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

Version: 5.1.1.0
Protocol Posting Date: April 2023
CAP Laboratory Accreditation Program Protocol Required Use Date: December 2023
The changes included in this current protocol version do not affect the prior accreditation date.

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

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resection</td>
<td>Includes radical tracheectomy, radical hysterectomy, or pelvic exenteration</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carcinoma</td>
<td></td>
</tr>
<tr>
<td>Carcinosarcoma</td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biopsy, includes Excision (Cone/LEEP) (consider Uterine Cervix Excision protocol)</td>
</tr>
<tr>
<td>Primary resection specimen with no residual cancer (eg, following neoadjuvant therapy)</td>
</tr>
<tr>
<td>Cytologic specimens</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Tumor Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphoma (consider the Hodgkin or non-Hodgkin Lymphoma protocols)</td>
</tr>
<tr>
<td>Sarcoma (consider Uterine Sarcoma protocol)</td>
</tr>
</tbody>
</table>

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With guidance from the CAP Cancer and CAP Pathology Electronic Reporting Committees.
* Denotes primary author.
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

v 5.1.0.0
- Updated "Lymphovascular Invasion" to "Lymphatic and / or Vascular Invasion"
- Updated pTNM Classification
- Updated display items associated with FIGO
- Updated Explanatory Notes B, C, D, E, and G

v 5.1.1.0
- Accelerated errata to update incorrect section text for pTNM Classification to AJCC 9th Version
- Please note staging classifications were not affected as they were already updated to the AJCC 9th Version in October 2020
**CASE SUMMARY: (UTERINE CERVIX: Resection)**

**Standard(s):** FIGO Cancer Report 2018, AJCC-UICC 9

**SPECIMEN (Note A)**

**Procedure (select all that apply)**

*For information about lymph node sampling, please refer to the Regional Lymph Node section.*

- ___ 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): _____________________

**+Hysterectomy Type**

- ___ Abdominal
- ___ Vaginal
- ___ Vaginal, laparoscopic-assisted
- ___ Laparoscopic
- ___ Laparoscopic, robotic-assisted
- ___ Other (specify): _____________________
- ___ Not specified

**TUMOR**

**+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

**Tumor Size (Note B)**
___ Greatest Dimension in Centimeters (cm): _________________ cm
   +Additional Dimension in Centimeters (cm): __ x ____ cm
___ Cannot be determined (explain): ____________________

*Per AJCC Staging Manual, Tumor Size is reported in Centimeters.*
All dimensions are important; see definition for “superficially invasive squamous cell carcinoma” under T1a1 / IA1

**Histologic Type (Note C)**
___ Squamous cell carcinoma, HPV-associated
___ Squamous cell carcinoma, HPV-independent
___ Squamous cell carcinoma, NOS (acceptable when p16 or HPV testing is not available)
___ Adenocarcinoma, NOS
___ Adenocarcinoma, HPV-associated
___ Adenocarcinoma, HPV-independent, NOS
___ Adenocarcinoma, HPV-independent, gastric type
___ Adenocarcinoma, HPV-independent, clear cell type
___ Adenocarcinoma, HPV-independent, mesonephric type
___ Endometrioid adenocarcinoma, NOS
___ Carcinosarcoma
___ Adenosquamous carcinoma
___ Adenoid basal carcinoma
___ Mucoepidermoid carcinoma
___ Carcinoma, unclassifiable (undifferentiated carcinoma)
___ Neuroendocrine tumor, NOS
___ Neuroendocrine tumor, grade 1
___ Neuroendocrine tumor, grade 2
___ Small cell neuroendocrine carcinoma, high grade
___ Large cell neuroendocrine carcinoma, high grade
___ Neuroendocrine carcinoma, NOS
___ Mixed neuroendocrine non-neuroendocrine carcinoma
___ Other histologic type not listed (specify): ____________________
___ Carcinoma, type cannot be determined: ____________________
   +Histologic Type Comment: ____________________

**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*
___ Specify in Millimeters (mm): _________________ mm
___ Not more than 3 mm
___ Greater than 3 mm but not more than 5 mm
___ Greater than 5 mm
___ Cannot be determined (explain): __________________________

+Extent of Depth of Stromal Invasion
___ Superficial one-third
___ Middle one-third
___ Deep one-third
___ Cannot be determined: __________________________

+Horizontal Extent of Stromal Invasion
___ Not applicable (in larger tumors that can be measured grossly)
___ Specify in Millimeters (mm): __________________________ mm
___ Estimated to be less than or equal to 7 Millimeters (mm)
  Number of Blocks Involved: __________________________
___ Estimated to be greater than 7 Millimeters (mm)
  Number of Blocks Involved: __________________________
___ Cannot be determined (explain): __________________________

+Silva System for Invasion#
  #Silva System (applicable only to HPV associated invasive endocervical adenocarcinomas)
___ Not applicable
___ Pattern A
___ Pattern B
___ Pattern C

