

Recommendations for the Reporting of Gastric Carcinoma

Prepared on behalf of the Association of Directors of Anatomic and Surgical Pathology

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Introduction for ADASP reporting Guidelines

It has been evident for decades that pathology reports are very variable even within a single institution. Standardization of reporting is the optimal way to insure that information necessary for patient management, prognostic and predictive factor assessment, grading, staging, analysis of outcomes and tumor registries is included in pathology reports. In recent years, two societies (first ADASP and then the CAP), have undertaken to publish guidelines for the reporting of common cancers. The CAP assigned multidisciplinary groups of pathologists, surgeons, radiation and medical oncologists to develop the protocols. They were then reviewed by other pathologists and clinicians. After those reviews the protocols were reviewed by multiple CAP committees and finally approved by the Board of Governors.

The ADASP, in contrast, chose a pathologist expert in each field to assemble a group from within the pathology community (with clinician input if desired) to write specific cancer protocols. These were then approved by the ADASP council and subsequently by the membership. While the ADASP and CAP formats are somewhat different, the contents are essentially the same.

The American College of Surgery (ACS) Commission on Cancer (COC) accredits cancer centers in the USA. Recently, the COC decided to require elements, deemed as essential by the CAP, to be described in all pathology reports in their accredited cancer centers as of January 2004. Importantly they do not require that the specific CAP protocols or synoptic reports be utilized. ADASP has updated all of its protocols to comply with the COC requirements in the form of 37 uniform checklists. The checklists use the staging criteria sited in the American Joint Committee on Cancer (AJCC) 2002 staging manual (sixth edition) but include a variety of other references listed in each of the checklists. Moreover, the checklists are formatted for ease of use. They may be used as templates for uniform reporting and are designed to be compatible with voice activated transcription.

The different elements in these revised ADASP Diagnostic Checklists have been divided into *Required* and *Optional* . The term *Required* in this context only signifies compliance with the COC guidelines. ADASP realizes that specimens and practices vary and it will not be possible to report these elements in every case. However, ADASP hopes that pathologists will find these checklists to be useful in daily clinical practice, while facilitating compliance with the new COC requirements.

The checklists are in standard PDF file format, and may be easily downloaded from the ADASP website. They are not to be reproduced, altered or used for commercial purposes without consent from ADASP.

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Introduction to Gastric Carcinoma Reporting Guideline

The purpose of this guideline is to facilitate uniform and complete reporting of the pathology of gastric carcinoma. Please refer both to this guideline and the accompanying checklist for a complete treatment of this topic. Guidelines for the reporting of gastric lymphoma and stromal tumors are described elsewhere. This guideline will describe the proper gross and microscopic assessment of gastric carcinoma on biopsies, endoscopic and surgical resections, and will discuss elements to be included in pathology reports. Refer also to the AJCC TNM (2002) and WHO (2000) manuals (1,2, 3).

Gross Examination

Gastric Biopsies:

Gastric biopsies should be carefully matched with patient identification. In the case of multiple specimen containers from the same patient, great care should be taken to further identify specific sites sampled as indicated by the clinician on the specimen jar and pathology requisition form (e.g., gastric fundus, gastric antrum, gastric mass, . . .etc). Any discrepancy between the number of specimens, specimen labels and the requisition sheet should be resolved immediately, prior to grossing by contacting the clinician. Documentation of specimen identification issues should be written and included with the requisition so that the pathologist is aware of the situation prior to sign out.

Many biopsies are submitted in formalin. If tissue arrives fresh, triage of tissue for special studies, such as flow cytometry or electron microscopy can occur as needed. Special handling is usually not needed for epithelial tumors.

The number of biopsies in each container should be exactly specified in the gross dictation. This helps to properly identify each specimen when there is a question of specimen mislabeling or other issues with tissue identification. Biopsies should be carefully oriented prior to placing in cassettes to ensure the best possible orientation on sections.

Gastric endoscopic mucosal resections (EMRs):

The specimen should be carefully matched with patient identification. Any concerns regarding identification or orientation should be resolved prior to gross

dissection. The number of tissue fragments in each container should be exactly specified in the gross dictation.

If not previously done in the endoscopy suite, EMRs should be carefully oriented (mucosa up), stretched, pinned down on a firm base and fixed for at least 12h in formalin. After fixation, the surgical margins (lateral and deep) must be carefully inked. The specimen must be entirely submitted in sequential sections after ensuring the best possible orientation, routinely processed and stained with hematoxylin and eosin. Care must be taken to orient the sections such that the circumferential (lateral) surgical margins are assessed, either in “en face” or cross-sections, depending on the size of the specimen. If provided by the clinician, further orientation as to specific margins should be documented and sections appropriately submitted (4).

