



NCCN Clinical Practice Guidelines in Oncology™

Ovarian Cancer

Including Fallopian Tube Cancer and Primary Peritoneal Cancer

V.1.2009

Continue

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These guidelines are a statement of evidence and consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult these guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network makes no representations or warranties of any kind, regarding their content use or application and disclaims any responsibility for their application or use in any way. These guidelines are copyrighted by National Comprehensive Cancer Network. All rights reserved. These guidelines and the illustrations herein may not be reproduced in any form without the express written permission of NCCN. ©2009.

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This manuscript is being updated to correspond with the newly updated algorithm.

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

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

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

See [NCCN Categories of Evidence and Consensus](#)

Summary of the Guidelines updates

Summary of the changes in the 1.2009 version of the Ovarian Cancer guidelines from the 1.2008 version include:

OV-1

- For clinical presentation, diagnosis by previous surgery or tissue biopsy, “cytopathology” was added for clarification.
- For suspicious/palpable pelvic mass..., “other tumor markers as clinically indicated” was added to CA-125.
- For both workup sections, “chest x-ray” was changed to “chest imaging”.
- Footnote ‘c’ was modified by adding, “Published data demonstrate that primary assessment and debulking by a gynecologic oncologist result in a survival advantage.” ([Also for OV-2](#))
- Footnote ‘e’ is new throughout the algorithm.

OV-2

- For Stage II, II, IV, suspect unresectable residual disease, primary treatment was clarified by adding, “Chemotherapy for a total of 6-8 cycles. Consider completion surgery after 3-6 cycles followed by postoperative chemotherapy.
- Footnote ‘g’ is new to the page.

OV-3

- For Stage II, II, IV, “Interval debulking” was clarified as, “Completion surgery” and intravenous taxane/carboplatin was clarified as “for a total of 6-8 cycles.”
- Footnote ‘j’ is new to the page.

OV-4

- Footnotes ‘k’ and ‘l’ are new to the page.

OV-5

- For monitoring/follow-up:
 - Visit interval was clarified as “3-6 months for 3 years and then annually after 5 years.”
 - “Consider family history evaluation if not previously done” was added.
 - PET scan was clarified as a category 2B.
- For rising CA-125, no previous chemotherapy, “surgical debulking” was removed after imaging studies and a link to primary treatment on OV-1 was added.
- For clinical relapse, previous chemotherapy and serially rising CA-125, “imaging studies” was added.

OV-6

- Progression or stable disease and complete remission and relapse for < 6 mo, 6-12 mo, and >12 mo respectively, “Clinical trial” was added as an option.

- Complete remission and relapse for both 6-12 mo and > 12 mo after stopping chemotherapy and the respective recurrence therapy options were added.

OV-7

- For incomplete previous surgery, suspect no residual disease, no invasive implants, “completion surgical staging” was added as a treatment option.
- For incomplete previous surgery, suspect no residual disease, invasive implants at previous surgery, “category 2B” was added to “observe”.

OV-A

- Principles of surgery was revised by separating into management of 1) patients with ovarian cancer apparently confined to an ovary or to the pelvis and 2) ovarian cancer involving the upper abdomen.

OV-B

- “Principles of Chemotherapy” is new to the guidelines.

OV-C

- “Management of Allergic Reactions” is new to the guidelines.

OV-E

- Cytotoxic therapy, preferred agents were separated into combination, if platinum sensitive; single-agent, if platinum sensitive; and single-agent non-platinum based if platinum resistant.
- “Cisplatin/gemcitabine” and “pemetrexed” were added to cytotoxic therapy, preferred agents.
- “Leuprolide and megestrol acetate” were added to hormonal therapy.
- Bevacizumab was moved to targeted therapy, preferred agents.

LCOH-3

- For persistently elevated markers, “with definitive residual disease” was added.
- Recurrent/persistent disease treatment options based on results after surgical resection were added.
- Footnote ‘a’, the regimen for etoposide/carboplatin was added.

LCOH-4

- For high-risk stage I, chemotherapy treatment option was clarified as “platinum-based”.

LCOH-5

- For treatment of Stage II-IV or Recurrence, a link to epithelial ovarian cancer replaced a link to uterine neoplasms.

CLINICAL
PRESENTATION

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

Diagnosis by previous surgery or tissue biopsy (cytopathology)

WORKUP

- 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 (LFT's)

- 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 LFT's
- Institutional pathology review

PRIMARY TREATMENT^c

Laparotomy/Total abdominal hysterectomy (TAH)/Bilateral salpingo-oophorectomy (BSO) with comprehensive staging^d or unilateral salpingo-oophorectomy (USO) (Clinical Stage 1A or 1C, all grades with comprehensive staging if patient desires fertility)
or
Cytoreductive surgery^d if clinical stage II, III, or IV
or
Consider neoadjuvant chemotherapy^e/primary interval cytoreduction for patients with bulky stage III/IV who are not surgical candidates (diagnosis by fine needle aspiration (FNA), biopsy or paracentesis)

[See Pathologic Staging \(OV-3\)](#)

[See Findings and Primary Treatment \(OV-2\)](#)

^aIm SS, Gordon AN, Buttin BM, et al. *Obstet Gynecol* 2005;105:35-41. [See Discussion.](#)

^bGoff BA, Mandel L, Drescher CW, et al. *Cancer* 2007;109:221-227.

^cStandard 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.

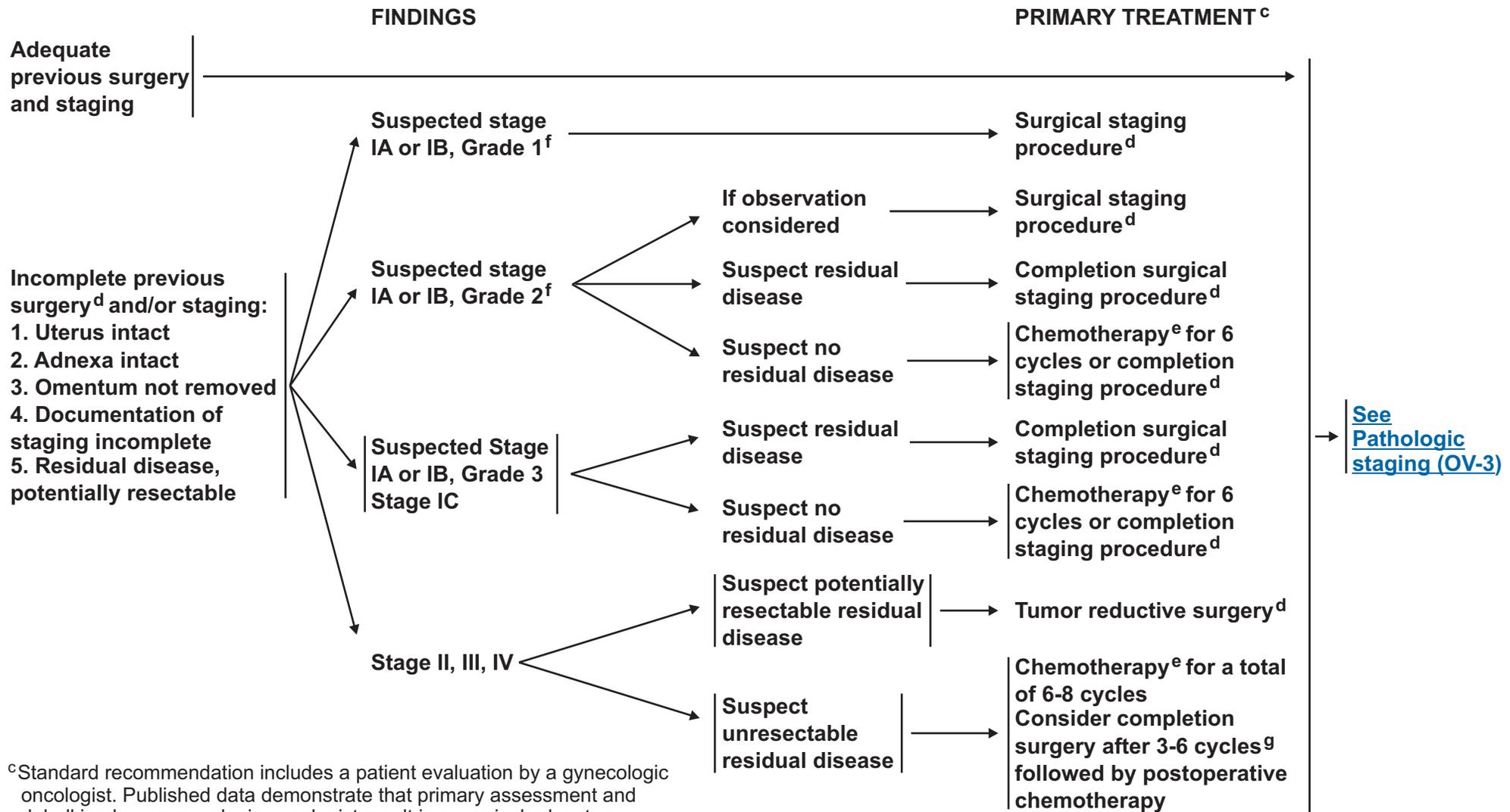
^d[See Principles of Primary Surgery \(OV-A\).](#)

^e[See Principles of Chemotherapy \(OV-B\)](#) and [Management of Allergic Reactions \(OV-C\).](#)

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

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

DIAGNOSIS BY PREVIOUS SURGERY



^cStandard 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.

