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

Version: 4.3.0.0
Protocol Posting Date: June 2025
CAP Laboratory Accreditation Program Protocol Required Use Date: March 2026
The changes included in this current protocol version affect accreditation requirements. The new deadline for implementing this protocol version is reflected in the above accreditation date.

For accreditation purposes, this protocol should be used for the following procedures AND tumor types:

Procedure	Description
Resection	Includes specimens designated pancreatectomy, partial or total, and pancreaticoduodenectomy (Whipple resection)
Tumor Type	**Description**
Carcinoma	Invasive carcinomas including small cell and large cell (poorly differentiated) neuroendocrine carcinoma.

This protocol is NOT required for accreditation purposes for the following:

Procedure
Biopsy
Enucleation (excisional biopsy)
Primary resection specimen with no residual cancer (e.g., following neoadjuvant therapy)
Cytologic specimens
Tumor Type
Intraductal papillary mucinous neoplasm without associated invasive carcinoma
Intraductal oncocytic papillary neoplasm without associated invasive carcinoma
Intraductal tubulopapillary neoplasm without associated invasive carcinoma
Mucinous cystic neoplasm without associated invasive carcinoma

The following tumor types should NOT be reported using this protocol:

Tumor Type
Well-differentiated neuroendocrine tumor (consider Pancreas Endocrine protocol)
Ampullary tumors (consider Ampulla of Vater protocol)
Lymphoma (consider the Precursor and Mature Lymphoid Malignancies protocol)
Sarcoma (consider the Soft Tissue protocol)

Version Contributors

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Glossary:
Author: Expert who is a current member of the Cancer Committee, or an expert designated by the chair of the Cancer Committee.
Expert Contributors: Includes members of other CAP committees or external subject matter experts who contribute to the current version of the protocol.

Accreditation Requirements

Synoptic reporting with core and conditional data elements for designated specimen types* is required for accreditation.

- Data elements designated as core must be reported.
- Data elements designated as conditional only need to be reported if applicable.
- Data elements designated as optional are identified with "+". Although not required for accreditation, they may be considered for reporting.

This protocol is not required for recurrent or metastatic tumors resected at a different time than the primary tumor. This protocol is also not required for pathology reviews performed at a second institution (i.e., second opinion and referrals to another institution).

Full accreditation requirements can be found on the CAP website under Accreditation Checklists.

A list of core and conditional data elements can be found in the Summary of Required Elements under Resources on the CAP Cancer Protocols website.

**Includes definitive primary cancer resection and pediatric biopsy tumor types.*

Synoptic Reporting

All core and conditionally required data elements outlined on the surgical case summary from this cancer protocol must be displayed in synoptic report format. Synoptic format is defined as:

- Data element: followed by its answer (response), outline format without the paired Data element: Response format is NOT considered synoptic.
- The data element should be represented in the report as it is listed in the case summary. The response for any data element may be modified from those listed in the case summary, including "Cannot be determined" if appropriate.
- Each diagnostic parameter pair (Data element: Response) is listed on a separate line or in a tabular format to achieve visual separation. The following exceptions are allowed to be listed on one line:
    - Anatomic site or specimen, laterality, and procedure
    - Pathologic Stage Classification (pTNM) elements
    - Negative margins, as long as all negative margins are specifically enumerated where applicable
- The synoptic portion of the report can appear in the diagnosis section of the pathology report, at the end of the report or in a separate section, but all Data element: Responses must be listed together in one location
- Organizations and pathologists may choose to list the required elements in any order, use additional methods in order to enhance or achieve visual separation, or add optional items within the synoptic report. The report may have required elements in a summary format elsewhere in the report IN ADDITION TO but not as replacement for the synoptic report i.e., all required elements must be in the synoptic portion of the report in the format defined above.

Summary of Changes

v 4.3.0.0

- Updates to cover page
- Updates to content and explanatory notes to include modifications to Histologic Type and Tumor Size questions, and MARGINS and SPECIAL STUDIES sections
- Addition of conditionally reported Pancreas Surface Involvement question
- Lymphovascular Invasion question updated to Lymphatic and / or Vascular Invasion
- Updates to pTNM Classification

Reporting Template

Protocol Posting Date: June 2025
Select a single response unless otherwise indicated.
CASE SUMMARY: (PANCREAS (EXOCRINE))
Standard(s): AJCC 8

SPECIMEN (Note A)

Procedure
___ Excisional biopsy (enucleation)
___ Pancreaticoduodenectomy (Whipple resection), partial pancreatectomy
___ Total pancreatectomy
___ Partial pancreatectomy, pancreatic body
___ Partial pancreatectomy, pancreatic tail
___ Other (specify): _____
___ Not specified

TUMOR

Tumor Site (Note B) (select all that apply)
___ Pancreatic head: _____
___ Uncinate process: _____
___ Pancreatic body: _____
___ Pancreatic tail: _____
___ Other (specify): _____
___ Cannot be determined: _____
___ Not specified

