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 2009

Procedures
- Endoscopic Resection
- Gastrectomy (Partial or Complete)

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The College of American Pathologists offers these protocols to assist pathologists in providing clinically useful and relevant information when reporting results of surgical specimen examinations of surgical specimens. The College regards the reporting elements in the “Surgical Pathology Cancer Case Summary (Checklist)” portion of the protocols as essential elements of the pathology report. However, the manner in which these elements are reported is at the discretion of each specific pathologist, taking into account clinician preferences, institutional policies, and individual practice.

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Surgical Pathology Cancer Case Summary (Checklist)

Protocol web posting date: October 2009

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 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)

* Data elements with asterisks are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.

Histologic Type (Note C)
___ Adenocarcinoma, intestinal type
___ Adenocarcinoma, diffuse type
___ Papillary adenocarcinoma
___ Tubular adenocarcinoma
___ Mucinous adenocarcinoma (greater than 50% mucinous)
___ Signet-ring cell carcinoma (greater than 50% signet-ring cells)
___ Other (specify): _____
___ Carcinoma, not otherwise specified

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
___ High-grade dysplasia/carcinoma in situ
___ Tumor invades lamina propria
___ Tumor invades muscularis mucosae
___ Tumor invades submucosa
___ Tumor invades muscularis propria
___ Tumor invades subserosal connective tissue
___ 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)

<u>Proximal Margin</u>
___ Cannot be assessed
___ Uninvolved by invasive carcinoma
___ Involved by invasive carcinoma
___ Carcinoma in situ/adenoma not identified at proximal margin
___ Carcinoma in situ/adenoma present at proximal margin

<u>Distal Margin</u>
___ Cannot be assessed
___ Uninvolved by invasive carcinoma
___ Involved by invasive carcinoma
___ Carcinoma in situ/adenoma not identified at distal margin
___ Carcinoma in situ/adenoma present at distal margin

* Data elements with asterisks are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.

Omental (Radial) Margins
___ Cannot be assessed
___ Uninvolved by invasive carcinoma
___ Lesser omental margin involved by invasive carcinoma
___ Greater omental margin involved by invasive carcinoma

Deep Margin (applies to endoscopic resections)
___ Cannot be assessed
___ Uninvolved by invasive carcinoma
___ Involved by invasive carcinoma
___ Not applicable

If all margins uninvolved by invasive carcinoma:
Distance of invasive carcinoma from closest margin: ___ mm
Specify margin: _____

Treatment Effect (applicable to carcinomas treated with neoadjuvant therapy) (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

***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 (post-treatment)

Primary Tumor (pT)
___ pTX: Cannot be assessed
___ pT0: No evidence of primary tumor
___ pTis: Carcinoma in situ
___ 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 involves 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
Specify: Number examined: ___
Number involved: ___

Distant Metastasis (pM)
___ Not applicable
___ pM1: Distant metastasis
*Specify site(s), if known: _____

***Additional Pathologic Findings (select all that apply) (Note K)**
*___ None identified
*___ Intestinal metaplasia
*___ Dysplasia
*___ Gastritis
* ___ *Helicobacter pylori*-type gastritis
* ____Other gastritis (specify): _____
*___ Polyp(s) (type[s]): _____
*___ Other (specify): _____

***Ancillary Studies**
***Specify: _____
*___ Not performed

***Clinical History (select all that apply) (Note L)**
*___ Previous gastric surgery (specify): _____
*___ Other (specify): _____
*___ Not known

***Comment(s)**

* Data elements with asterisks are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.

