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Ovary, Fallopian Tube and Primary Peritoneal Carcinoma Histopathology Reporting Guide

Family/Last name

Given name(s)

Date of birth DD – MM – YYYY

Patient identifiers

Date of request DD – MM – YYYY

Accession/Laboratory number

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

☐ indicates multi-select values ◯ indicates single select values

SCOPE OF THIS DATASET

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

- ◯ Information not provided
- ☐ Known gene predisposition (e.g., *BRCA1*, *BRCA2*, Lynch syndrome), *specify*
- ☐ Prior neoadjuvant therapy, *specify*
- ☐ Other, *specify*

SPECIMEN(S) SUBMITTED (select all that apply) (Note 2)

- ◯ Not specified
- ☐ Ovary
  - ☐ Left ☐ Right ◯ Laterality not specified
- ☐ Ovarian cystectomy
  - ☐ Left ☐ Right ◯ Laterality not specified
- ☐ Fallopian tube
  - ☐ Left ☐ Right ◯ Laterality not specified
- ☐ Uterus
- ☐ Cervix
- ☐ Omentum
- ☐ Peritoneal biopsies
- ☐ Peritoneal washings/peritoneal fluid
- ☐ Lymph nodes, *specify site(s)*
- ☐ Other, *specify*

SPECIMEN INTEGRITY (select all that apply) (Note 3)

(Required only if ovary(ies)/fallopian tube(s) are submitted)

Left ovary

- ☐ Ovarian capsule intact
- ☐ Ovarian capsule ruptured
  - ◯ Information not provided
  - ◯ Preoperatively
  - ◯ Intraoperatively
- ☐ Tumour on surface
- ☐ Fragmented specimen
- ☐ Other, *specify*

Right ovary

- ☐ Ovarian capsule intact
- ☐ Ovarian capsule ruptured
  - ◯ Information not provided
  - ◯ Preoperatively
  - ◯ Intraoperatively
- ☐ Tumour on surface
- ☐ Fragmented specimen
- ☐ Other, *specify*

Left fallopian tube

- ☐ Serosa intact
- ☐ Serosa ruptured
  - ◯ Information not provided
  - ◯ Preoperatively
  - ◯ Intraoperatively
- ☐ Tumour on serosal surface
- ☐ Fragmented specimen
- ☐ Other, *specify*

Right fallopian tube

- ☐ Serosa intact
- ☐ Serosa ruptured
  - ◯ Information not provided
  - ◯ Preoperatively
  - ◯ Intraoperatively
- ☐ Tumour on serosal surface
- ☐ Fragmented specimen
- ☐ Other, *specify*

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

- ◯ No macroscopically visible tumour
- ◯ Indeterminate
- ☐ Ovary
  - ☐ Left ☐ Right ◯ Laterality not specified
- ☐ Fallopian tube
  - ☐ Left ☐ Right ◯ Laterality not specified
    - ☐ Fimbrial ☐ Fimbrial
    - ☐ Non-fimbrial ☐ Non-fimbrial
- ☐ Peritoneum
- ☐ Other, *specify*

TUMOUR DIMENSIONS (Note 5)

(If separate tumours specify dimensions for each site)

mm x mm x mm

MACROSCOPIC DESCRIPTION OF OMENTUM (Note 6)

(Required only if omentum submitted)

Omentum dimensions

mm x mm x mm

Omental involvement

- ◯ Not involved
- ◯ Involved

Maximum dimension of largest tumour deposit mm

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BLOCK IDENTIFICATION KEY (Note 7)
(List overleaf or separately with an indication of the nature and origin of all tissue blocks)

HISTOLOGICAL TUMOUR TYPE (select all that apply) (Note 8)
(Value list based on the World Health Organization Classification of Female Genital Tumours (2020))

- ☐ Serous borderline tumour
- ☐ Low grade serous carcinoma
- ☐ High grade serous carcinoma
- ☐ Mucinous borderline tumour
- ☐ Mucinous carcinoma
- ☐ Endometrioid borderline tumour
- ☐ Endometrioid carcinoma
- ☐ Clear cell borderline tumour
- ☐ Clear cell carcinoma
- ☐ Seromucinous borderline tumour
- ☐ Borderline Brenner tumour
- ☐ Malignant Brenner tumour
- ☐ Mesonephric-like adenocarcinoma
- ☐ Carcinoma, undifferentiated
- ☐ Dedifferentiated carcinoma
- ☐ Carcinosarcoma
- ☐ Mixed carcinoma
- ☐ Other, *specify*

PATTERN OF INVASION (Note 9)
(Applicable for mucinous carcinomas only)

- ◯ Expansile
- ◯ Infiltrative/destructive

CARCINOSARCOMA COMPONENTS (select all that apply) (Note 10)

- ☐ Epithelial
  - Percentage ____ %
  - List components
- ☐ Sarcomatous
  - Percentage ____ %
  - Type ◯ Homologous ◯ Heterologous
  - List components

HISTOLOGICAL TUMOUR GRADE (Note 11)

Endometrioid carcinomas

- ◯ GX: Cannot be assessed
- ◯ G1: Well differentiated
- ◯ G2: Moderately differentiated
- ◯ G3: Poorly differentiated

Mucinous carcinomas

- ◯ GX: Cannot be assessed
- ◯ G1: Well differentiated
- ◯ G2: Moderately differentiated
- ◯ G3: Poorly differentiated

BORDERLINE TUMOUR - SPECIAL FEATURES (Note 12)
(Applicable only if borderline tumour is identified)

Micropapillary architecture for serous borderline tumour *(at least 5 mm in one dimension)*

- ◯ Not identified
- ◯ Present

Microinvasion *(upper limit 5 mm)*

- ◯ Not identified
- ◯ Present

Intraepithelial carcinoma for mucinous borderline tumour

- ◯ Not identified
- ◯ Present

Implants for serous and seromucinous borderline tumour (select all that apply)

- ☐ Non-invasive implants
  - ◯ Not identified
  - ◯ Present
    - ◯ Epithelial
    - ◯ Desmoplastic
    - Site(s) ☐ Pelvic ☐ Abdominal
- ☐ Invasive implants/Extra-ovarian low grade serous carcinoma
  - ◯ Not identified
  - ◯ Present
    - Site(s) ☐ Pelvic ☐ Abdominal
- ☐ Indeterminate
  - ◯ Not identified
  - ◯ Present
    - Site(s) ☐ Pelvic ☐ Abdominal

SEROUS TUBAL INTRAEPITHELIAL CARCINOMA (STIC)
(Required only if fallopian tube(s) are submitted) (Note 13)

Left fallopian tube

- ◯ Cannot be assessed
- ◯ Not identified
- ◯ Present (select all that apply)
  - ☐ Fimbrial
  - ☐ Non-fimbrial

Right fallopian tube

- ◯ Cannot be assessed
- ◯ Not identified
- ◯ Present (select all that apply)
  - ☐ Fimbrial
  - ☐ Non-fimbrial

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HISTOLOGICAL SITES OF TUMOUR INVOLVEMENT (Note 4)

Left ovary
- ◯ Not applicable
- ◯ Cannot be assessed
- ◯ Not involved
- ◯ Involved

Right ovary
- ◯ Not applicable
- ◯ Cannot be assessed
- ◯ Not involved
- ◯ Involved

Left fallopian tube
- ◯ Not applicable
- ◯ Cannot be assessed
- ◯ Not involved
- ◯ Involved

Right fallopian tube
- ◯ Not applicable
- ◯ Cannot be assessed
- ◯ Not involved
- ◯ Involved

Uterus
- ◯ Not applicable
- ◯ Cannot be assessed
- ◯ Not involved
- ◯ Involved (select all that apply)
  - Site(s)
    - ☐ Myometrium
    - ☐ Endometrium
    - ☐ Cervix

Omentum
- ◯ Not applicable
- ◯ Cannot be assessed
- ◯ Not involved
- ◯ Involved
  - Level of involvement
    - ◯ Macroscopic ◯ Microscopic

Peritoneum (including uterine serosa)
- ◯ Not applicable
- ◯ Cannot be assessed
- ◯ Not involved
- ◯ Involved (select all that apply)
  - Site(s)
    - ☐ Pelvis, *specify site(s)*
    - ☐ Abdomen, *specify site(s)*

Other involved organs(s)/sites(s), *specify*

PERITONEAL CYTOLOGY (Note 14)
- ◯ Not submitted
- ◯ Indeterminate
- ◯ Positive
- ◯ Negative

RESPONSE TO NEOADJUVANT THERAPY (Note 15)
- ◯ Cannot be assessed
- ◯ No prior treatment
- ◯ No definite or minimal response identified (chemotherapy response score (CRS 1))
- ◯ Moderate response identified (CRS 2)
- ◯ Marked response with no or minimal residual cancer (CRS 3)

LYMPH NODE STATUS (Note 16)
- ◯ Cannot be assessed
- ◯ No nodes submitted or found
- ◯ Not involved
- ◯ Involved (select all that apply)
  - ☐ **Regional**
    - ☐ **Left pelvic**
      - Number of nodes examined[a]
      - Number of positive nodes[a]
    - ☐ **Right pelvic**
      - Number of nodes examined[a]
      - Number of positive nodes[a]
    - ☐ **Para-aortic**
      - Number of nodes examined[a]
      - Number of positive nodes[a]
    - **Maximum dimension of largest deposit in regional node** mm
  - ☐ **Non-regional**
    - ☐ **Site 1**
      - Number of nodes examined[a]
      - Number of positive nodes[a]
    - ☐ **Site 2**
      - Number of nodes examined[a]
      - Number of positive nodes[a]

[a] *In some cases it may not be possible to record the actual number of nodes due to fragmentation of the specimen.*

COEXISTENT PATHOLOGY/PRECURSOR LESIONS (Note 17)
- ◯ None identified
- ◯ Present, *specify*

ANCILLARY STUDIES (Note 18)
- ◯ Not performed
- ◯ Performed (select all that apply)
  - ☐ Immunohistochemistry, *specify test(s) and result(s)*
  - ☐ Molecular findings, *specify test(s) and result(s)*
  - ☐ Other, *specify test(s) and result(s)*

ANCILLARY STUDIES (Cont.) (Note 18)

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

PROVISIONAL PATHOLOGICAL STAGING (Note 19)

FIGO (2014 edition)[b]

