The Royal College of Pathologists
Pathology: the science behind the cure

Standards and datasets for reporting cancers

Dataset for histopathological reporting of vulval carcinomas

January 2018

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Unique document number	G070
Document name	Dataset for histopathological reporting of vulval carcinomas
Version number	4
Produced by	Dr Asma Faruqi and Dr Brian Rous, on behalf of the Royal College of Pathologists' Working Group for Cancer Services. The authors are specialist gynaecological pathologists. Dr Faruqi has sat on committees relevant to quality assurance and policy in gynaecological pathology. Dr Rous is a gynaecological pathologist and chairs the Working Group of Cancer Services.
Date active	January 2018
Date for review	January 2021
Comments	This document will supersede the 2010 document *Dataset for histological reporting of vulval neoplasms (3rd edition).* In accordance with the College's pre-publications policy, this document was on The Royal College of Pathologists' website for consultation from 14 November to 12 December 2017. Responses and authors' comments are available to view on request. **Dr Lorna Williamson** Director of Publishing and Engagement

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Foreword

The cancer datasets published by The Royal College of Pathologists (RCPath) are a combination of textual guidance, educational information and reporting proformas. The datasets enable pathologists to grade and stage cancers in an accurate, consistent manner in compliance with international standards and provide prognostic information, thereby allowing clinicians to provide a high standard of care for patients and appropriate management for specific clinical circumstances. This guideline has been developed to cover most common circumstances. However, we recognise that guidelines cannot anticipate every pathological specimen type and clinical scenario. Occasional variation from the practice recommended in this guideline may therefore be required to report a specimen in a way that maximises benefit to the patient.

Each dataset contains core data items that are mandated for inclusion in the Cancer Outcomes and Services Dataset (COSD – previously the National Cancer Data Set) in England. Core data items are items that are supported by robust published evidence and are required for cancer staging, optimal patient management and prognosis. Core data items meet the requirements of professional standards (as defined by the Information Standards Board for Health and Social Care [ISB]) and it is recommended that at least 90% of reports on cancer resections should record a full set of core data items. Other non-core data items are described. These may be included to provide a comprehensive report or to meet local clinical or research requirements. All data items should be clearly defined to allow the unambiguous recording of data.

The following stakeholders have been consulted during the preparation of the dataset:

- Working Group of the British Association of Gynaecological Pathologists (BAGP) comprising BAGP Council and co-opted members
- British Gynaecological Cancer Society (BGCS)
- British Society for the Study of Vulval Diseases.

The evidence has been evaluated according to the modified SIGN guidance and the level of evidence for the recommendations has been summarised according to College guidance (see Appendix G).

No major organisational changes have been identified that would hinder the implementation of the dataset.

A formal revision cycle for all cancer datasets takes place on a three-yearly basis. However, each year, the College will ask the author of the dataset, in conjunction with the relevant subspecialty advisor to the College, to consider whether or not the dataset needs to be updated or revised. A full consultation process will be undertaken if major revisions are required, i.e. revisions to core data items (the only exception being changes to international tumour grading and staging schemes that have been approved by the Specialty Advisory Committee on Cellular Pathology and affiliated professional bodies; these changes will be implemented without further consultation). If minor revisions or changes to non-core data items are required, an abridged consultation process will be undertaken whereby a short note of the proposed changes will be placed on the College website for two weeks for members' attention. If members do not object to the changes, the short notice of change will be incorporated into the dataset and the full revised version (incorporating the changes) will replace the existing version on the College website.

The dataset has been reviewed by the Clinical Effectiveness department, Working Group on Cancer Services and Lay Governance Group. It was placed on the College website for consultation with the membership from 14 November to 12 December 2017. All comments received will be addressed by the authors to the satisfaction of the Chair of the Working Group and the Director of Publishing and Engagement.

This dataset was developed without external funding to the writing group. The College requires the authors of datasets to provide a list of potential conflicts of interest; these are monitored by the Clinical Effectiveness department and are available on request. The authors of this document have declared that there are no conflicts of interest.

1 Introduction

The dataset is intended to be used for the reporting of carcinomas only. For vulval melanomas, use of the *Dataset for the histological reporting of primary cutaneous malignant melanoma and regional lymph nodes*[1] is recommended.

In the context of gynaecological malignancies vulval cancer is relatively rare; nevertheless, there has been an increase over the past two decades. In 2013, there were 1,313 new cases diagnosed in the UK and in 2014, there were 453 deaths from vulval cancer.[2] Vulval cancer is associated with significant morbidity and mortality, particularly in older women where the disease is more likely to present at a later stage.[3] The incidence increases with age peaking at 80 years; however, since 1990, there has been a statistically significant increase in incidence in younger women that has been demonstrated in a number of studies. When analysing these data it is useful to consider the bimodal pathway in the development of vulval neoplasia;[4–6] broadly speaking tumours in the younger age group are associated with high-risk human papilloma virus (HPV) infection and those in older women present on a background of inflammatory dermatoses, especially lichen sclerosus.[7,8] With the increased incidence of HPV-related neoplasia at other sites (throat, penis, anus), it is reasonable to assume that the increase in vulval neoplasia in younger women is likely to be HPV related.

Primary surgery is the treatment choice for vulval cancer and in the UK, about 70% of patients undergo surgical resection as part of their cancer treatment.[2]

Prognostic features in vulval carcinoma are the site and size of the lesion, the depth of invasion or alternatively tumour thickness, the number of involved lymph nodes, the size of the nodal deposits, extra nodal spread and lymphovascular space invasion.

1.1 Precursor disease: vulval intraepithelial neoplasia (VIN)

1.1.1 Usual/classical VIN (HPV-associated neoplasia)

The nomenclature of precursor lesions in HPV-related neoplasia is varied and includes the terms usual type VIN and classical VIN. The terminology recommended by the World Health Organisation (WHO)[9] and the LAST project[10] refers to LSIL (low-grade squamous intraepithelial lesion that includes HPV-related changes and VIN1) and HSIL (high-grade squamous intraepithelial lesion, referring to VIN2, VIN3, Bowen's disease and Bowenoid dysplasia). The advantage of this approach is that it triages cases into prognostically relevant groups and puts HPV-independent precursor lesions, or differentiated VIN (dVIN), into a third, separate category. The terms LSIL and HSIL are not widely accepted within the UK and the use of the alternative terms low- and high-grade VIN can be used with subcategorisation as VIN2 or VIN3 in parentheses for the latter.

1.1.2 Differentiated VIN

This lesion is HPV independent. It is often seen in the older age group on a background of inflammatory dermatoses. It is characterised by basal cell atypia and abnormal keratinocyte differentiation.

