

# **Protocol for the Examination of Specimens From Patients With Carcinoma of the Ovary**

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

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**Based on AJCC/UICC TNM, 7th edition**

Protocol web posting date: October 2009

## **Procedures**

- Oophorectomy
- Salpingo-Oophorectomy
- Subtotal Resection or Removal of Tumor in Fragments
- Hysterectomy with Salpingo-Oophorectomy

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**Surgical Pathology Cancer Case Summary (Checklist)**

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**OVARY: Oophorectomy, Salpingo-Oophorectomy, Subtotal Oophorectomy or Removal of Tumor in Fragments, Hysterectomy with Salpingo-Oophorectomy**

***Note: Applies to ovarian primary tumor. If bilateral tumors of 2 different histologic types are present, separate checklists 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 salpingo-oophorectomy
- ☐ Left salpingo-oophorectomy
- ☐ Bilateral salpingo-oophorectomy
- ☐ Subtotal right oophorectomy
- ☐ Subtotal left oophorectomy
- ☐ Supracervical hysterectomy
- ☐ Hysterectomy
- ☐ Omentectomy
- ☐ Peritoneal biopsies
- ☐ Other (specify): \_\_\_\_\_
- ☐ Not specified

**Lymph Node Sampling**

- ☐ Performed
- ☐ Not performed
- ☐ Not known

\* Data elements with asterisks are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.

**Specimen Integrity (select all that apply) (Note B)**Right Ovary

- ☐ Not applicable
- ☐ Capsule intact
- ☐ Capsule ruptured
- ☐ Fragmented
- ☐ Other (specify): \_\_\_\_\_

Left Ovary

- ☐ Not applicable
- ☐ Capsule intact
- ☐ Capsule ruptured
- ☐ Fragmented
- ☐ Other (specify): \_\_\_\_\_

**Primary Tumor Site (select all that apply) (Notes C, D, and E)**

- ☐ Right ovary
- ☐ Left ovary
- ☐ Bilateral ovarian involvement
- ☐ Not specified

**Ovarian Surface Involvement**

- ☐ Present
- ☐ Absent
- ☐ Uncertain/cannot be determined

**Tumor Size**Right Ovary (if applicable)

Greatest dimension: \_\_\_\_ cm

\*Additional dimensions: \_\_\_\_ x \_\_\_\_ cm

☐ Cannot be determined (see "Comment")Left Ovary (if applicable)

Greatest dimension: \_\_\_\_ cm

\*Additional dimensions: \_\_\_\_ x \_\_\_\_ cm

☐ Cannot be determined (see "Comment")**Histologic Type (select all that apply) (Notes F and G)**

- ☐ Serous, borderline tumor
- ☐ Serous, carcinoma
- ☐ Mucinous, borderline tumor, intestinal type
- ☐ Mucinous, borderline tumor, endocervical type (seromucinous type)
- ☐ Mucinous carcinoma
- ☐ Endometrioid borderline tumor
- ☐ Endometrioid carcinoma
- ☐ Clear cell borderline tumor
- ☐ Clear cell carcinoma
- ☐ Transitional cell borderline tumor

\* Data elements with asterisks are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.

- ☐ Transitional cell carcinoma
- ☐ Brenner tumor, malignant type
- ☐ Squamous cell carcinoma
- ☐ Mixed epithelial borderline tumor (specify types and percentages): \_\_\_\_\_
- ☐ Mixed epithelial carcinoma (specify types and percentages): \_\_\_\_\_
- ☐ Undifferentiated carcinoma
- ☐ Carcinosarcoma (Malignant müllerian mixed tumor)
- ☐ Granulosa cell tumor
- ☐ Other sex cord-stromal tumor (specify type): \_\_\_\_\_
- ☐ Malignant germ cell tumor (specify types and percentages): \_\_\_\_\_
- ☐ Other(s) (specify): \_\_\_\_\_

