

GASTRIC CANCER STRUCTURED REPORTING PROTOCOL (1st Edition, 2011)

Core Document versions:

- AJCC Cancer Staging Manual 7th edition (including errata corrected with 5th reprint 10th Aug 2010).
- World Health Organization Classification of Tumours Pathology and Genetics of Tumours of the Digestive System, 2010, 4th edition

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The Royal College of Pathologists of Australasia ("College") has developed these protocols as an educational tool to assist pathologists in reporting of relevant information for specific cancers. While each protocol includes "standards" and "guidelines" which are indicators of 'minimum requirements' and 'recommendations', the protocols are a first edition and have not been through a full cycle of use, review and refinement. Therefore, in this edition, the inclusion of "standards" and "guidelines" in each document are provided as an indication of the opinion of the relevant expert authoring group, but should not be regarded as definitive or as widely accepted peer professional opinion. The use of these standards and guidelines is subject to the clinician's judgement in each individual case.

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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 will be prepared for endoscopic resections. Endoscopic biopsy specimens are excluded. The focus is on primary gastric epithelial malignancies excluding those of the gastro-oesophageal junction, which should be staged as oesophageal cancer according to the 2010 recommendations by the AJCC/UICC.¹

Synoptic reporting aims to improve the completeness and usability of pathology reports for clinicians, and in particular to improve decision support for cancer treatment. The protocol provides a framework for reporting of any gastric carcinoma, whether as a minimum data set or fully comprehensive report. This approach also allows easy extraction of relevant information for cancer registries and for clinical, translational and basic research. The structured report allows flexibility in the report to reflect the inherent heterogeneity of gastric carcinoma, including the provision of any appropriate additional information as free text.

Abbreviations

AJCC	American Joint Committee on Cancer
OGJ	Oesophagogastric junction
PBS	Pharmaceutical Benefits Scheme
RCPA	Royal College of Pathologists of Australasia
TNM	tumour-node-metastasis
UICC	International Union Against Cancer
WHO	World Health Organization

Definitions

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

Ancillary study An ancillary study is any pathology investigation that may form part of a cancer pathology report but is not part of routine histological assessment.

Clinical information Patient information required to inform pathological assessment, usually provided with the specimen request form, also referred to as "pre-test information".

Commentary Commentary is text, diagrams or photographs that clarify the standards (see below) and guidelines (see below), provide examples and help with interpretation, where necessary (not every standard or guideline has commentary).

Commentary is used to:

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

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

General commentary General commentary is text that is not associated with a specific standard or guideline. It is used:

- 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	<p>Guidelines are recommendations; they are not mandatory, as indicated by the use of the word 'should'. Guidelines cover items that are not essential for clinical management, staging or prognosis of a cancer, but are recommended.</p> <p>Guidelines include key observational and interpretative findings that are fundamental to the diagnosis and conclusion. Such findings are essential from a clinical governance perspective, because they provide a clear, evidentiary decision-making trail.</p> <p>Guidelines are not used for research items.</p> <p>In this document, guidelines are prefixed with 'G' and numbered consecutively within each chapter (eg G1.10).</p>
Macroscopic findings	Measurements, or assessment of a biopsy specimen made by the unaided eye.
Microscopic findings	In this document, the term 'microscopic findings' refers to morphological assessment using a microscope or equivalent.
Predictive factor	A <i>predictive factor</i> is a measurement that is associated with response or lack of response to a particular therapy.
Prognostic factor	A <i>prognostic factor</i> is a measurement that is associated with clinical outcome in the absence of therapy or with the application of a standard therapy. It can be thought of as a measure of the natural history of the disease.
Standard	<p>Standards are mandatory, as indicated by the use of the term 'must'. Their use is reserved for core items essential for the clinical management, staging or prognosis of the cancer.</p> <p>The summation of all standards represents the minimum dataset for the cancer.</p> <p>In this document, standards are prefixed with 'S' and numbered consecutively within each chapter (eg S1.02).</p>
Structured report	A report format which utilises standard headings, definitions and nomenclature with required information.
Synoptic report	A structured report in condensed form (as a synopsis or precis).
Synthesis	Synthesis is the process in which two or more pre-existing elements are combined, resulting in the formation of something new. 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

Nearly 2500 cases of gastric cancers are diagnosed yearly in Australia and New Zealand together²⁻³. Gastric cancer is ranked the 10th commonest cancer (2.2% of all cancers) and 7th among those responsible for mortality (6.2% of all cancer related deaths) in Australia.² Globally gastric cancer accounts for 10% of all cancers⁴ and is ranked as the 2nd most common cause of cancer death as at 2002⁵. Gastric cancer incidence and mortality rates in Australia and New Zealand are low compared to the rest of the world. They are similar to those of Canada and the United Kingdom and higher than those found in the United States.²

There has been a steady decline in both the incidence and mortality of gastric carcinoma worldwide over the last 15 years. However, the absolute number of diagnoses continues to rise, presumably due to the advancing age of the global population.⁴ Stomach cancer incidence fell by an average of 2.3% and 1.6% per year and the mortality rates decreased substantially by 3.4% and 3.6% in males and females on average, per annum over the 1991 to 2001 period in Australia² However gastric cancer remains a significant health care issue both in Australia and New Zealand. An annual average of 1203 (1998-2002) deaths with an annual total of 1902 new cases in the year 2001 was recorded in Australia.² Comparatively an annual average of 296 (1997-2007) deaths with an annual total of 382 new cases were reported in New Zealand in the year 2001.³

Gastric carcinoma has been traditionally divided on the basis of the location, into proximal ("cardia") and distal (mainly antro-pyloric) cancers. Proximal (cardia) tumours have a worse prognosis than distal tumours.⁵⁻⁷ Carcinomas of the "cardia" have been most commonly reported in North American and European populations.⁸ However the number of proximal (cardia) tumours is likely to reduce as a result of revision of the classification of adenocarcinomas of the gastro-esophageal junction by the UICC/AJCC.¹ Hence gastric antrum is likely to become the most common site of gastric carcinoma worldwide in the future.

Countries with a high incidence of gastric cancer where asymptomatic patients may be screened have a high proportion (30–50%) of early gastric cancer (EGC)⁹, in contrast to a lower proportion of (16–24%) in North America and European countries where overall gastric cancer incidence is low.¹⁰ Early gastric cancers (EGC) have a low incidence of vascular invasion and lymph-node metastasis and a good prognosis; approximately 90% of patients survive over 10 years.¹¹⁻¹² EGC is increasingly treated with mucosal/submucosal excisions with successful results in countries in which gastric cancer incidence is high and in other studies the technique has shown a diagnostic and staging advantage.¹³⁻¹⁴ Unfortunately, at the time of diagnosis most patients with advanced carcinoma already have lymph node metastases reflecting current dismal prognosis for advanced gastric cancer, according to local and global statistics.^{2,15-16} Currently the only curative treatment for gastric cancer is complete surgical resection of the primary tumour. The outcome of the surgical procedure is largely dependent on achieving adequately clear surgical margins. Current recommendations are that patients be considered for perioperative chemotherapy for the purpose of down staging and improvement in 5 year survival. For more advanced disease systemic chemotherapy has a role. Recent evidence has shown that the Her 2 status can have an impact on choice of systemic therapy and subsequent survival.¹⁷⁻¹⁸

Importance of histopathological reporting

The role of the histopathologist in the management of gastric carcinoma is to produce an accurate histological assessment that will inform clinicians about prognosis and the need for additional treatment. The most common types of specimen encountered include oesophagogastrectomy, total gastrectomy, distal gastrectomy and endoscopic resections. Endoscopic mucosal resections (EMR) and submucosal dissections (ESD) and laparoscopic resections may be offered as definitive therapy for EGC without adverse pathological features.

There is evidence to suggest that endoscopic resections are likely to be ineffective as complete cure for EGCs with adverse pathological features necessitating surgery.^{12,19} These features are submucosal invasion; tumour diameter > 3.0–3.5 cm; the presence of vascular invasion; the presence of lymphatic permeation; depressed or ulcerated lesions and undifferentiated histology.

Pathological assessment of resection specimens should provide information on the salient features of gastric cancer such as tumour location, type, size, stage, adequacy of resection/excision, tumour regression grade, and biological markers such as Her2 status where appropriate. Given the fact that the only curative treatment for gastric cancer is complete surgical resection of the primary tumour, it is imperative that the relevant information about adequacy of surgical margins is provided in the report.

The stage of gastric cancer with special reference to extension to the serosa and lymph nodes remains the strongest prognostic indicator for advanced gastric cancer. Lymphatic and vascular invasion often seen in advanced cases, specifically carry a poor prognosis. Published evidence support the value of a number-based classification scheme for reporting nodal involvement in gastric cancer.²⁰

There is recent evidence to suggest certain immunophenotypes of gastric carcinomas are more biologically aggressive.^{21,22} However the value of histological typing of gastric carcinomas in predicting prognosis is somewhat controversial. It has been recognised that a significant number of tumours classified as Lauren 'intestinal' type are in fact gastric immunophenotype or of mixed gastric/intestinal immunophenotype while some 'diffuse' carcinomas are intestinal immunophenotype.²³ (Refer to CG4.01b for further information.)

Benefits of structured reporting

It is not uncommon to find inconsistencies in pathology reports within single institutions, across organisations, states and countries. The single most effective way to overcome this situation is to create a standardised reporting system that will ensure that key pathological features necessary for patient management and prognostication are included. It is also desirable to document important features for the purposes of audits, tumour registries and research in a systematic fashion.

The College of American Pathologists (CAP), Association of Directors of Anatomic and Surgical Pathology (ADASP) and the Royal College of Pathologists (United Kingdom) have recently published protocols for the reporting of gastric cancer.²⁴⁻²⁶ These protocols by themselves or with modifications to suit local needs have been used in recent years in Australia and New Zealand. A uniform modified protocol prepared in agreement with all parties involved in patient management is

needed to cater for local requirements. This publication aims to fulfil this need incorporating relevant, currently available publications. The intention is to provide pathologists with a minimum dataset and guidelines that are comprehensive and easy to use. It is hoped that this will help the clinicians to manage the patients optimally.

