Pancreas (Exocrine)

Protocol applies to all carcinomas of the exocrine pancreas.

Protocol revision date: January 2004
Based on AJCC/UICC TNM, 6th edition

Procedures

- **Cytology** (No Accompanying Checklist)
- **Incisional Biopsy** (No Accompanying Checklist)
- **Partial Pancreatectomy**
- **Pancreaticoduodenectomy (Whipple Resection)**

Author
Carolyn C. Compton, MD, PhD
Department of Pathology, McGill University, Montreal, Quebec, Canada
For the Members of the Cancer Committee, College of American Pathologists

Previous contributors: Donald E. Henson, MD; Carlos Fernandez-del Castillo, MD; Andrew L. Warshaw, MD; Christopher Willett, MD

Surgical Pathology Cancer Case Summary (Checklist)

Protocol revision date: January 2004
Applies to invasive carcinomas only
Based on AJCC/UICC TNM, 6th edition

PANCREAS (EXOCRINE): Resection

Patient name:
Surgical pathology number:

Note: Check 1 response unless otherwise indicated.

MACROSCOPIC

Specimen Type
___ Pancreaticoduodenectomy (Whipple resection), partial pancreatectomy
___ Pancreaticoduodenectomy (Whipple resection), total pancreatectomy
___ Pylorus sparing pancreaticoduodenectomy, partial pancreatectomy
___ Pylorus sparing pancreaticoduodenectomy, total pancreatectomy
___ Partial pancreatectomy, pancreatic body
___ Partial pancreatectomy, pancreatic tail
___ Other (specify): _____
___ Not specified

Tumor Site (check all that apply)
___ Pancreatic head
___ Uncinate process
___ Pancreatic body
___ Pancreatic tail
___ Not specified

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

***Other Organs Resected**
*___ None
*___ Spleen
*___ Gallbladder
*___ Other(s) (specify): _____

* Data elements ***with asterisks*** are ***not required*** for accreditation purposes for the Commission on Cancer. These elements may be clinically important, but are not yet validated or regularly used in patient management. Alternatively, the necessary data may not be available to the pathologist at the time of pathologic assessment of this specimen.

MICROSCOPIC

Histologic Type

___ 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 – invasive
___ Invasive papillary-mucinous carcinoma
___ Acinar cell carcinoma
___ Acinar cell cystadenocarcinoma
___ Mixed acinar-endocrine carcinoma
___ Other (specify): _____
___ Carcinoma, type cannot be determined

Histologic Grade (ductal carcinoma only)

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

Pathologic Staging (pTNM)

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
___ N1a: Metastasis in single regional lymph node
___ N1b: Metastasis in multiple regional lymph nodes
Specify: Number examined ___

* Data elements ***with asterisks*** are ***not required*** for accreditation purposes for the Commission on Cancer. These elements may be clinically important, but are not yet validated or regularly used in patient management. Alternatively, the necessary data may not be available to the pathologist at the time of pathologic assessment of this specimen.

Number involved: ___

* Data elements ***with asterisks*** are ***not required*** for accreditation purposes for the Commission on Cancer. These elements may be clinically important, but are not yet validated or regularly used in patient management. Alternatively, the necessary data may not be available to the pathologist at the time of pathologic assessment of this specimen.

Distant Metastasis (pM)
___ pMX: Cannot be assessed
___ pM1: Distant metastasis
*Specify site(s), if known: _____

Margins (check all that apply)
___ Cannot be assessed
___ Margins uninvolved by invasive carcinoma
Distance of invasive carcinoma from closest margin: ___ mm
*Specify margin (if possible): _____
___ Carcinoma in situ absent at ductal margins
___ Carcinoma in situ present at common bile duct margin
___ Carcinoma in situ present at pancreatic parenchymal margin
___ Margin(s) involved by invasive carcinoma
___ Posterior retroperitoneal (radial) margin: posterior surface of pancreas
___ Uncinate process margin (non-peritonealized surface of the uncinate process)
___ Distal pancreatic margin
___ Common bile duct margin
___ Proximal pancreatic margin
___ Other (specify): _____

