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
Protocol web posting date: October 2009

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

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The College of American Pathologists offers these protocols to assist pathologists in providing clinically useful and relevant information when reporting results of surgical specimen examinations of surgical specimens. The College regards the reporting elements in the “Surgical Pathology Cancer Case Summary (Checklist)” portion of the protocols as essential elements of the pathology report. However, the manner in which these elements are reported is at the discretion of each specific pathologist, taking into account clinician preferences, institutional policies, and individual practice.

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Surgical Pathology Cancer Case Summary (Checklist)

Protocol web posting date: October 2009

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, and C)
___ Right superior quadrant (12 to 3 o'clock)
___ Right inferior quadrant (3 to 6 o'clock)
___ Left inferior quadrant (6 to 9 o'clock)
___ Left superior quadrant (9 to 12 o'clock)
___ Other (specify): _____
___ Not specified

Tumor Size
Greatest dimension: ___ cm
Additional dimensions: ___ x ___ cm
___ Cannot be determined (see Comment)

Note: all dimensions are important; see definition for "microinvasive carcinoma" under T1a1/IA1

* Data elements with asterisks are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.

Histologic Type (select all that apply) (Note D)
___ Squamous cell carcinoma
*___ Keratinizing
*___ Nonkeratinizing
*___ Other (specify): _____
___ Adenocarcinoma
___ Mucinous
*___ Endocervical type
*___ Intestinal type
*___ Other
___ Endometrioid
___ Clear cell
___ Other (specify): _____
___ 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)

<u>Endocervical Margin</u>
___ Not involved by invasive carcinoma
*Distance of invasive carcinoma from margin: ___ mm
*Specify location, if possible: _____
___ Involved by invasive carcinoma
*Specify location, if possible: _____
*___ Focal
*___ Diffuse
___ Not involved by intraepithelial squamous neoplasia
___ Involved by intraepithelial squamous neoplasia
*Specify grade: _____
___ Not involved by adenocarcinoma in situ
___ Involved by adenocarcinoma in situ

* Data elements with asterisks are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.

Exocervical Margin
___ Not involved by invasive carcinoma
*Distance of invasive carcinoma from margin: ___ mm
*Specify location, if possible: _____
___ Involved by invasive carcinoma
*Specify location, if possible: _____
*___ Focal
*___ Diffuse
___ Not involved by intraepithelial squamous neoplasia
___ Involved by intraepithelial squamous neoplasia
*Specify grade: _____
___ Not involved by adenocarcinoma in situ
___ Involved by adenocarcinoma in situ

Deep Margin
___ Not involved by invasive carcinoma
*Distance of invasive carcinoma from margin: ___ mm
*Specify location, if possible: _____
___ Involved by invasive carcinoma
*Specify location, if possible: _____
*___ Not involved by intraepithelial squamous neoplasia
*___ Involved by intraepithelial squamous neoplasia
*Specify grade: _____
___ Not involved by adenocarcinoma in situ
___ Involved by adenocarcinoma in situ

Lymph-Vascular Invasion (Note G)
___ Not identified
___ Present
___ Indeterminate

***Additional Pathologic Findings (select all that apply)**
*___ None identified
*___ Koilocytosis
*___ Inflammation
*___ Other (specify): _____

***Comment(s)**

Surgical Pathology Cancer Case Summary (Checklist)

Protocol web posting date: October 2009

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 (see Comment)

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

Histologic Type (select all that apply) (Note D)
___ Squamous cell carcinoma
    *___ Keratinizing
    *___ Nonkeratinizing
    *___ Other (specify): _____
___ Adenocarcinoma
    ___ Mucinous
        *___ Endocervical type
        *___ Intestinal type
        *___ Other
    ___ Endometrioid
    ___ Clear cell
    *___ Other (specify): _____
___ 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

Margins (select all that apply) (Note F)
___ Cannot be assessed
___ Margins uninvolved by invasive carcinoma
    Distance of invasive carcinoma from closest margin: ___ mm
    Specify margin, if possible: _____
    ___ Carcinoma in situ not identified at distal margin
    ___ Carcinoma in situ present at distal margin
___ Margin(s) involved by invasive carcinoma
    Specify margin(s), if possible: _____
___ Not applicable

Lymph-Vascular Invasion (Note G)
___ Not identified
___ Present
___ Indeterminate

* Data elements with asterisks are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.