**Histologic Grade (Note H)**World Health Organization (WHO) Grading System

(applies to all carcinomas, including serous carcinomas)

- ☐ GX: Cannot be assessed
- ☐ G1: Well differentiated
- ☐ G2: Moderately differentiated
- ☐ G3: Poorly differentiated
- ☐ G4: Undifferentiated

Two-Tier Grading System

(may be applied to serous carcinomas and immature teratomas only)

- ☐ Low grade
- ☐ High grade
- ☐ Other (specify): \_\_\_\_\_
- ☐ Not applicable

**Implants (only applies to advanced stage serous/seromucinous borderline tumors) (select all that apply) (Note I)**

- ☐ Not applicable/not sampled

Noninvasive Implant(s)

- ☐ Not present
- ☐ Present (specify sites): \_\_\_\_\_
  - \*Type of noninvasive implant(s)
  - \* ☐ Epithelial
  - \* ☐ Desmoplastic

Invasive Implant(s)

- ☐ Not present
- ☐ Present (specify sites): \_\_\_\_\_

\* Data elements with asterisks are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.

**Extent of Involvement of Other Tissues/Organs (select all that apply)**

- ☐ Right ovary  
    ☐ Involved  
    ☐ Not involved  
    ☐ Not applicable
- ☐ Left ovary  
    ☐ Involved  
    ☐ Not involved  
    ☐ Not applicable
- ☐ Right fallopian tube  
    ☐ Involved  
    ☐ Not involved  
    ☐ Not applicable
- ☐ Left fallopian tube  
    ☐ Involved  
    ☐ Not involved  
    ☐ Not applicable
- ☐ Omentum  
    ☐ Involved  
    ☐ Not involved  
    ☐ Not applicable
- ☐ Uterus  
    ☐ Involved (specify location: \_\_\_\_\_)  
    ☐ Not involved  
    ☐ Not applicable
- ☐ Peritoneum  
    ☐ Involved  
    ☐ Not involved  
    ☐ Not applicable
- ☐ Other organs/tissues (specify): \_\_\_\_\_

**\*Treatment Effect (applicable to carcinomas treated with neoadjuvant therapy)**

- \* ☐ No definite or minimal response identified (poor or no response)  
\* ☐ Marked response (minimal residual cancer)

**\*Lymph-Vascular Invasion (Note J)**

- \* ☐ Not identified  
\* ☐ Present  
\* ☐ Indeterminate

**Pathologic Staging (pTNM [FIGO]) (Note K)****TNM Descriptors** (required only if applicable) (select all that apply)

- ☐ m (multiple primary tumors)  
☐ r (recurrent)  
☐ y (posttreatment)

\* Data elements with asterisks are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.

Primary Tumor (pT)

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

<sup>#</sup> *Nonmalignant ascites is not classified. The presence of ascites does not affect staging unless malignant cells are present.*

Regional Lymph Nodes (pN)

- \_\_\_ pNX: Cannot be assessed
- \_\_\_ pN0: No regional lymph node metastasis
- \_\_\_ pN1 [IIIC]: Regional lymph node metastasis
- Specify: Number examined: \_\_\_
- Number involved: \_\_\_

Distant Metastasis (pM)

- \_\_\_ Not applicable
- \_\_\_ pM1 [IV]: 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.*

\* Data elements with asterisks are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.

**\*Additional Pathologic Findings (select all that apply) (Note L)**

\* ☐ None identified

\* ☐ Endometriosis

\* ☐ Ovarian

\* ☐ Extraovarian

\* ☐ Endosalpingiosis

\* ☐ Other(s)

\*Specify site(s) and type(s): \_\_\_\_\_

**\*Ancillary Studies (Note M)**

\*Specify: \_\_\_\_\_

**\*Clinical History (select all that apply)**

\* ☐ *BRCA1/2* family history

\* ☐ Hereditary breast/ovarian cancer

\* ☐ Other (specify): \_\_\_\_\_

**\*Comment(s)**

\* Data elements with asterisks are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.