Site of primary tumour

- ◯ Primary tumour, ovary (OV)
- ◯ Primary tumour, fallopian tube (FT)
- ◯ Primary tumour, peritoneum (P)
- ◯ Undesignated: site of primary tumour cannot be assessed (X)
- ◯ I Tumour is confined to ovaries or fallopian tube(s)
  - ◯ IA Tumour limited to 1 ovary (capsule intact) or fallopian tube; no tumor on ovarian or fallopian tube surface; no malignant cells in the ascites or peritoneal washings
  - ◯ IB Tumour limited to both ovaries (capsules intact) or fallopian tubes; no tumour on ovarian or fallopian tube surface; no malignant cells in the ascites or peritoneal washings
  - ◯ IC Tumour limited to 1 or both ovaries or fallopian tubes,with any of the following:
    - ◯ IC1 Surgical spill
    - ◯ IC2 Capsule ruptured before surgery or tumour on ovarian or fallopian tube surface
    - ◯ IC3 Malignant cells in the ascites or peritoneal washings
- ◯ II Tumour involves 1 or both ovaries or fallopian tubes with pelvic extension (below pelvic brim) or primary peritoneal cancer
  - ◯ IIA Extension and/or implants on uterus and/or fallopian tubes and/or ovaries
  - ◯ IIB Extension to other pelvic intraperitoneal tissues
- ◯ III Tumour involves 1 or both ovaries or fallopian tubes, or primary peritoneal cancer, with cytologically or histologically confirmed spread to the peritoneum outside the pelvis and/or metastasis to the retroperitoneal lymph nodes
  - ◯ IIIA1 Positive retroperitoneal lymph nodes only (cytologically or histologically proven):
    - ◯ IIIA1(i) Metastasis up to 10 mm in greatest dimension
    - ◯ IIIA1(ii) Metastasis more than 10 mm in greatest dimension
  - ◯ IIIA2 Microscopic extrapelvic (above the pelvic brim) peritoneal involvement with or without positive retroperitoneal lymph nodes
  - ◯ IIIB Macroscopic peritoneal metastasis beyond the pelvis up to 2 cm in greatest dimension, with or without metastasis to the retroperitoneal lymph nodes
  - ◯ IIIC Macroscopic peritoneal metastasis beyond the pelvis more than 2 cm in greatest dimension, with or without metastasis to the retroperitoneal lymph nodes (includes extension of tumor to capsule of liver and spleen without parenchymal involvement of either organ)
- ◯ IV Distant metastasis excluding peritoneal metastases
  - ◯ IVA Pleural effusion with positive cytology
  - ◯ IVB Parenchymal metastases and metastases to extra abdominal organs (including inguinal lymph nodes and lymph nodes outside of the abdominal cavity)

[b] *Reprinted from Int J Gynaecol Obstet., Volume 124, Prat J and FIGO Committee on Gynecologic Oncology, Staging classification for cancer of the ovary, fallopian tube, and peritoneum, pages 1-5, 2014, with permission from Wiley.*

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

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

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

Primary tumour (pT)

- ◯ TX Primary tumour can not be assessed
- ◯ T0 No evidence of primary tumour
- ◯ T1 Tumour limited to the ovaries (one or both) or fallopian tube(s)
  - ◯ T1a Tumour limited to one ovary (capsule intact) or fallopian tube; capsule intact, no tumor on ovarian surface or fallopian tube surface; no malignant cells in ascites or peritoneal washings
  - ◯ T1b Tumour limited to both ovaries or fallopian tubes; casule intact, no tumour on ovarian or fallopian tube surface; no malignant cells in ascites or peritoneal washings
  - ◯ T1c Tumour limited to one or both ovaries or fallopian tubes with any of the following:
    - ◯ T1c1 Surgical spill
    - ◯ T1c2 Capsule ruptured before surgery or tumour on ovarian or fallopian tube surface
    - ◯ T1c3 Malignant cells in ascites or peritoneal washings
- ◯ T2 Tumour involves one or both ovaries or fallopian tubes with pelvic extension (below pelvic brim) or primary peritoneal cancer
  - ◯ T2a Extension and/or implants on uterus and/or fallopian tube(s) and/or ovary(ies)
  - ◯ T2b Extension to other pelvic tissues, including bowel within the pelvis
- ◯ T3 and/or N1 Tumour involves one or both ovaries or fallopian tubes or primary peritoneal carcinoma with cytologically or histologically confirmed spread to the peritoneum outside the pelvis and/or metastasis to the retroperitoneal lymph nodes

Regional lymph nodes (pN)

- ◯ N1 Retroperitoneal lymph node metastasis only
  - ◯ N1a Lymph node metastasis not more than 10 mm in greatest dimension
  - ◯ N1b Lymph node metastasis more than 10 mm in greatest dimension
  - ◯ T3a any N Microscopic extrapelvic (above the pelvic brim) peritoneal involvement with or without retroperitoneal lymph node, including bowel involvement
  - ◯ T3b any N Macroscopic peritoneal metastasis beyond pelvic brim 2 cm, or less in greatest dimension, including bowel involvement outside the pelvis with or without retroperitoneal nodes
  - ◯ T3c any N Peritoneal metastasis beyond pelvic brim more than 2 cm in greatest dimension and/or retroperitoneal lymph node metastasis (includes extension of tumour to capsule of liver and spleen without parenchymal involvement of either organ)

[c] *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).*

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Definitions

CORE elements

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

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

NON-CORE elements

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

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

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Scope

The dataset has been developed for the pathology reporting of resection specimens of primary borderline and malignant epithelial tumours of the ovary, fallopian tubes and peritoneum. It does not include non-epithelial ovarian neoplasms such as germ cell or sex cord stromal tumours or other primary peritoneal neoplasms such as mesothelioma.[2] In those rare cases where more than one primary tumour of different morphological types is present, separate datasets should be completed for each neoplasm. These should include all the elements in this dataset, except for lymph node status which does not need to be documented separately for each tumour.

The 2nd edition of this dataset includes changes to align the dataset with the World Health Organization (WHO) Classification of Tumours, Female Genital Tumours, 5th edition, 2020.[3] The International Collaboration on Cancer Reporting (ICCR) dataset includes 5th edition Corrigenda, June 2021.[4]

The authors of this dataset can be accessed here.

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Note 1 – Clinical information (Non-core)

It is estimated that approximately 10% of primary tubo-ovarian and peritoneal carcinomas have a genetic basis,[5] and this figure may be as high as 17% for high grade serous carcinomas (HGSCs).[6] Germline mutations in *BRCA1* and *BRCA2* account for the majority of genetically related cases while up to 10% of patients with Lynch syndrome (LS) will develop ovarian carcinoma.

It is acknowledged that definitive genetic status is often not known or information about genetic status is not provided to the pathologist at the time of biopsy/surgery. Moreover, this information is not essential for the histological assessment and routine reporting of these tumours. Nevertheless, it is recommended that available information on genetic status be recorded for the following reasons:

1. High grade serous carcinomas (HGSCs) associated with BRCA mutations (germline or somatic) more commonly show certain morphological features such as solid, pseudoendometrioid or transitional-like ('SET') architectural patterns, very marked nuclear atypia, and tumour-infiltrating lymphocytes.[5,7,8] Thus, pathologists may be able to correlate the histological findings with any genetic data provided, better chemotherapy response, and consideration of specific therapeutic regimes such as those including poly ADP ribose polymerase inhibitors (PARPi).[5,6,9] Patients with suspected germline *BRCA* mutations and their relatives, may also be referred for genetic testing and counselling in regard to appropriate screening for *BRCA*-related neoplasia, although in many places this is done for all HGSCs irrespective of the tumour morphology.
2. Knowledge of proven or potential hereditary gynaecological cancer predisposition will affect pathological sampling of macroscopically normal tissues. This is most evident in the setting of prophylactic 'risk reduction surgery', especially in patients with known *BRCA1* or *BRCA2* mutation, where complete examination of tubal and ovarian tissues is essential.[5] Small, macroscopically occult tubal carcinomas, and their in situ precursor - serous tubal intraepithelial carcinoma (STIC) - is much more likely to be identified in this setting.

Approximately 1-2% of all ovarian carcinomas are associated with LS due to a germline mutation in one of the genes encoding the DNA mismatch repair (MMR) proteins.[10] In approximately 60% of women with LS, a gynaecological tumour (endometrial or ovarian) will represent the sentinel cancer.[11] Endometrioid and clear cell and endometriosis-associated carcinomas occur more frequently in LS and, therefore, immunohistochemical analysis of MMR proteins or molecular testing for microsatellite instability may be considered in these tumour types, or if there is relevant personal or family history of additional LS-related neoplasia.

Preoperative chemotherapy may significantly alter the gross and microscopic appearance of the tumour and result in difficulties in tumour typing and tumour down-staging. If neoadjuvant chemotherapy is being administered, a pretreatment tissue biopsy is recommended for tumour typing. If this is not possible then the diagnosis of malignancy can be made on cytological examination of ascitic fluid, preferably with immunohistochemistry (IHC) performed on a cell block preparation; however, there are limitations to the interpretation of immunohistochemical markers on cell blocks.[12] Markers of value in tumour typing are discussed in **Note 18 ANCILLARY STUDIES**.

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Note 2 – Specimen(s) submitted (Core)

Providing information about the specimen type is regarded as an integral part of the reporting of primary ovarian, tubal and peritoneal cancers. While the nature of the specimens submitted for pathological assessment may be deduced from the surgical procedure, specifying the nature of the specimen received provides complementary information and confirmation that entire organs have been resected and submitted.

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Note 3 – Specimen integrity (Core)

Assessment of the integrity of the specimen (ovary or tube) is important, particularly for substaging of organ-confined disease (Stage I). Core information should include whether the ovarian capsule or tubal serosa is intact or ruptured, and also if there is tumour on the surface, or whether the tumour was received fragmented or intact. In case of capsule rupture, it is recommended to try to ascertain if rupture occurred before or during surgery (this is important in substaging International Federation of Gynaecology and Obstetrics (FIGO) Stage IC disease).[13] Note that if the specimen ruptures within a bag during laparoscopic removal, or is cut into in the operating room, after removal from the patient, such that the peritoneal cavity is not exposed to the contents of the mass, it should be considered to be not ruptured i.e., 'intact', for surgical pathology reporting purposes.

