National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™)

Ovarian Cancer

Including Fallopian Tube Cancer and Primary Peritoneal Cancer

Version 2.2011

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Ovarian Cancer

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Discussion

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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

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NCCN Guidelines™ Version 2.2011 Updates Ovarian Cancer

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Updates to the 2.2011 version of the Ovarian Cancer guidelines from the 1.2011 version include:

Discussion (MS-7)

- **Based on recent clinical trial data, the panel revised the discussion regarding bevacizumab by adding information about the ICON7 trial and the following statement "Until there are more mature results from GOG 0218 and ICON7, the NCCN Ovarian Cancer panel does not recommend the routine addition of bevacizumab to upfront therapy with carboplatin/paclitaxel or as maintenance therapy at this time. 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."**

Updates to the 1.2011 version of the Ovarian Cancer guidelines from the 2.2010 version include:

OV-1

- **Foonote 'c' was modified by adding, "Patients being evaluated for neoadjuvant surgery should be seen by a fellowship-trained gynecologist oncologist prior to being considered a nonsurgical candidate."**

OV-3

- **Footnote i, number 1, was modified as, "Pelvic exams at least every 2 -*3* cycles."**
- **Footnote j, "The NCCN Ovarian Cancer panel recognizes that data for first-line and maintenance bevacizumab are becoming available and encourages participation in clinical trials" is new to the page.**

OV-6

- **Disease status, "Clinically low-volume or focal recurrence after disease-free interval > 6 mo" was removed.**
- **Footnote e, "See Principles of Primary Surgery" was added to the page. Also added as footnote 'g' to LCOH-4 and LCOH-5.**

OV-8

- **Follow-up with CA-125 tumor marker, footnote "n" is new to the page.**

OV-A 1 of 3

- **Patients with ovarian cancer involving the upper abdomen:**
  - **The statement "Residual disease < 1 cm defines optimal cytoreduction" was modified by adding, "however, maximal effort should be made to remove all gross disease".**

OV-A 2 of 3

- **"Distal pancreatectomy" was added as a procedure that may be considered for optimal surgical cytoreduction (in all stages).**
- **Special circumstances, first bullet was modified by adding, "This is particularly true in the *case of incidental finding of ovarian cancer* during prophylactic oophorectomy."**

OV-D

- **"Pemetrexed was moved from "preferred" to "other potentially active single agents".**
- **"Paclitaxel, albumin bound (nab-paclitaxel) was added to "other potentially active single agents".**

LCOH-1

- **Germ cell tumors was changed to "*malignan*t germ cell tumors".**

LCOH-2

- **Initial surgery, fertility desired, "and comprehensive staging" was added to fertility-sparing surgery.**
- **Footnote a, "Standard recommendation includes a patient evaluation by a gynecologic oncologist' was added to the page.**

LCOH-3

- **After recurrence therapy, for a complete clinical response, the algorithm is directed to "observe markers..." and for an incomplete clinical response to "see LCOH-A".**

LCOH-4

- **Footnote e, "Lymphadenetomy may be omitted" was added to "fertility-sparing surgery with complete staging."**
- **"Intermediate risk (eg, heterologous elements)" was added to "Stage I high risk."**

LCOH-A

- **Aromatase inhibitors (anastrozole, letrozole) were added to acceptable recurrence modalities for sex cord-stromal tumors.**

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NCCN Guidelines™ Version 2.2011
Epithelial Ovarian Cancer/ Fallopian Tube Cancer/ Primary Peritoneal Cancer

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CLINICAL PRESENTATION	WORKUP	PRIMARY TREATMENT[c,d]	
Suspicious[a]/palpable pelvic mass detected on abdominal/ pelvic exam and/or ascites, abdominal distention, and/or Symptoms such as bloating, pelvic or abdominal pain, difficulty eating or feeling full quickly or urinary symptoms (urgency or frequency)[b] without other obvious source of malignancy	• **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)	**Laparotomy/Total abdominal hysterectomy (TAH)/Bilateral salpingo-oophorectomy (BSO) with comprehensive staging[e] or unilateral salpingo-oophorectomy (USO) (Clinical Stage 1A or 1C, all grades with comprehensive staging if patient desires fertility)** **or** **Cytoreductive surgery[e] if clinical stage II, III, or IV** **or** **Consider neoadjuvant chemotherapy[f]/primary interval cytoreduction for patients with bulky stage III/IV who are not surgical candidates[c] (diagnosis by fine needle aspiration [FNA], biopsy or paracentesis)**	**See Pathologic Staging (OV-3)**
Diagnosis by previous surgery or tissue biopsy (cytopathology)	• Obtain family history and consider family history evaluation (See NCCN Genetic/Familial High-Risk Assessment Guidelines and NCCN Colorectal Cancer Screening Guidelines) • Ultrasound and/or abdominal/pelvic CT • Chest imaging • CA-125 or other tumor markers as clinically indicated • **CBC, chemistry profile with LFTs** • Institutional pathology review		**See Findings and Primary Treatment (OV-2)**

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

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

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

[d] 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. http://www.cancer.gov/clinicaltrials/developments/IPchemo-digest/page1/print

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

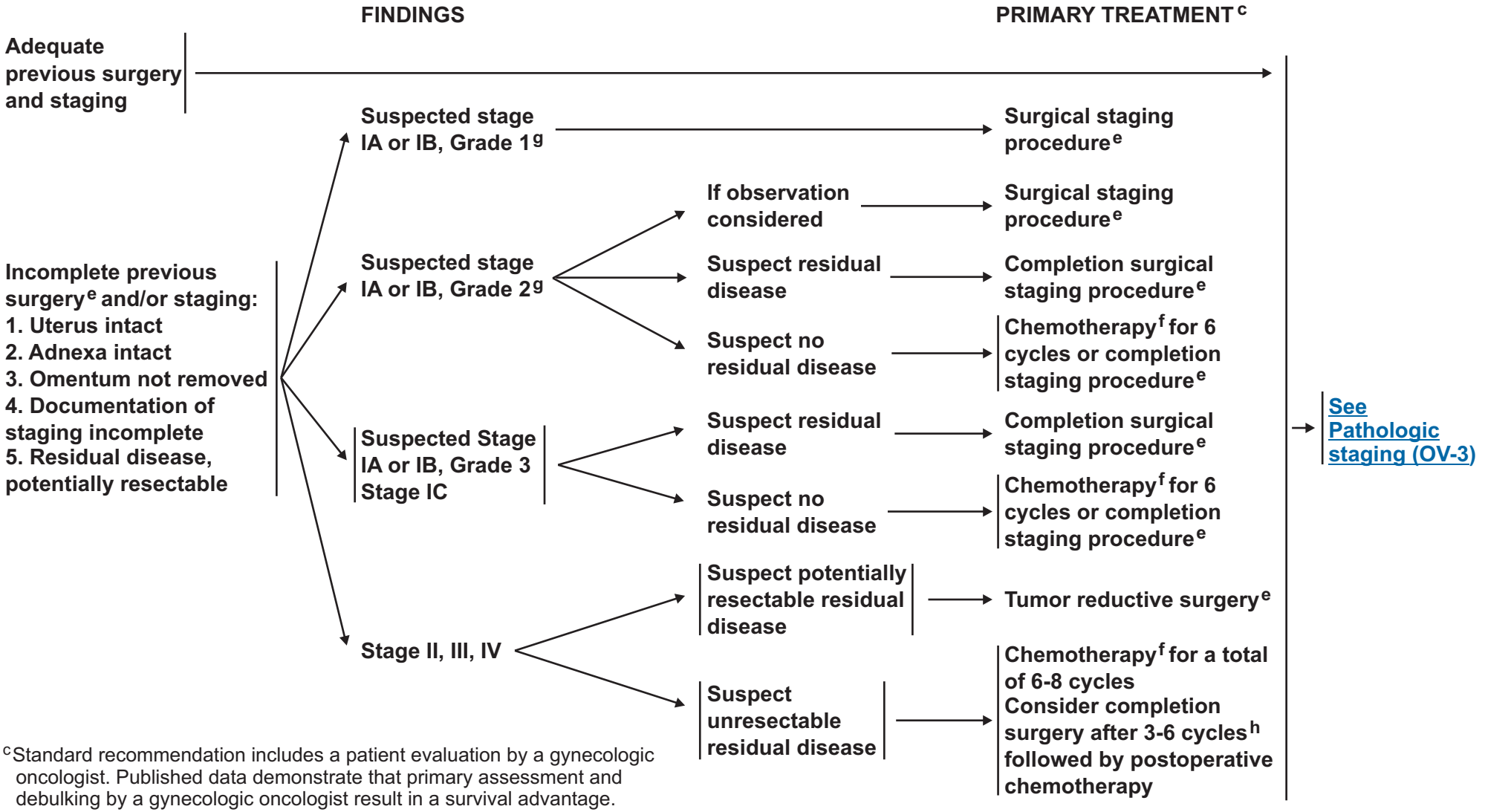
[f] See Principles of Chemotherapy (OV-B) and Management of Drug Reactions (OV-C).

