Protocol for the Examination of Resection Specimens From Patients With Primary Carcinoma of the Vagina

Version: 4.3.0.0
Protocol Posting Date: June 2021
CAP Laboratory Accreditation Program Protocol Required Use Date: March 2022
The changes included in this current protocol version affect accreditation requirements. The new deadline for implementing this protocol version is reflected in the above accreditation date.

For accreditation purposes, this protocol should be used for the following procedures AND tumor types:

Procedure	Description
Resection	Includes vaginectomy
Tumor Type	**Description**
Carcinoma	Includes squamous cell carcinoma, adenocarcinoma and variants, carcinosarcoma, adenosarcoma, neuroendocrine carcinoma, mixed epithelial – neuroendocrine tumors, and germ cell tumors

This protocol is NOT required for accreditation purposes for the following:

Procedure
Biopsy (consider Vagina Biopsy protocol)
Primary resection specimen with no residual cancer (eg, following neoadjuvant therapy)
Cytologic specimens

The following tumor types should NOT be reported using this protocol:

Tumor Type
Lymphoma (consider the Hodgkin or non-Hodgkin Lymphoma protocols)
Sarcoma other than adenosarcoma (consider the Soft Tissue protocol)
Melanoma (consider using the cutaneous Melanoma protocol)

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With guidance from the CAP Cancer and CAP Pathology Electronic Reporting Committees.
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Accreditation Requirements

This protocol can be utilized for a variety of procedures and tumor types for clinical care purposes. For accreditation purposes, only the definitive primary cancer resection specimen is required to have the core and conditional data elements reported in a synoptic format.

- Core data elements are required in reports to adequately describe appropriate malignancies. For accreditation purposes, essential data elements must be reported in all instances, even if the response is "not applicable" or "cannot be determined."
- Conditional data elements are only required to be reported if applicable as delineated in the protocol. For instance, the total number of lymph nodes examined must be reported, but only if nodes are present in the specimen.
- Optional data elements are identified with "+" and although not required for CAP accreditation purposes, may be considered for reporting as determined by local practice standards.

The use of this protocol is not required for recurrent tumors or for metastatic tumors that are resected at a different time than the primary tumor. Use of this protocol is also not required for pathology reviews performed at a second institution (ie, secondary consultation, second opinion, or review of outside case at second institution).

Synoptic Reporting

All core and conditionally required data elements outlined on the surgical case summary from this cancer protocol must be displayed in synoptic report format. Synoptic format is defined as:

- Data element: followed by its answer (response), outline format without the paired Data element: Response format is NOT considered synoptic.
- The data element should be represented in the report as it is listed in the case summary. The response for any data element may be modified from those listed in the case summary, including "Cannot be determined" if appropriate.
- Each diagnostic parameter pair (Data element: Response) is listed on a separate line or in a tabular format to achieve visual separation. The following exceptions are allowed to be listed on one line:
    - Anatomic site or specimen, laterality, and procedure
    - Pathologic Stage Classification (pTNM) elements
    - Negative margins, as long as all negative margins are specifically enumerated where applicable
- The synoptic portion of the report can appear in the diagnosis section of the pathology report, at the end of the report or in a separate section, but all Data element: Responses must be listed together in one location

Organizations and pathologists may choose to list the required elements in any order, use additional methods in order to enhance or achieve visual separation, or add optional items within the synoptic report. The report may have required elements in a summary format elsewhere in the report IN ADDITION TO but not as replacement for the synoptic report ie, all required elements must be in the synoptic portion of the report in the format defined above.

Summary of Changes

v 4.3.0.0

- General Reformatting
- Updated Histologic Grade
- New WHO 5th Edition Histological Updates
- Revised Margins Section
- Revised Lymph Nodes Section
- Added Distant Metastasis Section
- Removed pTX and pNX Staging Classification
- Updated Wording for FIGO Stage
- Additional Findings Section Updated
- Added p53 and p16 Immunohistochemistry plus HPV-ISH to Special Studies Section
- Modified Procedure

Reporting Template

Protocol Posting Date: June 2021
Select a single response unless otherwise indicated.

