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. Well-differentiated neuroendocrine neoplasms (carcinoid tumors) are not included.

Based on AJCC/UICC TNM, 7th edition
Protocol web posting date: October 2013

Procedures
• Ampullectomy
• Pancreatectoduodenectomy (Whipple Resection)

Authors
Kay Washington, MD, PhD, FCAP*
   Department of Pathology, Vanderbilt University Medical Center, Nashville, TN
Jordan Berlin, MD
   Department of Medicine, Vanderbilt University Medical Center, Nashville, TN
Philip Branton, MD, FCAP
   Department of Pathology, Inova Fairfax Hospital, Falls Church, VA
Lawrence J. Burgart, MD, FCAP
   Allina Laboratories, Abbott Northwestern Hospital, Minneapolis, MN
David K. Carter, MD, FCAP
   Department of Pathology, St. Mary’s/Duluth Clinic Health System, Duluth, MN
Carolyn C. Compton, MD, PhD, FCAP
   Critical Path Institute, Tucson, AZ
Patrick Fitzgibbons, MD, FCAP
   Department of Pathology, St. Jude Medical Center, Fullerton, CA
Wendy L. Frankel, MD, FCAP
   Department of Pathology, Ohio State University Medical Center, Columbus, OH
John Jessup, MD
   Division of Cancer Treatment and Diagnosis, National Cancer Institute, Bethesda, MD
Sanjay Kakar, MD, FCAP
   Department of Pathology, University of California San Francisco and the Veterans Affairs Medical Center, San Francisco, CA
Bruce Minsky, MD
   Department of Radiation Oncology, University of Chicago, Chicago, IL
Raouf Nakhleh, MD, FCAP
   Department of Pathology, Mayo Clinic, Jacksonville, FL
Laura H. Tang, MD, PhD, FCAP
   Department of Pathology, Memorial Sloan-Kettering Cancer Center, New York, NY
Jean-Nicolas Vauthey, MD
   Department of Surgical Oncology, University of Texas MD Anderson Cancer Center, Houston, TX†
For the Members of the Cancer Committee, College of American Pathologists

* Denotes primary author. All other contributing authors are listed alphabetically.
The College does not permit reproduction of any substantial portion of these protocols without its written authorization. The College hereby authorizes use of these protocols by physicians and other health care providers in reporting on surgical specimens, in teaching, and in carrying out medical research for nonprofit purposes. This authorization does not extend to reproduction or other use of any substantial portion of these protocols for commercial purposes without the written consent of the College.

The CAP also authorizes physicians and other health care practitioners to make modified versions of the Protocols solely for their individual use in reporting on surgical specimens for individual patients, teaching, and carrying out medical research for non-profit purposes.

The CAP further authorizes the following uses by physicians and other health care practitioners, in reporting on surgical specimens for individual patients, in teaching, and in carrying out medical research for non-profit purposes: (1) **Dictation** from the original or modified protocols for the purposes of creating a text-based patient record on paper, or in a word processing document; (2) **Copying** from the original or modified protocols into a text-based patient record on paper, or in a word processing document; (3) The use of a **computerized system** for items (1) and (2), provided that the protocol data is stored intact as a single text-based document, and is not stored as multiple discrete data fields.

Other than uses (1), (2), and (3) above, the CAP does not authorize any use of the Protocols in electronic medical records systems, pathology informatics systems, cancer registry computer systems, computerized databases, mappings between coding works, or any computerized system without a written license from the CAP.

Any public dissemination of the original or modified protocols is prohibited without a written license from the CAP.

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.

The inclusion of a product name or service in a CAP publication should not be construed as an endorsement of such product or service, nor is failure to include the name of a product or service to be construed as disapproval.
CAP Ampulla of Vater Protocol Revision History

Version Code
The definition of the version code can be found at www.cap.org/cancerprotocols.

Version: AmpullaVater 3.1.0.2

Summary of Changes
The following changes have been made since the June 2012 release.

