



# Protocol for the Examination of Resection Specimens From Patients With Primary Carcinoma of the Uterine Cervix

**Version:** Uterine Cervix Resection 4.2.0.0

**Protocol Posting Date:** August 2019

**CAP Laboratory Accreditation Program Protocol Required Use Date:** May 2020

Includes pTNM requirements from the 8<sup>th</sup> Edition, AJCC Staging Manual and 2018 FIGO Cancer Report

**For accreditation purposes, this protocol should be used for the following procedures AND tumor types:**

Procedure	Description
Resection	Includes radical trachelectomy, radical hysterectomy, or pelvic exenteration
Tumor Type	Description
Carcinoma	
Carcinosarcoma	

**This protocol is NOT required for accreditation purposes for the following:**

Procedure
Biopsy, includes Excision (Cone/LEEP) (consider Uterine Cervix Biopsy protocol)
Primary resection specimen with no residual cancer (eg, following neoadjuvant therapy)
Cytologic specimens

**The following tumor types should NOT be reported using this protocol:**

Tumor Type
Lymphoma (consider the Hodgkin or non-Hodgkin Lymphoma protocols)
Sarcoma (consider Uterine Sarcoma protocol)

## Authors

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With guidance from the CAP Cancer and CAP Pathology Electronic Reporting Committees.

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### Accreditation Requirements

This protocol can be utilized for a variety of procedures and tumor types for clinical care purposes. For accreditation purposes, only the definitive primary cancer resection specimen is required to have the core and conditional data elements reported in a synoptic format.

- Core data elements are required in reports to adequately describe appropriate malignancies. For accreditation purposes, essential data elements must be reported in all instances, even if the response is “not applicable” or “cannot be determined.”
- Conditional data elements are only required to be reported if applicable as delineated in the protocol. For instance, the total number of lymph nodes examined must be reported, but only if nodes are present in the specimen.
- Optional data elements are identified with “+” and although not required for CAP accreditation purposes, may be considered for reporting as determined by local practice standards.

The use of this protocol is not required for recurrent tumors or for metastatic tumors that are resected at a different time than the primary tumor. Use of this protocol is also not required for pathology reviews performed at a second institution (ie, secondary consultation, second opinion, or review of outside case at second institution).

### Synoptic Reporting

All core and conditionally required data elements outlined on the surgical case summary from this cancer protocol must be displayed in synoptic report format. Synoptic format is defined as:

- Data element: followed by its answer (response), outline format without the paired "Data element: Response" format is NOT considered synoptic.
- The data element should be represented in the report as it is listed in the case summary. The response for any data element may be modified from those listed in the case summary, including “Cannot be determined” if appropriate.
- Each diagnostic parameter pair (Data element: Response) is listed on a separate line or in a tabular format to achieve visual separation. The following exceptions are allowed to be listed on one line:
  - Anatomic site or specimen, laterality, and procedure
  - Pathologic Stage Classification (pTNM) elements
  - Negative margins, as long as all negative margins are specifically enumerated where applicable
- The synoptic portion of the report can appear in the diagnosis section of the pathology report, at the end of the report or in a separate section, but all Data element: Responses must be listed together in one location

Organizations and pathologists may choose to list the required elements in any order, use additional methods in order to enhance or achieve visual separation, or add optional items within the synoptic report. The report may have required elements in a summary format elsewhere in the report IN ADDITION TO but not as replacement for the synoptic report ie, all required elements must be in the synoptic portion of the report in the format defined above.

## Summary of Changes

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### Version 4.2.0.0

Resection and biopsy case summaries separated into discrete cancer protocols

#### The following were modified:

FIGO 2018 Update  
Stromal Invasion

#### The following was added:

Endocervical Margin/Lower uterine segment margin

**Surgical Pathology Cancer Case Summary**

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Protocol posting date: August 2019

**UTERINE CERVIX: Resection****Select a single response unless otherwise indicated.****Procedure (select all that apply) (Note A)**

- Trachelectomy
- Total hysterectomy and bilateral salpingo-oophorectomy
- Radical hysterectomy
- Simple hysterectomy
- Pelvic exenteration (specify included organs): \_\_\_\_\_
- Bilateral salpingo-oophorectomy
- Right salpingo-oophorectomy
- Left salpingo-oophorectomy
- Salpingo-oophorectomy, side not specified
- Right oophorectomy
- Left oophorectomy
- Oophorectomy, side not specified
- Bilateral salpingectomy
- Right salpingectomy
- Left salpingectomy
- Salpingectomy, side not specified
- Vaginal cuff resection
- Omentectomy
- Other (specify): \_\_\_\_\_

*Note: For information about lymph node sampling, please refer to the Regional Lymph Node section.***+ Hysterectomy Type**

