Pan Birmingham NHS
Cancer Network

Dataset for Histological Reporting of Vulval Neoplasms

Version History

Version	Date	Summary of Change/Process
0.1	20/05/09	Document circulated to Gynae and Cellular Pathology NSSGs for consultation
0.1	27/05/09	Both groups agreed to adopt Royal College guidance
1.0	10/06/09	Adopted by the Network Governance Committee Guidelines Sub Group
2.0	April 2012	Prepared for distribution and uploaded to Pan Birmingham Cancer Network website

Date Approved by Network Governance	**April 2012**

Date for Review	**April 2015**

This is a national document produced by the Royal College of Pathologists (www.rcpath.org) and is the latest version.

1. Scope of the guideline

This document is to inform and assist with the reporting of cervical neoplasia.

2. Guideline background

At Network Site Specific Group (NSSG) meetings the group acknowledged the need for pathology guidance for gynaecology. The NSSG recommended the guidance produced by the Royal College of Pathologists (RCP) and both Gynae and Cellular Pathology NSSGs agreed to adopt this guidance.

Monitoring of the guideline

Adherence to the Network guidelines may from time to time be formally monitored.

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Royal College of Pathologists

References

http://www.rcpath.org/resources/pdf/g070_vulvadataset_jun08.pdf

Approval Signatures

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

Standards and Datasets for Reporting Cancers

Dataset for histological reporting of vulval neoplasms (2nd edition)

June 2008

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Comments	In accordance with the College's pre-publications policy, this document was put on The Royal College of Pathologists' website for consultation from 9 January to 8 February 2008. Four pieces of feedback were received and the authors considered them and amended the document accordingly. Please email publications@rcpath.org if you wish to see the responses and comments. This edition replaces the 1st edition of the *Dataset for the histological reporting of vulval biopsy specimens and vulvectomy specimens for vulval cancer*, published in March 2001. **Professor Carrock Sewell** **Director of Communications**

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CONTENTS

1 INTRODUCTION

This is a revision of the vulval cancer dataset that was published in 2001. There has been an expansion of the clinico-pathological background and bibliography (up to June 2007), providing an evidence base for the expanded reporting proforma. The main changes in the proforma from 2001 are more precise specification of the nature of the submitted specimen with more detailed measurements, expansion of the resection margin parameters, inclusion of Paget's disease, mention of lichen planus as a risk factor for vulval squamous carcinoma, more detail on nodal involvement and the status of the sentinel node. Basal cell carcinoma is listed. Both TNM and SNOMED are requested.

Most gynaecological oncologists use the FIGO staging system for gynaecological cancers. However, TNM staging is included in this dataset to allow standardisation of staging across all cancer sites. Depending on local protocols, clinicians may elect to include TNM staging in gynaecological cancer datasets.

In the accompanying text, more guidance has been given on measuring the depth of invasion. A graphic has been provided (Appendix A) to assist identification of the abnormal areas on the request form and to give a format for recording findings.

Background

Vulval cancer is a rare disease, with 996 cases resulting in 364 deaths in 2002 in the United Kingdom. This is the 19th most common cause of death from cancer in women in the UK,[1] with a crude incidence of 0.8 per 100,000. Most (more than 90%) vulval cancers are squamous carcinomas.[2] In elderly women, squamous carcinoma is usually human papillomavirus (HPV) negative, often associated with lichen sclerosus and squamous hyperplasia[3] and is often accompanied by differentiated VIN.[4] In younger, usually pre-menopausal women, squamous carcinoma is often HPV related, associated with Bowenoid (warty) or basaloid VIN and associated with multifocal HPV associated disease of the cervix, vagina, perineum and anus.[5]

Adenocarcinoma of the vulva affects mainly women over 60 years, usually arises from Paget's disease with underlying carcinoma of a skin appendage in up to 10–20% of patients. Around 5% cases will have spread from local malignant disease of the anus, rectum, bladder or cervix.[6,7,8]

The prognosis of vulval carcinoma depends on the size of the lesion, depth of invasion,[9,10,11,12] the number of involved lymph nodes, presence or absence of extranodal spread and proportion of node replaced by metastasis[13,14]and the presence or absence of lymphovascular space involvement (LVSI).[13,15] The depth of invasion is measured from the epithelial-stromal junction of the adjacent most superficial dermal papillae to the deepest point of invasion by tumour.[16] Tumour grade is of questionable prognostic significance and most squamous carcinomas in elderly women are well differentiated.