Ampullectomy, Pancreaticoduodenectomy (Whipple Resection)

Microscopic Tumor Extension
“Carcinoma in situ” was changed to “carcinoma in situ/high-grade dysplasia, as follows:

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 invades peripancreatic soft tissues
___ Tumor invades extrapancreatic common bile duct
___ Tumor invades other adjacent organs or structures other than pancreas
   (specify): __________________

Margins
Pancreaticoduodenal Resection Specimen
“Proximal Mucosal Margin” was changed to “Proximal Margin,” as follows:

Proximal Margin (Gastric or Duodenal)
___ Cannot be assessed
___ Uninvolved by invasive carcinoma
___ Involved by invasive carcinoma
___ Intramucosal carcinoma /adenoma not identified at proximal margin
___ Intramucosal carcinoma/adenoma present at proximal margin
Surgical Pathology Cancer Case Summary

Protocol web posting date: October 2013

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
___ Peri-ampullary
___ Papilla of Vater (junction of ampullary and duodenal mucosa)
___ Other (specify): __________________________
___ Cannot be determined
___ Not specified

Tumor Size (Note B)
Greatest dimension: ___ cm
+ Additional dimensions: ___ x ___ cm
___ Cannot be determined (see Comment)
Histologic Type (select all that apply) (Note C)
___ Adenocarcinoma (not otherwise characterized, or select subtype below if applicable)
   + ___ Adenocarcinoma, pancreaticobiliary type
   + ___ Papillary adenocarcinoma
   + ___ 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
___ 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 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)

Ampullectomy Specimen
___ Cannot be assessed
___ Margins uninvolved by invasive carcinoma
   Distance of invasive carcinoma from closest margin: ___ mm
   Specify margin (if possible): ____________________________
___ Margins involved by invasive carcinoma
   Specify margin(s) (if possible): ____________________________
___ Not applicable

+ 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.
Pancreaticoduodenal Resection Specimen

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

Proximal Margin (Gastric or Duodenal)
  ___ Cannot be assessed
  ___ Uninvolved by invasive carcinoma
  ___ Involved by invasive carcinoma
  ___ Intramucosal carcinoma/adenoma not identified at proximal margin
  ___ Intramucosal carcinoma/adenoma present at proximal margin

Distal Margin (Distal Duodenal or Jejunal)
  ___ Cannot be assessed
  ___ Uninvolved by invasive carcinoma
  ___ Involved by invasive carcinoma
  ___ Intramucosal carcinoma/adenoma not identified at distal margin
  ___ Intramucosal carcinoma/adenoma present at distal margin

Pancreatic Retroperitoneal (Uncinate) Margin
  ___ Not applicable
  ___ Cannot be assessed
  ___ Uninvolved by invasive carcinoma
  ___ Involved by invasive carcinoma (tumor present 0-1 mm from margin)

Bile Duct Margin
  ___ Not applicable
  ___ Cannot be assessed
  ___ Margin uninvolved by invasive carcinoma
  ___ Margin involved by invasive carcinoma

Distal Pancreatic Resection Margin
  ___ Not applicable
  ___ Cannot be assessed
  ___ Margin uninvolved by invasive carcinoma
  ___ Margin 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
  ___ Indeterminate

+ 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.
+ Perineural Invasion (Note B)
  + ___ Not identified
  + ___ Present
  + ___ Indeterminate

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)
___ Not applicable
___ pM1: Distant metastasis
  + Specify site(s), if known: ______________________

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

+ Ancillary Studies
  + Specify: ____________________________
  + ___ Not performed

+ 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.
+ 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 invasion4 and perineural invasion5 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:

**WHO Classification of Ampullary Carcinoma**

Adenocarcinoma
Papillary adenocarcinoma#
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**
Large cell neuroendocrine carcinoma
Undifferentiated 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.\(^1\)

** 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 post-resection 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
pTis. 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. 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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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 (lymphatic 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.\(^1\)

**References**

---

**Figure 6.** T4 tumors invade peripancreatic soft tissues or other adjacent organs or structures. From Greene et al.\(^1\) 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.