Other Tissue / Organ Involvement# (select all that apply)
  # Any organ not selected is either not involved or was not submitted.
___ Not applicable
___ Not identified
___ Parametrium
___ Vagina, upper two-thirds
___ Vagina, lower one-third
___ Vagina (location not specified)
___ Pelvic wall
___ Bladder wall
  ## Tumor should involve the mucosal surface
___ Bladder mucosa##
___ Rectal wall
___ Bowel mucosa##
___ Other organs / tissue (specify): __________________________
___ Cannot be determined (explain): __________________________

Lymphatic and / or Vascular Invasion (Note E)
___ Not identified
___ Present
___ Equivocal (explain): __________________________
___ Cannot be determined: __________________________

+Tumor Comment: __________________________
MARGINS (Note F)

Margin Status for Invasive Carcinoma
___ All margins negative for invasive carcinoma
+ Closest Margin(s) to Invasive Carcinoma (select all that apply)
___ Ectocervical (specify location, if possible):
___ Radial / circumferential (specify location, if possible):
___ Endocervical / lower uterine segment (specify location, if possible):
___ Vaginal cuff:
___ Other (specify):
___ Cannot be determined:
+ Distance from Invasive Carcinoma to Closest Margin
  Specify in Millimeters (mm)
___ Exact distance: mm
___ Greater than: mm
___ At least: mm
___ Less than: mm
___ Less than 1 mm
___ Other (specify):
___ Cannot be determined:
___ Invasive carcinoma present at margin
Margin(s) Involved by Invasive Carcinoma (select all that apply)
___ Ectocervical (specify location, if possible):
___ Radial / circumferential (specify location, if possible):
___ Endocervical / lower uterine segment (specify location, if possible):
___ Vaginal cuff:
___ Other (specify):
___ Cannot be determined:
___ Other (specify):
___ Cannot be determined (explain):
___ Not applicable

Margin Status for HSIL or AIS# (select all that apply)
# Reporting high-grade squamous intraepithelial lesion (CIN 2-3 or VAIN 2-3) and / or AIS is not required if margin is involved by invasive carcinoma.
___ All margins negative for high-grade squamous intraepithelial lesion (HSIL) and / or adenocarcinoma in situ (AIS)
___ High-grade squamous intraepithelial lesion (HSIL) present at margin
Margin(s) Involved by HSIL (select all that apply)
___ Ectocervical (specify location, if possible):
___ Endocervical / lower uterine segment (specify location, if possible):
___ Vaginal cuff:
___ Other (specify):
___ Cannot be determined:
___ Adenocarcinoma in situ (AIS) present at margin
Margin(s) Involved by AIS (select all that apply)
___ Ectocervical (specify location, if possible):
____ Endocervical / lower uterine segment (specify location, if possible): _________________
____ Other (specify): _________________
____ Cannot be determined: _________________
____ Other (specify): _________________
____ Cannot be determined (explain if possible): _________________
____ Not applicable

+Margin Comment: _________________

REGIONAL LYMPH NODES (Note E)

Regional Lymph Node Status#
# 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 reported in the distant metastasis section. Presence of isolated tumor cells no greater than 0.2 mm in regional lymph node(s) is considered N0 (i+).

____ Not applicable (no regional lymph nodes submitted or found)
____ Regional lymph nodes present
____ All regional lymph nodes negative for tumor cells
## Macrometastases (greater than 2 mm), Micrometastases (greater than 0.2 mm to 2 mm), Isolated Tumor Cells (ITC: less than or equal to 0.2 mm or single cells or clusters of cells less than or equal to 200 cells in a single lymph node cross section). If pelvic and / or para-aortic lymph nodes are submitted and positive for tumor cells, reporting the number of nodes with or without macrometastases and micrometastases is required. Reporting isolated tumor cells is required only in the absence of macrometastasis or micrometastasis.

____ Tumor present in pelvic lymph node(s)##

Pelvic Lymph Nodes (required only if present)

Total Number of Pelvic Nodes with Macrometastasis (greater than 2 mm) (sentinel and non-sentinel)
____ Exact number: _________________
____ At least: _________________
____ Other (specify): _________________
____ Cannot be determined (explain): _________________

+Number of Pelvic Sentinel Nodes with Macrometastasis
____ Exact number: _________________
____ At least: _________________
____ Other (specify): _________________
____ Cannot be determined (explain): _________________

Total Number of Pelvic Nodes with Micrometastasis (greater than 0.2 mm up to 2 mm and / or greater than 200 cells) (sentinel and non-sentinel)
____ Exact number: _________________
____ At least: _________________
____ Other (specify): _________________
____ Cannot be determined (explain): _________________

