



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

Version: 4.2.0.0

Protocol Posting Date: June 2021

CAP Laboratory Accreditation Program Protocol Required Use Date: March 2022

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 (eg, 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 Hodgkin or non-Hodgkin Lymphoma protocols)
Sarcoma (consider the Soft Tissue 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 (ie, 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 ie, all required elements must be in the synoptic portion of the report in the format defined above.

Summary of Changes

v 4.2.0.0

- General Reformatting
- Updated Tumor General Modelling
- Updated Histologic Grade Responses
- New WHO 5th Edition Histological Updates
- Added Equivocal Response to Lymphovascular Invasion (LVI)
- Revised Margins Section
- Revised Lymph Nodes Section
- Added Distant Metastasis Section
- Removed pTX and pNX Staging Classification
- Updated FIGO Stage
- Additional Findings Section Updated
- Added p53 and p16 Immunohistochemistry plus HPV-ISH to Special Studies Section

Reporting Template

Protocol Posting Date: June 2021

Select a single response unless otherwise indicated.

CASE SUMMARY: (VULVA)

Standard(s): AJCC-UICC 8, FIGO Cancer Report 2018

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: _____
 Perineum: _____
 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
- Phyllodes tumor, borderline
- Phyllodes tumor, malignant
- Adenocarcinoma, NOS
- Adenocarcinoma of anogenital mammary-like glands
- Adenocarcinoma, intestinal type
- Paget disease, extramammary
- Sweat gland adenocarcinoma
- Apocrine adenocarcinoma
- Eccrine adenocarcinoma
- Porocarcinoma, NOS
- Adenoid cystic carcinoma
- Adenosquamous carcinoma
- Carcinoma, poorly differentiated, NOS
- Small cell neuroendocrine carcinoma
- Large cell neuroendocrine carcinoma
- Combined small cell neuroendocrine carcinoma
- Combined large cell neuroendocrine carcinoma
- Neuroendocrine tumor, NOS
- Neuroendocrine tumor, grade 1
- Neuroendocrine tumor, grade 2
- Myoepithelial carcinoma
- Epithelial-myoepithelial carcinoma
- Other histologic type not listed (specify): _____
- Carcinoma, type cannot be determined
- +Histologic Type Comment:** _____

Histologic Grade

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

Depth of Tumor Invasion (Note E)

- Specify in Millimeters (mm): _____ mm
- Other (specify): _____
- Cannot be determined (explain): _____

+Tumor Border (Note E)

- 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): _____

Lymphovascular Invasion (Note G)

- Not identified
- Present
- Equivocal (explain): _____
- Cannot be determined (explain): _____

+Tumor Comment: _____

MARGINS

Margin Status for Invasive Carcinoma

High-grade squamous intraepithelial lesion (VIN 2-3), dVIN, 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: _____

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 HSIL (VIN2-3) or dVIN (select all that apply)

All margins negative for high-grade squamous intraepithelial lesion (HSIL) and / or differentiated vulvar intraepithelial neoplasia (dVIN)

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): _____

Other (specify): _____

Cannot be determined (explain): _____

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): _____

Not applicable

+Margin Comment: _____

REGIONAL LYMPH NODES

Regional Lymph Node Status

Only inguinal and femoral nodes are considered regional lymph nodes. Any other involved nodes should be categorized as metastases (pM1) and be commented on in the distant metastasis section. Presence of isolated tumor cells no greater than 0.2 mm in regional lymph node(s) is considered NO (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 5 mm or Greater

Exact number (specify): _____

At least (specify): _____

Other (specify): _____

Cannot be determined (explain): _____

Number of Nodes with Metastasis Less than 5 mm (excluding 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)#

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): _____

+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 (select all that apply)

- None identified
 - Extranodal extension
 - Fixed / ulcerated nodes
 - Other (specify): _____
 - Cannot be determined (explain): _____
 - Not applicable
- 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

- 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

PATHOLOGIC STAGE CLASSIFICATION (pTNM, AJCC 8th ed.) (Note [H](#))

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.

