

Pathology Reporting of Gastric Endoscopic Resections: Recommendations from the International Collaboration on Cancer Reporting

Chanjuan Shi, Fleur Webster, Iris D. Nagtegaal, on behalf of the Dataset Authoring Committee for the development of the ICCR Dataset for Pathology Reporting of Gastric Endoscopic Resections

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Title: Pathology Reporting of Gastric Endoscopic Resections: Recommendations from the International Collaboration on Cancer Reporting

Short title: ICCR Stomach ER Dataset

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Abbreviations: International Collaboration on Cancer Reporting (ICCR), endoscopic resection (ER), Dataset Steering Committee (DSC), gastrointestinal (GI), Dataset Authoring Committee (DAC), National Health and Medical Research Council (NHMRC), endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD), millimeters (mm), European Society of Gastrointestinal Endoscopy (ESGE), American Gastroenterological Association (AGA), Japanese Gastric Cancer Association (JGCA), micrometers (μm), esophagogastric junction (EGJ), World Health Organization (WHO), Union for International Cancer Control (UICC), American Joint Committee on Cancer (AJCC), mixed neuroendocrine-non-neuroendocrine carcinomas (MiNECs), Epstein-Barr virus (EBV), EBV-associated gastric cancer (EBVaGC), microsatellite instability (MSI), Epstein-Bar encoding region (EBER).

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Data transparency statement: Analytic methods and are made available on the ICCR website to other researchers: <http://www.iccr-cancer.org/datasets/dataset-development>. The full dataset is available on the ICCR website: <http://www.iccr-cancer.org/datasets/published-datasets/digestive-tract/endoscopic-resection-of-the-stomach>.

Keywords: checklist; dataset; protocol; synoptic report; structured report; International Collaboration on Cancer Reporting (ICCR); guidelines; early gastric carcinoma; endoscopic resection.

Endoscopic resection (ER) has recently become an increasingly common treatment for early gastric cancer, despite being a relatively new approach in non-East-Asian countries.

Consistent, generalized data are needed for implementation of evidence-based clinical practice in the field.

Complete and accurate reporting of pathologic findings in ER specimens is extremely important in guiding follow-up management and surveillance. In addition, structured pathology reporting of ER specimens and inclusion of all clinically relevant information can help achieve the goal of implementing global best practice.

Datasets or checklists for pathology reporting of gastric carcinoma resections have been independently developed by several organizations across the world; however, a dataset specifically designed for early gastric carcinoma ER specimens has not been previously available. The aim of the International Collaboration on Cancer Reporting (ICCR) was to produce an evidence-based international pathology reporting dataset for ER of early gastric cancers. The development of a separate ER dataset will ensure comprehensive information acquisition and allow for more efficient updating. The dataset is freely available from the ICCR website at <http://www.iccr-cancer.org/datasets/published-datasets/digestive-tract/endoscopic-resection-of-the-stomach>.

Methods

The dataset was developed on the basis of guidelines agreed by the Dataset Steering Committee (DSC) of the ICCR at <http://www.iccr-cancer.org/datasets/dataset-development>.

The DSC appointed a Chair (CS) to develop a dataset for reporting of early gastric carcinomas in ER specimens. Eight expert gastrointestinal (GI) pathologists and a gastroenterologist were appointed, and together with the Chair, an ICCR Series Champion

(IDN) and Project Managers (FW and CIS), which formed the Dataset Authoring Committee (DAC). The DAC included one pathologist from the USA (GL), one from the UK (MO), two from Europe (CVDP, MV), two from Australia (PK, AKL), one from Japan (TU), and one from Korea (SH), together with a gastroenterologist (MB) from Australia. The Series Champion provided guidance and support to the Chair of the DAC regarding ICCR standards and ensured harmonization across GI tube datasets, while the Project Managers coordinated the development process. A separate dataset for the reporting of gastrectomy for gastric carcinomas was also developed by the ICCR and is available at <http://www.iccr-cancer.org/datasets/published-datasets/digestive-tract/carcinoma-of-the-stomach>.

