



## Protocol for the Examination of Specimens from Patients with Carcinoma of the Endometrium

Version: 5.1.0.0

Protocol Posting Date: December 2024

CAP Laboratory Accreditation Program Protocol Required Use Date: September 2025

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

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

Procedure	Description
Hysterectomy	This protocol should be completed for hysterectomies containing cancer as well as those with no residual cancer (e.g., following cancer diagnosis on previous biopsy / curettage)
Tumor Type	Description
Carcinoma	Applies to all endometrial carcinomas (including carcinosarcoma)

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

Procedure
Endometrial biopsy / curettage
Primary resection specimen with no residual cancer (e.g., following neoadjuvant therapy)
Cytologic specimens

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

Tumor Type
Carcinomas arising in the uterine cervix (consider the Uterine Cervix protocol)
Uterine sarcomas, including adenosarcoma (consider the Uterine Sarcoma protocol), and other non-epithelial malignancies
Metastatic carcinomas to the endometrium
Lymphoma (consider the Precursor and Mature Lymphoid Malignancies protocol)

### Version Contributors

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### Glossary:

**Author:** Expert who is a current member of the Cancer Committee, or an expert designated by the chair of the Cancer Committee.

**Expert Contributors:** Includes members of other CAP committees or external subject matter experts who contribute to the current version of the protocol.

### Accreditation Requirements

Synoptic reporting with core and conditional data elements for designated specimen types\* is required for accreditation.

- Data elements designated as core must be reported.
- Data elements designated as conditional only need to be reported if applicable.
- Data elements designated as optional are identified with “+”. Although not required for accreditation, they may be considered for reporting.

This protocol is not required for recurrent or metastatic tumors resected at a different time than the primary tumor. This protocol is also not required for pathology reviews performed at a second institution (i.e., second opinion and referrals to another institution).

Full accreditation requirements can be found on the CAP website under [Accreditation Checklists](#).

A list of core and conditional data elements can be found in the Summary of Required Elements under Resources on the CAP Cancer Protocols [website](#).

*\*Includes definitive primary cancer resection and pediatric biopsy tumor types.*

### 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 i.e., all required elements must be in the synoptic portion of the report in the format defined above.

**Summary of Changes**

**v 5.1.0.0**

- Cover page update
- Removed “Hysterectomy Type” and “Tumor Site” questions
- Updates to “Procedure”, “Tumor Size”, “Histologic Type”, “Histologic Grade”, “Molecular Type”, “Myometrial Invasion”, “Cervical Involvement”, “Lymphatic and / or Vascular Invasion”, “Margin Status” and “pN Category”
- Added back FIGO 2009 Staging while retaining FIGO 2023 Staging
- Updated explanatory notes

**Reporting Template**

**Protocol Posting Date:** December 2024

**Select a single response unless otherwise indicated.**

**CASE SUMMARY: (ENDOMETRIUM)**

**Standard(s):** AJCC 8, FIGO 2009 Staging (2018 Annual Report), FIGO 2023 Staging

**CLINICAL**

**+Clinical History (Note [A](#)) (select all that apply)**

- Lynch syndrome
- Other (specify): \_\_\_\_\_

**SPECIMEN (Note [B](#))**

**Procedure (select all that apply)**

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

- Total hysterectomy
- Supracervical hysterectomy
- Radical hysterectomy
- Hysterectomy
- 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
- Peritoneal biopsy(ies)
- Peritoneal / pelvic washing
- Other (specify): \_\_\_\_\_

**+Specimen Integrity**

- Intact
- Opened
- Morcellated
- Other (specify): \_\_\_\_\_

## TUMOR

### +Tumor Size

\_\_\_ Greatest gross dimension (if mass) in Centimeters (cm): \_\_\_\_\_ cm

**+Additional Dimension in Centimeters (cm): \_\_\_ x \_\_\_ cm**

\_\_\_ Greatest microscopic dimension (if no mass) in Centimeters (cm): \_\_\_\_\_ cm

**+Additional Dimension in Centimeters (cm): \_\_\_ x \_\_\_ cm**

\_\_\_ Cannot be determined (explain): \_\_\_\_\_

### Histologic Type (Note [C](#))

\_\_\_ Endometrioid carcinoma

\_\_\_ Serous carcinoma

\_\_\_ Clear cell carcinoma

\_\_\_ Dedifferentiated carcinoma

\_\_\_ Undifferentiated carcinoma

\_\_\_ Carcinosarcoma

\_\_\_ Mesonephric-like adenocarcinoma

\_\_\_ Squamous cell carcinoma

\_\_\_ Gastric (gastrointestinal)-type carcinoma

\_\_\_ Mixed carcinoma (specify types and percentages): \_\_\_\_\_

\_\_\_ Small cell neuroendocrine carcinoma

\_\_\_ Large cell neuroendocrine carcinoma

\_\_\_ Other histologic type not listed (specify): \_\_\_\_\_

**+Histologic Type Comment:** \_\_\_\_\_

### Histologic Grade# (Note [D](#))

*# International Federation of Gynecology and Obstetrics (FIGO) Grading System applies to endometrioid carcinomas only. All other subtypes are considered high-grade.*

\_\_\_ FIGO grade 1 (endometrioid carcinoma)

\_\_\_ FIGO grade 2 (endometrioid carcinoma)

\_\_\_ FIGO grade 3 (endometrioid carcinoma)

\_\_\_ High-grade (non-endometrioid carcinoma)

\_\_\_ Other (specify): \_\_\_\_\_

\_\_\_ Cannot be assessed (explain): \_\_\_\_\_

### +Molecular Type (Note [E](#)) (select all that apply)

\_\_\_ Mismatch Repair (MMR) / Microsatellite Instability (MSI) Status

#### MMR Immunohistochemistry

\_\_\_ Not performed

\_\_\_ Intact nuclear expression of MLH1, PMS2, MSH2 and MSH6

\_\_\_ Loss of nuclear MMR protein expression

*Select all that apply*

\_\_\_ MLH1

\_\_\_ PMS2

\_\_\_ MSH2

\_\_\_ MSH6

Subclonal loss of nuclear MMR protein expression

*Select all that apply*

MLH1

PMS2

MSH2

MSH6

MMR immunohistochemistry pending

**Microsatellite Instability (MSI) Testing**

Not performed

MSI-Stable (MSS)

MSI-Low (MSI-L)

MSI-High (MSI-H)

MSI testing pending

**MSI Testing Method (required only if applicable)**

Not applicable (not performed)

Polymerase chain reaction

Next generation sequencing

MSI testing pending

Cannot be determined (explain): \_\_\_\_\_

p53 Status

**p53 Immunohistochemistry**

Not performed

Normal (wild-type) expression

Abnormal (mutated) expression

Overexpression (strong, diffuse nuclear expression)

Null (complete lack of nuclear and cytoplasmic expression; internal positive control present)

Cytoplasmic staining (with or without nuclear expression)

Subclonal abnormal (mutated) expression

Overexpression (strong, diffuse nuclear expression)

Null (complete lack of nuclear and cytoplasmic expression; internal positive control present)

Cytoplasmic staining (with or without nuclear expression)

p53 immunohistochemistry pending

**TP53 Mutation Testing**

Not performed

Wild-type

Mutated (specify): \_\_\_\_\_

Cannot be determined (explain): \_\_\_\_\_

TP53 mutation testing pending

POLE Status

**POLE Status**

Wild-type

- Mutated (specify): \_\_\_\_\_
- POLE testing pending
- POLE testing cannot be performed / not available
- Cannot be determined (explain): \_\_\_\_\_

**+ProMisE Classification**

- POLE-mutated carcinoma
- Mismatch repair-deficient carcinoma
- p53-abnormal carcinoma
- No specific molecular profile (NSMP)
- Double classifier (explain): \_\_\_\_\_
- Testing pending (explain): \_\_\_\_\_
- Cannot be determined (explain): \_\_\_\_\_

