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

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

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

See NCCN Categories of Evidence and Consensus.

Staging (ST-1)
Updates to the 3.2012 version of the Ovarian Cancer Guidelines from the 2.2012 version include:

**OV-3**
- The chemotherapy regimens for Stage II-IV were moved from a footnote to a new page titled, “Primary Chemotherapy/Primary Adjuvant Therapy Regimens for Stage II-IV”. Footnote “I” was added to the page: “See specific regimens on Primary Chemotherapy/Primary Adjuvant Therapy Regimens for Stage II-IV (OV-D).”

**OV-D**
- Primary Chemotherapy/Primary Adjuvant Therapy Regimens for Stage II-IV, the following was added:
  - Bevacizumab-containing regimens per ICON-7 and GOG-218:
    - Paclitaxel 175 mg/m² IV over 3 hours, carboplatin 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)
    - Paclitaxel 175 mg/m² IV over 3 hours and carboplatin AUC 6 IV over 30 minutes 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)

**MS-1**
- The discussion has been updated to reflect the recent changes in the algorithm.

Updates to the 2.2012 version of the Ovarian Cancer Guidelines from the 1.2012 version include:
- The addition of the discussion to reflect the changes in the algorithm (MS-1).

Updates to the 1.2012 version of the Ovarian Cancer Guidelines from the 2.2011 version include:

**OV-1**
- Primary treatment
  - For patients with bulky stage III/IV who are determined not to be surgical candidates, “Consider neoadjuvant chemotherapy” was changed from a category 2A recommendation to a category 1 recommendation.
  - Footnotes
  - Footnote c, “See Discussion for usefulness of diagnostic tests” is new to the page.
  - Footnote “d” was modified by adding: “Standard recommendation includes a patient evaluation by a gynecologic oncologist prior to initiating chemotherapy. Patients being evaluated for neoadjuvant surgery chemotherapy should be seen...” (Also for OV-2)

**OV-5**
- Recurrent disease
  - Serially rising CA-125, previous chemotherapy, “Delay treatment until clinical relapse” was changed from a category 2B recommendation to a category 2A recommendation.
  - Footnote “o” was modified as: “There are preliminary data regarding...see...and Discussion”. (Also for OV-9)

**OV-6**
- Disease status
  - Complete remission and relapse > 6 mo after stopping chemotherapy, was separated into “radiographic and/or clinical relapse” and “biochemical relapse (rising CA-125 and no radiographic evidence of disease)”. For biochemical relapse, the following options for persistent disease or recurrence were added, “clinical trial, or delay treatment until clinical relapse or Immediate treatment for recurrent disease (recurrence therapy) (category 2B).”
  - Footnote “s” was added: “Clinical trials with newer agents should be strongly considered”.

**OV-7**
- Pelvic mass, fertility not desired, “standard surgery” was clarified as “completion surgery.”
  - Previous diagnosis of low malignant potential
  - “Previous surgical staging was complete” was changed to “....was comprehensive.”

**OV-8**
- Previous diagnosis of low malignant potential was expanded to clarify the options for fertility desired and no fertility desired when there was an incomplete previous surgery.

Continued on next page
Updates to the 1.2012 version of the Ovarian Cancer guidelines from the 2.2011 version include: (continued)

**OV-A 1 of 3**
- For both ovarian cancer apparently confined to an ovary or to the pelvis and ovarian cancer involving the upper abdomen:
  - Subbullet “Hysterectomy, bilateral salpingectomy, and bilateral oophorectomy should be performed...” was modified by removing “total” from hysterectomy.
  - New subbullet was added: “In low malignant potential, although data show upstaging with lymphadenectomy and omentectomy, other data show this surgery does not affect overall survival.”

**OV-B 1 of 2**
- 6th bullet was modified as: “Chemosensitivity/resistance and/or other biomarker assays are being used in some NCCN centers...”

**OV-B 2 of 2**
- 6th bullet was added: “Clinicians should be familiar with toxicity management and appropriate dose reduction.”

**OV-C 1 of 7 and OV-C 3 of 7**
- Algorithms for the management of “IV or IP drug reaction to platinum agents” and “IV or IP drug reaction to taxane, liposomal doxorubicin, or biotherapeutic agents” were added.

**OV-C 5 of 7**
- Preparation for a possible drug reaction, 5th subbullet was modified by adding, “In the setting of acute cardiopulmonary arrest, standard resuscitation (ACLS) procedures should be followed.”

**OV-E**
- Footnote “‡” was added: “In general, the panel would recommend combination regimens based on randomized trial data especially in first relapses” .

**LCOH-1**
- Footnote “a” was added: “See Sex Cord-Stromal Tumors - WHO Histologic Classification (LCOH-A).” (Also for LCOH-4 and LCOH-B)
- Malignant was added to “sex cord-stromal tumors” for clarification. (Also for LCOH-4)

**LCOH-2**
- Prior surgery, incompletely surgically staged pathway was expanded to include imaging and marker status in deciding primary treatment.
- Endodermal sinus tumor, “yolk sac tumor” was added as a descriptor. (Also for LCOH-3)

**LCOH-4**
- Stage I high risk and intermediate risk, “RT (category 2B)” was removed.
- Footnotes
  - Footnote “i” was modified as: “Inhibin levels can be followed if initially elevated for granulosa cell tumors (category 2B)”.
  - Footnote “j” was modified as: “Malignant germ cell regimens (See LCOH-3)...”

**LCOH-5**
- Stage I disease was combined with Stage II-IV to be treated per Epithelial Ovarian Cancer Guidelines (OV-3).

**LCOH-A**
- Sex cord-stromal tumors - WHO histologic classification is new to the guidelines.
**CLINICAL PRESENTATION**

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

**WORKUP**

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

**PRIMARY TREATMENT**

- Laparotomy/Hysterectomy (TAH)/Bilateral salpingo-oophorectomy (BSO) with comprehensive staging or unilateral salpingo-oophorectomy (USO) (Clinical Stage 1A or 1C, all grades with comprehensive staging if patient desires fertility)
- Cytoreductive surgery if clinical stage II, III, or IV
- For patients with bulky stage III/IV who are determined not to be surgical candidates, consider neoadjuvant chemotherapy (category 1)/primary interval cytoreduction (diagnosis by fine needle aspiration [FNA], biopsy or paracentesis)

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

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
**NCCN Guidelines Version 3.2012**

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

**DIAGNOSIS BY PREVIOUS SURGERY**

<table>
<thead>
<tr>
<th>Adequate previous surgery and staging</th>
<th>FINDINGS</th>
<th>PRIMARY TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Suspected stage IA or IB, Grade 1 (^h)</td>
<td>Surgical staging procedure (^f)</td>
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<tr>
<td></td>
<td>Suspected stage IA or IB, Grade 2 (^h)</td>
<td>Surgical staging procedure (^f)</td>
</tr>
<tr>
<td>Incomplete previous surgery and/or staging:</td>
<td></td>
<td>Completion surgical staging procedure (^f)</td>
</tr>
<tr>
<td>1. Uterus intact</td>
<td>Suspect residual disease</td>
<td>Chemotherapy (^g) for 6 cycles or completion staging surgery (^f)</td>
</tr>
<tr>
<td>2. Adnexa intact</td>
<td>Suspect no residual disease</td>
<td>Completion surgical staging surgery (^f)</td>
</tr>
<tr>
<td>3. Omentum not removed</td>
<td></td>
<td>Chemotherapy (^g) for 6 cycles or completion staging surgery (^f)</td>
</tr>
<tr>
<td>4. Documentation of staging incomplete</td>
<td></td>
<td>Chemotherapy (^g) for a total of 6-8 cycles</td>
</tr>
<tr>
<td>5. Residual disease, potentially resectable</td>
<td></td>
<td>Consider completion surgery after 3-6 cycles (^i) followed by postoperative chemotherapy</td>
</tr>
<tr>
<td>Stage II, III, IV</td>
<td></td>
<td>Tumor reductive surgery (^f)</td>
</tr>
</tbody>
</table>

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

\(^f\)See Principles of Primary Surgery (OV-A).

\(^g\)See Principles of Chemotherapy (OV-B) and Management of Drug Reactions (OV-C).

\(^h\)Clear-cell pathology is grade 3.

\(^i\)Based on clinical judgement of gynecologic oncologist, surgery may be performed after 6 cycles.

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PATHOLOGIC STAGING

**Stage IA or IB**
- **Grade 1**: Observe
- **Grade 2**: Observe or Intravenous (IV) taxane/carboplatin for 3-6 cycles
- **Grade 3**: IV taxane/carboplatin for 3-6 cycles

**Stage IC**
- Grade 1, 2, or 3: IV taxane/carboplatin for 3-6 cycles

**Stage II**
- Completion surgery as indicated by tumor response and potential resectability in selected patients

**Stage III**
- Intraperitoneal (IP) chemotherapy in < 1 cm optimally debulked Stage II patients and Stage III patients (category 1 for Stage III)
  - or
  - Intravenous taxane/carboplatin for a total of 6-8 cycles (category 1)

**Stage IV**

**Chemotherapy**
- Intraperitoneal (IP) chemotherapy in < 1 cm optimally debulked Stage II patients and Stage III patients (category 1 for Stage III)
  - or
  - Intravenous taxane/carboplatin for a total of 6-8 cycles (category 1)
  - Completion surgery as indicated by tumor response and potential resectability in selected patients

---

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.

See Principles of Primary Surgery (OV-A).

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

Clear-cell pathology is Grade 3.

Note: All recommendations are category 2A unless otherwise indicated. Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
**Stage II, III, IV post primary treatment**

**Secondary Adjuvant Therapy**

- **Complete clinical remission**<sup>m</sup>
  - Observe
  - or Clinical trial
  - or Postremission paclitaxel<sup>n</sup>
    (category 2B)

- **Partial remission or progression**
  - Observe
  - or Clinical trial
  - or Postremission paclitaxel<sup>n</sup>
    (category 2B)

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

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

<sup>m</sup>No objective evidence of disease (ie, negative physical exam, negative CA-125, negative CT with < 1 cm lymph nodes).

<sup>n</sup>See Discussion for dosing.

See Monitoring/Follow-Up (OV-5)

See Persistent Disease or Recurrence Therapy (OV-6)
MONITORING/FOLLOW-UP

Stage I, II, III, and IV complete response

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

STAGE I-IV COMPLETE RESPONSE

RECURRENT DISEASE

Rising CA-125, no previous chemotherapy or Clinical relapse, no previous chemotherapy

Imaging studies: Chest/abdominal/pelvic CT, MRI, PET-CT, or PET (category 2B for PET) as clinically indicated

Clinical relapse, previous chemotherapy

Imaging studies: Chest/abdominal/pelvic CT, MRI, PET-CT, or PET (category 2B for PET) as clinically indicated

Serially rising CA-125, previous chemotherapy

Imaging studies: Chest/abdominal/pelvic CT, MRI, PET-CT, or PET (category 2B for PET) as clinically indicated

Delay treatment until clinical relapse or Immediate treatment for recurrent disease (category 2B) or Clinical trial

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

<sup>®</sup>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.

See Primary Treatment (OV-1)
See Therapy for Persistent Disease or Recurrence (OV-6)
Epithelial Ovarian Cancer/ Fallopian Tube Cancer/ Primary Peritoneal Cancer

DISEASE STATUS

Progression, stable, or persistent disease on primary chemotherapy

Complete remission and relapse < 6 mo after stopping chemotherapy
or
Stage II, III, and IV with partial response

Clinical trials, or Supportive care only, or Recurrence therapy \(^p,q,r\)

Clinical trial \(^s\)
or
Recurrence therapy \(^p,r\)
or
Observe (category 2B)

THERAPY FOR PERSISTENT DISEASE OR RECURRENCE \(^p,q,r\)

Complete remission and relapse > 6 mo after stopping chemotherapy

Radiographic and/or clinical relapse

Biochemical relapse (rising CA-125 and no radiographic evidence of disease)

Consider secondary cytoreductive surgery \(^f\)

Clinical trial \(^s\)
or
Combination platinum-based chemotherapy \(^p,r\)
preferred for first recurrence (category 1)
or
Recurrence therapy \(^p,r\)

Clinical trial \(^s\)
or
Delay treatment until clinical relapse
or
Immediate treatment for recurrent disease (recurrence therapy \(^r\)) (category 2B)

\(^f\) See Principles of Primary Surgery (OV-A).

\(^p\) Patients who progress on two consecutive therapy regimens without evidence of clinical benefits have diminished likelihood of benefiting from additional therapy. Decisions to offer clinical trials, supportive care only, or additional therapy should be made on a highly individual basis.

