National Comprehensive Cancer Network

Clinical Practice Guidelines in Oncology – v.1.2003

Ovarian Cancer

Version 1.2003

Continue

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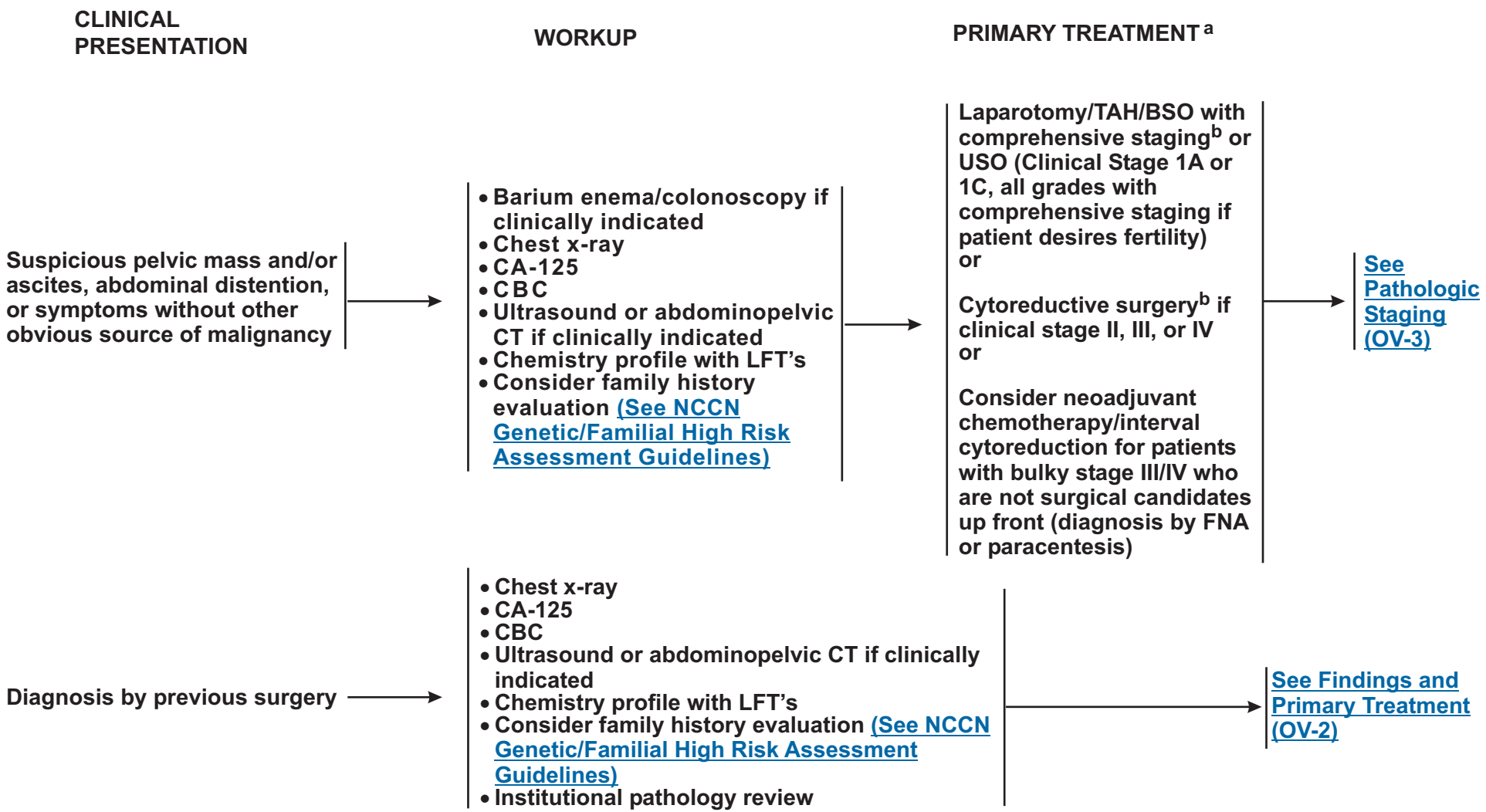
Clinical Trials: The NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

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

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

See NCCN Categories of Consensus

Epithelial Ovarian Cancer



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

[b] See Surgical Staging (OV-A).

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Epithelial Ovarian Cancer

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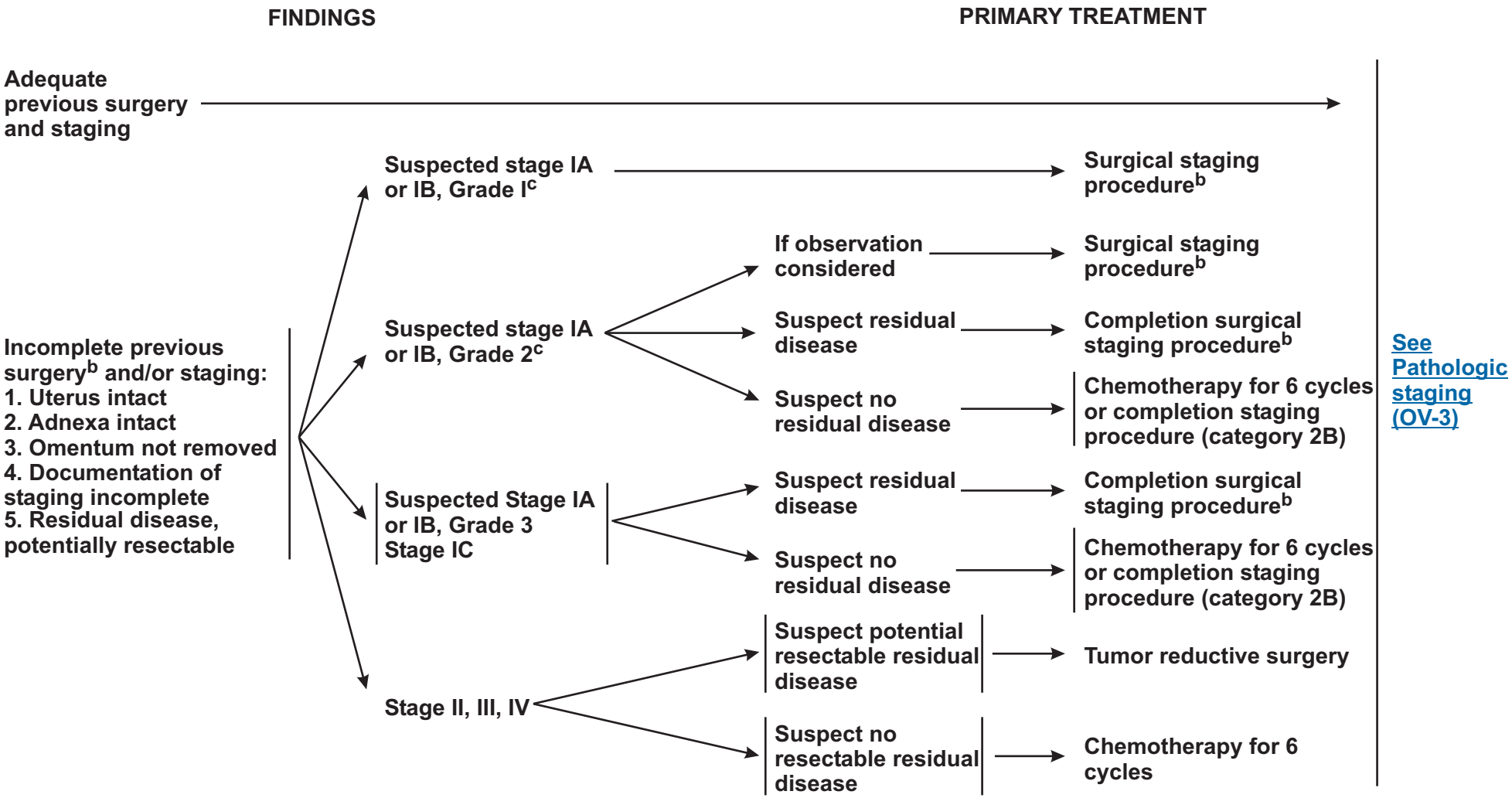
DIAGNOSIS BY PREVIOUS SURGERY



[b]See Surgical Staging (OV-A).

