Dataset for the Reporting of Ovarian, Fallopian Tube and Primary Peritoneal Carcinoma: Recommendations from the International Collaboration on Cancer Reporting (ICCR)

C. Blake Gilks, M.D., F.R.C.P.C., Christina I. Selinger, Ph.D., Ben Davidson, M.D., Martin Köbel, M.D., Jonathan A. Ledermann, M.D., F.Med.Sci., Diana Lim, M.D., F.R.C.Path., F.R.C.P.A., Anais Malpica, M.D., Yoshiki Mikami, M.D., Naveena Singh, M.D., F.R.C.Path., Radhika Srinivasan, M.D., Russell Vang, M.D., Sigurd F. Lax, M.D., W. Glenn McCluggage, F.R.C.Path.

Department of Pathology and Laboratory Medicine, University of British Columbia, Vancouver, British Columbia, Canada and Chair of ICCR Ovary Carcinoma expert panel (C.B.G.)

International Collaboration on Cancer Reporting, Sydney, NSW, Australia; Royal College of Pathologists of Australasia, Sydney, New South Wales, Australia and ICCR Project Manager (C.I.S.)

Department of Pathology, Oslo University Hospital, Norwegian Radium Hospital; Faculty of Medicine, Institute of Clinical Medicine, University of Oslo, Oslo, Norway (B.D.)

Department of Pathology and Laboratory Medicine, University of Calgary, Calgary, Alberta, Canada (M.K.)

Department of Oncology, UCL Cancer Institute, University College London and UCL Hospitals, London, UK (J.A.L.)

Department of Pathology, National University Hospital, Singapore (D.L.)

The University of Texas MD Anderson Cancer Center, Houston, Texas (A.M.)

Department of Diagnostic Pathology, Kumamoto University Hospital, Kumamoto, Japan (Y.M.)

Department of Cellular Pathology, Barts Health NHS Trust, London, UK (N.S.)

Department of Cytology and Gynecological Pathology, Postgraduate Institute of Medical Education and Research, Chandigarh, India (R.S.)

Department of Pathology and Gynecology & Obstetrics, The Johns Hopkins Hospital, Baltimore, Maryland, USA (R.V.)

Department of Pathology, General Hospital Graz II, Styrian Hospital Corporation and Medical University of Graz, and Johannes Kepler University, School of Medicine, Linz, Austria and ICCR Steering Committee Representative (S.F. L.)

Department of Pathology, Belfast Health and Social Care Trust, Belfast, UK and ICCR Series Champion for Gynecology Datasets (W.G.M)

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Corresponding author:

Blake Gilks

Department of Pathology and Laboratory Medicine,

University of British Columbia,

Vancouver, British Columbia, Canada

E-mail: Blake.Gilks@vch.ca

Tel: 1-604-789-7157

Fax: 1-604-875-4797

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ABSTRACT

The move towards consistent and comprehensive surgical pathology reports for cancer resection specimens has been a key development in supporting evidence-based patient management and consistent cancer staging. The International Collaboration on Cancer Reporting (ICCR) previously developed a dataset for reporting of ovarian, fallopian tube and primary peritoneal carcinomas which was published in 2015. In this paper we provide an update on this dataset, as a second edition, that reflects changes in the 2020 World Health Organization (WHO) Classification of Female Genital Tumours as well as some other minor modifications. The dataset has been developed by a panel of internationally recognised expert pathologists and a clinician and consists of 'core' and 'non-core' elements to be included in surgical pathology reports, with detailed commentary to guide users, including references. This dataset replaces the widely used first edition, and will facilitate consistent and accurate case reporting, data collection for quality assurance and research, and allow for comparison of epidemiological and pathological parameters between different populations.

INTRODUCTION

The formation of the International Collaboration on Cancer Reporting (ICCR) was initiated by the Australasian and United Kingdom Royal Colleges of Pathologists, the College of American Pathologists and the Canadian Association of Pathologists in association with the Canadian Partnership Against Cancer in 2011. The impetus for the ICCR initiative was to reduce the worldwide burden of cancer dataset development and reduplication of effort by various global organizations who were each commissioning, publishing and maintaining their own standardized cancer reporting datasets. A lack of standardization of data elements, terminology, dataset structure or recommended methodology has been linked to suboptimal comparability of essential data for research or benchmarking in cancer management. Uniformity of content and standardized nomenclature allows more efficient aggregation, comparison, benchmarking and epidemiological analysis of cancer data across large populations. An international collaborative approach encourages global alignment of best practice standards. In addition, the generation of freely available, internationally harmonized cancer reporting datasets, benefits countries which lack the resources to develop their own.

