

## **Pancreas (Endocrine)**

**Protocol applies to all endocrine tumors of the pancreas, including those with mixed endocrine and acinar cell differentiation.**

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*Protocol revision date: January 2004  
No AJCC/UICC staging system*

### **Procedures**

- **Incisional Biopsy**
- **Excisional Biopsy (Enucleation)**
- **Partial Pancreatectomy**
- **Pancreaticoduodenectomy (Whipple Resection)**

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**Surgical Pathology Cancer Case Summary (Checklist)***Protocol revision date: January 2004**Applies to endocrine tumors only**No AJCC/UICC staging system***PANCREAS (ENDOCRINE): 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 resection, pancreatic body
- Partial resection, pancreatic tail
- Other (specify): \_\_\_\_\_
- Not specified

**\*Tumor Site (check all that apply)**

- \*  Pancreatic head
- \*  Uncinate process
- \*  Pancreatic body
- \*  Pancreatic tail
- \*  Indeterminate
- \*  Not specified

**Tumor Focality**

- Unifocal
- Multifocal

**\*Tumor Configuration (check all that apply)**

- \*  Infiltrative
- \*  Circumscribed
- \*  Solid, entirely encapsulated
- \*  Solid, partially encapsulated
- \*  Cystic, entirely encapsulated
- \*  Cystic, partially encapsulated

2

\* 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.

**Tumor Size**

Greatest dimension: \_\_\_ cm

\*Additional dimensions: \_\_\_ x \_\_\_ cm

\_\_\_ Cannot be determined (see Comment)

**\*Other Organs Submitted (check all that apply)**

\* \_\_\_ None

\* \_\_\_ Spleen

\* \_\_\_ Gallbladder

\* \_\_\_ Other(s) (specify): \_\_\_\_\_

**MICROSCOPIC****\*Functional Type**

\* \_\_\_ Cannot be assessed

\* \_\_\_ Pancreatic endocrine tumor, functional  
(correlation with clinical syndrome and/or elevated serum levels of hormone product) (specify type): \_\_\_\_\_

\* \_\_\_ Pancreatic endocrine tumor, nonsecretory

\* \_\_\_ Pancreatic endocrine tumor, secretory status unknown

**Extent of Invasion**Primary Tumor

\_\_\_ Tumor limited to pancreas

\_\_\_ Tumor invades beyond pancreatic capsule, but does not invade adjacent structures/organs

\_\_\_ Tumor invades adjacent structures/organs (check all that apply):

\_\_\_ Duodenum

\_\_\_ Bile duct

\_\_\_ Stomach

\_\_\_ Spleen

\_\_\_ Colon

\_\_\_ Adjacent large vessels (eg, portal vein, celiac artery, superior mesenteric vessels, common hepatic vessels)

\_\_\_ Other (specify): \_\_\_\_\_

Regional Lymph Nodes

\_\_\_ Cannot be assessed

\_\_\_ No regional lymph node metastasis

\_\_\_ Regional lymph node metastasis

Specify: Number examined: \_\_\_\_\_

Number involved: \_\_\_\_\_

Distant Metastasis

\_\_\_ Cannot be assessed

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\_\_\_ Distant metastasis

\*Specify site(s) if known: \_\_\_\_\_

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**Margins (check all that apply)** Cannot be assessed Uninvolved by tumor

\*Distance of tumor from closest margin: \_\_\_\_ mm

\*Specify margin (if possible): \_\_\_\_\_

 Margin(s) involved by invasive carcinoma Posterior retroperitoneal (radial) margin: posterior surface of pancreas Uncinate process margin (non-peritonealized surface of the uncinata 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**\*Mitotic Activity**\*  Not applicable\*  Absent\*  Present; less than or equal to 4 mitoses/high-power field\*  Present; greater than 4 mitoses/high-power field**\*Additional Pathologic Findings (check all that apply)**\*  None identified\*  Chronic pancreatitis\*  Acute pancreatitis\*  Adenomatosis\*  Other (specify): \_\_\_\_\_**\*Comment(s)**

\* 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.

