



National
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NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Ovarian Cancer

Including Fallopian Tube Cancer and Primary Peritoneal Cancer

Version 1.2016

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Ovarian Cancer

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Clinical Trials: NCCN believes that the best management for any cancer patient 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/physician.html](#).

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

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

NCCN Guidelines for Patients® are available at www.nccn.org/patients.

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NCCN Guidelines Version 1.2016 Updates

Ovarian Cancer

Updates in Version 1.2016 of the NCCN Guidelines for Ovarian Cancer from Version 2.2015 include:

General

- "IV taxane/carboplatin x 6-8 cycles" has been changed to 6 cycles.
- The following footnote has been added to imaging recommendations:
"Imaging performed with contrast unless contraindicated."

OV-1

- Under workup:
 - ▶ "Refer for genetic risk evaluation" has been removed, but the recommendation remains after primary treatment.
 - ▶ Imaging options have been specified: "Chest x-ray or chest CT as clinically indicated imaging."
 - ▶ GI evaluation: Added "for mucinous histology"; removed "as clinically indicated."
 - ▶ Last bullet added after diagnosis by previous surgery: "Consider tissue diagnosis of metastatic sites."
- Third primary treatment option has been revised: "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 for consideration of neoadjuvant chemotherapy (category 1)/primary interval cytoreduction by fine-needle aspiration (FNA), biopsy, or paracentesis* for. *Tissue diagnosis prior to initiation of chemotherapy is required.*"
- Footnote "g" has been revised: "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."
- The following footnote has been removed: "For rare tumors including clear cell, mucinous, or low grade, see Discussion."

OV-2

- "Incomplete lymph node dissection" has been added as the last option under incomplete previous surgery and/or staging.
- Primary treatment has been revised for stage II,III,IV/suspected unresectable residual disease: "Chemotherapy for a total of 6–8 cycles. ~~Consider completion surgery after 3 cycles followed by postoperative chemotherapy~~ Evaluate for interval debulking surgery prior to fourth cycle of chemotherapy."
- Footnote "I" has been revised: "~~Some~~ Pathologists recommend that serous ovarian cancer ~~be is graded~~ either low-grade (most grade 1 serous tumors) or high-grade (most grade 2 or 3 serous tumors). See FIGO Guidelines (ST-5)."

OV-3

- Pathway has been added for "Less common histology (Carcinosarcoma, clear cell, mucinous, borderline epithelial, malignant sex cord-stromal/germ cell tumors)" and the following footnote has been removed: "See Discussion for more details about treatment of low-grade tumors."
- Stage IA or IB
 - ▶ "Serous/endometrioid" added to "Grade 1 (low-grade)" and "Grade 2"
 - ▶ "or High-grade" added to "Grade 3"
- Under primary treatment, where chemotherapy is listed a link to OV-B (3 of 7) has been added and the following footnote has been removed: "See specific regimens on Primary Chemotherapy/Primary Adjuvant Therapy Regimens for Stage II-IV (OV-B 3 of 7)."
- Footnote "n" added: "See WHO Histologic Classification (OV-D)."
- Footnote "o", #5 has been revised: "~~Radiographic imaging~~ Chest/abdominal/pelvic CT, MRI, PET-CT, or PET as indicated."
- Footnote "p" has been added: "Data suggests select patients with serous histology may benefit from 6 cycles. See Discussion."

OV-4

- Post-primary treatment, the following has been added: "Imaging as clinically indicated: Chest/abdominal/pelvic CT, MRI, PET-CT, or PET."
- Following complete clinical remission, postremission paclitaxel has been changed from a category 3 to a category 2B option.

OV-5

- Imaging with PET alone has been changed from a category 2B to a category 2A option.

OV-6

- Following consideration of secondary cytoreductive surgery for radiographic and/or clinical relapse:
 - ▶ The second treatment option has been revised: "Combination platinum-based chemotherapy x 6 cycles..."
 - ▶ "Best supportive care" has been added as an option.

[Continued on next page](#)

**Updates in Version 1.2016 of the NCCN Guidelines for Ovarian Cancer from Version 2.2015 include:****Less Common Ovarian Histopathologies****LCOH-1**

- Workup section has been removed and footnote "d" has been added: "Less common ovarian histopathologies are typically diagnosed after surgery. See Workup (OV-1)."
- Footnote "b" has been added: "Due 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."
- The first column has been revised: "Surgery and *histologic diagnosis frozen section*"
- Pathways have been added for clear cell carcinoma, mucinous carcinoma, and grade 1 (low-grade) serous/endometrioid epithelial carcinoma.

LCOH-2

- The following carcinosarcoma treatment options have been added for stage I-IV disease: cisplatin/ifosfamide, or carboplatin/ifosfamide, or paclitaxel/ifosfamide (category 2B)

LCOH-3

- New pathway and treatment options have been added for clear cell carcinoma.

LCOH-4

- New pathway and treatment options have been added for mucinous carcinoma.

LCOH-5

- New pathway and treatment options have been added for grade 1 (low-grade) serous/endometrioid epithelial carcinoma.

LCOH-6

- Clinical presentation and page header have been revised: "*Borderline epithelial tumors (LMP) Diagnosis of LMP tumor with institutional pathology review*"
- After invasive implants, the second primary treatment option has been revised: "Consider treatment as grade 1 (low-grade) serous epithelial ovarian cancer (~~category 2B~~) (See LCOH-5)."

LCOH-7

- Fertility desired, no invasive implants or unknown:
 - Observe was changed to a category 2B recommendation from 2A.
 - The second option has been revised: "Fertility-sparing surgery and *resection of residual disease comprehensive surgical staging, (category 2B for staging) if not previously done.*"
- Fertility desired, invasive implants at previous surgery:
 - The first option has been revised: "Fertility-sparing surgery and *resection of residual disease comprehensive surgical staging, (category 2B for staging) if not previously done.*"
 - Observe has been changed to a category 3 recommendation from 2B.
 - The third option has been revised: "Consider treatment as grade 1 (low-grade) serous epithelial ovarian cancer (~~category 2B~~) (See LCOH-5)."
- No fertility desired, no invasive implants or unknown:
 - Observe was changed to a category 2B recommendation from 2A.
 - The second option has been revised: "Completion surgery *and resection of residual disease.*"
- No fertility desired, invasive implants at previous surgery:
 - The first option has been revised: "Completion surgery *and resection of residual disease.*"
 - Observe has been changed to a category 3 recommendation from 2B.
 - The third option has been revised: "Consider treatment as grade 1 (low-grade) serous epithelial ovarian cancer (~~category 2B~~) (See LCOH-5)."
- The following footnote has been removed: "Observation is a reasonable option regardless of whether fertility is desired."

LCOH-8

- The sixth bullet has been added under monitoring/follow-up: "Imaging as clinically indicated: Chest/abdominal/pelvic CT, MRI, PET-CT, or PET."
- After surgical evaluation and debulking, "Low-grade invasive carcinoma" has been added to "Invasive implants of LMP," and "low grade" was removed from the third option.
- Recurrence therapy for low malignant potential/low grade has been revised: "See grade 1 (low-grade) serous epithelial carcinoma (LCOH-5)."

LCOH-9

- "See Surveillance, LCOH-12" has been added after treatment.

LCOH-10

- After surgery, for incompletely staged, "consider repeat imaging (CT, MRI, PET-CT) as indicated" has been added.

[Continued on next page](#)



NCCN Guidelines Version 1.2016 Updates

Ovarian Cancer

Updates in Version 1.2016 of the NCCN Guidelines for Ovarian Cancer from Version 2.2015 include:

LCOH-11

- After treatment with chemotherapy, added: "Imaging as clinically indicated: Chest/abdominal/pelvic CT, MRI, PET-CT, or PET"
- For benign teratoma, the following has been revised: "*Chest/abdominal/pelvic CT or MRI* ~~other imaging~~ as clinically indicated."
- For residual malignancy, "x 2 cycles" has been added to "Consider additional platinum-based chemotherapy."
- Footnote "t" has been added: "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."

LCOH-12

- Footnote "*" has been revised: "Chest x-ray, *chest/abdominal/pelvic CT, MRI, PET-CT, or PET; with contrast unless contraindicated.*"

OV-A (2 of 4)

- Under newly diagnosed invasive epithelial ovarian cancer apparently confined to an ovary or to the pelvis, the first line has been added: "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."
- Under newly diagnosed invasive epithelial ovarian cancer involving the pelvis and upper abdomen, the first line has been revised: "In general, every effort should be made *during a primary cytoreduction procedure to achieve maximum cytoreduction of all abdominal, pelvic, and retroperitoneal disease.*"

OV-A (3 of 4)

- A new section has been added, titled: "Interval cytoreduction after neoadjuvant chemotherapy of invasive epithelial ovarian cancer."
- Under the RRSO Protocol, the following has been added to the 10th bullet: "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."

OV-A (4 of 4)

- Special circumstances, the second bullet has been revised: "...and an appendectomy should be performed *at primary surgery* in patients with a *suspected or confirmed* mucinous ovarian neoplasm."

OV-B

- This section has been reorganized to include the primary therapy and recurrence therapy options for less common histopathologies.
- The section has been renamed Principles of Systemic Therapy ~~Chemotherapy~~.

OV-B (3 of 7)

- For stage II-IV epithelial ovarian/Fallopian tube/primary peritoneal/ carcinosarcoma/clear cell mucinous/low-grade serous/endometrioid/borderline epithelial cancer, the bevacizumab-containing regimens have been changed to category 2B recommendations from category 3.
- Footnote "b" has been revised: "IV regimens may be considered for neoadjuvant therapy *for epithelial ovarian cancer.*"

OV-B (5 of 7)

- Paclitaxel (weekly) ± pazopanib has been add as a category 2A, preferred option for platinum-resistant epithelial ovarian cancer, Fallopian tube cancer, or primary peritoneal cancer, based on the following reference: 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.
- Single-agent pazopanib has been added as a category 2B targeted therapy option for epithelial ovarian/Fallopian tube/primary peritoneal cancer based on the following reference: 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.

OV-B (6 of 7)

- Acceptable Recurrence Therapies for Malignant Germ Cell/Sex Cord-Stromal Tumors has been divided into options for "potentially curative therapy" and "palliative therapy only."
- Footnote "n" has been revised: "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."

OV-D

- The WHO Histologic Classification table has been updated and 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.

MS-1

- The Discussion section has been updated to reflect the changes in the algorithm.

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Epithelial Ovarian Cancer/Fallopian Tube Cancer/ Primary Peritoneal Cancer

CLINICAL PRESENTATION

Suspicious^a/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)^b without other obvious source of malignancy

WORKUP

- Obtain family history^{c,d}
- 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^{e,f}
- CA-125 or other tumor markers as clinically indicated^g

PRIMARY TREATMENT^{h,i,j}

Laparotomy/total abdominal hysterectomy (TAH)/bilateral salpingo-oophorectomy (BSO) with comprehensive staging^l or unilateral salpingo-oophorectomy (USO) (clinical stage 1A or 1C, all grades with comprehensive staging if patient desires fertility) or
Cytoreductive surgery^j 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^h for consideration of neoadjuvant chemotherapy^k (category 1)/primary interval cytoreduction^h. Tissue diagnosis prior to initiation of chemotherapy is required.

All patients with ovarian cancer, Fallopian tube cancer, or primary peritoneal cancer should be referred for genetic risk evaluation^{c,d}

[See Pathologic Staging \(OV-3\)](#)

Diagnosis by previous surgery or tissue biopsy (cytopathology)

- Obtain family history^c
- Refer for genetic risk evaluation^{c,d}
- Chest x-ray or chest CT as clinically indicated
- CBC, chemistry profile with LFTs
- Institutional pathology review
- Ultrasound and/or abdominal/pelvic CT/MRI as clinically indicated^e
- CA-125 or other tumor markers as clinically indicated^g
- Consider tissue diagnosis of metastatic sites

[See Findings and Primary Treatment \(OV-2\)](#)

^aIm SS, et al. Obstet Gynecol 2005;105:35-41. [See Discussion.](#)

^bGoff BA, Mandel L, Drescher CW, et al. Cancer 2007;109:221-227.

^c[See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian](#) and [NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal.](#)

^dPrimary treatment should not be delayed for a genetic counseling referral.

^eImaging performed with contrast unless contraindicated.

^fPET/CT scan or MRI may be indicated for indeterminate lesions if results will alter management.

^gOther 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.

^hStandard 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.

ⁱAll 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.](#)

^j[See Principles of Surgery \(OV-A\).](#)

^k[See Principles of Chemotherapy \(OV-B\)](#) and [Management of Drug Reactions \(OV-C\).](#)

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

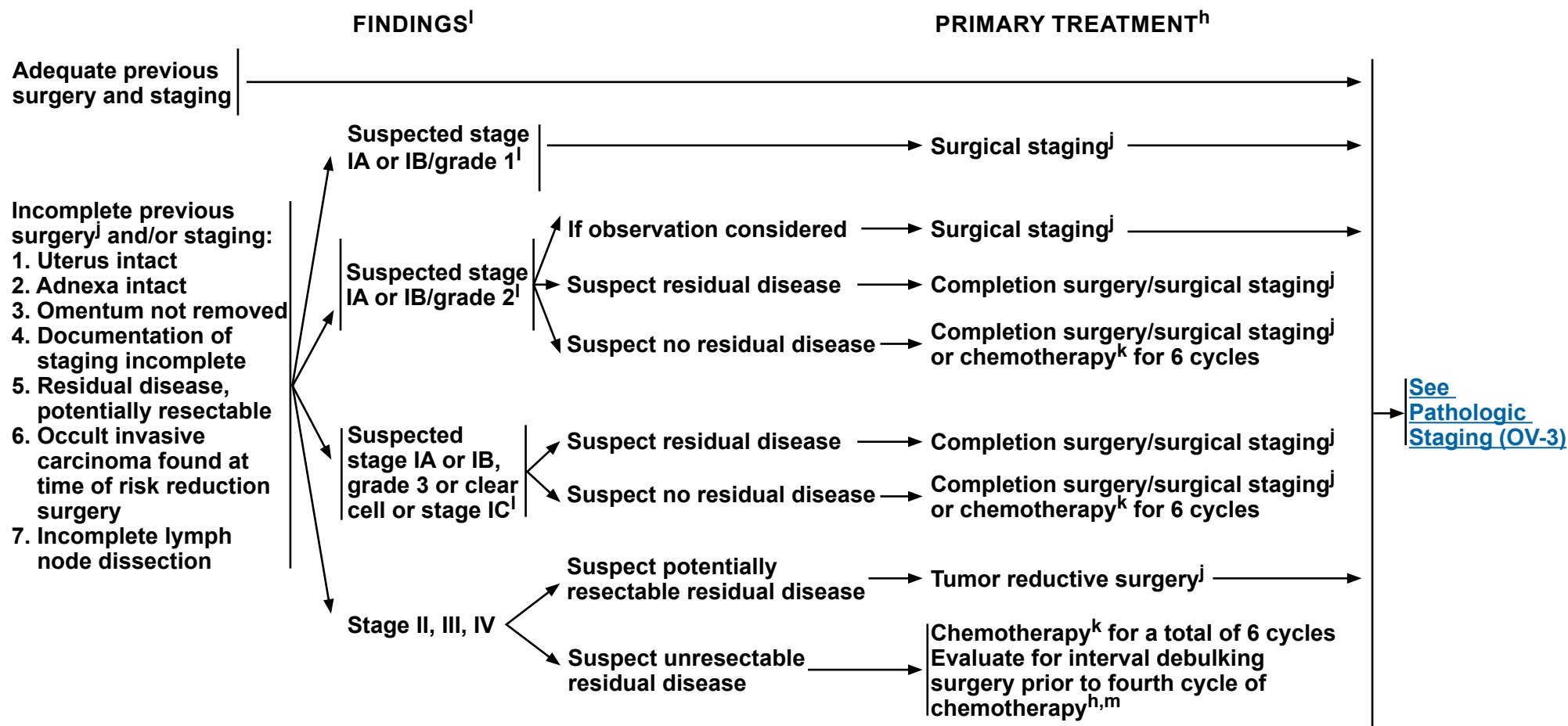
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Epithelial Ovarian Cancer/Fallopian Tube Cancer/ Primary Peritoneal Cancer

DIAGNOSIS BY PREVIOUS SURGERY



^hStandard 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 also recommended for management of occult serous tubal intraepithelial carcinomas.

^jSee [Principles of Surgery \(OV-A\)](#).

^kSee [Principles of Chemotherapy \(OV-B\)](#) and [Management of Drug Reactions \(OV-C\)](#).

^lPathologists 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 \(ST-5\)](#).

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

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Epithelial Ovarian Cancer/Fallopian Tube Cancer/ Primary Peritoneal Cancer

PATHOLOGIC STAGING^{l,n}

PRIMARY CHEMOTHERAPY/PRIMARY ADJUVANT THERAPY^o

Less common histology
(ie, carcinosarcoma, clear cell,
mucinous, grade 1 [low-grade] serous,
borderline epithelial, malignant sex
cord-stromal/germ cell tumors)ⁿ

→ [See LCOH-1](#)

Grade 1^l (low-grade)
serous/endometrioid

→ [See LCOH-5](#)

Stage IA or IB Grade 2^l
serous/endometrioid

Observe
or
Intravenous (IV) taxane/carboplatin^k
x 3–6 cycles^{o,p}

Stage IC
(Grade 1, 2, or 3)

Grade 3^l or high-grade

IV taxane/carboplatin^k x 3–6 cycles^{o,p}

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

→ [See Monitoring/
Follow-Up
\(OV-5\)](#)

Stage II
Stage III
Stage IV

- Chemotherapy (See Primary Regimens [\(OV-B, 3 of 7\)](#)^o
 - ▶ Intraperitoneal (IP) chemotherapy^{l,k} in <1 cm optimally debulked stage II and stage III patients (category 1 for stage III) or
 - ▶ IV taxane/carboplatin^k for a total of 6 cycles (category 1)^o
- Completion surgery as indicated by tumor response and potential resectability in selected patients^l

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

→ [See Secondary
Adjuvant
Therapy \(OV-4\)](#)

^lAll 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](#).

^j[See Principles of Surgery \(OV-A\)](#).

^k[See Principles of Chemotherapy \(OV-B\)](#) and [Management of Drug Reactions \(OV-C\)](#).

^lPathologists 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 \(ST-5\)](#).

ⁿSee WHO Histologic Classification (OV-D).

^oPatients 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.

^pData suggests select patients with serous histology may benefit from 6 cycles. [See Discussion](#).

