
Clinical Practice Guidelines in Oncology

Robert J. Morgan Jr, MD; Deborah K. Armstrong, MD; Ronald D. Alvarez, MD; Jamie N. Bakkum-Gamez, MD; Kian Behbakht, MD; Lee-may Chen, MD; Larry Copeland, MD; Marta Ann Crispens, MD; Maria DeRosa, RN; Oliver Dorigo, MD, PhD; David M. Gershenson, MD; Heidi J. Gray, MD; Arshed Hakam, MD; Laura J. Havrilesky, MD; Carolyn Johnston, MD; Shashikant Lele, MD; Lainie Martin, MD; Ursula A. Matulonis, MD; David M. O'Malley, MD; Richard T. Penson, MD, MRCP; Sanja Percac-Lima, MD, PhD; Mario Pineda, MD, PhD; Steven C. Plaxe, MD; Matthew A. Powell, MD; Elena Ratner, MD; Steven W. Remmenga, MD; Peter G. Rose, MD; Paul Sabbatini, MD; Joseph T. Santoso, MD; Theresa L. Werner, MD; Jennifer Burns; and Miranda Hughes, PhD

Overview

Ovarian neoplasms consist of several histopathologic entities; treatment depends on the specific tumor type.1 Epithelial ovarian cancer comprises the majority of malignant ovarian neoplasms (about 90%)2–4; however, other less common pathologic subtypes may occur. The less common ovarian histopathologies (LCOHs) include carcinosarcomas (malignant mixed Müllerian tumors [MMMTs] of the ovary), clear cell carcinomas, mucinous carcinomas, and grade 1 (low-grade) serous carcinomas/endometrioid epithelial carcinomas. The LCOHs also include carcinosarcomas (malignant mixed Müllerian tumors of the ovary), borderline epithelial tumors (also known as low malignant potential tumors), malignant sex cord-stromal tumors, and malignant germ cell tumors.

Abstract

This selection from the NCCN Guidelines for Ovarian Cancer focuses on the less common ovarian histopathologies (LCOHs), because new algorithms were added for LCOHs and current algorithms were revised for the 2016 update. The new LCOHs algorithms include clear cell carcinomas, mucinous carcinomas, and grade 1 (low-grade) serous carcinomas/endometrioid epithelial carcinomas. The LCOHs also include carcinosarcomas (malignant mixed Müllerian tumors of the ovary), borderline epithelial tumors (also known as low malignant potential tumors), malignant sex cord-stromal tumors, and malignant germ cell tumors.

J Natl Compr Canc Netw 2016;14(9):1134–1163

NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

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

Please Note

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) are a statement of consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult the NCCN Guidelines® is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient’s care or treatment. The National Comprehensive Cancer Network® (NCCN®) makes no representation or warranties of any kind regarding their content, use, or application and disclaims any responsibility for their applications or use in any way. The full NCCN Guidelines for Ovarian Cancer are not printed in this issue of JNCCN but can be accessed online at NCCN.org.

© National Comprehensive Cancer Network, Inc. 2016. All rights reserved. The NCCN Guidelines and the illustrations herein may not be reproduced in any form without the express written permission of NCCN.

Disclosures for the NCCN Ovarian Cancer Panel

At the beginning of each NCCN Guidelines panel meeting, panel members review all potential conflicts of interest. NCCN, in keeping with its commitment to public transparency, publishes these disclosures for panel members, staff, and NCCN itself.

Individual disclosures for the NCCN Ovarian Cancer Panel members can be found on page 1163. (The most recent version of these guidelines and accompanying disclosures are available on the NCCN Web site at NCCN.org.)

These guidelines are also available on the Internet. For the latest update, visit NCCN.org.
clear cell carcinomas, mucinous carcinomas, grade 1 (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. Fallopian tube cancer and primary peritoneal cancer are less common neoplasms that are managed in a similar manner to epithelial ovarian cancer. However, the LCOHs may be managed differently.

This selection from the NCCN Guidelines for Ovarian Cancer focuses on the LCOHs, because new algorithms were added to the LCOHs for the 2016 update (see LCOH-1, page 1139). The new algorithms include clear cell carcinomas, mucinous carcinomas, and grade 1 (low-grade) serous carcinomas/endometrioid epithelial carcinomas. Other rare histologies had been previously included in the LCOH guidelines and were also revised for 2016. These other rare histologies include MMMTs, borderline epithelial tumors, malignant sex cord-stromal tumors, and malignant germ cell tumors.

The complete version of the NCCN Guidelines for Ovarian Cancer addresses all aspects of management for the different types of ovarian cancer as well as for fallopian tube cancer and primary peritoneal cancer. These NCCN Guidelines for Ovarian Cancer were originally published 20 years ago and have been updated subsequently at least once every year.

A brief introduction to ovarian cancer is provided in the subsequent section. By definition, the NCCN Guidelines cannot incorporate all possible clinical variations and are not intended to replace good clinical judgment or individualization of treat-

---

**NCCN Ovarian Cancer Panel Members**

*Robert J. Morgan Jr, MD/Chair†‡
City of Hope Comprehensive Cancer Center

Deborah K. Armstrong, MD/Vice ChairΩ†
The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins

Ronald D. Alvarez, MDΩ
University of Alabama at Birmingham Comprehensive Cancer Center

Jamie N. Bakkum-Gamez, MDΩ
Mayo Clinic Cancer Center

Kian Behbakht, MDΩ
University of Colorado Cancer Center

Lee-may Chen, MDΩ
UCSF Helen Diller Family Comprehensive Cancer Center

Larry Copeland, MDΩ
The Ohio State University Comprehensive Cancer Center – James Cancer Hospital and Solove Research Institute

Marta Ann Crispens, MDΩ
Vanderbilt-Ingram Cancer Center

Maria DeRosa, RNW

Oliver Dorigo, MD, PhDΩ
Stanford Cancer Institute

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

Heidi J. Gray, MDΩ
University of Washington Medical Center/Seattle Cancer Care Alliance

Ardeshir Hakam, MD≠
Moffitt Cancer Center

Laura J. Havrilesky, MDΩ
Duke Cancer Institute

Carolyn Johnston, MDΩ
University of Michigan Comprehensive Cancer Center

Shashikant Lele, MDΩ
Roswell Park Cancer Institute

Lainie Martin, MD†
Fox Chase Cancer Center

Ursula A. Matulonis, MDΩ†
Dana-Farber/Brigham and Women’s Cancer Center

David M. O’Malley, MDΩ
The Ohio State University Comprehensive Cancer Center - James Cancer Hospital and Solove Research Institute

Richard T. Penson, MD, MRCPn
Massachusetts General Hospital Cancer Center

Sanja Percac-Lima, MDΩ
Massachusetts General Hospital Cancer Center

Mario Pineda, MD, PhDΩ
Robert H. Lurie Comprehensive Cancer Center of Northwestern University

Steven C. Plaxe, MDΩ
UC San Diego Moores Cancer Center

Matthew A. Powell, MDΩ
Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine

Elena Ratner, MDΩ
Yale Cancer Center/Smilow Cancer Hospital

Fred & Pamela Buffett Cancer Center

Peter G. Rose, MDΩ
Case Comprehensive Cancer Center/University Hospitals Seidman Cancer Center and Cleveland Clinic Taussig Cancer Institute

Paul Sabbatini, MDΩ†
Memorial Sloan Kettering Cancer Center

Joseph T. Santoso, MDΩ
St. Jude Children’s Research Hospital/University of Tennessee Health Science Center

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

NCCN Staff: Jennifer Burns and Miranda Hughes, PhD

KEY:

*Writing Committee member

Specialties: OGynecology Oncology; †Hematology/Hematology Oncology; ‡Medical Oncology; ΩInternal Medicine; ≠Pathology; ¥Patient Advocacy
**EPITHELIAL OVARIAN CANCER/FALLOPIAN TUBE CANCER/PRIMARY PERITONEAL CANCER**

### CLINICAL PRESENTATION

**Suspicious**
- Palpable pelvic mass detected on abdominal/pelvic exam and/or ascites, abdominal distention, and/or
- Symptoms such as bloating, pelvic or abdominal pain, difficulty eating or feeling full quickly, or urinary symptoms (urgency or frequency) without other obvious source of malignancy

