



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

Version: 4.4.0.0

Protocol Posting Date: October 2020

The use of this protocol is recommended for clinical care purposes but is not required for accreditation purposes.

This protocol may be used for the following procedures AND tumor types:

Procedure	Description
Excision	
Tumor Type	Description
Carcinoma	
Carcinosarcoma	

The following should NOT be reported using this protocol:

Procedure
Resection (consider Uterine Cervix Resection protocol)
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

The use of this biopsy case summary is recommended for clinical care purposes, but is not required for accreditation purposes. The core and conditional data elements are routinely reported for biopsy specimens. Non-core data elements are included to allow for reporting information that may be of clinical value.

Summary of Changes**v4.4.0.0**

- WHO 5th Edition Histologic Types
- Addition of “Equivocal” to Lymphovascular Invasion
- Margins Section Modifications
- Updated Explanatory Notes for Histologic Type, Silva Pattern, Lymphovascular Invasion

Reporting Template

Protocol Posting Date: October 2020

Note: + Data elements preceded by this symbol may be clinically important but are not yet validated or regularly used in patient management.

Select a single response unless otherwise indicated.

CASE SUMMARY: (UTERINE CERVIX: Excision)

Note: This case summary is recommended for reporting excision specimens, but is not required for accreditation purposes.

SPECIMEN

Procedure (Note [A](#))

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

TUMOR

+Tumor Site (select all that apply)

- Left superior (anterior) quadrant (12 to 3 o'clock)
 Left inferior (posterior) quadrant (3 to 6 o'clock)
 Right inferior (posterior) quadrant (6 to 9 o'clock)
 Right superior (anterior) quadrant (9 to 12 o'clock)
 Other (specify): _____
 Cannot be determined (explain): _____

Tumor Size (Note [B](#))

- Greatest dimension in Centimeters (cm): _____ cm
+Additional Dimension in Centimeters (cm): _____ cm
+Additional Dimension in Centimeters (cm): _____ cm
 Cannot be determined (explain): _____

Note: Per AJCC Staging Manual, Tumor Size is reported in Centimeters.

Histologic Type (Note [C](#))

- Squamous cell carcinoma, HPV-associated
 Squamous cell carcinoma, HPV-independent
 Squamous cell carcinoma, NOS (acceptable when p16 or HPV testing is not available)
 Adenocarcinoma, NOS
 Adenocarcinoma, HPV-associated
 Adenocarcinoma, HPV-independent, NOS
 Adenocarcinoma, HPV-independent, gastric type
 Adenocarcinoma, HPV-independent, clear cell type
 Adenocarcinoma, HPV-independent, mesonephric type
 Endometrioid adenocarcinoma, NOS
 Carcinosarcoma
 Adenosquamous carcinoma
 Adenoid basal carcinoma

- Mucoepidermoid carcinoma
 Carcinoma, unclassifiable (undifferentiated carcinoma)
 Neuroendocrine tumor, NOS
 Neuroendocrine tumor, grade 1
 Neuroendocrine tumor, grade 2
 Small cell neuroendocrine carcinoma, high grade
 Large cell neuroendocrine carcinoma, high grade
 Neuroendocrine carcinoma, NOS
 Mixed neuroendocrine non-neuroendocrine carcinoma
 Other histologic type not listed (specify): _____
 Carcinoma, type cannot be determined: _____
+Histologic Type Comments: _____

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 in Millimeters (mm)**

- Specify in Millimeters (mm): _____ mm
 At least in Millimeters (mm): _____ mm
 Cannot be determined (explain): _____

+Horizontal Extent of Stromal Invasion in Millimeters (mm)

- Not applicable (in larger tumors that can be measured grossly)
 Specify in Millimeters (mm): _____ mm
 Estimated as less than or equal to 7 Millimeters (mm)

Specify Number of Blocks Involved: _____

- Estimated as greater than 7 Millimeters (mm)

