GASTRIC CANCER
STRUCTURED REPORTING PROTOCOL
(2nd Edition, 2020)

Incorporating the:
International Collaboration on Cancer Reporting (ICCR)
Carcinoma of the Stomach Dataset
www.ICCR-Cancer.org
Core Document versions:

- ICCR dataset: Carcinoma of the Stomach 1st edition
- AJCC Cancer Staging Manual 8th edition
- Digestive System Tumours, World Health Organization Classification of Tumours, 5th Edition, Volume 1, 2019
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   - Numbering of Standards and Guidelines must be retained in the checklist, but can be reduced in size, moved to the end of the checklist item or greyed out or other means to minimise the visual impact.
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Gastric Cancer Structured Reporting Protocol 2nd edition
Scope

This protocol contains standards and guidelines for the preparation of structured reports for gastric cancer. Total and partial gastrectomies are included in this document and a separate protocol is available for endoscopic resections. Endoscopic biopsy specimens are excluded. Carcinomas involving the oesophagogastric junction (OGJ) with their epicentre >20 millimetres (mm) into the proximal stomach and cardia cancers that do not involve the OGJ are included. These criteria are set by the World Health Organization (WHO) and define the diagnosis ‘gastric cancer’. For all other tumours involving the OGJ, please refer to the protocol for oesophageal cancers.

Neuroendocrine carcinomas (NEC) and mixed neuroendocrine-non-neuroendocrine neoplasms (MiNENs) (with exception of mixed adenoma and well-differentiated neuroendocrine tumour (NET)) are included in this protocol. Well-differentiated NETs, non-epithelial malignancies, and secondary tumours are excluded from this protocol.

Structured reporting aims to improve the completeness and usability of pathology reports for clinicians and improve decision support for cancer treatment. This protocol can be used to define and report the minimum dataset, but the structure is scalable and can equally accommodate a maximum data set or fully comprehensive report.
# Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>AJCC</td>
<td>American Joint Committee on Cancer</td>
</tr>
<tr>
<td>CAP</td>
<td>College of American Pathologists</td>
</tr>
<tr>
<td>CIMP</td>
<td>CpG island methylation</td>
</tr>
<tr>
<td>CPS</td>
<td>Combined positive score</td>
</tr>
<tr>
<td>CRM</td>
<td>Circumferential resection margin</td>
</tr>
<tr>
<td>dMMR</td>
<td>Mismatch repair deficiency</td>
</tr>
<tr>
<td>EBER</td>
<td>Epstein Barr virus-encoded small RNAs</td>
</tr>
<tr>
<td>EBV</td>
<td>Epstein Barr virus</td>
</tr>
<tr>
<td>EGC</td>
<td>Early gastric cancer</td>
</tr>
<tr>
<td>EMR</td>
<td>Endoscopic mucosal resections</td>
</tr>
<tr>
<td>ESD</td>
<td>Endoscopic submucosal dissections</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>FISH</td>
<td>Fluorescence in situ hybridisation</td>
</tr>
<tr>
<td>IARC</td>
<td>International Agency for Research on Cancer</td>
</tr>
<tr>
<td>ICCR</td>
<td>International Collaboration on Cancer Reporting</td>
</tr>
<tr>
<td>IHC</td>
<td>Immunohistochemistry</td>
</tr>
<tr>
<td>ISH</td>
<td>In situ hybridisation</td>
</tr>
<tr>
<td>JGCA</td>
<td>Japanese Gastric Cancer Association</td>
</tr>
<tr>
<td>LBC</td>
<td>Lobular breast carcinoma</td>
</tr>
<tr>
<td>LIS</td>
<td>Laboratory information system</td>
</tr>
<tr>
<td>MiNEN</td>
<td>Mixed neuroendocrine-non-neuroendocrine neoplasm</td>
</tr>
<tr>
<td>MMR</td>
<td>Mismatch repair</td>
</tr>
<tr>
<td>MSI</td>
<td>Microsatellite instability</td>
</tr>
<tr>
<td>NEC</td>
<td>Neuroendocrine carcinoma</td>
</tr>
<tr>
<td>NET</td>
<td>Neuroendocrine tumour</td>
</tr>
<tr>
<td>NCCN</td>
<td>National Comprehensive Cancer Network</td>
</tr>
<tr>
<td>NHMRC</td>
<td>National Health and Medical Research Council</td>
</tr>
<tr>
<td>OGJ</td>
<td>Oesophaegogastric junction</td>
</tr>
<tr>
<td>PBS</td>
<td>Pharmaceutical Benefits Scheme</td>
</tr>
<tr>
<td>PCR</td>
<td>Polymerase chain reaction</td>
</tr>
<tr>
<td>RCPA</td>
<td>Royal College of Pathologists of Australasia</td>
</tr>
<tr>
<td>TGA</td>
<td>Therapeutic Goods Administration</td>
</tr>
<tr>
<td>TNM</td>
<td>Tumour-node-metastasis</td>
</tr>
<tr>
<td>UICC</td>
<td>Union for International Cancer Control</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
</tbody>
</table>
## 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.

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ancillary study</td>
<td>An ancillary study is any pathology investigation that may form part of a cancer pathology report but is not part of routine histological assessment.</td>
</tr>
<tr>
<td>Clinical information</td>
<td>Patient information required to inform pathological assessment, usually provided with the specimen request form, also referred to as “pre-test information”.</td>
</tr>
</tbody>
</table>
| 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 (e.g. CS1.01a, CG2.05b). |
| General commentary | General commentary is text that is not associated with a specific standard or guideline. It is used:  
  - 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). |
| Guideline      | 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 National Health and Medical Research Council (NHMRC) level III-2 evidence. These elements may be clinically... |
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.

Guidelines are not used for research items.

In this document, guidelines are prefixed with ‘G’ and numbered consecutively within each chapter (eg G1.10).

**Macroscopic findings**

Measurements, or assessment of a biopsy or resection specimen made by the unaided eye.

**Microscopic findings**

In this document, the term ‘microscopic findings’ refers to 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**

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 evidence 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 e.g. 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.

The summation of all standards represents the minimum dataset for the cancer.

In this document, standards are prefixed with ‘S’ and numbered consecutively within each chapter (e.g. 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 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

Gastric Cancer

Gastric cancer incidence and mortality varies according to geography, lifestyle factors, ethnicity and infectious agents. Globally gastric cancer has the third highest incidence of cancer-related deaths as at 2017. Although in Australia and New Zealand the gastric cancer incidence remains relatively low as does the 5-year relative survival rate, gastric cancer remains a significant healthcare issue. As advances have been made in the biological and molecular processes involved in this disease, there has been development of new surgical, immunotherapeutic and chemotherapeutic strategies.

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 Tumour-Node-Metastasis (TNM) 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 around the world. Both the United Kingdom and United States 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 i.e. cancer registries.

International Collaboration on Cancer Reporting

The International Collaboration on Cancer Reporting (ICCR), founded in 2011 by the Royal College of Pathologists of Australasia (RCPA), United States College of American Pathologists (US CAP) and Royal College of Pathologists United Kingdom (RCPath UK) and the Canadian Association of Pathology - Association Canadienne des Pathologistes (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 1
the ease and completeness of data capture\textsuperscript{9-12} 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](http://www.ICCR-Cancer.org)

**Design of this protocol**

This structured reporting protocol has been developed using the ICCR dataset on Carcinoma of the Stomach 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 stomach.

ICCR dataset elements for carcinomas of the stomach 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 is boarded by a grey box as shown below:

| ICCR G3.02 | The intraglandular extent should be recorded as a percentage. |

Additional commentary by the RCPA expert committee may be added to an ICCR element but is not included in the grey bordered area e.g.

| ICCR G2.03 | If present, the laterality of the lymph nodes submitted may be recorded as left, right or bilateral. |
| 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](http://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 documentation**

- *Guidelines for Authors of Structured Cancer Pathology Reporting Protocols*\(^\text{13}\)
- *The Pathology Request-Test-Report Cycle — Guidelines for Requesters and Pathology Provider*\(^\text{14}\)
- *ICCR dataset: Carcinoma of the Stomach 1\(^{st}\) edition*
- *WHO Classification of tumours, Pathology and Genetics of Tumours of the Digestive System, 2019, 5\(^{th}\) edition*\(^\text{15}\)
- *AJCC Cancer Staging Manual, 8\(^{th}\) edition, 2017*\(^\text{16}\)

**Changes since the last edition**

Inclusion of ICCR Core and Non-core elements.
Authority and development

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

This 2\textsuperscript{nd} edition of the protocol is an amalgam of two separate processes:

1. This protocol is based on the ICCR dataset for Carcinomas of the Stomach 1\textsuperscript{st} edition. 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 e.g. example reports, request information etc, have also been added.

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Acknowledgements
The gastric tumour expert committee wish to thank all the pathologists and clinicians who contributed to the discussion around this document.
Stakeholders

ACT Cancer Registry
ACT Health
Australasian Gastro-Intestinal Trials Group (AGITG)
Australian Gastrointestinal Pathology Society (AGPS)
Anatomical Pathology Advisory Committee (APAC)
Australian Commission on Safety and Quality in Health Care
Australian Digital Health Agency (ADHA)
Australian Institute of Health and Welfare (AIHW)
Cancer Australia
Cancer Council ACT
Cancer Council Australia and Australian Cancer Network (ACN)
Cancer Council NSW
Cancer Council Queensland
Cancer Council SA
Cancer Council Tasmania
Cancer Council Victoria
Cancer Council Western Australia
Cancer Institute NSW
Cancer Services Advisory Committee (CanSAC)
Cancer specific expert groups – engaged in the development of the protocols
Cancer Voices Australia
Cancer Voices NSW
Clinical Oncology Society of Australia (COSA)
Department of Health, Australian Government
Gastroenterological Society of Australia (GESA)
Health Informatics Society of Australia (HISA)
Independent Review Group of Pathologists
Medical Oncology Group of Australia (MOGA)
Medical Software Industry Association (MSIA)
National Pathology Accreditation Advisory Council (NPAAC)
New Zealand Committee of Pathologists
New Zealand Cancer Control Agency
New Zealand Cancer Registry
New Zealand Society of Gastroenterology (NZSG)
Australian Pathology
Public Pathology Australia
Queensland Cooperative Oncology Group (QCOG)
Representatives from laboratories specialising in anatomical pathology across Australia
Royal Australasian College of Physicians (RACP)
Royal Australasian College of Surgeons (RACS)
Royal Australian and New Zealand College of Radiologists (RANZCR)
Royal Australian College of General Practitioners (RACGP)
Royal College of Pathologists of Australasia (RCPA)
South Australia Cancer Registry
Southern Cancer Network, Christchurch, New Zealand
Standards Australia
Tasmanian Cancer Registry
Victorian Cancer Registry
Western Australia Clinical Oncology Group (WACOG)
Western Australian Cancer Registry

Development process
This protocol has been developed following the nine-step process set out in Guidelines for Authors of Structured Cancer Pathology Reporting Protocols.²⁷
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 gastric cancer, 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 must be adhered to.17 This document specifies the minimum information to be provided by the requesting clinician for any pathology test.

CS1.01b Ideally the laboratory information system (LIS) should include documentation as to whether or not the patient identifies as Aboriginal and/or Torres Strait Islander in Australia, or Māori in New Zealand. This is in support of government initiatives to monitor the health of those who identify as indigenous, particularly in relation to cancer.

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 Individual Healthcare Identifier (IHI) (Australia) or the National Healthcare Index (New Zealand).

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

CS1.02a In most cases all clinical information should be transcribed. However, in a small number of cases the pathologist may exercise discretion regarding the inclusion of provided clinical information, for instance, possibly erroneous information or information that may impact on patient privacy. In such case reference should be made as to the location of the complete clinical information e.g. “Further clinical information is available from the scanned request form.”

G1.01 The Copy To doctors requested on the request form should be recorded.

