Protocol for the Examination of Specimens From Patients With Tumors of the Endocrine Pancreas

Protocol applies to all well-differentiated neuroendocrine tumors of the pancreas.

Based on AJCC/UICC TNM, 7th edition
Protocol web posting date: January 2016

Procedures
• Excisional Biopsy (Enucleation)
• Partial Pancreatectomy
• Pancreaticoduodenectomy (Whipple Resection)
• Total Pancreatectomy

Authors
Laura H. Tang, MD, PhD*
Department of Pathology, Memorial Sloan-Kettering Cancer Center, New York, NY
Jordan Berlin, MD
Department of Medicine, Vanderbilt University Medical Center, Nashville, TN
Chanjuan Shi, MD, PhD
Department of Pathology, Microbiology and Immunology, Vanderbilt University Medical Center, Nashville, TN
Philip Branton, MD
Department of Pathology, Inova Fairfax Hospital, Falls Church, VA
Lawrence J. Burgart, MD
Allina Laboratories, Abbott Northwestern Hospital, Minneapolis, MN
David K. Carter, MD
Department of Pathology, St. Mary's/Duluth Clinic Health System, Duluth, MN
Carolyn C. Compton, MD, PhD
Critical Path Institute, Tucson, AZ
Patrick Fitzgibbons, MD
Department of Pathology, St. Jude Medical Center, Fullerton, CA
Wendy Frankel, MD
Department of Pathology, Ohio State University Medical Center, Columbus, OH
John Jessup, MD
Division of Cancer Treatment and Diagnosis, National Cancer Institute, Bethesda, MD
Sanjay Kakar, MD
Department of Pathology, University of California San Francisco and the Veterans Affairs Medical Center, San Francisco, CA
Bruce Minsky, MD
Department of Radiation Oncology, University of Chicago, Chicago, IL
Raouf Nakhleh, MD
Department of Pathology, Mayo Clinic, Jacksonville, FL
Kay Washington, MD, PhD†
Department of Pathology, Vanderbilt University Medical Center, Nashville, TN
For the Members of the Cancer Committee, College of American Pathologists

* Denotes primary author. † Denotes senior author. All other contributing authors are listed alphabetically.
The College does not permit reproduction of any substantial portion of these protocols without its written authorization. The College hereby authorizes use of these protocols by physicians and other health care providers in reporting on surgical specimens, in teaching, and in carrying out medical research for nonprofit purposes. This authorization does not extend to reproduction or other use of any substantial portion of these protocols for commercial purposes without the written consent of the College.

The CAP also authorizes physicians and other health care practitioners to make modified versions of the Protocols solely for their individual use in reporting on surgical specimens for individual patients, teaching, and carrying out medical research for non-profit purposes.

The CAP further authorizes the following uses by physicians and other health care practitioners, in reporting on surgical specimens for individual patients, in teaching, and in carrying out medical research for non-profit purposes: (1) Dictation from the original or modified protocols for the purposes of creating a text-based patient record on paper, or in a word processing document; (2) Copying from the original or modified protocols into a text-based patient record on paper, or in a word processing document; (3) The use of a computerized system for items (1) and (2), provided that the protocol data is stored intact as a single text-based document, and is not stored as multiple discrete data fields.

Other than uses (1), (2), and (3) above, the CAP does not authorize any use of the Protocols in electronic medical records systems, pathology informatics systems, cancer registry computer systems, computerized databases, mappings between coding works, or any computerized system without a written license from the CAP.

Any public dissemination of the original or modified protocols is prohibited without a written license from the CAP.

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” 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.

The College developed these protocols as an educational tool to assist pathologists in the useful reporting of relevant information. It did not issue the protocols for use in litigation, reimbursement, or other contexts. Nevertheless, the College recognizes that the protocols might be used by hospitals, attorneys, payers, and others. Indeed, effective January 1, 2004, the Commission on Cancer of the American College of Surgeons mandated the use of the required data elements of the protocols as part of its Cancer Program Standards for Approved Cancer Programs. Therefore, it becomes even more important for pathologists to familiarize themselves with these documents. At the same time, the College cautions that use of the protocols other than for their intended educational purpose may involve additional considerations that are beyond the scope of this document.

