Protocol for the Examination of Specimens from Patients with Carcinoma of the Endocrine Pancreas

Protocol applies to all endocrine tumors of the pancreas.

Based on AJCC/UICC TNM, 7th edition
Protocol web posting date: October 2009

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

Authors
Kay Washington, MD, PhD, FCAP*
Department of Pathology, Vanderbilt University Medical Center, Nashville, TN
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
Philip Branton, MD, FCAP
Department of Pathology, Inova Fairfax Hospital, Falls Church, VA
Lawrence J. Burgart, MD, FCAP
Allina Laboratories, Abbott Northwestern Hospital, Minneapolis, MN
David K. Carter, MD, FCAP
Department of Pathology, St. Mary's/Duluth Clinic Health System, Duluth, MN
Patrick Fitzgibbons, MD, FCAP
Department of Pathology, St. Jude Medical Center, Fullerton, CA
Wendy Frankel, MD, FCAP
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, FCAP
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, FCAP
Department of Pathology, Mayo Clinic, Jacksonville, FL
Carolyn C. Compton, MD, PhD, FCAP†
Office of Biorepositories and Biospecimen Research, National Cancer Institute, Bethesda, MD
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 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.

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 checklist 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 of service to be construed as disapproval.

Surgical Pathology Cancer Case Summary (Checklist)

Protocol web posting date: October 2009

PANCREAS (ENDOCRINE): 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)
___ Pancreaticoduodenectomy (Whipple resection), partial pancreatectomy
___ Pancreaticoduodenectomy (Whipple resection), total pancreatectomy
___ Partial pancreatectomy, pancreatic body
___ Partial pancreatectomy, pancreatic tail
___ Other (specify): _____
___ Not specified

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 (see Comment)

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

Histologic Type (Note E)
___ Well-differentiated endocrine neoplasm
___ Poorly differentiated endocrine carcinoma
*___ Small cell carcinoma
*___ Large cell endocrine carcinoma
___ Other (specify): _____
___ Carcinoma, type cannot be determined

***World Health Organization Classification (Note E)**
*___ Well-differentiated endocrine tumor, benign behavior
*___ Well-differentiated endocrine tumor, uncertain behavior
*___ Well-differentiated endocrine carcinoma
*___ Poorly differentiated endocrine carcinoma

***Functional Type (select all that apply) (Note F)**
*___ Cannot be assessed
*___ Pancreatic endocrine 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 (VIP-oma)
*___ Other (specify): _____
*___ Pancreatic endocrine tumor, nonfunctional
*___ Pancreatic endocrine tumor, functional status unknown

Mitotic Activity (select all that apply) (Note G)
___ Not applicable
___ Less than 2 mitoses/10 high-power fields (HPF)
Specify mitoses per 10 HPF: _____
___ Greater than or equal to 2 mitoses/10 HPF to 10 mitoses/10 HPF
Specify mitoses per 10 HPF: _____
___ Greater than 10 mitoses per 10 HPF
___ Cannot be determined

* Ki67 labeling index:
*___ ≤2% Ki67-positive cells
*___ 3%-20% Ki67-positive cells
*___ >20% Ki67-positive cells

***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): _____

Margins (select all that apply) (Note I)
___ Cannot be assessed
___ Margins uninvolved by tumor
Distance of tumor from closest margin: ___ mm
*Specify margin (if possible): _____
___ Margin(s) involved by tumor
___ Uncinate process (retroperitoneal) margin (nonperitonealized surface of the uncinate process)
___ Distal pancreatic margin
___ Common bile duct margin
___ Proximal pancreatic margin
___ Other (specify): _____
*___ Tumor involves posterior retroperitoneal surface of pancreas

Lymph-Vascular Invasion (Note J)
___ Not identified
___ Present
___ Indeterminate

Perineural Invasion (Note K)
___ Not identified
___ Present
___ Indeterminate

Pathologic Staging (pTNM) (Note L)

TNM Descriptors (required only if applicable) (select all that apply)
___ m (multiple primary tumors)
___ r (recurrent)
___ y (post-treatment)

* 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.

