Sponsored by

Endometrial Cancer Histopathology Reporting Guide

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 CORE. Elements in **grey text** are NON-CORE.

☐ indicates multi-select values ◯ indicates single select values

SCOPE OF THIS DATASET

CLINICAL INFORMATION (select all that apply) (Note 1)

- ◯ Information not provided
- ☐ Family history of cancer or cancer-associated syndrome, *specify*
- ☐ Prior history of cancer, *specify*
- ☐ Prior therapy, *specify*
- ☐ Other, *specify*

OPERATIVE PROCEDURE (select all that apply) (Note 2)

- ◯ Not specified
- ☐ Hysterectomy
  - ◯ Simple
  - ◯ Simple supracervical/subtotal
  - ◯ Radical
  - ◯ Type not specified
- ☐ Other procedure, *specify type*

SPECIMEN(S) SUBMITTED (select all that apply) (Note 3)

- ◯ Not specified
- ☐ Fallopian tube — ☐ Left ☐ Right ◯ Laterality not specified
- ☐ Ovary — ☐ Left ☐ Right ◯ Laterality not specified
- ☐ Parametrium — ☐ Left ☐ Right ◯ Laterality not specified
- ☐ Vaginal cuff
- ☐ Vaginal nodules
- ☐ Omentum
- ☐ Peritoneal biopsies
- ☐ Peritoneal washings//peritoneal fluid
- ☐ Lymphadenectomy specimen(s)
  - ☐ Sentinel node(s) — ☐ Left ☐ Right ◯ Laterality not specified
  - ☐ Regional node(s): pelvic — ☐ Left ☐ Right ◯ Laterality not specified
  - ☐ Regional node(s): para-aortic
  - ☐ Non-regional node(s): inguinal — ☐ Left ☐ Right ◯ Laterality not specified
  - ☐ Other node group, *specify*
- ☐ Other, *specify*

TUMOUR SITE (select all that apply) (Note 4)

- ☐ Isthmus/lower uterine segment
- ☐ Fundus
- ☐ Body
- ☐ Other, *specify*

MAXIMUM TUMOUR DIMENSION (Note 5)

mm

OMENTUM DIMENSIONS (Note 6)

mm x mm x mm

BLOCK IDENTIFICATION KEY (Note 7)

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

HISTOLOGICAL TUMOUR TYPE (select all that apply) (Note 8)

(Value list based on the World Health Organization Classification of Female Genital Tumours (2020))

- ☐ Endometrioid carcinoma
- ☐ Serous carcinoma
- ☐ Clear cell carcinoma
- ☐ Carcinoma, undifferentiated
- ☐ Mixed cell carcinoma
- ☐ Mesonephric carcinoma
- ☐ Squamous cell carcinoma
- ☐ Mucinous carcinoma, gastrointestinal type
- ☐ Mesonephric-like carcinoma
- ☐ Neuroendocrine carcinomas
  - Specify subtype
- ☐ Carcinosarcoma NOS → % Epithelial AND % Sarcomatous
  - ◯ Homologous
  - ◯ Heterologous
- ☐ Other, *specify*

Version 4.1 Published August 2021 ISBN: 978-1-922324-26-9

HISTOLOGICAL TUMOUR GRADE (Note 9)

- ◯ Not applicable
- ◯ Cannot be assessed
- ◯ Grade 1 (low)
- ◯ Grade 2 (low)
- ◯ Grade 3 (high)

MYOMETRIAL INVASION (Note 10)

◯ Not identified ◯ <50% ◯ ≥50%

Pattern of myometrial invasion, *specify*

Absolute percentage of myometrial wall thickness invaded by carcinoma ____ %

Distance of myoinvasive tumour to serosa ____ mm

LYMPHOVASCULAR INVASION (Note 11)

- ◯ Indeterminate
- ◯ Not identified
- ◯ Present
  - **Extent of lymphovascular invasion**
    - ◯ Focal
    - ◯ Extensive/Substantial

CERVICAL SURFACE OR CRYPT (Note 12)

- ◯ Not involved
- ◯ Involved

LOWER UTERINE SEGMENT (Note 13)

- ◯ Not involved
- ◯ Involved

CERVICAL STROMA (Note 14)

- ◯ Indeterminate
- ◯ Not involved
- ◯ Involved
  - **Depth of cervical stromal invasion** (Note 15) ____ mm
  - **Percentage of cervical stromal invasion** ____ %

PARAMETRIA[a] (Note 16)

- ◯ Not involved
- ◯ Involved

VAGINA[a] (Note 17)

- ◯ Not involved
- ◯ Involved

OMENTUM[a] (Note 18)

- ◯ Not involved
- ◯ Involved

[a] *If submitted.*

PERITONEAL BIOPSIES[a] (Note 19)

- ◯ Not involved
- ◯ Involved
  - **Site(s) of involvement** (select all that apply)
    - ☐ Pelvic ☐ Abdominal
    - Specify site ____

PERITONEAL CYTOLOGY (Note 20)

- ◯ Positive
- ◯ Negative
- ◯ Atypical/suspicous

UTERINE SEROSA (Note 21)

- ◯ Not involved
- ◯ Involved

ADNEXA[a] (Note 22)

- ◯ Not involved
- ◯ Involved
  - **Site(s) of involvement** (select all that apply)
    - ☐ Ovary(ies)
      - ☐ Left ☐ Right ◯ Laterality not specified
    - ☐ Fallopian tube(s)
      - ☐ Left ☐ Right ◯ Laterality not specified
    - Describe involvement (e.g., musocal) ____

[a] *If submitted.*

MARGIN STATUS (Note 23)

(Applicable only if appropriate anatomical structures submitted)

Paracervical soft tissue margin

- ◯ Cannot be assessed
- ◯ Not involved
  - Distance of tumour to closest margin ____ mm
- ◯ Involved

Ectocervical/vaginal cuff margin

- ◯ Cannot be assessed
- ◯ Not involved
  - Distance of tumour to closest margin ____ mm
- ◯ Involved

BACKGROUND ENDOMETRIUM (select all that apply) (Note 24)

- ☐ Cyclical
- ☐ Atrophic/inactive
- ☐ Hyperplasia without atypia
- ☐ Atypical hyperplasia/endometrioid intraepithelial neoplasia
- ☐ Other, *specify* ____

LYMPH NODE STATUS (Note 25)

- ◯ Cannot be assessed
- ◯ No nodes submitted or found

Maximum dimension of largest deposit in regional node

mm

Extracapsular spread

- ◯ Not identified
- ◯ Present

Lymph node type	Laterality	Number of nodes examined[b]	Number of positive nodes[b]	Degree of involvement (0=Negative for tumour, 1=Isolated tumour cells, 2=Micrometastasis, 3=Macrometastasis)
Sentinel node(s)	Left			
	Right			
Regional node(s): Pelvic	Left			
	Right			
Regional node(s): Para-aortic				

[b] *If the actual number of lymph nodes examined or the number of positive nodes cannot be determined due, for example, to fragmentation, then this should be indicated in the response.*

ANCILLARY STUDIES (Note 26)

◯ Performed (select all that apply) ◯ Not performed

- ☐ Mismatch repair testing, *specify*
- ☐ Immunohistochemistry, *specify test(s) and result(s)*
- ☐ Molecular findings, *specify test(s) and result(s)*
- ☐ TCGA-based molecular classification, *specify*
- ☐ Other, *specify test(s) and result(s)*

Representative blocks for ancillary studies, *specify those blocks best representing tumour and/or normal tissue for further study*

PATHOLOGICALLY CONFIRMED DISTANT METASTASIS

(Report when tissue submitted for evaluation) (Note 27)

- ◯ Not identified
- ◯ Present, *specify site(s)*

PROVISIONAL PATHOLOGICAL STAGING (Note 28)

FIGO (2009 edition)[c]

- ◯ I Tumour 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 Tumour invades cervical stroma, but does not extend beyond the uterus[d]
- ◯ III Local and/or regional spread of the tumour
  - ◯ IIIA Tumour invades the serosa of the corpus uteri and/or adnexae[e]
  - ◯ IIIB Vaginal involvement and/or parametrial involvement[e]

FIGO (2009 edition)[c] (Cont.)

- ◯ IIIC Metastases to pelvic and/or para-aortic lymph nodes[e]
  - ◯ IIIC1 Positive pelvic nodes
  - ◯ IIIC2 Positive para-aortic lymph nodes with/without positive pelvic lymph nodes
- ◯ IV Tumour invades bladder and/or bowel mucosa, and/or distant metastases
  - ◯ IVA Tumour invasion of bladder and/or bowel mucosa
  - ◯ IVB Distant metastases, including intra-abdominal metastases and/or inguinal nodes

[c] *Reprinted from Int J Gynaecol Obstet., Volume 143(Suppl. 2), Amant F, Cancer of the corpus uteri, pages 37-50, 2009, with permission from Wiley.*

[d] *Endocervical glandular involvement only should be considered as Stage I and no longer Stage II.*

[e] *Positive cytology has to be reported separately without changing the stage.*

TNM Staging (UICC TNM 8th edition 2016)[f]

TNM Descriptors (only if applicable) (select all that apply)

- ☐ m - multiple primary tumours
- ☐ r - recurrent
- ☐ y - post-therapy

Primary tumour (pT)

- ◯ TX Primary tumour can not be assessed
- ◯ T0 No evidence of primary tumour
- ◯ T1 Tumour confined to the corpus uteri[g]
  - ◯ T1a Tumour limited to endometrium or invading less than half of myometrium
  - ◯ T1b Tumour invades one half or more of myometrium
- ◯ T2 Tumour invades cervical stroma, but does not extend beyond the uterus
- ◯ T3 Local and/or regional spread as specified here:
  - ◯ T3a Tumour invades the serosa of the corpus uteri or adnexae (direct extension or metastasis)
  - ◯ T3b Vaginal or parametrial involvement (direct extension or metastasis)
- ◯ T4 Tumour invades bladder/bowel mucosa[h]

Regional lymph nodes (pN)

- ◯ NX Regional lymph nodes cannot be assessed
- ◯ N0 No regional lymph node metastasis
- ◯ N1 Metastasis to pelvic lymph nodes[i]
- ◯ N2 Metastasis to para-aortic lymph nodes with or without metastasis to pelvic lymph nodes[i]

[f] *Reproduced with permission. Source: UICC TNM Classification of Malignant Tumours, 8th Edition, eds by James D. Brierley, Mary K. Gospodarowicz, Christian Wittekind. 2016, Publisher Wiley (incorporating any errata published up until 6th October 2020).*

[g] *Endocervical glandular involvement only should be considered as Stage I.*

[h] *The presence of bullous oedema is not sufficient evidence to classify as T4.*

[i] *Positive cytology has to be reported separately without changing the stage.*

Definitions

CORE elements

CORE elements are those which are essential for the clinical management, staging or prognosis of the cancer. These elements will either have evidentiary support at Level III-2 or above (based on prognostic factors in the National Health and Medical Research Council levels of evidence[1]). In rare circumstances, where level III-2 evidence is not available an element may be made a core element where there is unanimous agreement by the Dataset Authoring Committee (DAC). An appropriate staging system e.g., Pathological TNM staging would normally be included as a CORE element.

Non-morphological testing e.g., molecular or immunohistochemical testing is a growing feature of cancer reporting. However, in many parts of the world this type of testing is limited by the available resources. In order to encourage the global adoption of ancillary tests for patient benefit, International Collaboration on Cancer Reporting (ICCR) recommends that some ancillary testing in ICCR Datasets is included as core elements. Where the technical capability does not yet exist, laboratories may consider temporarily using these data elements as NON-CORE items.

The summation of all CORE elements is considered to be the minimum reporting standard for a specific cancer.

NON-CORE elements

NON-CORE elements are those which are unanimously agreed should be included in the dataset but are not supported by level III-2 evidence. These elements may be clinically important and recommended as good practice but are not yet validated or regularly used in patient management.

Key information other than that which is essential for clinical management, staging or prognosis of the cancer such as macroscopic observations and interpretation, which are fundamental to the histological diagnosis and conclusion e.g., macroscopic tumour details, may be included as either CORE or NON-CORE elements by consensus of the DAC.

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Scope

The dataset has been developed for the pathology reporting of resection specimens of endometrial cancers, including carcinosarcomas. It is not applicable for small endometrial biopsy specimens. Haematopoietic neoplasms, mesenchymal neoplasms, adenosarcomas, malignant melanomas, other non-epithelial malignancies and metastatic tumours are excluded from this dataset. Adenosarcoma and other mesenchymal neoplasms are included in the International Collaboration on Cancer Reporting (ICCR) dataset for uterine malignant and potentially malignant mesenchymal tumours.[2]

The 4th edition of the ICCR Endometrial cancer dataset includes changes to align the dataset with the World Health Organization (WHO) Classification of Tumours, Female Genital Tumours, 5th edition, 2020.[3] The ICCR dataset includes 5th edition Corrigenda, June 2021.[4]

The authors of this dataset can be accessed here.

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Note 1 – Clinical information (Non-core)

Clinical information regarding history of familial cancer (particularly for Lynch syndrome, but also for other hereditary cancer syndromes) is important. In addition, the history of previous cancer, prior neoadjuvant therapy (including hormonal therapy), or any other clinical data that can be relevant for pathologic interpretation is of benefit to report.

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Note 2 – Operative procedure (Core)

Depending on the presumed extent of spread of the carcinoma as assessed clinically or radiologically, either a simple or radical hysterectomy is performed, which may or may not be part of a staging procedure. A simple hysterectomy is defined as the removal of the total uterus (including the cervix). Radical hysterectomy entails en bloc resection of the uterus and cervix along with the surrounding parametria, upper vagina and uterosacral ligaments.[5,6] These procedures can either be performed through a laparoscopy, robot-assisted laparoscopy or laparotomy.[7] Finally, a debulking procedure can be performed, if the tumour is macroscopically disseminated, to remove all visible tumour. Pelvic exenteration is not a frequent procedure, but is occasionally used in advanced and recurrent endometrial cancer,[8,9] and recognised in the European Society of Gynaecological Oncology (ESGO)-European Society for Radiotherapy and Oncology (ESTRO)-European Society of Pathology (ESP) guidelines.[10] In some instances, malignancy can be found in a morcellated hysterectomy specimen.[11] Morcellation should be avoided whenever there is suspicion of endometrial carcinoma. Primary hormonal treatment may be considered in a woman who desires fertility conservation.

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Note 3 – Specimen(s) submitted (Core)

Attached anatomical structures may include vaginal cuff, ovaries, fallopian tubes or parametria.[12] Further specimens may be submitted for pathological review including: omentum, sentinel lymph nodes,[13] pelvic and periaortic lymph nodes, peritoneal washings, and peritoneal biopsies from various sites.[12]

Inking of peritoneal and/or nonperitoneal surfaces is recommended in hysterectomy specimens and is essential in radical hysterectomy specimens in which a vaginal cuff is present. In addition, inking the peritoneal and nonperitoneal surfaces and extending the ink all the way to the vaginal cuff is useful to provide the status of the vaginal cuff margin.[12]

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Note 4 – Tumour site (Non-core)

Anatomically, the lower uterine segment begins where the body funnels towards the cervix and ends at the internal os. The fundus is that part of the uterus above the origin of the fallopian tubes.

Endometrial carcinoma involving the lower uterine segment has several implications. Tumours originating in this location are more frequently associated with mismatch repair (MMR) protein

deficiencies.[14,15] Lower uterine segment involvement in early endometrial carcinoma is predictive of lymph node metastasis and is an independent poor prognostic factor for distant recurrence and death.[16-19]

Endometrial carcinomas arising in the body of the uterus may extend to involve the lower uterine segment and this should also be recorded. Distinguishing lower uterine segment endometrial carcinoma from endocervical carcinoma is important for staging, prognosis and management, but this is not always straightforward.

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Note 5 – Maximum tumour dimension (Non-core)

Some studies have found that a larger tumour size is significantly associated with increased invasion of the lymphovascular space, lymph node metastasis, and/or risk of recurrence in endometrioid endometrial carcinoma (EEC); however the threshold defining a larger tumour size varies from ≥20 to ≥50 millimetres (mm).[20-27] Some studies have not found an association between a tumour size of ≥20 mm and prognosis.[28,29]

It is recommended that the largest dimension of the tumour should be reported; other dimensions are not required. This may be determined by macroscopic or microscopic assessment or the combination of both.[30]

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Note 6 – Omentum dimensions (Non-core)

Omentectomy is currently undertaken in many, but not all, institutions for all high grade endometrial carcinomas,[31] such as grade 3 endometrioid carcinoma, serous carcinoma, clear cell carcinoma, undifferentiated carcinoma and carcinosarcoma.[16] Grade 1 and 2 endometrioid carcinomas are subject to omentectomy in some centres.[16]

Thorough macroscopic examination of the omentum is essential.[32] The omentum should be cut at 5 mm intervals to detect small lesions.[12] Obvious lesions can be sampled in one or two blocks but if no lesion is seen then at least four blocks are recommended.[32] One study suggests improving the sensitivity for detection of microscopic disease in macroscopically normal omentum to 95% if at least 10 blocks are submitted.[33]

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Note 7 – Block identification key (Non-core)

The origin/designation of all tissue blocks should be recorded. This information should ideally be documented in the final pathology report and is particularly important should the need for internal or external review arise. The reviewer needs to be clear about the origin of each block in order to provide an informed specialist opinion. If this information is not included in the final pathology report, it should be available on the laboratory computer system and relayed to the reviewing pathologist. It may be useful to have a digital image of the specimen and record of the origin of the tumour blocks in some cases.

Recording the origin/designation of tissue blocks also facilitates retrieval of blocks for further immunohistochemical or molecular analysis, research studies or clinical trials.

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Note 8 – Histological tumour type (Core and Non-core)

All endometrial carcinomas should be classified according to the WHO Classification of Tumours, Female Genital Tumours, 5th edition, 2020 (Table 1).[3] The ICCR dataset includes 5th edition Corrigenda, June 2021.[4] It is beyond the scope of this dataset to provide detailed information about the microscopic features of each histologic type. However, some points are highlighted for clarification, particularly regarding the main modifications introduced in the 2020 WHO Classification.[34]

Histological tumour type has consistently been demonstrated as an important biological predictor in endometrial carcinoma. Accurate histological typing is important both in biopsy and resection specimens. Moreover, assessment of histological type determines the extent of the initial surgical procedure, and subsequent use of adjuvant therapy.[35]

Bokhman first described in 1984, two main pathogenetic types based on epidemiological studies and this concept was subsequently further expanded.[36,37] Type I carcinomas are considered low grade, estrogen-related, often clinically indolent and histologically mostly of endometrioid type. In contrast, type II carcinomas are clinically aggressive carcinomas and unrelated to estrogen stimulation and histologically non-endometrioid, particularly of serous and clear cell type. Although the type I versus type II classification is interesting for educational and epidemiological purposes, it is not useful for tumour stratification from the pathologic viewpoint, because there are significant overlapping features at the clinical, pathological, and molecular levels.[38-40]

Low grade (grade 1 and 2) endometrioid carcinomas are the most common tumours and are usually associated with favourable outcome. The prognosis for serous carcinoma is worse with recurrence occurring in about 50% of serous carcinomas compared with 20% recurrence in endometrioid carcinomas. Tumours that show combined or mixed features are rare but do occur. Although there is moderate to excellent (κ=0.62-0.87) reproducibility in histological typing, inter-observer agreement is worse in high grade carcinomas.[41-43]

Low grade endometrioid carcinoma is usually composed of cells arranged in a branching, maze-like glandular or complex papillary pattern of growth, while high grade endometrioid carcinoma has a predominant solid architecture,[44] and serous carcinoma has a complex architectural pattern with papillae and cellular budding.[45] However, serous carcinomas with a prominent glandular pattern can frequently be mistaken as low grade endometrioid carcinoma;[46,47] and endometrioid carcinoma with papillary pattern can sometimes be misinterpreted as serous carcinoma.[48]

Low grade endometrioid carcinoma exhibits some specific types of terminal differentiation such as squamous and mucinous differentiation or specific patterns of growth such as villoglandular, small non-villous papillae, microglandular, sex cord-like formations, corded and hyalinised patterns and sertoliform structures. The 2020 WHO Classification[34] incorporates mucinous carcinoma as a variant of low grade endometrioid carcinoma due to its shared molecular features and natural history. Predominant mucinous features do not significantly affect survival when compared with non-mucinous endometrial carcinomas, although, in some series, the mucinous type has a higher tendency to develop lymph node metastasis,[49] and distinction from proliferative, but not malignant, mucinous lesions may be challenging.[50] The 2020 WHO Classification clearly distinguishes the mucinous variant of endometrioid carcinoma from gastrointestinal-l type mucinous endometrioid carcinoma,[34,51] a rare type of tumour with different features and worse prognosis.

High grade endometrioid carcinoma is characterised by a solid growth pattern associated with mostly moderate nuclear atypia and an increased number of mitoses. Application of the Cancer Genome Atlas (TCGA)-molecular surrogate has demonstrated that this is a heterogeneous group of tumours.[52] This is one of the scenarios that shows the importance of integrating histologic typing with molecular classification.