In this document, standards and guidelines for pathology reporting of gastric epithelial tumours have been prepared considering the best available evidence-based information and collective suggestions and expert opinions of a multidisciplinary group.

Given this background structured gastric cancer reporting aims at "guiding/teaching" in order that the gastric cancer reporting is up to a desired standard, "enhancing" the practice of pathology with regards to gastric cancer, "inducing" the clinicians to undertake appropriate management and "promoting" advanced gastric cancer research in Australia.

Design of this protocol

This protocol defines the relevant information to be assessed and recorded in a pathology report for gastric cancer. Mandatory elements (standards) are differentiated from those that are not mandatory but represent best practice (guidelines). Also, items suited to tick boxes are distinguished from more complex elements requiring free text or narrative. The structure provided in the following chapters, headings and subheadings describe the elements of information and their groupings, but does not necessarily represent the format of either a pathology report (Chapter 7) or a 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.

It should be noted that if the resection specimen contains two or more primary carcinomas (as indicated by the term 'synchronous carcinomas' on the reporting checklist) then a separate reporting checklist must be completed for each primary carcinoma.

Key documentation

- Guidelines for Authors of Structured Cancer Pathology Reporting Protocols²⁷
- The Pathology Request-Test-Report Cycle — Guidelines for Requesters and Pathology Provider²⁸
- WHO Classification of tumours, *Pathology and Genetics of Tumours of the Digestive System, 2010*, 4th edition²³
- AJCC Cancer Staging Manual, 7th edition, 2010¹

Changes since the last edition

Not applicable.

Authority and development

This section provides details of the committee involved in developing this protocol and the process by which it was developed.

Protocol developers

This protocol was developed by an expert committee, with assistance from relevant stakeholders.

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Acknowledgements

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Stakeholders

ACT Health

Anatomical Pathology Advisory Committee (APAC)

Australian Association of Pathology Practices Inc (AAPP)

Australian Cancer Network
Australian Commission on Safety and Quality in Health Care
Cancer Australia
Cancer Control New Zealand
Cancer Council ACT
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
Clinical Oncology Society of Australia (COSA)
Colorectal Cancer Research Consortium
Department of Health and Ageing
Gastroenterological Society of Australia GESA
Grampians Integrated Cancer Services (GICS)
Health Informatics Society of Australia (HISA)
Medical Software Industry Association (MSIA)
National Breast and Ovarian Cancer Centre (NBOCC)
National Coalition of Public Pathology (NCOPP)
National E-Health Transition Authority (NEHTA)
National Pathology Accreditation Advisory Council (NPAAC)
National Round Table Working Party for Structured Pathology Reporting of Cancer.
New Zealand Guidelines Group (NZGG)
New Zealand Ministry of Health
New Zealand Society of Gastroenterology (NZSG)
NSW Department of Health
Peter MacCallum Cancer Institute
Queensland Cooperative Oncology Group (QCOG)
Representatives from laboratories specialising in anatomical pathology across Australia
Royal Australasian College of Physicians (RACP)
Southern Cancer Network, Christchurch, New Zealand
Southern Melbourne Integrated Cancer Service (SMICS)
Standards Australia

The Medical Oncology Group of Australia
The Royal Australasian College of Surgeons (RACS)
The Royal Australian and New Zealand College of Radiologists (RANZCR)
The Royal Australian College of General Practitioners (RACGP)
The Royal College of Pathologists of Australasia (RCPA)
Victorian Cooperative Oncology Group (VCOG)
Western Australia Clinical Oncology Group (WACOG)

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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 expert group.

1 Clinical information and surgical handling

This chapter relates to information that should be collected before the pathology test, and procedures that are required before handover of specimens to the laboratory.

The standards and guidelines below specify the particular information and specimens required for Gastric Cancer. Some of this information can be collected on generic pathology request forms; any additional information required specifically for the reporting of Gastric Cancer may be recorded on a separate data sheet. Appendix 1 provides a standardised data sheet that may be useful in obtaining all relevant information.

S1.01 Adequate demographic and request information must be provided with the specimen by the requesting clinician.

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.²⁸ This document specifies the minimum information to be provided by the requesting clinician for any pathology test. Items relevant to cancer reporting protocols include:

- patient name
- date of birth
- sex
- identification and contact details of requesting doctor
- date of request
- Additional information specified in the RCPA *The Pathology Request-Test-Report Cycle — Guidelines for Requesters and Pathology Providers* such as the specimen type and clinical information relevant to the investigation is catered for in the following standards and guidelines.

CS1.01b The patient's ethnicity must be recorded, if known.

G1.01 The patient's health identifiers should be recorded where provided.

CG1.01a The patient's health identifiers may include the patient's Medical Record Number as well as a national health number such as a NHI or the Individual Healthcare Identifier (IHI).

S1.02 The pathology accession number of the specimen must be recorded.

S1.03 The principal clinician involved in the patient's care and responsible for investigating the patient must be identified.

CS1.03a The requesting clinician (identified under S1.01) may be the doctor who performs the surgery or biopsy, and may not be the person with overall responsibility for investigating and managing the patient. Identification of the principal clinician is essential, to ensure that pathological and clinical information is communicated effectively.

S1.04 The surgeon or proceduralist's identity and contact details must be recorded.

CS1.04a Name of operating surgeon or proceduralist and contact details.

S1.05 The tumour location/site must be recorded.

CS1.05a Select all that apply:

- proximal 1/3
- middle 1/3
- distal 1/3

CS1.05b Cancers whose midpoint is in the lower thoracic oesophagus, OGJ or within the proximal 5cm of the stomach (cardia) that extend into the OGJ or oesophagus are staged as adenocarcinoma of the oesophagus. All other cancers with a midpoint in the stomach lying more than 5cm distal to the OGJ or those within 5cm of the OGJ but not extending into the OGJ or oesophagus are staged using the gastric (non-OGJ) cancer staging system.¹

CS1.05c It should be noted that true gastric proximal (cardia) tumours are rare; most involve the OGJ and should therefore be staged using the oesophageal cancer staging system.¹

S1.06 The type of operation or procedure must be recorded.

CS1.06a Choose from one of the following:

- Oesophago-gastrectomy
- Total gastrectomy
- Subtotal (proximal or distal) gastrectomy
- Other (specify)

S1.07 If preoperative therapy has been administered, this must be recorded.

CS1.07a Choose from one of the following:

- Preoperative chemotherapy
- Preoperative radiotherapy
- Preoperative chemoradiotherapy

S1.08 The involvement of adjacent organs must be recorded.

CS1.08a 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.

CS1.08b Select all that apply:

- Pancreas
- Spleen
- Liver
- Other (specify)

S1.09 The presence of any distant metastases must be recorded.

CS1.09a 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.

CS1.09b Additional specimens taken e.g. peritoneal nodules, liver biopsy, other etc should be labelled and recorded separately.

CS1.09c The presence of positive peritoneal cytology is classified as metastatic disease. This information should be provided to the reporting pathologist, in part because the diagnosis may have been made at a different laboratory.

S1.10 The Surgeon's opinion on the existence of local residual cancer following the operative procedure must be recorded.

CS1.10a This item relates to the overall completeness of resection of the tumour, including evidence of residual disease at surgical margins or within regions in which resection has not been attempted. It allows for residual tumour status (R) to be assessed.

G1.02 Any additional relevant information should be recorded.

CG1.02a 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.

Surgical handling

S1.11 The specimen must be capable of orientation if the status of specific surgical margins is critical in determining the need for, or extent of, further surgery.

CS1.11a Where there are no anatomical landmarks, specimen orientation may be indicated with marking sutures or other techniques. If a specimen is orientated, the orientation should be indicated on the specimen request form (this

may be facilitated by the use of a diagram).

- G1.03 The specimen should be sent to the laboratory in the fresh state without delay where possible.
 - CG1.03a The laboratory should be informed if the specimen is likely to be received outside normal working hours.
 - CG1.03b Where a specimen is unable to be received by the laboratory (eg outside normal working hours), it should be opened by the surgeon, (see S2.01b and c) gastric content drained, and placed in an adequate volume of formalin based solution.
- G1.04 The specimen should be sent to the laboratory intact where possible.
 - CG1.04a When a specimen needs to be opened eg to confirm adequate surgical margins or tumour localisation, the specimen should be opened by a single longitudinal incision usually anterior to the greater curvature and should avoid cutting through tumour if at all possible. (See S2.01b and S2.01c for additional information).

S1.12 Lymph nodes must be labelled clearly, identifying the site.

- CS1.12a Lymph nodes taken separately from the gastric resection specimen must be labelled as to site. Labelling must allow differentiation between regional nodes (refer to diagrams S1.12a and b) and non regional nodes. Refer to CS2.02b for the definition of regional and non regional lymph nodes.
- CS1.12b Non-regional nodes include retropancreatic, mesenteric, para-aortic, portal and retroperitoneal. Metastasis in non-regional nodes are staged as distant metastasis.

Figure S1.12a Regional lymph nodes. 1, 3, 5: perigastric nodes of the lesser curvature. 2, 4a, 4b, 6: perigastric nodes along the greater curvature. Involvement of nodes above the diaphragm is defined as distant metastasis.