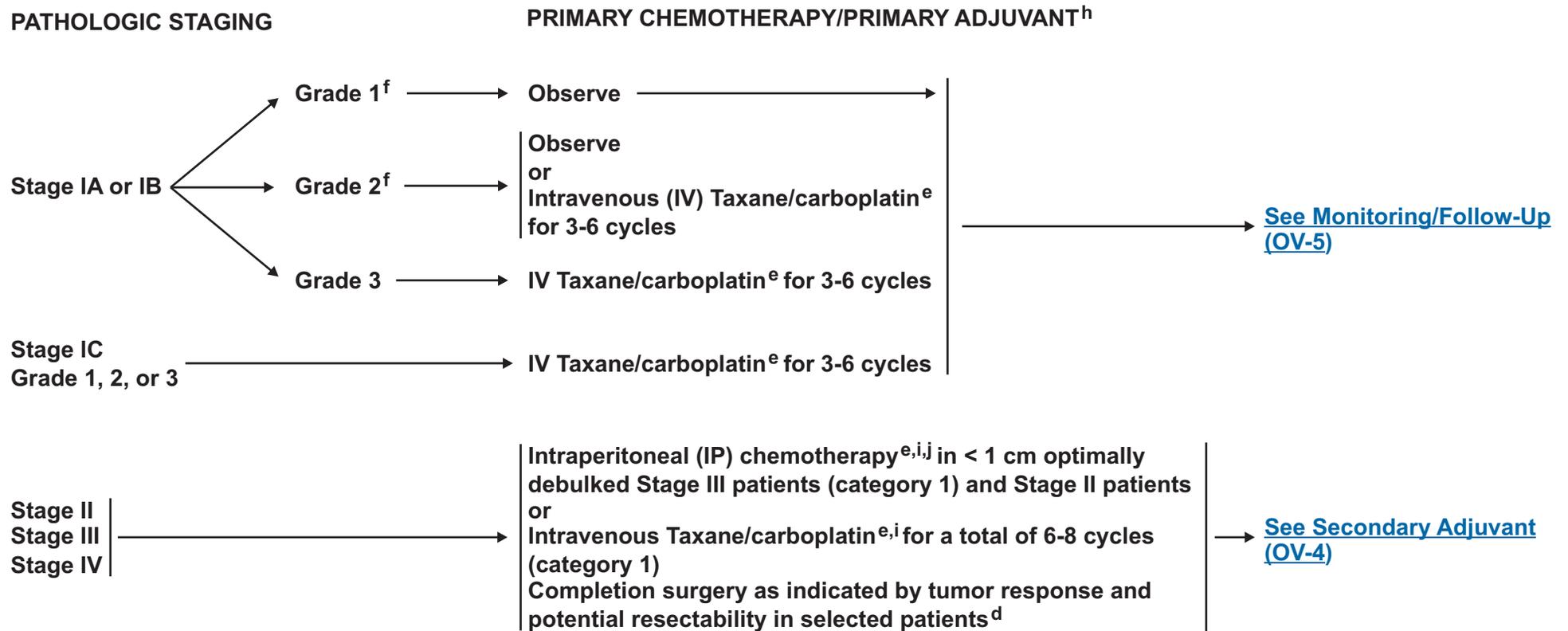
^dSee [Principles of Primary Surgery \(OV-A\)](#).

^eSee [Principles of Chemotherapy \(OV-B\)](#) and [Management of Allergic Reactions \(OV-C\)](#).

^fClear-cell pathology is grade 3.

^gBased on clinical judgement of gynecologic oncologist, surgery may be performed after 6 cycles.

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

^e See Principles of Chemotherapy (OV-B) and Management of Allergic Reactions (OV-C).

^f Clear-cell pathology is Grade 3.

^h Patients receiving primary chemotherapy will be monitored as follows:

1. Pelvic exams at least every 2 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

ⁱ Regimens:

1. Paclitaxel 135 mg/m² IV 24 h infusion day 1; cisplatin 100 mg/m² IP, day 2 after IV paclitaxel; paclitaxel 60 mg/m² IP, day 8 (max BSA 2.0 m²). Repeat every 3 weeks x 6 cycles (category 1).
2. Paclitaxel 175 mg/m² over 3 hours and carboplatin AUC 5-7.5 every 3 weeks x 6 cycles (category 1).
3. Docetaxel 60-75 mg/m² over 1 hour and carboplatin AUC 5 - 6 every 3 weeks x 6 cycles (category 1).

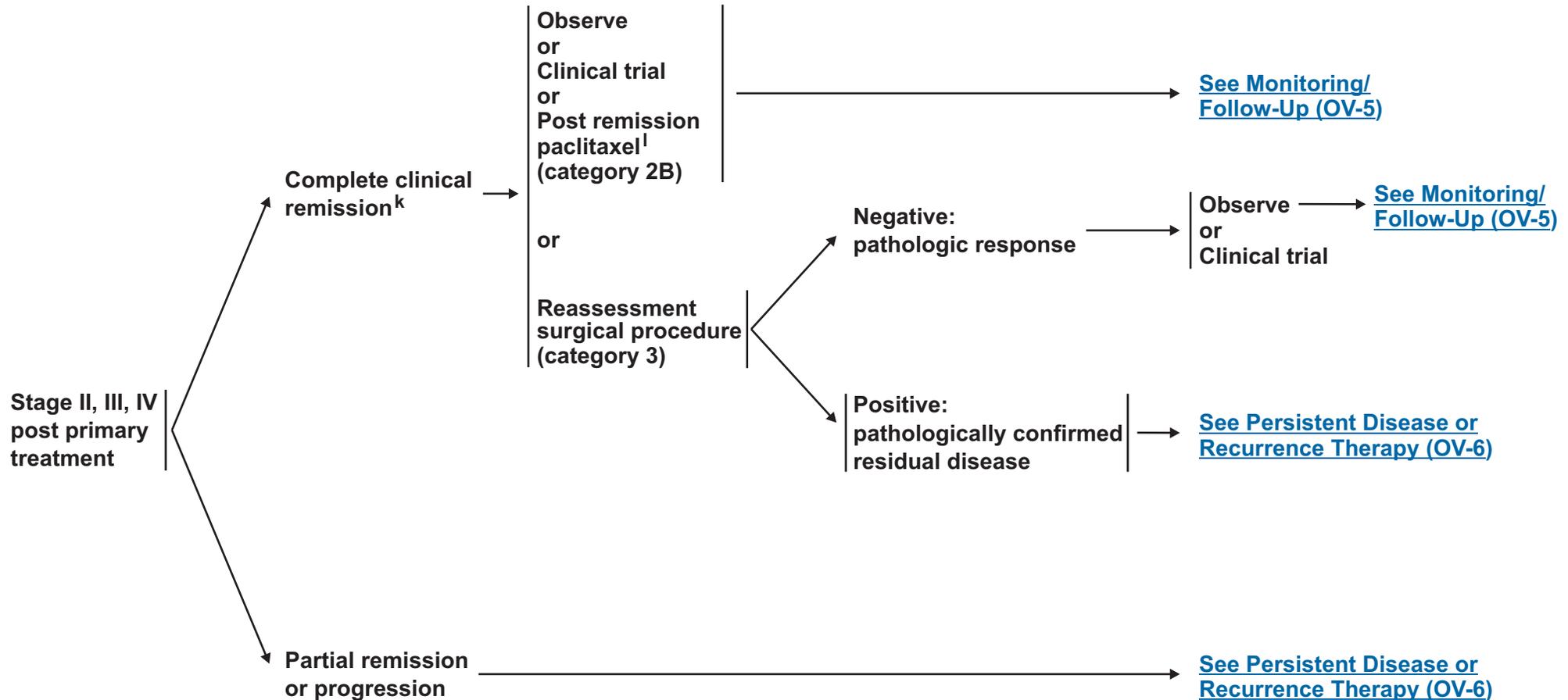
^j After primary surgery, women with optimally debulked FIGO stage III ovarian cancer should be counseled about the clinical benefit associated with combined IV and IP chemotherapy administration. <http://www.cancer.gov/clinicaltrials/developments/IPchemo-digest/page1/print>

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STAGE II, III, IV
POST PRIMARY TREATMENT