According to the 2014 FIGO Staging System for ovarian, tubal and primary peritoneal cancer,[13] ovarian capsular or tubal serosal rupture before surgery is considered Stage IC2 while intraoperative rupture is Stage IC1. There is some controversy as to whether rupture during surgery worsens the prognosis in the absence of surface excrescences, ascites or positive washings. Some studies showed a higher risk of recurrence in association with intraoperative ovarian capsular rupture,[14,15] while others did not.[16-18]

A 2014 meta-analysis assessed the impact of intraoperative rupture on prognosis, after analysing nine eligible studies which included 2,382 patients.[13] Patients with preoperative capsular rupture showed poorer progression-free survival (PFS) than those with no rupture or intraoperative rupture. In sub-analyses, preoperative rupture was associated with a worse prognosis, and intraoperative rupture had a poorer PFS than no rupture. However, no difference in PFS was found between intraoperative rupture and no rupture in patients who underwent a complete surgical staging operation, with or without adjuvant platinum-based chemotherapy. In a recent large study, the risk associated with intra-operative rupture/Stage IC1 ovarian carcinoma was histotype dependent and greatest for patients with clear cell carcinoma.[19]

There is some evidence to suggest that clear cell carcinomas exhibit a higher risk of rupture,[20] probably related to adhesions to the surrounding tissues, associated with tumour invasion or endometriosis.[21] Capsular rupture has also been associated with pregnancy.[22]

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Note 4 – Tumour site/Histological sites of tumour involvement (Core)

Sites of tumour involvement should be recorded as this is necessary for tumour staging. Although site assignment (tube versus ovary versus peritoneum) for clear cell, endometrioid, low grade serous and mucinous carcinomas is generally not problematic since almost all arise in the ovary, except for occasional cases arising in extraovarian endometriosis, the same is not true for HGSCs.

It was first recognised in 2001, that a high percentage of so-called ovarian HGSC in women with germline *BRCA1* mutations arise in the fimbrial end of the fallopian tube.[23,24] This was initially reported in risk reducing salpingo-oophorectomy specimens where early pre-invasive HGSCs were much more likely to be present in the fallopian tube than ovary. These STICs harbour identical *p53* mutations to the extratubal tumour, establishing that they are clonal.[25] Comparison of telomere length and centrosome amplification in matched STIC and ovarian HGSC suggests that the STICs develop before the ovarian tumours and are in fact a precursor and not a metastatic focus.[26,27] Finally, although numbers are small, early, incidental non-*BRCA1/2* associated (sporadic) HGSCs are predominantly detected in the fallopian tube mucosa, especially the fimbria, rather than the ovary.[28] In summary, there is compelling evidence that the precursors of HGSC originate in the fallopian tube in patients with germline *BRCA1* mutations, and there is accumulating and convincing evidence that this is also true for sporadic HGSC. Assignment of primary site should therefore reflect our current understanding of where HGSCs originate, based on data from the study of early incidental or pre-invasive HGSC. However, some cases of ovarian and primary peritoneal HGSCs do not show STIC lesions or tubal mucosal HGSC despite entire submission of the grossly normal fallopian tubes for histological evaluation. In a consecutive series of non-

uterine HGSCs classified as ovarian or peritoneal based on pre-FIGO 2014 criteria in which the fallopian tubes were examined in their entirety, STICs were identified in 59% of cases, and invasive HGSC of the mucosa of the fallopian tube in an additional 15% of cases.[13,29] In other cases, the fimbrial end of the fallopian tube was obliterated by a tubo-ovarian mass.

According to the 2014 FIGO Staging System, the primary site of non-uterine HGSC is designated as ovarian, tubal or primary peritoneal.[13] In some cases it may not be possible to ascertain the primary site of origin, and these should be categorised as 'undesignated' in the new staging system.[13] The descriptor 'tubo-ovarian HGSC' can also be used in practice for those cases of advanced stage HGSC where there is uncertainty about primary site, e.g., pre-treatment biopsy from the omentum. The problems in ascertaining the primary site and the variation in practice amongst pathologists have significant implications for epidemiological studies, determination of tumour incidence and mortality, data collection by cancer registries and entry into clinical trials. Based on the 2020 WHO Classification,[3] recommendations for assigning the site of origin of extra-uterine HGSC are provided in the following section. Using these criteria, assignment of primary site is no longer based on the site of greatest volume/size of tumour but the presence of STIC or tubal mucosa involvement by HGSC indicates a fallopian tube origin, as does partial or total obliteration of one or both fallopian tubes by a tumour mass. Application of these criteria will be important in ensuring consistency between different pathologists in assigning the site of origin of HGSC with obvious important implications for cancer registration and other parameters.[30]

Suggestions for assigning site of origin

The following suggestions are not intended to be an exhaustive list nor are they intended to be binding, and assignment of origin in an individual case (Figure 1) is left to the discretion of the pathologist and the clinical team, ideally in the setting of a multidisciplinary team meeting. Undoubtedly, there will be evolution over time in our ability to accurately assign the primary tumour site, but the following are intended as practical guidelines for handling cases at the present time:[30]

1. The fallopian tubes, or at least their fimbrial ends, should be well sampled – whenever possible - in all cases of HGSC by a sectioning and extensively examining the fimbriated end (SEE-FIM)-like protocol[25] to avoid missing this important site of disease, which probably represents the tumour origin in the large majority of cases.
2. The presence of STIC, in the absence of invasive HGSC involving the fallopian tube, should be considered as tubal primary for staging purposes, e.g., points 4 and 7.
3. The presence of STIC without invasion or extratubal spread should be staged as FIGO Stage IA tubal carcinoma (although these have a favourable prognosis, based on limited experience to date[31]) but with an annotation that there is no 'invasive' carcinoma.
4. Cases with only STIC in the fallopian tube, ovarian surface involvement or parenchymal involvement not exceeding 5 millimetres (mm) and widespread peritoneal involvement, which would traditionally be categorised as primary peritoneal carcinoma,[32] should be classified as tubal primaries.
5. Cases with HGSC located within the mucosa of the fallopian tube, including its fimbrial end, with or without STIC in any portion of the fallopian tube and with no, minimal or even substantial ovarian involvement should be categorised as tubal primaries. Note that the distinction between STIC and intramucosal HGSC of the fallopian tube is subjective, with the latter showing a greater degree of stratification and architectural complexity.
6. Cases in which the fallopian tube is not identifiable, having presumably been overgrown by the ipsilateral adnexal mass, or the distal end of the fallopian tube is incorporated into a large tubo-ovarian mass should also, based on current understanding, be diagnosed as tubal primaries. It is emphasised that a careful effort must be made to identify the tube in all cases.
7. Cases with a dominant ovarian mass(es) and identifiable fallopian tubes with STIC should be classified as tubal primaries.
8. Cases with a dominant ovarian mass(es) and identifiable fallopian tubes without STIC or mucosal involvement by HGSC, after SEE-FIM, should be classified as ovarian primaries.

9. Cases should be categorised as primary peritoneal carcinoma by the conventional criteria below[3] *and* only after complete histological examination of the fallopian tubes (including the non-fimbrial portions) has excluded the presence of STIC or a small tubal HGSC or ovarian involvement by HGSC.
10. All cases classified as 'undesignated' for FIGO staging purposes should be further described as 'tubo-ovarian' or 'tubal/ovarian' to distinguish them from serous carcinoma originating in the uterus. Using the suggestions presented here, these should represent a small proportion of HGSC.
11. Cases with unilateral or bilateral HGSC in the ovary and/or STIC or HGSC in the tube but with an endometrial serous intraepithelial or invasive carcinoma should be carefully evaluated for an endometrial versus a tubo-ovarian primary (WT1 may be of value in such cases - see **Note 18 ANCILLARY STUDIES**, to distinguish between ovarian and uterine carcinoma). The majority of such cases will represent adnexal metastases from an endometrial serous carcinoma.[33]

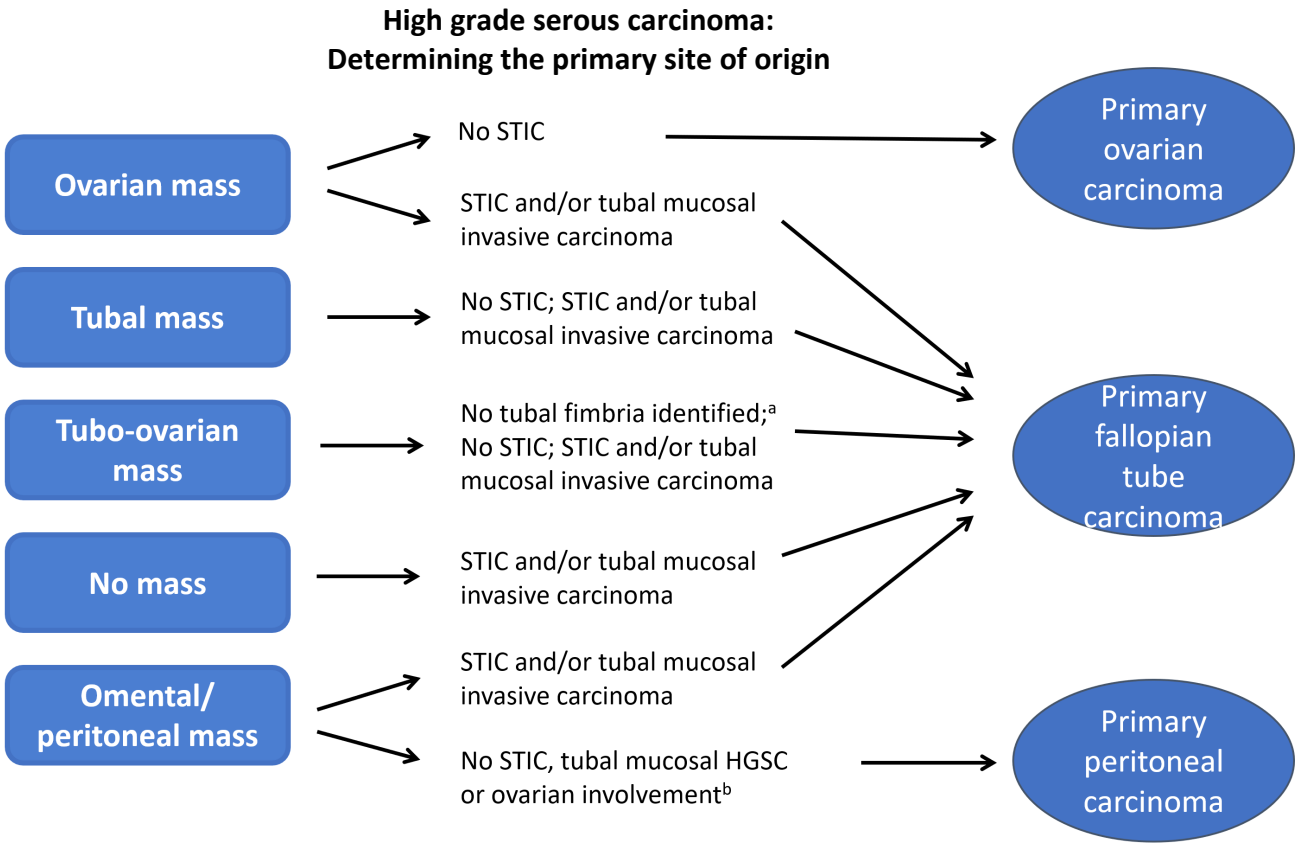

Figure 1: High grade serous carcinoma: determining the primary site of origin. Serous tubal intraepithelial carcinoma (STIC).

