



National
Comprehensive
Cancer
Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Ovarian Cancer

Including Fallopian Tube Cancer and Primary Peritoneal Cancer

Version 4.2017 — November 9, 2017

NCCN.org

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[NCCN Ovarian Cancer Panel Members](#)

[Summary of the Guidelines Updates](#)

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

[Clinical Presentation, Workup, Clinical Stage, Primary Treatment \(OV-1\)](#)

[Diagnosis by Previous Surgery: Findings and Primary Treatment \(OV-2\)](#)

[Pathologic Staging, Primary Chemotherapy/Primary Adjuvant Therapy \(OV-3\)](#)

[Post-Primary Treatment: Secondary Adjuvant Therapy \(OV-4\)](#)

[Monitoring/Follow-Up, Recurrent Disease \(OV-5\)](#)

[Disease Status, Therapy for Persistent Disease or Recurrence \(OV-6\)](#)

Less Common Ovarian Histopathologies:

[Diagnosis \(LCOH-1\)](#)

[Carcinosarcoma \(Malignant Mixed Müllerian Tumors\) \(LCOH-2\)](#)

[Clear Cell Carcinoma \(LCOH-3\)](#)

[Mucinous Carcinoma \(LCOH-4\)](#)

[Low-Grade \(Grade 1\) Serous/Endometrioid Epithelial Carcinoma \(LCOH-5\)](#)

[Borderline Epithelial Tumors \(Low Malignant Potential\) \(LCOH-6\)](#)

[Malignant Sex Cord-Stromal Tumors \(LCOH-9\)](#)

[Malignant Germ Cell Tumors \(LCOH-10\)](#)

[Surveillance for Malignant Germ Cell and Sex Cord-Stromal Tumors \(LCOH-12\)](#)

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

[Principles of Systemic Therapy \(OV-B\)](#)

• [Primary Systemic Therapy Regimens \(OV-B, 3 of 8\)](#)

• [Acceptable Recurrence Therapies \(OV-B, 5 of 8\)](#)

[Management of Drug Reactions \(OV-C\)](#)

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

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

To find clinical trials online at NCCN Member Institutions, [click here: nccn.org/clinical_trials/physician.html](#).

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

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

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[Staging \(ST-1\)](#)

The NCCN Guidelines® are a statement of evidence and consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult the NCCN Guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network® (NCCN®) makes no representations or warranties of any kind regarding their content, use or application and disclaims any responsibility for their application or use in any way. The NCCN Guidelines are copyrighted by National Comprehensive Cancer Network®. All rights reserved. The NCCN Guidelines and the illustrations herein may not be reproduced in any form without the express written permission of NCCN. ©2017.



Updates in Version 4.2017 of the NCCN Guidelines for Ovarian Cancer from Version 3.2017 include:

MS-1

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

Updates in Version 3.2017 of the NCCN Guidelines for Ovarian Cancer from Version 2.2017 include:

OV-6

- After platinum-based recurrence therapy for platinum-sensitive disease:
 - ▶ Olaparib was added as a maintenance therapy option: "Consider niraparib *or* *olaparib* maintenance therapy if partial or complete response."
 - ▶ Footnote "aa" added to olaparib: "For those with platinum-sensitive disease who have completed two or more lines of platinum-based therapy."

Updates in Version 2.2017 of the NCCN Guidelines for Ovarian Cancer from Version 1.2017 include:

OV-B (5 of 8)/(6 of 8)

- Footnote "i" revised: "In general, the panel would recommend combination regimens, *platinum-based regimens for platinum-sensitive recurrent disease* based on randomized trial data, especially in first relapses."
- Footnote "k" revised: ~~In patients who have not previously received bevacizumab.~~ *There are limited data on the efficacy of bevacizumab in the recurrence therapy setting for patients previously treated with bevacizumab.*
- Footnote "m" added: "If response after chemotherapy, bevacizumab can be continued as maintenance therapy until disease progression or unacceptable toxicity."

[Continued on next page](#)

Updates in Version 1.2017 of the NCCN Guidelines for Ovarian Cancer from Version 1.2016 include:

General

- Imaging recommendations have been clarified to include the target anatomy, and the recommended imaging modalities.

OV-1

- Workup, added: "Evaluate total serum protein and nutritional status."
- Clinical stage column added. Primary treatment options significantly revised and reorganized by clinical stage for those with a suspicious mass and/or symptoms.
- Footnote added: "May be an option for select patients with stage IC based on histology."

OV-3

- Stage II-IV, clarified that IP and IV chemotherapy options are category 2A recommendations for LCOH.
- Stage I-IV, following primary/adjuvant therapy, a link has been added to the NCCN Guidelines for Survivorship.

OV-4

- Footnote "r" revised: "No ~~objective definitive~~ evidence of disease (~~ie, negative physical exam, negative CA-125, negative CT with <1 cm lymph nodes~~)."
- Footnote "s" added: "There is limited evidence that postremission pazopanib may be less effective in east Asian women with ovarian cancer. (Kim JW, et al. Pazopanib maintenance therapy in East Asian women with advanced epithelial ovarian cancer: results from AGO-OVAR16 and an East Asian study. Int J Gynecol Cancer 2015.)"

OV-5

- Monitoring and follow-up, bullet added: "Long-term wellness care (See NCCN Guidelines for Survivorship)."

OV-6

- After platinum-based recurrence therapy for platinum-sensitive disease:
 - ▶ Added: "Repeat prior imaging: chest/abdominal/pelvic CT, MRI, PET/CT, or PET"
 - ▶ Maintenance option added: "Consider niraparib maintenance therapy if partial or complete response."
 - ▶ Footnote "aa" added: "For those with platinum-sensitive disease who have completed two or more lines of platinum-based therapy."

Less Common Ovarian Histopathologies

LCOH-1

- Reference added to footnote "b": "Committee on the State of the Science in Ovarian Cancer R, Board on Health Care S, Institute of M, et al. Ovarian Cancers: Evolving Paradigms in Research and Care. Washington (DC): National Academies Press (US) Copyright 2016 by the National Academy of Sciences. All rights reserved; 2016."

LCOH-2

- First adjuvant option revised: "~~Treat~~ Chemotherapy as per epithelial ovarian cancer (preferred) (See Primary Chemotherapy/Primary Adjuvant Therapy on OV-3)."

LCOH-3

- Adjuvant therapy for stage II-IV revised: "~~Treat~~ Chemotherapy as per epithelial ovarian cancer (See Primary Chemotherapy/Primary Adjuvant Therapy on OV-3)."

LCOH-4

- Added "if not previously done" to consider surgical staging after workup.
- For stages IA-IB and IC, the following option has been added: "Fertility-sparing surgery for select patients (if not previously done)."
- Footnote "f" revised: "Consider ~~molecular testing for additional testing to aid in the identification of metastatic~~ GI malignancies versus primary mucinous ovarian cancer."

LCOH-7

Added "Chest/abdomen/pelvic CT with contrast" for residual disease.

LCOH-10

- Prior surgery and incompletely staged, imaging recommendations revised: "~~consider repeat imaging (CT, MRI, PET-CT) as indicated~~ Chest/abdomen/pelvis CT with contrast (if not previously done)."

[Continued on next page](#)

Updates in Version 1.2017 of the NCCN Guidelines for Ovarian Cancer from Version 1.2016 include:

[LCOH-10 \(continued\)](#)

- For incompletely staged dysgerminoma or grade I immature teratoma, with negative tumor markers and negative imaging, the following option has been added: "Consider observation (category 2B) (See LCOH-12)"

[LCOH-11](#)

- Footnote "a" added: "See WHO histologic classification (OV-D)."

[LCOH-12](#)

- Footnote "w" added: "Chest/abdominal/pelvic CT with contrast if recurrence suspected. Other imaging modalities can be considered (ie, chest x-ray, MRI, PET/CT, or PET)."

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

- Interval "cytoreduction" changed to "debulking."
- First bullet revised: "Interval ~~cytoreductive~~ *debulking* surgery, including completion TAH and BSO with staging, should be performed after..."

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

- Fertility-sparing surgery, sub-bullet revised: "~~Fertility-sparing surgery with USO (preserving the uterus and contralateral ovary) or BSO (preserving the uterus) (fertility-sparing surgery)~~ can be considered for patients with apparent early-stage disease and/or low-risk tumors (early-stage invasive epithelial tumors, LMP lesions, malignant germ cell tumors, *mucinous*, or malignant sex cord-stromal tumors) who wish to preserve fertility..."
- Reference added: "Billmire D, Vinocur C, Rescorla F, et al. Outcome and staging evaluation in malignant germ cell tumors of the ovary in children and adolescents: an intergroup study. J Pediatr Surg 2004;39:424-429."
- Footnote "3" added: "Decisions on the use of ancillary procedures should be made in conjunction with a gynecologic oncology surgeon or a practitioner familiar with ovarian cancer patterns of recurrence."

[OV-B \(3 of 8\)](#)

- Heading revised: ~~Primary Systemic Therapy~~ *Chemotherapy/Primary Adjuvant Therapy Regimens, Epithelial Ovarian (including LCOH)/Fallopian Tube/Primary Peritoneal*
- Option added for stage II-IV: "Carboplatin AUC 5 + pegylated liposomal doxorubicin 30 mg/m² every 4 weeks for 6 cycles."
- Neoadjuvant therapy section added.
- Reference added: Mackay H, Gallagher CJ, Parulekar WR, et al. OV21/ PETROC: A randomized Gynecologic Cancer Intergroup (GCIG) phase II study of intraperitoneal (IP) versus intravenous (IV) chemotherapy following neoadjuvant chemotherapy and optimal debulking surgery in epithelial ovarian cancer (EOC) [abstract]. J Clin Oncol 2016;34: Abstract LBA5503.
- Additional options for LCOH moved onto OV-B (4 of 8).

[OV-B \(4 of 8\)](#)

- Page heading revised: "~~Primary Chemotherapy/Primary Adjuvant Systemic Therapy Regimens, Less Common Ovarian Histopathologies Malignant Germ Cell/Sex Cord-Stromal Tumors~~"
- Bullet added under carcinosarcoma, clear cell, mucinous, and borderline and low-grade (grade 1 serous/endometrioid epithelial carcinoma: "IP/IV and IV regimens (See options for stage II-IV disease on OV-B, 3 of 8)"

[OV-B \(5 of 8\)](#)

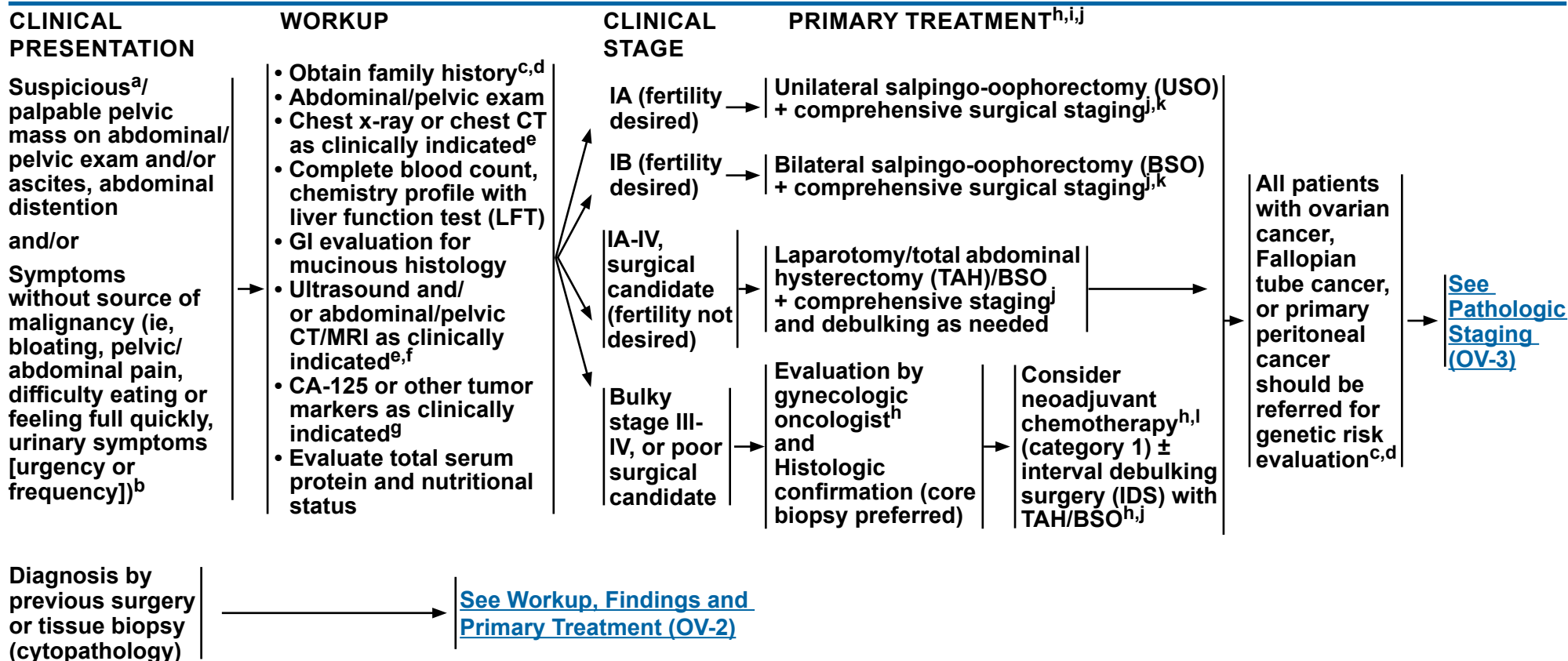
- Page heading revised: "Acceptable Recurrence Therapies for Epithelial (including LCOH)/Fallopian Tube/Primary Peritoneal Cancer"
- Cytotoxic therapy for platinum-sensitive disease:
 - Carboplatin/gemcitabine/bevacizumab has been changed from a category 2B recommendation to a category 2A.
 - Option added: Carboplatin/paclitaxel, albumin bound (for patients with confirmed taxane hypersensitivity)
 - The following options have been added for mucinous tumors only:
 - ◇ 5-FU/leucovorin/oxaliplatin ± bevacizumab (category 2B for bevacizumab)
 - ◇ Capecitabine + oxaliplatin
- Rucaparib added as a targeted recurrence therapy option (preferred option for platinum-resistant disease), with footnote "n": "For patients with deleterious germline and/or somatic BRCA mutated (as detected by an FDA-approved test or other validated test performed in a CLIA-approved facility) advanced ovarian cancer who have been treated with two or more lines of chemotherapy." Reference: Swisher EM, Lin KK, Oza AM, et al. Rucaparib in relapsed, platinum-sensitive high-grade ovarian carcinoma (ARIEL2 Part 1): an international, multicentre, open-label, phase 2 trial. Lancet Oncol 2017;18:75-87.
- A note has been added below the table: "For LCOH, all regimens are category 2A unless indicated." (Also on OV-B, 6 of 8)
- Footnote "g" added: "Chemotherapy has not been shown to be beneficial in ovarian borderline epithelial tumors (LMP)."
- List of other potentially active agents has been moved onto OV-B (6 of 8).

[OV-B \(6 of 8\)](#)

- Carboplatin/paclitaxel/bevacizumab has been added to the list of other potentially active agents for platinum-sensitive disease.

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Epithelial Ovarian Cancer/Fallopian Tube Cancer/ Primary Peritoneal Cancer



^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 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 \(OV-A\)](#).

^kMay be an option for select patients with stage IC based on histology.

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

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Epithelial Ovarian Cancer/Fallopian Tube Cancer/ Primary Peritoneal Cancer

DIAGNOSIS BY PREVIOUS SURGERY WORKUP

- Obtain family history^c
- Refer for genetic risk evaluation^{c,d}
- Chest x-ray or chest CT as clinically indicated^e
- 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

Incomplete previous surgery^j and/or staging:

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

Adequate previous surgery and staging

FINDINGS^l

Suspected stage
IA or IB/grade 1^m

Suspected
stage IA
or
IB/grade 2^m

Suspected
stage IA or
IB, grade 3
or clear cell
or stage IC^m

Stage
II, III, IV

PRIMARY TREATMENT^h

Surgical staging^j

Completion surgery/
surgical staging^j

Completion surgery/
surgical staging^j or
chemotherapy^l (6 cycles)

Completion surgery/
surgical staging^j

Tumor reductive surgery^j

Chemotherapy^l (6 cycles)
Evaluate for IDS prior
to fourth cycle of
chemotherapy^{h,n}

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

^cSee [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.

^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.

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

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

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

ⁿCompletion 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^{m,o}

PRIMARY CHEMOTHERAPY/PRIMARY ADJUVANT THERAPY^p

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

→ [See LCOH-1](#)

Stage IA or IB → Grade 1^m (low-grade)
serous/endometrioid

→ [See LCOH-5](#)

→ Grade 2^m
serous/endometrioid

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

Stage IC
(Grade 1, 2, or 3)

→ Grade 3^m (high-grade)

IV taxane/carboplatin^l x 3–6 cycles^{p,q}

Stage II
Stage III
Stage IV

- Chemotherapy [See Primary Regimens ([OV-B, 3 of 8](#))]^p
 - ▶ Intraperitoneal (IP) chemotherapy^{l,i} in <1 cm optimally debulked stage II and stage III patients (category 1 for stage III, category 2A for stage II and LCOH)
 - or
 - ▶ IV taxane/carboplatin^l for a total of 6 cycles (category 1, category 2A for LCOH)^p
- Completion surgery as indicated by tumor response and potential resectability in selected patients^j

Consider symptom
management and best
supportive care. Refer for
palliative care assessment,
if appropriate.

- [See NCCN Guidelines for Palliative Care](#)
- [See NCCN Guidelines for Survivorship](#)

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

Consider symptom
management and best
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if appropriate.

- [See NCCN Guidelines for Palliative Care](#)
- [See NCCN Guidelines for Survivorship](#)

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

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 \(OV-A\)](#).

