Data Set for Reporting Carcinoma of the Stomach in Gastrectomy

Recommendations From the International Collaboration on Cancer Reporting

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• ***Context.***—**A standardized detailed surgical pathology report is the cornerstone of gastric cancer management.**

Objective.—**To guide management and prognostication for patients with gastric carcinomas globally, the International Collaboration on Cancer Reporting aimed to produce an evidence-based international pathology reporting data set with a panel of globally recognized expert pathologists and clinicians.**

Design.—**Based on published guidelines/data sets for gastric carcinomas, a working draft was developed by the chair of the expert panel of pathologists and clinicians. The draft was then circulated to the panel and discussed in a series of teleconferences and email communications until consensus was achieved. The draft data set was uploaded on the International Collaboration on Cancer Reporting Web site for public comment. The data set was reviewed in consideration of the feedback, and a final version was approved by the panel.**

Results.—**This data set was developed for gastrectomy specimens for primary gastric carcinomas, including neuroendocrine carcinomas and mixed neuroendocrine-nonneuroendocrine neoplasms. Well-differentiated neuroendocrine tumors, nonepithelial malignancies, and secondary tumors were excluded from this data set. The final data set contains 15 core (required) elements and 8 noncore (recommended) elements. A commentary is provided for each element.**

Conclusions.—**The International Collaboration on Cancer Reporting has published freely available, evidence-based data sets for gastric cancer reporting. Standardized reporting has been shown to improve patient care and facilitates data exchange and analysis for quality assurance, cancer epidemiology, and clinical and basic research.**

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Gastric cancer is the fifth most common cancer and fourth leading cause of cancer-related death in the world. The estimated numbers of new gastric cancer cases and deaths in 2020 were 1 089 103 and 768 793, respectively, worldwide.[1] The incidence of gastric cancer is highly variable between different regions and racial and socioeconomic groups, with the highest incidence seen in Eastern Asia. The incidence rate is relatively low in Western countries. Treatment of gastric cancer patients depends on

the disease stage, patient performance status, and patient preferences. Early gastric cancer with negligible risk of lymph node metastasis can be managed by endoscopic resection, whereas patients with locally advanced resectable disease are typically treated with gastrectomy with chemotherapy or chemoradiation. Pathologic examination of gastrectomy for gastric cancer provides critical information, including primary tumor stage, lymph node status, margin status, treatment response, and other potentially prognostic factors. A standardized detailed surgical pathology report is therefore the cornerstone of gastric cancer patient management.

Structured reporting protocols facilitate pathology reporting of cancer specimens by ensuring inclusion of all clinically relevant information in a user-friendly format, thereby facilitating the use of the data for patient management, epidemiology, audit, and research. Data sets or checklists for pathology reporting have been independently developed by several organizations across the world, including the Royal College of Pathologists (RCPath), United Kingdom; the College of American Pathologists (CAP), United States; and the Royal College of Pathologists of Australasia. Although these protocols are broadly similar, there are significant differences in content and terminology that might hinder international comparison and research. Hence in 2011 the International Collaboration on Cancer Reporting (ICCR) was formed to harmonize the data sets, protocols, and checklists for pathologic reports of various cancers globally. The ICCR has since developed strategic alliances with other international cancer organizations, including the International Agency for Research on Cancer, the Union for International Cancer Control (UICC) and the American Joint Committee on Cancer (AJCC). Currently the ICCR coordinates the production of evidence-based international pathology reporting data sets developed by a panel of internationally recognized expert pathologists and clinicians. The data sets are freely available from the ICCR website: http://www.iccr-cancer.org.

The purpose of this paper was to specifically describe the development of an evidence-based pathology data set for reporting of gastric carcinomas in gastrectomy specimens.

MATERIALS AND METHODS

This data set was developed based on the guidelines agreed upon by the Dataset Steering Committee (DSC) of the ICCR. The DSC appointed a chair (C.S.) to develop 2 data sets for the reporting of carcinomas of the stomach, and together they identified 10 other expert gastrointestinal pathologists who, together with the chair, a medical oncologist, a surgical oncologist, an ICCR series champion (I.D.N.), and project managers (F.W. and C.I.S.) formed the Carcinoma of the Stomach Dataset Authoring Committee (DAC). The expert panel included 2 pathologists from the United States (G.L. and L.T.), 2 from the United Kingdom (M.O. and H.I.G.), 2 from Europe (R.S.P. and M.V.), 2 from Australia (P.K. and A.K.L.), 1 from Japan (T.U.), and 1 from Korea (S.H.), together with a medical oncologist (M.K.G.) and a surgical oncologist (B.D.B.) from the United States. The series champion provided guidance and support to the chair of the DAC regarding ICCR standards and ensured harmonization across data sets, whereas the project managers coordinated the development process.

In line with other ICCR data sets, this data set for the reporting of gastric carcinomas in gastrectomy specimens included a set of elements and value lists (responses) accompanied by a commentary. The elements were categorized as either core (required) or noncore (recommended). Core elements were those that are essential for the clinical management or staging of the cancer, or prognosis prediction. These elements will usually have evidentiary support at level III-2 or above (based on prognostic factors in the National Health and Medical Research Council levels of evidence[2]). In rare circumstances where level III-2 evidence is not available, an element may be made core when there is unanimous agreement by the DAC. Noncore elements were those that did not meet the above standard but were unanimously agreed upon by the DAC to be clinically important and/or representing good practice.

The commentary clarified the elements, explained the rationale behind the above categorization of individual data items, and cited published evidence that supported its inclusion.

The initial working draft of this data set was developed by the project managers following a review of all published cancer data sets pertaining to carcinoma of the stomach. Following editing by the chair, the draft was circulated to the DAC and discussed in a series of teleconferences. The chair then re-edited the data set based on these discussions and recirculated it to the members of the DAC for further review and discussion in a series of email communications until consensus was achieved. The draft data set was uploaded on the ICCR Web site for a period of 2 months for public comment. The data set was reviewed by the chair based on the feedback, approved by the DAC, and finally ratified by the ICCR DSC.

