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Carcinoma of the Vagina 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*
- ☐ Prior neoadjuvant therapy, *specify*
- ☐ In-utero exposure to diethylstilbestrol (DES)
- ☐ History of vaginal adenosis
- ☐ Other, *specify*

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

- ◯ Not specified
- ☐ Partial vaginectomy
- ☐ Total vaginectomy
- ☐ Pelvic exenteration
- ☐ 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)

- ◯ Vagina, site not known
- ☐ Vagina, upper third
- ☐ Vagina, middle third
- ☐ Vagina, lower third
- ☐ Vagina, anterior
- ☐ Vagina, posterior
- ☐ Vagina, lateral

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
- ◯ Adenocarcinoma, *specify type*
- ◯ Carcinosarcoma
- ◯ Adenosquamous carcinoma
- ◯ Adenoid basal carcinoma
- ◯ Neuroendocrine carcinoma, *specify type*
- ◯ Other, *specify*

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LYMPHOVASCULAR INVASION (Note 8)

- ◯ Indeterminate
- ◯ Not identified
- ◯ Present

MARGIN STATUS (Note 9)

Invasive tumour

- ◯ Cannot be assessed
- ◯ Not involved
  - Distance of tumour from closest margin ____ mm
  - Specify closest margin, if possible
  - Distance of tumour from deep margin ____ mm
- ◯ Involved
  - Specify margin, if possible

Precursor lesions

- ◯ Not applicable
- ◯ Cannot be assessed
- ◯ Not involved
  - Distance of high grade precursor lesion from closest margin ____ mm
  - Specify closest margin, if possible
- ◯ Involved
  - Specify margin, if possible

LYMPH NODE STATUS (Note 10)

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

Site 1

Number of nodes examined

Number of positive nodes

Size of maximum tumour deposit ____ mm

Extracapsular spread

- ◯ Not identified
- ◯ Present

Site 2

Number of nodes examined

Number of positive nodes

Size of maximum tumour deposit ____ mm

Extracapsular spread

- ◯ Not identified
- ◯ Present

COEXISTENT PATHOLOGY/PRECURSOR LESIONS (Note 11)

- ◯ None identified
- ◯ Present (select all that apply)
  - ☐ Low grade squamous intraepithelial lesion
  - ☐ High grade squamous intraepithelial lesion
  - ☐ Adenosis
  - ☐ Other, *specify*

ANCILLARY STUDIES (Note 12)

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

  AND/OR
  - ☐ HPV testing[a]
  - ☐ p53 immunohistochemistry
  - ☐ 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*

[a] *Core for squamous cell carcinomas.*

PATHOLOGICALLY CONFIRMED DISTANT METASTASIS (Note 13)

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

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PROVISIONAL PATHOLOGICAL STAGING (Note 14)

FIGO (2009 edition)[b]

- ◯ I — Carcinoma is limited to the vaginal wall. It has not spread to nearby lymph nodes (N0) or to distant sites (M0)
- ◯ II — Carcinoma has involved the para-vaginal tissue but has not extended to the pelvic wall. It has not spread to nearby lymph nodes (N0) or to distant sites (M0)
- ◯ III — Carcinoma has extended to the pelvic wall and/or involving the lower third of the vagina and/or causing hydronephrosis or nonfunctioning kidney or T1-T3 tumour that has also spread to nearby lymph nodes in the pelvis or groin (inguinal) area (N1) but not distant sites
- ◯ IV — Carcinoma has extended beyond the true pelvis or has involved the mucosa of the bladder or rectum (bullous edema as such does not permit a case to be allotted to stage IV)
  - ◯ IVA — Tumour invades bladder and/or rectal mucosa and or direct extension beyond the true pelvis. It might or might not have spread to lymph nodes in the pelvis or groin (inguinal area) (Any N). It has not spread to distant sites (M0)
  - ◯ IVB — Spread to distant organs (M1). It can be any size and might or might not have grown into nearby structures or organs (Any T). It might or might not have spread to nearby lymph nodes (Any N)

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

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)
- ◯ T1 — Tumour confirmed to vagina
- ◯ T2 — Tumour invades paravaginal tissues (paracolpium)
- ◯ T3 — Tumour extends to pelvic wall
- ◯ T4 — Tumour invades mucosa of bladder or rectum, or extends beyond the true pelvis[d]