- +  Abdominal
- +  Vaginal
- +  Vaginal, laparoscopic-assisted
- +  Laparoscopic
- +  Laparoscopic, robotic-assisted
- +  Other (specify): \_\_\_\_\_
- +  Not specified

**Tumor Size (Note B)**

- Greatest dimension (centimeters): \_\_\_ cm
- + Additional dimensions (centimeters): \_\_\_ x \_\_\_ cm
- Cannot be determined (explain): \_\_\_\_\_

*Note: All dimensions are important; see definition for "superficially invasive squamous cell carcinoma" under T1a1/IA1.***+ Tumor Site (select all that apply)**

- +  Left superior (anterior) quadrant (12 to 3 o'clock)
- +  Left inferior (posterior) quadrant (3 to 6 o'clock)
- +  Right inferior (posterior) quadrant (6 to 9 o'clock)
- +  Right superior (anterior) quadrant (9 to 12 o'clock)
- +  Other (specify): \_\_\_\_\_
- +  Not specified

+ Data elements preceded by this symbol are not required for accreditation purposes. These optional elements may be clinically important but are not yet validated or regularly used in patient management.

**Histologic Type (Note C)**

- Squamous cell carcinoma, NOS
- Squamous cell carcinoma, keratinizing
- Squamous cell carcinoma, nonkeratinizing
- Squamous cell carcinoma, basaloid
- Squamous cell carcinoma, verrucous
- Squamous cell carcinoma, warty
- Squamous cell carcinoma, papillary
- Squamous cell carcinoma, lymphoepithelioma-like
- Squamous cell carcinoma, squamotransitional
- Endocervical adenocarcinoma, usual type
- Mucinous carcinoma, NOS
- Mucinous carcinoma, intestinal type
- Mucinous carcinoma, signet-ring cell type
- Mucinous carcinoma, gastric type
- Villoglandular carcinoma
- Endometrioid carcinoma
- Clear cell carcinoma
- Serous carcinoma
- Mesonephric carcinoma
- Adenocarcinoma admixed with neuroendocrine carcinoma
- Adenosquamous carcinoma
- Adenosquamous carcinoma, glassy cell variant
- Adenoid cystic carcinoma
- Adenoid basal carcinoma
- Small cell neuroendocrine carcinoma
- Large cell neuroendocrine carcinoma
- Undifferentiated carcinoma
- Carcinosarcoma
- Other histologic type not listed (specify): \_\_\_\_\_
- Carcinoma, type cannot be determined

**Histologic Grade (Note D)**

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

**Stromal Invasion (Note B)**

**Depth of Stromal Invasion (millimeters):**

- Specify \_\_\_ mm
- At least \_\_\_ mm
- Cannot be determined (explain): \_\_\_\_\_

**+ Depth of Stromal Invasion**

- +  Superficial one-third
- +  Middle one-third
- +  Deep one-third

**Longitudinal Horizontal Extent/Length of Stromal Invasion (if applicable<sup>#</sup>) (millimeters): \_\_\_ mm**

- Cannot be determined (explain): \_\_\_\_\_

+ Data elements preceded by this symbol are not required for accreditation purposes. These optional elements may be clinically important but are not yet validated or regularly used in patient management.

**Circumferential Horizontal Extent/Width of Stromal Invasion (if applicable)# (millimeters):** \_\_\_ mm  
 \_\_\_ Cannot be determined (explain): \_\_\_\_\_

*#Not applicable in larger tumors that can be measured grossly.*

**Other Tissue/ Organ Involvement (select all that apply)**

*Note: Any organ not selected is either not involved or was not submitted.*

- \_\_\_ Not applicable
- \_\_\_ Not identified
- \_\_\_ Right parametrium
- \_\_\_ Left parametrium
- \_\_\_ Parametrium (side not specified)
- \_\_\_ Vagina, upper two-thirds
- \_\_\_ Vagina, lower one-third
- \_\_\_ Vagina (location not specified)
- \_\_\_ Right ovary
- \_\_\_ Left ovary
- \_\_\_ Ovary (side not specified)
- \_\_\_ Right fallopian tube
- \_\_\_ Left fallopian tube
- \_\_\_ Fallopian tube (side not specified)
- \_\_\_ Pelvic wall
- \_\_\_ Bladder wall
- \_\_\_ Bladder mucosa
- \_\_\_ Rectal wall
- \_\_\_ Bowel mucosa
- \_\_\_ Omentum
- \_\_\_ Other organs/tissue (specify): \_\_\_\_\_
- \_\_\_ Cannot be determined (explain): \_\_\_\_\_