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
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)**
*___ None identified
*___ Chronic pancreatitis
*___ Acute pancreatitis
*___ Adenomatosis (multiple endocrine tumors, each less than 5 mm in greatest dimension)
*___ Other (specify): _____

***Ancillary Studies (Note M)**
*****Specify: _____

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 endocrine tumors of the pancreas. Pancreatic endocrine tumors are also known as “islet cell tumors,” but this terminology is considered to be outdated and misleading because these tumors are not derived from pancreatic islets. Rather, they are believed to arise from pluripotential cells in the pancreatic ducts that have the capacity to differentiate along endocrine lines.

Currently, there are no definitive histopathologic criteria for differentiating benign from malignant endocrine tumors of the pancreas, and the presence of metastasis is the only absolute criterion for malignancy. Thus, in the absence of known metastasis or gross local invasion, it is suggested that the term “endocrine tumor” be used rather than definitive terms such as “adenoma” or “carcinoma,” which connote certainty about the biologic nature of the neoplasm.

Fewer than 5% to l0% of malignant tumors of the pancreas are neuroendocrine carcinomas. Surgical resection remains the only potentially curative approach for these tumors. The prognosis of pancreatic endocrine carcinomas is primarily dependent on the functional subtype, the completeness of the surgical resection, and the anatomic extent of disease.[1] The TNM staging system for carcinomas of the exocrine pancreas is also applied to pancreatic endocrine tumors.[2,3]

B. Tumor Site: Definition of Location

The anatomic subdivisions defining location of tumors of the pancreas (Figures 1 and 2) are as follows[3]:

- 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.

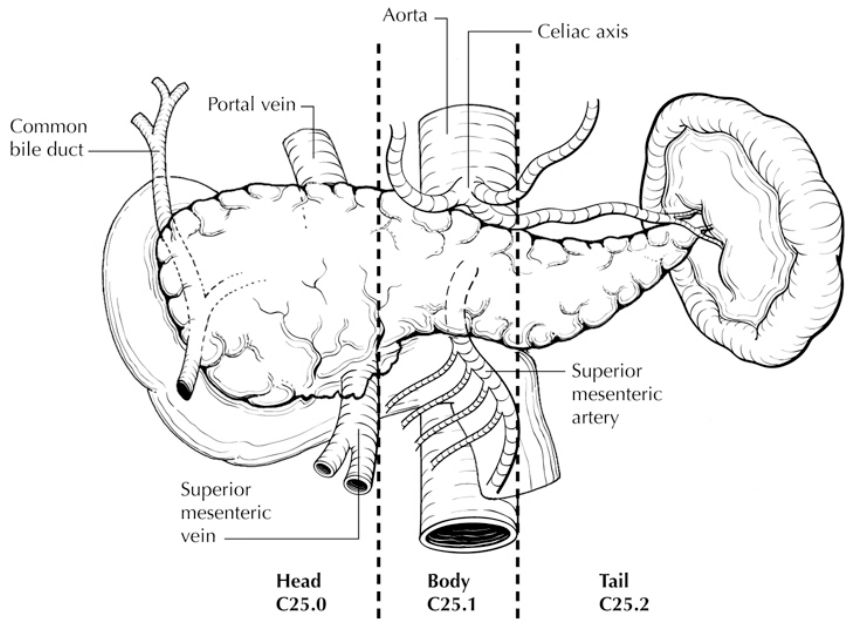


Figure 1. Anatomic subsites of the pancreas. From: Greene FL, Compton, CC, Fritz AG, et al, eds. *AJCC Cancer Staging Atlas.* New York: Springer; 2006. Copyright © American Joint Committee on Cancer. Used with permission.

