COLLEGE of AMERICAN PATHOLOGISTS

Protocol for the Examination of Specimens From Patients With Primary Carcinoma of the Vulva

Version: 5.1.0.0
Protocol Posting Date: June 2024
CAP Laboratory Accreditation Program Protocol Required Use Date: March 2025
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 vulvectomy (with or without removal of other organs and tissues)
Tumor Type	**Description**
Carcinoma	Includes squamous cell carcinoma, adenocarcinoma and variants, carcinosarcoma, neuroendocrine carcinoma, and mixed epithelial–neuroendocrine tumors

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

Procedure
Biopsy
Primary resection specimen with no residual cancer (e.g., following neoadjuvant therapy)
Cytologic specimens

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

Tumor Type
Melanoma (consider the Skin Melanoma protocol)
Lymphoma (consider the Precursor and Mature Lymphoid Malignancies protocol)
Sarcoma (consider the Soft Tissue protocol)
Phyllodes Tumor (consider the Breast Phyllodes Tumor 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 (i.e., 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 i.e., all required elements must be in the synoptic portion of the report in the format defined above.

Summary of Changes

v 5.1.0.0

- Separated “Margin Status for Paget Disease” elements from the “Margin Status for Precursor Lesions of Squamous Cell Carcinoma” question
- REGIONAL LYMPH NODE section typographical updates and the “Size of Largest Nodal Metastatic Deposit” question outdented
- Semantic change to pT3 and pN0(i+) staging terminology
- Typographical updates to SPECIAL STUDIES section
- Update to Explanatory Note A (resection margins)

Reporting Template

Protocol Posting Date: June 2024
Select a single response unless otherwise indicated.

CASE SUMMARY: (VULVA)
Standard(s): AJCC-UICC 9, FIGO Cancer Report 2021

SPECIMEN (Note A)

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

TUMOR

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

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

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

Histologic Type (Notes C,D)
___ Squamous cell carcinoma, HPV-associated

___ Squamous cell carcinoma, HPV-independent
___ Squamous cell carcinoma, NOS
___ Basal cell carcinoma, NOS
___ Adenocarcinoma, NOS
___ Adenocarcinoma of mammary gland type
___ Adenocarcinoma, intestinal type
___ Paget disease, extramammary
___ Sweat gland adenocarcinoma (specify subtype)
  ___ Apocrine adenocarcinoma
  ___ Eccrine adenocarcinoma
  ___ Porocarcinoma, NOS
  ___ Adenoid cystic carcinoma
___ Bartholin gland carcinoma (specify subtype)
  ___ Squamous cell carcinoma, NOS
  ___ Squamous cell carcinoma, HPV-positive
  ___ Adenocarcinoma
  ___ Adenosquamous carcinoma
  ___ Carcinoma, poorly differentiated, NOS
  ___ Adenoid cystic carcinoma
  ___ Neuroendocrine tumor, NOS
  ___ Myoepithelial carcinoma
  ___ Epithelial-myoepithelial carcinoma
___ Neuroendocrine tumor, NOS
___ Neuroendocrine tumor, grade 1
___ Neuroendocrine tumor, grade 2
___ Small cell neuroendocrine carcinoma
___ Large cell neuroendocrine carcinoma
___ Combined small cell neuroendocrine carcinoma
___ Combined large cell neuroendocrine carcinoma
___ Germ cell tumor, NOS
___ Yolk sac tumor, NOS
___ Other histologic type not listed (specify): _____
___ Carcinoma, type cannot be determined
  +Histologic Type Comment: _____

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

Depth of Invasion in Millimeters (mm) (FIGO 2021 method) (Note F)
___ Specify in Millimeters (mm): _____ mm
___ Other (specify): _____

___ Cannot be determined (explain): _____

+Depth of Invasion in Millimeters (mm) (conventional method) (Note F)
___ Specify in Millimeters (mm): _____ mm
___ Other (specify): _____
___ Cannot be determined (explain): _____

+Tumor Growth Pattern (Note G)
___ Pushing
___ Infiltrating
___ Other (specify): _____

