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Epithelial Ovarian Cancer

Clinical Practice Guidelines in Oncology

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Ovarian neoplasms consist of several histopathologic entities, and treatment depends on the specific tumor type. Epithelial ovarian cancer comprises most malignant ovarian neoplasms (~ 80%)[1]; however, other less-common pathologic subtypes must be considered in treatment guidelines. The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Ovarian Cancer 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

NCCN Clinical Practice Guidelines in Oncology for Epithelial Ovarian Cancer

Key Words

NCCN Clinical Practice Guidelines, NCCN Guidelines, treatment guidelines, ovarian cancer, staging, surgery, epithelial carcinoma, gynecologic malignancy, chemotherapy, chemosensitivity assay, minimally invasive surgery, in vitro chemosensitivity testing, laparoscopy *(JNCCN* 2011;9:82–113)

NCCN Categories of Evidence and Consensus

Category 1: The recommendation is based on high-level evidence (e.g., randomized controlled trials) and there is uniform NCCN consensus.

Category 2A: The recommendation is based on lower-level evidence and there is uniform NCCN consensus.

Category 2B: The recommendation is based on lower-level evidence and there is nonuniform NCCN consensus (but no major disagreement).

Category 3: The recommendation is based on any level of evidence but reflects major disagreement.

All recommendations are category 2A unless otherwise noted.

The full NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Ovarian Cancer are not printed in this issue of *JNCCN*, but can be accessed online at www.NCCN.org.

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

Please Note

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™) are a statement of consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult the NCCN Guidelines™ is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network® (NCCN®) makes no representation or warranties of any kind regarding their content, use, or application and disclaims any responsibility for their applications or use in any way.

Disclosures for the NCCN Guidelines Panel for Ovarian Cancer

At the beginning of each NCCN Guidelines panel meeting, panel members disclosed any financial support they have received from industry. Through 2008, this information was published in an aggregate statement in *JNCCN* and online. Furthering NCCN's commitment to public transparency, this disclosure process has now been expanded by listing all potential conflicts of interest respective to each individual expert panel member.

Individual disclosures for the NCCN Guidelines for Ovarian Cancer panel members can be found on page 113. (The most recent version of these guidelines and accompanying disclosures, including levels of compensation, are available on the NCCN Web site at www.NCCN.org.)

These guidelines are also available on the Internet. For the latest update, please visit www.NCCN.org.

fallopian tube and primary peritoneal cancers, which are less-common neoplasms that are managed similarly to epithelial ovarian cancer. However, the less-common histologies of ovarian cancer are managed differently. Information on the less-common ovarian histopathologies are not published in this issue of *JNCCN*, but can be found online at www.NCCN.org.

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 2010, an estimated 21,900 new diagnoses and 13,900 deaths will occur from this neoplasm in the United States; fewer than 40% of women with ovarian cancer are cured.[2,3] The incidence of ovarian cancer increases with age and is most prevalent in the eighth decade of life, with a rate of 57 per 100,000 women. The median age at diagnosis is 63 years, and 70% of patients present with advanced disease.[4]

Epidemiologic studies have identified risk factors for ovarian cancer. 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, or breast-feeding.[4] Conversely, nulliparity or older age at first birth (> 35 years) confers an increased risk of cancer. Recent data suggest that hormone therapy may increase the risk of ovarian cancer.[5]

Family history (primarily patients with ≥ 2 first-degree relatives with ovarian cancer), including linkage with *BRCA1* and *BRCA2* genotypes or families affected by hereditary nonpolyposis colorectal

Text continues on p. 99

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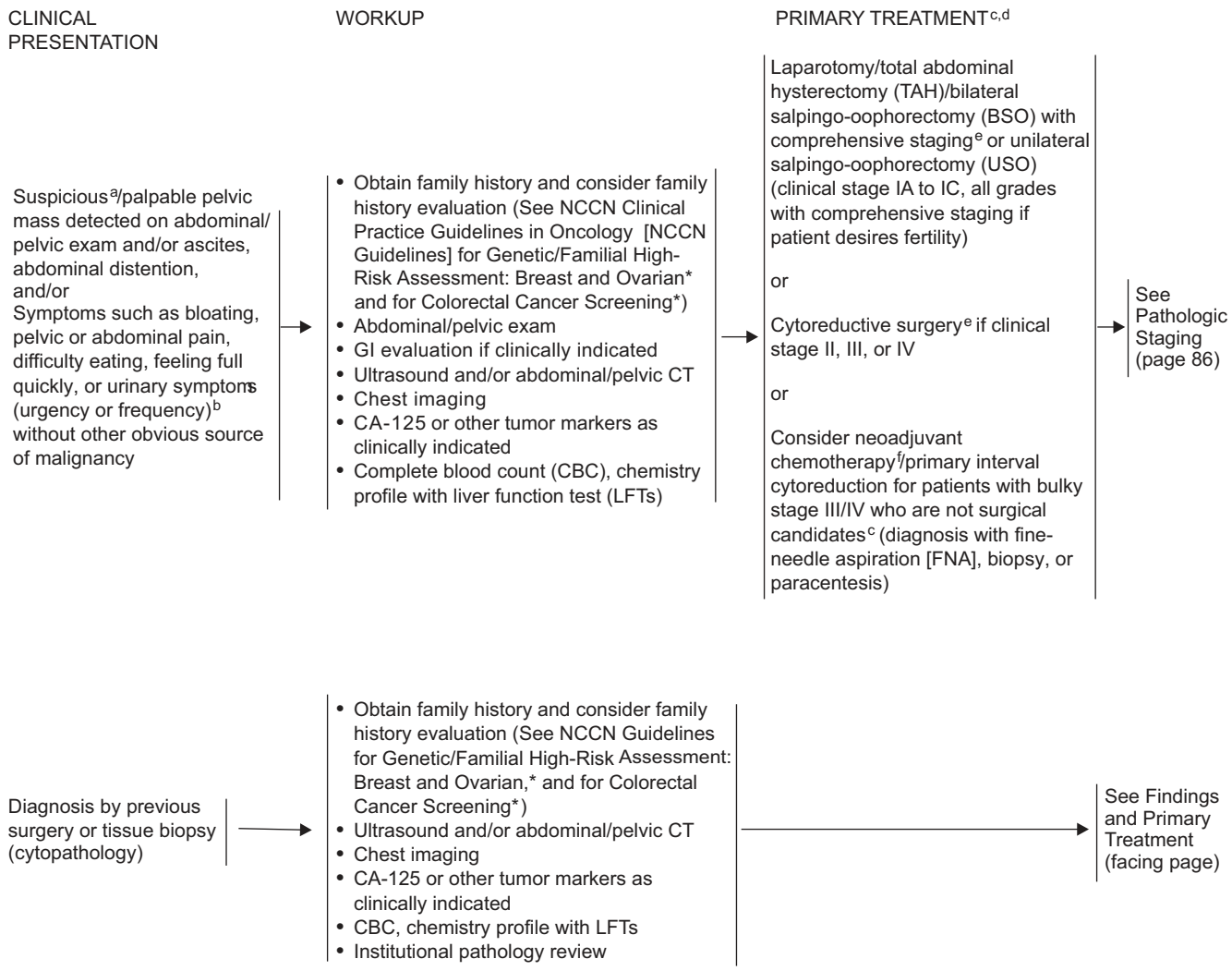
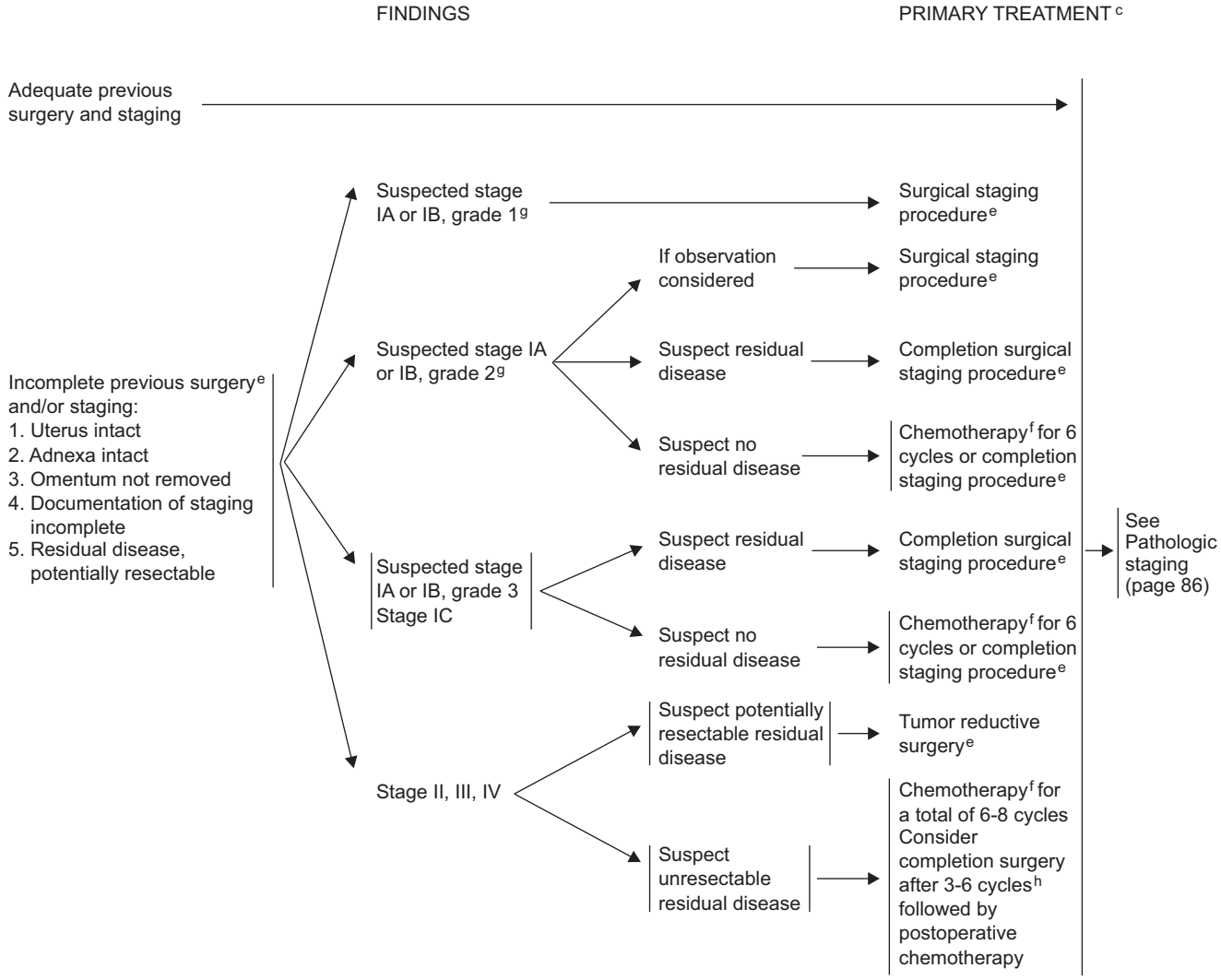