1.2 Target users and health benefits of this guideline

The dataset is primarily intended for use by consultant and trainee pathologists when reporting resection specimens of vulval cancers. Surgeons and oncologists can refer to the dataset when interpreting histopathology reports. The dataset should be available at the

multidisciplinary team (MDT) meetings for recording of accurate information and to inform discussions. It can also be used to assist in clinical trials. Many of the data items are collected for epidemiological analysis by Cancer Registries.

1.3 Changes to the 3rd edition

This is a revision of the last vulval cancer dataset[11] that was published in 2010. It takes into account changes in the WHO classification of vulval neoplasia[9] and includes the *TNM Classification of Malignant Tumours (8th edition)* from the Union for International Cancer Control (UICC).[12] An attempt has been made to simplify the dataset without sacrificing important prognostic information.

Other key changes that have been included in the dataset are as follows:

- addition of a proforma for biopsy reporting
- use of a two-tier system for grading VIN (LSIL/HSIL)
- addition of data items to allow recording of markers of high-risk HPV infection when performed
- recommendations for handling and reporting sentinel lymph nodes (SLN)
- proformas provided in list format to assist implementation in Laboratory Information Systems
- SNOMED-CT coding.

2 Clinical information required on the specimen request form

The specimen request form should include:

- full patient details
- history including results of previous biopsies/cytology
- details of surgical procedure; ideally a diagram should be included to assist orientation
- the specimen should be orientated, for example using sutures
- vaginal, urethral and anal margins, if present, should be marked by the surgeon and indicated on a diagram.

3 Preparation of specimens before dissection of resection specimens

Specimens should be prepared as follows:

- a photographic record or diagram of the orientated specimen is helpful as the blocks taken can be marked upon it and retained with the patient's record
- large specimens may be pinned onto a cork board prior to fixation
- surgical margins should be inked.

4 Specimen handling and block selection for resection specimens

4.1 Gross description

This should include:

- size of the specimen

- size of the tumour
- whether it is unifocal or multifocal
- distance to the margins in millimetres
- background skin should be examined for abnormalities.

4.2 Block selection

This should include:

- adequate tumour sampling (a representative megablock may be helpful)
- blocks should include tumour to the closest margins
- representative block(s) of non-neoplastic epithelial abnormality
- any other incidental abnormality.

4.3 Lymph nodes

Inguinofemoral lymph node resection is not usually performed if the depth of invasion is less than 1 mm and the horizontal size is less than 20 mm (FIGO stage IA) as studies have shown that there is a very low risk of nodal metastases in these patients.[13]

The following should be observed during lymph node resection:

- all lymph nodes must be sampled
- in most cases the nodes can be identified by careful palpation. The rest of the adipose tissue should be processed even if there are no palpable nodes. If there is excessive adipose tissue, it would be reasonable to sample up to five additional cassettes. If no lymph nodes are retrieved by these methods, all the adipose tissue should be sampled
- if a node has macroscopic tumour involvement, one or more representative blocks may be taken after careful examination, bearing in mind that the presence of extracapsular extension makes the tumour FIGO stage IIIC at least. If there is any doubt the entire node should be submitted for examination
- if a node appears normal, it should be submitted in it's entirety
- lymph nodes 4 mm or more should be serially sectioned at 2 mm intervals perpendicular to the long axis
- smaller nodes may be embedded in their entirety or after bisection.

4.4 Sentinel lymph nodes

Complete inguinofemoral lymph node dissection is associated with considerable morbidity and therefore SLN excision in the treatment of early stage vulval carcinoma is regarded as the standard of care in many institutes.[14–19]

The criteria for selection include unifocality, a tumour size of 4 cm or less and no clinically suspicious groin nodes. Intraoperative frozen sectioning of these lymph nodes may lead to tissue loss and therefore examination of paraffin-embedded tissue is recommended. All nodal tissue is sampled. If more than one lymph node is retrieved, then each lymph node must be clearly labelled and submitted in a separate cassette. Lymph nodes larger than 4 mm are sliced perpendicular to the long axis at 2 mm intervals. Each slice is placed face down with the equivalent face for each slice. Multiple slices may be submitted per cassette; however, care should be taken not to overcrowd the cassette and a maximum of three slices is recommended. Haematoxylin and eosin (H&E) is performed on each block. It is essential

to examine a full face of the tissue in which the sub-capsular sinus is evident. If metastasis is confirmed, the largest deposit is measured and no further action is required.

If there is no evidence of nodal metastasis on routine examination, then ultrastaging is recommended. This is a labour-intensive procedure, both in terms of laboratory workload and consultant time. Therefore, it requires prior discussion and agreement between the surgical and pathology teams and adequate support in terms of costing to reflect this. The current evidence indicates it is more effective at identifying micrometastases than routine sampling. A variety of methods have been employed for ultrastaging and there is no consensus about the most effective protocol. Mathematical models have been studied[20,21] and the probability of detecting metastases of 0.25 mm is estimated to be above 90% if the node is ultrasectioned at 200–250 µ step sections. In routine practice, a pragmatic approach is required that balances the probability of finding metastatic deposits with the work and cost involved. If the first H&E is negative, sets of three serial sections are cut 250 µ apart through the block. Slide 1 of each set is stained for H&E and if positive no further action is required. If negative, it is necessary to proceed to immunohistochemistry on slide 2 from each set using a broad spectrum cytokeratin such as AE1/3. Using this method, in a block approximately 2 mm thick, the initial trim to acquire a full face H&E would be around 0.5–1 mm. Further ultrasectioning should generate no more than four sets with a maximum of four H&E and four cytokeratin stains to be examined. Other studies have ultrasectioned the nodes at 500 µ, 400 µ, 200 µ and 40 µ.[22–26]

The size of lymph node metastases has implications for prognosis and treatment[27–29] and ultrastaging may bring to light very small tumour deposits. A micrometastasis is a deposit that measures 2 mm or less. This is similar to size criteria in breast cancer. In breast cancer the term isolated tumour cells is also used, which refers to cells or groups of cells that are 0.2 mm or less in size and are considered to be pN0, with the patient being treated as SLN negative. In reporting vulval carcinoma, it is not unreasonable to adopt a similar approach in the knowledge that micrometastasis may upstage a FIGO stage I tumour to FIGO stage III. The report should therefore state the size of the deposit and indicate that a dimension of 0.2 mm or less may be considered as SLN negative.

5 Core data items for resection specimens

5.1 Clinical

5.1.1 Procedure and lymph nodes

Documentation of the specimen submitted is good clinical practice. The femoral and inguinal lymph nodes are the sites of regional spread of vulval carcinoma.[30,31]

[Level of evidence – GPP.]

5.2 Macroscopy

5.2.1 Specimen size

Documentation of specimen size allows correlation between clinical appearances of the specimen, macroscopic assessment and microscopic assessment, and reduces the risk of laboratory error.

[Level of evidence – GPP.]

5.2.2 Tumour site

The anatomical subsites (labium majus, labium minus, central, clitoral) of the vulva that are involved by squamous cell carcinoma have been shown to have prognostic significance; patients with clitoral involvement have worse survival.[32]

[Level of evidence D – site of involvement has independent prognostic value.]

