**Endometrial Cancer Histopathology Reporting Guide**

**Elements in black text are CORE Elements in grey text are NON-CORE o indicates single select values □ indicates multi-select values**

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| --- | --- |
| Definition of 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 (NHMRC) levels of evidence1). 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.  **Reference**  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. |
| Definition of 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. |
| Scope of this dataset | 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](#_ENREF_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](#_ENREF_3)The ICCR dataset includes 5th edition Corrigenda, June 2021.[4](#_ENREF_4)  **References**  1 International Collaboration on Cancer Reporting (2021). *Uterine Malignant and Potentially Malignant Mesenchymal Tumours*. Available from: http://www.iccr-cancer.org/datasets/published-datasets/female-reproductive (Accessed 1st July 2021).  2 Kurman RJ, Carcangiu ML, Herrington CS and Young RH (2014). *WHO classification of tumours of the female reproductive organs*. IARC press, Lyon.  3 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). |

| **Core/**  **Non-core** | **Element name** | **Values** | **Commentary** | **Implementation notes** |
| --- | --- | --- | --- | --- |
| Non-core | CLINICAL INFORMATION | * Information not provided * Family history of cancer or cancer-associated syndrome,   *specify*   * Prior history of cancer, *specify* * Prior therapy, *specify* * Other, *specify* | 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. |  |
| Core | OPERATIVE PROCEDURE | * Not specified * Hysterectomy * Simple * Simple supracervical/subtotal * Radical * Type not specified * Other procedure, *specify type* | 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.[1](#_ENREF_1),[2](#_ENREF_2) These procedures can either be performed through a laparoscopy, robot-assisted laparoscopy or laparotomy.[3](#_ENREF_3) 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,[4](#_ENREF_4),[5](#_ENREF_5) and recognised in the European Society of Gynaecological Oncology (ESGO)-European Society for Radiotherapy and Oncology (ESTRO)-European Society of Pathology (ESP) guidelines.[6](#_ENREF_6) In some instances, malignancy can be found in a morcellated hysterectomy specimen.[7](#_ENREF_7) Morcellation should be avoided whenever there is suspicion of endometrial carcinoma. Primary hormonal treatment may be considered in a woman who desires fertility conservation. 0BReferences 1 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.  2 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.  3 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.  4 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.  5 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.  6 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.  7 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. |  |
| Core | SPECIMEN(S) SUBMITTED | * Not specified * Fallopian tube * Left * Right * Laterallity not specified * Ovary * Left * Right * Laterallity not specified * Parametrium * Left * Right * Laterallity not specified * Vaginal cuff * Vaginal nodules * Omentum * Peritoneal biopsies * Peritoneal washings/peritoneal fluid * Lymphadenectomy specimen(s) * Sentinel node(s)   □ Left  □ Right  o Laterallity not specified   * Regional node(s): pelvic   □ Left  □ Right  o Laterallity not specified   * Regional node(s): para-aortic * Non-regional node(s): inguinal   □ Left  □ Right  o Laterallity not specified   * Other node group, *specify* * Other, *specify* | Attached anatomical structures may include vaginal cuff, ovaries, fallopian tubes or parametria.[1](#_ENREF_1) Further specimens may be submitted for pathological review including: omentum, sentinel lymph nodes,[2](#_ENREF_2) pelvic and periaortic lymph nodes, peritoneal washings, and peritoneal biopsies from various sites.[1](#_ENREF_1)  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.[1](#_ENREF_1) 1BReferences 1 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.  2 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. |  |
| Non-core | TUMOUR SITE | * Isthmus/lower uterine segment * Fundus * Body * Other, *specify* | 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.[1](#_ENREF_1),[2](#_ENREF_2) 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.[3-6](#_ENREF_3)  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. 2BReferences 1 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.  2 Garg K and Soslow RA (2009). Lynch syndrome (hereditary non-polyposis colorectal cancer) and endometrial carcinoma. *J Clin Pathol* 62(8):679-684.  3 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.  4 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.  5 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.  6 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. |  |
| Non-core | MAXIMUM TUMOUR DIMENSION | \_\_\_\_ mm | 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).[1-8](#_ENREF_1) Some studies have not found an association between a tumour size of ≥20 mm and prognosis.[9](#_ENREF_9),[10](#_ENREF_10)  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.[11](#_ENREF_11) 3BReferences 1 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.  2 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.  3 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.  4 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.  5 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.  6 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.  7 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.  8 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.  9 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.  10 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.  11 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. |  |