Pathologic Staging (pTNM [FIGO]) (Notes H, I, and J)

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

Primary Tumor (pT)
___ pTX [--]: Cannot be assessed
pT1 [I]: Cervical carcinoma confined to uterus (extension to corpus should be disregarded)
- ___ pT1a [IA]: Invasive carcinoma diagnosed by microscopy only. All macroscopically visible lesions (even with superficial invasion) are pT1b/1B.
- ___ pT1a1 [IA1]: Stromal invasion ≤3.0 mm in depth and horizontal spread ≤7.0 mm
- ___ pT1a2 [IA2]: Stromal invasion >3.0 mm but not more than 5.0 mm in depth and horizontal spread ≤7.0 mm
- ___ pT1b [IB]: Clinically visible lesion confined to the cervix or microscopic lesion greater than T1a2/IA2
- ___ pT1b1 [IB1]: Clinically visible lesion ≤4.0 cm in greatest dimension
- ___ pT1b2 [IB2]: Clinically visible lesion >4.0 cm in greatest dimension

pT2 [II]: Tumor invades beyond the uterus but not to pelvic wall or to lower third of vagina
- ___ pT2a [IIA]: Tumor without parametrial invasion
- ___ pT2a1 [IIA1]: Clinically visible lesion ≤4.0 cm in greatest dimension
- ___ pT2a2 [IIA2] Clinically visible lesion >4.0 cm in greatest dimension
- ___ pT2b [IIB]: Tumor with parametrial invasion

pT3 [III]: Tumor extends to the pelvic wall and/or involves the lower third of the vagina and/or causes hydronephrosis or non-functioning kidney
- ___ pT3a [IIIA]: Tumor involves lower third of vagina, but not pelvic wall
- ___ pT3b [IIIB]: Tumor extends to pelvic wall and/or causes hydronephrosis or non-functioning kidney

___ pT4 [IVA]: 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)
___ pNX: Cannot be assessed
___ pN0: No regional lymph node metastasis
___ pN1: Regional lymph node metastasis
Specify: Number examined: ___
Number involved: ___

Distant Metastasis (pM)
___ Not applicable
___ pM1 [IVB]: Distant metastasis
*Specify site(s), if known: _____

* Data elements with asterisks are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.

***Additional Pathologic Findings (select all that apply)**
*___ None identified
*___ Intraepithelial neoplasia (specify type and grade): _____
*___ 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). However, specimens frequently are received without orientation. In these cases, the clock face orientation is designated by the pathologist and it 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 Oncologists (SGO) differs with the 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.[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.[6-8]

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-II lesions, and the most recent 2008 FIGO staging classification has adopted T subclassifications for T2 lesions (cervical carcinoma spreading beyond the cervix but not to the pelvic side wall or lower one-third of the vagina), based on tumor size ≤4 cm (T2a1) and >4 cm (T2a2).[6]

TNM Classification and FIGO Staging System for Cervical Carcinoma
Primary Tumor (T)