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.
The principal clinician can provide key information regarding the clinical presentation of the patient. Follow up may be required with the principal clinician for a number of reasons:

- The clinical assessment and staging may be incomplete at the time of biopsy.
- The pathology request is often authored by the clinician performing the biopsy 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.

In practice therefore, it is important in such cases that the reporting pathologist should be able to communicate with the managing clinician for clarification.

The Australian Healthcare identifiers ie Healthcare Provider Identifier - Individual (HPI-I) and Healthcare Provider Identifier - Organisation (HPI-O) should be included, where possible, to identify the principal clinician involved in the patient's care.

Any additional relevant information should be recorded.

There should be a free text field so that the referring doctor can add anything that is not addressed by the above points, such as previous cancers, risk factors, investigations, treatments and family history.
2 Specimen handling and macroscopic findings

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 if the pathologist is sure that the diagnostic process will not be compromised. As a safeguard, research use of the tissue samples may be put on hold until the diagnostic process is complete.
- If tissue is sampled for banking or research then this should be done in consultation with a pathologist and recorded in the report.

Specimen handling

- Detailed fixation and specimen handling instructions are available from the RCPA online Cut-up Manual:
- 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 including the measurement of maximum depth of invasion and other important parameters that influence patient prognosis and management will not be compromised. As a safeguard, research use of the specimen may be put on hold until the diagnostic process is complete so that the specimen can be retrieved.
- The specimen must be handled in a systematic and thorough fashion to ensure completeness and accuracy of pathological data.

Macroscopic findings

<table>
<thead>
<tr>
<th>S2.01</th>
<th>The labelling of the specimen(s) must be clearly recorded.</th>
</tr>
</thead>
<tbody>
<tr>
<td>S2.02</td>
<td>Clinical information must be recorded.</td>
</tr>
<tr>
<td>CS2.02a</td>
<td>Clinical information including preoperative neoadjuvant therapy and prior endoscopic resection can be provided by the clinician on the endoscopy report or the pathology</td>
</tr>
</tbody>
</table>
request form. Patient medical records may be another source of information if accessible.

Relevant biopsy results include the presence of carcinoma, dysplasia (glandular intraepithelial neoplasia), intestinal metaplasia, etc. Endoscopic tumour location or information on the tumour location as reported by the clinician are important guides as the tumour epicentre may be altered after neoadjuvant therapy.

Multiple tumours may occur in the stomach and previous history of cancer or cancer treatment is relevant. A number of conditions, including previous partial gastrectomy for benign disease and chronic atrophic gastritis, are risk factors for gastric cancer.

**S2.03** The operative procedure must be recorded.

**CS2.03a** Depending on the tumour location and tumour type, gastric resection can be described as:\(^{18}\)

1. Total gastrectomy: for tumours located in the body/corpus of the stomach, tumours in the cardia, and diffuse gastric cancer (including prophylactic gastrectomy for patients with hereditary diffuse gastric cancer).
2. Sub-total distal gastrectomy: for tumours located in the antrum (distal third and pylorus).
3. Oesophagogastrectomy: for gastric tumours extending into the lower oesophagus.

Prophylactic gastrectomy is a type of total gastrectomy specifically performed for patients with hereditary diffuse gastric cancer with a germline $CDH1$ or $CTNNA1$ mutation. The proximal and distal margins should not contain any gastric mucosa, which can be confirmed by frozen section during surgery.$^{19,20}$

**CS2.03b** Please refer to the relevant RCPA protocol for endoscopic resections.

**S2.04** The specimen dimensions must be recorded.

**CS2.04a** There is no official agreement or recommendation on how specimens should be measured and whether they should be measured fresh or after formalin-fixation. While most specimens are measured after fixation, gastrectomy specimens may be measured fresh for reasons such as frozen section evaluation of margins and biobanking of fresh tissue for research. Significant shrinkage of unpinned gastrointestinal tract specimens occurs after fixation. Pinning out the specimens on a card board during fixation helps to restore most of the specimen length.$^{21}$ It should be commented in the report if the dimensions are taken from a fixed but unpinned specimen.
**S2.05 Tumour focality must be recorded.**

| CS2.05a | While multifocal gastric carcinomas are rare, they should be documented. If multiple primary tumours are present, separate protocols should be used to describe this and all following elements for each primary tumour. |

---

**S2.06 The tumour site (location) must be recorded.**

| CS2.06a | The stomach is divided into the cardia, fundus, body, antrum and pylorus, but these regions are difficult to define macroscopically, especially for the cardia and fundus. The Japanese Gastric Cancer Association (JGCA) guidelines divide the stomach into upper third, middle third and distal third by the lines connecting the trisected points on the lesser and greater curvatures. Primary gastric cancer in the upper third of the stomach, especially at the OGJ/cardia, are reported to be more aggressive and associated with poor prognosis.

The OGJ is defined as the border between the oesophageal and gastric muscles, irrespective of the type of epithelial lining of the oesophagus. However, it can be challenging to determine the exact location of the OGJ, especially in individuals with conditions affecting OGJ landmarks. Four methods have been proposed to locate the OGJ anatomically:

1. The distal end of the longitudinal palisading small vessels in the lower oesophagus. It can be seen endoscopically as well as microscopically and is commonly used by Japanese pathologists. However, it can be obscured by inflammation.
2. The horizontal level of the angle of His (defined as starting from the peritoneal reflection of the stomach onto the diaphragm), as shown by barium meal examination. It can be altered by hiatal hernia or tumour invasion.
3. The proximal end of the gastric longitudinal mucosal folds, which is the most commonly used definition by endoscopists in Western countries. However, it can be obscured by the presence of gastric mucosal atrophy (i.e. post chemoradiation therapy and atrophic gastritis) or a large gastric mass.
4. The level of the macroscopic calibre changes of the resected oesophagus and stomach.

The current recommendation is to use the proximal end of the gastric longitudinal mucosal folds as the landmark for the OGJ. If it cannot be identified, use the distal end of the longitudinal palisading small vessels, which can also be identified microscopically. |
The Siewert classification categorizes OGJ cancer into Siewert type I (tumours with their epicentre located 1-5 cm above the OGJ), type II (tumour epicentre located from 1 cm above to 2 cm below the OGJ) and type III (tumour epicentre located from 2 cm - 5 cm below the OGJ). In the Siewert classification, the proximal end of the gastric longitudinal mucosa folds is used as pragmatic reference for the endoscopic cardia/OGJ (zero point). The current Union for International Cancer Control (UICC)/American Joint Committee on Cancer (AJCC) 8th edition definition of gastric cancer includes those involving OGJ but with epicentre >2 cm into proximal stomach and cardia cancer without involvement of OGJ (Figure 1). Refer to ICCR dataset for full commentary.

Preoperative chemotherapy/chemoradiation therapy can have an asymmetrical effect on the tumour, which might be problematic when attempting to determine the precise location of cancers adjacent to the OGJ. The asymmetric effect could alter the tumour epicentre in the resected specimen and may lead to misclassification of the tumour (oesophageal versus gastric cancer). Pretreatment tumour epicentre/tumour location information should be used as the tumour site if available.

<table>
<thead>
<tr>
<th>S2.07</th>
<th>The maximum tumour diameter must be recorded.</th>
</tr>
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<tbody>
<tr>
<td>CS2.07a</td>
<td>Tumour size is not used in staging gastric cancers. While some studies reported no prognostic role of tumour size, others suggest that tumour size may be an independent prognostic factor and that large tumour size is associated with undifferentiated cancer, serosal involvement, peritoneal metastasis, and poor survival in patients with stage II and III gastric cancers. Tumour size may vary, depending on measurements taken before or after fixation. A study on oesophageal cancers demonstrated 10% reduction in tumour size after fixation, which may also be true for gastric cancers. In most cases, tumour dimension/size can be measured macroscopically. Measurement of diffuse type gastric carcinoma (limitis plastica) requires both macroscopic and microscopic assessment. After neoadjuvant therapy, the presumed tumour bed should be measured, but the macroscopic tumour dimension needs to be confirmed microscopically. According to the UICC/AJCC 8th editions, acellular mucin pools and fibrosis with no viable tumour cells should be considered negative for residual carcinoma, and the size of viable tumour should be measured as the tumour dimension. If there is no tumour visible macroscopically, or for small residual tumours where the macroscopic dimensions may not be accurate, the microscopic dimensions should be documented. Precursors (e.g. low and high grade dysplasia) should be excluded from the measurement. For multiple discontinuous foci of residual carcinoma, it is recommended to measure the maximum dimension covering all foci.</td>
</tr>
</tbody>
</table>

13

*Gastric Cancer Structured Reporting Protocol 2nd edition*
<table>
<thead>
<tr>
<th>G2.01</th>
<th>The macroscopic tumour type should be recorded.</th>
</tr>
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<tbody>
<tr>
<td>CG2.01a</td>
<td>According to the Borrmann classification (Figure 2), growth patterns of advanced gastric cancer can be classified as polypoid mass (Borrmann type I), ulcerative (Borrmann type II), infiltrative ulcerative (Borrmann type III), or diffuse infiltrative (Borrmann type IV). Borrmann type II is the most common macroscopic type among advanced gastric cancers. Borrmann type IV is associated with a poor prognosis. Borrmann classification is based on untreated gastric cancers, and therefore may not be applicable after neoadjuvant treatment. ‘Other’ can be selected when Borrmann macroscopic tumour type cannot be assigned due to neoadjuvant treatment.</td>
</tr>
</tbody>
</table>

**CG2.01b** Early gastric cancer growth patterns are classified using criteria similar to those used in endoscopy, into protruded, elevated, flat, depressed or excavated (Figure 3). Depressed type has a higher risk for increased stage and lymphatic invasion.

**S2.08** The distance from the tumour to the nearest proximal or distal margin (cut end) must be recorded.

**CS2.08a** Tumour distance to margins is based on macroscopic assessment, confirmed or amended on microscopy, this is of particular relevance where the macroscopic size may be difficult to assess, such as early gastric carcinoma and diffuse carcinoma (linitis plastica).

**S2.09** For tumours of the cardia, the distance from the tumour to the circumferential resection margin (CRM) must be recorded.

**CS2.09a** Assessment of the distance between the tumour and the CRM is facilitated by horizontal sectioning through the tumour. To increase accuracy, the distance between the tumour and the CRM is subsequently measured microscopically. Involvement of the CRM is an indicator of poor prognosis.

**S2.10** The appearance of the serosa must be recorded.

**CS2.10a** Any abnormalities, nodule or plaques should be described as they may represent serosal involvement by carcinoma. Serosal involvement upstages a gastric carcinoma from T3 to T4.

**S2.11** The involvement of adjacent organs must be recorded.

**CS2.11a** Involvement of adjacent organs, either resected or not resected, is required for assessment of the tumour (T) stage of the tumour. Unless obvious, the area of involvement should be marked with a suture or other marker.

**CS2.11b** Select all that apply:
• Pancreas
• Spleen
• Liver
• Other, specify

S2.12 The presence of any distant metastases must be recorded.

CS2.12a The reporting of metastatic deposits, either resected or not resected, is required for assessment of the metastatic (M) stage of the tumour. The sites of such deposits should be stated.

CS2.12b Additional specimens taken e.g. peritoneal nodules, liver biopsy, other etc should be labelled and recorded separately.

CS2.12c The presence of positive peritoneal cytology is classified as metastatic disease.

S2.13 A block identification key listing the nature and origin of all tissue blocks must be recorded.

CS2.13a The origin/designation of all tissue blocks must 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. Where appropriate, specimen photographs and block diagrams should be utilised.

Recording the origin/designation of tissue blocks also facilitates retrieval of blocks for further immunohistochemical or molecular analysis, research studies or clinical trials. Ideally, the optimal block for molecular studies should be recorded.

