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

Protocol applies to all epithelial tumors of the exocrine pancreas. Endocrine tumors and tumors of the ampulla of Vater are not included.

Based on AJCC/UICC TNM, 7th edition
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Procedures
- Partial Pancreatectomy
- Pancreaticoduodenectomy (Whipple Resection)
- Total Pancreatectomy

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Surgical Pathology Cancer Case Summary (Checklist)

Protocol web posting date: October 2009

PANCREAS (EXOCRINE): 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
___ 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
Greatest dimension: ___ cm
*Additional dimensions: ___ x ___ cm
___ Cannot be determined (see Comment)

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

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

___ Ductal adenocarcinoma
___ Mucinous noncystic carcinoma
___ Signet-ring cell carcinoma
___ Adenosquamous carcinoma
___ Undifferentiated (anaplastic) carcinoma
___ Undifferentiated carcinoma with osteoclast-like giant cells
___ Mixed ductal-endocrine carcinoma
___ Serous cystadenocarcinoma
___ Mucinous cystic neoplasm
    ___ Noninvasive
    ___ Invasive
___ Intraductal papillary-mucinous carcinoma
    ___ Noninvasive
    ___ Invasive
___ Acinar cell carcinoma
___ Acinar cell cystadenocarcinoma
___ Mixed acinar-endocrine carcinoma
___ Other (specify): _____

Histologic Grade (ductal carcinoma only) (Note D)

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

Microscopic Tumor Extension (select all that apply)

___ Cannot be assessed
___ No evidence of primary tumor
___ Carcinoma in situ
___ Tumor is confined to pancreas
___ Tumor invades ampulla of Vater or sphincter of Oddi
___ Tumor invades duodenal wall
___ Tumor invades peripancreatic soft tissues
    *___ Tumor invades retroperitoneal soft tissue
    *___ Tumor invades mesenteric adipose tissue
    *___ Tumor invades mesocolon
    *___ Tumor invades other peripancreatic soft tissue (specify):_____
    ___ Tumor invades extrapancreatic common bile duct
___ Tumor invades other adjacent organs or structures (specify):_____

* 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.

Margins (select all that apply) (Note E)
___ Cannot be assessed
___ Margins uninvolved by invasive carcinoma
Distance of invasive carcinoma from closest margin: ___ mm
*Specify margin (if possible): _____
___ Margins uninvolved by carcinoma in situ
___ Margin(s) involved by carcinoma in situ
___ Carcinoma in situ present at common bile duct margin
___ Carcinoma in situ present at pancreatic parenchymal margin
___ Margin(s) involved by invasive carcinoma
___ Uncinate process (retroperitoneal) margin (nonperitonealized surface of the uncinate process)
___ Distal pancreatic margin
___ Common bile duct margin
___ Proximal pancreatic margin
___ Other (specify): _____
*___ Invasive carcinoma involves posterior retroperitoneal surface of pancreas

Treatment Effect (applicable to carcinomas treated with neoadjuvant therapy) (select all that apply) (Note F)
___ No prior treatment
___ Present
*____ No residual tumor (complete response, grade 0)
*____ Marked response (grade 1, minimal residual cancer)
*____ Moderate response (grade 2)
___ No definite response identified (grade 3, poor or no response)
___ Not known

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

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

Pathologic Staging (pTNM) (Note I)

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

* 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
___ pTis: Carcinoma in situ
___ 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) (Note J)**
*___ None identified
*___ Pancreatic intraepithelial neoplasia (highest grade: PanIN ___)
*___ Chronic pancreatitis
*___ Acute pancreatitis
*___ Other (specify): _____

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

Clinical History (select all that apply) (Note L)
___ Neoadjuvant therapy
___ Familial pancreatitis
___ Familial pancreatic cancer syndrome
___ Other (specify): _____
___ Not specified

***Comment(s)**

Explanatory Notes

A. Tumors

This protocol applies to epithelial tumors of the exocrine pancreas. It excludes endocrine tumors and tumors of the ampulla of Vater. More than 90% to 95% of malignant tumors of the pancreas are exocrine carcinomas.[1] For these tumors, surgical resection remains the only potentially curative approach, and the prognosis is primarily dependent on the anatomic extent of disease and performance status.[2]

B. Definition of Location

The anatomic subdivisions defining location of tumors of the pancreas (Figure 1) 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.