CASE SUMMARY: (VAGINA: Resection)
Standard(s): AJCC-UICC 8, FIGO Cancer Report 2018

SPECIMEN (Note A)

Procedure
___ Local excision
___ Partial vaginectomy
___ Radical vaginectomy
___ Trachelectomy
___ Other (specify): _____
___ Not specified

TUMOR

Tumor Site (select all that apply)
___ Vagina, upper third: _____
___ Vagina, middle third: _____
___ Vagina, lower third: _____
___ Vagina, not otherwise specified: _____

Tumor Size
___ Greatest dimension in Centimeters (cm): _____ cm
+Additional Dimension in Centimeters (cm): ____ x ____ cm
___ Cannot be determined (explain): _____

Histologic Type (Note B)
___ Squamous cell carcinoma, HPV-associated
___ Squamous cell carcinoma, HPV-independent
___ Squamous cell carcinoma, NOS
___ Adenocarcinoma, NOS
___ Adenocarcinoma, HPV-associated
___ Adenocarcinoma, Skene, Cowper and Littre gland origin
___ Mucinous carcinoma, NOS
___ Mucinous carcinoma, gastric type
___ Mucinous carcinoma, intestinal type
___ Endometrioid carcinoma
___ Clear cell carcinoma
___ Mesonephric adenocarcinoma
___ Adenosquamous carcinoma
___ Adenoid basal carcinoma
___ Small cell neuroendocrine carcinoma
___ Large cell neuroendocrine carcinoma
___ Combined small cell neuroendocrine carcinoma
___ Combined large cell neuroendocrine carcinoma

___ Neuroendocrine tumor, NOS
___ Undifferentiated carcinoma
___ Mixed tumor NOS
___ Carcinosarcoma
___ Adenosarcoma
___ Germ cell tumor (specify): _____
___ Other histologic type not listed (specify): _____
___ Carcinoma, type cannot be determined
+Histologic Type Comment: _____

Histologic Grade (Note C)
___ G1, well differentiated
___ G2, moderately differentiated
___ G3, poorly differentiated
___ Other (specify): _____
___ GX, cannot be assessed: _____
___ Not applicable: _____

Site(s) Involved by Direct Tumor Extension (select all that apply)
Any organ not selected is either not involved or was not submitted.
___ Confined to vaginal wall
___ Involves subepithelial soft tissue
___ Involves the muscular wall
___ Paravaginal tissues
___ Pelvic sidewall
___ Vagina, lower third
___ Bladder mucosa#
___ Rectal mucosa#
___ Site(s) beyond true pelvis (specify): _____
___ Other organs / tissue (specify): _____
___ Cannot be determined (explain): _____
___ Not applicable
 # Mucosal surface of bladder or rectum must be involved

Lymphovascular Invasion
___ Not identified
___ Present
___ Cannot be determined (explain): _____

+Tumor Comment: _____

MARGINS

Margin Status for Invasive Carcinoma
 # High-grade squamous intraepithelial lesion (VaIN 2-3) or adenocarcinoma in situ (AIS) should be reported if present, even if margin is involved by invasive carcinoma.
___ All margins negative for invasive carcinoma#
+Closest Margin(s) to Invasive Carcinoma (select all that apply)
___ Peripheral (specify location, if possible): _____
___ Deep (specify location, if possible): _____
___ Other (specify): _____

___ Cannot be determined (explain): _____

+Distance from Invasive Carcinoma to Closest Margin
Specify in Millimeters (mm)
___ Exact distance: _____ mm
___ Greater than: _____ mm
___ At least: _____ mm
___ Less than: _____ mm
___ Less than 1 mm
___ Other (specify): _____
___ Cannot be determined: _____