CS2.13b As per ICCR “If there is no tumour visible on macroscopic examination, the entire assumed tumour bed should be processed into paraffin blocks in order to correctly stage tumours and evaluate treatment response. However, there is no standard protocol for grossing specimens with macroscopically visible residual carcinoma. Most pathologists gross these specimens similar to those without pre-operative treatment.” (refer to S3.08a).

G2.02 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.

CG2.02a 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.

CG2.02b 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.

Figure 1: (A) OJG tumours with their epicentre located >2 cm into the proximal stomach are staged as stomach cancers. (B) Cardia cancers not involving the OJG are staged as stomach cancers. (C) Tumours involving the OJG with their epicentre <2 cm into the proximal stomach are staged as oesophageal cancer. Reproduced with permission from Amin MB, Edge SB and Greene FL et al (eds) (2017). American Joint Committee on Cancer Staging Manual. 8th ed., Springer, New York.16
Figure 2: Macroscopic types of advanced gastric cancer. Type 1 (mass): polypoid tumours, sharply demarcated from the surrounding mucosa. Type 2 (ulcerative): ulcerated tumours with raised margins surrounded by a thickened gastric wall with clear margins. Type 3 (infiltrative ulcerative): ulcerated tumours with raised margins, surrounded by a thickened gastric wall without clear margins. Type 4 (diffuse infiltrative): tumours without marked ulceration or raised margins; the gastric wall is thickened and indurated and the margin is unclear. © World Health Organization/International Agency for Research on Cancer (IARC). Reproduced with permission.
**Figure 3: Subclassification of Type 0.** Reproduced with permission from Japanese Gastric Cancer Association (2011). Japanese classification of gastric carcinoma: 3rd English edition. Springer; London. Copyright © The Author(s) 2016. Open Access - This content is distributed under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/)
3 Microscopic findings

Microscopic findings relate to purely histological (morphological) assessment. Information derived from multiple investigational modalities, or from two or more chapters, are described in Chapter 5.

S3.01 The microscopic tumour site (location) must be recorded.

CS3.01a The location should be stated in terms of the gastric region (cardia, fundus, body, antrum, pylorus), curvature (greater curvature, lesser curvature) and wall (anterior wall, posterior wall). See S2.05b.

CS3.01b For proximal (cardia) tumours: The tumour location should be explicitly recorded after microscopic confirmation as the microscopic location of the tumour may be different to the macroscopic location.

S3.02 The histological tumour type must be recorded.

CS3.02a Several classification schemes have been used for subtyping gastric carcinomas histologically, including the Lauren, Nakamura, JGCA, WHO (Appendix 4, Table 1) and Ming classifications. For consistency in reporting, the WHO histological classification of gastric carcinomas is recommended (Table 2). The Lauren classification is also widely used for gastric adenocarcinomas. In the Lauren classification, gastric adenocarcinomas are simply divided into two histological subtypes - intestinal type and diffuse type. Gastric carcinomas that do not fit into one of the two are placed into the mixed or indeterminate categories. The Lauren classification provides a simplified categorisation of common types of gastric carcinoma and may offer a better understanding of their biology and behaviour compared to the WHO classification. However, unlike the WHO classification, the Lauren classification cannot be applied to a variety of rare histologic subtypes.

Results on the prognostic value of histological types in gastric cancer are conflicting. While many studies have reported that diffuse, signet ring and anaplastic carcinomas confer an unfavourable prognosis, some multivariate studies show no effect of tumour type, independent of stage, on prognosis which might be explained by inconsistent histology typing by pathologists. See Appendix 4 Histological types.

CS3.02b The histological type of the tumour should be recorded based on the current WHO classification (refer to Appendix 5).

CS3.02c The histological type of the tumour should be recorded based on the Lauren classification.

S3.03 The histological grade must be recorded.
According to the WHO Classification of Tumours of the Digestive System, 5th edition, 2019, histological tumour grade applies primarily to tubular and papillary adenocarcinomas. The WHO classification recommends a two-tiered system: low grade (well and moderately differentiated) and high grade (poorly differentiated). The Stomach Carcinoma dataset authoring committee recommends the two-tiered WHO grading system because both well and moderately differentiated tumours are considered differentiated and this grading system is highly reproducible.

It is noted that a three-tiered system is recommended by the UICC/AJCC 8th edition staging system as follows:  
- G1: Well differentiated  
- G2: Moderately differentiated  
- G3: Poorly differentiated, undifferentiated

The AJCC 8th edition recommend that the highest is recorded if there is evidence of more than one grade or level of differentiation of the tumour. Histopathological grading does not independently affect patient survival after R0 resection; however, poor histopathological grade is associated with high rate of R1 and R2 resections. Assessment of histological grades may not be feasible in gastric cancers with prominent treatment response.

Signet-ring cell carcinomas are classified as grade 3. Small cell carcinomas and undifferentiated carcinomas are not graded.

The extent of invasion must be recorded.

Surgical resection specimens should be assessed for depth of tumour invasion, as this is an independent prognostic factor. Invasion into the serosa is associated with peritoneal recurrence and poor prognosis. Gastric cancer can directly invade into adjacent structures/organs, which include the spleen, transverse colon, liver, diaphragm, pancreas, abdominal wall, adrenal gland, kidney, small intestine and retroperitoneum. Direct infiltration of the duodenum or oesophagus is not considered invasion to adjacent organ. Refer to ICCR dataset for full commentary.

The presence or absence of perineural invasion should be recorded.

The prognostic value of perineural invasion remains under debate. Most studies demonstrate its significant prognostic impact in univariate analysis but not in multivariate analysis. For Lauren intestinal type gastric
cancer, perineural invasion may be an independent prognostic factor.\textsuperscript{44}

**S3.06** The presence or absence of lymphovascular invasion must be recorded.

Reports on the prognostic value of lymphovascular invasion are variable,\textsuperscript{49} but most studies demonstrate that lymphovascular invasion is an independent indicator of poor outcome following surgery.\textsuperscript{50,51} Lymphovascular invasion includes lymphatic and venous invasion. Prognostic differences between lymphatic and venous invasion have not been sufficiently evaluated in gastric cancers.

By the UICC\textsuperscript{31}/AJCC\textsuperscript{16} convention, lymphovascular invasion does not affect the T category.\textsuperscript{26,27} For example, a tumour invading the muscularis propria showing lymphovascular invasion in the subserosa is still considered pT2.

**S3.07** The response to neoadjuvant therapy must be recorded.

Several grading systems for histopathological tumour response to neoadjuvant therapy have been applied to treated gastrointestinal carcinomas. These include the Mandard,\textsuperscript{52} Becker,\textsuperscript{53} JGC\textsuperscript{22} and College of American Pathologists (CAP)/\textsuperscript{54}AJCC\textsuperscript{27} tumour regression grading schemes.\textsuperscript{55,56} While the Mandard system\textsuperscript{52} is based on the fibrosis/tumour ratio (Appendix 6, Table 3), the 4-tiered Becker system\textsuperscript{53} uses the estimated percentage of residual tumour in relation to the (assumed) previous tumour size (Table 4). The CAP grading system,\textsuperscript{54} which is also referred to by the AJCC staging system 8\textsuperscript{th} edition,\textsuperscript{27} is shown in Table 5 (Appendix 6).

Although many studies\textsuperscript{55,57-59} have evaluated and compared these schemes in assessing treatment response in gastrointestinal carcinomas after neoadjuvant therapy, there is no consensus on the optimal method to stratify tumour regression. In addition, the inter- and intra-observer variability is high in most schemes. Nevertheless, response to neoadjuvant therapy should be reported, as assessment of histological tumour regression may provide valuable prognostic information and may impact on choice of postoperative therapy.\textsuperscript{55} Patients with complete tumour regression have significantly better overall survival compared to patients with residual adenocarcinoma. As there is currently no consensus, the CAP grading system, which is a modified Ryan scheme\textsuperscript{60} is recommended by the Carcinoma of the Stomach Dataset Authoring Committee. The CAP grading system assesses the residual tumour cells rather than treatment-associated fibrosis.

The presence of lymph node metastasis is one of the most important prognosticators in gastrointestinal carcinomas, but a method to determine tumour regression in lymph nodes has not been established. Furthermore, so far only a few studies have demonstrated that regressive changes in lymph node metastasis is associated with patient outcome.\textsuperscript{55}
Therefore, tumour regression should only be assessed in the primary tumour for the time being.

If there is no tumour visible on macroscopic examination, the entire assumed tumour bed should be processed into paraffin blocks in order to correctly stage tumours and evaluate treatment response. However, there is no standard protocol for grossing specimens with macroscopically visible residual carcinoma. Most pathologists gross these specimens similar to those without preoperative treatment. Routine cytokeratin immunohistochemistry (IHC) is not recommended, but it may be helpful, if available, when there is morphologically suspicious for residual viable tumour. According to the UICC\textsuperscript{31}/AJCC\textsuperscript{16} 8th Edition Staging Manual, acellular mucin pools, necrosis, and degenerative/reactive changes without viable tumour cells after treatment should be interpreted as negative for tumour.\textsuperscript{26,27}

### S3.08 The margin status must be recorded.

|   | CS3.08a | Resection margins of gastrectomy specimens include proximal, distal and radial/circumferential margins. Depending on the location of the tumour or histological tumour type, proximal and distal margins may only be assessed macroscopically. The radial margin is often the closest margin, especially for tumours close to the OGJ. It is usually measured microscopically. In the gastric body and antrum, the lesser omental (hepatoduodenal and hepatogastric ligaments) can be considered as radial resection margins and distance between the tumour and these margins may be measured macroscopically.

The definition of what constitutes a positive resection margin differs between the US and UK/Europe. The CAP defines positive margin (incomplete resection, R1) as presence of the tumour cells directly at the resection margin,\textsuperscript{54} whereas the Royal College of Pathologists, UK defines R1 tumours as those having tumour cells present within 1 mm of the margin.\textsuperscript{61} A positive margin is associated with a poor prognosis. However, at this stage no consensus on the definition of margin positivity has been reached.

|   | CS3.08b | If dysplasia involves a margin this should be stated.

### S3.09 The number of regional lymph nodes involved and the total number of regional nodes identified must be recorded.

|   | CS3.09a | The UICC/AJCC\textsuperscript{26,27} 8th edition Staging Manuals and National Comprehensive Cancer Network (NCCN) guidelines\textsuperscript{19} recommend excision of a minimum of 15-16 lymph nodes in order to reliably stage the tumour, but efforts should be made to submit as many lymph nodes as possible for histological examination. A study on oesophagogastric adenocarcinoma showed that preoperative chemoradiation but not chemotherapy reduced total lymph node counts after total gastrectomy.\textsuperscript{62} Fat clearance of resection specimens
may increase lymph node yield and result in nodal upstaging.\textsuperscript{63}

D1 lymph node dissections include the removal of the perigastric lymph nodes while D2 resections include the removal of perigastric lymph nodes and the lymph nodes along the left gastric, common hepatic and splenic arteries, and the coeliac axis (Figure 4).

In Asian countries, D2 dissection yields superior outcomes compared with D1 dissection, however the results from other countries are conflicting. The Dutch D1D2 randomized clinical trial has recently demonstrated that D2 lymphadenectomy is associated with lower locoregional recurrence and gastric-cancer-related death rates compared with D1 surgery after long-term follow-up.\textsuperscript{64-66} Gastrectomy with D2 dissection has become more commonly used for advanced gastric cancer in Western countries.

Regional lymph nodes for gastric cancer includes perigastric lymph nodes along the greater curvature and lesser curvature, right paracardial lymph nodes, suprapyloric and infrapyloric lymph nodes, and lymph nodes along the left gastric artery, coeliac artery, common hepatic artery, hepatoduodenal vessels, splenic artery and splenic hilum (Figure 4).\textsuperscript{27} Reporting of the lymph node status by regional lymph node groups offers no significant prognostic information; thus, all regional nodes can be reported together.

