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Protocol for the Examination of Specimens From Patients With Carcinoma of the Stomach

Protocol applies to all invasive carcinomas of the stomach. Tumors of the esophagogastric junction and well-differentiated neuroendocrine tumors (carcinoid tumors) are not included.

Based on AJCC/UICC TNM, 7th edition

Protocol web posting date: October 2013

Procedures

- Endoscopic Mucosal Resection
- Gastrectomy (Partial or Complete)

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CAP Stomach Protocol Revision History

Version Code

The definition of the version code can be found at www.cap.org/cancerprotocols.

Version: Stomach 3.2.0.1

Summary of Changes

The following changes have been made since the June 2012 release.

Local Resection, Gastrectomy

Histologic Type

“Adenosquamous carcinoma” was added.

Explanatory Notes

A. Application

Edited second sentence to read: Tumors with midpoint in the proximal stomach within 5 cm of the EGJ and crossing the EGJ are not included...

C. Histologic Type

The note was edited to clarify that the WHO classification system is recommended but not required.

Table 1, Histologic Features, Neuroendocrine carcinoma:

Edited description to read:

Poorly differentiated high-grade carcinoma with diffuse synaptophysin expression and faint or focal positivity for chromogranin A. These tumors exhibit a high mitotic rate (>20 per 10 high power fields, or Ki-67 index >20%), marked nuclear atypia, and may have focal necrosis

Surgical Pathology Cancer Case Summary

Protocol web posting date: October 2013

STOMACH: Local Resection, Gastrectomy (Note A)**Select a single response unless otherwise indicated.****Specimen (select all that apply)**

- Stomach
 Portion of stomach
 Gastric body
 Gastric antrum
 Distal esophagus
 Proximal duodenum
 Not specified

Procedure

- Endoscopic mucosal resection
 Partial gastrectomy, proximal
 Partial gastrectomy, distal
 Partial gastrectomy, other (specify): _____
 Total gastrectomy
 Other (specify): _____
 Not specified

Tumor Site (select all that apply) (Note B)

- Fundus
 + Anterior wall
 + Posterior wall
 Body
 + Anterior wall
 + Posterior wall
 + Lesser curvature
 + Greater curvature
 Antrum
 + Anterior wall
 + Posterior wall
 + Lesser curvature
 + Greater curvature
 Other (specify): _____
 Not specified

Tumor Size

- Greatest dimension: ___ cm
 + Additional dimensions: ___ x ___ cm
 Cannot be determined (see Comment)

Histologic Type (select all that apply) (Note C)

- Adenocarcinoma
 Lauren classification of adenocarcinoma:

+ Data elements preceded by this symbol are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.

- Intestinal type
- Diffuse type (signet-ring carcinoma if >50% signet-ring cells)
- Mixed (approximately equal amounts of intestinal and diffuse)
- + Alternative optional classification (based on WHO classification):
 - + Tubular (intestinal) adenocarcinoma
 - + Poorly cohesive carcinoma (including mixed adenocarcinoma with >50% signet-ring cell features)
 - + Diffuse carcinoma (noncohesive carcinoma, >80% diffuse/signet-ring cells)
 - + Mucinous adenocarcinoma (>50% mucinous)
 - + Papillary adenocarcinoma
- Hepatoid adenocarcinoma
- Carcinoma with lymphoid stroma (medullary carcinoma)
- High-grade neuroendocrine carcinoma
 - Large cell neuroendocrine carcinoma
 - Small cell neuroendocrine carcinoma
- Mixed adenoneuroendocrine carcinoma
- Squamous cell carcinoma
- Adenosquamous carcinoma
- Undifferentiated carcinoma
- Other (specify): _____

Histologic Grade (Note D)

- Not applicable
- GX: Cannot be assessed
- G1: Well differentiated
- G2: Moderately differentiated
- G3: Poorly differentiated
- G4: Undifferentiated
- Other (specify): _____

Microscopic Extent of Tumor

- Cannot be assessed
- No evidence of residual primary tumor
- High-grade dysplasia/carcinoma in situ
- Tumor invades lamina propria
- Tumor invades into but not through muscularis mucosae
- Tumor invades submucosa
- Tumor invades muscularis propria
- Tumor invades subserosal connective tissue without involvement of visceral peritoneum
- Tumor penetrates serosa (visceral peritoneum)
- Tumor directly invades adjacent structures (specify): _____
- Tumor penetrates to the surface of the visceral peritoneum (serosa) and directly invades adjacent structures (specify: _____)

Margins (select all that apply) (Note E)

If all margins uninvolved by carcinoma:

Distance of carcinoma from closest margin: ___ mm or ___ cm

Specify margin: _____

Proximal Margin

- Cannot be assessed

+ Data elements preceded by this symbol are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.