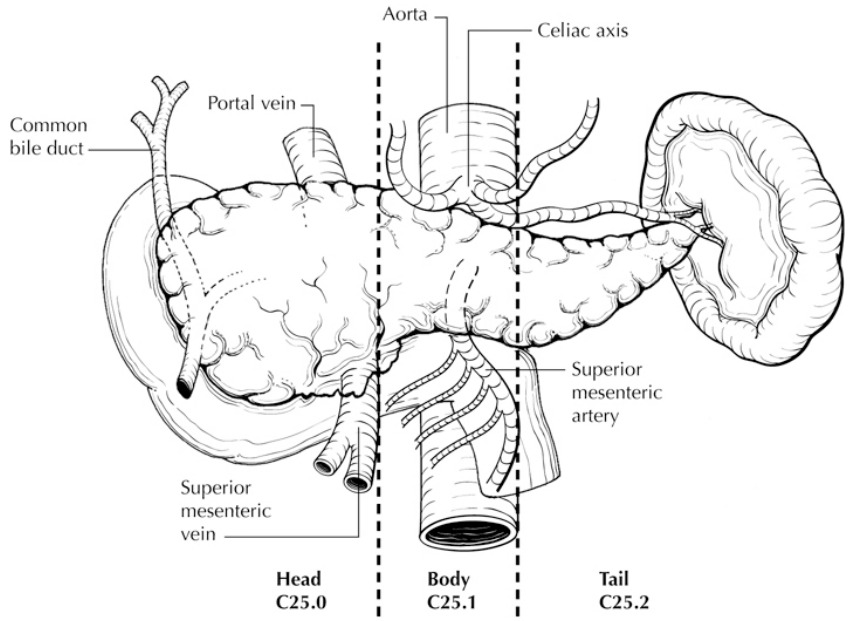


Figure 1. Anatomic subsites of the pancreas. From: Greene FL, Compton, CC, Fritz AG, et al, eds. *AJCC Cancer Staging Atlas.* New York: Springer; 2006. Copyright © American Joint Committee on Cancer. Used with permission.

C. Histologic Type

A classification of malignant and borderline (uncertain malignant potential) epithelial tumors of the exocrine pancreas recommended by the World Health Organization (WHO) is shown below.[4] However, this protocol does not preclude the use of other histologic types or systems of classification.

WHO Classification of Epithelial Tumors of the Exocrine Pancreas

Malignant Tumors
Ductal adenocarcinoma
- Mucinous noncystic carcinoma
- Signet-ring cell carcinoma[#]
- Adenosquamous carcinoma
- Undifferentiated (anaplastic) carcinoma[##]
- Undifferentiated carcinoma with osteoclast-like giant cells
- Mixed ductal-endocrine carcinoma

Serous cystadenocarcinoma[###]
Mucinous cystadenocarcinoma[###]
- Noninvasive
- Invasive

Intraductal papillary-mucinous carcinoma[###]
- Noninvasive
- Invasive (papillary-mucinous carcinoma)

Acinar cell carcinoma[###]
- Acinar cell cystadenocarcinoma[###]
- Mixed acinar-endocrine carcinoma[###]

Pancreatoblastoma[###]
Solid pseudopapillary carcinoma[###]
Others

[#] By convention, signet-ring cell carcinomas are assigned grade 3 (see below).

[##] By definition, undifferentiated carcinomas are grade 4 (see below).

[###] These histologic types are not usually graded.

D. Histopathologic Grade
For adenocarcinomas, a histologic grade based on the extent of glandular differentiation is suggested, as shown below:[3]

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

Tumors with no differentiation or minimal differentiation that is discernible only in rare, tiny foci (undifferentiated carcinomas by WHO classification) are categorized as grade 4.

For pancreatic ductal carcinoma, histologic grade has been shown to have prognostic significance, with high grade (grades 3 and 4) being an unfavorable prognostic factor.[5,6] In comparisons between the Klöppel grading system and the TNM grading system, no differences in predictive value have been demonstrated.[6] Other systems based on patterns of infiltration of predominant and secondary tumor patterns have been proposed[5] but not widely adopted to date.