## Background Documentation

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*Protocol revision date: January 2004*

### **I. Cytologic Material**

#### **A. Clinical Information**

1. Patient identification
  - a. Name
  - b. Patient identification number
  - c. Age (birth date)
  - d. Sex
2. Responsible physician(s)
3. Other clinical information
  - a. Relevant history
    - (1) jaundice
    - (2) pancreatitis
    - (3) diabetes mellitus
    - (4) Zollinger-Ellison syndrome
    - (5) personal or family history of other endocrine tumors or endocrine syndromes (eg, multiple endocrine neoplasia [MEN] syndromes)
  - b. Relevant findings (eg, serum studies, endoscopic, endoscopic retrograde cholangiopancreatography [ERCP], imaging studies)
  - c. Clinical diagnosis
  - d. Specific procedure (eg, brushing, washing)
  - e. Operative findings
  - f. Anatomic site(s) of specimen(s)

#### **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, special stains, immunocytochemistry)

#### **C. Microscopic Evaluation**

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

**II. Incisional Biopsy****A. Clinical Information**

1. Patient identification
  - a. Name
  - b. Patient identification number
  - c. Age (birth date)
  - d. Sex
2. Responsible physician(s)
3. Other clinical information
  - a. Relevant history
    - (1) jaundice
    - (2) pancreatitis
    - (3) diabetes mellitus
    - (4) Zollinger-Ellison syndrome
    - (5) personal or family history of other endocrine tumors or endocrine syndromes (eg, MEN syndromes)
  - b. Relevant findings (eg, serum studies, endoscopic, ERCP, imaging studies)
  - c. Clinical diagnosis
  - d. Procedure (endoscopic biopsy of ampulla, intraoperative pancreatic biopsy)
  - e. Operative findings
  - f. Anatomic site(s) of specimen(s)

**B. Macroscopic Examination**

1. Specimen
  - a. Unfixed/fixed (specify fixative)
  - b. Number of pieces
  - c. Range of dimensions
  - d. Results of intraoperative consultation
2. Submit entire specimen and frozen section tissue fragment(s) for microscopic evaluation (unless a portion is saved for special studies)
3. Special studies (specify) (eg, immunohistochemistry, electron microscopy)

**C. Microscopic Evaluation**

1. Tumor (Note **A**)
  - a. Functional type, if possible (Note **B**)
  - b. Other histologic features (eg, mitotic activity, pleomorphism, necrosis) (Note **C**)
  - c. Special features of extracellular matrix (eg, psammoma bodies, amyloid)
2. Additional pathologic findings, if present
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. Excision Biopsy  
(Enucleation)****A. Clinical Information**

1. Patient identification
  - a. Name
  - b. Patient identification number

- c. Age (birth date)
- d. Sex
- 2. Responsible physician(s)
- 3. Other clinical information
  - a. Relevant history
    - (1) jaundice
    - (2) pancreatitis
    - (3) diabetes mellitus
    - (4) Zollinger-Ellison syndrome
    - (5) personal or family history of other endocrine tumors or endocrine syndromes (eg, MEN syndromes)
  - b. Relevant findings (eg, serum studies, endoscopic, ERCP, imaging studies)
  - c. Clinical diagnosis
  - d. Procedure
  - e. Operative findings
  - f. Anatomic site(s) of specimen(s)

**B. Macroscopic Examination**

- 1. Specimen
  - a. Unfixed/fixated (specify fixative)
  - b. Types of tissues received
  - c. Number of pieces of each type
  - d. Largest dimension of each piece
  - e. Orientation, if designated by surgeon
  - f. Results of intraoperative consultation
- 2. Tumor
  - a. Dimensions (Note **D**)
  - b. Configuration (Note **E**)
  - c. Encapsulation, if present
  - d. Descriptive characteristics (eg, necrosis, cystification, hemorrhage)
- 3. Margins (Note **F**)
  - a. Orientation/location, if designated by surgeon
  - b. Distance of tumor from nearest margin(s)
  - c. Macroscopic involvement by tumor, if present
- 4. Other lesions, if present
- 5. Other tissues, if submitted
- 6. Tissues submitted for microscopic evaluation
  - a. Tumor
    - (1) representative sections
    - (2) encapsulated borders
    - (3) infiltrative borders
  - b. Closest margins
  - c. Frozen section tissue fragment(s) (unless saved for special studies)
  - d. Other lesions
  - e. Other organs/tissues
- 7. Special studies (specify) (eg, immunohistochemistry, electron microscopy)

**C. Microscopic Evaluation**

- 1. Tumor (Note **A**)
  - a. Functional type, if possible (Note **B**)