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

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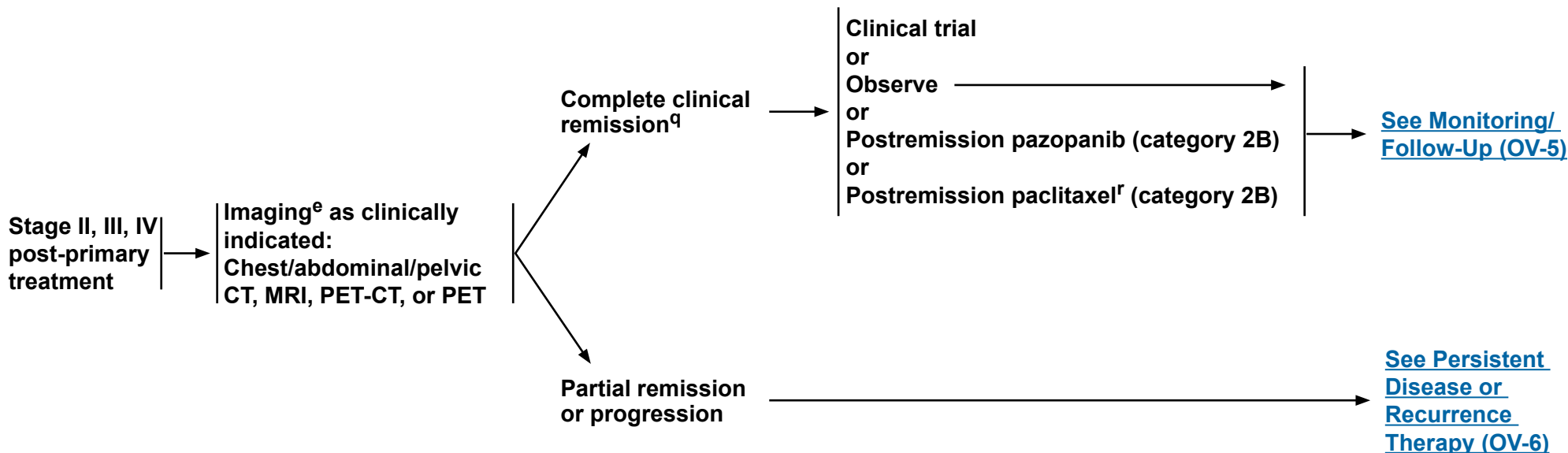


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Epithelial Ovarian Cancer/Fallopian Tube Cancer/ Primary Peritoneal Cancer

STAGE II, III, IV POST-PRIMARY TREATMENT

SECONDARY ADJUVANT THERAPY



^eImaging performed with contrast unless contraindicated.

^qNo objective evidence of disease (ie, negative physical exam, negative CA-125, negative CT with <1 cm lymph nodes).

^r[See Discussion](#) for dosing.

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

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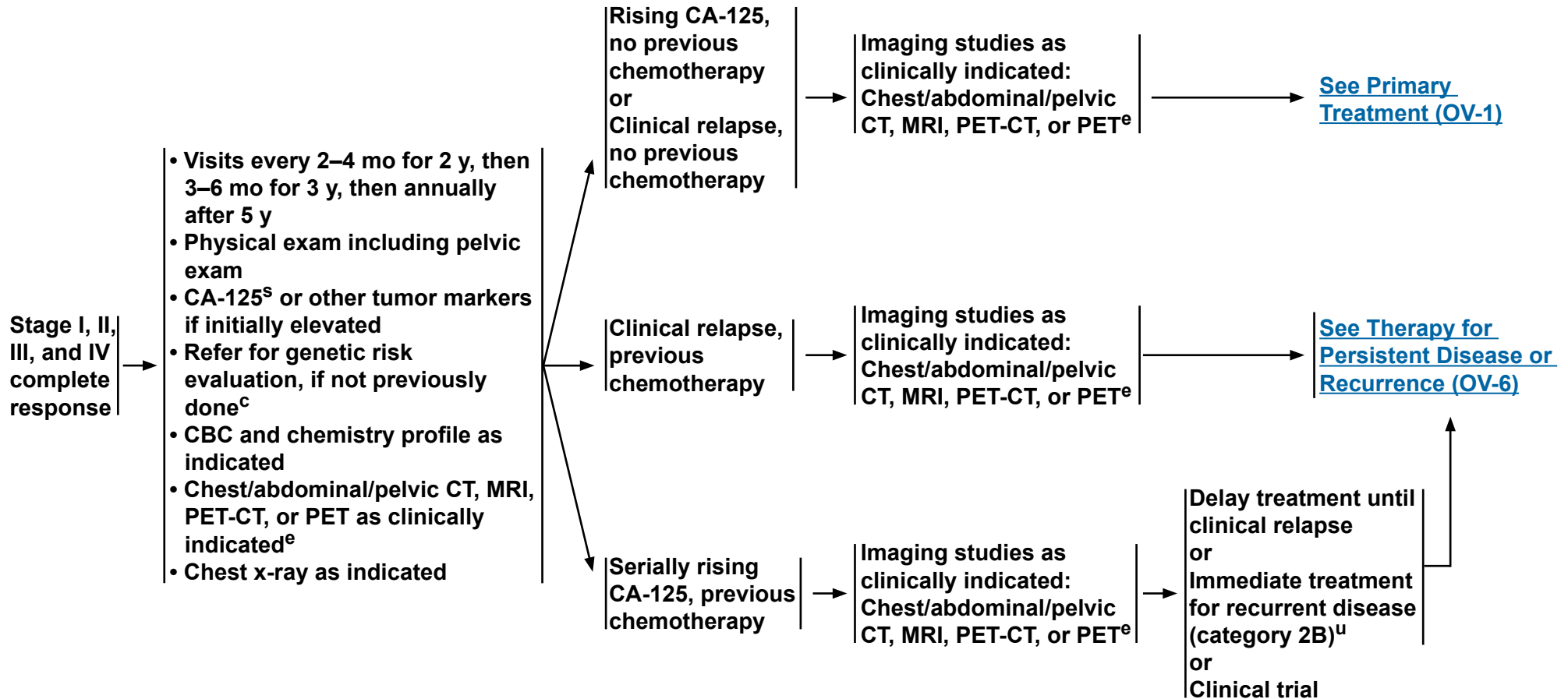


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Epithelial Ovarian Cancer/Fallopian Tube Cancer/ Primary Peritoneal Cancer

MONITORING/FOLLOW-UP

RECURRENT DISEASE[†]



^cSee [NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian](#) and [NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal](#).

^eImaging performed with contrast unless contraindicated.

[§]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](#).

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

^uSee [Acceptable Recurrence Therapies \(OV-B, 5 of 7\)](#).

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

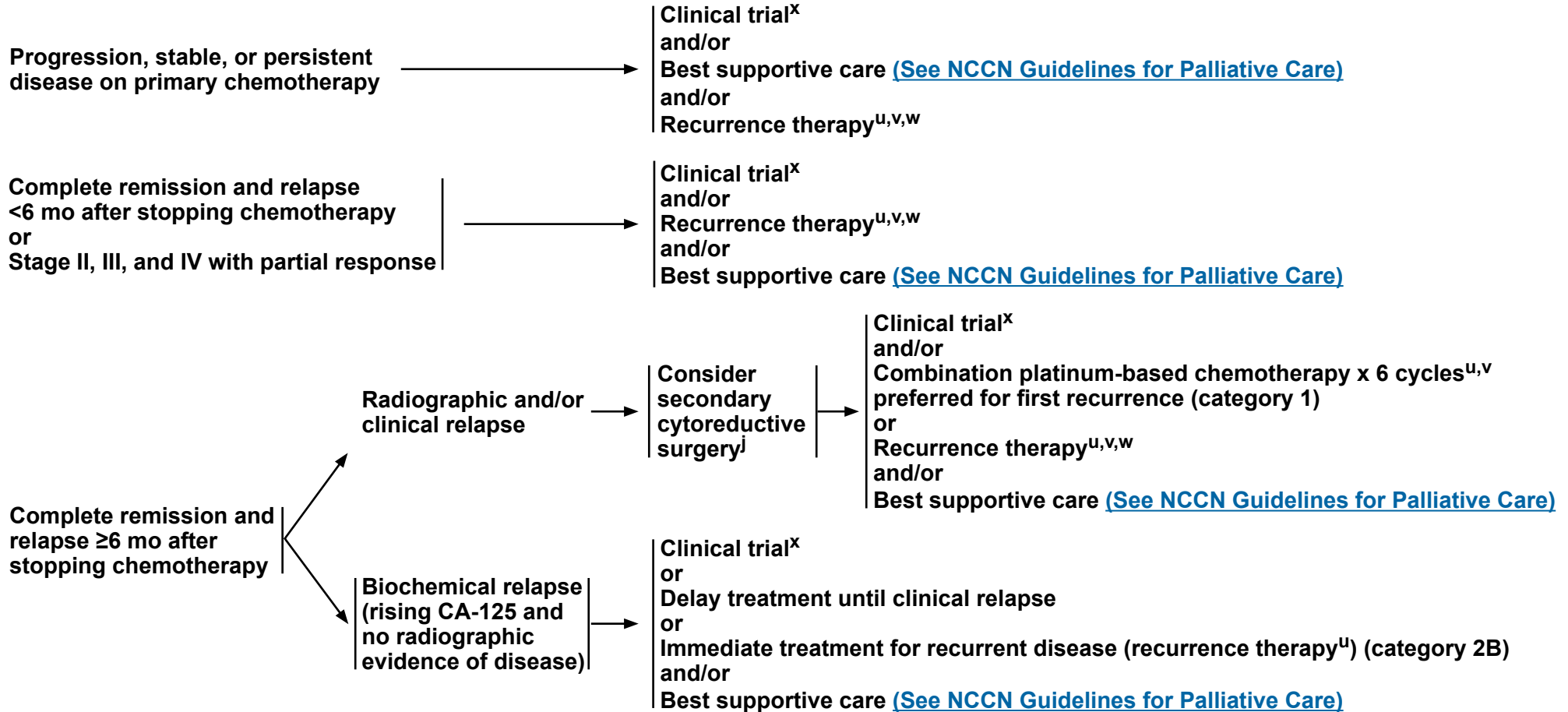
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Epithelial Ovarian Cancer/Fallopian Tube Cancer/ Primary Peritoneal Cancer

DISEASE STATUS^c

THERAPY FOR PERSISTENT DISEASE OR RECURRENCE^{u,v,w}



^cSee [NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian](#) and [NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal](#).
^jSee [Principles of Surgery \(OV-A\)](#).

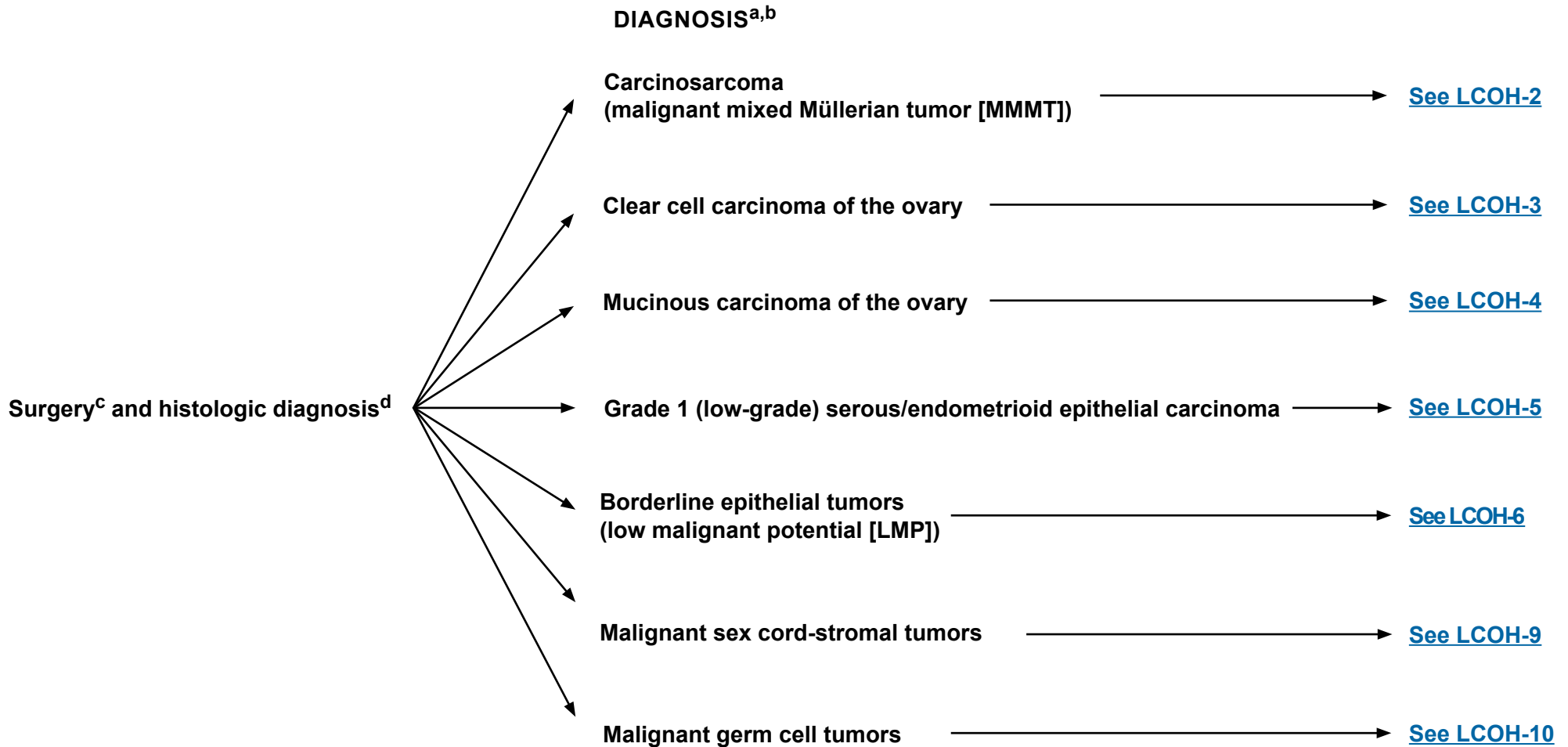
^uSee [Acceptable Recurrence Therapies \(OV-B, 5 of 7\)](#).

^vPatients 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.

^wSee [Ancillary Palliative Surgical Procedures in Principles of Surgery \(OV-A 4 of 4\)](#).

^xClinical trials with newer agents should be strongly considered.

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



^a[See 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.

^c[See Principles of Surgery \(OV-A\).](#)

^dLess common ovarian histopathologies are typically diagnosed after surgery. [See Workup \(OV-1\).](#)

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

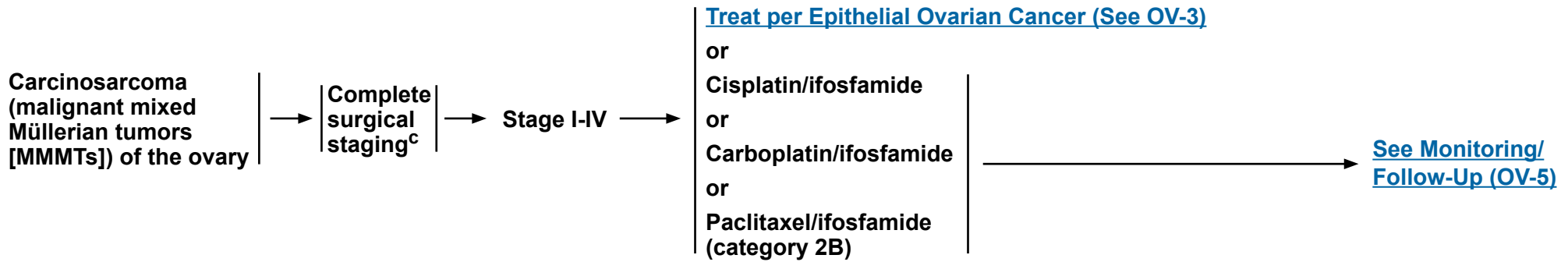
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Carcinosarcoma (Malignant Mixed Müllerian Tumors)

PATHOLOGIC DIAGNOSIS^a

ADJUVANT TREATMENT^e

MONITORING/FOLLOW-UP



^a[See WHO Histologic Classification \(OV-D\).](#)

^c[See Principles of Surgery \(OV-A\).](#)

^e[See Principles of Chemotherapy \(OV-B\)](#) and [Management of Drug Reactions \(OV-C\).](#)

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



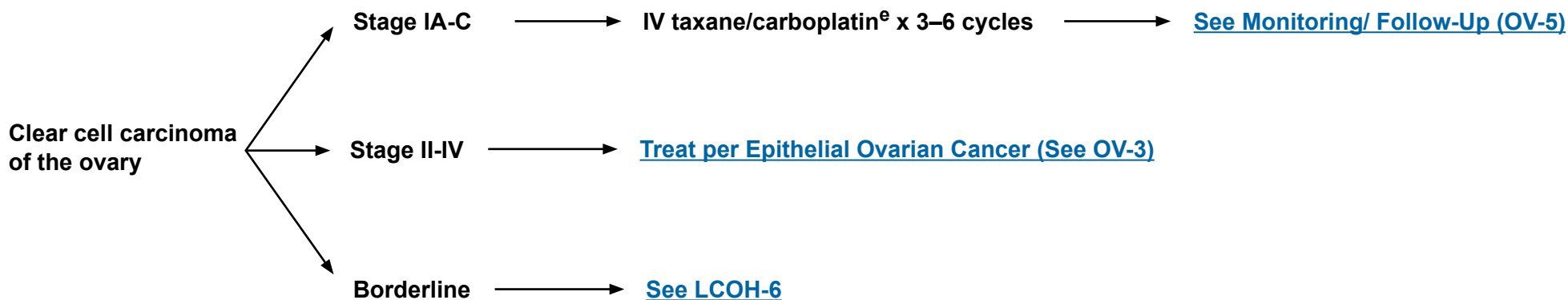
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Clear Cell Carcinoma of the Ovary

**PATHOLOGIC
DIAGNOSIS^a**

ADJUVANT TREATMENT

MONITORING/FOLLOW-UP



^aSee [WHO Histologic Classification \(OV-D\)](#).

^eSee [Principles of Chemotherapy \(OV-B\)](#) and [Management of Drug Reactions \(OV-C\)](#).

