Protocol for the Examination of Specimens From Patients With Carcinoma of the Endometrium

Based on AJCC/UICC TNM, 7th edition and FIGO 2008 Annual Report
Protocol web posting date: December 2013

Procedure
• Hysterectomy

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CAP Endometrium Protocol Revision History

Version Code
The definition of the version code can be found at www.cap.org/cancerprotocols.

Version: Endometrium 3.2.0.1

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

Explanatory Notes

I. TNM and FIGO Staging of Endometrial Carcinoma

Regional Lymph Nodes: Isolated Tumor Cells
“N1” was changed to “N0(i+)” in the last sentence, as follows:
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.

L. Clinical History
“MSH1” and “MSH2” were changed to “MLH1” and “MLH2.”

The following changes have been made since the June 2012 release.

Hysterectomy

Extent of Involvement of Other Organs
Added “Other (explain)” to Left/Right ovary and Left/Right fallopian tube. Deleted “Not applicable” from all organ sites.

Explanatory Notes

D. Myometrial Invasion
In the last sentence, “FIGO stage IB” was changed to “FIGO stage IA.”

L. Clinical History
“MLH6” was changed to “MSH6.”
Surgical Pathology Cancer Case Summary

Protocol web posting date: December 2013

ENDOMETRIUM: Hysterectomy, With or Without Other Organs or Tissues

Select a single response unless otherwise indicated.

Specimen (select all that apply)
___ Uterine corpus
___ Cervix
___ Right ovary
___ Left ovary
___ Right fallopian tube
___ Left fallopian tube
___ Left parametrium
___ Right parametrium
___ Vaginal cuff
___ Omentum
___ Other (specify): ____________________________
___ Not specified

Procedure (select all that apply) (Note A)
___ Supracervical hysterectomy
___ Simple hysterectomy
___ Radical hysterectomy
___ Right oophorectomy
___ Left oophorectomy
___ Right salpingectomy
___ Left salpingectomy
___ Right salpingo-oophorectomy
___ Left salpingo-oophorectomy
___ Bilateral salpingo-oophorectomy
___ Omentectomy
___ Peritoneal biopsies
___ Other (specify): ____________________________
___ Not specified

Lymph Node Sampling (select all that apply)
___ Performed:
   ___ Pelvic lymph nodes
   ___ Para-aortic lymph nodes
   ___ Other (specify): ____________________________
___ Not performed
___ Not known

Specimen Integrity (Note A)
___ Morcellated hysterectomy specimen
___ Intact hysterectomy specimen

+ Data elements preceded by this symbol are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.
+ Tumor Site
+ ___ Anterior endometrium
+ ___ Posterior endometrium
+ ___ Other (specify): _________________________________

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

Histologic Type (Note B)
___ Endometrioid adenocarcinoma, not otherwise characterized
___ Endometrioid adenocarcinoma, variant (specify): __________________________
___ Mucinous adenocarcinoma
___ Serous adenocarcinoma
___ Clear cell adenocarcinoma
___ Mixed carcinoma (specify types and percentages): __________________________
___ Squamous cell carcinoma
___ Transitional cell carcinoma
___ Small cell carcinoma
___ Undifferentiated carcinoma
___ Carcinosarcoma (malignant müllerian mixed tumor)
___ Other (specify): __________________________

Histologic Grade (Note C)
International Federation of Gynecology and Obstetrics (FIGO) Grading System (applies to endometrioid and mucinous adenocarcinomas only):
___ FIGO grade 1
___ FIGO grade 2
___ FIGO grade 3
For other carcinomas:
___ G1: Well differentiated
___ G2: Moderately differentiated
___ G3: Poorly differentiated
___ Other (specify): __________________________
___ Not applicable

Myometrial Invasion (Note D)
___ Not identified
___ Present
    Depth of invasion: ___ mm
    Myometrial thickness: ___ mm