**Margins (Note E)**

**Ectocervical Margin (select all that apply)#**

- \_\_\_ Cannot be assessed (explain): \_\_\_\_\_
- \_\_\_ Uninvolved by invasive carcinoma
  - + Distance of invasive carcinoma from margin (millimeters): \_\_\_ mm
  - + Specify location: \_\_\_\_\_
- \_\_\_ Involved by invasive carcinoma
  - Specify location, if possible: \_\_\_\_\_
- \_\_\_ Uninvolved by intraepithelial neoplasia
- \_\_\_ Involved by high-grade squamous intraepithelial lesion (CIN 2-3)
  - + Specify location: \_\_\_\_\_
- \_\_\_ Involved by adenocarcinoma in situ (AIS)
  - + Specify location: \_\_\_\_\_

*# Reporting high-grade squamous intraepithelial lesion (CIN 2-3) and/or AIS is not required if margin is involved by invasive carcinoma.*

**Radial (Circumferential) Margin**

- \_\_\_ Cannot be assessed (explain): \_\_\_\_\_
- \_\_\_ Uninvolved by invasive carcinoma
  - + Distance of invasive carcinoma from margin (millimeters): \_\_\_ mm
  - + Specify location: \_\_\_\_\_
- \_\_\_ Involved by invasive carcinoma
  - Specify location(s), if possible: \_\_\_\_\_

+ Data elements preceded by this symbol are not required for accreditation purposes. These optional elements may be clinically important but are not yet validated or regularly used in patient management.

**Endocervical Margin/Lower Uterine Segment Margin (if applicable, select all that apply)#**

- Cannot be assessed (explain): \_\_\_\_\_
- Uninvolved by invasive carcinoma
  - + Distance of invasive carcinoma from margin (millimeters): \_\_\_\_ mm
  - + Specify location: \_\_\_\_\_
- Involved by invasive carcinoma
  - Specify location, if possible: \_\_\_\_\_
- Uninvolved by intraepithelial neoplasia
- Involved by high-grade squamous intraepithelial lesion (CIN 2-3)
  - + Specify location: \_\_\_\_\_
- Involved by adenocarcinoma in situ (AIS)
  - + Specify location: \_\_\_\_\_

# Only applicable for trachelectomy specimens

**Vaginal Cuff Margin (if applicable, select all that apply)#**

- Cannot be assessed (explain): \_\_\_\_\_
- Uninvolved by invasive carcinoma
  - + Distance of invasive carcinoma from margin (millimeters): \_\_\_\_ mm
- Involved by invasive carcinoma
- Uninvolved by intraepithelial neoplasia
- Involved by high-grade squamous intraepithelial lesion (VAIN 2-3)

# Reporting high-grade squamous intraepithelial lesion (Vain 2-3) is not required if margin is involved by invasive carcinoma.

**Lymphovascular Invasion (Note F)**

- Not identified
- Present
- Cannot be determined

**Regional Lymph Nodes**

*Note: Lymph nodes designated as pelvic (parametrial, obturator, internal iliac (hypogastric), external iliac, common iliac, sacral, presacral) and para-aortic are considered regional lymph nodes. Any other involved nodes should be categorized as metastases (pM1) and commented on in the distant metastasis section. Presence of isolated tumor cells no greater than 0.2 mm in regional lymph node(s) is considered NO(i+).*

- No lymph nodes submitted or found

Lymph Node Examination (required only if lymph nodes are present in the specimen)

- All lymph nodes negative for tumor cells
- Positive for tumor cells (select all that apply)
  - Number of Nodes with Metastasis (excludes isolated tumor cells):** \_\_\_\_\_
  - Number of Nodes with Isolated Tumor Cells (0.2 mm or less) (if applicable):** \_\_\_\_\_
  - Number cannot be determined (explain):** \_\_\_\_\_

*Note: Reporting the number of lymph nodes with isolated tumor cells is required only in the absence of metastasis greater than 0.2 mm in other lymph nodes.*

**+ Nodal Site(s) with Tumor Cells (specify):** \_\_\_\_\_

- Total Number of Lymph Nodes Examined:** \_\_\_\_\_
- Number cannot be determined (explain): \_\_\_\_\_
- + Specify Site(s):** \_\_\_\_\_

- Number of Sentinel Nodes Examined (if applicable):** \_\_\_\_\_
- Number cannot be determined (explain): \_\_\_\_\_

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**Pathologic Stage Classification (pTNM, AJCC 8<sup>th</sup> Edition) (Note G)**

*Note: Reporting of pT, pN, and (when applicable) pM categories is based on information available to the pathologist at the time the report is issued. Only the applicable T, N, or M category is required for reporting; their definitions need not be included in the report. The categories (with modifiers when applicable) can be listed on 1 line or more than 1 line.*

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

- m (multiple primary tumors)  
 r (recurrent)  
 y (posttreatment)