E. Margins

The nonperitonealized surface of the uncinate process (uncinate margin) constitutes the retroperitoneal margin for pancreaticoduodenectomy specimens (Figure 2) and should be inked; sections through the tumor at its closest approach to this margin should be submitted.[3]

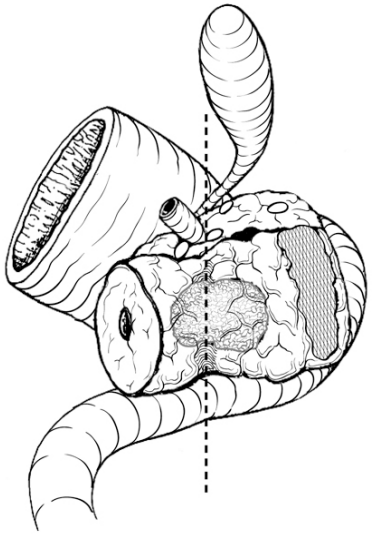


Figure 2. Posterior view of tumor arising in the pancreatic head, with dotted line indicating the location of the confluence of the portal and superior mesenteric veins. The hatched area shows the retroperitoneal (uncinate process) margin. From: Greene FL, Compton, CC, Fritz AG, et al, eds. *AJCC Cancer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

Because local recurrences of invasive pancreatic adenocarcinoma arise in the pancreatic bed corresponding to the retroperitoneal margin and to the deep retroperitoneal posterior surface of the pancreas, the American Joint Committee on Cancer (AJCC) and this protocol also recommend inking the posterior surface of the pancreas and submission of sections through the tumor at its closest approach to this surface, as well as the retroperitoneal (uncinate) margin.

When dealing with an intraductal tumor, the distal resection margin, the common bile duct margin (Whipple resection), or the proximal resection margin of the pancreas (distal pancreatectomy) are the most critical. Complete en face sections through the pancreatic margin and the common bile duct margin should be taken.

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.[7] The following system is suggested:

Tumor Regression Grade

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

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

This protocol does not preclude the use of other systems for assessment of tumor response, such as the scheme reported by investigators at MD Anderson Cancer Center.[8]

G. Venous/Lymphatic Vessel Invasion

Venous/lymphatic (small vessel) invasion has been shown to be an adverse prognostic factor.[9]

H. Perineural Invasion

Perineural invasion has been shown to be an adverse prognostic factor.[9]

I. TNM and Anatomic Stage/Prognostic Groupings

The TNM staging system for carcinoma of the exocrine pancreas of the AJCC and the International Union Against Cancer (UICC) is recommended and 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.[3,10]

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.

Primary Tumor[#] (T) (Figures 3 through 5)

TX Primary tumor cannot be assessed
T0 No evidence of primary tumor
Tis Carcinoma in situ[##]
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]). This applies only to grossly recognizable, synchronous primary carcinomas and not to a single, grossly detected tumor with multiple separate microscopic foci.[11]

Multiple synchronous carcinomas of the exocrine pancreas may be[11]:

- Multiple noninvasive tumors
- Multiple invasive tumors
- Multiple invasive tumors with associated carcinoma in situ

[##] PanIN-3 (see Note D) is the equivalent of carcinoma in situ and should be assigned pTis.

[###] Tumor size has been shown to have independent prognostic significance.[12-14]

^ For T3, extension beyond the pancreas may include invasion of soft tissues adjacent to the pancreas, the extrapancreatic biliary system, 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.[3]

^^ Invasion of the portal vein also has been shown to have independent prognostic significance as an adverse factor.[15]