Regional lymph nodes (pN)

- ◯ NX — Regional lymph nodes cannot be assessed
- ◯ N0 — No regional lymph node metastasis
- ◯ N1 — Regional lymph node metastasis

[b] *Reprinted from Int J Gynaecol Obstet., Volume 105(1), FIGO Committee on Gynecologic Oncology, Current FIGO staging for cancer of the vagina, fallopian tube, ovary, and gestational trophoblastic neoplasia, pages 3-4, 2009, with permission from Wiley.*

[c] *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 6th October 2020).*

[d] *The presence of bullous oedema is not sufficient evidence to classify a tumour as T4.*

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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 in the expert committee. An appropriate staging system e.g., Pathological TNM staging would normally be included as a CORE element.

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 the Dataset Authoring Committee.

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Scope

The dataset has been developed for the pathological reporting of resection specimens of primary carcinomas of the vagina (including carcinosarcomas).

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

Due to the rarity of primary vaginal carcinomas, there is little published research regarding some of the elements included in this dataset and some of the parameters included are 'extrapolated' from primary cervical and vulval carcinomas and/or represent the opinions and experience of the members of the International Collaboration on Cancer Reporting (ICCR) Carcinoma of the Vagina Dataset Authoring Committee (DAC).

The authors of this dataset can be accessed here.

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Note 1 – Clinical information (Core)

In most ICCR datasets, clinical information is a non-core element but the DAC felt that clinical information is vital in reporting vaginal carcinomas and thus this is included as a core element. In reporting a vaginal carcinoma, knowledge of a history of any prior tumour, 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 so with vaginal squamous cell carcinoma (SCC) since tumour recurrence is common. Knowledge of a history of a prior cervical carcinoma is important since before diagnosing a primary vaginal SCC, exclusion of a cervical primary is mandated; although there are no 'hard and fast' rules, a diagnosis of a cervical SCC concomitantly or in the past 5 years is usually taken as evidence for exclusion of a primary vaginal SCC.[2] Knowledge of a history of a prior malignancy is also important in reporting the very rare primary vaginal adenocarcinomas since a metastasis, from elsewhere in the female genital tract or outside this (especially the colorectum), should always be excluded before rendering such a diagnosis. A history of vaginal adenosis is also important since some primary vaginal adenocarcinomas of clear cell, gastric or human papillomavirus (HPV)-associated types arise in adenosis, which may be sporadic or secondary to in utero exposure to diethylstilbestrol.[3-6] Some primary vaginal endometrioid adenocarcinomas arise in endometriosis and this may be stimulated by hormones, including unopposed estrogens. Knowledge of a history of any prior neoadjuvant therapy (chemotherapy, radiotherapy, chemoradiation) is also 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)

Vaginectomy describes removal of the vaginal mucosa by either a vaginal or abdominal approach and may be partial or total.[7,8] The extent of vaginectomy depends on various parameters such as the location of the lesion, patient preference/expectations, prior hysterectomy, prior radiation, hormonal status and proximity to other vital structures.

Vaginectomy specimens may also be a component of a pelvic exenteration.

The 'other' category may be used to cover other organs, which have been removed as part of the operative procedure.

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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.[9,10] 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 (Non-core)

Most primary carcinomas arise in the upper two-thirds of the vagina. Recording the location within the vagina of a primary carcinoma may be important for several reasons and is facilitated by the specimen being orientated by the surgeon in the absence of attached anatomical structures. Exclusion of secondary involvement by a cervical (or upper genital tract) neoplasm is more important in tumours located in the upper two-thirds of the vagina.[2] HPV-associated SCC tend to arise in the upper two-thirds of the vagina, while HPV-independent SCC tend to involve the lower-third.[2,11] HPV-independent clear cell carcinomas related to in utero exposure to diethylstilbestrol show a predilection for the upper two-thirds,[2] mesonephric adenocarcinomas are usually located in the lateral walls[2] and mucinous carcinomas of intestinal type in the lower posterior third.[12] Additionally, there are different, albeit not always predictable, lymphatic drainage patterns of the upper, middle and lower thirds of the vagina.[13,14]

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Note 5 – Tumour dimensions (Core)

Measurement of tumour dimensions in vaginal carcinomas is important for accurate staging, patient management and prognostication. Tumours should be measured in millimetres (mm). The maximum horizontal dimension is the greatest tumour dimension measured parallel to the mucosal 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 mucosal surface is often included in the pathology report but this is not necessary for staging, management or prognostication. The depth of invasion must also be reported. While there are no widely used recommendations for measuring depth of invasion, it is recommended that this is taken from the base of the epithelium from which the tumour arises to the deepest point of invasion.