Tumour deposits, defined as discrete tumour nodules within the lymphatic drainage of the primary carcinoma without identifiable lymph node tissue or identifiable vascular or neural tissue, are considered regional lymph node metastases.\textsuperscript{27} Tumour deposit may be an independent predictor of prognosis in patients with gastric cancer.\textsuperscript{67}

Lymph nodes containing isolated tumour cells, defined as single tumour cells or small clusters of cells ≤0.2 mm in greatest diameter, without stromal reaction, are classified as pN0 in gastric cancer.\textsuperscript{27} There is no micro-metastasis (N1mi) category in staging gastric cancer.\textsuperscript{27} Lymph nodes containing clusters of cells >0.2 mm are considered positive. In pretreated gastric cancers, positive lymph nodes are defined as having at least one focus of residual tumour cells in the lymph nodes regardless of size. Lymph nodes with acellular mucin pool or fibrotic lymph nodes with no viable tumour are considered negative.\textsuperscript{27}

Involvement of non-regional lymph nodes is considered (y)pM1 and as such should be reported under ‘histologically confirmed distant metastases’. Non-regional lymph nodes include the retropancreatic, pancreaticoduodenal peripancreatic, superior mesenteric, middle colic, para-aortic, and retroperitoneal nodes.\textsuperscript{15}

The presence of lymph node metastasis is one of the strongest prognostic indicators in gastric cancer.\textsuperscript{68}
CS3.09b Record the number of lymph nodes from the main resection specimen, and the regional nodes from each separately labelled specimen.

S3.10 The presence or absence of coexistent pathology such as: gastritis, helicobacter infection, intestinal metaplasia, dysplasia, gastric polyps, Barrett mucosa (for those specimens with oesophagus) and other pathologies must be specified.

CS3.10a Based on the updated Sydney system, chronic gastritis is classified into *Helicobacter* gastritis, ex-*Helicobacter* gastritis, chemically induced/reactive gastritis, autoimmune gastritis and other special forms of gastritis. Helicobacter gastritis and autoimmune gastritis are recognized risk factors for gastric carcinoma. Both cause atrophic gastritis with intestinal metaplasia, which may develop into dysplasia/adenoma and further progress to intestinal-type adenocarcinoma. In addition, pyloric gland adenoma may arise in a background of autoimmune atrophic gastritis, which can also progress to gastric carcinoma.

Gastric polyps include fundic gland polyp, hyperplastic polyp and different types of adenoma. Hyperplastic polyps can be seen in the setting of long-term gastritis, and intestinal metaplasia may be seen in large hyperplastic polyps, which can progress to dysplasia and eventually to invasive carcinoma. Rarely dysplasia is seen in fundic polyps, but it almost never progresses to adenocarcinoma. Gastric adenomas include intestinal type, foveolar type, pyloric gland adenoma and oxyntic gland adenoma, all of which can progress to invasive carcinoma.

Other risk factors associated with gastric carcinoma include previous gastric surgery and Epstein-Barr virus (EBV) infection. In addition, approximately 10% of gastric cancers develop in a familial/ hereditary setting, including hereditary diffuse gastric cancer in patients with CDH1 mutations and patients with Lynch syndrome with microsatellite instability (MSI)-high gastric cancer. Some patients with familial adenomatous polyposis can have multiple foveolar type adenomas, which have a potential to become invasive carcinoma but at a consistently low rate. In addition, synchronous gastric carcinoma is rare; however, in one report from Asia, synchronous gastric cancer is seen in approximately 10% of gastric cancer patients.

CS3.10b Special stains for Helicobacter pylori (either histochemical or immunohistochemical), should be considered in any subtotal gastrectomy case showing inflammation in the mucosa away from the tumour.

S3.11 Histologically confirmed distant metastases must be recorded.

CS3.11a Common distant metastases in gastric cancer include peritoneal metastasis, liver metastasis and metastasis to the non-regional lymph node(s).
Involvement of non-regional lymph nodes is considered (y)pM1 and as such should be reported.

CS3.11b Disease classifiable as distant metastasis may sometimes be present within the primary tumour resection specimen (e.g. a positive peritoneal nodule, liver biopsy etc.

CS3.11c Positive peritoneal cytology is classified as M1. This may be separately reported. However, M1 would change the stage group to stage IV. This information if known should be indicated in the report preferably as a comment.

G3.02 Any additional relevant microscopic comments should be recorded.
**Figure 4: Regional lymph nodes of the stomach.** Reproduced with permission from the American Joint Committee on Cancer (AJCC).
4 Ancillary studies

Ancillary studies in gastric carcinoma may 1) predict response to medical therapy; 2) aid tumour classification; 3) detect a genetic aetiology for the carcinoma; 4) provide prognostic information and 5) establish the presence or absence of an infectious co-factor.

The Cancer Genome Atlas (TCGA) has proposed a classification categorising gastric cancers into four molecular subtypes: EBV-positive, microsatellite unstable, genomics stable, and chromosomally unstable. Each tumour subtype has characteristic morphology, prognosis, and therapeutic implications for specific chemo- and immunotherapy. Immunohistochemistry for mismatch repair proteins, p53, E-cadherin, and in situ hybridisation for EBV-encoded small RNA (EBER) may serve as a surrogate for molecular testing in routine practice (see Appendix 7, Table 6).

<table>
<thead>
<tr>
<th>CS4.01</th>
<th>Microsatellite instability (MSI)/mismatch repair (MMR) testing must be recorded.</th>
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<td></td>
<td><strong>CS4.01a</strong> Microsatellite instability/mismatch repair deficiency (dMMR) status and PD-L1 expression have been used as predictive biomarkers for checkpoint inhibitor therapy since the Food and Drug Administration (FDA) approved pembrolizumab for the treatment of MSI-H or PD-L1 positive unresectable or metastatic gastric cancers. While MSI status has been shown to be highly predictive of response to PD-1 blockage in several clinical trials, the value of PD-L1 expression in selecting patients for checkpoint inhibitors in oesophageal and gastric cancer needs to be further investigated. Approximately 40% of gastric/oesophageal cancers express PD-L1. Unlike other malignancies (i.e. non-small cell lung cancer), PD-L1 expression in gastric/oesophageal cancers is mainly observed in immune cells. The combined positive score (CPS), which takes into account of PD-L1 expression by both tumour and tumour-associated immune cells, has been developed and refined for scoring gastric and oesophageal cancers. CPS is calculated by dividing the total number of PD-L1 positive cells (including tumour and immune cells) by the total number of viable tumour cells. A CPS ≥ 1 as determined by an FDA-approved companion diagnostic test (the Dako PD-L1 IHC 22C3 PharmDx Assay) is currently used to classify a tumour as PD-L1 positive. A low overall response rate (ORR) has been reported when using CPS cutoff of &lt;1. Many studies are ongoing to explore if the ORR can be improved by using a different cutoff. Microsatellite status of a tumour can be determined by either polymerase chain reaction (PCR)-based MSI testing or by immunohistochemical (IHC) stains for MLH1, MSH2, MSH6 and PMS2. MMR IHC may be reported using the template outlined in Table 8. MSI-high/dMMR is seen in 8-25% of gastric cancer. While some of MSI-high/dMMR gastric cancers result from hypermethylation of MLH1 promotor, others develop in</td>
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association with Lynch syndrome, which is caused by germline mutations in one of mismatch repair genes, namely MLH1, MSH2, MSH6 and PMS2 or rarely in EPICAM. Germline mutational analyses are recommended for individuals suspicious for Lynch syndrome.

CS4.01b MSI-high/dMMR is seen in 7-22% of gastric cancer and these tumours constitute microsatellite unstable subtype in the TCGA molecular classification.

Pembrolizumab is approved in Australia and New Zealand for the treatment of advanced dMMR or MSI-H non-colorectal tumours that have progressed following prior treatment and when there are no satisfactory alternative options. Use of MMR immunohistochemistry is recommended for establishing MSI status (please see Appendix 8, Table 8 and Figure 11).

In Australia, pembrolizumab is also indicated for the treatment of patients with recurrent, unresectable or metastatic adenocarcinoma of the stomach or GOJ that have progressed during or following a first-line or second-line therapy and are PD-L1 positive (as determined by Combined Positive Score, or CPS).

PD-L1 staining should be performed using approved methods as clinically indicated or requested. PD-L1 IHC reports should include all relevant information including the clone and scoring method used. Testing and interpretation of PD-L1 IHC in clinical practice will ultimately be determined by the pharmaceutical agent/s that gain approval and their companion diagnostics.

<table>
<thead>
<tr>
<th>EC4.01</th>
<th>Any other ancillary testing performed should be noted and the results recorded in the pathology report.</th>
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<tr>
<td>CG4.01a</td>
<td>For gastric neuroendocrine carcinomas, including mixed neuroendocrine-non-neuroendocrine carcinomas, the reporting of neuroendocrine marker expression and Ki-67 proliferation index are core elements. These elements are non-core for other types of gastric carcinomas. Gastric neuroendocrine neoplasms are classified into NETs, NECs and MiNENs. NETs are graded 1-3 using the mitotic count and Ki-67 proliferation index. Pure NETs are not considered within the scope of this protocol. Most NECs show marked cytological atypia, brisk mitotic activity, and are subclassified into small cell and large cell subtypes. NECs are considered high grade by definition, typically with a Ki-67 proliferation index &gt;55%. MiNENs are usually composed of a poorly differentiated NEC component and an adenocarcinoma component. If a pure or mixed neuroendocrine carcinoma is suspected on morphology, IHC is required to confirm neuroendocrine differentiation, usually applying synaptophysin and chromogranin A as a minimum.</td>
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The NCCN guidelines recommend assessment of HER2 expression using IHC or HER2 amplification using in situ hybridisation (ISH) for patients with inoperable locally advanced, recurrent and metastatic gastric/OGJ adenocarcinoma for whom therapy with trastuzumab is considered.\(^{19}\) For IHC in resection specimens, both intensity and percentage of immunoreactive cancer cells is assessed with scores ranging from 0 to 3+ (Appendix 7, Table 7). ISH is used when IHC is equivocal (2+). IHC 3+ or ISH showing HER2 amplification (ISH positive) (including IHC 2+ with ISH positivity) is considered HER2 positive. The HER2 IHC report should include the IHC score and primary antibody used. The HER2 ISH report should include the result (amplified or not amplified), number of invasive cancer cells counted, and which assay used (dual-probe versus single-probe assay).

HER2 IHC can be performed up front, with the inclusion of a comment in the report that ISH can be performed on request for patients who meet criteria. Whilst HER2 testing is commonly performed on resection specimens, as the result of the prevalence of neoadjuvant therapy for advanced gastric cancer, it is practical to perform HER2 testing on biopsy tissue.

In Australia, the Therapeutic Goods Administration (TGA) and the Medical Services Advisory Committee (MSAC) approved the use of trastuzumab for patients whose tumours show both an IHC result of 2+ or 3+, in addition to an ISH result showing >6 copies of HER2 and a HER2/CEP17 ISH ratio >2. Trastuzumab is approved for advanced adenocarcinoma of stomach or OGJ in patients who have not received prior anticancer treatment for their metastatic disease.

Trastuzumab is approved in New Zealand by Medsafe for treatment of patients with HER2 positivity (HER2 3+ IHC or HER2/CEP17≥2 or HER2≥ 6 copies per nucleus) in advanced adenocarcinoma of the stomach or OGJ.

In summary, the current criteria for HER2 positive in Australia is HER2/CEP17 ratio >2 AND HER2 copy number >6 and ASCO/CAP for New Zealand, but that this may change in the future and pathologists should ensure they are up to date with current recommendations.

Please see Appendix 7 (Table 7, Figures 7, 8 and 9).

