

Ovarian Cancer

Version 1.2006

Continue

NCCN Ovarian Cancer Panel Members

*Robert J. Morgan, Jr., MD/Chair ‡ Ψ
City of Hope Cancer Center

*Ronald D. Alvarez, MD Ω
University of Alabama at Birmingham Comprehensive
Cancer Center

*Deborah K. Armstrong, MD Ω †
The Sidney Kimmel Comprehensive
Cancer Center at Johns Hopkins

*Lee-may Chen, MD Ω
UCSF Comprehensive Cancer Center

*Larry Copeland, MD Ω
Arthur G. James Cancer Hospital & Richard J. Solove
Research Institute at The Ohio State University

Jeff Fowler, MD Ω
Arthur G. James Cancer Hospital & Richard J. Solove
Research Institute at The Ohio State University

*David K. Gaffney, MD, PhD §
Huntsman Cancer Institute at the University of Utah

*David Gershenson, MD Ω
The University of Texas
M. D. Anderson Cancer Center

*Benjamin E. Greer, MD Ω
Fred Hutchinson Cancer Research Center/Seattle Cancer
Care Alliance

*Carolyn Johnston, MD Ω
University of Michigan Comprehensive Cancer Center

*Johnathan M. Lancaster, MD, PhD Ω
H. Lee Moffitt Cancer Center & Research Institute at
the University of South Florida

Shashikant Lele, MD Ω
Roswell Park Cancer Institute

*Ursula Matulonis, MD †
Dana-Farber/Partners CancerCare

*Robert F. Ozols, MD, PhD †
Fox Chase Cancer Center

*Steven W. Remmenga, MD Ω
UNMC Eppley Cancer Center at The Nebraska Medical
Center

*Paul Sabbatini, MD † ‡
Memorial Sloan-Kettering Cancer Center

John Soper, MD Ω
Duke Comprehensive Cancer Center

Nelson Teng, MD, PhD Ω
Stanford Hospital and Clinics

Continue

Ω Gyn oncology
‡ Hematology/Hematology oncology
§ Radiotherapy/Radiation oncology
† Medical Oncology
‡ Internal medicine
Ψ Neurology/neuro-oncology
* Writing committee member

Table of Contents

[NCCN Ovarian Cancer Panel Members](#)

Epithelial Ovarian Cancer:

- [Clinical Presentation, Workup, Primary Treatment \(OV-1\)](#)
- [Diagnosis by Previous Surgery: Findings and Primary Treatment \(OV-2\)](#)
- [Pathologic Staging, Primary Chemotherapy/Primary Adjuvant \(OV-3\)](#)
- [Secondary Adjuvant \(OV-4\)](#)
- [Monitoring/Follow-Up, Recurrent Disease \(OV-5\)](#)
- [Recurrence Therapy \(OV-6\)](#)

[Borderline Epithelial Ovarian Cancer \(Low Malignant Potential\) \(OV-7\)](#)

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

[Ancillary Palliative Surgical Procedures \(OV-B\)](#)

[Acceptable Recurrence Modalities \(OV-C\)](#)

[Less Common Ovarian Histopathologies \(LCOH-1\)](#)

[Germ Cell Tumors \(LCOH-2\)](#)

[Ovarian Stromal Tumors \(LCOH-4\)](#)

[Mixed Mullerian Tumors \(LCOH-5\)](#)

[Recurrence Modalities \(LCOH-A\)](#)

[Guidelines Index](#)

[Print the Ovarian Cancer Guideline](#)

[Order the Patient Version of the Ovarian Cancer Guidelines](#)

[For help using these documents, please click here](#)

[Staging](#)

[Manuscript](#)

[References](#)

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 Consensus: All recommendations are Category 2A unless otherwise specified.

See [NCCN Categories of Consensus](#)

[Summary of Guidelines Updates](#)

These guidelines are a statement of consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult 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. ©2006.

CLINICAL
PRESENTATION

WORKUP

PRIMARY TREATMENT^a

Suspicious^b pelvic mass
and/or ascites, abdominal
distention, or symptoms
without other obvious source
of malignancy

- GI evaluation if clinically indicated
- Chest x-ray
- CA-125
- CBC
- Ultrasound or abdominal/pelvic CT if clinically indicated
- Chemistry profile with LFT's
- Consider family history evaluation ([See NCCN Genetic/Familial High Risk Assessment Guidelines](#))

Laparotomy/TAH/BSO with comprehensive staging^c or USO (Clinical Stage 1A or 1C, all grades with comprehensive staging if patient desires fertility) or

Cytoreductive surgery^c if clinical stage II, III, or IV or

Consider neoadjuvant chemotherapy/primary interval cytoreduction for patients with bulky stage III/IV who are not surgical candidates up front (diagnosis by FNA, biopsy or paracentesis)

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

Diagnosis by previous surgery

- Chest x-ray
- CA-125
- CBC
- Ultrasound or abdominal/pelvic CT if clinically indicated
- Chemistry profile with LFT's
- Consider family history evaluation ([See NCCN Genetic/Familial High Risk Assessment Guidelines](#))
- Institutional pathology review

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

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

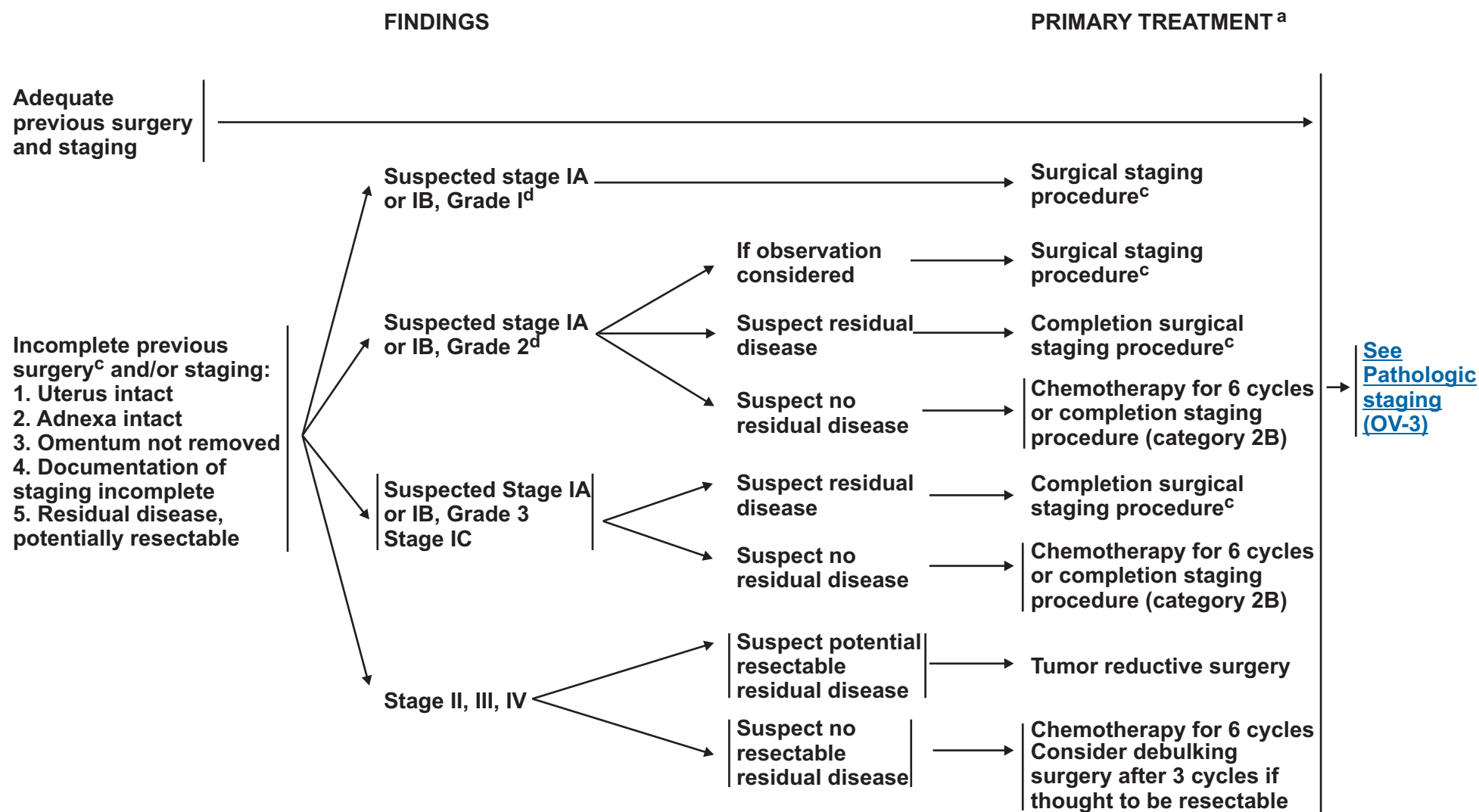
^bIm SS, Gordon AN, Buttin BM, et al. Validation of referral guidelines for women with pelvic masses. Obstet Gynecol 2005;105:35-41. [See Text.](#)

