

**CARCINOMA OF THE OVARY,
FALLOPIAN TUBE AND PRIMARY
PERITONEAL SITE**

**STRUCTURED REPORTING
PROTOCOL**

(1st Edition 2016)

Based on the:

International Collaboration on Cancer Reporting (ICCR)

Carcinoma of the Ovary, Fallopian tube and Primary Peritoneal
Site Dataset

www.ICCR-Cancer.org

Core Document versions:

- International Collaboration on Cancer Reporting (ICCR) Carcinoma of the Ovary, Fallopian tube and Primary Peritoneal Site Dataset as published to: www.ICCR-Cancer.org
- FIGO Committee on Gynecological Cancer (2014). Revised FIGO staging for carcinoma of the vulva, cervix and endometrium.
- World Health Organization Classification of Tumours Pathology and Genetics of Tumours of the Breast and Female Genital Organs (2014).

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Scope

This protocol contains standards and guidelines for the structured 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.

For risk reducing procedures, Appendix 6 describes the Protocol for Sectioning and Extensively Examining the Fimbriated End (SEE-FIM) of the Fallopian Tube.

Abbreviations

AJCC	American Joint Committee on Cancer
CRS	Chemotherapy Response Scores
ER	Estrogen receptor
FIGO	Federation Internationale de Gynecologie et d'Obstetrique (International Federation of Obstetricians and Gynecologists)
HGSC	High Grade Serous Carcinoma
IHC	Immunohistochemical tests on formalin fixed tissues
LS	Lynch Syndrome
LVSI	Lymphovascular space invasion by neoplastic cells
MMR	Mismatch repair
PBS	Pharmaceutical Benefits Scheme
PR	Progesterone receptor
RCPA	Royal College of Pathologists of Australasia
STIC	Serous Tubal Intraepithelial Carcinoma
TRG	Tumour Regression Grading
UICC	Union Internationale Contre le Cancer (International Union Against Cancer)
WHO	World Health Organization

Definitions

The table below provides definitions for general or technical terms used in this protocol. Readers should take particular note of the definitions for 'standard', 'guideline' and 'commentary', because these form the basis of the protocol.

Ancillary study	An ancillary study is any pathology investigation that may form part of a cancer pathology report but is not part of routine histological assessment.
Clinical information	Patient information required to inform pathological assessment, usually provided with the specimen request form, also referred to as "pre-test information".
Commentary	Commentary is text, diagrams or photographs that clarify the standards (see below) and guidelines (see below), provide examples and help with interpretation, where necessary (not every standard or guideline has commentary).

Commentary is used to:

- define the way an item should be reported, to foster reproducibility
- explain why an item is included (e.g. how does the item assist with clinical management or prognosis of the specific cancer).
- cite published evidence in support of the standard or guideline
- state any exceptions to a standard or guideline.

In this document, commentary is prefixed with 'CS' (for commentary on a standard) or 'CG' (for commentary on a guideline), numbered to be consistent with the relevant standard or guideline, and with sequential alphabetic lettering within each set of commentaries (eg CS1.01a, CG2.05b).

General commentary	General commentary is text that is not associated with a specific standard or guideline. It is used: <ul style="list-style-type: none">• to provide a brief introduction to a chapter, if necessary• for items that are not standards or guidelines but are included in the protocol as items of potential importance, for which there is currently insufficient evidence to recommend their inclusion. (Note: in future reviews of protocols, such items may be reclassified as either standards or guidelines, in line with diagnostic and prognostic advances, following evidentiary review).
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Guideline	<p>Guidelines are recommendations; they are not mandatory, as indicated by the use of the word 'should'. Guidelines cover items that are unanimously agreed should be included in the dataset but are not supported by NHMRC level III-2 evidence.¹ These elements may be clinically important and recommended as good practice but are not yet validated or regularly used in patient management.</p> <p>Guidelines include 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 eg macroscopic tumour details, block identification key, may be included as either required or recommended elements by consensus of the expert committee. Such findings are essential from a clinical governance perspective, because they provide a clear, evidentiary decision-making trail.</p> <p>Guidelines are not used for research items.</p> <p>In this document, guidelines are prefixed with 'G' and numbered consecutively within each chapter (eg G1.10).</p>
Macroscopic findings	Measurements, or assessment of a biopsy specimen, made by the unaided eye.
Microscopic findings	In this document, the term 'microscopic findings' refers to histo-morphological assessment.
Predictive factor	A predictive factor is a measurement that is associated with response or lack of response to a particular therapy.
Prognostic factor	A prognostic factor is a measurement that is associated with clinical outcome in the absence of therapy or with the application of a standard therapy. It can be thought of as a measure of the natural history of the disease.
Standard	<p>Standards are mandatory, as indicated by the use of the term 'must'. Standards 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 NHMRC levels of evidence¹ document). In rare circumstances, where level III-2 evidence is not available an element may be made a Standard where there is unanimous agreement in the expert committee. An appropriate staging system eg Pathological TNM staging would normally be included as a required element. These elements must be recorded and at the discretion of the pathologist included in the pathology report according to the needs of the recipient of the report.</p> <p>The summation of all standards represents the minimum dataset for the cancer.</p> <p>In this document, standards are prefixed with 'S' and</p>

numbered consecutively within each chapter (eg S1.02).

Structured report A report format which utilises standard headings, definitions and nomenclature with required information.

Synoptic report A structured report in condensed form (as a synopsis or precis).

Synthesis Synthesis is the process in which two or more pre-existing elements are combined, resulting in the formation of something new.

The Oxford dictionary defines synthesis as “the combination of components or elements to form a connected whole”.

In the context of structured pathology reporting, synthesis represents the integration and interpretation of information from two or more modalities to derive new information.

Introduction

Carcinoma of the ovary, fallopian tube and primary peritoneal site

Cancer of the ovary is the 7th most common cause of cancer death in Australian women² and the 5th leading cause of cancer death in New Zealand women.³ Numbers for fallopian tube cancers are much less, however this figure will change in the near future.

Site assignment (tube versus ovary versus peritoneum) for clear cell, endometrioid, low-grade serous and mucinous carcinomas is generally not problematic, however the same is not true for high-grade serous carcinomas (HGSCs). Recent evidence indicates that the precursors of HGSC originate in the fallopian tube in patients with germline BRCA1 mutations, and accumulating evidence suggests that this is also true for many sporadic HGSC. Therefore, in the presence of serous tubal intraepithelial carcinoma (STIC) or invasive HGSC in the tubal mucosa, assignment of a fallopian tube origin is now recommended. In approximately 15-10% of cases of HGSC the fallopian tube is normal in the presence of ovarian mass. Without a tubal lesion, these are classified as ovarian primary site.

Using the published criteria to assign the site of origin of HGSC will impact on relative numbers of ovarian versus fallopian tube cancers in the future with an increase in fallopian tube cancers and corresponding decrease in ovarian cancers. Many previously diagnosed ovarian cancers would today be reclassified as fallopian tube cancers.

The 2014 FIGO staging now includes assignment of primary site as part of the staging criteria.⁴

Importance of histopathological reporting

The information contained within a pathology report includes prognostic information for the patient and treating clinical team. The content will assist in subsequent management, whether this may be surveillance, further surgery, radiotherapy or chemotherapy, or a combination of these modalities.

Benefits of structured reporting

The pathology report lays the foundation for a patient's cancer journey and conveys information which:

- Provides the definitive diagnosis
- Includes critical information for FIGO staging
- Evaluates the adequacy of the surgical excision
- Provides morphological and biological prognostic markers which determine personalised cancer therapy

However, the rapid growth in ancillary testing such as immunohistochemistry, flow cytometry, cytogenetics, and molecular studies, have made the task of keeping abreast of advances on specific cancer investigations extremely difficult for pathologists. The use of structured reporting checklists by pathologists ensures that all key elements are included in the report specifically those which have clinical management, staging or prognostic implications. Consequently minimum or comprehensive datasets for the reporting of cancer have been developed^{5,6} around the world. Both the United Kingdom,⁷ and United States⁸ have produced standardised cancer reporting protocols or “datasets” for national use for many years.

The use of cancer reporting checklists improves completeness and quality of cancer reporting and thereby ensures an improved outcome for cancer patients. This has long term cost implications for public health by ensuring the most effective and timely treatment based on accurate and complete information.

The use of a structured reporting format also facilitates easy extraction of the necessary information by secondary users of the information ie cancer registries.

International Collaboration on Cancer Reporting

The International Collaboration on Cancer Reporting (ICCR), founded in 2011 by the Australasian (RCPA), US (CAP) and UK (RCPath) Colleges of Pathology and the Canadian Association of Pathology (Cap-ACP) in association with the Canadian Partnership Against Cancer (CPAC), was established to explore the possibilities of a collaborative approach to the development of common, internationally standardised and evidence-based cancer reporting protocols for surgical pathology specimens.

The ICCR, recognising that standardised cancer datasets have been shown to provide significant benefits for patients and efficiencies for organisations through the ease and completeness of data capture¹⁻⁴ undertook to use the best international approaches and the knowledge and experience of expert pathologists, and produce cancer datasets which would ensure that cancer reports across the world will be of the same high quality – ensuring completeness, consistency, clarity, conciseness and above all, clinical utility.

Representatives from the four countries participating in the initial collaboration undertook a pilot project in 2011 to develop four cancer datasets - Lung, Melanoma, Prostate (Radical Prostatectomy), and Endometrium. Following on from the success of this pilot project, the ICCR was joined by the European Society of Pathology (ESP) in 2013 and in 2014 incorporated a not-for-profit organisation focussed on the development of internationally agreed evidence-based datasets developed by world leading experts. The ICCR Datasets are made freely available from its website www.ICCR-Cancer.org

Design of this protocol

This structured reporting protocol has been developed using the ICCR dataset on Carcinoma of the Ovary, Fallopian Tube and Primary Peritoneal Site as the foundation.

This protocol includes all of the ICCR cancer dataset elements as well as additional information, elements and commentary as agreed by the RCPA expert committee. It provides a comprehensive framework for the assessment and documentation of pathological features of cancers of the ovary, fallopian tube and primary peritoneal site.

ICCR dataset elements for cancers of the ovary, fallopian tube and primary peritoneal site are included verbatim. ICCR Required elements are mandatory and therefore represented as standards in this document. ICCR Recommended elements, that is, those which are not mandatory but are recommended, may be included as guidelines or upgraded to a standard based on the consensus opinion of the local expert committee.

The ICCR elements are identified in each chapter with the ICCR logo placed before the Standard or Guideline number or bullet and the ICCR element description and commentary boarded by a grey box as shown below:

 G3.03	The histological grade for mucinous carcinomas may be recorded.
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Additional commentary by the RCPA expert committee may be added to an ICCR element but is not included in the grey bordered area eg

 G2.03	If present, the laterality of the lymph nodes submitted may be recorded as left, right or bilateral.
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CS2.03a If present, record site and number. All lymph node tissue should be submitted for histological examination.

Further information on the ICCR is available at www.iccr-cancer.org

Checklist

Consistency and speed of reporting is improved by the use of discrete data elements recorded from the checklist. Items suited to tick boxes are distinguished from more complex elements requiring free text or narrative. A structured or discrete approach to responses is favoured, however the pathologist is encouraged to include free text or narrative where necessary to document any other relevant issues, to give reasons for coming to a particular opinion and to explain any points of uncertainty.

Report format

The structure provided by the following chapters, headings and subheadings describes the elements of information and their groupings, but does not necessarily represent the format of either a pathology report (Chapter 7) or checklist (Chapter 6). These, and the structured pathology request form (Appendix 1) are templates that represent information from this protocol, organised and formatted differently to suit different purposes.

Key documents

- *International Collaboration on Cancer Reporting (ICCR) Carcinoma of the Ovary, Fallopian tube and Primary Peritoneal Site Dataset as published to: www.ICCR-Cancer.org.*
- *Guidelines for Authors of Structured Cancer Pathology Reporting Protocol, Royal College of Pathologists of Australasia, 2009⁹*
- *The Pathology Request-Test-Report Cycle — Guidelines for Requesters and Pathology Providers, Royal College of Pathologists of Australasia, 2004¹⁰*
- *FIGO Committee on Gynecologic Oncology (2014). Staging classification for cancer of the ovary, fallopian tube, and peritoneum.⁴*
- *WHO classification of tumours of the female reproductive organs. WHO classification of tumours. (2014). IARC press, Lyon.¹¹*
- *Berek and Hacker's Gynecologic Oncology, 5th edition. Walters Kluwer health/Lippincott Williams & Wilkins. 2010¹²*

Updates since last edition

Not applicable

Authority and development

This section provides information about the process undertaken to develop this protocol.

This 1st edition of the protocol is an amalgam of two separate processes:

1. This protocol is based on the 1st edition of the International Collaboration on Cancer Reporting (ICCR) Carcinoma of the Ovary, Fallopian tube and Primary Peritoneal Site Dataset. All ICCR elements from this dataset, both required (mandatory) and recommended (optional), are included in this protocol, verbatim. (It should be noted that RCPA feedback from all Anatomical Pathology fellows and specifically the local expert committee was sought during the development process of the ICCR dataset.) Details of the ICCR development process and the international expert authoring committee responsible for the ICCR dataset are available on the ICCR website: iccr-cancer.org.
2. Additional elements, values and commentary have been included as deemed necessary by the local expert committee. In addition, the standard inclusions of RCPA protocols eg example reports, request information etc, have also been added.

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Stakeholders

ACT Health

Anatomical Pathology Advisory Committee (APAC)

Australian Association of Pathology Practices Inc (AAPP)

Australian Cancer Network

Australian Commission on Safety and Quality in Health Care

Australian Society of Clinical Oncologists (ASCO)

Australian Society of Colposcopy and Cervical pathology (ASCCP)

Australian Society of Cytology (ASC)

Australian Society of Gynaecologic Oncologists (ASGO)

Cancer Australia

Cancer Council ACT

Cancer Council NSW

Cancer Council Queensland

Cancer Council SA

Cancer Council Tasmania

Cancer Council Victoria

Cancer Council Victoria Clinical Network

Cancer Council Western Australia

Cancer Institute NSW

Cancer Services Advisory Committee (CanSAC)

Cancer Voices

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Department of Health and Ageing

Grampians Integrated Cancer Services (GICS)

Health Informatics Society of Australia (HISA)

Independent Review Group of Pathologists

International Collaboration on Cancer Reporting (ICCR)

International Federation of Obstetricians and Gynecologists (FIGO)

International Gynecological Cancer Society (IGCS)

Medical Software Industry Association (MSIA)

National Breast and Ovarian Cancer Centre (NBOCC)

National E-Health Transition Authority (NEHTA)

National Pathology Accreditation Advisory Council (NPAAC)
National Round Table Working Party for Structured Pathology Reporting of Cancer.
New Zealand Guidelines Group (NZGG)
NSW Department of Health
Peter MacCallum Cancer Institute
Public Pathology Australia
Queensland Cooperative Oncology Group (QCOG)
Representatives from laboratories specialising in anatomical pathology across Australia
Royal Australasian College of Physicians (RACP)
Southern Cancer Network, Christchurch, New Zealand
Southern Melbourne Integrated Cancer Service (SMICS)
Standards Australia
The Medical Oncology Group of Australia
The Royal Australasian College of Surgeons (RACS)
The Royal Australian and New Zealand College of Obstetricians & Gynaecologists (RANZCOG)
The Royal Australian and New Zealand College of Radiologists (RANZCR)
The Royal Australian College of General Practitioners (RACGP)
The Royal College of Pathologists of Australasia (RCPA)
Western Australia Clinical Oncology Group (WACOG)

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Development process

This protocol has been developed following the ten-step process set out in *Guidelines for Authors of Structured Cancer Pathology Reporting Protocols*.⁹

Where no reference is provided, the authority is the consensus of the local expert group for local inclusions and the ICCR Dataset Authoring Committee for ICCR components denoted with the ICCR logo.

