Endometrial Cancer Histopathology Reporting Guide

International Collaboration on Cancer Reporting (ICCR)

Family/Last name

Given name(s)

Date of birth DD – MM – YYYY

Patient identifiers

Date of request DD – MM – YYYY

Accession/Laboratory number

Elements in **black text** are REQUIRED. Elements in **grey text** are RECOMMENDED.

Operative procedure

Simple hysterectomy ◯ Radical hysterectomy ◯ Other ◯

Attached anatomical structures

Vaginal cuff ☐ Left fallopian tube ☐
Left ovary ☐ Right fallopian tube ☐
Right ovary ☐ Parametria ☐

Accompanying specimens

None submitted ☐ Omentum ☐
Peritoneal biopsies ☐ Lymph nodes ☐
Other ☐

Tumour site (Note 1)

Fundus ☐ Body ☐ Isthmus/lower uterine segment ☐

Block identification key (Note 2)

(List overleaf or separately with an indication of the nature and origin of all tissue blocks)

Maximum tumour dimension (Note 3) mm

Histological tumour type (Note 4)

- ☐ Endometrioid carcinoma
- ☐ Mucinous carcinoma
- ☐ Serous endometrial intraepithelial carcinoma (SEIC)
- ☐ Serous carcinoma
- ☐ Clear cell carcinoma
- ☐ Mixed cell adenocarcinoma
- ☐ Undifferentiated carcinoma
- ☐ Dedifferentiated carcinoma
- ☐ Neuroendocrine tumour

Specify subtype

☐ Carcinosarcoma (Note 5) ⇒ % Epithelial & % Sarcomatous

⇩

Homologous ◯
Heterologous ◯

Histological grade (Note 6)

Grade 1 ◯ Grade 2 ◯ Grade 3 ◯
Not gradeable ◯ Not applicable ◯

Myometrial invasion (Note 7)

None ◯ <50% ◯ ≥ 50% ◯

⇩ ⇩

Percentage of myometrium infiltrated by carcinoma (Note 8) %

Distance of myoinvasive tumour to serosa (Note 9) mm

Lymphovascular invasion (Note 10)

Present ◯ Not identified ◯ Indeterminate ◯

Specify site

Cervical surface or crypt involvement (Note 11)

Present ◯ Not identified ◯ Indeterminate ◯

Cervical stromal invasion (Note 12)

Present ◯ Not identified ◯ Indeterminate ◯

Distance of tumour to cervical resection margins (Note 13) mm

Vagina

Involved ◯ Not involved ◯ Not applicable ◯

Omentum

Involved ◯ Not involved ◯ Not applicable ◯

Peritoneal biopsy/biopsies

Involved ◯ Not involved ◯ Not applicable ◯

Uterine serosa (Note 14)

Involved ◯ Not involved ◯ Indeterminate ◯

Parametria (Note 15)

Involved ◯ Not involved ◯ Not applicable ◯

Adnexa (Note 16)

Involved ◯ Not involved ◯ Not applicable ◯

Background endometrium (Note 17)

- ☐ Cyclical
- ☐ Hormone effect
- ☐ Atrophic
- ☐ Polyp/s
- ☐ Hyperplasia without atypia
- ☐ Atypical hyperplasia/Endometrial intraepithelial neoplasia

Peritoneal cytology (Note 18)

Positive ◯ Atypical/suspicous ◯
Negative ◯ Not submitted ◯

LYMPH NODE STATUS (Note 19)

Involved ◯ Not involved ◯ Not applicable ◯

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Left pelvic:
Number retrieved
Number involved

Right pelvic:
Number retrieved
Number involved

Para-aortic:
Number retrieved
Number involved

Extra-nodal spread:

Present ◯ Not identified ◯ Not applicable ◯

Histologically confirmed distant metastases

Present ◯ Not identified ◯ Indeterminate ◯

ANCILLARY STUDIES (Note 20)

- ☐ Immunohistochemical markers
- ☐ Molecular data

PROVISIONAL PATHOLOGICAL STAGING PRE-MDTM

Provisional FIGO stage (2009) (see table below) (Note 21)

Pathological staging (TNM and AJCC 7th ed.)(see table below)