***Venous/Lymphatic (Large/Small Vessel) Invasion (V/L)**
*___ Absent
*___ Present
*___ Indeterminate

***Perineural Invasion**
*___ Absent
*___ Present

***Additional Pathologic Findings (check all that apply)**
*___ None identified
*___ Pancreatic intraepithelial neoplasia (highest grade: PanIN ___)
*___ Chronic pancreatitis
*___ Acute pancreatitis
*___ Other (specify): _____

***Comment(s)**

Background Documentation

Protocol revision date: January 2004

I. Cytologic Material

A. Clinical Information

1. Patient identification
   a. Name
   b Identification Number
   c. Age (birth date)
   d. Sex
2. Responsible physician(s)
3. Date of procedure
4. Other clinical information
   a. Clinical history
      (1) jaundice
      (2) pancreatitis
      (3) previous pancreatic or biliary surgery
      (4) pseudocyst drainage
      (5) diabetes mellitus
   b. Clinical findings (eg, endoscopic retrograde cholangiopancreatography [ERCP] and/or imaging studies)
   c. Clinical diagnosis
   d. Procedure (eg, brushing, washing, other)
   e. Operative findings

B. Macroscopic Examination

1. Specimen
   a. Unfixed/fixed (specify fixative)
   b. Number of slides received, if appropriate
   c. Quantity and appearance of fluid specimen, if appropriate
   d. Other (eg, cytologic preparation from tissue)
   e. Results of intraprocedural consultation
2. Material submitted for microscopic evaluation
3. Special studies (specify) (eg, cytochemistry, immunocytochemistry)

C. Microscopic Evaluation

1. Adequacy of specimen (if unsatisfactory for evaluation, specify reason)
2. Tumor, if present (Note **A**)
   a. Histologic type, if possible (Note **B**)
   b. Histologic grade, if possible (Note **C**)
   c. Other features (eg, necrosis)
3. Additional pathologic findings, if present
4. Results/status of special studies (specify)
5. Comments
   a. Correlation with intraprocedural consultation, as appropriate
   b. Correlations with other specimens, as appropriate
   c. Correlation with clinical information, as appropriate

II. Incisional Biopsy

A. Clinical Information

1. Patient identification
   a. Name
   b. Identification Number
   c. Age (birth date)
   d. Sex
2. Responsible physician(s)
3. Date of procedure
4. Other clinical information
   a. Clinical history
      (1) jaundice
      (2) pancreatitis
      (3) previous pancreatic or biliary surgery
      (4) pseudocyst drainage
      (5) diabetes mellitus
   b. Clinical findings (eg, ERCP and/or imaging studies)
   c. Procedure (eg, ERCP biopsy, wedge biopsy)
   d. Operative findings
   e. Anatomic site(s) of specimen(s)

B. Macroscopic Examination

1. Specimen
   a. Unfixed/fixed (specify fixative)
   b. Number of pieces
   c. Largest dimension of each piece
   d. Results of intraoperative consultation
2. Tissues submitted for microscopic evaluation
   a. Submit entire specimen
   b. Frozen section tissue fragment(s) (unless saved for special studies)
3. Special studies (specify) (eg, histochemistry, immunohistochemistry)

C. Microscopic Evaluation

1. Tumor (Note A)
   a. Histologic type (Note B)
   b. Histologic grade (Note **C**)
   c. Invasion
2. Additional pathologic findings, if present
   a. Pancreatic intraepithelial neoplasia (PanIN) (Note **D**)
   b. Metaplasia
   c. Pancreatitis
   d. Other(s)
3. Results/status of special studies (specify)
4. Comments
   a. Correlation with intraoperative consultation, as appropriate
   b. Correlation with other specimens, as appropriate
   c. Correlation with clinical information, as appropriate

III. Partial Pancreatectomy
(Distal or Left Pancreatectomy)

A. Clinical Information

1. Patient identification
   a. Name
   b. Identification Number
   c. Age (birth date)
   d. Sex
2. Responsible physician(s)
3. Date of procedure
4. Other clinical information
   a. Clinical history
      (1) jaundice
      (2) pancreatitis
      (3) previous pancreatic or biliary surgery
      (4) pseudocyst drainage
      (5) diabetes mellitus
   b. Clinical findings (eg, ERCP and/or imaging studies)
   c. Clinical diagnosis
   d. Procedure (eg, distal pancreatectomy, local excision of tumor)
   e. Operative findings
   f. Anatomic site(s) of specimen(s)