Serous carcinoma is distinguished from endometrioid carcinoma by its marked nuclear pleomorphism and prominent nucleoli in the background of mostly well differentiated architecture, which is typically papillary, but can also be glandular or even solid. In contrast to the typical round, smooth and regular glandular lumens in endometrioid carcinoma, the luminal surface in serous carcinoma is irregular and the glandular structure often slit-like. Mitoses are prominent. The non-invasive type (formerly called serous endometrial intraepithelial carcinoma) is part of the spectrum of serous carcinoma, which is no longer included as a precursor lesion and can give rise to extrauterine metastasis.[53]

Clear cell carcinoma is infrequent and strict adherence to architectural and cytological diagnostic criteria is necessary, since clear cells are commonly present in endometrioid and serous carcinomas.[54-57] The major architectural patterns are tubulocystic, papillary and solid, and frequently these patterns are admixed. Tumour cells show cuboidal, polygonal, hobnail, or flat appearances, with clear or eosinophilic cytoplasm.

Undifferentiated carcinoma is usually composed of small to intermediate-sized, non-cohesive cells of relatively uniform size arranged in sheets. If a second component of differentiated carcinoma is present, which is most frequently a low grade endometrioid carcinoma occurring in approximately 40% of cases, the term dedifferentiated carcinoma is used.[58,59] The differentiated component can be low or high grade.[60] A significant number of un-/dedifferentiated carcinomas are characterised by an inactivating mutation resulting in loss of SMARCA4 or SMARCB1 protein.[61]

Mixed carcinomas are composed of two or more discrete histological types of endometrial carcinoma, of which at least one component is either serous or clear cell.[62-65] Rigorous criteria should be applied to distinguish them from heterogeneous endometrioid carcinomas (e.g., with a mixture of villoglandular, squamous and mucinous areas), which are frequently associated with MMR deficiency or *POLE* mutations.[66] Any percentage of high grade carcinoma is sufficient to classify the tumour as a mixed endometrial carcinoma. A diagnosis of mixed carcinoma should only be used when both components exhibit a characteristic morphology and immunophenotype.[65]

Carcinosarcoma, formerly included in the group of mixed epithelial and stromal tumours, is now classified as a distinct type of endometrial carcinoma and shows the typical biphasic pattern morphologically.[65] The carcinomatous component shows high grade morphology (serous, endometrioid, mixed or ambiguous), and shows a sharp demarcation from the sarcomatous component. The sarcomatous component can be homologous (no specific mesenchymal differentiation or differentiation towards smooth muscle of endometrial stroma phenotype) or heterologous (mesenchymal differentiation towards mesenchymal lineages not seen primarily in the uterus such as cartilaginous, osseous, skeletal muscle and adipocytic).

Several studies have shown that the presence of heterologous elements in carcinosarcomas is an important adverse prognostic feature particularly in Stage I tumours.[67,68] Reporting of the percentage of epithelial and sarcomatous elements and whether the sarcomatous component is homologous or heterologous is a non-core element. The rare instance of carcinoma arising in an adenosarcoma appears to be a distinct biologic process and should not be diagnosed as carcinosarcoma.[69]

The 2020 WHO Classification[34] includes novel tumour types, such as squamous cell carcinoma, mesonephric and mesonephric-like adenocarcinoma,[70,71] as well as gastrointestinal-type mucinous carcinoma.[51]

Neuroendocrine carcinomas of the endometrium are included in the section on neuroendocrine tumours of the female genital tract in the 2020 WHO Classification.[34,72] Reporting of the neuroendocrine carcinoma subtype is a non-core feature.

Endometrial carcinomas should be adequately sampled. The International Society of Gynecological Pathologists (ISGyP) 2019 guidelines recommend one section per 10 mm, considering the largest tumour dimension.[12] An alternative, when dealing with large tumours, is to submit at least four blocks of tumour. However, the entire endometrium and underlying inner myometrium should be submitted for microscopic examination in the setting of a preoperative endometrial specimen demonstrating malignancy, when no gross lesion is seen in the hysterectomy specimen.[12]

Table 1: World Health Organization classification of tumours of the uterine corpus.[3]

Descriptor	ICD-O codes[a]
Endometrial epithelial tumours and precursors	
Endometrial hyperplasia without atypia	
Atypical hyperplasia of the endometrium	8380/2
Endometrioid adenocarcinoma NOS	8380/3
POLE-ultramutated endometrioid carcinoma	
Mismatch repair-deficient endometrioid carcinoma	
P53-mutant endometrioid carcinoma	
No specific molecular profile (NSMP) endometrioid carcinoma	
Serous carcinoma NOS	8441/3
Clear cell adenocarcinoma NOS	8310/3
Carcinoma, undifferentiated, NOS	8020/3
Mixed cell adenocarcinoma	8323/3
Mesonephric adenocarcinoma	9110/3
Squamous cell carcinoma NOS	8070/3
Mucinous carcinoma, gastric (gastrointestinal)-type[b]	8144/3
Mesonephric-like adenocarcinoma	9113/3[c]
Carcinosarcoma NOS	8980/3
Neuroendocrine tumour NOS	8240/3

[a] These morphology codes are from the International Classification of Diseases for Oncology, third edition, second revision (ICD-O-3.2).[73] Behaviour is coded /0 for benign tumours; /1 for unspecified, borderline, or uncertain behaviour; /2 for carcinoma in situ and grade III intraepithelial neoplasia; and /3 for malignant tumours, primary site; and /6 for malignant tumours, metastatic site. Subtype labels are indented.
[b] Codes marked with an asterisk were approved by the International Agency for Research on Cancer (IARC)/World Health Organization (WHO) Committee for ICD-O at its meeting in June 2020. Incorporates all relevant changes from the 5th edition Corrigenda June 2021.

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Note 9 – Histological tumour grade (Core)

Evaluation of histopathological grade in endometrioid carcinoma is very important in both the initial biopsy/curettage and the final hysterectomy specimen, as risk stratification and decisions on the extent of surgical treatment and administration of adjuvant therapy take into account information on grading.[35]

Serous, clear cell, undifferentiated and neuroendocrine carcinomas and carcinosarcomas are considered high grade by definition. Entities that are high grade by definition should be recorded as 'not applicable' in the reporting guide. However, grading for endometrioid carcinoma is prognostically important.[35,74] The value of the figure (FIGO) grading system was shown in a univariate analysis of more than 600 patients with clinical Stage I or occult Stage II endometrioid carcinoma.[75] The 5-year relative survival was 94% for patients with grade 1 tumours, 84% for those with grade 2 tumours, and 72% for those with grade 3 tumours.[76]

The 2009 FIGO grading criteria for endometrioid carcinoma is primarily based on architectural features.[76] Grade 1, 2, and 3 tumours exhibit ≤5%, 6-50%, and >50% solid non-glandular growth, respectively.[76] In endometrioid carcinomas with squamous differentiation, the grade of the tumour should be assessed in the non-squamous areas. The presence of severe cytological atypia in the majority of cells (>50%) increases the grade by one level.

Overall, the κ statistic for interobserver variability has been shown to be fair to good for the FIGO grading system, with κ values ranging from 0.41 to 0.65.[77] In those studies that have looked at the individual components of the grading system, the interobserver agreement for architecture has ranged from 0.49 to 0.71.[77]

International Society of Gynecological Pathologists (ISGyP) guidelines and the 2020 WHO Classification, highlight the benefits of binary grading, whereby grade 1 and 2 tumours are categorised as low grade and grade 3 tumours as high grade.[34,78] This recommendation is based on the benefits of the binary grading system for easier clinical decision making and improved reproducibility. Classification and regression tree statistical analysis show that the distinction between low and high grade tumours was the second most informative predictor of survival after stage.[79,80] However, some reports show a small, but statistically significant survival difference of around 5% between low stage, grade 1 and 2 tumours,[78] and the distinction between grade 1 and 2 carcinomas may be still important in some institutions for patients desiring fertility-sparing treatments.[81-84]

Agreement in histopathological grade between biopsy and hysterectomy specimens varies, with concordance of only 35% reported in some series.[85,86] Tumour heterogeneity may explain this discrepancy, since biopsies may not be necessarily representative of the whole tumour.[87] When there is discrepancy between the reported histopathological grade in the biopsy and the hysterectomy specimen, it is recommended to review the initial biopsy, and to take this into account when assigning the final histological grade, particularly in cases in which the amount of tumour in the hysterectomy specimen is very limited.

Alternative proposals to FIGO grading have been suggested, which take into account several different parameters, such as nuclear grade, architectural grade, combination of architectural and nuclear features, necrosis, and pattern of myometrial invasion.[88-91] The alternate proposals have shown prognostic value but have not shown to be superior to the FIGO scheme in terms of reproducibility or prediction and some features, such as pattern of myometrial invasion, cannot be assessed on biopsies and curettage specimens.[88-91]

Histological grade may be difficult to apply for cases (especially hysterectomy specimens) in which the specimen was inappropriately fixed and/or the tumour is autolysed. The category of 'cannot be

assessed' should be used sparingly and only in cases where there is genuine doubt. In such cases, it may be useful to state the reason for a response of 'cannot be assessed' in the report and correlation with the preoperative biopsy may be valuable. The 'cannot be assessed' category may also be used in biopsy specimens containing extremely scant tissue.

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Note 10 – Myometrial invasion (Core and Non-core)

The extent of myometrial invasion has long been recognised to be an important risk factor for regional lymph node metastasis, and in some studies, for overall survival in Stage I endometrioid cancer patients.[92,93] Accordingly, the extent of myometrial invasion is a central component of most contemporary systems for prognostication, staging, intra- and post-operative risk stratification, and decision-making models for adjuvant therapy.[35,76,94]

Various methods of determining the extent of myometrial invasion have previously been evaluated. These have included the absolute depth of invasion (DOI) from the endomyometrial junction to the deepest focus of invasive carcinoma, the tumour free distance (TFD) to serosa, and the percentage of myometrium involved, expressed either as the percentage of the overall myometrial thickness that is infiltrated by carcinoma, or as one of three categories: none, <50%, or ≥50%.[95-105]

The widely used TNM and FIGO Staging Systems take the latter approach, with tumours limited to endometrium or invading less than half of myometrium categorised as Stage IA (pT1a), and tumours invading 50% or more categorised as Stage IB (pT1b).[76,106,107]

For cancer reporting, the absence or presence and depth of myometrial invasion should be recorded as none, <50%, or ≥50%; this is a core element. In addition, the absolute percentage of myometrial wall thickness that is invaded by carcinoma can be recorded as a non-core element.[30]

Depth of invasion (DOI) as an individual variable has received less investigation. Nevertheless, higher depths of invasion have been associated with an increased risk of lymphovascular invasion (LVI), lymph node involvement, high stage, recurrence and death of disease in some studies,[99,100,102,103] but not others.[97,98,101,104,105]

Tumour free distance (TFD) is the distance between the deepest point of myometrial invasion of the cancer and the nearest serosal surface.[97-105] TFD theoretically eliminates some of the difficulties that are inherent to determining the depth of myometrial invasion,[95,96] and is reportedly more reproducibly diagnosed by pathologists.[108] However, much like DOI, the prognostic significance of TFD is unclear, since the reported findings have been conflicting.[95,97-105] Most studies have found a statistically significant association, on univariate analyses, between shorter TFD and adverse clinicopathologic factors, including higher tumour grade, cervical involvement, LVI, and advanced patient age.[98,99,102,103] An association between TFD and lymph node involvement, adnexal involvement and/or larger tumour size has also been reported in some studies[98,99,101,102] but not others.[100,103,104] On multivariate analyses, TFD has been found to be an independent predictor of overall survival and recurrence free survival in only 50% and 33% of the studies that have evaluated these questions, respectively.[97-99,101,102,104] In two of the aforementioned studies, a TFD cut off of 10 mm was found to maximize sensitivity and specificity in predicting recurrences.[98,99] Both DOI and TFD are non-core elements. Additional studies are needed to clarify the prognostic roles of DOI and TFD.

Assessment of tumour invasion from adenomyosis is a controversial issue without strong scientific evidence. ISGyP guidelines state that "it is preferable to use the standard method for determining DOI, based on the location of the deepest focus of invasive carcinoma in relation to the total myometrial

thickness in this area, irrespective of its relationship to adenomyosis."[30] Thus, a tumour in which the only invasion arises from adenomyotic foci in the outer half of the myometrium, should be staged as FIGO Stage IB and accompanied by a comment that the clinical significance is unknown, and that this may be an overestimate of true DOI.[10,30]

Several patterns of myometrial invasion are recognised, and more than one pattern may be present within the same case.[109-112] The conventional *infiltrative* pattern is the most commonly encountered pattern, and has no specific prognostic significance.[109,110] This pattern is characterised by irregularly shaped glands that haphazardly infiltrate the myometrium, and are generally associated with a stromal response that may be granulation tissue-like, desmoplastic or inflammatory.[109,110,112] The *adenoma malignum-like pattern* is characterised by typically round, isolated glands that are unequivocally myoinvasive but are not associated with any significant stromal response. The glandular epithelium is generally less columnar than the non-myoinvasive component, and indeed may appear flattened.[112] Eosinophilic luminal secretions may be prominent, especially when the tumour involves the lower uterine segment or burrows into the cervix, potentially leading an endometrial carcinoma to be mistaken for mesonephric remnants or mesonephric proliferations. The *pushing or expansile pattern* is present in 9.4% to 21% of endometrioid carcinomas, and shows a broad, non-infiltrative myoinvasive front, generally without a significant stromal reaction.[109,110] The adenomyosis-like pattern is reminiscent of adenomyosis involved by cancer at scanning magnification, but tumour nests are smaller, overtly infiltrative and lack true endometrial stromal cells at the peripheries of myoinvasive nests.[109,110] The adenomyosis-like, adenoma-malignum, and expansile myoinvasive patterns are devoid of any specific prognostic significance.[109,110] The *microcystic, elongated and fragmented* (MELF) pattern is characterised by discrete foci of single cell clusters, cellular cords, or microcystic glands that are lined by variably flattened epithelium with eosinophilic or squamoid cytoplasm, and which are typically associated with a surrounding fibromyxoid stromal change with an interspersed, neutrophil-rich mixed inflammatory infiltrate.[111] In one meta-analysis comprising 14 studies and 588 patients, the MELF pattern was associated with larger tumour size, higher grade, lymph node metastasis, LVI and >50% myometrial invasion, but was not significantly associated with disease free survival, disease specific survival, or vaginal recurrence rates.[113] Nonetheless, the *diagnostic* significance of the MELF pattern of invasion is multi-fold: 1) the depth of myoinvasion may be underestimated if subtle epithelial cells within foci of MELF-associated fibromyxoid stroma in the myometrium are not recognised as such; 2) foci of MELF myoinvasion may be mistaken for LVI, or vice versa; and 3) lymph node metastases associated with the MELF pattern may be difficult to recognise, as they are frequently of small volume and a small subset of metastases may acquire a distinct histiocyte-like morphology.[114-117] Among the other potentially encountered myoinvasive patterns, single cell infiltration has been associated with an increased likelihood of extrauterine extension on multivariate analyses.[29] Tumour budding, which is probably a different iteration of the same biologic phenomenon, has also been associated with adverse clinicopathologic features and patient outcomes.[109,117-119] The pattern of myometrial invasion may be documented in the pathology report to facilitate future study, but is not a core item.

In most cases, determining the depth of myometrial invasion does not pose a challenge. However, a variety of circumstances may be encountered that may potentially render making this determination problematic.[120] The ICCR Endometrial Cancer Dataset Authoring Committee endorses the ISGyP recommendations for handling these diagnostic scenarios as summarised below:[30]

1. Exophytic tumours and endometrial polyps: Exophytic carcinomas not uncommonly have an 'incorporated' myomatous stroma that should not be mistaken for true myometrium for the purposes of measuring the depth of myometrial invasion. Tumour thickness, which encompasses the exophytic component of a myoinvasive tumour, is not synonymous with the depth of myometrial invasion, where measurement begins at the endomyometrial junction. The location of the true endomyometrial junction may be inferred by comparing the area in question with an adjacent section that is uninvolved by myoinvasive carcinoma. For tumours that infiltrate an endometrial polyp, the same approaches are applicable. In endometrial carcinomas in general, every attempt should be made to submit at least one section that

depicts any exophytic component, the most myoinvasive component, and an adjacent non-involved endomyometrial junction.

2. Uterine cornu and lower uterine segment: Given that the uterine wall thickness is thinnest at the cornu, the ISGyP recommendations are that the depth of myometrial invasion should not be measured at this focus, unless the tumour is entirely localised to the cornu, and/or extends to the serosa at that point. In contrast, for tumours whose maximal depth of myometrial invasion is in the lower uterine segment, measurements should be taken as they would be at other non-cornual areas of the uterine corpus.
3. Leiomyoma: For tumours that infiltrate a leiomyoma, measurements should be taken as if the leiomyoma represents non-leiomyomatous myometrium. Specifically, the thickness of the myometrial wall at the focus of myoinvasion should include the thickness of the leiomyoma, and the measurements of the depth of myometrial invasion should include the portion of the tumour that is invasive of the leiomyoma.
4. Lymphovascular invasion (LVI): Consistent with staging principles at other anatomic sites, LVI is not used, in and of itself, to upstage. Accordingly, in endometrial carcinoma, foci of LVI should not be used to determine the depth of myometrial invasion. For example, a Stage I tumour with <50% invasion of the myometrial wall but which shows LVI in the outer myometrium should be classified as Stage IA, rather than IB.

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Note 11 – Lymphovascular invasion (Core)

Lymphovascular invasion (LVI) is an important prognostic indicator in endometrial carcinoma and documenting the presence or absence of this is a core element. LVI can be confidently diagnosed at the invasive front of a carcinoma when there is a tumour embolus within an endothelial-lined channel.[30,121-123] The embolus frequently takes the shape of the vessel lumen and may be attached to the endothelium. The tumour embolus usually resembles the endometrial carcinoma, but LVI associated with MELF invasion may contain single or clustered histiocytoid or metaplastic-appearing cells that resemble the myometrial invasive cells of MELF.[121,124]

There are several types of artefact that simulate LVI: these include artefacts secondary to tumour disruption; MELF pattern myometrial invasion; and retraction artefacts.[121,122,125,126] The first situation is predominantly encountered in the setting of laparoscopic and/or robotic surgery followed by dissection of the uterus before adequate fixation.[125-129] Clues to the presence of this type of artefact include fragments of tumour and, sometimes, normal constituents around the cut surfaces of the section, in tissue 'cracks', in large, medium-sized and small vessels, both adjacent to the tumour's invasive front and in distant locations.[121,122] Often the amount of tumour within vessel appears disproportionate, for example in a tumour which is low grade and low stage. It may be impossible to distinguish 'real' LVI amongst all the artefact; this should be expressed in the surgical pathology report. Adequate fixation before prosection, generally lessens the degree of artefact. The second artefact type results from the morphologic similarity between MELF myometrial invasion and LVI.[130] Adding to the complexity is that MELF myometrial invasion is, indeed, associated with LVI.[113] The distinction between the two can usually be resolved by knowing about this type of artefact and careful examination to differentiate between endothelium on one hand (LVI) and tumour cells floating in a microcyst lined by flattened and attenuated epithelium (MELF myometrial invasion). Immunohistochemical endothelial markers can sometimes be used to confirm a suspicion of LVI, especially when there is extensive retraction artefact. Epithelial markers, in addition, may be added to the panel when MELF myometrial invasion is present, although the literature is not consistent on the added value of immunohistochemistry (IHC) after haematoxylin and eosin (H&E) evaluation.[30,131]

The absence of LVI is defined as no tumour cells within vessels.[78] There is controversial data regarding the cut off for 'extensive ' or 'substantial' LVI. 'Extensive' is defined as the presence of three or more vessels containing tumour, according to ISGyP recommendations,[78] but five or more vessels in the 2020 WHO Classification[34] and in the ESGO-ESTRO-ESP guidelines.[10]

Recent data indicate that 'substantial' or 'extensive' LVI is associated with adverse outcomes when compared to carcinomas with 'focal' or 'no' LVI.[132-134] Although there have been different proposals for what constitutes extensive LVI, it is a good rule of thumb to diagnose extensive LVI when it is easily recognisable at scanning magnification (and artefact is excluded) and when present in three or more vessels on closer inspection. Recording the degree of LVI (focal or substantial/extensive) is regarded as a core element. LVI should not be included in the assessment of depth of myometrial invasion, or indeed, in determining any element of pathologic staging.[30] LVI features in many (but not all) multivariate clinical outcomes analyses and is associated with lymph node metastasis, local and distant recurrence and poor survival.[132,133,135] Thus, the presence of substantial LVI may highlight the need for adjuvant treatment, such as recommended in the 2020 ESGO-ESTRO-ESP consensus guidelines.[10] A value of 'indeterminate' should be used sparingly and only in cases where there is genuine doubt. In such cases, it may be useful to report the reason for a response of 'indeterminate'.

