COLLEGE of AMERICAN PATHOLOGISTS

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

Protocol applies to all invasive carcinomas of the cervix.

Based on AJCC/UICC TNM, 7th edition, and FIGO 2014 Annual Report

Protocol web posting date: January 2016

Procedures
- Excision (Cone/LEEP)
- Radical Trachelectomy
- Radical Hysterectomy
- Pelvic Exenteration

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CAP Uterine Cervix Protocol Revision History

Version Code
The definition of version control and an explanation of version codes can be found at www.cap.org (search: cancer protocol terms).

Version: UterineCervix 3.3.0.0

Summary of Changes
The following changes have been made since the December 2013 release.

Excision (Cone/LEEP)

The following data elements were modified:
- Tumor Size
- Margins
- Lymph-Vascular Invasion

Trachelectomy, Hysterectomy, Pelvic Exenteration

The following data elements were modified:
- Tumor Size
- Margins
- Lymph-Vascular Invasion
- Distant Metastasis (changed to required only if confirmed pathologically)
- Additional Pathologic Findings

The following data element was added:
- FIGO Stage (not required)

Surgical Pathology Cancer Case Summary

Protocol web posting date: January 2016

UTERINE CERVIX: Excision (Cone/LEEP)

Select a single response unless otherwise indicated.

Specimen (select all that apply)
___ Cervix
___ Other (specify): _____
___ Not specified

Procedure
___ Cold knife cone excision
___ Loop electrical excision procedure (LEEP) / large loop excision of the transformation zone (LLETZ)
___ Other (specify): _____
___ Not specified

Tumor Site (select all that apply) (Notes A, B, C)
___ Left superior quadrant (12 to 3 o'clock)
___ Left inferior quadrant (3 to 6 o'clock)
___ Right inferior quadrant (6 to 9 o'clock)
___ Right superior quadrant (9 to 12 o'clock)
___ Other (specify): _____
___ Not specified

Tumor Size
Greatest dimension: ___ cm
+ Additional dimensions: ___ x ___ cm
___ Cannot be determined (explain): _____
Note: All dimensions are important; see definition for "superficially invasive squamous cell carcinoma" under T1a1/IA1.

Histologic Type (select all that apply) (Note D)
___ Superficial invasive squamous cell carcinoma (SISSCA)
___ Squamous cell carcinoma
- ___ Keratinizing
- ___ Non-keratinizing
- ___ Basaloid
- ___ Verrucous
- ___ Warty
- ___ Papillary
- ___ Lymphoepithelioma-like
- ___ Squamotransitional

___ Early invasive adenocarcinoma
___ Mucinous adenocarcinoma
- ___ Endocervical
- ___ Intestinal
- ___ Signet-ring cell
- ___ Minimal deviation
- ___ Villoglandular
- ___ Gastric

___ Endometrioid adenocarcinoma
___ Clear cell adenocarcinoma

+ Data elements preceded by this symbol are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.

___ Serous adenocarcinoma
___ Mesonephric adenocarcinoma
___ Adenosquamous carcinoma
___ Glassy cell carcinoma variant
___ Adenoid cystic carcinoma
___ Adenoid basal carcinoma
___ Carcinoid
___ Atypical carcinoid
___ Small cell carcinoma
___ Large cell neuroendocrine carcinoma
___ Undifferentiated carcinoma
___ Other (specify): _____
___ Carcinoma, type cannot be determined

Histologic Grade (Note E)
___ Not applicable
___ GX: Cannot be assessed
___ G1: Well differentiated
___ G2: Moderately differentiated
___ G3: Poorly differentiated

Stromal Invasion
Depth: ___ mm
Horizontal extent: ___ mm
___ Extent cannot be assessed

Margins (select all that apply) (Note F)
___ Margins cannot be assessed (eg, obscuring electrocautery artifact)

Endocervical Margin
___ Uninvolved by invasive carcinoma
+ Distance of invasive carcinoma from margin: ___ mm
+ Specify location: _____
___ Involved by invasive carcinoma
+ Specify location: _____
+ ___ Focal
+ ___ Diffuse
___ Uninvolved by squamous intraepithelial lesion
___ Involved by squamous intraepithelial lesion
+ Specify grade: _____
___ Uninvolved by adenocarcinoma in situ
___ Involved by adenocarcinoma in situ

Exocervical Margin
___ Uninvolved by invasive carcinoma
+ Distance of invasive carcinoma from margin: ___ mm
+ Specify location: _____
___ Involved by invasive carcinoma
+ Specify location: _____
+ ___ Focal
+ ___ Diffuse
___ Uninvolved by squamous intraepithelial lesion
___ Involved by squamous intraepithelial lesion
+ Specify grade: _____
___ Uninvolved by adenocarcinoma in situ
___ Involved by adenocarcinoma in situ

+ Data elements preceded by this symbol are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.