TNM Category	FIGO Stage	Definition
TX	(--)	Primary tumor cannot be assessed
T1	I	Cervical carcinoma confined to the uterus (extension to the corpus should be disregarded)
T1a	IA	Invasive carcinoma, diagnosed by microscopy only (all macroscopically visible lesions even those with superficial invasion are pT1b/stage IB) [#]
T1a1	IA1	Measured stromal invasion 3.0 mm or less in depth[##] and 7.0 mm or less in horizontal spread
T1a2	IA2	Measured stromal invasion more than 3.0 mm in depth[##] and not more than 5.0 mm[##] with a horizontal spread 7.0 mm or less
T1b	IB	Clinically visible lesion confined to the cervix or microscopic lesion greater than T1a2/IA2
T1b1	IB1	Clinically visible lesion 4.0 cm or less in greatest dimension
T1b2	IB2	Clinically visible lesion more than 4.0 cm in greatest dimension
T2	II	Tumor invades beyond the uterus but not to pelvic wall or to lower third of vagina
T2a	IIA	Tumor without parametrial invasion
T2a1	IIA1	Clinically visible lesion 4.0 cm or less in greatest dimension
T2a2	IIA2	Clinically visible lesion more than 4.0 cm in greatest dimension
T2b	IIB	Tumor with parametrial invasion
T3	III	Tumor extends to the pelvic wall and/or involves the lower third of the vagina, and/or causes hydronephrosis or non-functioning kidney
T3a	IIIA	Tumor involves lower third of vagina, no extension to pelvic wall
T3b	IIIB	Tumor extends to pelvic wall and/or causes hydronephrosis or non-functioning kidney
T4[###]	IVA	Tumor invades the mucosa of bladder or rectum and/or extends beyond true pelvis[###]
M1	IVB	Distant metastasis

[#] The current FIGO staging omits specific reference to glandular lesions in stage IA.[9]

[##] The depth of invasion is measured from the base of the epithelium, either surface or glandular, from which it originates. The depth of invasion is defined as the measurement of the tumor from the epithelial-stromal junction of the adjacent most superficial epithelial papilla to the deepest point of invasion. Vascular space involvement, either venous or lymphatic, does not alter the staging.

[###] Presence of bullous edema is not sufficient evidence to classify a tumor as T4. The lesion should be confirmed by biopsy.

Regional Lymph Nodes (N)[#] (TNM Staging System)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis

[#] Regional lymph nodes include paracervical, parametrial, hypogastric (obturator); common, internal and external iliac; presacral, sacral and para-aortic nodes. Metastasis to lymph nodes outside of the regional nodal group is classified as distant metastasis.

Distant Metastasis (M) (TNM Staging System)

M0	No distant metastasis
M1	Distant metastasis (including peritoneal spread, involvement of supraclavicular or mediastinal lymph nodes, lung, liver or bone)[#]

[#] Classified as stage IVB in the FIGO staging system.

TNM Stage Groupings (FIGO 2008)

Stage IA	T1a	Any N[#]	M0
Stage IA1	T1a1	Any N	M0
Stage IA2	T1a2	Any N	M0
Stage IB	T1b	Any N	M0
Stage IB1	T1b1	Any N	M0
Stage IB2	T1b2	Any N	M0
Stage IIA	T2a	Any N	M0
Stage IIB	T2b	Any N	M0
Stage III	T3	Any N	M0
Stage IIIA	T3a	Any N	M0
Stage IIIB	T1	Any N	M0
	T2	Any N	M0
	T3a	Any N	M0
	T3b	Any N	M0
Stage IVA	T4	Any N	M0
Stage IVB	Any T	Any N	M1

[#] Nodal status does not affect stage.

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 (pN0): 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.[10] 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 N1, with a comment noting how the cells were identified.

L. 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. Cytology Diagnosis

The updated Bethesda System of cytologic classification[11] is strongly recommended for consistency in reporting of Papanicolaou smears and is shown below. Although other classification systems may be used, the Papanicolaou class designation system is archaic and not recommended. The Bethesda System has been adopted by most cytology and pathology organizations for the classification of cytologic specimens from the female genital tract. According to this system, the terms “low-grade squamous intraepithelial lesion” (LSIL) and “high-grade squamous intraepithelial lesion” (HSIL) are used to encompass the spectrum of intraepithelial lesions otherwise classified as dysplasia/cervical intraepithelial neoplasia (CIN). Cellular changes characteristic of human papilloma virus (HPV), mild dysplasia, and a combination of both are classified as LSIL; and moderate (CIN 2) and severe dysplasia-carcinoma in situ (CIN 3) are classified as HSIL.

