. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21998762>.
478. Ray-Coquard I, Brown J, Harter P, et al. Gynecologic Cancer InterGroup (GCIG) consensus review for ovarian sex cord stromal tumors. *Int J Gynecol Cancer* 2014;24:S42-47. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25341579>.
479. Zhang M, Cheung MK, Shin JY, et al. Prognostic factors responsible for survival in sex cord stromal tumors of the ovary--an analysis of 376 women. *Gynecol Oncol* 2007;104:396-400. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17030354>.
480. Wolf J, Brown J. Management of stromal tumors of the ovary. ASCO Educational Book 2008:225-228.
481. Brown J, Sood AK, Deavers MT, et al. Patterns of metastasis in sex cord-stromal tumors of the ovary: can routine staging lymphadenectomy be omitted? *Gynecol Oncol* 2009;113:86-90. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19162310>.
482. Schumer ST, Cannistra SA. Granulosa cell tumor of the ovary. *J Clin Oncol* 2003;21:1180-1189. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12637488>.
483. Schneider DT, Calaminus G, Wessalowski R, et al. Ovarian sex cord-stromal tumors in children and adolescents. *J Clin Oncol* 2003;21:2357-2363. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12805338>.
484. Park JY, Jin KL, Kim DY, et al. Surgical staging and adjuvant chemotherapy in the management of patients with adult granulosa cell tumors of the ovary. *Gynecol Oncol* 2012;125:80-86. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22210469>.
485. Gurumurthy M, Bryant A, Shanbhag S. Effectiveness of different treatment modalities for the management of adult-onset granulosa cell tumours of the ovary (primary and recurrent). *Cochrane Database Syst Rev* 2014;4:CD006912. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24753008>.
486. Homesley HD, Bundy BN, Hurteau JA, Roth LM. Bleomycin, etoposide, and cisplatin combination therapy of ovarian granulosa cell tumors and other stromal malignancies: A Gynecologic Oncology Group study. *Gynecol Oncol* 1999;72:131-137. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10021290>.
487. Pautier P, Gutierrez-Bonnaire M, Rey A, et al. Combination of bleomycin, etoposide, and cisplatin for the treatment of advanced ovarian granulosa cell tumors. *Int J Gynecol Cancer* 2008;18:446-452. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18494093>.
488. Teoh D, Freedman R, Soliman PT. Nearly 30 years of treatment for recurrent granulosa cell tumor of the ovary: a case report and review of the literature. *Case Rep Oncol* 2010;3:14-18. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20740152>.
489. Alhilli MM, Long HJ, Podratz KC, Bakkum-Gamez JN. Aromatase inhibitors in the treatment of recurrent ovarian granulosa cell tumors: brief report and review of the literature. *J Obstet Gynaecol Res* 2012;38:340-344. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22136798>.
490. Korach J, Perri T, Beiner M, et al. Promising effect of aromatase inhibitors on recurrent granulosa cell tumors. *Int J Gynecol Cancer* 2009;19:830-833. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19574768>.
491. Fishman A, Kudelka AP, Tresukosol D, et al. Leuprolide acetate for treating refractory or persistent ovarian granulosa cell tumor. *J Reprod Med* 1996;41:393-396. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/8799913>.



492. Tao X, Sood AK, Deavers MT, et al. Anti-angiogenesis therapy with bevacizumab for patients with ovarian granulosa cell tumors. *Gynecol Oncol* 2009;114:431-436. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/19524286>.

493. Pacaut C, Bourmaud A, Rivoirard R, et al. Uterine and ovary carcinosarcomas: outcome, prognosis factors, and adjuvant therapy. *Am J Clin Oncol* 2015;38:272-277. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/23751320>.

494. George EM, Herzog TJ, Neugut AI, et al. Carcinosarcoma of the ovary: natural history, patterns of treatment, and outcome. *Gynecol Oncol* 2013;131:42-45. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/23838036>.

495. del Carmen MG, Birrer M, Schorge JO. Carcinosarcoma of the ovary: a review of the literature. *Gynecol Oncol* 2012;125:271-277. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/22155675>.

496. Mano MS, Rosa DD, Azambuja E, et al. Current management of ovarian carcinosarcoma. *Int J Gynecol Cancer* 2007;17:316-324. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/17362309>.

497. Berton-Rigaud D, Devouassoux-Shisheboran M, Ledermann JA, et al. Gynecologic Cancer InterGroup (GFIG) consensus review for uterine and ovarian carcinosarcoma. *Int J Gynecol Cancer* 2014;24:S55-60. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/25341582>.

498. Jernigan AM, Fader AN, Nutter B, et al. Ovarian carcinosarcoma: effects of cytoreductive status and platinum-based chemotherapy on survival. *Obstet Gynecol Int* 2013;2013:490508. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/23781249>.

499. Chun KC, Kim JJ, Kim DY, et al. Optimal debulking surgery followed by paclitaxel/platinum chemotherapy is very effective in treating ovarian carcinosarcomas: a single center experience. *Gynecol Obstet Invest* 2011;72:208-214. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/21968161>.

500. Brown E, Stewart M, Rye T, et al. Carcinosarcoma of the ovary: 19 years of prospective data from a single center. *Cancer* 2004;100:2148-2153. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/15139057>.

501. Silasi DA, Illuzzi JL, Kelly MG, et al. Carcinosarcoma of the ovary. *Int J Gynecol Cancer* 2008;18:22-29. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/17451459>.

502. Duska LR, Garrett A, Eltabbakh GH, et al. Paclitaxel and platinum chemotherapy for malignant mixed mullerian tumors of the ovary. *Gynecol Oncol* 2002;85:459-463. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/12051874>.

503. Inthasorn P, Beale P, Dalrymple C, Carter J. Malignant mixed mullerian tumour of the ovary: prognostic factor and response of adjuvant platinum-based chemotherapy. *Aust N Z J Obstet Gynaecol* 2003;43:61-64. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/12755351>.

504. Rauh-Hain JA, Growdon WB, Rodriguez N, et al. Carcinosarcoma of the ovary: a case-control study. *Gynecol Oncol* 2011;121:477-481. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/21420726>.

505. Leiser AL, Chi DS, Ishill NM, Tew WP. Carcinosarcoma of the ovary treated with platinum and taxane: the memorial Sloan-Kettering Cancer Center experience. *Gynecol Oncol* 2007;105:657-661. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/17395252>.

506. Loizzi V, Cormio G, Camporeale A, et al. Carcinosarcoma of the ovary: analysis of 13 cases and review of the literature. *Oncology* 2011;80:102-106. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/21677454>.

507. Rutledge TL, Gold MA, McMeekin DS, et al. Carcinosarcoma of the ovary—a case series. *Gynecol Oncol* 2006;100:128-132. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/16213011>.