If exact depth of invasion cannot be determined, state:
___ <50% myometrial invasion
___ ≥50% myometrial invasion
___ Extent of myometrial invasion cannot be determined (see Comment)
Involvement of Cervix (select all that apply) (Note E)
___ Not involved
___ Invasion of cervical stromal connective tissue
___ Cannot be determined (see Comment)

Extent of Involvement of Other Organs (select all that apply)
___ Right ovary
   ___ Involved
   ___ Not involved
   ___ Other (explain): ______________________
___ Left ovary
   ___ Involved
   ___ Not involved
   ___ Other (explain): ______________________
___ Right fallopian tube
   ___ Involved
   ___ Not involved
   ___ Other (explain): ______________________
___ Left fallopian tube
   ___ Involved
   ___ Not involved
   ___ Other (explain): ______________________
+ ___ Vagina
  + ___ Involved
  + ___ Not involved
+ ___ Right parametrium
  + ___ Involved
  + ___ Not involved
+ ___ Left parametrium
  + ___ Involved
  + ___ Not involved
+ ___ Omentum
  + ___ Involved
  + ___ Not involved
+ ___ Rectal wall
  + ___ Involved
  + ___ Not involved
+ ___ Bladder wall
  + ___ Involved
  + ___ Not involved
+ ___ Pelvic wall
  + ___ Involved
  + ___ Not involved
+ ___ Bladder mucosa and/or bowel mucosa
   + ___ Involved
   + ___ Not involved
+ ___ Other (specify): _________________________________

+ Data elements preceded by this symbol are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.
+ Peritoneal Ascitic Fluid (Note F)
+ ___ Negative for malignancy/normal/benign
+ ___ Atypical and/or suspicious (must qualify)
+ ___ Malignant (positive for malignancy)
+ ___ Unsatisfactory/nondiagnostic (provide reason): ______________________

+ Margins (Note G)
+ ___ Cannot be assessed
+ ___ Uninvolved by invasive carcinoma
   + Distance of invasive carcinoma from closest margin: ___ mm
   + Specify margin: ___________________________
+ ___ Involved by invasive carcinoma
   + Specify margin(s): ___________________________

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

Pathologic Staging (pTNM [FIGO]) (Note I)

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
___ pT1a [IA]: Tumor limited to endometrium or invades less than one-half of the myometrium
___ pT1b [IB]: Tumor invades greater than or equal to one-half of the myometrium
___ pT2 [II]: Tumor invades stromal connective tissue of the cervix, but does not extend beyond uterus
___ pT3a [IIIA]: Tumor involves serosa and/or adnexa (direct extension or metastasis)
___ pT3b [IIIB]: Vaginal involvement (direct extension or metastasis) or parametrial involvement
___ pT4 [IVA]: Tumor invades bladder mucosa and/or bowel mucosa (bullous edema is not sufficient to classify a tumor as T4)

Regional Lymph Nodes (pN)
___ pNX: Cannot be assessed
___ pN0: No regional lymph node metastasis
___ pN1 [IIIC1]: Regional lymph node metastasis to pelvic lymph nodes
___ pN2 [IIIC2]: Regional lymph node metastasis to para-aortic lymph nodes, with or without positive pelvic lymph nodes

Pelvic lymph nodes:
___ No nodes submitted or found

Number of Lymph Nodes Examined
Specify: ___
___ Number cannot be determined (explain): ______________________

+ Data elements preceded by this symbol are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.
Number of Lymph Nodes Involved
Specify: ____
___ Number cannot be determined (explain): ________________________

Para-aortic lymph nodes:
___ No nodes submitted or found

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

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

Distant Metastasis (pM)
___ Not applicable
___ pM1 [IVB]: Distant metastasis (includes metastasis to inguinal lymph nodes, intraperitoneal disease, or lung, liver, or bone metastasis. It excludes metastasis to para-aortic lymph nodes, vagina, pelvic serosa, or adnexa)
   Specify site(s), if known: ______________________________