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DIAGNOSIS BY PREVIOUS SURGERY



[c] Standard recommendation includes a patient evaluation by a gynecologic oncologist. Published data demonstrate that primary assessment and debulking by a gynecologic oncologist result in a survival advantage.

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

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

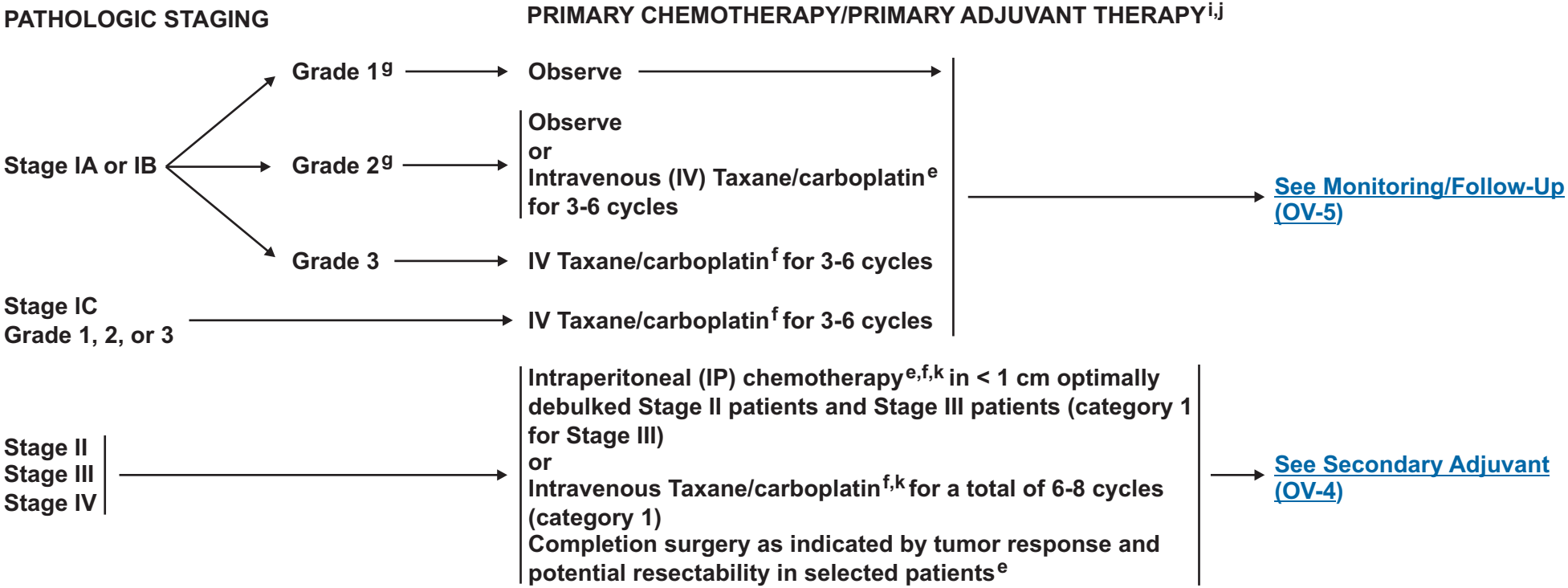
[g] Clear-cell pathology is grade 3.

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

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[d] 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. http://www.cancer.gov/clinicaltrials/developments/IPchemo-digest/page1/print

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

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

[g] Clear-cell pathology is Grade 3.

[i] Patients receiving primary chemotherapy will be monitored as follows:

1. Pelvic exams at least every 2-3 cycles
2. Interim CBC with platelets as indicated
3. Chemistry profiles if indicated
4. CA-125 levels or other tumor markers as clinically indicated prior to each cycle of chemotherapy
5. Radiographic imaging if indicated

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

[k] Regimens: (See Discussion for reference)

1. Paclitaxel 135 mg/m^2 IV continuous infusion over 24 h Day 1; cisplatin 75-100 mg/m^2 IP, Day 2 after IV paclitaxel; paclitaxel 60 mg/m^2 IP Day 8 (max BSA 2.0 m^2). Repeat every 3 weeks x 6 cycles (category 1).
2. Paclitaxel 175 mg/m^2 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/m^2 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/m^2 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)

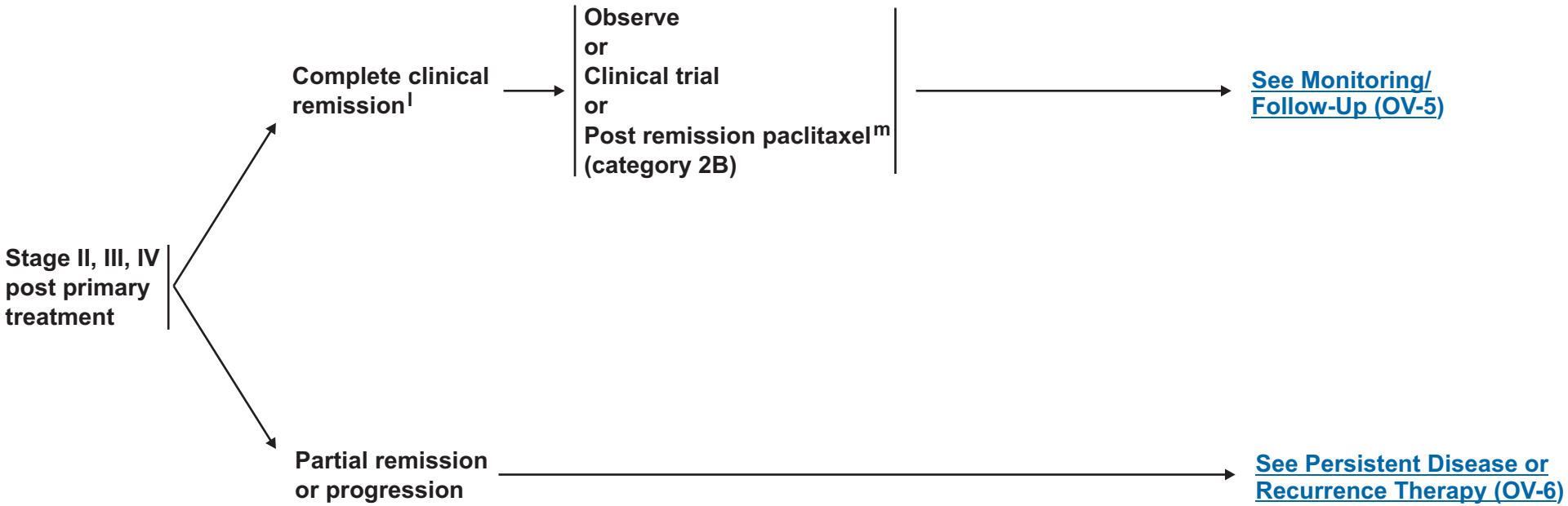
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STAGE II, III, IV
POST PRIMARY TREATMENT

SECONDARY ADJUVANT THERAPY



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

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STAGE I-IV COMPLETE RESPONSE

MONITORING/FOLLOW-UP

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

- Visits every 2-4 mo for 2 y, then 3-6 mo for 3 y, then annually after 5 y
- CA-125[n] 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**)

RECURRENT DISEASE

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

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

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

[n] There are preliminary data regarding the utility of CA-125 for monitoring of ovarian cancer after completion of primary therapy, see Society of Gynecologic Oncologists (SGO) position statement.

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

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

[o] 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.

