National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Ovarian Cancer

Including Fallopian Tube Cancer and Primary Peritoneal Cancer

Version 2.2013

NCCN.org

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Ovarian Cancer

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Discussion

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NCCN Guidelines Panel Disclosures

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

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

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

See NCCN Categories of Evidence and Consensus.

NCCN Guidelines for Patients™ are available at www.nccn.com.

NCCN Guidelines Version 2.2013 Updates
Ovarian Cancer

Updates to the 1.2013 version of the NCCN Guidelines for Ovarian Cancer from the 1.2013 version include:

MS-1

- The discussion section was updated to reflect the changes in the algorithm.

Updates to the 1.2013 version of the NCCN Guidelines for Ovarian Cancer from the 3.2012 version include:

OV-1

- Workup
  - "Ultrasound and/or abdominal/pelvic CT" was modified to include "as clinically indicated."
- Footnote "c" was added: "PET/CT scan may be indicated for indeterminate lesions if results will alter management."

OV-2

- The finding of "Suspected stage IA or IB, grade 3 stage IC" was modified as: "...grade 3 *or clear cell or* stage IC.*"*
- Footnote was removed: "Clear-cell pathology is grade 3." (Also for OV-3.)

OV-3

- Stage 1A or 1B, Grade 3 was modified to include: "or clear cell."
- Footnote was removed: "The NCCN Ovarian Cancer panel recognizes that data for first-line and maintenance bevacizumab are becoming available and encourages participation in clinical trials." (Also for OV-D.)

OV-4

- For Secondary Adjuvant Therapy, "Clinical trial" was moved to be the first option.

OV-6

- Disease Status,
  - For "Progression, stable, or persistent disease on primary chemotherapy," the option of "supportive care only" was modified by adding "palliative" and a corresponding link, "See NCCN Guidelines for Palliative Care."

OV-7

- Clinical presentation and primary treatment of "pelvic mass" was incorporated with "diagnosis of low malignant potential lesion with institutional pathology review."

OV-8

- For primary treatment options that include "comprehensive surgical staging," the category 2B recommendation was clarified to include "for staging."
- Footnotes:
  - Footnote "t" was added: "Observation is a reasonable option regardless of whether fertility is desired."
  - Footnote "u" was added: "For pathologically proven LMP, lymph node evaluation may be considered on a case-by-case basis."

OV-A 2 of 3

- "Procedures that may be considered for optimal surgical cytoreduction" was modified by adding: "appendectomy."
- Special circumstances, 1st bullet was modified as: "In ~~Stage I~~ *early-stage* disease..."

OV-D

- Number "1" was modified as: "Paclitaxel 135 mg/m^2 IV continuous infusion over *3 or* 24 h Day 1; cisplatin 75-100 mg/m^2 IP, Day 2 after IV paclitaxel; paclitaxel 60 mg/m^2 IP Day 8 (~~max BSA 2.0 m^2~~)..."
- Footnotes:
  - Footnote "2" was added: "The published randomized trial regimen used IV continuous infusion paclitaxel over 24 h."
  - Footnote "3" was added: "Due to changes in creatinine methodology, changes regarding carboplatin dosing can be considered. See FDA carboplatin dosing statement."

OV-E

- Under Cytotoxic therapy, an additional preferred regimen option was added: "Carboplatin/gemcitabine/bevacizumab" as a category 2B recommendation with a corresponding footnote, "In patients who have not previously received bevacizumab."

LCOH-B

- A new page was added: "Surveillance for Germ Cell and Sex Cord-Stromal Tumors" and links to this page were added throughout the "Less Common Ovarian Histopathologies" algorithms.

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CLINICAL PRESENTATION

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

→

WORKUP

- Obtain family history and consider family history evaluation (See NCCN Guidelines for Genetic/Familial High-Risk Assessment and NCCN Guidelines for Colorectal Cancer Screening)
- Abdominal/pelvic exam
- Chest imaging
- Complete blood count (CBC), chemistry profile with liver function test (LFT)
- GI evaluation as clinically indicated
- Ultrasound and/or abdominal/pelvic CT as clinically indicated[c]
- CA-125 or other tumor markers as clinically indicated[d]

→

PRIMARY TREATMENT[e,f]

Laparotomy/hysterectomy (TAH)/bilateral salpingo-oophorectomy (BSO) with comprehensive staging[g] or unilateral salpingo-oophorectomy (USO) (clinical stage 1A or 1C, all grades with comprehensive staging if patient desires fertility)
or
Cytoreductive surgery[g] if clinical stage II, III, or IV
or
Consider neoadjuvant chemotherapy[h] (category 1)/primary interval cytoreduction[e] (diagnosis by fine needle aspiration [FNA], biopsy, or paracentesis) for patients with bulky stage III/IV who are poor surgical candidates due to high-risk comorbidity conditions or disease factors

→ See Pathologic Staging (OV-3)

Diagnosis by previous surgery or tissue biopsy (cytopathology)

→

- Obtain family history and consider family history evaluation (See NCCN Guidelines for Genetic/Familial High-Risk Assessment and for Colorectal Cancer Screening)
- Chest imaging
- CBC, chemistry profile with LFTs
- Institutional pathology review
- Ultrasound and/or abdominal/pelvic CT as clinically indicated[c]
- CA-125 or other tumor markers as clinically indicated[d]

→ See Findings and Primary Treatment (OV-2)

[a] Im SS, Gordon AN, Buttin BM, et al. Obstet Gynecol 2005;105:35-41. See Discussion.

[b] Goff BA, Mandel L, Drescher CW, et al. Cancer 2007;109:221-227.

[c] PET/CT scan may be indicated for indeterminate lesions if results will alter management.

[d] See Discussion for usefulness of diagnostic tests.

[e] Standard recommendation includes a patient evaluation by a gynecologic oncologist prior to initiating chemotherapy. Published data demonstrate that primary assessment and debulking by a gynecologic oncologist result in a survival advantage. Patients being evaluated for neoadjuvant chemotherapy should be seen by a fellowship-trained gynecologist oncologist prior to being considered a poor surgical candidate.

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

[g] See Principles of Primary Surgery (OV-A).

[h] See Principles of Chemotherapy (OV-B) and Management of Drug Reactions (OV-C).

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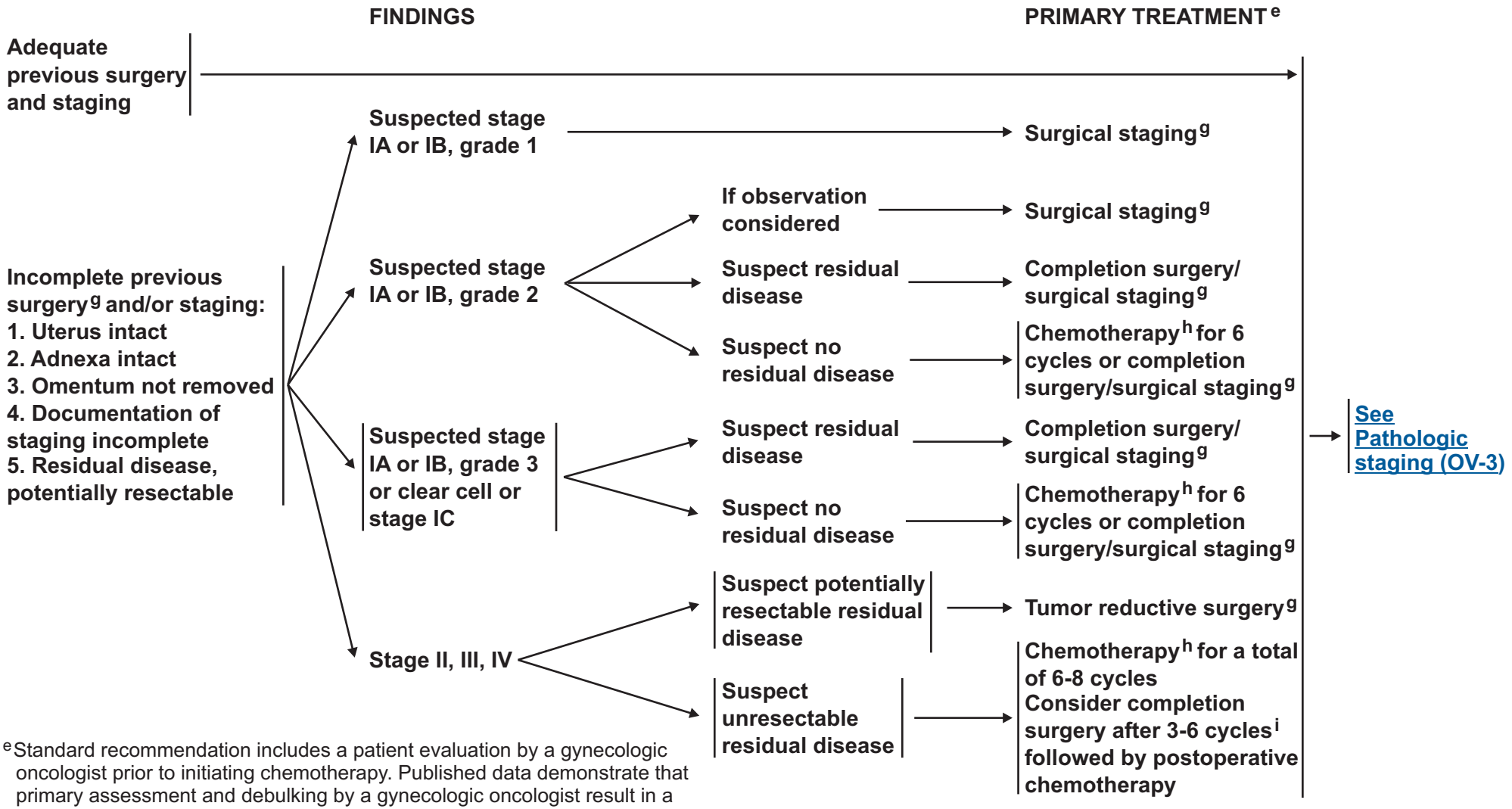
DIAGNOSIS BY PREVIOUS SURGERY



[e] Standard recommendation includes a patient evaluation by a gynecologic oncologist prior to initiating chemotherapy. Published data demonstrate that primary assessment and debulking by a gynecologic oncologist result in a survival advantage. Patients being evaluated for neoadjuvant chemotherapy should be seen by a fellowship-trained gynecologist oncologist prior to being considered a poor nonsurgical candidate.

[g] See Principles of Primary Surgery (OV-A).

[h] See Principles of Chemotherapy (OV-B) and Management of Drug Reactions (OV-C).

[i] Based on clinical judgement of gynecologic oncologist, surgery may be performed after 6 cycles.

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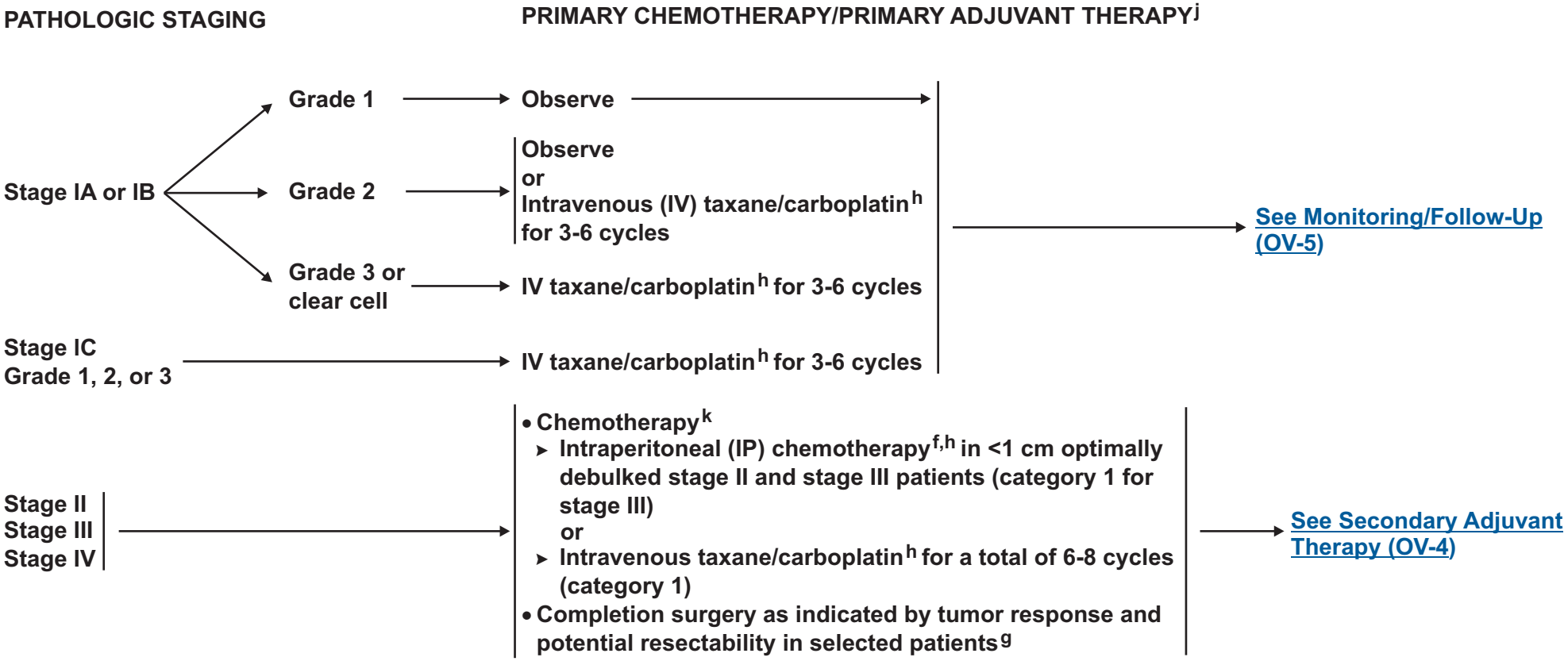

[f] All women undergoing surgery for ovarian cancer should be counseled about the clinical benefit associated with combined IV and IP chemotherapy administration prior to surgery. NCI Clinical Announcement.

[g] See Principles of Primary Surgery (OV-A).

[h] See Principles of Chemotherapy (OV-B) and Management of Drug Reactions (OV-C).

[j] Patients receiving primary chemotherapy will be monitored as follows:
1. Pelvic exams at least every 2-3 cycles
2. Interim CBC with platelets as indicated
3. Chemistry profiles if indicated
4. CA-125 levels or other tumor markers as clinically indicated prior to each cycle of chemotherapy
5. Radiographic imaging if indicated

[k] See specific regimens on Primary Chemotherapy/Primary Adjuvant Therapy Regimens for Stage II-IV (OV-D).