___ Invasive carcinoma present at margin
Margin(s) Involved by Invasive Carcinoma (select all that apply)
___ Peripheral (specify location, if possible): _____
___ Deep (specify location, if possible): _____
___ Other (specify): _____
___ Cannot be determined (explain): _____
___ Other (specify): _____
___ Cannot be determined (explain): _____
___ Not applicable

Margin Status for HSIL (VaIN 2-3) or AIS (select all that apply)
___ All margins negative for high-grade squamous intraepithelial lesion (HSIL) and / or adenocarcinoma in situ (AIS)
___ High-grade squamous intraepithelial lesion (HSIL) present at margin
+Margin(s) Involved by HSIL (select all that apply)
___ Peripheral (specify location, if possible): _____
___ Other (specify): _____
___ Cannot be determined (explain): _____

___ Adenocarcinoma in situ (AIS) present at margin
+Margin(s) Involved by AIS (select all that apply)
___ Peripheral (specify location, if possible): _____
___ Other (specify): _____
___ Cannot be determined (explain): _____

___ Other (specify): _____
___ Cannot be determined (explain): _____
___ Not applicable

+Margin Comment: _____

REGIONAL LYMPH NODES

Regional Lymph Node Status

 # For the upper two-thirds of the vagina, the following are considered regional lymph nodes: pelvic NOS, parametrial, obturator, internal iliac (hypogastric), external iliac, common iliac, sacral, presacral, and para-aortic lymph nodes. For the lower third of the vagina, the following are considered regional lymph nodes: inguinal and femoral lymph nodes. Any involved non-regional nodes should be categorized as metastases (pM1) with a comment in the distant metastasis section. Presence of isolated tumor cells no greater than 0.2 mm in regional lymph node(s) is considered N0(i+).

___ Not applicable (no regional lymph nodes submitted or found)
___ Regional lymph nodes present
  ___ All regional lymph nodes negative for tumor cells
  ___ Tumor present in regional lymph node(s)

Number of Nodes with Tumor (excluding isolated tumor cells)

___ Exact number (specify): _____
___ At least (specify): _____
___ Other (specify): _____
___ Cannot be determined (explain): _____

Number of Nodes with Isolated Tumor Cells (0.2 mm or less)#

 # Reporting the number of lymph nodes with isolated tumor cells is required only in the absence of metastasis greater than 0.2 mm in other lymph nodes.

___ Not applicable
___ Exact number (specify): _____
___ At least (specify): _____
___ Cannot be determined (explain): _____

+Nodal Site(s) with Tumor (select all that apply)

Right lymph nodes

___ Right inguinal: _____
___ Right femoral: _____
___ Right pelvic: _____
___ Right parametrial: _____
___ Right obturator: _____
___ Right internal iliac: _____
___ Right external iliac: _____
___ Right presacral: _____
___ Right sacral: _____
___ Right para-aortic: _____
___ Other right lymph nodes (specify): _____

Left lymph nodes

___ Left inguinal: _____
___ Left femoral: _____
___ Left pelvic: _____
___ Left parametrial: _____
___ Left obturator: _____
___ Left internal iliac: _____
___ Left external iliac: _____
___ Left presacral: _____
___ Left sacral: _____
___ Left para-aortic: _____
___ Other left lymph nodes (specify): _____

Lymph nodes, laterality not specified
___ Inguinal, NOS: _____
___ Femoral, NOS: _____
___ Pelvic, NOS: _____
___ Parametrial, NOS: _____
___ Obturator, NOS: _____
___ Internal iliac, NOS: _____
___ External iliac, NOS: _____
___ Presacral, NOS: _____
___ Sacral, NOS: _____
___ Para-aortic, NOS: _____
___ Other (specify): _____
___ Cannot be determined: _____

Additional Lymph Node Findings (select all that apply)
___ None identified
___ Extranodal extension
___ Fixed / ulcerated nodes
___ Other (specify): _____
___ Cannot be determined: _____
___ Not applicable