Other Tissue / Organ Involvement# (select all that apply)
 # Any organ not selected is either not involved or was not submitted.
___ Not applicable
___ Not identified
___ Vagina, lower one-third
___ Vagina, upper two-thirds
___ Urethra, lower one-third
___ Urethra, upper two-thirds
___ Anus
 # Mucosal surface of bladder or rectum should be involved by tumor
___ Bladder mucosa#
___ Rectal mucosa#
___ Pelvic bone
___ Other organs / tissue (specify): _____
___ Cannot be determined (explain): _____

Lymphatic and / or Vascular Invasion (Note H)
___ Not identified
___ Present
___ Equivocal (explain): _____
___ Cannot be determined (explain): _____

+Tumor Comment: _____

MARGINS

Margin Status for Invasive Carcinoma
 # Margin status for precursor lesions of squamous cell carcinoma and / or Paget disease 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 (explain): _____
___ 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 Precursor Lesions of Squamous Cell Carcinoma (select all that apply)
 # Includes high-grade squamous intraepithelial lesion (HSIL), differentiated vulvar intraepithelial neoplasia (dVIN) and / or vulvar aberrant maturation / HPV-independent, p53-wild-type verruciform acanthotic vulvar intraepithelial neoplasia (VAM / HPVi (p53wt) vaVIN).
___ All margins negative for squamous precursor lesions#
___ Squamous precursor lesion present at margin
+Margin(s) Involved by Squamous Precursor Lesion(s) (select all that apply)
___ Peripheral (specify location, if possible): _____
___ Deep (specify location, if possible): _____
___ Other (specify): _____
___ Cannot be determined (explain): _____
___ High-grade squamous intraepithelial lesion (HSIL) present at margin
+Margin(s) Involved by HSIL (select all that apply)
___ Peripheral (specify location, if possible): _____
___ Deep (specify location, if possible): _____
___ Other (specify): _____
___ Cannot be determined (explain): _____
___ Differentiated vulvar intraepithelial neoplasia (dVIN) present at margin
+Margin(s) Involved by dVIN (select all that apply)
___ Peripheral (specify location, if possible): _____
___ Deep (specify location, if possible): _____
___ Other (specify): _____
___ Cannot be determined (explain): _____
___ Vulvar aberrant maturation (VAM) / HPV-independent, p53-wild-type verruciform acanthotic vulvar intraepithelial neoplasia (HPVi (p53wt) vaVIN) present at margin
+Margin(s) Involved by VAM / HPVi (p53wt) vaVIN (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 Paget Disease (required only if applicable)

___ Not applicable
___ All margins negative for Paget disease
___ Paget disease present at margin
+Margin(s) Involved by Paget Disease (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): _____

+Margin Comment: _____

REGIONAL LYMPH NODES

Regional Lymph Node Status#

 # Only inguinal and femoral nodes are considered regional lymph nodes. Any other involved nodes are categorized as metastases (pM1) and should be described in a comment in the distant metastasis section. Presence of isolated tumor cells no greater than 0.2 mm, or single cells or cell clusters no more than 200 cells 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 Metastasis Greater than 5 mm

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

Number of Nodes with Metastasis 5 mm or Less but Greater than 2 mm

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

Number of Nodes with Micrometastasis 2 mm or Less but Greater than 0.2 mm (excludes 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, or Single Cells, or Cell Clusters not more than 200 Cells in a Single Node Cross-section) (required only if applicable)#

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

+Size of Largest Nodal Metastatic Deposit

Specify in Millimeters (mm)

___ Exact size (specify): _____ mm
___ Less than: _____ mm
___ Greater than: _____ mm
___ Other (specify): _____
___ Cannot be determined (explain): _____

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

___ Right inguinal: _____
___ Left inguinal: _____
___ Inguinal, NOS: _____
___ Right femoral: _____
___ Left femoral: _____
___ Femoral, NOS: _____
___ Other (specify): _____
___ Cannot be determined: _____

Additional Lymph Node Findings (required only if applicable) (select all that apply)

___ Not applicable
___ None identified
___ Extranodal extension / extracapsular spread
___ Fixed and / or ulcerated nodes
___ Other (specify): _____
___ Cannot be determined (explain): _____