[c]Clear-cell pathology is grade 3.

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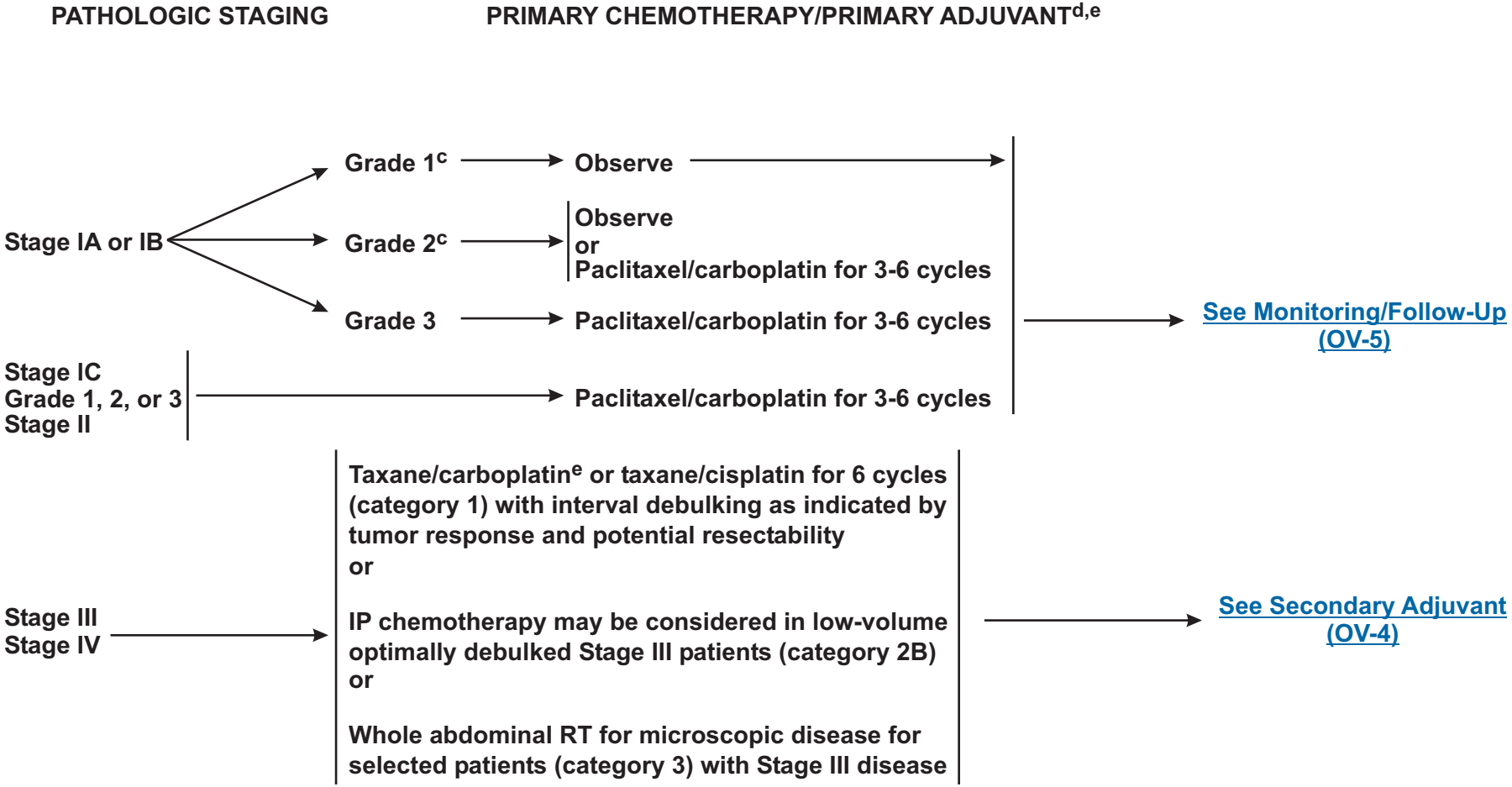
Epithelial Ovarian Cancer



[c]Clear-cell pathology is Grade 3.

[d]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 prior to each cycle of chemotherapy, if informative
5. Radiographic imaging if indicated

[e]Preferred regimens to be given for 6 cycles for Stage III/IV disease and for 3-6 cycles for lower stage disease (lesser number of courses preferred if possible to decrease toxicity):
1. Paclitaxel 175 mg/m^2 over 3 hours and carboplatin AUC 5.0-7.5 ever 3 weeks
2. Docetaxel 75 mg/m^2 over 1 hour and carboplatin AUC 5-6 every 3 weeks

Alternative regimen:
1. Paclitaxel 135 mg/m^2 over 24 hours and cisplatin 75 mg/m^2, every 3 weeks

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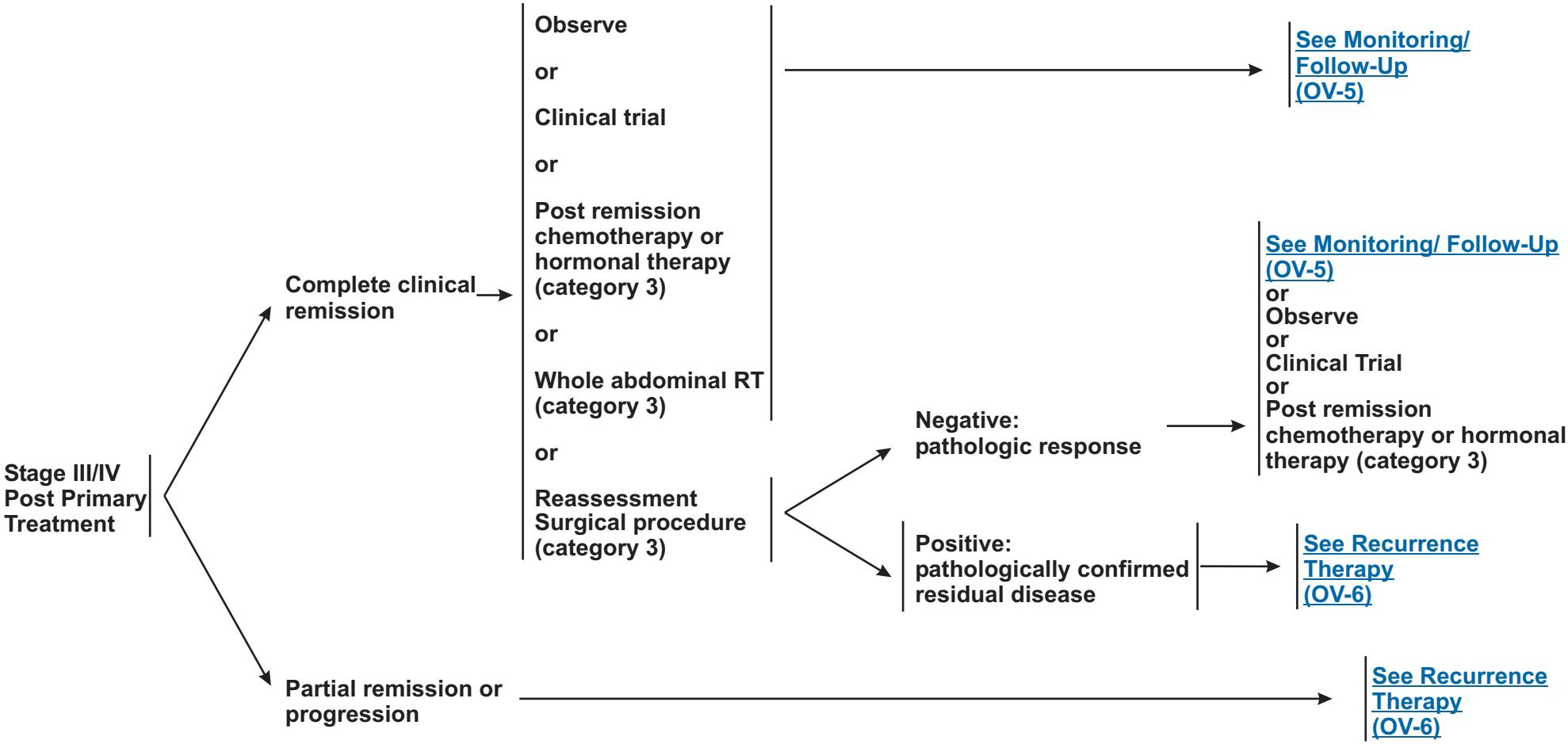
Epithelial Ovarian Cancer