- Uninvolved by invasive carcinoma, carcinoma in situ, and low-grade glandular dysplasia
- Involved by invasive carcinoma
- Involved by carcinoma in situ
- Involved by low-grade glandular dysplasia

Distal Margin

- Cannot be assessed
- Uninvolved by invasive carcinoma, carcinoma in situ, and low-grade glandular dysplasia
- Involved by invasive carcinoma
- Involved by carcinoma in situ
- Involved by low-grade glandular dysplasia

Omental (Radial) Margins

- Cannot be assessed
- Uninvolved by invasive carcinoma
- Omental margin involved by invasive carcinoma
 - + Greater omental margin involved by invasive carcinoma
 - + Lesser omental margin involved by invasive carcinoma

Deep Margin (endoscopic mucosal resections) (required only if applicable)

- Cannot be assessed
- Uninvolved by invasive carcinoma
- Involved by invasive carcinoma

Mucosal Margins (endoscopic resections) (required only if applicable)

- Cannot be assessed
- Uninvolved by invasive carcinoma, carcinoma in situ, and low-grade glandular dysplasia
- Involved by invasive carcinoma
- Involved by carcinoma in situ
- Involved by low-grade glandular dysplasia

Other Margin(s) (required only if applicable)

Specify margin(s): _____

- Cannot be assessed
- Involved by invasive carcinoma
- Uninvolved by invasive carcinoma

Treatment Effect (carcinomas treated with neoadjuvant therapy) (required only if applicable) (Note F)

- No prior treatment
- Present
 - + No residual tumor (complete response, grade 0)
 - + Marked response (grade 1, minimal residual cancer)
 - + Moderate response (grade 2)
- No definite response identified (grade 3, poor or no response)
- Not known

Lymph-Vascular Invasion (Note G)

- Not identified
- Present
- Indeterminate

+ Data elements preceded by this symbol are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.

+ Perineural Invasion (Note H)

- + ___ Not identified
- + ___ Present
- + ___ Indeterminate

Pathologic Staging (pTNM) (Note I)

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

- ___ m (multiple primary tumors)
- ___ r (recurrent)
- ___ y (posttreatment)

Primary Tumor (pT)

- ___ pTX: Cannot be assessed
- ___ pT0: No evidence of primary tumor
- ___ pTis: Carcinoma in situ/high-grade glandular dysplasia
- pT1: Tumor invades lamina propria, muscularis mucosae, or submucosa
- ___ pT1a: Tumor invades lamina propria or muscularis mucosae
- ___ pT1b: Tumor invades submucosa
- ___ pT2: Tumor invades muscularis propria
- ___ pT3: Tumor invades subserosal connective tissue, without involvement of visceral peritoneum or adjacent structures
- ___ pT4: Tumor invades serosa (visceral peritoneum) or adjacent structures
- ___ pT4a: Tumor invades serosa (visceral peritoneum)
- ___ pT4b: Tumor invades adjacent structures

Regional Lymph Nodes (pN) (Note J)

- ___ pNX: Cannot be assessed
- ___ pN0: No regional lymph node metastasis
- ___ pN1: Metastasis in 1 to 2 perigastric lymph nodes
- ___ pN2: Metastasis in 3 to 6 perigastric lymph nodes
- ___ pN3: Metastasis in 7 or more perigastric lymph nodes
- ___ pN3a: Metastasis in 7 to 15 perigastric lymph nodes
- ___ pN3b: Metastasis in 16 or more perigastric lymph nodes

___ No nodes submitted or found

Number of Lymph Nodes Examined

Specify: ___

___ Number cannot be determined (explain): _____

Number of Lymph Nodes Involved

Specify: ___

___ Number cannot be determined (explain): _____

Distant Metastasis (pM)

- ___ Not applicable
- ___ pM1: Distant metastasis
 - + Specify site(s), if known: _____

+ Additional Pathologic Findings (select all that apply) (Note K)

- + ___ None identified

+ Data elements preceded by this symbol are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.

- + ___ Intestinal metaplasia
- + ___ Dysplasia
 - + ___ Low-grade glandular dysplasia
 - + ___ High-grade glandular dysplasia
- + ___ Gastritis
 - + ___ *Helicobacter pylori*-type gastritis
 - + ___ Other gastritis (specify): _____
- + ___ Polyp(s) (type[s]): _____
- + ___ Other (specify): _____

+ Ancillary Studies (Note L)

+ HER2 Immunoperoxidase Studies

- + ___ Pending
- + ___ Not performed
- + ___ Negative (Score 0)
- + ___ Negative (Score 1+)
- + ___ Equivocal (Score 2+)
- + ___ Positive (Score 3+)
- + ___ Specify percentage of cells with positive membrane expression: _____
- + ___ Other (specify): _____

+ HER2 In Situ Hybridization Studies

- + ___ Pending
- + ___ Not performed

+ Interpretation

- + ___ Amplified (Specify amplification definition supplied by kit vendor: _____)
- + ___ Not amplified
- + ___ Cannot be determined (explain: _____)

- + Kit name: _____
- + ___ Fluorescence in situ hybridization (FISH)
- + ___ Chromogenic in situ hybridization (CISH)
- + ___ Other (specify): _____

- + Number of cells counted: _____
- + ___ Using HER2/CEP17 ratio (Dual probe assay)
 - + Number of HER2 signals/cell: _____
 - + Number of CEP17 signals/cell: _____
 - + Polyploidy (as defined by vendor kit used):
 - + ___ Not present
 - + ___ Present
 - + Other (specify): _____
- + ___ Using HER2 copy number (Single probe assay)
 - + Number of HER2 signals: _____
 - + Number of HER2 signals/cell: _____
 - + Other (specify): _____
- + ___ Other (specify): _____

+ Other Ancillary Studies

+ Specify: _____

+ ___ Not performed

+ **Clinical History (select all that apply) (Note M)**

+ ___ Previous gastric surgery (specify): _____

+ ___ Other (specify): _____

+ ___ Not known

+ **Comment(s)**

Explanatory Notes

A. Application

This protocol applies to all carcinomas that arise in the stomach and do not involve the esophagogastric junction (EGJ). Tumors with midpoint in the proximal stomach within 5 cm of the EGJ and crossing the EGJ are not included; the CAP protocol for carcinoma of the esophagus applies to such tumors.* Lymphomas, low-grade neuroendocrine tumors (carcinoid tumors), and sarcomas are also not included (separate TNM staging systems¹ and College of American Pathologists [CAP] protocols apply).