+Number of Pelvic Sentinel Nodes with Micrometastasis
____ Exact number: _________________
____ At least: _________________
____ Other (specify): _________________
____ Cannot be determined (explain): _________________
Total Number of Pelvic Nodes with Isolated Tumor Cells (0.2 mm or less and not more than 200 cells) (required only if present)###
### Reporting the number of lymph nodes with isolated tumor cells is required only in the absence of macrometastasis or micrometastasis in other lymph nodes.
___ Not applicable
___ Exact number: ____________________
___ At least: ____________________
___ Other (specify): ____________________
___ Cannot be determined (explain): ____________________

+Number of Pelvic Sentinel Nodes with ITCs
___ Exact number: ____________________
___ At least: ____________________
___ Other (specify): ____________________
___ Cannot be determined (explain): ____________________

Laterality of Pelvic Node(s) with Tumor (required only if present) (select all that apply)
___ Not applicable
___ Right sentinel: ____________________
___ Right non-sentinel: ____________________
___ Left sentinel: ____________________
___ Left non-sentinel: ____________________
___ Cannot be determined: ____________________

+Size of Largest Pelvic Nodal Metastatic Deposit
Specify in Millimeters (mm)
___ Exact size: ____________________ mm
___ Less than: ____________________ mm
___ Greater than: ____________________ mm
___ Other (specify): ____________________
___ Cannot be determined (explain): ____________________
___ Tumor present in para-aortic lymph node(s)

Para-aortic Nodes (required only if present)
Total Number of Para-aortic Nodes with Macrometastasis (greater than 2 mm) (sentinel and non-sentinel) (required only if present)
___ Not applicable
___ Exact number: ____________________
___ At least: ____________________
___ Other (specify): ____________________
___ Cannot be determined (explain): ____________________

+Number of Para-aortic Sentinel Nodes with Macrometastasis
___ Exact number: ____________________
___ At least: ____________________
___ Other (specify): ____________________
___ Cannot be determined (explain): ____________________

Total Number of Para-aortic Nodes with Micrometastasis (greater than 0.2 mm up to 2 mm and/or greater than 200 cells) (sentinel and non-sentinel) (required only if present)
___ Not applicable
___ Exact number: ____________________
___ At least: ____________________
___ Other (specify): ____________________
____ Cannot be determined (explain): ______________________

+ Number of Para-aortic Sentinel Nodes with Micrometastasis
  __ Exact number: ______________________
  __ At least: ______________________
  __ Other (specify): ______________________
  __ Cannot be determined (explain): ______________________

Total Number of Para-aortic Nodes with Isolated Tumor Cells (0.2 mm or less and not more than 200 cells) (required only if present) ####

### Reporting the number of lymph nodes with isolated tumor cells is required only in the absence of macrometastasis or micrometastasis in other lymph nodes.

__ Not applicable
__ Exact number: ______________________
__ At least: ______________________
__ Other (specify): ______________________
__ Cannot be determined (explain): ______________________

+ Number of Para-aortic Sentinel Nodes with ITCs
  __ Exact number: ______________________
  __ At least: ______________________
  __ Other (specify): ______________________
  __ Cannot be determined (explain): ______________________

Laterality of Para-aortic Node(s) with Tumor (required only if present) (select all that apply)
__ Not applicable
__ Right sentinel: ______________________
__ Right non-sentinel: ______________________
__ Left sentinel: ______________________
__ Left non-sentinel: ______________________
__ Cannot be determined: ______________________

+ Size of Largest Para-aortic Nodal Metastatic Deposit
  Specify in Millimeters (mm)
  __ Exact size: ______________________ mm
  __ Less than: ______________________ mm
  __ Greater than: ______________________ mm
  __ Other (specify): ______________________
  __ Cannot be determined (explain): ______________________

Lymph Nodes Examined

Total Number of Pelvic Nodes Examined (sentinel and non-sentinel)
__ Exact number: ______________________
__ At least: ______________________
__ Other (specify): ______________________
__ Cannot be determined (explain): ______________________

Number of Pelvic Sentinel Nodes Examined (required only if present)
__ Not applicable
__ Exact number: ______________________
__ At least: ______________________
Other (specify): __________________________  Cannot be determined (explain): __________________________  
Total Number of Para-aortic Nodes Examined (sentinel and non-sentinel)  
- Exact number: __________________________  
- At least: __________________________  
- Other (specify): __________________________  
- Cannot be determined (explain): __________________________  
Number of Para-aortic Sentinel Nodes Examined (required only if present)  
- Not applicable  
- Exact number: __________________________  
- At least: __________________________  
- Other (specify): __________________________  
- Cannot be determined (explain): __________________________  
Regional Lymph Node Comment: __________________________  

DISTANT METASTASIS  

Distant Site(s) Involved, if applicable# (select all that apply)  
# This excludes metastasis to pelvic or para-aortic lymph nodes, or vagina.  
- Not applicable  
- Uterine serosa: __________________________  
- Adnexa: __________________________  
- Inguinal lymph node(s): __________________________  
- Omentum: __________________________  
- Extrapelvic peritoneum: __________________________  
- Lung: __________________________  
- Liver: __________________________  
- Bone: __________________________  
- Other (specify): __________________________  
- Cannot be determined: __________________________  

pTNM CLASSIFICATION (AJCC 9th Version) (Note G)  
Reporting of pT, pN, and (when applicable) pM categories is based on information available to the pathologist at the time the report is issued. As per the AJCC (Chapter 1, 8th Ed.) it is the managing physician’s responsibility to establish the final pathologic stage based upon all pertinent information, including but potentially not limited to this pathology report.  

