

Family/Last name Date of birth Given name(s) Patient identifiers Date of request 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*
- Previous history of cancer, *specify*
- Previous therapy, *specify*
- Other clinical information, *specify*

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

- Not specified
- Hysterectomy
- Simple  Radical
- Simple supracervical/subtotal  Type not specified
- Other, *specify*

**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)**OMENTUM DIMENSIONS** (Note 6) x  x **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
- % AND  %
- Epithelial Sarcomatous
- Homologous
- Heterologous

Other, *specify*



**LYMPH NODE STATUS (Note 25)**

- Cannot be assessed
- No nodes submitted or found

**Maximum dimension of largest deposit in regional node**

**Extranodal spread**

- Not identified
- Present

Lymph node type	Laterality	Number of lymph nodes <sup>b</sup>	Number of lymph nodes with isolated tumour cells <sup>b,c</sup>	Number of lymph nodes with micrometastasis <sup>b,d</sup>	Number of lymph nodes with macrometastasis <sup>b,d</sup>
Sentinel node(s)	Left				
	Right				
Regional node(s): pelvic	Left				
	Right				
Regional node(s): para-aortic					

<sup>b</sup> 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.  
<sup>c</sup> Isolated tumour cells ( $\leq 0.2$  mm and  $\leq 200$  cells).  
<sup>d</sup> Micrometastasis ( $> 0.2$  mm and  $\leq 2$  mm); Macrometastasis ( $> 2$  mm).

**ANCILLARY STUDIES (Note 26)**

- Not performed
- Performed (select all that apply)
- 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, *record test(s), methodology 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 (2023 edition)<sup>c,d,e</sup>**

- I Confined to the uterine corpus and ovary<sup>f</sup>
- IA Disease limited to the endometrium OR non-aggressive histological type, i.e., low grade endometrioid, with invasion of less than half of myometrium with no or focal lymphovascular space involvement (LVSI) OR good prognosis disease
  - IA1 Non-aggressive histological type limited to an endometrial polyp OR confined to the endometrium
  - IA2 Non-aggressive histological types involving less than half of the myometrium with no or focal LVSI
  - IA3 Low grade endometrioid carcinomas limited to the uterus and ovary<sup>f</sup>
- IB Non-aggressive histological types with invasion of half or more of the myometrium, and with no or focal LVSI<sup>g</sup>
- IC Aggressive histological types<sup>h</sup> limited to a polyp or confined to the endometrium
- II Invasion of cervical stroma without extrauterine extension OR with substantial LVSI OR aggressive histological types with myometrial invasion
  - IIA Invasion of the cervical stroma of non-aggressive histological types
  - IIB Substantial LVSI<sup>g</sup> of non-aggressive histological types
  - IIC Aggressive histological types<sup>h</sup> with any myometrial involvement
- III Local and/or regional spread of the tumour of any histological subtype
  - IIIA Invasion of uterine serosa, adnexa, or both by direct extension or metastasis
    - IIIA1 Spread to ovary or fallopian tube (except when meeting stage IA3 criteria)<sup>f</sup>
    - IIIA2 Involvement of submesothelial fibroconnective tissue or the mesothelial layer<sup>i</sup> or spread through the uterine serosa
  - IIIB Metastasis or direct spread to the vagina and/or to the parametria or pelvic peritoneum
    - IIIB1 Metastasis or direct spread to the vagina and/or the parametria
    - IIIB2 Metastasis to the pelvic peritoneum

**PROVISIONAL PATHOLOGICAL STAGING CONT. (Note 28)****FIGO (2023 edition)<sup>c,d,e</sup> cont.**

- IIIC Metastasis to the pelvic or para-aortic lymph nodes or both<sup>j</sup>
- IIIC1 Metastasis to the pelvic lymph nodes
- IIIC1i Micrometastasis
- IIIC1ii Macrometastasis
- IIIC2 Metastasis to para-aortic lymph nodes up to the renal vessels, with or without metastasis to the pelvic lymph nodes
- IIIC2i Micrometastasis
- IIIC2ii Macrometastasis
- IV Spread to the bladder mucosa and/or intestinal mucosa and/or distance metastasis
- IVA Invasion of the bladder mucosa and/or the intestinal/bowel mucosa
- IVB Abdominal peritoneal metastasis beyond the pelvis
- IVC Distant metastasis, including metastasis to any extra- or intra-abdominal lymph nodes above the renal vessels, lungs, liver, brain, or bone

<sup>c</sup> Reprinted from *Int J Gynaecol Obstet.*, DOI: 10.1002/ijgo.14923, Berek JS, Matias-Guiu X, Creutzberg C, Fotopoulou C, Gaffney D, Kehoe S, Lindemann K, Mutch D and Concin N, FIGO staging of endometrial cancer:2023, pages 1-12, 2023, with permission from Wiley.

<sup>d</sup> Endometrial cancer is surgically staged and pathologically examined. In all stages, the grade of the lesion, the histological type and LVSI must be recorded. If available and feasible, molecular classification testing (POLEmut, MMRd, NSMP, p53abn) is encouraged in all patients with endometrial cancer for prognostic risk-group stratification and as factors that might influence adjuvant and systemic treatment decisions.