1 Pre-analytical

This chapter relates to information that should be recorded on receipt of the specimen in the laboratory.

The pathologist is reliant on the quality of information received from the clinicians or requestor. Some of this information may be received in generic pathology request forms; however, the additional information required by the pathologist specifically for the reporting of ovarian, fallopian tube or primary peritoneal site cancers is outlined in Appendix 1. Appendix 1 also includes a standardised request information sheet that may be useful in obtaining all relevant information from the requestor.

Surgical handling procedures affect the quality of the specimen and recommendations for appropriate surgical handling are included in Appendix 1.

S1.01 All demographic information provided on the request form and with the specimen must be recorded.

CS1.01a The Royal College of Pathologists of Australasia (RCPA) *The Pathology Request-Test-Report Cycle — Guidelines for Requesters and Pathology Providers*¹⁰ must be adhered to. This document specifies the minimum information to be provided by the requesting clinician for any pathology test.

CS1.01b In support of a government initiative to monitor the health of indigenous Australians particularly in relation to cancer, the patient's ethnicity must be recorded, if known. In particular whether the patient is of aboriginal or Torres Strait islander origin.

CS1.01c The patient's health identifiers may include the patient's Medical Record Number as well as a national health number such as a patient's Medicare number (Australia), Individual Healthcare Identifier (IHI) (Australia) or the National Healthcare Identifier (New Zealand).

S1.02 All clinical information as documented on the request form must be recorded verbatim.

CS1.02a The request information may be recorded as a single text (narrative) field or it may be recorded in a structured format.

S1.03 The pathology accession number of the specimen must be recorded.

S1.04 The principal clinician involved in the patient's care and responsible for investigating the patient must be recorded.

CS1.04a It is important that the reporting pathologist should be able to communicate with the managing clinician for clarification for a number of reasons:

- The clinical assessment and staging may be incomplete at the time of procedure.
- The pathology request is often authored by the clinician performing the procedure rather than the clinician who is investigating and managing the patient.

- The identity of this clinician is often not indicated on the pathology request form

G1.01 Any clinical information received in other communications from the requestor or other clinician should be recorded together with the source of that information.

2 Specimen handling in the laboratory

This chapter relates to the procedures required after the information has been handed over from the requesting clinician and the specimen has been received in the laboratory.

Tissue Banking

- Pathologists may be asked to provide tissue samples from fresh specimens for tissue banking or research purposes. The decision to provide tissue should only be made when the pathologist is sure that the diagnostic process and other important parameters that influence patient prognosis and management will not be compromised.

Specimen handling

- See Appendix 6 for the Protocol for Sectioning and Extensively Examining the Fimbriated End (SEE-FIM) of the Fallopian Tube, for prophylactic (risk-reducing) resections.
- Detailed fixation and specimen handling instructions are available from the RCPA online Cut-up Manual:

www.rcpa.edu.au/Library/Practising-Pathology/Macroscopic-Cut-Up

Macroscopic findings

S2.01 All measurements are in SI units.

S2.02 Record specimen labelling.

	S2.03	The specimen type must be recorded.
	CS2.03a	Providing information about the specimen type is regarded as an integral part of the reporting of ovarian, tubal and primary peritoneal cancers. While the nature of the specimen/s submitted for pathological assessment may be deduced from the surgical procedure, specifying the nature of specimen received provides complementary information and confirmation that entire organ/s have been resected and submitted.
	S2.04	The integrity of the ovaries and fallopian tubes must be recorded.

CS2.04a Assessment of the integrity of the specimen (ovary or tube) provides important information for substaging and may have prognostic implications. See appendix 8. If present, correlation with intra-operative findings is important (see appendix 1) to ascertain whether ovarian capsule rupture or tubal serosa disruption was pre-surgical or intraoperative ("spill").

G2.01 The specimen weight (ovary/adnexal mass weight) should be recorded where applicable.

CG2.01a Specimen weight is rarely relevant to tubal neoplasms and most often pertains to ovarian neoplasms.

G2.02 The specimen description and dimensions should be recorded.

CG2.02a The ovaries should be measured in 3 dimensions and a description including any abnormalities /tumour involvement noted.

CG2.02b The fallopian tubes should be measured in a minimum of 2 dimensions (length and diameter). In the presence of a macroscopic abnormality a third dimension may be warranted. A description including any abnormalities should be noted eg presence of clips, ligature or dilation. Evidence of tumour involvement should be noted.

The presence or absence of the fimbriae should be recorded.

CS2.06c In cases, where a large tumour has completely obliterated all discernible anatomical features, 'indeterminate' should be recorded for site. Designation of final site will be determined following microscopic analysis.

CG2.02d The uterus, if present, should be measured in 3 dimensions. Note, if uterus is present, this should be processed using the hysterectomy cut-up protocol.

Evidence of tumour involvement should be noted.

CG2.02e Any other specimens submitted should be described and measured eg appendix. Evidence of any tumour involvement should be noted.

 G2.03	Tumour size should be recorded in 3 dimensions. If there are separate tumours specify the dimensions for each site.
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CG2.03a Refer to Appendix 9 for notes on macroscopic reporting, and suggested tumour sampling.

CG2.03b Further useful information is available from the RCPA online Cut-up Manual:
www.rcpa.edu.au/Library/Practising-Pathology/Macroscopic-Cut-Up

G2.04 A description of each tumour should be recorded.

CG2.04a The description may include the presence or absence of cysts, papillary excrescences, proportion and description of solid component. For more detail refer to the RCPA online Cut-up Manual:
www.rcpa.edu.au/Library/Practising-Pathology/Macroscopic-Cut-Up

 S2.05	A macroscopic description on the omentum must be recorded, if submitted.
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Refer to Appendix 9 for notes on macroscopic reporting.

G2.05 In cases of omental involvement, the number and size of metastatic deposits should be reported.

 S2.06	Macroscopic tumour site(s) must be recorded.
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CS2.06a	Current evidence indicates that the presence of tubal involvement is best classified as a primary fallopian tube tumour. See Appendix 7.
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CS2.06b	Macroscopic tumour sites may be recorded under G2.02 as part of the macroscopic description of the submitted specimen(s). If G2.02 is not reported then S2.06 must be documented in the report.
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G2.06 Any lymph node tissue submitted should be described.

CG2.06a An estimation of the number of nodes per site may be given, however it should be noted that this requires microscopic confirmation.

 S2.07	A block identification key listing the nature and origin of all tissue blocks must be recorded.
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	CS2.07a The origin/designation of all tissue blocks should be recorded. This information should be documented in the final pathology report and is particularly important should the need for internal or external review arise. The reviewer needs to be clear about the origin of each block in order to provide an informed specialist opinion. If this information is not included in the final pathology report, it should be available on the
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		<p>laboratory computer system and relayed to the reviewing pathologist.</p> <p>Recording the origin/designation of tissue blocks also facilitates retrieval of blocks for further immunohistochemical or molecular analysis, research studies or clinical trials.</p>
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- G2.07 A descriptive or narrative field should be provided to record any macroscopic information that is not recorded in the above standards and guidelines, and that would normally form part of the macroscopic description.
- CG2.07a The traditional macroscopic narrative recorded at the time of specimen dissection is often reported separately from the cancer dataset. Although this remains an option, it is recommended that macroscopic information be recorded within the overall structure of this protocol.
- CG2.07b Much of the information recorded in a traditional macroscopic narrative is covered in the standards and guidelines above and in many cases, no further description is required.

3 Microscopic findings

Microscopic findings relate purely to histological assessment. Information derived from multiple investigational modalities, or from two or more chapters in this protocol is described in Chapter 5.

 S3.01	The histological tumour type must be recorded.	
<p>CS3.01a The WHO classification should be used. (Refer to Appendix 4). Information regarding tumour typing is documented in Appendix 10.</p>		
 G3.01	The pattern of invasion should be recorded, in mucinous carcinomas.	
	CG3.01a	<p>It is controversial as to whether the pattern of invasion in stage 1 mucinous ovarian carcinoma has prognostic significance.¹³⁻¹⁸ 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 to herald a better prognosis, a recent population-based registry study of mucinous ovarian carcinomas was not able to prognosticate based on the distinction between the two patterns of invasion.¹³⁻¹⁸ It is recommended that the pattern of invasion in mucinous ovarian carcinomas be recorded.</p>
 G3.02	Subtypes of carcinosarcoma should be recorded, if applicable.	
<p>CG3.02a Information regarding tumour typing of carcinosarcoma is found in Appendix 10.</p>		
 S3.02	The histological tumour grade for serous and endometrioid carcinoma must be recorded. Clear cell, undifferentiated carcinomas and carcinosarcoma are high grade by definition. Grading of mucinous is optional and may be recorded at G3.03.	
<p>CS3.02a Information regarding tumour grading is found in Appendix 11.</p>		
 G3.03	The histological grade for mucinous carcinomas may be recorded.	
 G3.04	The presence of nodules of anaplastic carcinoma in mucinous tumours should be recorded.	
 S3.03	The presence or absence of borderline tumours must be recorded.	
<p>If present, record:</p> <ul style="list-style-type: none"> • Histological tumour type of the borderline tumours - S3.04, 		

		<ul style="list-style-type: none"> • Special features - S3.05 and consider recording G3.05 • Implants for serous and seromucinous borderline tumour – S3.07
 S3.04	The histological tumour type of the borderline tumours must be recorded using the WHO classification of tumours (Appendix 4).	

CS3.04a Information regarding borderline tumours is found in Appendix 12.

 S3.05	Record the presence of special features of the borderline tumours.	
 G3.05	The presence of intraepithelial carcinoma may be recorded.	
	CG3.05a	In mucinous borderline tumours, intraepithelial carcinoma is diagnosed in non-invasive foci with marked nuclear atypia. ¹⁹⁻²¹ However, the reproducibility of this diagnosis has not been formally analysed.
 S3.06	The presence, type and site(s) of implants for serous and seromucinous borderline tumour must be recorded.	

CS3.06a Implants should be identified as invasive, non-invasive (epithelial and desmoplastic), or indeterminate (see appendix 12).

When diagnosing invasive implants, the report should state that these represent extra-ovarian low-grade carcinoma.
11,19,22-24

G3.06 The size of the largest implant should be recorded.

CG3.06a If outside the pelvis, the size of the largest implant may be important for staging.

 S3.07	The presence of serous tubal intraepithelial carcinoma (STIC) must be recorded.	
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CS3.07a The presence of STIC will assist in determining primary tumour site. Information on STIC is found in Appendix 13.

G3.07 Any other significant tubal lesions should be documented.

CG3.07a Fallopian tube may uncommonly be involved in primary carcinomas of non-serous type or metastases from uterine or non-gynaecological sites.²⁵⁻²⁷

G3.08 A description of histological features should be included (a traditional 'microscopic' description).

CG3.08a This can be used to describe the pattern of growth and morphology of tumour cells. In more unusual or complex cases this may be relevant to subsequent discussion of a differential diagnosis (synthesis and overview, and overarching comment, chapter 5), or may be beneficial to the pathologist in cases of subsequent tumour recurrence when slides are not immediately available for review.

	S3.08	The following sites must be evaluated for tumour involvement:
		<ul style="list-style-type: none"> • Right ovary • Left ovary • Right ovarian capsule/surface • Left ovarian capsule/surface • Right fallopian tube • Left fallopian tube • Uterus • Omentum • Peritoneum (including uterine serosa) • Other involved organs(s)/sites(s) (specify)

G3.09 The site of tubal involvement should be recorded as fimbrial or non-fimbrial.

CG3.09a Fimbrial tumours have previously been reported to have worse prognosis than non-fimbrial tumours.²⁸ In the context of recent change in tubal cancer reporting, collection of site data may contribute to further understanding prognostic indicators.

Measurement of the extent/depth of tubal wall involvement is not mandated. It does not contribute to FIGO stage, and, as the tubal wall is often expanded, assessment of tubal wall depth of invasion may be difficult.

G3.10 The presence or absence of lymphovascular invasion should be recorded.

	S3.09	Lymph node status must be recorded.
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CS3.09a Site and size of lymph node involvement is required for staging.

	CS3.09b	Data on lymph node involvement in borderline ovarian tumours is largely restricted to tumours of serous subtype (SBT) where approximately 25% of fully staged cases will show positive nodes. ^{29,30} 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. ³¹ Rarely, low-grade serous carcinoma appears to develop within the lymph nodes of patients with SBT, possibly from foci of endosalpingiosis. ³²
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	S3.10	The results of any peritoneal cytology must be recorded.
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	CS3.10a	The results of peritoneal cytology (peritoneal washings or ascitic 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. In the previous FIGO staging system, 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
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		indicate the need for adjuvant therapy in certain cases.
 G3.11	The response to any neoadjuvant therapy should be recorded.	

CG3.11a Patients with high stage high grade carcinomas may benefit from pre-operative chemotherapy to allow subsequent debulking surgery. Pathological assessment of response to neoadjuvant therapy is not well established, however may be of prognostic value, and a chemotherapy response score of 1-3 for high grade serous carcinoma has been proposed (see appendix 14).

CG3.11b Pre-chemotherapy tumour typing is highly recommended (see appendix 1). Neoadjuvant therapy can significantly alter tumour morphology. Disease at presentation may be advanced and tumour typing may be adequately performed on ascitic fluid cytology for example if there is good quality cell block material allowing for immunohistochemical studies.

 G3.12	The presence of any coexistent pathology should be recorded.	
	CG3.12a	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. The presence of endometriosis may also support a primary ovarian origin rather than metastasis from a primary uterine carcinoma of the same cell type.

G3.13 The optimal tumour block(s) for potential future ancillary studies may be documented.

CG3.13a Identification of optimal tumour block allows future studies (whether additional prognostic tests or research) to be more rapidly accessed.

G3.14 Any additional comments should be included, if appropriate.

CG3.14a Free text entry to allow any additional, unusual or unexpected findings to be reported.

4 Ancillary studies findings

G4.01 The results of any ancillary testing should be recorded.

CG4.01a It should be noted that this is a rapidly evolving field. The following section provides a useful, practical guide from the ICCR (also see appendix 15).

 G4.02	The results of any immunohistochemical markers should be documented.	
	CG4.02a	Immunohistochemistry has many important applications in the field of ovarian neoplasia. ³³⁻³⁵ There are a number of scenarios where immunohistochemical markers may assist in establishing a diagnosis of a primary ovarian epithelial malignancy or in tumour subtyping. It is beyond the scope of this dataset to present a detailed analysis of every scenario but major uses of immunohistochemistry are discussed (see appendix 15). 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 and the results of immunohistochemical studies should always be interpreted in conjunction with the clinical, gross and microscopic features.
 G4.03	The results of any molecular studies should be recorded.	

CG4.03a Information regarding molecular studies is found in Appendix 15.

5 Synthesis and overview

Information that is synthesized from multiple modalities and therefore cannot reside solely in any one of the preceding chapters is described here.

