NCCN Guidelines® Insights

Ovarian Cancer, Version 2.2013

Featured Updates to the NCCN Guidelines

Robert J. Morgan Jr, MD[1]; Ronald D. Alvarez, MD[2]; Deborah K. Armstrong, MD[3]; Robert A. Burger, MD[4]; Lee-may Chen, MD[5]; Larry Copeland, MD[6]; Marta Ann Crispens, MD[7]; David M. Gershenson, MD[8]; Heidi J. Gray, MD[9]; Ardeshir Hakam, MD[10]; Laura J. Havrilesky, MD[11]; Carolyn Johnston, MD[12]; Shashikant Lele, MD[13]; Lainie Martin, MD[4]; Ursula A. Matulonis, MD[14]; David M. O'Malley, MD[6]; Richard T. Penson, MD, MRCP[15]; Matthew A. Powell, MD[16]; Steven W. Remmenga, MD[17]; Paul Sabbatini, MD[18]; Joseph T. Santoso, MD[19]; Julian C. Schink, MD[20]; Nelson Teng, MD, PhD[21]; Theresa L. Werner, MD[22]; Mary A. Dwyer, MS[23]; and Miranda Hughes, PhD[23]

Abstract

These NCCN Guidelines Insights focus on the major updates to the 2013 NCCN Guidelines for Ovarian Cancer. Four updates were selected based on recent important updates in the guidelines and on debate among panel members about recent clinical trials. The topics include 1) intraperitoneal chemotherapy, 2) CA-125 monitoring for ovarian cancer recurrence, 3) surveillance recommendations for less common ovarian histopathologies, and 4) recent changes in therapy for recurrent epithelial ovarian cancer. These NCCN Guidelines Insights also discuss why some recommendations were not made. (*JNCCN* 2013;11:1199–1209)

From [1]City of Hope Comprehensive Cancer Center; [2]University of Alabama at Birmingham Comprehensive Cancer Center; [3]The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins; [4]Fox Chase Cancer Center; [5]UCSF Helen Diller Family Comprehensive Cancer Center; [6]The Ohio State University Comprehensive Cancer Center - James Cancer Hospital and Solove Research Institute; [7]Vanderbilt-Ingram Cancer Center; [8]The University of Texas MD Anderson Cancer Center; [9]University of Washington/Seattle Cancer Care Alliance; [10]Moffitt Cancer Center; [11]Duke Cancer Institute; [12]University of Michigan Comprehensive Cancer Center; [13]Roswell Park Cancer Institute; [14]Dana-Farber/Brigham and Women's Cancer Center; [15]Massachusetts General Hospital Cancer Center; [16]Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine; [17]Fred & Pamela Buffett Cancer Center at The Nebraska Medical Center; [18]Memorial Sloan-Kettering Cancer Center; [19]St. Jude Children's Research Hospital/The University of Tennessee Health Science Center; [20]Robert H. Lurie Comprehensive Cancer Center of Northwestern University; [21]Stanford Cancer Institute; [22]Huntsman Cancer Institute at the University of Utah; and [23]National Comprehensive Cancer Network.

Disclosures for the NCCN Ovarian Cancer Panel

Individual disclosures of potential conflicts of interest for the NCCN Ovarian Cancer Panel members can be found on page 1200.

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. **The NCCN Guidelines® Insights highlight important changes in the NCCN Guidelines® recommendations from previous versions. Colored markings in the algorithm show changes and the discussion aims to further understanding of these changes by summarizing salient portions of the panel's discussion, including the literature reviewed.**

The NCCN Guidelines Insights do not represent the full NCCN Guidelines; further, the National Comprehensive Cancer Network® (NCCN®) makes no representation or warranties of any kind regarding the content, use, or application of the NCCN Guidelines and NCCN Guidelines Insights and disclaims any responsibility for their applications or use in any way.

The full and most current version of these NCCN Guidelines are available at NCCN.org.

Ovarian Cancer, Version 2.2013

NCCN: Continuing Education

Accreditation Statement

This activity has been designated to meet the educational needs of physicians, nurses, and pharmacists involved in the management of patients with cancer. There is no fee for this article. The National Comprehensive Cancer Network (NCCN) is accredited by the ACCME to provide continuing medical education for physicians. NCCN designates this journal-based CE activity for a maximum of 1.0 *AMA PRA Category 1 Credit(s)*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

NCCN is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center`s Commission on Accreditation.

This activity is accredited for 1.0 contact hour. Accreditation as a provider refers to recognition of educational activities only; accredited status does not imply endorsement by NCCN or ANCC of any commercial products discussed/displayed in conjunction with the educational activity. Kristina M. Gregory, RN, MSN, OCN, is our nurse planner for this educational activity.

National Comprehensive Cancer Network is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. NCCN designates this continuing education activity for 1.0 contact hour(s) (0.1 CEUs) of continuing education credit in states that recognize ACPE accredited providers. This is a knowledge-based activity. UAN: 0836-0000-13-015-H01-P

All clinicians completing this activity will be issued a certificate of participation. To participate in this journal CE activity: 1) review the learning objectives and author disclosures; 2) study the education content; 3) take the posttest with a 66% minimum passing score and complete the evaluation at **http://education.nccn.org/node/30997;** and 4) view/print certificate.

Release date: October 25, 2013; Expiration date: October 25, 2014

Learning Objectives:

Upon completion of this activity, participants will be able to:

- Integrate into professional practice the updates to NCCN Guidelines for Ovarian Cancer
- Describe the rationale behind the decision-making process for developing the NCCN Guidelines for Ovarian Cancer

EDITOR: Kerrin M. Green, MA, Assistant Managing Editor, *JNCCN—Journal of the National Comprehensive Cancer Network,* has disclosed that she has no relevant financial relationships.

