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: June 2012

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 3.2.0.0

Summary of Changes
The following changes have been made since the February 2011 release.

This is a major revision to this protocol. Significant changes have been made throughout the document.

Local Resection, Gastrectomy

Histologic Type
Significant changes were made.

Microscopic Extent of Tumor
Significant changes were made.

Margins
Mucosal and other margins were added, as follows:

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

Pathologic Staging (pTNM)
Primary Tumor (pT)
pT1: was changed from a selectable to a nonselectable element.
pT4: “involves” was changed to “invades.”

Additional Pathologic Findings
Dysplasia was expanded to include low- and high-grade.

Ancillary Studies
Significant changes were made to include HER2 test results.

Explanatory Notes
Significant edits were made throughout.
Surgical Pathology Cancer Case Summary

Protocol web posting date: June 2012

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)

+ 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.
Histologic Type (select all that apply) (Note C)
___ Adenocarcinoma
   Lauren classification of adenocarcinoma:
   ___ 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
___ 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: ________________________________

+ 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.
Proximal 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

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
+ ___ 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 that arise in the proximal stomach within 5 cm of the EGJ and cross the EGJ are not included; the CAP protocol for carcinoma of the esophagus applies to such tumors.1 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](image)

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 controversial2,3 (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
Type II: true carcinoma of the gastric cardia, arising from the cardiac epithelium or short segments with intestinal metaplasia at the EGJ

1 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 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). 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. 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

Table 1. WHO Classification of Carcinoma of the Stomach5

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Histologic Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenocarcinoma</td>
<td></td>
</tr>
<tr>
<td>Papillary adenocarcinoma</td>
<td>Exophytic with elongated frond-like tumor extensions with fibrovascular cores; usually low grade.</td>
</tr>
<tr>
<td>Tubular adenocarcinoma</td>
<td>Dilated or slit-like branching tubules; usually low grade, although poorly differentiated variants are described.</td>
</tr>
<tr>
<td>Mucinous adenocarcinoma</td>
<td>Contains more than 50% extracellular mucin pools. May contain scattered signet-ring cells.</td>
</tr>
<tr>
<td>Poorly cohesive carcinomas, including diffuse and signet-ring cell carcinoma and other variants</td>
<td>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.</td>
</tr>
<tr>
<td>Mixed carcinoma</td>
<td>Mixture of morphologically identifiable components such as tubular, papillary, and poorly cohesive patterns.</td>
</tr>
<tr>
<td>Adenosquamous carcinoma</td>
<td>Mixture of glandular and squamous neoplastic components; the squamous component should comprise at least 25% of tumor volume</td>
</tr>
<tr>
<td>Carcinoma with lymphoid stroma (medullary carcinoma)</td>
<td>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.</td>
</tr>
<tr>
<td>Hepatoid adenocarcinoma</td>
<td>Large polygonal eosinophilic tumor cells resembling hepatocytes; may express alpha-fetoprotein.</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>Keratinizing and nonkeratinizing forms are encountered.</td>
</tr>
<tr>
<td>Undifferentiated carcinoma</td>
<td>High-grade carcinoma that cannot be further classified as adenocarcinoma, squamous cell carcinoma, or other recognized variants</td>
</tr>
</tbody>
</table>
### Tumor Type

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Histologic Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuroendocrine carcinoma</td>
<td>Poorly differentiated high-grade carcinoma with diffuse synaptophysin expression and faint or focal positivity for chromogranin A. These tumors exhibit a high mitotic rate (&gt;20 per high power field), marked nuclear atypia, and may have focal necrosis.</td>
</tr>
<tr>
<td>Large cell neuroendocrine carcinoma</td>
<td>Tumor cells are large, with moderate amount of cytoplasm, and may contain prominent nucleoli.</td>
</tr>
<tr>
<td>Small cell neuroendocrine carcinoma</td>
<td>Tumor cells are small, with finely granular chromatin and indistinct nucleoli.</td>
</tr>
<tr>
<td>Mixed adenoneuroendocrine carcinoma</td>
<td>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.</td>
</tr>
</tbody>
</table>