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

Total 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 inguinal: _____
___ Left inguinal: _____
___ Inguinal, NOS: _____
___ Right femoral: _____
___ Left femoral: _____
___ Femoral, NOS: _____
___ Other (specify): _____

___ Cannot be determined: _____

Number of Sentinel Nodes Examined (required only if applicable)

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

+Regional Lymph Node Comment: _____

DISTANT METASTASIS

Distant Site(s) Involved, if applicable (select all that apply)

___ Not applicable
___ Pelvic lymph node(s): _____
___ Internal iliac / hypogastric lymph node(s): _____
___ External iliac lymph node(s): _____
___ Common iliac lymph node(s): _____
___ Presacral lymph node(s): _____
___ Lung: _____
___ Liver: _____
___ Bone: _____
___ Other (specify): _____
___ Cannot be determined

pTNM CLASSIFICATION (AJCC Version 9) (Note I)

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.

Modified Classification (required only if applicable) (select all that apply)

___ Not applicable
___ y (post-neoadjuvant therapy)
___ r (recurrence)

pT Category

___ pT not assigned (cannot be determined based on available pathological information)
___ pT0: No evidence of primary tumor

pT1: Tumor confined to the vulva
 # Depth of invasion is measured from the basement membrane of the deepest adjacent tumor-free rete ridge to the deepest point of invasion.

___ pT1a: Tumor size less than or equal to 2 cm in greatest dimension and stromal invasion less than or equal to 1 mm#
___ pT1b: Tumor size greater than 2 cm in greatest dimension or stromal invasion greater than 1 mm#
___ pT1 (subcategory cannot be determined)
___ pT2: Tumor of any size with extension to lower one-third of urethra, lower one-third of vagina, or anus

___ pT3: Tumor of any size with disease extension to upper two-thirds of urethra, upper two-thirds of vagina, bladder mucosa, rectal mucosa
___ pT4: Tumor fixed to pelvic bone

T Suffix (required only if applicable)
___ Not applicable
___ (m) multiple primary synchronous tumors in a single organ

pN Category
Regional lymph nodes include inguinal and femoral nodes. Involvement of internal iliac / hypogastric, external iliac, and common iliac lymph nodes is considered distant metastases. The site, size, and laterality of lymph node metastases should be recorded.
___ pN not assigned (no nodes submitted or found)
 # Histologic examination of an inguinofemoral lymphadenectomy specimen will ordinarily include 6 or more lymph nodes. If the lymph nodes are negative, but the number ordinarily examined is not met, classify as pN not assigned (cannot be determined based on available pathological information).
___ 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) less than or equal to 0.2 mm, or single cells or clusters of cells less than or equal to 200 cells in a single lymph node cross-section
pN1: Tumor involvement of non-fixed, non-ulcerated regional lymph nodes
___ pN1mi: Tumor involvement greater than 0.2 mm but less than or equal to 2.0 mm in diameter of regional lymph nodes
___ pN1a: Tumor involvement greater than 2.0 mm but less than or equal to 5 mm of regional lymph nodes
___ pN1b: Tumor involvement greater than 5 mm of regional lymph nodes
___ pN1c: Tumor involvement of regional lymph nodes with extranodal extension (ENE)
___ pN1 (subcategory cannot be determined)
___ pN2: Tumor involvement of fixed or ulcerated regional lymph nodes

N Suffix (required only if applicable)
___ Not applicable
___ (sn) Sentinel node procedure
___ (f) FNA or core needle biopsy

pM Category (required only if confirmed pathologically)
___ Not applicable - pM cannot be determined from the submitted specimen(s)
___ pM1: Microscopic confirmation of distant metastasis

FIGO STAGE

+FIGO Stage (2021 FIGO staging for carcinoma of the vulva)
___ I: Tumor confined to the vulva
 # Depth of invasion is measured from the basement membrane of the deepest, adjacent (or nearest) dysplastic, tumor-free rete ridge to the deepest point of invasion.
___ IA: Tumor size less than or equal to 2 cm and stromal invasion less than or equal to 1 mm#
___ IB: Tumor size greater than 2 cm or stromal invasion greater than 1 mm#
___ II: Tumor of any size with extension to lower one-third of the urethra, lower one-third of the vagina, or lower one-third of the anus with negative nodes

___ III: Tumor of any size with extension to upper part of adjacent perineal structures, or with any number of non-fixed, non-ulcerated lymph node(s)

Regional lymph nodes include inguinal and femoral nodes.