CE AUTHORS: Deborah J. Moonan, RN, BSN, Manager, CE Supporter Outreach, has disclosed the following relationships with commercial interests: AstraZeneca: Stockholder/Former Employee. **Kristina M. Gregory, RN, MSN, OCN,** Vice President, Clinical Information Operations, has disclosed that she has no relevant financial relationships. **Mary A. Dwyer, MS,** Guidelines Coordinator, has disclosed no relevant financial relationships. **Miranda Hughes, PhD,** Oncology Scientist/Senior Medical Writer, has disclosed no relevant financial relationships.

Disclosure of Affiliations and Significant Relationships: NCCN Ovarian Cancer Panel

The following authors have no relevant financial interests to disclose: Dr. Chen, Dr. Copeland, Dr. Hakam, Dr. Lele, Dr. Martin, Dr. Remmenga, and Dr. Werner.

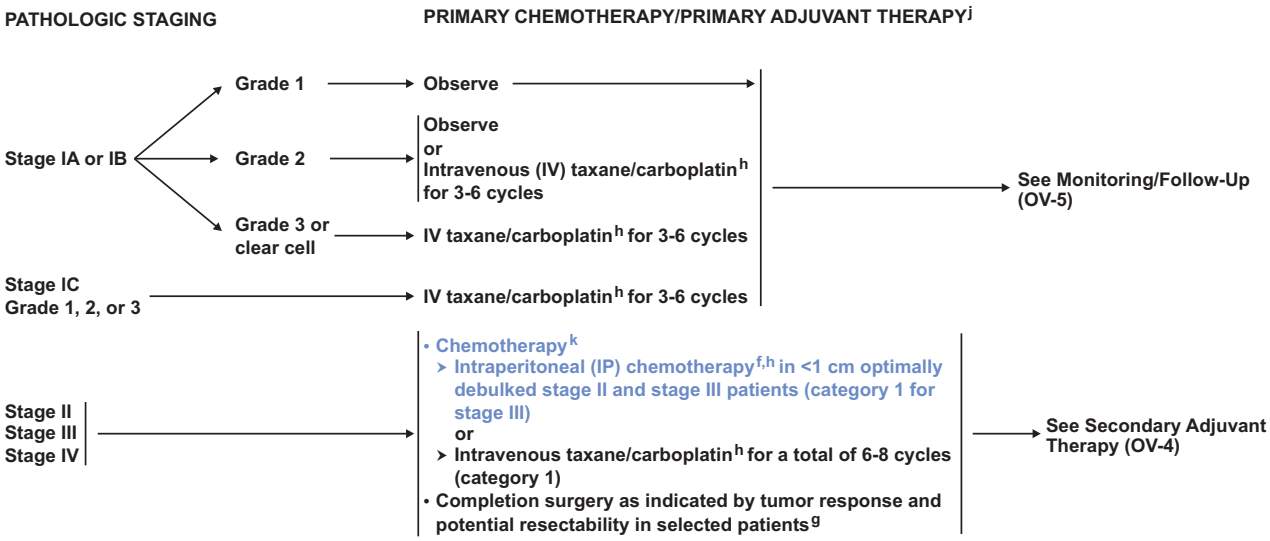
The following authors have disclosed the following relevant financial relationships:

Dr. Alvarez: Research funding from Morphotek, Inc. and Pfizer Inc. Advisory board member for Genentech, Inc. and Astellas Pharm US, Inc.
Dr. Armstrong: PI for Genentech, Inc.; MedImmune Inc.; Morphotek, Inc.; and Astellas Pharm US, Inc. Advisory board member for Genentech, Inc and Morphotek, Inc.
Dr. Burger: PI for Genentech, Inc. Advisory board member for Boehringer Ingelheim GmbH; Genentech, Inc.; GlaxoSmithKline; Chugai Pharmaceutical Co., Ltd; MEI Pharma (formerly Marshall Edwards); PharmaMar; and TESARO, Inc. Consultant for Champions Biotechnology Inc. and Fujirebio Diagnostics, Inc.
Dr. Crispens: PI for Morphotek, Inc. and Spirogen.
Dr. Gershenson: PI for AstraZeneca Pharmaceuticals LP; Genentech, Inc.; and National Cancer Institute. Co-Chair, Gynecologic Steering Committee for National Cancer Institute. Equity in Johnson & Johnson and Proctor and Gamble. Royalties from Elsevier; Informa; and Up-to-Date.
Dr. Gray: PI for Abbott Laboratories and Prima BioMed. Advisory board member for Prima BioMed.
Dr. Havrilesky: PI for and advisory board member for BD TriPath Oncology.
Dr. Johnston: Positions at American Cancer Society and Michigan Cancer Consortium.
Dr. Matulonis: PI for AstraZeneca Pharmaceuticals LP; Bristol-Myers Squibb Company; Eli Lilly and Company; Genentech, Inc.; and Merck & Co., Inc. Consultant for Clovis Oncology. Advisory board member for Pathway Therapeutics.
Dr. Morgan: Co-investigator for National Institutes of Health Cancer Therapy Evaluation Program.
Dr. O'Malley: PI for Genentech, Inc.
Dr. Penson: PI for Amgen Inc.; AstraZeneca Pharmaceuticals LP; Eisai Inc.; Eli Lilly and Company; Genentech, Inc.; ImClone Systems Incorporated; and Endocyte Inc. Data and Safety Monitoring Board chair for Genentech, Inc. Speakers bureau member for AstraZeneca Pharmaceuticals LP and Genentech, Inc. Advisory board member for BioMarin Pharmaceutical Inc.; Clovis Oncology; and Lifecore Biomedical LLC.
Dr. Powell: PI for Bristol-Myers Squibb Company. Protocol Steering Committee Member for Eisai Inc. Advisory board member for AnorMED Inc.
Dr. Sabbatini: Data and Safety Monitoring Board member for Prima BioMed.
Dr. Santoso: Speakers bureau member for Jannsen Pharmaceutica Products, LP and Vermillion, Inc. Consultant for LabCorp.
Dr. Schink: Consultant for Genentech, Inc. Intern for Precision Therapeutics, Inc.
Dr. Teng: PI for Gynecologic Oncology Group.