Specify Number of Blocks Involved: _____

- Cannot be determined

+Silva Pattern of Invasion#

#Silva System- applicable only to invasive endocervical adenocarcinomas

- Not applicable
 Pattern A
 Pattern B
 Pattern C

Lymphovascular Invasion (Note E)

- Not identified
 Present
 Equivocal (explain): _____
 Cannot be determined

MARGINS (Note E)**Margin Status for Invasive Carcinoma**

All margins negative for invasive carcinoma

+Closest Margin(s) to Invasive Carcinoma (select all that apply)

Ectocervical (specify location, if possible) : _____

Endocervical (specify location, if possible): _____

Deep margin

Other (specify): _____

Cannot be determined

+Distance of Invasive Carcinoma to Closest Margin

Specify in Millimeters (mm)

Exact distance: _____ mm

Greater than : _____ mm

At least: _____ mm

Less than: _____ mm

Less than 1 mm

Other (specify): _____

Cannot be determined

Invasive carcinoma present at margin

Margin(s) Involved by Invasive Carcinoma (select all that apply)

Ectocervical (specify location, if possible) : _____

Endocervical (specify location, if possible): _____

Deep margin

Other (specify): _____

Cannot be determined

Other (specify) : _____

Cannot be determined (explain): _____

Not applicable

Margin Status for HSIL/AIS#

All margins negative for high-grade squamous intraepithelial lesion (HSIL) and/or adenocarcinoma in situ (AIS)

High-grade squamous intraepithelial lesion (HSIL) present at margin

Margin(s) Involved by HSIL (select all that apply)

Ectocervical (specify location, if possible) : _____

Endocervical (specify location, if possible): _____

Other (specify): _____

Cannot be determined

Adenocarcinoma in situ (AIS) present at margin

Margin(s) Involved by AIS (select all that apply)

Ectocervical (specify location, if possible) : _____

Endocervical (specify location, if possible): _____

Other (specify): _____

Cannot be determined

Other (specify): _____

Cannot be determined

Not applicable

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

+Margins Comments: _____

ADDITIONAL FINDINGS

+Additional Findings (select all that apply)

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

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

B. Tumor Size

Tumor Size Measurement

Larger tumors are more accurately measured grossly, while smaller tumors and some larger tumors with a diffusely infiltrative pattern or with marked fibrosis are best measured microscopically. It is best to report only one set of tumor measurements based on a correlation of the gross and microscopic features to avoid confusion. According to the 2018 FIGO staging system for all stages the size of the primary tumor can be assessed by clinical evaluation (pre- or intraoperative), imaging, and/or pathological measurement.¹ However, in surgically treated cases, the pathologist's findings should take priority over clinical or image-based staging and should be used for the pathological staging.

The depth of invasion is required for the sub-staging of Stage 1 carcinomas in the latest FIGO staging system (2018)¹ and in the latest AJCC system (2020).² The depth of invasion is measured from its HSIL origin, that is, from the base of the epithelium, whether epithelial surface or an endocervical gland that is involved by HSIL to the deepest point of invasion. If the invasive focus or foci are not in continuity with the

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

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

Horizontal Extent

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

The horizontal extent may be the longitudinal extent (length) measured in the superior-inferior plane (ie, from the endocervical to ectocervical aspects of the section), or it may be the circumferential extent (width) that is measured or calculated perpendicular to the longitudinal axis of the cervix. When a gross lesion is not identified, the measurement accuracy of horizontal extent may be limited. If the extent is measured on a single glass slide, this may underestimate the true horizontal extent, because the tumor may involve multiple blocks and may have a greater “width” than “length”. The thickness of sections of the cervix, which are often taken as “wedges” of a cone may be variable and may range from less than 1.0 mm to greater than 3.0 mm. In addition, adding thicknesses of adjacent sections where the sections are taken as a cone are measuring the circumference rather than a linear “width”. Estimates using a thickness of 2.5 mm to 3.0 mm may overestimate the true tumor extent.^{5,6} The pathologist should report the maximum horizontal extent (when it on a single block) and where multiple blocks are involved, they should report the number of blocks involved and if it is estimated as less than or equal to 7.0 mm or greater than 7.0 mm.