Explanatory Notes

A. Application

This protocol applies to all carcinomas that arise in the stomach and do not involve the esophagogastric junction (EGJ). Tumors that arise in the proximal stomach within 5 cm of the EGJ and cross the EGJ are not included. Lymphomas, low-grade neuroendocrine tumors (carcinoid tumors), and sarcomas are also not included (separate TNM staging systems[1] 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, corpus, antrum, pylorus
- greater curvature, lesser curvature
- anterior wall, posterior wall

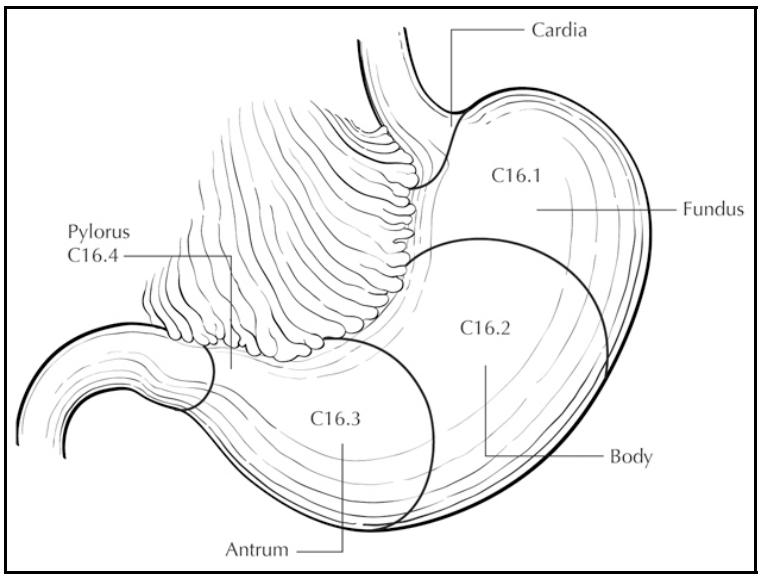

Figure 1. Anatomical subsites of the stomach. From: Greene FL, Compton, CC, Fritz AG, et al, eds. *AJCC Cancer Staging Atlas.* New York: Springer; 2006. Copyright © American Joint Committee on Cancer. Used with permission.

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 Chaves[4]), recent data support their classification as esophageal carcinomas.[1] The World Health Organization (WHO) defines esophageal tumors are 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 three 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
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 reflux,[2] reviewed by Carneiro and Chaves.[44]

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 histologic classification proposed by the World Health Organization (WHO) is recommended.[5] However, this protocol does not preclude the use of other systems of classification or histologic types, such as the Laurén classification,[10] which may be used in addition to 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]

WHO Classification of Carcinoma of the Stomach

Adenocarcinoma
    Intestinal type
    Diffuse type
Papillary adenocarcinoma
Tubular adenocarcinoma
Mucinous adenocarcinoma (greater than 50% mucinous)
Signet-ring cell carcinoma (greater than 50% signet-ring cells)
Adenosquamous carcinoma
Squamous cell carcinoma
Small cell carcinoma
Undifferentiated carcinoma
Other (specify)

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 in situ carcinoma as intraepithelial neoplasia. The term “carcinoma, NOS (not otherwise specified)” is not part of the WHO classification.

D. Histologic Grade

For adenocarcinomas, a histologic grade 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)

Tubular adenocarcinomas are not typically graded but are low grade and would correspond to grade 1.

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

Small cell 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 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 venous[16] and lymphatic vessel[9] invasion have been shown to be adverse prognostic factors[14] 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 factor[14] 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: 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.

