



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

Version: 5.0.1.0

Protocol Posting Date: June 2021

CAP Laboratory Accreditation Program Protocol Required Use Date: March 2022

The changes included in this current protocol version affect accreditation requirements. The new deadline for implementing this protocol version is reflected in the above accreditation date.

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 Excision 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

Uma G. Krishnamurti, MD, PhD*; Barbara A. Crothers, DO*; Saeid Movahedi-Lankarani, MD; George G. Birdsong, MD; Veronica Klepeis, MD, PhD; Christopher N. Otis, MD.

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 5.0.1.0

- General Reformatting
- Revisions to Depth of Stromal Invasion
- Revised Other Tissue / Organ Involvement

Reporting Template

Protocol Posting Date: June 2021

Select a single response unless otherwise indicated.

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
- Bladder mucosa[#]
- Rectal wall
- Bowel mucosa[#]
- Other organs / tissue (specify): _____
- Cannot be determined (explain): _____

[#] Tumor should involve the mucosal surface

Lymphovascular 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)

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

** 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.*

+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

___ Tumor present in pelvic lymph node(s)

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.

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)

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 (select all that apply)

- Right sentinel: _____
- Right non-sentinel: _____
- Left sentinel: _____
- Left non-sentinel: _____
- Cannot be determined: _____
- Not applicable

+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)

- 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)

- Not applicable
- Exact number: _____
- At least: _____
- 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)

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
- Specify number: _____
- At least: _____
- 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 (select all that apply)

- Right sentinel: _____
- Right non-sentinel: _____
- Left sentinel: _____
- Left non-sentinel: _____
- Cannot be determined: _____
- Not applicable

+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): _____

___ 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

___ 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

___ 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: _____

PATHOLOGIC STAGE CLASSIFICATION (pTNM, 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.

TNM Descriptors (select all that apply)

- Not applicable: _____
- m (multiple primary tumors)
- r (recurrent)
- y (post-treatment)

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 uteri with size measured by maximum tumor diameter. Note: The involvement of vascular/lymphatic 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 pelvic wall 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.)^{##}

Regional Lymph Node Modifier

*The suffix (sn) is added to the N category when metastasis is identified only by sentinel lymph node biopsy.

___ Not applicable

___ (sn)[#]

___ (sn)(i-)

___ (sn)(i+)

##The suffix (f) is added to the N category when metastasis is identified only by FNA or core biopsy.

___ (f)^{##}

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)

pM Category (required only if confirmed pathologically)

___ Not applicable - pM cannot be determined from the submitted specimen(s)

___ 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). Uterine serosa and adnexa involvement are considered M1 disease.

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.

^{##} The LAST definition of superficial invasive squamous cell carcinoma (SISCCA) conforms to FIGO 1A1.

___ 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

###Vascular/ lymphatic 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

___ 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

___ IVA: 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)

___ IVB: 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 (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 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.¹ 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)¹ and in the latest AJCC system (2020).² 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, 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.^{3,4}

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 (ie, 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.^{5,6} 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)⁷ 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 SISSCA 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.⁷

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 classification⁸ 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.

Silva Pattern ⁸	Histologic Appearance
A	Demarcated, complete, rounded glands, frequently forming groups on low power Cribriform and papillary growth is possible, but solid (nonglandular) growth is not No desmoplastic stroma Lacks single or detached cells No lymphovascular invasion Relationship of tumor to large cervical vessels and depth of tumor are not relevant to pattern
B	Localized or limited destructive (desmoplastic) stromal invasion arising in Pattern A Buds of small glands or individual cells from rounded glands (often in an inflamed or focally desmoplastic stroma), often with increased cytoplasm or maturation Single, multiple or linear (base of tumor) foci are acceptable No solid growth pattern Lymphovascular invasion may or may not be present
C	Diffuse growth pattern with destructive (often extensive desmoplastic) stromal invasion Confluent growth of glands, papillae, or mucin lakes filling 4X field (5 mm) Angulated, often incomplete or discontinuous glands (breaks opening into the stroma) Canalicular (labyrinthine, interconnected glandular) pattern with occasional open glands Solid or poorly differentiated component (high grade); nuclear grade is disregarded Lymphovascular invasion may or may not be present

References

1. Bhatla N, Berek JS, Cuello Fredes M, et al. Revised FIGO staging for carcinoma of the cervix uteri. *Int J Gynaecol Obstet.* 2019;145(1):129-135.
2. Olawaiye AB, Hagemann I, Otis C et al. 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).
3. 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: 352-35.
4. 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;73:177-83.
5. McCluggage WG, Judge MJ, Alvarado-Cabrero I, et al. Data set for the reporting of carcinomas of the cervix: recommendations from the International Collaboration on Cancer Reporting (ICCR). *Int J Gynecol Pathol.* 2018; 37(3):205-228.
6. Day E, Duffy S, Bryson G, et al. Multifocal FIGO Stage IA1 squamous carcinoma of the cervix: criteria for identification, staging, and its good clinical outcome. *Int J Gynecol Pathol.* 2016;35:467-474.
7. Darragh TM, Colgan TJ, Cox JT, et al. The Lower Anogenital Squamous Terminology Standardization Project for HPV-Associated Lesions: background and consensus recommendations from the College of American Pathologists and the American Society for Colposcopy and Cervical Pathology. *Arch Pathol Lab Med.* 2012; 136(10):1266-1297.
8. Roma AA, Diaz De Vivar A, Silva EG et al. Invasive endocervical adenocarcinoma: a new pattern-based classification system with important clinical significance. *Am J Surg Pathol.* 2015; 39(5):667-672.