The ICCR currently includes 18 representative member organizations covering six continents. The ICCR works closely in partnership with the International Agency for Research on Cancer (IARC) (the organization that is responsible for producing the World Health Organization (WHO) monographs, the ‘Blue books’ on tumor classification), the organizations responsible for tumor staging (the Union for International Cancer Control (UICC), American Joint Committee on Cancer (AJCC), the International Federation of Obstetricians and Gynecologists (FIGO)), the International Society of Gynecological Pathologists (ISGyP) and other bodies invested in improving the management of cancer. The ICCR have made a commitment to synchronize the development of harmonized international

datasets with each new WHO tumor classification (WHO Blue book) as well as with revised cancer staging systems (FIGO, UICC and AJCC).

In the last decade, the ICCR has developed 56 cancer datasets including updated editions for cervical and endometrial carcinomas and new datasets for vulval and vaginal carcinomas, gestational trophoblastic neoplasia and uterine malignant and potentially malignant mesenchymal tumors. These evidence-based datasets have been produced by a panel of internationally recognized expert pathologists as well as a specialist clinician in each field. All ICCR datasets are freely available for worldwide non-commercial use at the following website: http://www.iccr-cancer.org/datasets. The dataset development process has also been reported in other peer-reviewed journals (1-3). Herein, we describe the development of the updated (second edition) of the ovary/fallopian tube/primary peritoneal carcinoma dataset and present the 'core' and 'non-core' elements to be included on the pathology report.

METHODS

The purpose of the updated dataset was to revise the key pathological data that are required for cancer diagnosis, staging, prognosis and patient management in accordance with the updated WHO tumor classification (4) and to align with the most recent FIGO staging (5). The revision of the standardized dataset ensures that histopathology reports include all up-to-date, relevant information presented in a consistent, concise format that conforms to international best practice.

The ICCR has developed and ratified standard operating procedures for the process of dataset development (described in earlier publications (1-3)). Guidelines agreed by the ICCR Dataset Steering Committee (DSC) also define the selection process, roles and responsibilities of the chair, the DSC representative/s on the panel, and the expert panel

members. The DSC appointed a chair to develop the second edition dataset and they identified nine other expert gynecological pathologists who together with a medical oncologist, the ICCR Series Champion and project manager, formed, fallopian tube, primary peritoneal carcinoma Dataset Authoring Committee (DAC). The Series Champion provided guidance and support to the chair of the DAC regarding ICCR standards and ensured harmonization across datasets, while the project manager coordinated the development process.

As a result of the publication of the 5th edition of the WHO Classification of Tumors, Female Genital Tumors (4), the ICCR identified three gynecological datasets that required updating and four new gynecological datasets that required development. This suite of gynecological datasets was developed through a collaboration between the ICCR and the ISGyP. The datasets were developed and submitted to an eight-week period of international open consultation. Open consultation consists of sending the draft datasets to various international stakeholders comprising pathology societies and cancer organizations and requesting feedback on the datasets. The expert panel was convened via online meetings and email discussions to review and consider each of the elements in the dataset. The elements under discussion included core elements, defined as those which are unanimously agreed by the panel to be essential for the histological diagnosis, clinical management, staging or prognosis, and non-core elements, defined as non-essential, which are clinically important, recommended as good practice and should ideally be included in the dataset but which are not yet validated or regularly used in patient management. The necessary level of evidentiary support needed for core elements is Level III-2 or above (based on prognostic factors in the NHMRC levels of evidence document and defined as ‘Analysis of prognostic factors amongst persons in a single arm of a randomized controlled trial’) (6). Infrequently, where Level III-2 evidence is not available, an element can be categorized as core with unanimous agreement

of the expert panel. The minimum information which should be included in the pathology report is represented by the core elements.

The commentary comprises explanatory text, diagrams or tables to: (i) clarify core and non-core elements, (ii) provide relevant evidence, and explain why each element is necessary (e.g., how does it assist with diagnosis, clinical management or prognosis of the specific cancer); and (iii) define the way each element should be reported. The core elements and associated commentaries are presented below, followed by the non-core elements and commentaries. Some dataset elements include an admixture of core and non-core items, which are included in the core data elements section in this paper.

RESULTS

SCOPE OF THE DATASET

The dataset has been developed for the pathology reporting of resection specimens of primary borderline and malignant epithelial tumors of the ovary, fallopian tube and peritoneum. It does not include non-epithelial ovarian neoplasms such as germ cell or sex cord stromal tumors or other primary peritoneal neoplasms such as mesothelioma (7). In those rare cases where more than one primary tumor 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 tumor.

The 2nd edition of this dataset includes changes to align the dataset with the 2020 WHO Classification (4). The ICCR dataset includes 5th edition Corrigenda, June 2021 (8).

CORE DATA ELEMENTS

A list of the core elements for the reporting of ovarian, fallopian tube and primary peritoneal carcinomas is presented in Table 1 and described below:

Specimens submitted

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.

Specimen integrity

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 tumor on the surface, or whether the tumor 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 FIGO Stage IC disease) (5). 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 (5), 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 (9, 10), while others did not (11-13).