30% of patients have lymph node metastasis at presentation. The pattern of lymph node metastasis is well established and predictable[17] with spread first to the ipsilateral superficial inguinal nodes[18] and then to deep groin nodes, pelvic lymph nodes and distant sites. Five-year survival is affected by the number of nodes involved and whether involvement is unilateral (five-year survival 60–70%) or bilateral (five-year survival 25%). Extracapsular spread is an independent variable in two studies and may influence the decision on the type and dosage of post-operative radiotherapy.[13,14] Midline disease requires bilateral node dissection.[19] Lymphovascular space invasion (LVSI) is not an independent prognostic factor but is a good

marker of groin node metastasis: 88% with LVSI have nodal spread compared to 19% without LVSI.[20]

Evidence is accruing that sentinel lymph node examination is a reliable indicator of inguinal node involvement,[21, 22] with a negative predictive value of 95–100%. Step/serial sectioning (ultrastaging) with or without immunohistochemistry is currently under research. It has been shown to increase the yield of involved nodes that were negative on routine examination (4–11%), but as yet there has been no trial to assess the prognostic significance of this and there is no agreement as to whether this should form part of routine assessment.[23, 24,25,26] Until there is evidence that ultrastaging is relevant, sentinel nodes should be examined as detailed in the National breast screening recommendations.[27]

The risk of lymph node metastasis is very low if the depth of invasion is less than or equal to 1mm, (FIGO stage 1a) allowing the option of curative local excision for both squamous and glandular lesions. Lymph node dissection may not be undertaken if invasion is less than 1mm in a fully excised specimen.[28, 29, 30]

Lichen sclerosus, especially if associated with squamous hyperplasia,[31] and erosive lichen planus[32] are linked to the later development of squamous carcinoma in older, HPV negative women. Recurrent disease is linked to persisting VIN and lichen sclerosus.[33] Recurrence of VIN is associated with involved margins, multifocal disease and genital warts.[34] Untreated and recurrent VIN has a high risk of progression to squamous carcinoma.[35] Basal cell carcinoma accounts for 2–28% of vulval cancers, depending on the population[36] and generally behaves as an indolent, occasionally locally aggressive neoplasm in elderly women (average age 70) with a propensity to recur if incompletely excised; metastasis and death are rare.[37, 38,39,40,41]

Stakeholder groups:

The following organisations 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

2 CLINICAL INFORMATION REQUIRED ON THE SPECIMEN REQUEST FORM

- Full patient details, history and the results of previous biopsies.
- The results of ultrasound combined with fine needle aspiration cytology have been shown to be more accurate than computerised tomography (CT) and magnetic resonance imaging (MRI) in evaluating nodal involvement.[42] However, it may be advisable for results to be made available, although these might not be an accurate predictor of involvement.[12] The results of lymphangiography, including dye injections[43] and scintillogaphy[21, 22] are relevant to sentinel node assessment.
- Comprehensive details of the surgical procedure should be provided. It may be useful to use a diagram of the site of operation/biopsy with orientation markings/sutures (Appendix A).
- The details of surgical specimens from multiple sites should be provided.
- Specimen pots should be labelled to correspond to the specimen details on the request form.

3 PREPARATION OF SPECIMEN BEFORE DISSECTION

The usual surgical procedures for vulval carcinoma are:

- radical vulvectomy and lymph node dissection (with or without sentinel node dissection)
- partial vulvectomy and lymph node dissection (with or without sentinel node dissection)
- radical or partial vulvectomy
- wide local tumour excision
- diagnostic biopsy.

Preparation of radical vulvectomy specimens will depend upon the size of the vulval tumour and the extent of spread. Margins may require painting with ink/dye prior to block taking. A photographic record and/or schematic graphic of the orientated vulval specimen (Appendix A) may be useful. A vulvectomy specimen may be pinned out and fixed before block taking, but this is not essential. It is advisable to request that the surgeons mark the site of previous biopsy with a suture or ink if no gross lesion is visible.