Deep Margin
___ Uninvolved by invasive carcinoma
    + Distance of invasive carcinoma from margin: ___ mm
    + Specify location: _____
___ Involved by invasive carcinoma
    + Specify location: _____
+ ___ Uninvolved by squamous intraepithelial lesion
+ ___ Involved by squamous intraepithelial lesion
    + Specify grade: _____
___ Uninvolved by adenocarcinoma in situ
___ Involved by adenocarcinoma in situ

Lymph-Vascular Invasion (Note G)
___ Not identified
___ Present
___ Cannot be determined

+ Additional Pathologic Findings (select all that apply)
+ ___ None identified
+ ___ Low-grade squamous intraepithelial lesion (CIN 1)
+ ___ High-grade squamous intraepithelial lesion (CIN 2 or 3)
+ ___ Koilocytosis
+ ___ Inflammation
+ ___ Other (specify): _____

+ Comment(s)

Surgical Pathology Cancer Case Summary

Protocol web posting date:

UTERINE CERVIX: Trachelectomy, Hysterectomy, Pelvic Exenteration

Select a single response unless otherwise indicated.

Specimen (select all that apply) (Note H)
___ Cervix
___ Uterine corpus
___ Right ovary
___ Left ovary
___ Right fallopian tube
___ Left fallopian tube
___ Vagina
___ Urinary bladder
___ Rectum
___ Other (specify): _____
___ Not specified

Procedure
___ Trachelectomy
___ Radical hysterectomy
___ Pelvic exenteration
___ Other (specify): _____
___ Not specified

Tumor Size
Greatest dimension: ___ cm
+ Additional dimensions: ___ x ___ cm
___ Cannot be determined (explain): _____
Note: All dimensions are important; see definition for "superficially invasive squamous cell carcinoma" under T1a1/IA1.

Tumor Site (select all that apply)
___ Left superior quadrant (12 to 3 o'clock)
___ Left inferior quadrant (3 to 6 o'clock)
___ Right inferior quadrant (6 to 9 o'clock)
___ Right superior quadrant (9 to 12 o'clock)
___ Other (specify): _____
___ Not specified

Histologic Type (select all that apply) (Note D)
___ Superficial invasive squamous cell carcinoma (SISSCA)
___ Squamous cell carcinoma
- ___ Keratinizing
- ___ Non-keratinizing
- ___ Basaloid
- ___ Verrucous
- ___ Warty
- ___ Papillary
- ___ Lymphoepithelioma-like
- ___ Squamotransitional

___ Early invasive adenocarcinoma
___ Mucinous adenocarcinoma
    ___ Endocervical
    ___ Intestinal
    ___ Signet-ring cell
    ___ Minimal deviation
    ___ Villoglandular
    ___ Gastric
___ Endometrioid adenocarcinoma
___ Clear cell adenocarcinoma
___ Serous adenocarcinoma
___ Mesonephric adenocarcinoma
___ Adenosquamous carcinoma
___ Glassy cell carcinoma variant
___ Adenoid cystic carcinoma
___ Adenoid basal carcinoma
___ Carcinoid
___ Atypical carcinoid
___ Small cell carcinoma
___ Large cell neuroendocrine carcinoma
___ Undifferentiated carcinoma
___ Other (specify): _____
___ Carcinoma, type cannot be determined

Histologic Grade (Note E)
___ Not applicable
___ GX: Cannot be assessed
___ G1: Well differentiated
___ G2: Moderately differentiated
___ G3: Poorly differentiated

Stromal Invasion
Depth: ___ mm
Horizontal extent: ___ mm
___ Extent cannot be assessed

Margins (select all that apply) (Note F)
___ Cannot be assessed
___ Uninvolved by invasive carcinoma
    Distance of invasive carcinoma from closest margin: ___ mm
    Specify margin: _____
    ___ No HSIL identified at distal margin
    ___ HSIL present at distal margin
___ Involved by invasive carcinoma
    Specify margin(s): _____
___ Not applicable