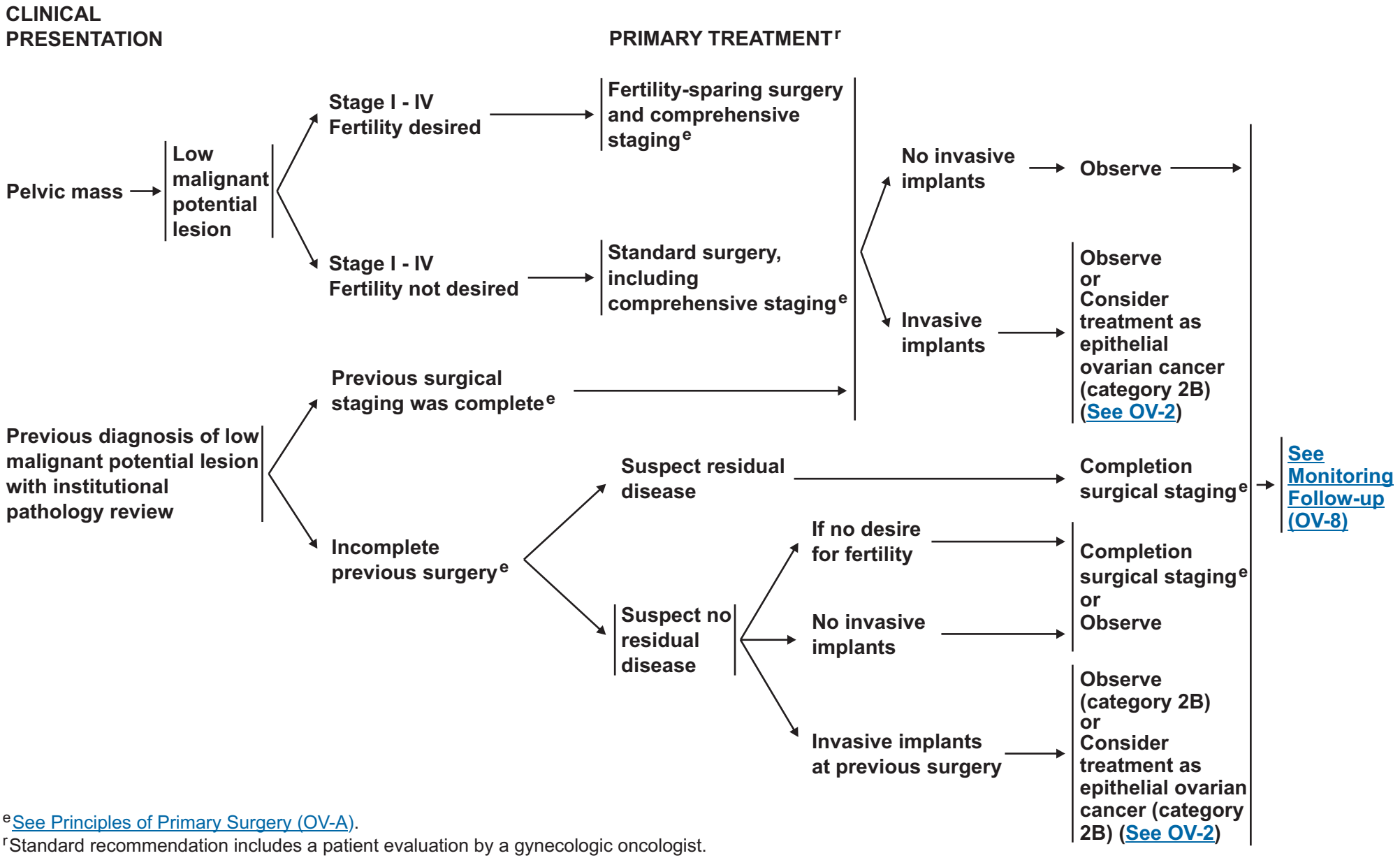
[p] See Ancillary Palliative Surgical Procedures in Principles of Surgery (OV-A).

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

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[e] See Principles of Primary Surgery (OV-A).
[r] Standard recommendation includes a patient evaluation by a gynecologic oncologist.

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MONITORING/FOLLOW-UP

- Visits every 3-6 mo for up to 5 y, then annually
- Physical exam including pelvic exam
- Ultrasound as indicated for patients with fertility-sparing surgery
- CA-125[n] or other tumor markers every visit if initially elevated
- CBC or chemistry profile as indicated
- After completion of childbearing in patients who underwent unilateral salpingo-oophorectomy, consider completion surgery (category 2B)

RECURRENT DISEASE

Clinical relapse → **Surgical evaluation + debulking if appropriate**

RECURRENCE THERAPY

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

[n]There are preliminary data regarding the utility of CA-125 for monitoring of ovarian cancer after completion of primary therapy, see Society of Gynecologic Oncologists (SGO) position statement.

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

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

Ovarian cancer involving the upper abdomen

In general, the following procedures should be part of the surgical management of patients with ovarian cancer involving the upper abdomen in an effort to achieve maximal cytoreduction. Residual disease < 1 cm defines optimal cytoreduction; however, maximal effort should be made to remove all gross disease.

- Aspiration of ascites or peritoneal lavage should be performed for peritoneal cytologic examinations. For obvious disease beyond ovaries, cytologic assessment of ascites and/or lavage specimens would not alter stage or management.
- Total hysterectomy, bilateral salpingectomy, and bilateral oophorectomy should be performed.
- All involved omentum should be removed.
- Suspicious and/or enlarged nodes should be resected, if possible.
- Those patients with tumor nodules outside the pelvis ≤ 2 cm (presumed stage IIIB) should have bilateral pelvic and para-aortic lymph node dissection as previously described.

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

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

Continued on OV-A 2 of 3

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

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

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 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.

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

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PRINCIPLES OF PRIMARY SURGERY (3 of 3)

- Ancillary Palliative Surgical Procedures

These procedures may be appropriate in select patients:

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

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

- 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 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.

Continued on OV-B 2 of 2

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

- For patients who have recurrent ovarian, fallopian tube, or primary peritoneal cancer:
- For all of the regimens listed in this NCCN Ovarian Cancer guideline, refer to the original references for toxicity, doses, schedules, and dose modifications (**See Discussion**).
- Patients should be informed about the following:
  1) availability of clinical trials, including the risks and benefits of various treatments, which will depend on the number of prior lines of chemotherapy the patient has received, and
  2) the patient's performance status, end-organ status, and 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).

- The schedule, toxicity, and potential benefits of any treatment should be thoroughly discussed with the patient and caregivers. Patient education should also include a discussion of precautions and measures to reduce the severity and duration of complications.

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MANAGEMENT OF DRUG REACTIONS (1 of 3)

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) 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) tend to occur following re-exposure to the inciting drug or less commonly at the completion of initial chemotherapy (ie, cycle 6 of a planned 6 treatments).[3]
- Preparation for a possible drug reaction
  - Patients and their families need to be counseled about the possibility of a drug reaction, and about the signs and symptoms of an adverse reaction (either infusion or allergic). Patients should be told to report any signs and symptoms of a drug reaction, especially after they have left the clinic.
  - Clinicians and nursing staff should be prepared for the possibility of a drug reaction every time a patient is infused with a drug.
  - Standing orders should be written for immediate intervention in case a severe drug reaction occurs.
  - The treatment area should have appropriate medical equipment in case of a life-threatening reaction.[5]
- Desensitization refers to a process of rendering the patient less likely to respond to an allergen and can be considered for patients who have had drug reactions.[1,7-9]
  - Although desensitization is more commonly used after allergic drug reactions, it can also be used after severe infusion reactions.
- If a mild reaction has previously occurred to a platinum agent, great caution should be undertaken if desensitization is pursued (see “Allergic Reactions”).
- If a patient has previously had a very severe life-threatening reaction, the implicated drug should not be used again.

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

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MANAGEMENT OF DRUG REACTIONS (2 of 3)

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, 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.[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.
  - 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]

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References on OV-C 3 of 3

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MANAGEMENT OF DRUG REACTIONS (3 of 3)

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ACCEPTABLE RECURRENCE THERAPIES (1 of 2)[1]

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

See Footnotes and References (OV-D 2 of 2)

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ACCEPTABLE RECURRENCE THERAPIES (2 of 2)