5.2.3 Maximum macroscopic tumour dimension

Documentation of macroscopic tumour size allows correlation between the clinical appearance of the specimen, macroscopic assessment and microscopic assessment, and reduces the risk of laboratory error. Size is an important prognostic factor and is included in FIGO and TNM staging. For large specimens, it may not be practical to measure microscopic size across multiple slides; in these circumstances, the macroscopic size may be more accurate.

[Level of evidence B – tumour size is an independent prognostic variable.]

5.2.4 Macroscopic margin, distance

Distance to margins correlates with risk of recurrence and as with tumour size, may not be measurable on histological sections.

[Level of evidence – D.]

5.3 Microscopy

5.3.1 Tumour type

Squamous cell carcinoma of the vulva is the most common vulval malignancy. Tumour type determines biological behaviour of the tumour. In contrast to squamous cell carcinoma, basal cell carcinoma is highly unlikely to metastasise.[33]

[Level of evidence C – tumour type is an independent prognostic factor.]

5.3.2 Tumour differentiation

Squamous carcinomas are graded as well differentiated (grade 1), moderately differentiated (grade 2) and poorly differentiated (grade 3) according to the degree of keratinisation, intercellular bridges and pleomorphism, following a modified version of Broders' grading system.[34] There is no agreed grading system for adenocarcinomas of the vulva.

Grade or differentiation in squamous tumours has been shown to be linked to five-year survival rates. Patients with grade 1 tumours have a greater chance of surviving five years than grade 3 tumours (64.4% vs 24.9%).[35] On the other hand, multiple large studies have now clearly demonstrated a significant difference in response to treatment and overall survival between HPV-related and HPV-independent vulval squamous carcinomas, and this parameter may well supersede the impact of conventional grading;[36–38] p16 immunohistochemistry is a good surrogate for HPV status in VIN and vulval squamous carcinomas and should be carried out in all cases.

[Level of evidence C – grade of differentiation is an independent prognostic factor.]

5.3.3 Maximum horizontal tumour size

This may require correlation with the macroscopic measurement if the tumour is very large or involves measurements across more than one block. If a tumour extends across seven or more blocks it may be greater than 20 mm in diameter (i.e. FIGO stage II or greater).

[Level of evidence B – tumour size in an independent prognostic factor.]

5.3.4 Tumour thickness OR depth of invasion

Accurate measurement of invasion requires a calibrated ocular eyepiece or similar method. It is recognised that many histopathologists may not have access to an ocular eyepiece and the Vernier scale present on the microscope can be used instead, although it may sometimes be difficult to measure perpendicularly from the surface using this method.

The report should state clearly whether the measurement represents depth of invasion or tumour thickness.

Depth of invasion is measured in millimetres from the adjacent most superficial dermal papilla to the deepest point of invasion (see Figure 1). If this is not possible, it can be estimated by measuring from the surface to the deepest point of invasion and subtracting from this the distance from the surface to the epithelial–stromal interface of the most superficial dermal papilla.

Tumour thickness is measured from the granular layer (in keratinised tumours) or from the base of the ulcer (in the case of ulcerated tumours) to the deepest point of invasion (see Figure 2).

It is important to measure depth of invasion whenever possible as FIGO staging uses this measurement to distinguish between stage IA and stage IB tumours. Tumour thickness should be measured when there is ulceration and it is not possible to determine the epithelial–stromal interface.

[Level of evidence B – depth of invasion is an independent prognostic factor.][13,35,39]

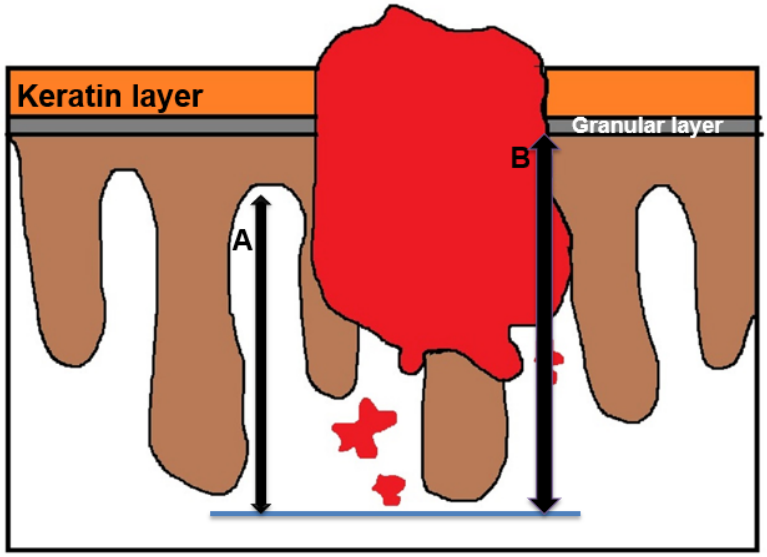

Figure 1: Diagram illustrating measurement of tumour thickness and depth of invasion.
A: Depth of invasion; B: tumour thickness.

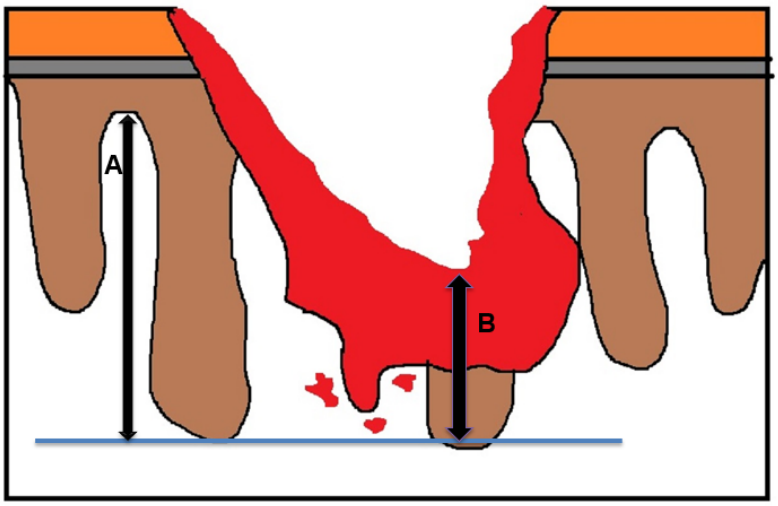

Figure 2: Diagram illustrating measurement of tumour thickness and depth of invasion in an ulcerated tumour. A: Depth of invasion; B: tumour thickness.

5.3.5 Lymphovascular and/or perineurial invasion (PNI)

Lymphovascular invasion does not affect tumour stage; however, it is important to recognise as there is an association with tumour spread and recurrence.

Retraction artefacts should be borne in mind and only tumour emboli in endothelium-lined spaces should be regarded as positive. Immunohistochemical staining for CD31 may be helpful in this regard.

