COLLEGE of AMERICAN PATHOLOGISTS

Protocol for the Examination of Specimens From Patients With Carcinoma of the Ampulla of Vater

Protocol applies to all intra-ampullary, peri-ampullary, and mixed intra- and peri-ampullary carcinomas. Low-grade neuroendocrine tumors (carcinoids) are not included.

Based on AJCC/UICC TNM, 7th edition
Protocol web posting date: January 2016

Procedures

- Ampullectomy
- Pancreaticoduodenectomy (Whipple Resection)

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The College of American Pathologists offers these protocols to assist pathologists in providing clinically useful and relevant information when reporting results of surgical specimen examinations of surgical specimens. The College regards the reporting elements in the “Surgical Pathology Cancer Case Summary” portion of the protocols as essential elements of the pathology report. However, the manner in which these elements are reported is at the discretion of each specific pathologist, taking into account clinician preferences, institutional policies, and individual practice.

The College developed these protocols as an educational tool to assist pathologists in the useful reporting of relevant information. It did not issue the protocols for use in litigation, reimbursement, or other contexts. Nevertheless, the College recognizes that the protocols might be used by hospitals, attorneys, payers, and others. Indeed, effective January 1, 2004, the Commission on Cancer of the American College of Surgeons mandated the use of the required data elements of the protocols as part of its Cancer Program Standards for Approved Cancer Programs. Therefore, it becomes even more important for pathologists to familiarize themselves with these documents. At the same time, the College cautions that use of the protocols other than for their intended educational purpose may involve additional considerations that are beyond the scope of this document.

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CAP Ampulla of Vater Protocol Revision History

Version Code
The definition of version control and an explanation of version codes can be found at www.cap.org (search: cancer protocol terms).

Version: AmpullaVater 3.2.0.0

Summary of Changes
The following changes have been made since the October 2013 release.

The following data elements were modified:

- Tumor Site
- Histologic Type
- Microscopic Tumor Extension
- Margins
- Lymph-Vascular Invasion
- Perineural Invasion
- Distant Metastasis (changed to required only if confirmed pathologically)

Surgical Pathology Cancer Case Summary

Protocol web posting date: January 2016

AMPULLA OF VATER: Ampullectomy, Pancreaticoduodenectomy (Whipple Resection)

Select a single response unless otherwise indicated.

Specimen (select all that apply)
___ Ampulla of Vater

Other organs received:
___ Stomach
___ Head of pancreas
___ Duodenum
___ Common bile duct
___ Gallbladder
___ Other (specify): _____
___ Not specified

Procedure
___ Ampullectomy
___ Pancreaticoduodenectomy (Whipple resection)
___ Other (specify): _____
___ Not specified

Tumor Site (Note A)
___ Intra-ampullary
    + ___ Arising from intra-ampullary papillary-tubular neoplasm (IAPN)
    + ___ Ampullary ductal (pancreaticobiliary-type)
___ Peri-ampullary/ampullary duodenal (arising from duodenal surface of the papilla)
___ Intra-ampullary and peri-ampullary (mixed type)
___ Other (specify): _____
___ Cannot be determined
___ Not specified

Tumor Size (Note B)
Greatest dimension: ___ cm
+ Additional dimensions: ___ x ___ cm
___ Cannot be determined (explain): _____

Histologic Type (select all that apply) (Note C)
___ Adenocarcinoma
+ ___ Adenocarcinoma, pancreaticobiliary type
+ ___ Adenocarcinoma, invasive intestinal type
___ Medullary carcinoma
___ Invasive papillary adenocarcinoma
___ Mucinous adenocarcinoma
___ Clear cell adenocarcinoma
___ Signet-ring cell carcinoma
___ Adenosquamous carcinoma
___ Squamous cell carcinoma
___ Hepatoid adenocarcinoma
___ High-grade neuroendocrine carcinoma
___ Large cell neuroendocrine carcinoma
___ Small cell neuroendocrine carcinoma
___ Undifferentiated carcinoma
___ Undifferentiated carcinoma with osteoclast giant cells
___ Mixed adenoneuroendocrine carcinoma
___ Other (specify): _____
___ Carcinoma, not otherwise specified