**+TCGA Classification**

- POLE-mutated (ultramutated) carcinoma
- Microsatellite instability high (hypermutated) carcinoma
- Copy number low carcinoma
- Copy number high carcinoma
- Double classifier (explain): \_\_\_\_\_
- Testing pending
- Cannot be determined (explain): \_\_\_\_\_

**Myometrial Invasion (required only if applicable) (Note [F](#))**

- Not applicable
- Not identified
- Present, inner half (less than 50%)
  - +Specify Percentage:** \_\_\_\_\_ %
  - +Myometrial Invasion Comment:** \_\_\_\_\_
- Present, outer half (greater than or equal to 50%)
  - +Specify Percentage:** \_\_\_\_\_ %
  - +Myometrial Invasion Comment:** \_\_\_\_\_
- Cannot be determined (explain): \_\_\_\_\_

**+Adenomyosis**

- Not identified
- Present, uninvolved by carcinoma
- Present, involved by carcinoma
- Cannot be determined: \_\_\_\_\_

**Uterine Serosal Involvement (Note [G](#))**

- Not identified
- Present
- Cannot be determined (explain): \_\_\_\_\_

**+Lower Uterine Segment Involvement (Note G)**

- Not identified
- Present, non-myoinvasive
- Present, myoinvasive
- Cannot be determined (explain): \_\_\_\_\_

**Cervical Involvement (Note H)**

- Cannot be assessed (supracervical hysterectomy)
- Not identified
- Cervical stromal invasion

**Percentage of Cervical Wall Involved**

- Specify percentage: \_\_\_\_\_ %
- Cannot be determined (explain): \_\_\_\_\_
- Endocervical glandular involvement only
- Cannot be determined (explain): \_\_\_\_\_

**Other Tissue / Organ Involvement# (Note H) (select all that apply)**

# Any organ not selected is either not involved or was not submitted.

- Not applicable (no other tissues / organs submitted)
- Not identified (other tissues / organs submitted and not involved)
- Right ovary
- Left ovary
- Ovary (side not specified)
- Right fallopian tube
- Left fallopian tube
- Fallopian tube (side not specified)
- Vagina
- Right parametrium
- Left parametrium
- Parametrium (side not specified)
- Pelvic wall
- Bladder wall without mucosal involvement
- Bladder wall with mucosal involvement
- Bowel wall without mucosal involvement
- Bowel wall with mucosal involvement
- Other organs / tissue (specify): \_\_\_\_\_
- Cannot be determined (explain): \_\_\_\_\_

**+Peritoneal / Pelvic Washings / Ascitic Fluid (Note I)**

- Not submitted
- Negative for malignant cells
- Malignant cells present
- Atypical (explain): \_\_\_\_\_
- Suspicious for malignancy (explain): \_\_\_\_\_
- Results pending



**Lymphatic and / or Vascular Invasion# (Note J)**

# Lymphatic and / or Vascular Invasion (LVI) is equivalent to the FIGO term Lymphovascular Space Invasion (LVSI). Report the maximum number of LVI foci present on the single slide with the highest number of foci.

- Not identified
- Present
  - Less than or equal to 4 foci
  - Specify Number of Foci:** \_\_\_\_\_
  - Greater than or equal to 5 foci
  - Cannot be determined (explain): \_\_\_\_\_

**+Tumor Comment:** \_\_\_\_\_

**MARGINS (Note K)**

**Margin Status (required only if cervix and / or parametrium / paracervix is involved by carcinoma)**

- Not applicable
- All margins negative for carcinoma
- +Closest Margin(s) to Carcinoma (select all that apply)**
  - Ectocervical (specify location, if possible): \_\_\_\_\_
  - Vaginal cuff (specify location, if possible): \_\_\_\_\_
  - Parametrial (specify location, if possible): \_\_\_\_\_
  - Paracervical (specify location, if possible): \_\_\_\_\_
  - Other (specify): \_\_\_\_\_
  - Cannot be determined: \_\_\_\_\_

**+Distance from Carcinoma to Closest Margin**

*Specify in Millimeters (mm)*

- Exact distance: \_\_\_\_\_ mm
- At least: \_\_\_\_\_ mm
- Less than: \_\_\_\_\_ mm
- Less than 1 mm
- Cannot be determined: \_\_\_\_\_
- Carcinoma present at margin

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

- Ectocervical (specify location, if possible): \_\_\_\_\_
- Vaginal cuff (specify location, if possible): \_\_\_\_\_
- Parametrial (specify location, if possible): \_\_\_\_\_
- Paracervical (specify location, if possible): \_\_\_\_\_
- Other (specify): \_\_\_\_\_
- Cannot be determined: \_\_\_\_\_
- Cannot be determined (explain): \_\_\_\_\_

**+Margin Comment:** \_\_\_\_\_

**REGIONAL LYMPH NODES (Note [L](#))**

**Regional Lymph Node Status#**

# Lymph nodes designated as pelvic (parametrial, obturator, internal iliac (hypogastric), external iliac, common iliac, sacral, presacral) and para-aortic are considered regional lymph nodes. Any other involved nodes should be categorized as metastases (pM1) and reported in the distant metastasis section. If pelvic and / or para-aortic lymph nodes are positive for metastatic carcinoma, reporting the number of nodes with or without macrometastases and micrometastases is required. Reporting isolated tumor cells (ITCs) is required only in the absence of macro- or micrometastasis in other nodes. The presence of ITCs in regional lymph node(s) is considered N0(i+).

- Not applicable (no regional lymph nodes submitted or found)
- Regional lymph nodes present
  - All regional lymph nodes negative for tumor cells
  - Tumor present in pelvic lymph node(s)

**Pelvic Lymph Nodes**

**Total Number of Pelvic Nodes with Macrometastasis (greater than 2 mm) (sentinel and non-sentinel)**

- Exact number: \_\_\_\_\_
- At least: \_\_\_\_\_
- Cannot be determined (explain): \_\_\_\_\_

**+Number of Pelvic Sentinel Nodes with Macrometastasis**

- Exact number: \_\_\_\_\_
- At least: \_\_\_\_\_
- Cannot be determined (explain): \_\_\_\_\_

**Total Number of Pelvic Nodes with Micrometastasis (greater than 0.2 mm up to 2 mm and / or greater than 200 cells) (sentinel and non-sentinel)**

- Exact number: \_\_\_\_\_
- At least: \_\_\_\_\_
- Cannot be determined (explain): \_\_\_\_\_

**+Number of Pelvic Sentinel Nodes with Micrometastasis**

- Exact number: \_\_\_\_\_
- At least: \_\_\_\_\_
- Cannot be determined (explain): \_\_\_\_\_

**Total Number of Pelvic Nodes with Isolated Tumor Cells (less than or equal to 0.2 mm, or clusters of cells less than or equal to 200 cells) (reported only if applicable)#**

# Reporting the number of lymph nodes with isolated tumor cells is required only in the absence of macrometastasis or micrometastasis in other lymph nodes.