**Primary Tumor (pT)**

- pTX: Primary tumor cannot be assessed  
 pT0: No evidence of primary tumor  
 pT1: Cervical carcinoma confined to uterus (extension to corpus should be disregarded)  
 pT1a: Invasive carcinoma diagnosed by microscopy only. Stromal invasion with a maximum depth of 5.0 mm, measured from the base of the epithelium, and a horizontal spread of 7.0 mm or less. Vascular space involvement, venous or lymphatic, does not affect classification.  
 pT1a1: Measured stromal invasion of 3.0 mm or less in depth and 7.0 mm or less in horizontal spread  
 pT1a2: Measured stromal invasion of more than 3.0 mm and not more than 5.0 mm, with a horizontal spread of 7.0 mm or less  
 pT1b: Clinically visible lesion confined to the cervix or microscopic lesion greater than T1a/1A2. Includes all macroscopically visible lesions, even those with superficial invasion.  
 pT1b1: Clinically visible lesion 4.0 cm or less in greatest dimension  
 pT1b2: Clinically visible lesion more than 4.0 cm in greatest dimension  
 pT2: Cervical carcinoma invading beyond the uterus but not to the pelvic wall or to lower third of the vagina  
 pT2a: Tumor without parametrial invasion  
 pT2a1: Clinically visible lesion 4.0 cm or less in greatest dimension  
 pT2a2: Clinically visible lesion more than 4.0 cm in greatest dimension  
 pT2b: Tumor with parametrial invasion  
 pT3: Tumor extending to the pelvic sidewall<sup>#</sup> and/or involving the lower third of the vagina and/or causing hydronephrosis or nonfunctioning kidney  
 pT3a: Tumor involving the lower third of the vagina but not extending to the pelvic wall  
 pT3b: Tumor extending to the pelvic wall and/or causing hydronephrosis or nonfunctioning kidney  
 pT4: Tumor invading the mucosa of the bladder or rectum and/or extending beyond the true pelvis (bullous edema is not sufficient to classify a tumor as T4)

<sup>#</sup> *The pelvic sidewall is defined as the muscle, fascia, neurovascular structures, and skeletal portions of the bony pelvis. On rectal examination, there is no cancer-free space between the tumor and pelvic sidewall.*

*Note: The LAST definition of superficial invasive squamous cell carcinoma (SISCCA) conforms to T1a1.*

**+ Regional Lymph Nodes Modifier**

- +  (sn)  
 +  (sn)(i-)  
 +  (sn)(i+)

**Regional Lymph Nodes (pN)**

- pNX: Regional lymph nodes cannot be assessed  
 pN0: No regional lymph node metastasis  
 pN0(i+): Isolated tumor cells in regional lymph node(s) no greater than 0.2 mm  
 pN1: Regional lymph node metastasis

**Distant Metastasis (pM) (required only if confirmed pathologically in this case)**

- pM1: Distant metastasis (including peritoneal spread or involvement of the supraclavicular, mediastinal, or distant lymph nodes; lung; liver; or bone)  
 Specify Site(s), if known: \_\_\_\_\_

+ Data elements preceded by this symbol are not required for accreditation purposes. These optional elements may be clinically important but are not yet validated or regularly used in patient management.

**+ FIGO Stage (2018 FIGO Cancer Report)**

- + \_\_\_ I: Carcinoma is strictly confined to the cervix (extension to the uterine corpus should be disregarded)
- + \_\_\_ IA: Invasive cancer identified only microscopically. (All gross lesions even with superficial invasion are stage IB cancers.) Invasion is limited to measured stromal invasion with a maximum depth of 5 mm<sup>#</sup>
- + \_\_\_ IA1: Measured invasion of stroma less than 3 mm in depth<sup>##</sup>
- + \_\_\_ IA2: Measured invasion of stroma at least 3 mm but less than 5 mm in depth
- + \_\_\_ IB: Invasive carcinoma with measured deepest invasion of 5 mm or greater and limited to the cervix uteri
- + \_\_\_ IB1: Invasive carcinoma that is less than 2 cm in greatest dimension with a depth of invasion of 5 mm or greater
- + \_\_\_ IB2: Invasive carcinoma with a greatest dimension of at least 2 cm but less than 4 cm
- + \_\_\_ IB3: Invasive carcinoma 4 cm or greater in greatest dimension
- + \_\_\_ II: The carcinoma extends beyond the uterus but has not extended onto the pelvic wall or to the lower third of vagina
- + \_\_\_ IIA: Involvement of up to the upper two-thirds of the vagina. No obvious parametrial involvement
- + \_\_\_ IIA1: Clinically visible lesion less than 4 cm
- + \_\_\_ IIA2: Clinically visible lesion 4 cm or greater
- + \_\_\_ IIB: Obvious parametrial involvement but not onto the pelvic sidewall
- + \_\_\_ III: The carcinoma involves the lower third of the vagina and/or extends to the pelvic wall and/or causes hydronephrosis or nonfunctioning kidney and/or involves pelvic and/or para- aortic lymph nodes
- + \_\_\_ IIIA: Involvement of the lower third of the vagina but no extension onto pelvic sidewall
- + \_\_\_ IIIB: Extension onto the pelvic sidewall, and/or causing hydronephrosis/nonfunctioning kidney (unless known to be due to another cause)
- + \_\_\_ IIIC: Involvement of pelvic and/or para- aortic lymph nodes, irrespective of tumor size and extent
- + \_\_\_ IIIC1: Pelvic lymph node metastasis only
- + \_\_\_ IIIC2: Para- aortic lymph node metastasis
- + \_\_\_ IV: Carcinoma has extended beyond the true pelvis or has involved (biopsy proven) the mucosa of the bladder and/or rectum (bullous edema is not sufficient) or spread to distant organs
- + \_\_\_ IVA: Spread to adjacent pelvic organs, ie, tumor invading the mucosa of the bladder and/or rectum (biopsy proven) and/or extending beyond the true pelvis (bullous edema is not sufficient)
- + \_\_\_ IVB: Spread to distant organs