The Bethesda System 2001 Cervical/Vaginal Classification

<u>Negative for Intraepithelial Lesion or Malignancy</u>

Organisms

- *Trichomonas vaginalis*
- Fungal organisms morphologically consistent with *Candida* spp
- Shift in flora suggestive of bacterial vaginosis
- Bacteria morphologically consistent with *Actinomyces* spp
- Cellular changes associated with Herpes simplex virus

Other non-neoplastic findings (optional to report, list not inclusive)

- Reactive cellular changes associated with
  - inflammation (includes typical repair)
  - Intrauterine contraceptive device (IUD)
  - irradiation
- Glandular cells status post hysterectomy
- Atrophy

<u>Other</u>

- Endometrial cells (in a woman greater than or equal to 40 years of age; specify if *“negative for squamous intraepithelial lesion”)*

<u>Epithelial Cell Abnormalities</u>

Squamous Cell

- Atypical squamous cells (ASC)
  - of undetermined significance (ASC-US)
  - cannot exclude HSIL (ASC-H)
- Low-grade squamous intraepithelial lesion (LSIL)
  - encompassing: HPV/mild dysplasia/CIN I
- High-grade squamous intraepithelial lesion (HSIL)
  - encompassing: moderate and severe dysplasia/ CIN2/CIN3/carcinoma in situ (CIS)

- with features suspicious for invasion (if invasion suspected)
- Squamous cell carcinoma

Glandular Cell
- Atypical
  - endocervical cells (NOS or specify in comment)
  - endometrial cells (NOS or specify in comment)
  - glandular cells (NOS or specify in comment)
- Atypical
  - endocervical cells, favor neoplastic
  - glandular cells, favor neoplastic
- Endocervical Adenocarcinoma *in situ* (AIS)
- Adenocarcinoma
  - endocervical
  - endometrial
  - extrauterine
  - not otherwise specified (NOS)

Other Malignant Neoplasms

Specify

L. Special Studies

HPV Testing

Human papillomaviruses are uniformly accepted to play an etiologic role in cervical carcinogenesis and are detectable in greater than 90% of preinvasive and invasive cervical epithelial neoplasms, with HPV types 16 and 18 being the most frequent types associated with invasive carcinoma.[12] While HPV genotyping assays to determine specific high-risk HPV type(s) have not yet become standard practice, the most recent 2006 consensus guidelines published through the American Society for Colposcopy and Cervical Pathology (ASCCP) have expanded the clinical indications for HPV testing. Based of large screening studies showing an improved sensitivity and negative predictive value of high-risk HPV testing in combination with cytology, the ASCCP is currently recommending the use of molecular testing for high-risk subtypes of HPV together with cervical cytology for screening in women 30 years of age and older.[13] Women who are negative on both tests can defer further screening for 3 years. Women who are positive for high-risk HPV DNA but show no evidence of dysplasia on cytology or colposcopic biopsy remain a particular management conundrum. Since the majority of HPV-positive women, even those 30 years and older, will clear the infection and become HPV negative on re-screening, the current consensus guidelines recommend conservative follow-up for the HPV-positive, cytology-negative patients, with repeat cytology and HPV testing at 12-month intervals.[13] Persistent high-risk HPV positivity at subsequent re-screening then warrants colposcopy.

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 HPV infection.[14,15] 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.[16] 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. 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).[17]

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 one antibody, is most useful; in most instances this includes vimentin, ER, p16 and monoclonal CEA.[18,19]

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. Despite these generalizations, the pattern of p16 expression should not be used to stratify dysplastic squamous intraepithelial lesions into LSIL versus HSIL; this distinction should be made on the basis of standard histologic criteria.

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