†Epithelial ovarian cancer/fallopian tube cancer/primary peritoneal cancer
*To view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org.

[a] Im SS, Gordon AN, Buttin BM, et al. Validation of referral guidelines for women with pelvic masses. Obstet Gynecol 2005;105:35-41. See also the Discussion.
[b] Goff BA, Mandel L, Drescher CW, et al. Development of an ovarian cancer symptom index: possibilities for earlier detection. Cancer 2007;109:221-227.
[c] Standard recommendation includes a patient evaluation by a gynecologic oncologist. Published data show that primary assessment and debulking by a gynecologic oncologist result in a survival advantage. Patients being evaluated for neoadjuvant surgery should be seen by a fellowship-trained gynecologist oncologist before being considered nonsurgical candidates.
[d] All women undergoing surgery for ovarian cancer should be counseled about the clinical benefit associated with combined intravenous (IV) and intraperitoneal (IP) chemotherapy administration before surgery (http://www.cancer.gov/clinicaltrials/developments/IPchemo-digest/page1/print).
[e] See Principles of Primary Surgery (pages 92 and 93).
[f] See Principles of Chemotherapy (page 94) and Management of Drug Reactions (pages 95 and 96).

DIAGNOSIS BY PREVIOUS SURGERY



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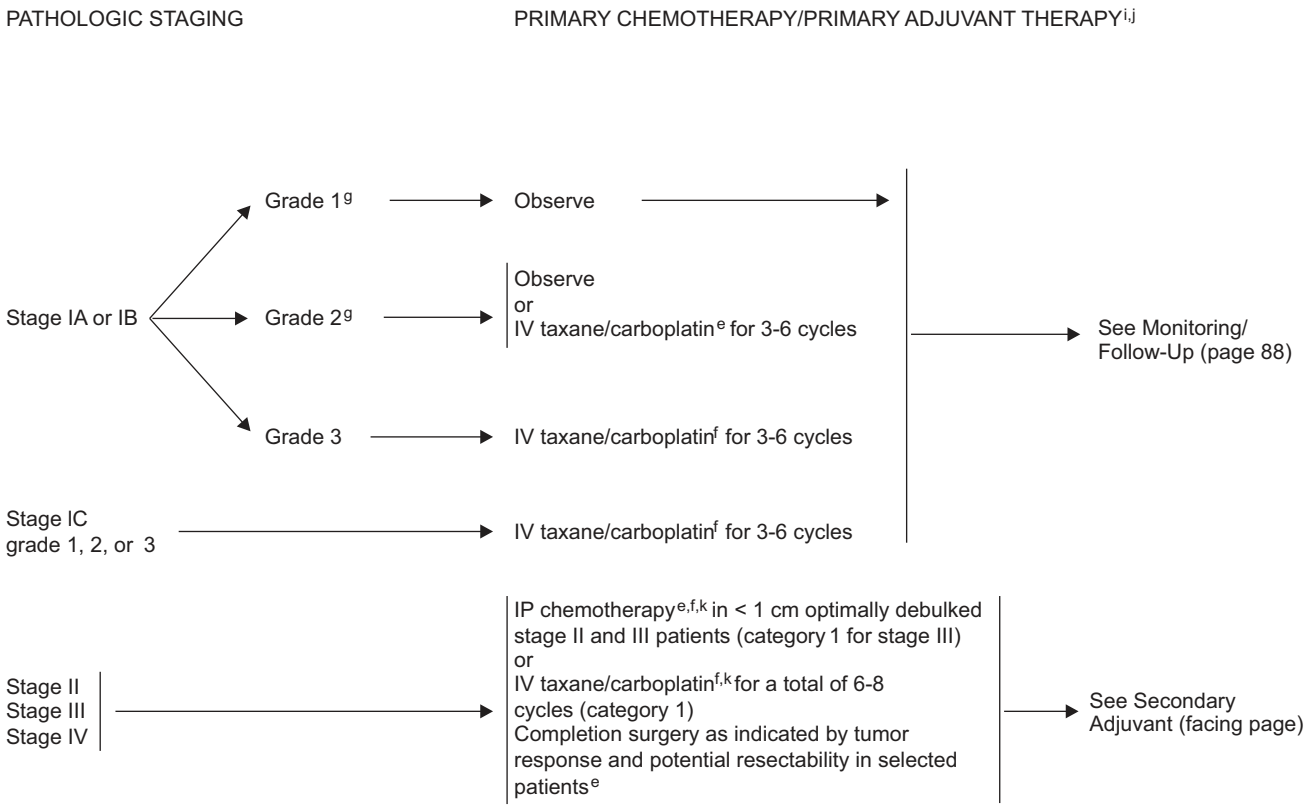
[e] See Principles of Primary Surgery (pages 92 and 93).
[f] See Principles of Chemotherapy (page 94) and Management of Drug Reactions (pages 95 and 96).
[g] Clear-cell pathology is grade 3.
[h] Based on clinical judgement of gynecologic oncologist, surgery may be performed after 6 cycles.



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[e] See Principles of Primary Surgery (pages 92 and 93).

[f] See Principles of Chemotherapy (page 94) and Management of Drug Reactions (pages 95 and 96).

[g] Clear-cell pathology is grade 3.