A 2014 meta-analysis assessed the impact of intraoperative rupture on prognosis, after analyzing nine eligible studies which included 2,382 patients (5). 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 (14).

There is some evidence to suggest that clear cell carcinomas exhibit a higher risk of rupture (15), probably related to adhesions to the surrounding tissues, associated with tumor invasion or endometriosis (16). Capsular rupture has also been associated with pregnancy (17).

Tumor site/Histological sites of tumor involvement

Sites of tumor involvement should be recorded as this is necessary for tumor 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 high grade serous carcinomas (HGSCs).

It was first recognized 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 (18,

19). This was first 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 serous tubal intraepithelial carcinomas (STICs) harbor identical *TP53* mutations to the extratubal tumor, establishing that they are clonal (20). Comparison of telomere length and centrosome amplification in matched STIC and ovarian HGSC suggests that the STICs develop before the ovarian tumors and are in fact a precursor and not a metastatic focus (21, 22). 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 (23). 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 HGSC 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 (5, 24). In other cases, the fimbrial end of the fallopian tube was obliterated by a tubo-ovarian mass.

According to the FIGO 2014 Staging System, the primary site of non-uterine HGSC is designated as ovarian, tubal or primary peritoneal (5). In some cases it may not be possible to ascertain the primary site of origin, and these should be categorized as ‘undesignated’ in the new staging system (5). 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 tumor incidence and mortality, data collection by cancer registries and entry into clinical trials. Based on the 2020 WHO Classification, recommendations for assigning the site of origin of extra-uterine HGSC are provided in the following section (4). Using these criteria, assignment of primary site is no longer based on the site of greatest volume/size of tumor 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 tumor 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 (25).

- **Suggestions for assigning site of origin of HGSC**

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 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 tumor site, but the following are intended as practical guidelines for handling cases at the present time (25).

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 (20) to avoid missing this important site of disease, which probably represents the tumor 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., point 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 favorable prognosis, based on limited experience to date (26)) 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 millimeters (mm) and widespread peritoneal involvement, which would traditionally be categorized as primary peritoneal carcinoma (27), 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 categorized as tubal primaries. Note that the distinction between STIC and intramucosal HGSC of the fallopian tube is subjective and not clinically significant; both are confined to the epithelium and are "non-invasive" but the latter shows 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 emphasized 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 categorized as primary peritoneal carcinoma by the conventional criteria below (4) *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 carcinoma should be carefully evaluated for an endometrial versus a tubo-ovarian primary (WT1 may be of value in such cases - see **Ancillary studies**, to distinguish between ovarian and uterine carcinoma). The majority of such cases will represent adnexal metastases from an endometrial serous carcinoma (28).

Macroscopic description of omentum

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 standardized guidelines have been developed for sampling

omental specimens in cases of ovarian carcinoma or borderline tumors. However, in the setting of a grossly involved omentum, submitting one block for histologic examination is probably sufficient (29, 30). In patients who have received neoadjuvant chemotherapy, where histological assessment of tumor response to therapy is recommended (see **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 (30), other studies suggest at least one block for every 20 mm of maximum omental dimension (31). Taking this information into account, 4-6 blocks in cases where the omentum is grossly negative in patients with an ovarian carcinoma or borderline tumor is recommended.

The size of the largest omental tumor deposit should be recorded in the pathology report. This is critical for determining the pathological stage (4, 5). Microscopic tumor which is not grossly evident, macroscopically evident tumor ≤20 mm, and macroscopically evident tumor >20 mm, correspond to FIGO Stages IIIA2, IIIB, and IIIC, respectively (5).

Histological tumor type

All tubo-ovarian epithelial malignancies and borderline tumors should be typed according to the 2020 WHO Classification (4). There are five major histotypes of primary ovarian carcinoma: low grade serous, high grade serous, clear cell, endometrioid and mucinous (32-35). There are also other uncommon minor types listed in the 2020 WHO Classification including malignant Brenner tumor, mesonephric-like and undifferentiated carcinoma (4). As seromucinous carcinoma is considered a morphologic variant of endometrioid carcinoma, it has thus been removed from the updated 2020 WHO Classification (4). 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) (36).

Although management of ovarian carcinoma is, at present, largely dependent on tumor 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 tumor types. This is in part because, although clinically often considered as one disease, there is an increasing realization 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 (32-35). Tumor 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 Lynch syndrome (LS) (37). The most common ovarian carcinoma is HGSC (approximately 70%) followed by clear cell and endometrioid (38, 39). Mucinous and low grade serous are less common. Approximately 90% of advanced stage ovarian carcinomas (Stage III/IV) are high grade serous in type (38, 39). 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 tumor 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 **Ancillary studies**).

Borderline tumors should also be typed according to 2020 WHO Classification criteria (4). The most common types are serous and mucinous. Seromucinous, endometrioid, and Brenner types also occur. Clear cell borderline tumor should only be diagnosed with the greatest caution, being certain to exclude carcinoma.