- b. Other histologic features (eg, mitotic activity, pleomorphism, necrosis) (Note **C**)
    - c. Special features of extracellular matrix (eg, psammoma bodies, amyloid)
    - d. Venous/lymphatic vessel invasion (Note **G**)
    - e. Perineural invasion (Note **G**)
  2. Additional pathologic findings, if present
  3. Other organs/tissues, if present
    - a. Involvement by tumor, if appropriate (Note **H**)
      - (1) direct extension
      - (2) metastasis
    - b. Other lesions, if present
  4. Results/status of special studies (specify)
  5. Comments
    - a. Correlation with intraoperative consultation, as appropriate
    - b. Correlations with other specimens, as appropriate
    - c. Correlations with clinical information, as appropriate

#### **IV. Partial Pancreatectomy**

##### **(Distal or Left Pancreatectomy)**

#### **A. Clinical Information**

1. Patient identification
  - a. Name
  - b. Patient identification number
  - c. Age (birth date)
  - d. Sex
2. Responsible physician(s)
3. Other clinical information
  - a. Relevant history
    - (1) jaundice
    - (2) pancreatitis
    - (3) diabetes mellitus
    - (4) Zollinger-Ellison syndrome
    - (5) personal or family history of other endocrine tumors or endocrine syndromes (eg, MEN syndromes)
  - b. Relevant findings (eg, serum studies, endoscopic, ERCP, 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(s)
  - a. Location (Note **I**)

- b. Dimensions (Note **D**)
- c. Configuration (Note **E**)
- d. Descriptive characteristics (eg, color, consistency, necrosis, hemorrhage, cavitation)
- e. Distance from margins (Note **F**)
  - (1) proximal
  - (2) distal
  - (3) radial (soft tissue margin closest to deepest tumor penetration)
- f. Estimated extent of invasion (Note **H**)
  - (1) confined to the pancreas
  - (2) into adjacent structures (bile duct; duodenum; peripancreatic tissues, which include surrounding retroperitoneal fat; mesentery; mesocolon; omentum)
  - (3) into stomach, spleen, or colon
  - (4) into adjacent large vessels (eg, portal vein, mesenteric or common hepatic arteries or veins)
  - (5) into other structure(s)
3. Additional pathologic findings, if present
  - 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)
5. Nonregional lymph nodes (identify by location, if possible or if specified by surgeon)
6. Other organ(s) or structure(s)
  - a. Tumor, if present
    - (1) direct extension
    - (2) metastasis
  - b. Other pathologic findings, if present
7. Tissues submitted for microscopic evaluation
  - a. Tumor(s), representative sections including:
    - (1) points of deepest penetration of surrounding structures
    - (2) interface with adjacent pancreas
    - (3) visceral serosa overlying tumor
  - b. Margins (Note **E**)
    - (1) proximal
    - (2) distal
    - (3) radial (posterior soft tissue margin closest to deepest tumor penetration)
  - c. All lymph nodes
    - (1) regional
    - (2) nonregional
  - d. Frozen section tissue fragment(s) (unless saved for special studies)
  - e. Noninvolved pancreas
  - f. Other tissue(s)/organ(s)
8. Special studies (specify) (eg, histochemistry, immunohistochemistry, electron microscopy)

**C. Microscopic Evaluation**

1. Tumor(s) (Note **A**)

- a. Functional type, if possible (Note **B**)
- b. Other histologic features (eg, mitotic activity, pleomorphism, necrosis) (Note **C**)
- c. Special features of extracellular matrix (eg, psammoma bodies, amyloid)
- d. Extent of local invasion (Note **G**)
  - (1) confined to the pancreas
  - (2) into adjacent structures (bile duct; duodenum; peripancreatic tissues, which include surrounding retroperitoneal fat; mesentery; mesocolon; omentum)
  - (3) into stomach, spleen, or colon
  - (4) into adjacent large vessels (eg, portal vein, mesenteric or common hepatic arteries or veins)
  - (5) into other structure(s)
- e. Venous/lymphatic vessel invasion (Note **G**)
- f. Perineural invasion (Note **G**)
2. Margins (Note **F**)
  - a. Proximal
  - b. Posterior pancreatic surface (deep radial margin)
  - c. Distal, if appropriate
3. Peritoneal surface
4. Lymph nodes (Note **I**)
  - a. Regional lymph nodes
    - (1) number
    - (2) number involved by tumor
  - b. Nonregional lymph nodes
    - (1) number
    - (2) number involved by tumor
5. Additional pathologic findings, if present
  - a. Islet cell dysplasia
  - b. Adenomatosis
  - c. Pancreatitis
  - d. Other(s)
6. Other organs/tissues, if present
  - a. Involvement by tumor (Note **K**)
    - (1) direct extension
    - (2) metastasis
  - b. Other lesions, if present
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