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

The Lower Anogenital Squamous Terminology (LAST)⁷ definition of superficial invasive squamous cell carcinoma (SISSCA) conforms to T1a1/ FIGO IA1 and defines what would have been previously reported as “microinvasive” squamous cell carcinoma. The LAST consensus recommends that SISSCA include multifocal disease and that reporting include the presence, number, and size of independent multifocal carcinoma. However, LAST makes no recommendation on the methodology to measure multifocal disease. Multifocal tumors should be defined as invasive foci separated by a tissue block within which there is no evidence of invasion, as invasive foci in the same tissue block that are more than 2.0 mm apart, or as invasive foci on different cervical lips. They recommend that multifocal tumors should be staged based on the largest focus.⁷

Silva Pattern of Invasion

Accurately measuring the depth of stromal invasion can be challenging in some endocervical adenocarcinomas. The Silva system of classification⁸ stratifies cases of invasive endocervical adenocarcinomas into three groups on the basis of the morphologic pattern of invasion and is predictive of the risk for LN metastasis. Briefly, Pattern A shows well-demarcated glands with rounded contours, frequently forming groups with no destructive stromal invasion, no single cells or cell detachment and no

LVI. Complex intraglandular growth such as cribriform or papillary architecture is acceptable but there is no solid growth. Pattern B shows localized (limited, early) destructive stromal invasion. There are individual or small groups of tumor cells, separated from the rounded gland, in a focally desmoplastic or inflamed stroma. There is no solid growth and LVI may or may not be present. Pattern C shows diffuse destructive stromal invasion. There are diffusely infiltrative glands with associated extensive desmoplastic response. Growth pattern is confluent or solid and LVI may or may not be present. Pattern A cases were all stage I with negative lymph nodes and no recurrences. Pattern B tumors rarely had metastatic lymph nodes and only 23.8% of cases with pattern C had lymph node metastases.

Silva Pattern ⁸	Histologic Appearance
A	<ul style="list-style-type: none"> • Demarcated, complete, rounded glands, frequently forming groups on low power • Cribriform and papillary growth is possible, but solid (nonglandular) growth is not • No desmoplastic stroma • Lacks single or detached cells • No lymphovascular invasion • Relationship of tumor to large cervical vessels and depth of tumor are not relevant to pattern
B	<ul style="list-style-type: none"> • Localized or limited destructive (desmoplastic) stromal invasion arising in Pattern A • Buds of small glands or individual cells from rounded glands (often in an inflamed or focally desmoplastic stroma), often with increased cytoplasm or maturation • Single, multiple or linear (base of tumor) foci are acceptable • No solid growth pattern • Lymphovascular invasion may or may not be present
C	<ul style="list-style-type: none"> • Diffuse growth pattern with destructive (often extensive desmoplastic) stromal invasion • Confluent growth of glands, papillae, or mucin lakes filling 4X field (5 mm) • Angulated, often incomplete or discontinuous glands (breaks opening into the stroma) • Canalicular (labyrinthine, interconnected glandular) pattern with occasional open glands • Solid or poorly differentiated component (high grade); nuclear grade is disregarded • Lymphovascular invasion may or may not be present

References

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4. Sedlis A, Bundy BN, Rotman MZ, Lentz SS, Muderspach LI, Zaino RJ. A randomized trial of pelvic radiation therapy versus no further therapy in selected patients with stage IB carcinoma of the cervix after radical hysterectomy and pelvic lymphadenectomy: a Gynecologic Oncology Group Study. *Gynecol Oncol.* 1999;73:177-83.
5. McCluggage WG, Judge MJ, Alvarado-Cabrero I, et al. Data set for the reporting of carcinomas of the cervix: recommendations from the International Collaboration on Cancer Reporting (ICCR). *Int J Gynecol Pathol.* 2018; 37(3):205-228.
6. Day E, Duffy S, Bryson G, et al. Multifocal FIGO Stage IA1 squamous carcinoma of the cervix: criteria for identification, staging, and its good clinical outcome. *Int J Gynecol Pathol.* 2016;35:467-474.

