National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Ovarian Cancer
Including Fallopian Tube Cancer and Primary Peritoneal Cancer

Version 2.2026 — March 12, 2026

NCCN recognizes the importance of clinical trials and encourages participation when applicable and available. Trials should be designed to maximize inclusiveness and broad representative enrollment.

NCCN Guidelines for Patients® available at www.nccn.org/patients

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Ovarian Cancer

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NCCN Guidelines Panel Disclosures

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NCCN Categories of Evidence and Consensus: All recommendations are category 2A unless otherwise indicated.

See NCCN Categories of Evidence and Consensus.

NCCN Categories of Preference: All recommendations are considered appropriate.

See NCCN Categories of Preference.

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Updates in Version 2.2026 of the NCCN Guidelines for Ovarian Cancer include:

LCOC-5A
• Small Cell Carcinoma of the Ovary (Hypercalcemic type), recurrence therapy, preferred, regimen removed: Tazemetostat.
LCOC-5B
• References for Small Cell Carcinoma of the Ovary (Hypercalcemic type), references removed for Tazemetostat.

Updates in Version 1.2026 of the NCCN Guidelines for Ovarian Cancer include:

Global
• Modifications made throughout the Guidelines related to terminology for biomarker testing and results.
• Imaging recommendations in algorithm and footnotes have been moved to Principles of Imaging (OV-A).
• References have been updated throughout the Guidelines.
OV-2
• Primary Treatment, Response, Bullet 1 modified: Consider hyperthermic intraperitoneal chemotherapy (HIPEC)*/Cisplatin*.
OV-4
• Pathologic Staging, first node modified: Less common ovarian cancers (LCOC), Any Stage *(including Grade 1 endometrioid)*.
• Footnote t added: Refer to the Distress Thermometer and Problem List, which includes social determinants of health. See NCCN Guidelines for Distress Management (DIS-A).
• Footnote u added: For high-grade serous histology, HRT can be considered for symptom management after assessing for individual factors.
OV-5
• Stage II, III, IV Post Primary Therapy and Maintenance Therapy sections extensively revised.
LCOC-1
• New diagnosis added: Small Cell Carcinoma of the Ovary (Hypercalcemic Type) (SCCOHT).
• Footnote f added: Individuals with LCOC may benefit from gynecologic oncology pathology confirmation and/or second opinion.
LCOC-5
• New algorithm added: Small Cell Carcinoma of the Ovary (Hypercalcemic Type) (SCCOHT).
LCOC-5A
• New page added: Systemic Therapy Regimens for Small Cell Carcinoma of the Ovary (Hypercalcemic Type) (SCCOHT).
LCOC-5B
• New page added: References for Small Cell Carcinoma of the Ovary (Hypercalcemic Type) (SCCOHT).
LCOC-9
• Footnote z added: Those with noninvasive implants (stage II–IV) are at risk for progression to low-grade serous carcinoma.
LCOC-A
• Systemic Therapy Regimens for Malignant Germ Cell Tumors, primary therapy, dosing moved to OV-D (7 of 12).
LCOC-B
• Surveillance for Malignant Germ Cell Tumors, last table row modified: C/A/P CT*/MRI*.
• Footnote d modified: ~~Chest x-ray, C/A/P CT, MRI, PET/CT, or PET; with contrast unless contraindicated. See~~ *Principles of Imaging (OV-A).*
OV-A
• New section added: Principles of Imaging.
OV-C (1 of 3)
• Principles of Pathology, General, bullet six, sub-bullet 5 added from OV-D (3 of 12): Current clinical HRD tests are proxy measures of HRD and lack accuracy in fully predicting functional HRD. HRD testing is recommended for those patients without germline BRCA1/2 P/LP variants as HRD test status may provide information on the magnitude of benefit of PARP inhibitor maintenance therapy in these patients. The Panel considers the use of PARPi in patients who have HRP tumors, at present, to be of minimal benefit.

Continued

Updates in Version 1.2026 of the NCCN Guidelines for Ovarian Cancer include:

OV-C (2 of 3)
- Principles of Pathology, Less Common Ovarian Cancers (LCOC)
  - Bullet 1 modified: A borderline tumor is a primary epithelial lesion with cytologic characteristics suggesting malignancy but without frank invasion. The terms for borderline epithelial tumors (also known as LMP tumors or atypical proliferative tumors) have changed over the years. The 2023 CAP protocol for ovarian cancer uses borderline and does not use LMP. Borderline epithelial tumors are typically serous or mucinous; other histologic subtypes can also occur (WHO Histologic Classification on OV-F). *Approximately 30% of serous borderline tumors are associated with peritoneal implants, which may be either noninvasive or invasive. According to WHO, invasive implants are synonymous with low-grade serous carcinoma and require adjuvant therapy.Noninvasive implants appear to confer at least a 15% to 20% increased risk of subsequent low grade serous carcinoma. While these patients do not require adjuvant therapy, they do require extended clinical follow-up as recurrences may occur 5 years or more after diagnosis.* ~~The characteristic pathologic hallmark of typical epithelial ovarian cancer is the identification of peritoneal implants, which microscopically and/or macroscopically invade the peritoneum. A borderline epithelial tumor may grossly resemble an invasive cancer. However, microscopic evaluation fails to reveal evidence of frank invasion by the tumor nodules, although rarely invasive implants (which continue to be consistent with the diagnosis of borderline epithelial lesions) can be identified microscopically by the pathologist.~~
  - Bullet 3 modified: It is difficult to distinguish based on histology between primary mucinous ovarian carcinomas and GI metastases. PAX8 immunostaining is typical of primary ovarian tumors, although the absence of PAX8 does not rule out ovary as the primary site, while SATB2 is consistent with colonic origin. Features favoring primary ovarian carcinoma versus metastasis are: unilateral, "expansile" pattern of invasion, complex papillary pattern, *size for mucinous carcinoma, >13~~10~~ cm for primary and <13 cm for metastatic*, smooth external surface, microscopic cystic glands, necrotic luminal debris, mural nodules and accompanying teratoma, adenofibroma, endometriosis, or Brenner tumor..

OV-D (1 of 12)
- Principles of Systemic Therapy, General
  - Bullet 9 added: Pembrolizumab and berahyaluronidase alfa-pmph subcutaneous injection may be substituted for IV pembrolizumab. Pembrolizumab and berahyaluronidase alfa-pmph has different dosing and administration instructions compared to IV pembrolizumab.
  - Bullet 10 added: For information regarding DPYD testing, see the NCCN Guidelines for Colon Cancer.

OV-D (3 of 12)
- Principles of Maintenance PARP Inhibitor (PARPi) Therapy, table extensively revised.

OV-D (6 of 12)
- Table header modified: Primary Therapy for Stage II–IV Disease *or Previously Untreated Recurrent Disease.*

OV-D (8 of 12)
- Recurrence Therapy for Platinum-Sensitive Disease
  - Other Recommended
    - ◊ Regimen removed: Melphalan
    - ◊ Targeted Therapy
      - – Regimen moved from Preferred: Bevacizumab
      - – Regimen removed: Niraparib (category 3)
      - – Regimen removed: Olaparib (category 3)
      - – Regimen removed: Rucaparib (category 3)

OV-D (9 of 12)
- Recurrence Therapy for Platinum-Resistant Disease
  - Other Recommended
    - ◊ Cytotoxic Chemotherapy
      - – Regimen moved from Preferred: Oral Etoposide.
      - – Regimen removed: Melphalan

Continued

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Updates in Version 1.2026 of the NCCN Guidelines for Ovarian Cancer include:

OV-D (9 of 12) (Continued)
- Recurrence Therapy for Platinum-Resistant Disease
  - Other Recommended
    - ◊ Targeted Therapy:
      - – Regimen moved from Preferred: Bevacizumab
      - – Regimen removed: Niraparib (category 3)
      - – Regimen removed: Olaparib (category 3)
- Recurrence Therapy for Platinum-Resistant Disease
  - ◊ Targeted Therapy:
    - – Regimen removed: Rucaparib (category 3)
  - Useful in Certain Circumstances
    - ◊ Immunotherapy
      - – Bullet 2 regimen added: Paclitaxel + Pembrolizumab ± Bevacizumab
      - – Bullet 4 added: For clear-cell carcinoma
        - ▪ Regimen added: Ipilimumab + Nivolumab

OV-D (9A of 12)
- Footnote z added: Tumors with a CPS ≥1 determined by an FDA-approved test are considered PD-L1 positive.
- Footnote removed: For patients treated with three or more prior chemotherapy regimens and whose cancer is associated with HRD defined by either: 1) a deleterious or suspected deleterious BRCA mutation; or 2) genomic instability and progression >6 months after response to the last platinum-based chemotherapy.
- Footnote removed: For patients with deleterious germline BRCA1/2-mutated (as detected by an FDA-approved test or other validated test performed in a CLIA-approved facility) advanced ovarian cancer who have been treated with two or more lines of chemotherapy.
- Footnote removed: For patients with deleterious germline and/or somatic BRCA mutation (as detected by an FDA-approved test or other validated test performed in a CLIA-approved facility) advanced ovarian cancer who have been treated with two or more lines of chemotherapy.

MS-1
- The Discussion section has been updated to reflect the changes in the algorithm.

CLINICAL PRESENTATION	WORKUP	CLINICAL STAGE[f]	PRIMARY TREATMENT[f,g,h]		
Suspicious/ palpable pelvic mass on abdomen/ pelvis exam and/or ascites, abdominal distention and/or Symptoms without source of malignancy (eg, bloating, pelvis/ abdomen pain, difficulty eating or feeling full quickly, urinary symptoms [urgency or frequency])	• Abdomen/pelvis exam • Imaging studies as clinically indicated. See Principles of Imaging (OV-A) • Complete blood count (CBC), chemistry profile with liver function test (LFT) • CA-125 or other tumor markers as clinically indicated[a] • Evaluate performance status and nutritional status • Gastrointestinal (GI) evaluation as clinically indicated • Reproductive endocrinology and infertility (REI) evaluation as clinically indicated[b] • Obtain family history[c,d,e] • Refer to gynecologic oncologist for clinically suspicious lesions[f]	IA (fertility desired)	→ Unilateral salpingo-oophorectomy (USO) + comprehensive surgical staging[g,h,i,j]	→ Patients with ovarian cancer, fallopian tube cancer, or primary peritoneal cancer should have genetic risk evaluation and germline and somatic biomarker testing (if not previously done)[c,d,e,h]	→ Pathologic Staging (OV-4) → For less common ovarian cancers (LCOC),[l] see LCOC-1
		IB (fertility desired)	→ Bilateral salpingo-oophorectomy (BSO) + comprehensive surgical staging[g,h,i,j]		
		IA–IV, surgical candidate, optimal cytoreduction likely (fertility not desired)	→ Hysterectomy/BSO + comprehensive staging[g,h] and debulking as needed		
		Poor surgical candidate or Low likelihood of optimal cytoreduction[g]	→ Neoadjuvant Therapy (OV-2)[k]		

Diagnosis by previous surgery or tissue biopsy (cytopathology) → Workup, Findings, and Primary Treatment (OV-3)

[a] Other tumor markers may include inhibin, beta-human chorionic gonadotropin (β-hCG), alpha-fetoprotein, lactate dehydrogenase (LDH), carcinoembryonic antigen (CEA), CA 19-9, and HE4. See Discussion for usefulness of diagnostic tests.
[b] Reconsider REI evaluation as clinically indicated once pathologic diagnosis is available.
[c] See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate and NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric.
[d] Germline and somatic *BRCA1/2* status informs maintenance therapy.
[e] In the absence of a *BRCA1/2* mutation, homologous recombination deficiency (HRD) status may provide information on the magnitude of benefit of PARP inhibitor (PARPi) therapy. For PARPi therapy in advanced stage disease, include measure of homologous recombination (HR) (OV-C).
[f] Evaluation by a gynecologic oncologist is recommended for:
- All patients with suspected ovarian malignancies; published data demonstrate that primary assessment and debulking by a gynecologic oncologist results in a survival advantage.
- Patients being evaluated for neoadjuvant therapy prior to being considered a poor surgical candidate.
- Management of occult serous tubal intraepithelial carcinomas (STICs).
- Consideration of laparoscopic evaluation to determine feasibility of debulking surgery in select patients.
- Endometrial biopsy as clinically indicated.

[g] Principles of Surgery (OV-B).
[h] Principles of Pathology (OV-C).
[i] May be an option for select patients with stage IC based on histology.
[j] Uterine preservation for potential future assisted reproductive approaches.
[k] See Principles of Systemic Therapy (OV-D) and Management of Drug Reactions (OV-E).
[l] Carcinosarcoma, clear cell, mucinous, low-grade serous, grade 1 endometrioid, borderline epithelial, malignant sex cord-stromal tumors, and germ cell tumors.

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

POOR SURGICAL CANDIDATE OR LOW LIKELIHOOD OF OPTIMAL CYTOREDUCTION
NEOADJUVANT THERAPY

PRIMARY TREATMENT

- Evaluation by gynecologic oncologist[f,g]

  and

  Histologic confirmation[h,m] (biopsy preferred)

  and/or

  Laparoscopic evaluation to determine feasibility of resection

  → Confirmed poor surgical candidate or low likelihood of optimal cytoreduction

  → Neoadjuvant therapy[f,k,n,o] (category 1)

  and

  Genetic risk evaluation and germline and somatic biomarker testing (if not previously done)[c,d,e,h]

  - Response → Interval debulking surgery (IDS) with completion hysterectomy/BSO[g,h] and cytoreduction
    - Consider hyperthermic intraperitoneal chemotherapy (HIPEC)/cisplatin[g]

    → Adjuvant therapy[k] → Maintenance Therapy (OV-5)
  - Stable disease → IDS with completion hysterectomy/BSO[g,h] and cytoreduction
    - Consider HIPEC[g]

    or

    Continue current therapy (for a total of at least 6 cycles)[k] → IDS with completion hysterectomy/BSO[g,h] and cytoreduction
    - Consider HIPEC[g] → Adjuvant therapy[k]

    or

    Therapy for Persistent Disease or Recurrence (OV-7)

    or

    Therapy for Persistent Disease or Recurrence (OV-7)

    (IDS with completion hysterectomy/BSO and cytoreduction → Adjuvant therapy[k])
  - Progressive disease → Therapy for Persistent Disease or Recurrence (OV-7)
  - LCOC → LCOC-1

[c] See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate and NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric.
[d] Germline and somatic *BRCA1/2* status informs maintenance therapy.
[e] In the absence of a *BRCA1/2* mutation, HRD status may provide information on the magnitude of benefit of PARPi therapy. For PARPi therapy in advanced stage disease, include measure of HR (OV-C).
[f] Evaluation by a gynecologic oncologist is recommended for:
- All patients with suspected ovarian malignancies; published data demonstrate that primary assessment and debulking by a gynecologic oncologist results in a survival advantage.
- Patients being evaluated for neoadjuvant therapy prior to being considered a poor surgical candidate.
- Management of occult STICs.
- Consideration of laparoscopic evaluation to determine feasibility of debulking surgery in select patients.
- Endometrial biopsy as clinically indicated.

[g] Principles of Surgery (OV-B).
[h] Principles of Pathology (OV-C).
[k] See Principles of Systemic Therapy (OV-D) and Management of Drug Reactions (OV-E).
[m] If biopsy is not feasible, cytopathology from ascites or pleural effusion combined with CA-125:CEA ratio of >25 can be used.
[n] Completion surgery after 3–4 cycles is preferred; however, surgery may be performed after 4–6 cycles based on the clinical judgment of the gynecologic oncologist.
[o] Neoadjuvant therapy does not apply to low malignant potential (LMP) or other noninvasive cancers (see LCOC-1).

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

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Epithelial Ovarian Cancer/Fallopian Tube Cancer/ Primary Peritoneal Cancer

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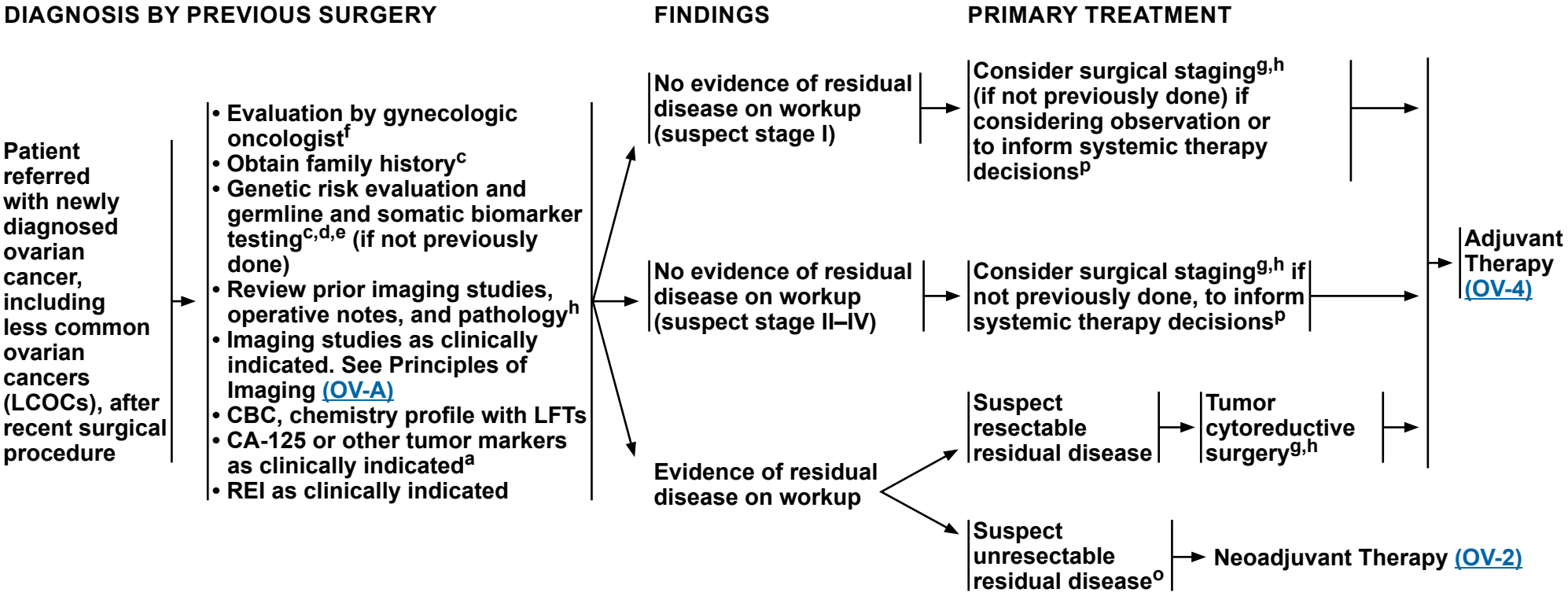

[a] Other tumor markers may include inhibin, β-hCG, alpha-fetoprotein, LDH, CEA, CA 19-9, and HE4. See Discussion for usefulness of diagnostic tests.
[c] See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate and NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric.
[d] Germline and somatic *BRCA1/2* status informs maintenance therapy.
[e] In the absence of a *BRCA1/2* mutation, HRD status may provide information on the magnitude of benefit of PARPi therapy. For PARPi therapy in advanced stage disease, include measure of HR (OV-C).
[f] Evaluation by a gynecologic oncologist is recommended for:
- All patients with suspected ovarian malignancies; published data demonstrate that primary assessment and debulking by a gynecologic oncologist results in a survival advantage.
- Patients being evaluated for neoadjuvant therapy prior to being considered a poor surgical candidate.
- Management of occult STICs.
- Consideration of laparoscopic evaluation to determine feasibility of debulking surgery in select patients.
- Endometrial biopsy as clinically indicated.

[g] Principles of Surgery (OV-B).
[h] Principles of Pathology (OV-C).
[o] Neoadjuvant therapy does not apply to LMP and other noninvasive cancers (see LCOC-1).
[p] Although comprehensive surgical staging has not been shown to improve survival in patients with no evidence of residual disease, it can be important for determining the most appropriate postoperative management options, including selection of adjuvant and maintenance therapy.

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

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Epithelial Ovarian Cancer/Fallopian Tube Cancer/ Primary Peritoneal Cancer

PATHOLOGIC STAGING[q,r]

PRIMARY CHEMOTHERAPY/PRIMARY ADJUVANT THERAPY[s]

Less common ovarian cancers (LCOC)
Any stage (including Grade 1 endometrioid)[l,r] → LCOC-1

Stage IA or IB
- Grade 2 endometrioid → **Observe or Intravenous (IV) platinum-based therapy[k,s] (see primary regimens for stage I disease [OV-D, 5 of 12])**
- **Grade 3 endometrioid/ high-grade serous carcinoma[q]** → **IV platinum-based therapy[k,s] (see primary regimens for stage I disease [OV-D, 5 of 12])**

Stage IC (High-grade serous or grade 2 or 3 endometrioid) → **IV platinum-based therapy[k,s] (see primary regimens for stage I disease [OV-D, 5 of 12])**

Provide symptom management and best supportive care[t,u]

Refer for palliative care assessment, if appropriate
- **See NCCN Guidelines for Palliative Care**
- **See NCCN Guidelines for Survivorship**

→ **Monitoring/ Follow-up (OV-6)**

Stage II
Stage III
Stage IV
→ **Platinum-based chemotherapy (see primary regimens for stage II–IV disease [OV-D, 6 of 12])[k,s]**

→
- **Provide symptom management and best supportive care[t,u]**
- **Refer for palliative care assessment, if appropriate**
  - **See NCCN Guidelines for Palliative Care**
  - **See NCCN Guidelines for Survivorship**

→ **Imaging studies as clinically indicated. See Principles of Imaging (OV-A)**

→
- **Complete Response (CR)[v]/ Partial Response (PR)** → **Maintenance Therapy (OV-5)**
- **Stable disease or progression** → **Therapy for Persistent Disease or Recurrence (OV-7)**

[k] See Principles of Systemic Therapy (OV-D) and Management of Drug Reactions (OV-E).
[l] Carcinosarcoma, clear cell, mucinous, low-grade serous, grade 1 endometrioid, borderline epithelial, malignant sex cord-stromal tumors, and germ cell tumors.
[q] Pathologists recommend categorizing serous ovarian cancer as either low-grade or high-grade. Grade 2 serous is considered high-grade.
[r] Consider expert pathologic review to confirm histologic diagnosis. See WHO Histologic Classification (OV-F).

[s] Patients receiving primary chemotherapy will be monitored as follows:
1. Every 1–3 cycles: Physical exam and consider pelvis exam
2. As indicated: Interim CBC and chemistry profiles
3. CA-125 levels or other tumor markers as clinically indicated prior to each cycle of chemotherapy
4. Imaging studies as clinically indicated. See Principles of Imaging (OV-A).

[t] Refer to the Distress Thermometer and Problem List, which includes social determinants of health. See NCCN Guidelines for Distress Management (DIS-A).
[u] For high-grade serous histology, HRT can be considered for symptom management after assessing for individual factors.
[v] No definitive evidence of disease.

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

STAGE II, III, IV[w]
POST PRIMARY THERAPY

MAINTENANCE THERAPY[e,k,x]

CR[v]/PR

Germline or somatic *BRCA1/2* pathogenic/ likely pathogenic (P/LP) variants

If bevacizumab not used during primary chemotherapy:
- **Olaparib (category 1) or Niraparib (category 1) or Rucaparib**

or
- **Observe for select stage II disease with CR[x]**

If bevacizumab used during primary chemotherapy:
- **Olaparib + Bevacizumab (category 1)**

or
- **Niraparib + Bevacizumab (if unable to tolerate Olaparib)**

or
- **Olaparib[y] or Niraparib[y] or Rucaparib[y]**

BRCA1/2 wild-type or unknown

and

HR Deficient

If bevacizumab not used during primary chemotherapy:
- **Olaparib or Niraparib or Rucaparib**

or
- **Observe (if CR)**

If bevacizumab used during primary chemotherapy:
- **Olaparib + Bevacizumab (category 1)**

or
- **Niraparib + Bevacizumab (if unable to tolerate Olaparib)**

or
- **Bevacizumab**

or
- **Olaparib**

BRCA1/2 wild-type or unknown

and

HR Proficient or HR unknown

If bevacizumab not used during primary chemotherapy:
- **Observe (if CR)**

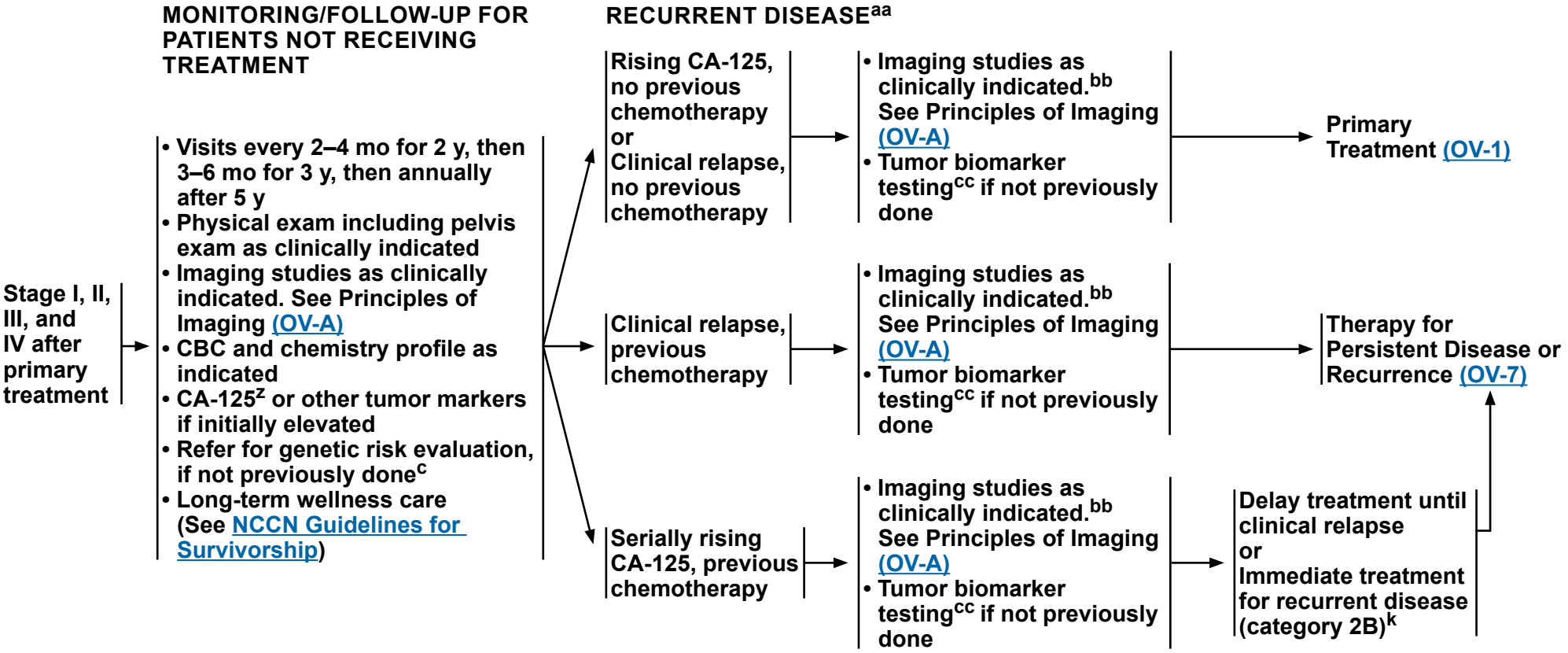
or
- **Therapy for Persistent Disease or Recurrence (OV-7)**

If bevacizumab used during primary chemotherapy:
- **Bevacizumab**

Monitoring/Follow-Up (OV-6)

[e] In the absence of a *BRCA1/2* mutation, HRD status has been correlated with magnitude of benefit from PARPi maintenance in clinical trials. For PARPi therapy in advanced stage disease, include measure of HR (OV-C).
[k] See Principles of Systemic Therapy (OV-D) and Management of Drug Reactions (OV-E).
[v] No definitive evidence of disease.
[w] Post primary treatment recommendations for stage II–IV high-grade serous or grade 2 or 3 endometrioid carcinoma; consider for clear cell carcinoma or carcinosarcoma with a *BRCA1/2* mutation.
[x] Data are limited for maintenance therapy with a PARPi for patients with stage II disease.
[y] After first-line therapy with bevacizumab, data are limited on maintenance therapy with a single-agent PARPi (olaparib, niraparib, or rucaparib) for patients with a germline or somatic *BRCA1/2* P/LP variants. However, based on the magnitude of benefit of PARPi maintenance therapy for other subgroups, single-agent PARPi can be considered.

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



[c] See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate and NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric.

[k] See Principles of Systemic Therapy (OV-D) and Management of Drug Reactions (OV-E).

[z] There are data regarding the utility of CA-125 for monitoring of ovarian cancer after completion of primary therapy. See The Society of Gynecologic Oncology (SGO) position statement and Discussion.

[aa] Consider symptom management and best supportive care. See NCCN Guidelines for Palliative Care. Refer for palliative care assessment, if appropriate.

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

[bb] Surveillance imaging may be indicated when tumor markers are considered unreliable, the physical exam is unreliable, and/or there is a high risk of recurrence.

[cc] Validated biomarker testing should be performed in a Clinical Laboratory Improvement Amendments (CLIA)-approved facility using the most recent available tumor tissue. Tumor biomarker analysis is recommended to include tests to identify potential benefit from targeted therapeutics that have tumor-specific or tumor-agnostic benefit including, but not limited to, HER2 status (by immunohistochemistry [IHC]), PD-L1 (IHC, combined positive score [CPS]), *BRCA1/2*, HRD status, microsatellite instability (MSI), mismatch repair (MMR), tumor mutational burden (TMB), *BRAF, KRAS*, FRα (FOLR1), *RET*, and *NTRK1/2/3* if prior testing did not include these markers. Multigene panel testing (MGPT) may be particularly important in LCOC with limited approved therapeutic options (OV-C).

DISEASE STATUS[c,cc,dd]	THERAPY FOR PERSISTENT DISEASE OR RECURRENCE[k,ff,gg,hh]
Platinum-resistant disease[ee]: • **Progression on primary, maintenance or recurrence therapy** **or** • **Stable or persistent disease (if not on maintenance therapy)** **or** • **Complete remission and relapse <6 mo after completing chemotherapy**	→ **Best supportive care (See NCCN Guidelines for Palliative Care)** **and/or** **Recurrence therapy (OV-D, 9 of 12)[k,ii,jj]**
Platinum-sensitive disease[ee]: • **Complete remission and relapse ≥6 mo after completing prior chemotherapy**	→ **OV-8**

[c] See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate and NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric.

[k] See Principles of Systemic Therapy (OV-D) and Management of Drug Reactions (OV-E).

[cc] Validated biomarker testing should be performed in a CLIA-approved facility using the most recent available tumor tissue. Tumor biomarker analysis is recommended to include tests to identify potential benefit from targeted therapeutics that have tumor-specific or tumor-agnostic benefit including, but not limited to, HER2 status (by IHC), PD-L1 (IHC, CPS), *BRCA1/2*, HRD status, MSI, MMR, TMB, *BRAF, KRAS,* FRα (FOLR1)*, RET,* and *NTRK1/2/3* if prior testing did not include these markers. MGPT may be particularly important in LCOC with limited approved therapeutic options (OV-C).

[dd] Tumor biomarker testing prior to initiation of therapy for persistent/recurrent disease, if not previously done.

[ee] Definitions of platinum-sensitive and platinum-resistant disease represent a spectrum of disease; clinical judgment and flexibility should be utilized in determining treatment options.

[ff] Data are limited on primary and maintenance therapy for recurrent/persistent LCOC.

[gg] During and after treatment for recurrence, patients should be evaluated as indicated with tumor markers and repeat imaging (with modalities previously used) to document response and/or disease status.

[hh] Ancillary Palliative Surgical Procedures (OV-B 5 of 5).

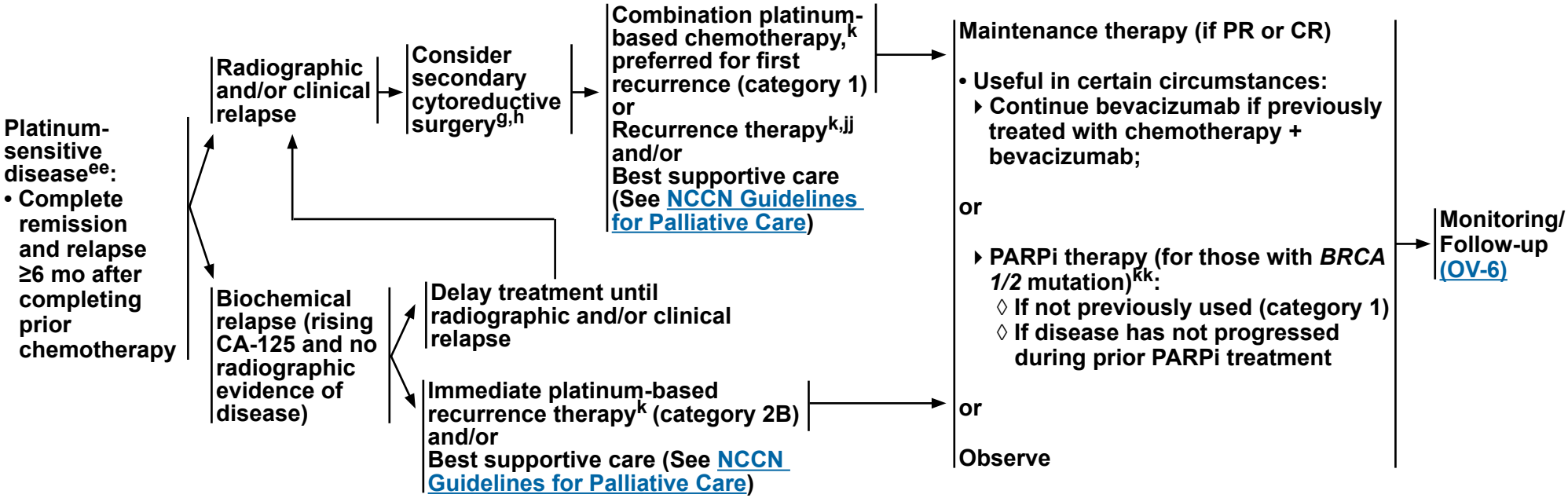
[ii] Patients who do not respond and progress on two consecutive regimens without evidence of clinical benefits have diminished likelihood of benefitting from additional therapy (Griffiths RW, et al. Int J Gynecol Cancer 2011;21:58-65). Decisions to offer clinical trials, supportive care, or additional therapy should be made on an individual basis.

[jj] Localized radiation therapy (RT) can be considered to palliate symptoms and/or for oligometastatic disease.

