Ampullary carcinoma: Epidemiology, clinical manifestations, diagnosis and staging

AUTHOR: John A Martin, MD
SECTION EDITORS: Douglas A Howell, MD, FASGE, FACG, Tracy Jaffe, MD
DEPUTY EDITORS: Sonali M Shah, MD, Shilpa Grover, MD, MPH, AGAF

All topics are updated as new evidence becomes available and our peer review process is complete.

Literature review current through: **Sep 2023.**
This topic last updated: **Feb 27, 2023.**

INTRODUCTION

Periampullary tumors are neoplasms that arise in the vicinity of the ampulla of Vater. They can originate from the pancreas, duodenum, distal common bile duct (CBD), or the structures of the ampullary (ampulla of Vater) complex. The ampulla of Vater is formed by the duodenal aspect of the sphincter of Oddi muscle, which surrounds the confluence of the distal CBD and main pancreatic duct, as well as the papilla of Vater, a mucosal papillary mound at the distal insertion of these ducts on the medial wall of the duodenum (figure 1). Ampullary carcinomas are defined as those that arise within the ampullary complex, distal to the bifurcation of the distal CBD and the pancreatic duct (figure 2).

The papilla is a nipple-like structure on the medial aspect of the second portion of the duodenum best visualized with a side-viewing endoscope. The distal bile and ventral pancreatic ducts traverse the duodenal wall in this location and open into the duodenal lumen through the small mucosal elevation of the papilla of Vater.

The epidemiology, clinical features, diagnosis, and staging of ampullary carcinoma will be reviewed here. Treatment of ampullary cancers and the approach to the patient with ampullary adenoma are presented separately. (See "Ampullary carcinoma: Treatment and prognosis" and "Ampullary adenomas: Clinical manifestations and diagnosis" and "Ampullary adenomas: Management".)

EPIDEMIOLOGY AND BIOLOGIC BEHAVIOR

Neoplastic transformation of the intestinal mucosa occurs more commonly near the ampulla than at any other site in the small intestine. Despite this, primary ampullary tumors are rare, with an incidence of approximately 4 to 10 cases per million population [1-4]. They account for only 6 percent of lesions that arise in the periampullary region [5] but are responsible for 20 percent of all tumor-related obstructions of the common bile duct [6]. There is some evidence that the incidence has increased over the last 30 years [2], although this has not been seen in all studies [4].

Both benign and malignant ampullary tumors can occur sporadically or in the setting of a genetic syndrome. The incidence of ampullary tumors is increased 200- to 300-fold among patients with hereditary polyposis syndromes, such as familial adenomatous polyposis (FAP) and hereditary nonpolyposis colorectal cancer (HNPCC, Lynch syndrome), compared with the general population [7-9]. Surveillance endoscopy is particularly important to detect early ampullary lesions in patients with FAP given the high incidence of coexisting premalignant duodenal adenomatous polyps. Up to 90 percent of patients with FAP develop adenomas in the upper gastrointestinal tract [10]. (See "Familial adenomatous polyposis: Screening and management of patients and families".)

Mismatch repair deficiency occurs in up to 18 percent of ampullary cancers, and often has a histopathologic profile that is suggestive of Lynch syndrome, which is caused by germline mutations in one or more DNA mismatch repair genes [11]; routine testing for Lynch syndrome is indicated in such cases. (See "Lynch syndrome (hereditary nonpolyposis colorectal cancer): Clinical manifestations and diagnosis", section on 'Identification of individuals at risk for Lynch syndrome' and "Lynch syndrome (hereditary nonpolyposis colorectal cancer): Clinical manifestations and diagnosis", section on 'When to suspect Lynch syndrome'.)

The average age at diagnosis of sporadic ampullary carcinomas is 60 to 70 years old [8,12-14]. By contrast, patients whose ampullary carcinomas arise in the setting of an inherited polyposis syndrome usually present at an earlier age, due in part to endoscopic screening and surveillance programs.