SECONDARY ADJUVANT



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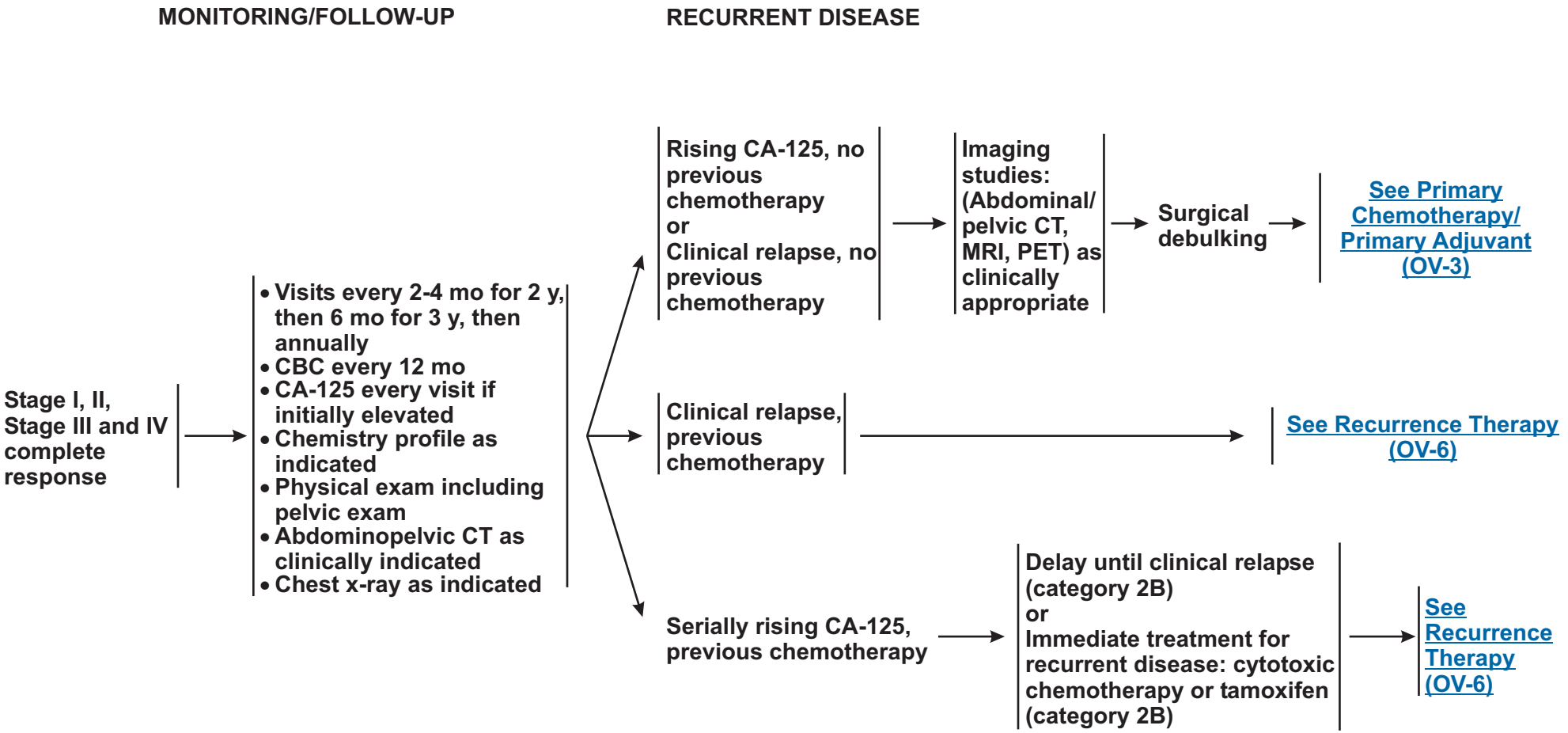
Epithelial Ovarian Cancer



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RECURRENCE REGIMEN[f,g,h]

Progression or stable disease on primary chemotherapy

or

Complete remission and relapse <6 mo after stopping chemotherapy

→ **Supportive care or Recurrence regimen[f,h]**

Stage III and IV with partial response →

Taxane or platinum
or Taxane + platinum
or Recurrence chemotherapy[f,h]
or Intraperitoneal therapy
or Whole-abdominopelvic RT in select patients with stage III disease (category 3)

Complete remission and relapse >6 mo after stopping chemotherapy →

Taxane or platinum or taxane + platinum
or Recurrence regimen[f,h]

Clinically low-volume or focal recurrence after disease-free interval 6 mo or greater →

Consider secondary cytoreductive surgery
or
Recurrence therapy → **Recurrence therapy[h]**

See NCCN Palliative Care Guidelines

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

[g] See Ancillary Palliative Surgical Procedures (OV-B).

[h] See Acceptable Recurrence Modalities (OV-C).

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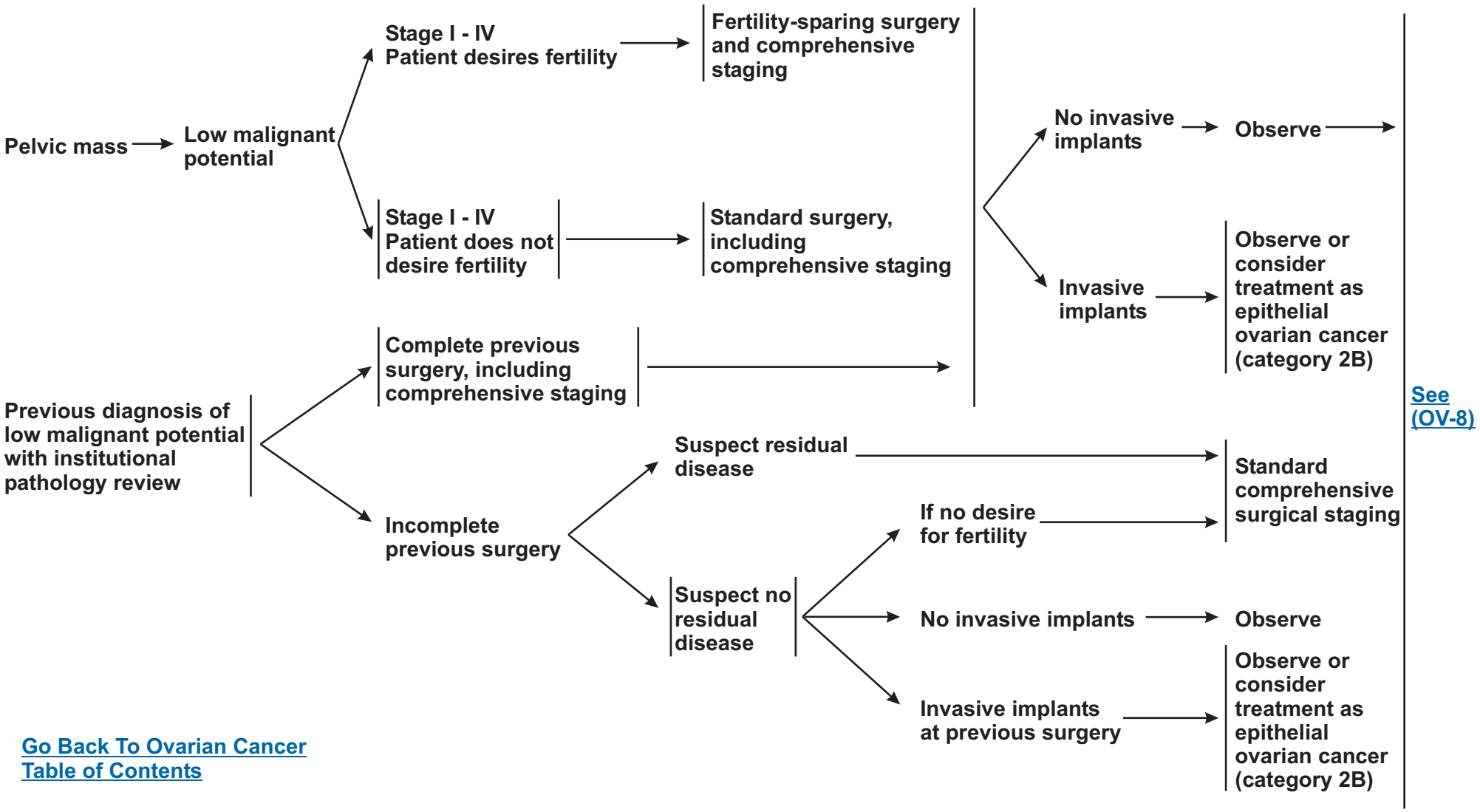
Borderline Epithelial Ovarian Cancer (Low Malignant Potential)



