Protocol for the Examination of Specimens From Patients With Primary Tumors of the Ovary or Fallopian Tube

Protocol applies to all primary borderline and malignant epithelial tumors, and also to germ cell tumors and sex cord-stromal tumors.

Based on AJCC/UICC TNM, 7th edition, and FIGO 2014

Protocol web posting date: January 2016

Procedures
• Oophorectomy
• Salpingo-Oophorectomy
• Salpingectomy
• Subtotal Resection or Removal of Tumor in Fragments
• Hysterectomy With Salpingo-Oophorectomy or Salpingectomy

Authors
* Blake Gilks, MD
Vancouver General Hospital, Vancouver, Canada
Saeid Movahedi-Lankarani, MD*
Department of Pathology, Abbott Northwestern Hospital, Minneapolis, Minnesota
Patricia M. Baker, MD
Pathology Department, Health Sciences Centre, Winnipeg, Canada
Christopher N. Otis, MD
Department of Pathology, Baystate Medical Center, Springfield, Massachusetts
Robert A. Soslow, MD
Memorial Sloan Kettering Cancer Center, New York, New York
Esther Oliva, MD†
Department of Pathology, Massachusetts General Hospital, Boston, Massachusetts
For the Members of the Cancer Committee, College of American Pathologists

* Denotes primary author. † Denotes senior author. All other contributing authors are listed alphabetically.

Previous contributors: Robert E. Scully, MD; Philip A. Branton, MD; Donald Earl Henson, MD; Mary L. Nielsen, MD; Stephen G. Ruby, MD; William T. Creasman, MD; Andrew Fried, MD; David M. Gershenson, MD; William R. Hart, MD; Richard L. Kempson, MD; David L. Page, MD; Suzanne M. Selvaggi, MD
Gynecologic • Ovary, Fallopian Tube

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**CAP Ovary Protocol Revision History**

**Version Code**
The definition of version control and an explanation of version codes can be found at www.cap.org (search: cancer protocol terms).

**Version:** OvaryFallopian 1.0.0.0

**Summary of Changes**
This is a new protocol. It replaces the previously separate Ovary and Fallopian Tube protocols.

**Important Note**
Recent observations including molecular findings have indicated that high-grade serous carcinoma of the fallopian tube/ovary/peritoneum are very often of fallopian tube origin. Serous intraepithelial carcinoma of the fallopian tube has been observed in patients undergoing prophylactic and routine salpingectomy/salpingo-oophorectomy for nonneoplastic disease, as the earliest lesions to appear in the genesis of high-grade serous carcinoma, providing supportive evidence for this change in the understanding of high-grade serous carcinoma carcinogenesis occurring in the adnexa and peritoneum. FIGO 2014 has acknowledged high-grade serous carcinoma of ovary/fallopian tube/peritoneum as a unified entity based on clinical behavior but recommends assigning a primary site if possible. In a recent publication, Singh et al describe 8 scenarios to illustrate assigning high-grade serous carcinoma to fallopian tube, ovary or peritoneum; these were adopted by the International Collaboration on Cancer Reporting (ICCR) and are in Note C, Table 1.¹⁻⁵
Surgical Pathology Cancer Case Summary

Protocol web posting date: January 2016

OVARY or FALLOPIAN TUBE: Oophorectomy, Salpingectomy, Salpingo-Oophorectomy, Subtotal Oophorectomy or Removal of Tumor in Fragments, Hysterectomy With Salpingo-Oophorectomy or Salpingectomy

Note: Applies to primary tumors of ovarian or fallopian tube origin. If bilateral tumors of 2 different histologic types are present, separate case summaries should be used for each tumor.

Select a single response unless otherwise indicated.

Specimen (select all that apply) (Note A)
___ Right ovary
___ Left ovary
___ Right fallopian tube
___ Left fallopian tube
___ Uterus
___ Cervix
___ Omentum
___ Peritoneum
___ Other (specify): ___________________________
___ Not specified
___ Cannot be determined

Procedure (select all that apply)
___ Right oophorectomy
___ Left oophorectomy
___ Right salpingectomy
___ Left salpingectomy
___ Right salpingo-oophorectomy
___ Left salpingo-oophorectomy
___ Bilateral salpingo-oophorectomy
___ Bilateral salpingectomy
___ Subtotal right oophorectomy
___ Subtotal left oophorectomy
___ Supracervical hysterectomy
___ Hysterectomy
___ Omentectomy
___ Peritoneal biopsies
___ Peritoneal washing
___ Pleural fluid
___ Other (specify): ___________________________
___ Not specified

Lymph Node Sampling (select all that apply)
___ Performed
   ___ Pelvic lymph nodes
   ___ Para-aortic lymph nodes
   ___ Other (specify): ___________________________
___ Not performed
___ Not known

+ Data elements preceded by this symbol are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.
Specimen Integrity (Note B)

**Right Ovary (if applicable)**
- Capsule intact
- Capsule ruptured
- Fragmented
- Other (specify): ____________________________

**Left Ovary (if applicable)**
- Capsule intact
- Capsule ruptured
- Fragmented
- Other (specify): ____________________________