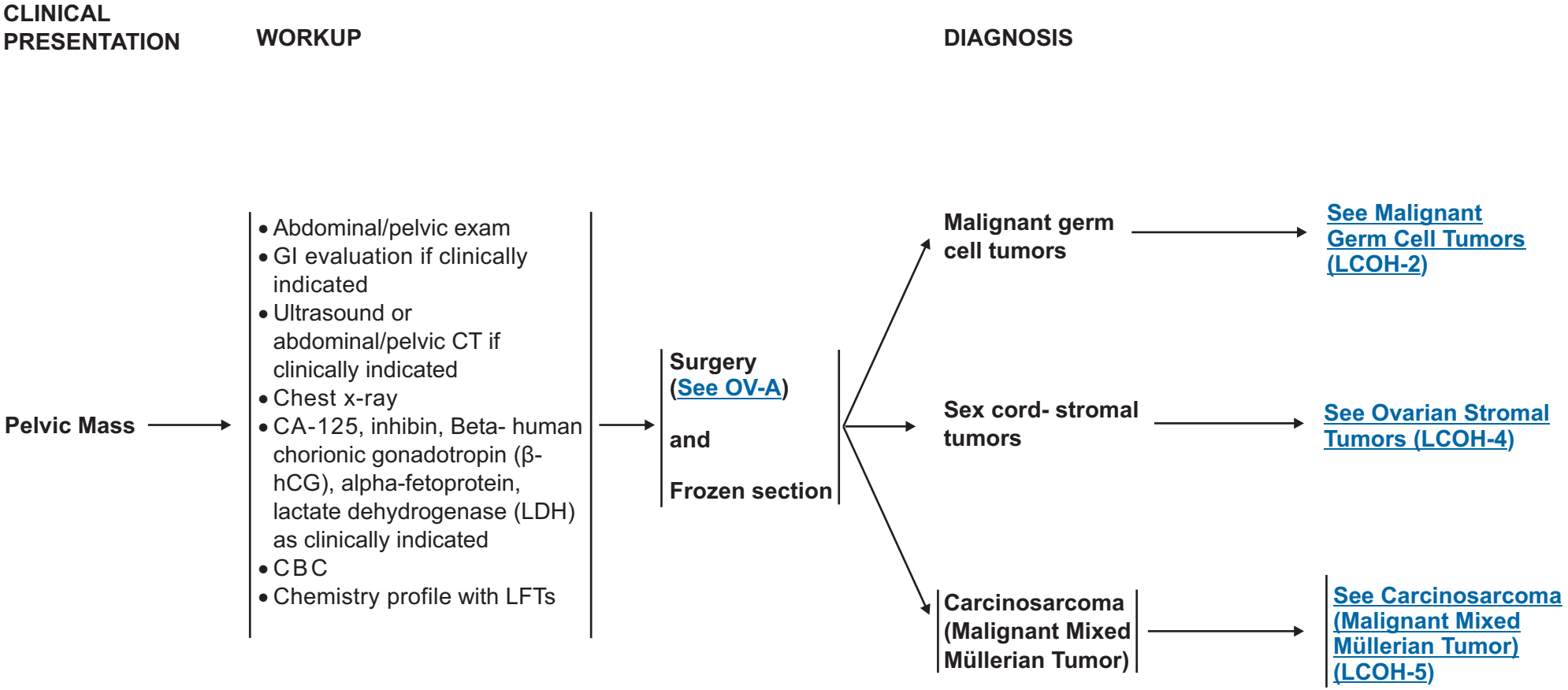
FOOTNOTES AND REFERENCES

[1]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, or additional therapy should be made on a highly individual basis.
[2]Platinum-based combination therapy should be considered for platinum-sensitive recurrences.
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[16]See Discussion for references.

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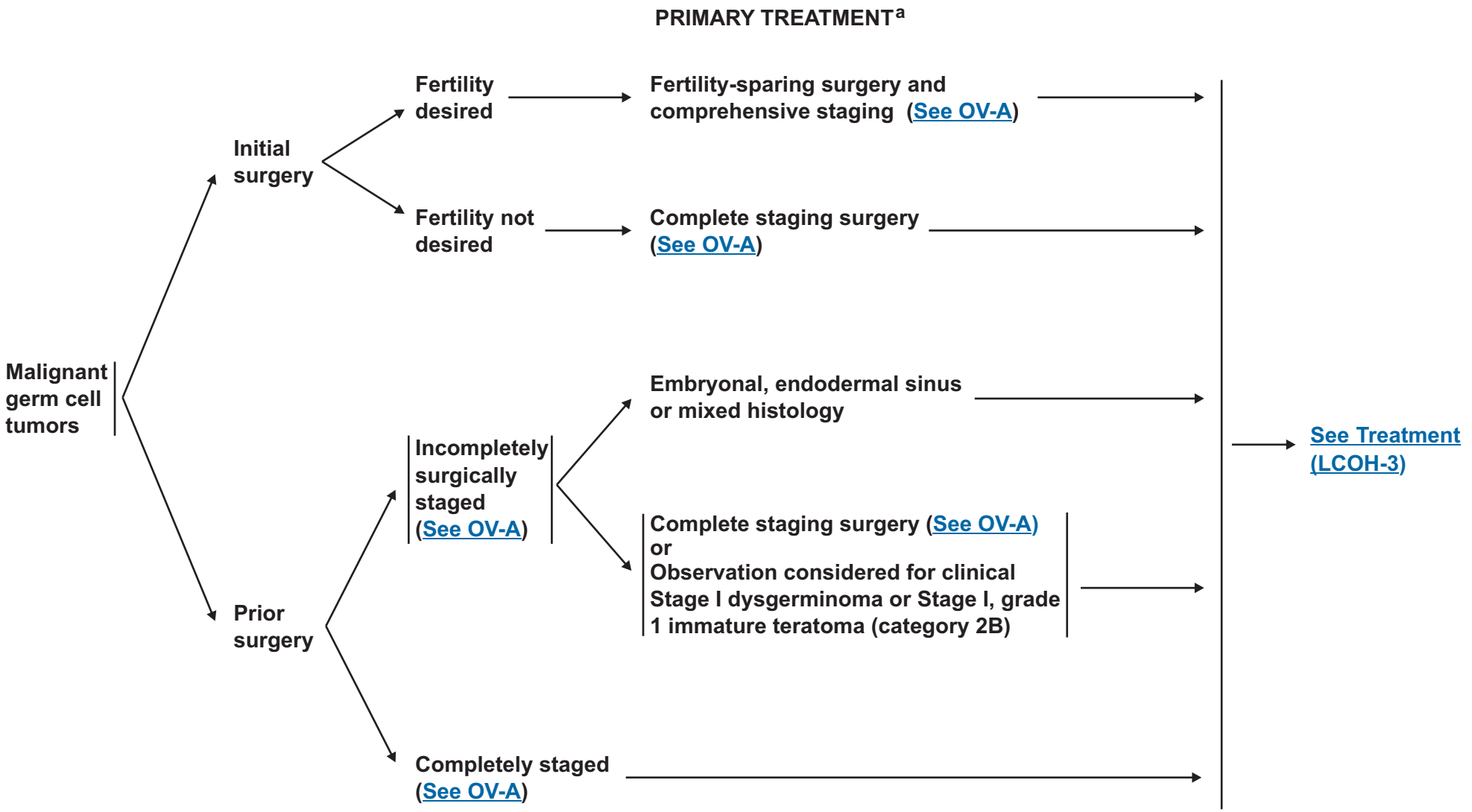
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[a]Standard recommendation includes a patient evaluation by a gynecologic oncologist.

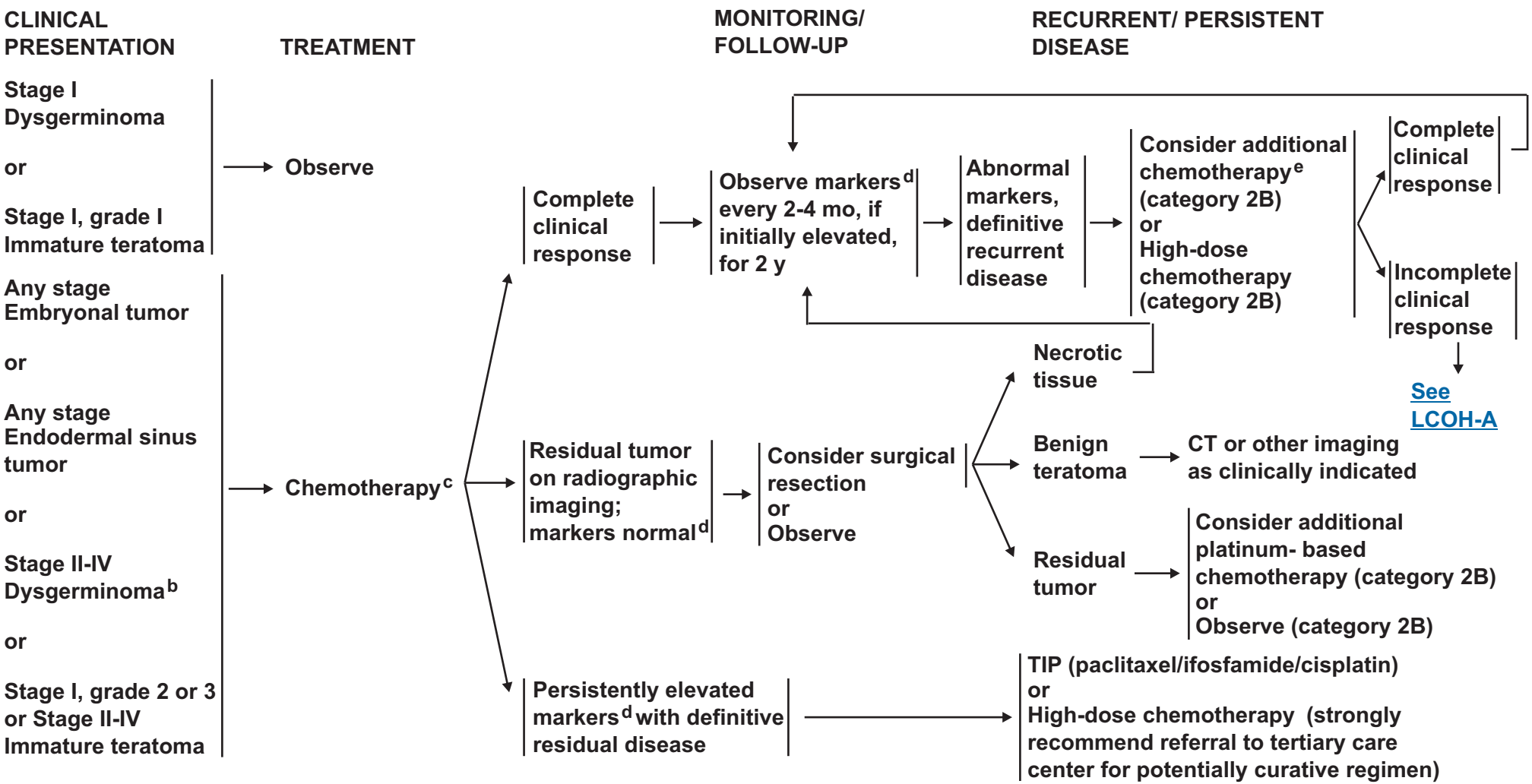
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NCCN Guidelines™ Version 2.2011
Malignant Germ Cell Tumors