*#Note: For FIGO IA cancers, the depth of invasion should not be more than 5 mm taken from the base of the epithelium, either surface or glandular, from which it originates. Vascular space invasion should not alter the staging.*

*##The LAST definition of superficial invasive squamous cell carcinoma (SISCCA) conforms to FIGO IA1.*

**+ Additional Pathologic Findings (select all that apply)**

- + \_\_\_ None identified
- + \_\_\_ Low-grade squamous intraepithelial lesion (CIN 1)
- + \_\_\_ High-grade squamous intraepithelial lesion (CIN 2 or 3)
- + \_\_\_ Inflammation
- + \_\_\_ Other (specify): \_\_\_\_\_

**+ Ancillary Studies (Note H)**

+ Specify: \_\_\_\_\_

**+ p16 Immunohistochemistry**

- + \_\_\_ Positive
- + \_\_\_ Negative

**+ Comment(s)**

+ Data elements preceded by this symbol are not required for accreditation purposes. These optional elements may be clinically important but are not yet validated or regularly used in patient management.



## Explanatory Notes

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### A. Procedure

#### Specimen Orientation

If the specimen is the product of a cone biopsy or an excisional biopsy, it is desirable for the surgeon to orient the specimen to facilitate assessment of the resection margins (eg, stitch at 12 o'clock). The laterality of the specimen is in reference to the patient's perspective. Clock values refer to the cervix from the viewer's perspective (face on). However, specimens frequently are received without orientation. In these cases, the clock face orientation is designated by the pathologist and is arbitrary.

#### Examination of Bladder and Rectum

Currently, pelvic exenterations are rarely seen, but typically when performed indicate advanced tumor stage. In these cases, the extent of tumor involvement of the urinary bladder and rectum and the relation of the tumor to the cervical carcinoma should be described. To evaluate these features, sections of the rectum and bladder should be taken perpendicular to the mucosa directly overlying the tumor in the cervix. A method that provides excellent orientation of the tumor to adjacent structures consists of inflation of the urinary bladder and rectum with formalin and fixation of the specimen for several hours. The entire specimen can then be hemisected through the neoplasm, and appropriate sections can be obtained.

### B. Tumor Size

#### Absence of Tumor

If no tumor or precursor lesion is present in a cytology or biopsy specimen, the adequacy of the specimen (ie, its content of both glandular and squamous epithelium) should receive comment. The absence of tumor or precursor lesions in resections must always be documented.

#### Tumor Size Measurement

Tumors should be measured in 3 dimensions in all cases, namely the depth of invasion and 2 measurements of horizontal extent (longitudinal/length and circumferential/width). Larger tumors are more accurately measured grossly, while smaller tumors and some larger tumors with a diffusely infiltrative pattern or with marked fibrosis are best measured microscopically. It is best to report only 1 set of tumor measurements based on a correlation of the gross and microscopic features to avoid confusion.

The depth of invasion is measured from its HSIL origin, that is, from the base of the epithelium either surface or glandular that is involved by HSIL to the deepest point of invasion. If the invasive focus or foci are not in continuity with the dysplastic epithelium, the depth of invasion should be measured from the deepest focus of tumor invasion to the base of the nearest dysplastic crypt or surface epithelium. If there is no obvious epithelial origin, the depth is measured from the deepest focus of tumor invasion to the base of the nearest surface epithelium, regardless of whether it is dysplastic or not. In situations where carcinomas are exclusively or predominantly exophytic, there may be little or no invasion of the underlying stroma. These should not be regarded as in situ lesions and the tumor thickness (from the surface of the tumor to the deepest point of invasion) should be measured in such cases. The depth of invasion below the level of the epithelial origin should not be provided in these cases as this may not truly reflect the biological potential of such tumors. If it is impossible to measure the depth of invasion, eg, in ulcerated tumors or in some adenocarcinomas, the tumor thickness may be measured instead, and this should be clearly stated on the pathology report along with an explanation for providing the thickness rather than the depth of invasion.