Tumour stage FIGO & pTNM##

Primary Tumour (T) (Surgical-Pathologic Findings)		
TNM	FIGO	
TX		Primary tumour cannot be assessed
T0		No evidence of primary tumour
Tis*		Carcinoma in situ (preinvasive carcinoma)
T1	I	Tumour confined to corpus uteri
T1a	IA	Tumour limited to endometrium or invades less than one-half of the myometrium
T1b	IB	Tumour invades one-half or more of the myometrium
T2	II	Tumour invades stromal connective tissue of the cervix but does not extend beyond uterus**
T3a	IIIA	Tumour involves serosa and /or adnexa (direct extension or metastasis)
T3b	IIIB	Vaginal involvement (direct extension or metastasis) or parametrial involvement.
T4	IVA	Tumour invades bladder mucosa and /or bowel mucosa (bullous oedema is not sufficient to classify a tumour as T4)
Regional Lymph Nodes (N)		
NX		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N1	IIIC1	Regional lymph nodes metastasis to pelvic lymph nodes
N2	IIIC2	Regional lymph nodes metastasis to para-aortic lymph nodes, with or without positive pelvic lymph nodes.
Distant Metastasis (M)		
M0		No distant metastasis
M1	IVB	Distant metastasis (includes metastasis to inguinal lymph nodes intraperitoneal disease, or lung, liver, or bone. It excludes metastasis to para-aortic lymph nodes, vagina, pelvic serosa, or adnexa.

* Note: FIGO no longer includes Stage 0(Tis)

** Endocervical glandular involvement only should be considered Stage I and not as Stage II.

American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Manual, Seventh Edition (2010) published by Springer Science and Business Media LLC, www.springerlink.com. Update: 1st July 2011. Copyright permission pending.

Note 1 - Tumour site (Recommended)

Reason/Evidentiary Support:
There may be an association between lower uterine segment/isthmic tumours and Lynch syndrome.[1,2]

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Note 2 – Block identification key (Recommended)

Reason/Evidentiary Support:
Complex cases are often referred for specialist review and the reviewer needs to know the origin and nature of the blocks for accurate assessment and staging of tumours. The block key should be recorded in the final pathology report. Recording the origin/designation of tissue blocks also facilitates retrieval of blocks for further immunohistochemical or molecular analysis, research studies and clinical trials.

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Note 3 - Maximum tumour dimension (Recommended)

Reason/Evidentiary Support:
There is a significant correlation between primary tumour diameter >20 mm and peritoneal failure. This does not yet reach III-2 evidence level.[3]

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Note 4 – Histological tumour type (Required)

Reason/Evidentiary Support:
Endometrial carcinomas should be typed according to the 2014 WHO Classification.[4] Accurate typing is necessary in both biopsies and resection specimens. Diagnosis of aggressive tumours such as serous carcinoma, clear cell carcinoma, carcinosarcoma, undifferentiated carcinoma and grade 3 endometrioid adenocarcinoma will usually result in full surgical staging including pelvic and para-aortic lymphadenectomy and omentectomy.

Mucinous adenocarcinoma refers to a subtype of endometrial adenocarcinoma in which more than 50% of the tumour cells contain intracytoplasmic mucin. Many endometrioid adenocarcinomas contain focal mucinous areas and endometrioid and mucinous adenocarcinomas form part of a spectrum. Although carcinosarcomas (malignant mixed MÜllerian tumours) are still classified as mixed epithelial and mesenchymal tumours in the 2014 WHO Classification,[4] their behaviour is similar to other high grade endometrial carcinomas and they are treated in the same way as aggressive endometrial carcinomas. Carcinosarcomas are believed to be epithelial neoplasms that have undergone sarcomatous metaplasia, the epithelial elements being the 'driving force'.