___ Other (specify): _____
___ Cannot be determined (explain): _____

Number of Lymph Nodes Examined
___ Exact number (specify): _____
___ At least (specify): _____
___ Other (specify): _____
___ Cannot be determined (explain): _____

+Nodal Site(s) Examined (select all that apply)
Right lymph nodes
___ Right inguinal: _____
___ Right femoral: _____
___ Right pelvic: _____
___ Right parametrial: _____
___ Right obturator: _____
___ Right internal iliac: _____
___ Right external iliac: _____
___ Right presacral: _____
___ Right sacral: _____
___ Right para-aortic: _____
___ Other right lymph nodes (specify): _____
Left lymph nodes
___ Left inguinal: _____
___ Left femoral: _____
___ Left pelvic: _____
___ Left parametrial: _____
___ Left obturator: _____
___ Left internal iliac: _____

___ Left external iliac: _____
___ Left presacral: _____
___ Left sacral: _____
___ Left para-aortic: _____
___ Other left lymph nodes (specify): _____
Lymph nodes, laterality not specified
___ Inguinal, NOS: _____
___ Femoral, NOS: _____
___ Pelvic, NOS: _____
___ Parametrial, NOS: _____
___ Obturator, NOS: _____
___ Internal iliac, NOS: _____
___ External iliac, NOS: _____
___ Presacral, NOS: _____
___ Sacral, NOS: _____
___ Para-aortic, NOS: _____
___ Other (specify): _____
___ Cannot be determined: _____

+Regional Lymph Node Comment: _____

DISTANT METASTASIS

Distant Site(s) Involved, if applicable
___ Not applicable
___ Specify site(s): _____
___ Cannot be determined: _____

PATHOLOGIC STAGE CLASSIFICATION (pTNM, AJCC 8th ed.) (Note D)
Reporting of pT, pN, and (when applicable) pM categories is based on information available to the pathologist at the time the report is issued. As per the AJCC (Chapter 1, 8th Ed.) it is the managing physician's responsibility to establish the final pathologic stage based upon all pertinent information, including but potentially not limited to this pathology report.

TNM Descriptors (select all that apply)
___ Not applicable: _____
___ m (multiple primary tumors)
___ r (recurrent)
___ y (post-treatment)

pT Category
___ pT not assigned (cannot be determined based on available pathological information)
___ pT0: No evidence of primary tumor
pT1: Tumor confined to the vagina
___ pT1a: Tumor confined to the vagina, measuring less than or equal to 2.0 cm
___ pT1b: Tumor confined to the vagina, measuring greater than 2.0 cm
___ pT1 (subcategory cannot be determined)
pT2: Tumor invading paravaginal tissues but not to pelvic sidewall
___ pT2a: Tumor invading paravaginal tissues but not to pelvic wall, measuring less than or equal to 2.0 cm
___ pT2b: Tumor invading paravaginal tissues but not to pelvic wall, measuring greater than 2.0 cm
___ pT2 (subcategory cannot be determined)

 # Pelvic sidewall is defined as the muscle, fascia, neurovascular structures, or skeletal portions of the bony pelvis. On rectal examination, there is no cancer-free space between the tumor and pelvic sidewall. Tumor causing hydronephrosis or nonfunctioning kidney is an indirect indication of pelvic sidewall involvement

___ pT3: Tumor extending to the pelvic sidewall# and / or causing hydronephrosis or nonfunctioning kidney

Mucosal surface of bladder or rectum must be involved

___ pT4: Tumor invading the mucosa of the bladder or rectum## and / or extending beyond the true pelvis (bullous edema is not sufficient evidence to classify a tumor as T4)

pN Category

___ pN not assigned (no nodes submitted or found)
___ pN not assigned (cannot be determined based on available pathological information)
___ pN0: No regional lymph node metastasis
___ pN0(i+): Isolated tumor cells in regional lymph node(s) no greater than 0.2 mm
___ pN1: Pelvic or inguinal lymph node metastasis

pM Category (required only if confirmed pathologically)