Overarching case comment is synthesis in narrative form. Although it may not necessarily be required in any given report, the provision of the facility for overarching commentary in a cancer report is essential.

By definition, synthetic elements are inferential rather than observational, often representing high-level information that is likely to form part of the 'diagnostic summary' section in the final formatted report.

 G5.01	Staging using the FIGO staging system should be recorded, if all applicable clinical and pathological information is available.	
	CG5.01a	<p>Tumour stage is amongst the strongest prognostic factors in ovarian carcinoma,³⁶ and patients with localised, regional and distant disease have 5-year relative survival rates of 92%, 72% and 27% based on U.S. 2014 figures.³⁷</p> <p>All ovarian carcinomas and borderline tumours, and carcinomas of the fallopian tube and peritoneum should be staged using the FIGO 2014 system.⁴</p>

CG5.01b In Australia staging is often performed in multidisciplinary meetings for gynaecological malignancies. In cases that are not reviewed at a multidisciplinary meeting staging is typically performed by the individual treating clinician, who correlates the clinical and pathological information.

FIGO stage may be appropriately recorded in the pathology report for the minority of 'current' cases that have been assessed in a multidisciplinary setting prior pathological 'sign out'. In Australia the treating clinician requires all pathological variables to allow for staging, but would not expect a 'pathological stage' to be documented as this is not an entity in gynaecological malignancies. The FIGO system is unique compared to the TNM system, the latter having a provision for a separate pathological ('p') stage. Indeed documenting a 'provisional pathological stage' is potentially misleading and could readily be misinterpreted as FIGO stage. The consensus of the Australian committee is that stage should not be document until the clinical and pathological data is integrated.

S5.01 The year of publication and edition of the cancer staging system used in S5.01 must be included in the report where applicable.

G5.02 The 'diagnostic summary' section of the final formatted report should include:

- a. Primary tumour site
- b. Histological type

- c. Tumour grade
- d. Ovarian surface involvement, if applicable
- e. Dimension of largest omental deposit, if applicable
- f. Involvement of other tissue/organs if present
- g. Peritoneal cytology status
- h. Lymph node status

In cases of borderline tumour document implants and type if present.

S5.02 The reporting system must allow for a field for free text or narrative in which the reporting pathologist can give overarching case comment.

CS5.02a This field may be used, for example, to:

- discuss the significance of ancillary tests
- discuss any noteworthy prognostic features
- express any diagnostic subtlety or nuance that is beyond synoptic capture
- document further consultation or results still pending
- highlight any further testing eg genetic counselling.³⁸

CS5.02b Use of this field is at the discretion of the reporting pathologist.

G5.03 The edition/version number of the RCPA protocol on which the report is based should be included on the final report.

CG5.03a For example, the pathology report may include the following wording at the end of the report: “the data fields within this formatted report align to the criteria as set out in the RCPA document “XXXXXXXXXX” XXXX Edition dated XXXXXXXX”.

6 Structured checklist

The following checklist includes the standards and guidelines for this protocol which must be considered when reporting, in the simplest possible form. The summation of all 'Standards' is equivalent to the 'minimum dataset' for ovarian, fallopian tube and peritoneal cancer. For emphasis, standards (mandatory elements) are formatted in bold font.

- S6.01 The structured checklist provided may be modified as required but with the following restrictions:**
 - a. All standards and their respective naming conventions, definitions and value lists must be adhered to.**
 - b. Guidelines are not mandatory but are recommendations and where used, must follow the naming conventions, definitions and value lists given in the protocol.**
- G6.01 The order of information and design of the checklist may be varied according to the laboratory information system (LIS) capabilities and as described in *Functional Requirements for Structured Pathology Reporting of Cancer Protocols*.³⁹
 - CG6.01a Where the LIS allows dissociation between data entry and report format, the structured checklist is usually best formatted to follow pathologist workflow. In this situation, the elements of synthesis or conclusions are necessarily at the end. The report format is then optimised independently by the LIS.
 - CG6.01b Where the LIS does not allow dissociation between data entry and report format, (for example where only a single text field is provided for the report), pathologists may elect to create a checklist in the format of the final report. In this situation, communication with the clinician takes precedence and the checklist design is according to principles given in Chapter 7.
- G6.02 Where the checklist is used as a report template (see G6.01), the principles in Chapter 7 and Appendix 2 apply.
 - CG6.02a All extraneous information, tick boxes and unused values should be deleted.
- G6.03 Additional comment may be added to an individual response where necessary to describe any uncertainty or nuance in the selection of a prescribed response in the checklist. Additional comment is not required where the prescribed response is adequate.

Values in italics are conditional on previous responses.

Values in all caps are headings with sub values.

S/G	Item description	Response type	Conditional
Pre-analytical			
S1.01	Demographic information provided		
S1.02	Clinical information provided on request form	Text OR Structured entry as below:	
	Genetic status	Multi selection value list (select all that apply): <ul style="list-style-type: none"> • BRCA1 • BRCA2 • Lynch syndrome • Other (specify) • Not known 	
	Prior chemotherapy	Single selection value list: <ul style="list-style-type: none"> • Prior chemotherapy administered • No chemotherapy administered • Not specified 	
	Previous gynaecological procedure/treatment	Text	

	Operative procedure	Multi select value list (select all that apply): <ul style="list-style-type: none"> • Left oophorectomy • Right oophorectomy • Left salpingo-oophorectomy • Right salpingo-oophorectomy • Left salpingectomy • Right salpingectomy • Peritoneal resection • Omentectomy • Total hysterectomy with bilateral salpingo-oophorectomy • Other, (specify) 	
	Operative findings	Text	
	New primary or recurrence	Single selection value list: <ul style="list-style-type: none"> • New primary tumour • Local recurrence • Distant metastasis 	If local recurrence or distant metastasis, provide details
	<i>Details</i>	<i>Text</i>	
S1.03	Pathology accession number	Alpha-numeric	
S1.04	Principal clinician caring for the patient	Text	
G1.01	Other clinical information received	Text	

Macroscopic findings			
	S2.02	Specimen labelled as	Text
	S2.03	Specimen type	<p>Multi select value list (select all that apply):</p> <ul style="list-style-type: none"> • Not specified • Right ovary • Left ovary • Right ovarian cystectomy • Left ovarian cystectomy • Right fallopian tube • Left fallopian tube • Uterus • Cervix • Omentum • Peritoneal biopsies • Peritoneal washings/ascitic fluid • Lymph nodes (specify site/s) • Other eg bowel, bladder, appendix (specify)
		RIGHT OVARY	
	S2.04	Specimen integrity	<ul style="list-style-type: none"> • Ovarian capsule intact • Ovarian capsule ruptured • Tumour on surface • Fragmented specimen

For each specimen received, record S2.04-6 and consider recording G2.01- 6 as applicable.

		<ul style="list-style-type: none"> Other (specify) 	
G2.01	Specimen weight	Numeric: ___g Note: This will primarily be the (ovary/adnexal mass weight)	
G2.02	Dimensions	Numeric: __x__x__mm	
G2.02	Description	Text	
 G2.03	Tumour dimensions	Numeric: __x__x__mm	Record only if tumour present macroscopically
G2.04	Tumour description	Text	Record only if tumour present macroscopically
	LEFT OVARY		
 S2.04	Specimen integrity	<ul style="list-style-type: none"> Ovarian capsule intact Ovarian capsule ruptured Tumour on surface Fragmented specimen Other (specify) Note: Only record 'tumour on surface' if the tumour is present macroscopically	
G2.01	Specimen weight	Numeric: ___g Note: This will primarily be the (ovary/adnexal mass weight)	

G2.02	Dimensions	Numeric: __x__x__mm	
G2.02	Description	Text	
 G2.03	Tumour dimensions	Numeric: __x__x__mm	Record only if tumour present macroscopically
G2.04	Tumour description	Text	Record only if tumour present macroscopically
RIGHT FALLOPIAN TUBE			
 S2.04	Specimen integrity	<ul style="list-style-type: none"> • Serosa intact • Serosa ruptured • Tumour on serosal surface • Fragmented specimen • Other (specify) <p>Note: Only record 'tumour on surface' if the tumour is present macroscopically</p>	
G2.02	Dimensions	Numeric: __x__x__*mm *Note: 2 dimensions (length x diameter) should be recorded as a minimum, if abnormal, a third dimension should be recorded.	
G2.02	Fimbriae	Single selection value list: <ul style="list-style-type: none"> • Not identified • Present 	
G2.02	Description	Text	
 G2.03	Tumour dimensions	Numeric: __x__x__mm	Record only if tumour present macroscopically

G2.04	Tumour description	Text	Record only if tumour present macroscopically
	LEFT FALLOPIAN TUBE		
 S2.04	Specimen integrity	<ul style="list-style-type: none"> • Serosa intact • Serosa ruptured • Tumour on serosal surface • Fragmented specimen • Other (specify) <p>Note: Only record 'tumour on serosal surface' if the tumour is present macroscopically</p>	
G2.02	Dimensions	<p>Numeric: __x__x__*mm</p> <p>* Note: 2 dimensions (length x diameter) should be recorded as a minimum, if abnormal, a third dimension should be recorded.</p>	
G2.02	Fimbriae	<p>Single selection value list:</p> <ul style="list-style-type: none"> • Not identified • Present 	
G2.02	Description	Text	
 G2.03	Tumour dimensions	Numeric: __x__x__mm	Record only if tumour present macroscopically
G2.04	Tumour description	Text	Record only if tumour present macroscopically

	UTERUS		
G2.01	Specimen weight	Numeric: ___g Note: This will primarily be the (ovary/adnexal mass weight). A comment should be added to state what is included.	
G2.02	Dimensions	Numeric: __x__x__mm Note: superior to inferior x distance between cornu x anterior to posterior	
G2.02	Description	Text	
 G2.03	Tumour dimensions	Numeric: __x__x__mm	Record only if tumour present macroscopically
G2.04	Tumour description	Text	Record only if tumour present macroscopically
G2.02	OTHER SPECIMEN(S)	Text	
 S2.05	MACROSCOPIC DESCRIPTION OF OMENTUM		Report only if omentum recorded in S2.03
	Omentum dimensions	Numeric: __x__x__mm	
	Omental involvement	Single selection value list: <ul style="list-style-type: none"> • Not involved • Involved 	If involved, record the maximum dimension of largest deposit. If involved consider reporting G2.06.
	Maximum dimension of	Numeric: __mm	

	<i>largest deposit</i>		
G2.05	Number of metastatic deposits	Numeric: ____ <i>OR</i> <i>Text</i>	
	Size of metastatic deposit	Numeric: ____mm Note: Repeat for each metastatic deposit.	
 S2.06	Macroscopic tumour site	Multi select value list (select all that apply): <ul style="list-style-type: none"> • Indeterminate • Left ovary • Right ovary • Left fallopian tube <ul style="list-style-type: none"> ○ Fimbrial ○ Non fimbrial • Right fallopian tube <ul style="list-style-type: none"> ○ Fimbrial ○ Non fimbrial • Peritoneum • Other (specify) 	Required only if not previously reported in G2.02.
G2.06	Lymph nodes	Text	
 S2.07	Block identification key	Text	
G2.07	Other macroscopic description	Text	
Microscopic findings			

 S3.01	Histological tumour type	Text Note: Use values from the WHO Classification of Tumours 2014 Appendix 4	
 G3.01	Pattern of invasion (<i>mucinous carcinoma only</i>)	Single selection value list: <ul style="list-style-type: none"> • Expansile • Infiltrative/destructive 	Applicable to mucinous carcinomas only
 G3.02	CARCINOSARCOMA SUBTYPES		
	Epithelial	Numeric: ____% AND Text: List subtypes	Applicable to carcinosarcomas only
	Sarcomatous	Numeric: ____% AND Type: <ul style="list-style-type: none"> • Homologous • Heterologous 	If Heterologous, record subtypes
	<i>Subtypes</i>	Text	
 S3.02	TUMOUR GRADE	Note: If chemotherapy has been administered the grade of the pre-chemotherapy biopsy should be noted.	Complete as applicable for the tumour type
	Serous carcinomas	Single selection value list:	

		<ul style="list-style-type: none"> • Low grade • High grade • Cannot be graded 	
	Endometrioid carcinomas	Single selection value list using FIGO grading <ul style="list-style-type: none"> • G1: Well differentiated • G2: Moderately differentiated • G3: Poorly differentiated • GX: Cannot be graded 	
	Clear cell carcinomas	Single selection value list: <ul style="list-style-type: none"> • High grade 	
	Undifferentiated carcinomas	Single selection value list: <ul style="list-style-type: none"> • High grade 	
	Carcinosarcomas	Single selection value list: <ul style="list-style-type: none"> • High grade 	
 G3.03	Mucinous carcinomas	Single selection value list: <ul style="list-style-type: none"> • G1: Well differentiated • G2: Moderately differentiated • G3: Poorly differentiated • GX: Cannot be graded 	
 G3.04	Nodules of anaplastic carcinoma <i>(mucinous carcinomas only)</i>	Single selection value list: <ul style="list-style-type: none"> • Not identified • Present 	

 S3.03	BORDERLINE TUMOUR	Single selection value list: <ul style="list-style-type: none"> • Absent • Present 	If present, record S3.04, S3.05, S3.06 and consider reporting G3.05
 S3.04	Histological tumour type	Text Note: Use values from the WHO Classification of Tumours 2014 Appendix 4	
 S3.05	SPECIAL FEATURES		
	Micropapillary architecture for serous borderline tumour (<i>at least 5 mm in one dimension</i>)	Single selection value list: <ul style="list-style-type: none"> • Absent • Present 	Applicable to serous borderline tumours only
	Microinvasion (<i>upper limit 5 mm</i>)	Single selection value list: <ul style="list-style-type: none"> • Absent • Present 	
 G3.05	Intraepithelial carcinoma for mucinous borderline tumour	Single selection value list: <ul style="list-style-type: none"> • Absent • Present 	Applicable to mucinous borderline tumours only
 S3.06	IMPLANTS FOR SEROUS & SEROMUCINOUS BORDERLINE TUMOUR		Applicable to serous and seromucinous borderline tumours only
	Non-invasive implants	Single selection value list: <ul style="list-style-type: none"> • Not identified 	If present, record type and site(s)

		<ul style="list-style-type: none"> • Present 	
	Type	Single selection value list: <ul style="list-style-type: none"> • Epithelial • Desmoplastic 	
	Site(s)	Multi select value list (select all that apply): <ul style="list-style-type: none"> • Pelvic • Abdominal 	
	Invasive implants/Extra-ovarian low grade serous carcinoma	Single selection value list: <ul style="list-style-type: none"> • Not identified • Present 	If present, record site(s)
	Site(s)	Multi select value list (select all that apply): <ul style="list-style-type: none"> • Pelvic • Abdominal 	
	Indeterminate	Single selection value list: <ul style="list-style-type: none"> • Not identified • Present 	If present, record site(s)
	Site(s)	Multi select value list (select all that apply): <ul style="list-style-type: none"> • Pelvic • Abdominal 	
G3.06	Size of the largest implant	Numeric: ____mm	
 S3.07	Serous tubal intraepithelial carcinoma (STIC) (only if fallopian tube(s) are submitted)	Single selection value list: Right FT <ul style="list-style-type: none"> • Present – fimbrial 	

		<ul style="list-style-type: none"> • Present - non-fimbrial • Not identified • Cannot be assessed <p>Left FT</p> <ul style="list-style-type: none"> • Present – fimbrial • Present - non-fimbrial • Not identified • Cannot be assessed 	
G3.07	Other significant tubal lesions	Text	
G3.08	Histological features	Text	
 S3.08	HISTOLOGICAL SITES OF TUMOUR INVOLVEMENT		Complete as applicable to the specimen submitted.
	Right ovary	<p>Single selection value list:</p> <ul style="list-style-type: none"> • Not involved • Involved • Cannot be assessed • Not applicable 	
	Left ovary	<p>Single selection value list:</p> <ul style="list-style-type: none"> • Not involved • Involved • Cannot be assessed • Not applicable 	

	Right ovarian capsule/surface	Single selection value list: <ul style="list-style-type: none"> • Not involved • Involved • Cannot be assessed • Not applicable 	
	Left ovarian capsule/surface	Single selection value list: <ul style="list-style-type: none"> • Not involved • Involved • Cannot be assessed • Not applicable 	
	Right fallopian tube	Single selection value list: <ul style="list-style-type: none"> • Not involved • Involved • Cannot be assessed • Not applicable 	
	Left fallopian tube	Single selection value list: <ul style="list-style-type: none"> • Not involved • Involved • Cannot be assessed • Not applicable 	
	Uterus	Single selection value list: <ul style="list-style-type: none"> • Not involved • Involved • Cannot be assessed 	If involved record site(s), for peritoneal involvement refer to Peritoneum (including uterine serosa) below.