PNI is defined as the presence of malignant cells in the layers of the nerve sheath (epineurium, perineurium and endoneurium). It was previously thought to be either a form of lymphatic invasion or spread along the path of least resistance. There is emerging evidence that it represents true invasion and is associated with a worse prognosis,[35,40,41] especially with regard to tumour recurrence. Tumour cells swirling around a nerve but not actually invading the nerve layers may not have the same clinical significance and the more accurate term intraneural or PNI is therefore recommended.

[Level of evidence – D.]

5.3.6 Margin status

Recurrence rates in vulval carcinoma and cancer-related deaths[42,43] have been shown to be related to pathological margin distance. Owing to factors such as tissue shrinkage and epithelial changes, the microscopic distance to the margin may not be the same as that measured macroscopically.[35,44–46] A clearance of at least 8 mm has been suggested as the pathological margin distance required to significantly reduce the risk of local recurrence.[42,47,48] Both measurements should therefore be stated.

[Level of evidence D – the distance of tumour from margin correlates with risk of recurrence.]

5.3.7 Precursor lesions

The presence of high-grade VIN (i.e. VIN 2/3), dVIN and Paget disease should be recorded. The report should also mention whether these lesions are completely excised or not.

Carcinomas associated with dVIN may be more likely to recur.[49]

[Level of evidence – D.]

5.3.8 Non-neoplastic epithelial disease (NNED)

The presence or absence of the following NNED should be recorded because there is an association with development of dVIN and invasive cancer:

- lichen sclerosus
- squamous hyperplasia
- mixed lichen sclerosus and squamous hyperplasia.

Lichen sclerosus has been associated with increased risk of recurrence.[50]

[Level of evidence D – the presence of NNED is associated with the development of cancer and increased risk of recurrence.]

5.3.9 Lymph node status

The number of involved lymph nodes, the size of the largest metastatic deposit and the presence or absence of extranodal spread should be recorded. Only inguinofemoral (groin) nodes are regarded as regional for FIGO and TNM staging; pelvic nodes are considered to represent distant metastatic disease.

[Level of evidence – B.]

5.3.10 Size of nodal deposits

Nodal deposits greater than 5 mm in size have been shown to correlate with poorer survival[30,31] and the tumour is upstaged in both the FIGO staging system and the TNM classification. In the FIGO system, the stage may prove problematic if there are two lymph nodes with deposits measuring 5 mm and less than 5 mm respectively, as it is not precisely covered in any of the stages; possibly the closest FIGO stage (as currently published) would be IIIA(i). Cutting levels on the lymph node with the smaller deposit may resolve this but if it does not, it might be advisable to include the TNM classification. In the TNM classification, this would be pN1b – one lymph node with metastasis 5 mm or more.

In the case of SLN, it is prudent to document the size of nodal metastases even if they are less than 5 mm. This is advisable for the purposes of data collection as there is emerging evidence that even when the size of the deposit is less than 5 mm, non-sentinel metastases may occur in a small minority of cases.[27]

[Level of evidence B – nodal deposit size is an independent prognostic factor.]

5.3.11 Extranodal extension

Tumour extension outside the lymph node has been shown to be an independent predictor of poorer survival and is included in the FIGO and TNM staging systems.[40,51]

[Level of evidence B – extranodal extension is an independent prognostic factor.]

5.3.12 Histological evidence of distant metastasis

The presence of distant metastatic disease may not always be known to the pathologist prior to the MDT meeting. If the relevant specimens that could indicate distant metastatic disease are received (e.g. biopsies of distant sites or pelvic lymph nodes), this should be recorded as pM1. Distant metastatic disease correlates with poorer survival.

[Level of evidence – B.]

5.3.13 Markers for high-risk HPV infection

There is now incontrovertible evidence that the presence or absence of HPV is an important prognostic factor with regards to radiotherapy response and survival.[36–38,52] Women with HPV-dependant carcinoma have a better response to radiotherapy, fewer in-field relapses and better survival. Thus, there appears to be clear stratification into two groups based on HPV status. Molecular methods for detection of high-risk HPV include PCR-based amplification of HPV DNA, DNA in situ hybridisation (ISH) and RNA ISH. Not all laboratories will have access to these tests and immunohistochemistry for p16 is a reliable surrogate marker for high-risk HPV infection. The pattern of p16 staining is important; it should only be regarded as positive if there is strong, linear, nuclear and cytoplasmic staining in the basal one-third to two-thirds of the epithelium ('block pattern'), although it may fade in the upper layers of epithelium.[36–38]

[Level of evidence D – high-risk HPV infection in the vulva may be associated with HPV infection at other gynaecological sites.]

6 Non-core data items

These may be recorded separately and include:

- koilocytosis as an indication HPV infection
- fibromyxoid stromal reaction as an adverse prognostic indicator[53]
- immunohistochemistry for p53 if dVIN is present. This may not always be conclusive but it can be overexpressed or have a 'null pattern' of staining.[54–58]

7 Small biopsies

Wide local excisions are handled in the same way as vulvectomy specimens. Ellipse and punch biopsies are handled according to size, in a manner similar to skin specimens. Larger ellipse biopsies may need inking of the margins. If a lesion is identified, transverse sectioning including the nearest resection margin is recommended.

8 Diagnostic coding and staging

Primary vulval carcinomas should be subtyped according to the WHO 2014 classification[9] and coded using SNOMED codes (Appendix B). Tumours should be staged using the 2009 FIGO staging system with the option to include the 7th or 8th edition of UICC TNM staging (Appendix A). Please note that apart from the prognostic grid, the 7th and 8th edition of UICC TNM staging are identical; for consistency of national data collection, the 7th edition should be stated until 31 December 2017 and the 8th edition should be stated from 1 January 2018.

9 Criteria for audit of the dataset

This dataset can be used as a standard in audits. Examples of audits include completeness of recording of all data items in histopathology reports, audits of numbers of lymph nodes retrieved and of variation between diagnostic biopsies and final histopathology reports.

Other audits are also recommended by the RCPath as key performance indicators (KPIs) (see Key Performance Indicators – Proposals for implementation [July 2013] on www.rcpath.org/clinical-effectiveness/kpi/KPI):

- cancer resections must be reported using a template or proforma, including items listed in the English COSD which are, by definition, core data items in RCPath cancer datasets. English Trusts were required to implement the structured recording of core pathology data in the COSD by January 2016.
  - standard: 95% of reports must contain structured data
- histopathology cases should be reported, confirmed and authorised within seven and ten calendar days of the procedure
  - standard: 80% of cases must be reported within seven calendar days and 90% within ten calendar days.

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Appendix A FIGO and TNM staging of vulval carcinoma

FIGO staging of vulval carcinoma

Stage I: confined to vulva, negative nodes

IA: Tumour confined to the vulva or perineum, ≤2 cm in size with stromal invasion* ≤1.0 mm, negative nodes.