| Non-core | OMENTUM DIMENSIONS | \_\_\_\_ mm x \_\_\_\_ mm x \_\_\_\_ mm | Omentectomy is currently undertaken in many, but not all, institutions for all high grade endometrial carcinomas,[1](#_ENREF_1) such as grade 3 endometrioid carcinoma, serous carcinoma, clear cell carcinoma, undifferentiated carcinoma and carcinosarcoma.[2](#_ENREF_2) Grade 1 and 2 endometrioid carcinomas are subject to omentectomy in some centres.[2](#_ENREF_2)  Thorough macroscopic examination of the omentum is essential.[3](#_ENREF_3) The omentum should be cut at 5 millimetre intervals to detect small lesions.[4](#_ENREF_4) Obvious lesions can be sampled in one or two blocks but if no lesion is seen then at least four blocks are recommended.[3](#_ENREF_3) One study suggests improving the sensitivity for detection of microscopic disease in macroscopically normal omentum to 95% if at least 10 blocks are submitted.[5](#_ENREF_5) 4BReferences 1 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.  2 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.  3 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.  4 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.  5 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. |  |
| Non-core | BLOCK IDENTIFICATION KEY | List overleaf or separately with an indication of the nature and origin of all tissue blocks | The origin/designation of all tissue blocks should be recorded, and it is preferable to document this information in the final pathology report. This 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. |  |
| Core and Non-core | HISTOLOGICAL TUMOUR TYPE | * 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* | All endometrial carcinomas should be classified according to the WHO Classification of Tumours, Female Genital Tumours, 5th edition, 2020 (Table 1).[1](#_ENREF_1) The ICCR dataset includes 5th edition Corrigenda, June 2021.[2](#_ENREF_2) 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.[3](#_ENREF_3)  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.[4](#_ENREF_4)  Bokhman first described in 1984, two main pathogenetic types based on epidemiological studies and this concept was subsequently further expanded.[5](#_ENREF_5),[6](#_ENREF_6) 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.[7-9](#_ENREF_7)  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.[10-12](#_ENREF_10)  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,[13](#_ENREF_13) and serous carcinoma has a complex architectural pattern with papillae and cellular budding.[14](#_ENREF_14) However, serous carcinomas with a prominent glandular pattern can frequently be mistaken as low grade endometrioid carcinoma;[15](#_ENREF_15),[16](#_ENREF_16) and endometrioid carcinoma with papillary pattern can sometimes be misinterpreted as serous carcinoma.[17](#_ENREF_17)  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[3](#_ENREF_3) 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,[18](#_ENREF_18) and distinction from proliferative, but not malignant, mucinous lesions may be challenging.[19](#_ENREF_19) The 2020 WHO Classification clearly distinguishes the mucinous variant of endometrioid carcinoma from gastrointestinal-l type mucinous endometrioid carcinoma,[3](#_ENREF_3),[20](#_ENREF_20) 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.[21](#_ENREF_21) 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.[22](#_ENREF_22)  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.[23-26](#_ENREF_23) 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.[27](#_ENREF_27),[28](#_ENREF_28) The differentiated component can be low or high grade.[29](#_ENREF_29) A significant number of un-/dedifferentiated carcinomas are characterised by an inactivating mutation resulting in loss of SMARCA4 or SMARCB1 protein.[30](#_ENREF_30)  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.[31-34](#_ENREF_31) 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.[35](#_ENREF_35) 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.[34](#_ENREF_34)  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.[34](#_ENREF_34) 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.[36](#_ENREF_36),[37](#_ENREF_37) 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.[38](#_ENREF_38" \o "El Hallani S, 2021 #5924)  The 2020 WHO Classification[3](#_ENREF_3) includes novel tumour types, such as squamous cell carcinoma, mesonephric and mesonephric-like adenocarcinoma,[39](#_ENREF_39),[40](#_ENREF_40) as well as gastrointestinal-type mucinous carcinoma.[20](#_ENREF_20)  Neuroendocrine carcinomas of the endometrium are included in the section on neuroendocrine tumours of the female genital tract in the 2020 WHO Classification.[3](#_ENREF_3),[41](#_ENREF_41) 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 millimetres, considering the largest tumour dimension.[42](#_ENREF_42) 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.[42](#_ENREF_42)  **Table 1 (See end of document for tables)** 5BReferences 1 Kurman RJ, Carcangiu ML, Herrington CS and Young RH (2014). *WHO classification of tumours of the female reproductive organs*. IARC press, Lyon.  2 WHO Classification of Tumours Editorial Board (2021). *Female Genital Tumours, WHO Classification of Tumours, 5th Edition, Volume 4 - Corrigenda June 2021*. 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Note that permission to publish the WHO Classification of Tumours may be needed in your implementation. It is advisable to check with the International Agency for Research on Cancer. |