[a] Failure to detect the tubal fimbria implies overgrowth by tumour.

[b] Apply criteria as specified in the commentary.

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Note 5 – Tumour dimensions (Non-core)

There is little or no published evidence to suggest that size of the primary tumour is of prognostic significance, and size is not important for staging or management. The principal reason for recording the tumour dimensions, especially the maximum diameter, is to provide evidence that the tumour has been adequately sampled for histology. There are no evidence-based guidelines as to the optimal sampling of solid or cystic ovarian tumours. By convention, however, most pathologists sample one block per 10 mm of maximum tumour diameter in solid tumours. These same recommendations appear in cancer datasets for tumours at a range of other anatomical sites.

Adequate sampling of ovarian tumours is important for a number of reasons; for example, to identify foci of microinvasion or invasion in borderline tumours, foci of sarcoma in an ovarian carcinoma (carcinosarcoma), or foci of undifferentiated carcinoma in an endometrioid carcinoma (dedifferentiated carcinoma).

It is recognised that ovarian mucinous neoplasms may exhibit considerable intratumoural heterogeneity with an admixture of benign, borderline and malignant areas. One study which assessed the 'adequacy' of sampling in epithelial ovarian neoplasms,[34] confirmed mucinous carcinomas to display more histological variation than serous carcinomas. The authors concluded that more extensive sampling was required in borderline tumours to exclude foci of invasion. According to the recommendations of the 2004 Bethesda Workshop for borderline ovarian tumours,[35] all borderline tumours should be well sampled – at least two sections per 10 mm (excluding smooth-walled cystic foci) with the exception that borderline tumours of less than 100 mm should be sampled with one block per 10 mm of maximum tumour diameter. The recommendation that there should be more extensive sampling of larger tumours, especially those of mucinous type, reflects their greater likelihood of harbouring foci of invasive carcinoma. Additional sampling of mucinous borderline tumours is also recommended when histological features such as intraepithelial carcinoma or microinvasion are identified in the original sections. Similarly, additional sampling in serous borderline tumours is recommended when micropapillary areas or microinvasion are present in initial sections since such neoplasms are more likely to harbour invasive foci.

In mucinous ovarian tumours, tumour size may be helpful in determining whether the ovarian neoplasm is primary or metastatic. Unilateral mucinous carcinomas ≥100 mm in diameter are more likely to be primary than metastatic.[36,37]

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Note 6 – Macroscopic description of omentum (Core)

Three dimensions of the omentum should be provided in the pathology report to document the size of the specimen received for pathological examination. This may be useful in certain scenarios to direct the need for further surgery. For example, if initially only an omental biopsy was performed, further surgery may be undertaken to remove the remainder of the omentum. The size of the specimen is also helpful to determine the extent of sampling for histologic examination. No standardised guidelines have been developed for sampling omental specimens in cases of ovarian carcinoma or borderline tumours. However, in the setting of a grossly involved omentum, submitting one block for histologic examination is probably sufficient.[38,39] In patients who have received neoadjuvant chemotherapy, where histological assessment of tumour response to therapy is recommended (see **Note 15 RESPONSE TO NEOADJUVANT THERAPY**), examination of 4-6 blocks of omentum is suggested. For grossly negative omental specimens the sampling recommendations are variable – sampling of 3-5 blocks is recommended in one study,[39] other studies suggest at least one block for every 20 mm of maximum omental dimension.[40] Taking this information into account, 4-6 blocks in cases where the omentum is grossly negative in patients with an ovarian carcinoma or borderline tumour is recommended.

The size of the largest omental tumour deposit should be recorded in the pathology report. This is critical for determining the pathological stage.[3,13] Microscopic tumour which is not grossly evident, macroscopically evident tumour ≤20 mm, and macroscopically evident tumour >20 mm, correspond to FIGO Stages IIIA2, IIIB, and IIIC, respectively.[13]

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Note 7 – Block identification key (Non-core)

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.

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Note 8 – Histological tumour type (Core)

All tubo-ovarian epithelial malignancies and borderline tumours should be typed according to the 2020 WHO Classification of Tumours, Female Genital Tumours, 5th edition (Tables 1-3).[3] There are five major histotypes of primary ovarian carcinoma: low grade serous, high grade serous, clear cell, endometrioid and mucinous.[41-44] There are also other uncommon minor types listed in the 2020 WHO Classification including malignant Brenner tumour, mesonephric-like and undifferentiated carcinoma.[3] As seromucinous carcinoma is considered a morphologic variant of endometrioid carcinoma, it has thus been removed from the updated 2020 WHO Classification.[3] Carcinomas formerly diagnosed as seromucinous carcinoma are now included in the endometrioid category. Carcinosarcoma is a mixed epithelial and mesenchymal malignancy but is included in the category of epithelial malignancies in this dataset and in the 2020 WHO Classification since most are of epithelial origin and histogenesis (epithelial mesenchymal transition).[3,45]

Although management of ovarian carcinoma is, at present, largely dependent on tumour stage and grade, accurate typing will almost certainly become more important in the future with the introduction of targeted therapies and specific treatments for different tumour types. This is in part because, although clinically often considered as one disease, there is an increasing realisation that the different histotypes of ovarian carcinoma have different origins, pathogenesis, are associated with distinct molecular alterations, and have a different natural history, response to traditional chemotherapy, and prognosis.[41-44] Tumour typing may also be important in identifying or initiating testing for an underlying genetic predisposition. For example, HGSC may be associated with underlying *BRCA1/2* mutation while endometrioid carcinomas can occur in patients with LS.[46] The most common ovarian carcinoma is HGSC (approximately 70%) followed by clear cell and endometrioid.[47,48] Mucinous and low grade serous are less common. Approximately 90% of advanced stage ovarian carcinomas (Stage III/IV) are high grade serous in type.[47,48] Most primary tubal carcinomas are high grade serous type.

Mixed ovarian carcinomas are now considered to be uncommon. It is recommended that all distinct morphological types in an ovarian carcinoma are documented, even if they comprise less than 10% of the neoplasm. As stated, mixed carcinomas in the ovary are uncommon, the most prevalent combination being clear cell and endometrioid (both of these tumour types often arise in endometriosis). Most neoplasms which were previously classified as mixed serous and endometrioid, and mixed serous and clear cell, represent HGSCs with pseudoendometrioid areas and areas of cytoplasmic clearing respectively. In such cases, immunohistochemical markers, especially WT1, may be useful (see **Note 18 ANCILLARY STUDIES**).

Borderline tumours should also be typed according to 2020 WHO Classification criteria.[3] The most common types are serous and mucinous. Seromucinous, endometrioid and Brenner types also occur. Clear cell borderline tumour should only be diagnosed with the greatest caution, being certain to exclude carcinoma.

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

Descriptor			ICD-O codes[a]
Epithelial tumours			
Serous tumours	Borderline	Serous borderline tumour NOS	8442/1
	Malignant	Low grade serous carcinoma	8460/3
	Malignant	High grade serous carcinoma	8461/3
Mucinous tumours	Borderline	Mucinous borderline tumour	8472/1
	Malignant	Mucinous adenocarcinoma	8480/3
Endometrioid tumours	Borderline	Endometrioid tumour, borderline	8380/1
	Malignant	Endometrioid adenocarcinoma NOS	8380/3
Clear cell tumours	Borderline	Clear cell borderline tumour	8313/1
	Malignant	Clear cell adenocarcinoma NOS	8310/3
Seromucinous tumours	Borderline	Seromucinous borderline tumour	8474/1
Brenner tumours	Borderline	Brenner tumour, borderline malignancy	9000/1
	Malignant	Brenner tumour, malignant	9000/3
Other carcinomas	Malignant	Mesonephric-like adenocarcinoma	9111/3
	Malignant	Carcinoma, undifferentiated, NOS	8020/3
	Malignant	Dedifferentiated carcinoma	8020/3
	Malignant	Carcinosarcoma NOS	8980/3
	Malignant	Mixed cell adenocarcinoma	8323/3

[a] These morphology codes are from the International Classification of Diseases for Oncology, third edition, second revision (ICD-O-3.2).[49] 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. This classification is modified from the previous WHO classification, taking into account changes in our understanding of these lesions. Incorporates all relevant changes from the 5th edition Corrigenda June 2021.

Table 2: World Health Organization classification of tumours of the fallopian tube.[3]

Descriptor		ICD-O codes[a]
Epithelial tumours		
Epithelial precursor lesion	Serous adenofibroma NOS	9014/0
Epithelial borderline tumour	Serous borderline tumour NOS	8442/1
Malignant epithelial tumours	High grade serous carcinoma	8461/3
	Endometrioid adenocarcinoma NOS	8380/3
	Carcinosarcoma NOS	8980/3

[a] These morphology codes are from the International Classification of Diseases for Oncology, third edition, second revision (ICD-O-3.2).[49] 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. This classification is modified from the previous WHO classification, taking into account changes in our understanding of these lesions. Incorporates all relevant changes from the 5th edition Corrigenda June 2021.

Table 3: World Health Organization classification of tumours of the peritoneum.[3]

Descriptor	ICD-O codes[a]
Epithelial tumours (of Müllerian type)	
Serous borderline tumour NOS	8442/1
Low grade serous carcinoma	8460/3
High grade serous carcinoma	8461/3

[a] These morphology codes are from the International Classification of Diseases for Oncology, third edition, second revision (ICD-O-3.2).[49] 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. This classification is modified from the previous WHO classification, taking into account changes in our understanding of these lesions. Incorporates all relevant changes from the 5th edition Corrigenda June 2021.