Histology and biologic behavior — Several lines of evidence suggest that the biology of primary ampullary adenomas and carcinomas is more analogous to intestinal rather than pancreaticobiliary neoplasms:

- True ampullary cancers have a better prognosis than periampullary malignancies of pancreatic [15-17] or extrahepatic biliary [18] origin. Resectability rates are higher (over 90

percent in some contemporary series), and five-year survival rates are approximately 30 to 50 percent, even in patients with lymph node involvement. By contrast, fewer than 10 percent of patients with completely resected, node-positive pancreatic cancer are alive at two years. (See "Overview of surgery in the treatment of exocrine pancreatic cancer and prognosis" and "Ampullary carcinoma: Treatment and prognosis".)

- The histology of primary ampullary neoplasms more often resembles that of adenomas and adenocarcinomas of intestinal origin rather than pancreaticobiliary origin. In one study of 170 ampullary carcinomas, the most common histologic subtype was intestinal (47 percent), followed by pancreatobiliary (24 percent), poorly differentiated adenocarcinomas (13 percent), intestinal-mucinous (8 percent), and invasive papillary (5 percent) [19].

- Ampullary carcinomas are thought to arise from ampullary adenomas, a premalignant precursor lesion displaying the adenoma-carcinoma sequence observed in colorectal neoplasia. Moreover, patients with FAP have a significantly increased incidence of both ampullary and colorectal cancers relative to the general population, suggesting that the mechanisms of ampullary and colorectal carcinogenesis may be similar [20].

- K-ras mutations are an early event in ampullary carcinogenesis, with an incidence (37 percent) that is similar to that in colon cancer (up to 50 percent) [21]. (See "Molecular genetics of colorectal cancer", section on 'Oncogenes'.)

- Immunohistochemistry may aid in classification [22,23]. Expression profiling of cyclooxygenase-2 (COX-2) by ampullary carcinomas is more consistent with a neoplasm of intestinal origin than with one of pancreaticobiliary origin. In one series, high COX-2 expression was detected in 78 percent of ampullary carcinomas [22]. Of the ampullary carcinomas classified as having an intestinal origin, 95 percent had high COX-2 expression, whereas only 50 percent of lesions with a pancreaticobiliary origin demonstrated high COX-2 expression.

Implications for prognosis and treatment — Subdividing adenocarcinomas of the ampulla of Vater according to histologic subtype and immunohistochemical staining pattern into distinct subsets with differing biologic behavior has prognostic importance [24-27]. In a retrospective study of 208 patients treated for ampullary adenocarcinoma in Sydney, Australia, those with a histomolecular pancreaticobiliary phenotype (CDX negative, MUC1 positive) had a significantly worse outcome than did those with an intestinal phenotype (CDX positive, MUC1 negative), with median survival of 16 versus 116 months [24]. When histomolecular phenotype was combined

with lymph node status, three subsets of ampullary adenocarcinomas emerged, with significantly different survival outcomes:

- Patients with a node-negative non-pancreaticobiliary histomolecular phenotype had an excellent prognosis (five-year survival 88 percent).
- Patients with a node-positive pancreaticobiliary phenotype had a poor prognosis (five-year survival 20 percent).
- The remaining patients (node-positive non-pancreaticobiliary phenotype, node-negative pancreaticobiliary phenotype) had an intermediate prognosis (five-year survival 47 percent).

The results were comparable in two additional independent cohorts of 90 patients from Glasgow, Scotland, and 46 from Verona, Italy. However, others have failed to find a significant overall survival difference between the intestinal and pancreaticobiliary subtypes of ampullary cancer [28]. Given the conflicting data, the most recent 2017 Tumor, Node, Metastasis (TNM) staging classification of the American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) did not include histomolecular phenotype as a component of its prognostic stage groups (table 1) [29].

Identification of prognostically relevant subgroups has also been achieved using gene expression profiling in conjunction with immunohistochemical staining for cytokeratins 7 and 20 [30]. However, molecular techniques such as these are not yet ready for clinical application.