___ IIIA: Tumor of any size with disease extension to upper two-thirds of the urethra, upper two-thirds of the vagina, bladder mucosa, rectal mucosa, or regional lymph node metastases less than or equal to 5 mm##

___ IIIB: Regional lymph node metastases greater than 5 mm##

___ IIIC: Regional lymph node metastases with extracapsular spread##

___ IV: Tumor of any size fixed to bone, or fixed, ulcerated lymph node metastases, or distant metastases

___ IVA: Disease fixed to pelvic bone, or fixed or ulcerated regional lymph node metastases##

___ IVB: Distant metastases

ADDITIONAL FINDINGS (Note J)

+Additional Findings (select all that apply)

___ None identified

___ Condyloma acuminatum

___ Low-grade squamous intraepithelial lesion / Vulvar intraepithelial neoplasia, grade 1

___ High-grade squamous intraepithelial lesion / Vulvar intraepithelial neoplasia, grade 2

___ High-grade squamous intraepithelial lesion / Vulvar intraepithelial neoplasia, grade 3

___ Differentiated vulvar intraepithelial neoplasia (dVIN)

___ Vulvar aberrant maturation / HPV-independent, p53-wild-type verruciform acanthotic vulvar intraepithelial neoplasia

___ Lichen sclerosus

___ Other (specify): _____

SPECIAL STUDIES (Note K)

+Ancillary Studies (specify): _____

+p16 Immunohistochemistry

___ Positive (diffuse, block-like expression)

___ Negative (no staining, or focal or patchy expression)

+p53 Immunohistochemistry

___ Normal (wild-type)

___ Abnormal (mutated)

- ___ Basal overexpression (uniform strong, diffuse nuclear expression in basal cells)
- ___ Parabasal / diffuse overexpression
- ___ Absent / null (lack of nuclear or cytoplasmic expression)
- ___ Cytoplasmic expression (with or without nuclear expression)

+HPV-ISH

___ Positive, high-risk, not otherwise specified

___ Positive, low-risk, not otherwise specified

___ Negative

COMMENTS

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 (perpendicular sections to margins may be particularly helpful, especially for human papillomavirus independent lesions, as they allow to more accurately assess margin clearance as well as the spectrum of morphologic and/or immunohistochemical changes leading up to the margin)
- Sections of abnormal epithelium or other tissue away from tumor
- Sections of area(s) marked by surgeon
- Sections of prior biopsy or resection site of tumor if no tumor is present grossly

Lymph Nodes

The femoral and inguinal lymph nodes are the sites of regional spread.[1,2] Involvement of pelvic or other lymph nodes is considered stage IV disease. Although inguinal-femoral lymphadenectomy is still performed in some patients, increasing evidence suggests that sentinel lymph node assessment is an alternative standard of care approach in select cases.[1,2,3,4,5]

Sections of grossly positive lymph nodes should demonstrate the maximum diameter of nodal metastasis and document the presence or absence of extranodal/extracapsular extension. Sentinel lymph nodes should be assessed in accordance with a locally agreed upon and established protocol. The pathology report should specify whether or not an ultrastaging procedure was performed and whether nodal metastases were identified on routine histologic examination (without ultrastaging) or by ultrastaging.[6] Reportedly, ultrastaging can improve the detection of nodal metastases from 8.6% to 41.7%. There is no universally accepted ultrastaging protocol; however, protocols used at the 2 largest cancer centers in USA are as follows:

1. Memorial Sloan Kettering Cancer Center Protocol: If the initial H&E-stained slide is negative for carcinoma, 2 additional levels at 50 µm apart are examined; at each level 2 slides are obtained, one for H&E and the second for keratin cocktail immunohistochemistry.
2. The University of Texas MD Anderson Cancer Center Protocol: If the initial H&E-stained slide is negative for carcinoma, 5 levels at 250 µm intervals are obtained (1 H&E and 2 unstained sections per level to be used for keratin cocktail immunohistochemistry if the additional H&E-stained slides are negative).[7]

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, post-frozen tissue fragment(s) should be submitted.