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Note 9 – Pattern of invasion (Non-core)

It is controversial as to whether the pattern of invasion in Stage I mucinous ovarian carcinoma has prognostic significance; therefore this is a non-core element.[50-55] The expansile/confluent/non-destructive pattern of invasion is characterised by architecturally complex glands, cysts or papillae lined by atypical epithelium with minimal to no intervening stroma. The destructive/infiltrative pattern is characterised by haphazardly arranged glands, tubules, nests and cords of malignant cells infiltrating stroma with an associated oedematous, inflammatory or desmoplastic response. While several studies have shown the expansile pattern heralds a better prognosis,[50-52,54-57] a population-based registry study of mucinous ovarian carcinomas was not able to prognosticate utilising the distinction between the two patterns of invasion.[53] It is recommended that the pattern of invasion in mucinous ovarian carcinomas be recorded. The focus of invasion should measure >5 mm in greatest linear extent; otherwise, this should be considered microinvasion or microinvasive carcinoma.

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Note 10 – Carcinosarcoma components (Non-core)

There is little published evidence suggesting any prognostic significance of the different morphological components within ovarian carcinosarcomas (although some prognostic evidence exists for uterine carcinosarcomas).[58-60] In view of the paucity of studies, the ICCR Ovary Carcinoma Dataset Authoring Committee (DAC) recommends that it would be useful to record the percentage of the epithelial and mesenchymal elements as well as the components of the epithelial and mesenchymal (homologous or heterologous) elements. This is a recommendation rather than a requirement as collection of these data may be informative for the future prognosis and management of these neoplasms.[58-60]

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Note 11 – Histological tumour grade (Core and Non-core)

Histological grade is part of current European Society for Medical Oncology (ESMO)-European Society of Gynaecological Oncology (ESGO) management guidelines for endometrioid and mucinous carcinomas.[61] Serous carcinomas are now classified as low grade serous or high grade serous,[3] and despite the names including the term grade, these are two different histotypes rather than low grade and high grade variants of the same tumour type. Hence, grading does not apply to serous carcinomas. Clear cell carcinomas, un-/dedifferentiated carcinomas, anaplastic carcinomas, carcinosarcomas and mesonephric-like carcinomas are aggressive tumours and grading does not apply. There is no grading system for malignant Brenner tumours. If chemotherapy has been administered, tumour grading (and typing) may need to be based on the pre-chemotherapy biopsy.

The independent prognostic significance of grade for ovarian endometrioid carcinomas has only recently been validated.[62] The 1988 FIGO grading system is widely used for grading endometrioid carcinomas of ovarian and endometrial origin.[13] The FIGO grading system is based on architecture; tumours with <5% non-squamous solid component are grade 1, those with 5-50% solid areas are grade 2, and tumours with >50% of solid architecture are classified as grade 3.[13] When grade 1 and 2 tumours show severe nuclear atypia in the majority of the tumour cells (grade 3 nuclei), the histological grade is increased by one.[13,63]

Dedifferentiation in endometrioid carcinoma, sometimes with Switch/Sucrose non-fermenting (SWI/SNF) alterations, results in highly aggressive behaviour and such tumours are high grade by definition.[64] A significant majority of ovarian endometrioid carcinomas are grade 1 and 2. However, there is a subset of grade 3 endometrioid carcinomas which should be diagnosed with caution, since a significant proportion of such tumours are in fact HGSC with so called SET features (solid, pseudoendometrioid, transitional cell). IHC is useful in this regard (see **Note 18 ANCILLARY STUDIES)**. The interobserver reproducibility of grading is limited and several studies have attempted to improve on it.[65-70] There are shortcomings of a primarily architecturally based grading system. Certain growth patterns of endometrioid carcinoma such as spindled with bland nuclear features may be over-graded. On the contrary, tumours with non-solid architecture but high grade nuclear atypia may be under-graded. For example, in a recent study a number of p53 abnormal (p53abn) ovarian endometrioid carcinomas with aggressive course were graded as 1.[62]

As compared to the FIGO grading system,[13] the Silverberg grading system[71] was found to correlate better with survival in a multivariate analysis, although outcome in ovarian endometrioid carcinoma is mostly dictated by stage.[63] The Silverberg system (Table 4) takes into account nuclear atypia and mitotic activity in addition to architecture. Thus, the scores for architecture (majority glandular=1, papillary=2, solid=3), nuclear atypia (mild=1, moderate=2, severe=3), mitotic activity per mm^2 of tumour area or in 10 high power fields (HPF) (based on each HPF being 0.345 mm^2 in area, as per the original study;[71] 0-3 mitotic figures/mm^2 (or 0 to 9 mitotic figures per 10 HPF) =1, 3-7 mitotic figures/mm^2 (or 10 to 24 mitotic figures per 10 HPF) =2, and >7 mitotic figures/mm^2 (or ≥25 mitotic figures per 10 HPF) =3) are added to obtain a score for determining the final grade (G1: 3 to 5, G2: 6 to 7, G3: 8 to 9). The better performance of the Silverberg system was attributed to the better separation of grade 2 from the grade 3 tumours, which had a poor outcome.[63]

Table 4: The Silverberg grading system.[71]

Criterion	Score
Architecture (majority pattern)	
Glandular	1
Papillary	2
Solid	3
Nuclear atypia	
Mild	1
Moderate	2
Severe	3
Mitotic count per mm^2	
<3 mitotic figures/mm^2	1
3-7 mitotic figures/mm^2	2
>7 mitotic figures/mm^2	3
Final Grade	**Total Score**
Grade 1	3-5
Grade 2	6-7
Grade 3	8-9

The DAC panel agrees that there is insufficient evidence for a change in the grading system of endometrioid carcinomas and continues to recommend the FIGO grading system.[13]

In addition to grading, molecular subtype assignment may further improve outcome prediction in the same way as for endometrioid carcinoma of the uterus; this is done with IHC for MMR proteins and p53 and by sequencing for exonuclease domain mutations (EDM) of *Polymerase epsilon* (*POLE*).[62,72]

Some management guidelines for mucinous carcinomas require grading.[61] The DAC previously suggest that if grading of mucinous carcinomas is undertaken (a non-core element rather than a core element), the same grading system for endometrioid carcinomas should be used. However, a recent study showed no prognostic significance of the FIGO grading system and reemphasised that mucinous carcinomas only rarely show a solid growth pattern.[73] In this study, the Silverberg grade was significantly associated with survival, although all mucinous carcinomas were graded as grade 1 or 2 by the Silverberg system, and none as grade 3.[73] The DAC now recommends the Silverberg grading system[71] for mucinous carcinomas as a non-core reporting element.

The same study also proposed a growth-based grading system based on the pattern of invasion.[73] Expansile/confluent invasion or infiltrative invasion ≤10% of the tumour is graded as 1 while infiltrative invasion >10% is graded as 2.[73] This was significantly associated with survival in univariable analysis in this relatively small study of 46 cases.[74] This corroborates earlier studies showing that while infiltrative invasion is associated with higher stage, it also predicts higher risk of recurrence at Stage I.[53,57,74,75] It is important to note, however, that an infiltrative pattern of invasion is a characteristic feature of metastatic mucinous carcinoma. In one study, the infiltrative pattern of invasion lost its significant association with survival after metastatic carcinomas to the ovary were excluded.[76] If an infiltrative/destructive pattern is present, metastatic carcinoma should carefully be ruled out. The quantification of the infiltrative component as focal (≤10%) or diffuse (>10%) may be recorded to allow more data to be gathered for future studies.

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Note 12 – Borderline tumour - special features (Core and Non-core)

Terminology for ovarian borderline tumours has evolved over several years.[40,77] The preferred terminology is borderline tumour, for example serous or mucinous borderline tumour, and this has been endorsed in the 2020 WHO Classification.[3] Serous borderline tumours can be of typical or micropapillary subtypes, as per the latest WHO Classification.[3] For mucinous, endometrioid, clear cell, Brenner, and seromucinous tumours, the designation 'borderline tumour' is also used in the 2020 WHO Classification.[3] The terms 'low malignant potential' or 'atypical proliferative' are not recommended.[3] Synonyms formerly used for seromucinous borderline tumours include endocervical-type mucinous borderline tumour, Müllerian mucinous borderline tumour, and atypical proliferative (borderline) Müllerian tumour.[78]

Determining the lowest threshold for the diagnosis of a borderline tumour in the setting of a cystadenoma/cystadenofibroma with minimal epithelial proliferation can be subjective and quantitative criteria have been suggested: cystadenomas/cystadenofibromas with qualitatively sufficient epithelial stratification/complexity involving ≥10% of the epithelial volume are designated as borderline tumours arising within a cystadenoma/cystadenofibroma.[40] A borderline tumour in which the epithelial stratification/complexity involves <10% of the epithelial volume should be diagnosed as cystadenoma/ cystadenofibroma with focal epithelial proliferation.

As serous borderline tumour can exhibit variable degrees of micropapillary or cribriform architecture, a diagnosis of micropapillary subtype of serous borderline tumour is based on the presence of ≥5 mm of confluent micropapillary (defined as micropapillae five times as long as they are wide) or cribriform growth.[3]

A standardised quantitative criterion for distinguishing microinvasion from frankly invasive carcinoma within a borderline tumour has not been established, with varying definitions used in different studies, including 1, 2, 3, 5 and 10 mm^2 as the upper limits of microinvasion.[40,77,79] The 2020 WHO Classification uses 5 mm^2 as a cut-off.[3] Some groups distinguish two patterns of stromal invasion in serous tumours which quantitatively falls short of frankly invasive carcinoma (<5 mm) - conventional 'microinvasion' (isolated and/or small clusters of eosinophilic cells and/ or small papillae cytologically similar to the non-invasive component within clear lacunar spaces) and 'microinvasive carcinoma' (glandular or micropapillary patterns qualitatively analogous to low grade serous carcinoma (LGSC)).[40,77] However, other investigators do not advocate this distinction. Due to insufficient numbers of cases in the literature, definitive conclusions regarding the clinical significance of this distinction cannot be drawn.[77,80] Analogous to the situation for serous tumours, some investigators advocate the separation of 'microinvasion' from 'microinvasive carcinoma' in mucinous borderline tumours while others use these two terms interchangeably.[79]

In mucinous borderline tumours, intraepithelial carcinoma is diagnosed in non-invasive foci with marked nuclear atypia, and is often associated with mitotic activity.[40,79] However, the reproducibility of this diagnosis has not been formally analysed. It has recently been suggested that p53 IHC could be used instead or in support of a diagnosis of intraepithelial carcinoma but this remains to be proven.[81] Intraepithelial carcinoma for mucinous borderline tumours is a non-core item for reporting and the term intraepithelial carcinoma is not applied to other types of borderline tumour. Mucinous borderline tumours can be associated with mural nodules, which are classified as reactive sarcoma-like, anaplastic carcinoma, or sarcoma.