Histologic Grade (Note D)
___ Not applicable (histologic type not usually graded)
___ GX: Cannot be assessed
___ G1: Well differentiated
___ G2: Moderately differentiated
___ G3: Poorly differentiated
___ G4: Undifferentiated
___ Other (specify): _____

Microscopic Tumor Extension (select all that apply)
___ Cannot be assessed
___ No evidence of primary tumor
___ Carcinoma in situ/high-grade dysplasia
___ Tumor limited to ampulla of Vater or sphincter of Oddi
___ Tumor invades duodenal wall
___ Tumor invades pancreas
+ ___ Tumor involves posterior surface of pancreas
+ ___ Tumor involves anterior surface of pancreas
+ ___ Tumor involves vascular bed/groove (corresponding to superior mesenteric vein/portal vein)
___ Tumor invades peripancreatic soft tissues
___ Tumor invades extrapancreatic common bile duct
___ Tumor invades other adjacent organs or structures other than pancreas (specify): _____

Margins (select all that apply) (Note E)

For ampullectomy specimens only:

Ampullectomy Margins
___ Cannot be assessed
___ Uninvolved by invasive carcinoma
    Distance of invasive carcinoma from closest margin: ___ mm *or* ___ cm
    Specify margin (if possible):
        ___ Deep (radial) margin
        ___ Duodenal mucosal margin
        ___ Other margin (eg, bile duct, pancreatic duct) (specify): _____
___ Involved by invasive carcinoma
    Specify margin(s) (if possible):
        ___ Deep (radial) margin
        ___ Duodenal mucosal margin
        ___ Other margin (eg, bile duct, pancreatic duct) (specify): _____
___ Not applicable

For pancreaticoduodenal resection specimens only:

If all margins uninvolved by invasive carcinoma:
    Distance of invasive carcinoma from closest margin: ___ mm *or* ___ cm
    Specify margin: _____

Pancreatic Neck/Parenchymal Margin
___ Cannot be assessed
___ Uninvolved by pancreatic high-grade intraepithelial neoplasia or invasive carcinoma
    + Distance of invasive carcinoma from margin: ___ mm *or* ___ cm
___ Involved by invasive carcinoma
___ Involved by pancreatic high-grade intraepithelial neoplasia

Uncinate (Retroperitoneal/Superior Mesenteric Artery) Margin
___ Cannot be assessed
___ Uninvolved by invasive carcinoma
    + Distance of invasive carcinoma from margin: ___ mm *or* ___ cm
___ Involved by invasive carcinoma

Bile Duct Margin
___ Cannot be assessed
___ Uninvolved by high-grade intraepithelial neoplasia or invasive carcinoma
    + Distance of invasive carcinoma from margin: ___ mm *or* ___ cm
___ Involved by invasive carcinoma
___ Involved by high-grade intraepithelial neoplasia

Proximal Margin (Gastric or Duodenal)
___ Cannot be assessed
___ Uninvolved by high-grade dysplasia or invasive carcinoma
___ Involved by invasive carcinoma

Distal Margin (Distal Duodenal or Jejunal)
___ Cannot be assessed
___ Uninvolved by high-grade dysplasia or invasive carcinoma
___ Involved by invasive carcinoma

Other Margin(s) (required only if applicable)
Specify margin(s): _____
___ Cannot be assessed
___ Uninvolved by invasive carcinoma
___ Involved by invasive carcinoma

Lymph-Vascular Invasion (Note B)
___ Not identified
___ Present
___ Cannot be determined

+ Perineural Invasion (Note B)
+ ___ Not identified
+ ___ Present
+ ___ Cannot be determined

Pathologic Staging (pTNM) (Note F)

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

Primary Tumor (pT)
___ pTX: Cannot be assessed
___ pT0: No evidence of primary tumor
___ pTis: Carcinoma in situ
___ pT1: Tumor limited to ampulla of Vater or sphincter of Oddi
___ pT2: Tumor invades duodenal wall
___ pT3: Tumor invades pancreas
___ pT4: Tumor invades peripancreatic soft tissues or other adjacent organs or structures