### WORKUP

- Obtain family history<sup>c,d</sup>
- Abdominal/pelvic exam
- Chest x-ray or chest CT as clinically indicated
- Complete blood count (CBC), chemistry profile with liver function test (LFT)
- GI evaluation for mucinous histology
- Ultrasound and/or abdominal/pelvic CT/MRI as clinically indicated<sup>d</sup>
- CA-125 or other tumor markers as clinically indicated<sup>d</sup>
- Ultrasound and/or abdominal/pelvic CT/MRI as clinically indicated<sup>d</sup>
- CA-125 or other tumor markers as clinically indicated<sup>d</sup>
- Consider tissue diagnosis of metastatic sites

### PRIMARY TREATMENT<sup>h,i,j</sup>

- Laparotomy/total abdominal hysterectomy (TAH)/bilateral salpingo-oophorectomy (BSO) with comprehensive staging or unilateral salpingo-oophorectomy (USO) (clinical stage 1A or 1C, all grades with comprehensive staging if patient desires fertility) or
- Cytoreductive surgery<sup>l</sup> if clinical stage II, III, IV or
- Patients with bulky stage III/IV who are poor surgical candidates due to high-risk comorbid conditions or disease factors require evaluation by a gynecologic oncologist<sup>k</sup> for consideration of neoadjuvant chemotherapy<sup>j</sup> (category 1/primary interval cytoreduction) Tissue diagnosis prior to initiation of chemotherapy is required

---

<sup>*Available online, in these guidelines, at NCCN.org.</sup>

---

<sup>11</sup>See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian and NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal.
<sup>12</sup>Primary treatment should not be delayed for a genetic counseling referral.
<sup>13</sup>Imaging performed with contrast unless contraindicated.
<sup>14</sup>PET/CT scan or MRI may be indicated for indeterminate lesions if results will alter management.
<sup>15</sup>Other tumor markers may include inhibin, beta-human chorionic gonadotropin (β-hCG), alpha-fetoprotein, lactate dehydrogenase (LDH), and carcinoembryonic antigen (CEA). See Discussion for usefulness of diagnostic tests.
<sup>16</sup>Standard recommendation includes a patient evaluation by a gynecologic oncologist prior to initiating chemotherapy. Published data demonstrate that primary assessment and debulking by a gynecologic oncologist results in a survival advantage. Patients being evaluated for neoadjuvant chemotherapy should be seen by a fellowship-trained gynecologic oncologist prior to being considered a poor surgical candidate. A referral to a gynecologic oncologist is also recommended for management of occult serous tubal intraepithelial carcinomas.
<sup>17</sup>All women undergoing surgery for ovarian cancer should be counseled about the clinical benefit associated with combined IV and IP chemotherapy administration prior to surgery. NCI Clinical Announcement.
<sup>18</sup>See Principles of Surgery (OV-A*).
<sup>19</sup>See Principles of Chemotherapy (OV-B*) and Management of Drug Reactions (OV-C*).
**DIAGNOSIS BY PREVIOUS SURGERY**

**FINDINGS**: 

- Adequate previous surgery and staging
- Incomplete previous surgery and/or staging:
  1. Uterus intact
  2. Adnexa intact
  3. Omentum not removed
  4. Documentation of staging incomplete
  5. Residual disease, potentially resectable
  6. Occult invasive carcinoma found at time of risk reduction surgery
  7. Incomplete lymph node dissection

**PRIMARY TREATMENT**: 

- Suspected stage IA or IB and/or grade 1:
  - Surgical staging
- Suspected stage IA or IB and/or grade 2:
  - If observation considered: Surgical staging
  - Suspect residual disease: Completion surgery/surgical staging
  - Suspect no residual disease: Completion surgery/surgical staging or chemotherapy for 6 cycles
- Suspected stage IA or IB, grade 3 or clear cell or stage IC:
  - Suspect residual disease: Completion surgery/surgical staging
  - Suspect no residual disease: Completion surgery/surgical staging or chemotherapy for 6 cycles
- Stage II, III, IV:
  - Suspect potentially resectable residual disease: Tumor reductive surgery
  - Suspect unresectable residual disease: Chemotherapy for a total of 6 cycles
    - Evaluate for interval debulking surgery prior to fourth cycle of chemotherapy

---

*Available online, in these guidelines, at NCCN.org.

---

*Standard recommendation includes a patient evaluation by a gynecologic oncologist prior to initiating chemotherapy. Published data demonstrate that primary assessment and debulking by a gynecologic oncologist results in a survival advantage. Patients being evaluated for neoadjuvant chemotherapy should be seen by a fellowship-trained gynecologic oncologist prior to being considered a poor nonsurgical candidate. A referral to a gynecologic oncologist is recommended for management of occult serous tubal intraepithelial carcinomas.

**See Principles of Surgery (OV-A**).

**See Principles of Chemotherapy (OV-B**), and Management of Drug Reactions (OV-C**).

**Pathologists recommend that serous ovarian cancer is either low-grade (most grade 1 serous tumors) or high-grade (most grade 2 or 3 serous tumors). See FIGO Guidelines (ST-5**).

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

---

```
OV-2
```
**Ovarian Cancer, Version 1.2016**

*EPITHELIAL OVARIAN CANCER/FALLOPIAN TUBE CANCER/PRIMARY PERITONEAL CANCER*

**PATHOLOGIC STAGING***

- Less common histology (e.g., carcinomas, clear cell, mucinous, grade 1 [low grade] serous, borderline epithelial, malignant sex cord-stromal/germ cell tumors)†

**PRIMARY CHEMOTHERAPY/PRIMARY ADJUVANT THERAPY**

- Stage IA or IB
  - Grade 1 (low grade) serous/endometrioid
  - Grade 2: serous/endometrioid
  - Grade 3: or high-grade

- Stage IC (Grade 1, 2, or 3)

- Stage II

- Stage III

- Stage IV

- Consider symptom management and best supportive care. See NCCN Guidelines for Palliative Care. Refer for palliative care assessment, if appropriate.

- Consider symptom management and best supportive care. See NCCN Guidelines for Palliative Care. Refer for palliative care assessment, if appropriate.

- Chemotherapy (See Primary Regimens (OV-B, 3 of 7))
  - Intrapertitoneal (IP) chemotherapy in <1 cm optimally debulked stage II and stage III patients (category 1 for stage III) or
  - IV taxane/carboplatin for a total of 6 cycles (category 1)
  - Completion surgery as indicated by tumor response and potential resectability in selected patients

- Cisplatin/ifosfamide
- Carboplatin/ifosfamide
- Paclitaxel/ifosfamide (category 2B)

- **Monitoring/Follow-Up**

- See Monitoring/Follow-Up (OV-5*)

- **Secondary Adjuvant Therapy**

- See Secondary Adjuvant Therapy (OV-4*)

- **Adjuvant Therapy**

- See Adjuvant Therapy (OV-4*)

**DIAGNOSIS**

- Carcinosarcoma (malignant mixed Müllerian tumors [MMMTs]) of the ovary

- Complete surgical staging

- Treat per Epithelial Ovarian Cancer (See OV-3)

- Cisplatin/ifosfamide
- Carboplatin/ifosfamide
- Paclitaxel/ifosfamide (category 2B)

**PATHOLOGIC DIAGNOSIS ADJUVANT TREATMENT**

- Carcinosarcoma (malignant mixed Müllerian tumors [MMMTs]) of the ovary

- Complete surgical staging

- Stage I-IV

- Treat per Epithelial Ovarian Cancer (See OV-3)

- Cisplatin/ifosfamide
- Carboplatin/ifosfamide
- Paclitaxel/ifosfamide (category 2B)

- **MONITORING/FOLLOW-UP**

- See Monitoring/Follow-Up (OV-5*)

- **Available online, in these guidelines, at NCCN.org.**

---

†All women undergoing surgery for ovarian cancer should be counseled about the clinical benefit associated with combined IV and IP chemotherapy administration prior to surgery. See NCI Clinical Announcement.

‡See Principles of Surgery (OV-A*).

§See Principles of Chemotherapy (OV-B*) and Management of Drug Reactions (OV-C*).

‖Pathologists recommend that serous ovarian cancer is either low-grade (most grade 1 serous tumors) or high-grade (most grade 2 or 3 serous tumors). See FIGO Guidelines (ST-5*).

¶See WHO Histologic Classification (OV-D*).

*Patients receiving primary chemotherapy will be monitored as follows:
1. Pelvic exams at least every 2–3 cycles
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, MRI, PET-CT, or PET as indicated.

Data suggests select patients with serous histology may benefit from 6 cycles. See Discussion.