C. Tumor Dimensions

Tumors less than 0.5 cm are regarded as endocrine microadenomas; these small nonfunctional tumors rarely come to clinical attention. Large tumor size (diameter 3.0 cm or greater) has been shown to correlate with aggressive biologic behavior,[4] such as local invasion and vascular invasion, and with metastasis. Large size also correlates with cystic radiographic appearance and calcification.[5] However, there is marked overlap in the size ranges of localized and malignant tumors (with metastasis), although tumors larger than 10 cm are highly likely to be malignant.[6]

D. Tumor Focality

Pancreatic endocrine 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.[6] 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 endocrine neoplasms are classified as well-differentiated neoplasms or as poorly differentiated (high-grade) carcinomas. The World Health Organization (WHO) classification of pancreatic endocrine tumors is based upon invasiveness, size, and mitotic rate (Table 1).[1] However, this protocol does not preclude the use of other histologic types or systems of classification.

The prognostic value of the WHO classification scheme has been confirmed,[7,8] although simpler schemes based upon tumor grade and stage have also been proposed.[7] High-

risk features in the WHO classification scheme are size ≥2 cm, angioinvasion, perineural invasion, and mitotic activity ≥2 per 10 HPF.

Table 1. WHO Classification of Pancreatic Endocrine Tumors

Classification	WHO Type	Local Invasion	Features
Well-differentiated endocrine tumor, benign behavior	1.1	Confined to pancreas	<2 cm, no angioinvasion or perineural invasion, <2 mitoses per 10 HPF; Ki67 labeling index less than 2%
Well-differentiated endocrine tumor, uncertain behavior (one or more high-risk features)	1.2	Confined to pancreas	One or more of the following features: ≥2 cm, angioinvasion, perineural invasion, 2 to 10 mitoses per 10 HPF; Ki67 labeling index 2% or greater
Well-differentiated endocrine carcinoma	2	Gross local invasion and/or metastases	Generally shows one or more of the following features: ≥2 cm, angioinvasion, perineural invasion, 2 to 10 mitoses per 10 HPF; Ki67 labeling index 2% or greater
Poorly differentiated endocrine carcinoma (small cell carcinoma or large cell endocrine carcinoma)	3	Often widely invasive or metastatic	High-grade carcinoma with >10 mitoses per 10 HPF

Pancreatic endocrine 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 activity. 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.[9]

F. Functional Type

Pancreatic endocrine 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.[1] Pancreatic endocrine 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 endocrine 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 to an impaired secretory pathway. Therefore, immunohistochemical demonstration of hormone products for purposes of tumor classification is of limited utility. Classification

of pancreatic endocrine tumors based on their functional status is shown below. The clinical features that define the functioning tumors are shown in parentheses.

Classification of Pancreatic Endocrine Tumors

Pancreatic endocrine tumor, functional
- Insulin-secreting (insulinoma) (hypoglycemia, neuropsychiatric disturbances)
- Glucagon-secreting (glucagonoma) (diabetes, skin rash [necrolytic migratory erythema], stomatitis)
- Gastrin-secreting (gastrinoma) (abdominal pain, ulcer disease, diarrhea, gastrointestinal bleeding)
- Somatostatin-secreting (somatostatinoma) (diabetes, steatorrhea, achlorhydria); rarely encountered.
- Pancreatic polypeptide (PP)-secreting (PP-oma) (clinically silent but with elevated serum PP levels)
- Vasoactive intestinal polypeptide (VIP)-secreting (VIP-oma[#]) (watery diarrhea, hypokalemia, achlorhydria)
- Adrenocorticotropic hormone-producing (Cushing's syndrome: central obesity, muscle weakness, glucose intolerance, hypertension)
- Carcinoid tumor (serotonin-producing) (carcinoid syndrome: flushing, diarrhea); rarely encountered as primary in the pancreas

Pancreatic endocrine tumor, nonsecretory
Mixed ductal-endocrine carcinoma[##]
Mixed acinar-endocrine carcinoma[##]

[#] Sometimes known as Verner-Morrison tumors.

[##] Biphasic tumors containing a significant proportion (greater than 25% to 30%) of tumor cells with differentiation along ductal or acinar cell lines are classified separately as subtypes of pancreatic endocrine carcinoma. The endocrine component in such tumors is often high grade.