Modified Classification (required only if applicable) (select all that apply)  
- Not applicable  
- y (post-neoadjuvant therapy)  
- r (recurrence)  

pT Category  
- pT not assigned (cannot be determined based on available pathological information)  
- pT0: No evidence of primary tumor  
- pT1: Carcinoma is strictly confined to the cervix (extension to the corpus should be disregarded).  
- pT1a: Invasive carcinoma that can be diagnosed only by microscopy with maximum depth of invasion less than or equal to 5 mm.  
# The LAST definition of superficial invasive squamous cell carcinoma (SISCCA) conforms to T1a1.
___ pT1a1: Measured stromal invasion less than or equal to 3 mm in depth
___ pT1a2: Measured stromal invasion greater than 3 mm and less than or equal to 5 mm in depth
___ pT1a (subcategory cannot be determined)

pT1b: Invasive carcinoma with measured deepest invasion greater than 5 mm (greater than stage IA); lesion limited to the cervix with size measured by maximum tumor diameter. Note: The involvement of lymphatic and / or vascular spaces should not change the staging. The lateral extent of the lesion is no longer considered.
___ pT1b1: Invasive carcinoma greater than 5 mm depth of stromal invasion and less than or equal to 2 cm in greatest dimension
___ pT1b2: Invasive carcinoma greater than 2 cm and less than or equal to 4 cm in greatest dimension
___ pT1b3: Invasive carcinoma greater than 4 cm in greatest dimension
___ pT1b (subcategory cannot be determined)
___ pT1 (subcategory cannot be determined)

pT2: Carcinoma invades beyond the uterus, but has not extended onto the lower third of the vagina or to the pelvic wall.
___ pT2a: Involvement limited to the upper two-thirds of the vagina without parametrial invasion.
___ pT2a1: Invasive carcinoma less than or equal to 4 cm in greatest dimension
___ pT2a2: Invasive carcinoma greater than 4 cm in greatest dimension
___ pT2a (subcategory cannot be determined)
___ pT2b: With parametrial invasion but not up to the pelvic wall
___ pT2 (subcategory cannot be determined)

pT3: Carcinoma involves the lower third of the vagina and/or extends to the pelvic wall and/or causes hydronephrosis or nonfunctioning kidney. Note: The pelvis is defined as the muscle, fascia, neurovascular structures, and skeletal portions of the bony pelvis. Cases with no cancer-free space between the tumor and pelvic wall by rectal examination are FIGO III.
___ pT3a: Carcinoma involves lower third of the vagina, with no extension to the pelvic wall
___ pT3b: Extension to the pelvic wall and/or hydronephrosis or nonfunctioning kidney (unless known to be due to another cause)
___ pT3 (subcategory cannot be determined)

## Tumor should involve the mucosal surface.
___ pT4: Carcinoma has involved (biopsy-proven) the mucosa of the bladder or rectum, or has spread to adjacent organs. (Bullous edema, as such, does not permit a case to be assigned to stage 4.)##

T Suffix (required only if applicable)
___ Not applicable
___ (m) multiple primary synchronous tumors in cervix

pN Category
___ pN not assigned (no nodes submitted or found)
___ pN not assigned (cannot be determined based on available pathological information)
___ pN0: No regional lymph node metastasis
___ pN0(i+): Isolated tumor cells in regional lymph node(s) less than or equal to 0.2 mm, or single cells or clusters of cells less than or equal to 200 cells in a single lymph node cross section

pN1: Regional lymph node metastasis to pelvic lymph nodes only.
___ pN1mi: Regional lymph node metastasis (greater than 0.2 mm but less than or equal to 2.0 mm) to pelvic lymph nodes
___ pN1a: Regional lymph node metastasis (greater than 2.0 mm diameter) to pelvic lymph nodes
___ pN1 (subcategory cannot be determined)

pN2: Regional lymph node metastasis to para-aortic lymph nodes, with or without positive pelvic lymph nodes.
___ pN2mi: Regional lymph node metastasis to para-aortic lymph nodes (greater than 0.2 mm but less than or equal to 2.0 mm), with or without positive pelvic lymph nodes
pN2a: Regional lymph node metastasis to para-aortic lymph nodes (greater than 2.0 mm in diameter), with or without positive pelvic lymph nodes

pN2 (subcategory cannot be determined)

**N Suffix (required only if applicable)**
- Not applicable
- (sn) metastasis is identified only by sentinel lymph node biopsy
- (sn)(i-)
- (sn)(i+)
- (f) metastasis is identified only by FNA or core biopsy

**pM Category (required only if confirmed pathologically)**
- Not applicable - pM cannot be determined from the submitted specimen(s)

# Uterine serosa and adnexa involvement are considered M1 disease. (Note G)

pM1: Distant metastasis (includes metastasis to inguinal lymph nodes, intraperitoneal disease, lung, liver, or bone) (excludes metastasis to pelvic or para-aortic lymph nodes, or vagina).