SECONDARY ADJUVANT

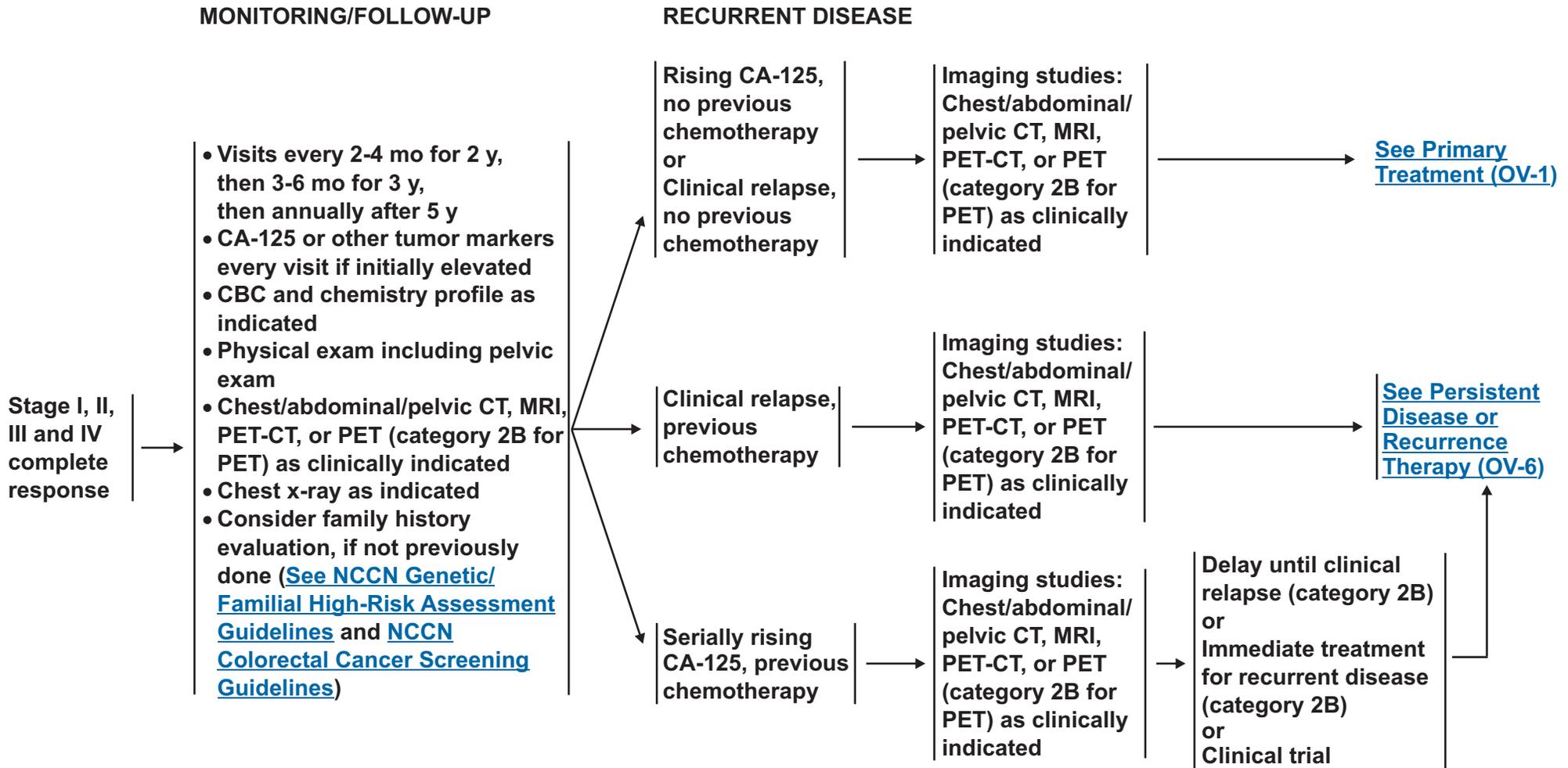


^kNo objective evidence of disease (ie, negative physical exam, negative CA-125, negative CT with < 1cm lymph nodes).

^l[See discussion](#) for dosing.

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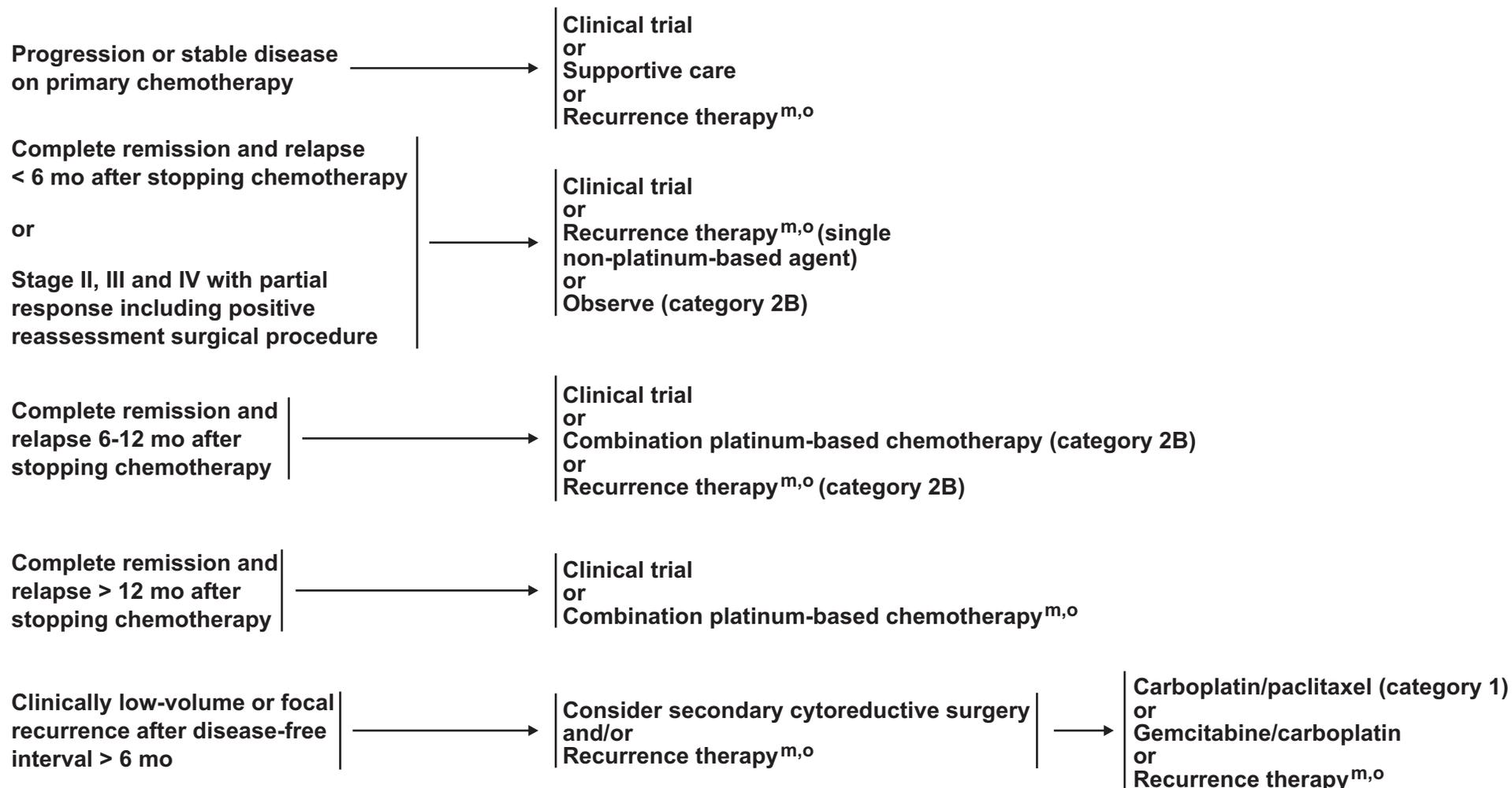
STAGE I-IV COMPLETE RESPONSE



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DISEASE STATUS

PERSISTENT DISEASE OR RECURRENCE THERAPY^{m,n,o}



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

ⁿ[See Ancillary Palliative Surgical Procedures \(OV-D\).](#)

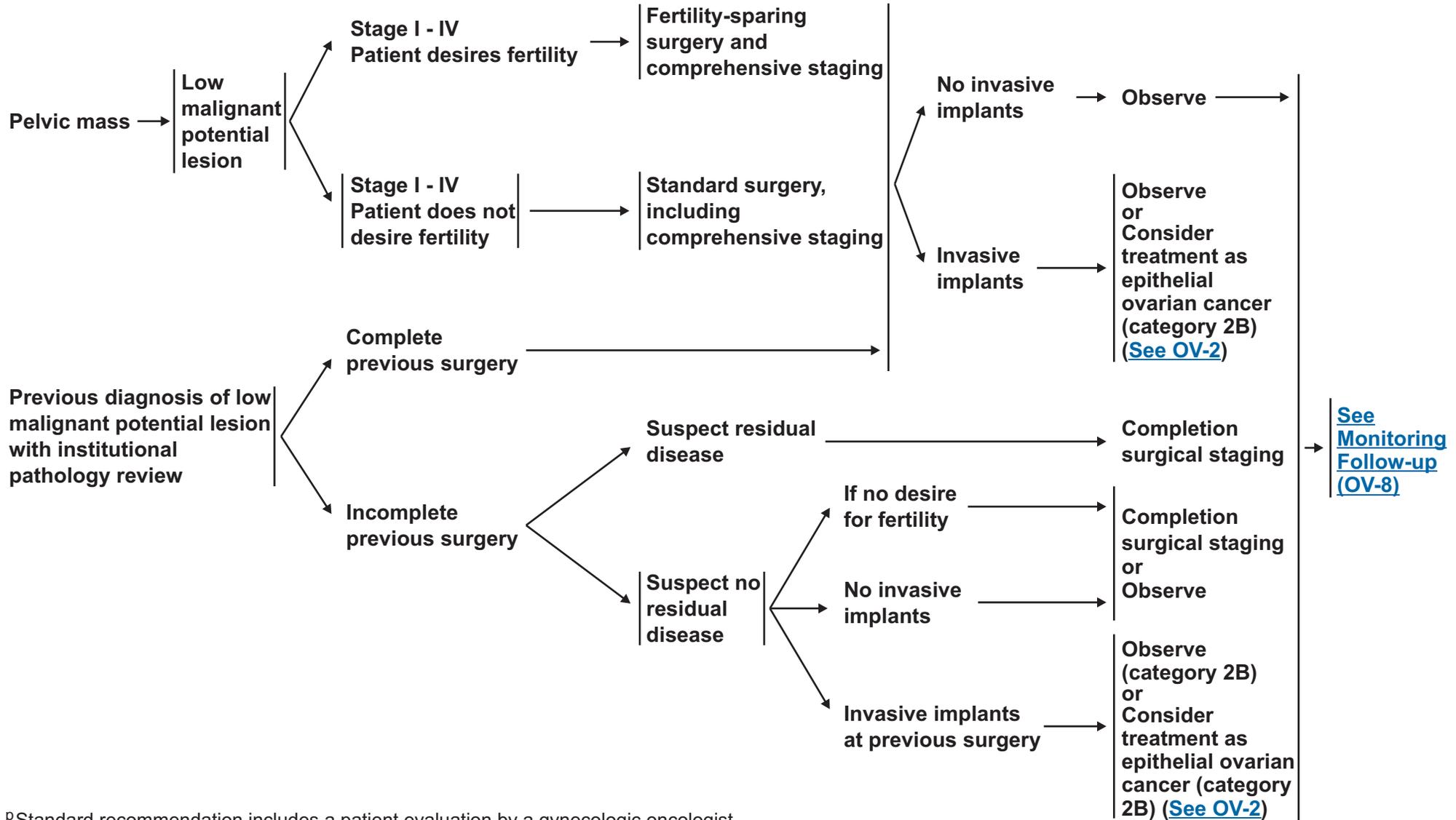
^o[See Acceptable Recurrence Therapies \(OV-E\).](#)

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CLINICAL
PRESENTATION

PRIMARY TREATMENT^P



^PStandard recommendation includes a patient evaluation by a gynecologic oncologist.