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



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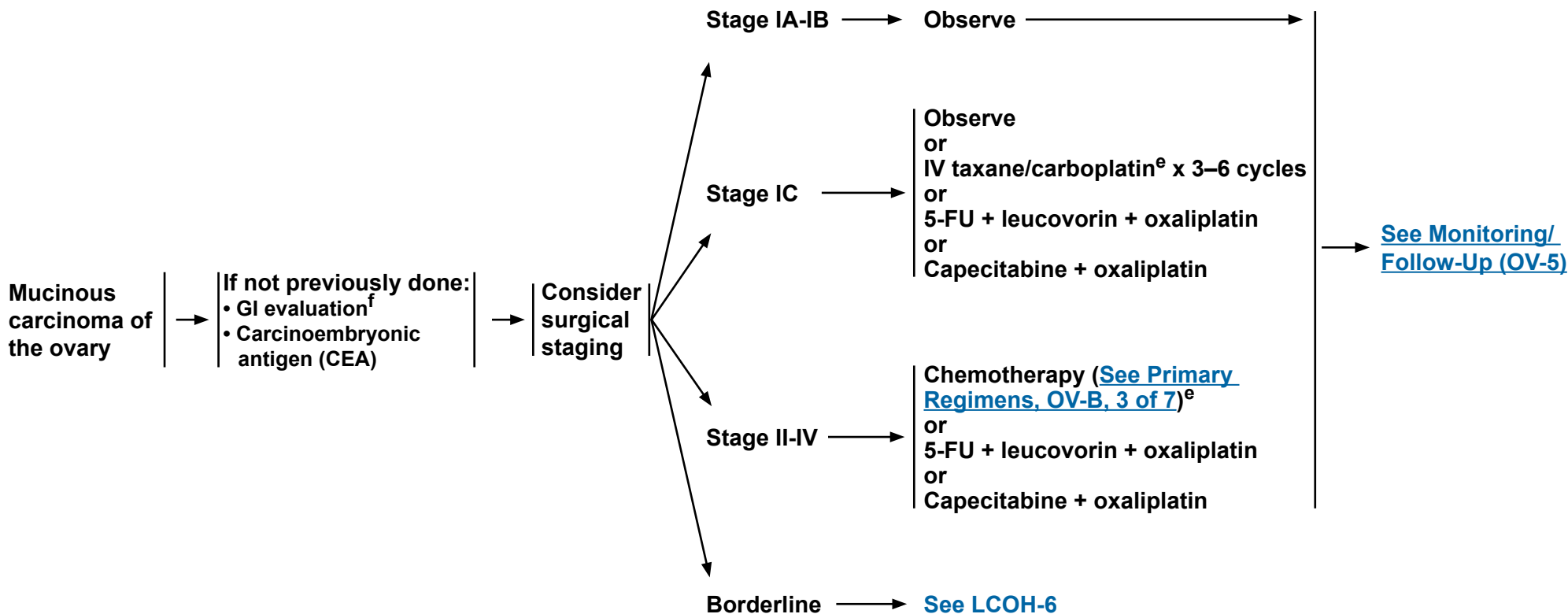
Mucinous Carcinoma of the Ovary

**PATHOLOGIC
DIAGNOSIS^a**

ADDITIONAL WORKUP

ADJUVANT TREATMENT^e

**MONITORING/
FOLLOW-UP**



^aSee [WHO Histologic Classification \(OV-D\)](#).

^eSee [Principles of Chemotherapy \(OV-B\)](#) and [Management of Drug Reactions \(OV-C\)](#).

^fConsider molecular testing for GI malignancies.

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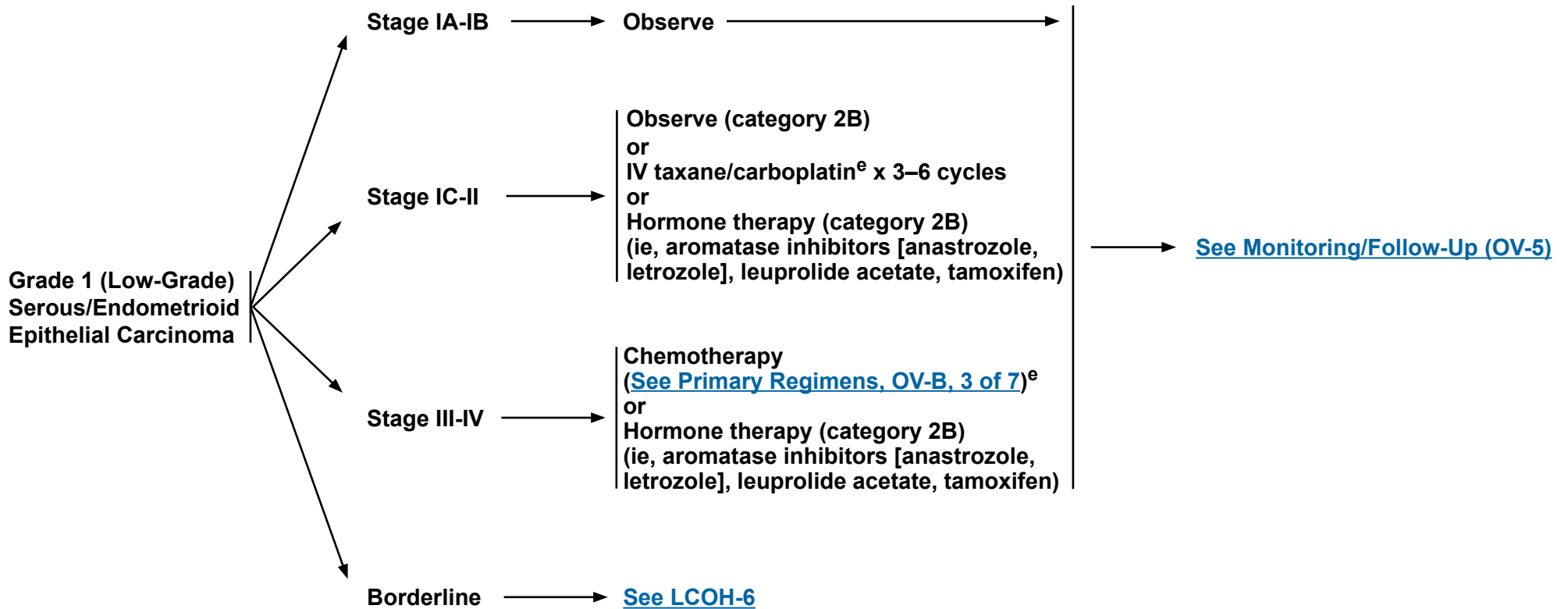
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Grade 1 (Low-Grade) Serous/Endometrioid Epithelial Carcinoma

**PATHOLOGIC
DIAGNOSIS^a**

ADJUVANT TREATMENT

MONITORING/FOLLOW-UP



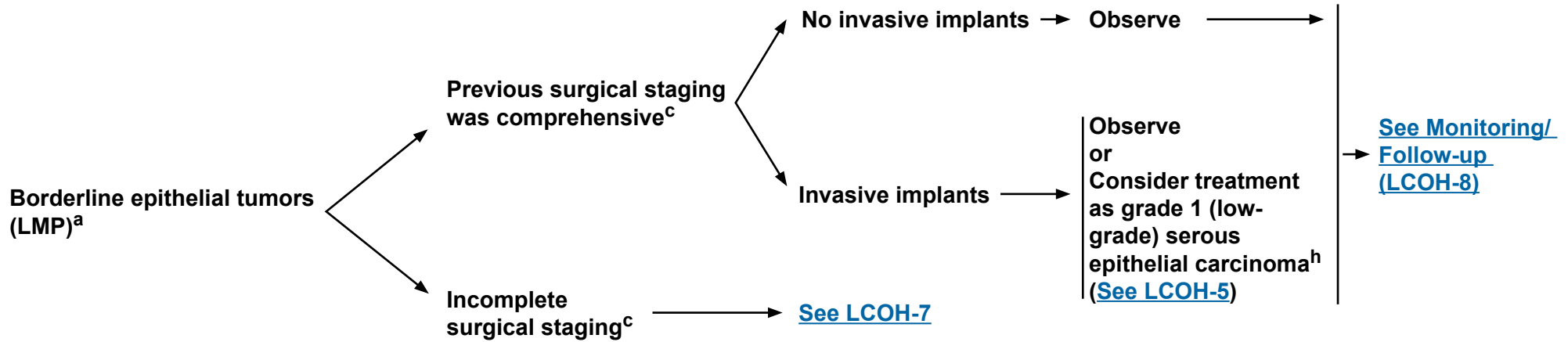
^aSee [WHO Histologic Classification \(OV-D\)](#).

^eSee [Principles of Chemotherapy \(OV-B\)](#) and [Management of Drug Reactions \(OV-C\)](#).

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

**PATHOLOGIC
DIAGNOSIS^a**

ADJUVANT TREATMENT^g



^aSee [WHO Histologic Classification \(OV-D\)](#).

^cSee [Principles of Surgery \(OV-A\)](#).

^gStandard recommendation includes a patient evaluation by a gynecologic oncologist.

^hChemotherapy (IV or IP) has not been shown to be beneficial in ovarian borderline epithelial tumors (LMP).

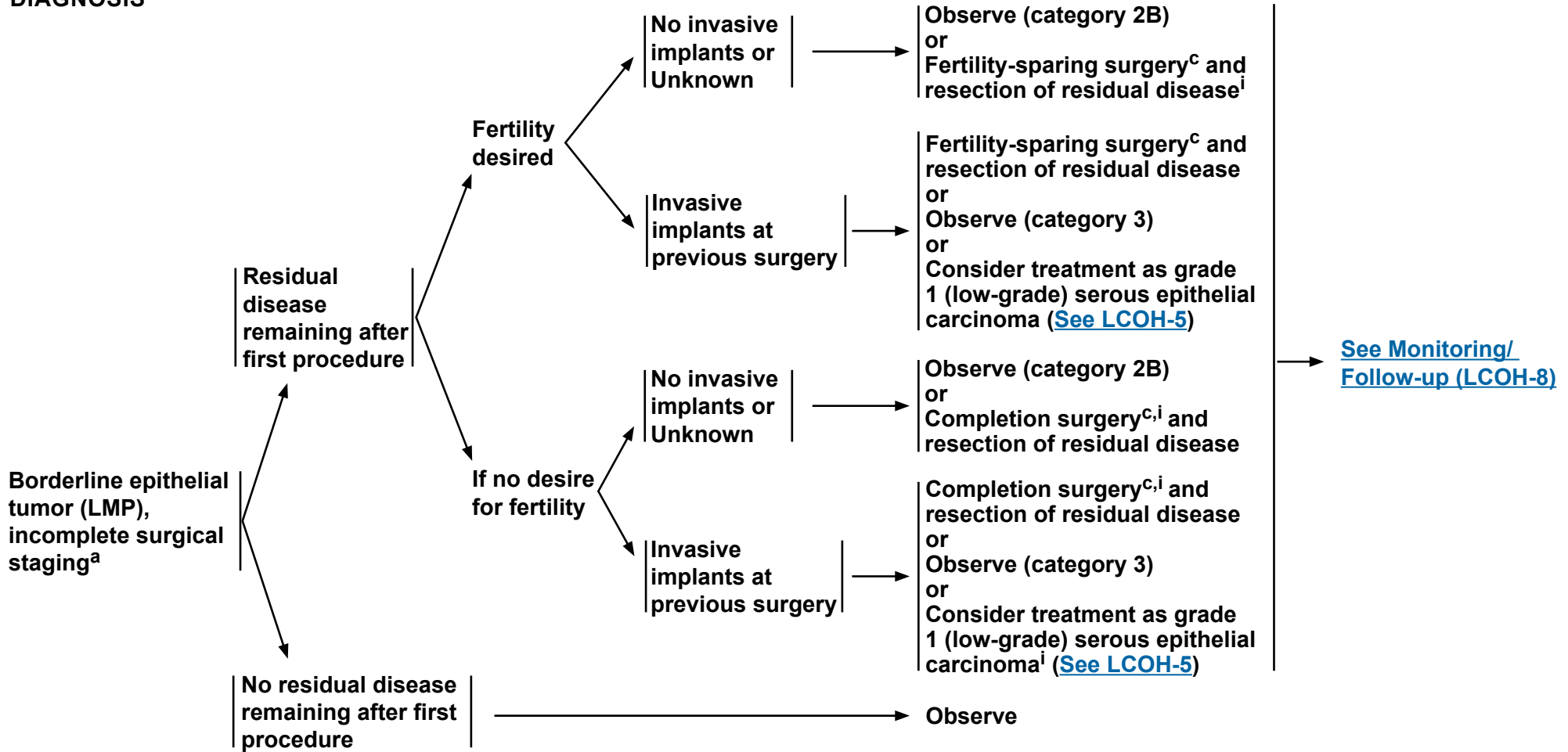
Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

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Borderline Epithelial Tumors (Low Malignant Potential)

PATHOLOGIC DIAGNOSIS^a

ADJUVANT TREATMENT^g



^aSee [WHO Histologic Classification \(OV-D\)](#).

^cSee [Principles of Surgery \(OV-A\)](#).

^gStandard recommendation includes a patient evaluation by a gynecologic oncologist.

^hChemotherapy (IV or IP) has not been shown to be beneficial in ovarian borderline epithelial tumors (LMP).

ⁱFor pathologically proven LMP, lymph node evaluation may be considered on a case-by-case basis.

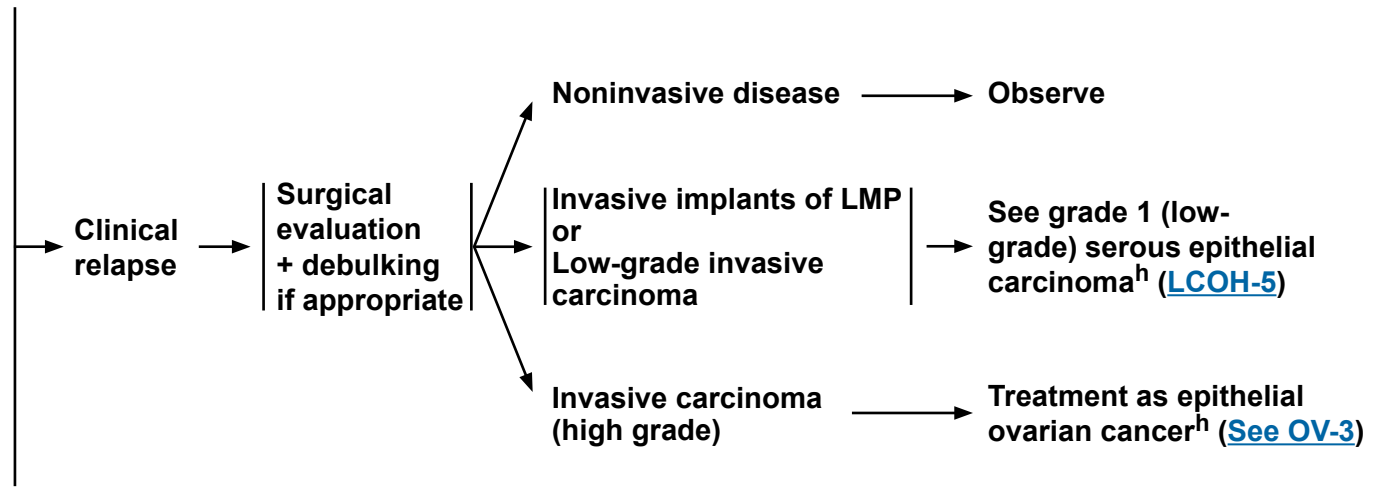
Note: All recommendations are category 2A unless otherwise indicated.

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

MONITORING/FOLLOW-UP

- Visits every 3–6 mo for up to 5 y, then annually
- Physical exam including pelvic exam
- CA-125^j 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^k
- Ultrasound as indicated for patients with fertility-sparing surgery

RECURRENT DISEASE



RECURRENCE THERAPY

^hChemotherapy (IV or IP) has not been shown to be beneficial in ovarian borderline epithelial tumors (LMP).

^jThere 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](#).

^kImaging performed with contrast unless contraindicated.

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

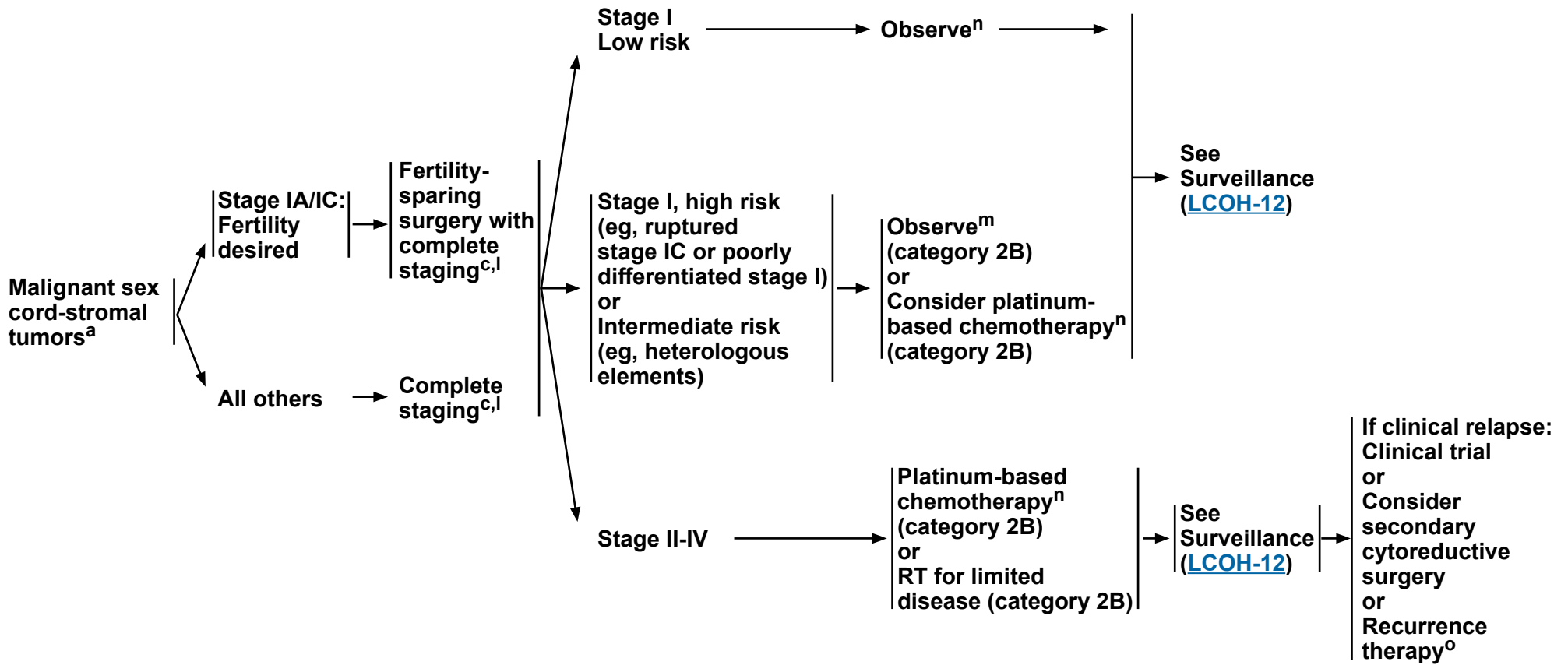
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Malignant Sex Cord-Stromal Tumors

**CLINICAL PRESENTATION/
DIAGNOSIS**

**ADJUVANT
TREATMENT**

**RECURRENCE
THERAPY**



^aSee [WHO Histologic Classification \(OV-D\)](#).

