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

Protocol applies to all invasive carcinomas of the vulva.

Based on AJCC/UICC TNM, 7th edition, and FIGO 2008 Annual Report
Protocol web posting date: October 2009

Procedures
- Excisional Biopsy
- Vulvectomy (With or Without Removal of Other Organs and Tissues)

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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

VULVA: Excisional Biopsy, Resection

Select a single response unless otherwise indicated.

Specimen (select all that apply) (Note A)
___ Vulva
___ Other (specify): _____
___ Not specified

Procedure
___ Local excision
___ Wide excision
___ Partial vulvectomy
___ Total vulvectomy
___ Radical vulvectomy
___ Other (specify): _____
___ Not specified

Lymph Node Sampling (select all that apply)
___ Not applicable
___ Sentinel lymph node biopsy
___ Inguinal-femoral nodes
___ Pelvic nodes
___ Other (specify): _____

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

Tumor Site (select all that apply)
___ Right vulva
    *___ Labium majus
    *___ Labium minus
___ Left vulva
    *___ Labium majus
    *___ Labium minus
___ Clitoris
___ Other (specify): _____
___ Not specified

* 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.

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

Tumor Focality
___ Unifocal
___ Multifocal
___ Cannot be determined (see Comment)
___ Not specified

Histologic Type (select all that apply) (Notes C and D)
___ Squamous cell carcinoma
- *___ Keratinizing
- *___ Nonkeratinizing
- *___ Basaloid
- *___ Warty
- *___ Verrucous
- *___ Other (specify):

___ Glandular tumors
- *___ Paget disease
- *___ Bartholin gland tumors
  - *___ Adenocarcinoma
  - *___ Squamous cell carcinoma
  - *___ Adenoid cystic carcinoma
  - *___ Adenosquamous carcinoma
  - *___ Transitional cell carcinoma
  - *___ Small cell carcinoma
- *___ Adenocarcinoma of mammary gland type
- *___ Adenocarcinoma of Skene gland origin
- *___ Malignant sweat gland tumors

___ Other (specify): _____
___ Carcinoma, type cannot be determined (see Comment)

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

Microscopic Tumor Extension (Note E)
Depth of invasion: ___ mm
___ Cannot be determined (see Comment)
___ Other (specify): _____

* 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.

***Tumor Border (Note F)**
*___ Pushing
*___ Infiltrating

Margins (select all that apply)
___ Cannot be determined (see Comment)
___ Uninvolved by invasive carcinoma
Distance of invasive carcinoma from closest margin: ___ mm
Specify margin, if possible: _____
___ Carcinoma in situ not identified at margin
___ Carcinoma in situ present at margin
___ Involved by invasive carcinoma
Specify margin(s): _____

Lymph-Vascular Invasion (Note G)
___ Not identified
___ Present
___ Cannot be determined (see Comment)

Lymph Nodes (Note H)
Number of lymph nodes examined: ____
Number of lymph nodes with metastasis: ____
Number of lymph nodes with metastasis(es) <5 mm: ____
Number of lymph nodes with metastasis(es) ≥5 mm: ____

Extranodal extension:
___ Present
___ Not identified
___ Cannot be determined (see Comment)

Fixed or ulcerated femoral-inguinal lymph nodes:
___ Present
___ Not identified
___ Cannot be determined (see Comment)

Laterality:
___ Unilateral
___ Bilateral

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
___ pT1 [FIGO IA]: Lesions ≤2 cm in size, confined to the vulva or perineum, and with stromal invasion ≤1.0 mm
___ pT2 [FIGO IB]: Lesions >2 cm in size or any size with stromal invasion >1.0 mm, confined to the vulva or perineum
___ pT3 [FIGO II]: Tumor of any size with extension to adjacent perineal structures (lower/distal 1/3 urethra, lower/distal 1/3 vagina, anal involvement)
___ pT4 [FIGO IVA]: Tumor invades any of the following: upper/proximal 2/3 of urethra, upper/proximal 2/3 vagina, bladder mucosa, rectal mucosa, or fixed to pelvic bone

Regional Lymph Nodes (pN) (select all that apply)
___ pNX: Cannot be assessed
___ pN0: No regional lymph node metastasis
___ pN1 [FIGO III]: Positive regional lymph nodes
    ___ pN1 [FIGO IIIA]: 1 node metastasis ≥5 mm
    ___ pN1 [FIGO IIIA]: 1-2 lymph node metastasis(es) <5 mm
___ pN2 [FIGO IIIB]:
    ___ 2 or more lymph node metastases ≥5 mm
    ___ 3 or more lymph node metastases<5 mm
___ pN3 [FIGO IIIC]: Lymph node(s) with extracapsular spread
___ pN4 [FIGO IVA]: Fixed or ulcerated femoral-inguinal lymph nodes

