



# Carcinoma of the Cervix Histopathology Reporting Guide

Family/Last name

Date of birth

DD – MM – YYYY

Given name(s)

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  
☐ Previous procedure performed  
     ☐ Loop excision<sup>a</sup>/Cone biopsy  
     ☐ Trachelectomy (simple or radical)  
☐ Prior therapy  
     ☐ Chemotherapy  
     ☐ Radiation  
☐ Other, *specify*

## SPECIMEN(S) SUBMITTED (select all that apply) (Note 2)

- ☐ Not specified  
☐ Loop excision<sup>a</sup>/Cone biopsy  
☐ Trachelectomy  
     ☐ Simple    ☐ Radical    ☐ Type not specified  
☐ Hysterectomy  
     ☐ Simple    ☐ Radical    ☐ Type not specified  
☐ Fallopian tube  
     ☐ Left    ☐ Right    ☐ Laterality not specified  
☐ Ovary  
     ☐ Left    ☐ Right    ☐ Laterality not specified  
☐ Parametrium  
     ☐ Left    ☐ Right    ☐ Laterality not specified  
☐ Vaginal cuff  
☐ Pelvic exenteration  
     ☐ Urinary bladder  
     ☐ Vagina  
     ☐ Uterus  
     ☐ Sigmoid colon  
☐ Other, *specify*

- ☐ Lymphadenectomy specimen(s)  
     ☐ Sentinel node(s)  
         ☐ Left    ☐ Right    ☐ Laterality not specified  
     ☐ Regional node(s): pelvic  
         ☐ Left    ☐ Right    ☐ Laterality not specified  
     ☐ Regional node(s): para-aortic  
     ☐ Non-regional node(s): inguinal  
         ☐ Left    ☐ Right    ☐ Laterality not specified  
☐ Other node group, *specify*

Other, *specify*


<sup>a</sup> Loop excision includes loop electrosurgical excision procedure (LEEP and large loop excision of the transformation zone (LLETZ)).

## SPECIMEN DIMENSIONS (Note 3)

- ☐ Cannot be assessed

Number of tissue pieces<sup>b</sup>

Tissue piece dimensions<sup>b</sup> (Note: Record for each piece)

<input type="text"/>	mm	x	<input type="text"/>	mm	x	<input type="text"/>	mm
<input type="text"/>	mm	x	<input type="text"/>	mm	x	<input type="text"/>	mm
<input type="text"/>	mm	x	<input type="text"/>	mm	x	<input type="text"/>	mm

### Cervix<sup>c</sup>

Diameter of ectocervix

 mm x  mm

Depth of specimen

 mm

### Vaginal cuff<sup>d</sup>

- ☐ Not applicable

Minimum length

 mm

Maximum length

 mm

### Left parametrium

- ☐ Not applicable

Lateral extent

 mm

### Right parametrium

- ☐ Not applicable

Lateral extent

 mm

<sup>b</sup> Applicable to loop/cone biopsies only.

<sup>c</sup> Applicable to loop/cone biopsies and trachelectomy specimens only.

<sup>d</sup> Applicable to trachelectomy and hysterectomy specimens.

## MACROSCOPIC APPEARANCE OF TUMOUR(S) (Note 4)

(select all that apply)

- ☐ No macroscopically visible tumour  
☐ Exophytic/polypoid  
☐ Flat  
☐ Ulcerated  
☐ Circumferential/barrel shaped cervix  
☐ Other, *specify*

**TUMOUR SITE** (select all that apply) (Note 5)

- ☐ No macroscopically visible tumour
- ☐ Ectocervix
- ☐ Anterior
- ☐ Posterior
- ☐ Left lateral
- ☐ Right lateral
- ☐ Circumference of cervix
- ☐ Endocervix
- ☐ Anterior
- ☐ Posterior
- ☐ Left lateral
- ☐ Right lateral
- ☐ Circumference of cervix
- ☐ Vagina
- ☐ Uterus
- ☐ Lower uterine segment
- ☐ Corpus
- ☐ Parametrium
- ☐ Left
- ☐ Right
- ☐ Laterality not specified
- ☐ Other organs or tissues, *specify*

**TUMOUR DIMENSIONS** (Note 6)

(If separate tumour foci, specify the dimensions for each)

☐ Cannot be assessed

Maximum horizontal tumour dimension  mm at least<sup>e</sup>

Depth of invasion  mm at least<sup>e</sup>

OR ☐ Not assessable

If not assessable record:

Thickness  mm

<sup>e</sup> It is advisable to include 'at least' for the tumour measurements in loop or cone excisions when tumour is present at a resection margin(s). If not applicable, delete 'at least'.

**BLOCK IDENTIFICATION KEY** (Note 7)

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

**HISTOLOGICAL TUMOUR TYPE** (Note 8)

(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, HPV-associated
- ☐ Adenocarcinoma, HPV-independent, gastric type
- ☐ Adenocarcinoma, HPV-independent, clear cell type
- ☐ Adenocarcinoma, HPV-independent, mesonephric type
- ☐ Adenosquamous carcinoma
- ☐ Small cell neuroendocrine carcinoma
- ☐ Carcinoma admixed with neuroendocrine carcinoma
- ☐ Other, *specify*

**HISTOLOGICAL TUMOUR GRADE** (Note 9)

(Applicable to some HPV-associated adenocarcinomas)

- ☐ GX: Cannot be assessed
- ☐ G1: Well differentiated
- ☐ G2: Moderately differentiated
- ☐ G3: Poorly differentiated

**LYMPHOVASCULAR INVASION** (Note 10)

- ☐ Indeterminate ☐ Not identified ☐ Present

**EXTENT OF INVASION** (Note 11)

- ☐ Not applicable

**Vagina**

- ☐ Not applicable
- ☐ Not involved
- ☐ Involved
- ☐ Upper two thirds
- ☐ Lower third

**Fallopian tube**

- ☐ Not applicable
- ☐ Not involved
- ☐ Involved
- ☐ Left
- ☐ Right

**Lower uterine segment**

- ☐ Not applicable
- ☐ Not involved
- ☐ Involved

**Endometrium**

- ☐ Not applicable
- ☐ Not involved
- ☐ Involved

**Parametrium**

- ☐ Not applicable
- ☐ Not involved
- ☐ Involved
- ☐ Left
- ☐ Right

**Myometrium**

- ☐ Not applicable
- ☐ Not involved
- ☐ Involved

**Ovary**

- ☐ Not applicable
- ☐ Not involved
- ☐ Involved
- ☐ Left
- ☐ Right

**Bladder**

- ☐ Not applicable
- ☐ Not involved
- ☐ Involved, *specify compartment*

**Rectum**

- ☐ Not applicable
- ☐ Not involved
- ☐ Involved, *specify compartment*

**Other organs or tissues**

- ☐ Not applicable
- ☐ Not involved
- ☐ Involved, *specify*

**PATTERN CLASSIFICATION FOR HPV-ASSOCIATED ADENOCARCINOMAS** (Note 12)

- ☐ A ☐ B ☐ C

**MARGIN STATUS** (Note 13)**Invasive tumour****HYSTERECTOMY/TRACHELECTOMY SPECIMEN**

Margin	Not involved	Involved	Distance of tumour from margin (mm)	Cannot be assessed
Ectocervical/vaginal cuff				
Endocervical <sup>f</sup>				
Radial/deep stromal				
Closest lateral		<input type="radio"/> Left <input type="radio"/> Right		

**LOOP/CONE**

Margin	Not involved	Involved	Distance of tumour from margin (mm)	Cannot be assessed
Ectocervical				
Endocervical				
Radial/deep stromal				
Unspecified <sup>g</sup>				

**Precursor lesions**

Margin	HSIL				AIS				SMILE				Margin is not applicable to specimen
	Not involved	Involved	Distance of tumour from margin	Cannot be assessed	Not involved	Involved	Distance of tumour from margin	Cannot be assessed	Not involved	Involved	Distance of tumour from margin	Cannot be assessed	
Ectocervical/vaginal cuff													
Endocervical													
Radial/deep stromal													
Unspecified <sup>g</sup>													

HSIL: High grade squamous intraepithelial lesion

AIS: Adenocarcinoma in situ

SMILE: Stratified mucin-producing intraepithelial lesion

<sup>f</sup> This is required only for trachelectomy specimens. Distance to endocervical margin is required for trachelectomy specimens as it is often used by surgeons to decide whether to undertake a followup hysterectomy or to remove another portion of the cervix if technically possible.

<sup>g</sup> Use for loop/cone biopsies where it is not possible to say whether the margin is ectocervical or endocervical.

**LYMPH NODE STATUS** (Note 14)

- ☐ Cannot be assessed  
☐ No nodes submitted or found

<sup>h</sup> If the actual number of lymph nodes examined or the number of positive nodes cannot be determined due, for example, to fragmentation, then this should be indicated in the response.

<sup>i</sup> Size of tumour deposit should be recorded for sentinel lymph nodes.

Lymph node type	Laterality	Number of nodes examined <sup>h</sup>	Number of positive nodes <sup>h</sup>	Size of maximum tumour deposit <sup>i</sup>
Sentinel node(s)	Left			
	Right			
Regional node(s): pelvic	Left			
	Right			
Regional node(s): para-aortic				
Non-regional node(s): inguinal	Left			
	Right			
Other node group, specify				

**COEXISTENT PATHOLOGY/PRECURSOR LESIONS<sup>j</sup>** (Note 15)**Squamous intraepithelial lesion (SIL) cervical intraepithelial lesion (CIN)**

- ☐ Not identified    ☐ Present  
                                     ↓  
                                     GRADE  
                                     ↓  
                                     ☐ Low grade SIL (LSIL) (CIN 1)  
                                     ☐ High grade SIL (HSIL) (CIN 2/3)

**HPV-associated adenocarcinoma in situ/High grade cervical glandular intraepithelial neoplasia (HG CGIN)**

- ☐ Not identified    ☐ Present

**Stratified mucin-producing intraepithelial lesion (SMILE)**

- ☐ Not identified    ☐ Present

**Other possible precursor lesions**

- ☐ Not identified  
☐ Present (select all that apply)  
☐ Adenocarcinoma in situ of gastric type  
☐ Lobular endocervical glandular hyperplasia  
☐ Atypical lobular endocervical glandular hyperplasia  
☐ Other, specify

**ANCILLARY STUDIES** (Note 16)

- ☐ Not performed  
☐ Performed (select all that apply)  
☐ HPV testing, record result(s)

- ☐ Immunohistochemistry, specify test(s) and result(s)

- ☐ 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

<sup>j</sup> Core for loop/cone excisions/trachelectomies only; non-core for other specimens.

## **PATHOLOGICALLY CONFIRMED DISTANT METASTASIS** (Report when tissue submitted for evaluation) (Note 17)

- ☐ Not identified  
☐ Present, specify site(s)

## **PROVISIONAL PATHOLOGICAL STAGING** (Note 18)

### **FIGO (2019 edition)<sup>k</sup>**

- ☐ I The carcinoma is strictly confined to the cervix (extension to the corpus should be disregarded)
- ☐ IA Invasive carcinoma that can be diagnosed only by microscopy with maximum depth of invasion  $\leq 5$  mm<sup>l</sup>
- ☐ IA1 Measured stromal invasion  $\leq 3$  mm in depth
- ☐ IA2 Measured stromal invasion  $> 3$  mm and  $\leq 5$  mm in depth
- ☐ IB Invasive carcinoma with measured deepest invasion  $> 5$  mm (greater than stage IA), lesion limited to the cervix uteri<sup>m</sup>
- ☐ IB1 Invasive carcinoma  $> 5$  mm depth of stromal invasion and  $\leq 2$  cm in greatest dimension
- ☐ IB2 Invasive carcinoma  $> 2$  cm and  $\leq 4$  cm in greatest dimension
- ☐ IB3 Invasive carcinoma  $> 4$  cm in greatest dimension
- ☐ II The carcinoma invades beyond the uterus, but has not extended onto the lower third of the vagina or to the pelvic wall
- ☐ IIA Involvement limited to the upper two-thirds of the vagina without parametrial invasion
- ☐ IIA1 Invasive carcinoma  $\leq 4$  cm in greatest dimension
- ☐ IIA2 Invasive carcinoma  $> 4$  cm in greatest dimension
- ☐ IIB With parametrial invasion but not up to the pelvic wall
- ☐ III The carcinoma involves the lower third of the vagina and/or extends to the pelvic wall and/or causes hydronephrosis or non-functioning kidney and/or involves pelvic and/or paraaortic lymph nodes<sup>n</sup>
- ☐ IIIA Carcinoma involves lower third of the vagina, with no extension to the pelvic wall
- ☐ IIIB Extension to the pelvic wall and/or hydronephrosis or non-functioning kidney (unless known to be due to another cause)
- ☐ IIIC Involvement of pelvic and/or paraaortic lymph nodes (including micrometastases), irrespective of tumour size and extent (with r and p notations)<sup>n</sup>
- ☐ IIIC1 Pelvic lymph node metastasis only
- ☐ IIIC2 Paraaortic lymph node metastasis
- ☐ IV The carcinoma has extended beyond the true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum. A bullous oedema, as such, does not permit a case to be allotted to stage IV
- ☐ IVA Spread of the growth to adjacent organs
- ☐ IVB Spread to distant organs

<sup>k</sup> Reprinted from *Int J Gynaecol Obstet.*, Volume 145(1), Bhatla N, Berek JS, Cuervo Fredes M, Denny LA, Grenman S, Karunaratne K, Kehoe ST, Konishi I, Olawaiye AB, Prat J, Sankaranarayanan R, Brierley J, Mutch D, Querleu D, Cibula D, Quinn M, Botha H, Sigurd L, Rice L, Ryu HS, Ngan H, Maenpaa J, Andrijono A, Purwoto G, Maheshwari A, Bafna UD, Plante M and Natarajan J, Revised FIGO staging for carcinoma of the cervix uteri, pages 129-135, 2019, with permission from Wiley.

<sup>l</sup> Imaging and pathology can be used, when available, to supplement clinical findings with respect to tumour size and extent, in all stages. Pathological findings supercede imaging and clinical findings.

<sup>m</sup> The involvement of vascular/lymphatic spaces does not change the staging. The lateral extent of the lesion is no longer considered.

<sup>n</sup> Adding notation of r (imaging) and p (pathology), to indicate the findings that are used to allocate the case to stage IIIC. For example, if imaging indicates pelvic lymph node metastasis, the stage allocation would be Stage IIIC1r and, if confirmed by pathological findings, it would be Stage IIIC1p. The type of imaging modality or pathology technique used should always be documented. When in doubt, the lower staging should be assigned.

## **TNM Staging (UICC TNM 8<sup>th</sup> edition 2021)<sup>o</sup>**

### **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 confined to the cervix (extension to the corpus should be disregarded)<sup>p</sup>
- ☐ T1a Invasive carcinoma diagnosed only by microscopy; stromal invasion with a maximum depth of 5.0 mm<sup>q</sup>
- ☐ T1a1 Measured depth of stromal invasion 3.0 mm or less in depth
- ☐ T1a2 Measured depth of stromal invasion more than 3.0 mm and not more than 5.0 mm<sup>r</sup>
- ☐ T1b Lesion confined to the cervix with depth of invasion greater than 5 mm
- ☐ T1b1 Lesion 2.0 cm or less in greatest dimension
- ☐ T1b2 Lesion more than 2.0 cm in greatest dimension but no more than 4.0 cm in greatest dimension
- ☐ T1b3 Lesion more than 4.0 cm in greatest diameter
- ☐ T2 Tumour invades beyond uterus but not to pelvic wall or to the lower third of vagina
- ☐ T2a Tumour without parametrial invasion
- ☐ T2a1 Lesion 4.0 cm or less in greatest dimension
- ☐ T2a2 Lesion more than 4.0 cm in greatest dimension
- ☐ T2b Tumour with parametrial invasion
- ☐ T3 Tumour involves lower third of vagina, or extends to pelvic wall, or causes hydronephrosis or nonfunctioning kidney
- ☐ T3a Tumour involves lower third of vagina
- ☐ T3b Tumour extends to pelvic wall, or causes hydronephrosis or nonfunctional kidney
- ☐ T4 Tumour invades mucosa of bladder or rectum, or extends beyond true pelvis<sup>s</sup>

### **Regional lymph nodes (pN)**

- ☐ NX Regional lymph nodes cannot be assessed
- ☐ N0 No regional lymph node metastasis
- ☐ N1 Regional lymph node metastasis to pelvic lymph nodes only<sup>t,u</sup>
- ☐ N2 Regional lymph node metastasis to paraaortic lymph nodes, with or without positive pelvic lymph nodes<sup>t,u</sup>

<sup>o</sup> Reproduced with permission. Source: *UICC TNM Classification for carcinoma of the cervix, Cervix Uteri TNM 2021*, eds by James D. Brierley, Mary K. Gospodarowicz, Christian Wittekind. 2021, Publisher Wiley (incorporating any errata published up until 6<sup>th</sup> October 2020).

<sup>p</sup> Extension to the corpus uteri should be disregarded.

<sup>q</sup> Vascular space involvement, venous or lymphatic, does not affect classification.

<sup>r</sup> The depth of invasion should be taken from the base of the epithelium, either surface or glandular, from which it originates. The depth of invasion is defined as the measurement of the tumour from the epithelial-stromal junction of the adjacent most superficial papillae to the deepest point of invasion.

<sup>s</sup> Bullous oedema is not sufficient to classify a tumour as T4.

<sup>t</sup> The suffix (mi) is added if the lymph node metastases is  $> 0.2$  mm but  $\leq 2$  mm.

<sup>u</sup> The suffix (sn) is added if the metastases is identified by sentinel node biopsy.

## 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 levels of evidence<sup>1</sup>). 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.

 [Back](#)

## Scope

The dataset has been developed for the pathology reporting of primary cervical carcinomas. Specimens reported using this dataset include loop/cone excisions, trachelectomies, simple and radical hysterectomies and exenterations. The dataset applies to epithelial neoplasms only. Small biopsy specimens are excluded from the dataset.

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

The 4<sup>th</sup> edition of this dataset incorporates the 2018 International Federation of Gynaecology and Obstetrics (FIGO) staging for cancer of the cervix uteri report,<sup>2</sup> with amendments as per the 2019 Corrigendum 'Revised FIGO staging for carcinoma of the cervix uteri.'<sup>3</sup> This dataset also includes changes to align the dataset with the World Health Organization (WHO) Classification of Tumours, Female Genital Tumours, 5<sup>th</sup> edition, 2020.<sup>4</sup> The International Collaboration on Cancer Reporting (ICCR) dataset includes 5<sup>th</sup> edition Corrigenda, June 2021.<sup>5</sup>

The authors of this dataset can be accessed [here](#).