G. Mitotic Activity

High mitotic activity, a high degree of pleomorphism, and tumor necrosis have all been shown to correlate strongly with malignant potential.[6] The WHO classification[1] and others[7] (see Note E) use mitoses per 10 or per 50 HPF as one of the criteria for potential for aggressive behavior. However, a low mitotic index is of little prognostic value, and many malignant tumors show little to no mitotic activity. Mitotic activity has also been proposed as the basis for a grading scheme for foregut endocrine tumors, including pancreatic endocrine tumors.[10]

Mitotic count 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.
Ki67 index is reported as percentage of positive tumor cells in area of highest nuclear labeling. It has been recommended that 2000 tumor cells be counted to determine the Ki67 index;[10] however, this practice may not be practical for routine clinical purposes, and it is acceptable to estimate the labeling index.

H. Tumor Necrosis

Tumor necrosis is uncommon in low-grade pancreatic endocrine neoplasms but is generally regarded as a malignancy-associated 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 malignant pancreatic endocrine tumors, complete resection of tumor is a strong determinant of long-term survival.[11,12] 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.[1]

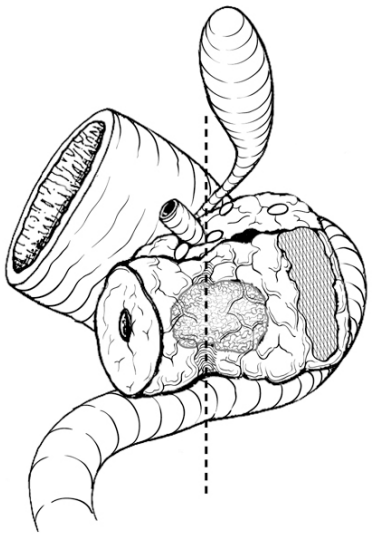


Figure 2. Posterior view of tumor arising in the pancreatic head, with dotted line indicating the location of the confluence of the portal and superior mesenteric veins. The hatched area shows the retroperitoneal (uncinate process) margin. From: Greene FL, Compton, CC, Fritz AG, et al, eds. *AJCC Cancer Staging Atlas.* New York: Springer; 2006. Copyright © American Joint Committee on Cancer. Used with permission.

J. Blood Vessel Invasion

The presence of blood vessel invasion,[13] 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.[14]

K. Perineural Invasion

Perineural invasion has been associated with malignancy and with shortened survival in some series[16] of pancreatic endocrine 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 endocrine tumors, as shown below.[3] The post-resection 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)

TX Primary tumor cannot be assessed
T0 No evidence of primary tumor
T1 Tumor limited to the pancreas, 2 cm or less in greatest dimension[##]
T2 Tumor limited to the pancreas, more than 2 cm in greatest dimension[##]
T3 Tumor extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery[###]
T4 Tumor involves the celiac axis or the superior mesenteric artery (unresectable primary tumor)^

[#] 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.[4,6]

[###] 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.[3]