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

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

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

^pPatients receiving primary chemotherapy will be monitored as follows:

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

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

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

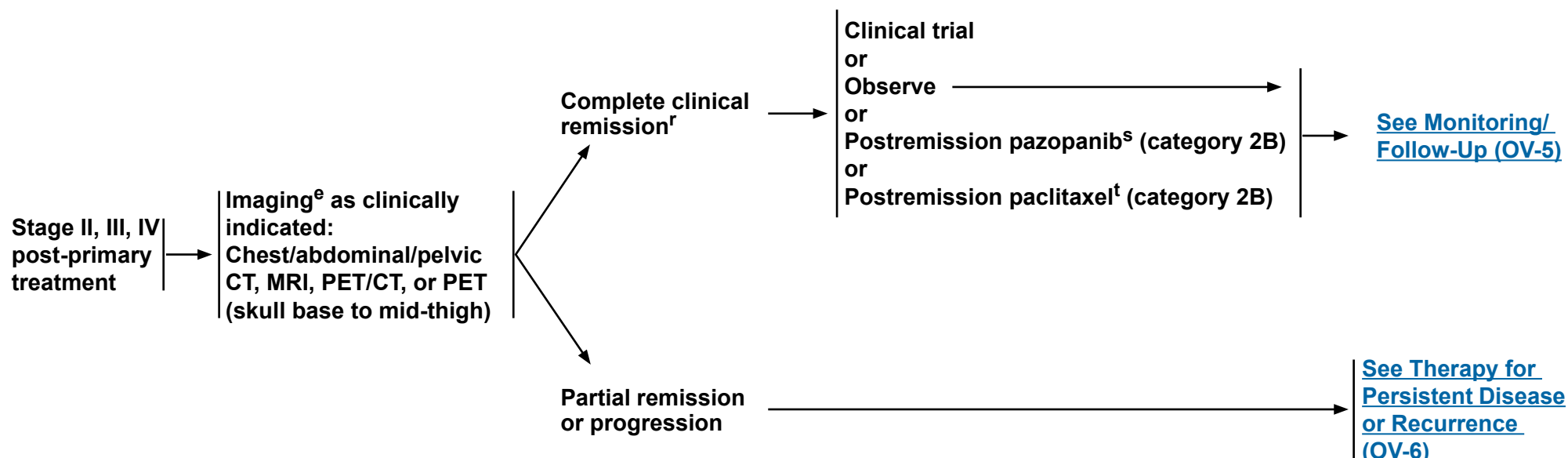
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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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.

^rNo definitive evidence of disease.

^sThere is limited evidence that postremission pazopanib may be less effective in east Asian women with ovarian cancer. (Kim JW, Mahner S, Wu LY, et al. Pazopanib maintenance therapy in East Asian women with advanced epithelial ovarian cancer: results from AGO-OVAR16 and an East Asian study. Int J Gynecol Cancer 2015.)

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

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

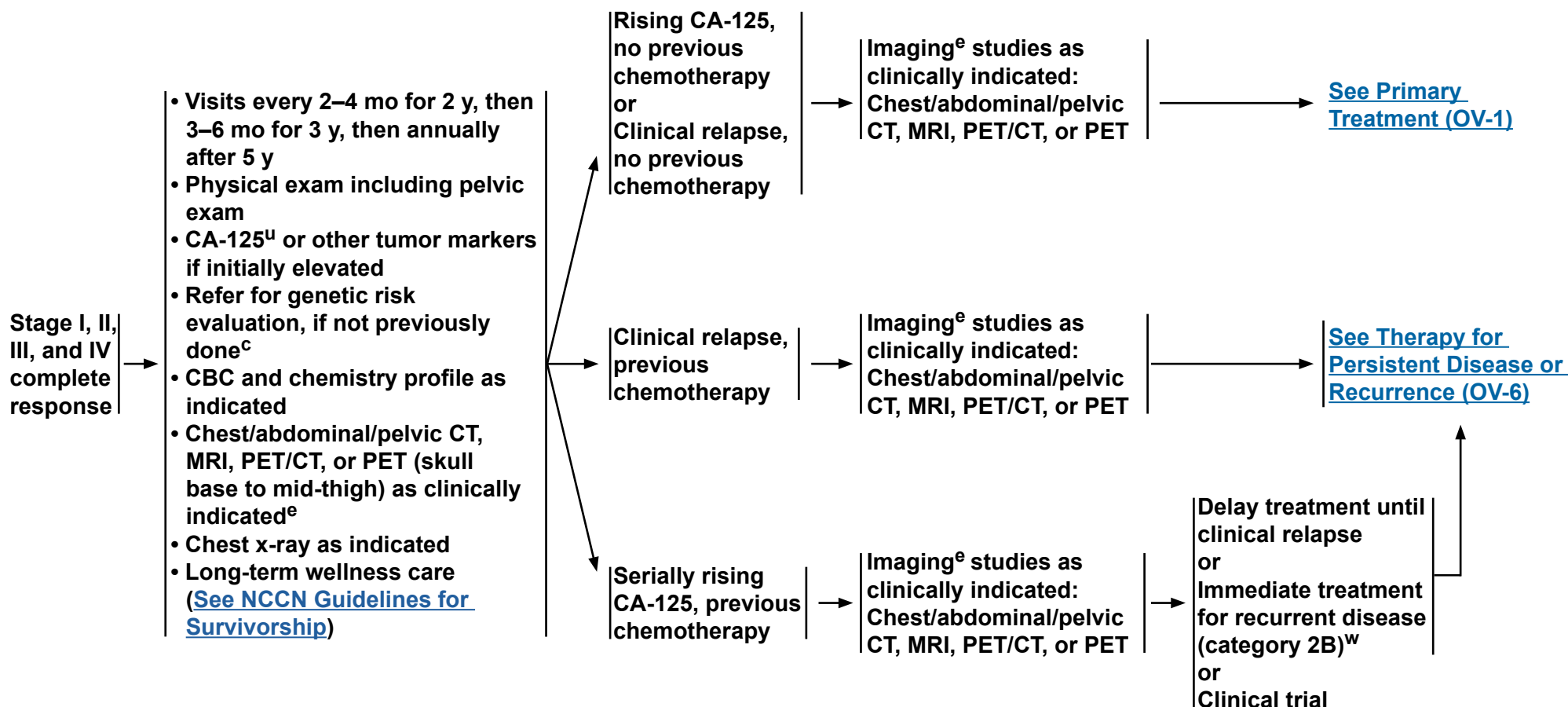
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Epithelial Ovarian Cancer/Fallopian Tube Cancer/ Primary Peritoneal Cancer

MONITORING/FOLLOW-UP

RECURRENT DISEASE^v



^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.

^uThere 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](#).

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

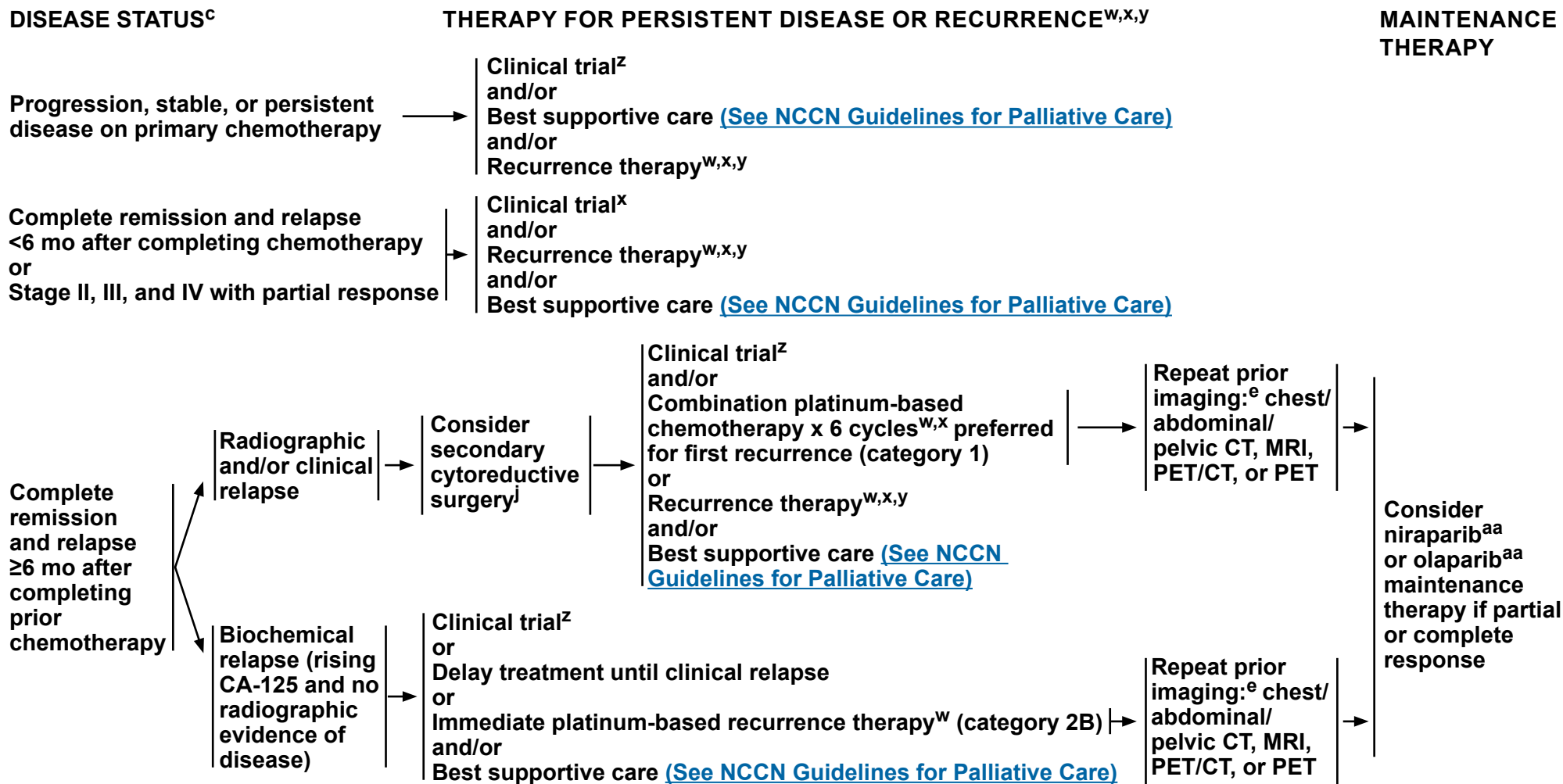
^wSee [Acceptable Recurrence Therapies \(OV-B, 5 of 8\)](#).

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Epithelial Ovarian Cancer/Fallopian Tube Cancer/ Primary Peritoneal Cancer



^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.

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

^wSee [Acceptable Recurrence Therapies \(OV-B, 5 of 8\)](#).

^xPatients 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.

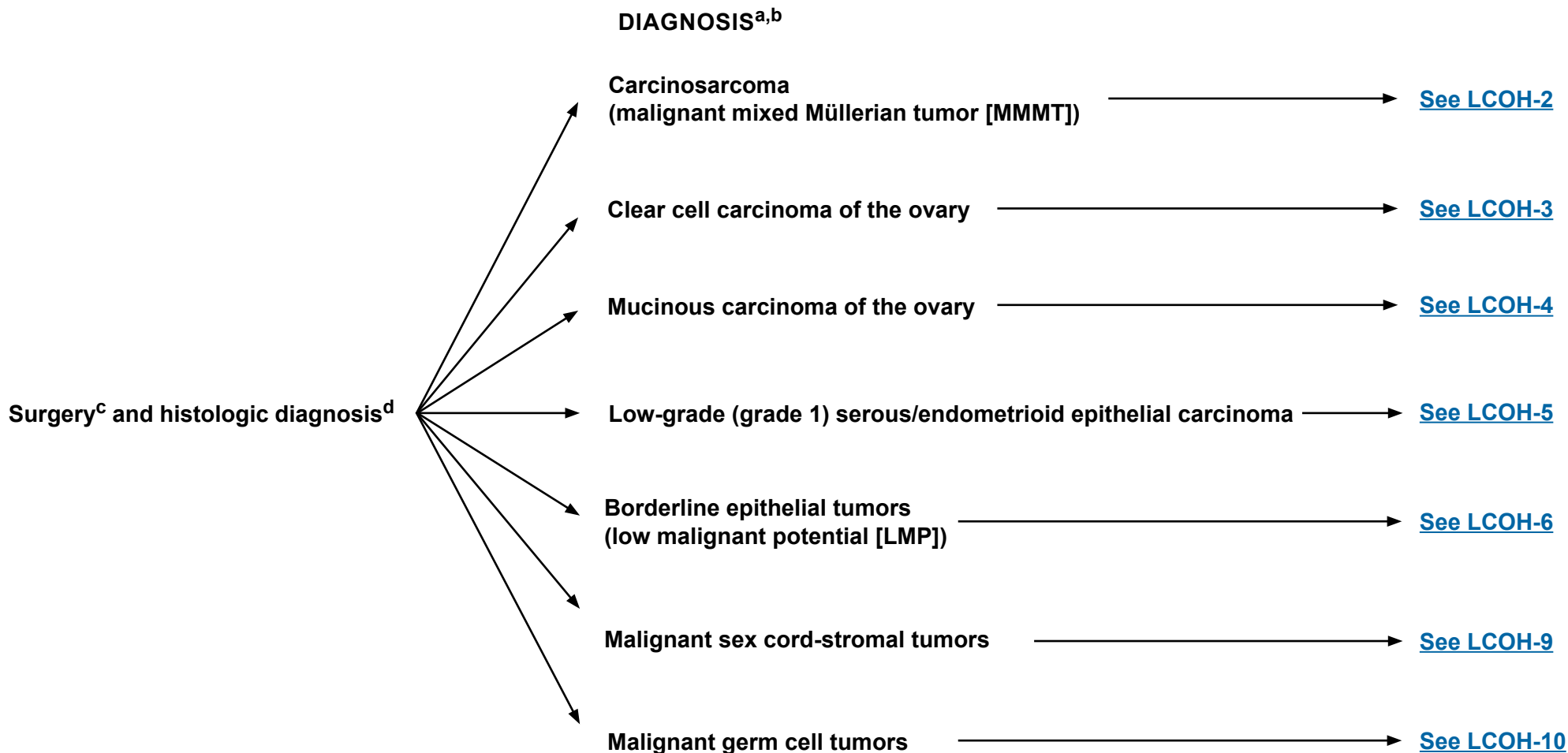
^ySee [Ancillary Palliative Surgical Procedures in Principles of Surgery \(OV-A 4 of 4\)](#).

^zClinical trials with newer agents should be strongly considered.

^{aa}For those with platinum-sensitive disease who have completed two or more lines of platinum-based therapy.

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^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. (Committee on the State of the Science in Ovarian Cancer R, Board on Health Care S, Institute of M, et al. Ovarian Cancers: Evolving Paradigms in Research and Care. Washington (DC): National Academies Press (US) Copyright 2016 by the National Academy of Sciences. All rights reserved; 2016.)

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

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

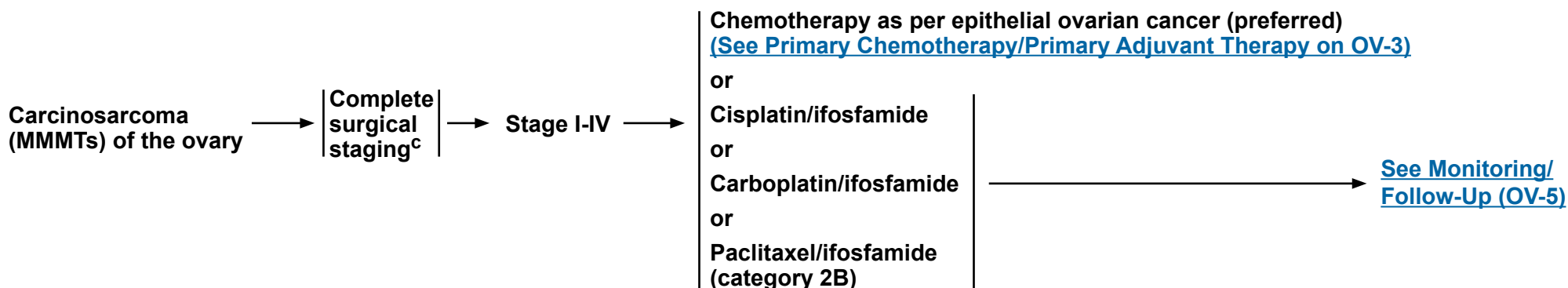
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PATHOLOGIC DIAGNOSIS^a

ADJUVANT TREATMENT^e

MONITORING/FOLLOW-UP



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

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

^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 patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



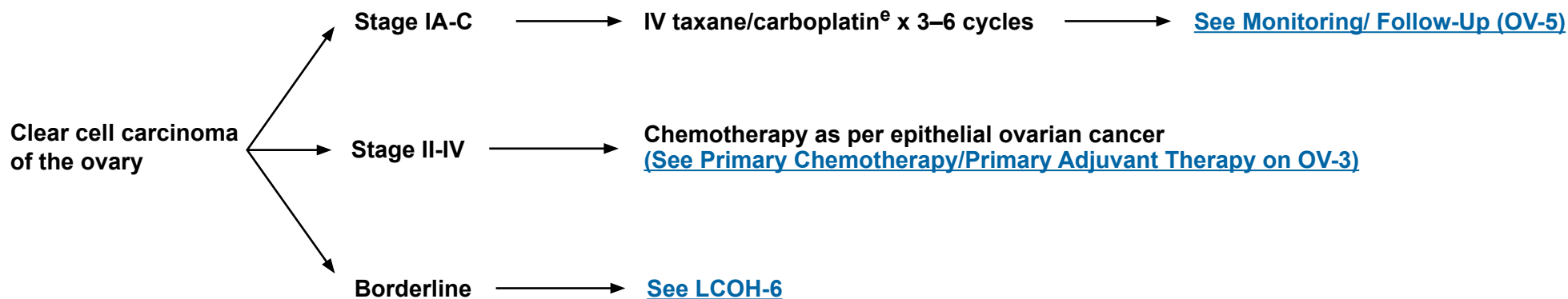
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Clear Cell Carcinoma of the Ovary