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Borderline Epithelial Ovarian Cancer (Low Malignant Potential)

MONITORING/FOLLOW-UP

- Visits every 2-4 mo for 2 y, then every 6 mo for up to 10 yrs
- 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 (catergory 2B)
- Consider family history
  (See NCCN Genetic/Familial High Risk Assessment Guidelines)

→ Clinical Relapse → Surgical evaluation + debulking if appropriate

- No invasive disease → Observe
- Invasive disease → Consider treatment as epithelial ovarian cancer (category 2B)

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PRINCIPLES OF PRIMARY SURGERY [1]

In general, a vertical incision should be used.[2]
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 intestinal 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 the level of the left renal hilus.**
- **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.**

[1]All procedures may not be indicated in all patients.
[2]However, in Stage I disease, minimally invasive techniques may be used to achieve the above.

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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*, 2nd ed, chap 32, pp 939-941. Philadelphia, Lippincott Williams & Wilkins, 1997.

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ANCILLARY PALLIATIVE SURGICAL PROCEDURES*

- Paracentesis
- Thoracentesis/pleurodesis/video-assisted thorascopy
- Ureteral stents/nephrostomy
- Surgical relief of intestinal obstruction
- Enteral feeding tube
- Gastrostomy tube
- Vascular access device

* These may be appropriate in select patients

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Ovarian Cancer

ACCEPTABLE RECURRENCE MODALITIES

Tamoxifen	**Topotecan**	**Gemcitabine**
Oral Etoposide	**Altretamine**	**Alkylating agent**
Vinorelbine	**Liposomal Doxorubicin**	**Radiation therapy**
Taxane	**Platinum compound**	

[1]Platinum-based combination therapy can be considered

[1]Patients 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.

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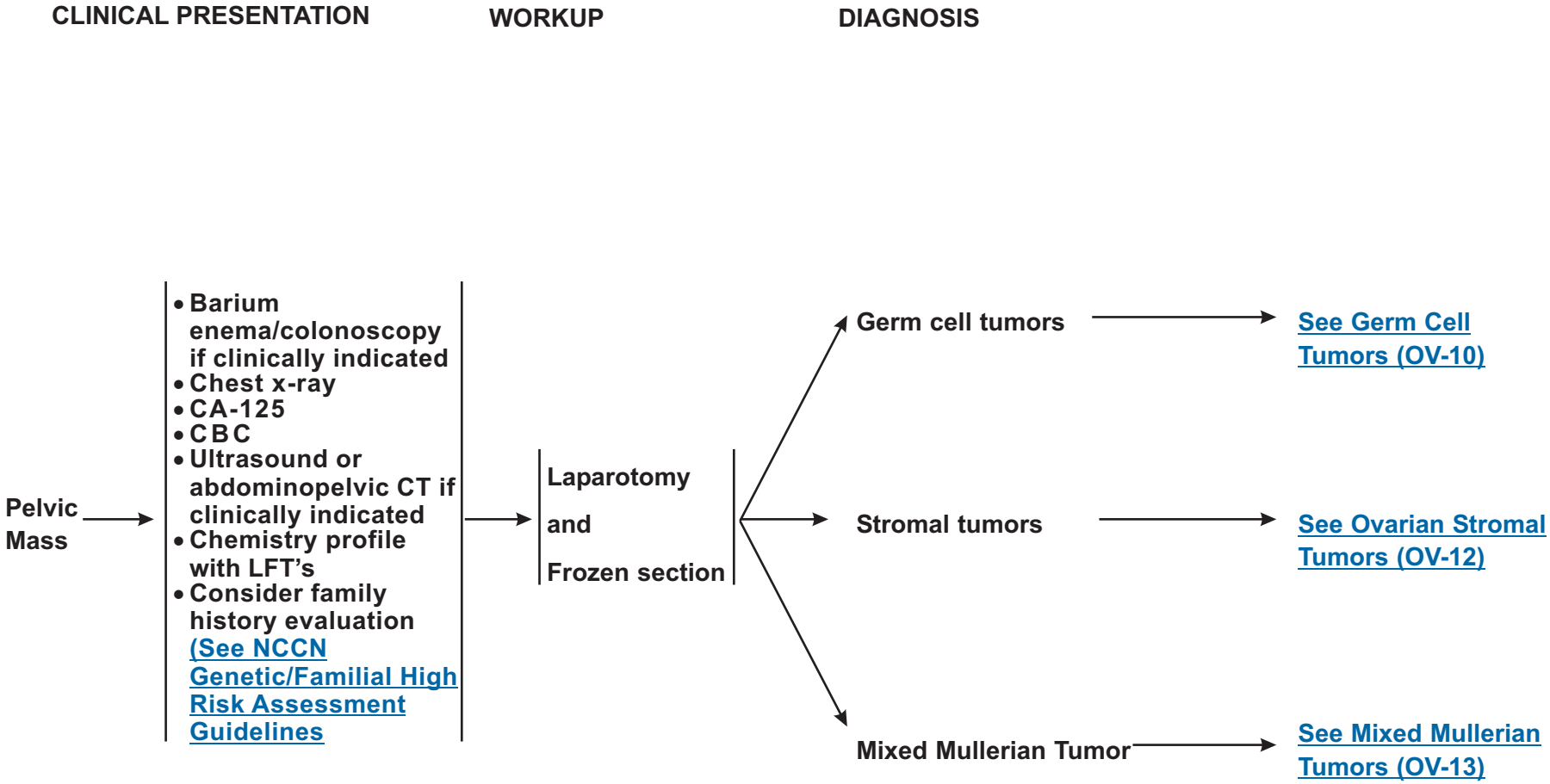
Less Common Ovarian Histopathologies