<sup>e</sup> In early endometrial cancer, the standard surgery is a total hysterectomy with bilateral salpingo-oophorectomy via a minimally invasive laparoscopic approach. Staging procedures include infracolic omentectomy in specific histological subtypes, such as serous and undifferentiated endometrial carcinoma, as well as carcinosarcoma, due to the high risk of microscopic omental metastases. Lymph node staging should be performed in patients with intermediate-high/high-risk patients. Sentinel lymph node (SLN) biopsy is an adequate alternative to systematic lymphadenectomy for staging purposes. SLN biopsy can also be considered in low-/low-intermediate-risk patients to rule out occult lymph node metastases and to identify disease truly confined to the uterus. Thus, the ESGO-ESTRO-ESP guidelines allow an approach of SLN in all patients with endometrial carcinoma, which is endorsed by FIGO. In assumed early endometrial cancer, an SLN biopsy in an adequate alternative to systematic lymphadenectomy in high-intermediate and high-risk cases for the purpose of lymph node staging and can also be considered in low-/intermediate-risk disease to rule out occult lymph node metastases. An SLN biopsy should be done in association with thorough (ultrastaging) staging as it will increase the detection of low-volume disease in lymph nodes.

<sup>f</sup> Low grade EECs involving both the endometrium and the ovary are considered to have a good prognosis, and no adjuvant treatment is recommended if all the below criteria are met. Disease limited to low grade endometrioid carcinomas involving the endometrium and ovaries (Stage IA3) must be distinguished from extensive spread of the endometrial carcinoma to the ovary (Stage IIIA1), by the following criteria: (1) no more than superficial myometrial invasion is present (<50%); (2) absence of extensive/substantial LVSI; (3) absence of additional metastases; and (4) the ovarian tumour is unilateral, limited to the ovary, without capsule invasion/rupture (equivalent to pT1a).

<sup>g</sup> LVSI as defined in WHO 2021: extensive/substantial, ≥5 vessels involved.

<sup>h</sup> Grade and histological type.

<sup>i</sup> The consensus of the dataset authors was to replace 'uterine subserosa' with 'submesothelial fibroconnective tissue or the mesothelial layer'.

<sup>j</sup> Micrometastases are considered to be metastatic involvement (pN1 (mi)). The prognostic significance of isolated tumour cells (ITCs) is unclear. The presence of ITCs should be documented and is regarded as pN0(i+). According to TNM8, macrometastases are >2 mm in size, micrometastases are >0.2–2 mm and/or >200 cells, and isolated tumour cells are ≤0.2 mm and ≤200 cells. Based on staging established by FIGO and the American Joint Committee on Cancer (AJCC). AJCC Cancer Staging Manual. 8<sup>th</sup> ed. New York: Springer, 2017.

**TNM Staging (UICC TNM 8<sup>th</sup> edition 2016)<sup>k</sup>****TNM Descriptors** (only if applicable) (select all that apply)

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

**Primary tumour (pT)**

- TX<sup>l</sup> Primary tumour can not be assessed
- T0 No evidence of primary tumour
- T1 Tumour confined to the corpus uteri<sup>m</sup>
- 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<sup>n</sup>

**Regional lymph nodes (pN)**

- NX<sup>l</sup> Regional lymph nodes cannot be assessed
- N0 No regional lymph node metastasis
- N1 Metastasis to pelvic lymph nodes<sup>o</sup>
- N2 Metastasis to para-aortic lymph nodes with or without metastasis to pelvic lymph nodes<sup>o</sup>

<sup>k</sup> Reproduced with permission. Source: UICC TNM Classification of Malignant Tumours, 8<sup>th</sup> Edition, eds by James D. Brierley, Mary K. Gospodarowicz, Christian Wittekind. 2016, Publisher Wiley (incorporating any errata published up until 8<sup>th</sup> July 2024).

<sup>l</sup> TX and NX should be used only if absolutely necessary.

<sup>m</sup> Endocervical glandular involvement only should be considered as Stage I.

<sup>n</sup> The presence of bullous oedema is not sufficient evidence to classify as T4.

<sup>o</sup> 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<sup>1</sup>). 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.

Molecular and 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) includes the most relevant ancillary testing in ICCR Datasets as CORE elements, especially when they are necessary for the diagnosis. 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 ICCR Uterine malignant and potentially malignant mesenchymal tumours dataset.<sup>2</sup>

The 5<sup>th</sup> edition of the ICCR Endometrial cancer dataset incorporates the International Federation of Gynaecology and Obstetrics (FIGO) staging for endometrial cancer (2023).<sup>3</sup> This dataset also includes changes to align the dataset with the World Health Organization (WHO) Classification of Tumours, Female Genital Tumours, 5<sup>th</sup> edition, 2020.<sup>4</sup> The ICCR dataset includes 5<sup>th</sup> edition Corrigenda, July 2024.<sup>5</sup>

A list of changes in this dataset edition can be accessed [here](#).

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, previous 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. These procedures can either be performed through a laparoscopy, robot-assisted laparoscopy or laparotomy. 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, and recognised in the 2020 European Society of Gynaecological Oncology (ESGO)-European Society for Radiotherapy and Oncology (ESTRO)-European Society of Pathology (ESP) guidelines.<sup>6</sup> In some instances, malignancy can be found in a morcellated hysterectomy specimen.<sup>7</sup> 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. Further specimens may be submitted for pathological review including: omentum, sentinel lymph nodes, pelvic and periaortic lymph nodes, peritoneal washings, and peritoneal biopsies from various sites.