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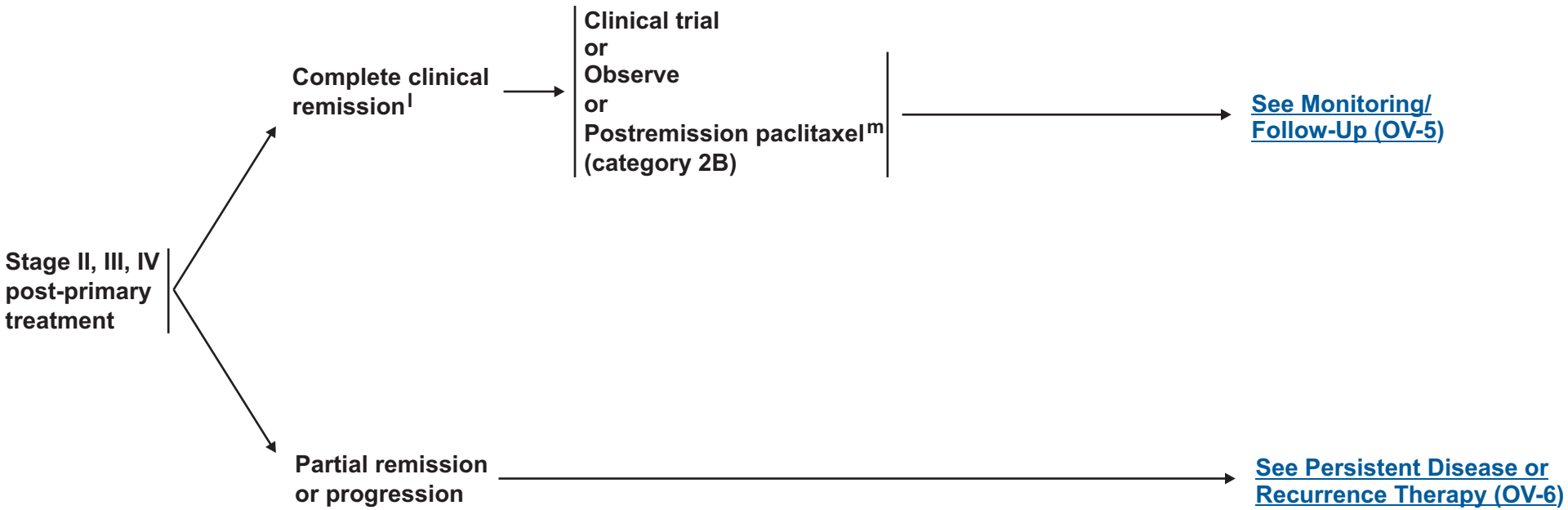
STAGE II, III, IV
POST-PRIMARY TREATMENT

SECONDARY ADJUVANT THERAPY



[l] No objective evidence of disease (ie, negative physical exam, negative CA-125, negative CT with <1 cm lymph nodes).
[m] See Discussion for dosing.

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STAGE I-IV COMPLETE RESPONSE

MONITORING/FOLLOW-UP

Stage I, II, III, and IV complete response →

- Visits every 2-4 mo for 2 y, then 3-6 mo for 3 y, then annually after 5 y
- Physical exam including pelvic exam
- CA-125[n] or other tumor markers every visit if initially elevated
- Consider family history evaluation, if not previously done (See NCCN Guidelines for Genetic/Familial High-Risk Assessment and NCCN Guidelines for Colorectal Cancer Screening)
- CBC and chemistry profile as indicated
- Chest/abdominal/pelvic CT, MRI, PET-CT, or PET (category 2B for PET) as clinically indicated
- Chest x-ray as indicated

RECURRENT DISEASE

Rising CA-125, no previous chemotherapy
or
Clinical relapse, no previous chemotherapy
→ Imaging studies: Chest/abdominal/pelvic CT, MRI, PET-CT, or PET (category 2B for PET) as clinically indicated
→ See Primary Treatment (OV-1)

Clinical relapse, previous chemotherapy
→ Imaging studies: Chest/abdominal/pelvic CT, MRI, PET-CT, or PET (category 2B for PET) as clinically indicated
→ See Therapy for Persistent Disease or Recurrence (OV-6)

Serially rising CA-125, previous chemotherapy
→ Imaging studies: Chest/abdominal/pelvic CT, MRI, PET-CT, or PET (category 2B for PET) as clinically indicated
→ Delay treatment until clinical relapse
or
Immediate treatment for recurrent disease (category 2B)
or
Clinical trial
→ See Therapy for Persistent Disease or Recurrence (OV-6)

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

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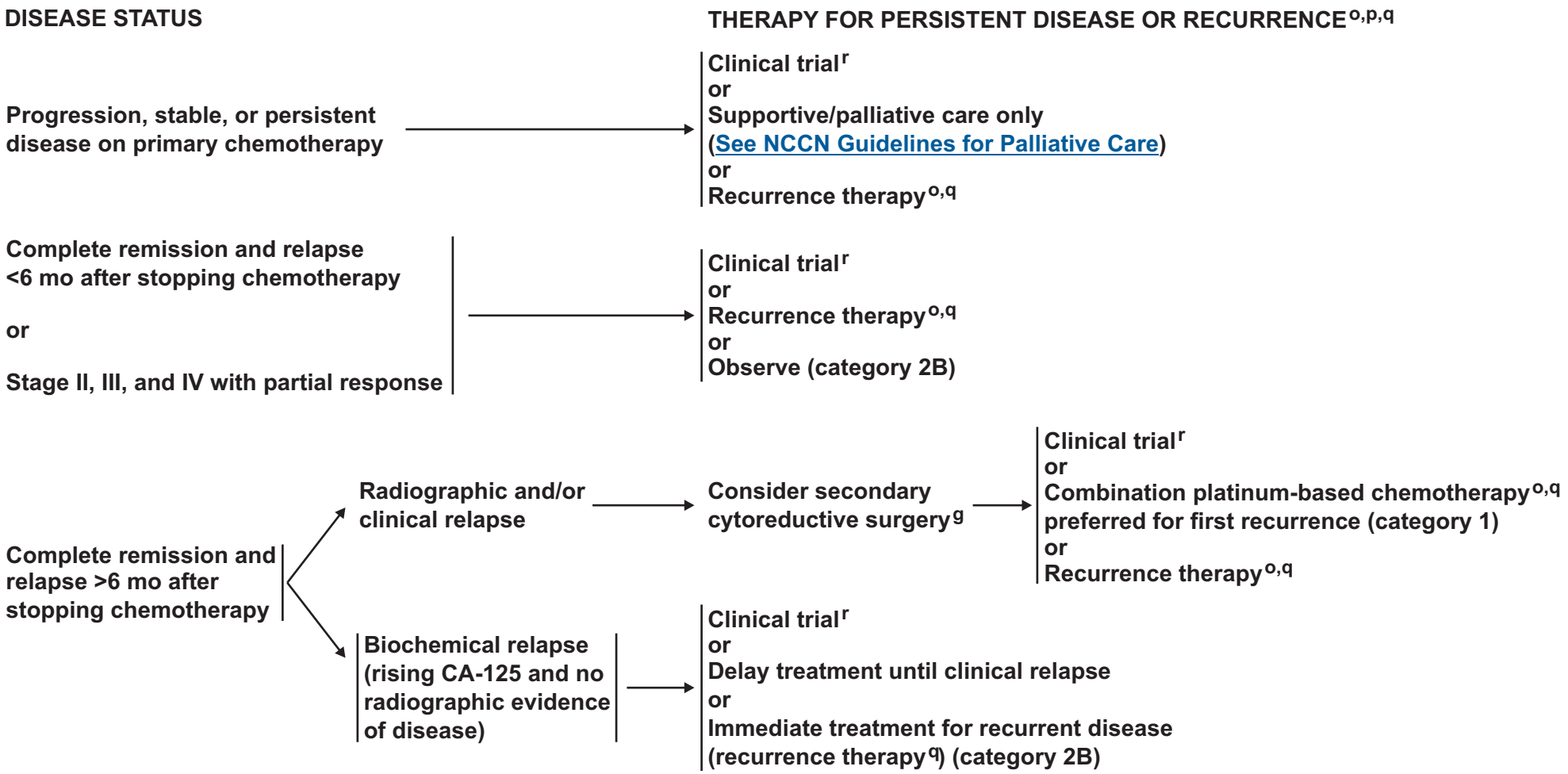

[g] See Principles of Primary Surgery (OV-A).

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

[p] See Ancillary Palliative Surgical Procedures in Principles of Primary Surgery (OV-A).

[q] See Acceptable Recurrence Therapies (OV-E).

[r] Clinical trials with newer agents should be strongly considered.

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Borderline Epithelial Ovarian Cancer (Low Malignant Potential)

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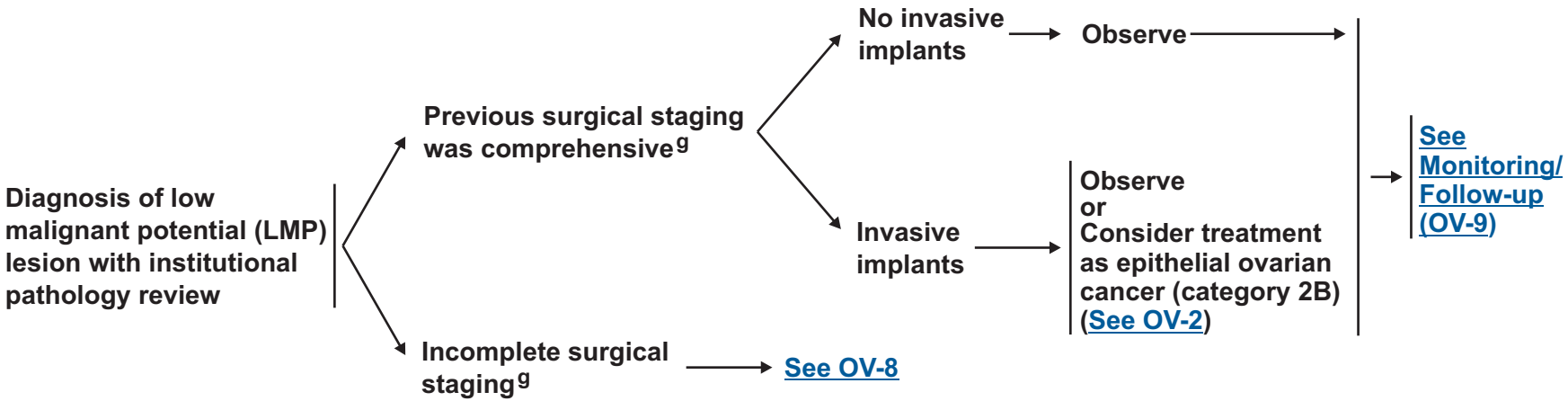
CLINICAL PRESENTATION

PRIMARY TREATMENT[s]



[g] See Principles of Primary Surgery (OV-A).

[s] Standard recommendation includes a patient evaluation by a gynecologic oncologist.

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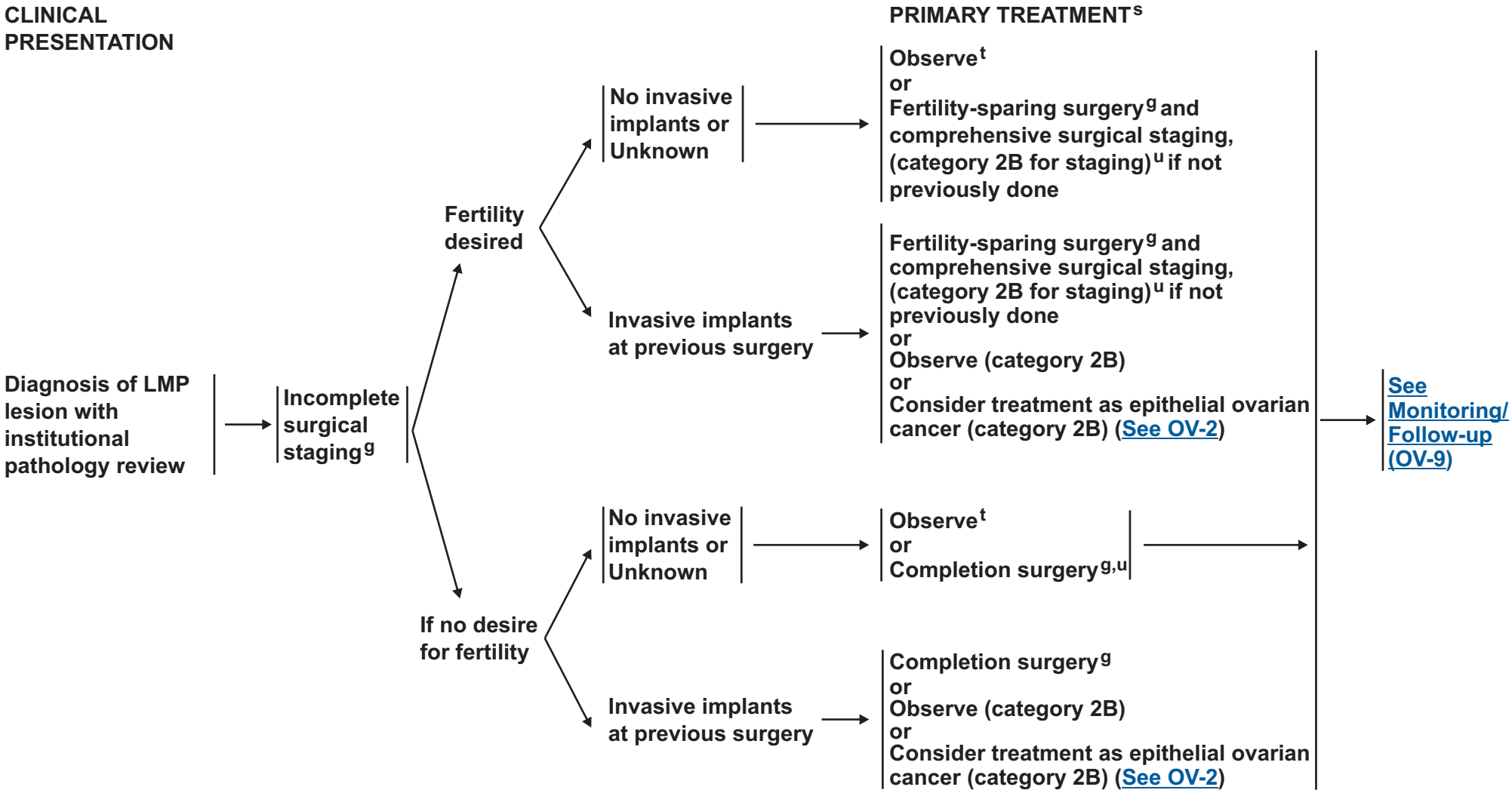

[g] See Principles of Primary Surgery (OV-A).
[s] Standard recommendation includes a patient evaluation by a gynecologic oncologist.
[t] Observation is a reasonable option regardless of whether fertility is desired.
[u] For pathologically proven LMP, lymph node evaluation may be considered on a case-by-case basis.