Histologic Type (Note C)
___ Ductal adenocarcinoma, NOS
___ Colloid carcinoma (mucinous carcinoma)
___ Poorly cohesive carcinoma
___ Signet-ring carcinoma
___ Intraductal papillary mucinous neoplasm with associated invasive carcinoma
___ Intraductal oncocytic papillary neoplasm with associated invasive carcinoma
___ Intraductal tubulopapillary neoplasm with associated invasive carcinoma
___ Mucinous cystic neoplasm with associated invasive carcinoma
___ Medullary carcinoma
___ Adenosquamous carcinoma
___ Hepatoid carcinoma
___ Large cell carcinoma with rhabdoid phenotype
___ Undifferentiated carcinoma, NOS
___ Undifferentiated carcinoma with osteoclast-like giant cells
___ Acinar cell carcinoma
___ Acinar cell cystadenocarcinoma
___ Mixed acinar-ductal carcinoma

___ Pancreatoblastoma
___ Solid-pseudopapillary neoplasm
___ Solid-pseudopapillary neoplasm with high grade carcinoma
___ Large cell neuroendocrine carcinoma
___ Small cell neuroendocrine carcinoma
___ Mixed neuroendocrine-non-neuroendocrine neoplasm (MiNEN) (specify components):
_____
___ Other histologic type not listed (specify): _____
+Histologic Type Comment: _____

Histologic Grade (required only for ductal carcinoma) (Note D)
___ Not applicable
___ G1, well-differentiated
___ G2, moderately differentiated
___ G3, poorly differentiated
___ Other (specify): _____
___ GX, cannot be assessed: _____

Tumor Size (Note E)
___ Unifocal invasive carcinoma
___ Greatest dimension in Centimeters (cm): _____ cm
+Additional Dimension in Centimeters (cm): ____ x ____ cm
___ Cannot be determined (explain): _____
___ Multifocal invasive carcinoma in association with intraductal neoplasms (intraductal papillary mucinous neoplasm, intraductal oncocytic papillary neoplasm, and intraductal tubulopapillary neoplasm) and mucinous cystic neoplasm
___ Size of the largest focus of invasive carcinoma in Centimeters (cm): _____ cm
Aggregate Size that Combines Sizes of all Foci of Invasive Carcinoma in Centimeters (cm) (specify, if known): _____ cm
Invasive Component as a Percentage of Entire Tumor (specify, if known): _____ %
___ Cannot be determined (explain): _____

Site(s) Involved by Direct Tumor Extension (select all that apply)
___ No invasion (carcinoma in situ / high-grade dysplasia)
___ Confined to pancreas
___ Vascular bed / groove (corresponding to superior mesenteric vein / portal vein)
___ Ampulla of Vater or sphincter of Oddi
___ Duodenal wall
___ Peripancreatic soft tissues
Select all that apply
___ Retroperitoneal soft tissue
___ Mesenteric adipose tissue
___ Mesocolon
___ Other peripancreatic soft tissue (specify): _____
___ Cannot be determined (explain): _____

___ Extrapancreatic common bile duct
___ Stomach
___ Superior mesenteric vein
___ Portal vein
___ Celiac axis
___ Superior mesenteric artery
___ Common hepatic artery
___ Other adjacent organ(s) or structure(s) (specify): _____
___ Cannot be determined: _____
___ No evidence of primary tumor

Pancreatic Surface Involvement (required only if applicable) (select all that apply)
___ Not applicable
___ Posterior surface: _____
___ Anterior surface: _____
___ Other (specify): _____
___ Cannot be determined (explain): _____

Lymphatic and / or Vascular Invasion (Note F)
___ Not identified
___ Present
___ Cannot be determined: _____

Perineural Invasion (Note G)
___ Not identified
___ Present
___ Cannot be determined: _____

Treatment Effect (Note H)
___ No known presurgical therapy
___ Present, with no viable cancer cells (complete response, score 0)
___ Present, with single cells or rare small groups of cancer cells (near complete response, score 1)
___ Present, with residual cancer showing evident tumor regression, but more than single cells or rare small groups of cancer cells (partial response, score 2)
___ Present, NOS
___ Absent, with extensive residual cancer and no evident tumor regression (poor or no response, score 3)
___ Cannot be determined: _____

+Tumor Comment: _____

MARGINS (Note I)

Margin Status for Invasive Carcinoma#
 # Includes surgical margins as well as surface involvement
___ All margins negative for invasive carcinoma

+Closest Margin(s) to Invasive Carcinoma (select all that apply)
___ Distal pancreatic parenchymal: _____
___ Proximal pancreatic parenchymal: _____
___ Pancreatic neck / parenchymal: _____
___ Uncinate (retroperitoneal / superior mesenteric artery): _____
___ Bile duct: _____
___ Proximal (gastric or duodenal): _____
___ Distal (duodenal or jejunal): _____
___ Anterior surface: _____
___ Posterior surface: _____
___ Vascular groove: _____
___ Other (specify): _____
___ Cannot be determined: _____

+Distance from Invasive Carcinoma to Closest Margin
Specify in Centimeters (cm)
___ Exact distance in cm: _____ cm
___ Greater than 1 cm
Specify in Millimeters (mm)
___ Exact distance in mm: _____ mm
___ Greater than 10 mm
Other
___ Other (specify): _____
___ Cannot be determined: _____