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

DISEASE STATUS[c,cc,dd]

RECURRENCE THERAPY FOR PLATINUM-SENSITIVE DISEASE[k,ff,gg,hh]



[c] See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate and NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric.
[g] Principles of Surgery (OV-B).
[h] Principles of Pathology (OV-C).
[k] See Principles of Systemic Therapy (OV-D) and Management of Drug Reactions (OV-E).
[cc] Validated biomarker testing should be performed in a CLIA-approved facility using the most recent available tumor tissue. Tumor biomarker analysis is recommended to include tests to identify potential benefit from targeted therapeutics that have tumor-specific or tumor-agnostic benefit including, but not limited to, HER2 status (by IHC), PD-L1 (IHC, CPS), *BRCA1/2*, HRD status, MSI, MMR, TMB, *BRAF, KRAS,* FRα (FOLR1), *RET,* and *NTRK1/2/3* if prior testing did not include these markers. MGPT may be particularly important in LCOC with limited approved therapeutic options (OV-C).
[dd] Tumor biomarker testing prior to initiation of therapy for persistent/recurrent disease, if not previously done.
[ee] Definitions of platinum-sensitive and platinum-resistant disease represent a spectrum of disease; clinical judgment and flexibility should be utilized in determining treatment options.
[ff] Data are limited on primary and maintenance therapy for recurrent/persistent LCOC.
[gg] During and after treatment for recurrence, patients should be evaluated as indicated with tumor markers and repeat imaging (with modalities previously used) to document response and/or disease status.
[hh] Ancillary Palliative Surgical Procedures (OV-B 5 of 5).
[jj] Localized RT can be considered to palliate symptoms and/or for oligometastatic disease.
[kk] PARPi options include niraparib, olaparib, or rucaparib in patients with *BRCA1/2*-mutated platinum-sensitive disease who have completed two or more lines of platinum-based therapy. Based on FDA indication, niraparib is limited to those with a P/LP germline *BRCA1/2* variants. Based on FDA indications, olaparib and rucaparib are limited to those with a *BRCA1/2* P/LP variants (germline or somatic). Caution should be used when using maintenance PARPi for longer than 24 months. There are limited data on the use of a maintenance PARPi in patients who previously received a PARPi. Combination PARPi + bevacizumab is not recommended for maintenance after recurrence therapy.

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

NCCN Guidelines Version 2.2026
Less Common Ovarian Cancers

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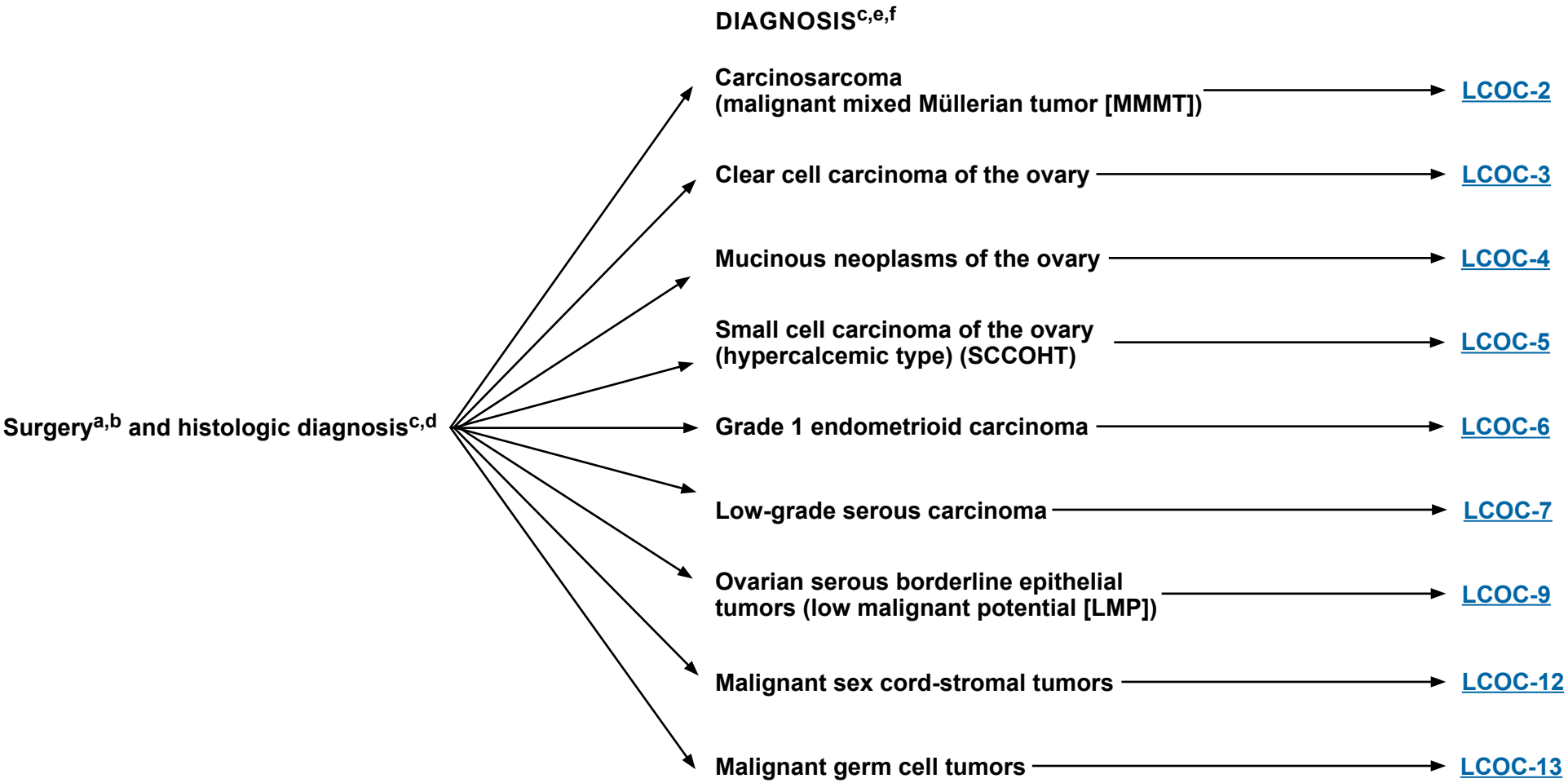
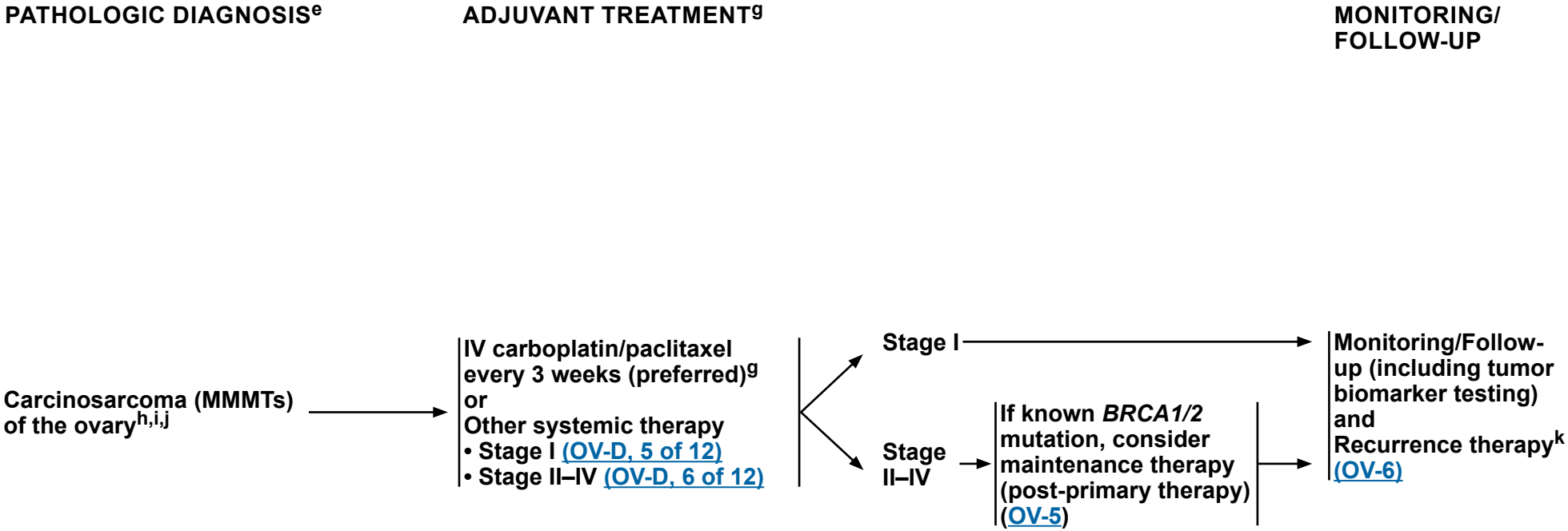


[a] Principles of Surgery (OV-B).
[b] Principles of Pathology (OV-C).
[c] Due to emerging therapeutics for LCOC, there is value in identifying potential pathways for rare cancers and it may be useful for clinical trial recruitment. Tumor biomarker testing can be considered, if not previously done, as it may help guide treatment. There are limited data in these cancers given their infrequency and it will be difficult to acquire prospective data. Individualized treatment may be the best treatment for these rare tumors. [Committee on the State of the Science in Ovarian Cancer, et al. Ovarian Cancers: Evolving Paradigms in Research and Care. Washington (DC): National Academies Press (US) Copyright 2016 by the National Academy of Sciences. All rights reserved; 2016.]
[d] LCOC are typically diagnosed after surgery. See Workup (OV-1).
[e] WHO Histologic Classification (OV-F).
[f] Individuals with LCOC may benefit from gynecologic oncology pathology confirmation and/or second opinion.

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



[e] WHO Histologic Classification (OV-F).
[g] See Principles of Systemic Therapy (OV-D) and Management of Drug Reactions (OV-E).
[h] If not previously done, consider surgical staging and resection of residual disease (OV-3).
[i] If not previously done, consider germline and somatic biomarker testing (OV-C).
[j] Germline and somatic *BRCA1/2* status informs maintenance therapy. In the absence of a *BRCA1/2* mutation, HRD status may provide information on the magnitude of benefit of PARPi therapy. For PARPi therapy in advanced stage disease, include measure of HR (OV-C).
[k] Data are limited on primary and maintenance therapy for recurrent/persistent LCOC.

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

NCCN Guidelines Version 2.2026
Clear Cell Carcinoma of the Ovary

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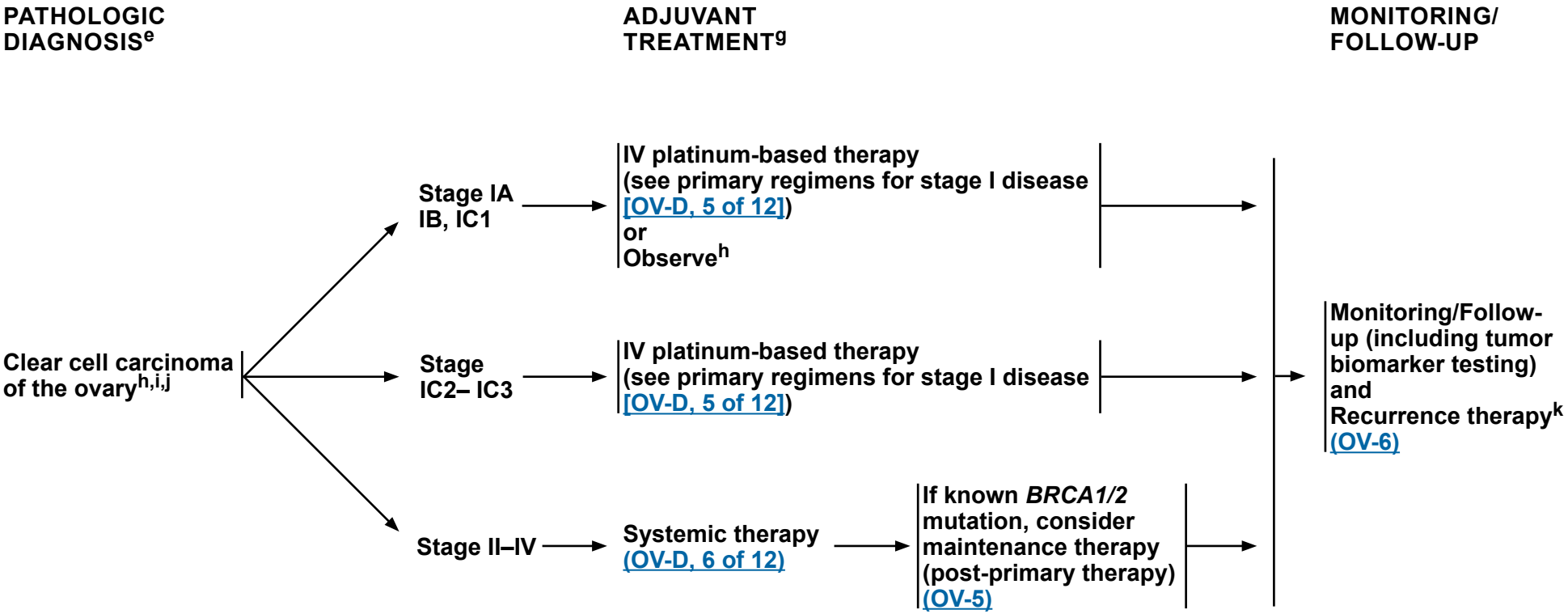

[e] WHO Histologic Classification (OV-F).
[g] See Principles of Systemic Therapy (OV-D) and Management of Drug Reactions (OV-E).
[h] If not previously done, consider surgical staging and resection of residual disease (OV-3).
[i] If not previously done, consider germline and somatic biomarker testing (OV-C).
[j] Germline and somatic *BRCA1/2* status informs maintenance therapy. In the absence of a *BRCA1/2* mutation, HRD status may provide information on the magnitude of benefit of PARPi therapy. For PARPi therapy in advanced stage disease, include measure of HR (OV-C).
[k] Data are limited on primary and maintenance therapy for recurrent/persistent LCOC.

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

NCCN Guidelines Version 2.2026
Mucinous Neoplasms of the Ovary

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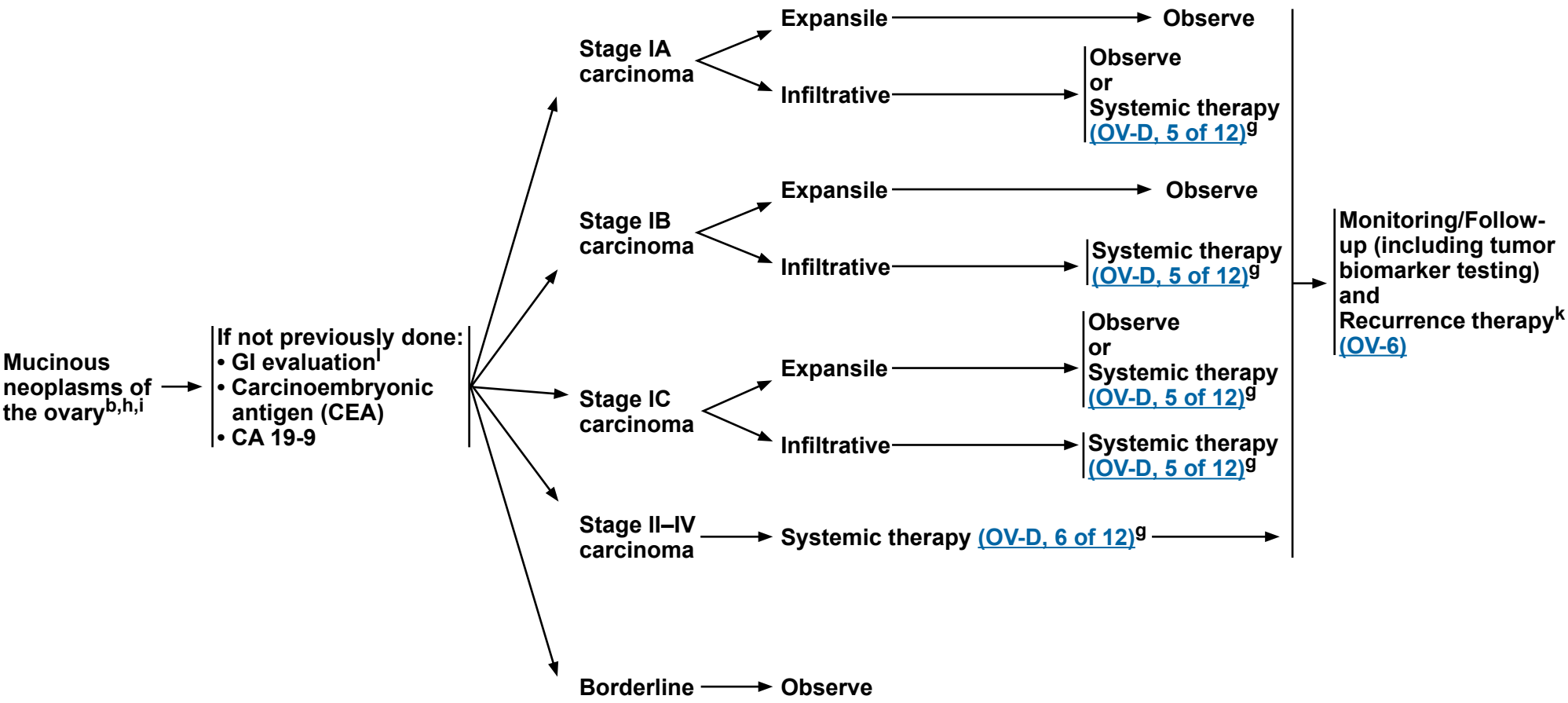

[b] Principles of Pathology (OV-C).
[e] WHO Histologic Classification (OV-F).
[g] See Principles of Systemic Therapy (OV-D) and Management of Drug Reactions (OV-E).
[h] If not previously done, consider surgical staging and resection of residual disease (OV-3).
[i] If not previously done, consider germline and somatic biomarker testing (OV-C).
[k] Data are limited on primary and maintenance therapy for recurrent/persistent LCOC.
[l] Consider additional testing, including but not limited to upper and lower endoscopic evaluation, to aid in the identification of metastatic GI malignancies versus primary mucinous ovarian cancer.

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

Small Cell Carcinoma of the Ovary (Hypercalcemic Type)

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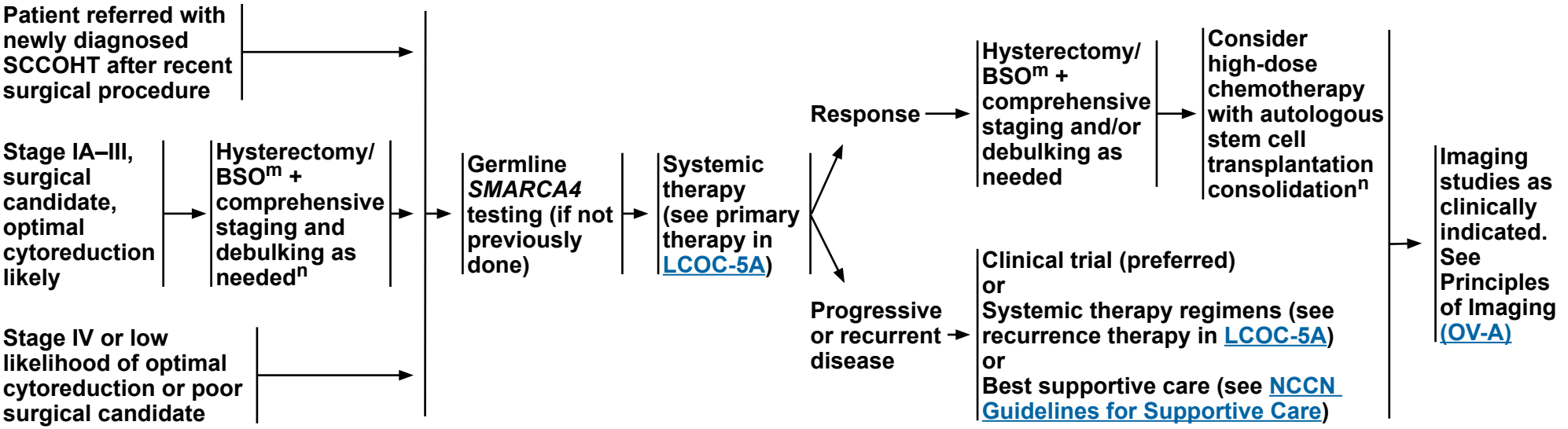
PATHOLOGIC DIAGNOSIS[e] | **ADJUVANT TREATMENT** | **POST-ADJUVANT THERAPY** | **MONITORING/ FOLLOW-UP**



[e] WHO Histologic Classification (OV-F).
[m] If germline *SMARCA4* negative, fertility sparing surgery can be considered after appropriate counseling. There are limited data on the safety and feasibility of this approach.
[n] Consider early referral to stem cell transplant center for autologous stem cell collection at the time of cycle 1.

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

SYSTEMIC THERAPY REGIMENS[g,n]
SMALL CELL CARCINOMA OF THE OVARY (HYPERCALCEMIC TYPE)

SMALL CELL CARCINOMA OF THE OVARY (HYPERCALCEMIC TYPE)			
	Preferred	**Other Recommended**	**Useful in Certain Circumstances**
Primary Therapy	• VPCBAE[1] (Vinblastine/Cisplatin/ Cyclophosphamide/Bleomycin/ Doxorubicin/Etoposide) ▸ up to 6 cycles	• PAVEP (Cisplatin/Doxorubicin/ Etoposide/Cyclophosphamide)[2,3] ▸ 4–6 cycles	• BEP[4] (Bleomycin/Etoposide/Cisplatin) ▸ 3–4 cycles • Cisplatin/Etoposide ▸ 4 cycles
Recurrence Therapy	• Pembrolizumab[5] • Ipilimumab + Nivolumab[6] • Paclitaxel + Bevacizumab[o]		

[g] See Principles of Systemic Therapy (OV-D) and Management of Drug Reactions (OV-E).
[n] Consider early referral to stem cell transplant center for autologous stem cell collection at the time of cycle 1.
[o] Based on activity in relapsed epithelial ovarian cancer and absence of a taxane in the primary therapy regimens

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

SYSTEMIC THERAPY REFERENCES
SMALL CELL CARCINOMA OF THE OVARY (HYPERCALCEMIC TYPE)

[1] Wallbillich JJ, Nick AM, Ramirez PT, et al. Vinblastine, cisplatin, cyclophosphamide, bleomycin, doxorubicin, and etoposide (VPCBAE) in the management of three patients with small-cell carcinoma of the ovary. Gyn Oncol Case Rep 2012;2:58-60.
[2] Blanc-Durand F, Lefeuvre-Plesse C, Ray-Coquard I, et al. Dose-intensive regimen treatment for small-cell carcinoma of the ovary of hypercalcemic type (SCCOHT). Gyn Oncol 2020;159:129-135.
[3] Pautier P, Ribrag V, Duvillard P, et al. Results of a prospective dose-intensive regimen in 27 patients with small cell carcinoma of the ovary of the hypercalcemic type. Ann Oncol 2007;18:1985-1989.
[4] Tischkowitz M, Huang S, Banerjee S, et al. Small-cell carcinoma of the ovary, hypercalcemic type-genetics, new treatment targets, and current management guidelines. Clin Canc Res 2020;26:3908-3917.
[5] Altman J, Schmitt W, Bashian N, Sehouli J. A dramatic response to checkpoint inhibitor in a woman with small cell carcinoma of the hypercalcemic type of the ovary. Gyn Oncol 2024;181:99-101.
[6] Chae YK, Othus M, Patel SP, et al. Abstract CT163: A phase II basket trial of dual anti-CTLA-4 and anti-PD-1 blockade in rare tumors (DART) SWOG S1609: the small cell carcinoma of the ovary, hypercalcemic type cohort. Canc Res 2023:83:[suppl 8] CT163.

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

NCCN Guidelines Version 2.2026
Grade 1 Endometrioid Carcinoma

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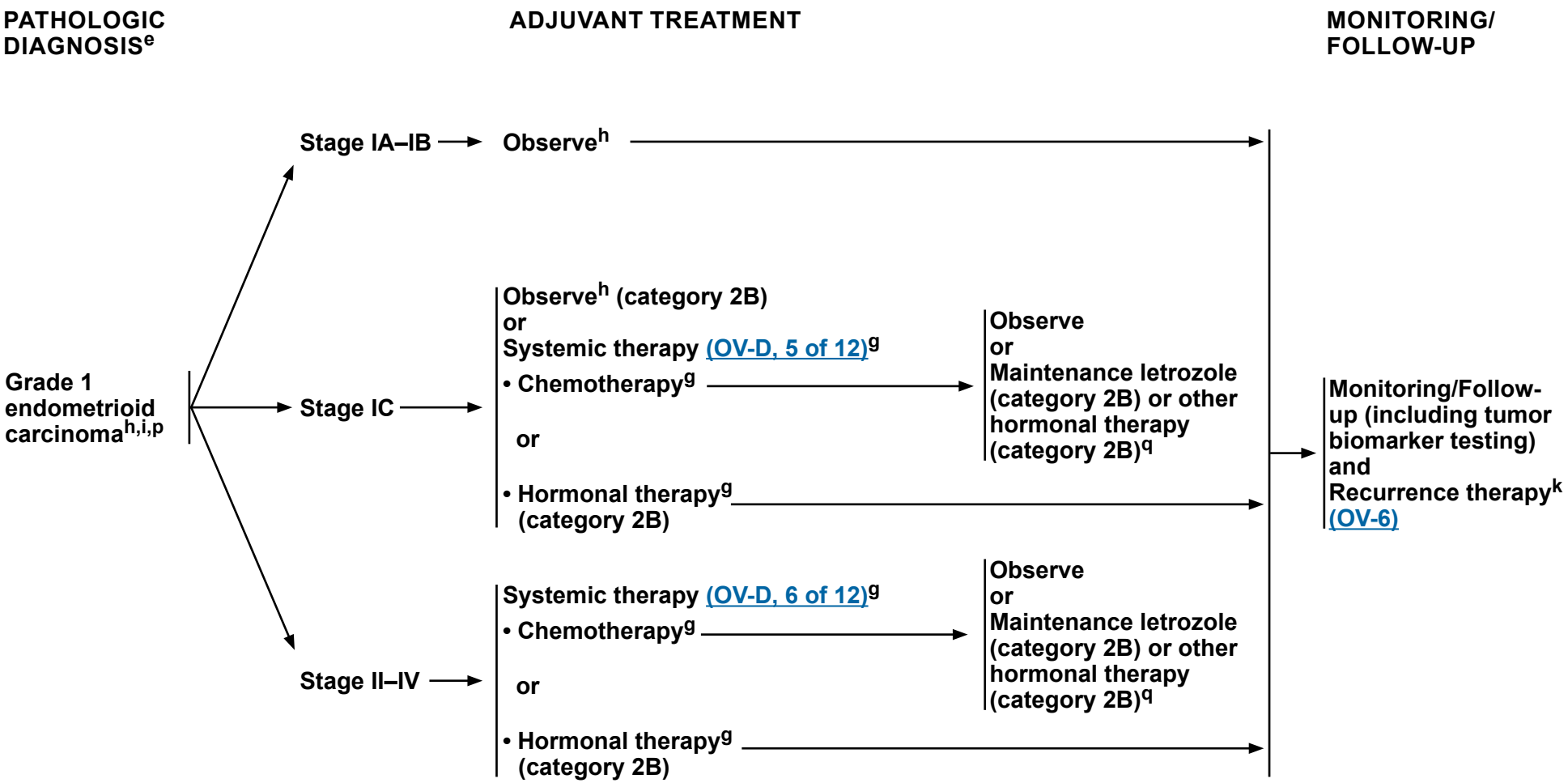

[e] WHO Histologic Classification (OV-F).
[g] See Principles of Systemic Therapy (OV-D) and Management of Drug Reactions (OV-E).
[h] If not previously done, consider surgical staging and resection of residual disease (OV-3).
[i] If not previously done, consider germline and somatic biomarker testing (OV-C).
[k] Data are limited on primary and maintenance therapy for recurrent/persistent LCOC.
[p] MSI/MMR testing is recommended for all patients with endometrioid carcinoma.
[q] Other hormonal therapy options include: aromatase inhibitors (eg, anastrozole, exemestane), leuprolide acetate, goserelin acetate, and tamoxifen.

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

NCCN Guidelines Version 2.2026
Low-Grade Serous Carcinoma

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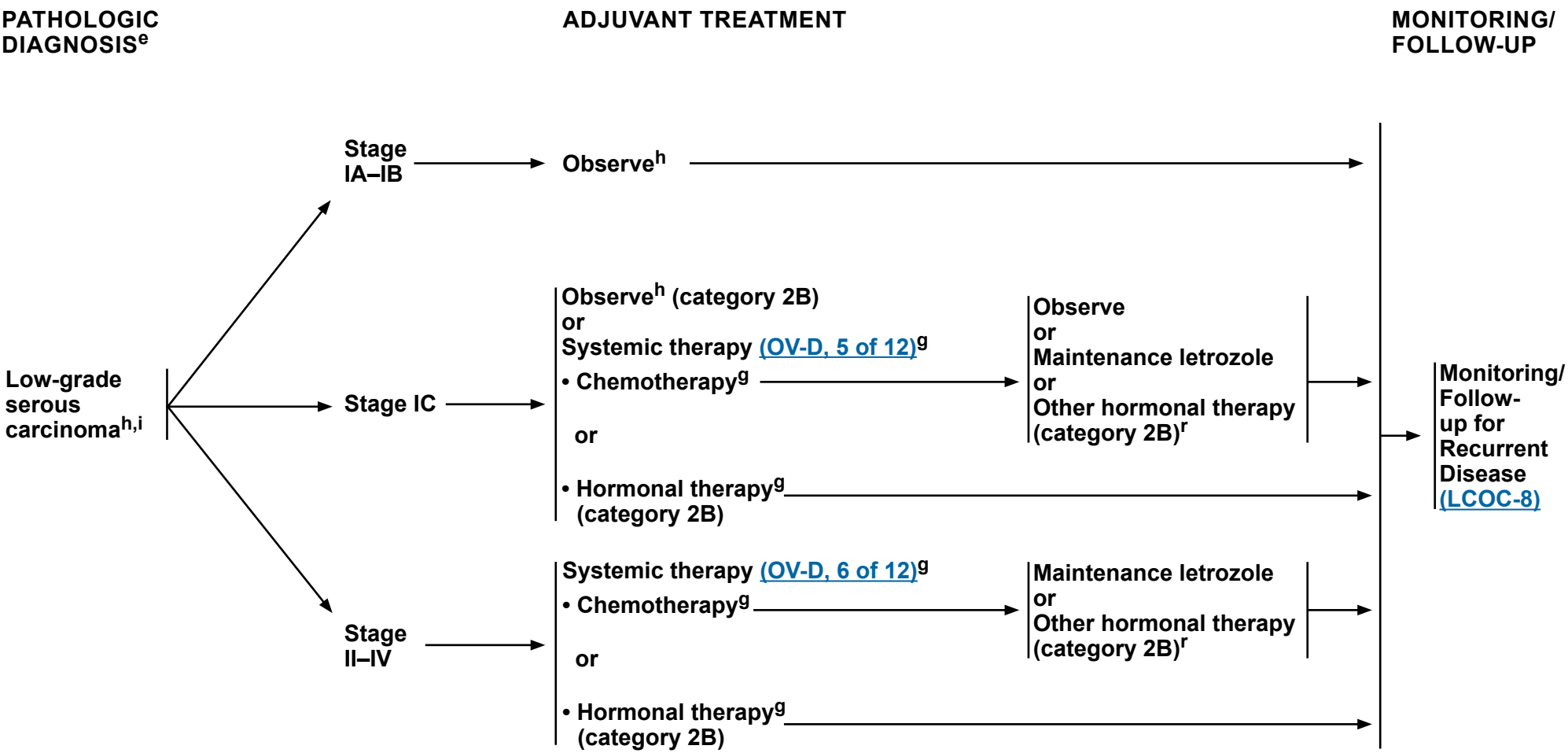


[e] WHO Histologic Classification (OV-F).
[g] See Principles of Systemic Therapy (OV-D) and Management of Drug Reactions (OV-E).
[h] If not previously done, consider surgical staging and resection of residual disease (OV-3).
[i] If not previously done, consider germline and somatic biomarker testing (OV-C).
[r] Other hormonal therapy options include: aromatase inhibitors (eg, anastrozole, exemestane), leuprolide acetate, and goserelin acetate.

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

MONITORING/FOLLOW-UP FOR RECURRENCE

- Visits every 2–4 mo for 2 y, then 3–6 mo for 3 y, then annually after 5 y
- Physical exam including pelvis exam as clinically indicated
- Tumor biomarker testing if not previously done[s]
- Imaging studies as clinically indicated. See Principles of Imaging (OV-A)
- CBC and chemistry profile as indicated
- CA-125[t] or other tumor markers if initially elevated
- Refer for genetic risk evaluation, if not previously done[u]
- Long-term wellness care (See NCCN Guidelines for Survivorship)

→ **Recurrent disease[v]** →

RECURRENCE THERAPY[w]

Hormonal therapy[x]

or

Chemotherapy (if not previously used), see OV-D (6 of 12)

or

Systemic therapy[g,y]
- For platinum-sensitive disease, see OV-D (8 of 12)
- For platinum-resistant disease, see OV-D (9 of 12)

or

Observation

[g] See Principles of Systemic Therapy (OV-D) and Management of Drug Reactions (OV-E).

[s] Validated biomarker testing should be performed in a CLIA-approved facility using the most recent available tumor tissue. Tumor biomarker analysis is recommended to include tests to identify potential benefit from targeted therapeutics that have tumor-specific or tumor-agnostic benefit including, but not limited to, HER2 status (by IHC), PD-L1 (IHC, CPS), *BRCA1/2*, HRD status, MSI, MMR, TMB, *BRAF, KRAS,* FRα (FOLR1)*, RET,* and *NTRK1/2/3* if prior testing did not include these markers. MGPT may be particularly important in LCOC with limited approved therapeutic options (OV-C).

[t] There are data regarding the utility of CA-125 for monitoring of ovarian cancer after completion of primary therapy. See The Society of Gynecologic Oncology (SGO) position statement and Discussion.

[u] See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate and NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric.

[v] Consider secondary cytoreduction in patients with long disease-free interval, isolated masses rather than diffuse carcinomatosis on imaging, and/or bowel obstruction.

[w] There is no standard sequencing of drugs for recurrent disease. Considerations include prior therapies, disease burden, relative efficacy, and relative toxicity profile.