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.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td>Cannot be assessed</td>
</tr>
<tr>
<td>1</td>
<td>Well differentiated (greater than 95% of tumor composed of glands)</td>
</tr>
<tr>
<td>2</td>
<td>Moderately differentiated (50% to 95% of tumor composed of glands)</td>
</tr>
<tr>
<td>3</td>
<td>Poorly differentiated (49% or less of tumor composed of glands)</td>
</tr>
</tbody>
</table>

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.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td>Grade cannot be assessed</td>
</tr>
<tr>
<td>1</td>
<td>Well differentiated</td>
</tr>
<tr>
<td>2</td>
<td>Moderately differentiated</td>
</tr>
<tr>
<td>3</td>
<td>Poorly differentiated</td>
</tr>
</tbody>
</table>

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,\textsuperscript{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.\textsuperscript{13} The following system is suggested:

<table>
<thead>
<tr>
<th>Description</th>
<th>Tumor Regression Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>No viable cancer cells</td>
<td>0 (Complete response)</td>
</tr>
<tr>
<td>Single cells or small groups of cancer cells</td>
<td>1 (Moderate response)</td>
</tr>
<tr>
<td>Residual cancer outgrown by fibrosis</td>
<td>2 (Minimal response)</td>
</tr>
<tr>
<td>Minimal or no tumor kill; extensive residual cancer</td>
<td>3 (Poor response)</td>
</tr>
</tbody>
</table>

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.\textsuperscript{14,15}

**G. Venous/Lymphatic Vessel Invasion**

Both venous\textsuperscript{16} and lymphatic vessel\textsuperscript{9} invasion have been shown to be adverse prognostic factors\textsuperscript{14} and are predictive of lymph node metastases in early gastric cancers.\textsuperscript{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.\textsuperscript{1}

**H. Perineural Invasion**

Perineural invasion has been shown to be an adverse prognostic factor\textsuperscript{14} and has been associated with lymph node metastases in early gastric cancer in univariate but not multivariate analyses.\textsuperscript{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.\textsuperscript{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)

<table>
<thead>
<tr>
<th>T Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>Primary tumor cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
</tr>
</tbody>
</table>
| 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 al.24 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 al 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 al. 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. 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. Nodules implanted on the peritoneal surface are considered distant metastases (M1).

Distant Metastasis (M)

- **M0**: No distant metastasis
- **M1**: Distant metastasis

Stage Groupings

<table>
<thead>
<tr>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0</td>
<td>Tis</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IA</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage 1B</td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T1</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIA</td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td></td>
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<td>M0</td>
</tr>
<tr>
<td></td>
<td>T1</td>
<td>N2</td>
<td>M0</td>
</tr>
</tbody>
</table>
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

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

**Pancreatic and Splenic Area:** Pancreaticocolienal, 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. 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, 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, 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.

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, 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. 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 Trial for Scoring HER2/neu Expression by immunohistochemistry (IHC) in Gastric and Esophagogastric Adenocarcinoma

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

<table>
<thead>
<tr>
<th>2+</th>
<th>Weak to moderate complete, basolateral or lateral membranous reactivity in &gt;10% of tumor cells</th>
<th>Cancer cell cluster with a weak to moderate complete, basolateral, or lateral membranous reactivity irrespective of percentage of cancer cells positive</th>
<th>Equivocal by IHC</th>
</tr>
</thead>
<tbody>
<tr>
<td>3+</td>
<td>Strong complete, basolateral or lateral membranous reactivity in ≥10% of cancer cells</td>
<td>Cancer cell cluster with a strong complete basolateral, or lateral membranous reactivity irrespective of percentage of cancer cells positive</td>
<td>Positive</td>
</tr>
</tbody>
</table>

M. Clinical History

Previous gastric surgery, such as Billroth I or Billroth 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

References