References

1. Van der Zee AG, Oonk MH, De Hullu JA, et al. Sentinel lymph node dissection is safe in the treatment of early-stage vulvar carcinoma. *J Clin Oncol.* 2008;26:884-889.
2. Levenback CF, Ali S, Coleman R, et al. Lymphatic mapping and sentinel lymph node biopsy in women with squamous cell carcinoma of the vulva: a gynecologic oncology group study. *J Clin Oncol.* 2012;30:3786-3791.
3. Abu-Rustum NR, Yashar C, et al. NCCN guidelines. Version 4.2024 Vulvar Cancer: National Comprehensive Cancer Network (NCCN), 2024.
4. Covens A, Vella ET, Kennedy EB, et al. Sentinel lymph node biopsy in vulvar cancer: Systematic review, meta-analysis and guideline recommendations. *Gynecol Oncol.* 2015;137:351-361.
5. Te Grootenhuis NC, van der Zee AG, van Doorn HC, et al. Sentinel nodes in vulvar cancer: Long-term follow-up of the GROningen INternational Study on Sentinel nodes in Vulvar cancer (GROINSS-V) I. *Gynecol Oncol.* 2016;140:8-14.
6. Hoang L, Webster F, Bosse T, et al. Data Set for the Reporting of Carcinomas of the Vulva: Recommendations From the International Collaboration on Cancer Reporting (ICCR). *Int J Gynecol Pathol.* 2022;41(Suppl 1):S8-S22.
7. Euscher ED, Malpica A. Gynaecological malignancies and sentinel lymph node mapping: an update. *Histopathol.* 2020;76(1):139-150.

B. Size of Tumor

Assessment of gross size of the tumor is important for staging. The tumor should be accurately measured to determine if its maximum dimension is less than or equal to 2 cm or greater than 2 cm. If there is a significant discrepancy between gross and microscopic measurements of the invasive tumor, careful microscopic assessment should be performed.

C. Etiology/Pathogenesis

Vulvar squamous cell carcinoma can be classified into three clinicopathologically distinct subgroups based on their human papillomavirus (HPV) and p53 status[1,2]: HPV-independent/p53-mutant, HPV-independent/p53-wild-type, and HPV-associated (see Table 1). The HPV-associated pathway involves high-grade squamous intraepithelial lesion (HSIL), which is associated with high-risk HPV subtypes (mostly HPV 16) and is histologically similar to cervical HSIL. It affects younger women and tends to be multifocal, with a relatively low risk of progression to squamous cell carcinoma. Both HSIL and HPV-associated squamous cell carcinoma usually show diffuse, block-like expression of p16 by immunohistochemistry (reflecting HPV association). HSIL is characterized by loss of maturation, nuclear hyperchromasia, increased nuclear-cytoplasmic ratio, and increased mitoses in the upper epidermal layers. The invasive component may display basaloid or warty morphology, but a significant subset are keratinizing.[3,4]

HPV-independent carcinomas can be p53-mutant or p53-wild-type. Differentiated VIN (dVIN) is usually seen in the setting of chronic inflammatory dermatoses, most commonly lichen sclerosus, in older women.[4] The morphologic features of dVIN are varied and may be subtle, but should include basal atypia.[4] dVIN should be distinguished from lichen simplex chronicus, hypertrophic lichen sclerosus, vulvar aberrant maturation (VAM), and lichen planus.[4] dVIN typically shows aberrant p53 expression and non-

block or negative staining pattern for p16. It remains unsettled whether a p53-wild-type immunophenotype is within the allowable spectrum for dVIN.[4,5,6] The invasive component that is associated with dVIN is frequently keratinizing and also often shows aberrant p53 expression.[3,7] Of note, the HPV-associated and HPV-independent squamous lesions may show overlapping morphologic features,[3] and immunohistochemistry for p53 and p16 is therefore recommended to classify a case into one of the aforementioned subgroups.