\(^q\) See Ancillary Palliative Surgical Procedures in Principles of Surgery (OV-A).

\(^r\) See Acceptable Recurrence Therapies (OV-E).

\(^s\) Clinical trials with newer agents should be strongly considered.

Note: All recommendations are category 2A unless otherwise indicated. Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
Borderline Epithelial Ovarian Cancer (Low Malignant Potential)

CLINICAL PRESENTATION

Pelvic mass

- Low malignant potential lesion

- Previous diagnosis of low malignant potential lesion with institutional pathology review

- Incomplete previous surgery

- Previous surgical staging was comprehensive

FERTILITY DESIRED

- Stage I - IV Fertility desired

- Fertility-sparing surgery and comprehensive staging

FERTILITY NOT DESIRED

- Stage I - IV Fertility not desired

- Completion surgery, including comprehensive staging

PRIMARY TREATMENT

- No invasive implants

- Observe

- Invasive implants

- Observe or consider treatment as epithelial ovarian cancer (category 2B) (See OV-2)

Monitoring Follow-up (OV-9)

See Principles of Primary Surgery (OV-A).

Standard recommendation includes a patient evaluation by a gynecologic oncologist.

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

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

- Previous diagnosis of low malignant potential lesion with institutional pathology review
  - Incomplete previous surgery
    - Fertility desired
      - Invasive implants at previous surgery
        - No invasive implants or Unknown
          - Observe
          - Fertility sparing surgery and comprehensive surgical staging, if not previously done
          - Fertility sparing surgery and comprehensive surgical staging, if not previously done (category 2B)
          - Observe (category 2B)
          - Consider treatment as epithelial ovarian cancer (category 2B) (See OV-2)
    - If no desire for fertility
      - Invasive implants at previous surgery
        - No invasive implants or Unknown
          - Completion surgery
          - Completion surgery
          - Observe
          - Observe (category 2B)
          - Consider treatment as epithelial ovarian cancer (category 2B) (See OV-2)

**PRINCIPLES OF PRIMARY SURGERY**

= See Principles of Primary Surgery (OV-A).

Standard recommendation includes a patient evaluation by a gynecologic oncologist.

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

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

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**See Principles of Primary Surgery (OV-A).**
Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
PRINCIPLES OF PRIMARY SURGERY (1 of 3)\textsuperscript{1,2}

- In general, a vertical midline abdominal incision should be used in patients with a suspected malignant ovarian neoplasm.\textsuperscript{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 of patients with ovarian cancer apparently confined to an ovary or to the pelvis:
  - On entering the abdomen, aspiration of ascites or peritoneal lavage should be performed for peritoneal cytologic examinations.
  - All peritoneal surfaces should be visualized, and any peritoneal surface or adhesion suspicious for harboring metastasis should be selectively excised or biopsied. In the absence of any suspicious areas, random peritoneal biopsies should be taken from the pelvis, paracolic gutters, and undersurfaces of the diaphragm (diaphragm scraping for Papanicolaou stain is an acceptable alternative).
  - Hysterectomy, bilateral salpingectomy, and bilateral oophorectomy should be performed with every effort made to keep an encapsulated mass intact during removal.
  - Unilateral salpingo-oophorectomy (USO) for patients desiring to preserve fertility may be considered in select patients. (See OV-A 2 of 3)
  - Omentectomy should be performed.
  - Aortic lymph node dissection should be performed by stripping the nodal tissue from the vena cava and the aorta bilaterally to at least the level of the inferior mesenteric artery and preferably to the level of the renal vessels.
  - Pelvic lymph nodes should be dissected. Removal of lymph nodes overlying and medial to the external iliac and hypogastric vessels, from the obturator fossa anterior to the obturator nerve, and overlying and anterolateral to the common iliac vessel is preferred.
  - In low malignant potential, although data show upstaging with lymphadenectomy and omentectomy, other data show this surgery does not affect overall survival.

**Ovarian cancer involving the upper abdomen**

- In general, the following procedures should be part of the surgical management of patients with ovarian cancer involving the upper abdomen in an effort to achieve maximal cytoreduction. Residual disease < 1 cm defines optimal cytoreduction; however, maximal effort should be made to remove all gross disease.
  - Aspiration of ascites or peritoneal lavage should be performed for peritoneal cytologic examinations. For obvious disease beyond ovaries, cytologic assessment of ascites and/or lavage specimens would not alter stage or management.
  - Hysterectomy, bilateral salpingectomy, and bilateral oophorectomy should be performed.
  - All involved omentum should be removed.
  - Suspicious and/or enlarged nodes should be resected, if possible.
  - Those patients with tumor nodules outside the pelvis \( \leq 2 \text{ cm} \) (presumed stage IIIB) should have bilateral pelvic and para-aortic lymph node dissection as previously described.


\textsuperscript{2} It is recommended that a gynecologic oncologist should perform primary surgery (category 1).

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

Continued on OV-A 2 of 3
PRINCIPLES OF PRIMARY SURGERY (2 of 3)

• 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

Special Circumstances

• In Stage I disease, minimally invasive techniques may be considered to achieve the surgical principles described on OV-A 1 of 3. Minimally invasive surgery performed by an experienced gynecologic oncologist may be considered in selected patients. 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.

• 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 malignant 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 GI tract should be carefully evaluated to rule out an occult GI primary with ovarian metastases.

• Appendectomy should be performed in all mucinous tumors and considered in all patients with epithelial malignancies suspicious for involvement of the appendix by metastases.

• Patients with low volume residual disease after surgical cytoreduction for invasive epithelial ovarian or peritoneal cancer are potential candidates for intraperitoneal (IP) therapy. In these patients, consideration should be given to placement of IP catheter with initial surgery.

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Ancillary Palliative Surgical Procedures

These procedures may be appropriate in select patients:

- Paracentesis
- Thoracentesis/pleurodesis
- Ureteral stents/nephrostomy
- Surgical relief of intestinal obstruction
- Gastrostomy tube
- Vascular access device
- Indwelling peritoneal or pleural catheter
- Intestinal stents
- Video-assisted thoracoscopy
PRINCIPLES OF CHEMOTHERAPY
(FOR OVARIAN, FALLOPIAN TUBE, AND PRIMARY PERITONEAL CANCER)

General

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

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

- If they are eligible for chemotherapy, patients should be informed about the different options that are available --- that is, intravenous (IV) chemotherapy, a combination of intraperitoneal (IP) and IV chemotherapy, or a clinical trial --- so they can decide which is most the appropriate option. (See OV-3 for dosing and schedule of these regimens).
- Prior to the administration of the combined IP and IV regimen, patients must be apprised of the increased toxicities with the combined regimen when compared to using IV chemotherapy alone (increased myelosuppression, renal toxicities, abdominal pain, neuropathy, gastrointestinal toxicities, metabolic toxicities, and hepatic toxicities).
- Patients considered for the IP cisplatin and IP/IV paclitaxel regimen should have normal renal function prior to starting, a medically appropriate performance status based on the future toxicities of the IP/IV regimen, and no prior evidence of medical problems that could significantly worsen during chemotherapy (for example, preexisting neuropathy).
- Prior to receiving and after receiving each cycle of IP cisplatin, adequate amounts of IV fluids need to be administered in order to prevent renal toxicity. After each cycle has been completed, patients need to be monitored carefully for myelosuppression, dehydration, electrolyte loss, end-organ toxicities (such as, renal and hepatic damage), and all other toxicities. Patients often require IV fluids postchemotherapy in the outpatient setting to prevent or help treat dehydration.
- Refer to the original references (See Discussion) for full toxicity data, doses, schedule, and dose modifications.

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

Continued on OV-B 2 of 2
For patients who have recurrent ovarian, fallopian tube, or primary peritoneal cancer:

- Refer to the original references (See Discussion) for full toxicity data, doses, schedule, and dose modifications.
- Patients should be informed about the following:
  1) availability of clinical trials, including the risks and benefits of various treatments, which will depend on the number of prior lines of chemotherapy the patient has received, and
  2) the patient’s performance status, end-organ status, and pre-existing toxicities from prior regimens. If appropriate, palliative care should also be discussed as a possible treatment choice. See NCCN Palliative Care Guidelines.
- Because of prior platinum exposure, myelosuppression occurs more frequently with any myelotoxic agent given in the recurrent setting.
- With repeat use of either carboplatin and/or cisplatin, patients are at an increased risk of developing a hypersensitivity reaction (also called an allergic reaction) that could be life threatening. Thus, patients should be counseled about the risk that a hypersensitivity reaction may occur, educated about the signs and symptoms of hypersensitivity reactions, treated by medical staff who know how to manage hypersensitivity reactions, and treated in a medical setting where appropriate medical equipment is available in case of an allergic reaction. See Management of Drug Reactions (OV-C).
- Before any chemotherapy drug is given in the recurrent setting, the clinician should be familiar with the drug’s metabolism (that is, renal, hepatic) and should make certain that the patient is an appropriate candidate for the drug (for example, that the patient has adequate renal or hepatic function).
- Clinicians should be familiar with toxicity management and appropriate dose reduction.
- The schedule, toxicity, and potential benefits of any treatment should be thoroughly discussed with the patient and caregivers. Patient education should also include a discussion of precautions and measures to reduce the severity and duration of complications.

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

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
MANAGEMENT OF DRUG REACTIONS (1 of 7)

**DRUG REACTION TO PLATINUM AGENTS**

**REACTION**

- **Mild reaction**
  - (hot flushing, rash, pruritus)
  - First exposure (platinum naive)

- **Second or further exposure**

**MANAGEMENT/TREATMENT**

- **First exposure (platinum naive)**
  - Decrease the infusion rate
  - Symptoms often resolve quickly after stopping infusion
  - Administer antihistamine

- **Second or further exposure**
  - Stop infusion
  - Administer antihistamine to treat symptoms
  - Corticosteroid ± IM epinephrine if symptoms do not quickly resolve

- **Severe reaction**
  - (shortness of breath, changes in blood pressure requiring treatment, dyspnea, GI symptoms [nausea, vomiting])

- **Life-threatening reaction**
  - (ie, anaphylaxis)
  - (acute onset, generalized hives, respiratory compromise, severe hypotension, GI symptoms [nausea, vomiting])

- **Consider allergy consultation**

- **If staff agree and vital signs remain stable, rechallenge with platinum drug**
  - Administer premedication with antihistamine, corticosteroids, H2 blockers

- **Allergist consultation, if possible**
  - Do not rechallenge/readminister drug until evaluated by allergist or specialist with desensitization expertise
  - Potential candidate for desensitization with each infusion

**See OV-C 2 of 7**

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**See Drug Reaction to Taxane, Liposomal Doxorubicin, or Biotherapeutic Agents on OV-C 3 of 7**

---

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

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

3. **Antihistamine**: eg, diphenhydramine or hydroxyzine; H2 blockers: eg, cimetidine, famotidine; corticosteroids: eg, methylprednisolone, hydrocortisone, dexamethasone.

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

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

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


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

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
MANAGEMENT OF DRUG REACTIONS (2 of 7)

**RECOVERY**

**MANAGEMENT/TREATMENT**

**Mild reaction** (hot flushing, rash, pruritus)
- See OV-C 1 of 7

**Severe reaction** (shortness of breath, changes in blood pressure requiring treatment, dyspnea, GI symptoms [nausea, vomiting])
- Stop infusion
- Administer oxygen, nebulized bronchodilators, H2 blockers, corticosteroid; IM epinephrine if needed

**Life-threatening reaction** (ie, anaphylaxis) (acute onset, generalized hives, respiratory compromise, severe hypotension, GI symptoms [nausea, vomiting])
- Stop infusion
- Administer IM epinephrine, oxygen, nebulized bronchodilators, H2 blockers, corticosteroid
- Saline bolus, if needed

- Allergist consultation, if possible
- Do not rechallenge/readminister drug until evaluated by allergist or specialist with desensitization expertise
- Potential candidate for desensitization with each infusion under guidance of an allergist or specialist with desensitization expertise

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

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

3 Antihistamine: eg, diphenhydramine or hydroxyzine; H2 blockers: eg, cimetidine, famotidine; corticosteroids: eg, methylprednisolone, hydrocortisone, dexamethasone.