B. Macroscopic Examination

1. Specimen
   a. Organs/tissues received (specify)
   b. Unfixed/fixed (specify fixative)
   c. Number of pieces
   d. Dimensions
   e. Orientation of specimen, if indicated by surgeon
   f. Results of intraoperative consultation
2. Tumor (Note **A**)
   a. Location (Note **E**)
   b. Configuration (Note **F**)
   c. Dimensions (best estimate) (Note **G**)
   d. Descriptive features (eg, color, consistency, necrosis, hemorrhage, cavitation)
   e. Estimated extent of invasion (Note **G**)
   f. Distance from margins (Note **H**)
      (1) proximal
      (2) distal
      (3) radial (retroperitoneal soft tissue margin closest to deepest tumor penetration)
3. Lesions in noncancerous pancreas
   a. Pancreatic duct obstruction
   b. Stones
   c. Pancreatitis
   d. Other(s)
4. Regional lymph nodes (identify by location, if possible or if specified by surgeon) (Note **G**)

5. Tissues submitted for microscopic evaluation
    a. Carcinoma, including:
        (1) points of deepest penetration of surrounding structures
        (2) interface with adjacent pancreas
        (3) interface with adjacent duodenum, if appropriate
        (4) visceral serosa overlying tumor
    b. Margins (Note **H**)
        (1) proximal
        (2) distal
        (3) radial (retroperitoneal posterior soft tissue margin closest to deepest tumor penetration)
    c. All lymph nodes (Note **G**)
        (1) specify node(s) when marked by surgeon
    d. Noninvolved pancreas
    e. Frozen section tissue fragment(s) (unless saved for special studies)
    f. Other tissue(s)/organ(s)
6. Special studies (specify) (eg, histochemistry, immunohistochemistry, electron microscopy, DNA analysis [specify type])

C. Microscopic Evaluation

1. Tumor (Note **A**)
    a. Histologic type (Note **B**)
    b. Histologic grade (Note **C**)
    c. Extent of invasion (Note **G**)
    d. Venous/lymphatic vessel invasion (Note **I**)
    e. Perineural invasion (Note **J**)
2. Margins (Note **H**)
    a. Proximal
    b. Posterior pancreatic surface (deep radial margin)
    c. Distal, if appropriate
3. Peritoneal surface
4. Regional lymph nodes (Note **G**)
    a. Number
    b. Number involved by tumor
5. Additional pathologic findings, if present
    a. Pancreatic intraepithelial neoplasia (PanIN) (Note **D**)
    b. Metaplasia
    c. Pancreatitis
    d. Other(s)
6. Distant metastasis (pM) (specify site)
7. Results/status of special studies (specify)
8. Comments
    a. Correlation with intraprocedural consultation, as appropriate
    b. Correlation with other specimens, as appropriate
    c. Correlation with clinical information, as appropriate

IV. Whipple Resection

(Pancreaticoduodenectomy, Partial or Total Pancreatectomy, With or Without Partial Gastrectomy)

A. Clinical Information

1. Identification Number
   a. Name
   b. Patient identification
   c. Age (birth date)
   d. Sex
2. Responsible physician(s)
3. Date of procedure
4. Other clinical information
   a. Clinical history
      (1) jaundice
      (2) pancreatitis
      (3) previous pancreatic or biliary surgery
      (4) pseudocyst drainage
      (5) diabetes mellitus
   b. Clinical findings (eg, ERCP and/or imaging studies)
   c. Clinical diagnosis
   d. Procedure (eg, pylorus-sparing Whipple resection)
   e. Operative findings
   f. Anatomic site(s) of specimen(s)