**FIGO STAGE (Note G)**

+FIGO Stage (2018 FIGO Cancer Report)

# Please note that this section includes the Corrigendum to Revised FIGO staging for carcinoma of the cervix uteri. See the appropriate reference in Note G.

I: Carcinoma is strictly confined to the cervix (extension to the uterine corpus should be disregarded)

For FIGO IA cancers, the depth of invasion should not be more than 5.0 mm taken from the base of the epithelium, either surface or glandular, from which it originates. Vascular space invasion does not alter the staging.

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 5.0 mm#

IA1: Measured stromal invasion of 3.0 mm or less in depth##

IA2: Measured stromal invasion of more than 3.0 mm and not more than 5.0 mm###

Lymphatic and / or vascular space invasion does not alter the staging.

IB: Invasive carcinoma with measured stromal invasion greater than 5.0 mm (greater than stage IA) and limited to the uterus####

IB1: Invasive carcinoma with measured stromal invasion greater than 5.0 mm and 2 cm or less in greatest dimension

IB2: Invasive carcinoma greater than 2 cm but 4 cm or less in greatest dimension

IB3: Invasive carcinoma greater than 4 cm in greatest dimension

II: Carcinoma extends beyond the uterus but has not extended onto the pelvic sidewall or to the lower third of vagina

IIA: Carcinoma involves the upper two-thirds of the vagina without parametrial invasion

IIA1: Invasive carcinoma 4 cm or less in greatest dimension

IIA2: Invasive carcinoma greater than 4 cm in greatest dimension

IIB: Parametrial involvement but not involving the pelvic sidewall

III: Carcinoma involves the lower third of the vagina and / or extends to the pelvic sidewall 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)
### Isolated tumor cells do not change the stage, but their presence should be recorded. Notations r refers to imaging and p refers to pathology.

- **IIIC**: Involvement of pelvic and / or para-aortic lymph nodes (including micrometastases), irrespective of tumor size and extent (with r and p notations)
- **IIIC1**: Pelvic lymph node metastasis only
- **IIIC2**: Para-aortic lymph node metastasis

### Involvement of the uterine or pelvic serosa and / or fallopian tubes alone does not constitute FIGO Stage IV disease, but is considered M1 disease in the AJCC / UICC system. (Note G)

- **IV**: Carcinoma extends beyond the true pelvis or involves (biopsy proven) the mucosa of the bladder and / or rectum (bullous edema is not sufficient) or spread to distant organs
- **IV A**: Spread to adjacent organs, i.e., tumor invading the mucosa of the bladder and / or rectum (biopsy proven) and / or extending beyond the true pelvis (bullous edema is not sufficient)
- **IV B**: Spread to distant organs

#### ADDITIONAL FINDINGS

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

- None identified
- Low-grade squamous intraepithelial lesion (CIN 1)
- High-grade squamous intraepithelial lesion (CIN 2 or 3)
- Endocervical adenocarcinoma in situ
- Inflammation
- Other (specify): ________________

#### SPECIAL STUDIES

**Ancillary Studies (specify) (Note H): ________________

- **p16 Immunohistochemistry**
  - Positive
  - Negative

#### COMMENTS

Comment(s): ________________
Explanatory Notes

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 (e.g., 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 that 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
   Tumor Size Measurement
   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 one set of tumor measurements based on a correlation of the gross and microscopic features to avoid confusion. According to the 2018 FIGO staging system for all stages the size of the primary tumor can be assessed by clinical evaluation (pre- or intraoperative), imaging, and/or pathological measurement. However, in surgically treated cases, the pathologist's findings should take priority over clinical or image-based staging and should be used for the pathological staging.

   The depth of invasion is required for the sub-staging of Stage 1 carcinomas in the latest FIGO staging system (2018) and in the latest AJCC system (2020). The depth of invasion is measured from its HSIL origin, that is, from the base of the epithelium, whether epithelial surface or an endocervical gland 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. 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 these tumors. If it is impossible to measure the depth of invasion, e.g., 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. 3,4

**FIGURE 1.** Measurement of Cervical Tumors in 3 Dimensions 5

**FIG. 1.** CIN3 with involvement of endocervical gland crypts is represented by the dark blue-colored areas, nondysplastic squamous epithelium is pink, and gray areas indicate foci of stromal invasion. The depth of invasion (a), and horizontal tumor dimension/width (b) are measured in unifocal disease. Third dimension: when stromal invasion is present in 3 or more consecutive blocks of a loop or cone biopsy the third tumor dimension (c), may exceed 7mm, that is the carcinoma may be more than International Federation of Obstetricians and Gynaecologists stage IA2. 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.