___ Invasive carcinoma present at margin

Margin(s) Involved by Invasive Carcinoma (select all that apply)
___ Proximal pancreatic parenchymal: _____
___ Distal pancreatic parenchymal: _____
___ Pancreatic neck / parenchymal: _____
___ Uncinate (retroperitoneal / superior mesenteric artery): _____
___ Bile duct: _____
___ Proximal (gastric or duodenal): _____
___ Distal (duodenal or jejunal): _____
___ Anterior surface: _____
___ Posterior surface: _____
___ Vascular groove: _____
___ Other (specify): _____
___ Cannot be determined: _____

___ Other (specify): _____
___ Cannot be determined (explain): _____
___ Not applicable

Margin Status for Dysplasia and Intraepithelial Neoplasia#
 # Includes surgical margins as well as surface involvement
___ All margins negative for high-grade dysplasia and / or high-grade intraepithelial neoplasia
___ High-grade dysplasia and / or high-grade intraepithelial neoplasia present at margin

Margin(s) Involved by High-Grade Dysplasia and / or High-Grade Intraepithelial Neoplasia (select all that apply)

___ Pancreatic neck / parenchymal: _____
___ Bile duct: _____
___ Proximal (gastric or duodenal): _____
___ Distal (duodenal or jejunal): _____
___ Anterior surface: _____
___ Posterior surface: _____
___ Vascular groove: _____
___ Other (specify): _____
___ Cannot be determined: _____
___ Other (specify): _____
___ Cannot be determined (explain): _____
___ Not applicable

+Margin Comment: _____

REGIONAL LYMPH NODES

Regional Lymph Node Status
___ Not applicable (no regional lymph nodes submitted or found)
___ Regional lymph nodes present
___ All regional lymph nodes negative for tumor
___ Tumor present in regional lymph node(s)
Number of Lymph Nodes with Tumor
___ Exact number (specify): _____
___ At least (specify): _____
___ Other (specify): _____
___ Cannot be determined (explain): _____
___ Other (specify): _____
___ Cannot be determined (explain): _____
Number of Lymph Nodes Examined
___ Exact number (specify): _____
___ At least (specify): _____
___ Other (specify): _____
___ Cannot be determined (explain): _____

+Regional Lymph Node Comment: _____

DISTANT METASTASIS

Distant Site(s) Involved, if applicable (select all that apply)
___ Not applicable
___ Non-regional lymph node(s): _____
___ Liver: _____
___ Other (specify): _____
___ Cannot be determined: _____

pTNM CLASSIFICATION (AJCC 8th Edition) (Note J)

Reporting of pT, pN, and (when applicable) pM categories is based on information available to the pathologist at the time the report is issued. As per the AJCC (Chapter 1, 8th Ed.) it is the managing physician's responsibility to establish the final pathologic stage based upon all pertinent information, including but potentially not limited to this pathology report.

Modified Classification (required only if applicable) (select all that apply)

___ Not applicable
___ y (post-neoadjuvant therapy)
___ r (recurrence)

pT Category#

___ pT not assigned (cannot be determined based on available pathological information)

 # Size of invasive component should be used for determining the T category.

___ pT0: No evidence of primary tumor
___ pTis: Carcinoma in situ (this includes high-grade pancreatic intraepithelial neoplasia (PanIN-3), intraductal papillary mucinous neoplasm with high-grade dysplasia, intraductal tubulopapillary neoplasm with high-grade dysplasia, and mucinous cystic neoplasm with high-grade dysplasia.)

pT1: Tumor less than or equal to 2 cm in greatest dimension

___ pT1a: Tumor less than or equal to 0.5 cm in greatest dimension
___ pT1b: Tumor greater than 0.5 cm and less than 1 cm in greatest dimension
___ pT1c: Tumor 1-2 cm in greatest dimension
___ pT1 (subcategory cannot be determined)
___ pT2: Tumor greater than 2 cm and less than or equal to 4 cm in greatest dimension
___ pT3: Tumor greater than 4 cm in greatest dimension
___ pT4: Tumor involves the celiac axis or the superior mesenteric artery, and / or common hepatic artery, regardless of size

T Suffix (required only if applicable)

___ Not applicable
___ (m) multiple primary synchronous tumors in a single organ

pN Category

___ pN not assigned (no nodes submitted or found)
___ pN not assigned (cannot be determined based on available pathological information)
___ pN0: No regional lymph node metastasis
___ pN1: Metastasis in one to three regional lymph nodes
___ pN2: Metastasis in four or more regional lymph nodes

pM Category (required only if confirmed pathologically)

___ Not applicable - pM cannot be determined from the submitted specimen(s)
___ pM1: Distant metastasis

ADDITIONAL FINDINGS (Note K)

+Additional Findings (select all that apply)

___ None identified
___ Pancreatic intraepithelial neoplasia (PanIN) (specify highest grade): _____
___ Chronic pancreatitis

___ Acute pancreatitis
___ Other (specify): _____

SPECIAL STUDIES

+Ancillary Studies (Note L)
___ Specify: _____
___ Not performed

COMMENTS

Comment(s): _____

Explanatory Notes

A. Tumors

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

B. Definition of Location

The anatomic subdivisions defining location of tumors of the pancreas (Figure 1) are as follows:[1]

- Tumors of the head of the pancreas are those arising to the right of the left border of the superior mesenteric vein. The uncinate process is part of the head.
- Tumors of the body of the pancreas are those arising between the left border of the superior mesenteric vein and the left border of the aorta.
- Tumors of the tail of the pancreas are those arising between the left border of the aorta and the hilum of the spleen.