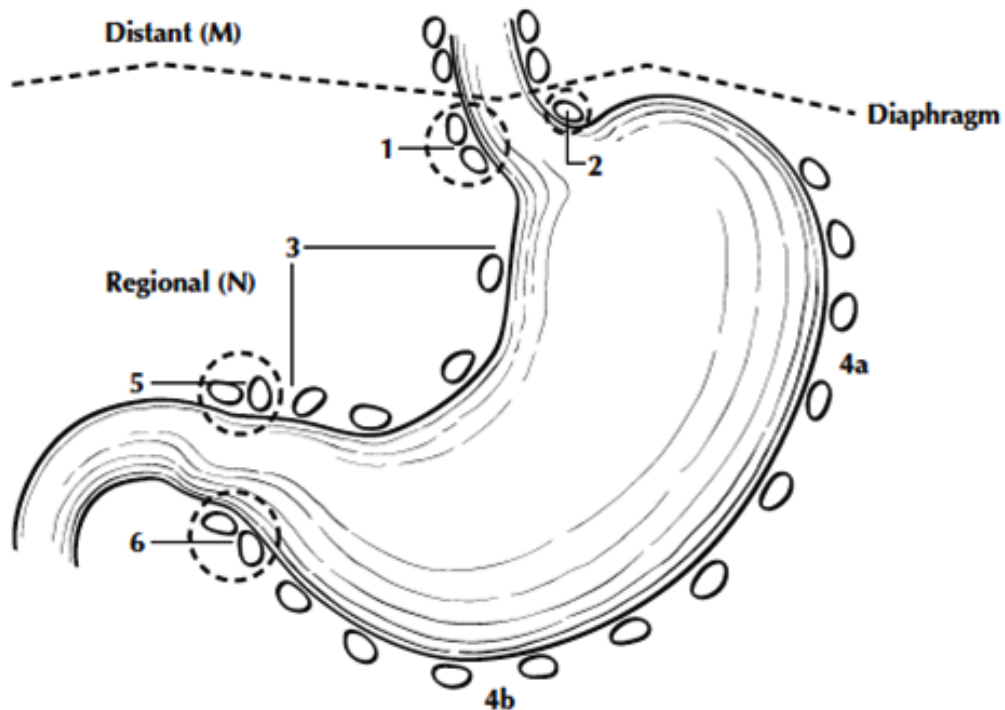
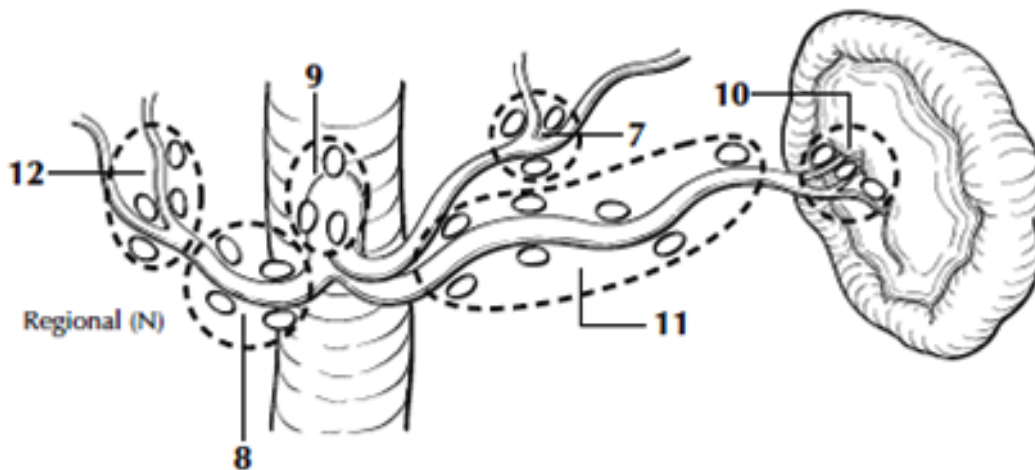


Figure S1.12b Regional lymph nodes of the stomach. 7: left gastric nodes; 8: nodes along the common hepatic artery; 9: nodes along the celiac artery; 10 and 11: nodes along the splenic artery; 12: hepatoduodenal



Figures 1.12a and b from AJCC Cancer Staging Atlas. Frederick L. Greene, Carolyn C. Compton, April G. Fritz, Jatin P. Shah and David P. Winchester. 2006 Springer. Reproduced with permission.

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.

Specimen handling

G2.01 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.

S2.01 The specimen must be handled in a systematic and thorough fashion to ensure completeness and accuracy of pathological data.

CS2.01a **Specimen reception:** specimens are best received fresh and without delay. This allows optimal orientation and sampling of non-fixed tissue e.g. tumour bank, research. Where receipt of fresh specimen is impractical, the specimen should be sent in an adequate volume of fixative (approximately 10 times greater than the tissue volume).²⁹

CS2.01b **Specimen, inspection, opening and fixing:** For non-proximal (cardia) tumours, the specimen is opened in such a way as to avoid cutting through the carcinoma. This is usually along the anterior border of the greater curve.²⁹ The specimen is then pinned onto a support and fixed in formalin, at least overnight. Some sources recommend at least 48 hours. Adequate fixation helps with cutting of thin slices and aids in lymph node identification.

CS2.01c For proximal (cardia) tumours (tumour within 5cm of the oesophagogastric junction, without extension into the oesophagus), the non peritonealised margin should be examined for macroscopic evidence of carcinoma penetration, then the non peritonealised margin of the lower oesophagus is inked, before opening. (Refer to the diagram S2.06b).

CS2.01d There are two methods of opening a specimen with a proximal (cardia) tumour. The first method involves opening the specimen with scissors along its length. If the tumour is not circumferential, then the specimen should be opened without cutting through the tumour. Alternatively, the specimen is opened above and below the carcinoma, without cutting through the tumour. A wick of formalin soaked paper is inserted into the unopened lumen to aid

fixation of the tumour. When fixed, the specimen is bread sliced horizontally through the tumour; this facilitates better visualisation of the non peritonealised margin.

- G2.02 Specific protocols should be followed for prophylactic gastrectomies from CDH1 mutation carriers.
- CG2.02a These stomachs are macroscopically normal²³, yet contain multifocal microscopic tumours. Specific pathologic protocols should be followed for this type of specimen.³⁰⁻³¹

S2.02 All lymph nodes must be harvested and examined histologically.

- CS2.02a In completely resected carcinomas, lymph node status is the most important independent prognostic indicator.²⁰
- CS2.02b Regional lymph nodes (see figures S1.12a & b) are the perigastric nodes along the lesser and greater curvatures and the nodes along the left gastric, common hepatic, hepatoduodenal, splenic and celiac arteries. Lymph node groups (as illustrated in figures S1.12a and b) offer no significant prognostic information, and thus all regional nodes can be reported together.¹
- Involvement of non-regional nodes such as retropancreatic, mesenteric, para-aortic, portal and retroperitoneal are classified as distant metastasis.
- CS2.02c Ideally, a minimum of 16 nodes should be examined for accurate staging.³²⁻³³ "Although it is suggested that at least 16 regional nodes be assessed pathologically, a pN0 determination may be assigned on the basis of the actual number of nodes evaluated microscopically."¹
- CS2.02d All macroscopically uninvolved nodes should be completely embedded. Macroscopically involved nodes require only one slice embedded for confirmation.
- CS2.02e Individually labelled lymph nodes (regional and non regional) should be reported separately.

Macroscopic findings

S2.03 The type of resection must be recorded.

- CS2.03a Options include:
- Oesophago-gastrectomy
 - Total gastrectomy
 - Subtotal (proximal or distal) gastrectomy
 - Other (specify)

S2.04 All linear measurements are in SI units, unless explicitly stated.

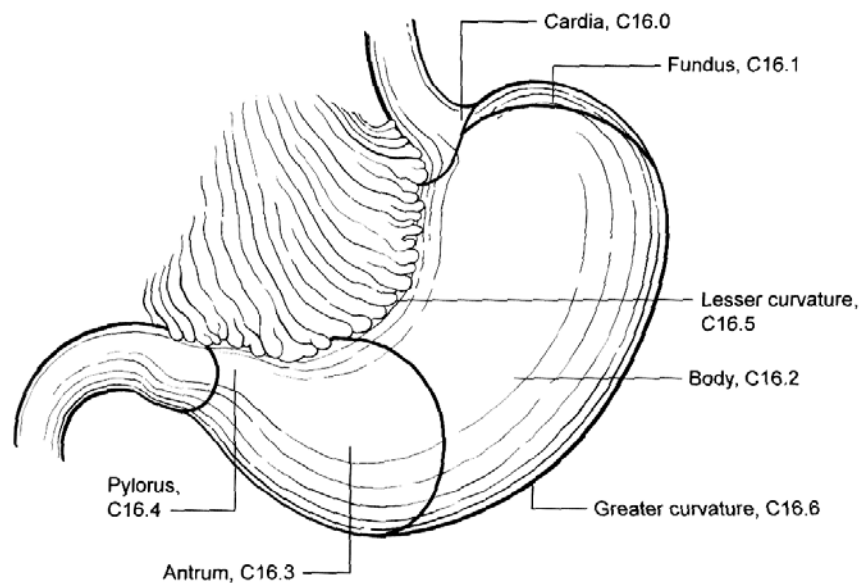
S2.05 The specimen dimensions must be recorded.

CS2.05a Length of the stomach greater curve, lesser curve, oesophagus, duodenum.

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

CS2.06a Record tumour site by anatomical location as in figure S2.06a. These sites conform to the ICD-O-3 topography codes.

Figure S2.06a Anatomical location of gastric cancer

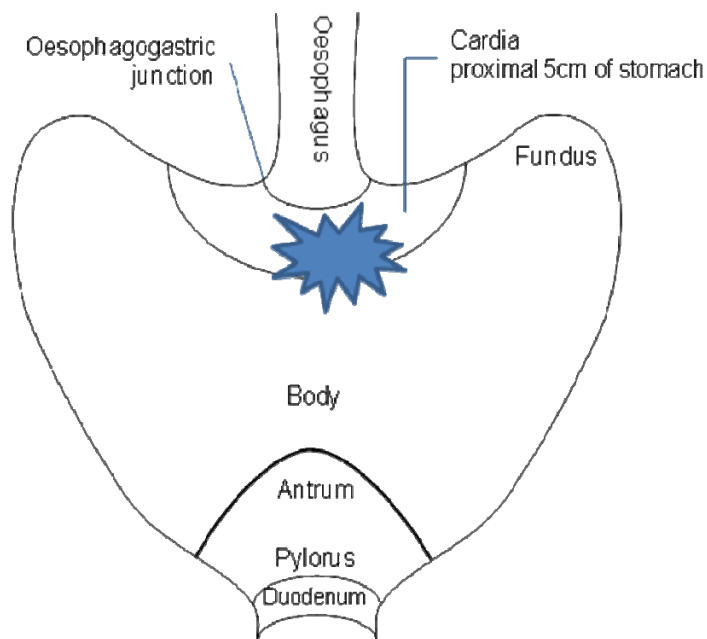


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CS2.06b For tumours of the proximal stomach (i.e., cardia; Siewert type 2⁰), this gastric structured reporting protocol uses the AJCC definition to distinguish between oesophagus and gastric tumours.