 [Back](#)

## Note 1 – Clinical information (Non-core)

Prior chemotherapy, chemoradiation and radiation therapy may significantly alter the original tumour size. Patients with FIGO 2018<sup>2</sup> clinical Stage IB3 and greater cervical cancer (with the exception of IIA1) usually receive chemotherapy, radiation or chemoradiation as definitive therapy. Although controversial, some institutions treat such patients with neoadjuvant chemoradiation followed by hysterectomy.<sup>6-12</sup> Studies have shown that the cervical tumour totally disappears in the majority of cases with only a third of hysterectomy specimens containing residual tumour after neoadjuvant chemoradiation. Chemotherapy, chemoradiation or radiation may also introduce histological changes that were not present in the untreated tumour, such as multinucleate tumour giant cells and degenerate nuclei. Metastatic carcinomas may mimic primary cervical malignancies and knowledge of the patient's cancer history is important for the diagnostic workup (immunohistochemistry or molecular studies) of a newly discovered cervical malignancy. Finally, histological findings (tumour size, histological type, grade and sometimes other parameters) in a prior cervical loop or cone excision may be important for the ultimate tumour staging and grading in a hysterectomy specimen. In patients with a prior loop excision, the size of the tumour in the original loop has to be taken into consideration in determining the overall tumour size (see **Note 6 TUMOUR DIMENSIONS**).<sup>6-11</sup>

 [Back](#)

## Note 2 – Specimen(s) submitted (Core)

The type of operative procedure undertaken, such as a simple or radical hysterectomy, is defined by the surgeon. A radical trachelectomy or hysterectomy includes resection of the parametrium including para-uterine node-bearing tissue. While the nature of the specimen(s) submitted for pathological assessment can usually be deduced from the procedure, in some cases the tissue submitted may be incomplete or include more components than expected and therefore specifying the anatomical structures included in the specimen(s) provides complementary information and confirmation that entire organ(s) have been resected and submitted.<sup>13</sup>

Gynaecological oncologists typically divide lymph nodes into anatomical subgroups, and this should be documented in the report.

 [Back](#)

## Note 3 – Specimen dimensions (Core)

Cervical specimens include loop/cone excisions, simple and radical hysterectomies, simple and radical trachelectomies, and pelvic exenterations. The cervix is a cylindrical structure and taking into account the various surgical procedures that are carried out to remove it, a conventional approach to measuring the size of the cervix in three dimensions is difficult to apply. Measurement is further complicated by differences between laboratories in how they fix and grossly examine the specimens. In loop/cone excisions and trachelectomies, the diameter of the ectocervix (two dimensions) and the length (corresponding to the length of the endocervical canal) of the specimen should be recorded in millimetres (mm). The metric should be accurate and reproducible since it may be important for documentation, diagnostic and prognostic purposes and therapeutic decision-making.<sup>13</sup>

The minimum and maximum cranio-caudal lengths of the vaginal cuff, when present, should be measured in mm. If a parametrectomy has been performed, a measurement from the side of the uterus to the lateral edge of each unstretched parametrium (lateral extent) should be recorded in mm and it may be useful to specify whether the measurement was taken pre- or post-fixation. Surgically dissected parametrium (formal

parametrectomy) is not part of a simple hysterectomy specimen. A small amount of paracervical/parametrial soft tissue may be included in the sections of cervix from a simple hysterectomy. Some pathologists submit this tissue as a paracervical/parametrial shave. Although paracervical/parametrial tissue is present, this does not represent a formal parametrial resection.

 [Back](#)

## Note 4 – Macroscopic appearance of tumour(s) (Non-core)

Documentation of the macroscopic appearance of cervical tumours allows correlation with the clinical and radiological assessment of the tumour. According to FIGO 2018, clinically visible cervical cancers are Stage IB.<sup>2,3</sup> However, it now allows for pathologic or radiologic measurements to assign final stage if available. Therefore, even if a tumour is clinically visible, if on histological examination the lesion has the dimensions of a Stage IA neoplasm, it is recommended that it should be categorised as Stage IA (for example, associated erosion with minimal tumour present).<sup>2,3</sup> This should also be discussed at the gynaecological oncology multidisciplinary tumour board.

Exophytic/polypoid carcinomas may have a growth pattern that results in very little or even no invasion of the underlying stroma and ulcerated tumours may entirely or predominantly supplant the surface epithelium. In both these circumstances, it may be necessary to measure tumour 'Thickness' rather than 'Depth of invasion' and it is helpful to document the macroscopic appearance to provide context and explanation for the use of the alternative measurements. In large circumferential tumours, there is a risk of overestimating the maximum horizontal extent of the tumour (see **Note 6 TUMOUR DIMENSIONS**). The type of growth pattern in bulky (>40 mm) tumours may be prognostic. In one study, barrel-shaped cervical tumours >40 mm had a significantly worse overall and disease-free survival compared to exophytic tumours >40 mm.<sup>14</sup>

The macroscopic appearance of the tumour influences tumour sampling. For cases where there is no macroscopically visible tumour either because there has been a prior surgical procedure or prior therapy the entire cervix should be blocked. For cases with a large visible tumour, it is not necessary to block the whole tumour, but instead careful block selection ensuring representative sampling of the tumour, accurate assessment of margins and tumour extent is required. The blocks should be taken to include the nearest margin(s) and show the maximum depth of stromal invasion. In departments where the facility for processing oversize blocks is available, a good overview of the tumour and resection margins can be obtained. In departments where this facility is not available, large blocks may need to be subdivided; in such cases, the relationship of the blocks to one another should be clearly documented.

 [Back](#)

## Note 5 – Tumour site (Core)

The gross location of cervical tumours in all resection specimens, including hysterectomy specimens and trachelectomies, must be documented. In addition to providing the tumour dimensions (see **Note 6 TUMOUR DIMENSIONS**) and the proximity of the tumour to surgical resection margins, the relationship to local anatomical structures such as the vaginal cuff, the resected parametrial tissue (if present) as well as involvement of the lower uterine segment and uterine corpus should be documented. Because there may be an increased risk of para-aortic lymph node spread<sup>15</sup> and a higher rate of ovarian metastases<sup>16</sup> in cases with invasion of the uterine corpus, the presence of macroscopic involvement of the uterine corpus should be recorded.

 [Back](#)



## Note 6 – Tumour dimensions (Core)

### Reasons for accurate tumour measurement

Measurement of tumour dimensions in cervical carcinomas is important for accurate FIGO staging of early cervical cancers, patient management and prognostication.<sup>17,18</sup> The largest measure of horizontal extent and the depth of invasion should be measured in millimetres for all tumours (Figure 1). Although the 2018 FIGO revision removed horizontal extent as a parameter for early stage cervical cancer, it should still be reported as this gives a more complete picture of the extent of tumour and also allows for data collection for future studies to assess the importance of horizontal extent (refer to **Note 18 PROVISIONAL PATHOLOGICAL STAGING**, Table 2).<sup>2,3</sup> Furthermore, the horizontal extent is also important to appreciate the tumour volume. There are multiple problems with regard to measuring cervical tumours and these are discussed in detail in this section. In addition, it may not be possible to provide accurate tumour dimensions in fragmented or thermally damaged specimens. In situations where the tumour extends to resection margins, the tumour dimensions should be qualified by use of the term ‘at least’ to indicate that the measurements may not indicate the true/final tumour size.<sup>13</sup>

In most datasets, separate gross and microscopic measurements are mandated but this may result in confusion if different measurements are given. Some tumours (especially larger ones) are more accurately measured grossly while others (especially smaller tumours and some larger tumours with a diffusely infiltrative pattern or with marked tumour associated fibrosis) are best measured (or can only be measured) microscopically. In this dataset, separate gross and microscopic measurements are not included but rather one set of measurements is required which is based on a correlation of the gross and microscopic features with gross examination being more important in some cases and microscopic examination in others. A few other points are emphasised:

1. In providing the final tumour dimensions, the measurements in any prior specimens, for example loop/cone excisions, will 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. However, adding the measurements of multiple specimens is sometimes challenging and may not always be possible. The depth of invasion can be taken as the maximum depth of invasion in any one specimen. Similar comments pertain if loop/cone excisions are received in more than one piece and where multifocal tumour can be excluded.
2. Many cervical carcinomas of large size or advanced stage are treated by chemoradiation, without surgical resection, once the diagnosis has been confirmed on a small biopsy specimen. In such cases, the tumour dimensions will be derived from clinical examination and the radiological appearances. As indicated previously, this dataset applies only to excision/resection specimens and not to small biopsy specimens.
3. Occasionally resections are undertaken following chemoradiation for cervical carcinoma. In such cases, there may be no residual tumour or only small microscopic foci making it impossible to assess the tumour dimensions. In such cases, the pre-treatment clinical or radiological tumour dimensions should be used for staging and the dimensions of the tumour in the resection should not be used for staging purposes. The exception is for those jurisdictions that use the TNM Staging System which includes the ‘y’ prefix for staging cancers post-treatment.

Specific situations where tumour measurements are important include:

1. Small carcinomas where accurate depth of invasion measurement is paramount in distinguishing between FIGO Stage IA1, IA2 and small IB1 neoplasms.<sup>2,3</sup> As well as providing an accurate stage, this may also be critical in dictating patient management. For example, FIGO IA1 neoplasms are often treated by local excision ensuring that the margins are clear of pre-invasive and invasive disease while IA2 and IB1 neoplasms are usually treated by radical surgery (radical hysterectomy or trachelectomy).



2. In patients with FIGO Stage IB tumours treated by radical hysterectomy, the tumour size is often one of the parameters used, in conjunction with depth of invasion of the cervical wall in thirds, presence or absence of lymphovascular invasion (LVI) (Sedlis criteria) and distance to margins in assessing the need for adjuvant therapy.<sup>19</sup>
3. The tumour measurements may be important in helping to determine whether radical hysterectomy or trachelectomy is performed; sometimes a cut-off size of 20 mm is used for performing a radical trachelectomy, although some surgeons would still perform this procedure for larger size lesions. Following radical trachelectomy, the recurrence rate is statistically higher with tumour size greater than 20 mm and rates of adjuvant treatment are higher.<sup>20,21</sup> There is also a trend towards more conservative surgery (simple as opposed to radical hysterectomy) in patients with tumours less than 20 mm as the probability of parametrial infiltration is very low.
4. Several studies have shown that in FIGO Stage IB1 cervical carcinomas, a cut-off size of 20 mm may be of prognostic value.<sup>22,23</sup> In the 2018 FIGO Staging System, a cut-off of 20 mm distinguishes between Stage IB1 and IB2 carcinomas.<sup>2,3</sup> A cut-off of 40 mm is also of prognostic significance and is used in FIGO 2018 to distinguish between FIGO Stage IB2 and IB3 neoplasms and between Stage IIA1 and IIA2 neoplasms.<sup>2,3,24</sup>

### Measurement of horizontal extent of tumour

Although the 2018 FIGO Staging System no longer utilises horizontal extent of tumour (Figures 1 and 2) to stage microscopic cervical carcinomas, it is still recommended to provide the information in pathology reports for a more complete assessment of tumour characteristics i.e., tumour length or width, measurements 'b' or 'c' in Figure 1.<sup>2,3</sup> Stage IB in the 2018 FIGO Staging System uses tumour size cut-off values of 20 mm and 40 mm to distinguish IB1 ( $\leq 20$  mm), IB2 ( $> 20$  mm and  $\leq 40$  mm) and IB3 ( $> 40$  mm).<sup>2,3</sup> Therefore, as discussed earlier for large tumours, this may best be done grossly if large block processing is not available, because in many cases these neoplasms will need to be submitted in multiple cassettes and the maximum tumour dimension may not be represented on a single slide. If a gross measurement is not performed in large circumferential tumours, there is a risk of overestimating the maximum horizontal extent of the tumour. This can occur when a circumferential tumour is 'opened-up' and submitted in several sequential cassettes. When the other horizontal dimension (the third dimension) is calculated by adding up sequential slices in this situation (see below), this may result in an artificially greater measurement than is accurate. In the cases where no grossly visible tumour is present, yet there is extensive stromal invasion (e.g., so called 'barrel cervix'), if tumour is present in multiple sections, the pathologist should attempt to give the most representative measurement based on the size of the cervix, the number of sections involved and possibly the quadrants that are involved. If a circumferential tumour without a grossly visible and measurable mass has full thickness stromal invasion of the cervical wall involving all quadrants, the diameter of the cervix can be used as a reasonable approximation of tumour size. If the circumferential tumour does not invade the full thickness of the cervical wall, then the deepest invasion and largest horizontal extent as measured on any single slide should be reported, along with the number of blocks involved by invasive carcinoma.

In smaller neoplasms, the horizontal extent is best determined histologically (Figure 2). One horizontal dimension is the measurement in a single slide in which the extent of invasion is the greatest (Figure 2, measurement 'e'). If the invasive focus is only represented in one block, then the other horizontal dimension is taken to be the thickness of the block (usually 2.5-3 mm or estimated as indicated below). In some cases, the maximum horizontal extent may need to be calculated in the manner below if this is not represented in one section but is spread over several adjacent sections (Figure 1, measurement 'c'). If invasive carcinoma is present in several adjacent sections of tissue and the invasive foci co-localise in the sections, the horizontal extent of the carcinoma should be calculated by an estimate of the thickness of the blocks, which is determined from the macroscopic dimensions of the specimen and the number of blocks taken. However, pathologists should be mindful that thickness of large or outsize blocks can vary from block to block, as compared with standard-sized blocks. Whilst it is acknowledged that measurements from calculating block thickness may be somewhat inaccurate, it will in some cases be the only way to determine the maximum

horizontal extent and this may affect staging, especially in small tumours. Some key points regarding measurement of the horizontal extent of tumours are outlined below:

1. In a case where a single tongue of stromal invasion is seen in continuity with the epithelium of origin (surface or glandular), the width of the single focus of invasion is measured across the invasive tongue.
2. Where clustered foci of stromal invasion arise close together from a single crypt or from dysplastic surface epithelium as detached cell groups, the maximum horizontal extent must encompass all the foci of invasion in the immediate area and the horizontal extent should be measured from the edge at which invasion is first seen to the most distant edge at which invasion is detected.
3. Where several foci of invasion arise in one single piece of cervical tissue as separate foci of invasion, but in close proximity (see section below on measurement of multifocal carcinomas), either as contiguous tongues of invasion or detached epithelial groups, the maximum horizontal extent is taken from the edge at which invasion is first seen to the most distant edge at which invasion is detected. The small amount of intervening tissue with no invasion (usually with in situ neoplasia) is included in the measurement.

### Measurement of depth of invasion

The maximum depth of invasion must be measured in all cases (Figure 2). This measurement is taken from the base of the epithelium (surface or crypt) from which the carcinoma arises to the deepest point of invasion, as specified in the FIGO Staging System.<sup>2,3</sup> If the deepest point of invasion involves the deep margin of the specimen, comment should be made regarding the possibility of underestimation of the depth of invasion; this is particularly applicable to loop/cone specimens. When the invasive focus is in continuity with the dysplastic epithelium from which it originates, this measurement is straightforward. If the invasive focus or foci are not in continuity with the dysplastic epithelium, the depth of invasion should be measured from the tumour base (deepest focus of tumour invasion) to the base of the nearest dysplastic crypt or surface epithelium (Figure 2, measurements 'a' and 'c'). If there is no obvious epithelial origin despite multiple levels of the tissue block, the depth is measured from the tumour base (deepest focus of tumour invasion) to the base of the nearest surface epithelium, regardless of whether it is dysplastic or not (Figure 2, measurement 'd').

There are some situations where it is impossible to measure the depth of invasion. In such cases, the tumour thickness may be measured, and this should be clearly stated on the pathology report along with the reasons for providing the thickness rather than the depth of invasion. In such cases, the pathologist and clinician should equate the tumour thickness with depth of invasion for staging and management purposes.

Situations where it may be necessary to measure the tumour thickness rather than the depth of invasion include:

- In some glandular lesions, it may be impossible to accurately assess where adenocarcinoma in situ (AIS) ends and where invasive adenocarcinoma (ACA) begins. This is because, in general, identification of invasion in a glandular lesion is more difficult than in a squamous lesion and this is an area where a specialist opinion may be of value. In some cases where the thickness is measured (from the epithelial surface to the deepest point of the tumour) because the point of origin is impossible to establish, this may result in overestimation of the depth of invasion.
- In ulcerated tumours with no obvious origin from overlying epithelium, the thickness may need to be measured. In this situation, measurement of tumour thickness may result in an underestimate of the depth of invasion.
- Uncommonly, squamous cell carcinomas (SCCs), ACAs and other morphological subtypes are polypoid with an exclusive or predominant exophytic growth pattern. In such cases, the carcinoma may be grossly visible and project above the surface with little or even no invasion of the underlying stroma. These should *not* be regarded as in situ lesions and the tumour thickness may need to be measured in such cases (from the surface of the tumour to the deepest point of invasion). Depth of invasion i.e., the extent of infiltration below the level of the epithelial origin, should also be provided

in these cases with a clear description of how each measurement was derived (see examples below). Exophytic tumours should be staged based on largest dimension, even if superficially invasive ( $\leq 5$  mm). If the depth of invasion is  $>5$  mm, it is staged as IB. The FIGO Staging System explicitly states that the depth of invasion measurements for staging in IA1 and IA2 apply to tumours that can be diagnosed only on microscopy, i.e., does not apply to grossly visible tumours.<sup>2,3</sup> It remains to be seen, however, whether staging in this manner truly reflects tumour behaviour and future studies may help to elucidate this controversial issue.

Some examples include:

Polypoid/exophytic tumour,  $\leq 20$  mm in largest dimension:

- with a total thickness of 15 mm (top of tumour to deepest invasion). The portion of the tumour with true destructive stromal invasion into the cervical wall (non-exophytic component) measures 4 mm in depth – Stage IB1.
- with total thickness of 15 mm (top of tumour to deepest invasion). The portion of the tumour with true destructive stromal invasion into cervical wall (non-exophytic component) measures 8 mm in depth – Stage IB1.
- with total thickness of 4 mm (top of tumour to deepest invasion) (shallow wide tumour). The portion of the tumour with true destructive stromal invasion into cervical wall (non-exophytic component) measures 1 mm in depth – Stage IA2.
- with total thickness of 2.5 mm (top of tumour to deepest invasion) (shallow wide tumour). The portion of the tumour with true destructive stromal invasion into cervical wall (non-exophytic component) measures 1 mm in depth – Stage IA1.

Polypoid/exophytic tumour,  $>20$  mm,  $\leq 40$  mm in largest dimension – Stage IB2 regardless of thickness or depth of invasion.

Polypoid/exophytic tumour  $>40$  mm in largest dimension – Stage IB3 regardless of thickness or depth of invasion.