© JNCCN—Journal of the National Comprehensive Cancer Network | Volume 14 Number 9 | September 2016
LESS COMMON OVARIAN HISTOPATHOLOGIES

DIAGNOSISa,b

Carcinosarcoma (malignant mixed Müllerian tumor [MMMT]) — See LCOH-2, below
Clear cell carcinoma of the ovary — See LCOH-3
Mucinous carcinoma of the ovary — See LCOH-4
Grade 1 (low grade) serous/endometrioid epithelial carcinoma — See LCOH-5
Borderline epithelial tumors (low malignant potential [LMP]) — See LCOH-6
Malignant sex cord-stromal tumors — See LCOH-9
Malignant germ cell tumors — See LCOH-10

Surgeryc and histologic diagnosisd

Carcinosarcoma (malignant mixed Müllerian tumors [MMMTs]) of the ovary — Complete surgical stagingc → Stage I-IV

TREATMENTa

Carcinosarcoma (malignant mixed Müllerian tumors [MMMTs]) of the ovary → Complete surgical stagingc

Treat per Epithelial Ovarian Cancer (See OV-3) or

Cisplatin/ifosfamide or
Carboplatin/ifosfamide or
Paclitaxel/ifosfamide (category 2B)

See Monitoring/Follow-Up (OV-5*)

CARCINOMA (MALIGNANT MÜLLERIAN TUMORS)

PATHOLOGIC DIAGNOSISa ADJUVANT TREATMENTa MONITORING/FOLLOW-UP

Carcinosarcoma (malignant mixed Müllerian tumors [MMMTs]) of the ovary Complete surgical stagingc Stage I-IV Treat per Epithelial Ovarian Cancer (See OV-3) or

Cisplatin/ifosfamide or
Carboplatin/ifosfamide or
Paclitaxel/ifosfamide (category 2B)

See Monitoring/Follow-Up (OV-5*)

*Available online, in these guidelines, at NCCN.org.

aSee WHO Histologic Classification (OV-D*).
bDue to emerging therapeutics for specific histologies, there is value in identifying potential pathways for rare histologies and it may be useful for clinical trial recruitment. There are limited data in these histologies given their infrequency and it will be difficult to acquire prospective data. Individualized treatment may be the best treatment for these rare tumors.
cSee Principles of Surgery (OV-A*).
dLess common ovarian histopathologies are typically diagnosed after surgery. See Workup (OV-1).
eSee Principles of Chemotherapy (OV-B*) and Management of Drug Reactions (OV-C*).

**CLEAR CELL CARCINOMA OF THE OVARY**

<table>
<thead>
<tr>
<th>PATHOLOGIC DIAGNOSIS</th>
<th>ADJUVANT TREATMENT</th>
<th>MONITORING/FOLLOW-UP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage IA-C</td>
<td>IV taxane/carboplatin x 3–6 cycles</td>
<td>See Monitoring/ Follow-Up (OV-5*)</td>
</tr>
<tr>
<td>Clear cell carcinoma of the ovary</td>
<td>Stage II-IV</td>
<td>Treat per Epithelial Ovarian Cancer (See OV-3)</td>
</tr>
<tr>
<td>Borderline</td>
<td>See LCOH-6</td>
<td></td>
</tr>
</tbody>
</table>

**MUCINOUS CARCINOMA OF THE OVARY**

<table>
<thead>
<tr>
<th>PATHOLOGIC DIAGNOSIS</th>
<th>ADDITIONAL WORKUP</th>
<th>ADJUVANT TREATMENT</th>
<th>MONITORING/FOLLOW-UP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage IA-IB</td>
<td>Observe</td>
<td>Observe or IV taxane/carboplatin x 3–6 cycles or 5-FU + leucovorin + oxaliplatin or Capecitabine + oxaliplatin</td>
<td>See Monitoring/ Follow-Up (OV-5*)</td>
</tr>
<tr>
<td>Stage IC</td>
<td>Observe (category 2B) or Consider surgical staging</td>
<td>Chemotherapy (See Primary Regimens, OV-B, 3 of 7)* or 5-FU + leucovorin + oxaliplatin or Capecitabine + oxaliplatin</td>
<td></td>
</tr>
<tr>
<td>Mucinous carcinoma of the ovary</td>
<td>If not previously done: • GI evaluation • Carcinoembryonic antigen (CEA)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Borderline</td>
<td>See LCOH-6</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Available online, in these guidelines, at NCCN.org.

*See WHO Histologic Classification (OV-D*).
*See Principles of Chemotherapy (OV-B*) and Management of Drug Reactions (OV-C*).
*Consider molecular testing for GI malignancies.
GRADE 1 (LOW-GRADE) SEROUS/ENDOMETROID EPITHELIAL CARCINOMA

PATHOLOGIC DIAGNOSIS

<table>
<thead>
<tr>
<th>Stage IA-IB</th>
<th>Observe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage IC-II</td>
<td>Observe (category 2B) or IV taxane/carboplatin (^\text{a}) x 3–6 cycles or Hormone therapy (category 2B) (ie, aromatase inhibitors [anastrozole, letrozole], leuprolide acetate, tamoxifen)</td>
</tr>
<tr>
<td>Stage III-IV</td>
<td>Chemotherapy (See Primary Regimens, OV-B, 3 of 7) (^\text{a}) or Hormone therapy (category 2B) (ie, aromatase inhibitors [anastrozole, letrozole], leuprolide acetate, tamoxifen)</td>
</tr>
</tbody>
</table>

ADJUVANT TREATMENT

| Borderline | See LCOH-6, below |

MONITORING/FOLLOW-UP

See Monitoring/Follow-Up (OV-5*)

BORDERLINE EPITHELIAL TUMORS (LOW MALIGNANT POTENTIAL)

PATHOLOGIC DIAGNOSIS

<table>
<thead>
<tr>
<th>Borderline epithelial tumors (LMP) (^\text{a})</th>
<th>Observe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous surgical staging was comprehensive (^\text{c})</td>
<td>Observe</td>
</tr>
<tr>
<td>Incomplete surgical staging (^\text{c})</td>
<td>See LCOH-7</td>
</tr>
</tbody>
</table>

ADJUVANT TREATMENT

<table>
<thead>
<tr>
<th>No invasive implants</th>
<th>Observe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invasive implants</td>
<td>Observe or Consider treatment as grade 1 (low-grade) serous epithelial carcinoma (^\text{a}) (See LCOH-5, above)</td>
</tr>
</tbody>
</table>

MONITORING/FOLLOW-UP

See Monitoring/Follow-up (LCOH-8, below)

*Available online, in these guidelines, at NCCN.org.

\(^\text{a}\)See WHO Histologic Classification (OV-D*).
\(^\text{b}\)See Principles of Surgery (OV-A*).
\(^\text{c}\)See Principles of Chemotherapy (OV-B*) and Management of Drug Reactions (OV-C*).
\(^\text{d}\)Standard recommendation includes a patient evaluation by a gynecologic oncologist.
\(^\text{e}\)Chemotherapy (IV or IP) has not been shown to be beneficial in ovarian borderline epithelial tumors (LMP).
BORDERLINE EPIDERMAL TUMORS (LOW MALIGNANT POTENTIAL)

PATHOLOGIC DIAGNOSIS

- Borderline epithelial tumor (LMP), incomplete surgical staging

ADJUVANT TREATMENT

- No invasive implants or Unknown
  - Fertility desired
    - Observation (category 2A)
  - If no desire for fertility
    - Invasive implants at previous surgery
      - Observation (category 2B)

MONITORING/FOLLOW-UP

- Visits every 3–6 mo for up to 5 y, then annually
- Physical exam including pelvic exam
- CA-125® or other tumor markers every visit if initially elevated
- After completion of childbearing in patients who underwent USO, consider completion surgery (category 2B)
- CBC, chemistry profile as indicated
- Imaging as clinically indicated: Chest, abdominal/pelvic CT, MRI, PET-CT, or PET
- Ultrasound as indicated for patients with fertility-sparing surgery

RECURRENT DISEASE

- Clinical relapse
  - Surgical evaluation + debulking if appropriate
    - Invasive implants of LMP or Low-grade invasive carcinoma
      - See grade 1 (low-grade) serous epithelial carcinoma (LCOH-5)
    - Invasive carcinoma (high grade)
      - Treatment as epithelial ovarian cancer (OV-3)
- Noninvasive disease
  - Observation

RECURRENT THERAPY

- See Monitoring/Follow-up (LCOH-8, below)

*Available online, in these guidelines, at NCCN.org.

a See WHO Histologic Classification (OV-D*).
b See Principles of Surgery (OV-A*).
c Standard recommendation includes a patient evaluation by a gynecologic oncologist.
d Chemotherapy (IV or IP) has not been shown to be beneficial in ovarian borderline epithelial tumors (LMP).
e For pathologically proven LMP, lymph node evaluation may be considered on a case-by-case basis.
f 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.