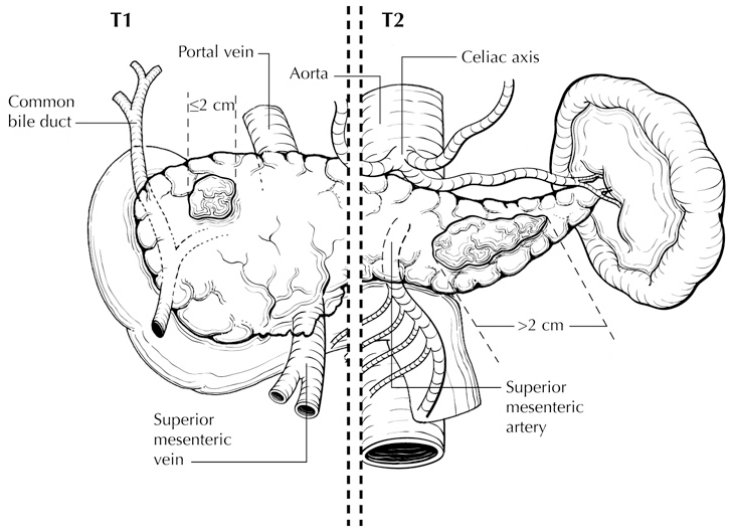
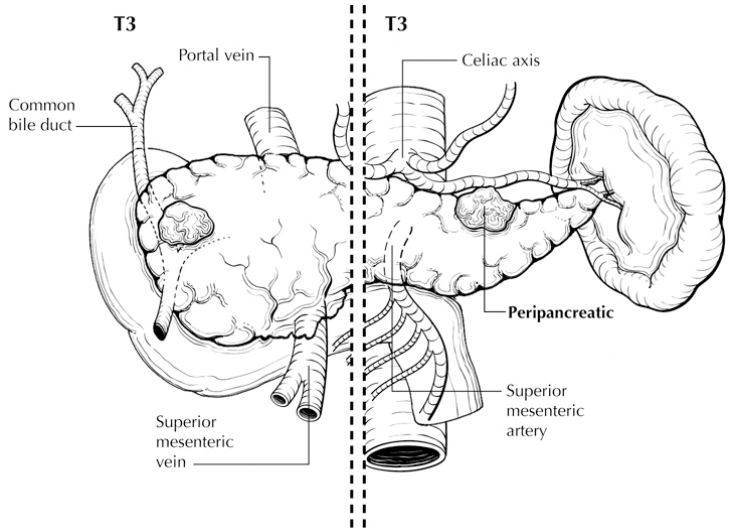
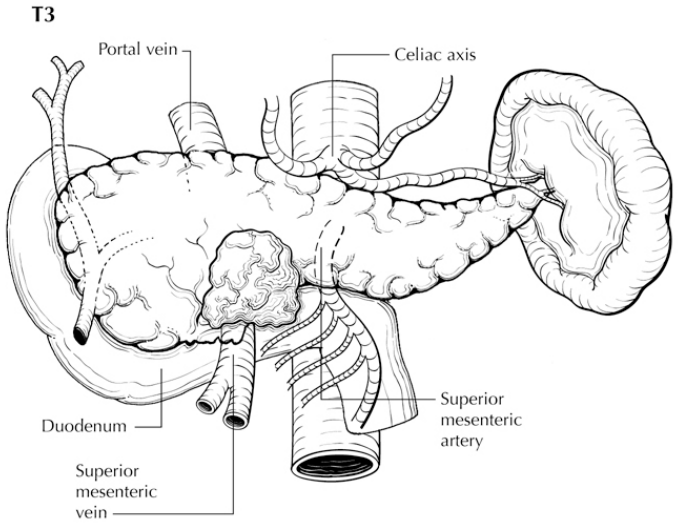


Figure 3. T1 (left of dotted line) is defined as tumor measuring 2 cm or less in greatest dimension and limited to the pancreas. T2 (right of dotted line) is defined as tumor measuring more than 2 cm in greatest dimension and limited to the pancreas. From: Greene FL, Compton, CC, Fritz AG, et al, eds. *AJCC Cancer Staging Atlas.* New York: Springer; 2006. Copyright © American Joint Committee on Cancer. Used with permission.

A.



B.



C.