- Not applicable
- Exact number: \_\_\_\_\_
- At least: \_\_\_\_\_
- Cannot be determined (explain): \_\_\_\_\_

**+Number of Pelvic Sentinel Nodes with Isolated Tumor Cells**

- Exact number: \_\_\_\_\_
- At least: \_\_\_\_\_
- Cannot be determined (explain): \_\_\_\_\_

**Laterality of Pelvic Node(s) with Tumor (select all that apply)**

- Right sentinel: \_\_\_\_\_
- Right non-sentinel: \_\_\_\_\_
- Left sentinel: \_\_\_\_\_
- Left non-sentinel: \_\_\_\_\_
- Cannot be determined: \_\_\_\_\_

**+Size of Largest Pelvic Nodal Metastatic Deposit**

*Specify in Millimeters (mm)*

- Specify exact size: \_\_\_\_\_ mm
- Less than: \_\_\_\_\_ mm
- Greater than: \_\_\_\_\_ mm
- Cannot be determined (explain): \_\_\_\_\_
- Tumor present in para-aortic lymph node(s)

**Para-aortic Nodes**

**Total Number of Para-aortic Nodes with Macrometastasis (greater than 2 mm) (sentinel and non-sentinel)**

- Exact number: \_\_\_\_\_
- At least: \_\_\_\_\_
- Cannot be determined (explain): \_\_\_\_\_

**+Number of Para-aortic Sentinel Nodes with Macrometastasis**

- Exact number: \_\_\_\_\_
- At least: \_\_\_\_\_
- Cannot be determined (explain): \_\_\_\_\_

**Total Number of Para-aortic Nodes with Micrometastasis (greater than 0.2 mm up to 2 mm and / or greater than 200 cells) (sentinel and non-sentinel)**

- Exact number: \_\_\_\_\_
- At least: \_\_\_\_\_
- Cannot be determined (explain): \_\_\_\_\_

**+Number of Para-aortic Sentinel Nodes with Micrometastasis**

- Exact number: \_\_\_\_\_
- At least: \_\_\_\_\_
- Cannot be determined (explain): \_\_\_\_\_

**Total Number of Para-aortic Nodes with Isolated Tumor Cells (less than or equal to 0.2 mm, or clusters of cells less than or equal to 200 cells) (required only if applicable)#**

*# Reporting the number of lymph nodes with isolated tumor cells is required only in the absence of macrometastasis or micrometastasis in other lymph nodes.*

- Not applicable
- Exact number: \_\_\_\_\_
- At least: \_\_\_\_\_
- Cannot be determined (explain): \_\_\_\_\_

**+Number of Para-aortic Sentinel Nodes with Isolated Tumor Cells**

- Exact number: \_\_\_\_\_
- At least: \_\_\_\_\_

\_\_\_ Cannot be determined (explain): \_\_\_\_\_

**Laterality of Para-aortic Node(s) with Tumor (select all that apply)**

- \_\_\_ Right sentinel: \_\_\_\_\_
- \_\_\_ Right non-sentinel: \_\_\_\_\_
- \_\_\_ Left sentinel: \_\_\_\_\_
- \_\_\_ Left non-sentinel: \_\_\_\_\_
- \_\_\_ Cannot be determined: \_\_\_\_\_

**+Size of Largest Para-aortic Nodal Metastatic Deposit**

*Specify in Millimeters (mm)*

- \_\_\_ Specify exact size: \_\_\_\_\_ mm
- \_\_\_ Less than: \_\_\_\_\_ mm
- \_\_\_ Greater than: \_\_\_\_\_ mm
- \_\_\_ Cannot be determined (explain): \_\_\_\_\_
- \_\_\_ Other (specify): \_\_\_\_\_
- \_\_\_ Cannot be determined (explain): \_\_\_\_\_

**Lymph Nodes Examined**

**Total Number of Pelvic Nodes Examined (sentinel and non-sentinel)**

- \_\_\_ Exact number: \_\_\_\_\_
- \_\_\_ At least: \_\_\_\_\_
- \_\_\_ Cannot be determined (explain): \_\_\_\_\_

**Number of Pelvic Sentinel Nodes Examined (required only if applicable)**

- \_\_\_ Not applicable
- \_\_\_ Exact number: \_\_\_\_\_
- \_\_\_ At least: \_\_\_\_\_
- \_\_\_ Cannot be determined (explain): \_\_\_\_\_

**Total Number of Para-aortic Nodes Examined (sentinel and non-sentinel)**

- \_\_\_ Exact number: \_\_\_\_\_
- \_\_\_ At least: \_\_\_\_\_
- \_\_\_ Cannot be determined (explain): \_\_\_\_\_

**Number of Para-aortic Sentinel Nodes Examined (required only if applicable)**

- \_\_\_ Not applicable
- \_\_\_ Exact number: \_\_\_\_\_
- \_\_\_ At least: \_\_\_\_\_
- \_\_\_ Cannot be determined (explain): \_\_\_\_\_

**+Regional Lymph Node Comment:** \_\_\_\_\_

## DISTANT METASTASIS

### Distant Site(s) Involved, if applicable# (select all that apply)

# This excludes metastasis to pelvic or para-aortic lymph nodes, vagina, uterine serosa, or adnexa

- Not applicable
- Omentum: \_\_\_\_\_
- Extrapelvic peritoneum: \_\_\_\_\_
- Inguinal lymph node(s): \_\_\_\_\_
- Lung: \_\_\_\_\_
- Liver: \_\_\_\_\_
- Bone: \_\_\_\_\_
- Other (specify): \_\_\_\_\_
- Cannot be determined: \_\_\_\_\_

### pTNM CLASSIFICATION (AJCC 8th Edition) (Note [M](#))

Reporting of pT, pN, and (when applicable) pM categories is based on information available to the pathologist at the time the report is issued. As per the AJCC (Chapter 1, 8th Ed.) it is the managing physician's responsibility to establish the final pathologic stage based upon all pertinent information, including but potentially not limited to this pathology report.

### Modified Classification (required only if applicable) (select all that apply)

- Not applicable
- y (post-neoadjuvant therapy)
- r (recurrence)

### pT Category

- pT not assigned (cannot be determined based on available pathological information)
- pT0: No evidence of primary tumor
- pT1: Tumor confined to the corpus uteri, including endocervical glandular involvement*
- pT1a: Tumor limited to the endometrium or invading less than half the myometrium
- pT1b: Tumor invading one half or more of the myometrium
- pT1 (subcategory cannot be determined)
- pT2: Tumor invading the stromal connective tissue of the cervix but not extending beyond the uterus.  
Does NOT include endocervical glandular involvement.
- pT3: Tumor involving serosa, adnexa, vagina, or parametrium*
- pT3a: Tumor involving the serosa and / or adnexa (direct extension or metastasis)
- pT3b: Vaginal involvement (direct extension or metastasis) or parametrial involvement
- pT3 (subcategory cannot be determined)
- # Tumor must involve the mucosal surface of urinary bladder or bowel.*
- pT4: Tumor invading bladder mucosa and / or bowel mucosa (bullous edema is not sufficient to classify a tumor as T4)#

### T Suffix (required only if applicable)

- Not applicable
- (m) multiple primary synchronous tumors in a single organ

### pN Category

- pN not assigned (no nodes submitted or found)

\_\_\_ pN not assigned (cannot be determined based on available pathological information)

\_\_\_ pN0: No regional lymph node metastasis

*# Isolated tumor cells (ITCs) are tumor cells less than or equal to 0.2 mm, or clusters of cells less than or equal to 200 cells. ITCs should be identified either only on hematoxylin-eosin (H&E) slide(s) or both the H&E slide(s) and keratin immunostain(s).*

\_\_\_ pN0(i+): Isolated tumor cells in regional lymph node(s) no greater than 0.2 mm#

*pN1: Regional lymph node metastasis to pelvic lymph nodes*

*## Even one metastasis greater than 2.0 mm would qualify as pN1a or pN2a.*

\_\_\_ pN1mi: Regional lymph node metastasis (greater than 0.2 mm but not greater than 2.0 mm in diameter) to pelvic lymph nodes##

\_\_\_ pN1a: Regional lymph node metastasis (greater than 2.0 mm in diameter) to pelvic lymph nodes

\_\_\_ pN1 (subcategory cannot be determined)

*pN2: Regional lymph node metastasis to para-aortic lymph nodes, with or without positive pelvic lymph nodes*

\_\_\_ pN2mi: Regional lymph node metastasis (greater than 0.2 mm but not greater than 2.0 mm in diameter) to para-aortic lymph nodes, with or without positive pelvic lymph nodes##