Gastric Resections for Carcinoma:

Gastric resections should be carefully matched with patient identification. All resections should be imaged fresh, in both the unopened and opened state to document the most important pathologic findings. Additional images can be taken at various stages of gross examination, including following fixation and after further sectioning as needed to document tumor location and depth. When opening the stomach, do not cut through tumor if at all possible. Cutting along the greater curvature is preferred.

When resections are sent for frozen section, it may be necessary to ink and cut certain aspects of the specimen in the fresh state. In most cases, only surgical margins need to be evaluated at the time of frozen section. The location of the tumor and distance to all surgical margins should be noted. If the tumor needs to be sampled for frozen section (a practice to be discouraged unless a true surgical decision will be made as a result) great care should be taken to cut the lesion in a manner that preserves anatomical relationships. Ink should be applied sparsely, so that it does not contaminate non-surgical margins. After frozen sections have been completed and prior to fixation, tissue for special studies should be procured if needed (flow cytometry, cytogenetics, electron microscopy). Again, for gastric epithelial tumors special studies are not usually needed or can be performed on paraffin sections.

Grossing gastrointestinal resections takes place in two stages, before and following fixation. After the specimen has been imaged and opened, a careful gross examination and description of the mucosal and serosal surfaces should be completed. If not already accomplished, careful measurements of the tumor, its location and the distance to all surgical margins should be noted. The serosal surface and any surgical margins not already sampled should be inked. The specimen should then be fixed overnight (if in formalin) or for a length of time suitable to the fixative used. Prior to fixing, the tumor can be thinly sectioned if needed to aid fixation. This is not necessary in most cases. The tumor should not be cut completely through if this can be avoided, as retraction of the serosal margin can result in the appearance of a false positive margin.

Following fixation, the gross dissection is completed. All lesions should be serially sectioned and thoroughly examined. Additional images can be taken at this time. The depth of invasion of the tumor through the gastric wall and relationship to the serosal margin should be stated in the gross description. Any other lesions should be described. Sections should be submitted for microscopy that demonstrate the lesion, the depth of invasion, relation to adjacent benign tissue, all surgical margins, including the serosal margin, random sections of uninvolved stomach, any other lesions and all lymph nodes. Following careful gross examination for lymph nodes, a clearing solution may be used if available to ensure the retrieval of all lymph nodes present within the specimen. This practice is institution dependent and may be of questionable value in terms of identifying metastases. However, the use of clearing solutions usually increases the number of lymph nodes retrieved. At least 15 lymph nodes should be retrieved to insure correct staging. However, the number of lymph nodes retrieved in gastrectomy specimens depends to some degree on the extent of the resection and amount of mesenteric fat included.

Summary of Recommended Sections:

Tumor for diagnosis

Depth of invasion

Margins- proximal, distal, radial*

Lymph nodes

Relation of tumor to adjacent stomach

Sections of uninvolved stomach to assess background mucosa

Gastritis and *Helicobacter pylori* status

Atrophy

Dysplasia

Other lesions (i.e., polyps)

* Radial margins in gastrectomy specimens are usually serosal lined surfaces. Tumors that extend into the esophagus may also have a pertinent margin that is a true surgical margin transected by the surgeon. The use of the term radial margin encompasses both settings.

Microscopic Examination

Gastric Biopsies:

Gastric biopsies obtained to confirm or exclude the clinical suspicion of malignancy can be extremely challenging for the pathologist, due to the usually small size of diagnostic material and the high rate of sampling error. Stated simply, biopsies from visible gastric lesions may be either (1) positive for invasive tumor, (2) positive for in situ neoplasia (dysplasia) (3) negative for neoplasia or (4) indeterminate for neoplasia. Each of these scenarios dictates a distinct recommendation from the pathologist. It is vital that the pathologist communicate directly with the clinician in order to make the correct recommendations. The following is a list of possible diagnoses on gastric biopsies from epithelial tumors and their consequences:

- Positive for carcinoma
 - There should be unequivocal evidence of invasive tumor present.
 - The neoplasm may be intramucosal with invasion limited to the lamina propria. The distinction from high grade dysplasia may be challenging with marked architectural changes. Desmoplasia may be absent. This diagnosis is best made on well oriented biopsies. Alternatively, there may be evidence of submucosal invasion with well developed desmoplasia
 - The histologic subtype should be stated if possible (e.g., intestinal type, signet ring carcinoma, etc).