		<ul style="list-style-type: none"> • Not applicable 	
	Site(s)	Multi select value list (select all that apply): <ul style="list-style-type: none"> • Myometrium • Endometrium • Cervix 	
	Peritoneum (including uterine serosa)	Single selection value list: <ul style="list-style-type: none"> • Not involved • Involved • Cannot be assessed • Not applicable 	If involved record site(s)
	Site(s)	Multi select value list (select all that apply): <ul style="list-style-type: none"> • Pelvis (specify site(s), including uterine serosa) • Abdomen (specify site(s)) 	
	Omentum	Single selection value list: <ul style="list-style-type: none"> • Not involved • Involved • Cannot be assessed • Not applicable 	If involved record level of involvement
	Level of involvement	Single selection value list: <ul style="list-style-type: none"> • Macroscopic • Microscopic 	
	Other involved organs(s)/sites(s)	Text	

G3.09	Site of tubal involvement	Indeterminate OR Multi select value list (select all that apply): <ul style="list-style-type: none"> • Fimbrial • Non-fimbrial 	
G3.10	Lymphovascular invasion	Single selection value list: <ul style="list-style-type: none"> • Present • Not identified • Cannot be assessed 	
 S3.09	Lymph node status	Single selection value list: <ul style="list-style-type: none"> • Not submitted • Not involved • Involved 	Required only if submitted. If involved, record involvement for regional and non regional lymph nodes as applicable. <i>Note: In some cases it may not be possible to record the actual number of nodes due to fragmentation of the specimen.</i>
	REGIONAL		
	LEFT PELVIC		
	Number of lymph nodes examined	Numeric	
	Number of positive lymph nodes	Numeric	

	RIGHT PELVIC		
	Number of lymph nodes examined	Numeric	
	Number of positive lymph nodes	Numeric	
	PARA-AORTIC		
	Number of lymph nodes examined	Numeric	
	Number of positive lymph nodes	Numeric	
	Maximum dimension of largest deposit in regional node	Numeric: ___mm	Record only if applicable
	NON - REGIONAL		
	Site	Text: (description of LN site) Note: Repeat "Site/Number of LN examined and Number of positive LN" segment as needed.	
	Number of lymph nodes examined	Numeric	
	Number of positive lymph nodes	Numeric	
 S3.10	Peritoneal cytology	Single selection value list: • Negative	

		<ul style="list-style-type: none"> • Positive • Indeterminate • Not received 	
 G3.11	Response to neoadjuvant therapy	TEXT OR Single selection value list: <ul style="list-style-type: none"> • No prior treatment • Cannot be assessed 	
 G3.12	COEXISTENT PATHOLOGY		
	Endometriosis	Text (specify sites)	
	Other	Text (specify)	
G3.13	Optimal tumour block(s)	Text	
G3.14	Additional microscopic comment	Text	
Ancillary test findings			
 G4.02	Immunohistochemical markers	Text	
 G4.03	Molecular data	Text	
G4.01	Other ancillary findings	Text	
Synthesis and overview			
 G5.01	FIGO STAGE (2014 edition) <i>(if</i>		

	<i>applicable)</i>		
	Site of primary tumour	Single selection value list: <ul style="list-style-type: none"> • Primary tumour, ovary (OV) • Primary tumour, fallopian tube (FT) • Primary tumour, peritoneum (P) • Undesignated: site of primary tumour cannot be assessed (X) 	In the case of undesignated, the term tubo-ovarian is recommended by the ICCR to be added to distinguish from an endometrial primary.
	Stage	Values per Appendix 5	
S5.01	Year and edition of staging system, if included	Text	
G5.02	Diagnostic summary Include: a. Primary tumour site b. Histological type c. Tumour grade d. Ovarian surface involvement, if applicable e. Dimension of largest omental deposit, if applicable f. Involvement of other tissue/organs if present g. Peritoneal cytology status h. Lymph node status In cases of borderline tumour document implants and type if present.	Text	

S5.02	Overarching comment (if applicable)	Text	
G5.03	Edition/version number of the RCPA protocol on which the report is based	Text	

7 Formatting of pathology reports

Good formatting of the pathology report is essential to optimise communication with the clinician, and will be an important contributor to the success of cancer reporting protocols. The report should be formatted to provide information clearly and unambiguously to the treating doctors, and should be organised with their use of the report in mind. In this sense, the report differs from the structured checklist, which is organised with the pathologists' workflow as a priority.

Uniformity in the format as well as in the data items of cancer reports between laboratories makes it easier for treating doctors to understand the reports; it is therefore seen as an important element of the systematic reporting of cancer.

Please see Appendix 2 for further guidance.

Appendix 1 Pathology request information and surgical handling procedures

This appendix describes the information that should be provided by the clinician prior to pathological examination.

Some of this information can be provided on generic pathology request forms; any additional information required specifically for the reporting of ovarian, fallopian tube or primary peritoneal site carcinoma may be provided by the clinician on a separate request information sheet. An example request information sheet is included below. Elements which are in bold text are those which pathologists consider to be required information. Those in non-bold text are recommended.

Also included in this appendix are the procedures that are recommended before handover of specimens to the laboratory.

Patient information

- **Adequate demographic and request information should be provided with the specimen.**
 - Items relevant to cancer reporting protocols include:
 - i patient name
 - ii date of birth
 - iii sex
 - iv identification and contact details of requesting doctor
 - v date of request
 - The patient’s ethnicity should be recorded, if known. In particular whether the patient is of aboriginal or Torres Strait islander origin. This is in support of a government initiative to monitor the health of indigenous Australians particularly in relation to cancer.
- The patient’s health identifiers should be provided.
 - The patient’s health identifiers may include the patient’s Medical Record Number as well as a national health number such as a patient’s Medicare number (Australia), Individual Healthcare Identifier (IHI) (Australia) or the National Healthcare Identifier (New Zealand).

Clinical Information

 ➤	The genetic status of the patient should be provided if known.
	<ul style="list-style-type: none"> • It is estimated that approximately 10% of primary tubo-ovarian and peritoneal carcinomas have a genetic basis,⁴⁰ and recent data suggest that this figure may be as high as 17% for high-grade serous carcinomas specifically.⁴¹ Germline mutations in <i>BRCA1</i> and <i>BRCA2</i> account for the majority of genetically related cases while up to 10% of such cases are related to Lynch syndrome (LS).

	<ul style="list-style-type: none"> • 	<p>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 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:</p> <ol style="list-style-type: none"> 1. High-grade serous carcinomas associated with <i>BRCA</i> mutations (germline or somatic) more commonly show certain morphological features such as solid, endometrioid or transitional-like ('SET') architectural patterns, very marked nuclear atypia, and tumour-infiltrating lymphocytes.^{40,42,43} Thus, pathologists may be able to correlate the histological findings with any genetic data provided, or raise the possibility of <i>BRCA</i> mutation in certain cases with implications regarding improved prognosis, better chemotherapy response, and consideration of specific therapeutic regimes such as those including PARP inhibitors.^{40,41,44} Patients with suspected germline <i>BRCA</i> mutations and their relatives, may also be referred for genetic testing and counselling in regard to appropriate screening for <i>BRCA</i>-related neoplasia. 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 <i>BRCA1</i> or <i>BRCA2</i> mutation, where complete examination of tubal and ovarian tissues is mandatory.⁴⁰ The identification of small, macroscopically occult tubal carcinomas, and their <i>in situ</i> precursor serous tubal intraepithelial carcinoma (STIC) is much more likely in this setting.
	<ul style="list-style-type: none"> • 	<p>Approximately 2% of all ovarian cancers are associated with LS due to a germline mutation in one of the genes encoding the DNA mismatch repair (MMR) proteins. In approximately 60% of women with LS, a gynaecological tumour (endometrial or ovarian) will represent the sentinel cancer.⁴⁵ Endometrioid and clear cell 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 subtypes, or if there is relevant personal or family history of additional LS-related neoplasia. Similar studies may be considered in those patients with synchronous primary ovarian and endometrial endometrioid carcinomas although most such cases are not associated with LS.⁴⁶ It has been suggested that in a women with an endometrial carcinoma, the presence of a synchronous ovarian clear cell carcinoma may be an indicator of LS.⁴⁷</p>
	<p>Any prior chemotherapy treatment of the patient should be included in the request information.</p>	



- Pre-operative chemotherapy may significantly alter the gross and microscopic appearance of the tumour and result in difficulties in tumour typing and grading and tumour down-staging. In some cases there may be no residual tumour. If neoadjuvant chemotherapy is being administered, a pre-treatment tissue biopsy should be obtained and used for tumour typing and grading. If this is not possible then the diagnosis of malignancy can be made on cytological examination of ascitic fluid, preferably with immunohistochemistry performed on a cell block preparation; however, this should only be in exceptional circumstances. Markers of value in tumour typing are discussed in G4.01 - IMMUNOHISTOCHEMICAL MARKERS.

- Any previous cancer history or gynaecological procedure should be documented.
 - Information relating to prior malignancy or previous gynaecological procedures may provide relevant information in the assessment of the current specimen
- Any additional relevant clinical information should be recorded.
- The operative procedure should be clearly documented.
 - For ovarian specimens for example, state whether oophorectomy or cystectomy, for accompanying cytology specimens, state whether ascitic fluid or peritoneal washings.
- Operative findings should be included with the request form.
 - Operative findings may assist in the identification of tumour rupture and to ascertain as to whether this was pre or intraoperative ('surgical spill'), which has implications for staging. Any coexistent pathology such as endometriosis should be included in the request information.

It should be noted as to whether peritoneal washing cytology was obtained upon access to the peritoneal cavity, or if they are collected following surgical handling of a cyst with rupture.
- **Record if this is a new primary tumour or a recurrence of a previous tumour, if known.**
 - This information also has implications for recording cancer incidence and evidence based research. This information will provide an opportunity for previous reports to be reviewed during the reporting process, which may provide valuable information to the pathologist.

Example Request Information Sheet

Ovary, Fallopian Tube and Primary Peritoneal Carcinoma Request Information	
<p>Family name</p> <input type="text"/>	<p>Ethnicity</p> <input type="checkbox"/> Unknown <input type="checkbox"/> Aboriginal/Torres Strait Islander <input type="checkbox"/> Other ethnicity: <input type="text"/>
<p>Given name(s)</p> <input type="text"/>	
<p>Date of birth</p> <input type="text" value="DD - MM - YYYY"/>	<p>Date of request</p> <input type="text" value="DD - MM - YYYY"/>
<p>Patient identifiers e.g. MRN, IHI or NHI (please indicate which)</p> <input type="text"/>	<p>Requesting doctor - name and contact details</p> <input type="text"/>
<p>Copy to doctor name and contact details</p> <input type="text"/>	
<p>GENETIC STATUS</p> <p><input type="radio"/> Not known</p> <p><input type="checkbox"/> BRCA1</p> <p><input type="checkbox"/> BRCA2</p> <p><input type="checkbox"/> Lynch syndrome</p> <p><input type="checkbox"/> Other</p> <input type="text"/>	<p>OPERATIVE PROCEDURE</p> <p><input type="checkbox"/> Left oophorectomy</p> <p><input type="checkbox"/> Right oophorectomy</p> <p><input type="checkbox"/> Left salpingo-oophorectomy</p> <p><input type="checkbox"/> Right salpingo-oophorectomy</p> <p><input type="checkbox"/> Left salpingectomy</p> <p><input type="checkbox"/> Right salpingectomy</p> <p><input type="checkbox"/> Peritoneal resection</p> <p><input type="checkbox"/> Omentectomy</p> <p><input type="checkbox"/> Total hysterectomy with bilateral salpingo-oophorectomy</p> <p><input type="checkbox"/> Other</p> <input type="text"/>
<p>PRIOR CHEMOTHERAPY</p> <p><input type="radio"/> Not known</p> <p><input type="radio"/> No chemotherapy administered</p> <p><input type="radio"/> Prior chemotherapy administered</p>	<p>OPERATIVE FINDINGS</p> <input type="text"/> <input type="text"/>
<p>PREVIOUS GYNAE. PROCEDURE OR TREATMENT</p> <input type="text"/> <input type="text"/>	<p>NEW PRIMARY CANCER OR RECURRENCE</p> <p>New primary <input type="radio"/> Regional (local) recurrence <input type="radio"/></p> <p>Distant metastases <input type="radio"/> Details:</p> <input type="text"/> <input type="text"/>
<p>ADDITIONAL RELEVANT CLINICAL INFORMATION</p> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<p>Note any other relevant information overleaf</p>

Vers. 1.0 Request Information Ovary, Fallopian Tube and Primary Peritoneal Carcinoma Protocol 1st Edition

The above Request Information Sheet is published to the RCPA website.

Appendix 2 Guidelines for formatting of a pathology report

Layout

Headings and spaces should be used to indicate subsections of the report, and heading hierarchies should be used where the LIS allows it. Heading hierarchies may be defined by a combination of case, font size, style and, if necessary, indentation.

Grouping like data elements under headings and using 'white space' assists in rapid transfer of information.⁴⁸

Descriptive titles and headings should be consistent across the protocol, checklist and report.

When reporting on different tumour types, similar layout of headings and blocks of data should be used, and this layout should be maintained over time.

Consistent positioning speeds data transfer and, over time, may reduce the need for field descriptions or headings, thus reducing unnecessary information or 'clutter'.

Within any given subsection, information density should be optimised to assist in data assimilation and recall.

- Configuring reports in such a way that they 'chunk' data elements into a single unit will help to improve recall for the clinician.⁴⁸
- 'Clutter' should be reduced to a minimum.⁴⁸ Thus, information that is not part of the protocol (eg billing information, Snomed codes, etc) should not appear on the reports or should be minimised.
- Injudicious use of formatting elements (eg too much bold, underlining or use of footnotes) also increases clutter and may distract the reader from the key information.

Where a structured report checklist is used as a template for the actual report, any values provided in the checklist but not applying to the case in question must be deleted from the formatted report.