B. Tumor Site

Tumor location should be described in relation to the following landmarks (Figure 1):

- gastric region: cardia (including EGJ), fundus, body, antrum, pylorus
- greater curvature, lesser curvature
- anterior wall, posterior wall

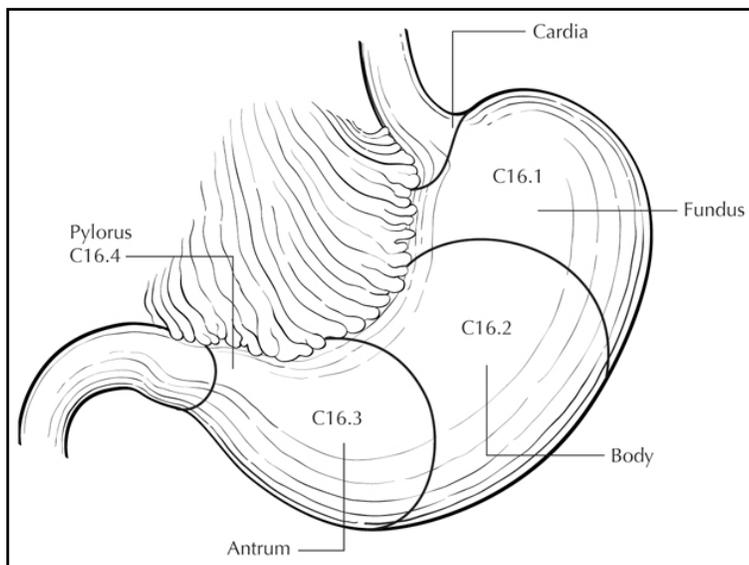


Figure 1. Anatomical subsites of the stomach. Used with permission of the American Joint Committee on Cancer (AJCC), Chicago, IL. The original source for this material is the *AJCC Cancer Staging Atlas* (2006) edited by Greene et al²⁴ and published by Springer Science and Business Media, LLC, www.springerlink.com.

Tumors involving the EGJ are classified for purposes of staging as esophageal carcinomas,¹ and the CAP protocol for the esophagus should be used for such tumors. The EGJ is defined as the junction of the tubular esophagus and the stomach irrespective of the type of epithelial lining of the esophagus. Although the nature of these tumors (gastric versus esophageal) has been controversial^{2,3} (reviewed by Carneiro and Chaves⁴), recent data support their classification as esophageal carcinomas.¹ The World Health Organization (WHO) defines esophageal tumors as those located entirely above the EGJ and proximal gastric tumors as those located entirely below the EGJ.⁵ Tumors crossing the EGJ are classified as EGJ tumors. An alternative system proposed by Siewart and colleagues divides adenocarcinomas involving the EGJ into 3 categories,⁶ based upon location of the midpoint of the tumor:

Type I: adenocarcinoma of the distal esophagus, with or without infiltration of the EGJ from above

* The CAP cancer protocols can be found in *Reporting on Cancer Specimens: Case Summaries and Background Documentation* published by the College of American Pathologists, Northfield, IL; or on the CAP website at cap.org/cancerprotocols.

Type II: true carcinoma of the gastric cardia, arising from the cardiac epithelium or short segments with intestinal metaplasia at the EGJ

Type III: subcardial gastric carcinoma, which infiltrates the EGJ and distal esophagus from below

Application of the Siewart system is complicated by lack of consensus as to the definition and nature of the gastric cardia, with some investigators regarding it as a normal anatomic finding,⁷ and others as a metaplastic response to injury from esophagogastric reflux² (reviewed by Carneiro and Chaves⁴).

Although some studies have shown no prognostic impact for tumor site,⁸ others have shown a poorer outcome for proximal gastric cancers than for distal tumors.⁹

C. Histologic Type

For consistency in reporting, the recently revised histologic classification proposed by the WHO is recommended⁵ (Table 1) but not required for clinical use. However, this classification scheme does not distinguish between intestinal and diffuse types of gastric carcinoma but includes signet-ring cell carcinoma in the poorly cohesive carcinoma category. Thus, the Laurén classification¹⁰ may be used in conjunction with the WHO system.

With the exception of the rare small cell carcinoma of the stomach, which has an unfavorable prognosis, most multivariate analyses show no effect of tumor type, independent of stage, on prognosis.⁹