RESULTS

Scope

Carcinomas involving the esophagogastric junction (EGJ) with their epicenter >20 mm into the proximal stomach and cardia cancers that do not involve the EGJ are included in this data set. These criteria are set by the AJCC 8th edition TNM classification and have been adopted by the World Health Organization (WHO) and define the diagnosis of "gastric cancer."[3,4] An ICCR data set for esophageal carcinomas is available for tumors not meeting these criteria.[5]

Neuroendocrine carcinomas (NECs) and mixed neuroendocrine-nonneuroendocrine neoplasms (except for mixed adenoma and well-differentiated neuroendocrine tumors [NETs]) are included in the data set. Neuroendocrine tumors, nonepithelial malignancies, and secondary tumors are excluded from this data set.

Because there are significant differences in the core and noncore elements, responses and commentaries between gastrectomy and endoscopic resection for gastric carcinomas, the chair and DAC in consultation with the ICCR DSC decided to separate the data sets for these 2 pathologic specimen types to maximize clarity and usability. The elements and associated commentaries presented below are for gastrectomy specimens. The core and noncore elements for the carcinoma of the stomach data set are listed in Table 1.

Core Elements

Neoadjuvant Therapy.—Assessment of treatment response is required for gastrectomy from patients with preoperative chemotherapy/chemoradiation. Therefore, history of neoadjuvant therapy should be documented. Perioperative (both preoperative and postoperative) therapy is currently recommended in patients with stage IB to stage III gastric cancer in Western countries. The efficacy of perioperative/preoperative chemotherapy has been evaluated in multiple clinical trials. Most studies observed improved overall survival compared with the group of patients treated with surgery alone.[6] The CROSS (the Dutch chemoradiotherapy for esophageal cancer followed by surgery study) trial documented the benefit of preoperative

Table 1. Core and Noncore Elements for the Pathology Reporting of Carcinoma of the Stomach	
Core	**Noncore**
Neoadjuvant therapy	Clinical information
Operative procedure	Specimen dimensions
Tumor focality	Tumor dimensions
Tumor site	Additional dimensions
Tumor dimensions	Macroscopic tumor type
Maximum tumor dimension	Histologic tumor type
Histologic tumor type	Laurén classification
World Health Organization Classification	Perineural invasion
Histologic tumor grade	Coexistent pathology
Extent of invasion	Ancillary studies
Lymphovascular invasion	HER2 testing performed
Response to neoadjuvant therapy	Microsatellite instability/mismatch repair testing
Margin status	Epstein-Barr virus status (eg, Epstein Barr virus–encoded RNA in situ hybridization)
Lymph node status	
Ancillary studies	
For neuroendocrine neoplasms only	
Neuroendocrine markers	
Ki-67 proliferation index	
Histologically confirmed distant metastases	
Pathologic staging	

chemoradiation in patients with EGJ adenocarcinomas[7]; however, its value in gastric cancers of other locations is unclear.

On the other hand, postoperative adjuvant therapy is currently the most common approach for stage II/III gastric cancer in Asia. The ACTS-GC (Adjuvant Chemotherapy Trial of TS-1 for Gastric Cancer) trial[8] in Japan and the CLASSIC (Capecitabine and Oxaliplatin Adjuvant Study in Stomach Cancer) trial[9] in South Korea, China, and Taiwan all showed improved overall survival in patients who received adjuvant therapy after gastrectomy with D2 lymphadenectomy. However, there are also 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 tumor size by preoperative chemotherapy/chemoradiation have been reported by multiple clinical trials.[6,11] Downstaging of the tumor may lead to a higher rate of R0 resection and increased survival. Pathologic tumor regression is evident in some cases, and complete tumor regression is achieved in up to 18% of patients.[12,13] Assessment of treatment response is recommended for gastrectomy from patients with preoperative chemotherapy/chemoradiation.

Operative Procedure.—The type of operative procedure should be documented. Depending on the tumor location and tumor type, the gastric resection specimen can be described as[14]: "total gastrectomy," which is used to resect tumors located in the body/corpus of the stomach, tumors in the cardia, and diffuse gastric cancer (including prophylactic gastrectomy for patients with hereditary diffuse gastric cancer); "sub-total distal gastrectomy," which is used to resect tumors located in the antrum (distal third and pylorus); or "esophagogastrectomy," which is used to resect gastric tumors extending into the lower esophagus.

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 and mapping is the gold standard for pathology examination. However, the routine workload may be incompatible with the elaborate workload of totally embedding these stomachs. Therefore, in the last hereditary diffuse gastric cancer guideline from the International Gastric Cancer Linkage Consortium, a 3-level protocol is proposed for pathologic examination of prophylactic gastrectomy specimens, depending on the local available resources (see supplementary materials from Blair et al[15]). Regardless of the level selected, the minimal examination of prophylactic gastrectomies should include: (1) proximal and distal 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 gastric zones; and (5) when no foci of gastric cancer are found on initial examination, going back to the specimen to retrieve additional blocks.[15] If no foci of signet ring cell 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]

Tumor Focality.—Although multifocal gastric carcinomas are rare, they should be documented. If multiple primary tumors are present, separate data sets should be used to describe each primary tumor. However, because of 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.

Tumor Site.—The stomach is divided into the cardia, fundus, body, antrum, and pylorus. However, these regions are difficult to define macroscopically, especially 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.[16] Primary gastric cancers located in the upper third of the stomach, especially at the EGJ/cardia, are reported to be more aggressive and associated with poorer prognosis.[17]

The EGJ is defined as the border between the esophageal and gastric muscles, irrespective of the type of epithelial lining of the esophagus. However, it can be challenging to determine the exact location of the EGJ, especially in individuals with conditions affecting EGJ landmarks. Four methods have been proposed to locate the EGJ anatomically as follows[16–18]:

1. The distal end of the longitudinal palisading small vessels in the lower esophagus. It can be seen

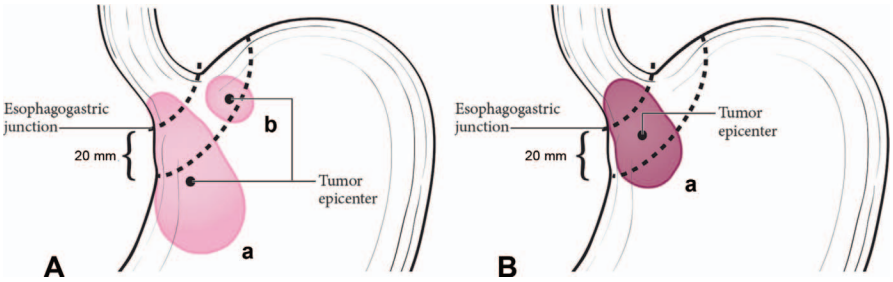

Figure 1. *Classification of esophagogastric junction tumors. A, A tumor that has its epicenter located >20 mm from the esophagogastric junction (a) or a tumor located within 20 mm of the esophagogastric junction (b) but not involving the esophagogastric junction is classified as stomach cancer. B, A tumor that has its epicenter located within 20 mm of the esophagogastric junction and involves the esophagogastric junction (a) is classified as esophageal cancer. Used with permission from the American College of Surgeons, Chicago, Illinois. The original source for this information is the American Joint Committee on Cancer Staging Manual, 8th edition (2016), published by Springer Science+Business Media.*[3]

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 tumor invasion.
3. The proximal end of the gastric longitudinal mucosal folds, which is the most used definition by endoscopists in Western countries. However, it can be obscured by the presence of gastric mucosal atrophy (ie, after chemoradiation therapy and atrophic gastritis) or a large gastric mass.
4. The level of the macroscopic caliber changes of the resected esophagus and stomach.

The current recommendation is to use the proximal end of the gastric longitudinal mucosal folds as the landmark for the EGJ. If it cannot be identified, use the distal end of the longitudinal palisading small vessels, which can also be identified microscopically.

The Siewert classification categorizes EGJ cancer into Siewert type I (tumors with their epicenter located 1–5 cm above the EGJ), type II (tumor epicenter located from 1 cm above to 2 cm below the EGJ), and type III (tumor epicenter located from 2–5 cm below the EGJ).[19] In the Siewert classification, the proximal end of the gastric longitudinal mucosa folds is used as pragmatic reference for the endoscopic cardia/EGJ (zero point).[19] The UICC[20]/AJCC[3] 8th edition TNM classification definition of gastric cancer includes those tumors involving the EGJ but with the epicenter >2 cm into the proximal stomach and cardia cancer without involvement of the EGJ (Figure 1).[3] Therefore, all Siewert type III and some Siewert type II tumors are classified as gastric cancer based on the UICC/AJCC 8th edition TNM classification.[3,20]

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

Tumor Dimensions.—Tumor size is not used in staging gastric cancers. Although some studies report no prognostic role for tumor size, others suggest that tumor size might be an independent prognostic factor.[21–23] Large tumor 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] Tumor size may vary, depending on measurements taken before or after fixation. A study on esophageal cancers demonstrated a 10% reduction in tumor size after fixation,[24] which may also be true for gastric cancers.

In most cases, tumor dimension/size can be measured macroscopically. Measurement of diffuse-type gastric carcinoma (linitis plastica) requires both macroscopic and microscopic assessment. However, accurate measurement of linitis plastica is sometimes impossible. Nevertheless, the tumor size is not used to stage gastric cancer, and linitis plastica is often associated with a poor prognosis.[25] After neoadjuvant therapy, the presumed tumor bed should be measured, but the macroscopic tumor dimension needs to be confirmed microscopically. According to the UICC[20]/AJCC[3] 8th edition TNM classification, acellular mucin pools and fibrosis with no viable tumor cells should be considered negative for residual carcinoma, and only the area with viable tumor should be measured to determine the tumor dimensions. For multiple discontinuous foci of posttreatment residual carcinoma, it is recommended to measure the maximum diameter including all foci (including nonneoplastic areas between foci).

If there is no tumor visible macroscopically, or for small residual tumors where the macroscopic dimensions may not be accurate, microscopic tumor dimensions should be documented. Precursors (eg, low- and high-grade dysplasia) should be excluded from the tumor size measurement.

Histologic Tumor Type.—Several classification schemes have been used for subtyping gastric carcinomas histologically, including the Laurén,[26] Nakamura et al,[27] JGCA,[28] WHO[4] (Table 2), and Ming[29] classifications. For consistency in reporting, the *WHO Classification of Tumours of the Digestive System*, 5th edition, is recommended (Table 3).[4] However, if a carcinoma does not fit the WHO classification for gastric carcinomas, a descriptive diagnosis should be given. The Laurén classification is widely used for gastric adenocarcinomas.[26] In the Laurén classification, gastric adenocarcinomas are divided into 2 histologic subtypes: intestinal type and diffuse type.[26] Gastric carcinomas that do not fit into 1 of the 2 categories are placed into the mixed or indeterminate categories. The Laurén classification provides a simplified categorization of common types of gastric carcinoma and facilitates a general understanding of the pathogenesis of most gastric carcinomas.[26] However, unlike

Table 2. Comparison of the Laurén, Nakamura, Japanese Gastric Cancer Association (JGCA), and World Health Organization (WHO) Classifications of Gastric Cancer[a]

Laurén (1965)[26]	Nakamura et al (1968)[27]	JGCA (2017)[28]	WHO (2019)[4]
Intestinal	Differentiated	Papillary: pap	Papillary
		Tubular 1, well differentiated: tub1	Tubular, well differentiated
		Tubular 2, moderately differentiated: tub2	Tubular, moderately differentiated
Indeterminate	Undifferentiated	Poorly 1 (solid type): por1	Tubular (solid), poorly differentiated
Diffuse	Undifferentiated	Signet ring cell: sig	Poorly cohesive, signet ring cell phenotype
		Poorly 2 (nonsolid type): por2	Poorly cohesive, other cell types
Intestinal/diffuse/ indeterminate	Differentiated/ undifferentiated	Mucinous	Mucinous
Mixed		Description according to the proportion (eg, por2 > sign > tub2)	Mixed
Not defined	Not defined	Special type:	Other histologic subtypes:
		Adenosquamous carcinoma	Adenosquamous carcinoma
		Squamous cell carcinoma	Squamous cell carcinoma
		Undifferentiated carcinoma	Undifferentiated carcinoma
		Carcinoma with lymphoid stroma	Carcinoma with lymphoid stroma
		Hepatoid adenocarcinoma	Hepatoid adenocarcinoma
		Adenocarcinoma with enteroblastic differentiation	Adenocarcinoma with enteroblastic differentiation
		Adenocarcinoma of fundic gland type	Adenocarcinoma of fundic gland type
			Micropapillary adenocarcinoma