PATHOLOGIC DIAGNOSIS^a

ADJUVANT TREATMENT

MONITORING/FOLLOW-UP



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

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

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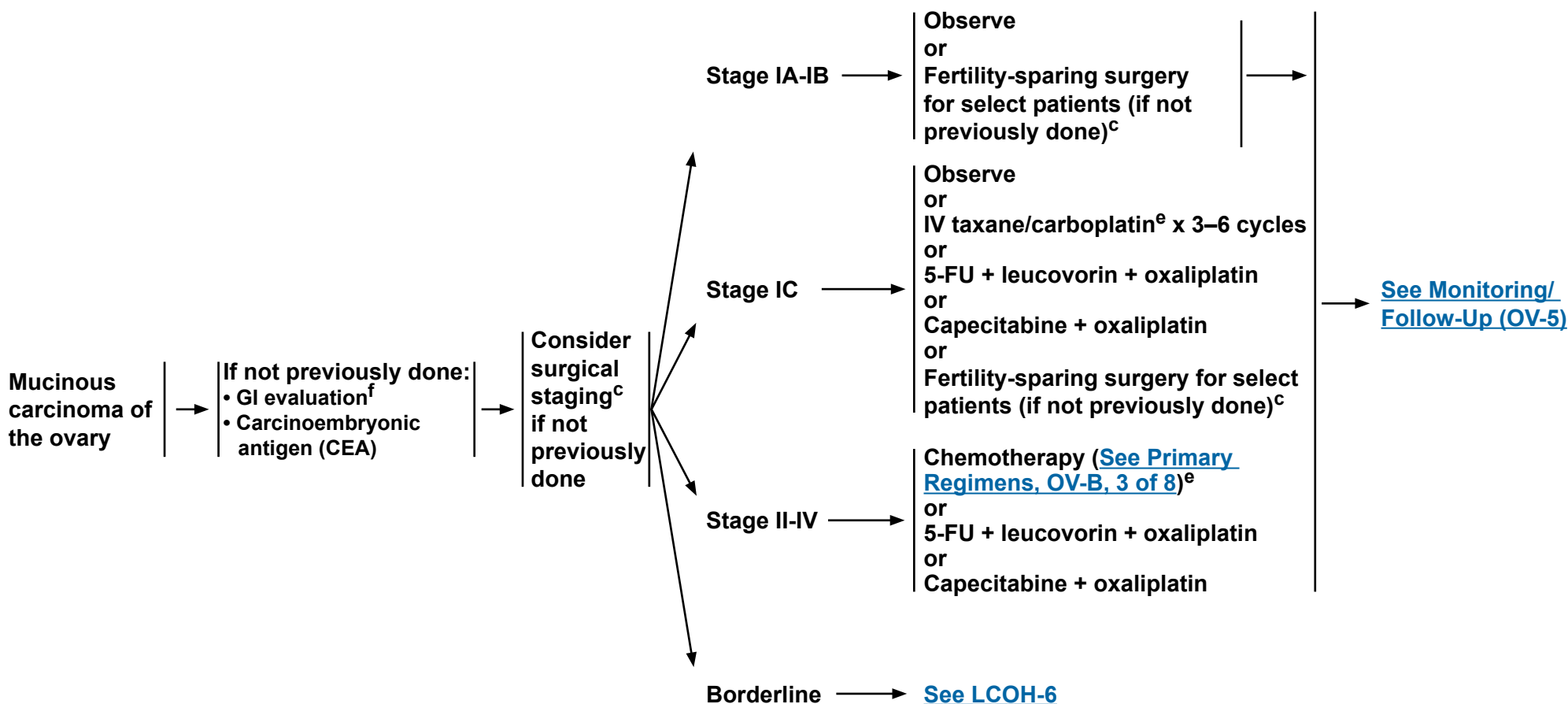
Mucinous Carcinoma of the Ovary

PATHOLOGIC DIAGNOSIS^a

ADDITIONAL WORKUP

ADJUVANT TREATMENT^e

MONITORING/ FOLLOW-UP



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

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

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

^fConsider additional testing to aid in the identification of metastatic GI malignancies versus primary mucinous ovarian cancer.

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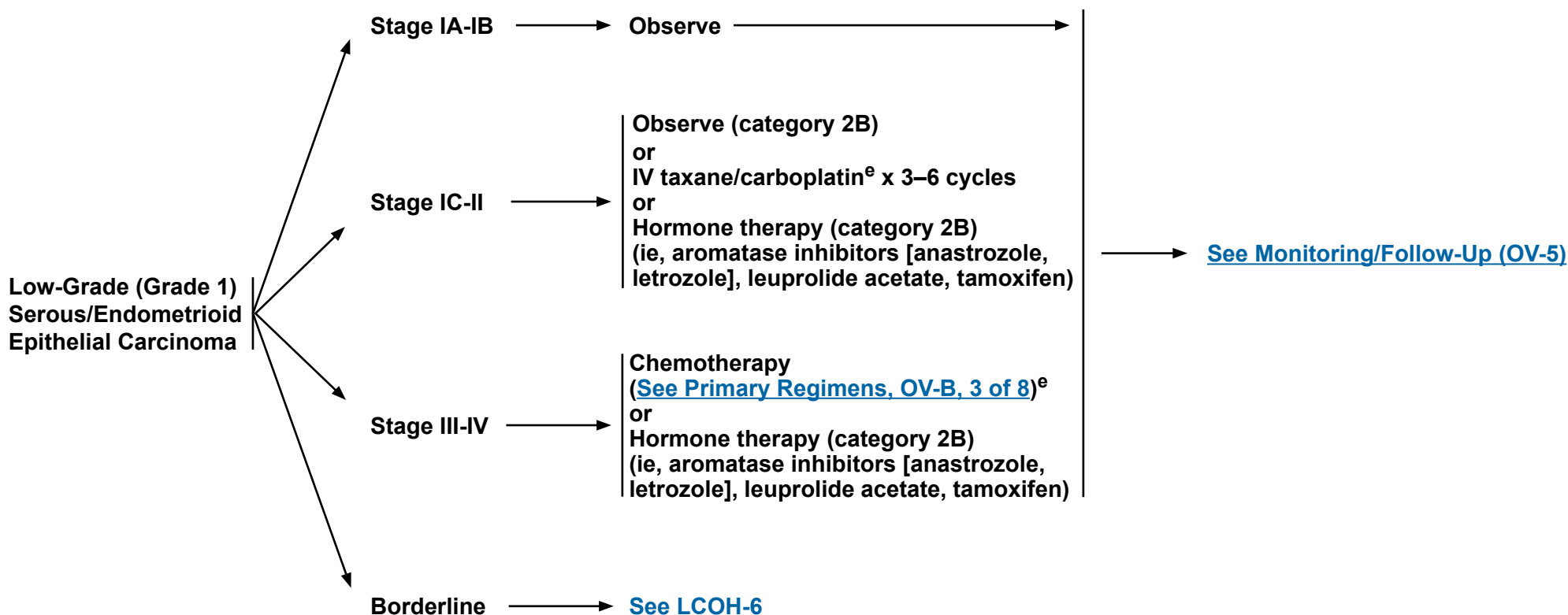
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Low-Grade (Grade 1) Serous/Endometrioid Epithelial Carcinoma

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.

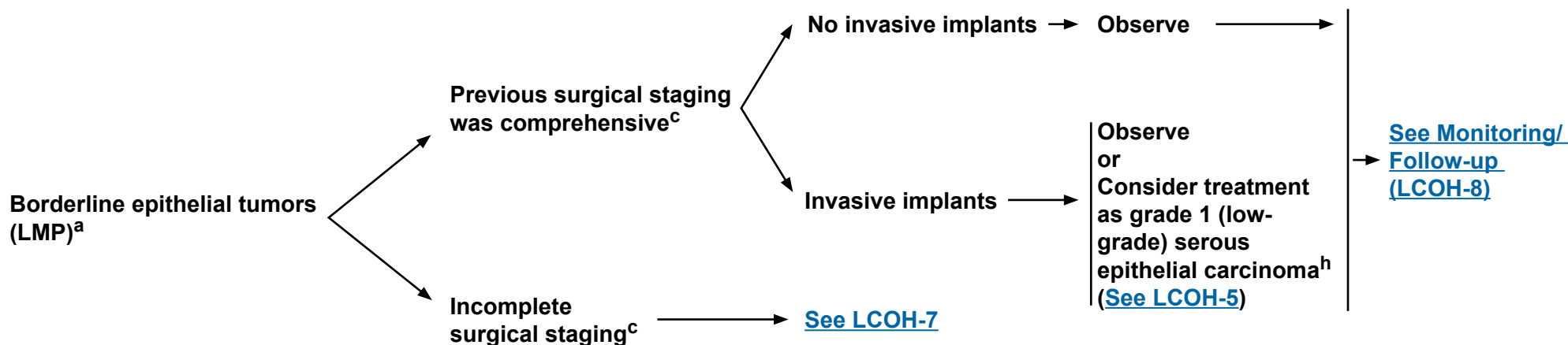
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

NCCN Guidelines Version 4.2017

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).

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

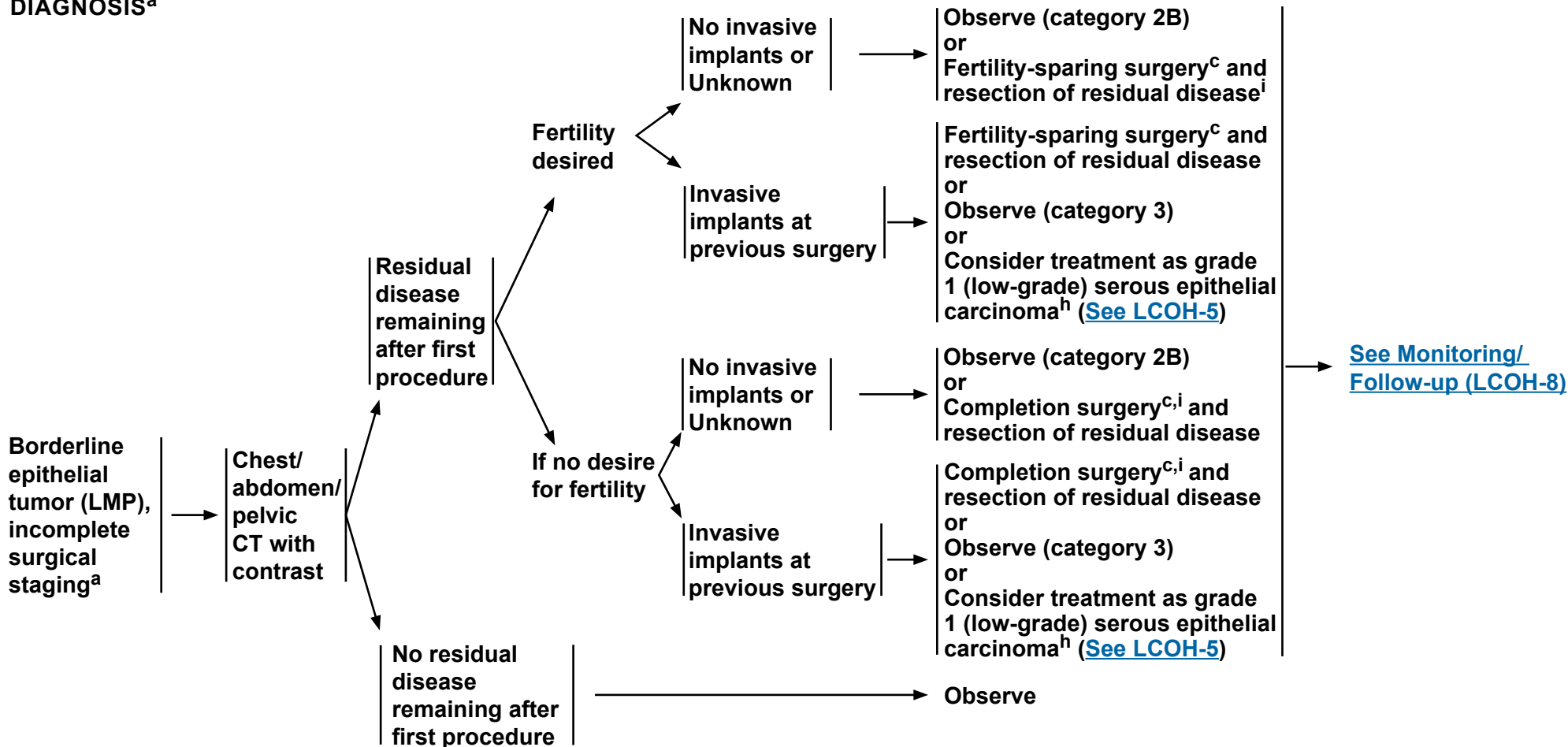
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NCCN Guidelines Version 4.2017

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.

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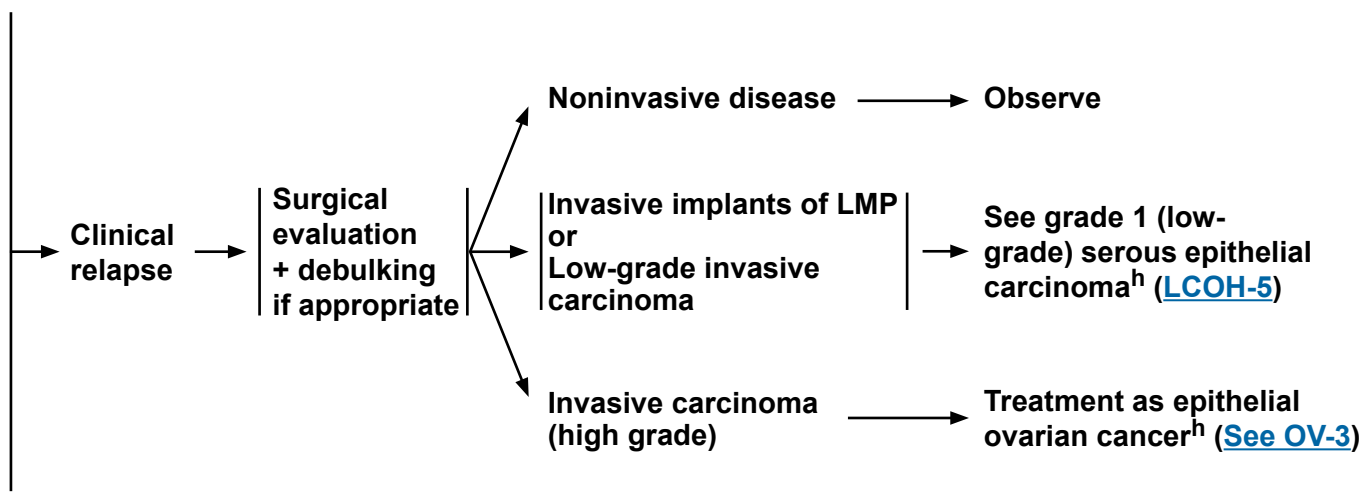
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Borderline Epithelial Tumors (Low Malignant Potential)

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^k as clinically indicated: Chest/abdominal/pelvic CT, MRI, PET/CT, or PET (skull base to mid-thigh)
- Ultrasound as indicated for patients with fertility-sparing surgery

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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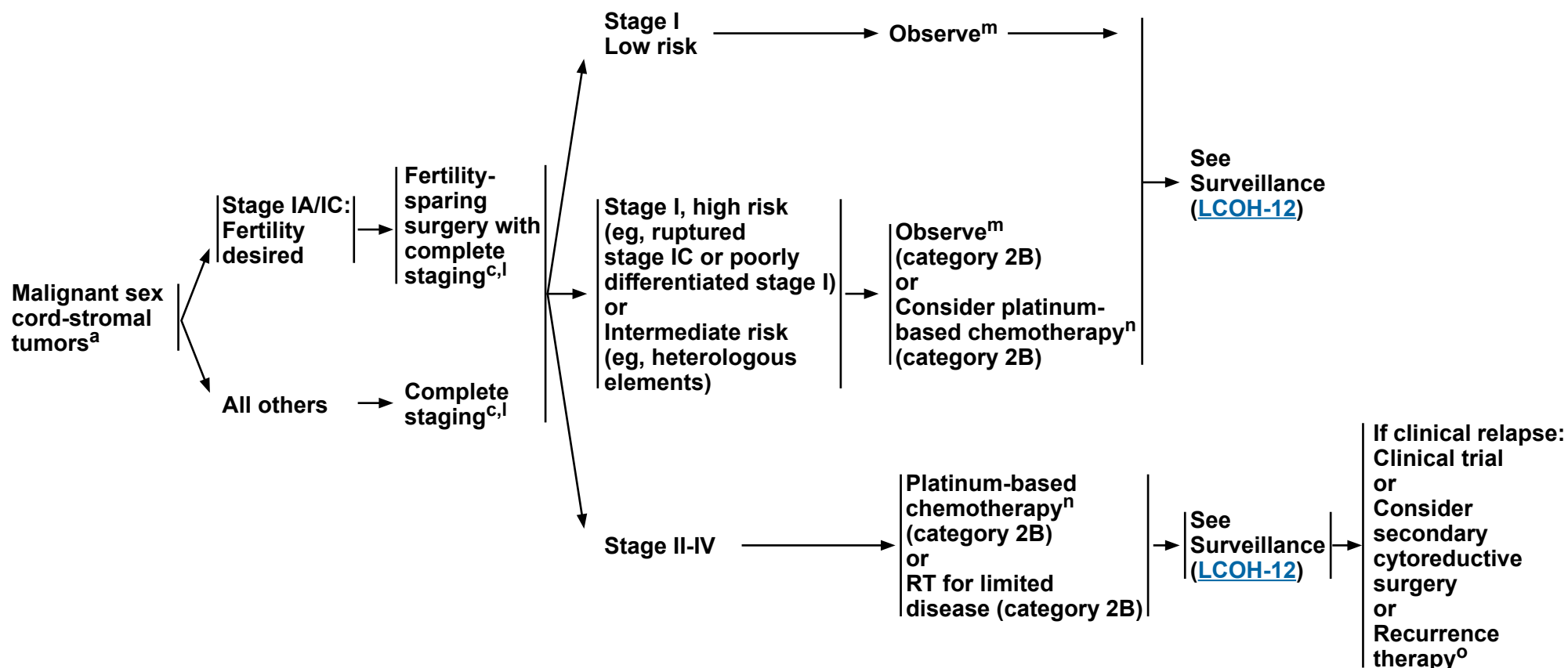
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Malignant Sex Cord-Stromal Tumors

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 \(OV-B, 4 of 8\)](#).