B. Macroscopic Examination

1. Specimen
   a. Organs/tissues received (specify)
   b. Unfixed/fixed (specify fixative)
   c. Number of pieces
   d. Dimensions (measure attached tissues individually)
   e. Orientation of specimen, if indicated by surgeon
   f. Results of intraoperative consultation
2. Tumor
   a. Location (Note **E**)
   b. Configuration (Note **F**)
   c. Dimensions (best estimate) (Note **G**)
   d. Descriptive characteristics (eg, color, consistency, necrosis, hemorrhage, cavitation)
   e. Estimated extent of invasion (Note **G**)
3. Margins (Note **H**)
   a. Distal pancreas
   b. Common bile duct
   c. Posterior pancreatic surface (deep radial margin)
   d. Proximal (gastric)
   e. Distal (duodenal)
   f. Other(s) (eg, uncinate)
4. Regional lymph nodes (Note **G**)
5. Additional pathologic findings, if present
   a. Common bile duct obstruction
   b. Pancreatic duct obstruction

   c. Calculi
   d. Pancreatitis
   e. Other(s)
6. Tissues submitted for microscopic evaluation
   a. Carcinoma, including
      (1) points of deepest penetration of surrounding structures
      (2) points of deepest penetration of closest margins
      (3) interface of tumor with adjacent tissues
   b. Ampulla of Vater (plus accessory papilla if present)
   c. Margins
      (1) distal pancreas
      (2) common bile duct
      (3) posterior pancreatic surface (deep radial margin)
      (4) proximal (gastric)
      (5) distal (duodenal)
   d. All lymph nodes
   e. Other lesions (eg, pseudocysts)
   f. Pancreas uninvolved by tumor
   g. Frozen section tissue fragment(s) (unless saved for special studies)
   h. Other tissue(s)/organ(s)
7. Special studies (specify) (eg, histochemistry, immunohistochemistry, electron microscopy, DNA analysis [specify type])

C. Microscopic Evaluation

1. Tumor (Note **A**)
   a. Histologic type (Note **B**)
   b. Histologic grade (Note **C**)
   c. Extent of invasion (Note **G**)
   d. Venous/lymphatic vessel invasion (Note **I**)
   e. Perineural invasion (Note **J**)
2. Margins (Note **H**)
   a. Distal pancreas
   b. Common bile duct
   c. Posterior pancreatic surface (deep radial margin)
   d. Proximal (gastric) (Note **K**)
   e. Distal (duodenal)
   f. Other(s)
3. Regional lymph nodes (Note **G**)
   a. Number
   b. Number with metastases
4. Distant metastasis (specify site)
5. Additional pathologic findings, if present
   a. Chronic pancreatitis
   b. Pancreatic intraepithelial neoplasia (PanIN) (Note **D**)
   c. Metaplasia
   d. Other(s)
6. Other tissue(s)/organ(s)
7. Results/status of special studies (specify)
8. Comments
   a. Correlation with intraoperative consultation, as appropriate

b. Correlation with other specimens, as appropriate
c. Correlation with clinical information, as appropriate

Explanatory Notes

A. Tumors

This protocol applies to epithelial tumors of the exocrine pancreas.[1] 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.[1,2] For these tumors, surgical resection remains the only potentially curative approach, and the prognosis is primarily dependent on the anatomic extent of disease.[2]

B. 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.[3] 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

<u>Malignant Tumors</u>
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[###]
- Non-invasive
- Invasive

Intraductal papillary-mucinous carcinoma[###]
- Non-invasive
- 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.

Borderline (Uncertain Malignant Potential)
Mucinous cystic neoplasm with moderate dysplasia[#]
Intraductal papillary-mucinous neoplasm with moderate dysplasia[##]
Solid-pseudopapillary neoplasm[##]

[#] Cured by complete surgical resection.

[##] Have a favorable prognosis compared to ductal adenocarcinoma.[3]

C. Histopathologic Grade
For adenocarcinomas, a histologic grade based on the extent of glandular differentiation is suggested as shown below.[4,5]

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.[6-8] In comparisons between the Klöppel grading system and the TNM grading system, no differences in predictive value have been demonstrated.[8]

D. 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.[9,10]

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 PanINs is unclear, but PanIN-3 is the equivalent of carcinoma in situ.

E. Definition of Location

The anatomic subdivisions defining location of tumors of the pancreas are as follows[5]:

- 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.