Table 1. WHO Classification of Carcinoma of the Stomach⁵

Tumor Type	Histologic Features
Adenocarcinoma	
Papillary adenocarcinoma	Exophytic with elongated frond-like tumor extensions with fibrovascular cores; usually low grade.
Tubular adenocarcinoma	Dilated or slit-like branching tubules; usually low grade, although poorly differentiated variants are described.
Mucinous adenocarcinoma	Contains more than 50% extracellular mucin pools. May contain scattered signet-ring cells.
Poorly cohesive carcinomas, including diffuse and signet-ring cell carcinoma and other variants	Tumor cells infiltrate as isolated single cells or small aggregates. Signet ring cell carcinoma is predominantly composed of signet-ring cells containing a clear droplet of cytoplasmic mucin displacing the nucleus. Other variants of poorly cohesive carcinoma may resemble mononuclear inflammatory cells.
Mixed carcinoma	Mixture of morphologically identifiable components such as tubular, papillary, and poorly cohesive patterns.
Adenosquamous carcinoma	Mixture of glandular and squamous neoplastic components; the squamous component should comprise at least 25% of tumor volume
Carcinoma with lymphoid stroma (medullary carcinoma)	Poorly developed glandular structures associated with a prominent lymphoid infiltrate in the stroma. Associated with Epstein-Barr virus infection and may have a more favorable prognosis.
Hepatoid adenocarcinoma	Large polygonal eosinophilic tumor cells resembling hepatocytes; may express alpha-fetoprotein.
Squamous cell carcinoma	Keratinizing and nonkeratinizing forms are encountered.
Undifferentiated carcinoma	High-grade carcinoma that cannot be further classified as adenocarcinoma, squamous cell carcinoma, or other recognized variants

Tumor Type	Histologic Features
Neuroendocrine carcinoma	Poorly differentiated high-grade carcinoma with diffuse synaptophysin expression and faint or focal positivity for chromogranin A. These tumors exhibit a high mitotic rate (>20 per 10 high power fields, or Ki-67 index >20%), marked nuclear atypia, and may have focal necrosis
Large cell neuroendocrine carcinoma	Tumor cells are large, with moderate amount of cytoplasm, and may contain prominent nucleoli.
Small cell neuroendocrine carcinoma	Tumor cells are small, with finely granular chromatin and indistinct nucleoli.
Mixed adenoneuroendocrine carcinoma	Composed of both gland-forming and neuroendocrine malignant elements, with at least 30% of each component. Identification of scattered neuroendocrine cells in adenocarcinomas by immunohistochemistry does not qualify as mixed carcinoma.

For well-differentiated neuroendocrine tumors (grade 1 [carcinoid] and grade 2 neuroendocrine tumors), the CAP protocol for neuroendocrine tumors (carcinoid tumors) of the stomach applies.

The Laurén classification, namely intestinal or diffuse type, and/or the Ming classification, namely expanding or infiltrating type, may also be included. In general, significant correlation is seen between the various classification systems.¹¹

The WHO classifies premalignant lesions of the gastrointestinal tract as intraepithelial neoplasia. For purposes of data reporting, high-grade glandular dysplasia in a gastric resection specimen is reported as “carcinoma in situ.” The term “carcinoma in situ” is not widely applied to glandular neoplastic lesions in the gastrointestinal tract but is retained for tumor registry reporting purposes as specified by law in many states.

D. Histologic Grade

For adenocarcinomas, a histologic grading system that is based on the extent of glandular differentiation is suggested, as shown below.

- Grade X Cannot be assessed
- Grade 1 Well differentiated (greater than 95% of tumor composed of glands)
- Grade 2 Moderately differentiated (50% to 95% of tumor composed of glands)
- Grade 3 Poorly differentiated (49% or less of tumor composed of glands)

Signet-ring cell carcinomas are high grade and are classified as grade 3.

Small cell neuroendocrine carcinomas and undifferentiated carcinomas are classified as grade 4.

For squamous cell carcinomas (rare), a suggested histologic grading system is shown below.

- Grade X Grade cannot be assessed
- Grade 1 Well differentiated
- Grade 2 Moderately differentiated
- Grade 3 Poorly differentiated

Note: Undifferentiated tumors cannot be specifically categorized as adenocarcinoma or squamous cell carcinoma. Instead, they are classified as undifferentiated carcinoma by the WHO classification and are assigned grade 4 (see Note C).

Although grade has been shown to have little impact on survival for patients undergoing complete tumor resection,¹² it has a significant impact on margin-negative resectability, with higher grade tumors less likely to be resectable.

E. Margins

For surgical resection specimens, margins include the proximal, distal, and radial margins. The radial margins represent the nonperitonealized soft tissue margins closest to the deepest penetration of tumor. In the stomach, the lesser omental (hepatoduodenal and hepatogastric ligaments) and greater omental resection margins are the only radial margins. For endoscopic resection specimens, margins include peripheral mucosal margins and the deep margin of resection. It may be helpful to mark the margin(s) closest to the tumor with ink. Margins marked by ink should be designated in the macroscopic description.

F. Treatment Effect

Response of tumor to previous chemotherapy or radiation therapy should be reported. Although grading systems for tumor response have not been established, in general, 3-category systems provide good interobserver reproducibility.¹³ The following system is suggested:

Tumor Regression Grade

Description	Tumor Regression Grade
No viable cancer cells	0 (Complete response)
Single cells or small groups of cancer cells	1 (Moderate response)
Residual cancer outgrown by fibrosis	2 (Minimal response)
Minimal or no tumor kill; extensive residual cancer	3 (Poor response)

Sizable pools of acellular mucin may be present after chemoradiation but should not be interpreted as representing residual tumor.