Precursors of HPV-independent, p53-wild-type squamous cell carcinoma are still poorly understood.[4,8] However, vulvar lesions with altered squamous maturation and verruciform acanthosis have previously been described using various terms such as vulvar acanthosis with altered differentiation (VAAD), differentiated exophytic vulvar intraepithelial lesion (DEVIL), vulvar aberrant maturation (VAM) and verruciform lichen simplex chronicus (vLSC), among others.[4,8] Although the available data are limited, a subset of these lesions may harbor recurrent alterations in oncogenes such as *PIK3CA*, *HRAS*, and *NOTCH1*[9] and they have been shown to be associated with significant rates of recurrence and/or progression to carcinoma.[10] The term VAM was proposed by the International Society of the Study of Vulvovaginal Diseases (ISSVD) Difficult Pathologic Diagnoses Committee and defined as “an umbrella term for HPV-independent lesions combining aberrant maturation with minimal nuclear atypia”.[4] In part to harmonize the nomenclature with the current World Health Organization (WHO) classification, an alternative term - HPV-independent, p53-wild-type verruciform acanthotic VIN (HPVi(p53wt) vaVIN) - has been proposed.[8]

Table 1. Clinicopathologic features of three subtypes of vulvar squamous cell carcinoma (SCC)

	HPV-associated SCC	**HPV-independent SCC, p53-mutant**	**HPV-independent SCC, p53-wild-type**
Prevalence[1,2]	17.4-18%	66-72%	10.5-15%
Median age[1]	59 years	75 years	73 years
Frequency of multifocality[2]	18.2%	20.4%	30%
Morphology	Varied and overlaps with the other subtypes; relative over-representation of warty or basaloid morphology	Varied and overlaps with the other subtypes; relative over-representation of keratinizing morphology	Varied and overlaps with the other subtypes; overrepresentation of verrucous morphology
Precursor	HSIL	dVIN	Unknown; may include VAM/HPVi(p53wt) vaVIN, VAAD, DEVIL
Association with HPV	Yes, HPV 16 > HPV 18	No	No
Immunohistochemistry	p53: Wild-type expression (often with basal sparing) p16: Block-like expression	p53: Aberrant p16: Negative or non-block expression	p53: Wild-type p16: Negative or non-block expression
HPV in situ hybridization	Positive	Negative	Negative
Prognosis[1,2]	Best of the three subtypes	Worst of the three subtypes	Intermediate between HPV-associated and HPV-independent p53-mutant subtypes

References

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D. Histologic Type

The protocol adheres to the standardized terminology proposed by the World Health Organization (WHO) classification of malignant and premalignant vulvar epithelial tumors.[1] The most common invasive tumor of the vulva is squamous cell carcinoma. Although the treatment of HPV-associated and HPV-independent squamous carcinoma is currently the same, their pathogenesis differs (see Note C).[1] In some instances, it may not be possible to distinguish between the two, and “squamous cell carcinoma, 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 determining whether a given tumor is HPV-associated or HPV-independent, but ancillary techniques are necessary for definitive classification. For HPV-associated precursors, low-grade or high-grade squamous intraepithelial lesion (SIL) is the preferred terminology but vulvar intraepithelial neoplasia (VIN) may also be used, with appropriate grades 1, 2, or 3 (e.g., VIN2). For the HPV-independent squamous cell carcinoma, a common precursor is differentiated VIN (dVIN), which is not graded.