+ Morcellated specimen (specify organ): ____________________________

Primary Tumor Site (Notes C, D, and E)
- Right ovary
- Left ovary
- Right fallopian tube
- Left fallopian tube
- Bilateral ovaries
- Bilateral fallopian tube
- Not specified

Ovarian Surface Involvement
- Present
- Absent
- Cannot be determined

Tumor Size

**Right Ovary (if applicable)**
Greatest dimension: ___ cm
+ Additional dimensions: ___ x ___ cm
- Cannot be determined (explain): ____________________________

**Left Ovary (if applicable)**
Greatest dimension: ___ cm
+ Additional dimensions: ___ x ___ cm
- Cannot be determined (explain): ____________________________

**Right Fallopian Tube (if applicable)**
Greatest dimension: ___ cm
+ Additional dimensions: ___ x ___ cm
- Cannot be determined (explain): ____________________________

**Left Fallopian Tube (if applicable)**
Greatest dimension: ___ cm
+ Additional dimensions: ___ x ___ cm
- Cannot be determined (explain): ____________________________

Histologic Type (select all that apply) (Notes F and G)
- Serous borderline tumor
- Serous low-grade carcinoma
- Serous high-grade carcinoma

+ Data elements preceded by this symbol are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.
Endometrioid borderline tumor
  + ___ With intraepithelial carcinoma
  + ___ With microinvasion
Endometrioid carcinoma
Clear cell borderline tumor
Clear cell carcinoma
Mucinous borderline tumor
  + ___ With intraepithelial carcinoma
  + ___ With microinvasion
Mucinous carcinoma
  + ___ Expansile
  + ___ Infiltrative
Seromucinous borderline tumor
  + ___ With intraepithelial carcinoma
  + ___ With microinvasion
Seromucinous carcinoma
Brenner tumor, borderline
Brenner tumor, malignant
Carcinoma, subtype cannot be determined
Mixed epithelial borderline tumor (specify types and percentages):
Mixed epithelial carcinoma (specify types and percentages):
Undifferentiated carcinoma
Carcinosarcoma (malignant mixed Mullerian tumor)
  ___ Homologous type
  ___ Heterologous type (specify heterologous elements):
  ___ Epithelial component(s) (specify epithelial cell types and percentages):
Granulosa cell tumor
Other sex cord-stromal tumor (specify type):
Dysgerminoma
Yolk sac tumor (endodermal sinus tumor)
Immature teratoma
Carcinoma arising from a teratoma
Mixed malignant germ cell tumor (specify types and percentages):
Other(s) (specify):

Histologic Grade (required for all carcinomas except clear cell carcinoma, low- and high-grade serous carcinoma, and Sertoli-Leydig cell tumors) (Note H)
  ___ GX: Cannot be assessed
  ___ G1: Well differentiated
  ___ G2: Moderately differentiated
  ___ G3: Poorly differentiated

Two-Tier Grading System (required for immature teratomas only)
  ___ Low grade
  ___ High grade
  ___ Other (specify):

Implants (required for advanced stage serous/seromucinous borderline tumors only)
(select all that apply) (Note I)
Note: Implants that were formerly classified as “invasive implants” are now classified as low-grade serous carcinoma of the peritoneum.
  ___ Not applicable/not sampled

+ Data elements preceded by this symbol are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.
**Noninvasive Implant(s) (select all that apply)**
- __Not present__
- __Present (specify sites): _______________________
  - + Type of noninvasive implant(s):
    - + ___ Epithelial
    - + ___ Desmoplastic

**Extent of Involvement of Other Tissues/Organs (select all that apply)**
- ___ Right ovary
  - ___ Involved
  - ___ Not involved
  - ___ Other (explain): _______________________
- ___ Left ovary
  - ___ Involved
  - ___ Not involved
  - ___ Other (explain): _______________________
- ___ Right fallopian tube
  - ___ Involved
  - ___ Not involved
  - ___ Other (explain): _______________________
- ___ Left fallopian tube
  - ___ Involved
  - ___ Not involved
  - ___ Other (explain): _______________________
- ___ Omentum
  - ___ Involved
  - ___ Not involved
  - ___ Other (explain): _______________________
- ___ Uterus
  - ___ Involved (specify location): _______________________
  - ___ Not involved
  - ___ Other (explain): _______________________
- ___ Peritoneum
  - ___ Involved
  - ___ Not involved
  - ___ Other (explain): _______________________
- ___ Other organs/tissues (specify): _______________________

**Peritoneal Ascitic Fluid (Note F)**
- ___ Not performed/ unknown
- ___ Negative for malignancy (normal/benign)
- ___ Atypical and/or suspicious (explain): _______________________
- ___ Malignant (positive for malignancy)
- ___ Unsatisfactory/nondiagnostic (explain): _______________________

**Pleural Fluid (Note F)**
- ___ Not performed/ unknown
- ___ Negative for malignancy (normal/benign)
- ___ Atypical and/or suspicious (explain): _______________________
- ___ Malignant (positive for malignancy)
- ___ Unsatisfactory/nondiagnostic (explain): _______________________

+ Data elements preceded by this symbol are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.
+ Treatment Effect (applicable to high-grade serous carcinomas treated with neoadjuvant therapy, based on assessment of residual tumor in the omentum) (Note J)
+ ___ No definite or minimal response identified (chemotherapy response score [CRS] 1)
+ ___ Moderate response identified (CRS score 2)
+ ___ Marked response with no or minimal residual cancer (CRS score 3)

Pathologic Staging (pTNM) (Note K)

Note: The International Federation of Gynecology and Obstetrics (FIGO) has developed new staging rules for ovarian, fallopian tube and primary peritoneal cancers. These new cancer staging rules will be incorporated into the 8th edition of the American Joint Committee on Cancer (AJCC) cancer staging system.


