Carcinoma of the Stomach
Histopathology Reporting Guide

Family/Last name

Given name(s)

Date of birth DD – MM – YYYY

Patient identifiers

Date of request DD – MM – YYYY

Accession/Laboratory number

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

☐ indicates multi-select values ◯ indicates single select values

SCOPE OF THIS DATASET

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

- ◯ Information not provided
- ☐ Relevant biopsy results, *specify*
- ☐ Previous diagnosis and treatment for gastric cancer, *specify*
- ☐ Endoscopic location of the tumour, *specify*
- ☐ Clinical staging, *specify level of involvement, distant metastases*
- ☐ Previous partial gastrectomy procedure, *specify*
- ☐ History of chronic gastritis, *specify*
- ☐ Other, *specify*

NEOADJUVANT THERAPY (Note 2)

- ◯ Information not provided
- ◯ Not administered
- ◯ Administered, *describe*

OPERATIVE PROCEDURE (Note 3)

- ◯ Not specified
- ◯ Gastrectomy
  - ◯ Sub-total
  - ◯ Total
- ◯ Oesophagogastrectomy
- ◯ Other, *specify*

SPECIMEN DIMENSIONS (Note 4)

Length of stomach greater curve	mm
Length of stomach lesser curve	mm
Length of oesophagus	mm
Length of duodenum	mm

TUMOUR FOCALITY[a] (Note 5)

- ◯ Unifocal
- ◯ Multifocal, *specify number of tumours in specimen*
- ◯ Cannot be assessed, *specify*

[a] *If multiple primary tumours are present, separate datasets should be used to record this and all following elements for each primary tumour.*

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TUMOUR SITE (select all that apply) (Note 6)

- ◯ Not specified
- ☐ Region
  - ☐ Upper third ☐ Middle third ☐ Distal third
- ☐ Curvature
  - ☐ Greater ☐ Lesser
- ☐ Wall
  - ☐ Anterior ☐ Posterior
- ☐ Other, *specify*

TUMOUR DIMENSIONS (Note 7)

Maximum tumour dimension

mm

Additional dimensions

mm x mm

◯ Cannot be assessed, *specify*

MACROSCOPIC TUMOUR TYPE (Note 8)

- ◯ 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*

HISTOLOGICAL TUMOUR TYPE (Note 9)

World Health Organization (WHO) Classification
(Value list based on the WHO Classification of Tumours of the Gastrointestinal Tract (2019))

- ◯ Cannot be assessed
- ◯ Tubular adenocarcinoma
- ◯ Papillary adenocarcinoma
- ◯ Mucinous adenocarcinoma
- ◯ Poorly cohesive carcinoma, including signet-ring cell carcinoma and other subtypes
- ◯ Mixed adenocarcinoma
- ◯ Other histological type/subtype, *specify*

Laurén Classification
(Applicable to gastric adenocarcinomas)

- ◯ Intestinal
- ◯ Diffuse
- ◯ Mixed
- ◯ Indeterminate

HISTOLOGICAL TUMOUR GRADE (Note 10)

- ◯ Not applicable
- ◯ Cannot be assessed
- ◯ Low grade (well and moderately differentiated)
- ◯ High grade (poorly differentiated)
- ◯ Other, *specify*

EXTENT OF INVASION (Note 11)

- ◯ Cannot be assessed
- ◯ No evidence of primary tumour
- ◯ Carcinoma in situ (intraepithelial tumour without invasion of the lamina propria, high grade dysplasia)
- ◯ Invasion into the lamina propria
- ◯ Invasion into the muscularis mucosae
- ◯ Invasion into the submucosa
- ◯ Invasion into the muscularis propria
- ◯ Invasion into the subserosal connective tissue (without invasion of the visceral peritoneum or adjacent structures)
- ◯ Invasion into the serosa (visceral peritoneum)
- ◯ Invasion into adjacent structure(s)/organ(s), *specify*

LYMPHOVASCULAR INVASION (Note 12)

- ◯ Not identified
- ◯ Present

PERINEURAL INVASION (Note 13)

- ◯ Not identified
- ◯ Present

RESPONSE TO NEOADJUVANT THERAPY (Note 14)

- ◯ 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)
- ◯ Cannot be assessed, *specify*

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MARGIN STATUS (Note 15)

Invasive carcinoma

- ◯ Cannot be assessed
- ◯ Not involved
  - Distance of tumour from closest margin: _____ mm
  - Specify closest margin, if possible: _____
- ◯ Involved (select all that apply)
  - ☐ Distal
  - ☐ Proximal
  - ☐ Circumferential/Radial

Dysplasia

- ◯ Cannot be assessed
- ◯ Not involved
- ◯ Involved
  - ◯ Carcinoma in situ/high grade dysplasia
  - ◯ Low grade

  Specify margin (select all that apply)
  - ☐ Distal
  - ☐ Proximal
  - ☐ Other, *specify*: _____

LYMPH NODE STATUS (Note 16)

- ◯ Cannot be assessed
- ◯ No nodes submitted or found

Number of lymph nodes examined: _____

- ◯ Not involved
- ◯ Involved

  Number of involved lymph nodes: _____

COEXISTENT PATHOLOGY (select all that apply) (Note 17)

- ◯ None identified
- ☐ *Helicobacter* gastritis
- ☐ Autoimmune gastritis
- ☐ Reactive gastritis
- ☐ Intestinal metaplasia
- ☐ Gastric polyps, *specify*: _____
- ☐ Dysplasia
  - ◯ Low grade
  - ◯ High grade
  - ◯ Indeterminate
- ☐ Synchronous carcinoma(s), *specify*: _____
- ☐ Other, *specify*: _____

ANCILLARY STUDIES (Note 18)

For neuroendocrine neoplasms only

- ◯ Not applicable
- ◯ Neuroendocrine markers (chromogranin A, synaptophysin, other), *specify test(s) performed and result(s) if available*: _____

AND

Ki-67 proliferation index: _____ %

Other gastric carcinomas

- ◯ Not performed
- ◯ Performed (select all that apply)
  - ☐ HER2 testing performed, *record result(s)*: _____
  - ☐ Microsatellite instability (MSI)/Mismatch repair (MMR) testing, *record result(s)*: _____
  - ☐ Epstein-Barr virus (EBV)-status (e.g., EBV encoded RNA (EBER) in situ hybridisation), *record result(s)*: _____
  - ☐ Other, *specify test(s) and result(s)*: _____

HISTOLOGICALLY CONFIRMED DISTANT METASTASES (Note 19)

- ◯ Not identified
- ◯ Present, *specify site(s)*: _____

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PATHOLOGICAL STAGING (UICC TNM 8th edition)[b] (Note 20)

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

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

Primary tumour (pT)