C. Histologic Type

For consistency in reporting, the histologic classification proposed by the World Health Organization (WHO) is recommended;¹ 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. Villoglandular, 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.

References

1. Herrington, CS, Ordi, J, Bray, F. Tumours of the uterine cervix In: WHO Classification of Tumours, Editorial Board. Female genital tumours [Internet]. Lyon (France): International Agency for Research on Cancer; 2020 [cited 2020 Sep 22]. (WHO classification of tumours series, 5th ed.; vol. 4). Available from: <https://tumourclassification.iarc.who.int/chapters/34>.

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:

- GX Cannot be assessed
- G1 Well differentiated
- G2 Moderately differentiated
- G3 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.^{1,2,3,4}

- 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.

Neuroendocrine tumors of the cervix have a separate grading system mirroring neuroendocrine tumors of other body sites. The 2020 WHO classifies uterine cervix neuroendocrine tumors into two categories: low-grade neuroendocrine tumor (including grades 1 and 2) and high-grade neuroendocrine carcinoma (including small cell neuroendocrine carcinoma and large cell neuroendocrine carcinoma), along with a “mixed” category with other carcinoma. By definition, the high-grade tumors are Grade 3.^{3,4,5} High-grade neuroendocrine tumors of the cervix are typically HPV-associated, most frequently HPV subtypes 16 or 18.

References

1. Kosary CL. FIGO stage, histology, histologic grade, age and race as prognostic factors in determining survival for cancers of the female gynecological system: an analysis of 1973-87 SEER cases of cancers of the endometrium, cervix, ovary, vulva, and vagina. *Semin Surg Oncol.* 1994;10:31-46.
2. Baalbergen A, Ewing-Graham PC, Hop WC, Struijk P, Helmerhorst TJ. Prognostic factors in adenocarcinoma of the uterine cervix. *Gynecol Oncol.* 2004;92:262-267.

3. Takeda N, Sakuragi N, Takeda M, et al. Multivariate analysis of histopathologic prognostic factors for invasive cervical cancer treated with radical hysterectomy and systematic retroperitoneal lymphadenectomy. *Acta Obstet Gynecol Scand.* 2002;8:1144-1151.
4. Lea JS, Sheets EE, Wenham RM, Duska LR, Coleman RL, Miller DS and Schorge JO (2002). Stage IIB-IVB cervical adenocarcinoma: prognostic factors and survival. *Gynecol Oncol* 2002; 84:115-119.
5. Howitt BE, Kelly P, McCluggage WG. Pathology of neuroendocrine tumors of the female genital tract. *Curr Oncol Rep.* 2017; 19:59. doi 10.1007/s11912-017-0617-2.

E. 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 and may be an independent risk factor for recurrence.^{1,2,3,4} At times, it may be difficult to evaluate a specimen for vascular/lymphatic vessel 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 vascular/lymphatic vessel 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.^{2,5,6,7}

References

1. Casarin J, Buda A, Bogani G, et al. Predictors of recurrence following laparoscopic radical hysterectomy for early-stage cervical cancer: a multi-institutional study. *Gynecol Oncol.* 2020; 159(1):164-170.
2. Margolis B, Cagle-Colon K, Chen L, Tergas AI, Boyd L, Wright JD. Prognostic significance of lymphovascular space invasion for stage IA2 and IA3 cervical cancer. *Int J Gynecol Cancer.* 2020; 30(6):735-743.
3. Qian Q, Yang J, Cao D, You Y, Chen J, Shen K. Analysis of treatment modalities and prognosis on microinvasive cervical cancer: a 10-year cohort study in China. *J Gynecol Oncol.* 2014; 25(4):293-300.
4. Kodama J, Mizutani Y, Hongo A, Yoshinouchi M, Kudo T, Okuda H. Optimal surgery and diagnostic approach of stage IA2 squamous cell carcinoma of the cervix. *Eur J Gynecol Reprod Biol.* 2002; 101(2):192-195.
5. Yan W, Qui S, Ding Y, Zhang Q, Si L, Lv S, Lui L. Prognostic value of lymphovascular space invasion in patients with early stage cervical cancer in Jilin, China: a retrospective study. *Medicine.* 2019; 98(40):e17302.
6. Weyl A, Illac C, Lusque A, et al. Prognostic value of lymphovascular space invasion in early-stage cervical cancer. *Int J Gynecol Cancer.* 2020; 30(10):1493-1499.
7. Pol FJ, Zusterzeel PL, vanHam MA, Kuijpers DA, Bulten J, Massuger LF. Satellite lymphovascular space invasion: an independent risk factor in early stage cervical cancer. *Gynecol Oncol.* 2015; 138(3):579-582.

