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Carcinoma of the Vulva Histopathology Reporting Guide

Family/Last name

Given name(s)

Date of birth DD – MM – YYYY

Patient identifiers

Date of request DD – MM – YYYY

Accession/Laboratory number

Elements in **black text** are CORE. Elements in **grey text** are NON-CORE.

☐ indicates multi-select values ◯ indicates single select values

SCOPE OF THIS DATASET

CLINICAL INFORMATION (select all that apply) (Note 1)

- ◯ Information not provided
- ☐ History of previous cancer, *specify*
- ☐ Previous neoadjuvant therapy, *specify*
- ☐ Other clinical information, *specify*

OPERATIVE PROCEDURE (select all that apply) (Note 2)

- ◯ Not specified
- ☐ Wide local excision
- ☐ Partial radical vulvectomy
- ☐ Total radical vulvectomy
- ☐ Lymph nodes, *specify site(s)*
- ☐ Other, *specify*

SPECIMEN DIMENSIONS (Note 3)

mm x mm x mm

◯ Cannot be assessed, *specify*

TUMOUR SITE (select all that apply) (Note 4)

- ☐ Vulva
  - ☐ Left
    - ◯ Not specified
    - ☐ Labium majus
    - ☐ Labium minus
    - ☐ Bartholin gland
  - ☐ Right
    - ◯ Not specified
    - ☐ Labium majus
    - ☐ Labium minus
    - ☐ Bartholin gland
  - ☐ Midline/central/clitoral
  - ☐ Vulva, site not known
  - ☐ Extension to adjacent structures
    - ☐ Vagina
    - ☐ Urethra
    - ☐ Anal/perianal
    - ☐ Other, *specify*
  - ☐ Other, *specify*

TUMOUR DIMENSIONS (Note 5)

Maximum horizontal tumour dimension mm

Depth of invasion mm

◯ Cannot be assessed, *specify*

BLOCK IDENTIFICATION KEY (Note 6)

(List overleaf or separately with an indication of the nature and origin of all tissue blocks)

HISTOLOGICAL TUMOUR TYPE (Note 7)

(Value list based on the World Health Organization Classification of Female Genital Tumours (2020))

- ◯ Squamous cell carcinoma, HPV-associated
- ◯ Squamous cell carcinoma, HPV-independent
- ◯ Squamous cell carcinoma, NOS
- ◯ Basal cell carcinoma
- ◯ Bartholin gland carcinoma, *specify type*
- ◯ Adenocarcinoma, *specify type*
- ◯ Neuroendocrine neoplasm, *specify type*
- ◯ Other, *specify*

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LYMPHOVASCULAR INVASION (Note 8)

- ◯ Indeterminate
- ◯ Not identified
- ◯ Present

PERINEURAL INVASION (Note 9)

- ◯ Not identified
- ◯ Present

MARGIN STATUS (Note 10)

Invasive carcinoma

- ◯ Cannot be assessed
- ◯ Not involved
  - Distance of tumour from closest skin or mucosal margin: ____ mm
  - Distance of tumour from deep margin: ____ mm
  - ◯ Distance not assessable
  - Specify closest margin(s), if possible: ____
- ◯ Involved
  - Specify margin(s), if possible: ____

High grade precursor lesions

- ◯ Not applicable
- ◯ Cannot be assessed
- ◯ Not involved
  - Distance of high grade precursor lesions from closest margin: ____ mm
  - Specify closest margin(s), if possible: ____
- ◯ Involved
  - Specify margin(s), if possible: ____

LYMPH NODE STATUS (Note 11)

Sentinel lymph nodes (inguinofemoral)

- ◯ Cannot be assessed
- ◯ No nodes submitted or found

Site 1 ____

- Number of nodes examined: ____
- Number of nodes with isolated tumour cells (ITCs): ____
- Number of positive nodes (other than ITCs): ____
- Maximum dimension of largest deposit: ____ mm

Extranodal extension[a]

- ◯ Not identified ◯ Present

Site 2 ____

- Number of nodes examined: ____
- Number of nodes with ITCs: ____
- Number of positive nodes (other than ITCs): ____
- Maximum dimension of largest deposit: ____ mm

Extranodal extension[a]

- ◯ Not identified ◯ Present

Classification of sentinel nodal metastasis

- ◯ ITCs (≤0.2 mm and ≤200 cells)
- ◯ Micrometastasis (>0.2 mm and ≤2 mm)
- ◯ Macrometastasis (>2 mm)

If sentinel node positive

- ◯ Identified with ultrastaging including immunohistochemistry
- ◯ Identified with ultrastaging without immunohistochemistry
- ◯ Identified without ultrastaging

Regional non-sentinel lymph nodes (inguinofemoral)

- ◯ Cannot be assessed
- ◯ No nodes submitted or found

Site 1 ____

- Number of nodes examined: ____
- Number of nodes with ITCs: ____
- Number of positive nodes (other than ITCs): ____
- Maximum dimension of largest deposit: ____ mm

Extranodal extension[a]

- ◯ Not identified ◯ Present

Site 2 ____

- Number of nodes examined: ____
- Number of nodes with ITCs: ____
- Number of positive nodes (other than ITCs): ____
- Maximum dimension of largest deposit: ____ mm

Extranodal extension[a]

- ◯ Not identified ◯ Present

Classification of nodal metastasis

- ◯ ITCs (≤0.2 mm and ≤200 cells)
- ◯ Micrometastasis (>0.2 mm and ≤2 mm)
- ◯ Macrometastasis (>2 mm)

Clinically fixed or ulcerated lymph nodes

- ◯ Not known ◯ Present

[a] *Extranodal extension is synonymous with extracapsular extension/spread.*

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Non-regional lymph nodes (other than inguinofemoral; includes pelvic or other sites)

- ◯ Cannot be assessed
- ◯ No nodes submitted or found

Site 1

Number of nodes examined

Number of nodes with ITCs

Number of positive nodes (other than ITCs)

Maximum dimension of largest deposit mm

Extranodal extension[a]

◯ Not identified ◯ Present

Site 2

Number of nodes examined

Number of nodes with ITCs

Number of positive nodes (other than ITCs)

Maximum dimension of largest deposit mm

Extranodal extension[a]

◯ Not identified ◯ Present

Classification of nodal metastasis

- ◯ ITCs (≤0.2 mm and ≤200 cells)
- ◯ Micrometastasis (>0.2 mm and ≤2 mm)
- ◯ Macrometastasis (>2 mm)

[a] *Extranodal extension is synonymous with extracapsular extension/spread.*

COEXISTENT PATHOLOGY/PRECURSOR LESIONS (Note 12)

- ◯ None identified
- ◯ Present (select all that apply)
  - ☐ Low grade squamous intraepithelial lesion (LSIL), HPV-associated
  - ☐ High grade squamous intraepithelial lesion (HSIL), HPV-associated
  - ☐ Vulval intraepithelial neoplasia (VIN), HPV-independent
  - ☐ Lichen sclerosus
  - ☐ Other, *specify*

ANCILLARY STUDIES (Note 13)

- ◯ Not performed
- ◯ Performed (select all that apply)
  - ☐ p16 immunohistochemistry[b]

  AND/OR
  - ☐ HPV testing[b]
  - ☐ p53 immunohistochemistry[b]
  - ☐ Other, *specify test(s) and result(s)*

Representative blocks for ancillary studies, *specify those blocks best representing tumour and/or normal tissue for further study*

[b] *Core for squamous cell carcinomas.*

PATHOLOGICALLY CONFIRMED DISTANT METASTASIS (Note 14)

- ◯ Not identified
- ◯ Present, *specify site(s)*

PROVISIONAL PATHOLOGICAL STAGING (Note 15)

FIGO (2021 edition)[c]

- ◯ I Tumour confined to the vulva
  - ◯ IA Tumour size ≤2 cm and stromal invasion ≤1 mm[d]
  - ◯ IB Tumour size >2 cm or stromal invasion >1 mm[d]
- ◯ II Tumour of any size with extension to lower one-third of the urethra, lower one-third of the vagina, lower one-third of the anus with negative nodes
- ◯ III Tumour of any size with extension to upper part of adjacent perineal structures, or with any number of nonfixed, nonulcerated lymph node
  - ◯ IIIA Tumour 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 ≤5 mm
  - ◯ IIIB Regional[e] lymph node metastases >5 mm
  - ◯ IIIC Regional[e] lymph node metastases with extracapsular spread
- ◯ IV Tumour 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[e] lymph node metastases
  - ◯ IVB Distant metastases

[c] *Reprinted from Int J Gynaecol Obstet., Volume 155, Olawaiye AB, Cotler J, Cuello MA, et al., FIGO staging for carcinoma of the vulva: 2021 revision, pages 43-47, 2021, with permission from Wiley.*

[d] *Depth of invasion is measured from the basement membrane of the deepest, adjacent, dysplastic, tumour-free rete ridge (or nearest dysplastic rete peg) to the deepest point of invasion.*

[e] *Regional refers to inguinal and femoral lymph nodes.*

TNM Staging (UICC TNM 8th edition 2016)[f]

TNM Descriptors (only if applicable) (select all that apply)

- ☐ m - multiple primary tumours
- ☐ r - recurrent
- ☐ y - post-therapy

Primary tumour (pT)

- ◯ TX Primary tumour cannot be assessed
- ◯ T0 No evidence of primary tumour
- ◯ Tis Carcinoma in situ (preinvasive carcinoma), intraepithelial neoplasia grade III (VIN III)
- ◯ T1 Tumour confirmed to vulva or vulva and perineum
  - ◯ T1a Tumour 2 cm or less in greatest dimension and with stromal invasion no greater than 1 mm[d]
  - ◯ T1b Tumour greater than 2 cm and or with stromal invasion greater than 1 mm[d]
- ◯ T2 Tumour invades any of the following structures: lower third urethra, lower third vagina, anus
- ◯ T3[g] Tumour invades any of the following perineal structures: upper 2/3 urethra, upper 2/3 vagina, bladder mucosa, rectal mucosa; or fixed to pelvic bone

Regional lymph nodes (pN)