The NCCN Guidelines Staff have no conflicts to disclose.

Supported by educational grants from Eisai, Inc.; Millennium: The Takeda Oncology Company; Teva Pharmaceuticals; Bayer HealthCare Pharmaceuticals Inc.; Celgene Corporation; Endo Pharmaceuticals and HealthTronics; Genentech; and ARIAD Pharmaceuticals, Inc.

Ovarian Cancer, Version 2.2013



[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).

OV-3

NCCN Categories of Evidence and Consensus

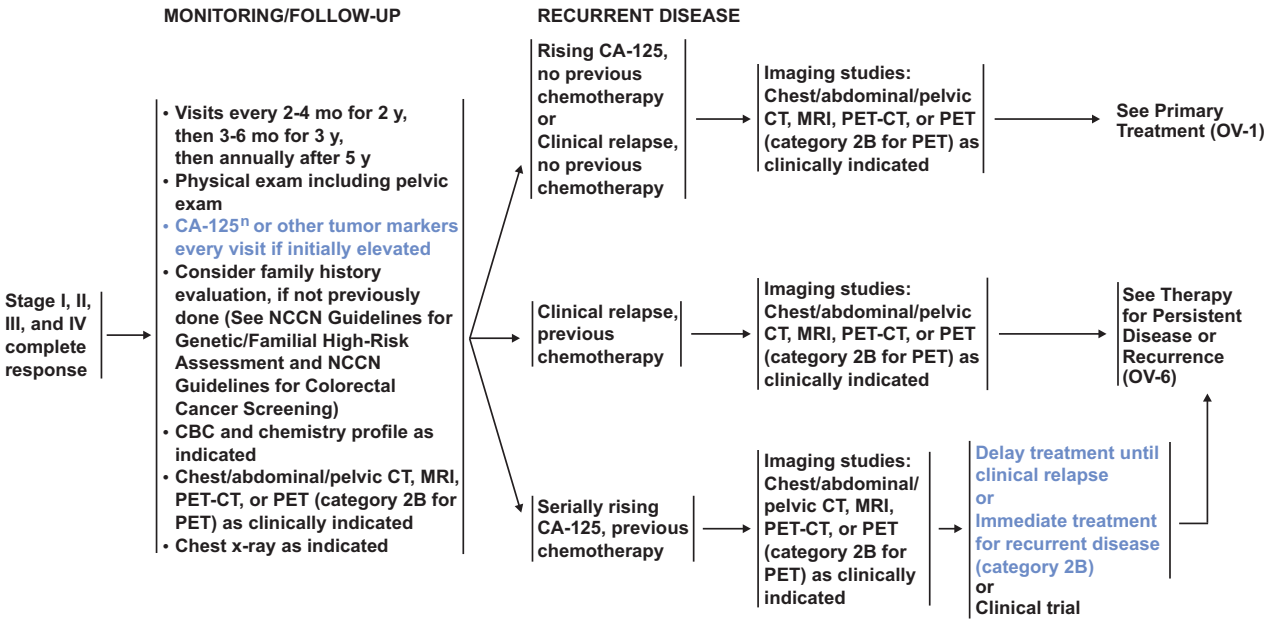
Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.
Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

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

Ovarian Cancer

These NCCN Guidelines Insights focus on the major updates to the 2013 NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Ovarian Cancer by describing how and why the new recommendations were made. Four topics were selected based on recent important updates in the NCCN Guidelines and debate among panel members about recent clinical trials. The topics include 1) intraperitoneal (IP) chemotherapy, 2) CA-125 monitoring for ovarian cancer recurrence, 3) surveillance recommendations for less common ovarian histopathologies, and 4) recent changes in therapy for recurrent epithelial ovarian cancer. The recently published NCCN Guidelines Insights on Ovarian Cancer discuss other topics, including 1) screening, 2) diagnostic tests for assessing pelvic masses, 3) primary treatment using neoadjuvant chemotherapy, 4) primary adjuvant treatment using bevacizumab in combination with chemotherapy,



[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.

OV-5

5) therapy for recurrent disease (mainly epithelial ovarian cancer), and 6) management of drug/hypersensitivity reactions.[1]

In 2013, an estimated 22,200 new diagnoses of and 14,000 deaths from ovarian cancer will occur in the United States.[2] The NCCN Guidelines for Ovarian Cancer discuss management of epithelial ovarian cancer, which is the most common type of ovarian cancer (to view the most recent version of these guidelines, visit NCCN.org). The 4 main histologic subtypes of epithelial ovarian cancer are serous, endometrioid, mucinous, and clear cell; however, most patients (≈70%) have serous histology.[3–7] Although some histologic subtypes respond differently, recommended primary treatment for these histologic subtypes does not currently differ; all are treated using the recommendations for epithelial ovarian cancer.[4]

The NCCN Guidelines also discuss less common cancers, such as Fallopian tube cancer and primary peritoneal cancer, which are managed in a similar manner to epithelial ovarian cancer. Less common ovarian histopathologies are also described, including malignant germ cell neoplasms, carcinosarcomas (malignant mixed Müllerian tumors of the ovary [MMMT]), and sex cord-stromal tumors. Another less common ovarian neoplasia is borderline epithelial ovarian tumor, which is less sensitive to chemotherapy than epithelial ovarian cancer and, in general, is managed surgically like malignant ovarian cancer except in specific circumstances.