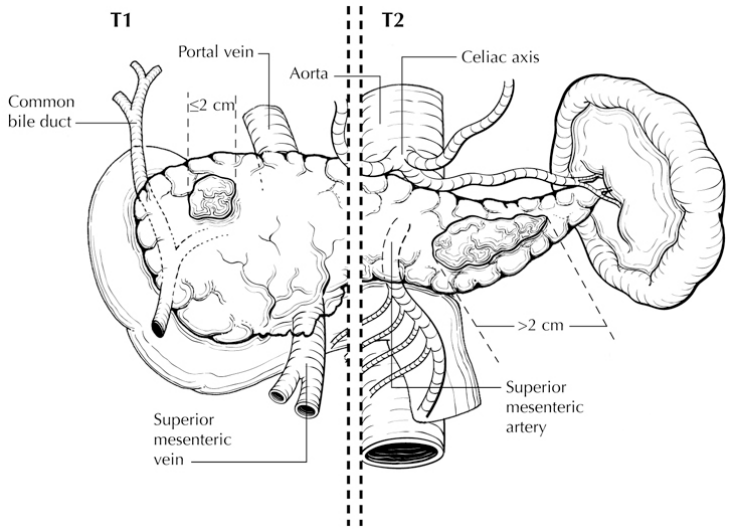
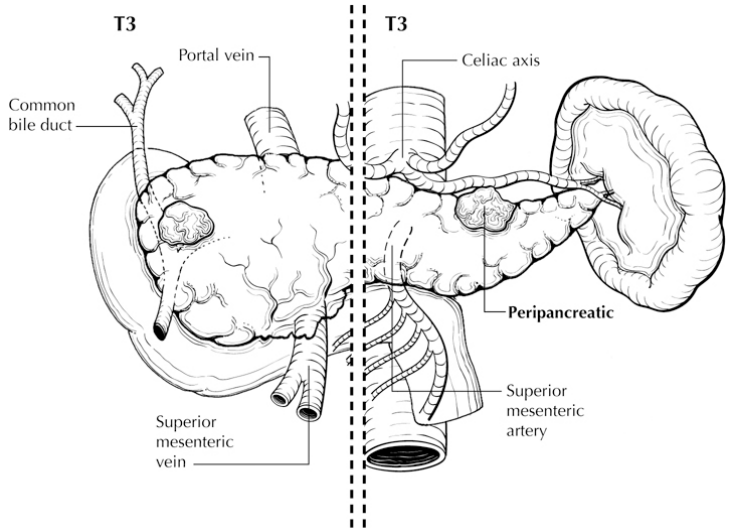


Figure 3. T1 (left of dotted line) is defined as tumor measuring 2 cm or less in greatest dimension and limited to the pancreas. T2 (right of dotted line) is defined as tumor measuring more than 2 cm in greatest dimension and limited to the pancreas. From: Greene FL, Compton, CC, Fritz AG, et al, eds.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

A.



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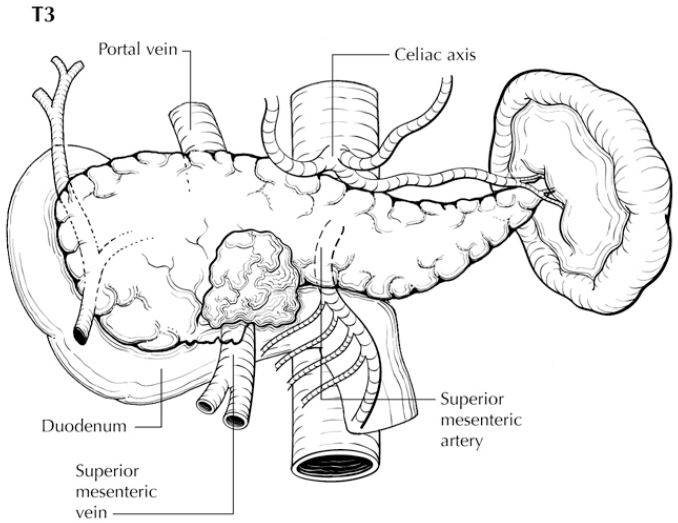

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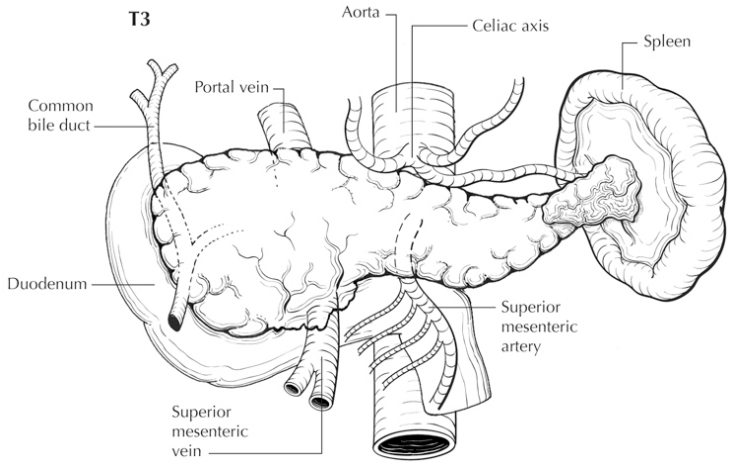

Figure 4. T3 is defined as tumor that extends beyond the pancreas but without involvement of the celiac axis or superior mesenteric artery. A. To the left of the dotted line, tumor invades the common bile duct without involving the superior mesenteric artery. To the right of the dotted line, tumor invades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