Histological tumor grade

Histological grade is part of current European Society for Medical Oncology (ESMO)-European Society of Gynecological Oncology (ESGO) management guidelines for endometrioid and mucinous carcinomas (40). Serous carcinomas are now classified as low grade serous or high grade serous (4), and despite the names including the term grade, these are two different histotypes rather than low grade and high grade variants of the same tumor type. Hence, grading does not apply to serous carcinomas. Clear cell carcinomas, un-/dedifferentiated carcinomas, anaplastic carcinomas, carcinosarcomas and mesonephric-like carcinomas are aggressive tumors and grading does not apply. There is no grading system for malignant Brenner tumors. If chemotherapy has been administered, tumor 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 (41). The 1988 FIGO grading system is widely used for grading endometrioid carcinomas of ovarian and endometrial origin (5). The FIGO grading system is based on architecture; tumors with <5% non-squamous solid component are grade 1, those with 5-50% solid areas are grade 2, and tumors with >50% of solid architecture are classified as grade 3 (5). When grade 1 and 2 tumors show severe nuclear atypia in the majority of the tumor cells (grade 3 nuclei), the histological grade is increased by one (5, 42).

Dedifferentiation in endometrioid carcinoma, sometimes with Switch/Sucrose non-fermenting (SWI/SNF) alterations, results in highly aggressive behavior and such tumors are high grade by definition (43). 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 tumors are in fact HGSC with so-called solid, pseudoendometrioid or transitional-like (SET) features. Immunohistochemistry (IHC) is useful in this regard (see **Ancillary studies**). The interobserver reproducibility of grading is limited and several studies have attempted to improve on it (44-49). 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, tumors 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 (41).

As compared to the FIGO grading, the Silverberg grading system(50) was found to correlate better with survival in a multivariate analysis, although outcome in ovarian endometrioid carcinoma is mostly dictated by stage (42). The Silverberg system (Table 2) 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 tumor area or in 10 high power fields (HPF) (based on each HPF being 0.345 mm^2 in area, as per the original study (50); 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 tumors, which had a poor outcome (42).

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 (5).

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 DNA mismatch repair (MMR) proteins and p53 and by sequencing for exonuclease domain mutations (EDM) of *Polymerase epsilon* (*POLE*) (41, 51).

Some management guidelines for mucinous carcinomas require grading (40). 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 reemphasized that mucinous carcinomas only rarely show a solid growth pattern (52). 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 (52). The DAC now recommends the Silverberg grading system (50) 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 (52). Expansile/confluent invasion or infiltrative invasion ≤10% of the tumor is graded as 1 while infiltrative invasion >10% is graded as 2 (52). This was significantly associated with survival in univariable analysis in this relatively small study of 46 cases (53). This corroborates earlier studies showing that while infiltrative invasion is associated with higher stage, it also predicts higher risk of recurrence at Stage I (53-56). 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 (57). 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.

Borderline tumor – special features

Terminology for ovarian borderline tumors has evolved over several years (31, 58). The preferred terminology is borderline tumor, for example serous or mucinous borderline tumor, and this has been endorsed in the 2020 WHO Classification (4). Serous borderline tumors can be of typical or micropapillary subtypes, as per the latest WHO Classification (4). For mucinous, endometrioid, clear cell, Brenner, and seromucinous tumors, the designation 'borderline tumor' is also used in the 2020 WHO Classification (4). The terms 'low malignant potential' or 'atypical proliferative' are not recommended (4). Synonyms formerly used for seromucinous borderline tumors include endocervical-type mucinous borderline tumor, Müllerian mucinous borderline tumor, and atypical proliferative (borderline) Müllerian tumor (59).

Determining the lowest threshold for the diagnosis of a borderline tumor 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 tumors arising within a cystadenoma/cystadenofibroma (31). A borderline tumor 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 tumor can exhibit variable degrees of micropapillary or cribriform architecture, a diagnosis of micropapillary subtype of serous borderline tumor 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 (4).

A standardized quantitative criterion for distinguishing microinvasion from frankly invasive carcinoma within a borderline tumor 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 (31, 58, 60). The 2020 WHO Classification uses a cut-off of 5 mm (4). Some groups distinguish two patterns of stromal invasion in serous tumors 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)) (31, 58). However, this distinction is not universally accepted as being clinically significant. Due to insufficient numbers of cases in the literature, definitive conclusions regarding the clinical significance of this distinction cannot be drawn (58, 61). Analogous to the situation for serous tumors, some investigators advocate the separation of 'microinvasion' from 'microinvasive carcinoma' in mucinous borderline tumors while others use these two terms interchangeably (60).