F. Tumor Configuration

Major types include intraductal, infiltrative, and circumscribed (if circumscribed: cystic or solid).

G. TNM and Stage Groupings

The TNM Staging System for carcinoma of the exocrine pancreas of the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC) is recommended and shown below.[4,5] 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.[2,5,7,8,11-16]

By 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 unfeasible) 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)

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 one 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 following the T category of the primary tumor (eg, pT3[m] or pT3[2]).[11] 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
- A single invasive tumor 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.[2,7,13,17-23]

^ 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.[5,11] Involvement of the peripancreatic soft tissues has been shown to have independent prognostic significance as an adverse factor.[14,20,22-26]

^^ Invasion of the portal vein also has been shown to have independent prognostic significance as an adverse factor.[14,20,27,28]

Regional Lymph Nodes (N)[#]

NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis[##]
N1 Regional lymph node metastasis[###]
N1a Metastasis in a single regional lymph node^
N1b Metastasis in multiple regional lymph nodes

[#] 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 (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.

[##] Regional Lymph Nodes (pN0): Isolated Tumor Cells
Isolated tumor cells (ITCs) are single cells or small clusters of cells not more than 0.2 mm in greatest dimension. Lymph nodes or distant sites with ITCs found by either histologic examination, immunohistochemistry, or nonmorphologic techniques (eg, flow cytometry, DNA analysis, polymerase chain reaction [PCR] amplification of a specific tumor marker) should be classified as N0 or M0, respectively. Specific denotation of the assigned N category is suggested as follows for cases in which ITCs are the only evidence of possible metastatic disease.[11,29]

pN0 No regional lymph node metastasis histologically, no examination for isolated tumor cells (ITCs)
pN0(i-) No regional lymph node metastasis histologically, negative morphologic (any morphologic technique, including hematoxylin-eosin and immunohistochemistry) findings for ITCs
pN0(i+) No regional lymph node metastasis histologically, positive morphologic (any morphologic technique, including hematoxylin-eosin and immunohistochemistry) findings for ITCs
pN0(mol-) No regional lymph node metastasis histologically, negative nonmorphologic (molecular) findings for ITCs
pN0(mol+) No regional lymph node metastasis histologically, positive nonmorphologic (molecular) findings for ITCs

[###]The presence of lymph node metastases has been shown to have independent prognostic significance as an adverse factor.[7,8,18,20,27,28,30-32]

^ Rationale: prognostic differences between N1a and N1b have been defined as follows.[12]

	2-Year (% ± SE)	**5-Year (% ± SE)**	**Median Survival (Months)**
pN1a	51 ± 17%	30 ± 16%	19.5
pN1b	18 ± 7%	0%	6.1

The difference between pN1a and pN1b is statistically significant ($p<0.01$).

Distant Metastasis (M)
MX Distant metastasis cannot be assessed
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.[5]

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 following 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 prior to 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.

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.[33]

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).

Vessel Invasion
By 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. In all other cases, lymphatic and venous invasion by tumor are coded separately as follows.

Lymphatic Vessel Invasion (L)
LX Lymphatic vessel invasion cannot be assessed
L0 No lymphatic vessel invasion
L1 Lymphatic vessel invasion

Venous Invasion (V)
VX Venous invasion cannot be assessed
V0 No venous invasion
V1 Microscopic venous invasion
V2 Macroscopic venous invasion

H. Margins
Most local recurrences of invasive pancreatic adenocarcinoma arise in the pancreatic bed corresponding to the deep radial posterior margin of the pancreas. Since this a critical margin, the AJCC and this protocol recommend inking the posterior surface of the pancreas and, if applicable to the specimen, the non-peritonealized surface of the uncinate process (the uncinate margin) and submitting sections through the tumor at its closest approach to this margin.[5]

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.

I. Venous/Lymphatic Vessel Invasion
Venous/lymphatic (small vessel) invasion has been shown to be an adverse prognostic factor.[24]

J. Perineural Invasion
Perineural invasion has been shown to be an adverse prognostic factor.[20,32]

K. Other Evaluation
In addition to the examination of other tissues/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.

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