These NCCN Guidelines Insights also discuss why some recommendations are category 2B and not category 2A or even category 1. For category 2A and 2B recommendations, the level of evidence to support the intervention is the same (eg, phase II randomized trial, phase III trial that has not been published yet). However, category 2A recommendations have greater consensus among panel members. A category 2B recommendation means that most panel members agree the intervention is appropri-

Ovarian Cancer, Version 2.2013

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 ~~(max BSA 2.0 m^2)~~. 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.

ate; however, some panel members would use other listed interventions (or may use other interventions in a different order), but do not feel that the listed intervention is inappropriate.

IP Chemotherapy

Surgical cytoreduction (debulking) is recommended as initial treatment for many women with ovarian cancer, even those with metastatic disease.[8–13] After surgical debulking, adjuvant systemic therapy (eg, taxane/platinum) is recommended for many patients (see OV-3, page 1201);[14] several different systemic regimens are recommended (see OV-D, page 1203).[15] Primary adjuvant therapy regimens include intravenous with (or without) IP options.[14,16–19] All of the regimens may be used for epithelial ovarian, primary peritoneal, and Fallopian tube cancers.

IP chemotherapy is recommended (category 1) for selected stage III patients with optimally debulked (<1 cm residual) disease (ie, low-volume residual disease) based on randomized controlled trials (see OV-3, page 1201).[16,20–24] Patients with optimally debulked stage II disease may also receive IP chemotherapy, although no randomized evidence has been published; therefore, this is a category 2A recommendation.[25–30] However, IP chemotherapy is not recommended for patients with stage I and IV disease in the NCCN Guidelines. In women with stage III cancer who had residual disease measuring less than 1 cm after debulking, 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).[15] Recent long-term follow-up data have confirmed this extraordinary survival advantage.[31] Overall survival was 110 months in patients with stage III ovarian cancer and no residual disease was found in those who received the IP regimen.[31] Although whether to use IP chemotherapy (vs intravenous chemotherapy alone) may be difficult to decide, the ex-

ACCEPTABLE RECURRENCE THERAPIES (1 of 2)†,Φ

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)

OV-E 1 of 2

Φ All references appearing on OV-E (1 of 2) can be accessed online, in these guidelines, at NCCN.org.

cellent survival rates for IP chemotherapy make this a valid option for selected patients.[31–37] Women with primary peritoneal cancer, Fallopian tube cancer, or MMMT can also be considered for IP chemotherapy, although MMMT has not been included in IP chemotherapy trials.[21,38] However, MMMT/carcinosarcoma is basically papillary serous carcinoma (ie, a poorly differentiated carcinoma); therefore, IP may be used for MMMT.

Potential toxicities associated with the IP paclitaxel/cisplatin regimen include leukopenia, infection, fatigue, renal toxicity, abdominal discomfort, neurotoxicity, and catheter complications.[24,32,39–41] Patients with poor performance status, comorbidities, or advanced age may not tolerate the IP regimen. Patients with stage IV disease have generally not been included in randomized trials of IP therapy; thus, its benefits have not been demonstrated in this group. Strategies to decrease toxicity and improve compliance with the IP chemotherapy regimen include using carefully selected patients, modifying dose and/or schedule, decreasing catheter complications, and using expert nursing care (see "Principles of Chemotherapy" and the discussion in the full version of these guidelines, available at NCCN.org).[14,32] The recommended IP chemotherapy regimen is paclitaxel, 135 mg/m^2 continuous intravenous infusion over 3 or 24 hours on day 1; cisplatin, 75 to 100 mg/m^2 IP on day 2 after intravenous paclitaxel; and paclitaxel, 60 mg/m^2 IP on day 8; repeated every 3 weeks for 6 cycles (category 1).[16] Note that this IP chemotherapy regimen includes intravenous paclitaxel, so that systemic disease can also be treated. The published randomized trial for this IP chemotherapy regimen used intravenous continuous infusion of paclitaxel over 24 hours.[16]

For the 2013 update of these NCCN Guidelines, the dosing for the IP chemotherapy regimen was revised to include a 3-hour infusion of paclitaxel, because it has been reported to be more convenient, easier to toler-

Ovarian Cancer, Version 2.2013

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.

LCOH-B

ate, and less toxic than a 24-hour infusion (see OV-D, page 1203).[42] However, a randomized trial comparing a 3-hour versus a 24-hour infusion of paclitaxel has not been performed to determine whether they are equivalent. Using a lower IP cisplatin dose of 75 mg/m^2 (GOG 252) or splitting the dose may also help to decrease toxicity.[28,42–44] Previously, capping doses at a maximum body surface area of 2.0 m^2 was recommended to reduce toxicity; however, this restriction was deleted in the 2013 update. If obese women receive doses based on their actual body weight, data suggest that they do not experience more toxicity; therefore, dose capping does not seem to be necessary and may result in suboptimal treatment.[45–48] Women should receive intravenous therapy if they are unable to complete IP therapy. Currently, the number of cycles of IP chemotherapy necessary to maintain a survival advantage is unclear,[28] although recent data suggest that survival correlates with the number of IP cycles received.[49] After 5 years, more women who received 5 or 6 cycles of IP chemotherapy were alive (59%) than those who only received 3 or 4 cycles (33%) or even 1 to 2 cycles (18%).[50]