7. Darragh TM, Colgan TJ, Cox JT, et al. The Lower Anogenital Squamous Terminology Standardization Project for HPV-Associated Lesions: background and consensus recommendations from the College of American Pathologists and the American Society for Colposcopy and Cervical Pathology. *Arch Pathol Lab Med.* 2012; 136(10):1266-1297.
8. Roma AA, Diaz De Vivar A, Silva EG et al. Invasive endocervical adenocarcinoma: a new pattern-based classification system with important clinical significance. *Am J Surg Pathol.* 2015; 39(5):667-672.

C. Histologic Type

For consistency in reporting, the histologic classification proposed by the World Health Organization (WHO) is recommended;¹ other classification systems may be used, however. A majority of cervical squamous cell carcinomas are HPV-associated. p16 testing and/or molecular HPV typing is recommended before making the diagnosis of HPV-associated cervical SCC. If these results are not available, the NOS category should be used. There is now a general consensus that most or all serous carcinomas detected in the cervix represent metastasis or direct extension from adnexal or endometrial serous carcinomas, although conclusive studies to support this have yet to be published.

References

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

D. Histologic Grade

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

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

It is uncertain whether grading has independent prognostic value in cervical ACA. Whilst a correlation between higher grade and adverse outcomes has been reported, at least for poorly differentiated tumors, this has not been a universal finding. Most grading systems are based on the tumor architecture (glandular and papillary versus solid areas) and its nuclear features. In contrast to squamous cell carcinoma, most authors who grade cervical adenocarcinoma have found the grade to have prognostic value.^{1,2,3,4}

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

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

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

References

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3. Takeda N, Sakuragi N, Takeda M, et al. Multivariate analysis of histopathologic prognostic factors for invasive cervical cancer treated with radical hysterectomy and systematic retroperitoneal lymphadenectomy. *Acta Obstet Gynecol Scand*. 2002;8:1144-1151.
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5. Howitt BE, Kelly P, McCluggage WG. Pathology of neuroendocrine tumors of the female genital tract. *Curr Oncol Rep*. 2017; 19:59. doi 10.1007/s11912-017-0617-2.

E. Lymphovascular Invasion

Many gynecologists feel that the presence of vascular/lymphatic vessel invasion is important because it may change the extent of their surgical treatment and may be an independent risk factor for recurrence.^{1,2,3,4} At times, it may be difficult to evaluate a specimen for vascular/lymphatic vessel invasion, as in cases with crush artifact or suboptimal fixation. In these cases, it can be categorized as “cannot be determined”. At other times, it may be difficult to be definitive whether vascular/lymphatic vessel invasion is present. This can include cases where retraction artifact or artifactual transfer of tumor cells is a consideration. In other cases, foci may be suspicious but not definitive for invasion. All of these situations can be categorized as “equivocal for invasion”. In cases where one cannot be definitive, a qualifying note explaining the interpretive difficulty and the extent of possible involvement is recommended, since it may help to direct medical management.^{2,5,6,7}

References

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F. Resection Margins

Margins can be involved, negative, or indeterminate for carcinoma. If a margin is involved, whether endocervical, ectocervical, deep, or other, it should be specified. If indeterminate, the reason should be specified (e.g., cautery artifact in electroexcision specimens may preclude evaluation of the status of the

margin). The severity and extent of a precursor lesion (e.g., focal or diffuse) involving a resection margin of a cone should be specified.

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