## Explanatory Notes

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### A. Suggestions for Sampling for Microscopic Examination

#### Ovarian Surface Epithelium

The surface of the ovary should be handled as gently as possible; rubbing or scraping it or allowing it to dry should be avoided. 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 oophorectomy because of a family history of ovarian and/or breast cancer, very small carcinomas centered in the ovarian surface may be present that may be potentially lethal and may be missed if the macroscopic inspection is not optimal.<sup>1</sup>

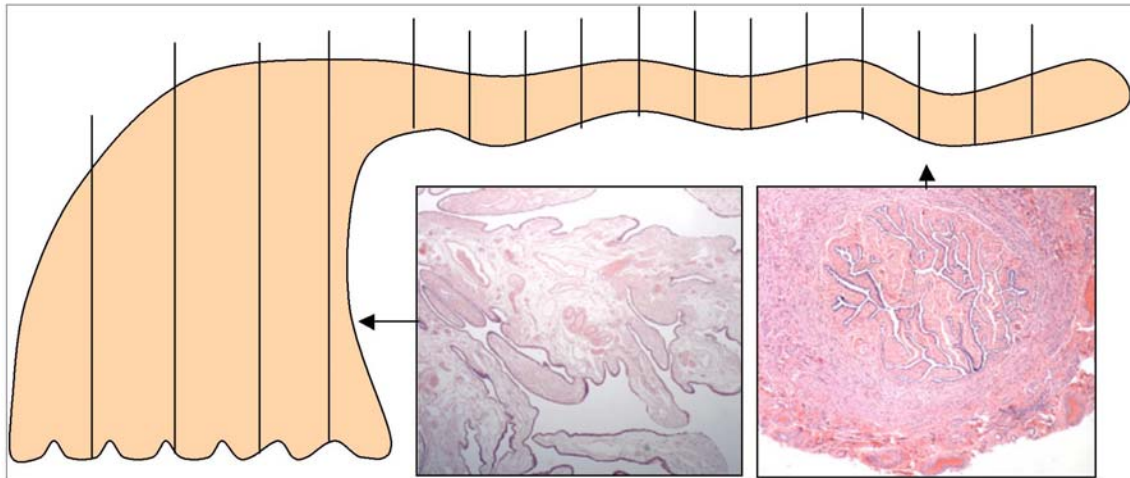
#### Primary Tumor

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.<sup>#</sup>

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, sites of rupture, and resection margins, if pertinent, should be sampled and labeled specifically for microscopic identification.

The ovary and fallopian tube should be submitted in toto in patients with *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.<sup>2</sup> Appropriate handling implies that all ovarian and tubal tissue should be serially sectioned and submitted.<sup>3,4</sup> 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)<sup>5</sup> (Figure 1). The remainder of the fallopian tube is submitted as serial cross-sections.



**Figure 1. 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.<sup>5</sup> Copyright © 2007 Lippincott Williams & Wilkins. Reproduced with permission.

Tumors showing predominant surface involvement of the ovary without parenchymal involvement are likely to be primary peritoneal or tubal in origin.<sup>3,6</sup>

<sup>#</sup> *Sampling Issues:* The recommendation for the number of sections to be taken of an ovarian 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, less numbers of 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 exclude a low-grade serous carcinoma. 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 is more informative than special studies.

### **Fallopian Tube(s)**

One section 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.

### **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 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<sup>7</sup> and from mature to immature,<sup>8</sup> respectively. Identification of a single invasive or immature implant may drastically 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.