Regional Lymph Nodes (pN)
___ pNX: Cannot be assessed
___ pN0: No regional lymph node metastasis
___ pN1: Regional lymph node metastasis
___ No nodes submitted or found

Number of Lymph Nodes Examined
Specify: ____
___ Number cannot be determined (explain): _____

Number of Lymph Nodes Involved
Specify: ____
___ Number cannot be determined (explain): _____

Distant Metastasis (pM) (required only if confirmed pathologically in this case)
___ pM1: Distant metastasis
Specify site(s), if known: _____

+ Additional Pathologic Findings (select all that apply)
+ ___ None identified
+ ___ Dysplasia/adenoma
+ ___ Other (specify): _____

+ Data elements preceded by this symbol are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.

+ Ancillary Studies
+ Specify: _____
+ ___ Not performed

+ Clinical History (select all that apply) (Note G)
+ ___ Familial adenomatous polyposis coli
+ ___ Other (specify): _____
+ ___ Not known

+ Comment(s)

Explanatory Notes

A. Anatomical Considerations

The ampulla of Vater is a complex structure that usually represents the confluence of the distal common bile duct and main pancreatic duct (Figure 1). In some individuals the ampulla includes only the distal common bile duct, with the pancreatic duct entering the duodenum elsewhere. The ampulla traverses the duodenal wall and opens into the duodenal lumen through a small mucosal elevation, the duodenal papilla (Figure 1). The ampulla is lined by pancreatico-biliary type ductal epithelium, whereas the duodenal papilla is covered by small intestinal epithelium. The sphincter of Oddi is part of the ampulla and consists of smooth muscle fibers that surround the distal end of the merged ducts.

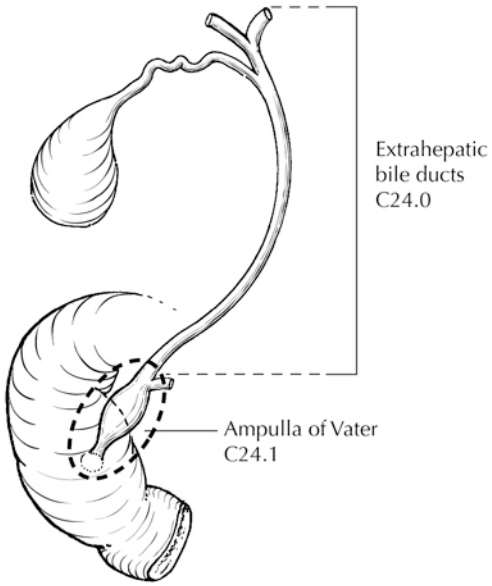

Figure 1. Anatomy of the ampulla of Vater. From Greene et al.[13] Used with permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the *AJCC Cancer Staging Atlas* (2006) published by Springer Science and Business Media LLC, www.springerlink.com.

Tumors of the ampulla of Vater may arise in the ampulla (intra-ampullary type) or on the duodenal surface of the papilla (peri-ampullary type),[1] or may involve both the intra-ampullary and peri-ampullary regions (mixed type). Thus, ampullary tumors may show biliary and/or intestinal features. The origin of the tumor may be difficult, and occasionally impossible, to determine; the differential diagnosis includes carcinoma of the distal common bile duct, main pancreatic duct, and duodenum. Tumors may be exophytic or ulcerated.

B. Non-TNM Prognostic Factors

Although not included in the TNM staging system for tumors of the ampulla of Vater, tumor size has been shown to have independent prognostic significance for local recurrence.[2] In some series, pancreatic invasion, not tumor size, appears to be the more important prognostic factor.[3]

Lymph and small blood vessel invasion[4] and perineural invasion[5] have also been shown to be adverse prognostic factors.