The inclusion of a product name or service in a CAP publication should not be construed as an endorsement of such product or service, nor is failure to include the name of a product or service to be construed as disapproval.
Version Code
The definition of version control and an explanation of version codes can be found at www.cap.org (search: cancer protocol terms).

Version: PancreasEndocrine 3.3.0.0

Summary of Changes
The following changes were made since the October 2013 release.

The following data elements were modified:
- Tumor Size
- Mitotic Rate
- Microscopic Tumor Extension
- Margins
- Lymph-Vascular Invasion
- Perineural Invasion
- Distant Metastasis (changed to required only if confirmed pathologically)
Surgical Pathology Cancer Case Summary

Protocol web posting date: January 2016

PANCREAS (NEUROENDOCRINE TUMOR): Resection (Note A)

Select a single response unless otherwise indicated.

Specimen (select all that apply)
___ Head of pancreas
___ Body of pancreas
___ Tail of pancreas
___ Duodenum
___ Stomach
___ Common bile duct
___ Gallbladder
___ Spleen
___ Adjacent large vessels
   ___ Portal vein
   ___ Superior mesenteric vein
   ___ Other large vessel (specify): ________________________________
___ Other (specify): ________________________________
___ Not specified
___ Cannot be determined

Procedure
___ Excisional biopsy (enucleation)
___ Pancreatoduodenectomy (Whipple resection), partial pancreatectomy
___ Pancreatoduodenectomy (Whipple resection), total pancreatectomy
___ Partial pancreatectomy, pancreatic body
___ Partial pancreatectomy, pancreatic tail
___ Other (specify): ________________________________
___ Not specified
___ Cannot be determined

Tumor Site (select all that apply) (Note B)
___ Pancreatic head
___ Uncinate process
___ Pancreatic body
___ Pancreatic tail
___ Other (specify): ________________________________
___ Cannot be determined
___ Not specified

Tumor Size (Note C)
Greatest dimension: ___ cm (specify size of largest tumor if multiple tumors are present)
+ Additional dimensions: ___ x ___ cm
___ Cannot be determined (explain): ________________________________________

Tumor Focality (Note D)
___ Unifocal
___ Multifocal (specify number of tumors): ______
___ Cannot be determined
___ Not specified

+ 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 and Grade (Note E)*
___ Not applicable
___ Well-differentiated neuroendocrine tumor; GX: Grade cannot be assessed
___ Well-differentiated neuroendocrine tumor; G1: Low grade
___ Well-differentiated neuroendocrine tumor; G2: Intermediate grade
___ Other (specify): __________________________

* For poorly differentiated (high-grade) neuroendocrine carcinomas, the College of American Pathologists (CAP) protocol for carcinoma of the pancreas should be used.

+ Functional Type (select all that apply) (Note F)
+ ___ Cannot be assessed
+ ___ Pancreatic neuroendocrine tumor, functional
   (correlation with clinical syndrome and elevated serum levels of hormone product)
   + ___ Insulin-producing (insulinoma)
   + ___ Glucagon-producing (glucagonoma)
   + ___ Somatostatin-producing (somatostatinoma)
   + ___ Gastrin-producing (gastrinoma)
   + ___ Vasoactive intestinal polypeptide (VIP)-producing (VIPoma)
   + ___ Serotonin-producing (carcinoid)
   + ___ Other (specify): __________________________
+ ___ Pancreatic neuroendocrine tumor, nonfunctional
+ ___ Pancreatic neuroendocrine tumor, functional status unknown

Mitotic Rate (select all that apply) (Note G)
___ Not applicable
___ <2 mitoses/10 high-power fields (HPF)*
___ 2 to 20 mitoses/10 HPF
   Specify mitoses per 10 HPF: ______
___ >20 mitoses per 10 HPF
   Specify mitoses per 10 HPF: ______
___ Cannot be determined

* Published criteria that rely upon determination of mitotic rate for grading of gastrointestinal and pancreatic neuroendocrine tumors have been reported using counts per HPF, and do not specify microscopic field size or number of mitoses per mm².