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

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

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

DIAGNOSIS BY PREVIOUS SURGERY



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

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

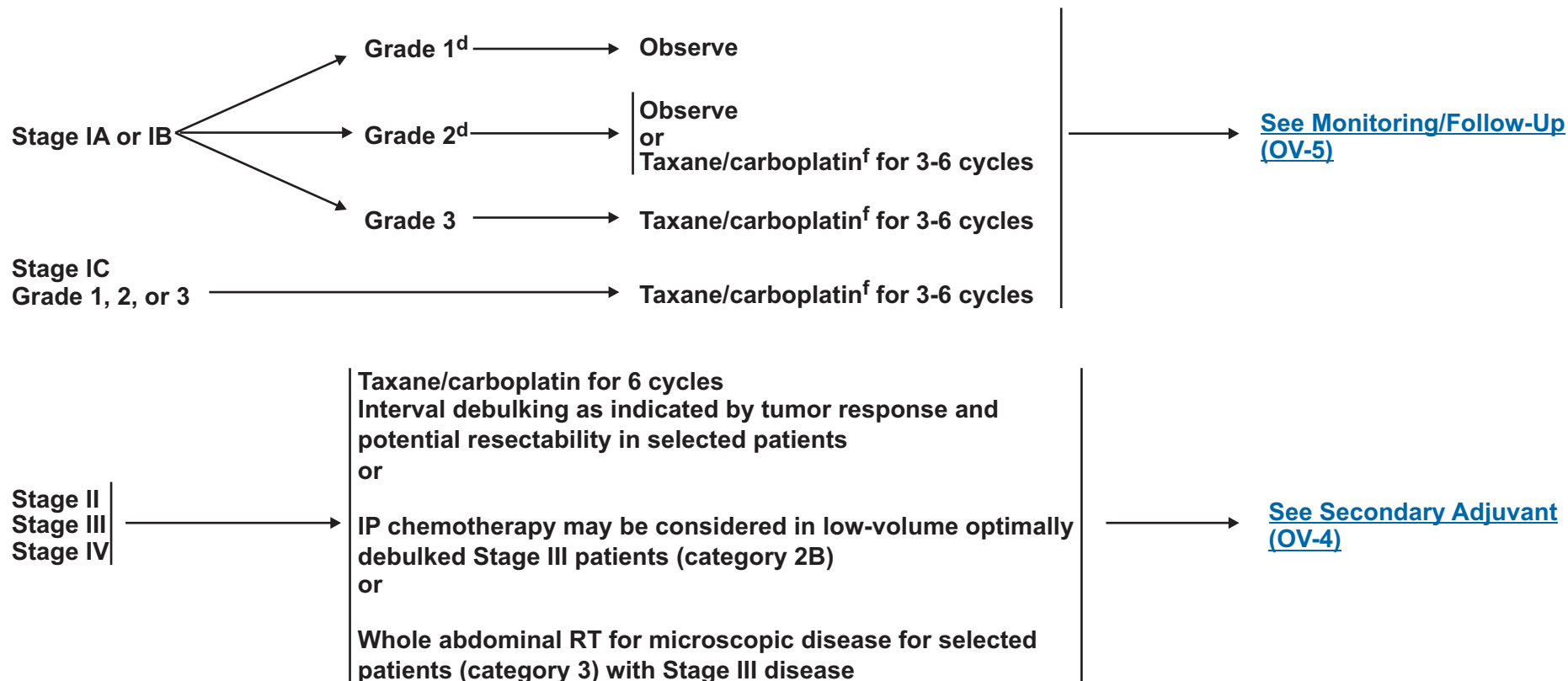
^dClear-cell pathology is grade 3.

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

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

PATHOLOGIC STAGING

PRIMARY CHEMOTHERAPY/PRIMARY ADJUVANT^e



^dClear-cell pathology is Grade 3.

^ePatients 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 prior to each cycle of chemotherapy, if informative
5. Radiographic imaging if indicated

^fPreferred regimen:

1. Paclitaxel 175 mg/m² over 3 hours and carboplatin AUC 5.0-7.5 every 3 weeks

Alternative regimens (category 2B):

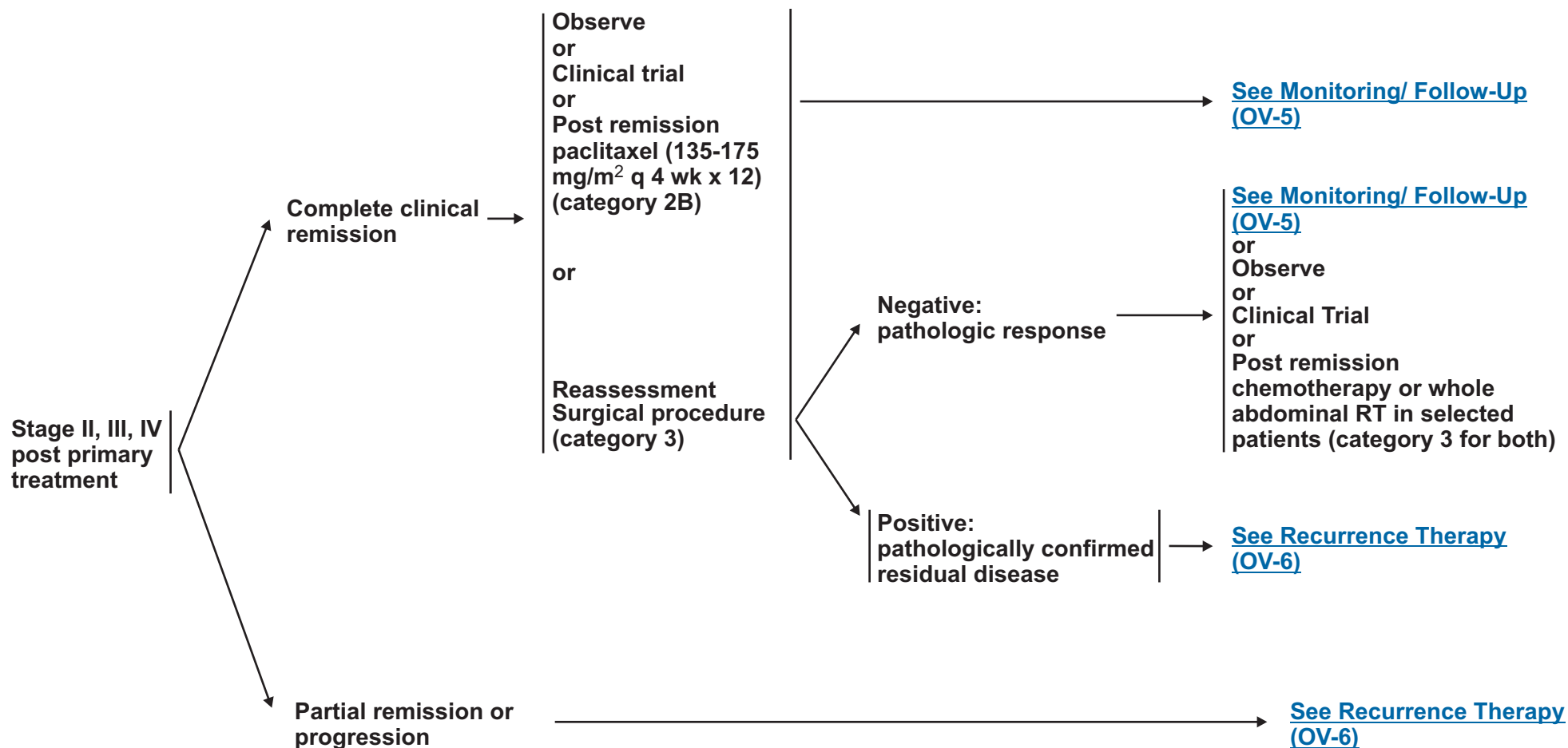
1. Docetaxel 60-75 mg/m² over 1 hour and carboplatin AUC 5-6 every 3 weeks
2. Paclitaxel 135 mg/m² IV 24 h infusion day 1; cisplatin 100 mg/m² IP, day 2 after IV paclitaxel; paclitaxel 60 mg/m² IP, day 8 (max BSA 2.0 m²). Repeat every 3 weeks x 6 courses.

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.

[Go Back To Ovarian Cancer Table of Contents](#)

SECONDARY ADJUVANT

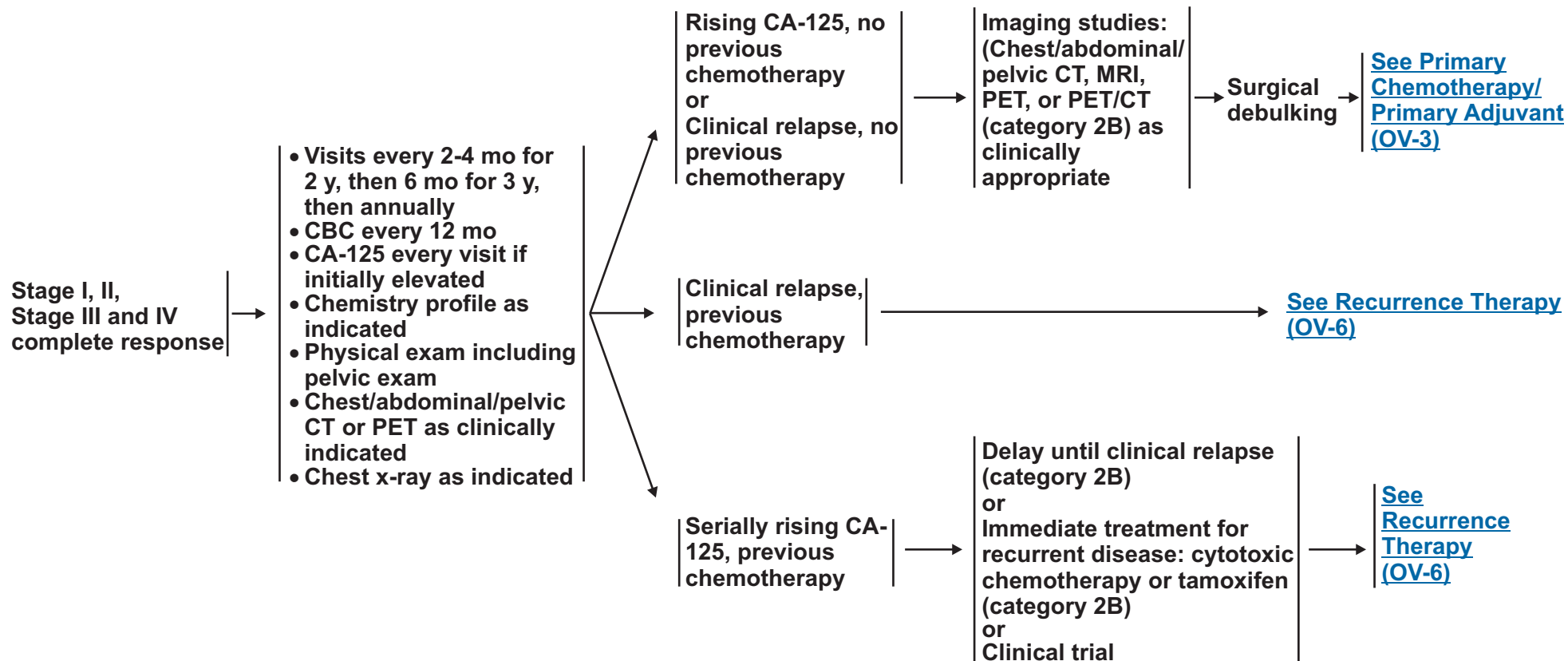
[Go Back To Ovarian Cancer Table of Contents](#)

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.