| Core | HISTOLOGICAL TUMOUR GRADE | * Not applicable * Cannot be assessed * Grade 1 (low) * Grade 2 (low) * Grade 3 (high) | 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.[1](#_ENREF_1)  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.[1](#_ENREF_1),[2](#_ENREF_2) The value of the International Federation of Gynaecology and Obstetrics (FIGO) grading system was shown in a univariate analysis of more than 600 patients with clinical Stage I or occult Stage II endometrioid carcinoma.[3](#_ENREF_3) 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.[4](#_ENREF_4)  The 2009 FIGO grading criteria for endometrioid carcinoma is primarily based on architectural features.[4](#_ENREF_4) Grade 1, 2, and 3 tumours exhibit ≤5%, 6-50%, and >50% solid non-glandular growth, respectively.[4](#_ENREF_4) 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.[5](#_ENREF_5) 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.[5](#_ENREF_5)  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.[6](#_ENREF_6),[7](#_ENREF_7) 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.[8](#_ENREF_8),[9](#_ENREF_9) However, some reports show a small, but statistically significant survival difference of around 5% between low stage, grade 1 and 2 tumours,[6](#_ENREF_6) and the distinction between grade 1 and 2 carcinomas may be still important in some institutions for patients desiring fertility-sparing treatments.[10-13](#_ENREF_10)  Agreement in histopathological grade between biopsy and hysterectomy specimens varies, with concordance of only 35% reported in some series.[14](#_ENREF_14),[15](#_ENREF_15) Tumour heterogeneity may explain this discrepancy, since biopsies may not be necessarily representative of the whole tumour.[16](#_ENREF_16) 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.[17-20](#_ENREF_17) 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.[17-20](#_ENREF_17)  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. 6BReferences 1 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.  2 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.  3 Prat J (2004). Prognostic parameters of endometrial carcinoma. *Hum Pathol* 35(6):649-662.  4 FIGO Committee on Gynecological Cancer (2009). Revised FIGO staging for carcinoma of the vulva, cervix and endometrium. *Int. J. Gynecol. 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| Non-core | MYOMETRIAL INVASION | * 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 | 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.[1](#_ENREF_1),[2](#_ENREF_2) 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.[3-5](#_ENREF_3)  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%.[6-16](#_ENREF_6)  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).[5](#_ENREF_5),[17](#_ENREF_17),[18](#_ENREF_18)  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.[19](#_ENREF_19)  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,[10](#_ENREF_10),[11](#_ENREF_11),[13](#_ENREF_13),[14](#_ENREF_14) but not others.[8](#_ENREF_8),[9](#_ENREF_9),[12](#_ENREF_12),[15](#_ENREF_15),[16](#_ENREF_16)  TFD is the distance between the deepest point of myometrial invasion of the cancer and the nearest serosal surface.[8-16](#_ENREF_8) TFD theoretically eliminates some of the difficulties that are inherent to determining the depth of myometrial invasion,[6](#_ENREF_6),[7](#_ENREF_7) and is reportedly more reproducibly diagnosed by pathologists.[20](#_ENREF_20) However, much like DOI, the prognostic significance of TFD is unclear, since the reported findings have been conflicting.[6](#_ENREF_6),[8-16](#_ENREF_8) 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.[9](#_ENREF_9),[10](#_ENREF_10),[13](#_ENREF_13),[14](#_ENREF_14) An association between TFD and lymph node involvement, adnexal involvement and/or larger tumour size has also been reported in some studies[9](#_ENREF_9),[10](#_ENREF_10),[12](#_ENREF_12),[13](#_ENREF_13) but not others.[11](#_ENREF_11),[14](#_ENREF_14),[15](#_ENREF_15) 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.[8-10](#_ENREF_8),[12](#_ENREF_12),[13](#_ENREF_13),[15](#_ENREF_15) In two of the aforementioned studies, a TFD cut off of 10 millimetres was found to maximize sensitivity and specificity in predicting recurrences.[9](#_ENREF_9),[10](#_ENREF_10) 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.”[19](#_ENREF_19) 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.[19](#_ENREF_19),[21](#_ENREF_21)  Several patterns of myometrial invasion are recognised, and more than one pattern may be present within the same case.[22-25](#_ENREF_22) The conventional *infiltrative* pattern is the most commonly encountered pattern, and has no specific prognostic significance.[22](#_ENREF_22),[23](#_ENREF_23) 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.[22](#_ENREF_22),[23](#_ENREF_23),[25](#_ENREF_25) 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.[25](#_ENREF_25) 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.[22](#_ENREF_22),[23](#_ENREF_23) 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.[22](#_ENREF_22),[23](#_ENREF_23) The adenomyosis-like, adenoma-malignum, and expansile myoinvasive patterns are devoid of any specific prognostic significance.[22](#_ENREF_22),[23](#_ENREF_23) 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.[24](#_ENREF_24) 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.[26](#_ENREF_26) 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.[27-30](#_ENREF_27) Among the other potentially encountered myoinvasive patterns, single cell infiltration has been associated with an increased likelihood of extrauterine extension on multivariate analyses.