The 2014 WHO classification of endometrial carcinomas (see below) now includes serous endometrial intraepithelial carcinoma (serous EIC).[4] Even in the absence of demonstrable stromal invasion, malignant cells can shed from serous EIC and metastasise widely to extra-uterine sites. Neuroendocrine tumours are also a new addition to the 2014 WHO Classification.[4] They are rare primary uterine neoplasms and the diagnosis should be confirmed immunohistochemically, although some small cell neuroendocrine carcinomas may not express neuroendocrine markers (see notes on ancillary studies). Neuroendocrine neoplasms of the endometrium are divided into low-grade neuroendocrine tumour (carcinoid tumour) which is extremely rare and high-grade neuroendocrine carcinoma (small cell and large cell neuroendocrine carcinoma) which is more common but also rare. Large cell neuroendocrine carcinoma should demonstrate a neuroendocrine growth pattern in at least part of the tumour, and show expression of one or more neuroendocrine markers (chromogranin, synaptophysin, CD56, PGP9.5) in >10% of the tumour. Undifferentiated carcinoma[5,6] is defined by WHO as a 'malignant epithelial neoplasm with no differentiation',[4] and may show immunohistochemical evidence of epithelial differentiation in only occasional tumour cells (see notes on ancillary studies). Dedifferentiated carcinoma[7] is defined as an

undifferentiated carcinoma that contains a second component of either FIGO grade 1 or 2 endometrioid adenocarcinoma; in such cases, it is believed that the undifferentiated component develops as a result of dedifferentiation in the low-grade endometrioid component.

Mixed carcinomas must contain two or more different histological types of endometrial carcinoma recognisable on H&E-stained sections. At least one of the subtypes must be a type II tumour and the second component, according to the 2014 WHO Classification,[4] must comprise at least 5% of the neoplasm. The most common mixture is endometrioid and serous carcinoma. Immunohistochemistry may assist in confirming the presence of a second, morphologically distinct subtype. All subtypes should be specified in the histopathology report, even if <5% of the neoplasm is composed of type II tumour, because the behaviour of these tumours is determined by the highest grade component.[4]

In cases where there is no residual tumour in the hysterectomy specimen or where there is a significant discrepancy between the reported tumour type in the biopsy and that in the hysterectomy, it may be necessary to review the prior biopsy. If high-risk/aggressive variants of carcinoma e.g. serous carcinoma, carcinosarcoma etc., are confirmed in the endometrial biopsy but are not identified in the final hysterectomy specimen, the carcinoma should be categorised according to the worst histology.

Adequate sampling of the tumour is required (minimum of 4 blocks) to allow meaningful assessment of this data item.

WHO histological classification (2014)[4]

Endometrial carcinoma - Epithelial tumours	**ICD-O code**
Endometrioid carcinoma	8380/3
Squamous differentiation	8570/3
Villoglandular	8263/3
Secretory	8382/3
Mucinous carcinoma	8480/3
Serous endometrial intraepithelial carcinoma (SEIC)	8441/2*
Serous carcinoma	8441/3
Clear cell carcinoma	8310/3
Neuroendocrine tumours	
Low-grade neuroendocrine tumour	
Carcinoid tumour	8240/3
High-grade neuroendocrine carcinoma	
Small cell neuroendocrine carcinoma	8041/3
Large cell neuroendocrine carcinoma	8013/3
Mixed cell adenocarcinoma	8323/3
Undifferentiated carcinoma	8020/3
Dedifferentiated carcinoma	
Mixed epithelial and mesenchymal tumours	
Carcinosarcoma	8980/3

* This new code was approved by the IARC/WHO committee for ICD-O in 2013.

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Note 5 – Carcinosarcoma (Recommended)

Reason/Evidentiary Support:
A recent study has shown that the presence of heterologous elements in stage I carcinosarcomas is an important adverse prognostic feature; this does not yet reach III-2 evidence level.[8]

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Note 6 - Histological grade (Required)

Reason/Evidentiary Support:
The FIGO grading system for endometrioid adenocarcinomas of the uterine corpus is based on the following architectural features:[9]

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

Notable nuclear atypia, which exceeds that which is routinely expected for the architectural grade, increases the tumour grade by 1. Notable nuclear atypia should be present in >50% of the tumour.[10]

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

(1) Non-gland forming squamous elements should be disregarded for grading purposes.
(2) Endometrioid and mucinous carcinomas should be graded using the FIGO grading system.
(3) Serous, clear cell and undifferentiated carcinomas and carcinosarcomas are not graded but are regarded as high grade neoplasms.[11] When the dataset is being completed, these should be designated as “not applicable” for histologic grade.
(4) In mixed carcinomas, the highest grade should be assigned.