LCOH-7
LCOH-8
<table>
<thead>
<tr>
<th>CLINICAL PRESENTATION/ DIAGNOSIS</th>
<th>ADJUVANT TREATMENT</th>
<th>RECURRENCE THERAPY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignant sex cord-stromal tumors&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Stage I Low risk</td>
<td>Observe&lt;sup&gt;n&lt;/sup&gt;</td>
</tr>
<tr>
<td>Fertility-sparing surgery with complete staging&lt;sup&gt;c,l&lt;/sup&gt;</td>
<td>Stage I, high risk (eg, ruptured stage IC or poorly differentiated stage I) or Intermediate risk (eg, heterologous elements)</td>
<td>Consider platinum-based chemotherapy&lt;sup&gt;n&lt;/sup&gt; (category 2B)</td>
</tr>
<tr>
<td>Stage II-IV</td>
<td>Platinum-based chemotherapy&lt;sup&gt;n&lt;/sup&gt; (category 2B) or RT for limited disease (category 2B)</td>
<td>See Surveillance (LCOH-12*)</td>
</tr>
<tr>
<td>All others</td>
<td>Complete staging&lt;sup&gt;c,l&lt;/sup&gt;</td>
<td>If clinical relapse: Clinical trial or Consider secondary cytoreductive surgery or Recurrence therapy&lt;sup&gt;y&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>Available online, in these guidelines, at NCCN.org.

<sup>b</sup>See WHO Histologic Classification (OV-D*).
<sup>c</sup>See Principles of Surgery (OV-A*).
<sup>d</sup>Lymphadenectomy may be omitted.
<sup>e</sup>Inhibin levels can be followed if initially elevated for granulosa cell tumors (category 2B).
<sup>f</sup>Malignant germ cell regimens or paclitaxel/carboplatin regimens are preferred. See Primary Chemotherapy Regimens for Malignant Germ Cell/Sex Cord-Stromal Tumors (OV-B, 4 of 7).
<sup>g</sup>See Acceptable Recurrence Therapies for Malignant Germ Cell/Sex Cord-Stromal Tumors (OV-B, 6 of 7).

**MALIGNANT GERM CELL TUMORS**

**CLINICAL PRESENTATION/DIAGNOSIS**

- **Fertility desired**
  - Malignant germ cell tumors
  - Initially staged:
    - Consider repeat imaging (CT, MRI, PET-CT) as indicated
    - Embryonal, endodermal sinus tumor (yolk sac tumor), grade 2–3 immature teratoma, or mixed histology
    - Dysgerminoma or Grade 1 immature teratoma
    - Fertility not desired
    - Incompletely staged, if necessary
  - Positively imaging and positive tumor markers
  - Positive imaging and positive tumor markers
  - Complete staging surgery
  - Fertility-sparing surgery and comprehensive staging
  - Fertility desired, then fertility-sparing surgery and comprehensive staging
  - Fertility not desired, then completion staging surgery

- **Fertility not desired**
  - Complete staging surgery
  - Consider observation (category 2B)

**ADJUVANT TREATMENT**

- See Treatment (LCOH-11)
- See Surveillance (LCOH-12*)
- Consider additional chemotherapy
- See Primary Chemotherapy Regimens for Malignant Germ Cell Tumors

---

*Available online, in these guidelines, at NCCN.org.*

9Standard recommendation includes a patient evaluation by a gynecologic oncologist.

*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 sinus tumor; stage I, grade 1 immature teratoma, or mixed histology.

**PERSISTENT DISEASE**

- Persistent disease on imaging:
  - Elevated tumor markers
  - Elevated tumor markers
  - Elevated tumor markers

- Persistent disease on imaging:
  - Elevated tumor markers
  - Elevated tumor markers
  - Elevated tumor markers

- Elevated tumor markers

- Elevated tumor markers

- Elevated tumor markers

---

Clinical trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged. All recommendations are category 2A unless otherwise indicated.

© JNCCN—Journal of the National Comprehensive Cancer Network | Volume 14 Number 9 | September 2016
MALIGNANT GERM CELL TUMORS

**PATHOLOGIC DIAGNOSIS**

| Stage I Dysgerminoma<sup>®</sup> or Stage I, grade 1 Immature teratoma<sup>®</sup> | Observe<br>See Surveillance (LCOH-12*)
|---|---
| Any stage Embryonal tumor<sup>®</sup> or Any stage Endodermal sinus tumor (yolk sac tumor)<sup>®</sup> or Stage II-IV Dysgerminoma or Stage I, grade 2 or 3 or Stage II-IV Immature teratoma | Imaging as clinically indicated: Chest/ abdominal/ pelvic CT, MRI, PET-CT, or PET<sup>®</sup> Complete clinical response
| Residual tumor on radiographic imaging; markers normal<sup>®</sup> Consider surgical resection or Observe (See Surveillance LCOH-12*)
| Residual malignancy Persistently elevated markers<sup>®</sup> with definitive residual disease TIP (paclitaxel/ifosfamide/cisplatin) or High-dose chemotherapy<sup>®</sup> (strongly recommend referral to tertiary care center for potentially curative regime) | Consider additional chemotherapy<sup>®</sup> (category 2B) or High-dose chemotherapy<sup>®</sup> (category 2B) Complete clinical response
| Incomplete clinical response
| See OV-B (6 of 7) See Surveillance (LCOH-12*) |

**TREATMENT**

<table>
<thead>
<tr>
<th>Observe (LCOH-12*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consider additional chemotherapy&lt;sup&gt;®&lt;/sup&gt; (category 2B) or High-dose chemotherapy&lt;sup&gt;®&lt;/sup&gt; (category 2B)</td>
</tr>
</tbody>
</table>

**MONITORING/FOLLOW-UP**

<table>
<thead>
<tr>
<th>Abnormal markers, definitive recurrent disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest/abdominal/ pelvic CT&lt;sup&gt;®&lt;/sup&gt; or MRI as clinically indicated</td>
</tr>
<tr>
<td>Residual malignancy</td>
</tr>
</tbody>
</table>

**RECURRENT/PERSISTENT DISEASE**

<table>
<thead>
<tr>
<th>Complete staging surgery (See OV-A*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consider observation (category 2B)</td>
</tr>
<tr>
<td>Fertility not desired, then completion surgery and comprehensive staging; Fertility desired, then fertility-sparing surgery (See OV-A*)</td>
</tr>
<tr>
<td>(LCOH-11)</td>
</tr>
</tbody>
</table>

| LCOH-11 |

*Available online, in these guidelines, at NCCN.org.

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

<sup>®</sup>See Acceptable Recurrence Therapies for Malignant Germ Cell/Sex Cord- Stromal Tumors (OV-B, 6 of 7).

<sup>®</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>®</sup>See Primary Chemotherapy Regimens for Malignant Germ Cell Tumors (OV-B, 4 of 7).

<sup>®</sup>See LCOH-1 for markers.