4 SPECIMEN HANDLING AND BLOCK SELECTION[44]

Specimens may be fixed and pinned out or, if appropriate, sampled fresh. It might be appropriate to map the lesion(s) on a graphic (Appendix A) or photograph. The tumour must be adequately sampled to allow typing, grading and measurement of depth and width.

Blocks should be taken to document:

- distance to epithelial resection margin
- distance to urethral resection margin (if appropriate)
- distance to vaginal resection margin (if appropriate)
- distance to anal resection margin (if appropriate)
- distance to soft tissue (deep) resection margin
- any grossly normal or abnormal epithelium to identify non-neoplastic epithelial diseases (NNED)
- any incidental cysts or other abnormalities.

All lymph nodes should be sampled from each side. The presence of macroscopic involvement of lymph nodes should be recorded together with the dimensions of involved nodes. The sentinel node is highly predictive for inguinofemoral node involvement with a negative predictive value of 95–100%.[23] Although step sectioning and immunohistochemistry have been performed in some studies,[2] there is no evidence that ultrastaging is prognostically significant.

The following is advised for all inguinal (including sentinel) nodes.

- Each lymph node must be examined histologically
- Resected lymph nodes not obviously involved by tumour must be examined in their entirety
- Larger nodes may require more than one block
- Nodes larger than 5mm should be blocked out at 2–3mm intervals cut perpendicular to the long axis

- Nodes smaller than 5mm can be bisected or embedded whole
- Only one block is necessary from any grossly involved node
- Levels are only required for clarification of suspicious groups of cells. [23,24,25,26]

In departments where the facility for processing of oversize blocks is available a good overview of the tumour and resection margins can be obtained, but standard blocks of tumours should also be processed, to enable immunohistochemistry or other special stains to be performed more readily should these be required.

The origin/designation of all tissue blocks should be recorded on the pathology report. This is particularly important should the need for internal or external review arise. The reviewer needs to be clear about the origin, relevant resection margin and laterality of each block.

5 CORE HISTOLOGICAL DATA ITEMS

The following information must be recorded:

- tumour type according to the WHO classification (see section 7)
- tumour differentiation
- tumour size (in at least 2 dimensions)
- thickness/depth of invasion
- presence or absence of lymphovascular invasion
- status of all resection margins
- minimum tumour free margins
- presence of associated VIN or Paget's disease
- status of resection margins for VIN or Paget's disease
- minimum distance to margins for VIN or Paget's disease
- presence or absence of non-neoplastic epithelial disease
- presence or absence of lymph nodes metastases
- presence of extranodal spread
- whether >50% of any one node is involved.

Tumour differentiation

Squamous carcinomas should be graded according to a modified version of Broders system as well differentiated (keratinising), moderately or poorly differentiated.[45] There is no agreed grading system for adenocarcinoma but it is suggested that these tumours be graded according to the FIGO system for endometrial adenocarcinomas.[46]

Maximum horizontal dimension (width of lesion)

Where a tumour involves more than one adjacent block a third dimension may be calculated from an estimate of the block thickness. A tumour occupying 7 or more adjacent blocks may exceed 20mm i.e. the carcinoma may be more than FIGO stage I.[47] The microscopic maximum horizontal dimension should be correlated with the gross measurements.

Thickness/depth of invasion

The depth of invasion is defined as the measurement from the epithelial-stromal junction of the adjacent most superficial dermal papilla to the deepest point of invasion. Where this is not easily achievable, an estimate can be made by measuring from the surface to the deepest point of invasion and then subtracting the distance from the surface to the epithelial stromal junction of the most superficial dermal papilla. If the lesion is ulcerated, a maximum tumour thickness may be given. It is important to correlate the macroscopic and microscopic measurements to avoid error and to permit measurements of tumours larger than a standard slide. Vascular space involvement, either venous or lymphatic, does not alter the staging.[48,49]

Vulval intraepithelial neoplasia[50]

The following features should be recorded for instances of vulval intraepithelial neoplasia:

- VIN-warty, basaloid, mixed (warty/basaloid) type
- Grades I, II, III
- VIN-differentiated type – this is not graded
- Paget's disease
- Assessment of margins
- Minimum distance from resection margins, where applicable.

Non-neoplastic epithelial diseases (NNED)[51]

Evidence for the following diseases should be sought and recorded, if present.