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

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

[d] See LCOH-1 for markers.

[e] See Acceptable RecurrenceTherapies (LCOH-A).

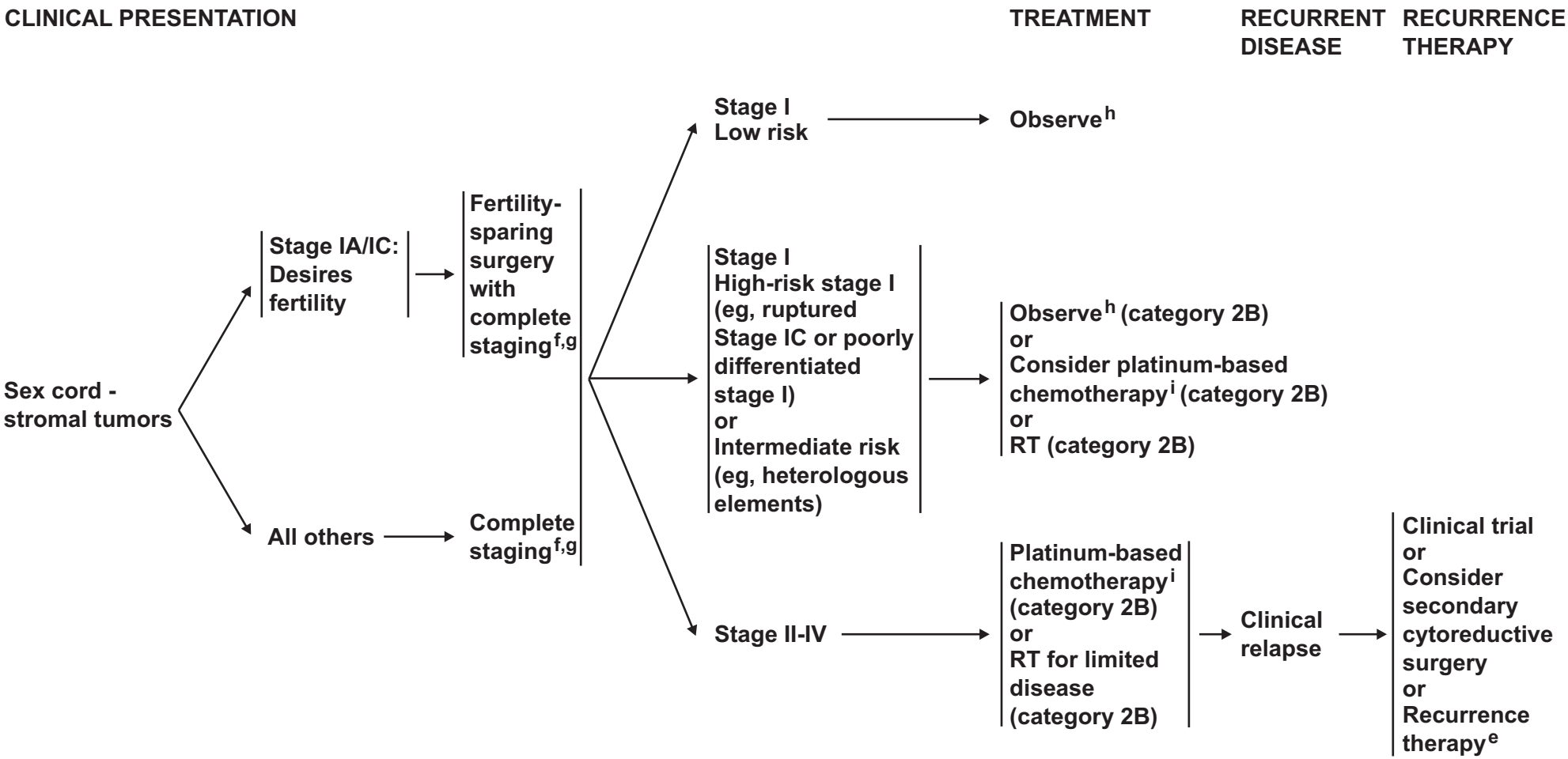
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Sex Cord-Stromal Tumors

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e See Acceptable RecurrenceTherapies (LCOH-A).
f Lymphadenectomy may be omitted.
g See Principles of Primary Surgery (OV-A).
h Inhibin levels can be followed if initially elevated (category 2B)
i Germ cell regimens (See LCOH-3) or paclitaxel/carboplatin regimens are preferred.

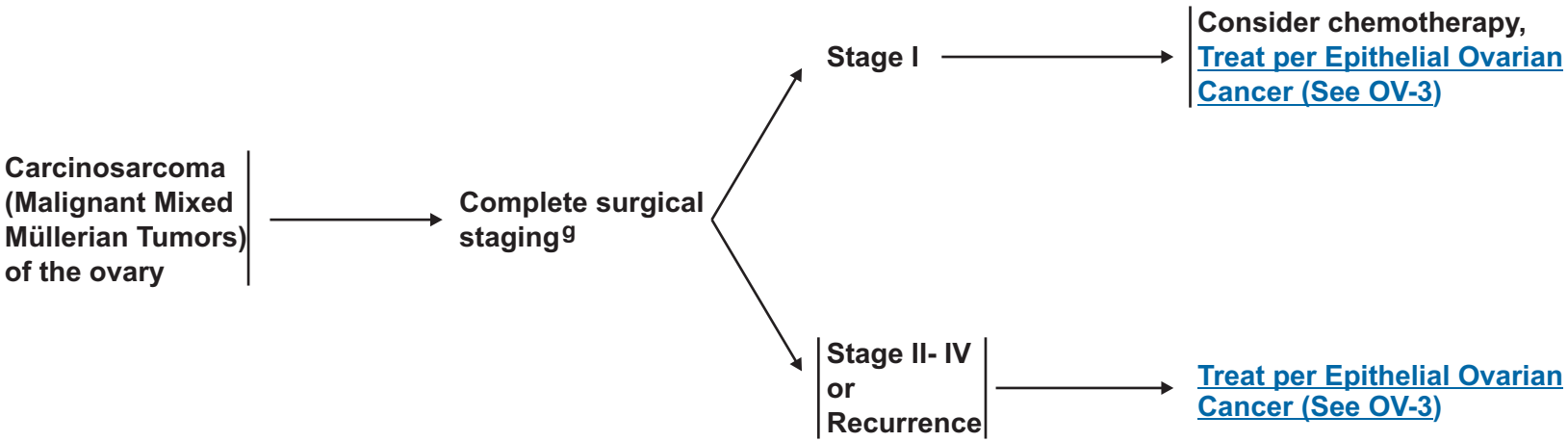
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CLINICAL PRESENTATION

TREATMENT



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

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ACCEPTABLE RECURRENCE THERAPIES

MALIGNANT GERM CELL TUMORS[1]

High-dose chemotherapy[1,2]

Cisplatin/etoposide

Docetaxel

Docetaxel/carboplatin

Paclitaxel

Paclitaxel/ifosfamide

Paclitaxel/carboplatin

Paclitaxel/gemcitabine

VIP (etoposide, ifosfamide, cisplatin)

VeIP (vinblastine, ifosfamide, cisplatin)

VAC (vincristine, dactinomycin, cyclophosphamide)

TIP (paclitaxel, ifosfamide, cisplatin)

Radiation therapy

Supportive care only

SEX CORD-STROMAL TUMORS

Aromatase inhibitors (anastrozole, letrozole)

Bevacizumab may be considered for granulosa cell tumors

Leuprolide may be used as hormonal therapy for granulosa cell tumors

Docetaxel

Paclitaxel

Paclitaxel/ifosfamide

Paclitaxel/carboplatin

Tamoxifen

VAC (vincristine, dactinomycin, cyclophosphamide)

Radiation therapy

Supportive care only

[1] Patients with potentially curable recurrent germ cell disease should be referred to a tertiary care institution for potentially curative therapy.
[2] High-dose chemotherapy regimens vary among institutions.