**Horizontal Extent**

This is now an optional element in the synoptic template. It is no longer included in the AJCC staging update and is no longer used for sub-staging of Stage I carcinomas in the 2018 FIGO staging system. 1 However, some still feel that horizontal spread may have prognostic significance in early stage cervical cancer. The collection of horizontal spread data is encouraged to create an opportunity for future analysis and individual clinicians may request a horizontal extent for their practice.

The horizontal extent may be the longitudinal extent (length) measured in the superior-inferior plane (i.e., from the endocervical to ectocervical aspects of the section), or it may be the circumferential extent (width) that is measured or calculated perpendicular to the longitudinal axis of the cervix. When a gross lesion is not identified, the measurement accuracy of horizontal extent may be limited. If the extent is measured on a single glass slide, this may underestimate the true horizontal extent, because the tumor may involve multiple blocks and may have a greater “width” than “length”. The thickness of sections of the cervix, which are often taken as “wedges” of a cone may be variable and may range from less than 1.0 mm to greater than 3.0 mm. In addition, adding thicknesses of adjacent sections where the sections are
taken as a cone are measuring the circumference rather than a linear “width”. Estimates using a thickness of 2.5 mm to 3.0 mm may overestimate the true tumor extent. The pathologist should report the maximum horizontal extent (when it is on a single block) and where multiple blocks are involved, they should report the number of blocks involved and if it is estimated as less than or equal to 7.0 mm or greater than 7.0 mm.

To summarize, horizontal extent data is an optional element and has been excluded from the staging update. However, the collection of horizontal spread data is encouraged.

The Lower Anogenital Squamous Terminology (LAST) definition of superficial invasive squamous cell carcinoma (SISSCA) conforms to T1a1/FIGO IA1 and defines what would have been previously reported as “microinvasive” squamous cell carcinoma. The LAST consensus recommends that SISCCA include multifocal disease and that reporting include the presence, number, and size of independent multifocal carcinoma. However, LAST makes no recommendation 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, as invasive foci in the same tissue block that are more than 2.0 mm apart, or as invasive foci on different cervical lips. They recommend that multifocal tumors should be staged based on the largest focus.

Silva Pattern of Invasion

Silva patterns of invasion are applicable only to HPV-associated invasive endocervical adenocarcinomas. Accurately measuring the depth of stromal invasion can be challenging in some endocervical adenocarcinomas. The Silva system of classification stratifies cases of invasive endocervical adenocarcinomas into three groups on the basis of the morphologic pattern of invasion and is predictive of the risk for LN metastasis. Briefly, Pattern A shows well-demarcated glands with rounded contours, frequently forming groups with no destructive stromal invasion, no single cells or cell detachment and no LVI. Complex intraglandular growth such as cribriform or papillary architecture is acceptable but there is no solid growth. Pattern B shows localized (limited, early) destructive stromal invasion. There are individual or small groups of tumor cells, separated from the rounded gland, in a focally desmoplastic or inflamed stroma. There is no solid growth and LVI may or may not be present. Pattern C shows diffuse destructive stromal invasion. There are diffusely infiltrative glands with associated extensive desmoplastic response. Growth pattern is confluent or solid and LVI may or may not be present. Pattern A cases were all stage I with negative lymph nodes and no recurrences. Pattern B tumors rarely had metastatic lymph nodes and only 23.8% of cases with pattern C had lymph node metastases.

<table>
<thead>
<tr>
<th>Silva Pattern</th>
<th>Histologic Appearance</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Demarcated, complete, rounded glands, frequently forming groups on low power</td>
</tr>
<tr>
<td></td>
<td>Cribriform and papillary growth is possible, but solid (nonglandular) growth is not</td>
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<tr>
<td></td>
<td>No desmoplastic stroma</td>
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<tr>
<td></td>
<td>Lacks single or detached cells</td>
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<tr>
<td></td>
<td>No lymphovascular invasion</td>
</tr>
<tr>
<td></td>
<td>Relationship of tumor to large cervical vessels and depth of tumor are not relevant to pattern</td>
</tr>
<tr>
<td>B</td>
<td>Localized or limited destructive (desmoplastic) stromal invasion arising in Pattern A</td>
</tr>
<tr>
<td></td>
<td>Buds of small glands or individual cells from rounded glands (often in an inflamed or focally desmoplastic stroma), often with increased cytoplasm or maturation</td>
</tr>
<tr>
<td></td>
<td>Single, multiple or linear (base of tumor) foci are acceptable</td>
</tr>
<tr>
<td></td>
<td>No solid growth pattern</td>
</tr>
</tbody>
</table>
Cervix Uteri. Used with permission of the American College of Surgeons, Chicago, Illinois. The original source for this information is the AJCC Cancer Staging System (2020).