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.<sup>8</sup>

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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.<sup>9</sup> 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.<sup>10</sup>

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  $\geq 20$  to  $\geq 50$  millimetres (mm).<sup>11,12</sup> Some studies have not found an association between a tumour size of  $\geq 20$  mm and prognosis.<sup>13,14</sup>

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.

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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, such as grade 3 endometrioid carcinoma, serous carcinoma, clear cell carcinoma, undifferentiated and dedifferentiated carcinoma and carcinosarcoma. Grade 1 and 2 endometrioid carcinomas are subject to omentectomy in some centres.

Thorough macroscopic examination of the omentum is essential.<sup>8</sup> The omentum should be cut at 5 mm intervals to detect small lesions.<sup>8</sup> Obvious lesions can be sampled in one or two blocks but if no lesion is seen then at least four blocks are recommended.

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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, 5<sup>th</sup> edition, 2020 (Table 1).<sup>4</sup> The ICCR dataset includes 5<sup>th</sup> edition Corrigenda, July 2024.<sup>5</sup> 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.<sup>4</sup>

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.<sup>6</sup>

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. Although there is moderate to excellent ( $\kappa=0.62-0.87$ ) reproducibility in histological typing, inter-observer agreement is worse in high grade carcinomas.<sup>15-17</sup>

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, and serous carcinoma has a complex architectural pattern with papillae and cellular budding.<sup>18</sup> However, serous carcinomas with a prominent glandular pattern can frequently be mistaken as low grade endometrioid carcinoma;<sup>19,20</sup> and endometrioid carcinoma with papillary pattern can sometimes be misinterpreted as serous carcinoma.<sup>21</sup>

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.<sup>22</sup> This is one of the scenarios that shows the importance of integrating histologic typing with molecular classification.

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.<sup>23-26</sup> Rigorous criteria should be applied to make this diagnosis and a diagnosis of mixed carcinoma should only be used when both components exhibit a characteristic morphology and immunophenotype.<sup>26</sup> There is no minimum percentage of one of the components to classify the tumour as a mixed endometrial carcinoma.

Several studies have shown that the presence of heterologous elements in carcinosarcomas is an important adverse prognostic feature particularly *in low stage* tumours.<sup>27,28</sup> 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.<sup>29</sup>

Neuroendocrine carcinomas of the endometrium are included in the section on neuroendocrine tumours of the female genital tract in the 2020 WHO Classification.<sup>4</sup> Reporting of the neuroendocrine carcinoma subtype is a non-core feature.

For staging purposes, the 2023 FIGO staging system<sup>3</sup> distinguishes two main groups of tumours regarding histological type:

1. Non-aggressive histological types are composed of low grade (G1, G2) endometrioid carcinomas.
2. Aggressive histological types are composed of high grade endometrioid carcinomas, serous, mixed, clear cell, undifferentiated, dedifferentiated, mesonephric-like and gastrointestinal type mucinous carcinomas and carcinosarcomas.

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.<sup>8</sup> 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.<sup>8</sup>

**Table 1: World Health Organization classification of tumours of the uterine corpus.<sup>4</sup>**

Descriptor	ICD-O codes <sup>a</sup>
<b>Endometrial epithelial tumours and precursors</b>	
Endometrial hyperplasia without atypia	
Atypical hyperplasia of the endometrium	8380/2
Endometrioid adenocarcinoma NOS	8380/3
<i>POLE</i> -ultramutated endometrioid carcinoma <sup>b</sup>	
Mismatch repair-deficient endometrioid carcinoma <sup>b</sup>	
P53-mutant endometrioid carcinoma <sup>b</sup>	
No specific molecular profile (NSMP) endometrioid carcinoma <sup>b</sup>	
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	8144/3
Mesonephric-like adenocarcinoma	9113/3
Carcinosarcoma NOS	8980/3
Neuroendocrine tumour NOS	8240/3

<sup>a</sup> These morphology codes are from the International Classification of Diseases for Oncology, third edition, second revision (ICD-O-3.2).<sup>30</sup> Behaviour is coded /0 for benign tumours; /1 for unspecified, borderline, or uncertain behaviour; /2 for carcinoma in situ and grade III intraepithelial neoplasia; /3 for malignant tumours, primary site; and /6 for malignant tumours, metastatic site. Subtype labels are indented.

Incorporates all relevant changes from the 5<sup>th</sup> edition Corrigenda July 2024.<sup>5</sup>

<sup>b</sup> These molecular types apply to all endometrial carcinomas (not just endometrioid carcinomas).

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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.<sup>31</sup>

Serous, clear cell, undifferentiated, dedifferentiated, mesonephric-like, gastrointestinal type mucinous and neuroendocrine carcinomas and carcinosarcomas are considered high grade by definition. Tumours that are high grade by definition should be recorded as ‘not applicable’ in the reporting guide. The value of the FIGO grading system was shown in a univariate analysis of more than 600 patients with clinical Stage I or occult Stage II endometrioid carcinomas.<sup>32</sup> 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.<sup>3</sup>

The 2023 FIGO grading criteria for endometrioid carcinoma is primarily based on architectural features.<sup>3</sup> Grade 1, 2, and 3 tumours exhibit ≤5%, 6-50%, and >50% solid non-glandular growth, respectively.<sup>3</sup> 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.