- Implied in this diagnosis is 100% certainty. Definitive therapy will be based on the pathology report, with no need for additional biopsies to confirm the pathologic diagnosis. If there is any doubt as to the diagnosis, review by a second pathologist is encouraged. Any concerns regarding the diagnosis that preclude definitive therapy as a next step should be communicated with the clinician at least in writing and preferably verbally as well.
- Positive for dysplasia (intraepithelial neoplasia)
 - Dysplasia should be classified as low or high grade using published criteria (5-10).
 - If in a visible lesion, the lesion must be completely excised to exclude an invasive component. (This must be communicated to the clinician.) Sometimes a biopsy showing dysplasia is from a lesion that was obviously malignant at endoscopy, but was inadequately sampled. If the diagnosis of dysplasia is certain in this setting, there is usually no need to obtain additional biopsies just to demonstrate the invasive component.
 - If dysplasia is found in a random biopsy (usually in the setting of gastric atrophy), a recommendation for gastric mapping. Frequent follow up is appropriate. Gastric mapping involves extensive sampling of the body and antrum at intervals depending on the extent and severity of dysplasia discovered (low versus high grade). The decision of when to perform gastrectomy for dysplasia (low or high grade) in the setting of gastric atrophy is center dependent (11-13).
- Negative for dysplasia or carcinoma
 - In the setting of a visible lesion, a negative biopsy raises the concern for a false negative due to sampling error. Signet ring cell carcinoma is often difficult to sample with standard biopsy forceps. Large malignant ulcers are also notoriously difficult to sample due to necrosis and inflammation. All clinically suspicious lesions must be rebiopsied, often with endoscopic ultrasound, and other radiologic evaluation.
- Indeterminate for neoplasia (either in situ or invasive)

- Because of ulceration and small sample size, gastric biopsies from suspicious lesions may show worrisome atypia that is insufficient for a definitive diagnosis of malignancy. In this setting, deeper sections, a second opinion and special stains may be valuable. However, there should be no hesitation to request additional biopsies in order to obtain a firm diagnosis. Equivocal histology should never be “overcalled”. A good guideline to use when deciding how to phrase the report is to ask yourself the question, “Do I want to receive the resected stomach as a specimen?”
- Additional information to be included in the report
 - If non-lesional gastric mucosa is present, it should be assessed for gastritis, *Helicobacter pylori*, atrophy, intestinal metaplasia and any other changes (13-16).
- Gastroesophageal junction tumors
 - Adenocarcinomas that straddle the GE junction can be difficult to classify as to site of origin (stomach vs. esophagus). Since adenocarcinoma of the distal esophagus is treated differently from gastric cancer, it is important to clarify the site of origin if at all possible. This distinction frequently requires correlation of pathologic, endoscopic and radiologic information. The decision cannot be made on the basis of tumor morphology at biopsy or resection alone. However, the presence of intestinal metaplasia in the esophagus adjacent to tumor (Barrett esophagus) lends support to an esophageal primary origin in ambiguous cases. Otherwise, the site of primary tumor is usually determined by location of the dominant or central portion of tumor.

Gastric Endoscopic Mucosal Resections:

Gastric EMRs are usually obtained after a diagnosis of high-grade dysplasia or malignancy has been established on biopsy. EMRs have 3 functions: (a) diagnostic, (b) therapeutic and (c) guidance with regard to determination of further treatment. Since endoscopic mucosal resections are performed with a curative intent, they should be handled and reported as surgical specimens and therefore, the role of the surgical

pathologist is crucial. Appropriate reporting is essential in guiding additional therapeutic options (4).

The list of possible diagnoses on gastric EMRs include:

- Positive for carcinoma

Three features should be evaluated and reported: 1) the degree of differentiation, 2) the depth of invasion and 3) the status of the margins (lateral and deep) and overall completeness of excision. Finally, the status of vascular invasion should also be reported, especially in cases with submucosal extension.

- Positive for dysplasia or intraepithelial neoplasia
 - Dysplasia should be classified as low or high grade using published criteria. All reports should include the status of the lateral mucosal surgical margins regarding dysplasia.
- Negative for dysplasia or intraepithelial neoplasia

Technical artifacts such as hemorrhage and electrodiathermic burns should be mentioned in the report if they limit the histologic interpretation.