CA-125 Monitoring for Ovarian Cancer Recurrence

Patients who have been treated for ovarian cancer and have experienced a complete response are carefully followed (monitored) to determine whether the disease has recurred. Monitoring includes measuring blood CA-125 levels if they were initially increased, physical and pelvic examinations, and other tests if indicated, such as imaging (see OV-5, page 1202).[51–55] For asymptomatic patients with only biochemical evidence of relapse (ie, with increased CA-125 levels but without radiographic and/or clinical evidence of relapse), treatment options include delaying treatment until clinical evidence of relapse (category 2A) or providing immediate treatment (category 2B). The NCCN Guidelines recommend (category 2A)

that treatment should be delayed until clinical evidence of relapse (eg, ascites, abdominal/pelvic/back pain, weight loss, bloating, obstruction) based on a recent European trial (see OV-5, page 1202).[56]

A recent multi-institutional European trial assessed the use of CA-125 monitoring for ovarian cancer recurrence after primary therapy.[56,57] Data suggest that treating recurrences early (based on detectable CA-125 levels in otherwise asymptomatic patients) is not associated with an increase in survival, and is associated with a decrease in quality of life.[58] The NCCN Ovarian Cancer Panel recommends that patients discuss the pros and cons of CA-125 monitoring with their physicians. However, patients often prefer to have CA-125 monitoring.[59] Several articles discuss CA-125 monitoring in greater detail.[60–63]

Surveillance Recommendations for Less Common Ovarian Histopathologies

Malignant germ cell tumors and sex cord-stromal tumors are rare. For the 2013 update, panel members added surveillance recommendations for germ cell neoplasms and sex cord-stromal tumors based on recent recommendations from the Society for Gynecology Oncology (see LCOH-B, page 1205).[60] The recommendations are different for the 2 types of tumors, because sex cord-stromal tumors can recur many years after initial diagnosis and treatment.

Therapy for Recurrent Disease

Although most patients with ovarian cancer experience a response to initial treatment, 75% to 80% will experience a relapse of their disease. Patients with ovarian cancer will often receive multiple types of recurrence therapy, because their disease frequently responds to sequential therapies. Recurrence therapy for patients with epithelial ovarian cancer, Fallopian tube cancer, and primary peritoneal cancer was discussed in detail in a recent NCCN Guidelines Insights.[1] The recommended options for recurrence therapy are shown in the NCCN Guidelines for Ovarian Cancer, including the preferred agents (available at NCCN.org). For the 2013 update, panel members added a new preferred regimen—carboplatin/gemcitabine/bevacizumab (category 2B)—based on the recent OCEANS trial (see OV-E, page 1204). This phase III randomized trial assessed carboplatin/gemcitabine with and without bevacizumab in patients with platinum-sensitive recurrent ovarian cancer who had not previously received bevacizumab. In patients receiving the chemotherapy/bevacizumab arm, progression-free survival was increased when compared with chemotherapy alone (12.4 vs 8.4 months; $P<.0001$).[64] However, overall survival was not increased in the chemotherapy/bevacizumab arms. Combination therapy with bevacizumab is a category 2B recommendation, because there is less consensus that this intervention would be routinely used by the panel members. Many of the panel members feel that other combination regimens may be 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 potentially active in patients who have recurrent disease (especially those with ascites), which is reflected in the category 2A recommendation for single-agent bevacizumab.[65–68]

Summary of the Major Updates

Four update topics are discussed in these NCCN Guidelines Insights. The 4 update topics include 1) IP chemotherapy, 2) CA-125 monitoring for ovarian cancer recurrence, 3) surveillance recommendations for less common ovarian histopathologies, and 4) recent changes in therapy for recurrent disease (mainly epithelial ovarian cancer).

After initial surgery, IP chemotherapy is recommended (category 1) for selected stage III patients with low-volume residual disease.[16,20–24] For the 2013 update, the dosing for the IP chemotherapy regimen was revised to include a 3-hour infusion of paclitaxel, because it has been reported to be more convenient, easier to tolerate, and less toxic (see OV-D, page 1203).[42] However, a 3-hour infusion of paclitaxel has not been proven to be equivalent to a 24-hour infusion in a randomized controlled trial. Previously, capping doses at a maximum body surface area of 2.0 m^2 was recommended to reduce toxicity; however, for the 2013 update, this restriction was deleted in the NCCN Guidelines. If obese women receive doses based on their actual body weight, data suggest that they do not have increased toxicity; therefore, dose capping does not seem to be necessary and may result in suboptimal treatment.[45–48]

Ovarian Cancer, Version 2.2013

For the 2013 update, the panel added surveillance recommendations for germ cell neoplasms and sex cords-tromal tumors based on recent recommendations from the Society for Gynecology Oncology (see LCOH-B, page 1205).[60]

Patients who have been treated for ovarian cancer and have had a complete response are carefully monitored to determine whether the disease has recurred. The NCCN Guidelines recommend (category 2A) that treatment for ovarian cancer should be delayed until radiographic and/or clinical evidence of relapse (eg, ascites, abdominal/pelvic/back pain, weight loss, bloating, and obstruction; see OV-5, page 1202).[56] A recent trial suggests that treating recurrences early (based only on detectable CA-125 levels in otherwise asymptomatic patients) is not associated with an increase in survival but is associated with a decrease in quality of life.[56–58] Therefore, early immediate treatment is only a category 2B recommendation in the NCCN Guidelines.

For the 2013 update, panel members have added a new preferred recurrence therapy regimen of carboplatin/gemcitabine/bevacizumab (category 2B) based on the recent OCEANS trial (see OV-E, page 1204).[64] However, combination therapy with bevacizumab is a category 2B recommendation, because less consensus exists among the panel that this intervention would be routinely used. Many of the panel members feel that other combination regimens are potentially more beneficial and effective than those with bevacizumab. Recurrence therapy for patients with epithelial ovarian cancer, Fallopian tube cancer, and primary peritoneal cancer was discussed in detail in a recent NCCN Guidelines Insights.[1] The recommended options for recurrence therapy are shown in the NCCN Guidelines for Ovarian Cancer, including the preferred agents (see OV-E, page 1204).