TNM Descriptors (required only if applicable) (select all that apply)
___ m (multiple primary tumors)
___ r (recurrent)
___ y (posttreatment)

Primary Tumor (pT)

Ovary
___ pTX: Cannot be assessed
___ pT0: No evidence of primary tumor
pT1: Tumor limited to ovaries (1 or both)
___ pT1a: Tumor limited to 1 ovary; capsule intact, no tumor on ovarian surface. No malignant cells in ascites or peritoneal washings*
___ pT1b: Tumor limited to both ovaries; capsule intact, no tumor on ovarian surface. No malignant cells in ascites or peritoneal washings
___ pT1c: Tumor limited to 1 or both ovaries with any of the following: capsule ruptured, tumor on ovarian surface, malignant cells in ascites or peritoneal washings
pT2: Tumor involves one or both ovaries with pelvic extension and/or implants
___ pT2a: Extension and/or implants on uterus and/or tube(s). No malignant cells in ascites or peritoneal washings
___ pT2b: Extension to other pelvic tissues. No malignant cells in ascites or peritoneal washings
___ pT2c: Pelvic extension and/or implants (T2a or T2b/IIA or IIB) with malignant cells in ascites or peritoneal washings
pT3 and/or N1: Tumor involves 1 or both ovaries with confirmed peritoneal metastasis outside the pelvis (including liver capsule metastasis and/or regional lymph node metastasis [N1])
___ pT3a: Microscopic peritoneal metastasis beyond pelvis (no macroscopic tumor)
___ pT3b: Macroscopic peritoneal metastasis beyond pelvis ≤2 cm in greatest dimension
___ pT3c and/or N1: Peritoneal metastasis beyond pelvis >2 cm in greatest dimension and/or regional lymph node metastasis

*Nonmalignant ascites is not classified. The presence of ascites does not affect staging unless malignant cells are present.
Fallopian Tube

- **pTX:** Primary tumor cannot be assessed
- **pT0:** No evidence of primary tumor
- **pTis:** Tubal intraepithelial carcinoma (limited to tubal mucosa)

**pT1:** Tumor limited to fallopian tube(s)
  + **pT1a:** Tumor limited to 1 tube without penetrating the serosal surface; no ascites
  + **pT1b:** Tumor limited to both tubes without penetrating the serosal surface; no ascites
  + **pT1c:** Tumor limited to 1 or both tube(s) with extension into or through the tubal serosa; or with malignant cells in ascites or peritoneal washings

**pT2:** Tumor involves 1 or both tube(s) with pelvic extension
  + **pT2a:** Extension and/or metastasis to the uterus and/or ovaries
  + **pT2b:** Extension to other pelvic structures
  + **pT2c:** Pelvic extension (T2a or T2b/IIA or IIB) with malignant cells in ascites or peritoneal washings

**pT3 and/or N1:** Tumor involves 1 or both tube(s) with peritoneal implants outside the pelvis and/or regional lymph node metastasis
  + **pT3a:** Microscopic peritoneal metastasis beyond pelvis
  + **pT3b:** Macroscopic peritoneal metastasis beyond pelvis 2 cm or less in greatest dimension
  + **pT3c/N1:** Peritoneal metastasis beyond pelvis more than 2 cm in greatest dimension and/or regional lymph node metastasis

**Any T/Any N and M1:** Distant metastasis including presence of malignant cells in pleural fluid or parenchymal hepatic metastasis

Regional Lymph Nodes (pN) (select all that apply)

- **pNX:** Cannot be assessed
- **pN0:** No regional lymph node metastasis
- **pN1:** Regional lymph node metastasis
  + **pN1a:** Lymph node metastasis up to 10 mm in greatest dimension
  + **pN1b:** Lymph node metastasis greater than 10 mm in greatest dimension

*Note: Although not noted specifically in AJCC 7th edition, WHO 2014 defines pN1a and pN1b based on FIGO.

- **No nodes submitted or found**

Pelvic lymph nodes:

- **No pelvic nodes submitted or found**

**Number of Pelvic Lymph Nodes Examined**

Specify: _____

**Number cannot be determined (explain): ________________

**Number of Pelvic Lymph Nodes Involved**

Specify: _____

**Number cannot be determined (explain): ________________

**Size of greatest metastasis (if applicable): ______mm**

Para-aortic lymph nodes:

- **No para-aortic nodes submitted or found**

**Number of Para-aortic Lymph Nodes Examined**

Specify: _____

**Number cannot be determined (explain): ________________

+ Data elements preceded by this symbol are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.
Number of Para-aortic Lymph Nodes Involved
Specify: _____
___ Number cannot be determined (explain): ______________________

Other lymph nodes:
Specify site: ______________________

Number of Other Lymph Nodes Examined
Specify: _____
___ Number cannot be determined (explain): ______________________

Number of Other Lymph Nodes Involved
Specify: _____
___ Number cannot be determined (explain): ______________________

Size of largest metastasis (if applicable): _____ mm

Distant Metastasis (pM) (required only if confirmed pathologically in this case)
___ pM1: Distant metastases (excludes peritoneal metastasis)
Specify site(s), if known: ______________________

Note: If pleural effusion is present, there must be a positive cytology for a stage IV designation. Parenchymal liver metastasis is classified as stage IV disease, whereas liver capsule metastasis is classified as stage III disease.