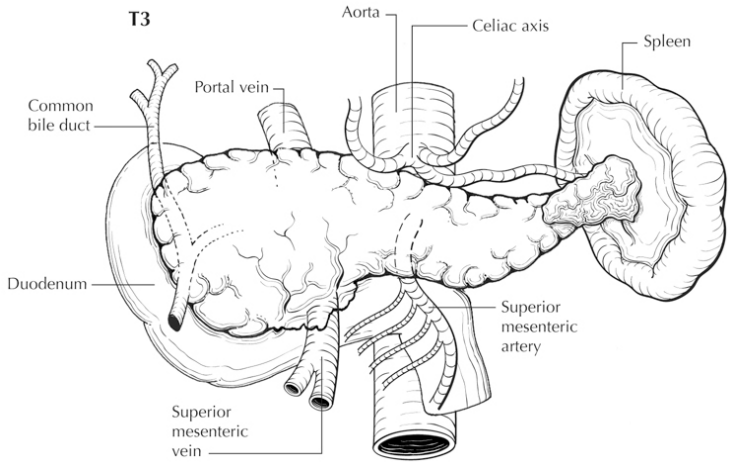


Figure 4. T3 is defined as tumor that extends beyond the pancreas but without involvement of the celiac axis or superior mesenteric artery. A. To the left of the dotted line, tumor invades the common bile duct without involving the superior mesenteric artery. To the right of the dotted line, tumor invades 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 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.

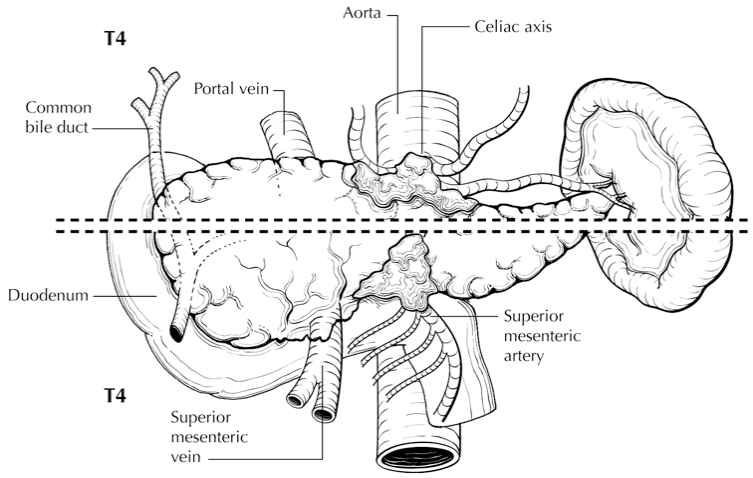


Figure 5. T4 tumor involves the celiac axis (above dotted line) or the superior mesenteric artery (below dotted line). T4 tumors are considered unresectable and are rarely encountered in surgical pathology specimens. From: Greene FL, Compton, CC, Fritz AG, et al, eds. *AJCC Cancer Staging Atlas.* New York: Springer; 2006. Copyright © American Joint Committee on Cancer. Used with permission.

Regional Lymph Nodes (N)[#] (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, pancreaticolieno 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.[2,12] The minimum number of lymph nodes needed for adequate staging for pancreatic endocrine tumors in pancreaticoduodenectomy specimens has not been determined, although a minimum of 12 lymph nodes has been suggested for pancreatic adenocarcinoma specimens.