In line with other ICCR datasets, this dataset included a set of elements and value lists (responses) accompanied by commentary. The elements were categorized as either core (required) or non-core (recommended). Core elements were those which were 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 (NHMRC) levels of evidence).¹ In some circumstances, where level III-2 evidence is not available, an element may be made a core element where there is unanimous agreement of the DAC. Non-core elements were those that did not meet the above standard but were considered by the DAC to be clinically important and/or representing good practice. The commentary clarified the elements; explained the rationale behind the categorization; and, where possible, cited published evidence that supported its inclusion.

Based on published datasets/guidelines for early gastric carcinomas, a working draft was first developed by the Project Managers and then edited by the Chair. The draft was circulated to the DAC and discussed in a series of teleconferences and email communications until

consensus was achieved. The draft dataset was uploaded on the ICCR website for public comment. The dataset was reviewed in response to feedback and a final version was approved by the DAC and ratified by the DSC.

Recommendations

The list of core and non-core elements is provided in Table 1 and discussed below:

Core elements

a. Clinically relevant information, including performed endoscopic procedure and tumor site should be communicated.

ER, including endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD), is recommended for selected early gastric carcinomas. En bloc resection may be necessary to obtain precise pathological diagnosis. EMR cannot be used to resect lesions larger than 15 millimeters (mm) in one piece, and piecemeal EMR of larger lesions is potentially associated with risk of local recurrence.² Therefore, for larger lesions, ESD is the better option.² The European Society of Gastrointestinal Endoscopy (ESGE), American Gastroenterological Association (AGA) and Japanese Gastric Cancer Association (JGCA) recommend ESD as the treatment of choice for most gastric superficial neoplastic lesions.³⁻⁶

To determine whether ER is sufficient treatment, these organizations have defined standard criteria,³⁻⁵ with extended criteria^{4, 5} for ESD which include: 1) well/moderately differentiated intramucosal carcinoma with no ulcer, size >20 mm; 2) well/moderately differentiated intramucosal carcinomas, with ulcer, size ≤30 mm; 3) well/moderately differentiated carcinomas with early submucosal invasion (SM1) ≤500 micrometers (μm), with no ulcer and

size ≤ 30 mm; and 4) poorly differentiated intramucosal carcinoma ≤ 20 mm, with no ulcer.

Reliable long-term results have not been established for the extended criteria.²

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 dataset. The stomach is 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 JGCA guidelines divide the stomach into upper third, middle third and distal third by the lines connecting the trisected points on the lesser and greater curvatures,⁶ which is adopted by this dataset. Primary gastric cancer located in the upper third of the stomach, especially at the EGJ/cardia, are reported to be more aggressive and associated with poor prognosis.⁷ For ER specimens, tumor site can be provided by endoscopists, or can be found in the endoscopy report or the patient electronic medical records.

b. The description of the specimen should include specimen and tumor dimensions, presence of different tissue layers, as well as tumor focality.

There is no internationally agreed recommendation on how specimens should be measured and whether they should be measured fresh or after formalin fixation. However, the DAC unanimously recommended that the reporting of specimen dimensions should be a core element as this allows for good clinical correlation.

For early gastric carcinoma, the tumor dimension is usually measured microscopically. However, when the tumor size is large, macroscopic mapping of the entire tumor and a thorough pathologic examination may be necessary. Reporting of tissue layers present in the specimen is very important as limited tissue layers prevent accurately staging the tumor.

While multifocal gastric carcinomas are rare, they should be documented. If multiple primary tumors are present, separate datasets should be used.

c. For tumor typing the World Health Organization (WHO) classification should be used, while for grading, the Union for International Cancer Control (UICC)/American Joint Committee on Cancer (AJCC) staging systems should be used.

Several classification schemes have been used for subtyping gastric carcinomas histologically, including the Laurén, Nakamura, JGCA, Ming, and WHO classifications.⁸ For consistency in reporting, the WHO classification of gastric carcinomas is a core element.⁸ The Laurén classification is also widely used for gastric adenocarcinomas and provides a simplified and valuable categorization of common types of gastric carcinoma.⁹ However, unlike the WHO classification, the Laurén classification cannot be applied to a variety of rare histologic subtypes and is therefore a non-core element. In the Laurén classification, gastric adenocarcinomas are simply divided into two histological subtypes - intestinal type and diffuse type.⁹ Gastric carcinomas that do not fit into one of these two histological subtypes are placed into the mixed or indeterminate categories. 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.¹⁰ Close endoscopic surveillance is required for patients with these histological subtypes.