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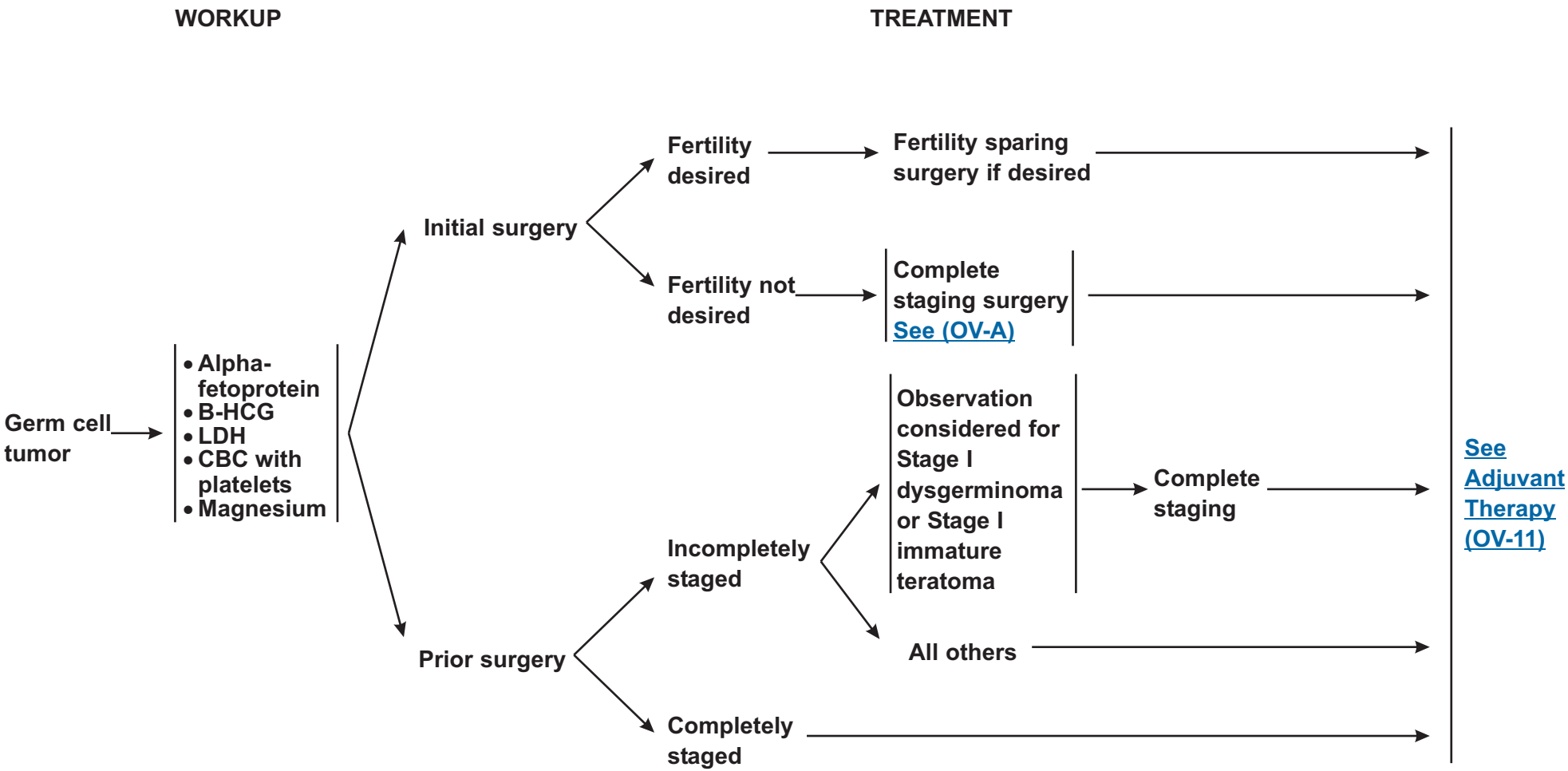
Germ Cell Tumors



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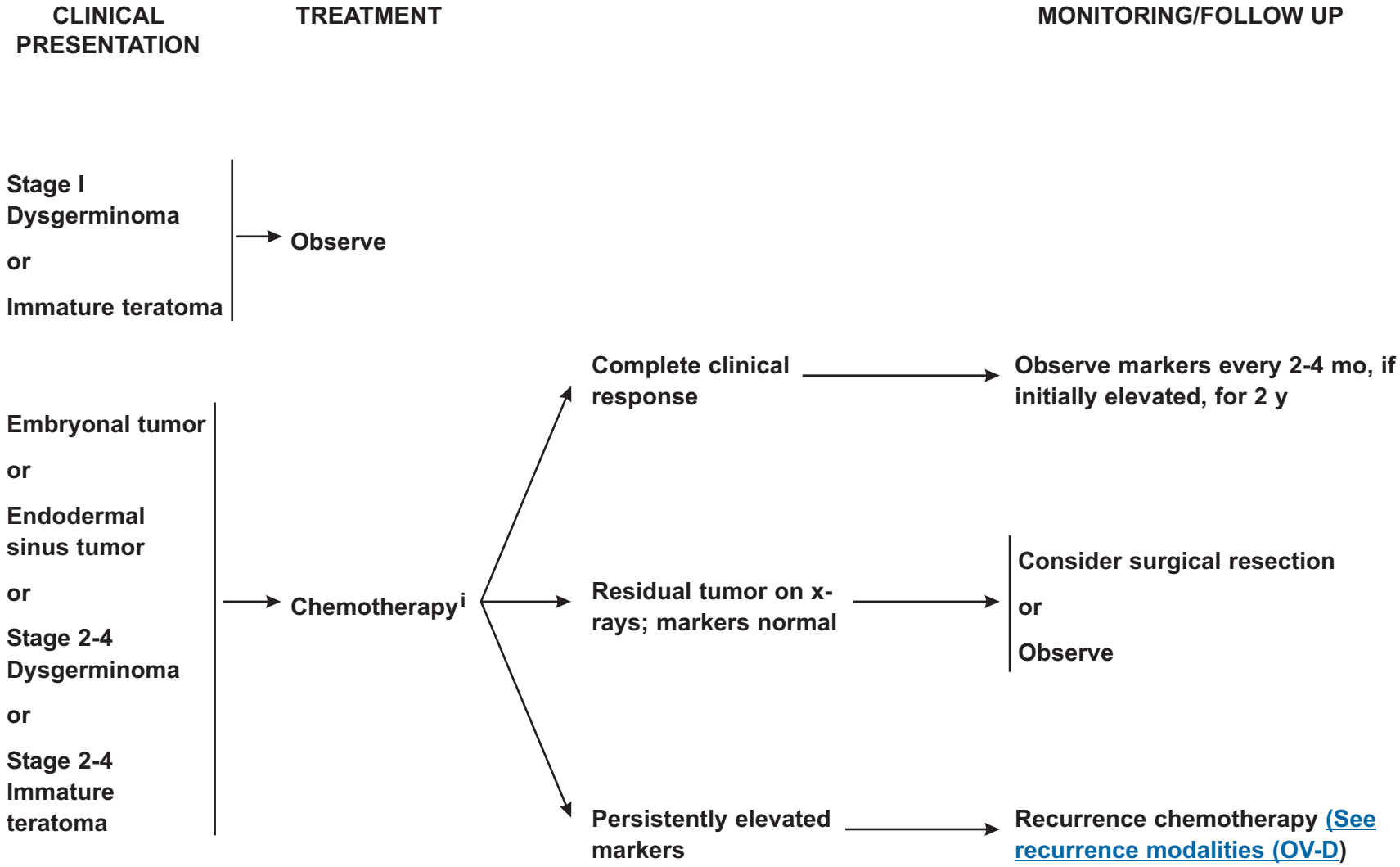
Germ Cell Tumors



[i]BEP (Bleomycin, Etoposide, Cisplatin) for three cycles.