References

1. Morgan RJ Jr, Alvarez RD, Armstrong DK, et al. Ovarian Cancer, Version 3.2012. J Natl Compr Canc Netw 2012;10:1339–1349.
2. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. CA Cancer J Clin 2013;63:11–30.
3. Prat J. New insights into ovarian cancer pathology. Ann Oncol 2012;23(Suppl 10):x111–117.
4. McCluggage WG. Morphological subtypes of ovarian carcinoma: a review with emphasis on new developments and pathogenesis. Pathology 2011;43:420–432.
5. Edge SB, Byrd DR, Compton CC, et al. AJCC Cancer Staging Manual, 7th ed. New York, NY: Springer; 2010.
6. Kobel M, Kalloger SE, Huntsman DG, et al. Differences in tumor type in low-stage versus high-stage ovarian carcinomas. Int J Gynecol Pathol 2010;29:203–211.
7. Seidman JD, Horkayne-Szakaly I, Haiba M, et al. The histologic type and stage distribution of ovarian carcinomas of surface epithelial origin. Int J Gynecol Pathol 2004;23:41–44.
8. Bristow RE, Tomacruz RS, Armstrong DK, et al. Survival effect of maximal cytoreductive surgery for advanced ovarian carcinoma during the platinum era: a meta-analysis. J Clin Oncol 2002;20:1248–1259.
9. Chi DS, Franklin CC, Levine DA, et al. Improved optimal cytoreduction rates for stages IIIC and IV epithelial ovarian, fallopian tube, and primary peritoneal cancer: a change in surgical approach. Gynecol Oncol 2004;94:650–654.
10. Elattar A, Bryant A, Winter-Roach BA, et al. Optimal primary surgical treatment for advanced epithelial ovarian cancer. Cochrane Database Syst Rev 2011:CD007565.
11. Luyckx M, Leblanc E, Filleron T, et al. Maximal cytoreduction in patients with FIGO stage IIIC to stage IV ovarian, fallopian, and peritoneal cancer in day-to-day practice: a retrospective French multicentric study. Int J Gynecol Cancer 2012;22:1337–1343.
12. Chang SJ, Bristow RE, Ryu HS. Impact of complete cytoreduction leaving no gross residual disease associated with radical cytoreductive surgical procedures on survival in advanced ovarian cancer. Ann Surg Oncol 2012;19:4059–4067.
13. Goff BA. Advanced ovarian cancer: what should be the standard of care? J Gynecol Oncol 2013;24:83–91.
14. Cristea M, Han E, Salmon L, Morgan RJ. Practical considerations in ovarian cancer chemotherapy. Ther Adv Med Oncol 2010;2:175–187.
15. Armstrong DK. New issues in systemic therapy for ovarian cancer. J Natl Compr Canc Netw 2013;11:690–693.
16. Armstrong DK, Bundy B, Wenzel L, et al. Intraperitoneal cisplatin and paclitaxel in ovarian cancer. N Engl J Med 2006;354:34–43.
17. Ozols RF, Bundy BN, Greer BE, et al. Phase III trial of carboplatin and paclitaxel compared with cisplatin and paclitaxel in patients with optimally resected stage III ovarian cancer: a Gynecologic Oncology Group study. J Clin Oncol 2003;21:3194–3200.
18. Vasey PA, Jayson GC, Gordon A, et al. Phase III randomized trial of docetaxel-carboplatin versus paclitaxel-carboplatin as first-line chemotherapy for ovarian carcinoma. J Natl Cancer Inst 2004;96:1682–1691.
19. Katsumata N, Yasuda M, Takahashi F, et al. Dose-dense paclitaxel once a week in combination with carboplatin every 3 weeks for advanced ovarian cancer: a phase 3, open-label, randomised controlled trial. Lancet 2009;374:1331–1338.
20. Markman M, Walker JL. Intraperitoneal chemotherapy of ovarian cancer: a review, with a focus on practical aspects of treatment. J Clin Oncol 2006;24:988–994.
21. Marth C, Walker JL, Barakat RR, et al. Results of the 2006 Innsbruck International Consensus Conference on intraperitoneal chemotherapy in patients with ovarian cancer. Cancer 2007;109:645–649.
22. Alberts DS, Liu PY, Hannigan EV, et al. Intraperitoneal cisplatin plus intravenous cyclophosphamide versus intravenous cisplatin plus intravenous cyclophosphamide for stage III ovarian cancer. N Engl J Med 1996;335:1950–1955.
23. Markman M, Bundy BN, Alberts DS, et al. Phase III trial of standard-dose intravenous cisplatin plus paclitaxel versus

moderately high-dose carboplatin followed by intravenous paclitaxel and intraperitoneal cisplatin in small-volume stage III ovarian carcinoma: an intergroup study of the Gynecologic Oncology Group, Southwestern Oncology Group, and Eastern Cooperative Oncology Group. J Clin Oncol 2001;19:1001–1007.