In mucinous borderline tumors, intraepithelial carcinoma is diagnosed in non-invasive foci with marked nuclear atypia, and is often associated with mitotic activity (31, 60). 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 (62). Intraepithelial carcinoma for mucinous borderline tumors is a non-core item for reporting and the term intraepithelial carcinoma is not applied to other types of borderline tumor. Mucinous borderline tumors 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 tumors and are more common with exophytic neoplasms. The most important adverse prognostic factor for ovarian serous borderline tumors 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 favorable prognosis. Specifying the location and size of implants is important for determining the FIGO stage (5). Non-invasive and invasive implants/LGSC may co-exist in the same specimen. Non-invasive implants are subclassified as epithelial or desmoplastic types (31). Epithelial-type non-invasive implants resemble detached fragments of a serous borderline tumor 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 (58).

The most widely used criterion for diagnosing extra-ovarian LGSC/invasive implants in a patient with an ovarian serous borderline tumor is destructive invasion of underlying tissue (63). 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 (31, 58).

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 (64). This terminology should only be used sparingly, and obtaining a specialist gynecological 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; this has been endorsed in the 2020 WHO Classification (4, 31, 58, 65). It is unclear whether invasive implants involving extra-ovarian sites in association with an ovarian serous borderline tumor represent metastases from the serous borderline tumor or an independent primary peritoneal tumor. A number of molecular studies analyzing primary ovarian tumors with their associated implants have yielded varying results (58). However, Ardighieri et al (2014) showed in a large population-based cohort, that the vast majority of implants are clonally related to the primary ovarian tumor (66). 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 tumor, suggesting that invasive implants are clonally related to the primary ovarian tumor as opposed to representing independent primary peritoneal lesions (66). 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 tumor are mostly LGSCs and most are clonally related to the serous

borderline tumor i.e., represent tumor progression (67). From a practical point of view, for cases of invasive implants in association with an ovarian tumor diagnosed as serous borderline tumor, it is recommended to consider additional sampling of ovarian tissue to demonstrate LGSC or micropapillary serous borderline tumor (68).

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

Serous tubal intraepithelial carcinoma (STIC)

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 **Histological sites of tumor involvement**). STIC comprises a population of cytologically malignant epithelial cells replacing the normal tubal mucosa, most commonly involving the fimbria, and characterized 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 (69-71). 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 (3

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-gynecological primary tumors can occur and mimic STIC (72-74). 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 **Ancillary studies**) (75). A diagnosis of STIC always requires consideration of clinical and pathological findings and the exclusion of secondary involvement of the fallopian tube.

Peritoneal cytology

The results of peritoneal cytology (peritoneal washings or peritoneal fluid) are important for the substaging of Stage I ovarian tumors (borderline and malignant). Positive peritoneal washings in a Stage I tumor signify Stage IC3 in the 2014 FIGO Staging System (5). Positive peritoneal cytology in a Stage I carcinoma may indicate the need for adjuvant therapy in certain cases. Cells of LGSC and serous borderline tumor cannot be reliably

distinguished in a cytology specimen; in such cases, the cytology findings should be correlated with the histopathological findings

Lymph node status

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 (5). 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 favorable outcome - although it should be noted that the data are based mainly on cases of HGSC (76, 77). Positive extra-abdominal lymph nodes including inguinal metastases represent Stage IVB disease.

FIGO specifically restricts the definition of Stage IIIA1 disease to retroperitoneal lymph nodes (pelvic and para-aortic) but does not indicate how tumor 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 (5). According to FIGO (personal communication), this should be regarded as intra-abdominal disease, i.e., Stage IIIC (78, 79). At present there are also limited data to justify the subdivision of Stage IIIA1 according to the size of the nodal metastases (5). 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 tumors is largely restricted to tumors of serous subtype where approximately 25% of fully staged cases will show positive

nodes (80, 81). While this finding does not appear to influence overall survival, cases with nodular epithelial tumor aggregates >1 mm in extent may show decreased disease-free survival (82). Rarely, LGSC appears to develop within the lymph nodes of patients with ovarian serous borderline tumors (83).

According to TNM8 (84), nodal involvement should be recorded as the presence of isolated tumor cells (ITC, <0.2 mm), micrometastases (MIC, 0.2-2 mm) or macrometastases (MAC, >2 mm).

Provisional pathological staging

Tumor stage is amongst the strongest prognostic factors in tubo-ovarian carcinoma (85). Patients with localized, 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 (86). 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 tumor stage which should be determined at the multidisciplinary tumor board meeting where all the pathological, clinical and radiological features are available (5, 84, 87, 88).

All ovarian carcinomas and borderline tumors, as well as carcinomas of the fallopian tube and peritoneum should be staged (5). The latest version of either FIGO *or* TNM staging, *or* both, can be used depending on local preferences (5, 84, 87, 88). The FIGO system is in widespread use internationally and is the system used in most clinical trials and research studies. However, UICC or AJCC 8th edition TNM Staging Systems are used or mandated in many parts of the world (84, 87). 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 (84, 87).