MONITORING/
FOLLOW-UP

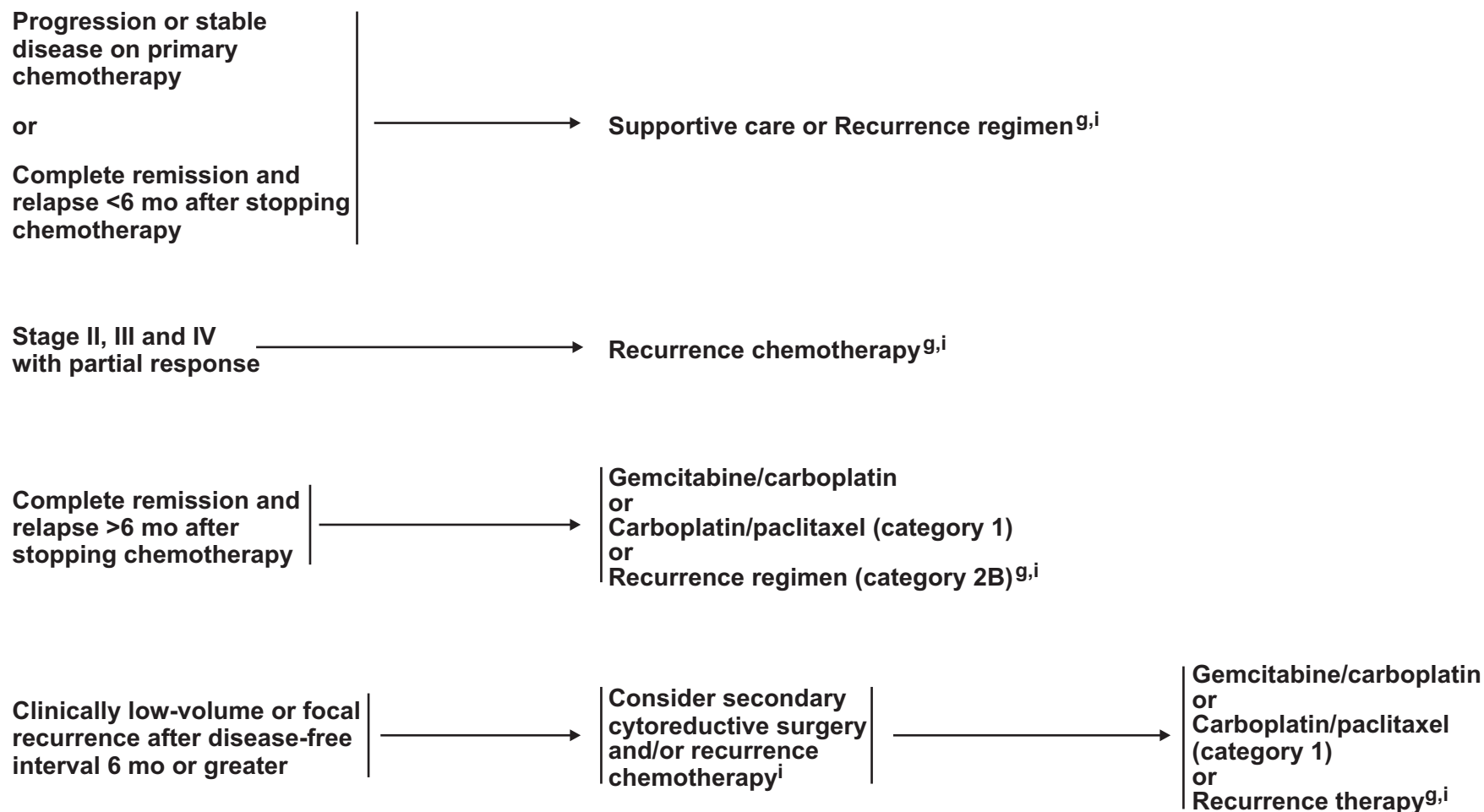
RECURRENT DISEASE



[Go Back To Ovarian Cancer Table of Contents](#)

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.

RECURRENCE THERAPY^{g,h,i}

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

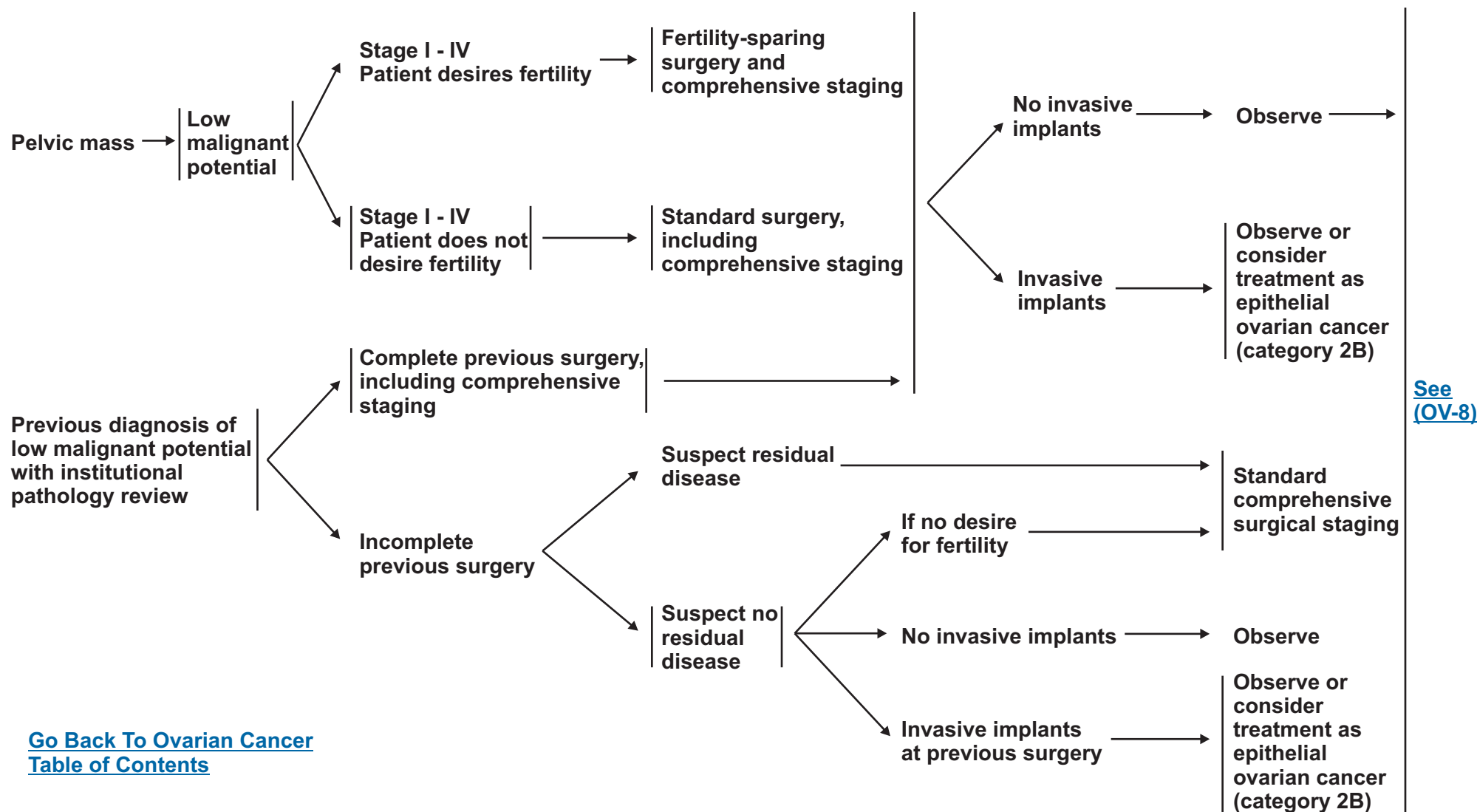
^h[See Ancillary Palliative Surgical Procedures \(OV-B\).](#)

ⁱ[See Acceptable Recurrence Modalities \(OV-C\).](#)

[See NCCN Palliative Care Guidelines](#)

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.

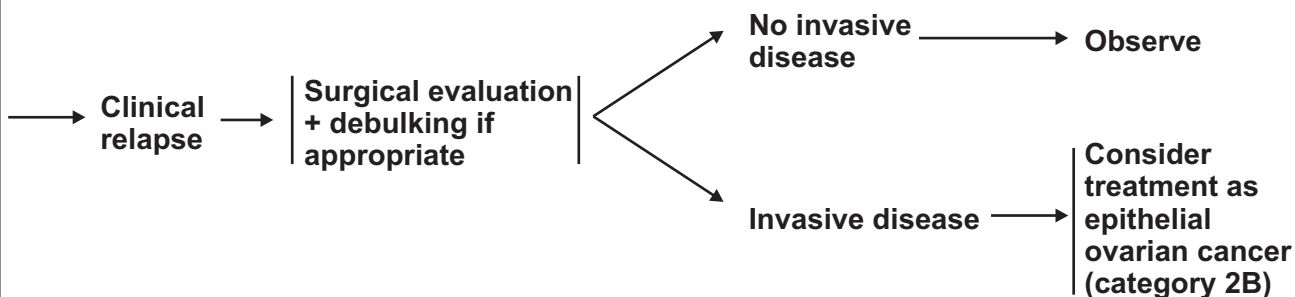


Note: All recommendations are category 2A unless otherwise indicated.