[a] Reproduced with permission from WHO Classification of Tumors Editorial Board. *WHO Classification of Digestive System Tumors*. 5th ed. Lyon, France: IARC Press. © World Health Organization/International Agency for Research on Cancer.[4]

the WHO classification, the Laurén classification is difficult to apply to all histologic gastric cancer subtypes.[4,26]

Results on the prognostic value of histologic types in gastric cancer are conflicting. While many studies have reported that diffuse, signet ring, and anaplastic carcinomas confer an unfavorable prognosis, some multivariate studies showed no relationship between tumor types and prognosis when stage was included in the model, which might be explained by inconsistent histology typing by pathologists.[30,31]

A high incidence of intragastric recurrence is observed in certain histologic subtypes, including undifferentiated carcinoma and mixed adenocarcinoma with both signet ring cell carcinoma and poorly differentiated adenocarcinoma.[32] Close endoscopic surveillance is required for these patients.

Histologic Tumor Grade.—According to the WHO classification, histologic tumor grading applies primarily to tubular and papillary adenocarcinomas.[4] The WHO classification recommends a 2-tiered system: low-grade (well and moderately differentiated) and high-grade (poorly differentiated).[4] The DAC recommends the 2-tiered WHO grading system for stomach resection specimens because both well and moderately differentiated tumors are considered more differentiated than poorly differentiated tumors, and this grading system is highly reproducible.

It is noted that a 3-tiered system is recommended by the UICC[20]/AJCC[3] 8th edition TNM classification: G1, well differentiated; G2, moderately differentiated; and G3, poorly differentiated or undifferentiated. The AJCC 8th edition TNM classification also recommends that the highest grade be recorded if there is evidence of more than 1 grade or level of differentiation of the tumor.[3]

Histopathologic grading does not independently affect patient survival after R0 resection; however, poor histopathologic grade is associated with a high rate of R1 and R2 resections.[33] Assessment of histologic grade may not be feasible in gastric cancers with prominent treatment response.

Extent of Invasion.—Surgical resection specimens should be assessed for depth of tumor invasion because this is an independent prognostic factor. Invasion into the serosa is associated with peritoneal recurrence and poor prognosis.[34] 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.[3] Direct infiltration of the duodenum or esophagus is not considered as 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[20]/AJCC[3] 8th edition TNM classification, mainly for tumor registry reporting purposes.

Lymphovascular Invasion.—Reports on the prognostic value of lymphovascular invasion are variable,[35] but most studies demonstrate that lymphovascular invasion is an independent indicator of poor outcome following surgery.[36,37] 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[20]/AJCC[3] staging convention, lymphovascular invasion does not affect the depth of invasion ((y)pT) category. For example, a tumor invading the muscularis propria showing lymphovascular invasion in the subserosa is still considered pT2.

Response to Neoadjuvant Therapy.—Several grading systems to assess the histopathologic tumor response to neoadjuvant therapy have been applied to treated gastrointestinal carcinomas.[38,39] These include the Mandard,[40] Becker,[41] JGCA,[16] and CAP[42]/AJCC[3] tumor regression

Table 3. World Health Organization Histologic Classification of Gastric Carcinomas[a]

Tumor Type	Histologic Features
Adenocarcinoma, main histologic types	
Tubular adenocarcinoma	Most common subtype; composed of dilated or slitlike branching tubules of variable diameter or acinar structures
Papillary adenocarcinoma	Exophytic growth pattern and most commonly well differentiated; composed of elongated fingerlike 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 tumor area)
Mixed adenocarcinoma	Composed of signet ring cell/poorly cohesive component and 1 or more other distinct histologic components, such as tubular/papillary carcinoma
Adenocarcinoma, other histologic subtypes	
Gastric (adeno)carcinoma with lymphoid stroma	Characterized by irregular sheets, trabeculae, ill-defined tubules, or syncytia of polygonal cells embedded within a prominent lymphocytic infiltrate, with intraepithelial lymphocytes; frequently associated with 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 α-fetoprotein expression; other α-fetoprotein–producing carcinomas, including well-differentiated papillary/tubular-type adenocarcinoma with clear cytoplasm, adenocarcinoma with enteroblastic differentiation, and yolk-sac tumor–like carcinoma
Micropapillary adenocarcinoma	Composed of micropapillary component (10%–90% of the tumor 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 histologic subtypes	Mucoepidermoid carcinoma, paneth cell carcinoma, and parietal cell carcinoma
Gastric squamous cell carcinoma	Only composed of squamous cell carcinoma with no other histologic 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 sized polygonal cells, with frequent pleomorphic tumor 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 NEC	
Small cell NEC	Resembles its lung counterpart; frequent necrosis
Large cell NEC	Resembles its lung counterpart; frequent necrosis
Mixed neuroendocrine-nonneuroendocrine neoplasm	
Mixed adenocarcinoma-NEC	Composed of both adenocarcinoma and NEC with each component ≥30%
Mixed adenocarcinoma-neuroendocrine tumor	Composed of both adenocarcinoma and neuroendocrine tumor with each component ≥30%

Abbreviation: NEC, neuroendocrine carcinoma.

[a] Data derived from WHO Classification of Tumours Editorial Board, ed. *Digestive System Tumours*. WHO Classification of Tumours, 5th ed. Lyon, France: International Agency for Research on Cancer Press; 2019.[4]

grading schemes.[38,39] Although the Mandard system[40] is based on the fibrosis/tumor ratio (Table 4), the 4-tiered Becker system[41] uses the estimated percentage of residual tumor in relation to the (assumed) pretherapy tumor size (Table 4). The CAP modified Ryan grading system,[43] which is also referred to by the AJCC 8th edition TNM classification,[3] is shown in Table 4.