+ Tumor Necrosis (Note H)
+ ___ Not identified
+ ___ Present
+ ___ Not applicable
+ ___ Cannot be determined

Microscopic Tumor Extension (select all that apply)
___ Cannot be determined
___ No evidence of primary tumor
___ Tumor is confined to pancreas
___ Tumor invades ampulla of Vater
___ Tumor invades common bile duct
___ Tumor invades duodenal wall
___ Tumor invades peripancreatic soft tissues
___ Tumor invades other adjacent organs or structures (specify): __________________________
+ ___ Tumor involves posterior surface of pancreas
+ ___ Tumor involves anterior surface of pancreas
+ ___ Tumor involves vascular bed/groove (corresponding to superior mesenteric vein/portal vein)
Margins (select all that apply) (Note I)
If all margins uninvolved by tumor:

Distance of tumor from closest margin: ____ mm or ____ cm
Specify margin: __________________________

For Segmental Resection (including Distal Pancreatectomy) Specimens Only:

Proximal Pancreatic Parenchymal Margin
___ Cannot be assessed
___ Uninvolved by tumor
   + Distance of tumor from margin: ____ mm or ____ cm
___ Involved by tumor

Distal Pancreatic Parenchymal Margin (required only if applicable)
___ Cannot be assessed
___ Uninvolved by tumor
   + Distance of tumor from margin: ____ mm or ____ cm
___ Involved by tumor

Other Margin(s) (required only if applicable)
Specify margin(s): ________________________
___ Cannot be assessed
___ Uninvolved by tumor
___ Involved by tumor

For Enucleation Specimens Only:

Pancreatic Parenchymal Margin
___ Cannot be assessed
___ Uninvolved by tumor
   + Distance of tumor from margin: ____ mm or ____ cm
___ Involved by tumor

Other Margin(s) (required only if applicable)
Specify margin(s): ________________________
___ Cannot be assessed
___ Uninvolved by tumor
___ Involved by tumor

For Pancreaticoduodenal Resection Specimens Only:

Pancreatic Neck/Parenchymal Margin
___ Cannot be assessed
___ Uninvolved by tumor
   + Distance of tumor from margin: ____ mm or ____ cm
___ Involved by tumor

Uncinate (Retropertoneal/Superior Mesenteric Artery) Margin
___ Cannot be assessed
___ Uninvolved by tumor
   + Distance of tumor from margin: ____ mm or ____ cm
___ Involved by tumor

+ 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.
Bile Duct Margin
- Cannot be assessed
- Uninvolved by tumor
  + Distance of tumor from margin: ___ mm or ___ cm
- Involved by tumor

Proximal Margin (Gastric or Duodenal)
- Cannot be assessed
- Uninvolved by tumor
- Involved by tumor

Distal Margin (Distal Duodenal or Jejunal)
- Cannot be assessed
- Uninvolved by tumor
- Involved by tumor

Other Margin(s) (required only if applicable)
Specify margin(s): _____________________________
- Cannot be assessed
- Uninvolved by tumor
- Involved by tumor

Lymph-Vascular Invasion (Note J)
- Not identified
- Present
- Cannot be determined

Perineural Invasion (Note K)
- Not identified
- Present
- Cannot be determined

Pathologic Staging (pTNM) (Note L)

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
- pT1: Tumor limited to the pancreas, 2 cm or less in greatest dimension
- pT2: Tumor limited to the pancreas, more than 2 cm in greatest dimension
- pT3: Tumor extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery
- pT4: Tumor involves the celiac axis or the superior mesenteric artery

Regional Lymph Nodes (pN)
- pNX: Cannot be assessed
- pN0: No regional lymph node metastasis
- pN1: Regional lymph node metastasis
- No nodes submitted or found