TNM Descriptors (select all that apply)

- Not applicable: _____
- m (multiple primary tumors)
- r (recurrent)
- y (post-treatment)

pT Category

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

** Multifocal lesions should be designated as such. The largest lesion or the lesion with the greatest depth of invasion will be the target lesion identified to address the highest pT stage. 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.*

*pT1: Tumor confined to the vulva and / or perineum**

The LAST definition of superficial invasive squamous cell carcinoma (SISCCA) conforms to AJCC pT1a/FIGO IA

pT1a: Lesions 2 cm or less, confined to the vulva and / or perineum, and with stromal invasion of 1.0 mm or less##

pT1b: Lesions more than 2 cm, or any size with stromal invasion of more than 1.0 mm, confined to the vulva and / or perineum

pT1 (subcategory cannot be determined)

pT2: Tumor of any size with extension to adjacent perineal structures (lower / distal third of the urethra, lower / distal third of the vagina, anal involvement)

Mucosal surface of bladder or rectum must be involved

___ pT3: Tumor of any size with extension to any of the following: upper / proximal two-thirds of the urethra, upper / proximal two-thirds of the vagina, bladder mucosa, rectal mucosa,### or fixed to pelvic bone

+pN Modifier

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

pN Category

___ 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

Isolated tumor cells (ITCs) are single cells or small clusters of cells not more than 0.2 mm in greatest dimension.

___ pN0(i+): Isolated tumor cells in regional lymph node(s) no greater than 0.2 mm###

pN1: Regional lymph node metastasis with one or two lymph node metastases each less than 5 mm, or one lymph node metastasis greater than or equal to 5 mm

___ pN1a: One or two lymph node metastases each less than 5 mm###

___ pN1b: One lymph node metastasis greater than or equal to 5 mm

___ pN1 (subcategory cannot be determined)

pN2: Regional lymph node metastasis with three or more lymph node metastases each less than 5 mm, or two or more lymph node metastases greater than 5 mm, or lymph node(s) with extranodal extension

___ pN2a: Three or more lymph node metastases each less than 5 mm###

___ pN2b: Two or more lymph node metastases greater than or equal to 5 mm

___ pN2c: Lymph node metastasis with extranodal extension

___ pN2 (subcategory cannot be determined)

___ pN3: Fixed or ulcerated regional lymph node metastasis

The site, size, and laterality of lymph node metastases should be recorded.

pM Category (required only if confirmed pathologically)

___ Not applicable - pM cannot be determined from the submitted specimen(s)

Internal iliac / hypogastric, external iliac, and common iliac lymph nodes are considered distant metastasis.

___ pM1: Distant metastasis (including pelvic lymph node metastasis)#

FIGO STAGE

+FIGO Stage (2018 FIGO Cancer Report)

___ I: Tumor confined to the vulva and / or peritoneum, without lymph node metastasis

The LAST definition of superficial invasive squamous cell carcinoma (SISCCA) conforms to AJCC pT1a/FIGO IA.

___ IA: Tumor less than or equal to 2 cm in size, confined to the vulva and / or perineum and with stromal invasion less than or equal to 1.0 mm, no nodal metastasis#

___ IB: Tumor greater than 2 cm in size or with stromal invasion greater than 1.0 mm, confined to the vulva and / or perineum

___ II: Tumor of any size with extension to adjacent perineal structures (lower third of urethra, lower third of vagina, anus) without lymph node metastasis

___ III: Tumor of any size with or without extension to adjacent perineal structures (lower third of urethra, lower third of vagina, anus) with metastasis to inguinofemoral lymph nodes

___ IIIA: With 1 lymph node metastasis (greater than or equal to 5 mm)

___ IIIA: With 1 to 2 lymph node metastasis(es) (less than 5 mm)

- IIIB: With 2 or more lymph node metastases (greater than or equal to 5 mm)
- IIIB: With 3 or more lymph node metastases (less than 5 mm)
- IIIC: With positive nodes with extranodal extension
- 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 inguinofemoral lymph nodes
- IVB: Any distant metastasis including pelvic lymph nodes

ADDITIONAL FINDINGS (Note I)

+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)
- Lichen sclerosus
- Other (specify): _____

SPECIAL STUDIES (Note J)

+Ancillary Studies (specify): _____

+p16 Immunohistochemistry

- Positive
- Negative

+p53 Immunohistochemistry

- Normal (wild type)
- Abnormal (mutated)
 - Overexpression (strong, diffuse basilar nuclear expression)
 - Null (lack of nuclear or cytoplasmic expression)
 - Cytoplasmic only (lacks 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.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 the 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.