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 (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.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

1. McCluggage WG, Judge MJ, Alvarado-Cabrero I, et al. Data set for the reporting of carcinomas of the cervix: recommendations from the International Collaboration on Cancer Reporting (ICCR). *Intl J Gynecol Pathol.* 2018;37(3):205–228.

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 recommended.^{1,2,3,4,5,6}

By AJCC/UICC convention, the designation “T” refers to a primary tumor that has not been previously treated. The symbol “p” refers to the pathological classification of the TNM, as opposed to the clinical ‘c’ 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.

Pathological classification is usually performed after surgical resection of the primary tumor. Pathological classification 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 infeasible) and if the highest T and N categories or the M1 category of the tumor can be confirmed microscopically, the criteria for pathological 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 2018 FIGO staging classification uses tumor size for the subclassification of stage I and stage IIa tumors.

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 total number of primary tumors may be (optionally) reported in parentheses after the (m) pT(m)(2)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

Sentinel lymph node sampling in cervical carcinoma has been recently implemented.⁷ 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 pankeratin immunohistochemistry.^{8,9,10}

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 (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.

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.

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).
2. Brierley JD, Gospodarowicz M, Wittekind CH, eds. TNM Classification of Malignant Tumors. 8th ed. Oxford, UK: Wiley; 2016.

3. Bhatla N, Berek JS, Cuello Fredes M, et al. Revised FIGO staging for carcinoma of the cervix uteri. *Int J Gynaecol Obstet.* 2019;145:129-135.
4. Bhatla N, Berek JS, Cuello Fredes M, et al: Corrigendum to “Revised FIGO staging for carcinoma of the cervix uteri” [*Int J Gynecol Obstet* 145(2019) 129–135]; *Int J Gynecol Obstet.* 2019; 147: 279–280.
5. Bhatla N, Denny L FIGO Cancer Report 2018. *Int J Gynecol Obstet.* 2018; 142 (Suppl 2): i-iv, 1-158.
6. Bhatla N, Aoki D, Sharma DN, Sankaranarayanan R. Cancer of the cervix uteri. *Int J Gynecol Obstet.* 2018; 143 (Suppl 2):22-36.
7. Cibula D, McCluggage WG. Sentinel lymph node (SLN) concept in cervical cancer: current limitations and unanswered questions. *Gynecol Oncol.* 2019;152(1):202-207.
8. Diaz JP, Gemignani ML, Pandit-Taskar N, et al. Sentinel lymph node biopsy in the management of early-stage cervical carcinoma. *Gynecol Oncol.* 2011;120(3):347-352.
9. Euscher ED, Malpica A, Atkinson EN, Levenback CF, Frumovitz, M, Deavers MT. Ultrastaging improves detection of metastases in sentinel lymph nodes of uterine cervix squamous cell carcinoma. *Am J Surg Pathol.* 2008;32(9):1336-1343.
10. Dunch P, Cibula D, Němejcová K, Tichá I, Bártů M, Jakša R. Pathologic protocols for sentinel lymph nodes ultrastaging in cervical cancer. *Arch Pathol Lab Med.* 2020; 144(8):1011-1020.

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.^{1,2} 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.³ 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.⁴ 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

1. Kalof AN, Evans MF, Simmons-Arnold L, Beatty BG, Cooper K. p16INK4A immunoreactivity and HPV in situ hybridization signal patterns: potential markers of high-grade cervical intraepithelial neoplasia. *Am J Surg Pathol.* 2005;29:674-679.

2. Kalof AN, Cooper K. p16INK4a immunoexpression: surrogate marker of high-risk HPV and high-grade cervical intraepithelial neoplasia. *Adv Anat Pathol*. 2006;13:190-194.
3. Kong CS, Balzer BL, Troxell ML, Patterson BK, Longacre TA. p16INK4A immunohistochemistry is superior to HPV in situ hybridization for the detection of high-risk HPV in atypical squamous metaplasia. *Am J Surg Pathol*. 2007;31:33-43.
4. Darragh TM, Colgan TJ, Cox JT, et al. The Lower Anogenital Squamous Terminology Standardization Project for HPV-Associated Lesions: background and consensus recommendations from the College of American Pathologists and the American Society for Colposcopy and Cervical Pathology. *Arch Pathol Lab Med*. 2012;136(10):1266-1297.
5. Badr RE, Walts AE, Chung F, Bose S. BD ProEx C: a sensitive and specific marker of HPV-associated squamous lesions of the cervix. *Am J Surg Pathol*. 2008;32:899-906.
6. Castrillon DH, Lee KR, Nucci MR. Distinction between endometrial and endocervical adenocarcinoma: an immunohistochemical study. *Int J Gynecol Pathol*. 2002;21:4-10.
7. Kamoi S, AlJuboury MI, Akin MR, Silverberg SG. Immunohistochemical staining in the distinction between primary endometrial and endocervical adenocarcinomas: another viewpoint. *Int J Gynecol Pathol*. 2002;21:217-223.