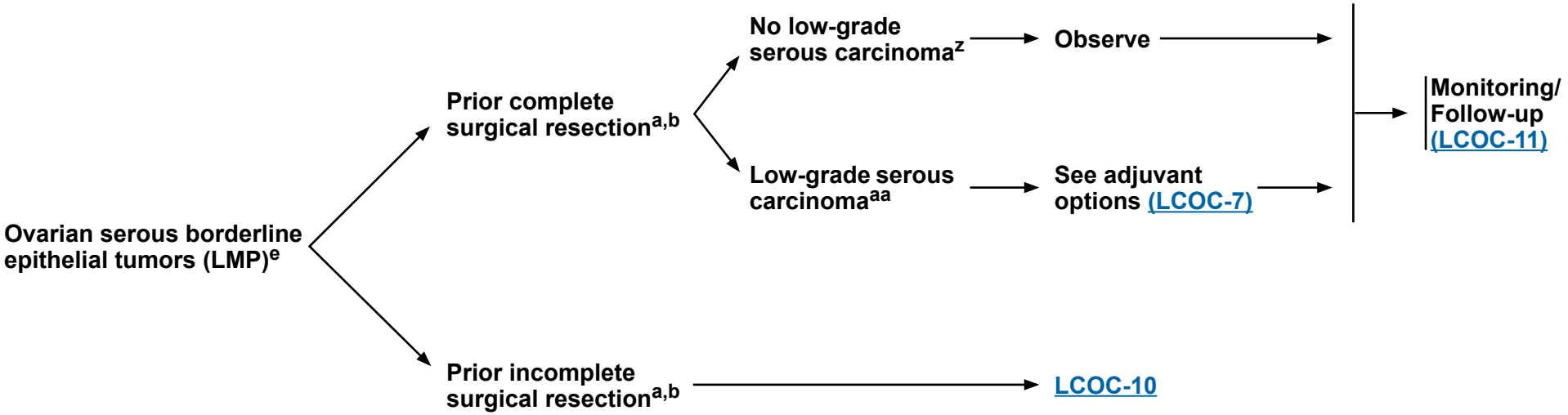
[x] An aromatase inhibitor (eg, letrozole, anastrozole, exemestane) is preferred if not used previously. Fulvestrant, leuprolide acetate, or goserelin acetate is recommended if an aromatase inhibitor was given previously.

[y] Data are limited on maintenance therapy for recurrent/resistant LCOC. See OV-8 for maintenance options after platinum-based therapy, and patient selection criteria.

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

PATHOLOGIC DIAGNOSIS[e]

ADJUVANT TREATMENT[bb]



[a] Principles of Surgery (OV-B).
[b] Principles of Pathology (OV-C).
[e] WHO Histologic Classification (OV-F).
[z] Those with noninvasive implants (stage II–IV) are at risk for progression to low-grade serous carcinoma.
[aa] Chemotherapy (IV or IP) has not been shown to be beneficial in ovarian borderline epithelial tumors (LMP).
[bb] Standard recommendation includes a patient evaluation by a gynecologic oncologist.

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

NCCN Guidelines Version 2.2026
Ovarian Serous Borderline Epithelial Tumors (Low Malignant Potential)

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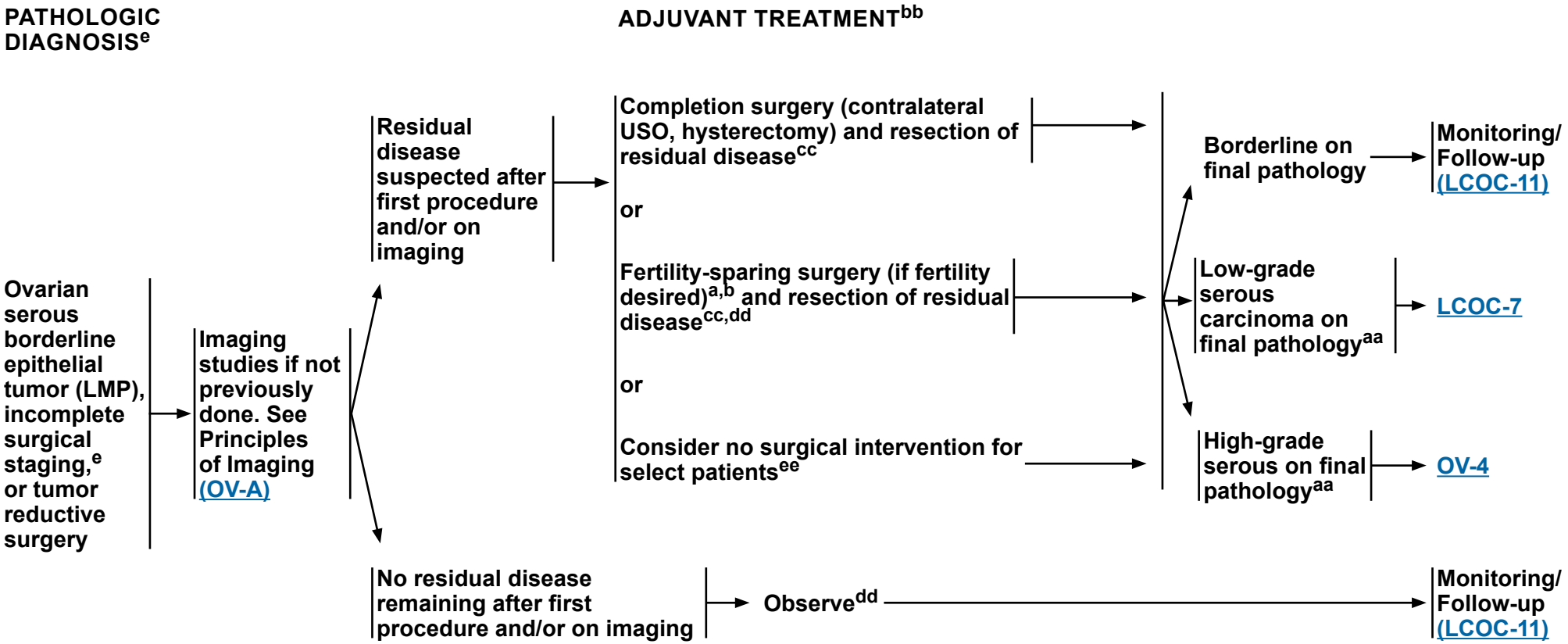

[a] Principles of Surgery (OV-B).
[b] Principles of Pathology (OV-C).
[e] WHO Histologic Classification (OV-F).
[aa] Chemotherapy (IV or IP) has not been shown to be beneficial in ovarian borderline epithelial tumors (LMP).
[bb] Standard recommendation includes a patient evaluation by a gynecologic oncologist.
[cc] For pathologically proven ovarian borderline epithelial tumors, lymph node evaluation may be considered on a case-by-case basis.
[dd] In patients who underwent USO, consider completion surgery (eg, contralateral USO, hysterectomy) after completion of childbearing (category 2B).
[ee] If patient is medically unfit, or for those with unresectable residual disease.

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

Ovarian Serous Borderline Epithelial Tumors (Low Malignant Potential)

NCCN Guidelines Index
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MONITORING/FOLLOW-UP

- Visits every 3–12 mo for up to 5 y, then as clinically indicated
- Physical exam including pelvis exam as clinically indicated
- CA-125[t] or other tumor markers every visit if initially elevated
- CBC, chemistry profile as indicated
- Imaging as clinically indicated. See Principles of Imaging (OV-A)

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

RECURRENT DISEASE

- **Noninvasive disease** → **Observe**
- **Low-grade invasive carcinoma** → **See appropriate LCOC page based on histology[aa] (LCOC-1)**
- **High-grade invasive carcinoma** → **Treatment as epithelial ovarian cancer[aa] (OV-4)**

RECURRENCE THERAPY

[t] There are data regarding the utility of CA-125 for monitoring of ovarian cancer after completion of primary therapy. See The Society of Gynecologic Oncology (SGO) position statement and Discussion.

[aa] Chemotherapy (IV or IP) has not been shown to be beneficial in ovarian borderline epithelial tumors (LMP).

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

NCCN Guidelines Version 2.2026
Malignant Sex Cord-Stromal Tumors

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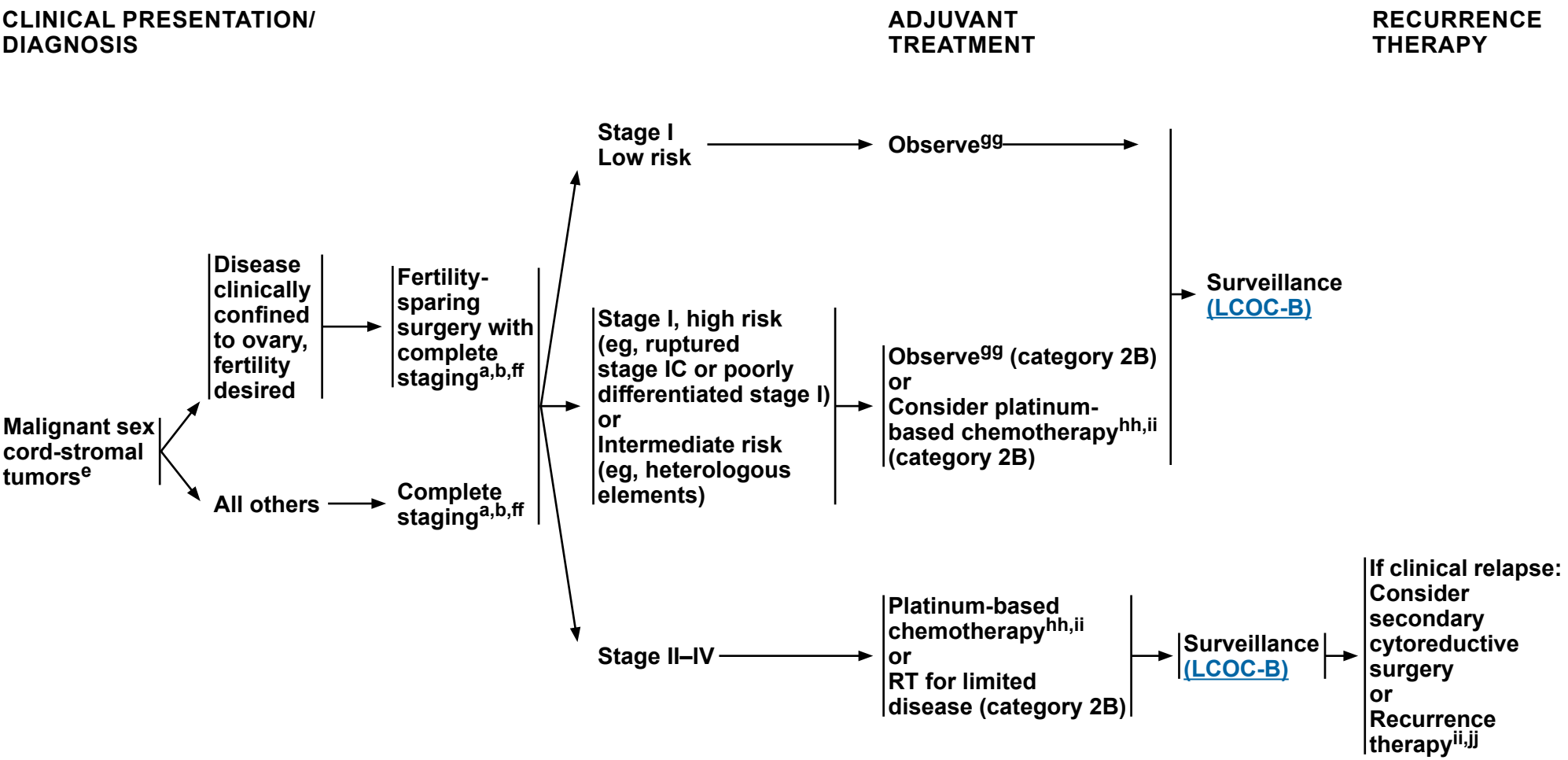
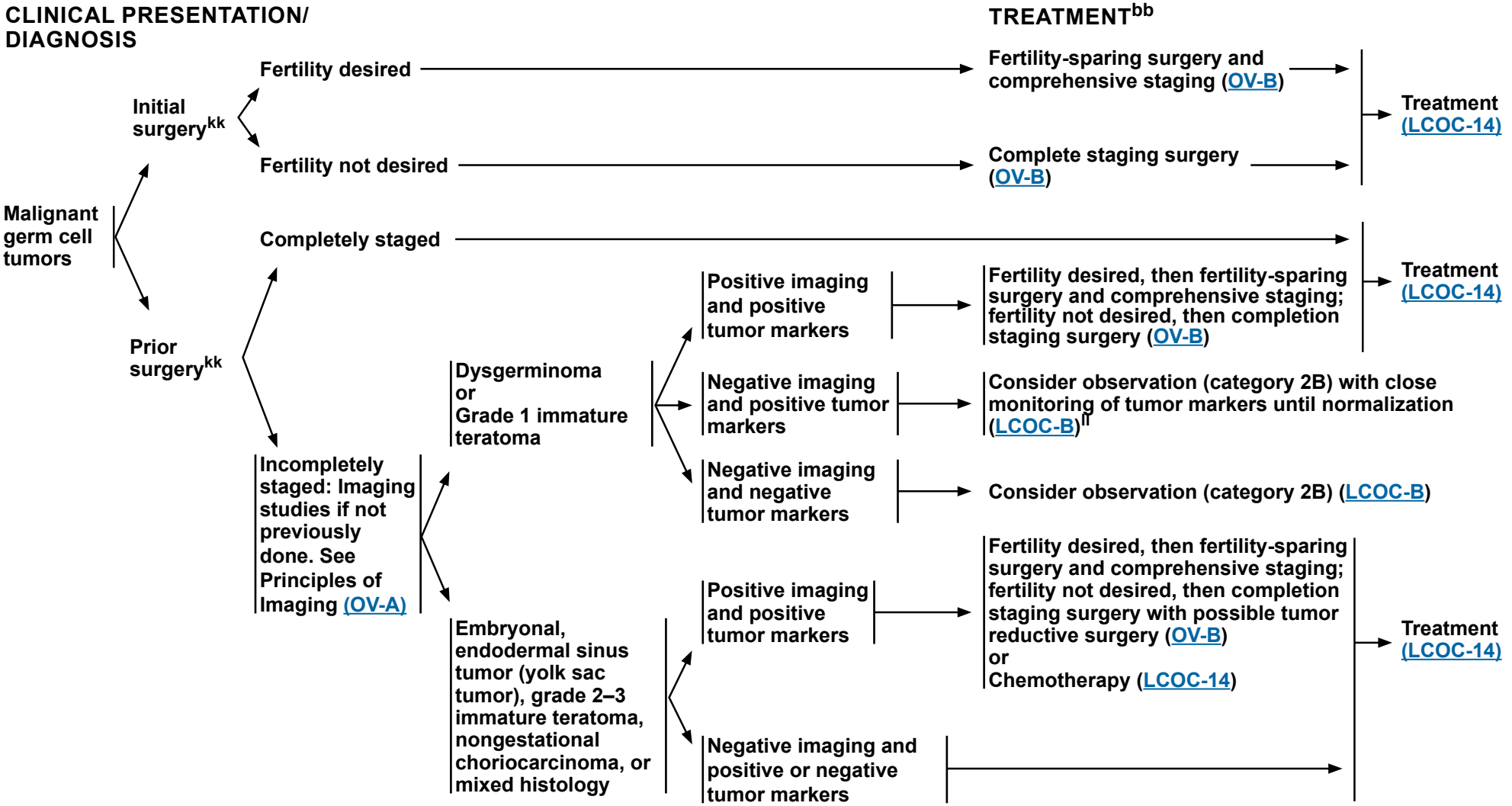


[a] Principles of Surgery (OV-B).
[b] Principles of Pathology (OV-C).
[e] WHO Histologic Classification (OV-F).
[ff] Lymphadenectomy may be omitted.
[gg] Inhibin levels can be followed for granulosa cell tumors.
[hh] Acceptable options include carboplatin/paclitaxel (preferred), EP (etoposide/cisplatin), or BEP (bleomycin/etoposide/cisplatin) (category 2B).
[ii] See Principles of Systemic Therapy (OV-D) and Systemic Therapy Regimens for Malignant Germ Cell/Sex Cord-Stromal Tumors (LCOC-A).
[jj] Localized RT can be considered to palliate symptoms and/or for oligometastatic disease.

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



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

[kk] Surgical principles for pediatric/young adult patients may differ from those for adult patients. See Principles of Surgery (OV-B).

[ll] Repeat imaging if tumor markers plateau at significant abnormal level or rise. If imaging positive, follow pathway above for positive imaging and positive tumor markers.

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

NCCN Guidelines Version 2.2026
Malignant Germ Cell Tumors

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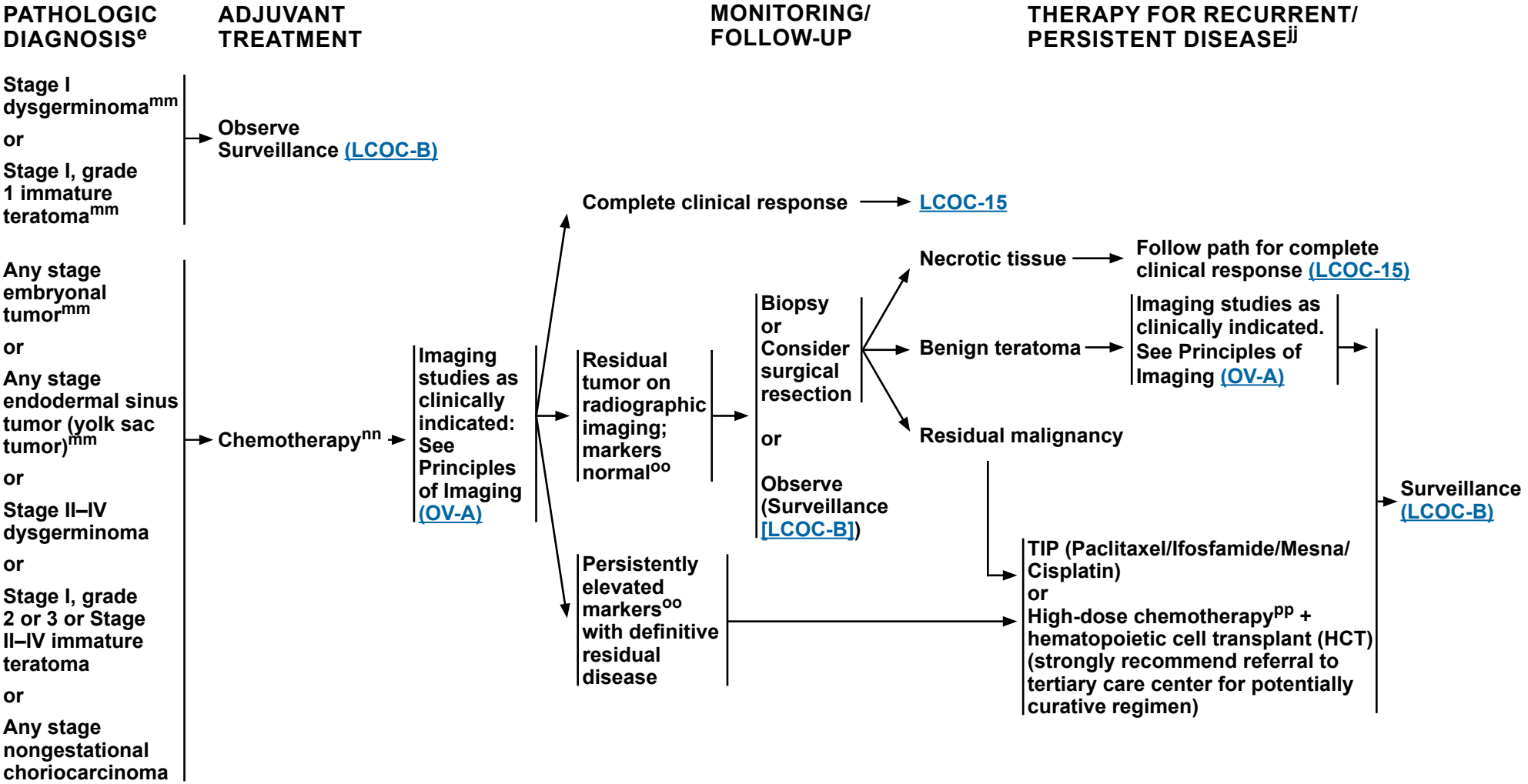


[e] WHO Histologic Classification (OV-F).

[jj] Localized RT can be considered to palliate symptoms and/or for oligometastatic disease.

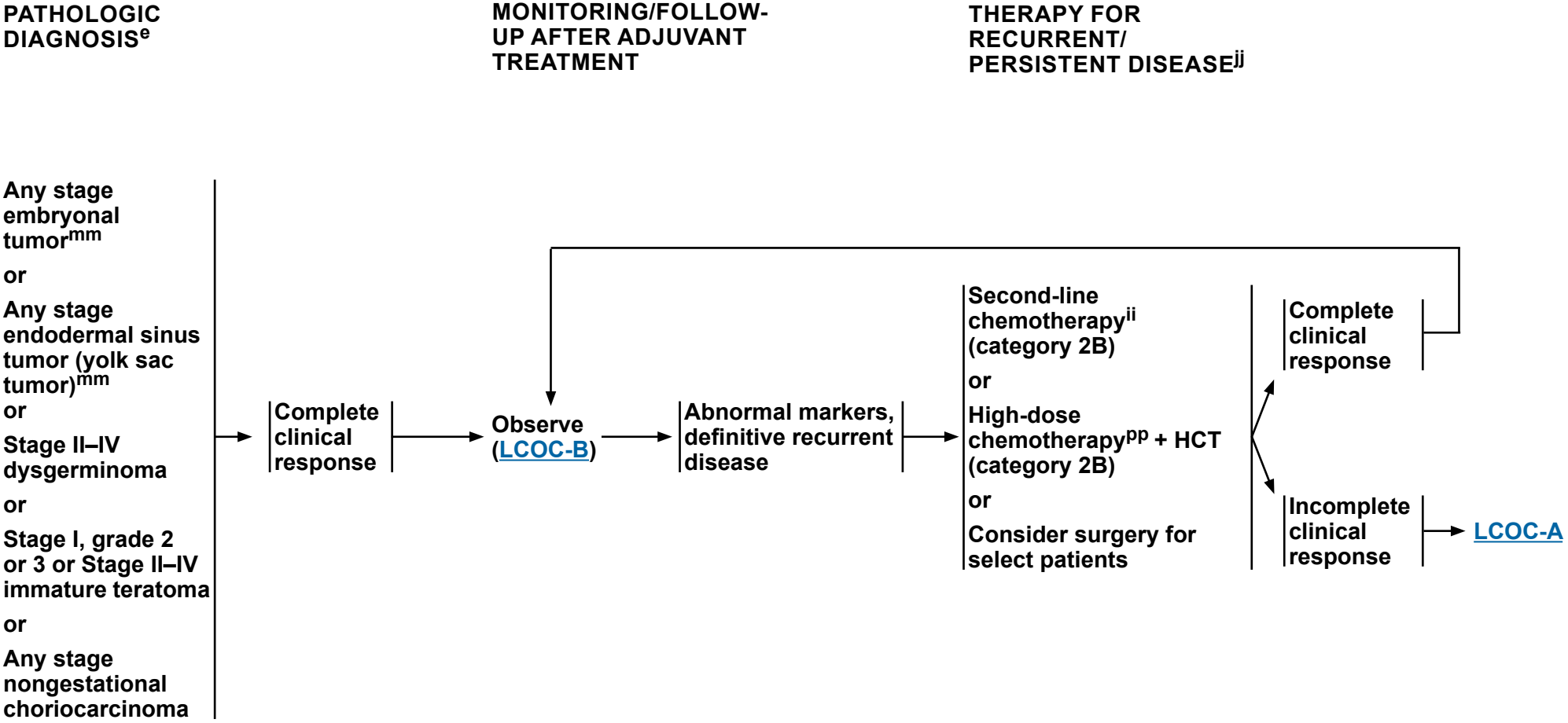
[mm] Pediatric/adolescent patients with the following clinical presentations may consider observation or chemotherapy as treatment options: stage IA, IB dysgerminoma; stage IA, grade 1 immature teratoma; stage IA embryonal carcinomas; or stage IA yolk sac tumors. Consultation with a pediatric oncologist for pediatric/adolescent patients is recommended.

[nn] Primary Systemic Therapy Regimens for Malignant Germ Cell Tumors (LCOC-A).

[oo] See OV-1 for markers.

[pp] High-dose chemotherapy regimens vary among institutions. Some patients are potentially curable with HCT. Patients with potentially curable recurrent germ cell disease should be referred to a tertiary care institution for HCT consultation and potentially curative therapy.

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



[e] WHO Histologic Classification (OV-F).
[ii] See Principles of Systemic Therapy (OV-D) and Systemic Therapy Regimens for Malignant Germ Cell/Sex Cord-Stromal Tumors (LCOC-A).
[jj] Localized RT can be considered to palliate symptoms and/or for oligometastatic disease.
[mm] Pediatric/adolescent patients with the following clinical presentations may consider observation or chemotherapy as treatment options: stage IA, IB dysgerminoma; stage IA, grade 1 immature teratoma; stage IA embryonal carcinomas; or stage IA yolk sac tumors. Consultation with a pediatric oncologist for pediatric/adolescent patients is recommended.
[pp] High-dose chemotherapy regimens vary among institutions. Some patients are potentially curable with HCT. Patients with potentially curable recurrent germ cell disease should be referred to a tertiary care institution for HCT consultation and potentially curative therapy.

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

SYSTEMIC THERAPY REGIMENS[a]
MALIGNANT GERM CELL/SEX CORD-STROMAL TUMORS

MALIGNANT GERM CELL TUMORS[a,b,c]

	Preferred	Useful in Certain Circumstances		
Primary Therapy	• BEP (Bleomycin, Etoposide, Cisplatin)[d] ▸ For good risk (category 2B) or poor risk	• Carboplatin/Etoposide[a,e] (for select patients with stage II–III resected dysgerminoma for whom minimizing toxicity is critical)		
Recurrence Therapy	**Preferred** (Potentially curative)	**Other Recommended** (Palliative only)		
	• High-dose chemotherapy[b] • TIP (Paclitaxel/Ifosfamide/Mesna/Cisplatin)	• Carboplatin/Docetaxel • Carboplatin/Paclitaxel • Docetaxel • Oral Etoposide • EP (Etoposide/Cisplatin), if not previously used • Gemcitabine/Oxaliplatin/Paclitaxel • Gemcitabine/Oxaliplatin • Gemcitabine/Paclitaxel	• Ifosfamide/Mesna/Paclitaxel • Paclitaxel • Pembrolizumab (if microsatellite instability-high [MSI-H]/mismatch repair deficient [dMMR] or tumor mutational burden-high [TMB-H]) • VAC (Vincristine, Dactinomycin, Cyclophosphamide)	• VEIP (Vinblastine/ Ifosfamide/Mesna/Cisplatin) • VIP (Etoposide/Ifosfamide/ Mesna/Cisplatin) • Supportive care (See NCCN Supportive Care Guidelines)

MALIGNANT SEX CORD-STROMAL TUMORS[a,c]

	Preferred	Other Recommended	Useful in Certain Circumstances
Primary Therapy	• Carboplatin/Paclitaxel	• Etoposide/Cisplatin (EP)	• BEP (category 2B)[d]
Recurrence Therapy	• Carboplatin/Paclitaxel	• Docetaxel • EP, if not previously used • Ifosfamide/Paclitaxel • Paclitaxel • Supportive care only (See NCCN Supportive Care Guidelines) • Targeted therapy: Bevacizumab (single agent)	• Aromatase inhibitors (eg, Anastrozole, Exemestane, Letrozole) • Leuprolide acetate or Goserelin acetate (for granulosa cell tumors) • Tamoxifen • BEP (category 2B),[d] if not previously used • VAC (category 2B)

[a] See Principles of Systemic Therapy (OV-D) and see Discussion for references.
[b] High-dose chemotherapy regimens vary among institutions. Some patients are potentially curable with HCT. Patients with potentially curable recurrent germ cell disease should be referred to a tertiary care institution for HCT consultation and potentially curative therapy.
[c] WHO Histologic Classification (OV-F).
[d] Recommend pulmonary function test if considering bleomycin.
[e] Consultation with a pediatric oncologist for pediatric/adolescent patients is recommended.

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

SURVEILLANCE
MALIGNANT GERM CELL/SEX CORD-STROMAL TUMORS

Malignant Germ Cell Tumors					
	Year 1	**Year 2**	**Year 3**	**Years 4–5**	**After 5 Years**
Clinical evaluation	Every 3 mo	Every 3 mo	Every 6 mo	Every 12 mo	Every 12 mo
Pelvic US[a]	Every 3 mo	Every 3 mo	Every 6 mo	--	--
Tumor markers[b]	Every 2 mo	Every 3 mo	Every 6 mo	Every 12 mo	Every 12 mo up to 10 y
Chest x-ray[c]	--	--	--	Every 6 mo	As clinically indicated
C/A/P CT/MRI[c]	Every 3 mo	Every 3 mo	Every 6–12 mo	As clinically indicated	As clinically indicated

Malignant Sex Cord-Stromal Tumors[d]		
	0–2 Years	**After 2 Years**
Physical exam	• As clinically indicated based on stage (6–12 mo if early-stage, low-risk disease; 4–6 mo if high-risk disease)	• As clinically indicated based on stage (6–12 mo if early-stage, low-risk disease; 4–6 mo if high-risk disease)
Serum tumor markers[b]	• Testing as clinically indicated, if applicable • If done, frequency based on stage (6–12 mo if early-stage, low-risk disease; 4–6 mo if high-risk disease)	• Testing as clinically indicated, if applicable • If done, frequency based on stage (6–12 mo if early-stage, low-risk disease; 4–6 mo if high-risk disease)
Imaging[c]	• Reserved for patients with symptoms, elevated biomarkers, or suspicious findings on physical exam	• Reserved for patients with symptoms, elevated biomarkers, or suspicious findings on physical exam

[a] Only for those patients who have a residual ovary.
[b] See OV-1 for markers.
[c] Principles of Imaging (OV-A).
[d] Salani R, Khanna N, Frimer M, et al. An update on post-treatment surveillance and diagnosis of recurrence in women with gynecologic malignancies: Society of Gynecologic Oncology (SGO) recommendations. Gynecol Oncol 2017;146:3-10.

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

PRINCIPLES OF IMAGING

General:

- CT is performed with oral and iodinated IV contrast (unless contraindicated due to anaphylaxis or significant renal dysfunction) with or without rectal contrast.
- MRI is performed with gadolinium-based contrast agents (unless contraindicated due to anaphylaxis) and is preferred in select patients with renal dysfunction over CT.
  - Chest CT can be done with or without iodinated IV contrast.

Imaging Recommendations:

- For imaging workup of epithelial ovarian cancer, fallopian tube cancer, and primary peritoneal cancer, including LCOCs, see Table 1 on OV-A (2 of 4)
- For treatment response assessment and monitoring/follow-up/surveillance of epithelial ovarian cancer, fallopian tube cancer, and primary peritoneal cancer, see Table 2 on OV-A (2 of 4)
- For monitoring/follow-up for LCOCs, see Table 3 on OV-A (3 of 4)
- For surveillance of malignant germ cell tumors and malignant sex cord-stromal tumors, see Table 4 on OV-A (4 of 4)

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

PRINCIPLES OF IMAGING

Table 1. General Imaging Recommendations for Workup of Epithelial Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer, including LCOCs

Workup	Imaging as Clinically Indicated
• Suspicious/palpable pelvic mass on abdomen/pelvis exam and/or • Ascites, abdominal distention and/or • Symptoms without source of malignancy	• Pelvis ultrasound • A/P CT/MRI If there is concern for metastatic or disseminated disease: • Chest CT May be indicated for indeterminate ovarian lesions, if results will alter management: • PET/CT, MRI, or PET/MRI
• Patient referred with newly diagnosed ovarian cancer, including LCOCs, after recent surgical procedure	• Chest/abdomen/pelvis (C/A/P) CT • Chest CT & A/P MRI • PET/MRI or PET/CT (skull base to mid-thigh)

Table 2. Treatment Response Assessment and Monitoring/Follow-Up/Surveillance Imaging Recommendations for Epithelial Ovarian Cancer/ Fallopian Tube Cancer/Primary Peritoneal Cancer

Treatment Response Assessment	Imaging as Clinically Indicated
• Patients receiving primary chemotherapy ▸ Stage IA ▸ Stage IB ▸ Stage IC	• C/A/P CT • Chest CT & A/P MRI • PET/MRI or PET/CT (skull base to mid-thigh)
• Patients receiving platinum-based chemotherapy ▸ Stage II–IV	
• Patients receiving primary chemotherapy and primary adjuvant therapy ▸ Stage II–IV	
Monitoring/Follow-Up/Surveillance	**Imaging as Clinically Indicated**
• For patients not receiving treatment ▸ Stage I–IV	• C/A/P CT • Chest CT & A/P MRI • PET/MRI or PET/CT (skull base to mid-thigh)
• Recurrent disease	

For Monitoring/Follow-Up of LCOCs, see OV-A (3 of 4)
For Surveillance of LCOCs, see OV-A (4 of 4)

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

PRINCIPLES OF IMAGING

Table 3. Imaging Recommendations for Monitoring/Follow-Up of LCOCs

Monitoring/Follow-Up	Imaging as Clinically Indicated
• Low-grade serous carcinoma	Imaging for recurrence: • C/A/P CT • Chest CT & A/P MRI • PET/MRI or PET/CT (skull base to mid-thigh)
• Ovarian serous borderline epithelial tumor (LMP) ▸ Incomplete surgical staging or tumor reductive surgery	Imaging if not previously done: • C/A/P CT • Chest CT & A/P MRI • PET/MRI or PET/CT (skull base to mid-thigh)
• Ovarian serous borderline epithelial tumors (LMP) ▸ Borderline on final pathology	• C/A/P CT • Chest CT & A/P MRI • PET/MRI or PET/CT (skull base to mid-thigh) For patients with fertility-sparing surgery: • Ultrasound
• Malignant germ cell tumors ▸ Prior surgery; incompletely staged ▸ Post-adjuvant treatment ◊ Any stage embryonal tumor ◊ Any stage endodermal sinus tumor (yolk sac tumor) ◊ Stage II–IV dysgerminoma ◊ Stage I, grade 2 or 3, or Stage II–IV immature teratoma ◊ Any stage non-gestational choriocarcinoma	• C/A/P CT • Chest CT & A/P MRI • PET/MRI or PET/CT (skull base to mid-thigh)
• Benign teratoma	• C/A/P CT or A/P MRI
• Small cell carcinoma of the ovary (hypercalcemic type)	• PET/CT (skull-base to mid-thigh) ▸ Every 3–6 months for 2 years ▸ Then annually

For Surveillance of LCOCs, see OV-A (4 of 4)

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

PRINCIPLES OF IMAGING

Table 4. Imaging Recommendations for Surveillance of Malignant Germ Cell Tumors and Sex Cord-Stromal Tumors

Surveillance	Imaging as Clinically Indicated
• Malignant germ cell tumors	• Chest x-ray ▸ Every 6 months for years 4–5 ▸ As indicated after 5 years • C/A/P CT or A/P MRI ▸ Every 3 months for years 1–2 ▸ Every 6–12 months for year 3 ▸ As clinically indicated for years 4–5 ▸ As clinically indicated after 5 years For patients who have a residual ovary: • Pelvis ultrasound ▸ Every 3 months for years 1–2 ▸ Every 6 months for year 3
• Malignant sex cord-stromal tumors	Imaging for patients with symptoms, elevated biomarkers or suspicious findings on physical exam: • Chest x-ray • C/A/P CT • A/P MRI • PET/CT or PET

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

PRINCIPLES OF SURGERY[1]

General Considerations

- It is recommended that a gynecologic oncologist perform the appropriate surgery.
- An open laparotomy including a vertical midline abdominal incision should be used in most patients with a suspected malignant ovarian/fallopian tube/primary peritoneal neoplasm in whom a surgical staging procedure, a primary debulking procedure, an interval debulking procedure, or secondary cytoreduction is planned.
  - For select patients, a minimally invasive surgical approach may be used by an experienced surgeon to manage early-stage disease.
  - Laparoscopy may be useful to evaluate whether optimal cytoreduction can be achieved in patients with newly diagnosed advanced-stage or recurrent disease.
  - Minimally invasive techniques can be used for select patients for interval debulking procedures. Patients who are unable to be optimally debulked using minimally invasive techniques should be converted to an open procedure.
- Intraoperative pathologic evaluation with frozen sections may assist in management.
- Prior to surgery for ovarian cancer, counsel patients about port placement if intraperitoneal (IP) chemotherapy is being considered.