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NCCN Guidelines Version 2.2013
Borderline Epithelial Ovarian Cancer (Low Malignant Potential)

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MONITORING/FOLLOW-UP

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

RECURRENT DISEASE

→ Clinical relapse → Surgical evaluation + debulking if appropriate

RECURRENCE THERAPY

- Noninvasive disease → Observe
- Invasive disease → Treatment as epithelial ovarian cancer (category 2B) (See OV-3)

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

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PRINCIPLES OF PRIMARY SURGERY (1 of 3)[1,2]

- **In general, a vertical midline abdominal incision should be used in patients with a suspected malignant ovarian neoplasm.[2] Intraoperative pathologic evaluation with frozen sections may assist in management.**
- **Quantify the extent of initial and residual disease, and document in operative notes.**

Ovarian cancer apparently confined to an ovary or to the pelvis

- **The following procedures should be considered part of the surgical management of patients with ovarian cancer apparently confined to an ovary or to the pelvis:**
  - **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).**
  - **Hysterectomy, bilateral salpingectomy, and bilateral oophorectomy should be performed with every effort made to keep an encapsulated mass intact during removal.**
  - **USO for patients desiring to preserve fertility may be considered in select patients. (See OV-A 2 of 3)**
  - **Omentectomy should be performed.**
  - **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.**
  - **Pelvic lymph nodes should be dissected. Removal of lymph nodes overlying and medial to the external iliac and hypogastric vessels, from the obturator fossa anterior to the obturator nerve, and overlying and anterolateral to the common iliac vessel is preferred.**
  - **In LMP, although data show upstaging with lymphadenectomy and omentectomy, other data show that this surgery does not affect overall survival.**

Ovarian cancer involving the upper abdomen

- **In general, the following procedures should be part of the surgical management of patients with ovarian cancer involving the upper abdomen in an effort to achieve maximal cytoreduction. Residual disease <1 cm defines optimal cytoreduction; however, maximal effort should be made to remove all gross disease.**
  - **Aspiration of ascites or peritoneal lavage should be performed for peritoneal cytologic examinations. For obvious disease beyond ovaries, cytologic assessment of ascites and/or lavage specimens would not alter stage or management.**
  - **Hysterectomy, bilateral salpingectomy, and bilateral oophorectomy should be performed.**
  - **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.**

[1] Fleming GF, Ronnett BM, Seidman J, et al: Epithelial ovarian cancer. In Barakat RR, Markman M, Randall ME (eds): Principles and Practice of Gynecologic Oncology, 5th ed, Philadelphia, Lippincott Williams & Wilkins, 2009:763-835. Amended by panel.

[2] It is recommended that a gynecologic oncologist perform primary surgery (category 1).

Continued on OV-A 2 of 3

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PRINCIPLES OF PRIMARY SURGERY (2 of 3)[1]

- **Procedures that may be considered for optimal surgical cytoreduction (in all stages) may include:**
  - **Radical pelvic dissection**
  - **Bowel resection**
  - **Diaphragm or other peritoneal surface stripping**
  - **Splenectomy**
  - **Partial hepatectomy**
  - **Cholecystectomy**
  - **Partial gastrectomy**
  - **Partial cystectomy**
  - **Ureteroneocystostomy**
  - **Distal pancreatectomy**
  - **Appendectomy**

Special Circumstances

- **In early-stage disease, minimally invasive techniques may be considered to achieve the surgical principles described on OV-A 1 of 3. Minimally invasive surgery performed by an experienced gynecologic oncologist may be considered in selected patients, particularly for an incidental finding of ovarian cancer during prophylactic oophorectomy. See the College of American Pathologists, Protocol for the Examination of Specimens from Patients with Carcinoma of the Ovary.**
- **For patients with apparent early-stage disease and/or good risk tumors (early-stage invasive epithelial tumors, LMP lesion, malignant germ cell tumors, or malignant sex cord-stromal tumors) who wish to preserve fertility, USO preserving the uterus and contralateral ovary (fertility-sparing surgery) can be considered. Comprehensive surgical staging should still be performed to rule out occult higher stage disease.**
- **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.**
- **Appendectomy should be performed in all mucinous tumors and considered in all patients with epithelial malignancies suspicious for involvement of the appendix by metastases.**
- **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.**

Continued on OV-A 3 of 3

[1] Fleming GF, Ronnett BM, Seidman J, et al: Epithelial ovarian cancer. In Barakat RR, Markman M, Randall ME (eds): Principles and Practice of Gynecologic Oncology, 5th ed, Philadelphia, Lippincott Williams & Wilkins, 2009:763-835. Amended by panel.

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PRINCIPLES OF PRIMARY SURGERY (3 of 3)

- **Ancillary Palliative Surgical Procedures**

These procedures may be appropriate in select patients:

- **Paracentesis**
- **Thoracentesis/pleurodesis**
- **Ureteral stents/nephrostomy**
- **Surgical relief of intestinal obstruction**
- **Gastrostomy tube**
- **Vascular access device**
- **Indwelling peritoneal or pleural catheter**
- **Intestinal stents**
- **Video-assisted thoracoscopy**

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PRINCIPLES OF CHEMOTHERAPY
(FOR OVARIAN, FALLOPIAN TUBE, AND PRIMARY PERITONEAL CANCER)
(1 of 2)

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.
- Goals of systemic therapy should be discussed with patients prior to initiation of any therapy.
- Prior to recommending chemotherapy, requirements for adequate organ function and performance status should be met.
- Patients should be observed closely and treated for any complications during chemotherapy. Appropriate blood chemistry tests should be monitored. Appropriate dose reductions and modifications of chemotherapy should be performed depending on toxicities experienced and goals of therapy.
- After completion of chemotherapy, patients should be assessed for response during and following treatment and monitored for any long-term complications.
- Chemosensitivity/resistance and/or other biomarker assays are being used in some NCCN Member Institutions for decisions related to future chemotherapy in situations where there are multiple equivalent chemotherapy options available. The current level of evidence is not sufficient to supplant standard-of-care chemotherapy. (category 3)

For patients with newly diagnosed ovarian, fallopian tube, or primary peritoneal cancer:

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

Continued on OV-B 2 of 2

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PRINCIPLES OF CHEMOTHERAPY
(FOR OVARIAN, FALLOPIAN TUBE, AND PRIMARY PERITONEAL CANCER)
(2 of 2)

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.

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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).
  - Symptoms can overlap, whether caused by infusion or allergic reactions. In addition, patients can have mild allergic reactions or severe infusion reactions.
- 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). Reactions can occur with either IV or IP administration.
- 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 need to be counseled about the possibility of a drug reaction, and about the signs and symptoms of an adverse reaction (either infusion or allergic). Patients should be told to report any signs and symptoms of a drug reaction, especially after they have left the clinic.
  - 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.
  - The treatment area should have appropriate medical equipment in case of a life-threatening reaction.[5]
  - Epinephrine (intramuscular 0.3 mL of 1 mg/mL solution/Epipen) should be used for any patient experiencing hypotension (systolic BP of <90 mm Hg) with or without other symptoms of an allergic/hypersensitivity reaction during or shortly after any chemotherapy drug treatment. In the setting of acute cardiopulmonary arrest, standard resuscitation (ACLS) procedures should be followed.
- Desensitization refers to a process of rendering the patient less likely to respond to an allergen and can be considered for patients who have had drug reactions.[1,7-9]
  - Although desensitization is more commonly used after allergic drug reactions, it can also be used after infusion reactions.
  - If a mild reaction has previously occurred to a platinum agent, great caution should be undertaken if desensitization is pursued (see Allergic Reactions).
- If a patient has previously had a very severe life-threatening reaction, the implicated drug should not be used again unless under guidance of an allergist or specialist with desensitization experience.

Continued on OV-C 2 of 7
References on OV-C 3 of 7

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

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, syncope or pre-syncope, chest pain, tachycardia, hives/itching, changes in blood pressure, nausea, vomiting, chills, and changes in bowel function. Patients with severe reactions may have the following symptoms: cardiac problems, bronchospasm, blood pressure changes that require treatment, and feeling of impending doom.[11]
- Symptoms 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
  - Intravenous administration of the drug rather than oral or intraperitoneal 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] The desensitization treatment of these patients should be managed by a physician with expertise and experience in platinum desensitization.
  - 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, hypoxia--the treating clinician should consult an allergist 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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MANAGEMENT OF DRUG REACTIONS (3 of 7)

REFERENCES

[1]Castells MC, Tennant NM, Sloane DE, et al. Hypersensitivity reactions to chemotherapy: Outcomes and safety of rapid desensitization in 413 cases. J Allergy Clin Immunol 2008;122:574-580.
[2]Dizon DS, Sabbatini PJ, Aghajanian C, et al. Analysis of patients with epithelial ovarian cancer or fallopian tube carcinoma retreated with cisplatin after the development of a carboplatin allergy. Gynecol Oncol 2002;84:378-382.
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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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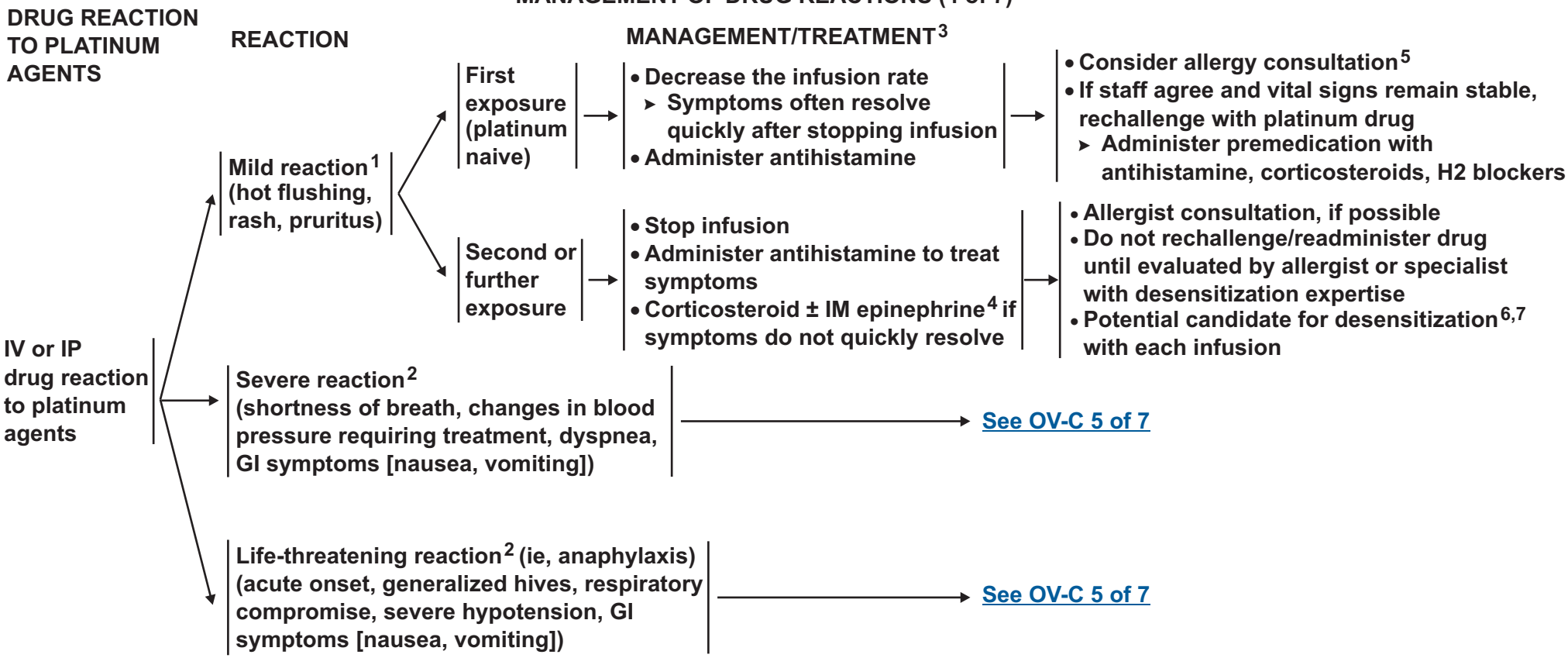
MANAGEMENT OF DRUG REACTIONS (4 of 7)



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

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

[3] Antihistamine (eg, diphenhydramine or hydroxyzine); H2 blockers (eg, cimetidine, famotidine); corticosteroids (eg, methylprednisolone, hydrocortisone, dexamethasone).

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

See Drug Reaction to Taxane, Liposomal Doxorubicin, or Biotherapeutic Agents on OV-C 6 of 7

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

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

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

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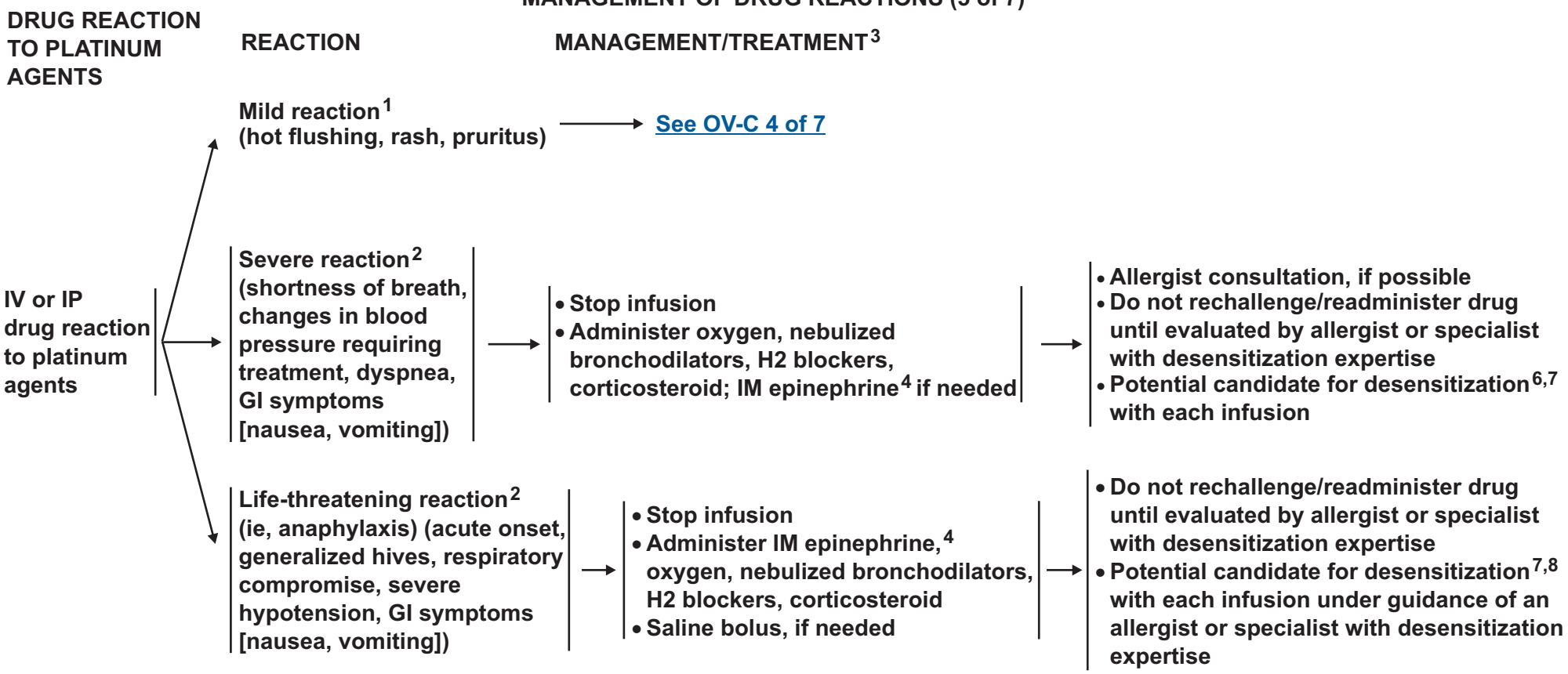
MANAGEMENT OF DRUG REACTIONS (5 of 7)



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

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

[3]Antihistamine (eg, diphenhydramine or hydroxyzine); H2 blockers (eg, cimetidine, famotidine); corticosteroids (eg, methylprednisolone, hydrocortisone, dexamethasone).