^cSee [Principles of Surgery \(OV-A\)](#).

^lLymphadenectomy may be omitted.

^mInhibin levels can be followed if initially elevated for granulosa cell tumors (category 2B).

ⁿMalignant germ cell regimens or paclitaxel/carboplatin regimens are preferred. See [Primary Chemotherapy Regimens for Malignant Germ Cell/Sex Cord-Stromal Tumors \(OV-B, 4 of 7\)](#).

^oSee [Acceptable Recurrence Therapies for Malignant Germ Cell/Sex Cord-Stromal Tumors \(OV-B, 6 of 7\)](#).

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

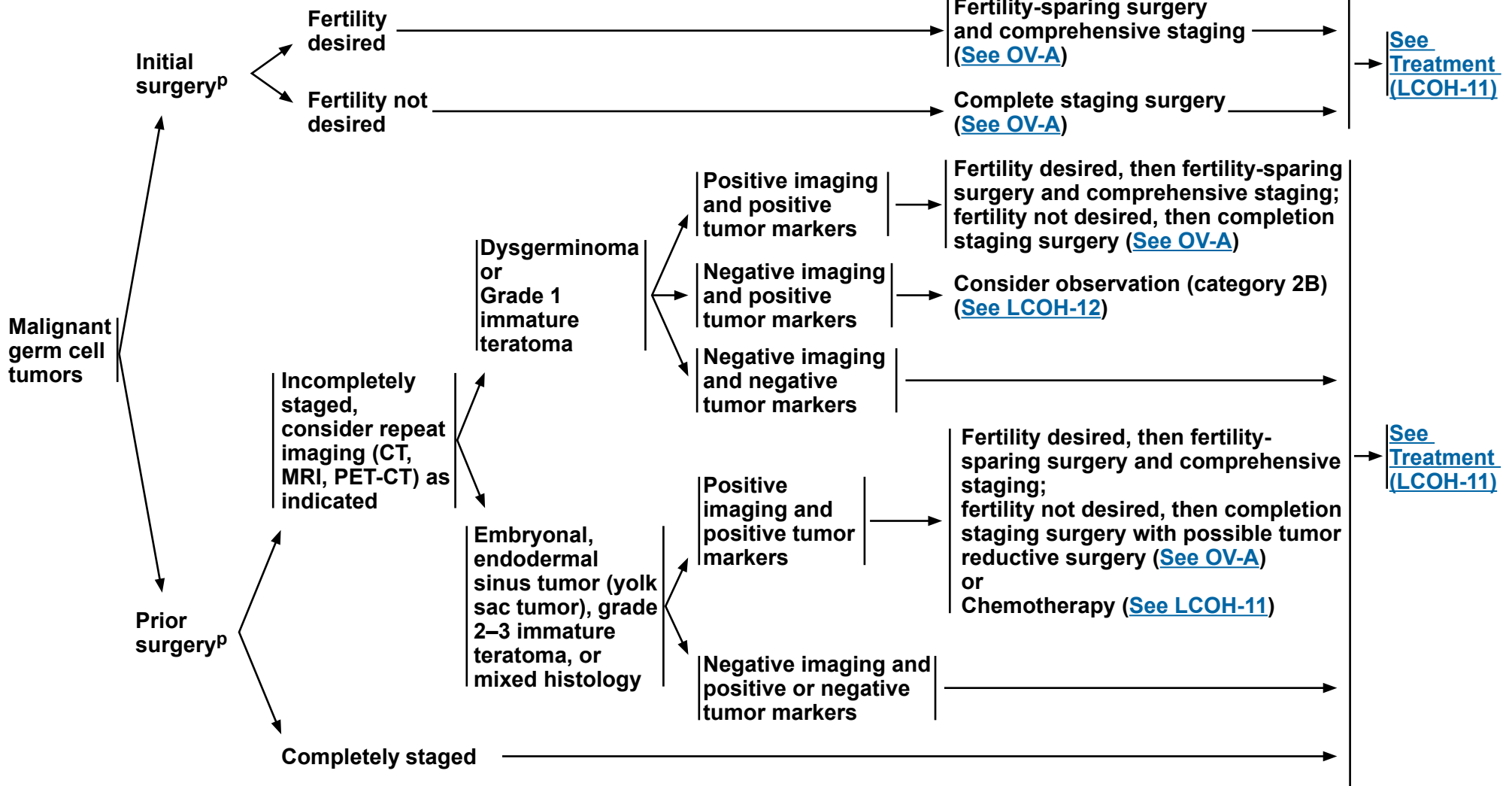


NCCN Guidelines Version 1.2016

Malignant Germ Cell Tumors

CLINICAL PRESENTATION/ DIAGNOSIS

ADJUVANT TREATMENT⁹



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

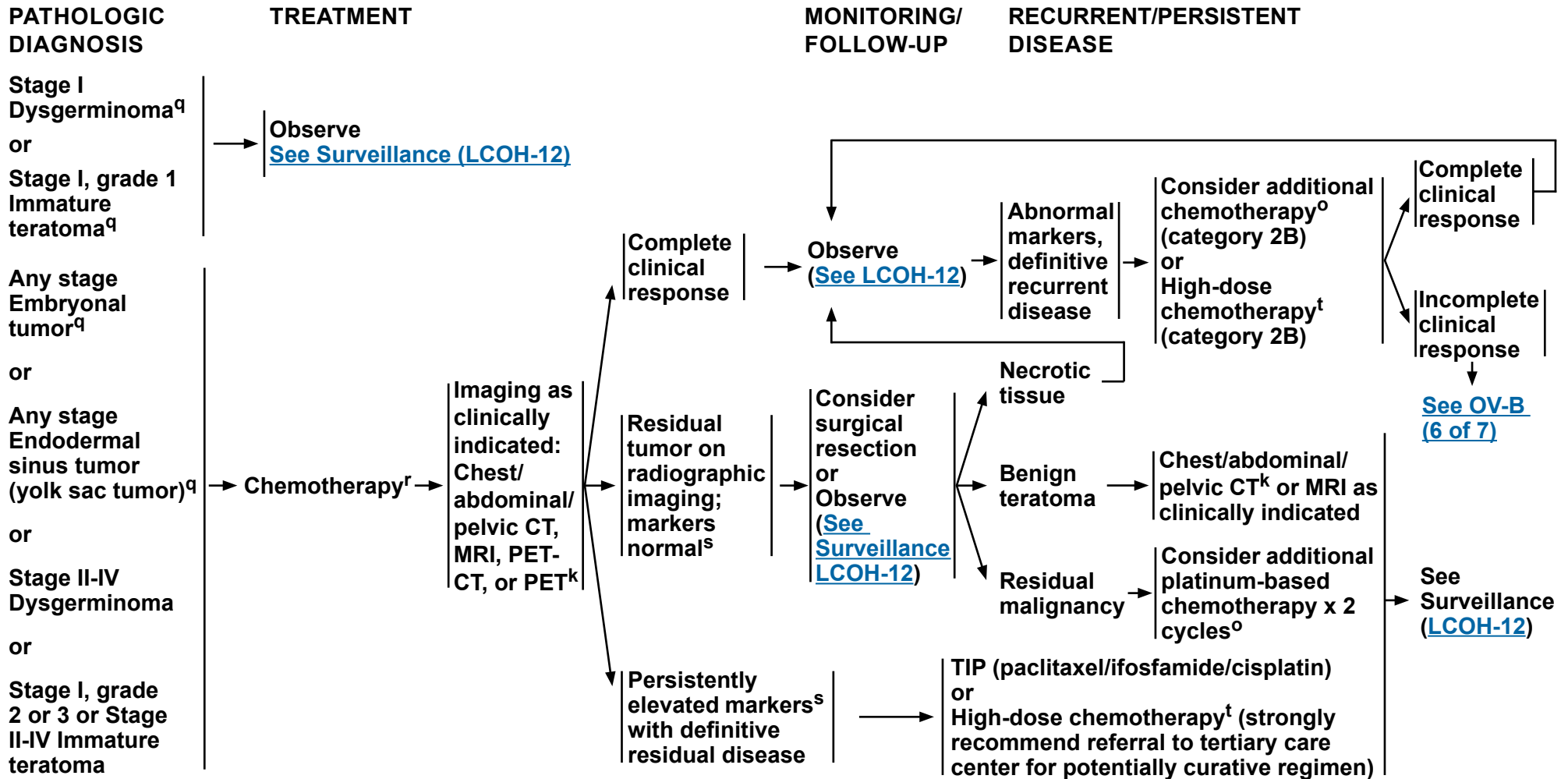
^PSurgical principles for pediatric/young adult patients may differ from those for adult patients. [See Principles of Surgery \(OV-A\)](#).

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

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

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Malignant Germ Cell Tumors



^kImaging performed with contrast unless contraindicated.

^o[See Acceptable Recurrence Therapies for Malignant Germ Cell/Sex Cord-Stromal Tumors \(OV-B, 6 of 7\).](#)

^qPediatric/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.

^r[See Primary Chemotherapy Regimens for Malignant Germ Cell Tumors \(OV-B, 4 of 7\).](#)

^s[See LCOH-1 for markers.](#)

^tHigh-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 1.2016

Malignant Germ Cell and Sex Cord-Stromal Tumors

SURVEILLANCE FOR GERM CELL AND SEX CORD-STROMAL TUMORS^u

	Years				
	<1	1–2	2–3	3–5	>5
<u>Physical exam</u>					
Germ cell tumors	Every 2–4 mo	Every 2–4 mo	Yearly	Yearly	Yearly
Sex cord-stromal tumors	Every 2–4 mo	Every 2–4 mo	Every 6 mo	Every 6 mo	Every 6 mo
<u>Serum tumor markers**</u>					
Germ cell tumors	Every 2–4 mo	Every 2–4 mo	Not indicated	Not indicated	Not indicated
Sex cord-stromal tumors	Every 2–4 mo	Every 2–4 mo	Every 6 mo	Every 6 mo	Every 6 mo
<u>Radiographic imaging*</u>					
Germ cell tumors	As clinically indicated unless markers normal at initial presentation	As clinically indicated unless markers normal at initial presentation	As clinically indicated	As clinically indicated	As clinically indicated
Sex cord-stromal tumors	Insufficient data to support routine use	Insufficient data to support routine use	Insufficient data to support routine use	Insufficient data to support routine use	Insufficient data to support routine use
<u>Recurrence suspected</u>	CT scan and tumor markers**	CT scan and tumor markers**	CT scan and tumor markers**	CT scan and tumor markers**	CT scan and tumor markers**

*Chest x-ray, chest/abdominal/pelvic CT, MRI, PET-CT, or PET; with contrast unless contraindicated.

**See [OV-1](#) for markers.

^uAdapted with permission, 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.

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NCCN Guidelines Version 1.2016

Epithelial Ovarian Cancer/Fallopian Tube Cancer/ Primary Peritoneal Cancer & Less Common Histopathologies

PRINCIPLES OF SURGERY (1 of 4)¹

General considerations

- An open laparotomy including a vertical midline abdominal incision should be used in 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.
- Intraoperative pathologic evaluation with frozen sections may assist in management.
- For select patients, a minimally invasive surgical approach may be employed by an experienced surgeon to achieve the surgical staging and debulking principles subsequently described.
- Patients who are unable to be optimally debulked using minimally invasive techniques should be converted to an open procedure.
- Minimally invasive surgical approaches may be useful when evaluating whether maximum cytoreduction can be achieved in patients with newly diagnosed or recurrent ovarian cancer. If clinical judgment indicates that maximum cytoreduction cannot be achieved, neoadjuvant chemotherapy should be considered.
- It is recommended that a gynecologic oncologist perform the appropriate surgery.

Operative reports

- Surgeons should describe the following in the operative report:
 - ▶ Extent of initial disease before debulking pelvis, midabdomen, 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.

[Continued on OV-A \(2 of 4\)](#)

¹Fleming GF, Seidman J, Lengyel E, et al: Epithelial ovarian cancer. In Barakat RR, Berchuck A, Markman M, et al. (eds): Principles and Practice of Gynecologic Oncology, 6th ed, Philadelphia, Lippincott Williams & Wilkins, 2013:757-847. Amended by panel.

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

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NCCN Guidelines Version 1.2016

Epithelial Ovarian Cancer/Fallopian Tube Cancer/ Primary Peritoneal Cancer & Less Common Histopathologies

PRINCIPLES OF SURGERY (2 of 4)¹

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 may be considered.
- 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.²

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.³

- 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.
- Those patients with tumor nodules outside the pelvis ≤ 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 ureteroneocystotomy, 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.

¹Fleming GF, Seidman J, Lengyel E, et al: Epithelial ovarian cancer. In Barakat RR, Berchuck A, Markman M, et al. (eds): Principles and Practice of Gynecologic Oncology, 6th ed, Philadelphia, Lippincott Williams & Wilkins, 2013:757-847. Amended by panel.

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

³Chi 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 on OV-A \(3 of 4\)](#)

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

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NCCN Guidelines Version 1.2016

Epithelial Ovarian Cancer/Fallopian Tube Cancer/ Primary Peritoneal Cancer & Less Common Histopathologies

PRINCIPLES OF SURGERY (3 of 4)¹

Interval cytoreduction after neoadjuvant chemotherapy of invasive epithelial ovarian cancer

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

- Interval cytoreductive surgery should be performed after ≤ 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.
- 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 cytoreduction include bowel resection and/or appendectomy, stripping of the diaphragm or other peritoneal surfaces, splenectomy, partial cystectomy and/or ureteroneocystotomy, partial hepatectomy, partial gastrectomy, cholecystectomy, and/or distal pancreatectomy.

Risk-Reducing Salpingo-Oophorectomy (RRSO) Protocol

- Perform operative laparoscopy.
- 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.⁴
- Engage in minimal instrument handling of the tubes and ovaries to avoid traumatic exfoliation of cells.⁴
- 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.⁵
- If occult malignancy or 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 by 50%. [See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian.](#)

¹Fleming GF, Seidman J, Lengyel E, et al: Epithelial ovarian cancer. In Barakat RR, Berchuck A, Markman M, et al. (eds): Principles and Practice of Gynecologic Oncology, 6th ed, Philadelphia, Lippincott Williams & Wilkins, 2013:757-847. Amended by panel.

⁴Powell 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.

⁵Mingels 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.

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

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

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NCCN Guidelines Version 1.2016

Epithelial Ovarian Cancer/Fallopian Tube Cancer/ Primary Peritoneal Cancer & Less Common Histopathologies

PRINCIPLES OF SURGERY (4 of 4)¹

Special Circumstances

- **Fertility-sparing surgery:** USO preserving the uterus and contralateral ovary (fertility-sparing surgery) can be considered for patients with apparent early-stage disease and/or good-risk tumors (early-stage invasive epithelial tumors, LMP lesions, malignant germ cell tumors, or malignant sex cord-stromal tumors) who wish to preserve fertility. 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.
- **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 should be performed at primary surgery in patients with a suspected or confirmed mucinous ovarian neoplasm.
- **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. Patients are encouraged to participate in ongoing trials evaluating the true benefit of secondary cytoreduction.

Ancillary Palliative Surgical Procedures

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

¹Fleming GF, Seidman J, Lengyel E, et al: Epithelial ovarian cancer. In Barakat RR, Berchuck A, Markman M, et al. (eds): Principles and Practice of Gynecologic Oncology, 6th ed, Philadelphia, Lippincott Williams & Wilkins, 2013:757-847. Amended by panel.

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NCCN Guidelines Version 1.2016

Epithelial Ovarian Cancer/Fallopian Tube Cancer/ Primary Peritoneal Cancer & Less Common Histopathologies

PRINCIPLES OF SYSTEMIC THERAPY (1 of 7)

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 the initiation of any therapy:
 - ▶ 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.
- Prior to recommending chemotherapy, requirements for adequate organ function and performance status should be met.
- 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 in 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)

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 the appropriate option. ([See OV-B 3 of 7](#) for dosing and schedule of these regimens).
- 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.

[Continued on OV-B 2 of 7](#)

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

NCCN Guidelines Version 1.2016

Epithelial Ovarian Cancer/Fallopian Tube Cancer/ Primary Peritoneal Cancer & Less Common Histopathologies

PRINCIPLES OF SYSTEMIC THERAPY (2 of 7)

For patients who have 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) The patient's 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.](#)
- 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.

For elderly patients (>age 65) and/or those with comorbidities

- Elderly patients and those with comorbidities may be intolerant to the combination chemotherapy regimens recommended in these NCCN Guidelines. Single-agent platinum agents may be appropriate in selected patients.
 - ▶ Algorithms have been developed for predicting chemotherapy toxicity. See the [NCCN Guidelines for Older Adult Oncology.](#)

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.

[Continued on OV-B 3 of 7](#)

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NCCN Guidelines Version 1.2016

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^a

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^c 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^b

- ▶ Paclitaxel 175 mg/m² IV over 3 hours followed by carboplatin^d 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 carboplatin^d 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.^e (category 1)
- ▶ Docetaxel 60–75 mg/m² IV over 1 hour followed by carboplatin^d 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 carboplatin^d 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)
or
Paclitaxel 175 mg/m² IV over 3 hours followed by carboplatin^d 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
- ▶ Capecitabine/oxaliplatin

• Borderline epithelial carcinoma and grade 1 (low-grade) serous/endometrioid

- ▶ Hormone therapy (Aromatase inhibitors [ie, anastrozole, letrozole], leuprolide acetate, tamoxifen) (category 2B)

^aSee [Discussion](#) for references.

^bIV regimens may be considered for neoadjuvant therapy for epithelial ovarian cancer.

^cThe published randomized trial regimen used IV continuous infusion paclitaxel over 24 h.