Reports should be formatted with an understanding of the potential for the information to 'mutate' or be degraded as the report is transferred from the LIS to other health information systems.

As a report is transferred between systems:

- text characteristics such as font type, size, bold, italics and colour are often lost
- tables are likely to be corrupted as vertical alignment of text is lost when fixed font widths of the LIS are rendered as proportional fonts on screen or in print
- spaces, tabs and blank lines may be stripped from the report, disrupting the formatting
- supplementary reports may merge into the initial report.

Appendix 3 Example pathology report

Example report 1: High Grade Serous Carcinoma

Page 1 of 4	
<p>Citizen, Geraldine W. C/O Paradise Close Wreck Bay Resort Nar Nar Goon East, 3181</p> <p>Female</p> <p>DOB 1/7/1959 MRN M1196785</p>	<p>Lab Ref: 16/P7846 Referred: 30/3/2016</p>
<p>Copy to: Dr N.G. Chappie Rainforest Cancer Centre, 46 Smith Road, Wood Wood, 3478</p>	<p>Referred by: Dr V. Brown Suite 3, A/C Medical Centre, Bunyip Crescent Nar Nar Goon West, 3182</p>
OVARIAN/FALLOPIAN TUBE CANCER STRUCTURED REPORT	
Diagnostic Summary	
<p><i>High grade serous carcinoma, right tube, also involving ovaries bilaterally, with right ovarian surface involvement; uterine serosa, right pelvic side wall and omentum (33mm). Peritoneal washing cytology positive. No metastasis to pelvic lymph nodes. Genetic testing may be appropriate in this patient.</i></p>	
Supporting Information	
CLINICAL	
Genetic status:	Not known. Family history: Breast cancer, mother and sister.
Prior chemotherapy:	Not specified
Prev. gynae treatment:	Tubal ligation
Operative findings:	Right ovarian mass, tumour right pelvic side wall
Operative procedure:	Total hysterectomy with bilateral salpingo-oophorectomy; omentectomy; right and left pelvic lymph nodes, right pelvic side wall biopsy, peritoneal washings
New primary cancer or recurrence:	New primary
MACROSCOPIC	
Specimen labelled:	"1. Uterus tubes, ovaries, 2. Omentum, 3. Left pelvic lymph nodes, 4. Right pelvic nodes; 5. Right pelvic side wall, 6. Peritoneal washings" (see separate cytology report 16-C6543)
Specimen type:	Right ovary Left ovary Right fallopian tube Left fallopian tube Uterus Omentum Peritoneal washings Lymph nodes: left and right pelvic Right pelvic side wall biopsy
RIGHT OVARY	
Specimen integrity:	Tumour on surface
Specimen weight:	110g
Dimensions:	80x60x50mm
Tumour dimensions:	70x50x50mm
Tumour description:	cream firm focally necrotic
<p>The data fields within this formatted report conform to criteria as set out in the RCPA document "CARCINOMA OF THE OVARY, FALLOPIAN TUBE AND PRIMARY PERITONEAL SITE STRUCTURED REPORTING PROTOCOL 1st Ed. 2016.</p>	

LEFT OVARY

Specimen integrity: Ovarian capsule intact
Dimensions: 25x22x12mm
Description: Involved by tumour
Tumour dimensions: 10mm

RIGHT FALLOPIAN TUBE

Specimen integrity: Serosa intact
Dimensions: 50x8x8mm
Fimbriae: Present
Description: **Fimbrial** end of tube adherent to and predominantly obscured by right ovarian mass

LEFT FALLOPIAN TUBE

Specimen integrity: Serosa intact
Dimensions: 55x10x8mm
Fimbriae: Present

UTERUS

Dimensions: 70x35x25mm
Description: Anterior uterine serosa appears involved by tumour. Endometrium 2mm thickness with 8mm polyp anterior endometrium
Tumour dimensions: 22x15mm

RIGHT PELVIC SIDE WALL

Dimensions: 25x15x10mm
Description: Involved by tumour

OMENTUM

Dimensions: 220x180x30mm
Omental involvement: Involved
Max. dimension of largest deposit: 33mm
Number of metastatic deposits: Multiple (>8)

Lymph nodes:

Left pelvic lymph nodes - **fibrofatty** tissue
 35x25x12mm containing 4 probable lymph nodes
 Right pelvic lymph nodes - **fibrofatty** tissue
 30x20x15mm containing 6 possible lymph nodes

Block identification key:

1.1-1.4 right ovarian tumour, 1.5 **fimbrial** right tube, 1.6 remainder right tube, 1.7-1.10 left ovarian tumour, 1.11 left **fimbrial** tube, 1.12 remainder left tube, 1.12 uterine serosal lesion, 1.13, anterior **endomyometrium**, 1.14 posterior **endomyometrium**, 1.15 anterior cervix, 1.16 posterior cervix
 2.1, 2.2 Omental nodules

3.1 – 3.4 Left pelvic LN, one per block, 3.5 remaining fatty tissue
 4.1- 4.6 Right pelvic LN, one per block, 4.7 remaining fatty tissue
 5.1 Right pelvic side wall nodule, serially sectioned

MICROSCOPIC:

Histological tumour type: High grade serous carcinoma
Tumour grade: High grade; by definition.
Borderline tumour: Absent
Serous tubal intraepithelial carcinoma (STIC): Right tube: Present - **fimbrial**
 Left tube: Not identified

Histological features:

1. Tumour in both ovaries comprises pleomorphic tumour cells with a papillary and solid architecture, and areas of slit like glands. There is involvement of the **fimbrial** portion of the right tube with associated intraepithelial carcinoma. Focal cytoplasmic clearing identified, without other morphological features of clear cell carcinoma.
2. The omental tumour nodules have a similar appearance to the adnexal tumours.
- 3&4. The pelvic lymph nodes show mild sinus **histiocytosis** with no malignancy.

HISTOLOGICAL SITES OF TUMOUR INVOLVEMENT

Right ovary: Involved
Left ovary: Involved
Right ovarian capsule/surface: Involved
Left ovarian capsule/surface: Not involved
Right fallopian tube: Involved
Left fallopian tube: Not involved
Uterus: Not involved
Peritoneum (including uterine serosa): Involved. Pelvis - right side wall, anterior uterine serosa
Omentum: Involved
Level of involvement: Macroscopic
Site of tubal involvement: **Fimbrial**
Lymphovascular invasion: Not identified

LYMPH NODE STATUS:

Not involved

REGIONAL**Left pelvic**

Number of LN examined: x4
Number of positive LN: x0

The data fields within this formatted report conform to criteria as set out in the RCPA document "CARCINOMA OF THE OVARY, FALLOPIAN TUBE AND PRIMARY PERITONEAL SITE STRUCTURED REPORTING" PROTOCOL 1st Ed. 2016.

Right pelvic

Number of LN examined: x6
Number of positive LN: x0

Peritoneal cytology: Positive (see cytology report 16-C6543)

Response to neoadjuvant therapy: Not applicable, no prior treatment

COEXISTENT PATHOLOGY

Endometriosis: Not identified

Other: Inactive endometrium, benign endometrial polyp, cervix within normal limits

Optimal tumour block(s): Block 2.1

ANCILLARY TESTS

Immunohistochemical markers: p16 positive (>80% strong cytoplasmic and nuclear)
p53 positive (90% strong nuclear)
WT1 positive
ER positive (2+ intensity 60% tumour cell nuclei)
PR positive (2+ intensity 30% tumour cell nuclei)

Reported by Dr Sarah Nguyen

Authorised 4/4/2016

Example report 2: Borderline tumour

Page 1 of 3	
Citizen, Geraldine W. C/O Paradise Close Wreck Bay Resort Nar Nar Goon East, 3181 Female DOB 1/7/1979 MRN M1196785	Lab Ref: 16/P7846 Referred: 30/3/2016
Copy to: Dr N.G. Chappie Rainforest Cancer Centre, 46 Smith Road, Wood Wood, 3478	Referred by: Dr V. Brown Suite 3, AJC Medical Centre, Bunyip Crescent Nar Nar Goon West, 3182
OVARIAN/FALLOPIAN TUBE TUMOUR STRUCTURED REPORT	
Diagnostic Summary	
<i>Serous borderline tumours of left and right ovaries, with surface involvement and non-invasive implants involving omentum.</i>	
Supporting Information	
CLINICAL	
Genetic status:	Not known
Prior chemotherapy:	No chemotherapy administered
Prev. gynaec treatment:	LUSCS
Operative findings:	Bilateral ovarian masses
Operative procedure:	Hysterectomy, bilateral salpingoophorectomy, omentectomy, peritoneal washing cytology
New primary or recurrence:	New primary tumour
MACROSCOPIC	
Specimen labelled:	1. Left ovary and tube, 2. Right ovary and tube, 3. Uterus, 4. Omentum Peritoneal washings
Specimen type:	Right ovary Left ovary Right fallopian tube Left fallopian tube Uterus Omentum Peritoneal washings (see separate cytology report 16-C9975)
RIGHT OVARY	
Specimen integrity:	Tumour on surface.
Specimen weight:	40g
Dimensions:	50x30x25mm
Tumour dimensions:	50x30x25mm
Tumour description:	Cystic and focally solid, with surface papillary excrescences
<small>The data fields within this formatted report conform to criteria as set out in the RCPA document "CARCINOMA OF THE OVARY, FALLOPIAN TUBE AND PRIMARY PERITONEAL SITE STRUCTURED REPORTING PROTOCOL 1st Ed. 2016.</small>	

LEFT OVARY

Specimen integrity:	Tumour on surface. Specimen received previously incised.
Specimen weight:	115g
Dimensions:	120x120x100mm
Tumour dimensions:	120x120x100mm
Tumour description:	Predominantly cystic, no normal ovary identified

RIGHT FALLOPIAN TUBE

Specimen integrity:	Serosa intact
Dimensions:	70x10mm
Fimbria:	Present
Description:	No abnormality

LEFT FALLOPIAN TUBE

Specimen integrity:	Serosa intact
Dimensions:	65x8mm
Fimbria:	Present
Description:	No abnormality

UTERUS

Specimen weight:	103g
Dimensions:	95x70x60mm
Description:	Endometrium smooth, 3mm in thickness, cervix 25x23mm without abnormality, whorled white mass posterior myometrium 25mm

OMENTUM

Dimensions:	180x100x25mm
Description:	Congested fibrofatty tissue with firm areas but no discrete nodules
Omental involvement:	Not involved

Block identification key:

1.1-1.5 left ovarian tumour, 1.6 left fallopian tube fimbrial end, 1.7 representative non-fimbrial tube
 2.1- 2.12 right ovarian tumour, 2.13 right fallopian tube fimbrial end, 2.14 representative non-fimbrial tube
 3.1 anterior cervix, 3.2 posterior cervix, 3.3 anterior endomyometrium, 3.4 and 3.5 posterior endomyometrium with myometrial tumour
 4.1- 4.6 omentum

MICROSCOPIC:

BORDERLINE TUMOUR:	Present
Histological tumour type:	Serous borderline tumour
Micropapillary architecture:	Absent
Microinvasion:	Absent

The data fields within this formatted report conform to criteria as set out in the RCPA document "CARCINOMA OF THE OVARY, FALLOPIAN TUBE AND PRIMARY PERITONEAL SITE STRUCTURED REPORTING PROTOCOL 1st Ed. 2016.

Histological features:

- 1&2. Both ovarian tumours show similar microscopic features with complex papillae showing hierarchical branching. The lining epithelium is focally stratified columnar, with minimal atypia. Some cells have apical cilia. The fallopian tubes are within normal limits.
3. Proliferative endometrium, cervix within normal limits. The myometrial lesion is of low cellularity comprising interlacing bundles of smooth muscle without atypical features.
4. Clusters of cells with hierarchical branching within a dense fibrous stroma involve the surface of the omentum. Endosalpingiosis is also present.

IMPLANTS

Non-invasive implants:	Present, desmoplastic, involving omentum
Invasive implants/Extra-ovarian low grade serous carcinoma:	Not identified
Indeterminate:	Not identified
Size of largest implant:	6mm

HISTOLOGICAL SITES OF TUMOUR INVOLVEMENT

Right ovary:	Involved (serous borderline tumour)
Left ovary:	Involved (serous borderline tumour)
Right ovarian capsule/surface:	Involved (serous borderline tumour)
Left ovarian capsule/surface:	Involved (serous borderline tumour)
Right fallopian tube:	Not involved
Left fallopian tube:	Not involved
Uterus:	Not involved
Peritoneum (including uterine serosa):	Not involved
Omentum:	Involved (non-invasive implant)

Peritoneal cytology:	Negative (see cytology report 16-C9975)
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COEXISTENT PATHOLOGY

Endometriosis:	Not identified
Other:	Proliferative endometrium, posterior myometrial leiomyoma, 25mm. Endosalpingiosis, omentum.

ANCILLARY TESTS

Immunohistochemical markers:	Not performed
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Reported by Dr Sarah Nguyen

Authorised 4/4/2016

The data fields within this formatted report conform to criteria as set out in the RCRA document "CARCINOMA OF THE OVARY, FALLOPIAN TUBE AND PRIMARY PERITONEAL SITE STRUCTURED REPORTING PROTOCOL 1st Ed. 2016.

Example report 3: Post chemotherapy

Smith, Maggie
C/O Paradise Close
Wreck Bay Resort
Nar Nar Goon East, 3181

Female

DOB 1/7/1932
MRN M1196785

Lab Ref: **16/P1234**

Referred: 30/3/2016

Copy to: ~~Dr N.G. Chappie~~
Rainforest Cancer Centre,
46 Smith Road,
Wood Wood, 2478

Referred by: Dr V. Brown
Suite 3, AJC Medical Centre,
Bunyip Crescent
Nar Nar Goon West, 3182

OVARIAN/FALLOPIAN TUBE CANCER STRUCTURED REPORT

Diagnostic Summary

~~Residual high grade serous carcinoma (post neoadjuvant therapy) of the right fallopian tube with involvement of the right and left ovary, serosa of left fallopian tube and omentum with positive ascitic fluid cytology. Chemotherapy Response Score (CRS) 2: Partial tumour response.~~

Supporting Information

CLINICAL

Genetic status:	Not known
Prior chemotherapy:	Prior chemotherapy administered. 3 cycles.
Prev. gynae treatment:	Vaginal hysterectomy (benign) 2006
Additional clinical information:	Previous diagnosis on CT-guided biopsy. Interval cytoreduction after three cycles of Paclitaxel and carboplatin. Reduction in tumour volume, normalisation of Ca125, and marked reduction of ascites.
Operative findings:	Omental cake
Operative procedure:	Tumour debulking BSO, omentectomy
New primary or recurrence:	New primary

MACROSCOPIC

Specimen labelled:	"1. Right ovary and tube 2. Left ovary and tube 3. Omentum Ascitic fluid cytology (see cytology ref 16C1234)"
---------------------------	--

Specimen type:	Right ovary Left ovary Right fallopian tube Left fallopian tube Omentum Ascitic fluid
-----------------------	--

RIGHT OVARY

Specimen integrity:	Tumour on surface.
Specimen weight:	40g
Dimensions:	40x35x30mm (tubo-ovarian mass)
Description:	Replaced by tumour
Tumour dimensions:	As above
Tumour description:	Nodular cream tubo-ovarian mass

LEFT OVARY

Specimen integrity: Tumour on surface.
Specimen weight: 30g
Dimensions: 30x25x20mm
Description: Replaced by tumour
Tumour dimensions: As above
Tumour description: Nodular cream tumour

RIGHT FALLOPIAN TUBE

Specimen integrity: Right tubo-ovarian mass (see above)
Dimensions: 20mm x 12mm. Portion of tube visible adherent to the surface of the right ovary
Fimbria: Not identified
Description: Tube disappears into tubo-ovarian mass
Tumour dimensions: Tubo-ovarian mass (as above)
Tumour description: Nodular cream tubo-ovarian mass

LEFT FALLOPIAN TUBE

Specimen integrity: Serosa intact
Dimensions: 85mm x 12mm
Fimbria: Present
Description: Within normal limits

OMENTUM

Dimensions: 180x180x45mm
Omental involvement: Involved
Max. dimension of largest deposit: >85mm
Number of metastatic deposits: Multiple diffuse abnormality, firm throughout, without discrete nodules

Block identification key:

1.1-1.8 Right ovary, 1.9-1.11 - Right fallopian tube, 1.12 interface of tube and ovary (all visible tube processed)
 2.1-2.6 Left ovary 2.7-2.10 - Left fallopian tube (all tube processed)
 3.1-3.6 Omentum

MICROSCOPIC:

Histological tumour type: High grade serous carcinoma
Tumour grade: High grade
Borderline tumour: Absent
Serous tubal intraepithelial carcinoma (STIC): Right tube: not identified
 Left tube: not identified
Histological features: High grade serous carcinoma with multifocal regression, but viable tumour easily identified at all sites of described macroscopic tumour involvement. ~~Widespread response seen. Ovarian with macrophages and psammoma bodies.~~ Fimbriae not identified histologically in the widely sampled mass.