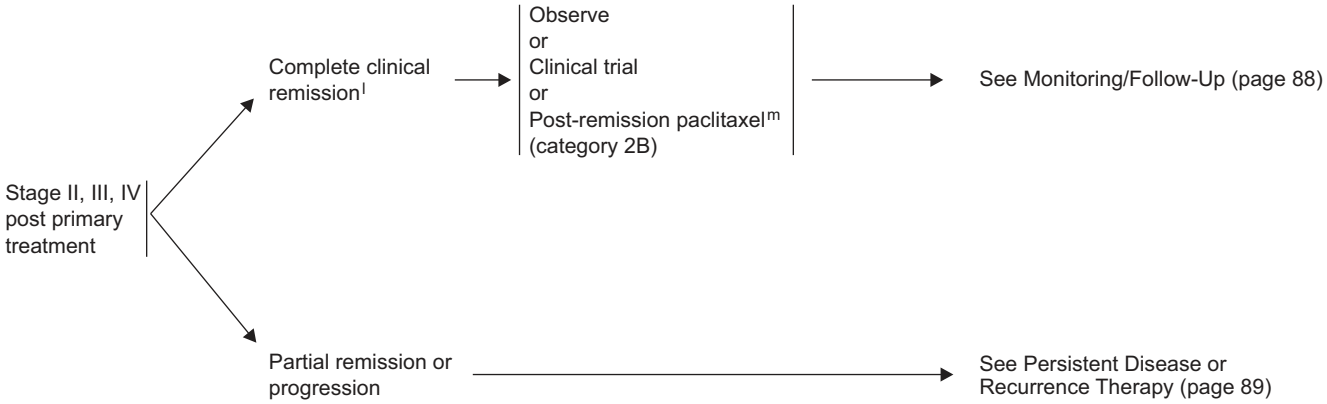
[i] Patients undergoing primary chemotherapy will be monitored as follows:
1. Pelvic exams at least every 2-3 cycles
2. Interim CBC with platelets as indicated
3. Chemistry profiles if indicated
4. CA-125 levels or other tumor markers as clinically indicated before each cycle of chemotherapy

[j] The NCCN Ovarian Cancer Panel recognizes that data for first-line and maintenance bevacizumab are becoming available and encourages participation in clinical trials.

[k] Regimens (see Discussion for references):
1. Paclitaxel, 135 mg/m^2, IV continuous infusion over 24 h on day 1; cisplatin, 75-100 mg/m^2, IP on day 2 after IV paclitaxel; paclitaxel, 60 mg/m^2, IP on day 8 (maximum body surface area 2.0 m^2). Repeat every 3 wk x 6 cycles (category 1).
2. Paclitaxel, 175 mg/m^2, IV over 3 h followed by carboplatin, AUC 5-7.5, IV over 1 h on day 1. Repeat every 3 wk x 6 cycles (category 1).
3. Docetaxel, 60-75 mg/m^2, IV over 1 h followed by carboplatin, AUC 5-6, IV over 1 h on day 1. Repeat every 3 wk x 6 cycles (category 1).
4. Dose-dense paclitaxel, 80 mg/m^2, IV over 1 h on days 1, 8, and 15, and carboplatin, AUC 6, IV over 1 h on day 1. Repeat every3 wk x 6 cycles. (category 1)

STAGE II, III, IV
POST PRIMARY TREATMENT

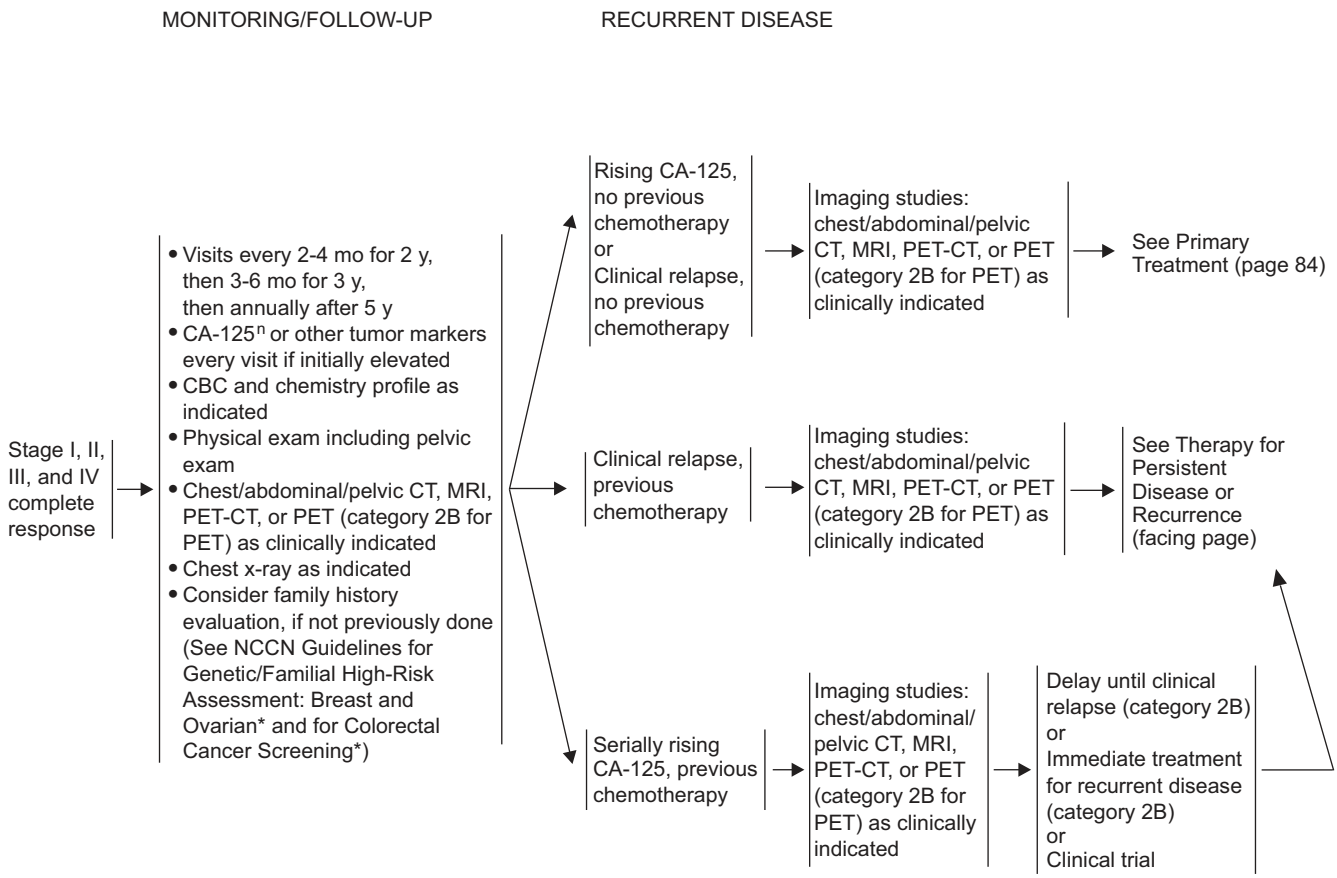
SECONDARY ADJUVANT THERAPY



†Epithelial ovarian cancer/fallopian tube cancer/primary peritoneal cancer

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

STAGE I-IV COMPLETE RESPONSE



†Epithelial ovarian cancer/fallopian tube cancer/primary peritoneal cancer

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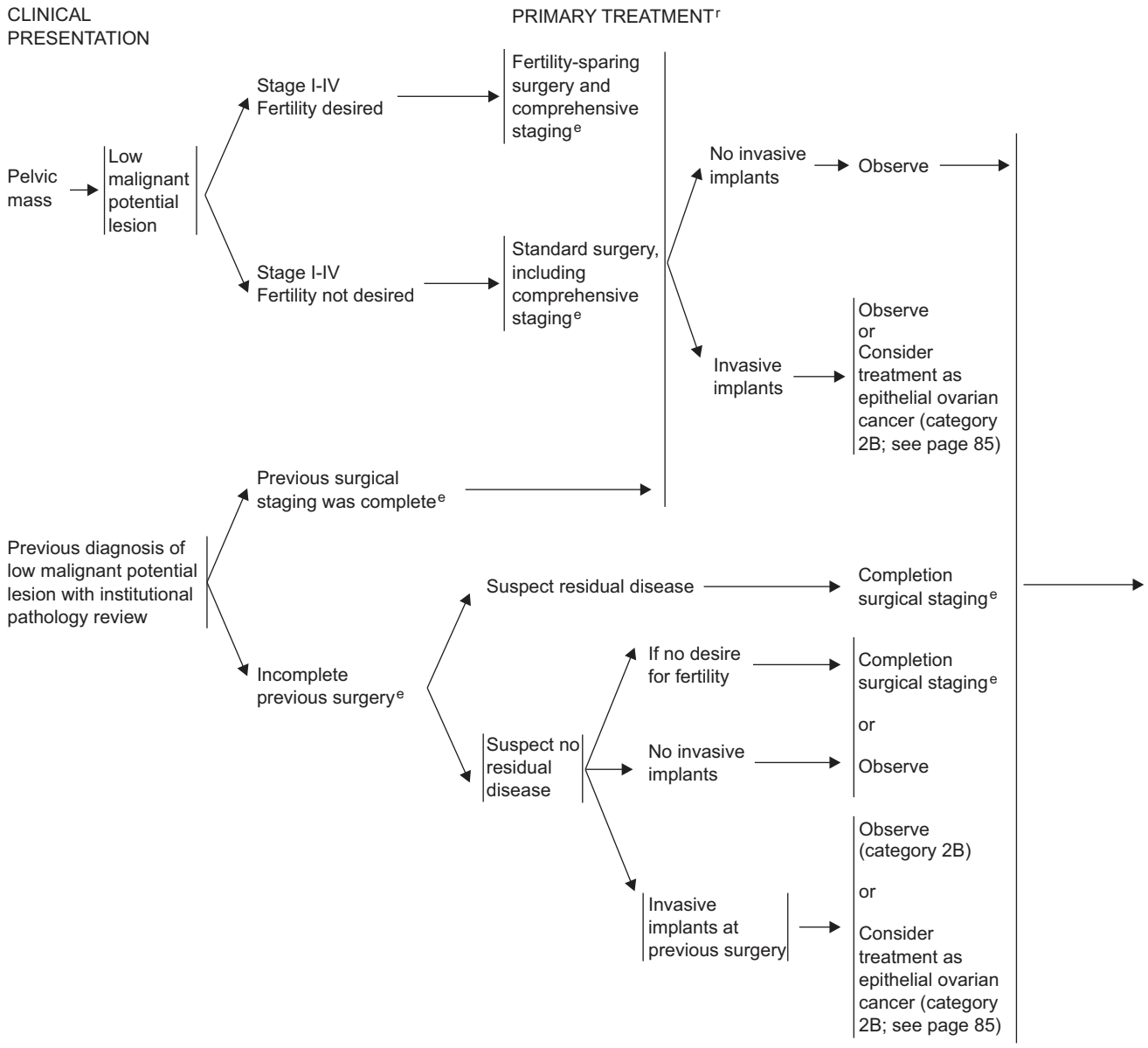
[n] There are preliminary data regarding the utility of CA-125 for monitoring of ovarian cancer after completion of primary therapy; see Society of Gynecologic Oncologists (SGO) position statement (http://www.sgo.org/WorkArea/showcontent.aspx?id=2702).