Epstein Barr virus (EBV) positive gastric cancers are associated with a better prognosis. In addition, EBV positive tumours are more likely associated with overexpression of PD-L1 and PD-L2. A recent study demonstrated that EBV positive tumours could be a strong marker for efficacy of immunotherapy.\(^{74}\)

These cancers show prominent lymphocytic stromal reaction and intraepithelial lymphocytes, and gastric cancers are associated with a better prognosis.
Approximately 3-9% of gastric cancers are EBV positive and constitute EBV positive subtype in the TCGA molecular classification.

| CG4.01f | Other molecular testing includes targeted next generation sequencing. The testing is usually only performed to identify other actionable targets. |

CG4.01g **Hereditary gastric carcinomas**

Approximately 90% of gastric cancer is sporadic while up to 10% shows familial clustering with 1-3% arising in a clearly hereditary setting.\(^{15,80}\)

**Hereditary diffuse gastric carcinoma** – results from a germline mutation in e-cadherin (CDH1). This results in early age onset of multifocal diffuse signet ring pattern gastric carcinoma in all mucosal zones of the stomach. Up to 40% of affected females also develop lobular breast carcinoma. Referral for genetic counselling for CDH-1 mutation analysis is recommended in patients who fulfil the 2015 International Gastric Cancer Linkage Consortium guidelines\(^{81}\) established criteria:

1. Two or more cases of gastric cancer at any age in first or second degree relatives, with at least 1 confirmed as diffuse-type gastric carcinoma
2. Diffuse gastric cancer with onset before the age of 40
3. Personal or family history of diffuse gastric cancer and lobular breast cancer, with one diagnosed before the age of 50

Families in whom testing could be considered:

1. Bilateral lobular breast carcinoma (LBC) or family history of 2 or more cases of LBC before the age of 50
2. A personal or family history of cleft lip/palate in a patient with diffuse-type gastric cancer
3. In situ signet ring cells and/or pagetoid spread of signet ring cells

**Lynch syndrome** – gastric adenocarcinoma can infrequently arise in this syndrome\(^{45}\) and universal MMR IHC testing is recommended in all patients, for purposes of Lynch syndrome screening and predictive indications for immune checkpoint inhibitor therapy (Figure 11). If the tumour shows loss of MLH1 and PMS2, MLH1 promoter hypermethylation testing should be performed. Lynch syndrome is unlikely if the hypermethylation is positive.

**Familial adenomatous polyposis (FAP)** – patients frequently develop multiple fundic gland polyps which are at risk for developing gastric dysplasia and adenocarcinoma. This is seldom the only manifestation of this syndrome.
**Gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS)** – an autosomal dominant cancer predisposition syndrome with a unique phenotype but considered part of FAP.2 GAPPS is caused by germline point mutations in the APC promoter,83 and is associated with an increased risk of tubular (WHO)/intestinal (Lauren) gastric adenocarcinoma, along with proximal polyposis of the stomach.2

**Other genetic syndromes that increase the risk of gastric carcinoma**

- Peutz Jeghers syndrome
- Li-Fraumeni syndrome
- Juvenile polyposis

CG4.01h Surgical resection (or selective endomucosal resection) remains the only potential curative procedure in gastric carcinoma and is recommended for suitable patients with disease stages Tis-T3, N0-N2, M0 or T4N0M0.83 Other patients may be offered chemotherapy with the potential addition of targeted therapies currently under trial. While research in this area is still evolving, in the near future, ancillary tests may guide the use of these molecular targeted therapies.
5 Synthesis and overview

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

For example, tumour stage is synthesised from multiple classes of information – clinical, macroscopic and microscopic.

By definition, synthetic elements are inferential rather than observational, often representing high-level information that is likely to form part of the report ‘Summary’ or ‘Diagnosis’ section in the final formatted report.

Overarching case comment is synthesis in narrative format. 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.

<table>
<thead>
<tr>
<th>S5.01</th>
<th>The tumour stage and stage grouping must be recorded, incorporating clinical and pathological data, based on the TNM staging system of the AJCC Cancer Staging Manual (8th Edition).16</th>
</tr>
</thead>
</table>
| CS5.01a | The AJCC/UICC 8th Edition Staging Systems for gastric carcinoma are recommended as shown in Figures 5 and 6.26,27  
According to the UICC/AJCC convention, the designation “T” refers to a primary tumour that has not been previously treated. The symbol ‘p’ refers to the pathologic classification of the TNM, as opposed to the clinical classification, and is based on gross and microscopic examination of surgically resected specimens.26,27 pT entails a resection of the primary tumour adequate to evaluate the highest pT category, pN entails removal of nodes adequate to validate lymph node metastasis, and pM implies microscopic examination of distant lesions.  
**TNM descriptors**  
For identification of special cases of TNM or pTNM classifications, the “m” suffix and “y,” and “r” prefixes are used.  
The “m” suffix indicates the presence of multiple primary tumours in a single site. For multifocal gastric cancers, T is assigned to the highest T category.  
The “y” prefix indicates those cases in which classification is performed after neoadjuvant therapy. The ypTNM categorizes the extent of tumour actually present at the time of that examination. The “y” categorisation is not an estimate of tumour before neoadjuvant therapy.  
The “r” prefix indicates a recurrent tumour when staged after a documented disease-free interval and is identified by the “r” prefix: rTNM. |
<table>
<thead>
<tr>
<th></th>
<th>A tumour may penetrate the muscularis propria with extension into the gastrocolic or gastrohepatic ligaments, or into the greater or lesser omentum, without perforation of the visceral peritoneum covering these structures. In this case, the tumour is classified as T3.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N Category considerations</strong></td>
<td>As per AJCC 8th edition, a designation of N0 should be used if all examined lymph nodes are negative, regardless of the total number removed and examined.</td>
</tr>
<tr>
<td>CS5.01b</td>
<td>Thus, there must be a recognition that staging based on examination of the gastrectomy specimen may not reflect the stage of disease in the patient.</td>
</tr>
</tbody>
</table>

This can be indicated in the “synthesis and diagnostic summary” section of the report by including a statement such as: Note: the staging given is based on examination of the specimens received. Stage IV cannot normally be assigned on these examinations.

**S5.02 The year of publication and edition of the cancer staging system used in S5.01 must be included in the report.**

**G5.01** The ‘Diagnostic summary’ section of the final formatted report should include:
- a) Specimen type
- b) Tumour site
- c) Histologic type
- d) Involved or close margins with measurements
- e) Pathologic stage and stage grouping

**G5.02** A field for free text or narrative in which the reporting pathologist can give overarching case comment must be provided.

**CG5.02a** This field may be used, for example, to:
- list any relevant ancillary tests
- document any noteworthy adverse gross and/or histological features
- express any diagnostic subtlety or nuance that is beyond synoptic capture
- document further consultation or results still pending.

**CG5.02b** 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 are aligned with the criteria as
Figure 5: T1a is defined as tumour that invades the lamina propria. T1b is defined as tumour that invades the submucosa. T2 is defined as tumour that invades the muscularis propria, whereas T3 is defined as tumour that extends through the muscularis propria into the subserosal tissue. Reproduced with permission of the American Joint Committee on Cancer (AJCC).²⁷

Figure 6: T4a is defined as tumour that penetrates the serosa (visceral peritoneum) without invasion of adjacent structures, whereas T4b is defined as tumour that radially invades adjacent structures, shown here invading the pancreas. Reproduced with permission of the American Joint Committee on Cancer (AJCC).²⁷
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 data set’ for gastric 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 LIS capabilities and as described in Functional Requirements for Structured Pathology Reporting of Cancer Protocols.

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.
Item descriptions in italics are conditional on previous responses.

Values in all caps are headings with sub values.

<table>
<thead>
<tr>
<th>S/G</th>
<th>Item description</th>
<th>Response type</th>
<th>Conditional</th>
</tr>
</thead>
<tbody>
<tr>
<td>S1.01</td>
<td>Demographic information provided</td>
<td>Information not provided</td>
<td></td>
</tr>
<tr>
<td>S1.02</td>
<td>Clinical information provided on request form</td>
<td>Information not provided OR Text OR Structured entry as below:</td>
<td></td>
</tr>
</tbody>
</table>

Relevant biopsy results | Text |
Previous diagnosis and treatment for gastric cancer | Text |
Endoscopic location of the tumour | Text |
Clinical staging | Text |
Previous partial gastrectomy | Text |
History of chronic gastritis | Text |
Other clinical information | Text |
Neoadjuvant therapy | Single selection value list: |

*Specify level of involvement, distant metastases*
<table>
<thead>
<tr>
<th>ID</th>
<th>Description</th>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1.01</td>
<td>Copy To doctors recorded</td>
<td>Text</td>
</tr>
<tr>
<td>S1.03</td>
<td>Pathology accession number</td>
<td>Alpha-numeric</td>
</tr>
<tr>
<td>S1.04</td>
<td>Principal clinician</td>
<td>Text</td>
</tr>
<tr>
<td>G1.02</td>
<td>Comments</td>
<td>Text</td>
</tr>
</tbody>
</table>

**Macroscopic findings**

<table>
<thead>
<tr>
<th>ID</th>
<th>Description</th>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>S2.01</td>
<td>Specimen labelled as</td>
<td>Text</td>
</tr>
<tr>
<td>S2.02</td>
<td>Clinical information</td>
<td>Text</td>
</tr>
<tr>
<td>S2.03</td>
<td>Operative procedure</td>
<td>Text OR</td>
</tr>
</tbody>
</table>
| S2.04 Specimen dimensions | **Multi selection value list (select all that apply):**  
| | • Not specified  
| | • Gastrectomy  
| | o Sub-total  
| | o Total  
| | • Oesophagogastrectomy  
| | • Other, specify  
| | **Numeric:** Length of stomach greater curve ___mm  
| | **Numeric:** Length of stomach lesser curve ___mm  
| | **Numeric:** Length of oesophagus ___mm  
| | **Numeric:** Length of duodenum ___mm |

| S2.05 Tumour focality | **Single selection value list:**  
| | • Unifocal  
| | • Multifocal, specify number of tumours in specimen  
| | • Cannot be assessed, specify  
| | **Note:** If multiple primary tumours are present, separate protocols should be used to record this an all following elements for each primary tumour.  
| | **Tumours in specimen** | **Numeric:** ___ |

| S2.06 Tumour site | Not specified |
**Maximum tumour dimension**

<table>
<thead>
<tr>
<th>Cannot be assessed, specify</th>
</tr>
</thead>
<tbody>
<tr>
<td>OR</td>
</tr>
<tr>
<td>Text: Tumour identification</td>
</tr>
<tr>
<td>AND</td>
</tr>
<tr>
<td><strong>Numeric:</strong> maximum tumour dimension ___mm</td>
</tr>
</tbody>
</table>

**Notes:**

Repeat tumour identification and maximum dimension for each tumour identified.