\_\_\_ pN2a: Regional lymph node metastasis (greater than 2.0 mm in diameter) to para-aortic lymph nodes, with or without positive pelvic lymph nodes

\_\_\_ pN2 (subcategory cannot be determined)

#### **N Suffix (required only if applicable)**

\_\_\_ Not applicable

\_\_\_ (sn) Sentinel node procedure

\_\_\_ (f) FNA or core biopsy

#### **pM Category (required only if confirmed pathologically)**

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

*# Involvement of pelvic serosal structures (cul-de-sac, urinary bladder, sigmoid serosa) is classified as stage pT3a, while involvement of the omentum and abdominal peritoneum is considered pM1 disease.*

\_\_\_ pM1: Distant metastasis (includes metastasis to inguinal lymph nodes, intraperitoneal disease, lung, liver, or bone). (It excludes metastasis to pelvic or para-aortic lymph nodes, vagina, uterine serosa, or adnexa)#

#### **FIGO STAGE**

##### **+FIGO Stage (FIGO 2009 Staging / 2018 FIGO Cancer Report) (Note [N](#))**

\_\_\_ I: Tumor confined to the corpus uteri

\_\_\_ IA: No or less than half myometrial invasion

\_\_\_ IB: Invasion equal to or more than half of the myometrium

\_\_\_ II: Tumor invades cervical stroma, but does not extend beyond the uterus

\_\_\_ III: Local and / or regional spread of the tumor

\_\_\_ IIIA: Tumor invades the serosa of the corpus uteri and / or adnexae

\_\_\_ IIIB: Vaginal and / or parametrial involvement

\_\_\_ IIIC: Metastases to pelvic and / or para-aortic lymph nodes

\_\_\_ IIIC1: Positive pelvic nodes

\_\_\_ IIIC2: Positive para-aortic nodes with or without positive pelvic lymph nodes

\_\_\_ IV: Tumor invades bladder and / or bowel mucosa, and / or distant metastases

\_\_\_ IVA: Tumor invasion of bladder and / or bowel mucosa

*# Involvement of pelvic serosal structures (cul-de-sac, urinary bladder, sigmoid serosa) is classified as stage IIIA, while involvement of the omentum and abdominal peritoneum is considered IVB disease.*

\_\_\_ IVB: Distant metastasis, including intra-abdominal metastases and / or inguinal nodes#

**+FIGO Stage (2023 Staging for Cancer of the Endometrium) (Note [N](#))**

\_\_\_ I: Confined to the uterine corpus and ovary

\_\_\_ IA: Disease limited to the endometrium OR non-aggressive histological type, i.e., low-grade endometrioid, with invasion of less than half of the myometrium with no or focal lymphovascular space involvement (LVSI) OR good prognosis disease

\_\_\_ IA1: Non-aggressive histological type limited to an endometrial polyp OR confined to the endometrium

\_\_\_ IA2: Non-aggressive histological types involving less than half of the myometrium with no or focal LVSI

\_\_\_ IA3: Low-grade endometrioid carcinomas limited to the uterus and ovary

+ \_\_\_ IAm (POLEmut): POLE mutated endometrial carcinoma, confined to the uterine corpus or with cervical extension, regardless of the degree of LVSI or histological type

\_\_\_ IB: Non-aggressive histological types with invasion of half or more of the myometrium, and with no or focal LVSI

\_\_\_ IC: Aggressive histological types limited to a polyp or confined to the endometrium

\_\_\_ II: Invasion of cervical stroma without extrauterine extension OR with substantial LVSI OR aggressive histological types with myometrial invasion

\_\_\_ IIA: Invasion of the cervical stroma of non-aggressive histological types

\_\_\_ IIB: Substantial LVSI of non-aggressive histological types

\_\_\_ IIC: Aggressive histological types with any myometrial involvement

+ \_\_\_ IICm (p53abn): p53 abnormal endometrial carcinoma confined to the uterine corpus with any myometrial invasion, with or without cervical invasion, and regardless of the degree of LVSI or histological type

\_\_\_ III: Local and / or regional spread of the tumor of any histological subtype

\_\_\_ IIIA: Invasion of uterine serosa, adnexa, or both by direct extension or metastasis

\_\_\_ IIIA1: Spread to ovary or fallopian tube (except when meeting stage IA3 criteria)

\_\_\_ IIIA2: Involvement of uterine subserosa or spread through the uterine serosa

\_\_\_ IIIB: Metastasis or direct spread to the vagina and / or to the parametria or pelvic peritoneum

\_\_\_ IIIB1: Metastasis or direct spread to the vagina and / or the parametria

\_\_\_ IIIB2: Metastasis to the pelvic peritoneum

\_\_\_ IIIC: Metastasis to pelvic or para-aortic lymph nodes or both

\_\_\_ IIIC1: Metastasis to the pelvic lymph nodes

\_\_\_ IIIC1i: Micrometastasis (to pelvic nodes)

\_\_\_ IIIC1ii: Macrometastasis (to pelvic nodes)

\_\_\_ IIIC2: Metastasis to para-aortic lymph nodes up to the renal vessels, with or without metastasis to the pelvic lymph nodes

\_\_\_ IIIC2i: Micrometastasis (to para-aortic lymph nodes up to the renal vessels, with or without metastasis to the pelvic nodes)

\_\_\_ IIIC2ii: Macrometastasis (to para-aortic lymph nodes up to the renal vessels, with or without metastasis to the pelvic nodes)

\_\_\_ IV: Spread to the bladder mucosa and / or intestinal mucosa and / or distant metastasis

\_\_\_ IVA: Invasion of the bladder mucosa and / or intestine / bowel mucosa

\_\_\_ IVB: Abdominal peritoneal metastasis beyond the pelvis

\_\_\_ IVC: Distant metastasis, including metastasis to any extra- or intra-abdominal lymph nodes above the

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renal vessels, lungs, liver, brain or bone

**ADDITIONAL FINDINGS (Note [O](#))**

**+Additional Findings (select all that apply)**

None identified

Atypical hyperplasia / endometrioid intraepithelial neoplasia (EIN)

Other (specify): \_\_\_\_\_

**SPECIAL STUDIES**

*For reporting molecular testing, immunohistochemistry, and other cancer biomarker testing results, the CAP gynecologic origin biomarker template should be used. Pending biomarker studies should be listed in the Comments section of this report.*

**COMMENTS**

Comment(s): \_\_\_\_\_



## Explanatory Notes

### A. Clinical History

Approximately 3-5% of endometrial carcinomas can be attributed to Lynch syndrome (LS) / hereditary nonpolyposis colorectal cancer (HNPCC), which is caused by germline mutations in DNA mismatch repair (MMR) genes (*MLH1*, *PMS2*, *MSH2*, *MSH6*). Patients with LS have a 40-60% lifetime risk for endometrial and colorectal cancer, and endometrial cancer develops before colorectal cancer in more than 50% of cases.<sup>1,2</sup> Women with Cowden syndrome (*PTEN* mutations) also have a 20-30% lifetime risk of developing endometrial cancer. Such clinical history, if known, may be specified in the synoptic report. Results of MMR immunohistochemistry and other prognostic or therapeutic markers should be reported using the CAP Gynecologic Biomarker Protocol.<sup>3</sup> Please refer to this protocol for further details. See also Explanatory Note E.