- Lichen sclerosus
- Squamous hyperplasia
- Mixed lichen sclerosus and squamous hyperplasia
- Lichen planus

Nodal involvement

The number of identified and involved nodes at each site must be recorded. The presence of extranodal spread may indicate increased risk of local recurrence and must be reported if present. Note whether >50% of any one node is involved by tumour.[13,14]

6 NON-CORE DATA ITEMS

These may be recorded as a separate comment or within a complementary text report. Such items include the presence of human papillomavirus associated features (koilocytosis, epithelial multinucleation, dyskeratosis, parakeratosis, acanthosis, papillomatosis), inflammatory dermatoses or other benign lesions such as cysts. The presence of a fibromyxoid stromal reaction is reported, in one study, to be an indicator of an adverse prognosis and may be recorded as a separate comment.[52]

7 WHO CLASSIFICATION AND SNOMED CODES OF VULVAR EPITHELIAL TUMORS AND RELATED LESIONS

Squamous lesions	
Intraepithelial neoplasia (vulvar intraepithelial neoplasia VIN 3)	80772
Carcinoma in situ	80702
Squamous cell carcinoma	80703
Keratinizing	80713
Nonkeratinizing	80723
Basaloid	80833
Verrucous	80513
Warty (condylomatous)	80513
Others	
Basal cell carcinoma	80903
Glandular lesions	
Paget disease	85423
Bartholin gland tumours	
Adenocarcinoma	81403
Squamous carcinoma	80703
Adenoid cystic carcinoma	82003
Adenosquamous carcinoma	85603
Transitional cell carcinoma	81203
Small cell carcinoma	80413
Carcinoma of mammary type gland	85003
Adenocarcinoma of Skene gland	81403
Carcinoma of sweat gland origin	84003
Adenocarcinomas of other types	81403

8 SMALL BIOPSIES[44]

These may be received as fresh or fixed material. Wide local excisions are treated in a similar manner to vulvectomy specimens. Small diagnostic punch biopsies may be taken for confirmation of malignancy and the site must be clearly identified to allow orientation of margins and sampling of the biopsy site in any subsequent vulvectomy specimen.

The biopsy will vary according to the size of the lesion, and range from small punch biopsies that are up to several millimetres long and 2–4mm diameter, to larger ellipse biopsies of similar size to skin or vulval excisional biopsies. In some institutions small biopsies may be mounted onto a card.
Careful handling of these specimens is recommended to prevent surface trauma and disruption or loss of surface epithelium. It is important to search the container and the under surface of its lid to ensure that stray fragments of tissue are recovered. Fragments should be counted and embedded as received. Larger pieces are measured individually.

Punch biopsies are bisected if larger than 3mm and the epithelium is clearly visible for orientation.Ellipse excisions are embedded as received if narrower than 3mm, and bisected longitudinally if wider.

Wider biopsies, or larger biopsies with an identifiable lesion are cut in transverse section to include the nearest resection margins. The blocks containing the end slices are noted – these will usually be the first and last blocks in the sequence. It may be appropriate to ink the margins as orientated by the clinician with marking sutures or pinned to a cork board. Identifiable surface lesions are described and measured and the macroscopic distance from the closest margin noted.

9 FROZEN SECTIONS

Frozen section assessment is not routinely used for the assessment of margins. Frozen sections have been used for the assessment of sentinel nodes intraoperatively in research studies, but this is not currently recommended for routine practice due to sampling and interpretational errors.[15,24,25,27]

10 ANCILLARY INVESTIGATIONS

Immunohistochemistry has a limited role in diagnosis and prognostication of vulval cancers. For invasive vulval carcinoma, stage remains the most important prognostic factor. Diffuse p16 positivity may indicate an HPV-associated neoplasm. Neither ploidy, retinoblastoma protein (pRb) or p53 are prognostically significant.[53] Neither p53 nor Ki67 can determine prognosis in Paget's disease of the vulva.[54]

Immunohistochemistry for broad spectrum cytokeratins, such as AE1/AE3, can reveal micrometastases in up to 23% of inguinal nodes,[25, 55] but not all studies support this,[24, 56] and the prognostic implications of micrometastases have not been established.[2]