Operative Reports

- Surgeons should describe the following in the operative report:
  - Extent of initial disease before debulking pelvis, mid-abdomen, or upper abdomen (cutoffs: pelvic brim to lower ribs).
  - Amount of residual disease in the same areas after debulking.
  - Complete or incomplete resection; if incomplete, indicate the size of the major lesion and total number of lesions. Indicate if miliary or small lesions.

[1] Fleming GF, Seidman J, Yemelyanova A, Lengyl E. Epithelial Ovarian Cancer. In: Chi DS, Berchuck A, Dizon D, et al (eds). Principles and Practice of Gynecologic Oncology, 7th ed. Philadelphia: Lippincott Williams & Wilkins; 2017:611-705.

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

PRINCIPLES OF SURGERY[1]

Newly Diagnosed Invasive Epithelial Ovarian Cancer Apparently Confined to the Ovaries, Fallopian Tubes, and Uterus (apparent stage IA–IIA)

In general, every effort should be made during a primary cytoreduction procedure to achieve maximum cytoreduction of all pelvic disease and to evaluate for occult disease in the upper abdomen or retroperitoneum.

- On entering the abdomen, aspiration of ascites or peritoneal lavage should be performed for peritoneal cytologic examinations.
- All peritoneal surfaces should be visualized, and any peritoneal surface or adhesion suspicious for harboring metastasis should be selectively excised or biopsied. In the absence of any suspicious areas, random peritoneal biopsies should be taken from the pelvis, paracolic gutters, and undersurfaces of the diaphragm (diaphragm scraping for Papanicolaou stain is an acceptable alternative).
- BSO and hysterectomy should be performed with every effort to keep an encapsulated mass intact during removal.
- For selected patients desiring to preserve fertility, USO or BSO with uterine preservation may be considered. Uterine preservation allows for potential future assisted reproductive approaches.
- Omentectomy should be performed.
- Para-aortic lymph node dissection should be performed by stripping the nodal tissue from the vena cava and the aorta bilaterally to at least the level of the inferior mesenteric artery and preferably to the level of the renal vessels.
- The preferred method of dissecting pelvic lymph nodes is bilateral removal of lymph nodes overlying and anterolateral to the common iliac vessel, overlying and medial to the external iliac vessel, overlying and medial to the hypogastric vessels, and from the obturator fossa at a minimum anterior to the obturator nerve.[2]

Newly Diagnosed Invasive Epithelial Ovarian Cancer Involving the Pelvis and Upper Abdomen (stage >IIB)

In general, every effort should be made during a primary cytoreduction procedure to achieve maximum cytoreduction of all abdominal, pelvic, and retroperitoneal disease. Residual disease <1 cm defines optimal cytoreduction; however, maximal effort should be made to remove all gross disease since this offers superior survival outcomes.[3]

- Aspiration of ascites (if present) should be performed for peritoneal cytologic examinations. All involved omentum should be removed.
- Suspicious and/or enlarged nodes, identified on preoperative imaging or during surgical exploration, should be resected, if possible. Resection of clinically negative nodes is not required.[4]
- Procedures that may be considered for optimal surgical cytoreduction (in all stages) include bowel resection and/or appendectomy, stripping of the diaphragm or other peritoneal surfaces, splenectomy, partial cystectomy and/or ureteroneocystostomy, partial hepatectomy, partial gastrectomy, cholecystectomy, and/or distal pancreatectomy.
- Select patients with low-volume residual disease after surgical cytoreduction for invasive epithelial ovarian or peritoneal cancer are potential candidates for IP therapy. In these patients, consideration should be given to placement of IP catheter with initial surgery.

[1] Fleming GF, Seidman J, Yemelyanova A, Lengyl E. Epithelial Ovarian Cancer. In: Chi DS, Berchuck A, Dizon D, et al (eds). Principles and Practice of Gynecologic Oncology, 7th ed. Philadelphia: Lippincott Williams & Wilkins; 2017:611-705.
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[3] Chi DS, Eisenhauer EL, Zivanovic O, et al. Improved progression-free and overall survival in advanced ovarian cancer as a result of a change in surgical paradigm. Gynecol Oncol 2009;114:26-31.
[4] Harter P, Sehouli J, Lorusso D, et al. A randomized trial of lymphadenectomy in patients with advanced ovarian neoplasms. N Engl J Med 2019;380:822-832.

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

PRINCIPLES OF SURGERY[1]

Interval Debulking Surgery After Neoadjuvant Chemotherapy of Invasive Epithelial Ovarian Cancer

As with a primary debulking procedure, every effort should be made to achieve maximum cytoreduction during an interval debulking procedure. Maximal effort should be made to remove all gross disease in the abdomen, pelvis, and retroperitoneum. Consultation with a gynecologic oncologist is recommended.

- IDS, including completion hysterectomy and BSO with staging, should be performed after 3–4 cycles of neoadjuvant chemotherapy for patients with a response to chemotherapy or stable disease. Alternate timing of surgery has not been prospectively evaluated but may be considered based on individual patient-centered factors.
- HIPEC with cisplatin (100 mg/m^2) can be considered at the time of IDS for stage III disease. HIPEC can also be considered for suitable stage IV patients (category 2B) who have had a favorable response to neoadjuvant therapy both intraperitoneally and extraperitoneally, or in whom stage IV disease sites have completely resolved (eg, resolution of malignant pleural effusion) or are now deemed resectable. Sodium thiosulfate may be administered at the start of perfusion, followed by a continuous infusion, to allow for renal protection during HIPEC.
- All peritoneal surfaces should be visualized, and any peritoneal surface or adhesion suspicious for harboring metastasis should be selectively excised or biopsied.
- An omentectomy should be performed.
- While systematic lymphadenectomy of clinical-negative nodes is not recommended, suspicious and/or enlarged nodes should be resected, if possible.
- Procedures that may be considered for optimal surgical debulking include bowel resection and/or appendectomy, stripping of the diaphragm or other peritoneal surfaces, splenectomy, partial cystectomy and/or ureteroneocystostomy, partial hepatectomy, partial gastrectomy, cholecystectomy, and/or distal pancreatectomy.

[1] Fleming GF, Seidman J, Yemelyanova A, Lengyl E. Epithelial Ovarian Cancer. In: Chi DS, Berchuck A, Dizon D, et al (eds). Principles and Practice of Gynecologic Oncology, 7th ed. Philadelphia: Lippincott Williams & Wilkins; 2017:611-705.

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

PRINCIPLES OF SURGERY[1]

Risk-Reducing Salpingo-Oophorectomy (RRSO) Protocol

- For information on when RRSO is indicated, see NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate.
- Perform minimally invasive laparoscopic surgery.
- Survey upper abdomen, bowel surfaces, omentum, appendix (if present), and pelvic organs.
- Biopsy any abnormal peritoneal findings.
- Obtain pelvic washing for cytology (50 cc normal saline instilled and aspirated immediately).
- Perform total BSO, removing 2 cm of proximal ovarian vasculature/IP ligament, all tube up to the cornua, and all peritoneum surrounding the ovaries and tubes, especially peritoneum underlying areas of adhesion between tube and/or ovary and the pelvic sidewall.[5]
- Engage in minimal instrument handling of the tubes and ovaries to avoid traumatic exfoliation of cells.[5]
- Both ovaries and tubes should be placed in an endobag for retrieval from the pelvis.
- Both ovaries and tubes should be processed by sectioning and extensively examining the fimbriated end (SEE-FIM) protocol.[6]
- If occult malignancy or serous tubal intraepithelial carcinoma (STIC) is identified, refer to a gynecologic oncologist.
- The prevention benefits of salpingectomy alone are not yet proven. If considered, the fallopian tube from the fimbria to its insertion into the uterus should be removed. In addition, the fallopian tube should be processed and assessed as described above. The concern for risk-reducing salpingectomy alone is that patients are still at risk for developing ovarian cancer. In addition, in premenopausal patients, oophorectomy reduces the risk of developing breast cancer but the magnitude is uncertain. See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate.

[1] Fleming GF, Seidman J, Yemelyanova A, Lengyl E. Epithelial Ovarian Cancer. In: Chi DS, Berchuck A, Dizon D, et al (eds). Principles and Practice of Gynecologic Oncology, 7th ed. Philadelphia: Lippincott Williams & Wilkins; 2017:611-705.
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Note: All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF SURGERY[1]

Special Circumstances

- *Fertility-sparing surgery:*
  - Fertility-sparing surgery with USO (preserving the uterus and contralateral ovary) or BSO (preserving the uterus) can be considered for patients with apparent early-stage disease and/or low-risk tumors (early-stage invasive epithelial tumors, LMP lesions, malignant germ cell tumors, mucinous tumors, or malignant sex cord-stromal tumors) who wish to preserve fertility. Consider endometrial sampling to exclude synchronous primary or hyperplasia. Refer to reproductive endocrinologist for evaluation and REI consultation as clinically indicated. Comprehensive surgical staging should still be performed to rule out occult higher stage disease but may be omitted in pediatric, adolescent, and young adult patients with clinically apparent early-stage malignant germ cell tumors based on the pediatric surgical literature.[7]
- *Mucinous tumors:*
  - Primary invasive mucinous tumors of the ovary are uncommon. Thus, the upper and lower GI tract should be carefully evaluated to rule out an occult GI primary with ovarian metastases, and an appendectomy need only be performed in patients with a suspected or confirmed mucinous ovarian neoplasm if it appears to be abnormal. A normal appendix does not require surgical resection in this setting. If mucinous histology is confirmed by intraoperative frozen section analysis and there are no suspicious lymph nodes, consider omitting lymphadenectomy.
- *Ovarian borderline epithelial (LMP) tumors:*
  - Although data show upstaging with lymphadenectomy, other data show that lymphadenectomy does not affect overall survival. However, omentectomy and multiple biopsies of peritoneum (the most common sites of peritoneal implants) may upstage patients in approximately 30% of cases and may affect prognosis.
- *Secondary cytoreduction:*
  - A secondary cytoreduction procedure can be considered in patients with recurrent ovarian cancer who develop a recurrence more than 6 months since completion of initial chemotherapy, have a good performance status, have no ascites, and have an isolated focus or limited foci of disease amenable to complete resection. In addition to preoperative imaging, laparoscopy may be used to determine if complete resection can be achieved. Secondary cytoreduction can be performed with either open or minimally invasive approaches. Consider using validated scoring methods to assess suitability for secondary cytoreduction.

Ancillary Palliative Surgical Procedures[a]

These procedures may be appropriate in select patients:
- Paracentesis/indwelling peritoneal catheter
- Thoracentesis/pleurodesis/video-assisted thoracoscopy/indwelling pleural catheter
- Ureteral stents/nephrostomy
- Gastrostomy tube/intestinal stents/surgical relief of intestinal obstruction

[a] Decisions on the use of ancillary procedures should be made in conjunction with a gynecologic oncology surgeon or a practitioner familiar with ovarian cancer patterns of recurrence.

[1] Fleming GF, Seidman J, Yemelyanova A, Lengyl E. Epithelial Ovarian Cancer. In: Chi DS, Berchuck A, Dizon D, et al (eds). Principles and Practice of Gynecologic Oncology. 7th ed. Philadelphia: Lippincott Williams & Wilkins; 2017:611-705.
[7] Billmire D, Vinocur C, Rescorla F, et al. Outcome and staging evaluation in malignant germ cell tumors of the ovary in children and adolescents: an intergroup study. J Pediatr Surg 2004;39:424-429.

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

PRINCIPLES OF PATHOLOGY

General

- The complete histologic classification from the WHO is included in the NCCN Guidelines (WHO Histologic Classification on OV-F).[1] The WHO pathology manual is also a useful resource.[1]
- Most ovarian cancers, including the LCOC, are diagnosed after pathologic analysis of a biopsy or surgical specimen. Fine-needle aspiration (FNA) should be avoided for diagnosis of ovarian cancer in patients with presumed early-stage disease to prevent rupturing the cyst and spilling malignant cells into the peritoneal cavity. However, FNA may be necessary in patients with bulky disease who are not candidates for primary debulking.[2,3]
- Both primary peritoneal and fallopian tube cancers are usually diagnosed postoperatively (if there is no major involvement of the ovary) or preoperatively (if there is a biopsy and the patient has already had a bilateral salpingo-oophorectomy). Primary peritoneal and fallopian tube cancers are treated in the same manner as epithelial ovarian cancer.
- The College of American Pathologists (CAP) protocol is a useful tool for pathology reports.[4]
- Pathologic assessment should include:
  - Elements from CAP protocol[4]:
    - ◊ Tumor site(s) (eg, ovary, fallopian tube, or primary peritoneum)
    - ◊ Tumor size(s)
    - ◊ Other tissue/organ involvement
    - ◊ Ovarian/fallopian tumors: surface involvement (present/absent/cannot determine), specimen integrity (capsule/serosa intact/fractured/fragmented)
    - ◊ Histologic type and grade
    - ◊ Extension and/or implants (if sampled/identified)
    - ◊ Cytology: peritoneal or ascitic fluid or washings/pleural fluid
    - ◊ Lymph nodes: number and location of nodes examined, size of largest metastatic deposits
    - ◊ STIC, endometriosis (particularly if in continuity with endometrioid or clear cell carcinoma), and/or endosalpingiosis
    - ◊ Staging information (FIGO and TNM)
- Tumor biomarker testing
  - In the upfront setting, choice of somatic testing should, at a minimum, optimize identification of molecular alterations that can inform use of interventions that have demonstrated benefit in this setting, including *BRCA1/2*, loss of heterozygosity (LOH), or homologous recombination deficiency (HRD) status in the absence of a germline *BRCA1/2* P/LP variants.
  - In the recurrence setting, tumor biomarker testing is recommended to include, as appropriate, tests to identify potential benefit from targeted therapeutics that have tumor-specific or tumor-agnostic benefit including, but not limited to, HER2 status (by IHC), PD-L1 (IHC, CPS), *BRCA1/2*, HRD status, microsatellite instability (MSI), mismatch repair (MMR), tumor mutational burden (TMB), *BRAF*, *KRAS,* FRα (FOLR1)*, RET,* and *NTRK1/2/3* if prior testing did not include these markers. Multigene panel testing (MGPT) may be particularly important in less common histologies with limited approved therapeutic options. It is recommended that such testing be performed on the most recent available tumor tissue.
  - Biomarker testing may be performed on circulating tumor DNA (ctDNA) when tissue-based analysis is not clinically feasible.
  - Validated biomarker testing should be performed in a Clinical Laboratory Improvement Amendments (CLIA)-approved facility.
  - Current clinical HRD tests are proxy measures of HRD and lack accuracy in fully predicting functional HRD. HRD testing is recommended for those patients without germline *BRCA1/2* P/LP variants as HRD test status may provide information on the magnitude of benefit of PARP inhibitor maintenance therapy in these patients. The Panel considers the use of PARPi in patients who have HRP tumors, at present, to be of minimal benefit.

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

References

PRINCIPLES OF PATHOLOGY

Less Common Ovarian Cancers (LCOC)

- A borderline tumor is a primary epithelial lesion with cytologic characteristics suggesting malignancy but without frank invasion. The terms for borderline epithelial tumors (also known as LMP tumors or atypical proliferative tumors) have changed over the years.[5] The 2023 CAP protocol for ovarian cancer uses borderline and does not use LMP.[4] Borderline epithelial tumors are typically serous or mucinous; other histologic subtypes can also occur (WHO Histologic Classification on OV-F).[1,6] Approximately 30% of serous borderline tumors are associated with peritoneal implants, which may be either noninvasive or invasive. According to WHO, invasive implants are synonymous with low-grade serous carcinoma and require adjuvant therapy.[1] Noninvasive implants appear to confer at least a 15% to 20% increased risk of subsequent low-grade serous carcinoma. While these patients do not require adjuvant therapy, they do require extended clinical follow-up as recurrences may occur 5 years or more after diagnosis.[7]
- Clear cell carcinomas are high-grade tumors that may arise in endometriosis. Most clear cell carcinomas express napsin A and are negative for WT1 and estrogen receptors.[5]
- It is difficult to distinguish based on histology between primary mucinous ovarian carcinomas and GI metastases.[8,9,10] PAX8 immunostaining is typical of primary ovarian tumors, although the absence of PAX8 does not rule out ovary as the primary site,[11] while SATB2 is consistent with colonic origin.[12] Features favoring primary ovarian carcinoma versus metastasis are: unilateral, "expansile" pattern of invasion, complex papillary pattern, size for mucinous carcinoma, >13 cm for primary and <13 cm for metastatic, smooth external surface, microscopic cystic glands, necrotic luminal debris, mural nodules and accompanying teratoma, adenofibroma, endometriosis, or Brenner tumor.[13]
- Most early stage invasive mucinous ovarian cancers have an expansile pattern of growth characterized by complex glandular, papillary and/or cribriform architecture with a labyrinthine or anastomosing pattern and little or no intervening stroma. About 20% have an infiltrative pattern of destructive invasion of haphazardly arranged and angulated tumor cell nests into a desmoplastic stroma and measuring at least 5 mm in linear extent–and this has been associated with an increased risk of relapse and mortality.[14,15]
- Metastatic colorectal adenocarcinomas also usually are positive for CK20.
- Endometrioid carcinomas may be associated with endometriosis.[11,16] Endometrioid adenocarcinomas are usually positive for cytokeratin 7 (CK7), PAX8, and estrogen receptors. Endometrioid tumors are also very similar in appearance to sex cord-stromal tumors.[5]
- Most pathologists now consider MMMTs to be a variant of poorly differentiated epithelial ovarian cancer (metaplastic carcinoma).[17]

Special Circumstances

- Other cancers[18,19] that can commonly involve the adnexa include:
  - Uterine
  - Cervical
  - GI (small and large bowel, pancreatic)
  - Lymphoma
- For risk-reducing surgery, pathologic assessment should include the following:
  - Fallopian tubes should be processed by SEE-FIM of the tubes and then assessed to determine whether any evidence of cancer is present.[4]
  - The ovaries should also be carefully sectioned, processed, and assessed.[4] The 2023 CAP protocol describes the process for sectioning the fallopian tubes and ovaries.[4]
- Patients who have equivocal pathologic findings or who are referred to NCCN Member Institutions after having a previous diagnosis of ovarian cancer should have their pathology reviewed by pathologists at NCCN Member Institutions.

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

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

NCCN Guidelines Version 2.2026
Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer

PRINCIPLES OF SYSTEMIC THERAPY

General Principles

Primary Systemic Therapy Regimens - Epithelial Ovarian/Fallopian Tube/Primary Peritoneal

Acceptable Recurrence Therapies - Epithelial Ovarian/Fallopian Tube/Primary Peritoneal

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

PRINCIPLES OF SYSTEMIC THERAPY

General

- Patients with ovarian, fallopian tube, or peritoneal cancer should be encouraged to participate in clinical trials during all aspects of their diagnosis and treatment.
- Prior to recommending chemotherapy, requirements for adequate organ function and performance status should be met.
- Prior to the initiation of any therapy:
  - All patients with suspected stage IIIC or IV invasive epithelial ovarian cancer should be evaluated by a gynecologic oncologist prior to initiation of therapy to determine whether they are candidates for primary cytoreductive surgery (PCS).
  - Patients of childbearing potential who desire fertility-sparing procedures should be referred to an appropriate fertility specialist (see Fertility, Reproductive Endocrine, and Sexual Health Considerations for Individuals with Ovaries in the NCCN Guidelines for Adolescent and Young Adult [AYA] Oncology).
  - Goals of systemic therapy should be discussed.
- Consider scalp cooling to reduce incidence of alopecia for patients receiving chemotherapy with high rates of alopecia.
- Patients should be observed closely and treated for any complications during chemotherapy. Appropriate blood chemistry tests should be monitored. Appropriate dose reductions and modifications of chemotherapy should be performed depending on toxicities experienced and goals of therapy.
- After completion of chemotherapy, patients should be assessed for response during and following treatment and monitored for any long-term complications.
- Chemosensitivity/resistance and/or other biomarker assays are being used at some NCCN Member Institutions for decisions related to future chemotherapy in situations where there are multiple equivalent chemotherapy options available. The current level of evidence is not sufficient to supplant standard-of-care chemotherapy.
- An FDA-approved biosimilar is an appropriate substitute for any recommended systemic biologic therapy in the NCCN Guidelines.
- Pembrolizumab and berahyaluronidase alfa-pmph subcutaneous injection may be substituted for IV pembrolizumab. Pembrolizumab and berahyaluronidase alfa-pmph has different dosing and administration instructions compared to IV pembrolizumab.
- For information regarding *DPYD* testing, see the NCCN Guidelines for Colon Cancer.

Definitions Used in the NCCN Guidelines for Ovarian Cancer

- **Adjuvant therapy:** Drugs, radiation, or other forms of supplemental treatment following cancer surgery intended to decrease the risk of disease recurrence or to primarily treat residual disease, whether gross or microscopic, following surgical cytoreduction.
- **Neoadjuvant therapy:** Drugs, radiation, or other forms of treatment given prior to cancer surgery intended to reduce tumor burden in preparation for surgery.
- **Recurrence therapy:** Drugs, radiation, or other forms of treatment used to treat recurrent cancer, control symptoms, or increase length and/or quality of life at the time of clinical, biochemical, or radiographic evidence of recurrent cancer following the initial treatment.

For Patients with Newly Diagnosed Ovarian, Fallopian Tube, or Primary Peritoneal Cancer:

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

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

PRINCIPLES OF SYSTEMIC THERAPY

Principles of Neoadjuvant Therapy

- Consider the histology of the primary tumor and the potential response to primary chemotherapy when evaluating for neoadjuvant chemotherapy.
- Any of the primary IV regimens for stage II–IV high-grade serous carcinoma and respective LCOCs can be used as neoadjuvant therapy before surgery. Neoadjuvant therapy does not apply to LMP and other noninvasive cancers. See OV-D (6 of 12), LCOC-5A, and LCOC-A.
- Bevacizumab-containing regimens should be used with caution before surgery due to potential interference with postoperative healing. If Bevacizumab is being used as part of a neoadjuvant regimen, Bevacizumab should be withheld from therapy for 4–6 weeks prior to surgery.
- After neoadjuvant therapy and surgery, any of the adjuvant therapy options for high-grade serous carcinoma (IV or IP/IV) and respective LCOCs can be considered. Neoadjuvant therapy does not apply to LMP and other noninvasive cancers. See OV-D (6 of 12), LCOC-5A, and LCOC-A.
- There are limited data for the use of IP chemotherapy regimens after neoadjuvant therapy and surgery. The following is an additional IP option after surgery: Paclitaxel 135 mg/m^2 IV on Day 1, Carboplatin area under the curve (AUC) 6 IP on Day 1, and Paclitaxel 60 mg/m^2 IP on Day 8.[1]
- A minimum of 6 cycles of treatment is recommended, including at least 3 cycles of adjuvant therapy after surgery. Patients with stable disease who are tolerating therapy may continue past 6 cycles.

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

References

PRINCIPLES OF SYSTEMIC THERAPY

Principles of Maintenance PARP Inhibitor (PARPi) Therapy

- *Post Primary Treatment*
  - Certain patients with newly diagnosed stage II–IV disease (high-grade serous, grade 2/3 endometrioid, or *BRCA1/2*-mutated clear cell carcinoma or carcinosarcoma) may benefit from maintenance therapy with PARPi if CR or PR is achieved after primary treatment with surgery and platinum-based first-line therapy. See OV-5 for PARPi options and patient selection criteria.
  - Data are limited for use of maintenance PARPi post primary treatment in patients with stage II disease and for those with LCOC.
- *Post Recurrence Treatment*
  - Patients with *BRCA1*/2-mutated recurrent disease may benefit from maintenance therapy with PARPi after recurrence therapy, if in CR or PR after platinum-based recurrence therapy, and if no prior progression on a PARPi. See OV-8 for PARPi options and patient selection criteria.
- *General Information on PARPi*
  - For patients receiving PARPi, careful monitoring of blood counts is required.
  - Monitoring of renal and hepatic function is recommended.
  - Monitoring of blood pressure is required for Niraparib, and recommended for all other PARPi.
  - Appropriate dose holds and modifications should be made depending on the toxicity noted.
  - Data are limited on the use of maintenance PARPi in LCOC.
  - Refer to the package insert for more detailed information.

Regimen	Dose/Administration	Maintenance Setting	Duration
Niraparib monotherapy[2,3]	• 300 mg PO once daily (or an initial dose of 200 mg once daily for patients with a baseline body weight of <77 kg, and/or a platelet count of <150,000/mm^3	Post-primary chemotherapy	• Up to 36 Months unless disease progression or unacceptable toxicity[b]
		Post-recurrence chemotherapy[a]	• Until disease progression or unacceptable toxicity[c]
Olaparib monotherapy[4-6]	• 300 mg PO twice daily	Post-primary chemotherapy	• Up to 2 Years unless disease progression or unacceptable toxicity[b]
		Post-recurrence chemotherapy[a]	• Until disease progression or unacceptable toxicity[c]
Rucaparib monotherapy[7,8]	• 600 mg PO twice daily	Post-primary chemotherapy	• Up to 2 Years unless disease progression or unacceptable toxicity[b]
		Post-recurrence chemotherapy[a]	• Until disease progression or unacceptable toxicity[c]
Olaparib + Bevacizumab[9]	• Olaparib 300 mg PO twice daily • Bevacizumab 15 mg/kg IV every 21 days	Post-primary chemotherapy + Bevacizumab	• Olaparib: Up to 2 Years unless disease progression or unacceptable toxicity • Bevacizumab: Up to 15 Months (total including chemotherapy) unless disease progression or unacceptable toxicity
Niraparib + Bevacizumab[10]	• Niraparib: 300 mg PO once daily (or 200 mg once daily for patients with a baseline body weight of <77 kg, and/or a platelet count of <150,000/mm^3) • Bevacizumab: 15 mg/kg IV every 21 Days	Post-primary chemotherapy + Bevacizumab	• Niraparib: Up to 3 Years unless disease progression or unacceptable toxicity • Bevacizumab: Up to 15 Months (total including chemotherapy) unless disease progression or unacceptable toxicity

[a] Use of PARPi maintenance in post recurrence setting is restricted to *BRCA1/2* mutated setting
[b] In studies, treatment was continued for those whose disease was not in CR at 2 years (olaparib, rucaparib) or 3 years (rucaparib).
[c] Clinical trials in the recurrent setting included PARPi maintenance until progression. However, exposure to prolonged PARPi maintenance >2 years in the recurrent setting may increase risk of MDS/AML development.

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

References

PRINCIPLES OF SYSTEMIC THERAPY

Recurrent Ovarian, Fallopian Tube, or Primary Peritoneal Cancer:

- Refer to the original references (Discussion) for full toxicity data, doses, schedule, and dose modifications.
- Patients should be informed about the following:
  1) Availability of clinical trials, including the risks and benefits of various treatments, which will depend on the number of prior lines of chemotherapy the patient has received, and
  2) Performance status, end-organ status, and pre-existing toxicities from prior regimens. If appropriate, palliative care should also be discussed as a possible treatment choice. See NCCN Guidelines for Palliative Care.
- Tumor biomarker testing is recommended if not previously done for persistent/recurrent disease. See Principles of Pathology (OV-C).
- Because of prior platinum exposure, myelosuppression occurs more frequently with any myelotoxic agent given in the recurrent setting.
- With repeat use of either carboplatin and/or cisplatin, patients are at an increased risk of developing a hypersensitivity reaction (also called an allergic reaction) that could be life-threatening. Thus, patients should be counseled about the risk that a hypersensitivity reaction may occur, educated about the signs and symptoms of hypersensitivity reactions, treated by medical staff who know how to manage hypersensitivity reactions, and treated in a medical setting where appropriate medical equipment is available in case of an allergic reaction. See Management of Drug Reactions (OV-E).
- Before any chemotherapy drug is given in the recurrent setting, the clinician should be familiar with the drug's metabolism (eg, renal, hepatic) and should make certain that the patient is an appropriate candidate for the drug (eg, that the patient has adequate renal or hepatic function).
- Clinicians should be familiar with toxicity management and appropriate dose reduction.
- The schedule, toxicity, and potential benefits of any treatment should be thoroughly discussed with the patient and caregivers. Patient education should also include a discussion of precautions and measures to reduce the severity and duration of complications.
- Patients who do not respond and progress on two consecutive regimens without evidence of clinical benefits have diminished likelihood of benefitting from additional therapy (Griffiths RW, et al. Int J Gynecol Cancer 2011;21:58-65). Decisions to offer clinical trials, supportive care, or additional therapy should be made on an individual basis.

Acceptable Recurrence Therapies for Platinum-Sensitive Disease (OV-D, 8 of 12)

Acceptable Recurrence Therapies for Platinum-Resistant Disease (OV-D, 9 of 12)

References

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

PRINCIPLES OF SYSTEMIC THERAPY
Primary Systemic Therapy Regimens[d] - Epithelial Ovarian/Fallopian Tube/Primary Peritoneal

Primary Therapy for Stage I Disease			
	Preferred	**Other Recommended**	**Useful in Certain Circumstances**
• High-grade serous • Endometrioid (grade 2/3) • Clear cell carcinoma[e] • Carcinosarcoma[e]	• Carboplatin/Paclitaxel every 3 Weeks[h,i]	• Carboplatin/Liposomal Doxorubicin • Carboplatin/Docetaxel	• Cisplatin/Paclitaxel For carcinosarcoma: • Carboplatin/Ifosfamide • Cisplatin/Ifosfamide/Mesna • Ifosfamide/Mesna/Paclitaxel (category 2B)[h]
Mucinous carcinoma (stage IA, IB, and IC, grades 1–3)[e]	• Capecitabine/Oxaliplatin • Carboplatin/Paclitaxel every 3 Weeks[h,i] • Fluorouracil/Leucovorin/Oxaliplatin	• Carboplatin/Docetaxel • Carboplatin/Liposomal Doxorubicin	• Cisplatin/Paclitaxel
Low-grade serous (stage IC)/Grade I endometrioid (stage IC)[e,f,g]	• Carboplatin/Paclitaxel every 3 Weeks[h,i] ± maintenance Letrozole (category 2B[g]) or other hormonal therapy (category 2B)[j] • Hormone therapy (aromatase inhibitors: Anastrozole, Exemestane, Letrozole) (category 2B)	• Carboplatin/Docetaxel ± maintenance Letrozole (category 2B[g]) or other hormonal therapy (category 2B)[j] • Carboplatin/Liposomal Doxorubicin ± maintenance Letrozole (category 2B[g]) or other hormonal therapy (category 2B)[j] • Hormone therapy (Leuprolide acetate, Goserelin acetate, Tamoxifen,[k] Fulvestrant) (category 2B)	• Cisplatin/Paclitaxel

Stage II–IV (OV-D, 6 of 12)
Primary Systemic Therapy Dosing (OV-D, 7 of 12)

[d] See Discussion for references.
[e] There are limited data on the primary systemic therapy regimens for these LCOC.
[f] Borderline disease with invasive implants may be treated as low-grade serous disease. See LCOC-7 and LCOC-9.
[g] For low-grade serous, maintenance letrozole is a category 2A recommendation. For grade I endometrioid, maintenance letrozole is a category 2B recommendation.
[h] Albumin-bound paclitaxel may be substituted for those experiencing a hypersensitivity reaction to paclitaxel. However, albumin-bound paclitaxel will not overcome infusion reactions in all patients.
[i] Individuals >70 years of age and those with comorbidities may be intolerant to the combination chemotherapy regimens recommended in these NCCN Guidelines. Based on clinical judgment and expected tolerance to therapies, alternate dosing (OV-D, 7 of 12) may be appropriate for these individuals with epithelial ovarian cancer (including carcinosarcoma, clear cell, mucinous, and low-grade serous). Algorithms have been developed for predicting chemotherapy toxicity.
[j] Other hormonal therapy options include: aromatase inhibitors (eg, anastrozole, exemestane), leuprolide acetate, goserelin acetate, or tamoxifen.
[k] Tamoxifen is not recommended for low-grade serous carcinoma.