<sup>®</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.
**EPITHELIAL OVARIAN CANCER/FALLOPIAN TUBE CANCER/PRIMARY PERITONEAL CANCER & LESS COMMON HISTOPATHOLOGIES**

**PRINCIPLES OF SYSTEMIC THERAPY (3 of 7)**

Primary Chemotherapy/Primary Adjuvant Therapy Regimens

Ovarian/Fallopian Tube/Primary Peritoneal/Carcinosarcoma/Clear Cell/Mucinous/Borderline Epithelial/Grade 1 (Low-Grade) Serous/Endometrioid

**Stage II-IV**

- **IP/IV Regimen**
  - Paclitaxel 135 mg/m² IV continuous infusion over 3 or 24 h on Day 1; cisplatin 75–100 mg/m² IP, Day 2 after IV paclitaxel; paclitaxel 60 mg/m² IP Day 8. Repeat every 3 weeks x 6 cycles. (category 1)
  - **IV Regimens**
    - Paclitaxel 175 mg/m² IV over 3 hours followed by carboplatin² AUC 5–6 IV over 1 hour Day 1. Repeat every 3 weeks x 6 cycles. (category 1)
    - Dose-dense paclitaxel 80 mg/m² IV over 1 hour Days 1, 8, and 15 followed by carboplatin² AUC 5–6 IV over 1 hour Day 1. Repeat every 3 weeks x 6 cycles. (category 1)
    - Paclitaxel 60 mg/m² IV over 1 hour followed by carboplatin AUC 2 IV over 30 minutes. Weekly for 18 weeks. (category 1)
    - Docetaxel 60–75 mg/m² IV over 1 hour followed by carboplatin² AUC 5–6 IV over 1 hour Day 1. Repeat every 3 weeks x 6 cycles. (category 1)
    - Bevacizumab-containing regimens per ICON-7 and GOG-218:
      - Paclitaxel 175 mg/m² IV over 3 hours followed by carboplatin² AUC 5–6 IV over 1 hour, and bevacizumab 7.5 mg/kg IV over 30–90 minutes Day 1. Repeat every 3 weeks x 5–6 cycles. Continue bevacizumab for up to 12 additional cycles. (category 2B)
      - Paclitaxel 175 mg/m² IV over 3 hours followed by carboplatin² AUC 6 IV over 1 hour Day 1. Repeat every 3 weeks x 6 cycles. Starting Day 1 of cycle 2, give bevacizumab 15 mg/kg IV over 30–90 minutes every 3 weeks for up to 22 cycles. (category 2B)

**Additional options for the following less common histopathologies:**

- Carcinosarcoma (MMMT)
  - Carboplatin/ifosfamide
  - Cisplatin/ifosfamide
  - Paclitaxel/ifosfamide (category 2B)

- Mucinous tumors
  - 5-FU/leucovorin/oxaliplatin
  - Capetitabine/oxaliplatin

- Grade 1 (low-grade) serous/endometrioid and borderline epithelial carcinoma
  - Hormone therapy (Aromatase inhibitors [ie, anastrozole, letrozole], leuprolide acetate, tamoxifen) (category 2B)

**PRINCIPLES OF SYSTEMIC THERAPY (4 of 7)**

Primary Chemotherapy/Primary Adjuvant Therapy Regimens

Malignant Germ Cell/Sex Cord-Stromal Tumors

- **BEP (bleomycin, etoposide, cisplatin)**
  - Bleomycin 30 units per week
  - Etoposide 100 mg/m² daily for days 1–5, cisplatin 20 mg/m² daily for days 1–5
  - Repeat every 21 days for 3 cycles for good risk (category 2B), or 4 cycles for poor risk.
  - Etoposide/carboplatin³
    - For select patients with stage IB-II resected dysgerminoma for whom minimizing toxicity is critical, 3 cycles of etoposide/carboplatin can be used.
    - Carboplatin 400 mg/m² on day 1 plus etoposide 120 mg/m² on days 1, 2, and 3 every 4 weeks for 3 cycles.

Malignant Sex Cord-Stromal Tumors

- **BEP (category 2B)**
- Paclitaxel/carboplatin (category 2B)

Continued on OV-B 5 of 7

(available online, in these guidelines, at NCCN.org)

---

²See Discussion for references.

³IV regimens may be considered for neoadjuvant therapy for epithelial ovarian cancer.

⁴The published randomized trial regimen used IV continuous infusion paclitaxel over 24 h.

⁵Due to changes in creatinine methodology, changes regarding carboplatin dosing can be considered. See FDA carboplatin dosing statement.

⁶This regimen may be considered for elderly patients or those with poor performance status.

⁷Recommend pulmonary function test if considering bleomycin.
### Acceptable Recurrence Therapies For Malignant Germ Cell/Sex Cord-Stromal Tumors

<table>
<thead>
<tr>
<th>Cytotoxic Therapy (In alphabetical order)</th>
<th>Hormonal Therapy</th>
<th>Targeted Therapy</th>
<th>Radiation Therapy</th>
</tr>
</thead>
</table>
| **Malignant Germ Cell Tumors**<sup>a</sup> | **Potentially Curative Therapy:**  
High-dose chemotherapy<sup>b</sup>  
TIP (paclitaxel, ifosfamide, cisplatin)  
Palliative Therapy Only:  
Cisplatin/etoposide  
Docetaxel  
Docetaxel/carboplatin  
Paclitaxel  
Paclitaxel/ifosfamide  
Paclitaxel/carboplatin  
Paclitaxel/gemcitabine  
VIP (etoposide, ifosfamide, cisplatin)  
VelIP (vinblastine, ifosfamide, cisplatin)  
VAC (vincristine, daunorubicin, cyclophosphamide)  
TIP  
Supportive care only (See NCCN Supportive Care Guidelines, available at NCCN.org) | Hormonal Therapy | Targeted Therapy | Palliative localized radiation therapy |
| **Malignant Sex Cord-Stromal Tumors**<sup>b</sup> | Docetaxel  
Paclitaxel  
Paclitaxel/ifosfamide  
Paclitaxel/carboplatin  
VAC  
Supportive care only (See NCCN Supportive Care Guidelines, available at NCCN.org) | Aromatase inhibitors (ie, anastrozole, letrozole)  
Leuprolide acetate (for granulosa cell tumors)  
Tamoxifen | Bevacizumab (single agent) | Palliative localized radiation therapy |

<sup>a</sup>Available online, in these guidelines, at NCCN.org.

<sup>b</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>c</sup>See WHO Histologic Classification (OV-D*).
mments. Exceptions to the rule were discussed among the panel members while developing these NCCN Guidelines.

**Epidemiology**

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. However, LCOHs are rare cancers that present at an earlier age than epithelial ovarian cancer. The risk for borderline epithelial tumors may be increased after ovarian stimulation for in vitro fertilization. Family history (primarily patients having ≥2 first-degree relatives with ovarian cancer)—including linkage with BRCA1 and BRCA2 genotypes (hereditary breast and ovarian cancer syndrome) or families affected by Lynch syndrome (hereditary nonpolyposis colorectal cancer syndrome)—is associated with early-onset disease. Lynch syndrome is associated with risk for endometrioid carcinomas, clear cell carcinomas, and papillary serous carcinomas. In women at high risk (with either BRCA1 or BRCA2 mutations), prophylactic bilateral salpingooophorectomy (BSO) is associated with a reduced risk for breast, ovarian, fallopian tube, and primary peritoneal cancers.

Occult ovarian cancer is sometimes found after prophylactic salpingooophorectomy, thus emphasizing the need for careful pathologic review of the ovaries and tubes (see “Risk-Reducing Salpingo-Oophorectomy [RRSO] Protocol” in the complete version of these guidelines, available at NCCN.org [OV-A]). The risks of surgery include injury to the bowel, bladder, ureter, and vessels.

**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. However, evaluations of patients with newly diagnosed ovarian cancer have resulted in consensus guidelines for ovarian cancer symptoms, which may enable earlier identification of patients possibly at an increased risk of having early-stage ovarian cancer. 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). Physicians evaluating women with this constellation of symptoms must be cognizant of the possibility that ovarian pathology may be causing these symptoms. However, 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.

Randomized data do not yet support routine screening for ovarian cancer in the general population, and routine screening is not currently recommended by any professional society. Some physicians follow-up women with high-risk factors (eg, BRCA mutations, family history) using cancer antigen 125 (CA 125) monitoring and endovaginal ultrasound; however, prospective validation of these tests remains elusive.

**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 complete version of these guidelines, available at NCCN.org [ST-1–5]).

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). Pathologists may use histologic grades 1, 2, or 3 for endometrioid carcinomas, mucinous carcinomas, and stage IC tumors. Staging for the LCOHs is performed using the ovarian cancer staging system.

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 complete version of these guidelines [ST-1–5]). In the new staging guidelines, old stages IC, IIIA, and IV are now subdivided, and the old stage IIC has been eliminated. These changes will be included in the next edition of the AJCC Cancer Staging Manual (8th edition), which will be published in 2016 and will be effective for all cancer cases recorded on or after January 1, 2017. The 2016 protocol from the College of American Pathologists (CAP) for ovarian cancer includes the LCOHs.