The three-tiered system, applicable to tubular and papillary adenocarcinomas, is recommended by the UICC¹¹/AJCC¹² 8th Edition Staging Systems and includes: 1) G1: well differentiated; 2) G2: moderately differentiated; and 3) 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 tumor.¹² The DAC recommended that the UICC¹¹/AJCC¹² grading system for endoscopic specimens should be a core element because tumor grade may be more relevant in this setting. Some studies have shown that poorly differentiated/undifferentiated mucosal and submucosal gastric cancer are associated with a higher risk for lymphovascular invasion/lymph node metastasis.^{5, 13, 14}

d. For specimens with invasive carcinoma the extent of invasion should be reported, while for staging, the UICC/AJCC staging systems should be used.

The depth of invasion is associated with increased risk of lymph node metastasis in early gastric cancer,⁵ and is therefore a core element. Tumor invasion into the submucosa >500 µm (0.5 mm) from the muscularis mucosa has been reported as an independent risk factor for lymph node metastasis after noncurative ER.⁵ The depth of submucosal invasion is measured from the lower border of the muscularis mucosae to the point of the deepest tumor penetration (Figure 1). Submucosal invasion of <500 µm in depth has been included as one of the extended criteria for ESD.

The UICC¹¹/AJCC¹² 8th Edition Staging Systems for gastric carcinoma should be used (core element) (Figure 1). The term ‘carcinoma in situ’ is not commonly applied to glandular epithelium. However, high-grade dysplasia in ER specimens can be reported as ‘carcinoma in situ’ as recommended by the UICC¹¹/AJCC¹² 8th Edition Staging Systems mainly for tumour registry reporting purposes. Staging is only applicable to ER specimens with sufficient tissue layers present.

e. For specimens with invasive carcinoma the presence or absence of lymphovascular invasion should be reported.

Lymphovascular invasion is an independent predictor of lymph node metastasis in endoscopically resected early gastric cancers,^{15, 16} and a core element. Therefore, additional gastrectomy is recommended for patients who have ER showing lymphovascular invasion.

f. For all specimens the margin status should be reported.

Margins include mucosal and deep margins. ER can be an en bloc or piecemeal resection. Mucosal margin status is impossible to assess if it is a piecemeal resection with no orientation provided. Presence or absence of low-grade and high-grade dysplasia at the mucosal margin should also be recorded.

g. For carcinomas with neuroendocrine differentiation neuroendocrine marker expression and Ki-67 proliferation index should be reported.

For gastric carcinomas with neuroendocrine differentiation, including gastric neuroendocrine carcinomas and mixed neuroendocrine-non-neuroendocrine carcinomas (MiNECs), the reporting of neuroendocrine marker expression and Ki-67 proliferation index are core elements.

Non-core elements

a. Additional clinical information can be communicated.

Additional clinical information can be provided by the clinician in 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, intestinal metaplasia, etc. Multiple tumors may occur in the stomach and previous history of cancer or cancer treatment is relevant. In addition, several conditions, including previous partial gastrectomy for a benign disease and chronic atrophic gastritis, are risk factors for gastric cancer.

b. Reporting of macroscopic tumor type is recommended.

Early gastric carcinoma is defined as an invasive carcinoma involving only the mucosa (T1a) or submucosa (T1b). Growth patterns of early gastric carcinoma are classified into type 0-I (protruding), type 0-II (superficial), and type 0-III (excavated). Type 0-II tumors are further divided into type 0-IIa (superficial, elevated), type 0-IIb (superficial, flat) and type 0-IIc (superficial depressed).^{6, 8, 17} Tumor ulceration may be a negative determinant in selecting patients for ER, which can be recorded in the dataset. Early gastric carcinomas are usually small, and the corresponding macroscopic tumor type may only be accurately assessed by the endoscopist.

c. Reporting of coexistent pathology is recommended.

