COLLEGE of AMERICAN PATHOLOGISTS

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

Version: Uterine Cervix Resection 4.3.0.0 **Protocol Posting Date:** February 2020

CAP Laboratory Accreditation Program Protocol Required Use Date: November 2020

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

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

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

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

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

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

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

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

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

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

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

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

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

Summary of Changes

Version 4.3.0.0
The following data element was modified:
Extent of Invasion

Surgical Pathology Cancer Case Summary

Protocol posting date: February 2020

UTERINE CERVIX: Resection

Select a single response unless otherwise indicated.

Procedure (select all that apply) (Note A)
___ Trachelectomy
___ Total hysterectomy and bilateral salpingo-oophorectomy
___ Radical hysterectomy
___ Simple hysterectomy
___ Pelvic exenteration (specify included organs): _____
___ Bilateral salpingo-oophorectomy
___ Right salpingo-oophorectomy
___ Left salpingo-oophorectomy
___ Salpingo-oophorectomy, side not specified
___ Right oophorectomy
___ Left oophorectomy
___ Oophorectomy, side not specified
___ Bilateral salpingectomy
___ Right salpingectomy
___ Left salpingectomy
___ Salpingectomy, side not specified
___ Vaginal cuff resection
___ Omentectomy
___ Other (specify): _____

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

+ Hysterectomy Type
+ ___ Abdominal
+ ___ Vaginal
+ ___ Vaginal, laparoscopic-assisted
+ ___ Laparoscopic
+ ___ Laparoscopic, robotic-assisted
+ ___ Other (specify): _____
+ ___ Not specified

Tumor Size (Note B)
Greatest dimension (centimeters): ___ cm
+ Additional dimensions (centimeters): ___ x ___ cm
___ Cannot be determined (explain): _____

Note: All dimensions are important; see definition for "superficially invasive squamous cell carcinoma" under T1a1/IA1.

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

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

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

Stromal Invasion (Note B)

Depth of Stromal Invasion (millimeters):
___ Specify ___ mm
___ At least ___ mm
___ Cannot be determined (explain): _____

+ Depth of Stromal Invasion
+ ___ Superficial one-third
+ ___ Middle one-third
+ ___ Deep one-third

Horizontal Extent of Stromal Invasion[#]
___ Not applicable
___ Specify ___ mm
___ Estimated as less than or equal to 7 mm
Specify Number of Block(s) Involved: _____

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

___ Estimated as greater than 7 mm
Specify Number of Block(s) Involved: _____
___ Cannot be determined

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

Pattern of Invasion[#]
___ Pattern A
___ Pattern B
___ Pattern C

[#]*Silva System- applicable only to invasive endocervical adenocarcinomas*

Other Tissue/ Organ Involvement (select all that apply)
Note: Any organ not selected is either not involved or was not submitted.
___ Not applicable
___ Not identified
___ Right parametrium
___ Left parametrium
___ Parametrium (side not specified)
___ Vagina, upper two-thirds
___ Vagina, lower one-third
___ Vagina (location not specified)
___ Right ovary
___ Left ovary
___ Ovary (side not specified)
___ Right fallopian tube
___ Left fallopian tube
___ Fallopian tube (side not specified)
___ Pelvic wall
___ Bladder wall
___ Bladder mucosa[#]
___ Rectal wall
___ Bowel mucosa[#]
___ Omentum
___ Other organs/tissue (specify): _____
___ Cannot be determined (explain):_____

[#]*Note: Tumor should involve the mucosal surface*

Margins (Note E)

Ectocervical Margin (select all that apply)[#]
___ Cannot be assessed (explain): _____
___ Uninvolved by invasive carcinoma
+ Distance of invasive carcinoma from margin (millimeters): ___ mm
+ Specify location: _____
___ Involved by invasive carcinoma
Specify location, if possible: _____
___ Uninvolved by intraepithelial neoplasia
___ Involved by high-grade squamous intraepithelial lesion (CIN 2-3)
+ Specify location: _____
___ Involved by adenocarcinoma in situ (AIS)
+ Specify location: _____