^dDue to changes in creatinine methodology, changes regarding carboplatin dosing can be considered. See [FDA carboplatin dosing statement](#).

^eThis regimen may be considered for elderly patients or those with poor performance status.

[Continued on
OV-B \(4 of 7\)](#)

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

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Epithelial Ovarian Cancer/Fallopian Tube Cancer/ Primary Peritoneal Cancer & Less Common Histopathologies

PRINCIPLES OF SYSTEMIC THERAPY (4 of 7) Primary Chemotherapy/Primary Adjuvant Therapy Regimens^a Malignant Germ Cell/Sex Cord-Stromal Tumors

Malignant Germ Cell Tumors^a

- BEP (bleomycin, etoposide, cisplatin)^f
 - ▶ 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/carboplatin^a
 - ▶ For select patients with stage IB-III 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)^f
- Paclitaxel/carboplatin (category 2B)

^aSee [Discussion](#) for references.

^fRecommend pulmonary function test if considering bleomycin.

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[Continued on OV-B \(5 of 7\)](#)

NCCN Guidelines Version 1.2016

Epithelial Ovarian Cancer/Fallopian Tube Cancer/ Primary Peritoneal Cancer & Less Common Histopathologies

PRINCIPLES OF SYSTEMIC THERAPY (5 of 7)

Acceptable Recurrence Therapies for Epithelial Ovarian/Fallopian Tube/Primary Peritoneal Cancer^g

	Cytotoxic Therapy (In alphabetical order)	Hormonal Therapy	Targeted Therapy	Radiation Therapy
Preferred Agents	Platinum-Sensitive Disease^{h,i} Carboplatin ¹ Carboplatin/docetaxel ^{2,3} Carboplatin/gemcitabine ¹ Carboplatin/gemcitabine/bevacizumab ^{j,k} (category 2B) ⁴ Carboplatin/liposomal doxorubicin ⁵ (category 1) Carboplatin/paclitaxel (category 1) ⁶ Carboplatin/paclitaxel (weekly) ⁷ Cisplatin ⁶ Cisplatin/gemcitabine ⁸		Single Agents Bevacizumab ^{j,k,18,19} Olaparib ^{m,20,21}	
	Platinum-Resistant Disease Docetaxel ⁹ Etoposide, oral ¹⁰ Gemcitabine ^{11,12} Liposomal doxorubicin ^{11,12} Liposomal doxorubicin/bevacizumab ^{j,k,13} Paclitaxel (weekly) ¹⁴ ± pazopanib ¹⁵ Paclitaxel (weekly)/bevacizumab ^{j,k,13} Topotecan ^{16,17} Topotecan/bevacizumab ^{j,k,13}		Single Agents Bevacizumab ^{j,k,18,19} Olaparib ^{m,20,21}	
Other Potentially Active Agents	Single Agents^{1,22} Altretamine Capecitabine Cyclophosphamide Doxorubicin Ifosfamide Irinotecan Melphalan Oxaliplatin Paclitaxel Paclitaxel, albumin bound (nab-paclitaxel) Pemetrexed Vinorelbine	Aromatase inhibitors Leuprolide acetate Megestrol acetate Tamoxifen	Pazopanib (category 2B) ²³	Palliative localized radiation therapy

^gPatients who progress on two consecutive therapy 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.

^hIn general, the panel would recommend combination regimens based on randomized trial data, especially in first relapses.

ⁱPlatinum-based combination therapy should be considered for platinum-sensitive recurrences.

^jIn patients who have not previously received bevacizumab.

^kContraindicated for patients at increased risk of gastrointestinal perforation.

^lMany of these agents have not been tested in patients who have been treated with modern chemotherapy regimens.

^mFor 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 or more lines of chemotherapy.²

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[Continued on OV-B \(6 of 7\)](#)

[References on OV-B \(7 of 7\)](#)

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Epithelial Ovarian Cancer/Fallopian Tube Cancer/ Primary Peritoneal Cancer & Less Common Histopathologies

PRINCIPLES OF SYSTEMIC THERAPY (6 of 7)

Acceptable Recurrence Therapies For Malignant Germ Cell/Sex Cord-Stromal Tumors

	Cytotoxic Therapy (In alphabetical order)	Hormonal Therapy	Targeted Therapy	Radiation Therapy
Malignant Germ Cell Tumorsⁿ	<p>Potentially Curative Therapy: High-dose chemotherapyⁿ TIP (paclitaxel, ifosfamide, cisplatin)</p> <p>Palliative Therapy Only: Cisplatin/etoposide Docetaxel Docetaxel/carboplatin Paclitaxel Paclitaxel/ifosfamide Paclitaxel/carboplatin Paclitaxel/gemcitabine VIP (etoposide, ifosfamide, cisplatin) VeIP (vinblastine, ifosfamide, cisplatin) VAC (vincristine, dactinomycin, cyclophosphamide) TIP Supportive care only (See NCCN Supportive Care Guidelines)</p>			Palliative localized radiation therapy
Malignant Sex Cord-Stromal Tumors^o	<p>Docetaxel Paclitaxel Paclitaxel/ifosfamide Paclitaxel/carboplatin VAC Supportive care only (See NCCN Supportive Care Guidelines)</p>	<p>Aromatase inhibitors (ie, anastrozole, letrozole) Leuprolide acetate (for granulosa cell tumors) Tamoxifen</p>	Bevacizumab (single agent)	Palliative localized radiation therapy

ⁿHigh-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.

^oSee [WHO Histologic Classification \(OV-D\)](#).

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Epithelial Ovarian Cancer/Fallopian Tube Cancer/ Primary Peritoneal Cancer & Less Common Histopathologies

PRINCIPLES OF SYSTEMIC THERAPY (7 of 7)

REFERENCES FOR ACCEPTABLE RECURRENT THERAPIES

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NCCN Guidelines Version 1.2016

Epithelial Ovarian Cancer/Fallopian Tube Cancer/ Primary Peritoneal Cancer & Less Common Histopathologies

MANAGEMENT OF DRUG REACTIONS (1 of 7)

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.¹
 - ▶ 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.^{2,3}
 - ▶ 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.⁴⁻⁶
 - ▶ 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.¹
 - ▶ 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).³
- 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.⁵
 - ▶ 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 respond to an allergen and can be considered an option for patients who have had drug reactions.^{1,7-9}
- 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.

[References on OV-C 3 of 7](#)

[Continued on OV-C 2 of 7](#)

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MANAGEMENT OF DRUG REACTIONS (2 of 7)

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.¹⁰
- More common with paclitaxel (27% of patients); however, mild reactions can occur with liposomal doxorubicin.¹⁰
- If an infusion reaction has previously occurred 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.^{7,11} 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, and changes in bowel function and occasionally feeling of impending doom.
- Symptoms may continue to persist after stopping infusion and/or after treatment interventions.
- More common with platinum drugs such as carboplatin (16% of patients), cisplatin, and oxaliplatin.¹¹ Mild reactions can occur with platinum agents.¹¹
- 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).¹¹⁻¹³
 - ▶ Patients who have had mild reactions may develop more serious reactions even when the platinum drug is slowly infused.¹¹
 - ▶ For very severe life-threatening reactions (ie, anaphylaxis), the implicated drug should not be used again unless under guidance of an allergist or specialist with desensitization experience.
 - ▶ For more severe reactions--such as those involving blood pressure changes, dyspnea, tachycardia, widespread urticaria, or hypoxia--the treating clinician should consult an allergist or specialist with desensitization expertise prior to rechallenge.
 - ▶ 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.⁷⁻⁹

[References on OV-C 3 of 7](#)

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Epithelial Ovarian Cancer/Fallopian Tube Cancer/ Primary Peritoneal Cancer & Less Common Histopathologies

MANAGEMENT OF DRUG REACTIONS (3 of 7)

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

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

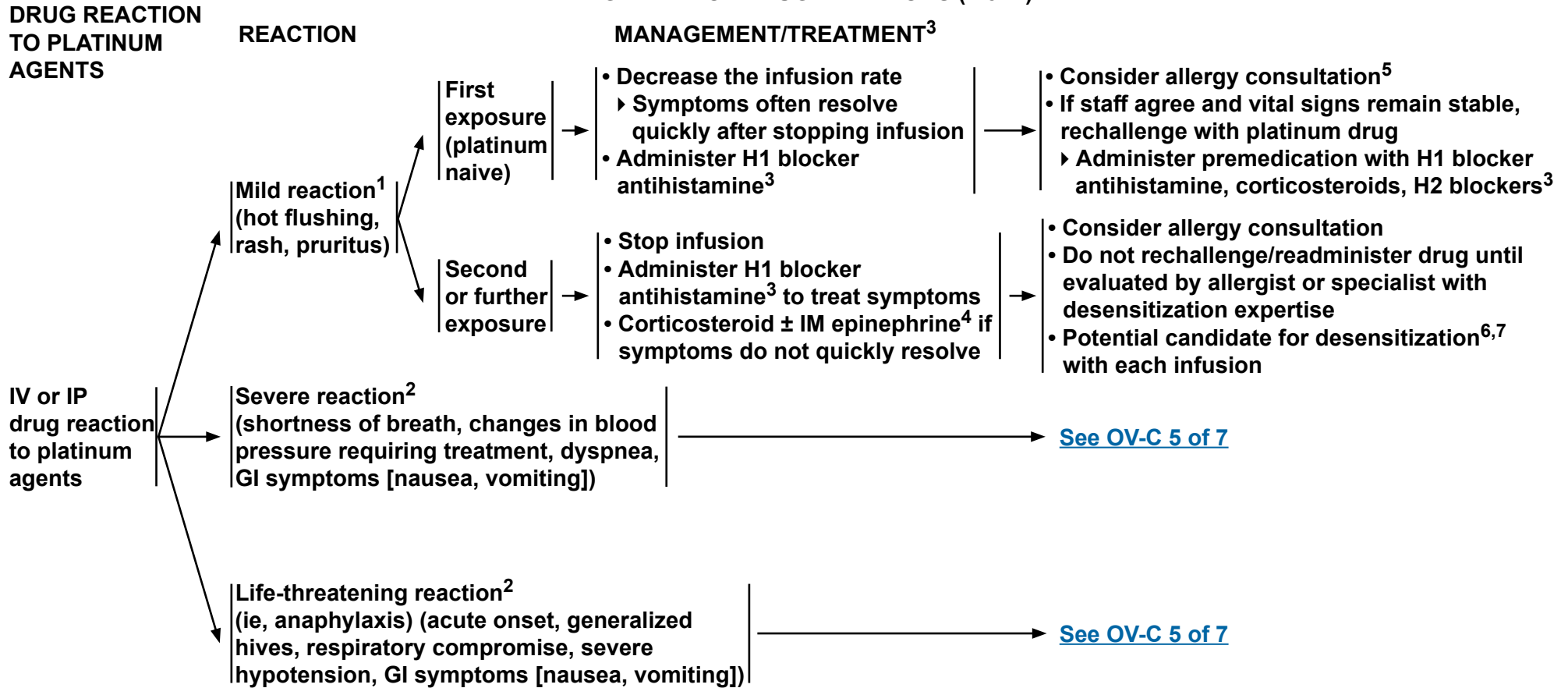
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Epithelial Ovarian Cancer/Fallopian Tube Cancer/ Primary Peritoneal Cancer & Less Common Histopathologies

MANAGEMENT OF DRUG REACTIONS (4 of 7)



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

¹Most 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).

²Most severe reactions are allergic reactions and more commonly are caused by platinum agents.

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

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

⁵Mild 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.

⁶Referral to academic center with expertise in desensitization is preferred.

⁷Castells 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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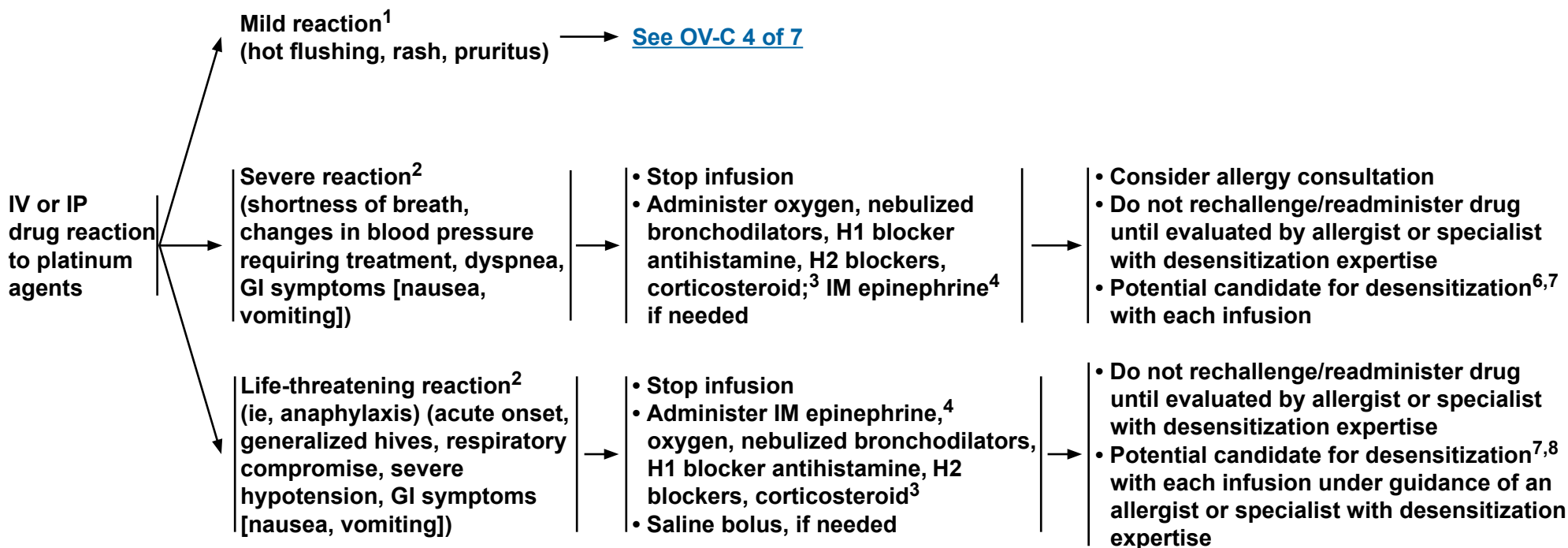


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Epithelial Ovarian Cancer/Fallopian Tube Cancer/ Primary Peritoneal Cancer & Less Common Histopathologies

MANAGEMENT OF DRUG REACTIONS (5 of 7)

DRUG REACTION TO PLATINUM AGENTS



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

¹Most 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).

²Most severe reactions are allergic reactions and more commonly are caused by platinum agents.

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

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

⁶Referral to academic center with expertise in desensitization is preferred.

⁷Castells 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.

⁸For 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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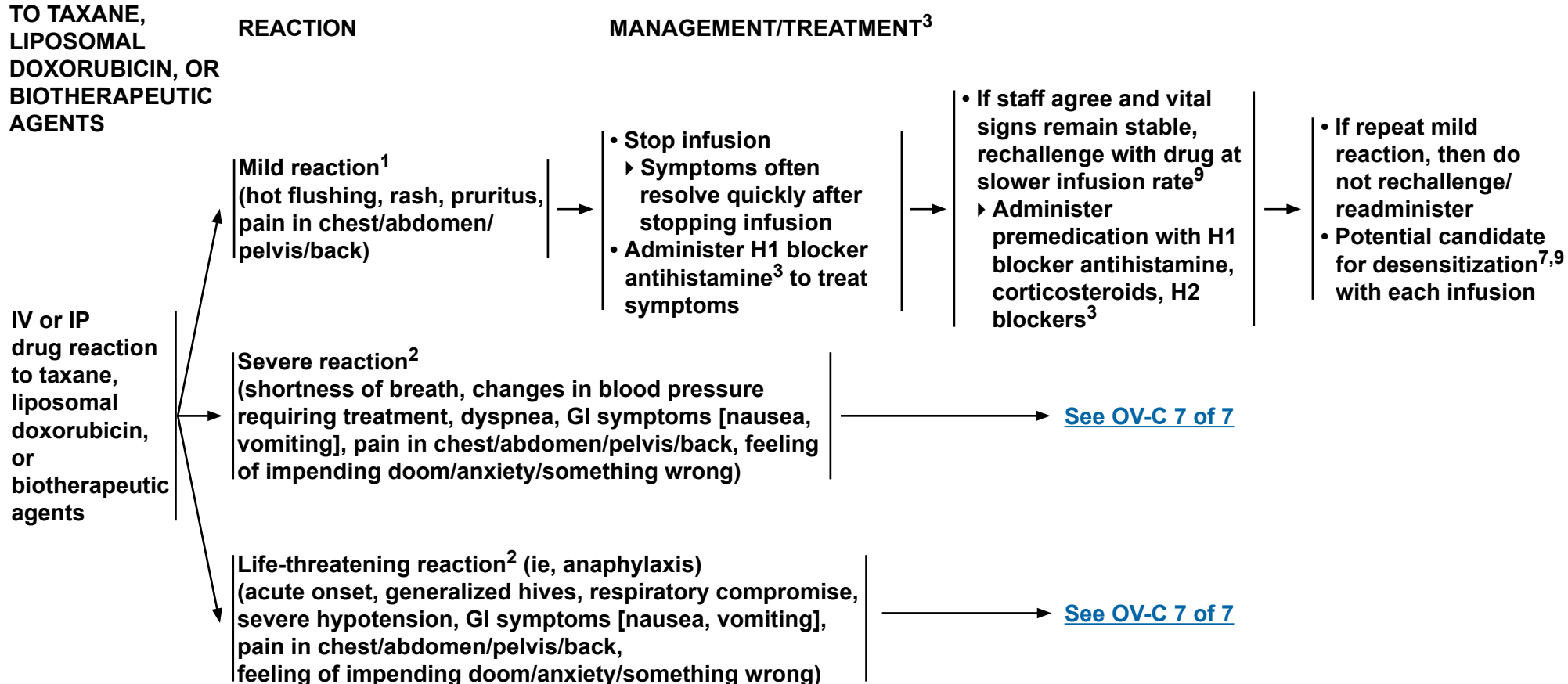


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Epithelial Ovarian Cancer/Fallopian Tube Cancer/ Primary Peritoneal Cancer & Less Common Histopathologies

DRUG REACTION TO TAXANE, LIPOSOMAL DOXORUBICIN, OR BIOTHERAPEUTIC AGENTS

MANAGEMENT OF DRUG REACTIONS (6 of 7)



¹Most 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).

²Most severe reactions are allergic reactions and more commonly are caused by platinum agents.

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

⁷Castells 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.

