

# **Pancreas (Endocrine)**

**Protocol applies to all endocrine tumors of the pancreas.**

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*Protocol revision date: January 2005  
No AJCC/UICC staging system*

## **Procedures**

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

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## Summary of Changes to Checklist(s)

*Protocol revision date: January 2005*

The following changes have been made to the data elements of the checklist(s) since the January 2004 protocol revision.

### **Protocol in General**

Tumors with mixed endocrine and acinar cell differentiation are no longer included in this protocol (see Exocrine Pancreas protocol).

### **Excisional Biopsy (Enucleation), Resection Checklist**

#### **Macroscopic**

Specimen Type: Excisional biopsy (enucleation) was added, as shown below

#### **Specimen Type**

- Excisional biopsy (enucleation)
- 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

**Surgical Pathology Cancer Case Summary (Checklist)***Protocol revision date: January 2005**Applies to endocrine tumors only**No AJCC/UICC staging system***PANCREAS (ENDOCRINE): Excisional Biopsy (Enucleation),  
Resection**

Patient name:

Surgical pathology number:

**Note: Check 1 response unless otherwise indicated.****MACROSCOPIC****Specimen Type**

- Excisional biopsy (enucleation)  
 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

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\* 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

\_\_\_ Distant metastasis

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

\* 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.

**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/10 high-power fields\*  Present; greater than 4 mitoses/10 high-power fields**\*Additional Pathologic Findings (check all that apply)**\*  None identified\*  Chronic pancreatitis\*  Acute pancreatitis\*  Adenomatosis\*  Other (specify): \_\_\_\_\_**\*Comment(s)**

## Background Documentation

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Protocol revision date: January 2005

### 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. Excisional 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/fixed (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/fixated (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>

<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 exocrine 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 uncinata 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>

## References

1. Moffat FL, Ketcham A. Metastatic proclivities and patterns among APUD cell neoplasms. *Semin Surg Oncol*. 1993;9:443-452.
2. Greene FL, Page DL, Fleming ID, et al. eds. *AJCC Cancer Staging Manual*. 6<sup>th</sup> ed. New York: Springer; 2002.
3. Heitz PU, Kasper M, Polak JM, Kloppel G. Pancreatic endocrine tumors: immunocytochemical analysis of 125 tumors. *Hum Pathol*. 1982;13:263-271.
4. Larsson L. Endocrine pancreatic tumors. *Hum Pathol*. 1978;9(4):401-416.
5. White TJ, Edney JA, Thompson JS, Karrer FW, Moor BJ. Is there a prognostic difference between functional and nonfunctional islet cell tumors? *Am J Surg*. 1994;168:627-630.
6. Amikura K, Alexander HR, Norton JA, et al. Role of surgery in management of adrenocorticotrophic hormone-producing islet cell tumors of the pancreas. *Surgery*. 1995;118(6):1125-1130.
7. Solcia E, Capella C, Kloppel G. *Tumors of the Exocrine Pancreas. Atlas of Tumor Pathology*. Third Series, Fascicle 20. Washington, DC: Armed Forces Institute of Pathology; 1997.
8. Buetow PC, Parrino TV, Buck J, 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*. 1995;165:1175-1179.
9. Kenny BD, Sloan JM, Hamilton PW, et al. The role of morphometry in predicting prognosis in pancreatic islet cell tumors. *Cancer*. 1989;64:460-465.
10. Kent RB, Van Heerden JA, Weiland LH. Nonfunctioning islet cell tumors. *Ann Surg*. 1981;193:185-190.
11. Dial PF, Braasch JW, Rossi RL, Lee AK, Jin G. Management of nonfunctioning islet cell tumors of the pancreas. *Surg Clin North Am*. 1985;65:291-299.
12. Cubilla AL, Hajdu IS. Islet cell carcinoma of the pancreas. *Arch Pathol Lab Med*. 1975;99:204-207.