### **Avoid the term ‘microinvasive carcinoma’**

The term ‘microinvasive carcinoma’ appears in the 2018 FIGO Staging System for cervical cancer where it is equated with Stage IA disease.<sup>2,3</sup> However, use of the term ‘microinvasive carcinoma’ has different connotations in different geographical areas. For example, in the United Kingdom and in several other European countries, ‘microinvasive carcinoma’ was considered to be synonymous with FIGO Stage IA1 and IA2 disease in most, but not all, institutions (some used the term ‘microinvasive carcinoma’ to denote only FIGO Stage IA1 tumours).<sup>2,3</sup> In the United States and Canada where the Lower Anogenital Squamous Terminology (LAST)<sup>25</sup> recommendations have been adopted, the term superficially invasive squamous cell carcinoma (SISCCA) is used to describe FIGO Stage 1A1 tumours with negative margins, and the term ‘microinvasive squamous cell carcinoma’ is no longer in routine use. Thus, to avoid confusion, it is recommended to avoid using the term ‘microinvasive carcinoma’ for all morphological subtypes and to use the specific FIGO stage.

### **Measurement of multifocal carcinomas**

Early invasive carcinomas of the cervix, especially squamous, are sometimes multifocal comprising tumours that show multiple foci of invasion arising from separate sites in the cervix and separated by uninvolved cervical tissue. In those rare cases where more than one primary tumour is present, separate datasets should be completed for each neoplasm. These should include all the elements in this dataset, except for lymph node status which does not need to be documented separately for each tumour.

Specifically, multifocal tumours should be diagnosed if foci of invasion are:

- separated by blocks of uninvolved cervical tissue (levels must be cut to confirm this)
- located on separate cervical lips with discontinuous tumour, not involving the curvature of the canal
- situated far apart from each other in the same section (see below).

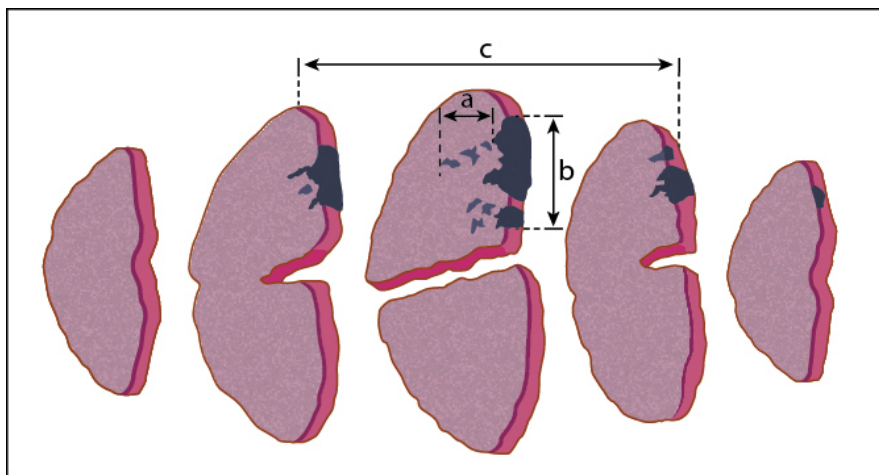
Again, because FIGO 2018 no longer requires horizontal extent to be measured for staging of early carcinoma, the measuring of multifocal tumours is less of an issue in determining stage, especially since most multifocal tumours tend to be superficially invasive.<sup>2,3</sup> The individual foci of stromal invasion may be attached to, or discontinuous from, the epithelium from which they arise. Multifocal carcinomas should not be confused with the scenario in which tongues or buds of invasion originate from more than one place in a single zone of transformed epithelium and will, over time, coalesce to form a single invasive tumour which represents unifocal disease (and should be measured, as indicated above, in three dimensions).

The frequency of multifocality in FIGO Stage IA1 cervical squamous carcinomas has been reported to be between 12% and 25%<sup>26-28</sup> although multifocality in larger, advanced tumours is uncommon. There are few (and some rather dated) guidelines regarding measurement of multifocal carcinomas.<sup>26,28,29</sup> Although pre-invasive disease may be present, when foci of stromal invasion arise from separate sites or are separated by cervical tissue without invasion (after levels/deeper sections have been cut to confirm this), the foci of invasion should be measured separately, in three dimensions, as described above, and staged according to the dimensions of the larger/largest tumour with a clear statement that the tumour is multifocal. However, in the last of the scenarios mentioned above (foci of stromal invasion situated far apart from each other in the same section) measurement of the multifocal disease is problematical. Options include measuring from the edge of one invasive focus to the edge of the furthest invasive focus according to 2018 FIGO guidelines (irrespective of the distance between foci of invasion), adding the maximum horizontal extent of each invasive focus together (which clearly does not reflect the biological potential of the individual invasive foci) or regarding widely separated foci as representing small independent areas of invasion.<sup>2,3,26-30</sup> Two studies have regarded such lesions as representing multiple foci of invasion (multifocal FIGO IA1 carcinomas) if the foci of invasion are clearly separated.<sup>26,27</sup> An arbitrary minimum distance of 2 mm between each separate focus of invasion was applied in these studies.<sup>26,27</sup> Follow-up of patients in these studies, which include a combined total of 46 cases of 'multifocal IA1 cervical squamous carcinomas' treated by local excisional methods (loop/cone excision) with margins clear of premalignant and malignant disease, showed no evidence of recurrent premalignant or malignant disease with median follow-up periods of 45 months and 7 years respectively.<sup>26,27</sup> Moreover, one of the studies showed that the prevalence of residual pre-invasive (20%) and invasive disease (5%) on repeat excision were comparable to data available for unifocal FIGO Stage IA1 cases.<sup>27</sup> These studies included cases which would have been regarded as FIGO Stage IB1 in the 2009 Staging System (but IA in the 2018 Staging System) had the horizontal extent been measured from the edge of one invasive focus to the edge of the furthest invasive focus, as per FIGO guidelines.<sup>2,3,31</sup> Although limited by a relatively small number of cases and the selection of an arbitrary distance of separation of 2 mm, the findings support the hypothesis that with regard to tumour staging and management, it may be appropriate to consider superficial, widely separated foci of invasion as representing multifocal lesions. In addition, it may be appropriate to measure each focus separately, and to determine the FIGO stage on the basis of the invasive focus with the higher/highest FIGO stage. Although the ICCR Carcinoma of the Cervix Dataset Authoring Committee (DAC) cannot justify implementation of an approach based only on two studies involving 46 patients in total, the DAC recommends that this approach be considered and discussed at multidisciplinary tumour board meetings to avoid unnecessary surgery in young patients who wish to preserve their fertility in this specific clinical situation. This approach needs to be verified by additional larger collaborative studies and trials. It is also stressed that in such cases, the tissue blocks containing the invasive foci and those in between should be levelled to confirm that the invasive foci are truly separate and ensure that there is no occult stromal invasion in the intervening areas. If this approach is adopted, the pathology report should clearly indicate how the measurements have been obtained to arrive at a diagnosis of multifocal invasion, provide the dimensions of the separate foci of invasion and indicate how the FIGO stage has been ascertained. Such cases may need to be referred to cancer centres for review and, as indicated above, should be discussed individually at the multidisciplinary tumour board meeting. There have been no

similar studies for multifocal ACAs but anecdotally these are less common than multifocal squamous carcinomas and until further evidence becomes available, a similar approach is recommended.

### Measurement of tumour volume

In most studies, tumour size is based on measurement of two dimensions but in a few studies, tumour volume (based on the three measured tumour dimensions) has been shown to predict prognosis more reliably than measurements in only one or two dimensions.<sup>32-34</sup> Some older studies have suggested tumour volume as a reliable prognostic factor for early stage tumours: a volume of less than 420 mm<sup>3</sup> has been suggested to be associated with no lymph node metastasis.<sup>32-34</sup> This is one of the main reasons for recommending that three tumour dimensions (two of horizontal extent and one of depth of invasion or tumour thickness) are provided. However, only a few centres continue to routinely factor tumour volume into patient management.

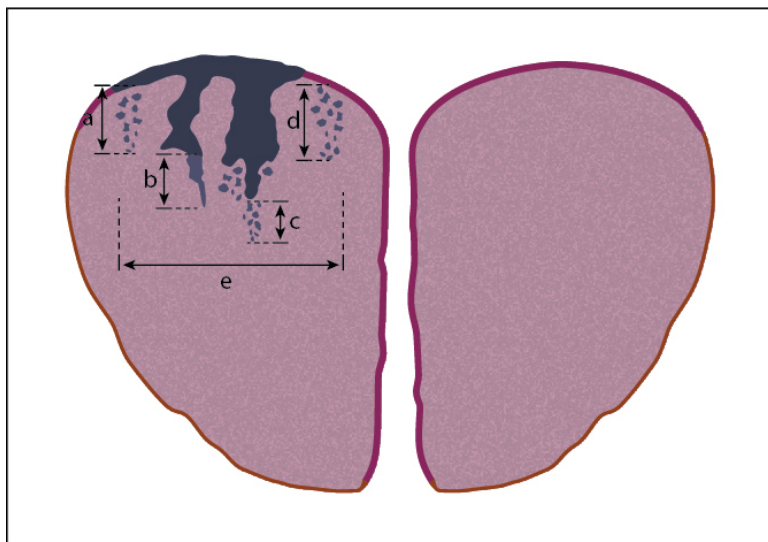


**Figure 1: Measurement of cervical tumours in three dimensions.**

High grade squamous intraepithelial lesion/Cervical intraepithelial neoplasia 3 (CIN3) with involvement of endocervical gland crypts is represented by the dark blue-coloured areas, non-dysplastic squamous epithelium is pink, and grey areas indicate foci of stromal invasion. The depth of invasion, **a** and horizontal tumour dimension/width **b** are measured in unifocal disease.

**Third dimension c**, this dimension is determined by calculating the block thickness (usually 2.5 - 3.0 mm) from the macroscopic specimen dimensions and multiplying this by the number of sequential blocks through which the invasion extends.

© 2021 International Collaboration on Cancer Reporting Limited (ICCR).



**Figure 2: Measurement of width and depth of invasion in cervical tumours.**

The dark blue areas represent high grade squamous intraepithelial lesion/Cervical intraepithelial neoplasia 3 (CIN3) with involvement of endocervical gland crypts, non-dysplastic squamous epithelium is pink, and grey areas indicate foci of stromal invasion.

**Depth of invasion:** when invasion originates from the surface epithelium **a**, or gland crypts **b** and **c**, the depth of invasion is taken from the base of the epithelium from which the invasive carcinoma arises, to the deepest focus of invasion, as specified in the FIGO Staging System. Measurements are taken in the same way, regardless of whether the invasive foci remain attached to the gland crypt **b** or not **c**. Where invasion occurs and no obvious surface (or crypt) epithelial origin is seen, the depth of invasion is measured from the deepest focus of tumour invasion, to the base of the nearest non-neoplastic surface epithelium **d**.

**Horizontal dimension/width in unifocal tumours e**, this is measured in the slice of tissue in which the width is greatest (from the edge at which invasion is first seen, to the most distant edge at which invasion is identified), in sections where the foci of invasion arise in close proximity to each other, even if those foci are separated by short stretches of normal epithelium.

© 2021 International Collaboration on Cancer Reporting Limited (ICCR).

↑ Back

## Note 7 – 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.

↑ Back

## Note 8 – Histological tumour type (Core)

The major subtypes of cervical carcinoma are SCC, ACA (with various subtypes), adenosquamous carcinoma and neuroendocrine tumours (NETs). In the era of molecular characterisation and targeted therapy, correct identification of the tumour subtypes will be even more crucial for understanding tumour biology and discovery of potential therapeutic targets. While it is beyond the remit of this document to detail the morphological appearances of the different tumour types in detail, a few points should be noted. All cervical carcinomas should be typed according to the 2020 WHO Classification of Tumours, Female Genital Tumours, 5<sup>th</sup> edition (Table 1).<sup>4</sup> The ICCR dataset includes 5<sup>th</sup> edition Corrigenda, June 2021.<sup>5</sup> This 2020 edition of the WHO Classification divides epithelial tumours of the cervix on the basis of their association (or lack thereof) with human papillomavirus (HPV) infection, which results in a classification that allows more accurate assessment of the success of HPV testing in cervical screening programmes, as well as the role of HPV vaccination. In addition, as in other anatomical areas, HPV-independent cervical carcinomas have been shown to have worse prognosis compared with HPV-associated neoplasms.<sup>35,36</sup>

To harmonise the classification across lower genital tract sites and other anatomical sites such as the head and neck region, SCCs are subdivided in the 2020 WHO Classification into HPV-associated and HPV-independent categories. Histological growth patterns, the presence of keratinisation and other morphologic variations (e.g., papillary, basaloid, warty, verrucous, etc.) are no longer the basis for subclassification, as they have no bearing on clinical behaviour. However, it may be useful to record unusual subtypes, for example lymphoepithelioma-like carcinoma, since the behaviour is not well established. Unfortunately, the two categories of cervical SCC, HPV-associated and HPV-independent, cannot be reliably distinguished on the basis of morphological criteria. Thus, p16 immunostaining and/or HPV testing are considered essential criteria, required to classify SCC of the cervix into the two categories. It is recognised that routinely performing these ancillary techniques on all cervical carcinomas is not feasible in many pathology laboratories. *Thus, a diagnosis of SCC not otherwise specified (NOS), without differentiating the two categories, is an acceptable alternative where the facilities necessary to make this distinction are not available.* However, the presence of concomitant high grade squamous intraepithelial lesion (HSIL) and/or a recent history of HSIL or high-risk HPV positivity is considered sufficient to classify a tumour as HPV-associated. There is no evidence, as yet, that an HPV-independent precursor lesion exists, and squamous intraepithelial lesions are therefore grouped into a single, HPV-associated, category. However, it should be emphasised that although HPV-independent SCCs have been described<sup>37</sup>, the vast majority of cervical SCC are HPV-associated. HPV-independent tumours represent a small percentage of all SCC, even in countries with active cervical cancer screening programs, where HPV-independent tumours are probably over-represented.

Recent comprehensive studies have shown that although the majority (85%) of endocervical ACAs are associated with HPV infection, about 15% are not and there are clinically significant outcomes based on association with HPV infection.<sup>38,39</sup> The 2020 WHO Classification recognises this by separating HPV-associated and HPV-independent ACAs.<sup>4</sup> Contrary to SCC, HPV-associated and HPV-independent ACAs of the cervix can be distinguished based on morphology alone with easily identifiable luminal mitoses and apoptotic bodies typically being identified at scanning magnification in HPV-associated ACAs. The HPV-independent ACAs can be further subcategorised by traditional nuclear, cytoplasmic and architectural features, and comprise gastric, clear cell, mesonephric, and endometrioid types. It should be emphasised that most ACAs with an 'endometrioid' appearance represent HPV-associated ACAs with mucin depletion and should be classified as usual type, HPV-associated. In addition, most true endometrioid neoplasms involving the cervix are likely due to direct extension from an endometrioid carcinoma in the corpus or, rarely, arises from cervical endometriosis. Thus, true endometrioid carcinoma should be diagnosed only when HPV-associated ACA and other mimics (e.g., extension from an endometrial carcinoma) have been rigorously excluded. Of note, mismatch repair deficiency is not thought to be a feature of endocervical carcinoma and the loss of mismatch repair protein expression should raise considerable suspicion for an endometrial primary, particularly given the predilection of MLH1/PMS2-deficient, *MLH1* hypermethylated tumours to involve the lower uterine segment.<sup>40</sup> p16 and/or HPV testing are considered desirable (not essential) criteria, as the morphological



features usually allow accurate differentiation. The ubiquitous use of and reliance on p16 immunohistochemistry to diagnose cervical ACA may cause diagnostic problems for HPV-independent tumours, since these typically do not exhibit the diffuse strong immunoreactivity characteristic of HPV-associated tumours (see **Note 17 ANCILLARY STUDIES**).<sup>41,42</sup> Invasive stratified mucin-producing carcinoma (iSMC) is the invasive counterpart of stratified mucin-producing intraepithelial lesion (SMILE) and a variant of HPV-associated ACA characterised by solid nests of tumour cells with mucin vacuoles scattered throughout the entire thickness of the nests; the term invasive SMILE (iSMILE) can also be used. These can mimic squamous carcinomas when mucin-poor and have likely been categorised as adenosquamous carcinomas in the past. This ACA subtype appears to have more aggressive behaviour than usual type ACA or adenosquamous carcinoma and should be mentioned in the diagnostic report.<sup>43-45</sup>

Primary serous carcinoma of the cervix is likely non-existent and is no longer included in the 2020 WHO Classification.<sup>4</sup> Most cases reported as primary cervical serous carcinoma are likely to represent a metastasis from the corpus or extrauterine sites or a usual HPV-related ACA with marked nuclear atypia, including the micropapillary variant. Metastasis should be excluded in cases that are morphologically consistent with serous carcinoma in the cervix. Both HPV-associated usual type cervical ACAs, adenosquamous carcinomas and HPV-independent gastric type ACAs can have a papillary and micropapillary growth pattern with high grade nuclear atypia, mimicking serous carcinoma.<sup>46</sup>

Adenosquamous carcinomas (defined in the WHO 2020 Classification<sup>4</sup> as a malignant epithelial tumour exhibiting both squamous and glandular differentiation) are usually related to high-risk HPV. To make a diagnosis of adenosquamous carcinoma, unequivocal malignant squamous and glandular components should be identifiable on routine haematoxylin and eosin (H&E) stained sections. The demonstration of foci of intracytoplasmic mucin by mucin stains in an otherwise typical squamous cell carcinoma should not result in diagnosis of an adenosquamous carcinoma. Carcinomas which lack evidence of squamous differentiation (intercellular bridges, keratinisation) but have abundant mucin-producing cells should be diagnosed as poorly differentiated ACAs. Adenosquamous carcinoma should also be distinguished from a spatially separate squamous carcinoma and ACA, which occasionally occurs. While some studies have indicated a worse outcome than pure squamous or ACAs, there is not robust evidence to confirm these findings and recent studies suggest similar outcomes to ACA.<sup>43,45,47,48</sup>

Carcinosarcoma is also included in the WHO 2020 Classification in the category of epithelial neoplasms of the cervix since it is considered a carcinoma which has undergone sarcomatous differentiation.<sup>4</sup>