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 depth of invasion can be taken as the maximum depth of invasion in the two different specimens.

If the tumour involves a margin, a comment should be made regarding the possibility of underestimation of the horizontal dimension or depth of invasion.

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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 vaginal carcinomas should be typed according to the most recent edition of the World Health Organization (WHO) Classification of Tumours of Female Genital Tumours, 5th edition, 2020 (Table 1).[15] The ICCR dataset includes 5th edition Corrigenda, June 2021.[16] While SCC is by far the most common carcinoma to arise in the vagina, these neoplasms are uncommon and thus care should be taken to rule out secondary involvement from adjacent sites, especially the cervix and vulva. Although there are no 'hard and fast' rules, a diagnosis of a cervical SCC in the past five years is usually taken as evidence for exclusion of a primary vaginal SCC. Aligning with SCC of the vulva and cervix, SCC of the vagina is divided in the 2020 WHO Classification[15] into HPV-associated and HPV-independent types. HPV-associated SCC are secondary to persistent infection by oncogenic high-risk HPV (most commonly type 16) and are associated with smoking, immunosuppression and often multifocal disease including HPV-associated lesions in other areas of the lower female genital tract (vulva, cervix) and anal/perianal regions.[17,18] Similar to the vulva, primary vaginal HPV-associated SCC are more likely to be non-keratinizing, basaloid and warty, while HPV-independent SCC are more likely to be keratinizing. The presence of an adjacent high grade squamous intraepithelial lesion (HSIL) may be useful in suggesting an HPV-associated lesion. However, as in the vulva, in practice, ancillary testing is necessary to determine the HPV status given the overlap in morphology in some cases (see **Note 12 ANCILLARY STUDIES**).[18,19] 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. Although because of the rarity of these neoplasms within the vagina, evidence is much more limited compared to the vulva, HPV-independent SCC have worse disease-free and overall survival compared to HPV-associated SCC, independent of age and stage.[11]

Grading of vaginal SCC is not recommended and is not included as a core or non-core item in this dataset. Grading has not been shown to correlate with clinical outcome. In fact, as with vulval SCC, 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 primary vaginal SCC.

Primary adenocarcinomas of the vagina are extremely rare and of various morphological types, including HPV-associated, endometrioid, clear cell, mucinous (gastric-type or intestinal-type) and mesonephric; adenocarcinoma of periurethral Skene gland origin may also occur and present as a primary vaginal neoplasm.[3,4,12,20,21] The specific histologic type should be specified in the report. These categories of adenocarcinoma are broadly similar to those described in the cervix and before diagnosing a primary vaginal adenocarcinoma, a metastasis from elsewhere should always be excluded. The most likely alternative site of primary depends on the morphological type. For example, before diagnosing an HPV-associated adenocarcinoma or a gastric-type adenocarcinoma, a primary in the cervix should be excluded and before diagnosing an intestinal-type adenocarcinoma, a large intestinal primary should be ruled out. Some primary vaginal adenocarcinomas, for example those of gastric, HPV-associated and clear cell type may be associated with and arise from vaginal adenosis via 'atypical adenosis' which is usually sporadic but which may be secondary to in-utero exposure to diethylstilbestrol.

Carcinosarcomas, adenosquamous carcinomas and adenoid basal carcinomas are extremely rare as primary neoplasms in the vagina and before diagnosing a primary vaginal carcinosarcoma or adenosquamous carcinoma, a metastasis from another site in the female genital tract should be excluded. Neuroendocrine neoplasia is classified according to the 2020 WHO Classification[15] (neuroendocrine tumour, small cell neuroendocrine carcinoma, large cell neuroendocrine carcinoma, mixed neuroendocrine-non-neuroendocrine carcinoma); again these are extremely rare primary vaginal neoplasms.