Gastric Resections:

The role of the pathologist in examining gastric resections is usually not to determine the diagnosis, but to accurately stage and categorize a lesion that has been previously diagnosed by biopsy or other techniques. Nonetheless, care should be taken to ensure that tissues are adequately sampled and saved for special techniques prior to fixation if needed to confirm a diagnosis (e.g., flow cytometry, electron microscopy, cytogenetics, etc). The following discussion pertains to gastric carcinoma. Refer to the AJCC staging manual and WHO classification of gastric tumors for additional detail. This guideline emphasizes the elements to be assessed and included in the pathology report for the purposes of uniformity and completeness:

- Tumor Location
 - Cardia, Fundus, Body, Antrum, pylorus
 - Lesser or Greater Curvature, anterior wall, posterior wall

Note: The distinction between gastric cardia cancer and lower esophageal adenocarcinoma arising in the setting of Barrett esophagus can be difficult. In general, if the center of the lesion is within the stomach, gastric carcinoma is favored and vice versa. If esophageal tissue (either from previous biopsies or the resection) reveals intestinal metaplasia, this can be used as evidence of esophageal adenocarcinoma in cases where the lesion is predominantly within the gastroesophageal junction. It should be understood that there will be cases where the designation as to gastric or esophageal primary will have to be made arbitrarily, using all information available. However, a three tiered classification scheme of gastroesophageal junction (GEJ) tumors has been proposed (Siewert Dis Esophagus 1996;9:173-182). Type I are tumors with an epicenter located entirely in the distal esophagus and within 1 to 5 cm above but not involving the GEJ. Type III cancers have epicenters entirely within the proximal stomach and 2-5cm below the GEJ. Type II are tumors with their epicenters between 1 cm above and 2cm below the GEJ.

- Growth Pattern of advanced cancer- This is an optional feature that may be included in pathology reports (from Bormann's classification, 17)
 - Type 1- Polypoid
 - Type 2- Fungating
 - Type 3- Ulcerated
 - Type 4- Diffusely infiltrative (Linitis Plastica)
- Tumor type (Modified from WHO classification)
 - Adenocarcinoma
 - Intestinal type
 - Diffuse type (implies a significant component of signet ring cell carcinoma)*
 - Papillary adenocarcinoma
 - Tubular adenocarcinoma
 - Mucinous adenocarcinoma
 - Adenosquamous carcinoma
 - Squamous cell carcinoma

- Lymphoepithelioma-like carcinoma (18,19)
- Carcinoid tumor
- Atypical carcinoid tumor
- Small cell carcinoma
- Undifferentiated carcinoma
- Other
 - E.g., Hepatoid variant of adenocarcinoma (20-22)

***Note:** Frequently both intestinal and signet ring morphology are present in the same tumor

- Grade- Applies primarily to gland forming variants
 - Well differentiated- well formed glands
 - Moderately differentiated- some gland formation and areas with single cells or islands
 - Poorly differentiated- irregular glands, single cells, nests

Note: By definition, signet ring cell carcinoma is poorly differentiated

- TNM staging-see ADASP checklist and AJCC staging manual
- Certain subtypes of carcinoma may require additional studies or be associated with syndromes
 - EBV testing in lymphoepithelioma like carcinoma (18,19)
 - E Cadherin (CDH1) molecular analysis in patients with a strong family history of diffuse gastric carcinoma. This should be at the request of the clinician and with consideration for family genetic counseling (23,24).
 - Microsatellite instability testing in patients with a suspicion of hereditary non-polyposis colon cancer syndrome (25,26)
 - Rarely, gastric cancer is seen in the setting of familial polyposis syndrome and Peutz-Jeghers syndrome (27-29)
- Status of non-neoplastic stomach
 - Every report of gastric carcinoma should state *Helicobacter pylori* status and degree and type of gastritis (i.e. multifocal atrophic or autoimmune), if

present. Specifically, the presence of intestinal metaplasia and dysplasia should be noted.

References

1. Hamilton SR, Aaltonen LA. World Health Organization Classification of Tumours. Pathology and Genetics. Tumours of the Digestive System. Lyon: IARC Press, 2000, 38-52).
2. AJCC Cancer Staging Manual. 6th ed. Philadelphia: Lipincott-Raven Press, 2002, 99-103.
3. Sobin LH, Wittekind C. TNM Classification of Malignant Tumours. 6th ed. New York: Wiley-Liss, 2002.
4. Hull MJ, Mino-Kneudson M, Nishioka NS, Ban S, Sepehr A, Puricelli W, Nakatsuka L, Ota S, Shimizu M, Brugge W, and Lauwers GY. Endoscopic mucosal resection: an improved diagnostic procedure for early gastroesophageal epithelial neoplasms. *AJSP* 30:114-118
5. Lauwers GY, Riddell RH: Gastric epithelial dysplasia. *Gut* 45:784-790, 1999.
6. Jass JR: A classification of gastric dysplasia. *Histopathology* 7:181-193, 1983.
7. Ming SC, Bajtai A, Correa P, et al. Gastric dysplasia: Significance and pathologic criteria. *Cancer* 54:1794-1801, 1984.
8. Zhang Y. Typing and grading of gastric dysplasia. In Zhang Y, Kawai K (eds): *Precancerous Conditions and Lesions of the Stomach*. Berlin, Springer-Verlag, 1993, pp. 64-84.
9. Lansdown M, Quirke P, Dixon MF, et al. High-grade dysplasia of the gastric mucosa: A marker for gastric carcinoma. *Gut* 31:977-983, 1990.
10. Correa P. Human gastric carcinogenesis: A multistep and multifactorial process-First American Cancer Society Award Lecture on Cancer Epidemiology and Prevention. *Cancer Res* 6740, 1992.