- ◯ TX Primary tumour cannot be assessed
- ◯ T0 No evidence of primary tumour
- ◯ Tis Carcinoma in situ: intraepithelial tumour without invasion of the lamina propria, high grade dysplasia
- ◯ 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 invades subserosa
- ◯ T4 Tumour perforates serosa (visceral peritoneum) or invades adjacent structures[c,d,e]
  - ◯ T4a Tumour perforates serosa
  - ◯ T4b Tumour invades adjacent structures[c,d]

Regional lymph nodes (pN)

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

[b] *Reproduced with permission. Source: UICC TNM Classification of Malignant Tumours, 8th Edition, eds by James D. Brierley, Mary K. Gospodarowicz, Christian Wittekind. 2016, Publisher Wiley.*

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

[d] *Intramural extension to the duodenum or oesophagus is classified by the depth of greatest invasion in any of these sites including stomach.*

[e] *Tumour that extends into gastrocolic or gastrohepatic ligaments or into greater or lesser omentum, without perforation of visceral peritoneum, is T3.*

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Definitions

CORE elements

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

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

NON-CORE elements

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

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

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Scope

The dataset has been developed for the pathology reporting of gastrectomy for gastric carcinomas. A separate International Collaboration on Cancer Reporting (ICCR) dataset is available for endoscopic resections of the stomach.[2]

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 Union for International Cancer Control (UICC)[3]/American Joint Committee on Cancer (AJCC)[4] 8th edition Classifications and have been adopted by the World Health Organization (WHO) to define the diagnosis 'gastric cancer'. For all other tumours involving the OGJ, refer to the ICCR dataset for carcinomas of the oesophagus.[5]

Neuroendocrine carcinomas (NECs) and mixed neuroendocrine-non-neuroendocrine neoplasms (MiNENs) (with the exception of mixed adenoma and neuroendocrine tumours (NETs)) are included in this dataset.

Neuroendocrine tumours (NETs), non-epithelial malignancies and secondary tumours are excluded from this dataset.

The authors of this dataset can be accessed here.

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Note 1 – Clinical information (Non-core)

Clinical information including preoperative neoadjuvant therapy and previous endoscopic resection should ideally 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) and intestinal metaplasia. 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.

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Note 2 – Neoadjuvant therapy (Core)

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 of patients treated with surgery alone.[6] The CROSS trial documented the benefit of preoperative chemoradiation in patients with OGJ adenocarcinomas,[7] but its value in gastric cancers of other locations is unclear.

On the other hand, postoperative adjuvant therapy is currently recommended for stage II/III gastric cancer in Asia. The ACTS-GC trial[8] in Japan and the CLASSIC trial[9] in South Korea, China and Taiwan all showed improved overall survival in patients who received adjuvant chemotherapy after gastrectomy with D2 lymphadenectomy. However, there are studies demonstrating no additional benefit from postoperative chemoradiation in patients after D2 and D1+ nodal dissection.[10]

Downstaging of lymph node metastases and/or reduction of tumour size by preoperative chemotherapy/chemoradiation have been reported by multiple clinical trials.[6,11] Downstaging of the tumour may lead to a 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.[12,13] Assessment of treatment response is recommended in gastrectomy specimens from patients with preoperative chemotherapy/chemoradiation (see **Note 14 RESPONSE TO NEOADJUVANT THERAPY**).

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Note 3 – Operative procedure (Core)

Depending on the tumour location and tumour type, gastric resection can be described as:[14]

1. Total gastrectomy: for tumours located in the body/corpus of the stomach, tumours in the cardia, and diffuse-type 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 due to a germline *CDH1* or *CTNNA1* mutation. Total gastric mucosa embedding with mapping is the gold standard for pathology examination. However, the routine workload may be incompatible with the workload of complete embedding of these stomachs. Therefore, in the last hereditary diffuse gastric cancer guideline from the International Gastric Cancer Linkage Consortium, a three level protocol is proposed for pathological examination of prophylactic gastrectomy specimens, depending on the locally available resources (see supplementary materials from Blair et al (2020)).[15] Regardless of the level selected, the minimal examination of prophylactic gastrectomies should include: 1) proximal and distal resection margins to confirm that all gastric mucosa have been resected, which can be confirmed by frozen section during surgery; 2) examination of all lymph nodes; 3) photographing the specimen; 4) sampling of all anatomic regions of the stomach (Figure 1); and 5) when no foci of gastric cancer are found on initial examination, go back to the specimen to retrieve additional blocks.[15] If no foci of diffuse type cancer are found, the gastrectomy should not be reported as negative for cancer, but as 'no carcinoma found in xx% of the mucosa examined'.[15]

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Note 4 – Specimen dimensions (Non-core)

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. Significant shrinkage of unpinned gastrointestinal tract specimens occurs after fixation. Pinning out the specimens on a cardboard during fixation helps preserving most of the original specimen length.[16] It should be commented in the report if the dimensions are taken from a fixed but unpinned specimen.

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Note 5 – Tumour focality (Core)

While multifocal gastric carcinomas are rare, they should be documented. If multiple primary tumours are present, separate datasets should be used to describe this and all following elements for each primary tumour. However, due to the fact that regional lymph nodes in gastrectomies for gastric carcinomas of different locations are the same, the same 'N' category can be used for multifocal gastric carcinomas.

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Note 6 – Tumour site (Core)

The stomach is anatomically divided into the cardia, fundus, body, antrum and pylorus, but these regions are difficult to define macroscopically, which is especially true for the cardia and fundus. The current recommendation is to use the Japanese Gastric Cancer Association (JGCA) guidelines, which divide the stomach into upper third, middle third and distal third by the lines connecting the trisected points on the lesser and greater curvatures (Figure 1).[17] Primary gastric cancer located in the upper third of the stomach, especially at the OGJ/cardia, are reported to be more aggressive and associated with poor prognosis.[18]

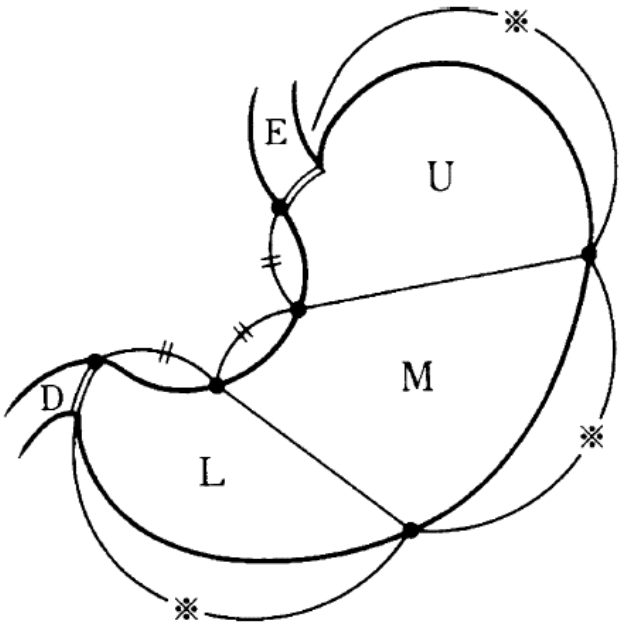

Figure 1: The stomach can be divided into 3 portions: upper third (U), middle third (M) and distal third (L). (E) oesophagus and (D) duodenum. Reproduced with permission from Japanese Gastric Cancer Association (2011). *Japanese classification of gastric carcinoma: 3rd English Edition.* Springer; London.[17]