- ◯ NX Regional lymph nodes cannot be assessed
- ◯ N0 No regional lymph node metastasis
- ◯ N1 Regional lymph node metastasis with the following features:
  - ◯ N1a One or two lymph node metastasis each less than 5 mm
  - ◯ N1b One lymph node metastasis 5 mm or greater
- ◯ N2 Regional lymph node metastasis with the following features:
  - ◯ N2a Three or more lymph nodes metastases each less than 5 mm
  - ◯ N2b Two or more lymph node metastases 5 mm or greater
  - ◯ N2c Lymph node metastasis with extracapsular spread
- ◯ N3 Fixed or ulcerated regional lymph node metastasis

[d] *Depth of invasion is measured from the basement membrane of the deepest, adjacent, dysplastic, tumour-free rete ridge (or nearest dysplastic rete peg) to the deepest point of invasion.*

[f] *Reproduced with permission. Source: UICC TNM Classification of Malignant Tumours, 8th Edition, eds by James D. Brierley, Mary K. Gospodarowicz, Christian Wittekind. 2016, Publisher Wiley (incorporating any errata published up until 25th January 2022).*

[g] *T3 is not used by FIGO.*

Definitions

CORE elements

CORE elements are those which are essential for the clinical management, staging or prognosis of the cancer. These elements will either have evidentiary support at Level III-2 or above (based on prognostic factors in the National Health and Medical Research Council (NHMRC) levels of evidence[1]). In rare circumstances, where level III-2 evidence is not available an element may be made a CORE element where there is unanimous agreement by the Dataset Authoring Committee (DAC). An appropriate staging system e.g., Pathological TNM staging would normally be included as a CORE element.

Non-morphological testing e.g., molecular or immunohistochemical testing is a growing feature of cancer reporting. However, in many parts of the world this type of testing is limited by the available resources. In order to encourage the global adoption of ancillary tests for patient benefit, International Collaboration on Cancer Reporting (ICCR) includes the most relevant ancillary testing in ICCR Datasets as CORE elements, especially when they are necessary for the diagnosis. Where the technical capability does not yet exist, laboratories may consider temporarily using these data elements as NON-CORE items.

The summation of all CORE elements is considered to be the minimum reporting standard for a specific cancer.

NON-CORE elements

NON-CORE elements are those which are unanimously agreed should be included in the dataset but are not supported by level III-2 evidence. These elements may be clinically important and recommended as good practice but are not yet validated or regularly used in patient management.

Key information other than that which is essential for clinical management, staging or prognosis of the cancer such as macroscopic observations and interpretation, which are fundamental to the histological diagnosis and conclusion e.g., macroscopic tumour details, may be included as either CORE or NON-CORE elements by consensus of DAC.

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Scope

The dataset has been developed for the pathological reporting of resection specimens of primary carcinomas of the vulva.

In some patients with a prior diagnosis of vulval carcinoma (especially squamous), it is not clear whether a 'new' lesion is a recurrence or an independent neoplasm and the dataset can also be used for such tumours, especially when these 'arise' from the surface squamous epithelium. Molecular studies have shown that some of these 'recurrent' neoplasms exhibit similar mutations and are clonally related to the original tumour and are likely to represent true recurrences while others are clonally unrelated with different mutations and are likely to represent new neoplasms.[2]

In those rare cases where more than one primary tumour is present, separate datasets should be completed for each neoplasm. These should include all the elements in this dataset, except for lymph node status which does not need to be documented separately for each tumour.

Haematopoietic neoplasms, mesenchymal neoplasms, mixed epithelial and mesenchymal neoplasms, malignant melanomas, other non-epithelial malignancies and metastatic tumours are excluded from this dataset.

The 2nd edition of this dataset incorporates the 2021 International Federation of Gynaecology and Obstetrics (FIGO) staging for carcinoma of the vulva.[3]

A list of changes in this dataset edition can be accessed here.

The authors of this dataset can be accessed here.

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Note 1 – Clinical information (Core)

In some ICCR datasets, clinical information is a non-core element. However, the Carcinoma of the vulva DAC agreed that clinical information is vital in reporting vulval carcinomas, and thus this is included as a core element. In reporting a vulval carcinoma, knowledge of a history of any prior vulval tumour (including the site), precursor lesion or treatment is important. While in many cases, this information can be identified from the laboratory information system/electronic care record, this is not always the case, and this information should be provided by the clinician on the specimen request form. This is especially important with vulval squamous carcinomas since tumour recurrence is common. In some patients with a prior vulval squamous carcinoma, it is not clear from a pathological perspective whether a 'new' lesion is a recurrence or an independent neoplasm and the dataset can also be used for such tumours if an 'origin' can be seen from the overlying squamous epithelium. Knowledge of a history of a prior precursor lesion or inflammatory dermatosis is also important. Information regarding a history of a prior malignancy is important in reporting those rare primary vulval adenocarcinomas since a metastasis should always be excluded before rendering such a diagnosis. Knowledge of a history of any prior neoadjuvant therapy (chemotherapy, radiotherapy, chemoradiation) is important since this can have a marked effect on the pathological appearances of the neoplasm (gross and morphological).

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Note 2 – Operative procedure (Core)

Wide local excision refers to removal of the full thickness of vulval skin or mucosa with preservation of subcutaneous fat and other deep tissues (older terminologies include partial vulvectomy, superficial vulvectomy, skinning vulvectomy).[4-6] Wide local excision is usually performed for pre-invasive or non-malignant lesions or for diagnostic purposes where cancer has not been ruled out.

Radical vulvectomy (partial or total) is usually performed for biopsy confirmed invasive carcinoma and involves removing the vulval tissue down to the deep fascia. Radical vulvectomy may include removal of the clitoris with prepuce, the labia majora, labia minora, a portion of vagina, urethra, and/or anus.[4-6] It is desirable that orientation of the specimen is provided by the surgeon to enable evaluation of margin status; this may be achieved by the placing of sutures or by provision of a diagram or photograph.

Wide local excision and radical vulvectomy procedures will be tailored depending on the tumour size, pathological diagnosis, patient wishes/expectations, likely impact on psychosexual function and tumour location with respect to proximity to other vital structures.

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Note 3 – Specimen dimensions (Core)

Although not necessary for staging, clinical management or prognosis, it is recommended that the specimen dimensions be recorded on the pathology report.[7-10] This gives clinicians dealing with the patient an indication as to how radical a resection has been undertaken.

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Note 4 – Tumour site (Core and Non-core)

Detailing the anatomical site of a vulval carcinoma is important for the following reasons: tumours located close to or in the midline can be associated with bilateral or contralateral lymph node involvement because the lymphatic vessels anastomose across the midline, particularly in the clitoral and the anterior labium minus regions and midline/clitoral involvement is associated with a worse prognosis which is possibly related to unfavourable histopathological characteristics of the tumours (more likely to be human papillomavirus (HPV)-independent).[11-13]

The tumour site should be provided by the surgeon and the placing of sutures or the provision of a diagram or photograph may be helpful. If determination of the tumour site is not possible, it may be necessary to liaise with the surgeon.

The tumour laterality (right vulva, left vulva, midline, involvement of other structures) is regarded as a core item, while involvement of the labium majus, labium minus and Bartholin gland is regarded as non-core.

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Note 5 – Tumour dimensions (Core)

Accurate measurement of tumour dimensions in vulval carcinomas is important for staging, patient management and prognostication. Tumour dimensions should be measured in millimetres (mm). The maximum horizontal dimension is the greatest tumour dimension measured parallel to the skin surface. This measurement is typically made based on macroscopic assessment for larger tumours but for very small tumours this may be best measured or can only be measured on the histological section. A second horizontal dimension taken perpendicular to the first and also parallel to the skin surface is often included in the pathology report but this is not necessary for staging, management or prognostication. The depth of invasion (DOI) must also be reported and this is discussed in more detail below.

Note that the final pathology report should only contain one set of measurements; in other words, there should not be separate gross and microscopic measurements in the report. The single set of measurements provided should be based on a correlation of the gross and microscopic features, with gross examination being more important for some tumour measurements and microscopic examination for others.

In providing the final tumour dimensions, the measurements in a prior specimen, for example an excisional biopsy, may need to be taken into account. Although it may overestimate the maximum horizontal extent, it is recommended to add together the maximum horizontal measurement in different specimens when calculating the final horizontal extent. The DOI can be taken as the maximum (largest) DOI in the two different specimens.

If the tumour involves a margin (skin, mucosal or deep), a comment should be made regarding the possibility of underestimation of the horizontal dimension or DOI.

Measurement of depth of invasion (DOI)

As discussed, the maximum DOI of tumour must be measured in all cases since invasion >1 mm signifies greater than Stage IA and typically results in inguinofemoral lymphadenectomy being undertaken. Traditionally, this measurement is taken from the most superficial dermal papilla adjacent to the tumour to the deepest point of invasion (conventional measurement) (refer to Figure 1). An alternative method of measuring the DOI has been proposed whereby the DOI is measured from the basement membrane of the deepest adjacent dysplastic (tumour free) rete ridge (or nearest dysplastic rete peg) to the deepest point of invasion.[14,15] This method of measuring DOI results in 'downstaging' of some Stage IB tumours to IA. In one study, the downstaged patients developed less recurrences and had a higher disease-specific survival compared with the patients who remained Stage IB.[14] Using the alternative method for measuring DOI would have resulted in 19% of patients with vulval squamous cell carcinoma (SCC) not undergoing lymphadenectomy with less treatment-related morbidity. In another study, all tumours which were downstaged using this method of measuring DOI had no nodal metastasis, lymphovascular or perineural invasion.[15] There remains significant interobserver variability in assessment of superficial invasion, including disagreements as to whether or not there is invasion and whether the invasion is ≤1 mm or >1 mm (Stage IA versus Stage IB),[16,17] and this can result in changes in stage assignment (Stage IA versus IB) between pre-operative biopsy and the subsequent resection.[18]

