Protocol for the Examination of Specimens from Patients with Carcinoma of the Fallopian Tube

Protocol applies to all carcinomas presumed to be arising from the mucosa of the fallopian tube.

Based on AJCC/UICC TNM, 7th edition, and FIGO 2006 Annual Report
Protocol web posting date: October 2009

Procedures
- Unilateral Salpingectomy
- Salpingo-oophorectomy
- Hysterectomy with Salpingo-oophorectomy

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Surgical Pathology Cancer Case Summary (Checklist)

Protocol web posting date: October 2009

FALLOPIAN TUBE: Unilateral Salpingectomy, Salpingo-oophorectomy, or Hysterectomy with Salpingo-oophorectomy

Select a single response unless otherwise indicated.

Specimen (select all that apply)
___ Right fallopian tube
___ Left fallopian tube
___ Right ovary
___ Left ovary
___ Uterus
___ Other (specify): _____
___ Not specified

Procedure (select all that apply)
___ Right salpingectomy
___ Left salpingectomy
___ Right salpingo-oophorectomy
___ Left salpingo-oophorectomy
___ Hysterectomy with salpingo-oophorectomy
___ Other (specify): _____
___ Not specified

Lymph Node Sampling
___ Common iliac
___ External iliac
___ Internal iliac (hypogastric)
___ Obturator
___ Para-aortic
___ Inguinal
___ Pelvic nodes, not otherwise specified (NOS)

Tumor Site (select all that apply) (Note A)
___ Right fallopian tube
    Relationship to ovary:
    ___ Not fused
    ___ Fused
    Status of fimbriated end: **(Note B)**
    ___ Open
    ___ Closed

* 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.

___ Left fallopian tube
    Relationship to ovary:
    ___ Not fused
    ___ Fused
    Status of fimbriated end: **(Note B)**
    ___ Open
    ___ Closed
___ Not specified

Tumor Location (select all that apply)
___ Fimbria(e)
___ Ampulla
___ Infundibular portion
___ Isthmus
___ Cannot be determined

Specimen Integrity
Specify side: _____
___ Intact
___ Ruptured
___ Fragmented
___ Other (specify): _____

Tumor Size
Greatest dimension: ___ cm
*Additional dimensions: ___ x ___ cm
___ Cannot be determined (see Comment)

Histologic Type (Notes D and E)
___ Tubal intraepithelial carcinoma (specify type): _____
___ Serous carcinoma
___ Mucinous carcinoma
___ Endometrioid carcinoma
___ Clear cell carcinoma
___ Transitional cell carcinoma
___ Squamous cell carcinoma
___ Undifferentiated carcinoma
___ Other (specify): _____
___ Carcinoma, type cannot be determined

Histologic Grade (Note F)
___ Not applicable
___ GX: Cannot be assessed
___ G1: Well differentiated
___ G2: Moderately differentiated
___ G3: Poorly differentiated

* 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.

***Microscopic Tumor Extension (select all that apply)**
*___ Fallopian tube
*___ Other organs/tissues (specify): _____

Lymph-Vascular Invasion
___ Not identified
___ Present
___ Indeterminate

Lymph Nodes
___ Common iliac
Number examined: ___
Number positive: ___
___ External iliac
Number examined: ___
Number positive: ___
___ Internal iliac (hypogastric)
Number examined: ___
Number positive: ___
___ Obturator
Number examined: ___
Number positive: ___
___ Para-aortic
Number examined: ___
Number positive: ___
___ Pelvic nodes, NOS
Number examined: ___
Number positive: ___

Pathologic Staging (pTNM [FIGO]) (Note G)

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

Primary Tumor (pT)

___ pTX:	Primary tumor cannot be assessed
___ pT0:	No evidence of primary tumor
___ pTis:	Tubal intraepithelial carcinoma (limited to tubal mucosa)
___ pT1 [I]:	Tumor limited to fallopian tube(s)
*___ pT1a [IA]:	Tumor limited to 1 tube without penetrating the serosal surface; no ascites
*___ pT1b [IB]:	Tumor limited to both tubes without penetrating the serosal surface; no ascites
*___ pT1c [IC]:	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 [II]:	Tumor involves 1 or both tube(s) with pelvic extension
___ pT2a [IIA]:	Extension and/or metastasis to the uterus and/or ovaries

