Protocol for the Examination of Specimens from Patients with Carcinoma of the Vagina

Protocol applies to all invasive carcinomas of the vagina.

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

Procedures
- Biopsy
- Excisional biopsy
- Vaginectomy
- Radical Vaginectomy

Authors
Dina H. Kandil, MD, FCAP*
Department of Pathology, University of Vermont, Burlington, VT
Philip A. Branton, MD
Department of Pathology, Inova Fairfax Hospital, Fairfax, VA
Anthony Montag, MD
Department of Pathology, University of Chicago Medical Center, Chicago, IL
Esther Oliva, MD
Department of Pathology, Massachusetts General Hospital, Boston, MA
Kumarasen Cooper, MBChB, DPhil, FRCPath†
Department of Pathology, University of Vermont, Burlington, VT
For the Members of the Cancer Committee, College of American Pathologists

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

Previous lead contributors: Arthur L. Herbst, MD; Esther Oliva, MD; Patricia M Baker, MD; Robert J. Kurman, MD; Robert E. Scully, MD

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 (Checklist)” 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.

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Surgical Pathology Cancer Case Summary (Checklist)

Protocol web posting date: October 2009

***VAGINA: Biopsy**
(Note: Use of checklist for biopsy specimens is optional)

Select a single response unless otherwise indicated.

***Procedure (Notes A through D)**
*___ Incisional biopsy
*___ Other (specify): _____
*___ Not specified

***Tumor Site**
*___ Upper third
*___ Middle third
*___ Lower third
*___ Not specified

***Histologic Type (select all that apply) (Note E)**
*___ Squamous cell carcinoma
  *___ Keratinizing
  *___ Non-keratinizing
  *___ Basaloid
  *___ Verrucous
  *___ Warty
  *___ Not otherwise specified
*___ Adenocarcinoma
  *___ Clear cell
  *___ Mucinous
  *___ Endometrioid
  *___ Mesonephric
  *___ Intestinal type
  *___ Not otherwise specified
*___ Adenosquamous carcinoma
*___ Undifferentiated carcinoma
*Other (specify): _____

***Histologic Grade (Note F)**
*___ Not applicable
*___ GX: Cannot be assessed
*___ G1: Well differentiated
*___ G2: Moderately differentiated
*___ G3: Poorly differentiated
*___ G4: Undifferentiated
*___ Other (specify): _____

***Microscopic Tumor Extension**
*___ Cannot be assessed
*___ Stromal invasion
*___ Muscle invasion

***Margins**
*___ Not applicable
*___ Cannot be assessed
*___ Uninvolved by tumor
*___ Involved by tumor
Specify site: _____

***Additional Pathologic Findings (select all that apply) (Note G)**
*___ None identified
*___ Condyloma accuminatum
*___ Squamous dysplasia
*___ Carcinoma in-situ
*___ Adenocarcinoma in-situ
*___ Atypical adenosis
*___ Other (specify): _____

***Comment(s)**

Surgical Pathology Cancer Case Summary (Checklist)

Protocol web posting date: October 2009

VAGINA: Excisional Biopsy, Resection (Vaginectomy, Radical Vaginectomy)

Select a single response unless otherwise indicated.

Procedure
___ Excisional biopsy
___ Partial vaginectomy
___ Radical vaginectomy
___ Other (specify): _____
___ Not specified

Tumor Site (select all that apply)
___ Upper third
- *___ Circumferential
- *___ Anterior
- *___ Posterior
- *___ Left lateral
- *___ Right lateral

___ Middle third
- *___ Circumferential
- *___ Anterior
- *___ Posterior
- *___ Left lateral
- *___ Right lateral

___ Lower third
- *___ Circumferential
- *___ Anterior
- *___ Posterior
- *___ Left lateral
- *___ Right lateral

___ Not specified

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

* 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.