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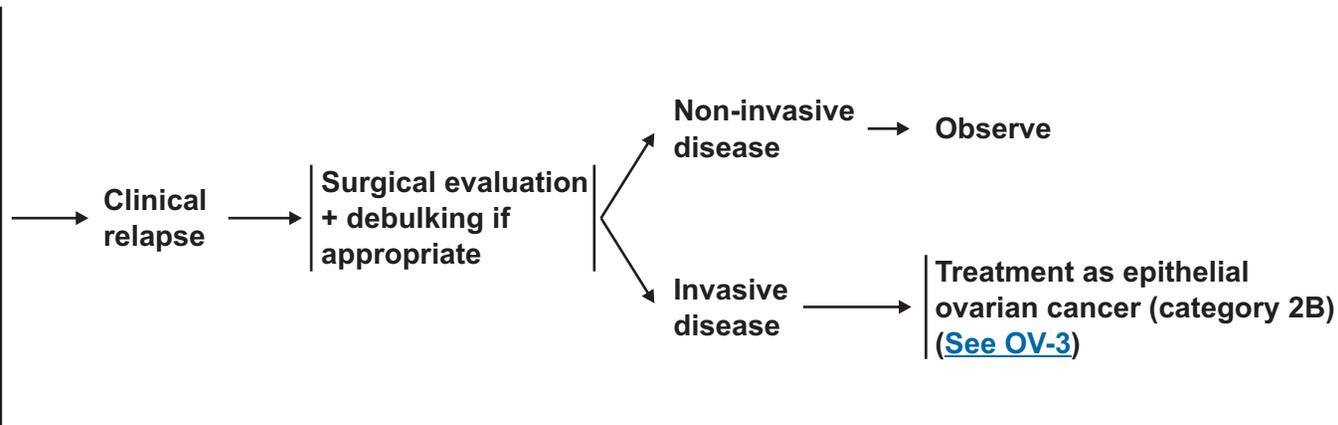
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

MONITORING/FOLLOW-UP

RECURRENT DISEASE

RECURRENCE THERAPY

- 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 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)



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PRINCIPLES OF PRIMARY SURGERY (1 of 2)^{1,2}

In general, a vertical midline abdominal incision should be used in patients with a suspected malignant ovarian neoplasm.²

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 2](#))
- 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 lateral to the common iliac vessel is preferred.

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 to < 1 cm residual disease in appropriate circumstances:

- On entering the abdomen, aspiration of ascites or peritoneal lavage should be performed for cytologic examinations.
- 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 periaortic lymph node dissection as previously described.
- Procedures that may be considered for optimal surgical cytoreduction (in all stages) may include:
 - ▶ Radical pelvic dissection
 - ▶ Bowel resection
 - ▶ Diaphragm or other peritoneal surface stripping
 - ▶ Splenectomy

[Continued on OV-A 2 of 2](#)

¹Ozols RF, Rubin SC, Thomas G, et al: Epithelial ovarian cancer, in Hoskins WJ, Perez CA, Young RC (eds): Principles and Practice of Gynecologic Oncology, 4th ed, Philadelphia, Lippincott Williams & Wilkins, 2005:919-922. Amended by panel.

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

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PRINCIPLES OF PRIMARY SURGERY (2 of 2)¹**Special Circumstances**

- In Stage I disease, minimally invasive techniques may be considered to achieve the surgical principles described on [OV-A 1 of 2](#). Minimally invasive surgery performed by an experienced gynecologic oncologist may be considered in selected patients.
- For patients with apparent early stage disease and/or good risk tumors (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.

¹Ozols RF, Rubin SC, Thomas G, et al: Epithelial ovarian cancer, in Hoskins WJ, Perez CA, Young RC (eds): Principles and Practice of Gynecologic Oncology, 4th ed, Philadelphia, Lippincott Williams & Wilkins, 2005:919-922. Amended by panel.

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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 and monitored for any long-term complications.

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.
- 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 infusion 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 Allergic 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 ALLERGIC REACTIONS (1 of 3)

- Virtually all chemotherapy drugs have the potential to cause infusion reactions, either occurring during the infusion or following completion of the infusion (even days later).
- Most drug reactions that occur are mild infusion reactions, but more severe reactions (such as, anaphylaxis) can occur. Anaphylaxis is a type of infusion reaction that is more rare, can occur with the platinum and taxane agents (and others less commonly), and can be life threatening.
- Drugs used in gynecologic oncology cancer treatment that can more commonly cause infusion reactions include: carboplatin, cisplatin, oxaliplatin, paclitaxel, docetaxel, and liposomal doxorubicin.
- Reactions that are associated with paclitaxel and other taxanes 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). Reactions associated with platinum drugs (carboplatin, cisplatin) tend to occur following re-exposure to the inciting drug.

Signs and symptoms of infusion reactions:

The most common signs and symptoms of infusion reactions are the following:

- 1) Flushing
- 2) Changes in blood pressure – either elevated blood pressure or hypotension
- 3) Shortness of breath, fever, chills
- 4) Back pain, abdominal pain, leg pain
- 5) Hives or other types of rashes
- 6) Nausea, vomiting, or change in bowels

More rare types of reactions involve anaphylaxis and resultant cardiovascular collapse.

Patients who are at higher risk of developing an infusion reaction include those in the following settings:

- 1) Re-introduction of the drug after a period of no exposure and following multiple cycles of the drug during the first and subsequent exposures
- 2) Intravenous administration of the drug rather than oral or intraperitoneal administration
- 3) With allergies to other drugs

[Continued on OV-C 2 of 3](#)

[References on OV-C 3 of 3](#)

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MANAGEMENT OF ALLERGIC REACTIONS (2 of 3)

Preparation for a possible allergic infusion reaction:

- Clinicians and nursing staff should be prepared for the possibility of an infusion reaction every time the patient is infused with the drug; patients and their families need to be counseled about the possibility of a reaction and about the signs and symptoms of the reaction. Standing orders should be written for immediate intervention in case a reaction occurs. The treatment area should have appropriate medical equipment in case of a life-threatening allergic reaction.

Once an infusion reaction occurs:

- Consider consult with an allergist and skin testing in the case of platinum reactions (either carboplatin or cisplatin). Various desensitization protocols have been published and should be followed to maximize safety. For severe life-threatening reactions, the implicated drug should not be used again.
- In the case of mild taxane reactions --- such as those causing flushing, urticaria, chills --- patients may be rechallenged with the taxane if the patient, physician, and nursing staff are all comfortable with this plan, the patient has been counseled appropriately, and emergency equipment is available in the clinic area. For more severe reactions --- such as those involving blood pressure changes, rashes, hypoxia --- the treating clinician should consult an allergist prior to rechallenge.

[References on OV-C 3 of 3](#)

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MANAGEMENT OF ALLERGIC REACTIONS (3 of 3)

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

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

ANCILLARY PALLIATIVE SURGICAL PROCEDURES¹

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

¹These may be appropriate in select patients.

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

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

ACCEPTABLE RECURRENCE THERAPIES¹

Agents	Cytotoxic Therapy	Hormonal Therapy	Targeted Therapy	Radiation Therapy
Preferred Agents	<p><u>Combination if platinum sensitive</u> Carboplatin/paclitaxel (category 1)² Carboplatin/docetaxel² Carboplatin/gemcitabine² Cisplatin/gemcitabine²</p> <p><u>Single-agent if platinum sensitive</u> Carboplatin Cisplatin</p> <p><u>Single-agent non-platinum based if platinum resistant</u> Docetaxel Etoposide, oral Gemcitabine Liposomal doxorubicin Paclitaxel, weekly Pemetrexed Topotecan</p>		Bevacizumab ³	
Other Potentially Active Agents	Altretamine Capecitabine Cyclophosphamide Ifosfamide Irinotecan Melphalan Oxaliplatin Paclitaxel Vinorelbine	Anastrozole Letrozole Leuprolide Megestrol acetate Tamoxifen		Palliative localized radiation therapy

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

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

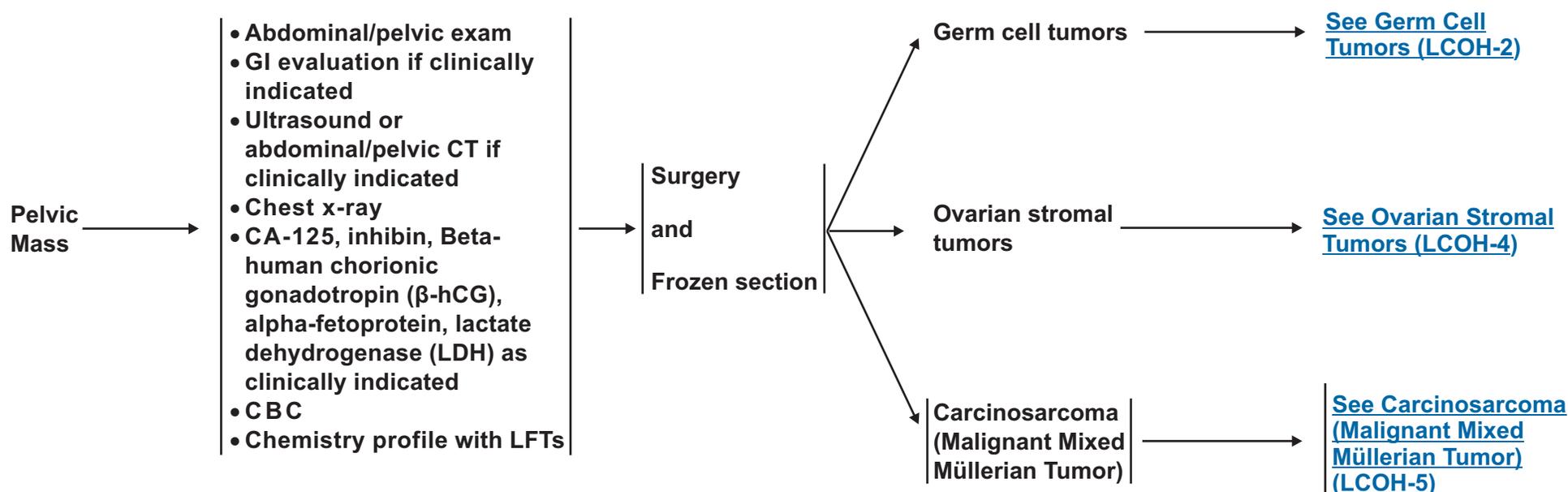
³Combination therapy with bevacizumab may be considered.