___ Not applicable - pM cannot be determined from the submitted specimen(s)
___ pM1: Distant metastasis

FIGO STAGE

+FIGO Stage (2018 FIGO Cancer Report)

___ I: Tumor of any size confined to the vagina
___ II: Tumor of any size that invades paravaginal tissue but not the pelvic sidewall
___ III: Tumor extends to the pelvic sidewall and / or involves the lower third of the vagina and / or causes hydronephrosis or nonfunctioning kidney or T1-T3 tumor involving pelvic or inguinal lymph nodes (N1) but not distant sites
___ IV: Tumor extends beyond the true pelvis or involves the bladder and / rectal mucosa (bullous edema alone does not constitute stage IV)
___ IVA: Tumor invades bladder and / or rectal mucosa and / or extends beyond the true pelvis, regardless of lymph node involvement (any N)
___ IVB: Tumor of any size with spread to distant sites (M1), with or without involvement of adjacent structures (any T) or lymph nodes (any N)

ADDITIONAL FINDINGS (Note E)

Additional Findings (select all that apply)

___ None identified
___ High grade squamous intraepithelial lesion / vaginal intraepithelial neoplasia, grade 3 (VaIN3)
___ High grade squamous intraepithelial lesion / vaginal intraepithelial neoplasia, grade 2 (VaIN2)
___ Low grade squamous intraepithelial lesion / vaginal intraepithelial neoplasia, grade 1 (VaIN1)
___ Condyloma acuminatum
___ Adenocarcinoma in situ (AIS)
___ Atypical adenosis
___ Adenoma: _____
___ Other (specify): _____

SPECIAL STUDIES

+Ancillary Studies (specify) : _____

+p16 Immunohistochemistry
___ Positive
___ Negative
___ Other (specify): _____

COMMENTS

Comment(s): _____

Explanatory Notes

A. Procedure

Local excision (wide local excision) is employed primarily for smaller lesions and should have margins surgically oriented. A partial vaginectomy leaves a portion of the vagina intact as a conduit to drain menses (if the uterus is retained). Radical (complete) vaginectomy removes the entire vagina and may be part of infralevatoric exenteration, radical hysterectomy and/or bilateral lymphadenectomy. Trachelectomy (removal of the lower portion of the cervix along with the upper vagina) may be employed when the cervix is involved for fertility-sparing. The peripheral margin is the tumor resection margin with mucosa and may be designated as proximal and distal (upper vaginal / lower vaginal). The deep margin is the tumor resection margin with soft tissue and may be designated as anterior, posterior, right or left lateral vaginal wall.

Squamous cell carcinoma, the most frequent tumor, typically involves the posterior vagina, while adenocarcinoma almost exclusively involves the anterior vaginal wall. Both are most common in the upper 1/3 of the vagina.[1]

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 21 century, most patients with clear cell adenocarcinoma of the vagina had a history of DES exposure.[2] 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 a history of DES exposure and patients with squamous cell carcinoma.[3] A bimodal age peak for DES-related carcinoma has, however, been 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.[4,5]

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 DES in utero (but is often seen in unexposed women as well). Approximately one-third of patients exposed to DES have 1 or more gross structural abnormalities of the cervix.[2,5] The fallopian tubes are abnormal in some women exposed to DES in the form of hypoplasia or defects demonstrated on hysterosalpingographic examination.[5]

Third-generation exposure to DES is associated with decreased fertility, irregular menses, continued risk for clear cell adenocarcinoma, pregnancy mishaps such as preterm delivery, and psychosomatic disorders, indicating that DES adverse effects are genetically transmissible, possibly through epigenetics and transformation of protein 63 (TRP63.p63) that drives differentiation of Mullerian duct epithelium to squamous differentiation.[6,7,8]

Prior Tumors and Operations

A history of dysplasia, carcinoma in situ, or invasive carcinoma of the cervix, as well as knowledge of the tumor's microscopic features, may be essential to determine 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.