Neuroendocrine carcinomas (NECs) (small cell and large cell NEC) are uncommon but well described in the cervix and can occur in pure form or associated with another tumour type, ACA (most common), SCC or adenosquamous carcinoma. The vast majority of cervical NECs are associated with high-risk HPV, typically HPV 18, with only rare exceptions. The WHO 2020 Classification has separated neuroendocrine neoplasia of the gynaecologic tract as a stand-alone section.<sup>4</sup> A unified terminology across all organs has been incorporated into the 2020 WHO Classification, following the agreement reached at a consensus conference held at the International Agency for Research on Cancer (IARC) in November 2017, and subsequently published.<sup>4,49</sup> Neuroendocrine neoplasia is categorised into NET and NEC, the former defined as low or intermediate grade epithelial neoplasms with morphologic and immunohistochemical features of neuroendocrine differentiation (formerly carcinoid and atypical carcinoid tumour), the latter as either small cell or large cell NEC. When mixed with another tumour type, the percentage of the neuroendocrine component should be given. Regardless of the percentage of NEC, it is recommended that the tumour be reported as mixed since all tumours containing a component of NEC have a very poor prognosis and the NEC component may be underestimated in a limited sample.<sup>50</sup> Several studies of small cell NECs of the cervix have shown that adjuvant chemotherapy after surgery for early stage disease provides significant clinical benefit compared to surgery alone and therefore, it is extremely important to correctly diagnose any component of NEC. Additionally, in many institutions surgical resection is not undertaken for a NEC even if early stage but instead chemotherapy treatment is given. Diagnosing NEC or a component of NEC can be difficult, especially in small samples, but a combination of synaptophysin, chromogranin A, CD56, TTF1,

INSM-1, p40, p63 and somatostatin analogues (SST2 and SST5) has been shown to be helpful in making the distinction between NEC and poorly differentiated non-NEC (see **Note 17 ANCILLARY STUDIES**).<sup>51-53</sup>

**Table 1: World Health Organization classification of tumours of the uterine cervix.<sup>4</sup>**

Descriptor	ICD-O codes <sup>a</sup>
<b>Squamous epithelial tumours</b>	
Squamous metaplasia	
Atrophy	
Condyloma acuminatum	
Low grade squamous intraepithelial lesion	8077/0
Cervical intraepithelial neoplasia, grade 1	8077/0
High grade squamous intraepithelial lesion	8077/2
Cervical intraepithelial neoplasia, grade 2	8077/2
Cervical intraepithelial neoplasia, grade 3	8077/2
Squamous cell carcinoma, HPV-associated	8085/3
Squamous cell carcinoma, HPV-independent	8086/3
Squamous cell carcinoma NOS	8070/3
<b>Glandular tumours and precursors</b>	
Endocervical polyp	
Müllerian papilloma	
Nabothian cyst	
Tunnel clusters	
Microglandular hyperplasia	
Lobular endocervical glandular hyperplasia	
Diffuse laminar endocervical hyperplasia	
Mesonephric remnants and hyperplasia	
Arias-Stella reaction	
Endocervicosis	
Tuboendometrioid metaplasia	
Ectopic prostate tissue	
Adenocarcinoma in situ NOS	8140/2
Adenocarcinoma in situ, HPV-associated	8483/2*
Adenocarcinoma in situ, HPV-independent	8484/2*
Adenocarcinoma NOS	8140/3
Adenocarcinoma, HPV-associated	8483/3*
Adenocarcinoma, HPV-independent, gastric type	8482/3
Adenocarcinoma, HPV-independent, clear cell type	8310/3
Adenocarcinoma, HPV-independent, mesonephric type	9110/3
Adenocarcinoma, HPV-independent, NOS	8484/3*
Other adenocarcinoma NOS	8380/3
<b>Other epithelial tumours</b>	
Carcinosarcoma NOS	8980/3
Adenosquamous carcinoma	8560/3
Mucoepidermoid carcinoma	8430/3
Adenoid basal carcinoma	8098/3
Carcinoma, undifferentiated, NOS <sup>b</sup>	8020/3
<b>Mixed epithelial and mesenchymal tumours</b>	
Adenomyoma	8932/0
Mesonephric-type adenomyoma	
Endocervical-type adenomyoma	
Adenosarcoma	8933/3

Descriptor	ICD-O codes <sup>a</sup>
<b>Germ cell tumours</b>	
Germ cell tumour NOS	9064/3
Mature teratoma NOS	9080/0
Dermoid cyst NOS	9084/0
Yolk sac tumour NOS <sup>c</sup>	9071/3
Choriocarcinoma NOS	9100/3

<sup>a</sup> These morphology codes are from the International Classification of Diseases for Oncology, third edition, second revision (ICD-O-3.2).<sup>54</sup> Behaviour is coded /0 for benign tumours; /1 for unspecified, borderline, or uncertain behaviour; /2 for carcinoma in situ and grade III intraepithelial neoplasia; and /3 for malignant tumours, primary site; and /6 for malignant tumours, metastatic site. Subtype labels are indented. Incorporates all relevant changes from the 5<sup>th</sup> edition Corrigenda June 2021.

<sup>b</sup> Carcinoma of the uterine cervix, unclassifiable.

<sup>c</sup> Endodermal sinus tumour.

© World Health Organization/International Agency for Research on Cancer. Reproduced with permission.

 **Back**

## Note 9 – Histological tumour grade (Non-core)

### Grading of cervical carcinoma

Tumour grade is regularly included in histopathology reports of cervical SCC and ACA. However, at present no particular grading system has achieved universal acceptance and grading of these tumours remains of uncertain clinical value.<sup>55-57</sup> For example, grade is not amongst the factors considered in determining the Gynaecology Oncology Group (GOG) score which is used to assess the need for adjuvant therapy following surgery for low-stage cervical carcinomas.<sup>58</sup> Not uncommonly, studies that assess grade as a potential prognostic variable provide no details of the grading system employed, and this is also true of large multicentre investigations utilising data from the Surveillance Epidemiology and End Results (SEER) program of the National Cancer Institute (NCI).<sup>59,60</sup> For these and other reasons (discussed below), tumour grading is not listed as core but rather a non-core element. While no particular grading system for squamous carcinoma is recommended, the International Society of Gynecological Pathologists (ISGyP) has recently published a consensus statement on grading cervical ACA.<sup>61</sup>

### General considerations

1. As with tumours arising in other anatomical sites, grading of cervical carcinomas has a considerable subjective component and this probably explains, at least in part, the variable proportion of well, moderately, and poorly differentiated tumours reported in different studies. However, some investigators have demonstrated reasonable intra- and inter-observer agreement using more complex multifactor grading schemes in SCC (discussed below).
2. Almost all cervical SCCs are HPV-associated and given that HPV-associated SCCs very commonly have a 'basaloid' morphology with minimal keratinisation, they are very commonly poorly differentiated.
3. Most clinically advanced cervical carcinomas are treated with primary chemoradiation rather than surgery and histological sampling may be limited to a small diagnostic biopsy. This may not be fully representative due to tumour heterogeneity and could be potentially misleading as regards tumour differentiation or grade.<sup>55</sup> This may be particularly relevant since less differentiated appearing tumour elements may be located more deeply towards the invasive margin.<sup>56</sup>

4. There is an implicit correlation between tumour type and grade in certain cervical carcinomas and therefore a separate grade may not be applicable. For example, pure villoglandular ACA of the cervix (considered a morphological variant of usual-type HPV-associated ACA) is by definition a low grade neoplasm while clear cell carcinoma, as in the endometrium, is considered high grade by default.<sup>62</sup> Similarly, 'gastric-type' cervical ACAs and NECs are clinically aggressive regardless of their histological pattern and therefore are best considered high grade automatically.<sup>63,64</sup> There is no published grading system for cervical mesonephric ACAs. Several variants of cervical SCC are also recognised, although most do not differ from conventional SCC in terms of prognosis or therapy.<sup>65</sup>
5. It is uncertain whether a truly 'undifferentiated' cervical carcinoma should be regarded as a separate tumour subtype analogous, for example, to similar tumours arising in the endometrium.
6. Grading of very small superficially ('early') invasive carcinomas of either squamous or glandular type is probably not possible or relevant.

### **Grading of cervical squamous cell carcinoma**

Historically, cervical SCCs were graded using the Broder system or modifications thereof based upon the degree of keratinisation, cytological atypia and mitotic activity.<sup>66</sup> In some schemes, the pattern of invasion (pushing versus infiltrating) has also been taken into account. As noted above, this raises the issue whether such categorisation represents a tumour subtype (arguably not further graded), or a grade within a spectrum of a single type of tumour. It should be noted that some studies have found that the keratinising variant of large cell SCC actually has a poorer prognosis than the non-keratinising variant, an apparently paradoxical finding if keratinisation is deemed to be evidence of better differentiation. This may be because unlike in skin, evidence of keratinisation in the cervix is abnormal and therefore, should not be equated with being well-differentiated. It is also possible that some keratinising SCCs of the cervix are not driven by HPV (HPV-independent SCCs), and these tumours, in the cervix and other organs, generally have a worse prognosis than HPV-associated tumours. It is also uncertain what proportion of small cell SCCs reported in the older literature would now be classified as high grade NECs (small cell NECs), and this could potentially bias the supposedly poor outcome of this tumour category.

At present, no single grading system has been widely adopted in routine diagnostic practice and it is recommended at this time to *not grade* SCCs.

### **Grading of cervical adenocarcinoma**

As with SCC, it is controversial whether grading has independent prognostic value in cervical ACA. Whilst a correlation between higher grade and adverse outcomes has been reported,<sup>67-71</sup> at least for poorly differentiated tumours, this has not been a universal finding.<sup>72,73</sup> It should also be noted that some studies have included a variable proportion of less common histological subtypes such as adenosquamous carcinoma, mesonephric, gastric-type and clear cell carcinoma,<sup>67,70,71</sup> and often tumour details are not provided. Therefore, it is not clear whether the reported grading data are applicable to usual-type cervical ACA or have been biased by the inclusion of other more aggressive tumour subtypes (for example, gastric-type ACA).

There is a lack of consensus regarding the prognostic value of grading of endocervical ACAs and no universally adopted, validated system for grading exists. Despite this, clinicians expect tumour grade to be included in the pathology report, irrespective of whether it will influence treatment. Several grading schemes have been proposed, most combining an evaluation of the extent of solid tumour growth and nuclear grade, similar to the FIGO Staging System for grading endometrial endometrioid carcinoma,<sup>2,3</sup> although some schemes modify the proportion of solid tumour required to separate Grades 1 and 2 from 5% to 10%. Two sizeable studies using a three-tier system with cut-off points for the proportion of solid architecture set at ≤10%, 11-50% and >50%, with tumours upgraded for marked nuclear atypia, have demonstrated the independent prognostic value of tumour grade by multivariate analysis.<sup>71,74</sup> Other studies have reached varied conclusions, although some, including large multicentre population analyses, have similarly found tumour grade to have independent prognostic value, although the grading systems used and histological tumour types examined were not always reported.<sup>35,59,60,75-78</sup>

Based on the available evidence, the ISGyP recommends that HPV-associated ACAs with  $\leq 10\%$  solid growth is designated Grade 1, 11-50% solid growth is designated Grade 2, and  $>50\%$  solid growth is designated Grade 3. Tumours should be upgraded in the presence of marked nuclear atypia involving the majority ( $>50\%$ ) of the tumour, and a confluent microacinar pattern is regarded as solid tumour growth. Tumours with a micropapillary, signet ring or invasive stratified mucinous carcinoma component should not be graded as these are automatically considered high grade. Grading is also not recommended for HPV-independent ACAs as most of these neoplasms exhibit intrinsically aggressive behaviour regardless of their morphologic appearance. Importantly, grading should not be performed for gastric-type ACAs, particularly as these tumours may appear deceptively 'low grade' yet still exhibit aggressive behaviour. With the emergence of new aetiology and pattern-based classification systems for endocervical ACA, both of which offer effective risk stratification, traditional grading of these tumours may, in future, become redundant.

### Grading of cervical adenosquamous carcinoma

Although it has been suggested that adenosquamous carcinomas are graded on the basis of the degree of differentiation of both the glandular and squamous components, there is no well established grading system for these neoplasms which has been shown to be of prognostic significance.

 [Back](#)

## Note 10 – Lymphovascular invasion (Core)

Lymphovascular invasion (LVI) does not affect FIGO or TNM staging (for example if there is LVI in tissues outside the cervix but the tumour itself is confined to the cervix, this is still FIGO Stage I) but should be clearly documented in the pathology report.<sup>2,3,79,80</sup> The significance of LVI in cervical carcinoma has been debated for predicting overall survival, disease-free interval (DFI), recurrence-free survival and regional lymph node metastasis for decades. Although studies conflict, there is general agreement that LVI is an independent predictor of adverse outcome.<sup>56,81-90</sup> Early studies indicated that LVI was an independent predictor of DFI, with one study reporting a 1.7 times higher rate of recurrence in patients with LVI compared to those without LVI in low-stage cervical carcinoma.<sup>83</sup> This has been confirmed in later studies, particularly in low-stage (FIGO Stage IB) cervical carcinoma.<sup>56</sup> The significance of LVI in SISCCA is unclear, likely due to the rarity of adverse outcomes including lymph node metastasis in SISCCA. Studies have shown that LVI does not predict lymph node metastasis in cases of SISCCA with a depth of invasion of  $\leq 3$  mm.<sup>91-94</sup>

Lack of standardised criteria and marked variability in recognition of LVI have undoubtedly led to conflicting outcomes in previous studies. Fixation retraction around tumour cell groups is a well recognised artefact which mimics LVI. Features that may help in the recognition of LVI include a tumour nest within a space associated with other vascular structures, the presence of an endothelial lining, adherence of the tumour cell group to the side of the space, the contour of the intravascular component matching the contour of the vessel and the presence of adherent fibrin. Immunohistochemical demonstration of an endothelial cell lining may assist but is not performed routinely. D2-40 (recognising lymphatic endothelium) and CD31 and CD34 (recognising both lymphatic and blood vascular endothelium) may be useful in confirming the presence of LVI.<sup>95-98</sup>

In rare situations when specimens are severely traumatised or cauterised, LVI may be suspected but it may not be possible to reliably determine whether or not LVI is present. In these circumstances 'indeterminate' should be recorded in the reporting guide, although it is expected this will be a rare response and should be used sparingly.

Most studies which have examined the significance of LVI in cervical carcinoma have not distinguished between lymphatic and blood vessel invasion and there is little evidence to support separating out the type of invasion, especially since this is not reliable in haematoxylin and eosin-stained sections. Occasional studies have found blood vessel invasion to have a worse prognosis than lymphatic invasion and to be a predictor of

ovarian involvement.<sup>99</sup> However, there is insufficient evidence to warrant inclusion of blood vessel and lymphatic invasion as separate data items. Likewise, there is currently no evidence to support counting the number of blood vessels containing tumour. A comment may be made if there is obvious extensive LVI, and there are no standard cut off values that can be applied currently.

 [Back](#)

## Note 11 – Extent of invasion (Core)

The involvement of any extracervical structures by invasive tumour should be documented. Documentation of the involvement of various extracervical tissues is prognostically significant and is important for tumour staging. Involvement of the pelvic side-wall, vagina, parametria, rectum and bladder upstage the tumour. Involvement of the uterine body, whilst not formally part of FIGO or 8<sup>th</sup> edition TNM Staging,<sup>2,3,79,80</sup> has also been shown to be of prognostic significance.<sup>100</sup> Adnexal involvement also does not upstage cervical cancer though the presence of tubo-ovarian tumour generally results in some form of adjuvant therapy. Documentation of the extent of invasion is also important for correlation with clinical and radiological findings.

The **parametria** are composed of fibrous tissue, which surrounds the supravaginal part of the cervix and separates this part of the cervix anteriorly from the bladder and posteriorly from the rectum. The fibrous parametrial tissue extends onto the sides of the supravaginal cervix and between the layers of the broad ligaments. The fibrous connective tissue around the isthmus at the cervix/lower uterine segment junction should be regarded as part of the parametria and included in the sampling of parametrial tissue. Lymph nodes and the uterine blood vessels and lymphatics that supply and drain the cervix are contained within the fibrous parametrial tissue.

The **uterine body** includes both endometrial (glandular/stromal) and myometrial structures.

If the **bladder or rectum** is involved, the pathologist should state which compartments are infiltrated; in particular, if the bladder or rectal mucosa is involved, this implies that the tumour is Stage IVA at least.

Lymphovascular invasion (LVI) should be documented wherever it is identified, but anatomical structures where there is *only* LVI and no direct stromal infiltration, should not be recorded as being involved by tumour and the presence of LVI should not alter the FIGO stage.

 [Back](#)

## Note 12 – Pattern of invasion for HPV-associated adenocarcinomas (Non-core)

Recently, a system of assessing cervical ACAs based upon their invasive growth pattern has been developed, the Silva Pattern Classification, and this has been shown to be reproducible amongst pathologists and to correlate with the risk of lymph node metastasis and patient outcomes.<sup>101-105</sup> If these findings are confirmed by additional studies it may be argued whether this system could be considered a complement to, or even an alternative to, conventional grading. The latter has traditionally been based upon the cytoarchitectural pattern of the neoplasm itself but as noted above, tumour-stromal relationships including the pattern of stromal invasion have been included in earlier grading schemes of cervical SCC. It is important to highlight that the pattern classification is only applicable to HPV-associated cervical ACAs on complete resections (loop electrosurgical excision procedure (LEEP) or cone with negative margins, trachelectomies, hysterectomies). Studies have shown that the pattern classification is not clinically relevant in HPV independent cervical

ACAs,<sup>106</sup> and therefore, should not be applied in those scenarios. One study has also shown that the pattern classification is highly concordant between LEEP and hysterectomy, but this was not shown for biopsies and hysterectomies.<sup>105</sup>

The Silva Pattern Classification system for HPV-associated cervical ACAs was developed in 2013 in an attempt to correlate histologic invasion patterns to outcomes, regardless of tumour size or stage so that patients could potentially be spared unnecessary lymphadenectomies for cases with no risk of nodal involvement.<sup>102</sup> Pattern A endocervical ACAs are characterised by well-formed glands frequently forming groups with relatively well preserved lobular architecture without destructive stromal invasion, single cells or detached clusters of tumour cells. There should be no solid growth or high grade cytology but complex intraglandular proliferations are acceptable (cribriforming or papillae). LVI should be absent in these lesions. Pattern B tumours show localised (limited/early) destructive invasion arising in a background of pattern A glands. Individual cells or clusters of tumour cells are seen in desmoplastic or inflamed stroma, and these foci can be single, multiple or linear at the base of the tumour, but should not exceed 5 mm contiguously. Pattern C tumours show diffuse destructive invasion that usually elicits a desmoplastic/inflammatory response. The glands can be angulated, or have a canalicular/labyrinthine appearance, and incomplete/fragmented (as seen in microcystic, elongated and fragmented (MELF) pattern of endometrioid carcinomas) glands are frequent, sometimes associated with mucin lakes. Solid or confluent growth can also be seen. LVI can be present in either pattern B or C and should be documented separately. In the original study, the risk of lymph node metastases for the various patterns was 0%, 4.4%, 23.8% for patterns A, B and C, respectively. Subsequent studies have reproduced the original findings and also showed good reproducibility amongst pathologists.<sup>104,107-109</sup> While more and larger prospective studies to evaluate and confirm these retrospective results are necessary, gynaecologic surgeons are increasingly becoming aware of the classification system and this may in the future become an important part of surgical planning and prognostication. It should be emphasised that the classification can only be applied in HPV-associated ACAs which have been completely resected on loop/cone/trachelectomy/hysterectomy specimens.