DISEASE STATUS		THERAPY FOR PERSISTENT DISEASE OR RECURRENCE[o,p,q]
Progression, stable, or persistent disease on primary chemotherapy	→	Clinical trial or Supportive care only or Recurrence therapy[o,q]
Complete remission and relapse < 6 mo after stopping chemotherapy or Stage II, III, and IV with partial response	→	Clinical trial or Recurrence therapy[o,q] or Observe (category 2B)
Complete remission and relapse > 6 mo after stopping chemotherapy	→ Consider secondary cytoreductive surgery[e] →	Clinical trial or Combination platinum-based chemotherapy[o,q] preferred for first recurrence (category 1) or Recurrence therapy[o,q]

†Epithelial ovarian cancer/fallopian tube cancer/primary peritoneal cancer

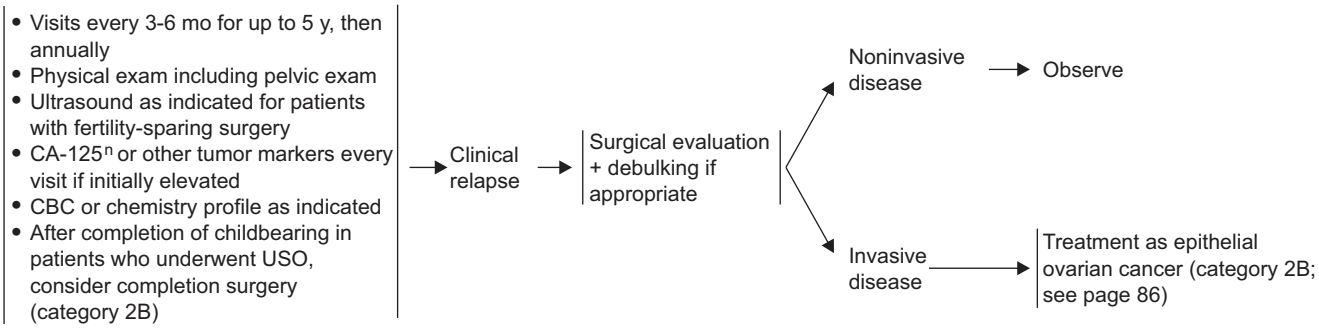
[e]See Principles of Primary Surgery (pages 92 and 93).
[o]Patients who progress on 2 consecutive therapy regimens without evidence of clinical benefits have diminished likelihood of benefitting from additional therapy. Decisions to offer clinical trials, supportive care only, or additional therapy should be made on a highly individual basis.
[p]See Principles of Surgery: Ancillary Palliative Surgical Procedures (page 93).
[q]See Acceptable Recurrence Therapies (pages 97 and 98).



†Borderline epithelial ovarian cancer (low malignant potential)

[e]See Principles of Primary Surgery (pages 92 and 93).
[r]Standard recommendation includes a patient evaluation by a gynecologic oncologist.

MONITORING/FOLLOW-UP | RECURRENT DISEASE | RECURRENCE THERAPY



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PRINCIPLES OF PRIMARY SURGERY[1,2]
(FOR EPITHELIAL OVARIAN, FALLOPIAN TUBE, AND PRIMARY PERITONEAL CANCERS)

- 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; 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 for 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).
  - Total 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 page 93).
  - 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.

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.
- Total 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.

- 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

[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, PA: Lippincott Williams & Wilkins; 2009:763-835. Amended by panel.
[2] It is recommended that a gynecologic oncologist should perform primary surgery (category 1).

PRINCIPLES OF PRIMARY SURGERY (Cont.)[1]

Special Circumstances

- In stage I disease, minimally invasive techniques may be considered to achieve the surgical principles described on the previous page. Minimally invasive surgery performed by an experienced gynecologic oncologist may be considered in selected patients. This is particularly true in the case of 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 (http://www.cap.org/apps/docs/committees/cancer/cancer_protocols/2009/Ovary_09protocol.pdf).
- For patients with apparent early-stage disease and/or good-risk tumors (malignant germ cell tumors, low malignant potential [LMP] lesion, early-stage invasive epithelial tumors or sex cord-stromal tumors) who wish to preserve fertility, USO, preserving the uterus and contralateral ovary, 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 gastrointestinal tract should be carefully evaluated to rule out an occult gastrointestinal 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.

Ancillary Palliative Surgical Procedures

These procedures may be appropriate in select patients:

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

[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, PA: Lippincott Williams & Wilkins; 2009:763-835. Amended by panel.

PRINCIPLES OF CHEMOTHERAPY
(FOR OVARIAN, FALLOPIAN TUBE, AND PRIMARY PERITONEAL CANCERS)

- 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 before initiation of any therapy.
- Before 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 assays are being used in some NCCN Member Institutions for decisions related to future chemotherapy when multiple equivalent chemotherapy options are 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 (e.g., intravenous [IV] chemotherapy, a combination of IP and IV chemotherapy, or a clinical trial) so they can decide which is most the appropriate option. (See page 86 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 associated with the combined regimen compared with using IV chemotherapy alone (e.g., increased myelosuppression, renal toxicities, abdominal pain, neuropathy, gastrointestinal toxicities, metabolic toxicities, hepatic toxicities).
- Patients considered for the IP cisplatin and IP/IV paclitaxel regimen should have normal renal function before 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 (e.g., preexisting neuropathy).
- Before and after patients receive 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 (e.g., 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.

For patients who have recurrent ovarian, fallopian tube, or primary peritoneal cancer:

- For all of the regimens listed in these guidelines, refer to the original references for toxicity, doses, schedules, and dose modifications (see Discussion).
- 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 preexisting toxicities from prior regimens. If appropriate, palliative care should also be discussed as a possible treatment choice. See NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Palliative Care (to view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org).
- 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 (pages 95 and 96).
- Before any chemotherapy drug is given in the recurrent setting, the clinician should be familiar with the drug's metabolism (i.e., renal, hepatic) and should make certain that the patient is an appropriate candidate for the drug (e.g., that the patient has adequate renal or hepatic function).

- 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.

MANAGEMENT OF DRUG REACTIONS
(FOR EPITHELIAL OVARIAN, FALLOPIAN TUBE, AND PRIMARY PERITONEAL CANCERS)

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 (e.g., hot flushing, rash).
  - Hypersensitivity (allergic) reactions are often characterized by more severe symptoms (e.g., 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 after 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 (i.e., docetaxel, paclitaxel) 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 (i.e., carboplatin, cisplatin) tend to occur after reexposure to the inciting drug or less commonly at the completion of initial chemotherapy (i.e., cycle 6 of a planned 6 treatments).[3]
- Preparation for a possible drug reaction
  - Patients and their families must 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]
- 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 severe 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, page 96).
- If a patient has previously had a very severe life-threatening reaction, the implicated drug should not be used again.