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

Radial (Circumferential) Margin
___ Cannot be assessed (explain): _____
___ Uninvolved by invasive carcinoma
+ Distance of invasive carcinoma from margin (millimeters): ___ mm
+ Specify location: _____
___ Involved by invasive carcinoma
Specify location(s), if possible: _____

Endocervical Margin/Lower Uterine Segment Margin (if applicable, select all that apply)#
___ Cannot be assessed (explain): _____
___ Uninvolved by invasive carcinoma
+ Distance of invasive carcinoma from margin (millimeters): ___ mm
+ Specify location: _____
___ Involved by invasive carcinoma
Specify location, if possible: _____
___ Uninvolved by intraepithelial neoplasia
___ Involved by high-grade squamous intraepithelial lesion (CIN 2-3)
+ Specify location: _____
___ Involved by adenocarcinoma in situ (AIS)
+ Specify location: _____
 # Only applicable for trachelectomy specimens

Vaginal Cuff Margin (if applicable, select all that apply)#
___ Cannot be assessed (explain): _____
___ Uninvolved by invasive carcinoma
+ Distance of invasive carcinoma from margin (millimeters): ___ mm
___ Involved by invasive carcinoma
___ Uninvolved by intraepithelial neoplasia
___ Involved by high-grade squamous intraepithelial lesion (VAIN 2-3)
 # Reporting high-grade squamous intraepithelial lesion (Vain 2-3) is not required if margin is involved by invasive carcinoma.

Lymphovascular Invasion (Note F)
___ Not identified
___ Present
___ Cannot be determined

Regional Lymph Nodes
Note: Lymph nodes designated as pelvic (parametrial, obturator, internal iliac (hypogastric), external iliac, common iliac, sacral, presacral) and para-aortic are considered regional lymph nodes. Any other involved nodes should be categorized as metastases (pM1) and commented on in the distant metastasis section. Presence of isolated tumor cells no greater than 0.2 mm in regional lymph node(s) is considered N0(i+).

___ No lymph nodes submitted or found

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

___ All lymph nodes negative for tumor cells

___ Positive for tumor cells (select all that apply)
Number of Nodes with Metastasis (excludes isolated tumor cells): _____
Number of Nodes with Isolated Tumor Cells (0.2 mm or less) (if applicable): _____
Number cannot be determined (explain): _____

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

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

+ Nodal Site(s) with Tumor Cells (specify): _____

Total Number of Lymph Nodes Examined: _____
___ Number cannot be determined (explain): _____
+ Specify Site(s): _____

Number of Sentinel Nodes Examined (if applicable): _____
___ Number cannot be determined (explain): _____

Pathologic Stage Classification (pTNM, AJCC 8th Edition) (Note G)

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

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

Primary Tumor (pT)
___ pTX: Primary tumor cannot be assessed
___ pT0: No evidence of primary tumor
___ pT1: Cervical carcinoma confined to uterus (extension to corpus should be disregarded)
___ pT1a: Invasive carcinoma diagnosed by microscopy only. Stromal invasion with a maximum depth of 5.0 mm, measured from the base of the epithelium, and a horizontal spread of 7.0 mm or less. Vascular space involvement, venous or lymphatic, does not affect classification.
___ pT1a1: Measured stromal invasion of 3.0 mm or less in depth and 7.0 mm or less in horizontal spread
___ pT1a2: Measured stromal invasion of more than 3.0 mm and not more than 5.0 mm, with a horizontal spread of 7.0 mm or less
___ pT1b: Clinically visible lesion confined to the cervix or microscopic lesion greater than T1a/IA2. Includes all macroscopically visible lesions, even those with superficial invasion.
___ pT1b1: Clinically visible lesion 4.0 cm or less in greatest dimension
___ pT1b2: Clinically visible lesion more than 4.0 cm in greatest dimension
___ pT2: Cervical carcinoma invading beyond the uterus but not to the pelvic wall or to lower third of the vagina
___ pT2a: Tumor without parametrial invasion
___ pT2a1: Clinically visible lesion 4.0 cm or less in greatest dimension
___ pT2a2: Clinically visible lesion more than 4.0 cm in greatest dimension
___ pT2b: Tumor with parametrial invasion
___ pT3: Tumor extending to the pelvic sidewall[#] and/or involving the lower third of the vagina and/or causing hydronephrosis or nonfunctioning kidney
___ pT3a: Tumor involving the lower third of the vagina but not extending to the pelvic wall
___ pT3b: Tumor extending to the pelvic wall and/or causing hydronephrosis or nonfunctioning kidney
___ pT4: Tumor invading the mucosa of the bladder or rectum and/or extending beyond the true pelvis (bullous edema is not sufficient to classify a tumor as T4)[##]