 [Back](#)

## Note 13 – Margin status (Core and Non-core)

The status of all surgical resection margins should be recorded (ectocervical, endocervical, radial/deep stromal and vaginal cuff). At the time of specimen grossing, it may be useful to ink the various resection margins with different colours to assist precise margin recognition.

The recording of margin involvement by tumour is a core data element. When invasive carcinoma is close to a surgical margin, documentation of the distance to the margin is non-core. No data are available to indicate the optimal margin of clearance of carcinoma in simple hysterectomy, trachelectomy, cone or loop biopsy specimens. Consistent recording of the distance to the margins will enable data to be collected prospectively and provide evidence for future practice. A small number of retrospective studies has assessed the impact of close margins on local and overall recurrence in patients undergoing radical hysterectomy for cervical cancer.<sup>110</sup> The crude local recurrence rate was 20% in 284 patients with FIGO Stage IB carcinomas with ‘close’ margins (close was defined as <10 mm) in one study.<sup>111</sup> In the same study, patients with negative margins, defined as a clearance of ≥10 mm, had a crude recurrence rate of 11%.<sup>111</sup> Another study of close surgical margins after radical hysterectomy in early-stage cervical cancer found that close surgical margins, defined as ≤5 mm, were associated with recurrence rates of 24% as compared with recurrence rates of only 9% in patients with negative margins.<sup>112</sup> In the same study, close surgical margins were significantly associated with positive lymph nodes, parametrial involvement, larger tumour size, deeper stromal invasion and LVI.<sup>112</sup>

In occasional cases where tumour involvement of the margin cannot be determined for various reasons (processing artefact, multiple pieces or poor tissue orientation), the margin status should be specified as ‘cannot be assessed’ and the reason explained. In hysterectomy or trachelectomy specimens, the lateral



radial margin may consist of parametrial soft tissue, which should be measured (see **Note 3 SPECIMEN DIMENSIONS**), based on gross examination, and calculated into the margin evaluation. In contrast, anterior and posterior radial/deep stromal margins in a hysterectomy specimen will consist of cervical stromal tissue.

The presence of margin involvement by HSIL, AIS or SMILE should be documented (core element). If not involved, the distance to the resection margin is a non-core element, although, as with invasive tumour, there are no data available to indicate the optimal margin of clearance. In hysterectomy specimens with Stage IA or small IB carcinomas, the entire cervix should be assessed histologically to ensure an accurate measurement of the extent of the disease and surgical margins.<sup>113-116</sup>

 [Back](#)

## Note 14 – Lymph node status (Core and Non-core)

Lymph node status is one of the most important prognostic factors for survival in patients with cervical cancer.<sup>117</sup> The 5 year survival rate decreases from 85% to 50% when lymph node metastases are identified.<sup>118</sup>

Radical hysterectomy or trachelectomy and pelvic lymphadenectomy are the standard of treatment in most centres for FIGO Stage IB1, IB2 and IIA1 cervical carcinomas and, in some centres, for Stage IA2 carcinomas. There is an increasing trend for a more conservative approach, such as loop/cone excision, in the treatment of FIGO Stage IA2 and small Stage IB1 carcinomas, particularly if additional risk factors such as LVI are absent.<sup>12</sup> In such cases, lymphadenectomy is often performed. Lymphadenectomy may also occasionally be performed for bulky nodal metastases (>20 mm) which are resistant to radiotherapy and/or chemotherapy; debulking of enlarged pelvic nodes has been shown to reduce the risk of pelvic recurrence but does not benefit survival.<sup>119,120</sup>

Core data items regarding lymph node status are restricted to the number of lymph nodes identified from the various sites and the number involved by tumour. The size of the tumour deposit is included as a non-core item. Some of the other parameters discussed below (extracapsular spread and lymph node ratio) may be recorded if locally agreed. Recording these parameters may be useful for future research.

Resected lymph nodes are categorised as regional (paracervical, parametrial, various pelvic lymph node groups, including obturator, internal, common or external iliac, presacral and lateral sacral, and para-aortic) or non-regional nodes (inguinal and other nodes).<sup>79</sup> The FIGO 2018 Staging System,<sup>2,3</sup> unlike previous systems, includes lymph node status and is thus now closely aligned with the structure of the Union for International Cancer Control (UICC) and American Joint Committee on Cancer (AJCC) 8<sup>th</sup> edition TNM Classifications (see **Note 18 PROVISIONAL PATHOLOGICAL STAGING**).<sup>79,80</sup> In the FIGO 2018 Staging System, pelvic lymph node involvement is Stage IIIC1 and para-aortic nodal involvement Stage IIIC2.<sup>2,3</sup> In applying a TNM stage, regional lymph node metastases contribute to the N category, but non-regional node involvement is regarded as distant metastasis. One point to emphasise is that the TNM8 Classification takes into account the size of the nodal metastasis in assigning the N category.<sup>79,80</sup> According to TNM8, {Brierley JD, 2016 #5267} macrometastases (MAC) are >2 mm, micrometastases (MIC) are >0.2-2 mm and isolated tumour cells (ITCs) are up to 0.2 mm. MAC are regarded as pN1, MIC as pN1 (mi) and ITCs are pN0 (i+); ITCs do not upstage a carcinoma. The 2018 FIGO Staging System originally stated that MIC and ITCs can be recorded but this does not alter the tumour stage.<sup>2,3</sup> However, a corrigendum was later issued stating that MIC should be counted as nodal involvement and FIGO Stage IIIC.<sup>121</sup>

According to the UICC, a pelvic lymphadenectomy specimen should normally include six or more lymph nodes, but if this node count is not met and the resected lymph nodes are negative, the carcinoma should still be classified as pN0.<sup>79</sup> The mean or median number of lymph nodes removed during pelvic lymphadenectomy varies widely in different studies and ranges from 13 to 56 nodes. Apart from the arbitrary minimum number of nodes proposed by the UICC, there is no internationally accepted minimum for

the number of resected lymph nodes required as part of a lymphadenectomy for cervical cancer. A study by Inoue et al (1990) reported that the number of positive nodes was of greater prognostic significance than the presence of nodal metastasis per se.<sup>122</sup> While a more recent study by Park and Bae (2016), showed that the number of lymph nodes with metastases is an independent risk factor for reduced survival in patients with cervical cancer.<sup>123</sup>

In many centres, sentinel lymph node (SLN) biopsy is now being undertaken in patients with presumed low-stage cervical carcinoma.<sup>114,124,125</sup> Overall, in FIGO Stage I cervical cancer the incidence of pelvic lymph node metastasis is approximately 10%.<sup>126</sup> If the SLN is negative, this avoids the morbidity associated with full pelvic lymphadenectomy in the remaining 90% of patients, i.e., SLN biopsy is of value in reducing the requirement for a complete lymphadenectomy with its attendant morbidity in a patient population at low risk for lymph node metastases. With regard to the issue of MIC (which, as discussed, should be staged as pN1 (mi)) and the use of immunohistochemistry (usually cytokeratin AE1/AE3), a study by Juretzka et al (2004) found immunohistochemically-detected MIC in 8.1% of patients with initially reported 'negative' nodes (comprising 4 of 976 or 0.41% of pelvic lymph nodes examined).<sup>127</sup> The immunohistochemically-detected MIC were more frequent in tumours with LVI; another study showed that immunohistochemically-detected MIC were a risk factor for tumour recurrence.<sup>128</sup> Other studies have shown higher rates of lymph node MIC in early stage cervical carcinomas for example, 10.1% of cases in a study by Cibula et al (2012)<sup>129</sup> and 15% in a study by Lentz et al (2004).<sup>130</sup> The latter study also showed that MIC were more likely in patients in whom larger numbers of lymph nodes were removed. A study by Horn et al (2008) revealed that lymph node MIC were prognostically significant; patients with MIC had a reduced 5 year survival rate compared with node-negative patients, but fared better than those patients with MAC.<sup>131</sup> In the study by Cibula et al (2012)<sup>129</sup> ITCs were detected in 4.5% of cases and were found to be of no prognostic significance. If SLN biopsy is carried out, the number of nodes examined, the number of positive nodes and the size of the tumour deposit should be recorded. It is acknowledged that there are few published data regarding MIC and ITCs in cervical cancer and until further data emerge it is recommended that these should be reported in the same way as ITCs at other sites.

Frozen section of SLNs is also performed routinely in some institutions, while others may take a more selective approach in choosing SLNs to send for frozen. If positive lymph nodes are detected at the time of surgery, the procedure is abandoned, and the patient receives adjuvant chemoradiation therapy and is spared also undergoing a radical surgical procedure. The sensitivity for detecting metastases at frozen section varies depending on the method of sectioning the lymph nodes and appears to be better in high volume centres. In general, frozen section has low sensitivity (47%-56%)<sup>132,133</sup> for detecting clinically relevant metastases.<sup>132-134</sup> In addition, performing frozen section on all SLNs is resource heavy and may not be feasible in under resourced areas. It may be more efficient to only send clinically or radiologically suspicious lymph nodes for frozen section evaluation.

The size of lymph nodes with metastatic carcinoma has been reported to be a prognostic factor in one study; patients with lymph nodes >15 mm in short-axis diameter had significantly lower survival rates than nodes of smaller size.<sup>135</sup>

Lymph node ratio (LNR), the ratio of positive to negative lymph nodes, has been assessed in a wide range of different cancers. The significance of LNR in cervical carcinoma has only recently been evaluated and there is insufficient evidence to include this as a data item in the current dataset. However, in early stage cervical cancer, the LNR identifies node-positive patients with a worse prognosis<sup>136</sup> and has been found to be an independent prognostic indicator of overall survival and disease-free survival in patients with SCC.<sup>137</sup>

There are very few studies that assess the significance of extracapsular/extranodal spread of metastatic cervical carcinoma, and the item has not been included in this dataset. One study showed extracapsular spread to correlate with advanced stage disease, the number of involved nodes and the size of metastatic deposits.<sup>138</sup> In another study, patients with extracapsular lymph node spread had a significantly lower 5 year recurrence-free survival rate compared to patients whose nodes showed no extracapsular spread.<sup>139</sup>

The lymph node parameters, LNR and extracapsular spread have not been included as specific data items due to a lack of supporting evidence. However, as indicated above, individual pathologists or institutions may choose to include some or all these items in their own protocols. This may be useful for prospective data collection.

 [Back](#)

## **Note 15 – Coexistent pathology/precursor lesions (Core and Non-core)**

Carcinomas of the cervix are often associated with premalignant precursor lesions, which are mostly squamous or glandular in type. Their pathology is well described and illustrated in the WHO 2020 Classification and a number of reviews.<sup>4,140,141</sup> There are also numerous benign squamous or glandular lesions which can be broadly classified as inflammatory, metaplastic and neoplastic. Their importance is in recognising the lesions as benign as they can morphologically mimic premalignant or malignant glandular or squamous lesions and result in a false positive diagnosis.

It is important to report co-existing premalignant lesions and document whether they involve resection margins since this may influence patient management and follow up. Most clearly defined premalignant lesions are caused by HPV. The terminology of HPV-associated premalignant squamous lesions was revised in the 2014 WHO Classification to squamous intraepithelial lesion (SIL).<sup>25</sup> The change also harmonises with The Bethesda System<sup>142</sup> for the reporting of cytological abnormalities in cervical smears. SILs are divided into low grade SIL (LSIL) which is a viral infection with a high spontaneous resolution rate, and HSIL which is a true premalignant lesion that can progress to SCC. The corresponding cervical intraepithelial neoplasia (CIN) terms can be included in parentheses.

Adenocarcinoma in situ (AIS) HPV-associated is the precursor lesion of usual HPV-related cervical ACA. High grade cervical glandular intraepithelial neoplasia (HG CGIN) is an alternative terminology used in some jurisdictions.<sup>143</sup> SMILE is a variant of AIS (and should be coded as such) according to the WHO 2020 Classification<sup>4</sup> but others consider it a form of high grade reserve cell dysplasia and report it separately.<sup>144,145</sup>

In the WHO 2020 Classification, the precursor lesions of HPV-independent gastric-type cervical ACA is listed as AIS, HPV-independent.<sup>4</sup> Atypical lobular endocervical glandular hyperplasia (ALEGH) and gastric-type AIS comprise these precursor lesions.<sup>146,147</sup>

 [Back](#)

## **Note 16 – Ancillary studies (Non-core)**

Ancillary testing is becoming increasingly important for diagnosis and treatment across all tumour types. In the cervix, immunohistochemistry for p16 and in-situ hybridisation for *HPV* play vital roles in the diagnostic setting, and PD-L1 immunohistochemistry is necessary to determine eligibility for immunotherapy in treating recurrent/metastatic cervical cancer. In low resource countries, it may not be possible to perform immunohistochemical or molecular studies; however, histochemical stains can also be of value in certain situations.

Given the importance of the performance and accuracy of these markers, one should ensure proper, timely fixation of surgical specimens. It is also recommended that the best representative block(s) be designated in the pathology report block key to facilitate any future testing.

## Human papillomavirus (HPV) testing

Human papillomavirus (HPV) is universally accepted to play a key aetiological role in cervical carcinogenesis. HPV is detectable in over 95% of pre-invasive and invasive cervical carcinomas, with HPV 16 and 18 being the most frequent types.<sup>148</sup> Molecular testing for HPV is useful for separating HPV-associated and HPV-independent cervical cancer. It may also be useful in confirming metastatic HPV-associated cervical neoplasms.

## Immunohistochemistry

It is beyond the scope of this document to provide a detailed review of the immunophenotype of cervical neoplasms, but some relevant issues should be noted.

### p16 Immunohistochemistry

Diffuse immunoreactivity (nuclear and cytoplasmic) for p16 is a surrogate marker of integrated high-risk HPV and is seen in malignant or high grade, premalignant epithelial lesions associated with high-risk HPV infections.<sup>149</sup> In high grade squamous intraepithelial lesions, the staining is typically contiguous involving two-thirds to full thickness of the epithelium, referred to as 'block type' immunoreactivity. p16 is useful in the separation of HPV-associated and HPV-independent cervical cancers. AIS and high-risk HPV-associated cervical cancers also show strong diffuse p16 nuclear and cytoplasmic staining in nearly all tumour cells (close to 100%). However, it should be noted that other gynaecological malignancies, for example uterine serous carcinoma and high grade serous carcinoma of the ovary/fallopian tube typically exhibit strong diffuse immunoreactivity with p16. This should be distinguished from focal/patchy (so-called 'mosaic-type') staining, which is not in keeping with a high-risk HPV-associated neoplasm.

### Immunohistochemistry: Cervical versus endometrial adenocarcinoma

Immunohistochemistry can be helpful in the differential diagnosis between a cervical and an endometrial ACA.<sup>150</sup> In the distinction between an endometrial and a cervical origin for an ACA, the panels of markers which are useful will depend on the morphological type and not just the site of origin. In the distinction between a high-risk HPV-associated (usual type) cervical ACA and a low grade endometrial endometrioid ACA, the most useful immunohistochemical markers are p16 and hormone receptors (estrogen receptor and progesterone receptor) with cervical ACAs exhibiting diffuse (near every cell) immunoreactivity with p16 and usually negative or only focally positive staining with hormone receptors (with occasional exceptions). In contrast, low grade endometrial endometrioid ACAs are usually diffusely positive with hormone receptors and exhibit patchy 'mosaic-type' staining with p16. Even when low grade endometrial endometrioid ACAs exhibit diffuse positivity with p16, this is still usually patchy with alternating positive and negative areas. Vimentin (usually positive in low grade endometrial endometrioid ACA and negative in cervical ACAs) and CEA (usually positive in cervical ACAs and negative in low grade endometrial endometrioid ACAs) may also be of value. However, it should be emphasised that there may be unexpected positive and negative staining reactions with any of the markers. HPV studies will be of value in such cases.

In the distinction between a high-risk HPV-associated (usual type) cervical ACA and a high grade endometrial ACA, p16 and hormone receptors are often of limited value. p53 immunohistochemistry and HPV studies may be of value in this scenario. Most uterine serous carcinomas and many other high grade endometrial carcinomas exhibit mutation-type p53 staining ('all or nothing' staining) and are HPV negative. High-risk HPV-related cervical ACAs rarely, if ever, exhibit 'mutation-type' p53 expression.

### Immunohistochemistry of HPV-independent cervical adenocarcinomas

Human papillomavirus (HPV)-independent cervical ACAs have a different immunophenotype than usual HPV-associated ACAs. They tend to be negative or only focally positive with p16 and some, such as gastric type ACAs, may exhibit mutation-type staining with p53.<sup>151</sup> Gastric type ACAs are usually positive with gastric markers such as MUC6 and HIK1083 and are flat negative with hormone receptors.<sup>151</sup> There is no specific immunohistochemical marker of mesonephric ACAs but they tend to be flat negative with hormone receptors and may stain with CD10, TTF1 and GATA3.<sup>152,153</sup> Clear cell carcinomas are usually

hormone receptor negative, exhibit wild-type staining with p53 and may be positive with napsin A and hepatocyte nuclear factor 1-beta.

#### Immunohistochemistry of cervical neuroendocrine carcinomas

Cervical NECs are variably positive with the neuroendocrine markers chromogranin A, CD56, synaptophysin and INSM1. Of these, INSM1<sup>154</sup> and synaptophysin are highly sensitive and specific, while CD56 is sensitive but lacks specificity. Chromogranin A is the most specific neuroendocrine marker but lacks sensitivity with only about 50% of these neoplasms being positive.<sup>52</sup> Chromogranin A positivity is often very focal in small cell NECs with punctate cytoplasmic immunoreactivity which is only visible on high-power magnification. A diagnosis of small cell NEC can be made in the absence of neuroendocrine marker positivity if the morphological appearances are typical. Small cell NEC may be only focally positive (often punctate cytoplasmic staining) or even negative with broad-spectrum cytokeratins. A diagnosis of large cell NEC requires neuroendocrine marker positivity and most of these neoplasms are diffusely positive with broad-spectrum cytokeratins.

A high percentage of primary cervical NECs are TTF1 positive, including some with diffuse immunoreactivity, and this marker is of no value in the distinction from a pulmonary metastasis.<sup>52</sup> Most cervical NECs are diffusely positive with p16 secondary to the presence of high-risk HPV.<sup>52</sup> Diffuse p63 nuclear positivity is useful in confirming a small cell variant of squamous carcinoma rather than small cell NEC. However, occasional cervical NECs exhibit p63 nuclear immunoreactivity.<sup>52</sup>

#### PD-L1

PD-L1 immunostaining is approved as a biomarker for anti-PD-1-based immunotherapy in some countries.<sup>155-160</sup> The United States Food and Drug Administration has approved the use of immunotherapy based on the Combined Positive Score (CPS), which comprises membranous staining in tumour cells as well as membranous or cytoplasmic staining in tumour-associated (both immediately peritumoural and intratumoural) lymphocytes and macrophages.<sup>155-157</sup> Importantly, PD-L1 expression in inflammatory cells associated with normal adjacent epithelium and dysplasia should not be included in this assessment, nor should inflammation in stroma distant from the tumour. The CPS is averaged across the entire tumour, rather than focused exclusively on hot spots. The CPS equation is as follows: ((PD-L1-positive tumour cells + lymphocytes + macrophages)/(total number of tumour cells)) x100. The maximum CPS is 100.