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

PRINCIPLES OF SYSTEMIC THERAPY
Primary Systemic Therapy Regimens[d] - Epithelial Ovarian/Fallopian Tube/Primary Peritoneal

Primary Therapy for Stage II–IV Disease or Previously Untreated Recurrent Disease (Principles of Maintenance PARPi Therapy on OV-D, 3 of 12)			
	Preferred	**Other Recommended**	**Useful in Certain Circumstances**
• High-grade serous • Endometrioid (grade 2/3) • Clear cell carcinoma[e] • Carcinosarcoma[e]	• Carboplatin/Paclitaxel every 3 Weeks[h,i] • ICON-7 Carboplatin/Paclitaxel + Bevacizumab[h] • GOG-218 Carboplatin/Paclitaxel + Bevacizumab[h]	• Carboplatin Weekly/Paclitaxel Weekly[h,i,l] • Carboplatin/Docetaxel • Carboplatin/Liposomal Doxorubicin • Carboplatin every 3 Weeks/Paclitaxel weekly[h] • GOG-218 Carboplatin/Docetaxel + Bevacizumab	• Cisplatin/Paclitaxel • Docetaxel/Oxaliplatin + Bevacizumab • IP/IV Carboplatin/Paclitaxel • IP/IV Cisplatin/Paclitaxel (for optimally debulked stage II–III disease) • For carcinosarcoma: ▸ Carboplatin/Ifosfamide ▸ Cisplatin/Ifosfamide/Mesna ▸ Ifosfamide/Mesna/Paclitaxel (category 2B)[h]
Mucinous carcinoma[e]	• Fluorouracil/Leucovorin/Oxaliplatin ± Bevacizumab (category 2B for Bevacizumab) • Capecitabine/Oxaliplatin ± Bevacizumab (category 2B for Bevacizumab) • Carboplatin/Paclitaxel every 3 Weeks[h,i] • Carboplatin/Paclitaxel + Bevacizumab[h] (ICON-7 & GOG-218)	• Carboplatin Weekly/Paclitaxel Weekly[h,i,l] • Carboplatin/Docetaxel • Carboplatin/Liposomal Doxorubicin • Carboplatin every 3 Weeks/Paclitaxel Weekly[h] • Carboplatin/Docetaxel + Bevacizumab (GOG-218)	• Cisplatin/Paclitaxel • Docetaxel/Oxaliplatin + Bevacizumab
Low-grade serous/Grade I endometrioid[e,f,g]	• Carboplatin/Paclitaxel every 3 Weeks[h,i] ± maintenance Letrozole (category 2B[g]) or other hormonal therapy (category 2B)[j] • Carboplatin/Paclitaxel/Bevacizumab + maintenance Bevacizumab[h] (ICON-7 & GOG-218) • Hormone therapy (aromatase inhibitors: Anastrozole, Letrozole, Exemestane) (category 2B)	• Carboplatin Weekly/Paclitaxel Weekly[h,i,l] • Carboplatin/Docetaxel ± maintenance Letrozole (category 2B[g]) or other hormonal therapy (category 2B)[j] • Carboplatin/Liposomal Doxorubicin ± maintenance Letrozole (category 2B[g]) or other hormonal therapy (category 2B)[j] • Carboplatin every 3 Weeks/Paclitaxel Weekly[h] • Carboplatin/Docetaxel + Bevacizumab (GOG-218) • Hormone therapy (Leuprolide acetate, Goserelin acetate, Tamoxifen,[k] Fulvestrant) (category 2B)	• Cisplatin/Paclitaxel • Docetaxel/Oxaliplatin + Bevacizumab (category 2B)

Primary Systemic Therapy Dosing

[d] See Discussion for references.
[e] There are limited data on the primary systemic therapy regimens for these LCOC.
[f] Borderline disease with invasive implants may be treated as low-grade serous disease. See LCOC-7 and LCOC-9.
[g] For low-grade serous, maintenance letrozole is a category 2A recommendation. For grade I endometrioid, maintenance letrozole is a category 2B recommendation.
[h] Albumin-bound paclitaxel may be substituted for those experiencing a hypersensitivity reaction to paclitaxel. However, albumin-bound paclitaxel will not overcome infusion reactions in all patients.
[i] Individuals >70 years of age and those with comorbidities may be intolerant to the combination chemotherapy regimens recommended in these NCCN Guidelines. Based on clinical judgment and expected tolerance to therapies, alternate dosing (OV-D, 7 of 12) may be appropriate for these individuals with epithelial ovarian cancer (including carcinosarcoma, clear cell, mucinous, and low-grade serous). Algorithms have been developed for predicting chemotherapy toxicity.
[j] Other hormonal therapy options include: aromatase inhibitors (eg, anastrozole, exemestane), leuprolide acetate, goserelin acetate, or tamoxifen.
[k] Tamoxifen is not recommended for low-grade serous carcinoma.
[l] Regimen may be considered for those with poor performance status.

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

PRINCIPLES OF SYSTEMIC THERAPY
Primary Systemic Therapy Regimens[d] - Epithelial Ovarian (including LCOC)/Fallopian Tube/Primary Peritoneal

Primary Systemic Therapy Recommended Dosing

Carboplatin/Paclitaxel every 3 Weeks[h,m]
- Paclitaxel 175 mg/m² IV followed by Carboplatin[n] AUC 5–6 IV Day 1
- Repeat every 21 Days x 3–6 cycles[m]

Cisplatin/Paclitaxel every 3 Weeks[11,12]
- Paclitaxel 175 mg/m² IV followed by Cisplatin 75 mg/m² IV
- Repeat every 21 Days x 3–9 cycles

IP/IV Cisplatin/Paclitaxel
- Paclitaxel 135 mg/m² IV continuous infusion[o] Day 1; Cisplatin 75–100 mg/m² IP Day 2 after IV Paclitaxel; Paclitaxel 60 mg/m² IP Day 8
- Repeat every 21 Days x 6 cycles

IP/IV Carboplatin/Paclitaxel[13]
- Paclitaxel 80 mg/m² IV on Days 1, 8, and 15; Carboplatin AUC 6 IP Day 1 after IV Paclitaxel
- Repeat every 21 Days x 6–8 cycles

Carboplatin every 3 Weeks/Paclitaxel Weekly[h]
- Dose-dense Paclitaxel 80 mg/m² IV Days 1, 8, and 15 followed by Carboplatin[o] AUC 5–6 IV Day 1
- Repeat every 21 Days x 6 cycles

Carboplatin Weekly/Paclitaxel Weekly[h]
- Paclitaxel 60 mg/m² IV followed by Carboplatin AUC 2 IV
- Days 1, 8, and 15; repeat every 21 Days x 6 cycles (18 Weeks)[l]

Docetaxel/Oxaliplatin + Bevacizumab
- Docetaxel 75 mg/m² IV followed by Oxaliplatin 85 mg/m² IV, and Bevacizumab 15 mg/kg IV
- Repeat every 21 Days x 6 cycles
- Continue Bevacizumab 15 mg/kg IV every 21 Days to complete 1 Year of therapy

Carboplatin/Docetaxel[m]
- Docetaxel 60–75 mg/m² IV followed by Carboplatin[n] AUC 5–6 IV Day 1
- Repeat every 21 Days x 3–6 cycles[l]

Carboplatin/Liposomal Doxorubicin[m]
- Carboplatin AUC 5 IV + pegylated Liposomal Doxorubicin 30 mg/m² IV
- Repeat every 28 Days for 3–6 cycles[l]

Carboplatin/Paclitaxel + Bevacizumab[h] (ICON-7)
- Paclitaxel 175 mg/m² IV followed by Carboplatin[n] AUC 5–6 IV, and Bevacizumab 7.5 mg/kg IV Day 1
- Repeat every 21 Days x 5–6 cycles
- Continue Bevacizumab for up to 12 additional cycles

Carboplatin/Paclitaxel + Bevacizumab[h] (GOG-218)
- Paclitaxel 175 mg/m² IV followed by Carboplatin[n] AUC 6 IV Day 1. Repeat every 21 Days x 6 cycles
- Starting Day 1 of cycle 2, give Bevacizumab 15 mg/kg IV every 21 Days for up to 22 cycles

Carboplatin/Docetaxel + Bevacizumab (GOG-218)
- Docetaxel 75 mg/m² IV followed by Carboplatin[n] AUC 6 IV Day 1. Repeat every 21 Days x 6 cycles
- Starting Day 1 of cycle 2, give Bevacizumab 15 mg/kg IV every 21 Days for up to 22 cycles

Individuals >70 Years and/or Those with Comorbidities

Carboplatin/Paclitaxel 135[h,14]
- Paclitaxel 135 mg/m² IV + Carboplatin AUC 5 IV given every 21 Days x 3–6 cycles[m]

Carboplatin weekly/Paclitaxel weekly[h]
- Paclitaxel 60 mg/m² IV over 1 Hour followed by Carboplatin AUC 2 IV over 30 Minutes
- Days 1, 8, and 15; repeat every 21 Days x 6 cycles (18 Weeks)

Primary Systemic Therapy for Malignant Germ Cell Tumors

Carboplatin/Etoposide
- Carboplatin 400 mg/m² IV on Day 1 plus Etoposide 120 mg/m² IV on Days 1, 2, and 3 every 28 Days for 3 cycles

BEP
- Bleomycin 30 units IV per Week plus Etoposide 100 mg/m² IV daily on Days 1–5 plus Cisplatin 20 mg/m² IV daily on Days 1–5; repeat every 21 Days for 3 cycles for good risk (category 2B), or 4 cycles for poor risk

[d] See Discussion for references.
[h] Albumin-bound paclitaxel may be substituted for those experiencing a hypersensitivity reaction to paclitaxel. However, albumin-bound paclitaxel will not overcome infusion reactions in all patients.
[l] Regimen may be considered for those with poor performance status.
[m] For stage I disease: 6 cycles is recommended for high-grade serous; 3–6 cycles for all other ovarian cancer types. For stage II–IV disease: 6 cycles is recommended.
[n] Due to changes in creatinine methodology, changes regarding carboplatin dosing can be considered. See carboplatin dosing guidelines.
[o] The published randomized trial regimen used IV continuous infusion paclitaxel over 24 hours.

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

References

PRINCIPLES OF SYSTEMIC THERAPY
Acceptable Recurrence Therapies for Epithelial Ovarian (including LCOC)[p]/Fallopian Tube/Primary Peritoneal Cancer

Recurrence Therapy for Platinum-Sensitive Disease[q] (alphabetical order)

Preferred	Other Recommended[t]	Useful in Certain Circumstances
• Carboplatin/Gemcitabine[15] ± Bevacizumab[r,s,16] • Carboplatin/Liposomal Doxorubicin[17] ± Bevacizumab[r,18] • Carboplatin/Paclitaxel[h,19] ± Bevacizumab[r,s,20] • Cisplatin/Gemcitabine[21]	• Capecitabine • Carboplatin[15] • Carboplatin/Docetaxel[22,23] • Carboplatin/Paclitaxel (Weekly)[h,24] • Cisplatin[19] • Cyclophosphamide • Doxorubicin • Ifosfamide/Mesna • Irinotecan • Oxaliplatin • Paclitaxel • Albumin-bound Paclitaxel • Pemetrexed • Vinorelbine **Targeted Therapy** • Bevacizumab[r,25,26] • Niraparib + Bevacizumab (category 2B)[r,27] • Pazopanib (category 2B)[28] **Hormone Therapy** • Aromatase inhibitors (Anastrozole, Exemestane, Letrozole) • Goserelin acetate • Leuprolide acetate • Megestrol acetate • Tamoxifen[k]	• For mucinous carcinoma: ▸ Fluorouracil/Leucovorin/Oxaliplatin ± Bevacizumab (category 2B for Bevacizumab)[r] ▸ Capecitabine/Oxaliplatin ± Bevacizumab (category 2B for Bevacizumab)[r] • Carboplatin/Paclitaxel (for age >70)[h,u] • Albumin-bound Paclitaxel/Carboplatin (for confirmed taxane hypersensitivity) • Irinotecan/Cisplatin (for clear cell carcinoma)[29] **Targeted Therapy[v]** • Dabrafenib/Trametinib (for *BRAF* V600E-positive tumors)[30] • Entrectinib[31] or Larotrectinib[32] or Repotrectinib[33] (for *NTRK1/2/3* gene fusion-positive tumors) • Fam-trastuzumab deruxtecan-nxki (for HER2-positive tumors [IHC 3+ or 2+]) (category 2B)[34] • Mirvetuximab soravtansine-gynx[w] (for FRα-expressing tumors [≥75% positive tumor cells])[35] • Mirvetuximab soravtansine-gynx + Bevacizumab[r] (for FRα-expressing tumors [≥50% positive tumor cells]) (category 2B)[36] • Selpercatinib (for *RET* gene fusion-positive tumors)[37] • For low-grade serous carcinoma: ▸ Avutometinib/Defactinib (for *KRAS*-mutated tumors)[38] ▸ Trametinib[39] ▸ Binimetinib (category 2B)[40,41] **Hormone Therapy** • Fulvestrant (for low-grade serous carcinoma) **Immunotherapy[v]** • Dostarlimab-gxly (for dMMR/MSI-H recurrent or advanced tumors)[42] • Pembrolizumab (for MSI-H or dMMR solid tumors, or patients with TMB-H tumors ≥10 mutations/megabase)[43]

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

Footnotes
References

PRINCIPLES OF SYSTEMIC THERAPY
Acceptable Recurrence Therapies for Epithelial Ovarian (including LCOC)[p]/Fallopian Tube/Primary Peritoneal Cancer

Recurrence Therapy for Platinum-Resistant Disease (alphabetical order)

Preferred	Other Recommended	Useful in Certain Circumstances
Cytotoxic Therapy • Oral Cyclophosphamide + Bevacizumab[r,44] • Docetaxel[45] • Gemcitabine[46,47] • Liposomal Doxorubicin[46,47] • Liposomal Doxorubicin + Bevacizumab[r,48] • Paclitaxel (Weekly)[h,49] • Paclitaxel (Weekly) + Bevacizumab[h,r,48] • Topotecan[50,51] • Topotecan + Bevacizumab[r,48] **Targeted Therapy (single agents)** • Mirvetuximab soravtansine-gynx (for FRα-expressing tumors [≥75% positive tumor cells])(category 1)[v,52,53]	**Cytotoxic Therapy**[t] • Capecitabine • Carboplatin[x] • Carboplatin/Docetaxel[x] • Carboplatin/Paclitaxel (Weekly)[h,x] • Carboplatin/Gemcitabine[15] ± Bevacizumab[r,s,x,16] • Carboplatin/Liposomal Doxorubicin[17] ± Bevacizumab[r,x,18] • Carboplatin/Paclitaxel[h,19] ± Bevacizumab[r,s,x,20] • Cisplatin/Gemcitabine[x,21] • Cyclophosphamide • Oral Cyclophosphamide + Pembrolizumab + Bevacizumab[r,54,55] • Doxorubicin • Oral Etoposide[56] • Gemcitabine + Bevacizumab[r,57] • Ifosfamide/Mesna • Irinotecan • Ixabepilone + Bevacizumab (category 2B)[r,y,58] • Oxaliplatin • Paclitaxel • Albumin-bound Paclitaxel • Pemetrexed • Sorafenib/Topotecan[59] • Vinorelbine **Targeted Therapy (single agents)** • Bevacizumab[r,25,26] • Pazopanib (category 2B)[28] **Hormone Therapy** • Aromatase inhibitors (Anastrozole, Exemestane, Letrozole) • Goserelin acetate • Leuprolide acetate • Megestrol acetate • Tamoxifen[k]	• Carboplatin/Paclitaxel (for age >70)[h,u,x] • Albumin-bound Paclitaxel/Carboplatin (for confirmed taxane hypersensitivity)[x] **Immunotherapy**[v] • Dostarlimab-gxly (for dMMR/MSI-H recurrent or advanced tumors)[41] • Paclitaxel + Pembrolizumab ± Bevacizumab (for PD-L1-positive tumors [CPS≥1])[h,r,s,z,60] • Pembrolizumab (for patients with MSI-H or dMMR solid tumors, or TMB-H tumors ≥10 mutations/megabase)[42] • For clear-cell carcinoma ▸ Ipilimumab + Nivolumab[61,62] **Hormone Therapy** • Fulvestrant (for low-grade serous carcinoma) **Targeted Therapy**[v] • Dabrafenib/Trametinib (for *BRAF* V600E positive tumors)[30] • Entrectinib[31] or Larotrectinib[32] or Repotrectinib[33] (for *NTRK1/2/3* gene fusion-positive tumors) • Fam-trastuzumab deruxtecan-nxki (for HER2-positive tumors [IHC 3+ or 2+])[34] • Mirvetuximab soravtansine-gynx + Bevacizumab (for FRα-expressing tumors [≥25% positive tumor cells])[r,36,63,64] • Selpercatinib (for *RET* gene fusion-positive tumors)[37] • For low-grade serous carcinoma: ▸ Avutometinib/Defactinib (for *KRAS*-mutated tumors)[38] ▸ Trametinib[39] ▸ Binimetinib (category 2B)[40,41] • For mucinous carcinoma: ▸ FOLFIRI ± Bevacizumab[r] (category 2B)[65-68]

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

Footnotes
References

PRINCIPLES OF SYSTEMIC THERAPY
Acceptable Recurrence Therapies for Epithelial Ovarian (including LCOC)[p]/Fallopian Tube/Primary Peritoneal Cancer[q]
FOOTNOTES

[h] Albumin-bound paclitaxel may be substituted for those experiencing a hypersensitivity reaction to paclitaxel. However, albumin-bound paclitaxel will not overcome infusion reactions in all patients.
[k] Tamoxifen is not recommended for low-grade serous carcinoma.
[p] Chemotherapy has not been shown to be beneficial in ovarian borderline epithelial tumors (LMP).
[q] In general, the Panel would recommend combination, platinum-based regimens for platinum-sensitive recurrent disease based on randomized trial data, especially in first relapses.
[r] Contraindicated for patients at increased risk of GI perforation.
[s] If response after chemotherapy, bevacizumab can be continued as maintenance therapy until disease progression or unacceptable toxicity. Discontinue bevacizumab before initiating maintenance therapy with a PARPi.
[t] Many of these single-agent cytotoxic therapy options have not been tested in patients who have been treated with modern chemotherapy regimens.
[u] For recommended dosing for individuals >70 years, see OV-D, 7 of 12.
[v] Validated biomarker testing should be performed in a CLIA-approved facility using the most recent available tumor tissue. Tumor biomarker testing is recommended to include tests to identify potential benefit from targeted therapeutics that have tumor-specific or tumor-agnostic benefit including, but not limited to, HER2 status (by IHC), PD-L1 (IHC, CPS), *BRCA1/2*, HRD status, MSI, MMR, TMB, *BRAF*, *KRAS,* FRα (FOLR1), *RET*, and *NTRK1/2/3* if prior testing did not include these markers. MGPT may be particularly important in LCOC with limited approved therapeutic options (OV-C).
[w] For patients treated with two prior lines of platinum-based therapy.
[x] Platinum agents have limited activity when the disease has demonstrated growth through a platinum-based regimen, and platinum rechallenge is generally not recommended in this setting.
[y] For those previously treated with taxanes.
[z] Tumors with a CPS ≥1 determined by an FDA-approved test are considered PD-L1 positive.

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

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

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

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

MANAGEMENT OF DRUG REACTIONS

Overview

- Virtually all drugs used in oncology have the potential to cause adverse drug reactions while being infused, which can be classified as either infusion or allergic reactions.[1]
  - Infusion reactions are often characterized by milder symptoms (eg, hot flushing, rash).
  - Hypersensitivity (allergic) reactions are often characterized by more severe symptoms (eg, shortness of breath, generalized hives/itching, changes in blood pressure).
- Most adverse drug reactions that occur are mild reactions, but more severe reactions can occur.[2,3]
  - Anaphylaxis is a rare type of very severe allergic reaction that can occur with platinum and taxane agents (and others less commonly), can cause cardiovascular collapse, and can be life-threatening.[4-6]
  - Drug reactions can occur either during infusion or following completion of infusion (and can even occur days later).
- In gynecologic oncology treatment, drugs that more commonly cause adverse reactions include carboplatin, cisplatin, docetaxel, liposomal doxorubicin, oxaliplatin, and paclitaxel.[1]
  - Adverse reactions associated with biotherapeutic agents and taxane drugs (eg, docetaxel, paclitaxel) tend to be infusion-related and, in taxanes, are often attributed to the excipient (eg, Cremophor EL in paclitaxel, polysorbate 80 in docetaxel). These tend to occur during the first few cycles of treatment (although they can be seen during any infusion regardless of how many previous cycles were administered).
  - Adverse reactions associated with platinum drugs (eg, carboplatin, cisplatin), a true allergy, tend to occur following re-exposure to the inciting drug or less commonly at the completion of initial chemotherapy (eg, cycle 6 of a planned 6 treatments).3
- Preparation for a possible drug reaction
  - Patients and their families should be counseled about the possibility of a drug reaction and the signs and symptoms of one. Patients should be told to report any signs and symptoms of a drug reaction, especially after they have left the clinic (eg, delayed rash).
  - Clinicians and nursing staff should be prepared for the possibility of a drug reaction every time a patient is infused with a drug. Standing orders should be written for immediate intervention in case a severe drug reaction occurs and the treatment area should have appropriate medical equipment in case of a life-threatening reaction.[5]
  - Epinephrine (intramuscular [IM] 0.3 mL of 1 mg/mL solution/Epipen) should be used for any patient experiencing hypotension (systolic blood pressure of <90 mm Hg) with or without other symptoms of an allergic/hypersensitivity reaction during or shortly after any chemotherapy drug treatment. In the setting of acute cardiopulmonary arrest, standard resuscitation (advanced cardiovascular life support [ACLS]) procedures should be followed.
- Desensitization refers to a process of rendering the patient less likely to react in response to an allergen and can be considered an option for patients who have had drug reactions.[1,7-10]
- If a patient has previously had a very severe life-threatening reaction, the implicated drug should not be used again unless under guidance of an allergist or specialist with desensitization experience.

References on OV-E, 3 of 7

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

MANAGEMENT OF DRUG REACTIONS

Infusion Reactions

- Symptoms include: hot flushing, rash, fever, chest tightness, mild blood pressure changes, back pain, and chills.
- Symptoms usually can be treated by decreasing the infusion rate and resolve quickly after stopping the infusion. However, patients who have had mild reactions to carboplatin, cisplatin, or oxaliplatin may develop more serious reactions even when the platinum drug is slowly infused; therefore, consider consultation with an allergist.[11]
- Infusion reactions are more common with paclitaxel (27% of patients); however, mild reactions can occur with liposomal doxorubicin.[11]
- If an infusion reaction has previously occurred in response to a taxane:
  - For mild infusion reactions (eg, flushing, rash, chills), patients may be rechallenged with the taxane if:
    1) the patient, physician, and nursing staff are all comfortable with this plan;
    2) the patient has been counseled appropriately; and
    3) emergency equipment is available in the clinic area.
  - Typically the taxane infusion can be restarted at a much slower rate, and the rate can be slowly increased as tolerated as per the treating clinician's judgment.[7,12] Note that this slow infusion is different from desensitization.
  - Many institutions have nursing policies that stipulate how to reinfuse the drug if the patient has had a prior infusion reaction.

Allergic Reactions (ie, True Drug Allergies)

- Symptoms include: rash, edema, shortness of breath (bronchospasm), syncope or pre-syncope, chest pain, tachycardia, hives/itching, changes in blood pressure, nausea, vomiting, chills, changes in bowel function, and occasionally feeling of impending doom.
- Symptoms may continue to persist after stopping infusion and/or after treatment interventions.
- Allergic reactions are more common with platinum drugs such as carboplatin (16% of patients), cisplatin, and oxaliplatin.[12] Mild reactions can occur with platinum agents.[12]
- Patients who are at higher risk of developing a hypersensitivity (allergic) reaction include those in the following settings:
  - Reintroduction of the drug after a period of no exposure and following multiple cycles of the drug during the first and subsequent exposures
  - IV administration of the drug rather than oral or IP administration
  - Those with allergies to other drugs
  - Those who have previously had a reaction
- If an allergic reaction has previously occurred:
  - Consider consultation with an allergist (or qualified medical or gynecologic oncologist) and skin testing for patients who have experienced a platinum reaction (eg, carboplatin-hypersensitivity reaction).[12-14]
  - Patients who have had mild reactions may develop more serious reactions even when the platinum drug is slowly infused.[12]
  - For more severe or life-threatening reactions—such as those involving blood pressure changes, dyspnea, tachycardia, widespread urticaria, anaphylaxis, or hypoxia—the implicated drug should not be used again unless under guidance of a specialist with desensitization experience.
  - If it is appropriate to give the drug again, patients should be desensitized prior to resuming chemotherapy even if the symptoms have resolved. Patients must be desensitized with each infusion if they previously had a drug reaction.[1,7-10]

References on OV-E, 3 of 7

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

MANAGEMENT OF DRUG REACTIONS
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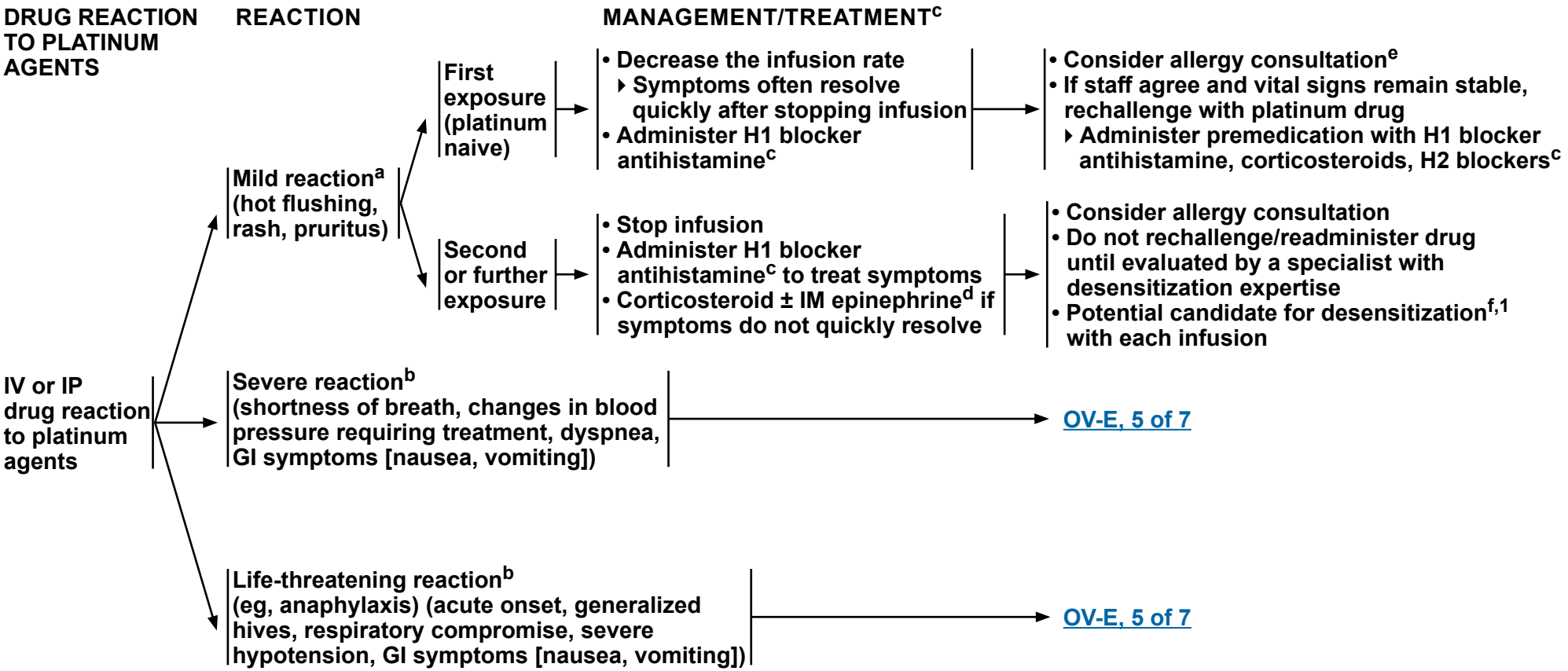
Drug Reaction to Platinum Agents (OV-E, 4 of 7)

Drug Reaction to Taxane, Liposomal Doxorubicin, or Biotherapeutic Agents (OV-E, 6 of 7)

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

MANAGEMENT OF DRUG REACTIONS



Drug Reaction to Taxane, Liposomal Doxorubicin, or Biotherapeutic Agents (OV-E, 6 of 7)

[a] Most mild reactions are infusion reactions and more commonly are caused by taxanes (eg, docetaxel, paclitaxel), but can also occur with platinum agents (eg, carboplatin, cisplatin).
[b] Most severe reactions are allergic reactions and more commonly are caused by platinum agents.
[c] H1 blocker antihistamine (eg, diphenhydramine, hydroxyzine); H2 blockers (eg, cimetidine, famotidine); corticosteroids (eg, methylprednisolone, hydrocortisone, dexamethasone).
[d] In the setting of acute cardiopulmonary arrest, standard resuscitation (ACLS) procedures should be followed.
[e] Mild reactions can progress to severe reactions by re-exposure. An allergy consultation may provide skin testing and evaluate sensitization and the risk for further, more severe reactions.
[f] Referral to an academic center with expertise in desensitization is preferred.
[1] Castells MC, Tennant NM, Sloane DE, et al. Hypersensitivity reactions to chemotherapy: Outcomes and safety of rapid desensitization in 413 cases. J Allergy Clin Immunol 2008;122:574-580.

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

MANAGEMENT OF DRUG REACTIONS

DRUG REACTION TO PLATINUM AGENTS

IV or IP drug reaction to platinum agents

REACTION	MANAGEMENT/TREATMENT[c]
Mild reaction[a] (hot flushing, rash, pruritus)	→ OV-E, 4 of 7
Severe reaction[b] (shortness of breath, changes in blood pressure requiring treatment, dyspnea, GI symptoms [nausea, vomiting])	• Stop infusion • Administer oxygen, nebulized bronchodilators, H1 blocker antihistamine, H2 blockers, corticosteroid[c]; IM epinephrine[d] if needed → • Consider allergy consultation • Do not rechallenge/readminister drug until evaluated by allergist or specialist with desensitization expertise • Potential candidate for desensitization[f,1] with each infusion
Life-threatening reaction[b] (eg, anaphylaxis) (acute onset, generalized hives, respiratory compromise, severe hypotension, GI symptoms [nausea, vomiting])	• Stop infusion • Administer IM epinephrine,[d] oxygen, nebulized bronchodilators, H1 blocker antihistamine, H2 blockers, corticosteroid[c] • Saline bolus, if needed → • Do not rechallenge/readminister drug until evaluated by allergist or specialist with desensitization expertise • Potential candidate for desensitization[g,1] with each infusion under guidance of an allergist or specialist with desensitization expertise

Drug Reaction to Taxane, Liposomal Doxorubicin, or Biotherapeutic Agents (OV-E, 6 of 7)

[a] Most mild reactions are infusion reactions and more commonly are caused by taxanes (eg, docetaxel, paclitaxel), but can also occur with platinum agents (eg, carboplatin, cisplatin).
[b] Most severe reactions are allergic reactions and more commonly are caused by platinum agents.
[c] H1 blocker antihistamine (eg, diphenhydramine, hydroxyzine); H2 blockers (eg, cimetidine, famotidine); corticosteroids (eg, methylprednisolone, hydrocortisone, dexamethasone).
[d] In the setting of acute cardiopulmonary arrest, standard resuscitation (ACLS) procedures should be followed.
[f] Referral to an academic center with expertise in desensitization is preferred.
[g] For both taxanes and platinum analogues, it is preferred that anyone with a life-threatening reaction be evaluated and referred to an academic center if the drug is still considered first line.
[1] Castells MC, Tennant NM, Sloane DE, et al. Hypersensitivity reactions to chemotherapy: Outcomes and safety of rapid desensitization in 413 cases. J Allergy Clin Immunol 2008;122:574-580.

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MANAGEMENT OF DRUG REACTIONS

DRUG REACTION TO TAXANE, LIPOSOMAL DOXORUBICIN, OR BIOTHERAPEUTIC AGENTS

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

REACTION	MANAGEMENT/TREATMENT[c]
Mild reaction[a] (hot flushing, rash, pruritus, pain in chest/abdomen/pelvis/back)	• Stop infusion ▸ Symptoms often resolve quickly after stopping infusion • Administer H1 blocker antihistamine[c] to treat symptoms • If staff agree and vital signs remain stable, rechallenge with drug at slower infusion rate[h] ▸ Administer premedication with H1 blocker antihistamine, corticosteroids, H2 blockers[c] • If repeat mild reaction, then do not rechallenge/readminister • Potential candidate for desensitization[h,1] with each infusion
Severe reaction[b] (shortness of breath, changes in blood pressure requiring treatment, dyspnea, GI symptoms [nausea, vomiting], pain in chest/abdomen/pelvis/back, feeling of impending doom/anxiety/something wrong)	OV-E, 7 of 7
Life-threatening reaction[b] (eg, anaphylaxis) (acute onset, generalized hives, respiratory compromise, severe hypotension, GI symptoms [nausea, vomiting], pain in chest/abdomen/pelvis/back, feeling of impending doom/anxiety/something wrong)	OV-E, 7 of 7

Drug Reaction to Platinum Agents (OV-E, 4 of 7)

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

[b] Most severe reactions are allergic reactions and more commonly are caused by platinum agents.

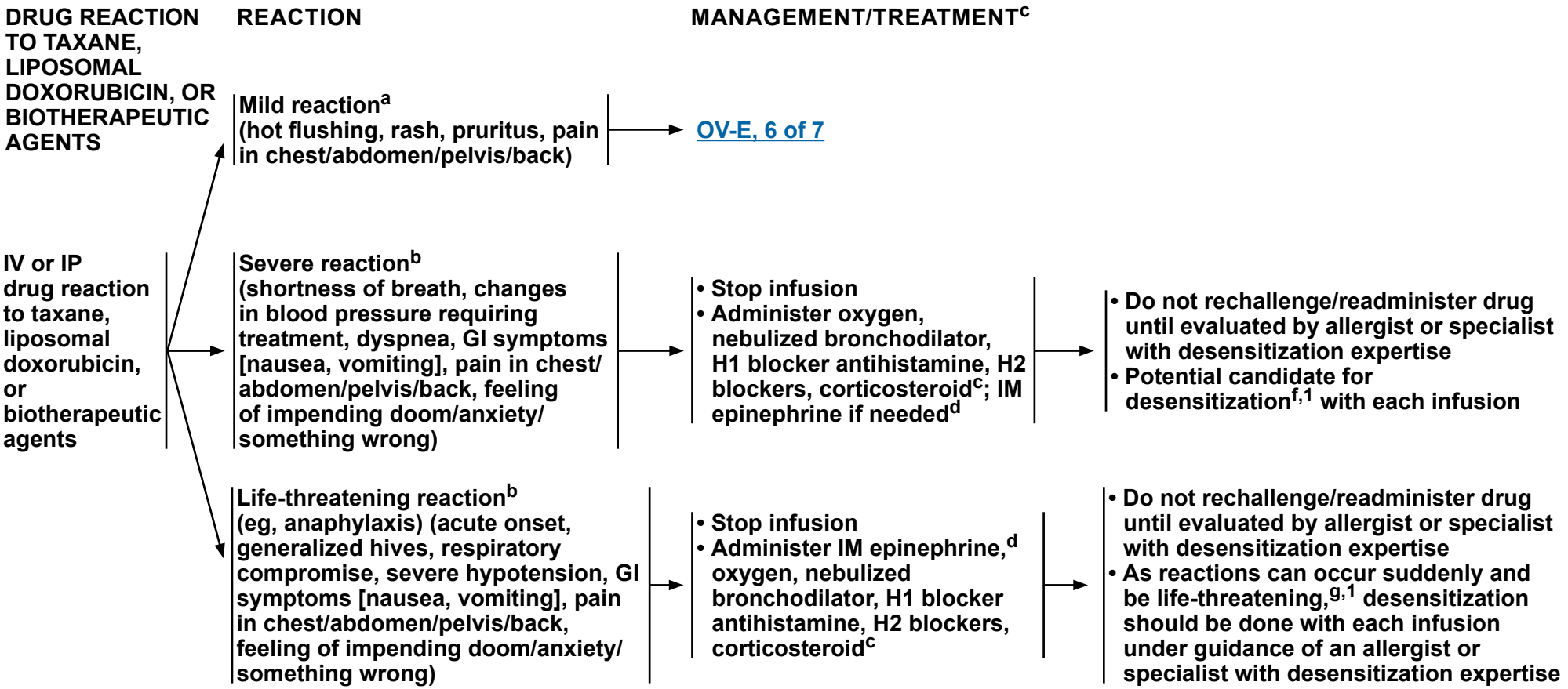
[c] H1 blocker antihistamine (eg, diphenhydramine, hydroxyzine); H2 blockers (eg, cimetidine, famotidine); corticosteroids (eg, methylprednisolone, hydrocortisone, dexamethasone).