In alignment with the updated 2021 FIGO staging publication,[3] this revised ICCR dataset also endorses the alternative method for measuring DOI. This harmonises the method of measuring DOI with cervical carcinomas and will potentially reduce morbidity to patients by reducing the number of lymphadenectomy procedures. The FIGO Committee on Women's Cancer acknowledges that the evidence for the oncological safety of this alternative method of measuring DOI is limited and FIGO will collect new information prospectively to evaluate this change in methodology. It is noted here that the recent European Society of Gynaecological Oncology (ESGO) guidelines (2023 update) for the management of patients with vulval cancer advises to record the DOI using both methods but to base treatment on the traditional method of measuring DOI.[19]

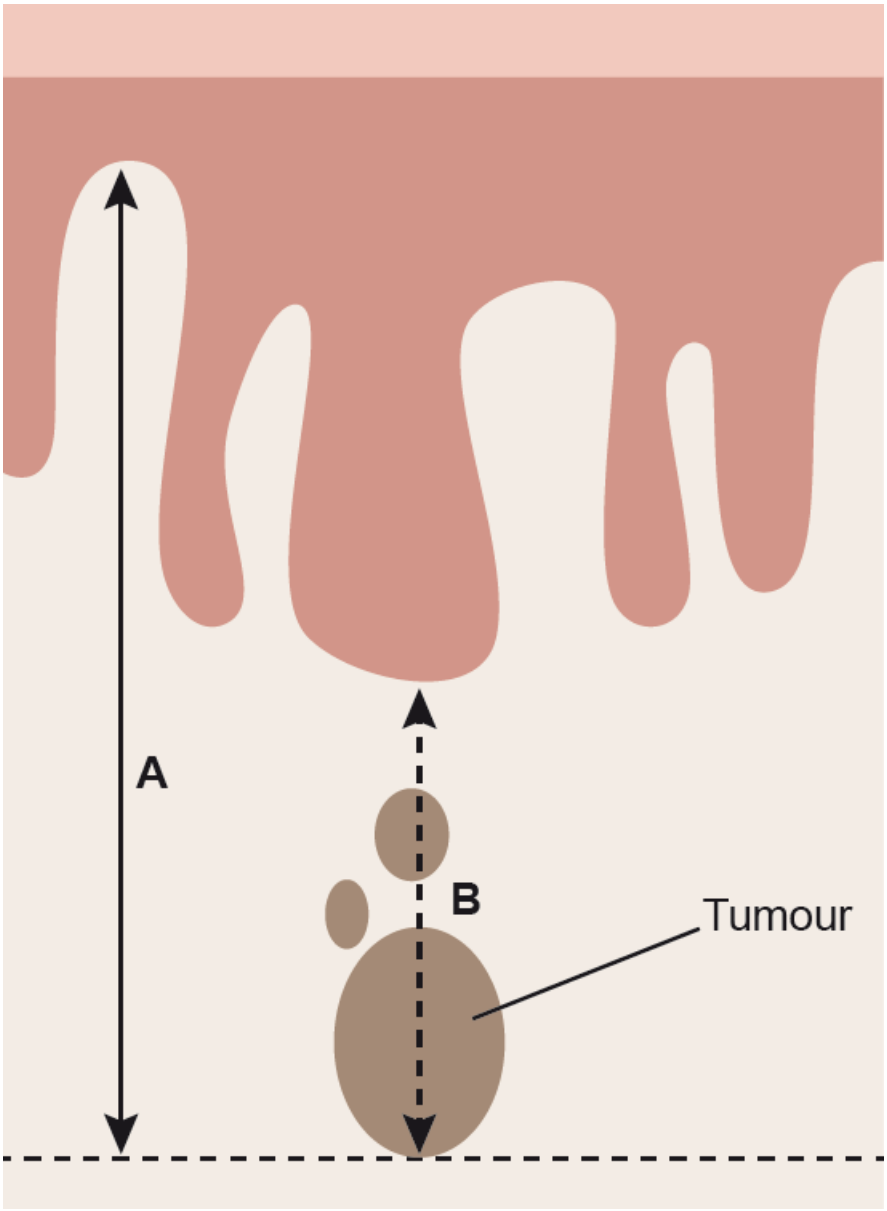

Figure 1: Schematic diagram showing measurement of depth of invasion in vulval carcinomas. A shows the traditional method of measurement from the adjacent most superficial dermal papilla to the deepest point of invasion while B shows the alternative (now recommended by FIGO and ICCR) method from the basement membrane of the deepest adjacent dysplastic (tumour free) rete ridge to the deepest point of invasion. Permission courtesy of Mr Norm Cyr.

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Note 6 – Block identification key (Non-core)

The origin/designation of all tissue blocks should be recorded. This information should ideally be documented in the final pathology report and is particularly important should the need for internal or external review arise. The reviewer needs to be clear about the origin of each block in order to provide an informed specialist opinion. If this information is not included in the final pathology report, it should be

available on the laboratory computer system and relayed to the reviewing pathologist. It may be useful to have a digital image of the specimen and record of the origin of the tumour blocks in some cases.

Recording the origin/designation of tissue blocks also facilitates retrieval of blocks for further immunohistochemical or molecular analysis, research studies or clinical trials.

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Note 7 – Histological tumour type (Core)

All tumours should be typed according to most recent edition of the World Health Organization (WHO) Classification of Tumours of Female Genital Tumours, 5th edition, 2020.[20] The ICCR dataset includes 5th edition Corrigenda, June 2021.[21]

Squamous cell carcinoma (SCC) is by far the most common carcinoma to arise on the vulva. Traditional histologic subtyping of SCC, using terms such as keratinising, non-keratinising, basaloid and warty, has been superseded by HPV status as the major determinant of classification. Vulval SCC is divided into HPV-associated and HPV-independent types. HPV-independent SCC have a worse prognosis with significantly worse recurrence free and overall survival compared to HPV-associated SCC.[22-25] There is also growing evidence that HPV-independent SCC are less responsive to radiotherapy.[26,27] HPV-associated SCC are secondary to persistent infection by oncogenic high-risk HPV (most commonly types 16 and 18) and are associated with smoking, immunosuppression and often multifocal disease including HPV-associated lesions in other areas of the lower female genital tract (vagina, cervix) and anal/perianal regions. HPV-independent SCC often arises in the setting of lichen sclerosus and chronic inflammation.[28] Verrucous carcinoma falls under the umbrella of HPV-independent SCC. The majority of HPV-associated SCC exhibit basaloid or warty morphology, while HPV-independent SCC tend to be keratinising. However, a significant percentage of cases (15-20%) will show overlapping morphologic features.[29,30] The nature of any adjacent precursor lesion may be useful in helping to determine the HPV status. However, in practice, ancillary testing is necessary to determine the HPV status given the overlap in morphology in some cases (see **Note 13 ANCILLARY STUDIES**). When HPV status cannot be confidently determined or resources are not available to undertake ancillary testing, a morphological diagnosis of SCC, not otherwise specified (NOS) is acceptable, although this is not recommended.

Most, but not all, HPV-independent vulval SCC are associated with *TP53* mutations. A proportion are *TP53* wild-type and there is growing evidence that these may have an intermediate prognosis between HPV-associated SCC and HPV-independent *TP53* mutated neoplasms.[23,31,32]

Grading of vulval SCC is not recommended and is not included in this dataset. Grading has not been shown to consistently correlate with clinical outcome.[33] In fact, there is a paradox in that HPV-independent SCC, which tend to be keratinising and often well-differentiated have a worse prognosis than HPV-associated SCC which are typically non-keratinising, basaloid and poorly differentiated. In addition, no validated grading system exists for vulval SCC.

Basal cell carcinomas are histologically identical to their counterparts occurring in other cutaneous locations. A variety of adenocarcinomas rarely arise in the vulva and these should be diagnosed using the 2020 WHO Classification.[20] These may be of mammary gland type (various types as in the breast), of sweat gland origin (various types), intestinal type or arise from Paget disease (invasive Paget).[34,35] Before diagnosing a primary vulval adenocarcinoma, a metastasis from elsewhere should always be considered, and correlation of the clinical picture (including the past history) with pathological features, including immunohistochemical studies, may assist.

A variety of carcinomas (squamous, glandular, 'salivary-type' and other) can arise from the Bartholin gland.[36] To be considered a Bartholin gland primary, the tumour should involve the anatomic region of the Bartholin gland and be histologically compatible with an origin in Bartholin gland with no alternative primary site identified elsewhere; preferably normal Bartholin gland tissue should be present in the vicinity of the neoplasm.

Neuroendocrine neoplasia is classified according to the 2020 WHO , although Merkel cell carcinoma also exists at this site.[20] Some vulval neuroendocrine carcinomas are driven by HPV-infection, while some Merkel cell carcinomas are driven by polyomavirus.[37,38]

Table 1: World Health Organization classification of malignant epithelial tumours of the vulva.[20]

Descriptor	**ICD-O codes[a]**
Squamous cell carcinoma, HPV-associated	8085/3
Squamous cell carcinoma, HPV-independent	8086/3
Squamous cell carcinoma NOS	8070/3
Basal cell carcinoma NOS	8090/3
Adenocarcinoma of anogenital mammary-like glands	8500/3
Bartholin gland lesions	
Squamous cell carcinoma NOS	8070/3
Adenoid cystic carcinoma	8200/3
Carcinoma, poorly differentiated, NOS	8020/3
Adenosquamous carcinoma	8560/3
Myoepithelial carcinoma	8982/3
Epithelial-myoepithelial carcinoma	8562/3
Paget disease, extramammary	8542/3
Sweat gland adenocarcinoma	8400/3
Apocrine adenocarcinoma	8401/3
Eccrine adenocarcinoma	8413/3
Porocarcinoma NOS	8409/3
Adenoid cystic carcinoma	8200/3
Adenocarcinoma, intestinal type	8144/3
Neuroendocrine neoplasia	
Neuroendocrine tumour NOS	8240/3
Neuroendocrine tumour, grade 1	8240/3
Neuroendocrine tumour, grade 2	8249/3
Small cell neuroendocrine carcinoma	8041/3
Large cell neuroendocrine carcinoma	8013/3
Carcinoma admixed with small cell neuroendocrine carcinoma[b]	8045/3
Carcinoma admixed with large cell neuroendocrine carcinoma[b]	8013/3
Merkel cell carcinoma	8247/3

[a] These morphology codes are from the International Classification of Diseases for Oncology, third edition, second revision (ICD-O-3.2).[39] Behaviour is coded /0 for benign tumours; /1 for unspecified, borderline, or uncertain behaviour;

/2 for carcinoma in situ and grade III intraepithelial neoplasia; /3 for malignant tumours, primary site; and /6 for malignant tumours, metastatic site. Subtype labels are indented. Incorporates all relevant changes from the 5th edition Corrigenda, June 2021.[21]

[b] This terminology is synonymous with the ICD-0 terminology of combined small/large cell neuroendocrine carcinomas.