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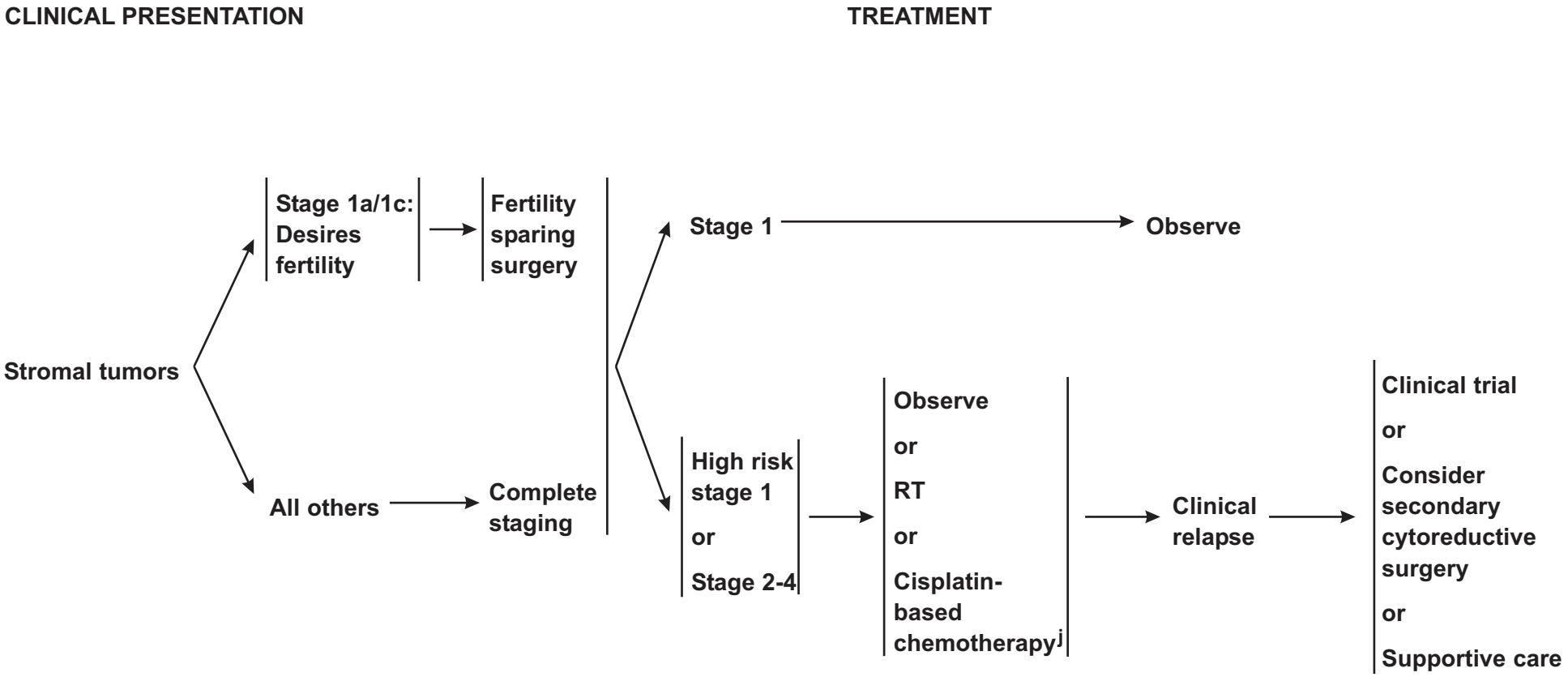
Ovarian Stromal Tumors



[j]Germ cell regimens are preferred.

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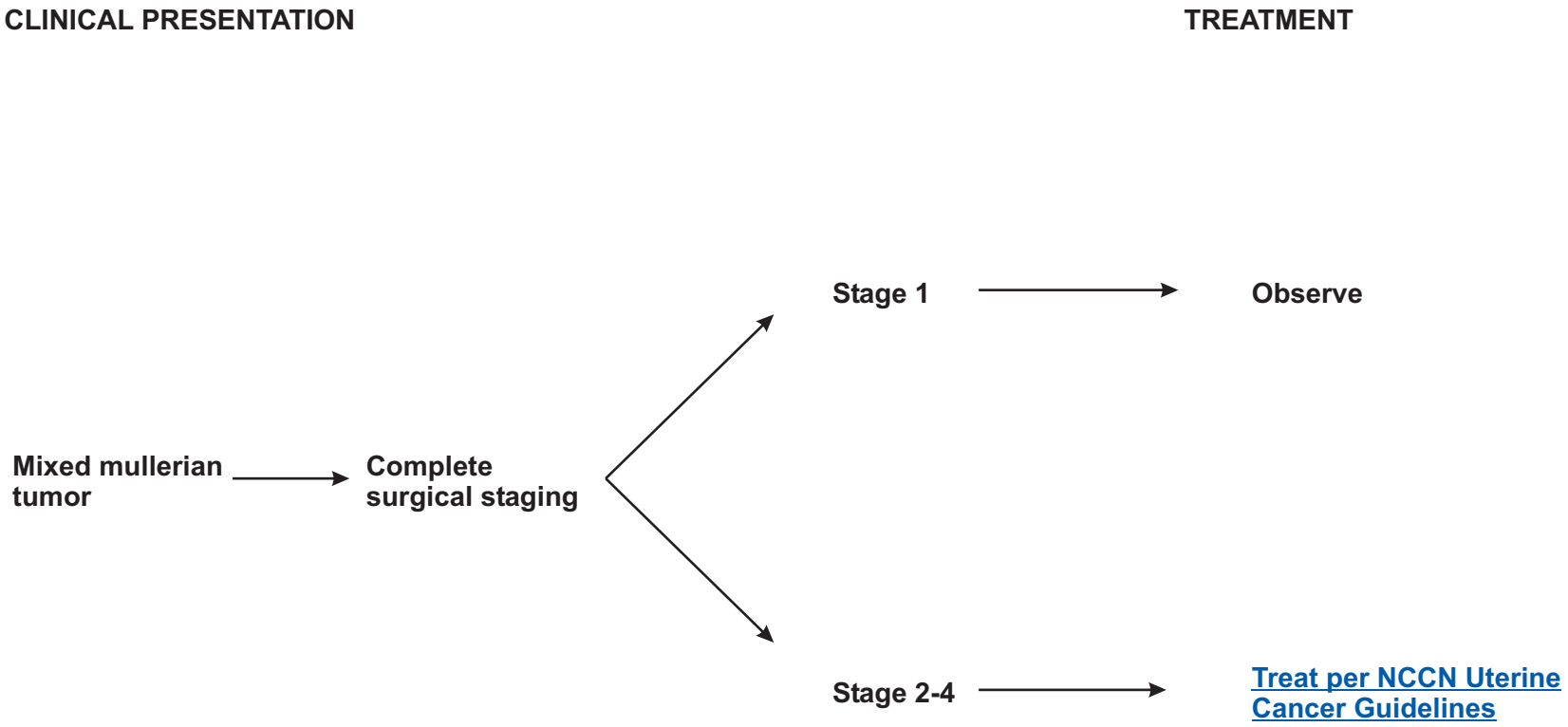
Mixed Mullerian Tumors (Carcinosarcoma)



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Less Common Ovarian Histopathologies

ACCEPTABLE RECURRENCE MODALITIES

- Clinical trial
- Cisplatin/Etoposide
- VIP (etoposide, ifosfamide, cisplatin)
- VeIP (vinblastine, ifosfamide, cisplatin)
- VAC (vincristine, dactinomycin, cyclophosphamide)
- Taxanes
- Radiation therapy
- Supportive care

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Staging

Table 1

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

Primary Tumor (T)

TNM Categories	FIGO Stages	
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 orT 2b) with malignant cells in ascites or peritoneal washings
T3	III	Tumor involves one or both ovaries with microscopically confirmed peritoneal metastasis outside the pelvis
T3a	IIIA	Microscopic peritoneal metastasis beyond pelvis (no macroscopic tumor)
T3b	IIIB	Macroscopic peritoneal metastasis beyond pelvis 2 cm or less in greatest dimension
T3c	IIIC	Peritoneal metastasis beyond pelvis more than 2 cm in greatest dimension and/or regional lymph node metastasis
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 I	T1	N0	M0
Stage IA	T1a	N0	M0
Stage IB	T1b	N0	M0
Stage IC	T1c	N0	M0
Stage II	T2	N0	M0
Stage IIA	T2a	N0	M0
Stage IIB	T2b	N0	M0
Stage IIC	T2c	N0	M0
Stage III	T3	N0	M0
Stage IIIA	T3a	N0	M0
Stage IIIB	T3b	N0	M0
Stage IIIC	T3c	N0	M0
	Any T	N1	M0
Stage IV	Any T	Any N	M1

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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

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 2003, there will be an estimated 25,400 new diagnoses and an estimated 14,300 deaths from this neoplasm (Jemal et al, 2003). 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 (Ozols et al, 1997).

