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

Version: 4.2.0.1
Protocol Posting Date: July 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)

Authors
Uma G. Krishnamurti, MD, PhD*; Barbara A. Crothers, DO*; Christopher N. Otis, MD; George G. Birdsong, MD; Saeid Movahedi-Lankarani, MD; Veronica Klepeis, MD, PhD.

With guidance from the CAP Cancer and CAP Pathology Electronic Reporting Committees.
* Denotes primary author.

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 4.2.0.1

- Fixed incorrect staging classification note for pN2
    - Changed "...or two or more lymph node metastases greater than 5 mm..." to "...or two or more lymph node metastases greater than *or equal to* 5 mm..."

v 4.2.0.0

- General Reformatting

Reporting Template

Protocol Posting Date: July 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 F)
___ 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 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 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 lymphadectomy 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 or equal to 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 intraepitheilal 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, Dvoretsky 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 "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 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/chpters/1.
2. Ouldamer L, Chraibi 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.
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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]

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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]

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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]

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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

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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]

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