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Note 8 – Lymphovascular invasion (Core)

Lymphovascular invasion is an adverse prognostic factor associated with increased risk of local recurrence, lymph node metastasis and poorer survival in vulval SCC.[40-43] Two recent systematic reviews have highlighted some conflicting data on the prognostic significance of lymphovascular invasion from different studies,[33,44] but it should be noted that the criteria for lymphovascular invasion were often not specified and there might be substantial variability in terms of diagnostic thresholds. The published studies also did not distinguish between focal or extensive lymphovascular invasion.[33,44]

Caution is needed when distinguishing genuine lymphovascular invasion from mimickers, such as 'carry-over' of tumour cells into lymphovascular spaces or retraction artefacts. In one study of vulval carcinomas, the use of D2-40 immunohistochemistry as a marker of lymphatic vessels demonstrated improved detection of lymphovascular invasion as compared to morphology alone.[45]

While usually straightforward, the assessment of lymphovascular invasion may be difficult in a minority of cases, for which the reasons may include (but are not limited to) suboptimal fixation or cauterisation artefacts. In such cases, examination of multiple levels and/or immunostaining for endothelial or lymphatic markers (such as CD31, CD34, D2-40) may be employed to assist with the decision-making. Cases that are still equivocal after taking additional steps may be reported as 'indeterminate' for lymphovascular invasion, but this designation should only be sparingly used and it is useful to provide the reason in a comment in the report.

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Note 9 – Perineural invasion (Non-core)

Perineural invasion has been specifically evaluated by several retrospective studies, which demonstrated an association with significantly shorter overall survival and disease-free survival in patients with vulval SCC.[46-48] Perineural invasion is also an independent predictor of local recurrence based on multivariate analysis in two studies.[48,49]

Immunohistochemistry was used as an adjunct to identify perineural invasion in several studies which showed its prognostic value,[47-49] either by S100 alone or dual immunohistochemistry with S100 and AE1/3. Immunohistochemistry may be useful to assist with cases that are morphologically inconclusive or suspicious for perineural invasion.

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Note 10 – Margin status (Core and Non-core)

Appropriate sections need to be taken to include the nearest peripheral epithelial/ mucosal margin and the deep margin.

Vulval cancer patients with positive or 'close' surgical margins are at high risk of local recurrence. A histological clearance of at least 8 mm (clinical clearance of 10-20 mm) from the tumour has been suggested as the distance required to significantly reduce this risk of local recurrence. Recent studies, however, show no difference in recurrence between <8 mm and ≥8 mm tumour free surgical margin.[50,51] It is also likely that the risk of recurrence with regard to tumour distance to the nearest margin differs between HPV-associated and HPV-independent SCC.[22] It is clear that there are multiple problems in measuring the distance to surgical margins with no clear guidelines as to how measurements should be undertaken. Separate gross and microscopic distances to margins should not be provided on the pathology report, but rather a single set of measurements.

To ensure a standardised approach regarding margin measurements for vulval carcinomas, it is recommended that surgical margins should be inked and the following recommendations adhered to:[52]

- Involvement of a peripheral (skin, mucosal) surgical margin by tumour should be recorded and the margin specified if possible.
- The minimum distance from invasive carcinoma to the peripheral margin should be reported and the margin specified if possible.
- This peripheral surgical margin should be roughly perpendicular to the skin/mucosal surface; this includes the epithelial surface and deeper soft tissue.
- The peripheral margin should be measured toward the peripheral stromal edge or surface-epithelial edge, whichever is shorter.
- The minimum peripheral margin should be measured through tissue and preferably in a straight uninterrupted line; however, in some situations (e.g., collarette), a composite measurement including separate linear measurements joined at an angle may be required.
- Measuring the distance to the margin by a curved line in the context of an irregular surface, which is now possible due to the increased use of digital pathology, is not recommended, unless this is felt to represent a truer measurement, for example, when a length of uninvolved skin is embedded curved/folded in order to fit into a paraffin block.
- Involvement of a peripheral margin by a high grade precursor lesion (HPV-associated high grade squamous intraepithelial lesion (HSIL) or HPV-independent vulval intraepithelial neoplasia (VIN)) should be recorded and the margin specified if possible; p53 immunohistochemical staining may be of value in assessing margin involvement by HPV-independent VIN (see **Note 13 ANCILLARY STUDIES**). Margin involvement by a low grade precursor lesion (low grade squamous intraepithelial lesion (LSIL)) does not need to be recorded.
- Although there is no clear evidence to support the value of recording the distance of high grade precursor lesions from the nearest peripheral margin and thus this cannot be considered a core element, it is recommended that this measurement be included in the report and collection of this data prospectively may facilitate future studies which will determine the importance of this. This measurement is made along the epithelial surface. The distance from the margin of a LSIL does not need to be recorded.
- The minimum distance of invasive tumour to the deep soft tissue margin should also be recorded. In general, this should be measured from the deepest infiltrating tumour nest to the deep soft tissue margin. However, if the deep margin is irregular, the closest deep margin may not necessarily be at the point of deepest invasion; in such cases, this should be taken into account when providing this measurement.

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Note 11 – Lymph node status (Core)

Lymph node involvement in vulval cancer is one of the most important adverse prognostic parameters,[33] and the appropriate management and pathological assessment of regional (inguinofemoral) lymph nodes is considered the most important factor in reducing mortality from early vulval cancer.[53] Regional nodal assessment is therefore typically indicated in all carcinomas (with the exception of basal cell carcinomas) that are greater than FIGO Stage IA (pT1a) on clinicopathological assessment, i.e., those that exceed 20 mm in maximum size, those with greater than 1 mm DOI and those of any size that involve adjacent structures (lower third of urethra, lower third of vagina or anus).[54,55] Clinically suspicious/palpable inguinal nodes should be biopsied. Tumours that are <40 mm in size and ≥20 mm from the midline are usually managed by an ipsilateral inguinofemoral lymphadenectomy. Bilateral inguinofemoral lymphadenectomy is typically undertaken in tumours larger than 40 mm, those that cross or are located within 20 mm of the midline, or those that clinically or radiologically are felt to have positive ipsilateral lymph nodes.[56] Significant changes in surgical practice in the last decades, both in terms of vulvar excision and nodal assessment have led to publication of algorithms to help direct surgical procedure.

When lymphadenectomy is performed, one or more sections of all identified nodes should be submitted for histological examination, including sections containing perinodal fat to confirm the presence or absence of extranodal extension, especially if grossly suspected. For nodes which are grossly involved by tumour, representative sampling is acceptable whereas nodes which are not suspicious should be submitted in their entirety after sectioning at 2 mm intervals perpendicular to the long axis of the node. Ultrastaging does not need to be performed for lymphadenectomies (see discussion on sentinel lymph node biopsy (SLNB) below).

Lymph node status is a powerful indicator of local recurrence and survival. The site, size and nature of nodal metastasis all influence prognosis and are integral to tumour stage. Involvement of regional lymph nodes represents Stage III, and this is further subdivided according to the number of involved nodes, the maximum size of the deposit and the presence or absence of extranodal extension (extranodal extension refers to extension of tumour outside the capsule of a lymph node and into the perinodal soft tissue; this is the preferred terminology to extracapsular extension).

It has been shown in multivariate analysis that extranodal extension is an independent prognostic factor for earlier recurrence and overall survival.[48] The presence of fixed or ulcerated inguinofemoral lymph nodes as determined by clinical examination, or involvement of non-regional, including pelvic, lymph nodes, upstages the carcinoma to Stage IVA or IVB, respectively. The anatomic location and number of lymph nodes dissected, the number containing tumour and the size of the largest tumour deposit should be accurately documented in the pathology report.

In recent years, owing to the high morbidity of groin dissection, SLNB has become the standard of care in some vulval cancers.[57-60] SLNB can be performed for unifocal lesions which are confined to the vulva and less than 40 mm in size, with no prior vulval or groin surgery or radiation, and in the absence of clinically palpable or radiologically suspicious nodes.

The evaluation of sentinel lymph nodes should follow an established locally agreed protocol. It should be documented whether or not an ultrastaging procedure has been carried out and whether nodal metastases have been detected on routine histological examination (without ultrastaging) or by ultrastaging, including cytokeratin immunohistochemistry. Sentinel (and non-sentinel) nodal involvement should be recorded as presence of isolated tumour cells (ITC), micrometastases (MIC) or macrometastases (MAC). An ideal ultrastaging protocol used should detect almost all MIC (>0.2 and ≤2 mm). The anatomic location and number of lymph nodes dissected, the number containing tumour, the size of the largest tumour deposit and the presence or absence of extranodal extension should be accurately documented in the pathology report. According to TNM8,[61,62] nodal involvement should be recorded as the presence of ITC (≤0.2 mm and

≤200 cells), MIC (>0.2 mm and ≤2 mm) or MAC (>2 mm). MAC are regarded as pN1, MIC as pN1 (mi) and ITCs are pN0 (i+); ITCs do not upstage a carcinoma. In the 2021 FIGO staging system, it is now stated that ITCs within lymph nodes does not result in tumour upstaging.[3] The possibility of performing radiologically-guided fine needle aspiration cytology (FNAC) of suspicious lymph nodes should be considered. A positive result enables the surgeon to immediately perform a bilateral inguinofemoral lymphadenectomy, thus avoiding an unnecessary SLNB.

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Note 12 – Coexistent pathology/precursor lesions (Core)

Recording the presence of precursor lesions and coexistent pathology is important for vulval SCC since this gives insight into the pathogenesis of the tumour, specifically whether it is HPV-associated or HPV independent.[23] Margin involvement by a high grade precursor lesion is also important.