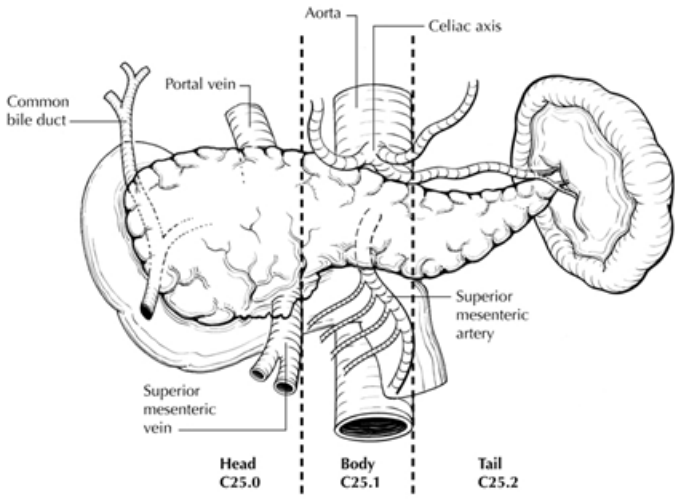

Figure 1. Anatomic subsites of the pancreas. From Greene et al.[2] Used with permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the *AJCC Cancer Staging Atlas* (2006) published by Springer Science and Business Media LLC, www.springerlink.com.

References

1. Amin MB, Edge SB, Greene FL, et al, eds. *AJCC Cancer Staging Manual*. 8th ed. New York, NY: Springer; 2017.
2. Greene FL, Compton, CC, Fritz AG, et al, eds. *AJCC Cancer Staging Atlas.* New York, NY: Springer; 2006.

C. Histologic Type

A classification of malignant epithelial tumors of the exocrine pancreas is recommended by the World Health Organization (WHO),[1] however; this protocol does not preclude the use of other histologic types or systems of classification.

References
1. Gill AJ, Klimstra DS, Lam AK, Washington MK eds. *Tumours of the pancreas.* In: WHO Classification of Tumours Editorial Board. Digestive system tumours. Lyon, France 2019. pp 295-371.

D. Histopathologic Grade
For adenocarcinomas, a histologic grade based on the extent of glandular differentiation is shown below:[1]

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)

Certain histologic subtypes, including acinar cell carcinoma, acinar cell cystadenocarcinoma, serous cystadenocarcinoma, and solid-pseudopapillary neoplasm, are not assigned a grade. By convention, signet-ring cell carcinomas are assigned grade 3. Undifferentiated carcinomas lack morphologic or immunohistochemical evidence of glandular, squamous, or neuroendocrine differentiation. This grading scheme is not applicable to poorly differentiated neuroendocrine carcinomas.

For pancreatic ductal carcinoma, histologic grade has been shown to have prognostic significance, with high grade (grade 3) being an unfavorable prognostic factor.[1,2] Kloeppel grading scheme uses a combination of glandular differentiation, mucin production, mitoses, and nuclear pleomorphism. No differences in predictive value have been demonstrated in comparisons between the Klöppel grading system and the grading system based on glandular differentiation alone.[2] Other systems based on patterns of infiltration of predominant and secondary tumor patterns have been proposed[1] but have not been widely adopted.

References
1. Adsay NV, Basturk O, Bonnett M, et al. A proposal for a new and more practical grading scheme for pancreatic ductal adenocarcinoma. *Am J Surg Pathol.* 2005;29(6):724-733.
2. Giulianotti PC, Boggi U, Fornaciari G, et al. Prognostic value of histological grading in ductal adenocarcinoma of the pancreas: Kloppel vs TNM grading. *Int J Pancreatol.* 1995;17(3):279-289.

E. Tumor Size Evaluation Associated Invasive Carcinoma Associated with Intraductal Neoplasms and Mucinous Cystic Neoplasm
The invasive component in intraductal neoplasms (intraductal papillary mucinous neoplasm, intraductal oncocytic papillary neoplasm, and intraductal tubulopapillary neoplasm) and mucinous cystic neoplasm may be unifocal or multifocal. In multifocal invasive carcinoma, it is recommended to include the size of the largest focus, the combined size of all invasive foci, and/or the percentage of invasive tumor relative to the gross tumor size (See also Note J).

F. Lymphatic and / or Vascular Invasion
Venous as well as lymphatic (small vessel) invasion has been shown to be an adverse prognostic factor.[1,2]

References
1. Garcea G, Dennison AR, Ong SL, et al. Tumour characteristics predictive of survival following resection for ductal adenocarcinoma of the head of pancreas. *Eur J Surg Oncol.* 2007;33(7):892-897.
2. Chen JW, Bhandari M, Astill DS, et al. Predicting patient survival after pancreaticoduodenectomy for malignancy: histopathological criteria based on perineural infiltration and lymphovascular invasion. *HPB (Oxford).* 2010;12(2):101-108.