^oSee [Acceptable Recurrence Therapies for Malignant Germ Cell/Sex Cord-Stromal Tumors \(OV-B, 7 of 8\)](#).

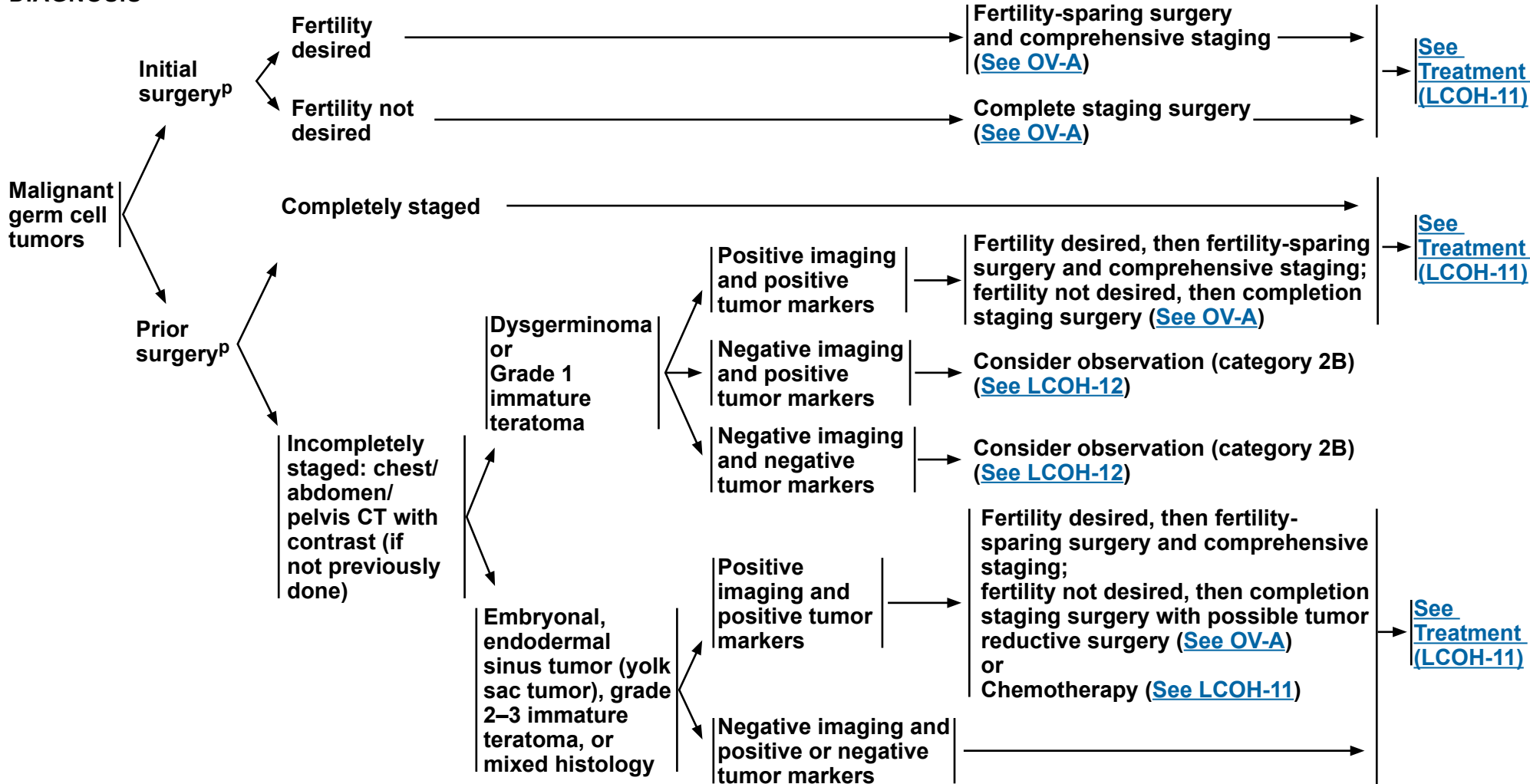
Note: All recommendations are category 2A unless otherwise indicated.

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Malignant Germ Cell Tumors

CLINICAL PRESENTATION/ DIAGNOSIS



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

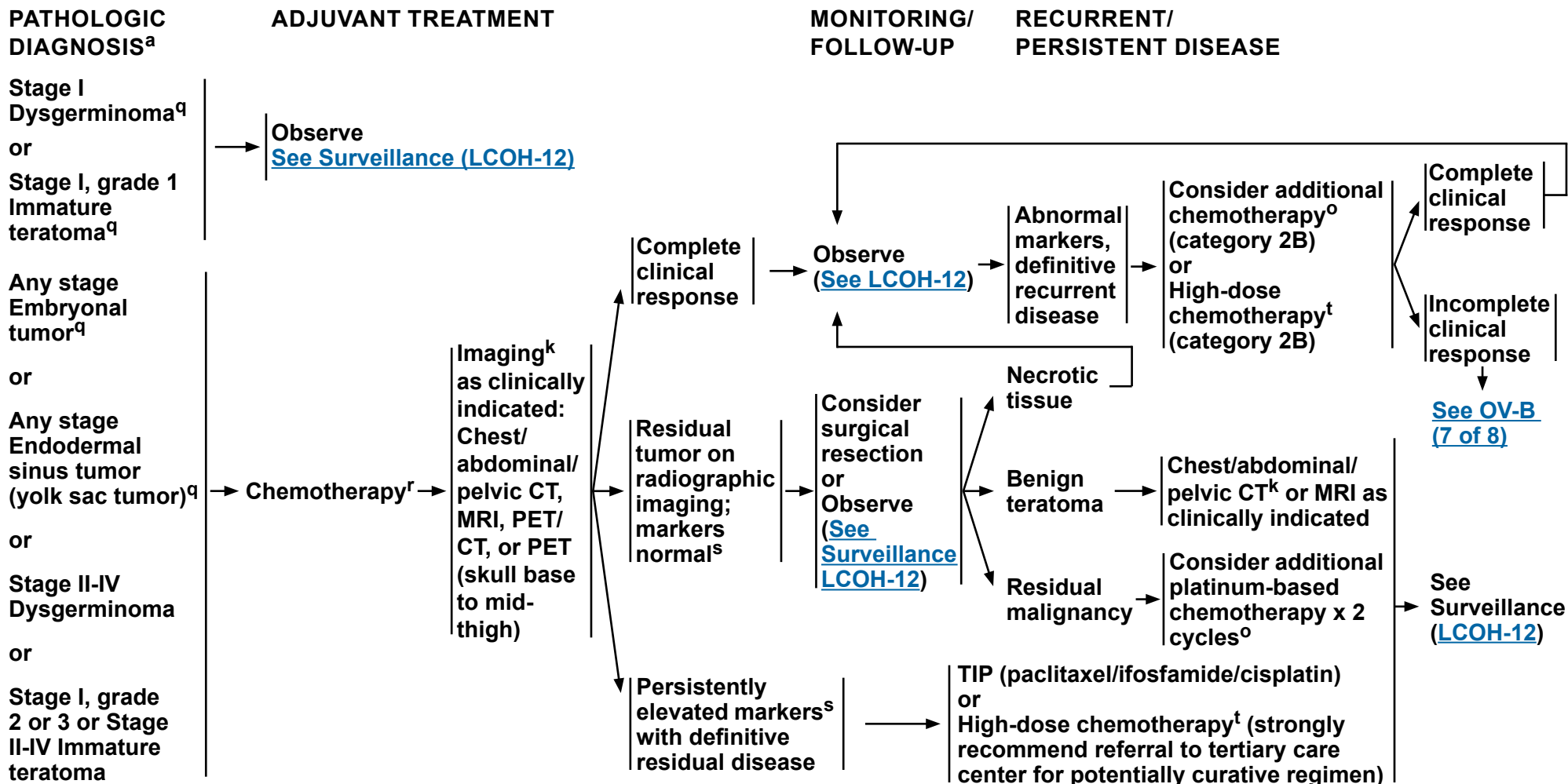
^PSurgical principles for pediatric/young adult patients may differ from those for adult patients. [See Principles of Surgery \(OV-A\)](#).

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NCCN Guidelines Version 4.2017

Malignant Germ Cell Tumors



^aSee WHO Histologic Classification (OV-D).

^kImaging performed with contrast unless contraindicated.

^oSee Acceptable Recurrence Therapies for Malignant Germ Cell/Sex Cord-Stromal Tumors (OV-B, 7 of 8).

^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.

^rSee Primary Chemotherapy Regimens for Malignant Germ Cell Tumors (OV-B, 4 of 8).

^sSee OV-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 4.2017

Malignant Germ Cell and Sex Cord-Stromal Tumors

SURVEILLANCE FOR MALIGNANT 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^v</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^w</u>	CT scan and tumor markers ^{x,w}	CT scan and tumor markers ^{x,w}	CT scan and tumor markers ^{x,w}	CT scan and tumor markers ^{x,w}	CT scan and tumor markers ^{x,w}

^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.

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

^wChest/abdominal/pelvic CT with contrast if recurrence suspected. Other imaging modalities can be considered (ie, chest x-ray, MRI, PET/CT, or PET).

^xSee [OV-1](#) for markers.

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NCCN Guidelines Version 4.2017

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.

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NCCN Guidelines Version 4.2017

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 ureteroneocystostomy, partial hepatectomy, partial gastrectomy, cholecystectomy, and/or distal pancreatectomy.
- Select patients with low-volume residual disease after surgical cytoreduction for invasive epithelial ovarian or peritoneal cancer are potential candidates for IP therapy. In these patients, consideration should be given to placement of IP catheter with initial surgery.

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 \(3 of 4\)](#)

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NCCN Guidelines Version 4.2017

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

PRINCIPLES OF SURGERY (3 of 4)¹

Interval debulking surgery after neoadjuvant chemotherapy of invasive epithelial ovarian cancer

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

- Interval debulking surgery, including completion TAH and BSO with staging, 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 debulking include bowel resection and/or appendectomy, stripping of the diaphragm or other peritoneal surfaces, splenectomy, partial cystectomy and/or ureteroneocystostomy, partial hepatectomy, partial gastrectomy, cholecystectomy, and/or distal pancreatectomy.

Risk-Reducing Salpingo-Oophorectomy (RRSO) Protocol

- 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 \(4 of 4\)](#)

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NCCN Guidelines Version 4.2017

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

PRINCIPLES OF SURGERY (4 of 4)¹

Special Circumstances

- **Fertility-sparing surgery:**
 - Fertility-sparing surgery with USO (preserving the uterus and contralateral ovary) or BSO (preserving the uterus) can be considered for patients with apparent early-stage disease and/or low-risk tumors (early-stage invasive epithelial tumors, LMP lesions, malignant germ cell tumors, mucinous, or malignant sex cord-stromal tumors) who wish to preserve fertility. 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.²
- **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 Procedures³

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.

²Billmire D, Vinocur C, Rescorla F, et al. Outcome and staging evaluation in malignant germ cell tumors of the ovary in children and adolescents: an intergroup study. J Pediatr Surg 2004;39:424-429.

³Decisions on the use of ancillary procedures should be made in conjunction with a gynecologic oncology surgeon or a practitioner familiar with ovarian cancer patterns of recurrence.

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NCCN Guidelines Version 4.2017

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

PRINCIPLES OF SYSTEMIC THERAPY (1 of 8)

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 appropriate option. ([See OV-B 3 of 8](#) 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](#)

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

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NCCN Guidelines Version 4.2017

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

PRINCIPLES OF SYSTEMIC THERAPY (2 of 8)

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](#)

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NCCN Guidelines Version 4.2017

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

PRINCIPLES OF SYSTEMIC THERAPY (3 of 8)

Primary Systemic Therapy Regimens^a

Epithelial Ovarian (including LCOH)/Fallopian Tube/Primary Peritoneal

Stage II-IV

- **IP/IV Regimen (for optimally debulked stage II-III disease)**
 - ▶ **Paclitaxel 135 mg/m² IV continuous infusion over 3 or 24 h^b Day 1; cisplatin 75–100 mg/m² IP Day 2 after IV paclitaxel; paclitaxel 60 mg/m² IP Day 8. Repeat every 3 weeks x 6 cycles. (category 1)**
- **IV Regimens**
 - ▶ **Paclitaxel 175 mg/m² IV over 3 hours followed by carboplatin^c 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^c 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.^d (category 1)**
 - ▶ **Docetaxel 60–75 mg/m² IV over 1 hour followed by carboplatin^c AUC 5–6 IV over 1 hour Day 1. Repeat every 3 weeks x 6 cycles. (category 1)**
 - ▶ **Carboplatin AUC 5 + pegylated liposomal doxorubicin 30 mg/m² every 4 weeks for 6 cycles.**
 - ▶ **Bevacizumab-containing regimens per ICON-7 and GOG-218:**
 - Paclitaxel 175 mg/m² IV over 3 hours followed by carboplatin^c 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^c 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)**

Neoadjuvant Therapy

- **Any of the above IV regimens can be used as neoadjuvant therapy before IDS.**
- **Bevacizumab-containing regimens should be used with caution before IDS due to potential interference with postoperative healing.**
- **After neoadjuvant therapy and IDS any of the above regimens (IV or IP/IV) can be considered as adjuvant therapy options.**
- **There are limited data for the use of IP chemotherapy regimens after neoadjuvant therapy and IDS. The following is an additional IP option after IDS: IV paclitaxel 135 mg/m² over 3 hours on Day 1, IP carboplatin AUC 6 IP Day 1, paclitaxel 60 mg/m² IP Day 8.^e**
- **A minimum of 6 cycles of treatment is recommended, including at least three cycles of adjuvant therapy after IDS.**

^aSee [Discussion](#) for references.

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

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

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

^eMackay H, Gallagher CJ, Parulekar WR, et al. OV21/PETROC: A randomized Gynecologic Cancer Intergroup (GCIg) phase II study of intraperitoneal (IP) versus intravenous (IV) chemotherapy following neoadjuvant chemotherapy and optimal debulking surgery in epithelial ovarian cancer (EOC) [abstract]. J Clin Oncol 2016;34: Abstract LBA5503.

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

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

[Continued](#)

NCCN Guidelines Version 4.2017

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

PRINCIPLES OF SYSTEMIC THERAPY (4 of 8) Primary Systemic Therapy Regimens^a Less Common Ovarian Histopathologies (LCOH)

Carcinosarcoma (MMMT)

- ▶ IP/IV and IV regimens ([See options for stage II-IV disease on OV-B, 3 of 8](#))
- ▶ Carboplatin/ifosfamide
- ▶ Cisplatin/ifosfamide
- ▶ Paclitaxel/ifosfamide (category 2B)

Clear Cell Carcinoma

- ▶ IP/IV and IV regimens ([See options for stage II-IV disease on OV-B, 3 of 8](#))

Mucinous tumors

- ▶ IP/IV and IV regimens ([See options for stage II-IV disease on OV-B, 3 of 8](#))
- ▶ 5-FU/leucovorin/oxaliplatin
- ▶ Capecitabine/oxaliplatin

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

- ▶ IP/IV and IV regimens ([See options for stage II-IV disease on OV-B, 3 of 8](#))
- ▶ Hormone therapy (Aromatase inhibitors [ie, anastrozole, letrozole], leuprolide acetate, tamoxifen) (category 2B)

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

PRINCIPLES OF SYSTEMIC THERAPY (5 of 8)

Acceptable Recurrence Therapies for Epithelial (including LCOH^g)/Fallopian Tube/Primary Peritoneal Cancer^h

	Cytotoxic Therapy (In alphabetical order)*		Targeted Therapy*
Preferred Agents	Platinum-Sensitive Disease^{i,j} Carboplatin ¹ Carboplatin/docetaxel ^{2,3} Carboplatin/gemcitabine ¹ Carboplatin/gemcitabine/bevacizumab ^{k,l,m,4} Carboplatin/liposomal doxorubicin ⁵ (category 1) Carboplatin/paclitaxel, albumin bound (for patients with confirmed taxane hypersensitivity) Carboplatin/paclitaxel (category 1) ⁶ Carboplatin/paclitaxel (weekly) ⁷ Cisplatin ⁶ Cisplatin/gemcitabine ⁸ Additional options for mucinous carcinoma only: 5-FU/leucovorin/oxaliplatin ± bevacizumab (category 2B for bevacizumab) ^{k,l} Capecitabine + oxaliplatin	Platinum-Resistant Disease Docetaxel ⁹ Etoposide, oral ¹⁰ Gemcitabine ^{11,12} Liposomal doxorubicin ^{11,12} Liposomal doxorubicin/bevacizumab ^{k,l,13} Paclitaxel (weekly) ¹⁴ ± pazopanib ¹⁵ Paclitaxel (weekly)/bevacizumab ^{k,l,13} Topotecan ^{16,17} Topotecan/bevacizumab ^{k,l,13}	Single Agents Bevacizumab ^{k,l,18,19} Olaparib ^{n,20,21} Rucaparib ^{o,24} (platinum-resistant disease)

*NOTE: For LCOH, all regimens are category 2A unless indicated.