+ FIGO Stage
+ I: Tumor confined to ovaries or fallopian tube(s)
+ ___ IA: Tumor limited to 1 ovary (capsule intact) or fallopian tube; no tumor on ovarian or fallopian tube surface; no malignant cells in the ascites or peritoneal washings
+ ___ IB: Tumor limited to both ovaries (capsules intact) or fallopian tubes; no tumor on ovarian or fallopian tube surface; no malignant cells in the ascites or peritoneal washings
+ IC: Tumor limited to 1 or both ovaries or fallopian tubes, with any of the following:
+ ___ IC1: Surgical spill intraoperatively
+ ___ IC2: Capsule ruptured before surgery or tumor on ovarian or fallopian tube surface
+ ___ IC3: Malignant cells present in the ascites or peritoneal washings
+ II: Tumor involves 1 or both ovaries or fallopian tubes with pelvic extension (below pelvic brim) or peritoneal cancer
+ ___ IIA: Extension and/or implants on the uterus and/or fallopian tubes and/or ovaries
+ ___ IIB: Extension to other pelvic intraperitoneal tissues
+ III: Tumor involves 1 or both ovaries, or fallopian tubes, or primary peritoneal cancer, with cytologically or histologically confirmed spread to the peritoneum outside the pelvis and/or metastasis to the retroperitoneal lymph nodes
+ IIIA: Metastasis to the retroperitoneal lymph nodes with or without microscopic peritoneal involvement beyond the pelvis
+ ___ IIIA1: Positive retroperitoneal lymph nodes only (cytologically or histologically proven)
+ ___ IIIA1(i): Metastasis ≤10 mm in greatest dimension
+ ___ IIIA1(ii): Metastasis >10 mm in greatest dimension
+ ___ IIIA2: Microscopic extrapelvic (above the pelvic brim) peritoneal involvement with or without positive retroperitoneal lymph nodes
+ ___ IIIB: Macroscopic peritoneal metastases beyond the pelvic brim ≤2 cm in greatest dimension, with or without metastasis to the retroperitoneal lymph nodes
+ ___ IIIC: Macroscopic peritoneal metastases beyond the pelvic brim >2 cm in greatest dimension, with or without metastases to the retroperitoneal nodes
+ IV: Distant metastasis excluding peritoneal metastases
+ ___ IVA: Pleural effusion with positive cytology
+ ___ IVB: Metastases to extraabdominal organs (including inguinal lymph nodes and lymph nodes outside of abdominal cavity)

+ Data elements preceded by this symbol are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.
# This is tumor dimension and not lymph node dimension.
## Includes extension of tumor to capsule of liver and spleen without parenchymal involvement of either organ.
### Parenchymal metastases are stage IVB. Disease invading through the bowel wall and into the mucosa increases the stage to IVB, and transmural involvement of a visceral structure also represents stage IVB disease.

+ **Additional Pathologic Findings (select all that apply) (Note L)**
  + ___ None identified
  + ___ Endometriosis
    + ___ Ovarian
    + ___ Extraovarian
  + ___ Endosalpingiosis
  + ___ Other (specify): ______________________________

+ **Ancillary Studies (Note M)**
  + Specify: ______________________________

+ **Clinical History (select all that apply)**
  + ___ BRCA1/2 family history
  + ___ Hereditary breast/ovarian cancer
  + ___ Lynch syndrome
  + ___ Other (specify): ______________________________

+ **Comment(s)**
Explanatory Notes

A. Suggestions for Sampling for Microscopic Examination

Ovarian Surface
Involvement of the ovarian surface is an important element in staging tumors limited to the ovary, and the presence of surface involvement may influence treatment. Therefore, careful examination of the ovarian surface is crucial. Furthermore, in patients who undergo prophylactic (salpingo-) oophorectomy because of a family history of ovarian and/or breast cancer, very small foci of involvement of the ovarian surface may be present that may be potentially lethal and may be missed if the macroscopic inspection is not optimal.\(^1\)

Ovarian/Adnexal Tumor
One section for each centimeter of the tumor’s largest dimension is generally recommended, with modification based on the degree of heterogeneity of the tumor and the difficulty of diagnosis. Mucinous tumors, particularly borderline tumors, may require more sections.

Some sections should include the ovarian surface where it is most closely approached by tumor on gross examination, with the number of sections depending on the degree of suspicion of surface involvement.

Tumor adhesions and sites of rupture should be sampled and labeled specifically for microscopic identification.