G. Perineural Invasion

Perineural invasion has been shown to be an adverse prognostic factor.[1,2]

References
1. Chen JW, Bhandari M, Astill DS, et al. Predicting patient survival after pancreaticoduodenectomy for malignancy: histopathological criteria based on perineural infiltration and lymphovascular invasion. *HPB (Oxford).* 2010;12(2):101-108.
2. Chatterjee D, Katz MH, Rashid A, et al. Perineural and intra-neural invasion in posttherapy pancreaticoduodenectomy specimens predicts poor prognosis in patients with pancreatic ductal adenocarcinoma. *Am J Surg Pathol.* 2012;36(3):409.

H. Treatment Effect

Response of tumor to previous chemotherapy or radiation therapy should be reported. Several scoring systems have been described, and a modified Ryan scheme[1] is recommended, as below:

Modified Ryan Scheme for Tumor Regression Score[1]

Description	Tumor Regression Score
No viable cancer cells (complete response)	0
Single cells or rare small groups of cancer cells (near complete response)	1
Residual cancer with evident tumor regression, but more than single cells or rare small groups of cancer cells (partial response)	2
Extensive residual cancer with no evident tumor regression (poor or no response)	3

Sizable pools of acellular mucin may be present after chemoradiation but should not be interpreted as representing residual tumor. It is suggested that to estimate the approximate size of the tumor by adding the size of all the viable tumor foci within the tumor mass based in the histologic evaluation. Only the extent or the size of the viable tumor should be used to assign the ypT category as site appropriate, and this requires a combined assessment of both gross and microscopic findings.

This protocol does not preclude the use of other systems for assessment of tumor response.[2,3,4,5,6] A modification of the above scoring scheme into a 3-tier scheme has been shown to correlate better with outcome: no residual carcinoma (grade 0), minimal residual carcinoma defined as single cells or small groups of cancer cells, <5% residual carcinoma (grade 1), 5% or more residual carcinoma (grade 2).[7,8]

References

1. Ryan R, Gibbons D, Hyland JMP, et al. Pathological response following long-course neoadjuvant chemoradiotherapy for locally advanced rectal cancer. *Histopathology.* 2005; 47:141-146.
2. Evans DB, Rich TA, Byrd DR, et al. Preoperative chemoradiation and pancreaticoduodenectomy for adenocarcinoma of the pancreas. *Arch Surg.* 1992; 127:1335-1339.
3. Breslin TM, Hess KR, Harbison DB, et al. Neoadjuvant chemoradiotherapy for adenocarcinoma of the pancreas: treatment variables and survival duration. *Ann Surg Oncol.* 2001;8(2):123-132.
4. Wang H, Chetty R, Hosseini M, et al. Pathologic Examination of Pancreatic Specimens Resected for Treated Pancreatic Ductal Adenocarcinoma: Recommendations from the Pancreatobiliary Pathology Society. *Am J Surg Pathol.* 2022;46(6):754-764.
5. Janssen BV, Tutucu F, Roessel S, et al. Amsterdam International Consensus Meeting: Tumor Response Scoring in the Pathology Assessment of Resected Pancreatic Cancer After Neoadjuvant Therapy. *Mod Pathol.* 2021;34(1):4-12.
6. Janssen BV, Roessel S, Dieren S, et al. Histopathological Tumor Response Scoring in Resected Pancreatic Cancer Following Neoadjuvant Therapy: International Interobserver Study (ISGPP-1). *Br J Surg.* 2022;110(1):67-75.
7. Chatterjee D, Katz MH, Rashid A, et al. Histologic grading of the extent of residual carcinoma following neoadjuvant chemoradiation in pancreatic ductal adenocarcinoma: a predictor for patient outcome. *Cancer.* 2012;118(12):3182-3190.
8. Lee SM, Katz MH, Liu L, et al. Validation of a proposed tumor regression grading scheme for pancreatic ductal adenocarcinoma after neoadjuvant therapy as a prognostic indicator for survival. *Am J Surg Pathol.* 2016;40(12):1653-1660.

I. Margins

The nonperitonealized surface of the uncinate process (uncinate margin) constitutes the inferior-posterior retroperitoneal margin of pancreaticoduodenectomy specimens (Figure 2) and should be inked; sections through the tumor at its closest approach to this margin should be submitted.[1] This margin has also been referred to as *retroperitoneal margin* and *superior mesenteric artery margin*.

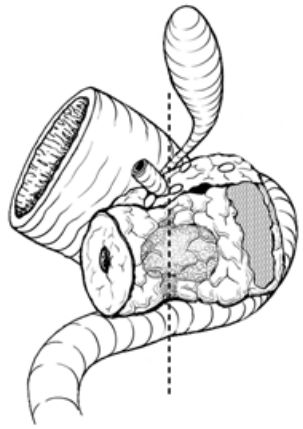

Figure 2. Posterior view of tumor arising in the pancreatic head, with dotted line indicating the location of the confluence of the portal and superior mesenteric veins. The hatched area shows the retroperitoneal (uncinate process) margin. From Greene et al.[2] Used with permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the *AJCC Cancer Staging Atlas* (2006) published by Springer Science and Business Media LLC, www.springerlink.com.