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Note 12 – Cervical surface or crypt (Non-core)

Cervical surface mucosal or crypt epithelial involvement (without cervical stromal invasion) does not affect tumour stage in the 2009 FIGO Staging System and is regarded as a non-core element.[76] However, it is a potential adverse risk factor for locoregional recurrence and may be taken into consideration for adjuvant radiotherapy.[30] In the Post Operative Radiation Therapy in Endometrial Carcinoma-2 (PORTEC-2) and Gynecology Oncology Group trial 99 (GOG #99) prospective randomised trials, patients with high-intermediate risk factors, including cervical surface or crypt involvement (FIGO 1988 Stage IIA), were found to have improved locoregional disease control (reduced recurrence rate) with postoperative radiation (vaginal brachytherapy or pelvic radiation).[136-139] While the above studies lacked an overall survival benefit, a recent large retrospective cohort (analysing over 14,000 patients) demonstrated improved overall survival in FIGO 1988 Stage IIA patients receiving adjuvant radiation.[140]

The current clinical practice guidelines of the American Society for Radiation Oncology and the Society of Gynecologic Oncology are based on the results of the PORTEC-2 and GOG #99 trials for adjuvant radiotherapy.[141,142]

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Note 13 – Lower uterine segment (Non-core)

As stated in **Note 4 TUMOUR SITE**, similar to cervical surface or crypt involvement, although not affecting the FIGO tumour stage, lower uterine segment involvement is a potential adverse risk factor for locoregional and distant recurrence and may be taken into consideration for adjuvant radiotherapy.[17] It is regarded as a non-core element for reporting. As tumours arising in the lower uterine segment also show frequent association with Lynch syndrome, documentation of lower uterine segment involvement has important risk implications.[14]

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Note 14 – Cervical stroma (Core)

Cervical stromal invasion indicates Stage II endometrial carcinoma according to the current FIGO Staging System and is a core element for reporting.[76] Cervical stromal invasion is associated with a significant risk of recurrence and is a predictor of pelvic lymph node metastases.[143,144] However, the role of cervical stromal involvement as an independent prognosticator per se has been questioned.[35] Cervical stromal invasion often occurs in the presence of other adverse features such as high histologic grade, deep myometrial invasion and LVI.[145] In one study, the presence of these factors conferred worse disease-free survival in patients with Stage II endometrial cancer.[146]

Cervical stromal invasion is defined as infiltrative or expansile (pushing) tumour growth into the cervical stroma. Characteristics of infiltrative invasion include irregular glands, single cells or tumour cell clusters, and desmoplastic stromal reaction. In the absence of infiltrative features, assessment of stromal invasion is facilitated by comparing the architecture of the carcinoma with the normal endocervical crypts: expansile (pushing) invasion is favoured if there is altered architecture with complex cribriform or microacinar growth (exceeding what would normally be accepted as just intraglandular growth).[30]

Determination of cervical stromal invasion can be complicated by difficulties in demarcating the cervix from the lower uterine segment. By convention, the boundary is defined by the most proximal benign endocervical crypt.[121,147] Consequently, any invasion identified at the level of, or distal to, a benign endocervical crypt should be considered cervical stromal invasion.

Significant interobserver variation in the assessment of cervical involvement by endometrial carcinoma has been documented. McCluggage et al (2011) showed fair to good agreement among six experienced gynaecologic pathologists in this exercise.[147] While Zaino et al (2013) showed high agreement in determining whether the cervix is involved or not, but only slight agreement in the distinction between glandular and stromal involvement.[148] Problematic scenarios include: determination of the junction between the lower uterine segment and upper endocervix; the distinction between 'floaters' and true cervical glandular involvement; the distinction between cervical glandular involvement and stromal involvement; and the distinction between cervical glandular involvement and reactive non-neoplastic glandular lesions such as tuboendometrial metaplasia or changes secondary to recent biopsy.[147] Strict definitions as to what constitutes cervical stromal invasion and the boundary between cervix and lower uterine segment, as provided above, are likely to improve reproducibility. In addition, consensus diagnosis via intra- or inter-departmental consultation is encouraged.

A value of 'indeterminate' should be used sparingly and only in cases where there is genuine doubt; in such cases, it may be useful to state the reason for a response of indeterminate in the report.

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Note 15 – Depth of cervical stromal invasion (Non-Core)

The National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology Uterine Neoplasms lists deep cervical stromal invasion as an adverse risk factor in patients with Stage II endometrial carcinoma.[149] While external beam radiation therapy (EBRT) is preferred in patients with surgically staged Stage II endometrial carcinoma, vaginal brachytherapy is listed as a valid option for those patients with low grade disease with minimal cervical stromal invasion and no tumour outside the corpus and cervix.[149]

There is no clear definition of what constitutes 'minimal cervical stromal invasion'. A retrospective, single institution study by Orezzoli et al (2009) stratified cervical stromal invasion into four subcategories (≤1 mm; >1 mm and ≤3 mm; >3 mm and ≤5 mm; >5 mm), and found no statistical association with survival.[150] Barnes et al (2019) reported on their retrospective, single institution experience study on brachytherapy alone in patients with low grade endometrial carcinoma and cervical stromal invasion confined to the inner half of the cervix, which showed good results.[151] Absolute depth of cervical stromal invasion and percentage of cervical stromal invasion are non-core elements.

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Note 16 – Parametria (Core)

Most hysterectomies for endometrial cancer are simple hysterectomies and do not have parametrial resections, although occasionally parametrial resection is undertaken when cervical stromal invasion is suspected preoperatively (radical or modified radical hysterectomy). Endometrial carcinomas with parametrial invasion are staged as FIGO Stage IIIB.[76] Although not an independent prognostic indicator, parametrial involvement by direct extension is a poor prognostic factor.[152-154] It is associated not only with cervical stromal invasion but also with outer half myometrial invasion, pelvic and/or paraaortic lymph node metastasis, ovarian metastasis, positive peritoneal cytology and LVI.[152-154] Reporting of the presence or absence of parametrial involvement in hysterectomy specimens containing parametrial tissue is a core element.

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Note 17 – Vagina (Core)

In endometrial carcinoma, vaginal involvement may occur in two different scenarios:

- Vaginal involvement at diagnosis (uncommon scenario)
- Vaginal recurrence of endometrial carcinoma (common scenario).

Vaginal involvement at the time of diagnosis is uncommon, and places the disease in FIGO Stage IIIB (pT3b).[107] Vaginal involvement occurs either via direct extension from the corpus to the cervix and vagina or metastasis through lymphatic pathways. It is essential to report vaginal involvement for staging of disease and prognosis. Vaginal involvement at diagnosis is rare (less than 1% of cases) and it is very unusual that patients present with vaginal extension without lymph node metastasis or spread to other distant sites. The 5-year survival rate for these patients is approximately 25%, with a median survival of 1-2 years.[155] Vaginal metastasis may be identified in a vaginal nodule submitted separately by the surgeon or from sampling the vaginal cuff tissue from a radical hysterectomy specimen.

The vagina represents the most common site of recurrence of endometrial carcinoma.[138,156] In the majority of cases, recurrence involves the upper vagina, while recurrence in the middle third or distal vagina is less common.[157] In a study by Moschiano et al (2014),[157] there were no disease-related deaths in patients with vaginal recurrence only, suggesting that vaginal recurrence is not a marker of aggressive tumour biology. Vaginal recurrences are also associated with cervical tumour involvement.[157] Endometrial carcinoma with vaginal recurrence show different features compared with tumours that recur at other sites, in particular: older age, superficial myometrial invasion, low nuclear grade, no greater than 1 focus of LVI, LVI not deeper than the invasive front, <5% MELF pattern at the invasive tumour front, and no lymph node metastasis at presentation.[158] Stolnicu et al (2020) suggests that vaginal recurrence in patients with endometrial carcinoma might be caused by distal migration of tumour cells in the vagina as a result of tumour cells dropping off from polypoid tumours, tumours involving the cervix, or tumour bleeding during surgical treatment.[159]

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Note 18 – Omentum (Core)

Omentectomy is part of the surgical staging procedure for some high grade endometrial cancers. Omental spread by endometrial carcinoma is associated with decreased overall survival.[160,161] Omental metastases are associated with other adverse prognostic features such as high tumour grade, serous histology, deep myometrial invasion, LVI and adnexal involvement.[160,162]

Spread of endometrial carcinoma to the omentum, either supracolic or infracolic, is regarded as a distant metastasis and places the disease in FIGO Stage IVB (pM1).[163,164] The previous version of the ICCR Endometrial cancer dataset did not make recommendations on this staging component.[16]

Omental metastases by endometrial carcinomas are uncommon. One study documented that 92.7% of omentectomy specimens for staging of endometrial adenocarcinoma showed no tumour.

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Note 19 – Peritoneal biopsies (Core and Non-core)

Reporting of peritoneal involvement is core when biopsy specimens are submitted as part of staging of endometrial carcinoma. The site of the peritoneal biopsies and the presence or absence of tumour involvement should be documented. Taking of blind peritoneal biopsies is routine in some institutions.[165]

It is important to distinguish between abdominal and pelvic peritoneal involvement since this denotes a different Stage (IIIA for pelvic peritoneal involvement and IVB for upper abdominal peritoneal involvement).

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Note 20 – Peritoneal cytology (Non-core)

Positive peritoneal cytology is no longer part of the FIGO Staging System, but the results of the peritoneal cytology may provide risk-stratification. As a consequence, consideration for adjuvant therapy may be discussed in multidisciplinary tumour board meetings. Positive peritoneal cytology has been shown to be an independent prognostic factor for serous carcinoma regardless of stage and it will be important to report for other invasive carcinomas.[76,149,166,167]

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, and it is also unclear whether the method of hysteroscopy or operative procedure may influence the likelihood of positive peritoneal washings.[30] FIGO and the Union for International Cancer Control (UICC) recommend to record positive peritoneal washings but without altering the tumour stage.[76,106]

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Note 21 – Uterine serosa (Core)

Documentation of the presence or absence of serosal involvement is a core element. According to ESGO/ESTRO/ESP[10] and ISGyP guidelines,[30] tumour infiltrating the full myometrial thickness and reaching submesothelial fibroconnective tissue or the mesothelial layer should be reported as serosal involvement. Tumour may or may not be present on the surface of the uterus and a desmoplastic response may or may not be present. *It should be noted that, when present, a desmoplastic stromal reaction can obscure evaluation of the serosa.* Locating the serosal plane flanking the area in question and extending the plane through the area of desmoplasia can be helpful. Serosal involvement is considered present if there is disruption of that plane or carcinoma extends beyond the plane. Involvement of the serosa (FIGO Stage IIIA) carries a higher risk of locoregional recurrence than does adnexal involvement (also FIGO Stage IIIA).[168]

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Note 22 – Adnexa (Core)

The presence or absence of adnexal involvement is a core element. Adnexal involvement has an impact on overall survival rate. [76,106,107] The presence of adnexal involvement categorises a tumour as Stage IIIA in FIGO and pT3a in TNM Staging Systems, respectively.[76,106,107] Prognosis is worse when ovarian metastases are associated with metastases at other sites.[169] The involved adnexa should also be documented, particularly specifying which ovary and which fallopian tube is involved as well as the location of tubal involvement.

It is important to distinguish between endometrial carcinoma with ovarian metastasis and synchronous primary tumours of the endometrium and the ovary.[170] For high grade tumours, including serous carcinoma, ovarian involvement is almost always categorised as metastatic. However, there is always the possibility of coincidental independent primary serous carcinomas in the endometrium and the tube/ovary, although this situation is exceedingly unusual. Furthermore, metastasis from the adnexa to the endometrium rarely occurs. Ancillary techniques (such as WT1 and p53 staining) and evaluation of the fallopian tube by Sectioning and Extensively Examining the Fimbria (SEE-FIM) protocol may be helpful.[12]

Five percent of endometrioid adenocarcinomas are associated with an endometrioid carcinoma of the ovary. Cases with simultaneous involvement of endometrium and ovary by low grade endometrioid carcinomas are often associated with indolent outcome.

Clinicopathologic criteria can help to distinguish patients with good prognosis (such as those with two independent primary tumours/'low-risk') and patients with bad prognosis (such as those with an endometrial carcinoma with ovarian metastasis/'high-risk'). Distinction between these two prognostic types is based on several criteria including: 1) size of the tumour, 2) histologic type and grade, 3) extent/depth of myometrial invasion, 4) presence of LVI, 5) tubal invasion, 6) presence of endometrial hyperplasia, 7) presence of ovarian endometriosis, 8) pattern of ovarian invasion, including bilaterality, and 9) presence of additional metastases.

Recent molecular studies have shown that for low grade endometrioid carcinomas, there is a clonal relationship between the endometrial and ovarian tumour in the vast majority of cases, suggesting that the tumour arises in the endometrium, and secondarily extends to the ovary .[171-174] However, this clonal relationship should not be equated with the clinical outcomes expected of metastatic endometrial carcinoma.

In the 2020 edition of the WHO Classification,[34] it is suggested that patients with clonally related low-risk tumours be managed conservatively (as if they were two independent primaries) 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.[3,175] This is an evolving field, and it is not clear at this time why a subset of metastatic tumours are associated with good prognosis. This phenomenon is also seen in endocervical adenocarcinomas metastatic to the ovaries.[176,177] Potential explanations are: 1) that clonal ovarian metastasis occurs early in the process of endometrial tumour development, thereby allowing tumours in each site to acquire additional, sometimes distinct genetic abnormalities; and 2) tumour cells follow retrograde uterine/transtubal spread, possibly with ovarian implantation, rather than destructive invasion. It is recommended to discuss these cases in multidisciplinary tumour boards.

Although true independent simultaneous endometrial and ovarian carcinomas do exist, they are relatively infrequent, and share characteristics of tumours arising in the setting of Lynch syndrome.[174] In this scenario, endometrioid carcinomas of the endometrium may coexist with ovarian clear cell carcinoma.[15,178]

It is important to remember that the presence of LVI in ovarian hilar or parenchymal vessels or tubal vessels without stromal invasion does not affect stage.

Tumour involvement of the fallopian tube should also be recorded.[169] It is important to stress that the presence of detached aggregates of tumour cells in the tubal lumen, without involvement of the fallopian wall, should not be considered tubal involvement,[127] since this is thought to be an artefact related to the type of surgery performed and/or specimen fixation. However, it has been reported that the presence of serous carcinoma cells in the lumen of the fallopian tube is often associated with peritoneal metastasis.[179] Floating tumour cells in the fallopian tube lumen should not lead to upstaging of the tumour, although this should prompt a careful review of the peritoneal/pelvic washings.

Tubal involvement by endometrial carcinoma in the form of intramucosal spread has controversial prognostic significance. Tubal tumour is generally considered metastatic from the endometrium, but it is sometimes considered to represent a coincidental low-risk 'synchronous' endometrioid carcinoma of the fallopian tube. The approach to distinguishing between low- and high-risk carcinomas could theoretically follow the same paradigm used for tumours involving endometrium and ovary. The prognostic significance of tubal mucosal involvement by endometrioid carcinoma (either low- or high-risk) is unknown.[30]

Tubal involvement by serous carcinoma, with or without stromal invasion is usually a manifestation of metastatic serous carcinoma. Recent studies have shown that endometrial serous carcinoma frequently extends to the fallopian tube, giving rise to a lesion that may be indistinguishable from serous tubal intraepithelial carcinoma (STIC)/STIC-like lesion.[180] There is also the possibility that a bona fide STIC can be the nidus from which serous carcinoma cells detach and implant in the endometrium, simulating a primary endometrial serous carcinoma.[181] Furthermore, there is also the possibility of the coincidental presence of an endometrial serous carcinoma and a primary STIC, but in these cases ancillary techniques are required. Assessment of WT1 expression may be helpful in these scenarios. WT1 immunoreactivity is negative in the majority of primary endometrial carcinomas but positive in almost all carcinomas arising from the ovaries or the fallopian tube.[182]

Endometrial carcinomas metastatic to the fallopian tube wall or its serosa should be interpreted as metastatic unless there is evidence of an origin in endometriosis.

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Note 23 – Margin status (Core and Non-core)

It is important to record the status of paracervical soft tissue and ectocervical/vaginal cuff margins, and this is a core reporting element. The term paracervical soft tissue refers to the small part of the parametrium that is included in simple hysterectomy specimens, which is the common surgical procedure for endometrial carcinoma.

Vaginal (direct extension or metastasis) or parametrial involvement by endometrial carcinoma is currently staged as IIIB.[76,107] Positive margin status has been identified as a risk factor for local recurrence and mortality, and patients with positive margins are more likely to receive a vaginal vault brachytherapy boost.[183,184] Vascular invasion at the cervical/parametrial/vaginal resection margin is not considered a positive margin.

Close cervical/parametrial/vaginal margins may indicate an increased risk of recurrence and may be taken into consideration for adjuvant radiotherapy.[185] However, there are no criteria regarding the distance to margins that would be considered 'close'. The distance to the margins is a non-core reporting element; when reported, the distance to margins should be stated in mm.

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Note 24 – Background endometrium (Non-core)

The background endometrium may provide useful information regarding tumour pathogenesis and may have prognostic implications.[16] The presence of stromal predecidual change and Arias-Stella reaction may serve as evidence of preoperative hormonal therapy.[186] These should be reported under 'other'.

Hyperplasia without atypia may occur due to prolonged exposure to unopposed estrogen, whereas atypical hyperplasia/endometrioid intraepithelial neoplasia is a manifestation of clonal expansion of neoplastic glands.[187,188] These lesions predispose to endometrioid carcinoma.[189-191] Serous carcinoma typically arises in a background of atrophic endometrium although it remains controversial as to what constitutes a precise precursor lesion. Serous endometrial intraepithelial carcinoma is regarded as a serous carcinoma which grows along pre-existing glands but still has the potential to metastasize to extrauterine sites. Therefore, it is considered a carcinoma rather than a precursor lesion.[192,193] A precursor of clear cell carcinoma has not yet been defined.[194,195]

Carcinomas arising in an endometrial polyp, may be endometrioid or serous in type, with the latter being more common.[196] To prove that a carcinoma has arisen within an endometrial polyp rather than secondarily involving it, the tumour should be confined to the polyp. Usually this needs to be confirmed on a hysterectomy specimen.

Although metaplasias are common in benign endometrium, some subtypes, such as papillary proliferation and morular metaplasia, may be associated with concurrent or subsequent atypical endometrial hyperplasia and endometrial carcinoma.[197,198] Papillary mucinous metaplasia and complex mucinous glandular proliferation predispose to endometrioid carcinoma with mucinous differentiation.[50,199]

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Note 25 – Lymph node status (Core and Non-core)

Lymph node status is an important prognostic factor for endometrial carcinoma and its assessment is crucial for determining both stage and appropriate adjuvant therapy. According to the FIGO Staging System, metastatic involvement of lymph nodes increases tumour stage (IIIC1 and IIIC2 for pelvic and para-aortic nodes, respectively).[76] In contrast, a therapeutic benefit from lymph node resection has not been shown yet in randomised trials,[200-202] although a large retrospective study has shown benefit from extensive nodal dissection especially in serous tumours.[202]

Intraoperative frozen section analysis can be useful to assess lymph node metastases.[203] The technique has its limitations for the detection of micrometastasis and isolated tumour cells.[204] Notably, intraoperative frozen section is only justified if the results have immediate therapeutic consequences. Serial sections from different levels are not recommended to avoid tissue depletion. The tissue block used for frozen section needs to be fixed in formalin and embedded in paraffin and, if negative for metastasis, submitted for ultrastaging.

Resected lymph nodes are categorised as regional (paracervical, parametrial, various pelvic lymph node groups, including obturator, internal, common or external iliac, presacral and lateral sacral, and para-aortic) or non-regional nodes (inguinal and other nodes). It should be noted that non-regional lymph nodes (including inguinal nodes) are considered to be distant metastases.

Core data regarding lymph node status includes the number of lymph nodes identified from the various sites, the number of lymph nodes involved by metastatic tumour and the size of largest metastasis (maximum diameter in mm). Some other parameters which may be useful for future research may be recorded, such as extranodal spread. Extranodal spread is a non-core element. Occasionally, metastatic tumour is present in the specimen removed, but no lymph node tissue is identified.

The FIGO Staging System includes lymph node status, and its structure is similar to that of the TNM system.[76,106,107] Pelvic lymph node involvement is Stage IIIC1 and para-aortic nodal involvement Stage IIIC2. For TNM stage, regional lymph node metastases contribute to the N category, whereas metastases in non-regional nodes are regarded as distant metastasis and belong to the M category.[106,107] According to TNM8,[106] macrometastases are >2 mm, micrometastases are >0.2 to 2 mm and/or >200 cells, and isolated tumour cells are up to 0.2 mm and ≤200 cells. Macrometastases are regarded as pN1 or pN2 depending on location (pelvic for pN1, para-aortic for pN2), micrometastases as pN1mi or pN2mi (depending again on location of the involved lymph nodes) and isolated tumour cells are pN0(i+); isolated tumour cells do not upstage a carcinoma.[106,107,205,206]

Grossing of the lymph nodes is an important step for a thorough histologic evaluation. Lymph nodes up to 2 mm are embedded whole. If lymph nodes are larger than 2 mm, they should be sliced perpendicular to the long axis at 2 to 3 mm intervals and entirely submitted.