Sarcoma-like nodules are composed of a variable mixture of spindled/round mononucleated cells, often associated with marked inflammation.

Extra-ovarian implants occur in approximately 20% of serous borderline tumours and are more common with exophytic neoplasms. The most important adverse prognostic factor for ovarian serous borderline tumours in which there is extra-ovarian disease, is the presence of invasive implants, i.e., LGSC, in extra-ovarian tissues as this portends an adverse prognosis, with non-invasive implants having a favourable prognosis. Specifying the location and size of implants is important for determining the FIGO stage.[13] Non-invasive and invasive implants/LGSC may co-exist in the same specimen. Non-invasive implants are subclassified as epithelial or desmoplastic types.[40] Epithelial-type non-invasive implants resemble detached fragments of a serous

borderline tumour involving extra-ovarian tissues. They do not exhibit infiltration of underlying tissue, and they are often present within mesothelial or epithelial-lined spaces although they may be adherent to the serosal surface. Desmoplastic non-invasive implants are composed of glands or papillary clusters within fibroblastic or granulation tissue-like stroma, but they do not exhibit infiltration of adjacent tissue. Often these are located on serosal surfaces or within septa in the omentum. Note that the presence of isolated individual or small clusters of eosinophilic epithelial cells within the stroma is generally considered to be within the spectrum of desmoplastic non-invasive implants rather than representing an invasive implant/LGSC.[77]

The most widely used criterion for diagnosing extra-ovarian LGSC/invasive implants in a patient with an ovarian serous borderline tumour is destructive invasion of underlying tissue.[82] Invasive implants often feature markedly crowded epithelial nests, glands or micropapillary clusters with a haphazard arrangement. The nests, glands and papillae are sometimes surrounded by clefts.[40,77]

In occasional cases, it may not be possible to definitively distinguish non-invasive from invasive implants/LGSC and the recommendation is to designate such implants as being of indeterminate type.[83] This terminology should only be used sparingly, and obtaining a specialist gynaecological pathology opinion and submitting additional sections for histological examination (if an omentectomy specimen), may be useful.

When invasive implants are present this should be diagnosed in the final pathology report as extra-ovarian LGSC;[40,77,84] this has been endorsed in the 2020 WHO Classification.[3] It is unclear whether invasive implants involving extra-ovarian sites in association with an ovarian serous borderline tumour represent metastases from the serous borderline tumour or an independent primary peritoneal tumour. A number of molecular studies analysing primary ovarian tumours with their associated implants have yielded varying results.[77] However, Ardighieri et al (2014) showed in a large population-based cohort has shown that the vast majority of implants are clonally related to the primary ovarian tumour.[85] Most of the cases from this study were non-invasive implants; however, all 10 invasive implants had the same mutational status (*KRAS* mutation, *BRAF* mutation, or wild-type *KRAS/BRAF*) as the corresponding serous borderline tumour, suggesting that invasive implants are clonally related to the primary ovarian tumour as opposed to representing independent primary peritoneal lesions.[85] Nevertheless, the number of invasive implants evaluated by molecular methods in the entire literature is limited. Carcinoma developing in patients with a previous diagnosis of serous borderline tumour are mostly LGSCs and most are clonally related to the serous borderline tumour i.e., represent tumour progression.[86] From a practical point of view, for cases of invasive implants in association with an ovarian tumour diagnosed as serous borderline tumour, it is recommended to consider additional sampling of ovarian tissue to demonstrate LGSC or micropapillary serous borderline tumour.[87]

Implants may also be encountered in the setting of seromucinous borderline tumours, and the same issues for serous tumours pertain. In general implants do not occur in the setting of mucinous, endometrioid, clear cell or Brenner borderline tumours.

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Note 13 – Serous tubal intraepithelial carcinoma (STIC) (Core)

Recently, STIC has been implicated in the pathogenesis of extra-uterine HGSC. The evidence indicating that STIC is a precursor of most HGSCs that were formerly considered to be of tubal, ovarian or primary peritoneal origin, as well as guidelines for assigning primary site in cases of advanced stage non-uterine, HGSC, have already been provided (see **Note 4 HISTOLOGICAL SITES OF TUMOUR INVOLVEMENT**). STIC comprises a population of cytologically malignant epithelial cells replacing the normal tubal mucosa, most commonly involving the fimbria, and characterised by increased nuclear to cytoplasmic ratio with rounded nuclei, loss of cell polarity, coarsely clumped chromatin, prominent nucleoli and absence of ciliated cells. Additional features that may be present include epithelial stratification, small fracture lines in the epithelium and tufting and exfoliation from the tubal surface of small epithelial cell clusters.

The diagnostic criteria for STIC have evolved and guidelines for diagnosis, which include the use of p53 and Ki-67 (MIB1) immunostaining, have been published.[88-90] Use of these criteria results in a high degree of inter-observer diagnostic agreement. In discrete fallopian tube mucosal lesions (usually, but not always, located in the fimbria) with high grade atypia in non-ciliated epithelium, the presence of abnormal p53 immunostaining (three mutation-type patterns: overexpression, complete absence and cytoplasmic) and high Ki-67 proliferation index (≥10%) support a diagnosis of STIC. Although immunostains are a valuable adjunct in the diagnosis of isolated lesions of the fallopian tube, they are usually not needed to diagnosis STIC in the context of advanced stage HGSC, where comparison between the tubal mucosal lesion and HGSC elsewhere reveals identical cytological features, with high grade atypia and numerous mitotic figures. Fallopian tube epithelial lesions with atypia that do not meet all the criteria for STIC (e.g., tubal intraepithelial lesion in transition/serous tubal intraepithelial lesion, synonymous terms for lesions that have some but not all features of STIC) are of uncertain significance at present with poor reproducibility and these are not reportable diagnoses and should generally not be used in routine practice; additional research is required to determine the clinical significance, if any, of such lesions. Similarly, p53 signatures should not be reported as a diagnosis.

Fallopian tube mucosal involvement by uterine or non-gynaecological primary tumours can occur and mimic STIC.[91-93] Most cases with unilateral or bilateral HGSC in the ovary and/or STIC or HGSC in the tube but with an endometrial serous intraepithelial or invasive carcinoma will represent adnexal metastases from an endometrial serous carcinoma (see **Note 18 ANCILLARY STUDIES**).[94] A diagnosis of STIC always requires consideration of clinical and pathological findings and the exclusion of secondary involvement of the fallopian tube.

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Note 14 – Peritoneal cytology (Core)

The results of peritoneal cytology (peritoneal washings or peritoneal fluid) are important for the substaging of Stage I ovarian tumours (borderline and malignant). Positive peritoneal washings in a Stage I tumour signify Stage IC3 in the 2014 FIGO Staging System.[13] In the previous 2006 FIGO Staging System,[95] the results of peritoneal cytology were used for the substaging of Stage II neoplasms, but this is no longer the case. Positive peritoneal cytology in a Stage I carcinoma may indicate the need for adjuvant therapy in certain cases. Cells of LGSC and serous borderline tumour cannot be reliably distinguished in a cytology specimen; in such cases, the cytology findings should be correlated with the histopathological findings.

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Note 15 – Response to neoadjuvant therapy (Non-core)

Histological assessment of chemotherapy response is only applicable to HGSC at this time. An initial study has tested and validated the prognostic significance of chemotherapy response criteria, and assessed reproducibility in two independent series of tubo-ovarian HGSC.[96,97] This three-tier scoring system (the Chemotherapy Response Score (CRS)) is reproducible, simple to apply in practice, and has been validated in an international multicentre study.[98] This is the grading system currently recommended by the DAC. The method is as follows:

1. Scoring should be carried out on a single haematoxylin and eosin (H&E)-stained section (refer to discussion of omental sampling in Note 6 Macroscopic description of omentum).
2. A single block of involved omental tissue that shows the least response to chemotherapy should be selected (if there is no residual omental tumour a CRS score of 3 is given - see Table 5).
3. The amount of viable tumour should be assessed; this may or may not show degenerative changes in the form of nuclear atypia, smudging of the nuclear chromatin and cytoplasmic clearing.

4. The presence of fibrosis may be helpful in marking the site of previous tumour infiltration:
    a. When found in the absence of tumour, fibrosis is likely to indicate regression.
    b. If fibrosis occurs in association with tumour, this may simply reflect tumour-associated desmoplasia rather than regression.
    c. However, when fibrosis in association with tumour is accompanied by an inflammatory response (so-called 'fibro-inflammatory' response – fibrosis with associated macrophages and a mixed population of inflammatory cells), this indicates regression.
    d. Psammoma bodies may mark the site of previous tumour and can sometimes appear more numerous because their density increases in areas where tumour has disappeared.
5. As a guide, >95% of tumour should be viable for a score of 1, and <5% for a score of 3.
6. In studies to date using this system or a closely related system, a difference in prognosis was shown only when tumours with a CRS score of 1 or 2 were compared with those having a CRS score of 3.[96,97] However, the DAC recommends use of the three-tier system to gather more data for future studies.
7. Note that this system has only been applied to HGSCs to date.
8. If the omental tissue appears normal, with neither tumour cells nor fibrosis, it is important to ascertain that there was omental involvement prior to the start of chemotherapy, that has completely regressed, by review of the clinical and radiological findings, before assigning a CRS score of 3. If there was no omental involvement prior to starting chemotherapy, then a CRS score cannot be applied.

Table 5: Chemotherapy response score (CRS).[96]

Score	Criterion	Tumour regression
1	Mainly viable tumour with no or minimal regression-associated fibro-inflammatory changes[a] limited to a few foci	No definite or minimal tumour response identified
2	Multifocal or diffuse regression-associated fibro-inflammatory changes, [a] with viable tumour ranging from diffuse sheets, streaks or nodules, to extensive regression with multifocal but easily identifiable residual tumour.	Moderate response identified
3	Mainly regression, with few irregularly scattered individual tumour cells or cell groups (all measuring less than 2 mm), or no residual tumour identified.	Marked response with no or minimal residual cancer

[a] Regression associated fibro-inflammatory changes: fibrosis associated with macrophages, including foam cells, mixed inflammatory cells and psammoma bodies; to be distinguished from tumour-related inflammation or desmoplasia.