The data fields within this formatted report conform to criteria as set out in the RCPA document "CARCINOMA OF THE OVARY, FALLOPIAN TUBE AND PRIMARY PERITONEAL SITE STRUCTURED REPORTING PROTOCOL 1st Ed. 2016.

HISTOLOGICAL SITES OF TUMOUR INVOLVEMENT

Right ovary:	Involved
Left ovary:	Involved
Right ovarian capsule/surface:	Involved
Left ovarian capsule/surface:	Involved
Right fallopian tube:	Involved
Left fallopian tube:	Involved (serosa)
Peritoneum:	Not involved.
Omentum:	Involved. Level of involvement macroscopic
Site of tubal involvement:	Indeterminate
Lymphovascular invasion:	Present
Peritoneal cytology:	Positive (ascitic fluid cytology)
Response to neoadjuvant therapy:	Score 2 (CRS partial tumour response)
COEXISTENT PATHOLOGY	
Endometriosis:	Not identified
Optimal tumour block(s):	3.1 (omentum – extensive viable tumour in this section)

ANCILLARY TESTS

Immunohistochemical markers:	WT1 positive, p53 positive (mutant pattern), Ki67 = 15% ER 40%, 2+, PR 25%, 2+
-------------------------------------	--

Reported by Dr Sarah Nguyen

Authorised 4/4/2016

Appendix 4 WHO classification of tumours¹¹

The 2014 WHO classification of tumours for carcinomas of the ovary, fallopian tube and peritoneum

Ovary

Epithelial tumours	Serous Tumours	Borderline	Serous borderline tumour / Atypical proliferative serous tumour	8442/1
			Serous borderline tumour- micropapillary variant / Non-invasive low-grade serous carcinoma	8460/2
		Malignant	Low-grade serous carcinoma	8460/3
			High-grade serous carcinoma	8461/3
	Mucinous tumours	Borderline	Mucinous borderline tumour / Atypical proliferative mucinous tumour	8472/1
		Malignant	Mucinous carcinoma	8480/3
	Endometrioid tumours	Borderline	Endometrioid borderline tumour / Atypical proliferative endometrioid tumour	8380/1
		Malignant	Endometrioid carcinoma	8380/3
	Clear cell tumours	Borderline	Clear cell borderline tumour / Atypical proliferative clear cell tumour	8313/1
		Malignant	Clear cell carcinoma	8310/3
	Brenner tumours	Borderline	Borderline Brenner tumour / Atypical proliferative Brenner tumour	9000/1
		Malignant	Malignant Brenner tumour	9000/3
	Seromucinous tumours	Borderline	Seromucinous borderline tumour / Atypical proliferative seromucinous tumour	8474/1
		Malignant	Seromucinous carcinoma	8474/3
	Undifferentiated carcinoma			8020/3
Mixed epithelial and mesenchymal tumours			Carcinosarcoma	8980/3

Fallopian tube

Epithelial tumours	Epithelial precursor lesion		Serous tubal intraepithelial carcinoma	8441/2
	Epithelial borderline tumour		Serous borderline tumour / Atypical proliferative serous tumour	8442/1
	Malignant epithelial tumours		Low-grade serous carcinoma	8460/3

		High-grade serous carcinoma	8461/3
		Endometrioid carcinoma	8380/3
		Undifferentiated carcinoma	8020/3
	Others	Mucinous carcinoma	8480/3
		Transitional cell carcinoma	8120/3
		Clear cell carcinoma	8130/3
Mixed epithelial-mesenchymal tumours		Carcinosarcoma	

Peritoneum

Epithelial tumours of Müllerian type	Serous borderline tumour / Atypical proliferative serous tumour	8442/1
	Low-grade serous carcinoma	8460/3
	High-grade serous carcinoma	8461/3
	Others	

Note: a code for mixed cell adenocarcinoma is not included in the above list but the code M8323/3 is recommended if this diagnosis is made.

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Appendix 5 FIGO Cancer staging(2014)^{4,49,50}

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)

Stage

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 10mm in greatest dimension
IIIA1(ii)	Metastasis more than 10mm 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 2cm 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)

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Comments on staging:

In occasional cases of advanced stage high grade serous carcinoma it may not be possible to ascertain the primary site of origin, and these tumours should be categorised as “undesignated” as above. In practice, the additional term “tubo-ovarian” is suggested as a descriptor to assist in distinguishing these cases from endometrial primaries (see appendix 7).



Lymph node status

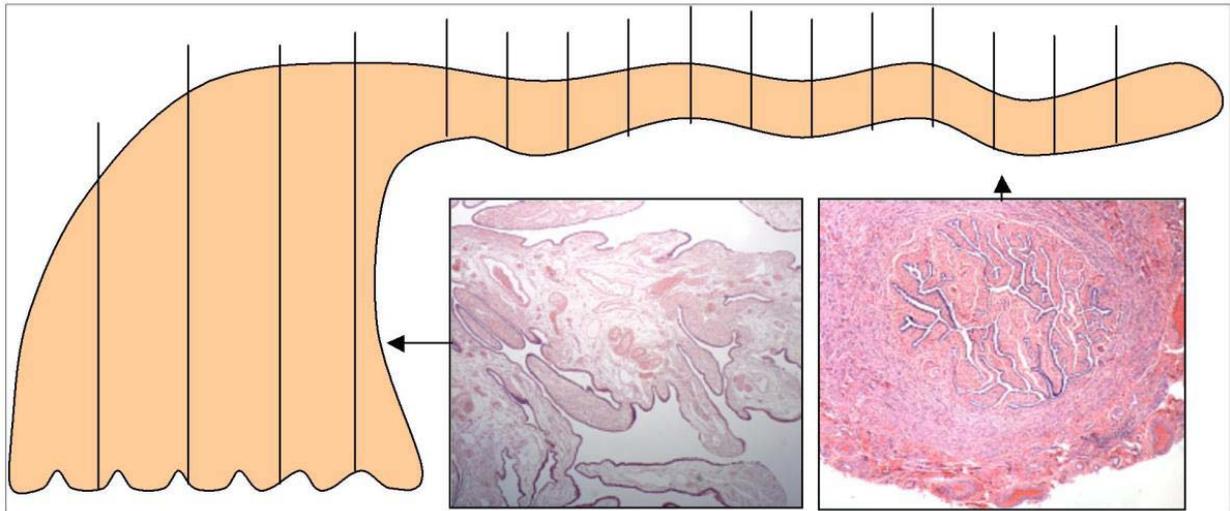


In the revised 2014 FIGO staging system metastases involving retroperitoneal lymph nodes, in the absence of peritoneal spread above the pelvic brim or distant metastases, represent stage IIIA1 disease. This stage is further subdivided into stages IIIA1(i) and IIIA1(ii) for nodal metastases ≤ 10 mm and > 10 mm, respectively.⁴ 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 serous carcinoma.^{51,52} 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 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. According to FIGO (personal communication), this should be regarded as intra-abdominal disease, i.e. stage IIIC. At present there are also limited data to justify the subdivision of stage IIIA1 according to the size of the nodal metastases.⁴ 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.

Appendix 6 SEE-FIM protocol



Protocol for Sectioning and Extensively Examining the FIMbriated End (SEE-FIM) of the Fallopian Tube. This protocol entails amputation and longitudinal sectioning of the infundibulum and fimbrial segment (distal 2 cm) to allow maximal exposure of the tubal plicae. The isthmus and ampulla are cut transversely at 2- to 3-mm intervals.

From Crum et al.⁵³ Copyright © 2007 Lippincott Williams & Wilkins. Reproduced with permission.

Appendix 7 Notes on assigning primary tumour site



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, the same is not true for high-grade serous carcinomas (HGSCs).



It was first recognised in 2001^{54,55} that a high percentage of so-called ovarian HGSC in women with germline *BRCA1* mutations arise in the fimbrial end of the fallopian tube. This was first noticed in risk reducing salpingo-oophorectomy specimens (RRSO) where early, pre-invasive, high-grade serous carcinomas are much more likely to be present in the fallopian tube than ovary. These serous tubal intraepithelial carcinomas (STICs) harbour identical p53 mutations to the extratubal tumour, establishing that they are clonal.⁵⁶ Comparison of telomere length and centrosome amplification in matched STIC and ovarian HGSC suggests that the STICs develop before the ovarian tumours.^{57,58} 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.⁵⁹ In summary, there is compelling evidence that the precursors of HGSC originate in the fallopian tube in patients with germline *BRCA1* mutations, and accumulating 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. It is also relevant that some cases of ovarian and primary peritoneal HGSCs do not show STIC lesions despite complete examination of the fallopian tube. 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.⁶⁰ 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.⁴ 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.⁴ 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. 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 a recent publication, recommendations for assigning the site of origin of extra-uterine HGSC are provided in the following section.⁶¹ Using these criteria, assignment of primary site is no longer based on the site of greatest volume/size of tumour but in the presence of STIC or invasive HGSC in the tubal mucosa, a fallopian tube origin is rendered. 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.



Suggestions for Assigning Site of Origin⁶¹ (see Fig 1)

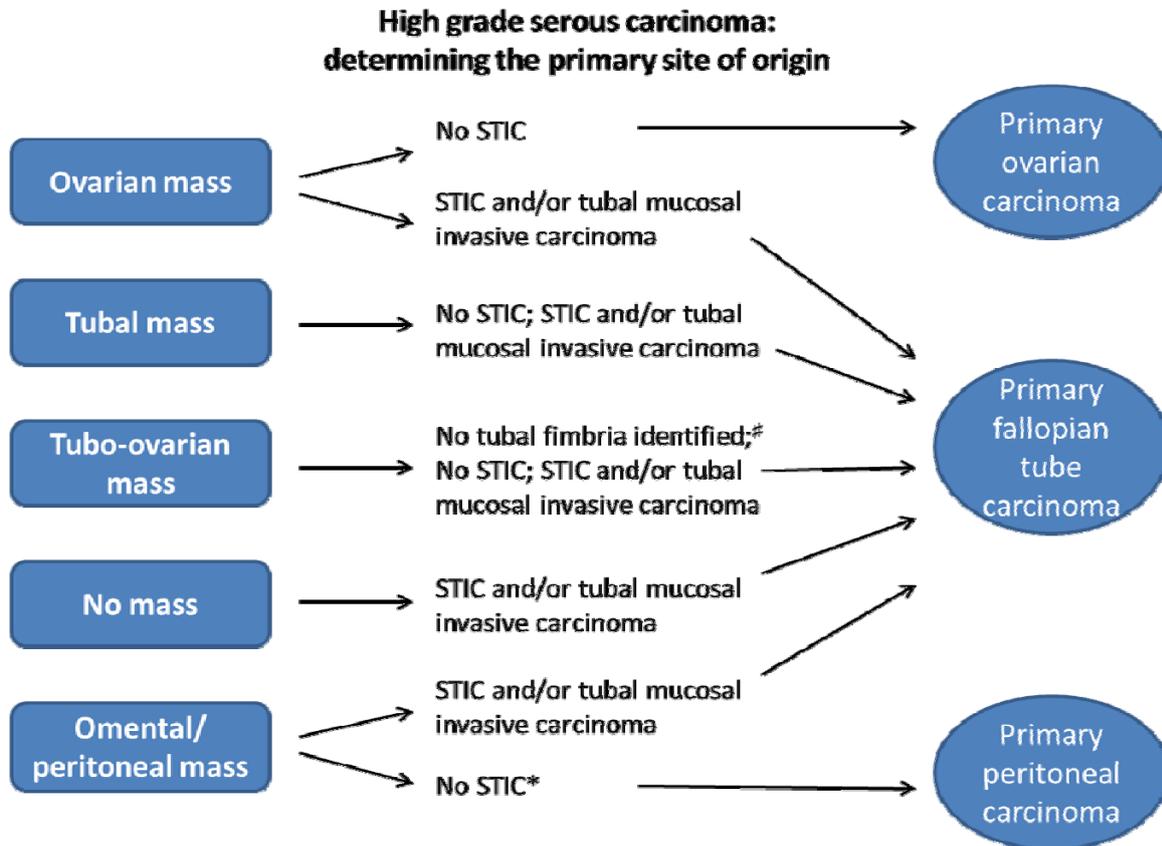
The following suggestions are not intended to be an exhaustive list nor are they intended to be binding, and assignment of origin in an individual case is left to the discretion of the pathologist and the clinical team, ideally in the setting of a multidisciplinary team meeting. Undoubtedly, there will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

1. The fallopian tubes, or at least their fimbrial ends, should be totally sampled in all cases of HGSC by a SEE-FIM-like protocol⁵⁶ (see appendix 6) to avoid missing this important site of disease, which probably represents the tumour origin in the majority of cases.
2. The presence of STIC, in the absence of invasive disease in the fallopian tube, should be considered as tubal involvement for staging purposes.
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 date⁶²) but with an annotation that there is no invasive carcinoma.
4. Cases with only STIC, ovarian surface involvement or parenchymal involvement not exceeding 5 mm and widespread peritoneal involvement, which would traditionally be categorised as primary peritoneal carcinoma,⁶³ should be classified as tubal primaries.
5. Cases with invasive 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.
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 should be classified as ovarian primaries.
9. Cases should be categorised as primary peritoneal carcinoma by the conventional criteria below⁶³ and only after complete examination of the fallopian tubes (including the non-fimbrial portions) has excluded the presence of STIC or a small tubal HGSC
 - both ovaries must be normal in size or enlarged by a benign process
 - the involvement in the extra-ovarian sites must be greater than the involvement on the surface of either ovary
 - the ovarian tumour involvement must be non-existent, confined to the ovarian surface without stromal invasion or involve the cortical stroma with tumour size less than 5 mm x 5 mm.
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.