Because local recurrences of invasive pancreatic adenocarcinoma arise in the pancreatic bed corresponding to the uncinate margin and vascular groove, inking of the vascular groove corresponding to portal and superior mesenteric veins and submission of sections through the tumor at its closest approach to this surface is recommended. The classification of the vascular groove, anterior, and posterior surfaces as either anatomical "surfaces" or true margins remains a matter of debate. However, regardless of the terminology, it is essential to document their involvement, as this plays a critical role in evaluating the risk of local tumor spread and recurrence.[1,2,3]

When dealing with an intraductal tumor, the pancreatic (neck/parenchymal) resection margin and the common bile duct margin (Whipple resection) are the most critical. Complete en face sections through the pancreatic resection margin and the common bile duct margin should be taken.[1] The presence of tumor at or within 1 mm of resection margin constitutes a positive margin.[4,5,6] Margin status can be reported as negative (R0, no residual disease), R1 (positive, microscopic residual disease) and R2 (positive, macroscopic residual disease).[3]

References

1. Dhall D, Shi J, Allende DS, et al. Towards a more standardized approach to pathologic reporting of pancreatoduodenectomy specimens for pancreatic ductal adenocarcinoma. *Am J Surg Pathol.* 2021; 45(10): 1364-1373.
2. Greene FL, Compton, CC, Fritz AG, et al, eds. *AJCC Cancer Staging Atlas.* New York, NY: Springer;2006.
3. Adsay NV, Basturk O, Saka B, et al. Whipple made simple for surgical pathologists: orientation, dissection, and sampling of pancreaticoduodenectomy specimens for a more practical and accurate evaluation of pancreatic, distal common bile duct, and ampullary tumors. *Am J Surg Pathol.* 2014;38(4):480-493.
4. Amin MB, Edge SB, Greene FL, et al, eds. *AJCC Cancer Staging Manual.* 8th ed. New York, NY: Springer; 2017.
5. Campbell F, Smith RA, Whelan P, et al. Classification of R1 resections for pancreatic cancer: the prognostic relevance of tumour involvement within 1 mm of a resection margin. *Histopathol.* 2009;55(3):277-283.
6. Verbeke CS, Menon KV. Redefining resection margin status in pancreatic cancer. *HPB (Oxford).* 2009;11(4):282-289.

J. pTNM Classification

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.[1] 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.

According to AJCC/UICC convention, the designation “T” refers to a primary tumor that has not been previously treated. The symbol “p” refers to the pathologic classification of the TNM, as opposed to the clinical classification, and is based on gross and microscopic examination. pT entails a resection of the primary tumor or biopsy adequate to evaluate the highest pT category, pN entails removal of nodes adequate to validate lymph node metastasis, and pM implies microscopic examination of distant lesions.

Clinical classification (cTNM) is usually carried out by the referring physician before treatment during initial evaluation of the patient or when pathologic classification is not possible.

Pathologic staging is usually performed after surgical resection of the primary tumor. Pathologic staging depends on pathologic documentation of the anatomic extent of disease, whether or not the primary tumor has been completely removed. If a biopsied tumor is not resected for any reason (e.g., when technically infeasible) and if the highest T and N categories or the M1 category of the tumor can be confirmed microscopically, the criteria for pathologic classification and staging have been satisfied without total removal of the primary cancer.

TNM Descriptors
For identification of special cases of TNM or pTNM classifications, the “m” suffix and “y,” “r,” and “a” prefixes are used. Although they do not affect the stage grouping, they indicate cases needing separate analysis.

The “m” suffix indicates the presence of multiple primary tumors in a single site and is recorded in parentheses: pT(m)NM.

The “y” prefix indicates those cases in which classification is performed during or after initial multimodality therapy (ie, neoadjuvant chemotherapy, radiation therapy, or both chemotherapy and radiation therapy). The cTNM or pTNM category is identified by a “y” prefix. The ycTNM or ypTNM categorizes the extent of tumor actually present at the time of that examination. The “y” categorization is not an estimate of tumor before multimodality therapy (i.e., before initiation of neoadjuvant therapy).

The “r” prefix indicates a recurrent tumor when staged after a documented disease-free interval and is identified by the “r” prefix: rTNM.

The “a” prefix designates the stage determined at autopsy: aTNM.

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

T Category Considerations (Figures 3 and 4)
If more than 1 tumor is present in the pancreas, the tumor with the highest T category should be classified according to the pT definitions and either the multiplicity (“m”) or the actual number of simultaneous multiple tumors (e.g., “3”) should be indicated in parentheses after the T category of the primary tumor (e.g., pT3[m] or pT3[2]).

This applies only to grossly recognizable, synchronous primary carcinomas and not to a single, grossly detected tumor with multiple separate microscopic foci.[2]

Tis includes high-grade pancreatic intraepithelial neoplasia (PanIn-3), intraductal papillary mucinous neoplasm with high-grade dysplasia, intraductal oncocytic papillary neoplasm with high-grade dysplasia, intraductal tubulopapillary neoplasm with high-grade dysplasia, and mucinous cystic neoplasm with high-grade dysplasia.