[Other Potentially Active Agents on OV-B \(6 of 8\)](#)

^gChemotherapy has not been shown to be beneficial in ovarian borderline epithelial tumors (LMP).

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

ⁱIn general, the panel would recommend combination, platinum-based regimens for platinum-sensitive recurrent disease based on randomized trial data, especially in first relapses.

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

^kThere are limited data on the efficacy of bevacizumab in the recurrence therapy setting for patients previously treated with bevacizumab.

^lContraindicated for patients at increased risk of GI perforation.

^mIf response after chemotherapy, bevacizumab can be continued as maintenance therapy until disease progression or unacceptable toxicity.

ⁿFor 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.

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

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NCCN Guidelines Version 4.2017

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

PRINCIPLES OF SYSTEMIC THERAPY (6 of 8)

Acceptable Recurrence Therapies for Epithelial (including LCOH^g)/Fallopian Tube/Primary Peritoneal^h

	Cytotoxic Therapy (In alphabetical order)*	Hormonal Therapy*	Targeted Therapy*	Radiation Therapy*
Other Potentially Active Agents	<p>Single Agents^{p,22}</p> <p>Altretamine Capecitabine Cyclophosphamide Doxorubicin Ifosfamide Irinotecan Melphalan Oxaliplatin Paclitaxel Paclitaxel, albumin bound Pemetrexed Vinorelbine</p> <p>Combinations</p> <p>Carboplatin/paclitaxel/bevacizumab^{i,k,l,m} (platinum-sensitive disease)</p>	<p>Aromatase inhibitors Leuprolide acetate Megestrol acetate Tamoxifen</p>	<p>Pazopanib (category 2B)²³ Rucaparib^{o,24} (platinum-sensitive disease)</p>	<p>Palliative localized radiation therapy</p>

*NOTE: For LCOH, all regimens are category 2A unless indicated.

^gChemotherapy has not been shown to be beneficial in ovarian borderline epithelial tumors (LMP).

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

ⁱIn general, the panel would recommend combination, platinum-based regimens for platinum-sensitive recurrent disease based on randomized trial data, especially in first relapses.

^kThere are limited data on the efficacy of bevacizumab in the recurrence therapy setting for patients previously treated with bevacizumab.

^lContraindicated for patients at increased risk of GI perforation.

^mIf response after chemotherapy, bevacizumab can be continued as maintenance therapy until disease progression or unacceptable toxicity.

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

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

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[Continued](#)

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

PRINCIPLES OF SYSTEMIC THERAPY (7 of 8)

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 Tumors^q	<p>Potentially Curative Therapy: High-dose chemotherapy^q 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^r	<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

^qHigh-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.

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

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[Continued](#)

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

PRINCIPLES OF SYSTEMIC THERAPY (8 of 8)

REFERENCES FOR ACCEPTABLE RECURRENCE THERAPIES

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NCCN Guidelines Version 4.2017

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

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, 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](#)

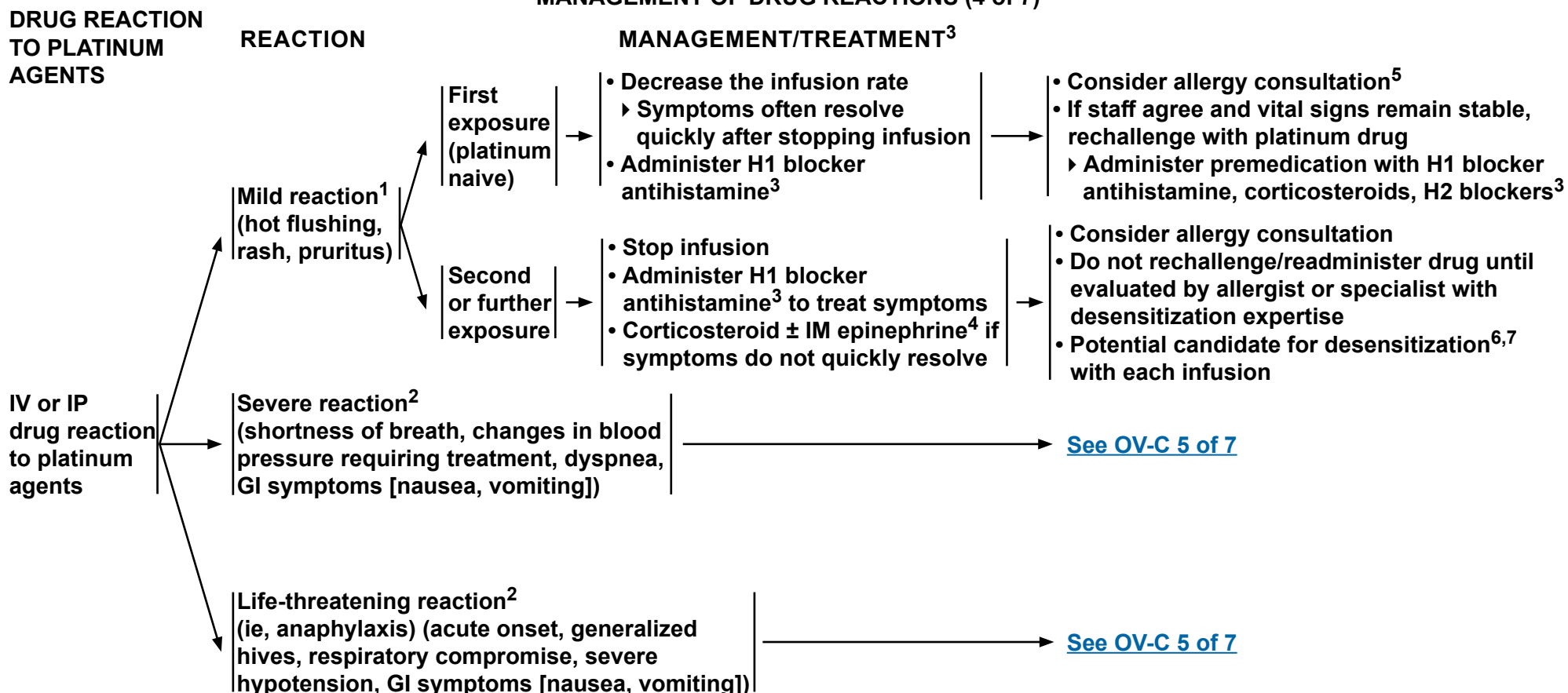
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Epithelial Ovarian Cancer/Fallopian Tube Cancer/ Primary Peritoneal Cancer & Less Common Histopathologies

MANAGEMENT OF DRUG REACTIONS (4 of 7)



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.

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

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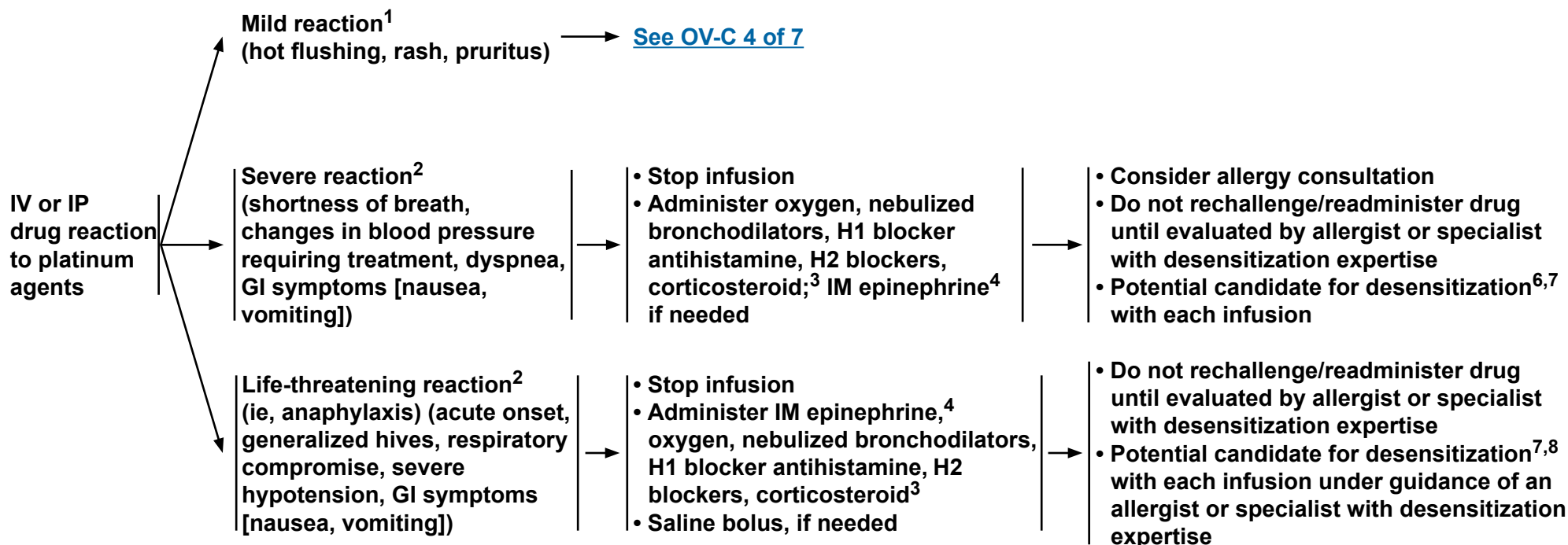
Epithelial Ovarian Cancer/Fallopian Tube Cancer/ Primary Peritoneal Cancer & Less Common Histopathologies

MANAGEMENT OF DRUG REACTIONS (5 of 7)

DRUG REACTION TO PLATINUM AGENTS

REACTION

MANAGEMENT/TREATMENT³



[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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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)

REACTION

MANAGEMENT/TREATMENT³

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

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

- Stop infusion
 - Symptoms often resolve quickly after stopping infusion
- Administer H1 blocker antihistamine³ to treat symptoms

- If staff agree and vital signs remain stable, rechallenge with drug at slower infusion rate⁹
 - Administer premedication with H1 blocker antihistamine, corticosteroids, H2 blockers³

- If repeat mild reaction, then do not rechallenge/ readminister
- Potential candidate for desensitization^{7,9} with each infusion

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)

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

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)

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

[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).

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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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.

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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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Ovarian Cancer Histopathologies

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

<u>Serous Tumors</u> <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 	Benign Benign Benign Borderline Carcinoma in-situ/ grade III intraepithelial neoplasia Malignant Malignant
<u>Mucinous Tumors</u> <ul style="list-style-type: none"> • Mucinous cystadenoma • Mucinous adenofibroma • Mucinous borderline tumor/atypical proliferative mucinous tumor • Mucinous carcinoma 	Benign Benign Borderline Malignant
<u>Endometrioid Tumors</u> <ul style="list-style-type: none"> • Endometriotic cyst • Endometriotic cystadenoma • Endometriotic adenofibroma • Endometrioid borderline tumor/atypical proliferative endometrioid tumor • Endometrioid carcinoma 	Benign Benign Benign Borderline Malignant
<u>Clear Cell Tumors</u> <ul style="list-style-type: none"> • Clear cell cystadenoma • Clear cell adenofibroma • Clear cell borderline tumor/atypical proliferative clear cell tumor • Clear cell carcinoma 	Benign Benign Borderline Malignant

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

[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.

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

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Ovarian Cancer Histopathologies

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

<u>Sex Cord-Stromal Tumors:</u> <u>Pure Stromal Tumors</u> <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>	<u>Germ Cell Tumors</u> <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>	<u>Miscellaneous Tumors</u> <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>
<u>Sex Cord-Stromal Tumors:</u> <u>Pure Sex Cord Tumors</u> <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>	<u>Monodermal Teratoma & Somatic-type Tumors from Dermoid Cyst</u> <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>	<u>Mesothelial Tumors</u> <ul style="list-style-type: none"> • Adenomatoid tumor • Mesothelioma 	<p>Benign Malignant</p>
<u>Mixed Sex Cord-Stromal Tumors</u> <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>	<u>Germ Cell- Sex Cord-Stromal Tumors</u> <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>	<u>Soft Tissue Tumors</u> <ul style="list-style-type: none"> • Myxoma • Others 	<p>Benign</p>
				<u>Tumor-like Lesions</u> <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 	
				<u>Lymphoid and Myeloid Tumors</u> <ul style="list-style-type: none"> • Lymphomas • Plasmacytoma • Myeloid neoplasms 	<p>Malignant</p>

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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.

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	
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	
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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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
IC		Tumor limited to 1 or both ovaries or Fallopian tubes, with any of the following:	IIIA1(ii)		Metastasis more than 10 mm in greatest dimension
IC1	T1c1	Surgical spill	IIIA2	T3a2-N0/N1	Microscopic extrapelvic (above the pelvic brim) peritoneal involvement with or without positive retroperitoneal lymph nodes
IC2	T1c2	Capsule ruptured before surgery or tumor on ovarian or Fallopian tube surface	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
IC3	T1c3	Malignant cells in the ascites or peritoneal washings	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)
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.

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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 indicated.

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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 other less common pathologic subtypes may occur such as malignant germ cell and sex-cord stromal cell tumors. The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Ovarian Cancer were originally published more than 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, low-grade (also known as grade 1) serous carcinomas/endometrioid epithelial carcinomas, borderline epithelial tumors (also known as low malignant potential tumors), malignant sex cord-stromal tumors, and malignant germ cell tumors. The NCCN Guidelines also discuss Fallopian tube cancer and primary peritoneal cancer, which are less common neoplasms that are managed in a similar manner to epithelial ovarian cancer. The LCOH may be managed differently.

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

NCCN Guidelines unless otherwise indicated. Category 2A recommendations are based on lower level evidence (such as phase 2 trials) and uniform NCCN consensus (at least 85% of panel members) that the intervention is appropriate.

Epithelial ovarian cancer is the leading cause of death from gynecologic cancer in the United States and is the country's fifth most common cause of cancer mortality in women. In 2017, it is estimated that 22,440 new diagnoses and 14,080 deaths from this neoplasm will occur in the United States; less than 40% of women with ovarian cancer are cured.⁶ Five-year survival is about 46.5%, although survival is longer for select patients with some of the LCOH.⁷ 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.^{4,8,9} A 30% to 60% decreased risk for cancer is associated with younger age at first pregnancy and first birth (≤ 25 years), the use of oral contraceptives, and/or breastfeeding.¹⁰ Conversely, nulliparity or older age (>35 years) at first pregnancy and first birth confers an increased risk for ovarian cancer. Data suggest that postmenopausal hormone therapy and pelvic inflammatory disease may increase the risk for ovarian cancer.¹¹⁻¹³ The risk for borderline epithelial tumors (also known as low malignant potential tumors) may be increased after ovarian stimulation for in vitro fertilization.^{14,15} Smoking is associated with an increased risk for mucinous carcinomas but a decreased risk for clear cell carcinomas.⁸ Obesity does not appear to be associated with the most aggressive types of ovarian cancer.¹⁶ 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.¹⁷⁻²⁹ These patients account for only 15% of all women who have ovarian cancer.^{10,25,30,31} In women at high risk (with either *BRCA1* or *BRCA2* mutations), risk-reducing bilateral salpingo-oophorectomy (BSO) is associated with a reduced risk for breast, ovarian, Fallopian tube, and primary peritoneal cancers (see *Risk-Reducing Salpingo-Oophorectomy [RRSO] Protocol [BRCA/HBOC syndrome]* in the NCCN Guidelines for Ovarian Cancer, *Cytoreductive Surgery* in this Discussion, and *Risk Reduction Surgery* in the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian, available at [NCCN.org](#)).³¹⁻³⁶ There is a residual risk for primary peritoneal cancer after risk-reducing BSO in these women at high risk for cancer. Occult ovarian cancer is sometimes found after RRSO, thus emphasizing the need for careful pathologic review of the ovaries and tubes (see *Risk-Reducing Salpingo-Oophorectomy [RRSO] Protocol [BRCA/HBOC syndrome]* in the NCCN Guidelines for Ovarian Cancer).³⁷⁻⁴⁰ The risks of surgery include injury to the bowel, bladder, ureter, and vessels.⁴¹

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

Screening

Because of the location of the ovaries and the biology of most epithelial cancers, it has been difficult to diagnose ovarian cancer at an earlier, more curable stage. Evaluations of patients with newly diagnosed ovarian cancer have resulted in consensus guidelines for ovarian cancer symptoms, which may enable earlier identification of patients who may be at an increased risk of having developed early-stage ovarian cancer.^{47,48} 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).⁴⁷ Physicians evaluating women with this constellation of symptoms must be cognizant of the possibility that ovarian pathology may be causing these symptoms.⁴⁹ 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.^{41,50-52}

The literature does not support routine screening for ovarian cancer in the general population, and routine screening is not currently recommended by any professional society.^{41,49,53-61} 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;⁵⁴ however, prospective validation of these tests remains elusive. An intriguing study suggests that ovarian cancer is associated with unique odors that can be detected.⁶²⁻⁶⁵

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.^{66,67} Preliminary results suggested that multimodality

screening was more effective at detecting early-stage cancer; however, after a median of 11 years of follow-up, a significant mortality reduction was not observed.^{68,69} Some feel that this UKCTOCS screening approach may be useful for women at high risk such as those with *BRCA* mutations.³⁹ 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.^{56,70,71} 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.⁷²

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.⁷³ 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).^{49,74-77} The NCCN Panel believes that the OvaSure screening test should not be used to detect ovarian cancer.⁷⁸⁻⁸¹ The OvaSure test uses 6 biomarkers, including leptin, prolactin, osteopontin, insulin-like growth factor II,

macrophage inhibitory factor, and CA-125.⁸² 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.⁸³⁻⁸⁵

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).⁸⁶ Most patients present with stage 3 disease.⁸⁷ 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).⁸⁷⁻⁹² Pathologists may use histologic grades 1, 2, or 3 for endometrioid carcinomas, mucinous carcinomas, and stage IC tumors.⁸⁸ Primary peritoneal adenocarcinoma and LCOH are also staged using the ovarian cancer staging system (see Table 1 in the NCCN Guidelines for Ovarian Cancer).⁸⁶ Until January 1, 2018, Fallopian tube carcinomas will be staged using a separate FIGO and AJCC staging system (see Table 2 in the NCCN Guidelines for Ovarian Cancer and see next paragraph).⁸⁶ The new AJCC/FIGO staging guidelines (8th edition) will combine staging for Fallopian tube carcinoma and ovarian cancer, and will be effective on January 1, 2018 (see *Staging* in the NCCN Guidelines for Ovarian Cancer).⁹³ 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).^{87,89} For example, in the new staging guidelines, old stages IC, IIIA, and IV are now subdivided; the old stage IIC has been eliminated. These changes are included in the 8th edition of the AJCC Cancer Staging Manual, which was published in late 2016 and will be effective for all cancer cases recorded on or after January 1, 2018.⁹³ A pathology and staging cancer protocol is available from the College of American Pathologists (CAP) for Fallopian tube carcinoma and ovarian cancer that is based on the 8th edition of the AJCC; earlier editions are also available.⁹⁴

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 October 1, 2015 and October 1, 2016 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.⁹⁵ The search results were narrowed by selecting studies in humans published in English. Results were

confined to the following article types: Clinical Trial, Phase 3; Clinical Trial, Phase IV; Guideline; Randomized Controlled Trial; Meta-Analysis; Systematic Reviews; and Validation Studies.