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

See Drug Reaction to Taxane, Liposomal Doxorubicin, or Biotherapeutic Agents on OV-C 3 of 7

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


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

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

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
**MANAGEMENT OF DRUG REACTIONS (3 of 7)**

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

- **Mild reaction**
  - (hot flushing, rash, pruritus, pain in chest/abdomen/pelvis/back)
  - Stop infusion
  - Symptoms often resolve quickly after stopping infusion
  - Administer antihistamine to treat symptoms

- **Severe reaction**
  - (shortness of breath, changes in blood pressure requiring treatment, dyspnea, GI symptoms [nausea, vomiting]), pain in chest/abdomen/pelvis/back, feeling of impending doom/anxiety/something wrong)
  - If staff agree and vital signs remain stable, rechallenge with drug at slower infusion rate
  - Administer premedication with antihistamine, corticosteroids, H2 blockers

- **Life-threatening reaction**
  - (ie, anaphylaxis)
  - (acute onset, generalized hives, respiratory compromise, severe hypotension, GI symptoms [nausea, vomiting]), pain in chest/abdomen/pelvis/back, feeling of impending doom/anxiety/something wrong)
  - If repeat mild reaction, then do not rechallenge/readminister
  - Potential candidate for desensitization with each infusion

---

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

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

---

**See Drug Reaction to Platinum Agents on OV-C 1 of 7**

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

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

3 Antihistamine: eg, diphenhydramine or hydroxyzine; H2 blockers: eg, cimetidine, famotidine; corticosteroids: eg, methylprednisolone, hydrocortisone, dexamethasone.


9 Consider switching to docetaxel; however, there are no data to support switching taxanes. Cross reactions have occurred and have been life-threatening. Some reactions to paclitaxel may occur because of the diluent.
DRUG REACTION TO TAXANE, LIPOSOMAL DOxorubicin, OR BIOtherAPEUtic AGENTS

MANAGEMENT OF DRUG REACTIONS (4 of 7)

<table>
<thead>
<tr>
<th>REACTION</th>
<th>MANAGEMENT/ TREATMENT</th>
</tr>
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<tbody>
<tr>
<td>Mild reaction¹ (hot flushing, rash, pruritus, pain in chest/abdomen/pelvis/back)</td>
<td>→ See OV-C 3 of 7</td>
</tr>
</tbody>
</table>
| Severe reaction² (shortness of breath, changes in blood pressure requiring treatment, dyspnea, GI symptoms [nausea, vomiting]), pain in chest/abdomen/pelvis/back, feeling of impending doom/ anxiety/something wrong) | • Stop infusion  
• Administer oxygen, nebulized bronchodilator, antihistamine, H2 blockers, corticosteroid; IM epinephrine if needed⁴ |
| Life-threatening reaction² (ie, anaphylaxis) (acute onset, generalized hives, respiratory compromise, severe hypotension, GI symptoms [nausea, vomiting]), pain in chest/abdomen/pelvis/back, feeling of impending doom/ anxiety/something wrong) | • Do not rechallenge/readminister drug until evaluated by allergist or specialist with desensitization expertise  
• Potential candidate for desensitization⁶,⁷ with each infusion |

¹ Most mild reactions are infusion reactions and more commonly are caused by taxanes (ie, docetaxel, paclitaxel) but can also occur with platinum agents (ie, carboplatin, cisplatin).
² Most severe reactions are allergic reactions and more commonly are caused by platinum agents.
³ Antihistamine: eg, diphenhydramine or hydroxyzine; H2 blockers: eg, cimetidine, famotidine; corticosteroids: eg, methylprednisolone, hydrocortisone, dexamethasone.
⁴ In the setting of acute cardiopulmonary arrest, standard resuscitation (ACLS) procedures should be followed.
⁵ Referral to academic center with expertise in desensitization is preferred.
⁶ For both taxanes and platinum analogues, it is preferred that anyone with a life-threatening reaction should be evaluated and referred to an academic center if the drug is still considered first line.

See Drug Reaction to Platinum Agents on OV-C 1 of 7

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

- Virtually all drugs used in oncology have the potential to cause adverse drug reactions while being infused, which can be classified as either infusion or allergic reactions.\(^1\)
  - Infusion reactions are often characterized by milder symptoms (eg, hot flushing, rash).
  - Hypersensitivity (allergic) reactions are often characterized by more severe symptoms (eg, shortness of breath, generalized hives/itching, changes in blood pressure).
  - Symptoms can overlap, whether caused by infusion or allergic reactions. In addition, patients can have mild allergic reactions or severe infusion reactions.
- Most adverse drug reactions that occur are mild reactions, but more severe reactions can occur.\(^2,3\)
  - Anaphylaxis is a rare type of very severe allergic reaction that can occur with the platinum and taxane agents (and others less commonly), can cause cardiovascular collapse, and can be life threatening.\(^4-6\)
  - Drug reactions can occur either during the infusion or following completion of the infusion (and can even occur days later). Reactions can occur with either intravenous (IV) or intraperitoneal (IP) administration.
- In gynecologic oncology treatment, drugs that more commonly cause adverse reactions include carboplatin, cisplatin, docetaxel, liposomal doxorubicin, oxaliplatin, and paclitaxel.\(^1\)
  - Adverse reactions associated with taxane drugs (ie, docetaxel, paclitaxel) and biotherapeutic agents tend to be infusion related often attributed to cremaphor in paclitaxel and tend to occur during the first few cycles of treatment (although they can be seen during any infusion regardless of how many previous cycles were administered).
  - Adverse reactions associated with platinum drugs (ie, carboplatin, cisplatin), a true allergy, tend to occur following re-exposure to the inciting drug or less commonly at the completion of initial chemotherapy (ie, cycle 6 of a planned 6 treatments).\(^3\)
- Preparation for a possible drug reaction
  - Patients and their families need to be counseled about the possibility of a drug reaction, and about the signs and symptoms of an adverse reaction (either infusion or allergic). Patients should be told to report any signs and symptoms of a drug reaction, especially after they have left the clinic.
  - Clinicians and nursing staff should be prepared for the possibility of a drug reaction every time a patient is infused with a drug.
  - Standing orders should be written for immediate intervention in case a severe drug reaction occurs.
  - The treatment area should have appropriate medical equipment in case of a life-threatening reaction.
- Desensitization refers to a process of rendering the patient less likely to respond to an allergen and can be considered for patients who have had drug reactions.\(^1,7-9\)
  - Although desensitization is more commonly used after allergic drug reactions, it can also be used after infusion reactions.
  - If a mild reaction has previously occurred to a platinum agent, great caution should be undertaken if desensitization is pursued (see “Allergic Reactions”).
  - If a patient has previously had a very severe life-threatening reaction, the implicated drug should not be used again unless under guidance of an allergist or specialist with desensitization experience.

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

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

- Symptoms include: hot flushing, rash, fever, chest tightness, mild blood pressure changes, back pain, and chills.
- Symptoms usually can be treated by decreasing the infusion rate and resolve quickly after stopping the infusion. However, patients who have had mild reactions to carboplatin, cisplatin, or oxaliplatin may develop more serious reactions even when the platinum drug is slowly infused; therefore, consider consultation with an allergist.\(^{10}\)

- More common with paclitaxel (27% of patients); however, mild reactions can occur with liposomal doxorubicin.\(^{10}\)

- If an infusion reaction has previously occurred to a taxane:
  - For mild infusion reactions (eg, flushing, rash, chills), patients may be rechallenged with the taxane if:
    1) the patient, physician, and nursing staff are all comfortable with this plan;
    2) the patient has been counseled appropriately; and
    3) emergency equipment is available in the clinic area.
  - Typically the taxane infusion can be re-started at a much slower rate, and the rate can be slowly increased as tolerated as per the treating clinician's judgment.\(^{7,11}\) Note that this slow infusion is different from desensitization.
  - Many institutions have nursing policies that stipulate how to reinfuse the drug if the patient has had a prior infusion reaction.

Allergic Reactions (ie, True Drug Allergies)

- Symptoms include: rash, edema, shortness of breath, syncope or pre-syncope, chest pain, tachycardia, hives/itching, changes in blood pressure, nausea, vomiting, chills, and changes in bowel function. Patients with severe reactions may have the following symptoms: cardiac problems, bronchospasm, and blood pressure changes that require treatment, feeling of impending doom.\(^{11}\)

- Symptoms continue to persist after stopping infusion and/or after treatment interventions.

- More common with platinum drugs such as carboplatin (16% of patients), cisplatin, and oxaliplatin.\(^{11}\) Mild reactions can occur with platinum agents.\(^{11}\)

- Patients who are at higher risk of developing a hypersensitivity (allergic) reaction include those in the following settings:
  - Re-introduction of the drug after a period of no exposure and following multiple cycles of the drug during the first and subsequent exposures
  - Intravenous administration of the drug rather than oral or intraperitoneal administration
  - With allergies to other drugs
  - Those who have previously had a reaction

- If an allergic reaction has previously occurred:
  - Consider consultation with an allergist (or qualified medical or gynecologic oncologist) and skin testing for patients who have experienced a platinum reaction (eg, carboplatin-hypersensitivity reaction).\(^{11,13}\)
  - Patients who have had mild reactions may develop more serious reactions even when the platinum drug is slowly infused.\(^{11}\) The desensitization treatment of these patients should be managed by a physician with expertise and experience in platinum desensitization.
  - For very severe life-threatening reactions (ie, anaphylaxis), the implicated drug should not be used again unless under guidance of an allergist or specialist with desensitization experience.
  - For more severe reactions --- such as those involving blood pressure changes, dyspnea, tachycardia, widespread urticaria, hypoxia --- the treating clinician should consult an allergist prior to rechallenge.
  - If it is appropriate to give the drug again, patients should be desensitized prior to resuming chemotherapy even if the symptoms resolved. Patients must be desensitized with each infusion if they previously had a drug reaction.\(^{7-9}\)
MANAGEMENT OF DRUG REACTIONS (7 of 7)

REFERENCES


1. Paclitaxel 135 mg/m² IV continuous infusion over 24 h Day 1; cisplatin 75-100 mg/m² IP, Day 2 after IV paclitaxel; paclitaxel 60 mg/m² IP Day 8 (max BSA 2.0 m²). Repeat every 3 weeks x 6 cycles. (category 1)

2. Paclitaxel 175 mg/m² IV over 3 hours followed by carboplatin AUC 5-7.5 IV over 1 hour Day 1. Repeat every 3 weeks x 6 cycles. (category 1)

3. Docetaxel 60-75 mg/m² IV over 1 hour followed by carboplatin AUC 5-6 IV over 1 hour Day 1. Repeat every 3 weeks x 6 cycles. (category 1)

4. Dose-dense paclitaxel 80 mg/m² IV over 1 hour Days 1, 8, and 15 and carboplatin 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/m² IV over 3 hours, carboplatin 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/m² IV over 3 hours and carboplatin AUC 6 IV over 30 minutes 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)

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a See Discussion for references.
b The NCCN Ovarian Cancer panel recognizes that data for first-line and maintenance bevacizumab are becoming available and encourages participation in clinical trials.
### ACCEPTABLE RECURRENCE THERAPIES (1 of 2)†

<table>
<thead>
<tr>
<th>Agents</th>
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<th>Hormonal Therapy</th>
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<td>Paclitaxel, weekly¹²</td>
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<td><strong>Other Potentially Active Agents</strong></td>
<td><strong>Single Agents</strong>¹⁵</td>
<td>Anastrozole</td>
<td>Palliative localized radiation therapy</td>
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<td>Altretamine</td>
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<td>Capecitabine</td>
<td>Leuprolide acetate</td>
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<td>Vinorelbine</td>
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†Patients who progress on two consecutive therapy regimens without evidence of clinical benefits have diminished likelihood of benefiting 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.