Although many studies[38,44–46] have evaluated and compared these grading schemes in assessing treatment response in gastrointestinal carcinomas after neoadjuvant therapy, there is no consensus on the optimal method to stratify tumor regression. In addition, the interobserver and intraobserver variability is high for most grading schemes.[38,39] Nevertheless, response to neoadjuvant therapy should be reported, because assessment of histologic tumor regression may provide valuable prognostic information and may impact the choice of postoperative therapy.[38] Patients with complete tumor regression have significantly better overall survival compared with patients with residual adenocarcinoma.[38] Because there is currently no consensus, the CAP grading system, which is a modified Ryan scheme,[43] is recommended by the DAC. The CAP grading system assesses the residual tumor cells rather than treatment-associated fibrosis.[43]

The presence of lymph node metastasis is one of the most important prognosticators in gastrointestinal carcinomas, but a consensus method to determine tumor regression in lymph nodes has not been established. Furthermore, so far only few studies have demonstrated that regressive changes in lymph node metastasis were associated with patient

Table 4. Tumor Regression Grading Systems					
Mandard et al[40]		Becker et al[41]		College of American Pathologists[42]	
Description	TRS	Description	TRS	Description	TRS
Complete regression: fibrosis without detectable tumor	1	No residual carcinoma	1	No viable cancer cells (complete response)	0
Fibrosis with rare, scattered residual cancer cells	2	1%–10% residual carcinoma	2	Single cells or rare small groups of cancer cells (near complete response)	1
Fibrosis and tumor cells with a predominance of fibrosis	3	11%–50% residual carcinoma	3	Residual cancer with evident tumor regression, but more than single cells or rare small groups of cancer cells (partial response)	2
Fibrosis and tumor cells with predominance of tumor cells	4	>50% residual carcinoma	4	Extensive residual cancer with no evident tumor regression (poor or no response)	3
No signs of regression	5				

Abbreviation: TRS, tumor regression score.

outcome.[38] Therefore, tumor regression should only be assessed in the primary tumor for the time being.

If there is no tumor visible on macroscopic examination, the entire assumed tumor bed should be processed into paraffin blocks to correctly stage tumors 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 may be helpful, if available, when the specimen is morphologically suspicious for residual tumor. According to the UICC[20]/AJCC[3] 8th edition TNM classification, acellular mucin pools, necrosis, and degenerative/reactive changes without viable tumor cells after treatment should be interpreted as negative for tumor.

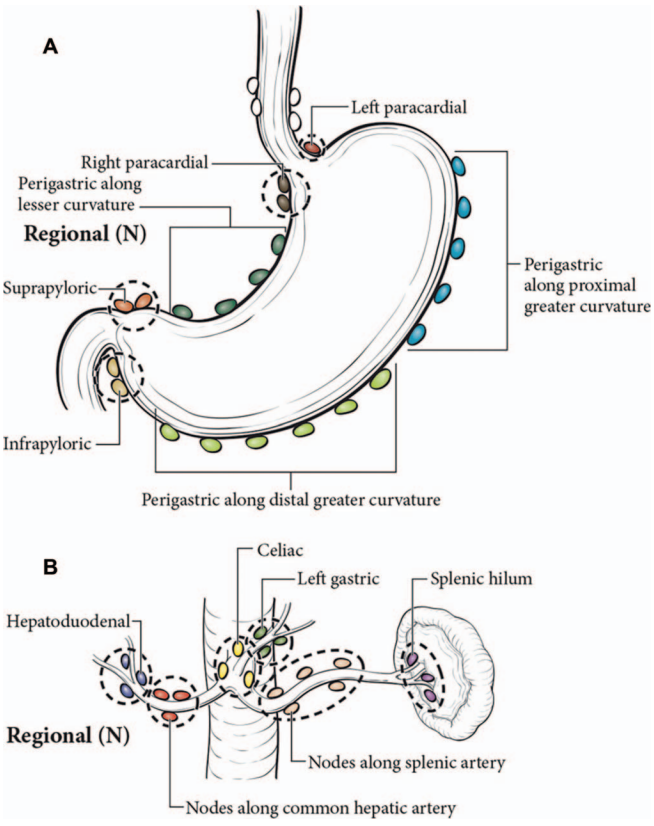

Figure 2. *Regional lymph nodes of the stomach. A, Perigastric lymph nodes. B, Extraperigastric lymph nodes. Used with permission from the American College of Surgeons, Chicago, Illinois. The original source for this information is the American Joint Committee on Cancer Staging Manual, 8th edition (2016), published by Springer Science+Business Media.*[3]

Margin Status.—Resection margins of gastrectomy specimens include proximal, distal, and radial/circumferential margins. Depending on tumor location and/or histologic tumor type, proximal and distal margins may only be assessed macroscopically. The radial margin is often the closest margin, especially for tumors close to the EGJ, and is usually measured microscopically. In the gastric body and antrum, the lesser omental (hepatoduodenal and hepatogastric ligaments) can be considered as radial resection margins, and distance between the tumor and these margins may be measured macroscopically.

The definition of what constitutes a positive resection margin differs between the United States and the United Kingdom/Europe. The CAP defines a positive margin (incomplete resection, R1) as the presence of tumor cells directly at the resection margin,[42] whereas RCPath defines R1 tumors as those having tumor cells present within 1 mm of the margin.[47] A positive margin is associated with a poor prognosis.[48] However, at this stage no consensus on the definition of margin positivity has been reached. It is recommended that pathologists follow their countries' guidelines. However, there is not sufficient evidence whether a 1-mm resection margin cutoff is clinically relevant in gastric cancer.

Lymph Node Status.—The presence of lymph node metastasis is one of the strongest prognostic indicators in gastric cancer.[49] The UICC[20]/AJCC[3] 8th edition TNM classification and National Comprehensive Cancer Network (NCCN) guidelines[50] recommend excision of a minimum of 15 to 16 lymph nodes in order to reliably stage the tumor, but efforts should be made to submit as many lymph nodes as possible for histologic examination. A study on esophagogastric adenocarcinoma showed that preoperative chemoradiation, but not chemotherapy, reduced the total lymph node count after total gastrectomy.[51] Fat clearance of resection specimens may increase lymph node yield and result in nodal upstaging.[52]

D1 lymph node resections include the removal of the perigastric lymph nodes (Figure 2, A), whereas D2 resections include the removal of perigastric lymph nodes

Table 5. Criteria Used in the ToGA Trial for Scoring HER2 Expression by Immunohistochemistry (IHC) in Gastric and Esophagogastric Junction Adenocarcinoma[a]		
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 cancer cells	Equivocal (do in situ hybridization)
3+	Strong complete, basolateral, or lateral membranous reactivity in ≥10% of cancer cells	Positive

[a] Data derived from Hofmann et al.[63]

and the lymph nodes along the left gastric, common hepatic, and splenic arteries and the celiac axis (Figure 2, B).