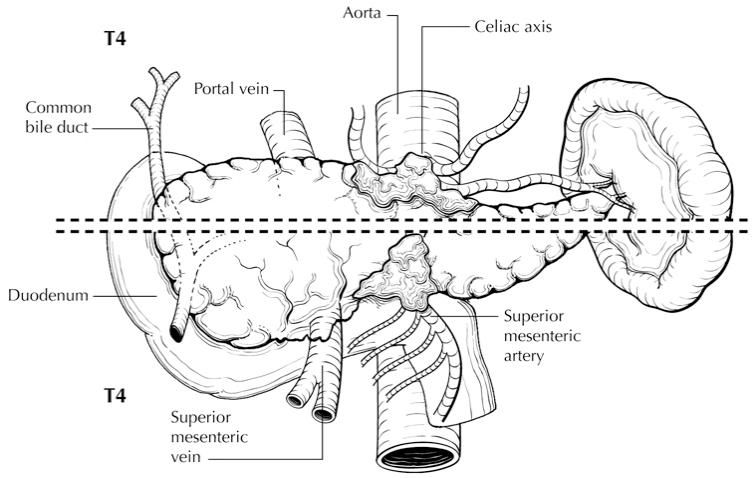

Figure 5. T4 tumor involves the celiac axis (above dotted line) or the superior mesenteric artery (below dotted line). T4 tumors are considered unresectable and are rarely encountered in surgical pathology specimens. From: Greene FL, Compton, CC, Fritz AG, et al, eds. *AJCC Cancer Staging Atlas.* New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

Regional Lymph Nodes (N)[#]

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 (Figures 6 and 7):

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.[9,12,14,16-18] A minimum of 15 lymph nodes has been suggested to achieve optimal staging for node-negative pancreatic cancer;[19] however, this proposed guideline requires further study before its widespread adoption is recommended.

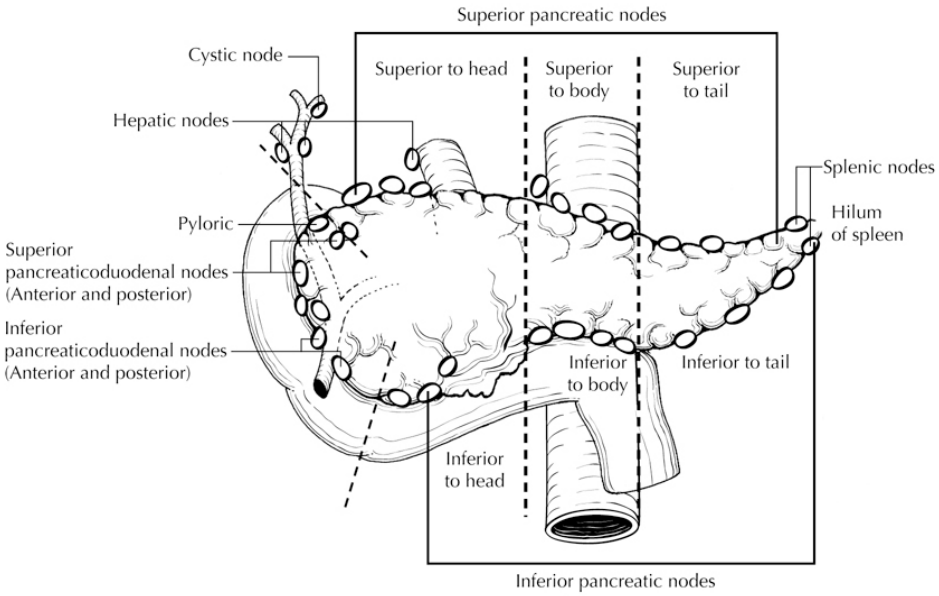

Figure 6. Regional lymph nodes of the pancreas (anterior view). From: Greene FL, Compton, CC, Fritz AG, et al, eds. *AJCC Cancer Staging Atlas.* New York: Springer; 2006. Copyright © American Joint Committee on Cancer. Used with permission.