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

See Drug Reaction to Taxane, Liposomal Doxorubicin, or Biotherapeutic Agents on OV-C 6 of 7

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

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

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

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MANAGEMENT OF DRUG REACTIONS (6 of 7)

DRUG REACTION TO TAXANE, LIPOSOMAL DOXORUBICIN, OR BIOTHERAPEUTIC AGENTS

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

REACTION	MANAGEMENT/TREATMENT[3]			
Mild reaction[1] (hot flushing, rash, pruritus, pain in chest/abdomen/pelvis/back)	• Stop infusion ➤ Symptoms often resolve quickly after stopping infusion • Administer antihistamine to treat symptoms	→	• If staff agree and vital signs remain stable, rechallenge with drug at slower infusion rate[9] ➤ Administer premedication with antihistamine, corticosteroids, H2 blockers	→ • If repeat mild reaction, then do not rechallenge/ readminister • Potential candidate for desensitization[7,9] with each infusion
Severe reaction[2] (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 reaction[2] (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

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

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

[3] Antihistamine (eg, diphenhydramine or hydroxyzine); H2 blockers (eg, cimetidine, famotidine); corticosteroids (eg, methylprednisolone, hydrocortisone, dexamethasone).

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

[9] Consider switching to docetaxel; however, there are no data to support switching taxanes. Cross reactions have occurred and have been life-threatening. Some reactions to paclitaxel may occur because of the diluent.

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MANAGEMENT OF DRUG REACTIONS (7 of 7)

DRUG REACTION TO TAXANE, LIPOSOMAL DOXORUBICIN, OR BIOTHERAPEUTIC AGENTS

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

REACTION	MANAGEMENT/TREATMENT[3]	
Mild reaction[1] (hot flushing, rash, pruritus, pain in chest/abdomen/ pelvis/back)	→ See OV-C 6 of 7	
Severe reaction[2] (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)	• Stop infusion • Administer oxygen, nebulized bronchodilator, antihistamine, H2 blockers, corticosteroid; IM epinephrine if needed[4]	• Do not rechallenge/readminister drug until evaluated by allergist or specialist with desensitization expertise • Potential candidate for desensitization[6,7] with each infusion
Life-threatening reaction[2] (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)	• Stop infusion • Administer IM epinephrine,[4] oxygen, nebulized bronchodilator, antihistamine, H2 blockers, corticosteroid	• 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

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

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

[3] Antihistamine (eg, diphenhydramine or hydroxyzine); H2 blockers (eg, cimetidine, famotidine); corticosteroids (eg, methylprednisolone, hydrocortisone, dexamethasone).

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

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

See Drug Reaction to Platinum Agents on OV-C 4 of 7

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

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

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PRIMARY CHEMOTHERAPY/PRIMARY ADJUVANT THERAPY REGIMENS FOR STAGE II-IV[1]

1. **Paclitaxel 135 mg/m^2 IV continuous infusion over 3 or 24 h[2] Day 1; cisplatin 75-100 mg/m^2 IP, Day 2 after IV paclitaxel; paclitaxel 60 mg/m^2 IP Day 8. Repeat every 3 weeks x 6 cycles. (category 1)**
2. **Paclitaxel 175 mg/m^2 IV over 3 hours followed by carboplatin[3] AUC 5- 7.5 IV over 1 hour Day 1. Repeat every 3 weeks x 6 cycles. (category 1)**
3. **Docetaxel 60-75 mg/m^2 IV over 1 hour followed by carboplatin[3] AUC 5 - 6 IV over 1 hour Day 1. Repeat every 3 weeks x 6 cycles. (category 1)**
4. **Dose-dense paclitaxel 80 mg/m^2 IV over 1 hour Days 1, 8, and 15 and carboplatin[3] AUC 6 IV over 1 hour Day 1. Repeat every 3 weeks x 6 cycles. (category 1)**
5. **Bevacizumab-containing regimens per ICON-7 and GOG-218:**
   Paclitaxel 175 mg/m^2 IV over 3 hours, carboplatin[3] AUC 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 3)
   or
   Paclitaxel 175 mg/m^2 IV over 3 hours and carboplatin[3] 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 3)

See Management (OV-3)

[1] See Discussion for references.
[2] The published randomized trial regimen used IV continuous infusion paclitaxel over 24 h.
[3] Due to changes in creatinine methodology, changes regarding carboplatin dosing can be considered. See FDA carboplatin dosing statement.

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ACCEPTABLE RECURRENCE THERAPIES (1 of 2)†

Agents	Cytotoxic Therapy	Hormonal Therapy	Targeted Therapy	Radiation Therapy
Preferred Agents	**Combination if platinum sensitive** ‡ ¶ Carboplatin/paclitaxel (category 1)[1] Carboplatin/weekly paclitaxel[2] Carboplatin/docetaxel[3,4] Carboplatin/gemcitabine[5] Carboplatin/gemcitabine/bevacizumab* (category 2B)[6] Carboplatin/liposomal doxorubicin[7] Cisplatin/gemcitabine[8] **Single-agent if platinum sensitive** Carboplatin[6] Cisplatin[6] **Single-agent non-platinum-based if platinum resistant** Docetaxel[9] Etoposide, oral[10] Gemcitabine[11,12] Liposomal doxorubicin[11,12] Paclitaxel, weekly[13] Topotecan[14,15]		Bevacizumab	
Other Potentially Active Agents	**Single agents**[16] Altretamine Capecitabine Cyclophosphamide Ifosfamide Irinotecan Melphalan Oxaliplatin Paclitaxel Paclitaxel, albumin bound (nab-paclitaxel) Pemetrexed Vinorelbine	Anastrozole Letrozole Leuprolide acetate Megestrol acetate Tamoxifen		Palliative localized radiation therapy

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

‡In general, the Panel would recommend combination regimens based on randomized trial data, especially in first relapses.

*In patients who have not previously received bevacizumab.

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

See References (OV-E 2 of 2)

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ACCEPTABLE RECURRENCE THERAPIES (2 of 2)

REFERENCES

[1]Parmar MK, Ledermann JA, Colombo N, et al. Paclitaxel plus platinum-based chemotherapy versus conventional platinum-based chemotherapy in women with relapsed ovarian cancer: the ICON4/AGO-OVAR-2.2 trial. Lancet 2003;361:2099-2106.
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[16]See Discussion for references.

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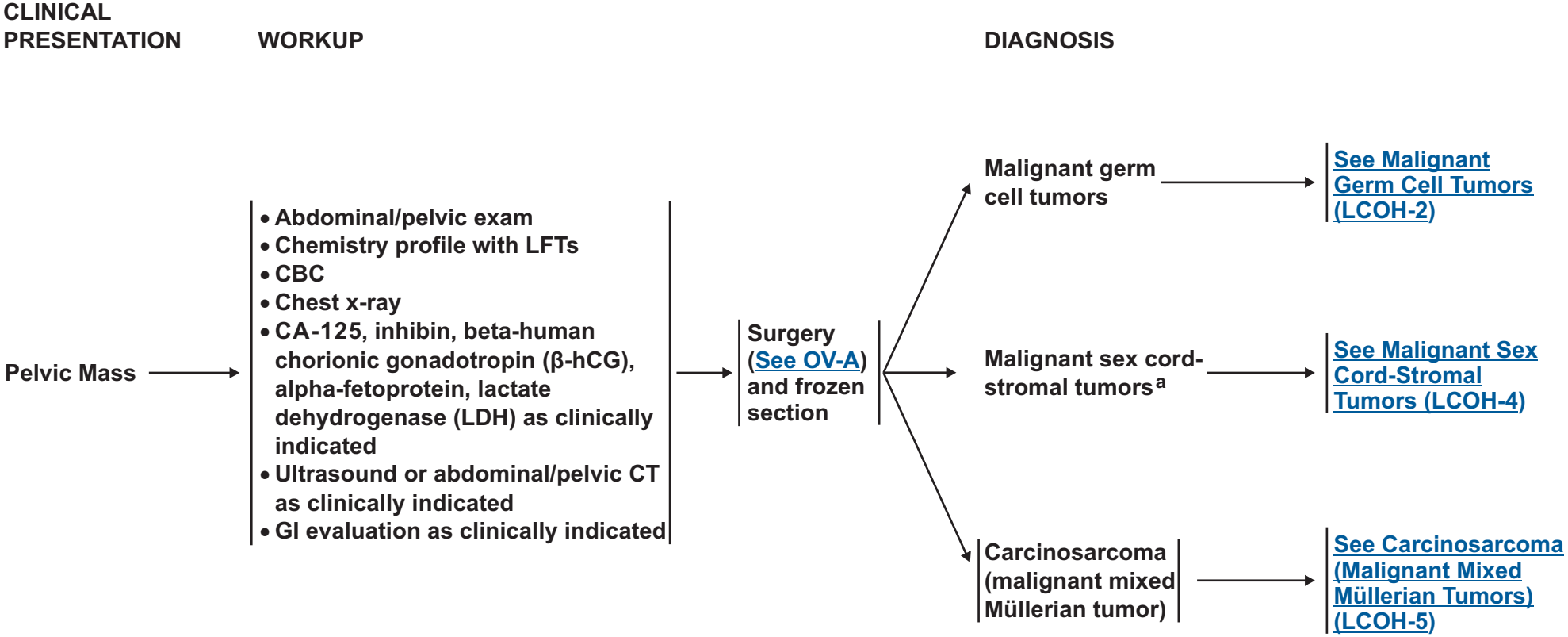

[a] See Sex Cord-Stromal Tumors - WHO Histologic Classification (LCOH-A).

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Malignant Germ Cell Tumors

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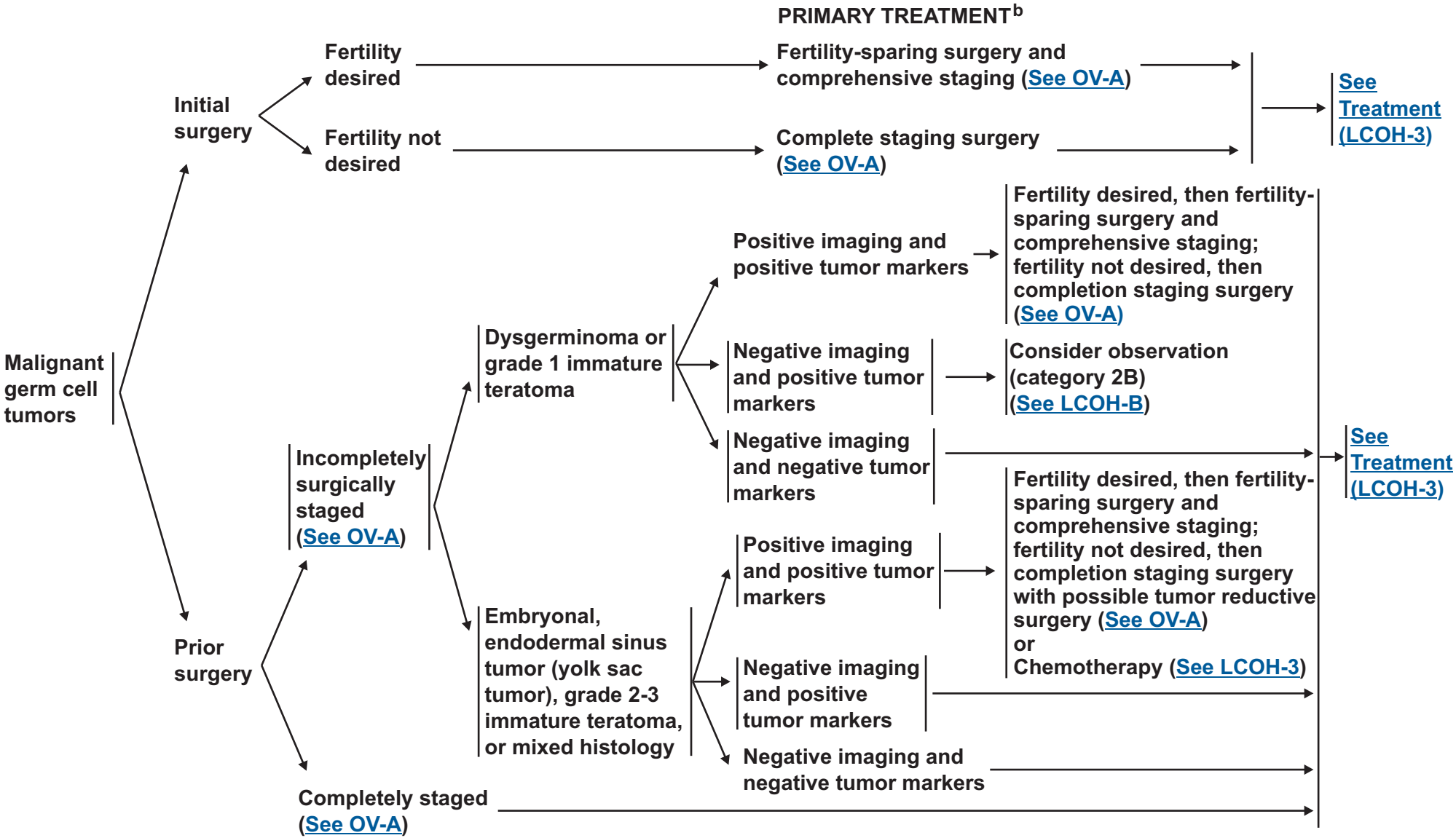
Discussion



[b] Standard recommendation includes a patient evaluation by a gynecologic oncologist.