Histologic Type (select all that apply) (Note E)
___ Squamous cell carcinoma
*___ Keratinizing
*___ Non-keratinizing
*___ Basaloid
*___ Verrucous
*___ Warty
*___ Not otherwise specified
___ Adenocarcinoma
*___ Clear cell
*___ Endometrioid
*___ Mucinous
*___ Mesonephric
*___ Intestinal type
*___ Not otherwise specified
___ Adenosquamous carcinoma
___ Undifferentiated carcinoma
___ Other (specify): _____

Histologic Grade (Note F)
___ Not applicable
___ GX: Cannot be assessed
___ G1: Well differentiated
___ G2: Moderately differentiated
___ G3: Poorly differentiated
___ G4: Undifferentiated
___ Other (specify): _____

Margins (select all that apply)
___ Cannot be assessed
___ Margins uninvolved by invasive carcinoma
Distance of invasive carcinoma from closest margin: ___ mm
Specify margin, if possible: _____
___ Dysplasia/carcinoma in situ not identified at margin
___ Dysplasia present at margin (specify grade: _____)
___ Margin(s) involved by invasive carcinoma
Specify margin(s), if possible: _____

***Lymph-Vascular Invasion**
*___ Not identified
*___ Present
*___ Indeterminate

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

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

* 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
___ pTis [0]: Carcinoma in situ
___ pT1 [I]: Tumor confined to vaginal wall
___ pT2 [II]: Tumor invades paravaginal tissues but not the pelvic wall
___ pT3 [III]: Tumor extends to pelvic wall
___ pT4 [IVA]: Tumor invades mucosa of bladder or rectum and/or extends beyond true pelvis

Regional Lymph Nodes (pN)
___ pNX: Cannot be assessed
___ pN0: No regional lymph node metastasis
___ pN1 [IVB]: Pelvic or inguinal lymph node metastasis
Specify: Number examined: ___
Number involved: ___

Distant Metastasis (pM)
___ Not applicable
___ pM1 [IVB]: Distant metastasis
*Specify site(s), if known: _____

***Additional Pathologic Findings (select all that apply) (Note G)**
*___ None identified
*___ Condyloma acuminatum
*___ Squamous dysplasia
*___ Carcinoma in-situ
*___ Adenocarcinoma in-situ
*___ Atypical adenosis
*___ Other (specify): _____

***Comment(s)**

Explanatory Notes

A. Prenatal DES Exposure

Prenatal exposure to diethylstilbestrol (DES) or related synthetic drugs was relatively common in the United States and other countries until 1971, when its relation to clear cell adenocarcinomas of the vagina and cervix led to proscription of these drugs by the Food and Drug Administration. From the 1970s to the turn of the 21st century, most patients with clear cell adenocarcinoma of the vagina had a history of DES exposure.[1] As this cohort ages, the diagnosis has been less common, and most women with this diagnosis currently have no DES exposure history. Furthermore, it has been reported that these patients have significantly worse outcomes than do patients with history of DES exposure and patients with squamous cell carcinoma.[2] A bimodal age peak for DES-related carcinoma has, however, been recently reported, and therefore a history of this type of prenatal drug exposure should alert the pathologist to the possible presence of those tumors and associated lesions.[3,4]

B. Prior Tumors and Operations

A history of dysplasia, carcinoma in situ or invasive carcinoma of the cervix as well as knowledge of its microscopic features may be essential in the determination whether a subsequent vaginal tumor is a recurrent or new tumor. Also, a history of a carcinoma higher in the female genital tract may influence the interpretation of a neoplasm that is detected in a specimen from the vagina. Prior pathology slides and reports should be obtained and reviewed if a review is deemed essential by the clinician or pathologist for optimal pathologic evaluation of the present specimen.

C. Clinical Findings and DES Exposure

Naked-eye examination, colposcopy, and iodine staining of the cervix and vagina may disclose a variety of changes highly suspicious of prenatal diethylstilbestrol (DES) exposure, such as cervical hypoplasia, pseudopolyp, or coxcomb deformity, and vaginal adenosis or ridge, any of which should alert the pathologist to look carefully for DES changes.[4]

D. Bethesda Classification System of Cervical/Vaginal Cytology

For consistency in reporting, the cytologic classification proposed in The Bethesda System 2001 is recommended.[5] Although this protocol does not preclude the use of other systems of classification, use of the Papanicolaou class designation system is strongly discouraged.