+ 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.
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) (required only if confirmed pathologically in this case)
___ pM1: Distant metastasis
      Specify site(s), if known: ________________________________

Additional Pathologic Findings (select all that apply)
+ ___ None identified
+ ___ Chronic pancreatitis
+ ___ Acute pancreatitis
+ ___ Adenomatosis (multiple neuroendocrine tumors, each less than 5 mm in greatest dimension)
+ ___ Other (specify): ________________________________

Ancillary Studies (select all that apply) (Note M)
+ ___ Ki-67 labeling index (specify: _____)
   + ___ ≤2%
   + ___ 3% to 20%
   + ___ >20%
+ ___ Other (specify): ________________________________
+ ___ Not performed

Clinical History (select all that apply) (Note N)
+ ___ Von Hippel-Lindau disease
+ ___ Multiple endocrine neoplasia type 1
+ ___ Familial pancreatic cancer syndrome
+ ___ Hypoglycemic syndrome
+ ___ Necrolytic migratory erythema
+ ___ Watery diarrhea
+ ___ Hypergastrinemia
+ ___ Zollinger-Ellison syndrome
+ ___ Other (specify): ________________________________
+ ___ Not specified

Comment(s)
Explanatory Notes

A. Application
This protocol applies to well-differentiated neuroendocrine tumors of the pancreas. Use of the protocol is not required for incidentally identified pancreatic neuroendocrine tumors ≤5 mm (defined as neuroendocrine microadenoma) in specimens removed for other indications. Pancreatic neuroendocrine tumors are also known as islet cell tumors, but this terminology is considered to be outdated and misleading because these tumors may not be derived from pancreatic islets. Rather, they are believed to arise from pluripotential cells in the pancreatic ducts that have the capacity to differentiate along neuroendocrine lines.

Fewer than 5% to 10% of malignant tumors of the pancreas are neuroendocrine tumors. Surgical resection remains the only potentially curative approach for these tumors. The prognosis of pancreatic neuroendocrine tumors is primarily dependent on the functional subtype, the completeness of the surgical resection, the anatomic extent of disease, and the tumor grade. The TNM staging system for carcinomas of the exocrine pancreas is also applied to pancreatic neuroendocrine tumors.

B. Tumor Site: Definition of Location
The anatomic subdivisions defining location of tumors of the pancreas (Figures 1 and 2) are as follows:

- Tumors of the head of the pancreas are those arising to the right of the left border of the superior mesenteric vein. The uncinate process is part of the head.
- Tumors of the body of the pancreas are those arising between the left border of the superior mesenteric vein and the left border of the aorta.
- Tumors of the tail of the pancreas are those arising between the left border of the aorta and the hilum of the spleen.

![Figure 1. Anatomic subsites of the pancreas. From Greene et al. Used with permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Atlas (2006) published by Springer Science and Business Media LLC, www.springerlink.com.](image)

C. Tumor Dimensions
Tumors less than 0.5 cm are regarded as neuroendocrine microadenomas; these small nonfunctional tumors rarely come to clinical attention. A separate case summary does not need to be completed for incidentally identified neuroendocrine microadenomas. Large tumor size (diameter 3.0 cm or greater) has been shown to correlate with aggressive biologic behavior, such as local invasion and vascular invasion, and with metastasis.
Large size also correlates with cystic radiographic appearance and calcification. However, there is marked overlap in the size ranges of localized and metastatic tumors, although tumors larger than 10 cm are highly likely to be metastatic.

D. Tumor Focality
Pancreatic neuroendocrine tumors are multifocal in the majority of multiple endocrine neoplasia type 1 (MEN 1) cases and in up to 30% of gastrinomas and 13% of insulinomas. Careful gross examination of the resection specimen with systematic sectioning at 3- to 5-mm intervals is necessary to detect small lesions within the pancreatic parenchyma.