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Malignant Germ Cell Tumors

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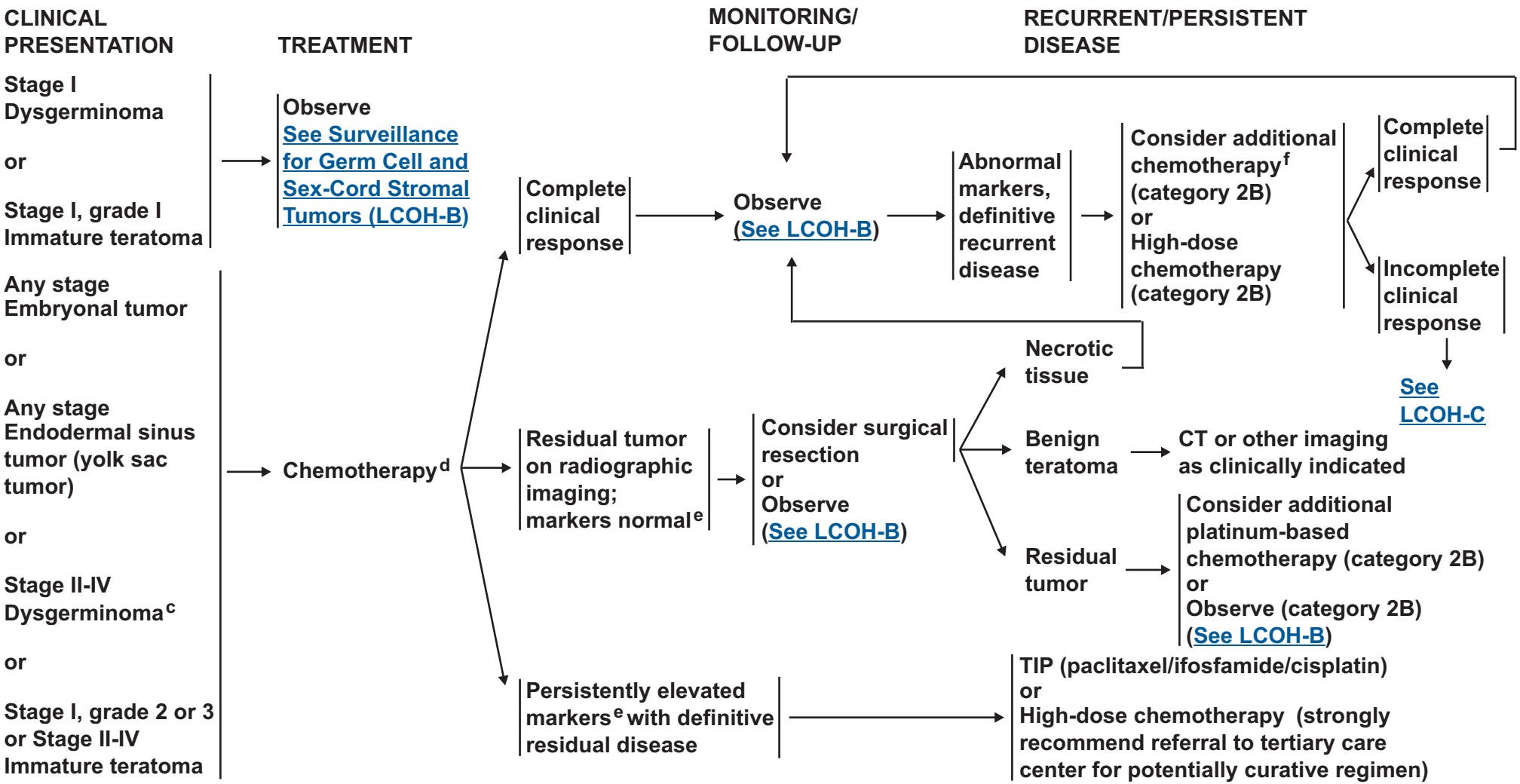
Ovarian Cancer TOC
Discussion



[c] For select patients with stage IB-III dysgerminoma for whom minimizing toxicity is critical, 3 courses of etoposide/carboplatin can be used (3 courses of carboplatin 400 mg/m^2 on day 1 plus etoposide 120 mg/m^2 on days 1, 2, and 3 every 4 weeks).

[d] BEP (bleomycin, 30 units per week; etoposide, 100 mg/m^2/d daily for days 1-5; cisplatin 20 mg/m^2/d daily for days 1-5) for 3-4 cycles (category 2B for 3 versus 4 cycles). Recommend pulmonary function tests if considering bleomycin.

[e] See LCOH-1 for markers.

[f] See Acceptable Recurrence Therapies (LCOH-C).

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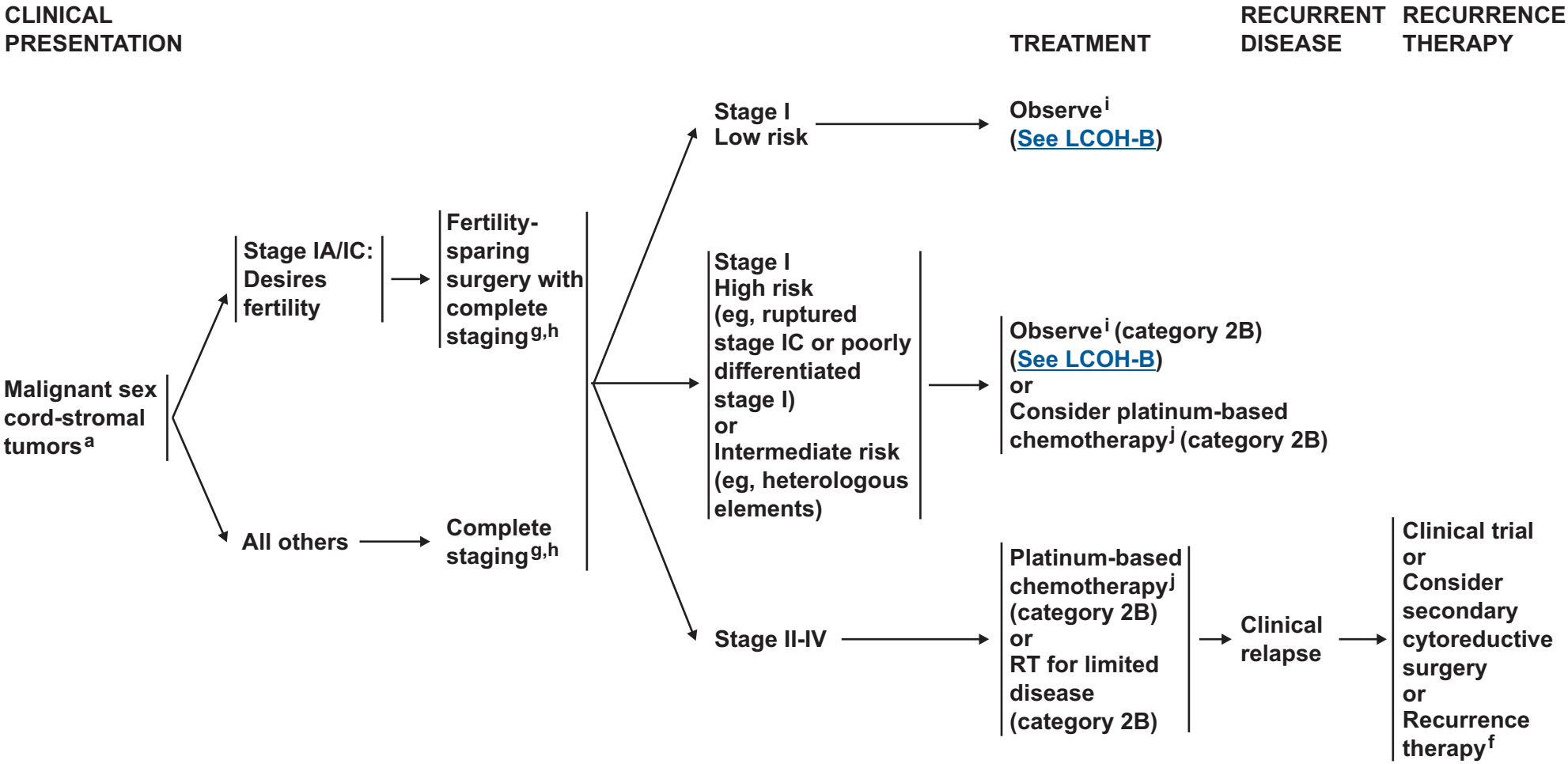
NCCN Guidelines Version 2.2013
Malignant Sex Cord-Stromal Tumors

NCCN Guidelines Index
Ovarian Cancer TOC
Discussion



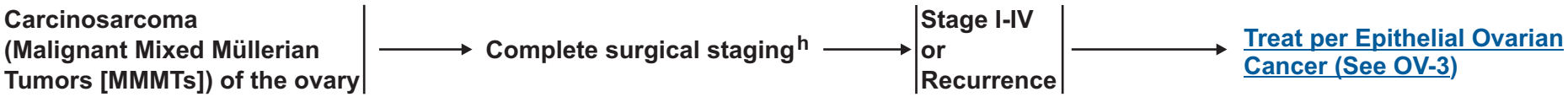
[a] See Sex Cord-Stromal Tumors - WHO Histologic Classification (LCOH-A).
[f] See Acceptable Recurrence Therapies (LCOH-C).
[g] Lymphadenectomy may be omitted.
[h] See Principles of Primary Surgery (OV-A).
[i] Inhibin levels can be followed if initially elevated for granulosa cell tumors (category 2B).
[j] Malignant germ cell regimens (See LCOH-3) or paclitaxel/carboplatin regimens are preferred.

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

NCCN Guidelines Version 2.2013
Carcinosarcoma (Malignant Mixed Müllerian Tumors)

CLINICAL PRESENTATION

TREATMENT



[h] See Principles of Primary Surgery (OV-A).

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

SEX CORD-STROMAL TUMORS - WHO HISTOLOGIC CLASSIFICATION[1]

- **Sex cord-stromal tumors are a heterogenous group of very rare tumors from benign to aggressive, and each histology has a range of often well differentiated to undifferentiated. Therefore, it should be determined whether a patient has a malignant or benign sex cord-stromal tumor.**
- **Treatment decisions and the decision whether to preserve fertility must be individualized based on the patient's specific tumor features.**

WHO Histologic Classification	Pathology
Granulosa cell tumors	
Adult	**Malignant**
Juvenile	**Malignant**
Thecoma	
Thecomas typical	**Benign**
Thecomas, luteinized	**Malignant potential**
Thecoma with increased mitotic figures	**Malignant potential**
Fibroma	
Cellular fibroma	**Malignant potential**
Cellular fibroma with increased mitotic figures	**Malignant potential**
Fibrosarcoma	**Malignant**
Stromal tumor with minor sex cord elements	**Benign**
Sclerosing stromal tumor	**Benign**
Signet ring stromal tumors	**Benign**
Unclassified	**Malignant potential**
Sertoli-Leydig cell tumors	
Well differentiated	**Malignant potential**
Intermediate differentiation	**Malignant**
Poorly differentiated	**Malignant**
Sertoli-Leydig tumors with heterologous elements	**Malignant**
Sertoli cell tumors	**Malignant potential**
Leydig cell tumors	**Benign**
Stromal-Leydig cell tumors	**Benign**
Sex cord tumors with annular tubules (SCTAT)	**Malignant**
Microscopic SCTAT associated with Peutz-Jeghers syndrome	**Benign**
Gynandroblastoma	**Malignant/Malignant potential**
Unclassified sex cord stromal tumors	**Malignant potential**
Steroid cell tumors	**Malignant**

[1]Adapted from Tavassoeli FA, Devilee P (Eds): WHO Classification of Tumours, Pathology and Genetics: Tumours of the Breast and Female Genital Organs. IARC, Lyon, 2003.

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

SURVEILLANCE FOR GERM CELL AND SEX CORD-STROMAL TUMORS[1]

	Years				
	<1	1-2	2-3	3-5	>5
Physical exam					
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
Serum tumor markers**					
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
Radiographic imaging*					
Germ cell tumors	Not indicated unless markers normal at initial presentation	Not indicated unless markers normal at initial presentation	Not indicated	Not indicated	Not 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
Recurrence suspected	CT scan and tumor markers**	CT scan and tumor markers**	CT scan and tumor markers**	CT scan and tumor markers**	CT scan and tumor markers**

*Chest x-ray, CT, MRI

**See LCOH-1 for markers.

[1]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.

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

ACCEPTABLE RECURRENCE THERAPIES

MALIGNANT GERM CELL TUMORS[1]

High-dose chemotherapy[1,2]

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 (paclitaxel, ifosfamide, cisplatin)

Radiation therapy

Supportive care only

MALIGNANT SEX CORD-STROMAL TUMORS[3]

Aromatase inhibitors (anastrozole, letrozole)

Bevacizumab may be considered for granulosa cell tumors

Leuprolide may be used as hormonal therapy for granulosa cell tumors

Docetaxel

Paclitaxel

Paclitaxel/ifosfamide

Paclitaxel/carboplatin

Tamoxifen

VAC

Radiation therapy

Supportive care only

[1] Patients with potentially curable recurrent germ cell disease should be referred to a tertiary care institution for potentially curative therapy.
[2] High-dose chemotherapy regimens vary among institutions.
[3] See Sex Cord-Stromal Tumors - WHO Histologic Classification (LCOH-A).

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

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
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.

Continued

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.

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
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.

Continued

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.

Discussion

NCCN Categories of Evidence and Consensus

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

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

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

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

All recommendations are category 2A unless otherwise noted.

Table of Contents

Overview

Ovarian neoplasms consist of several histopathological entities; treatment depends on the specific tumor type. Epithelial ovarian cancer comprises the majority of malignant ovarian neoplasms (about 90%);[1-3] however, other less common pathologic subtypes should be mentioned in guidelines describing treatment recommendations. These NCCN Guidelines discuss epithelial ovarian cancer (including borderline or low malignant potential) and, less common histopathologies, including malignant germ cell neoplasms, carcinosarcomas (malignant mixed Müllerian tumors of the ovary [MMMT]), and sex cord–stromal tumors. The guidelines also discuss Fallopian tube cancer and primary peritoneal cancer, which are less common neoplasms that are managed in a similar manner to epithelial ovarian cancer. However, the less common histologies of ovarian cancer are managed differently. These NCCN Guidelines also include sections on *Principles of Chemotherapy* (including *Acceptable Recurrence Therapies*), *Principles of Primary Surgery*, and *Management of Drug Reactions*. The *Updates* section in the algorithm briefly describes the new changes for 2013 (see the NCCN Guidelines for Ovarian Cancer).

Epithelial ovarian cancer is the leading cause of death from gynecologic cancer in the United States and the country's fifth most common cause of cancer mortality in women. In 2013, there will be an estimated 22,240 new diagnoses and an estimated 14,030 deaths from this neoplasm in the United States; less than 40% of women with ovarian cancer are cured.[4] The incidence of ovarian cancer increases with age and is most prevalent in the sixth and seventh decades of life.[3] The median age at the time of diagnosis is 63 years, and more than 70% of patients present with advanced disease.[5,6]

Epidemiologic studies have identified risk factors in the etiology of ovarian cancer.[3,7] A 30% to 60% decreased risk of cancer is associated with younger age at pregnancy and first birth (≤25 years), the use of oral contraceptives, and/or breast-feeding.[5] Conversely, nulliparity or older age (> 35 years) at pregnancy and first birth confers an increased risk of cancer. Recent data suggest that hormone therapy and pelvic inflammatory disease may increase the risk of ovarian cancer.[8-10] The risk of borderline ovarian cancer may be increased after ovarian stimulation for in vitro fertilization.[11,12] Obesity does not appear to be associated with the most aggressive types of ovarian cancer.[13]

Family history (primarily patients having 2 or more first-degree relatives with ovarian cancer)—including linkage with BRCA1 and BRCA2 genotypes or families affected by Lynch syndrome (hereditary nonpolyposis colorectal cancer [HNPCC] syndrome)—is associated with early-onset disease.[14-21] However, these patients account for only 5% of all women who have ovarian cancer.[5,22] In high-risk women (with either BRCA1 or BRCA2 mutations), oophorectomy is associated with a reduced risk of ovarian and Fallopian tube cancer; however, there is a residual risk for primary peritoneal cancer in these high-risk women after prophylactic salpingo-oophorectomy.[22-25] The risks of surgery include injury to the bowel, bladder, ureter, and vessels.[26] Recently, it has been suggested that the Fallopian tube may be the origin of some ovarian and primary peritoneal cancers.[27-42] Environmental factors have been investigated, but so far they have not been conclusively associated with the development of this neoplasm.