A variety of non-invasive lesions may be present in association with SCC. Some are considered to be precursor lesions while others, such as lichen sclerosus, are not considered to be a precursor lesion but rather a chronic inflammatory condition that increases the risk of HPV-independent SCC and cancer recurrence when present at surgical margins.[63,64]

The presence of the following should be noted in the setting of vulval SCC: HPV-associated squamous intraepithelial lesion (LSIL or HSIL), HPV-independent VIN and lichen sclerosus.

Vulval squamous precursor lesions are classified into HPV-associated and HPV-independent. The HPV-associated lesions predominantly comprise HSIL (VIN 2/3). LSIL in the vulva is uncommon aside from condylomatous lesions. HPV-associated precursor lesions are associated with smoking, immunosuppression and often multifocal disease including HPV-associated lesions in other areas of the lower female genital tract (vagina, cervix) and anal/perianal regions. HPV-independent precursor lesions, collectively termed 'HPV-independent VIN', include a spectrum of lesions with varying terminology and often overlapping morphology, such as differentiated VIN (dVIN), and two uncommon lesions termed vulvar acanthosis with altered differentiation (VAAD), differentiated exophytic vulvar intraepithelial lesion (DEVIL), verruciform lichen simplex chronicus, vulvar aberrant maturation and verruciform acanthotic VIN (vaVIN).[65-71] (refs 69-71 new) Recently, it has been proposed that HPV-independent VIN be subcategorised by p53 status, and that this can be used as a replacement or supplement to the above morphologic descriptors.[71]

Although not a core item, biomarkers may also be useful for appropriate classification of precursor lesions given that both HPV-independent premalignant lesions morphologically indistinguishable from HSIL and HPV-associated intraepithelial precursors simulating dVIN have been described (see **Note 13 ANCILLARY STUDIES**).[72-75] Recent evidence suggests that HPV-independent SCC arising on intraepithelial precursors mimicking HSIL are more likely to recur than tumours arising on conventional dVIN.[76]

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Note 13 – Ancillary studies (Core and Non-core)

As discussed (see **Note 7 HISTOLOGICAL TUMOUR TYPE**), the 2020 WHO Classification categorises vulval SCC into two main types, HPV-associated and HPV-independent,[77] with prognostic implications which have already been discussed.[23,25-27,78] This new diagnostic approach has consequences since, as discussed,

morphology is not always reliable in distinguishing between the two types.[29,79] It implies that the use of ancillary techniques, namely p16 immunohistochemistry and/or HPV molecular testing, are considered as essential to correctly classify vulval SCC.[77] Similarly, although the HPV-associated and HPV-independent intraepithelial precursors of SCC have distinctive features (see **Note 12 COEXISTENT PATHOLOGY/ PRECURSOR LESIONS**), both HPV-independent premalignant lesions morphologically indistinguishable from HSIL and HPV-associated intraepithelial precursors simulating dVIN have been described.[72-75] Therefore, p16 staining and/or molecular testing (see below) are also highly desirable in classifying precursor lesions. p16 immunohistochemistry and/or HPV testing is considered a core element in cases of vulval SCC. In practice, almost all laboratories will perform p16 immunohistochemistry rather than HPV testing. As discussed earlier, when HPV status cannot be confidently determined or resources are not available to undertake ancillary testing, a morphological diagnosis of SCC, NOS is acceptable, although this is not recommended. This is especially likely in laboratories in developing countries and including these ancillary techniques as a core element may enable laboratories to introduce these tests. If p16 immunohistochemistry and/or HPV testing has been performed on a diagnostic biopsy, it does not need to be repeated on the resection specimen, although it is useful to record the results on the report of the resection specimen. Similarly, these tests do not need to be repeated on a tumour recurrence.

As discussed, the two accepted tools for confirming an HPV-association are the direct identification of HPV products (DNA or mRNA) and block-type immunohistochemical staining for p16, a cell protein typically overexpressed in transforming HPV infections. Although the results of both methods are usually in agreement and it has been proposed that a positive result with both techniques is the gold standard for classifying a tumour as HPV-associated,[80] discrepancies are observed in a small number of cases when the two techniques are applied.[29] Moreover, most laboratories are not likely to have access to HPV testing and, as discussed, p16 immunohistochemistry is likely to be the method of choice in most laboratories.

One of the main challenges of HPV molecular testing methods in vulval samples is that HPV identification is usually performed on formalin-fixed, paraffin-embedded tissues, which may result in limitations due to fragmentation of DNA and RNA, associated with the tissue processing.[79] Thus, highly sensitive methods, such as SPF10 polymerase chain reaction (PCR) testing are the most used tests, but large series have reported both false positive and false negative results with this test.[29,79,80] In situ hybridisation for HPV E7 mRNA, one of the oncogenic HPV genes has shown good results in tumours of the uterine cervix,[81] but the experience in vulval lesions is limited.

p16 immunohistochemical staining has shown a good correlation with HPV testing.[25,26,29,78-80] Although isolated cases of HPV-associated tumours with 'negative' p16 staining have been reported in the cervix and vulva,[82] there is evidence indicating that the accuracy to classify a tumour as HPV-associated or HPV-independent is probably higher for p16 than for most of the available HPV tests.[29] It has also been shown that p16 expression alone is closely associated with prognosis.[23,25-27,78] In addition to its high accuracy, p16 immunohistochemistry is available in most pathology laboratories. It is important to stress that only so-called 'block-type' p16 staining in a squamous lesion (in situ or malignant) is supportive of an association with oncogenic high-risk HPV. Block-type staining in an in-situ lesion is defined as strong and continuous typically nuclear and cytoplasmic (less frequently only nuclear) immunoreactivity in all epithelial cells in the basal and parabasal layers with upward extension. Upward extension must involve at least the lower one-third of the epithelial thickness and expression must extend for at least 6 cells across.[83] It is acknowledged that the criteria defining the horizontal and upward extent are arbitrary but these serve to improve specificity. In HPV-associated SCC, there is typically diffuse positive staining involving almost every tumour cell but keratinous areas may be negative. It also needs to be stressed that p16 staining should not be reported simply as positive since HPV-independent premalignant and malignant lesions and non-neoplastic tissues may exhibit focal (so-called mosaic) staining. Instead terms such as 'block-type', 'abnormal' or 'aberrant' should be used in the pathology report, or alternatively when the term positive is used this should be qualified as diffuse or 'block-type'.

p53 immunohistochemistry is now considered a core item for SCC of the vulva for classification and prognostication as previously discussed (see **Note 7 HISTOLOGICAL TUMOUR TYPE**). Almost all HPV-associated vulval SCC and high grade precursor lesions exhibit a 'wild-type' pattern of p53 immunoreactivity while many, but importantly not all, HPV-independent SCC and precursor lesions exhibit 'mutation-type' immunoreactivity. Classification of p53 staining in such lesions as 'wild-type' or 'mutation-type' is not always straightforward and requires a pattern-based approach.[84,85] An algorithm combining the use of p16 and p53 immunohistochemistry to classify SCC of the vulva into HPV-associated, HPV-independent p53 wild-type and HPV-independent p53 abnormal has been described.[86] Although not currently a requisite, p53 staining may also be helpful in assessing margin involvement by HPV-independent dVIN; this may be subtle histologically and mutation-type p53 staining at a margin may be useful in confirming margin involvement.[32,87,88]

Additional biomarkers, such as PD-L1, may become useful in the future as the role of immune checkpoint inhibitor therapy in vulval squamous carcinomas becomes established through ongoing clinical trials.[89]

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Note 14 – Pathologically confirmed distant metastasis (Core)

Documentation of known metastatic disease is an important part of the pathology report. Such information, if available, should be recorded with as much detail as is available including the site, whether the specimen is a histopathology or cytopathology specimen and with reference to any relevant prior surgical pathology or cytopathology specimens.

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Note 15 – Provisional pathological staging (Core)

The pathological staging must be provided on the pathology report and is therefore a core element. The term 'provisional pathological staging' is used in this dataset to indicate that the stage that is provided may not represent the final tumour stage which should be determined at the multidisciplinary tumour board meeting where all the pathological, clinical and radiological features are available.[53,61,62,90]

The latest version of either FIGO *or* TNM staging, *or* both, can be used depending on local preferences.[53,61,62,90] The FIGO Staging System is in widespread use internationally and is the system used in most clinical trials and research studies. This updated version of the ICCR Carcinoma of the vulva dataset incorporates the FIGO 2021 update to vulval cancer reporting.[3,91] However, Union for International Cancer Control (UICC) or American Joint Committee on Cancer (AJCC) versions of TNM are used or mandated in many parts of the world.[61,62] With regards to updating of staging systems, there is collaboration between FIGO and those agencies responsible for TNM with an agreement to adopt changes to FIGO staging. Following the introduction of a new FIGO Staging System, the amendments are usually incorporated into TNM (both UICC and AJCC) versions at a later date. Apart from minor discrepancies in terminology, the UICC and AJCC systems are broadly concurrent.

A tumour should be staged following diagnosis using various appropriate modalities (clinical, radiological, pathological). While the original tumour stage should not be altered following treatment, TNM systems allow staging to be performed on a resection specimen following non-surgical treatment (for example chemotherapy, radiotherapy); in such cases, if a stage is being provided on the pathology report (this is optional), it should be prefixed by 'y' to indicate that this is a post-therapy stage.

In cases where more than one primary tumour is present, a separate pathological stage should be provided for each tumour and, as stated in the scope, separate datasets should be completed for each neoplasm.

Reporting of pathological staging categories is based on the evidence available to the pathologist at the time of reporting. As indicated in UICC TNM8 and AJCC TNM8,[56,78] the final stage grouping of a patient's tumour is based on a combination of pathological staging and other clinical and imaging information.

The reference document TNM Supplement: A commentary on uniform use, 5th Edition (C Wittekind et al. editors) may be of assistance when staging.[92]

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References

1 Merlin T, Weston A and Tooher R (2009). Extending an evidence hierarchy to include topics other than treatment: revising the Australian 'levels of evidence'. *BMC Med Res Methodol* 9:34.