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

MONITORING/FOLLOW-UP

- Visits every 2-6 mo for 2 y, then every 3-6 mo for up to 5 y, then annually
- Ultrasound as indicated for patients with fertility sparing surgery
- CA-125 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)
- Consider family history
([See NCCN Genetic/Familial High Risk Assessment Guidelines](#))



[Go Back To Ovarian Cancer Table of Contents](#)

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

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

PRINCIPLES OF PRIMARY SURGERY ^{1,2}

In general, a vertical incision should be used.³

On entering the abdomen, aspiration of ascites or peritoneal lavage should be performed for peritoneal cytologic examinations. Specimens should be taken from:

- Pelvis
- Right and left paracolic gutters
- The undersurfaces of the right and left hemidiaphragms
- An encapsulated mass should be removed intact if possible.
- Adhesions should be noted and marked.
- All peritoneal surfaces should be evaluated and any suspicious area should be biopsied.
- Omentectomy and random peritoneal biopsies should be performed.
- Aortic lymph node sampling should be performed by stripping the nodal tissue from the vena cava and the aorta to at least the level of the inferior mesenteric artery.
- Pelvic lymph nodes should be sampled.
- Total hysterectomy, bilateral salpingectomy, and bilateral oophorectomy should be performed.

Surgical Cytoreduction

- Every attempt should be made to achieve maximal cytoreduction in appropriate circumstances.
- USO for patients desiring to preserve fertility may be considered in select patients.
- Patients with stromal tumors or borderline tumors may be desirous of fertility sparing surgery.

Special Circumstances

- In Stage I disease, minimally invasive techniques may be considered to achieve the above. This remains a controversial area and is not a standard approach. Laparoscopic surgery performed by an experienced gynecologic oncologist may be considered in selected patients (category 2B).
- Mucinous tumors.
- Consideration of IP catheter placement.

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 committee.

²Appendectomy may be performed in selected patients.

³It is recommended that a gynecologic oncologist should perform primary surgery (category 1).

[Go Back To Ovarian
Cancer Table of Contents](#)

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
- Enteral feeding tube
- Gastrostomy tube
- Vascular access device
- Indwelling peritoneal or pleural catheter
- Intestinal stents
- Video-assisted thoracoscopy

[Go Back To Ovarian Cancer
Table of Contents](#)

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 MODALITIES¹
(Listed in Alphabetical Order)

Altretamine	Docetaxel	Oral Etoposide
Anastrozole	Gemcitabine	Oxaliplatin
Bevacizumab²	Ifosfamide	Paclitaxel
Carboplatin	Irinotecan	Radiation therapy
Cisplatin	Letrozole	Tamoxifen
Cyclophosphamide	Liposomal Doxorubicin	Topotecan
	Melphalan	Vinorelbine

Platinum-based combination therapy can be considered³

¹Patients who progress on two consecutive single-agent regimens without evidence of clinical benefit are unlikely to benefit from additional chemotherapy regimens and may be offered best supportive care or clinical trial.

²May cause arterial thrombosis or intestinal perforation.

³Some evidence suggests that platinum-based combination therapy may be efficacious.

[Go Back To Ovarian Cancer Table of Contents](#)

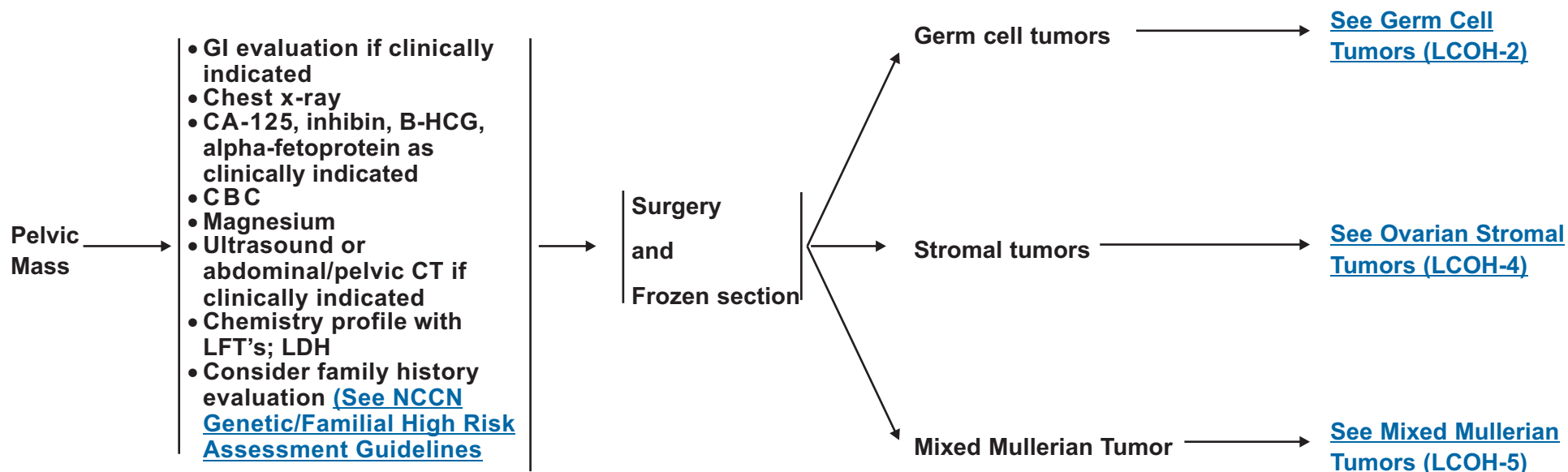
Note: All recommendations are category 2A unless otherwise indicated.

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

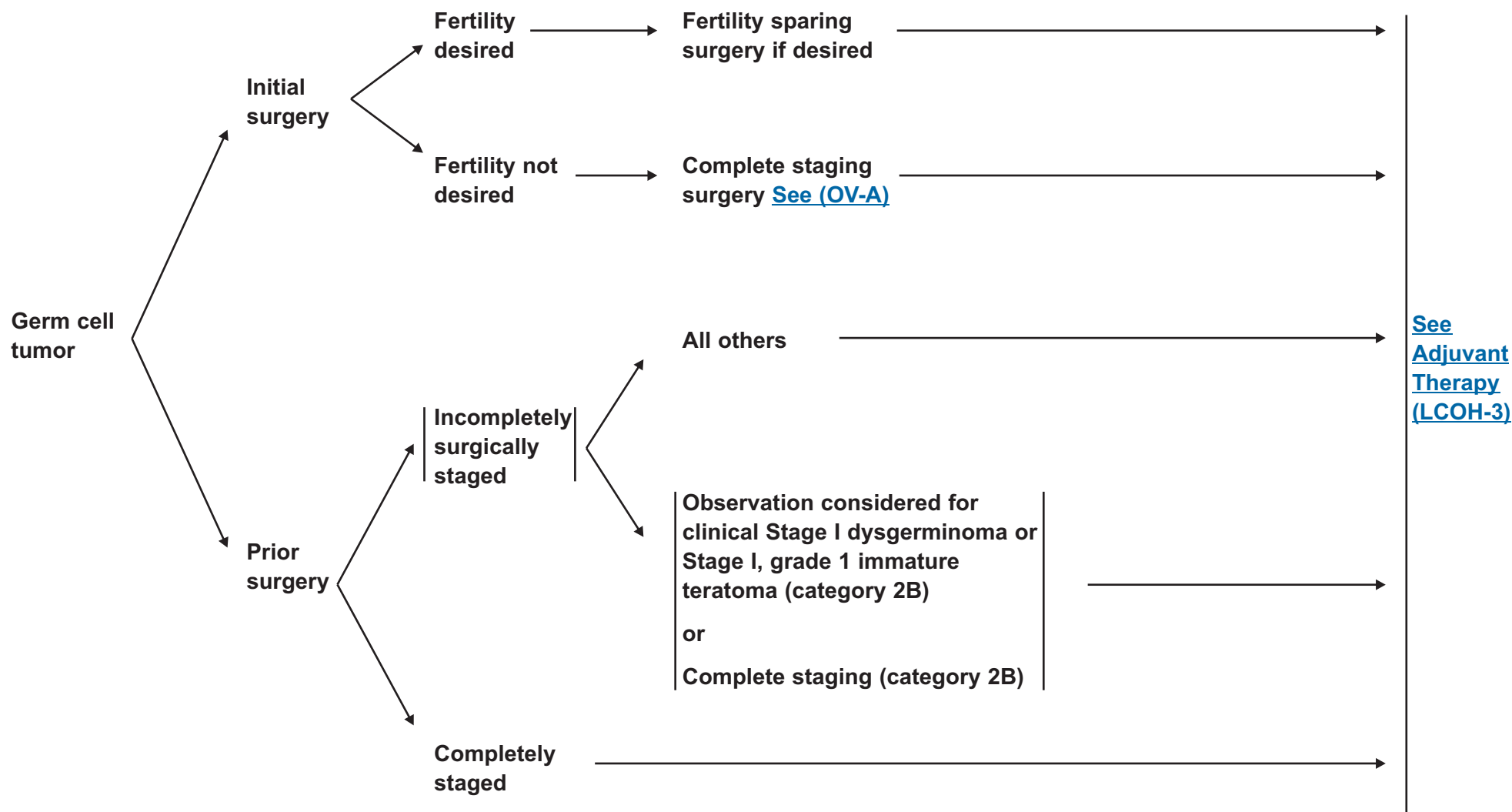
DIAGNOSIS



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.