The depth of stromal invasion in fractional thirds in resections is a data point in the NCCN guidelines that guides clinical management.<sup>1,2</sup>

Horizontal extent: The longitudinal extent (length) of horizontal extent is measured in the superior-inferior plane (ie, from the endocervical to ectocervical aspects of the section), whereas the circumferential extent (width) is measured or calculated perpendicular to the longitudinal axis of the cervix. If the tumor involves only 1 block, the circumferential extent (width) will be 2.5 mm to 3 mm (thickness of 1 block). When more than 1 block is involved, it is the product of the number of consecutive blocks with tumor and thickness of a block.

The LAST definition of superficial invasive squamous cell carcinoma (SISCCA) conforms to T1a1/ FIGO 1A1. The LAST consensus recommends SISCCA to include multifocal disease and that reporting include presence, number, and size of independent multifocal carcinoma, however, no LAST recommendation was made on the methodology to measure multifocal disease. Multifocal tumors should be defined as invasive foci separated by a tissue block within which there is no evidence of invasion or as invasive foci in the same tissue block that are more than 2 mm apart, or as invasive foci on different cervical lips. They recommend that multifocal tumors should be staged based on the largest focus.<sup>3</sup>

#### References

1. Delgado G, Bundy B, Zaino R, Sevin B, Creasman WT, Major F: 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.* 1990; 38 (3): 352-35.
2. Sedlis A, Bundy BN, Rotman MZ, Lentz SS, Muderspach LI, Zaino RJ: 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.* 1999 ;73(2):177-83.
3. Day E, Duffy S, Bryson G, Syed S, Shanbhag S, Burton K, Lindsay R, Siddiqui N, Millan D: Multifocal FIGO Stage IA1 Squamous Carcinoma of the Cervix: Criteria for Identification, Staging, and its Good Clinical Outcome. *Int J Gynecol Pathol.* 2016 ;35(5):467-74.

#### C. Histologic Type

For consistency in reporting, the histologic classification proposed by the World Health Organization (WHO) is recommended<sup>1</sup>; other classification systems may be used, however.

#### WHO Histologic Classification of Cervical Carcinoma and Precursor Lesions

##### Epithelial Tumors and Related Lesions

##### Squamous lesions

- Squamous intraepithelial lesions/cervical intraepithelial neoplasia (SIL/CIN)
  - Low-grade squamous intraepithelial lesion [LSIL]/Mild dysplasia (CIN 1)
  - High-grade squamous intraepithelial lesion [HSIL]/Moderate dysplasia (CIN 2)
  - HSIL/Severe dysplasia (CIN 3)
  - HSIL/Carcinoma in situ (CIS)

- Squamous cell carcinoma, NOS
- Squamous cell carcinoma, keratinizing
- Squamous cell carcinoma, non-keratinizing
- Squamous cell carcinoma, basaloid
- Squamous cell carcinoma, verrucous
- Squamous cell carcinoma, warty
- Squamous cell carcinoma, papillary
- Squamous cell carcinoma, lymphoepithelioma-like
- Squamous cell carcinoma, squamotransitional

Endocervical adenocarcinoma, usual type

- Mucinous carcinoma, NOS
- Mucinous carcinoma, intestinal type
- Mucinous carcinoma, signet-ring cell type
- Mucinous carcinoma, gastric type

- Villoglandular carcinoma
- Endometrioid carcinoma
- Clear cell carcinoma
- Serous carcinoma
- Mesonephric carcinoma

Adenocarcinoma admixed with neuroendocrine carcinoma  
 Adenosquamous carcinoma  
 Adenosquamous carcinoma, glassy cell variant  
 Adenoid cystic carcinoma  
 Adenoid basal carcinoma  
 Small cell neuroendocrine carcinoma  
 Large cell neuroendocrine carcinoma  
 Undifferentiated carcinoma  
 Carcinosarcoma

#### References

1. Kurman RJ, Carcangiu ML, Harrington CS, Young RH, eds. *WHO Classification of Tumors of the Female Reproductive Organs*. Geneva, Switzerland: WHO Press; 2014.

#### D. Histologic Grade

A wide variety of grading systems, including some that evaluate only the extent of cellular differentiation and others that assess additional features such as the appearance of the tumor margin, the extent of inflammatory cell infiltration, and vascular invasion, have been used for squamous cell carcinoma of the cervix. However, there is no consensus emerging from the literature that any of these systems are reproducible or that they provide useful prognostic information.

For the grading of invasive squamous tumors, it is suggested that 3 grades be used:

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

In contrast to squamous cell carcinoma, most authors who grade cervical adenocarcinoma on the basis of its architecture (glandular and papillary versus solid areas) and its nuclear features have found the grade to have prognostic value.<sup>1-3</sup>

- |    |   |
|----|---|
| G1 | Small component of solid growth and mild to moderate nuclear atypia |
| G2 | Intermediate between grades 1 and 3                                 |
| G3 | Solid pattern with severe nuclear atypia                            |

Tumors with no differentiation or minimal differentiation that is discernible only in rare, tiny foci (undifferentiated carcinomas by WHO classification) are categorized as grade 4.