OR

For a large number of tumours include a range:
<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Additional tumour dimension</strong></td>
<td><strong>__mm to __mm</strong></td>
<td></td>
</tr>
<tr>
<td><strong>ICCR</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| **G2.01** | **Macroscopic tumour type** | **Single selection value list:**  
  - Not applicable  
  - Cannot be assessed  
  - Polypoid mass (Borrmann type I)  
  - Ulcerative (Borrmann type II)  
  - Infiltrative ulcerative (Borrmann type III)  
  - Diffuse Infiltrative (Borrmann type IV)  
  - Other, specify |
| **S2.08** | **Distance of tumour to nearest proximal or distal margin** | **Numeric: ____mm**  
  AND  
  Text (margin, if possible) |
<p>| <strong>S2.09</strong> | <strong>Distance of tumour to the circumferential resection margin (applicable to tumours of the cardia)</strong> | <strong>Numeric: ____mm</strong> |
| <strong>S2.10</strong> | <strong>Serosa appearance</strong> | <strong>Text</strong> |
| <strong>S2.11</strong> | <strong>Involvement of adjacent organs</strong> | <strong>Text</strong> |
| <strong>S2.12</strong> | <strong>Distant metastases</strong> | <strong>Text</strong> |
| <strong>S2.13</strong> | <strong>Block identification key</strong> | <strong>Text</strong> |</p>
<table>
<thead>
<tr>
<th>G2.02</th>
<th>Additional macroscopic comments</th>
<th>Text</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Microscopic findings</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>S3.01</strong> Tumour site</td>
</tr>
<tr>
<td><strong>S3.02</strong> Histological tumour type</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Single selection value list:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Tubular adenocarcinoma</td>
</tr>
<tr>
<td>• Papillary adenocarcinoma</td>
</tr>
<tr>
<td>• Mucinous adenocarcinoma</td>
</tr>
<tr>
<td>• Poorly cohesive carcinoma, including signet-ring cell carcinoma and other subtypes</td>
</tr>
<tr>
<td>• Mixed adenocarcinoma</td>
</tr>
<tr>
<td>• Other histological type/subtype, specify</td>
</tr>
<tr>
<td>• Cannot be assessed</td>
</tr>
</tbody>
</table>

| **S3.02** Histological tumour type |
| **S3.03** Histological grade |

| Lauren classification (applicable to adenocarcinoma) |
| Single selection value list: |
| • Intestinal |
| • Diffuse |
| • Mixed |
| • Indeterminate |

<table>
<thead>
<tr>
<th>Single selection value list:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Not applicable</td>
</tr>
<tr>
<td>• Cannot be assessed</td>
</tr>
<tr>
<td>S3.04</td>
</tr>
<tr>
<td>-------</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>S3.05</th>
<th>Serosal surface involvement</th>
<th>Single selection value list:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>• Indeterminate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Absent</td>
</tr>
<tr>
<td>Code</td>
<td>Description</td>
<td>Single selection value list:</td>
</tr>
<tr>
<td>------</td>
<td>-------------</td>
<td>-----------------------------</td>
</tr>
</tbody>
</table>
| G3.01 | Perineural invasion | • Not identified  
• Present |
| S3.06 | Lymphovascular invasion | • Not identified  
• Present |
| S3.07 | Response to neoadjuvant therapy | • Cannot be assessed, specify  
• No neoadjuvant treatment  
• Complete response - no viable cancer cells (score 0)  
• Near complete response - single cells or rare small groups of cancer cells (score 1)  
• Partial response - residual cancer with evident tumour regression, but more than single cells or rare groups of cancer cells (score 2)  
• Poor or no response - extensive residual cancer with no evident tumour regression (score 3) |
| S3.08 | MARGIN STATUS | Invasive carcinoma  
• Cannot be assessed  
• Not involved |
<table>
<thead>
<tr>
<th><strong>Dysplasia</strong></th>
<th><strong>Lymph node status</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>- Cannot be assessed</td>
<td></td>
</tr>
<tr>
<td>- Not involved</td>
<td></td>
</tr>
<tr>
<td>- Involved</td>
<td></td>
</tr>
<tr>
<td>- Carcinoma in situ/high grade dysplasia</td>
<td></td>
</tr>
<tr>
<td>- Low grade</td>
<td></td>
</tr>
<tr>
<td>- Specify margin</td>
<td></td>
</tr>
<tr>
<td>- Distal</td>
<td></td>
</tr>
<tr>
<td>- Proximal</td>
<td></td>
</tr>
<tr>
<td>- Other, specify</td>
<td></td>
</tr>
<tr>
<td><strong>Number of lymph nodes examined</strong></td>
<td><strong>Single selection value list:</strong></td>
</tr>
<tr>
<td>No nodes submitted</td>
<td>If involved record the number of positive LNs</td>
</tr>
<tr>
<td>OR</td>
<td></td>
</tr>
<tr>
<td><strong>Numeric:</strong> ____</td>
<td></td>
</tr>
<tr>
<td><strong>S3.10</strong></td>
<td><strong>COEXISTENT PATHOLOGY</strong></td>
</tr>
<tr>
<td>----------------</td>
<td>--------------------------</td>
</tr>
</tbody>
</table>

**Multi selection value list (select all that apply):**
- *Helicobacter* gastritis
- Autoimmune gastritis
- Reactive gastritis
- Gastric polyps, *specify*
- Intestinal metaplasia
- Dysplasia
  - Low grade
  - High grade
  - Indeterminate
- Synchronous carcinoma(s), *specify*
- Other, *specify*

| **S3.11** | **Histologically confirmed distant metastases** | **Single selection value list:**
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Not identified</td>
</tr>
<tr>
<td></td>
<td>Present, <em>specify site(s)</em></td>
</tr>
</tbody>
</table>

**Ancillary findings**

<table>
<thead>
<tr>
<th><strong>S4.01</strong></th>
<th><strong>MSI/MMR testing</strong></th>
<th><strong>Single selection value list:</strong></th>
</tr>
</thead>
</table>
| G4.01 | Other ancillary studies | Multi selection value list (select all that apply):
- HER2 testing performed, record results
- Epstein-Barr virus (EBV)-status (e.g. EBV encoded RNA (EBER) in situ hybridisation), record result(s)
- PD-L1 IHC, record results
- Other, specify |

| | Neuroendocrine neoplasms only | Not applicable OR Neuroendocrine markers (chromogranin A, synaptophysin, other), specify test(s) performed and result(s) if available |

| | Ki-67 proliferation index | Percentage: ____ |

**Synthesis and overview**

<table>
<thead>
<tr>
<th>S5.01</th>
<th>PATHOLOGICAL STAGING (AJCC 8TH EDITION)</th>
</tr>
</thead>
</table>

| | TNM descriptors | Multi select value list : |
| | | • m - multiple primary tumours |
| | | • y - post therapy |
| | | • r - recurrent |

<p>| | Primary tumour (T) | Single select value list : |</p>
<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>Primary tumour cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumour</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ: intraepithelial tumour without invasion of the lamina propria, high grade dysplasia</td>
</tr>
</tbody>
</table>
| T1    | Tumour invades lamina propria, muscularis mucosae, or submucosa  
  | o pT1a: Tumour invades lamina propria or muscularis mucosae  
  | o pT1b: Tumour invades submucosa |
| T2    | Tumour invades muscularis propria* |
| T3    | Tumour invades subserosal connective tissue without invasion of the visceral peritoneum or adjacent structures^~ |
| T4    | Tumour perforates serosa (visceral peritoneum) or adjacent structures^~  
  | o pT4a: Tumour perforates serosa (visceral peritoneum)  
  | o pT4b: Tumour invades adjacent structures/organs |

* A tumour may penetrate the muscularis propria with extension into the gastrocolic or gastrohepatic ligaments, or into the greater or lesser omentum, without perforation of the visceral peritoneum covering these structures. In this case, the tumour is classified as T3. If there is perforation of the visceral peritoneum covering the gastric ligaments or the omentum, the tumour should be classified as T4.

^ The adjacent structures of the stomach are the spleen, transverse colon, liver, diaphragm, pancreas, abdominal wall, adrenal gland, kidney, small intestine, and retroperitoneum.

~ Intramural extension to the duodenum or oesophagus is not considered invasion of an adjacent structure, but is classified using the depth of the greatest invasion in any of these sites.
### Regional lymph nodes (N)

<table>
<thead>
<tr>
<th>Single selection value list</th>
</tr>
</thead>
<tbody>
<tr>
<td>NX</td>
</tr>
<tr>
<td>N0</td>
</tr>
<tr>
<td>N1</td>
</tr>
<tr>
<td>N2</td>
</tr>
<tr>
<td>N3</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

### Year and edition of staging system

- **Numeric:** year
- **AND**
- **Text:** Edition eg 1\textsuperscript{st}, 2\textsuperscript{nd} etc

### Diagnostic summary

Include:
- a. specimen submitted
- b. tumour type
- c. tumour stage
- d. whether or not the specimen margins are involved

### Overarching comment

**Text**

### 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 for optimising 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. For guidance on formatting pathology reports, please refer to Appendix 2.
Appendix 1  Pathology request form for gastric tumours

This appendix describes the information that should be collected before the pathology test. Some of this information can be provided on generic pathology request forms; any additional information required specifically for the reporting of gastric carcinomas 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:
  - patient name
  - date of birth
  - sex
  - identification and contact details of requesting doctor
  - date of request
- Document whether or not the patient identifies as Aboriginal and/ or Torres Strait Islander in Australia, or Māori in New Zealand. This is in support of government initiatives to monitor the health of those who identify as indigenous, 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 Individual Healthcare Identifier (IHI) (Australia) or the National Healthcare Index (New Zealand).

➢ The Australian Healthcare identifiers ie Healthcare Provider Identifier - Individual (HPI-I) and Healthcare Provider Identifier - Organisation (HPI-O) should be use, where possible, to identify the requesting doctor.
Clinical Information

- Clinical information should be recorded

- Clinical information including pre-operative neoadjuvant therapy and prior endoscopic resection can be provided by the clinician on the endoscopy report or the pathology request form. Patient medical records may be another source of information if accessible.
- Relevant biopsy results include the presence of carcinoma, dysplasia (glandular intraepithelial neoplasia), intestinal metaplasia, etc. Endoscopic tumour location or information on the tumour location as reported by the clinician are important guides as the tumour epicentre may be altered after neoadjuvant therapy.
- Multiple tumours may occur in the stomach and previous history of cancer or cancer treatment is relevant. A number of conditions, including previous partial gastrectomy for a benign disease condition and chronic atrophic gastritis, are risk factors for gastric cancer.

| ➢ | Relevant biopsy results should be recorded. |
| ➢ | Record any previous diagnosis and treatment for gastric cancer. |
| ➢ | The endoscopic location of the tumour should be recorded. |
| ➢ | Clinical staging should be recorded. |
| ➢ | Record any previous partial gastrectomy. |
| ➢ | Any history of chronic gastritis should be recorded. |
| ➢ | **If neoadjuvant therapy has been administered, this must be recorded.** |

- Perioperative (both pre- and postoperative) therapy is currently recommended in patients with stage IB to stage III gastric cancer in Western countries. Efficacy of perioperative/preoperative chemotherapy has been evaluated in multiple clinical trials. Most studies observed improved overall survival compared to the group treated with surgery alone. The CROSS trial documented the benefit of preoperative chemoradiation in patients with OGJ adenocarcinomas, but its value in gastric cancers of other locations is unclear.
- On the other hand, postoperative adjuvant therapy is currently the most common approach for stage II/III gastric cancer in Asia. The ACTS-GC trial in Japan and the CLASSIC trial in South Korea, China and Taiwan showed improved overall survival in patients who received adjuvant therapy after gastrectomy with D2 lymphadenectomy. However, there are also studies demonstrating no additional benefits from postoperative chemoradiation in patients after D2 and D1+ nodal dissection.
- Downstaging of lymph node metastases and/or reduction of tumour size by preoperative chemotherapy/chemoradiation have been reported by multiple clinical trials.\textsuperscript{85,90} Downstaging of the tumour may lead to higher rate of R0 resection and increased survival. Pathological tumour regression is evident in some cases, and complete tumour regression is achieved in up to 18\% of patients.\textsuperscript{91,92} Assessment of treatment response is recommended for gastrectomy from patients with preoperative chemotherapy/chemoradiation.

<table>
<thead>
<tr>
<th>The type of operation or procedure must be recorded.</th>
</tr>
</thead>
</table>

Depending on the tumour location and tumour type, gastric resection can be described as:\textsuperscript{18}

1. Total gastrectomy: for tumours located in the body/corpus of the stomach, tumours in the cardia, and diffuse gastric cancer (including prophylactic gastrectomy for patients with hereditary diffuse gastric cancer).
2. Sub-total distal gastrectomy: for tumours located in the antrum (distal third and pylorus).
3. Oesophagogastrectomy: for tumours extending to the lower oesophagus.