In Asian countries, D2 dissection yields superior outcomes compared with D1 dissection; however, the results from other countries are conflicting.[53–55] The Dutch D1D2 randomized clinical trial has recently demonstrated that D2 lymphadenectomy is associated with lower locoregional recurrence and gastric cancer–related death rates compared with D1 surgery after long-term follow-up.[56] Gastrectomy with D2 dissection has become more commonly used for advanced gastric cancer in Western countries.[57,58]

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 (Figure 2, A); and lymph nodes along the left gastric artery, celiac artery, common hepatic artery, hepatoduodenal vessels, splenic artery, and splenic hilum (Figure 2, B).[3] 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.

Tumor deposits, defined as discrete tumor nodules within the lymphatic drainage of the primary carcinoma without identifiable lymph node tissue, vascular tissue, or neural tissue, are considered regional lymph node metastases.[3] Tumor deposits may be an independent predictor of prognosis in patients with gastric cancer.[59]

Lymph nodes containing isolated tumor cells, defined as single tumor cells or small clusters of cells ≤0.2 mm in greatest diameter, without stromal reaction, are classified as pN0 in gastric cancer.[3] However, it is recommended to add a comment in the report to describe the finding. There is no micrometastasis (N1mi) category in staging gastric cancer.[3] 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 1 focus of residual tumor cells in the lymph nodes regardless of size.[60] Lymph nodes with acellular mucin pool or fibrotic lymph nodes with no viable tumor are considered negative.[60] Immunohistochemistry for cytokeratin should be performed if there is suspicion of tumor cells.

Involvement of nonregional lymph nodes is considered (y)pM1 and as such should be reported under "histologically confirmed distant metastases." Nonregional lymph nodes include the retropancreatic, pancreaticoduodenal peripancreatic, superior mesenteric, middle colic, para-aortic, and retroperitoneal nodes.[60]

Ancillary Studies.—For gastric neuroendocrine carcinomas, including mixed neuroendocrine-nonneuroendocrine carcinomas, the reporting of neuroendocrine marker expression and Ki-67 proliferation index is a core element. These elements are noncore for other types of gastric carcinomas. Gastric neuroendocrine neoplasms are classified into neuroendocrine tumors, NECs, or mixed neuroendocrine-nonneuroendocrine neoplasms. The neuroendocrine tumors are graded 1 to 3 using the mitotic count and Ki-67 proliferation index. Pure neuroendocrine tumors are not considered within the scope of this data set.[61] Most NECs show marked cytologic atypia and brisk mitotic activity and are subclassified into small cell and large cell subtypes. NECs are considered high grade by definition, typically with a Ki-67 proliferation index >55%.[62] Mixed neuroendocrine-nonneuroendocrine neoplasms are usually composed of a poorly differentiated NEC component and an adenocarcinoma component. If a pure or mixed neuroendocrine carcinoma is suspected on morphology, IHC is required to confirm neuroendocrine differentiation, usually applying synaptophysin and chromogranin A as a minimum.[60]

The National Comprehensive Cancer Network guidelines recommend assessment of human epidermal growth factor receptor 2 (HER2) expression using IHC or *HER2* amplification using in situ hybridization (ISH) for patients with inoperable locally advanced, recurrent, and metastatic gastric/EGJ adenocarcinoma for whom therapy with trastuzumab is considered.[50] For HER2 IHC in resection specimens, both intensity and percentage of immunoreactive cancer cells are assessed with scores ranging from 0 to 3+ (Table 5).[63] In situ hybridization is used when IHC is equivocal (2+). IHC 3+ or ISH showing *HER2* amplification (including IHC 2+ with *HER2* amplification by ISH) is considered HER2$^+$. 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 was used (dual-probe versus single-probe assay). The HER2 scoring system by Hofmann et al[63] can be used to evaluate HER2 expression in gastric cancers.[63]

Microsatellite instability/mismatch repair deficiency (dMMR) status and programmed death ligand-1 (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 microsatellite instability (MSI)-high or PD-L1$^+$ unresectable or metastatic gastric cancers.[64] Although MSI status has been highly predictive of response to programmed death receptor-1 (PD-1) pathway blockage in several clinical trials,[65] the value of PD-L1 expression in selecting patients for checkpoint inhibitors in esophageal and gastric cancer needs further investigation.

Approximately 40% of gastric/esophageal cancers express PD-L1. Unlike other malignancies (ie, non–small cell lung cancer), PD-L1 expression in gastric/esophageal cancers is