The 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.<sup>4,33</sup> This recommendation has been endorsed in the 2023 FIGO staging criteria.<sup>3</sup> It 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.<sup>34,35</sup> However, some reports show a small, but statistically significant survival difference of around 5% between low stage, grade 1 and 2 tumours,<sup>33</sup> and the distinction between grade 1 and 2 carcinomas may be still important in some institutions for patients desiring fertility-sparing treatments.<sup>36-39</sup>

Agreement in histopathological grade between biopsy and hysterectomy specimens varies, with concordance of only 35% reported in some series.<sup>40,41</sup> Tumour heterogeneity may explain some of this discrepancy, since biopsies may not be necessarily representative of the whole tumour.<sup>42</sup> When there is discrepancy between the reported histological 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.

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 low stage endometrioid cancer patients.<sup>43</sup> 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.<sup>3,31,44,45</sup>

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%.<sup>46-56</sup>

In the 2023 FIGO staging system, myometrial involvement is important in determining Stage I and II tumours.<sup>3</sup> 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.

Depth of invasion (DOI) as an individual variable has received less investigation. Nevertheless, higher DOI has been associated with an increased risk of lymphovascular invasion (LVI), lymph node involvement, high stage, recurrence and death of disease in some studies but not others.<sup>43</sup>

Tumour free distance (TFD) is the distance between the deepest point of myometrial invasion of the cancer and the nearest serosal surface.<sup>4</sup> TFD theoretically eliminates some of the difficulties that are inherent in determining the depth of myometrial invasion, and is reportedly more reproducibly diagnosed by pathologists.<sup>57</sup> However, much like DOI, the prognostic significance of TFD is unclear, since the reported findings have been conflicting.<sup>53-56</sup> 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."<sup>10</sup> Thus, a tumour in which the only invasion arises from adenomyotic foci in the outer half of the myometrium, should be regarded as involving the outer half of the myometrium and accompanied by a comment that the clinical significance is unknown, and that this may be an overestimate of true DOI.<sup>3,6,10</sup>

Several patterns of myometrial invasion are recognised, and more than one pattern may be present within the same case.<sup>58-61</sup> The pattern of myometrial invasion may be documented in the pathology report to facilitate future study, but it is a non-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.<sup>62</sup>

The ICCR Endometrial Cancer Dataset Authoring Committee endorses the ISGyP recommendations for handling these diagnostic scenarios as summarised below:<sup>10</sup>

1. Exophytic tumours and endometrial polyps: Exophytic carcinomas not uncommonly contain bundles of smooth muscle within the 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.

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## Note 11 – Lymphovascular invasion (Core)

Lymphovascular invasion (LVI) is an important prognostic indicator in endometrial carcinoma and documenting the presence and extent of LVI or documenting if LVI is not identified is a core element.

Lymphovascular invasion (LVI) is diagnosed when there is a tumour embolus within an endothelial-lined channel.<sup>10,63-65</sup> There are several morphological features that may simulate LVI: these include spreading artefact, artefactual pseudoinvasion secondary to tumour disruption; microcystic elongated and fragmented (MELF) pattern myometrial invasion; and retraction artefacts.<sup>63,64</sup>

Artefactual pseudoinvasion secondary to tumour disruption is predominantly encountered in the setting of laparoscopic and/or robotic surgery.<sup>66</sup> 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 invasive front and in distant locations.<sup>63,64</sup> Often the amount of tumour within vessel appears disproportionate, for example in a tumour which is low grade and low stage. Adequate fixation before prosection, generally lessens the degree of artefact.

Microcystic elongated and fragmented (MELF) myometrial invasion may also mimic LVI. Adding to the complexity is that MELF myometrial invasion is also associated with LVI. 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) on the other.

Immunohistochemical staining with endothelial markers can sometimes be used to confirm a suspicion of LVI, especially when there is extensive retraction artefact, although the literature is inconsistent on the added value of immunohistochemistry (IHC) after haematoxylin and eosin (H&E) evaluation.<sup>10</sup>

The absence of LVI is defined as no tumour cells within vessels.<sup>33</sup> There is controversial data regarding the cut off for 'substantial (extensive)' LVI. 'Substantial LVI' is defined as the presence of three or more vessels containing tumour, according to ISGyP recommendations,<sup>33</sup> but five or more vessels in the 2020 WHO Classification<sup>4</sup>, the FIGO 2023 staging system, and in the 2020 ESGO-ESTRO-ESP guidelines.<sup>6</sup> None of these recommendations explicitly state whether assessment of the number of involved vessels should be on the slide containing the greatest number of involved vessels or whether the number of involved vessels on all the slides should be added together. The WHO classification is expected to be updated in 2025 and it is hoped that this issue will be clarified.

For staging purposes, the 2023 FIGO staging system includes substantial LVI as an important parameter for non-aggressive histological types (low grade endometrioid carcinoma). By following the WHO rule of five or more vessels, cases with substantial LVI are categorised as Stage IIB tumours.<sup>3</sup> However, in the FIGO 2023 system, and as previously stated, it is not clear as to whether the number of vessels is to be counted in a single section or across all the sections.

Some data indicate that 'substantial' LVI is associated with adverse outcomes when compared to carcinomas with 'focal' or 'no' LVI.<sup>67-69</sup> Recording the degree of LVI (focal or substantial/extensive) is regarded as a core element.