**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.<sup>9,10</sup>

**C. Site(s) of Origin of Tumor**

When a tumor involves both the ovary and the fallopian tube, it may be difficult or impossible to determine the primary site of the tumor. Typically, the tumor predominates in one or the other organ, almost always the ovary. Although the convention is to designate these tumors as primary ovarian carcinomas, there is increasing evidence that at least some (and perhaps most) of them arise primarily in the fallopian tube.<sup>3</sup>

Although this is an important area of academic activity, with ramifications particularly for screening, there is insufficient evidence at this time to change the accepted convention regarding designation of primary site on the basis of the site of the dominant mass. For example, the ovary and tube are not infrequently fused to form a solid or cystic mass with destruction of most or all landmarks, and the convention in such cases is to designate the tumor as a primary ovarian carcinoma. Even though it may be difficult to determine with certainty the primary site in some cases, patient management is not

influenced by designation of the tumor as tubal, ovarian, or peritoneal (except in cases where the patient may be eligible for a clinical trial on the basis of a certain diagnosis).

When carcinomas of the same cell type involve ovary and uterus simultaneously, it may be difficult to determine whether the tumor is a primary ovarian carcinoma with spread to the uterus, a primary uterine carcinoma spreading to the ovary, or independent primary tumors. There are several criteria to help determine the primary origin of the tumor. Size and distribution of the tumors, presence of a precancerous lesion in either organ (atypical hyperplasia of the endometrium, endometriosis or adenofibroma of the ovary), microscopic appearance of the tumors, DNA ploidy findings, and molecular genetic studies have all been used to facilitate this differential diagnosis. Regardless, when synchronous low-grade endometrioid ovarian and endometrial carcinomas coexist, they are typically associated with good prognosis.

#### **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 a primary peritoneal neoplasm with secondary ovarian involvement.<sup>6</sup> If a tumor is centered or mainly involves the ovarian hilus, it is most likely to be a metastasis or a primary tumor originating from some structure in this area.<sup>11</sup>

#### **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 WHO classification and nomenclature of ovarian tumors be used because of its wide acceptance.<sup>12</sup> An abbreviated form of this classification is shown below.

### **WHO Classification of Malignant Ovarian Tumors**

#### Surface Epithelial-Stromal Tumors<sup>#</sup>

##### Histologic Type (Epithelial Component)

- Serous
- Mucinous<sup>##</sup>
- Endometrioid
- Clear cell
- Transitional (including Brenner)
- Squamous
- Mixed
- Undifferentiated

## Degree of Malignancy of Epithelial and/or Stromal Component

Borderline (of low malignant potential)<sup>###</sup>

Malignant

Carcinoma

Sarcoma

Both (malignant mesodermal mixed tumor)

Germ Cell Tumors

Dysgerminoma

Yolk sac tumor (endodermal sinus tumor)

Immature teratoma

Mixed malignant germ cell tumors (specify types)

Malignancy in dermoid cyst (specify type)

Other (specify)

Sex Cord-Stromal Tumors

Granulosa cell tumor

Other (specify)

# When the stromal component predominates in a surface epithelial stromal tumor, “adenofibro-” appears in the diagnostic term. This addition may be important because malignant ovarian tumors in which the neoplastic cells are surrounded by abundant benign fibromatous tissue appear to have a better prognosis than those without such a component. Surface involvement by neoplastic cells elevates the substage in stage I tumors and indicates a higher likelihood of extraovarian peritoneal involvement.

## Mucinous tumors of the ovary, when bilateral, should be considered metastases until proven otherwise. Bilateral, histologically well-differentiated tumors accompanied by pseudomyxoma peritonei are likely to be appendiceal in origin.<sup>13</sup> Only rare ovarian teratomas may be associated with pseudomyxoma ovarii.<sup>14,15</sup>

### Kurman and his group<sup>16</sup> have challenged the concept of borderline neoplasia, providing evidence that most so-called borderline tumors in the serous category should be designated “atypical proliferative” because they are rarely fatal.