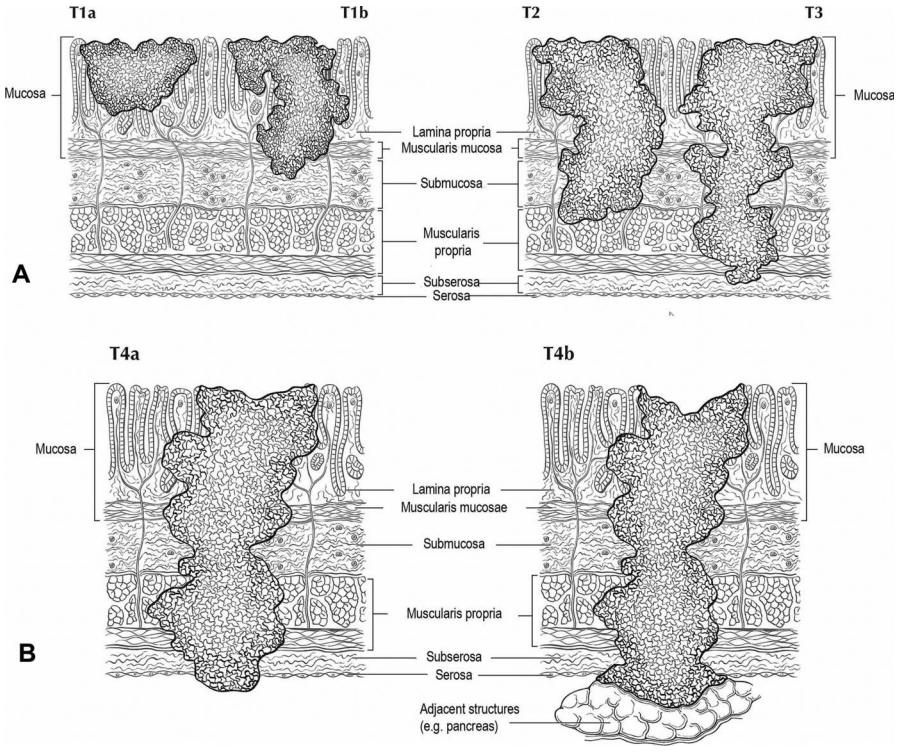

Figure 3. *Extent of invasion. A, T1a is defined as tumor that invades the lamina propria. T1b is defined as tumor that invades the submucosa. T2 is defined as tumor that invades the muscularis propria, whereas T3 is defined as tumor that extends through the muscularis propria into the subserosal tissue. B, T4a is defined as tumor that penetrates the serosa (visceral peritoneum) without invasion of adjacent structures, whereas T4b is defined as tumor that radially invades adjacent structures, shown here invading the pancreas. Used with permission from the American College of Surgeons, Chicago, Illinois. The original source for this information is the American Joint Committee on Cancer Staging Manual, 8th edition (2016), published by Springer Science+Business Media.*[3]

mainly observed in immune cells. The combined positive score, which takes into account PD-L1 expression by both tumor cells and tumor-associated immune cells, was developed and refined for scoring gastric and esophageal cancers.[66] Combined positive score is calculated by dividing the total number of PD-L1$^+$ cells (including tumor and immune cells) by the total number of viable tumor cells. A combined positive score $\geq$1, as determined by an FDA-approved companion diagnostic test (the Dako PD-L1 IHC 22C3 PharmDx Assay), is currently used to classify a tumor as PD-L1$^+$. A low overall response rate has been reported when using a combined positive score cutoff of $<$1.[67] Studies are ongoing to investigate whether the overall response rate can be improved by using a different cutoff.

DNA mismatch repair defect can be determined by either polymerase chain reaction–based MSI testing or by IHC stains for MutL homolog 1 (MLH1), MutS homolog 2 (MSH2), MutS homolog 6 (MSH6), and postmeiotic segregation increased 2 (PMS2). The CAP template for reporting results for DNA mismatch repair testing in patients being considered for checkpoint inhibitor immunotherapy can be used to report MMR protein immunohistochemistry and MSI testing results.[68] MSI-high/dMMR is seen in 8% to 25% of gastric cancers. Although some 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 epithelial cellular adhesion molecule (*EPCAM*). Germline mutational analyses are recommended for individuals suspected of having Lynch syndrome.

Epstein-Barr virus (EBV)–positive gastric cancers are associated with a better prognosis.[69] In addition, EBV-positive gastric cancers are more likely associated with overexpression of PD-L1 and PD-L2. A recent study suggested that EBV-positive tumors could be a strong marker for efficacy of immunotherapy.[67] EBV-positive gastric cancers account for approximately 10% of all gastric cancers, most of which are located in the proximal stomach.[70] Histologically, EBV-positive gastric cancers can be subclassified into: (1) poorly differentiated carcinoma with abundant tumor-infiltrating lymphocytes (gastric [adeno]carcinoma with lymphoid stroma); (2) tubular adenocarcinoma with prominent lymphoid follicles and active germinal centers (also termed carcinoma with Crohn disease–like lymphoid reaction); and (3) conventional-type adenocarcinoma with scant lymphocytic infiltrate.[69] Although EBV-positive gastric cancer can be poorly differentiated, EBV-positive gastric cancer is a distinct subtype with a low risk of lymph node metastasis.[71]

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

Histologically Confirmed Distant Metastases.—Common distant metastases in gastric cancer include peritoneal metastasis, liver metastasis, and metastasis to nonregional lymph nodes. Involvement of nonregional lymph nodes is considered (y)pM1 and should be reported as such.

Pathologic Staging.—The UICC[20]/AJCC[3] 8th edition TNM classification for gastric carcinoma is recommended, as shown in Figure 3.[3]

Noncore Elements

Clinical Information.—Clinical information, including preoperative neoadjuvant therapy and prior 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 tumor location or other clinical

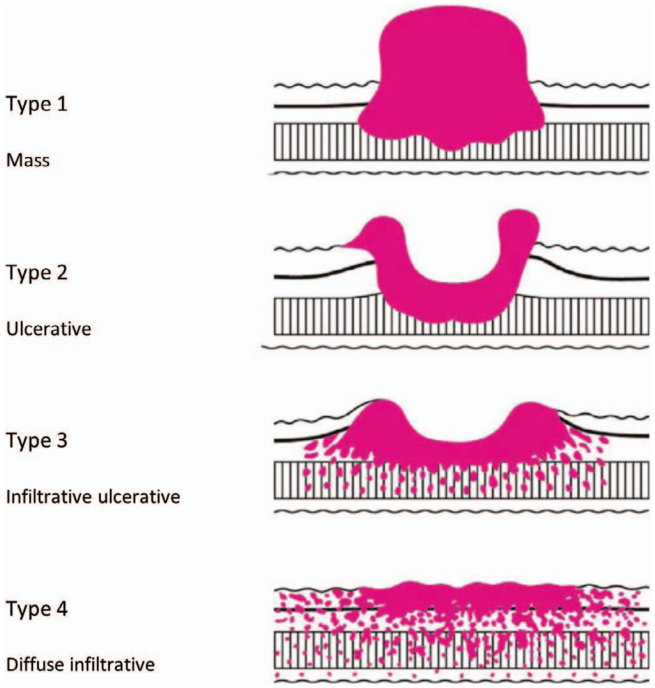

Figure 4. *Macroscopic types of advanced gastric cancer (Borrmann Classification). Type 1 (mass): polypoid tumors, sharply demarcated from the surrounding mucosa. Type 2 (ulcerative): ulcerated tumors with raised margins surrounded by a thickened gastric wall with clear margins. Type 3 (infiltrative ulcerative): ulcerated tumors with raised margins, surrounded by a thickened gastric wall without clear margins. Type 4 (diffuse infiltrative): tumors without marked ulceration or raised margins; the gastric wall is thickened and indurated and the margin is unclear. Reprinted by permission from Springer Nature: Gastric Cancer (Japanese Gastric Cancer Association [2011]. Japanese classification of gastric carcinoma: 3rd English Edition), Copyright 2011.*[16]

information on the tumor location is an important guide because the tumor epicenter may be altered after neoadjuvant therapy.