Lymphovascular invasion (LVI) should not be included in the assessment of depth of myometrial invasion.<sup>10</sup> 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.<sup>67,68,70</sup> Thus, the presence of substantial LVI may highlight the need for adjuvant treatment, such as recommended in the 2020 ESGO-ESTRO-ESP guidelines.<sup>6</sup>

A value of 'indeterminate' should be used sparingly and only in cases where there is genuine doubt as to whether LVI is present or not. 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 or 2023 FIGO staging system and is regarded as a non-core element.<sup>3,71</sup> However, it is a potential adverse risk factor for locoregional recurrence and may be taken into consideration for adjuvant radiotherapy.<sup>10</sup>

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## **Note 13 – Lower uterine segment (Non-core)**

Anatomically, the lower uterine segment begins where the body funnels towards the cervix and ends at the internal os. As stated in **Note 4 – TUMOUR SITE**, lower uterine segment involvement is a potential adverse risk factor for locoregional and distant recurrence and may be taken into consideration for adjuvant

radiotherapy, although it does not affect the FIGO tumour stage.<sup>10</sup> 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 origin in the lower uterine segment has important risk implications.<sup>9</sup>

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## **Note 14 – Cervical stroma (Core)**

Cervical stromal invasion indicates Stage IIA endometrial carcinoma according to the FIGO 2023 staging system for non-aggressive histological types (low grade endometrioid carcinomas) and is a core element for reporting.<sup>3</sup>

Cervical stromal invasion is associated with a significant risk of recurrence and is a predictor of pelvic lymph node metastases.<sup>72-74</sup> However, the role of cervical stromal involvement as an independent prognosticator per se has been questioned.<sup>31</sup> Cervical stromal invasion often occurs in the presence of other adverse features such as high histologic grade, deep myometrial invasion and LVI. In one study, the presence of these factors conferred worse disease-free survival in patients with Stage II endometrial cancer.<sup>75</sup>

Determination of cervical stromal invasion can be complicated by difficulties in demarcating the upper cervix from the lower uterine segment. By convention, the boundary is defined by the most proximal mucinous gland/crypt.<sup>63,76</sup> Consequently, any invasion identified at the level of, or distal to, a benign mucinous gland should be considered cervical stromal invasion.

Significant interobserver variation in the assessment of cervical involvement by endometrial carcinoma has been documented. A study by McCluggage et al (2011) demonstrated fair to good agreement among six experienced gynaecologic pathologists in this exercise.<sup>76</sup> While, a study by 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.<sup>77</sup> 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 a recent biopsy.<sup>76</sup>

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.<sup>78</sup> 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 2023 Stage IIIB1.<sup>3</sup> Although not an independent prognostic indicator, parametrial involvement by direct extension is a poor prognostic factor.<sup>79-81</sup> 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.<sup>79-81</sup> 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 carcinomas, 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 2023 Stage IIIB1.<sup>3</sup> 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.<sup>82</sup>

The vagina represents the most common site of recurrence of endometrial carcinoma.<sup>83,84</sup> In the majority of cases, recurrence involves the upper vagina, while recurrence in the middle third or distal vagina is less common.<sup>85</sup> In a study by Moschiano et al (2014) there were no disease-related deaths in patients with vaginal recurrence only, suggesting that vaginal recurrence is not a marker of aggressive tumour biology.<sup>85</sup>

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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.<sup>86</sup> Omental metastases are associated with other adverse prognostic features such as high tumour grade, serous histology, deep myometrial invasion, LVI and adnexal involvement.<sup>86</sup>

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).<sup>3,87</sup>

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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.

It is important to distinguish between abdominal and pelvic peritoneal involvement since this denotes a different FIGO Stage (IIIB2 for pelvic peritoneal involvement and IVB for abdominal peritoneal involvement).<sup>3</sup>

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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 meeting. Positive peritoneal cytology has been shown to be an independent prognostic factor for serous carcinoma regardless of stage and it is important to report for other carcinomas.<sup>3,78,88,89</sup>

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.<sup>10</sup> It is also unclear whether the method of hysteroscopy or operative procedure may influence the likelihood of positive peritoneal washings.<sup>10</sup>

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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<sup>6</sup> and ISGyP guidelines,<sup>10</sup> tumour infiltrating the full myometrial thickness and reaching submesothelial fibroconnective tissue or the mesothelial layer should be reported as serosal involvement. This criteria has been endorsed in the 2023 FIGO staging system.<sup>3</sup>

Involvement of the serosa (FIGO Stage IIIA2) carries a higher risk of locoregional recurrence than does adnexal involvement ( FIGO Stage IIIA1).<sup>3</sup>

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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.<sup>3,90,91</sup> The involved adnexa should be documented, particularly specifying which ovary and which fallopian tube is involved as well as the location of tubal involvement.

It is sometimes difficult to distinguish between endometrial carcinoma with ovarian metastasis and synchronous primary tumours of the endometrium and the ovary.<sup>92</sup> 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.<sup>8</sup>

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

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.<sup>93-96</sup> However, this clonal relationship should not be equated with the clinical outcomes expected of metastatic endometrial carcinoma.