For reasons of comparability, FIGO continue to classify umbilical metastases as Stage IVB (personal communication) (5). 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 tumor should be staged following diagnosis using various appropriate modalities (clinical, radiological, pathological). While the original tumor 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 (89).

NON-CORE DATA ELEMENTS

A list of the non-core elements for the reporting of ovarian, fallopian tube and primary peritoneal carcinomas is presented in Table 3 and described below:

Clinical information

It is estimated that approximately 10% of primary tubo-ovarian and peritoneal carcinomas have a genetic basis (90), and this figure may be as high as 17% for HGSCs (91).

Germline mutations in *BRCA1* and *BRCA2* account for the majority of genetically related cases while up to 10% of patients with 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 tumors. Nevertheless, it is recommended that available information on genetic status be recorded for the following reasons:

1. HGSCs associated with *BRCA* mutations (germline or somatic) more commonly show certain morphological features such as 'SET' architectural patterns, very marked nuclear atypia, and tumor-infiltrating lymphocytes (90, 92, 93). 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) (90, 91, 94). 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 tumor morphology.
2. Knowledge of proven or potential hereditary gynecological 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 (90). Small, macroscopically occult tubal carcinomas, and their in situ precursor - 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 MMR proteins (95). In approximately 60% of women with LS, a gynecological tumor (endometrial or ovarian) will represent the sentinel cancer (96). 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 tumor 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 tumor and result in difficulties in tumor typing and tumor down-staging. If neoadjuvant chemotherapy is being administered, a pretreatment tissue biopsy is recommended for tumor typing. If this is not possible then the diagnosis of malignancy can be made on cytological examination of ascitic fluid, preferably with IHC performed on a cell block preparation; however, there are limitations to the interpretation of immunohistochemical markers on cell blocks (97). Markers of value in tumor typing are discussed in **Ancillary studies**.

Tumor dimensions

There is little or no published evidence to suggest that size of the primary tumor is of prognostic significance, and size is not important for staging or management. The principal reason for recording the tumor dimensions, especially the maximum diameter, is to provide evidence that the tumor has been adequately sampled for histology. There are no evidence-based guidelines as to the optimal sampling of solid or cystic ovarian tumors. By convention, however, most pathologists sample one block per 10 mm of maximum tumor diameter in

solid tumors. These same recommendations appear in cancer datasets for tumors at a range of other anatomical sites.

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

It is recognized that ovarian mucinous neoplasms may exhibit considerable intratumoral heterogeneity with an admixture of benign, borderline and malignant areas. One study which assessed the 'adequacy' of sampling in epithelial ovarian neoplasms (98), confirmed mucinous carcinomas to display more histological variation than serous carcinomas. The authors concluded that more extensive sampling was required in borderline tumors to exclude foci of invasion. According to the recommendations of the 2004 Bethesda Workshop for borderline ovarian tumors (99), all borderline tumors should be well sampled – at least two sections per 10 mm (excluding smooth-walled cystic foci) with the exception that borderline tumors of less than 100 mm should be sampled with one block per 10 mm of maximum tumor diameter. The recommendation that there should be more extensive sampling of larger tumors, especially those of mucinous type, reflects their greater likelihood of harboring foci of invasive carcinoma. Additional sampling of mucinous borderline tumors is also recommended when histological features such as intraepithelial carcinoma or microinvasion are identified in the original sections. Similarly, additional sampling in serous borderline tumors is recommended when micropapillary areas or microinvasion are present in initial sections since such neoplasms are more likely to harbor invasive foci.

In mucinous ovarian tumors, tumor 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 (100, 101).

Block identification key

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 tumor 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.

Pattern of invasion

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 (54, 102-106). The expansile/confluent/non-destructive pattern of invasion is characterized by architecturally complex glands, cysts or papillae lined by atypical epithelium with minimal to no intervening stroma. The destructive/infiltrative pattern is characterized by haphazardly arranged glands, tubules, nests and cords of malignant cells infiltrating stroma with an associated edematous, inflammatory or desmoplastic response. While several studies have shown the expansile pattern heralds a better prognosis (56, 102-107), a population-based registry study of mucinous ovarian carcinomas was not able to prognosticate utilizing the distinction between the two patterns of invasion (54). 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.

Carcinosarcoma components

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) (108-110). In view of the paucity of studies, the 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 (108-110).

Response to neoadjuvant therapy

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 (111, 112). This three-tier scoring system (the Chemotherapy Response Score (CRS)) is reproducible, simple to apply in practice, and has been validated in an international multicenter study (113). This is the grading system currently recommended by the DAC. The method is as follows:

1. Scoring should be carried out on a single hematoxylin and eosin (H&E)-stained section (see discussion of omental sampling in **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 tumor a CRS score of 3 is given - see Table 4).
3. The amount of *viable* tumor 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 tumor infiltration:
    a. When found in the absence of tumor, fibrosis is likely to indicate regression.
    b. If fibrosis occurs in association with tumor, this may simply reflect tumor-associated desmoplasia rather than regression.
    c. However, when fibrosis in association with tumor 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 tumor and can sometimes appear more numerous because their density increases in areas where tumor has disappeared.
5. As a guide, >95% of tumor 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 tumors with a CRS score of 1 or 2 were compared with those having a CRS score of 3 (111, 112). 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 tumor 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.