## Bibliography

- Ahstrom H, Eriksson B, Bergstrom M, Bjurling P, Langstrom B, Oberg K. Pancreatic neuroendocrine tumors: diagnosis with PET. *Radiology*. 1995;195:333-337.
- Bordi C, De Vita O, Pilato F, et al. Multiple islet cell tumors with predominance of glucagon-producing cells and ulcer disease. *Am J Clin Pathol*. 1987;88:153-161.
- Bretherton-Watt D, Ghatel MA, Bloom SE, Williams S, Bloom SR. Islet amyloid polypeptide-like immunoreactivity in human tissue and endocrine tumors. *J Clin Endocrinol Metab*. 1993;76:1072-1074.
- Broughan TA, Leslie JD, Soto JM, Hermann RE. Pancreatic islet cell tumors. *Surgery*. 1986;99:671-678.
- Bussolati G, Gugliotta P, Sapino A, Eusebi V, Lloyd RV. Chromogranin-reactive endocrine cells in argyrophilic carcinomas ("carcinoids") and normal tissue of the breast. *Am J Pathol*. 1985;120:186-192.
- Capella C, Polak JM, Buffa R, et al. Morphologic patterns and diagnostic criteria of VIP-producing endocrine tumors: a histologic, histochemical, ultrastructural, and biochemical study of 32 cases. *Cancer*. 1983;52:1860-1874.
- Cefis F, Cattaneo M, Carnavale-Ricci PM. Primary polypeptide hormones and mucin-producing malignant carcinoid of the larynx. *Ultrastruct Pathol*. 1983;5:45-53.
- Creutzfeldt W, Arnold R, Creutzfeldt C, Track NS. Pathomorphologic, biochemical, and diagnostic aspects of gastrinomas (Zollinger-Ellison Syndrome). *Hum Pathol*. 1975;6:47-76.
- Delcore R, Cheung L, Friesen S. Outcome of lymph node involvement in patients with the Zollinger-Ellison syndrome. *Ann Surg*. 1988;208:291-298.

- Doppman JL, Shawker TH, Miller DL. Localization of islet cell tumors. *Gastroenterol Clin North Am.* 1989;18:793-804.
- Eckhauser FE, Cheung PS, Vinik AI, Strodel WE, Lloyd RV, Thompson NW. Nonfunctioning malignant neuroendocrine tumors of the pancreas. *Surgery.* 1986;100(6):978-988.
- Fajans SS, Vinik AI. Insulin-producing islet cell tumors. *Endocrinol Metab Clin North Am.* 1989;18:45-74.
- Friesen SR. Tumors of the endocrine pancreas. *N Engl J Med.* 1982;306:580-590.
- Giercksky KE, Halse J, Mathison W, Gione E, Flatmark A. Endocrine tumors of the pancreas. *Scand J Gastroenterol.* 1980;15:129-135.
- Graeme-Cook F, Nardi G, Compton CC. Human chorionic gonadotrophin subunits as predictors of malignancy in insulinomas. *Am J Clin Pathol.* 1990;93:273-276.
- Graeme-Cook F, Bell DA, Flotte TJ, Pfeffer F, Pastel-Levy C, Compton CC. Aneuploidy in pancreatic insulinomas does not predict malignancy. *Cancer.* 1990;66:2365-2368.
- Goudswaard WB, Houthott HJ, Koudstaai J, Zwierstra RP. Nesidioblastosis and endocrine hyperplasia of the pancreas: a secondary phenomenon. *Hum Pathol.* 1986;17:46-53.
- Hammar S, Sale G. Multiple hormone producing islet cell carcinomas of the pancreas. *Hum Pathol.* 1975;6:349-362.
- Heitz PU, Kasper M, Polak JK, Kloppel G. Pathology of the endocrine pancreas. *J Histochem Cytochem.* 1979;27:1401-1402.
- Heitz PU, Von Herbay G, Kloppel G, et al. The expression of subunits of human chorionic gonadotropin (hCG) by nontrophoblastic, nonendocrine, and endocrine tumors. *Am J Clin Pathol.* 1987;88:467-472.
- Ivy EJ, Sarr MG, Reiman HM. Nonendocrine cancer of the pancreas in patients under age forty years. *Surgery.* 1990;108:481-487.
- Jaksic T, Yaman M, Thorner P, et al. A 20-year review of pediatric pancreatic tumors. *J Pediatr Surg.* 1992;27:1315-1317.
- Kahn CR, Rosen SW, Weintraub BD, Faians SS, Gorden P. Ectopic production of chorionic gonadotropin and its subunits by islet-cell tumors: a specific marker for malignancy. *N Engl J Med.* 1977;297:565-569.
- Klimstra DS, Hettess CS, Oertel JE, et al. Acinar cell carcinoma of the pancreas: a clinicopathologic study of 28 cases. *Am J Surg Pathol.* 1992;16:815-837.
- Kniffin WD, Spencer SK, Memoli VA, et al. Metastatic islet cell amphoteric carcinoma of the pancreas: association with an eosinophilic infiltration of the skin. *Cancer.* 1988;62:1999-2004.
- Lewin K. Carcinoid tumors and the mixed (composite) glandular - endocrine cell carcinomas. *Am J Surg Pathol.* 1987;11:71-86.
- Liu TH, Tseng HC, Zhu Y, Zhong SX, Chen J, Cui QC. Insulinoma: an immunocytochemical and morphologic analysis of 95 cases. *Cancer.* 1985;56:1420-1429.
- Liu T, Zhu Y, Cui Q, et al. Nonfunctioning pancreatic endocrine tumors: an immunohistochemical and electron microscopic analysis of 26 cases. *Path Res Pract.* 1992;188:191-198.
- McPherson GA, Williamson RC. Massive hemorrhage as the initial appearance of "nonfunctioning" islet cell tumors of the pancreas. *Pancreas.* 1989;4:381-385.
- Mukai K, Greider MH, Grotting JC, et al. Retrospective study of 77 pancreatic endocrine tumors using the immunoperoxidase method. *Am J Surg Pathol.* 1982;6:387-399.
- Nojima T, Kojima T, Kato H, Inoue K, Hagashima K. Cystic endocrine tumor of the pancreas. *Int J Pancreatol.* 1991;10:65-72.
- Patchefsky AS, Gordon G, Harrer WV, Hoch WS. Carcinoid tumor of the pancreas: ultrastructural observations of a lymph node metastasis and comparison with bronchial carcinoid. *Cancer.* 1974;33:1349-1354.
- Pelosi G, Zamboni G, Doglioni C, et al. Immunodetection of proliferating cell nuclear antigen assesses the growth fraction and predicts malignancy in endocrine tumors of the pancreas. *Am J Surg Pathol.* 1992;16:1215-1225.