Traditionally, lymph node status has been assessed either by removal of enlarged and grossly suspicious lymph nodes or systematic lymphadenectomy. More recently, the technique of sentinel node biopsy has been developed and established for endometrial carcinoma as an alternative to systematic and selective lymphadenectomy. Multiple studies confirm the high sensitivity of the sentinel lymph node approach for determining the lymph node status in early-stage endometrial carcinoma and underscore the value of sentinel node biopsy in selecting therapeutic approaches.[207-210] Currently, indocyanine green is considered the most reliable tracer and the highest detection rate can be achieved when the substance is injected into the cervix.[211,212]

One of the strengths of sentinel lymph node biopsy is the detection of a high percentage of lymph node positive cases by accurate analysis of one or a few lymph nodes. Isolated tumour cells, micrometastases, and small macrometastases are detected by ultra-staging of the lymph nodes in

combination with IHC. In addition, sentinel lymph node biopsy is associated with a substantially lower risk of post-operative morbidity, especially lower leg lymphoedema when the dissection of other pelvic lymph nodes is avoided.[213,214]

A study by Kim et al (2013) on low risk endometrial carcinoma patients (myometrial invasion <50%, low histologic grade) has shown involvement of sentinel lymph nodes in 6% of patients, of which half were identified by pathological ultra-staging.[215] Patients with carcinomas limited to the endometrium were not identified with positive sentinel lymph nodes and, therefore, sentinel node biopsy could be omitted in this patient population.[216] However, this usually is confirmed after hysterectomy only.

The presence of nodal micrometastases is associated with worse prognosis, particularly in patients not receiving adjuvant treatment.[217] There is no evidence that the presence of isolated tumour cells which would be classified as pN0(i+) has prognostic ramifications. Based on large randomised trials,[200-202] lymph node staging does not show any impact on survival but provides information on extent of the disease and decisions about adjuvant treatment. According to recent European (ESGO-ESTRO-ESP 2020) guidelines,[10] sentinel lymph node biopsy can be considered for staging purposes in patients with low/intermediate risk disease and can be omitted in cases without myometrial invasion. Systematic lymphadenectomy is not recommended for these carcinomas due to the morbidity associated with the procedure and low incidence of positive nodes. For high-intermediate/high-risk carcinomas in Stages I/II, surgical lymph node staging should be performed and sentinel lymph node biopsy is an acceptable alternative to systematic lymphadenectomy.[218]

Ultrastaging is recommended for the analysis of sentinel nodes negative for metastasis by routine histopathologic analysis since it provides valuable clinical information.[219,220] Notably, if sentinel nodes are negative by ultrastaging the occurrence of isolated nodal paraaortic metastasis is less likely.[10,220] Several ultrastaging protocols have been published, however there is no preferred standardised technique. Ultrastaging consists of additional sections cut at defined intervals and stained by H&E and pankeratin for improved detection of micrometastases and isolated tumour cells. There is some evidence that the results between different protocols do not reveal significant differences.[219-222] Two different methods were compared without significant differences: five H&E levels at 250 micrometres (µm) intervals with two unstained slides at each level; pankeratin IHC performed on level 1 in cases with negative H&E levels; or one H&E level plus two unstained slides cut 250 µm into the tissue block and pankeratin IHC performed in cases with negative H&E.[219] Another protocol uses H&E and pankeratin IHC at 50 µm into the tissue block with a total of five sections per block.

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Note 26 – Ancillary studies (Core and Non-core)

Immunohistochemistry for mismatch repair proteins and MLH1 promoter methylation

Immunohistochemistry (IHC) for MMR proteins is recommended in addition to analysis for MLH1 promoter methylation when there is immunohistochemical loss of MLH1 or PMS2 as a core reporting parameter.[223]

Endometrial cancer is one of the most common tumours in patients with Lynch syndrome (also known as hereditary non-polyposis colorectal cancer).[224,225] Around 3% of all endometrial carcinomas and approximately 10% of MMR deficient (MMRd)/microsatellite unstable endometrial carcinomas are causally related to germline mutations of one of the MMR genes MLH1, PMS2, MSH2 and MSH6 or a related gene, EPCAM.[226] 'Constitutive methylation' is also a rare cause of Lynch syndrome.[227]

Testing for MMR status/microsatellite instability (MSI) in endometrial carcinoma patients has been shown to be important for four key reasons:

1. Diagnostic, since MMRd/MSI is helpful to diagnose endometrioid carcinomas (as opposed to serous carcinoma or human papillomavirus (HPV)-associated cervical carcinoma);
2. It is part of the screening algorithm to identify potential patients with Lynch syndrome;[228]
3. Prognostic, as part of the TCGA surrogate molecular classification;[229] and
4. Therapeutically as a predictive biomarker for potential utility of immune checkpoint inhibitor therapy.[230]

Systematic clinical screening of personal and family history misses a significant proportion of women with Lynch syndrome, since up to 75% of patients do not fulfill the revised Bethesda Guidelines criteria.[231] ISGyP has recommended testing for MMR status/MSI in all endometrial carcinomas (preferably curettings or biopsy), irrespective of age.[223] This has also been recommended whenever resources are available by other societies/groups, such as the Manchester International Consensus Group.[232] The identification of Lynch syndrome in women with endometrial carcinoma can lead to the prevention of a second cancer in the patient and reduced incidence of cancers in family members through risk reducing strategies and heightened surveillance.

Microsatellite instability (MSI) can be detected by different methods, including polymerase chain reaction (PCR)-based approaches[231,233,234] and next generation sequencing (NGS).[235] NGS is in the process of being validated for this scenario. MSI can also be accurately predicted using IHC.

Immunohistochemistry (IHC) is cost effective and is implemented in most pathology departments. ISGyP guidelines recommend IHC as the best test for MMR deficiency and, indirectly, for MSI.[223] The IHC approach consists of an assessment of the expression of four DNA MMR proteins; MLH1, PMS2, MSH6, and MSH2. A simplified version includes only PMS2 and MSH6, with expanded analysis of MLH1 when PMS2 is lost, and of MSH2 when MSH6 is lost.[236] Carcinomas showing loss of MLH1 and PMS2 expression should be investigated for MLH1 promoter hypermethylation,[237] as its presence essentially excludes Lynch syndrome. Endometrial cancer patients whose tumours are MMRd, but not methylated at the MLH1 promoter, should undergo genetic counselling with consideration for germline testing.

Immunohistochemistry (IHC) may be not informative when the specimen has been subjected to poor pre-analytical conditions, such as inappropriate or delayed fixation. Furthermore, occasionally there are germline genetic abnormalities that do not result in abnormal expression of MMR proteins. In these cases, PCR-based techniques to assess MSI may be appropriate, particularly when the family history is highly suspicious for Lynch syndrome. MSI detected by PCR-based methods usually requires testing both normal and tumour tissue, although there is a recently described method that only requires tumour tissue.[238]

The cumulative incidences of colorectal, endometrial, ovarian, upper gastrointestinal, urinary and brain cancers in women aged 75 years with Lynch syndrome, depend on the specific mutation. The cumulative incidences have been reported as: germline *MLH1* mutation (46%,43% 10%, 21%, 8%, 1%); germline *MSH2* mutation (43%, 57%, 17%, 10%, 25%, 5%); germline *MSH6* mutation (15%, 46%, 13%, 7%, 11%, 1%), respectively.[239] In contrast, PMS2 is mostly associated with a moderate increase in colon and endometrial cancer risk, with a cumulative incidence at age 80 years of 12% and 13%, respectively.[240]

The Cancer Genome Atlas (TCGA)-based molecular classification of endometrial carcinomas

Reporting of TCGA-based molecular classification of endometrial carcinomas is a non-core parameter. Diagnosis and classification of endometrial carcinoma has up until now largely been based on the microscopic appearance of the tumours.[3] The different histologic types have different molecular features, microscopic appearances, precursor lesions, and natural history, although in multivariate analyses,[38] FIGO stage and grade have more prognostic significance than histotype. Unfortunately, histological typing engenders problems with interobserver reproducibility and prognostication. While diagnosis is quite reproducible in low grade (FIGO grades 1 and 2) endometrioid carcinomas, which account for 70% of endometrial carcinomas, in typical serous and clear cell carcinomas, there is poor interobserver agreement in approximately 10% of tumours. This is particularly evident in a subset of endometrial carcinomas with high grade morphology[41-43] with microscopic and immunohistochemical features that are shared between high grade endometrioid and serous carcinomas.

The TCGA performed an integrated genomic, transcriptomic and proteomic characterisation of endometrial carcinoma.[241] Exome sequence analysis revealed four groups of tumours. Group 1 carcinomas (7% of endometrial carcinomas) have somatic inactivating hotspot mutations in the *POLE* exonuclease domain and a very high mutational burden (ultramutated). FIGO grade 3 endometrioid carcinomas are highly represented in group 1, some of which resemble serous carcinomas. Irrespective of grade, group 1 tumours have an excellent prognosis, although this is not confirmed in all of the recent literature.[241-244] Group 2 and Group 3 show similar progression-free survival rates that are intermediate between groups 1 and 4. With additional research, it is becoming apparent that groups 2 and 3 are heterogeneous, each having genomically-defined subgroups of tumours, some of which are prognostically favourable and others that are unfavourable.[241,245-247] Group 2 (28% of tumours) include endometrioid carcinomas with MSI (hypermutated), frequently with MLH1 promoter hypermethylation and high mutation rates. Group 3 tumours (39% of endometrial carcinomas) include endometrioid carcinoma with low copy number alterations, and low mutational burden, while lacking *POLE* mutations and MSI-high (MSI-H). Group 3 tumours have also been referred to as 'no specific molecular profile (NSMP)'. Finally, Group 4 (serous-like or copy-number high; 26% of carcinomas) show a low mutation rate, nearly universal (95%) *TP53* mutations, and a highly unfavourable prognosis. Most of these tumours are serous carcinomas, but up to 25% of endometrioid (mostly high grade) and clear cell carcinomas, along with carcinosarcomas, can be found in this group.

In an attempt to bring the TCGA molecular-based classification into clinical practice, different groups have proposed a surrogate (simplified) algorithm precluding comprehensive tumour profiling.[229,246,247] The algorithm includes three immunohistochemical markers (p53, MSH6 and PMS2) and one molecular test (mutation analysis of *POLE*). Several studies have demonstrated the prognostic value of this TCGA-surrogate approach, and ISGyP have recommended this scheme.[78,223,245]

According to this simplified algorithm, tumours with pathogenic *POLE* mutations correspond to ultramutated tumours. MSH6 or PMS2 abnormal expression defines tumours in the hypermutated group. Abnormal expression of p53 (mutated pattern), characterises the high copy number group. Finally, NSMP is defined by the absence of *POLE* mutation, and a normal expression pattern for MSH6, PMS2 and p53.[229,247]

The TCGA surrogate approach has been shown to be particularly helpful in the group of high grade endometrioid carcinomas, including cases in the grey zone between endometrioid and serous carcinomas. High grade endometrioid carcinoma had been regarded as an aggressive tumour type with some similarities to serous carcinoma. However, application of the TCGA surrogate shows that there is a group of high grade endometrioid carcinomas with an improved prognosis (tumours with pathogenic *POLE* mutations), and a group with a very poor prognosis (p53-abnormal tumours). MSI-H and NSMP grade 3 endometrioid carcinomas have an intermediate prognosis.[52] Application of this algorithm for clear cell carcinoma,[248] undifferentiated carcinoma,[58] neuroendocrine carcinoma,[249] and carcinosarcoma[250] is possible, but this is currently considered investigational as these tumours were not

included in the original TCGA paper.[241] The vast majority of low grade endometrioid carcinomas are NSMP or MSI, with *POLE*-mutated, or *TP53*-abnormal tumours accounting for less than 10%. Moreover, the vast majority (95%) of serous carcinoma are *TP53* abnormal.

There is still discussion about whether to apply the molecular classifier to all endometrial carcinomas or just in diagnostically challenging high grade tumours. An important factor in the decision to base therapy selection on genomic subgrouping, includes that most evidence is still retrospective. Prospective studies are awaited and ongoing (e.g., PORTEC 4a). The availability of resources, particularly for *POLE* mutation analysis, are not always accessible. However, perhaps the most important argument against generalised introduction of the molecular classifier is that studies so far have not shown that risk stratification using TCGA molecular data is superior to the European Society for Medical Oncology (ESMO) classification, which relies on clinicopathological data.[229] Also, most evidence in support of the TCGA classification is based on two large but retrospective cohorts.[229,247] There are two additional complexities to *POLE* testing: distinguishing between pathogenic and non-pathogenic mutations,[251] and coexistence of ultramutation (i.e., pathogenic *POLE* mutation) with secondary mutations in *TP53* and/or one or more of the DNA MMR genes.[252] These 'multiple classifier' cases are currently thought to retain the favourable
prognosis of *POLE* mutated tumours, regardless of the MMR or p53 status but this is still an evolving field.

Other markers

Immunohistochemistry (IHC) may be helpful for diagnosis. With a differential diagnosis involving endometrioid and serous carcinomas, loss of expression of DNA MMR proteins, PTEN and/or ARID1A expression would favour endometrioid carcinoma, whereas both serous and endometrioid carcinomas can show aberrant p53 staining and p16 overexpression (both more common in serous carcinoma).[253] Napsin A, HNF1-beta and AMACR (together with negative estrogen receptor (ER))[254,255] may be helpful in diagnosing clear cell carcinoma. A combination of cytokeratin staining, EMA, PAX8 and E-cadherin may also be useful in distinguishing between undifferentiated carcinomas and high grade endometrioid carcinomas since the former generally shows markedly reduced staining with these markers compared to the latter. Neuroendocrine markers can help in recognition of neuroendocrine tumours,[72] and GATA3, TTF1, CD10 and calretinin may help in recognising mesonephric-like carcinoma.[70,71] Finally, a panel including p16, ER, progesterone receptor (PR), and high risk *HPV* in situ hybridisation may be useful in ruling out an HPV-associated endocervical adenocarcinoma.[169]

There are also immunohistochemical markers of prognostic and predictive value. HER2 protein overexpression and/or *HER2* gene amplification is encountered in approximately 25-30% of endometrial serous carcinomas,[256-258] and 14% of endometrial carcinosarcomas.[259] Intratumoural heterogeneity of HER2 expression and gene amplification are common in these tumours and should be taken into consideration when evaluating their HER2 status.[256,260] HER2 positivity in endometrial serous carcinomas is associated with worse progression free and overall survival,[261] but they can be therapeutically targeted by adding trastuzumab to the standard chemotherapy regimen.[262,263] It has been recently shown that *HER2* amplification is characteristic of p53-abnormal endometrial carcinomas as defined in the molecular classification, and is not restricted to the serous carcinoma category.[264] Although currently no official endometrial cancer-specific pathology HER2 scoring guidelines exist, a new set of criteria have been recently proposed based on the successful clinical trial experience.[265]

L1CAM expression has been touted as a marker of aggressive behaviour amongst the NSMP carcinomas and is associated with non-endometrioid histology, distant metastasis and poor survival.[266-268] Mutations in *CTNNB1* (but not necessarily nuclear expression of beta-catenin with IHC) are considered by some to be associated with diminished survival in low grade endometrioid carcinomas, but this is not universally accepted.[247,269,270]

Estrogen receptor (ER) expression has been associated with tumour behaviour and survival in endometrioid tumours.[271,272] ER/PR may assist with tumour classification and may be important to some clinicians for treatment planning, although there is some controversy on whether the expression status of the initial hysterectomy specimen reflects the status of the progressive disease at a later stage. A recent systematic review confirmed improved response rates to endocrine therapy in tumours with positive ER and PR, especially when determined in the metastatic tissue.[273]

WT1 expression may be helpful to distinguish between a primary endometrial serous carcinoma and a tubo-ovarian high grade serous carcinoma since the latter is more likely to be positive. However, up to 30-40% of endometrial serous carcinomas may exhibit some degree of WT1 positivity.[274]

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Note 27 – Pathologically confirmed distant metastases (Core)

Documentation of known metastatic disease is an important part of the pathology report. Such information, if available, should be recorded with as much detail as is available including the site, whether the specimen is a histopathology or cytopathology specimen and with reference to any relevant prior surgical pathology or cytopathology specimens.

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Note 28 – Provisional pathological staging (Core)

The pathological staging must be provided on the pathology report and is therefore a core element. The term 'provisional pathological staging' is used in this dataset to indicate that the stage that is provided may not represent the final tumour stage which should be determined at the multidisciplinary tumour board meeting where all the pathological, clinical and radiological features are available.[76,106,107,275]

The latest version of either FIGO *or* TNM staging, *or* both, can be used depending on local preferences.[76,106,107,275] The FIGO system is in widespread use internationally and is the system used in most clinical trials and research studies. However, UICC or American Joint Committee on Cancer (AJCC) versions of TNM are used or mandated in many parts of the world.[106,107] With regards to updating of staging systems, there is collaboration between FIGO and those agencies responsible for TNM with an agreement to adopt changes to FIGO staging. Following the introduction of a new FIGO Staging System, this is usually incorporated into TNM (both UICC and AJCC versions) at a later date. Apart from minor discrepancies in terminology, the UICC and AJCC 8th edition systems are broadly concurrent.

A tumour should be staged following diagnosis using various appropriate modalities (clinical, radiological, pathological). While the original tumour stage should not be altered following treatment, TNM systems allow staging to be performed on a resection specimen following non-surgical treatment (for example chemotherapy, radiotherapy); in such cases, if a stage is being provided on the pathology report (this is optional), it should be prefixed by 'y' to indicate that this is a post-therapy stage.

McCluggage (2018) suggests "there are several scenarios where tumour involves sites which are not specifically mentioned in the FIGO (or TNM) Staging Systems and it is useful for the pathologist to know the correct staging in these scenarios. Involvement of pelvic serosal structures (cul-de-sac, bladder, sigmoid serosa) are all Stage IIIA, whereas involvement of the omentum and the abdominal peritoneum is Stage IVB."[121]

The reference document TNM Supplement: A commentary on uniform use, 5th edition (C Wittekind et al. editors) may be of assistance when staging.[276]

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References

1 Merlin T, Weston A and Tooher R (2009). Extending an evidence hierarchy to include topics other than treatment: revising the Australian 'levels of evidence'. *BMC Med Res Methodol* 9:34.

2 International Collaboration on Cancer Reporting (2021). *Uterine Malignant and Potentially Malignant Mesenchymal Tumours Histopathology Reporting Guide*. Available from: http://www.iccr-cancer.org/datasets/published-datasets/female-reproductive (Accessed 31st August 2021).

3 Kurman RJ, Carcangiu ML, Herrington CS and Young RH (2014). *WHO classification of tumours of the female reproductive organs*. IARC press, Lyon.

4 WHO Classification of Tumours Editorial Board (2021). *Female Genital Tumours, WHO Classification of Tumours, 5th Edition, Volume 4 - Corrigenda June 2021*. Available from: https://publications.iarc.fr/Book-And-Report-Series/Who-Classification-Of-Tumours/Female-Genital-Tumours-2020 (Accessed 16th June 2021).

5 Landoni F, Maneo A, Zapardiel I, Zanagnolo V and Mangioni C (2012). Class I versus class III radical hysterectomy in stage IB1-IIA cervical cancer. A prospective randomized study. *Eur J Surg Oncol* 38(3):203-209.

6 Ware RA and van Nagell JR (2010). Radical hysterectomy with pelvic lymphadenectomy: indications, technique, and complications. *Obstet Gynecol Int* 2010:DOI:10.1155/2010/587610.

7 Marin F, Plesca M, Bordea CI, Moga MA and Blidaru A (2014). Types of radical hysterectomies : From Thoma Ionescu and Wertheim to present day. *J Med Life* 7(2):172-176.

8 Chiantera V, Rossi M, De Iaco P, Koehler C, Marnitz S, Gallotta V, Margariti AP, Parazzini F, Scambia G, Schneider A and Vercellino GF (2014). Pelvic exenteration for recurrent endometrial adenocarcinoma: a retrospective multi-institutional study about 21 patients. *Int J Gynecol Cancer* 24(5):880-884.

9 Schmidt AM, Imesch P, Fink D and Egger H (2016). Pelvic exenterations for advanced and recurrent endometrial cancer: clinical outcomes of 40 patients. *Int J Gynecol Cancer* 26(4):716-721.

10 Concin N, Creutzberg CL, Vergote I, Cibula D, Mirza MR, Marnitz S, Ledermann JA, Bosse T, Chargari C, Fagotti A, Fotopoulou C, González-Martín A, Lax SF, Lorusso D, Marth C, Morice P, Nout RA, O'Donnell DE, Querleu D, Raspollini MR, Sehouli J, Sturdza AE, Taylor A, Westermann AM, Wimberger P, Colombo N, Planchamp F and Matias-Guiu X (2021). ESGO/ESTRO/ESP Guidelines for the management of patients with endometrial carcinoma. *Virchows Arch*:DOI: 10.1007/s00428-00020-03007-z.

11 Picerno TM, Wasson MN, Gonzalez Rios AR, Zuber MJ, Taylor NP, Hoffman MK and Borowsky ME (2016). Morcellation and the incidence of occult uterine malignancy: a dual-institution review. *Int J Gynecol Cancer* 26(1):149-155.

12 Malpica A, Euscher ED, Hecht JL, Ali-Fehmi R, Quick CM, Singh N, Horn LC, Alvarado-Cabrero I, Matias-Guiu X, Hirschowitz L, Duggan M, Ordi J, Parkash V, Mikami Y, Ruhul Quddus M, Zaino R, Staebler A, Zaloudek C, McCluggage WG and Oliva E (2019). Endometrial carcinoma, grossing and processing issues: recommendations of the international society of gynecologic pathologists. *Int J Gynecol Pathol* 38 Suppl 1(Iss 1 Suppl 1):S9-s24.

13 Holloway RW, Abu-Rustum NR, Backes FJ, Boggess JF, Gotlieb WH, Jeffrey Lowery W, Rossi EC, Tanner EJ and Wolsky RJ (2017). Sentinel lymph node mapping and staging in endometrial cancer: A Society of Gynecologic Oncology literature review with consensus recommendations. *Gynecol Oncol* 146(2):405-415.