Whether and how this information could be used to individualize treatment decisions, particularly about adjuvant therapy, are unclear. The impact of adjuvant therapy on outcomes according to histomolecular phenotype could not be addressed in the study described above, since only a minority of patients (64 of 208) in all three cohorts received adjuvant chemotherapy, and it was not randomly assigned [24]. A retrospective analysis of a prospective, randomized, cooperative group study exploring the role of adjuvant therapy in periampullary cancers found no significant improvement in the pancreaticobiliary type compared with the intestinal type of ampullary cancers when adjuvant therapy was compared with no adjuvant therapy [31]. However, prospective study of treatment selection based on histomolecular phenotype is needed before conclusions can be drawn as to the clinical significance of histomolecular phenotype. At present, adjuvant therapy recommendations for patients with ampullary cancer follow guidelines established for pancreatic cancer rather than intestinal cancer. (See "Ampullary carcinoma: Treatment and prognosis", section on 'Adjuvant therapy'.)

CLINICAL MANIFESTATIONS

As with ampullary adenomas, the most common presenting symptom of ampullary carcinoma is obstructive jaundice (80 percent) caused by compression of the distal bile duct by the tumor [12,32]. (See "Ampullary adenomas: Clinical manifestations and diagnosis".)

Ampullary cancers are not usually suspected as a cause of obstructive jaundice because of their lower incidence relative to other periampullary malignancies. Additional symptoms may include diarrhea due to fat malabsorption (steatorrhea), mild weight loss, and fatigue.

Up to one-third of patients have chronic, frequently occult gastrointestinal blood loss with an associated microcytic anemia or heme-positive stools. Patients occasionally present with frank bleeding due to sloughing of the tumor, a condition exacerbated by the use of antiplatelet agents such as aspirin and clopidogrel. In one report, nonspecific symptoms included abdominal pain (45 percent), fever (45 percent), mild nausea, and dyspepsia [33]. Large lesions may produce gastric outlet obstruction associated with severe nausea and vomiting.

DIAGNOSIS AND STAGING

The diagnosis of an ampullary carcinoma is established by a combination of endoscopic, radiologic, and histologic features. Accurate staging is essential for planning surgical treatment.

TNM staging system — The most commonly used staging system is the Tumor, Node, Metastasis (TNM) system of the combined American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) (table 1) [34]. The current (eighth edition, 2017) version contains a number of significant changes compared with the seventh (2010) edition, including modified definitions of T1, T2, T3, and T4 disease, the redefining of N1 disease as one to three positive regional nodes, and the defining of a new category, N2, as four or more positive regional nodes. The prognostic relevance of the new T and N stage definitions and stage groupings is depicted in the figure (figure 3) [35].

In the absence of metastases, the prognosis of an ampullary carcinoma depends primarily on two factors: the degree of local tumor invasion, as reflected by the T stage, and the presence of lymphatic spread, as reflected by the N stage.

Diagnostic evaluation — The diagnostic evaluation of a jaundiced patient with a suspected malignant bile duct obstruction is designed to eliminate benign tumors or gallstones from the differential and to establish the extent of tumor invasion and spread. Although advanced

endoscopic techniques can help to differentiate ampullary adenomas from carcinomas, it may be difficult to completely exclude a carcinoma without complete resection of the lesion. Ampullary adenomas have the potential to undergo malignant transformation, and an occult focus of carcinoma may be present within a predominantly benign adenoma. (See "Ampullary adenomas: Clinical manifestations and diagnosis".)

A transabdominal ultrasound is a reasonable first test in patients presenting with obstructive jaundice, but it will generally not show the tumor. Helical computed tomography (CT) scanning should be obtained to visualize the pancreas and surrounding structures. Although its spatial resolution is inadequate to determine the degree of local tumor invasion, it is the most useful test to exclude the presence of distant metastases. (See 'Transabdominal ultrasonography' below and 'Abdominal computed tomography' below.)

Endoscopic retrograde cholangiopancreatography (ERCP) is the single most useful endoscopic study for diagnosing ampullary carcinoma because it permits identification of the tumor, biopsy, and biliary decompression, if needed. While endoscopic ultrasound (EUS) is as sensitive as ERCP and superior to CT and transabdominal ultrasound for detecting small ampullary tumors, it is typically not required for diagnosis. It may have a role in preoperative staging but may result in overstaging. As a result, we do not routinely employ EUS for the diagnosis and staging of ampullary carcinoma. (See 'Endoscopic retrograde cholangiopancreatography' below and 'Endoscopic ultrasonography' below.)

