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 2014 Annual Report

Protocol web posting date: January 2016

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

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CAP Vulva Protocol Revision History

Version Code
The definition of version control and an explanation of version codes can be found at www.cap.org (search: cancer protocol terms).

Version: Vulva 3.2.0.0

Summary of Changes
The following changes have been made since the November 2011 release.

The following data elements were modified:
- Histologic Type
- Microscopic Tumor Extension
- Margins
- Primary Tumor (pT)
- Regional Lymph Nodes (pN)
- Distant Metastasis (changed to required only if confirmed pathologically)
- Additional Pathologic Findings

The following data element was added:
- FIGO Stage

The following data element was deleted:
- Specimen Size
- Lymph Nodes
CAP Approved Gynecologic • Vulva

Surgical Pathology Cancer Case Summary

Protocol web posting date: January 2016

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): ____________________________

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

Tumor Size (Note B)
Greatest dimension: ___ cm
+ Additional dimensions: ___ x ___ cm
___ Cannot be determined (explain): ____________________________

Tumor Focality
___ Unifocal
___ Multifocal
___ Cannot be determined (explain): ____________________________
___ Not specified

Data elements preceded by this symbol 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) (Notes C and D)
___ Superficial invasive squamous cell carcinoma (SISSCA)
___ Squamous cell carcinoma
    ___ Keratinizing
    ___ Non-keratinizing
    ___ Basaloid
    ___ Warty
    ___ Verrucous
___ Paget disease
___ Bartholin gland tumors
    ___ Adenocarcinoma
    ___ Squamous cell carcinoma
    ___ Adenoid cystic carcinoma
    ___ Adenosquamous carcinoma
    ___ Transitional cell carcinoma
___ Adenocarcinoma of mammary gland type
___ Adenocarcinoma of Skene gland origin
___ Malignant sweat gland tumor
___ Small cell neuroendocrine carcinoma
___ Large cell neuroendocrine carcinoma
___ Merkel cell carcinoma
___ Other (specify): ____________________________
___ Carcinoma, type cannot be determined (explain): ____________________________

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 (explain): ____________________________

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

Margins (select all that apply)
___ Cannot be determined (explain): ____________________________
___ Uninvolved by invasive carcinoma
    Distance of invasive carcinoma from closest margin: ___ mm
    Specify margin: ____________________________
___ Involved by invasive carcinoma
    Specify margin(s):
    ___ Uninvolved by high-grade squamous intraepithelial lesion (VIN 2-3)
    ___ Involved by high-grade squamous intraepithelial lesion (VIN 2-3)
    Specify margin(s):
___ Uninvolved by vulvar intraepithelial neoplasia, differentiated type
___ Involved by vulvar intraepithelial neoplasia, differentiated type
    Specify margin(s): ____________________________
Lymph-Vascular Invasion (Note G)
___ Not identified
___ Present
___ Cannot be determined (explain): ________________________________

Pathologic Staging (pTNM) (Note H)

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

Primary Tumor (pT)
___ pTX: Primary tumor cannot be assessed
___ pT0: No evidence of primary tumor
___ pTis: High-grade squamous intraepithelial lesion (carcinoma in situ, VIN 2-3, preinvasive carcinoma)
___ pT1a: Lesions 2 cm or less in size, confined to the vulva or perineum, and with stromal invasion 1.0 mm or less
___ pT1b: Lesions more than 2 cm in size or any size with stromal invasion more than 1.0 mm, confined to the vulva or perineum
___ pT2: Tumor of any size with extension to adjacent perineal structures (lower/distal one-third urethra, lower/distal one-third vagina, anal involvement)
___ pT3: Tumor of any size with extension to any of the following: upper/proximal two-thirds of urethra, upper/proximal two-thirds vagina, bladder mucosa, rectal mucosa, or fixed to pelvic bone

Regional Lymph Nodes (pN) (select all that apply)

+ Modifier
+ ___ (sn)
+ ___ (sn)(i-)
+ ___ (sn)(i+)

Category (pN)
___ pNX: Regional lymph nodes cannot be assessed
___ pN0: No regional lymph node metastasis
___ pN1: 1 or 2 regional lymph nodes with the following features
___ pN1a: 1 or 2 lymph node metastasis each 5 mm or less
___ pN1b: 1 lymph node metastasis 5 mm or greater
___ pN2: Regional lymph node metastasis with the following features
___ pN2a: 3 or more lymph node metastases each less than 5 mm
___ pN2b: 2 or more lymph node metastases 5 mm or greater
___ pN2c: Lymph node metastasis with extracapsular extension
___ pN3: Fixed or ulcerated regional lymph node metastasis