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, consultation with an allergist should be considered.[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 (e.g., 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 restarted at a much slower rate, and the rate can be slowly increased as tolerated as perthe 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.

MANAGEMENT OF DRUG REACTIONS (Cont.)

Allergic Reactions (i.e., True Drug Allergies)

- Symptoms include: rash, edema, shortness of breath, chest pain, tachycardia, hives/itching, changes in blood pressure, nausea, vomiting, chills, and changes in bowel function. Patients with severe reactions may have cardiac problems, bronchospasm, and blood pressure changes that require treatment.[11]
- Symptoms 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:
  - Reintroduction of the drug after a period of no exposure and after multiple cycles of the drug during the first and subsequent exposures
  - IV administration of the drug rather than oral or IP administration
  - Allergies to other drugs
  - Previous 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 (e.g., 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 (i.e., anaphylaxis), the implicated drug should not be used again.
  - For more severe reactions, such as those involving blood pressure changes, dyspnea, tachycardia, widespread urticaria, or hypoxia, the treating clinician should consult an allergist before rechallenge.
  - If it is appropriate to give the drug again, patients should be desensitized before resuming chemotherapy even if the symptoms resolved. Patients must be desensitized with each infusion if they previously had a drug reaction.[7-9]

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ACCEPTABLE RECURRENCE THERAPIES[1]
(FOR EPITHELIAL OVARIAN, FALLOPIAN TUBE, AND PRIMARY PERITONEAL CANCERS)

Agents	Cytotoxic Therapy	Hormonal Therapy	Targeted Therapy	Radiation Therapy
Preferred agents	Combination if platinum-sensitive: Carboplatin/paclitaxel (category 1)[2,3] Carboplatin/weekly paclitaxel[2,4] Carboplatin/docetaxel[2,5,6] Carboplatin/gemcitabine[2,7] Carboplatin/liposomal doxorubicin[2,8] Cisplatin/gemcitabine[2,9] Single-agent if platinum-sensitive: Carboplatin[7] Cisplatin[7] Single-agent non-platinum-based if platinum-resistant: Docetaxel[10] Etoposide, oral[11] Gemcitabine[12,13] Liposomal doxorubicin[12,13] Paclitaxel, weekly[14] Topotecan[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

See Footnotes and References (page 98)

ACCEPTABLE RECURRENCE THERAPIES (Cont.)

FOOTNOTES AND REFERENCES

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

[2]Platinum-based combination therapy should be considered for platinum-sensitive recurrences.

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[16]See Discussion for references.

Text continued from p.83

cancer (HNPCC), has been found to be associated with early-onset disease; however, these patients account for only 5% of all women who have ovarian cancer.[4,6] In high-risk women (with either *BRCA1* or *BRCA2* mutations), oophorectomy is associated with a reduced risk of ovarian and fallopian tube cancer; however, these high-risk women have a residual risk for primary peritoneal cancer after prophylactic salpingo-oophorectomy.[6,7] The risks of surgery include injury to the bowel, bladder, ureter, and vessels.[8] Recent data suggest that the fallopian tube may be the origin of some ovarian and primary peritoneal cancers.[9–13] 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, ovarian cancer has been difficult to diagnose at an earlier, more curable stage. However, evaluations of patients with newly diagnosed ovarian cancer have resulted in consensus guidelines for symptoms, which may enable earlier identification of patients who may be at increased risk for having developed early-stage ovarian cancer (http://www.wcn.org/articles/types_of_cancer/ovarian/symptoms/index.html).[14,15] Symptoms suggestive of ovarian cancer include bloating, pelvic or abdominal pain, difficulty eating, feeling full quickly, and urinary symptoms (urgency or frequency), especially if these symptoms are new and frequent (> 12 days per month).[14] When evaluating women with this constellation of symptoms, physicians must be cognizant that ovarian pathology may be the cause. However, some evidence suggests that the screening test for these symptoms is not as sensitive or specific as necessary, especially in those with early-stage disease.[8,16]

An ongoing trial (UK Collaborative Trial of Ovarian Cancer Screening [UKCTOCS]) is assessing multimodality screening with ultrasound and CA-125 versus either ultrasound alone or no screening, with preliminary results suggesting that multimodality screening is more effective at detecting early-stage ovarian cancer.[17] However, a similar trial in the United States assessing screening with transvaginal ultrasonography and CA-125 did not find that screening increased detection of early-stage cancer (72% of cancers detected through screening were late-stage).[18] Another recent study comparing CA-125 alone versus ultrasound with or without CA-125 found that CA-125 did not increase the detection of cancer compared with ultrasound alone.[19]

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.[8,20] Some physicians monitor women with high-risk factors (e.g., *BRCA* mutations, a family history) using CA-125 levels and endovaginal ultrasound; however, prospective validation of these tests remains elusive. An intriguing study suggests that ovarian cancer is associated with unique odors that can be detected.[21,22]

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.[23] However, the Society of Gynecologic Oncologists (SGO) and others have stated that until data from larger randomized controlled trials are published (e.g., UKCTOCS), evidence is insufficient to support this screening approach for low-risk women (http://www.sgo.org/WorkArea/showcontent.aspx?id=3664). Some feel that the ROCA algorithm may be useful for high-risk women (e.g., those with *BRCA* mutations).

The SGO and FDA state that the OVA1 test (Vermillion, Inc., Austin, Texas) should not be used as a screening tool to detect ovarian cancer (http://www.sgo.org/WorkArea/showcontent.aspx?id=2940). The OVA1 screening test uses 5 markers (transthyretin, apolipoprotein A1, transferrin, beta-2 microglobulin, and CA-125) to assess who should be referred to an experienced gynecologic oncologist for surgery. The NCCN Ovarian Cancer Panel recommends that all patients should have surgery performed by an experienced gynecologic oncologist (category 1) based on data documenting increased survival.[24–26]

The SGO has stated that additional research is necessary to validate the OvaSure screening test (LabCorp, Burlington, North Carolina) before it can be made available outside of a clinical trial (http://www.sgo.org/WorkArea/showcontent.aspx?id=1754). The OvaSure test uses 6 biomarkers: leptin, prolactin, osteopontin, insulin-like growth factor II, macrophage inhibitory factor, and CA-125.[27] Although human epididymis protein 4 (HE4) and CA-125 seem to be useful in detecting ovarian

cancer,[28,29] 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.[30]

Staging

These guidelines reflect the importance of stage and grade of disease on prognosis and treatment recommendations. Ovarian cancer is classified primarily as stages I through 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 online, in these guidelines, at www.NCCN.org [ST-1 and -2]).[31] 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 women with stage I, grade 1 tumors (in whom survival is > 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, available at www.NCCN.org [ST-1 and -2]).[31] Fallopian tube carcinomas are also staged using the TNM and FIGO staging systems (see Table 2, available at www.NCCN.org [ST-3 and -4]).[31]

Caveat

By definition, these NCCN Guidelines cannot incorporate all possible clinical variations and are not intended to replace good clinical judgment or individualization of treatments. Exceptions to the rule were discussed among the members of the panel 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 prior diagnosis of a malignant epithelial ovarian tumor. Many patients with this diagnosis come to NCCN Member Institutions after having undergone previous surgery.

Undiagnosed Pelvic Mass: The primary workup of a patient with a suspicious pelvic mass detected on abdominal/pelvic examination and/or ascites, abdominal distention, and/or symptoms (i.e., bloating, pelvic or abdominal pain, difficulty eating or feeling full quickly, or 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 page 84).[14,32–36] Ultrasound is typically used for initial evaluation; however, CT is useful to assess for metastases.[33] When diagnosing ovarian cancer in patients with presumed early-stage disease, fine-needle aspiration (FNA) should be avoided if possible 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.[37,38] Other cancers that should be ruled out include bowel, uterine, and pancreatic cancers and lymphoma.

Primary peritoneal and fallopian tube cancers are usually diagnosed postoperatively (if no major involvement of the ovary is present) or preoperatively (if a biopsy is performed and the patient has already had a bilateral oophorectomy). Primary peritoneal and fallopian tube cancers are treated in the same manner as ovarian cancer.

Although no direct evidence shows that chest imaging is necessary, the panel believes that it should be part of the overall evaluation before surgical staging. Additional diagnostic studies, such as gastrointestinal tract evaluation, are not routinely recommended, although they could be useful in specific clinical situations.