24. Elit L, Oliver TK, Covens A, et al. Intraperitoneal chemotherapy in the first-line treatment of women with stage III epithelial ovarian cancer: a systematic review with metaanalyses. Cancer 2007;109:692–702.
25. Kirmani S, Braly PS, McClay EF, et al. A comparison of intravenous versus intraperitoneal chemotherapy for the initial treatment of ovarian cancer. Gynecol Oncol 1994;54:338–344.
26. Gadducci A, Carnino F, Chiara S, et al. Intraperitoneal versus intravenous cisplatin in combination with intravenous cyclophosphamide and epidoxorubicin in optimally cytoreduced advanced epithelial ovarian cancer: a randomized trial of the Gruppo Oncologico Nord-Ovest. Gynecol Oncol 2000;76:157–162.
27. Fujiwara K, Nagao S, Kigawa J, et al. Phase II study of intraperitoneal carboplatin with intravenous paclitaxel in patients with suboptimal residual epithelial ovarian or primary peritoneal cancer: a Sankai Gynecology Cancer Study Group Study. Int J Gynecol Cancer 2009;19:834–837.
28. Fujiwara K. Three ongoing intraperitoneal chemotherapy trials in ovarian cancer. J Gynecol Oncol 2012;23:75–77.
29. Nagao S, Fujiwara K, Ohishi R, et al. Combination chemotherapy of intraperitoneal carboplatin and intravenous paclitaxel in suboptimally debulked epithelial ovarian cancer. Int J Gynecol Cancer 2008;18:1210–1214.
30. Fujiwara K, Sakuragi N, Suzuki S, et al. First-line intraperitoneal carboplatin-based chemotherapy for 165 patients with epithelial ovarian carcinoma: results of long-term follow-up. Gynecol Oncol 2003;90:637–643.
31. Landrum LM, Java J, Mathews CA, et al. Prognostic factors for stage III epithelial ovarian cancer treated with intraperitoneal chemotherapy: a Gynecologic Oncology Group study. Gynecol Oncol 2013;130:12–18.
32. Jaaback K, Johnson N, Lawrie TA. Intraperitoneal chemotherapy for the initial management of primary epithelial ovarian cancer. Cochrane Database Syst Rev 2011:CD005340.
33. Rowan K. Intraperitoneal therapy for ovarian cancer: why has it not become standard? J Natl Cancer Inst 2009;101:775–777.
34. Zeimet AG, Reimer D, Radl AC, et al. Pros and cons of intraperitoneal chemotherapy in the treatment of epithelial ovarian cancer. Anticancer Res 2009;29:2803–2808.
35. Gore M, du Bois A, Vergote I. Intraperitoneal chemotherapy in ovarian cancer remains experimental. J Clin Oncol 2006;24:4528–4530.
36. Armstrong DK, Brady MF. Intraperitoneal therapy for ovarian cancer: a treatment ready for prime time. J Clin Oncol 2006;24:4531–4533.
37. Ozols RF, Bookman MA, du Bois A, et al. Intraperitoneal cisplatin therapy in ovarian cancer: comparison with standard intravenous carboplatin and paclitaxel. Gynecol Oncol 2006;103:1–6.
38. Walker JL, Armstrong DK, Huang HQ, et al. Intraperitoneal catheter outcomes in a phase III trial of intravenous versus intraperitoneal chemotherapy in optimal stage III ovarian and primary peritoneal cancer: a Gynecologic Oncology Group study. Gynecol Oncol 2006;100:27–32.
39. Markman M. Management of ovarian cancer. An impressive history of improvement in survival and quality of life. Oncology (Williston Park) 2006;20:347–354.
40. Wenzel LB, Huang HQ, Armstrong DK, et al. Health-related quality of life during and after intraperitoneal versus intravenous chemotherapy for optimally debulked ovarian cancer: a Gynecologic Oncology Group Study. J Clin Oncol 2007;25:437–443.
41. Tummala MK, Alagarsamy S, McGuire WP. Intraperitoneal chemotherapy: standard of care for patients with minimal residual stage III ovarian cancer? Expert Rev Anticancer Ther 2008;8:1135–1147.
42. Barlin JN, Dao F, Zgheib NB, et al. Progression-free and overall survival of a modified outpatient regimen of primary intravenous/intraperitoneal paclitaxel and intraperitoneal cisplatin in ovarian, fallopian tube, and primary peritoneal cancer. Gynecol Oncol 2012;125:621–624.
43. Landrum LM, Hyde J Jr, Mannel RS, et al. Phase II trial of intraperitoneal cisplatin combined with intravenous paclitaxel in patients with ovarian, primary peritoneal and fallopian tube cancer. Gynecol Oncol 2011;122:527–531.
44. Markman M. An update on the use of intraperitoneal chemotherapy in the management of ovarian cancer. Cancer J 2009;15:105–109.
45. Schwartz J, Toste B, Dizon DS. Chemotherapy toxicity in gynecologic cancer patients with a body surface area (BSA)>2 m2. Gynecol Oncol 2009;114:53–56.
46. Griggs JJ, Mangu PB, Anderson H, et al. Appropriate chemotherapy dosing for obese adult patients with cancer: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol 2012;30:1553–1561.
47. Wright JD, Tian C, Mutch DG, et al. Carboplatin dosing in obese women with ovarian cancer: a Gynecologic Oncology Group study. Gynecol Oncol 2008;109:353–358.
48. Hunter RJ, Navo MA, Thaker PH, et al. Dosing chemotherapy in obese patients: actual versus assigned body surface area (BSA). Cancer Treat Rev 2009;35:69–78.
49. Tewari D, Java J, Salani R, et al. Long-term survival advantage of intraperitoneal chemotherapy treatment in advanced ovarian cancer: an analysis of a Gynecologic Oncology Group ancillary data study (GOG#114/172) [abstract]. Presented at the Society of Gynecologic Oncology Annual Meeting on Women's Cancer; March 9–12, 2013; Los Angeles, CA. Abstract 6.
50. Sullivan EJ. Bathing abdomen in chemotherapy gives ovarian cancer patients better chance of survival. Society of Gynecologic Oncology Web site. Available at: https://www.sgo.org/newsroom/newsreleases/eninchemotherapygivesovariancancerpatientsbetterchanceofsurvival/. Accessed September 6, 2013.
51. Risum S, Hogdall C, Markova E, et al. Influence of 2-(18F) fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography on recurrent ovarian cancer diagnosis and on selection of patients for secondary cytoreductive surgery. Int J Gynecol Cancer 2009;19:600–604.
52. Fulham MJ, Carter J, Baldey A, et al. The impact of PET-CT in suspected recurrent ovarian cancer: a prospective multi-centre study as part of the Australian PET Data Collection Project. Gynecol Oncol 2009;112:462–468.
53. Bhosale P, Peungjesada S, Wei W, et al. Clinical utility of positron emission tomography/computed tomography in the evaluation of suspected recurrent ovarian cancer in the setting of normal CA-125 levels. Int J Gynecol Cancer 2010;20:936–944.
54. Son H, Khan SM, Rahaman J, et al. Role of FDG PET/CT in staging of recurrent ovarian cancer. Radiographics 2011;31:569–583.