E. Histologic Type
Pancreatic neuroendocrine neoplasms are classified as well-differentiated pancreatic neuroendocrine tumors or as poorly differentiated (high-grade) neuroendocrine carcinomas. The World Health Organization (WHO) classification of pancreatic neuroendocrine tumors is based upon mitotic rate and tumor proliferative index as assessed by Ki-67 immunoreactivity (Table 1). However, this protocol does not preclude the use of other histologic types or systems of classification.

Table 1. WHO Classification of Pancreatic Neuroendocrine Tumors

<table>
<thead>
<tr>
<th>Classification</th>
<th>WHO Grade</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Well-differentiated neuroendocrine tumor, grade 1</td>
<td>G1</td>
<td>&lt;2 mitoses per 10 HPF; Ki-67 labeling index ≤2%</td>
</tr>
<tr>
<td>Well-differentiated neuroendocrine tumor, grade 2</td>
<td>G2</td>
<td>2 to 20 mitoses per 10 HPF; Ki-67 labeling index 3%-20%</td>
</tr>
<tr>
<td>Poorly differentiated neuroendocrine carcinoma (small cell carcinoma or large cell endocrine carcinoma), grade 3</td>
<td>G3</td>
<td>&gt;20 mitoses per 10 HPF; Ki-67 labeling index &gt;20%</td>
</tr>
</tbody>
</table>

For poorly differentiated (high-grade) neuroendocrine carcinomas, the College of American Pathologists (CAP) protocol for carcinoma of the pancreas should be used.

Pancreatic neuroendocrine tumors typically display a variety of growth patterns, including (1) gyriform patterns that resemble the structure of normal islets, in which thin cords of tumor cells form loops separated by a delicate stroma; (2) solid or medullary patterns, in which the tumor cells grow in sheets and have little intervening stroma; and (3) glandular patterns, in which the tumor cells form acini or pseudorosettes. Sarcomatoid or anaplastic growth may also occur. Cytologically, most tumors are composed of monomorphic cells with clear to eosinophilic cytoplasm and variable mitotic rate. Many tumors show more than 1 growth pattern. There is no correlation between growth pattern and biologic behavior or between growth pattern and functional type.

F. Functional Type
Pancreatic neuroendocrine tumors that secrete large amounts of hormonal cell product into the systemic circulation are known as “functioning” tumors, and their classification is often based on the clinical syndrome produced by the predominant secretory product. Pancreatic neuroendocrine tumors are classified as “nonfunctioning” if they produce no hormonally related clinical syndrome. Some tumors assigned to the nonfunctioning category may secrete hormones that produce no clinical sequelae (such as pancreatic polypeptide) and are detectable only by specific serum analysis for the polypeptide. Most nonfunctioning pancreatic neuroendocrine tumors actually produce 1 or more peptide hormones (detectable by immunolocalization within the cells of the excised tumor tissue) but are clinically silent because they do not export their cell products because of an impaired secretory pathway. Therefore, immunohistochemical demonstration of hormone products for purposes of tumor classification is of limited utility. Classification of pancreatic neuroendocrine tumors based on their functional status is shown below. The clinical features that define the functioning tumors are shown in parentheses.
Classification of Pancreatic Neuroendocrine Tumors

Pancreatic neuroendocrine microadenoma (<0.5 cm and nonfunctional)
- Neuroendocrine tumor (NET) (nonfunctional)
  - NET G1
  - NET G2

Neuroendocrine carcinoma (NEC)
- Large cell NEC
- Small cell NEC

Pancreatic neuroendocrine tumor, functional
- EC cell, serotonin-producing NET (carcinoid) (carcinoid syndrome, flashing, diarrhea); rarely encountered as primary in the pancreas
- Gastrin-secreting (gastrinoma) (abdominal pain, ulcer disease, diarrhea, gastrointestinal bleeding)
- Glucagon-secreting (glucagonoma) (diabetes, skin rash [necrolytic migratory erythema], stomatitis)
- Insulin-secreting (insulinoma) (hypoglycemia, neuropsychiatric disturbances)
- Somatostatin-secreting (somatostatinoma) (diabetes, steatorrhea, achlorhydria); rarely encountered
- Vasoactive intestinal polypeptide (VIP)-secreting (VIPoma) (watery diarrhea, hypokalemia, achlorhydria)