Prior Diagnosis of Malignancy: Often patients are referred to NCCN Member Institutions after ovarian cancer has been diagnosed through surgery or tissue biopsy (cytopathology), and they have already undergone cytoreductive surgery and comprehensive staging procedures (i.e., having met the Gynecologic Oncology Group [GOG] standards for surgical staging). However, referral sometimes occurs after incomplete surgery and/or staging (e.g., 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 pages

92 and 93). Identical workup procedures are recommended for patients with undiagnosed or diagnosed pelvic masses at referral. NCCN institutional pathology review is recommended in all patients. The College of American Pathologists "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/2009/Ovary_09protocol.pdf).

Primary Treatment

Primary treatment for presumed ovarian cancer consists of appropriate surgical staging and cytoreduction, followed by systemic chemotherapy in most patients. Initial surgery should consist of a comprehensive staging laparotomy, including a total abdominal hysterectomy and bilateral salpingo-oophorectomy. Based on published improved outcomes, the panel recommends that a gynecologic oncologist perform the primary surgery (category 1).[24–26] For young patients who wish to maintain fertility, a unilateral salpingo-oophorectomy (preserving the uterus and contralateral ovary) may be adequate for stage I and/or low-risk tumors (e.g., early-stage, low-grade, invasive tumors; low malignant potential [LMP] lesions).[39–42]

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.[43] In stage I disease, minimally invasive techniques to achieve the surgical goals (see pages 92 and 93) may be considered in select patients if performed by an experienced gynecologic oncologist. For example, minimally invasive techniques may be considered for prophylactic oophorectomy.

Cytoreductive surgery is the initial treatment recommendation for patients with clinical stage II, III, or IV disease (see page 84).[26,40,43–45] To fully stage the disease and achieve maximal cytoreduction to less than 1 cm residual disease or resection of all visible disease in appropriate circumstances, the procedures outlined in the next paragraph should be part of the surgical management of patients with ovarian, fallopian tube, or primary peritoneal cancer.[46–48]

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. Total hysterectomy and bilateral salpingo-oophorectomy should be performed. The encapsulated mass should be removed intact. All involved omentum should be removed. Suspicious and/or enlarged nodes should be resected, if possible.[49,50] Patients with tumor nodules of 2 cm or less (presumed stage IIIB) outside the pelvis should undergo bilateral pelvic and para-aortic lymph node dissection (see pages 92 and 93).

In patients with advanced ovarian cancer who have had complete debulking, data indicate that overall survival is increased in those who undergo systematic lymphadenectomy.[51] Patients with low-volume residual disease after surgical cytoreduction for invasive epithelial ovarian or peritoneal cancer are potential candidates for intraperitoneal therapy. In these patients, consideration should be given to placement of an intraperitoneal catheter at 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, or distal pancreatectomy.[52]

The therapeutic benefit of neoadjuvant chemotherapy followed by interval cytoreduction remains controversial (see next paragraph).[53–55] It may be considered for patients with bulky stage III to IV disease who are not surgical candidates.[56–59] Before initiation of chemotherapy, the pathologic diagnosis should be confirmed (through FNA, biopsy, or paracentesis) in this group of patients.

A recent randomized phase III trial assessed neoadjuvant chemotherapy with interval debulking surgery versus up-front primary debulking surgery in patients with extensive-stage IIIC/IV ovarian, primary peritoneal, and fallopian tube carcinoma (sponsored by the EORTC Gynaecological Cancer Group [EORTC-GCG] and the National Cancer Institute of Canada Clinical Trials Group [NCIC CTG]).[60] Median overall survival was equivalent in these patients (29 vs. 30 months), but patients undergoing neoadjuvant chemotherapy with interval debulking surgery experienced 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 survivals averaging 50 months).[61] Although the median overall survival in the international trial is 20 months lower than that reported in United States trials using the customary sequence of therapeutic interventions (i.e., 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). However, in the opinion of the NCCN Ovarian Cancer Guideline panel, more data will be necessary before recommending neoadjuvant chemotherapy in patients with potentially resectable ovarian cancer, and up-front debulking surgery remains the preferred treatment in the United States. Note that the authors of the international trial believe that up-front debulking surgery should remain the standard of care for patients with stage IIIB or earlier-stage disease but that neoadjuvant chemotherapy with interval debulking surgery is an option for patients with extensive stage IIIC/IV disease.

Incompletely Staged Patients: For patients with incomplete previous surgery, treatment recommendations are outlined in the algorithm (see page 85). Completion surgery after 3 to 6 cycles of chemotherapy should be considered for patients with stage II through IV disease who have residual disease that is considered unresectable. Depending on the surgical results, patients would then undergo postoperative chemotherapy. Tumor reductive surgery is recommended for all patients with stage II through IV disease with suspected potentially resectable residual disease.

Chemotherapy: Most patients with epithelial ovarian cancer undergo 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.[62] 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 and intraperitoneal options. All of the regimens (including the intraperitoneal chemotherapy) may be used for epithelial ovarian, primary peritoneal, and fallopian tube cancers. Principles of chemotherapy are described in the algorithm (see page 94).

Intraperitoneal chemotherapy is recommended for patients with stage III, optimally debulked (< 1 cm residual) disease based on randomized controlled trials (category 1; http://www.cancer.gov/clinicaltrials/developments/IPchemo-digest/page1/print); patients with stage II disease may also undergo intraperitoneal chemotherapy, although no randomized evidence for stage II disease has been published.[61,63,64] In women with stage III cancer, survival was increased by 16 months after intraperitoneal therapy using cisplatin/paclitaxel 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 (e.g., those with poor performance status), the combination of intravenous paclitaxel plus carboplatin (category 1) may be used (see page 86).[24,65] Intravenous docetaxel plus carboplatin (category 1)[66] or paclitaxel plus cisplatin (category 1) are options for alternative regimens.[67] The docetaxel/carboplatin regimen may be considered for patients who are at high risk for neuropathy (e.g., 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.[68]

The recommended intravenous regimens accepted by a consensus of the 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 to 7.5 intravenously over 1 hour on day 1, given every 3 weeks for 6 cycles (category 1)[65]; 2) docetaxel, 60 to 75 mg/m^2, 1-hour intravenous infusion followed by carboplatin, dosed at AUC of 5 to 6 intravenously over 1 hour on day 1, every 3 weeks for 6 cycles (category 1)[66]; and 3) dose-dense paclitaxel, 80 mg/m^2, intravenously over 1 hour on days 1, 8, and 15 plus carboplatin AUC 6 intravenously over 1 hour on day 1, every 3 weeks for 6 cycles (category 1).[69] The recommended intraperitoneal regimen is paclitaxel, 135 mg/m^2, continuous intravenous infusion over 24 hours on day 1; intraperitoneal cisplatin, 75 to 100 mg/m^2, day 2 after

intravenous paclitaxel; intraperitoneal paclitaxel, 60 mg/m^2, day 8 (maximum body surface area, 2.0 m^2); repeat every 3 weeks for 6 cycles (category 1).[61]

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.[66,69] The intraperitoneal paclitaxel/cisplatin regimen is associated with leukopenia, infection, fatigue, renal toxicity, abdominal discomfort, and neurotoxicity.[70,71] In the initial studies, only 42% of women were able to complete all 6 treatment cycles because of toxicity; however, with more experience, this percentage has improved in the major cancer centers. Using a lower intraperitoneal dose of cisplatin of 75 mg/m^2 may help to decrease toxicity.[72] Patients considered for the intraperitoneal cisplatin and intraperitoneal/intravenous paclitaxel regimen should have normal renal function before starting, a medically appropriate performance status based on the future toxicities of the intraperitoneal/intravenous regimen, and no previous evidence of medical problems that could significantly worsen during chemotherapy (e.g., preexisting neuropathy; see page 94).