Risk Reducing Salpingo-Oophorectomy Specimens
The ovary and fallopian tube should be submitted in toto in patients with \textit{BRCA} mutations or suspected to be at increased risk of hereditary breast/ovarian cancer, even when grossly normal. This detailed examination results in an approximately 4-fold increase in detection of precursor lesions or early microscopic carcinoma.\(^7\) Appropriate handling implies that all ovarian and tubal tissue should be serially sectioned and submitted.\(^8,9\) For fallopian tubes, amputate the fimbriated ends and section parallel to the long axis of the fallopian tube to maximize the amount of tubal epithelium available for histological examination (SEE-FIM protocol)\(^10\) (Figure 1). The remainder of the fallopian tube is submitted as serial cross-sections. Fixation for 1 to 2 hours prior to sectioning and/or manipulation may help prevent sloughing of the epithelium.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{Protocol for Sectioning and Extensively Examining the FIMbriated End (SEE-FIM) of the Fallopian Tube.}
This protocol entails amputation and longitudinal sectioning of the infundibulum and fimbrial segment (distal 2 cm) to allow maximal exposure of the tubal plicae. The isthmus and ampulla are cut transversely at 2- to 3-mm intervals. From Crum et al.\(^10\) Copyright © 2007 Lippincott Williams & Wilkins. Reproduced with permission.
\end{figure}

Sampling Issues: The recommendation for the number of sections to be taken of an ovarian/adnexal tumor is a general guideline, with the pathologist determining how many sections are necessary. If a tumor is obviously malignant and homogeneous throughout on gross examination, fewer sections may be needed. In contrast, if
there is great variability in the gross appearance of the sectioned surfaces or opened cysts, it may be necessary to take more sections to sample the tumor adequately. In addition, as a general recommendation, borderline serous tumors with micropapillary foci or with microinvasion should be extensively sampled to ensure adequate assessment of the extent of invasion, when present. Mucinous tumors (particularly those with solid areas), solid teratomas, and malignant germ cell tumors often require careful gross examination and judicious sampling. Of note, additional sampling of a tumor that poses problems in differential diagnosis may be more informative than special studies.

**Fallopian Tube(s)**

The fimbrial end of each fallopian tube, if no gross lesion is present, is recommended. Representative sections of tumor, if present, to determine its distribution and relationship to tubal epithelium are recommended.

For patients with high-grade serous carcinoma, in contrast to other tumor histologic types covered by this protocol, a small, sometimes microscopic focus of tumor may be present in the mucosa of the fallopian tube that, as explained previously, is the probable primary site. The identification of tubal involvement can usually be accomplished by careful macroscopic examination and, if nothing is identified grossly, by submitting the fimbrial end of the fallopian tubes in toto for microscopic examination.

**Uterus**

If tumor is grossly present, sections should be taken to determine its extent, including depth of invasion of myometrium if tumor possibly originated in endometrium, and to determine its relation to ovarian tumor (metastatic to, metastatic from, independent primary).

**Omentum**

If tumor is grossly identifiable, representative sections are enough. It is recommended to take multiple sections when no tumor is detected grossly.

For patients who have received neoadjuvant chemotherapy for advanced stage tubo-ovarian carcinoma (typically of high-grade serous type), 4 to 6 sections of omentum, to sample the most abnormal areas, are recommended to allow assessment of response to chemotherapy (see Note J).

For borderline tumors or immature teratoma with grossly apparent implants, multiple sections of the implants should be taken.

Although there is no general consensus regarding the number of sections that should be taken on a grossly normal omentum of a patient with an ovarian serous borderline tumor, serous carcinoma, or immature teratoma, a general recommendation would be to take 5 to 10 sections. Implants in serous borderline tumors and immature teratomas may vary from noninvasive to invasive low-grade serous carcinoma and from mature to immature, respectively. Identification of invasive carcinoma or an immature implant may considerably alter the prognosis and therapy.

**Lymph Nodes**

If the lymph nodes are grossly involved by tumor, representative sections are enough. However, if the lymph nodes appear grossly free of tumor, they should be entirely submitted. In either case, the dimension of the largest metastatic deposit should be documented.

**Other Staging Biopsy Specimens**

Staging biopsy tissues should be entirely processed unless grossly positive for tumor. If tumor is grossly seen, representative sections are usually sufficient. For borderline tumors or immature teratomas with grossly apparent implants, multiple sections of the implants should be taken (as in omental sampling).

**Other Organ or Tissue Removed**

Sections should be taken to determine the presence or absence, as well as location and extent, of tumor, if present. Resection margins should be taken, if applicable.
B. Rupture of Tumor
It is important to know if the tumor is intact or ruptured, because in the latter situation, malignant cells may have spilled into the abdominal cavity. In tumors that have an admixture of benign, borderline, and/or malignant areas, it may also be important to know which area ruptured.\(^{13,14}\)

C. Site of Origin
Although determination of primary site for most histologic types of tumor is relatively straightforward, as they present with tumor confined to the ovary, when a tumor involves ovary, fallopian tube, uterus, and multiple intraperitoneal sites it may be difficult or impossible to determine the primary site of the tumor.