This protocol does not preclude the use of other systems for assessment of tumor response, such as the schemes reported by Memorial Sloan-Kettering Cancer Center investigators and others.^{14,15}

G. Venous/Lymphatic Vessel Invasion

Both venous¹⁶ and lymphatic vessel⁹ invasion have been shown to be adverse prognostic factors¹⁴ and are predictive of lymph node metastases in early gastric cancers.¹⁷ However, the microscopic presence of tumor in lymphatic vessels or veins does not qualify as local extension of tumor as defined by the T classification.¹

H. Perineural Invasion

Perineural invasion has been shown to be an adverse prognostic factor¹⁴ and has been associated with lymph node metastases in early gastric cancer in univariate but not multivariate analyses.¹⁷

I. TNM and Anatomic Stage/Prognostic Groupings

The TNM staging system for gastric carcinoma of the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC) is recommended and shown below.¹

According to AJCC/UICC convention, the designation "T" refers to a primary tumor that has not been previously treated. The symbol "p" refers to the pathologic classification of the TNM, as opposed to the clinical classification, and is based on gross and microscopic examination. pT entails a resection of the primary tumor or biopsy adequate to evaluate the highest pT category, pN entails removal of nodes adequate to validate lymph node metastasis, and pM implies microscopic examination of distant

lesions. Clinical classification (cTNM) is usually carried out by the referring physician before treatment during initial evaluation of the patient or when pathologic classification is not possible.

Pathologic staging is usually performed after surgical resection of the primary tumor. Pathologic staging depends on pathologic documentation of the anatomic extent of disease, whether or not the primary tumor has been completely removed. If a biopsied tumor is not resected for any reason (eg, when technically infeasible) and if the highest T and N categories or the M1 category of the tumor can be confirmed microscopically, the criteria for pathologic classification and staging have been satisfied without total removal of the primary cancer.

TNM Descriptors

For identification of special cases of TNM or pTNM classifications, the “m” suffix and “y,” “r,” and “a” prefixes are used. Although they do not affect the stage grouping, they indicate cases needing separate analysis.

The “m” suffix indicates the presence of multiple primary tumors in a single site and is recorded in parentheses: pT(m)NM.

The “y” prefix indicates those cases in which classification is performed during or after initial multimodality therapy (ie, neoadjuvant chemotherapy, radiation therapy, or both chemotherapy and radiation therapy). The cTNM or pTNM category is identified by a “y” prefix. The ycTNM or ypTNM categorizes the extent of tumor actually present at the time of that examination. The “y” categorization is not an estimate of tumor before multimodality therapy (ie, before initiation of neoadjuvant therapy).

The “r” prefix indicates a recurrent tumor when staged after a documented disease-free interval and is identified by the “r” prefix: rTNM.

The “a” prefix designates the stage determined at autopsy: aTNM.

Primary Tumor (T) (Figures 2-4)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ (including high-grade dysplasia): intraepithelial tumor without invasion of the lamina propria
T1	Tumor invades lamina propria, muscularis mucosae, or submucosa
T1a	Tumor invades lamina propria [#]
T1b	Tumor invades submucosa [#]
T2	Tumor invades muscularis propria ^{##}
T3	Tumor penetrates subserosal connective tissue without invasion of visceral peritoneum or adjacent structures
T4	Tumor invades serosa (visceral peritoneum) or adjacent structures
T4a	Tumor invades serosa (visceral peritoneum)
T4b	Tumor invades adjacent structures ^{###}

[#] The T1 category has been expanded on the basis of the observed difference in frequency of lymph node metastasis. In addition, the substratifications may be important as indicators for treatment by limited procedures.⁸

^{##} A tumor may penetrate the muscularis propria with extension into the gastrocolic or gastrohepatic ligaments or into the greater or lesser omentum without perforation of the visceral peritoneum covering these structures. In this case, the tumor would be classified as T3. If there is perforation of the visceral peritoneum covering the gastric ligaments or omenta, the tumor is classified as T4.