___ No nodes submitted or found

Inguinal lymph nodes:
___ No inguinal nodes submitted or found

Number of Inguinal Lymph Nodes Examined
Specify number of right inguinal lymph nodes: _____
Specify number of left inguinal lymph nodes: _____
___ Number cannot be determined (explain): ________________________________

+ Data elements preceded by this symbol are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.
Number of Inguinal Lymph Nodes Involved
Specify number of right inguinal lymph nodes: ____
Specify number of left inguinal lymph nodes: ____
___ Number cannot be determined (explain): ______________________________

Other lymph nodes:

Specify site and laterality ______________________________

Number of Other Lymph Nodes Examined
Specify: ____
___ Number cannot be determined (explain): ______________________________

Number of Other Lymph Nodes Involved
Specify: ____
___ Number cannot be determined (explain): ______________________________

Number of lymph nodes with metastasis(es) <5 mm (required only if applicable): ____
Number of lymph nodes with metastasis(es) ≥ 5 mm (required only if applicable): ____
+ Number of lymph nodes with isolated tumor cells (<0.2 mm): ____
+ Number of lymph nodes with micrometastasis (>0.2 mm to 2 mm): ____

Extranodal Extension (required only if applicable) (Note I)
___ Present
___ Not identified
___ Cannot be determined (explain): ______________________________

Fixed or Ulcerated Femoral-inguinal Lymph Nodes (required only if applicable)
___ Present
___ Not identified
___ Cannot be determined (explain): ______________________________

Distant Metastasis (pM) (required only if confirmed pathologically in this case)
___ pM1: Distant metastasis (including pelvic lymph node metastasis)
   Specify site(s), if known: ______________________________

+ FIGO Stage
+ I: Tumor confined to the vulva
  +__ IA: Lesions ≤ 2 cm in size, confined to the vulva or perineum and with stromal invasion ≤ 1.0 mm, no nodal metastasis
  +__ IB: Lesions > 2 cm in size or with stromal invasion > 1.0 mm, confined to the vulva or perineum, with negative nodes
  +__ II: Tumor of any size with extension to adjacent perineal structures (lower third of urethra, lower third of vagina, anus) with negative nodes
  +__ III: Tumor of any size with or without extension to adjacent perineal structures (lower third of urethra, lower third of vagina, anus) with positive inguinal/femoral nodes
  +__ IIIA: With 1 lymph node metastasis (≥ 5 mm)
  +__ IIIB: With 2 or more lymph node metastases (≥ 5 mm)
  +__ IIIC: With positive nodes with extracapsular spread
+ IV: Tumor invades other regional (upper two-thirds urethra, upper two-thirds vagina), or distant structures
  +__ IVA: Tumor invades any of the following: upper urethral and/or vaginal mucosa, bladder mucosa, rectal mucosa, or fixed to pelvic bone, or fixed or ulcerated inguinal/femoral lymph nodes
  +__ IVB: Any distant metastasis including pelvic lymph nodes

+ Data elements preceded by this symbol are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.
**Additional Pathologic Findings (select all that apply) (Note I)**

+ ___ None identified
+ ___ Condyloma accuminatum
+ ___ High grade squamous intraepithelial neoplasia
+ ___ Low grade squamous intraepithelial neoplasia
+ ___ Vulvar intraepithelial neoplasia, differentiated type
+ ___ 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 the surgeon. 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. When inguinal-femoral lymphadenectomy is performed, 6 or more lymph nodes will normally be included. 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 metastatic)
- 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.

C. Etiology/Pathogenesis
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. Of note, overlap does exist between the 2 pathways, with some tumors exhibiting morphologic and/or clinical features of each.
<table>
<thead>
<tr>
<th>Prevalence</th>
<th>Keratinizing Squamous Carcinoma</th>
<th>Basaloid Squamous Carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>More common (approximately 80%)</td>
<td>Less common (approximately 20%)</td>
</tr>
<tr>
<td>Age</td>
<td>Older females</td>
<td>Younger females</td>
</tr>
<tr>
<td>Distribution</td>
<td>Usually unifocal, may be multifocal</td>
<td>Often multifocal</td>
</tr>
<tr>
<td>Association with multifocal lower genital tract neoplasia</td>
<td>Rare</td>
<td>Common</td>
</tr>
<tr>
<td>Morphology</td>
<td>Keratinizing</td>
<td>Warty</td>
</tr>
<tr>
<td>Associated vulvar intraepithelial neoplasia (VIN)</td>
<td>Uncommon: differentiated type</td>
<td>Common: classic type</td>
</tr>
<tr>
<td>Association with human papillomavirus (HPV)</td>
<td>Yes, beta (cutaneous)$^8$ 5,8</td>
<td>Yes, alpha 16&gt;18</td>
</tr>
<tr>
<td>Association with vulvar dystrophy</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>Immunohistochemistry</td>
<td>p53: Some cases positive p16: Negative or focally positive at stromal interface</td>
<td>p53: Negative p16: Positive</td>
</tr>
</tbody>
</table>