 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 G4.01 IMMUNOHISTOCHEMICAL MARKERS Distinction between ovarian and uterine carcinoma and Appendix 15); a majority of such cases will represent adnexal metastases from an endometrial serous carcinoma.

 **Figure 1: Determining the primary site**



Failure to detect the tubal fimbria implies overgrowth by tumour

* Apply criteria as specified in the commentary above

In summary, any tubal mucosal involvement designates tube as primary site.

In cases diagnosed on omental or peritoneal biopsy, or a cytology sample, where chemotherapy (rather than surgery) is the initial form of treatment, the presumed primary site should be assigned as 'tubo-ovarian' to avoid the assignment of site of origin as 'undesignated' where possible.⁶⁴

Appendix 8 Notes on Specimen Integrity



Assessment of the integrity of the specimen (ovary or tube) is important, particularly for substaging of organ-confined disease (Stage I). 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 FIGO stage IC disease - see next paragraph), although obviously this information should be provided by the surgeon. (Refer to Appendix 1) Occasionally there is microscopic ovarian surface involvement in the absence of gross capsular deficiency and this should be recorded (see S2.05 - SITES OF TUMOUR INVOLVEMENT).



Approximately 25% of ovarian cancers are FIGO stage I at diagnosis, with a 5-year-survival of 83-90%.^{65,66} According to the 2014 FIGO staging system for ovarian, tubal and primary peritoneal cancer,⁴ ovarian capsular or tubal serosal rupture before surgery is considered stage IC2 while intraoperative rupture is 1C1. 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,^{67,68} while others did not.⁶⁹⁻⁷¹



A recent meta-analysis⁴ assessed the impact of intraoperative rupture on prognosis, after analysing nine eligible studies which included 2382 patients. Patients with preoperative capsular rupture showed poorer progression free survival (PFS) than those with no rupture or intraoperative rupture. In subanalyses, 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.



There is some evidence to suggest that clear cell carcinomas exhibit a higher risk of rupture,⁷² probably related to adhesions to the surrounding tissues, associated with tumour invasion or endometriosis.⁷³ Capsular rupture has also been associated with pregnancy.⁷⁴

Appendix 9 Notes on Macroscopic reporting

Tumour size

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 1 block per cm of maximum tumour diameter in solid tumours. For example, it has been recommended that soft tissue tumours <2 cm in diameter be blocked in their entirety, and that a minimum of 1 section per cm of maximum diameter be examined for larger tumours.⁷⁵ These same recommendations appear in cancer datasets for tumours at a range of anatomical sites.

 Adequate sampling of ovarian tumours is important for a number of reasons; for example to identify small foci of carcinosarcoma in ovarian carcinomas, histological heterogeneity (e.g. different epithelial subtypes in mixed carcinomas) and to identify foci of microinvasion or invasion in borderline tumours. Adequate sampling may also assist in identifying diagnostic areas in poorly-differentiated neoplasms or features which suggest a particular tumour subtype. For example, the presence of squamous differentiation may help to confirm an endometrioid neoplasm, and identification of endometriosis supports a diagnosis of endometrioid, clear cell or seromucinous tumours.

 It is recognised 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 of one section per 1–2 cm of maximum tumour diameter in epithelial ovarian neoplasms,⁷⁶ 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,⁷⁷ all borderline tumours should be well sampled – at least 1 block per centimetre of maximum tumour diameter for neoplasms <10 cm and 2 sections per centimetre for larger tumours (excluding smooth-walled cystic foci). 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.

 Seidman et al⁷⁸ suggested that in mucinous ovarian tumours, tumour size may be helpful in determining whether the ovarian neoplasm is primary or metastatic. The authors found that unilateral mucinous carcinomas ≥ 10 cm in diameter were more likely to be primary than metastatic. Similar findings were reported by others.⁷⁹

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 tumours. However, in the setting of a grossly involved omentum, submitting 1 block for histologic examination is probably sufficient.^{80,81} In patients who have received neoadjuvant chemotherapy, where histological assessment of tumour response to therapy is recommended (see G3.06 - 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,⁸¹ other studies suggest 1 block for every 67 mm of maximal dimension of omentum⁸⁰ or at least 1 block for every 20 mm of maximum omental dimension.¹⁹ Taking 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 tumour deposit should be recorded in the pathology report. This is critical for determining the pathological stage. 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 (FIGO 2014).⁴

Appendix 10 Notes on Tumour Typing



All ovarian epithelial malignancies and borderline tumours should be typed according to the WHO classification.¹¹ There are 5 major subtypes of primary ovarian carcinoma, high-grade serous, clear cell, endometrioid, mucinous and low-grade serous.⁸²⁻⁸⁵ There are also other uncommon minor subtypes, those listed by the WHO including malignant Brenner tumour, seromucinous carcinoma and undifferentiated carcinoma.¹¹ Carcinosarcoma is a mixed epithelial and mesenchymal malignancy but is included in the category of epithelial malignancies in this dataset since most are of epithelial origin and histogenesis.⁸⁶



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 morphological subtypes of ovarian carcinoma have a different pathogenesis, are associated with distinct molecular alterations and have a different natural history, response to traditional chemotherapy and prognosis.⁸²⁻⁸⁵ Tumour typing may also be important in identifying or initiating testing for an underlying genetic predisposition; for example, high-grade serous carcinoma may be associated with underlying *BRCA1/2* mutation while endometrioid and clear cell carcinomas can occur in patients with Lynch syndrome.⁸⁷ The most common ovarian carcinoma is high-grade serous carcinoma (approximately 70%) followed by clear cell and endometrioid.^{88,89} Mucinous and low-grade serous are less common. Approximately 90% of advanced stage ovarian carcinomas (stage III/IV) are high-grade serous in type.^{88,89}



Most primary tubal carcinomas are high-grade serous or endometrioid and most primary peritoneal carcinomas are of high-grade serous type. As discussed in the sections on tumour site, it may be difficult to ascertain the origin of a high-grade serous carcinoma since multiple sites are often involved.



Mixed ovarian carcinomas are now considered to be uncommon. The current 2014 WHO classification does not include a category of mixed carcinoma⁸² but the prior classification stated that a diagnosis of mixed carcinoma should only be made if the minor component represents more than 10% of the neoplasm.⁸² However, it is recommended that all different morphological subtypes 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 high-grade serous carcinomas with pseudoendometrioid areas and areas of cytoplasmic clearing respectively. In such cases, immunohistochemical markers, especially WT1, may be useful (see G4.01 - IMMUNOHISTOCHEMICAL MARKERS).



Borderline tumours should also be typed according to WHO criteria. The most common subtypes are serous and mucinous (intestinal type). Seromucinous, endometrioid, clear cell and Brenner subtypes also occur.



Subtyping of Carcinosarcoma

There is little published evidence suggesting any prognostic significance of the different morphological subtypes within ovarian carcinosarcomas (evidence exists for uterine carcinosarcomas).⁹⁰⁻⁹² However, in view of the paucity of studies, the ICCR recommends that it would be useful to record the percentage of the epithelial and mesenchymal elements as well as the subtypes of the epithelial and mesenchymal components. This is a recommended rather than a required element and collection of these data may be informative for the future regarding the prognosis and management of these neoplasms.⁹⁰⁻⁹²

Appendix 11 Notes on Tumour Grading



Assessment of histological grade is important for patient management and prognosis and is a required element.⁹³ Although some universal grading systems, for example the Shimizu-Silverberg system,⁹⁴ are in use which are applicable to all ovarian epithelial malignancies, the ICCR recommends that different grading systems should be used for the different morphological subtypes.



Serous carcinoma

Improvements in the understanding of the natural history and molecular pathology of serous carcinoma have demonstrated that high-grade serous carcinoma and low-grade serous carcinoma are different tumour types with a different underlying pathogenesis and associated with different molecular events and prognosis.⁹⁴⁻⁹⁷ Serous carcinomas are now classified as low-grade or high-grade and this has been endorsed by WHO 2014,¹¹ with the recognition that these are two different tumour types rather than low-grade and high-grade variants of the same tumour type.



Endometrioid carcinoma

Grading of endometrioid carcinomas is identical to that of uterine endometrioid carcinomas⁹⁸⁻¹⁰³ and is of prognostic and therapeutic significance. A significant majority of ovarian endometrioid carcinomas is 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 high-grade serous carcinomas with a glandular growth pattern. Immunohistochemistry is useful in this regard (see G4.01 - IMMUNOHISTOCHEMICAL MARKERS). The 1988 International Federation of Gynaecology and Obstetrics (FIGO) grading system is widely used for grading endometrioid carcinomas and is recommended by the ICCR. The FIGO system is based on architecture; tumours with <5% solid glandular component are grade 1, those with 5-50% solid areas are grade 2, and tumours with >50% of solid glandular component are classified as grade 3. When grade 1 and 2 tumours show notable nuclear atypia, the histological grade is increased by one.



Clear cell, undifferentiated carcinoma, carcinosarcoma

Clear cell and undifferentiated carcinomas and carcinosarcomas are high-grade tumours by definition. Although some publications suggest that clear cell carcinomas should be graded according to a three-tier system,¹⁰⁴ there is no consensus about this.



Mucinous carcinomas

There is also little evidence for grading mucinous carcinomas, although oncologists often ask for a tumour grade. The ICCR panel suggests that if grading of these neoplasms is undertaken (a recommended rather than required element in the case of mucinous carcinomas), the same grading system for endometrioid carcinomas should be used (see next paragraph). Malignant mural nodules in ovarian mucinous neoplasms are automatically grade 3.



There are no published recommendations for the grading of seromucinous carcinomas and malignant Brenner tumours, two rare ovarian malignancies, which are included in the recent WHO Classification and for which no grading recommendations have been provided.¹¹ Since seromucinous carcinomas have some features in common with endometrioid carcinomas the ICCR recommends that they should be graded in the

same way as endometrioid ovarian carcinomas, i.e. according to the 1988 FIGO grading system.⁹⁸

Since ICCR protocol release, a review of 19 cases of seromucinous carcinoma has reinforced that grading of this uncommon but distinct entity should be analogous to that of ovarian endometrioid adenocarcinoma.¹⁰⁵

 If chemotherapy has been administered, tumour grading (and typing) may need to be based on the pre-chemotherapy biopsy.

Appendix 12 Notes on Borderline Tumours

Tumour typing

Terminology for ovarian borderline tumours has evolved over several years.^{19,22} The preferred terminology is borderline tumour, for example serous or mucinous borderline tumour, and this has been endorsed in the 2014 WHO Classification.¹¹ An acceptable synonym is atypical proliferative tumour.¹¹ Serous borderline tumours which have been previously designated typical and micropapillary types, are now classified as serous borderline tumour/atypical proliferative serous tumour and micropapillary variant of serous borderline tumour/non-invasive low-grade serous carcinoma respectively, in the 2014 WHO Classification for gynecologic tumours.^{11,23} For mucinous, endometrioid, clear cell, Brenner, and seromucinous tumours, borderline tumour/atypical proliferative tumour terminology is also used in the 2014 WHO Classification.^{11,20,106-109} The term low malignant potential is not recommended.^{11,20,23,106-109} Synonyms for seromucinous tumours include endocervical-type mucinous borderline tumour, Müllerian mucinous borderline tumour, and atypical proliferative (borderline) Müllerian tumour.¹⁰⁹

Special Features

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 $\geq 10\%$ of the epithelial volume are designated as borderline tumours arising within a cystadenoma/cystadenofibroma.^{19,20,23} However, many would still diagnose a borderline tumour in which the epithelial stratification/complexity involves $< 10\%$ of the epithelial volume.

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

As serous borderline tumour/atypical proliferative serous tumour can exhibit variable degrees of micropapillary architecture, a diagnosis of micropapillary variant of serous borderline tumour is based on the presence of ≥ 5 mm of confluent micropapillary growth.²³

Microinvasion

A standardized quantitative criterion for distinguishing microinvasion from frankly invasive carcinoma within a borderline tumour has not been established, and varying definitions have been used in different studies, including 1 mm, 2 mm, 3 mm, 5 mm, and 10 mm² as the upper limits of microinvasion.¹⁹⁻²³ The 2014 WHO Classification suggests a cut-off of 5 mm.¹¹ Some groups distinguish 2 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 "microinvasive carcinoma" (glandular or micropapillary patterns qualitatively analogous to low-grade serous carcinoma).^{19,22,23} 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.^{22,23,110} 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 2 terms synonymously.^{20,21}

Implants and microinvasion

 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 serous borderline tumours is the presence of invasive implants in extra-ovarian tissues with non-invasive implants having a favourable prognosis. Specifying the location and size of implants is important for determining the FIGO stage.⁴ Non-invasive and invasive implants may co-exist in the same specimen. Non-invasive implants are subclassified as epithelial or desmoplastic types.¹⁹ 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.^{22,23}

 The most widely used criterion for diagnosing invasive implants is destructive invasion of underlying tissue.¹¹¹ 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. As some peritoneal staging biopsies may be superficial without sufficient underlying tissue to assess invasion, expanded criteria for invasive implants have been proposed for cases without classic patterns of invasion.²⁴ These criteria include micropapillary architecture resembling micropapillary serous borderline tumour and clusters of tumour within clear lacunar spaces. Not all gynaecological pathologists accept these expanded criteria,^{19,22} but they have been shown to correlate with poor outcome.²⁴

 In occasional cases, it may not be possible to definitively distinguish non-invasive from invasive implants and the recommendation is to designate such implants as being of indeterminate type.¹¹² 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 diagnosing invasive implants, the report should state that these represent extra-ovarian low-grade serous carcinoma; this has been endorsed in the 2014 WHO blue book.^{11,19,22-24} 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 results²² but a recent study of a large population-based cohort has shown that the vast majority of implants are clonally related to the primary ovarian tumour.¹¹³ Most of the cases from that 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. Nevertheless, the number of invasive implants evaluated by molecular methods in the entire literature is limited.

 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 borderline mucinous, endometrioid, clear cell or Brenner tumours. In the presence of an "implant" in association with an ovarian mucinous borderline tumour, an undiagnosed or unsampled primary ovarian mucinous carcinoma

or a metastasis from a non-gynaecological primary tumour involving the ovary should be excluded.

Appendix 13 Notes on Serous tubal intra-epithelial carcinoma (STIC).



Recently, serous tubal intraepithelial carcinoma (STIC) has been implicated in the pathogenesis of extra-uterine high-grade serous carcinoma. The evidence indicating that STIC is a precursor of most high-grade serous carcinomas 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, high-grade serous carcinoma, have already been provided (see S2.05 - SITES OF TUMOUR 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.¹¹⁴⁻¹¹⁶ 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 (strong diffuse staining or complete absence of staining) and high Ki-67 labelling index ($\geq 10\%$) 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 such lesions that have some but not all features of STIC) are of uncertain significance at present and these diagnoses should 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.



A last consideration is that fallopian tube mucosal involvement by uterine or non-gynaecological primary tumours can occur and mimic STIC.^{25-27,117} 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, and WT1 may be of value in these cases (see G4.01 - IMMUNOHISTOCHEMICAL MARKERS).¹¹⁸ A diagnosis of STIC always requires consideration of clinical and pathological findings and the exclusion of secondary involvement of the fallopian tube.