References

1. Rouzier R, Haddad B, Atallah D, Dubois P, Paniel BJ. Surgery for vulvar cancer. Clin Obstet Gynecol. 2005;48:869-878.
2. Amin MB, Edge SB, Greene FL, et al, eds. AJCC Cancer Staging Manual. 8th ed. New York, NY: Springer; 2017.

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 ≤ 2 cm or >2 cm.

C. Etiology/Pathogenesis

Two pathways have been elucidated in the pathogenesis of invasive vulvar squamous carcinoma.^{1,2,3} The first pathway (HPV-associated) involves classic vulvar intraepithelial neoplasia (VIN) / high-grade squamous intraepithelial lesion (HSIL), which is associated with high-risk human papillomavirus (HPV) subtypes (mostly HPV 16) and is histologically similar to that seen in the cervix. It tends to be multifocal and is more common in younger women, with a relatively low risk of progression into invasive squamous cell carcinoma. It is usually diffusely, block-positive with p16 immunostain (reflecting HPV association).

The associated invasive component is often basaloid or warty in morphology. The second pathway is referred to as HPV-independent and manifests as differentiated VIN (dVIN). dVIN is not associated with HPV, but instead with vulvar dystrophy such as lichen sclerosus, vulvar acanthosis with altered differentiation (VAAM), differentiated exophytic vulvar intraepithelial lesion (DEVIL), lichen simplex chronicus, and squamous cell hyperplasia. The morphologic features of dVIN are subtle. Helpful features include basal cell nuclear atypia, dyskeratosis, and elongated or clubbed, anastomosing rete ridges, but there are a variety of patterns.^{4,5,6} At a minimum, the diagnosis of dVIN should be contingent on basal atypia (abnormal chromatin with hyperchromasia or vesicular spacing, nuclear enlargement, nuclear pleomorphism, or mitotic figures), p53 aberrant expression (null, contiguous strong basal overexpression, diffuse overexpression or cytoplasmic overexpression, or occasionally wild type) and p16 non-block or negative expression.⁵ Basal overexpression of p53 occurs in up to 80% of dVIN and is defined by intense nuclear staining in 90% or greater cells of the basal layers, but other patterns exist and some investigators have advocated against using percentages.⁵ The associated invasive component is keratinizing and also often associated with p53 mutations. P53 immunostains are helpful in confirming dVIN^{5,6,7} and well-differentiated invasive squamous carcinoma.⁸ The HPV-independent subtype usually occurs in older women. Of note, overlap does exist between the 2 pathways, with some tumors exhibiting morphologic and/or clinical features of both.

Table 1. Features to differentiate keratinizing from basaloid squamous cell carcinoma

	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 high risk human papillomavirus (HPV)	No	Yes Type 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.¹

References

1. McCluggage WG. Recent developments in vulvovaginal pathology. *Histopathology*. 2009;54:156-173.
2. Hart WR. Vulvar intraepithelial neoplasia: historical aspects and current status. *Int J Gynecol Pathol*. 2001;20:16-30.
3. Chiesa-Vottero A, Dvoretzky PM, and Hart WR. Histopathologic study of thin vulvar squamous carcinomas and associated cutaneous lesions. *Am J Surg Pathol*. 2006;30:310-318.
4. Jin C, Liang S. Differentiated vulvar intraepithelial neoplasia: a brief review of clinicopathologic features. *Arch Pathol Lab Med*. 2019;143(9):768-771.
5. Heller DS, Day T, Allbritton JI, et al; ISSVD Difficult Pathologic Diagnoses Committee. Diagnostic criteria for differentiated vulvar intraepithelial neoplasia and vulvar aberrant maturation. *J Low Genit Tract Dis*. 2021;25(1):57-70.
6. Day T, Marzol A, Pagano R, Jaaback K, Scurry J. Clinicopathologic diagnosis of differentiated vulvar intraepithelial neoplasia and vulvar aberrant maturation. *J Low Genit Tract Dis*. 2020;24(4):392-398.