[31](#_ENREF_31) Tumour budding, which is probably a different iteration of the same biologic phenomenon, has also been associated with adverse clinicopathologic features and patient outcomes.[22](#_ENREF_22),[30](#_ENREF_30),[32](#_ENREF_32),[33](#_ENREF_33) 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.[34](#_ENREF_34) The ICCR Endometrial Cancer Dataset Authoring Committee endorses the ISGyP recommendations for handling these diagnostic scenarios as summarised below:[19](#_ENREF_19)   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. 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.  7BReferences 1 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). 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| Core | LYMPHOVASCULAR INVASION | * Indeterminate * Not identified * Present   **Extent of LVI**   * Focal * Extensive/Substantial | 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.[1-4](#_ENREF_1) 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.[1](#_ENREF_1),[5](#_ENREF_5)  There are several types of artefact that simulate LVI: these include artefacts secondary to tumour disruption; MELF pattern myometrial invasion; and retraction artefacts.[1](#_ENREF_1),[2](#_ENREF_2),[6](#_ENREF_6),[7](#_ENREF_7) The first situation is predominantly encountered in the setting of laparoscopic and/or robotic surgery followed by dissection of the uterus before adequate fixation.[6-10](#_ENREF_6) 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.[1](#_ENREF_1),[2](#_ENREF_2) 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.[11](#_ENREF_11) Adding to the complexity is that MELF myometrial invasion is, indeed, associated with LVI.[12](#_ENREF_12) 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.[4](#_ENREF_4),[13](#_ENREF_13)  The absence of LVI is defined as no tumour cells within vessels.[14](#_ENREF_14) 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,[14](#_ENREF_14) but five or more vessels in the 2020 WHO Classification[15](#_ENREF_15) and in the ESGO-ESTRO-ESP guidelines.[16](#_ENREF_16)  Recent data indicate that ’substantial’ or ‘extensive’ LVI is associated with adverse outcomes when compared to carcinomas with ‘focal’ or ‘no’ LVI.[17-19](#_ENREF_17) 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.[4](#_ENREF_4) 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.[17](#_ENREF_17),[18](#_ENREF_18),[20](#_ENREF_20) Thus, the presence of substantial LVI may highlight the need for adjuvant treatment, such as recommended in the 2020 ESGO-ESTRO-ESP consensus guidelines.[16](#_ENREF_16) 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’.  **References**  1 McCluggage WG (2018). Pathologic staging of endometrial carcinomas: selected areas of difficulty. *Adv Anat Pathol* 25(2):71-84.  2 Soslow RA (2016). 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| Non-core | CERVICAL SURFACE OR CRYPT | * Not involved * Involved | 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.[1](#_ENREF_1) However, it is a potential adverse risk factor for locoregional recurrence and may be taken into consideration for adjuvant radiotherapy.[2](#_ENREF_2) 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).[3-6](#_ENREF_3) 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.[7](#_ENREF_7)  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.[8](#_ENREF_8),[9](#_ENREF_9) 8BReferences 1 FIGO Committee on Gynecological Cancer (2009). Revised FIGO staging for carcinoma of the vulva, cervix and endometrium. *Int. J. Gynecol. Obstet.* 105:103-104.  2 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.  3 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.  4 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.  5 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.  6 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.  7 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.  8 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.  9 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. |  |
| Non-core | LOWER UTERINE SEGMENT | * Not involved * Involved | As stated in **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.[1](#_ENREF_1) 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.[2](#_ENREF_2) 9BReferences 1 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.  2 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. |  |
| Core and  Non-core | CERVICAL STROMA | * Indeterminate * Not involved * Involved   **Depth of cervical stromal**  **invasion** (see Note in  commentary) \_\_\_\_ mm    **Percentage of cervical stromal**  **Invasion** \_\_\_\_ % | Cervical stromal invasion indicates Stage II endometrial carcinoma according to the current FIGO Staging System and is a core element for reporting.[1](#_ENREF_1) Cervical stromal invasion is associated with a significant risk of recurrence and is a predictor of pelvic lymph node metastases.[2](#_ENREF_2),[3](#_ENREF_3) However, the role of cervical stromal involvement as an independent prognosticator per se has been questioned.[4](#_ENREF_4) Cervical stromal invasion often occurs in the presence of other adverse features such as high histologic grade, deep myometrial invasion and LVI.[5](#_ENREF_5) In one study, the presence of these factors conferred worse disease-free survival in patients with Stage II endometrial cancer.[6](#_ENREF_6)  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).[7](#_ENREF_7)  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.[8](#_ENREF_8),[9](#_ENREF_9) 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.[8](#_ENREF_8) 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.