Reasons for discontinuing the intraperitoneal regimen included catheter complications, nausea/vomiting/dehydration, and abdominal pain.[73] Women unable to complete intraperitoneal therapy should receive intravenous therapy. Techniques to decrease catheter complications include catheter choice and timing of insertion.[63,74] Giving intravenous hydration before and after intraperitoneal chemotherapy is a useful strategy to prevent renal toxicity. After chemotherapy, patients often require intravenous fluids (5–7 days) in the outpatient setting to prevent or help treat dehydration. Whether to use intraperitoneal or intravenous chemotherapy remains controversial.[73,75–77]

Dose-dense weekly paclitaxel with carboplatin has been shown to increase both progression-free (28 vs. 17 months; $P = .0015$) and 3-year overall survival (72% vs. 65%; $P = .03$) compared with standard therapy given every 3 weeks (i.e., intravenous carboplatin/paclitaxel).[69] However, the dose-dense regimen is more toxic, and patients discontinued dose-dense paclitaxel therapy more often than those undergoing standard therapy. Future studies will compare the effects of weekly paclitaxel and intraperitoneal chemotherapy on overall survival benefit.[78]

Preliminary results have been presented from a phase III randomized trial (GOG 0218) assessing bevacizumab combined with carboplatin/paclitaxel in the up-front setting compared with carboplatin/paclitaxel alone. Although data regarding overall survival and/or quality of life have not been reported yet, the median progression-free survival was significantly increased (10.3–14.1 months; $P < .0001$) in patients receiving bevacizumab up-front and as maintenance therapy compared with chemotherapy alone.[79] However, progression-free survival was not significantly increased in patients receiving bevacizumab up-front with placebo maintenance versus chemotherapy alone (i.e., bevacizumab/carboplatin/paclitaxel vs. carboplatin/paclitaxel).

Another phase III randomized trial (ICON7) has also assessed bevacizumab/carboplatin/paclitaxel in the up-front setting. The trial design of ICON7, which has some important differences compared to GOG 0218, was presented at ESMO in October 2010. Although the progression-free survival data from ICON7 confirm the findings of GOG 0218, the benefits seem to be modest and data are immature regarding overall survival.

Until more mature results from GOG 0218 and ICON 7 are available, the panel does not recommend the routine addition of bevacizumab to up-front therapy with carboplatin/paclitaxel or as maintenance therapy. The panel encourages participation in ongoing clinical trials that are further investigating the role of antiangiogenesis agents in the treatment of ovarian cancer, in the up-front and recurrence settings. Note that the SGO has stated that if patients are interested in bevacizumab therapy, they should discuss the risks, benefits, and utility with their health care providers (http://www.sgo.org/WorkArea/showcontent.aspx?id=3666).

Patients with poor performance status, comorbidities, stage IV disease, or advanced age may not tolerate the intraperitoneal regimen. The intraperitoneal regimen published by Armstrong et al.[61] has, however, documented the longest median survival (65.6 months) that has been described to date in patients with optimally debulked stage III disease. Patients with primary peritoneal cancer, fallopian tube cancer, or MMMT can also be considered for intraperitoneal chemotherapy.[64,74] All women should be

counseled about the clinical benefit associated with combined intravenous and intraperitoneal chemotherapy administration before undergoing surgery for ovarian, fallopian tube cancer, primary peritoneal cancer, or MMMT.

Dose Intensity: Panel members also discussed dose-intensification using high-dose chemotherapy with peripheral blood stem cell transplantation in select patients with previously untreated ovarian cancer, or as a consolidation strategy after induction therapy with standard drug doses. Results from phase III randomized high-dose chemotherapy trials with carboplatin and paclitaxel and with high-dose melphalan consolidation did not show an improvement in overall survival compared with standard-dose chemotherapy.[80,81] The panel agrees that this approach remains investigational and should not be performed outside of an approved clinical trial.

Number of Chemotherapy Cycles and Agents: Panel members had an extensive discussion about the number of chemotherapy cycles that should be recommended for patients with advanced-stage disease. No evidence confirms that more than 6 to 8 cycles of combination chemotherapy are required for initial chemotherapy.[82] Patients can also have 3 to 6 cycles of chemotherapy followed by completion surgery and then postoperative chemotherapy (see page 85).[54]

Maintenance therapy is an option in patients who experience a complete clinical remission after 6 to 8 cycles of chemotherapy based on the results from GOG 178. This trial randomly assigned patients to 3 or 12 months of further paclitaxel (135–175 mg/m^2 every 4 weeks for 12 cycles) after initial chemotherapy.[83] The study treated patients at 175 mg/m^2, with the plan 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 undergoing 12 months of therapy sustained a progression-free survival advantage. Postremission paclitaxel chemotherapy is a category 2B recommendation.

Drug Reactions: Virtually all drugs have the potential to cause drug reactions, either during or after infusion.[84] 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 intraperitoneal administration of these drugs.[85] Most of these drug reactions are mild infusion reactions (e.g., skin reactions, cardiovascular reactions, respiratory or throat tightness), but more severe allergic reactions (e.g., life-threatening anaphylaxis) can occur.[86,87] Infusion reactions are more common with paclitaxel,[88] but mild reactions can also occur with liposomal doxorubicin.[89] Allergic reactions (i.e., true drug allergies) are more common with platinum agents (e.g., carboplatin, cisplatin, oxaliplatin).[88]

Management of drug reactions is discussed in the algorithm (see pages 95 and 96).[90] 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.[84] Almost all patients can be desensitized (~ 90%).[84] For severe life-threatening reactions, the implicated agent should not be used again. 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. Patients who previously experienced a drug reaction must be desensitized with each infusion.[91–93]

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 at NCCN Member Institutions, it is not included as a treatment recommendation in the 2011 guidelines. Palliative localized radiation therapy is an option for symptom control in patients with recurrent disease (see page 97).[94,95] Patients who undergo 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 radiation therapy is completed and can be performed indefinitely (http://www.owenmumford.com/en/download.asp?id=59).

Recommendations After Primary Treatment

After initial treatment (e.g., 6 cycles of chemotherapy), patients should undergo a clinical reevaluation. Patients with no evidence of disease progression (i.e., complete clinical remission) after initial treatment can undergo observation with follow-up (see Follow-Up Recommendations, opposite page, and see page 88); other options are discussed later. Patients with partial remission or progression during initial treatment should be treated with second-line approaches (see Recurrent Disease, opposite page, and see page 87).

Options for maintenance treatment of patients with advanced-stage disease (stages II–IV) who experience complete clinical remission after the initial therapeutic regimen include observation alone, clinical trial, or additional chemotherapy[83] (paclitaxel, category 2B), preferably in a controlled clinical trial (see page 87). 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 (i.e., negative physical examination, negative CA-125 levels, and negative CT with lymph nodes < 1 cm).

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), the standard recommendation is observation with follow-up. Recommendations for monitoring are described in the algorithm (see page 88). Chest/abdominal/pelvic CT, MRI, PET scans (category 2B for PET), PET-CT, and chest imaging may be ordered if clinically necessary.[96,97] Measurement of a CA-125 level or other tumor markers at each follow-up evaluation is recommended if the level was initially elevated.[98]

Preliminary data are available from a recent multi-institutional European trial assessing the use of CA-125 for monitoring ovarian cancer after primary therapy.[99] 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.[100] The panel concurs with the SGO opinion, which states that this study has limitations and that patients should discuss the pros and cons of CA-125 monitoring with their physicians (http://www.sgo.org/WorkArea/showcontent.aspx?id=2702). In addition, patients seem reluctant to give up monitoring.[101] Others have discussed this study in greater detail.[102,103]

Management of an Increasing CA-125 Level: The management of patients experiencing 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 after an evaluation, including a negative pelvic examination and negative chest/abdominal/pelvic CT scans, is somewhat controversial. Patients who have never undergone chemotherapy (i.e., naïve to chemotherapy) should be managed as newly diagnosed patients, undergo clinically appropriate imaging studies and surgical debulking, and be treated as previously described (see page 84).

After the documentation of an increased CA-125 level, the median time for a clinical relapse is 2 to 6 months. A lack of consensus exists regarding the timing of recurrence therapy for patients who have undergone previous chemotherapy. Because tamoxifen and other hormonally active agents have a defined response rate in recurrent disease after progression on platinum-based chemotherapy,[104] they are frequently administered to patients who have only a rising CA-125 level[105] as evidence of tumor progression. Tamoxifen, other hormonal agents, or other recurrence therapy are acceptable recommendations for this clinical situation (category 2B). Other alternatives include enrollment in a clinical trial or delaying treatment (i.e., observation) until clinical symptoms arise (category 2B for observation; see page 88).

Recurrent Disease

The prognosis is poor for patients whose disease progresses after 2 consecutive chemotherapy regimens without ever sustaining a clinical benefit (refractory), or recurs in less than 6 months (platinum-resistant). Note that progression is typically defined using traditional RECIST (Response Evaluation Criteria in Solid Tumor) criteria (i.e., a 20% increase in tumor diameter).[106] Panel members emphasized the importance of clinical trials to identify agents active in this group of patients. Because these patients disease was resistant to the primary induction regimen, retreatment with a platinum compound or paclitaxel is not generally recommended. Although panel members do not recommend retreatment with platinum agents, they recognize that altering the schedule of paclitaxel may produce secondary responses.[107,108] Before any drug is given in the recurrent setting, clinicians should be familiar with the drug's metabolism and ensure that patients are appropriate candidates for the drug (e.g., have adequate renal or hepatic function). Clinical judgment must be used when selecting postoperative chemotherapy.