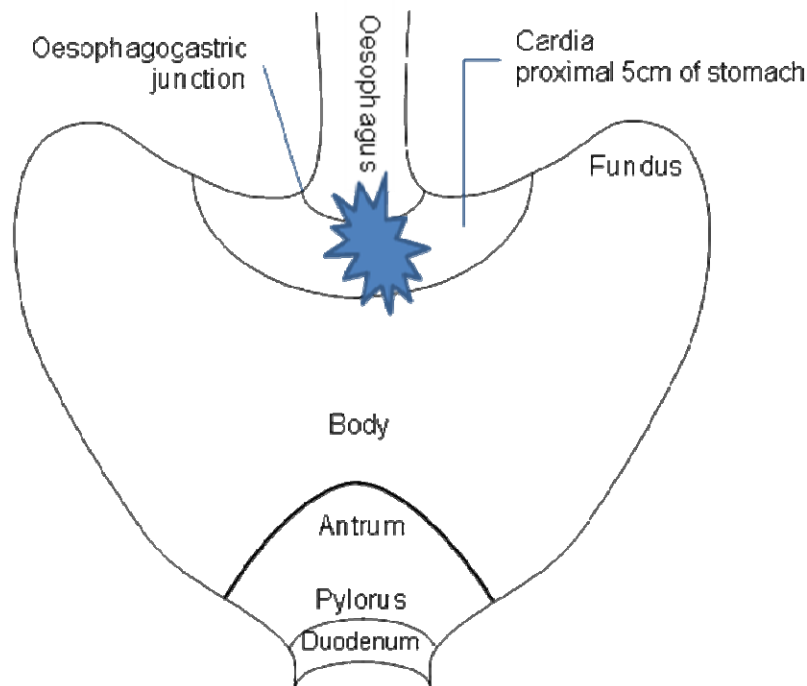
Tumours with an epicenter in the stomach within 5 cm of the oesophagogastric junction, without extension in the oesophagus (macroscopically or microscopically) are classified and staged using this gastric cancer reporting protocol, fig S2.06b.

Figure S2.06b Stage and classify as gastric carcinoma



CS2.06c Tumours of the cardia (Siewert type 2), that extend into the oesophagus (macroscopically or microscopically) are staged using the oesophageal cancer scheme, figure S2.06c.

Figure S2.06c Stage as oesophageal carcinoma (see comment CS3.01b)



CS2.06d The oesophagogastric junction can be identified by the upper limit of gastric rugal folds. If this mucosal landmark is obscured by extensive tumour involvement or columnar lined oesophagus, the junction can be located at the highest point of the peritoneal reflection on the serosal surface.

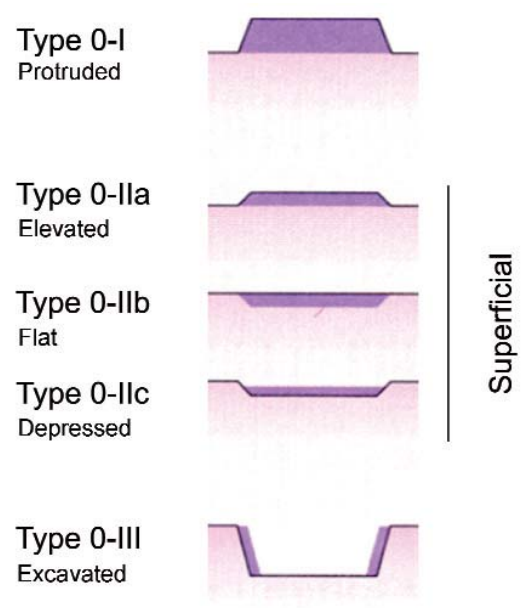
S2.07 The maximum tumour diameter must be recorded.

CS2.07a Tumour size 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).

S2.08 The macroscopic tumour type must be recorded.

CS2.08a Early gastric cancer growth patterns are classified using criteria similar to those used in endoscopy, into protruded, elevated, flat, depressed or excavated. Depressed type has a higher risk for increased stage and lymphatic invasion.²³ (refer to figure S2.08a below).

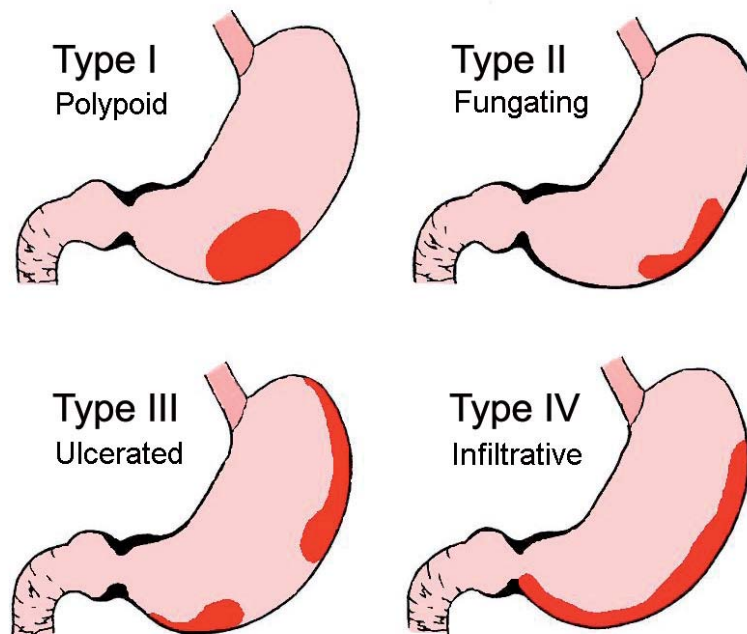
Figure S2.08a Growth patterns of early gastric carcinoma²³



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CS2.08b Advanced gastric cancer growth patterns are classified using the Borrmann criteria, into polypoid, fungating, ulcerated and infiltrative. Infiltrative type is associated with a poorer prognosis³⁴ (refer to figure S2.08b below).

Figure S2.08b Growth patterns of advanced gastric cancer according to the Borrmann classification.



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S2.09 The distance from the tumour to the nearest proximal or distal margin (cut end) must be recorded.

CS2.09a 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).

S2.10 For tumours of the cardia, the distance from the tumour to the circumferential resection margin (CRM) must be recorded.

CS2.10a 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 circumferential resection margin is an indicator of poor prognosis.

S2.11 The appearance of the serosa must be recorded.

- CS2.11a 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.

S2.12 The nature and site of all blocks must be recorded.

- CS2.12a Following the macroscopic description, dissection and block selection is performed. Proximal and distal resection margins should be sampled, usually parallel to the cut edge. If the tumour is very close to the margin, perpendicular slices can aid microscopic measurement.

The tumour is cut in serial 3mm slices, and the slices laid out sequentially. Select at least four blocks of tumour²⁹, including the greatest depth of invasion, tumour closest to or at, the serosa, and if applicable, the closest circumferential radial margin. If the tumour is perforated, then a block is taken for the histologic record.

- CS2.12b For tumours involving the cardia, sample the adjacent (proximal and distal) mucosa to assess for background chronic inflammation, atrophy, intestinal metaplasia and *Helicobacter pylori* as well as to detect columnar lined oesophagus and dysplasia. This may be important in the aetiology of tumour carcinogenesis.
- CS2.12c Sample non neoplastic mucosa from the antrum and body to assess for background chronic inflammation, atrophy, intestinal metaplasia and *Helicobacter pylori*.
- CS2.12d Neoadjuvant chemotherapy may result in the shrinkage or complete loss of macroscopic abnormality. In the absence of macroscopic abnormality, clinical and radiologic data regarding tumour location is used to localise sampling. Following slicing, thickening or fibrosis in the submucosa and muscularis propria may indicate the site of previous tumour.

A minimum of five blocks from the tumour site should be taken. If no carcinoma is found in the initial sections, then examine three levels of each block. If no carcinoma is found, then in most cases, embedding of the whole site is required before a complete response to neoadjuvant therapy can be reported.

- G2.03 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.

- CG2.03a 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.

CG2.03b Much of the information recorded in a traditional macroscopic narrative is covered in the standards and guidelines above and in many cases, no further description is required.

3 Microscopic findings

Microscopic findings relates 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 S2.06 and figure S2.06a-c.

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. In the AJCC classification tumours "arising in the stomach <5cm from the oesophagogastric junction and crossing the oesophagogastric junction are staged using the TNM system for oesophageal adenocarcinoma".¹ In the event that the location on microscopic evaluation involves the oesophagus, even when not obvious macroscopically, then the cancer is reported using the oesophageal cancer structured report.

By adhering to the AJCC classification, it is recognised that there will be tumours that are present in the upper stomach and oesophagus, which appear to be of gastric origin (eg unassociated with Barrett's metaplasia/dysplasia and predominantly located in the stomach), and will be somewhat artificially placed into the category of tumours of the "oesophagus and oesophagogastric junction". Such tumours are not reported using the protocol for gastric cancer. Nevertheless, in reporting such tumours it is recommended that the likelihood that such tumours have arisen within the stomach is recorded.

S3.02 The WHO histological tumour type must be recorded.

CS3.02a The histological type of the tumour should be recorded based on the current WHO classification²³ (refer to Appendix 4). These types are:

- Tubular adenocarcinoma
- Papillary adenocarcinoma
- Mucinous adenocarcinoma (*requires more than 50% of the tumour to be mucinous*)
- Poorly cohesive carcinomas, including signet-ring cell carcinoma
- Mixed carcinoma
- Other (specify)

S3.03 The tumour type according to the Lauren classification must be recorded.

CS3.03a The histological type of the tumour should be recorded based on the Lauren classification.^{23,35} These types are:

- Diffuse
- Intestinal
- Mixed
- Indeterminate (Undifferentiated)

S3.04 The histological grade must be recorded.

CS3.04a The tumour should receive a histological grade based on the AJCC grading system^a:

Grade X	Grade cannot be assessed
Grade 1	Well differentiated (greater than 95% of tumour composed of glands).
Grade 2	Moderately differentiated (50% to 95% of tumour composed of glands)
Grade 3	Poorly differentiated (49% or less of tumour composed of glands).
Grade 4	Undifferentiated.