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

CLINICAL
PRESENTATION

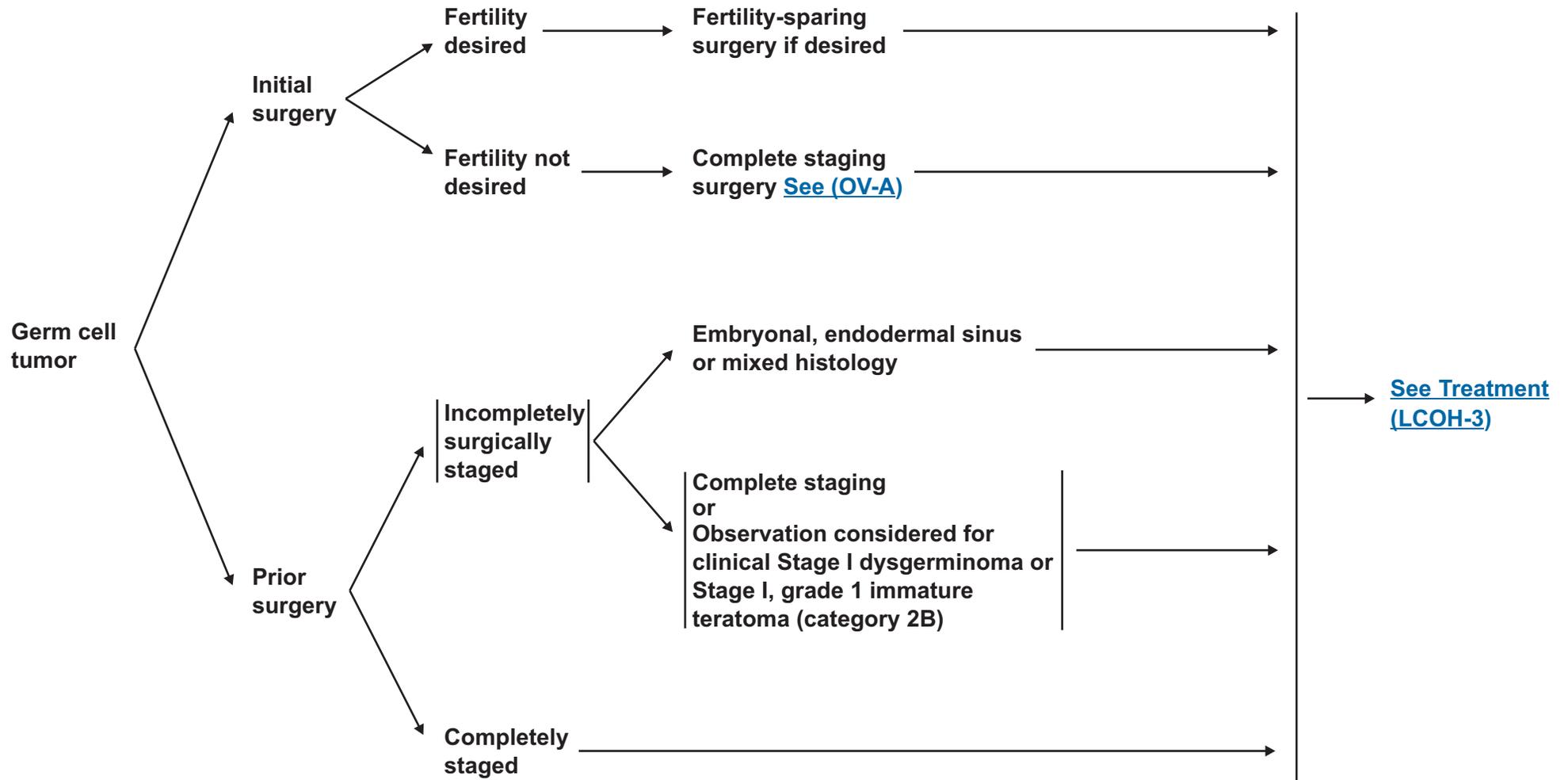
WORKUP

DIAGNOSIS

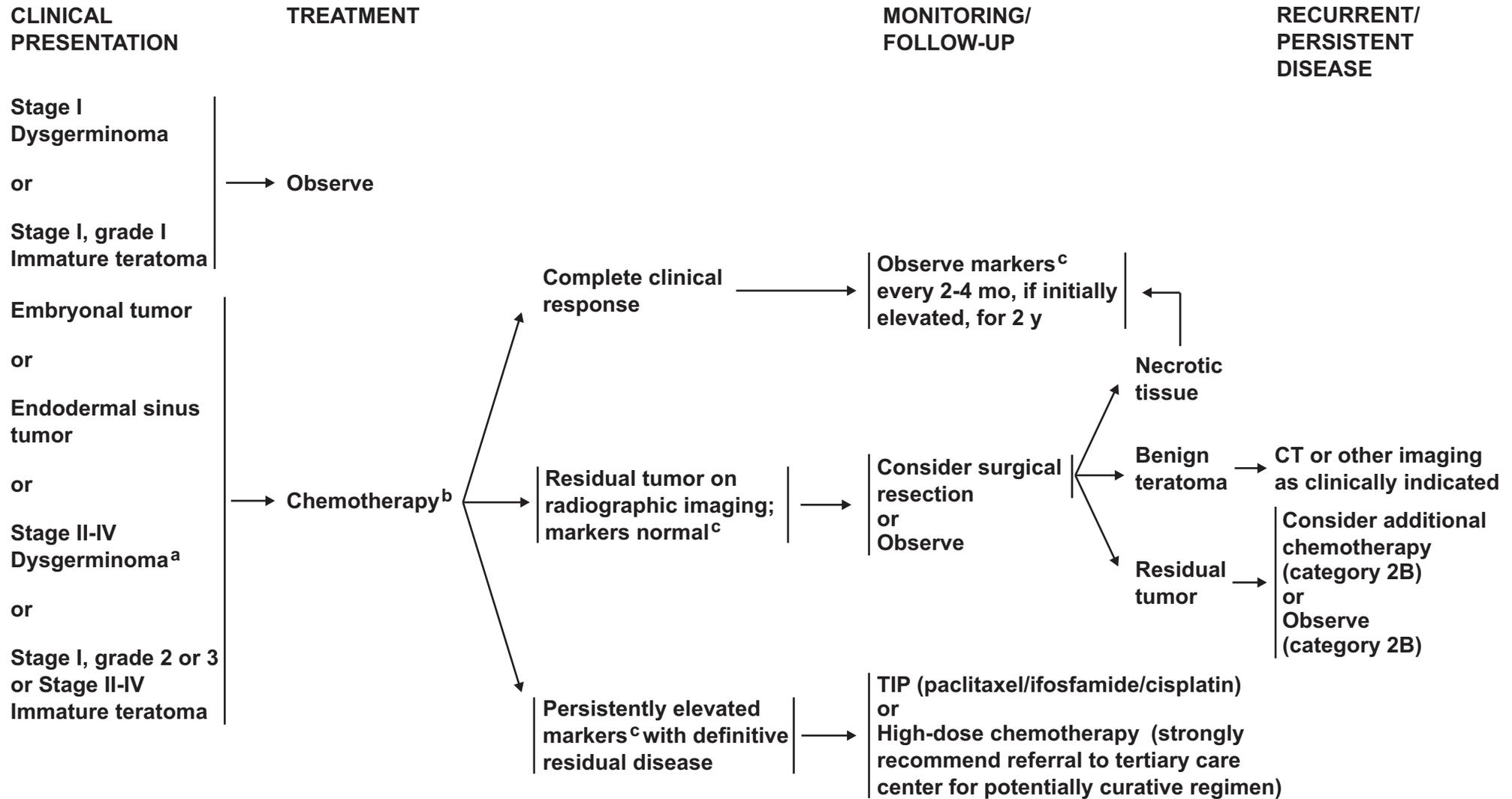


Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

PRIMARY TREATMENT



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



^aFor 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/m² on day 1 plus etoposide 120 mg/m² on days 1, 2, and 3 every 4 weeks).

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

^cSee [LCOH-1 for markers](#).