Mixed ductal-neuroendocrine carcinoma

Mixed acinar-neuroendocrine carcinoma

# Sometimes known as Verner-Morrison tumors.

## Biphase tumors containing a significant proportion (greater than 30%) of tumor cells with differentiation along ductal or acinar cell lines are classified separately as subtypes of pancreatic neuroendocrine carcinoma. The neuroendocrine component in such tumors is often high grade. The CAP protocol for carcinoma of the pancreas should be used for these tumors.

G. Mitotic Rate

High mitotic rate, a high degree of pleomorphism, and tumor necrosis have all been shown to correlate strongly with an aggressive behavior. The WHO classification and others (see Note E) use mitoses per 10 or per 50 HPF and/or Ki67 index as one of the criteria for potential for aggressive behavior. Mitotic rate should be based upon counting 50 HPF (40x objective) and in the area of highest mitotic activity, and reported as number of mitoses per 10 HPF.

Ki-67 index is reported as percent positive tumor cells in area of highest nuclear labeling, although the precise method of assessment has not been standardized. It has been recommended that 500 to 2000 tumor cells be counted to determine the Ki-67 index. Published criteria that rely upon determination of mitotic count for grading of GI and pancreatic neuroendocrine tumors have been reported using counts per high-power field and do not specify microscopic field size or number of mitoses per mm². Grade assigned based on Ki-67 index may be higher than that based on mitotic count. Reporting the higher grade by either method is preferred if both are performed.

It is important to note that there are a small group of well-differentiated pancreatic neuroendocrine tumors with a Ki67 index >20% but a low mitotic rate (usually much less than 20 mitoses per 10 HPF) and no features of poorly differentiated neuroendocrine carcinoma. Although they have a Ki67 index >20%, these tumors should still be considered as well-differentiated neuroendocrine tumors. In the histologic type and grade section of the case summary, “other” should be selected, followed by well-differentiated neuroendocrine tumor with a specific Ki67 index and mitotic rate.

H. Tumor Necrosis

Tumor necrosis is uncommon in well-differentiated pancreatic neuroendocrine tumors but is generally regarded as an aggressive feature. When possible, a distinction should be made between nonischemic necrosis (usually punctate or geographic), which is associated with higher tumor grade, and ischemic necrosis.
I. Margins
For enucleation procedures, the periphery of the resection specimen tissue may be inked, and radial sections at the closest approach of tumor can be examined microscopically.

For partial pancreatectomy and pancreaticoduodenectomy specimens, sections through the closest approach of the tumor to the pancreatic parenchymal resection margin(s) and to the retroperitoneal (uncinate) (Figure 2) are recommended. Sampling of the deep radial surface (representing the posterior retroperitoneal surface of the specimen) is also indicated. In cases of MEN 1, tumors are frequently multiple, and microscopic tumors that are not seen on macroscopic examination may be found at the margin(s).

Overall, for pancreatic neuroendocrine tumors, complete resection of tumor is a strong determinant of long-term survival. However, in some cases, long-term survival is possible even when the tumor cannot be completely excised. Surgical debulking procedures are of value in controlling tumor-related endocrinopathies and may prolong survival in some patients.

Figure 2. Posterior view of tumor arising in the pancreatic head, with dotted line indicating the location of the confluence of the portal and superior mesenteric veins. The hatched area shows the retroperitoneal (uncinate process) margin. From Greene et al. Used with permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Atlas (2006) published by Springer Science and Business Media LLC, www.springerlink.com.

J. Blood Vessel Invasion
The presence of blood vessel invasion, perineural invasion, or both have been regarded by some authors as histopathologic criteria for malignancy. Invasion of blood vessels (particularly veins within the tumor capsule) or perineural spaces have been observed in 90% of cases with distant metastases in some studies.