The T categories T1-T3 are defined by tumor size as it provides better prognostic stratification than classification based on extension into peripancreatic tissue.[3,4,5,6,7] Tumor size is determined by measurement of the gross lesion and should be corroborated on microscopic assessment. For invasive carcinoma associated with intraductal papillary mucinous neoplasms, intraductal oncocytic papillary neoplasms, intraductal tubulopapillary neoplasms, and mucinous cystic neoplasms, only the invasive component should be used to determine the T category. A synoptic report is not required for accreditation if no invasive component is present. The invasive component may be unifocal or multifocal. In multifocal invasive carcinoma, it is unclear whether tumor outcome is determined by the size of the largest focus, the combined size of all invasive foci, or the percentage of invasive tumor relative to the gross tumor size. It is recommended to include these measurements in the pathology report (i.e., the dimension of the largest invasive focus, and the estimated aggregate size of all invasive foci, or the percentage of invasive tumor relative to the gross tumor size), and to apply the maximum linear dimension of the largest invasive focus for staging (see also Note E).[8] Extension beyond the pancreas may include invasion of peripancreatic soft tissue, peritoneum (including mesocolon, greater/lesser omentum), extrapancreatic biliary system, and/or duodenum (including the ampulla of Vater) for pancreatic head tumors, while stomach, spleen, left adrenal, and peritoneum can be involved by direct extension of body/tail tumors. Tumor extension in these areas does not affect staging but should be noted in the pathology report. Invasion of the portal vein does not affect staging but has been shown to be an independent prognostic factor.[9] T4 tumors are characterized by involvement of superior mesenteric artery, celiac axis and/or common hepatic artery. In most instances, these tumors are considered unresectable and hence T4 category is determined by radiologic studies and is not usually assigned by pathologists.

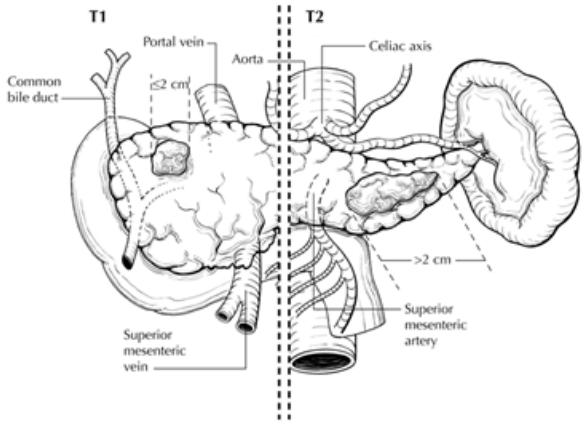

Figure 3. T1 (left of dotted line) is defined as tumor measuring 2 cm or less in greatest dimension and limited to the pancreas. T2 (right of dotted line) is defined as tumor measuring more than 2 cm in greatest dimension and less than 4 cm in greatest dimension. From Greene et al.[10] Used with permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Atlas (2006) published by Springer Science and Business Media LLC, www.springerlink.com.

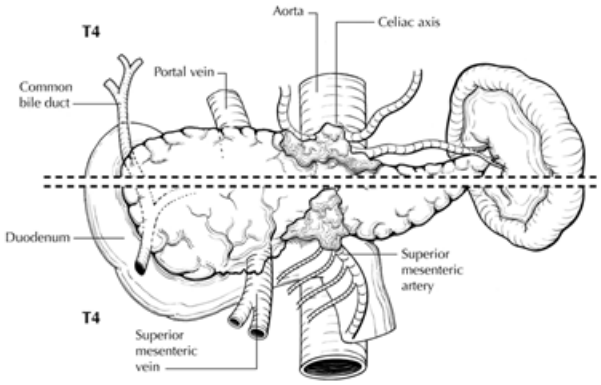

Figure 4. T4 tumor involves the celiac axis (above dotted line) or the superior mesenteric artery (below dotted line). T4 tumors are considered unresectable and are rarely encountered in surgical pathology specimens. From Greene et al.[10] Used with permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the *AJCC Cancer Staging Atlas* (2006) published by Springer Science and Business Media LLC, www.springerlink.com.

N Category Considerations

The regional lymph nodes for head and neck cancers include lymph nodes along common bile duct, common hepatic artery, portal vein, pyloric, anterior and posterior pancreaticoduodenal arcades, superior mesenteric vein and right lateral wall of superior mesenteric artery (Figures 5 and 6). The regional lymph nodes for the pancreatic body and tail cancers include lymph nodes along common hepatic artery, celiac axis, splenic artery, and splenic hilum. Tumor involvement of other nodal groups is considered distant metastasis. Anatomic division of lymph nodes is not necessary but separately submitted lymph nodes should be individually reported as received.