Lymph-Vascular Invasion (Note G)
___ Not identified
___ Present
___ Cannot be determined

Pathologic Staging (pTNM) (Notes H, I, and J)

TNM Descriptors (required only if applicable) (select all that apply)
___ m (multiple primary tumors)
___ r (recurrent)
___ y (posttreatment)

Primary Tumor (pT)
___ pTX: Cannot be assessed
pT1: Cervical carcinoma confined to uterus (extension to corpus should be disregarded)
___ pT1a: Invasive carcinoma diagnosed by microscopy only. All macroscopically visible lesions (even with superficial invasion) are pT1b/1B.
___ pT1a1: Stromal invasion ≤3.0 mm in depth and horizontal spread ≤7.0 mm
___ pT1a2: Stromal invasion >3.0 mm but not more than 5.0 mm in depth and horizontal spread ≤7.0 mm
___ pT1b: Clinically visible lesion confined to the cervix or microscopic lesion greater than T1a2/IA2
___ pT1b1: Clinically visible lesion ≤4.0 cm in greatest dimension
___ pT1b2: Clinically visible lesion >4.0 cm in greatest dimension
pT2: Tumor invades beyond the uterus but not to pelvic wall or to lower third of vagina
___ pT2a: Tumor without parametrial invasion
___ pT2a1: Clinically visible lesion ≤4.0 cm in greatest dimension
___ pT2a2: Clinically visible lesion >4.0 cm in greatest dimension
___ pT2b: Tumor with parametrial invasion
pT3: Tumor extends to the pelvic wall and/or involves the lower third of the vagina and/or causes hydronephrosis or nonfunctioning kidney
___ pT3a: Tumor involves lower third of vagina, but not pelvic wall
___ pT3b: Tumor extends to pelvic wall and/or causes hydronephrosis or nonfunctioning kidney
___ pT4: Tumor invades the mucosa of bladder or rectum and/or extends beyond true pelvis (bullous edema is not sufficient evidence to classify a tumor as pT4)

Regional Lymph Nodes (pN) (select all that apply)

+ *Modifier*

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

Category (pN)

___ pNX: Cannot be assessed
___ pN0: No regional lymph node metastasis
___ pN1: Regional lymph node metastasis

___ No nodes submitted or found

Pelvic lymph nodes:

___ No pelvic nodes submitted or found

Number of Pelvic Lymph Nodes Examined
Specify: ____
___ Number cannot be determined (explain): _____

Number of Pelvic Lymph Nodes Involved
Specify: ____
___ Number cannot be determined (explain): _____

+ Data elements preceded by this symbol are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.

Para-aortic lymph nodes:

___ No para-aortic nodes submitted or found

Number of Para-aortic Lymph Nodes Examined
Specify: ____
___ Number cannot be determined (explain): _____

Number of Para-aortic Lymph Nodes Involved
Specify: ____
___ Number cannot be determined (explain): _____

Other lymph nodes:

Specify site: _____

Number of Other Lymph Nodes Examined
Specify: ____
___ Number cannot be determined (explain): _____

Number of Other Lymph Nodes Involved
Specify: ____
___ Number cannot be determined (explain): _____

+ Number of lymph nodes with isolated tumor cells (<0.2 mm): ____
+ Number of lymph nodes with micrometastasis (>0.2 mm to 2 mm): ____

Distant Metastasis (pM) (required only if confirmed pathologically in this case)
___ pM1: Distant metastasis
Specify site(s), if known: _____