The differential diagnosis of Paget's disease of the vulva includes malignant melanoma. Paget's disease is often positive for CAM 5.2, CEA, EMA and CK7, with variable positivity for CK20 and GCDFP15 (gross cystic disease fluid protein 15). Although Paget cells may contain melanin, they are negative with the melanoma markers HMB45 and S100; melanoma reacts for HMB45 and S100.[29] CK20 positivity in Paget's disease, especially if strong and diffuse, suggests metastatic involvement from the colorectum or urinary bladder, although some primary vulval Paget's disease may be positive with these markers. Similarly, positivity for uroplakin suggest urothelial origin.[8, 57]

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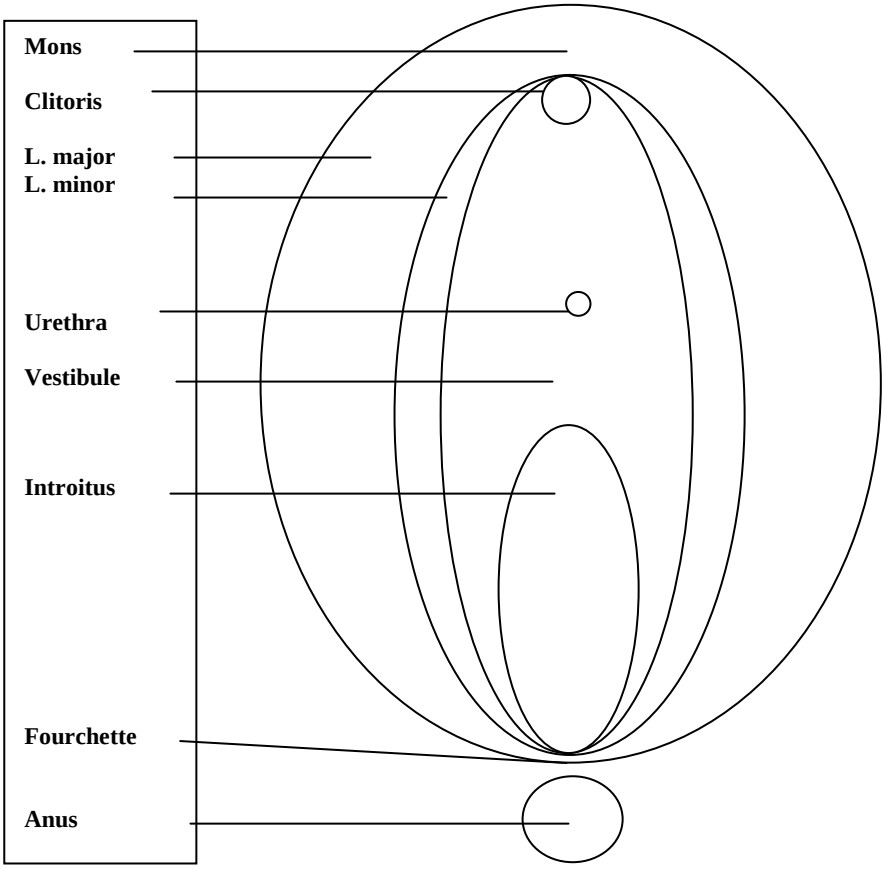
APPENDIX A DIAGRAM TO ASSIST THE ORIENTATION OF SPECIMENS AND SELECTED BLOCKS



APPENDIX B FIGO and TNM PATHOLOGICAL STAGING OF VULVAL CARCINOMA[57]

Most gynaecological oncologists use the FIGO staging system for gynaecological cancers. However, TNM staging is included in this dataset to allow standardisation of staging across all cancer sites. Depending on local protocols, clinicians may elect to include TNM staging in gynaecological cancer datasets.

FIGO stage	TNM category	Definition
–	TX	Tumour cannot be assessed
–	TO	No evidence of primary tumour
0	Tis	Carcinoma in situ, VIN III
I		Lesions =/<2cm in size, confined to the vulva or perineum, no nodal metastasis
Ia	T1a	Lesions =/<2cm in size, confined to the vulva or perineum, and with stromal invasion =/<1.00mm*, no nodal metastasis
Ib	T1b	Lesions =/<2cm in size, confined to the vulva or perineum, and with stromal invasion >1.00mm*, no nodal metastasis
II	T2	Tumour confined to the vulva or perineum; >2cm in greatest dimension; no nodal metastasis
III	T3	Tumour of any size with adjacent spread to the lower urethra and/or the vagina, or the anus, and/or unilateral lymph node metastasis
IV		
IVa	T4	Tumour invades any of the following: upper urethra, bladder mucosa, rectal mucosa, pelvic bone, and/or bilateral regional node metastases
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 epithelial papilla to the deepest point of invasion. Vascular space involvement, either venous or lymphatic, does not alter the staging[6,7].