14 Westin SN, Lacour RA, Urbauer DL, Luthra R, Bodurka DC, Lu KH and Broaddus RR (2008). Carcinoma of the lower uterine segment: a newly described association with Lynch syndrome. *J Clin Oncol* 26(36):5965-5971.

15 Garg K and Soslow RA (2009). Lynch syndrome (hereditary non-polyposis colorectal cancer) and endometrial carcinoma. *J Clin Pathol* 62(8):679-684.

16 McCluggage WG, Colgan T, Duggan M, Hacker NF, Mulvany N, Otis C, Wilkinson N, Zaino RJ and Hirschowitz L (2013). Data set for reporting of endometrial carcinomas: recommendations from the International Collaboration on Cancer Reporting (ICCR) between United Kingdom, United States, Canada, and Australasia. *Int J Gynecol Pathol* 32(1):45-65.

17 Gemer O, Gdalevich M, Voldarsky M, Barak F, Ben Arie A, Schneider D, Levy T, Anteby EY and Lavie O (2009). Lower uterine segment involvement is associated with adverse outcome in patients with stage I endometroid endometrial cancer: results of a multicenter study. *Eur J Surg Oncol* 35(8):865-869.

18 Kizer NT, Gao F, Guntupalli S, Thaker PH, Powell MA, Goodfellow PJ, Mutch DG and Zighelboim I (2011). Lower uterine segment involvement is associated with poor outcomes in early-stage endometrioid endometrial carcinoma. *Ann Surg Oncol* 18(5):1419-1424.

19 Madom LM, Brown AK, Lui F, Moore RG, Granai CO and Disilvestro PA (2007). Lower uterine segment involvement as a predictor for lymph node spread in endometrial carcinoma. *Gynecol Oncol* 107(1):75-78.

20 Ytre-Hauge S, Husby JA, Magnussen IJ, Werner HM, Salvesen Ø O, Bjørge L, Trovik J, Stefansson IM, Salvesen HB and Haldorsen IS (2015). Preoperative tumor size at MRI predicts deep myometrial invasion, lymph node metastases, and patient outcome in endometrial carcinomas. *Int J Gynecol Cancer* 25(3):459-466.

21 Cox Bauer CM, Greer DM, Kram JJF and Kamelle SA (2016). Tumor diameter as a predictor of lymphatic dissemination in endometrioid endometrial cancer. *Gynecol Oncol* 141(2):199-205.

22 Sozzi G, Uccella S, Berretta R, Petrillo M, Fanfani F, Monterossi G, Ghizzoni V, Frusca T, Ghezzi F, Chiantera V and Scambia G (2018). Tumor size, an additional risk factor of local recurrence in low-risk endometrial cancer: a large multicentric retrospective study. *Int J Gynecol Cancer* 28(4):684-691.

23 Pavlakis K, Rodolakis A, Vagios S, Voulgaris Z, Messini I, Yiannou P, Vlachos A and Panoskaltsis T (2017). Identifiable risk factors for lymph node metastases in grade 1 endometrial carcinoma. *Int J Gynecol Cancer* 27(8):1694-1700.

24 Canlorbe G, Bendifallah S, Laas E, Raimond E, Graesslin O, Hudry D, Coutant C, Touboul C, Bleu G, Collinet P, Cortez A, Daraï E and Ballester M (2016). Tumor size, an additional prognostic factor to include in low-risk endometrial cancer: results of a French multicenter study. *Ann Surg Oncol* 23(1):171-177.

25 Mahdi H, Munkarah AR, Ali-Fehmi R, Woessner J, Shah SN and Moslemi-Kebria M (2015). Tumor size is an independent predictor of lymph node metastasis and survival in early stage endometrioid endometrial cancer. *Arch Gynecol Obstet* 292(1):183-190.

26 Capozzi VA, Sozzi G, Uccella S, Ceni V, Cianciolo A, Gambino G, Armano G, Pugliese M, Scambia G, Chiantera V and Berretta R (2020). Novel preoperative predictive score to evaluate lymphovascular space involvement in endometrial cancer: an aid to the sentinel lymph node algorithm. *Int J Gynecol Cancer* 30(6):806-812.

27 Boyraz G, Salman MC, Gultekin M, Basaran D, Cagan M, Ozgul N and Yuce K (2017). Incidence of lymph node metastasis in surgically staged FIGO IA G1/G2 endometrial cancer with a tumor size of more than 2 cm. *Int J Gynecol Cancer* 27(3):486-492.

28 Oz M, Korkmaz V, Meydanli MM, Sari ME, Cuylan ZF and Gungor T (2017). Is tumor size really important for prediction of lymphatic dissemination in grade 1 endometrial carcinoma with superficial myometrial invasion? *Int J Gynecol Cancer* 27(7):1393-1398.

29 Euscher E, Fox P, Bassett R, Al-Ghawi H, Ali-Fehmi R, Barbuto D, Djordjevic B, Frauenhoffer E, Kim I, Hong SR, Montiel D, Moschiano E, Roma A, Silva E and Malpica A (2013). The pattern of myometrial invasion as a predictor of lymph node metastasis or extrauterine disease in low-grade endometrial carcinoma. *Am J Surg Pathol* 37(11):1728-1736.

30 Singh N, Hirschowitz L, Zaino R, Alvarado-Cabrero I, Duggan MA, Ali-Fehmi R, Euscher E, Hecht JL, Horn LC, Ioffe O, Matias-Guiu X, McCluggage WG, Mikami Y, Ordi J, Parkash V, Quddus MR, Quick CM, Staebler A, Zaloudek C, Nucci M, Malpica A and Oliva E (2019). Pathologic prognostic factors in endometrial carcinoma (other than tumor type and grade). *Int J Gynecol Pathol* 38 Suppl 1(Iss 1 Suppl 1):S93-s113.

31 Amin MB, Edge S, Greene FL, Byrd DR, Brookland RK, Washington MK, Gershenwald JE, Compton CC, Hess KR, Sullivan DC, Jessup JM, Brierley JD, Gaspar LE, Schilsky RL, Balch CM, Winchester DP, Asare EA, Madera M, Gress DM and Meyer LR (eds) (2017). *AJCC Cancer Staging Manual 8th ed.*, Springer, New York.

32 Usubütün A, Ozseker HS, Himmetoglu C, Balci S and Ayhan A (2007). Omentectomy for gynecologic cancer: how much sampling is adequate for microscopic examination? *Arch Pathol Lab Med* 131(10):1578-1581.

33 Skala SL and Hagemann IS (2015). Optimal sampling of grossly normal omentum in staging of gynecologic malignancies. *Int J Gynecol Pathol* 34(3):281-287.

34 WHO Classification of Tumours Editorial Board (2020). *Female Genital Tumours, WHO Classification of Tumours, 5th Edition, Volume 4*. IARC Press, Lyon.

35 Colombo N, Creutzberg C, Amant F, Bosse T, González-Martín A, Ledermann J, Marth C, Nout R, Querleu D, Mirza MR and Sessa C (2016). ESMO-ESGO-ESTRO Consensus Conference on Endometrial Cancer: diagnosis, treatment and follow-up. *Ann Oncol* 27(1):16-41.

36 Lax SF and Kurman RJ (1997). A dualistic model for endometrial carcinogenesis based on immunohistochemical and molecular genetic analyses. *Verh Dtsch Ges Pathol* 81:228-232.

37 Bokhman Ia V and Vishnevskiĭ AS (1984). [2 pathogenetic variants of corpus uteri cancer]. *Akush Ginekol (Mosk)*(4):34-37.

38 Piulats JM, Guerra E, Gil-Martín M, Roman-Canal B, Gatius S, Sanz-Pamplona R, Velasco A, Vidal A and Matias-Guiu X (2017). Molecular approaches for classifying endometrial carcinoma. *Gynecol Oncol* 145(1):200-207.

39 Yeramian A, Moreno-Bueno G, Dolcet X, Catasus L, Abal M, Colas E, Reventos J, Palacios J, Prat J and Matias-Guiu X (2013). Endometrial carcinoma: molecular alterations involved in tumor development and progression. *Oncogene* 32(4):403-413.

40 Kurman RJ, Visvanathan K and Shih Ie M (2013). Bokhman's dualistic model of endometrial carcinoma. Revisited. *Gynecol Oncol* 129(2):271-272.

41 Gilks CB, Oliva E and Soslow RA (2013). Poor interobserver reproducibility in the diagnosis of high-grade endometrial carcinoma. *Am J Surg Pathol* 37(6):874-881.

42 Hoang LN, McConechy MK, Köbel M, Han G, Rouzbahman M, Davidson B, Irving J, Ali RH, Leung S, McAlpine JN, Oliva E, Nucci MR, Soslow RA, Huntsman DG, Gilks CB and Lee CH (2013). Histotype-genotype correlation in 36 high-grade endometrial carcinomas. *Am J Surg Pathol* 37(9):1421-1432.

43 Murali R, Davidson B, Fadare O, Carlson JA, Crum CP, Gilks CB, Irving JA, Malpica A, Matias-Guiu X, McCluggage WG, Mittal K, Oliva E, Parkash V, Rutgers JKL, Staats PN, Stewart CJR, Tornos C and Soslow RA (2019). High-grade Endometrial Carcinomas: Morphologic and Immunohistochemical Features, Diagnostic Challenges and Recommendations. *Int J Gynecol Pathol* 38 Suppl 1(Iss 1 Suppl 1):S40-s63.

44 Azueta A, Gatius S and Matias-Guiu X (2010). Endometrioid carcinoma of the endometrium: pathologic and molecular features. *Semin Diagn Pathol* 27(4):226-240.

45 Gatius S and Matias-Guiu X (2016). Practical issues in the diagnosis of serous carcinoma of the endometrium. *Mod Pathol* 29 Suppl 1:S45-58.

46 Darvishian F, Hummer AJ, Thaler HT, Bhargava R, Linkov I, Asher M and Soslow RA (2004). Serous endometrial cancers that mimic endometrioid adenocarcinomas: a clinicopathologic and immunohistochemical study of a group of problematic cases. *Am J Surg Pathol* 28(12):1568-1578.

47 Garg K and Soslow RA (2012). Strategies for distinguishing low-grade endometrioid and serous carcinomas of endometrium. *Adv Anat Pathol* 19(1):1-10.

48 Bartosch C, Manuel Lopes J and Oliva E (2011). Endometrial carcinomas: a review emphasizing overlapping and distinctive morphological and immunohistochemical features. *Adv Anat Pathol* 18(6):415-437.

49 Rauh-Hain JA, Vargas RJ, Clemmer J, Clark RM, Bradford LS, Growdon WB, Goodman A, Boruta DM, 2nd, Schorge JO and del Carmen MG (2016). Mucinous adenocarcinoma of the endometrium compared with endometrioid endometrial cancer: a SEER analysis. *Am J Clin Oncol* 39(1):43-48.

50 Rawish KR, Desouki MM and Fadare O (2017). Atypical mucinous glandular proliferations in endometrial samplings: follow-up and other clinicopathological findings in 41 cases. *Hum Pathol* 63:53-62.

51 Wong RW, Ralte A, Grondin K, Talia KL and McCluggage WG (2020). Endometrial Gastric (Gastrointestinal)-type Mucinous Lesions: Report of a Series Illustrating the Spectrum of Benign and Malignant Lesions. *Am J Surg Pathol* 44(3):406-419.

52 Bosse T, Nout RA, McAlpine JN, McConechy MK, Britton H, Hussein YR, Gonzalez C, Ganesan R, Steele JC, Harrison BT, Oliva E, Vidal A, Matias-Guiu X, Abu-Rustum NR, Levine DA, Gilks CB and Soslow RA (2018). Molecular classification of grade 3 endometrioid endometrial cancers identifies distinct prognostic subgroups. *Am J Surg Pathol* 42(5):561-568.

53 Soslow RA, Pirog E and Isacson C (2000). Endometrial intraepithelial carcinoma with associated peritoneal carcinomatosis. *Am J Surg Pathol* 24(5):726-732.

54 Fadare O, Zheng W, Crispens MA, Jones HW, Khabele D, Gwin K, Liang SX, Mohammed K, Desouki MM, Parkash V and Hecht JL (2013). Morphologic and other clinicopathologic features of endometrial clear cell carcinoma: a comprehensive analysis of 50 rigorously classified cases. *Am J Cancer Res* 3(1):70-95.

55 Fadare O, Parkash V, Dupont WD, Acs G, Atkins KA, Irving JA, Pirog EC, Quade BJ, Quddus MR, Rabban JT, 3rd, Vang R and Hecht JL (2012). The diagnosis of endometrial carcinomas with clear cells by gynecologic pathologists: an assessment of interobserver variability and associated morphologic features. *Am J Surg Pathol* 36(8):1107-1118.

56 Hariri N, Qarmali M and Fadare O (2018). Endometrial serous carcinoma with clear-cell change: frequency and immunohistochemical analysis. *Int J Surg Pathol* 26(2):126-134.

57 Han G, Soslow RA, Wethington S, Levine DA, Bogomolniy F, Clement PB, Köbel M, Gilks B and DeLair D (2015). Endometrial carcinomas with clear cells: a study of a heterogeneous group of tumors including interobserver variability, mutation analysis, and immunohistochemistry with HNF-1β. *Int J Gynecol Pathol* 34(4):323-333.

58 Rosa-Rosa JM, Leskelä S, Cristóbal-Lana E, Santón A, López-García M, Muñoz G, Pérez-Mies B, Biscuola M, Prat J, Esther O, Soslow RA, Matias-Guiu X and Palacios J (2016). Molecular genetic heterogeneity in undifferentiated endometrial carcinomas. *Mod Pathol* 29(11):1390-1398.

59 Silva EG, Deavers MT and Malpica A (2007). Undifferentiated carcinoma of the endometrium: a review. *Pathology* 39(1):134-138.

60 Busca A, Parra-Herran C, Nofech-Mozes S, Djordjevic B, Ismiil N, Cesari M, Nucci MR and Mirkovic J (2020). Undifferentiated endometrial carcinoma arising in the background of high-grade endometrial carcinoma - Expanding the definition of dedifferentiated endometrial carcinoma. *Histopathology* 77(5):769-780.

61 Tessier-Cloutier B, Coatham M, Carey M, Nelson GS, Hamilton S, Lum A, Soslow RA, Stewart CJ, Postovit LM, Köbel M and Lee CH (2020). SWI/SNF-deficiency defines highly aggressive undifferentiated endometrial carcinoma. *J Pathol Clin Res*:DOI: 10.1002/cjp1002.1188.

62 Matrai CE, Pirog EC and Ellenson LH (2018). Despite diagnostic morphology, many mixed endometrial carcinomas show unexpected immunohistochemical staining patterns. *Int J Gynecol Pathol* 37(5):405-413.

63 Coenegrachts L, Garcia-Dios DA, Depreeuw J, Santacana M, Gatius S, Zikan M, Moerman P, Verbist L, Lambrechts D, Matias-Guiu X and Amant F (2015). Mutation profile and clinical outcome of mixed endometrioid-serous endometrial carcinomas are different from that of pure endometrioid or serous carcinomas. *Virchows Arch* 466(4):415-422.

64 Köbel M, Meng B, Hoang LN, Almadani N, Li X, Soslow RA, Gilks CB and Lee CH (2016). Molecular analysis of mixed endometrial carcinomas shows clonality in most cases. *Am J Surg Pathol* 40(2):166-180.

65 Rabban JT, Gilks CB, Malpica A, Matias-Guiu X, Mittal K, Mutter GL, Oliva E, Parkash V, Ronnett BM, Staats P, Stewart CJR and McCluggage WG (2019). Issues in the differential diagnosis of uterine low-grade endometrioid carcinoma, including mixed endometrial carcinomas: recommendations from the international society of gynecological pathologists. *Int J Gynecol Pathol* 38 Suppl 1(Iss 1 Suppl 1):S25-s39.

66 Hussein YR, Weigelt B, Levine DA, Schoolmeester JK, Dao LN, Balzer BL, Liles G, Karlan B, Köbel M, Lee CH and Soslow RA (2015). Clinicopathological analysis of endometrial carcinomas harboring somatic POLE exonuclease domain mutations. *Mod Pathol* 28(4):505-514.

67 Abdulfatah E, Lordello L, Khurram M, Van de Vijver K, Alosh B, Bandyopadhyay S, Oliva E and Ali-Fehmi R (2019). Predictive histologic factors in carcinosarcomas of the uterus: a multi-institutional study. *Int J Gynecol Pathol* 38(3):205-215.

68 Ferguson SE, Tornos C, Hummer A, Barakat R and Soslow R (2007). Prognostic features of surgical stage I uterine carcinosarcoma. *Am J Surg Pathol* 31(11):1653-1661.

69 El Hallani S AR, Lin D, Måsbäc A, Mateoiu C, McCluggage WG, Nucci MR, Otis CN, Parkash V, Parra-Herran C, Longacre TA, (2021). Mixed endometrioid adenocarcinoma and Müllerian adenosarcoma of the uterus and ovary clinicopathologic characterization with emphasis on its distinction from carcinosarcoma. *American Journal of Surgical Pathology* DOI: 10.1097/PAS.0000000000001643.

70 Euscher ED, Bassett R, Duose DY, Lan C, Wistuba I, Ramondetta L, Ramalingam P and Malpica A (2020). Mesonephric-like carcinoma of the endometrium: a subset of endometrial carcinoma with an aggressive behavior. *Am J Surg Pathol* 44(4):429-443.

71 Horn LC, Höhn AK, Krücken I, Stiller M, Obeck U and Brambs CE (2020). Mesonephric-like adenocarcinomas of the uterine corpus: report of a case series and review of the literature indicating poor prognosis for this subtype of endometrial adenocarcinoma. *J Cancer Res Clin Oncol* 146(4):971-983.

72 Pocrnich CE, Ramalingam P, Euscher ED and Malpica A (2016). Neuroendocrine carcinoma of the endometrium: a clinicopathologic study of 25 cases. *Am J Surg Pathol* 40(5):577-586.

73 Fritz A, Percy C, Jack A, Shanmugaratnam K, Sobin LH, Parkin DM, Whelan SL (eds) (2020). *International Classification of Diseases for Oncology, Third edition, Second revision ICD-O-3.2*. Available from: http://www.iacr.com.fr/index.php?option=com_content&view=category&layout=blog&id=100&Itemid=577 (Accessed 21st January 2021).

74 Abeler VM, Kjørstad KE and Berle E (1992). Carcinoma of the endometrium in Norway: a histopathological and prognostic survey of a total population. *Int J Gynecol Cancer* 2(1):9-22.

75 Prat J (2004). Prognostic parameters of endometrial carcinoma. *Hum Pathol* 35(6):649-662.

76 FIGO Committee on Gynecological Cancer (2009). Revised FIGO staging for carcinoma of the vulva, cervix and endometrium. *Int. J. Gynecol. Obstet.* 105:103-104.

77 Clarke BA and Gilks CB (2010). Endometrial carcinoma: controversies in histopathological assessment of grade and tumour cell type. *J Clin Pathol* 63(5):410-415.

78 Soslow RA, Tornos C, Park KJ, Malpica A, Matias-Guiu X, Oliva E, Parkash V, Carlson J, McCluggage WG and Gilks CB (2019). Endometrial carcinoma diagnosis: use of FIGO grading and genomic subcategories in clinical practice: recommendations of the International Society of Gynecological Pathologists. *Int J Gynecol Pathol* 38 Suppl 1(Iss 1 Suppl 1):S64-s74.

79 Barlin JN, Soslow RA, Lutz M, Zhou QC, St Clair CM, Leitao MM, Jr., Iasonos A, Hensley ML, Barakat RR, Matias-Guiu X and Abu-Rustum NR (2013). Redefining stage I endometrial cancer: incorporating histology, a binary grading system, myometrial invasion, and lymph node assessment. *Int J Gynecol Cancer* 23(9):1620-1628.

80 Barlin JN, Zhou Q, St Clair CM, Iasonos A, Soslow RA, Alektiar KM, Hensley ML, Leitao MM, Jr., Barakat RR and Abu-Rustum NR (2013). Classification and regression tree (CART) analysis of endometrial carcinoma: Seeing the forest for the trees. *Gynecol Oncol* 130(3):452-456.

81 Zhang Q, Qi G, Kanis MJ, Dong R, Cui B, Yang X and Kong B (2017). Comparison among fertility-sparing therapies for well differentiated early-stage endometrial carcinoma and complex atypical hyperplasia. *Oncotarget* 8(34):57642-57653.

82 Wei J, Zhang W, Feng L and Gao W (2017). Comparison of fertility-sparing treatments in patients with early endometrial cancer and atypical complex hyperplasia: A meta-analysis and systematic review. *Medicine (Baltimore)* 96(37):e8034.

83 Qin Y, Yu Z, Yang J, Cao D, Yu M, Wang Y and Shen K (2016). Oral progestin treatment for early-stage endometrial cancer: a systematic review and meta-analysis. *Int J Gynecol Cancer* 26(6):1081-1091.

84 Luo L, Luo B, Zheng Y, Zhang H, Li J and Sidell N (2018). Oral and intrauterine progestogens for atypical endometrial hyperplasia. *Cochrane Database Syst Rev* 12(12):Cd009458.