In the 2020 WHO Classification,<sup>4</sup> it is suggested that patients with synchronous endometrioid carcinomas in the endometrium and ovary be managed conservatively (as if they were two independent primaries) when the following criteria are met: 1) low grade endometrioid morphology at both sites, 2) no more than superficial myometrial invasion, 3) absence of LVI, and 4) absence of additional metastases.<sup>4,97</sup>

This is an evolving field, and it is not clear at this time why a subset of metastatic low grade endometrioid carcinomas involving the endometrium and ovary are associated with good prognosis. 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 molecular abnormalities; and 2) tumour cells follow retrograde transtubal spread, with ovarian implantation, rather than destructive invasion. It is recommended to discuss these cases in multidisciplinary tumour board meetings.

The 2023 FIGO staging system endorses criteria proposed by the WHO and ESGO-ESTRO-ESP for endometrial carcinomas with ovarian involvement.<sup>3</sup> The system establishes the category of Stage IA3 when the following criteria are met in a low grade endometrioid carcinoma: 1) no more than superficial myometrial invasion is present (<50%), 2) absence of substantial LVI, 3) absence of additional metastases, and 4) the ovarian tumour is unilateral, limited to the ovary, without capsule invasion/breach. Cases which do not fulfill these criteria should be categorised as Stage IIIA1.

Although true independent simultaneous endometrial and ovarian carcinomas do exist, they are relatively infrequent, and may occur in the setting of Lynch syndrome.<sup>96</sup> In this scenario, these may represent synchronous endometrioid carcinomas of the endometrium and ovary or an endometrioid carcinoma of the endometrium may coexist with ovarian clear cell carcinoma.<sup>98</sup>

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.<sup>99</sup> It is important to stress that the presence of detached aggregates of tumour cells in the tubal lumen, without involvement of the wall, should not be considered tubal involvement,<sup>66</sup> since this is thought to be an artefact related to the type of surgery performed and/or specimen fixation. However, the presence of serous carcinoma cells in the lumen of the fallopian tube may be associated with peritoneal metastasis.<sup>10</sup> 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 if performed.

Tubal involvement by endometrial carcinoma in the form of intramucosal spread has controversial prognostic significance. Tubal tumour is generally considered metastatic from the endometrium, rather than 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 is unknown.<sup>10</sup>

Tubal involvement by serous carcinoma, with or without stromal invasion is usually a manifestation of metastatic serous carcinoma. 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); this is referred to as a STIC-like lesion.<sup>100</sup> 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. 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 serous carcinomas, although a significant proportion are positive, but positive in almost all serous carcinomas arising from the ovary or the fallopian tube.<sup>101</sup>

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.<sup>3,90</sup> 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.<sup>102,103</sup> LVI 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.<sup>104</sup> 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.<sup>105</sup> The presence of stromal pseudodecidualisation may serve as evidence of preoperative hormonal therapy.<sup>106</sup> These should be reported under 'other'.

Atypical hyperplasia/endometrioid intraepithelial neoplasia is a manifestation of clonal expansion of neoplastic glands. This lesion predisposes to endometrioid carcinoma.<sup>107-109</sup>

Serous carcinoma typically arises in a background of atrophic endometrium although it remains controversial as to what constitutes a 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.<sup>110</sup> The literature on a precursor of clear cell carcinoma is limited.<sup>111-113</sup>

Various types of carcinoma, including endometrioid and serous, may occasionally arise in an endometrial polyp.<sup>114</sup> 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.

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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).<sup>3</sup> A therapeutic benefit from lymph node resection has not been shown yet in randomised trials.<sup>115-118</sup> Although a large retrospective study has shown benefit from extensive nodal dissection especially in serous tumours.<sup>117</sup>

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 node involvement (including inguinal nodes) is considered to be distant metastases.

Core data elements regarding lymph node status include 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.<sup>3,45,90,91</sup> 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.<sup>90,91</sup>

The 2023 FIGO staging system aligns with the TNM 8<sup>th</sup> edition staging systems.<sup>3,45,90,91</sup> Stage IIIC is further divided into micrometastasis (0.2 to 2 mm and/or >200 cells) (IIIC1i, IIIC2i) and macrometastasis (>2 mm) (IIIC1ii, IIIC2ii), while isolated tumour cells (up to 0.2 mm and ≤200 cells) are not considered metastatic, are not included in FIGO 2023 and in TNM are regarded as pN0(i+).<sup>3</sup>

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.

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 lymph node biopsy in selecting therapeutic approaches.<sup>119-122</sup> One of the strengths of sentinel lymph node biopsy is the detection

of a high percentage of lymph node positive cases by intense analysis (ultrastaging) of one or a few lymph nodes. Micrometastases and small macrometastases should be detected by ultrastaging of the lymph nodes. In addition, sentinel lymph node biopsy is associated with a substantially lower risk of post-operative morbidity, especially lower leg lymphoedema, since the dissection of other pelvic lymph nodes is avoided.<sup>123,124</sup>

The presence of nodal micrometastases is associated with worse prognosis, particularly in patients not receiving adjuvant treatment.<sup>125</sup> There is no evidence that the presence of isolated tumour cells has prognostic ramifications. Based on large randomised trials,<sup>118</sup> lymph node staging does not impact survival, but provides information on extent of the disease and decisions about adjuvant treatment.