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

***Additional Pathologic Findings (select all that apply) (Note I)**
*___ None identified
*___ Dysplasia
*___ Condyloma accuminatum
*___ Vulvar intraepithelial neoplasia (VIN) 3 (severe dysplasia/carcinoma in situ)
*___ Other (specify): _____

***Comment(s)**

Explanatory Notes

A. Suggestions for Sampling of Tissue Removed for Diagnosis or Treatment of Vulvar Carcinoma

Tumor
Sections taken will vary with procedure, as designated by surgeon.[1] Sections to include the following should be taken (if appropriate):

- Tumor, representative sections, including site of deepest invasion and interface of tumor with adjacent epithelium
- Resection margins
- Sections of abnormal epithelium or other tissue remote from tumor
- Sections of areas(s) marked by surgeon
- Sections of prior biopsy or resection site of tumor if no tumor present grossly

Lymph Nodes
The femoral and inguinal lymph nodes are the sites of regional spread.[1,2] When inguinal-femoral lymphadenectomy is performed, 6 or more lymph nodes will normally be included.[1,2] One or more sections of all lymph nodes identified should be taken, depending on presence or absence of gross tumor as well as size of lymph node. In addition, sections to confirm presence or absence of extranodal extension should be taken.

Other Organs and Tissues
Other organs and tissues may be submitted with the vulva specimen. Sections to include the following should be taken (if appropriate):

- Sections to demonstrate presence or absence of tumor
- Sections to demonstrate its relation, if present, to vulvar tumor (contiguous or metastastic
- Sections of other lesions, if present
- Resection margins

If frozen section analysis was performed, those tissue fragment(s) should be submitted.

B. Thickness of Tumor
The thickness of a squamous cell carcinoma is measured in millimeters from the surface of the tumor or, if there is surface keratinization, from the bottom of the granular layer to the deepest point of invasion.[3,4]

C. Etiology/Pathogenesis[5-7]
Two pathways have been elucidated in the pathogenesis of invasive vulvar carcinoma. The first pathway involves classic vulvar intraepithelial neoplasia (VIN), which is associated with high-grade human papillomavirus (HPV) subtypes (16 >18), and is histologically similar to dysplasia seen in the cervix. It tends to be multifocal and more common in younger women, with a relatively low risk of progression into an invasive squamous cell carcinoma. It is diffusely positive with p16 (reflecting HPV association) and is negative with p53. The associated invasive component is basaloid or warty in morphology. The second pathway is referred to as differentiated VIN (VIN simplex). VIN simplex is not associated with HPV, but instead with vulvar dystrophy such as that seen in the context of lichen sclerosus or squamous hyperplasia. The morphologic features

are more subtle, with atypia noted in the parabasal cells. The associated invasive component is keratinizing and can be associated with p53 mutations. This subtype usually occurs in older women. Most recently, cutaneous HPV subtypes (5,8) were found to be associated with this form.[8] Of note, overlap does exist between the two pathways, with some tumors exhibiting morphologic and/or clinical features of each.

	Keratinizing Squamous Carcinoma	**Basaloid Squamous Carcinoma**
Prevalence	More common (approximately 80%)	Less common (approximately 20%)
Age	Older females	Younger females
Distribution	Usually unifocal, may be multifocal	Often multifocal
Association with multifocal lower genital tract neoplasia	Rare	Common
Morphology	Keratinizing	Warty
Associated vulvar intraepithelial neoplasia (VIN)	Uncommon: differentiated type	Common: classic type
Association with HPV	Yes, beta (cutaneous)[8] 5,8	Yes, alpha 16>18
Association with vulvar dystrophy	Common	Rare
Immunohistochemistry	p53: Some cases positive p16: Negative or focally positive at stromal interface	p53: Negative p16: Positive

Adapted from McCluggage.[5]

D. Histologic Type

The following is an abbreviated, slightly modified version of the World Health Organization (WHO) classification of histologic types of malignant and premalignant vulvar epithelial tumors[3,9]:

WHO Classification of Vulvar Epithelial Tumors and Related Lesions

Squamous Lesions

Intraepithelial neoplasia (VIN)
- Mild dysplasia (VIN 1)
- Moderate dysplasia (VIN 2)
- Severe dysplasia (VIN 3)
- Carcinoma in situ (VIN 3)

Squamous cell carcinoma
- Keratinizing
- Nonkeratinizing
- Basaloid
- Warty
- Verrucous

Keratoacanthoma-like
Variant with tumor giant cells
Others
Basal cell carcinoma

Glandular Lesions
Paget disease
Bartholin gland tumors
Adenocarcinoma
Squamous cell carcinoma
Adenoid cystic carcinoma
Adenosquamous carcinoma
Transitional cell carcinoma
Small cell carcinoma
Adenocarcinoma of mammary gland type
Adenocarcinoma of Skene gland origin
Malignant sweat gland tumors
Adenocarcinomas of other types

E. Depth of Invasion

The depth of invasion of squamous cell carcinoma is defined as the measurement in millimeters from the epithelial-stromal junction of the adjacent most superficial dermal papilla to the deepest point of invasion.[2-4]

F. Tumor Growth Pattern

Vulvar squamous cell carcinomas can generally be separated into those tumors that have a predominately infiltrating (fingerlike) pattern and those that invade with a broad, pushing front (verrucous carcinoma). In some studies, infiltrating invasion is associated with a higher frequency of regional lymph node metastasis and should be noted in the report.[10]

G. Lymphatic/Blood Vessel Invasion

Vascular space invasion by squamous cell carcinoma has been associated with a poorer prognosis, including a risk factor for regional lymph node metastasis, and should be noted in the report.[11-13]

H. Extranodal Extension/Nodal Replacement

Both extranodal extension as well as the size of lymph node metastasis have been shown to reflect prognosis and should be noted in the report.[2,12,14,15]

I. TNM and International Federation of Gynecology and Obstetrics (FIGO) Stage Groupings

The TNM staging system of the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC) for carcinoma of the vulva is recommended and is shown below.[2,16] Comparison with FIGO staging is also shown.[17,18]

According to 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 infeasible) 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 Vulvar Carcinoma

Primary Tumor (T)

TNM Categories	FIGO Stages	
TX		Primary tumor cannot be assessed
T1	IA	Lesions ≤2 cm in size, confined to the vulva or perineum and with stromal invasion ≤1.0 mm*
T2	IB	Lesions >2 cm in size **or** any size with stromal invasion >1.0 mm, confined to the vulva or perineum
T3	II	Tumor of any size with extension to adjacent perineal structures (lower/distal 1/3 urethra, lower/distal 1/3 vagina, anal involvement)
T4	IVA	Tumor invades any of the following: upper/proximal 2/3 of urethra, upper/proximal 2/3 vagina, bladder mucosa, rectal mucosa, or fixed to pelvic bone

**Note:* The depth of invasion is defined as the measurement of the tumor from the epithelial-stromal junction of the adjacent most superficial dermal papilla to the deepest point of invasion.

Regional Lymph Nodes (N)

NX		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N1	III	Positive regional lymph nodes
N1	IIIA	1 lymph node metastasis ≥5 mm
		or
N1	IIIA	1-2 lymph node metastasis(es) <5 mm
N2	IIIB	2 or more lymph node metastases ≥5 mm
		or
N2	IIIB	3 or more lymph node metastases (<5 mm)
N3	IIIC	Lymph node(s) with extracapsular spread
N4	IVA	Fixed or ulcerated femoral-inguinal lymph nodes

An effort should be made to describe the site and laterality of lymph node metastases.

Distant Metastasis (M)

M0		No distant metastasis
M1	IVB	Distant metastasis (including pelvic lymph node metastasis)

Anatomic Stage/Prognostic Groups

Stage I	T1-2	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage II	T3	N0	M0
Stage III	T1-T3	N1-3	M0
Stage IIIA	T1-3	N1	M0
Stage IIIB	T1-3	N2	M0
Stage IIIC	T1-3	N3	M0
Stage IVA	T4	Any N	M0
Stage IVA	Any T	N4	M0
Stage IVB	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 after 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 before 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

Lymph-vascular invasion (LVI) indicates whether microscopic lymph-vascular invasion is identified. LVI includes lymphatic invasion, vascular invasion, or lymph-vascular invasion. According to 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.

Sentinel Lymph Nodes

The sentinel lymph node is the first node to receive drainage from a primary tumor. There may be more than one 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.[1,13]

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