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

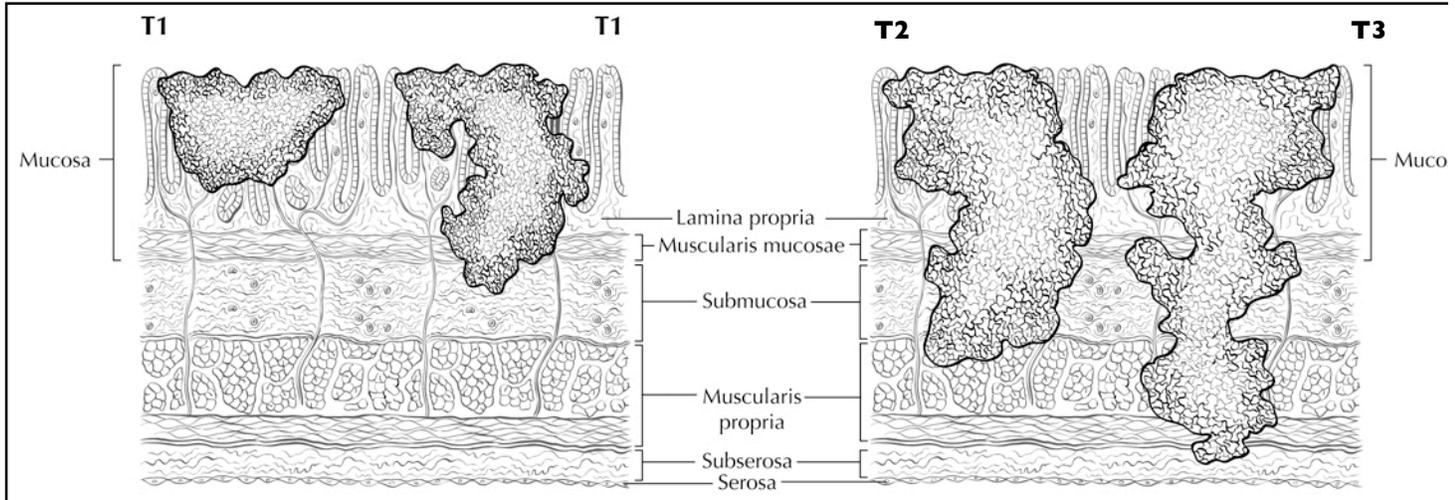


Figure 2. Definitions of T1, T2, and T3. Tumor invading the lamina propria is classified as T1a (left side or T1 illustration), whereas tumor invading the submucosa is classified as T1b (right side). T2 tumor invades the muscularis propria. T3 tumor invades the subserosal adipose tissue. Used with permission of the American Joint Committee on Cancer (AJCC), Chicago, IL. The original source for this material is the *AJCC Cancer Staging Atlas* (2006) edited by Greene et al²⁴ and published by Springer Science and Business Media, LLC, www.springerlink.com.

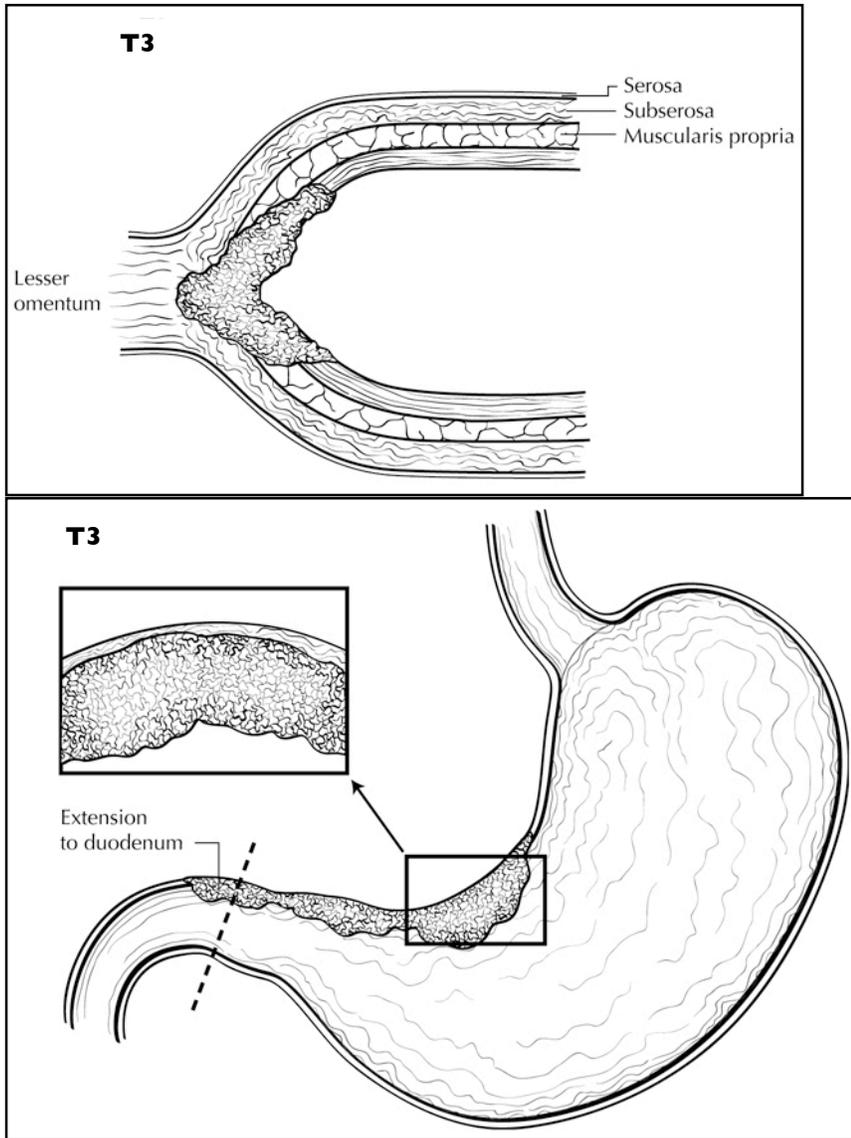


Figure 3. T3 is defined as tumor that invades the subserosa. Distal extension to duodenum does not affect T category. Used with permission of the American Joint Committee on Cancer (AJCC), Chicago, IL. The original source for this material is the *AJCC Cancer Staging Atlas (2006)* edited by Greene et al²⁴ and published by Springer Science and Business Media, LLC, www.springerlink.com.