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Note 16 – Lymph node status (Core)

In the revised 2014 FIGO Staging System, metastases involving retroperitoneal lymph nodes, in the absence of peritoneal spread above the pelvic brim or distant metastases, represent Stage IIIA1 disease.[13] This stage is further subdivided into Stages IIIA1(i) and IIIA1(ii) for nodal metastases ≤10 mm and >10 mm, respectively. Formerly, regional node metastases were a criterion for Stage IIIC disease and this amendment is based upon evidence that patients with only nodal metastases (in the absence of peritoneal disease) have a relatively favourable outcome - although it should be noted that the data are based mainly on cases of HGSC.[99,100] Positive extra-abdominal lymph nodes including inguinal metastases represent Stage IVB disease.

International Federation of Gynaecology and Obstetrics (FIGO) specifically restricts the definition of Stage IIIA1 disease to retroperitoneal lymph nodes (pelvic and para-aortic) but does not indicate how tumour spread to intraperitoneal nodes (such as those in the mesentery or omentum) should be interpreted, although it would be very unusual to have isolated nodal metastases at these sites.[13] According to FIGO (personal communication), this should be regarded as intra-abdominal disease, i.e., Stage IIIC.[101,102] At present there are also limited data to justify the subdivision of Stage IIIA1 according to the size of the nodal metastases.[13] It is also not clear how the extent of nodal involvement (≤10 mm or >10 mm) should be measured if the diagnosis is based only upon cytological sampling. According to FIGO (personal communication), this should be regarded as Stage IIIA(i) disease.

Data on lymph node involvement in borderline ovarian tumours is largely restricted to tumours of serous subtype where approximately 25% of fully staged cases will show positive nodes.[103,104] While this finding does not appear to influence overall survival, cases with nodular epithelial tumour aggregates >1 mm in extent may show decreased disease-free survival.[105] Rarely, LGSC appears to develop within the lymph nodes of patients with ovarian serous borderline tumours.[106]

According to TNM8,[107] nodal involvement should be recorded as the presence of isolated tumour cells (ITC, <0.2 mm), micrometastases (MIC, 0.2-2 mm) or macrometastases (MAC, >2 mm).

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Note 17 – Coexistent pathology/Precursor lesions (Non-core)

Borderline and malignant endometrioid, clear cell and seromucinous ovarian tumours may arise from endometriosis. Thus, the presence of endometriosis, although not of prognostic or therapeutic significance, particularly if contiguous with the tumour, may assist in determining the histotype in problematic cases.[108,109]

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Note 18 – Ancillary studies (Non-core)

Morphology remains the mainstay in ovarian carcinoma diagnosis. Diagnostic ancillary testing is currently based primarily on IHC. Diagnostic immunohistochemical markers may assist in establishing a diagnosis of a primary ovarian carcinoma or aid in histotyping. It is beyond the scope of this dataset to present a detailed analysis (sensitivity, specificity, cut-off interpretation) but the most commonly used first-line immunohistochemical panels are discussed. In general, panels of markers are better than reliance on individual markers and it should be remembered that no marker is totally specific or sensitive for any tumour type. Unexpected positive and negative staining reactions may occur. Therefore, the results of immunohistochemical studies should always be interpreted in conjunction with the clinical, gross and microscopic features.[109,110]

The choice of ancillary tests for the distinction of a primary ovarian carcinoma from a metastatic malignancy (Table 6) depends on its morphological context and can be problematic particularly on small or cytological specimens.

Table 6: Ancillary tests to distinguish primary ovarian carcinoma from a metastasis.

Comparator #1	Comparator #2	Expressed/abnormal in comparator #1	Expressed/abnormal in comparator #2	References
Primary ovarian carcinoma	Benign mesothelial proliferation	Claudin 4, B72.3, Ber-EP4	Desmin	111-117
Primary ovarian carcinoma	Mesothelioma	Claudin 4, B72.3, Ber-EP4, Estrogen receptor (ER)[a]	Calretinin, BAP1	112,118-120
Ovarian endometrioid carcinoma	Lower gastrointestinal tract (colorectal and appendiceal)	CK7, PAX8[b], ER[a]	SATB2, CK20	121
Ovarian endometrioid carcinoma	Sex cord stromal tumour	EMA, CK7	Inhibin, Calretinin, SF1	122
Ovarian mucinous carcinoma	Lower gastrointestinal tract (colorectal and appendiceal)	CK7	SATB2, CK20	36,37,121
Ovarian mucinous carcinoma	Endocervical adenocarcinoma (human papilloma virus (HPV)-associated)		P16, HPV-PCR	123,124
Tubo-ovarian high grade serous carcinoma	Metastatic breast carcinoma	PAX8, WT1	GATA3	125
Tubo-ovarian high grade serous carcinoma	Endometrial serous carcinoma	WT1, p53	p53	33,126

[a] ER is absent in ovarian clear cell and mucinous carcinomas as well about 20% of endometrioid and high grade serous carcinomas.
[b] PAX8 is absent in 15% of ovarian endometrioid carcinomas.

In the distinction between a primary ovarian carcinoma and a benign mesothelial proliferation, a first line panel of claudin 4, B72.3 and desmin is slightly better than the traditional panel of MOC31 (or BerEP4), estrogen receptor (ER) and calretinin.[114] Claudin 4 can be superior to MOC31, BerEP4, or PAX8.[116] Expression of PAX8 in reactive mesothelial proliferations has been noted.[117,127-129] However, claudin 4 or BP72.3 may not be widely available. Desmin is an excellent second marker for differentiating primary ovarian carcinoma from reactive mesothelial proliferation,[111] which outperforms calretinin (positive, at least focally, in some serous carcinomas). WT1 is consistently positive in both serous and mesothelial proliferations but the combination of WT1 expression with abnormal p53 is characteristic of tubo-ovarian HGSC, although some mesotheliomas can harbor a *TP53* mutation. If mesothelioma is in the differential diagnosis, BAP1 should be added. Bernardi et al (2020) showed that claudin 4 expression was completely sensitive and specific for metastatic carcinoma versus mesothelioma.[112]

Metastatic colorectal adenocarcinomas may mimic an endometrioid carcinoma or a mucinous neoplasm, either borderline or malignant. In the distinction between an ovarian endometrioid carcinoma and a metastatic colorectal adenocarcinoma, the following panel of markers may assist: CK7, CK20, PAX8, ER and SATB2.

Endometrioid carcinoma may closely mimic an ovarian sex cord-stromal tumour, either a granulosa cell tumour or a Sertoli cell tumour. Conversely, some Sertoli-Leydig cell tumours have a pseudoendometrioid appearance and can mimic an endometrioid neoplasm.[130] Markers which are useful to distinguish between them include inhibin, calretinin and SF-1 versus EMA, PAX8, BerEP4 and CK7.[130-135]

Simultaneous involvement of the endometrium and ovaries by an endometrioid carcinoma is not uncommon.[136,137] IHC and molecular testing are of little value in ascertaining the relationship between the tumours as synchronous dual primaries versus metastasis since it has been shown that in almost all such the tumours are clonally related.[138-140] However, an indolent behaviour can be anticipated if both tumours are low grade; the endometrial tumour shows less than 50% myometrial invasion; substantial lymphovascular invasion is absent; and only the endometrium and one ovary and no other site is involved.[141] These tumours can be designated as synchronous.

In the distinction between an ovarian mucinous carcinoma and a metastatic colorectal adenocarcinoma or appendiceal neoplasm, as well as the macroscopic and microscopic findings, with large size and unilaterality being more in keeping with primary ovarian mucinous carcinoma, a panel of CK7, CK20, CDX2 and SATB2 may assist.[36,37,121] The use of IHC to distinguish primary ovarian mucinous carcinoma from metastatic adenocarcinoma of upper gastrointestinal origin (pancreatic, hepatobiliary, gastric) is limited. An absence of staining with SMAD4 (DPC4) may suggest a pancreatic adenocarcinoma since staining of this nuclear transcription factor is lost in about 50% of pancreatic adenocarcinomas.[142] Conversely, DPC4 is expressed in virtually all primary ovarian mucinous neoplasms. Rarely, a metastatic human papillomavirus (HPV)-associated endocervical adenocarcinoma may mimic a primary ovarian mucinous or endometrioid neoplasm.[143] Diffuse p16 immunoreactivity in such cases may be useful in suggesting a metastatic cervical adenocarcinoma, but performing HPV testing is more specific.[123,124,144]

Metastatic triple negative ductal breast carcinomas may mimic a tubo-ovarian HGSC. In a patient with a history of breast carcinoma and germline *BRCA1*/2 mutation who is found to have a pelvic mass or a disseminated peritoneal malignancy, most often this will represent a new tubo-ovarian HGSC. A panel of PAX8, WT1 and GATA3 is helpful.[125,145-147] However, in the setting of triple negative breast carcinomas, GATA3 expression is often limited or completely negative.

With a serous carcinoma involving the endometrium and one or both tubes/ovaries, correct site assignment becomes important because only tubo-ovarian HGSC are eligible for PARPi at this time, but this could change. WT1 and p53 staining may be of some value in distinguishing between an endometrial serous carcinoma with metastasis to the tube/ovary, a 'drop metastasis' in the endometrium from a tubo-ovarian HGSC or independent synchronous neoplasms. Differences in staining between the sites, especially with both markers, suggest the latter. Absence of WT1 staining is a relatively specific indicator of endometrial primary site because almost all tubo-ovarian HGSC show diffuse WT1 staining (approximately 2% show partial or complete absence).[94,148] On the contrary, while WT1 expression is consistent with a tubo-ovarian HGSC, approximately one third of endometrial serous carcinoma exhibit WT1 staining (often focal).[33,94,126,148-153]

While most primary ovarian carcinomas are straightforward to histotype on well sampled specimens, on occasion it is difficult to distinguish between a HGSC and a high grade endometrioid carcinoma (Table 7). The recommended panel is a combination of WT1 and p53.[154] Diffuse strong WT1 expression in combination with abnormal mutation-type p53 staining is highly sensitive and specific for HGSC. If it is not possible to distinguish between high grade serous and endometrioid carcinoma, these cases could be submitted for cancer susceptibility screening and predictive testing for both histotypes (*BRCA1/2* mutation testing and MMR protein expression). HGSC with clear cell areas and clear cell carcinoma can be distinguished by a combination of WT1, napsin A/HNF1B and ER.[109] HGSC can be distinguished from LGSC by p53 and from mucinous carcinoma by WT1.[155] Endometrioid carcinoma can be distinguished from clear cell carcinoma by napsin A, HNF1B and progesterone receptor (PR).[110] Endometrioid and mucinous carcinomas can be distinguished by PR and vimentin.[76,108,155]

Table 7: Ancillary tests to distinguish serous and endometrioid carcinomas.