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:[17-19]

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 utilised 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 categorises OGJ cancer into Siewert type I (tumours with their epicentre located 10-50 mm above the OGJ), type II (tumour epicentre located from 10 mm above to 20 mm below the OGJ) and type III (tumour epicentre located from 20 mm - 50 mm below the OGJ).[20] 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).[20] The current UICC[3]/AJCC[4] 8th edition Staging System definition of gastric cancer includes those tumours involving the OGJ but with the epicentre >20 mm into the proximal stomach and cardia cancer without involvement of the OGJ (Figure 2).[4] Therefore, all Siewert type III and some Siewert type II tumours are classified as gastric cancer based on the UICC/AJCC 8th edition Staging Systems.[3,4]

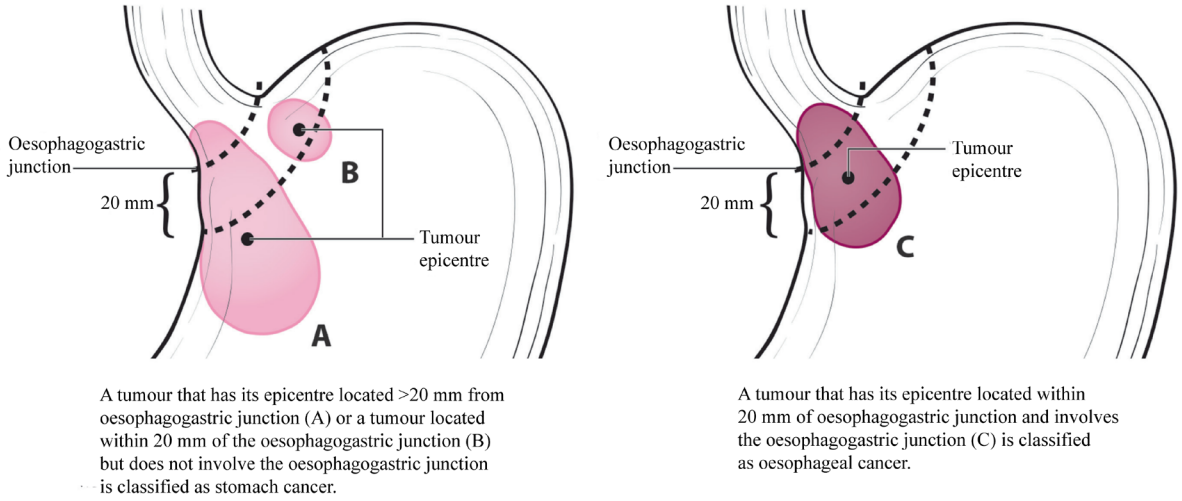

Figure 2: (A) Oesophagogastric junction (OGJ) tumours with their epicentre located >20 mm into the proximal stomach are staged as stomach cancers. (B) Cardia cancers not involving the OGJ are staged as stomach cancers. (C) Tumours involving the OGJ with their epicentre <20 mm into the proximal stomach are staged as oesophageal cancer. Modified with permission of the American College of Surgeons, Chicago, Illinois. The original source for this information is the American Joint Committee on Cancer Staging Manual, Eighth Edition (2016) published by Springer Science+Business Media.[4]

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 after chemo/radiotherapy. 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 to determine the tumour site if available.

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Note 7 – Tumour dimensions (Core and Non-core)

Tumour size is not used in staging gastric cancers. While some studies report no prognostic role for tumour size, others suggest that tumour size may be an independent prognostic factor.[21-23] Large tumour size has been associated with undifferentiated type cancer, serosal involvement, peritoneal metastasis, and poor survival in patients with stage II and III gastric cancers.[21-23] 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,[16] which may also be true for gastric cancers.

In most cases, tumour dimension/size can be measured macroscopically. Measurement of diffuse-type gastric cancer (especially linitis plastica) requires both macroscopic and microscopic assessment. However, accurate measurement of linitis plastica is sometimes impossible. The presence of linitis plastica has been associated with a poor prognosis.[24] After neoadjuvant therapy, the presumed tumour bed should be measured, but the macroscopic tumour dimension needs to be confirmed microscopically. According to the UICC[3]/AJCC[4] 8th editions, acellular mucin pools and fibrosis with no viable tumour cells should be considered negative for residual carcinoma, and only the area with viable tumour should be measured to determine the tumour dimension. For multiple discontinuous foci of post-treatment residual carcinoma, it is recommended to measure the maximum diameter including all foci and non-neoplastic areas between foci.[4]

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 tumour size measurement.

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Note 8 – Macroscopic tumour type (Non-core)

According to the Borrmann Classification (Figure 3), the 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).[25,26] Borrmann type II is the most common macroscopic type among advanced gastric cancers. Borrmann type IV is associated with a poor prognosis.[27,28] The 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.

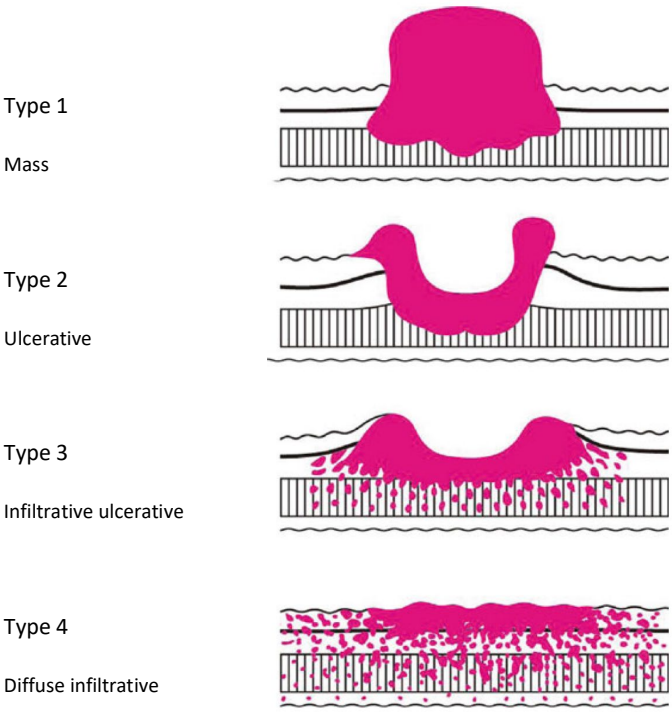

Figure 3: Macroscopic types of advanced gastric cancer. **Type 1 (mass): polypoid tumours, sharply demarcated from the surrounding mucosa. Type 2 (ulcerative): ulcerated tumours with raised margins surrounded by a thickened gastric wall with clear margins. Type 3 (infiltrative ulcerative): ulcerated 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**. Reproduced with permission from Japanese Gastric Cancer Association, Sano T and Kodera Y (2011). Japanese classification of gastric carcinoma: 3rd English Edition*, Gastric Cancer* 14(2):101-112.[17]