7. Tessier-Cloutier B, Kortekaas KE, Thompson E, et al. Major p53 immunohistochemical patterns in in-situ and invasive squamous cell carcinomas of the vulva and correlation with TP53 mutation status. *Mod Pathol*.33(8):1565-1605.
8. Rakislova N, Alemany L, Clavero O, et al; VVAP Study Group. P53 immunohistochemical patterns in HPV-independent squamous cell carcinoma of the vulva and associated skin lesions: a study of 779 cases. *Int J Mol Sci*. 2020;21(21):8091.

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 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 “wart”, “basaloid”, “verrucous” and “papillary” are no longer necessary components of the histologic type. Adjacent squamous intraepithelial lesions, the putative precursors, are a helpful clue to subtype. For HPV-associated precursors, low grade or high grade “squamous intraepithelial lesion” (SIL) is the preferred terminology but vulvar intraepithelial lesion (VIN) may also be used, with appropriate grades 1,2 or 3 (eg. VIN2). For the HPV-independent precursor of keratinizing squamous cell carcinoma, differentiated VIN (dVIN) is used; there is otherwise no grading for this lesion.

The vulva may harbor tumors arising from mammary-like anogenital glands, such as phyllodes tumors and adenocarcinoma mimicking breast primaries. Carcinomas of sweat gland origin occur but are rare, as are neuroendocrine tumors. Bartholin’s glands with chronic inflammation or marsupialization are susceptible to malignant transformation; these have been categorized based upon similarities to their histologic counterparts in other organs.^{1,2,3} 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 (often with a papillary architecture). There are numerous other patterns, including adenosquamous carcinoma, mucinous adenocarcinoma, myoepithelial carcinoma, epithelial-myoepithelial carcinoma and neuroendocrine carcinoma. Carcinomas derived from sweat gland origin include apocrine adenocarcinoma, eccrine adenocarcinoma, porocarcinoma and adenoid cystic carcinoma subtypes and usually arise in the labia majora in older patients.

References

1. Herrington CS, Kim K-R, McCluggage WG, Ordi J. Tumours of the vulva. In: WHO Classification of Tumours Editorial Board. Female genital tumours [Internet]. Lyon (France): International Agency for Research on Cancer; 2020 [cited 2020 Dec 30]. (WHO classification of tumours series, 5th ed; vol 4). Available from <https://tumoursclassification.iarc.who.int/chapters/1>.
2. Ouldamer L, Chraïbi Z, Arbion F, Barillot I, Body G. Bartholin’s gland carcinoma: epidemiology and therapeutic management. Review. *Surg Oncol*. 2013;22:117-122.
3. Nazeran T, Cheng AS, Karnezis AN, Tinker AV, Gilks CB. Bartholin gland carcinoma: clinicopathologic features, including p16 expression and clinical outcome. *Int J Gynecol Pathol*. 2018;38:189-195.

E. 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.^{1,2} Tumor thickness is not a

parameter used in staging, but may be used when the tumor is exophytic, the surface is ulcerated, or there is no adjacent epithelial-stromal junction, preventing measurement of 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.^{2,3} This parameter is important for tumor staging, especially for small tumors. However, depth of invasion can be difficult to measure when it is superficial and pathologists may disagree as to what constitutes true invasion.⁴ A proposed alternative method of measuring invasion is from the basement membrane of the deepest adjacent dysplastic rete ridge to the deepest point of invasion.^{5,6} This approach effectively down-stages some stage 1B to 1A tumors. Two studies have shown that down-staged patients had fewer recurrences and higher survival compared with stage 1B patients and this approach might prevent the need for lymphadenectomy.^{5,6} Currently, there is no consensus for the adoption of this approach but further studies are in progress and reporting of the alternative method measurement in a note is acceptable.