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 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.[5]

References

1. Lima M, Rio G, Horta M, Cunha TM. Primary vaginal malignancies: a single oncology centre experience. *J Obstet Gynecol*. 2019;39(6):827-832.
2. Herbst AL, Ulfelder H, Poskanzer DC. Adenocarcinoma of the vagina: association of maternal stilbestrol therapy with tumor appearance in young women. *N Engl J Med*. 1971;284:878-881.
3. Frank SJ, Deavers MT, Jhingran A, et al. Primary adenocarcinoma of the vagina not associated with diethylstilbestrol (DES) exposure. *Gynecol Oncol*. 2007;105:470-474.
4. Hanselaar A, van Loosbroek M, Schuurbiers O, et al. Clear cell adenocarcinoma of the vagina and cervix: an update of the central Netherlands registry showing twin age incidence peaks. *Cancer*. 1997;79:2229-2236.
5. Kaufman RH, Noller K, Adam E, et al. Upper genital tract abnormalities and pregnancy outcome in diethylstilbestrol-exposed progeny. *Am J Obstet Gynecol*. 1984;148:973-984.
6. Clement R, Guilbaud E, Barrios L, Rouge-Maillart C, Jousset N, Rodat O. DES daughters in France: experts' points of view on the various genital, uterine and obstetric pathologies, and in utero DES exposure. *Med Sci Law*. 2014;54(4):219-29.
7. Titus L, Hatch EE, Drake KM, et al. Reproductive and hormone-related outcomes in women whose mothers were exposed to in utero diethylstilbestrol (DES): a report from the UN National Cancer Institute DES Third Generation Study. *Reprod Toxicol*. 2019;84:32-38.
8. Laronda MM, Unno K, Butler LM, Kurita T. The development of cervical and vaginal adenosis as a result of diethylstilbestrol exposure in utero. *Differentiation*. 2012;84(3):252-60.

B. Histologic Type

The protocol adheres to the standardized terminology proposed by the World Health Organization (WHO) classification of malignant and premalignant vaginal epithelial tumors.[1] This protocol is also used for adenosarcoma. The most common tumor 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, with secondary extension to the vagina. Categorization of squamous cell carcinoma has been simplified into HPV-associated and HPV-independent types based upon their pathogenesis. If this association is unknown or unable to be determined, "not otherwise specified (NOS)" is appropriate. Former descriptive terms such as "warty", "basaloid", "verrucous" and "papillary" are no longer necessary components of the histologic type. Adjacent squamous intraepithelial lesions, the putative precursors, are a helpful clue to subtype. For HPV-associated precursors, low grade or high grade squamous intraepithelial lesion (SIL) is the preferred terminology but vaginal intraepithelial lesion (VaIN) may also be used, with appropriate grades 1, 2 or 3 (eg. VaIN2). Microinvasive / superficially invasive carcinoma is not a recognized entity in the vagina, and thus the term is not used.

If adenocarcinoma is present in the vagina, it is important to remember that many of those tumors represent secondary involvement either by direct extension or metastases, most commonly from the endometrium, colorectum, ovary, vulva, urethra, or urinary bladder. Although rare, primary intestinal-type mucinous (adeno)carcinoma has been described in the vagina.[2,3] These tumors usually arise in a background of a benign adenomatous lesion or polyp. Awareness of this subtype is necessary to avoid misdiagnosis of a metastatic colorectal adenocarcinoma.[3,4,5] Primary gastric-type adenocarcinoma is also rare and usually associated with non-DES vaginal adenosis. The most differentiated form was previously known as "adenoma malignum" or "minimal deviation adenocarcinoma" but these tumors are now recognized as part of a spectrum of malignancy with gastric-type epithelium under the rubric of mucinous

carcinoma, gastric-type. It has features identical to this entity in the cervix.[6,7] The tall columnar cells are characterized by abundant pale pink cytoplasm, distinct cell borders, basal nuclei and often minimal nuclear atypia, with immunoreactivity for MUC6 (more specific) and HIK1083, and mutation-type p53 patterns.[8] It is not associated with HPV or DES. p16 is block-like; ER and PR are generally nonreactive. Goblet and neuroendocrine cells may be present. Glandular patterns of invasion are subtle, typically lack stromal reaction, and are characterized by haphazardly arranged “claw-like” glands deep in the stroma, with focal or extensive glandular dilatation.[8]