[h] Consider switching to albumin-bound paclitaxel due to medical necessity (eg, hypersensitivity reaction), or consider switching to docetaxel; however, there are no data to support switching taxanes. Cross reactions have occurred and have been life-threatening. Some reactions to paclitaxel may occur because of the diluent.

[1] Castells MC, Tennant NM, Sloane DE, et al. Hypersensitivity reactions to chemotherapy: Outcomes and safety of rapid desensitization in 413 cases. J Allergy Clin Immunol 2008;122:574-580.

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

MANAGEMENT OF DRUG REACTIONS



Drug Reaction to Platinum Agents (OV-E, 4 of 7)

[a] Most mild reactions are infusion reactions and more commonly are caused by taxanes (eg, docetaxel, paclitaxel), but can also occur with platinum agents (eg, carboplatin, cisplatin).
[b] Most severe reactions are allergic reactions and more commonly are caused by platinum agents.
[c] H1 blocker antihistamine (eg, diphenhydramine, hydroxyzine); H2 blockers (eg, cimetidine, famotidine); corticosteroids (eg, methylprednisolone, hydrocortisone, dexamethasone).
[d] In the setting of acute cardiopulmonary arrest, standard resuscitation (ACLS) procedures should be followed.
[f] Referral to academic center with expertise in desensitization is preferred.
[g] For both taxanes and platinum analogues, it is preferred that anyone with a life-threatening reaction be evaluated and referred to an academic center if the drug is still considered first line.

[1] Castells MC, Tennant NM, Sloane DE, et al. Hypersensitivity reactions to chemotherapy: Outcomes and safety of rapid desensitization in 413 cases. J Allergy Clin Immunol 2008;122:574-580.

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WHO HISTOLOGIC CLASSIFICATION[1,2]

Serous Tumors	
• Serous cystadenoma NOS	0
▸ Serous surface papilloma	0
▸ Serous adenofibroma NOS	0
▸ Serous cystadenofibroma NOS	0
• Serous borderline tumor NOS	1
▸ Serous borderline tumor, micropapillary variant	2
• Serous carcinoma, non-invasive, low-grade	2
• Low-grade serous carcinoma	3
• High-grade serous carcinoma	3
Mucinous Tumors	
• Mucinous cystadenoma NOS	0
• Mucinous adenofibroma NOS	0
• Mucinous borderline tumor	1
• Mucinous adenocarcinoma	3
Endometrioid Tumors	
• Endometrioid cystadenoma NOS	0
• Endometrioid adenofibroma NOS	0
• Endometrioid tumor, borderline	1
• Endometrioid adenocarcinoma NOS	3
▸ Seromucinous carcinoma	3
Clear Cell Tumors	
• Clear cell cystadenoma	0
• Clear cell cystadenofibroma	0
• Clear cell borderline tumor	1
• Clear cell adenocarcinoma NOS	3

Brenner Tumors	
• Brenner tumor, NOS	0
• Brenner tumor, borderline malignancy	1
• Brenner tumor, malignant	3
Seromucinous Tumors	
• Seromucinous cystadenoma	0
• Seromucinous adenofibroma	0
• Seromucinous borderline tumor	1
Other carcinomas	
• Mesonephric-like adenocarcinoma	3
• Carcinoma, undifferentiated, NOS	3
• Dedifferentiated carcinoma	3
• Carcinosarcoma NOS	3
• Mixed cell adenocarcinoma	3
Mesenchymal Tumors	
• Endometrioid stromal sarcoma, low-grade	3
• Endometrioid stromal sarcoma, high-grade	3
• Leiomyoma NOS	0
• Leiomyosarcoma NOS	3
• Smooth muscle tumor of uncertain malignant potential	1
• Myxoma NOS	0
Mixed Epithelial & Mesenchymal Tumors	
• Adenosarcoma	3

[1] Reproduced with permission from Adhikari L, Hassell LA. World Health Organization Classification of Female Genital Tumours, 5th edition. IARC, 2020.
[2] Behavior is coded 0 for benign tumors; 1 for unspecified, borderline, or uncertain behavior; 2 for carcinoma in situ and grade III intraepithelial neoplasia; 3 for malignant tumors, primary site.

Continued

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

NCCN Guidelines Version 2.2026
Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer

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WHO HISTOLOGIC CLASSIFICATION[1,2]

Sex Cord-Stromal Tumors: Pure Stromal Tumors	
• Fibroma NOS	0
▸ Cellular fibroma	1
• Thecoma NOS	0
• Thecoma, luteinized	0
• Sclerosing stromal tumor	0
• Microcystic stromal tumor	0
• Signet-ring stromal tumor	0
• Leydig cell tumor of the ovary NOS	0
• Steroid cell tumor NOS	0
• Steroid cell tumor, malignant	3
• Fibrosarcoma NOS	3
Sex Cord-Stromal Tumors: Pure Sex Cord Tumors	
• Adult granulosa cell tumor of the ovary	3
• Granulosa cell tumor, juvenile	1
• Sertoli cell tumor NOS	1
• Sex cord tumor with annular tubules	1
Mixed Sex Cord-Stromal Tumors	
• Sertoli-Leydig cell tumor NOS	1
▸ Sertoli-Leydig cell tumor, well differentiated	0
▸ Sertoli-Leydig cell tumor, moderately differentiated	1
▸ Sertoli-Leydig cell tumor, poorly differentiated	3
▸ Sertoli-Leydig cell tumor, retiform	1
• Sex cord tumor NOS	1
• Gynandroblastoma	1

Germ Cell Tumors	
• Teratoma, benign	0
• Immature teratoma NOS	3
• Dysgerminoma	3
• Yolk sac tumor NOS	3
• Embryonal carcinoma NOS	3
• Choriocarcinoma NOS	3
• Mixed germ cell tumor	3
Monodermal Teratoma & Somatic-type Tumors from Dermoid Cyst	
• Struma ovarii, NOS	0
• Struma ovarii, malignant	3
• Strumal carcinoid	1
• Teratoma with malignant transformation	3
• Cystic teratoma NOS	0
Germ Cell- Sex Cord-Stromal Tumors	
• Gonadoblastoma	1
▸ Dissecting gonadoblastoma	
▸ Undifferentiated gonadal tissue	
• Mixed germ cell- sex cord-stromal tumor, NOS	1

Miscellaneous Tumors	
• Adenoma of rete ovarii	0
• Adenocarcinoma of rete ovarii	3
• Wolffian tumor	1
• Solid pseudopapillary tumor of ovary	1
• Small cell carcinoma, hypercalcaemic type	3
▸ Small cell carcinoma, large cell variant	
• Wilms tumor	3
Tumor-like Lesions	
• Follicle cyst	0
• Corpus luteum cyst	0
• Large solitary luteinized follicle cyst	0
• Hyperreactio luteinalis	0
• Pregnancy luteoma	0
• Stromal hyperplasia and hyperthecosis	0
• Fibromatosis and massive oedema	0
• Leydig cell hyperplasia	0
Metastases to the ovary	

[1] Reproduced with permission from Adhikari L, Hassell LA. World Health Organization Classification of Female Genital Tumours, 5th edition. IARC, 2020.
[2] Behavior is coded 0 for benign tumors; 1 for unspecified, borderline, or uncertain behavior; 2 for carcinoma in situ and grade III intraepithelial neoplasia; 3 for malignant tumors, primary site.

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

Staging

Table 1
American Joint Committee on Cancer (AJCC)
TNM and FIGO Staging System for Ovarian, Fallopian Tube, and Primary Peritoneal Cancer (8th ed., 2017)

Primary Tumor (T)

TNM	FIGO	
TX		Primary tumor cannot be assessed
T0		No evidence of primary tumor
T1	**I**	Tumor limited to ovaries (one or both) or fallopian tube(s)
T1a	**IA**	Tumor limited to one ovary (capsule intact) or fallopian tube, no tumor on ovarian or fallopian tube surface; no malignant cells in ascites or peritoneal washings
T1b	**IB**	Tumor limited to both ovaries; (capsules intact) or fallopian tubes; no tumor on ovarian or fallopian tube surface; no malignant cells in ascites or peritoneal washings
T1c	**IC**	Tumor limited to one or both ovaries or fallopian tubes, with any of the following:
T1c1	**IC1**	Surgical spill
T1c2	**IC2**	Capsule ruptured before surgery or tumor on ovarian or fallopian tube surface
T1c3	**IC3**	Malignant cells in ascites or peritoneal washings
T2	**II**	Tumor involves one or both ovaries or fallopian tubes with pelvic extension below pelvic brim or primary peritoneal cancer
T2a	**IIA**	Extension and/or implants on the uterus and/or fallopian tube(s) and/or ovaries
T2b	**IIB**	Extension to and/or implants on other pelvic tissues
T3	**III**	Tumor involves one or both ovaries or fallopian tubes, or primary peritoneal cancer, with microscopically confirmed peritoneal metastasis outside the pelvis and/or metastasis to the retroperitoneal (pelvic and/or para-aortic) lymph nodes
T3a	**IIIA2**	Microscopic extrapelvic (above the pelvic brim) peritoneal involvement with or without positive retroperitoneal lymph nodes
T3b	**IIIB**	Macroscopic peritoneal metastasis beyond pelvis 2 cm or less in greatest dimension with or without metastasis to the retroperitoneal lymph nodes
T3c	**IIIC**	Macroscopic peritoneal metastasis beyond the pelvis more than 2 cm in greatest dimension with or without metastasis to the retroperitoneal lymph nodes (includes extension of tumor to capsule of liver and spleen without parenchymal involvement of either organ)

Used with the permission of the American College of Surgeons, Chicago, Illinois. The original source for this information is the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer International Publishing.

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

Continued

Staging

Table 1 (Continued)
American Joint Committee on Cancer (AJCC)
TNM and FIGO Staging System for Ovarian, Fallopian Tube, and Primary Peritoneal Cancer (8th ed., 2017)

Regional Lymph Nodes (N)

TNM	FIGO	
NX		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N0(i+)		Isolated tumor cells in regional lymph node(s) no greater than 0.2 mm
N1	**IIIA1**	Positive retroperitoneal lymph nodes only (histologically confirmed)
N1a	**IIIAi**	Metastasis up to and including 10 mm in greatest dimension
N1b	**IIIAii**	Metastasis more than 10 mm in greatest dimension

Distant Metastasis (M)

TNM	FIGO	
M0		No distant metastasis
M1	**IV**	Distant metastasis, including pleural effusion with positive cytology; liver or splenic parenchymal metastasis; metastasis to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside the abdominal cavity); and transmural involvement of intestine
M1a	**IVA**	Pleural effusion with positive cytology
M1b	**IVB**	Liver or splenic parenchymal metastases; metastases to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside the abdominal cavity); transmural involvement of intestine

Used with the permission of the American College of Surgeons, Chicago, Illinois. The original source for this information is the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer International Publishing.

Continued

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

Staging

Table 2. **AJCC Prognostic Groups**
TNM and FIGO Staging System for Ovarian, Fallopian Tube, and Primary Peritoneal Cancer (8th ed., 2017)

	T	N	M
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 IIIA1	T1/T2	N1	M0
Stage IIIA2	T3a	NX/N0/N1	M0
Stage IIIB	T3b	NX/N0/N1	M0
Stage IIIC	T3c	NX/N0/N1	M0
Stage IV	Any T	Any N	M1
Stage IVA	Any T	Any N	M1a
Stage IVB	Any T	Any N	M1b

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NCCN Guidelines Version 2.2026
Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer

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ABBREVIATIONS

ACLS	advanced cardiovascular life support
AUC	area under the curve
BSO	bilateral salpingo-oophorectomy
β-hCG	beta-human chorionic gonadotropin
CAP	College of American Pathologists
CBC	complete blood count
CEA	carcinoembryonic antigen
CLIA	Clinical Laboratory Improvement Amendments
CR	complete response
ctDNA	circulating tumor DNA
C/A/P	chest/abdomen/pelvis
dMMR	mismatch repair deficient
FIGO	International Federation of Gynecology and Obstetrics
FNA	fine-needle aspiration
GI	gastrointestinal
HCT	hematopoietic cell transplant
HIPEC	hyperthermic intraperitoneal chemotherapy
HR	homologous recombination
HRD	homologous recombination deficiency
IDS	interval debulking surgery
IHC	immunohistochemistry
IM	intramuscular
IP	intraperitoneal
LCOC	less common ovarian cancers
LDH	lactate dehydrogenase
LFT	liver function test
LMP	low malignant potential
LOH	loss of heterozygosity
MGPT	multigene panel testing
MMMT	malignant mixed Müllerian tumor
MMR	mismatch repair
MSI	microsatellite instability
MSI-H	microsatellite instability-high
PARPi	PARP inhibitor
PCS	primary cytoreductive surgery
P/LP	pathogenic/likely pathogenic
PR	partial response
REI	reproductive endocrinology and infertility
RRSO	risk-reducing salpingo-oophorectomy
SEE-FIM	sectioning and extensively examining the fimbriated end
SCCOHT	small cell carcinoma of the ovary (hypercalcemic type)
STIC	serous tubal intraepithelial carcinoma
TMB	tumor mutational burden
TMB-H	tumor mutational burden-high
TNM	tumor node metastasis
USO	unilateral salpingo-oophorectomy

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

NCCN Categories of Evidence and Consensus	
Category 1	Based upon high-level evidence (≥1 randomized phase 3 trials or high-quality, robust meta-analyses), there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.
Category 2B	Based upon lower-level evidence, there is NCCN consensus (≥50%, but <85% support of the Panel) that the intervention is appropriate.
Category 3	Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise indicated.

NCCN Categories of Preference	
Preferred	Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability.
Other recommended	Other interventions that may be somewhat less efficacious, more toxic, or based on less mature data; or significantly less affordable for similar outcomes.
Useful in certain circumstances	Other interventions that may be used for selected patient populations (defined with recommendation).

All recommendations are considered appropriate.

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

NCCN Guidelines Version 2.2026
Ovarian Cancer Including Fallopian Tube Cancer and Primary Peritoneal Cancer

Discussion

This discussion corresponds to the NCCN Guidelines for Ovarian Cancer Including Fallopian Tube Cancer and Primary Peritoneal Cancer. Last updated on: March 12, 2026

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Overview

Epithelial ovarian cancer is the sixth most common cause of cancer mortality in females in the United States.[1] In 2026 it is estimated that 21,010 new diagnoses and 12,450 deaths from this malignancy will occur in the United States.[1] Five-year survival is about 52%, although survival is longer for select patients with early-stage disease and certain histologic subtypes.[2,3] These guidelines include recommendations for patients with the most common subtypes—high-grade serous and grade 2/3 endometrioid along with less common ovarian cancers (LCOC): carcinosarcoma, clear cell carcinoma, mucinous carcinoma, low-grade serous, small cell carcinoma of the ovary hypercalcemic type, grade 1 endometrioid, borderline epithelial, malignant sex cord-stromal, and malignant germ cell tumors. The 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 Panel members during the process of developing these guidelines. A 5% rule (omitting clinical scenarios that comprise <5% of all cases) was used to eliminate uncommon clinical occurrences or conditions from these guidelines.

Guidelines Update Methodology

The complete details of the Development and Update of the NCCN Guidelines are available at www.NCCN.org.

Literature Search Criteria

Prior to the update of the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Ovarian Cancer Including Fallopian Tube Cancer and Primary Peritoneal Cancer, an electronic search of the PubMed database was performed to obtain key literature published since the previous Guidelines update, using the following search terms: *ovarian OR fallopian OR (primary and peritoneal) OR (ovary) AND (carcinoma OR carcinomas OR cancer OR cancers OR malignant OR malignancy OR malignancies OR lesion OR lesions OR tumor OR tumors OR carcinosarcoma OR carcinosarcomas)*. The PubMed database was chosen because it is the most widely used resource for medical literature and it indexes peer-reviewed biomedical literature.[4] The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: Clinical Trial, Phase 2; Clinical Trial, Phase 3; Clinical Trial, Phase 4; Clinical Conference; Guideline; Practice Guideline; Randomized Controlled Trials; Meta-Analysis; Systematic Reviews; and Validation Studies. The data from key PubMed articles as well as articles from additional sources deemed as relevant to these NCCN Guidelines have been included in this version of the Discussion section. Recommendations for which high-level evidence is lacking are based on the Panel's review of lower-level evidence and expert opinion.

Sensitive/Inclusive Language Usage

NCCN Guidelines strive to use language that advances the goals of equity, inclusion, and representation.[5] NCCN Guidelines endeavor to use language that is person-first; not stigmatizing; anti-racist, anti-classist, anti-misogynist, anti-ageist, anti-ableist, and anti-weight-biased; and inclusive of individuals of all sexual orientations and gender identities. NCCN Guidelines incorporate non-gendered language, instead focusing on organ-specific recommendations. This language is both more accurate and more inclusive and can help fully address the needs of individuals of all sexual orientations and gender identities. NCCN Guidelines will continue to use the terms men, women, female, and male when citing statistics, recommendations, or data from organizations or sources that do not use inclusive terms. Most studies do not report how sex and gender data are collected and use these terms interchangeably or inconsistently. If sources do not differentiate gender from sex assigned at birth or organs present, the information is presumed to predominantly represent cisgender individuals. NCCN encourages researchers to collect more specific data in future studies and

organizations to use more inclusive and accurate language in subsequent analyses.

Risk Factors for Ovarian Cancer

Carriers of confirmed BRCA1/2 P/LP variants are at increased risk for ovarian cancers.[6,7] The effectiveness of risk-reducing salpingo-oophorectomy (RRSO) in reducing the risk for ovarian cancer in carriers of a BRCA1/2 P/LP variant has been demonstrated in a number of studies.[8,9] For detailed information about genetic/familial risks and risk reducing strategies please refer to the NCCN guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate (available at www.NCCN.org).

Additionally, 30% to 60% decreased risk for cancer is associated with ≥1 pregnancies/births, the use of oral contraceptives, and/or breastfeeding.[10-13] Conversely, nulliparity confers an increased risk for ovarian cancer. Data suggest that postmenopausal hormone therapy may increase the risk for ovarian cancer, although results vary across studies.[12,14-16] The risk for ovarian borderline epithelial tumors (also known as low malignant potential [LMP] tumors) may be increased after ovarian stimulation for in vitro fertilization.[17,18] Other factors including obesity and smoking have been shown to be associated with increased risk of ovarian cancers, but the data are inconsistent. [12,13,19-22]

Clinical Signs and/or Symptoms

Clinical signs include abdominal distension/ascites, and a mass noted on abdomen/pelvis examination. Symptoms suggestive of ovarian cancer include bloating, pelvic or abdominal pain, difficulty eating or feeling full quickly, and urinary symptoms (urgency or frequency), especially if these symptoms are new and frequent (>12 times/mo), and cannot be attributed to any known or previously identified malignancy/cause. Physicians evaluating those with this constellation of symptoms must be cognizant of the possibility that ovarian pathology.[23,24]

Workup

Workup for patients with ovarian cancer presenting with clinical signs and/or symptoms includes abdominal/pelvic exam, imaging, laboratory studies, biomarker tests, assessment of nutritional, and performance status, and gastrointestinal (GI) evaluation, as clinically indicated. These are described in the following sections.

Imaging

The primary workup for patients with clinical signs or symptoms of ovarian cancer should include a pelvis ultrasound (US) and/or abdomen/pelvis (A/P) CT/MRI scan or chest CT as clinically indicated. US is typically used for initial evaluation since it can be effective in triaging the majority of adnexal masses into benign or malignant categories.[25,26] If US is not reliable or results are indeterminate, A/P MRI for determining malignant potential of adnexal masses or FDG-PET/CT scan may be useful.[25-30] For assessment of A/P metastases for preoperative staging, estimation of resectability, and surgical planning, A/P CT or MRI are generally more useful than US.[28,31] MRI has been shown to provide equivalent accuracy for staging and comparable accuracy for predicting peritoneal tumor volume, and can be useful if CT results are inconclusive. FDG-PET/CT for assessing advanced disease may also be useful if CT results are indeterminate and may be able to detect distant metastases.[32,33] The Panel recommends PET/CT, MRI, or PET/MRI for indeterminate lesions if the results of the scan will alter management. Although there is no direct evidence that chest CT is necessary, Panel members felt that it should be part of the overall evaluation of a patient if clinically indicated. Chest CT can detect metastatic or disseminated disease, which may help with treatment planning. These imaging modalities can also be utilized for patients referred after recent surgical procedures and with newly diagnosed disease.

Laboratory Studies and Biomarker Tests

Appropriate laboratory studies for patients presenting with clinical symptoms/signs of ovarian cancer include complete blood count (CBC) and chemistry profile with liver function test. If clinically indicated, cancer antigen 125 (CA-125) testing or other tumor markers can be included in the preoperative workup. Serum CA-125 levels tend to correlate with the clinical course of disease, especially in those with elevated pretreatment levels.[34,35] Therefore, serum CA-125 can be useful in treatment planning, monitoring response to therapy, and surveillance for recurrence.

HE4 may be a useful prognostic marker in patients with ovarian cancer during treatment and may improve early detection of recurrence relative to CA-125 alone.[35-37] Other tumor markers elevated in stromal or germ cell tumors include inhibin, alpha-fetoprotein [AFP], beta–human chorionic gonadotropin [β-hCG], lactate dehydrogenase [LDH], carcinoembryonic antigen [CEA], and CA 19-9.[38-42] Serum levels of these markers can be elevated and correlate with clinical course of disease in patients with epithelial and certain LCOCs. In young patients with an ovarian mass, high levels of AFP and β-hCG correlated with higher likelihood of malignancy, poor prognosis, or specific histologic subtypes.[38] These studies also suggested that AFP and β-hCG can help with intraoperative diagnosis to determine whether fertility-sparing surgery is an option. Similarly, high levels of serum LDH have been shown to correlate with more extensive disease and poor outcomes in patients with certain types of ovarian cancer.[43] Elevated serum CEA is a marker associated with GI primary cancers, but can also occur in patients with ovarian malignancies, particularly mucinous tumors. When biopsy is not feasible, the Panel recommends considering a ratio of serum CA-125 to CEA >25 suspicious for ovarian cancer combined with cytopathology from ascites or pleural effusion. CA 19-9 is another marker that is elevated more often in mucinous tumors compared with other ovarian cancer types.[42] Results from some studies suggest that serum CA 19-9 may be useful for monitoring for recurrence, especially in patients with mucinous ovarian cancers and in those with high CA 19-9 levels prior to treatment.

Nutritional Status, Performance Status, and Gastrointestinal (GI) Evaluation

Workup should also include evaluation of the patient's nutritional status, performance status, and if clinically indicated, an additional GI evaluation.[44] Performance status (PS) (Eastern Cooperative Oncology Group [ECOG] > 0) in patients with high-grade serous carcinoma was significantly associated with longer overall survival (OS) ($P < .05$).[45] In another study, patients with stage III epithelial carcinoma and PS 1 or 2 were at an increased risk for recurrence compared to patients PS 0 (HR = 1.12; 95% CI, 1.01 to 1.24).[46] PS is utilized to assess the patient's ability to tolerate treatment. The Panel recommends that performance status be used to determine whether patients can be considered for secondary cytoreductive surgery and systemic therapy.

Patients with ovarian cancer often present with bloating, pelvic or abdominal pain, difficulty eating, or feeling full quickly, which leads to changes in dietary habits and results in poor nutritional status. Poor nutritional status is associated with higher risk of suboptimal surgery, surgical complications, and poor survival, especially in patients ≥75 years.[47-49] Evaluation of nutritional status is recommended as part of baseline workup as it is important for determining whether a patient is a good surgical candidate, and for preoperative planning. Poor nutritional status in the context of a GI mass may be an indication for prioritizing surgery to remove or reduce the GI mass, especially if the patient is a good surgical candidate. GI tract evaluation is especially important in those with elevated serum CEA and adnexal mass to distinguish between a GI primary tumor that has metastasized to the ovary and primary mucinous carcinoma of the ovary.[50] The presence of a pancreatic mass or widespread abdominal disease should also increase suspicion for primary GI cancer.

Family History and Genetic Testing

Obtaining a family history of cancer and referral to a genetic counselor and/or genetic testing is important, as some patients may carry germline mutations in ovarian cancer risk genes that inform future treatment. Primary treatment (surgery and chemotherapy) should not be delayed for a genetic counselling referral. Recommendations regarding screening, genetic testing, and risk management, including risk-reducing surgeries, can be found in the NCCN Guidelines® for Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate (available at www.NCCN.org).

Referral to Gynecologic Oncologist for Clinically Suspicious Lesions

Primary assessment and debulking by a gynecologic oncologist are associated with improved survival; therefore, all patients with clinically suspicious lesions should be referred to an experienced gynecologic oncologist for evaluation.[51] A gynecologic oncologist assesses whether a patient is a suitable surgical candidate and/or an appropriate candidate for neoadjuvant therapy (NACT). A gynecologic oncologist can also perform laparoscopic evaluation to determine whether debulking surgery is feasible and the best method for obtaining tissue needed for definitive diagnosis.[24,52]

Reproductive Endocrinology and Infertility (REI) Evaluation

Patients who wish to retain fertility should be referred to a reproductive endocrinologist for consultation, including possibility of oocyte collection before chemotherapy is initiated. Fertility-sparing surgery may be considered for patients who wish to preserve fertility and have apparent early-stage disease and/or low-risk tumors, such as early-stage invasive epithelial tumors, LMP lesions, malignant germ cell tumors, or malignant sex cord-stromal tumors. Even if the contralateral ovary cannot be spared, uterine preservation can be considered as it allows for potential future assisted reproductive approaches. Reconsider REI as clinically indicated once pathologic diagnosis is available or if patient was diagnosed by previous surgery.

Diagnosis by Previous Surgery

Patients are occasionally referred to cancer centers after a previous diagnosis of ovarian cancer by surgery or tissue biopsy (cytopathology). Referrals can also occur after incomplete surgery and/or staging, eg, uterus and/or adnexa intact, omentum not removed, incomplete lymph node dissection, residual disease that is potentially resectable, incomplete documentation of surgical staging, or occult invasive carcinoma found at time of risk reduction surgery. Occult serous tubal intraepithelial carcinomas (STICs) are considered as precursors of high-grade serous carcinomas and there is no clear understanding of how to diagnose and manage these.[53] Therefore, the Panel recommends a gynecologic oncologist should be consulted for management of STICs. In such cases, evaluation by a gynecologic oncologist is important for determining whether the previous surgery was adequate or an additional surgery is required. Prior imaging studies and operative notes should be reviewed to determine if additional workup is needed. Additional imaging may be needed to screen for distant disease and evaluate for residual disease not removed during the previous surgery. Pathologic review of tissue from the previous surgery is important for confirming diagnosis and cancer type. CBC and chemistry profile with LFTs should be obtained, and CA-125 or other tumor markers should be measured as clinically indicated to corroborate likely diagnosis and to serve as baseline for future follow-up. If not previously done, workup should include obtaining a family history, genetic risk evaluation, and germline/somatic testing.

Histopathology, Staging, and Molecular Testing

Most ovarian cancers, including the LCOC, are diagnosed after pathologic analysis of a biopsy or surgical specimen, which may occur preoperatively, intraoperatively, or postoperatively. Based on the College

of American Pathologists (CAP) protocol that is updated frequently and Panel consensus, components that should be included in the pathologic assessment are described in the guidelines.

Histopathology at Diagnosis

The complete histologic classification from the WHO is listed in the guidelines.[54] Epithelial ovarian cancer has four main subtypes, including serous, endometrioid, mucinous, and clear cell.[55] The pathologic hallmark of typical epithelial ovarian tumors are peritoneal implants that invade the peritoneum microscopically and/or macroscopically. Ovarian borderline epithelial tumors, also called atypical proliferative tumors, are another type of primary epithelial lesions. Borderline tumors have cytologic characteristics suggesting malignancy and may grossly resemble an invasive cancer, but microscopic evaluation will usually show no evidence of frank tumor invasion. Borderline epithelial tumors are typically serous or mucinous; but other less common histologic subtypes can also occur.[56] A rare and aggressive type of tumors that arise in the ovary, fallopian tubes, or peritoneum are carcinosarcomas, also called carcinomas of Müllerian origin (malignant mixed Müllerian tumors [MMMTs]). MMMTs are biphasic, with both malignant epithelial and sarcomatous components.[57] Non-epithelial tumors of the ovary include germ cell tumors and malignant sex cord-stromal tumors.[58] Germ cell tumors encompass dysgerminomas, immature teratomas, embryonal tumors, and endodermal sinus (yolk sac) tumors. Malignant sex cord-stromal tumors are rare and include granulosa cell tumors and Sertoli-Leydig cell tumors.

In some cases, it can be difficult to distinguish between ovarian cancer subtypes. For example, high-grade endometrioid tumors can be difficult to distinguish from high-grade serous tumors or resemble either clear cell or sex cord-stromal tumors. In complex cases, immunohistochemistry (IHC) analyses of most recent available tissue may help with differential diagnosis. Consistent with the Society of Gynecologic Oncology (SGO) and American Society of Clinical Oncology (ASCO), the Panel emphasizes that evaluation by a gynecologic oncologist is important for determining the most appropriate method of obtaining tissue for histologic confirmation.[59]

Most serous carcinomas (80%–90%) are positive for WT1, whereas endometrioid and clear cell carcinomas are usually negative for WT1.[60] Endometriosis can also be an indication for certain subtypes such as clear cell carcinomas and endometrioid tumors.[61] Napsin A is a specific IHC marker and is expressed in most clear cell carcinomas. It can also be difficult to distinguish between primary mucinous ovarian carcinomas and GI metastases. In such cases, PAX8 immunostaining can be helpful since it is typical of primary ovarian tumors. However, the absence of PAX8 does not completely rule out ovary as the primary site.[62]

Staging

Ovarian cancer is classified as stages I to IV using FIGO (International Federation of Gynecology and Obstetrics) staging, which was approved and incorporated into the AJCC Cancer Staging Manual, 8th Edition.[63,64] A pathology and staging cancer protocol is available from CAP for examination of specimens from patients with primary tumors of the ovary, fallopian tube, or peritoneum, including pTNM requirements from the AJCC Staging Manual, 8th edition and FIGO staging.[65] Data show that ~30% of patients with presumed early-stage disease are upstaged after undergoing complete surgical staging.[66-69] Therefore, the Panel recommends comprehensive surgical staging in most patients undergoing unilateral salpingo-oophorectomy (USO) or bilateral salpingo-oophorectomy (BSO) to rule out occult higher-stage disease. The Panel notes that the extent of surgical staging does not affect overall survival (OS) and comprehensive surgical staging may be omitted in pediatric/adolescent patients with clinically apparent early-stage malignant germ cell tumors.[70,71]

Molecular Testing

Upon pathologic confirmation of ovarian cancer, fallopian tube cancer, or primary peritoneal cancer, patients should be referred for a genetic risk evaluation and germline and somatic testing (if not previously done). This recommendation for germline and somatic testing is intentionally broad so that the genetic counselor and treating oncologist have the latitude to order whichever tests they consider necessary based on evaluation of the individual patient and their cancer family history. All testing should be performed on the most recent available tumor tissue in a CLIA (Clinical Laboratory Improvement Amendments)-approved facility. The goal of tumor testing in the upfront setting is to identify molecular alterations that can inform the use of interventions with demonstrated benefit in this setting. Molecular alterations that should be probed, at a minimum, in this setting include *BRCA1/2* mutation status and loss of heterozygosity or homologous recombination status. Since germline and/or somatic *BRCA1/2* testing informs selection of maintenance therapy, the Panel agrees that it is important to establish *BRCA1/2* mutation status for patients who may be eligible for maintenance therapy following completion of platinum-based first-line chemotherapy. In the absence of *BRCA* mutations, the Panel recommends testing homologous recombination status (eg, homologous recombination deficient ([HRD] vs. homologous recombination proficient [HRP]). HRD status may provide information on the magnitude of benefit of maintenance PARP inhibitor therapy. The Panel notes that current clinical HRD tests are proxy measures of HRD and lack accuracy in fully predicting functional HRD. The Panel discussed whether comprehensive tumor biomarker analysis should be recommended for all patients. Comprehensive tumor testing may not be necessary for certain patients in the upfront setting, specifically those with germline *BRCA1/2* pathogenic/likely pathogenic (P/LP) variants or other homologous recombination/DNA repair pathway genes. However, some patients (such as those who lack *BRCA1/2* alterations or experience disease recurrence) may benefit from a more thorough tumor-biomarker analysis. In the recurrence setting, the Panel recommends that tumor biomarker analysis should include tests to identify potential benefits from targeted therapeutics that have tumor-specific or -agnostic benefit. These include, but are not limited to: HER2 status (by IHC), *BRCA1/2*, HRD status, microsatellite instability (MSI), mismatch repair (MMR), tumor mutational burden (TMB), *BRAF, FRα* (FOLR1; by IHC)*, RET,* and *NTRK*, if prior testing did not include these markers. More comprehensive tumor analyses may be particularly important for less common histologies with limited approved treatment options.

Primary Treatment Recommendations

For all patients with suspected or confirmed ovarian cancer a gynecologic oncologist should be involved in assessing whether a patient is a suitable surgical candidate, laparoscopically and/or radiographically evaluate the feasibility of debulking surgery, and determine if they are an appropriate candidate for NACT. NACT with interval debulking surgery (IDS) should be considered in patients with advanced-stage ovarian cancer who have a relatively poor performance status or have disease with low likelihood of optimal cytoreduction. Depending on stage, grade and histology, in certain patients' surgery could be followed by observation with appropriate monitoring/follow-up, while others would be recommended to receive adjuvant therapy and for some this would be followed by maintenance therapy such as bevacizumab or PARP inhibitors. Whole abdominal radiation therapy (RT) is rarely used for epithelial ovarian, primary peritoneal, and fallopian tube cancers at NCCN Member Institutions because of their low efficacy and high toxicity and therefore is not included in the guidelines. Palliative localized RT can be considered for symptom control in patients with recurrent disease and/or for oligometastatic disease.