#### Histochemical stains for mucin detection

Mucicarmine, PAS or alcian blue can be used to detect intracytoplasmic mucin in tumours that are morphologically ambiguous (squamous vs adenocarcinoma). This may be particularly helpful in differentiating between HSIL and SMILE or between squamous cell carcinoma and poorly differentiated adenocarcinoma or between squamous cell carcinoma and iSMC. Gastric type adenocarcinoma expresses neutral gastric mucin that stains bright pink/magenta with the combined PAS/alcian blue stain, while endocervical and intestinal type acidic mucin stains dark blue/navy. This can be a helpful tool in detecting gastric type mucin in glandular neoplasias and preneoplastic lesions.

 [Back](#)

## **Note 17 – Pathologically confirmed distant metastases (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.

 [Back](#)

## Note 18 – Provisional pathological staging (Core)

The ‘pathological staging’ must be provided on the pathology report and is therefore a core element. The term ‘provisional pathological staging’ is used in this dataset to indicate that the stage that is provided may not represent the final tumour stage which should be determined at the multidisciplinary tumour board meeting where all the pathological, clinical and radiological features are available.<sup>2,3,79,80</sup>

The latest version of either FIGO *or* TNM staging, *or* both, can be used depending on local preferences.<sup>2,3,79,80</sup> The FIGO Staging System is in widespread use internationally and is the system used in most clinical trials and research studies. However, UICC or AJCC versions of TNM are used or mandated in many parts of the world.<sup>79,80</sup> 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 8<sup>th</sup> edition systems are broadly concurrent.

A new FIGO Staging System for cervical cancer was introduced in 2018.<sup>2,3</sup> The main changes from the prior 2009 FIGO Staging System are outlined below and summarised in Table 2:

- The horizontal dimension of 7 mm is no longer considered in defining the upper boundary of a Stage IA carcinoma.
- Stage IB has been subdivided into IB1, IB2 and IB3 based on maximum tumour size.
- Nodal status is included; the presence of nodal involvement upstages a tumour to Stage IIIC, with IIIC1 indicating pelvic and IIIC2 indicating para-aortic nodal involvement. As discussed, the revised FIGO Staging System is now more closely aligned with the TNM Classification.
- Prior FIGO Staging Systems were based mainly on clinical examination, while the 2018 Staging System allows imaging and pathology findings to be taken into account to supplement clinical staging with respect to tumour size and extent in all stages. The notation of r (imaging) or p (pathology) should indicate the parameters that are used to allocate the case to Stage IIIC; for example, if imaging indicates pelvic lymph node metastasis, the stage would be Stage IIIC1r, and if confirmed by pathologic findings, it would be Stage IIIC1p.

**Table 2: 2009 and 2018 International Federation of Gynaecology and Obstetrics (FIGO) staging of carcinoma of the cervix uteri.<sup>a</sup>**

FIGO staging of carcinoma of the cervix uteri		
	2009	2018
<b>Stage I</b>	Carcinoma is strictly confined to the cervix (extension to the corpus would be disregarded).	The carcinoma is strictly confined to the cervix (extension to the corpus should be disregarded).
<b>IA</b>	Invasive cancer identified only by microscopy, with deepest invasion $\leq 5$ mm and largest extension $\leq 7$ mm.	Invasive carcinoma that can be diagnosed only by microscopy with maximum depth of invasion $\leq 5$ mm. <sup>b</sup>
<b>IA1</b>	Measured stromal invasion $\leq 3.0$ mm in depth and extension $\leq 7$ mm.	Measured stromal invasion $\leq 3$ mm in depth.
<b>IA2</b>	Measured stromal invasion $> 3$ mm and $\leq 5$ mm with an extension $\leq 7$ mm.	Measured stromal invasion $> 3$ mm and $\leq 5$ mm in depth.
<b>IB</b>	Clinically visible lesions limited to the cervix uteri or preclinical lesions greater than Stage IA.	Invasive carcinoma with measured deepest invasion $> 5$ mm (greater than Stage IA); lesion limited to the cervix uteri with size measured by maximum tumour diameter. <sup>c</sup>
<b>IB1</b>	Clinically visible lesions $\leq 4$ cm in greatest diameter.	Invasive carcinoma $> 5$ mm depth of stromal invasion and $\leq 2$ cm in greatest dimension.
<b>IB2</b>	Clinically visible lesions $> 4$ cm in greatest diameter.	Invasive carcinoma $> 2$ cm and $\leq 4$ cm in greatest dimension.
<b>IB3</b>		Invasive carcinoma $> 4$ cm in greatest dimension.
<b>Stage II</b>	Cervical carcinoma extends beyond the uterus, but not to the pelvic wall or to the lower third of the vagina.	The cervical carcinoma invades beyond the uterus, but has not extended onto the lower third of the vagina or to the pelvic wall.
<b>IIA</b>	Without parametrial invasion.	Involvement limited to the upper two-thirds of the vagina without parametrial involvement.
<b>IIA1</b>	Clinically visible lesion $\leq 4.0$ cm in greatest diameter.	Invasive carcinoma $\leq 4$ cm in greatest dimension.
<b>IIA2</b>	Clinically visible lesion $> 4$ cm in greatest dimension.	Invasive carcinoma $> 4$ cm in greatest dimension.
<b>IIB</b>	With obvious parametrial invasion.	With parametrial involvement but not up to the pelvic wall.
<b>Stage III</b>	The tumour extends to the pelvic wall and/or involves lower third of the vagina and/or causes hydronephrosis or non-functioning kidney. On rectal examination, there is no cancer-free space between the tumour and the pelvic wall.	The carcinoma involves the lower third of the vagina and/or extends to the pelvic wall and/or causes hydronephrosis or non-functioning kidney and/or involves pelvic and/or para-aortic lymph nodes.
<b>IIIA</b>	No extension to the pelvic wall but involvement of the lower third of vagina.	Carcinoma involves the lower third of the vagina, with no extension to the pelvic wall.
<b>IIIB</b>	Extension on to pelvic wall and/or hydronephrosis or non-functioning kidney.	Extension to the pelvic wall and/or hydronephrosis or non-functioning kidney (unless known to be due to another cause).
<b>IIIC</b>		Involvement of pelvic and/or para-aortic lymph nodes (including micrometastases), <sup>d</sup> irrespective of tumour size and extent (with r and p notations). <sup>e</sup>
<b>IIIC1</b>		Pelvic lymph node metastasis only.
<b>IIIC2</b>		Para-aortic lymph node metastasis.



<b>Stage IV</b>	The carcinoma has extended beyond the true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum. A bullous oedema, as such, does not permit a case to be allotted to Stage IV.	The carcinoma has extended beyond the true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum. A bullous edema, as such, does not permit a case to be allotted to Stage IV.
<b>IVA</b>	Spread of growth to adjacent organs.	Spread of the growth to adjacent organs.
<b>IVB</b>	Spread to distant organs.	Spread to distant organs.
<b>Notes</b>		
<sup>a</sup> Differences in the two staging systems are highlighted in red text.		
		<sup>b</sup> Imaging and pathology can be used, when available, to supplement clinical findings with respect to tumour size and extent, in all stages. Pathological findings supersede imaging and clinical findings. <sup>c</sup> The involvement of vascular/lymphatic spaces should not change the staging. The lateral extent of the lesion is no longer considered. <sup>d</sup> Isolated tumour cells do not change the stage but their presence should be recorded <sup>e</sup> Adding notation of r (imaging) and p (pathology), to indicate the findings that are used to allocate the case to Stage IIIC. For example, if imaging indicates pelvic lymph node metastasis, the stage allocation would be Stage IIIC1r; if confirmed by pathological findings, it would be Stage IIIC1p. The type of imaging modality or pathology technique used should always be documented. When in doubt, the lower staging should be assigned.

There are several difficulties inherent in the staging of carcinoma of the uterine cervix as follows:<sup>2,3</sup>

1. There are difficulties in obtaining precise tumour measurements in low-stage disease (FIGO Stage IA and IB); this has been discussed in **Note 6 TUMOUR DIMENSIONS**.
2. Clinical staging, as previously recommended by FIGO, may under- or overestimate true anatomical extent of disease as it does not include information obtained from post-surgical pathology specimens or radiological/surgical techniques which may not be universally available. Reliance on clinical staging tends to occur in underdeveloped or under-resourced countries where surgical facilities and ancillary investigations (such as radiology and pathology) may be limited.<sup>2,3</sup> A provisional FIGO stage should be provided on the pathology report but the definitive stage is assigned at the multidisciplinary tumour board meeting.

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, 5<sup>th</sup> edition (C Wittekind et al. editors) may be of assistance when staging.<sup>161</sup>

 **Back**

## References

- 1 Merlin T, Weston A and Tooher R (2009). Extending an evidence hierarchy to include topics other than treatment: revising the Australian 'levels of evidence'. *BMC Med Res Methodol* 9:34.
- 2 Bhatla N, Aoki D, Sharma DN and Sankaranarayanan R (2018). Cancer of the cervix uteri. *Int J Gynaecol Obstet* 143 Suppl 2:22-36.
- 3 Bhatla N, Berek JS, Cuello Fredes M, Denny LA, Grenman S, Karunaratne K, Kehoe ST, Konishi I, Olawaiye AB, Prat J, Sankaranarayanan R, Brierley J, Mutch D, Querleu D, Cibula D, Quinn M, Botha H, Sigurd L, Rice L, Ryu HS, Ngan H, Maenpaa J, Andrijono A, Purwoto G, Maheshwari A, Bafna UD, Plante M and Natarajan J (2019). Revised FIGO staging for carcinoma of the cervix uteri. *Int J Gynaecol Obstet* 145(1):129-135.
- 4 WHO Classification of Tumours Editorial Board (2020). *Female Genital Tumours, WHO Classification of Tumours, 5th Edition, Volume 4*. IARC Press, Lyon.
- 5 WHO Classification of Tumours Editorial Board (2021). *Female Genital Tumours, WHO Classification of Tumours, 5th Edition, Volume 4 - Corrigenda June 2021*. Available from: <https://publications.iarc.fr/Book-And-Report-Series/Who-Classification-Of-Tumours/Female-Genital-Tumours-2020> (Accessed 16th June 2021).
- 6 Landoni F, Maneo A, Colombo A, Placa F, Milani R, Perego P, Favini G, Ferri L and Mangioni C (1997). Randomised study of radical surgery versus radiotherapy for stage Ib-IIa cervical cancer. *Lancet* 350(9077):535-540.
- 7 Benedet JL, Odicino F, Maisonneuve P, Beller U, Creasman WT, Heintz AP, Ngan HY and Pecorelli S (2003). Carcinoma of the cervix uteri. *Int J Gynaecol Obstet* 83 Suppl 1:41-78.
- 8 Mabuchi S, Isohashi F, Yoshioka Y, Temma K, Takeda T, Yamamoto T, Enomoto T, Morishige K, Inoue T and Kimura T (2010). Prognostic factors for survival in patients with recurrent cervical cancer previously treated with radiotherapy. *Int J Gynecol Cancer* 20(5):834-840.
- 9 McCluggage WG, Hurrell DP and Kennedy K (2010). Metastatic carcinomas in the cervix mimicking primary cervical adenocarcinoma and adenocarcinoma in situ: report of a series of cases. *Am J Surg Pathol* 34(5):735-741.
- 10 Monnier L, Touboul E, Darai E, Lefranc JP, Lauratet B, Ballester M and Huguet F (2016). [Stage IB2, IIA and IIB cervical carcinoma without lymph node extension treated with neoadjuvant chemoradiotherapy]. *Bull Cancer* 103(2):164-172.
- 11 Musaev A, Guzel AB, Khatib G, Gulec UK, Vardar MA, Altintas A and Gumurdulu D (2015). Assessment of primary radical hysterectomy and neoadjuvant chemotherapy followed by radical hysterectomy in Stage IB2, IIA bulky cervical cancer. *Eur J Gynaecol Oncol* 36(5):579-584.
- 12 Cibula D, Pötter R, Planchamp F, Avall-Lundqvist E, Fischerova D, Haie Meder C, Köhler C, Landoni F, Lax S, Lindegaard JC, Mahantshetty U, Mathevet P, McCluggage WG, McCormack M, Naik R, Nout R, Pignata S, Ponce J, Querleu D, Raspagliesi F, Rodolakis A, Tamussino K, Wimberger P and Raspollini MR (2018). The European Society of Gynaecological Oncology/European Society for Radiotherapy and Oncology/European Society of Pathology guidelines for the management of patients with cervical cancer. *Radiother Oncol* 127(3):404-416.

- 13 Raspollini MR, Lax SF and McCluggage WG (2018). The central role of the pathologist in the management of patients with cervical cancer: ESGO/ESTRO/ESP guidelines. *Virchows Arch* 473(1):45-54.
- 14 Trimpos JB, Lambeek AF, Peters AA, Wolterbeek R, Gaarenstroom KN, Fleuren GJ and Kenter GG (2004). Prognostic difference of surgical treatment of exophytic versus barrel-shaped bulky cervical cancer. *Gynecol Oncol* 95(1):77-81.
- 15 Mileschkin L, Paramanathan A, Kondalsamy-Chennakesavan S, Bernshaw D, Khaw P and Narayan K (2014). Smokers with cervix cancer have more uterine corpus invasive disease and an increased risk of recurrence after treatment with chemoradiation. *Int J Gynecol Cancer* 24(7):1286-1291.
- 16 Kato T, Watari H, Takeda M, Hosaka M, Mitamura T, Kobayashi N, Sudo S, Kaneuchi M, Kudo M and Sakuragi N (2013). Multivariate prognostic analysis of adenocarcinoma of the uterine cervix treated with radical hysterectomy and systematic lymphadenectomy. *J Gynecol Oncol* 24(3):222-228.
- 17 Salvo G, Odetto D, Saez Perrotta MC, Noll F, Perrotta M, Pareja R, Wernicke A and Ramirez PT (2020). Measurement of tumor size in early cervical cancer: an ever-evolving paradigm. *Int J Gynecol Cancer* 30(8):1215-1223.
- 18 Zyla RE, Gien LT, Vicus D, Olkhov-Mitsel E, Mirkovic J, Nofech-Mozes S, Djordjevic B and Parra-Herran C (2020). The prognostic role of horizontal and circumferential tumor extent in cervical cancer: Implications for the 2019 FIGO staging system. *Gynecol Oncol* 158(2):266-272.
- 19 Sedlis A, Bundy BN, Rotman MZ, Lentz SS, Muderspach LI and Zaino RJ (1999). A randomized trial of pelvic radiation therapy versus no further therapy in selected patients with stage IB carcinoma of the cervix after radical hysterectomy and pelvic lymphadenectomy: A Gynecologic Oncology Group Study. *Gynecol Oncol* 73(2):177-183.
- 20 Plante M, Gregoire J, Renaud MC and Roy M (2011). The vaginal radical trachelectomy: an update of a series of 125 cases and 106 pregnancies. *Gynecol Oncol* 121(2):290-297.
- 21 Park JY, Joo WD, Chang SJ, Kim DY, Kim JH, Kim YM, Kim YT and Nam JH (2014). Long-term outcomes after fertility-sparing laparoscopic radical trachelectomy in young women with early-stage cervical cancer: an Asan Gynecologic Cancer Group (AGCG) study. *J Surg Oncol* 110(3):252-257.
- 22 Turan T, Yildirim BA, Tulunay G, Boran N and Kose MF (2010). Prognostic effect of different cut-off values (20mm, 30mm and 40mm) for clinical tumor size in FIGO stage IB cervical cancer. *J Surg Oncol* 19(2):106-113.
- 23 Horn LC, Bilek K, Fischer U, Eimenkel J and Hentschel B (2014). A cut-off value of 2 cm in tumor size is of prognostic value in surgically treated FIGO stage IB cervical cancer. *Gynecol Oncol* 134(1):42-46.
- 24 Horn LC, Fischer U, Raptis G, Bilek K and Hentschel B (2007). Tumor size is of prognostic value in surgically treated FIGO stage II cervical cancer. *Gynecol Oncol* 107(2):310-315.
- 25 Darragh TM, Colgan TJ, Cox JT, Heller DS, Henry MR, Luff RD, McCalmont T, Nayar R, Palefsky JM, Stoler MH, Wilkinson EJ, Zaino RJ, Wilbur DC and Members of LAST Project Work Groups (2012). The Lower Anogenital Squamous Terminology Standardization Project for HPV-Associated Lesions: background and consensus recommendations from the College of American Pathologists and the American Society for Colposcopy and Cervical Pathology. *Int J Gynecol Pathol* 32:76-115.