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Staging

Table 1

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

Primary Tumor (T)

TNM	FIGO	
TX		Primary tumor cannot be assessed
T0		No evidence of primary tumor
T1	**I**	Tumor limited to ovaries (one or both)
T1a	**IA**	Tumor limited to one ovary; capsule intact, no tumor on ovarian surface. No malignant cells in ascites or peritoneal washings
T1b	**IB**	Tumor limited to both ovaries; capsules intact, no tumor on ovarian surface. No malignant cells in ascites or peritoneal washings
T1c	**IC**	Tumor limited to one or both ovaries with any of the following: capsule ruptured, tumor on ovarian surface, malignant cells in ascites or peritoneal washings
T2	**II**	Tumor involves one or both ovaries with pelvic extension
T2a	**IIA**	Extension and/or implants on uterus and/or tube(s). No malignant cells in ascites or peritoneal washings
T2b	**IIB**	Extension to and/or implants on other pelvic tissues. No malignant cells in ascites or peritoneal washings
T2c	**IIC**	Pelvic extension and/or implants (T2a or T2b) with malignant cells in ascites or peritoneal washings
T3	**III**	Tumor involves one or both ovaries with microscopically confirmed peritoneal metastasis outside the pelvis
T3a	**IIIA**	Microscopic peritoneal metastasis beyond pelvis (no macroscopic tumor)
T3b	**IIIB**	Macroscopic peritoneal metastasis beyond pelvis 2 cm or less in greatest dimension
T3c	**IIIC**	Peritoneal metastasis beyond pelvis more than 2 cm in greatest dimension and/or regional lymph node metastasis

Regional Lymph Nodes (N)

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

Distant Metastasis (M)

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

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

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Staging

Table 1 (Continued)

American Joint Committee on Cancer (AJCC)

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

Stage Grouping			
Stage 1	T1	N0	M0
Stage IA	T1a	N0	M0
Stage IB	T1b	N0	M0
Stage IC	T1c	N0	M0
Stage II	T2	N0	M0
Stage IIA	T2a	N0	M0
Stage IIB	T2b	N0	M0
Stage IIC	T2c	N0	M0
Stage III	T3	N0	M0
Stage IIIA	T3a	N0	M0
Stage IIIB	T3b	N0	M0
Stage IIIC	T3c	N0	M0
	Any T	N1	M0
Stage IV	Any T	Any N	M1

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

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Staging

Table 2

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

Primary Tumor (T)

TNM	FIGO	
TX		Primary tumor cannot be assessed
T0		No evidence of primary tumor
Tis*		Carcinoma in situ (limited to tubal mucosa)
T1	**I**	Tumor limited to the fallopian tube(s)
T1a	**IA**	Tumor limited to one tube, without penetrating the serosal surface; no ascites
T1b	**IB**	Tumor limited to both tubes, without penetrating the serosal surface; no ascites
T1c	**IC**	Tumor limited to one or both tubes with extension onto or through the tubal serosa, or with malignant cells in ascites or peritoneal washings
T2	**II**	Tumor involves one or both fallopian tubes with pelvic extension
T2a	**IIA**	Extension and/or metastasis to the uterus and/or ovaries
T2b	**IIB**	Extension to other pelvic structures
T2c	**IIC**	Pelvic extension with malignant cells in ascites or peritoneal washings
T3	**III**	Tumor involves one or both fallopian tubes, with peritoneal implants outside the pelvis
T3a	**IIIA**	Microscopic peritoneal metastasis outside the pelvis
T3b	**IIIB**	Macroscopic peritoneal metastasis outside the pelvis 2 cm or less in greatest dimension
T3c	**IIIC**	Peritoneal metastasis outside the pelvis and more than 2 cm in diameter

Regional Lymph Nodes (N)

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

Distant Metastasis (M)

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

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

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

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Staging

Table 2 (Continued)

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

Stage Grouping			
Stage 0*	Tis	N0	M0
Stage 1	T1	N0	M0
Stage IA	T1a	N0	M0
Stage IB	T1b	N0	M0
Stage IC	T1c	N0	M0
Stage II	T2	N0	M0
Stage IIA	T2a	N0	M0
Stage IIB	T2b	N0	M0
Stage IIC	T2c	N0	M0
Stage III	T3	N0	M0
Stage IIIA	T3a	N0	M0
Stage IIIB	T3b	N0	M0
Stage IIIC	T3c	N0	M0
	Any T	N1	M0
Stage IV	Any T	Any N	M1

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

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

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Discussion

NCCN Categories of Evidence and Consensus

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

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

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

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

All recommendations are category 2A unless otherwise noted.

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

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.[4] 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.[5]

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 hereditary nonpolyposis colorectal cancer (HNPCC), has been found to be associated with early-onset disease; however, these patients account for only 5% of all women who have ovarian cancer.[4, 6] In high-risk women (with either BRCA1 or BRCA2 mutations), oophorectomy is associated with a reduced risk of ovarian and Fallopian tube cancer; however, there is a residual risk for primary peritoneal cancer in these high-risk women after prophylactic

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salpingo-oophorectomy.[6, 7] The risks of surgery include injury to the bowel, bladder, ureter, and vessels.[8] Recent data suggest that the Fallopian tube may be the origin of some ovarian and primary peritoneal cancers.[9-13] Environmental factors have been investigated, but so far they have not been conclusively associated with the development of this neoplasm.

Screening

Because of the location of the ovaries and the biology of most epithelial cancers, 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).[14, 15] 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).[14] 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.[8, 16]

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.[17] However, a similar trial in the United States assessing screening with transvaginal ultrasonography and CA-125 did not find that screening increased the detection of early-stage cancer (72% of cancers detected by screening were late stage).[18] Another recent study comparing CA-125 alone versus ultrasound with or without CA-125 found that CA-125 did not increase the detection of cancer over ultrasound alone.[19]

Randomized data do not yet support routine screening for ovarian cancer in the general population, and routine screening is not currently recommended by any professional society.[8, 20] Some physicians follow women with high-risk factors (e.g., those with BRCA mutations, those with a family history) using CA-125 monitoring and endovaginal ultrasound; however, prospective validation of these tests remains elusive. An intriguing study suggests that ovarian cancer is associated with unique odors that can be detected.[21, 22]

A recent screening trial assessed an algorithm that used age and longitudinal changes in CA-125 levels to determine whether women at average risk would develop ovarian cancer (Risk of Ovarian Cancer Algorithm [ROCA]); women deemed at risk were referred for transvaginal sonography (TVS).[23] However, the Society of Gynecologic Oncologists (SGO) and others have stated that until data from larger randomized controlled trials are published (e.g., UKCTOCS), 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 Society of Gynecologic Oncologists (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.

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(http://www.sgo.org/WorkArea/showcontent.aspx?id=2940). The OVA-1 screening 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).[24-26]

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.[27] Although human epididymis protein 4 (HE4) and CA-125 appear to be useful in detecting ovarian cancer,[28, 29] recent data show that several markers (including CA-125, HE4, mesothelin, B7-H4, decoy receptor 3 [DcR3], and spondin-2) do not increase early enough to be useful in detecting early-stage ovarian cancer.[30]

Staging

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).[31] Pathologic grading continues to be an important prognostic factor and is used in the selection of therapy, primarily for early-stage disease. Grading is labeled as 1, 2, or 3. Except for 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).[31] Fallopian tube carcinomas are also staged using the TNM and FIGO staging systems (see Table 2).[31]

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 OV-1).[14, 32-36] Ultrasound is

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typically used for initial evaluation; however, CT is useful to assess for metastases.[33] 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.[37, 38] Other cancers that should be ruled out include bowel, uterine, and pancreatic cancers or lymphoma.