C. Histologic Type
For consistency in reporting, the histologic classification proposed by the World Health Organization (WHO) is recommended; other classification systems may be used, however. A majority of cervical squamous cell carcinomas are HPV-associated. p16 testing and/or molecular HPV typing is recommended before making the diagnosis of HPV-associated cervical SCC. If these results are not available, the NOS category should be used. 75% of HPV-associated adenocarcinomas are of the usual type. Villo glandular, mucinous NOS, intestinal, signet ring cell, and SMILE (stratified mucin-producing) carcinoma are all patterns of HPV-associated adenocarcinomas. There is now a general consensus that most or all serous carcinomas detected in the cervix represent metastasis or direct extension from adnexal or endometrial serous carcinomas, although conclusive studies to support this have yet to be published.
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, so no particular system is recommended. For the grading of invasive squamous tumors, it is suggested that three grades be used:

- GradeGX: Cannot be assessed
- GradeG1: Well differentiated
- GradeG2: Moderately differentiated
- GradeG3: Poorly differentiated

It is uncertain whether grading has independent prognostic value in cervical ACA. Whilst a correlation between higher grade and adverse outcomes has been reported, at least for poorly differentiated tumors, this has not been a universal finding. Most grading systems are based on the tumor architecture (glandular and papillary versus solid areas) and its nuclear features. In contrast to squamous cell carcinoma, most authors who grade cervical adenocarcinoma have found the grade to have prognostic value. By definition, the high-grade tumors are grade 3. High-grade neuroendocrine tumors of the cervix are typically HPV-associated, most frequently HPV subtypes 16 or 18.

References


### E. Lymphatic and/or Vascular Invasion

Many gynecologists feel that the presence of lymphatic and/or vascular invasion is important because it may change the extent of their surgical treatment and may be an independent risk factor for recurrence. At times, it may be difficult to evaluate a specimen for lymphatic and/or vascular invasion, as in cases with crush artifact or suboptimal fixation. In these cases, it can be categorized as "cannot be determined". At other times, it may be difficult to be definitive whether lymphatic and/or vascular invasion is present. This can include cases where retraction artifact or artifactual transfer of tumor cells is a consideration. In other cases, foci may be suspicious but not definitive for invasion. All of these situations can be categorized as "equivocal for invasion". In cases where one cannot be definitive, a qualifying note explaining the interpretive difficulty and the extent of possible involvement is recommended, since it may help to direct medical management.

### References


### F. 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 (e.g., cautery artifact in electroexcision specimens may preclude evaluation of the status of the
margin). The severity and extent of a precursor lesion (e.g., 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.1 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.

References

G. Pathological Classification
The TNM categories 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 recommended1,2,3,4,5,6 This does not preclude the use of other staging systems.

By AJCC/UICC convention, the designation “cT” 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 the pathologist's contribution is based on gross and microscopic examination after primary surgical treatment. pT entails a surgical treatment resection of the primary tumor or biopsy adequate to evaluate the highest pT category and highest pN categories, pN entails removal or biopsy 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. Pathological classification (pTNM) must be assigned by the managing physician based on the clinical stage information, the operative findings, and the gross and microscopic examination of the surgical resection specimen. The pathologist provides vital information, but it is not the patient’s final pT, pN, and/or pM categories.

TNM Stage Classifications
The “y” prefix indicates those cases in which classification is performed during or following initial multimodality therapy (i.e., 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 (i.e., 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.

TNM Suffixes
For identification of special cases of TNM or pTNM classifications, the “(m)” T suffix and “(sn)” and “(f)” N suffixes are used. Although they do not affect the stage grouping, they indicate cases needing special analysis.

The “(m)” T suffix indicates the presence of multiple primary synchronous tumors in a single site and is recorded in parentheses: e.g., pT1(m).

The “(sn)” N suffix indicates a sentinel node procedure only, without resection of the nodal basin, was performed and is recorded in parentheses: e.g., pN1(sn).

The “(f)” N suffix indicates a fine needle aspiration (FNA) or core needle biopsy, without a sentinel node procedure or resection of nodal basin, was performed and is recorded in parentheses: e.g., pN1(f).

Of note, tumor size has been shown to have prognostic utility for stage I to stage II lesions, and the 2018 FIGO staging classification uses tumor size for the subclassification of stage I and stage IIa tumors.

The CAP protocols follow the AJCC/UICC staging guidance and vocabulary, which may predate staging guidance from editions of the WHO Classification of Tumours and/or conflict with FIGO staging guidance. Although the ultimate goal is harmonization of these 3 guidelines, discrepancies in the CAP protocol may occur due to release date variability of these manuscripts. The AJCC Cancer Staging System, 9th Version (2020), cervical cancer staging chapter includes guidance for pM1 that contains the statement, “Uterine serosa and adnexal involvement are considered M1 disease” (Table 1) and this conflicts with the definition of M - Distant Metastasis in the WHO Classification of Tumours, 5th edition, Female Genital Tumours, which states for cervix: “M1 – Distant metastasis (includes inguinal lymph nodes and intraperitoneal disease). It excludes metastasis to the vagina, pelvic serosa, and adnexa.” The AJCC/UICC, WHO and FIGO criteria for stage IV disease differ due to limited evidence for consensus. Involvement of the ovary and/or fallopian tube for tumors limited to the cervix constitutes M1 disease in AJCC (involves the fallopian tube and/or ovary), but is stage I in FIGO, (organs are within the true pelvis).