## V. Whipple Resection

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

### A. Clinical Information

1. Patient identification
  - a. Name

- b. Patient identification number
- c. Age (birth date)
- d. Sex
2. Responsible physician(s)
3. Other clinical information
  - a. Relevant history
    - (1) jaundice
    - (2) pancreatitis
    - (3) diabetes mellitus
    - (4) Zollinger-Ellison syndrome
    - (5) personal or family history of other endocrine tumors or endocrine syndromes (eg, MEN syndromes)
  - b. Relevant findings (eg, serum studies, endoscopic, ERCP, imaging studies)
  - c. Clinical diagnosis
  - d. Procedure (eg, gastroduodenal pancreatectomy, partial or complete)
  - e. Operative findings
  - f. Anatomic site(s) of specimen(s)

**B. Macroscopic Examination**

1. Specimen
  - a. Organs/tissues received
  - 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 **I**)
  - b. Dimensions (Note **D**)
  - c. Configuration (Note **E**)
  - d. Descriptive characteristics (eg, color, consistency, necrosis, hemorrhage, cavitation)
  - e. Estimated extent of invasion (Note **G**)
    - (1) confined to the pancreas or ampulla
    - (2) into adjacent structures (bile duct; duodenum; peripancreatic tissues, which include surrounding retroperitoneal fat; mesentery; mesocolon; omentum)
    - (3) into stomach, spleen, or colon
    - (4) into adjacent large vessels (eg, portal vein, mesenteric or common hepatic arteries or veins)
    - (5) into other structure(s) (eg, peritoneal seeding)
3. Additional pathologic findings, if present
  - a. Common bile duct obstruction
  - b. Pancreatic duct obstruction
  - c. Calculi
  - d. Pancreatitis
  - e. Other(s)
4. Regional lymph nodes (identify by location, if possible or if specified by surgeon)
5. Nonregional lymph nodes (identify by location, if possible or if specified by surgeon)

6. Other tissue(s)/organ(s) (specify)
  - a. Tumor, if present
    - (1) direct extension
    - (2) metastasis
  - b. Other lesions
7. Tissues submitted for microscopic evaluation
  - a. Tumor, 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) posterior pancreatic surface (deep radial margin)
    - (3) bile duct
  - d. All lymph nodes
    - (1) regional
    - (2) nonregional
  - e. Frozen section tissue fragment(s) (unless saved for special studies)
  - f. Other lesions (eg, pseudocysts)
  - g. Pancreas uninvolved by tumor
  - h. Other tissue(s)/organ(s) (specify)
8. Special studies (specify) (eg, histochemistry, immunohistochemistry, electron microscopy)

**C. Microscopic Evaluation**

1. Tumor
  - a. Functional type, if possible (Note **B**)
  - b. Other histologic features (eg, mitotic activity, pleomorphism, necrosis) (Note **C**)
  - c. Special features of extracellular matrix (eg, psammoma bodies, amyloid)
  - d. Extent of invasion (Note **G**)
    - (1) confined to the pancreas
    - (2) into adjacent structures (bile duct; duodenum; peripancreatic tissues, which include surrounding retroperitoneal fat; mesentery; mesocolon; omentum)
    - (3) into stomach, spleen, or colon
    - (4) into adjacent large vessels (eg, portal vein, mesenteric or common hepatic arteries or veins)
    - (5) into other structure(s)
  - e. Venous/lymphatic vessel invasion (Note **G**)
  - f. Perineural invasion (Note **G**)
2. Margins (Note **E**)
  - a. Distal pancreas
  - b. Posterior pancreatic surface (deep radial margin)
3. Peritoneal surface
4. Lymph nodes (Note **J**)
  - a. Regional lymph nodes
    - (1) number
    - (2) number involved by tumor

- b. Nonregional lymph nodes
    - (1) number
    - (2) number involved by tumor
- 5. Additional pathologic findings, if present
  - a. Islet cell dysplasia
  - b. Adenomatosis
  - c. Pancreatitis
  - d. Other(s)
- 6. Other organ(s)/tissue(s), if present
  - a. Involvement by tumor (Note J)
  - b. Other lesions, if present
- 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. Application

This protocol applies to endocrine tumors of the pancreas. Pancreatic endocrine tumors are also known as “islet cell tumors,” but this terminology is misleading since these tumors do not derive from pancreatic islets. Rather, they are believed to arise from pluripotential ductal cells that have the capacity to differentiate along neuroendocrine 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, it is suggested that the term “neuroendocrine 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 10% 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.<sup>1</sup> There is no TNM staging system for these neoplasms.<sup>2</sup>