Additional Pathologic Findings (select all that apply) (Note J)
___ None identified
___ Hyperplasia
   ___ Simple without cytologic atypia
   ___ Complex without cytologic atypia
___ Atypical hyperplasia
   ___ Simple
   ___ Complex
___ Endometrial intraepithelial neoplasia (EIN)
___ Other (specify): ___________________________

Ancillary Studies (Note K)
Specify: ___________________________
___ Not performed

Clinical History (select all that apply) (Note L)
___ Lynch syndrome
___ Other (specify): ___________________________

Comment(s)

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

A. Specimen Type
In rare occasions when an endometrial carcinoma is not suspected, the pathologist may receive a supracervical hysterectomy specimen removed by laparoscopy. The type of procedure should be recorded. It has been reported that hysterectomies performed using certain laparoscopic techniques result in the finding of venous tumor emboli that are likely to be iatrogenic.^1 The significance of morcellation techniques in unsuspected endometrial cancer cases is not known, but there is theoretical risk of spreading tumor cells to the pelvis and peritoneal cavity. Therefore, reporting of such a procedure is important (and listed under Specimen Integrity in the case summary).

B. Histologic Type
For consistency in reporting, the histologic classification of endometrial carcinoma and hyperplasia proposed by the World Health Organization (WHO), shown below, is recommended.^2

**Carcinoma**

- **Endometrioid carcinoma**
  - Variants:
    - With squamous differentiation
    - Villoglandular
    - Secretory
    - Ciliated cell
  - Mucinous adenocarcinoma
  - Serous adenocarcinoma
  - Clear cell adenocarcinoma
  - Mixed carcinoma^*^
  - Squamous cell carcinoma
  - Transitional cell carcinoma
  - Small cell carcinoma
  - Undifferentiated carcinoma

^*The term **mixed carcinoma** should only be used when two or more distinctive subtypes of endometrial carcinoma are identified, each representing more than 10% of the tumor. Optimally, the diagnosis is made on examination of a hysterectomy specimen, but if only a smaller specimen is available, any amount of a second tumor category suffices for the diagnosis. When a carcinoma is classified as “mixed,” the major and minor types and their relative proportions should be specified. High-grade tumors with ambiguous features should be classified as “carcinoma, subtype can not be determined”; however, this is a very infrequent situation and every effort should be made to subclassify such tumors. It should be noted that for mixed endometrioid and serous carcinomas, studies have found variable results regarding tumor behavior based on percentage of the serous component. Some studies have found that tumors with >25% serous component behave like pure serous carcinomas, whereas other studies have shown that tumors with <10% serous component also behave like pure serous carcinomas.^3,4 It is important to be aware that some serous carcinomas may display a glandular architecture.^5 Thus, when a gland-forming endometrial carcinoma shows high-grade nuclear features, the diagnosis of serous carcinoma should be considered. Finally, the term **endometrial intraepithelial carcinoma** is discouraged because it is not uncommon for these lesions to be associated with extrauterine spread.^6,7,8

In addition, carcinosarcoma (also referred to as malignant müllerian mixed tumor [MMMT]) has been added to the above list of tumors in the case summary. Carcinosarcoma is a high-grade endometrial neoplasm that is staged like endometrial carcinomas because it is thought to represent a high-grade metaplastic carcinoma. The diagnosis of carcinosarcoma requires presence of both a malignant
epithelial component and a malignant mesenchymal (sarcomatous) component in the neoplasm, which should not merge.