- Pelosi G, Bresaola E, Bogina G, et al. Endocrine tumors of the pancreas: Ki-67 immunoreactivity on paraffin sections is an independent predictor for malignancy: a comparative study with proliferating-cell nuclear antigen and progesterone receptor protein immunostaining, mitotic index, and other clinicopathologic variables. *Hum Pathol.* 1996;27:1124-1134.
- Permert J, Mogaki M, Andron-Sandberg A, et al. Pancreatic mixed ductal-islet tumors. *Int J Pancreatol.* 1992;11:23-29.
- Prinz RA, Badrinath K, Chejfec G, Freeark RJ, Greenlee HB. "Nonfunctioning" islet cell carcinoma of the pancreas. *Am Surg.* 1983;49:345-349.
- Prinz RA, Bermes EW, Kimmel JR, Marangos PJ. Serum markers for pancreatic islet cell and intestinal carcinoid tumors: a comparison of neuron-specific enolase, beta-human chorionic gonadotropin and pancreatic polypeptide. *Surgery.* 1983;94:1019-1023.
- Ruschoff J, Willemer S, Brunzel M, et al. Nucleolar organizer regions and glycoprotein-hormone alpha-chain reaction as markers of malignancy in endocrine tumours of the pancreas. *Histopathology.* 1993;22:51-57.
- Sakai H, Kodaira S, Ono K, et al. Disseminated pancreatic polypeptidoma. *Intern Med.* 1993;32:737-741.
- Shield CF, Haff RC, Murray HM. Islet cell tumors of the pancreas. *Am J Surg.* 1974;128:709-714.
- Solcia E, Capella C, Buffa R, et al. The contribution of immunohistochemistry to the diagnosis of neuroendocrine tumors. *Semin Diagn Pathol.* 1984;1;285-296.
- Udelsman R, Yeo CJ, Hruban RH, et al. Pancreaticoduodenectomy for selected pancreatic endocrine tumors. *Surg Gynecol Obstet.* 1993;177:269-278.
- Wahlstrom T, Seppala M. Immunological evidence for the occurrence of luteinizing hormone releasing factor and the alpha subunit of glycoprotein hormones in carcinoid tumors. *J Clin Endocrinol Metab.* 1981;53:209-212.
- Weber HC, Venzon DJ, Lin J, et al. Determinants of metastatic rate and survival in patients with Zollinger-Ellison Syndrome: a prospective long-term study. *Gastroenterology.* 1995;108:1637-1649.
- Wolfe MM, Jensen RT. Zollinger-Ellison Syndrome: current concepts in diagnosis and management. *N Engl J Med.* 1987;317:1200-1209.
- Zollinger RM, Martin EW, Carey LC, Sparks J, Minton JP. Observations on the postoperative tumor growth behavior of certain islet cell tumors. *Ann Surg.* 1976;184:525-530.