- 26 McIlwaine P, Nagar H and McCluggage WG (2014). Multifocal FIGO stage 1A1 cervical squamous carcinomas have an extremely good prognosis equivalent to unifocal lesions. *Int J Gynecol Pathol* 33(3):213-217.
- 27 Day E, Duffy S, Bryson G, Syed S, Shanbhag S, Burton K, Lindsay R, Siddiqui N and Millan D (2016). Multifocal FIGO Stage IA1 squamous carcinoma of the cervix: criteria for identification, staging, and its good clinical outcome. *Int J Gynecol Pathol* 35(5):467-474.
- 28 Reich O, Pickel H, Tamussino K and Winter R (2001). Microinvasive carcinoma of the cervix: site of first focus of invasion. *Obstet Gynecol* 97(6):890-892.
- 29 Reich O and Pickel H (2002). Multifocal stromal invasion in microinvasive squamous cell carcinoma of the cervix: how to measure and stage these lesions. *Int J Gynecol Pathol* 21:416-417.
- 30 Hirschowitz L, Nucci M and Zaino RJ (2013). Problematic issues in the staging of endometrial, cervical and vulval carcinomas. *Histopathology* 62(1):176-202.
- 31 Pecorelli S, Zigliani L and Odicino F (2009). Revised FIGO staging for carcinoma of the cervix. *Int J Gynaecol Obstet*. 105(2):107-108. Epub 2009 Apr 2001.
- 32 Burghardt E, Baltzer J, Tulusan AH and Haas J (1992). Results of surgical treatment of 1028 cervical cancers studied with volumetry. *Cancer* 70(3):648-655.
- 33 Burghardt E and Holzer E (1977). Diagnosis and treatment of microinvasive carcinoma of the cervix uteri. *Obstet Gynecol* 49(6):641-653.
- 34 Trattner M, Graf AH, Lax S, Forstner R, Dandachi N, Haas J, Pickel H, Reich O, Staudach A and Winter R (2001). Prognostic factors in surgically treated stage ib-iiB cervical carcinomas with special emphasis on the importance of tumor volume. *Gynecol Oncol* 82(1):11-16.
- 35 Stolnicu S, Hoang L, Chiu D, Hanco-Bauer O, Terinte C, Pesci A, Aviel-Ronen S, Kiyokawa T, Alvarado-Cabrero I, Oliva E, Park KJ, Abu-Rustum NR and Soslow RA (2019). Clinical Outcomes of HPV-associated and Unassociated Endocervical Adenocarcinomas Categorized by the International Endocervical Adenocarcinoma Criteria and Classification (IECC). *Am J Surg Pathol* 43(4):466-474.
- 36 Nicolás I, Marimon L, Barnadas E, Saco A, Rodríguez-Carunchio L, Fusté P, Martí C, Rodríguez-Trujillo A, Torne A, Del Pino M and Ordi J (2019). HPV-negative tumors of the uterine cervix. *Mod Pathol* 32(8):1189-1196.
- 37 Casey S, Harley I, Jamison J, Molijn A, van den Munckhof H and McCluggage WG (2015). A rare case of HPV-negative cervical squamous cell carcinoma. *Int J Gynecol Pathol* 34(2):208-212.
- 38 Hodgson A, Park KJ, Djordjevic B, Howitt BE, Nucci MR, Oliva E, Stolnicu S, Xu B, Soslow RA and Parra-Herran C (2019). International Endocervical Adenocarcinoma Criteria and Classification: validation and interobserver reproducibility. *Am J Surg Pathol* 43(1):75-83.
- 39 Stolnicu S, Barsan I, Hoang L, Patel P, Terinte C, Pesci A, Aviel-Ronen S, Kiyokawa T, Alvarado-Cabrero I, Pike MC, Oliva E, Park KJ and Soslow RA (2018). International Endocervical Adenocarcinoma Criteria and Classification (IECC): A new pathogenetic classification for invasive adenocarcinomas of the endocervix. *Am J Surg Pathol* 42(2):214-226.

- 40 Mills AM, Liou S, Kong CS and Longacre TA (2012). Are women with endocervical adenocarcinoma at risk for lynch syndrome? Evaluation of 101 cases including unusual subtypes and lower uterine segment tumors. *Int J Gynecol Pathol* 31(5):463-469.
- 41 Howitt BE, Herfs M, Brister K, Oliva E, Longtine J, Hecht JL and Nucci MR (2013). Intestinal-type endocervical adenocarcinoma in situ: an immunophenotypically distinct subset of AIS affecting older women. *Am J Surg Pathol* 37(5):625-633.
- 42 Vang R, Gown AM, Farinola M, Barry TS, Wheeler DT, Yemelyanova A, Seidman JD, Judson K and Ronnett BM (2007). p16 expression in primary ovarian mucinous and endometrioid tumors and metastatic adenocarcinomas in the ovary: utility for identification of metastatic HPV-related endocervical adenocarcinomas. *Am J Surg Pathol* 31(5):653-663.
- 43 Stolnicu S, Boros M, Segura S, Horn LC, Parra-Herran C, Oliva E, Abu-Rustum N, Soslow RA and Park KJ (2020). Invasive stratified mucinous carcinoma (iSMC) of the cervix often presents with high-risk features that are determinants of poor outcome: an international multicenter study. *Am J Surg Pathol* 44(10):1374-1380.
- 44 Hodgson A, Olkhov-Mitsel E, Howitt BE, Nucci MR and Parra-Herran C (2019). International Endocervical Adenocarcinoma Criteria and Classification (IECC): correlation with adverse clinicopathological features and patient outcome. *J Clin Pathol* 72(5):347-353.
- 45 Stolnicu S, Hoang L, Hanko-Bauer O, Barsan I, Terinte C, Pesci A, Aviel-Ronen S, Kiyokawa T, Alvarado-Cabrero I, Oliva E, Park KJ and Soslow RA (2019). Cervical adenosquamous carcinoma: detailed analysis of morphology, immunohistochemical profile, and clinical outcomes in 59 cases. *Mod Pathol* 32(2):269-279.
- 46 Wong RW, Ng JHY, Han KC, Leung YP, Shek CM, Cheung KN, Choi CKM, Tse KY and Ip PPC (2020). Cervical carcinomas with serous-like papillary and micropapillary components: illustrating the heterogeneity of primary cervical carcinomas. *Mod Pathol* 34(1):207-221.
- 47 Look KY, Brunetto VL, Clarke-Pearson DL, Averette HE, Major FJ, Alvarez RD, Homesley HD and Zaino RJ (1996). An analysis of cell type in patients with surgically staged stage IB carcinoma of the cervix: a Gynecologic Oncology Group study. *Gynecol Oncol* 63(3):304-311.
- 48 Lea JS, Coleman RL, Garner EO, Duska LR, Miller DS and Schorge JO (2003). Adenosquamous histology predicts poor outcome in low-risk stage IB1 cervical adenocarcinoma. *Gynecol Oncol* 91(3):558-562.
- 49 Rindi G, Klimstra DS, Abedi-Ardekani B, Asa SL, Bosman FT, Brambilla E, Busam KJ, de Krijger RR, Dietel M, El-Naggar AK, Fernandez-Cuesta L, Klöppel G, McCluggage WG, Moch H, Ohgaki H, Rakha EA, Reed NS, Rous BA, Sasano H, Scarpa A, Scoazec JY, Travis WD, Tallini G, Trouillas J, van Krieken JH and Cree IA (2018). A common classification framework for neuroendocrine neoplasms: an International Agency for Research on Cancer (IARC) and World Health Organization (WHO) expert consensus proposal. *Mod Pathol* 31(12):1770-1786.
- 50 Horn LC, Hentschel B, Bilek K, Richter CE, Eibenkel J and Leo C (2006). Mixed small cell carcinomas of the uterine cervix: prognostic impact of focal neuroendocrine differentiation but not of Ki-67 labeling index. *Ann Diagn Pathol* 10(3):140-143.
- 51 Ganesan R, Hirschowitz L, Dawson P, Askew S, Pearmain P, Jones PW, Singh K, Chan KK and Moss EL (2016). Neuroendocrine carcinoma of the cervix: review of a series of cases and correlation with outcome. *Int J Surg Pathol* 24(6):490-496.

- 52 McCluggage WG, Kennedy K and Busam KJ (2010). An immunohistochemical study of cervical neuroendocrine carcinomas: Neoplasms that are commonly TTF1 positive and which may express CK20 and P63. *Am J Surg Pathol* 34(4):525-532.
- 53 Inzani F, Santoro A, Angelico G, Feraco A, Spadola S, Arciuolo D, Valente M, Carlino A, Piermattei A, Scaglione G, Scambia G, Rindi G and Zannoni GF (2020). Neuroendocrine carcinoma of the uterine cervix: a clinicopathologic and immunohistochemical study with focus on novel markers (Sst2-Sst5). *Cancers (Basel)* 12(5).
- 54 Fritz A, Percy C, Jack A, Shanmugaratnam K, Sobin LH, Parkin DM, Whelan SL (eds) (2020). *International Classification of Diseases for Oncology, Third Edition, Second revision ICD-O-3.2*. Available from: [http://www.iacr.com.fr/index.php?option=com\\_content&view=category&layout=blog&id=100&Itemid=577](http://www.iacr.com.fr/index.php?option=com_content&view=category&layout=blog&id=100&Itemid=577) (Accessed 21st January 2021).
- 55 Benda JA (1996). Histopathologic prognostic factors in early stage cervical carcinoma. *J Natl Cancer Inst Monogr*(21):27-34.
- 56 Zaino R, Ward S, Delgado G, Bundy B, Gore H, Fetter G, Ganjei P and Fraumeni E (1992). Histopathologic predictors of the behavior of surgically treated Stage IB squamous cell carcinoma of the cervix. A gynecologic oncology group study. *Cancer* 69(7):1750-1758.
- 57 Tiltman AJ (2005). The pathology of cervical tumours. *Best Pract Res Clin Obstet Gynaecol* 19(4):485-500.
- 58 Delgado G, Bundy B, Zaino R, Sevin BU, Creasman WT and Major F (1990). Prospective surgical-pathological study of disease-free interval in patients with stage IB squamous cell carcinoma of the cervix: a Gynecologic Oncology Group study. *Gynecol Oncol* 38:352-357.
- 59 Vinh-Hung V, Bourgain C, Vlastos G, Cserni G, De Ridder M, Storme G and Vlastos AT (2007). Prognostic value of histopathology and trends in cervical cancer: a SEER population study. *BMC Cancer* 7:164.
- 60 Macdonald OK, Chen J, Dodson M, Lee CM and Gaffney DK (2009). Prognostic significance of histology and positive lymph node involvement following radical hysterectomy in carcinoma of the cervix. *Am J Clin Oncol* 32(4):411-416.
- 61 Talia KL, Oliva E, Rabban JT, Singh N, Stolnicu S and McCluggage WG (2021). Grading of endocervical adenocarcinomas: review of the literature and recommendations from the International Society of Gynecological Pathologists. *Int J Gynecol Pathol* 40(Suppl 1):S66-S74.
- 62 Chen JH, Duan H, Yu XB, Zhao HW, Chen X, Li P, Li ZQ, Li BX, Pan LY, Yan X and Chen C (2021). Clinical features and prognostic factors of cervical villoglandular adenocarcinoma. *Int J Gynecol Cancer* 31(4):512-517.
- 63 Kojima A, Mikami Y, Sudo T, Yamaguchi S, Kusanagi Y, Ito M and Nishimura R (2007). Gastric morphology and immunophenotype predict poor outcome in mucinous adenocarcinoma of the uterine cervix. *Am J Surg Pathol* 31(5):664-672.
- 64 Karamurzin YS, Kiyokawa T, Parkash V, Jotwani AR, Patel P, Pike MC, Soslow RA and Park KJ (2015). Gastric-type endocervical adenocarcinoma: an aggressive tumor with unusual metastatic patterns and poor prognosis. *Am J Surg Pathol* 39(11):1449-1457.

- 65 Stoler M, Bergeron C and Colgan TJ et al (2014). Squamous cell tumours and precursors. In: *WHO Classification of Tumours of Female Reproductive Organs, 4th ed.*, Kurman RJ, Carcangiu ML, Herrington CS and Young RH (eds), IARC, Lyon, 172-182.
- 66 Broders AC (1920). Squamous cell cancer of the lip: a study of five hundred and thirty-seven cases. *JAMA* 74:656-664.
- 67 McLellan R, Dillon MB, Woodruff JD, Heatley GJ, Fields AL and Rosenshein NB (1994). Long-term follow-up of stage I cervical adenocarcinoma treated by radical surgery. *Gynecol Oncol* 52(2):253-259.
- 68 Goodman HM, Buttlar CA, Niloff JM, Welch WR, Marck A, Feuer EJ, Lahman EA, Jenison EL and Knapp RC (1989). Adenocarcinoma of the uterine cervix: prognostic factors and patterns of recurrence. *Gynecol Oncol* 33(2):241-247.
- 69 Lea JS, Sheets EE, Wenham RM, Duska LR, Coleman RL, Miller DS and Schorge JO (2002). Stage IIB-IVB cervical adenocarcinoma: prognostic factors and survival. *Gynecol Oncol* 84(1):115-119.
- 70 Eifel PJ, Morris M, Oswald MJ, Wharton JT and Delclos L (1990). Adenocarcinoma of the uterine cervix. Prognosis and patterns of failure in 367 cases. *Cancer* 65(11):2507-2514.
- 71 Baalbergen A, Ewing-Graham PC, Hop WC, Struijk P and Helmerhorst TJ (2004). Prognostic factors in adenocarcinoma of the uterine cervix. *Gynecol Oncol* 92(1):262-267.
- 72 Alfsen GC, Kristensen GB, Skovlund E, Pettersen EO and Abeler VM (2001). Histologic subtype has minor importance for overall survival in patients with adenocarcinoma of the uterine cervix. A population-based study of prognostic factors in 505 patients with nonsquamous cell carcinomas of the cervix. *Cancer* 92(9):2471-2483.
- 73 Leminen A, Paavonen J, Forss M, Wahlstrom T and Vesterinen E (1990). Adenocarcinoma of the uterine cervix. *Cancer* 65(1):53-59.
- 74 Satabongkoch N, Khunamornpong S, Pongsuwareeyakul T, Settakorn J, Sukpan K, Soongkhaw A, intaraphet S, Suprasert P and Siriaunkgul S (2017). Prognostic value of tumor budding in early-stage cervical adenocarcinomas. *Asian Pac J Cancer Prev* 18(6):1717-1722.
- 75 Chargui R, Damak T, Khomsi F, Ben Hassouna J, Chaieb W, Hechiche M, Gamoudi A, Boussen H, Benna F and Rahal K (2006). Prognostic factors and clinicopathologic characteristics of invasive adenocarcinoma of the uterine cervix. *Am J Obstet Gynecol* 194(1):43-48.
- 76 Khalil J, Bellefqih S, Afif M, Elkacemi H, Kebdani T and Benjaafar N (2015). Prognostic factors affecting cervical adenocarcinoma: 10 years experience in a single institution. *Arch Gynecol Obstet* 292(4):915-921.
- 77 Rivera-Colon G, Chen H, Niu S, Lucas E, Holloway S, Carrick K, Gwin K, Lea J and Zheng W (2020). Cervical adenocarcinoma: histopathologic features from biopsies to predict tumor behavior. *Am J Surg Pathol* 44(2):247-254.
- 78 Nola M, Tomicic I, Dotlic S, Morovic A, Petroveckii M and Jukic S (2005). Adenocarcinoma of uterine cervix - prognostic significance of clinicopathologic parameters. *Croat Med J* 46(3):397-403.
- 79 Brierley JD, Gospodarowicz MK and Wittekind C (eds) (2016). *UICC TNM Classification of Malignant Tumours, 8th Edition*, Wiley, USA.



- 80 Olawaiye A, Mutch D, Bhosale P, Gress D, Vandenberg J, Rous B, Hagemann I, Otis C, Sullivan D and Washington M (eds) (2020). *AJCC Cancer Staging System for Cervix Uteri, Version 9*, Springer, New York.
- 81 Benson WL and Norris HJ (1977). A critical review of the frequency of lymph node metastasis and death from microinvasive carcinoma of the cervix. *Obstet Gynecol* 49(5):632-638.
- 82 Maiman MA, Fruchter RG, DiMaio TM and Boyce JG (1988). Superficially invasive squamous cell carcinoma of the cervix. *Obstet Gynecol* 72(3 Pt 1):399-403.
- 83 Delgado G, Bundy BN, Fowler WC, Jr., Stehman FB, Sevin B, Creasman WT, Major F, DiSaia P and Zaino R (1989). A prospective surgical pathological study of stage I squamous carcinoma of the cervix: a Gynecologic Oncology Group Study. *Gynecol Oncol* 35(3):314-320.
- 84 Copeland LJ, Silva EG, Gershenson DM, Morris M, Young DC and Wharton JT (1992). Superficially invasive squamous cell carcinoma of the cervix. *Gynecol Oncol* 45(3):307-312.
- 85 Buckley SL, Tritz DM, Van Le L, Higgins R, Sevin BU, Ueland FR, DePriest PD, Gallion HH, Bailey CL, Kryscio RJ, Fowler W, Averette H and van Nagell JR, Jr. (1996). Lymph node metastases and prognosis in patients with stage IA2 cervical cancer. *Gynecol Oncol* 63(1):4-9.
- 86 Obermair A, Wanner C, Bilgi S, Speiser P, Reisenberger K, Kaider A, Kainz C, Leodolter S, Breiteneker G and Gitsch G (1998). The influence of vascular space involvement on the prognosis of patients with stage IB cervical carcinoma: correlation of results from hematoxylin and eosin staining with results from immunostaining for factor VIII-related antigen. *Cancer* 82(4):689-696.
- 87 Morimura Y, Nishiyama H, Hashimoto T, Fujimori K, Yamada H, Yanagida K and Sato A (1999). Re-assessment of stage I uterine cervical carcinoma according to revised JSGO (1997) staging. *Fukushima J Med Sci* 45(2):109-116.
- 88 Elliott P, Coppleson M, Russell P, Liouros P, Carter J, MacLeod C and Jones M (2000). Early invasive (FIGO stage IA) carcinoma of the cervix: a clinico-pathologic study of 476 cases. *Int J Gynecol Cancer* 10(1):42-52.
- 89 Morice P, Piovesan P, Rey A, Atallah D, Haie-Meder C, Pautier P, Sideris L, Pomel C, Duvillard P and Castaigne D (2003). Prognostic value of lymphovascular space invasion determined with hematoxylin-eosin staining in early stage cervical carcinoma: results of a multivariate analysis. *Ann Oncol* 14(10):1511-1517.
- 90 Singh N and Arif S (2004). Histopathologic parameters of prognosis in cervical cancer - a review. *Int J Gynecol Cancer*. 14(5):741-750.
- 91 Benedet JL (1997). Cervical cancer staging systems: the endless debate. *Gynecol Oncol* 65(1):6-7.
- 92 Lee SW, Kim YM, Son WS, You HJ, Kim DY, Kim JH, Kim YT and Nam JH (2009). The efficacy of conservative management after conization in patients with stage IA1 microinvasive cervical carcinoma. *Acta Obstet Gynecol Scand* 88(2):209-215.
- 93 Ostor AG and Rome RM (1994). Micro-invasive squamous cell carcinoma of the cervix: a clinico-pathologic study of 200 cases with long-term follow-up. *Int J Gynecol Cancer* 4(4):257-264.
- 94 Robert ME and Fu YS (1990). Squamous cell carcinoma of the uterine cervix-a review with emphasis on prognostic factors and unusual variants. *Semin Diagn Pathol* 7(3):173-189.