#### References

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#### E. Resection Margins

Margins can be involved, negative, or indeterminate for carcinoma. If a margin is involved, whether endocervical, ectocervical, deep, or other, it should be specified. If indeterminate, the reason should be specified (eg, cautery artifact in electroexcision specimens may preclude evaluation of the status of the margin). The severity and extent of a precursor lesion (eg, focal or diffuse) involving a resection margin of a cone should be specified.

If an invasive tumor approximates but does not directly involve a resection margin, the distance between the tumor and the margin should be measured in millimeters. If the tumor involves the uterine corpus, a determination of whether the cervix or corpus is the primary site should be made.

In hysterectomy or trachelectomy specimens, the lateral radial margin may consist of parametrial soft tissue, which should be measured if present.<sup>1</sup> 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 and calculated into the margin evaluation. If parametrectomy has been performed, careful microscopic examination of the parametria is important for evaluation of the lateral margins and/or soft tissue extension. Fragments of paracervical/ parametrial soft tissue that may be present in sections of cervix from a simple hysterectomy do not represent a formal parametrectomy. Anterior and posterior radial/deep stromal margins in a hysterectomy specimen will consist of cervical stromal tissue.

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#### F. Lymphovascular Invasion

Many gynecologists feel that the presence of vascular/lymphatic vessel invasion is important because it may change the extent of their surgical treatment. Specifically, the Society of Gynecologic Oncology (SGO) differs with the International Federation of Gynecology and Obstetrics (FIGO) in the definition of early invasive carcinoma. The SGO defines such tumors as being invasive to a depth <3 mm, with a width of <7 mm, but most importantly lacking lymphovascular invasion. At times, it may be difficult to determine whether vascular/lymphatic vessel invasion is present; in such cases, its presence should be categorized as indeterminate (cannot be determined).<sup>1</sup>

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#### G. Pathologic Stage Classification

The TNM staging system for cervical cancer endorsed by the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC), and the parallel system formulated by the International Federation of Gynecology and Obstetrics (FIGO), are recommended.<sup>1-5</sup>

By AJCC/UICC convention, the designation “T” refers to a primary tumor that has not been previously treated. The symbol “p” refers to the pathologic classification of the TNM, as opposed to the clinical classification, and is based on gross and microscopic examination. pT entails a resection of the primary tumor or biopsy adequate to evaluate the highest pT category, pN entails removal of nodes adequate to validate lymph node metastasis, and pM implies microscopic examination of distant lesions. Clinical classification (cTNM) is usually carried out by the referring physician before treatment during initial evaluation of the patient or when pathologic classification is not possible.

Pathologic staging is usually performed after surgical resection of the primary tumor. Pathologic staging depends on pathologic documentation of the anatomic extent of disease, whether or not the primary tumor has been completely removed. If a biopsied tumor is not resected for any reason (eg, when technically unfeasible) and if the highest T and N categories or the M1 category of the tumor can be confirmed microscopically, the criteria for pathologic classification and staging have been satisfied without total removal of the primary cancer.

Of note, tumor size has been shown to have prognostic utility for stage I to stage II lesions, and the 2014 FIGO staging classification has adopted T subclassifications for T2 lesions (cervical carcinoma spreading beyond the cervix but not to the pelvic side wall or lower one-third of the vagina), based on tumor size ≤4 cm (T2a1) and >4 cm (T2a2).<sup>1, 5</sup>

**TNM Descriptors**

For identification of special cases of TNM or pTNM classifications, the “m” suffix and “y,” “r,” and “a” prefixes are used. Although they do not affect the stage grouping, they indicate cases needing separate analysis.

The “m” suffix indicates the presence of multiple primary tumors in a single site and is recorded in parentheses: pT(m)NM.

The “y” prefix indicates those cases in which classification is performed during or following initial multimodality therapy (ie, neoadjuvant chemotherapy, radiation therapy, or both chemotherapy and radiation therapy). The cTNM or pTNM category is identified by a “y” prefix. The ycTNM or ypTNM categorizes the extent of tumor actually present at the time of that examination. The “y” categorization is not an estimate of tumor prior to multimodality therapy (ie, before initiation of neoadjuvant therapy).

The “r” prefix indicates a recurrent tumor when staged after a documented disease-free interval, and is identified by the “r” prefix: rTNM.

The “a” prefix designates the stage determined at autopsy: aTNM.

**T Category Considerations**Lymphovascular Invasion (LVI)

LVI indicates whether microscopic lymphovascular invasion is identified. LVI includes lymphatic invasion, vascular invasion, or lymphovascular invasion. By AJCC/UICC convention, LVI does not affect the T category indicating local extent of tumor unless specifically included in the definition of a T category.