Ovarian Cancer, Version 2.2013

55. Rettenmaier NB, Rettenmaier CR, Wojciechowski T, et al. The utility and cost of routine follow-up procedures in the surveillance of ovarian and primary peritoneal carcinoma: a 16-year institutional review. Br J Cancer 2010;103:1657–1662.
56. Rustin GJ, van der Burg ME, Griffin CL, et al. Early versus delayed treatment of relapsed ovarian cancer (MRC OV05/EORTC 55955): a randomised trial. Lancet 2010;376:1155–1163.
57. Rustin G, van der Burg M, Griffin C, et al. Early versus delayed treatment of relapsed ovarian cancer. Lancet 2011;377:380–381.
58. Miller RE, Rustin GJ. How to follow-up patients with epithelial ovarian cancer. Curr Opin Oncol 2010;22:498–502.
59. Markman M, Petersen J, Belland A, Burg K. CA-125 monitoring in ovarian cancer: patient survey responses to the results of the MRC/EORTC CA-125 Surveillance Trial. Oncology 2010;78:1–2.
60. 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.
61. Morris RT, Monk BJ. Ovarian cancer: relevant therapy, not timing, is paramount. Lancet 2010;376:1120–1122.
62. Karam AK, Karlan BY. Ovarian cancer: the duplicity of CA125 measurement. Nat Rev Clin Oncol 2010;7:335–339.
63. Bast RC Jr. CA 125 and the detection of recurrent ovarian cancer: a reasonably accurate biomarker for a difficult disease. Cancer 2010;116:2850–2853.
64. Aghajanian C, Blank SV, Goff BA, et al. OCEANS: a randomized, double-blind, placebo-controlled phase III trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer. J Clin Oncol 2012;30:2039–2045.
65. Burger RA, Sill MW, Monk BJ, et al. Phase II trial of bevacizumab in persistent or recurrent epithelial ovarian cancer or primary peritoneal cancer: a Gynecologic Oncology Group Study. J Clin Oncol 2007;25:5165–5171.
66. Cannistra SA, Matulonis UA, Penson RT, et al. Phase II study of bevacizumab in patients with platinum-resistant ovarian cancer or peritoneal serous cancer. J Clin Oncol 2007;25:5180–5186.
67. Elit L, Hirte H. Palliative systemic therapy for women with recurrent epithelial ovarian cancer: current options. Onco Targets Ther 2013;6:107–118.
68. Emile G, Chauvenet L, Tigaud JM, et al. A clinical experience of single agent bevacizumab in relapsing ovarian cancer. Gynecol Oncol 2013;129:459–462.

Instructions for Completion

To participate in this journal CE activity: 1) review the learning objectives and author disclosures; 2) study the education content; 3) take the posttest with a 66% minimum passing score and complete the evaluation at **http://education.nccn.org/node/30997;** and 4) view/print certificate. After reading the article, you should be able to answer the following multiple-choice questions. Credit cannot be obtained for tests completed on paper. You must be a registered user on NCCN.org. If you are not registered on NCCN.org, click on "New Member? Sign up here" link on the left hand side of the Web site to register. Only one answer is correct for each question. Once you successfully answer all posttest questions you will be able to view and/or print your certificate. Software requirements: Internet.

Posttest Questions

1. Which of the following is FALSE about IP chemotherapy using cisplatin/paclitaxel for select women with ovarian cancer?
   a. Capping doses at a maximum body surface area of 2.0 m^2 is recommended to reduce toxicity.
   b. Dose capping at a maximum body surface area of 2.0 m^2 does not seem to be necessary and is no longer recommended.
   c. A 3-hour infusion of paclitaxel has not been shown to be equivalent to a 24-hour infusion in a randomized trial.
   d. A 3-hour infusion of paclitaxel appears to be more convenient, easier to tolerate, and less toxic than a 24-hour infusion.
   e. Reported survival averages about 66 months in select women with stage III ovarian cancer who complete an IP chemotherapy regimen.
2. Which of the following is TRUE about epithelial ovarian cancer?
   a. Most patients have serous histology.
   b. It is the most common type of ovarian cancer.
   c. Initial treatment includes surgical cytoreduction (debulking), even in those with metastatic disease.
   d. All of the above
   e. None of the above
3. In patients with complete response after primary treatment for ovarian cancer, which of the following is FALSE about surveillance and treatment for recurrent disease?
   a. Surveillance includes measuring CA-125 levels if they were initially increased.
   b. For asymptomatic patients who only have increased CA-125 levels, treatment should be delayed until clinical evidence of relapse, such as ascites, abdominal/pelvic/back pain, weight loss, bloating, and obstruction.
   c. For asymptomatic patients who only have increased CA-125 levels but no clinical evidence of relapse, immediate treatment is recommended.
   d. All of the above
   e. None of the above