Lymph node metastasis is an independent adverse prognostic factor.[3,5,11,12,13,14] Microscopic evaluation of at least 12 lymph nodes is recommended for Whipple resections.[15,16] Based on outcome data, tumors with positive lymph nodes are now categorized as N1 or N2.[17,18]

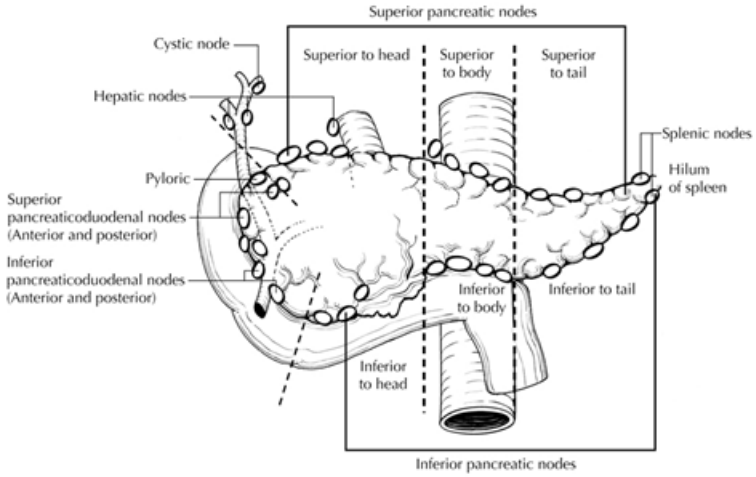

Figure 5. Regional lymph nodes of the pancreas (anterior view). From Greene et al.[10] Used with permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material

is the *AJCC Cancer Staging Atlas* (2006) published by Springer Science and Business Media LLC, www.springerlink.com.

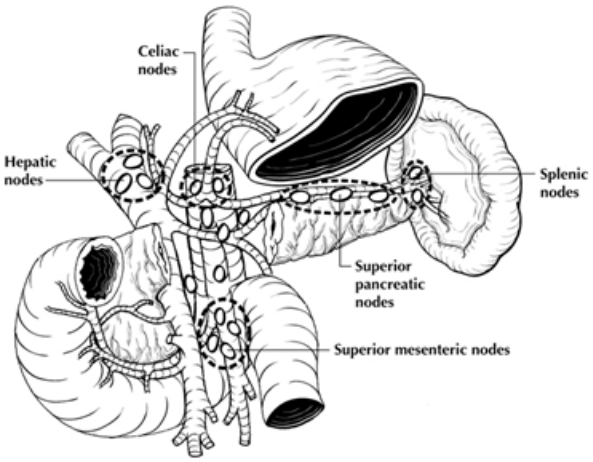

Figure 6. Regional lymph nodes of the pancreas (anterior view with pancreatic body removed to reveal retroperitoneal vessels and lymph nodes). From Greene et al.[10] Used with permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the *AJCC Cancer Staging Atlas* (2006) published by Springer Science and Business Media LLC, www.springerlink.com.

M Category Considerations

Peritoneal seeding or positive peritoneal cytology is considered M1.[1,19]

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K. Additional Findings

Pancreatic Intraepithelial Neoplasia (PanIN)

Noninvasive 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 were previously classified into 3 grades.[1] The most recent consensus recommends a 2-tier grading scheme for better reproducibility and for better alignment of the grades with treatment options.[2] A similar 2-tier scheme is recommended for noninvasive mucinous cystic neoplasm (MCN), intraductal papillary mucinous neoplasm (IPMN), and intraductal tubulopapillary neoplasm.[3]

Normal	Nonmucinous flattened or cuboidal epithelium without dysplasia
PanIN, low grade	Includes flat mucinous epithelium without dysplasia (PanIN-1A), papillary mucinous epithelium without dysplasia (PanIN-1B) and flat or papillary mucinous epithelium with mild-to-moderate dysplasia featuring mild-to-moderate nuclear irregularity, hyperchromasia, and loss of polarity (PanIN-2)
PanIN, high grade	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), corresponds to carcinoma in situ

High-grade PanIN at the resection margins of an otherwise completely resected malignancy should be noted in the pathology report. In this setting, the biologic significance of PanIN of any grade remains unclear. The presence of dysplasia at the margin of a noninvasive IPMN is also uncertain. The highest grade, even if focal, determines the final grade. For IPMN and MCN, the extent of high-grade dysplasia can be recorded, but does not currently have clinical relevance.

Other Findings

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

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L. Ancillary Studies

Immunohistochemistry (MMR IHC) and/or microsatellite instability (MSI) testing are now essential not only for identifying Lynch syndrome but also for detecting mismatch repair deficient (dMMR) tumors because FDA approved immune checkpoint inhibitors are now available for any malignancy irrespective of histologic type or location.[1,2] Now NCCN also suggests considering testing it for adenocarcinomas of the

small intestine, stomach, pancreas, and biliary tract.[3] Similarly, targeted therapies for HER2 have expanded beyond non-breast and non-gastric gastrointestinal cancers.[4,5] HER2 testing for advanced gastrointestinal cancers (stage IV, recurrent, or unresectable) is becoming more common, although standardized reporting guidelines for non-gastric gastrointestinal cancers are still lacking. While criteria applicable for colorectal cancer have been developed,[6,7] the ASCO/College of American Pathology guidelines for gastric cancer HER2 scoring have been applied in recent clinical trials for other gastrointestinal cancers.[8] It is suggested that while reporting HER2 it is a good practice to indicate the criteria used. Further details about mismatch repair enzyme immunohistochemistry and PCR for MSI testing, as well as other ancillary molecular testing can be found in the CAP Biomarkers protocol.

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