IB: Tumour confined to the vulva or perineum, greater than 2 cm in size OR with stromal invasion* greater than 1.0 mm, negative nodes.

Stage II: tumour of any size extending to adjacent structures

II: Tumour of any size with adjacent spread (lower third of urethra, lower third of vagina, anus) with negative nodes.

Stage III: tumour of any size with or without extension to adjacent perineal structures (lower third of urethra, lower third of vagina, anus) but with positive inguinofemoral lymph nodes

IIIA: (i) With one lymph node metastasis ≥5.0 mm.

(ii) With one or two lymph node metastasis(es) of less than 5.0 mm.

IIIB: (i) With two or more lymph nodes metastases ≥5.0 mm.

(ii) With three or more lymph nodes metastases, less than 5.0 mm.

IIIC: Positive node(s) with extracapsular spread.

Stage IV: invasion of other regional structures (upper two-thirds of urethra, upper two-thirds of vagina or distant metastases)

IVA: (i) Upper two-thirds of urethra, upper two-thirds of vagina, bladder mucosa, rectal mucosa OR fixed to pelvic bone.

(ii) Fixed or ulcerated inguinofemoral lymph nodes.

IVB: Any distant metastasis including pelvic lymph nodes.

*The depth of invasion is defined as the measurement of the tumour from the epithelial–stromal junction of the adjacent most superficial dermal papilla to the deepest point of invasion.

UICC TNM Classification (7th/8th edition)

T – Primary tumour

TX Primary tumour cannot be assessed

T0 No evidence of primary tumour

Tis Carcinoma in situ (preinvasive carcinoma)

T1 Tumour confined to vulva

- T1a Tumour 2 cm or less in greatest dimension and with stromal invasion no greater than 1.0 mm
- T1b Tumour greater than 2 cm and/or stromal invasion greater than 1.0 mm

T2 Tumour invades any of the following structures: lower third of urethra, lower third of vagina, anus

T3 Tumour includes any of the following perineal structures: upper two-thirds of urethra, upper two-thirds of vagina, bladder mucosa, rectal mucosa; or fixed to pelvic bone

N – Regional lymph nodes

NX Regional lymph nodes cannot be assessed

N0 No regional lymph nodes metastasis

N1 Regional lymph node metastasis with the following features:

- N1a One or two lymph node metastases 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

M – Distant metastasis

M0 No distant metastasis

M1 Distant metastasis (including pelvic lymph nodes)

Appendix B WHO classification and SNOMED codes

Tumour site	ICD-10	SNOMED 2/3 Code	SNOMED-CT terminology	SNOMED-CT code
Vulva	C51	T-80000/T-81000	Entire vulva (body structure)	265796001

The morphology codes are from the International Classification of Diseases for Oncology (ICD-O)

Morphological codes	SNOMED 2/3 /ICD-O code	SNOMED-CT terminology	SNOMED-CT code
Intraepithelial tumours			
HSIL (VIN 2/3)	M-80772	Squamous intraepithelial neoplasia, grade III (morphologic abnormality)	20365006
dVIN	M-80712	No code yet	No code yet
Squamous cell carcinoma			
Keratinising or non-keratinising	M-80703	Squamous cell carcinoma, no ICD-O subtype (morphologic abnormality)	28899001
Basaloid	M-8083	Basaloid squamous cell carcinoma (morphologic abnormality)	128634009
Warty	M-80513	Warty (condylomatous) carcinoma (morphologic abnormality)	399408005
Verrucous	M-80513	Verrucous carcinoma (morphologic abnormality)	89906000
Basal cell carcinoma			
Basal cell carcinoma	M-80903	Basal cell carcinoma (morphologic abnormality)	1338007
Glandular tumours			
Paget disease	M-85423	Paget disease, extramammary (except Paget disease of bone) (morphologic abnormality)	71447003
Adenocarcinoma of mammary gland type	M-85003	Infiltrating duct carcinoma (morphologic abnormality)	82711006
Adenocarcinoma of Skene gland origin	M-81403	Adenocarcinoma, no subtype (morphologic abnormality)	35917007
Phyllodes tumour, malignant	M-90203	Phyllodes tumour, malignant (morphologic abnormality)	87913009

Adenocarcinoma, sweat gland type	M-81403	Adenocarcinoma, no subtype (morphologic abnormality)	35917007
Adenocarcinoma, intestinal type	M-81403	Adenocarcinoma, no subtype (morphologic abnormality)	35917007
Bartholin's gland tumours and other specialised anogenital gland			
Adenocarcinoma	M-81403	Adenocarcinoma, no subtype (morphologic abnormality)	35917007
Squamous cell carcinoma	M-81403	Squamous cell carcinoma, no ICD-O subtype (morphologic abnormality)	28899001
Adenosquamous carcinoma	M-85603	Adenosquamous carcinoma (morphologic abnormality)	59367005
Adenoid cystic carcinoma	M-82003	Adenoid cystic carcinoma (morphologic abnormality)	11671000
Transitional cell carcinoma	M-81203	Transitional cell carcinoma (morphologic abnormality)	27090000
Neuroendocrine tumours			
Small cell neuroendocrine carcinoma	M-80413	Small cell carcinoma (morphologic abnormality)	74364000
Large cell neuroendocrine carcinoma	M-80133	Large cell neuroendocrine carcinoma (morphologic abnormality)	128628002
Merkel cell tumour	M-82473	Merkel cell carcinoma (morphologic abnormality)	5052009

Procedure codes (P)

These are used in SNOMED 2 and SNOMED 3 to distinguish biopsies, partial resections and radical resections to indicate the nature of the procedure.

Local P codes should be recorded. At present, P codes vary according to the SNOMED system in use in different institutions.

Appendix C Reporting proforma for vulval cancer resection specimens

Surname ..... Forenames ..... Date of birth .....
Hospital ..... Hospital no ..... NHS/CHI no .....
Date of receipt ..... Date of report ..... Report no .....
Pathologist ..... Surgeon .....