Differentiating a primary ampullary carcinoma from other more common periampullary malignancies (arising in the pancreas, duodenum, or bile duct) is challenging. Although the distinction may be evident after radiographic and endoscopic evaluation, it may not be possible to determine the tissue origin of a malignant periampullary neoplasm until resection and a histopathologic evaluation of the entire surgical specimen are completed [36]. This is particularly true if the lesion is large and obstructs the duodenal lumen. From a surgical standpoint, the distinction between ampullary and periampullary cancers is not essential preoperatively since the treatment is the same for both lesions. However, the oncologic implications for adjuvant therapy and prognosis of ampullary and periampullary tumors are substantially different. (See "Ampullary carcinoma: Treatment and prognosis", section on 'Adjuvant therapy' and "Overview of surgery in the treatment of exocrine pancreatic cancer and prognosis" and "Treatment of localized cholangiocarcinoma: Adjuvant and neoadjuvant therapy and prognosis", section on 'Distal cholangiocarcinoma'.)

Transabdominal ultrasonography — Transabdominal ultrasound should be the first imaging study ordered for patients with jaundice, since ultrasound can identify intrahepatic and extrahepatic bile duct dilatation and gallstones. However, overlying bowel gas frequently

obscures the distal bile duct, ampulla, and pancreas. In one study, only 10 of 127 ampullary masses were detected by ultrasound [37]. The overall accuracy was 15 percent according to one study [38]. As a result, abdominal CT should be ordered as the next diagnostic procedure if ultrasound does not demonstrate gallstones or an obvious pancreatic head mass in a jaundiced patient.

Abdominal computed tomography — CT is more sensitive than ultrasound for evaluating the periampullary region (image 1). A "pancreatic mass protocol" CT should be ordered. Specifically, patients should receive water as the oral "contrast agent" (to distend the duodenum and improve visualization of the duodenal lumen and adjacent pancreas), and intravenous contrast is injected as a bolus to permit both arterial- and venous-phase imaging. Images are reconstructed at 1 to 2.5 mm intervals to improve the sensitivity of pancreatic imaging. (See "Clinical manifestations, diagnosis, and staging of exocrine pancreatic cancer", section on 'Imaging studies'.)

Although helical CT can detect masses obstructing the distal common bile duct (CBD), its sensitivity usually does not permit the visualization of small ampullary neoplasms within the duodenal lumen [39]. In one report, the overall accuracy was only 20 percent [38].However, a small retrospective study demonstrated multidetector CT to be 67 percent sensitive in detection of ampullary adenoma if adequate duodenal distention was achieved [40]. Furthermore, CT by itself is inadequate for staging ampullary cancers because it lacks the spatial resolution to determine the degree of local tumor invasion into the duodenal wall or adjacent pancreas, or the presence of major vascular involvement [41]. On the other hand, CT is generally the most useful study to evaluate for the presence of distant metastatic disease, which most frequently involves the regional lymph nodes, liver, peritoneum, lungs, and bone.

Endoscopic retrograde cholangiopancreatography — In a jaundiced patient with suspected malignant bile duct obstruction, ERCP is the preferred initial endoscopic study since it permits simultaneous endoscopic visualization of the ampulla, contrast-enhanced radiographic imaging of the pancreatic and bile ducts, biopsy from the papilla and ampullary segment of the CBD or pancreatic duct, and placement of a stent for biliary decompression, if necessary and technically feasible. However, ERCP cannot determine the extent of local tumor invasion of an ampullary carcinoma into the adjacent duodenum or pancreatic parenchyma, information that is essential for preoperative staging and surgical planning.

Most ampullary cancers are obvious endoscopically (image 2). If an exophytic ampullary tumor is identified that has the appearance of an adenoma, malignancy should be strongly suspected if the mass is ulcerated or over 3 cm in size. However, because the false negative rate of endoscopic biopsy is as high as 50 percent, a negative result is insufficient to exclude the

presence of malignancy in an ampullary lesion [42-47]. The overall accuracy of diagnosis with ERCP in one report was 88 percent (p >0.05) [48].