**Proposed Criteria Defining Endometrial Carcinoma versus Endometrial Hyperplasia**

1. Irregular infiltration of glands associated with an altered fibroblastic stroma (desmoplastic response), or
2. Confluent glandular pattern (cribriform growth) or
3. Extensive papillary growth pattern or
4. Severe cytologic atypia (G3 nuclear atypia)

Some investigators have offered specific measurements to assess confluent glandular growth more objectively. Kurman and Norris proposed 1.9 mm as a cutoff, whereas Longacre and colleagues proposed 30% as a cutoff. Extensive papillary growth has also been quantitatively measured in one study and defined to be at least 4.2 mm in diameter to warrant the diagnosis of carcinoma. However, it is important to note that different investigators did not find these parameters to have the same predictive value.

**C. Histologic Grading**

The FIGO grading system for carcinomas of the uterine corpus is only officially designated for endometrioid carcinomas and is based on architectural features as follows:

1. Grade 1: 5% or less nonsquamous solid growth pattern
2. Grade 2: 6% to 50% nonsquamous solid growth pattern
3. Grade 3: > 50% nonsquamous solid growth pattern

Notable nuclear atypica, which exceeds that which is routinely expected for the architectural grade, increases the tumor grade by 1.

In addition, the following guidelines should be used in grading:

1. The squamous component of endometrioid adenocarcinoma should not be graded because the degree of differentiation typically parallels that of the glandular component.
2. Because mucinous carcinomas are closely related to endometrioid carcinomas, they can be graded by the same criteria.
3. Serous, clear cell, transitional, small cell, undifferentiated carcinomas, and carcinosarcomas are generally considered to be high grade and it is not recommended to assign a FIGO grade to these tumor types. When the case summary is being completed, these should be designated as “not applicable” for histologic grade.
4. In mixed carcinomas, the highest grade should be assigned.

**D. Myometrial Invasion**

Assessing myometrial invasion may be difficult. Depth of invasion should be measured from the endomyometrial junction to the deepest point of invasion, which may not be easy because the endomyometrial junction in normal conditions is often irregular. In these cases, it is always helpful to look for compressed, nonneoplastic endometrial glands at the nearby endomyometrial junction or even at the base of the tumor. Carcinoma involving adenomyotic foci should not be interpreted as invasive carcinoma. However, the distinction between invasive carcinoma and carcinoma involving adenomyosis may be difficult, because in some cases invasive carcinoma may not elicit stromal response. In the absence of adenomyosis uninvolved by tumor in other sections of the specimen, a diagnosis of adenomyosis involved by adenocarcinoma should be made with caution. CD10 staining is not helpful in this differential diagnosis because stromal cells surrounding foci of invasive carcinoma are also frequently CD10 positive. There are no rules for determining how to measure the depth of invasion in the rare cases where myoinvasive carcinoma is only encountered in foci of adenomyosis involved by
carcinoma. In such cases, it is advised that the distance from the adenomyotic focus to the deepest area of invasion be measured (Figure 1). Therefore, if there is a tumor with a 2-mm focus of myoinvasion from a focus of adenomyosis in the deep myometrium, it is still considered as having <50% myometrial invasion (FIGO stage IA).

Figure 1. Schematic of measurement of depth of invasion in (A) tumor with a regular interface; (B) tumor with an irregular endomyometrial interface; (C) and (D) tumor with an exophytic growth; (E) tumor arising from adenomyosis. From Ali A, Black D, Soslow RA. Difficulties in assessing the depth of myometrial invasion in endometrial carcinoma. Int J Gynecol Pathol. 2007;26:115-123. Copyright © 2007, Wolters Kluwer Health. Reproduced with permission.

E. Cervical Involvement
Cervical involvement by endometrial carcinoma has been traditionally divided into 2A when there was only secondary involvement of the endocervical epithelium and 2B when the endometrial carcinoma invaded the cervical stroma. Recently, it has been shown that involvement of the surface endocervical epithelium and/or endocervical glands (either by direct extension or drop metastases) does not have any prognostic significance. Therefore, the new American Joint Committee on Cancer (AJCC)/FIGO staging system considers stage II disease only when cervical stromal involvement is seen.