CS3.04b Signet-ring cell carcinomas are classified as grade 3 and small cell carcinomas and undifferentiated carcinomas are classified as grade 4.²⁶

G3.01 The pattern of growth should be recorded.

CG3.01a The pattern of growth³⁶ should be recorded as either:

1. Expanding: Tumour cells grow en masse by expansion resulting in tumour nodules, or
2. Infiltrating: Tumour cells penetrate individually and widely resulting in diffuse infiltration of the stomach.

S3.05 The maximal dimension of tumour must be recorded.

CS3.05a A final estimate of the maximum dimension of the tumour should be given based on both the macroscopic and histological findings.

S3.06 The level of invasion relative to the anatomical layers of the stomach (lamina propria, muscularis mucosae, submucosa, muscularis propria and subserosal connective tissue) must be

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recorded.

S3.07 The presence or absence of serosal surface involvement must be recorded.

S3.08 The presence or absence of vascular space invasion in small (lymphatic and capillary) and large (vein and artery) caliber vessels as well as perineural growth must be recorded.

S3.09 The degree of regression after preoperative chemoradiation must be recorded.

CS3.09a The following schema, though based on a study originally applied to rectal cancer, is recommended by the College of American Pathologists. In the absence of other widely used schemas, the following grading system is recommended.^b

Description	Tumour regression grade
No viable cancer cells	0 (complete response)
Single cells or small groups of cancer cells	1 (moderate response)
Residual cancer outgrown by fibrosis	2 (minimal response)
Minimal or no tumour kill; extensive residual cancer	3 (poor response)

S3.10 The distance of carcinoma from the proximal, distal and radial/circumferential margins must be recorded.

CS3.10a For tumours close to the gastro-oesophageal junction, the radial margin of the oesophagus will commonly be the closest margin. This margin should be recorded separately if included. Away from the gastro-oesophageal junction, the only radial/circumferential margins are the lesser omental ligaments and the greater omental resection margin.

S3.11 The number of regional lymph nodes involved and the total number of regional nodes identified must be recorded.

CS3.11a Regional lymph nodes are the perigastric nodes along the lesser and greater curvatures and the nodes along the left gastric, common hepatic, hepatoduodenal, splenic and celiac arteries (see figures S1.12a and b). Lymph node groups offer no significant prognostic information, and thus all regional nodes can be reported together.¹

CS3.11b Record the number of lymph nodes from the main resection specimen, and the regional nodes from each

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separately labelled specimen.

- CS3.11c According to the AJCC, a "tumour nodule with smooth contour in regional node area" is classified as a positive node. In reference to the stomach specifically: "metastatic nodules in the fat adjacent to a gastric carcinoma, without evidence of residual lymph node tissue, are considered regional lymph node metastases". Note that similar nodules on the peritoneal surface are considered M1.

S3.12 The number of involved non regional lymph nodes and the total number of non regional nodes identified/submitted must be recorded.

- CS3.12a Non-regional lymph nodes include other intra-abdominal nodes such as retropancreatic, mesenteric, and para-aortic.
- CS3.12b Metastasis to non regional lymph nodes is staged as distant metastasis (M1).

S3.13 The presence or absence of histologically confirmed metastatic sites must be recorded.

- CS3.13a Disease classifiable as distant metastasis may sometimes be present within the primary tumour resection specimen (eg a positive peritoneal nodule, liver biopsy etc)
- CS3.13b 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.

S3.14 The presence or absence of gastritis, helicobacter infection, intestinal metaplasia, dysplasia, gastric polyps, Barrett's mucosa (for those specimens with oesophagus) and other pathologies must be specified.

- CS3.14a If dysplasia involves a margin this should be stated.

G3.02 Any additional relevant microscopic comments should be recorded.

4 Ancillary studies findings

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

G4.01 Any ancillary testing performed should be noted and the results recorded in the pathology report.

CG4.01a Therapeutic guidance

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 T4N0M0.³⁷ 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.

1) Her 2

Up to one third of gastric carcinomas show over-expression and amplification of Her 2.¹⁷⁻¹⁸ Intestinal type gastric cancers show a significantly higher rate of Her2 positivity than diffuse cancers.¹⁷⁻¹⁸ Results from the recent ToGA trial have shown that the Her 2 antagonist trastuzumab combined with chemotherapy in Her 2 positive tumours resulted in improved overall survival and overall response rate.¹⁷⁻¹⁸ A modified Her 2 scoring system for gastric cancer was used for the ToGA trial based on a validation study.³⁸ Trastuzumab was recently approved in Australia by the Therapeutic Goods Administration (TGA) for treatment of patients with Her2 positive (IHC3+ or ISH positive with any IHC result) advanced adenocarcinoma of stomach or gastro oesophageal junction who have not received prior anticancer treatment for their metastatic disease.³⁹ In Australia a gastric HER2 testing algorithm has been recommended by the Her2 gastric cancer advisory committee. The recommendations are also partly based on the GATHER (Gastric Her2 testing) validation study.⁴⁰ Trastuzumab has also been approved for metastatic gastric carcinoma in the European Union with eligibility criteria based on tumours that show IHC 2+ and a confirmatory FISH+ result, or IHC3+, as determined by an accurate and validated study⁴¹. Similar approval was granted by the Food & Drug Administration (FDA) in the USA recently.⁴² In other countries such exercises are being carried out currently. It is likely that Her 2 testing will become standard of care in gastric carcinoma globally. As a result pathologists will be expected to report on Her2 status of gastric cancers.

2) EGFR (Her1)

Large molecule antagonists of EGFR (cetuximab and

panitumumab) are currently in phase 3 trials as adjunctive therapy in advanced gastric carcinoma. Although data is limited there appears to be a lower rate of both KRAS and BRAF mutations in gastric carcinoma⁴³ than in colorectal carcinoma. Despite this, preliminary data for these drugs is disappointing and there is no current role for EGFR, KRAS or BRAF testing in gastric carcinoma.

3) Others

Trials are underway into other targeted therapy for MAPK and PI3K-AKT signalling pathway targets.

CG4.01b Tumour classification

A problem with the widely used Lauren classification scheme for gastric carcinoma is that a significant number of tumours classified as 'intestinal' are in fact gastric or of mixed gastric/intestinal immunophenotype while some 'diffuse' carcinomas are intestinal immunophenotype. It is now possible with the use of commercially available immunohistochemical stains to establish lines of differentiation in gastric carcinoma. A panel of gastric mucin stains (MUC5AC and MUC6) and intestinal markers (MUC2, CDX2 and CD10) can allow separation into gastric, intestinal, mixed (hybrid) and unclassified ("null") subtypes. We see this as a desirable, but not mandatory, step toward a more accurate and reproducible gastric cancer classification. In addition, some studies have shown that carcinomas of certain mucin immunophenotypes are more biologically aggressive and this may have implications for the treatment of early stage disease because of the increased potential for lymph node metastases.^{21,22}

CG4.01c Detection of hereditary gastric carcinoma

Approximately 90% of gastric cancer is sporadic while up to 10% shows familial clustering with 1-3% arising in a clearly hereditary setting.^{44,23}

- **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 2010 International Gastric Cancer Linkage Consortium guidelines^{23,30} as follows^c:

1.	Two or more documented cases of gastric cancer in first-degree relatives, with at least one documented case of diffuse gastric cancer diagnosed before the age of 50 years
2.	Three or more cases of documented diffuse gastric

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	cancer in first- or second-degree relatives, independent of age of onset
3.	Diffuse gastric cancer before the age of 40 years without a family history
4.	Families with diagnoses of both diffuse gastric cancer and lobular breast cancer, with one case before the age of 50 years
5.	In addition, in cases where expert pathologists detect carcinoma <i>in situ</i> adjacent to diffuse-type gastric cancer, genetic testing should be considered since this is rarely, if ever, seen in sporadic cases.

- **Hereditary non polyposis colon cancer (HNPCC)** – gastric adenocarcinoma can infrequently arise in this syndrome⁴⁵ and immunohistochemistry for mismatch repair markers and/or formal genetic testing is warranted in all patients who fulfil revised Bethesda criteria.⁴⁶
- **Familial adenomatous polyposis** – 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.

CG4.01d **Prognostic information**

Three main genetic pathways are implicated in gastric carcinogenesis: 1) Chromosomal instability; 2) Microsatellite instability (MSI); and 3) CpG island methylation. While there has been less research into these pathways and their prognostic significance or therapeutic implications than exists for colorectal carcinoma, there is evidence that gastric carcinomas arising on the basis of MSI (approximately 20% of the total) have better overall survival.⁴⁷ These tumours are characterised by older age of presentation, distal gastric location, large size, intestinal glandular or solid morphology and a usual absence of lymph node metastases.⁴⁴ Data also suggests that gastric carcinomas that have high levels of CpG island methylation (CIMP-high) have significantly better survival than non CIMP-high tumours.⁴⁸ At present it is not recommended that either MSI or CIMP status testing be undertaken for prognostic prediction. Her 2 expression (discussed above) has been shown to be an independent poor prognostic factor in some studies⁴⁹⁻⁵¹ but it is not recommended that testing for this be done solely as a prognostic instrument.

CG4.01e **Infectious co-factor**

The role of **Helicobacter pylori** infection in gastric carcinogenesis is well established. Special stains, either histochemical or immunohistochemical, should be considered in any subtotal gastrectomy case showing inflammation in the

mucosa away from the tumour.

The finding of **Epstein-Barr virus** in gastric cancer has been recently appreciated. Worldwide as many of 10% of all gastric cancers show evidence of tumour cell infection although the significance of this is not clear.⁵² A pathogenic mechanism involving DNA hypermethylation has been proposed.¹⁴ Twenty percent (20%) of EBV infected gastric cancers have a distinctive clinicopathological presentation characterised by solid tumour growth with lymphoid cell infiltration ('lymphoepithelioma' or 'medullary' like), proximal gastric location (or gastric stump), male sex and improved prognosis – possibly related to frequent concomitant CIMP-high status.⁵³ While we do not see a role for EBV testing (EBER in situ hybridization) in all gastric carcinomas, we believe it is good practice to investigate EBV infection in poorly differentiated gastric carcinomas with lymphoid stroma.

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.