Table 1: World Health Organization classification of malignant epithelial tumours of the vagina.[15]

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
Adenocarcinoma NOS	8140/3
Adenocarcinoma, HPV-associated	8483/3
Endometrioid adenocarcinoma NOS	8380/3
Clear cell adenocarcinoma NOS	8310/3
Mucinous carcinoma, gastric type	8482/3
Mucinous adenocarcinoma	8480/3
Mesonephric adenocarcinoma	9110/3
Carcinosarcoma NOS	8980/3
Carcinoma of Skene, Cowper, and Littré glands	8140/3
Adenosquamous carcinoma	8560/3
Adenoid basal carcinoma	8098/3

[a] These morphology codes are from the International Classification of Diseases for Oncology, third edition, second revision (ICD-O-3.2).[22] 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. Incorporates all relevant changes from the 5th Edition Corrigenda June 2021.

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Note 8 – Lymphovascular invasion (Core)

There is a lack of published evidence regarding the prognostic significance of lymphovascular invasion in primary vaginal carcinomas probably due to the rarity of these neoplasms. Two studies evaluated lymphovascular invasion as a prognostic factor for primary vaginal carcinoma;[23,24] this was not statistically significant in one study[23] and no conclusion was documented in the other.[24] The consensus of the DAC supports including lymphovascular invasion as a core item, based on its possible role in altering clinical management in some cases, and also by extrapolating from cervical and vulvar carcinomas, many of which are biologically analogous to vaginal carcinomas.

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, 'carry-over' or cauterization 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 – Margin status (Core and Non-core)

Due to the rarity of primary vaginal carcinomas, there is little published research regarding the value of positive tumour margins or distance from tumour to the various margins in predicting tumour recurrence and prognosis. However, by extrapolation from primary cervical and vulval carcinomas and the opinions and experience of the members of the DAC, tumour involvement of or distance from the margins are considered to represent a core element. Appropriate sections need to be taken to include the nearest peripheral mucosal margin and the deep margin and assessment of the margins may be facilitated by the placing of sutures or provision of a diagram or photograph by the clinician. 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 vaginal carcinomas, it is recommended that surgical margins should be inked and the following recommendations adhered to:

- Involvement of a peripheral 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.
- Involvement of a peripheral margin by a high grade precursor lesion (HPV-associated HSIL) should be recorded and the margin specified if possible. Margin involvement by a low grade precursor lesion (low grade squamous intraepithelial lesion (LSIL)) does not need to be recorded.
- The distance of a high grade precursor lesion from the nearest peripheral margin is regarded as a non-core element but 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.
- The minimum distance of invasive tumour to the deep soft tissue margin should also be recorded. This should be measured from the deepest infiltrating tumour nest to the deep soft tissue margin.

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Note 10 – Lymph node status (Core)

The vagina has complex lymphatic drainage. The upper two-thirds of the vagina, the location of the majority of carcinomas, drains into pelvic lymph nodes (obturator, internal iliac/hypogastric and external iliac), and rarely to the para-aortic lymph nodes. The lower one-third drains into the inguinofemoral lymph nodes. Tumours arising in the middle third of the vagina may spread to both pelvic and inguinofemoral nodes and defining 'regional' nodes may not be possible in each case, especially as the pathologist may not be aware of the location of the tumour. This is reflected in the International Federation of Gynecology and Obstetrics (FIGO) Staging System,[25,26] where only involvement of 'nearby lymph nodes', i.e., pelvic or groin, is taken into account.

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 extracapsular 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.

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 extracapsular spread should be accurately documented in the pathology report. According to TNM8,[27] nodal involvement should be recorded as the presence of isolated tumour cells (ITC, <0.2 mm), micrometastases (MIC, 0.2-2 mm) or macrometastases (MAC, >2 mm). MAC are regarded as pN1, MIC as pN1 (mi) and ITCs are pN0 (i+); ITCs do not upstage a carcinoma.

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Note 11 – Coexistent pathology/precursor lesions (Core)

Recording the presence of precursor lesions and coexistent pathology is important for vaginal SCC since this gives insight into the pathogenesis of the tumour, specifically whether it is HPV-associated or HPV-independent. Margin involvement by a high grade precursor lesion is also important (see **Note 9 MARGIN STATUS**). The presence of HPV-associated squamous intraepithelial lesion (LSIL or HSIL) should be recorded. HSIL (vaginal intraepithelial neoplasia grades 2/3) is the precursor of HPV-associated vaginal SCC and, as discussed earlier (see **Note 7 HISTOLOGICAL TUMOUR TYPE**), is associated with smoking, immunosuppression and often multifocal disease including HPV-associated lesions in other areas of the lower female genital tract (vulva, cervix) and anal/perianal regions.[17,18] Unlike in the vulva, there is currently no recognised precursor lesion of HPV-independent vaginal SCC. p16 may be useful in diagnosing HSIL and in distinguishing this from morphological mimics (see **Note 12 ANCILLARY STUDIES**).