[10](#_ENREF_10) 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.[8](#_ENREF_8) 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. 10BReferences 1 FIGO Committee on Gynecological Cancer (2009). Revised FIGO staging for carcinoma of the vulva, cervix and endometrium. *Int. J. Gynecol. Obstet.* 105:103-104.  2 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.  3 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.  4 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). 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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.  8 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.  9 McCluggage WG (2018). Pathologic staging of endometrial carcinomas: selected areas of difficulty. *Adv Anat Pathol* 25(2):71-84.  10 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.  **Depth of cervical stromal invasion**  The National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology Uterine Neoplasms lists deep cervical stromal invasion as an adverse risk factor in patients with Stage II endometrial carcinoma.[1](#_ENREF_1) While external beam radiation therapy 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.[1](#_ENREF_1)  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 millimetre (mm); >1 mm and ≤3 mm; >3 mm and ≤5 mm; >5 mm), and found no statistical association with survival.[2](#_ENREF_2) 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.[3](#_ENREF_3) Absolute depth of cervical stromal invasion and percentage of cervical stromal invasion are non-core elements. 11BReferences 1 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).  2 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.  3 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. |  |
| Core | PARAMETRIAa | * Not involved * Involved | 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.[1](#_ENREF_1) Although not an independent prognostic indicator, parametrial involvement by direct extension is a poor prognostic factor.[2-4](#_ENREF_2) 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.[2-4](#_ENREF_2) Reporting of the presence or absence of parametrial involvement in hysterectomy specimens containing parametrial tissue is a core element. 12BReferences 1 FIGO Committee on Gynecological Cancer (2009). Revised FIGO staging for carcinoma of the vulva, cervix and endometrium. *Int. J. Gynecol. Obstet.* 105:103-104.  2 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.  3 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.  4 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. | a If submitted |
| Core | VAGINAa | * Not involved * Involved | 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).[1](#_ENREF_1) 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.[2](#_ENREF_2) 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.[3](#_ENREF_3),[4](#_ENREF_4)In the majority of cases, recurrence involves the upper vagina, while recurrence in the middle third or distal vagina is less common.[5](#_ENREF_5) In a study by Moschiano et al (2014),[5](#_ENREF_5) 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.[5](#_ENREF_5)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.[6](#_ENREF_6)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.[7](#_ENREF_7)  **References**  1 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.  2 Hirschowitz L, Nucci M and Zaino RJ (2013). Problematic issues in the staging of endometrial, cervical and vulval carcinomas. *Histopathology* 62(1):176-202.  3 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.  4 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.  5 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.  6 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.  7 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. | a If submitted |
| Core | OMENTUMa | * Not involved * Involved | 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.[1](#_ENREF_1),[2](#_ENREF_2) Omental metastases are associated with other adverse prognostic features such as high tumour grade, serous histology, deep myometrial invasion, LVI and adnexal involvement.[1](#_ENREF_1),[3](#_ENREF_3)  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).[4](#_ENREF_4),[5](#_ENREF_5) The previous version of the ICCR Endometrial cancer dataset did not make recommendations on this staging component.[6](#_ENREF_6)  Omental metastases by endometrial carcinomas are uncommon. One study documented that 92.7% of omentectomy specimens for staging of endometrial adenocarcinoma showed no tumour. 13BReferences 1 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.  2 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.  3 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.  4 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.  5 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.  6 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. | a If submitted |
| Core and Non-core | PERITONEAL BIOPSIESa | * Not involved * Involved   **Site(s) of involvement**   * Pelvic * Abdominal   Specify site \_\_\_\_ | 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.[1](#_ENREF_1)  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). 14BReference 1 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. | a If submitted |