___ pT2b [IIB]: Extension to other pelvic structures
*___ pT2c [IIC]: Pelvic extension (T2a or T2b/IIA or IIB) with malignant cells in ascites or peritoneal washings
___ pT3 and/or N1 [III]: Tumor involves 1 or both tube(s) with peritoneal implants outside the pelvis and/or regional lymph node metastasis
___ pT3a [IIIA]: Microscopic peritoneal metastasis beyond pelvis
___ pT3b [IIIB]: Macroscopic peritoneal metastasis beyond pelvis 2 cm or less in greatest dimension
___ pT3c/N1 [IIIC]: Peritoneal metastasis beyond pelvis more than 2 cm in greatest dimension and/or regional lymph node metastasis
___ Any T/Any N and M1 [IV]: Distant metastasis including presence of malignant cells in pleural fluid or parenchymal hepatic metastasis

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 metastasis
*Specify site(s), if known: _____

***Additional Pathologic Findings (select all that apply)**
*___ None identified
*___ Salpingitis (type): _____ **(Note H)**
*___ Other (specify): _____

***Ancillary Studies (select all that apply)**
*___ P53 immunostaining
*___ Positive
*___ Negative
*___ Other (specify): _____

***Clinical History (select all that apply)**
*___ *BRCA1/BRCA2* family history
*___ Other (specify): _____

***Comment(s)**

Explanatory Notes

A. Site(s) of Origin of Tumor

When a tumor (typically of serous subtype) involves both the fallopian tube and the ovary, it may be difficult to determine the primary site of the tumor. Historically, serous carcinomas involving both the ovary and fallopian tube have been assumed to arise from the ovary[1]; however, recent data suggests that the fallopian tube may be the primary source for at least a significant number of these tumors.[2-5] Examination of prophylactic salpingo-oophorectomy specimens from BRCA+ patients has provided the opportunity to extensively evaluate both the fallopian tubes and ovaries from women at high risk to develop ovarian cancer, and therefore detect "very early" tumors. Interestingly, studies have shown that most early carcinomas detected in these specimens occur in the tubal fimbria, and many of them are still confined to the mucosa in the form of tubal intraepithelial carcinoma.[3] These findings raise an important paradox, namely BRCA+ women that are known to have an increased risk of ovarian cancer, rather have a significant portion of early cancers arising in the fallopian tube. Thus, it has been postulated that the fimbriated end of the fallopian tube is the portion of the tubal mucosa that is at greatest risk to develop early serous carcinoma in BRCA+ women.

Medeiros and colleagues[3] have developed a meticulous protocol (SEE-FIM [see Figure 1]) for carefully evaluating the fallopian tube that maximizes examination of the fimbriated end in order to detect these "early carcinomas." In addition, the ovaries should be sectioned at 2- to 3-mm intervals and submitted in toto for histological examination. Using this protocol, 7 early carcinomas were detected in BRCA+ patients over a 2-year period. All cancers involved the fallopian tube, and 6 were centered in the fimbria. Thus, the distal fallopian tube appears to be most frequently involved in cases of early serous carcinoma in BRCA+ women.

Fallopian tube carcinoma does not appear to be unique to BRCA+ women, as the topography of tubal carcinoma from BRCA+ and BRCA- women seems to be equivalent. Cass and colleagues[4] studied 28 patients with fallopian tube carcinoma, 16 of which (48%) were not associated with BRCA mutations; in both groups, fallopian tube carcinoma involved the distal portion with no proximal involvement. When combining the studies from Medeiros et al,[3] Colgan et al,[5] and Callahan et al,[6] 12 of 14 (86%) early serous carcinomas were found to arise in the distal fallopian tube, indicating that virtually all fallopian tube carcinomas arise in the distal (fimbriated) segment of the fallopian tube irrespective of BRCA status, and that a high percentage of early serous carcinoma in BRCA+ patients arise in the distal fallopian tube.[3,5,6] In a blinded review by Shaw et al[7] of fallopian tubes from 176 BRCA + (103 BRCA1 and 73 BRCA2) patients compared with 64 control patients, tubal intraepithelial carcinomas (TICs) were identified in 8% of the BRCA group and 3% of the control group. Other than 1 case in which TIC was located in the midportion of the isthmus, all TICs were found in the fimbria.[7] Review of the literature has shown that in women with pelvic serous carcinoma whose BRCA status is unknown, TICs are present in about 50% of cases, leading to the conclusion that the fallopian tube is a major site of origin for pelvic serous carcinoma, regardless of BRCA status.[8]