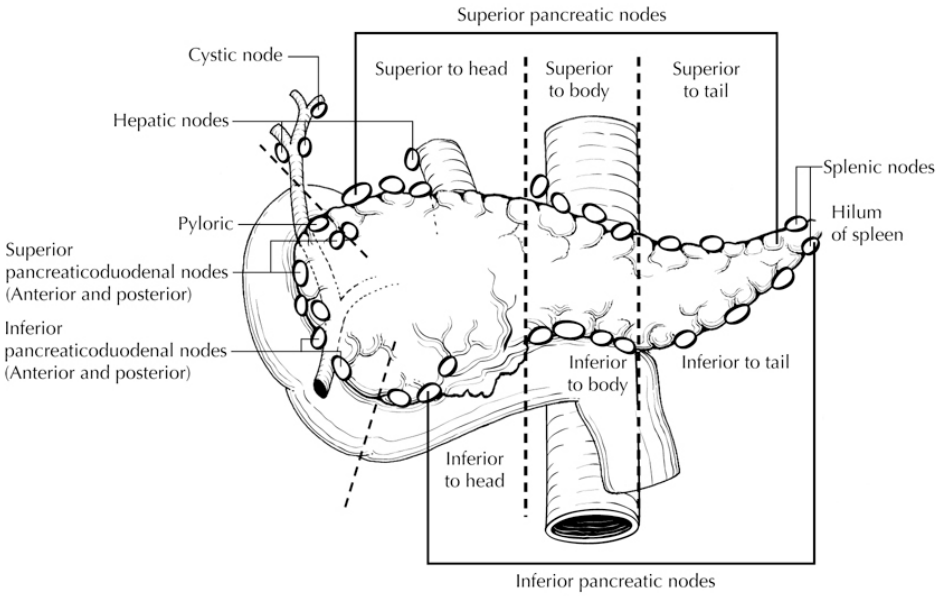


Figure 6. Regional lymph nodes of the pancreas (anterior view). From: Greene FL, Compton, CC, Fritz AG, et al, eds. *AJCC Cancer Staging Atlas.* New York: Springer; 2006. Copyright © American Joint Committee on Cancer. Used with permission.

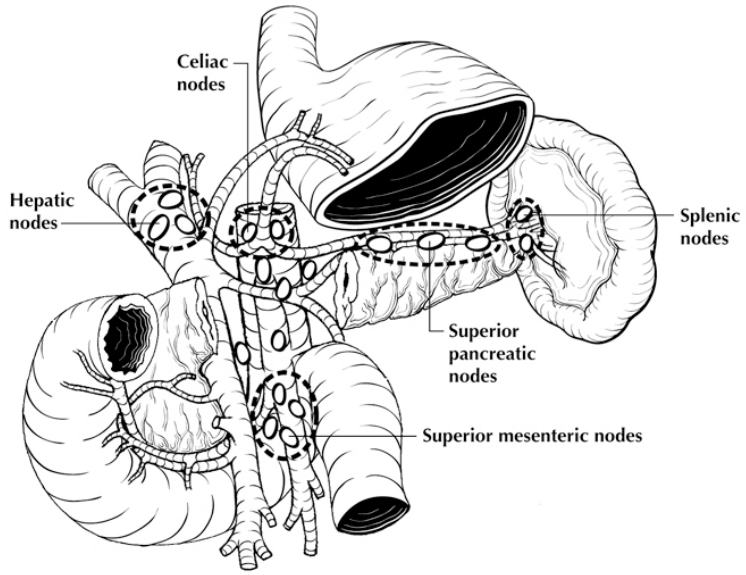


Figure 7. Regional lymph nodes of the pancreas (anterior view with pancreatic body removed to reveal retroperitoneal vessels and lymph nodes). From: Greene FL, Compton, CC, Fritz AG, et al, eds. *AJCC Cancer Staging Atlas.* New York: Springer; 2006. Copyright © American Joint Committee on Cancer. Used with permission.

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.[6]

Anatomic Stage/Prognostic Groupings

Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage III	T4	Any N	M0
Stage IV	Any T	Any N	M1

Additional Descriptors

Residual Tumor (R)

Tumor remaining in a patient after therapy with curative intent (eg, 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 endocrine neoplasms are strongly positive for synaptophysin and chromogranin A. Some investigators,[8, 16] but not all,[15] have found that expression of cytokeratin 19, which is found in normal pancreatic ductal cells but not in pancreatic endocrine cells, is strongly predictive of poor outcome. It is hypothesized that CK19 positivity in pancreatic endocrine tumors may indicate differentiation along pancreatic ductal lines, thus accounting for the poorer outcome.

Ki67 is used routinely by some investigators to assess proliferative activity in pancreatic endocrine tumors,[1,8,10,15-17] but it is unclear if use of the Ki67 index is superior to assessment of mitotic activity in routinely stained sections.

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 endocrine tumors of the pancreas is not known. However, MEN 1, von Hippel-Lindau disease, and, more rarely, neurofibromatosis type 1[1] are associated with pancreatic endocrine 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 endocrine tumor is associated with a functional syndrome, which is an important predictor of malignancy (see Note F). In particular, insulinomas behave in a benign fashion, probably because they are discovered early due to the production of a hypoglycemic state. Other functioning tumors are generally malignant.