CLINICAL
PRESENTATION

TREATMENT

MONITORING/FOLLOW UP

Stage I
Dysgerminoma
or
Stage I, grade I
Immature teratoma

→ Observe

Embryonal tumor
or
Endodermal sinus
tumor
or
Stage II-IV
Dysgerminoma^a
or
Stage I, grade 2 or 3
or Stage II-IV
Immature teratoma

→ Chemotherapy^b

Complete clinical
response

→ Observe markers every 2-4 mo, if
initially elevated, for 2 y

Residual tumor on x-
rays; markers normal

→ Consider surgical resection
or
Observe

Persistently elevated
markers^c

→ TIP (paclitaxel/ifosfamide/cisplatin) or high-
dose chemotherapy (strongly recommend
referral to tertiary care center for potentially
curative regimen)^d

^aFor select patients with Stage IB-III dysgerminoma for whom minimizing toxicity is critical, three courses of etoposide/carboplatin can be used.

^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.

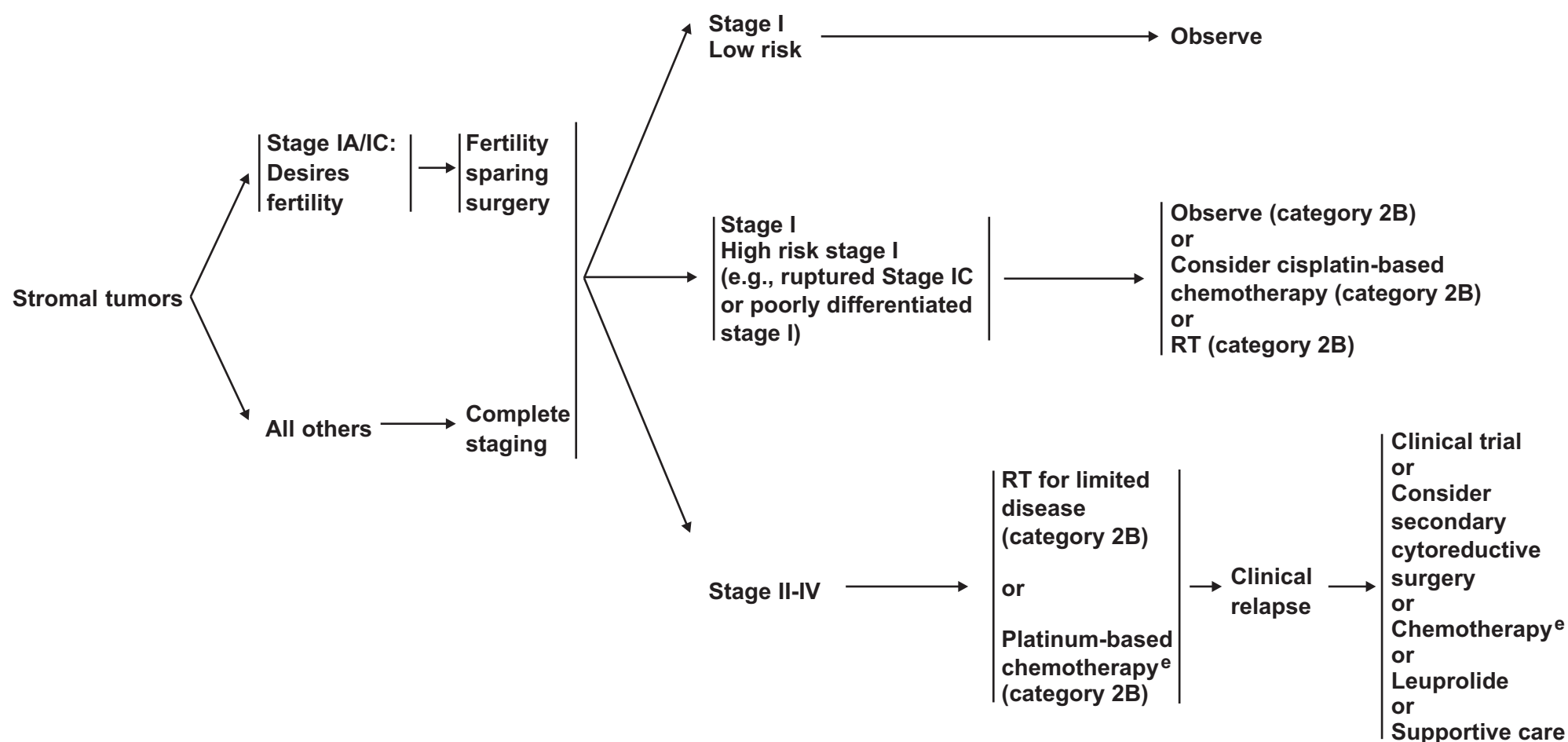
^cSee [LCOH-1 for markers](#).

^dPatients with recurrent or residual disease after multiple chemotherapeutic regimens for whom no curative options are considered possible may be treated with a recurrence regimen. See [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^d

^dPatients with recurrent or residual disease after multiple chemotherapeutic regimens for whom no curative options are considered possible may be treated with a recurrence regimen. [See LCOH-A.](#)

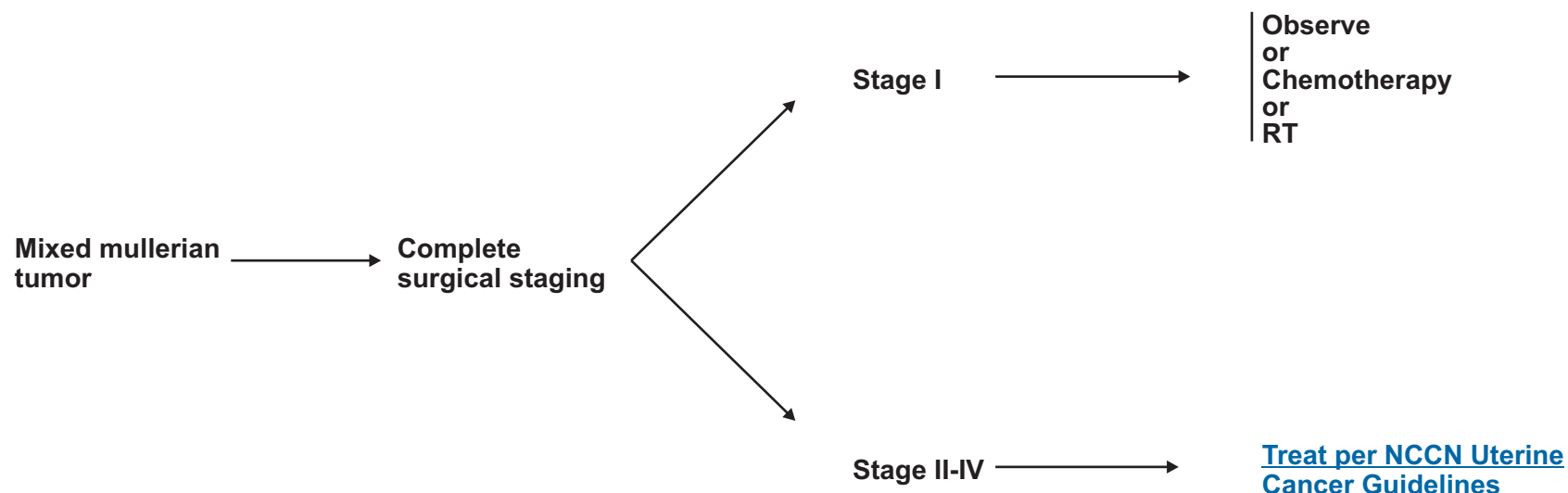
^eGerm cell or paclitaxel/carboplatin regimens are preferred.

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



[Go Back To Ovarian Cancer Table of Contents](#)

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 MODALITIES¹**Cisplatin/etoposide****TIP (paclitaxel/ifosfamide/cisplatin)****Docetaxel/carboplatin****VIP (etoposide, ifosfamide, cisplatin)****VeIP (vinblastine, ifosfamide, cisplatin)****VAC (vincristine, dactinomycin, cyclophosphamide)****Paclitaxel****Docetaxel****Radiation therapy****Supportive care****Leuprolide may be used as hormonal therapy for
granulosa cell tumors**[Go Back To Ovarian Cancer
Table of Contents](#)

¹These modalities are acceptable for palliation in patients for whom all potentially curative options have been exhausted. Patients with potentially curable recurrent disease should not be treated with these regimens, but rather should be referred to a tertiary care institution for potential treatment with high-dose chemotherapy.

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.

Summary of the Guidelines updates

Highlights of major changes in the 2006 version of the Ovarian Cancer guidelines from the 2005 version include:

- GI evaluation replaced barium enema/colonoscopy ([OV-1 and LCOH-1](#)).
- Under primary treatment, biopsy was added as an option for some patients ([OV-1](#)).
- Debulking was added as a consideration for Stage II, III, IV with no suspicion of residual disease ([OV-2](#)).
- Stage II was included with Stage III and IV and primary treatment for this group was clarified ([OV-3](#)).
- Footnote 'f' alternative regimens were updated ([OV-3](#)).
- Secondary adjuvant treatment for complete clinical remission was changed to delete WART and add specific paclitaxel treatment ([OV-4](#)).
- WART was added as a treatment option for negatively reassessed patients and hormonal therapy was deleted ([OV-4](#)).
- Imaging studies for recurrent disease were specified ([OV-5](#)).
- Clinical trials were added as an option for serially rising CA-125 levels ([OV-5](#)).
- Recurrent regimens for all stages were updated ([OV-6](#)).
- A list of special circumstances was added to The Principles of Primary Surgery ([OV-A](#)).
- Intestinal stents were added to Ancillary Palliative Surgical Procedures ([OV-B](#)).
- Anastrozole, bevacizumab, irinotecan and letrozole were added to recurrence modalities ([OV-C](#)).
- A footnote indicated that bowel perforation is a potential risk when using bevacizumab was added ([OV-C](#)).
- Additional tests were added to the workup ([LCOH-1](#)).
- Laparotomy was changed to "surgery" ([LCOH-1](#)).
- Structure of algorithm changed for primary treatment of germ cell tumors ([LCOH-2](#)).
- TIP or high-dose chemotherapy was added as a treatment option for persistently elevated markers ([LCOH-3](#)).
- PFT's were recommended when using bleomycin ([LCOH-3](#)).
- Etoposide/carboplatin was added as treatment for some Stage 2-4 dysgerminomas ([LCOH-3](#)).
- Treatment options for Stage 1 and for Stage 2-4 were updated ([LCOH-4](#)).
- Chemotherapy or RT were added as treatment options for mixed mullerian tumors ([LCOH-5](#)).
- TIP and paclitaxel/carboplatin were added as recurrence modalities ([LCOH-A](#)).