85 Leitao MM, Jr., Kehoe S, Barakat RR, Alektiar K, Gattoc LP, Rabbitt C, Chi DS, Soslow RA and Abu-Rustum NR (2009). Comparison of D&C and office endometrial biopsy accuracy in patients with FIGO grade 1 endometrial adenocarcinoma. *Gynecol Oncol* 113(1):105-108.

86 Mitchard J and Hirschowitz L (2003). Concordance of FIGO grade of endometrial adenocarcinomas in biopsy and hysterectomy specimens. *Histopathology* 42(4):372-378.

87 Gatius S, Cuevas D, Fernández C, Roman-Canal B, Adamoli V, Piulats JM, Eritja N, Martin-Satue M, Moreno-Bueno G and Matias-Guiu X (2018). Tumor heterogeneity in endometrial carcinoma: practical consequences. *Pathobiology* 85(1-2):35-40.

88 Taylor RR, Zeller J, Lieberman RW and O'Connor DM (1999). An analysis of two versus three grades for endometrial carcinoma. *Gynecol Oncol* 74(1):3-6.

89 Alkushi A, Abdul-Rahman ZH, Lim P, Schulzer M, Coldman A, Kalloger SE, Miller D and Gilks CB (2005). Description of a novel system for grading of endometrial carcinoma and comparison with existing grading systems. *Am J Surg Pathol* 29(3):295-304.

90 Scholten AN, Smit VT, Beerman H, van Putten WL and Creutzberg CL (2004). Prognostic significance and interobserver variability of histologic grading systems for endometrial carcinoma. *Cancer* 100(4):764-772.

91 Lax SF, Kurman RJ, Pizer ES, Wu L and Ronnett BM (2000). A binary architectural grading system for uterine endometrial endometrioid carcinoma has superior reproducibility compared with FIGO grading and identifies subsets of advance-stage tumors with favorable and unfavorable prognosis. *Am J Surg Pathol* 24(9):1201-1208.

92 Creutzberg CL, Nout RA, Lybeert ML, Wárlám-Rodenhuis CC, Jobsen JJ, Mens JW, Lutgens LC, Pras E, van de Poll-Franse LV and van Putten WL (2011). Fifteen-year radiotherapy outcomes of the randomized PORTEC-1 trial for endometrial carcinoma. *Int J Radiat Oncol Biol Phys* 81(4):e631-638.

93 Creasman WT, Morrow CP, Bundy BN, Homesley HD, Graham JE and Heller PB (1987). Surgical pathologic spread patterns of endometrial cancer. A Gynecologic Oncology Group Study. *Cancer* 60(8 Suppl):2035-2041.

94 Koh WJ, Abu-Rustum NR, Bean S, Bradley K, Campos SM, Cho KR, Chon HS, Chu C, Cohn D, Crispens MA, Damast S, Dorigo O, Eifel PJ, Fisher CM, Frederick P, Gaffney DK, George S, Han E, Higgins S, Huh WK, Lurain JR, 3rd, Mariani A, Mutch D, Nagel C, Nekhlyudov L, Fader AN, Remmenga SW, Reynolds RK, Tillmanns T, Ueda S, Wyse E, Yashar CM, McMillian NR and Scavone JL (2018). Uterine Neoplasms, Version 1.2018, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw* 16(2):170-199.

95 Lutz MH, Underwood PB, Jr., Kreutner A, Jr. and Miller MC (1978). Endometrial carcinoma: a new method of classification of therapeutic and prognostic significance. *Gynecol Oncol* 6(1):83-94.

96 Templeton AC (1982). Reporting of myometrial invasion by endometrial cancer. *Histopathology* 6(6):733-737.

97 Kaku T, Tsuruchi N, Tsukamoto N, Hirakawa T, Kamura T and Nakano H (1994). Reassessment of myometrial invasion in endometrial carcinoma. *Obstet Gynecol* 84(6):979-982.

98 Lindauer J, Fowler JM, Manolitsas TP, Copeland LJ, Eaton LA, Ramirez NC and Cohn DE (2003). Is there a prognostic difference between depth of myometrial invasion and the tumor-free distance from the uterine serosa in endometrial cancer? *Gynecol Oncol* 91(3):547-551.

99 Schwab KV, O'Malley DM, Fowler JM, Copeland LJ and Cohn DE (2009). Prospective evaluation of prognostic significance of the tumor-free distance from uterine serosa in surgically staged endometrial adenocarcinoma. *Gynecol Oncol* 112(1):146-149.

100 Kondalsamy-Chennakesavan S, van Vugt S, Sanday K, Nicklin J, Land R, Perrin L, Crandon A and Obermair A (2010). Evaluation of tumor-free distance and depth of myometrial invasion as prognostic factors for lymph node metastases in endometrial cancer. *Int J Gynecol Cancer* 20(7):1217-1221.

101 Chattopadhyay S, Galaal KA, Patel A, Fisher A, Nayar A, Cross P and Naik R (2012). Tumour-free distance from serosa is a better prognostic indicator than depth of invasion and percentage myometrial invasion in endometrioid endometrial cancer. *Bjog* 119(10):1162-1170.

102 Geels YP, Pijnenborg JM, van den Berg-van Erp SH, Snijders MP, Bulten J and Massuger LF (2013). Absolute depth of myometrial invasion in endometrial cancer is superior to the currently used cut-off value of 50%. *Gynecol Oncol* 129(2):285-291.

103 Ozbilen O, Sakarya DK, Bezircioglu I, Kasap B, Yetimalar H and Yigit S (2015). Comparison of myometrial invasion and tumor free distance from uterine serosa in endometrial cancer. *Asian Pac J Cancer Prev* 16(2):519-522.

104 Doghri R, Chaabouni S, Houcine Y, Charfi L, Boujelbene N, Driss M and Mrad K (2018). Evaluation of tumor-free distance and depth of myometrial invasion as prognostic factors in endometrial cancer. *Mol Clin Oncol* 9(1):87-91.

105 Oge T, Comert DK, Cakmak Y and Arık D (2020). Is tumor-free distance an independent prognostic factor for early-stage endometrioid endometrial cancer? *J Oncol* 2020: ID:2934291.

106 Brierley JD, Gospodarowicz MK and Wittekind C (eds) (2016). *UICC TNM Classification of Malignant Tumours, 8th Edition*, Wiley, USA.

107 Amin MB, Edge SB, Greene FL, Byrd DR, Brookland RK, Washington MK, Gershenwald JE, Compton CC, Hess KR, Sullivan DC, Jessup JM, Brierley JD, Gaspar LE, Schilsky RL, Balch CM, Winchester DP, Asare EA, Madera M, Gress DM and Meyer LR (eds) (2017). *AJCC Cancer Staging Manual. 8th Edition*, Springer, New York.

108 van der Putten LJ, van de Vijver K, Bartosch C, Davidson B, Gatius S, Matias-Guiu X, McCluggage WG, Toledo G, van der Wurff AA, Pijnenborg JM, Massuger LF and Bulten J (2017). Reproducibility of measurement of myometrial invasion in endometrial carcinoma. *Virchows Arch* 470(1):63-68.

109 Park JY, Hong DG, Chong GO and Park JY (2019). Tumor budding is a valuable diagnostic parameter in prediction of disease progression of endometrial endometrioid carcinoma. *Pathol Oncol Res* 25(2):723-730.

110 Quick CM, May T, Horowitz NS and Nucci MR (2012). Low-grade, low-stage endometrioid endometrial adenocarcinoma: a clinicopathologic analysis of 324 cases focusing on frequency and pattern of myoinvasion. *Int J Gynecol Pathol* 31(4):337-343.

111 Murray SK, Young RH and Scully RE (2003). Unusual epithelial and stromal changes in myoinvasive endometrioid adenocarcinoma: a study of their frequency, associated diagnostic problems, and prognostic significance. *Int J Gynecol Pathol* 22(4):324-333.

112 Longacre TA and Hendrickson MR (1999). Diffusely infiltrative endometrial adenocarcinoma: an adenoma malignum pattern of myoinvasion. *Am J Surg Pathol* 23(1):69-78.

113 Prodromidou A, Vorgias G, Bakogiannis K, Kalinoglou N and Iavazzo C (2018). MELF pattern of myometrial invasion and role in possible endometrial cancer diagnostic pathway: A systematic review of the literature. *Eur J Obstet Gynecol Reprod Biol* 230:147-152.

114 Joehlin-Price AS, McHugh KE, Stephens JA, Li Z, Backes FJ, Cohn DE, Cohen DW and Suarez AA (2017). The microcystic, elongated, and fragmented (MELF) pattern of invasion: a single institution report of 464 consecutive FIGO grade 1 endometrial endometrioid adenocarcinomas. *Am J Surg Pathol* 41(1):49-55.

115 Pelletier MP, Trinh VQ, Stephenson P, Mes-Masson AM, Samouelian V, Provencher DM and Rahimi K (2017). Microcystic, elongated, and fragmented pattern invasion is mainly associated with isolated tumor cell pattern metastases in International Federation of Gynecology and Obstetrics grade I endometrioid endometrial cancer. *Hum Pathol* 62:33-39.

116 Espinosa I, Serrat N, Zannoni GF, Rovira R, D'Angelo E and Prat J (2017). Endometrioid endometrial carcinomas with microcystic, elongated, and fragmented (MELF) type of myoinvasion: role of immunohistochemistry in the detection of occult lymph node metastases and their clinical significance. *Hum Pathol* 70:6-13.

117 Han G, Lim D, Leitao MM, Jr., Abu-Rustum NR and Soslow RA (2014). Histological features associated with occult lymph node metastasis in FIGO clinical stage I, grade I endometrioid carcinoma. *Histopathology* 64(3):389-398.

118 Kluz T, Łoziński T, Czekierdowska S, Stachowicz N, Gurynowicz G, Chróściel M and Czekierdowski A (2020). Tumor budding index and microvessel density assessment in patients with endometrial cancer: A pilot study. *Oncol Lett* 20(3):2701-2710.

119 Rau TT, Bettschen E, Büchi C, Christe L, Rohner A, Müller MD, Carlson JW, Imboden S and Zlobec I (2020). Prognostic impact of tumor budding in endometrial carcinoma within distinct molecular subgroups. *Mod Pathol*: DOI: 10.1038/s41379-41020-40626-41379.

120 Ali A, Black D and Soslow RA (2007). Difficulties in assessing the depth of myometrial invasion in endometrial carcinoma. *Int J Gynecol Pathol* 26(2):115-123.

121 McCluggage WG (2018). Pathologic staging of endometrial carcinomas: selected areas of difficulty. *Adv Anat Pathol* 25(2):71-84.

122 Soslow RA (2016). Practical issues related to uterine pathology: staging, frozen section, artifacts, and Lynch syndrome. *Mod Pathol* 29 Suppl 1(Suppl 1):S59-77.

123 Peters EEM, Bartosch C, McCluggage WG, Genestie C, Lax SF, Nout R, Oosting J, Singh N, Smit H, Smit V, Van de Vijver KK and Bosse T (2019). Reproducibility of lymphovascular space invasion (LVSI) assessment in endometrial cancer. *Histopathology* 75(1):128-136.

124 McKenney JK, Kong CS and Longacre TA (2005). Endometrial adenocarcinoma associated with subtle lymph-vascular space invasion and lymph node metastasis: a histologic pattern mimicking intravascular and sinusoidal histiocytes. *Int J Gynecol Pathol* 24(1):73-78.

125 Krizova A, Clarke BA, Bernardini MQ, James S, Kalloger SE, Boerner SL and Mulligan AM (2011). Histologic artifacts in abdominal, vaginal, laparoscopic, and robotic hysterectomy specimens: a blinded, retrospective review. *Am J Surg Pathol* 35(1):115-126.

126 Logani S, Herdman AV, Little JV and Moller KA (2008). Vascular "pseudo invasion" in laparoscopic hysterectomy specimens: a diagnostic pitfall. *Am J Surg Pathol* 32(4):560-565.

127 Delair D, Soslow RA, Gardner GJ, Barakat RR and Leitao MM, Jr. (2013). Tumoral displacement into fallopian tubes in patients undergoing robotically assisted hysterectomy for newly diagnosed endometrial cancer. *Int J Gynecol Pathol* 32(2):188-192.

128 Folkins AK, Nevadunsky NS, Saleemuddin A, Jarboe EA, Muto MG, Feltmate CM, Crum CP and Hirsch MS (2010). Evaluation of vascular space involvement in endometrial adenocarcinomas: laparoscopic vs abdominal hysterectomies. *Mod Pathol* 23(8):1073-1079.

129 Kitahara S, Walsh C, Frumovitz M, Malpica A and Silva EG (2009). Vascular pseudoinvasion in laparoscopic hysterectomy specimens for endometrial carcinoma: a grossing artifact? *Am J Surg Pathol* 33(2):298-303.

130 Stewart CJ, Brennan BA, Leung YC and Little L (2009). MELF pattern invasion in endometrial carcinoma: association with low grade, myoinvasive endometrioid tumours, focal mucinous differentiation and vascular invasion. *Pathology* 41(5):454-459.

131 Alexander-Sefre F, Nibbs R, Rafferty T, Ayhan A, Singh N and Jacobs I (2009). Clinical value of immunohistochemically detected lymphatic and vascular invasions in clinically staged endometrioid endometrial cancer. *Int J Gynecol Cancer* 19(6):1074-1079.

132 Pifer PM, Bhargava R, Patel AK, Ling DC, Vargo JA, Orr BC, Sukumvanich P, Courtney-Brooks MB, Boisen MM, Berger JL, Taylor S, Olawaiye AB, Comerci JT, Lesnock JL, Edwards RP and Beriwal S (2020). Is the risk of substantial LVSI in stage I endometrial cancer similar to PORTEC in the North American population? - A single-institution study. *Gynecol Oncol* 159(1):23-29.

133 Bosse T, Peters EE, Creutzberg CL, Jürgenliemk-Schulz IM, Jobsen JJ, Mens JW, Lutgens LC, van der Steen-Banasik EM, Smit VT and Nout RA (2015). Substantial lymph-vascular space invasion (LVSI) is a significant risk factor for recurrence in endometrial cancer--A pooled analysis of PORTEC 1 and 2 trials. *Eur J Cancer* 51(13):1742-1750.

134 Barnes EA, Martell K, Parra-Herran C, Taggar AS, Donovan E and Leung E (2021). Substantial lymphovascular space invasion predicts worse outcomes in early-stage endometrioid endometrial cancer. *Brachytherapy*:DOI: 10.1016/j.brachy.2020.1012.1006.

135 Stålberg K, Bjurberg M, Borgfeldt C, Carlson J, Dahm-Kähler P, Flöter-Rådestad A, Hellman K, Hjerpe E, Holmberg E, Kjølhede P, Marcickiewicz J, Rosenberg P, Tholander B, Åvall-Lundqvist E and Högberg T (2019). Lymphovascular space invasion as a predictive factor for lymph node metastases and survival in endometrioid endometrial cancer - a Swedish Gynecologic Cancer Group (SweGCG) study. *Acta Oncol* 58(11):1628-1633.

136 Nout RA, Smit VT, Putter H, Jürgenliemk-Schulz IM, Jobsen JJ, Lutgens LC, van der Steen-Banasik EM, Mens JW, Slot A, Kroese MC, van Bunningen BN, Ansink AC, van Putten WL and Creutzberg CL (2010). Vaginal brachytherapy versus pelvic external beam radiotherapy for patients with endometrial cancer of high-intermediate risk (PORTEC-2): an open-label, non-inferiority, randomised trial. *Lancet* 375(9717):816-823.

137 Keys HM, Roberts JA, Brunetto VL, Zaino RJ, Spirtos NM, Bloss JD, Pearlman A, Maiman MA and Bell JG (2004). A phase III trial of surgery with or without adjunctive external pelvic radiation therapy in intermediate risk endometrial adenocarcinoma: a Gynecologic Oncology Group study. *Gynecol Oncol* 92(3):744-751.

138 Creutzberg CL, van Putten WL, Koper PC, Lybeert ML, Jobsen JJ, Wárlám-Rodenhuis CC, De Winter KA, Lutgens LC, van den Bergh AC, van de Steen-Banasik E, Beerman H and van Lent M (2000). Surgery and postoperative radiotherapy versus surgery alone for patients with stage-1 endometrial carcinoma: multicentre randomised trial. PORTEC Study Group. Post Operative Radiation Therapy in Endometrial Carcinoma. *Lancet* 355(9213):1404-1411.

139 Wortman BG, Creutzberg CL, Putter H, Jürgenliemk-Schulz IM, Jobsen JJ, Lutgens L, van der Steen-Banasik EM, Mens JWM, Slot A, Kroese MCS, van Triest B, Nijman HW, Stelloo E, Bosse T, de Boer SM, van Putten WLJ, Smit V and Nout RA (2018). Ten-year results of the PORTEC-2 trial for high-intermediate risk endometrial carcinoma: improving patient selection for adjuvant therapy. *Br J Cancer* 119(9):1067-1074.

140 Cahan B, Kim JH, Schultheiss TE, Wong JYC and Chen YJ (2018). Stage I and II endometrial adenocarcinoma: analysis of 2009 FIGO staging revision and impact on survival by adjuvant therapy. *Am J Clin Oncol* 41(3):302-306.

141 Klopp A, Smith BD, Alektiar K, Cabrera A, Damato AL, Erickson B, Fleming G, Gaffney D, Greven K, Lu K, Miller D, Moore D, Petereit D, Schefter T, Small W, Jr., Yashar C and Viswanathan AN (2014). The role of postoperative radiation therapy for endometrial cancer: Executive summary of an American Society for Radiation Oncology evidence-based guideline. *Pract Radiat Oncol* 4(3):137-144.

142 Burke WM, Orr J, Leitao M, Salom E, Gehrig P, Olawaiye AB, Brewer M, Boruta D, Herzog TJ and Shahin FA (2014). Endometrial cancer: a review and current management strategies: part II. *Gynecol Oncol* 134(2):393-402.

143 Fanning J, Alvarez PM, Tsukada Y and Piver MS (1991). Prognostic significance of the extent of cervical involvement by endometrial cancer. *Gynecol Oncol* 40(1):46-47.

144 Mariani A, Webb MJ, Keeney GL and Podratz KC (2001). Routes of lymphatic spread: a study of 112 consecutive patients with endometrial cancer. *Gynecol Oncol* 81(1):100-104.

145 Morrow CP, Bundy BN, Kurman RJ, Creasman WT, Heller P, Homesley HD and Graham JE (1991). Relationship between surgical-pathological risk factors and outcome in clinical stage I and II carcinoma of the endometrium: a Gynecologic Oncology Group study. *Gynecol Oncol* 40(1):55-65.

146 Pitson G, Colgan T, Levin W, Lockwood G, Manchul L, Milosevic M, Murphy J and Fyles A (2002). Stage II endometrial carcinoma: prognostic factors and risk classification in 170 patients. *Int J Radiat Oncol Biol Phys* 53(4):862-867.

147 McCluggage WG, Hirschowitz L, Wilson GE, Oliva E, Soslow RA and Zaino RJ (2011). Significant variation in the assessment of cervical involvement in endometrial carcinoma: an interobserver variation study. *Am J Surg Pathol* 35(2):289-294.

148 Zaino RJ, Abendroth C, Yemelyanova A, Oliva E, Lim D, Soslow R, DeLair D, Hagemann IS, Montone K and Zhu J (2013). Endocervical involvement in endometrial adenocarcinoma is not prognostically significant and the pathologic assessment of the pattern of involvement is not reproducible. *Gynecol Oncol* 128(1):83-87.

149 Abu-Rustum N, Yashar C, Bradley K, Campos SM, Chon HS, Chu C, Clinton L, Cohn D, Crispens MA, Damast S, Diver E, Fisher C, Frederick P, Gaffney DK, George S, Giuntoli R, Han E, Huh WK, Lea J, Mariani A, Mutch D, Nagel C, Nekhlyudov L, Nickles Fader A, Remmenga SW, Reynolds RK, Salani R, Sisodi R, Soliman P, Tanner E, Tillmanns T, Ueda S, Urban R, Wyse E (2020). *NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) Uterine Neoplasms*. Available from: https://www.nccn.org/professionals/physician_gls/pdf/uterine.pdf (Accessed 3rd December 2020).

150 Orezzoli JP, Sioletic S, Olawaiye A, Oliva E and del Carmen MG (2009). Stage II endometrioid adenocarcinoma of the endometrium: clinical implications of cervical stromal invasion. *Gynecol Oncol* 113(3):316-323.

151 Barnes EA, Parra-Herran C, Martell K, Barbera L, Taggar A and Leung E (2019). Vaginal brachytherapy alone for patients with Stage II endometrial cancer with inner half cervical stromal invasion. *Brachytherapy* 18(5):606-611.

152 Sato R, Jobo T and Kuramoto H (2003). Parametrial spread is a prognostic factor in endometrial carcinoma. *Eur J Gynaecol Oncol* 24(3-4):241-245.

153 Watanabe Y, Satou T, Nakai H, Etoh T, Dote K, Fujinami N and Hoshiai H (2010). Evaluation of parametrial spread in endometrial carcinoma. *Obstet Gynecol* 116(5):1027-1034.

154 Yura Y, Tauchi K, Koshiyama M, Konishi I, Yura S, Mori T, Matsushita K, Hayashi M and Yoshida M (1996). Parametrial involvement in endometrial carcinomas: its incidence and correlation with other histological parameters. *Gynecol Oncol* 63(1):114-119.