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

Epithelial Ovarian Cancer

Recommended Workup

The NCCN Guidelines for Epithelial Ovarian Cancer begin with the management of an undiagnosed pelvic mass or a prior diagnosis of a malignant epithelial ovarian tumor. Many patients with this diagnosis come to NCCN Member Institutions after having had previous surgery. The NCCN Guidelines recommend symptom management and best supportive care for all patients; women should be referred for palliative care assessment if appropriate (see the NCCN Guidelines for Palliative Care, available at [NCCN.org](#)).^{53,96}

Undiagnosed Pelvic Mass

The primary workup should include an abdominal/pelvic ultrasound and/or abdominal/pelvic CT/MRI scan (after an abdominal/pelvic examination) and appropriate laboratory studies for a patient with a suspicious pelvic mass (detected on abdominal/pelvic exam) and/or ascites, abdominal distention, and/or symptoms (ie, bloating, pelvic or

abdominal pain, difficulty eating or feeling full quickly, urinary symptoms) without other obvious sources of malignancy (see *Workup* in the NCCN Guidelines for Epithelial Ovarian Cancer).^{47,97-104} 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).¹⁰⁵⁻¹⁰⁷ For example, clinicians should consider measuring AFP levels to assess for germ cell tumors in women younger than 35 years with a pelvic mass.¹⁰⁵⁻¹⁰⁷ Ultrasound is typically used for initial evaluation; abdominal/pelvic CT is useful to assess for metastases.⁹⁹ Abdominal/pelvic MRI may be useful for determining malignant potential if ultrasound is not reliable.^{103,104} CT/MRI imaging should be performed with contrast unless contraindicated. FDG-PET/CT scan or MRI may be useful for indeterminate lesions.¹⁰⁸⁻¹¹⁰

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.^{111,112} Other cancers that should be ruled out include bowel, uterine, and pancreatic cancers or lymphoma;^{113,114} benign ovarian and non-ovarian conditions also need to be ruled out

(eg, serous cystadenoma).¹¹⁵ 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.^{116,117} 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.¹¹⁸⁻¹²¹ Although there is no direct evidence that chest x-ray or chest CT is necessary, panel members felt that it should be part of the overall evaluation of a patient before surgical staging if clinically indicated. Gastrointestinal tract evaluation should be done for mucinous histology to determine whether patients have metastases to the ovary or primary mucinous carcinoma of the ovary (see *Mucinous Carcinomas* in this Discussion).¹²²

Prior Diagnosis of Malignancy

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

masses at the time of referral. Tissue diagnosis of metastatic sites can be considered.

Histologic Subtypes

Epithelial ovarian cancer has 4 main histologic subtypes, including serous, endometrioid, mucinous, and clear cell; most patients (about 70%) have serous histology.^{3,86,90,123,124} Primary treatment recommendations for the LCOH subtypes—mucinous, clear cell, and low-grade (grade 1) serous/endometrioid—may be different from the treatment recommendations for the high-grade serous/endometrioid subtypes (see the NCCN Guidelines for Epithelial Ovarian Cancer and the NCCN Guidelines for Less Common Ovarian Histopathologies).⁹⁰ Molecular characterization of clear cell, mucinous, or low-grade (grade 1) serous tumors suggests that mutations in these histologies are different from those in higher grade tumors.¹²⁵⁻¹²⁷ 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).^{87,89-92,128,129} High-grade endometrioid tumors are difficult to distinguish from high-grade serous tumors.⁹⁰ Low-grade (grade 1) serous tumors are relatively resistant to standard chemotherapy regimens.^{90,130} Pathology review at NCCN Member Institutions is recommended for all patients. The CAP protocol is a useful tool for pathology reports; it was revised for 2016 and 2017.^{88,94,131} The complete histologic classification from the WHO is included in the NCCN Guidelines (see *WHO Histologic Classification* in the NCCN Guidelines for Ovarian Cancer Histopathologies).¹ The WHO pathology manual is also a useful resource.^{1,132}

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](#)).³⁹ 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.^{37,133} The ovaries should also be carefully sectioned, processed, and assessed.¹³⁴ The 2016 and 2017 CAP protocols describe the process for sectioning the Fallopian tubes and ovaries.^{88,94,134} Note that it is controversial whether a hysterectomy should also be done.³⁰ The prevention benefits of salpingectomy alone are not yet proven.¹³⁵⁻¹⁴⁰ 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.¹³⁵

Primary Treatment

Primary treatment for presumed ovarian cancer consists of appropriate surgical staging and debulking surgery, followed in most (but not all) patients by systemic chemotherapy.^{74,141-143} The surgeon should describe the following in the operative report: 1) the extent of initial disease; 2) the amount of residual disease; and 3) whether a complete or incomplete resection (including a description of the lesions) was achieved (see *Principles of Surgery: Operative Reports* in the NCCN Guidelines for Epithelial Ovarian Cancer).¹⁴⁴ For most patients, initial surgery should include a total abdominal hysterectomy (TAH) and BSO with comprehensive staging and debulking as indicated (see the *Principles of Surgery* in the NCCN Guidelines for Ovarian Cancer).^{10,145,146} Based on published improved outcomes, it is recommended (category 1) that a gynecologic oncologist perform the primary surgery.⁷⁵⁻⁷⁷ For a young patient who wishes to maintain fertility,

a unilateral salpingo-oophorectomy (USO) (preserving the uterus and contralateral ovary) and comprehensive surgical staging may be adequate for select unilateral stage I tumors (stage 1A and 1C, but not stage 1B) and/or low-risk ovarian tumors (ie, early-stage, grade 1 tumors; borderline tumors).¹⁴⁷⁻¹⁵² For those with stage IB tumors who wish to maintain fertility, a BSO (preserving the uterus) and comprehensive surgical staging are needed.

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

Debulking Surgery

Debulking surgery is the initial treatment recommendation for patients with clinical stage II, III, or IV disease (see *Primary Treatment* in the NCCN Guidelines for Epithelial Ovarian Cancer and the NCCN Guidelines for Less Common Ovarian Histopathologies).^{74,77,143,149,153,161-163} Although debulking surgery is the standard of care, this recommendation is based on retrospective data (and thus is not a category 1 recommendation).¹⁶⁴ In general, the procedures outlined in the next paragraph should be part of the surgical

management of patients with ovarian, Fallopian tube, or primary peritoneal cancer in an effort to fully stage patients and to achieve maximal debulking to less than 1-cm residual disease or resection of all visible disease in appropriate circumstances.¹⁶⁵⁻¹⁶⁷ These procedures also apply to many of the LCOH. Surgical debulking is optimal if the residual tumor nodules are less than 1 cm in maximum diameter or thickness.^{146,149,164,168,169} the goal is resection to R0. Extensive resection of upper abdominal metastases is recommended for patients who can tolerate this surgery.^{162,170}

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

A maximal effort should be made to remove all gross disease, because the more complete the debulking the better the outcomes.¹⁶¹ 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.^{112,155} All involved omentum should be removed. Suspicious and/or enlarged nodes should be resected, if possible.^{174,175} 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.¹⁷⁶⁻¹⁷⁹

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.¹⁸⁰ Patients with low-volume residual disease after surgical debulking for stage II or III invasive epithelial ovarian or peritoneal cancer are candidates for intraperitoneal (IP) therapy.^{181,182} In these patients, consideration should be given to placement of an IP catheter with initial surgery.¹⁴⁵ Procedures that may be considered for optimal surgical debulking include: radical pelvic dissection, bowel resection and/or appendectomy, lymphadenectomy, diaphragm or other peritoneal surface stripping, splenectomy, partial hepatectomy, partial gastrectomy, or partial cystectomy and/or ureteroneocystostomy, cholecystectomy, and/or distal pancreatectomy.^{162,170,183}

The surgical guidelines emphasize that an open laparotomy should be used for patients with suspected malignant ovarian cancer if the treatment plan involves surgical staging, primary debulking, interval debulking, or secondary debulking surgery (see *Principles of Surgery* in the NCCN Guidelines for Epithelial Ovarian Cancer). The surgical guidelines also state that if patients cannot be optimally debulked using minimally invasive techniques, they should be converted to an open procedure. Neoadjuvant therapy can be considered if maximal

debulking cannot be achieved (see *Neoadjuvant Chemotherapy* in this Discussion).^{184,185} For patients with incomplete previous surgery and/or staging, treatment recommendations are outlined in the algorithm (see *Diagnosis by Previous Surgery* in the NCCN Guidelines for Epithelial Ovarian Cancer).

Neoadjuvant Chemotherapy

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

Neoadjuvant therapy refers to treatment (eg, drugs, radiation, other treatment) that is given to reduce the tumor burden before cancer surgery (see *Principles of Systemic Therapy: Primary*

Chemotherapy/Primary Adjuvant Therapy Regimens in the NCCN Guidelines for Epithelial Ovarian Cancer). Intravenous taxane/carboplatin and liposomal doxorubicin/carboplatin regimens are recommended for neoadjuvant chemotherapy and adjuvant therapy after interval debulking surgery.

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

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

averages about 50 months in the United States).^{182,201} 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).¹⁶⁴

A retrospective analysis of the EORTC-NCIC trial reported that patients with stage IV disease with bulky tumors had longer survival with neoadjuvant therapy, whereas those with stage IIIC disease and less bulky tumors had longer survival with upfront surgery.¹⁸⁵ 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.^{145,204} A large (586 patients) single-institution study in the United States reported that patients with advanced ovarian cancer who had standard debulking surgery had improved median overall survival (71.7 months [CI, 59.8–not reached]) when compared with those who had neoadjuvant chemotherapy (42.9 months [CI, 37.1–56.3]).²⁰⁵ A report of more than 14,000 patients reported that median survival is improved by almost 2 years in those receiving upfront debulking surgery when compared with those receiving neoadjuvant chemotherapy (69 vs. 45 months).²⁰⁶ A recent retrospective Italian study in women in complete response after primary treatment reported better outcomes with upfront surgery (n = 322) when compared with neoadjuvant therapy followed by surgery (n = 62); overall survival at 2 years, 5 years, and 7 years was

96.4%, 69.3%, and 50.4% for upfront surgery versus 87.1%, 41.8%, and 32.6% for neoadjuvant therapy ($P = .001$).¹⁸⁶

Interval Debulking Surgery

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

Incomplete Surgery and/or Staging

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

Depending on the surgical results, postoperative chemotherapy may be recommended. Tumor reductive surgery is recommended for all patients with stage II to IV disease with suspected residual disease that is potentially resectable.

Postoperative Chemotherapy

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

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

increased by 16 months after IP therapy using cisplatin/paclitaxel when compared with standard intravenous therapy (65.6 vs. 49.7 months, $P=.03$) in the GOG 172 trial. For patients who are not candidates for IP therapy (eg, those with poor performance status [PS]), other regimens may be recommended (see *Primary Chemotherapy/Primary Adjuvant Therapy Regimens* in the NCCN Guidelines for Epithelial Ovarian Cancer).^{75,213} Intravenous docetaxel plus carboplatin (category 1)²¹⁴ or paclitaxel plus carboplatin (category 1) are options for alternative regimens.^{215,216} The docetaxel/carboplatin or liposomal doxorubicin/carboplatin regimens may be considered for patients who are at high risk for neuropathy (eg, patients with diabetes).²¹⁷

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

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);^{213,215} 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);²²¹ 3) paclitaxel 60 mg/m² over 1 hour followed by carboplatin AUC 2 intravenous over 30 minutes, weekly for 18 weeks (category 1);²²² 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);²¹⁴ and 5) carboplatin AUC 5 plus pegylated liposomal doxorubicin 30 mg/m² every 4 weeks for 6 cycles (category 2A).²¹⁵ For the 2017 update, the NCCN Panel added the fifth regimen (see last paragraph in this section). These intravenous regimens may also be used for neoadjuvant chemotherapy (see *Principles of Systemic Therapy* in the NCCN Guidelines for Ovarian Cancer). The weekly carboplatin/paclitaxel regimen may be considered for elderly patients or those with poor PS based on the phase 3 MITO-7 trial.²²² Note that carboplatin dosing may be revised based on changes in serum creatinine methodology (see FDA carboplatin dosing statement). The AUC of 5 to 6 for carboplatin reflects contemporary treatment.

The recommended IP chemotherapy regimen is paclitaxel, 135 mg/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).¹⁸² The randomized phase 3 trial for this IP/intravenous regimen used intravenous continuous infusion of paclitaxel over 24 hours. A 3-hour infusion of paclitaxel has not been proven to be equivalent to a 24-hour infusion, although a 3-hour infusion has been reported to be more convenient, easier to tolerate, and less toxic.²²³ 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.^{214,215,221,224} Note that there are no agents to prevent chemotherapy-induced peripheral neuropathy.²²⁵

The IP paclitaxel/cisplatin regimen is associated with leukopenia, infection, fatigue, renal toxicity, abdominal discomfort, and neurotoxicity.²²⁶⁻²²⁸ In the initial studies, only 42% of women were able to complete all 6 treatment cycles of the IP regimen because of toxicity; with more experience, this percentage has improved in the major cancer centers.²²⁹ 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.^{223,229-231} Patients who are candidates for the IP cisplatin and IP/intravenous paclitaxel regimen should have normal renal function before starting, a medically appropriate PS based on the future toxicities of the IP/intravenous regimen, and no previous evidence of medical problems that could significantly worsen during chemotherapy, such as preexisting neuropathy (see *Principles of Systemic Therapy* in the NCCN Guidelines for Epithelial Ovarian Cancer). Reasons for discontinuing the IP regimen included catheter complications, nausea/vomiting/dehydration, and abdominal pain.²³² Women unable to complete IP therapy should receive intravenous therapy. Techniques to decrease catheter complications include catheter choice and timing of insertion.^{211,233} Expert nursing care may help to decrease complications.²¹⁰ Giving intravenous hydration before and after IP chemotherapy is a useful strategy to prevent renal toxicity.²²⁹ 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.^{232,234-237}

Patients with poor PS, comorbidities, stage IV disease, or advanced age (>65 years) may not tolerate the IP regimen or the other

combination intravenous regimens described in the NCCN Guidelines. Single-agent platinum agents, such as cisplatin or carboplatin, may be more appropriate for these patients. A phase 3 randomized trial (MITO-7) assessed carboplatin/paclitaxel every week compared with standard therapy given every 3 weeks (ie, intravenous carboplatin/paclitaxel) in women with advanced epithelial ovarian cancer.²²² Median PFS was similar between the 2 regimens. The weekly carboplatin/paclitaxel regimen was associated with fewer side effects and yielded a better quality of life. For example, fewer patients receiving the weekly regimen had grade 3 to 4 neutropenia (167 [42%] of 399 patients vs. 200 [50%] of 400 patients). Therefore, this weekly carboplatin/paclitaxel regimen may be considered for elderly patients or those with poor PS based on the phase 3 MITO-7 trial.²²² 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 reported a median survival of 65.6 months in women with optimally debulked stage III cancer.^{182,194} A study reported overall survival of 110 months in patients with stage III ovarian cancer and no residual disease who received the IP regimen.¹⁹⁴ Another study showed that survival improves with each cycle of IP chemotherapy.²³⁸ Patients with optimally debulked stage II or III primary peritoneal cancer, Fallopian tube cancer, or MMT can also be considered for IP chemotherapy.^{212,233} If the NCCN Guidelines state that treatment as per epithelial ovarian cancer is an option, then IP chemotherapy can be considered an option for other LCOH including clear cell carcinoma, mucinous carcinoma, low-grade serous carcinoma, endometrioid carcinoma, and borderline epithelial tumors with invasive implants (see the NCCN Guidelines for Less Common Ovarian Histopathologies). All women should be counseled about the clinical benefit associated with combined intravenous and IP

chemotherapy administration before undergoing surgery for epithelial ovarian cancer, Fallopian tube cancer, primary peritoneal cancer, or MMMT.^{181,239} A study reported that women with aberrant *BRCA1* expression had increased survival when treated with IP cisplatin/paclitaxel.²⁴⁰ A recent study reported that young women with some residual disease (1–10 mm) remaining after debulking still benefited from IP chemotherapy, although removing all gross disease yielded the longest survival.²⁴¹

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

For the 2017 update, the NCCN Panel added carboplatin/liposomal doxorubicin as another first-line postoperative intravenous option for patients with stages II to IV ovarian cancer; this regimen has a category 2A recommendation. The regimen was added based on a phase 3 randomized trial in 820 patients with stages III and IV ovarian cancer comparing carboplatin/liposomal doxorubicin versus carboplatin/paclitaxel.²¹⁵ There was no significant difference in the median overall survival with carboplatin/liposomal doxorubicin versus carboplatin/paclitaxel (61.6 and 53.2 months, respectively; HR, 0.89; 95% CI, 0.72–1.12; $P = .32$). Toxicity was different in the 2 groups.