Furthermore, there is controversy regarding the appropriate terminology for noninvasive micropapillary serous tumors of the ovary. Kurman's group refers to them as “noninvasive micropapillary serous carcinoma,” whereas most other groups prefer the term “serous borderline tumor, micropapillary type.” Differences in opinions stem from differences regarding whether the term “carcinoma” should be applied to tumors associated with peritoneal invasive implants that occur in 15% to 25% of these cases. Pathologists advocating the “serous borderline” terminology argue that the presence of invasive implants, irrespective of micropapillary architecture, places the patient at substantial risk of recurrence as occurs with overt low-grade serous carcinoma.<sup>17,18</sup> The most recent and extensive study on serous borderline tumors conducted by Longacre and colleagues has shown that the risk for recurrence in these tumors is driven by many factors, micropapillary architecture being only one of them.<sup>19</sup>

### 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 representing >10% of the tumor. When a carcinoma is classified as “mixed,” the major and minor types and their relative proportions should be specified. High-grade tumors with ambiguous features 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. 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.<sup>20,21</sup>

### H. Histologic Grade for Surface Epithelial-Stromal Tumors

Numerous grading systems, including architectural, nuclear, and combined architectural and nuclear systems, as well as schemas that incorporate additional features (eg, appearance of tumor margin, inflammatory cell reaction, and vascular space invasion) have been used for ovarian cancers. This protocol does not recommend any specific grading system because several have proved to have prognostic significance. Below is the WHO grading system.<sup>12</sup>

Grade X	Cannot be assessed
Grade 1	Well differentiated
Grade 2	Moderately differentiated
Grade 3	Poorly differentiated (tumors with minimal differentiation seen in very small foci)

Silverberg and colleagues have proposed a new grading system for invasive ovarian carcinomas modeled on the Nottingham system of breast cancer grading, which takes into account architectural pattern, nuclear pleomorphism, and mitotic activity with some modifications.<sup>22</sup>

Malpica and colleagues have also proposed a 2-tier system for grading serous carcinomas of the ovary into low and high grade.<sup>23</sup> Criteria are primarily based on nuclear variability (>3-fold nuclear atypia) with secondary use of mitotic activity (>12 mitoses). Such a system has molecular and prognostic validity and far less interobserver variability than a 3-tier system.

### Epithelial Cancers

As a rule, both architectural and nuclear features are evaluated in ovarian carcinomas. The prognostic significance of grading varies with each tumor type.

Serous. Usually, architectural features parallel nuclear features (ie, the extent of gland and papillae formation versus the quantity of solid growth correlates with low versus high grade). However, exceptions exist; for example certain tumors exhibit a solid growth pattern in the form of small nests associated with high degree of nuclear maturation and often containing numerous psammoma bodies. Tumors in the latter category are assigned grade 1 (or low grade) despite their solid architecture.

Mucinous. Architectural and nuclear features are both evaluated. Most important, however, is whether the tumor falls in the borderline or carcinoma category. Many mucinous tumors that lack obvious stromal invasion contain cysts and glands lined by

malignant epithelium. Such tumors have been designated as borderline tumor “with intraepithelial carcinoma.” They appear to have an excellent prognosis but one that is slightly worse than that of borderline tumors lacking this feature.

Endometrioid. These tumors can be graded according to the International Federation of Gynecology and Obstetrics (FIGO) system suggested for similar tumors of the uterine corpus.<sup>12</sup>

Grade 1	≤5% of a nonsquamous, solid growth
Grade 2	6% to 50% of nonsquamous solid growth
Grade 3	>50% of nonsquamous, solid growth

*Note:* Notable nuclear atypia, inappropriate for the architectural grade, raises the grade of a grade 1 or grade 2 tumor by 1 grade. Adenocarcinomas with squamous differentiation are graded according to the nuclear grade of the glandular component.

Clear cell and transitional cell. In general, these tumors are all high grade.

Squamous cell. Pure squamous cell carcinoma primary of the ovary is very rare. Such tumors can be graded in a 3-tier system.