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

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

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
ACCEPTABLE RECURRENCE THERAPIES (2 of 2)

REFERENCES


15. See Discussion for references.
**CLINICAL PRESENTATION**

Pelvic Mass

**WORKUP**

- Abdominal/pelvic exam
- GI evaluation if clinically indicated
- Ultrasound or abdominal/pelvic CT if clinically indicated
- Chest x-ray
- CA-125, inhibin, Beta-human chorionic gonadotropin (β-hCG), alpha-fetoprotein, lactate dehydrogenase (LDH) as clinically indicated
- CBC
- Chemistry profile with LFTs

**DIAGNOSIS**

- Malignant germ cell tumors
  - Surgery (See OV-A) and Frozen section
- Malignant sex cord-stromal tumors
  - Carcinosarcoma (Malignant Mixed Müllerian Tumor)

- See Malignant Germ Cell Tumors (LCOH-2)
- See Malignant Sex Cord-Stromal Tumors (LCOH-4)
- See Carcinosarcoma (Malignant Mixed Müllerian Tumor) (LCOH-5)

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

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**See Sex Cord-Stromal Tumors - WHO Histologic Classification (LCOH-A).**
Malignant Germ Cell Tumors

Malignant germ cell tumors

Initial surgery

Fertility desired
Fertility not desired

Prior surgery

Incompletely surgically staged

Embryonal, endodermal sinus tumor (yolk sac tumor), grade 2-3 immature teratoma, or mixed histology

Dysgerminoma or grade 1 immature teratoma

Completely staged

PRIMARY TREATMENT
Fertility-sparing surgery and comprehensive staging (See OV-A)

Complete staging surgery (See OV-A)

Positive imaging and tumor markers

Negative imaging and tumor markers

Fertility desired, then fertility-sparing surgery and comprehensive staging; fertility not desired, completion staging surgery (See OV-A)

Consider observation (category 2B)

Fertility desired, then fertility-sparing surgery and comprehensive staging; fertility not desired, completion staging surgery with possible tumor reductive surgery (See OV-A) or Chemotherapy (See LCOH-3)

Negative imaging and tumor markers

Positive imaging and tumor markers

Negative imaging and tumor markers

Negative imaging and tumor markers

See Treatment (LCOH-3)

See Treatment (LCOH-3)

See Treatment (LCOH-3)

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

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

bStandard recommendation includes a patient evaluation by a gynecologic oncologist.
**NCCN Guidelines Version 3.2012**

**Malignant Germ Cell Tumors**

### CLINICAL PRESENTATION

- **Stage I**
  - Dysgerminoma
  - or
  - Immature teratoma
- **Stage I, grade I**
  - Dysgerminoma
- **Any stage**
  - Embryonal tumor
  - or
  - Endodermal sinus tumor (yolk sac tumor)
- **Stage II-IV**
  - Dysgerminoma
  - or
  - Immature teratoma
  - Stage I, grade 2 or 3

### TREATMENT

- **Stage I**, **Immature teratoma**
  - Observe
- **Any stage**, **Embryonal tumor**
  - Chemotherapy
- **Stage I, grade I**, **Dysgerminoma**
  - Observe
- **Any stage**, **Endodermal sinus tumor**
  - Chemotherapy
- **Stage II-IV**, **Dysgerminoma**
  - Observed markers every 2-4 mo, if initially elevated, for 2 y
  - Abnormal markers, definitive recurrent disease
  - Consider additional chemotherapy (category 2B)
  - High-dose chemotherapy (category 2B)
- **Stage I, grade 2 or 3**, **Immature teratoma**
  - Persistently elevated markers with definitive residual disease
  - TIP (paclitaxel/ifosfamide/cisplatin)
  - or
  - High-dose chemotherapy (strongly recommend referral to tertiary care center for potentially curative regimen)

### MONITORING/FOLLOW-UP

- Complete clinical response
- Residual tumor on radiographic imaging; markers normal
- Consider surgical resection or Observe
- Abnormal markers, definitive recurrent disease
- Consider additional chemotherapy (category 2B)
- High-dose chemotherapy (category 2B)
- Observe marker every 2-4 mo, if initially elevated, for 2 y
- Persistently elevated markers with definitive residual disease
- Necrotic tissue
- Benign teratoma
- CT or other imaging as clinically indicated
- Residual tumor
- Consider additional platinum-based chemotherapy (category 2B)
- Observe (category 2B)
- Complete clinical response

### RECURRENT/PERSISTENT DISEASE

- Necrotic tissue
- Observe
- Consider surgical resection
- Persistent clinical response

---

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

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

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<sup>c</sup> For select patients with Stage IB-III dysgerminoma for whom minimizing toxicity is critical, three courses of etoposide/cisplatin can be used (three courses of carboplatin 400 mg/m² on day 1 plus etoposide 120 mg/m² on days 1, 2, and 3 every 4 weeks).

<sup>d</sup> BEP (Bleomycin, 30 units per week, Etoposide, 100 mg/m²/d daily for days 1-5, Cisplatin 20 mg/m²/d daily for days 1-5) for 3-4 cycles (category 2B for 3 versus 4 cycles). Recommend pulmonary function tests if considering bleomycin.

<sup>e</sup> See LCOH-1 for markers.

<sup>f</sup> See Acceptable Recurrence Therapies (LCOH-B).
CLINICAL PRESENTATION

Malignant sex cord - stromal tumors

Stage IA/IC: Desires fertility
- Fertility-sparing surgery with complete staging

Stage I Low risk
- Observe

Stage I High-risk (eg, ruptured Stage IC or poorly differentiated stage I) or Intermediate risk (eg, heterologous elements)
- Observe (category 2B)
- Consider platinum-based chemotherapy (category 2B)
- Platinum-based chemotherapy (category 2B) or RT for limited disease (category 2B)
- Clinical relapse
- Clinical trial or Consider secondary cytoreductive surgery or Recurrence therapy

Stage II-IV
- Observe (category 2B)
- Consider platinum-based chemotherapy (category 2B)
- Platinum-based chemotherapy (category 2B) or RT for limited disease (category 2B)
- Clinical relapse
- Clinical trial or Consider secondary cytoreductive surgery or Recurrence therapy

RECURRENT DISEASE

RECURRENT THERAPY

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

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

Complete surgical staging$^h$

Stage I-IV or Recurrence

Treat per Epithelial Ovarian Cancer (See OV-3)

$^h$See Principles of Primary Surgery (OV-A).

Note: All recommendations are category 2A unless otherwise indicated. Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
### SEX CORD-STROMAL TUMORS - WHO HISTOLOGIC CLASSIFICATION

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

<table>
<thead>
<tr>
<th>WHO Histologic Classification</th>
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</tr>
<tr>
<td>Cellular fibroma with increased mitotic figures</td>
<td>Malignant potential</td>
</tr>
<tr>
<td>Fibrosarcoma</td>
<td>Malignant</td>
</tr>
<tr>
<td>Stromal tumor with minor sex cord elements</td>
<td>Benign</td>
</tr>
<tr>
<td>Sclerosing stromal tumor</td>
<td>Benign</td>
</tr>
<tr>
<td>Signet ring stromal tumors</td>
<td>Benign</td>
</tr>
<tr>
<td>Unclassified</td>
<td>Malignant potential</td>
</tr>
<tr>
<td><strong>Sertoli-Leydig cell tumors</strong></td>
<td>Malignant potential</td>
</tr>
<tr>
<td>Well differentiated</td>
<td></td>
</tr>
<tr>
<td>Intermediate differentiation</td>
<td>Malignant</td>
</tr>
<tr>
<td>Poorly differentiated</td>
<td>Malignant</td>
</tr>
<tr>
<td>Sertoli-Leydig tumors with heterologous elements</td>
<td>Malignant</td>
</tr>
<tr>
<td>Sertoli cell tumors</td>
<td>Malignant potential</td>
</tr>
<tr>
<td>Leydig cell tumors</td>
<td>Benign</td>
</tr>
<tr>
<td>Stromal-Leydig cell tumors</td>
<td>Benign</td>
</tr>
<tr>
<td>Sex cord tumors with annular tubules (SCTAT)</td>
<td>Malignant</td>
</tr>
<tr>
<td>Microscopic SCTAT associated with Peutz-Jeghers syndrome</td>
<td>Benign</td>
</tr>
<tr>
<td>Gynandroblastoma</td>
<td>Malignant/Malignant potential</td>
</tr>
<tr>
<td>Unclassified sex cord stromal tumors</td>
<td>Malignant potential</td>
</tr>
<tr>
<td>Steroid cell tumors</td>
<td>Malignant</td>
</tr>
</tbody>
</table>

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

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

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

<table>
<thead>
<tr>
<th>MALIGNANT GERM CELL TUMORS&lt;sup&gt;1&lt;/sup&gt;</th>
<th>MALIGNANT SEX CORD-STROMAL TUMORS&lt;sup&gt;3&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-dose chemotherapy&lt;sup&gt;1,2&lt;/sup&gt;</td>
<td>Aromatase inhibitors (anastrozole, letrozole)</td>
</tr>
<tr>
<td>Cisplatin/etoposide</td>
<td>Bevacizumab may be considered for granulosa cell tumors</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>Leuprolide may be used as hormonal therapy for granulosa cell tumors</td>
</tr>
<tr>
<td>Docetaxel/carboplatin</td>
<td>Docetaxel</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>Paclitaxel</td>
</tr>
<tr>
<td>Paclitaxel/ifosfamide</td>
<td>Paclitaxel/ifosfamide</td>
</tr>
<tr>
<td>Paclitaxel/carboplatin</td>
<td>Paclitaxel/carboplatin</td>
</tr>
<tr>
<td>Paclitaxel/gemcitabine</td>
<td>Tamoxifen</td>
</tr>
<tr>
<td>VIP (etoposide, ifosfamide, cisplatin)</td>
<td>VAC (vincristine, dactinomycin, cyclophosphamide)</td>
</tr>
<tr>
<td>VelP (vinblastine, ifosfamide, cisplatin)</td>
<td>Radiation therapy</td>
</tr>
<tr>
<td>VAC (vincristine, dactinomycin, cyclophosphamide)</td>
<td>Supportive care only</td>
</tr>
<tr>
<td>TIP (paclitaxel, ifosfamide, cisplatin)</td>
<td></td>
</tr>
<tr>
<td>Radiation therapy</td>
<td></td>
</tr>
<tr>
<td>Supportive care only</td>
<td></td>
</tr>
</tbody>
</table>

---

<sup>1</sup>Patients with potentially curable recurrent germ cell disease should be referred to a tertiary care institution for potentially curative therapy.

<sup>2</sup>High-dose chemotherapy regimens vary among institutions.

<sup>3</sup>See Sex Cord-Stromal Tumors - WHO Histologic Classification (LCOH-A).

---

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

**Table 1**  
American Joint Committee on Cancer (AJCC)  
TNM and FIGO Staging System for Ovarian and Primary Peritoneal Cancer (7th ed., 2010)

### Primary Tumor (T)

<table>
<thead>
<tr>
<th>TNM</th>
<th>FIGO</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td></td>
<td>Primary tumor cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>I</td>
<td>No evidence of primary tumor</td>
</tr>
<tr>
<td>T1a</td>
<td>IA</td>
<td>Tumor limited to one ovary; capsule intact, no tumor on ovarian surface. No malignant cells in ascites or peritoneal washings</td>
</tr>
<tr>
<td>T1b</td>
<td>IB</td>
<td>Tumor limited to both ovaries; capsules intact, no tumor on ovarian surface. No malignant cells in ascites or peritoneal washings</td>
</tr>
<tr>
<td>T1c</td>
<td>IC</td>
<td>Tumor limited to one or both ovaries with any of the following: capsule ruptured, tumor on ovarian surface, malignant cells in ascites or peritoneal washings</td>
</tr>
<tr>
<td>T2</td>
<td>II</td>
<td>Tumor involves one or both ovaries with pelvic extension</td>
</tr>
<tr>
<td>T2a</td>
<td>IIA</td>
<td>Extension and/or implants on uterus and/or tube(s). No malignant cells in ascites or peritoneal washings</td>
</tr>
<tr>
<td>T2b</td>
<td>IIB</td>
<td>Extension to and/or implants on other pelvic tissues. No malignant cells in ascites or peritoneal washings</td>
</tr>
<tr>
<td>T2c</td>
<td>IIC</td>
<td>Pelvic extension and/or implants (T2a or T2b) with malignant cells in ascites or peritoneal washings</td>
</tr>
<tr>
<td>T3</td>
<td>III</td>
<td>Tumor involves one or both ovaries with microscopically confirmed peritoneal metastasis outside the pelvis</td>
</tr>
<tr>
<td>T3a</td>
<td>IIIA</td>
<td>Microscopic peritoneal metastasis beyond pelvis (no macroscopic tumor)</td>
</tr>
<tr>
<td>T3b</td>
<td>IIIB</td>
<td>Macroscopic peritoneal metastasis beyond pelvis 2 cm or less in greatest dimension</td>
</tr>
<tr>
<td>T3c</td>
<td>IIIC</td>
<td>Peritoneal metastasis beyond pelvis more than 2 cm in greatest dimension and/or regional lymph node metastasis</td>
</tr>
</tbody>
</table>

### Regional Lymph Nodes (N)

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

### Distant Metastasis (M)

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

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

*Continued*
### Table 1 (Continued)

**American Joint Committee on Cancer (AJCC)**

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

<table>
<thead>
<tr>
<th>Stage Grouping</th>
<th>T</th>
<th>N</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stage 1</strong></td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td><strong>Stage IA</strong></td>
<td>T1a</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td><strong>Stage IB</strong></td>
<td>T1b</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td><strong>Stage IC</strong></td>
<td>T1c</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td><strong>Stage II</strong></td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td><strong>Stage IIA</strong></td>
<td>T2a</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td><strong>Stage IIB</strong></td>
<td>T2b</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td><strong>Stage IIC</strong></td>
<td>T2c</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td><strong>Stage III</strong></td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td><strong>Stage IIIA</strong></td>
<td>T3a</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td><strong>Stage IIIB</strong></td>
<td>T3b</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td><strong>Stage IIIC</strong></td>
<td>T3c</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>Any T</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td><strong>Stage IV</strong></td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
</tr>
</tbody>
</table>

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

Note: For histologic grade and histopathologic type, see AJCC staging manual.