Epidemiologic studies have identified risk factors as important in the etiology of ovarian cancer. A history of pregnancy with age at first birth 25 years or younger, the use of oral contraceptives, and/or breast-feeding confers a 30% to 60% decreased risk (Ozols et al, 1997). Conversely, nulliparity or age at first birth older than 35 years confers an increased risk. 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 (Ozols et al, 1997). Environmental factors have been investigated, but so far have not been conclusively associated with the development of this neoplasm.

The basic structure of the ovarian cancer guidelines has not changed since their 1997 publication. The guidelines continue to reflect the importance of stage and grade of disease. Ovarian cancer is classified primarily as stage I, II, III, or IV. In the past year, there have not been any significant changes in the TNM and FIGO (International Federation of Gynecology and Obstetrics) staging system for ovarian cancer (ST-1, ST-2).

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 with stage I, grade 1 tumors, in whom survival is greater than 95% following comprehensive laparotomy, patients in all other stages of ovarian cancer should be encouraged to enter clinical trials for both primary and recurrence therapy.

Recommended Work-up

The NCCN ovarian cancer guidelines begin with the management of an undiagnosed pelvic mass or a prior diagnosis of a malignant epithelial ovarian tumor. Many such patients come to NCCN member institutions after having had previous surgery at other institutions.

Undiagnosed Pelvic Mass

There was general agreement on the primary work-up of a patient with an undiagnosed pelvic mass, and there have not been any significant changes made to the previous guidelines. The standard work-up for such patients 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 (LFT's), and a CA 125 determination, have been completed. Patients having a family history of ovarian and/or breast cancer should also be considered for consultation by Clinical Cancer Genetics. (see the NCCN Genetics/Cancer Screening Guidelines).

While there continues to be 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 colonoscopy or barium studies of the gastrointestinal tract, are not routinely recommended, although they could prove useful in specific clinical situations.

Prior Diagnosis of Malignancy

Patients are often referred to NCCN institutions 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" staging (eg uterus and/or adnexa intact, omentum not removed, or absence of complete documentation of surgical stage). The components of surgical staging are listed in (OV-A). Identical work-up procedures are recommended to 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). For a young patient who wants to maintain fertility, a unilateral salpingo-oophorectomy (USO) may be adequate for stage I tumors.

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

Incompletely Staged Patients

Recommendations regarding the treatment of incompletely staged patients continue to generate discussion. There was consensus on the following three treatment possibilities:

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 and 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 six cycles is recommended. 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 (Category 2B).

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.

Primary Adjuvant Chemotherapy

The majority of patients with epithelial ovarian cancer will receive postoperative systemic chemotherapy. Observation, however, is recommended for patients with Stage 1A or IB, Grade 1 tumors, as survival is greater than 90% for surgical treatment alone (Young et al, 1990). Some disagreement continues regarding stage IA or IB, grade 2 tumors. If residual disease is suspected, or observation without the addition of chemotherapy is considered as definitive therapy, a completion surgical staging procedure is recommended for all patients. If no residual disease is suspected, surgical staging is an option, or, alternatively, patients may be treated with six cycles of chemotherapy. For patients with higher-grade and/or higher-stage tumors, systemic chemotherapy is indicated following appropriate surgery for potentially resectable disease.

The recommendations for specific primary chemotherapy/primary adjuvant therapy have been changed from previous guidelines. Regimens including paclitaxel plus carboplatin or docetaxel plus carboplatin are considered preferred regimens. These combinations have been shown to exhibit comparable toxicity (Vasey, 2002). Paclitaxel plus cisplatin remains an alternative regimen (Bookman et al, 1996; McGuire et al, 1996; Vasey et al, 2001)). Recommendations for the number of cycles of treatment vary with the stage of the disease. For patients with advanced-stage disease (Stages III or IV), six cycles of chemotherapy are recommended (Category 1), whereas for earlier-stage disease, three to six cycles are recommended, pending the results of an ongoing GOG study in this group of patients.

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/m^2 given over 3 hours. Alternative regimens include cisplatin, 75 mg/m^2 plus paclitaxel, 135 mg/m^2 given over 24 hours, or carboplatin, dosed at an area under the curve (AUC) of 5 to 6 plus docetaxel, 75 mg/m^2.

Radiation Therapy

There was a debate among the panel members regarding the role of whole abdominal radiation therapy in patients with low-bulk stage III or IV disease. Based primarily on historical data (Thomas, 1994), whole-abdominopelvic radiotherapy was listed as a primary chemotherapy/primary adjuvant therapy option for patients with low-bulk disease (Category 3).

Other Areas of Controversy

Intraperitoneal (IP) Cisplatin: The panel also considered the role of IP cisplatin, as opposed to intravenous (IV) cisplatin, based upon the results of recent clinical trials of IP chemotherapy in patients with stage III ovarian cancer (Alberts et al, 1996, 2002). These studies suggest that IP chemotherapy may result in improved overall or progression-free survivals. The panelists felt that IP 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 have begun recently of high-dose

chemotherapy, requiring peripheral blood stem cell transplantation in selected patients with previously untreated ovarian cancer, or as a consolidation strategy following 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 be considered investigational, and not part of the current practice guidelines.

Number of Chemotherapy Cycles: There was considerable 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 six cycles of combination chemotherapy are required for initial chemotherapy. However, the role of maintenance therapy in patients who achieve a complete remission after six cycles of chemotherapy has recently gained support due to the results of GOG 178, which randomized patients to three versus twelve months of further paclitaxel following initial chemotherapy. The results of this trial suggested that patients receiving twelve months of therapy sustained a progression-free survival advantage. Because of the preliminary nature of these results, however, post-remission chemotherapy is not considered a definitive recommendation.

Follow-up Recommendations

Stage I and Stage II Disease

Following the completion of primary surgery and chemotherapy in patients having stages I or II disease and poor prognostic features, the standard recommendation would be observation with follow-up. Monitoring should include a history and physical exam 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 considered if clinically indicated. No role has been established for routine abdominopelvic CT scans in this group of patients, but these 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. A consultation with Clinical Cancer Genetics is recommended if a family history suggests a genetic syndrome, as recommended in the NCCN Genetics/Cancer Screening Guidelines.

Stage III and Stage IV Disease

Patients with advanced-stage disease who have no evidence of progression of cancer following initial treatment should undergo a clinical reevaluation after six cycles of chemotherapy. Patients who progress during initial therapy should be treated with second-line approaches (“recurrence therapy”).

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 to additional chemotherapy (Markman et al, 2003) or hormonal therapy (Category 3), preferably in a controlled clinical trial. Consolidation therapy with whole abdominal radiotherapy (Category 3) has been shown to have potential therapeutic value, however, should not be considered standard (Pickel et al, 1999). In addition, the roles of 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. 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 a Rising CA125 Level

There was considerable discussion regarding the management of patients in a clinical complete remission who, during routine monitoring and follow-up, are found to have a rising CA 125 level but no symptoms of recurrent disease, following an evaluation which includes a negative pelvic examination, and abdominopelvic CT scan. Patients who have never received chemotherapy should be managed as newly diagnosed patients, undergo clinically appropriate imaging studies and surgical debulking, and be treated as described under the primary chemotherapy/primary adjuvant chemotherapy guidelines.