Clinical

Procedure‡*:*

Local excision ☐ Left wide local excision ☐ Right wide local excision☐
Partial vulvectomy: Left ☐ Right ☐ Anterior ☐ Posterior ☐
Total vulvectomy ☐

Lymph nodes: Present ☐ Absent ☐

If present, tick all received:

	Left	Right
Sentinel nodes	☐	☐
Inguinofemoral nodes	☐	☐
Pelvic nodes	☐	☐
Other, specify ……	☐	

Macroscopy

Specimen size: ….. x …… x …… (L x W x thickness in mm)

Tumour site (tick all that apply)‡*:*

Labium majus: Left ☐ Right ☐
Labium minus: Left ☐ Right ☐
Central ☐ Clitoral ☐ Cannot be determined ☐

OR

No visible tumour☐

Maximum macroscopic tumour dimension (if visible)‡*:* …… mm

Nearest macroscopic margin (specify): ……
Nearest macroscopic margin distance …… mm

Microscopy

Histological type‡*:*

Squamous tumours
- Squamous cell carcinoma, NOS☐
  - Keratinising SCC ☐
  - Non-keratinising SCC ☐
  - Basaloid SCC ☐
  - Warty SCC ☐
  - Verrucous SCC ☐
- Basal cell carcinoma ☐

Glandular tumours
- Bartholin gland carcinomas
  - Adenocarcinoma ☐
  - Adenoid cystic carcinoma ☐
  - Adenosquamous carcinoma ☐
  - Transitional cell carcinoma
- Adenocarcinoma of mammary gland type ☐
- Adenocarcinoma of Skene gland origin ☐
- Adenocarcinoma of sweat gland type ☐
- Adenocarcinoma of intestinal type ☐

Neuroendocrine tumours
- Small cell neuroendocrine carcinoma ☐
- Large cell neuroendocrine carcinoma ☐
- Merkel cell carcinoma ☐

Carcinoma, type cannot be determined ☐

Other (specify): ....

Differentiation‡*:*

Well (grade 1) ☐ Moderate (grade 2) ☐ Poor (grade 3) ☐
Undifferentiated (grade 4) ☐ Not applicable ☐

Tumour size:
Maximum horizontal dimension‡*:* …… mm
Depth of invasion‡*:* …….. mm
AND/OR
Tumour thickness‡: …….. mm

Lymphovascular invasion‡*:* Present ☐ Not identified ☐ Uncertain ☐
Perineurial (intraneural) invasion: Present ☐ Not identified ☐ Uncertain ☐

Margins:
Extension to margin‡: No ☐. Yes ☐

If yes specify:
Left ☐ Right ☐
Anterior ☐ Posterior ☐
Deep ☐ Unorientated ☐
Other (specify) …….

If margins are not involved, which is the closest margin?
Left ☐ Right ☐
Anterior ☐ Posterior ☐
Deep ☐ Unorientated ☐
Other (specify) ……..

What is the distance of the tumour to the closest margin: …. mm

High-grade VIN/HSIL (VIN2/3): Present ☐ Not identified ☐ Uncertain ☐

If present:
Excised ☐ Not excised ☐
If not excised, *which margins are involved?*:
Left ☐ Right ☐
Anterior ☐ Posterior ☐
Other (specify): ☐…….

Differentiated VIN: Present ☐ Not identified ☐ Uncertain ☐

If present:

Excised ☐ Not excised ☐

If not excised, *which margins are involved?*:

Left ☐ Right ☐

Anterior ☐ Posterior ☐

Other (specify): ☐…….

Paget disease: Present ☐ Not identified ☐ Uncertain ☐

If present:

Excised ☐ Not excised ☐

If not excised, *which margins are involved?*:

Left ☐ Right ☐

Anterior ☐ Posterior ☐

Other (specify): ☐…….

Non-neoplastic epithelial disease:

Lichen sclerosus ☐ Lichen planus ☐ Squamous hyperplasia ☐

Lymph nodes, if received‡:

	Left		Right	
	Number positive	Number received	Number positive	Number received
Sentinel lymph nodes				
Inguinofemoral lymph nodes				
Pelvic lymph nodes				
Other, specify ……				

Size of sentinel lymph node deposit(s) in mm: ……

Largest lymph node deposit in mm: ……..

Extranodal extension‡ Yes ☐ No ☐

Histological evidence of distant metastasis‡: Present ☐ Not identified ☐

Markers for high-risk HPV infection:

HPV ISH Positive ☐ Negative ☐ Not performed ☐

p16 immunohistochemistry Positive ☐ Negative ☐ Not performed ☐

Staging

Provisional FIGO stage (may change following MDT discussion): …….

TNM‡ T... N... M... UICC TNM edition ……

SNOMED codes‡*:* …….

Reporting pathologist ……. Date……./……./…….

‡Data items that are currently part of the Cancer Outcomes and Services Dataset (COSD) version 7.

Appendix D Reporting proforma for vulval cancer biopsy specimens

Surname ..... Forenames ..... Date of birth .....
Hospital ..... Hospital no ..... NHS/CHI no .....
Date of receipt ..... Date of report ..... Report no .....
Pathologist ..... Surgeon .....

Clinical

Procedure‡*:*

Punch biopsy ☐ Wedge biopsy ☐

Laterality‡*:*

Left ☐ Right ☐ Midline ☐ Not known ☐

Microscopy

Histological type‡*:*

Squamous tumours
- Squamous cell carcinoma, NOS ☐
  - Keratinising SCC ☐
  - Non-keratinising SCC ☐
  - Basaloid SCC ☐
  - Warty SCC ☐
  - Verrucous SCC ☐
- Basal cell carcinoma ☐

Glandular tumours
- Bartholin gland carcinomas
  - Adenocarcinoma ☐
  - Adenoid cystic carcinoma ☐
  - Adenosquamous carcinoma ☐
  - Transitional cell carcinoma
- Adenocarcinoma of mammary gland type ☐
- Adenocarcinoma of Skene gland origin ☐
- Adenocarcinoma of sweat gland type ☐
- Adenocarcinoma of intestinal type ☐

Neuroendocrine tumours
- Small cell neuroendocrine carcinoma ☐
- Large cell neuroendocrine carcinoma ☐
- Merkel cell carcinoma ☐

Carcinoma, type cannot be determined ☐
Other (specify): ....

Differentiation‡*:*

Well (grade1) ☐ Moderate (grade 2) ☐ Poor (grade 3) ☐
Undifferentiated (grade 4) ☐ Not applicable ☐

Lymphovascular invasion‡*:*	Present ☐	Not identified ☐	Uncertain ☐
Perineurial invasion:	Present ☐	Not identified ☐	Uncertain ☐
High-grade VIN/HSIL (VIN2/3):	Present ☐	Not identified ☐	Uncertain ☐
Differentiated VIN:	Present ☐	Not identified ☐	Uncertain ☐
Paget disease:	Present ☐	Not identified ☐	Uncertain ☐

Markers for high-risk HPV infection:

HPV ISH	Positive ☐	Negative ☐	Not performed ☐
p16 immunohistochemistry	Positive ☐	Negative ☐	Not performed ☐

SNOMED codes‡*:* ……

Reporting pathologist …….. Date……/……./…….

‡Data items that are currently part of the Cancer Outcomes and Services Dataset (COSD) version 7.