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Note 9 – Histological tumour type (Core and Non-core)

Several classification schemes have been used for subtyping gastric carcinomas histologically, including the Laurén,[29] Nakamura,[30] JGCA,[31] WHO[25] (Table 1) and Ming[32] classifications. For consistency in reporting, the WHO Classification of Tumours of the Digestive System, 5th edition, is recommended (Tables 2 and 3).[25] However, if a carcinoma does not fit into a category of the WHO Classification for gastric carcinomas, a descriptive diagnosis should be given. The Laurén Classification is widely used for gastric adenocarcinomas. In the Laurén Classification, gastric adenocarcinomas are divided into two histological subtypes - intestinal type and diffuse type.[29] Gastric carcinomas that do not fit into one of the two are placed into the mixed or indeterminate categories. The Laurén Classification provides a simplified categorisation of common types of gastric carcinoma and facilitates a general understanding of pathogenesis of most gastric carcinomas .[33] However, unlike the WHO Classification, the Laurén Classification is difficult to apply to all histologic gastric cancer subtypes and is therefore a non-core element.[29,34]

Table 1: Comparison of the Laurén, Nakamura, Japanese Gastric Cancer Association (JGCA) and World Health Organization (WHO) Classification of gastric cancer.

Laurén (1965)	Nakamura et al (1968)	JGCA (2017)	WHO (2019)
Intestinal	Differentiated	Papillary: pap Tubular 1, well differentiated: tub1 Tubular 2, moderately differentiated: tub2	Papillary Tubular, well differentiated Tubular, moderately differentiated
Indeterminate	Undifferentiated	Poorly 1 (solid type): por1	Tubular (solid), poorly differentiated
Diffuse	Undifferentiated	Signet-ring cell: sig Poorly 2 (non-solid type): por2	Poorly cohesive, signet-ring cell phenotype Poorly cohesive, other cell types
Intestinal/ diffuse/ indeterminate	Differentiated/ undifferentiated	Mucinous	Mucinous
Mixed		Description according to the proportion (e.g., por2>sign>tub2)	Mixed
Not defined	Not defined	**Special type:** Adenosquamous carcinoma Squamous cell carcinoma Undifferentiated carcinoma Carcinoma with lymphoid stroma Hepatoid adenocarcinoma Adenocarcinoma with enteroblastic differentiation Adenocarcinoma of fundic gland type	**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

Reproduced with permission from Frayling I et al (2016). Association for Clinical Genomic Science (ACGS) Best practice guidelines for genetic testing and diagnosis of Lynch syndrome. https://www.acgs.uk.com/quality/best-practice-guidelines/, derived from van Lier et al etc.; and from World Health Organization (WHO) Classification of Tumours Editorial Board. *WHO Classification of Digestive System Tumours, 5th Edition,* IARC Press, Lyon.[25]

Table 2: World Health Organization histological classification of gastric carcinomas.[26]

Tumour type	Histologic features
Adenocarcinoma, main histologic types	
Tubular adenocarcinoma	Most common subtype; composed of dilated or slit-like branching tubules of variable diameter or acinar structures
Papillary adenocarcinoma	Exophytic growth pattern and most commonly well differentiated; composed of elongated finger-like processes lined by columnar or cuboidal cells supported by fibrovascular cores
Poorly cohesive carcinoma, including signet ring cell carcinoma and other subtypes	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
Mucinous adenocarcinoma	Composed of malignant epithelium and extracellular mucin pools (mucin pools >50% of the tumour area)
Mixed adenocarcinoma	Composed of signet ring cell/poorly cohesive component and one or more other distinct histological components such as tubular/papillary carcinoma
Adenocarcinoma, other histological subtypes	
Gastric (adeno)carcinoma with lymphoid stroma	Characterised by irregular sheets, trabeculae, ill-defined tubules or syncytia of polygonal cells embedded within a prominent lymphocytic infiltrate, with intraepithelial lymphocytes; frequently associated with Epstein-Barr virus infection; less commonly associated with microsatellite instability or DNA mismatch repair deficiency
Hepatoid adenocarcinoma and related entities	Composed of large polygonal eosinophilic hepatocyte-like neoplastic cells with alpha fetoprotein (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
Micropapillary adenocarcinoma	Composed of micropapillary component (10-90% of the tumour area) and tubular/papillary adenocarcinoma
Gastric adenocarcinoma of fundic-gland type	Likely develop from oxyntic gland adenoma with oxyntic gland differentiation; include chief-cell predominant (most common), parietal cell-predominant, and mixed phenotype
Rare histological subtypes	Mucoepidermoid carcinoma, paneth cell carcinoma, and parietal cell carcinoma
Gastric squamous cell carcinoma	Only composed of squamous cell carcinoma with no other histological component after thorough sampling
Gastric adenosquamous cell carcinoma	Admixture of adenocarcinoma and squamous cell carcinoma with the squamous cell component ≥25%
Gastric undifferentiated (anaplastic) carcinoma	Composed of diffuse sheets of anaplastic, large to medium size polygonal cells, with frequent pleomorphic tumour giant cells; other morphologies that may be seen include rhabdoid cell, sarcomatoid pleomorphic pattern, undifferentiated carcinoma with osteoclast-like giant cells, carcinoma with lymphoepithelioma-like feature, and a glandular component

Gastroblastoma	Composed of uniform spindle cells and uniform epithelial cells arranged in nests
Gastric neuroendocrine carcinoma (NEC)	
Small cell NEC	Resemble its lung counterpart; frequent necrosis
Large cell NEC	Resemble its lung counterpart; frequent necrosis
Mixed neuroendocrine-non-neuroendocrine neoplasm	
Mixed adenocarcinoma-NEC	Composed of both adenocarcinoma and NEC with each component ≥30%
Mixed adenocarcinoma-neuroendocrine tumour	Composed of both adenocarcinoma and neuroendocrine tumour with each component ≥30%

Results on the prognostic value of histological types in gastric cancer are conflicting. While many studies have reported that diffuse, signet ring or anaplastic carcinomas confer an unfavourable prognosis, some multivariate studies showed no relationship between histological tumour types, and prognosis when stage was included in the model, which might be explained by inconsistent histology typing by pathologists.[35,36]