Although historically primary site was assigned based on the dominant mass, this resulted in ovarian metastases from a number of extra-ovarian primary sites (eg, stomach, vermiform appendix, colon, endocervix, endometrium) being mistaken for primary ovarian neoplasms. Increased awareness of the ability of small extra-ovarian primary tumors to metastasize to the ovary and their characteristic morphological features, and the introduction of immunostains that aid in primary site determination, have led to improved recognition of ovarian metastases in practice.

There remain challenges in assignment of primary site in cases of advanced stage high-grade serous carcinoma. The following Table reflects current recommendations for site assignment in such cases.

### Table 1. Criteria for Assignment of Primary Site in Tubo-Ovarian High-Grade Serous Carcinoma (HGSC)\(^{1,3,5}\)

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Primary Site</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serous tubal intraepithelial carcinoma (STIC) present</td>
<td>Fallopian tube</td>
<td>Regardless of presence and size of ovarian and peritoneal disease.</td>
</tr>
<tr>
<td>Invasive mucosal carcinoma in tube, with or without STIC</td>
<td>Fallopian tube</td>
<td>Regardless of presence and size of ovarian and peritoneal disease.</td>
</tr>
<tr>
<td>Fallopian tube partially or entirely incorporated into tubo-ovarian mass</td>
<td>Fallopian tube</td>
<td>Regardless of presence and size of ovarian and peritoneal disease.</td>
</tr>
<tr>
<td>No STIC or invasive mucosal carcinoma in either tube in presence of ovarian mass or microscopic ovarian involvement</td>
<td>Ovary</td>
<td>Both tubes should be clearly visible and fully examined by a standardized SEE-FIM protocol. Regardless of presence and size of peritoneal disease.</td>
</tr>
<tr>
<td>Both tubes and both ovaries grossly and microscopically normal (when examined entirely) or involved by benign process in presence of peritoneal HGSC</td>
<td>Primary peritoneal HGSC</td>
<td>As recommended in World Health Organization (WHO) 2014 classification. This diagnosis should only be made in specimens removed at primary surgery prior to any chemotherapy; see below for samples following chemotherapy.</td>
</tr>
<tr>
<td>HGSC diagnosed on small sample, peritoneal/omental biopsy or cytology</td>
<td>Tubo-ovarian</td>
<td>Note: this should be supported by clinicopathological findings including immunohistochemistry to exclude mimics, principally uterine serous carcinoma</td>
</tr>
<tr>
<td>Postchemotherapy with residual disease</td>
<td>Same criteria as described above</td>
<td></td>
</tr>
<tr>
<td>Postchemotherapy with no residual disease</td>
<td>Tubo-ovarian</td>
<td></td>
</tr>
</tbody>
</table>

Site assignment as “undesignated” should be avoided as far as possible and used only in the rare event that a case does not fit into any of the above categories and/or there remains doubt over whether it is of tubo-ovarian or endometrial origin.

It is important to note that serous carcinomas of endometrium may present with adnexal mass(es). In such cases there is often not the extensive omental involvement characteristic of primary tubo-ovarian high-grade serous carcinoma. Within the endometrium there may be a co-existent low-grade component or precursor lesion (atypical hyperplasia/endometrial intraepithelial neoplasia) features in support of a primary endometrial carcinoma. WT1 staining is typically strong and diffuse in tubo-ovarian high-grade serous carcinoma and weak/focal or negative in endometrial serous carcinoma, but is not completely sensitive or specific in determining primary site.\(^{1,3}\) Further study is needed to improve the ability to distinguish between high-grade serous carcinoma of endometrial and tubo-ovarian origin; however, it is likely that most instances where high-grade serous carcinoma involves the endometrium, the tumor is primary endometrial serous carcinoma.
D. Tumor Location
Distribution of tumor in the ovary may be a clue to its origin. If the tumor is mainly present on the surface of the ovary without forming a discrete lesion, the tumor is more likely to be secondary ovarian involvement. If a tumor is centered or mainly involves the ovarian hilus, it is most likely to be a metastasis. In the case of mucinous neoplasms, if they are bilateral or associated with mucinous ascites or peritoneal/ovarian surface involvement, they are more likely to be metastatic.\(^\text{15}\)

E. Contralateral Ovary
Contralateral ovary refers to the ovary that is nondominant because it is either (1) involved by a tumor that is similar to but smaller than the dominant ovarian tumor, (2) contains only what appears to be metastatic tumor on gross examination, or (3) is negative for tumor. If the contralateral ovary contains only focal tumor, the gross and microscopic examination should concentrate on determining whether the tumor is an independent primary or it is metastatic from the dominant ovary. Metastatic involvement is supported by the same criteria that are used to distinguish primary and metastatic cancers to the ovary (multiple nodules, surface implants, and hilar vascular space invasion favor metastasis).

F. Histologic Type
It is recommended that the World Health Organization (WHO) classification and nomenclature of ovarian tumors be used because of its wide acceptance.\(^\text{16}\) An abbreviated form of this classification is shown below.