Screening

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

cancer patients 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.[43,44] 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 days/month).[43] Physicians evaluating women with this constellation of symptoms must be cognizant of the possibility that ovarian pathology may be causing these symptoms.[45] However, some evidence suggests that the screening test using these symptoms is not as sensitive or specific as necessary, especially in those with early-stage disease.[26,46,47]

An ongoing trial is assessing screening for ovarian cancer (UK Collaborative Trial of Ovarian Cancer Screening [UKCTOCS]) using multimodality screening with ultrasound and cancer antigen 125 (CA-125) versus either ultrasound alone or no screening.[48] Preliminary results suggest that multimodality screening is more effective at detecting early-stage cancer.[49] However, a large randomized trial in more than 78,000 women (the Prostate, Lung, Colorectal and Ovarian [PLCO] Cancer trial) in the United States found that screening with transvaginal ultrasonography and CA-125 did not decrease mortality from ovarian cancer.[50-52] 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.[53]

Randomized data do not yet support routine screening for ovarian cancer in the general population, and routine screening is not currently recommended by any professional society.[26,45,50,54-59] Some physicians follow women with high-risk factors (eg, those with BRCA mutations, those with a family history) using CA-125 monitoring and endovaginal ultrasound;[57] however, prospective validation of these tests remains elusive. An intriguing study suggests that ovarian cancer is associated with unique odors that can be detected.[60,61]

A recent screening trial assessed an algorithm that used age and longitudinal changes in CA-125 levels to determine whether women at average risk would develop ovarian cancer (Risk of Ovarian Cancer Algorithm [ROCA]); women deemed at risk were referred for transvaginal sonography (TVS).[62,63] However, until data from larger randomized controlled trials are published (eg, UKCTOCS), there is not enough evidence to support this screening approach for low-risk women.[55,56] Some feel that the ROCA algorithm may be useful for high-risk women (eg, those with BRCA mutations). The Society of Gynecologic Oncology (SGO) and the FDA have stated that the OVA1 test should not be used as a screening tool to detect ovarian cancer (https://www.sgo.org/newsroom/position-statements-2/ova1/). 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. Based on data documenting an increased survival, NCCN panel members recommend that all patients should undergo surgery by an experienced gynecologic oncologist (category 1).[45,64-66]

NCCN panel members believe that the OvaSure screening test should not be used to detect ovarian cancer.[67-70] The OvaSure test uses 6 biomarkers, including leptin, prolactin, osteopontin, insulin-like growth factor II, macrophage inhibitory factor, and CA-125.[71] Although human epididymis protein 4 (HE4) and CA-125 appear to be useful in detecting ovarian cancer,[72,73] recent 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.[74-76]

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–IV. Since 1997, no significant changes have been made in the TNM and FIGO (International Federation of Gynecology and Obstetrics) staging systems for ovarian cancer (see Table 1).[77] Pathologic grading continues to be an important prognostic factor and is used in the selection of therapy, primarily for early-stage disease. Grading is labeled as 1, 2, or 3. Except for those 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. Primary peritoneal adenocarcinoma is staged using the ovarian cancer staging system (see Table 1).[77] Fallopian tube carcinomas are also staged using the TNM and FIGO staging systems (see Table 2).[77]

Caveat

By definition, the NCCN Practice 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.

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.

Undiagnosed Pelvic Mass

The primary workup of 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 should include an ultrasound and/or abdominal/pelvic CT scan after an abdominal/pelvic examination and appropriate laboratory studies (see *Workup* in the NCCN Guidelines for Epithelial Ovarian Cancer).[43,78-84] Tumor markers (including CA-125, inhibin, alpha-fetoprotein [AFP], and beta–human chorionic gonadotropin [beta-HCG]) can be measured if clinically indicated.[85-87] Ultrasound is typically used for initial evaluation; however, CT is useful to assess for metastases.[79] PET/CT scan may be useful for indeterminate lesions.[88-90]

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.[91-93] Other cancers that should be ruled out include bowel, uterine, and pancreatic cancers or lymphoma;[94,95] benign ovarian and non-ovarian conditions also need to be ruled out (eg, serous cystadenoma).[96]

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.[97] The FDA has approved the use of HE4 and CA 125 for estimating the risk of 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.[98-100] 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. Although there is no direct evidence that chest imaging is necessary, panel members felt that it should be part of the overall evaluation of a patient before surgical staging. Additional diagnostic studies, such as gastrointestinal tract evaluation, are not routinely recommended, although they could prove useful in specific clinical situations.

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 undergone cytoreductive surgery and have undergone comprehensive staging procedures (ie, having met the standards for surgical staging of the Gynecologic Oncology Group [GOG]). However, in some instances, referral occurs after *incomplete* surgery and/or staging (eg, uterus and/or adnexa intact, omentum not removed, residual disease that is potentially resectable, surgical stage not completely documented). The components of surgical staging are listed in the algorithm (see *Principles of Primary 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.

Epithelial ovarian cancer has 4 main histologic subtypes (eg, serous, endometrioid, mucinous, clear cell); however, most patients (about 70%) have serous histology.[2,77,101-103] Primary treatment for these histologic subtypes does not differ; they are all treated using the recommendations for epithelial ovarian cancer (see the NCCN Guidelines for Epithelial Ovarian Cancer).[101] However, stage I clear cell carcinoma is treated using recommendations for stage I, grade 3 epithelial ovarian cancer. Pathology review at NCCN Member Institutions is recommended in all patients. The College of American Pathologists (CAP) *Protocol for Examining Specimens from Patients with Carcinoma of the Ovary* is a useful tool for pathology reports (http://www.cap.org/apps/docs/committees/cancer/cancer_protocols/2012/Ovary_12protocol.pdf).

Primary Treatment

Primary treatment for presumed ovarian cancer consists of appropriate surgical staging and cytoreduction, followed in most (but not all) patients by systemic chemotherapy. Initial surgery should be a comprehensive staging laparotomy, including a total abdominal hysterectomy (TAH) and bilateral salpingo-oophorectomy (BSO).[104] Based on published improved outcomes, it is recommended (category 1) that a gynecologic oncologist perform the primary surgery.[64-66] For a young patient who wishes to maintain fertility, a unilateral salpingo-oophorectomy (USO) (preserving the uterus and contralateral ovary) may be adequate for select stage I tumors (stage 1A and 1C, but not stage 1B) and/or low-risk tumors (ie, early-stage, low-grade invasive tumors; low malignant potential [LMP] lesions).[105-110]

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.[111]

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.[84] Minimally invasive techniques may be considered for prophylactic salpingo-oophorectomy.

Cytoreductive surgery is the initial treatment recommendation for patients with clinical stage II, III, or IV disease (see *Primary Treatment* in the NCCN Guidelines for Epithelial Ovarian Cancer).[66,107,111-114] Although cytoreductive surgery is the standard of care, this recommendation is based on retrospective data (and thus is not a category 1 recommendation).[115] In general, the following 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 and to achieve maximal cytoreduction to less than 1-cm residual disease or resection of all visible disease in appropriate circumstances.[116-118] Surgical cytoreduction is optimal if the residual tumor nodules are less than 1 cm in maximum diameter or thickness;[104,107,115,119] extensive resection of upper abdominal ovarian metastases is recommended for patients who can tolerate this surgery.[113]

A maximal effort should be made to remove all gross disease. 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 bilateral salpingo-oophorectomy 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. All involved omentum should be removed. Suspicious and/or enlarged nodes should be resected, if possible.[120,121] Those patients with tumor nodules, outside the pelvis, of 2 cm or less (presumed stage IIIB) should have bilateral pelvic and para-aortic lymph node dissection (see *Principles of Primary Surgery* in the NCCN Guidelines for Epithelial Ovarian Cancer). For young patients who will abruptly enter menopause after surgery, various supportive care measures are available to decrease hot flashes and other symptoms.[122-124]

In patients with advanced ovarian cancer who have had complete debulking, data indicate that overall survival is increased in those who receive systematic lymphadenectomy.[125] Patients with low-volume residual disease after surgical cytoreduction for invasive epithelial ovarian or peritoneal cancer are potential candidates for intraperitoneal (IP) therapy. In these patients, consideration should be given to placement of an IP catheter with initial surgery. Procedures that may be considered for optimal surgical cytoreduction (in all stages) include: radical pelvic dissection, bowel resection, diaphragm or other peritoneal surface stripping, splenectomy, partial hepatectomy, cholecystectomy, partial gastrectomy or cystectomy, ureteroneocystostomy, distal pancreatectomy, or appendectomy.[126]

The therapeutic benefit of neoadjuvant chemotherapy followed by interval cytoreduction remains controversial (see next paragraph).[115,127-132] It may be considered (category 1) for patients with bulky stage III–IV disease who are not surgical candidates; however, a gynecologic oncologist should make this assessment before neoadjuvant chemotherapy is administered.[133-138] Before initiation of chemotherapy, the pathologic diagnosis should be confirmed (by FNA, biopsy, or paracentesis) in this group of patients.

A randomized phase III trial assessed neoadjuvant chemotherapy with interval debulking surgery versus upfront primary debulking surgery in patients with extensive-stage IIIC/IV ovarian, primary peritoneal, and

Fallopian tube carcinoma (sponsored by the EORTC-GCG and the NCIC-CTG).[133] 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 and overall survivals were inferior to those reported more recently in randomized studies in the United States of patients undergoing primary debulking surgery followed by postoperative intravenous chemotherapy for advanced ovarian cancer (overall survival averages 50 months).[138,139] Although the median overall survival in the International trial is 20 months lower than that reported in US 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 higher risk patients 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 not have been optimal (ie, patients may have had had >1 cm of residual disease).[115]

In the opinion of the subcommittee for the NCCN Guidelines for Ovarian Cancer, more data will be necessary prior to recommending neoadjuvant chemotherapy in potentially resectable ovarian cancer patients, and upfront debulking surgery remains the treatment of choice in the United States.[140] Note that the authors of the International trial believe that upfront debulking surgery should remain the standard of care for stage IIIB or earlier-stage patients but that neoadjuvant chemotherapy with interval debulking surgery is an option for patients with extensive-stage IIIC/IV disease.[133]

Incompletely Staged Patients

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–IV disease who have residual disease that is considered unresectable, consider completion surgery after 3 to 6 cycles of chemotherapy. Depending on the surgical results, patients would then receive postoperative chemotherapy. Tumor reductive surgery is recommended for all patients with stage II–IV diseases with suspected potentially resectable residual disease.

Chemotherapy

Most patients with epithelial ovarian cancer receive postoperative systemic chemotherapy. Observation, however, is recommended for patients with stage IA or IB, grade 1 tumors, because survival is greater than 90% for this group with surgical treatment alone.[141-143] If observation (without the addition of chemotherapy) is considered for stage IA or IB, grade 2 tumors, a surgical staging procedure is recommended for all patients. Recommendations regarding initial primary chemotherapy/primary adjuvant therapy include intravenous with [or without] IP options (see *Primary Chemotherapy/Adjuvant Chemotherapy Regimens for Stage II–IV* in the NCCN Guidelines for Epithelial Ovarian Cancer).[144] All of the regimens (including the combined intravenous/IP chemotherapy) may be used for epithelial ovarian, primary peritoneal, and Fallopian tube cancers. *Principles of Chemotherapy* are also described in the algorithm (see the NCCN Guidelines for Ovarian Cancer). The intravenous/IP chemotherapy regimen (IP chemotherapy) is recommended for stage III patients with optimally debulked (<1 cm residual) disease based on randomized controlled trials (category 1) (http://www.cancer.gov/clinicaltrials/conducting/developments/ipchemo-digest/Page1); stage II patients may also receive IP chemotherapy,

although no randomized evidence for stage II has been published.[139,145,146] 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 for whom this does not apply (eg, those with poor performance status [PS]), the combination of intravenous paclitaxel plus carboplatin (category 1) may be used (see *Primary Chemotherapy/Primary Adjuvant Therapy* in the NCCN Guidelines for Epithelial Ovarian Cancer).[64,147] Intravenous docetaxel plus carboplatin (category 1)[148] or paclitaxel plus cisplatin (category 1) are options for alternative regimens.[149] The docetaxel/carboplatin regimen may be considered for patients who are at high risk for neuropathy (eg, patients with diabetes). Recommendations for the number of cycles of treatment vary with the stage of the disease. For patients with advanced-stage disease (stages II–IV), 6 to 8 cycles of chemotherapy are recommended, whereas 3 to 6 cycles are recommended for earlier-stage disease.[150] Some clinicians feel there is a potential survival advantage for 6 cycles of chemotherapy in patients with serous cytology.[151]

The recommended intravenous regimens accepted by a consensus of the NCCN Panel include: (1) paclitaxel, 175 mg/m^2 over 3-hour intravenous infusion, followed by carboplatin, dosed at an area under the curve (AUC) of 5-7.5 intravenous over 1 hour on day 1, given every 3 weeks for 6 cycles (category 1);[147,152] (2) docetaxel, 60-75 mg/m^2 1-hour intravenous infusion followed by carboplatin, dosed at AUC of 5-6 intravenous over 1 hour on day 1, every 3 weeks for 6 cycles (category 1);[148] and 3) dose-dense paclitaxel, 80 mg/m^2 intravenous over 1 hour on days 1, 8, and 15 plus carboplatin AUC 6 intravenous over 1 hour on day 1, every 3 weeks for 6 cycles (category 1).[153] Note that carboplatin dosing may be revised based on changes in serum creatinine methodology (http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm228974.htm).

The recommended IP chemotherapy regimen is paclitaxel, 135 mg/m^2 continuous intravenous infusion over 3 or 24 hours on day 1; cisplatin 75-100 mg/m^2 IP on day 2 after intravenous paclitaxel; paclitaxel, 60 mg/m^2 IP on day 8; repeat every 3 weeks times 6 cycles (category 1).[139] The published randomized trial for this IP/intravenous regimen used intravenous continuous infusion of paclitaxel over 24 hours. A 3-hour infusion of paclitaxel has not been proven to be equivalent to a 24-hour infusion, although a 3-hour infusion has been reported to be more convenient, easier to tolerate, and less toxic.[154] Note that these IP regimens include intravenous regimens, so that systemic disease can also be treated.

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.[148,152,153] The IP paclitaxel/cisplatin regimen is associated with leukopenia, infection, fatigue, renal toxicity, abdominal discomfort, and neurotoxicity.[155,156] In the initial studies, only 42% of women were able to complete all 6 treatment cycles (of the IP regimen) because of toxicity; however, with more experience, this percentage has improved in the major cancer centers.[157] Using a lower IP cisplatin dose of 75 mg/m^2 or splitting the dose may help to decrease toxicity.[154,157,158] This approach is currently under investigation in an ongoing Gynecologic Oncology Group clinical trial.