Staging

Table 1

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

Primary Tumor (T)

TNM	FIGO
-----	------

categories	stages
------------	--------

TX	Primary tumor cannot be assessed
-----------	----------------------------------

T0 No evidence of primary tumor

T1 | 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 other pelvic tissues. No malignant cells in ascites or peritoneal washings.

T2c IIC Pelvic extension (2a or 2b) with malignant cells in ascites or peritoneal washings

TNM

T3

111

and/or

N1

T3a IIIA Microscopic peritoneal metastasis beyond pelvis

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

and/or lymph node metastasis

N1

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.

Manuscript

NCCN Categories of Consensus

Category 1: There is uniform NCCN consensus, based on high-level evidence, that the recommendation is appropriate.

Category 2A: There is uniform NCCN consensus, based on lower-level evidence including clinical experience, that the recommendation is appropriate.

Category 2B: There is nonuniform NCCN consensus (but no major disagreement), based on lower-level evidence including clinical experience, that the recommendation is appropriate.

Category 3: There is major NCCN disagreement that the recommendation is appropriate.

All recommendations are category 2A unless otherwise noted.

Overview

Ovarian neoplasms consist of several histopathological entities, and treatment depends on the specific tumor type. Epithelial ovarian cancer comprises most malignant ovarian neoplasms; however, other pathologic subtypes (such as less common ovarian histopathologies) must be considered in guidelines describing treatment recommendations. These NCCN guidelines discuss epithelial ovarian cancer and less common ovarian histopathologies in separate sections of the document.

Epithelial ovarian cancer is the leading cause of death from gynecologic cancer in the United States and the country's fourth most common cause of cancer mortality in women. In the year 2005,

there will be an estimated 22,220 new diagnoses and an estimated 16,210 deaths from this neoplasm.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 two 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.

The NCCN Ovarian Cancer Guidelines reflect the importance of stage and grade of disease. 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 (see [Table 1](#)).

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 compre-

hensive 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 and/or ascites, abdominal distention, or symptoms without other obvious sources of malignancy should include an ultrasound or abdominopelvic computed tomography (CT) scan (if clinically indicated) after a complete physical examination and appropriate laboratory studies, including complete blood count (CBC), chemistry profile with liver function tests (LFTs), and a CA-125 determination.³ Patients with a family history of ovarian and/or breast cancer should also be considered for genetic counseling (see the [NCCN Genetics/Familial High Risk Assessment Guidelines](#)).

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 prior to 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. Often they have undergone cytoreductive surgery and been completely staged (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, absence of complete documentation of surgical stage). 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.

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). It is recommended (category 1) that a gynecologic oncologist perform the primary surgery based on published improved outcomes.^{4,5} For a young patient who wishes to maintain fertility, a unilateral salpingo-oophorectomy (USO) may be adequate for stage I tumors. In stage I disease, minimally invasive techniques may be considered to achieve the surgical goals (see [OV-A](#)); however, this remains a

controversial area and is not a standard approach. Laparoscopic surgery performed by an experienced gynecologic oncologist may be considered in select patients (category 2B).

The treatment recommendation continues to be cytoreductive surgery for patients having clinical stage II, III, or IV disease. Neoadjuvant chemotherapy followed by interval cytoreduction may be considered for patients with bulky stage II-IV disease who are not surgical candidates. The pathologic diagnosis should be confirmed, however, by fine-needle aspiration, biopsy, or paracentesis in this group of patients.

Incompletely Staged Patients. For patients with incomplete previous surgery or who were incompletely staged, there was consensus on the following treatment recommendations:

1. A surgical staging procedure is recommended for all patients with suspected stage IA, grade 1 or stage 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, grade 1 or stage IB, grade 1, if no residual disease is suspected, chemotherapy for 6 cycles is recommended. For patients with stage II-IV disease, consider debulking surgery after 3 cycles of chemotherapy if residual tumor is judged to be resectable. A completion surgical staging procedure (category 2B) 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, grade 2 or stage 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.

Primary Adjuvant Chemotherapy. Most patients with epithelial ovarian cancer will receive postoperative systemic chemotherapy. Observation, however, is recommended for patients with stage 1A or 1B, grade 1 tumors because survival is greater than 90% for surgical treatment alone.⁶ If observation (without the addition of chemotherapy) is considered for stage 1A or 1B, grade 2 tumors, a comprehensive surgical staging procedure is recommended for all patients.

For specific primary chemotherapy/primary adjuvant therapy, the preferred regimen is the combination of paclitaxel plus carboplatin.⁷ Docetaxel plus carboplatin⁸ or paclitaxel plus cisplatin are options for alternative regimens (category 2B).⁹ 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.

The recommended doses 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 six courses.⁷ Alternative regimens (category 2B) include (1) docetaxel, 60-75 mg/m² 1-hour intravenous infusion plus carboplatin, dosed at AUC of 5 to 6 every 3 weeks;⁸ 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.¹⁰

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,¹¹ whole-abdominopelvic radiotherapy is a primary adjuvant therapy option for patients with low-bulk disease (category 3). Results of a recent prospective trial¹² suggest that whole abdominal radiotherapy may be an option to be used as consolidation therapy in selected subgroups of patients following chemotherapy.

Other Areas of Controversy.

Intraperitoneal Cisplatin. The panel also discussed the role of intraperitoneal cisplatin, as opposed to intravenous cisplatin, based on the results of clinical trials of intraperitoneal chemotherapy in patients with stage III ovarian cancer.^{10,13} These studies suggest that intraperitoneal chemotherapy results in improved overall and progression-free survivals. The panelists felt that intraperitoneal therapy could be considered in low-volume, optimally debulked, stage III patients (category 2B).

Dose Intensity. Panel members also discussed the issue of dose intensity. Clinical trials are ongoing of high-dose chemotherapy, requiring 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. Panel members recommended that patients participate in these trials, but uniformly felt that high-dose chemotherapy that requires stem cell support is investigational and not part of the current practice guidelines.

Number of Chemotherapy Cycles. There was extensive discussion regarding the number of cycles of chemotherapy that should be recommended for patients with advanced-stage disease. There is no existing 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 recently gained support due to the results of GOG 178, which randomly assigned patients to 3 versus 12 months of further paclitaxel following initial chemotherapy.¹⁴ The results of this trial suggested that patients receiving 12 months of therapy sustained a progression-free survival advantage. Postremission chemotherapy is a category 2B recommendation.

Follow-up Recommendations

Stage I Disease. After the completion of primary surgery and chemotherapy in patients having stage I disease and poor prognostic features, the standard recommendation would be 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 should be tested every 12 months. In addition, a chemistry profile and a chest x-ray should be done if clinically indicated. Chest/abdominal/pelvic CT or positron emission tomography (PET) scans 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, as recommended in the [NCCN Genetics/Familial High-Risk Assessment Guidelines](#).

Stage II, III, or IV Disease. Patients with advanced-stage disease who have no evidence of progression of cancer following 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).

There was substantial disagreement among panel members regarding the further management of advanced-stage patients who are in complete clinical remission following their initial therapeutic regimen. Options range from observation alone, clinical trial, or additional chemotherapy¹⁴ (paclitaxel, category 2B), preferably in a controlled clinical trial. In addition, second-look laparotomy or laparoscopy and debulking after primary chemotherapy remain controversial in this group of patients (category 3).

If a 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; whole abdominal RT is an option in selected patients, although the panel disagreed about this option (category 3). If the second-look findings are positive and the patient is thought to have been responding to initial chemotherapy, then the same chemotherapy regimen may be continued. In some patients, however, the second-look surgical procedure will demonstrate non-response to initial chemotherapy. These patients should be treated with recurrence therapy.

Management of an Increasing CA-125 Level. There was extensive discussion regarding 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 symptoms of recurrent disease, following an evaluation which includes a negative pelvic examination and chest/abdominal/pelvic CT scan. Patients who have never received chemotherapy should be managed as newly diagnosed patients, undergo clinically appropriate imaging studies (including MRI, PET, or PET/CT [category 2B] if clinically appropriate) and surgical debulking, and be treated as described

under the primary chemotherapy/primary adjuvant chemotherapy guidelines.

After finding an elevated CA-125 level, the median time for a clinical relapse is 2 to 6 months. For patients who have received previous chemotherapy, there was a lack of consensus regarding the timing of recurrence therapy. Because tamoxifen has a defined response rate in recurrent disease following progression on cisplatin-based chemotherapy,¹⁵ it is frequently administered to patients who have only a rising CA-125 level¹⁶ as evidence of tumor progression. Consequently, the panel included tamoxifen as an acceptable recommendation for this clinical situation (category 2B). Other alternatives include observation until clinical symptoms arise (category 2B), the immediate institution of cytotoxic chemotherapy (category 2B), or clinical trial.

Recurrent Disease

The prognosis for those who progress without ever sustaining a clinical benefit on two consecutive chemotherapy regimens or whose disease recurs in less than 6 months is poor. The importance of clinical trials to identify agents active in this group was emphasized. Because these patients are primarily resistant to their 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.¹⁷ Treatment with a recurrence regimen is suggested¹⁸ or supportive care as outlined by the [NCCN Palliative Care Guidelines](#). Potential ancillary surgical and/or supportive care procedures for selected patients are summarized (see [OV-B](#)).