C. Histologic Type

This protocol uses the following histologic classification but does not preclude the use of other histologic types or systems of classification. A modified classification of carcinomas of the gallbladder and extrahepatic bile ducts published by the World Health Organization (WHO) that is applicable to the ampulla of Vater is as follows[6]:

WHO Classification of Ampullary Carcinoma
Adenocarcinoma (not otherwise characterized)
    Adenocarcinoma, pancreaticobiliary type
    Invasive papillary adenocarcinoma
    Medullary carcinoma
Adenocarcinoma, intestinal type
Mucinous adenocarcinoma
Clear cell adenocarcinoma
Signet-ring cell carcinoma
Adenosquamous carcinoma
Squamous cell carcinoma
High-grade neuroendocrine carcinoma
    Large cell neuroendocrine carcinoma
    Small cell neuroendocrine carcinoma
Undifferentiated carcinoma
Undifferentiated carcinoma with osteoclast giant cells
Mixed adenoneuroendocrine carcinoma

The term *carcinoma, NOS (not otherwise specified)* is not part of the WHO classification.

[#] Ampullary tumors of the papillary histologic type have been shown to have a favorable prognosis as compared with tumors of nonpapillary histologic types. Many of these tumors have a noninvasive exophytic growth pattern and hence a favorable prognosis. These tumors are more common in the gallbladder than in the ampullary region.[1] The term *ampullary tubular-papillary neoplasm, invasive,* has also been used for these tumors.

[##] Signet-ring cell carcinomas are, by convention, classified as poorly differentiated (grade 3) adenocarcinomas.

[###] Small cell carcinomas and undifferentiated (histologic type) carcinomas are assigned grade 4 (see below).

D. Histologic Grade
For nonpapillary adenocarcinomas, the following grading system is suggested:
GX Grade cannot be assessed
G1 Well differentiated (greater than 95% of tumor composed of glands)
G2 Moderately differentiated (50% to 95% of tumor composed of glands)
G3 Poorly differentiated[#] (49% or less of tumor composed of glands)

[#] Poor differentiation has been shown to be an adverse prognostic factor on univariate analysis in some, but not all, series.[2,7]

Grade 4 carcinomas include both undifferentiated carcinomas (histologic type) and small cell carcinoma (high-grade neuroendocrine carcinomas) in the WHO classification (see above). Undifferentiated carcinomas should show less than 5% glandular structures.

E. Margins
Local recurrence from invasive carcinoma in the region of the pancreatic head, including ampullary cancers invading the pancreas, most often occurs at the uncinate margin of the pancreatic head (retroperitoneal margin). Because this is a critical margin, inking the retroperitoneal surface of the pancreas and submitting sections through the tumor at its closest approach to this margin is recommended. Complete en face sections through the distal pancreatic resection margin (representing the distal margin of the main pancreatic duct) and the resection margin of the common bile duct should also be taken. Microscopically positive margins of resection (R1) have been shown to have an adverse impact on prognosis in ampullary carcinoma.[8]

F. TNM and Anatomic Stage/Prognostic Groupings
The TNM staging system for tumors of the ampulla of Vater of the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC) is recommended and shown below.[9] The postresection

prognosis of a patient with ampullary carcinoma is primarily determined by the anatomic extent of disease as defined by the TNM classification and stage groupings.[2,7,8]

By AJCC/UICC convention, the designation "T" refers to a primary tumor that has not been previously treated. The symbol "p" refers to the pathologic classification of the TNM, as opposed to the clinical classification, and is based on gross and microscopic examination. pT entails a resection of the primary tumor or biopsy adequate to evaluate the highest pT category, pN entails removal of nodes adequate to validate lymph node metastasis, and pM implies microscopic examination of distant lesions. Clinical classification (cTNM) is usually carried out by the referring physician before treatment during initial evaluation of the patient or when pathologic classification is not possible.

Pathologic staging is usually performed after surgical resection of the primary tumor. Pathologic staging depends on pathologic documentation of the anatomic extent of disease, whether or not the primary tumor has been completely removed. If a biopsied tumor is not resected for any reason (eg, when technically 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" and "r" prefixes are used. Although they do not affect the stage grouping, they indicate cases needing separate analysis.

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

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

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

T Category Considerations
For ampullary carcinomas, *carcinoma in situ* (pTis) as a staging term includes cancer cells confined within the glandular basement membrane (high-grade dysplasia). The term *carcinoma in situ* is not widely applied to glandular neoplastic lesions in the gastrointestinal tract but is retained for tumor registry reporting purposes as specified by law in many states. Noninvasive ampullary carcinomas with a papillary growth pattern are classified as pTis.