| Non-core | PERITONEAL CYTOLOGY | * Positive * Negative * Atypical/suspicous | 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.[1-4](#_ENREF_1)  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.[5](#_ENREF_5) FIGO and the Union for International Cancer Control (UICC) recommend to record positive peritoneal washings but without altering the tumour stage.[4](#_ENREF_4),[6](#_ENREF_6) 15BReferences 1 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).  2 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.  3 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.  4 FIGO Committee on Gynecological Cancer (2009). Revised FIGO staging for carcinoma of the vulva, cervix and endometrium. *Int. J. Gynecol. Obstet.* 105:103-104.  5 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.  6 Brierley JD, Gospodarowicz MK and Wittekind C (eds) (2016). *UICC TNM Classification of Malignant Tumours, 8th Edition*, Wiley, USA. |  |
| Core | UTERINE SEROSA | * Not involved * Involved | Documentation of the presence or absence of serosal involvement is a core element. According to ESGO-ESTRO-ESP[1](#_ENREF_1) and ISGyP guidelines,[2](#_ENREF_2) 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).[3](#_ENREF_3) 16BReferences 1 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.  2 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.  3 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. |  |
| Core | ADNEXAa | * Not involved * Involved   **Site(s) of involvement**   * Ovary(ies) * Left * Right * Laterallity not specified * Fallopian tube(s) * Left * Right * Laterallity not specified   Describe involvement (e.g., musocal) \_\_\_\_ | The presence or absence of adnexal involvement is a core element. Adnexal involvement has an impact on overall survival rate.[1-3](#_ENREF_1) The presence of adnexal involvement categorises a tumour as Stage IIIA in FIGO and pT3a in TNM Staging Systems, respectively.[1-3](#_ENREF_1) Prognosis is worse when ovarian metastases are associated with metastases at other sites.[4](#_ENREF_4) 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.[5](#_ENREF_5) 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.[6](#_ENREF_6)  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 .[7-10](#_ENREF_7) 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,[11](#_ENREF_11) 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.[12](#_ENREF_12),[13](#_ENREF_13) 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.[14](#_ENREF_14),[15](#_ENREF_15) 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.[10](#_ENREF_10) In this scenario, endometrioid carcinomas of the endometrium may coexist with ovarian clear cell carcinoma.[16](#_ENREF_16),[17](#_ENREF_17)  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.[4](#_ENREF_4) 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,[18](#_ENREF_18) 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.[19](#_ENREF_19) 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.[20](#_ENREF_20)  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.[21](#_ENREF_21) 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.[22](#_ENREF_22) 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.[23](#_ENREF_23)  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. 17BReferences 1 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.  2 Brierley JD, Gospodarowicz MK and Wittekind C (eds) (2016). *UICC TNM Classification of Malignant Tumours, 8th Edition*, Wiley, USA.  3 FIGO Committee on Gynecological Cancer (2009). Revised FIGO staging for carcinoma of the vulva, cervix and endometrium. *Int. J. Gynecol. 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| Core and Non-core | MARGIN STATUS | **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 | 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.[1](#_ENREF_1),[2](#_ENREF_2) 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.[3](#_ENREF_3),[4](#_ENREF_4) 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.[5](#_ENREF_5) 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 millimetres. 18BReferences 1 FIGO Committee on Gynecological Cancer (2009). Revised FIGO staging for carcinoma of the vulva, cervix and endometrium. *Int. J. Gynecol. Obstet.* 105:103-104.  2 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.  3 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.  4 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.  5 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. | Applicable only if appropriate anatomical structures  Submitted*.* |
| Non-core | BACKGROUND ENDOMETRIUM | * Cyclical * Atrophic/inactive * Hyperplasia without atypia * Atypical hyperplasia /endometrioid intraepithelial neoplasia * Other, *specify* | The background endometrium may provide useful information regarding tumour pathogenesis and may have prognostic implications.[1](#_ENREF_1) The presence of stromal predecidual change and Arias-Stella reaction may serve as evidence of preoperative hormonal therapy.[2](#_ENREF_2) 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.[3](#_ENREF_3),[4](#_ENREF_4) These lesions predispose to endometrioid carcinoma.[5-7](#_ENREF_5) 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.[8](#_ENREF_8),[9](#_ENREF_9) A precursor of clear cell carcinoma has not yet been defined.[10](#_ENREF_10),[11](#_ENREF_11)  Carcinomas arising in an endometrial polyp, may be endometrioid or serous in type, with the latter being more common.[12](#_ENREF_12) 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.[13](#_ENREF_13),[14](#_ENREF_14) Papillary mucinous metaplasia and complex mucinous glandular proliferation predispose to endometrioid carcinoma with mucinous differentiation.[15](#_ENREF_15),[16](#_ENREF_16)   19BReferences 1 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.  2 Yamani F and Fadare O (2016). 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| Core and Non-core | LYMPH NODE STATUS | * Cannot be assessed * No nodes submitted or found   **Maximum dimension of**  **largest deposit in regional node**  \_\_\_ mm  Extracapsular spread   * Not identified * Present   **Other values are listed in Table 2.