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

[##]*Note: Ttumor should involve the mucosal surface*

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

+ Regional Lymph Nodes Modifier

+ ___ (sn)

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

Regional Lymph Nodes (pN)

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

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

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

+ FIGO Stage (2018 FIGO Cancer Report)

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

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

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

+ Additional Pathologic Findings (select all that apply)

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

+ Ancillary Studies (Note H)
+ Specify: _____

+ p16 Immunohistochemistry
+ ___ Positive
+ ___ Negative

+ Comment(s)

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 the tumor to the cervical carcinoma should be described. To evaluate these features, sections of the rectum and bladder should be taken perpendicular to the mucosa directly overlying the tumor in the cervix. A method that provides excellent orientation of the tumor to adjacent structures consists of inflation of the urinary bladder and rectum with formalin and fixation of the specimen for several hours. The entire specimen can then be hemisected through the neoplasm, and appropriate sections can be obtained.

B. Tumor Size

Absence of Tumor

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

Tumor Size Measurement

Larger tumors are more accurately measured grossly, while smaller tumors and some larger tumors with a diffusely infiltrative pattern or with marked fibrosis are best measured microscopically. It is best to report only 1 set of tumor measurements based on a correlation of the gross and microscopic features to avoid confusion. 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]

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 (2017)[2]. The depth of invasion is measured from its HSIL origin, that is, from the base of the epithelium either surface or glandular that is involved by HSIL to the deepest point of invasion. If the invasive focus or foci are not in continuity with the dysplastic epithelium, the depth of invasion should be measured from the deepest focus of tumor invasion to the base of the nearest dysplastic crypt or surface epithelium. If there is no obvious epithelial origin, the depth is measured from the deepest focus of tumor invasion to the base of the nearest surface epithelium, regardless of whether it is dysplastic or not. In situations where carcinomas are exclusively or predominantly exophytic, there may be little or no invasion of the underlying stroma. These should not be regarded as in situ lesions and the tumor thickness (from the surface of the tumor to the deepest point of invasion) should be measured in such cases. The depth of invasion below the level of the epithelial origin should not be provided in these cases as this may not truly reflect the biological potential of such tumors. If it is impossible to measure the depth of invasion, eg, in ulcerated tumors or in some adenocarcinomas, the tumor thickness may be measured instead, and this should be clearly stated on the pathology report along with an explanation for providing the thickness rather than the depth of invasion.

The depth of stromal invasion in fractional thirds in resections is a data point in the NCCN guidelines that guides clinical management.[3,4]

Horizontal extent: It is only relevant to stage 1 tumors, and larger tumors can be reported as "not applicable". This is no longer used for sub-staging of Stage I carcinomas in the FIGO staging system 2018.1 However, is still used in the latest AJCC system (2017)2 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 accuracy of measuring the 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 1mm to greater than 3 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 mm may overestimate the true tumor extent.[5] The pathologist should report the maximum horizontal extent (when it 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 7mm or greater than 7 mm. It is also acceptable to report a tumor as pT1 without further substaging as long as the depth of invasion is reported, although individual clinicians may request a horizontal extent for their practice.