The vulva may harbor malignancies arising from mammary-like anogenital glands, such as adenocarcinoma of mammary gland type and malignant phyllodes tumors.[1] Carcinomas of sweat gland origin are rare and include apocrine adenocarcinoma, eccrine adenocarcinoma, porocarcinoma and adenoid cystic carcinoma; these usually arise in the labia majora of older patients.[1] Paget disease of the vulva may be associated with an invasive component, which may be a non-specific adenocarcinoma, an adenocarcinoma of mammary gland type, or a carcinoma of sweat gland type.[1] Basal cell carcinomas and sebaceous carcinomas occur but are uncommon. Bartholin glands may be the site of malignant transformation; these neoplasms have been categorized based upon similarities to their histologic counterparts in other organs.[1,2,3] Ideally, to designate a tumor as arising from a Bartholin gland, it should involve the region housing Bartholin glands, be histologically compatible with that origin, demonstrate a transition from a benign gland or cyst, and have no alternative primary site.[3] Squamous cell carcinoma predominates, followed by adenocarcinoma.[1] Numerous other subtypes have been described in the Bartholin glands, including adenosquamous carcinoma, mucinous adenocarcinoma, salivary gland-type carcinomas and neuroendocrine carcinoma. Exceptionally rare adenocarcinomas that may be seen in the vulva include endometriosis-related adenocarcinomas (clear cell and endometrioid carcinomas), adenocarcinomas of the intestinal type, and HPV-related adenocarcinoma.[4] Notably, a significant subset of glandular malignancies that involve the vulva are secondary to this site.[5]

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E. Histologic Grade

Current evidence suggests that histologic grading is not consistently associated with prognosis of vulvar squamous cell carcinoma.[1,2] Although HPV-independent tumors are often keratinizing and well-differentiated, their prognosis is paradoxically worse than HPV-associated tumors which are usually non-keratinizing, basaloid and poorly differentiated. Furthermore, there is no validated grading system. Therefore, grading of vulvar squamous cell carcinoma is not recommended,[2] and grade may be included as an optional element.

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F. Depth of Invasion

Tumor thickness and depth of invasion are separate measurements. Tumor 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.[1] Tumor thickness is not a parameter used in staging and should not be used for depth of invasion, because vulvar carcinoma can have a significant exophytic component.

Assessment of the maximum depth of tumor invasion is important because invasion >1 mm requires regional lymph node evaluation. The depth of invasion has traditionally been measured from the most superficial dermal papilla adjacent to the tumor to the deepest point of invasion (conventional measurement),[2] and there is significant interobserver variability in assessment of superficial invasion, including invasion vs VIN and invasion ≤1 vs >1 mm (i.e., stage IA vs IB).[3] An alternative method has been adopted by FIGO and AJCC for all vulvar carcinomas, irrespective of type or HPV status, which measures the depth of invasion from the basement membrane of the deepest adjacent (or nearest) dysplastic tumor-free rete ridge or the nearest dysplastic rete peg to the deepest point of invasion.[4,5] This alternative method "down-stages" some conventional stage IB tumors to IA. Down-staged patients have been shown to develop fewer inguinal recurrences[4,5] with higher disease-specific survival[4] and a lower risk of inguinal node involvement at diagnosis[5] compared with conventional stage 1B patients, raising the possibility that they may be spared a lymphadenectomy. Some investigators suggest that in cases where the deepest rete ridge is deeper than the tumor, the most adjacent basement membrane of the rete ridge may be used to measure the depth of invasion, regardless of whether it is dysplastic or not.[4] When depth of invasion is ambiguous or difficult to determine, this should be clearly stated in the pathology report. The AJCC recommends using the conventional method of measurement as an ancillary data point.

In early stage disease, there are insufficient data on other features to identify patients at higher risk for recurrence, such as distance from margins, inguinal lymph node metastases, tumor size or focality, and depth of invasion.[6,7] Tumor stage and lymph node status are the strongest predictors of overall progression-free survival. Measuring the distance of tumor from the nearest surgical margin may be challenging, but one study showed that most pathologists measure in a straight line from the tumor to the nearest inked edge, rather than measuring along the epithelial surface.[8]

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G. Tumor Growth Pattern

Vulvar squamous cell carcinomas can generally be separated into those tumors that have a predominately infiltrating pattern and those that invade with a broad, pushing front.[1] Related parameters include high tumor budding,[2] a distinctive spray-like infiltration pattern,[1,3] and a prominent fibromyxoid response.[4] Some studies have associated these features with worsened patient outcomes, but as a group, they are understudied.[1,2]

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H. Lymphatic and/or Vascular Invasion