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.$^{3,9,10}$

WHO and Lower Anogenital Squamous Terminology (LAST) Classification of Vulvar Epithelial Tumors and Related Lesions

**Squamous Lesions**
LAST classification
- Low-grade squamous intraepithelial lesion (VIN 1)
- High-grade squamous intraepithelial lesion (VIN 2-3)

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
Neuroendocrine tumors
   High-grade neuroendocrine carcinoma
   Small cell neuroendocrine carcinoma
   Large cell neuroendocrine carcinoma
   Merkel cell carcinoma

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 (finger-like) 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. 11

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. 12-14

H. 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. 2,15 Comparison with FIGO staging is also shown. 16-18

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

<table>
<thead>
<tr>
<th>Primary Tumor (T)</th>
<th>TNM Categories</th>
<th>FIGO Stages</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>Primary tumor cannot be assessed</td>
<td></td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
<td></td>
</tr>
<tr>
<td>Tis</td>
<td>High-grade squamous intraepithelial lesion (VIN 2-3)</td>
<td></td>
</tr>
<tr>
<td>T1a</td>
<td>Lesions 2 cm or less in size, confined to the vulva or perineum and with stromal invasion 1.0 mm or less</td>
<td>IA</td>
</tr>
<tr>
<td>T1b</td>
<td>Lesions more than 2 cm in size or any size with stromal invasion more than 1.0 mm, confined to the vulva or perineum</td>
<td>IB</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor of any size with extension to adjacent perineal structures (lower/distal one-third urethra, lower/distal one-third vagina, anal involvement)</td>
<td>II</td>
</tr>
</tbody>
</table>
T3  IVA  Tumor of any size with extension to any of the following: upper/proximal two-thirds of urethra, upper/proximal two-thirds 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  1 or 2 regional lymph nodes with the following features
N1a  IIA  1 or 2 lymph node metastasis each 5 mm or less
N1b  IIA  1 lymph node metastasis 5 mm or greater
N2  IIIB  Regional lymph nodes metastasis with the following features
N2a  IIIB  3 or more lymph node metastases each less than 5 mm
N2b  IIIB  2 or more lymph node metastases 5 mm or greater
N2c  IIIC  Lymph node metastasis with extracapsular spread
N3  IVA  Fixed or ulcerated regional lymph node metastasis

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

Although N0(sn)(i-) and N0(sn)(i+) are not explicitly mentioned in the vulva chapter of the AJCC 7th edition, AJCC acknowledges use of (sn) and (i) modifiers for cancers other than breast cancer. This nomenclature is currently being adopted and used by pathologists for vulvar cancer.

**Distant Metastasis (M)**

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

**Anatomic Stage/Prognostic Groups**

<table>
<thead>
<tr>
<th>Stage 0</th>
<th>Tis</th>
<th>N0</th>
<th>M0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IA</td>
<td>T1a</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IB</td>
<td>T1b</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage II</td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage II A</td>
<td>T1, T2</td>
<td>N1a, N1b</td>
<td>M0</td>
</tr>
<tr>
<td>Stage II B</td>
<td>T1, T2</td>
<td>N2a, N2b</td>
<td>M0</td>
</tr>
<tr>
<td>Stage II C</td>
<td>T1, T2</td>
<td>N2c</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IV A</td>
<td>T1, T2</td>
<td>N3</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>T3</td>
<td>Any</td>
</tr>
<tr>
<td>Stage IV B</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
</tr>
</tbody>
</table>

**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. 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.

The “r” prefix indicates a recurrent tumor when staged after a 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)
The absence or presence of residual tumor after treatment. In some cases treated with surgery and/or neoadjuvant therapy there will be residual tumor at the primary site after treatment because of incomplete resection or local and regional disease that extends beyond the limit of ability of resection.

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 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.1,14

I. 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.2,13,19,20

References
8. Glazyrin A, Rohwedder A, Carlson, JA. Beta-human papillomaviruses (HPV) are common in vulvar squamous cell carcinomas and surrounding skin. Mod Pathol. 2009;22[suppl 1]:103A. Poster presentation at 98th annual meeting, USCAP.