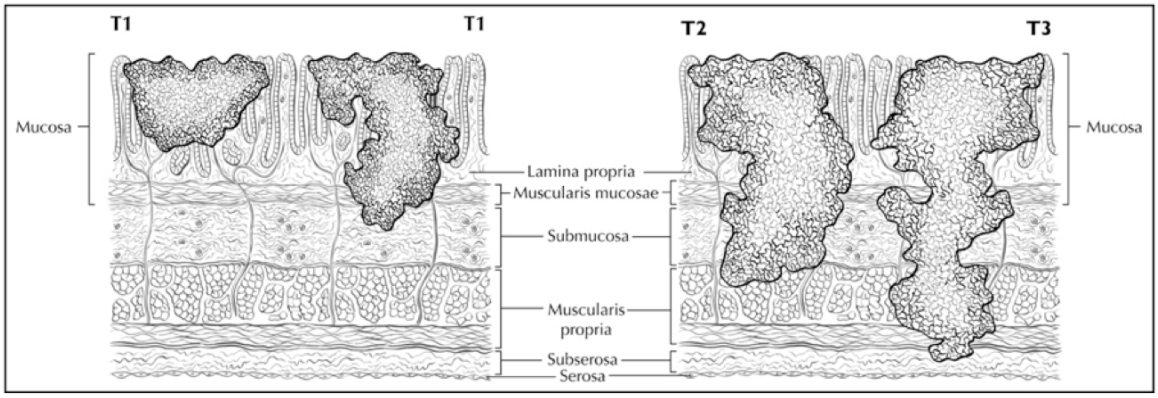

Figure 2. Definitions of T1, T2, and T3. Tumor invading the lamina propria is classified as T1a (left side or T1 illustration), whereas tumor invading the submucosa is classified as T1b (right side). T2 tumor invades the muscularis propria. T3 tumor invades the subserosal adipose tissue. Modified from: Greene FL, Compton, CC, Fritz AG, et al, eds. *AJCC Cancer Staging Atlas.* New York: Springer; 2006. Copyright © American Joint Committee on Cancer. Used with permission.

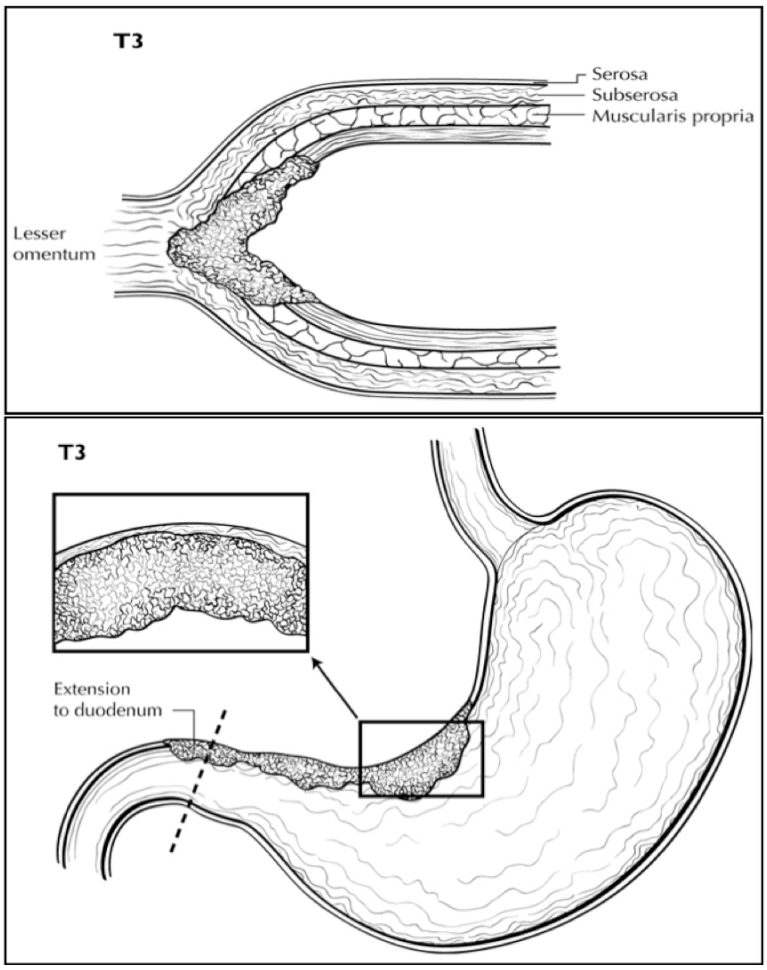

Figure 3. T3 is defined as tumor that invades the subserosa. Distal extension to duodenum does not affect T category. Modified from: Greene FL, Compton, CC, Fritz AG, et al, eds. *AJCC Cancer Staging Atlas.* New York: Springer; 2006. Copyright © American Joint Committee on Cancer. Used with permission.