A high incidence of intragastric recurrence is observed in certain histological subtypes, including undifferentiated carcinoma and mixed adenocarcinoma with both signet ring cell carcinoma and poorly differentiated adenocarcinoma.[37]

Table 3: World Health Organization Classification of tumours of the stomach.[26]

Descriptor	**ICD-O codes[a]**
Benign epithelial tumours and precursors	
Glandular intraepithelial neoplasia, low grade	8148/0
Glandular intraepithelial neoplasia, high grade	8148/2
Serrated dysplasia, low grade	8213/0*
Serrated dysplasia, high grade	8213/2*
Intestinal-type dysplasia	
Foveolar-type (gastric-type) dysplasia	
Gastric pit/crypt dysplasia	
Intestinal-type adenoma, low grade	8144/0*
Intestinal-type adenoma, high grade	8144/2*
Sporadic intestinal-type gastric adenoma	
Syndromic intestinal-type gastric adenoma	
Adenomatous polyp, low-grade dysplasia	8210/0*
Adenomatous polyp, high-grade dysplasia	8210/2*
Malignant epithelial tumours	
Adenocarcinoma NOS	8140/3
Tubular adenocarcinoma	8211/3
Parietal cell carcinoma	8214/3
Adenocarcinoma with mixed subtypes	8255/3
Papillary adenocarcinoma NOS	8260/3
Micropapillary carcinoma NOS	8265/3
Mucoepidermoid carcinoma	8430/3
Mucinous adenocarcinoma	8480/3

Descriptor	ICD-O codes[a]
Signet-ring cell carcinoma	8490/3
Poorly cohesive carcinoma	8490/3
Medullary carcinoma with lymphoid stroma	8512/3
Hepatoid adenocarcinoma	8576/3
Paneth cell carcinoma	
Squamous cell carcinoma NOS	8070/3
Adenosquamous carcinoma	8560/3
Carcinoma, undifferentiated, NOS	8020/3
Large cell carcinoma with rhabdoid phenotype	8014/3
Pleomorphic carcinoma	8022/3
Sarcomatoid carcinoma	8033/3
Carcinoma with osteoclast-like giant cells	8035/3
Gastroblastoma	8976/3*
Neuroendocrine tumour NOS	8240/3
Neuroendocrine tumour, grade 1	8240/3
Neuroendocrine tumour, grade 2	8249/3
Neuroendocrine tumour, grade 3	8249/3
Gastrinoma NOS	8153/3
Somatostatinoma NOS	8156/3
Enterochromaffin-cell carcinoid	8241/3
ECL-cell carcinoid, malignant	8242/3
Neuroendocrine carcinoma NOS	8246/3
Large cell neuroendocrine carcinoma	8013/3
Small cell neuroendocrine carcinoma	8041/3
Mixed neuroendocrine–non-neuroendocrine neoplasm (MiNEN)	8154/3

[a] These morphology codes are from the International Classification of Diseases for Oncology, third Edition, second revision (ICD-O-3.2).[38] Behaviour is coded /0 for benign tumours; /1 for unspecified, borderline, or uncertain behaviour; /2 for carcinoma in situ and grade III intraepithelial neoplasia; and /3 for malignant tumours, primary site; and /6 for malignant tumours, metastatic site. Subtype labels are indented. Incorporates all relevant changes from the 5th edition Corrigenda, January 2022.[39]

* Codes marked with an asterisk were approved by the International Agency for Research on Cancer /World Health Organization Committee for ICD-O at its meeting in April 2019.

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Note 10 – Histological tumour grade (Core)

According to the WHO Classification of Tumours, Digestive System Tumours, 5th edition, 2019, histological tumour grading applies primarily to tubular and papillary adenocarcinomas.[25] The WHO Classification recommends a two-tiered system: low grade (well and moderately differentiated) and high grade (poorly differentiated).[25] The Carcinoma of the Stomach 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.

However, it is noted that a three-tiered system is recommended by the UICC[3]/AJCC[4] 8th edition Staging Systems as follows:

- G1: Well differentiated
- G2: Moderately differentiated
- G3: Poorly differentiated, undifferentiated

The AJCC 8th edition Staging System also recommends that the highest grade is recorded if there is evidence of more than one grade or level of differentiation of the tumour.[4]

Histopathological grading is not independently related to patient survival after R0 resection; however, poor histopathological grade is associated with high rate of R1 and R2 resections.[40] Assessment of histological grade may not be feasible in gastric cancers with prominent treatment response.

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Note 11 – Extent of invasion (Core)

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.[41] 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.[4] Direct infiltration of the duodenum or oesophagus is not considered invasion into an adjacent organ.

The term 'carcinoma in situ' is not commonly applied to glandular epithelium. However, high grade dysplasia in a gastric resection specimen can be reported as 'carcinoma in situ' as recommended by the UICC[3]/AJCC[4] 8th edition Staging Systems mainly for tumour registry reporting purposes.

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Note 12 – Lymphovascular invasion (Core)

Reports on the prognostic value of lymphovascular invasion in gastric cancer are variable,[42] but most studies demonstrate that lymphovascular invasion is an independent indicator of poor outcome following surgery.[43,44] Lymphovascular invasion includes lymphatic and venous invasion. Prognostic differences between lymphatic and venous invasion have not been sufficiently evaluated in gastric cancers.

According to UICC[3]/AJCC[4] staging convention, lymphovascular invasion does not affect the ((y)pT) category. For example, a tumour invading the muscularis propria showing lymphovascular invasion in the subserosa is still considered pT2.

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Note 13 – Perineural invasion (Non-core)

The prognostic value of perineural invasion in gastric cancer remains under debate.[45-49] Most studies demonstrate its significant prognostic impact in univariate analysis but not in multivariate analysis. For Laurén intestinal type gastric cancer, perineural invasion may be an independent prognostic factor.[45]

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Note 14 – Response to neoadjuvant therapy (Core)

Several grading systems for histopathological primary tumour response to neoadjuvant therapy have been applied to treated gastrointestinal carcinomas. These include the Mandard,[50] Becker,[51] JGCA[17] and College of American Pathologists (CAP)[52]/AJCC[4] tumour regression grading schemes.[53,54] While the Mandard system[50] is based on the fibrosis/tumour ratio (Table 4), the four-tiered Becker system[51] uses the estimated percentage of residual tumour in relation to the (assumed) pre-therapy tumour size (Table 5). The CAP modified Ryan grading system,[55] which is also referred to by the AJCC Staging System 8th edition,[4] is shown in Table 6.