2 Pors J, Tessier-Cloutier B, Thompson E, Almadani N, Ho J, Gilks B, Huntsman D and Hoang L (2020). Targeted Molecular Sequencing of Recurrent and Multifocal Non-HPV-associated Squamous Cell Carcinoma of the Vulva. *Int J Gynecol Pathol*.

3 Olawaiye AB, Cotler J, Cuello MA, Bhatla N, Okamoto A, Wilailak S, Purandare CN, Lindeque G, Berek JS and Kehoe S (2021). FIGO staging for carcinoma of the vulva: 2021 revision. *Int J Gynaecol Obstet* 155(1):43-47.

4 de Hullu JA, van der Avoort IA, Oonk MH and van der Zee AG (2006). Management of vulvar cancers. *Eur J Surg Oncol* 32(8):825-831.

5 American College of Obstetricians and Gynecologists' Committee on Gynecologic Practice and the American Society for Colposcopy and Cervical Pathology (2016). *Management of Vulvar Intraepithelial Neoplasia*. Available at: https://www.acog.org/clinical/clinical-guidance/committee-opinion/articles/2016/10/management-of-vulvar-intraepithelial-neoplasia (Accessed 19th February 2021).

6 C. Paul Morrow and John P. Curtin. (1996). *Gynecologic Cancer Surgery*. Churchill Livingstone.

7 Heatley MK (2008). Dissection and reporting of the organs of the female genital tract. *J Clin Pathol* 61(3):241-257.

8 College of American Pathologists (2021). *Protocol for the Examination of Specimens From Patients With Primary Carcinoma of the Vulva*. Available at: https://documents.cap.org/protocols/Vulva_4.2.0.2.REL_CAPCP.pdf (Accessed 1st July 2023).

9 Royal College of Pathologists (2018). *Dataset for histopathological reporting of vulval carcinomas*. Available at: https://www.rcpath.org/static/79003d03-8e27-4bf9-9732d2f3ffc5291d/G070-Dataset-for-histopathological-reporting-of-vulval-carcinomas.pdf (Accessed 19th February 2021).

10 Royal College of Pathologists of Australasia (2013). *Vulva Cancer Structured Reporting Protocol*. Available at: https://www.rcpa.edu.au/getattachment/9cdcbca0-6523-4a13-b716-370d5bc945c3/Protocol-vulva-cancer.aspx (Accessed 19th February 2021).

11 Hinten F, Molijn A, Eckhardt L, Massuger L, Quint W, Bult P, Bulten J, Melchers WJG and de Hullu JA (2018). Vulvar cancer: Two pathways with different localization and prognosis. *Gynecol Oncol* 149(2):310-317.

12 Iversen T and Aas M (1983). Lymph drainage from the vulva. *Gynecol Oncol* 16(2):179-189.

13 Hinten F, van den Einden LC, Cissen M, IntHout J, Massuger LF and de Hullu JA (2015). Clitoral involvement of squamous cell carcinoma of the vulva: localization with the worst prognosis. *Eur J Surg Oncol* 41(4):592-598.

14 van den Einden LC, Massuger LF, Jonkman JK, Bult P, de Hullu JA and Bulten J (2015). An alternative way to measure the depth of invasion of vulvar squamous cell carcinoma in relation to prognosis. *Mod Pathol* 28(2):295-302.

15 Skala SL, Ebott JA, Zhao L and Lieberman RW (2020). Predictive Value of an Alternative Strategy for Measuring Depth and Size of Stage 1 Vulvar Squamous Cell Carcinoma. *J Low Genit Tract Dis* 24(3):265-271.

16 Abdel-Mesih A, Daya D, Onuma K, Sur M, Tang S, Akhtar-Danesh N, Boutross-Tadross O, Ceballos KM, Chapman W, Colgan T, Deb P, Nucci MR, Oliva E and Lytwyn A (2013). Interobserver agreement for assessing invasion in stage 1A vulvar squamous cell carcinoma. *Am J Surg Pathol* 37(9):1336-1341.

17 Pouwer AW, Bult P, Otte I, van der Brand M, van der Horst J, Harterink LJV, van de Vijver KK, Guerra E, Aliredjo RP, Bosch SL, J MMG, Zomer S, Hollema H, de Heus B, Satumalaij S, Ewing-Graham PC, IntHout J, de Hullu JA and Bulten J (2019). Measuring the depth of invasion in vulvar squamous cell carcinoma: interobserver agreement and pitfalls. *Histopathology* 75(3):413-420.

18 Grimm D, Prieske K, Mathey S, Kuerti S, Burandt E, Schmalfeldt B and Woelber L (2019). Superficially invasive stage IA vulvar squamous cell carcinoma-therapy and prognosis. *Int J Gynecol Cancer* 29(3):466-473.

19 Oonk MHM, Planchamp F, Baldwin P, Mahner S, Mirza MR, Fischerová D, Creutzberg CL, Guillot E, Garganese G, Lax S, Redondo A, Sturdza A, Taylor A, Ulrikh E, Vandecaveye V, van der Zee A, Wölber L, Zach D, Zannoni GF and Zapardiel I (2023). European Society of Gynaecological Oncology Guidelines for the Management of Patients with Vulvar Cancer - Update 2023. *Int J Gynecol Cancer* 33(7):1023-1043.

20 WHO Classification of Tumours Editorial Board (2020). *Female Genital Tumours, WHO Classification of Tumours, 5th Edition, Volume 4*. IARC Press, Lyon.

21 WHO Classification of Tumours Editorial Board (2021). *Female Genital Tumours, WHO Classification of Tumours, 5th Edition, Volume 4 - Corrigenda June 2021*. Available from: https://publications.iarc.fr/Book-And-Report-Series/Who-Classification-Of-Tumours/Female-Genital-Tumours-2020 (Accessed 16th June 2021).

22 McAlpine JN, Leung SCY, Cheng A, Miller D, Talhouk A, Gilks CB and Karnezis AN (2017). Human papillomavirus (HPV)-independent vulvar squamous cell carcinoma has a worse prognosis than HPV-associated disease: a retrospective cohort study. *Histopathology* 71(2):238-246.

23 Nooij LS, Ter Haar NT, Ruano D, Rakislova N, van Wezel T, Smit V, Trimbos B, Ordi J, van Poelgeest MIE and Bosse T (2017). Genomic Characterization of Vulvar (Pre)cancers Identifies Distinct Molecular Subtypes with Prognostic Significance. *Clin Cancer Res* 23(22):6781-6789.

24 Allo G, Yap ML, Cuartero J, Milosevic M, Ferguson S, Mackay H, Kamel-Reid S, Weinreb I, Ghazarian D, Pintilie M and Clarke BA (2020). HPV-independent Vulvar Squamous Cell Carcinoma is Associated With Significantly Worse Prognosis Compared With HPV-associated Tumors. *Int J Gynecol Pathol* 39(4):391-399.

25 Lee LJ, Howitt B, Catalano P, Tanaka C, Murphy R, Cimbak N, DeMaria R, Bu P, Crum C, Horowitz N, Matulonis U and Viswanathan AN (2016). Prognostic importance of human papillomavirus (HPV) and p16 positivity in squamous cell carcinoma of the vulva treated with radiotherapy. *Gynecol Oncol* 142(2):293-298.

26 Proctor L, Hoang L, Moore J, Thompson E, Leung S, Natesan D, Chino J, Gilks B and McAlpine JN (2020). Association of human papilloma virus status and response to radiotherapy in vulvar squamous cell carcinoma. *Int J Gynecol Cancer* 30(1):100-106.

27 Horne ZD, Dohopolski MJ, Pradhan D, Bhargava R, Edwards RP, Kelley JL, Comerci JT, Olawaiye AB, Courtney-Brooks MB, Bockmeier MM, Berger JL, Taylor SE, Sukumvanich P and Beriwal S (2018). Human papillomavirus infection mediates response and outcome of vulvar squamous cell carcinomas treated with radiation therapy. *Gynecol Oncol* 151(1):96-101.

28 McCluggage WG (2009). Recent developments in vulvovaginal pathology. *Histopathology* 54(2):156-173.

29 Rakislova N, Clavero O, Alemany L, Saco A, Quirós B, Lloveras B, Alejo M, Pawlita M, Quint W, Del Pino M, de Sanjose S and Ordi J (2017). "Histological characteristics of HPV-associated and -independent squamous cell carcinomas of the vulva: A study of 1,594 cases". *Int J Cancer* 141(12):2517-2527.

30 Dong F, Kojiro S, Borger DR, Growdon WB and Oliva E (2015). Squamous Cell Carcinoma of the Vulva: A Subclassification of 97 Cases by Clinicopathologic, Immunohistochemical, and Molecular Features (p16, p53, and EGFR). *Am J Surg Pathol* 39(8):1045-1053.

31 Kortekaas KE, Bastiaannet E, van Doorn HC, de Vos van Steenwijk PJ, Ewing-Graham PC, Creutzberg CL, Akdeniz K, Nooij LS, van der Burg SH, Bosse T and van Poelgeest MIE (2020). Vulvar cancer subclassification by HPV and p53 status results in three clinically distinct subtypes. *Gynecol Oncol* 159(3):649-656.

32 Carreras-Dieguez N, Saco A, Del Pino M, Marimon L, López Del Campo R, Manzotti C, Fusté P, Pumarola C, Torné A, Garcia A and Rakislova N (2023). Human papillomavirus and p53 status define three types of vulvar squamous cell carcinomas with distinct clinical, pathological, and prognostic features. *Histopathology* 83(1):17-30.

33 Chen J and Ln H (2020). A review of prognostic factors in squamous cell carcinoma of the vulva: Evidence from the last decade. *Semin Diagn Pathol*(38(1):37-49).

34 Tessier-Cloutier B, Asleh-Aburaya K, Shah V, McCluggage WG, Tinker A and Gilks CB (2017). Molecular subtyping of mammary-like adenocarcinoma of the vulva shows molecular similarity to breast carcinomas. *Histopathology* 71(3):446-452.

35 He SR, Deng WH, Yang L, Yang K, Cui D and Liu DG (2017). Cloacogenic adenocarcinoma of the vulva: one new case and literature review. *Eur J Gynaecol Oncol* 38(2):296-302.

