COLLEGE of AMERICAN PATHOLOGISTS

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.

Based on AJCC/UICC TNM, 7th edition
Protocol web posting date: August 2015

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

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The College of American Pathologists offers these protocols to assist pathologists in providing clinically useful and relevant information when reporting results of surgical specimen examinations of surgical specimens. The College regards the reporting elements in the “Surgical Pathology Cancer Case Summary” portion of the protocols as essential elements of the pathology report. However, the manner in which these elements are reported is at the discretion of each specific pathologist, taking into account clinician preferences, institutional policies, and individual practice.

The College developed these protocols as an educational tool to assist pathologists in the useful reporting of relevant information. It did not issue the protocols for use in litigation, reimbursement, or other contexts. Nevertheless, the College recognizes that the protocols might be used by hospitals, attorneys, payers, and others. Indeed, effective January 1, 2004, the Commission on Cancer of the American College of Surgeons mandated the use of the required data elements of the protocols as part of its Cancer Program Standards for Approved Cancer Programs. Therefore, it becomes even more important for pathologists to familiarize themselves with these documents. At the same time, the College cautions that use of the protocols other than for their intended educational purpose may involve additional considerations that are beyond the scope of this document.

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CAP Ovary Protocol Revision History

Version Code
The definition of the version code can be found at www.cap.org/cancerprotocols.

Version: Ovary 3.2.0.1

Summary of Changes

The only change to the October 2013 version is the addition of the following:

Important Note
Recent observations including molecular findings have indicated that high-grade serous carcinoma of the fallopian tube/ovary/and peritoneum is very often of fallopian tube origin. Serous intraepithelial carcinoma of the fallopian tube has been observed in patients undergoing prophylactic and routine salpingectomy/salpingooophorectomy for nonneoplastic disease, 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 as a unified entity based on clinical behavior but recommends assigning a primary site if possible. In a recent publication, Singh et al describe 10 scenarios to illustrate assigning high-grade serous carcinoma to fallopian tube, ovary, or peritoneum.

Bibliography
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McCluggage WG, Judge MJ, Clarke BA, et al. Data set for reporting of ovary, fallopian tube and primary peritoneal carcinoma: recommendations from the International Collaboration on Cancer Reporting (ICCR). *Mod Pathol.* 2015;28(8):1101-1122.

Singh N, Gilks CB, Wilkinson N. Assessment of a new system for primary site assignment in high-grade serous carcinoma of the fallopian tube, ovary, and peritoneum. *Histopathology.* 2015;67(3):331-337.

Surgical Pathology Cancer Case Summary

Protocol web posting date: August 2015

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 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 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

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 (if applicable)
___ Fragmented
___ Other (specify): _____

Primary Tumor Site (Notes C, D, and E)
___ Right ovary
___ Left ovary
___ Bilateral ovaries
___ 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
___ Transitional cell carcinoma
___ Brenner tumor, borderline
___ Brenner tumor, malignant
___ 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): _____
___ Dysgerminoma
___ Yolk sac tumor (endodermal sinus tumor)
___ Immature teratoma

+ 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.

___ Carcinoma in teratoma
___ Mixed 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 (applies only 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): _____

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): _____

+ 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.

___ Uterus
    ___ Involved (specify location: _____)
    ___ Not involved
    ___ Other (explain): _____
___ Peritoneum
    ___ Involved
    ___ Not involved
    ___ Other (explain): _____
___ 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)

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[#]
___ 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

[#] *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

___ No nodes submitted or found

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

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

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.

+ 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)

Explanatory Notes

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.[1]

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.[#]

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.[2] Appropriate handling implies that all ovarian and tubal tissue should be serially sectioned and submitted.[3,4] 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)[5] (Figure 1). The remainder of the fallopian tube is submitted as serial cross-sections.

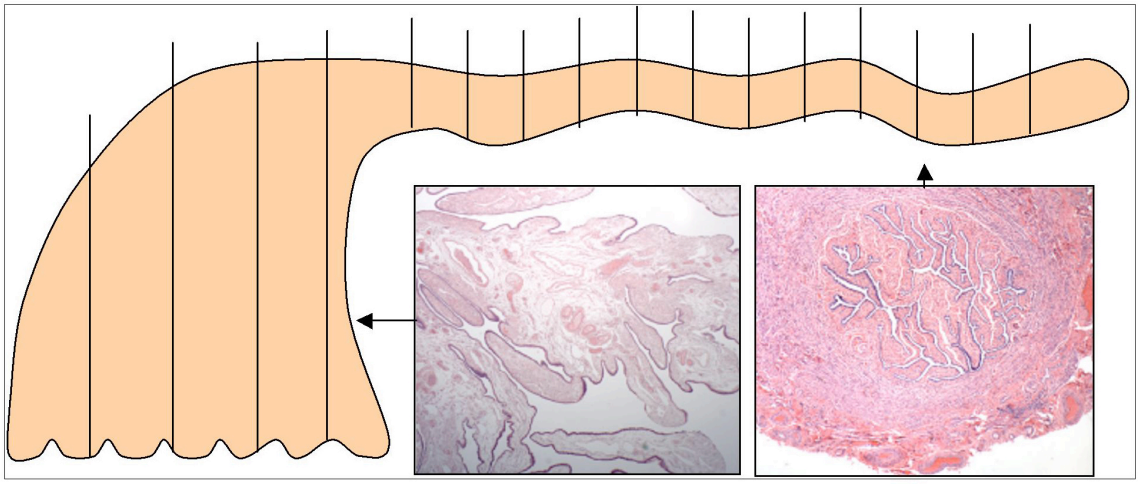

Figure 1. Protocol for Sectioning and Extensively Examining the FIMbriated End (SEE-FIM) of the Fallopian Tube. This protocol entails amputation and longitudinal sectioning of the infundibulum and fimbrial segment (distal 2 cm) to allow maximal exposure of the tubal plicae. The isthmus and ampulla are cut transversely at 2- to 3-mm intervals. From Crum et al.[5]

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

[#] *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[7] and from mature to immature,[8] 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.[9,10]

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.[3] 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.[6] 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.[11]

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.[12] An abbreviated form of this classification is shown below.

WHO Classification of Malignant Ovarian Tumors

<u>Surface Epithelial-Stromal Tumors</u>[#]
Histologic Type (Epithelial Component)
- Serous
- Mucinous[##]
- Endometrioid
- Clear cell
- Transitional (including Brenner)
- Squamous
- Mixed
- Undifferentiated

Degree of Malignancy of Epithelial and/or Stromal Component
- Borderline (of low malignant potential)[###]
- Malignant
  - Carcinoma
  - Sarcoma
  - Both (malignant mesodermal mixed tumor)

<u>Germ Cell Tumors</u>
- 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.[13] Only rare ovarian teratomas may be associated with pseudomyxoma ovarii.[14,15]

[###] Kurman and his group[16] 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.[17,18] 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.[19]

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.[20,21]

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.[12]

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.[22]

Malpica and colleagues have also proposed a 2-tier system for grading serous carcinomas of the ovary into low and high grade.[23] 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.

Endometrioid carcinomas may be graded according to FIGO. Notable nuclear atypia, inappropriate for the architectural grade, raises the grade of a grade 1 or grade 2 tumor by 1 grade.

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.[12]

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.[24] 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.[25] 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,[26,27] the vast majority of gynecologic pathologists do not grade granulosa cell tumors because the most important prognostic parameter is stage.[28,29]

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.[30]

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.[31-35]

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[#]	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

[#] 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. At present, immunohistochemical stains are the most commonly used to determine tumor differentiation and diagnosis.

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