S5.01 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 (7th Edition).¹ (See Tables S5.01a, b, c and d below.)

Table S5.01a AJCC gastric cancer primary tumour definitions.^d

Primary Tumour (T)	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carcinoma <i>in situ</i> : intraepithelial tumour without invasion of the lamina propria
T1	Tumour invades lamina propria, muscularis mucosae, or submucosa
T1a	Tumour invades lamina propria or muscularis mucosae
T1b	Tumour invades submucosa
T2	Tumour invades muscularis propria*
T3	Tumour penetrates subserosal connective tissue without invasion of visceral peritoneum or adjacent structures****
T4	Tumour invades serosa (visceral peritoneum) or adjacent structures****
T4a	Tumour invades serosa (visceral peritoneum)
T4b	Tumour invades adjacent structures

* Note: A tumour may penetrate the muscularis propria with extension into the 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 T4.

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- ** The adjacent structures of the stomach include the spleen, transverse colon, liver, diaphragm, pancreas, abdominal wall, adrenal gland, kidney, small intestine and retroperitoneum.
- *** Intramural extension to the duodenum or esophagus is classified by the depth of the greatest invasion in any of these sites, including the stomach.

Table S5.01b AJCC gastric cancer regional lymph node classifications.^e

Regional Lymph Nodes (N)	
NX	Regional lymph node(s) cannot be assessed
N0	No regional lymph node metastasis*
N1	Metastasis in 1-2 regional lymph nodes
N2	Metastasis in 3-6 regional lymph nodes
N3	Metastasis in seven or more regional lymph nodes
N3a	Metastasis in 7-15 regional lymph nodes
N3b	Metastasis in 16 or more regional lymph nodes

* Note: A designation of pN0 should be used if all examined lymph nodes are negative, regardless of the total number removed and examined.

Table S5.01c AJCC gastric cancer distant metastasis classifications.^e

Distant Metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis

NOTE that the designation "MX" has been dropped from the 7th edition of the AJCC/UICC TNM system.

The terminology pM1 (distant metastases present) can only be used by pathologists on the basis of pathological assessment of a relevant tissue sample.

The pathologist may not be in possession either of the clinical information that indicates a cM1 stage or of specimens received from other procedures that indicate a pM1 stage.

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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.

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.

Note that positive peritoneal cytology is classified as M1. Often this is separately reported. Positive cytology would change the stage group to stage IV. This information if available should be indicated in the report preferably as a comment.

Table S5.01d AJCC/UICC pathological stage grouping.^f

Anatomic Stage/Prognostic Groups			
Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
	T1	N1	M0
Stage IIA	T3	N0	M0
	T2	N1	M0
	T1	N2	M0
Stage IIB	T4a	N0	M0
	T3	N1	M0
	T2	N2	M0
	T1	N3	M0
Stage IIIA	T4a	N1	M0
	T3	N2	M0
	T2	N3	M0
Stage IIIB	T4b	N0	M0
	T4b	N1	M0
	T4a	N2	M0
	T3	N3	M0
Stage IIIC	T4b	N2	M0
	T4b	N3	M0
	T4a	N3	M0
Stage IV	Any T	Any N	M1

S5.02 The year of publication and edition of the cancer staging system

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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 (S2.03)
- b) Tumour site (S3.01)
- c) Histologic type (S3.02 WHO and S3.03 Lauren)
- d) Involved or close margins with measurements (S3.10)
- e) Pathologic stage and stage grouping (S5.01)

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.

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 tumours. For emphasis, standards (mandatory elements) are formatted in bold font.

S6.01 The structured checklist provided below may be modified as required but with the following restrictions:

- a. All standards and their respective naming conventions, definitions and value lists must be adhered to.**
- b. Guidelines are not mandatory but are recommendations and where used, must follow the naming conventions, definitions and value lists given in the protocol.**

G6.01 The order of information and design of the checklist may be varied according to the laboratory information system (LIS) capabilities.

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.

CLINICAL INFORMATION AND SURGICAL HANDLING

S1.01 Patient name _____

Date of birth _____

Sex _____

Identification and contact details of requesting doctor _____

Date of request _____

Ethnicity:

Aboriginal or Torres Strait Islander _____

Other ethnicity _____

Unknown _____

G1.01 Patient identifiers (eg MRN, IHI, NHI) _____

S1.02 Pathology accession number _____

S1.03 Principal clinician _____

S1.04 Surgeon/proceduralist name and contact details _____

S1.05 Tumour site(location):

proximal 1/3 _____

middle 1/3 _____

distal 1/3 _____

S1.06 Type of operation:

Oesophago-gastrectomy _____

Total gastrectomy _____

Subtotal gastrectomy (proximal) _____

Subtotal gastrectomy (distal) _____

Other (specify) _____

S1.07 Preoperative therapy

Nil

**Preoperative
chemotherapy**

**Preoperative
radiotherapy**

**Preoperative
chemoradiotherapy**

Not stated

**S1.08 Involvement of adjacent
organs:**

Absent

Present

Not stated

If present: Pancreas

Spleen

Liver

**Other
(specify)** _____

S1.09 Distant metastases:

Absent

Present

Not stated

**If present,
specify sites** _____

**S1.10 Surgeon's opinion –
residual tumour**

Not stated

G1.02 Comments

MACROSCOPIC FINDINGS

S2.03 Type of resection:

Oesophago-
gastrectomy —

Total gastrectomy —

Subtotal gastrectomy
(proximal) —

Subtotal gastrectomy
(distal) —

Other (specify) _____

S2.05 Specimen dimensions

Length of stomach
greater curve — mm

Length of stomach
lesser curve — mm

Length of oesophagus — mm

Length of duodenum — mm

S2.06 Macroscopic tumour site (location) (tick all that apply)

Region Cardia —

Fundus —

Antrum —

Body —

Pylorus —

Curvature Greater —

Lesser —

Wall Anterior —

Posterior —

S2.07 Maximum tumour diameter — mm

S2.08 Macroscopic tumour type

Early gastric cancer
pT1 or T2:

Type 0-I Protruded —

Type 0-IIa Elevated —

Type 0-IIb Flat —

Type 0-III Excavated —

Type 0-IIc Depressed —

Advanced gastric cancer
pT3 or T4:

Type I Polypoid —

Type II Fungating —

Type III Ulcerated —

Type IV Infiltrative —

S2.09 Distance from tumour to nearest proximal or distal margin (cut end) — mm

S2.10 Distance from tumour to the circumferential resection margin (proximal /cardia tumours) — mm

— Not applicable

S2.11 Serosal appearance _____

S2.12 Nature and site of blocks _____

G2.03 Other relevant information and comments _____

MICROSCOPIC FINDINGS

S3.01 Tumour site (location)

Region	Cardia	___
	Fundus	___
	Antrum	___
	Body	___
	Pylorus	___
Curvature	Greater	___
	Lesser	___
Wall	Anterior	___
	Posterior	___

S3.02 WHO Histological tumour type:

Tubular adenocarcinoma	___
Papillary adenocarcinoma	___
Mucinous adenocarcinoma <i>(require more than 50% of the tumour to be mucinous)</i>	___
Poorly cohesive carcinomas, including signet-ring cell carcinoma	___
Mixed carcinoma	___
Other (specify)	_____

S3.03 Lauren histological tumour type:

Diffuse	___
Intestinal	___
Mixed	___
Indeterminate (Undifferentiated)	___

Other (specify) _____

S3.04 Histological grade:

Grade X ___

Grade 1 ___

Grade 2 ___

Grade 3 ___

Grade 4 ___

G3.01 Growth pattern:

Expanding ___

Infiltrating ___

S3.05 Maximal dimension of tumour _____ mm

S3.06 Level of invasion:

Mucosa /lamina propria ___

Muscularis mucosa ___

Submucosa ___

Muscularis propria ___

Subserosal connective tissue ___

S3.07 Serosal surface involvement:

Absent ___

Present ___

S3.08 Vascular space invasion:

Small vessels (lymphatic and capillary)

Absent ___

Present ___

Large vessels (vein and artery)

Absent ___

Present ___

Perineural growth

Absent ___

Present ___

S3.09 Degree of regression after preoperative chemoradiation, if applicable:

0 (complete response) ___

1 (moderate response) ___

2 (minimal response) ___

3 (poor response) ___

S3.10 Distance of tumour from margins

From proximal ___ mm

From distal ___ mm

From radial/
circumferential ___ mm
(proximal/cardia
tumours)

S3.11 Number of involved regional nodes/total number of regional nodes (pN) ___/___

S3.12 Number of involved non-regional lymph nodes/total number of non-regional lymph nodes (pM) ___/___

S3.13 Metastatic sites

Absent ___

Present ___

If present, specify site _____

S3.14 Other pathologies:

conclusion _____

Person responsible for reporting _____

SYNTHESIS AND OVERVIEW

S5.01 Tumour stage

T _____

N _____

M _____

Stage group _____

S5.02 Year of publication and edition of cancer staging system _____

G5.01 Diagnostic summary _____

G5.02 Other relevant comments _____

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

S1.01 Patient name _____

Date of birth _____

Sex _____

Identification and contact details of requesting doctor _____

Date of request _____

Ethnicity:

Aboriginal or Torres Strait Islander _____

Other ethnicity _____

Unknown _____

G1.01 Patient identifiers (eg MRN, IHI, NHI) _____

S1.03 Principal clinician _____

S1.04 Surgeon/proceduralist name and contact details _____

S1.05 Tumour site (location):

proximal 1/3 _____

middle 1/3 _____

distal 1/3 _____

S1.06 Type of operation:

Oesophago-gastrectomy _____

Total gastrectomy _____

Subtotal gastrectomy (proximal) _____

Subtotal gastrectomy (distal) _____

Other (specify) _____

S1.07 Preoperative therapy

Nil ___

Preoperative
chemotherapy ___

Preoperative radiotherapy ___

Preoperative
chemoradiotherapy ___

**S1.08 Involvement of adjacent
organs:**

Absent ___

Present ___

If present: Pancreas ___

Spleen ___

Liver ___

Other
(specify) _____

S1.09 Distant metastases:

Absent ___

Present ___

If present,
specify sites _____

**S1.10 Surgeon's opinion – residual
tumour**

G1.02 Comments

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.⁵⁴

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.⁵⁴
- 'Clutter' should be reduced to a minimum.⁵⁴ 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

Citizen, Georgina W. C/O Paradise Close Wreck Bay Resort Nar Nar Goon East, 3181 Female DOB 1/7/1951 MRN FMC1096785	Lab Ref: 10/P28460 Referred: 30/8/2010	Copy to: Dr N.G.Chapman Rainforest Cancer Centre. 46 Smith Road, Woop Woop, 3478	Referred by: Dr V. Smith Suite 3, AJC Medical Centre, Bunyip Crescent Nar Nar Goon West, 3182
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GASTRIC CANCER STRUCTURED REPORT

Page 1 of 3

Diagnostic Summary

Total Gastrectomy

Gastric adenocarcinoma of the antrum; tubular (WHO); intestinal (Lauren); grade 2; surgical margins clear; 2/16 nodes involved; pT3, pN1, cM0; Stage IIB (AJCC 7th edition, 2010)

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

Supporting Information

CLINICAL

Tumour site:	Antrum
Type of operation:	Total gastrectomy
Preoperative therapy:	Nil
Involvement of adjacent organs:	Absent
Distant metastases:	Nil
Surgeon's opinion – residual tumour:	Nil

MACROSCOPIC

Type of resection:	Total gastrectomy
Specimen dimensions	
Length of stomach greater curve:	250mm
Length of stomach lesser curve:	150mm
Tumour site:	Antrum
Maximum tumour diameter:	30mm
Macroscopic tumour type:	Polypoid
Distance to nearest (distal) margin:	30mm
Serosal appearance:	Normal

Nature and site of blocks:	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
Other relevant information and comments	Gastric mucosa appears atrophic

MICROSCOPIC

Tumour

Tumour site:	Antrum
WHO Histological tumour type:	Tubular adenocarcinoma
Lauren histological tumour type:	Intestinal
Histological grade:	Grade 2 (AJCC)- Moderately differentiated
Growth pattern:	Infiltrating
Dimensions of tumour	30mm
Level of invasion:	invasion of subserosal connective tissue
Invasion beyond the muscularis propria	2mm
Serosal surface involvement:	Absent
Vascular space invasion	
Small vessel invasion:	Present
Large vessel invasion:	Absent
Perineural growth:	Absent
Distance of tumour from margins	
From proximal:	180mm
From distal:	30mm
From radial:	Not applicable

Lymph nodes

Regional lymph nodes	
Number received (main specimen + separately labelled)	16
Number involved:	2
Non regional nodes:	Not received
Metastatic sites:	Absent

Other pathologies

Gastritis:	Present
Helicobacter infection:	Absent
Intestinal metaplasia:	Present

Dysplasia:	Absent
Gastric polyps:	Absent
Other pathologies:	None

ANCILLARY TESTS

None performed

Reported by Dr Bernard Beckstein

Authorised 4/9/2010

Appendix 4: WHO Classification^a of Gastric Tumours 4th edition.

Epithelial tumours

Premalignant lesions

Adenoma	8140/0
Intraepithelial neoplasia (dysplasia), low grade	8148/0*
Intraepithelial neoplasia (dysplasia), high grade	8148/2*

Carcinoma

Adenocarcinoma	8140/3
Papillary adenocarcinoma	8260/3
Tubular adenocarcinoma	8211/3
Mucinous adenocarcinoma	8480/3
Poorly cohesive carcinoma (including signet ring cell carcinoma and other variants)	8490/3*
Mixed adenocarcinoma	8255/3
Adenosquamous carcinoma	8560/3
Carcinoma with lymphoid stroma (medullary carcinoma)	8512/3
Hepatoid adenocarcinoma	8576/3
Squamous cell carcinoma	8070/3
Undifferentiated carcinoma	8020/3

Neuroendocrine neoplasms^b

Neuroendocrine tumour (NET)	
NET G1 (carcinoid)	8240/3
NET G2	8249/3
Neuroendocrine carcinoma (NEC)	8246/3
Large cell NEC	8013/3
Small cell NEC	8041/3
Mixed adenoneuroendocrine carcinoma	8244/3
EC cell, serotonin-producing NET	8241/3
Gastrin-producing NET (gastrinoma)	8153/3

Mesenchymal tumours

Glomus tumour	8711/0
Granular cell tumour	9580/0
Leiomyoma	8890/0
Plexiform fibromyxoma	8811/0*
Schwannoma	9560/0
Inflammatory myofibroblastic tumour	8825/1
Gastrointestinal stromal tumour	8936/3
Kaposi sarcoma	
9140/3	
Leiomyosarcoma	8890/3
Synovial sarcoma	9040/3

Lymphomas

Secondary tumours

^a The morphology codes are from the International Classification of Diseases for Oncology (ICD-O)⁵⁵ Behaviour is coded /0 for benign tumours, /1 for unspecified, borderline or uncertain behaviour, /2 for carcinoma *in situ* and grade III intraepithelial neoplasia, and /3 for malignant tumours;

^b The classification is modified from the previous WHO histological classification of tumours⁵⁶ taking into account changes in our understanding of these lesions. In the case of neuroendocrine neoplasms, the classification has been simplified to be of more practical utility in morphological classification;

* These new codes were approved by the IARC/WHO Committee for ICD-O at its meeting in March 2010.

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References

- 1 Edge SE, Byrd DR, Compton CC, Fritz AG, Greene FL and Trotti A (eds) (2010). *AJCC Cancer Staging Manual 7th ed.*, New York, NY.: Springer.
- 2 AIHW (Australian Institute of Health and Welfare) and AACR (Australasian Association of Cancer Registries) (2008). *Cancer in Australia: an overview, 2008*. Cancer Series No.46 (AIHW cat. no. CAN 42). AIHW, Canberra. Available from <http://www.aihw.gov.au/publications/index.cfm/title/10607>
- 3 New Zealand Ministry of Health (2002). *Cancer in New Zealand: Trends and Projections. Chapter 31. Stomach Cancer* Available from: www.moh.govt.nz/moh.nsf/indexmh/dataandstatistics-subjects-cancer
- 4 Munoz N and Francheschi S (1997). Epidemiology of gastric cancer and perspectives for prevention. *Salud pública Méx, Cuernavaca* 39(4).
- 5 Kajiyama Y, Tsurumaru M, Udagawa H, Tsutsumi K, Kinoshita Y and Ueno M et al (1997). Prognostic factors in adenocarcinoma of the gastric cardia: pathologic stage analysis and multivariate regression analysis. *J Clin Oncol* 15:2015-2021.
- 6 Pinto-De-Sousa J, David L, Seixas M and Pimenta A (2001). Clinicopathologic profiles and prognosis of gastric carcinomas from the cardia, fundus/body and antrum. *Dig Surg* 18:102–110.
- 7 Yokota T, Ishiyama S, Saito T, Teshima S, Yamada Y and Iwamoto K et al (2002). Is tumor size a prognostic indicator for gastric carcinoma? *Anticancer Res* 22:3673–3677.
- 8 Ectors N et al (2005). Is adenocarcinoma of the esophagogastric junction or cardia different from Barrett adenocarcinoma. *Arch Pathol Lab Med* 129:183-185.
- 9 Ohta H and Noguchi Y et al (1987). Early gastric carcinoma with special reference to macroscopic classification. *Cancer* 60:1099-1106.
- 10 Green PH and O'Toole KM et al (1981). Early gastric cancer. *Gastroenterology*. 2:247-256.
- 11 Gotoda T (2007). Endoscopic resection of early gastric cancer. *Gastric Cancer* 10(1):1-11.
- 12 Gotoda T, Yamamoto H and Soetikno RM (2006). Endoscopic submucosal dissection of early gastric cancer. *J Gastroenterol* 41:929-942.
- 13 Isomoto H, Shikuwa S, Yamaguchi N, Fukuda E, Ikeda K, Nishiyama H, Ohnita K, Mizuta Y, Shiozawa J, Kohno S. (2009). Endoscopic submucosal dissection for early gastric cancer: A large scale follow-up study. *Gut* 58(3):331-336 Published Online First: 10 November 2008. Available from: <http://gut.bmj.com/content/58/3/331.long>
- 14 Hull MJ, Mino-Kenudson M, Nishioka NS, Ban S, Sepehr A, Puricelli W, Nakatsuka L, Ota S, Shimizu M, Brugge WR and Lauwers GY (2006). Endoscopic Mucosal Resection. An Improved Diagnostic Procedure for Early

Gastroesophageal Epithelial Neoplasms. *American Journal of Surgical Pathology* 30(1): 114-118.

- 15 Gotoda T (2006). Endoscopic resection of early gastric cancer: the Japanese perspective. *Curr Opin Gastroenterol* 22:561-569.
- 16 Roder JD et al (1998). Classification of regional lymph node metastases from gastric carcinoma. German gastric cancer study group. *Cancer* 82:621-631. Available from:
<http://onlinelibrary.wiley.com/doi/10.1002/%28SICI%291097-0142%2819980215%2982:4%3C621::AID-CNCR2%3E3.0.CO;2-O/abstract>
- 17 Cutsem EV, Kang Y and Chung H et al. (2009). Efficacy results from the ToGA trial: A phase III study of trastuzumab added to standard chemotherapy (CT) in first-line human epidermal growth factor receptor 2 (HER2)-positive advanced gastric cancer (GC). *J Clin Oncol* 27: (suppl; abstr LBA4509).
- 18 Bang Y-J, Cutsem EV, Feyereislova A, Chung HC, Shen L, Sawaki A, Lordick F, Ohtsu A, Omuro Y, Satoh T, Aprile G, Kulikov E, Hill J, Lehle M, Rüschoff J and Kang Y-K for the ToGA Trial Investigators (2010). Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. *Lancet* 376:687-697.
- 19 Hyun Jeong Kang, Dae Hwan Kim, Tae-Yong Jeon, Soo-Han Lee, Shin N, Sue-Hye Chae, Gwang Ha Kim, Geum Am Song, Dong-Heon Kim, Srivastava A, Do Youn Park and Lauwers GY (2010). Lymph node metastasis from intestinal-type early gastric cancer: experience in a single institution and reassessment of the extended criteria for endoscopic submucosal dissection. *GASTROINTESTINAL ENDOSCOPY* 72(3):508-515.
- 20 Siewert JR, Böttcher K, Stein HJ and Roder JD (1998 Oct.). Relevant prognostic factors in gastric cancer: ten-year results of the German Gastric Cancer Study. *Ann Surg.* 228(4):449-461. Available from:
<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1191515/?tool=pubmed>
- 21 Nakamoto J, Torisu R and Aoki R et al. (2007). Clinicopathological evaluation of biological behaviour of submucosal invasive gastric carcinomas: relationship among lymph node metastasis, mucin phenotype and proliferative activity. *J Med Invest.* 54:99-108. Available from:
http://www.jstage.jst.go.jp/article/jmi/54/1,2/54_99/article
- 22 Han HS, Lee SY and Lee KY et al (2009). Unclassified mucin phenotype of gastric adenocarcinoma exhibits the highest invasiveness. *Journal of gastroenterology and hepatology* 24:658-666.
- 23 WHO (World Health Organization) (2010). *Classification of Tumours. Pathology and Genetics of Tumours of the Digestive System (4th edition)*. Bosman FT, Carneiro F, Hruban RH and Theise ND. IARC Press, Lyon.
- 24 Robert ME et al (2008). Recommendations for the reporting of gastric carcinoma. *Human Pathology.* 39:9-14.