K. Perineural Invasion
Perineural invasion has been associated with aggressive behavior and with shortened survival in some series of pancreatic neuroendocrine tumors.

L. Pathologic Staging
The same TNM staging system of the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC) is recommended for staging both carcinoma of the exocrine pancreas and pancreatic neuroendocrine tumors, as shown below. The postresection prognosis of a patient with pancreatic carcinoma is primarily determined by the anatomic extent of disease as defined by the TNM stage groupings.

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 3 through 5)

<table>
<thead>
<tr>
<th>TX</th>
<th>Primary tumor cannot be assessed</th>
</tr>
</thead>
<tbody>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
</tr>
<tr>
<td>T1</td>
<td>Tumor limited to the pancreas, 2 cm or less in greatest dimension</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor limited to the pancreas, more than 2 cm in greatest dimension</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery</td>
</tr>
<tr>
<td>T4</td>
<td>Tumor involves the celiac axis or the superior mesenteric artery (unresectable primary tumor)</td>
</tr>
</tbody>
</table>

If more than 1 tumor is present in the pancreas, the tumor with the highest T category should be classified according to the pT definitions, and either the multiplicity (“m”) or the actual number of simultaneous multiple tumors (eg, “3”) should be indicated in parentheses after the T category of the primary tumor (eg, pT3[m] or pT3[2]).

The “m” designation applies only to grossly recognizable, synchronous primary carcinomas and not to a single, grossly detected tumor with multiple separate microscopic foci.

**Tumor size has been shown to have independent prognostic significance.5,7**

For T3, extension beyond the pancreas may include invasion of soft tissues adjacent to the pancreas, the common bile duct, and/or duodenum (including the ampulla of Vater). Specifically, peripancreatic tissues include the surrounding retroperitoneal fat (retroperitoneal soft tissue), including mesentery (mesenteric fat), mesocolon, greater and lesser omentum, and peritoneum.
Invasion of the portal vein also has been shown to have independent prognostic significance as an adverse factor.\textsuperscript{4}

**Figure 3.** T1 (left of dotted line) is defined as tumor measuring 2 cm or less in greatest dimension and limited to the pancreas. T2 (right of dotted line) is defined as tumor measuring more than 2 cm in greatest dimension and limited to the pancreas. From Greene et al.\textsuperscript{21} Used with permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the *AJCC Cancer Staging Atlas* (2006) published by Springer Science and Business Media LLC, www.springerlink.com.

**Figure 4.** T3 is defined as tumor that extends beyond the pancreas but without involvement of the celiac axis or superior mesenteric artery. A. To the left of the dotted line, tumor invades the common bile duct without involving the superior mesenteric artery. To the right of the dotted line, tumor invades the peripancreatic tissues without involving the celiac axis. B. Tumor invades duodenum without involvement of superior mesenteric artery. C. Tumor invades spleen without involvement of celiac axis or superior mesenteric artery. From Greene et al.\textsuperscript{21} Used with permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the *AJCC Cancer Staging Atlas* (2006) published by Springer Science and Business Media LLC, www.springerlink.com.
Figure 5. T4 tumor involves the celiac axis (above dotted line) or the superior mesenteric artery (below dotted line). T4 tumors are considered unresectable and are rarely encountered in surgical pathology specimens. From Greene et al. Used with
Regional Lymph Nodes (N)* (Figures 6 and 7)
NX  Regional lymph nodes cannot be assessed
N0  No regional lymph node metastasis
N1  Regional lymph node metastasis #

The regional nodes may be subdivided as follows #:

Superior  Lymph nodes superior to head and body of pancreas
Inferior  Lymph nodes inferior to head and body of pancreas
Anterior  Anterior pancreaticoduodenal, pyloric, and proximal mesenteric lymph nodes
Posterior  Posterior pancreaticoduodenal, common bile duct or pericholedochal, and proximal mesenteric nodes
Splenic  (For tumors in body and tail only) Nodes of the splenic hilum and tail of pancreas.