Appendix E Reporting proforma for vulval cancer resection specimens in list format

Element name	Values	Implementation comments
Procedure	Single selection value list: • Local excision • Left wide local excision • Right wide local excision • Partial vulvectomy, left • Partial vulvectomy, right • Partial vulvectomy, anterior • Partial vulvectomy, posterior • Total vulvectomy	
Lymph nodes	Single selection value list: • Present • Absent	
Lymph nodes, present	Multiple selection value list: • Sentinel nodes, left • Sentinel nodes, right • Inguinofemoral nodes, left • Inguinofemoral nodes, right • Pelvic nodes, left • Pelvic nodes, right • Other	Only applicable if 'Lymph nodes, Present' is selected.
Lymph nodes, present, other	Free text	Only applicable if 'Lymph nodes, Present' is selected.
Macroscopic size, length	Size in mm	
Macroscopic size, width	Size in mm	
Macroscopic size, thickness	Size in mm	
Tumour site	Multiple selection value list: • Labium majus, left • Labium majus, right • Labium minus, left • Labium minus, right • Central • Clitoral • Cannot be determined • No visible tumour	

Element name	Values	Implementation comments
Maximum macroscopic tumour dimensions	Size in mm	Not applicable if 'Tumour site, No visible tumour' is selected.
Nearest macroscopic margin	Free text	Not applicable if 'Tumour site, No visible tumour' is selected.
Nearest macroscopic margin, distance	Size in mm	Not applicable if 'Tumour site, No visible tumour' is selected.
Histological type	Single selection value list: • Squamous cell carcinoma, NOS • Keratinising SCC • Non-keratinising SCC • Basaloid SCC • Warty SCC • Verrucous SCC • Basal cell carcinoma • Adenocarcinoma • Adenoid cystic carcinoma • Adenosquamous carcinoma • Transitional cell carcinoma • Adenocarcinoma of mammary gland type • Adenocarcinoma of Skene gland origin • Adenocarcinoma of sweat gland type • Adenocarcinoma of intestinal type • Small cell neuroendocrine carcinoma • Large cell neuroendocrine carcinoma • Merkel cell carcinoma • Carcinoma, type cannot be determined • Other	
Histological type, other	Free text	Only applicable if 'Histological type, Other' is selected.

Element name	Values	Implementation comments
Differentiation	Single selection value list: • Well (grade1) • Moderate (grade 2) • Poor (grade 3) • Undifferentiated (grade 4) • Not applicable	
Microscopic, horizontal dimension	Size in mm	
Microscopic, depth of invasion	Size in mm	
Microscopic, tumour thickness	Size in mm	
Lymphovascular invasion	Single selection value list: • Present • Not identified • Uncertain	
Perineurial (intraneural) invasion	Single selection value list: • Present • Not identified • Uncertain	
Extension to margin	Single selection value list: • Yes • No	
Margins involved	Multiple selection value list: • Left • Right • Anterior • Posterior • Deep • Unorientated • Other	Only applicable if ‘Extension to margin, Yes’ is selected.
Margins involved, other	Free text	Only applicable if ‘Margins involved, Other’ is selected.
Distance to closest margin	Size in mm	Only applicable if ‘Extension to margin, No’ is selected.

Element name	Values	Implementation comments
Closest margin	Single selection value list: • Left • Right • Anterior • Posterior • Deep • Unorientated • Other	Only applicable if 'Extension to margin, No' is selected.
Closest margin, other	Free text	Only applicable if 'Closest margin, Other' is selected.
High-grade VIN/HSIL (VIN2/3)	Single selection value list: • Present • Not identified • Uncertain	
High-grade VIN/HSIL (VIN2/3), excision status	Single selection value list: • Excised • Not excised	Only applicable if 'VIN2/3 (HSIL), Present' is selected.
High-grade VIN/HSIL (VIN2/3), margins involved	Multiple selection value list: • Left • Right • Anterior • Posterior • Other	Only applicable if 'VIN2/3 (HSIL), excision status, Not excised' is selected.
High-grade VIN/HSIL (VIN2/3), margins involved, other	Free text	Only applicable if 'VIN2/3 (HSIL), margins involved, Other' is selected.
Differentiated VIN	Single selection value list: • Present • Not identified • Uncertain	
Differentiated VIN, excision status	Single selection value list: • Excised • Not excised	Only applicable if 'Differentiated VIN, Present' is selected.

Element name	Values	Implementation comments
Differentiated VIN, margins involved	Multiple selection value list: • Left • Right • Anterior • Posterior • Other	Only applicable if 'Differentiated VIN, excision status, Not excised' is selected.
Differentiated VIN, margins involved	Free text	Only applicable if 'Differentiated VIN, margins involved, Other' is selected.
Paget disease	Single selection value list: • Present • Not identified • Uncertain	
Paget disease, excision status	Single selection value list: • Excised • Not excised	Only applicable if 'Paget disease, Present' is selected.
Paget disease, margins involved	Multiple selection value list: • Left • Right • Anterior • Posterior • Other	Only applicable if 'Paget disease, excision status, Not excised' is selected.
Paget disease, margins involved, other	Free text	Only applicable if 'Paget disease, margins involved, Other' is selected.
Non-neoplastic epithelial disease	Multiple selection value list: • Lichen sclerosus • Lichen planus • Squamous hyperplasia	
Sentinel lymph nodes, left, number received	Integer	Only applicable if 'Lymph nodes, present' includes 'Sentinel lymph nodes'.
Sentinel lymph nodes, left, number positive	Integer	Only applicable if 'Lymph nodes, present' includes 'Sentinel lymph nodes'.
Sentinel lymph nodes, right, number received	Integer	Only applicable if 'Lymph nodes, present' includes 'Sentinel lymph nodes'.

Element name	Values	Implementation comments
Sentinel lymph nodes, right, number positive	Integer	Only applicable if 'Lymph nodes, present' includes 'Sentinel lymph nodes'.
Inguinofemoral lymph nodes, left, number received	Integer	Only applicable if 'Lymph nodes, present' includes 'Inguinofemoral lymph nodes'.
Inguinofemoral lymph nodes, left, number positive	Integer	Only applicable if 'Lymph nodes, present' includes 'Inguinofemoral lymph nodes'.
Inguinofemoral lymph nodes, right, number received	Integer	Only applicable if 'Lymph nodes, present' includes 'Inguinofemoral lymph nodes'.
Inguinofemoral nodes, right, number positive	Integer	Only applicable if 'Lymph nodes, present' includes 'Inguinofemoral lymph nodes'.
Pelvic lymph nodes, left, number received	Integer	Only applicable if 'Lymph nodes, present' includes 'Pelvic lymph nodes'.
Pelvic lymph nodes, left, number positive	Integer	Only applicable if 'Lymph nodes, present' includes 'Pelvic lymph nodes'.
Pelvic lymph nodes, right, number received	Integer	Only applicable if 'Lymph nodes, present' includes 'Pelvic lymph nodes'.
Pelvic lymph nodes, right, number positive	Integer	Only applicable if 'Lymph nodes, present' includes 'Pelvic lymph nodes'.
Other lymph nodes, specify	Free text	Only applicable if 'Lymph nodes, present, Other' is selected.
Other lymph nodes, left, number received	Integer	Only applicable if 'Lymph nodes, present, Other' is selected.
Other lymph nodes, left, number positive	Integer	Only applicable if 'Lymph nodes, present, Other' is selected.
Other lymph nodes, right, number received	Integer	Only applicable if 'Lymph nodes, present, Other' is selected.
Other lymph nodes, right, number positive	Integer	Only applicable if 'Lymph nodes, present, Other' is selected.
Size of sentinel lymph node deposits in mm	Size in mm (may have multiple sizes)	Only applicable if either 'Sentinel lymph nodes, Right, Number positive' OR 'Sentinel lymph nodes, Left, Number positive' is >0.