36 Nazeran T, Cheng AS, Karnezis AN, Tinker AV and Gilks CB (2019). Bartholin Gland Carcinoma: Clinicopathologic Features, Including p16 Expression and Clinical Outcome. *Int J Gynecol Pathol* 38(2):189-195.

37 Chen PP, Ramalingam P, Alvarado-Cabrero I, Euscher ED, Nagarajan P, Lawson BC and Malpica A (2020). High-grade Neuroendocrine Carcinomas of the Vulva: A Clinicopathologic Study of 16 Cases. *Am J Surg Pathol*.

38 Coggshall K, Tello TL, North JP and Yu SS (2018). Merkel cell carcinoma: An update and review: Pathogenesis, diagnosis, and staging. *J Am Acad Dermatol* 78(3):433-442.

39 Fritz A, Percy C, Jack A, Shanmugaratnam K, Sobin L, Parkin DM and Whelan S (eds) (2020). *International Classification of Diseases for Oncology, Third edition, Second revision ICD-O-3.2*. Available from: http://www.iacr.com.fr/index.php?option=com_content&view=category&layout=blog&id=100&Itemid=577 (Accessed 16th June 2021).

40 Raspagliesi F, Hanozet F, Ditto A, Solima E, Zanaboni F, Vecchione F and Kusamura S (2006). Clinical and pathological prognostic factors in squamous cell carcinoma of the vulva. *Gynecol Oncol* 102(2):333-337.

41 Chan JK, Sugiyama V, Pham H, Gu M, Rutgers J, Osann K, Cheung MK, Berman ML and Disaia PJ (2007). Margin distance and other clinico-pathologic prognostic factors in vulvar carcinoma: a multivariate analysis. *Gynecol Oncol* 104(3):636-641.

42 Aragona AM, Cuneo NA, Soderini AH and Alcoba EB (2014). An analysis of reported independent prognostic factors for survival in squamous cell carcinoma of the vulva: is tumor size significance being underrated? *Gynecol Oncol* 132(3):643-648.

43 Dabi Y, Gosset M, Bastuji-Garin S, Mitri-Frangieh R, Bendifallah S, Darai E, Paniel BJ, Rouzier R, Haddad B and Touboul C (2020). Associated Lichen Sclerosis Increases the Risk of Lymph Node Metastases of Vulvar Cancer. *J Clin Med* 9(1):250.

44 Te Grootenhuis NC, Pouwer AW, de Bock GH, Hollema H, Bulten J, van der Zee AGJ, de Hullu JA and Oonk MHM (2018). Prognostic factors for local recurrence of squamous cell carcinoma of the vulva: A systematic review. *Gynecol Oncol* 148(3):622-631.

45 Braun M, Wardelmann E, Debald M, Walgenbach-Bruenagel G, Höller T, Wolfgarten M, Sauerwald A, Rudlowski C, Büttner R, Kuhn W and Pölcher M (2009). Detection of lymphovascular invasion in vulvar cancer by D2-40 (podoplanin) as a predictor for inguinal lymph node metastases. *Onkologie* 32(12):732-738.

46 Salcedo MP, Sood AK, Dos Reis R, Ramalingam P, Chen C, Frumovitz M, Jhingran A, Pitcher B, Ramirez PT and Schmeler KM (2019). Perineural invasion (PNI) in vulvar carcinoma: A review of 421 cases. *Gynecol Oncol* 152(1):101-105.

47 Long Y, Yao DS, Wei YS, Wei CH and Chen XY (2019). Prognostic significance of perineural invasion in vulvar squamous cell carcinoma. *Cancer Manag Res* 11:4461-4469.

48 Ferrari F, Forte S, Ardighieri L, Bonetti E, Fernando B, Sartori E and Odicino F (2019). Multivariate analysis of prognostic factors in primary squamous cell vulvar cancer: The role of perineural invasion in recurrence and survival. *Eur J Surg Oncol* 45(11):2115-2119.

49 Holthoff ER, Jeffus SK, Gehlot A, Stone R, Erickson SW, Kelly T, Quick CM and Post SR (2015). Perineural Invasion Is an Independent Pathologic Indicator of Recurrence in Vulvar Squamous Cell Carcinoma. *Am J Surg Pathol* 39(8):1070-1074.

50 Woelber L, Griebel LF, Eulenburg C, Sehouli J, Jueckstock J, Hilpert F, de Gregorio N, Hasenburg A, Ignatov A, Hillemanns P, Fuerst S, Strauss HG, Baumann KH, Thiel FC, Mustea A, Meier W, Harter P, Wimberger P, Hanker LC, Schmalfeldt B, Canzler U, Fehm T, Luyten A, Hellriegel M, Kosse J, Heiss C, Hantschmann P, Mallmann P, Tanner B, Pfisterer J, Richter B, Neuser P and Mahner S (2016). Role of tumour-free margin distance for loco-regional control in vulvar cancer-a subset analysis of the Arbeitsgemeinschaft Gynäkologische Onkologie CaRE-1 multicenter study. *Eur J Cancer* 69:180-188.

51 Nooij LS, van der Slot MA, Dekkers OM, Stijnen T, Gaarenstroom KN, Creutzberg CL, Smit VT, Bosse T and van Poelgeest MI (2016). Tumour-free margins in vulvar squamous cell carcinoma: Does distance really matter? *Eur J Cancer* 65:139-149.

52 Kortekaas KE, Van de Vijver KK, van Poelgeest MIE, Gilks CB, Smit V, Arif S, Arora D, Faruqi A, Ganesan R, Griffin NR, Hale R, Hock YE, Horn LC, McCluggage WG, Mukonoweshuro P, Park KJ, Rous B, Tanchel B, Van Rompuy AS, van Schalkwyk G, Vella J, Vergine M, Singh N and Bosse T (2020). Practical Guidance for Measuring and Reporting Surgical Margins in Vulvar Cancer. *Int J Gynecol Pathol* 39(5):420-427.

53 Rogers LJ and Cuello MA (2018). Cancer of the vulva. *Int J Gynaecol Obstet* 143 Suppl 2:4-13.

54 Koh WJ, Greer BE, Abu-Rustum NR, Campos SM, Cho KR, Chon HS, Chu C, Cohn D, Crispens MA, Dizon DS, Dorigo O, Eifel PJ, Fisher CM, Frederick P, Gaffney DK, Han E, Higgins S, Huh WK, Lurain JR, 3rd, Mariani A, Mutch D, Nagel C, Nekhlyudov L, Fader AN, Remmenga SW, Reynolds RK, Tillmanns T, Ueda S, Valea FA, Wyse E, Yashar CM, McMillian N and Scavone J (2017). Vulvar Cancer, Version 1.2017, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw* 15(1):92-120.

55 Dellinger TH, Hakim AA, Lee SJ, Wakabayashi MT, Morgan RJ and Han ES (2017). Surgical Management of Vulvar Cancer. *J Natl Compr Canc Netw* 15(1):121-128.

56 Stehman FB and Look KY (2006). Carcinoma of the vulva. *Obstet Gynecol* 107(3):719-733.

57 Coleman RL, Ali S, Levenback CF, Gold MA, Fowler JM, Judson PL, Bell MC, De Geest K, Spirtos NM, Potkul RK, Leitao MM, Jr., Bakkum-Gamez JN, Rossi EC, Lentz SS, Burke JJ, 2nd, Van Le L and Trimble CL (2013). Is bilateral lymphadenectomy for midline squamous carcinoma of the vulva always necessary? An analysis from Gynecologic Oncology Group (GOG) 173. *Gynecol Oncol* 128(2):155-159.

58 Van der Zee AG, Oonk MH, De Hullu JA, Ansink AC, Vergote I, Verheijen RH, Maggioni A, Gaarenstroom KN, Baldwin PJ, Van Dorst EB, Van der Velden J, Hermans RH, van der Putten H, Drouin P, Schneider A and Sluiter WJ (2008). Sentinel node dissection is safe in the treatment of early-stage vulvar cancer. *J Clin Oncol* 26(6):884-889.

59 Fotopoulou C, Ind T, Baldwin P, Crawford R, Devaja O, Dobbs S, Frost J, Gajjar K, Ganesan R, Kaushik S, Morrison J, Nobbenhuis M, Ratnavelu N, Rolland P, Singh N, Taylor A, Sundar S and Nordin A (2019). Sentinel lymph node consensus document of the British Gynaecological Cancer Society for endometrial, vulvar, and cervical cancers. *Int J Gynecol Cancer* 29(9):1348-1350.

60 Te Grootenhuis NC, van der Zee AG, van Doorn HC, van der Velden J, Vergote I, Zanagnolo V, Baldwin PJ, Gaarenstroom KN, van Dorst EB, Trum JW, Slangen BF, Runnebaum IB, Tamussino K, Hermans RH, Provencher DM, de Bock GH, de Hullu JA and Oonk MH (2016). 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* 140(1):8-14.

61 Brierley JD, Gospodarowicz MK and Wittekind C (eds) (2016). *Union for International Cancer Control. TNM Classification of Malignant Tumours, 8th Edition*, Wiley, USA.

62 Amin MB, Edge SB, Greene FL, Byrd DR, Brookland RK, Washington MK, Gershenwald JE, Compton CC, Hess KR, Sullivan DC, Jessup JM, Brierley JD, Gaspar LE, Schilsky RL, Balch CM, Winchester DP, Asare EA, Madera M, Gress DM and Meyer LR (eds) (2017). *AJCC Cancer Staging Manual. 8th Edition*, Springer, New York.

63 Satmary W, Holschneider CH, Brunette LL and Natarajan S (2018). Vulvar intraepithelial neoplasia: Risk factors for recurrence. *Gynecol Oncol* 148(1):126-131.

64 Te Grootenhuis NC, Pouwer AW, de Bock GH, Hollema H, Bulten J, van der Zee AGJ, de Hullu JA and Oonk MHM (2019). Margin status revisited in vulvar squamous cell carcinoma. *Gynecol Oncol* 154(2):266-275.