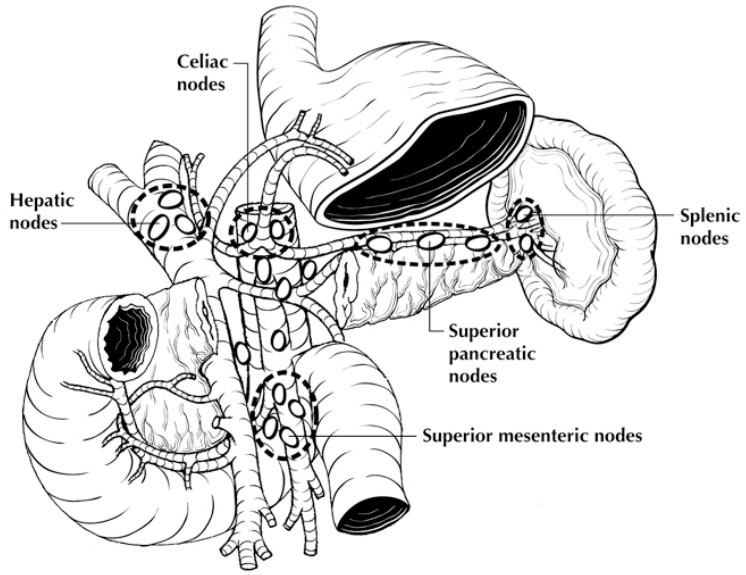

Figure 7. Regional lymph nodes of the pancreas (anterior view with pancreatic body removed to reveal retroperitoneal vessels and lymph nodes). From: Greene FL, Compton, CC, Fritz AG, et al, eds. *AJCC Cancer Staging Atlas.* New York: Springer; 2006. Copyright © American Joint Committee on Cancer. Used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

Distant Metastasis (M)

M0 No distant metastasis
M1 Distant metastasis[#]

[#] Peritoneal seeding or ascitic peritoneal fluid containing cytologic evidence of malignancy is considered M1.[11] Positive peritoneal cytology in patients without ascites is also considered M1 because the data suggest that this finding predicts a short survival.[3]

Stage Groupings

Stage 0	Tis	N0	M0
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

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.

Vessel Invasion

According to AJCC/UICC convention, vessel invasion (lymphatic or venous) does not affect the T category indicating local extent of tumor unless specifically included in the definition of a T category.

J. Additional Pathologic Findings

Pancreatic Intraepithelial Neoplasia (PanIN)

Noninvasive dysplastic lesions of the ductal epithelium often are found in the pancreatic parenchyma surrounding ductal adenocarcinoma. These lesions are collectively known as pancreatic intraepithelial neoplasia (PanIN). PanINs have been classified at a National Cancer Institute Think Tank as follows:[20]

Normal	Nonmucinous flattened or cuboidal epithelium without dysplasia
PanIN-1A	Flat mucinous epithelium without dysplasia
PanIN-1B	Papillary mucinous epithelium without dysplasia
PanIN-2	Flat or papillary mucinous epithelium with mild-to-moderate dysplasia (mild-to-moderate nuclear irregularity, hyperchromasia, and loss of polarity)
PanIN-3	Flat or papillary mucinous epithelium with severe dysplasia (marked nuclear irregularity, hyperchromasia, and loss of polarity), often with cribriforming and intraluminal blebbing (budding off of noncohesive cells)

PanINs are thought to progress from flat to papillary lesions with increasing degrees of dysplasia and increasing numbers of alterations in cancer-associated genes. PanINs are believed to be the precursor lesions of ductal adenocarcinoma of the pancreas. Many of the cytological changes included in the PanIN spectrum are seen in cystic tumors of the pancreas, such as mucinous cystic neoplasms and papillary mucinous neoplasms, but PanINs, by definition, occur in nondilated ducts.

PanIN occurring at the resection margins of an otherwise completely resected malignancy should be noted in the pathology report. In this setting, the biologic significance of low-grade PanIN remains unclear, because these ductal changes may be seen in pancreata with benign lesions, but PanIN-3 is the equivalent of carcinoma in situ and should be reported as Tis.

Other Findings

In addition to the examination of other tissues and organs that are part of pancreaticoduodenectomy specimens, pathologic evaluation may also include examination of the gastric antrum for gastritis (eg, *Helicobacter pylori* gastritis or chemical gastritis) and the duodenum for duodenitis, peptic ulcer disease, and ampullitis.

K. Ancillary Studies

No specific molecular or immunohistochemical studies are recommended at this time for pancreatic cancer.

L. Clinical History

Predisposing conditions for pancreatic cancer include familial pancreatic cancer syndromes, which are relatively rare and account for less than 10% of cases.[1] Germline mutations in BRCA2 and p16 have been linked to increased risk, and patients with hereditary pancreatitis have at least a 4-fold higher risk. Pre-existing chronic pancreatitis probably accounts for a small minority of cases. Diabetes mellitus and smoking have also been associated with increased risk.

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