



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

Version: Vagina Biopsy 4.2.0.0

Protocol Posting Date: August 2019

Accreditation Requirements

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, neuroendocrine carcinoma, and mixed epithelial – neuroendocrine 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 (consider the Soft Tissue protocol)

Authors

Saeid Movahedi-Lankarani, MD*; Uma Krishnamurti, MD, PhD*; Debra A. Bell, MD; George G. Birdsong, MD; Charles V. Biscotti, MD; Christopher N. Chapman Jr, MD; Dina H. Kandil, MD; Veronica Klepeis, MD, PhD; Anthony G. Montag, MD; Christopher N. Otis, MD

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

* Denotes primary authors. All other contributing authors are listed alphabetically.

Summary of Changes

Version 4.2.0.0

Resection and biopsy case summaries separated into discrete cancer protocols

Surgical Pathology Cancer Case Summary

Protocol posting date: August 2019

VAGINA: Biopsy**Note: This case summary is recommended for reporting biopsy specimens, but is not required for accreditation purposes. Core data elements are bolded to help identify routinely reported elements.****Select a single response unless otherwise indicated.****Procedure (Note A)**

- Incisional biopsy
 Other (specify): _____
 Not specified

Tumor Site

- Vagina, upper third
 Vagina, middle third
 Vagina, lower third
 Not specified

Histologic Type (Note B)

- Squamous cell carcinoma, NOS
 Squamous cell carcinoma, keratinizing
 Squamous cell carcinoma, nonkeratinizing
 Squamous cell carcinoma, basaloid
 Squamous cell carcinoma, verrucous
 Squamous cell carcinoma, warty
 Squamous cell carcinoma, papillary
 Adenocarcinoma, NOS
 Mucinous carcinoma, NOS
 Endometrioid carcinoma
 Clear cell carcinoma
 Mesonephric carcinoma
 Adenosquamous carcinoma
 Adenoid basal carcinoma
 Small cell neuroendocrine carcinoma
 Large cell neuroendocrine carcinoma
 Undifferentiated carcinoma
 Carcinosarcoma
 Other histologic type not listed (specify): _____
 Carcinoma, type cannot be determined

*Note: Microinvasive/superficial invasive carcinoma is not currently a recognized entity in the vagina, and thus the term is not used.***Histologic Grade (Note C)**

- G1: Well differentiated
 G2: Moderately differentiated
 G3: Poorly differentiated
 G4: Undifferentiated
 Other (specify): _____
 GX: Cannot be assessed
 Not applicable

Tumor Extension

- Stromal invasion
- Muscle invasion
- Cannot be assessed

Margins

- Not applicable
 - Cannot be assessed
 - Uninvolved by tumor
 - Involved by tumor
- Specify site: _____

Additional Pathologic Findings (select all that apply) (Note D)

- None identified
- High-grade squamous intraepithelial neoplasia (VAIN 2-3)
- Low-grade squamous intraepithelial neoplasia (VAIN 1)
- Condyloma accuminatum
- Adenocarcinoma in situ (AIS)
- Atypical adenosis
- Other (specify): _____

Comment(s)

Explanatory Notes

A. Procedure

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}

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 nonexposed women as well). Approximately one-third of patients exposed to DES have 1 or more gross structural abnormalities of the cervix.^{1,4}

The fallopian tubes are abnormal in some women exposed to DES in the form of hypoplasia or defects demonstrated on hysterosalpingographic examination.⁴

References

1. 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.
2. 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.
3. Hanselaar A, van Loosbroek M, Schuurbiens 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.
4. 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.

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 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.

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.¹

References

1. 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.

B. Histologic Type

The World Health Organization (WHO) classification and nomenclature of vaginal tumors is recommended because of its wide acceptance.¹ 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, 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.² 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.²⁻⁴

WHO Classification¹

Precancerous Lesions and Carcinomas of the Vagina (Modified)

Epithelial Tumors

Squamous tumors and precursors

Squamous intraepithelial lesions (SIL)	Vaginal intraepithelial neoplasia (VAIN)
Low-grade SIL (LSIL)	VAIN 1
High-grade SIL (HSIL)	VAIN 2-3

Squamous cell carcinoma, not otherwise specified

- Keratinizing
- Nonkeratinizing
- Papillary
- Basaloid
- Verrucous
- Warty

Glandular tumors

- Clear cell carcinoma
- Endometrioid adenocarcinoma
- Mucinous adenocarcinoma
- Mesonephric adenocarcinoma

High-grade neuroendocrine carcinoma

- Small cell neuroendocrine carcinoma
- Large cell neuroendocrine carcinoma

Other epithelial tumors

- Adenosquamous carcinoma
- Adenoid basal carcinoma
- Undifferentiated carcinoma

References

1. Kurman RJ, Carcangiu ML, Harrington CS, Young RH, eds. *WHO Classification of Tumors of the Female Reproductive Organs*. Geneva, Switzerland: WHO Press; 2014. World Health Organization Classification of Tumors. 4th edition
2. Tjalma WA, Colpaert CG. Primary vaginal adenocarcinoma of intestinal type arising from a tubulovillous adenoma. *Int J Gynecol Cancer*. 2006;16:1461-1465.
3. Mudhar HS, Smith JH, Tidy J. Primary vaginal adenocarcinoma of intestinal type arising from an adenoma: case report and review of the literature. *Int J Gynecol Pathol*. 2001;20:204-209.
4. 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;26:490-493.

C. 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

D. 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.¹⁻³

References

1. Iavazzo C, Vorgias G, Vecchini G, et al. Vaginal carcinoma in a completely prolapsed uterus: a case report. *Arch Gynecol Obstet.* 2007;275:503-505.
2. Batista TP, Morais JA, Reis TJ, et al. A rare case of invasive vaginal carcinoma associated with vaginal prolapse. *Arch Gynecol Obstet.* 2009;280(5):845-848.
3. Gupta N, Mittal S, Dalmia S, et al. A rare case of primary invasive carcinoma of vagina associated with irreducible third degree uterovaginal prolapse. *Arch Gynecol Obstet.* 2007; 276:563-4.