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

**Table 2**

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

**Primary Tumor (T)**

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

<table>
<thead>
<tr>
<th>TNM</th>
<th>FIGO</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>T3</td>
<td>III</td>
<td>Tumor involves one or both fallopian tubes, with peritoneal implants outside the pelvis</td>
</tr>
<tr>
<td>T3a</td>
<td>IIIA</td>
<td>Microscopic peritoneal metastasis outside the pelvis</td>
</tr>
<tr>
<td>T3b</td>
<td>IIIB</td>
<td>Macroscopic peritoneal metastasis outside the pelvis</td>
</tr>
<tr>
<td>T3c</td>
<td>IIIC</td>
<td>Peritoneal metastasis outside the pelvis and more than 2 cm in diameter</td>
</tr>
</tbody>
</table>

**Regional Lymph Nodes (N)**

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

**Distant Metastasis (M)**

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

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

Note: Liver capsule metastasis is T3/Stage III; liver parenchymal metastasis, M1/Stage IV. Pleural effusion must have positive cytology for M1/Stage IV.
### Table 2 (Continued)

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

<table>
<thead>
<tr>
<th>Stage Grouping</th>
<th>Tis</th>
<th>N0</th>
<th>M0</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stage 0</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage 1</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IA</td>
<td>T1a</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IB</td>
<td>T1b</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IC</td>
<td>T1c</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage II</td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIA</td>
<td>T2a</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIB</td>
<td>T2b</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIC</td>
<td>T2c</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage III</td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIIA</td>
<td>T3a</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIIB</td>
<td>T3b</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIIC</td>
<td>T3c</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>Any T</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td><strong>Stage IV</strong></td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
</tr>
</tbody>
</table>

*Note: FIGO no longer includes Stage 0 (Tis)*  
Note: For histologic grade and histopathologic type, see AJCC staging manual.

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Discussion

NCCN Categories of Evidence and Consensus

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

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

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

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

All recommendations are category 2A unless otherwise noted.

Overview

Ovarian neoplasms consist of several histopathological entities; treatment depends on the specific tumor type. Epithelial ovarian cancer comprises the majority of malignant ovarian neoplasms (about 80%); however, other less common pathologic subtypes must be considered in guidelines describing treatment recommendations. These NCCN guidelines discuss epithelial ovarian cancer (including borderline or low malignant potential) and, less common histopathologies, including malignant germ cell neoplasms, carcinosarcomas (malignant mixed Müllerian tumors of the ovary [MMMT]), and sex cord-stromal tumors. The guidelines also discuss Fallopian tube cancer and primary peritoneal cancer, which are less common neoplasms that are managed in a similar manner to epithelial ovarian cancer. However, the less common histologies of ovarian cancer are managed differently. These NCCN guidelines also include sections on “Principles of Chemotherapy” (including Acceptable Recurrence Therapies), “Principles of Primary Surgery,” and “Management of Drug Reactions.”

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 2011, there will be an estimated 21,990 new diagnoses and an estimated 15,460 deaths from this neoplasm in the United States; less than 40% of women with ovarian cancer are cured. The incidence of ovarian cancer increases with age and is most prevalent in the eighth decade of life, with a rate of 57/100,000 women. The median age at the time of diagnosis is 63 years, and more than 70% of patients present with advanced disease.

Epidemiologic studies have identified risk factors in the etiology of ovarian cancer. A 30% to 60% decreased risk of cancer is associated with younger age at pregnancy and first birth (25 years or younger), the use of oral contraceptives, and/or breast-feeding. Conversely, nulliparity or older age at first birth (older than 35 years) confers an increased risk of cancer. Recent data suggest that hormone therapy may increase the risk of ovarian cancer. Pelvic inflammatory disease may increase the risk for ovarian cancer. The risk of borderline ovarian cancer may be increased after ovarian stimulation for in vitro fertilization.

Family history (primarily patients having 2 or more first-degree relatives with ovarian cancer)—including linkage with BRCA1 and BRCA2 genotypes or families affected by Lynch syndrome (hereditary nonpolyposis colorectal cancer [HNPCC] syndrome)—is associated with early-onset disease. However, these patients account for only 5% of all women who have ovarian cancer. In high-risk women (with either BRCA1 or BRCA2 mutations), oophorectomy is associated with a reduced risk of ovarian and Fallopian tube cancer; however, there is a
residual risk for primary peritoneal cancer in these high-risk women after prophylactic salpingo-oophorectomy.15-17 The risks of surgery include injury to the bowel, bladder, ureter, and vessels.18 Recently, it has been suggested that the Fallopian tube may be the origin of some ovarian and primary peritoneal cancers.19-27 Environmental factors have been investigated, but so far they have not been conclusively associated with the development of this neoplasm.

Screening

Because of the location of the ovaries and the biology of most epithelial cancers, it has been difficult to diagnose ovarian cancer at an earlier more curable stage. However, evaluations of newly diagnosed ovarian cancer patients have resulted in consensus guidelines for ovarian cancer symptoms which may enable earlier identification of patients who may be at an increased risk of having developed early-stage ovarian cancer (http://www.wcn.org/articles/types_of_cancer/ovarian/symptoms/index.html).28,29 Symptoms suggestive of ovarian cancer include: bloating, pelvic or abdominal pain, difficulty eating or feeling full quickly, and urinary symptoms (urgency or frequency), especially if these symptoms are new and frequent (> 12 days/month).28 Physicians evaluating women with this constellation of symptoms must be cognizant of the possibility that ovarian pathology may be causing these symptoms. However, some evidence suggests that the screening test using these symptoms is not as sensitive or specific as necessary, especially in those with early-stage disease.18,30

An ongoing trial is assessing screening for ovarian cancer (UK Collaborative Trial of Ovarian Cancer Screening [UKCTOCS]) using multimodality screening with ultrasound and cancer antigen 125 (CA-125) versus either ultrasound alone or no screening. Preliminary results suggest that multimodality screening is more effective at detecting early-stage cancer.31 However, a large randomized trial in more than 78,000 women (the Prostate, Lung, Colorectal and Ovarian [PLCO] Cancer trial) in the United States found that screening with transvaginal ultrasonography and CA-125 did not decrease mortality from ovarian cancer.32,33 In addition, false-positive results led to serious complications in some women (n = 163) in the PLCO trial. 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 over ultrasound alone.34

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.18,32,35 Some physicians follow women with high-risk factors (e.g., those with BRCA mutations, those with a family history) using CA-125 alone or CA-125 with transvaginal 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.36,37

A recent screening trial assessed an algorithm that used age and longitudinal changes in CA-125 levels to determine whether women at average risk would develop ovarian cancer (Risk of Ovarian Cancer Algorithm [ROCA]); women deemed at risk were referred for transvaginal sonography (TVS).38 However, the Society of Gynecologic Oncology (SGO) and others have stated that until data from larger randomized controlled trials are published (e.g., UKCTOCS), there is not enough evidence 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 the Food and Drug Administration (FDA) have stated that the OVA-1 test should not be...
used as a screening tool to detect ovarian cancer. The OVA-1 test uses 5 markers (including transthyretin, apolipoprotein A1, transferrin, beta-2 microglobulin, and CA-125) to assess who should undergo surgery by an experienced gynecologic oncologist and who can have surgery in the community. Based on data documenting an increased survival, the NCCN panel recommends that all patients should undergo surgery by an experienced gynecologic oncologist (category 1).39-41

The SGO has stated that additional research is necessary to validate the OvaSure screening test before making it available outside of a clinical trial (http://www.sgo.org/WorkArea/showcontent.aspx?id=1754). The OvaSure test uses 6 biomarkers, including leptin, prolactin, osteopontin, insulin-like growth factor II, macrophage inhibitory factor, and CA-125.42 Although human epididymis protein 4 (HE4) and CA-125 appear to be useful in detecting ovarian cancer,43,44 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.45,46

**Staging**
The NCCN Ovarian Cancer Guidelines reflect the importance of stage and grade of disease on prognosis and treatment recommendations. Ovarian cancer is classified primarily as stages I-IV. Since 1997, no significant changes have been made in the TNM and FIGO (International Federation of Gynecology and Obstetrics) staging systems for ovarian cancer (see Table 1).47 Pathologic grading continues to be an important prognostic factor and is used in the selection of therapy, primarily for early-stage disease. Grading is labeled as 1, 2, or 3. Except for those women with stage I, grade 1 tumors (in whom survival is greater than 95% after comprehensive laparotomy), patients in all other stages of ovarian cancer should be encouraged to enter clinical trials for both primary and recurrence therapy.

Primary peritoneal adenocarcinoma is staged using the ovarian cancer staging system (see Table 1).47 Fallopian tube carcinomas are also staged using the TNM and FIGO staging systems (see Table 2).47

**Caveat**
By definition, the NCCN practice guidelines cannot incorporate all possible clinical variations and are not intended to replace good clinical judgment or individualization of treatments. Exceptions to the rule were discussed among 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 a prior diagnosis of a malignant epithelial ovarian tumor. Many patients with this diagnosis come to NCCN member institutions after having had previous surgery.

**Undiagnosed Pelvic Mass**
The primary workup of a patient with a suspicious pelvic mass detected on abdominal/pelvic exam and/or ascites, abdominal distention, and/or symptoms (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 computed tomography (CT) scan after an abdominal/pelvic examination and appropriate laboratory studies (see "Workup" in the NCCN Ovarian...
Cancer algorithm). Tumor markers (including CA-125, inhibin, alpha-fetoprotein [AFP], and beta–human chorionic gonadotropin [beta-HCG]) can be measured if clinically indicated. Ultrasound is typically used for initial evaluation; however, CT is useful to assess for metastases.

If possible, fine-needle aspiration (FNA) should be avoided for diagnosis of ovarian cancer in patients with presumed early-stage disease to prevent rupturing the cyst and spilling malignant cells into the peritoneal cavity; however, FNA may be necessary in patients with bulky disease who are not surgical candidates. Other cancers that should be ruled out include bowel, uterine, and pancreatic cancers or lymphoma; benign ovarian and non-ovarian conditions also need to be ruled out (e.g., serous cystadenoma).

It has been suggested that specific biomarkers (serum HE4 and CA 125) along with an algorithm (Risk of Ovarian Malignancy Algorithm [ROMA]) may be useful for determining whether a pelvic mass is malignant or benign. The FDA has approved the use of HE4 and CA 125 for estimating the risk of ovarian cancer in women with a pelvic mass. Currently, the NCCN panel does not recommend the use of these biomarkers for determining the status of an undiagnosed pelvic mass. Both primary peritoneal and Fallopian tube cancers are usually diagnosed postoperatively (if there is no major involvement of the ovary) or preoperatively (if there is a biopsy and the patient has already had a bilateral oophorectomy). Primary peritoneal and Fallopian tube cancers are treated in the same manner as ovarian cancer.

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

**Prior Diagnosis of Malignancy**

Patients are often referred to NCCN institutions after having a previous diagnosis of ovarian cancer by surgery or tissue biopsy (cytopathology). Often they have undergone cytoreductive surgery and have undergone comprehensive staging procedures (i.e., having met the standards for surgical staging of the Gynecologic Oncology Group [GOG]). However, in some instances, referral occurs after “incomplete” surgery and/or staging (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 “Principles of Primary Surgery” in the NCCN Ovarian Cancer algorithm). Identical workup procedures are recommended for patients having undiagnosed or diagnosed pelvic masses at the time of 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/2011/Ovary_11protocol.pdf).