- 95 Birner P, Obermair A, Schindl M, Kowalski H, Breitenecker G and Oberhuber G (2001). Selective immunohistochemical staining of blood and lymphatic vessels reveals independent prognostic influence of blood and lymphatic vessel invasion in early-stage cervical cancer. *Clin Cancer Res* 7(1):93-97.
- 96 Alexander-Sefre F, Singh N, Ayhan A, Salveson HB, Wilbanks G and Jacobs IJ (2003). Detection of tumour lymphovascular space invasion using dual cytokeratin and CD31 immunohistochemistry. *J Clin Pathol* 56(10):786-788.
- 97 Urabe A, Matsumoto T, Kimura M, Sonoue H and Kinoshita K (2006). Grading system of lymphatic invasion according to D2-40 immunostaining is useful for the prediction of nodal metastasis in squamous cell carcinoma of the uterine cervix. *Histopathology* 49(5):493-497.
- 98 Lim CS, Alexander-Sefre F, Allam M, Singh N, Aleong JC, Al-Rawi H and Jacobs IJ (2008). Clinical value of immunohistochemically detected lymphovascular space invasion in early stage cervical carcinoma. *Ann Surg Oncol* 15(9):2581-2588.
- 99 Sakuragi N, Takeda N, Hareyama H, Fujimoto T, Todo Y, Okamoto K, Takeda M, Wada S, Yamamoto R and Fujimoto S (2000). A multivariate analysis of blood vessel and lymph vessel invasion as predictors of ovarian and lymph node metastases in patients with cervical carcinoma. *Cancer* 88:2578-2583.
- 100 Narayan K, Fisher R and Bernshaw D (2006). Significance of tumor volume and corpus uteri invasion in cervical cancer patients treated by radiotherapy. *Int J Gynecol Cancer* 16:623-630.
- 101 Roma AA, Diaz De Vivar A, Park KJ, Alvarado-Cabrero I, Rasty G, Chanona-Vilchis JG, Mikami Y, Hong SR, Teramoto N, Ali-Fehmi R, Rutgers JK, Barbuto D and Silva EG (2015). Invasive endocervical adenocarcinoma: a new pattern-based classification system with important clinical significance. *Am J Surg Pathol* 39(5):667-672.
- 102 Diaz De Vivar A, Roma AA, Park KJ, Alvarado-Cabrero I, Rasty G, Chanona-Vilchis JG, Mikami Y, Hong SR, Arville B, Teramoto N, Ali-Fehmi R, Rutgers JK, Tabassum F, Barbuto D, Aguilera-Barrantes I, Shaye-Brown A, Daya D and Silva EG (2013). Invasive endocervical adenocarcinoma: proposal for a new pattern-based classification system with significant clinical implications: a multi-institutional study. *Int J Gynecol Pathol* 32(6):592-601.
- 103 Roma AA, Mistretta TA, De Vivar AD, Park KJ, Alvarado-Cabrero I, Rasty G, Chanona-Vilchis JG, Mikami Y, Hong SR, Teramoto N, Ali-Fehmi R, Barbuto D, Rutgers JK and Silva EG (2016). New pattern-based personalized risk stratification system for endocervical adenocarcinoma with important clinical implications and surgical outcome. *Gynecol Oncol* 141(1):36-42.
- 104 Rutgers JK, Roma AA, Park KJ, Zaino RJ, Johnson A, Alvarado I, Daya D, Rasty G, Longacre TA, Ronnett BM and Silva EG (2016). Pattern classification of endocervical adenocarcinoma: reproducibility and review of criteria. *Mod Pathol* 29(9):1083-1094.
- 105 Djordjevic B and Parra-Herran C (2016). Application of a pattern-based classification system for invasive endocervical adenocarcinoma in cervical biopsy, cone and loop electrosurgical excision (LEEP) material: pattern on cone and LEEP is predictive of pattern in the overall tumor. *Int J Gynecol Pathol* 35(5):456-466.

- 106 Stolnicu S, Barsan I, Hoang L, Patel P, Terinte C, Pesci A, Aviel-Ronen S, Kiyokawa T, Alvarado-Cabrero I, Oliva E, Park KJ, Abu-Rustum NR, Pike MC and Soslow RA (2018). Stromal invasion pattern identifies patients at lowest risk of lymph node metastasis in HPV-associated endocervical adenocarcinomas, but is irrelevant in adenocarcinomas unassociated with HPV. *Gynecol Oncol* 150(1):56-60.
- 107 Parra-Herran C, Taljaard M, Djordjevic B, Reyes MC, Schwartz L, Schoolmeester JK, Lastra RR, Quick CM, Laury A, Rasty G, Nucci MR and Howitt BE (2016). Pattern-based classification of invasive endocervical adenocarcinoma, depth of invasion measurement and distinction from adenocarcinoma in situ: interobserver variation among gynecologic pathologists. *Mod Pathol* 29(8):879-892.
- 108 Paquette C, Jeffus SK, Quick CM, Conaway MR, Stoler MH and Atkins KA (2015). Interobserver variability in the application of a proposed histologic subclassification of endocervical adenocarcinoma. *Am J Surg Pathol* 39(1):93-100.
- 109 Spaans VM, Scheunhage DA, Barzaghi B, de Kroon CD, Fleuren GJ, Bosse T and Jordanova ES (2018). Independent validation of the prognostic significance of invasion patterns in endocervical adenocarcinoma: Pattern A predicts excellent survival. *Gynecol Oncol* 151(2):196-201.
- 110 Khanna N, Rauh LA, Lachiewicz MP and Horowitz IR (2016). Margins for cervical and vulvar cancer. *J Surg Oncol* 113:304-309.
- 111 Viswanathan AN, Lee H, Hanson E, Berkowitz RS and Crum CP (2006). Influence of margin status and radiation on recurrence after radical hysterectomy in Stage IB cervical cancer. *Int. J. Radiation Oncology Biol. Phys* 65(5):1501-1507.
- 112 McCann GA, Taege SK, Boutsicaris CE, Phillips GS, Eisenhauer EL, Fowler JM, O'Malley DM, Copeland LJ, Cohn DE and Salani R (2013). The impact of close surgical margins after radical hysterectomy for early-stage cervical cancer. *Gynecol Oncol*. 128(1):44-48.
- 113 Tanquay C, Plante M, Renauld M-C, Roy M and Tetu B (2004). Vaginal radical trachelectomy in the treatment of cervical cancer: the role of frozen section. *Int J Gynecol Pathol* 23:170-175.
- 114 Andikyan V, Khoury-Collado F, Denesopolis J, Park KJ, Hussein YR, Brown CL, Sonoda Y, Chi DS, Barakat RR and Abu-Rustum NR (2014). Cervical conization and sentinel lymph node mapping in the treatment of stage I cervical cancer: is less enough? *Int J Gynecol Cancer* 24(1):113-117.
- 115 Tierney KE, Lin PS, Amezcua C, Matsuo K, Ye W, Felix JC and Roman LD (2014). Cervical conization of adenocarcinoma in situ: a predicting model of residual disease. *Am J Obstet Gynecol* 210(4):366.e361-365.
- 116 Lea JS, Shin CH, Sheets EE, Coleman RL, Gehrig PA, Duska LR, Miller DS and Schorge JO (2002). Endocervical curettage at conization to predict residual cervical adenocarcinoma in situ. *Gynecol Oncol* 87(1):129-132.
- 117 Uno T, Ito H, Itami J, Yasuda S, Isobe K, Hara R, Sato T, Minoura S, Shigematsu N and Kubo A (2000). Postoperative radiation therapy for stage IB-IIb carcinoma of the cervix with poor prognostic factors. *Anticancer Res* 20(3b):2235-2239.
- 118 Peters WA, 3rd, Liu PY, Barrett RJ, 2nd, Stock RJ, Monk BJ, Berek JS, Souhami L, Grigsby P, Gordon W, Jr. and Alberts DS (2000). Concurrent chemotherapy and pelvic radiation therapy compared with pelvic radiation therapy alone as adjuvant therapy after radical surgery in high-risk early-stage cancer of the cervix. *J Clin Oncol* 18(8):1606-1613.

- 119 Cheung TH, Lo KW, Yim SF, Yau SH, Yu MM and Yeung WK (2011). Debulking metastatic pelvic nodes before radiotherapy in cervical cancer patients: a long-term follow-up result. *Int J Clin Oncol* 16(5):546-552.
- 120 Yaegashi N, Sato S, Inoue Y, Noda K and Yajima A (1994). Conservative surgical treatment in cervical cancer with 3 to 5 mm stromal invasion in the absence of confluent invasion and lymph-vascular space involvement. *Gynecol Oncol* 54(3):333-337.
- 121 International Federation of Gynecology and Obstetrics (2019). Corrigendum to "Revised FIGO staging for carcinoma of the cervix uteri" [Int J Gynecol Obstet 145(2019) 129-135]. *Int J Gynaecol Obstet* 147(2):279-280.
- 122 Inoue T and Morita K (1990). The prognostic significance of number of positive nodes in cervical carcinoma stages IB, IIA, and IIB. *Cancer* 65(9):1923-1927.
- 123 Park JW and Bae JW (2016). Prognostic significance of positive lymph node number in early cervical cancer. *Mol Clin Oncol* 4(6):1052-1056.
- 124 Gortzak-Uzan L, Jimenez W, Nofech-Mozes S, Ismiil N, Khalifa MA, Dube V, Rosen B, Murphy J, Laframboise S and Covens A (2010). Sentinel lymph node biopsy vs. pelvic lymphadenectomy in early stage cervical cancer: is it time to change the gold standard? *Gynecol Oncol* 116(1):28-32.
- 125 van de Lande J, Torrenge B, Raijmakers PG, Hoekstra OS, van Baal MW, Brolmann HA and Verheijen RH (2007). Sentinel lymph node detection in early stage uterine cervix carcinoma: a systematic review. *Gynecol Oncol* 106(3):604-613.
- 126 Steed H, Rosen B, Murphy J, Laframboise S, De Petrillo D and Covens A (2004). A comparison of laparoscopic-assisted radical vaginal hysterectomy and radical abdominal hysterectomy in the treatment of cervical cancer. *Gynecol Oncol* 93(3):588-593.
- 127 Juretzka MM, Jensen KC, Longacre TA, Teng NN and Husain A (2004). Detection of pelvic lymph node micrometastasis in stage IA2-IB2 cervical cancer by immunohistochemical analysis. *Gynecol Oncol* 93(1):107-111.
- 128 Colturato LF, Signorini Filho RC, Fernandes RC, Gebrim LH and Olini AH (2016). Lymph node micrometastases in initial stage cervical cancer and tumoral recurrence. *Int J Gynaecol Obstet* 133(1):69-75.
- 129 Cibula D, Abu-Rustum NR, Dusek L, Zikan M, Zaal A, Sevcik L, Kenter GG, Querleu D, Jach R, Bats AS, Dyduch G, Graf P, Klat J, Lacheta J, Meijer CJ, Mery E, Verheijen R and Zweemer RP (2012). Prognostic significance of low volume sentinel lymph node disease in early-stage cervical cancer. *Gynecol Oncol* 124(3):496-501.
- 130 Lentz SE, Muderspach LI, Felix JC, Ye W, Groshen S and Amezcuca CA (2004). Identification of micrometastases in histologically negative lymph nodes of early-stage cervical cancer patients. *Obstet Gynecol* 103(6):1204-1210.
- 131 Horn LC, Hentschel B, Fischer U, Peter D and Bilek K (2008). Detection of micrometastases in pelvic lymph nodes in patients with carcinoma of the cervix uteri using step sectioning: Frequency, topographic distribution and prognostic impact. *Gynecol Oncol* 111(2):276-281.

- 132 Balaya V, Guani B, Benoit L, Magaud L, Bonsang-Kitzis H, Ngô C, Le Frère-Belda MA, Mathevet P and Lécure F (2020). Diagnostic value of frozen section examination of sentinel lymph nodes in early-stage cervical cancer at the time of ultrastaging. *Gynecol Oncol* 158(3):576-583.
- 133 Tu H, Gu HF, Huang H, Liu KJ, Yun JP, Chen JP, Zhang XK, Yahata H, Sonoda K, Zhang HY and Liu JH (2020). Sectioning protocol determines accuracy of intraoperative pathological examination of sentinel lymph node in cervical cancer: A systematic review and meta-analysis. *Gynecol Oncol* 158(2):489-497.
- 134 Dostalek L, Slama J, Fisherova D, Kocian R, Germanova A, Fruhauf F, Dusek L, Dundr P, Nemejcova K, Jarkovsky J and Cibula D (2020). Impact of sentinel lymph node frozen section evaluation to avoid combined treatment in early-stage cervical cancer. *Int J Gynecol Cancer* 30(6):744-748.
- 135 Song S, Kim JY, Kim YJ, Yoo HJ, Kim SH, Kim SK, Lim MC, Kang S, Seo SS and Park SY (2013). The size of the metastatic lymph node is an independent prognostic factor for the patients with cervical cancer treated by definitive radiotherapy. *Radiother Oncol* 108(1):168-173.
- 136 Fleming ND, Frumovitz M, Schmeler KM, dos Reis R, Munsell MF, Eifel PJ, Soliman PT, Nick AM, Westin SN and Ramirez PT (2015). Significance of lymph node ratio in defining risk category in node-positive early stage cervical cancer. *Gynecol Oncol* 136(1):48-53.
- 137 Li C, Liu W and Cheng Y (2016). Prognostic significance of metastatic lymph node ratio in squamous cell carcinoma of the cervix. *Onco Targets Ther* 9:3791-3797.
- 138 Horn L-C, Hentschel B, Galle D and Bilek K (2008). Extracapsular extension of pelvic lymph node metastases is of prognostic value in carcinoma of the cervix uteri. *Gynecologic Oncology* 108:63-67.
- 139 Metindir J and Bilir Dilek G (2008). Evaluation of prognostic significance in extracapsular spread of pelvic lymph node metastasis in patients with cervical cancer. *Eur J Gynaecol Oncol* 29(5):476-478.
- 140 McCluggage WG (2013). Premalignant lesions of the lower female genital tract: cervix, vagina and vulva. *Pathology* 45(3):214-228.
- 141 Nucci MR (2014). Pseudoneoplastic glandular lesions of the uterine cervix: a selective review. *Int J Gynecol Pathol* 33(4):330-338.
- 142 Oren A and Fernandes J (1991). The Bethesda system for the reporting of cervical/vaginal cytology. *J Am Osteopath Assoc* 91(5):476-479.
- 143 McCluggage WG (2013). New developments in endocervical glandular lesions. *Histopathology* 62(1):138-160.
- 144 Park JJ, Sun D, Quade BJ, Flynn C, Sheets EE, Yang A, McKeon F and Crum CP (2000). Stratified mucin-producing intraepithelial lesions of the cervix: adenosquamous or columnar cell neoplasia? *Am J Surg Pathol* 24(10):1414-1419.
- 145 Boyle DP and McCluggage WG (2015). Stratified mucin-producing intraepithelial lesion (SMILE): report of a case series with associated pathological findings. *Histopathology* 66(5):658-663.
- 146 Mikami Y and McCluggage WG (2013). Endocervical glandular lesions exhibiting gastric differentiation: an emerging spectrum of benign, premalignant, and malignant lesions. *Adv Anat Pathol* 20(4):227-237.

- 147 Talia KL, Stewart CJR, Howitt BE, Nucci MR and McCluggage WG (2017). HPV-negative gastric type adenocarcinoma in situ of the cervix: a spectrum of rare lesions exhibiting gastric and intestinal differentiation. *Am J Surg Pathol* 41(8):1023-1033.
- 148 Wheeler CM, Hunt WC, Joste NE, Key CR, Quint WG and Castle PE (2009). Human papillomavirus genotype distributions: implications for vaccination and cancer screening in the United States. *J Natl Cancer Inst* 101(7):475-487.
- 149 Kalof AN and Cooper K (2006). p16INK4a immunoexpression: surrogate marker of high-risk HPV and high-grade cervical intraepithelial neoplasia. *Adv Anat Pathol* 13(4):190-194.
- 150 Castrillon DH, Lee KR and Nucci MR (2002). Distinction between endometrial and endocervical adenocarcinoma: an immunohistochemical study. *Int J Gynecol Pathol* 21:4-10.
- 151 Carleton C, Hoang L, Sah S, Kiyokawa T, Karamurzin YS, Talia KL, Park KJ and McCluggage WG (2016). A detailed immunohistochemical analysis of a large series of cervical and vaginal gastric-type adenocarcinomas. *Am J Surg Pathol* 40(5):636-644.
- 152 Howitt BE, Emori MM, Drapkin R, Gaspar C, Barletta JA, Nucci MR, McCluggage WG, Oliva E and Hirsch MS (2015). GATA3 is a sensitive and specific marker of benign and malignant mesonephric lesions in the lower female genital tract. *Am J Surg Pathol* 39(10):1411-1419.
- 153 Kenny SL, McBride HA, Jamison J and McCluggage WG (2012). Mesonephric adenocarcinomas of the uterine cervix and corpus: HPV-negative neoplasms that are commonly PAX8, CA125, and HMGA2 positive and that may be immunoreactive with TTF1 and hepatocyte nuclear factor 1-beta. *Am J Surg Pathol* 36(6):799-807.
- 154 Kuji S, Watanabe R, Sato Y, Iwata T, Hirashima Y, Takekuma M, Ito I, Abe M, Nagashio R, Omae K, Aoki D and Kameya T (2017). A new marker, insulinoma-associated protein 1 (INSM1), for high-grade neuroendocrine carcinoma of the uterine cervix: Analysis of 37 cases. *Gynecol Oncol* 144(2):384-390.
- 155 Paxton, A. (2018). *Scoring gastric, GEJ cancers for PD-L1 expression*. Available from: <https://www.captodayonline.com/scoring-gastric-gej-cancers-pd-l1-expression/> (Accessed 6th October 2020).
- 156 Kulangara K, Zhang N, Corigliano E, Guerrero L, Waldroup S, Jaiswal D, Ms MJ, Shah S, Hanks D, Wang J, Lunceford J, Savage MJ, Juco J and Emancipator K (2019). Clinical utility of the combined positive score for programmed death ligand-1 expression and the approval of pembrolizumab for treatment of gastric cancer. *Arch Pathol Lab Med* 143(3):330-337.
- 157 Kulangara K, Hanks DA, Waldroup S, Peltz L, Shah S, Roach C, Juco JW, Emancipator K and Stanforth D (2017). Development of the combined positive score (CPS) for the evaluation of PD-L1 in solid tumors with the immunohistochemistry assay PD-L1 IHC 22C3 pharmDx. *Journal of Clinical Oncology* 35(15\_suppl):e14589-e14589.
- 158 Shields LBE and Gordinier ME (2019). Pembrolizumab in recurrent squamous cell carcinoma of the vulva: case report and review of the literature. *Gynecol Obstet Invest* 84(1):94-98.
- 159 Chung HC, Ros W, Delord JP, Perets R, Italiano A, Shapira-Frommer R, Manzuk L, Piha-Paul SA, Xu L, Zeigenfuss S, Pruitt SK and Leary A (2019). Efficacy and safety of pembrolizumab in previously treated advanced cervical cancer: Results from the Phase II KEYNOTE-158 Study. *J Clin Oncol* 37(17):1470-1478.

- 160 United States Food & Drug Administration (2018). *FDA approves pembrolizumab for advanced cervical cancer with disease progression during or after chemotherapy*. Available from: <https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-pembrolizumab-advanced-cervical-cancer-disease-progression-during-or-after-chemotherapy> (Accessed 6th October 2020).
- 161 Wittekind C, Brierley JD, Lee A and van Eycken E (eds) (2019). *TNM Supplement: A Commentary on Uniform Use, 5th Edition*, Wiley, USA.