⁹Consider 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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NCCN Guidelines Version 1.2016

Epithelial Ovarian Cancer/Fallopian Tube Cancer/ Primary Peritoneal Cancer & Less Common Histopathologies

DRUG REACTION TO TAXANE, LIPOSOMAL DOXORUBICIN, OR BIOTHERAPEUTIC AGENTS

IV or IP drug reaction to taxane, liposomal doxorubicin, or biotherapeutic agents

REACTION

Mild reaction¹
(hot flushing, rash, pruritus, pain in chest/abdomen/pelvis/back)

Severe reaction²
(shortness of breath, changes in blood pressure requiring treatment, dyspnea, GI symptoms [nausea, vomiting], pain in chest/abdomen/pelvis/back, feeling of impending doom/ anxiety/ something wrong)

Life-threatening reaction²
(ie, anaphylaxis) (acute onset, generalized hives, respiratory compromise, severe hypotension, GI symptoms [nausea, vomiting], pain in chest/abdomen/pelvis/back, feeling of impending doom/ anxiety/ something wrong)

MANAGEMENT OF DRUG REACTIONS (7 of 7)

MANAGEMENT/TREATMENT³

[See OV-C 6 of 7](#)

- Stop infusion
- Administer oxygen, nebulized bronchodilator, H1 blocker antihistamine, H2 blockers, corticosteroid;³ IM epinephrine if needed⁴

- Do not rechallenge/readminister drug until evaluated by allergist or specialist with desensitization expertise
- Potential candidate for desensitization^{6,7} with each infusion

- Stop infusion
- Administer IM epinephrine,⁴ oxygen, nebulized bronchodilator, H1 blocker antihistamine, H2 blockers, corticosteroid³

- Do not rechallenge/readminister drug until evaluated by allergist or specialist with desensitization expertise
- As reactions can occur suddenly and be life-threatening;^{7,8} desensitization should be done with each infusion under guidance of an allergist or specialist with desensitization expertise

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

¹Most 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).

²Most severe reactions are allergic reactions and more commonly are caused by platinum agents.

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

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

⁶Referral to academic center with expertise in desensitization is preferred.

⁷Castells 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.

⁸For 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.

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

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

NCCN Guidelines Version 1.2016

Ovarian Cancer Histopathologies

WHO HISTOLOGIC CLASSIFICATION (1 of 2)^{1,2}

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

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

[Continued on next page](#)

¹Reproduced 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.

²Borderline = Unspecified, borderline, or uncertain behavior.

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NCCN Guidelines Version 1.2016

Ovarian Cancer Histopathologies

WHO HISTOLOGIC CLASSIFICATION (2 of 2) ^{1,2}

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

¹Reproduced 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.

²Borderline= Unspecified, borderline, or uncertain behavior.

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NCCN Guidelines Version 1.2016

Epithelial Ovarian Cancer/Primary Peritoneal Cancer

Staging*

Table 1

American Joint Committee on Cancer (AJCC)

TNM and FIGO Staging System for Ovarian and Primary Peritoneal Cancer (7th ed., 2010)

Primary Tumor (T)

TNM FIGO

TX		Primary tumor cannot be assessed
T0		No evidence of primary tumor
T1	I	Tumor limited to ovaries (one or both)
T1a	IA	Tumor limited to one ovary; capsule intact, no tumor on ovarian surface. No malignant cells in ascites or peritoneal washings
T1b	IB	Tumor limited to both ovaries; capsules intact, no tumor on ovarian surface. No malignant cells in ascites or peritoneal washings
T1c	IC	Tumor limited to one or both ovaries with any of the following: capsule ruptured, tumor on ovarian surface, malignant cells in ascites or peritoneal washings
T2	II	Tumor involves one or both ovaries with pelvic extension
T2a	IIA	Extension and/or implants on uterus and/or tube(s). No malignant cells in ascites or peritoneal washings
T2b	IIB	Extension to and/or implants on other pelvic tissues. No malignant cells in ascites or peritoneal washings
T2c	IIC	Pelvic extension and/or implants (T2a or T2b) with malignant cells in ascites or peritoneal washings

TNM FIGO

T3	III	Tumor involves one or both ovaries with microscopically confirmed peritoneal metastasis outside the pelvis
T3a	IIIA	Microscopic peritoneal metastasis beyond pelvis (no macroscopic tumor)
T3b	IIIB	Macroscopic peritoneal metastasis beyond pelvis 2 cm or less in greatest dimension
T3c	IIIC	Peritoneal metastasis beyond pelvis more than 2 cm in greatest dimension and/or regional lymph node metastasis

Regional Lymph Nodes (N)

NX		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N1	IIIC	Regional lymph node metastasis

Distant Metastasis (M)

M0		No distant metastasis
M1	IV	Distant metastasis (excludes peritoneal metastasis)

Note: Liver capsule metastasis is T3/stage III; liver parenchymal metastasis, M1/stage IV. Pleural effusion must have positive cytology for M1/stage IV.

*An update to the FIGO staging guidelines is available. [See FIGO Guidelines \(ST-5\).](#)

[Continued](#)

Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago Illinois. The original and primary source for this information is the AJCC Cancer Staging Manual, Seventh Edition (2010) published by Springer Science+Business Media, LLC (SBM). (For complete information and data supporting the staging tables, visit www.cancerstaging.net.) Any citation or quotation of this material must be credited to the AJCC as its primary source. The inclusion of this information herein does not authorize any reuse or further distribution without the expressed, written permission of Springer SBM, on behalf of the AJCC.



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Epithelial Ovarian Cancer/Primary Peritoneal Cancer

Staging*

Table 1 (Continued)

American Joint Committee on Cancer (AJCC)

TNM and FIGO Staging System for Ovarian and Primary Peritoneal Cancer (7th ed., 2010)

Stage Grouping

Stage 1	T1	N0	M0
Stage IA	T1a	N0	M0
Stage IB	T1b	N0	M0
Stage IC	T1c	N0	M0
Stage II	T2	N0	M0
Stage IIA	T2a	N0	M0
Stage IIB	T2b	N0	M0
Stage IIC	T2c	N0	M0
Stage III	T3	N0	M0
Stage IIIA	T3a	N0	M0
Stage IIIB	T3b	N0	M0
Stage IIIC	T3c	N0	M0
	Any T	N1	M0
Stage IV	Any T	Any N	M1

The staging system for ovarian and primary peritoneal cancer is also used for malignant germ cell tumors, malignant sex cord-stromal tumors, and carcinosarcoma (malignant mixed Müllerian tumors).

Note: For histologic grade and histopathologic type, see AJCC Staging Manual.

*An update to the FIGO staging guidelines is available. [See FIGO Guidelines \(ST-5\).](#)

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Staging*

Table 2
American Joint Committee on Cancer (AJCC)
TNM and FIGO Staging System for Fallopian Tube Cancer (7th ed., 2010)

Primary Tumor (T)

TNM	FIGO	Description
TX		Primary tumor cannot be assessed
T0		No evidence of primary tumor
Tis**		Carcinoma in situ (limited to tubal mucosa)
T1	I	Tumor limited to the Fallopian tube(s)
T1a	IA	Tumor limited to one tube, without penetrating the serosal surface; no ascites
T1b	IB	Tumor limited to both tubes, without penetrating the serosal surface; no ascites
T1c	IC	Tumor limited to one or both tubes with extension onto or through the tubal serosa, or with malignant cells in ascites or peritoneal washings
T2	II	Tumor involves one or both Fallopian tubes with pelvic extension
T2a	IIA	Extension and/or metastasis to the uterus and/or ovaries
T2b	IIB	Extension to other pelvic structures
T2c	IIC	Pelvic extension with malignant cells in ascites or peritoneal washings

TNM	FIGO	Description
T3	III	Tumor involves one or both Fallopian tubes, with peritoneal implants outside the pelvis
T3a	IIIA	Microscopic peritoneal metastasis outside the pelvis
T3b	IIIB	Macroscopic peritoneal metastasis outside the pelvis 2 cm or less in greatest dimension
T3c	IIIC	Peritoneal metastasis outside the pelvis and more than 2 cm in diameter

Regional Lymph Nodes (N)

NX		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N1	IIIC	Regional lymph node metastasis

Distant Metastasis (M)

M0		No distant metastasis
M1	IV	Distant metastasis (excludes metastasis within the peritoneal cavity)

**Note: FIGO no longer includes stage 0 (Tis)

Note: Liver capsule metastasis is T3/stage III; liver parenchymal metastasis, M1/stage IV. Pleural effusion must have positive cytology for M1/stage IV.

*An update to the FIGO staging guidelines is available. [See FIGO Guidelines \(ST-5\)](#).

[Continued](#)

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Staging*

Table 2 (Continued)

American Joint Committee on Cancer (AJCC)

TNM and FIGO Staging System for Fallopian Tube Cancer (7th ed., 2010)

Stage Grouping

Stage 0**	Tis	N0	M0
Stage 1	T1	N0	M0
Stage IA	T1a	N0	M0
Stage IB	T1b	N0	M0
Stage IC	T1c	N0	M0
Stage II	T2	N0	M0
Stage IIA	T2a	N0	M0
Stage IIB	T2b	N0	M0
Stage IIC	T2c	N0	M0
Stage III	T3	N0	M0
Stage IIIA	T3a	N0	M0
Stage IIIB	T3b	N0	M0
Stage IIIC	T3c	N0	M0
	Any T	N1	M0
Stage IV	Any T	Any N	M1

**Note: FIGO no longer includes stage 0 (Tis)

Note: For histologic grade and histopathologic type, see AJCC Staging Manual.

*An update to the FIGO staging guidelines is available. [See FIGO Guidelines \(ST-5\)](#).

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NCCN Guidelines Version 1.2016

Epithelial Ovarian Cancer/Fallopian Tube Cancer/ Primary Peritoneal Cancer

Staging

International Federation of Gynecology and Obstetrics (FIGO)

FIGO Guidelines: Staging Classification for Cancer of the Ovary, Fallopian Tube, and Peritoneum

FIGO	TNM		FIGO	TNM	
I	T1	Tumor confined to ovaries or Fallopian tube(s)	III	T1/T2-N1	Tumor involves 1 or both ovaries or Fallopian tubes, or primary peritoneal cancer, with cytologically or histologically confirmed spread to the peritoneum outside the pelvis and/or metastasis to the retroperitoneal lymph nodes
IA	T1a	Tumor limited to 1 ovary (capsule intact) or Fallopian tube; no tumor on ovarian or Fallopian tube surface; no malignant cells in the ascites or peritoneal washings	IIIA1		Positive retroperitoneal lymph nodes only (cytologically or histologically proven):
IB	T1b	Tumor limited to both ovaries (capsules intact) or Fallopian tubes; no tumor on ovarian or Fallopian tube surface; no malignant cells in the ascites or peritoneal washings	IIIA1(i)		Metastasis up to 10 mm in greatest dimension
			IIIA1(ii)		Metastasis more than 10 mm in greatest dimension
IC		Tumor limited to 1 or both ovaries or Fallopian tubes, with any of the following:	IIIA2	T3a2-N0/N1	Microscopic extrapelvic (above the pelvic brim) peritoneal involvement with or without positive retroperitoneal lymph nodes
IC1	T1c1	Surgical spill	IIIB	T3b-N0/N1	Macroscopic peritoneal metastasis beyond the pelvis up to 2 cm in greatest dimension, with or without metastasis to the retroperitoneal lymph nodes
IC2	T1c2	Capsule ruptured before surgery or tumor on ovarian or Fallopian tube surface	IIIC	T3c-N0/N1	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)
IC3	T1c3	Malignant cells in the ascites or peritoneal washings			
II	T2	Tumor involves 1 or both ovaries or Fallopian tubes with pelvic extension (below pelvic brim) or primary peritoneal cancer	IV	Any T, any N, M1	Distant metastasis excluding peritoneal metastases
IIA	T2a	Extension and/or implants on uterus and/or Fallopian tubes and/or ovaries	IVA		Pleural effusion with positive cytology
IIB	T2b	Extension to other pelvic intraperitoneal tissues	IVB		Parenchymal metastases and metastases to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside of the abdominal cavity)

Reprinted with permission: Prat J, FIGO Committee on Gynecologic Oncology. Staging classification for cancer of the ovary, Fallopian tube, and peritoneum. Int J Gynaecol Obstet 2014; 124(1):1-5.

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

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



Discussion

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.

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Ovarian Cancer

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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. These NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Ovarian Cancer were originally published 20 years ago and have been subsequently updated at least once every year.⁵ These NCCN Guidelines® 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, 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. 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. However, 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 2016 (see the NCCN Guidelines for Ovarian Cancer). The section on LCOH was extensively revised for 2016 (see *Less Common Ovarian Histopathologies* in this Discussion and the NCCN Guidelines for Less Common Ovarian Histopathologies).

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 2016, it is estimated that 22,280 new diagnoses and 14,240 deaths from this neoplasm will occur in the United States; less than 40% of women with ovarian cancer are cured.⁶ The incidence of ovarian cancer increases with age and is most prevalent in the sixth and seventh decades of life.⁴ The median age at the time of diagnosis is 63 years, and more than 70% of patients present with advanced disease.^{6,7}

Epidemiologic studies have identified risk factors in the etiology of ovarian cancer.^{4,8} A 30% to 60% decreased risk for cancer is associated with younger age at pregnancy and first birth (≤ 25 years), the use of oral contraceptives, and/or breastfeeding.⁹ Conversely, nulliparity or older age (>35 years) at 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.¹⁰⁻¹² The risk for borderline epithelial tumors (also known as low malignant potential tumors) may be increased after ovarian stimulation for in vitro fertilization.^{13,14} Obesity does not appear to be associated with the most aggressive types of ovarian cancer.¹⁵ 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 families affected by Lynch syndrome (hereditary nonpolyposis colorectal cancer [HNPCC] syndrome)—is associated with early-onset disease.¹⁶⁻²⁸ However, these patients account for only 15% of all women who have ovarian cancer.^{9,24,29,30} In women at high risk (with either *BRCA1* or *BRCA2* mutations), prophylactic 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 NCCN.org.³⁰⁻³⁵ However, there is a residual risk for primary peritoneal cancer after prophylactic BSO in these women at high risk for cancer. Occult ovarian cancer is sometimes found after prophylactic salpingo-oophorectomy, 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).³⁶⁻³⁹ The risks of surgery include injury to the bowel, bladder, ureter, and vessels.⁴⁰ Recently, it has been suggested that the Fallopian tube may be the origin of serous ovarian and primary peritoneal cancers, including serous intraepithelial carcinoma of the Fallopian tube (also known as serous tubal intraepithelial carcinoma [STIC]).^{32,36,41-61} A referral to a gynecologic oncologist/comprehensive cancer center is recommended for management of occult 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. 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 who may be at an increased risk of having developed early-stage ovarian cancer.^{62,63} 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).⁶² Physicians evaluating women with this constellation of symptoms must be cognizant of the possibility that ovarian pathology may be causing these

symptoms.⁶⁴ 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.^{40,65-67}

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.^{40,64,68-75} 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;⁶⁸ however, prospective validation of these tests remains elusive. An intriguing study suggests that ovarian cancer is associated with unique odors that can be detected.⁷⁶⁻⁷⁹

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.^{80,81} Preliminary results suggested that multimodality screening is more effective at detecting early-stage cancer; however, after a median of 11 years of follow-up, a significant mortality reduction was not observed.^{82,83} Some feel that this UKCTOCS screening approach may be useful for women at high risk such as those with *BRCA* mutations.³⁸ 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.^{70,84,85} 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.⁸⁶



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Ovarian Cancer

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.⁸⁷ 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).^{64,88-91} NCCN Guidelines Panel Members believe that the OvaSure screening test should not be used to detect ovarian cancer.⁹²⁻⁹⁵ The OvaSure test uses 6 biomarkers, including leptin, prolactin, osteopontin, insulin-like growth factor II, macrophage inhibitory factor, and CA-125.⁹⁶ 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.⁹⁷⁻⁹⁹

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).¹⁰⁰ Most patients present with stage III disease.¹⁰¹ 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).¹⁰¹⁻¹⁰⁶ Pathologists may use

histologic grades 1, 2, or 3 for endometrioid carcinomas, mucinous carcinomas, and stage IC tumors.¹⁰² Primary peritoneal adenocarcinoma and LCOH are also staged using the ovarian cancer staging system (see Table 1 in the NCCN Guidelines for Ovarian Cancer).¹⁰⁰ Until January 1, 2017, 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).¹⁰⁰ The new AJCC/FIGO staging guidelines will combine staging for Fallopian tube carcinoma and ovarian cancer, and will be effective on January 1, 2017 (see *Staging* in the NCCN Guidelines for Ovarian Cancer). 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).^{101,103} 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 will be included in the next edition of the AJCC Cancer Staging Manual (8th edition), which will be published in mid-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 now includes Fallopian tube carcinomas.^{102,107}

Caveat

By definition, the NCCN Guidelines cannot incorporate all possible clinical variations and are not 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

Prior to the update of this version of the NCCN Guidelines for Ovarian Cancer, an electronic search of the PubMed database was performed to obtain key literature in ovarian cancer published between September 1, 2014 and October 1, 2015 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.¹⁰⁸ The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: Clinical Trial, Phase III; Clinical Trial, Phase IV; Guideline; Randomized Controlled Trial; Meta-Analysis; Systematic Reviews; and Validation Studies.

The PubMed search resulted in 139 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](#).

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; patients should be referred for palliative care assessment if appropriate (see the NCCN Guidelines for Palliative Care, available at [NCCN.org](#)).