**Primary Treatment**

Primary treatment for presumed ovarian cancer consists of appropriate surgical staging and cytoreduction, followed in most (but not all) patients by systemic chemotherapy. Initial surgery should be a comprehensive staging laparotomy, including a total abdominal hysterectomy (TAH) and bilateral salpingo-oophorectomy (BSO). Based on published improved outcomes, it is recommended (category 1) that a gynecologic oncologist perform the primary surgery. For a young patient who wishes to maintain fertility, a unilateral...
salpingo-oophorectomy (USO) (preserving the uterus and contralateral ovary) may be adequate for select stage I tumors (stage 1A and 1C, but not stage 1B) and/or low-risk tumors (i.e., early-stage, low-grade invasive tumors; low malignant potential [LMP] lesions).66-70

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.71 In stage I disease, minimally invasive techniques to achieve the surgical goals may be considered in selected 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 “Primary Treatment” in the NCCN Ovarian Cancer algorithm).61,68,71-74 Although cytoreductive surgery is the standard of care, this recommendation is based on retrospective data (and thus is not a category 1 recommendation).75 In general, the following procedures (outlined in the next paragraph) should be part of the surgical management of patients with ovarian, Fallopian tube, or primary peritoneal cancer in an effort to fully stage and to achieve maximal cytoreduction to less than 1 cm residual disease or resection of all visible disease in appropriate circumstances.76-78 Surgical cytoreduction is optimal if the residual tumor nodules are less than 1 cm in maximum diameter or thickness;68,75,79 extensive resection of upper abdominal ovarian metastases is recommended for patients who can tolerate this surgery.73

A maximal effort should be made to remove all gross disease. On entering the abdomen, aspiration of ascites or peritoneal lavage should be performed for cytologic examinations. For obvious disease beyond the ovaries, cytologic assessment of ascites and/or lavage specimens will not alter stage or management. Hysterectomy and bilateral salpingo-oophorectomy should be performed. Although total hysterectomy is recommended for most patients, a supracervical hysterectomy is appropriate in some circumstances. An encapsulated mass should be removed intact, if possible. All involved omentum should be removed. Suspicious and/or enlarged nodes should be resected, if possible.80,81 Those patients with tumor nodules, outside the pelvis, of 2 cm or less (presumed stage IIIB) should have bilateral pelvic and para-aortic lymph node dissection (see “Principles of Primary Surgery” in the NCCN Ovarian Cancer algorithm).

In patients with advanced ovarian cancer who have had complete debulking, data indicate that overall survival is increased in those who receive systematic lymphadenectomy.82 Patients with low-volume residual disease after surgical cytoreduction for invasive epithelial ovarian or peritoneal cancer are potential candidates for intraperitoneal (IP) therapy. In these patients, consideration should be given to placement of an IP catheter with initial surgery.

Procedures that may be considered for optimal surgical cytoreduction (in all stages) include: radical pelvic dissection, bowel resection, diaphragm or other peritoneal surface stripping, splenectomy, partial heptectomy, cholecystectomy, partial gastrectomy or cystectomy, ureteroneocystostomy, or distal pancreatectomy.83 The therapeutic benefit of neoadjuvant chemotherapy followed by interval cytoreduction remains controversial (see next paragraph).75,84-88 It may be considered (category 1) for patients with bulky stage III to IV disease who are not surgical candidates (however, a gynecologic oncologist should make this assessment before neoadjuvant chemotherapy is administered).89-93 Before initiation of chemotherapy,
the pathologic diagnosis should be confirmed (by FNA, biopsy, or paracentesis) in this group of patients.

A recent randomized phase III trial assessed neoadjuvant chemotherapy with interval debulking surgery versus upfront primary debulking surgery in patients with extensive stage IIIC/IV ovarian, primary peritoneal, and Fallopian tube carcinoma (sponsored by the European Organization for Research and Treatment of Cancer-Gynaecological Cancer Group [EORTC-GCG] and the National Cancer Institute Canada-Clinical Trial Group [NCIC-CTG]).

Median overall survival was equivalent in these patients (29 versus 30 months), but patients receiving neoadjuvant chemotherapy with interval debulking surgery had fewer complications.

A major criticism of this International trial is that reported progression-free and overall survivals were inferior to those reported more recently in randomized studies in the United States of patients undergoing primary debulking surgery followed by postoperative intravenous chemotherapy for advanced ovarian cancer (overall survival averages 50 months). Although the median overall survival in the International trial is 20 months lower than that reported in US trials using the customary sequence of therapeutic interventions (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). It has also been pointed out that primary or interval debulking surgery in the International trial may not have been optimal (i.e., patients may have had had > 1 cm of residual disease).

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

**Incompletely Staged Patients**

For patients with incomplete previous surgery and/or staging, treatment recommendations are outlined in the NCCN Ovarian Cancer algorithm (see “Diagnosis by Previous Surgery”). For patients with stage II-IV disease who have residual disease that is considered unresectable, consider completion surgery after 3-6 cycles of chemotherapy. Depending on the surgical results, patients would then receive postoperative chemotherapy. Tumor reductive surgery is recommended for all patients with stage II-IV diseases with suspected potentially resectable residual disease.

**Chemotherapy**

Most patients with epithelial ovarian cancer receive postoperative systemic chemotherapy. Observation, however, is recommended for patients with stage IA or IB, grade 1 tumors, because survival is greater than 90% for this group with surgical treatment alone. 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 IV and IP options. All of the regimens (including the IP chemotherapy) may be used for epithelial ovarian, primary peritoneal and Fallopian tube cancers. Principles of chemotherapy are described in the NCCN Ovarian Cancer algorithm.
Intraperitoneal chemotherapy is recommended for stage III patients with optimally debulked (<1 cm residual) disease based on randomized controlled trials (category 1) (http://www.cancer.gov/clinicaltrials/conducting/developments/ipchemo-digest/Page1); stage II patients may also receive IP chemotherapy, although no randomized evidence for stage II has been published. In women with stage III cancer, survival was increased by 16 months after IP therapy using cisplatin/paclitaxel when compared with standard IV therapy (65.6 versus 49.7 months, \( P = .03 \)) in the Gynecologic Oncology Group (GOG) 172 trial. For patients for whom this does not apply (e.g., those with poor performance status [PS]), the combination of intravenous paclitaxel plus carboplatin (category 1) may be used (see “Primary Chemotherapy/Primary Adjuvant Therapy” in the NCCN Ovarian Cancer algorithm). Intravenous docetaxel plus carboplatin (category 1) or paclitaxel plus cisplatin (category 1) are options for alternative regimens. 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), 6-8 cycles of chemotherapy are recommended, whereas 3 to 6 cycles are recommended for earlier-stage disease.

The recommended IV regimens accepted by a consensus of the panel include: (1) paclitaxel, 175 mg/m\(^2\) over 3-hour IV infusion, followed by carboplatin, dosed at an area under the curve (AUC) of 5-7.5 IV over 1 hour on day 1, given every 3 weeks for 6 cycles (category 1); (2) docetaxel, 60-75 mg/m\(^2\) 1-hour IV infusion followed by carboplatin, dosed at AUC of 5 to 6 IV over 1 hour on day 1, every 3 weeks for 6 cycles (category 1); and (3) dose-dense paclitaxel, 80 mg/m\(^2\) IV over 1 hour on days 1, 8, and 15 plus carboplatin AUC 6 IV over 1 hour on day 1, every 3 weeks for 6 cycles (category 1).

The recommended IP regimen is paclitaxel, 135 mg/m\(^2\) continuous IV infusion over 24 hours 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 times 6 cycles (category 1).

These regimens have different toxicity profiles. The docetaxel/carboplatin regimen is associated with increased risk for neutropenia; the IV paclitaxel/carboplatin regimen is associated with sensory peripheral neuropathy, and dose-dense paclitaxel is associated with increased anemia. The IP paclitaxel/cisplatin regimen is associated with leukopenia, infection, fatigue, renal toxicity, abdominal discomfort, and neurotoxicity. In the initial studies, only 42% of women were able to complete all 6 treatment cycles (of the IP regimen) because of toxicity; however, with more experience, this percentage has improved in the major cancer centers. Using a lower IP dose of cisplatin of 75 mg/m\(^2\) or splitting the dose may help to decrease toxicity. This approach is currently under investigation in an ongoing Gynecologic Oncology Group clinical trial.

Patients considered for the IP cisplatin and IP/IV paclitaxel regimen should have normal renal function before starting, a medically appropriate PS based on the future toxicities of the IP/IV regimen, and no previous evidence of medical problems that could significantly worsen during chemotherapy (e.g., preexisting neuropathy) (see “Principles of Chemotherapy” in the NCCN Ovarian Cancer algorithm). Reasons for discontinuing the IP regimen included catheter complications, nausea/vomiting/dehydration, and abdominal pain. Women unable to complete IP therapy should receive IV therapy. Techniques to decrease catheter complications include catheter choice...
and timing of insertion.\textsuperscript{96,111} Giving intravenous hydration before and after IP chemotherapy is a useful strategy to prevent renal toxicity.\textsuperscript{108} Expert nursing care may help to decrease complications.\textsuperscript{97} After chemotherapy, patients often require IV fluids (5-7 days) in the outpatient setting to prevent or help treat dehydration. Whether to use IP or IV chemotherapy remains controversial.\textsuperscript{110,112-115}

Patients with poor PS, comorbidities, stage IV disease, or advanced age may not tolerate the IP regimen. The IP regimen published by Armstrong and colleagues has, however, documented the longest median survival (65.6 months) that has been described to date in optimally debulked stage III patients.\textsuperscript{94} Patients with primary peritoneal cancer, Fallopian tube cancer, or MMMT can also be considered for IP chemotherapy.\textsuperscript{99,111} All women should be counseled about the clinical benefit associated with combined IV and IP chemotherapy administration before undergoing surgery for ovarian, Fallopian tube cancer, primary peritoneal cancer, or MMMT.

Dose-dense weekly paclitaxel with carboplatin has been shown to increase both PFS (28 versus 17 months, \( P = .0015 \)) and 3-year overall survival (72\% versus 65\%, \( P = .03 \)) when compared with standard therapy given every 3 weeks (i.e., IV carboplatin/paclitaxel).\textsuperscript{105} However, the dose-dense regimen is more toxic, and patients discontinued dose-dense paclitaxel therapy more often than did those receiving standard therapy. Future studies will compare the effect of weekly paclitaxel on the overall survival benefit with that of using IP chemotherapy.\textsuperscript{116}

**Anti-Angiogenesis Agents**

A recent phase III randomized trial (GOG-0218) assessed bevacizumab with carboplatin/paclitaxel in the upfront setting compared to carboplatin/paclitaxel alone. The median PFS was significantly increased (14.1 versus 10.3 months; HR for progression or death, 0.717 \( P<.001 \)) in patients receiving bevacizumab upfront and as maintenance therapy when compared with chemotherapy alone.\textsuperscript{117} However, PFS was not significantly increased in patients receiving bevacizumab upfront with placebo maintenance versus chemotherapy alone (i.e., bevacizumab/carboplatin/paclitaxel versus carboplatin/paclitaxel). No significant differences in overall survival or quality of life were reported between the groups. Of note, the primary endpoint of overall survival was converted to PFS midway through the GOG-0218 trial, because maintaining the blind was deemed infeasible. Many patients and investigators requested information at disease progression regarding whether patients had received bevacizumab.

Another recent phase III randomized trial (ICON7) also assessed bevacizumab with carboplatin/paclitaxel in the upfront setting followed by bevacizumab as maintenance therapy. The trial design of ICON7 had some important differences compared to GOG-0218 (e.g., the dose of bevacizumab was decreased by 50\% to 7.5 mg/kg).\textsuperscript{118} Although the PFS data from ICON7 confirm the findings of GOG-0218, the benefits were modest (1.7 month increase in PFS); data are immature regarding survival. Quality of life was similar between the 2 arms. After an unplanned post-hoc subset analysis in ICON7, an apparent overall survival advantage was reported in patients with stage III suboptimal and stage IV disease (30\% of participants). However, this overall survival advantage was not seen in GOG-0218 where 65\%-70\% of patients had similar high-risk features; any potential benefit may have been obscured by the availability of bevacizumab after progression of disease in the United States. Currently, no ongoing studies are addressing this issue in first-line therapy. Final overall survival results for ICON7 will be available in 2013.
The Gynecologic Cancer Intergroup (GCIG) has previously stated that “…in the front-line setting, both PFS as a surrogate end point and overall survival as a true end point…are reasonable primary end points.” Many agree that PFS may be a valid surrogate end point for overall survival in advanced ovarian cancer. Recently the GCIG stated that “Both PFS and overall survival are important end points to understand the full impact of any new treatment. Although overall survival is an important end point, PFS is most often the preferred primary end point for trials because of the confounding effect of the post-recurrence/progression therapy on overall survival. Each protocol should specify if PFS or overall survival is the preferred end point. Regardless of which is selected, the study should be designed and powered for both PFS and overall survival when feasible.”