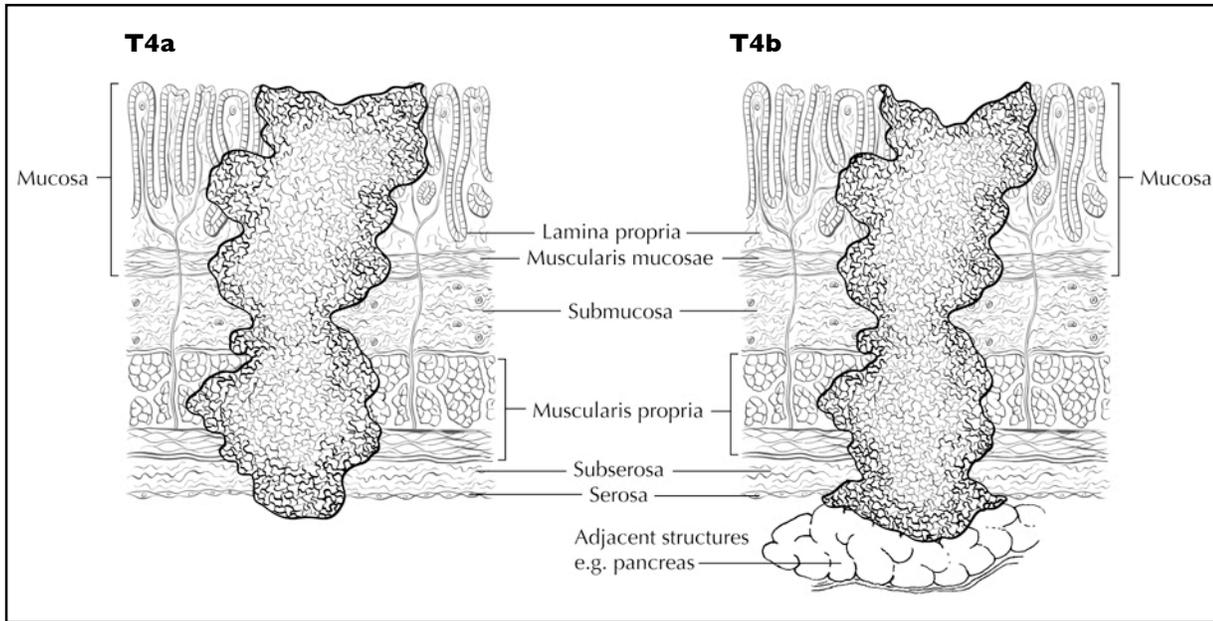


Figure 4. T4a tumor penetrates serosa (visceral peritoneum) without invasion of adjacent structures, whereas T4b tumor invades adjacent structures, such as the pancreas (shown). Used with permission of the American Joint Committee on Cancer (AJCC), Chicago, IL. The original source for this material is the *AJCC Cancer Staging Atlas* (2006) edited by Greene et al²⁴ and published by Springer Science and Business Media, LLC, www.springerlink.com.

Regional Lymph Nodes (N) (also see Note K)

- NX Regional lymph nodes cannot be assessed
- N0 No regional lymph node metastasis[#]
- N1 Metastasis in 1 to 2 perigastric lymph nodes
- N2 Metastasis in 3 to 6 perigastric lymph nodes
- N3 Metastasis in more than 6 lymph nodes

[#] A designation of N0 should be used if all examined lymph nodes are negative, regardless of the total number removed and examined.¹ Lymph nodes containing isolated tumor cells, defined as single tumor cells or small clusters of cells not more than 0.2 mm in diameter, are classified as pN0.

Discontinuous tumor deposits without evidence of residual lymph node and located in the subserosal tissue adjacent to a gastric carcinoma are considered regional lymph node metastases, according to the AJCC TNM 7th edition.¹ Nodules implanted on the peritoneal surface are considered distant metastases (M1).

Distant Metastasis (M)

- M0 No distant metastasis
- M1 Distant metastasis

Stage Groupings

Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage 1B	T2	N0	M0
	T1	N1	M0
Stage IIA	T3	N0	M0
	T2	N1	M0
	T1	N2	M0

Stage IIB	T4a	N0	M0
	T3	N1	M0
	T2	N2	M0
Stage IIIA	T4a	N1	M0
	T3	N2	M0
	T2	N3	M0
Stage IIIB	T4b	N0 or N1	M0
	T4a	N2	M0
	T3	N3	M0
Stage IIIC	T4b	N2 or N3	M0
	T4a	N3	M0
Stage IV	Any T	Any N	M1

Additional Descriptors

Lymph-Vascular Invasion

Lymph-vascular invasion (LVI) indicates whether microscopic lymph-vascular invasion is identified in the pathology report. LVI includes lymphatic invasion, vascular invasion, or lymph-vascular invasion. By AJCC/UICC convention, LVI does not affect the T category indicating local extent of tumor unless specifically included in the definition of a T category.