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### B. Specimen Type and Sampling

The typical operative procedure for endometrial cancer is a hysterectomy. A total hysterectomy is defined as the removal of the uterus, including the cervix. Radical hysterectomy comprises the parametria, upper vagina and uterosacral ligaments, and should preferably be identified as such by the surgeon. Hysterectomy may be performed through a laparoscopy, robot-assisted laparoscopy or laparotomy.<sup>1</sup> Laparoscopic and robot-assisted laparoscopic hysterectomies may show intravascular and intraluminal (fallopian tubes) tumor fragments and other artifacts, such as myometrial clefts.<sup>2,3</sup>

Institutional practices vary. However, according to the International Society of Gynecological Pathologists (ISGyP) 2019 guidelines,<sup>4</sup> sections submitted for microscopic examination should include the following:

- a) One section per 1 cm of maximal tumor dimension should be submitted. Alternatively, at least 4 blocks of tumor should be taken, including sections to demonstrate the deepest point of myometrial invasion. In cases of a preoperative diagnosis of atypical hyperplasia or carcinoma but no grossly visible lesion in the hysterectomy specimen, the entire endometrium and underlying myometrium should be submitted.
- b) Ovaries should be sliced perpendicularly to the long axis at 2-3 mm intervals and submitted entirely for non-endometrioid carcinomas (albeit there is no supporting evidence). At least 2 sections of each ovary should be taken in endometrioid carcinomas.
- c) Fallopian tubes should be submitted entirely for non-endometrioid carcinomas per the SEE-FIM (Sectioning and Extensively Examining the FIMbriated End) protocol. At least the entire fimbriae and representative cross-sections should be taken in endometrioid carcinomas.
- d) The omentum should be grossly inspected and sectioned at 5 mm intervals. Gross lesions can be sampled in 1-2 blocks. At least 4 sections or 1 section per 2-3 cm of maximal dimension should be

submitted from grossly normal omentum,<sup>5</sup> although submitting at least 10 sections improves the sensitivity for detection of microscopic disease to 95%.<sup>6</sup>

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#### C. Histologic Type

Endometrioid carcinoma displays varying proportions of glandular, papillary, and solid architecture.<sup>1,2</sup> Growth patterns such as villoglandular, small non-villous papillae, microglandular, sex cord-like, corded and hyalinized, and sertoliform can be seen. In high-grade tumors, the presence of confirmatory endometrioid features such as squamous, mucinous, secretory or ciliated (tubal) differentiation combined with loss of expression of ARID1A, PTEN, or mismatch repair (MMR) protein(s) by immunohistochemistry (IHC) favors endometrioid carcinoma over other histotypes.<sup>3</sup> Abnormal/mutation-type p53 expression is seen in 2-5% of low-grade and approximately 20% of high-grade endometrioid carcinomas.<sup>1</sup>

Serous carcinoma usually shows papillary, glandular and/or solid architecture with high-grade cytology (marked nuclear pleomorphism, prominent nucleoli, brisk mitoses), associated with abnormal p53 expression and often block-like p16 expression.<sup>4</sup> It can be differentiated from endometrioid carcinoma based on slit-like glands with irregular luminal outlines, contrasting with round, smooth and regular luminal outlines typical for endometrioid differentiation.

Clear cell carcinoma is characterized by an admixture of tubulocystic, papillary, and/or solid patterns with clear to eosinophilic cuboidal, polygonal, hobnail, or flat cells. Helpful immunostains include expression of napsin A, AMACR (P504S), and HNF-1Beta (although these may also be expressed in endometrioid carcinoma), and lack of reactivity for estrogen and progesterone receptors (ER, PR).<sup>1</sup>

Undifferentiated carcinoma consists of sheets of uniform, small to intermediate-sized, non-cohesive cells. Dedifferentiated carcinoma is composed of an undifferentiated carcinoma and a second differentiated component, usually a FIGO grade 1 or 2 endometrioid carcinoma or, rarely, a high-grade carcinoma.<sup>5,6</sup> The typical immunoprofile includes absent or focal expression of PAX8, ER, e-cadherin, and epithelial markers. EMA and CK8/18 expression may be present in rare cells, and a subset shows abnormal p53 expression.

Published criteria set an upper limit of 10% for the extent of allowable neuroendocrine marker expression, but in practice more extensive staining can be encountered. Differentiation from a high-grade neuroendocrine carcinoma in such a case rests on morphology, MMR-deficiency (more common in un/dedifferentiated carcinoma) and/or loss of expression of SWI/SNF complex proteins such as SMARCA4 (BRG1), SMARCB1 (INI-1), SMARCA2 (BRM), ARID1A or ARID1B (favoring un/dedifferentiated carcinoma).

Carcinosarcoma comprises high-grade carcinomatous and sarcomatous components. The carcinomatous component often shows serous or endometrioid differentiation, but other non-endometrioid carcinomas or high-grade carcinoma with ambiguous morphology may also be encountered. The sarcomatous component usually consists of high-grade sarcoma NOS (homologous differentiation), but heterologous elements (rhabdomyosarcoma, chondrosarcoma, and rarely osteosarcoma) may be seen.<sup>1</sup> The presence of rhabdomyosarcomatous elements has been shown to predict poor prognosis.<sup>7,8</sup>

Rare aggressive types of endometrial carcinoma include:<sup>1</sup> **a) Neuroendocrine carcinomas (NECs)** show high-grade hyperchromatic nuclei and scant cytoplasm (small cell NEC), or moderate amounts of cytoplasm and large nuclei with coarse chromatin and prominent nucleoli (large cell NEC). **b) Mesonephric-like adenocarcinoma** exhibits an admixture of growth patterns, including papillary, ductal, retiform, solid, or spindled, with intraluminal eosinophilic colloid-like material, and moderately atypical vesicular nuclei with angulation and overlapping. The typical immunoprofile is absent or focal ER and PR, wild-type p53 expression, and variable positivity for GATA3, TTF1, and CD10 (luminal). Most cases exhibit *KRAS* mutations and an aggressive behavior.<sup>9,10</sup> **c) Squamous cell carcinoma** is human papillomavirus independent and may develop secondary to long-standing obstruction with squamous metaplasia (ichthyosis uteri). **d) Gastric (gastrointestinal)-type carcinoma** is composed of glands lined by mucin-secreting epithelium with or without goblet cells and should be differentiated from low-grade endometrioid carcinoma with extensive mucinous differentiation (previously known as mucinous carcinoma). In all these types, extension from a cervical primary must be excluded. **e) Endometrial carcinomas with yolk sac-like, choriocarcinoma-like, trophoblastic-like or neuroectodermal-like features** are regarded as somatic transdifferentiation of carcinoma and are not considered a mixed tumor of carcinoma and germ cell tumor. They are characterized by a particularly aggressive clinical behavior and poor response to therapy.<sup>11,12,13</sup>

Mixed carcinomas are composed of two distinct histologic types, in which at least one component is usually either serous or clear cell carcinoma.<sup>1</sup> These are graded as high-grade carcinoma irrespective of the relative percentages of serous or clear cell carcinoma present. IHC support for two distinct types is desirable for diagnosis.<sup>1</sup> “Combined small cell and/or large cell NECs” (ICD-0 terms) with another tumor type (for example, endometrioid) is also a mixed carcinoma and should be classified as “carcinoma admixed with neuroendocrine carcinoma”.<sup>1</sup> The percentages of each tumor type and associated myoinvasion should be specified in mixed carcinomas.

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#### D. Histologic Grading

All non-endometrioid histotypes are considered high-grade.<sup>1,2</sup> Only endometrioid carcinoma (including variants) is graded which has a prognostic impact.<sup>3</sup> The International Federation of Gynecology and Obstetrics (FIGO) grading system is based on the proportion of non-squamous solid growth as follows:

FIGO Grade 1	5% or less non-squamous solid growth pattern
FIGO Grade 2	6% to 50% non-squamous solid growth pattern
FIGO Grade 3	>50% non-squamous solid growth pattern

Severe cytologic atypia in >50% of tumor cells increases the tumor grade by 1. This should raise suspicion for serous carcinoma, and *TP53*-mutated or *POLE*-mutated endometrioid carcinoma.