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

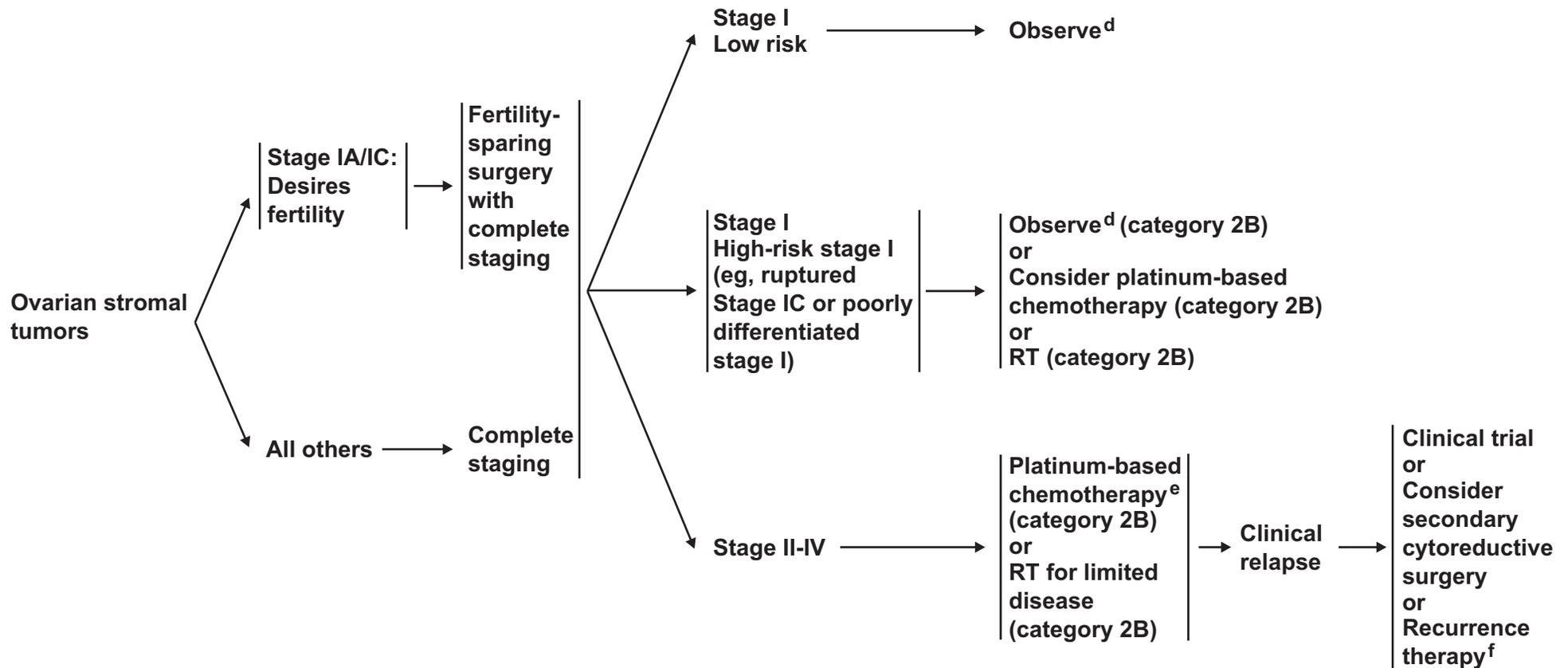
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

CLINICAL PRESENTATION

TREATMENT

RECURRENT
DISEASE

RECURRENCE
THERAPY



^dInhibin levels can be followed if initially elevated (category 2B)

^eGerm cell regimens ([See LCOH-3](#)) or paclitaxel/carboplatin regimens are preferred.

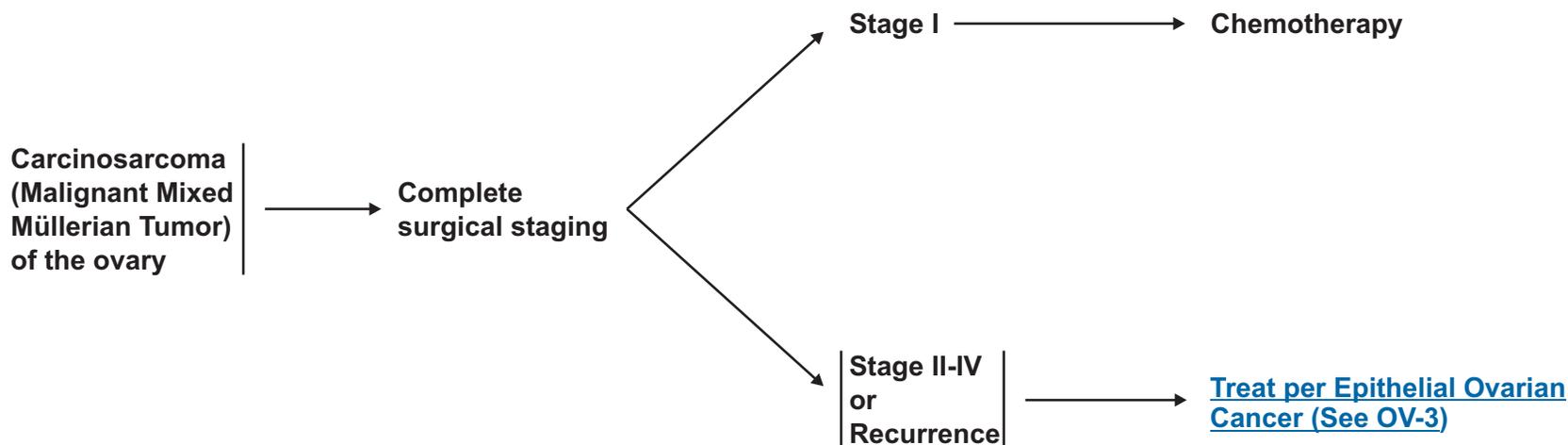
^f[See Acceptable Recurrence Therapies \(LCOH-A\)](#).

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

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

CLINICAL PRESENTATION

TREATMENT



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

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

ACCEPTABLE RECURRENCE THERAPIES

GERM CELL TUMORS¹High-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

OVARIAN STROMAL TUMORSLeuprolide 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

¹Patients with potentially curable recurrent germ cell disease should be referred to a tertiary care institution for potentially curative therapy.²High-dose chemotherapy regimens vary among institutions.**Note:** All recommendations are category 2A unless otherwise indicated.**Clinical Trials:** NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Staging

Table 1

**American Joint Committee on Cancer (AJCC)
TNM and FIGO Staging System for Ovarian Cancer**

Primary Tumor (T)

TNM	FIGO	Description
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 and/or implants
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

TNM FIGO

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
N1	IIIC	Regional lymph node metastasis
M1	IV	Distant metastasis (excludes peritoneal metastasis)

*Note: The presence of nonmalignant ascites is not classified. The presence of ascites does not affect staging unless malignant cells are present.

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

[Continued](#)

Table 1 Continued

Regional Lymph Nodes (N)

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

Distant Metastasis (M)

- MX** Distant metastasis cannot be assessed
- M0** No distant metastasis
- M1** Distant metastasis (excludes peritoneal metastasis)

Stage Grouping

Stage IA	T1a	N0	M0
Stage IB	T1b	N0	M0
Stage IC	T1c	N0	M0
Stage IIA	T2a	N0	M0
Stage IIB	T2b	N0	M0
Stage IIC	T2c	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

Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original and primary source for this information is the AJCC Cancer Staging Manual, Sixth Edition (2002) published by Springer-Verlag New York. (For more information, visit www.cancerstaging.net.) Any citation or quotation of this material must be credited to the AJCC as its primary source. The inclusion of this information herein does not authorize any reuse or further distribution without the expressed, written permission of Springer-Verlag New York, Inc., on behalf of the AJCC.

Discussion

This discussion is being updated to correspond with the newly updated algorithm. Last updated 03/13/08

NCCN Categories of Evidence and Consensus

Category 1: The recommendation is based on high-level evidence, and there is uniform NCCN consensus.

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

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

Category 3: 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; however, other less common pathologic subtypes must be considered in guidelines describing treatment recommendations. These NCCN guidelines discuss epithelial ovarian cancer and, in addition, less common ovarian histopathologies, including germ cell neoplasms, carcinosarcomas (malignant mixed Müllerian tumors of the ovary [MMMT]), and ovarian stromal tumors.

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 2008, there will be an estimated 21,650 new diagnoses and an estimated 15,520 deaths from this neoplasm in the United States; less than 40% of women with ovarian cancer are cured.¹ The incidence increases with age and is

most prevalent in the eighth decade of life, with an incidence 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.²

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.² Conversely, nulliparity or older age at first birth (older than 35 years) confers an increased risk of cancer. Family history (primarily patients having 2 or more first-degree relatives with ovarian cancer), including linkage with BRCA1 and BRCA2 genotypes, has been found to be associated with early-onset disease; however, these patients account for only 5% of all women who have ovarian cancer.² Environmental factors have been investigated, but so far they have not been conclusively associated with the development of this neoplasm.

Because of the location of the ovaries, it has been difficult to diagnose ovarian cancer at an earlier more curable stage. However, recent evaluations of newly diagnosed ovarian cancer patients have resulted in new 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.³ Symptoms suggestive of ovarian cancer include: bloating, pelvic or abdominal pain, difficulty eating or feeling full quickly, and urinary symptoms (urgency or frequency). Physicians evaluating women with this constellation of symptoms must be cognizant of the possibility that ovarian pathology may be causing these symptoms.

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 stage I, II, III, or IV. Since 1997, there have not been any significant changes in the TNM and

FIGO (International Federation of Gynecology and Obstetrics) staging systems for ovarian cancer.

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.

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 at other institutions.

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 (such as 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 (if clinically indicated) after a complete physical examination and appropriate laboratory studies.⁴ Laboratory studies should include a complete blood count (CBC), chemistry profile with liver function tests (LFTs), and CA-125 determination. Patients with a family history of ovarian and/or breast cancer should also be considered for genetic counseling.