In early stage disease, there are insufficient data on 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.⁷ Tumor stage and lymph node status are the strongest predictors of overall progression-free survival.⁸

References

1. Tavassoli FA, Devilee P, eds. World Health Organization Classification of Tumours: Pathology and Genetics of Tumours of the Breast and Female Genital Organs. Lyon, France: IARC Press; 2003.
2. Yoder BJ, Rufforny I, Massoll NA, Wilkinson EJ. Stage 1A vulvar squamous cell carcinoma: an analysis of tumor invasive characteristics and risk. *Am J Surg Pathol.* 2008;32:765-772.
3. Amin MB, Edge SB, Greene FL, et al, eds. *AJCC Cancer Staging Manual.* 8th ed. New York, NY: Springer; 2017.
4. Pouwer AW, Bult P, Otte I, et al. Measuring the depth of invasion in vulvar squamous cell carcinoma: interobserver agreement and pitfalls. *Histopathol.* 2019; 75(3):413-420.
5. van den Eindin LC, Massuger LF, Jonkman JK, Bult P, de Hullu JA, Bulten J. An alternative way to measure the depth of invasion of vulvar squamous cell carcinoma in relation to prognosis. 2015; *Mod Pathol.* 28(2):295-302.
6. Skala SL, Ebot JA, Zhao L, Lieberman RW. Predictive value of an alternative strategy for measuring depth and size of stage 1 vulvar squamous cell carcinoma, *J Low Genit Tract Dis.* 2020; 24(3):265-271.
7. Te Grootenhuis NC, Pouwer AFW, de Bock GH et al. Prognostic factors for local recurrence of squamous cell carcinoma of the vulva: a systematic review. *Gynecol Oncol.* 2018;148(3):622-631.
8. Julia CJ, Hoang LN. A review of prognostic factors in squamous cell carcinoma of the vulva: evidence from the last decade. *Semin Diagn Pathol.* 2021;38(1):37-49.

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, but this feature is understudied.^{1,2}

References

1. Drew PA, Al-Abbadi MA, Orlando CA, Hendricks JB, Kubilis PS, Wilkinson EJ. Prognostic factors in carcinoma of the vulva: a clinicopathologic and DNA flow cytometric study. *Int J Gynecol Pathol.* 1996;15:235-241.
2. Julia CJ, Hoang LN. A review of prognostic factors in squamous cell carcinoma of the vulva: evidence from the last decade. *Semin Diagn Pathol.* 2021;38(1):37-49.

G. Lymphatic/Blood Vessel Invasion

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}

References

1. Chan JK, Sugiyama V, Pham H, et al. Margin distance and other clinico-pathologic prognostic factors in vulvar carcinoma: a multivariate analysis. *Gynecol Oncol.* 2007;104:636-641.
2. Raspagliesi F, Hanozet F, Ditto A, et al. Clinical and pathologic prognostic factors in squamous cell carcinoma of the vulva. *Gynecol Oncol.* 2006;102:333-337.
3. Hauspy J, Beiner M, Harley I, et al. Sentinel lymph node in vulvar cancer. *Cancer.* 2007;110:1015-1022.

H. Pathologic Stage Classification

The TNM staging system of the American Joint Committee on Cancer (AJCC) for carcinoma of the vulva is recommended.^{1,2} FIGO staging is desirable but optional.³

According to AJCC 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 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

T Category Considerations

Lymphovascular invasion (LVI) indicates whether microscopic lymphovascular invasion is identified. LVI includes lymphatic invasion, vascular invasion, or lymphovascular invasion. According to AJCC convention, LVI does not affect the T category indicating local extent of tumor unless specifically included in the definition of a T category.

N Category Considerations

Only femoral and inguinal lymph nodes are considered regional nodes in vulvar cancers. An effort should be made to describe the site and laterality of lymph node metastases.