Binary grading (low-grade: FIGO grade 1-2; high-grade: FIGO grade 3) has been endorsed by the International Society of Gynecological Pathologists (ISGyP), International Collaboration on Cancer

Reporting (ICCR), and the 2020 World Health Organization (WHO) Classification due to improved reproducibility.<sup>1,2,4</sup> However, it has not been widely adopted in practice.

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#### E. Molecular Type

In 2013, The Cancer Genome Atlas (TCGA) identified 4 distinct molecular types of endometrial carcinoma with significant differences in progression-free survival:<sup>1</sup> 1) *POLE*-mutated (ultramutated) carcinomas account for ~7% of endometrial carcinomas and have inactivating hotspot mutations in the *POLE* exonuclease domain with an extremely high tumor mutation burden (TMB); 2) Microsatellite instability high (MSI-H; hypermutated) carcinomas account for ~28% of cases and often show *MLH1* promoter methylation and high TMB; 3) Copy number low (CNL) carcinomas account for ~39% of cases and show low copy number alterations, and low TMB; and 4) Copy number high (CNH) carcinomas account for ~26% of cases and show frequent (95%) *TP53* mutations and low TMB. Most *POLE*-mutated tumors have an excellent prognosis, CNH tumors have a poor prognosis, while MSI-H and CNL tumors are heterogeneous with variable outcomes. FIGO grade 3 endometrioid carcinomas are highly represented in all 4 groups. *POLE*-mutated tumors may resemble serous carcinomas. MSI-H and CNL groups predominantly include endometrioid carcinomas, while most CNH tumors are serous carcinomas.

Although molecular type assignment has predictive implications, this approach has not been widely validated clinically. Instead, there has been extensive validation of a surrogate marker approach such as ProMisE (Proactive Molecular Risk Classifier for Endometrial Cancer),<sup>2,3,4</sup> recommended by the World Health Organization (WHO),<sup>5</sup> and an independently validated TransPORTEC classifier.<sup>6</sup> ProMisE combines *POLE* mutation testing and immunohistochemistry (IHC) for p53 and mismatch repair proteins (MMR) to identify *POLE*-mutated, MMR-deficient, p53-abnormal, and no specific molecular profile (NSMP) groups. Adjuvant chemotherapy is associated with more favorable outcomes for patients with p53-abnormal tumors (including stage I disease and non-serous morphology) but not for MMR-deficient tumors.<sup>6,7</sup> Molecular classification of all endometrial carcinomas is encouraged and can be performed on biopsies/curettings or hysterectomy specimens, because having the results upfront (on biopsy material) may influence surgical management.<sup>8</sup> However, in contrast to MMR and p53 IHC, limited availability of *POLE* mutational analysis hinders the universal adoption of this classifier as well as the FIGO 2023 staging system (see Explanatory Note N). Selective ProMisE classifier may be used in routine practice, according to which MMR and p53 IHC is performed in all cases, while *POLE* testing is restricted to patients in whom *POLE* status would alter adjuvant therapy.<sup>9</sup> Grade 1 or 2 tumors, endometrioid morphology, wild-type p53

expression, MMR-proficient status, stage IA and absence of substantial lymphovascular invasion (LVI) can be regarded as “very low-risk” with no further testing. Postsurgically, tumors staged higher than IA, grade 3 and tumors with substantial LVI should also be molecularly characterized.<sup>9</sup>

MMR IHC is reported as intact expression, loss of expression, or subclonal loss of expression. **Intact (normal) expression** of MMR proteins is nuclear staining with similar or stronger intensity compared with the background (non-neoplastic) internal control cells. **Loss of expression** denotes absence of nuclear expression in tumor cells and should only be reported if internal control cells are positive.<sup>10,11</sup> **Subclonal loss** of MMR protein expression occurs when there are discrete areas of tumor with complete loss of nuclear expression adjacent to tumor cells with retained expression. Subclonal loss of expression should be distinguished from patchy staining that can be seen in cases of intact expression. Subclonal loss of MLH1/ PMS2 and MSH6 expression has been described in 7% of endometrial endometrioid carcinomas, and may be due to epigenetic silencing such as *MLH1* promoter methylation or *POLE* mutations.<sup>10,12</sup> Subclonal loss may rarely occur in Lynch syndrome associated endometrial carcinomas;<sup>12</sup> therefore, it is important not to regard any positive nuclear staining as intact expression. Microsatellite instability is determined by polymerase chain reaction or next generation sequencing (refer to the CAP Gynecologic Biomarker Protocol for further details).

The normal or “wild-type” pattern of p53 expression denotes nuclear staining of varying intensity, usually in association with non-mutated *TP53* gene. There are 3 **abnormal/mutation-type patterns** (Table 1)<sup>13,14,15,16</sup> and rarely, loss of function mutations in the *TP53* gene are associated with wild-type p53 pattern by IHC.<sup>12</sup> **Subclonal abnormal p53 pattern** has been described in up to 21% of endometrial carcinomas, usually suggesting a secondary mutation in the setting of MMR-deficiency or *POLE* mutations.<sup>14,15,17</sup> In addition, subclonal abnormal p53 pattern may indicate a mixed (e.g., serous and endometrioid or clear cell) carcinoma. Correlation between the p53 protein expression and morphologic features can help identify a mixed carcinoma. Subclonal abnormal p53 expression should be reported along with the most likely explanation (such as MMR-deficiency or *POLE* mutation). Endometrial carcinomas with combined p53-abnormal/MMR-deficient, p53-abnormal/*POLE* mutated or *POLE* mutated/MMR-deficient profiles (“double classifiers”) do not have the same prognosis as pure molecular types.<sup>18</sup>

**Table 1. Reporting Results of p53 Status by Immunohistochemistry (IHC)**

Result	Criteria
Wild-type expression	Nuclear staining of varying intensity admixed with negative nuclei
<b>Abnormal (mutated) expression patterns</b>	
Abnormal expression (overexpression)	Diffuse, strong nuclear positivity in at least 80% of tumor cells
Abnormal expression (null-type)	Complete absence of nuclear and cytoplasmic reactivity in tumor cells (with satisfactory internal positive control)
Abnormal expression (cytoplasmic)	Cytoplasmic staining that may be accompanied by nuclear reactivity
Subclonal abnormal expression	Abnormal expression (any of the above) in a subset of tumor cells

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## F. Myometrial Invasion

The depth of myometrial invasion is an important variable for pTNM and FIGO 2009 staging (inner half: pT1a/IA, outer half: pT1b/IB) as it represents a risk factor for regional nodal metastasis and overall survival in stage I endometrioid carcinomas.<sup>1</sup> The conventional pattern of myometrial invasion shows infiltrating glands associated with a stromal response.<sup>2</sup> Additional patterns include:

- a) The adenoma malignum-like pattern comprising round glands lined by bland epithelium, sometimes with eosinophilic secretions, lacking an associated stromal response. When involving the lower uterine segment (LUS) or cervix, these glands may be misdiagnosed as mesonephric remnants/hyperplasia.
- b) The adenomyosis-like pattern shows neoplastic glands forming irregular “islands” without surrounding endometrial stromal cells.<sup>2</sup>
- c) The microcystic, elongated and fragmented (MELF) pattern shows single cell clusters, cords, or microcystic glands lined by variably flattened epithelium with eosinophilic cytoplasm, and surrounded by reactive, inflamed (neutrophil-rich), sometimes fibromyxoid, stroma. The foci of MELF invasion may be missed and/or mistaken for lymphovascular invasion (LVI). MELF pattern is associated with LVI and lymph node metastasis, although it is not an independent predictor of overall survival.<sup>3</sup> Nodal metastases are often small and resemble histiocytes and identification may be facilitated by keratin staining.<sup>4,5</sup>
- d) Single cell infiltration is associated with an increased risk of extrauterine extension in one study.<sup>6</sup>