Lymphatic and/or vascular space invasion by squamous cell carcinoma has been associated with a poorer prognosis and increased risk for regional lymph node metastasis.[1,2,3]

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I. pTNM Classification

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

By AJCC/UICC convention, the designation “cT” 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 the pathologist's contribution is based on gross and microscopic examination after primary surgical treatment. pT entails a surgical treatment resection of the primary tumor or biopsy adequate to evaluate the highest pT category and highest pN categories, pN entails removal or biopsy 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 the initial evaluation of the patient. Pathological classification (pTNM) must be assigned by the managing physician based on the clinical stage information, the operative findings, and the gross and microscopic examination of the surgical resection specimen. The pathologist provides vital information, but it is not the patient's final pT, pN, and/or pM categories.

TNM Stage Classifications

The "y" prefix indicates those cases in which classification is performed during or following initial multimodality therapy (i.e., 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 (i.e., 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.

TNM Suffixes

For identification of special cases of TNM or pTNM classifications, the "(m)" T suffix and "(sn)" and "(f)" N suffixes are used. Although they do not affect the stage grouping, they indicate cases needing special analysis.

The "(m)" T suffix indicates the presence of multiple primary synchronous tumors in a single site and is recorded in parentheses: e.g., pT1(m).

The "(sn)" N suffix indicates a sentinel node procedure only, without resection of the nodal basin, was performed and is recorded in parentheses: e.g., pN1(sn).

The "(f)" N suffix indicates a fine needle aspiration (FNA) or core needle biopsy, without a sentinel node procedure or resection of nodal basin, was performed and is recorded in parentheses: e.g., pN1(f).
Isolated tumor cells (ITCs) are single cells or small cell clusters not more than 0.2 mm in greatest dimension or more than 200 cells. Lymph nodes or distant sites with ITCs found by either histologic examination (e.g., immunohistochemical evaluation for cytokeratin) or nonmorphologic techniques (e.g., 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 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.[3,4] Patients with metastases <2 mm in sentinel nodes may be candidates to forego groin dissection.[4]

Extranodal Extension/Extracapsular spread

Both extranodal extension and the size of lymph node metastasis have been shown to reflect prognosis and should be noted in the report.[5,6]

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J. Additional Findings

The presence of adjacent lesions such as lichen sclerosus may increase the risk of recurrence and development of new primary tumors in patients with HPV-independent squamous cell carcinoma.[1] Therefore, reporting the presence of this finding should be considered.

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K. Ancillary Tests

Reporting ancillary tests in synoptic format is optional. However, distinguishing between HPV-associated and HPV-independent squamous cell lesions of the vulva has diagnostic and prognostic significance. Given that HPV-associated and HPV-independent vulvar lesions often show significant morphologic overlap, their differential diagnosis often requires immunohistochemical studies for p16 and p53. Accurate classification is important because the prognosis for HPV-associated squamous cell carcinoma is superior to that of HPV-independent types.[1]

Diffuse, block-like expression of p16 indicates association with HPV. Focal or patchy expression, or absence of staining is seen in HPV-independent lesions.[2]

There are two normal (wild-type) and 4 abnormal (aberrant, mutated) patterns of p53 expression. Wild-type expression is usually patchy with scattered basal/parabasal cells showing heterogeneous staining of variable intensity.[3] HPV-associated squamous lesions often show strong mid-epithelial expression of p53

that spares the basal layer (negative to weak basal cell staining) and is associated with block-like p16 expression.[3]

The 4 abnormal patterns of p53 are as follows: 1) Basal overexpression with strong, diffuse nuclear expression in basal cells; 2) Parabasal/diffuse overexpression; 3) Absent “null” phenotype, lacking nuclear or cytoplasmic expression; 4) Cytoplasmic expression with moderate to strong cytoplasmic staining and with or without nuclear staining.[3]

Of note, although the basal expression pattern has been associated with the presence of an underlying *TP53* mutation,[3] this pattern is considered non-specific, since it may also be observed in non-neoplastic lesions such as lichen sclerosus, lichen planus, and spongiotic dermatitis.[4]

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