N Category Considerations
Regional lymph node metastases have been shown to have independent significance as an adverse prognostic factor in multiple series.[2,10,11] Although a minimum number of lymph nodes has not been determined for optimal staging, retrieval and examination of at least 10 lymph nodes is recommended for pancreaticoduodenectomy.

The regional nodes (Figure 2) may be subdivided as follows:

Superior:	Lymph nodes superior to head and body of pancreas
Inferior:	Lymph nodes inferior to head and body of pancreas
Anterior:	Anterior pancreaticoduodenal, pyloric, and proximal mesenteric lymph nodes
Posterior:	Posterior pancreaticoduodenal, common bile duct or pericholedochal, and proximal mesenteric nodes

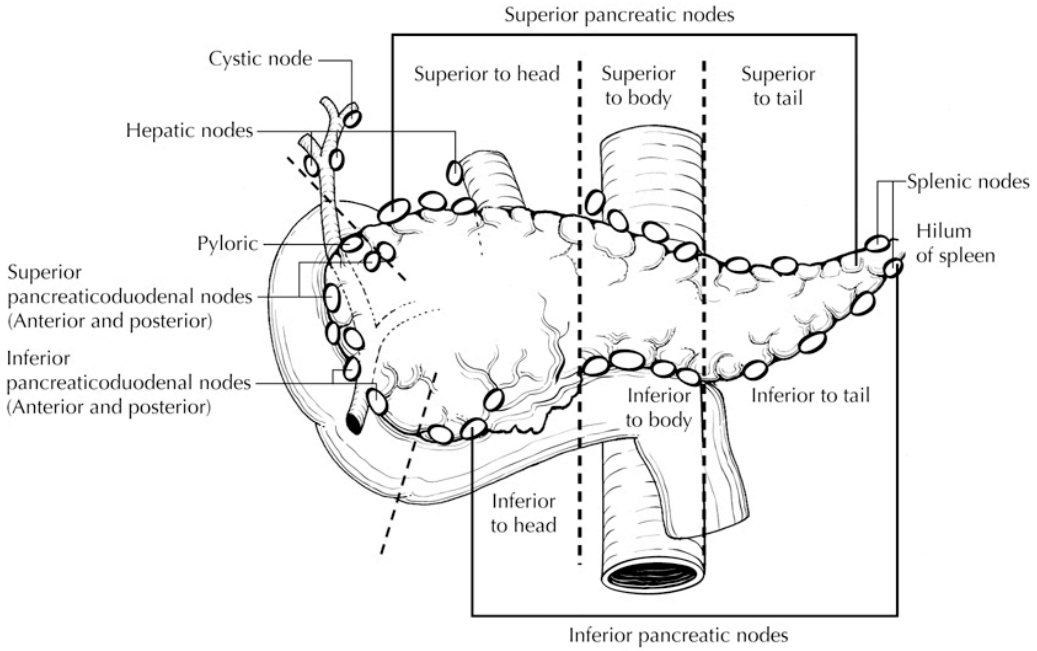

Figure 2. Regional lymph nodes of the ampulla of Vater. From Greene et al.[13] Used with permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the *AJCC Cancer Staging Atlas* (2006) published by Springer Science and Business Media LLC, www.springerlink.com.

The following lymph nodes are also considered regional: hepatic artery nodes, infrapyloric nodes, subpyloric nodes, celiac nodes, superior mesenteric nodes, retroperitoneal nodes, and lateral aortic nodes. Tumor involvement of other nodal groups is considered distant metastasis. Anatomic division of regional lymph nodes is not necessary, but separately submitted lymph nodes should be reported as submitted.[1]

Routine assessment of regional lymph nodes is limited to conventional pathologic techniques (gross assessment and histologic examination), and data are currently insufficient to recommend special measures to detect micrometastasis or isolated tumor cells. Thus, neither multiple levels of paraffin blocks nor the use of special/ancillary techniques such as immunohistochemistry are recommended for routine examination of regional lymph nodes.