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 OV-A). 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/2009/Ovary_09protocol.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.[24-26] For a young patient who wishes to maintain fertility, a unilateral salpingo-oophorectomy (USO) (preserving the uterus and contralateral ovary) may be adequate for stage I tumors and/or low-risk tumors (i.e., early-stage, low-grade invasive tumors; low malignant potential [LMP] lesions).[39-42]

Comprehensive surgical staging should still be performed to rule out occult higher-stage disease, because data show that approximately 30% of patients undergoing complete staging surgery are upstaged.[43] In stage I disease, minimally invasive techniques to achieve the surgical goals 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 OV-1).[26, 40, 43-45] In

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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.[46-48]

A maximal effort should be made to remove all gross disease. On entering the abdomen, aspiration of ascites or peritoneal lavage should be performed for cytologic examinations. For obvious disease beyond the ovaries, cytologic assessment of ascites and/or lavage specimens will not alter stage or management. Total hysterectomy and bilateral salpingo-oophorectomy should be performed. The encapsulated mass should be removed intact. All involved omentum should be removed. Suspicious and/or enlarged nodes should be resected, if possible.[49, 50] 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 OV-A).

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

Procedures that may be considered for optimal surgical cytoreduction (in all stages) include: radical pelvic dissection, bowel resection, diaphragm or other peritoneal surface stripping, splenectomy, partial hepatectomy, cholecystectomy, partial gastrectomy or cystectomy, ureteroneocystostomy, or distal pancreatectomy.[52]

The therapeutic benefit of neoadjuvant chemotherapy followed by interval cytoreduction remains controversial (see next paragraph).[53-55] It may be considered for patients with bulky stage III to IV disease who are not surgical candidates.[56-59] Before initiation of chemotherapy, the pathologic diagnosis should be confirmed (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]).[60] Median overall survival was the 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 survivals averaging 50 months).[61] 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). However, in the opinion of the Ovarian Cancer Guideline subcommittee, more data will be necessary prior to recommending neoadjuvant chemotherapy in potentially resectable ovarian cancer

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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, treatment recommendations are outlined in the algorithm (see OV-2). 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.[62] If observation (without the addition of chemotherapy) is considered for stage IA or IB, grade 2 tumors, a surgical staging procedure is recommended for all patients.

Recommendations regarding initial primary chemotherapy/primary adjuvant therapy include 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 algorithm (see OV-B).

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/developments/IPchemo-digest/page1/print); stage II patients may also receive IP chemotherapy, although no randomized evidence for stage II has been published.[61, 63, 64] 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 OV-3).[24, 65] Intravenous docetaxel plus carboplatin (category 1)[66] or paclitaxel plus cisplatin (category 1) are options for alternative regimens.[67] The docetaxel/carboplatin regimen may be considered for patients who are at high risk for neuropathy (e.g., patients with diabetes).

Recommendations for the number of cycles of treatment vary with the stage of the disease. For patients with advanced-stage disease (stages II-IV), 6-8 cycles of chemotherapy are recommended, whereas 3 to 6 cycles are recommended for earlier-stage disease.[68]

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);[65] (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);[66] 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).[69] The recommended IP

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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).[61]

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.[66, 69] The IP paclitaxel/cisplatin regimen is associated with leukopenia, infection, fatigue, renal toxicity, abdominal discomfort, and neurotoxicity.[70, 71] In the initial studies, only 42% of women were able to complete all 6 treatment cycles because of toxicity; however, with more experience, this percentage has improved in the major cancer centers. Using a lower IP dose of cisplatin of 75 mg/m^2 may help to decrease toxicity.[72] 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 OV-B). Reasons for discontinuing the IP regimen included catheter complications, nausea/vomiting/dehydration, and abdominal pain.[73] Women unable to complete IP therapy should receive IV therapy. Techniques to decrease catheter complications include catheter choice and timing of insertion.[63, 74] Giving intravenous hydration before and after IP chemotherapy is a useful strategy to prevent renal toxicity. 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.[73, 75-77]

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).[69] 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.[78]

Preliminary results have been presented from a phase III randomized trial (GOG 0218) assessing bevacizumab combined with carboplatin/paclitaxel in the upfront setting compared to carboplatin/paclitaxel alone. Although data regarding overall survival and/or quality of life have not been reported yet, the median PFS was significantly increased (14.1 versus 10.3 months, *P*<.0001) in patients receiving bevacizumab upfront and as maintenance therapy when compared with chemotherapy alone.[79] 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).

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

Until there are more mature results from GOG 0218 and ICON7, the NCCN Ovarian Cancer panel does not recommend the routine addition of bevacizumab to upfront therapy with carboplatin/paclitaxel or as

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maintenance therapy at this time. 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).

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.[61] Patients with either primary peritoneal cancer, Fallopian tube cancer, or MMMT can also be considered for IP chemotherapy.[64, 74] 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 Intensity

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

Number of Chemotherapy Cycles and Agents

Panel members had an extensive discussion about the number of 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.[82] Patients can also have 3-6 cycles of chemotherapy followed by completion surgery and then postoperative chemotherapy (see OV-2).[54]

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/m^2 every 4 weeks for 12 cycles) after initial chemotherapy.[83] The published study treated patients at 175 mg/m^2; the plan was to decrease the dose to 135 mg/m^2, but the protocol closed before any patients were treated at the lower dose. The results of this trial suggest that patients receiving 12 months of therapy sustained a PFS advantage. Postremission paclitaxel chemotherapy is a category 2B recommendation.

Drug Reactions

Virtually all drugs have the potential to cause drug reactions, either during or after the infusion.[84] Drugs used in gynecologic oncology treatment that more commonly cause adverse reactions include carboplatin, cisplatin, docetaxel, liposomal doxorubicin, oxaliplatin, and paclitaxel. Drug reactions can occur with either IV or IP administration of these drugs.[85] 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.[86, 87] Infusion reactions are more common with paclitaxel,[88] but mild reactions can also occur with liposomal doxorubicin.[89] Allergic reactions (i.e., true drug allergies) are

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more common with platinum agents (i.e., carboplatin, cisplatin, oxaliplatin).[88]

Management of drug reactions is discussed in the algorithm (see OV-C).[90] For patients with allergic reactions, various desensitization protocols have been published and should be followed. To maximize safety; patients may be desensitized in the intensive care unit.[84] Almost all patients can be desensitized (about 90%).[84] For severe life-threatening reactions, the implicated agent should not be used again. If a mild allergic reaction is suspected, and it is appropriate to administer the drug again, a desensitization regimen should be used even if the symptoms have resolved. Patients must be desensitized with each infusion if they previously had a drug reaction.[91-93]

Radiation Therapy

Whole abdominal radiation therapy (WART) in patients with low-bulk stage III disease is no longer included as an option for initial treatment or consolidation treatment in ovarian cancer. Because WART is rarely used in NCCN institutions, it is not included as a treatment recommendation in the 2011 guidelines. Palliative localized RT is an option for symptom control in patients with recurrent disease (see OV-D).[94, 95] 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") (see OV-5); 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") (see OV-4).

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[83] (paclitaxel, category 2B), preferably in a controlled clinical trial (see OV-4). If used, the paclitaxel regimen is 135-175 mg/m^2 every 4 weeks for 12 cycles. Note that complete clinical remission is defined as no objective evidence of disease (i.e., negative physical examination, negative CA-125 levels, and negative CT with <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), the standard recommendation is observation with follow-up. Recommendations for monitoring are described in the algorithm (see OV-5). 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.[96, 97] Measurement of a CA-125 level or other tumor markers at each follow-up evaluation is recommended if the level was initially elevated.[98]

Preliminary data are available from a recent multi-institutional European trial assessing the use of CA-125 for monitoring ovarian cancer after primary therapy.[99] The data suggest that treating recurrences early (based on detectable CA-125 levels in asymptomatic patients) is not associated with an increase in survival and is associated with a decrease in quality of life.[100] The NCCN panel concurs with the SGO

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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 (http://www.sgo.org/WorkArea/showcontent.aspx?id=2702). In addition, patients seem reluctant to give up monitoring.[101] Others have discussed this study in greater detail.[102, 103]

Management of an Increasing CA-125 Level

The management of patients 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, 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 be treated as previously described (see OV-1).