Patients considered for the IP cisplatin and IP/intravenous paclitaxel regimen should have normal renal function before starting, a medically appropriate PS based on the future toxicities of the IP/intravenous regimen, and no previous evidence of medical problems that could significantly worsen during chemotherapy (eg, preexisting neuropathy) (see *Principles of Chemotherapy* in the NCCN Guidelines for Epithelial Ovarian Cancer). Reasons for discontinuing the IP regimen included catheter complications, nausea/vomiting/dehydration, and abdominal pain.[159] Women unable to complete IP therapy should receive intravenous therapy. Techniques to decrease catheter complications include catheter choice and timing of insertion.[145,160] Expert nursing care may help to decrease complications.[144] Giving intravenous hydration before and after IP chemotherapy is a useful strategy to prevent renal toxicity.[157] 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.[159,161-164]

Patients with poor PS, comorbidities, stage IV disease, or advanced age may not tolerate the IP regimen. The IP regimen published by Armstrong et al. has, however, documented the longest median survival (65.6 months) that has been described to date in optimally debulked stage III patients.[139,165] A recent study reported overall survival of 110 months in patients with stage III ovarian cancer and no residual disease who received the IP regimen.[165] Patients with primary peritoneal cancer, Fallopian tube cancer, or MMMT can also be considered for IP chemotherapy.[146,160] 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. A recent study reported that women with aberrant BRCA1 expression had increased survival when treated with intraperitoneal cisplatin/paclitaxel.[166]

Dose-dense weekly paclitaxel with carboplatin has been shown to increase both PFS (28 vs. 17 months, $P = .0015$) and 3-year overall survival (72% vs. 65%, $P = .03$) when compared with standard therapy given every 3 weeks (ie, intravenous carboplatin/paclitaxel) in women with advanced epithelial ovarian cancer.[153] After 5 years, overall survival was 58.6% versus 51% ($P = .044$).[167] However, the dose-dense regimen is more toxic, and patients discontinued dose-dense paclitaxel therapy more often than did those receiving standard therapy. Future studies will compare the effect of weekly paclitaxel on the overall survival benefit with that of using IP chemotherapy.[168] A recent phase II study reported that dose-dense paclitaxel/carboplatin regimen yielded overall survival of 31.5 months, which is inferior to the median survival with an IP regimen (61 months).[165,169]

Anti-Angiogenesis Agents

A recent phase III randomized trial (GOG 0218) assessed bevacizumab combined with carboplatin/paclitaxel in the upfront setting compared to carboplatin/paclitaxel alone. The median PFS was significantly increased (14.1 vs. 10.3 months, $P < .001$) in patients receiving prolonged bevacizumab (upfront and as maintenance therapy) when compared with chemotherapy alone.[170,171] However, PFS was not significantly increased in patients who did not receive maintenance bevacizumab (upfront with placebo maintenance) versus chemotherapy alone (ie, bevacizumab/carboplatin/paclitaxel vs. carboplatin/paclitaxel). Quality of life was not improved in GOG 0218.[172]

Another phase III randomized trial (ICON7) also assessed bevacizumab/carboplatin/paclitaxel in the upfront setting. The trial design of ICON7 differs from GOG 0218 (see next paragraph).[173,174]

Although the PFS data from ICON7 confirm the findings of GOG 0218, the benefits appear to be modest (2.4-month increase in PFS) and mature survival data have not been reported.[172,173]

Panel members had a major disagreement about recommending the addition of bevacizumab to up-front chemotherapy with carboplatin/paclitaxel or using bevacizumab as maintenance therapy, which is reflected in the category 3 recommendations for these regimens (see *Primary Chemotherapy/Adjuvant Chemotherapy Regimens for Stage II–IV* in the NCCN Guidelines for Epithelial Ovarian Cancer).[175] Many panel members believe that bevacizumab should not be added to up-front chemotherapy in patients with ovarian cancer, because data from these 2 phase III randomized trials (ie, GOG-0218 and ICON7) have not shown a statistically significant increase in overall survival and/or improved quality of life.[171,172,174,176-178]

The NCCN Panel recommends (category 3) 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/Adjuvant Chemotherapy Regimens for Stage II–IV* in the NCCN Guidelines for Epithelial Ovarian Cancer).[171,174] The only GOG-0218 regimen that is recommended (category 3) is the prolonged bevacizumab regimen (upfront with carboplatin/paclitaxel followed by maintenance bevacizumab).[171] This topic is discussed in greater detail in a recent JNCCN Guidelines Insight on Ovarian Cancer.[175] 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.[179]

Number of Chemotherapy Cycles and Agents

Panel members had an extensive discussion about the number of cycles of chemotherapy that should be recommended for patients with advanced-stage disease. There is no evidence confirming that more than 6 to 8 cycles of combination chemotherapy are required for initial chemotherapy.[180] Patients can also have 3 to 6 cycles of chemotherapy followed by completion surgery and then postoperative chemotherapy (see *Primary Treatment* in the NCCN Guidelines for Epithelial Ovarian Cancer).[130]

The role of maintenance (or postremission) therapy in patients who achieve a complete clinical remission after 6-8 cycles of chemotherapy is an option based on the results from GOG 178. This trial randomly assigned patients to 3 versus 12 months of further paclitaxel (135–175 mg/m^2 every 4 weeks for 12 cycles) after initial chemotherapy.[181] The published study treated patients at 175 mg/m^2; the plan was to decrease the dose to 135 mg/m^2, 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. However, postremission paclitaxel chemotherapy is a category 2B recommendation because it is associated with toxicity and it only increased PFS. Another study suggests that postremission paclitaxel is not beneficial.[182] Note that a category 2B recommendation is based on lower level evidence (eg, phase II randomized trials) and a majority vote (>50% but <85%) from panel members who agree that the intervention is appropriate.

Drug Reactions

Virtually all drugs have the potential to cause drug reactions, either during or after the infusion.[183-185] 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.[186] 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.[187,188] Infusion reactions are more common with paclitaxel,[189] but mild reactions can also occur with liposomal doxorubicin.[190] Allergic reactions (ie, true drug allergies) are more common with platinum agents (ie, carboplatin, cisplatin, oxaliplatin).[189,191]

Management of drug reactions is discussed in the NCCN Guidelines for Ovarian Cancer. Algorithms are provided for management of mild, severe, and life-threatening reactions.[192] These drug reaction algorithms are also useful for patients with other gynecologic cancers (eg, cervical and uterine cancers) who are receiving carboplatin, cisplatin, docetaxel, liposomal doxorubicin, oxaliplatin, or paclitaxel. Typically, the infusion should be stopped for patients having a reaction; further management is provided in the algorithms. Standard resuscitation procedures (ie, Advanced Cardiac Life Support [ACLS]) should be followed for patients with acute cardiopulmonary arrest (http://acls-algorithms.com/2010-acls-guidelines).[193]

For patients with allergic reactions, various desensitization protocols have been published and should be followed. To maximize safety; patients may be desensitized in the intensive care unit.[185] Almost all patients can be desensitized (about 90%).[185] 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.[183] Patients must be desensitized with each infusion if they previously had a drug reaction.[194-196] Data suggest that an extended infusion schedule and use of premedication may decrease the number of hypersensitivity reactions to carboplatin.[197] Skin testing is associated with false-negative results.[198,199]

Radiation Therapy

Whole abdominal radiation therapy (WART) in patients with low-bulk stage III disease is no longer included as an option for initial treatment or consolidation treatment in ovarian cancer. Because WART is rarely used 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 *Acceptable Recurrence Therapies* in the NCCN Guidelines for Epithelial Ovarian Cancer).[200-204] Patients who receive radiation are prone to vaginal stenosis, which can impair sexual function. 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 (http://www2.mskcc.org/patient_education/_assets/downloads-english/571.pdf).

Recommendations After Primary Treatment

After initial treatment (eg, 6 cycles of chemotherapy), patients should undergo a clinical re-evaluation. Patients who have no evidence of progression of cancer (ie, complete clinical remission) after initial treatment can undergo observation with follow-up (see next section on *Follow-Up Recommendations*) (also see *Monitoring/Follow-up* in the NCCN Guidelines for Epithelial Ovarian Cancer); other options are discussed below. Patients with partial remission or progression during initial treatment should be treated with second-line approaches (see section on *Recurrent Disease* in this Discussion) (see *Therapy for Persistent Disease or Recurrence* in the NCCN Guidelines for Epithelial Ovarian Cancer).

Options for maintenance treatment—for the management of advanced-stage (stages II–IV) patients who are in complete clinical remission after their initial therapeutic regimen—include observation alone, a clinical trial, or additional chemotherapy[181] (paclitaxel, category 2B), preferably in a controlled clinical trial (see *Secondary Adjuvant Therapy* in the NCCN Guidelines for Epithelial Ovarian Cancer). If used, the paclitaxel regimen is 135 to 175 mg/m^2 every 4 weeks for 12 cycles. Note that complete clinical remission is defined as no objective evidence of disease (ie, negative physical examination, negative CA-125 levels, negative CT with <1 cm lymph nodes).

Follow-up Recommendations

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 a complete response, the standard recommendation is observation with follow-up. Recommendations for monitoring are described in the algorithm (see *Monitoring/Follow-up* in the NCCN Guidelines for Epithelial Ovarian Cancer). Chest/abdominal/pelvic CT, MRI, PET scans (category 2B for PET), PET-CT, and chest imaging may be ordered if clinically necessary.[205-208] Patients should be educated about the signs and symptoms suggestive of recurrence (eg, pelvic pain, bloating, early satiety, obstruction, weight loss, fatigue). Patients who chose fertility-sparing surgery should be monitored by ultrasound examinations if necessary; completion surgery should be considered (category 2B) after they finish childbearing.

If the CA-125 level was initially elevated, the measurement of a CA-125 level or other tumor markers at each follow-up evaluation is recommended. A multi-institutional European trial assessed the use of CA-125 for monitoring for ovarian cancer recurrence after primary therapy.[209-211] The data suggest that treating recurrences early (based on detectable CA-125 levels in asymptomatic patients) is not associated with an increase in survival and is associated with a decrease in quality of life.[212] Recent recommendations from the SGO state that use of CA-125 levels for surveillance is optional.[207] The NCCN Panel concurs with the SGO opinion which states that the European trial has limitations and that patients should discuss the pros and cons of CA-125 monitoring with their physicians (https://www.sgo.org/newsroom/position-statements-2/use-of-ca125-for-monitoring-ovarian-cancer/). In addition, patients seem reluctant to give up monitoring.[213] Others have discussed this study in greater detail.[214-216]

Management of an Increasing CA-125 Level

The management of patients in a clinical complete remission who (during routine monitoring and follow-up) are found to have an increasing CA-125 level 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 is somewhat controversial. Patients who have never received chemotherapy (ie, naïve to chemotherapy) should be managed as 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).

After the documentation of an increased CA-125 level (ie, biochemical relapse), the median time for a clinical relapse is 2 to 6 months. However, data suggest that immediate treatment for biochemical relapse is not beneficial; therefore, immediate treatment is a category 2B recommendation in the NCCN Guidelines.[209] After biochemical relapse, recommended options include enrollment on a clinical trial or delaying treatment (ie, observation) until clinical symptoms arise (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,[217] these agents are frequently administered to patients who have only a rising CA-125 level[218] as evidence of tumor progression.[219] Tamoxifen, other hormonal agents, or other recurrence therapy are acceptable recommendations for this clinical situation (category 2B).

Recurrent Disease

The prognosis is poor either 1) for patients who progress after 2 consecutive chemotherapy regimens without ever sustaining a clinical benefit (refractory);[220] or 2) for those whose disease recurs in less than 6 months (platinum resistant). Note that progression is typically defined using traditional RECIST (Response Evaluation Criteria in Solid Tumor) criteria (ie, a 20% increase in tumor diameter).[221] Panel members emphasized the importance of clinical trials to identify agents active in this group of patients. Because these patients were resistant to their 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.[222,223] 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 platinum-resistant patients or for those with stages II–IV disease who have a partial response include recurrence therapy (see *Acceptable Recurrence Therapies* in the NCCN Guidelines for Epithelial Ovarian Cancer),[224] clinical trial, or observation (category 2B for observation). Patients who relapse 6 months or more after initial chemotherapy are termed *platinum sensitive*.[225,226] Combination platinum-based chemotherapy is preferred for first recurrence (category 1) in platinum-sensitive patients (see *Therapy for Persistent Disease or Recurrence* in the NCCN Guidelines for Epithelial Ovarian Cancer).[226] Possible regimens are discussed in the following section (see *Acceptable Recurrence Modalities*).

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 Chemotherapy* 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 Primary Surgery* in the NCCN Guidelines for Epithelial Ovarian Cancer) (http://emedicine.medscape.com/article/270646-overview#aw2aab6b4).[227-232] The SGO has a position statement on *Principles of Palliative Care* (https://www.sgo.org/newsroom/position-statements-2/delivery-of-palliative-care-services/).

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).[115,233,234] A recent meta-analysis suggests that survival increases for patients with recurrent disease who have complete cytoreduction.[116] 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 should be considered.[235]

Acceptable Recurrence Modalities

The NCCN Panel felt that no single therapeutic agent should be currently recommended as the treatment of choice for recurrent ovarian carcinoma. However, some agents are preferred based on expert opinion (primarily for reasons of decreased toxicity and/or marginally increased effectiveness) (see *Acceptable Recurrence Therapies* in the NCCN Guidelines for Epithelial Ovarian Cancer).[144] A meta-analysis of 13 randomized studies in recurrent ovarian cancer has been published.[225]

The consensus of the NCCN Panel for the treatment of recurrent disease is shown in the algorithm (see *Acceptable Recurrence Therapies* in the NCCN Guidelines for Epithelial Ovarian Cancer). Platinum-based combination chemotherapy is recommended (category 1) for platinum-sensitive recurrence (see *Therapy for Persistent Disease or Recurrence* in the NCCN Guidelines for Epithelial Ovarian Cancer).[225,226] Preferred combinations for platinum-sensitive recurrent disease include carboplatin/paclitaxel (category 1),[226] carboplatin/weekly paclitaxel,[153] carboplatin/docetaxel,[236,237] carboplatin/gemcitabine (which has been shown to improve progression-free survival),[226,238,239] carboplatin/liposomal doxorubicin (also has been shown to improve progression-free survival) [240] or cisplatin/gemcitabine.[238]

For platinum-resistant disease, the preferred agent is a single non-platinum–based agent (ie, docetaxel, oral etoposide, gemcitabine, liposomal doxorubicin, weekly paclitaxel, topotecan); sequential therapy using single agents is typically used.[241] The response rate of the following agents appears to be similar: topotecan, 20%;[242] gemcitabine, 19%;[243,244] vinorelbine, 20%;[245,246] liposomal doxorubicin, 26%;[243,244,247] and oral etoposide, 27%.[248] In platinum-resistant patients, the response rate for docetaxel is 22% and for weekly paclitaxel is 21%.[222,249,250] For platinum-sensitive disease in patients who cannot tolerate combination therapy, the preferred single agent is carboplatin or cisplatin.[238,239] Recent reports suggest that weekly topotecan is less toxic than the daily regimen.[251,252]

Other potentially active agents include altretamine, capecitabine, cyclophosphamide, ifosfamide, irinotecan, melphalan, oxaliplatin, paclitaxel, nanoparticle albumin-bound paclitaxel (ie, nab-paclitaxel), pemetrexed, and vinorelbine (see *Acceptable Recurrence Therapies* in the NCCN Guidelines for Epithelial Ovarian Cancer). Nab-paclitaxel has an overall response rate of 64%.[253] Altretamine has a 14% response rate[254] and ifosfamide has a 12% response rate,[255] although less information regarding their use in paclitaxel-refractory patients is available. In platinum-resistant patients, the response rate for pemetrexed is 21%.[222,249,250] Bevacizumab is also active (21%) in both platinum-sensitive and platinum-resistant patients,[172,256-260] although it may cause hypertension, arterial thrombosis, or intestinal perforation.