For patients with platinum-resistant disease or stages II through IV disease who experience a partial response, options include recurrence therapy (see page 97),[109] clinical trial, or observation (category 2B for observation). Patients who experience disease

relapse 6 months or more after initial chemotherapy are considered platinum-sensitive (see page 89).[110,111] Combination platinum-based chemotherapy is preferred for first recurrence (category 1).[111] Possible regimens are discussed in Acceptable Recurrence Modalities, below.

Patients with ovarian cancer will often undergo retreatment with multiple courses of recurrence therapy. Caution should be used in patients who undergo 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 page 94). Potential ancillary palliative surgical and/or supportive care procedures for select patients are summarized in the algorithm (see pages 92 and 93).

Secondary cytoreductive surgery can be considered for patients who experience recurrence after a long disease-free interval (≥ 6 months).[112] A recent meta-analysis suggests that survival increases for patients with recurrent disease who undergo complete cytoreduction.[46] 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 be considered.

Acceptable Recurrence Modalities: Panel members felt that no single therapeutic agent should be currently recommended as the preferred treatment for recurrent ovarian carcinoma. However, some agents are preferred based on expert opinion (primarily because of decreased toxicity and/or marginally increased effectiveness; see page 97). A meta-analysis of 13 randomized studies in recurrent ovarian cancer has been published.[110]

The panel consensus on the treatment of recurrent disease appears on page 97. Platinum-based combination chemotherapy is recommended (category 1) for platinum-sensitive recurrence (see page 89).[110,111] Preferred combinations for platinum-sensitive recurrent disease include carboplatin/paclitaxel (category 1),[111] carboplatin/weekly paclitaxel,[69] carboplatin/docetaxel,[113,114] carboplatin/gemcitabine (shown to improve progression-free survival),[111,115,116] carboplatin/liposomal doxorubicin (also shown to improve progression-free survival),[117] or cisplatin/gemcitabine.[115]

For platinum-resistant disease, the preferred agent is a single non–platinum-based agent (i.e., docetaxel, oral etoposide, gemcitabine, liposomal doxorubicin, weekly paclitaxel, topotecan). The activity of the following agents seems to be similar: topotecan, 20%[118]; gemcitabine, 19%[119,120]; vinorelbine, 20%[121,122]; liposomal doxorubicin, 26%[119,120]; and oral etoposide, 27%.[123] In patients with platinum-resistant disease, the activity for docetaxel is 22%, weekly paclitaxel is 21%, and pemetrexed is 21%.[107,124,125] For platinum-sensitive disease, the preferred single agent is carboplatin or cisplatin in patients who cannot tolerate combination therapy.[115,116]

Other potentially active agents include altretamine, capecitabine, cyclophosphamide, ifosfamide, irinotecan, melphalan, oxaliplatin, paclitaxel, nanoparticle albumin-bound paclitaxel (i.e., nab-paclitaxel), and vinorelbine (see page 97). Nab-paclitaxel has an overall response rate of 64%.[126] Altretamine has a 14% response rate[127] and ifosfamide a 12% response rate,[128] although less information is available regarding their use in patients who are refractory to paclitaxel. Bevacizumab is also active (21%) in both platinum-sensitive and platinum-resistant patients,[129–133] although it may cause arterial thrombosis or intestinal perforation. Several trials are assessing combination therapy with bevacizumab for recurrent ovarian cancer (i.e., OCEANS, AURELIA).

Taxanes (including docetaxel and paclitaxel) and platinum compounds (including cisplatin, carboplatin, and oxaliplatin) can be used in appropriate patients.[83,111,134] Capecitabine has activity in patients whose disease is resistant to platinum and taxanes.[135] Other alkylating agents, including cyclophosphamide and melphalan, can also be used. In addition, for patients who cannot tolerate cytotoxic regimens or for whom treatment with these regimens has been unsuccessful, hormonal therapy with tamoxifen or other agents (including anastrozole, letrozole, leuprolide acetate, or megestrol acetate) continues to be a viable therapeutic option.[136–140]

Recent data suggest that olaparib (AZD2281), which is a PARP (poly ADP-ribose polymerase) inhibitor, is active in select patients (those with *BRCA1* and *BRCA2* mutations have higher response rates than those without a mutation) with chemotherapy-refractory ovarian cancer, especially those with platinum-sensitive disease.[141–143] Olaparib has a lower response rate in patients whose disease is resistant or refractory to platinum.[142,143] Note that olapa-

rib is not FDA-approved for this indication and is only available in a clinical trial. Localized radiation therapy can also provide effective palliation when radiation ports are tailored to specific symptomatic disease sites.[94,95]

Chemotherapy/resistance assays are used in some NCCN Member Institutions to help select chemotherapy when multiple equivalent chemotherapy options are available; the current level of evidence (category 3) is not sufficient to supplant standard of care chemotherapy.[144,145] The panel believes that in vitro chemosensitivity testing to help choose a chemotherapy regimen for recurrent disease situations should not be recommended because of the lack of demonstrable efficacy for this approach. However, regardless of which regimen is selected initially, patients should be reevaluated after 2 to 4 cycles of chemotherapy (depending on the agent) to determine whether they benefited from chemotherapy. Patients on 2 consecutive chemotherapy regimens who experience disease progression without evidence of clinical benefit have diminished likelihood of benefitting from additional therapy. Decisions to offer supportive care, additional therapy, or enrollment in clinical trials should be made on a highly individual basis.

Borderline Epithelial Ovarian Cancer

Diagnosis

Borderline epithelial ovarian cancer (also known as *epithelial ovarian cancer of LMP* or *borderline ovarian cancer*) is a primary epithelial ovarian lesion with cytologic characteristics suggesting malignancy but without frank invasion and with a clinically indolent course and good prognosis.[146] Five-year survival exceeds 80%.[147] 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 show evidence of frank invasion by the tumor nodules, although invasive implants that continue to be consistent with the diagnosis of LMP lesions can rarely be identified microscopically by the pathologist.

Some investigators believe that the appearance of invasive implants on the peritoneal surfaces in patients with ovarian cancer of LMP portends a less favorable prognosis; therefore, the same treatments used for epithelial ovarian cancer (i.e., postoperative chemotherapy) can be considered (category 2B) for these patients (see page 90).[148] 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.[149,150] The benefit of postoperative chemotherapy has not been shown for patients who have no microscopically demonstrable invasive implants.[151]

Treatment

Treatment guidelines for borderline epithelial ovarian cancer depend on the histologic and clinical characteristics, patient age,[150] and disease stage at 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. Patients with an LMP lesion who desire to maintain their fertility may undergo surgery limited to a unilateral salpingo-oophorectomy (preserving the uterus and contralateral ovary) when comprehensive staging is performed.[39,40] If the patient does not desire fertility-sparing surgery, standard ovarian cancer debulking surgery is recommended, accompanied by comprehensive staging.

For patients with known LMP disease who were incompletely staged at initial laparotomy, options include either completion surgical staging or observation, depending on whether residual disease is present (see page 90).

Follow-Up

Treatment recommendations after comprehensive staging depend on the presence or absence of invasive implants. The initial therapeutic approach for patients with invasive implants may include observation or, alternatively, treatment according to the guidelines for epithelial ovarian cancer can be considered (category 2B; see page 85). Patients with no invasive implants should be observed and monitored (see page 91).[149,152] Patients who chose fertility–sparing surgery should be monitored with ultrasound examinations if necessary, and should be considered for completion surgery (category 2B) after finishing childbearing.

At clinical relapse, a surgical evaluation and debulking are recommended if appropriate. Patients who have invasive disease at this time may be treat-

ed according to the guidelines for epithelial ovarian cancer (category 2B; see page 86); those without invasive implants should be observed or enrolled in a clinical trial.

Less-Common Ovarian Histopathologies

Information on less-common ovarian histopathologies can be found in the full NCCN Guidelines for Ovarian Cancer, available online at www.NCCN.org.

Recommended Readings

Recommended readings can be found in the full NCCN Guidelines for Ovarian Cancer, available online at www.NCCN.org.

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References 153–187 are referenced in the "Less-Common Ovarian Histopathologies" section of these guidelines, available online, at www.NCCN.org.

Individual Disclosures for the NCCN Ovarian Cancer Panel					
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Dr. Hughes has disclosed that she has a patent, equity, or royality in Myriad Genetic Laboratories, Inc.; Affymetrix; and Qiagen NV. The remaining guidelines staff have disclosed that they have no conflicts of interest.