* The following lymph nodes are also considered regional: hepatic artery nodes, infrapyloric nodes (for tumors in head only), subpyloric nodes (for tumors in head only), celiac nodes (for tumors in head only), superior mesenteric nodes, pancreaticocolic nodes (for tumors in body and tail only), splenic nodes (for tumors in body and tail only), retroperitoneal nodes, and lateral aortic nodes. Tumor involvement of other nodal groups is considered distant metastasis.

** The presence of lymph node metastases has been shown to have independent prognostic significance as an adverse factor. 3,11 The minimum number of lymph nodes needed for adequate staging for pancreatic neuroendocrine tumors in pancreaticoduodenectomy specimens has not been determined, although a minimum of 12 lymph nodes has been suggested for pancreatic adenocarcinoma specimens.

Figure 6. Regional lymph nodes of the pancreas (anterior view). From Greene et al. 21 Used with permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Atlas (2006) published by Springer Science and Business Media LLC, www.springerlink.com.
**Background Documentation**

**Endocrine • Pancreas (Neuroendocrine Tumor)**

PancreasEndocrine 3.3.0.0

---

**Figure 7.** Regional lymph nodes of the pancreas (anterior view with pancreatic body removed to reveal retroperitoneal vessels and lymph nodes). From Greene et al. Used with permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the *AJCC Cancer Staging Atlas* (2006) published by Springer Science and Business Media LLC, www.springerlink.com.

**Distant Metastasis (M)**

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

* The most common site of distant metastasis is liver. In many cases, metastasis is found only in the liver, without regional lymph node metastasis.

**Anatomic Stage/Prognostic Groupings**

<table>
<thead>
<tr>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IB</td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IIA</td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IIB</td>
<td>T1</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T2</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td>III</td>
<td>T4</td>
<td>Any N</td>
<td>M0</td>
</tr>
<tr>
<td>IV</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
</tr>
</tbody>
</table>

**Additional Descriptors**

**Residual Tumor (R)**

Tumor remaining in a patient after therapy with curative intent (e.g., surgical resection for cure) is categorized by a system known as R classification, shown below.

- **RX** Presence of residual tumor cannot be assessed
- **R0** No residual tumor
- **R1** Microscopic residual tumor
- **R2** Macroscopic residual tumor

For the surgeon, the R classification may be useful to indicate the known or assumed status of the completeness of a surgical excision. For the pathologist, the R classification is relevant to the status of the margins of a surgical resection specimen. That is, tumor involving the resection margin on pathologic examination may be assumed to
correspond to residual tumor in the patient and may be classified as macroscopic or microscopic according to the findings at the specimen margin(s).

**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.

**M. Ancillary Studies**
Most pancreatic neuroendocrine tumors are strongly positive for synaptophysin and chromogranin A.

Ki-67 is now used routinely by most practices to assess proliferative activity in pancreatic neuroendocrine tumors, and it has been shown that Ki67 labeling in addition to mitotic rate determination helps define more accurately tumor grade and prognosis.

Immunohistochemical studies to determine production of hormonal products are not indicated for routine assessment, because determination of tumor functionality is made on the basis of presence or absence of clinical syndromes.

**N. Clinical History**
The etiology of most sporadic neuroendocrine tumors of the pancreas is not known. However, MEN 1, von Hippel-Lindau disease, and, more rarely, tuberous sclerosis complex and neurofibromatosis type 1 are associated with pancreatic neuroendocrine tumors. It is important to know whether the patient has a history of a genetic syndrome because tumors from such patients are more likely to be multifocal.

Knowledge of the clinical history is important for determining whether a pancreatic neuroendocrine tumor is associated with a functional syndrome, which is an important predictor of clinical course (see Note F). In particular, insulinomas behave indolently, probably because they are discovered early due to the production of a hypoglycemic state. Other functioning tumors are generally aggressive.

**References**