In practice, because of the diffuse distribution of pelvic serous carcinoma, it may be challenging to assign site of origin: ovarian, tubal or peritoneal. Traditionally, this has

based on the location of the bulk of the tumor, with ovarian carcinoma demonstrating predominant involvement of the ovarian parenchyma, whereas the salpinx is implicated if the tumor is centered mainly in the tube with minimal ovarian surface involvement. Primary peritoneal carcinoma requires the presence of extensive and predominant peritoneal disease with normal ovaries or involvement confined to ovarian serosal surface or cortical invasion limited to 5 mm by 5 mm. The immunophenotype of serous carcinomas in these sites (ovary, tube and peritoneum) is similar, suggesting a common cell of origin, regardless of site. In the presence of diffuse disease, if tubal intraepithelial carcinoma is present, these should be regarded as tubal carcinomas. This requires processing of the fimbrial end of the fallopian tube (see Figure 1).[3] It is acknowledged that in cases of diffuse serous carcinoma, tumor implants may be seen on the tubal mucosa, making definitive assessment of tubal intraepithelial carcinoma impossible. In such cases, the phrase "serous carcinoma of tubal/ovarian origin" may be used.

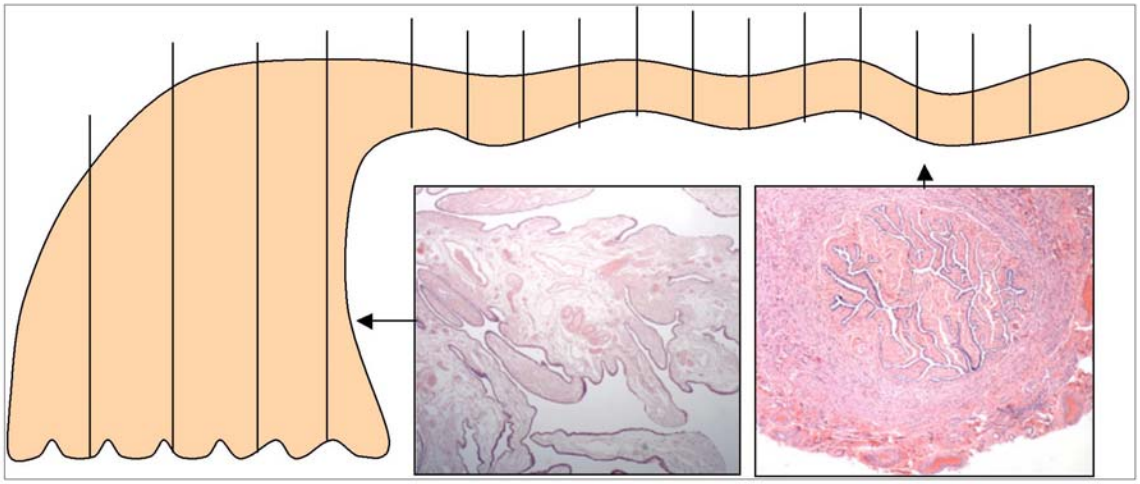

Figure 1. Protocol for Sectioning and Extensively Examining the FIMbriated End (SEE-FIM) of the Fallopian Tube. This protocol entails amputation and longitudinal sectioning of the infundibulum and fimbrial segment (distal 2 cm) to allow maximal exposure of the tubal plicae. The isthmus and ampulla are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

From Crum CP, Drapkin R, Miron A, et al. The distal fallopian tube: a new model for pelvic serous carcinogenesis. *Curr Opin Obstet Gynecol.* 2007;19:5. Copyright © 2007 Lippincott Williams & Wilkins. Reproduced with permission.

B. Fimbriated End

Although most investigators have not commented on the possible prognostic significance of the status of the fimbriated end, in 2 series of cases of tubal carcinoma,[9,10] closure of the fimbriated end was associated with lower stage of the tubal carcinoma.

C. Selection of Specimens for Microscopic Examination

Primary Tumor

- If visible mass: sections adequate to demonstrate extent of tumor, including maximal depth of invasion and relationship to surrounding organs/tissues, if present, should

be taken. Sections showing transition to grossly uninvolved areas of fallopian tube are also helpful.
- If no visible tumor (typically in prophylactic oophorectomy): entirely submit the fimbriated end of the fallopian tube to search for carcinoma in situ (tubal intraepithelial carcinoma) or a small carcinoma, as the fimbriated end of the fallopian tube appears to be the most common site for "early carcinoma" (Note A) either in BRCA+ or BCRA– patients. Serial longitudinal sections of the fallopian tube fimbria at 2- to 3-mm intervals should be performed to examine the most surface of the plicae (see Figure 1). The rest of the fallopian tube can be serially sectioned transversally[3].

Uterus
- Tumor grossly present: sections necessary to determine tumor extent, including depth of invasion of myometrium if tumor originates in endometrium, and to determine relation to tubal tumor (for primary tumors of endometrium, see CAP endometrium protocol).