**Recommended Workup**

The LCOH algorithms begin after surgery and histologic diagnosis of a suspicious pelvic mass (see LCOH-1;
Undiagnosed Pelvic Mass: The primary workup should include an 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 examination) 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 LCOH-1; page 1139). 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,” page 1150, and LCOH-1, page 1139). For example, AFP levels should be considered to assess for germ cell tumors in women younger than 35 years with a pelvic mass. Ultrasound is typically used for initial evaluation; however, CT is useful to assess for metastases. MRI may be useful for determining malignant potential if ultrasound is not reliable. CT/MRI imaging should be performed with contrast unless contraindicated. FDG-PET/CT scan may be useful for indeterminate lesions.

Most ovarian cancers, including the LCOHs, are diagnosed after pathologic analysis of a biopsy or surgical specimen, which may occur preoperatively, intraoperatively, or postoperatively. If possible, fine-needle aspiration (FNA) should be avoided for diagnosing 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. Other cancers that should be ruled out include bowel, uterine, and pancreatic cancers and lymphoma. Benign ovarian and nonovarian conditions also need to be ruled out (eg, serous cystadenoma), as do metastases to the ovaries (see “Mucinous Carcinomas,” page 1152).

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. The FDA has approved the use of HE4 and CA 125 for estimating the risk for ovarian cancer in women with a pelvic mass, however, the NCCN Panel does not currently recommend the use of these biomarkers for determining the status of an undiagnosed pelvic mass. Although no direct evidence exists that chest radiography or 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 if patients have metastases to the ovary or primary mucinous carcinoma of the ovary (see “Mucinous Carcinomas,” page 1152).

Prior Diagnosis of Malignancy: Patients are often referred to NCCN Member Institutions after a previous diagnosis of ovarian cancer through surgery or tissue biopsy (cytopathology). Often these patients have undergone cytoreductive surgery and comprehensive staging procedures. However, referral may occur after incomplete surgery and/or staging; for example, the uterus and/or adnexa may still be intact (see OV-2; page 1137). The components of surgical staging are listed in the algorithm (see “Principles of Surgery” in the complete version of these guidelines, available at NCCN.org [OV-A]). Identical workup procedures are recommended for patients with 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: serous, endometrioid, mucinous, and clear cell; however, most patients (about 70%) have serous histology. For the 2016 update, primary treatment recommendations for the LCOH subtypes—mucinous, clear cell, and grade 1 (low-grade) serous/endometrioid—may be different from the treatment recommendations for the high-grade serous/endometrioid subtypes (see OV-3 and LCOH-1;
Primary Treatment
Primary treatment for presumed ovarian cancer consists of appropriate surgical staging and cytoreduction, followed in most (but not all) patients by systemic therapy. Neoadjuvant therapy refers to drugs, radiation, or other treatment that is given to reduce the tumor burden before cancer surgery. The therapeutic benefit of neoadjuvant chemotherapy followed by interval cytoreduction remains controversial for epithelial ovarian cancer. Neoadjuvant chemotherapy may be considered (category 1) for patients with bulky stage III to IV disease who are not surgical candidates; however, a gynecologic oncologist should make this assessment before neoadjuvant chemotherapy is administered. Because many patients with LCOH are diagnosed after surgery and/or present with early-stage disease, neoadjuvant chemotherapy does not apply for the LCOHs.

Initial surgery should be a comprehensive staging laparotomy, including a total abdominal hysterectomy and BSO (see LCOH-1 and “Principles of Surgery” in the complete version of these guidelines [OV-A]). Based on published improved outcomes, it is recommended (category 1) that a gynecologic oncologist perform the primary surgery. For a young patient who wishes to maintain fertility, a unilateral salpingooophorectomy (USO; preserving the uterus and contralateral ovary) 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; see LCOH-6, LCOH-9, LCOH-10; pages 1141, 1143, and 1144, respectively). Comprehensive staging may not be necessary for select patients, such as those with borderline epithelial tumors (see LCOH-6, page 1141).

Most patients have a hysterectomy with BSO, omentectomy, and lymphadenectomy of suspicious/enlarged nodes. Cytoreductive surgery is the initial treatment recommendation for patients with clinical stage II, III, or IV disease (see OV-1, page 1136, and “Principles of Surgery” in the complete version of these guidelines, available at NCCN.org [OV-A]). These procedures also apply to many of the LCOHs. Surgical cytoreduction is optimal if the residual tumor nodules are less than 1 cm in maximum diameter or thickness, extensive resection of upper abdominal ovarian metastases is recommended for patients who can tolerate this surgery. In select patients, minimally invasive procedures may be used to assess whether cytoreductive surgery is feasible and to achieve cytoreduction.

Young patients who will abruptly enter menopause after surgery, various supportive care measures may be used to help decrease hot flashes and other symptoms. Procedures that may be considered for optimal surgical cytoreduction (in all stages) include radical pelvic dissection, bowel resection and/or appendectomy, diaphragm or other peritoneal surface stripping, splenectomy, partial hepatectomy, partial gastrectomy, or partial cystectomy and/or ureteroneocystostomy, cholecystectomy, and/or distal pancreatectomy. For patients with incomplete previous surgery and/or staging, treatment recommendations are outlined in the algorithm (see OV-2 and LCOH-7; pages 1137 and 1142, respectively).

Less Common Ovarian Histopathologies
For the 2016 update, the NCCN Panel extensively revised the section on LCOHs. As previously mentioned, new algorithms for clear cell carcinoma, mucinous carcinoma, and grade 1 (low-grade) serous/endometrioid epithelial carcinoma were added to
Fertility-sparing surgery may be recommended for women who would like to maintain their fertility (see “Surgery,” subsequent section).

Surgery
In contrast to high-grade serous epithelial ovarian cancer or MMMTs, many patients with other LCOHs present at an early stage. Some of the tumors may be confined to one ovary. Thus, some of the younger patients are candidates for fertility-sparing surgery, which may be performed laparoscopically (see “Principles of Surgery” in the complete version of these guidelines, available at NCCN.org [OV-A]).

Fertility-sparing surgery may be performed (if technically feasible) if the intraoperative frozen section results are positive for malignant germ cell tumors, borderline epithelial tumors, unilateral stage I epithelial ovarian tumors, or unilateral stage I sex cord-stromal tumors. Patients who do not desire fertility preservation; those who have a clinical stage IB, II, III, or IV epithelial ovarian cancer; those with clinical stage IB, II, III, or IV sex cord-stromal tumor; or those with MMMT should undergo comprehensive surgical staging as per these guidelines (see “Principles of Surgery” in the complete version of these guidelines [OV-A]).

Clear Cell Carcinoma
For the 2016 update, the NCCN Ovarian Cancer Panel added a new algorithm for patients with clear cell carcinoma of the ovary (see LCOH-3; page 1143). Clear cell carcinomas are considered high-grade tumors; they are more common than the other LCOHs. Most clear cell carcinomas are negative for WT1 and estrogen receptors. 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 performed before surgery, as described in the algorithm (see OV-1; page 1136).

Primary treatment for these patients includes completion surgery with comprehensive staging...
followed by postoperative therapy (see LCOH-3; page 1140). Lymphadenectomy has been shown to improve survival. The staging system for ovarian and primary peritoneal cancer is also used for clear cell carcinomas (see Table 1 in the complete version of these guidelines, available at NCCN.org [ST-1]). Lynch syndrome is associated with risk for clear cell carcinomas, endometrioid carcinomas, and papillary serous carcinomas. For patients with stage IA to IC disease, recommended postoperative treatment is either intravenous paclitaxel/carboplatin or docetaxel/carboplatin. Fertility-sparing surgery and/or observation/monitoring are options for patients with unilateral clear cell borderline tumors (see LCOH-6; page 1141). For patients with stage II to IV clear cell carcinoma, postoperative treatment is similar to that recommended for epithelial ovarian cancer. Patients with advanced clear cell carcinoma have a poor prognosis.

Mucinous Carcinomas
For the 2016 update, the NCCN Panel added a new algorithm for mucinous carcinoma of the ovary (see LCOH-4; page 1140). 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 approximately 80% to 90%. Mucinous tumors are unusual because they may be very large cystic masses that may fill the entire abdominal pelvic cavity; this presentation often suggests mucinous histology. Patients with mucinous tumors typically present at a younger age (20–40 years) than women with high-grade serous ovarian cancer.

Patients are typically diagnosed with mucinous carcinoma after surgery for a suspicious pelvic mass (see LCOH-4; page 1140). Therefore, the initial workup is the same as for other types of ovarian cancer (see OV-1; page 1136). Primary treatment for these patients includes completion surgery with comprehensive staging followed by postoperative therapy or observation (see LCOH-4; page 1140). An appendectomy is also recommended at primary surgery in patients with suspected or confirmed mucinous ovarian tumors. The staging system for ovarian and primary peritoneal cancer is also used for mucinous carcinomas (see Table 1 in the complete version of these guidelines [ST-1]).