**  **Table 2 (See the end of the document for Tables)** | 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).[1](#_ENREF_1) In contrast, a therapeutic benefit from lymph node resection has not been shown yet in randomised trials,[2-4](#_ENREF_2) although a large retrospective study has shown benefit from extensive nodal dissection especially in serous tumours.[4](#_ENREF_4)  Intraoperative frozen section analysis can be useful to assess lymph node metastases.[5](#_ENREF_5) The technique has its limitations for the detection of micrometastasis and isolated tumour cells.[6](#_ENREF_6) 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 millimetres (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.[1](#_ENREF_1),[7](#_ENREF_7),[8](#_ENREF_8) 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.[7](#_ENREF_7),[8](#_ENREF_8) According to TNM8,[8](#_ENREF_8) 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.[7-10](#_ENREF_7)  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.[11-14](#_ENREF_11) 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.[15](#_ENREF_15),[16](#_ENREF_16)  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.[17](#_ENREF_17),[18](#_ENREF_18)  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.[19](#_ENREF_19) 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.[20](#_ENREF_20) 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.[21](#_ENREF_21) 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,[2-4](#_ENREF_2) 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 ESGO-ESTRO-ESP 2020 guidelines,[22](#_ENREF_22) 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.[23](#_ENREF_23)  Ultrastaging is recommended for the analysis of sentinel nodes negative for metastasis by routine histopathologic analysis since it provides valuable clinical information.[24](#_ENREF_24),[25](#_ENREF_25) Notably, if sentinel nodes are negative by ultrastaging the occurrence of isolated nodal paraaortic metastasis is less likely.[22](#_ENREF_22),[25](#_ENREF_25) 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.[24-27](#_ENREF_24) 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.[24](#_ENREF_24) Another protocol uses H&E and pankeratin IHC at 50 μm into the tissue block with a total of five sections per block. 20BReferences 1 FIGO Committee on Gynecological Cancer (2009). Revised FIGO staging for carcinoma of the vulva, cervix and endometrium. *Int. J. Gynecol. Obstet.* 105:103-104.  2 Kitchener H, Swart AM, Qian Q, Amos C and Parmar MK (2009). 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| Core and Non-core | ANCILLARY STUDIES | * Not performed * 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* | **Immunohistochemistry for mismatch repair proteins and MLH1 promoter methylation**  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.[1](#_ENREF_1)  Endometrial cancer is one of the most common tumours in patients with Lynch syndrome (also known as hereditary non-polyposis colorectal cancer).[2](#_ENREF_2),[3](#_ENREF_3) 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.[4](#_ENREF_4) ‘Constitutive methylation’ is also a rare cause of Lynch syndrome.[5](#_ENREF_5)  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;[6](#_ENREF_6) 3. Prognostic, as part of the TCGA surrogate molecular classification;[7](#_ENREF_7) and 4. Therapeutically as a predictive biomarker for potential utility of immune checkpoint inhibitor therapy.[8](#_ENREF_8)   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.[9](#_ENREF_9) ISGyP has recommended testing for MMR status/MSI in all endometrial carcinomas (preferably curettings or biopsy), irrespective of age.[1](#_ENREF_1) This has also been recommended whenever resources are available by other societies/groups, such as the Manchester International Consensus Group.[10](#_ENREF_10) 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.  MSI can be detected by different methods, including polymerase chain reaction (PCR)-based approaches[9](#_ENREF_9),[11](#_ENREF_11),[12](#_ENREF_12) and next generation sequencing (NGS).[13](#_ENREF_13) NGS is in the process of being validated for this scenario. MSI can also be accurately predicted using IHC.  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.[1](#_ENREF_1) 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.[14](#_ENREF_14) Carcinomas showing loss of MLH1 and PMS2 expression should be investigated for MLH1 promoter hypermethylation,[15](#_ENREF_15) 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.  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.[16](#_ENREF_16)  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.[17](#_ENREF_17) 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.[18](#_ENREF_18)  **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.[19](#_ENREF_19) The different histologic types have different molecular features, microscopic appearances, precursor lesions, and natural history, although in multivariate analyses,[20](#_ENREF_20) 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[21-23](#_ENREF_21) 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.[24](#_ENREF_24) 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.[24-27](#_ENREF_24) 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.[24](#_ENREF_24),[28-30](#_ENREF_28) 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.[7](#_ENREF_7),[29](#_ENREF_29),[30](#_ENREF_30) 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.[1](#_ENREF_1),[28](#_ENREF_28),[31](#_ENREF_31)  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.[7](#_ENREF_7),[30](#_ENREF_30)  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.