155 Hirschowitz L, Nucci M and Zaino RJ (2013). Problematic issues in the staging of endometrial, cervical and vulval carcinomas. *Histopathology* 62(1):176-202.

156 Ng TY, Perrin LC, Nicklin JL, Cheuk R and Crandon AJ (2000). Local recurrence in high-risk node-negative stage I endometrial carcinoma treated with postoperative vaginal vault brachytherapy. *Gynecol Oncol* 79(3):490-494.

157 Moschiano EJ, Barbuto DA, Walsh C, Singh K, Euscher ED, Roma AA, Ali-Fehmi R, Frauenhoffer EE, Montiel DP, Kim I, Djordjevic B, Malpica A, Hong SR and Silva EG (2014). Risk factors for recurrence and prognosis of low-grade endometrial adenocarcinoma; vaginal versus other sites. *Int J Gynecol Pathol* 33(3):268-273.

158 Roma AA, Rybicki LA, Barbuto D, Euscher E, Djordjevic B, Frauenhoffer E, Kim I, Hong SR, Montiel D, Ali-Fehmi R, Malpica A and Silva EG (2015). Risk factor analysis of recurrence in low-grade endometrial adenocarcinoma. *Hum Pathol* 46(10):1529-1539.

159 Stolnicu S, Terinte C, Ioanid N and Silva E (2020). Presence of tumor cells in the vagina during surgical treatment could be the source of vaginal recurrence in patients with endometrial carcinoma - A pilot prospective study. *Ann Diagn Pathol* 46:151503.

160 Fujiwara H, Saga Y, Takahashi K, Ohwada M, Enomoto A, Konno R, Tanaka A and Suzuki M (2008). Omental metastases in clinical stage I endometrioid adenocarcinoma. *Int J Gynecol Cancer* 18(1):165-167.

161 Faratian D, Stillie A, Busby-Earle RM, Cowie VJ and Monaghan H (2006). A review of the pathology and management of uterine papillary serous carcinoma and correlation with outcome. *Int J Gynecol Cancer* 16(3):972-978.

162 Usubütün A, Ozseker HS, Himmetoglu C, Balci S and Ayhan A (2007). Omentectomy for gynecologic cancer: how much sampling is adequate for microscopic examination? *Arch Pathol Lab Med* 131:1578-1581.

163 Singh N, Hirschowitz L, Zaino R, Alvarado-Cabrero I, Duggan MA, Ali-Fehmi R, Euscher E, Hecht JL, Horn LC, Ioffe O, Matias-Guiu X, McCluggage WG, Mikami Y, Ordi J, Parkash V, Quddus MR, Quick CM, Staebler A, Zaloudek C, Nucci M, Malpica A and Oliva E (2019). Pathologic prognostic factors in endometrial carcinoma (other than tumor type and grade). *Int J Gynecol Pathol* 38 Suppl 1:S93-s113.

164 McCluggage WG, Judge MJ, Alvarado-Cabrero I, Duggan MA, Horn LC, Hui P, Ordi J, Otis CN, Park KJ, Plante M, Stewart CJR, Wiredu EK, Rous B and Hirschowitz L (2018). Data Set for the Reporting of Carcinomas of the Cervix: Recommendations From the International Collaboration on Cancer Reporting (ICCR). *Int J Gynecol Pathol* 37(3):205-228.

165 Timmers PJ, Zwinderman K, Coens C, Vergote I and Trimbos JB (2010). Lymph node sampling and taking of blind biopsies are important elements of the surgical staging of early ovarian cancer. *Int J Gynecol Cancer* 20(7):1142-1147.

166 Han KH, Park NH, Kim HS, Chung HH, Kim JW and Song YS (2014). Peritoneal cytology: a risk factor of recurrence for non-endometrioid endometrial cancer. *Gynecol Oncol* 134(2):293-296.

167 Hanley KZ, Fadare O, Fisher KE, Atkins KA and Mosunjac MB (2016). Clinical significance of positive pelvic washings in uterine papillary serous carcinoma confined to an endometrial polyp. *Int J Gynecol Pathol* 35(3):249-255.

168 Jobsen JJ, Naudin Ten Cate L, Lybeert ML, Scholten A, van der Steen-Banasik EM, van der Palen J, Stenfert Kroese MC, Slot A, Schutter EM and Siesling S (2011). Outcome of endometrial cancer Stage IIIA with adnexa or serosal involvement only. *Obstet Gynecol Int* 2011:962518.

169 Stewart CJR, Crum CP, McCluggage WG, Park KJ, Rutgers JK, Oliva E, Malpica A, Parkash V, Matias-Guiu X and Ronnett BM (2019). Guidelines to aid in the distinction of endometrial and endocervical carcinomas, and the distinction of independent primary carcinomas of the endometrium and adnexa from metastatic spread between these and other sites. *Int J Gynecol Pathol* 38 Suppl 1(Iss 1 Suppl 1):S75-s92.

170 Heitz F, Amant F, Fotopoulou C, Battista MJ, Wimberger P, Traut A, Fisseler-Eckhoff A, Harter P, Vandenput I, Sehouli J, Schmidt M, Kimmig R, du Bois R and du Bois A (2014). Synchronous ovarian and endometrial cancer--an international multicenter case-control study. *Int J Gynecol Cancer* 24(1):54-60.

171 Reijnen C, Küsters-Vandevelde HVN, Ligtenberg MJL, Bulten J, Oosterwegel M, Snijders M, Sweegers S, de Hullu JA, Vos MC, van der Wurff AAM, van Altena AM, Eijkelenboom A and Pijnenborg JMA (2020). Molecular profiling identifies synchronous endometrial and ovarian cancers as metastatic endometrial cancer with favorable clinical outcome. *Int J Cancer* 147(2):478-489.

172 Chao A, Wu RC, Jung SM, Lee YS, Chen SJ, Lu YL, Tsai CL, Lin CY, Tang YH, Chen MY, Huang HJ, Chou HH, Huang KG, Chang TC, Wang TH and Lai CH (2016). Implication of genomic characterization in synchronous endometrial and ovarian cancers of endometrioid histology. *Gynecol Oncol* 143(1):60-67.

173 Anglesio MS, Wang YK, Maassen M, Horlings HM, Bashashati A, Senz J, Mackenzie R, Grewal DS, Li-Chang H, Karnezis AN, Sheffield BS, McConechy MK, Kommoss F, Taran FA, Staebler A, Shah SP, Wallwiener D, Brucker S, Gilks CB, Kommoss S and Huntsman DG (2016). Synchronous endometrial and ovarian carcinomas: evidence of clonality. *J Natl Cancer Inst* 108(6):djv428.

174 Schultheis AM, Ng CK, De Filippo MR, Piscuoglio S, Macedo GS, Gatius S, Perez Mies B, Soslow RA, Lim RS, Viale A, Huberman KH, Palacios JC, Reis-Filho JS, Matias-Guiu X and Weigelt B (2016). Massively parallel sequencing-based clonality analysis of synchronous endometrioid endometrial and ovarian carcinomas. *J Natl Cancer Inst* 108(6):djv427.

175 Turashvili G, Gómez-Hidalgo NR, Flynn J, Gonen M, Leitao MM, Jr., Soslow RA and Murali R (2019). Risk-based stratification of carcinomas concurrently involving the endometrium and ovary. *Gynecol Oncol* 152(1):38-45.

176 Elishaev E, Gilks CB, Miller D, Srodon M, Kurman RJ and Ronnett BM (2005). Synchronous and metachronous endocervical and ovarian neoplasms: evidence supporting interpretation of the ovarian neoplasms as metastatic endocervical adenocarcinomas simulating primary ovarian surface epithelial neoplasms. *Am J Surg Pathol* 29(3):281-294.

177 Ronnett BM, Yemelyanova AV, Vang R, Gilks CB, Miller D, Gravitt PE and Kurman RJ (2008). Endocervical adenocarcinomas with ovarian metastases: analysis of 29 cases with emphasis on minimally invasive cervical tumors and the ability of the metastases to simulate primary ovarian neoplasms. *Am J Surg Pathol* 32(12):1835-1853.

178 Garg K, Shih K, Barakat R, Zhou Q, Iasonos A and Soslow RA (2009). Endometrial carcinomas in women aged 40 years and younger: tumors associated with loss of DNA mismatch repair proteins comprise a distinct clinicopathologic subset. *Am J Surg Pathol* 33(12):1869-1877.

179 Snyder MJ, Bentley R and Robboy SJ (2006). Transtubal spread of serous adenocarcinoma of the endometrium: an underrecognized mechanism of metastasis. *Int J Gynecol Pathol* 25(2):155-160.

180 Kommoss F, Faruqi A, Gilks CB, Lamshang Leen S, Singh N, Wilkinson N and McCluggage WG (2017). Uterine serous carcinomas frequently metastasize to the fallopian tube and can mimic serous tubal intraepithelial carcinoma. *Am J Surg Pathol* 41(2):161-170.

181 Stewart CJ, Armstrong M, Brennan BA, Hammond IG, Havlat M, Rene Kee A, Koay E, Leung Y, Netreba AN and Ruba S (2010). Coexisting serous carcinoma of the endometrium and the fallopian tube. *Int J Gynecol Pathol* 29(3):278-281.

182 Angelico G, Santoro A, Straccia P, Inzani F, Cianfrini F, Spadola S, Arciuolo D, Valente M, D'Alessandris N, Mulè A and Zannoni GF (2020). Diagnostic and prognostic role of WT1 immunohistochemical expression in uterine carcinoma: a systematic review and meta-analysis across all endometrial carcinoma histotypes. *Diagnostics (Basel)* 10(9):637.

183 Martell K, Doll C, Barnes EA, Phan T, Leung E and Taggar A (2019). Radiotherapy practices in postoperative endometrial cancer: A survey of the ABS membership. *Brachytherapy* 18(6):741-746.

184 Bingham B, Orton A, Boothe D, Stoddard G, Huang YJ, Gaffney DK and Poppe MM (2017). Brachytherapy improves survival in stage III endometrial cancer with cervical involvement. *Int J Radiat Oncol Biol Phys* 97(5):1040-1050.

185 Mitra D, Klopp AH and Viswanathan AN (2016). Pros and cons of vaginal brachytherapy after external beam radiation therapy in endometrial cancer. *Gynecol Oncol* 140(1):167-175.

186 Yamani F and Fadare O (2016). Arias-Stella reaction in progestin-treated endometrioid adenocarcinoma: a potential diagnostic pitfall. *Int J Surg Pathol* 24(4):330-331.

187 Mutter GL, Baak JP, Crum CP, Richart RM, Ferenczy A and Faquin WC (2000). Endometrial precancer diagnosis by histopathology, clonal analysis, and computerized morphometry. *J Pathol* 190(4):462-469.

188 Lacey JV, Jr., Chia VM, Rush BB, Carreon DJ, Richesson DA, Ioffe OB, Ronnett BM, Chatterjee N, Langholz B, Sherman ME and Glass AG (2012). Incidence rates of endometrial hyperplasia, endometrial cancer and hysterectomy from 1980 to 2003 within a large prepaid health plan. *Int J Cancer* 131(8):1921-1929.

189 Lacey JV, Jr., Sherman ME, Rush BB, Ronnett BM, Ioffe OB, Duggan MA, Glass AG, Richesson DA, Chatterjee N and Langholz B (2010). Absolute risk of endometrial carcinoma during 20-year follow-up among women with endometrial hyperplasia. *J Clin Oncol* 28(5):788-792.

190 Semere LG, Ko E, Johnson NR, Vitonis AF, Phang LJ, Cramer DW and Mutter GL (2011). Endometrial intraepithelial neoplasia: clinical correlates and outcomes. *Obstet Gynecol* 118(1):21-28.

191 Trimble CL, Kauderer J, Zaino R, Silverberg S, Lim PC, Burke JJ, 2nd, Alberts D and Curtin J (2006). Concurrent endometrial carcinoma in women with a biopsy diagnosis of atypical endometrial hyperplasia: a Gynecologic Oncology Group study. *Cancer* 106(4):812-819.

192 Baergen RN, Warren CD, Isacson C and Ellenson LH (2001). Early uterine serous carcinoma: clonal origin of extrauterine disease. *Int J Gynecol Pathol* 20(3):214-219.

193 Wheeler DT, Bell KA, Kurman RJ and Sherman ME (2000). Minimal uterine serous carcinoma: diagnosis and clinicopathologic correlation. *Am J Surg Pathol* 24(6):797-806.

194 Fadare O, Liang SX, Ulukus EC, Chambers SK and Zheng W (2006). Precursors of endometrial clear cell carcinoma. *Am J Surg Pathol* 30(12):1519-1530.

195 Fadare O and Zheng W (2009). Insights into endometrial serous carcinogenesis and progression. *Int J Clin Exp Pathol* 2(5):411-432.

196 Trinh VQ, Pelletier MP, Echelard P, Warkus T, Sauthier P, Gougeon F, Mès-Masson AM, Provencher DM and Rahimi K (2020). Distinct histologic, immunohistochemical and clinical features associated with serous endometrial intraepithelial carcinoma involving polyps. *Int J Gynecol Pathol* 39(2):128-135.

197 Lin MC, Lomo L, Baak JP, Eng C, Ince TA, Crum CP and Mutter GL (2009). Squamous morules are functionally inert elements of premalignant endometrial neoplasia. *Mod Pathol* 22(2):167-174.

198 Ip PP, Irving JA, McCluggage WG, Clement PB and Young RH (2013). Papillary proliferation of the endometrium: a clinicopathologic study of 59 cases of simple and complex papillae without cytologic atypia. *Am J Surg Pathol* 37(2):167-177.

199 Stewart CJR, Bigby S, Giardina T, Grieu-Iacopetta F and Amanuel B (2018). An immunohistochemical and molecular analysis of papillary proliferation of the endometrium. *Pathology* 50(3):286-292.

200 Kitchener H, Swart AM, Qian Q, Amos C and Parmar MK (2009). Efficacy of systematic pelvic lymphadenectomy in endometrial cancer (MRC ASTEC trial): a randomised study. *Lancet* 373(9658):125-136.

201 Benedetti Panici P, Basile S, Maneschi F, Alberto Lissoni A, Signorelli M, Scambia G, Angioli R, Tateo S, Mangili G, Katsaros D, Garozzo G, Campagnutta E, Donadello N, Greggi S, Melpignano M, Raspagliesi F, Ragni N, Cormio G, Grassi R, Franchi M, Giannarelli D, Fossati R, Torri V, Amoroso M, Crocè C and Mangioni C (2008). Systematic pelvic lymphadenectomy vs. no lymphadenectomy in early-stage endometrial carcinoma: randomized clinical trial. *J Natl Cancer Inst* 100(23):1707-1716.

202 Todo Y, Kato H, Kaneuchi M, Watari H, Takeda M and Sakuragi N (2010). Survival effect of para-aortic lymphadenectomy in endometrial cancer (SEPAL study): a retrospective cohort analysis. *Lancet* 375(9721):1165-1172.

203 Renz M, Marjon N, Devereaux K, Raghavan S, Folkins AK and Karam A (2020). Immediate intraoperative sentinel lymph node analysis by frozen section is predictive of lymph node metastasis in endometrial cancer. *J Robot Surg* 14(1):35-40.

204 Ballester M, Dubernard G, Bats AS, Heitz D, Mathevet P, Marret H, Querleu D, Golfier F, Leblanc E, Rouzier R and Daraï E (2012). Comparison of diagnostic accuracy of frozen section with imprint cytology for intraoperative examination of sentinel lymph node in early-stage endometrial cancer: results of Senti-Endo study. *Ann Surg Oncol* 19(11):3515-3521.

205 Blakely M, Liu Y, Rahaman J, Prasad-Hayes M, Tismenetsky M, Wang X, Nair N, Dresser KA, Nagarsheth N and Kalir T (2019). Sentinel lymph node ultra-staging as a supplement for endometrial cancer intraoperative frozen section deficiencies. *Int J Gynecol Pathol* 38(1):52-58.

206 Sinno AK, Fader AN, Roche KL, Giuntoli RL, 2nd and Tanner EJ (2014). A comparison of colorimetric versus fluorometric sentinel lymph node mapping during robotic surgery for endometrial cancer. *Gynecol Oncol* 134(2):281-286.

207 Bodurtha Smith AJ, Fader AN and Tanner EJ (2017). Sentinel lymph node assessment in endometrial cancer: a systematic review and meta-analysis. *Am J Obstet Gynecol* 216(5):459-476.e410.

208 Bogani G, Murgia F, Ditto A and Raspagliesi F (2019). Sentinel node mapping vs. lymphadenectomy in endometrial cancer: A systematic review and meta-analysis. *Gynecol Oncol* 153(3):676-683.

209 Buda A, Di Martino G, Restaino S, De Ponti E, Monterossi G, Giuliani D, Ercoli A, Dell'Orto F, Dinoi G, Grassi T, Scambia G and Fanfani F (2017). The impact on survival of two different staging strategies in apparent early stage endometrial cancer comparing sentinel lymph nodes mapping algorithm and selective lymphadenectomy: An Italian retrospective analysis of two reference centers. *Gynecol Oncol* 147(3):528-534.

210 Tschernichovsky R, Diver EJ, Schorge JO and Goodman A (2016). The role of lymphadenectomy versus sentinel lymph node biopsy in early-stage endometrial cancer: a review of the literature. *Am J Clin Oncol* 39(5):516-521.

211 Frumovitz M, Plante M, Lee PS, Sandadi S, Lilja JF, Escobar PF, Gien LT, Urbauer DL and Abu-Rustum NR (2018). Near-infrared fluorescence for detection of sentinel lymph nodes in women with cervical and uterine cancers (FILM): a randomised, phase 3, multicentre, non-inferiority trial. *Lancet Oncol* 19(10):1394-1403.

212 Leitao MM, Jr. (2016). Sentinel lymph node mapping in patients with endometrial carcinoma: less can be more. *Curr Obstet Gynecol Rep* 5(4):279-285.

213 Accorsi GS, Paiva LL, Schmidt R, Vieira M, Reis R and Andrade C (2020). Sentinel lymph node mapping vs systematic lymphadenectomy for endometrial cancer: surgical morbidity and lymphatic complications. *J Minim Invasive Gynecol* 27(4):938-945.e932.

214 Helgers RJA, Winkens B, Slangen BFM and Werner HMJ (2020). Lymphedema and post-operative complications after sentinel lymph node biopsy versus lymphadenectomy in endometrial carcinomas- a systematic review and meta-analysis. *J Clin Med* 10(1):120.

215 Kim CH, Khoury-Collado F, Barber EL, Soslow RA, Makker V, Leitao MM, Jr., Sonoda Y, Alektiar KM, Barakat RR and Abu-Rustum NR (2013). Sentinel lymph node mapping with pathologic ultrastaging: a valuable tool for assessing nodal metastasis in low-grade endometrial cancer with superficial myoinvasion. *Gynecol Oncol* 131(3):714-719.

216 Daraï E, Dubernard G, Bats AS, Heitz D, Mathevet P, Marret H, Querleu D, Golfier F, Leblanc E, Rouzier R and Ballester M (2015). Sentinel node biopsy for the management of early stage endometrial cancer: long-term results of the SENTI-ENDO study. *Gynecol Oncol* 136(1):54-59.

217 Ignatov A, Lebius C, Ignatov T, Ivros S, Knueppel R, Papathemelis T, Ortmann O and Eggemann H (2019). Lymph node micrometastases and outcome of endometrial cancer. *Gynecol Oncol* 154(3):475-479.

218 Concin N, Matias-Guiu X, Vergote I, Cibula D, Mirza MR, Marnitz S, Ledermann J, Bosse T, Chargari C, Fagotti A, Fotopoulou C, Gonzalez Martin A, Lax S, Lorusso D, Marth C, Morice P, Nout RA, O'Donnell D, Querleu D, Raspollini MR, Sehouli J, Sturdza A, Taylor A, Westermann A, Wimberger P, Colombo N, Planchamp F and Creutzberg CL (2021). ESGO/ESTRO/ESP guidelines for the management of patients with endometrial carcinoma. *Int J Gynecol Cancer* 31(1):12-39.

219 Euscher E, Sui D, Soliman P, Westin S, Ramalingam P, Bassett R and Malpica A (2018). Ultrastaging of sentinel lymph nodes in endometrial carcinoma according to use of 2 different methods. *Int J Gynecol Pathol* 37(3):242-251.

220 Kim CH, Soslow RA, Park KJ, Barber EL, Khoury-Collado F, Barlin JN, Sonoda Y, Hensley ML, Barakat RR and Abu-Rustum NR (2013). Pathologic ultrastaging improves micrometastasis detection in sentinel lymph nodes during endometrial cancer staging. *Int J Gynecol Cancer* 23(5):964-970.

221 Grassi T, Dell'Orto F, Jaconi M, Lamanna M, De Ponti E, Paderno M, Landoni F, Leone BE, Fruscio R and Buda A (2020). Two ultrastaging protocols for the detection of lymph node metastases in early-stage cervical and endometrial cancers. *Int J Gynecol Cancer* 30(9):1404-1410.

222 Mueller JJ, Pedra Nobre S, Braxton K, Alektiar KM, Leitao MM, Jr., Aghajanian C, Ellenson LH and Abu-Rustum NR (2020). Incidence of pelvic lymph node metastasis using modern FIGO staging and sentinel lymph node mapping with ultrastaging in surgically staged patients with endometrioid and serous endometrial carcinoma. *Gynecol Oncol* 157(3):619-623.