Although there is no direct evidence that a chest x-ray 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. Often they have undergone cytoreductive surgery and have undergone comprehensive staging procedures (ie, having met the standards for surgical staging of the Gynecologic Oncology Group [GOG]). However, in some instances, referral occurs after “incomplete” surgery and/or staging (eg, uterus and/or adnexa intact, omentum not removed, residual disease that is potentially resectable, surgical stage not completely documented). The components of surgical staging are listed in the algorithm. 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.

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.^{5,6} 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 (ie, low malignant potential [LMP] lesions, early-stage invasive tumors).^{7,8} Comprehensive surgical staging should still be performed to rule out occult higher-stage disease.

In stage I disease, minimally invasive techniques may be considered to achieve the surgical goals. Laparoscopic surgery performed by an experienced gynecologic oncologist may be considered in selected patients.

Cytoreductive surgery for patients having clinical stage II, III, or IV disease remains the initial treatment recommendation. Every attempt should be made to achieve maximal cytoreduction to less than 1 cm residual disease in appropriate circumstances.⁹ Procedures that may be considered for optimal surgical cytoreduction include: radical pelvic dissection, bowel resection, diaphragm stripping, or splenectomy. The therapeutic benefit of neoadjuvant chemotherapy followed by interval cytoreduction remains controversial.^{10,11} It may be considered for patients with bulky stage II to IV disease who are not surgical candidates. The pathologic diagnosis should be confirmed, however, before initiation of chemotherapy, by fine-needle aspiration, biopsy, or paracentesis in this group of patients.

Incompletely Staged Patients

For patients with incomplete previous surgery, there was consensus on the following treatment recommendations:

1. A surgical staging procedure is recommended for all patients with suspected stage IA or IB, grade 1 tumors because, if this stage is confirmed, no further adjuvant therapy is indicated.
2. If potentially resectable residual disease is suspected, a completion surgical staging procedure with debulking is recommended for all stages.
3. For stages higher than stage IA or IB, grade 1, if no residual disease is suspected, chemotherapy for 6 cycles is recommended. Controversy persists regarding the treatment of stage IA or IB, grade 2 disease. Observation after careful surgical staging is considered an option. For patients with stage II-IV disease, consider interval debulking surgery after 3 cycles of chemotherapy followed by postoperative chemotherapy. A completion surgical staging procedure with debulking is, however, an option for all patients with stage IA or IB, grade 2 or 3, and stage IC tumors.

For patients with stage IA or IB, grade 2, who are suspected of harboring residual disease, a completion surgical staging procedure is recommended. Tumor reductive surgery is conducted for 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 surgical treatment alone.¹² If observation (without the addition of chemotherapy) is considered for stage IA or IB, grade 2 tumors, a comprehensive surgical staging procedure is recommended for all patients.

Recommendations regarding initial primary chemotherapy/primary adjuvant therapy include intravenous and intraperitoneal options. Evidence for superiority of intraperitoneal chemotherapy for less than 1 cm optimally debulked stage III patients has recently been published

and is now a category 1 recommendation; stage II patients may also receive chemotherapy via the intraperitoneal route of administration.^{13,14} In women with stage III cancer, survival was increased by 16 months after intraperitoneal therapy using cisplatin/paclitaxel when compared with standard intravenous therapy (65.6 versus 49.7 months, $P = .03$) in this GOG 172 trial. For patients for whom this does not apply (eg, those with poor performance status), the preferred intravenous regimen is the combination of paclitaxel plus carboplatin (category 1).^{15,16} Docetaxel plus carboplatin (category 1)¹⁷ or paclitaxel plus cisplatin (category 1) are options for alternative regimens.¹⁸ The docetaxel/carboplatin regimen may be considered for patients who are at high risk for neuropathy (eg, patients with diabetes). Recommendations for the number of cycles of treatment vary with the stage of the disease. For patients with advanced-stage disease (stages II-IV), 6 cycles of chemotherapy are recommended, whereas 3 to 6 cycles are recommended for earlier-stage disease.¹⁹

The recommended regimens accepted by a consensus of the panel include: carboplatin, dosed at an area under the curve (AUC) of 5-7.5, plus paclitaxel, 175 mg/m² 3-hour intravenous infusion given every 3 weeks for 6 courses (category 1), which is the preferred IV regimen.¹⁵ Alternative regimens include (1) docetaxel, 60-75 mg/m² 1-hour intravenous infusion plus carboplatin, dosed at AUC of 5 to 6 every 3 weeks (category 1);¹⁷ and (2) paclitaxel, 135 mg/m² intravenous 24-h infusion day 1; cisplatin 100 mg/m² intraperitoneal, day 2 after intravenous paclitaxel; paclitaxel, 60 mg/m² intraperitoneal, day 8 (max BSA 2.0 m²); repeat every 3 weeks times 6 courses (category 1).¹³ These regimens have different toxicity profiles. The docetaxel/carboplatin regimen is associated with increased risk for neutropenia; the intravenous paclitaxel/carboplatin regimen is associated with sensory peripheral neuropathy. The intraperitoneal paclitaxel/cisplatin regimen is associated with leukopenia, infection, fatigue, and pain; only 42% of women were able to complete all 6

treatment cycles.²⁰ Reasons for discontinuing the intraperitoneal regimen included catheter complications, nausea/vomiting/dehydration, and abdominal pain. Women unable to complete intraperitoneal therapy should receive intravenous therapy. Techniques to decrease catheter complications include catheter choice and timing of insertion.^{14,21} Intraperitoneal chemotherapy is controversial;^{22,23} some investigators feel that intraperitoneal paclitaxel/cisplatin therapy should be considered an optional approach until it is assessed in a trial with intravenous carboplatin/paclitaxel, which has been considered the standard treatment.²⁴ Patients with poor performance status, comorbidities, stage IV disease, or advanced age may not tolerate the intraperitoneal regimen. The intraperitoneal regimen published by Armstrong and colleagues has, however, documented the longest median survival that has been described to date in optimally debulked stage 3 patients.

Dose Intensity

Panel members also discussed the issue of 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 recent 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.^{25,26} The consensus of the panel is that this approach remains investigational and should not be performed outside of an approved clinical trial.

Number of Chemotherapy Cycles

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 cycles of combination chemotherapy are required for initial

chemotherapy. However, the role of maintenance therapy in patients who achieve a complete remission after 6 cycles of chemotherapy has gained support because of the results of GOG 178, which randomly assigned patients to 3 versus 12 months of further paclitaxel after initial chemotherapy.²⁷ The results of this trial suggest that patients receiving 12 months of therapy sustained a progression-free survival advantage. Postremission chemotherapy is a category 2B recommendation. When using a cisplatin/paclitaxel regimen, prolonging the infusion of paclitaxel did not improve median overall survival.²⁸

Radiation Therapy

The panel members disagreed about the role of whole abdominal radiation therapy (RT) in patients with low-bulk stage III disease. Based on historical data,²⁹ whole-abdominopelvic radiotherapy was previously a primary adjuvant therapy option for patients with low-bulk disease, although the panel members had a major disagreement (category 3). Results of a prospective trial³⁰ suggest that whole abdominal radiotherapy may be an option to be used as consolidation therapy in selected subgroups of patients after chemotherapy. Because it is rarely used in NCCN institutions, it is not included as a treatment recommendation in the 2008 guidelines.

Follow-up Recommendations

After the completion of primary surgery and chemotherapy in patients having all stages of ovarian cancer, the standard recommendation is observation with follow-up. Monitoring should include a history and physical examination (including pelvic exam) every 2 to 4 months for 2 years, followed by every 6 months for 3 years, and then annually. Laboratory studies including a CBC and chemistry profile should be done if indicated. Chest/abdominal/pelvic CT or positron emission tomography (PET) scans and chest x-ray may be ordered if clinically necessary. Measurement of a CA-125 level at each follow-up evaluation is recommended if the level was initially elevated. Genetic

counseling is recommended if a family history suggests a genetic syndrome. Patients who have no evidence of progression of cancer after initial treatment should undergo a clinical re-evaluation after 6 cycles of chemotherapy. Patients who progress during initial therapy should be treated with second-line approaches (see next section on “Recurrent Disease”).

Panel members had a substantial disagreement about the role of further treatment for the management of advanced-stage (stages II-IV) patients who are in complete clinical remission after their initial therapeutic regimen. Options range from observation alone, clinical trial, or additional chemotherapy²⁷ (paclitaxel, category 2B), preferably in a controlled clinical trial. In addition, reassessment surgical procedures (such as, second-look laparotomy or laparoscopy and debulking after primary chemotherapy) remain controversial in this group of patients (category 3).³¹

If a reassessment (second-look) laparotomy or laparoscopy is performed, the findings should dictate further treatment. If the findings are negative, the patient should be monitored as described previously. If the reassessment findings are positive and the patient is thought to have been responding to initial chemotherapy, the initial chemotherapy regimen may be continued. In some patients, however, the reassessment (second-look) surgical procedure demonstrates that the patient did not respond to initial chemotherapy. These patients should be treated with recurrence therapy.

Management of an Increasing CA-125 Level

Panel members had an extensive discussion about 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. Patients who have never received

chemotherapy (ie, naïve to chemotherapy) should be managed as newly diagnosed patients, should undergo clinically appropriate imaging studies (including MRI, PET, or PET/CT [category 2B] if clinically appropriate) and surgical debulking, and be treated as previously described.

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 chemotherapy 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,³² they are frequently administered to patients who have only a rising CA-125 level³³ as evidence of tumor progression. Tamoxifen or other hormonal agents are acceptable recommendations for this clinical situation (category 2B). Other alternatives include enrollment on a clinical trial, observation until clinical symptoms arise (category 2B), or immediate treatment for recurrent disease (category 2B).