- 25 RCP (Royal College of Pathologists) (2009). *Datasets and tissue pathways* RCP Available from: <http://www.rcpath.org/index.asp?PageID=254> (Accessed 13th Oct 09).
- 26 CAP (College of American Pathologists) (2009). *Cancer protocols and checklists*. Available from: http://www.cap.org/apps/cap.portal?nfpb=true&cntvwrPtlit_actionOverride=%2Fportlets%2FcontentViewer%2Fshow&_windowLabel=cntvwrPtlit&cntvwrPtlit%7BactionForm.contentReference%7D=committees%2Fcancer%2Fcancer_protocols%2Fprotocols_index.html&_state=maximized&_pageLabel=cntvwr (Accessed 13 October 2009).
- 27 RCPA (Royal College of Pathologists of Australasia) (2009). *Guidelines for Authors of Structured Cancer Pathology Reporting Protocols*. RCPA, Surry Hills, NSW. Available from: www.rcpa.edu.au/Publications/StructuredReporting/ProtocolDevelopment.htm
- 28 RCPA (Royal College of Pathologists of Australasia) (2004). *The Pathology Request-Test-Report Cycle — Guidelines for Requesters and Pathology Providers*, RCPA, Surry Hills, NSW. Available from: [www.rcpa.edu.au/static/File/Asset_library/public_documents/Policy_Manual/Guidelines/The Pathology Request-Test-Report Cycle.pdf](http://www.rcpa.edu.au/static/File/Asset_library/public_documents/Policy_Manual/Guidelines/The_Pathology_Request-Test-Report_Cycle.pdf)
- 29 Pritchard SA (2008 Feb.). Best practice in macroscopic examination of gastric resections. *J Clin Pathol.* 61(2):172-178.
- 30 Fitzgerald RC, Hardwick R, Huntsman D, Carneiro F, Guilford P, Blair V, Chung DC, Norton J, Ragnath K, Han Van Krieken J, Dwerryhouse S, Caldas C on behalf of the International Gastric Cancer Linkage Consortium (2010). Hereditary Diffuse Gastric Cancer: updated consensus guidelines for clinical management and directions for future research *Journal of Medical Genetics.* 47(7):436-444. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2991043/?tool=pubmed>
- 31 Lee AF, Rees H, Owen DA and Huntsman DG (2010). Periodic Acid-Schiff Is Superior to Hematoxylin and Eosin for Screening Prophylactic Gastrectomies From CDH1 Mutation Carriers. *Am J Surg Pathol* 34(7):1007-1013.
- 32 Karpeh MS, Leon L, Klimstra D and Brennan MF (2000 Sep.). Lymph node staging in gastric cancer: Is location more important than number? An analysis of 1,038 patients. *Ann Surg.* 232(3):362-371. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1421150/?tool=pubmed>
- 33 Lee HK, Yang HK, Kim WH, Lee KU, Choe KJ and Kim JP (2001 Oct). Influence of the number of lymph nodes examined on staging of gastric cancer. *Br J Surg.* 88(10):1408-1412.
- 34 Nakamura K, Ueyama T, Yao T, Xuan ZX, Ambe K, Adachi Y, Yakeishi Y, Matsukuma A and Enjoji M (1992). Pathology and prognosis of gastric carcinoma. Findings in 10,000 patients who underwent primary gastrectomy. *Cancer* 70(5):1030-1037.

- 35 Lauren P (1965). The two histological main types of gastric carcinoma: diffuse and so-called intestinal-type carcinoma. An attempt at a histoclinical classification. *Acta Pathol Microbiol Scand* 64: 31-49.
- 36 Ming S-C (1977). Gastric carcinoma. A pathobiological classification. *Cancer* 39: 2475-2485.
- 37 Van Cutsem E, Van de Velde C and Roth A et al. (2008). Expert opinion on management of gastric and gastro-oesophageal junction adenocarcinoma on behalf of the European Organisation for Research and Treatment of Cancer (EORTC)-gastrointestinal cancer group. *Eur J Cancer* 44: 182-194.
- 38 Hofmann M, Stoss O, Shi D, Buttner R, van de Vijver M, Kim W, Ochiai A, Ruschoff R and Henkel T (2008). Modified HER2 scoring system for gastric cancer: results from a validation study. *Histopathology* 52: 797-805.
- 39 Roche (*HERCEPTIN trastuzumab CAS-180288-69-1 data sheet*. Available from: <http://www.roche-australia.com/fmfiles/re7229005/downloads/oncology/herceptin-pi.pdf>
- 40 Kumarasinghe MP, Fox S and Armes J et al for GaTHER study group (Gastric HER2 Testing Study (GaTHER): An evaluation of gastric cancer testing accuracy in Australia. Proceedings of ASCO 2011, citation in *J Clin Oncol* 29: 2011 (suppl 4; abstract 15)
- 41 European Medicines Agency (2010). *ASSESSMENT REPORT FOR HERCEPTIN International non-proprietary name/Common name: trastuzumab. Procedure No. EMEA/H/C/278/II/0047*. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/000278/WC500074921.pdf.
- 42 *FDA Approval for Trastuzumab: HER2 - overexpressing Metastatic Gastric or Gastroesophageal (GE) Junction Adenocarcinoma. 2010. (Accessed Nov 29, 2010, at <http://www.cancer.gov/cancertopics/druginfo/fda-trastuzumab>)*
- 43 Stella G, Llimpe FR and Barone C et al. (2009). KRAS and BRAF mutational status as response biomarkers to cetuximab combination therapy in advanced gastric cancer patients. *J Clin Oncol* 27: (suppl; abstr e15503).
- 44 Carneiro F, Oliviera C and Leite M et al. (2008). Molecular targets and biological modifiers in gastric cancer. *Sem. Diag. Pathol.* 25: 274-287.
- 45 Watson P, Vasen HFA and Mecklin J-P et al. (2008). The risk of extra-colonic, extraendometrial cancer in the Lynch syndrome. *Int J Cancer* 123: 444-449. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2627772/?tool=pubmed>
- 46 Umar A, Boland CR and Terdiman JP et al. (2004). Revised Bethesda guidelines for hereditary nonpolyposis colorectal cancer (Lynch syndrome) and microsatellite instability. *J Natl Cancer Inst* 96: 261-268. Available from: <http://jnci.oxfordjournals.org/content/96/4/261.long>
- 47 Hayden JD, Cawkwell L and Quirke P et al. (1997). Prognostic significance of microsatellite instability in patients with gastric carcinoma. *Eur J Cancer* 33: 2342-2346.

- 48 Kusano M, Toyota M and Suzuki H et al. (2006). Genetic, epigenetic, and clinicopathologic features of gastric carcinoma with CpG island methylator phenotype and an association with Epstein-Barr virus. *Cancer* 106(7): 1467-1479. Available from: <http://onlinelibrary.wiley.com/doi/10.1002/cncr.21789/abstract>
- 49 Park DI, Yun JW, Park JH et al. and (2006). HER-2/neu amplification is an independent prognostic factor in gastric cancer. *Dig Dis Sci* 51: 1371-1379.
- 50 Tanner M, Hollmen M and Junttila TT et al. (2005). Amplification of HER-2 in gastric carcinoma: association with Topoisomerase IIalpha gene amplification, intestinal type, poor prognosis and sensitivity to trastuzumab. *Ann Oncol* 16:273-278. Available from: <http://annonc.oxfordjournals.org/content/16/2/273.long>
- 51 García I, Vizoso F, Martín A, Sanz L, Abdel-Lah O, Raigoso P and García-Muñiz JL Clinical Significance of the Epidermal Growth Factor Receptor and HER2 Receptor in Resectable Gastric Cancer. *Annals of Surgical Oncology* 10(3): 234-241.
- 52 Sousa H, Pinto-Correia AL and Medeiros R et al. (2008). Epstein-Barr virus is associated with gastric carcinoma: The question is what is the significance? *World J Gastroenterol* 14(27): 4347-4351. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2731187/?tool=pubmed>
- 53 Uozaki H and Fukayama M (2008). Epstein-Barr Virus and Gastric Carcinoma – Viral Carcinogenesis through Epigenetic Mechanisms *Int J Clin Exp Pathol* 1: 198-216. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2480567/?tool=pubmed>
- 54 Valenstein PN (2008). Formatting pathology reports: applying four design principles to improve communication and patient safety. *Archives of Pathology and Laboratory Medicine* 132(1): 84–94.
- 55 Fritz A, Percy C, Jack A, Shanmugaratnam K, Lobin L, Parkin DM and Whelan S (eds) (2000). *International Classification of Diseases for Oncology. Third edition*, World Health Organisation, Geneva.
- 56 WHO (World Health Organization) (2004). *World Health Organization Classification of Tumours . Pathology and Genetics Tumours of Endocrine Organs*. DeLellis RA, Lloyd RV, Heitz PU and Eng C. IARC Press, Lyon.