In general, if there is a discrepancy between the grade of an endometrioid adenocarcinoma in the pre-operative biopsy and the final resection specimen, the final histological tumour grade should be based on findings in the hysterectomy specimen, which usually contains a larger volume of tumour for assessment. This is particularly important if the hysterectomy specimen contains abundant low-grade tumour and the biopsy showed grade 3 endometrioid adenocarcinoma. In this specific situation, application of the guidelines for FIGO grading may result in the tumour being downgraded, although this will not always be the case; for example, where the biopsy contained abundant grade 3 endometrioid adenocarcinoma and the hysterectomy a limited amount of low-grade tumour, the final diagnosis might still be grade 3 endometrioid adenocarcinoma.

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Note 7 – Myometrial invasion (Required)

Reason/Evidentiary Support:
Depth of invasion should be measured from the endomyometrial junction (not the surface of exophytic tumours) to the deepest focus of tumour invasion. Measurement of the depth of invasion may be rendered difficult by irregularity of the endomyometrial junction, polypoid tumour growth, intramural leiomyomas, adenomyosis and uncommonly by smooth muscle metaplasia within polypoid neoplasms.[12] Deep myometrial invasion has repeatedly been shown to be an important poor prognostic indicator in endometrial carcinoma. This is an independent predictor of haematogenous dissemination by endometrial carcinoma and it is therefore an important determinant of adjuvant therapy.[13]

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Note 8 – Percentage of myometrium infiltrated by carcinoma (Recommended)

Reason/Evidentiary Support:
Tumour-free distance (to the uterine serosa) and percentage of myometrium infiltrated are independent prognostic factors for lymph node metastasis in endometrial carcinoma but studies do not reach level III-2 evidence.[14]

The percentage of myometrium infiltrated by carcinoma is defined as the percentage of myometrium involved as determined by the depth of myometrial invasion from the endomyometrial junction to the deepest focus of invasive carcinoma in comparison to the overall myometrial thickness.

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Note 9 – Distance of myoinvasive tumour to serosa (Recommended)

Reason/Evidentiary Support:
Tumour-free distance and percentage of myometrium infiltrated are independent prognostic factors for lymph node metastasis in endometrial carcinoma; studies do not reach level III-2 evidence.[14]

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Note 10 – Lymphovascular invasion (Required)

Reason/Evidentiary Support:
Lymphovascular invasion is a predictor of tumour recurrence and lymph node metastasis.[15] However, lymphovascular space invasion does not alter the tumour stage. For example, if an endometrial adenocarcinoma is confined to the inner half of the myometrium but shows lymphovascular invasion in the outer half of the myometrium, this should still be staged as FIGO 1A. Similarly lymphovascular invasion alone in cervical, parametrial or para-ovarian vessels does not upstage the tumour. There is an increased incidence of vascular pseudoinvasion in laparoscopic hysterectomy specimens associated with the use of an intrauterine balloon manipulator.[15,16]

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Note 11 – Cervical surface or crypt involvement (Recommended)

Reason/Evidentiary Support:
Not necessary for staging but some oncologists administer vault brachytherapy if this is identified. Level III-2 evidence currently not available.

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Note 12 – Cervical stromal invasion (Required)

Reason/Evidentiary Support:
Cervical stromal infiltration by endometrial carcinoma is associated with a risk of recurrence and is a predictor of pelvic lymph node metastases.[17,18]

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Note 13 – Distance of tumour to cervical resection margins (Recommended)

Reason/Evidentiary Support:
Close margins may indicate a need for vault brachytherapy. Vascular invasion at cervical resection margin should be documented but does not upstage the tumour.

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Note 14 – Uterine serosa (Required)

Reason/Evidentiary Support:
Carcinoma should penetrate through the serosa in order to be classified as serosal involvement. Involvement of the serosa (FIGO stage IIIA) carries a higher risk of locoregional recurrence than does adnexal involvement (also FIGO stage IIIA).[19]

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Note 15 – Parametria (Required)

Reason/Evidentiary Support:
Most hysterectomies for endometrial cancer will be simple hysterectomies and will not have parametrial resections. Endometrial carcinomas with parametrial invasion are staged as FIGO IIIB. Although not an independent prognostic indicator, parametrial involvement by direct extension is a poor prognostic factor and also correlates with other poor prognostic factors. The presence of lymphovascular invasion in parametrial tissues should be documented but does not constitute parametrial involvement.[20,21]