PFS can be used as a surrogate for overall survival not because it is a better end point, but because PFS requires less follow-up time to observe statistical significance. Concordance between PFS and overall survival has not been shown yet in the GOG-0218 and ICON7 trials (i.e., although slight increases in PFS have been reported in both trials, overall survival did not increase in GOG-0218; mature survival data have not been reported yet for ICON7). Detected differences in PFS are subject to bias. Thus, it is critical to report final overall survival data so that clinicians are fully informed. “The primary goal [of clinical research] should be to obtain a statistically reliable evaluation about whether the experimental intervention is safe and provides a clinically meaningful benefit.”

The NCCN Ovarian Cancer panel had a major disagreement about recommending the addition of bevacizumab to upfront therapy with carboplatin/paclitaxel followed by maintenance bevacizumab therapy; this disagreement is reflected in the category 3 recommendation. A majority of panel members feel that bevacizumab should not be added to upfront chemotherapy in patients with ovarian cancer, because data from GOG-0218 and ICON7 have not shown a statistically significant increase in overall survival and/or improved quality of life. The magnitude of the clinical benefit versus the potential for serious side effects (e.g., < 3% of patients had GI perforation or fistula) as well as cost were also discussed by the panel with varying opinions. It is not clear whether use of maintenance bevacizumab therapy alone in GOG-0218 would have yielded the same PFS results.

The NCCN panel recommends (category 3) that if bevacizumab is used with upfront chemotherapy followed by maintenance therapy, then either the GOG-0218 or ICON7 regimens should be used (see OV-D). Note that the only GOG-0218 regimen that is recommended (category 3) is bevacizumab upfront with carboplatin/paclitaxel followed by maintenance bevacizumab. A recent phase II trial of upfront bevacizumab with IP cisplatin (75 mg/m²)/paclitaxel followed by maintenance bevacizumab reported PFS within the range reported with chemotherapy alone in GOG172. There was an increased risk of GI perforation (7%). The issues of clinical trial endpoints, use of peer-reviewed publications for evidence-based decisions, and cost effectiveness are controversial and challenging. The high cost of bevacizumab warrants more cost-effectiveness research. The NCCN panel encourages participation in ongoing clinical trials that are further investigating the role of anti-angiogenesis agents in the treatment of ovarian cancer, both in the upfront and recurrence settings. Note that the SGO has stated that if patients are interested in bevacizumab therapy, they should discuss the risks, benefits, and utility with their healthcare providers (http://www.sgo.org/WorkArea/showcontent.aspx?id=3666).
The NCCN panel encourages participation in ongoing clinical trials that are further investigating the role of anti-angiogenesis agents in the treatment of ovarian cancer, both in the upfront and recurrence settings. Note that the SGO has stated that if patients are interested in bevacizumab therapy, they should discuss the risks, benefits, and utility with their healthcare providers (http://www.sgo.org/WorkArea/showcontent.aspx?id=3666).

**Number of Chemotherapy Cycles and Agents**

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

The role of maintenance therapy in patients who achieve a complete clinical remission after 6-8 cycles of chemotherapy is an option based on the results from GOG 178. This trial randomly assigned patients to 3 versus 12 months of further paclitaxel (135-175 mg/m² every 4 weeks for 12 cycles) after initial chemotherapy. The published study treated patients at 175 mg/m²; the plan was to decrease the dose to 135 mg/m², but the protocol closed before any patients were treated at the lower dose. The results of this trial suggest that patients receiving 12 months of therapy sustained a PFS advantage. However, postremission paclitaxel chemotherapy is a category 2B recommendation because it is associated with toxicity and it only increased PFS.

**Drug Reactions**

Virtually all drugs have the potential to cause drug reactions, either during or after the infusion. 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 IV or IP administration of these drugs. Most of these drug reactions are mild infusion reactions (i.e., skin reactions, cardiovascular reactions, respiratory or throat tightness), but more severe allergic reactions (i.e., life-threatening anaphylaxis) can occur. Infusion reactions are more common with paclitaxel, but mild reactions can also occur with liposomal doxorubicin. Allergic reactions (i.e., true drug allergies) are more common with platinum agents (i.e., carboplatin, cisplatin, oxaliplatin).

Management of drug reactions is discussed in the NCCN Ovarian Cancer guidelines. New algorithms are provided for management of mild, severe, and life-threatening reactions in the 2012 guidelines. These drug reaction algorithms are also useful for patients with other gynecologic cancers (e.g., cervical and uterine cancers) who are receiving carboplatin, cisplatin, docetaxel, liposomal doxorubicin, oxaliplatin, or paclitaxel. Typically the infusion should be stopped for patients having a reaction; further management is provided in the new algorithms. Standard resuscitation procedures (i.e., Advanced Cardiac Life Support [ACLS]) should be followed for patients with acute cardiopulmonary arrest (http://acls-algorithms.com/2010-acls-guidelines).

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. Almost all patients can be desensitized (about 90%). For severe life-threatening...
reactions, the implicated agent should not be used again unless under the supervision and guidance of an allergist or specialist with expertise in desensitization. If a mild allergic reaction is suspected, and it is appropriate to administer the drug again, a desensitization regimen should be used even if the symptoms have resolved. Patients must be desensitized with each infusion if they previously had a drug reaction. Data suggest that an extended infusion schedule and use of premedication may decrease the number of hypersensitivity reactions to carboplatin.

**Radiation Therapy**

Whole abdominal radiation therapy (WART) in patients with low-bulk stage III disease is no longer included as an option for initial treatment or consolidation treatment in ovarian cancer. Because WART is rarely used in NCCN institutions, it is not included as a treatment recommendation in the Ovarian Cancer guidelines. Palliative localized RT is an option for symptom control in patients with recurrent disease (see “Acceptable Recurrence Therapies” in the NCCN Ovarian Cancer algorithm). Patients who receive radiation are prone to vaginal stenosis, which can impair sexual function. Women can use vaginal dilators to prevent or treat vaginal stenosis. Dilator use can start 2-4 weeks after RT is completed and can be done 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 re-evaluation. Patients who have no evidence of progression of cancer (i.e., complete clinical remission) after initial treatment can undergo observation with follow-up (see next section on “Follow-Up Recommendations”) (also see “Monitoring/Follow-up” in the NCCN Ovarian Cancer algorithm); other options are discussed below. Patients with partial remission or progression during initial treatment should be treated with second-line approaches (see section on “Recurrent Disease” in this Discussion) (see “Therapy for Persistent Disease or Recurrence” in the NCCN Ovarian Cancer algorithm).

Options for maintenance treatment for the management of advanced-stage (stages II-IV) patients who are in complete clinical remission after their initial therapeutic regimen include observation alone, a clinical trial, or additional chemotherapy (paclitaxel, category 2B), preferably in a controlled clinical trial (see “Secondary Adjuvant Therapy” in the NCCN Ovarian Cancer algorithm). If used, the paclitaxel regimen is 135-175 mg/m² 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 <1 cm lymph nodes).

**Follow-up Recommendations**

After the completion of primary surgery and chemotherapy in patients with all stages of ovarian cancer (or Fallopian tube cancer or primary peritoneal cancer) who have a complete response, the standard recommendation is observation with follow-up. Recommendations for monitoring are described in the algorithm (see “Monitoring/Follow-up” in the NCCN Ovarian Cancer algorithm). Chest/abdominal/pelvic CT, MRI, positron emission tomography (PET) scans (category 2B for PET), PET-CT, and chest imaging may be ordered if clinically necessary. Measurement of a CA-125 level or other tumor markers at each follow-up evaluation is recommended if the level was initially elevated. Patients should be educated about the signs and symptoms suggestive of recurrence (e.g., pelvic pain, bloating, obstruction, weight loss, fatigue). Patients who chose fertility-sparing surgery should be monitored by ultrasound examinations if necessary; they should be considered for completion surgery (category 2B) after finishing childbearing.
A recent multi-institutional European trial assessed the use of CA-125 for monitoring for ovarian cancer recurrence after primary therapy. 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. The NCCN panel concurs with the SGO opinion which states that there are limitations to this study and that patients should discuss the pros and cons of CA-125 monitoring with their physicians. In addition, patients seem reluctant to give up monitoring. Others have discussed this study in greater detail.

Management of an Increasing CA-125 Level

The management of patients in a clinical complete remission who (during routine monitoring and follow-up) are found to have an increasing CA-125 level but no signs or symptoms of recurrent disease (e.g., pelvic pain, bloating, obstruction), following an evaluation including a negative pelvic examination and negative chest/abdominal/pelvic CT scans is somewhat controversial. Patients who have never received chemotherapy (i.e., naïve to chemotherapy) should be managed as newly diagnosed patients, should undergo clinically appropriate imaging studies and surgical debulking, and should be treated as previously described (see “Primary Treatment” in the NCCN Ovarian Cancer algorithm).

After the documentation of an increased CA-125 level (i.e., biochemical relapse), the median time for a clinical relapse is 2 to 6 months. However, recent data suggest that immediate treatment for biochemical relapse is not beneficial; therefore, immediate treatment is a category 2B recommendation in the NCCN guidelines. Recommendations for biochemical relapse include enrollment on a clinical trial or delaying treatment (i.e., observation) until clinical symptoms arise (see “Recurrent Disease” in the NCCN Ovarian Cancer algorithm).

Because tamoxifen and other hormonally active agents have a defined response rate in recurrent disease after progression on platinum-based chemotherapy, they are frequently administered to patients who have only a rising CA-125 level as evidence of tumor progression. Tamoxifen, other hormonal agents, or other recurrence therapy are acceptable recommendations for this clinical situation (category 2B).

Recurrent Disease

The prognosis is poor (1) for patients who progress after 2 consecutive chemotherapy regimens without ever sustaining a clinical benefit (refractory); or (2) for those whose disease recurs in less than 6 months (platinum resistant). Note that progression is typically defined using traditional RECIST (Response Evaluation Criteria in Solid Tumor) criteria (i.e., a 20% increase in tumor diameter). Panel members emphasized the importance of clinical trials to identify agents active in this group of patients. Because these patients were resistant to their primary induction regimen, retreatment with a platinum compound or paclitaxel is not generally recommended. Although panel members do not recommend retreatment with platinum agents, they recognize that altering the schedule of paclitaxel may produce secondary responses. Before any drug is given in the recurrent setting, the clinician should be familiar with the drug’s metabolism and should make certain that the patient is an appropriate candidate for the drug (e.g., that the patient has adequate renal or hepatic function). Clinical judgment must be used when selecting postoperative chemotherapy.

Options for platinum-resistant patients or for those with stages II-IV disease who have a partial response include recurrence therapy (see “Acceptable Recurrence Therapies” in the NCCN Ovarian Cancer
algorithm). Combination platinum-based chemotherapy is preferred for first recurrence (category 1) in platinum-sensitive patients (see “Therapy for Persistent Disease or Recurrence” in the NCCN Ovarian Cancer algorithm). Possible regimens are discussed in the following section (see “Acceptable Recurrence Modalities”).

Patients with ovarian cancer will often be retreated with multiple courses of recurrence therapy. Caution should be used in patients who receive multiple sequential courses of chemotherapy, because they may experience excessive toxicity and may not be able to tolerate doses used for first-line recurrence therapy; thus, clinical judgment should be used when selecting doses (see “Principles of Chemotherapy” in the NCCN Ovarian Cancer algorithm). Potential ancillary palliative surgical and/or supportive care procedures for selected patients are summarized in the algorithm (see “Principles of Primary Surgery” in the NCCN Ovarian Cancer algorithm) (http://emedicine.medscape.com/article/270646-overview#aw2aab6b4).

Secondary cytoreductive surgery can be considered for patients who recur (i.e., radiographic and/or clinical relapse) after a long disease-free interval (6 months or more). A recent meta-analysis suggests that survival increases for patients with recurrent disease who have complete cytoreduction. The duration of the disease-free interval has not been established, although panel members agreed that it should be at least 6 months before surgery should be considered.

**Acceptable Recurrence Modalities**

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

The consensus of the NCCN panel for the treatment of recurrent disease is shown in the NCCN Ovarian Cancer algorithm (see “Acceptable Recurrence Therapies”). Platinum-based combination chemotherapy is recommended (category 1) for platinum-sensitive recurrence (see “Therapy for Persistent Disease or Recurrence” in the NCCN Ovarian Cancer algorithm). Preferred combinations for platinum-sensitive recurrent disease include carboplatin/paclitaxel (category 1), carboplatin/weekly paclitaxel, carboplatin/docetaxel, carboplatin/gemcitabine (which has been shown to improve progression-free survival), carboplatin/liposomal doxorubicin (also has been shown to improve progression-free survival) or cisplatin/gemcitabine.