Recurrent Disease

The prognosis is poor (1) for patients who progress after 2 consecutive chemotherapy regimens without ever sustaining a clinical benefit; or (2) for those whose disease recurs in less than 6 months. 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 recommended (although clinical trials suggest that altering the schedule of paclitaxel may produce secondary responses).³⁴ Options include treatment with a recurrence regimen that does not contain platinum³⁵ or supportive care. Potential ancillary surgical and/or supportive care procedures for selected patients are summarized.

Patients who relapse more than 6 months after initial chemotherapy are considered “platinum-sensitive” and have the greatest number of potential options for second-line therapy. Evidence suggests that combination chemotherapy may be superior to single-agent therapy in this situation.³⁶ Options include carboplatin/paclitaxel (category 1),³⁶ gemcitabine/carboplatin (which has been shown to improve progression-free survival),³⁶⁻³⁸ or a recurrence regimen (category 2B). A recent study found that an oxaliplatin and docetaxel regimen was active (67%) in women with recurrent cancer.³⁹

For stage II, III, and IV patients with partial responses (including positive reassessment surgical procedure, microscopic disease), recurrence chemotherapy regimens include single-agent therapy as described in the next section; observation is also an option (category 2B). Secondary cytoreductive surgery and/or recurrence chemotherapy can be considered for patients who have a low-grade or focal recurrence after a long disease-free interval (6 months or more).⁴⁰ 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 efficacy of several newer agents in ovarian cancer has been described. The activity of the following agents appears to be similar: topotecan, 20%;⁴¹ gemcitabine, 19%;⁴² vinorelbine, 20%;^{43,44} liposomal doxorubicin, 26%;⁴⁵ and oral etoposide, 27% in platinum-resistant patients and 35% in platinum-sensitive patients.⁴⁶ A recent meta-analysis of 13 randomized studies in recurrent ovarian cancer has been published.⁴⁷ Platinum-based combination chemotherapy should be considered for platinum-sensitive recurrence.^{36,47} Altretamine, with a 14% response rate,⁴⁸ and ifosfamide, with a 12% response rate,⁴⁹ have also been proven to be active in recurrent ovarian cancer, although less information regarding their use in paclitaxel-refractory patients is

available. Bevacizumab is also active,⁵⁰⁻⁵⁴ although it may cause arterial thrombosis or intestinal perforation. Taxanes (including docetaxel and paclitaxel) and platinum compounds (including cisplatin, carboplatin, and oxaliplatin) can be used in appropriate patients.^{27,36} Capecitabine has activity in patients resistant to platinum and taxanes.⁵⁵ 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 aromatase inhibitors (including letrozole, anastrozole, or exemestane) continues to be a viable therapeutic option.⁵⁶⁻⁵⁹ Pertuzumab has slight activity.⁶⁰ RT can also provide effective palliation when radiation ports are tailored to specific symptomatic disease sites.⁶¹

The NCCN panel felt that no single chemotherapeutic agent should be currently recommended as the treatment of choice for recurrent ovarian carcinoma. They also 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 progress on 2 consecutive chemotherapy regimens without evidence of clinical benefit will probably not benefit from additional chemotherapy. 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 LMP) identifies a primary epithelial ovarian lesion with specific histological characteristics suggesting malignancy but with a

clinically indolent course and good prognosis. Five-year survivals exceed 80%.⁶² 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 treatment used for epithelial ovarian cancer (category 2B) (such as postoperative chemotherapy) can be considered for these patients.⁶³ 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.^{64,65} The benefit of postoperative chemotherapy has not been demonstrated for patients who have no microscopically demonstrable invasive implants.⁶⁶

Treatment

Treatment guidelines for borderline epithelial ovarian cancer depend on the histological and clinical characteristics, the age of the patient,⁶⁵ and the stage of the disease at the time of diagnosis. At NCCN institutions, patients may be initially evaluated with an undiagnosed pelvic mass or with an established diagnosis of ovarian cancer of LMP. Patients with an LMP lesion who desire to maintain their fertility may undergo surgery limited to a USO at the time of comprehensive staging. If the patient does not desire fertility-sparing surgery, standard ovarian cancer debulking surgery is recommended, accompanied by comprehensive staging.

Patients with known LMP disease who were incompletely staged at the time of their initial laparotomy should undergo completion surgical staging (1) if residual disease is suspected, or (2) if residual disease is not suspected (suspected stage I) but they have no desire to maintain fertility. Conversely, these patients should be observed if residual disease is not suspected but they desire to maintain fertility.

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). Patients with noninvasive implants should be observed and monitored^{64,67} every 3 to 6 months for up to 5 years followed by annual evaluations. If the CA-125 level is initially elevated, it should be monitored at each visit. In addition, a CBC and chemistry profile should be monitored as clinically indicated.

Patients who chose fertility-sparing surgery should be monitored by ultrasound examinations if necessary; they should be considered for exploratory surgery and standard debulking after the completion of childbearing (category 2B). All patients should be considered for a family history evaluation.

At the time of clinical relapse, a surgical evaluation and debulking should be considered. Patients who have invasive implants at this time may be considered for treatment according to the recommended guidelines for epithelial ovarian cancer (category 2B); those without invasive implants should be observed or enrolled in a clinical trial.

Less Common Ovarian Histopathologies

Overview

Less common histopathologies of ovarian cancer include: germ cell neoplasms, carcinosarcoma (MMMT), and ovarian stromal tumors. These tumors account for approximately 3% to 7% 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.

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, including abdominal/pelvic examination, ultrasound or abdominal/pelvic CT, and GI evaluation if clinically indicated. The recommended laboratory evaluation for a pelvic mass should include a comprehensive metabolic panel, CBC, magnesium level, liver function studies, and lactic dehydrogenase. Tumor markers (including CA-125, inhibin, alpha-fetoprotein [AFP]) and beta-human chorionic gonadotropin (HCG) levels can be obtained 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 germ cell tumor, ovarian cancer of LMP, or clinical stages I epithelial ovarian or stromal tumors.⁶⁸⁻⁷⁰ Patients who do not want to preserve their fertility; those who have a clinical stage II, III, or IV epithelial ovarian cancer or stromal tumor; or those with

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

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. Many times, 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 (eg, uterus and/or adnexa intact, omentum not removed, or surgical stage not documented). The components of surgical staging are listed in the epithelial ovarian cancer guidelines.

Germ Cell Tumors

The recommended workup (see “Recommended Workup” as previously discussed) for germ cell tumors should include a comprehensive metabolic panel, CBC with platelets, magnesium level, lactic dehydrogenase, alpha-fetoprotein, and beta-HCG levels and may include pulmonary function studies if bleomycin is being considered. Fertility-sparing surgery should be considered for those desiring fertility preservation. Otherwise, comprehensive surgical staging is recommended as initial surgery.

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, then options include observation (category 2B) or a completion staging procedure (category 2B). If there is no evidence of disease, these patients may be observed. If tumor is found, patients should then receive bleomycin/etoposide/platinum (BEP) in the postoperative period; taxanes may be less toxic than BEP.⁷¹⁻⁷³ Pulmonary function tests are recommended if considering the use of bleomycin.

Patients should receive chemotherapy for 3 to 4 cycles with 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.^{72,73} In select patients with stage IB-III dysgerminoma for whom minimizing toxicity is critical, 3 courses of etoposide/carboplatin can be used.⁷⁴ 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 patients having radiographic evidence of residual tumor but with normal AFP and beta-HCG, consideration should be given to surgical resection of the tumor; observation is also an option. For patients having persistently elevated AFP and/or beta-HCG after first-line chemotherapy, recommendations include TIP (paclitaxel, ifosfamide, cisplatin)⁷⁵ or high-dose chemotherapy (for example, TIP at high doses) with stem cell support (strongly recommend referral to a tertiary care center for potentially curative regimen).

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, including TIP, VIP (etoposide, ifosfamide, cisplatin), VeIP (vinblastine, ifosfamide, cisplatin), VAC (vincristine, dactinomycin, cyclophosphamide), cisplatin/etoposide, docetaxel/carboplatin, paclitaxel/carboplatin, paclitaxel/gemcitabine, paclitaxel/ifosfamide, docetaxel, paclitaxel, RT, or supportive care.⁷⁶⁻⁸⁰ Combination chemotherapy is not recommended for recurrent or residual disease with no curative options. These recurrence regimens are not generalizable for all of the uncommon histology tumors; therefore, patients should be referred to tertiary care institutions for treatment.

Ovarian Stromal Tumors

Patients with stage IA-C ovarian stromal tumors desiring to preserve their fertility should be treated with fertility-sparing surgery with complete staging. Complete staging is also recommended for all other patients. 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 cm⁸¹), recommendations (all are category 2B) include observation, RT, or consideration of cisplatin-based chemotherapy.⁸² For patients being observed, inhibin levels can be followed if they were initially elevated (category 2B). For patients with stages 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; docetaxel/carboplatin can also be used). For patients subsequently having a clinical relapse, options include clinical trial, supportive care, chemotherapy (germ cell regimens or paclitaxel/carboplatin regimens are preferred); recurrence regimens can also be used. Leuprolide or secondary cytoreductive surgery may also be considered.

Carcinosarcoma (Malignant Mixed Müllerian Tumors)

After complete surgical staging, patients found to have stage I carcinosarcoma (MMMT) at the time of surgery should have post-operative chemotherapy. The type of chemotherapy (category 2B) is variable, because there are no data to specifically define the optimal chemotherapeutic regimen; ifosfamide-based regimens can be used. Patients with stages II-IV carcinosarcoma (MMMT) or recurrence are often treated as papillary serous or clear cell carcinomas.

Discussion
update in
progress

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& References marked with this symbol provided the basis for the algorithms.