223 Cho KR, Cooper K, Croce S, Djordevic B, Herrington S, Howitt B, Hui P, Ip P, Koebel M, Lax S, Quade BJ, Shaw P, Vidal A, Yemelyanova A, Clarke B, Hedrick Ellenson L, Longacre TA, Shih IM, McCluggage WG, Malpica A, Oliva E, Parkash V and Matias-Guiu X (2019). International Society of Gynecological Pathologists (ISGyP) endometrial cancer project: guidelines from the special techniques and ancillary studies group. *Int J Gynecol Pathol* 38 Suppl 1(Iss 1 Suppl 1):S114-s122.

224 Egoavil C, Alenda C, Castillejo A, Paya A, Peiro G, Sánchez-Heras AB, Castillejo MI, Rojas E, Barberá VM, Cigüenza S, Lopez JA, Piñero O, Román MJ, Martínez-Escoriza JC, Guarinos C, Perez-Carbonell L, Aranda FI and Soto JL (2013). Prevalence of Lynch syndrome among patients with newly diagnosed endometrial cancers. *PLoS One* 8(11):e79737.

225 Stoffel E, Mukherjee B, Raymond VM, Tayob N, Kastrinos F, Sparr J, Wang F, Bandipalliam P, Syngal S and Gruber SB (2009). Calculation of risk of colorectal and endometrial cancer among patients with Lynch syndrome. *Gastroenterology* 137(5):1621-1627.

226 Cuatrecasas M, Gorostiaga I, Riera C, Saperas E, Llort G, Costa I, Matias-Guiu X, Carrato C, Navarro M, Pineda M, Dueñas N, Brunet J, Marco V, Trias I, Busteros JI, Mateu G, Balaguer F, Fernández-Figueras MT, Esteller M and Musulén E (2020). Complete loss of EPCAM immunoexpression identifies EPCAM deletion carriers in MSH2-negative colorectal neoplasia. *Cancers (Basel)* 12(10):2803.

227 Dámaso E, González-Acosta M, Vargas-Parra G, Navarro M, Balmaña J, Ramon YCT, Tuset N, Thompson BA, Marín F, Fernández A, Gómez C, Velasco À, Solanes A, Iglesias S, Urgel G, López C, Del Valle J, Campos O, Santacana M, Matias-Guiu X, Lázaro C, Valle L, Brunet J, Pineda M and Capellá G (2020). Comprehensive constitutional genetic and epigenetic characterization of Lynch-like individuals. *Cancers (Basel)* 12(7):1799.

228 Frolova AI, Babb SA, Zantow E, Hagemann AR, Powell MA, Thaker PH, Gao F and Mutch DG (2015). Impact of an immunohistochemistry-based universal screening protocol for Lynch syndrome in endometrial cancer on genetic counseling and testing. *Gynecol Oncol* 137(1):7-13.

229 Talhouk A, McConechy MK, Leung S, Li-Chang HH, Kwon JS, Melnyk N, Yang W, Senz J, Boyd N, Karnezis AN, Huntsman DG, Gilks CB and McAlpine JN (2015). A clinically applicable molecular-based classification for endometrial cancers. *Br J Cancer* 113(2):299-310.

230 Green AK, Feinberg J and Makker V (2020). A review of immune checkpoint blockade therapy in endometrial cancer. *Am Soc Clin Oncol Educ Book* 40:1-7.

231 Umar A, Boland CR, Terdiman JP, Syngal S, de la Chapelle A, Rüschoff J, Fishel R, Lindor NM, Burgart LJ, Hamelin R, Hamilton SR, Hiatt RA, Jass J, Lindblom A, Lynch HT, Peltomaki P, Ramsey SD, Rodriguez-Bigas MA, Vasen HF, Hawk ET, Barrett JC, Freedman AN and Srivastava S (2004). Revised Bethesda Guidelines for hereditary nonpolyposis colorectal cancer (Lynch syndrome) and microsatellite instability. *J Natl Cancer Inst* 96(4):261-268.

232 Crosbie EJ, Ryan NAJ, Arends MJ, Bosse T, Burn J, Cornes JM, Crawford R, Eccles D, Frayling IM, Ghaem-Maghami S, Hampel H, Kauff ND, Kitchener HC, Kitson SJ, Manchanda R, McMahon RFT, Monahan KJ, Menon U, Møller P, Möslein G, Rosenthal A, Sasieni P, Seif MW, Singh N, Skarrott P, Snowsill TM, Steele R, Tischkowitz M and Evans DG (2019). The Manchester International Consensus Group recommendations for the management of gynecological cancers in Lynch syndrome. *Genet Med* 21(10):2390-2400.

233 Hissong E, Crowe EP, Yantiss RK and Chen YT (2018). Assessing colorectal cancer mismatch repair status in the modern era: a survey of current practices and re-evaluation of the role of microsatellite instability testing. *Mod Pathol* 31(11):1756-1766.

234 Pécriaux A, Favre L, Calderaro J, Charpy C, Derman J and Pujals A (2021). Detection of microsatellite instability in a panel of solid tumours with the Idylla MSI Test using extracted DNA. *J Clin Pathol* 74(1):36-42.

235 Middha S, Zhang L, Nafa K, Jayakumaran G, Wong D, Kim HR, Sadowska J, Berger MF, Delair DF, Shia J, Stadler Z, Klimstra DS, Ladanyi M, Zehir A and Hechtman JF (2017). Reliable pan-cancer microsatellite instability assessment by using targeted next-generation sequencing data. *JCO Precis Oncol* 2017:DOI: 10.1200/PO.1217.00084.

236 Mojtahed A, Schrijver I, Ford JM, Longacre TA and Pai RK (2011). A two-antibody mismatch repair protein immunohistochemistry screening approach for colorectal carcinomas, skin sebaceous tumors, and gynecologic tract carcinomas. *Mod Pathol* 24(7):1004-1014.

237 Ryan NAJ, Glaire MA, Blake D, Cabrera-Dandy M, Evans DG and Crosbie EJ (2019). The proportion of endometrial cancers associated with Lynch syndrome: a systematic review of the literature and meta-analysis. *Genet Med* 21(10):2167-2180.

238 Samaison L, Grall M, Staroz F and Uguen A (2019). Microsatellite instability diagnosis using the fully automated Idylla platform: feasibility study of an in-house rapid molecular testing ancillary to immunohistochemistry in pathology laboratories. *J Clin Pathol* 72(12):830-835.

239 Møller P, Seppälä TT, Bernstein I, Holinski-Feder E, Sala P, Gareth Evans D, Lindblom A, Macrae F, Blanco I, Sijmons RH, Jeffries J, Vasen HFA, Burn J, Nakken S, Hovig E, Rødland EA, Tharmaratnam K, de Vos Tot Nederveen Cappel WH, Hill J, Wijnen JT, Jenkins MA, Green K, Lalloo F, Sunde L, Mints M, Bertario L, Pineda M, Navarro M, Morak M, Renkonen-Sinisalo L, Valentin MD, Frayling IM, Plazzer JP, Pylvanainen K, Genuardi M, Mecklin JP, Moeslein G, Sampson JR and Capella G (2018). Cancer risk and survival in path_MMR carriers by gene and gender up to 75 years of age: a report from the Prospective Lynch Syndrome Database. *Gut* 67(7):1306-1316.

240 Ten Broeke SW, van der Klift HM, Tops CMJ, Aretz S, Bernstein I, Buchanan DD, de la Chapelle A, Capella G, Clendenning M, Engel C, Gallinger S, Gomez Garcia E, Figueiredo JC, Haile R, Hampel HL, Hopper JL, Hoogerbrugge N, von Knebel Doeberitz M, Le Marchand L, Letteboer TGW, Jenkins MA, Lindblom A, Lindor NM, Mensenkamp AR, Møller P, Newcomb PA, van Os TAM, Pearlman R, Pineda M, Rahner N, Redeker EJW, Olderode-Berends MJW, Rosty C, Schackert HK, Scott R, Senter L, Spruijt L, Steinke-Lange V, Suerink M, Thibodeau S, Vos YJ, Wagner A, Winship I, Hes FJ, Vasen HFA, Wijnen JT, Nielsen M and Win AK (2018). Cancer risks for PMS2-associated Lynch Syndrome. *J Clin Oncol* 36(29):2961-2968.

241 Kandoth C, Schultz N, Cherniack AD, Akbani R, Liu Y, Shen H, Robertson AG, Pashtan I, Shen R, Benz CC, Yau C, Laird PW, Ding L, Zhang W, Mills GB, Kucherlapati R, Mardis ER and Levine DA (2013). Integrated genomic characterization of endometrial carcinoma. *Nature* 497(7447):67-73.

242 Billingsley CC, Cohn DE, Mutch DG, Hade EM and Goodfellow PJ (2016). Prognostic significance of POLE exonuclease domain mutations in high-grade endometrioid endometrial cancer on survival and recurrence: a subanalysis. *Int J Gynecol Cancer* 26(5):933-938.

243 Church DN, Stelloo E, Nout RA, Valtcheva N, Depreeuw J, ter Haar N, Noske A, Amant F, Tomlinson IP, Wild PJ, Lambrechts D, Jürgenliemk-Schulz IM, Jobsen JJ, Smit VT, Creutzberg CL and Bosse T (2015). Prognostic significance of POLE proofreading mutations in endometrial cancer. *J Natl Cancer Inst* 107(1):402.

244 Stasenko M, Tunnage I, Ashley CW, Rubinstein MM, Latham AJ, Da Cruz Paula A, Mueller JJ, Leitao MM, Jr., Friedman CF, Makker V, Soslow RA, DeLair DF, Hyman DM, Zamarin D, Alektiar KM, Aghajanian CA, Abu-Rustum NR, Weigelt B and Cadoo KA (2020). Clinical outcomes of patients with POLE mutated endometrioid endometrial cancer. *Gynecol Oncol* 156(1):194-202.

245 Kommoss S, McConechy MK, Kommoss F, Leung S, Bunz A, Magrill J, Britton H, Kommoss F, Grevenkamp F, Karnezis A, Yang W, Lum A, Krämer B, Taran F, Staebler A, Lax S, Brucker SY, Huntsman DG, Gilks CB, McAlpine JN and Talhouk A (2018). Final validation of the ProMisE molecular classifier for endometrial carcinoma in a large population-based case series. *Ann Oncol* 29(5):1180-1188.

246 McAlpine J, Leon-Castillo A and Bosse T (2018). The rise of a novel classification system for endometrial carcinoma; integration of molecular subclasses. *J Pathol* 244(5):538-549.

247 Stelloo E, Nout RA, Osse EM, Jürgenliemk-Schulz IJ, Jobsen JJ, Lutgens LC, van der Steen-Banasik EM, Nijman HW, Putter H, Bosse T, Creutzberg CL and Smit VT (2016). Improved risk assessment by integrating molecular and clinicopathological factors in early-stage endometrial cancer-combined analysis of the PORTEC cohorts. *Clin Cancer Res* 22(16):4215-4224.

248 DeLair DF, Burke KA, Selenica P, Lim RS, Scott SN, Middha S, Mohanty AS, Cheng DT, Berger MF, Soslow RA and Weigelt B (2017). The genetic landscape of endometrial clear cell carcinomas. *J Pathol* 243(2):230-241.

249 Howitt BE, Dong F, Vivero M, Shah V, Lindeman N, Schoolmeester JK, Baltay M, MacConaill L, Sholl LM, Nucci MR and McCluggage WG (2020). Molecular characterization of neuroendocrine carcinomas of the endometrium: representation in all 4 TCGA groups. *Am J Surg Pathol* 44(11):1541-1548.

250 Travaglino A, Raffone A, Gencarelli A, Mollo A, Guida M, Insabato L, Santoro A, Zannoni GF and Zullo F (2020). TCGA classification of endometrial cancer: the place of carcinosarcoma. *Pathol Oncol Res* 26(4):2067-2073.

251 León-Castillo A, Britton H, McConechy MK, McAlpine JN, Nout R, Kommoss S, Brucker SY, Carlson JW, Epstein E, Rau TT, Bosse T, Church DN and Gilks CB (2020). Interpretation of somatic POLE mutations in endometrial carcinoma. *J Pathol* 250(3):323-335.

252 León-Castillo A, Gilvazquez E, Nout R, Smit VT, McAlpine JN, McConechy M, Kommoss S, Brucker SY, Carlson JW, Epstein E, Rau TT, Soslow RA, Ganesan R, Matias-Guiu X, Oliva E, Harrison BT, Church DN, Gilks CB and Bosse T (2020). Clinicopathological and molecular characterisation of 'multiple-classifier' endometrial carcinomas. *J Pathol* 250(3):312-322.

253 Soslow RA (2013). High-grade endometrial carcinomas - strategies for typing. *Histopathology* 62(1):89-110.

254 Fadare O, Parkash V, Gwin K, Hanley KZ, Jarboe EA, Liang SX, Quick CM, Zheng W, Rawish KR, Hecht JL and Desouki MM (2013). Utility of α-methylacyl-coenzyme-A racemase (p504s) immunohistochemistry in distinguishing endometrial clear cell carcinomas from serous and endometrioid carcinomas. *Hum Pathol* 44(12):2814-2821.

255 Fadare O, Desouki MM, Gwin K, Hanley KZ, Jarboe EA, Liang SX, Quick CM, Zheng W, Parkash V and Hecht JL (2014). Frequent expression of napsin A in clear cell carcinoma of the endometrium: potential diagnostic utility. *Am J Surg Pathol* 38(2):189-196.

256 Buza N, English DP, Santin AD and Hui P (2013). Toward standard HER2 testing of endometrial serous carcinoma: 4-year experience at a large academic center and recommendations for clinical practice. *Mod Pathol* 26(12):1605-1612.

257 Halle MK, Tangen IL, Berg HF, Hoivik EA, Mauland KK, Kusonmano K, Berg A, Hurtado A, Kalland KH, Øyan AM, Stefansson I, Vintermyr OK, Werner HM, Haldorsen IS, Trovik J, Salvesen HB and Krakstad C (2018). HER2 expression patterns in paired primary and metastatic endometrial cancer lesions. *Br J Cancer* 118(3):378-387.

258 Zhao S, Choi M, Overton JD, Bellone S, Roque DM, Cocco E, Guzzo F, English DP, Varughese J, Gasparrini S, Bortolomai I, Buza N, Hui P, Abu-Khalaf M, Ravaggi A, Bignotti E, Bandiera E, Romani C, Todeschini P, Tassi R, Zanotti L, Carrara L, Pecorelli S, Silasi DA, Ratner E, Azodi M, Schwartz PE, Rutherford TJ, Stiegler AL, Mane S, Boggon TJ, Schlessinger J, Lifton RP and Santin AD (2013). Landscape of somatic single-nucleotide and copy-number mutations in uterine serous carcinoma. *Proc Natl Acad Sci U S A* 110(8):2916-2921.

259 Rottmann D, Snir OL, Wu X, Wong S, Hui P, Santin AD and Buza N (2020). HER2 testing of gynecologic carcinosarcomas: tumor stratification for potential targeted therapy. *Mod Pathol* 33(1):118-127.

260 Buza N and Hui P (2013). Marked heterogeneity of HER2/NEU gene amplification in endometrial serous carcinoma. *Genes Chromosomes Cancer* 52(12):1178-1186.

261 Erickson BK, Najjar O, Damast S, Blakaj A, Tymon-Rosario J, Shahi M, Santin A, Klein M, Dolan M, Cimino-Mathews A, Buza N, Ferriss JS, Stone RL, Khalifa M and Fader AN (2020). Human epidermal growth factor 2 (HER2) in early stage uterine serous carcinoma: A multi-institutional cohort study. *Gynecol Oncol* 159(1):17-22.

262 Fader AN, Roque DM, Siegel E, Buza N, Hui P, Abdelghany O, Chambers S, Secord AA, Havrilesky L, O'Malley DM, Backes FJ, Nevadunsky N, Edraki B, Pikaart D, Lowery W, ElSahwi K, Celano P, Bellone S, Azodi M, Litkouhi B, Ratner E, Silasi DA, Schwartz PE and Santin AD (2020). Randomized phase II trial of carboplatin-paclitaxel compared with carboplatin-paclitaxel-trastuzumab in advanced (stage III-IV) or recurrent uterine serous carcinomas that overexpress Her2/Neu (NCT01367002): updated overall survival analysis. *Clin Cancer Res* 26(15):3928-3935.

263 Fader AN, Roque DM, Siegel E, Buza N, Hui P, Abdelghany O, Chambers SK, Secord AA, Havrilesky L, O'Malley DM, Backes F, Nevadunsky N, Edraki B, Pikaart D, Lowery W, ElSahwi KS, Celano P, Bellone S, Azodi M, Litkouhi B, Ratner E, Silasi DA, Schwartz PE and Santin AD (2018). Randomized phase II trial of carboplatin-paclitaxel versus carboplatin-paclitaxel-trastuzumab in uterine serous carcinomas that overexpress human epidermal growth factor receptor 2/neu. *J Clin Oncol* 36(20):2044-2051.

264 Vermij L, Horeweg N, Leon-Castillo A, Rutten TA, Mileshkin LR, Mackay HJ, Leary A, Powell ME, Singh N, Crosbie EJ, Smit V, Creutzberg CL and Bosse T (2020). HER2 Status in high-risk endometrial cancers (PORTEC-3): relationship with histotype, molecular classification, and clinical outcomes. *Cancers (Basel)* 13(1):44.

265 Buza N (2020). HER2 testing in endometrial serous carcinoma. *Arch Pathol Lab Med* 145(6):687-691.

266 van der Putten LJ, Visser NC, van de Vijver K, Santacana M, Bronsert P, Bulten J, Hirschfeld M, Colas E, Gil-Moreno A, Garcia A, Mancebo G, Alameda F, Trovik J, Kopperud RK, Huvila J, Schrauwen S, Koskas M, Walker F, Weinberger V, Minar L, Jandakova E, Snijders MP, van den Berg-van Erp S, Matias-Guiu X, Salvesen HB, Amant F, Massuger LF and Pijnenborg JM (2016). L1CAM expression in endometrial carcinomas: an ENITEC collaboration study. *Br J Cancer* 115(6):716-724.

267 Van Gool IC, Stelloo E, Nout RA, Nijman HW, Edmondson RJ, Church DN, MacKay HJ, Leary A, Powell ME, Mileshkin L, Creutzberg CL, Smit VT and Bosse T (2016). Prognostic significance of L1CAM expression and its association with mutant p53 expression in high-risk endometrial cancer. *Mod Pathol* 29(2):174-181.

268 Zeimet AG, Reimer D, Huszar M, Winterhoff B, Puistola U, Azim SA, Müller-Holzner E, Ben-Arie A, van Kempen LC, Petru E, Jahn S, Geels YP, Massuger LF, Amant F, Polterauer S, Lappi-Blanco E, Bulten J, Meuter A, Tanouye S, Oppelt P, Stroh-Weigert M, Reinthaller A, Mariani A, Hackl W, Netzer M, Schirmer U, Vergote I, Altevogt P, Marth C and Fogel M (2013). L1CAM in early-stage type I endometrial cancer: results of a large multicenter evaluation. *J Natl Cancer Inst* 105(15):1142-1150.

269 Myers A, Barry WT, Hirsch MS, Matulonis U and Lee L (2014). β-Catenin mutations in recurrent FIGO IA grade I endometrioid endometrial cancers. *Gynecol Oncol* 134(2):426-427.

270 Kurnit KC, Kim GN, Fellman BM, Urbauer DL, Mills GB, Zhang W and Broaddus RR (2017). CTNNB1 (beta-catenin) mutation identifies low grade, early stage endometrial cancer patients at increased risk of recurrence. *Mod Pathol* 30(7):1032-1041.

271 Backes FJ, Walker CJ, Goodfellow PJ, Hade EM, Agarwal G, Mutch D, Cohn DE and Suarez AA (2016). Estrogen receptor-alpha as a predictive biomarker in endometrioid endometrial cancer. *Gynecol Oncol* 141(2):312-317.

272 Trovik J, Wik E, Werner HM, Krakstad C, Helland H, Vandenput I, Njolstad TS, Stefansson IM, Marcickiewicz J, Tingulstad S, Staff AC, Amant F, Akslen LA and Salvesen HB (2013). Hormone receptor loss in endometrial carcinoma curettage predicts lymph node metastasis and poor outcome in prospective multicentre trial. *Eur J Cancer* 49(16):3431-3441.

273 van Weelden WJ, Massuger L, Pijnenborg JMA and Romano A (2019). Anti-estrogen treatment in endometrial cancer: a systematic review. *Front Oncol* 9:359.

274 Hedley C, Sriraksa R, Showeil R, Van Noorden S and El-Bahrawy M (2014). The frequency and significance of WT-1 expression in serous endometrial carcinoma. *Hum Pathol* 45(9):1879-1884.

275 Amant F, Mirza MR, Koskas M and Creutzberg CL (2018). Cancer of the corpus uteri. *Int J Gynaecol Obstet* 143 Suppl 2:37-50.

276 Wittekind C, Brierley JD, Lee A and van Eycken E (eds) (2019). *TNM Supplement: A Commentary on Uniform Use, 5th Edition*, Wiley, USA.