The depth of myometrial invasion should be estimated from the endomyometrial junction to the deepest point of invasion in relation to the myometrial thickness. The following challenging scenarios may be encountered:<sup>7,8</sup>

- a) In cases of irregular endomyometrial junction, it is helpful to look for compressed, non-neoplastic endometrial glands adjacent to or at the base of the tumor.
- b) In exophytic tumors and endometrial polyps, the exophytic component should be excluded from assessing the myometrial thickness. The endomyometrial junction may be inferred by comparing the area in question and an adjacent area without myoinvasion.
- c) Given the thin uterine wall at the cornu, the depth of invasion should not be assessed at this site, unless the tumor entirely involves the cornu and/or serosa.
- d) If the deepest invasion is seen in the LUS, the depth of myometrial invasion should be estimated similarly to the uterine corpus.
- e) For tumors infiltrating a leiomyoma and where this represents the deepest invasion, the depth of invasion should include the portion of the tumor invading into the leiomyoma, and the myometrial thickness should include the leiomyoma.
- f) If myometrial invasion appears to have arisen from adenomyosis, determining pT1a versus pT1b stage is controversial. If the deepest point of invasion is in the outer half of the myometrium, the International Collaboration on Cancer Reporting (ICCR)<sup>7</sup> and International Society for Gynecological Pathologists (ISGyP)<sup>8</sup> guidelines recommend staging the tumor as pT1b with a comment that the invasion arose from the focus of adenomyosis.
- g) Foci of LVI should not be included in determining pT1a versus pT1b stage.



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## G. Uterine Serosal and Lower Uterine Segment (LUS) Involvement

Uterine serosa is involved when the tumor infiltrates the entire myometrium and reaches submesothelial fibroconnective tissue or the mesothelial layer, irrespective of the presence of tumor cells or desmoplastic response on the serosal surface.<sup>1</sup> Desmoplastic reaction may make serosal assessment challenging. It may be helpful to identify the serosal plane within the area of interest and desmoplastic area, whereby disruption of the plane or extension of carcinoma beyond the plane would be considered positive for serosal involvement. Although both constitute a stage IIIA disease (FIGO 2009 staging), uterine serosal involvement is associated with a higher risk of locoregional recurrence than adnexal involvement.<sup>2</sup>

The prevalence of Lynch syndrome has been shown to be greater in patients with endometrial carcinoma arising in the LUS compared with the general patient population.<sup>3</sup> In addition, LUS involvement predicts nodal metastasis, distant recurrence and death in some studies.<sup>4,5,6</sup>

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#### **H. Cervical, Adnexal, and Other Organ Involvement**

Cervical stromal invasion by endometrial carcinoma constitutes a pT2/FIGO stage II disease and increases the risk of recurrence and regional nodal metastases.<sup>1</sup> Cervical stromal invasion can be identified by the presence of a desmoplastic stromal response and/or altered architecture relative to pre-existing normal endocervical glands.<sup>2</sup> The upper limit of the endocervix is defined by the most proximal endocervical gland(s), and stromal invasion can be diagnosed when tumor is present either at the level of, or distal to, non-neoplastic endocervical glands.<sup>3</sup> Patients with low-grade endometrial carcinoma and cervical stromal invasion within the inner half of the cervix treated with brachytherapy alone have favorable outcomes.<sup>4</sup> Therefore, the percentage of cervical wall involvement should be reported.

Endocervical glandular involvement should not be classified as stage pT2/II. However, adjuvant radiation in these patients improves the risk of locoregional recurrence and overall survival, and some oncologists administer brachytherapy.<sup>5,6</sup> Therefore, endocervical glandular involvement should be reported.<sup>7</sup>

Adnexal involvement in endometrial cancer signifies stage pT3a/IIIA in FIGO 2009 and 2023 (some cases; see below) staging. Most high-grade carcinomas simultaneously involving the endometrium and adnexa are endometrial primaries with adnexal metastases rather than synchronous primaries. However, classification of low-grade endometrioid carcinomas is controversial.<sup>2</sup> These tumors are often associated with favorable outcomes, although recent studies have revealed a clonal relationship between the endometrial and ovarian carcinomas in most patients.<sup>8,9,10,11</sup> Consequently, the World Health Organization (WHO),<sup>12</sup> European Society of Gynecologic Oncology (ESGO), European Society for Therapeutic Radiology and Oncology (ESTRO), and European Society of Pathology (ESP)<sup>13</sup> recommend conservative management without adjuvant therapy when the following criteria are met: 1) low-grade endometrioid morphology, 2) no more than superficial myometrial invasion, 3) absence of LVI, and 4) absence of additional metastases.<sup>12,14</sup> The FIGO 2023 staging system endorses this view and establishes the category of stage IA3 for low-grade endometrial endometrioid carcinomas based on the above 4 criteria with the additional requirement of a unilateral ovarian tumor without surface involvement (pT1a).<sup>15</sup>

Tumor invading into the fallopian tube (mucosa or wall) also constitutes stage pT3a/IIIA in both FIGO 2009 and 2023 staging systems, but intraluminal tumor fragments alone should be disregarded. However, intraluminal fragments of serous carcinoma may be associated with peritoneal metastasis,<sup>16</sup> and peritoneal/pelvic washings (if performed) should be reviewed in such cases. The finding of tubal intramucosal endometrioid carcinoma in association with an endometrial endometrioid carcinoma is controversial. It could theoretically represent either direct spread/metastasis from the endometrium or a synchronous carcinoma, with the former interpretation usually favored unless a precursor lesion (e.g. endometriosis) is present. Tubal involvement by serous carcinoma may form a serous tubal intraepithelial carcinoma (STIC)-like lesion and must be distinguished from true STIC.<sup>17</sup> Immunohistochemistry for WT1 may be helpful, with expected negative to minimal staining in most endometrial serous carcinomas but diffuse expression in most adnexal high-grade serous carcinomas.<sup>18</sup>

The presence of LVI in the ovary or fallopian tube without stromal invasion does not affect staging.

Stage IV disease includes mucosal involvement of the urinary bladder or bowel, and peritoneal or omental involvement beyond the pelvic brim.

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### **I. Peritoneal/Pelvic Washings or Ascites Fluid**

The prognostic significance of positive cytology in endometrial cancer is controversial with contradictory results in various studies. It is uncertain whether the type of operative procedure affects the probability of positive cytology.<sup>1</sup> Consequently, positive cytology no longer alters staging and many clinicians do not routinely perform peritoneal/pelvic washings.

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### **J. Lymphatic and / or Vascular Invasion**

Lymphovascular invasion (LVI) or lymphovascular space invasion (LVSI) has prognostic significance in endometrial carcinoma and should be reported. LVI is usually seen at the invasive front of a tumor and is characterized by the presence of a tumor embolus within an endothelial-lined space, often taking the shape of the vascular lumen and sometimes attached to the endothelium.<sup>1,2,3</sup> LVI mimics include retraction, artifactually displaced tumor cells, and MELF (microcystic, elongated, fragmented) pattern myoinvasion. Retraction may show fine strands of cytoplasm between the tumor embolus and the vessel wall.<sup>3</sup> Artifactually displaced tumor fragments or normal tissue on the cut surfaces of tissue sections, in tissue “cracks” and/or large, medium and small vessels at the invasive front and distant locations are usually seen in the setting of grossing the uterus before adequate fixation following laparoscopic and/or robotic surgery.<sup>2</sup> MELF pattern myoinvasion is usually seen in low-grade endometrioid carcinomas.<sup>4,5</sup> Both the foci of LVI and MELF invasion can be seen in the same section.<sup>6</sup> If there is uncertainty regarding true versus artifactual LVI, this should be clearly explained in the report.