Appendix 14 Notes on Response to Neoadjuvant therapy



There is no recommended or agreed system for tumour regression grading (TRG) of ovarian/tubal/peritoneal carcinomas that have been treated with neoadjuvant chemotherapy (this largely applies to pelvic high-grade serous carcinomas) despite the fact that oncologists often request this information because it is potentially a helpful morphological marker to assess the response to neoadjuvant treatment after surgery and identify patients who may be eligible for entry into trials. TRG has been shown to provide valuable prognostic information in patients with carcinomas of the breast, stomach, oesophagus and colorectum who have been treated with neoadjuvant chemotherapy and serves as a morphological marker to guide further treatment after surgery.¹¹⁹⁻¹²³ The applicability of several well-known and widely used systems for TRG has been considered for pelvic gynaecological carcinomas. Some of the systems that are used for breast carcinoma are unduly complex and include the separate assessment of both the primary tumour and involved lymph nodes.¹²⁴⁻¹²⁶ Most of the different TRG systems for gastrointestinal tumours are relatively simple to use,^{120,127,128} although the reported reproducibility of these systems is variable.¹²⁹⁻¹³² TRG is usually applied to the primary site of unifocal tumours in the breast and gastrointestinal tract. In contrast, pelvic high-grade serous carcinomas tend to affect multiple intra-abdominal sites in addition to the primary site of origin. They also typically evoke a desmoplastic host reaction and the inclusions of fibrosis as a criterion for tumour regression has the potential to provide misleading data.



Four studies have assessed tumour regression after neoadjuvant chemotherapy in advanced-stage ovarian cancer and all showed a correlation between response and survival; however, all used different scoring criteria, did not validate their criteria in an independent series of cases, and did not assess reproducibility of their criteria.¹³³⁻¹³⁶ A more recent study has tested and validated the prognostic significance of response criteria, and assessed reproducibility in two independent series of high-grade pelvic serous carcinoma.^{133,137} The latter study suggests that a 3-tier scoring system (the Chemotherapy Response Score [CRS]) is most reproducible and that the system is simple and easy for all pathologists to apply, irrespective of their level of experience in gynaecological pathology. In this study the prognostic significance of the CRS as applied to omental tumour deposits was superior to the CRS of the primary tumour. The study (which included 60 patients in the test cohort and 71 in the validation cohort) used a modification of the Dworak system¹²⁸ and demonstrated good inter-observer reproducibility and significant association with clinical outcome.



Although further studies are needed to confirm the findings, this is the grading system currently recommended by the ICCR. The method is as follows:

1. Scoring should be carried out on a single H&E-stained section (refer to discussion of omental sampling in S2.06 - 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 Chemotherapy Response Score/CRS score of 3 is given - see table below)
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. A 3-tier system for CRS should be used:

Chemotherapy Response Score (CRS)¹³⁷

Score	Criterion	TRG
1	Mainly viable tumour with minimal regression-associated fibro-inflammatory changes* limited to a few foci (>95% tumour viable)	No or minimal tumour response
2	Multifocal or diffuse regression associated fibro-inflammatory changes*, with viable tumour ranging from diffuse sheets, streaks or nodules, to extensive regression with multifocal but easily identifiable residual tumour.	Partial tumour response
3	Mainly regression, with few irregularly scattered individual tumour cells or cell groups (all measuring less than 2 mm), or no residual tumour identified.(<5% tumour viable)	Complete or near-complete response

* 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.

5. 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.
6. As a guide, >95% of tumour should be viable for a score of 1, and <5% for a score of 3.
7. 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.^{133,137} However, the ICCR recommends use of the 3-tier system to gather more data for future studies.

Note that this system has only been applied to high-grade serous carcinomas to date.

Appendix 15 Notes on IHC and Molecular studies



Markers of Use in Typing Ovarian Carcinomas

While most primary ovarian carcinomas are straightforward to type, on occasion it is difficult to distinguish between a high-grade serous carcinoma and a high-grade endometrioid carcinoma, or between a clear cell carcinoma and clear cell areas within a high-grade serous carcinoma or an endometrioid carcinoma. A panel of markers may help which should be tailored depending on the differential diagnosis. Approximately 80-90% of serous carcinomas (low-grade and high-grade) are positive with WT1, usually with diffuse immunoreactivity.^{118,138-142} In contrast, endometrioid and clear cell carcinomas are usually negative, although a small percentage of endometrioid carcinomas are positive.¹⁴³ High-grade serous carcinomas exhibit aberrant "mutation-type" staining with p53 (see below) while low-grade serous carcinomas, clear cell carcinomas and most endometrioid carcinomas exhibit "wild-type" staining (focal and heterogenous); some high-grade endometrioid carcinomas exhibit aberrant p53 staining. p16 is diffusely positive ("block-type" staining) in most high-grade serous carcinomas while most low-grade serous carcinomas, clear cell carcinomas and endometrioid carcinomas exhibit patchy immunoreactivity.¹⁴⁴ Clear cell carcinomas usually exhibit diffuse strong nuclear staining with hepatocyte nuclear factor 1-beta while other primary ovarian epithelial neoplasms are usually negative or focally positive.^{145,146} Napsin A is also a useful marker of clear cell carcinomas.¹⁴⁷ ER is positive in most high-grade and low-grade serous carcinomas and endometrioid carcinomas while clear cell carcinomas are usually negative. Some of these markers have helped establish that most neoplasms which were previously classified as mixed high-grade serous and endometrioid and mixed high-grade serous and clear cell represent high-grade serous carcinomas with pseudoendometrioid areas and areas of cytoplasmic clearing.



On occasion, especially in a biopsy specimen, it may be problematic to differentiate between a low-grade and a high-grade serous small carcinoma. The most useful marker in this scenario is p53 ("mutation-type" staining in high-grade serous carcinoma; "wild-type" staining in low-grade serous carcinoma).



Distinction Between Primary and Secondary Ovarian Adenocarcinoma

The distinction between a primary ovarian adenocarcinoma and metastatic adenocarcinoma from various sites may be problematic.¹⁴⁸ Metastatic colorectal adenocarcinomas may mimic an endometrioid carcinoma or a mucinous neoplasm of intestinal type, either borderline or malignant. In the distinction between an ovarian endometrioid adenocarcinoma and a metastatic colorectal adenocarcinoma with a pseudoendometrioid pattern, a panel of markers may assist. While there may be immunophenotypic overlap of individual markers, primary ovarian endometrioid carcinomas are usually positive with CK7, ER, CA125 and PAX8 and negative with CK20, CEA and CDX2 while the converse immunophenotype is the rule in metastatic colorectal adenocarcinomas.³³⁻³⁵ In distinguishing between a primary ovarian mucinous tumour and a metastatic colorectal adenocarcinoma, immunohistochemistry is less helpful. This is because many primary ovarian mucinous neoplasms exhibit CK20 positivity, usually focal but sometimes widespread. They are also commonly positive, sometimes diffusely so, with CEA, CDX2 and CA19.9. The expression of these enteric markers is a reflection of intestinal differentiation in primary ovarian mucinous neoplasms. However, the pattern of coordinate expression of CK7/CK20 may assist in distinguishing between

a primary ovarian mucinous tumour and a metastatic colorectal adenocarcinoma with a mucinous appearance. Although either marker can be positive in both tumours, primary ovarian mucinous neoplasms are often diffusely positive with CK7 while CK20 is variable; conversely metastatic colonic adenocarcinoma is usually diffusely positive with CK20 and focally positive with CK7 when this marker is expressed. Thus, CK7 immunopositivity is typically of greater extent than CK20 immunopositivity in primary ovarian mucinous tumours and CK20 staining is more extensive than CK7 in metastatic colonic adenocarcinoma.¹⁴⁹

 Metastatic pancreatic or biliary adenocarcinoma may mimic a primary ovarian mucinous neoplasm of intestinal type, either borderline or malignant and immunohistochemistry is of limited value. Most commonly, these tumour types are diffusely positive with CK7 while CK20 is variable, being negative, focally or diffusely positive. CEA, CA19.9 and CDX2 may be positive. An absence of staining with DPC4 (DPC = deleted in pancreatic cancer) may be a useful pointer towards a pancreatic adenocarcinoma since this nuclear transcription factor is inactivated in about 50% of pancreatic adenocarcinomas with the result that approximately half of these are negative.¹⁵⁰ Conversely, DPC4 is expressed in virtually all primary ovarian mucinous neoplasms.

 Metastatic breast carcinomas of ductal type may mimic a high grade serous carcinoma or an endometrioid carcinoma. It is a not uncommon scenario that a patient with a history of breast carcinoma is found to have a pelvic mass or a disseminated peritoneal malignancy. In most cases, this will represent a new tubo-ovarian high grade serous carcinoma; such patients may or may not have underlying *BRCA1/2* mutation. In distinguishing between a metastatic breast carcinoma and a tubo-ovarian high grade serous carcinoma, markers which may be useful are PAX8, CA125 and WT1 (usually positive in high grade serous carcinomas and negative in breast carcinomas, although occasionally the latter are CA125 or WT1 positive) and GCDFP15, mammoglobin and GATA3 (usually negative in high grade serous carcinomas and positive in breast carcinomas).¹⁵¹⁻¹⁵³ A similar panel of markers is useful in the distinction between an endometrioid carcinoma and a metastatic breast carcinoma, although WT1 is negative in endometrioid carcinomas and a proportion of these may be mammoglobin positive.¹⁵⁴

 Rarely, a metastatic cervical adenocarcinoma of usual type (HPV related) in the ovary may mimic a primary ovarian mucinous or endometrioid neoplasm.¹⁵⁵ Diffuse p16 immunoreactivity in such cases may be useful in suggesting a metastatic cervical adenocarcinoma.

Distinction Between Ovarian Endometrioid Carcinoma and Sex Cord-Stromal Tumour

Some primary ovarian carcinomas, especially of endometrioid type, 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.¹⁵⁶ Markers which are useful to distinguish between an endometrioid neoplasm and a sex cord-stromal tumour include inhibin, calretinin and steroidogenic factor-1 (SF-1; positive in sex cord-stromal tumours) and epithelial membrane antigen and CK7 (positive in epithelial neoplasms).^{33-35,156-158}

Diagnosis of Serous Tubal Intraepithelial Carcinoma (STIC)

Biomarkers are not necessary if the features are unequivocally those of STIC but if there is diagnostic uncertainty, both p53 and MIB1 staining should be performed.¹⁵⁹ The cells must exhibit aberrant p53 staining (see definition below). The MIB1 proliferative

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 MIB1 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 immunohistochemistry is undertaken (morphological features and aberrant p53 staining are also needed).¹⁵⁹

Two Patterns of Aberrant p53 Staining

There is significant variability amongst pathologists in the interpretation of p53 staining. Pathologists are often unaware that many normal tissues and tumours unassociated with *TP53* abnormalities express p53 protein. Such staining is usually focal and weak and somewhat variable from area to area (referred to as "wild-type" p53 staining), although on occasions many of the nuclei are positive, albeit with variable intensity. The degree of positive staining can be affected by varying the antibody concentration used.¹⁶⁰ This pattern of staining is found in many normal tissues (non-neoplastic epithelia, stromal and lymphoid cells which can act as an internal positive control) and neoplasms not related to *TP53* mutation. Rather than this "wild-type" staining, it is the diffuse intense pattern of nuclear immunoreactivity which should be interpreted as "positive" and which is correlated with *TP53* missense mutations. Typically in excess of 75% and sometimes almost all of the nuclei are intensely positive. It should also be appreciated that totally absent p53 staining (as stated, there is usually an inbuilt positive control with "wild-type" staining of non-neoplastic tissues) is also indicative of aberrant p53 immunoreactivity.^{161,162} This pattern of immunoreactivity is in keeping with a null (including non-sense, frame shift or splice site) *TP53* mutation resulting in complete absence of detectable protein. To summarise, it is not simply negative or positive staining but rather patterns of p53 immunoreactivity which are of importance. Diffuse intense nuclear immunoreactivity and totally absent staining ("all or nothing") are aberrant patterns ("mutation-type" staining) and in keeping with an underlying *TP53* mutation while "wild-type" staining is not.

Distinction Between Ovarian and Uterine Carcinoma

A not uncommon scenario is simultaneous involvement of the uterine corpus and one or both ovaries by an adenocarcinoma. Most commonly, the adenocarcinomas are endometrioid in type but sometimes they are serous.^{163,164} With endometrioid adenocarcinomas involving the uterus and one or both ovaries, immunohistochemistry is of little or no value in ascertaining the relationship between the tumours as the immunophenotype of a primary ovarian and uterine endometrioid adenocarcinoma is essentially identical.

 With a serous carcinoma involving the uterus and one or both ovaries, WT1 staining may be of some value in distinguishing between a uterine serous carcinoma with metastasis to the ovary, metastasis from the ovary/tube to the endometrium ("drop metastasis") and independent synchronous neoplasms, the latter being unlikely.^{118,138-142,165} Most tubo-ovarian serous carcinomas exhibit diffuse nuclear positivity with WT1 while most uterine serous carcinomas are negative. However, there is some overlap in that a proportion of uterine serous carcinomas are WT1 positive (the percentage has varied between studies) and a small percentage of tubo-ovarian high-grade serous carcinomas are WT1 negative.^{118,138-142} It can be summarized that, although there is some overlap, diffuse WT1 positivity in a serous neoplasm favours a tubo-ovarian origin. In contrast, negative staining is a pointer towards a primary uterine neoplasm.



Distinction Between Serous and Mesothelial Proliferation

On occasion it may be difficult to distinguish between a serous proliferation (borderline or malignant) and a mesothelial proliferation (reactive or neoplastic). Florid reactive mesothelial proliferation may occur in association with endometriosis and mimic an endometrioid carcinoma.¹⁶⁶ A suggested panel of markers in this situation would include BerEP4, ER and PAX8 (usually positive in serous proliferations and endometrioid carcinomas) and calretinin and CK5/6 (usually positive in mesothelial proliferations). WT1 is usually positive in both serous and mesothelial proliferations.



Molecular studies



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.¹⁶⁷ 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



High-grade serous carcinomas are chromosomally unstable tumours, in which *TP53* mutations are ubiquitous. Germ-line 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.¹⁶⁸ 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. 33% of the tumours showed alterations in *BRCA* genes, either somatic or germline mutations or promoter hypermethylation.



Low-grade serous carcinomas are closely related to serous borderline tumours, and show frequent mutations in *KRAS* (19%) and *BRAF* (38 %), which are mutually exclusive events.



The molecular events in endometrioid adenocarcinoma are similar to the uterine counterpart. The main molecular alterations are: microsatellite instability (12 - 20%), and mutations in the *PTEN* (20%), *KRAS*, and *PIK3CA* genes. Mutations in exon 3 of *CTNNB1* with nuclear accumulation of beta-catenin occur in 38 - 50% of cases. Mutation of the *ARID1A* gene has recently been described.¹⁶⁹



Clear cell carcinoma shows frequent *PIK3CA* mutations, and also *PTEN* inactivation. Alterations in *KRAS* and *Tp53* are unusual. Mutation of the *ARID1A* gene and loss of the corresponding protein BAF250a has recently been described, occurring in 50% of the tumours. They also show up-regulation of *HNF-1-beta*.



Mucinous carcinomas frequently contain *KRAS* mutations.¹⁷⁰ 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 tumorigenesis. However, in general, *KRAS* mutations are more frequent

in carcinomas in comparison with benign mucinous tumours. Amplification of *c-erbB2* is sometimes seen in mucinous carcinomas.

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