Isolated tumor cells (ITCs) are single cells or small clusters of cells not more than 0.2 mm in greatest dimension. Lymph nodes or distant sites with ITCs found by either histologic examination (eg, immunohistochemical evaluation for cytokeratin) or nonmorphological techniques (eg, 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.^{4,5,6} Patients with a negative or micro-metastatic sentinel node may be candidates to forego groin dissection.^{7,8}

Extranodal Extension/Nodal Replacement

Both extranodal extension and the size of lymph node metastasis have been shown to reflect prognosis and should be noted in the report.^{1,6,9}

References

1. Amin MB, Edge SB, Greene FL, et al, eds. AJCC Cancer Staging Manual. 8th ed. New York, NY: Springer; 2017.
2. Brierley JD, Gospodarowicz M, Wittekind Ch, eds. TNM Classification of Malignant Tumors. 8th ed. Oxford, UK: Wiley; 2016.
3. Bhatla N, Denny L. FIGO Cancer Report 2018. Int J Gynecol Obstet. 2018;142(Suppl 2):i-iv, 1-158.
4. Paladini D, Cross P, Lopes A, Monaghan JM. Prognostic significance of lymph node variables in squamous cell carcinoma of the vulva. Cancer. 1994;74:2491-2494.
5. Rouzier R, Haddad B, Atallah D, Dubois P, Paniel BJ. Surgery for vulvar cancer. Clin Obstet Gynecol. 2005;48:869-878.
6. Raspagliesi F, Hanozet F, Ditto A, et al. Clinical and pathologic prognostic factors in squamous cell carcinoma of the vulva. Gynecol Oncol. 2006;102:333-337.
7. Nica A, Covens A, Vicus D, et al. Sentinel lymph nodes in vulvar cancer: management dilemmas in patients with positive nodes and larger tumors. Gynecol Oncol. 2019;152(1):94-100.

8. Brincat MR, Baron YM. Sentinel lymph node biopsy in the management of vulvar carcinoma: an evidence-based insight. *Int J Gynecol Cancer*. 2017;27(8):1769-1773.
9. van der Velden J, van Lindert AC, Lammes FB, et al. Extracapsular growth of lymph node metastases in squamous cell carcinoma of the vulva: the impact on recurrence and survival. *Cancer*. 1995;75:2885-2890.

I. Additional Findings

Presence of adjacent lesions such as lichen sclerosus may increase the risk of recurrence and development of new primary tumors in patients with vulvar squamous cell carcinoma.¹ Therefore, reporting the presence of this finding is recommended.

References

1. Yap JK, Fox R, Leonard S, et al. Adjacent lichen sclerosus predicts local recurrence and second field tumour in women with vulvar squamous cell carcinoma. *Gynecol Oncol*. 2016;142(3):420-426.

J. Ancillary Tests

Reporting ancillary tests in synoptic format is optional, but their importance is increasing for diagnostic, therapeutic and prognostic purposes. Reporting p16 status is encouraged because the prognosis for HPV-associated squamous cell carcinoma is much better than for HPV-independent types. Additionally, p53 is useful diagnostically to identify HPV-independent vulvar squamous cell carcinoma harboring TP53 mutations that behave aggressively and precursor vulvar lesions such as dVIN.¹ It is included here to emphasize reporting terminology. There are 3 abnormal patterns of p53 expression that differ from normal (“wild type”) tissue expression, which is patchy and has variable weak to strong nuclear expression. An abnormal uniformly strong, continuous basal cell nuclear overexpression is consistent with dVIN. An abnormal “null” phenotype is the lack of nuclear or cytoplasmic expression. Recently recognized is an abnormal cytoplasmic overexpression, where the cytoplasm is diffusely and contiguously moderate to strongly positive while the nuclei are negative or variably stained. A strong, contiguous nuclear stain with a cytoplasmic blush is interpreted as nuclear overexpression.² Of note, strong midepithelial expression of p53 that spares the basal layer and is associated with strong block p16 positivity has been detected in HPV-associated squamous lesions.³

References

1. Nooij LS, Ter Haar NT, Ruano D, et al. Genomic characterization of vulvar (pre)cancers identifies distinct molecular subtypes with prognostic significance. *Clin Cancer Res*. 2017; 23:6781-6789.
2. Köbel M, Kang, EY. The many uses of p53 immunohistochemistry in gynecologic pathology: proceedings of the ISGyP Companion Society session at the 2020 USCAP annual meeting. *Int J Gynecol Pathol*. 2021; 40(1):32-40.
3. Tessier-Cloutier B, Kortekaas KE, Thompson E, et al. Major p53 immunohistochemical patterns in situ and invasive squamous cell carcinomas of the vulva and correlation with TP53 mutation status. *Mod Pathol*. 2020; 33:1595-1605.