Comparator #1	Comparator #2	Expressed/abnormal in comparator #1	Expressed/abnormal in comparator #2	References
High grade serous carcinoma	Endometrioid carcinoma (grade 3)	WT1, p53		[154]
High grade serous carcinoma	Clear cell carcinoma	WT1, Estrogen receptor	Napsin A, HNF1B	[109,156]
High grade serous carcinoma	Low grade serous carcinoma	p53		[155]
High grade serous carcinoma	Mucinous carcinoma	WT1		[109]
Endometrioid carcinoma	Clear cell carcinoma	Progesterone receptor	Napsin A, HNF1B	[157]
Endometrioid carcinoma	Mucinous carcinoma	Progesterone receptor, Vimentin		[76]
Low grade serous carcinoma	Endometrioid, clear cell, mucinous	WT1		[109]

Biomarkers are not necessary if the features are unequivocally those of STIC, however if there is diagnostic uncertainty, both p53 and Ki-67 staining should be performed.[158] The cells must exhibit abnormal (mutation-type) p53 staining.[159,160] The Ki-67 proliferation index is increased, typically in the region of 40% to nearly 100% with most cases showing focal areas exceeding 70%. However, some cases of STIC exhibit a lower Ki-67 proliferation index and it has been suggested that at least 10% of the nuclei should be positive for a diagnosis of STIC in cases where IHC is undertaken (morphological features and aberrant p53 staining are also needed).[158]

While many prognostic biomarker studies have been published for HGSC, none provide sufficient stratification to influence management.

This is different for endometrioid carcinoma where three recent studies validated that the same molecular subtype assignment of their uterine counterparts showed prognostic stratification.[62,72,161] The four molecular subtypes are *POLE* mutated with the longest survival, mismatch repair deficient (MMRd) and no specific molecular profile (NSMP) cases with intermediate survival and p53abn cases with the shortest survival. In particular, assessing the latter may supplant grading. Assessing the MMR status also serves genetic LS screening and might provide predictive information. The NSMP group is the largest in ovarian endometrioid carcinoma, as it is in endometrial endometrioid carcinoma. Further stratification of this group might require other biomarkers. For example, PR expression status and/or *CTNNB1* mutation status both have been shown to be associated with survival across all ovarian endometrioid carcinomas, but have not been studied within the NSMP group.[162-166]

There are no validated prognostic biomarkers for ovarian clear cell or mucinous carcinoma. However, p53 status might inform about the course of mucinous borderline tumours. A recent study showed that p53abn mucinous borderline tumours were associated with a higher risk of death.[167] While there are no current therapeutic options for these patients, the converse information that p53 normal mucinous borderline tumours are at very low risk of disease progression can be useful in some clinical circumstances.[81]

Tubo-ovarian HGSCs with proven *BRCA1/2* mutations (germline or somatic) are likely to respond to PARPi. If modern IHC supported histotyping is performed, *BRCA1/2* mutations are confined to HGSC so *BRCA1/2* testing can be restricted to this histotype.[168] Difficult cases (e.g., differential diagnosis with grade 3 endometrioid) can also be tested at the discretion of the pathologist. Several clinical trials showed effects of PARPi in the *BRCA1/2* wild-type but homologous repair deficient group.[169] It can be anticipated that eligibility for PARPi will be expanded. Several competing proprietary homologous repair deficiency (HRD) tests (mutational signatures,

genomic scars etc.) are being marketed, with an alternative approach to testing being an expanded gene panel that includes proven HRD genes such as *RAD51C, RAD51D, BRIP1, PALB2* among others.[170]

The United States Food and Drug Administration (FDA) has approved immunotherapy for MMRd tumours irrespective of site. Universal MMRd testing is recommended for ovarian endometrioid carcinoma to screen for hereditary LS.[171] While MMRd is rarely observed in prototypical clear cell carcinomas, some cases with ambiguous morphology between endometrioid and clear cell carcinoma are MMRd and even with the use of diagnostic IHC panels these cases might be diagnosed as clear cell carcinoma. While MMRd in clear cell carcinoma is uncommon, all cases reported in the literature were proven or probable LS.[172-175] Hence, if funding is not restricted, clear cell carcinoma might also be tested for LS. Alternatively, a features-based screening for clear cell carcinoma is possible (ambiguous/mixed morphology between endometrioid/clear cell carcinoma, microcystic architecture and intratumoural stromal lymphocytic infiltrate, presence of synchronous endometrial and ovarian carcinoma).[172] Age cut-offs have limited value.

No other molecular targeted therapies are approved. Hormone receptor expression assessment might be requested by oncologists before commencing hormonal therapy for endometrioid or LGSC.[165] No predictive cut-offs have been established and the expression of ER and PR should be reported descriptively. About 5% of LGSCs harbor a *BRAF* V600E mutation and case reports suggest promising results with BRAF inhibitors.[176] *HER2* amplifications occur in 18% of ovarian mucinous[177] and 7-14% of ovarian clear cell carcinoma.[178]

Ovarian carcinomas represent a heterogeneous group of tumours. In recent years, molecular pathology has been instrumental in demonstrating that ovarian carcinomas are not a single entity, but a group of tumours with diverse morphology, natural history, and pathogenesis.[179] While molecular investigations at present do not have a significant role in diagnosis, prediction of prognosis or determination of treatment in ovarian, tubal and peritoneal carcinomas, this may change in the future, especially with the introduction of PARPi therapy for HGSC.

High grade serous carcinomas (HGSCs) are chromosomally unstable tumours, in which *TP53* mutations are ubiquitous. Germline or sporadic, genetic or epigenetic, alterations in *BRCA1* and *BRCA2* also occur. A pathogenetic model has been proposed, starting with early *TP53* alteration, followed by *BRCA1* loss, leading to deficiency in homologous recombination repair of double strand breaks, triggering chromosomal instability with gene copy number variation. The Cancer Genome Atlas (TCGA) performed an integrated genomic analysis of 489 high grade ovarian serous carcinomas.[180] Mutations in *TP53* were seen in 96% of the cases. There was a low prevalence, but there were statistically recurrent somatic mutations in nine further genes, including *NF1, BRCA1, BRCA2, RB1* and *CDK12*. Copy number alterations and promoter hypermethylation events were detected in 168 genes. The most common amplifications were detected in *CCNE1, MYC* and *MECOM*. Deletions were identified in *RB1, NF1* and *PTEN*. Hierarchical clustering analysis identified four transcriptional subtypes, three microRNA subtypes, four promoter methylation subtypes, and a transcriptional signature associated with survival. In 33% of the tumours, alterations in *BRCA* genes, either somatic or germline mutations or promoter hypermethylation were present. Defects in DNA repair by homologous recombination, secondary to mutations in *BRCA1*, *BRCA2* or related genes, or by mechanisms not yet elucidated, are seen in approximately 50% of HGSCs, and HRD is a predictive marker for response to PARPi therapy.[181,182] At present there is no single agreed upon predictive assay for HRD/prediction of response to PARPi.

Low grade serous carcinomas (LGSCs) are closely related to serous borderline tumours, and show frequent mutations in the MAPK pathway (*KRAS*, *BRAF*, *NRAS*), prognostically unfavourable alterations in *CDK2A* and mutations in *USP9X* [164,183] PR is an unfavourable prognostic marker.[165]

The molecular events in endometrioid carcinoma are similar to the uterine counterpart. The main molecular alterations are: *CTNNB1* mutation (50%), microsatellite instability (13%), and mutations in the *PTEN* (20%), *KRAS*, *PIK3CA, TP53, and POLE* genes. The molecular subtypes from the uterine counterpart are equally prognostic in ovarian endometrioid carcinomas, as discussed earlier.[62,184]

Clear cell carcinoma shows frequent *ARID1A* and *PIK3CA* mutations. Alterations in *KRAS* and *TP53* are unusual. *HER2* amplifications are uncommon.

Mucinous carcinomas frequently harbour genomic loss of *CDKN2A*, *KRAS* and *TP53* mutations often co-occurring and *HER2* amplifications.[185] In mucinous tumours with areas of carcinoma admixed with foci of benign or borderline mucinous tumour, *KRAS* mutations have been demonstrated in all components, suggesting that this represents an early event during tumourigenesis. *TP53* mutations are implicated in the progression from mucinous borderline tumour to carcinoma and, as discussed earlier, a recent study demonstrated a higher risk of death for patient with mucinous borderline tumour harbouring a *TP53* mutation.[167]

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Note 19 – Provisional pathological staging (Core)

Tumour stage is amongst the strongest prognostic factors in tubo-ovarian carcinoma.[186] Patients with localised, regional and distant disease have been shown to have 5 year relative survival rates of 92%, 72% and 27%, based on United States figures from 2014.[187] Therefore pathological staging must be provided on the pathology report and is 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.[13,107,188,189]

All ovarian carcinomas and borderline tumours, as well as carcinomas of the fallopian tube and peritoneum should be staged.[13,189] The latest version of either FIGO[13,189] *or* TNM staging,[107,188] *or* both, can be used depending on local preferences. The FIGO system is in widespread use internationally and is the system used in most clinical trials and research studies. However, Union for International Cancer Control (UICC) or American Joint Committee on Cancer (AJCC) 8th edition TNM Staging Systems are used or mandated in many parts of the world.[107,188] With regards to updating of staging systems, there is collaboration between FIGO and those agencies responsible for TNM with an agreement to adopt FIGO staging but no coordination of timing of revisions; generally, what happens is that following the introduction of a new FIGO Staging System, this is 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.[107,188]

For reasons of comparability, FIGO continue to classify umbilical metastases as Stage IVB (personal communication).[13,189] It is recommended that these cases are reported separately to keep track of and obtain further insight into the prognostic value of umbilical involvement in tubo-ovarian cancer and whether this may be best regarded as Stage III.

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

The reference document TNM Supplement: A commentary on uniform use, 5th edition (C Wittekind et al. editors) may be of assistance when staging.[190]

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