Serous, borderline tumor
Serous, low-grade carcinoma
Serous, high-grade carcinoma
Endometrioid borderline tumor
Endometrioid carcinoma
Clear cell borderline tumor
Clear cell carcinoma
Mucinous borderline tumor
Mucinous carcinoma
Seromucinous borderline tumor
Seromucinous carcinoma
Brenner tumor, borderline
Brenner tumor, malignant
Carcinoma, subtype cannot be determined
Mixed epithelial borderline tumor
Mixed epithelial carcinoma
Undifferentiated carcinoma
Carcinosarcoma (malignant mixed Mullerian tumor)
  Homologous type
  Heterologous type
  Epithelial component(s)
Granulosa cell tumor
Other sex cord-stromal tumor
Dysgerminoma
Yolk sac tumor (endodermal sinus tumor)
Immature teratoma
Carcinoma arising from a teratoma
Mixed malignant germ cell tumor

Histologic type of ovarian carcinoma can be diagnosed with a high degree of reproducibility in routine practice and does have clinical implications.\(^\text{16}\) For example, hereditary breast and ovarian cancer syndrome is associated with high-grade serous carcinoma, while Lynch syndrome is associated with endometrioid and clear cell histotypes, so accurate diagnosis is important.
The distinction between high-grade serous carcinoma and low-grade serous carcinoma is not an assignment of grade based on a continuum. They differ with respect to risk factors, precursor lesions, response to chemotherapy, and genetic events during oncogenesis, and merit consideration as distinct histologic types. The criteria for distinguishing between high-grade serous carcinoma and low-grade serous carcinoma are primarily based on nuclear variability (>3-fold nuclear size variation). In cases where the distinction is difficult, p53 immunostaining and assessment of mitotic activity (>12 mitoses/10 high-power field). Such a system has molecular and prognostic validity and excellent interobserver agreement.\(^{16}\)

High-grade tumors with ambiguous features, such that 1 of the specific histologic types listed cannot be diagnosed, should be classified as “carcinoma, subtype cannot be determined”; however, this is a very infrequent situation, and every effort should be made to subclassify such tumors.

G. Mixtures of Histologic Types of Tumors

The term *mixed carcinoma* should only be used when 2 or more distinctive subtypes of surface epithelial carcinomas are identified. When a carcinoma is classified as “mixed,” the major and minor types and their relative proportions should be specified.

The diagnosis of mixed carcinoma was relatively common in the past, but with application of current histopathologic criteria, fewer than 1% of tubo-ovarian carcinomas are mixed, and the most common admixture is of endometrioid and clear cell carcinoma.\(^ {17}\) It is now appreciated that high-grade serous carcinomas show a wide range of histopathologic features, and glandular (pseudoinfiametroid) differentiation, solid architecture, transitional growth pattern, or clear cell change are now accepted as being within the spectrum of high-grade serous carcinoma, and the presence of these variants does not warrant diagnosis as mixed carcinoma.\(^ {16,17}\)

Quantitation of various epithelial cell types within a carcinoma, as well as quantitation of tumor types within primitive germ cell tumors, may be prognostically important.\(^{18}\)

H. Histologic Grade

Epithelial Carcinomas

High-grade serous carcinoma, low-grade serous carcinoma, and clear cell carcinoma are not graded; at present there is no grading system that has consistently been shown to prognosticate for these histologic types. Endometrioid carcinomas may be graded according to the FIGO system used for endometrioid carcinomas of the endometrium, as shown below.

\[
\begin{align*}
\text{Grade 1} & \leq 5\% \text{ of nonsquamous, solid growth} \\
\text{Grade 2} & 6\% \text{ to } 50\% \text{ of nonsquamous solid growth} \\
\text{Grade 3} & >50\% \text{ of nonsquamous, solid growth}
\end{align*}
\]

Notable nuclear atypia, inappropriate for the architectural grade, raises the grade of a grade 1 or grade 2 tumor by 1 grade.

There are no defined grading systems in widespread use for the remaining histologic types of ovarian carcinoma (eg, mucinous, seromucinous, malignant Brenner), and a gestalt 3-part grading system can be used, acknowledging that it is not well validated.

\[
\begin{align*}
\text{Grade X} & \text{ Cannot be assessed} \\
\text{Grade 1} & \text{ Well differentiated} \\
\text{Grade 2} & \text{ Moderately differentiated} \\
\text{Grade 3} & \text{ Poorly differentiated (tumors with minimal differentiation seen in very small foci)}
\end{align*}
\]

Germ Cell Tumors

Immature teratomas are the only malignant germ cell tumors that are graded. They are classically graded on the basis of the quantity of immature/embryonal elements (almost always neuroectodermal tissue) that are present.\(^ {19}\) Even though in the past a 3-tier system was used to classify immature teratomas (G1 = immature neural tissue occupying <1 low-power field in any slide, and G3 = immature neural tissue occupying ≥4 low-power fields in any...
slide), a 2-tiered grading system (low versus high grade) has been proposed by some experts.\textsuperscript{20} Also, implants associated with immature teratomas must be assessed for the presence of immature elements, typically glial tissue (gliomatosis peritonei).

**Sertoli-Leydig Cell Tumors**
Sertoli-Leydig cell tumors are graded in a 3-part grading system, as described in the WHO 2014 classification.\textsuperscript{16} Briefly, in well differentiated grade 1 tumors, the Sertoli cells are present in open or closed tubules; in moderately differentiated grade 2 tumors, the Sertoli cells are present in lobular aggregates, although there may be some tubular architecture present; and in poorly differentiated grade 3 tumors, there is sarcomatous stroma, and the lobulated Sertoliiform growth typical of grade 2 tumors, if present, is only focal.