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 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).^{62,109-116} 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).¹¹⁷⁻¹¹⁹ For example, AFP levels should be considered to assess for germ cell tumors in women younger than 35 years with a pelvic mass.¹¹⁷⁻¹¹⁹ Ultrasound is typically used for initial evaluation; however, CT is useful to assess for metastases.¹¹¹ MRI may be useful for determining malignant potential if ultrasound is not reliable.^{115,116} CT/MRI imaging should be performed with contrast unless contraindicated. FDG-PET/CT scan may be useful for indeterminate lesions.¹²⁰⁻¹²²

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 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.^{123,124} Other cancers that should be ruled out include bowel, uterine, and pancreatic cancers or lymphoma;^{125,126} benign ovarian and non-ovarian conditions also need to be ruled out (eg, serous cystadenoma).¹²⁷ 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.^{128,129} 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.¹³⁰⁻¹³³ 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 if patients have metastases to the ovary or primary mucinous carcinoma of the ovary (see *Mucinous Carcinomas* in this Discussion).¹³⁴

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]). However, 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; however, most patients (about 70%) have serous histology.^{3,100,104,135,136} 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 the NCCN Guidelines for Epithelial Ovarian Cancer and the NCCN Guidelines for Less Common Ovarian Histopathologies).¹⁰⁴ Recent molecular characterization of clear cell, mucinous, or grade 1 (low-grade) tumors suggests that mutations in these histologies are different from those in higher grade tumors.^{45,137,138} 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).^{101,103-106,139,140} High-grade



endometrioid tumors are difficult to distinguish from high-grade serous tumors.¹⁰⁴ Grade 1 (low-grade) serous tumors are relatively resistant to standard chemotherapy regimens.^{104,141} Pathology review at NCCN Member Institutions is recommended for all patients. The CAP protocol is a useful tool for pathology reports, which was recently revised for 2016.^{102,107} For the 2016 update, the complete histologic classification from the WHO was added to the NCCN Guidelines (see *WHO Histologic Classification* in the NCCN Guidelines for Ovarian Cancer Histopathologies).¹ The WHO pathology manual is also a useful resource.^{1,142}

Primary Treatment

Primary treatment for presumed ovarian cancer consists of appropriate surgical staging and cytoreduction, followed in most (but not all) patients by systemic chemotherapy.^{88,143-145} Initial surgery should be a comprehensive staging laparotomy, including a total abdominal hysterectomy (TAH) and BSO (see the *Principles of Surgery* in the NCCN Guidelines for Ovarian Cancer).^{9,146,147} Based on published improved outcomes, it is recommended (category 1) that a gynecologic oncologist perform the primary surgery.⁸⁹⁻⁹¹ For a young patient who wishes to maintain fertility, a unilateral salpingo-oophorectomy (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).¹⁴⁸⁻¹⁵³

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.¹⁵⁴ In select patients, minimally invasive procedures may be used for surgical staging.^{146,155-158} 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.^{116,146,159,160} Surgeons tend to use an open laparotomy for patients with more widespread disease.^{160,161} Minimally invasive techniques may be considered for prophylactic 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).

For the 2016 update, the surgical guidelines were extensively revised. For example, a new section was added on interval cytoreduction after neoadjuvant chemotherapy (see *Principles of Surgery* in the NCCN Guidelines for Ovarian Cancer). Two other sections were recently added to the *Principles of Surgery: Operative Reports* and a *Risk-Reducing Salpingo-Oophorectomy (RRSO) Protocol (BRCA/HBOC syndrome)* (see the NCCN Guidelines for Epithelial Ovarian Cancer). To summarize the new operative report, the surgeon should describe the following: 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.¹⁶²

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 NCCN.org).³⁸ 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.^{36,54} The ovaries should also be carefully sectioned,



processed, and assessed.¹⁶³ The 2016 CAP protocol describes the process for sectioning the Fallopian tubes and ovaries.^{102,163} Note that it is controversial whether a hysterectomy should also be done after RRSO.²⁹ The prevention benefits of salpingectomy alone are not yet proven.¹⁶⁴⁻¹⁶⁹ 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.¹⁶⁴

Cytoreductive Surgery

Cytoreductive 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 Histopathologies).^{88,91,145,150,154,170-172} Although cytoreductive surgery is the standard of care, this recommendation is based on retrospective data (and thus is not a category 1 recommendation).¹⁷³ 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 cytoreduction to less than 1-cm residual disease or resection of all visible disease in appropriate circumstances.¹⁷⁴⁻¹⁷⁶ These procedures also apply to many of the LCOH. Surgical cytoreduction is optimal if the residual tumor nodules are less than 1 cm in maximum diameter or thickness;^{147,150,173,177,178} extensive resection of upper abdominal ovarian metastases is recommended for patients who can tolerate this surgery.^{171,179} In select patients, minimally invasive procedures may be used to assess whether cytoreductive surgery is feasible and to achieve cytoreduction.^{146,159,160,180,181}

A maximal effort should be made to remove all gross disease, because the more complete the debulking the better the outcomes.¹⁷⁰ 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.^{124,156} All involved omentum should be removed. Suspicious and/or enlarged nodes should be resected, if possible.^{182,183} 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.¹⁸⁴⁻¹⁸⁶

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.¹⁸⁷ Patients with low-volume residual disease after surgical cytoreduction for invasive epithelial ovarian or peritoneal cancer are potential candidates for intraperitoneal (IP) therapy.^{188,189} In these patients, consideration should be given to placement of an IP catheter with initial surgery.¹⁴⁶ 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.^{171,179,190}

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 cytoreduction (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 cytoreduction cannot be achieved (see *Neoadjuvant Chemotherapy* in this Discussion).¹⁹¹ The RRSO protocol is used for patients at risk for HBOC and is described in detail in the algorithm; this protocol recommends that the Fallopian tubes should be processed by SEE-Fim of the tubes and then assessed to determine whether any evidence of cancer is present.^{36,54,102,163} The ovaries should also be carefully sectioned, processed, and assessed.¹⁶³

Neoadjuvant Chemotherapy

The therapeutic benefit of neoadjuvant chemotherapy followed by interval cytoreduction remains controversial (see next paragraph).^{173,192-198} 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.¹⁹⁹⁻²⁰⁵ 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 chemotherapy, a tissue diagnosis should be obtained (by FNA, biopsy,

or paracentesis) in this group of patients. If there are concerns about the histology, a core biopsy can be obtained; minimally invasive techniques may be used to obtain the biopsy.

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). A randomized phase III 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).²⁰⁰ 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 more recently 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).^{189,205} 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).¹⁷³ A recent 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.¹⁹¹ 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.^{146,206} A recent 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]).²⁰⁷

Interval Cytoreduction

For the 2016 update, the algorithm now states that patients should be evaluated for potential interval debulking surgery before the fourth cycle of neoadjuvant chemotherapy (see *Primary Treatment* in the NCCN Guidelines for Epithelial Ovarian Cancer). A new section was added to the surgical guidelines describing the procedures for interval cytoreduction 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 cytoreduction. For example, every effort should be made to achieve maximal cytoreduction during an interval cytoreduction. 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; however, 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.

Chemotherapy

Most patients with epithelial ovarian cancer receive postoperative systemic chemotherapy, which is also referred to as adjuvant therapy (see *Principles of Systemic Therapy* in the NCCN Guidelines for Epithelial Ovarian Cancer). Observation is recommended for patients with stage IA or IB, grade 1 endometrioid carcinomas, because survival is greater than 90% for this group with surgical treatment alone.²⁰⁸⁻²¹⁰ If observation (without the addition of chemotherapy) is considered for stage IA or IB grade 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).²¹¹ All of the regimens (including the combined intravenous/IP chemotherapy) may be used for epithelial ovarian, primary peritoneal, and Fallopian tube cancers. 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).^{188,189,212,213} Women with stage II disease may also receive IP chemotherapy, although no randomized evidence for stage II has been published.

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).^{89,214} Intravenous docetaxel plus carboplatin (category 1)²¹⁵ or paclitaxel plus carboplatin (category 1) are options for alternative regimens.^{216,217} The docetaxel/carboplatin regimen may be considered for patients who are at high risk for neuropathy (eg, patients with diabetes).

Recommendations for the number of cycles of treatment vary with the stage of the disease. For patients with advanced-stage disease (stages II–IV), 6 cycles of chemotherapy are recommended, whereas 3 to 6 cycles are recommended for earlier-stage disease.^{216,218} Data suggest there is a potential survival advantage for 6 cycles of chemotherapy in select patients with serous cytology.²¹⁹

The recommended intravenous regimens accepted by a consensus of the NCCN Panel include: 1) paclitaxel, 175 mg/m² 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);^{214,216} 2) dose-dense paclitaxel, 80 mg/m² 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);²²⁰ 3) paclitaxel 60 mg/m² over 1 hour followed by

carboplatin AUC 2 intravenous over 30 minutes, weekly for 18 weeks (category 1);²²¹ and 4) docetaxel, 60 to 75 mg/m² 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).²¹⁵ 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 III MITO-7 trial.²²¹ Note that carboplatin dosing may be revised based on changes in serum creatinine methodology. The AUC of 5 to 6 for carboplatin reflects contemporary treatment.

The recommended IP chemotherapy regimen is paclitaxel, 135 mg/m² continuous intravenous infusion over 3 or 24 hours on day 1; cisplatin, 75 to 100 mg/m² IP on day 2 after intravenous paclitaxel; paclitaxel, 60 mg/m² IP on day 8; repeat every 3 weeks for 6 cycles (category 1).¹⁸⁹ The published randomized 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.²²² 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.^{215,216,220,223} Note that there are no agents to prevent chemotherapy-induced peripheral neuropathy.²²⁴

The IP paclitaxel/cisplatin regimen is associated with leukopenia, infection, fatigue, renal toxicity, abdominal discomfort, and



neurotoxicity.²²⁵⁻²²⁷ In the initial studies, only 42% of women were able to complete all 6 treatment cycles (of the IP regimen) because of toxicity; however, with more experience, this percentage has improved in the major cancer centers.²²⁸ Although it has been suggested that a lower IP cisplatin dose of 75 mg/m² may help to decrease toxicity, preliminary data from GOG 252 suggest that the reduced-dose IP regimen should not be used.^{222,228-230} 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 (eg, 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.²³¹ Women unable to complete IP therapy should receive intravenous therapy. Techniques to decrease catheter complications include catheter choice and timing of insertion.^{212,232} Expert nursing care may help to decrease complications.²¹¹ Giving intravenous hydration before and after IP chemotherapy is a useful strategy to prevent renal toxicity.²²⁸ 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.^{231,233-236}

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 recent phase III 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.²²¹ 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 III MITO-7 trial.²²¹ Algorithms are available for predicting chemotherapy toxicity (see the NCCN Guidelines for Senior Adult Oncology, available at [NCCN.org](#)).

The IP regimen published by Armstrong et al has, however, documented the longest median survival (65.6 months) that has been described to date in women with optimally debulked stage III cancer.^{189,237} A recent study reported overall survival of 110 months in patients with stage III ovarian cancer and no residual disease who received the IP regimen.²³⁷ Another recent study showed that survival improves with each cycle of IP chemotherapy.²³⁸ Patients with primary peritoneal cancer, Fallopian tube cancer, or MMT can also be considered for IP chemotherapy.^{213,232} 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 (see the NCCN Guidelines for Less Common 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 MMT.^{188,239} A recent study reported that women with aberrant *BRCA1* expression had increased survival when treated with IP cisplatin/paclitaxel.²⁴⁰

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.^{220,241} In the dose-dense group, median overall survival was 100.5 months versus 62.2 months in the conventional treatment group (HR 0.79; 95% CI, 0.63–0.99; $P = .039$). However, the dose-dense regimen is more toxic, and patients discontinued dose-dense paclitaxel therapy more often than did those receiving standard therapy. A recent study reported that dose-dense weekly paclitaxel did not prolong PFS.²⁴² Future studies will compare the effect of weekly paclitaxel on the overall survival benefit with that of using IP chemotherapy.²⁴³

Anti-Angiogenesis Agents

A phase III randomized trial (GOG 0218) assessed bevacizumab combined with carboplatin/paclitaxel in the upfront setting compared to 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.^{244,245} However, 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 0218.²⁴⁶ A recent analysis of the data from GOG 0218 suggests that upfront therapy with carboplatin/paclitaxel/bevacizumab may be beneficial in patients with ascites.²⁴⁷ 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 III randomized trial (ICON7) also assessed bevacizumab/carboplatin/paclitaxel in the upfront setting. The trial design of ICON7 differs from GOG 0218 (see next paragraph).²⁴⁸ Although the PFS data from ICON7 confirm the findings of GOG 0218, the benefits appear to be modest (2.4-month increase in PFS).²⁴⁶ Recent 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 whole study population.²⁴⁹ 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; $P = .03$).

For the 2016 update, panel members revised the recommendation to category 2B (previously it was category 3) for the addition of bevacizumab to upfront chemotherapy with carboplatin/paclitaxel followed by bevacizumab as maintenance therapy (see *Primary Chemotherapy/Primary Adjuvant Therapy Regimens: Ovarian, Fallopian Tube, and Primary Peritoneal Cancer* in the NCCN Guidelines for Epithelial Ovarian Cancer).^{249,250} Some panel members believe that bevacizumab should not be added to upfront chemotherapy in patients with ovarian cancer, because data from these 2 phase III 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.^{245,246,248,250-253} Note that a category 2B recommendation indicates that more ($\geq 50\%$ 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).^{245,248} The only GOG 0218 regimen that is recommended (category 2B) is the prolonged bevacizumab regimen (upfront with carboplatin/paclitaxel followed by maintenance bevacizumab).²⁴⁵ 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.²⁵⁴

Number of Chemotherapy Cycles and Agents

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.²⁵⁵ Patients with stage II to IV disease may receive 3 to 6 cycles of chemotherapy followed by completion surgery and postoperative chemotherapy (see *Primary Treatment* in the NCCN Guidelines for Epithelial Ovarian Cancer).¹⁹⁶

The role of maintenance (or postremission) therapy in patients who achieve a complete clinical remission after 6 cycles of chemotherapy 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/m² every 4 weeks for 12 cycles) after initial chemotherapy.²⁵⁶ The published study treated patients at 175 mg/m²; the plan was to decrease the dose to 135 mg/m², but the 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.²⁵⁷ Another study suggests that postremission paclitaxel is not beneficial.²⁵⁸ For the 2016 update, the panel revised the recommendation for postremission paclitaxel to category 2B (from category 3).

The NCCN Panel recommends adding pazopanib (category 2B) as postremission therapy 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 recent phase III randomized trial showing an increase in PFS (17.9 vs. 12.3 months) in patients treated with pazopanib compared with placebo.²⁵⁹ However, pazopanib is a category 2B recommendation for maintenance therapy because the FDA has not approved this indication, there was no increase in overall survival data, and patients had increased toxicity with pazopanib such as grade 3 or 4 hypertension. 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.²⁶⁰⁻²⁶⁴ 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.²⁶⁵ 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.^{266,267} Infusion reactions are more common with paclitaxel,²⁶⁸ but



mild reactions can also occur with liposomal doxorubicin.²⁶⁹ Allergic reactions (ie, true drug allergies) are more common with platinum agents (ie, carboplatin, cisplatin, oxaliplatin).^{268,270}

Algorithms are provided for management of mild, severe, and life-threatening reactions (see *Management of Drug Reactions* in the NCCN Guidelines for Ovarian Cancer).²⁷¹ These drug reaction algorithms are also useful for patients with other gynecologic cancers (eg, cervical 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.²⁷²⁻²⁷⁵

For patients with allergic reactions, various desensitization protocols have been published.^{261,264,276,277} To maximize safety, patients may be desensitized in the intensive care unit.^{264,277} Almost all patients can be desensitized (about 90%).²⁶⁴ 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.²⁶² Patients must be desensitized with each infusion if they previously had a drug reaction.²⁷⁸⁻²⁸⁰ Data suggest that an extended infusion schedule and use of premedication may decrease the number of hypersensitivity reactions to carboplatin.²⁸¹ Skin testing is associated with false-negative results.^{282,283}

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).²⁸⁴⁻²⁸⁸ Patients who receive radiation are prone to vaginal stenosis, which can impair sexual function.²⁸⁹ 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.²⁹⁰

Recommendations After Primary Treatment

After initial treatment (eg, surgery followed by 6 cycles of 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 partial remission or progression 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).^{291,292} The NCCN Guidelines recommend symptom management and best supportive care for all patients; patients should be referred for palliative care assessment if appropriate (see the NCCN Guidelines for Palliative Care, available at 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 NCCN.org).^{293,294} Primary treatment should not be delayed for genetic counseling.

Options for maintenance treatment—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)²⁵⁶, preferably in a controlled clinical trial (see *Secondary Adjuvant Therapy* in the NCCN Guidelines for Epithelial Ovarian Cancer). The NCCN Panel recommends postremission pazopanib (category 2B) for management of stage II to IV disease (see *Number of Chemotherapy Cycles and Agents* in this Discussion).²⁵⁹ As previously described, postremission pazopanib increases PFS when administered following initial chemotherapy. If used, the recommended paclitaxel regimen is 135 to 175 mg/m² every 4 weeks for 12 cycles.²⁵⁶ 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). Note that complete clinical remission is defined as no objective evidence of disease (ie, negative physical examination, negative CA-125 levels, negative CT with <1 cm lymph nodes).^{291,292}

Follow-up Recommendations

Recurrent disease may be identified clinically (eg, pelvic pain, weight loss), biochemically (ie, elevated CA-125 levels), and/or with imaging following initial treatment. 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 (see *Monitoring/Follow-up* in the NCCN Guidelines for Epithelial Ovarian Cancer). Chest/abdominal/pelvic CT, MRI, FDG-PET/CT, FDG-PET scans (category 2B for PET alone), and chest x-ray may be ordered if clinically indicated.²⁹⁵⁻²⁹⁸ 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 if indicated; completion surgery should be considered (category 2B) after they finish childbearing.

If the CA-125 level was initially elevated, the 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.^{299,300} 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.³⁰¹ Recommendations from the SGO state that use of CA-125 levels for surveillance is optional.²⁹⁷ 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.³⁰² Others have discussed this study in greater detail.³⁰³⁻³⁰⁵

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. 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. However, data suggest that immediate treatment for biochemical relapse is not beneficial; therefore, immediate treatment is a category 2B recommendation in the NCCN Guidelines.²⁹⁹ After biochemical relapse, recommended options include enrollment in a clinical trial, delaying treatment (ie, observation) until clinical symptoms arise, and/or best supportive care (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,³⁰⁶ these agents are frequently administered to patients who have only a rising CA-125 level³⁰⁷ as evidence of tumor progression.³⁰⁸ 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);³⁰⁹ 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.^{291,292} Panel members emphasized the importance of clinical trials to identify agents active in this group of patients.³¹⁰ 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.^{311,312} 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),³¹³ and/or best supportive care (see NCCN Guidelines for Palliative Care, available at 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*.^{314,315} 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.^{315,316} 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).³¹⁷⁻³²² 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).^{173,323-328} A meta-analysis suggests that survival increases for patients with recurrent disease who have complete cytoreduction.¹⁷⁴ 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.^{146,329}

Acceptable Recurrence Modalities

The NCCN Panel felt that no single therapeutic agent should be currently recommended as the treatment of choice for recurrent ovarian carcinoma. However, some 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).²¹¹ A meta-analysis of chemotherapy for recurrent ovarian cancer was published in 2007.³¹⁴ 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.