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Note 16 – Adnexa (Required)

Reason/Evidentiary Support:
FIGO staging is based on tumour involvement of either the fallopian tube or ovary (stage IIIA). Especially with low-grade endometrioid adenocarcinomas, involvement of the uterine corpus and adnexa may indicate synchronous, independent neoplasms rather than metastasis from the endometrium to the adnexa; a variety of pathological parameters is useful in the distinction between synchronous independent and metastatic neoplasms. As for other sites in the gynaecological tract in which lymphovascular invasion by endometrial adenocarcinoma may be identified e.g., myometrium and parametrial tissue, the identification of lymphovascular space invasion alone in adnexal structures does not alter the tumour stage i.e. endometrial carcinoma should not be upstaged if there is vascular involvement in the adnexa in the absence of tumour outside of vascular channels.

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Note 17 – Background endometrium (Recommended)

Reason/Evidentiary Support:
The appearance of the background endometrium and the presence of abnormalities such as hyperplasia or polyps, should be documented.

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Note 18 – Peritoneal cytology (Recommended)

Reason/Evidentiary Support:
This data item is not necessary for staging but there is lack of consensus in the literature regarding the prognostic significance of positive peritoneal washings in the absence of other evidence of extrauterine spread. A recommendation is made by FIGO and UICC to record positive peritoneal washings without altering the tumour stage.[22,23]

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Note 19 – Lymph node status (Required)

Reason/Evidentiary Support:
Pelvic and para-aortic node status should be recorded separately since this affects tumour stage. Pelvic node involvement without para-aortic involvement is stage IIIC1 while para-aortic node involvement is stage IIIC2.[24,25]

The number of nodes involved and the site of involvement is prognostically important and may direct adjuvant treatment.

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Note 20 – Ancillary studies (Recommended)

Reason/Evidentiary Support:
Immunohistochemistry may be useful in certain diagnostic scenarios. For example, a panel of markers (ER, PR, vimentin, CEA, p16) may be useful in the distinction between a primary endometrial and cervical adenocarcinoma.[26-27] Other markers (ER, PR, p53, p16, PTEN, IMP3) may be useful in the distinction between an endometrioid and a serous adenocarcinoma.[28-29] p53 and p16 may help to highlight serous EIC and distinguish this from surface atypias which can mimic it. Immunohistochemistry for mismatch repair proteins (MLH1, MSH2, MSH6, PMS2) may be useful in helping to establish whether endometrial carcinomas are associated with underlying mismatch repair gene abnormalities and Lynch syndrome (hereditary non-polyposis colorectal cancer) .[30-31]

Undifferentiated endometrial carcinomas are often only focally, but characteristically intensely, positive with broad spectrum cytokeratins, CK18 and epithelial membrane antigen (EMA). This may be useful in the distinction from an undifferentiated sarcoma or other neoplasms and may also help to establish a diagnosis of dedifferentiated carcinoma when a component of low-grade endometrioid adenocarcinoma is present.[5-7] Some undifferentiated carcinomas exhibit focal expression of neuroendocrine markers.[32]

High-grade neuroendocrine carcinomas are usually positive with the neuroendocrine markers chromogranin, synaptophysin, CD56 and PGP9.5. Some small cell neuroendocrine markers are negative with these markers but usually at least one is positive. Large cell neuroendocrine carcinomas should be positive with at least one of these markers in >10% of tumour cells.

Different morphological subtypes of endometrial adenocarcinoma are associated with distinct molecular abnormalities. However, at present molecular analysis has little role in diagnosis or as an independent prognostic or predictive factor. However, this may change in the future and it is likely that targeted therapies will be developed against carcinomas exhibiting specific molecular abnormalities.

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Note 21 – Provisional Pathological FIGO Stage Pre-MDTM (Required)

Reason/Evidentiary Support:
Staging is provisional since final stage should be determined at multidisciplinary team/tumour board meeting when all relevant clinical and radiological information is available.[11,33]

The reference document TNM Supplement: A commentary on uniform use, 4th Edition (C Wittekind editor) may be of assistance when staging.[34]

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