



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

Version: 4.3.0.0

Protocol Posting Date: June 2021

The use of this protocol is recommended for clinical care purposes but is not required for accreditation purposes.

This protocol may be used for the following procedures AND tumor types:

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

The following should NOT be reported using this protocol:

Procedure
Resection (consider the Vagina Resection protocol)
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

The use of this case summary is recommended for clinical care purposes but is not required for accreditation purposes. The core and conditional data elements are routinely reported. Non-core data elements are indicated with a plus sign (+) to allow for reporting information that may be of clinical value.

Summary of Changes**v 4.3.0.0**

- General Reformatting
- Updated Histologic Grade
- New WHO 5th Edition Histological Updates
- Revised Margins Section
- Additional Findings Section Updated
- Added p53 and p16 Immunohistochemistry plus HPV-ISH to Special Studies Section
- Elements that are recommended for clinical care purposes are designated as Core and Conditional (indicated by bolded text), while Non-core elements are now indicated with a plus (+) sign

Reporting Template

Protocol Posting Date: June 2021

Select a single response unless otherwise indicated.

CASE SUMMARY: (VAGINA: Biopsy)

This case summary is recommended for reporting biopsy specimens, but is not required for accreditation purposes.

SPECIMEN

Procedure (Note [A](#))

- Incisional biopsy
- Other (specify): _____
- Not specified

TUMOR

Tumor Site

- Vagina, upper third
- Vagina, middle third
- Vagina, lower third
- Vagina, not otherwise specified

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: _____

+Tumor Extent

- ___ Subepithelial stromal invasion
- ___ Muscle invasion
- ___ Other (specify): _____
- ___ Cannot be determined: _____

+Tumor Comment: _____

MARGINS

+Margin Status

- ___ All margins negative for tumor
- ___ Tumor present at margin

+Margin(s) Involved by Tumor

- ___ Specify involved margin(s): _____
- ___ Cannot be determined: _____
- ___ Cannot be determined: _____
- ___ Not applicable: _____

+Margin Comment: _____

ADDITIONAL FINDINGS

Additional Findings (Note D) (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 1/3rd 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 21st 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

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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 "wartlike", "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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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. Other Lesions

Squamous dysplasia or carcinoma in situ, adenocarcinoma in situ, adenomatous lesions 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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