The LAST definition of superficial invasive squamous cell carcinoma (SISSCA) conforms to T1a1/ FIGO 1A1. The LAST consensus recommends SISCCA to include multifocal disease and that reporting include presence, number, and size of independent multifocal carcinoma, however, no LAST recommendation was made on the methodology to measure multifocal disease. Multifocal tumors should be defined as invasive foci separated by a tissue block within which there is no evidence of invasion or as invasive foci in the same tissue block that are more than 2 mm apart, or as invasive foci on different cervical lips. They recommend that multifocal tumors should be staged based on the largest focus.[6]

Pattern of invasion

Accurately measuring the depth of stromal invasion can be challenging in some endocervical adenocarcinomas. The Silva system of classification [7] 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 is ±. 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 is ±. Pattern A cases were all stage I, had negative lymph nodes, and no recurrences. 23.8% of cases with pattern C had lymph node metastases, while pattern B tumors had metastatic lymph nodes rarely.

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. *AJCC Cancer Staging Manual.* Springer; 2017.
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 (3): 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(2):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, Syed S, Shanbhag S, Burton K, Lindsay R, Siddiqui N, Millan D: Multifocal FIGO Stage IA1 Squamous Carcinoma of the Cervix: Criteria for Identification, Staging, and its Good Clinical Outcome. Int J Gynecol Pathol. 2016 ;35(5):467-74.

7. Roma AA, Diaz De Vivar A, Silva EG et al. 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.

References

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

D. Histologic Grade

A wide variety of grading systems, including some that evaluate only the extent of cellular differentiation and others that assess additional features such as the appearance of the tumor margin, the extent of inflammatory cell infiltration, and vascular invasion, have been used for squamous cell carcinoma of the cervix. However, there is no consensus emerging from the literature that any of these systems are reproducible or that they provide useful prognostic information. For the grading of invasive squamous tumors, it is suggested that 3 grades be used:

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

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

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

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

References

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, Okamoto K, Kuwabara M, Negishi H, Oikawa M, Yamamoto R, Yamada H, Fujimoto S 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.

E. Resection Margins

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

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

In hysterectomy or trachelectomy specimens, the lateral radial margin may consist of parametrial soft tissue, which should be measured if present.[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
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F. Lymphovascular Invasion

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

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G. Pathologic Stage Classification

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

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

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

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

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

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

Sentinel nodes should be sliced at 2.0 mm intervals. The sentinel nodes should undergo ultrastaging, Currently, there is no universal ultrastaging protocol. However, all institutions undertaking sentinel lymph node examination should have a standard procedure in place for sentinel lymph nodes. One protocol is as follows: For any section that is negative on initial H&E section, 2 sections are taken from each of two levels that are 50 µm apart, with one for H&E and the second for keratin cocktail IHC.[6]
There is little data to assign risk for nonsentinel lymph node metastasis based on the size of the metastasis in the sentinel lymph node. However, the size criteria for micrometastasis and macrometastasis is adopted from the experience in breast carcinoma. Micrometastasis is defined as a metastasis measuring greater than 0.2 mm but less than 2 mm.

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

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H. Special Studies
p16 Immunohistochemistry
Immunohistochemistry has served as an important adjunct to the histologic diagnosis of CIN in difficult lesions, with p16 immunoreactivity being a good surrogate marker for high-risk human papillomavirus (HPV) infection.[1, 2] 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.[3] Given the heterogeneous staining patterns seen in low-grade CIN lesions, however, immunohistochemistry for p16 is generally reserved for lesions that are morphologically suspicious or indeterminate for high-grade dysplasia. The LAST project proposed p16 be used in 3 specific situations. First, to distinguish inflammatory lesions from HSIL; second, to distinguish LSIL from HSIL; and third, to evaluate specimens such as endocervical curettage on patients who have previously had a recent HSIL diagnosis. ProEx C, an immunohistochemical assay targeting both topoisomerase II-alpha and minichromosome maintenance protein-2 (MMP-2), has recently been shown to have high sensitivity and specificity for HPV-associated lesions of the cervix, with similar staining patterns as those seen for p16 and MIB-1 (Ki-67).[4]

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.[5, 6]

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/ 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).*[7]

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