### B. Histologic 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.<sup>1,3-5</sup> 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. 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)

Pancreatic polypeptide (PP)-secreting (PP-oma) (clinically silent but with elevated serum PP levels)

Vasoactive intestinal polypeptide (VIP)-secreting (VIP-oma<sup>#</sup>) (watery diarrhea, hypokalemia, achlorhydria)

Adrenocorticotrophic hormone-producing (Cushing's syndrome: central obesity, muscle weakness, glucose intolerance, hypertension)<sup>6</sup>

Carcinoid tumor (serotonin-producing) (carcinoid syndrome: flushing, diarrhea)

Pancreatic endocrine tumor, nonsecretory

Mixed ductal-endocrine carcinoma<sup>##</sup>

Mixed acinar-endocrine carcinoma<sup>##</sup>

<sup>#</sup> Sometimes known as Verner-Morrison tumors.<sup>4</sup>

<sup>##</sup> 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. Although the prognostic significance of biphasic differentiation has not been clearly defined, these tumors are staged according to the TNM staging system of the pancreatic endocrine carcinomas of the American Joint Committee on Cancer/International Union Against Cancer (see Exocrine Pancreas protocol).

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.<sup>3</sup> For these reasons, pancreatic endocrine tumors are not usually graded.

### C. Mitotic Activity, Pleomorphism, and Necrosis

High mitotic activity, a high degree of pleomorphism, and tumor necrosis have all been shown to correlate strongly with malignant potential.<sup>7</sup> It has been suggested that a mitotic index of greater than 4 mitoses per 10 high-power fields predicts malignant

behavior in more than 80% of cases.<sup>7</sup> However, a lower mitotic index is of no prognostic value, and many malignant tumors evidence little to no mitotic activity. Nuclear pleomorphism is of no prognostic value,<sup>7</sup> but poorly differentiated endocrine or small cell tumors with a high degree of pleomorphism are generally regarded as malignant.<sup>7</sup> Tumor necrosis is uncommon, and although it is generally regarded as a malignancy-associated feature, it is not a reliable criterion for diagnosing malignancy in pancreatic endocrine tumors.

#### **D. Tumor Dimensions**

Large size (diameter 2.5 cm or greater) has been shown to correlate with aggressive biologic behavior, such as local invasion and vascular invasion, and with metastasis. Large size also correlates with cystification and calcification.<sup>1,8</sup> Although there is marked overlap in the size ranges of localized and malignant tumors (with metastasis), tumors smaller than 2.5 cm are almost always benign, and tumors larger than 10 cm are highly likely to be malignant.<sup>7,9</sup>

#### **E. Tumor Configuration**

Types include infiltrative and circumscribed (if circumscribed, cystic or solid). Circumscribed tumors may be entirely or partially encapsulated.

#### **F. 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 deep radial margin (representing the posterior retroperitoneal surface of the specimen) are recommended. In cases of multiple endocrine neoplasia syndrome type I (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.<sup>1</sup> 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.<sup>1</sup>

#### **G. Blood Vessel and Perineural Invasion**

The presence of blood vessel invasion, perineural invasion, or both have been regarded by some authors as histopathologic criteria for malignancy.<sup>8,10</sup> In particular, it has been suggested that blood vessel invasion is the only histologic marker of malignancy.<sup>7</sup> 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.<sup>7</sup> Other authors regard these criteria as useful indicators of aggressive behavior, but not as absolute indicators of malignancy.<sup>10,11</sup>

**H. Invasion of Local Structures**

Infiltration of organs adjacent to the pancreas has been regarded as a criterion for malignancy by some authors.<sup>3,8</sup>

**I. Definition of Location**

The anatomic subdivisions defining location of tumors of the pancreas are as follows<sup>2</sup>:

- 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.

**J. Regional Lymph Nodes**

The regional nodes of the pancreas may be subdivided as follows<sup>2</sup>:

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, pancreaticolienal (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.<sup>2</sup>

Metastasis, whether to regional lymph nodes or to distant sites, constitutes the only universally accepted criterion for malignancy in pancreatic endocrine tumors.<sup>3,8,11,12</sup>

**K. Distant Metastasis**

Common sites of distant metastasis include the liver and bone. Less common metastatic sites include peritoneum, lung, periaortic lymph nodes, kidney, and thyroid.<sup>1,10</sup> In many cases, metastasis is found only in the liver without regional lymph node metastasis.<sup>1</sup>

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