Table 4: Mandard tumour regression grading system.[50]

Description	Tumour Regression Score
Complete regression: fibrosis without detectable tumour	1
Fibrosis with rare, scattered residual cancer cells	2
Fibrosis and tumour cells with a predominance of fibrosis	3
Fibrosis and tumour cells with predominance of tumour cells	4
No signs of regression	5

Table 5: Becker Tumour Regression Grading System.[51]

Description	Tumour Regression Score
No residual carcinoma	1
1-10% residual carcinoma	2
11-50% residual carcinoma	3
>50% residual carcinoma	4

Table 6: College of American Pathologists modified Ryan tumour regression grading system.[52]

Description	Tumour Regression Score
No viable cancer cells (complete response)	0
Single cells or rare small groups of cancer cells (near complete response)	1
Residual cancer with evident tumour regression, but more than single cells or rare small groups of cancer cells (partial response)	2
Extensive residual cancer with no evident tumour regression (poor or no response)	3

Reproduced with permission from Ryan R et al (2005). Pathological response following long-course neoadjuvant chemoradiotherapy for locally advanced rectal cancer. *Histopathology* 47(2):141-146.[55]

Although many studies have evaluated and compared these grading schemes in assessing treatment response in gastrointestinal carcinomas after neoadjuvant therapy,[53,56-58] there is no consensus on the optimal method to stratify tumour regression. In addition, the inter- and intra-observer variability is high for most grading schemes.[53,54] Nevertheless, response to neoadjuvant therapy should be reported, as assessment of histological tumour regression may provide valuable prognostic information and may impact on the choice of postoperative therapy.[53] Patients with complete tumour regression of the primary cancer have significantly better overall survival compared to patients with residual adenocarcinoma.[53] As there is currently no consensus, the CAP grading system,[52] which is a modified Ryan scheme,[55] 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.[55]

The presence of lymph node metastasis is one of the most important prognosticators in gastrointestinal carcinomas, but a consensus 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 were associated with patient outcome.[53] Therefore, tumour regression should only be graded in the primary tumour at present.

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 like those without preoperative treatment. Routine cytokeratin immunohistochemistry (IHC) is not recommended, but it may be helpful, if available, when the specimen is morphologically suspicious for residual viable tumour. According to the UICC[3]/AJCC[4] 8th edition Staging Manuals, acellular mucin pools, necrosis, and degenerative/ reactive changes without viable tumour cells after treatment should be interpreted as negative for tumour.

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Note 15 – Margin status (Core)

Resection margins of gastrectomy specimens include proximal, distal and radial/circumferential margins. Depending on the tumour location 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, and it is usually assessed 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 United States (US) and United Kingdom (UK)/Europe. The CAP defines a positive margin (incomplete resection, R1) as the presence of tumour cells directly at the resection margin,[52] whereas The Royal College of Pathologists, UK, defines R1 tumours as those having tumour cells present within 1 mm of the margin.[59] A positive margin is associated with a poor prognosis.[60] However, there is not sufficient evidence whether a 1 mm resection margin cutoff is clinically relevant in gastric cancer, and at this stage no consensus on the definition of margin positivity has been reached. Pathologists may follow their local guidelines.

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Note 16 – Lymph node status (Core)

The UICC[3]/AJCC[4] 8th edition Staging Manuals and National Comprehensive Cancer Network (NCCN) guidelines[61] 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 the total lymph node count after total gastrectomy.[62] Fat clearance of resection specimens may increase lymph node yield and result in nodal upstaging.[63]

D1 lymph node resections 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.[64-66] The Dutch D1D2 randomized clinical trial has recently demonstrated that D2 lymphadenectomy is associated with lower locoregional recurrence and reduced gastric cancer related death rates compared with D1 surgery after long-term follow-up.[67-69] Gastrectomy with D2 dissection has become more commonly used for advanced gastric cancer in Western countries.

Regional lymph nodes for gastric cancer include the perigastric lymph nodes along the greater curvature and lesser curvature, right and left 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).[4] Reporting of the lymph node status by regional lymph node groups (stations) 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.[4] Tumour deposits may be an independent predictor of prognosis in patients with gastric cancer.[70]

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.[4] There is no micro-metastasis (N1mi) category in staging gastric cancer.[4] 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.[26] Lymph nodes with acellular mucin pool or fibrotic lymph nodes with no viable tumour are considered negative.[26]

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.[26]

The presence of lymph node metastasis is one of the strongest prognostic indicators in gastric cancer.[71]