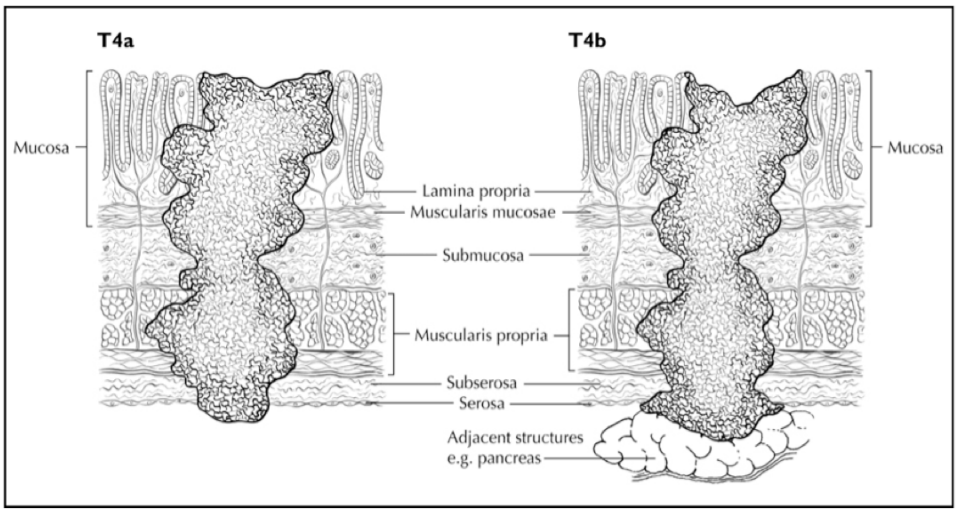

Figure 4. T4a tumor penetrates serosa (visceral peritoneum) without invasion of adjacent structures, whereas T4b tumor invades adjacent structures, such as the pancreas (shown). Modified from: Greene FL, Compton, CC, Fritz AG, et al, eds. *AJCC Cancer Staging Atlas.* New York: Springer; 2006. Copyright © American Joint Committee on Cancer. Used with permission.

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]

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]

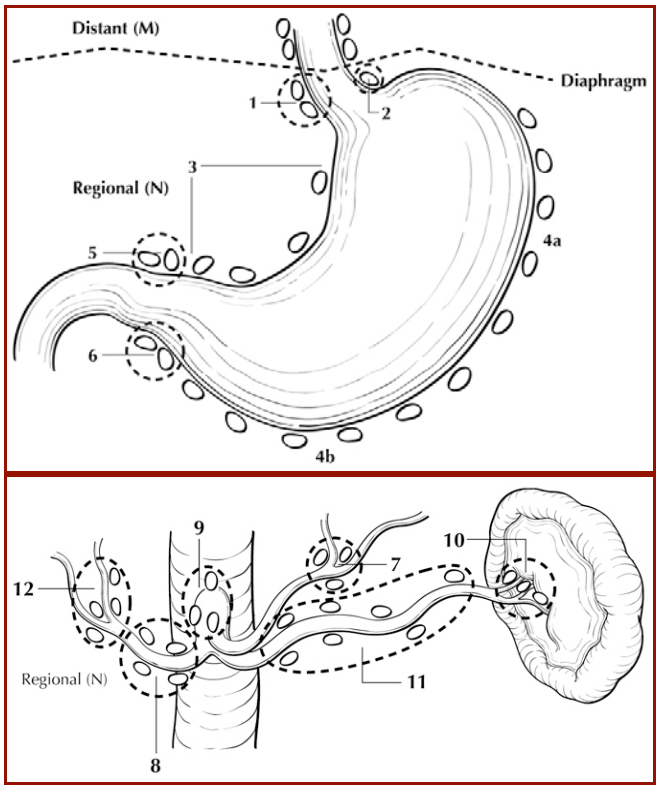

Figure 5. Regional lymph nodes of the stomach. From: Greene FL, Compton, CC, Fritz AG, et al, eds. *AJCC Cancer Staging Atlas.* New York: Springer; 2006. Copyright © American Joint Committee on Cancer. Used with permission.

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

Pancreatic and Splenic Area: Pancreaticolienal, 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. 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.[19]

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