Several trials are assessing combination therapy with bevacizumab for recurrent ovarian cancer (ie, OCEANS, AURELIA). [261-263] A phase III randomized trial (OCEANS) assessed carboplatin/gemcitabine with and without bevacizumab in patients with platinum-sensitive recurrent ovarian cancer who had not previously received bevacizumab. In the OCEANS trial, PFS was increased in patients receiving the chemotherapy/bevacizumab arm when compared with chemotherapy alone (12.4 vs. 8.4 months, $P<.0001$).[262] Combination therapy with bevacizumab is a category 2B recommendation because there is less consensus among the NCCN Panel (>50% but < 85%) that this intervention is appropriate. Panel members feel other combination regimens are more beneficial and effective than those with bevacizumab. In addition, the carboplatin/gemcitabine/bevacizumab regimen is only recommended in patients who have not previously received bevacizumab. Based on 2 phase II trials, panel members feel

that bevacizumab alone is useful in patients who have recurrent disease (especially those with ascites), which is reflected in the category 2A recommendation for single-agent bevacizumab.[241,258,259,264]

Taxanes (including docetaxel and paclitaxel) and platinum compounds (including cisplatin, carboplatin, and oxaliplatin) can be used in appropriate patients.[181,226,265] Capecitabine has activity in patients resistant to platinum and taxanes.[266] Other alkylating agents, including cyclophosphamide and melphalan, can also be used. In addition, for patients who cannot tolerate or have not responded to cytotoxic regimens, hormonal therapy with tamoxifen or other agents (including anastrozole, letrozole, leuprolide acetate, or megestrol acetate) continues to be a viable therapeutic option.[267-272]

Recent data suggest that olaparib (AZD2281), which is a PARP (poly ADP-ribose polymerase) inhibitor, is active in select patients (those with BRCA-1 and BRCA-2 mutations have higher response rates than BRCA-negative patients) with chemotherapy-refractory ovarian cancer, especially those with platinum-sensitive disease.[241,273-277] Patients who are resistant or refractory to platinum have a lower response rate to olaparib.[273,275,276] A phase II study found that olaparib was similar to pegylated liposomal doxorubicin. Note that olaparib is not FDA approved for this indication and is only available in a clinical trial. Localized RT can also provide effective palliation when radiation ports are tailored to specific symptomatic disease sites.[200,201]

Chemotherapy/resistance assays and/or other biomarker assays are being used in some NCCN Member Institutions to aid in selecting chemotherapy in situations where there are multiple equivalent chemotherapy options available; however, the current level of evidence (category 3) is not sufficient to supplant standard of care chemotherapy.[278,279] Thus, the NCCN Panel felt that in vitro chemosensitivity testing to choose a chemotherapy regimen for recurrent disease situations should not be recommended (category 3), owing to the lack of demonstrable efficacy for such an approach. The ASCO also does not recommend use of chemotherapy sensitivity and resistance assays, unless in a clinical trial setting.[280]

However, regardless of which regimen is selected initially, reevaluation should follow after 2 to 4 cycles of chemotherapy (depending on the agent) to determine if patients benefited from chemotherapy. Patients who primarily progress on 2 consecutive chemotherapy regimens without evidence of clinical benefit may not benefit from additional therapy.[220] Decisions to offer supportive care, additional therapy, or clinical trials should be made on a highly individual basis.

Borderline Epithelial Ovarian Cancer (Low Malignant Potential)

Diagnosis

Borderline epithelial ovarian cancer (also known as ovarian cancer of low malignant potential [LMP], borderline ovarian cancer) is a primary epithelial ovarian lesion with cytological characteristics suggesting malignancy but without frank invasion and with a clinically indolent course and good prognosis.[281] Five-year survival exceeds 80%.[282] In contrast to patients with frankly invasive ovarian carcinoma, women with borderline disease tend to be younger and are often diagnosed with stage I disease.[283,284]

The characteristic pathologic hallmark of typical epithelial ovarian cancer is the identification of peritoneal implants, which microscopically and/or macroscopically invade the peritoneum. Borderline epithelial ovarian cancer has the visual appearance of peritoneal carcinomatosis; however, microscopic evaluation fails to reveal evidence of frank invasion by the tumor nodules, although rarely invasive implants (which

continue to be consistent with the diagnosis of LMP lesions) can be identified microscopically by the pathologist.

Some investigators feel that the appearance of invasive implants on the peritoneal surfaces in patients having ovarian cancer of LMP portends a less favorable prognosis; therefore, the same treatments used for epithelial ovarian cancer (ie, postoperative chemotherapy) can be considered (category 2B) for these patients (see *Primary Treatment* in the NCCN Guidelines for Borderline Epithelial Ovarian Cancer).[283-285] The benefit of postoperative chemotherapy has not been demonstrated for patients who have no microscopically demonstrable invasive implants; therefore, observation is recommended for these patients.[286]

Treatment

Treatment guidelines for borderline epithelial ovarian cancer depend on the histological and clinical characteristics, the age of the patient,[284] and the stage of the disease at the time of diagnosis. 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 ovarian cancer of LMP. For the 2013 update, panel members are now less likely to recommend aggressive surgery; observation is one of several possible approaches. Patients with an LMP lesion who desire to maintain their fertility may undergo surgery limited to a unilateral salpingo-oophorectomy (USO) (preserving the uterus, contralateral ovary, and contralateral Fallopian tube) at the time of comprehensive staging.[106,107,287] If the patient does not desire fertility-sparing surgery, observation or standard ovarian cancer debulking surgery is recommended. However, data do not show increased survival with lymphadenectomy and omentectomy for LMP, although upstaging does occur.[288,289]

For patients with known LMP disease 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 Ovarian Cancer). Patients who want to preserve their fertility should have comprehensive fertility-sparing surgical staging (if not previously done).

Follow-up

Treatment recommendations after comprehensive staging depend on the presence or absence of invasive implants. The initial therapeutic approach for patients having invasive implants may include observation or, alternatively, consideration can be given to treating patients according to the guidelines for epithelial ovarian cancer (category 2B for postoperative chemotherapy) (see *Primary Treatment* in the NCCN Guidelines for Borderline Epithelial Ovarian Cancer).[290] Patients with no invasive implants should be observed and monitored (see *Monitoring/Follow-Up* in the NCCN Guidelines for Borderline Epithelial Ovarian Cancer).[283,291]

Patients who chose fertility-sparing surgery should be monitored by ultrasound examinations if necessary. After child-bearing is completed, completion surgery should be considered (category 2B). At the time of clinical relapse, a surgical evaluation and debulking are recommended if appropriate. Patients who have invasive disease at this time may be treated using the guidelines for epithelial ovarian cancer (category 2B) (see *Primary Chemotherapy/Primary Adjuvant Therapy* in the NCCN Guidelines for Borderline Epithelial Ovarian Cancer); those without invasive implants should be observed.

Less Common Ovarian Histopathologies (LCOH)

Overview

Less common histopathologies of ovarian cancer include: malignant germ cell neoplasms, carcinosarcoma (MMMT), and malignant sex cord-stromal tumors. These tumors account for approximately 5% of all ovarian cancers and differ from epithelial ovarian cancer in their biology and recommended approaches to treatment. In contrast to epithelial ovarian cancer, many patients with these tumors present at an early stage and tumors may be confined to one ovary; thus, some of these patients are candidates for fertility-sparing surgery. The diagnosis of LCOH is often not made until after surgery.

Recommended Workup

The NCCN Guidelines recognize that 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 Less Common Ovarian Histopathologies). Tumor markers (including CA-125, inhibin, AFP, and beta-HCG) can be measured if clinically indicated.

Patients desiring to potentially maintain fertility should have an intraoperative frozen section evaluation. Fertility-sparing surgery may be performed (if technically feasible) if the frozen section results are positive for malignant germ cell tumor, ovarian cancer of LMP, or clinical stage I epithelial ovarian or stromal tumors.[106,107,110,292-295] Patients who do not desire fertility preservation; those who have a clinical stage II, III, or IV epithelial ovarian cancer or stromal tumor; or those with carcinosarcoma (MMMT) should undergo comprehensive surgical staging as per the ovarian cancer guidelines (see *Principles of Primary Surgery* in the NCCN Guidelines for Ovarian Cancer).

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

Malignant Germ Cell Tumors

These tumors include dysgerminomas, immature teratomas, embryonal tumors, and endodermal sinus (yolk sac) tumors; they mainly occur in younger women who are often diagnosed with stage I disease.[296,297] The recommended workup (see *Recommended Workup* as previously discussed) for malignant germ cell tumors may include pulmonary function studies if bleomycin is being considered.[85,298] Women younger than 35 years with a pelvic mass should have AFP levels measured to assess for germ cell tumors.[85-87] Malignant germ cell tumors have an excellent prognosis. After appropriate treatment, 5-year survival is more than 85%.[296,299,300]

Completion surgery with comprehensive staging is recommended as initial surgery for patients who do not desire fertility preservation. The staging system for ovarian and primary peritoneal cancer is also used for malignant germ cell tumors (see Table 1). After comprehensive surgical staging, observation is recommended for patients with stage I dysgerminoma or immature teratoma.[301] If these patients have had

incomplete surgical staging, recommended options depend on the type of tumor, the results of imaging and tumor marker testing (eg, AFP and beta-HCG), and whether the patient desires fertility preservation (see *Malignant Germ Cell Tumors* in the NCCN Guidelines for Less Common Ovarian Histopathologies).

Fertility-sparing surgery should be considered for those desiring fertility preservation, regardless of stage (see *Primary Treatment* for *Malignant Germ Cell Tumors* in the NCCN Guidelines for Less Common Ovarian Histopathologies).[110,297,300,302,303] 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, surveillance is the recommended option for patients with stage I dysgerminoma or stage I, grade I immature teratoma based on European and pediatric reports.[297] For patients with stage II to IV malignant germ cell tumors, postoperative chemotherapy is recommended. Patients should receive postoperative chemotherapy for 3–4 cycles with bleomycin/etoposide/platinum (BEP) (category 2B for 3 vs. 4 cycles) if they have (1) embryonal or endodermal sinus tumors; (2) stages III–V dysgerminoma; or (3) stage I, grade 2–3 or stage II to IV immature teratoma.[298,304-306] If considering the use of bleomycin, pulmonary function tests are recommended.[298,299] In select patients with stage IB–III dysgerminoma for whom minimizing toxicity is critical, 3 courses of etoposide/carboplatin can be used (carboplatin 400 mg/m^2 [AUC =~5–6] on day 1 plus etoposide 120 mg/m^2 on days 1–3 every 4 weeks for 3 courses).[307] Dose reductions or delays are not recommended even in the setting of neutropenia.

Patients achieving a complete clinical response after chemotherapy should be observed clinically every 2–4 months with AFP and beta-HCG levels (if initially elevated) for 2 years. For those with abnormal markers and definitive recurrent disease, options (category 2B) include 1) high-dose chemotherapy; or 2) consider additional chemotherapy (see *Acceptable Recurrence Therapies* in the NCCN Guidelines for Less Common Ovarian Histopathologies). Referral of these patients to a tertiary care center for potentially curative therapy is strongly recommended. The NCCN Panel added surveillance recommendations for germ cell tumors for the 2013 update, which are based on the SGO recommendations.[207]

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 is also an option. Further options depend on which findings are present: residual tumor, 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 having persistently elevated AFP and/or beta-HCG after first-line chemotherapy, recommendations include TIP (paclitaxel, ifosfamide, cisplatin)[308] or high-dose chemotherapy with stem cell support. Referral to a tertiary care center for potentially curative treatment is strongly recommended.[309] Observation is an option (category 2B) for patients with residual malignancy after surgical resection of residual masses; this is an area of continued study and controversy.[297] Others may recommend further chemotherapy (category 2B). There are small series but no major trials in adult patients. Clinical judgment should be used regarding the frequency of imaging.[310]

Patients with recurrent or residual disease after multiple chemotherapeutic regimens for whom no curative options are considered possible may be treated with a recurrence modality (see *Acceptable Recurrence Therapies* for *Malignant Germ Cell Tumors* in

the NCCN Guidelines for Less Common Ovarian Histopathologies), including TIP, VAC (vincristine, dactinomycin, cyclophosphamide), VeIP (vinblastine, ifosfamide, cisplatin), VIP (etoposide, ifosfamide, cisplatin), cisplatin/etoposide, docetaxel/carboplatin, paclitaxel/carboplatin, paclitaxel/gemcitabine, paclitaxel/ifosfamide, docetaxel, paclitaxel, high-dose chemotherapy, RT, or supportive care only.[309,311-315] Combination chemotherapy is not recommended for patients with recurrent or residual disease who have no curative options. These recurrence regimens (see *Acceptable Recurrence Therapies* for *Malignant Germ Cell Tumors* in the NCCN Guidelines for Less Common Ovarian Histopathologies) 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 stromal tumors are rare and include granulosa cell tumors (most common), granulosa-theca tumors, and Sertoli-Leydig cell tumors; they are typically associated with a good prognosis.[316] Most patients with granulosa tumors present with early-stage disease.[317] It is important to determine whether the sex cord–stromal tumor is benign or malignant (see *Sex Cord Stromal Tumors—WHO Histologic Classification* in the NCCN Guidelines for Less Common Ovarian Histopathologies).[318] The staging system for ovarian and primary peritoneal cancer is also used for sex cord–stromal tumors (see Table 1).

Patients with stage IA or IC sex cord–stromal tumors desiring to preserve their fertility should be treated with fertility-sparing surgery with complete staging.[317,319,320] Complete staging is also recommended for all other patients; however, lymphadenectomy may be omitted.[321] Patients who chose fertility-sparing surgery should be monitored by ultrasound examinations if necessary; they should be considered for completion surgery (category 2B) after finishing childbearing.

For patients with high-risk stage I tumors (tumor rupture, stage 1C, poorly differentiated tumor, tumor size >10–15 cm[322]), recommendations (all are category 2B) include observation or consideration of platinum-based chemotherapy.[323] Those with surgical findings of low-risk stage I tumor (ie, without high-risk features)) should be observed. 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–IV tumors, recommended options (all are category 2B) include RT for limited disease or platinum-based chemotherapy (BEP or paclitaxel/carboplatin regimens are preferred).[324,325]

The NCCN Panel added surveillance recommendations for sex cord-stromal tumors for the 2013 update, which are based on the SGO recommendations.[207] Prolonged surveillance is recommended for granulosa cell tumors, because they can recur years later (eg, 30 years).[302,316,326] For patients with stage II–IV tumors who subsequently have a clinical relapse, options include a clinical trial or recurrence therapy (see *Acceptable Recurrence Therapies* for *Malignant Sex Cord–Stromal Tumors* in the NCCN Guidelines for Less Common Ovarian Histopathologies).[316,326,327] Note that bevacizumab or leuprolide may be considered for patients with recurrent granulosa cell tumors.[327,328] Secondary cytoreductive surgery may also be considered.

Carcinosarcoma (Malignant Mixed Müllerian Tumors)

MMMT are rare tumors with a poor prognosis.[329,330] Most pathologists now consider MMMT to be a variant of poor risk, poorly differentiated epithelial ovarian cancer (metaplastic carcinoma). Patients with MMMT are not candidates for fertility-sparing surgery. The staging system for

ovarian and primary peritoneal cancer is also used for MMMT (see Table 1).[329]

Optimal surgical debulking is recommended for patients with MMMT (see *Principles of Primary Surgery* in the NCCN Guidelines for Epithelial Ovarian Cancer).[329,331] After complete surgical staging, patients with stage I–IV carcinosarcoma (MMMT) at the time of surgery should have postoperative chemotherapy. Patients with stage I–IV MMMT or recurrence are treated using the same chemotherapy regimens that are recommended for epithelial ovarian cancer (see *Primary Chemotherapy/Primary Adjuvant Therapy* in the NCCN Guidelines for Epithelial Ovarian Cancer).[332-336] For example, the IP chemotherapy regimen described for ovarian cancer can be used for select patients with MMMT.

Recommended Readings

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