Table 1: AJCC Cancer Staging System, 9th Version, Cervix Uteri Cancer Staging

<table>
<thead>
<tr>
<th>pNX</th>
<th>Not for use by pathologist; assigned only by managing physician</th>
<th>May assign if unable to determine pN category</th>
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<tr>
<td>pNO</td>
<td>Fine Needle Aspiration (FNA), core needle biopsy, sentinel node biopsy, lymph node dissection (including procedures performed prior to definitive surgical resection) Note: These procedures in the absence of a surgical resection are cN</td>
<td>- No regional node(s) sampled or resected</td>
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<tr>
<td>pNO(i+)</td>
<td>Requires: - At least one lymph node sampled</td>
<td></td>
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<tr>
<td>pN1</td>
<td>Requires: - May require information from a previous node biopsy procedure to assign pN category</td>
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<tr>
<td>pN1mi</td>
<td>- For FNA or core biopsy: use (f) modifier</td>
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<tr>
<td>pN1a</td>
<td>- For sentinel node biopsy: use (sn) modifier</td>
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</tr>
<tr>
<td>pN2</td>
<td>Requires: - Same information as the pathologist</td>
<td></td>
</tr>
<tr>
<td>pN2mi</td>
<td>- Supplement with clinically positive nodes from examination or imaging</td>
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<td>pN2a</td>
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<tr>
<td></td>
<td>cM0</td>
<td>cM1</td>
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<tr>
<td></td>
<td>Primary site surgical resection is</td>
<td>Not assigned by pathologist</td>
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<tr>
<td></td>
<td>required to assign pN</td>
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<tr>
<td></td>
<td>When no clinical or pathologic evidence</td>
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<tr>
<td></td>
<td>of metastatic disease, assign cM0</td>
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**T Category Considerations**

**Lymphatic and/or Vascular Invasion (LVI)**

LVI indicates whether microscopic lymphatic and/or vascular invasion is identified. 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**

Sentinel lymph node sampling in cervical carcinoma has been recently implemented. 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 pan-keratin immunohistochemistry.

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 or equal to 2.0 mm.

Isolated tumor cells (ITCs) are single cells or small clusters of cells not more than 0.2 mm in greatest dimension, or single cells or clusters of cells less than or equal to 200 cells in a single lymph node cross section. Lymph nodes or distant sites with ITCs found by either histologic examination (e.g., immunohistochemical evaluation for cytokeratin) or nonmorphological techniques (e.g., 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.

**Examination of Parametria**
The parametria may be measured grossly, but their width varies according to the elasticity of the tissue. The parametria should not be stretched during measurement. Careful microscopic examination of the parametria is important for evaluation of the lateral margins and/or soft tissue extension.

**References**
1. Used with permission of the American College of Surgeons, Chicago, Illinois. The original source for this information is the AJCC Cancer Staging System (2020).

**H. Special Studies**

**p16 Immunohistochemistry**
Immunohistochemistry (IHC) serves as an important adjunct to the histologic diagnosis of high grade squamous intraepithelial lesion (HSIL) in difficult cases, with p16 immunoreactivity serving as a surrogate marker for high-risk human papillomavirus (HPV) infection. Squamous epithelial p16 immunostaining should be diffuse and strong in both nuclei and cytoplasm to support HPV etiology. Focally strong nuclear and cytoplasmic p16 staining may be identified not only in dysplastic squamous epithelium, but also in benign squamous epithelium. 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 HSIL, given its wide availability, easy interpretation, and high sensitivity and specificity. However, due to the heterogeneous staining patterns seen in low-grade squamous intraepithelial lesions (LSIL), p16 immunohistochemistry is generally reserved for lesions that are morphologically suspicious or indeterminate for HSIL. The LAST project proposed that 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 in patients who have previously had a recent HSIL diagnosis.
It should not be used if the biopsy shows identifiable LSIL or HSIL. ProEx C, an immunohistochemical assay targeting both topoisomerase II-alpha and minichromosome maintenance protein-2 (MMP-2), has 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).\(^5\)

**Immunohistochemistry: Endocervical versus Endometrial Adenocarcinoma**

Immunohistochemistry can also be helpful in the differential diagnosis between endocervical and endometrial carcinoma, especially in curettage specimens, since 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.\(^6,7\) Typically, endometrioid adenocarcinoma is positive for vimentin and ER, whereas endocervical adenocarcinoma is positive for p16 and mCEA, but exceptions occur.

**References**