11. Filipe MI, Munoz N, Matko I, et al. Intestinal metaplasia types and the risk of gastric cancer: A cohort study in Slovenia. *Int J Cancer* 57:324-329, 1994.
12. Hattori T, Sugihara H. The pathological sequence in the development of gastric cancer: I. *Scand J Gastroenterol Suppl* 214:34-35, 1996.
13. Siurala M, Sipponen P, Kekki M. Chronic gastritis: Dynamic and clinical aspects. *Scand J Gastroenterol Suppl* 109:69-76, 1985.
14. Kuipers EJ, Uytterlinde AM, Pena AS, et al. Long-term sequelae of *Helicobacter pylori* gastritis. *Lancet* 345:1525-1528, 1995.
15. Forman D, Newell DG, Fullerton F, et al. Association between infection with *Helicobacter pylori* and risk of gastric cancer: Evidence from a prospective investigation. *BMJ* 302:1302-1305, 1991.
16. Parsonnet J, Friedman GD, Vandersteen DP, et al. *Helicobacter pylori* infection and the risk of gastric carcinoma. *N Engl J Med* 325:1127-1131, 1991.
17. Borrmann R. Geshwulste des Magens und Duodenums. In Henke F, Lubarsch O (eds): *Handbuch des speziellen Pathologischen Anatomie und Histologie*, vol 4. Berlin, Springer-Verlag, 1926, p 865.
18. Watanabe H, Enjoji M, Imai T. Gastric carcinoma with lymphoid stroma: Its morphologic characteristics and prognostic correlations. *Cancer* 38:232-243, 1976.
19. Kang GH, Lee S, Kim WH, et al. Epstein-Barr virus-positive gastric carcinoma demonstrates frequent aberrant methylation of multiple genes and constitutes CpG island methylator phenotype-positive gastric carcinoma. *Am J Pathol* 160:787-794, 2002.
20. Inagawa S, Shimazaki J, Hori M, et al. Hepatoid adenocarcinoma of the stomach. *Gastric Cancer* 4:43-52, 2001.

21. Ishikura H, Kirimoto K, Shamoto M, et al. Hepatoid adenocarcinomas of the stomach: An analysis of seven cases. *Cancer* 58:119-126, 1986.
22. Motoyama T, Aizawa K, Watanabe H, et al. Alpha-fetoprotein producing gastric carcinomas: A comparative study of three different subtypes. *Acta Pathol Jpn* 43:654-661, 1993.
23. Guilford P, Hopkins J, Harraway J, et al. E-cadherin germline mutations in familial gastric cancer. *Nature* 392:402-405, 1998.
24. Huntsman DG, Carneiro F, Lewis FR, et al. Early gastric cancer in young, asymptomatic carriers of germ-line E-cadherin mutations. *N Engl J Med* 344:1904-1909, 2001.
25. Aarnio M, Salovaara R, Aaltonen LA, et al. Features of gastric cancer in hereditary non-polyposis colorectal cancer syndrome. *Int J Cancer* 74:551-555, 1997.
26. Mecklin JP, Jarvinen HJ, Peltokallio P. Cancer family syndrome: Genetic analysis of 22 Finnish kindreds. *Gastroenterology* 90:328-333, 1986.
27. Hofgartner WT, Thorp M, Ramus MW, et al. Gastric adenocarcinoma associated with fundic gland polyps in a patient with attenuated familial adenomatous polyposis. *Am J Gastroenterol* 94:2275-2281, 1999.
28. Zwick A, Munir M, Ryan CK, et al. Gastric adenocarcinoma and dysplasia in fundic gland polyps of a patient with attenuated adenomatous polyposis coli. *Gastroenterology* 113:659-663, 1997.
29. Entius MM, Westerman AM, van Velthuisen ML, et al. Molecular and phenotypic markers of hamartomatous polyposis syndromes in the gastrointestinal tract. *Hepatogastroenterology* 46:661-666, 1999.