Coexistent pathology/Precursor lesions

Borderline and malignant endometrioid, clear cell and seromucinous ovarian tumors may arise from endometriosis. Thus, the presence of endometriosis, although not of prognostic or therapeutic significance, particularly if contiguous with the tumor, may assist in determining the histotype in problematic cases (114, 115).

Ancillary studies

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 tumor 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 (115, 116).

The choice of ancillary tests for the distinction of a primary ovarian carcinoma from a metastatic malignancy (Table 5) depends on its morphological context and can be problematic particularly on small or cytological specimens.

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 (117). Claudin 4 can be superior to MOC31, BerEP4, or PAX8 (118). Expression of PAX8 in reactive mesothelial proliferations has been noted (119-122). However, claudin 4 or B72.3 may not be widely available. Desmin is an excellent second marker for differentiating primary ovarian carcinoma from reactive mesothelial proliferation (123), 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 (124).

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 tumor, either a granulosa cell tumor or a Sertoli cell tumor. Conversely, some Sertoli-Leydig cell tumors have a pseudoendometrioid appearance and can mimic an endometrioid neoplasm (125). Markers which are useful to distinguish between them include inhibin, calretinin and SF-1 versus EMA, PAX8, BerEP4 and CK7 (125-130).

Simultaneous involvement of the endometrium and ovaries by an endometrioid carcinoma is not uncommon (131, 132). IHC and molecular testing are of little value in ascertaining the relationship between the tumors as synchronous dual primaries versus metastasis since it has been shown that in almost all such the tumors are clonally related (133-135). However, an indolent behavior can be anticipated if both tumors are low grade; the endometrial tumor shows less than 50% myometrial invasion; substantial lymphovascular invasion is absent; and only the endometrium and one ovary and no other site is involved (136). These tumors 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 (100, 101, 137). 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 (138). 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 (139). Diffuse p16 immunoreactivity in such cases may be useful in suggesting a metastatic cervical adenocarcinoma, but performing HPV testing is more specific (140-142).

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 (143-146).

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) (75, 147). 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) (28, 75, 147-153). HER2 overexpression is rare in tubo-ovarian HGSC but is seen in up to 30% of endometrial serous carcinomas; although relatively insensitive the presence of HER2 overexpression favors an endometrial primary site (154).

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 6). The recommended panel is a combination of WT1 and p53 (155). 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 (*BRCA 1/2* 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 (115). HGSC can

be distinguished from LGSC by p53 and from mucinous carcinoma by WT1 (156). Endometrioid carcinoma can be distinguished from clear cell carcinoma by napsin A, HNF1B and progesterone receptor (PR) (116). Endometrioid and mucinous carcinomas can be distinguished by PR and vimentin (57, 114, 156).

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 (157). The cells must exhibit abnormal (mutation-type) p53 staining (158, 159). 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) (157).

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 (41, 51, 160). 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 (161-165).

There are no validated prognostic biomarkers for ovarian clear cell or mucinous carcinoma. However, p53 status might inform about the course of mucinous borderline tumors. A recent study showed that p53abn mucinous borderline tumors were associated with a higher risk of death. While there are no current therapeutic options for these patients, the converse information that p53 normal mucinous borderline tumors are at very low risk of disease progression can be useful in some clinical circumstances (62).

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 (166). 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 (167). 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 (168).

The United States Food and Drug Administration (FDA) has approved immunotherapy for MMRd tumors irrespective of site. Universal MMRd testing is recommended for ovarian endometrioid carcinoma to screen for hereditary LS (169). 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 (170-173). 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 intratumoral stromal lymphocytic infiltrate, presence of synchronous endometrial and ovarian carcinoma) (170). 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 (164). 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 (174). *HER2* amplifications occur in 18% of ovarian mucinous(175) and 7-14% of ovarian clear cell carcinoma (176).

Ovarian carcinomas represent a heterogeneous group of tumors. In recent years, molecular pathology has been instrumental in demonstrating that ovarian carcinomas are not a single entity, but a group of tumors with diverse morphology, natural history, and pathogenesis (177). 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.

HGSCs are chromosomally unstable tumors, 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 (178). 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 tumors, 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 (179, 180). At present there is no single agreed upon predictive assay for HRD/prediction of response to PARPi.

LGSCs are closely related to serous borderline tumors, and show frequent mutations in the MAPK pathway (*KRAS, BRAF*, *NRAS*), prognostically unfavorable alterations in *CDK2A* and mutations in *USP9X* (163, 181). PR is an unfavorable prognostic marker (164).

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 (41, 182).