The additional workup includes a gastrointestinal tract evaluation and CEA level for patients with mucinous histology to determine whether patients have either an occult gastrointestinal primary that has metastasized to the ovaries or primary mucinous carcinoma of the ovaries (see OV-1; page 1136). 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. PAX8 immunostaining may be useful. Postoperative observation and monitoring are recommended for patients with stage IA or IB mucinous tumors, because most of these tumors are benign or borderline. Fertility-sparing surgery is an option for patients with a unilateral mucinous borderline tumor (see LCOH-6; page 1141). 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). Some clinicians feel the gastrointestinal regimens are appropriate, because mucinous carcinomas of the ovary are similar to gastrointestinal tumors. For patients with stages II to IV mucinous carcinomas, postoperative options include (1) chemotherapy using the regimens for epithelial ovarian cancer; (2) 5-FU/leucovorin/oxaliplatin (gastrointestinal regimen); or (3) capecitabine/oxaliplatin (gastrointestinal regimen).

Grade 1 (Low-Grade) Serous/Endometrioid Epithelial Carcinomas
For the 2016 update, the NCCN Panel added a new algorithm for grade 1 (low-grade) endometrioid serous/endometrioid epithelial carcinomas (see LCOH-5; page 1141). Endometrioid carcinomas may be associated with endometriosis. 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. Endometrioid tumors are also very similar in appearance to sex cord-stromal tumors. Lynch syndrome is associated with risk for endometrioid carcinomas, clear cell carcinomas, and serous carcinomas.

 Patients with grade 1 (low-grade) serous carcinomas may present with more advanced disease, but they often have more indolent disease and present at a younger age than those with high-grade serous carci-
Serous carcinomas are usually positive for WT1 and estrogen receptors. Primary treatment for these patients includes completion surgery with comprehensive staging followed by postoperative therapy or observation; patients are typically diagnosed after surgery (see OV-3; page 1138). Fertility-sparing surgery is an option for patients with serous and endometrioid borderline tumors (see LCOH-6; page 1141). Some clinicians feel that neoadjuvant therapy should not be recommended for patients with grade 1 (low-grade) serous carcinomas, because they often respond poorly to chemotherapy.

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; or (2) hormone therapy (category 2B) as previously described (see OV-B, 3 of 7; page 1146).

Malignant Germ Cell Tumors

These malignant tumors include dysgerminomas, immature teratomas, embryonal tumors, and endodermal sinus (yolk sac) tumors (see LCOH-10; page 1144). 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. Germ cell tumors are the predominant ovarian tumor in this age group. The recommended workup may include pulmonary function studies if bleomycin is being considered (see OV-B, 4 of 7; page 1146). In young women (<35 years of age) with a pelvic mass, AFP levels can indicate the presence of germ cell tumors. Gonadal dysgenesis is a risk factor for germ cell tumors. Women with malignant germ cell tumors have an excellent prognosis. After appropriate treatment, the 5-year survival rate is more than 85%.

Treatment: Completion surgery with comprehensive staging is recommended as initial surgery for patients who do not desire fertility preservation (see LCOH-10; page 1144). The staging system for ovarian and primary peritoneal cancer is also used for malignant germ cell tumors (see Table 1 in the complete version of these guidelines, available at NCCN.org [ST-1]). After comprehensive surgical staging, observation with monitoring is recommended for patients with stage I dysgerminoma or stage I, grade 1 immature teratoma. Surgery for children or adolescents may differ from that for adult women (see “Principles of Surgery” in the complete version of these guidelines [OV-A]). In children or adolescents with early-stage germ cell tumors, comprehensive staging may be omitted. If these 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 LCOH-10; page 1144). Fertility-sparing surgery should be considered for those desiring fertility preservation, regardless of stage (see LCOH-10; page 1144). Patients who chose fertility-sparing surgery should be monitored by ultrasound examinations if necessary; completion surgery (category 2B) should be considered afterchildbearing is finished.

After surgery, observation with surveillance is the recommended option for patients with stage I dysgerminoma or stage I, grade 1 immature teratoma based on European and pediatric reports. Observation or chemotherapy may be considered for children or adolescents with select stage IA or IB tumors (see LCOH-11; page 1145). For patients with stage II to IV malignant dysgerminomas or immature teratomas, postoperative chemotherapy is recommended (see OV-B, 4 of 7; page 1146).

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 OV-B, 4 of 7; page 1146). If considering the use of bleomycin, pulmonary function tests are recommended. 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 I 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. 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/m² [area under the curve, ≈5–6] on day 1 plus etoposide, 120 mg/m² on days 1–3 every 4 weeks for 3 courses). 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 complete version of these guidelines, available at NCCN.org [LCOH-12]). Patients experiencing 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 or (2) consider additional chemotherapy (see OV-B, 6 of 7; page 1147). 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.

**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. Further options depend on which findings are present: residual malignancy, benign teratoma, or necrotic tissue (see LCOH-11; page 1145). For patients with definitive residual disease and with persistently elevated AFP and/or beta-hCG after first-line chemotherapy, recommendations include paclitaxel/ifosfamide/cisplatin (TIP) or high-dose chemotherapy. Referral to a tertiary care center for potentially curative treatment is strongly recommended. 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, including TIP, vincristine/dactinomycin/cyclophosphamide (VAC), vinblastine/ifosfamide/cisplatin (VeIP), etoposide/ifosfamide/cisplatin (VIP), cisplatin/etoposide, docetaxel/carboplatin, paclitaxel/carboplatin, paclitaxel/gemcitabine, paclitaxel/ifosfamide, docetaxel, paclitaxel, high-dose chemotherapy, radiotherapy, or supportive care only (see OV-B, 6 of 7 page 1147). Most of the combination chemotherapy regimens are recommended as palliative options for patients with recurrent or residual disease who have no curative options. These recurrence regimens (see OV-B, 6 of 7 page 1147) 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. Most patients with granulosa tumors present with early-stage disease; the disease is typically indolent. For the 2016 update, the complete histologic classification for ovarian cancer from the WHO was added to the NCCN Guidelines, which includes the different types of sex cord-stromal tumors and whether they are benign or malignant (see “WHO Histologic Classification” in the complete version of these guidelines [OV-D]). The staging system for ovarian and primary peritoneal cancer is also used for sex cord-stromal tumors (see Table 1 in the complete version of these guidelines [ST-1]).

Patients with stage IA or IC sex cord-stromal tumors desiring to preserve their fertility should be treated with fertility-sparing surgery (see LCOH-9; page 1143). Although complete staging is recommended for all other patients, lymphadenectomy may be omitted for patients with stage IA or IC tumors. 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 LCOH-9; page 1143). For patients with high-risk stage I tumors (tumor rupture, stage 1C, poorly differentiated tumor, and tumor size >10–15 cm), postoperative recommendations (all are category 2B) include observation or consideration of platinum-based chemotherapy (see LCOH-9 and OV-B, 4 of 7; pages 1143 and 1146, respectively). Those with surgical findings of low-risk stage I tumor (ie, without high-risk features)
Borderline epithelial tumors are rare tumors and are considered atypical tumors. They are most commonly seen in young women with stage I disease, and the 5-year survival rate exceeds 80%. 

Diagnosis: The terms for borderline epithelial tumors (also known as low malignant potential tumors or atypical proliferative tumors) have changed over the years. The 2016 CAP cancer protocol for ovarian cancer uses “borderline” and does not use “low malignant potential.” Borderline epithelial tumors are typically serous or mucinous; other histologic subtypes can also occur (see “WHO Histologic Classification” in the complete version of these guidelines [OV-D]). 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. The 5-year survival rate exceeds 80%. 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.

Borderline epithelial tumors are rare tumors and are managed differently from high-grade carcinomas (see LCOH-6; page 1141). 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 has the visual appearance of peritoneal carcinomatosis. 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 as discussed in the subsequent paragraphs (see “Principles of Surgery” in the complete version of these guidelines, available at NCCN.org [OV-A]).

Treatment guidelines for borderline epithelial tumors depend on the histologic and clinical characteristics, the age of the patient, 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 (see LCOH-6; page 1141). 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 LCOH-6; page 1141).