Substantial/extensive LVI (with variable definitions) has been shown to be a strong independent prognostic factor for regional and distant recurrence, and overall survival.<sup>7,8,9,10,11,12</sup> However, there have been conflicting recommendations for the LVI extent (focal versus substantial). Substantial LVI is defined as 5 or more involved vessels by the World Health Organization (WHO),<sup>13</sup> the FIGO 2023 Staging System,<sup>14</sup> and the 2021 ESGO/ESTRO/ESP risk grouping guidelines,<sup>15</sup> and 3 or more involved vessels by the 2022 International Collaboration on Cancer Reporting (ICCR) guidelines<sup>16</sup> and the 2019 International Society of Gynecological Pathologists guidelines.<sup>1</sup> However, in these publications it is not always clear whether the highest number of LVI foci is determined in a single section or across multiple sections. In the most recent study based on PORTEC-1 and PORTEC-2 cohorts of 926 cases and the Danish Gynecological Cancer Database cohort of 401 cases, 4 pathologists evaluated the extent of LVI and proposed a cut-off of at least 4 involved vessels in at least one slide for substantial LVI.<sup>7</sup> Given that the only evidence-based numeric threshold for defining clinically relevant LVI is 4 or more vessels in a single section,<sup>17,18</sup> the CAP

recommends using this cut-off (estimated on the single slide with the highest number of vessels involved) when the AJCC and FIGO 2009 staging systems are used. The cut-off of 5 or more vessels can be used for the FIGO 2023 staging. Nevertheless, given the conflicting recommendations, specific number of LVI foci (if less than 5) can be specified in the synoptic report.

The presence of LVI in the cervix, ovary, fallopian tube, or parametrium without stromal invasion does not affect tumor stage.

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### K. Margins

In total hysterectomy specimens, the parametrial/paracervical soft tissue and ectocervical/vaginal cuff margins are the only true margins. It is required to report these margins if the cervical stroma and/or parametrium/paracervix is involved by carcinoma. In supracervical hysterectomies, the status of the lower uterine segment margin should be reported.

### L. Lymph Node Status

Regional lymph nodes in endometrial cancer patients include the **pelvic** (parametrial, obturator, internal iliac/hypogastric, external iliac, common iliac, sacral, presacral) and **para-aortic** nodes. Any other involved nodes should be categorized as metastases (pM1) and reported in the distant metastasis section. In FIGO 2009 staging, positive pelvic nodes indicate stage IIIC and positive para-aortic nodes IIIC. Other positive non-regional nodes constitute stage IVB.

The AJCC and FIGO definitions of micro- and macrometastasis are identical. Micrometastases (pN1(mi)) are deposits greater than 0.2 mm but no greater than 2 mm, and macrometastases are greater than 2 mm. Both micro- and macrometastases result in tumor upstaging. The presence of isolated tumor cells (ITCs), defined as no greater than 0.2 mm or clusters of no more than 200 cells in regional lymph node(s), is considered stage pN0(i+). ITCs should only be reported in the absence of micro- or macrometastases. ITCs can be seen only on hematoxylin-eosin (H&E) stained slides or both the H&E stain and keratin immunostain(s). Caution should be exercised when diagnosing ITCs on a keratin immunostain alone without morphologic correlation.

Patients at intermediate- or high-risk for recurrence benefit from lymph node assessment. Sentinel lymph node sampling is widely used for staging low - or intermediate-risk patients, but is also an alternative to systematic lymphadenectomy in presumed early-stage cancers for higher-risk patients.<sup>1</sup> Sentinel lymph nodes should be examined in accordance with a locally agreed upon and established protocol. The pathology report should specify whether or not an ultrastaging procedure was performed and whether nodal metastases were identified on routine histologic examination (without ultrastaging) or by ultrastaging.<sup>2</sup> There is no universally used ultrastaging protocol; however, protocols used at the 2 largest cancer centers in USA are as follows:<sup>3,4,5</sup>

1. Memorial Sloan Kettering Cancer Center Protocol: If the initial H&E-stained slide is negative for carcinoma, 2 additional levels at 50 µm apart are examined; at each level 2 slides are obtained, one for H&E and the second for keratin cocktail immunohistochemistry.
2. The University of Texas MD Anderson Cancer Center Protocol: If the initial H&E-stained slide is negative for carcinoma, 5 levels at 250 µm intervals are obtained (1 H&E and 2 unstained sections per level to be used for keratin cocktail immunohistochemistry if the additional H&E-stained slides are negative).

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#### **M. pTNM Classification**

The TNM staging system for endometrial cancer endorsed by the AJCC and the UICC<sup>1</sup> is recommended. The parallel systems formulated by FIGO<sup>2,3</sup> are optional for endometrial cancer patients.

According to 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 necessitates a resection of the primary tumor or biopsy adequate to evaluate the highest pT category, pN necessitates removal of nodes adequate to validate lymph node metastasis, and pM implies microscopic examination of distant lesions. The referring physician usually carries out clinical classification (cTNM) 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 (e.g., 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.

#### **TNM Descriptors**

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

The “y” prefix indicates those cases in which classification is performed during or after initial multimodality therapy (i.e., neoadjuvant chemotherapy, radiation therapy, or both chemotherapy and radiation therapy). The “y” may also be added in patients treated with progestin. 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 before multimodality therapy (i.e., 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.

### **T Category Considerations**

It is important to note that in endometrial cancer, as in cancer of other organs, the validity of T stage depends upon the adequacy and completeness of the surgical staging.

### **N Category Considerations**

The size criteria for micrometastasis and macrometastasis are adopted from experience in breast carcinoma. Micrometastasis is defined as a metastasis measuring greater than 0.2 mm but less than 2 mm. Macrometastases measure more than 2 mm. Isolated tumor cells (ITCs) are single cells or small clusters of cells no more than 0.2 mm in greatest dimension or no more than 200 cells. ITCs are identified by either only histologic examination (hematoxylin-eosin (H&E) stained slides) or both the H&E stained slides and cytokeratin immunohistochemistry. Until more data are available, they should be coded as “N0(i+)” with a comment describing how the cells were identified.

### **M Category Considerations**

Involvement of the intrapelvic peritoneum (cul-de-sac, urinary bladder, sigmoid serosa) without extension beyond the pelvic brim is considered pT3 and not pM1 disease. Distant metastases are required to be beyond the pelvic brim, i.e., involvement of the omentum and abdominal peritoneum is considered pM1 disease.<sup>1</sup> In complex cases, it may be necessary to confer with the surgeon to determine the appropriate stage.

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### **N. FIGO Staging**

In 2023, the International Federation of Gynaecology and Obstetrics (FIGO) released a new staging system for endometrial carcinoma, which includes non-anatomic variables such as tumor histotype (aggressive versus non-aggressive), tumor grade, lymphovascular space invasion, and molecular classification.<sup>1,2</sup> There has been considerable debate about and criticism of this system as the incorporation of these “non-anatomical” parameters, some of which are controversial or poorly reproducible, poses significant challenges in accurate reporting of endometrial cancer with the potential for major negative



impact on optimal patient management.<sup>3,4</sup> In the absence of robust supporting evidence and wide acceptance for the proposed changes, the CAP has elected to revert to the 2009 FIGO staging (FIGO 2018 Cancer Report)<sup>5</sup> and make both the 2023 and 2009 FIGO staging systems optional reporting elements until more data becomes available.

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#### O. Additional Findings

Endometrioid carcinomas may be associated with atypical hyperplasia/endometrioid intraepithelial neoplasia (AH/EIN). AH/EIN is diagnosed when there are crowded glands (increased gland-to-stroma ratio) with altered cytology (nuclear enlargement, pleomorphism, rounding, loss of polarity, prominent nucleoli) that are distinct from adjacent/entrapped benign glands. Confluent glandular (cribriform or maze-like growth) or solid patterns and myoinvasion must be absent.<sup>1</sup> Common mimics such as artifacts, metaplasia, glands from stratum basalis, polyp, or dyssynchronous endometrium must be excluded.

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