References

1. Heitz PU, Komminoth P, Perren A, et al. Tumours of the endocrine pancreas. In: DeLellis RA, Lloyd RV, Heitz PU, Eng C, eds. *World Health Organization Classification of Tumours: Pathology and Genetics of Tumours of Endocrine Organs*. Lyon, France: IARC Press; 2004:177-182.
2. Bilimoria KY, Bentrem DJ, Merkow RP, et al. Application of the pancreatic adenocarcinoma staging system to pancreatic neuroendocrine tumors. *J Am Coll Surg.* 2007;205(4):558-563.
3. Edge SB, Byrd DR, Carducci MA, Compton CC, eds. *AJCC Cancer Staging Manual*. 7th ed. New York, NY: Springer; 2009.
4. Panzuto F, Nasoni S, Falconi M, et al. Prognostic factors and survival in endocrine tumor patients: comparison between gastrointestinal and pancreatic localization. *Endocr Relat Cancer.* 2005;12(4):1083-1092.
5. Buetow PC, Parrino TV, Buck JL, et al. Islet cell tumors of the pancreas: pathologic-imaging correlation among size, necrosis and cysts, calcification, malignant behavior, and functional status. *AJR Am J Roentgenol.* Nov 1995;165(5):1175-1179.
6. Hruban RH, Pitman MB, Klimstra DS. *Tumors of the Pancreas.* Fourth series, Fascicle 6 ed. Washington, DC: Armed Forces Institute of Pathology; 2007.
7. Ferrone CR, Tang LH, Tomlinson J, et al. Determining prognosis in patients with pancreatic endocrine neoplasms: can the WHO classification system be simplified? *J Clin Oncol.* Dec 2007;25(35):5609-5615.
8. Schmitt AM, Anlauf M, Rousson V, et al. WHO 2004 criteria and CK19 are reliable prognostic markers in pancreatic endocrine tumors. *Am J Surg Pathol.* Nov 2007;31(11):1677-1682.
9. Heitz PU, Kasper M, Polak JM, Kloeppel G. Pancreatic endocrine tumors: immunocytochemical analysis of 125 tumors. *Hum Pathol.* 1982;13:263-271.

10. Rindi G, Kloppel G, Ahlman H, et al. TNM staging of foregut (neuro)endocrine tumors: a consensus proposal including a grading system. *Virchows Archiv.* Oct 2006;449(4):395-401.
11. Chung JC, Choi DW, Jo SH, Heo JS, Choi SH, Kim YI. Malignant nonfunctioning endocrine tumors of the pancreas: predictive factors for survival after surgical treatment. *World J Surg.* 2007;31(3):579-585.
12. Tomassetti P, Campana D, Piscitelli L, et al. Endocrine pancreatic tumors: factors correlated with survival. *Ann Oncol.* Nov 2005;16(11):1806-1810.
13. Kazanjian KK, Reber HA, Hines OJ. Resection of pancreatic neuroendocrine tumors: results of 70 cases. *Arch Surg.* 2006;141(8):765-769; discussion 769-770.
14. La Rosa S, Sessa F, Capella C, et al. Prognostic criteria in nonfunctioning pancreatic endocrine tumours. *Virchows Arch.* 1996;429(6):323-333.
15. La Rosa S, Rigoli E, Uccella S, Novario R, Capella C. Prognostic and biological significance of cytokeratin 19 in pancreatic endocrine tumours. *Histopathology.* Apr 2007;50(5):597-606.
16. Deshpande V, Fernandez-del Castillo C, Muzikansky A, et al. Cytokeratin 19 is a powerful predictor of survival in pancreatic endocrine tumors. *Am J Surg Pathol.* Sep 2004;28(9):1145-1153.
17. Bordi C, D'Adda T, Azzoni C, et al. Criteria for malignancy in gastrointestinal endocrine tumors. *Endocr Pathol.* 2006;17(2):119-129.