J. Regional Lymph Nodes

The specific nodal areas of the stomach (Figure 5) are listed below.¹

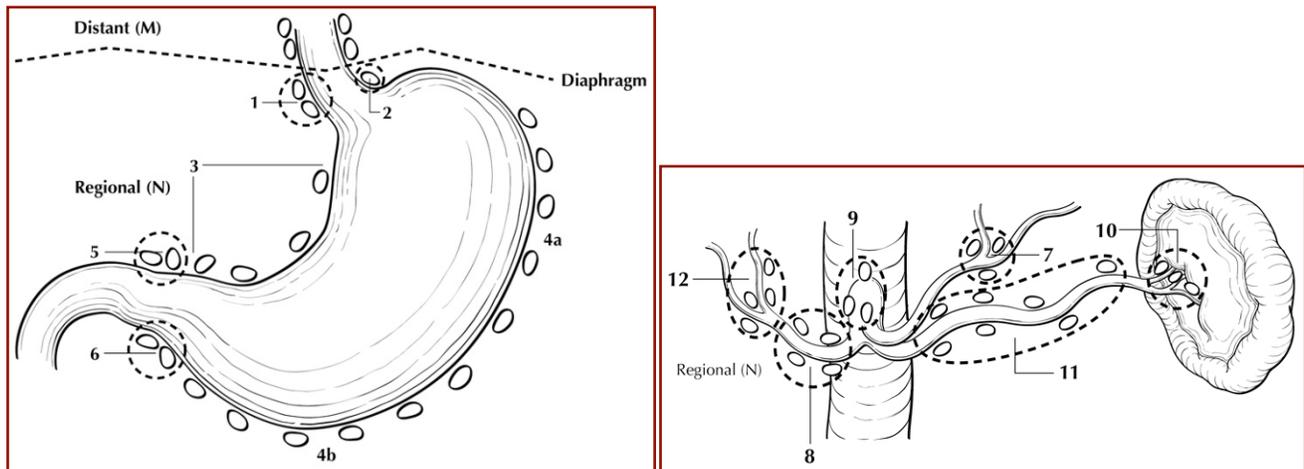


Figure 5. Regional lymph nodes of the stomach. Used with permission of the American Joint Committee on Cancer (AJCC), Chicago, IL. The original source for this material is the *AJCC Cancer Staging Atlas (2006)* edited by Greene et al²⁴ and published by Springer Science and Business Media, LLC, www.springerlink.com.

Greater Curvature of Stomach: Greater curvature, greater omental, gastroduodenal, gastroepiploic, pyloric, and pancreaticoduodenal

Pancreatic and Splenic Area: Pancreaticocolic, peripancreatic, splenic

Lesser Curvature of Stomach: Lesser curvature, lesser omental, left gastric, cardioesophageal, common hepatic, celiac, and hepatoduodenal

Involvement of other intra-abdominal lymph nodes, such as hepatoduodenal, retropancreatic, mesenteric, and para-aortic, is classified as distant metastasis.¹

K. Other Findings

One of the most important risk factors for development of gastric carcinoma is long-standing infection with *Helicobacter pylori*, which leads to chronic gastritis and mucosal atrophy with intestinal metaplasia; autoimmune gastritis, also a chronic inflammatory condition, is also associated with increased risk.¹⁸ Occasionally, gastric carcinoma arises in a preexisting gastric polyp, most commonly large hyperplastic polyps in the setting of atrophic gastritis.

L. Ancillary Studies

The ToGA trial,¹⁹ an international multicenter Phase III clinical study involving 24 countries globally, has shown that the anti-HER2/*neu* humanized monoclonal antibody trastuzumab (Herceptin) is effective in prolonging survival in patients with HER2/*neu*-positive adenocarcinoma of the stomach and the gastroesophageal junction. Comparable to breast carcinoma, ~20% of gastric carcinomas overall show HER2/*neu* overexpression/amplification, more commonly in intestinal type and proximal tumors. Molecular therapy targeting HER2/*neu*, an established treatment in breast carcinoma, is now approved for patients with inoperable locally advanced, recurrent, or metastatic adenocarcinoma of the stomach or esophagogastric junction if the tumor shows unequivocal HER2/*neu* overexpression by IHC (score 3+) or amplification by FISH or CISH. Therefore, HER2 testing in gastric carcinoma is warranted for determination of treatment eligibility.

As validated in the ToGA trial,¹⁹ a phase III randomized clinical trial of trastuzumab treatment in gastric cancer, the HER2/*neu* testing criteria used in evaluating both gastric carcinoma biopsies and surgical specimens differ from those routinely applied in breast carcinoma (Table 2). Because of the heterogeneity of expression of HER2/*neu* in gastric carcinomas, clusters of as few as 5 strongly positive tumor cells on IHC are considered positive in biopsy samples.²⁰

While some centers use immunohistochemistry (IHC) for HER2/*neu* as a first line assay followed by fluorescence or chromogen in situ hybridization (FISH or CISH) in 2+ equivocal cases,²¹ discordance between IHC and FISH or CISH results is not uncommon, and consideration should be given to testing by both methods, regardless of IHC results.²² In the ToGA trial, FISH was regarded as positive when the HER2/CEN17 ratio was >2.0. For gastric carcinoma, in contrast to breast carcinoma, there are few available data on the borderline ratio of 1.8 <R< 2.2 and polysomy of CEN17.

Table 2: Criteria Used in the ToGA Trial¹⁹ for Scoring HER2/*neu* Expression by immunohistochemistry (IHC) in Gastric and Esophagogastric Adenocarcinoma

HER2/ <i>neu</i> IHC Score	HER2/ <i>neu</i> IHC Pattern in Surgical Specimen	HER2/ <i>neu</i> IHC Pattern in Biopsy Specimen	HER2/ <i>neu</i> Expression Assessment
0	No reactivity or membranous reactivity in <10% of cancer cells	No reactivity or no membranous reactivity in any cancer cell	Negative by IHC
1+	Faint or barely perceptible membranous reactivity in ≥10% of cancer cells; cells are reactive only in part of their membrane	Cancer cell cluster with a faint or barely perceptible membranous reactivity irrespective of percentage of cancer cells positive	Negative by IHC

2+	Weak to moderate complete, basolateral or lateral membranous reactivity in >10% of tumor cells	Cancer cell cluster with a weak to moderate complete, basolateral, or lateral membranous reactivity irrespective of percentage of cancer cells positive	Equivocal by IHC
3+	Strong complete, basolateral or lateral membranous reactivity in ≥10% of cancer cells	Cancer cell cluster with a strong complete basolateral, or lateral membranous reactivity irrespective of percentage of cancer cells positive	Positive

M. Clinical History

Previous gastric surgery, such as Bilroth I or Bilroth II procedures, predisposes to the development of carcinoma in the remnant stomach; such tumors typically arise approximately 25 years after surgery for benign diseases.²³

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