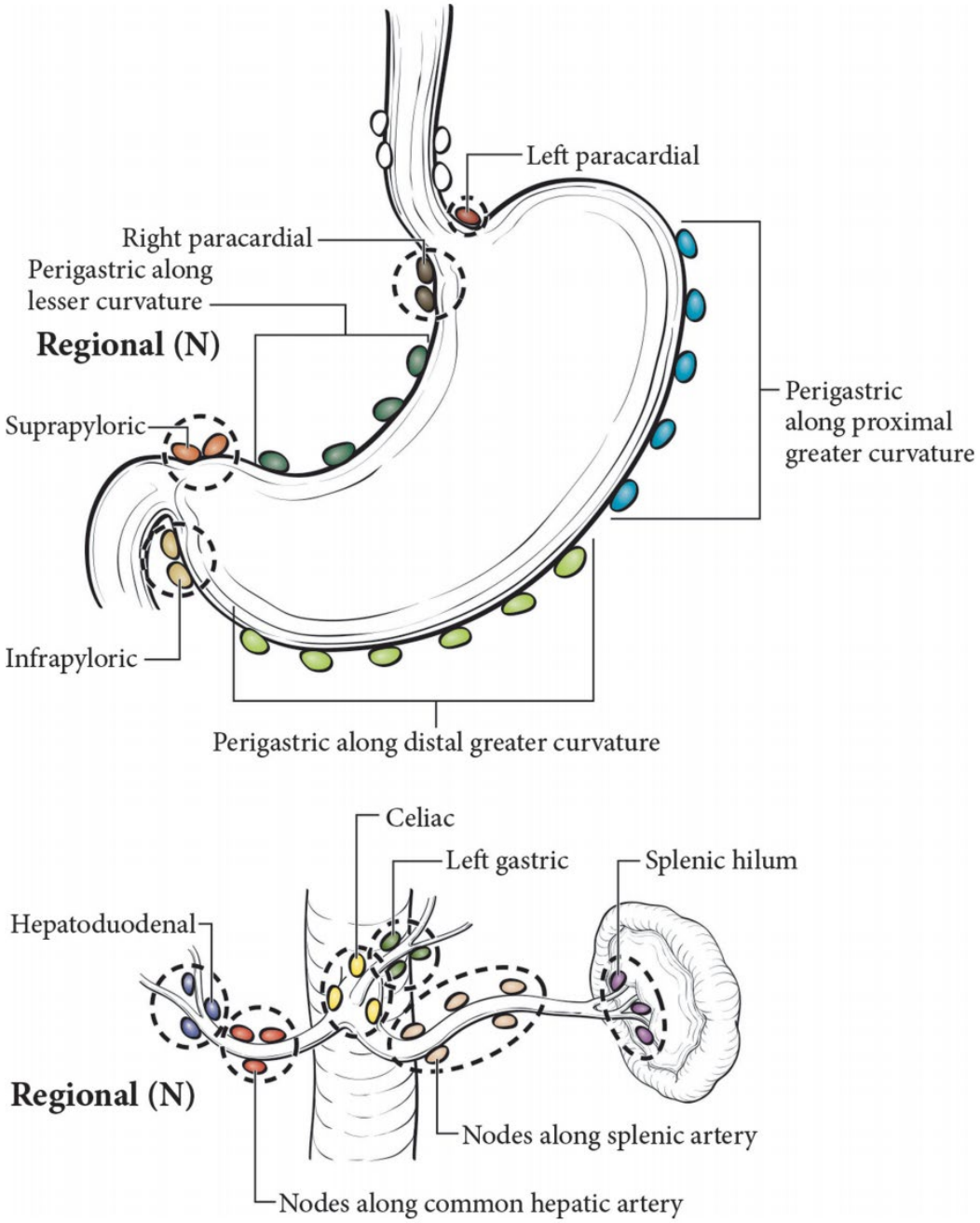

Figure 4: Regional lymph nodes of the stomach. Used with permission of the American College of Surgeons, Chicago, Illinois. The original source for this information is the American Joint Committee on Cancer Staging Manual, Eighth Edition (2016) published by Springer Science+Business Media.[4]

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Note 17 – Coexistent pathology (Non-core)

Based on the updated Sydney system, chronic gastritis is classified into *Helicobacter pylori* gastritis, ex-*Helicobacter pylori* gastritis, chemically induced/reactive gastritis, autoimmune gastritis and other special forms of gastritis.[72] *Helicobacter pylori* gastritis and autoimmune gastritis are recognised 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,[73] 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 may progress to dysplasia and eventually to invasive carcinoma. Rarely, dysplasia is seen in fundic gland polyps, but it almost never progresses to adenocarcinoma. Gastric adenomas include intestinal type, foveolar type, pyloric gland adenoma and oxyntic gland (chief cell) adenoma, all of which can progress to invasive carcinoma.[4]

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* or *CTNNA1* mutations, patients with Lynch syndrome with microsatellite instability (MSI)-high gastric cancer, familial intestinal gastric cancer, gastric adenocarcinoma, and proximal polyposis of the stomach due to germline mutations in promoter 1B of *APC*. 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.[4] 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.[74]

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Note 18 – Ancillary studies (Core and Non-core)

For gastric carcinomas, where there is a suspicion based on morphology, of neuroendocrine differentiation, including gastric NECs and 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.[26] However, pure NETs are not considered within the scope of this dataset.[75] Most NECs show marked cytological atypia, brisk mitotic activity, and are subclassified into small cell and large cell subtypes.[26] NECs are considered high grade by definition, typically with a Ki-67 proliferation index >55%.[76] MiNENs are usually composed of a poorly differentiated NEC component and an adenocarcinoma component. If a pure or mixed NEC is suspected on morphology, IHC is required to confirm neuroendocrine differentiation, usually applying synaptophysin and chromogranin A as a minimum.[26]

The NCCN guidelines recommend assessment of HER2 expression using IHC, followed up by assessment of *HER2* amplification using in situ hybridization (ISH) when ISH is equivocal, for patients with inoperable locally advanced, recurrent and metastatic gastric/OGJ adenocarcinoma for whom therapy with trastuzumab is considered.[61] For HER2 IHC in resection specimens, both intensity and percentage of immunoreactive cancer cells is assessed with scores ranging from 0 to 3+ (Table 7). ISH

is used if IHC is equivocal (2+). IHC 3+ or ISH showing *HER2* amplification (including IHC 2+ with *HER2* amplification by ISH) 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). The HER2 scoring system by Hofmann et al (2008) can be used to evaluate HER2 expression in gastric cancers.[77]

Table 7: Criteria used in the ToGA trial for scoring HER2 expression by immunohistochemistry (IHC) in gastric and oesophagogastric junction adenocarcinoma.[77]

HER2 IHC Score	HER2 IHC pattern in surgical specimen	HER2 Expression assessment
0	No reactivity or membranous reactivity in <10% of cancer cells	Negative
1+	Faint or barely perceptible membranous reactivity in ≥10% of cancer cells; cells are reactive only in part of their membrane	Negative
2+	Weak to moderate complete, basolateral or lateral membranous reactivity in ≥10% of tumour cells	Equivocal (perform in situ hybridisation (ISH))
3+	Strong complete, basolateral or lateral membranous reactivity in ≥10% of cancer cells	Positive

Microsatellite instability/mismatch repair deficiency (dMMR) status and PD-L1 expression have been used as predictive biomarkers for checkpoint inhibitor therapy since the US Food and Drug Administration (FDA) approved pembrolizumab for the treatment of patients with MSI-H or PD-L1 positive unresectable or metastatic gastric cancers.[78] While MSI status has been highly predictive of response to PD-1 pathway 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 based on the combined positive score (CPS). Unlike other malignancies (i.e., non-small cell lung cancer), PD-L1 expression in gastric/oesophageal cancers is mainly observed in immune cells. The CPS, which takes into account PD-L1 expression by both tumour cells and tumour-associated immune cells, was developed and refined for scoring gastric and oesophageal cancers.[79] 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 a CPS cutoff of <1.[80] Practices may differ in other countries. Studies are ongoing to investigate whether the ORR can be improved by using a different cutoff.

DNA mismatch repair defect can be determined by either polymerase chain reaction (PCR)-based MSI testing or by IHC stains for MLH1, MSH2, MSH6 and PMS2. Mismatch repair (MMR) IHC may be reported using the template outlined in Table 8.[81] 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 association with Lynch syndrome, which is caused by germline mutations in one of the mismatch repair genes, namely *MLH1*, *MSH2*, *MSH6* and *PMS2* or rarely *EPCAM*. Germline mutational analyses can be performed if there is a suspicion of Lynch syndrome.