**I. Implants (Serous/Seromucinous Borderline Tumors Only)**
In both serous borderline and seromucinous borderline tumors, peritoneal implants must be assessed for invasiveness. Noninvasive implants can be subdivided into epithelial and desmoplastic types, and both are typically associated with favorable prognosis.

Note that implants with invasive carcinoma (formerly designated as “invasive implants,” as per Bell and Scully criteria) result in a diagnosis of low-grade serous carcinoma or seromucinous carcinoma, based on the WHO 2014 classification,\textsuperscript{16} as they are associated with a poor prognosis (identical to that of low-grade serous carcinomas).

**J. Chemotherapy Response Score**
A system for histopathologic assessment of response to neoadjuvant chemotherapy (chemotherapy response score or CRS) for high-grade serous carcinoma has been developed and validated, and shown to be highly reproducible.\textsuperscript{21} This 3-tiered scoring system is based on assessment of the section of omentum that shows the least response to chemotherapy. The criteria are shown in Table 2.

**Table 2. Criteria of the Chemotherapy Response Score**

| CRS 1: No or minimal tumor response | Mainly viable tumor with no or minimal regression-associated fibro-inflammatory changes\textsuperscript{8}, limited to a few foci; cases in which it is difficult to decide between regression and tumor-associated desmoplasia or inflammatory cell infiltration |
| CRS 2: Appreciable tumor response amidst viable tumor, both readily identifiable and tumor regularly distributed | Ranging from multifocal or diffuse regression associated fibro-inflammatory changes\textsuperscript{8}, with viable tumor in sheets, streaks or nodules, to extensive regression associated fibro-inflammatory changes\textsuperscript{8} with multifocal residual tumor which is easily identifiable |
| CRS 3: Complete or near-complete response with no residual tumor OR minimal irregularly scattered tumor foci seen as individual cells, cell groups, or nodules up to 2 mm in maximum size | Mainly regression-associated fibro-inflammatory changes or, in rare cases, no/very little residual tumor in complete absence of any inflammatory response; advisable to record whether “no residual tumor” or “microscopic residual tumor present” |

\textsuperscript{8} Regression-associated fibro-inflammatory changes: Fibrosis associated with macrophages, including foam cells, mixed inflammatory cells, and psammoma bodies; to distinguish from tumor-related inflammation or desmoplasia.
K. **TNM and Stage Groupings**

In view of the role of the pathologist in the staging of cancers, the staging system for ovarian cancer endorsed by the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC), as well as the parallel system formulated by the International Federation of Gynecology and Obstetrics (FIGO), are recommended.22-25

According to AJCC/UICC convention, the designation “T” refers to a primary tumor that has not been previously treated. The symbol “p” refers to the pathologic classification of the TNM, as opposed to the clinical classification, and is based on gross and microscopic examination. pT entails a resection of the primary tumor or biopsy adequate to evaluate the highest pT category, pN entails removal of nodes adequate to validate lymph node metastasis, and pM implies microscopic examination of distant lesions. Clinical classification (cTNM) is usually carried out by the referring physician before treatment during initial evaluation of the patient or when pathologic classification is not possible.

Pathologic staging is usually performed after surgical resection of the primary tumor. Pathologic staging depends on pathologic documentation of the anatomic extent of disease, whether or not the primary tumor has been completely removed. If a biopsied tumor is not resected for any reason (eg, when technically infeasible), and if the highest T and N categories or the M1 category of the tumor can be confirmed microscopically, the criteria for pathologic classification and staging have been satisfied without total removal of the primary cancer.

**TNM Descriptors**

For identification of special cases of TNM or pTNM classifications, the “m” suffix and “y,” “r,” and “a” prefixes are used. Although they do not affect the stage grouping, they indicate cases needing separate analysis.

- The “m” suffix indicates the presence of multiple primary tumors in a single site and is recorded in parentheses: pT(m)NM.
- The “y” prefix indicates those cases in which classification is performed during or after initial multimodality therapy (ie, neoadjuvant chemotherapy, radiation therapy, or both chemotherapy and radiation therapy). The cTNM or pTNM category is identified by a “y” prefix. The ycTNM or ypTNM categorizes the extent of tumor actually present at the time of that examination. The “y” categorization is not an estimate of tumor before multimodality therapy (ie, before initiation of neoadjuvant therapy).
- The “r” prefix indicates a recurrent tumor when staged after a documented disease-free interval and is identified by the “r” prefix: rTNM.
- The “a” prefix designates the stage determined at autopsy: aTNM.

L. **Other Lesions**

The presence of endometriosis, particularly if it is in continuity with either an endometrioid or clear cell carcinoma, is an important clue as to the primary nature of the ovarian tumor.

M. **Special Studies**

Special studies include histochemical and immunohistochemical staining, which are helpful diagnostically in occasional cases. Fluorescence in situ hybridization or molecular genetic studies may be used in some cases. Evaluation for microsatellite instability and Lynch syndrome may be performed on ovarian tumors, particularly endometrioid and clear cell types.

**References**