According to the 2020 ESGO-ESTRO-ESP guidelines,<sup>6</sup> 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.<sup>86</sup>

Ultrastaging is recommended for the analysis of sentinel nodes which are negative on examination of initial H&E stained slides.<sup>126,127</sup> Notably, if sentinel nodes are negative by ultrastaging, the occurrence of isolated nodal paraaortic metastasis is very unlikely.<sup>6,127</sup>

Several ultrastaging protocols have been published, but there is no preferred standardised technique. Ultrastaging consists of additional sections cut at defined intervals and stained by H&E and pankeratins.

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

### Immunohistochemistry for mismatch repair (MMR) proteins and MLH1 promoter methylation (Core)

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 in all endometrial carcinomas.<sup>128</sup>

Endometrial cancer is one of the most common tumours in patients with Lynch syndrome (also known as hereditary non-polyposis colorectal cancer).<sup>9,129</sup> 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.<sup>130</sup> 'Constitutive methylation' is also a rare cause of Lynch syndrome.<sup>131</sup>

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;<sup>132</sup>
3. Prognostic, as part of the TCGA molecular classification;<sup>133</sup>
4. Therapeutically as a predictive biomarker for potential utility of immune checkpoint inhibitor therapy.<sup>134</sup>

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.<sup>135</sup> ISGyP has recommended testing for MMR status/MSI in all endometrial carcinomas (preferably curettings or biopsy), irrespective of age.<sup>128</sup> This has also been recommended whenever resources are available by other societies/groups, such as the Manchester International Consensus Group.<sup>136</sup> The identification of Lynch syndrome in women with endometrial carcinoma can lead to the prevention of a second cancer in the patient and prevention 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<sup>135,137,138</sup> and next generation sequencing (NGS).<sup>139</sup>

Immunohistochemistry (IHC) is cost effective and is used in most pathology departments. ISGyP guidelines recommend IHC as the best test to identify MMR deficiency and, indirectly, for MSI.<sup>128</sup> The IHC approach consists of staining with the four DNA MMR proteins: MLH1, PMS2, MSH2, and MSH6. An alternative is to use only PMS2 and MSH6, with addition of MLH1 when PMS2 is lost, and of MSH2 when MSH6 is lost.<sup>140</sup> Carcinomas showing loss of MLH1 and PMS2 expression should be investigated for MLH1 promoter hypermethylation,<sup>141</sup> 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 an alternative method that only requires tumour tissue.<sup>142</sup>

### **The Cancer Genome Atlas (TCGA)-based molecular classification of endometrial carcinomas (Non-core)**

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, often supplemented by IHC.<sup>4</sup> The different histologic types have different molecular features, microscopic appearances, precursor lesions, and natural history, although in multivariate analyses,<sup>143</sup> 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, there is less interobserver agreement in classifying high grade endometrial carcinomas.<sup>15-17</sup>

The TCGA performed an integrated genomic, transcriptomic and proteomic characterisation of endometrial carcinomas.<sup>144</sup> This revealed four groups of tumours.

One group (approximately 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 this group, some of which resemble serous carcinomas. Irrespective of grade, this group of tumours have an excellent prognosis, although this is not confirmed in all of the literature.<sup>144-147</sup>

There are also two groups which show similar progression-free survival rates that are intermediate between the other two groups. With additional research, it is becoming apparent that these groups are heterogeneous, each having genomically-defined subgroups of tumours, some of which are prognostically

favourable and others that are unfavourable.<sup>144,148-150</sup> One group (approximately 30% of tumours) comprises carcinomas with MSI (hypermutated), frequently with MLH1 promoter hypermethylation and high mutation rates.

The other 'intermediate' group (approximately 39% of endometrial carcinomas) includes endometrioid carcinomas with low copy number alterations, and low mutational burden, which lack *POLE* and *TP53* mutations and which are not MSI-high (MSI-H). These tumours are commonly referred to as 'no specific molecular profile (NSMP)'.

The last group is referred to as serous-like or copy-number high (approximately 26% of endometrial carcinomas). These exhibit 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), some clear cell carcinomas, and most carcinosarcomas, are in this group.

In an attempt to bring TCGA molecular-based classification into clinical practice, different groups have proposed a surrogate (simplified) algorithm which does not include comprehensive tumour profiling.<sup>133,149,150</sup> 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.<sup>33,128,148</sup>

According to this simplified algorithm, tumours with pathogenic *POLE* mutation correspond to ultramutated tumours. MSH6 or PMS2 abnormal expression defines tumours in the hypermutated group. Abnormal expression of p53 (mutated pattern), characterises the copy number high group. Finally, NSMP is defined by the absence of *POLE* mutation, and a normal expression pattern of MSH6, PMS2 and p53.<sup>133,150</sup>

The Cancer Genome Atlas (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 has 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 (p53abn)). MSI-H and NSMP grade 3 endometrioid carcinomas have an intermediate prognosis.<sup>22</sup> Application of this algorithm for clear cell carcinoma,<sup>151</sup> undifferentiated/dedifferentiated carcinoma,<sup>152</sup> neuroendocrine carcinoma,<sup>153</sup> and carcinosarcoma<sup>154</sup> is possible, although there has been limited study regarding these tumours and they were not included in the original TCGA paper.<sup>144</sup> The vast majority of low grade endometrioid carcinomas are NSMP or MSI, with *POLE*-mutated, or p53abn tumours accounting for less than 10%. Moreover, the vast majority (95%) of serous carcinoma are p53abn.