65 Watkins JC, Howitt BE, Horowitz NS, Ritterhouse LL, Dong F, MacConaill LE, Garcia E, Lindeman NI, Lee LJ, Berkowitz RS, Nucci MR and Crum CP (2017). Differentiated exophytic vulvar intraepithelial lesions are genetically distinct from keratinizing squamous cell carcinomas and contain mutations in PIK3CA. *Mod Pathol* 30(3):448-458.

66 Akbari A, Pinto A, Amemiya Y, Seth A, Mirkovic J and Parra-Herran C (2020). Differentiated exophytic vulvar intraepithelial lesion: Clinicopathologic and molecular analysis documenting its relationship with verrucous carcinoma of the vulva. *Mod Pathol* 33(10):2011-2018.

67 Singh N and Gilks CB (2020). Vulval squamous cell carcinoma and its precursors. *Histopathology* 76(1):128-138.

68 McCluggage WG (2013). Premalignant lesions of the lower female genital tract: cervix, vagina and vulva. *Pathology* 45(3):214-228.

69 Roy SF, Wong J, Le Page C, Tran-Thanh D, Barkati M, Pina A, Trinh VQ and Rahimi K (2021). DEVIL, VAAD and vLSC constitute a spectrum of HPV-independent, p53-independent intra-epithelial neoplasia of the vulva. *Histopathology* 79(6):975-988.

70 Heller DS, Day T, Allbritton JI, Scurry J, Radici G, Welch K and Preti M (2021). Diagnostic Criteria for Differentiated Vulvar Intraepithelial Neoplasia and Vulvar Aberrant Maturation. *J Low Genit Tract Dis* 25(1):57-70.

71 Parra-Herran C, Nucci MR, Singh N, Rakislova N, Howitt BE, Hoang L, Gilks CB, Bosse T and Watkins JC (2022). HPV-independent, p53-wild-type vulvar intraepithelial neoplasia: a review of nomenclature and the journey to characterize verruciform and acanthotic precursor lesions of the vulva. *Mod Pathol* 35(10):1317-1326.

72 Ordi J, Alejo M, Fusté V, Lloveras B, Del Pino M, Alonso I and Torné A (2009). HPV-negative vulvar intraepithelial neoplasia (VIN) with basaloid histologic pattern: an unrecognized variant of simplex (differentiated) VIN. *Am J Surg Pathol* 33(11):1659-1665.

73 Rakislova N, Alemany L, Clavero O, Del Pino M, Saco A, Marimon L, Quirós B, Lloveras B, Ribera-Cortada I, Alejo M, Pawlita M, Quint W, de Sanjose S and Ordi J (2020). HPV-independent Precursors Mimicking High-grade Squamous Intraepithelial Lesions (HSIL) of the Vulva. *Am J Surg Pathol* 44(11):1506-1514.

74 Rakislova N, Alemany L, Clavero O, Del Pino M, Saco A, Quirós B, Lloveras B, Alejo M, Halec G, Quint W, de Sanjosé S and Ordi J (2018). Differentiated Vulvar Intraepithelial Neoplasia-like and Lichen Sclerosus-like Lesions in HPV-associated Squamous Cell Carcinomas of the Vulva. *Am J Surg Pathol* 42(6):828-835.

75 Griesinger LM, Walline H, Wang GY, Lorenzatti Hiles G, Welch KC, Haefner HK, Lieberman RW and Skala SL (2020). Expanding the Morphologic, Immunohistochemical, and HPV Genotypic Features of High-grade Squamous Intraepithelial Lesions of the Vulva With Morphology Mimicking Differentiated Vulvar Intraepithelial Neoplasia and/or Lichen Sclerosus. *Int J Gynecol Pathol*.

76 Carreras-Dieguez N, Saco A, Del Pino M, Pumarola C, Del Campo RL, Manzotti C, Garcia A, Marimon L, Diaz-Mercedes S, Fuste P, Rodrigo-Calvo MT, Vega N, Torné A and Rakislova N (2023). Vulvar squamous cell carcinoma arising on human papillomavirus-independent precursors mimicking high-grade squamous intra-epithelial lesion: a distinct and highly recurrent subtype of vulvar cancer. *Histopathology* 82(5):731-744.

77 Herrington CS, Kim KR, McCluggage WG and Ordi J (2020). Tumours of the vulva. In: *Female Genital Tumours, WHO Classification of Tumours, 5th Edition, Volume 4*, WHO Classification of Tumours Editorial Board (ed), IARC Press, Lyon.

78 Hay CM, Lachance JA, Lucas FL, Smith KA and Jones MA (2016). Biomarkers p16, Human Papillomavirus and p53 Predict Recurrence and Survival in Early Stage Squamous Cell Carcinoma of the Vulva. *J Low Genit Tract Dis* 20(3):252-256.

79 Santos M, Landolfi S, Olivella A, Lloveras B, Klaustermeier J, Suárez H, Alòs L, Puig-Tintoré LM, Campo E and Ordi J (2006). p16 overexpression identifies HPV-positive vulvar squamous cell carcinomas. *Am J Surg Pathol* 30(11):1347-1356.

80 de Sanjosé S, Alemany L, Ordi J, Tous S, Alejo M, Bigby SM, Joura EA, Maldonado P, Laco J, Bravo IG, Vidal A, Guimerà N, Cross P, Wain GV, Petry KU, Mariani L, Bergeron C, Mandys V, Sica AR, Félix A, Usubutun A, Seoud M, Hernández-Suárez G, Nowakowski AM, Wilson G, Dalstein V, Hampl M, Kasamatsu ES, Lombardi LE, Tinoco L, Alvarado-Cabrero I, Perrotta M, Bhatla N, Agorastos T, Lynch CF, Goodman MT, Shin HR, Viarheichyk H, Jach R, Cruz MO, Velasco J, Molina C, Bornstein J, Ferrera A, Domingo EJ, Chou CY, Banjo AF, Castellsagué X, Pawlita M, Lloveras B, Quint WG, Muñoz N and Bosch FX (2013). Worldwide human papillomavirus genotype attribution in over 2000 cases of intraepithelial and invasive lesions of the vulva. *Eur J Cancer* 49(16):3450-3461.

81 Hodgson A, Park KJ, Djordjevic B, Howitt BE, Nucci MR, Oliva E, Stolnicu S, Xu B, Soslow RA and Parra-Herran C (2019). International Endocervical Adenocarcinoma Criteria and Classification: Validation and Interobserver Reproducibility. *Am J Surg Pathol* 43(1):75-83.

82 Nicolás I, Saco A, Barnadas E, Marimon L, Rakislova N, Fusté P, Rovirosa A, Gaba L, Buñesch L, Gil-Ibañez B, Pahisa J, Díaz-Feijoo B, Torne A, Ordi J and Del Pino M (2020). Prognostic implications of genotyping and p16 immunostaining in HPV-positive tumors of the uterine cervix. *Mod Pathol* 33(1):128-137.

83 Naveena Singh, C Blake Gilks, Richard Wing-Cheuk Wong, W Glenn McCluggage and C Simon Herrington (2018). *Interpretation of p16 Immunohistochemistry In Lower Anogenital Tract Neoplasia.* Available at: https://www.bgcs.org.uk/wp-content/uploads/2019/05/BAGP-UKNEQAS-cIQC-project-p16-interpretation-guide-2018.pdf (Accessed 14th February 2021).

84 Tessier-Cloutier B, Kortekaas KE, Thompson E, Pors J, Chen J, Ho J, Prentice LM, McConechy MK, Chow C, Proctor L, McAlpine JN, Huntsman DG, Gilks CB, Bosse T and Hoang LN (2020). 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):1595-1605.

85 Kortekaas KE, Solleveld-Westerink N, Tessier-Cloutier B, Rutten TA, Poelgeest MIE, Gilks CB, Hoang LN and Bosse T (2020). Performance of the pattern-based interpretation of p53 immunohistochemistry as a surrogate for TP53 mutations in vulvar squamous cell carcinoma. *Histopathology* 77(1):92-99.

86 Yang H, Almadani N, Thompson EF, Tessier-Cloutier B, Chen J, Ho J, Senz J, McConechy MK, Chow C, Ta M, Cheng A, Karnezis A, Huvila J, McAlpine JN, Gilks B, Jamieson A and Hoang LN (2023). Classification of Vulvar Squamous Cell Carcinoma and Precursor Lesions by p16 and p53 Immunohistochemistry: Considerations, Caveats, and an Algorithmic Approach. *Mod Pathol* 36(6):100145.

87 Singh N, Leen SL, Han G, Faruqi A, Kokka F, Rosenthal A, Jiang XR, Kim R, McAlpine JN and Gilks CB (2015). Expanding the morphologic spectrum of differentiated VIN (dVIN) through detailed mapping of cases with p53 loss. *Am J Surg Pathol* 39(1):52-60.

88 Thompson EF, Wong RWC, Trevisan G, Tessier-Cloutier B, Almadani N, Chen J, Cheng A, Karnezis A, McConechy MK, Lum A, Senz J, McAlpine JN, Huntsman DG, Gilks B, Jamieson A and Hoang LN (2023). p53-Abnormal "Fields of Dysplasia" in Human Papillomavirus-Independent Vulvar Squamous Cell Carcinoma Impacts Margins and Recurrence Risk. *Mod Pathol* 36(2):100010.

89 Borella F, Preti M, Bertero L, Collemi G, Castellano I, Cassoni P, Cosma S, Carosso AR, Bevilacqua F, Gallio N, Benedetto C and Micheletti L (2020). Is There a Place for Immune Checkpoint Inhibitors in Vulvar Neoplasms? A State of the Art Review. *Int J Mol Sci* 22(1).

90 Hacker NF (2009). Revised FIGO staging for carcinoma of the vulva. *Int J Gynaecol Obstet* 105(2):105-106.

91 Olawaiye AB, Cuello MA and Rogers LJ (2021). Cancer of the vulva: 2021 update. *Int J Gynaecol Obstet* 155 Suppl 1(Suppl 1):7-18.

92 Wittekind C, Brierley JD, Lee A and van Eycken E (eds) (2019). *TNM Supplement: A Commentary on Uniform Use, 5th Edition*, Wiley, USA.