More hematologic adverse effects but less neurotoxicity and alopecia occurred with carboplatin/liposomal doxorubicin; therefore, this regimen may be useful in select patients at high risk for neurotoxicity or those who would like to avoid alopecia.

Anti-Angiogenesis Agents

A phase 3 randomized trial (GOG 0218) assessed bevacizumab combined with carboplatin/paclitaxel in the upfront setting compared to 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.^{245,246} 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 0218.²⁴⁷ An analysis of the data from GOG 0218 suggests that upfront therapy with carboplatin/paclitaxel/bevacizumab may be beneficial in patients with ascites.²⁴⁸ Women with ascites who received the bevacizumab regimen had significantly improved PFS (adjusted hazard ratio [AHR] 0.71; 95% CI, 0.62–0.81; $P < .001$) and overall survival (AHR 0.82; 95% CI, 0.70–0.96; $P = .014$) when compared with those only receiving chemotherapy.

Another phase 3 randomized trial (ICON7) also assessed bevacizumab/carboplatin/paclitaxel in the upfront setting. The trial design of ICON7 differs from GOG 0218 (see next paragraph).²⁴⁹ Although the PFS data from ICON7 confirm the findings of GOG 0218, the benefits appear to be modest (2.4-month increase in PFS).²⁴⁷ Data for ICON7 suggest that overall survival was increased in the subset of patients with a poor prognosis, although overall survival was not increased in the whole study population.²⁵⁰ In women with a poor

prognosis who received bevacizumab plus chemotherapy, overall survival was increased when compared with those receiving chemotherapy alone (restricted mean survival time 39.3 months [37.0–41.7] with bevacizumab vs. 34.5 months [95% CI, 32.0–37.0] with chemotherapy alone; $P = .03$).

The addition of bevacizumab to upfront chemotherapy with carboplatin/paclitaxel followed by bevacizumab as maintenance therapy is a category 2B recommendation (see *Primary Chemotherapy/Primary Adjuvant Therapy Regimens: Ovarian, Fallopian Tube, and Primary Peritoneal Cancer* in the NCCN Guidelines for Epithelial Ovarian Cancer).^{250,251} Some panel members believe that bevacizumab should not be added to upfront chemotherapy in patients with ovarian cancer, because data from these 2 phase 3 randomized trials (ie, GOG 0218, ICON7) have not shown a statistically significant increase in overall survival in the whole study population and/or improved quality of life.^{246,247,249,251–254} Note that a category 2B recommendation indicates that many but not all ($\geq 50\%$ and $< 85\%$) panel members agree that the intervention is appropriate.

The NCCN Panel recommends (category 2B) that if bevacizumab is used with upfront chemotherapy followed by maintenance therapy, then either the GOG 0218 or ICON7 regimens should be used (see *Primary Chemotherapy/Primary Adjuvant Therapy Regimens: Ovarian, Fallopian Tube, and Primary Peritoneal Cancer* in the NCCN Guidelines for Epithelial Ovarian Cancer).^{246,249} The only GOG 0218 regimen that is recommended (category 2B) is the prolonged bevacizumab regimen (upfront with carboplatin/paclitaxel followed by maintenance bevacizumab).²⁴⁶ 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.²⁵⁵

Postremission Therapy

Paclitaxel (category 2B) is a postremission therapy option for patients with stages II to IV epithelial ovarian cancer, Fallopian tube cancer, or primary peritoneal cancer who have had complete clinical remission after first-line therapy. Maintenance (or postremission) therapy is an option based on the results from GOG 178. This trial randomly assigned patients to 3 versus 12 months of further paclitaxel (135–175 mg/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

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

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.²⁶¹⁻²⁶⁵

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.²⁶⁶

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.^{267,268} Infusion reactions are more common with paclitaxel,²⁶⁹ but mild reactions can also occur with liposomal doxorubicin.²⁷⁰ Allergic reactions (ie, true drug allergies) are more common with platinum agents (ie, carboplatin, cisplatin, oxaliplatin).^{269,271}

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

For patients with allergic reactions, various desensitization protocols have been published.^{262,265,277,278} To maximize safety, patients may be desensitized in the intensive care unit.^{265,278} Almost all patients can be desensitized (about 90%).²⁶⁵ 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.²⁶³ Patients must be desensitized with each infusion if they previously had a drug reaction.²⁷⁹⁻²⁸¹ Data suggest that an extended infusion schedule and use of premedication may decrease the number of hypersensitivity reactions to carboplatin.^{282,283} Skin testing is associated with false-negative results.^{284,285}

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).²⁸⁶⁻²⁹⁰ Patients who receive radiation are prone to vaginal stenosis, which can impair sexual function.²⁹¹ 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.²⁹²

Recommendations After Primary Treatment

After initial treatment (eg, surgery followed by chemotherapy), patients should undergo a clinical re-evaluation. Observation with follow-up is

recommended for patients who have no evidence of progression of cancer (ie, complete clinical remission) after initial treatment (see *Follow-Up Recommendations* in this Discussion) (also see *Monitoring/Follow-up* in the NCCN Guidelines for Epithelial Ovarian Cancer); other options are discussed below. Patients with progression, persistent disease, or stable disease during initial treatment should be treated with second-line approaches (see *Recurrent Disease* in this Discussion) (see *Therapy for Persistent Disease or Recurrence* in the NCCN Guidelines for Epithelial Ovarian Cancer).^{293,294} The NCCN Guidelines recommend symptom management, best supportive care, and long-term wellness care for all patients; patients should be referred for palliative care assessment if appropriate (see the NCCN Guidelines for Palliative Care and the NCCN Guidelines for Survivorship, available at 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).^{295,296} Primary treatment should not be delayed for genetic counseling.

Options for the management of patients with advanced-stage (stages II–IV) disease who are in complete clinical remission after their initial therapeutic regimen include observation alone, a clinical trial, or postremission systemic therapy (category 2B)²⁵⁶ (see the NCCN Guidelines for Epithelial Ovarian Cancer). The NCCN Panel recommends postremission paclitaxel or pazopanib (category 2B) for management of stage II to IV disease (see *Postremission Therapy* in this Discussion).²⁵⁹ As previously described, postremission paclitaxel or pazopanib prolong PFS when administered following initial chemotherapy. If used, the recommended paclitaxel regimen is 135 to

175 mg/m² every 4 weeks for 12 cycles.²⁵⁶ Note that complete clinical remission is defined as no definitive evidence of disease.^{293,294}

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

Follow-up Recommendations

Recurrent disease may be identified clinically (eg, pelvic pain, weight loss), biochemically (ie, elevated CA-125 levels), and/or with imaging. After the completion of primary surgery and chemotherapy in patients with all stages of ovarian cancer (or Fallopian tube cancer or primary peritoneal cancer) who have had a complete response, the standard recommendation is observation with follow-up to monitor for recurrent disease. Recommendations for monitoring are described in the algorithm and also apply to some of the LCOH (see *Monitoring/Follow-up* in the NCCN Guidelines for Epithelial Ovarian Cancer). Chest/abdominal/pelvic CT, MRI, FDG-PET/CT, FDG-PET scans (skull base to mid-thigh), and chest x-ray may be ordered if clinically indicated; imaging is done with contrast unless contraindicated.²⁹⁷⁻³⁰⁰ Patients should be educated about the signs and symptoms suggestive of recurrence (eg, pelvic pain, bloating, early satiety, obstruction, weight loss, fatigue). Patients who have had fertility-sparing surgery should be monitored by ultrasound examinations of the abdomen and pelvis if indicated; completion surgery should be considered (category 2B) after they finish childbearing. For the 2017 update (Version 1), the NCCN Panel added a recommendation for

long-term wellness care (see the NCCN Guidelines for Survivorship, available at NCCN.org).

If the CA-125 level was initially elevated, then measurement of a CA-125 level or other tumor markers is recommended. A multi-institutional European trial assessed the use of CA-125 for monitoring for ovarian cancer recurrence after primary therapy.^{301,302} 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.³⁰³ Recommendations from the SGO state that use of CA-125 levels for surveillance is optional.²⁹⁹ 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.³⁰⁴ Others have discussed this study in greater detail.³⁰⁵⁻³⁰⁷

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.³⁰⁸ Patients who have never received chemotherapy (ie, naïve to chemotherapy) should be managed using recommendations for newly diagnosed patients, should undergo clinically appropriate imaging studies and surgical debulking, and should be treated as previously described (see *Primary Treatment* in the NCCN Guidelines for Epithelial Ovarian Cancer).

Recurrence therapy refers to drugs, radiation, or other treatment that is given to decrease tumor burden, control symptoms, or increase length and/or quality of life for patients with recurrent disease. After the documentation of an increased CA-125 level (ie, biochemical relapse), the median time for a clinical relapse is 2 to 6 months. Data suggest that immediate treatment for biochemical relapse is not beneficial; therefore, immediate treatment is a category 2B recommendation in the NCCN Guidelines.³⁰¹ After biochemical relapse, recommended options include enrollment in a clinical trial, delaying treatment (ie, observation) until clinical symptoms arise, or immediate treatment (category 2B) (see *Recurrent Disease* in the NCCN Guidelines for Epithelial Ovarian Cancer). Because tamoxifen and other hormonally active agents have a defined response rate for patients with recurrent disease who have progressed after platinum-based chemotherapy,³⁰⁹ these agents are frequently administered to patients who have only a rising CA-125 level³¹⁰ as evidence of tumor progression.³¹¹ 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);³¹² 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.^{293,294} Panel members emphasized the importance of clinical trials to identify agents active in this group of patients.^{313,314} 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.^{315,316} 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),³¹⁷ 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*.^{318,319} 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.^{319,320} 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).³²¹⁻³²⁶ 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).^{164,327-332} A meta-analysis suggests that survival increases for patients with recurrent disease who have complete debulking.¹⁶⁵ 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.^{145,333}

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

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.³¹² 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.^{286,287}

Acceptable Recurrence Modalities

The NCCN Panel feels that no single therapeutic agent should be currently recommended as the treatment of choice for recurrent ovarian carcinoma. Some regimens and agents are preferred based on expert opinion primarily for reasons of decreased toxicity and/or marginally increased effectiveness (see *Principles of Systemic Therapy: Acceptable Recurrence Therapies* in the NCCN Guidelines for Epithelial Ovarian Cancer).²¹⁰ A meta-analysis of chemotherapy for recurrent ovarian cancer was published in 2007.³¹⁸ Recurrence therapy refers to therapy (eg, drugs, radiation, or other treatment) that is given for recurrent cancer to control symptoms and increase length or quality of life for clinical, biochemical, or radiographic evidence of recurrent cancer following initial treatment.

Preferred Therapies

The consensus of the NCCN Panel for the treatment of recurrent disease is summarized in the algorithm (see *Principles of Systemic Therapy: Acceptable Recurrence Therapies* in the NCCN Guidelines for Epithelial Ovarian Cancer). Platinum-based combination chemotherapy is recommended (category 1) for a total of 6 cycles for platinum-sensitive recurrence (see *Therapy for Persistent Disease or Recurrence* in the NCCN Guidelines for Epithelial Ovarian Cancer).^{318,319} For patients with platinum-sensitive disease who cannot tolerate combination therapy, the preferred single agent is carboplatin or cisplatin.^{319,337,338} Preferred combinations for platinum-sensitive recurrent disease include carboplatin/paclitaxel (category 1),³¹⁹ carboplatin/liposomal doxorubicin (category 1),³³⁹⁻³⁴¹ carboplatin/weekly paclitaxel,²²¹ carboplatin/albumin-bound paclitaxel (for taxane

hypersensitivity), carboplatin/docetaxel,^{342,343} carboplatin/gemcitabine (which has been shown to improve PFS),^{319,337,338} cisplatin/gemcitabine, or carboplatin/gemcitabine/bevacizumab.³³⁷

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

For platinum-resistant disease, non-platinum-based agents or regimens are preferred (ie, docetaxel, oral etoposide, gemcitabine, weekly paclitaxel with or without pazopanib, liposomal doxorubicin with or without bevacizumab, weekly paclitaxel/bevacizumab, topotecan with or without bevacizumab); sequential therapy using single agents is typically used.^{350,351} A phase 2 trial (MITO-11) assessed weekly paclitaxel with (or without) pazopanib in patients with platinum-resistant or refractory advanced ovarian cancer.³⁵⁰ The data show that PFS was increased in the paclitaxel/pazopanib arm when compared with

paclitaxel alone (median 6.35 months [95% CI, 5.36–11.02] vs. 3.49 months [2.01–5.66]; HR, 0.42 [95% CI, 0.25–0.69]; $P = .0002$). Combination regimens with bevacizumab (AURELIA trial) are described later in this section (see *Bevacizumab* in this Discussion). Combination therapy is not preferred over single-agent therapy for platinum-resistant disease. For the 2017 update (Version 2), the NCCN Panel clarified this point by adding a footnote stating that the panel recommends combination, platinum-based regimens for platinum-sensitive recurrent disease, especially first relapses.

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

Other Potentially Active Agents

Other potentially active agents include altretamine, capecitabine, cyclophosphamide, doxorubicin, ifosfamide, irinotecan, melphalan, oxaliplatin, paclitaxel, nanoparticle albumin-bound paclitaxel (nab-paclitaxel), pemetrexed, and vinorelbine (see *Principles of Systemic Therapy: Acceptable Recurrence Therapies* in the NCCN Guidelines for Epithelial Ovarian Cancer).^{358,362-366} Nab-paclitaxel has an overall response rate of 64%.³⁶⁷ Vinorelbine has a response rate of 20%.^{368,369} Altretamine has a 14% response rate³⁷⁰ and ifosfamide has a 12% response rate,³⁷¹ 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%.^{315,357,358} Single-agent paclitaxel, nab-paclitaxel, and oxaliplatin can

be used in appropriate patients.^{256,319,357,372} Capecitabine has activity if disease was resistant to platinum and taxanes.³⁷³ Other alkylating agents, including cyclophosphamide and melphalan, can also be used.^{216,374} In addition, hormonal therapy with tamoxifen or other agents including aromatase inhibitors (such as anastrozole and letrozole), leuprolide acetate, or megestrol acetate continues to be a viable therapeutic option for patients who cannot tolerate or have not responded to cytotoxic regimens.³⁷⁵⁻³⁸¹ Studies are ongoing for new agents to treat platinum-resistant disease.³⁸² The NCCN Panel also recommends (category 2B) single-agent pazopanib as a potentially active targeted recurrence therapy in patients who had a complete response to initial therapy.³⁸³ In a phase 2 trial in 36 patients, the overall response rate was 18% with grade 3 elevations in ALT and AST in a few patients (8%).

Bevacizumab

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

progression or unacceptable toxicity if patients respond to the initial recurrence chemotherapy/bevacizumab regimens described in the following paragraphs (see *Principles of Systemic Therapy: Acceptable Recurrence Therapies* in the NCCN Guidelines for Epithelial Ovarian Cancer).

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

A phase 3 randomized trial (OCEANS) assessed carboplatin/gemcitabine with and without bevacizumab in patients with platinum-sensitive recurrent ovarian cancer who had not previously received bevacizumab. In the OCEANS trial, PFS was increased in patients receiving the chemotherapy/bevacizumab arm when compared

with chemotherapy alone (12.4 vs. 8.4 months, $P < .0001$).³⁹¹ The final survival analysis did not show an increase in overall survival with the chemotherapy/bevacizumab arm when compared with chemotherapy alone (bevacizumab/chemotherapy: 33.6 months; chemotherapy alone: 32.9 months; HR, 0.95; $P = .65$).³⁹³ Gastrointestinal perforation occurred in 2 patients in the chemotherapy/bevacizumab arm. One patient died from intracranial hemorrhage in the chemotherapy/bevacizumab arm. For the 2017 update, the NCCN Panel revised the recommendation for carboplatin/gemcitabine/bevacizumab to category 2A (from category 2B) based on clinical experience. However, category 1 combination regimens are recommended over this bevacizumab regimen. The carboplatin/gemcitabine/bevacizumab regimen is not recommended in patients who are at risk for gastrointestinal perforation.

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

PARP Inhibitors

Olaparib

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

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

serious (grade 3 or worse) adverse events included anemia (19% [38/195] in the olaparib group vs. 2% [2/99] in the placebo group), fatigue or asthenia (4% [8/195] vs. 2% [2/99]), and neutropenia (5% [10/195] vs. 4% [4/99]). In the olaparib group, one (1%) patient died from a treatment-related adverse event (acute myeloid leukemia). The FDA recently approved olaparib (tablets) as maintenance therapy for women with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who have had complete or partial responses to platinum-based chemotherapy.