Primary Tumor (T) (Figures 3-6)

TX	Cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor limited to ampulla of Vater or sphincter of Oddi
T2	Tumor invades duodenal wall
T3	Tumor invades pancreas
T4	Tumor invades peripancreatic soft tissues or other adjacent organs or structures other than pancreas

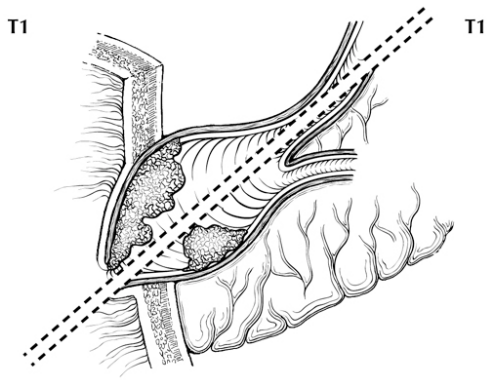

Figure 3. T1 tumors are limited to the ampulla of Vater (below the dotted line) or sphincter of Oddi (above the dotted line). From Greene et al.[13] Used with permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the *AJCC Cancer Staging Atlas* (2006) published by Springer Science and Business Media LLC, www.springerlink.com.

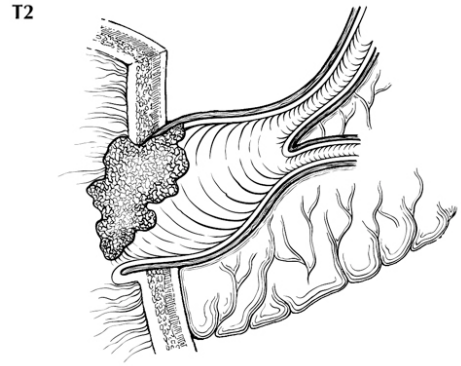

Figure 4. T2 tumors invade the duodenal wall. From Greene et al.[13] Used with permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the *AJCC Cancer Staging Atlas* (2006) published by Springer Science and Business Media LLC, www.springerlink.com.

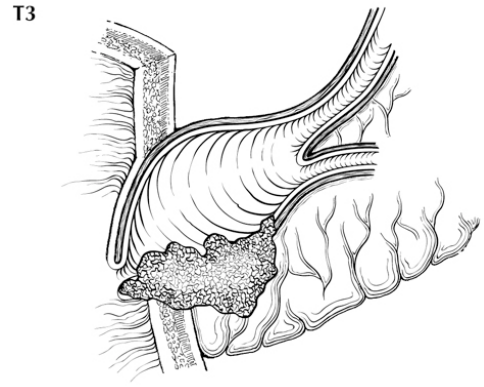

Figure 5. T3 tumors invade pancreas. From Greene et al.[13] Used with permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the *AJCC Cancer Staging Atlas* (2006) published by Springer Science and Business Media LLC, www.springerlink.com.

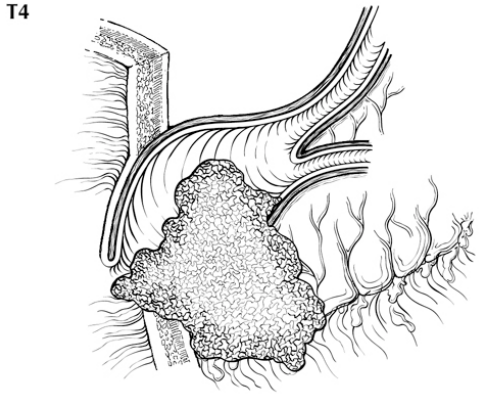

Figure 6. T4 tumors invade peripancreatic soft tissues or other adjacent organs or structures. From Greene et al.[13] Used with permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the *AJCC Cancer Staging Atlas* (2006) published by Springer Science and Business Media LLC, www.springerlink.com.

Regional Lymph Nodes (N)

NX	Cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis

Distant Metastasis (M)

M0	No distant metastasis
M1	Distant metastasis

Stage Groupings

Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage III	T4	Any N	M0
Stage IV	Any T	Any N	M1

Vessel Invasion

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

G. Relevant Clinical History

Ampullary adenomas are common in patients with familial adenomatous polyposis coli, and such patients are at increased risk for ampullary adenocarcinomas. Estimated lifetime incidence is roughly 12% for ampullary carcinoma in this population.[12]

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