[32](#_ENREF_32) Application of this algorithm for clear cell carcinoma,[33](#_ENREF_33) undifferentiated carcinoma,[34](#_ENREF_34) neuroendocrine carcinoma,[35](#_ENREF_35) and carcinosarcoma[36](#_ENREF_36) is possible, but this is currently considered investigational as these tumours were not included in the original TCGA paper.[24](#_ENREF_24) 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., Post Operative Radiation Therapy in Endometrial Carcinoma-2 (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.[7](#_ENREF_7) Also, most evidence in support of the TCGA classification is based on two large but retrospective cohorts.[7](#_ENREF_7),[30](#_ENREF_30) There are two additional complexities to *POLE* testing: distinguishing between pathogenic and non-pathogenic mutations,[37](#_ENREF_37) and coexistence of ultramutation (i.e., pathogenic *POLE* mutation) with secondary mutations in *TP53* and/or one or more of the DNA MMR genes.[38](#_ENREF_38) 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**  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).[39](#_ENREF_39) Napsin A, HNF1-beta and AMACR (together with negative estrogen receptor (ER))[40](#_ENREF_40),[41](#_ENREF_41) 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,[42](#_ENREF_42) and GATA3, TTF1, CD10 and calretinin may help in recognising mesonephric-like carcinoma.[43](#_ENREF_43),[44](#_ENREF_44) 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.[45](#_ENREF_45)  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,[46-48](#_ENREF_46) and 14% of endometrial carcinosarcomas.[49](#_ENREF_49) Intratumoural heterogeneity of HER2 expression and gene amplification are common in these tumours and should be taken into consideration when evaluating their HER2 status.[46](#_ENREF_46),[50](#_ENREF_50) HER2 positivity in endometrial serous carcinomas is associated with worse progression free and overall survival,[51](#_ENREF_51) but they can be therapeutically targeted by adding trastuzumab to the standard chemotherapy regimen.[52](#_ENREF_52),[53](#_ENREF_53) 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.[54](#_ENREF_54) 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.[55](#_ENREF_55)  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.[56-58](#_ENREF_56) 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.[30](#_ENREF_30),[59](#_ENREF_59),[60](#_ENREF_60)  ER expression has been associated with tumour behaviour and survival in endometrioid tumours.[61](#_ENREF_61),[62](#_ENREF_62) 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.[63](#_ENREF_63)  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.[64](#_ENREF_64) 21BReferences 1 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). 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| Core | PATHOLOGICALLY CONFIRMED DISTANT METASTASIS | * None identified * Present, *specify* | 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. | Report when tissue submitted for evaluation. |
| Core | PROVISIONAL PATHOLOGICAL STAGING | **FIGO (2014 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 uterusd   * III Local and/or regional spread of the tumour * IIIA Tumour invades the serosa of the corpus uteri and/or * adnexaee * IIIB Vaginal involvement and/or parametrial involvemente * IIIC Metastases to pelvic and/or para-aortic lymph nodese * 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   **TNM Staging (UICC TNM 8th edition 2016)f**  **TNM Descriptors**  (only if applicable)   * 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 uterig * 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 mucosah   **Regional lymph nodes (pN)**   * NX Regional lymph nodes cannot be assessed * N0 No regional lymph node metastasis * N1 Metastasis to pelvic lymph nodesi * N2 Metastasis to para-aortic lymph nodes with or without metastasis to pelvic lymph nodesi | 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.[1-4](#_ENREF_1)  The latest version of either FIGO *or* TNM staging, *or* both, can be used depending on local preferences.[1-4](#_ENREF_1) 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.[3](#_ENREF_3),[4](#_ENREF_4) 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.”[5](#_ENREF_5) 22BThe reference document TNM Supplement: A commentary on uniform use, 5th edition (C Wittekind et al. editors) [may](http://au.wiley.com/WileyCDA/Section/id-370022.html?query=Christian+Wittekind) be of assistance when staging.[6](#_ENREF_6)23BReferences 1 FIGO Committee on Gynecological Cancer (2009). Revised FIGO staging for carcinoma of the vulva, cervix and endometrium. *Int. J. Gynecol. Obstet.* 105:103-104.  2 Amant F, Mirza MR, Koskas M and Creutzberg CL (2018). 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Note that permission to publish the TNM cancer staging tables may be needed in your implementation. It is advisable to check.  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.  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. |

**Tables**

**Table 1: World Health Organization classification of tumours of the uterine corpus.**[**1**](#_ENREF_1)

| **Descriptor** | **ICD-O codesa** |
| --- | --- |
| **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).[43](#_ENREF_43) 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)/WHO Committee for ICD-O at its meeting in June 2020. Incorporates all relevant changes from the 5th edition Corrigenda June 2021.

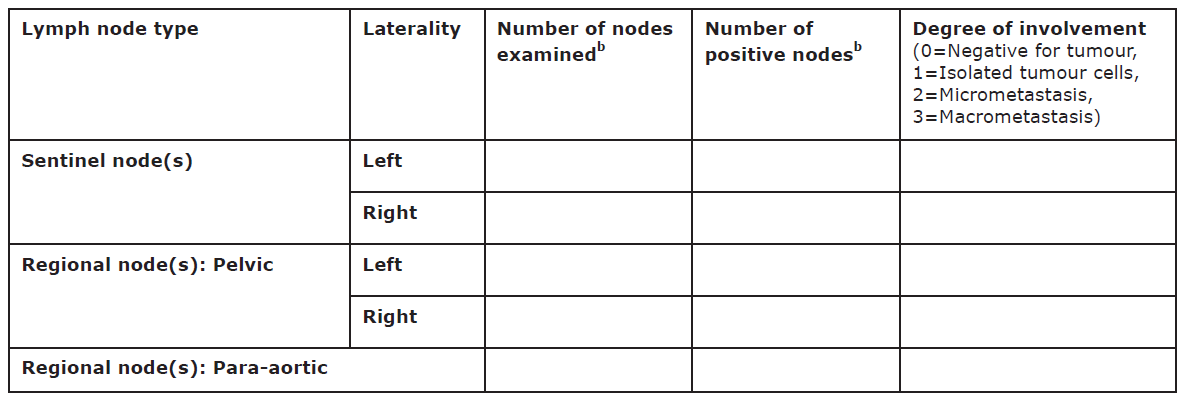
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**Table 2: Lymph node status – core and non-core element. All feilds listed in this table are core.**



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.