+ FIGO Stage
+ I: Carcinoma is strictly confined to the cervix (extension to the uterine corpus should be disregarded).
+ ___ IA: Invasive cancer identified only microscopically. (All gross lesions even with superficial invasion are stage IB cancers.) Invasion is limited to measured stromal invasion with a maximum depth of 5 mm and no wider than 7 mm.
+ ___ IA1: Measured invasion of stroma ≤3 mm in depth and ≤7 mm width.
+ ___ IA2: Measured invasion of stroma >3 mm and <5 mm in depth and ≤7 mm width.
+ ___ IB: Clinical lesions confined to the cervix, or preclinical lesions greater than stage IA.
+ ___ IB1: Clinical lesions ≤4 cm in size.
+ ___ IB2: Clinical lesions >4cm in size.
+ II: The carcinoma extends beyond the uterus, but has not extended onto the pelvic wall or to the lower third of vagina.
+ ___ IIA: Involvement of up to the upper two-thirds of the vagina. No obvious parametrial involvement.
+ ___ IIA1: Clinically visible lesion ≤4 cm
+ ___ IIA2: Clinically visible lesion >4 cm
+ ___ IIB: Obvious parametrial involvement but not onto the pelvic sidewall.
+ III: The carcinoma has extended onto the pelvic sidewall. On rectal examination, there is no cancer-free space between the tumor and pelvic sidewall. The tumor involves the lower third of the vagina. All cases of hydronephrosis or nonfunctioning kidney should be included unless they are known to be due to other causes.
+ ___ IIIA: Involvement of the lower vagina but no extension onto pelvic sidewall.
+ ___ IIIB: Extension onto the pelvic sidewall, or hydronephrosis/nonfunctioning kidney.
+ IV: Carcinoma has extended beyond the true pelvis or has clinically involved the mucosa of the bladder and/or rectum.
+___ IVA: Spread to adjacent pelvic organs.

+___ IVB: Spread to distant organs.

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

+ Additional Pathologic Findings (select all that apply)
+ ___ None identified
+ ___ Low-grade squamous intraepithelial lesion (CIN 1)
+ ___ High-grade squamous intraepithelial lesion (CIN 2 or 3)
+ ___ Koilocytosis
+ ___ Inflammation
+ ___ Other (specify): _____

+ Ancillary Studies
+ Specify: _____

+ Comment(s)

Explanatory Notes

A. 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.

B. Specimen Handling (Cone/LEEP)

Specimens should have their margins inked and be step-sectioned with orientation by quadrant. For large, unfixed, cervical cone/loop electrical excision procedure (LEEP) specimens, the endocervical margin may be marked with ink and pinned on a corkboard with the mucosa facing up. Three hours of fixation before cutting is optimal. The specimen should be sectioned entirely at 1- to 3-mm intervals. Each tissue section may be marked with India ink or a dye such as eosin in order to orient embedding and facilitate evaluation of margins. For optimal evaluation, the sections are placed into separate cassettes, which are numbered consecutively.

C. Absence of Tumor

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

D. 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.

WHO Histologic Classification of Cervical Carcinoma and Precursor Lesions

<u>Epithelial Tumors and Related Lesions</u>

- Squamous lesions
  - Squamous intraepithelial lesions (cervical intraepithelial neoplasia/ squamous intraepithelial lesion [CIN/SIL])
    - Mild dysplasia (CIN 1/low-grade squamous intraepithelial lesion [LSIL])
    - Moderate dysplasia (CIN 2/high-grade squamous intraepithelial lesion [HSIL])
    - Severe dysplasia (CIN 3/HSIL)
    - Carcinoma in situ (CIN 3/HSIL)
  - Early invasive squamous cell carcinoma
  - Squamous cell carcinoma, not otherwise specified (NOS)
    - Keratinizing
    - Non-keratinizing
    - Basaloid
    - Verrucous
    - Warty
    - Papillary
    - Lymphoepithelioma-like
    - Squamotransitional
- Glandular lesions
  - Adenocarcinoma in-situ
  - Early invasive adenocarcinoma
  - Adenocarcinoma
    - Mucinous adenocarcinoma
      - Endocervical
      - Intestinal
      - Signet-ring cell
      - Minimal deviation

Villoglandular
Endometrioid adenocarcinoma
Clear cell adenocarcinoma
Serous adenocarcinoma
Mesonephric adenocarcinoma
Other epithelial tumors
Adenosquamous carcinoma
Glassy cell carcinoma variant
Adenoid cystic carcinoma
Adenoid basal carcinoma
Neuroendocrine tumors
Carcinoid
Atypical carcinoid
Small cell carcinoma
Large cell neuroendocrine carcinoma
Undifferentiated carcinoma

E. 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. Grading is considered optional at the present time.

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

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

In contrast to squamous cell carcinoma, most authors who grade cervical adenocarcinoma on the basis of its architecture (glandular and papillary versus solid areas) and its nuclear features have found the grade to have prognostic value.[2-4]

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.

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.

G. Lymph-Vascular Invasion
Many gynecologists feel that the presence of vascular/lymphatic vessel invasion is important because it may change the extent of their surgical treatment. Specifically, the Society of Gynecologic Oncology (SGO) differs with the International Federation of Gynecology and Obstetrics (FIGO) in the definition of early invasive carcinoma.