### **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.<sup>24</sup> 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), recently a 2-tiered grading system (low versus high grade) has been proposed by some experts.<sup>25</sup> Also, implants associated with immature teratomas must be assessed for the presence of immature elements, typically glial tissue (gliomatosis peritonei).

### **Granulosa Cell Tumors**

Even though two groups of investigators have found that nuclear grading is effective in determining prognosis in these tumors,<sup>26,27</sup> the vast majority of gynecologic pathologists do not grade granulosa cell tumors because the most important prognostic parameter is stage.<sup>28,29</sup>

### **I. Implants (Serous/Seromucinous Borderline Tumors Only)**

In both serous borderline and endocervical type mucinous (ie, seromucinous) tumors, peritoneal implants are divided into 2 main categories:

- Noninvasive implants. They are subdivided into epithelial and desmoplastic types and are typically associated with favorable prognosis.
- Invasive implants are associated with a poor prognosis.

### **J. Lymph-Vascular Invasion**

Lymph-vascular invasion (LVI) indicates whether microscopic lymph-vascular invasion is identified. LVI includes lymphatic invasion, vascular invasion, or lymph-vascular invasion. According to the American Joint Committee on Cancer (AJCC) / International

Union Against Cancer (UICC) convention, LVI does not affect the T category indicating local extent of tumor unless specifically included in the definition of a T category.

The prognostic significance of vascular space invasion in primary ovarian cancer has not been demonstrated. The finding of lymph-vascular space invasion should raise suspicion for metastatic carcinoma to the ovary.<sup>30</sup>

### 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 AJCC and the UICC, as well as the parallel system formulated by the International Federation of Gynecology and Obstetrics (FIGO), are recommended.<sup>31-35</sup>

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.

### Stage Groupings

TNM Stage Groupings				FIGO Stage
Stage IA	T1a	N0	M0 <sup>#</sup>	Stage IA
Stage IB	T1b	N0	M0	Stage IB
Stage IC	T1c	N0	M0	Stage IC
Stage IIA	T2a	N0	M0	Stage IIA
Stage IIB	T2b	N0	M0	Stage IIB
Stage IIC	T2c	N0	M0	Stage IIC
Stage IIIA	T3a	N0	M0	Stage IIIA
Stage IIIB	T3b	N0	M0	Stage IIIB
Stage IIIC	T3c	N0	M0	Stage IIIC
	Any T	N1	M0	Stage IIIC
Stage IV	Any T	Any N	M1	Stage IV

<sup>#</sup> M0 is defined as no distant metastasis.



**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.

**Additional Descriptors****Residual Tumor (R)**

Tumor remaining in a patient after therapy with curative intent (eg, surgical resection for cure) is categorized by a system known as R classification, shown below.

RX	Presence of residual tumor cannot be assessed
R0	No residual tumor
R1	Microscopic residual tumor
R2	Macroscopic residual tumor

For the surgeon, the R classification may be useful to indicate the known or assumed status of the completeness of a surgical excision. For the pathologist, the R classification is relevant to the status of the margins of a surgical resection specimen. That is, tumor involving the resection margin on pathologic examination may be assumed to correspond to residual tumor in the patient and may be classified as macroscopic or microscopic according to the findings at the specimen margin(s).

**L. Other Lesions**

The presence of endometriosis, particularly if it is in continuity with either an endometrioid or clear cell carcinoma, is a very important clue as to the primary nature of the ovarian tumor, especially in cases in which it may be difficult otherwise to exclude metastasis from a synchronous or asynchronous cancer of the uterine corpus.

**M. Special Studies**

Special studies include histochemical and immunohistochemical staining, which are helpful diagnostically in occasional cases; flow cytometry; DNA image analysis; quantitative microscopy; hormone receptor studies; molecular genetic studies; and

chromosome analysis analysis. At present, immunohistochemical stains are the most commonly used to determine tumor differentiation and diagnosis.

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