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

Mucinous carcinomas frequently harbor genomic loss of *CDKN2A, KRAS* and *TP53* mutations often co-occurring and *HER2* amplifications (183). In mucinous tumors with areas

of carcinoma admixed with foci of benign or borderline mucinous tumor, *KRAS* mutations have been demonstrated in all components, suggesting that this represents an early event during tumorigenesis. *TP53* mutations are implicated in the progression from mucinous borderline tumor to carcinoma and, as discussed earlier, a recent study demonstrated a higher risk of death for patient with mucinous borderline tumor harboring a *TP53* mutation (62).

DISCUSSION

The first edition of the ICCR dataset for reporting ovarian, fallopian tube and primary peritoneal carcinomas emphasized the importance of accurate histotype diagnosis and the differences between histotypes with respect to pathogenesis and patient management and outcome (1). For example, HGSC and LGSC are distinct diagnostic entities rather than grades of serous carcinoma, a seemingly minor change but one that reflects the understanding that HGSC and LGSC are distinct diagnostic entities rather than simply different grades of a single tumor type.

The first edition adopted criteria to be used for primary site assignment for extrauterine HGSC that was novel at the time but has now been widely adopted, including in the 2020 WHO Classification (4). The second edition includes a slight modification from the first and aligns with the WHO criteria. This concerns the criteria for diagnosing a primary peritoneal HGSC which should be diagnosed 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 and there should be no ovarian involvement by HGSC. This contrasts with the first edition where ovarian stromal involvement up to 5mm was allowed for a primary peritoneal neoplasm. The first edition also included criteria for assignment of CRS in assessing response of HGSC to neoadjuvant chemotherapy, a system since validated in a large international study (113). These aspects are unchanged in this second edition of the

ICCR dataset (with the exception of the minor change just discussed). The revisions in this edition are relatively minor, predominantly reflecting those changes adopted in the 2020 WHO Classification, along with updated references where new information has become available. It is noteworthy that the WHO 5th edition includes harmonization of terminology across the three sites (ovary, fallopian tube, peritoneum).

Changes in this second edition, which largely align with WHO 2020, include dropping the terminology of 'atypical proliferative tumor' as a synonym for 'borderline tumor'. This is in recognition that a single standardized nomenclature is in all regards preferable to use. The diagnosis of 'non-invasive low grade serous carcinoma' is no longer used and these are considered to be micropapillary variants of serous borderline tumor (4). The diagnosis of seromucinous carcinoma is also no longer included, as these are now considered mostly to be morphological variants of endometrioid carcinoma, based on morphology and molecular features (184). The list of possible histotypes includes the relatively recently described mesonephric-like adenocarcinoma and dedifferentiated carcinoma (an admixture of endometrioid and undifferentiated carcinoma) (4); these have histopathological features identical to their more common counterparts in the endometrium. Mixed carcinoma, which was absent from the first edition of the ICCR dataset, is present in the second edition and was reintroduced in the WHO 2020 Classification; it is recognized that mixed carcinomas, especially admixtures of histotypes associated with endometriosis, while rare, do occur, accounting for <1% of ovarian carcinomas (185). There is one modification in the second edition regarding tumor grading which applies to mucinous carcinomas. Grading of these neoplasms remains a non-core element but while in the first edition it was recommended to grade these neoplasms using the FIGO grading system for endometrioid carcinomas, it is now recommended to use the Silverberg grading system if a grade is to be appended to a mucinous carcinoma.

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FIGURE LEGENDS

Table 1. Core data elements for pathological reporting of ovarian, fallopian tube and primary peritoneal carcinoma.

STIC, Serous tubal intraepithelial carcinoma; FIGO, International Federation of Obstetricians and Gynecologists; UICC, Union for International Cancer Control; AJCC, American Joint Committee on Cancer.

† Specification of endometrioid carcinoma grade is core; specification of mucinous carcinoma grade is considered non-core (see Table 2).

Micropapillary architecture for serous borderline tumor, microinvasion and implants for serous and seromucinous borderline tumor is core; specification of presence or absence of intraepithelial carcinoma for mucinous borderline tumor is considered non-core (see Table 2).

Table 2

The Silverberg grading system (50).

Table 3. Non-core data elements for pathological reporting of ovarian, fallopian tube and primary peritoneal carcinoma.

† Specification of mucinous carcinoma grade is non-core; specification of endometrioid carcinoma grade is considered core (see Table 1).

Specification of presence or absence of intraepithelial carcinoma for mucinous borderline tumor is non-core; micropapillary architecture for serous borderline tumor, microinvasion and implants for serous and seromucinous borderline tumor is considered core (see Table 1).

Table 4

Chemotherapy response score (CRS) (111).

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

Table 5

Ancillary tests to distinguish primary ovarian carcinoma from other entities.

[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.

Table 6

Ancillary tests to distinguish ovarian carcinomas of various histotypes.

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