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).^{314,315} Preferred combinations for platinum-sensitive recurrent disease include carboplatin/paclitaxel (category 1),³¹⁵ carboplatin/liposomal doxorubicin (category 1),³³⁰⁻³³² carboplatin/weekly paclitaxel,²²⁰ carboplatin/docetaxel,^{333,334} carboplatin/gemcitabine (which has been shown to improve PFS),^{315,335,336} or cisplatin/gemcitabine.³³⁵ The NCCN Panel recently revised the recommendation for carboplatin/liposomal doxorubicin to category 1 (from category 2A) based on recent data and uniform consensus from the panel.^{330,331,337-340} Carboplatin/liposomal doxorubicin is equivalent to carboplatin/paclitaxel but both have different toxicity profiles. 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 platinum-resistant disease, the preferred single agent is a non-platinum-based agent (ie, docetaxel, oral etoposide, gemcitabine, liposomal doxorubicin, weekly paclitaxel with or without pazopanib, topotecan); sequential therapy using single agents is typically used.^{341,342} The response rate of the following agents appears to be similar: topotecan, 20%;³⁴³ gemcitabine, 19%;^{344,345} liposomal doxorubicin, 26%;³⁴⁴⁻³⁴⁶ and oral etoposide, 27%.³⁴⁷ In patients with



platinum-resistant disease, the response rate for docetaxel is 22% and for weekly paclitaxel is 21%.^{311,348,349} For platinum-sensitive disease in patients who cannot tolerate combination therapy, the preferred single agent is carboplatin or cisplatin.^{315,335,336} Recent reports suggest that weekly topotecan is less toxic than the daily regimen.^{350,351} Palliative chemotherapy has been shown to reduce symptoms in patients with platinum-resistant disease.³⁵² A recent phase 2 trial (MITO-11) assessed weekly paclitaxel with (or without) pazopanib in patients with platinum-resistant or refractory advanced ovarian cancer.³⁴¹ 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]; hazard ratio, 0.42 [95% CI, 0.25–0.69]; $P = .0002$).

Other potentially active agents include altretamine, capecitabine, cyclophosphamide, doxorubicin, ifosfamide, irinotecan, melphalan, oxaliplatin, paclitaxel, nanoparticle albumin-bound paclitaxel (ie, nab-paclitaxel), pemetrexed, and vinorelbine (see *Principles of Systemic Therapy: Acceptable Recurrence Therapies* in the NCCN Guidelines for Epithelial Ovarian Cancer).^{349,353-357} Nab-paclitaxel has an overall response rate of 64%.³⁵⁸ Vinorelbine has a response rate of 20%.^{359,360} Altretamine has a 14% response rate³⁶¹ and ifosfamide has a 12% response rate,³⁶² 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%.^{311,348,349} Single-agent bevacizumab is also active (21%) in patients with both platinum-sensitive and platinum-resistant disease,^{123,246,363-366} although it may cause hypertension, arterial thrombosis, or intestinal perforation.

Several phase III randomized trials have recently assessed combination therapy with bevacizumab for recurrent ovarian cancer (ie, AURELIA,

OCEANS).^{367,368} 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 hazard ratio 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 now recommends the following combination regimens for patients with platinum-resistant recurrent ovarian cancer: weekly paclitaxel/bevacizumab, liposomal doxorubicin/bevacizumab, and topotecan/bevacizumab.^{368,369} These bevacizumab combination regimens are contraindicated in patients at increased risk of gastrointestinal perforation or those who have previously received bevacizumab.^{368,370} Previously, only single-agent therapy was recommended for platinum-resistant disease.

A phase III 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, $P < .0001$).³⁶⁷ 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; hazard ratio, 0.95; $P = .65$).³⁷¹ Combination therapy with



bevacizumab is a category 2B recommendation for platinum-sensitive disease, because there is less consensus among the NCCN Panel (>50% but < 85%) that this intervention is appropriate. Panel members feel other combination regimens may be more preferred for platinum-sensitive disease than regimens with bevacizumab. In addition, the carboplatin/gemcitabine/bevacizumab regimen is only recommended in patients who have not previously received bevacizumab. Based on phase II trials, panel members feel that bevacizumab alone is useful in patients who have recurrent disease (especially those with ascites), which is reflected in the category 2A recommendation for single-agent bevacizumab for women with either platinum-sensitive or platinum-resistant disease.^{123,342,365,372}

Single-agent paclitaxel, nab-paclitaxel, and oxaliplatin are listed as other potentially active agents that can be used in appropriate patients.^{256,315,348,373} Capecitabine has activity if their disease was resistant to platinum and taxanes.³⁷⁴ Other alkylating agents, including cyclophosphamide and melphalan, can also be used.^{217,375} In addition, hormonal therapy with tamoxifen or other agents including aromatase inhibitors (such as exemestane, 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.³⁷⁶⁻³⁸² Studies are ongoing for new agents to treat platinum-resistant disease.³⁸³

Recent 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) with chemotherapy-refractory ovarian cancer, especially those with platinum-sensitive disease.^{342,384-388} If disease is resistant or refractory to platinum, then a lower response rate to olaparib is observed.^{385,387} A recent trial assessed olaparib in women

with recurrent advanced ovarian cancer; the overall response rate was 34% (complete response, 2%; and partial response, 32%).^{389,390} 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.^{390,391} The NCCN Panel recommends single-agent olaparib as recurrence therapy for patients with advanced ovarian cancer 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. However, the NCCN Panel decided not to recommend olaparib as maintenance therapy for patients with platinum-sensitive disease, because panel members feel that current data are not sufficient for recommending olaparib in this setting.^{388,392} Studies are ongoing for olaparib in other rare populations such as patients with HR deficiency.^{393,394} The NCCN Panel also recommends (category 2B) single-agent pazopanib as a potentially active targeted therapy in patients who had a complete response to initial therapy.³⁹⁵ 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%).

Chemotherapy/resistance assays and/or other biomarker assays are being used in some NCCN Member Institutions to aid in selecting chemotherapy in situations where there are multiple equivalent chemotherapy options available; however, the current level of evidence (category 3) is not sufficient to supplant standard-of-care chemotherapy.^{396,397} Thus, the NCCN Panel felt 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.³⁹⁸ Note that a

category 3 recommendation reflects strong disagreement about the intervention; at least 3 different NCCN Member Institutions must agree to include the category 3 intervention in the guideline; otherwise it is deleted.

However, 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.³⁰⁹ 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.^{284,285}

Less Common Ovarian Histopathologies

For the 2016 update, the NCCN Panel extensively revised the section on LCOH (see the NCCN Guidelines for Less Common Ovarian Histopathologies). New algorithms for clear cell carcinoma, mucinous carcinoma, and grade 1 (low-grade) serous/endometrioid epithelial carcinoma were added to the NCCN Guidelines. Previously, these rare histologies had been included in the algorithm for epithelial ovarian cancer. Panel members believe there is value in identifying potential pathways for these rare histologies because of emerging therapeutics for specific histologies. However, there are limited data for these rare histologies because of their infrequency and it will be difficult to acquire prospective data. Therefore, individualized treatment may be the best treatment for patients with these rare histologies.

The complete histologic classification for ovarian cancer from the WHO was added to the NCCN Guidelines for 2016, which includes the different types of LCOH (see *WHO Histologic Classification* in the

NCCN Guidelines for Ovarian Cancer Histopathologies).¹ Other LCOH include: carcinosarcomas (MMMTs), borderline epithelial tumors, malignant sex cord-stromal tumors, and malignant germ cell tumors; these rare histologies had previously been included in the LCOH guidelines and were also revised for 2016.

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.¹¹⁷⁻¹¹⁹ A gastrointestinal tract evaluation is recommended for mucinous histology to determine whether an occult gastrointestinal primary has metastasized to the ovaries.¹³⁴ 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).^{149,150,153,399-403} 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, clinical stage I epithelial ovarian tumors, or clinical stage I sex cord-stromal tumors.^{149,150,153,400-403} Patients who do not desire fertility preservation; those who have a clinical stage II, III, or IV epithelial ovarian cancer; those with 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. However, 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

For the 2016 update, the NCCN Panel added a new algorithm for patients with clear cell carcinoma of the ovary (see the NCCN Guidelines for Clear Cell Carcinoma and the *WHO Histologic Classification* in the NCCN Guidelines for Ovarian Cancer

Histopathologies).¹ Clear cell carcinomas are considered high-grade tumors; they are more common than the other LCOH.⁴¹ Most clear cell carcinomas are negative for WT1 and estrogen receptors.⁴¹ 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).⁴⁰⁴ Lymphadenectomy has been shown to improve survival.⁴⁰⁵ The staging system for ovarian and primary peritoneal cancer is also used for clear cell carcinomas (see Table 1 in the NCCN Guidelines for Ovarian Cancer). Lynch syndrome is associated with risk for endometrioid carcinomas, clear cell carcinomas, and papillary serous carcinomas.¹⁶⁻¹⁸ For patients with stage IA to IC disease, recommended postoperative treatment is either intravenous paclitaxel/carboplatin or docetaxel/carboplatin.⁴⁰⁵ 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 similar to that recommended for epithelial ovarian cancer. Patients with advanced clear cell carcinoma have a poor prognosis.^{404,405}

Mucinous Carcinomas

For the 2016 update, the NCCN Panel added a new algorithm for mucinous carcinoma of the ovary (see the NCCN Guidelines for Mucinous Carcinoma and the *WHO Histologic Classification* in the NCCN Guidelines for Ovarian Cancer Histopathologies).¹ 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%.^{134,406} 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 *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).¹³⁴ 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 NCCN Guidelines for Ovarian Cancer).

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 *Workup* in the NCCN Guidelines for Epithelial Ovarian Cancer).¹³⁴ 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.^{407–409} PAX8 immunostaining may be useful.⁴⁰⁷

Postoperative observation and monitoring are recommended for patients with stage IA or IB mucinous tumors because most of these tumors are benign or borderline.^{41,134} Fertility-sparing surgery is an option for patients with a unilateral mucinous borderline tumor (see the NCCN Guidelines for Borderline Epithelial Tumors [Low Malignant Potential]). 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).¹³⁴ Some clinicians feel the gastrointestinal regimens are appropriate because mucinous carcinomas of the ovary are similar to gastrointestinal tumors.⁴¹⁰ 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) 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).¹ Endometrioid carcinomas may be associated with endometriosis.^{411,412} 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 CDX2.⁴¹ Endometrioid tumors are also very similar in appearance to sex cord-stromal tumors.⁴¹ Lynch syndrome is associated with risk for endometrioid carcinomas, clear cell carcinomas, and serous carcinomas.^{16–18}



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 carcinomas.^{141,413} Serous carcinomas are usually positive for WT1 and estrogen receptors.⁴¹ 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 Grade 1 (Low-Grade) Serous Carcinomas/Endometrioid Epithelial Carcinomas).¹⁴¹ 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).¹ 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.¹⁴¹

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 *Principles of Systemic Therapy: Primary Chemotherapy/Primary Adjuvant Therapy Regimens* in the NCCN Guidelines for Epithelial Ovarian Cancer).^{141,414-416}

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).¹ 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.^{417,418} Germ cell tumors are the predominant ovarian tumor in this age group.⁴¹⁹ The recommended workup may include pulmonary function studies if bleomycin is being considered (see *Recommended Workup* in the NCCN Guidelines for Epithelial Ovarian Cancer).^{117,420} In young women (<35 years) with a pelvic mass, AFP levels can indicate the presence of germ cell tumors.¹¹⁷⁻¹¹⁹ Gonadal dysgenesis is a risk factor for germ cell tumors.⁴¹⁹ Malignant germ cell tumors have an excellent prognosis. After appropriate treatment, 5-year survival is more than 85%.^{417,421,422}

Treatment

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).⁴¹⁹ The staging system for ovarian and primary peritoneal cancer is also used for malignant germ cell tumors (see Table 1 in the NCCN Guidelines for Epithelial Ovarian Cancer). After comprehensive surgical staging, observation with monitoring is recommended for patients with stage I dysgerminoma or stage I, grade 1 immature teratoma.⁴²³ 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.^{424,425} 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 the NCCN Guidelines for Malignant Germ Cell Tumors). Fertility-sparing surgery should be considered for those desiring fertility preservation, regardless of stage (see the NCCN Guidelines for Malignant Germ Cell Tumors).^{153,418,422,426-428} 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.⁴²⁹⁻⁴³² 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).^{418,429,431,433-435} 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).^{420,436-438} If considering the use of bleomycin, pulmonary function tests are recommended.^{420,421} 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.^{429,439-446} 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 [AUC =~5–6] on day 1 plus etoposide 120 mg/m² on days 1–3 every 4 weeks for 3 courses).⁴⁴⁷ 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 Germ Cell and Sex Cord-Stromal Tumors* in the NCCN Guidelines for Malignant Germ Cell and Sex Cord-Stromal Tumors).²⁹⁷ 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,⁴⁴⁸ 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.⁴⁴⁹⁻⁴⁵²

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.⁴⁵³ 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)⁴⁵⁴ or high-dose chemotherapy. Referral to a tertiary care center for potentially curative treatment is strongly recommended.⁴⁵⁵ 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 TIP, VAC (vincristine, dactinomycin, cyclophosphamide), VeIP (vinblastine, ifosfamide, cisplatin), VIP (etoposide, ifosfamide, cisplatin), cisplatin/etoposide, docetaxel/carboplatin, paclitaxel/carboplatin, paclitaxel/gemcitabine, paclitaxel/ifosfamide, docetaxel, paclitaxel, high-dose chemotherapy, RT, or supportive care only.^{442,455-459} 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 *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.^{460,461} Most patients with granulosa tumors present with early-stage disease; the disease is typically indolent.⁴⁶² 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; 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).¹ The staging system for ovarian and primary peritoneal cancer is also used for sex cord-stromal tumors (see Table 1 in the NCCN Guidelines for Ovarian Cancer).

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).⁴⁶²⁻⁴⁶⁵ Although complete staging is recommended for all other patients, lymphadenectomy may be omitted for stage IA or IC tumors.⁴⁶⁶ 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).⁴⁶³ For patients with high-risk stage I tumors (tumor rupture, stage 1C, poorly differentiated tumor, and tumor size >10–15 cm⁴⁶⁷), postoperative recommendations (all are category 2B) include observation or consideration of platinum-based chemotherapy.⁴⁶⁸ Those with surgical findings of low-risk stage I tumor (ie, without high-risk features) should be observed (see *Surveillance for 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).⁴⁶⁹⁻⁴⁷²

Surveillance recommendations for malignant sex cord-stromal tumors are provided in the algorithm, which are based on the SGO recommendations (see *Surveillance for Germ Cell and Sex Cord-Stromal Tumors* in the NCCN Guidelines for Less Common Ovarian Histopathologies).²⁹⁷ Prolonged surveillance is recommended for granulosa cell tumors, because they can recur years later (eg, 30 years).^{427,460,461,473} 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).^{461,473-476} 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.^{476,477} 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).⁴⁷⁸⁻⁴⁸¹ Most pathologists now consider MMMTs to be a variant of poor risk, poorly differentiated

epithelial ovarian cancer (metaplastic carcinoma).⁴⁸² Patients with MMMTs are not candidates for fertility-sparing surgery regardless of age. The staging system for ovarian and primary peritoneal cancer is also used for MMMTs (see Table 1 in the NCCN Guidelines for Ovarian Cancer).⁴⁸⁰

Optimal surgical debulking is recommended for patients with MMMTs (see *Principles of Surgery* in the NCCN Guidelines for Ovarian Cancer).^{480,483-485} After complete surgical staging, several postoperative chemotherapy regimens are recommended for patients with stage I to IV MMMT. Patients with stage I to IV MMMT or recurrence may be treated using the same primary chemotherapy regimens that are recommended for epithelial ovarian cancer (see *Primary Chemotherapy/Primary Adjuvant Therapy* in the NCCN Guidelines for Ovarian Cancer).^{482,486-491} The IP chemotherapy regimen described for ovarian cancer can be used for select patients with MMMT. For the 2016 update, the NCCN Panel also added 3 new postoperative chemotherapy options for patients with stage I to IV MMMT or recurrence: cisplatin/ifosfamide (category 2A), carboplatin/ifosfamide (category 2A), and ifosfamide/paclitaxel (category 2B).^{478,482,486,492} After treatment, the surveillance and follow-up recommendations for epithelial ovarian cancer are also used for MMMTs.

Borderline Epithelial Tumors (Low Malignant Potential Tumors)

Diagnosis

The terms for borderline epithelial tumors (also known as low malignant potential tumors or atypical proliferative tumors) have changed over the years.⁴¹ The 2016 CAP cancer protocol for ovarian cancer uses borderline and does not use low malignant potential.¹⁰² 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).^{1,399} 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.^{493,494} Five-year survival exceeds 80%.⁴⁹⁵ 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.^{496,497}

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 Tumors]).^{399,498} 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 (see the NCCN Guidelines for Borderline Epithelial Tumors [Low Malignant Potential Tumors]).⁴⁹⁹ Treatment guidelines for borderline epithelial tumors depend on the histologic and clinical characteristics, the age of the patient,⁴⁹⁷ 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.^{399,500} 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 Tumors]).

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.^{149,150,501} 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.^{502,503} 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 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 *Primary Treatment for Incomplete Previous Surgery* in the NCCN Guidelines for Borderline Epithelial Tumors [Low Malignant Potential Tumors]). 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 grade 1 (low-grade) serous epithelial ovarian cancer can be considered for these patients (see *Primary Treatment* in



the NCCN Guidelines for Borderline Epithelial Tumors [Low Malignant Potential Tumors]).^{496,497,504} 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 IP or intravenous, is controversial in patients with borderline epithelial tumors. The significance of invasive implants remains under investigation.^{399,505} The benefit of postoperative chemotherapy has not been demonstrated for patients who have no microscopically demonstrable invasive implants.⁵⁰⁶ 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; these recommendations were revised for the 2016 update (see *Primary Treatment* for Borderline Epithelial Tumors [Low Malignant Potential Tumors]).

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 *Primary Treatment* in the NCCN Guidelines for Borderline Epithelial Tumors [Low Malignant Potential Tumors]).⁵⁰⁵ 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 Tumors]).^{496,507} 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).³⁹⁹

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 grade 1 (low-grade) serous epithelial ovarian cancer; those with high-grade invasive implants may be treated as per epithelial ovarian cancer (see *Primary Chemotherapy/Primary Adjuvant Therapy* in the NCCN Guidelines for Borderline Epithelial Tumors [Low Malignant Potential Tumors]). Observation is recommended for those with noninvasive disease.

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& References marked with this symbol provided the basis for the algorithms.



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