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

Specimen Dimensions.—There is no official agreement or recommendation on how specimens should be measured and whether they should be measured fresh or after formalin fixation. Although most specimens are measured after fixation, gastrectomy specimens may be measured fresh for reasons such as frozen section evaluation of margins and biobanking of fresh tissue for research. Significant shrinkage of unpinned gastrointestinal tract specimens occurs after fixation. Pinning out the specimens on cardboard during fixation helps restore most of the specimen length.[24] A comment should be included in the report if the dimensions are taken from a fixed but unpinned specimen.

Macroscopic Tumor Type.—According to the Borrmann Classification (Figure 4), 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).[4,60] Borrmann type II is the most common macroscopic type among advanced gastric cancers. Borrmann type IV is associated with a poor prognosis.[72,73] The Borrmann classification is based on untreated gastric cancers, and therefore may not be applicable after neoadjuvant treatment.

Perineural Invasion.—The prognostic value of perineural invasion remains under debate. Most studies demonstrate its significant prognostic impact in univariate analysis but not in multivariate analysis.[74–78] For Laurén intestinal-type gastric cancer, perineural invasion may be an independent prognostic factor.[74]

Coexistent Pathology.—Based on the updated Sydney system, chronic gastritis is classified into *Helicobacter pylori* gastritis, ex–*H pylori* gastritis, chemically induced/reactive gastritis, autoimmune gastritis, and other special forms of gastritis.[79] *Helicobacter pylori* gastritis and autoimmune gastritis are recognized risk factors for gastric carcinoma. Both cause atrophic gastritis with intestinal metaplasia, which may develop into dysplasia/adenoma and further progress to intestinal-type adenocarcinoma. In addition, pyloric gland adenoma may arise in a background of autoimmune atrophic gastritis,[80] 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 adenoma, all of which can progress to invasive carcinoma.[3]

Other risk factors associated with gastric carcinoma include previous gastric surgery and EBV infection. In addition, approximately 10% of gastric cancers develop in a familial/hereditary setting, such as hereditary diffuse gastric cancer in patients with e-cadherin (*CDH1*) or catenin alpha-1 (*CTNNA1*) mutations, patients with Lynch syndrome with MSI-high gastric cancer, familial intestinal gastric cancer, gastric adenocarcinoma, and proximal polyposis of the stomach due to germline mutations in promoter 1B of adenomatous polyposis coli (*APC*).[81] Some patients with familial adenomatous polyposis can have multiple foveolar-type adenomas, which have the potential to become invasive carcinoma but at a consistently low rate.[3] In addition, synchronous gastric carcinoma is rare. However, in 1 report from Asia, synchronous gastric cancer is seen in approximately 10% of gastric cancer patients.[82]

DISCUSSION

Synoptic cancer reporting helps improve patient care and facilitates data exchange and analyses for quality assurance, cancer epidemiology, and clinical and basic research. A complete and accurate pathology report is crucial to diagnostic workup, therapeutic management, and posttherapeutic follow-up of every cancer patient. Baranov et al[83] analyzed more than 1000 narrative and synoptic (structured) esophageal and gastric cancer pathology reports for completeness. Completeness significantly increased from 56% to 97% in the structured reports compared with unstructured narrative reports.[83] The ICCR data sets contain all the parameters needed to guide management and prognostication for various cancers. In addition, synoptic reporting may increase awareness of quality indicators,

thereby improving the quality of pathologic specimen evaluation. For example, increased numbers of lymph nodes have been obtained from colorectal cancer resections since the implementation of synoptic reporting.[84] Furthermore, the commentaries contained in the data sets provide an important tool to educate and train individual pathologists, thereby increasing accuracy of the data. Finally, the ICCR harmonizes data sets from various pathology organizations, which allows data exchange globally, thereby facilitating clinical and basic research around the world.

Gastric cancer is a heterogeneous disease, with different etiologies and diverse genetic and epigenetic alterations. Since the early 1990s when infection with *H pylori* was discovered to be the main risk factor for gastric cancer, several other factors have been associated with an increased risk for gastric cancer. These factors include autoimmune (autoimmune atrophic gastritis), infectious (EBV infection), and hereditary (Lynch syndrome and hereditary diffuse gastric cancer) causes. In addition, the incidence of proximal gastric adenocarcinoma has been increasing in Western countries, which has been attributed to gastroesophageal reflux disease and obesity.[85] Based on genomic data, the Cancer Genome Atlas has classified gastric adenocarcinomas into 4 distinct molecular subtypes: (1) EBV-positive, (2) MSI tumors, (3) genomically stable tumors, and (4) tumors with chromosomal instability.[86] Similarly, the Asian Cancer Research Group has identified 4 subtypes of gastric cancers based on gene expression: (1) microsatellite stable/epithelial-mesenchymal transition; (2) MSI; 3) microsatellite stable–TP53 active; and (4) microsatellite stable–TP53 negative.[87]

Recent advances in molecular understanding of gastric cancer have introduced targeted therapies for advanced gastric cancer. Addition of trastuzumab to chemotherapy in patients with $HER2^+$ gastric cancers significantly improves survival in these patients. Recently, immune checkpoint inhibitors have been used to treat MSI-high/dMMR or PD-L1–positive gastric cancers. In addition, with the discovery of inhibitors for neurotrophic tropomyosin-related kinase (NTRK), *NTRK* gene fusions are currently included in the clinical management of metastatic gastric cancer.[50] Despite these developments, the prognosis remains poor in most patients with advanced gastric cancer. Wide implementation of next-generation sequencing in gastric cancers may lead to the discovery of new therapeutic targets, potentially improving clinical care, survival, and quality of life of patients with gastric cancer in the future.

In the present day, treatment of gastric cancer patients depends on tumor stage, patient performance status, and patient preferences. In the future, more therapeutic and prognostic biomarkers are expected to be discovered, which will be integrated into the ICCR Carcinoma of the Stomach data set, guiding fine-tuning of the treatment for gastric cancer patients.

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