Laparoscopic Evaluation Prior to Resection

In select patients with advanced-stage disease, minimally invasive procedures may be used to assess whether optimal cytoreduction is likely to be achieved by primary debulking surgery or whether NACT may be a

better initial treatment option.[72-75] A randomized trial assessed whether laparoscopy would be useful to predict the ability to achieve optimal cytoreduction (<1 cm residual disease). Only 10% of patients randomized to the assessment laparoscopy arm had >1 cm of residual disease after surgery compared to 39% of patients who were randomized to primary cytoreductive surgery (relative risk [RR], 0.25; 95% CI, 0.13–0.47; P < .001). The survival rates were comparable between the two groups.[73]

Fertility-Sparing Options for Stage I and/or Low-Risk Disease

Patients who wish to retain fertility options should be referred to a reproductive endocrinologist for preoperative evaluation and consultation. Fertility-sparing surgery may be considered for patients who wish to preserve fertility and have apparent early-stage disease and/or low-risk tumors, such as early-stage invasive epithelial tumors, LMP lesions, malignant germ cell tumors, or malignant sex cord-stromal tumors.[76] Fertility-sparing surgery did not appear to compromise disease-free survival (DFS) or OS compared with radical surgery for stage I ovarian cancer, regardless of histology.[77-81] USO to preserve the uterus and contralateral ovary/fallopian tube with comprehensive surgical staging may be adequate for select patients who wish to preserve fertility and appear to have stage IA unilateral tumors.[82-84] For those with bilateral stage IB tumors who wish to maintain fertility, a BSO to preserve the uterus with comprehensive surgical staging can be considered. Even if the contralateral ovary cannot be spared, uterine preservation can be considered as it allows for potential assisted reproductive approaches in the future.

Surgery

Since multiple studies have shown improved outcomes, it is recommended that a gynecologic oncologist be the provider to determine and use the best surgical debulking approach.[52,85,86] An open laparotomy is recommended for most patients, but minimally invasive techniques may be appropriate in certain circumstances. For most patients presenting with suspected malignant ovarian, fallopian tube, or primary peritoneal neoplasm, initial surgery should include a hysterectomy (if uterus is present) and BSO with comprehensive staging and debulking as indicated.[87-89] This approach is recommended for most patients with stage IA–IV disease who are good surgical candidates, when optimal cytoreduction appears feasible and fertility is not a concern. For patients with advanced-stage ovarian cancer who are not good candidates for primary debulking surgery due to advanced age, frailty, poor performance status, comorbidities, or who have disease unlikely to be optimally cytoreduced, NACT with IDS should be considered.[59,90] The anticipated benefit from NACT is the improvement in clinical symptoms and/or response that would increase the likelihood of optimal IDS as well as less need for procedures such as intestinal resection that increase morbidity. For other patients with bulky disease, a minimally invasive procedure may be appropriate to obtain biopsy tissue for confirming diagnosis and/or biomarker testing and determine whether optimal cytoreduction is possible. Enhanced recovery after surgery (ERAS) programs, when implemented, have shown to reduce the length of hospital stay, especially for patients who underwent complex surgeries.[91]

Open Laparotomy Versus Minimally Invasive Techniques

The Panel notes that minimally invasive techniques, if performed by an experienced gynecologic oncologist, may be considered in select patients with early-stage disease (IA–IIA) or presumed early-study disease. Studies have shown no difference in surgical outcomes, recurrence rates, or survival between patients who underwent minimally invasive surgery versus open surgical staging.[66,92-95] If signs of lymph node metastasis or localized carcinomatosis are found, lymphadenectomy and complete pelvic peritonectomy may still be feasible using minimally invasive techniques.[96] Minimally invasive techniques to debulk tumors and perform surgical staging along with hysterectomy and USO or BSO are also feasible and can achieve optimal cytoreduction in patients with advanced disease.[97-101] The Panel recommends that minimally invasive procedures

may be used for IDS provided that optimal debulking can be achieved. If the disease cannot be optimally debulked using minimally invasive techniques, then an open procedure should be utilized.

Debulking Surgery for Newly Diagnosed Disease

The recommendation for debulking surgery for patients with clinical stage >IIB disease is based on retrospective data.[102-104] Optimal cytoreduction is defined as residual disease <1 cm in maximum diameter or thickness; however, maximal effort should be made to remove all gross disease since R0 resection offers superior survival outcomes. [102,105-108] Optimal secondary or tertiary cytoreductive surgeries improved OS and disease-specific survival (DSS) or progression-free survival (PFS) compared to suboptimal cytoreductive surgeries.[109,110] Additionally, randomized studies show no difference between secondary cytoreduction plus chemotherapy compared to chemotherapy alone.[111,112] Extensive resection of upper abdominal metastases is associated with improved PFS and OS and therefore is recommended as part of debulking for patients who can tolerate it.[103,106]

Surgical Considerations for Mucinous Tumors

Since primary invasive mucinous tumors of the ovary are uncommon, it is important to first establish the primary site in patients with these tumors. The upper and lower GI tract should be carefully evaluated to rule out an occult GI primary with ovarian metastases. A normal appendix does not require surgical resection in this setting. An appendectomy needs to be performed only if it appears to be abnormal in patients with a suspected or confirmed mucinous ovarian neoplasm.[113-115]

Surgical Considerations for Ovarian Borderline Epithelial (LMP) Tumors

Although data show upstaging with lymphadenectomy, there is no association with OS.[116-118] Although retrospective studies did not find an association with prognosis, omentectomy and multiple biopsies of the peritoneum (the most common sites of peritoneal implants) may result in upstaging.[119-121]

Interval Debulking Surgery After Neoadjuvant Chemotherapy

All interval debulking procedures should include completion hysterectomy/BSO with comprehensive staging and cytoreduction. Maximal effort should be made to remove all gross disease in the abdomen, pelvis, and retroperitoneum. Neoadjuvant chemotherapy followed by debulking surgery/primary chemotherapy is not inferior to debulking surgery/primary chemotherapy.[122-124] The Panel notes that the non-inferiority studies were mostly investigated in patients with high risk in whom initial optional cytoreduction was unlikely. In patients ≥75 years, IDS following NACT is associated with greater OS compared to chemotherapy alone.[125]

Hyperthermic Intraperitoneal Chemotherapy at the Time of IDS

Hyperthermic intraperitoneal chemotherapy (HIPEC) aims to enhance clinical outcomes by delivering heated chemotherapy directly in the peritoneal cavity to eliminate any remaining residual disease. HIPEC involves perfusion of chemotherapy agents, heated to approximately 41°C to 43°C, administered immediately after cytoreductive surgery. The goal is to expose peritoneal surfaces to high chemotherapy concentrations while minimizing systemic toxicity. The rationale for hyperthermic intraperitoneal (IP) delivery is that heat can increase penetration of the chemotherapy at the peritoneal surface and enhance the sensitivity of cancer cells to chemotherapy.[126-128] Selection bias and variations in chemotherapy agents used during HIPEC across studies impact the generalizability of observed results. Ongoing studies such as the HOTT trial (NCT05659381) will add to existing data regarding outcomes with HIPEC use in ovarian cancer.

In some studies, HIPEC has improved relapse-free survival (RFS) and OS in specific patient subgroups compared to surgery alone.[129,130] A

single-center, prospective, randomized phase III trial demonstrated that NACT followed by surgery/HIPEC was associated with better DFS and OS without affecting quality of life (QOL).[131] Although HIPEC is associated with certain risks, such as abdominal pain, infection, and ileus, studies report that grade ≥3 toxicities are similar between HIPEC and non-HIPEC groups. Sodium thiosulfate may be administered, at the start of perfusion, for renal protection to mitigate potential nephrotoxic effects. Further studies with standardized protocols and longer duration of follow-up are needed to clarify long-term benefits and potential risks associated with HIPEC.

HIPEC is an option for patients with stage III or IV epithelial ovarian (category 2B for stage IV), fallopian tube, or primary peritoneal cancer who have undergone neoadjuvant chemotherapy and achieved optimal cytoreduction. Eligible stage IV patients include those who have had a favorable response to NACT both intraperitoneally and extraperitoneally, or in whom stage IV disease sites have completely resolved (eg, resolution of malignant pleural effusion) or are now deemed resectable. Exclusion criteria for HIPEC typically involve those with unresectable disease, poor performance status, or excessive residual disease post-surgery (eg, >1 cm residual tumors).

Systematic Lymphadenectomy

The use of systematic lymphadenectomy is an area of controversy. For patients with presumed early-stage disease, a randomized trial (N = 268) showed that systematic aortic and pelvic lymphadenectomy improved detection of positive nodes compared with lymph node sampling (9% vs. 22%; P = .007).[132] Operating time and the proportion of patients requiring blood transfusions were significantly higher for those who underwent systematic lymphadenectomy.[132] A randomized trial found that lymphadenectomy in patients with stage IIB–IV ovarian cancer with macroscopically complete resection and normal nodes both before and during surgery did not improve PFS or OS, and was associated with increased rates of serious postoperative complications and mortality within 60 days after surgery.[133] Other prospective studies using systematic lymphadenectomy have shown positive lymph node detection in 3% to 14% of patients.[134-137] Meta-analyses show that systematic lymphadenectomy improves OS in patients with early-stage disease, even though it does not improve PFS.[138] Based on existing data, the Panel does not recommend systematic lymphadenectomy of clinically negative nodes; however, suspicious and/or enlarged nodes should be resected if possible.

Supportive Care After Surgery

For young patients who will abruptly enter menopause after surgery, various supportive care measures may be used to help decrease hot flashes and other symptoms, and potentially reduce the risk of other systemic comorbidities that are more likely with surgical menopause.[139,140] Hormone replacement therapy (HRT) has not been shown to worsen survival in premenopausal patients with gynecologic cancers, but limited prospective data exist.[141,142] For high-grade serous histology, HRT can be considered—and may be beneficial—for symptom management after assessing individual risk factors such as personal history of estrogen receptor-positive breast cancer, thromboembolic disease, or cardiovascular risk. Some patients with newly diagnosed ovarian cancer who are past the age of natural menopause and already taking HRT may wish to continue.[143] Most will have had the uterus removed and could take estrogen alone, which avoids adverse effects of progestins. Studies suggest that HRT does not adversely impact recurrence risk or survival for high-grade serous cancers, which comprise the majority of ovarian cancer cases. For germ cell tumors, which are not hormone-dependent, HRT is generally considered safe. However, HRT should be avoided in hormonally responsive types including low-grade serous cancers, endometrioid ovarian cancers, and sex cord-stromal tumors such as advanced granulosa cell tumors.[91,144] For clear cell carcinomas, data are

limited but current evidence does not suggest a strong contraindication; individualized assessment is recommended.[145]

Patients Referred with New Diagnoses After Recent Surgical Procedure

For patients diagnosed with ovarian cancer after a recent surgical procedure, primary treatment depends on the findings noted during the workup and evaluation performed by a gynecologic oncologist. Primary treatment can include surgical staging followed by observation or systemic therapy, NACT for suspected residual disease, or a secondary/tertiary cytoreductive surgery followed by adjuvant therapy.

Select Patients Who Undergo Observation After Surgery

Observation has been shown to have similar clinical outcomes compared to adjuvant therapy for certain early stage diagnoses with a low risk of recurrence.[146,147] Observation after surgical staging is an option for patients with certain histologic subtypes as long as pathology confirms stage IA/IB with no evidence of residual disease. For those with low-risk disease and who have had complete surgical staging, adjuvant chemotherapy, compared with observation alone, has not been demonstrated to provide clear clinical benefit.[148-151] For some of the less common epithelial cancer types (eg, mucinous, grade 1 endometrioid, low-grade serous), observation is an option since the benefit of adjuvant systemic therapy has not been demonstrated. If analysis of a biopsy or surgical specimen shows a non-epithelial cancer type, such as sex cord-stromal or germ cell tumors, treatment recommendations for non-epithelial cancers should be followed (described in a later section).

Systemic Therapy for High-Grade Serous and Endometrioid Epithelial Tumors

Neoadjuvant Chemotherapy

NACT refers to treatment that is given to reduce the tumor burden in preparation for surgery. Randomized trials demonstrate that NACT improves surgical outcomes in a multitude of ways, including shorter operative time, less blood loss, fewer high-grade surgical complications or surgery-related adverse events (AEs), shorter hospital stay, less extensive and complicated surgeries needed to achieve optimal cytoreduction, and a lower risk of postoperative death.[122-124,152] Most of the trials show that NACT increases the likelihood of achieving optimal cytoreduction and/or removal of all macroscopic disease. However, there are no significant differences in PFS and OS between patients who receive NACT compared to those who do not receive NACT. A pooled analysis of EORTC 55971 and CHORUS trials showed that although there was no difference in median OS or PFS in the overall population, NACT could improve clinical outcomes in patients with more extensive disease.[153] The Panel recommends NACT for patients with confirmed bulky disease that is unlikely to be optimally cytoreduced by up-front surgery and for those who are not ideal surgical candidates due to advanced age, frailty, poor performance status, or comorbidities. NACT in patients who are not ideal surgical candidates can reduce tumor load to improve their condition, allowing for the possibility of surgery, and to reduce perioperative risks. At least one randomized trial showed that among patients (aged 60–75 years) with stage III/IV disease, NACT improved the rate of successful cytoreduction and other surgical outcomes.[124]

In the absence of data supporting specific regimens, the Panel recommends all of the IV regimens for conventional treatment of stage II–IV high-grade serous carcinoma as options for NACT. Prospective trials indicate that although platinum-based regimens that include bevacizumab have acceptable safety when used as a NACT regimen, its impact on

survival is unclear.[154,155] It is important to note that these studies used a washout period before (and sometimes after) IDS when bevacizumab was utilized in the NACT setting.[152,154-156] The Panel added a caveat to the use of bevacizumab-containing regimens before IDS due to potential interference with postoperative healing. If bevacizumab is used as part of NACT, it should be withheld for 4 to 6 weeks prior to IDS.

Adjuvant Therapy

Adjuvant therapy is a form of supplemental treatment following surgery intended to decrease the risk of disease recurrence or to treat gross/microscopic residual disease. Most patients with epithelial ovarian, fallopian tube, or primary peritoneal cancer should receive adjuvant systemic chemotherapy after primary surgery once requirements for adequate organ function and performance status are met. Many regimens and approaches have been tested in prospective randomized trials as postoperative therapy for patients with newly diagnosed ovarian cancer. Based on phase III randomized trials, the Panel has listed several options as adjuvant therapy options. These include platinum-based IV chemotherapy with or without bevacizumab and platinum-based IV/IP chemotherapy with or without bevacizumab. Data are limited for stage I disease. While the Panel has included some platinum-based IV options, IV/IP regimens and bevacizumab are not recommended for stage I disease.

Platinum-Based Regimens

Results from early trials suggested that regimens that included platinum agents resulted in better response rates and PFS.[157,158] Randomized studies comparing different dosing schedules for IV carboplatin and paclitaxel regimens as first-line adjuvant therapy for ovarian cancer showed variation in clinical outcomes.[159-164] These trials also showed increased rates of neutropenia and signs of worse QOL among patients treated with dose-dense regimens. Studies investigating standard paclitaxel/carboplatin dosing and weekly paclitaxel/weekly carboplatin found no significant differences in efficacy.[159,160] Different AEs were reported for the two regimens; however, the weekly paclitaxel regimen was associated with significant improvement in QOL compared to the weekly dose-dense regimen.[159,160,165] Randomized studies also show equivalent efficacy between carboplatin versus cisplatin, either alone or in combination, but reported differences in toxicity profiles and QOL.[166-173] Cisplatin was associated with higher rates of neurotoxicity, GI toxicities (eg, nausea, emesis), renal toxicity, metabolic toxicities, anemia, and alopecia, while carboplatin was associated with higher rates of thrombocytopenia and granulocytopenia.[166-170,174,175] The AGO-OVAR-3 study found that global QOL and various subscales were significantly better with carboplatin/paclitaxel than cisplatin/paclitaxel.[175] A study comparing alternate carboplatin and cisplatin schedules with only the carboplatin schedule found similar efficacy; however, toxicity was worse in the alternate cisplatin/carboplatin arm.[172] Based on these data, the Panel chose to include carboplatin/paclitaxel-based regimens as preferred options for adjuvant therapy.

Docetaxel/carboplatin have similar PFS, OS, and global QOL scores as paclitaxel/carboplatin with both regimens associated with certain AEs.[176] Pegylated liposomal doxorubicin/carboplatin is associated with a higher response rate but similar PFS and OS as paclitaxel/carboplatin.[177] This regimen may be useful in select patients at high risk for neurotoxicity or to avoid alopecia. Both docetaxel/carboplatin and liposomal doxorubicin/carboplatin may be considered for patients who are at high risk for neuropathy (eg, patients with diabetes).[178] Most patients in the abovementioned trials had stage III–IV disease with only some including patients with stage I or stage II disease.[159,160,165,176,177,179] Therefore, the list of recommended options, which includes paclitaxel/carboplatin, docetaxel/carboplatin, and pegylated liposomal doxorubicin/carboplatin, is smaller for patients with stage I disease. Weekly paclitaxel/carboplatin is more logistically challenging to administer and is therefore often not used in stage I disease. The Panel also had extensive discussions about the

number of cycles of chemotherapy that should be recommended for different disease stages. There are no data showing that >6 cycles of combination regimens is required for initial chemotherapy. Continuation beyond 6 cycles is unlikely to provide additional clinical benefit.[158,173,180] In fact, increasing the number of cycles may be associated with higher grades of AEs, including neurotoxicity, granulocytopenia, and anemia.[181,182] Therefore, the Panel recommends 6 cycles for stage I high-grade serous disease, with 3–6 cycles recommended for all other ovarian cancer types. For any stage II–IV disease, 6 cycles is recommended.

Patients ≥70 years and/or with comorbidities are less likely to tolerate certain drug combinations, leading to discontinuation before the full course of chemotherapy is completed.[178,183-185] For example, patients ≥70 years receiving paclitaxel/carboplatin-based therapy may be at higher risk of febrile neutropenia, anemia, diarrhea, asthenia, thromboembolic events, or bevacizumab-associated hypertension.[183,184] Studies have suggested that risk of severe toxicity, discontinuation of adjuvant chemotherapy, and even worse OS may be correlated with increased age, functional status or depression at baseline, lymphopenia, hypoalbuminemia, and a number of co-medications.[186-191] For these reasons, alternate dosing is recommended for patients ≥70 years and/or those with comorbidities. For guidance on how potential chemotherapy toxicity can be assessed, refer to the NCCN Guidelines for Older Adult Oncology (available at www.NCCN.org). The Panel no longer recommends carboplatin monotherapy as an option for patients who are ≥70 years and/or those with comorbidities based on the termination of the GINECO/GCIG trial, which showed worse survival outcomes associated with carboplatin monotherapy, by the independent data monitoring committee.[192]

IP chemotherapy has been explored as an option based on the idea that localized delivery with an acceptable safety profile could improve efficacy, particularly against microscopic spread and peritoneal carcinomatosis. IP/IV administration significantly increases risk of certain high-grade hematologic and non-hematologic toxicities.[193-195] Contradictory data exist, with some studies showing improved PFS and OS with IP/IV administration compared to IV-only administration.[193,194,196,197] In patients who had platinum-based NACT followed by IDS, adjuvant IP/IV regimens were well tolerated with moderate improvement in OS/PFS.[198-200] Based on these results, the Panel decided to add IP/IV options for stage II–IV disease. The Panel notes that enthusiasm for IP/IV chemotherapy has waned considerably since IP carboplatin as part of the paclitaxel/carboplatin/bevacizumab combination did not improve PFS or OS compared to IV administration.[201] The PFS benefit in this study is thought to have mostly come from the addition of bevacizumab.

Bevacizumab

Studies show that high-risk disease associated with poor prognosis tends to derive greater benefit from the addition of bevacizumab to upfront paclitaxel/carboplatin.[202-204] Subgroup analyses have identified high-risk groups as those with either stage IV, inoperable stage III, or suboptimally debulked stage III disease (residual disease >1 cm).[204] Exploratory data suggest that stage may be more important than the extent of residual disease to identify patients who may benefit from bevacizumab.[205] There was no difference in PFS in patients who received bevacizumab, in addition to platinum-based therapy, based on the presence or absence of *BRCA1*, *BRCA2*, or non-*BRCA* homologous recombination repair (HRR) alterations.[206] Most toxicities developed during the initial therapy, although there were a few AEs of concern that continued to develop during the maintenance portion of bevacizumab treatment. These included hypertension, high-grade pain, proteinuria, and thromboembolism.[202]

The trials investigating bevacizumab excluded stage I–II disease entirely or included only stage I–IIA disease with “high-risk” features including poor differentiation or clear cell histology. These studies included primarily ovarian cancer, but a small percentage of primary peritoneal or fallopian tube cancer or other histologic subtypes (eg, mucinous, clear cell, endometrioid) were also part of the studies.[202,203] Therefore, the Panel

decided to recommend bevacizumab-containing regimens as an option for any of these histologic subtypes and stage II–IV disease.

Primary Maintenance Therapy

Maintenance therapy after adjuvant platinum-based therapy can have a positive impact on PFS and OS in patients with advanced disease.[207-209] Therefore, integration of maintenance therapy, which includes PARP inhibitors, to adjuvant treatment has increased in prevalence and importance. PARP inhibitors, including olaparib, rucaparib, and niraparib, have been widely studied in ovarian cancer and established as maintenance treatment options. The Panel recommends testing for *BRCA1* and *BRCA2* mutations as part of genetic risk evaluation and germline and somatic testing earlier during workup and primary treatment. In the absence of *BRCA* mutations, homologous recombination repair (HR) status might provide information on the magnitude of the benefit of maintenance PARP inhibitor. The Panel recognizes that the current clinical HRD tests are proxy measures of HRD and lack accuracy in fully predicting functional HRD. The current recommendations for PARP inhibitors as first-line maintenance therapy post primary treatment for stage II–IV tumors are based on: 1) complete response ([CR], defined as no definitive evidence of disease)/partial response (PR) status after first-line treatment; 2) presence of germline or somatic *BRCA1/2* pathogenic/likely pathogenic(P/LP) variants or HRD; and 3) prior use of bevacizumab. These recommendations have been and will be revised several times due to emerging data from several clinical trials.

Bevacizumab in First-Line Setting

Phase III trials support the use of single-agent bevacizumab maintenance therapy for patients with stage II–IV disease who experience response or stable disease (SD) after platinum/bevacizumab regimens.[204,206] Based on these results, bevacizumab monotherapy is an option for maintenance therapy. It is important to note that the trials with bevacizumab maintenance were done prior to the introduction of PARP inhibitors as maintenance therapy options and the studies that showed an association of response to PARP inhibitors with *BRCA* and/or HR status. Therefore, when subsequent trials showed benefit from PARP inhibitors (described below), bevacizumab monotherapy was removed as an option for patients with *BRCA1/2* P/LP variants; however, it is still recommended for patients who have wild-type or unknown *BRCA1/2* status. Currently, there are no data to support bevacizumab as maintenance therapy if it was not used during primary treatment.

PARP Inhibitors in First-Line Setting

The SOLO-1 trial investigated 2 years of maintenance olaparib (vs. placebo) in patients with newly diagnosed advanced ovarian cancer harboring germline or somatic *BRCA1/2* P/LP variants.[207,210] Patients with CR or PR after first-line platinum-based chemotherapy were included, while those who received bevacizumab as part of primary systemic therapy were excluded.[207,210] After a median follow-up of ~41 months, patients receiving olaparib demonstrated a remarkable improvement in PFS. Longer follow-up at 7 years showed that a higher percentage of patients treated with olaparib were still alive compared to those treated with placebo (67%–46%).[211] Additionally, the time to first subsequent therapy was delayed in the olaparib arm compared to the placebo arm. Unlike SOLO-1, PAOLA-1 included patients with newly diagnosed high-grade serous ovarian cancer regardless of *BRCA1/2* status and compared the combination of maintenance olaparib (administered for up to 24 months)/bevacizumab with bevacizumab monotherapy.[212] Although there was no statistically significant improvement in OS in the intent-to-treat (ITT) population, a clinically meaningful OS benefit was observed for those with HRD tumors(which included patients with somatic *BRCA 1/2* mutations) and treated with olaparib/bevacizumab (HR, 0.62; 95% CI, 0.45–0.85).[212] The trial did not include an olaparib single-agent arm.

Other PARP inhibitors, niraparib and rucaparib, were investigated in different clinical trials around the same time. The PRIMA trial examined single-agent niraparib for 3 years or until disease progression, as maintenance therapy, in patients with advanced-stage disease in CR/PR after first-line platinum-based chemotherapy. This trial demonstrated a significant improvement in PFS with niraparib compared to placebo in the patients with HRD, with or without a *BRCA1/2* mutation (21.9 months vs. 10.4 months, $P < .001$).[209] In the ITT population, which included patients who had HRP tumors, median PFS was 13.8 months versus 8.2 months.[209] The final analysis from PRIMA study confirmed the PFS benefit reported in the initial analysis, but no difference in OS was observed between the niraparib maintenance and placebo arms in the overall population or by HRD/*BRCA* status.[213] In the PRIMA study about half of the patients in the placebo group received a PARP inhibitor in subsequent lines of therapy, which could have compromised the ability to demonstrate improved OS. Single-agent maintenance rucaparib for up to 2 years demonstrated significant clinical benefit in those with HRD as well as the overall ITT population when compared to placebo in the ATHENA-MONO trial, which included patients regardless of *BRCA* or HRD status.[214] In the ARIEL3 trial, 21% of patients in the rucaparib arm had a PFS of ≥2 years compared to 2% in the placebo arm. Niraparib in combination with bevacizumab for up to 3 years has also been studied in a single-arm phase II study, OVARIO, which reported that 62% of all patients, 76% of HRD patients, 47% of HRP patients, and 56% of the HR unknown subgroups remained progression-free at 18 months.[215] In the 5-year follow-up analysis of the OVARIO study, the median OS in the overall population was 61.1 months; not reached in the HRD subgroup; 38.7 months in the HRP subgroup; and 39.8 months in the HR not determined.[216]

The landscape of maintenance PARP therapy is evolving, and the Panel strives to update recommendations that are in line with the most recent data. For detailed recommendations about PARP maintenance therapy after primary platinum-based treatment, please see OV-5 within the algorithm. Data regarding PARP inhibitor use in patients with stage II ovarian cancer are limited and it is unlikely that future trials of PARP inhibitors as maintenance therapy post-primary treatment will address this question. Diagnosis of stage II disease is rare, especially among patients who have undergone complete surgical staging. For these reasons, the Panel decided that PARP inhibitor maintenance therapy options that are recommended for patients with stage III–IV disease and who have completed first-line chemotherapy should also be considered for patients who have stage II disease. The recommendations for maintenance options specifically apply to patients with high-grade serous or grade 2/3 endometrioid cancer types and may apply to clear cell carcinoma or carcinosarcoma with a *BRCA1/2* mutation. Whether these maintenance therapies are appropriate for patients with less common epithelial ovarian cancer types (ie, carcinosarcoma, mucinous carcinoma, grade 1 endometrioid, low grade serous) has not been studied.

Monitoring and Follow-up Recommendations

Monitoring and follow-up recommendations after the completion of primary surgery and chemotherapy in patients (with any disease stage) who are not currently receiving active treatment are described in the algorithm. These include physical examination as part of clinical visits, imaging studies, and monitoring labs/blood work. Patients should be educated about the signs and symptoms suggestive of recurrence (eg, pelvic pain, bloating, early satiety, obstruction, weight loss, fatigue). Recurrent disease may be identified clinically (eg, pelvic pain, weight loss; suspicious findings during physical examination), biochemically (ie, elevated CA-125 levels), and/or through imaging.

Management of an Increasing CA-125 Level

The care of patients in clinically complete remission is somewhat controversial. This includes patients with increasing CA-125 levels during

routine monitoring and follow-up but who present with no other signs or symptoms of recurrent disease (eg, pelvic pain, bloating, obstruction) with a negative pelvic examination, negative chest/abdomen/pelvis (C/A/P) CT and PET scans.[217] The median time for clinical relapse after documented increase in CA-125 levels is 2 to 6 months. Data suggest that immediate treatment for biochemical relapse is not beneficial; therefore, this is a category 2B recommendation.[218]

Use of Circulating Tumor DNA Assays

Circulating tumor DNA (ctDNA) assays represent a new experimental diagnostic test for monitoring disease status in ovarian cancer. Different roles may potentially exist for the use of ctDNA in the management of ovarian cancer, including early detection/diagnosis and monitoring for disease recurrence. A systematic review in ovarian cancer detection, which included 19 studies, found the diagnostic accuracy of ctDNA varied widely with sensitivity (40.6%–94.7%) and specificity (56%–100%).[219] The presence of ctDNA in blood samples after initial surgical treatment and platinum therapy is likely indicative of worse prognosis.[220,221] Among 44 patients who underwent second look laparoscopy and had ctDNA testing, 34% (15/44) were ctDNA-positive, which was associated with worse PFS (6.4 vs. 28.1 months; $P < .001$) and OS (32.4 months vs. not reached; $P = .008$). In a study of patients with serially samples collected post-surgery (n = 12) and in surveillance (n =13) with a median follow-up of 2 years, ctDNA was only detected in patients who relapsed (100% sensitivity and specificity) and preceded radiologic findings by an average of 10 months.[222]

Various technologies are being used to assess ctDNA status including PCR assays, methylation assays, and next-generation sequencing.[223] In the future, ctDNA may be able to allow for prediction of genomic alterations or resistance pathways that develop in ovarian cancer.[224] In a real-world retrospective study of patients with ovarian cancer receiving PARP inhibitor maintenance, ctDNA status was a stronger predictor of disease progression compared to CA-125 or BRCA/HR status.[225] Despite the growing body of literature, existing studies lack standardization with ctDNA assays, making it hard to draw conclusions from these data sets. There are no clinical trials to date that have demonstrated an improvement in survival with the use of ctDNA over CA-125. Prospective trials with standardized assays and pre-specified endpoints are needed to better characterize the role of ctDNA in the management of ovarian cancer. At this time, ctDNA assays should be considered experimental when incorporated in the diagnosis, treatment, and surveillance for patients impacted by ovarian cancer. Additionally, the Panel notes that ctDNA alone has not been validated as an indication for selecting treatment options.

Therapy for Recurrent Disease

Recurrence therapy refers to treatments that are administered to decrease tumor burden, control symptoms, or increase length and/or QOL for patients with evidence of recurrent disease. Secondary cytoreductive surgery can be considered for disease that recurs (ie, radiographic and/or clinical relapse) after long disease-free intervals (≥6 months).[226-229] A meta-analysis suggests that complete debulking increases survival in patients with recurrent disease.[230] The duration of the disease-free interval has not been established, although the Panel agreed that it should be ≥6 months before surgery is considered.[88,231] Platinum-sensitive disease is defined as disease that was in complete remission and relapse occurred ≥6 months after completing prior chemotherapy. Platinum-resistant disease is defined as progression on primary, maintenance, or recurrence therapy, or stable or persistent disease (if not on maintenance therapy) or complete remission and relapse <6 months after completing platinum-based chemotherapy. However, the Panel notes definitions of platinum-sensitive and platinum-resistant disease represent a spectrum of disease; clinical judgment and flexibility should be utilized in determining treatment options.

Patients with recurrent ovarian cancer will often be treated with multiple courses of therapy. Caution should be used when selecting doses for patients who have received multiple sequential courses of chemotherapy, as they may experience excessive toxicity and may not be able to tolerate doses used for first-line recurrence therapy or dose-dense regimens.[232] Patients who do not respond and progress on two consecutive regimens without evidence of clinical benefits have diminished likelihood of benefitting from additional therapy.[233] Decisions to offer clinical trials, supportive care, or additional therapy should be made on an individual basis.

Platinum-Sensitive High-Grade Disease

Based on randomized trials, the Panel recommends multiple platinum-based combination regimens for platinum-sensitive disease, especially during first relapses. Platinum-based combination chemotherapy is preferred for first recurrence (category 1) in patients with platinum-sensitive disease. Carboplatin/liposomal doxorubicin is equivalent to carboplatin/paclitaxel but has a different toxicity profile.[234-239] Patients tend to discontinue carboplatin/paclitaxel more often than carboplatin/liposomal doxorubicin since it is easier to tolerate. The Panel added carboplatin/albumin-bound paclitaxel as a recurrence therapy option for those with confirmed taxane hypersensitivity. Albumin-bound paclitaxel may be substituted for those experiencing a hypersensitivity reaction to paclitaxel. However, albumin-bound paclitaxel will not overcome infusion reactions in all patients. Carboplatin/albumin-bound paclitaxel in patients with gynecologic tumors, including 22 patients with ovarian cancer, was well tolerated with no hypersensitivity reactions and some clinical benefit.[240,241] Platinum/gemcitabine regimens with or without bevacizumab improve PFS and response rates compared to platinum monotherapy or platinum/gemcitabine without bevacizumab, respectively, without severely affecting the QOL and dose-limiting toxicities.[242-244] Therefore, the Panel includes platinum/gemcitabine regimens with or without bevacizumab as options for recurrent disease. A randomized trial showed that in platinum-sensitive disease carboplatin combination therapy with bevacizumab slightly increased median OS when compared with chemotherapy alone (HR, 0.829; 95% CI, 0.683–1.005; P = .056).[245] Most patients in both arms had at least one grade 3 or worse AE—96% (317/325) of patients in the chemotherapy/bevacizumab group versus 86% (282/332) with chemotherapy alone. The most common of these AEs were hypertension, fatigue, and proteinuria. Three percent of treatment-related deaths occurred in the bevacizumab arm versus 1% of deaths in the chemotherapy-alone arm.

Maintenance Therapy in Recurrent Platinum-Sensitive High-Grade Disease

Bevacizumab

A multicenter, open-label, randomized phase 3 trial evaluated bevacizumab with platinum-based chemotherapy followed by maintenance bevacizumab in patients who had been disease-free for >6 months following last cycle of platinum.[245] The addition of bevacizumab to standard chemotherapy followed by maintenance therapy until progression improved median OS in this patient population. The most common AEs observed in this trial were hypertension, fatigue, and proteinuria. Another phase 3 trial compared carboplatin/doxorubicin/bevacizumab and carboplatin/gemcitabine/bevacizumab; both of these regimens were followed by maintenance bevacizumab.[246] The carboplatin/doxorubicin/bevacizumab followed by maintenance bevacizumab arm showed better median PFS with similar rates of serious AEs in both groups. Based on these data, the Panel recommends continuing bevacizumab if previously treated with a bevacizumab-containing regimen in patients with platinum-sensitive disease.

PARP Inhibitors

The recommendations for PARP inhibitors as second-line maintenance therapy options have been updated based on the following studies and FDA indications. In 2017, the FDA approved niraparib and olaparib for maintenance therapy after response to platinum-based therapy for recurrent platinum-sensitive disease based on the results of 3 phase III randomized controlled trials, NOVA, SOLO-2, and Study 19. In 2018, the FDA approved rucaparib as maintenance therapy in recurrent disease. Retrospective subset analyses of several studies in recurrent disease did not demonstrate a statistically significant improvement in OS with the use of PARP inhibitors as second-line maintenance therapy and further raised the question whether there could be negative impact in patients with wild-type *BRCA*. Therefore, the FDA approached manufacturers and requested that they voluntarily restrict second-line maintenance PARP inhibitor indications to only those patients with germline/somatic *BRCA*-mutated cancers. Following the FDA's request, second-line maintenance indications were modified for all three PARP inhibitors: rucaparib and olaparib are limited to patients with germline or somatic *BRCA* P/LP variants while niraparib is limited to patients with germline *BRCA* P/LP variants.