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 appears to be similar: topotecan, 20%; gemcitabine, 19%; vinorelbine, 20%; liposomal doxorubicin, 26%; and oral etoposide, 27%. In platinum-resistant patients, the activity for docetaxel is 22%, and for weekly paclitaxel is 21%. For platinum-sensitive disease, the preferred single agent is carboplatin or cisplatin in patients who cannot tolerate combination therapy. Recent reports suggest that weekly topotecan is less toxic than the daily regimen.
Other potentially active agents include altretamine, capecitabine, cyclophosphamide, ifosfamide, irinotecan, melphalan, oxaliplatin, paclitaxel, nanoparticle albumin-bound paclitaxel (i.e., nab-paclitaxel), pemetrexed, and vinorelbine (see “Acceptable Recurrence Therapies” in the NCCN Ovarian Cancer algorithm). Nab-paclitaxel has an overall response rate of 64%. Altretamine has a 14% response rate and ifosfamide has a 12% response rate, although less information regarding their use in paclitaxel-refractory patients is available. In platinum-resistant patients, the activity for pemetrexed is 21%. Bevacizumab is also active (21%) in both platinum-sensitive and platinum-resistant patients, 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. Capecitabine has activity in patients resistant to platinum and taxanes. Other alkylating agents, including cyclophosphamide and melphalan, can also be used. In addition, for patients who cannot tolerate or who have been unsuccessful with cytotoxic regimens, hormonal therapy with tamoxifen or other agents (including anastrozole, letrozole, leuprolide acetate, or megestrol acetate) continues to be a viable therapeutic option.

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

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

However, regardless of which regimen is selected initially, reevaluation should follow after 2 to 4 cycles of chemotherapy (depending on the agent) to determine if patients benefited from chemotherapy. Patients who primarily progress on 2 consecutive chemotherapy regimens without evidence of clinical benefit may not benefit from additional therapy. Decisions to offer supportive care, additional therapy, or 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 low malignant potential [LMP] or borderline ovarian cancer) is a primary epithelial ovarian lesion with cytological characteristics suggesting malignancy but without frank invasion and with a clinically indolent course and good prognosis. Five-year survival exceeds
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. \(^{212,213}\)

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

Some investigators feel that the appearance of invasive implants on the peritoneal surfaces in patients having ovarian cancer of LMP portends a less favorable prognosis; therefore, the same treatments used for epithelial ovarian cancer (i.e., postoperative chemotherapy) can be considered (category 2B) for these patients (see “Primary Treatment for Borderline Epithelial Ovarian Cancer” in the NCCN Ovarian Cancer algorithm). \(^{212-214}\) The benefit of postoperative chemotherapy has not been demonstrated for patients who have no microscopically demonstrable invasive implants; therefore, observation is recommended for these patients. \(^{215}\)

### Treatment

Treatment guidelines for borderline epithelial ovarian cancer depend on the histological and clinical characteristics, the age of the patient, \(^{213}\) and the stage of the disease at the time of diagnosis. Patients should be evaluated by a gynecologic oncologist. At NCCN 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 USO (preserving the uterus, contralateral ovary, and contralateral Fallopian tube) at the time of comprehensive staging. \(^{67,68,216}\) If the patient does not desire fertility-sparing surgery, standard ovarian cancer debulking surgery is recommended, accompanied by comprehensive surgical staging (i.e., completion surgery). However, data do not show increased survival with lymphadenectomy and omentectomy for LMP, although upstaging does occur. \(^{217,218}\)

For patients with known LMP disease who had incomplete previous surgery and/or were incompletely staged at the time of their initial laparotomy, recommendations depend on whether invasive implants are present and whether fertility preservation is desired (see “Primary Treatment” for Incomplete Previous Surgery in the NCCN Borderline Epithelial Ovarian Cancer algorithm). Patients who want to preserve their fertility should have comprehensive fertility-sparing surgical staging (if not previously done).

### Follow-up

Treatment recommendations after comprehensive staging depend on the presence or absence of invasive implants. The initial therapeutic approach for patients having invasive implants may include observation or, alternatively, consideration can be given to treating patients according to the guidelines for epithelial ovarian cancer (category 2B for postoperative chemotherapy) (see “Primary Treatment” in the NCCN Ovarian Cancer algorithm). Patients with no invasive implants should be observed and monitored (see “Monitoring/Follow-Up” in the NCCN Borderline Epithelial Ovarian Cancer algorithm). \(^{212,219}\)

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

Less Common Ovarian Histopathologies (LCOH)

Overview

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

Recommended Workup

The NCCN guidelines for ovarian neoplasms recognize that patients may obtain consultation at an NCCN institution for recommendations and treatment of an undiagnosed pelvic mass, or for management of a previously biopsied malignant ovarian tumor. Many such patients come to NCCN member institutions after having had previous surgery at other institutions. Patients having a histologically undiagnosed pelvic mass should undergo evaluation and staging as described in the algorithm (see “Workup” in the NCCN Less Common Ovarian Histopathologies algorithm). Tumor markers (including CA-125, inhibin, AFP, and beta-HCG) can be measured if clinically indicated.

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

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

Malignant Germ Cell Tumors

These tumors include dysgerminomas, immature teratomas, embryonal tumors, and endodermal sinus (yolk sac) tumors; they mainly occur in younger women who are often diagnosed with stage I disease. The recommended workup (see “Recommended Workup” as previously discussed) for malignant germ cell tumors may include pulmonary function studies if bleomycin is being considered. Women younger than 35 years with a pelvic mass should have AFP levels measured to assess for germ cell tumors. Malignant germ cell tumors have an excellent prognosis. After appropriate treatment, 5-year survival is more than 85%.
Completion surgery with comprehensive staging is recommended as initial surgery for patients who do not desire fertility preservation. The staging system for ovarian and primary peritoneal cancer is also used for malignant germ cell tumors (see Table 1). After comprehensive surgical staging, observation is recommended for patients with stage I dysgerminoma or immature teratoma. If these patients have had incomplete surgical staging, recommended options depend on the type of tumor, the results of imaging and tumor marker testing (e.g., AFP and beta-HCG), and whether the patients wants to preserve her fertility (see the “Malignant Germ Cell Tumors” algorithm in the NCCN guideline).

Fertility-sparing surgery should be considered for those desiring fertility preservation, regardless of stage (see “Primary Treatment” in the NCCN Malignant Germ Cell Tumors algorithm). Patients who chose fertility-sparing surgery should be monitored by ultrasound examinations if necessary; completion surgery (category 2B) should be considered after finishing childbearing.

After surgery, surveillance is the recommended option for patients with stage I dysgerminoma or stage I, grade I immature teratoma based on European and pediatric reports. For patients with stage II-IV malignant germ cell tumors, postoperative chemotherapy is recommended. Patients should receive postoperative chemotherapy for 3 to 4 cycles with bleomycin/etoposide/platinum (BEP) (category 2B for 3 versus 4 cycles) if they have (1) embryonal or endodermal sinus tumors; (2) stages II-IV dysgerminoma; or (3) stage I, grade 2-3 or stage II-IV immature teratoma. If considering the use of bleomycin, pulmonary function tests are recommended. In select patients with stage IB-III dysgerminoma for whom minimizing toxicity is critical, 3 courses of etoposide/carboplatin can be used (carboplatin 400 mg/m² (AUC =5-6) on day 1 plus etoposide 120 mg/m² on days 1-3 every 4 weeks for 3 courses).

Patients achieving a complete clinical response after chemotherapy should be observed clinically every 2 to 4 months with AFP and beta-HCG levels (if initially elevated) for 2 years. For those with abnormal markers and definitive recurrent disease, options (category 2B) include 1) high-dose chemotherapy; or 2) consider additional chemotherapy (see “Acceptable Recurrence Therapies” in the NCCN Less Common Ovarian Histopathologies algorithm). Referral of these patients to a tertiary care center for potentially curative therapy is strongly recommended.

For patients having radiographic evidence of residual tumor (after surgery and chemotherapy) but with normal AFP and beta-HCG, consider surgical resection of the tumor; observation is also an option. Further options depend on which findings are present: residual tumor, benign teratoma, or necrotic tissue (see “Recurrent/Persistent Disease” in the NCCN Malignant Germ Cell Tumors algorithm). For patients having persistently elevated AFP and/or beta-HCG after first-line chemotherapy, recommendations include TIP (paclitaxel, ifosfamide, cisplatin) or high-dose chemotherapy with stem cell support. Referral to a tertiary care center for potentially curative treatment is strongly recommended. Observation is an option (category 2B) for patients with residual malignancy after surgical resection of residual masses; this is an area of continued study and controversy. Others may recommend further chemotherapy (category 2B). There are small series but no major trials in adult patients. Clinical judgment should be used regarding the frequency of imaging.

Patients with recurrent or residual disease after multiple chemotherapeutic regimens for whom no curative options are
considered possible may be treated with a recurrence modality (see “Acceptable Recurrence Therapies” in the NCCN Less Common Ovarian Histopathologies algorithm), including TIP, VAC (vincristine, dactinomycin, cyclophosphamide), VeiP (vinblastine, ifosfamide, cisplatin), VIP (etoposide, ifosfamide, cisplatin), cisplatin/etoposide, docetaxel/carboplatin, paclitaxel/carboplatin, paclitaxel/gemcitabine, paclitaxel/ifosfamide, docetaxel, paclitaxel, high-dose chemotherapy, RT, or supportive care only. Combination chemotherapy is not recommended for patients with recurrent or residual disease who have no curative options. These recurrence regimens (see “Acceptable Recurrence Therapies” in the NCCN Less Common Ovarian Histopathologies algorithm) are not generalizable for all of the uncommon histology tumors; therefore, patients should be referred to tertiary care institutions for treatment.

Malignant Sex Cord-Stromal Tumors

Malignant stromal tumors are rare and include granulosa cell tumors (most common), granulosa-theca tumors, and Sertoli-Leydig cell tumors; they are typically associated with a good prognosis. Most patients with granulosa tumors present with early-stage disease. It is important to determine whether the sex cord-stromal tumor is benign or malignant (see “Sex Cord Stromal Tumors—World Health Organization (WHO) Histologic Classification” in the NCCN Less Common Ovarian Histopathologies algorithm). The staging system for ovarian and primary peritoneal cancer is also used for sex cord-stromal tumors (see Table 1).

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

Those with surgical findings of stage I tumor (low risk) should be observed. For patients with high-risk stage I tumors (tumor rupture, stage 1C, poorly differentiated tumor, tumor size greater than 10-15 cm), recommendations (all are category 2B) include observation or consideration of platinum-based chemotherapy. For patients with granulosa cell tumors who are being observed, inhibin levels can be followed if they were initially elevated (category 2B). For patients with stage II-IV tumors, recommended options (all are category 2B) include RT for limited disease or platinum-based chemotherapy (BEP or paclitaxel/carboplatin regimens are preferred).

Prolonged surveillance is recommended for granulosa cell tumors, because they can recur years later (e.g., 30 years). For patients with stage II-IV tumors who subsequently have a clinical relapse, options include a clinical trial or recurrence therapy (see “Acceptable Recurrence Therapies” in the NCCN Less Common Ovarian Histopathologies algorithm). Note that bevacizumab or leuprolide may be considered for patients with recurrent granulosa cell tumors. Secondary cytoreductive surgery may also be considered.

Carcinosarcoma (Malignant Mixed Müllerian Tumors)

MMMT are rare tumors with a poor prognosis. Most pathologists now consider MMMT to be a variant of poor risk, poorly differentiated epithelial ovarian cancer (metaplastic carcinoma. Patients with MMMT are not candidates for fertility-sparing surgery. The staging system for ovarian and primary peritoneal cancer is also used for MMMT (see Table 1).
After complete surgical staging, patients with stage I-IV carcinosarcoma (MMMT) at the time of surgery should have postoperative chemotherapy. Patients with stage I-IV MMMT or recurrence are treated using the same chemotherapy regimens that are recommended for epithelial ovarian cancer (see “Primary Chemotherapy/Primary Adjuvant Therapy” in the NCCN Ovarian Cancer algorithm). For example, the IP chemotherapy regimen described for ovarian cancer can be used for select patients with MMMT.

**Recommended Readings**


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