Cervical/Vaginal Cytology Classification (The Bethesda 2001 System)

<u>Negative for Intraepithelial Lesion or Malignancy</u>

Organisms

- *Trichomonas vaginalis*
- Fungal organisms morphologically consistent with *Candida* spp
- Shift in flora suggestive of bacterial vaginosis
- Bacteria morphologically consistent with *Actinomyces* spp
- Cellular changes associated with Herpes simplex virus

Other non-neoplastic findings (optional to report, list not inclusive)
- Reactive cellular changes associated with
  - inflammation (includes typical repair)
  - irradiation
- Glandular cells status post hysterectomy
- Atrophy

Other

Epithelial Cell Abnormalities

Squamous cell
- Atypical squamous cells
  - of undetermined significance (ASC-US)
  - cannot exclude HSIL (ASC-H)
- Low grade squamous intraepithelial lesion (LSIL)[#] encompassing: HPV/mild dysplasia/vaginal intraepithelial neoplasia (VAIN) I
- High grade squamous intraepithelial lesion (HSIL) encompassing: moderate and severe dysplasia/ VAIN2/VAIN3/VACIS
  - with features suspicious for invasion (if invasion suspected)
- Squamous cell carcinoma

Glandular cell
- Atypical
  - glandular cells (NOS or specify in comment)
  - glandular cells, favor neoplastic
- Adenocarcinoma
  - not otherwise specified (NOS)

Other Malignant Neoplasms
- Specify

[#] Cellular changes of HPV cytopathic effect, previously termed “koilocytosis,” “koilocytotic atypia,” or “condylomatous atypia,” are included in the category of LSIL.

E. Histologic Type

The World Health Organization (WHO) classification and nomenclature of vaginal tumors is recommended because of its wide acceptance.[6] The most common subtype is squamous cell carcinoma. However, when such tumor simultaneously involves the cervix or the vulva and the vagina, the tumor is considered to originate from the cervix or vulva respectively with secondary extension to the vagina. Also, when an adenocarcinoma is present in the vagina, it is important to keep in mind that many of those tumors represent secondary involvement either by direct extension or metastases, more commonly from the endometrium, colorectal, ovary, vulva, urethra, and urinary bladder. Although not included in the current WHO classification, primary intestinal type adenocarcinoma has recently been described in the vagina.[7] These tumors usually arise in a background of benign adenomatous lesion. Awareness of this new subtype is necessary to avoid misdiagnosis of a metastatic colorectal adenocarcinoma.[7-9]

WHO Classification
Precancerous Lesions and Carcinomas of the Vagina (Modified)

Epithelial tumors		
Squamous tumors and precursors		
Squamous intraepithelial lesions	Vaginal intraepithelial neoplasia (VAIN)	
Mild dysplasia	VAIN 1	LSIL
Moderate dysplasia	VAIN 2	HSIL
Severe dysplasia	VAIN 3	HSIL
Carcinoma in situ	VAIN 3	HSIL
Squamous cell carcinoma, not otherwise specified		
Keratinizing		
Non-keratinizing		
Basaloid		
Verrucous		
Warty		
Glandular tumors		
Clear cell carcinoma		
Endometrioid adenocarcinoma		
Mucinous adenocarcinoma		
Mesonephric adenocarcinoma		
Other epithelial tumors		
Adenosquamous carcinoma		
Adenoid cystic carcinoma		
Adenoid basal carcinoma		
Carcinoid		
Small cell carcinoma		
Undifferentiated carcinoma		

F. Histologic Grade
No specific grading system for vaginal cancers is recommended. For the sake of uniformity, however, it is suggested that 3 grades be used, as shown below, with grades 1 to 3 assigned to carcinomas showing squamous or glandular differentiation.