The Panel does not recommend bevacizumab and PARP inhibitor combination as a maintenance option for recurrent disease. PARP inhibitor use is limited to those with *BRCA1/2* P/LP variants if not previously used (category 1) or if disease did not progress during prior PARP inhibitor treatment (category 2A). The Panel notes that these regimens significantly improve outcomes in patients with *BRCA* P/LP variants and who are PARP inhibitor naïve, suggesting that patients who most likely benefit from PARP inhibitors are those who receive them in the front-line setting. Patients who have *BRCA* P/LP variants, who are PARP inhibitor naïve, and whose disease responds to platinum in the recurrent setting should still be offered a maintenance PARP inhibitor. For patients who have received prior PARP inhibitors, the Panel recognizes that there are limited data in those who receive repeat PARP inhibitors as second-line maintenance therapy.

In a meta-analysis of 28 randomized control trials, the risk of hematologic malignancies, including myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML), were higher in patients treated with long-term PARP inhibitors.[247] Analysis of the PAOLA-1 trial at 5 years showed that the rates of MDS, AML, aplastic anemia, and new primary malignancy incidence remained low and at a similar rate between the olaparib/bevacizumab and placebo/bevacizumab arms.[212] The authors note that a higher proportion of patients in the placebo arm received subsequent PARP inhibitor therapy and could be a reason for similar rates observed between the two arms.[212] Patients with *BRCA* P/LP variants and prolonged PARP exposure (≥2 years) show increased risk of developing MDS and AML.[248-250] Therefore, the Panel urges caution when using PARP inhibitors as maintenance therapy for >24 months, especially in the recurrence setting, and emphasizes the need for careful evaluation of risks and benefits when considering PARP inhibitor use in subsequent lines of therapy.

Platinum-Resistant High-Grade Disease

Platinum agents have limited activity when the disease has demonstrated growth on a platinum-based regimen, and platinum rechallenge is generally not recommended in this setting. Although the Panel does not recommend retreatment with platinum agents, it recognizes that altering paclitaxel schedule can elicit secondary responses.[251,252] The Panel also recommends palliative care, which is appropriate at any stage of the disease course; however, this is especially appropriate in the resistant setting since patients may have been receiving continuous systemic therapy.

Non–platinum-based regimens are preferred for platinum-resistant disease and these include a number of targeted therapies as well as chemotherapy regimens. These include but not limited to oral

cyclophosphamide, docetaxel, gemcitabine, liposomal doxorubicin with or without bevacizumab, weekly paclitaxel with or without bevacizumab, and topotecan with or without bevacizumab.[253-255] A phase 2 trial showed an increase in PFS when platinum-resistant disease was treated with the paclitaxel/pazopanib arm when compared with paclitaxel alone (HR, 0.42; 95% CI, 0.25–0.69; *P* = .0002).[253] Randomized trials have assessed a number of chemotherapy agents with bevacizumab for recurrent ovarian cancer (ie, AURELIA).[256,257] Compared to chemotherapy alone, bevacizumab/chemotherapy has demonstrated improved overall response rate (ORR) and PFS. Hypertension and proteinuria (≥ grade 2) are more common with bevacizumab. The response rate for single-agent bevacizumab is about 20% and it may cause hypertension, arterial thrombosis, or intestinal perforation.[258-263] Bevacizumab combination regimens, or single-agent bevacizumab, are contraindicated in patients at increased risk of GI perforation.[256,264]

Other potentially active agents include capecitabine, doxorubicin, ifosfamide, irinotecan, oxaliplatin, paclitaxel, albumin-bound paclitaxel, pemetrexed, and vinorelbine.[157,158] In addition, hormonal therapy with tamoxifen or other agents including aromatase inhibitors (eg, anastrozole, letrozole), leuprolide acetate, goserelin acetate, or megestrol acetate continue to be a viable options for patients who cannot tolerate or whose disease has not responded to cytotoxic regimens.[265-271] The Panel notes that many of the single-agent cytotoxic therapy options have not been tested in patients who have been treated with modern chemotherapy regimens in both the sensitive and resistant setting.

Select Indications for Targeted Agents in Recurrent Disease

Mirvetuximab Soravtansine-gynx

A randomized, open-label, phase III study (FORWARD I) compared mirvetuximab soravtansine-gynx (*N* = 366) with investigator's choice chemotherapy to treat platinum-resistant disease with ≥50% of tumor cells with any FRα membrane staining.[272] There was no significant difference in PFS between the two groups in the ITT population. Effects were observed in secondary endpoints for patients in the protocol-defined high FRα subgroup; however, these were not significantly different, and the trial was not powered to show a difference in OS. Following this study, a phase 3 randomized controlled trial compared the efficacy and safety of mirvetuximab soravtansine-gynx (*N* = 453) with the investigator's choice of chemotherapy (paclitaxel or pegylated liposomal doxorubicin or topotecan) to treat platinum-resistant disease with ≥75% of viable tumor cells with moderate [2+] or strong [3+] staining intensity (a population with the most effect in the first trial).[273] OS was significantly longer with mirvetuximab soravtansine-gynx than with chemotherapy (median, 16.46 months vs. 12.75 months; HR for death, 0.67; 95% CI, 0.50–0.89; *P* = .005). In addition to these trials testing mirvetuximab soravtansine-gynx monotherapy, the regimen was also investigated in combination with bevacizumab in platinum-resistant disease.[274,275] Promising activity was observed in the platinum-resistant setting regardless of the level of FRα expression or prior bevacizumab treatment. Mirvetuximab soravtansine-gynx was also tested in platinum-sensitive disease treated with > 2 lines of prior therapy and was found to have consistent efficacy with tolerable safety in this setting.[276] The Panel carefully evaluated the data presented in these trials including efficacy, safety, and the population with the most benefit in relation to FRα expression. Based on careful considerations, the Panel recommends mirvetuximab soravtansine-gynx monotherapy and the combination with bevacizumab in both platinum-sensitive and platinum-recurrent disease at different cut-offs of FRα expression.

Fam-trastuzumab Deruxtecan-nxki

The DESTINY-PanTumor2 trial included a total of 40 patients with ovarian tumors who had received at least two lines of prior therapy and had HER2-expressing tumors (IHC3+ or IHC2+ by local or central testing).[277] Most patients did not receive prior HER2 treatment. Objective response rates were observed in 63.6% of IHC 3+ tumors and 36.8% of IHC 2+ tumors. The Panel notes that patients with ovarian cancer were

not randomized in this trial and it is a small dataset; however, the Panel acknowledges that response rates are good especially in IHC 3+ tumors. In 2024, the FDA granted accelerated approval to fam-trastuzumab deruxtecan-nxki for adult patients with unresectable or metastatic HER2-positive (IHC3+) solid tumors who have received prior systemic treatment and have no satisfactory alternative treatment options. Based on these data, FDA approval, and discussions, the Panel recommends fam-trastuzumab deruxtecan-nxki for recurrent disease with HER2-positivity (IHC 3+ or 2+; category 2A for platinum-resistant and category 2B for platinum-sensitive).

Dabrafenib/Trametinib

A phase 2, open-label, single-arm NCI-MATCH trial (subprotocol H), evaluated dabrafenib in combination with trametinib in patients with solid tumors, lymphoma, or multiple myeloma who had a somatic BRAF V600E mutation and who progressed on at least one standard therapy.[278] Out of the 29 patients included in the primary analysis, five had low-grade serous carcinoma and one had mucinous-papillary serous adenocarcinoma of peritoneum. The ORR of the overall population was 38%, with a PFS of 11.4 months. Notably, clinical benefits were observed in all 6 patients with primary gynecologic cancer; 5 patients achieved a PR (>12 months for 3 patients) and 1 patient had SD for 8 months following treatment. Following FDA approval, the Panel included dabrafenib in combination with trametinib for the treatment of *BRAF* V600E-positive recurrent ovarian cancer.

Targeted agents with tumor agnostic indications

NTRK Inhibitors

NTRK gene fusions are rarely found in ovarian cancer. The efficacy and safety of larotrectinib, an NTRK inhibitor, was investigated in three multicenter, open-label, single-arm trials (a phase I study in adults, a phase I/II study in children, and a phase II study in adolescents and adults).[279] Seventy-nine percent of patients had an objective response (95% CI, 72%–85%), with 16% showing a CR.[280] Similarly, entrectinib induced durable and clinically meaningful responses in patients with *NTRK* fusion-positive solid tumors (*N* = 1 for ovarian cancer) and was well tolerated with a manageable safety profile.[281] In TRIDENT-1, with 8.7 months minimum follow-up, repotrectinib showed robust responses and durable clinical activity in patients with *NTRK*+ solid tumors; this study did not include any patients with ovarian cancer.[282] Based on these data, the FDA approved NTRK inhibitors for the treatment of *NTRK* gene fusion-positive solid tumors in adult and pediatric patients who have no satisfactory alternative treatments or whose cancer has progressed following treatment. The Panel includes these inhibitors for those rare ovarian tumors with *NTRK* gene fusions.

Selpercatinib

Selpercatinib, a kinase inhibitor, received accelerated approval from the FDA based on treatment of *RET* fusion-positive non-small cell lung, medullary thyroid, and thyroid cancers. In the basket trial that included a tumor agnostic population (excluding lung or thyroid tumors), the objective response rate was 43.9% (95% CI, 28.5–60.3; 18 of 41 patients).[283] Based on these observations, selpercatinib is recommended for recurrent ovarian tumors with *RET* gene fusion positivity.

Immunotherapy

Trials of immunotherapy alone in treatment of ovarian cancer have largely shown minimal responses. A phase 3 trial evaluated pembrolizumab plus weekly paclitaxel with or without bevacizumab in patients with platinum-resistant disease and who received at least one prior systemic regimen (n = 643).[284] A large proportion of tumors (72%) had a programmed death ligand 1 (PD-L1), combined positive score (CPS) ≥1. Interim analysis (median follow-up, 15.6 months) showed that pembrolizumab significantly improved PFS in the PD-L1 CPS ≥1 population (8.3 vs. 7.2 months; *P* = .0014) and OS (18.2 vs. 14 months;

P = .0053). There were no new safety signals observed in this study population. Following the FDA approval of this combination regimen based on the interim analysis, the Panel added weekly paclitaxel + pembrolizumab with or without bevacizumab as an option for patients with platinum-resistant disease with PD-L1 CPS ≥1 expression. In patients with mismatch repair deficient disease, dostarlimab-gxly was active across multiple tumor types, with an ORR of 44.1%.[285] The safety profile of dostarlimab-gxly across different tumor types was acceptable with manageable toxicities. This trial included 7 patients with ovarian cancer. Three of the 7 (43%) ovarian cancer patients had a partial response to dostarlimab-gxly treatment. Dostarlimab-gxly received an accelerated approval for the treatment of adult patients with dMMR recurrent or advanced solid tumors that have progressed on or following prior treatment with no satisfactory alternative treatments. Similarly, in patients with MSI-H/dMMR pembrolizumab was active across multiple tumor types.[286] This phase II study included 15 patients with ovarian cancer, with 3 complete responses and 2 partial responses observed in those treated with pembrolizumab. Based on FDA approvals for tumor agnostic indications, both dostarlimab-gxly and pembrolizumab are included as options to treat recurrent disease.

Pazopanib

In a phase 2 trial (*N* = 36), patients with recurrent disease were treated with pazopanib. The ORR was 18%, with grade 3 elevations in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) in a few patients (8%). Therefore, the Panel also recommends single-agent pazopanib (category 2B) as a potentially active targeted recurrence therapy.[287]

Single-Agent PARP Inhibitors

Previous versions of the guidelines had PARP inhibitor monotherapy as options for recurrent disease. However, the long-term efficacy and safety data on the use of PARP inhibitors as therapy for recurrent disease were not as complimentary as the initial data and resulted in FDA withdrawal announcements. Therefore, for V.1.2026 of the guidelines the Panel removed PARP inhibitor monotherapy as options for recurrent disease.[288,289]

Less Common Ovarian Cancers (LCOCs)

The LCOC recommendations in the current guideline cover carcinosarcomas (MMMTs), clear cell carcinoma, mucinous carcinoma, low-grade (grade 1) serous/endometrioid epithelial carcinoma, small cell carcinoma of the ovary, hypercalcemic type (SCCHOT), borderline epithelial tumors, malignant sex cord-stromal tumors, and malignant germ cell tumors.[290] There are limited data for these rare histologies because of their infrequency, and it will be difficult to acquire prospective data. Clinical trials for eligible patients and individualized treatment plans, for those who are ineligible for trials, may be the most suitable approaches to treatment for these patients at this time.

Workup

Since the diagnosis of LCOC is often not made until after surgery for a suspicious pelvic mass, many patients with LCOCs are referred to higher volume cancer centers after having had previous surgery at other institutions. Patients with a histologically undiagnosed pelvic mass should undergo evaluation and staging. Individuals with LCOC may benefit from gynecologic oncology pathology confirmation and/or second opinion. The workup for LCOC is the same as for other types of ovarian cancer, except that tumor markers are measured and other testing is done to determine the specific histopathology. Tumor markers may include CA-125, inhibin, β-hCG, alfa-fetoprotein, CA 19-9, and CEA. Individuals <35 years with a pelvic mass should have AFP levels measured to assess for germ cell tumors and rule out pregnancy.[291-293] A GI tract evaluation is recommended for mucinous histology to determine whether an occult GI primary has metastasized to the ovaries.[50] An intraoperative frozen section

evaluation is recommended for those who would like to maintain their fertility.

Surgery

Many patients with LCOCs, except MMMTs, present with early-stage disease that may be confined to one ovary. Therefore, some of these patients are candidates for laparoscopic fertility-sparing surgery. The initial surgical recommendation depends on the specific histologic diagnosis. Often, patients have been comprehensively staged (having met the standards for surgical staging of the Gynecologic Oncology Group [GOG]) and have undergone cytoreductive surgery. In some instances, they are referred after having had *incomplete* staging (ie, uterus and/or adnexa intact, omentum not removed, surgical stage not documented). Fertility-sparing surgery may be performed if technically feasible and the intraoperative frozen section results are positive for apparent early-stage and/or low-risk tumors.[294-300] Patients who do not desire fertility preservation or those with clinical stage II, III, or IV sex cord-stromal tumor/MMMT should undergo comprehensive surgical staging per recommendations for high-grade serous epithelial tumors.

Carcinosarcomas (Malignant Mixed Müllerian Tumors)

MMMTs are rare aggressive tumors with poor prognosis.[301-304] Patients with MMMTs are not candidates for fertility-sparing surgery regardless of age or stage. Optimal surgical debulking is recommended for patients with MMMTs.[303,305-307] After complete surgical staging, several adjuvant platinum-based regimens, similar to high-grade serous disease, are recommended for patients with stage I to IV MMMT. [308-314] Monitoring/follow-up and recurrence therapy recommendations for carcinosarcomas are the same as for high-grade serous disease (described in the previous sections).

Clear Cell Carcinoma

Clear cell carcinomas are the most common type of LCOC diagnosed and are considered to be high-grade tumors that are rarely positive for estrogen receptors.[60] Patients with advanced clear cell carcinoma have a poor prognosis.[315,316] Primary treatment for these patients includes surgery with comprehensive staging followed by adjuvant therapy.[315] Fertility-sparing surgery is not recommended for stage IA to C clear cell carcinomas, while lymphadenectomy has been shown to improve survival.[316] Fertility-sparing surgery and/or observation/monitoring are options for patients with unilateral clear cell borderline tumors. Adjuvant treatment for clear cell carcinoma is the usual platinum-based regimens used to treat high-grade serous ovarian cancer.[316]

Across ovarian cancer immunotherapy trials, ovarian clear cell carcinoma have a greater response to immunotherapy than the more common ovarian cancer histologies. A phase 2 non-randomized clinical trial, which included advanced clear cell ovarian cancer, investigated ipilimumab/nivolumab in patients with at least 1 prior line of therapy.[317] The ORR was 55% and the median duration of response has not been reached yet. Grade 3 or 4 AEs were observed in 35% of patients. Another randomized phase 2 non-comparative trial studied nivolumab alone and ipilimumab/nivolumab in patients with relapsed clear cell carcinoma outside the kidney and no prior immunotherapy.[318] The ORR with nivolumab alone and ipilimumab/nivolumab was 14.2 and 26.7%, respectively. There were no treatment-related deaths and no new safety signals. The second stage of this study is set to enroll more patients to receive the combination arm. Based on these studies, the Panel added ipilimumab/nivolumab as an option for platinum-resistant clear cell carcinoma.

Evidence suggests support for the use of bevacizumab in combination with chemotherapy for primary treatment of stage III and IV clear cell carcinoma.[202-204,319,320] Although ICON7 demonstrated improvement in PFS

with the addition of bevacizumab to chemotherapy compared to chemotherapy alone in the overall population, no benefit of bevacizumab on OS was reported for the subset of patients with clear cell carcinoma.[203,204] GOG 218 reported a benefit associated with bevacizumab in the overall ovarian cancer population. The median PFS was 10.3 months in the chemotherapy group and 14.1 months in the bevacizumab-throughout group.[202] In a final report of GOG 218, there was no difference in OS between these two groups, and there was no subset analysis of patients with clear cell carcinoma.[319] In a retrospective Japanese study of 183 patients with stage III and IV clear cell carcinoma, the median PFS was 10.5 months in the adjuvant chemotherapy group versus 29.7 months in the chemotherapy plus bevacizumab group (P < .001).[321] In addition, the median OS increased from 27.4 months in the chemotherapy group to 51.4 months in the chemotherapy plus bevacizumab group (P < .001).[321] While further information is needed, the totality of the data to date support the use of bevacizumab in the treatment of patients with stage III and IV clear cell ovarian cancer.

Monitoring/follow-up and recurrence therapy recommendations for clear cell carcinomas are the same as for high-grade serous disease (described in the previous sections).

Mucinous Carcinomas

Mucinous tumors are unusual and present as very large cystic masses that fill the abdomen and pelvis. Patients with mucinous carcinoma of the ovary are often diagnosed with early-stage disease and have a good prognosis; the 5-year DFS is about 80% to 90%.[50,322] Individuals with mucinous tumors typically present at a younger age (20–40 years) than those with high-grade serous ovarian cancer.

The Panel added a recommendation for fertility-sparing surgery, if not previously done, for select patients with stage IA to C disease. Primary treatment for these patients includes completion surgery with comprehensive staging followed by adjuvant therapy or observation.[50] Patients with infiltrative tumors are more likely to have bilateral tumors and have an advanced FIGO stage at diagnosis compared to expansile tumors.[323] Therefore, observation is typically reserved for stage 1A–IC tumors that have an expansile pattern of invasion and only 1A tumors with infiltrative pattern of invasion. Since primary invasive mucinous tumors of the ovary are uncommon, it is important to establish the primary site in patients with these tumors. The upper and lower GI tract should be carefully evaluated to rule out occult GI primary with ovarian metastases. An appendectomy should only be performed in patients with a suspected or confirmed mucinous ovarian neoplasm if it appears to be abnormal.[113-115] A normal appendix does not require surgical resection in this setting. Fertility-sparing surgery is an option for select patients with stage I mucinous tumors. Some clinicians feel the GI regimens are appropriate because mucinous carcinomas of the ovary are similar to GI tumors.[324] In a retrospective study that included 52 patients with ovarian mucinous carcinoma, use of GI regimens, such as 5-fluorouracil, capecitabine, oxaliplatin, or irinotecan, was associated with improved PFS (HR 0.4, 95% CI 0.1–0.97) and OS (HR 0.2, 95% CI 0.1–0.8) compared with the use of a gynecologic regimens, such as a carboplatin- or cisplatin-containing agents.[325] The Panel added 5-fluorouracil/irinotecan/leucovorin (FOLFIRI) ± bevacizumab as an option to treat recurrent mucinous carcinomas.[326,327] Monitoring/follow-up and recurrence therapy recommendations for mucinous carcinomas are the same as for high-grade serous disease (described in the previous sections).

Small Cell Carcinoma of the Ovary, Hypercalcemic Type (SCCHOT)

SCCOHT is a rare disease with a poor prognosis that is associated with *SMARCA4* gene mutations as well as molecular and genetic similarities to malignant rhabdoid tumors.[328] As for other LCOCs, surgery followed by staging is recommended for all stages of SCCHOT. If germline SMARCA4 negative, fertility-sparing surgery can be considered after appropriate counseling. There are limited data on the safety and feasibility of this

approach. Germline *SMARCA4* testing, if not previously done, should be performed after surgery. Adjuvant therapy options include VPCBAE(Vinblastine/Cisplatin/Cyclophosphamide/Bleomycin/Doxorubicin/Etoposide), PAVEP (Cisplatin/Doxorubicin/Etoposide/Cyclophosphamide), BEP (Bleomycin/Etoposide/Cisplatin), and cisplatin/etoposide. Since these are rare tumors, the chemotherapy regimens are based on studies from small case series studies.[329,330] If the tumor responds to primary adjuvant therapy, additional surgery can be considered. This may be followed by high-dose chemotherapy with early referral to autologous stem cell transplant center. For disease that does not respond, clinical trials, as well as systemic therapies including immunotherapy or supportive care are options.[331] SCCOHT as such is not hypermutated, which may suggest that immunotherapies may not be as effective. However, activity of programmed cell death protein 1 (PD-1)/ PD-L1 blockade in these tumors has not been reported in detail. In a small subset of 11 patients, tumors demonstrated significant levels of T-cell infiltration and PD-L1 expression, suggesting SCCOHTs are immunogenic tumors.[332]

Low-Grade Serous Carcinoma

Low-grade serous carcinoma is considered pathologically distinct from the more commonly diagnosed high-grade serous carcinoma and represents <5% of epithelial ovarian cancers.[290,333] Low-grade serous carcinomas are more indolent and present at a younger age than high-grade serous carcinomas, but by the time of diagnosis they are often at an advanced stage.[334-337] Additionally, activating mutations in the MAPK pathway are frequently identified in low-grade, but not high-grade, serous carcinomas. In contrast, *TP53* mutations are generally associated with high-grade, but not low-grade, serous carcinomas.[338-343]

Primary treatment for low-grade serous carcinomas is comprised of surgery with comprehensive staging, followed by observation for select stage IA–IC disease or adjuvant therapy.[334] Low-grade serous carcinomas often respond poorly to chemotherapy compared with high-grade serous carcinomas[344]; therefore, neoadjuvant chemotherapy is less favored for patients with low-grade serous carcinoma.[334] Several adjuvant systemic therapy options, including paclitaxel/platinum-containing regimens, are recommended for patients with stage IC or stage II–IV disease. The Panel notes there are limited data on systemic therapy regimens in patients with low-grade serous carcinoma.

Select patients with low-grade serous carcinomas may also benefit from maintenance hormone therapy following adjuvant chemotherapy. One database study observed that patients with stage II–IV low-grade serous carcinoma who received maintenance hormone therapy after completing primary cytoreductive surgery and first-line platinum-based chemotherapy experienced longer PFS than those who did not receive maintenance hormone therapy (median PFS, 64.9 vs. 26.4 months; $P < .001$).[345] The majority of patients in the study received letrozole (54.3%), with a lower proportion receiving tamoxifen (28.6%). Based on these data, maintenance hormone therapy (letrozole, anastrozole, exemestane, leuprolide acetate, goserelin acetate, or tamoxifen) is a category 2B recommendation in the guidelines. A randomized trial will evaluate if maintenance hormonal therapy versus hormonal therapy alone following paclitaxel/carboplatin has clinical benefits in patients with low-grade serous carcinoma.[346]

Since disease relapse is a concern in patients with advanced low-grade serous carcinoma, continued monitoring is essential. Monitoring/follow-up recommendations are slightly different from those for high-grade serous carcinoma. The Panel recommends several options for patients with recurrent low-serous carcinoma. Patients are monitored more frequently in the first 2 years (2–4 months), which drops to 3 to 6 months in the third year and annually thereafter. Additional testing includes imaging, measuring tumor markers, chemistry profile, tumor biomarker testing, and long-term wellness care (see the NCCN Guidelines for

Survivorship at www.NCCN.org). For recurrent disease, secondary cytoreduction can be considered for patients with long disease-free interval, isolated masses rather than diffuse carcinomatosis on imaging, and/or bowel obstruction. Systemic therapy and observation are the other options for recurrent low-grade serous carcinoma. The Panel emphasizes that there is no particular sequence of systemic therapy sequencing. Each patient should be evaluated on an individual basis, taking into consideration prior therapies, disease burden, molecular profile, and the relative efficacy and toxicity profile before initiating systemic therapy. Recommended systemic therapies for this patient population in this setting include chemotherapy (if not previously used), targeted agents if any molecular markers are present, and hormonal therapy.[334,347]

Since activating *MAPK* mutations are frequently found, MEK inhibitors including avutometinib/defactinib, trametinib, and binimetinib (category 2B) are options for low-grade serous carcinoma. A phase 2/3 open-label, randomized study evaluated the efficacy and safety of trametinib, a MEK1/2 inhibitor, compared with five chemotherapy options (paclitaxel, pegylated liposomal doxorubicin, topotecan, letrozole, or tamoxifen) in 260 patients with recurrent low-grade serous carcinoma.[348] The median PFS was 13.0 months in the trametinib arm, compared with 7.2 months in the chemotherapy group (HR, 0.48; 95% CI, 0.36–0.64; $P < .0001$). The ORR of the trametinib group was significantly higher than the ORR of the chemotherapy group (26% vs. 6%, $P < .0001$). The ORR to trametinib in those with KRAS, BRAF, or NRAS mutated disease was 50% vs 8.3% in the wild-type group.[349] The most common grade 3 or 4 AEs reported in the trametinib group were skin rash, anemia, hypertension, diarrhea, nausea, and fatigue. A phase 3 open-label study evaluated the efficacy and safety of binimetinib in comparison to physician's choice chemotherapy (PCC; pegylated liposomal doxorubicin, paclitaxel, or topotecan) in 303 patients with recurrent low-grade serous carcinoma.[350] The median PFS for the binimetinib group was 9.1 versus 10.6 months in the PCC group (HR, 1.21; 95% CI, 0.79–1.86; $P = .807$). However, binimetinib was numerically superior to PCC across certain endpoints, such as PFS by local investigator assessment (12.5 months vs. 11.6 months) and ORR (16% vs. 13%). The efficacy and safety of avutometinib alone or in combination with defactinib has been tested in patients with recurrent low-grade serous ovarian cancer.[351] The phase II trial showed that ORR was 44% in *KRAS*-mutant and 17% in *KRAS* wild-type cohorts.[352] The median PFS was 22.0 months versus 12.8 months in *KRAS*-mutant and wild-type cohorts, respectively. The most frequent grade ≥3 treatment-related AEs were elevated creatine phosphokinase, diarrhea, and anemia.

Grade 1 Endometrioid Carcinoma

Treatment options for primary and recurrent disease are similar to those for low-grade serous carcinoma and are described in the previous section. Monitoring/follow-up and recurrence therapy recommendations for endometrioid carcinoma are the same as for high-grade serous disease (described in the previous sections).

Borderline Epithelial Tumors (Low Malignant Potential)

In contrast to patients with frankly invasive ovarian carcinoma, those with borderline epithelial tumors tend to be younger, are often diagnosed with stage I disease, and are candidates for fertility-sparing surgery.[353,354] A borderline tumor is a primary epithelial lesion with cytologic characteristics suggesting malignancy but without frank invasion and with a clinically indolent course and good prognosis.[355,356] Five-year survival exceeds 80%.[357] A borderline epithelial tumor may grossly resemble an invasive cancer. However, microscopic evaluation does not reveal evidence of frank invasion by the tumor nodules, although rarely invasive implants (which continue to be consistent with the diagnosis of borderline epithelial lesions) can be identified microscopically by the pathologist.

Surgery is the primary treatment for borderline epithelial tumors, including debulking or fertility-sparing surgery. Patients with a borderline epithelial tumor who desire to maintain their fertility may undergo surgery limited to a USO with resection of residual disease.[294,295,358] BSO and preserving the uterus is an option for select patients. If the patient does not desire fertility-sparing surgery, total abdominal hysterectomy (TAH), BSO, and debulking are options and resection of residual disease is recommended. Increased survival has not been observed with lymphadenectomy and omentectomy for borderline epithelial tumor, although upstaging does occur.[359,360] Lymph node evaluation may be considered on a case-by-case basis. The Panel does not recommend systemic therapies for confirmed cases of LMP tumors. At the time of clinical relapse, surgical evaluation and debulking are recommended. Those with noninvasive implants (stage II–IV) are at risk for progression to low-grade serous disease.

Malignant Germ Cell Tumors

These malignant tumors include dysgerminomas, immature teratomas, embryonal tumors, and endodermal sinus (yolk sac) tumors. They mainly occur in younger individuals who are often diagnosed with stage I disease; the median age at diagnosis is 16 to 20 years but with excellent prognosis.[361-363] Germ cell tumors are the predominant ovarian tumor in this age group.[364] Gonadal dysgenesis is a risk factor for germ cell tumors.[364] The recommended workup may include pulmonary function studies if bleomycin is being considered.[291,365] In individuals <35 years with a pelvic mass, AFP, LDH, and β-hCG, levels can indicate the presence of germ cell tumors.[291-293] Pregnancy should also be ruled out.

Fertility-sparing surgery is recommended for those desiring fertility preservation, regardless of stage.[300,366-368] In children or adolescents with early-stage germ cell tumors, comprehensive staging may be omitted.[70,369] Completion surgery with comprehensive staging is recommended as initial surgery for patients who do not desire fertility preservation.[364] If patients have had incomplete surgical staging, recommended options depend on the type of tumor, the results of imaging and tumor marker testing (eg, AFP, LDH, β-hCG), the age of the patient, and whether the patient desires fertility preservation. Patients who chose fertility-sparing surgery should be monitored by US examinations if necessary; completion surgery can be considered after finishing childbearing. After surgery, observation with surveillance is the recommended option for patients with stage I dysgerminoma or stage I, grade I immature teratoma.[370-374] Observation or chemotherapy may be considered for children or adolescents with select stage IA or IB tumors.[362,370,372,375-377] For patients with stage II to IV malignant dysgerminomas or immature teratomas, postoperative chemotherapy is recommended.

Postoperative chemotherapy for 3 to 4 cycles with BEP is recommended for: 1) any stage embryonal tumors or endodermal sinus tumors; 2) stages II to V dysgerminoma; or 3) stage I, grade 2 to 3, or stage II to IV immature teratoma.[365,378-380] If considering the use of bleomycin, pulmonary function tests are recommended.[365,381] The Memorial Sloan Kettering Cancer Center criteria can be used to identify tumors that are low risk.[370,382-389] In select patients with stage IB to III dysgerminoma for whom minimizing toxicity is critical, 3 courses of etoposide/carboplatin can be used.[390] Dose reductions or delays are not recommended even in the setting of neutropenia. Detailed recommendations for surveillance including physical exam, measuring tumor biomarker, and imaging, are described in detail in the algorithm.

For those with abnormal markers and definitive recurrent disease, options include: 1) high-dose chemotherapy[391]; or 2) consider additional chemotherapy. Referral of these patients to a tertiary care center for hematopoietic cell transplant consultation and potentially curative therapy is strongly recommended. Patients who have received chemotherapy for germ cell tumors may later present with growing teratoma syndrome.[392-395]

For patients having radiographic evidence of residual tumor (after surgery and chemotherapy) but with normal AFP, LDH, and β-hCG, consider surgical resection of the tumor; observation with monitoring is also an option. Clinical judgment should be used regarding the frequency of imaging.[396] Further options depend on which findings are present: residual malignancy, benign teratoma, or necrotic tissue. Patients with recurrent or residual malignancy after multiple chemotherapeutic regimens may be treated with a recurrence modality, including potentially curative high-dose chemotherapy or TIP (paclitaxel, ifosfamide, cisplatin).[385,397-401] These regimens are not generalizable for all of the uncommon histology tumors; therefore, patients should be referred to tertiary care institutions for treatment.

Malignant Sex Cord-Stromal Tumors

Malignant sex cord-stromal tumors are rare and include granulosa cell tumors (most common) and Sertoli-Leydig cell tumors; they are typically associated with a good prognosis.[402,403] Most patients with granulosa tumors present with early-stage disease; the disease is typically indolent.[404] Surgery followed by observation or adjuvant therapy are the recommended treatment options for these tumors based on stage. Adjuvant therapy usually consists of platinum-based chemotherapy including carboplatin/paclitaxel, etoposide/cisplatin, and BEP. The Panel notes that localized RT can be considered for palliate symptoms and/or for oligometastatic disease. Surveillance recommendations for malignant sex cord-stromal tumors are provided in the algorithm, which are based on the SGO recommendations. Secondary cytoreductive surgery may also be considered. Palliative localized RT may also be useful.

Management of Drug Toxicities

Patients should be observed closely and treated for any complications during systemic therapy. Appropriate blood chemistry tests should be monitored. Appropriate dose reductions and modifications of chemotherapy should be performed depending on toxicities experienced and goals of therapy. Consider scalp cooling to reduce incidence of alopecia for patients receiving chemotherapy with high rates of alopecia.[405]

Patients must be informed of the increased toxicities with the combined IP/IV regimen when compared to using IV chemotherapy alone prior to the start of therapy. Those unable to complete IP therapy should receive IV therapy. Expert nursing care may help to decrease complications.[406] Giving IV hydration before and after IP chemotherapy is a useful strategy to prevent certain toxicities including nausea, vomiting, electrolyte imbalances, and metabolic toxicities.[407] Adequate amounts of IV fluids need to be administered prior to and after each cycle of IP cisplatin in order to prevent renal toxicity. After each cycle, patients need to be monitored carefully for all toxicities including myelosuppression, dehydration, electrolyte loss, end-organ toxicities such as renal and hepatic damage. After chemotherapy, patients often require IV fluids to prevent or help treat dehydration in the outpatient setting.

Drugs used in gynecologic oncology treatment that more commonly cause adverse reactions include carboplatin, cisplatin, docetaxel, liposomal doxorubicin, oxaliplatin, and paclitaxel.[408] Drug reactions can occur with either IV or IP administration of these drugs.[409] Most of these drug reactions are mild infusion reactions, but more severe hypersensitivity (allergic) reactions and life-threatening anaphylaxis can occur.[409-411] Refer to the management of drug reactions in the algorithm pages for detailed recommendations.

Summary

In summary, these guidelines discuss epithelial ovarian cancer and LCOC, which are mostly diagnosed after pathologic analysis of a biopsy or surgical specimen. Primary treatment for presumed ovarian cancer consists of appropriate surgical staging and debulking surgery, followed in most but not all patients by systemic chemotherapy. Most patients with epithelial ovarian cancer receive postoperative systemic therapy.

Palliative care intervention is appropriate at several stages during the disease course. The guidelines also include recommendations for monitoring and treating AEs to therapies delivered by infusion.

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