Element name	Values	Implementation comments
Largest lymph node deposit in mm	Size in mm	
Extranodal extension	Single selection value list: • Yes • No	
Histological evidence of distant metastasis	Single selection value list: • Present • Not identified	
HPV ISH	Single selection value list: • Positive • Negative • Not performed	
p16 immunohistochemistry	Single selection value list: • Positive • Negative • Not performed	
Provisional FIGO stage	Single selection value list: • IA • IB • II • IIIA(i) • IIIA(ii) • IIIB(i) • IIIB(ii) • IIIC • IVA(i) • IVA(ii) • IVB	
pT category	Single selection value list: • TX • T0 • Tis • T1a • T1b • T2 • T3	

Element name	Values	Implementation comments
pN category	Single selection value list: • NX • N0 • N1a • N1b • N2a • N2b • N2c • N3	
pM category	Single selection value list: • Not applicable • M1	
UICC TNM version	Single selection value list: • 7 • 8 • 9	
SNOMED Topography code	May have multiple codes. Look up from SNOMED tables.	
SNOMED Morphology code	May have multiple codes. Look up from SNOMED tables.	

Appendix F Reporting proforma for vulval cancer biopsy specimens in list format

Element name	Values	Implementation comments
Procedure	Single selection value list: • Punch biopsy • Wedge biopsy	
Laterality	Single selection value list: • Left • Right • Midline • Not known	
Histological type	Single selection value list: • Squamous cell carcinoma, NOS • Keratinising SCC • Non-keratinising SCC • Basaloid SCC • Warty SCC • Verrucous SCC • Basal cell carcinoma • Adenocarcinoma • Adenoid cystic carcinoma • Adenosquamous carcinoma • Transitional cell carcinoma • Adenocarcinoma of mammary gland type • Adenocarcinoma of Skene gland origin • Adenocarcinoma of sweat gland type • Adenocarcinoma of intestinal type • Small cell neuroendocrine carcinoma • Large cell neuroendocrine carcinoma • Merkel cell carcinoma • Carcinoma, type cannot be determined • Other	

Element name	Values	Implementation comments
Histological type, other	Free text	Only applicable if 'Histological type, Other' is selected.
Differentiation	Single selection value list: • Well (grade1) • Moderate (grade 2) • Poor (grade 3) • Undifferentiated (grade 4) • Not applicable	
Lymphovascular invasion	Single selection value list: • Present • Not identified • Uncertain	
Perineurial (intraneural) invasion	Single selection value list: • Present • Not identified • Uncertain	
High-grade VIN/HSIL (VIN2/3)	Single selection value list: • Present • Not identified • Uncertain	
Differentiated VIN	Single selection value list: • Present • Not identified • Uncertain	
Paget disease	Single selection value list: • Present • Not identified • Uncertain	
HPV ISH	Single selection value list: • Positive • Negative • Not performed	
p16 immunohistochemistry	Single selection value list: • Positive • Negative • Not performed	

Element name	Values	Implementation comments
SNOMED Topography code	May have multiple codes. Look up from SNOMED tables.	
SNOMED Morphology code	May have multiple codes. Look up from SNOMED tables.	

Appendix G Summary table – explanation of levels of evidence

(modified from Palmer K *et al. BMJ* 2008;337:1832)

Level of evidence	Nature of evidence
Level A	At least one high-quality meta-analysis, systematic review of randomised controlled trials or a randomised controlled trial with a very low risk of bias and directly attributable to the target cancer type or A body of evidence demonstrating consistency of results and comprising mainly well-conducted meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a low risk of bias, directly applicable to the target cancer type.
Level B	A body of evidence demonstrating consistency of results and comprising mainly high-quality systematic reviews of case-control or cohort studies and high-quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relation is causal and which are directly applicable to the target cancer type or Extrapolation evidence from studies described in A.
Level C	A body of evidence demonstrating consistency of results and including well-conducted case-control or cohort studies and high quality case-control or cohort studies with a low risk of confounding or bias and a moderate probability that the relation is causal and which are directly applicable to the target cancer type or Extrapolation evidence from studies described in B.
Level D	Non-analytic studies such as case reports, case series or expert opinion or Extrapolation evidence from studies described in C.
Good practice point (GPP)	Recommended best practice based on the clinical experience of the authors of the writing group.

Appendix H AGREE compliance monitoring sheet

The cancer datasets of The Royal College of Pathologists comply with the AGREE II standards for good quality clinical guidelines (www.agreetrust.org). The sections of this dataset that indicate compliance with each of the AGREE II standards are indicated in the table.

AGREE standard	Section of guideline
Scope and purpose	
1 The overall objective(s) of the guideline is (are) specifically described	1
2 The health question(s) covered by the guideline is (are) specifically described	1
3 The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described	Foreword, 1
Stakeholder involvement	
4 The guideline development group includes individuals from all the relevant professional groups	Foreword
5 The views and preferences of the target population (patients, public, etc.) have been sought	Foreword
6 The target users of the guideline are clearly defined	1
Rigour of development	
7 Systematic methods were used to search for evidence	Foreword
8 The criteria for selecting the evidence are clearly described	Foreword
9 The strengths and limitations of the body of evidence are clearly described	Foreword
10 The methods for formulating the recommendations are clearly described	Foreword
11 The health benefits, side effects and risks have been considered in formulating the recommendations	Foreword
12 There is an explicit link between the recommendations and the supporting evidence	4–6
13 The guideline has been externally reviewed by experts prior to its publication	Foreword
14 A procedure for updating the guideline is provided	Foreword
Clarity of presentation	
15 The recommendations are specific and unambiguous	4–8
16 The different options for management of the condition or health issue are clearly presented	4–8
17 Key recommendations are easily identifiable	4–8
Applicability	
18 The guideline describes facilitators and barriers to its application	Foreword, 1
19 The guideline provides advice and/or tools on how the recommendations can be put into practice	Appendices A–F
20 The potential resource implications of applying the recommendations have been considered	Foreword
21 The guideline presents monitoring and/or auditing criteria	9
Editorial independence	
22 The views of the funding body have not influenced the content of the guideline	Foreword
23 Competing interest of guideline development group members have been recorded and addressed	Foreword