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

Rucaparib

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

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

Niraparib

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

most recent line of recurrence therapy based on this trial and the FDA approval.^{408,409}

Less Common Ovarian Histopathologies

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

Recommended Workup

Patients may obtain consultation at an NCCN Member Institution for recommendations and treatment of an undiagnosed pelvic mass, or for management of a previously biopsied malignant ovarian tumor. Many

such patients come to NCCN Member Institutions after having had previous surgery at other institutions. Patients having a histologically undiagnosed pelvic mass should undergo evaluation and staging as described in the algorithm (see *Workup* in the NCCN Guidelines for Epithelial Ovarian Cancer). The diagnosis of LCOH is often not made until after surgery for a suspicious pelvic mass (see *Primary Treatment* in the NCCN Guidelines for Epithelial Ovarian Cancer). Therefore, the workup for LCOH is the same as for other types of ovarian cancer except that tumor markers are measured and other testing is done to determine the specific histopathology (see *Workup* in the NCCN Guidelines for Epithelial Ovarian Cancer). Tumor markers may include CA-125, inhibin, beta-hCG, alfa-fetoprotein, and carcinoembryonic antigen (CEA). Women younger than 35 years with a pelvic mass should have AFP levels measured to assess for germ cell tumors and to rule out pregnancy.¹⁰⁵⁻¹⁰⁷ A gastrointestinal tract evaluation is recommended for mucinous histology to determine whether an occult gastrointestinal primary has metastasized to the ovaries.¹²² 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).^{148,149,152,410-414} Fertility-sparing surgery may be performed (if technically feasible) if the intraoperative frozen section results are positive for apparent early-stage tumors and/or low-risk tumors (ie, malignant germ cell tumors, borderline epithelial tumors, clinical stage I epithelial ovarian tumors, clinical stage I mucinous

tumors, or clinical stage I sex cord-stromal tumors).^{148,149,152,411-414}

Patients who do not desire fertility preservation; those who have a clinical stage II, III, or IV epithelial ovarian cancer; those with a clinical stage II, III, or IV sex cord-stromal tumor; or those with MMMT should undergo comprehensive surgical staging as per the ovarian cancer guidelines (see *Principles of Surgery* in the NCCN Guidelines for Ovarian Cancer).

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

Clear Cell Carcinoma

Clear cell carcinomas are considered high-grade tumors; they are more common than the other LCOH.⁴¹⁵ Most clear cell carcinomas are negative for WT1 and estrogen receptors.⁴¹⁵ The NCCN Guidelines provide an algorithm for clear cell carcinomas (see the NCCN Guidelines for Clear Cell Carcinoma and the *WHO Histologic Classification* in the NCCN Guidelines for Ovarian Cancer Histopathologies).¹ 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).⁴¹⁶ Fertility-sparing surgery is not recommended for stage IA to C clear cell carcinomas. Lymphadenectomy has been shown to improve survival.⁴¹⁷ The staging system for high-grade serous ovarian and primary peritoneal cancer is also used for clear cell carcinomas (see Table 1 in the NCCN Guidelines for Ovarian Cancer).⁹³ Lynch syndrome is associated with risk for endometrioid carcinomas, clear cell carcinomas, and papillary serous carcinomas.¹⁷⁻¹⁹ For patients with stage IA to IC disease, recommended postoperative treatment is the standard intravenous taxane-carboplatin regimens (with paclitaxel or docetaxel) used for high-grade serous ovarian cancer.⁴¹⁷ Fertility-sparing surgery and/or observation/monitoring are an option for patients with unilateral clear cell borderline tumors (see the NCCN Guidelines for Borderline Epithelial Tumors [Low Malignant Potential]). For patients with stage II to IV clear cell carcinoma, postoperative treatment is standard regimens used for epithelial ovarian cancer (eg, intravenous carboplatin with paclitaxel, docetaxel, or liposomal doxorubicin). Patients with advanced clear cell carcinoma have a poor prognosis.^{416,417} Data suggest that 6 or 3 cycles of postoperative chemotherapy are equivalent for patients with clear cell carcinoma.^{220,418}

Mucinous Carcinomas

Mucinous tumors are unusual because they may be very large cystic masses that may fill the abdomen and pelvis; this presentation often suggests mucinous histology. Patients with mucinous carcinoma of the ovary are often diagnosed with early-stage disease and have a good prognosis; the 5-year disease-free survival is about 80% to 90%.^{122,419} Women with mucinous tumors typically present at a younger age (20–40 years) than those with high-grade serous ovarian cancer. The NCCN Guidelines provide an algorithm for mucinous carcinoma (see the NCCN Guidelines for Mucinous Carcinoma and the *WHO Histologic*

Classification in the NCCN Guidelines for Ovarian Cancer Histopathologies).¹ For the 2017 update (Version 1), the NCCN Panel added a recommendation for fertility-sparing surgery, if not previously done, for select patients with stage IA to C disease.

Patients are typically diagnosed with mucinous carcinoma after surgery for a suspicious pelvic mass (see *Primary Treatment* in the NCCN Guidelines for Epithelial Ovarian Cancer). Therefore, the initial workup is the same as for other types of ovarian cancer (see *Workup* in the NCCN Guidelines for Epithelial Ovarian Cancer). Primary treatment for these patients includes completion surgery with comprehensive staging followed by postoperative therapy or observation (see the NCCN Guidelines for Mucinous Carcinoma).¹²² An appendectomy is also recommended at primary surgery in patients with suspected or confirmed mucinous ovarian tumors. Fertility-sparing surgery is an option for select patients with stage I mucinous tumors (see the NCCN Guidelines for Borderline Epithelial Tumors [Low Malignant Potential]). The staging system for high-grade serous epithelial ovarian cancer and primary peritoneal cancer is also used for mucinous carcinomas (see Table 1 in the NCCN Guidelines for Ovarian Cancer).⁹³

The additional workup includes a gastrointestinal tract evaluation and CEA level for patients with mucinous histology to determine whether patients have either occult gastrointestinal primary that has metastasized to the ovaries or primary mucinous carcinoma of the ovaries (see *Workup* in the NCCN Guidelines for Epithelial Ovarian Cancer).¹²² 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.⁴²⁰⁻⁴²² PAX8 immunostaining may be useful.⁴²⁰

Postoperative observation and monitoring are recommended for patients with stage IA or IB mucinous tumors because most of these tumors are benign or borderline.^{122,415} 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).¹²² Some clinicians feel the gastrointestinal regimens are appropriate because mucinous carcinomas of the ovary are similar to gastrointestinal tumors.⁴²³ For patients with stages II to IV mucinous carcinomas, postoperative options include: 1) chemotherapy using the regimens for epithelial ovarian cancer (eg, intravenous carboplatin with paclitaxel, docetaxel, or liposomal doxorubicin); 2) 5-FU/leucovorin/oxaliplatin (gastrointestinal regimen); or 3) capecitabine/oxaliplatin (gastrointestinal regimen). For the 2017 update (Version 1), the NCCN Panel added recommendations for recurrence therapy for mucinous carcinomas: 1) 5-FU/leucovorin/oxaliplatin with or without bevacizumab (category 2B for bevacizumab); or 2) capecitabine/oxaliplatin.

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

The NCCN Guidelines provide an algorithm for grade 1 (low-grade) serous carcinomas/endometrioid epithelial carcinomas (see the NCCN Guidelines for Grade 1 (Low-Grade) Serous Carcinomas/Endometrioid Epithelial Carcinomas and the *WHO Histologic Classification* in the NCCN Guidelines for Ovarian Cancer Histopathologies).¹ Endometrioid carcinomas may be associated with endometriosis.^{424,425} 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 CDX2.⁴¹⁵ Endometrioid tumors are also very similar in appearance to sex cord-stromal tumors.⁴¹⁵ Lynch syndrome is associated with risk for

endometrioid carcinomas, clear cell carcinomas, and serous carcinomas.¹⁷⁻¹⁹

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

Primary treatment for these patients includes completion surgery with comprehensive staging followed by postoperative therapy or observation; patients are typically diagnosed after surgery (see the NCCN Guidelines for Low-Grade (Grade 1) Serous Carcinomas/Endometrioid Epithelial Carcinomas).¹³⁰ The staging system for high-grade serous ovarian and primary peritoneal cancer is also used for low-grade (grade 1) serous/endometrioid carcinomas (see Table 1 in the NCCN Guidelines for Ovarian Cancer).⁹³ 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 low-grade (grade 1) serous carcinomas, because they often respond poorly to chemotherapy.¹³⁰

Postoperative observation and monitoring are recommended for patients with stage IA or IB disease. For patients with stage IC to II disease, postoperative options include: 1) intravenous carboplatin with either paclitaxel or docetaxel; 2) observation (category 2B); or 3)

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

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.^{431,432} Germ cell tumors are the predominant ovarian tumor in this age group.⁴³³ The recommended workup may include pulmonary function studies if bleomycin is being considered (see *Recommended Workup* in the NCCN Guidelines for Epithelial Ovarian Cancer).^{105,434} In young women (<35 years) with a pelvic mass, AFP levels can indicate the presence of germ cell tumors.¹⁰⁵⁻¹⁰⁷ However, pregnancy should also be ruled out. Gonadal dysgenesis is a risk factor for germ cell tumors.⁴³³ Malignant germ cell

tumors have an excellent prognosis.⁴³⁵ After appropriate treatment, 5-year survival is more than 85%.^{431,436,437}

Treatment

Fertility-sparing surgery is recommended for those desiring fertility preservation, regardless of stage (see the NCCN Guidelines for Malignant Germ Cell Tumors).^{152,432,437-440} 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.^{441,442} 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).⁴³³ The staging system for high-grade serous ovarian and primary peritoneal cancer is also used for malignant germ cell tumors (see Table 1 in the NCCN Guidelines for Epithelial Ovarian Cancer).⁹³ After comprehensive surgical staging, observation with monitoring is recommended for patients with stage I dysgerminoma or stage I, grade 1 immature teratoma.⁴⁴³ If patients have had incomplete surgical staging, recommended options depend on the type of tumor, the results of imaging and tumor marker testing (eg, AFP, beta-HCG), the age of the patient, and whether the patient desires fertility preservation (see the NCCN Guidelines for Malignant Germ Cell Tumors). Patients who chose fertility-sparing surgery should be monitored by ultrasound examinations if necessary; completion surgery (category 2B) should be considered after finishing childbearing.

After surgery, observation with surveillance is the recommended option for patients with stage I dysgerminoma or stage I, grade I immature teratoma based on European and pediatric reports.⁴⁴⁴⁻⁴⁴⁷ 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).^{432,444,446,448-450} 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).^{434,451-453} If considering the use of bleomycin, pulmonary function tests are recommended.^{434,436} 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.^{444,454-461} 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).⁴⁶² Dose reductions or delays are not recommended even in the setting of neutropenia.

Surveillance recommendations for germ cell tumors are described in the algorithm (see *Surveillance for Malignant Germ Cell and Sex Cord-Stromal Tumors* in the NCCN Guidelines for Malignant Germ Cell and Sex Cord-Stromal Tumors).²⁹⁹ 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;⁴⁶³ 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.⁴⁶⁴⁻⁴⁶⁷

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.⁴⁶⁸ 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)⁴⁶⁹ or high-dose chemotherapy. Referral to a tertiary care center for potentially curative treatment is strongly recommended.⁴⁷⁰ There are small series but no major trials in adult patients.

Patients with recurrent or residual malignancy after multiple chemotherapeutic regimens may be treated with a recurrence modality (see *Principles of Systemic Therapy: Acceptable Recurrence Therapies for Malignant Germ Cell/Sex Cord-Stromal Tumors* in the NCCN Guidelines for Epithelial Ovarian Cancer), including potentially curative

high-dose chemotherapy or TIP. Other regimens include VAC (vincristine, dactinomycin, cyclophosphamide), VeIP (vinblastine, ifosfamide, cisplatin), VIP (etoposide, ifosfamide, cisplatin), cisplatin/etoposide, docetaxel/carboplatin, paclitaxel/carboplatin, paclitaxel/gemcitabine, paclitaxel/ifosfamide, docetaxel, paclitaxel, RT, or supportive care only.^{457,470-474} 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.^{475,476} Most patients with granulosa tumors present with early-stage disease; the disease is typically indolent.⁴⁷⁷ The complete histologic classification for ovarian cancer from the WHO includes the different types of sex cord-stromal tumors; it is important to determine whether the sex cord-stromal tumor is benign or malignant (see *WHO Histologic Classification: Sex Cord-Stromal Tumors* in the NCCN Guidelines for Ovarian Cancer Histopathologies).¹ The staging system for high-grade serous ovarian and primary peritoneal cancer is also used for sex cord-stromal tumors (see Table 1 in the NCCN Guidelines for Ovarian Cancer).⁹³

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).⁴⁷⁷⁻⁴⁸⁰ Although complete staging is recommended for all other patients, lymphadenectomy may be omitted for tumors grossly confined

to the ovary.⁴⁸¹ 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).⁴⁷⁸ For patients with high-risk stage I tumors (tumor rupture, stage 1C, poorly differentiated tumor, and tumor size >10–15 cm⁴⁸²), postoperative recommendations (all are category 2B) include observation or consideration of platinum-based chemotherapy.⁴⁸³ Observation is recommended for those with surgical findings of low-risk stage I tumor (ie, without high-risk features) (see *Surveillance for Malignant Germ Cell and Sex Cord-Stromal Tumors* in the NCCN Guidelines for Less Common Ovarian Histopathologies). For patients with granulosa cell tumors who are being observed, inhibin levels can be followed if they were initially elevated (category 2B). For patients with stage II to IV tumors, recommended options (all are category 2B) include RT for limited disease or platinum-based chemotherapy (BEP or paclitaxel/carboplatin regimens are preferred).⁴⁸⁴⁻⁴⁸⁷

Surveillance recommendations for malignant sex cord-stromal tumors are provided in the algorithm, which are based on the SGO recommendations (see *Surveillance for Malignant Germ Cell and Sex Cord-Stromal Tumors* in the NCCN Guidelines for Less Common Ovarian Histopathologies).²⁹⁹ Prolonged surveillance is recommended for granulosa cell tumors, because they can recur years later (eg, 30 years).^{439,475,476,488} 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).^{476,488-491} 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.^{491,492} 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).⁴⁹³⁻⁴⁹⁶ Most pathologists now consider MMMTs to be a variant of poorly differentiated epithelial ovarian cancer (metaplastic carcinoma).⁴⁹⁷ Patients with MMMTs are not candidates for fertility-sparing surgery regardless of age or stage. The staging system for ovarian and primary peritoneal cancer is also used for MMMTs (see Table 1 in the NCCN Guidelines for Ovarian Cancer).^{93,495}

Optimal surgical debulking is recommended for patients with MMMTs (see *Principles of Surgery* in the NCCN Guidelines for Ovarian Cancer).^{495,498-500} 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; for the 2017 update (Version 1), the panel decided these chemotherapy regimens are preferred options (see *Primary Chemotherapy/Primary Adjuvant Therapy* in the NCCN Guidelines for Ovarian Cancer).^{497,501-506} For example, intravenous carboplatin with either paclitaxel, docetaxel, or liposomal doxorubicin are recommended for patients with stage I-IV MMMT. The IP chemotherapy regimen described for ovarian cancer can

be used for select patients with MMMT. Other recommended postoperative chemotherapy options include cisplatin/ifosfamide (category 2A), carboplatin/ifosfamide (category 2A), and ifosfamide/paclitaxel (category 2B).^{493,497,501,507} After treatment, the surveillance and follow-up recommendations for epithelial ovarian cancer are also used for MMMTs.

Borderline Epithelial Tumors (Low Malignant Potential)

Diagnosis

Borderline epithelial tumors are rare tumors and are managed differently than high-grade carcinomas (see the NCCN Guidelines for Borderline Epithelial Tumors [Low Malignant Potential]).^{410,508} Five-year survival exceeds 80%.⁵⁰⁹ 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.^{510,511} 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.^{512,513}

The terms for borderline epithelial tumors (also known as low malignant potential tumors or atypical proliferative tumors) have changed over the years.⁴¹⁵ The 2016 and 2017 CAP cancer protocols for ovarian cancer use borderline and do not use low malignant potential.^{88,94} 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).^{1,410}

The characteristic pathologic hallmark of typical epithelial ovarian cancer is the identification of peritoneal implants, which microscopically and/or macroscopically invade the peritoneum. A borderline epithelial tumor may grossly resemble an invasive cancer. However, microscopic

evaluation fails to reveal evidence of frank invasion by the tumor nodules, although rarely invasive implants (which continue to be consistent with the diagnosis of borderline epithelial lesions) can be identified microscopically by the pathologist.

Treatment

Surgery is the primary treatment for borderline epithelial tumors, including standard ovarian cancer debulking surgery or fertility-sparing surgery depending on the surgical evaluation and other factors (see the NCCN Guidelines for Borderline Epithelial Tumors [Low Malignant Potential]).⁵¹⁴ Treatment guidelines for borderline epithelial tumors depend on the histologic and clinical characteristics, the age of the patient,⁵¹¹ 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.^{410,515} Although the staging system for epithelial ovarian cancer is used for borderline epithelial tumors, the NCCN Guidelines use the presence or absence of invasive implants to determine the need for postoperative therapy (see the NCCN Guidelines for Borderline Epithelial Tumors [Low Malignant Potential]).

Patients with a borderline epithelial tumor who desire to maintain their fertility may undergo surgery limited to a USO (preserving the uterus, contralateral ovary, and contralateral Fallopian tube) with resection of residual disease.^{148,149,516} BSO and preserving the uterus is an option for select patients. If the patient does not desire fertility-sparing surgery, standard ovarian cancer surgery (TAH, BSO, and debulking as needed) and resection of residual disease are recommended. Data do not show increased survival with lymphadenectomy and omentectomy for

borderline epithelial tumor, although upstaging does occur.^{517,518} Lymph node evaluation may be considered on a case-by-case basis.

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

Follow-up

Treatment recommendations after surgery depend on the presence or absence of invasive implants. The initial therapeutic approach for

patients having invasive implants may include treatment with the same chemotherapeutic regimens used for low-grade (grade 1) serous epithelial ovarian cancer or observation (category 3) (see *Primary Treatment* in the NCCN Guidelines for Borderline Epithelial Tumors [Low Malignant Potential]).⁵²⁰ 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]).^{510,522} 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).⁴¹⁰

Relapse

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

Summary

Epithelial ovarian cancer is the leading cause of death from gynecologic cancer in the United States and is the country's fifth most common cause of cancer mortality in women. More than 70% of patients present with advanced disease. The literature does not support routine screening for ovarian cancer in the general population, and routine screening is not currently recommended by any professional society. These NCCN Guidelines discuss epithelial ovarian cancer and LCOH,

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

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

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

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

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

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

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

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