**N Category Considerations**

Isolated tumor cells (ITCs) are single cells or small clusters of cells not more than 0.2 mm in greatest dimension. Lymph nodes or distant sites with ITCs found by either histologic examination (eg, immunohistochemical evaluation for cytokeratin) or nonmorphological techniques (eg, flow cytometry, DNA analysis, polymerase chain reaction [PCR] amplification of a specific tumor marker) should be so identified. There is currently no guidance in the literature as to how these patients should be coded; until more data are available, they should be coded as “N0(i+)” with a comment noting how the cells were identified.

Sentinel nodes should be sliced at 2.0 mm intervals. The sentinel nodes should undergo ultrastaging. Currently, there is no universal ultrastaging protocol. However, all institutions undertaking sentinel lymph node examination should have a standard procedure in place for sentinel lymph nodes. One protocol is as follows: For any section that is negative on initial H&E section, 2 sections are taken from each of two levels that are 50 µm apart, with one for H&E and the second for keratin cocktail IHC.<sup>6</sup>

There is little data to assign risk for nonsentinel lymph node metastasis based on the size of the metastasis in the sentinel lymph node. However, the size criteria for micrometastasis and macrometastasis is adopted from the experience in breast carcinoma. Micrometastasis is defined as a metastasis measuring greater than 0.2 mm but less than 2 mm.

Examination of Parametria

The parametria may be measured grossly, but their width varies according to the elasticity of the tissue. Careful microscopic examination of the parametria is important for evaluation of the lateral margins and/or soft tissue extension.

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## H. Special Studies

### p16 Immunohistochemistry

Immunohistochemistry has served as an important adjunct to the histologic diagnosis of CIN in difficult lesions, with p16 immunoreactivity being a good surrogate marker for high-risk human papillomavirus (HPV) infection.<sup>1, 2</sup> p16 immunostaining in the squamous epithelium, however, should be diffuse; strong nuclear and cytoplasmic staining, as focal strong p16 reactivity, may be identified not only in dysplastic squamous epithelium, but also in benign squamous epithelium (Table 1). p16 immunostaining is also considered a better candidate (rather than HPV in situ hybridization) for the initial assessment of cervical biopsies that are histologically indeterminate for dysplasia, given its wide availability, easy interpretation, and high sensitivity and specificity.<sup>3</sup> Given the heterogeneous staining patterns seen in low-grade CIN lesions, however, immunohistochemistry for p16 is generally reserved for lesions that are morphologically suspicious or indeterminate for high-grade dysplasia. The LAST project proposed p16 be used in 3 specific situations. First, to distinguish inflammatory lesions from HSIL; second, to distinguish LSIL from HSIL; and third, to evaluate specimens such as endocervical curettage on patients who have previously had a recent HSIL diagnosis. ProEx C, an immunohistochemical assay targeting both topoisomerase II-alpha and minichromosome maintenance protein-2 (MMP-2), has recently been shown to have high sensitivity and specificity for HPV-associated lesions of the cervix, with similar staining patterns as those seen for p16 and MIB-1 (Ki-67).<sup>4</sup>

### Immunohistochemistry: Endocervical versus Endometrial Adenocarcinoma

Immunohistochemistry can also be helpful in the differential diagnosis between endocervical and endometrial carcinoma, especially in curettage specimens, as endometrial carcinomas may show mucinous differentiation. A panel of antibodies, rather than a single antibody, is most useful; in most instances this includes vimentin, ER, p16, and monoclonal CEA.<sup>5, 6</sup>

**Table 1. p16 Immunohistochemistry in the Differential Diagnosis of Squamous and Glandular Lesions of the Uterine Cervix**

	p16 <sup>#</sup>	MIB-1 (Ki-67)
LSIL (CIN I)	+/-	increased
HSIL (CIN II-III)	+	increased (full thickness)
AIS	+	+
AIM	-/+	-/+
Reactive squamous or glandular atypia	-/+	+
Tubal metaplasia	+/-	-

LSIL, low-grade squamous intraepithelial neoplasia; HSIL, high-grade squamous intraepithelial neoplasia; CIN, cervical intraepithelial neoplasia; AIS, adenocarcinoma in situ; AIM, atypical immature metaplasia.

<sup>#</sup> p16 expression (nuclear and cytoplasmic) is a surrogate marker of high-risk HPV (eg, HPV 16, 18). In LSIL, the p16 expression may be confined to the lower one-third/lower one-half of the squamous epithelium or show focal immunoreactivity (the latter being a pattern of expression, albeit cytoplasmic only, that may also be seen in reactive squamous epithelia). HSIL p16 immunoreactivity usually involves two-thirds or full thickness of the squamous epithelium (so-called block like positivity).<sup>7</sup>

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