The SGO defines such tumors as being invasive to a depth <3 mm, with a width of <7 mm, but most importantly lacking lymphovascular invasion. At times, it may be difficult to determine whether vascular/lymphatic vessel invasion is present; in such cases, its presence should be categorized as indeterminate (cannot be determined).[5]

H. Examination of Bladder and Rectum

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

I. Staging

The TNM staging system for cervical cancer endorsed by the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC), and the parallel system formulated by the International Federation of Gynecology and Obstetrics (FIGO) are recommended as shown below.[6-10]

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

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

Of note, tumor size has been shown to have prognostic utility for stage I to stage II lesions, and the 2014FIGO staging classification has adopted T subclassifications for T2 lesions (cervical carcinoma spreading beyond the cervix but not to the pelvic side wall or lower one-third of the vagina), based on tumor size ≤4 cm (T2a1) and >4 cm (T2a2).[6,10]

TNM Descriptors

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

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

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

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

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

Additional Descriptors

Residual Tumor (R)
Tumor remaining in a patient after therapy with curative intent (eg, surgical resection for cure) is categorized by a system known as R classification, shown below.

RX Presence of residual tumor cannot be assessed
R0 No residual tumor
R1 Microscopic residual tumor
R2 Macroscopic residual tumor

For the surgeon, the R classification may be useful to indicate the known or assumed status of the completeness of a surgical excision. For the pathologist, the R classification is relevant to the status of the margins of a surgical resection specimen. That is, tumor involving the resection margin on pathologic examination may be assumed to correspond to residual tumor in the patient and may be classified as macroscopic or microscopic according to the findings at the specimen margin(s).

Lymph-Vascular Invasion (LVI)
LVI indicates whether microscopic lymph-vascular invasion is identified. LVI includes lymphatic invasion, vascular invasion, or lymph-vascular 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.

Regional Lymph Nodes: Isolated Tumor Cells
Isolated tumor cells (ITC) are single cells or small clusters of cells not more than 0.2 mm in greatest dimension. Lymph nodes or distant sites with ITC found by either immunohistochemical (eg, cytokeratin) examination or non-morphological/molecular techniques (eg, flow cytometry, DNA analysis, polymerase chain reaction [PCR] amplification of a specific tumor marker) should be so identified.[11] There is currently no guidance in the literature as to how these patients should be coded (in contrast to similar patients with breast carcinoma); until further studies are available, these patients should be coded as N0(i+), with a comment noting how the cells were identified.

J. 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.

K. Special Studies

p16 Immunohistochemistry
Immunohistochemistry has served as an important adjunct to the histologic diagnosis of CIN in difficult lesions, with p16 immunoreactivity being a good surrogate marker for high-risk human papillomavirus (HPV) infection.[12,13] p16 immunostaining in the squamous epithelium, however, should be diffuse; strong nuclear and cytoplasmic staining, as focal strong p16 reactivity, may be identified not only in dysplastic squamous epithelium, but also in benign squamous epithelium (Table 1). p16 immunostaining is also considered a better candidate (rather than HPV in situ hybridization) for the initial assessment of cervical biopsies that are histologically indeterminate for dysplasia, given its wide availability, easy interpretation, and high sensitivity and specificity.[14] Given the heterogenous staining patterns seen in low-grade CIN lesions, however, immunohistochemistry for p16 is generally reserved for lesions that are morphologically suspicious or indeterminate for high-grade dysplasia. The LAST project proposed p16 be used in 3 specific situations. First, to distinguish inflammatory lesions from HSIL; second, to distinguish LSIL from HSIL; and third, to evaluate specimens such as endocervical curettage on patients who have previously had a recent HSIL diagnosis. ProEx C, an immunohistochemical assay targeting both topoisomerase II-alpha and minichromosome maintenance protein-2 (MMP-2), has recently been shown to have high sensitivity and specificity for HPV-associated lesions of the cervix, with similar staining patterns as those seen for p16 and MIB-1 (Ki-67).[15]

Immunohistochemistry: Endocervical versus Endometrial Adenocarcinoma

Immunohistochemistry can also be helpful in the differential diagnosis between endocervical and endometrial carcinoma, especially in curettage specimens, as endometrial carcinomas may show mucinous differentiation. A panel of antibodies, rather than a single antibody, is most useful; in most instances this includes vimentin, ER, p16, and monoclonal CEA.[16,17]

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

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

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

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

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