The median time for a clinical relapse following the finding of an elevated CA 125 level 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 (Hatch et al, 1991), it is frequently administered to patients who have only a rising CA 125 level (van der Velden et al, 1995) 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) and the immediate institution of cytotoxic chemotherapy (Category 2B).

Recurrent Disease

The prognosis for those who progress on primary chemotherapy or whose disease recurs in less than six months is extremely poor. In light of this fact, panel members recommended several ancillary surgical and supportive care procedures for selected patients (OV-B). The importance of clinical trials to identify agents active in this group was also emphasized. Since these patients are primarily resistant to their induction regimen, retreatment with a platinum compound or paclitaxel is not recommended, although recent clinical trials suggest that altering the schedule of paclitaxel may produce secondary responses (Fennelly et al, 1997). Treatment with a recurrence regimen is suggested (Markman et al, 1991) or supportive care as outlined by the NCCN Palliative Care Guideline.

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 (OV-C). Recent evidence suggests that combination chemotherapy may be superior to single-agent therapy in this situation (Parmar et al, 2003) although sequential therapy may provide the same results; many of these patients are treated with the combination that produced their initial remission. Alternatively, patients can be treated with a single-agent taxane or platinum and then crossed over to the other agent as dictated by clinical response. Additionally, there is no evidence that retreatment with a taxane or a platinum compound in patients with chemotherapy-sensitive recurrent ovarian cancer that recurs is superior to using newer agents as the first chemotherapy option for recurrent disease.

For stage III and IV patients with partial responses, recurrence regimens include single agent therapy or a combination of a taxane and a platinum, recurrence chemotherapy (OV-C), or intraperitoneal

therapy. The recommendation for whole abdominal radiotherapy (Category 3) in lieu of chemotherapy for patients with small-volume residual disease or recurrent disease remained controversial among panel members (Schray et al, 1988).

Secondary cytoreductive surgery or recurrence therapy was endorsed for patients who have a low-grade or focal recurrence after a long disease-free interval (Hoskins et al, 1989). The exact length of the disease-free interval has not been established, although there was a consensus among panel members that it should be at least 6 months for surgery to be considered.

Acceptable Recurrence Modalities

In the last 8 years, the efficacy of several newer agents in ovarian cancer has been described. The activity of the following agents appears to be similar: topotecan, 20% (ten Bokkel Huinink et al, 1997); gemcitabine, 19% (Lund et al, 1994); vinorelbine, 20% (Bajetta et al, 1996); liposomal doxorubicin, 26% (Muggia et al, 1997); and oral etoposide, 27% in platinum-resistant patients and 35% in platinum-sensitive patients (Rose et al, 1992). Altretamine, with a 14% response rate (Vergote et al, 1992), and ifosfamide, with a 12% response rate (Markman et al, 1992), have also been proven to be active in recurrent ovarian cancer, although less information regarding their use in paclitaxel-refractory patients is available. 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. Radiation therapy can also provide effective palliation when radiation ports are tailored to specific symptomatic disease sites (Corn et al, 1994).

Most patients in the GOG Phase II trial of etoposide (Rose et al, 1992) had previously received therapy with paclitaxel, making these results particularly relevant to the management of those whose initial therapy consisted of paclitaxel plus a platinum compound. Gemcitabine has been shown to be synergistic with platinum in ovarian cancer cell lines and treatment with platinum-based combinations can also be considered. Liposomal doxorubicin is associated with a prolonged survival (progression-free survival, 5.7 months; and median survival, 11 months) in heavily pre-treated patients.

The panel felt that no single chemotherapeutic agent should be considered 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 two cycles of chemotherapy to determine the presence of potential clinical benefit. Patients experiencing two successive therapeutic failures should be offered supportive care or a clinical trial if further therapy is desired.

Borderline Epithelial Ovarian Cancer

Diagnosis

Borderline epithelial ovarian cancer (also known as epithelial ovarian cancer of low malignant potential) identifies a tumor whose histological characteristics suggest malignancy, but whose clinical behavior is known to confer an excellent prognosis (Fort et al, 1989), with a 5-year survival exceeding 80% (Barakat et al, 1995). 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 and postoperative chemotherapy can be considered for these patients (Gershenson and Silva, 1990). 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 (Leake et al, 1992; Barnhill et al, 1995). The benefit of postoperative chemotherapy has not been demonstrated for patients who have no microscopically demonstrable invasive implants (Sutton et al, 1991; Trope et al, 1993).

Treatment

Treatment guidelines for this tumor depend on the histological and clinical characteristics, the age of the patient (Barnhill et al, 1995), 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 orchiectomy 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 (OV-A).

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 (Leake et al, 1992; Kennedy and Hail, 1996) every 2 to 4 months for 2 years and every 6 months for 3 years followed by annual evaluations after five years. 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 as considered necessary, and 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/Cancer Screening 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; those without invasive implants should be observed or enrolled in a clinical trial.

Guidelines for the Treatment of Less Common Ovarian Histopathologies

Overview

Ovarian tumors of less common histopathologies for which these guidelines have been outlined include germ cell neoplasms, mixed Mullerian tumors of the ovary (MMT, carcinosarcoma) and ovarian stromal tumors. These tumors account for approximately 37% 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 Work-up

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 unconfirmed pelvic mass should undergo evaluation and staging as per OV-1 of the NCCN Epithelial Ovarian Cancer Guidelines. Patients desiring to potentially maintain fertility should have an intraoperative frozen section evaluation. Fertility-sparing surgery may be considered (if technically feasible) if the frozen section results are germ cell tumor, ovarian cancer of low malignant potential, clinical stages IA/C epithelial ovarian cancer or stromal tumors (Ayhan et al, 2003; Zanetta et al, 2001). Patients not desirous of preserving fertility, or those who have a clinical stage II, III, or IV epithelial ovarian cancer or stromal tumor, or those with Mixed Mullerian Tumor (carcinosarcoma) should under complete surgical staging as per OV-A of the NCCN 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 OV-A of the NCCN 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.

Patients found to have a Stage I Dysgerminoma or Immature Teratoma who have had complete surgical staging according to OV-A should be observed. Patients who have had incomplete surgical staging for whom observation without chemotherapy is being considered should undergo a completion staging procedure. If there is no evidence of disease, these patients may be observed. If tumor is found, patients should then receive platinum/etoposide/bleomycin (BEP) for three cycles in the post-operative period (Williams et al, 1994; Gershonson et al, 1990).

Patients found to have stages II-IV immature teratoma or dysgerminoma, or embryonal or endodermal sinus tumors should receive chemotherapy for three cycles with BEP. Patients achieving a complete clinical response should be observed clinically every 2-4

months with AFP and Beta-HCG levels (if initially elevated) for two years. For patients having radiographic evidence of residual tumor but with normal AFP and BHCG, consideration should be given to surgical resection of the tumor; observation can be considered. Patients having persistently elevated AFP and/or BHCG following chemotherapy, (or who relapse with these markers elevated) or with clinically or radiographically evident disease, should receive recurrence chemotherapy. Acceptable recurrence regimens include clinical trial enrollment, Cisplatin/etoposide, VIP, VeIP, VAC, radiation therapy, or supportive care, and can be found on page OV-D.

Mixed Mullerian Tumors (Carcinosarcoma)

Following complete surgical staging, patients found to have Stage I mixed Mullerian tumor (MMT) at the time of surgery should be observed. Patients having Stages II-IV MMT should be treated as per the NCCN UterineSarcoma Guidelines.

Ovarian Stromal Tumors

Patients found to have Stage I ovarian stromal tumors following complete surgery should be observed. Patients having high-risk stage I (tumor rupture, high mitotic index, tumor size greater than 10-15 cm (Schumer et al, 2002)) or Stages II-IV tumors could be observed or consider radiation therapy or undergo platinum-based chemotherapy (Schneider et al, 2003) with germ cell regimens preferred. Patients subsequently having a clinical relapse may consider secondary cytoreductive surgery, enter a clinical trial, or be offered supportive care.

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