Patients whose disease relapses more than 6 months after initial chemotherapy are considered “platinum-sensitive” and have the

greatest number of potential options for second-line therapy. Recent evidence suggests that combination chemotherapy may be superior to single-agent therapy in this situation.¹⁹ Options include carboplatin/paclitaxel (category 1),¹⁹ gemcitabine/carboplatin,²⁰ or a recurrence regimen (category 2B).

For stage II, III, and IV patients with partial responses, recurrence chemotherapy regimens include single-agent therapy as described in the next section. 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).²¹ 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%;²² gemcitabine, 19%;²³ vinorelbine, 20%;^{24,25} liposomal doxorubicin, 26%;²⁶ and oral etoposide, 27% in platinum-resistant patients and 35% in platinum-sensitive patients.²⁷ Altretamine, with a 14% response rate,²⁸ and ifosfamide, with a 12% response rate,²⁹ 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,³⁰ 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.^{14,19} 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 continues to be a viable

therapeutic option. RT can also provide effective palliation when radiation ports are tailored to specific symptomatic disease sites.³¹

The NCCN panel felt that no single chemotherapeutic agent can 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 could 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 cycles of chemotherapy to determine the presence of potential clinical benefit. Patients who progress on two consecutive chemotherapy regimens without evidence of clinical benefits have diminished likelihood of benefiting 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 low malignant potential) identifies a primary epithelial ovarian tumor with specific histological characteristics suggesting malignancy but having a clinically excellent prognosis, with a 5-year survival exceeding 80%.³² The diagnostic pathologic characteristic of typical epithelial ovarian cancer consists of peritoneal implants, which microscopically and/or macroscopically invade the peritoneum. Borderline epithelial ovarian cancer is manifested by the gross appearance of peritoneal carcinomatosis but a microscopic appearance that characteristically fails to reveal evidence of frank invasion by the tumor nodules.

The appearance of invasive implants on the peritoneal surfaces portends a less favorable prognosis; therefore, treatment as for epithelial ovarian cancer (category 2B) (such as postoperative chemotherapy) can be considered for these patients.³³ 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.^{34,35} The benefit of postoperative chemotherapy has not been demonstrated for patients who have no microscopically demonstrable invasive implants.³⁶

Treatment

Treatment guidelines for borderline epithelial ovarian cancer depend on the histological and clinical characteristics, the age of the patient,³⁵ 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 low malignant potential. Patients having a low-malignant potential lesion who desire to maintain their fertility may undergo surgery limited to a unilateral oophorectomy 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 low malignant potential disease who were incompletely staged at the time of their initial laparotomy should undergo standard comprehensive staging for those having suspected residual disease and for those patients without suspected residual disease who have no desire to maintain fertility. Conversely, patients who are suspected of having no residual disease (suspected stage I) and desire to maintain fertility should be observed.

Follow-up

Treatment recommendations following comprehensive staging depend on the presence or absence of invasive implants. There was nonuniform consensus among the panel regarding the initial therapeutic approach for patients having invasive implants. These recommendations 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^{34,37} every 2 to 6 months for 2 years and every 3-6 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 complete blood count and chemistry profiles should be monitored as clinically indicated.

Patients who had chosen fertility-sparing surgery should be monitored by ultrasound examinations if necessary, and should be considered for exploratory surgery and standard debulking following the completion of childbearing (category 2B). All patients should be considered for a family history evaluation according to the [NCCN Genetics/Familial High Risk Assessment Guidelines](#).

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, mixed Müllerian tumors of the ovary (MMT),

carcinosarcoma), 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 of these tumors present at an early stage and 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 regarding 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. The recommended laboratory evaluation for a pelvic mass should include a comprehensive metabolic panel, complete blood count, magnesium level, 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 low malignant potential, or clinical stages I epithelial ovarian or stromal tumors.^{38,39} 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 mixed Müllerian tumor (carcinosarcoma) should undergo complete surgical staging as per the epithelial ovarian cancer guidelines.

Patients may have been referred to an NCCN institution after having been histologically confirmed to have an ovarian neoplasm of a less common type. The recommended initial surgical recommendation depends on the specific histologic diagnosis. Many times, patients have been completely staged (having met the standards for surgical staging of the Gynecologic Oncology Group [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 absence of documentation of surgical stage). The components of surgical staging are listed in the epithelial ovarian cancer guidelines.

Germ Cell Tumors

The recommended laboratory evaluation for germ cell tumors should include a comprehensive metabolic panel, complete blood count with platelets, magnesium level, lactic dehydrogenase, alpha-fetoprotein, and beta-HCG levels. Additionally, pulmonary function studies (category 2B) may be obtained. Fertility-sparing surgery should be considered for those desiring fertility preservation. Otherwise, complete staging surgery is recommended as initial surgery.

Patients found to have a stage I dysgerminoma or immature teratoma who have had complete surgical staging should be observed. If these patients have had incomplete surgical staging, then options include observation or a completion staging procedure (category 2B for both). 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.⁴⁰⁻⁴² Pulmonary function tests are recommended if considering the use of bleomycin.

Patients found to have embryonal or endodermal sinus tumors; stages

II-IV dysgerminoma; or stage I, grade 2-3 immature teratoma should receive chemotherapy for 3 to 4 cycles with BEP (category 2B for 3 versus 4 cycles).^{41,42} In select patients with stage IB-III dysgerminoma for whom minimizing toxicity is critical, three courses of etoposide/carboplatin can be used.⁴³ 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)⁴⁴ or high-dose chemotherapy (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 regimen (see [LCOH-A](#)), including CDDP (cisplatin)/etoposide, VIP (etoposide, ifosfamide, cisplatin), VeIP (vinblastine, ifosfamide, cisplatin), VAC (vincristine, dactinomycin, cyclophosphamide), RT, docetaxel, paclitaxel, or supportive care.

Ovarian Stromal Tumors

Patients with stage IA-C ovarian stromal tumors desiring to preserve their fertility should be treated with fertility sparing surgery. Otherwise, complete staging is recommended to 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, poorly differentiated tumor, tumor size greater than 10-15 cm⁴⁵), recommendations (all are category 2B) include observation, RT, or consider cisplatin-based chemotherapy.⁴⁶

For patients with stages II-IV tumors, recommended options (all are category 2B) include RT for limited disease or platinum-based chemotherapy (germ cell or paclitaxel/carboplatin regimens are preferred). For patients subsequently having a clinical relapse, options include clinical trial, supportive care, chemotherapy (germ cell or paclitaxel/carboplatin regimens are preferred), or leuprolide; these patients may also consider secondary cytoreductive surgery.

Mixed Müllerian Tumors (Carcinosarcoma)

After complete surgical staging, patients found to have stage I mixed Müllerian tumor (MMT) at the time of surgery have several options including observation, chemotherapy, or RT. Patients with stages II-IV MMT should be treated as per the [NCCN Uterine Cancer Guidelines](#) for uterine sarcoma.

Disclosures for the NCCN Ovarian Cancer Guidelines Panel

At the beginning of each panel meeting to develop NCCN guidelines, panel members disclosed the names of companies, foundations, and/or funding agencies from which they received research support; for which they participate in speakers' bureau, advisory boards; and/or in which they have equity interest or patents. Members of the panel indicated that they have received support from the following: American College of Radiology; Amgen Inc; Bristol Myers-Squibb; Cardinal Health; Cell Control Inc; Department of Defense; Eli Lilly; EMD Pharmaceuticals; Genentech Inc; GlaxoSmithKline; ImClone Systems Inc; InterMune; Merck & Co, Inc; National Cancer Institute; Novartis Pharmaceuticals; Ortho-McNeil Pharmaceutical, Inc.; Pfizer Inc; RTOG; Sanofi-Aventis; Schering-Plough; Unither Pharmaceuticals; and Wyeth. Some panel members do not accept any support from industry. The panel did not regard any potential conflicts of interest as sufficient reason to disallow participation in panel deliberations by any member.

References

1. Jemal A, Murray T, Ward E, et al. Cancer Statistics, 2005. *CA Cancer J Clin* 2005;55:10-30.
2. Ozols 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.
3. Im SS, Gordon AN, Buttin BM, et al. Validation of referral guidelines for women with pelvic masses. *Obstet Gynecol* 2005;105:35-41.
4. du Bois A, Quinn M, Thigpen T, et al. 2004 consensus statements on the management of ovarian cancer: final document of the 3rd International Gynecologic Cancer Intergroup Ovarian Cancer Consensus Conference (GCIG OCCC 2004). *Ann Oncol* 2005;16 Suppl 8:viii7-viii12.
5. Edwards BK, Brown ML, Wingo PA, et al. Annual report to the nation on the status of cancer 1975-2002, featuring population-based trends in cancer treatment. *J Natl Cancer Inst* 2005;97:1407-1427.
6. Young RC, Walton LA, Ellenberg SS, et al. Adjuvant therapy in stage I and stage II epithelial ovarian cancer. *N Engl J Med* 1990;322:1021-1027. &.
7. Ozols RF, Bundy BN, Greer BE, et al. Phase III trial of carboplatin and paclitaxel compared with cisplatin and paclitaxel in patients with optimally resected stage III ovarian cancer: a Gynecologic Oncology Group study. *J Clin Oncol* 2003;21:3194-3200.
8. Vasey PA, Jayson GC, Gordon A, et al. Phase III randomized trial of docetaxel-carboplatin versus paclitaxel-carboplatin as first-line chemotherapy for ovarian carcinoma. *J Natl Cancer Inst* 2004;96:1682-1691.
9. McGuire WP, Hoskins WJ, Brady MF, et al. Cyclophosphamide and cisplatin compared with paclitaxel and cisplatin in patients with stage III and stage IV ovarian cancer. *N Engl J Med* 1996;334:1-6.
10. Armstrong D, Bundy B, Wenzel L, et al. Intraperitoneal cisplatin and paclitaxel in ovarian cancer. *N Engl J Med* 2006;354:34-43.
11. Thomas GM. Radiotherapy in early ovarian cancer. *Gynecol Oncol* 1994;55(suppl):S73-79.
12. Sorbe B. Consolidation treatment of advanced (FIGO stage III) ovarian carcinoma in complete surgical remission after induction chemotherapy: randomized, controlled, clinical trial comparing whole abdominal radiotherapy, chemotherapy, and no further treatment. *Int J Gynecol Cancer* 2003;13:278-286.
13. Alberts DS, Liu PY, Hannigan EV, et al. Intraperitoneal cisplatin plus intravenous cyclophosphamide vs intravenous cisplatin plus intravenous cyclophosphamide for stage III ovarian cancer. *N Engl J Med* 1996;335:1950-1955.
14. Markman M, Liu PY, Wilczynski S, et al. Phase III randomized trial of 12 versus 3 months of maintenance paclitaxel in patients with advanced ovarian cancer after complete response to platinum and paclitaxel-based chemotherapy: a Southwest Oncology Group and Gynecologic Oncology Group trial. *J Clin Oncol* 2003;21:2460-2465.
15. Hatch KD, Beecham JB, Blessing JA, et al. Responsiveness of patients with advanced ovarian carcinoma to tamoxifen. *Cancer* 1991;68:269-271.