Prophylactic gastrectomy is a type of total gastrectomy specifically performed for patients with hereditary diffuse gastric cancer with a germline \textit{CDH1} or \textit{CTNNA1} mutation. The proximal and distal margins should not contain any gastric mucosa, which can be confirmed by frozen section during surgery.\textsuperscript{19,20}

- Comments should be included, if appropriate.
  - Space for free text should be included to encourage reporting of ambiguity, or for the addition of other comments.
Example Request Information Sheet

V2.0 Request Info from Gastric Cancer Structured Reporting Protocol 2nd Edition

The above Request Information Sheet is also available on the RCPA Cancer Protocols webpage.
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.

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.

- Clutter should be reduced to a minimum. Thus, information that is not part of the protocol (e.g. billing information, SNOMED codes, etc) should not appear on the reports or should be minimized.

- Injudicious use of formatting elements (e.g. too much bold, underlining or use of footnotes) constitutes 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 of a pathology report

GASTRIC CANCER STRUCTURED REPORT

Diagnostic Summary

Total Gastrectomy

Gastric adenocarcinoma of the antrum; tubular (WHO); intestinal (Lauren); low grade; surgical margins clear; 2/16 nodes involved; pT3, pN1; Stage IIb (AJCC 8th edition, 2017)

Comment: The staging is based on examination of the specimens received and the clinical information provided

Supporting Information

CLINICAL

Neoadjuvant therapy: Not administered
Operative procedure: Total gastrectomy

Tumour site: Antrum
Preoperative therapy: Nil
Surgeon’s opinion – residual tumour: Nil

MACROSCOPIC

Specimen labelled as: "Total gastrectomy"
Specimen dimensions
  Length of stomach greater curve: 250 mm
  Length of stomach lesser curve: 150 mm
  Length of oesophagus: 10 mm
  Length of duodenum: 10 mm
Tumour focality: Unifocal
Tumour site: Greater curvature
Maximum tumour dimension: 30 mm
Macroscopic tumour type: Polypoid mass (Borrmann Type I)
Distance to nearest (distal) margin: 30 mm
Serosal appearance: Normal
Involvement of adjacent organs: Absent
**Distant metastases:** Nil

**Block identification key:**
- Block 1: proximal resection margin,
- Block 2: distal resection margin,
- Blocks 3-8: tumour,
- Blocks 9-23: lymph nodes (one in each block),
- Blocks 24, 25: random gastric mucosa

**Additional macroscopic comments:**
Gastric mucosa appears atrophic

---

**MICROSCOPIC**

**Microscopic tumour site:** Antrum / Greater curvature

**Histological tumour type:** Tubular adenocarcinoma

**Lauren classification:** Intestinal

**Histological grade:** Low grade - Moderately differentiated

**Growth pattern:** Infiltrating

**Extent of invasion:** Invasion into subserosal connective tissue

**Serosal surface involvement:** Absent

**Perineural invasion:** Not identified

**Lymphovascular invasion:** Not identified

**Response to neoadjuvant therapy:** No prior treatment

**Distance of tumour from margins**
- From proximal: 180 mm
- From distal: 30 mm
- From radial: Not applicable

**Lymph node status**

| Number examined (main specimen + separately labelled): | 16 |
| Number of positive lymph nodes: | 2 |
| Number of involved non regional nodes: | Not received |

**Coexistent pathologies**

- **Helicobacter infection:** Absent
- **Gastritis:** Present
- **Gastric polyps:** Absent
- **Intestinal metaplasia:** Present
- **Dysplasia:** Absent
- **Other pathologies:** None

**Histologically confirmed distance metastases:** Not identified
ANCILLARY TESTS

None performed

Reported by Dr Bernard Beckstein

Authorised 4/9/2020
Appendix 4  

Histological subtypes

Table 1: Comparison of the Lauren, Nakamura, Japanese Gastric Cancer Association and World Health Organization classification of gastric cancer

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Intestinal</td>
<td>Differentiated</td>
<td>Papillary: pap Tubular 1, well-differentiated: tub1 Tubular 2, moderately differentiated: tub2</td>
<td>Papillary Tubular, well-differentiated Tubular, moderately differentiated</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>Undifferentiated</td>
<td>Poorly 1 (solid type): por1</td>
<td>Tubular (solid), poorly differentiated</td>
</tr>
<tr>
<td>Diffuse</td>
<td>Undifferentiated</td>
<td>Signet-ring cell: sig Poorly 2 (non-solid type): por2</td>
<td>Poorly cohesive, signet-ring cell phenotype Poorly cohesive, other cell types</td>
</tr>
<tr>
<td>Intestinal/diff use/ indeterminate</td>
<td>Differentiated/ undifferentiated</td>
<td>Mucinous</td>
<td>Mucinous</td>
</tr>
<tr>
<td>Mixed</td>
<td>Not defined</td>
<td>Description according to the proportion (e.g. por2&gt;sign&gt;tub2)</td>
<td>Mixed</td>
</tr>
<tr>
<td>Not defined</td>
<td>Not defined</td>
<td>Special type: Adenosquamous carcinoma Squamous cell carcinoma Undifferentiated carcinoma Carcinoma with lymphoid stroma Hepatoid adenocarcinoma Adenocarcinoma with enteroblastic differentiation Adenocarcinoma of fundic gland type</td>
<td>Other histological subtypes: Adenosquamous carcinoma Squamous cell carcinoma Undifferentiated carcinoma Carcinoma with lymphoid stroma Hepatoid adenocarcinoma Adenocarcinoma with enteroblastic differentiation Adenocarcinoma of fundic gland type Micropapillary adenocarcinoma</td>
</tr>
</tbody>
</table>


Table 2: World Health Organization histological classification of gastric carcinoma

<table>
<thead>
<tr>
<th>Tumour type</th>
<th>Histologic features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenocarcinoma, main histologic types</td>
<td></td>
</tr>
<tr>
<td>Tubular adenocarcinoma</td>
<td>Most common subtype; composed of dilated or slit-like branching tubules of variable diameter or acinar structures</td>
</tr>
<tr>
<td>Papillary adenocarcinoma</td>
<td>Exophytic growth pattern and most commonly well-differentiated; composed of elongated finger-like processes lined by columnar or cuboidal cells supported by fibrovascular cores.</td>
</tr>
<tr>
<td>Poorly cohesive carcinoma, including signet ring cell carcinoma and other subtypes</td>
<td>Accounting for 20-54% of gastric cancers; composed of neoplastic cells that are isolated or arranged in small aggregates without well-formed glands; either signet-ring cell type (composed predominantly or exclusively of signet-ring cells) or non-signet ring cell type with marked desmoplasia</td>
</tr>
<tr>
<td>Mucinous adenocarcinoma</td>
<td>Composed of malignant epithelium and extracellular mucin pools (mucin pools &gt;50% of the tumour area)</td>
</tr>
<tr>
<td>------------------------</td>
<td>--------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Mixed adenocarcinoma</td>
<td>Composed of poorly cohesive component and one or more other distinct histological components such as glandular carcinoma.</td>
</tr>
</tbody>
</table>

**Adenocarcinoma, other histological subtypes**

<table>
<thead>
<tr>
<th>Gastric (adeno)carcinoma with lymphoid stroma</th>
<th>Characterized by irregular sheets, trabeculae, ill-defined tubules or syncytia of polygonal cells embedded within a prominent lymphocytic infiltrate, with intraepithelial lymphocytes; frequently associated with EBV infection; less commonly associated with microsatellite instability and/or mismatch repair deficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatoid adenocarcinoma and related entities</td>
<td>Composed of large polygonal eosinophilic hepatocyte-like neoplastic cells with AFP expression; other AFP-producing carcinomas including well-differentiated papillary/tubular-type adenocarcinoma with clear cytoplasm, adenocarcinoma with enteroblastic differentiation and yolk-sac tumour-like carcinoma.</td>
</tr>
<tr>
<td>Micropapillary adenocarcinoma</td>
<td>Composed of micropapillary component (10-90% of the tumour area) and tubular/papillary adenocarcinoma</td>
</tr>
<tr>
<td>Gastric adenocarcinoma of fundic-gland type</td>
<td>Likely develop from oxyntic gland adenoma with oxyntic gland differentiation; include chief-cell predominant (most common), parietal cell-predominant, and mixed phenotype</td>
</tr>
<tr>
<td>Rare histological subtypes</td>
<td>Mucocoeipidermoid carcinoma, paneth cell carcinoma, and parietal cell carcinoma</td>
</tr>
<tr>
<td>Gastric squamous cell carcinoma</td>
<td>Only composed of squamous cell carcinoma with no other histological component on thorough sampling</td>
</tr>
<tr>
<td>Gastric adenosquamous cell carcinoma</td>
<td>Admixture of adenocarcinoma and squamous cell carcinoma with the squamous cell component ≥25%</td>
</tr>
<tr>
<td>Gastric undifferentiated (anaplastic) carcinoma</td>
<td>Composed of diffuse sheets of anaplastic, large to medium size polygonal cells, with frequent pleomorphic tumour giant cells; other morphologies include rhabdoid cell, sarcomatoid pleomorphic pattern, undifferentiated carcinoma with osteoclast-like giant cells, carcinoma with lymphoepithelioma-like feature, and glandular</td>
</tr>
<tr>
<td>Gastroblastoma</td>
<td>Composed of uniform spindle cells and uniform epithelial cells arranged in nests.</td>
</tr>
<tr>
<td>Gastric neuroendocrine carcinoma (NEC)</td>
<td></td>
</tr>
<tr>
<td>Small cell NEC</td>
<td>Resemble its lung counterpart; frequent necrosis</td>
</tr>
<tr>
<td>Large cell NEC</td>
<td>Resemble its lung counterpart; frequent necrosis</td>
</tr>
<tr>
<td>Mixed neuroendocrine-non-neuroendocrine neoplasm</td>
<td></td>
</tr>
<tr>
<td>Mixed adenocarcinoma-NEC</td>
<td>Composed of both adenocarcinoma and NEC with each component ≥30%</td>
</tr>
<tr>
<td>Mixed adenocarcinoma-neuroendocrine tumour</td>
<td>Composed of both adenocarcinoma and NET with each component ≥30%</td>
</tr>
</tbody>
</table>
Appendix 5   WHO Classification of Gastric Tumours 5th edition

Benign epithelial tumours and precursors
8148/0  Glandular intraepithelial neoplasia, low grade
8148/2  Glandular intraepithelial neoplasia, high grade
8213/0*  Serrated dysplasia, low grade
8213/2*  Serrated dysplasia, high grade
  Intestinal-type dysplasia
  Foveolar-type (gastric-type) dysplasia
  Gastric pit/crypt dysplasia
8144/0*  Intestinal-type adenoma, low grade
8144/2*  Intestinal-type adenoma, high grade
  Sporadic intestinal-type gastric adenoma
  Syndromic intestinal-type gastric adenoma
8210/0*  Adenomatous polyp, low-grade dysplasia
8210/2*  Adenomatous polyp, high-grade dysplasia

Malignant epithelial tumours
8140/3  Adenocarcinoma NOS
8211/3  Tubular adenocarcinoma
8214/3  Parietal cell carcinoma
8255/3  Adenocarcinoma with mixed subtypes
8260/3  Papillary adenocarcinoma NOS
8265/3  Micropapillary carcinoma NOS
8430/3  Mucoepidermoid carcinoma
8480/3  Mucinous adenocarcinoma
8490/3  Signet-ring cell carcinoma
8490/3  Poorly cohesive carcinoma
8512/3  Medullary carcinoma with lymphoid stroma
8576/3  Hepatoid adenocarcinoma
  Paneth cell carcinoma
8070/3  Squamous cell carcinoma NOS
8560/3  Adenosquamous carcinoma
8020/3  Carcinoma, undifferentiated, NOS
8014/3  Large cell carcinoma with rhabdoid phenotype
8022/3  Pleomorphic carcinoma
8033/3  Sarcomatoid carcinoma
8035/3  Carcinoma with osteoclast-like giant cells
8976/1*  Gastroblastoma
8240/3  Neuroendocrine tumour NOS
8240/3  Neuroendocrine tumour, grade 1
8249/3  Neuroendocrine tumour, grade 2
8249/3  Neuroendocrine tumour, grade 3
8153/3  Gastrinoma NOS
8156/3  Somatostatinoma NOS
8241/3  Enterochromaffin-cell carcinoid
8242/3  ECL-cell carcinoid, malignant
8246/3  Neuroendocrine carcinoma NOS
8013/3  Large cell neuroendocrine carcinoma
8041/3  Small cell neuroendocrine carcinoma
8154/3  Mixed neuroendocrine–non-neuroendocrine neoplasm (MiNEN)

These morphology codes are from the International Classification of Diseases for Oncology, third edition, second revision (ICD-O-3.2).\(^4\) Behaviour is coded /0 for benign tumours; /1 for unspecified, borderline, or uncertain behaviour; /2 for carcinoma in situ and grade III intraepithelial neoplasia; /3 for malignant tumours, primary site; and /6 for malignant tumours, metastatic site. Behaviour code /6 is not generally used by cancer registries.