Grade X	Cannot be assessed
Grade 1	Well differentiated
Grade 2	Moderately differentiated
Grade 3	Poorly differentiated
Grade 4	Undifferentiated

G. Other Lesions
Squamous dysplasia or carcinoma in situ, adenocarcinoma in situ, or atypical adenosis, particularly if such changes are at the resection margin, may increase the frequency of recurrent tumor. Also, few cases of primary invasive carcinoma of vagina have been reported to occur in association with severe vaginal prolapse.[10-12]

H. Staining of Mucosal Surface
Schiller's or Lugol's solutions stain glycogenated epithelium brown. Therefore, they stain glycogenated squamous epithelium and well-glycogenated tumors. The stains are useful in identifying sites of nonstaining vaginal adenosis or immature squamous metaplasia of

adenosis in patients exposed to diethylstilbestrol (DES), which may not be detectable before staining.

I. TNM and FIGO Stage Groupings

The TNM staging system for vaginal cancer endorsed by the American Joint Committee on Cancer (AJCC) and the International Union against Cancer (UICC),[13,14] and the parallel system formulated by the International Federation of Gynecology and Obstetrics (FIGO)[15] are recommended.

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.

TNM and FIGO Staging Systems for Vaginal Carcinoma

Primary Tumor (T)

TNM Category	FIGO Stage	Definition
TX	(--)	Primary tumor cannot be assessed
T0	(--)	No evidence of primary tumor
Tis	0	Carcinoma in situ
T1	I	Tumor confined to vaginal wall
T2	II	Tumor invades paravaginal tissues but not the pelvic wall[#]
T3	III	Tumor extends to pelvic wall
T4	IVA	Tumor invades mucosa of bladder or rectum and/or extends beyond the true pelvis (bullous edema is not sufficient to classify a tumor as T4)
(M1)	IVB	Distant metastasis (excludes peritoneal metastasis)

[#] Pelvic wall is defined as muscle, fascia, neurovascular structures, or skeletal portions of the bony pelvis.

Microinvasive/early carcinoma is not, currently, a recognized entity in the vagina, in contradistinction to the cervix, and the term is therefore not used. Superficially invasive tumors which invade 3 mm or less without lymphovascular invasion (LVI) have a low incidence of lymph node metastasis.[16]

Regional Lymph Nodes (N): TNM

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

Distant Metastasis (M): TNM

M0	No distant metastasis
M1	Distant metastasis

Stage Groupings

AJCC/UICC TNM				FIGO
Stage 0	Tis	N0	M0	Stage 0
Stage I	T1	N0	M0	Stage I
Stage II	T2	N0	M0	Stage II
Stage III	T1	N1	M0	Stage III
	T2	N1	M0	
	T3	N0, N1	M0	
Stage IVA	T4	Any N	M0	Stage IVA
Stage IVB	Any T	Any N	M1	Stage IVB

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 (i.e., 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 (e.g., 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.

Regional Lymph Nodes: Isolated Tumor Cells
Isolated tumor cells (ITC) are single cells or small clusters of cells not more than 0.2 mm in greatest dimension. Lymph nodes or distant sites with ITC found by either standard histologic examination, immunohistochemical stains (eg, cytokeratin), or nonmorphological techniques (eg, flow cytometry, DNA analysis, polymerase chain reaction [PCR] amplification of a specific tumor marker) should be so identified. There is currently no guidance in the literature as to how these patients should be coded; until further studies are available, they should be coded as “N1” with a comment noting how the cells were identified.

Sentinel Lymph Nodes
The sentinel lymph node is the first node to receive drainage from a primary tumor. There may be more than 1 sentinel node for some tumors. If a sentinel node contains metastatic tumor, it indicates that other more distant nodes may also contain metastatic disease. If sentinel nodes are negative, other regional nodes are less likely to contain metastasis.

J. Cervical Abnormalities
Ectropion (erosion, eversion) of the cervix, which is characterized by the appearance of glandular (columnar) epithelium outside the external os of the cervix, is seen in approximately 90% of women exposed to diethylstilbestrol (DES) in utero (but is often seen in nonexposed women as well). Approximately one-third of patients exposed to DES have 1 or more gross structural abnormalities of the cervix.[1,4]

K. Fallopian Tubes
The fallopian tubes are abnormal in some women exposed to diethylstilbestrol (DES) in the form of hypoplasia or defects demonstrated on hysterosalpingographic examination.[4]

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