The very rare adenocarcinoma of Skene gland origin mimics prostatic adenocarcinoma and is reactive with prostatic markers.[9] Equally rare is mesonephric adenocarcinoma, which is typically para-urethral and characterized by a diversity of architectural patterns within the tumor. They are presumed to arise from vaginal mesonephric remnants and thus are most often located in the lateral vaginal wall.[9,10]

Neuroendocrine tumor are extremely rare in the gynecologic tract other than ovary or cervix. The “combined” category must include the presence of a non-neuroendocrine carcinoma along with a neuroendocrine tumor.

References

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3. Ditto A, Martinelli F, Carcangiu ML, et al. Incidental diagnosis of primary vaginal adenocarcinoma of intestinal type: a case report and review of the literature. *Int J Gynecol Pathol*. 2007;26(4):490-493.
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C. Histologic Grade

A wide variety of grading systems, including some that evaluate only the extent of cellular differentiation and others that assess additional features such as the appearance of the tumor margin, the extent of inflammatory cell infiltration, and vascular invasion, have been used for squamous cell carcinoma of the cervix. However, there is no consensus emerging from the literature that any of these systems are reproducible or that they provide useful prognostic information. Similar problems arise with grading adenocarcinoma. Therefore, no specific grading system for vaginal cancers is recommended.

For the sake of uniformity, 3 grades may be used, as shown below, with the understanding that these have not been clinically validated. Grades 1 to 3 are assigned to carcinoma showing squamous or glandular differentiation; undifferentiated carcinoma is not graded (not applicable).

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

D. Pathologic Stage Classification

The TNM staging system of the American Joint Committee on Cancer (AJCC) for carcinoma of the vulva is recommended.[1,2] FIGO staging is desirable but optional.[3]

By AJCC 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 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

T Category Considerations
Lymphovascular Invasion (LVI) indicates whether microscopic lymphovascular invasion is identified. LVI includes lymphatic invasion, vascular invasion, or lymphovascular invasion. By AJCC convention, LVI does not affect the T category indicating local extent of tumor unless specifically included in the definition of a T category.

N Category Considerations
Regional lymph nodes in vaginal resections are based on vaginal lymphatic drainage. For the upper two-thirds of the vagina, the following are considered regional lymph nodes: pelvic, parametrial, obturator, internal iliac (hypogastric), external iliac, common iliac, sacral, presacral, and para-aortic. For the lower third of the vagina, the following are considered regional lymph nodes: inguinal and femoral. Any involved nonregional nodes should be categorized as metastases (pM1) with a comment on their location in the distant metastasis section.

Isolated tumor cells (ITCs) are single cells or small clusters of cells not more than 0.2 mm in greatest dimension. Reporting the number of lymph nodes with isolated tumor cells is required only in the absence of metastasis greater than 0.2 mm in other lymph nodes. Lymph nodes or distant sites with ITCs found by either histologic examination (eg, immunohistochemical evaluation for 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 more data are available, they should be coded as “N0(i+)” with a comment noting how the cells were identified.

Sentinel lymph node evaluation is undergoing investigation in early stage vaginal carcinoma but is not widely employed.[4,5,6] Sentinel nodes may be reported under “other, specify” with the site.

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E. 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. A few cases of primary invasive carcinoma of vagina have been reported to occur in association with severe vaginal prolapse.[1,2,3]

References
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