16. van der Velden J, Gitsch G, Wain GV, et al. Tamoxifen in patients with advanced epithelial ovarian cancer. *Int J Gynecol Cancer* 1995;5:301-305.
17. Fennelly D, Aghajanian C, Shapiro F, et al. Phase I and pharmacologic study of paclitaxel administered weekly in patients with relapsed ovarian cancer. *J Clin Oncol* 1997;15:187-192.
18. Markman M, Rothman R, Hakes T, et al. Second-line platinum therapy in patients with ovarian cancer previously treated with cisplatin. *J Clin Oncol* 1991;9:389-393.
19. Parmar MK, Ledermann JA, Colombo N, et al. ICON and AGO Collaborators. Paclitaxel plus platinum-based chemotherapy versus conventional platinum-based chemotherapy in women with relapsed ovarian cancer: the ICON4/AGO-OVAR-2.2 trial. *Lancet* 2003;361:2099-2106.
20. Rose PG. Gemcitabine reverses platinum resistance in platinum-resistant ovarian and peritoneal carcinoma. *Int J Gynecol Cancer* 2005;15:18-22.
21. Eisenkop SM, Friedman RL, Spirtos NM. The role of secondary cytoreductive surgery in the treatment of patients with recurrent epithelial ovarian carcinoma. *Cancer* 2000;88:144-153.
22. ten Bokkel Huinink W, Gore M, Carmichael J, et al. Topotecan vs paclitaxel for the treatment of recurrent epithelial ovarian cancer. *J Clin Oncol* 1997;15:2183-2193.
23. Lund B, Hansen OP, Theilade K, et al. Phase II study of gemcitabine (2', 2' -difluorodeoxycytidine) in previously treated ovarian cancer patients. *J Natl Cancer Inst* 1994;86:1530-1533.
24. Rothenberg ML, Liu PY, Wilczynski S, et al. Phase II trial of vinorelbine for relapsed ovarian cancer: a Southwest Oncology Group study. *Gynecol Oncol* 2004;95:506-512.
25. Bajetta E, Di Leo A, Biganzoli L, et al. Phase II study of vinorelbine in patients with pretreated advanced ovarian cancer: Activity in platinum-resistant disease. *J Clin Oncol* 1996;14:2546-2551.
26. Muggia FM, Hainsworth JD, Jeffers S, et al. Phase II study of liposomal doxorubicin refractory ovarian cancer: Antitumor activity and toxicity modification by liposomal encapsulation. *J Clin Oncol* 1997;15:987-993.
27. Rose PG, Blessing JA, Mayer AR, et al. Prolonged oral etoposide as second line therapy for platinum resistant (PLATR) and platinum sensitive (PLATS) ovarian carcinoma: A Gynecologic Oncology Group study. *J Clin Oncol* 1998;16:405-410.
28. Alberts DS, Jiang C, Liu PY, et al. Long-term follow-up of a phase II trial of oral altretamine for consolidation of clinical complete remission in women with stage III epithelial ovarian cancer in the Southwest Oncology Group. *Int J Gynecol Cancer* 2004;14:224-228.
29. Markman M, Hakes T, Reichman B, et al. Ifosfamide and mesna in previously-treated advanced epithelial ovarian cancer: Activity in platinum-resistant disease. *J Clin Oncol* 1992;10:243-248.
30. Monk BJ, Choi DC, Pugmire G, et al. Activity of bevacizumab (rhuMAB VEGF) in advanced refractory epithelial ovarian cancer. *Gynecol Oncol* 2005;96:902-905.
31. Corn BW, Lanciano RM, Boente M, et al. Recurrent ovarian cancer. Effective radiotherapeutic palliation after chemotherapy failure. *Cancer* 1994;74:2979-2983.

32. Barakat RR, Benjamin I, Lewis JL, et al. Platinum-based chemotherapy for advanced-stage serous ovarian carcinoma of low malignant potential. *Gynecol Oncol* 1995;59:390-393.
33. Gershenson DM, Silva EG. Serous ovarian tumors of low malignant potential with peritoneal implants. *Cancer* 1990;65:578-585.
34. Leake JF, Currie JL, Rosenshein NB, et al. Long-term follow-up of serous ovarian tumors of low malignant potential. *Gynecol Oncol* 1992;47:150-158.
35. Barnhill DR, Kurman RJ, Brady MF, et al. Preliminary analysis of the behavior of stage I ovarian serous tumors of low malignant potential: A Gynecologic Oncology Group study. *J Clin Oncol* 1995;13:2752-2756.
36. Sutton GP, Bundy BN, Omura GA, et al. Stage III ovarian tumors of low malignant potential treated with cisplatin combination therapy (a Gynecologic Oncology Group study). *Gynecol Oncol* 1991;41:230-233.
37. Kennedy AW, Hart WR. Ovarian papillary serous tumors of low malignant potential (serous borderline tumors): A long-term followup study, including patients with microinvasion; lymph node metastasis, and transformation to invasive serous carcinoma. *Cancer* 1996;78:278-286.
38. Ayhan A, Celik H, Taskiran C, et al. Oncologic and reproductive outcome after fertility-saving surgery in ovarian cancer. *Eur J Gynaecol Oncol* 2003;24:223-232.
39. Zanetta G, Bonazzi C, Cantu M, et al. Survival and reproductive function after treatment of malignant germ cell ovarian tumors. *J Clin Oncol* 2001;19:1015-1020.
40. Brown J, Shvartsman HS, Deavers MT, et al. The activity of taxanes compared with bleomycin, etoposide, and cisplatin in the treatment of sex cord-stromal ovarian tumors. *Gynecol Oncol* 2005;97:489-496.
41. Williams S, Blessing JA, Liao SY, et al. Adjuvant therapy of ovarian germ cell tumors with cisplatin, etoposide, and bleomycin: a trial of the Gynecologic Oncology Group. *J Clin Oncol* 1994;12:701-706.
42. Gershenson DM, Morris M, Cangir A, et al. Treatment of malignant germ cell tumors of the ovary with bleomycin, etoposide, and cisplatin. *J Clin Oncol* 1990;8:715-720.
43. Williams SD, Kauderer J, Burnett AF, et al. Adjuvant therapy of completely resected dysgerminoma with carboplatin and etoposide: a trial of the Gynecologic Oncology Group. *Gynecol Oncol* 2004;95:496-499.
44. Kondagunta GV, Bacik J, Donadio A, et al. Combination of paclitaxel, ifosfamide, and cisplatin is an effective second-line therapy for patients with relapsed testicular germ cell tumors. *J Clin Oncol* 2005;23:6549-6555.
45. Schumer ST, Cannistra SA. Granulosa cell tumor of the ovary. *J Clin Oncol* 2003;21:1180-1189.
46. Schneider DT, Calaminus G, Wessalowski R, et al. Ovarian sex cord-stromal tumors in children and adolescents. *J Clin Oncol* 2003;21:2357-2363.
- Recommended Readings**
- Alberts DS, Green S, Hannigan EV, et al. Improved therapeutic index of carboplatin plus cyclophosphamide versus cisplatin plus cyclophosphamide: Final report by the Southwest Oncology Group

of a phase III randomized trial in stage III and IV ovarian cancer. J Clin Oncol 1992;10:706-717. &

Bell JG, Brady M, Lage J, et al. A randomized phase III trial of three versus six cycles of carboplatin and paclitaxel as adjuvant treatment in early stage ovarian epithelial carcinoma: a Gynecologic Oncology Group Study [abstract]. Gynecol Oncol 2003;85:156.

Ozols RF, Bundy BN, Greer BE, et al. Phase III trial of carboplatin and paclitaxel compared with cisplatin and paclitaxel in patients with optimally resected stage III ovarian cancer: a Gynecologic Oncology Group study. J Clin Oncol 2003;21:3194-3200. &

Swenerton K, Jeffrey J, Stuart G, et al. Cisplatin-cyclophosphamide versus carboplatin-cyclophosphamide in advanced ovarian cancer: a randomized phase III study of the National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol 1992;10:718-726. &

Trimbos JB, Parmar M, Vergote I, et al. International Collaborative Ovarian Neoplasm trial 1 and Adjuvant Chemotherapy In Ovarian Neoplasm trial: two parallel randomized phase III trials of adjuvant chemotherapy in patients with early-stage ovarian carcinoma. J Natl Cancer Inst 2003;95:105-112.

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