Table 8: College of American Pathologists template for reporting mismatch repair protein immunohistochemistry results.[81]

Immunohistochemistry results for mismatch repair (MMR) proteins	
MLH1	
	Intact nuclear expression
	Loss of nuclear expression
	Cannot be determined (explain)
MSH2	
	Intact nuclear expression
	Loss of nuclear expression
	Cannot be determined (explain)
MSH6	
	Intact nuclear expression
	Loss of nuclear expression
	Cannot be determined (explain)
PMS2	
	Intact nuclear expression
	Loss of nuclear expression
	Cannot be determined (explain)
Background non-neoplastic tissue/internal control shows intact nuclear expression	
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	

Reproduced with permission from College of American Pathologists (2021). *Template for reporting results of DNA mismatch repair testing.* College of American Pathologists.[81]

Epstein-Barr virus associated gastric cancers (EBVaGC) are associated with a better prognosis.[82] In addition, EBVaGCs are more likely associated with overexpression of PD-L1 and PD-L2. A recent study suggested that EBVaGC could be a marker for efficacy of immunotherapy.[80] EBVaGC accounts for approximately 10% of all gastric cancers, most of which are located in the proximal stomach.[83] Histologically, EBVaGC can be sub-classified into: 1) poorly differentiated carcinoma with abundant tumour-infiltrating lymphocytes (gastric (adeno)carcinoma with lymphoid stroma); 2) tubular adenocarcinoma with prominent lymphoid follicles and active germinal centres (also termed carcinoma with Crohn disease-like lymphoid reaction); and 3) conventional-type adenocarcinoma with scant lymphocytic infiltrate.[82] Although EBVaGC can be poorly differentiated, EBVaGC is a distinct subtype with a low risk of lymph node metastasis.[84] Epstein-Barr encoded region (EBER) ISH is widely used to detect EBVaGC.

Other molecular testing includes targeted next generation sequencing. This testing is usually only performed to identify other actionable targets.

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Note 19 – Histologically confirmed distant metastases (Core)

Common distant metastases in gastric cancer include peritoneal metastasis, liver metastasis and metastasis to non-regional lymph node(s) (see **Note 16 LYMPH NODE STATUS**).

Involvement of non-regional lymph nodes is considered (y)pM1 and as such should be reported.

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Note 20 – Pathological staging (Core)

The UICC[3]/AJCC[4] 8th edition Staging Systems for gastric carcinoma are recommended (Figures 5 and 6).

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 'c' which refers to the clinical classification, and is based on gross and microscopic examination of surgically resected specimens.[3,4] 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 categorises 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.

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.

N Category considerations

As per AJCC 8th edition,[4] a designation of N0 should be used if all examined lymph nodes are negative, regardless of the total number removed and examined.

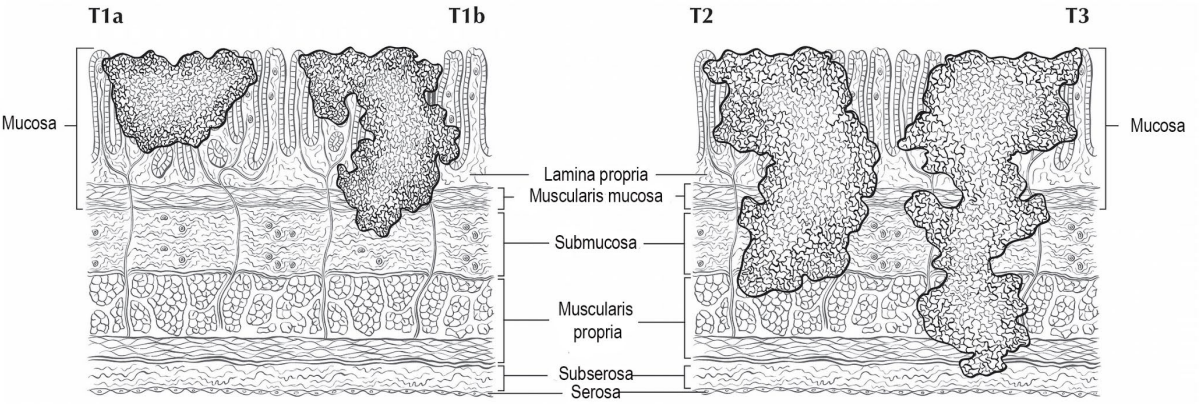

Figure 5: T1a is defined as tumour that invades the lamina propria. T1b is defined as tumour that invades the submucosa. T2 is defined as tumour that invades the muscularis propria, whereas T3 is defined as tumour that extends through the muscularis propria into the subserosal tissue. Used with permission of the American College of Surgeons, Chicago, Illinois. The original source for this information is the American Joint Committee on Cancer Staging Manual, Eighth Edition (2016) published by Springer Science+Business Media.[4]

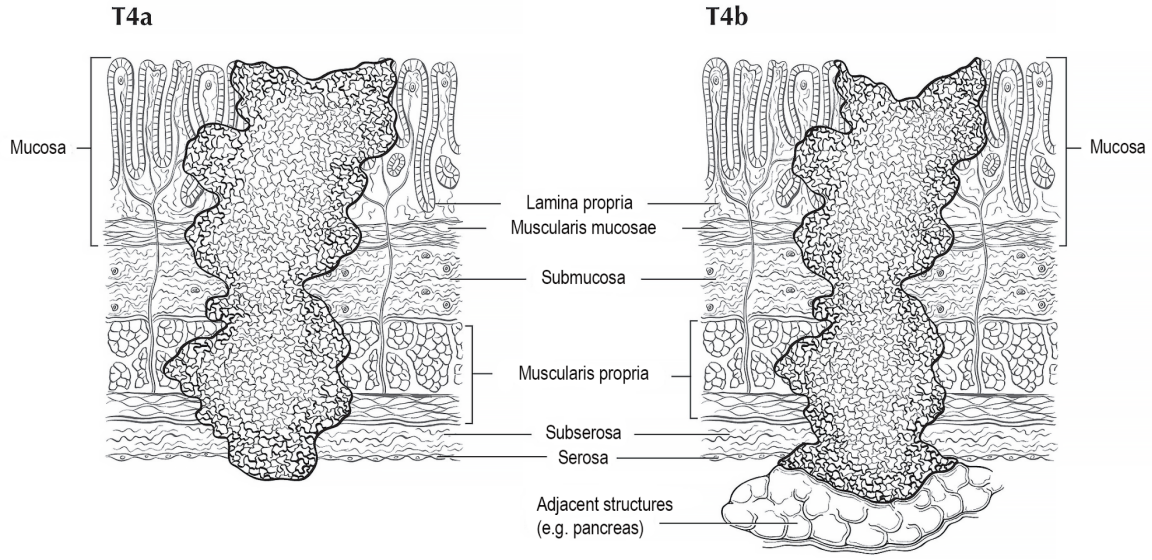

Figure 6: T4a is defined as tumour that penetrates the serosa (visceral peritoneum) without invasion of adjacent structures, whereas T4b is defined as tumour that radially invades adjacent structures, shown here invading the pancreas. Used with permission of the American College of Surgeons, Chicago, Illinois. The original source for this information is the American Joint Committee on Cancer Staging Manual, Eighth Edition (2016) published by Springer Science+Business Media.[4]

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