Helicobacter gastritis and autoimmune gastritis are recognized risk factors for gastric carcinoma. Both cause atrophic gastritis with intestinal metaplasia, which may develop into dysplasia/adenoma and further progress to intestinal-type adenocarcinoma. In addition,

pyloric gland adenoma may arise in a background of autoimmune atrophic gastritis,¹⁸ 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.¹²

Other risk factors associated with gastric carcinoma include previous gastric surgery and Epstein-Barr virus (EBV) infection. In addition, approximately 10% of gastric cancers develop in a familial/ hereditary setting, including hereditary diffuse gastric cancer in patients with *CDH1* mutations and patients with Lynch syndrome with microsatellite instability (MSI)-high gastric cancer. Some patients with familial adenomatous polyposis can have multiple foveolar type adenomas, which have a potential to become invasive carcinoma but at a consistently low rate.¹²

d. Reporting of Epstein-Barr virus (EBV) and microsatellite instability (MSI) status is recommended.

Additional immunohistochemical stains for mismatch repair proteins can be performed where there is a suspicion for Lynch syndrome-associated gastric cancer, or to predict response to immune checkpoint inhibitor therapy, where appropriate.¹⁹ Testing for PD-L1 expression and *HER2* amplification/overexpression are only useful for patients with advanced/metastatic

gastric cancer. Therefore, these tests are not normally performed on the ER specimens but may be helpful for patients who develop metastases.

EBV-associated gastric cancer (EBVaGC) accounts for approximately 10% of total gastric cancers, most of which occur in men, and are located in the upper part of the stomach.²⁰

Morphologic features associated with EBVaGC include abundant tumor-infiltrating lymphocytes and Crohn disease-like reaction. Epstein-Bar encoding region (EBER) in situ hybridization is used to identify EBVaGC, particularly for proximal gastric cancers with the above-mentioned demographic and morphologic features. EBVaGC has a low risk of lymph node metastasis.²¹ Extension of the criteria for ESD in early EBVaGC is still under discussion.

Remarks

The consensus of the DAC was to not include tumor budding as a reporting element in the dataset. The rationale for this decision was that although there is an international consensus definition of tumor budding for colorectal cancer, in gastric cancer the evidence is growing but has not yet met the standard for inclusion in the ICCR Endoscopic Resection of the Stomach dataset. It was the consensus of the DAC that tumor budding could be reported locally where appropriate.

Conclusion

ER for early gastric cancer is a relatively new approach. The ICCR is the first organization to publish an evidence-based dataset for the pathology reporting of ER for early gastric cancer, which is freely available from the ICCR website. With increasing global uptake and ever more well-designed clinical studies underway, pathology reporting of early gastric cancer in ER specimens is an evolving field. A structured approach to reporting of ER of early gastric cancer dataset by pathologists worldwide will help ensure all of the necessary information for patient management is captured and allow for comparison of data between countries.

Figure legend

Figure 1 - Extent of invasion in early gastric cancers. T1a is defined as tumor invading the lamina propria; T1b is defined as tumor invading the submucosa. Note: depth of submucosal invasion is measured from the lower border of the muscularis mucosae to the point of the deepest tumor penetration.

Table 1 - Core and non-core elements for the pathology reporting of endoscopic resections of the stomach.

Core elements	Non-core elements
<ul style="list-style-type: none"> - Endoscopic procedure - Specimen dimensions - Tumor focality - Tumor site - Maximum tumor dimension - Tissue layers present - Margin status 	<ul style="list-style-type: none"> - Clinical information - Macroscopic tumor type - Histological tumor type (Laurén classification) - Coexistent pathology
For specimens with carcinoma only	
<ul style="list-style-type: none"> - Histological tumour type (World Health Organization classification) - Histological tumor grade - Extent of invasion - Lymphovascular invasion - Pathological staging 	<ul style="list-style-type: none"> - Additional tumor dimensions - Ancillary studies for other gastric carcinomas with no neuroendocrine differentiation
For gastric carcinomas with combined neuroendocrine neoplasms	
<ul style="list-style-type: none"> - Neuroendocrine markers - Ki-67 proliferation index 	

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