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., RAINBO trial).<sup>155 156</sup> The availability of resources, particularly for *POLE* mutation analysis, is inconsistent.<sup>133</sup> Also, most evidence in support of the TCGA classification is based on two large but retrospective cohorts.<sup>133,150</sup> There are two additional complexities to *POLE* testing: distinguishing between pathogenic and non-pathogenic mutations,<sup>157</sup> and coexistence of ultramutation (i.e., pathogenic *POLE* mutation) with secondary mutations in *TP53* and/or one or more of the MMR genes.<sup>158</sup> These 'multiple classifier' cases are currently thought to retain the favourable prognosis of *POLE* mutated tumours, regardless of MMR or p53 status but this is still an evolving field.

The 2023 FIGO staging system encourages performance of the complete molecular classification in all endometrial carcinomas for prognostic risk-group stratification and as potential influencing factors for

adjuvant and systemic treatment decisions.<sup>3</sup> Although not mandatory for appropriate staging, identification of *POLE* mutations and p53 abnormalities result in upstaging or downstaging the disease when molecular classification is performed in stage I and II tumours.<sup>3</sup> For FIGO Stages I and II, based on surgical/anatomical and histological findings, the FIGO stage is modified when molecular classification reveals either POLEmut or p53abn. This is depicted in the FIGO stage by the addition of 'm' for molecular classification, and a subscript is added to denote POLEmut or p53abn status. MMRd or NSMP status do not modify early FIGO stages; however, these molecular classifications should be recorded for the purpose of data collection. No changes occur through the molecular features in stages III and IV, but cases for which the molecular classification is known should be recorded as Stage III<sub>m</sub> and Stage IV<sub>m</sub> with specification of the molecular class for purposes of data collection.

### Other markers (Non-core)

Immunohistochemistry (IHC) may be helpful for diagnosis of endometrial carcinomas. With a differential diagnosis involving endometrioid and serous carcinomas, loss of expression of MMR proteins, PTEN and/or ARID1A would favour endometrioid carcinoma. Both serous and endometrioid carcinomas can show aberrant p53 staining and p16 overexpression (both more common in serous carcinoma).<sup>159</sup> Napsin A, HNF1-beta and AMACR (together with negative estrogen receptor (ER))<sup>160,161</sup> may be helpful in diagnosing clear cell carcinoma. A combination of broad spectrum cytokeratin, EMA, PAX8, ER and E-cadherin may 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 (INSM1, chromogranin, synaptophysin) can help in recognition of neuroendocrine tumours,<sup>162</sup> and GATA3, TTF1 and CD10 may help in diagnosing mesonephric-like carcinoma.<sup>163,164</sup> 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.<sup>99</sup>

There are also immunohistochemical markers of prognostic and predictive value. HER2 protein overexpression and/or *HER2* gene amplification is present in approximately 25-30% of endometrial serous carcinomas,<sup>165-167</sup> and 14% of endometrial carcinosarcomas.<sup>168</sup> Intratumoral heterogeneity of HER2 expression and gene amplification are common in these tumours and this should be taken into consideration when evaluating their HER2 status.<sup>165,169</sup> HER2 positivity in endometrial serous carcinomas is associated with worse progression free and overall survival,<sup>170</sup> but can be therapeutically targeted by adding trastuzumab to the standard chemotherapy regimen.<sup>171,172</sup> It has been shown that *HER2* amplification is characteristic of p53abn endometrial carcinomas as defined in the molecular classification, and is not restricted to the serous carcinoma category.<sup>173</sup> Although currently no official endometrial cancer-specific pathology HER2 scoring guidelines exist, a new set of criteria have been proposed based on successful clinical trial experience.<sup>174</sup>

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.<sup>175-177</sup> Mutations in *CTNNB1* (often, but not always, associated with nuclear expression of beta-catenin with IHC) have been some in some studies to be associated with diminished survival in low grade endometrioid carcinomas, but this is not universally accepted.<sup>150,178,179</sup>

Estrogen receptor (ER) expression has been associated with tumour behaviour and survival in endometrioid carcinomas.<sup>180,181</sup> ER/PR may assist with tumour classification and may be important to clinicians for treatment planning. A systematic review by van Weeldon et al (2019) confirmed improved response rates to endocrine therapy in ER and PR positive tumours, especially when determined in the metastatic tissue.<sup>182</sup>

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.<sup>183</sup>



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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 previous 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.<sup>3,90,91,184</sup>

Either FIGO (2009 or 2023) or TNM staging, or both, can be used depending on local preferences.<sup>3,90,91,184</sup> The FIGO staging system is used internationally and is the system used in most clinical trials and research studies. However, the revised 2023 FIGO staging system<sup>3</sup> is currently in the process of being incorporated and is not yet in widespread use, with many jurisdictions still using the FIGO 2009 staging system. The Union for International Cancer Control (UICC) or American Joint Committee on Cancer (AJCC) versions of TNM are used or required in many parts of the world.<sup>90,91</sup>

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.

The revised 2023 FIGO staging system<sup>3</sup> incorporates many of the core elements of the ICCR Endometrial cancer dataset 5<sup>th</sup> Edition.

The reference document TNM Supplement: A commentary on uniform use, 5<sup>th</sup> edition (C Wittekind et al. editors) may be of assistance when staging.<sup>185</sup>

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