Nonfused Ovary or Ovaries
- Tumor visible in the ovary: sections to determine relation to tubal tumor(s).
- No tumor in the ovary but visible tumor in the fallopian tube: representative section(s).
- No tumor visible in the fallopian tube or ovary (mainly in prophylactic oophorectomy); serial sections of the ovary along the shorter axis to be able to evaluate the maximum ovarian surface.

Omentum
- Representative sampling of grossly identifiable tumor.
- If no visible tumor, multiple sections are generally optimal because of the possible impact of microscopically detected disease on prognosis and therapy.

Lymph Nodes
- Representative sections of grossly positive lymph nodes are generally adequate.
- If lymph nodes appear to be grossly free of tumor, an attempt should be made to identify and submit the entire lymph node(s). If they are large, they should be bivalved along their long axis, and both halves should be entirely submitted.

Other Staging Biopsy Specimens
- Submit entirely (unless grossly positive, in which case a representative section usually suffices).

Other Excised Organ(s) or Tissue(s)
- Sections adequate to determine presence or absence, and location and extent of tumor, if present.
- Resection margins, if applicable.

D. Histologic Type
The histologic classification proposed by the World Health Organization (WHO) is recommended, as shown below.[11]

WHO Classification of Carcinoma of the Fallopian Tube
Carcinoma in situ
Serous carcinoma
Mucinous carcinoma
Endometrioid carcinoma
Clear cell carcinoma
Transitional cell carcinoma
Squamous cell carcinoma
Mixed carcinoma
Undifferentiated carcinoma

E. Immunohistochemistry
Immunohistochemistry is a useful adjunct in recognition and classification of precursor lesions and carcinomas of the fallopian tube. Although there is no universally accepted classification schema for the precursor lesions encountered in prophylactic BSO specimens, Jarboe and colleagues have proposed a serous carcinogenesis sequence which incorporates immunohistochemical profiles.[12] These lesions can be focal, and serial sections may be required.

Serous tubal intraepithelial carcinoma (STIC) comprises a discreetly different population of epithelial cells replacing the normal tubal mucosa and characterized by (1) increased nuclear to cytoplasmic ratio with more rounded nuclei, (2) loss of cell polarity, (3) prominent nucleoli, and (4) absence of ciliated cells. Additional features that may be encountered include (5) epithelial stratification, (6) small fracture lines in the epithelium, and (7) exfoliation from the tubal surface of small epithelial cell clusters with or without degenerative changes. The cells exhibit uniformly strong nuclear staining for p53. The MIB-1 index ranges from 40% to nearly 100%, with the majority of cases showing focal areas exceeding 70%.

The latent precursor (p53 signature) refers to foci of at least 12 consecutive morphologically benign, p53 positive secretory cells with low MIB-1 proliferative index. Tubal intraepithelial lesion in transition refers to p53 positive foci with features intermediate between p53 signatures and STICs. The p53 signature and tubal intraepithelial lesion in transition are NOT recommended as diagnostic terms because their reproducibility and clinical significance is as yet uncertain. Use of biomarkers is not necessary in the presence of STIC, but if there is diagnostic uncertainty, both p53 and MIB-1 staining should be performed.

Panels of biomarkers have been used to distinguish cell type in ovarian carcinoma and similar markers could be used to classify fallopian tube carcinomas. Using individual markers, WT-1 is a marker of ovarian/tubal serous carcinoma[13] and HNF-1β a marker of clear cell carcinoma. [14] WT-1 has a sensitivity of 79.9% and specificity of 97.4% for ovarian/tubal serous carcinoma and HNF-1β a sensitivity of 82.5% and specificity of 95.2% for clear cell carcinoma. However, a diagnostic panel consisting of ER, WT-1 and HNF-1β has been recommended to distinguish serous and clear cell types in ovary, with the former being positive for ER and WT-1 and the latter positive for HNF-1β.[14] Other authors have suggested a combination of p16 and WT-1 (both positive in serous carcinoma) as a reliable panel for discriminating high-grade serous carcinoma from other subtypes of ovarian carcinoma.[15]

F. Histologic Grade

No specific grading system for tubal cancers is recommended. However, it is suggested that 3 grades be used to parallel the grading systems of endometrial and ovarian tumors, which are histologically similar to those encountered in the fallopian tube.

GX Cannot be assessed
G1 Well differentiated
G2 Moderately differentiated
G3 Poorly differentiated

Undifferentiated carcinoma equals grade 4, and it is applied to tumors with no differentiation or minimal differentiation that is discernible in only rare tiny foci.