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. If the patient does not desire fertility-sparing surgery, standard ovarian cancer debulking surgery 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. For the 2016 update, the NCCN Panel deleted the recommendation for comprehensive surgical staging (category 2B); lymph node evaluation may be considered on a case-by-case basis.

For patients with a known borderline epithelial tumor 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 LCOH-7; page 1142). Patients who want to preserve their fertility should undergo 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 grade 1 (low-grade) serous epithelial ovarian cancer can be considered for these patients (see LCOH-5 and LCOH-7; pages 1141 and 1142, respectively). For the 2016 update, the NCCN Panel revised this recommendation for postoperative chemotherapy to category 2A (from category 2B); intravenous carboplatin with either docetaxel or paclitaxel is recommended. However, the benefit of chemotherapy, either intraperitoneal or intravenous, is controversial in patients with borderline epithelial tumors. The significance of invasive implants remains under investigation. The benefit of postoperative chemotherapy has not been demonstrated for patients who have no microscopically demonstrable invasive implants. 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 those without invasive implants; these recommendations were revised for the 2016 update (see LCOH-7; page 1142).

**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 grade 1 (low-grade) serous epithelial ovarian cancer, or observation (category 3) (see LCOH-6; page 1141). Patients with no invasive implants may be observed (category 2B) and monitored (see LCOH-8; page 1142). 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).

**Relapse:** At the time of clinical relapse, surgical evaluation and debulking are recommended if appropriate. For the 2016 update, the NCCN Panel revised the algorithm by clarifying the recommendations for low-grade and high-grade disease. Patients who have low-grade invasive carcinoma or invasive implants from borderline epithelial tumors may be treated as per patients with grade 1 (low-grade) serous epithelial ovarian cancer; those with high-grade invasive carcinoma may be treated as per patients with epithelial ovarian cancer (see LCOH-5 and LCOH-8; pages 1141 and 1142, respectively). Observation is recommended for those with noninvasive disease.
References


ovarian malignancy algorithm (ROMA) as diagnostic tools for ovarian and cystic components that mimic malignancy. AJR Am J Roentgenol


& Practice of Oncology, 10th ed. Philadelphia, PA: Lippincott Williams &


### Individual Disclosures of the Ovarian Cancer Panel

<table>
<thead>
<tr>
<th>Panel Member</th>
<th>Clinical Research Support/Data Safety Monitoring Board</th>
<th>Scientific Advisory Boards, Consultant, or Expert Witness</th>
<th>Promotional Advisory Boards, Consultant, or Speakers Bureau</th>
<th>Date Completed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deborah K. Armstrong, MD</td>
<td>Astellas LLC; AstraZeneca Pharmaceuticals LP; and Clovis Oncology</td>
<td>None</td>
<td>None</td>
<td>10/27/15</td>
</tr>
<tr>
<td>Ronald D. Alvarez, MD</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>7/13/16</td>
</tr>
<tr>
<td>Jamie N. Bakkum-Gamez, MD</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>4/13/16</td>
</tr>
<tr>
<td>Kian Behbakht, MD</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>7/18/15</td>
</tr>
<tr>
<td>Lee-may Chen, MD</td>
<td>None</td>
<td>None</td>
<td>Genentech, Inc.</td>
<td>5/11/16</td>
</tr>
<tr>
<td>Larry Copeland, MD</td>
<td>GOG Foundation; NRG Oncology; and TESARO, Inc.</td>
<td>Advaxis, Inc.; Bayer HealthCare; Cerulean Pharma Inc; Endocyte, Inc.; Helomics, Inc.; and Johnson &amp; Johnson</td>
<td>None</td>
<td>9/30/15</td>
</tr>
<tr>
<td>Marta Ann Crispens, MD</td>
<td>AstraZeneca Pharmaceuticals LP; and Janssen Pharmaceuticals Product, LP</td>
<td>None</td>
<td>None</td>
<td>5/8/16</td>
</tr>
<tr>
<td>Marie DeRosa, RN</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>3/18/16</td>
</tr>
<tr>
<td>Oliver Dorigo, MD, PhD</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>5/4/16</td>
</tr>
<tr>
<td>David M. Gershenson, MD</td>
<td>NCI</td>
<td>None</td>
<td>None</td>
<td>8/7/15</td>
</tr>
<tr>
<td>Heidi J. Gray, MD</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>4/21/16</td>
</tr>
<tr>
<td>Ardeshir Hakam, MD</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>2/29/16</td>
</tr>
<tr>
<td>Laura J. Havrilesky, MD</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>10/2/15</td>
</tr>
<tr>
<td>Carolyn Johnston, MD</td>
<td>None</td>
<td>None</td>
<td>Michigan Cancer Consortium; and MPRO</td>
<td>3/29/16</td>
</tr>
<tr>
<td>Shashikant Lele, MD</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>10/13/15</td>
</tr>
<tr>
<td>Lainie Martin, MD</td>
<td>Novartis Pharmaceuticals Corporation; and Synta Pharmaceuticals Corp.</td>
<td>None</td>
<td>None</td>
<td>9/29/15</td>
</tr>
<tr>
<td>Ursula A. Matulonis, MD</td>
<td>None</td>
<td>AstraZeneca Pharmaceuticals LP; Genentech, Inc.; Immunogen, Inc.; Merck &amp; Co., Inc.; and Pfizer Inc.</td>
<td>None</td>
<td>5/11/16</td>
</tr>
<tr>
<td>Robert J. Morgan Jr, MD</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>3/14/16</td>
</tr>
<tr>
<td>David M. O'Malley, MD</td>
<td>None</td>
<td>AstraZeneca Pharmaceuticals LP; Clovis Oncology; and Janssen Pharmaceutical Product, LP</td>
<td>None</td>
<td>4/18/16</td>
</tr>
<tr>
<td>Richard T. Penson, MD, MRCR</td>
<td>Amgen Inc.; AstraZeneca Pharmaceuticals LP; Endocyte, Inc.; Genentech, Inc.; and Vascular Biogenics Ltd</td>
<td>AstraZeneca Pharmaceuticals LP; Genentech, Inc.; and Vascular Biogenics, Ltd</td>
<td>None</td>
<td>3/9/16</td>
</tr>
<tr>
<td>Sanja Percac-Lima, MD, PhD</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>7/31/16</td>
</tr>
<tr>
<td>Mario Pineda, MD, PhD</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>1/7/16</td>
</tr>
<tr>
<td>Steven C. Piaxe, MD</td>
<td>Amgen Inc.; AstraZeneca Pharmaceuticals LP; Azaya Therapeutics, Inc; BIND Therapeutics, Inc.; Endocyte, Inc.; Janssen Pharmaceutical Products, LP; Millennium Pharmaceuticals, Inc.; Navidea Biopharmaceuticals; Novartis Pharmaceuticals Corporation; Pfizer Inc.; PharmaMar; and TESARO, Inc.</td>
<td>Ambrx, Inc.; and Insys Therapeutics, Inc.</td>
<td>Insys Therapeutics, Inc.</td>
<td>11/6/15</td>
</tr>
<tr>
<td>Matthew A. Powell, MD</td>
<td>Bristol-Myers Squibb Company; and Eisai Inc.</td>
<td>AnorMED Inc.; and Genentech, Inc.</td>
<td>Genentech, Inc.</td>
<td>7/13/15</td>
</tr>
<tr>
<td>Elena Ratner, MD</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>11/11/15</td>
</tr>
<tr>
<td>Steven W. Remmenga, MD</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>5/10/16</td>
</tr>
<tr>
<td>Peter G. Rose, MD</td>
<td>None</td>
<td>None</td>
<td>Pfizer Inc.</td>
<td>5/19/16</td>
</tr>
<tr>
<td>Paul Sabbatini, MD</td>
<td>Bristol-Myers Squibb Company</td>
<td>None</td>
<td>None</td>
<td>10/5/15</td>
</tr>
<tr>
<td>Joseph T. Santoso, MD</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>9/19/15</td>
</tr>
<tr>
<td>Theresa L. Werner, MD</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>10/1/15</td>
</tr>
</tbody>
</table>

*The following individuals have disclosed that they have an employment/governing board, patent, equity, or royalty conflict:

- David M. Gershenson, MD: Biogen Idec, Celgene Corporation, Elsevier, Johnson & Johnson, NCI, Proctor and Gamble, UpToDate
- Steven C. Piaxe, MD: Abbott Laboratories, Abb Vie Inc., Bristol-Myers Squibb Company, Pfizer Inc.

The NCCN Guidelines Staff have no conflicts to disclose.*