F. Peritoneal Washings or Ascites Fluid
The prognostic significance of presence of tumor cells in peritoneal washings or ascites fluid is controversial. There are studies that indicate either a worse prognosis or no alteration of prognosis on the basis of positive cytology. Consequently, the newly adopted staging system no longer utilizes positive cytology to alter stage. When collected, however, cytology results should be recorded.

G. Margins
The paracervical soft tissue is the only true margin in total hysterectomy specimens, and reporting the status of this margin is usually not performed; conversely, reporting the status of the vaginal and parametrial margins in a radical hysterectomy specimen is optional.

H. Lymph-Vascular Invasion
Lymph-vascular invasion (LVI) indicates whether microscopic lymph-vascular invasion is identified. LVI includes lymphatic invasion, vascular invasion, or lymph-vascular invasion. According to AJCC/International Union Against Cancer (UICC) convention, LVI does not affect the T category indicating local extent of tumor unless specifically included in the definition of a T category.
I. TNM and FIGO Staging of Endometrial Carcinoma

The TNM staging system for endometrial cancer endorsed by the AJCC and the UICC,\textsuperscript{14-16} and the parallel system formulated by FIGO are recommended, as shown below.

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 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.

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.

<table>
<thead>
<tr>
<th>Primary Tumor (T)</th>
<th>TNM Category</th>
<th>FIGO Stage</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>(-)</td>
<td></td>
<td>Primary tumor cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>(-)</td>
<td>I</td>
<td>No evidence of primary tumor</td>
</tr>
<tr>
<td>T1</td>
<td>I</td>
<td>IA</td>
<td>Tumor confined to corpus uteri</td>
</tr>
<tr>
<td>T1a</td>
<td>IA</td>
<td>I</td>
<td>Tumor limited to endometrium or invades less than one-half of the myometrium</td>
</tr>
<tr>
<td>T1b</td>
<td>IB</td>
<td>II</td>
<td>Tumor invades one-half or more of the myometrium</td>
</tr>
<tr>
<td>T2</td>
<td>II</td>
<td>III</td>
<td>Tumor invades stromal connective tissue of the cervix</td>
</tr>
<tr>
<td>T3</td>
<td>III</td>
<td>IIIA</td>
<td>Local and/or regional spread as specified in T3a and T3b, and in FIGO IIIA and IIIB</td>
</tr>
<tr>
<td>T3a</td>
<td>IIIA</td>
<td></td>
<td>Tumor involves serosa and/or adnexa (direct extension or metastasis)</td>
</tr>
<tr>
<td>T3b</td>
<td>IIIB</td>
<td></td>
<td>Vaginal involvement (direct extension or metastasis) or parametrial involvement</td>
</tr>
<tr>
<td>T4*</td>
<td>IVA</td>
<td></td>
<td>Tumor invades bladder mucosa* and/or bowel mucosa*</td>
</tr>
</tbody>
</table>

* Presence of bullous edema is not sufficient evidence to classify a tumor as T4.

Regional Lymph Nodes (N):# TNM Staging System

| NX               | Regional lymph nodes cannot be assessed |
| N0               | No regional lymph node metastasis |
| N1               | IIIC1 Regional lymph node metastasis to pelvic lymph nodes |
| N2               | IIIC2 Regional lymph node metastasis to para-aortic lymph nodes with or without positive pelvic lymph nodes |

* Regional lymph nodes include the pelvic, obturator, internal iliac (hypogastric), external iliac, common iliac, para-aortic, presacral, and parametrial lymph nodes.
Distant Metastasis (M): TNM Staging System

M0 No distant metastasis
M1 IVB Distant metastasis (includes metastasis to abdominal lymph nodes [other than para-aortic], and/or inguinal lymph nodes; excludes metastasis to vagina, pelvic serosa, or adnexa)

TNM Stage Groupings

<table>
<thead>
<tr>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Tis</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IA</td>
<td>T1a</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IB</td>
<td>T1b</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>II</td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IIIA</td>
<td>T3a</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IIIB</td>
<td>T3b</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IIIC1</td>
<td>T1-T3</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td>IIIC2</td>
<td>T1-T3</td>
<td>N2</td>
<td>M0</td>
</tr>
<tr>
<td>IVA</td>
<td>T4</td>
<td>Any N</td>
<td>M0</td>
</tr>
<tr>
<td>IVB</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
</tr>
</tbody>
</table>

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 after 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 before multimodality therapy (ie, before initiation of neoadjuvant therapy).