G. TNM and Stage Groupings

The TNM staging system for fallopian tube endorsed by the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC), and the parallel system formulated by the International Federation of Gynecology and Obstetrics (FIGO) are recommended as shown below.[16-19]

By 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 unfeasible) 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.

Primary Tumor (T)

TNM Category	FIGO Stage	Definition
TX	(--)	Primary tumor cannot be assessed
T0	(--)	No evidence of primary tumor
Tis	(--)	Carcinoma in situ (limited to tubal mucosa)
T1	Stage I	Tumor limited to fallopian tube(s)
T1a	Stage IA	Tumor limited to 1 tube without penetrating the serosal surface; no ascites
T1b	Stage IB	Tumor limited to both tubes without penetrating the serosal surface; no ascites

T1c	Stage IC	Tumor limited to 1 or both tube(s) with extension onto or through the tubal serosa, or with malignant cells in ascites or peritoneal washings
T2	Stage II	Tumor involves 1 or both fallopian tube(s) with pelvic extension
T2a	Stage IIA	Extension and/or metastasis to the uterus and/or ovaries
T2b	Stage IIB	Extension to other pelvic structures
T2c	Stage IIC	Pelvic extension (T2a or T2b/IIA or IIB) with malignant cells in ascites or peritoneal washings
T3 and/or N1	Stage III	Tumor involves 1 or both fallopian tube(s) with peritoneal implants outside of the pelvis and/or positive regional lymph nodes
T3a	Stage IIIA	Microscopic peritoneal metastasis outside the pelvis
T3b	Stage IIIB	Macroscopic peritoneal metastasis outside the pelvis 2 cm or less in greatest dimension
T3c and/or N1	Stage IIIC	Peritoneal metastasis more than 2 cm in greatest dimension and/or positive regional lymph nodes
M1	Stage IV	Distant metastasis (excludes peritoneal metastasis)

Note: Liver capsule metastasis is T3/stage III; liver parenchymal metastasis is MI/stage IV. Pleural effusion must have positive cytology for MI/stage IV.

Some authors recommend a modified FIGO staging system for fallopian tube carcinomas subdividing stage IA and IB in 3 subcategories, as they found depth of invasion to be a very important prognostic factor in these tumors.[19] Those include:

Stage IA-0: Growth limited to 1 tube with no extension into lamina propria
Stage IA-1: Growth limited to 1 tube with extension into the lamina propria, but no extension into muscularis
Stage IA-2: Growth limited to 1 tube with extension into muscularis

The same substagings are applied to stage IB tubal carcinomas.

Some authors also recommend using stage IF for fimbrial carcinomas, as they seem to be associated with worse prognosis because the tumor cells are exposed directly to the peritoneal cavity even though they do not invade the tubal wall.[8]

The above proposals for altering the FIGO classification are particularly important in staging of early carcinomas such those that have been detected in salpingo-oophorectomy specimens from BRCA-positive patients undergoing prophylactic oophorectomy.[5, 20]

Regional Lymph Nodes (N) (TNM Staging System)

NX Regional lymph nodes cannot be assessed
N0 No regional lymph nodes metastasis
N1 Regional lymph node metastasis

Distant Metastasis (M) (TNM Staging System)

M0	No distant metastasis
M1	Distant metastasis

TNM Stage Groupings

Stage 0	Tis	N0	M0
Stage IA	T1a	N0	M0
Stage IB	T1b	N0	M0
Stage IC	T1c	N0	M0
Stage IIA	T2a	N0	M0
Stage IIB	T2b	N0	M0
Stage IIC	T2c	N0	M0
Stage IIIA	T3a	N0	M0
Stage IIIB	T3b	N0	M0
Stage IIIC	T3c	N0	M0
	Any T	N1	M0
Stage IV	Any T	Any N	M1

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 following 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 prior to 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).

Lymph-Vascular Invasion (LVI)
LVI indicates whether microscopic lymph-vascular invasion is identified. LVI includes lymphatic invasion, vascular invasion, or lymph-vascular invasion. By AJCC/UICC convention, LVI does not affect the T category indicating local extent of tumor unless specifically included in the definition of a T category.

H. Other Lesions
Severe salpingitis, including tuberculous salpingitis, can be associated with severe cytologic atypia (pseudocarcinomatous changes) in the fallopian tube.[21] In contrast, carcinoma is rarely associated with severe salpingitis. Therefore, the presence of severe inflammation should alert the pathologist to the possibility of a pseudocarcinomatous change. p53 may be helpful to distinguish between reactive cytologic changes and carcinoma in situ in the fallopian tube, the latter being typically positive.[3] Endometriosis may be present in the background of endometrioid carcinoma of the tube.[9]

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