This classification is modified from the previous WHO classification, taking into account changes in our understanding of these lesions.\(^2\)

* Codes marked with an asterisk were approved by the IARC/WHO Committee for ICD-O at its meeting in April 2019.

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## Appendix 6  Tumour regression grading

### Table 3: Mandard tumour regression grading system\textsuperscript{52}

<table>
<thead>
<tr>
<th>Description</th>
<th>Tumour Regression Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete regression: fibrosis without detectable tumour</td>
<td>1</td>
</tr>
<tr>
<td>Fibrosis with rare, scattered residual cancer cells</td>
<td>2</td>
</tr>
<tr>
<td>Fibrosis and tumour cells with a predominance of fibrosis</td>
<td>3</td>
</tr>
<tr>
<td>Fibrosis and tumour cells with predominance of tumour cells</td>
<td>4</td>
</tr>
<tr>
<td>No signs of regression</td>
<td>5</td>
</tr>
</tbody>
</table>

### Table 4: Becker Tumour Regression Grading System\textsuperscript{53}

<table>
<thead>
<tr>
<th>Description</th>
<th>Tumour Regression Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>No residual carcinoma</td>
<td>1</td>
</tr>
<tr>
<td>1-10% residual carcinoma</td>
<td>2</td>
</tr>
<tr>
<td>11-50% residual carcinoma</td>
<td>3</td>
</tr>
<tr>
<td>&gt;50% residual carcinoma</td>
<td>4</td>
</tr>
</tbody>
</table>

### Table 5: CAP modified Ryan tumour regression grading system\textsuperscript{54}

<table>
<thead>
<tr>
<th>Description</th>
<th>Tumour Regression Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>No viable cancer cells (complete response)</td>
<td>0</td>
</tr>
<tr>
<td>Single cells or rare small groups of cancer cells (near complete response)</td>
<td>1</td>
</tr>
<tr>
<td>Residual cancer with evident tumour regression, but more than single cells or rare small groups of cancer cells (partial response)</td>
<td>2</td>
</tr>
<tr>
<td>Extensive residual cancer with no evident tumour regression (poor or no response)</td>
<td>3</td>
</tr>
</tbody>
</table>
Appendix 7  Ancillary studies

Table 6. Molecular classifications of gastric adenocarcinoma by the Cancer Genome Atlas (TCGA) and their clinicopathologic applications

<table>
<thead>
<tr>
<th></th>
<th>EBV-positive</th>
<th>Microsatellite instability</th>
<th>Genomically stable</th>
<th>Chromosomal instability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence</td>
<td>3-9%</td>
<td>7-22%</td>
<td>15-25%</td>
<td>50-68%</td>
</tr>
<tr>
<td>Surrogate immunohistochemistry</td>
<td>EBER in situ hybridization</td>
<td>Mismatch repair proteins (MLH1/PMS2/MSH2/MSH6)</td>
<td>E-cadherin</td>
<td>p53</td>
</tr>
<tr>
<td>Histology</td>
<td>Gastric carcinoma with lymphoid stroma</td>
<td>Component of poorly differentiated solid type</td>
<td>Diffuse/poorly cohesive type</td>
<td>Intestinal/tubular type</td>
</tr>
<tr>
<td>Her2(ERBB2) amplification</td>
<td>Very rare</td>
<td>Very rare</td>
<td>Vary rare</td>
<td>Present</td>
</tr>
<tr>
<td>Prognostic significance</td>
<td>Favorable</td>
<td>Favorable</td>
<td>Poor</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Predictive significance</td>
<td>Possible indication for immunotherapy due to increased expression of PD-L1</td>
<td>Chemotherapy less beneficial Indication for immunotherapy due to high tumour mutational burden</td>
<td></td>
<td>Indication for Trastuzumab for Her2 positive tumour</td>
</tr>
</tbody>
</table>

HER2

Up to one third of gastric carcinomas show over-expression and amplification of HER2.\textsuperscript{95} Intestinal type gastric cancers show a significantly higher rate of HER2 positivity than diffuse cancers.\textsuperscript{95} Results from the ToGA trial have shown that the HER2 antagonist trastuzumab combined with chemotherapy in HER2 positive tumours resulted in improved overall survival and overall response rate.\textsuperscript{95} A modified HER2 scoring system for gastric cancer was used for the ToGA trial based on a validation study.\textsuperscript{96}

Trastuzumab is approved in New Zealand by Medsafe for treatment of patients with HER2 positivity (HER2 3+ IHC or HER2/CEP17>2 or HER2> 6 copies per nucleus) in advanced adenocarcinoma of the stomach or GOJ.

In Australia, the Therapeutic Goods Administration (TGA) approved the use of trastuzumab for patients whose tumours show an ISH ratio of >2 as well as an IHC result of 2+ or 3+. Similarly, trastuzumab is approved for advanced adenocarcinoma of stomach or OGJ in patients who have not received prior anticancer treatment for their metastatic disease.

As a result, pathologists are expected to report on the HER2 status of gastric cancers (Table 1).
Figure 7. HER2 testing algorithm in gastric and GOJ. Reproduced with permission from Kumarasinghe et al (2017). HER2 testing in advanced gastric and gastro-oesophageal cancer: analysis of an Australia-wide testing program. Pathology 49(6):575-581.97
Figure 8. HER2 algorithm for pathologists. Tumour cell cluster is defined as a cluster of five or more tumour cells. Additional recommendations: Pathologists should ensure that biopsy or resection specimens used for HER2 testing are rapidly placed in fixative, ideally within 1 hour (cold ischemic time), and are fixed in 10% neutral buffered formalin for 6 to 72 hours. Routine histology processing and HER2 testing should be performed according to analytically validated protocols. Pathologists should identify areas of invasive adenocarcinoma and also mark areas with strongest intensity of HER2 expression by immunohistochemistry (IHC) in the gastroesophageal adenocarcinoma specimen for subsequent scoring when in situ hybridisation (ISH) is required. Note - currently in Australia, access to anti-HER2 therapy requires that HER2 positivity must also be confirmed by ISH. Reproduced with permission from Bartley et al (2016). HER2 testing and clinical decision making in gastroesophageal adenocarcinoma: guideline from the College of American Pathologists, American Society for Clinical Pathology, and the American Society of Clinical Oncology. Arch Pathol Lab Med 140(12):1345-1363.
### Table 7. HER2 scoring (immunohistochemistry) table

<table>
<thead>
<tr>
<th>Surgical specimen</th>
<th>Biopsy specimen</th>
<th>Score</th>
<th>HER2 status (protein over-expression)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No reactivity or membranous reactivity in &lt;10% of tumour cells</td>
<td>No reactivity or no membranous reactivity in any tumour cells</td>
<td>0</td>
<td>Negative</td>
</tr>
<tr>
<td>Faint/barely perceptible membranous reactivity in ≥10% of tumour cells; cells are reactive only in part of their membrane</td>
<td>Tumour cell cluster with a faint/barely perceptible membranous reactivity irrespective of percentage of tumour cells stained</td>
<td>1+</td>
<td>Negative</td>
</tr>
<tr>
<td>Weak to moderate complete, basolateral or lateral membranous reactivity in ≥10% of tumour cells</td>
<td>Tumour cell cluster with a weak to moderate complete, basolateral or lateral membranous reactivity irrespective of percentage of tumour cells stained</td>
<td>2+</td>
<td>Equivocal</td>
</tr>
<tr>
<td>Strong complete, basolateral or lateral membranous reactivity in ≥10% of tumour cells</td>
<td>Tumour cell cluster with a strong complete, basolateral or lateral membranous reactivity irrespective of percentage of tumour cells stained</td>
<td>3+</td>
<td>Positive</td>
</tr>
</tbody>
</table>
Figure 9. IHC for HER2 demonstrating heterogeneous patterns

Score 3+
Left score 1+
Right score 3+
Mix of scores 1+, 2+ and 3+
Figure 10. HER2 gene amplification by SISH on the left half of the tumour in contrast to non-amplification on the right half. This example also highlights HER2 heterogeneity.
### Table 8. Template for reporting mismatch repair (MMR) protein immunohistochemistry results.99

<table>
<thead>
<tr>
<th>Specimen site:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Testing performed on block number(s):</td>
<td></td>
</tr>
<tr>
<td><strong>Immunohistochemistry (IHC) Results for Mismatch Repair (MMR) Proteins (select all that apply)</strong></td>
<td></td>
</tr>
<tr>
<td><strong>MLH1</strong></td>
<td></td>
</tr>
<tr>
<td>Intact nuclear expression</td>
<td></td>
</tr>
<tr>
<td>Loss of nuclear expression</td>
<td></td>
</tr>
<tr>
<td>Cannot be determined (explain):</td>
<td></td>
</tr>
<tr>
<td><strong>MSH2</strong></td>
<td></td>
</tr>
<tr>
<td>Intact nuclear expression</td>
<td></td>
</tr>
<tr>
<td>Loss of nuclear expression</td>
<td></td>
</tr>
<tr>
<td>Cannot be determined (explain):</td>
<td></td>
</tr>
<tr>
<td><strong>MSH6</strong></td>
<td></td>
</tr>
<tr>
<td>Intact nuclear expression</td>
<td></td>
</tr>
<tr>
<td>Loss of nuclear expression</td>
<td></td>
</tr>
<tr>
<td>Cannot be determined (explain):</td>
<td></td>
</tr>
<tr>
<td><strong>PMS2</strong></td>
<td></td>
</tr>
<tr>
<td>Intact nuclear expression</td>
<td></td>
</tr>
<tr>
<td>Loss of nuclear expression</td>
<td></td>
</tr>
<tr>
<td>Cannot be determined (explain):</td>
<td></td>
</tr>
</tbody>
</table>

**Background non-neoplastic tissue/internal control shows intact nuclear expression**

**Mismatch Repair (MMR) Interpretation**

- No loss of nuclear expression of MMR proteins: No evidence of deficient mismatch repair (low probability of MSI-H)
- Loss of nuclear expression of one or more MMR proteins: deficient mismatch repair

**Note:** All reporting elements listed in this table are not required by the CAP. However, these elements may be clinically important but are not yet validated or regularly used in patient management.

Figure 11. Screening for Lynch syndrome in gastric malignancy

Methylation studies to be performed on all cases which are MLH1-ve and PMS2-ve. If MLH1 promoter methylation is present, Lynch Syndrome is unlikely.

Referral to familial cancer service is indicated:
1. For all MLH1-ve, PMS2-ve, MSH2-ve, MSH6-ve cases
2. For all MLH1-ve, PMS2-ve, MSH2-ve, MSH6-ve cases
3. For all MLH1-ve, PMS2-ve, MSH2-ve, MSH6-ve cases
4. For all MLH1-ve, PMS2-ve, MSH2-ve, MSH6-ve cases which are not hypermethylated
References


RCPA (Royal College of Pathologists of Australasia) (2009). Guidelines for Authors of Structured Cancer Pathology Reporting Protocols. RCPA, Surry Hills NSW.


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