After the documentation of an increased CA-125 level, the median time for a clinical relapse is 2 to 6 months. There is a lack of consensus regarding the timing of recurrence therapy for patients who have received previous chemotherapy. Because tamoxifen and other hormonally active agents have a defined response rate in recurrent disease after progression on platinum-based chemotherapy,[104] they are frequently administered to patients who have only a rising CA-125 level[105] as evidence of tumor progression. Tamoxifen, other hormonal agents, or other recurrence therapy are acceptable recommendations for this clinical situation (category 2B). Other alternatives include enrollment on a clinical trial or delaying treatment (i.e., observation) until clinical symptoms arise (category 2B for observation) (see OV-5).

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).[106] 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.[107, 108] 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 OV-D),[109] clinical trial, or observation (category 2B for observation). Patients who relapse 6 months or more after initial chemotherapy are considered "platinum sensitive" (see OV-6).[110, 111] Combination platinum-based chemotherapy is preferred for first recurrence (category 1).[111] 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

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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 OV-B). Potential ancillary palliative surgical and/or supportive care procedures for selected patients are summarized in the algorithm (see OV-A).

Secondary cytoreductive surgery can be considered for patients who recur after a long disease-free interval (6 months or more).[112] A recent meta-analysis suggests that survival increases for patients with recurrent disease who have complete cytoreduction.[46] The duration of the disease-free interval has not been established, although panel members agreed that it should be at least 6 months before surgery 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 OV-D). A meta-analysis of 13 randomized studies in recurrent ovarian cancer has been published.[110]

The consensus of the NCCN panel for the treatment of recurrent disease appears on OV-D. Platinum-based combination chemotherapy is recommended (category 1) for platinum-sensitive recurrence (see OV-6).[110, 111] Preferred combinations for platinum-sensitive recurrent disease include carboplatin/paclitaxel (category 1),[111] carboplatin/weekly paclitaxel,[69] carboplatin/docetaxel,[113, 114] carboplatin/gemcitabine (which has been shown to improve progression-free survival),[111, 115, 116] carboplatin/liposomal doxorubicin (also has been shown to improve progression-free survival) [117] or cisplatin/gemcitabine.[115]

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

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

Taxanes (including docetaxel and paclitaxel) and platinum compounds (including cisplatin, carboplatin, and oxaliplatin) can be used in appropriate patients.[83, 111, 134] Capecitabine has activity in patients resistant to platinum and taxanes.[135] 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.[136-140]

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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.[141-143] Patients who are resistant or refractory to platinum have a lower response rate to olaparib.[142, 143] 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.[94, 95]

Chemotherapy/resistance assays are being used in some NCCN centers to aid in selecting chemotherapy in situations where there are multiple equivalent chemotherapy options available; the current level of evidence (category 3) is not sufficient to supplant standard of care chemotherapy.[144, 145] The NCCN panel felt that in vitro chemosensitivity testing to choose a chemotherapy regimen for recurrent disease situations should not be recommended, owing to the lack of demonstrable efficacy for such an approach. 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 have diminished likelihood of benefitting 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.[146] Five-year survival exceeds 80%.[147] The characteristic pathologic hallmark of typical epithelial ovarian cancer is the identification of peritoneal implants, which microscopically and/or macroscopically invade the peritoneum. Borderline epithelial ovarian cancer has the visual appearance of peritoneal carcinomatosis; however, microscopic evaluation fails to reveal evidence of frank invasion by the tumor nodules, although rarely invasive implants that 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 OV-7).[148] In contrast to patients with frankly invasive ovarian carcinoma, women with borderline disease tend to be younger and are often diagnosed with stage I disease.[149, 150] The benefit of postoperative chemotherapy has not been demonstrated for patients who have no microscopically demonstrable invasive implants.[151]

Treatment

Treatment guidelines for borderline epithelial ovarian cancer depend on the histological and clinical characteristics, the age of the patient,[150] 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

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limited to a USO (preserving the uterus and contralateral ovary) at the time of comprehensive staging.[39, 40] If the patient does not desire fertility-sparing surgery, standard ovarian cancer debulking surgery is recommended, accompanied by comprehensive staging.

For patients with known LMP disease who were incompletely staged at the time of their initial laparotomy, options include either completion surgical staging or observation, depending on whether residual disease is present (see OV-7).

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) (see OV-2). Patients with no invasive implants should be observed and monitored (see OV-8).[149, 152]

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.

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 OV-3); those without invasive implants should be observed or enrolled in a clinical trial.

Less Common Ovarian Histopathologies (LCOH)

Overview

Less common histopathologies of ovarian cancer include: malignant germ cell neoplasms, carcinosarcoma (MMMT), and 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 LCOH-1). Tumor markers (including CA-125, inhibin, alpha-fetoprotein [AFP], and beta–human chorionic gonadotropin [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.[39, 40, 153-156] 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

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carcinosarcoma (MMMT) should undergo comprehensive surgical staging as per the epithelial ovarian cancer guidelines (see OV-A).

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

The recommended workup (see “Recommended Workup” as previously discussed) for malignant germ cell tumors may include pulmonary function studies if bleomycin is being considered.[157, 158] Women younger than 35 years with a pelvic mass should have AFP levels measured to assess for germ cell tumors.[158-160] Fertility-sparing surgery should be considered for those desiring fertility preservation.[161, 162] Otherwise, comprehensive surgical staging is recommended as initial surgery. The staging system for ovarian and primary peritoneal cancer is also used for malignant germ cell tumors (see Table 1). Patients who have had comprehensive surgical staging should be observed if they have a stage I dysgerminoma or immature teratoma. If these patients have had incomplete surgical staging, options include a completion staging procedure or observation may be considered for clinical stage I dysgerminoma or clinical stage I, grade 1 immature teratoma (category 2B for observation). If there is no evidence of If disease is not evident following a completion staging procedure, these patients may be observed. Otherwise recommended treatment depends on the surgical findings.

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.[157, 163-165] Pulmonary function tests are recommended if considering the use of bleomycin.[157] In select patients with stage IB-III dysgerminoma for whom minimizing toxicity is critical, 3 courses of etoposide/carboplatin can be used (carboplatin 400 mg/m^2 (AUC =~5-6) on day 1 plus etoposide 120 mg/m^2 on days 1-3 every 4 weeks for 3 courses).[166]

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 LCOH-A). Referral of these patients to a tertiary care center for potentially curative therapy is strongly recommended. For patients having radiographic evidence of residual tumor 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 LCOH-3). For patients having persistently elevated AFP and/or beta-HCG after first-line chemotherapy, recommendations include TIP (paclitaxel, ifosfamide, cisplatin)[167] or high-dose chemotherapy with stem cell support. Referral to a tertiary care center for potentially curative treatment is strongly recommended.[168]

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Surveillance is an option (category 2B) for patients who have germ cell tumors with residual malignancy after surgical resection of residual masses; this is an area of continued study and controversy.[169] 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.[170]

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 LCOH-A), 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.[168, 171-175] Combination chemotherapy is not recommended for patients with recurrent or residual disease who have no curative options. These recurrence regimens (see LCOH-A) are not generalizable for all of the uncommon histology tumors; therefore, patients should be referred to tertiary care institutions for treatment.

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. The staging system for ovarian and primary peritoneal cancer is also used for sex cord-stromal tumors (see Table 1). Patients with stage IA-C sex cord-stromal tumors desiring to preserve their fertility should be treated with fertility-sparing surgery with complete staging.[176, 177] Complete staging is also recommended for all other patients; however, lymphadenectomy may be omitted.[178] 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[179]), recommendations (all are category 2B) include observation, RT, or consideration of platinum-based chemotherapy.[180] For patients 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).[181] For patients with stage II-IV tumors who subsequently have a clinical relapse, options include a clinical trial or recurrence therapy (see LCOH-A). Note that bevacizumab may be considered for patients with recurrent granulosa cell tumors.[182] Secondary cytoreductive surgery may also be considered.

Carcinosarcoma (Malignant Mixed Müllerian Tumors)

MMMT are rare tumors with a poor prognosis. Many pathologists now consider MMMT to be a variant of poor risk, poorly differentiated epithelial ovarian cancer. The staging system for ovarian and primary peritoneal cancer is also used for MMMT (see Table 1). After complete surgical staging, patients with stage II-IV carcinosarcoma (MMMT) at the time of surgery should have postoperative chemotherapy; chemotherapy can be considered for stage I MMMT (see LCOH-5). The type of chemotherapy is variable, because there are no data to specifically define the optimal chemotherapeutic regimen; ifosfamide-based regimens have been used.[183-185] Patients with stage II-IV MMMT or recurrence are treated using recommendations for epithelial ovarian cancer (see OV-3).[186, 187] For example, the IP chemotherapy regimen described for ovarian cancer (see OV-3) can be used for select patients with MMMT.

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Recommended Readings

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