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

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

Additional Descriptors

Residual Tumor (R)

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

<table>
<thead>
<tr>
<th>RX</th>
<th>Presence of residual tumor cannot be assessed</th>
</tr>
</thead>
<tbody>
<tr>
<td>R0</td>
<td>No residual tumor</td>
</tr>
<tr>
<td>R1</td>
<td>Microscopic residual tumor</td>
</tr>
<tr>
<td>R2</td>
<td>Macroscopic residual tumor</td>
</tr>
</tbody>
</table>

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

**Regional Lymph Nodes: Isolated Tumor Cells**

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.

**J. Additional Findings**

**Endometrial Intraepithelial Neoplasia**

In part because of poor agreement in the diagnosis of atypical hyperplasia of the endometrium under the WHO criteria, a new diagnostic terminology, *endometrial intraepithelial neoplasia* (EIN), has been proposed. EIN describes a clonal expansion of premalignant endometrial glands with endometrioid features, but without invasion. Microscopic criteria proposed to diagnose this lesion include:

1. Architecturally crowded glands whose volume percentage stroma (VPS) is <55%  
2. Measurement of at least 1 to 2 mm in diameter  
3. Altered/demarcated cytology from the background endometrial glands; not part of a benign mimic with focal glandular crowding (such as a polyp).

**K. Ancillary Studies**

In some instances—more often in biopsy/curettage specimens, but also in hysterectomy specimens—it may be difficult to assess the origin of an adenocarcinoma, especially determining its origin in the endometrium versus endocervix. In these cases, a panel of immunohistochemical stains may be useful, although clinicoradiologic correlation is usually informative.

In some instances, clinicians may ask that estrogen and progesterone receptor immunohistochemistry studies be performed on a tumor. The results of such studies should always be added to the report. In addition, in younger patients with a family history of endometrial or colorectal carcinoma, immunohistochemical studies on DNA mismatch repair gene products (see Note L) may be requested and the results should be added to the report.

**L. Clinical History**

Colon carcinoma is the most common malignancy in hereditary nonpolyposis colon cancer (HNPCC; Lynch syndrome). However, endometrial carcinoma develops before colon carcinoma in >50% of women with HNPCC. Still, the reported series of HNPCC-related endometrial carcinomas are much smaller in number than those reported for HNPCC colonic carcinoma. Histopathologic features suggestive of HNPCC-related carcinoma are well characterized in the colon but not in the uterus. However, when examining an endometrial carcinoma in a patient under 50 years of age or with a personal or family history of colon carcinoma, it is important to consider the possibility of an HNPCC-related endometrial carcinoma. In these cases, testing for defective DNA mismatch repair may be performed by immunohistochemistry (MLH1, MLH2, MSH6, and PMS2 antibodies are commercially available). Loss of MLH2 expression essentially always indicates Lynch syndrome and MSH6 is related to MLH2. HNPCC-related endometrial carcinoma is predominantly associated with MLH2 mutations, and MSH6 mutations in particular. PMS2 loss is often associated with loss of MLH1 and is only independently meaningful if MLH1 is intact (see Colon protocol for further details). In addition, PCR assays can be used to detect high levels of microsatellite alterations (MSI), a condition that is definitional
for defective DNA mismatch repair. This testing is performed on paraffin-embedded tissue and compares the results of tumor DNA to those of nonneoplastic tissues from the same patient.

References