Regional lymph nodes (N)* (TNM staging system)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Unilateral regional lymph node metastasis
N2	Bilateral regional lymph node metastasis

*Regional lymph nodes are the femoral and inguinal nodes. Metastasis to lymph nodes outside of the regional nodal groups is classified as distant metastasis.

Distant metastasis (M) (TNM staging system)

MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis (including pelvic lymph node metastasis)

Histopathological grading

GX	Grade of tumour cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated or undifferentiated

pTNM pathological classification

The pT, pN, pM categories correspond to the TNM catgories

Stage grouping

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage IA	T1a	N0	M0
Stage IB	T1b	N0	M0
Stage II	T2	N0	M0
Stage III	T1, T2,	N1	M0
	T3	N0, N1	M0
Stage IVA	T1,T2,T3	N2	M0
	T4	Any N	M0
Stage IVB	Any T	Any N	M1

APPENDIX C REPORTING PROFORMA FOR VULVAL CANCER RESECTION SPECIMENS

Surname..... Forenames.....Date of birth....…….....
Hospital.....……..…….....Hospital No .....…....……..NHS No .....……..…....……
Date of receipt…….....…….....Date of reporting……...…….....Report No..……....……...
Pathologist…….....…..…Surgeon…….....……...…….

Nature of vulvectomy specimen:

Radical☐ simple ☐ anterior☐ posterior ☐
left hemi☐ left nodes ☐ right hemi ☐ right nodes ☐
3 part with nodes ☐ Y excision with nodes ☐ local excision ☐
Other……..

Gross description

Size of specimen: Length .....mm Width ...…...mm Thickness .....mm
Size of tumour: Length .....mm Width ...…...mm Thickness .....mm Site(s) of tumour – state ……
No macroscopic residual tumour: ☐

Histology

Histological type: squamous (usual) ☐ verrucous☐
adenocarcinoma ☐ basal cell ☐
(for melanoma use appropriate skin dataset)
other (please specify) ☐……
Histological differentiation: well ☐ moderate ☐ poor ☐
Tumour size (for staging): maximum horizontal dimension ……(mm)
Thickness/depth of invasion……...……....(mm)
(**NB** requires correlation of macro/micro measurements)
Lymphovascular invasion: present ☐ absent ☐
Minimum tumour-free margin
skin/epithelial…….(mm) N/A☐ involved ☐ (position)……o'clock
urethral..…….(mm) N/A☐ involved ☐
vaginal ……...….....(mm) N/A☐ involved ☐
anal …….. .....(mm) N/A☐ involved ☐
soft tissue ……...(mm) N/A☐ involved ☐

VIN 1 ☐ VIN 2☐ VIN 3 ☐ Differentiated VIN ☐ Paget's ☐
Is VIN or Paget's excised? Yes☐ No☐
Minimum margin
skin/epithelial…….(mm) N/A☐ involved ☐ (position)……o'clock
urethral..…….(mm) N/A☐ involved ☐
vaginal ……...….....(mm) N/A☐ involved ☐
anal …….. .....(mm) N/A☐ involved ☐

Presence of non-neoplastic epithelial disease (NNED):

lichen sclerosus ☐ lichen planus ☐ Squamous hyperplasia ☐ HPV-associated features ☐
Is NNED excised? Yes☐ No☐

Groin nodes:

Sentinel node – if sent - (right) positive ☐ Sentinel node – if sent - (left) positive ☐
Total number of nodes (right) …..… …… Total number of nodes (left) ……..
Total number of positive nodes (right) …..… Total number of positive nodes (left) …….
Extranodal extension: yes ☐ no ☐ >50% of any one node involved? yes ☐ no ☐

Pathological FIGO stage:……pT…… N…….M……
(**N.B.** may alter following MDT)

Comments

SNOMED codes: T: M:

Signature .....……. Date ……..../……../……...