There are also recognised precursor lesions of some primary vaginal adenocarcinomas and these should be recorded on the pathology report; the presence of these lesions may be useful in helping to confirm a vaginal primary and in excluding a metastasis from elsewhere. Some of these adenocarcinomas, for example those of gastric, HPV-associated and clear cell type may be associated with and arise from vaginal adenosis via 'atypical adenosis' which is usually sporadic but which may be secondary to in utero exposure to diethylstilbestrol.[3] Primary vaginal endometrioid adenocarcinomas may arise in endometriosis,[20] and intestinal-type adenocarcinomas may arise in tubular and tubulovillous adenomas.[12] Mesonephric adenocarcinomas may arise from benign mesonephric remnants.

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Note 12 – Ancillary studies (Core and Non-core)

As discussed (see **Note 7 HISTOLOGICAL TUMOUR TYPE**), the 2020 WHO Classification categorises vaginal SCC into two main types, HPV-associated and HPV-independent,[2] with prognostic implications which have already been discussed.[11,17,19,28,29] This new diagnostic approach has consequences since, as discussed, morphology is not always reliable in distinguishing between the two types. It implies that the use of ancillary techniques, namely p16 immunohistochemistry and/or HPV molecular testing, are considered as essential to correctly classify vaginal SCC.[2] p16 immunohistochemistry and/or HPV testing is considered a core element in cases of vaginal 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, not otherwise specified (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.

The two accepted tools for confirming an HPV-association are the direct identification of HPV products (DNA or mRNA) and the presence of immunohistochemical overexpression of 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, a small number of discrepancies are observed when the two techniques are applied. 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 tissue 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. Thus, highly sensitive methods, such as SPF10 PCR testing are the most used tests, but large series have reported both false positive and false negative results with this test.[30-32] In situ hybridisation for HPV E7 mRNA, one of the oncogenic HPV genes, has shown good results in tumours of the uterine cervix[33] but the experience in vaginal lesions is limited.

p16 immunohistochemical staining generally shows a good correlation with HPV testing, although there are few studies specifically focusing on vaginal lesions. Although isolated cases of HPV-associated tumours with 'negative' p16 staining have been reported in the cervix and vulva,[34] 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.[30] 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 nuclear or more typically nuclear and cytoplasmic expression 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 six cells across.[35] 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 is also 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'.

Other ancillary studies are regarded as non-core and when undertaken the results should be documented on the pathology report. One of the most useful markers is p53 and many HPV-independent vaginal SCC contain *TP53* mutations. Almost all HPV-associated SCC and high grade precursor lesions exhibit a 'wild-type' pattern of p53 immunoreactivity while many HPV-independent SCC exhibit 'mutation-type' immunoreactivity.

Other immunohistochemical markers and ancillary studies may be of value in helping to classify primary vaginal adenocarcinomas. For example, HPV-associated adenocarcinomas exhibit diffuse block-type p16 immunoreactivity and are HPV positive. Intestinal-type adenocarcinomas may be positive with intestinal markers such as CK20 and CDX2, mesonephric carcinomas with GATA3, CD10 and TTF1 and clear cell carcinomas are typically positive with napsin A and hepatocyte nuclear factor 1-beta. Skene gland adenocarcinomas are usually positive with prostatic markers such as prostate specific antigen, prostatic acid phosphatase and NKX3.1.

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Note 13 – 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 14 – 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 board meeting where all the pathological, clinical and radiological features are available.[25-27,36]

The latest version of either FIGO *or* TNM staging *or* both, can be used depending on local preferences.[25-27,36] The FIGO Staging System is in widespread use internationally and is the system used in most clinical trials and research studies. 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.[27,36] 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, this is 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.

The reference document TNM Supplement: A commentary on uniform use, 5th Edition (C Wittekind et al. editors) may be of assistance when staging.[37]

Back

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