Attempts to enhance the accuracy of endoscopic biopsy include the acquisition of tissue at least 48 hours following sphincterotomy [49,50], the performance of multiple biopsies [51], and the use of polymerase chain reaction (PCR) or immunohistochemical staining to detect p53 (a tumor suppressor gene that is frequently lost in periampullary neoplasms) or K-ras gene mutations [21,52-56]. Neither PCR nor immunohistochemical staining for p53 or K-ras gene mutations is used routinely in current clinical practice.

Magnetic resonance cholangiopancreatography and percutaneous transhepatic cholangiography — Ampullary obstruction can also be evaluated by magnetic resonance imaging with cholangiopancreatography (MRI-MRCP) or percutaneous transhepatic cholangiography (PTC) in patients with contraindications to ERCP or in whom ERCP can be technically limited (eg, those who have undergone gastric surgery, such as a Roux-en-Y gastrojejunostomy, with resultant anatomy that may make endoscopic access of the duodenum technically challenging or impossible, even with deep enteroscopy techniques). However, neither of these imaging modalities permits direct luminal visualization of the papillary aspect of the ampulla, nor do they provide access for tissue acquisition via direct forceps biopsy.

MRCP is a noninvasive method of imaging the pancreaticobiliary tree via MRI. MRCP is done in conjunction with an MRI of the abdomen with contrast (gadolinium). Some authors recommend this approach in place of ERCP in patients who will not tolerate invasive procedures or in whom a large tumor occludes the orifice of the pancreaticobiliary ducts, thus preventing cannulation and duct opacification at the time of ERCP. Ampullary carcinomas may appear as masses (filling defects) protruding into the duodenal lumen, with characteristic delayed enhancement and hyperintensity on diffusion-weighted imaging [57,58]. In one report, the overall accuracy of diagnosis with MRCP was 76 percent [48].

By contrast, PTC is an invasive procedure during which the biliary tree is accessed percutaneously using a needle inserted through the parenchyma of the liver into an intrahepatic bile duct, then contrast opacified under fluoroscopy. PTC is most commonly performed when the biliary tree is dilated and ERCP has failed to cannulate or adequately demonstrate the biliary anatomy. PTC provides not only cholangiography but also the opportunity for brush cytology (although not forceps biopsy for histology) of radiographic strictures, although ampullary lesions that do not extend into the distal CBD may not be amenable to tissue acquisition via this route. Another limitation of PTC is that it cannot directly visualize ampullary lesions, duodenal tumor ingrowth, or involvement of the pancreatic duct. (See "Percutaneous transhepatic cholangiography in adults".)

Endoscopic ultrasonography — EUS is as sensitive as ERCP and superior to CT and transabdominal ultrasound for detecting small ampullary tumors, although it is typically not required for diagnosis [38,57,59-67]. It may have a role in preoperative staging to look for tumor extension and to determine the depth of tumor invasion, but it may result in overstaging. As a result, we do not routinely employ EUS for the diagnosis and staging of ampullary carcinoma.

Because biliary and pancreatic sphincterotomy and stent placement cannot be performed using EUS equipment, patients who require therapeutic intervention must also undergo an ERCP, which can often be performed concomitantly. However, when a large ampullary neoplasm or duodenal obstruction preclude direct biliary drainage via ERCP, therapeutic EUS techniques offer an endoscopic alternative to percutaneous drainage. (See "Therapeutic endoscopic ultrasound", section on 'EUS-guided cholangiopancreatography'.)

Role in diagnosis — Most cancers are clearly seen endoscopically, and ampullectomy will provide tissue for histologic diagnosis, so EUS is generally not required for diagnosis. In addition, EUS will not be helpful for identifying foci of carcinoma within otherwise benign lesions. EUS may be indicated for the occasional biopsy-negative ampullary lesion that has equivocal endoscopic features of malignancy. (See "Ampullary adenomas: Management", section on 'Endoscopic papillectomy'.)

If malignancy is suspected in a patient undergoing EUS, fine-needle aspiration (FNA) of the ampulla, papilla, and surrounding deeper structures, including the local lymph nodes, can be obtained during the procedure. However, a negative result does not exclude the presence of a malignant focus within an adenoma. (See "Endoscopic ultrasound-guided fine needle aspiration in the gastrointestinal tract".)

In one report, the overall accuracy of EUS-guided FNA biopsy for primary masses of the ampullary region was 89 percent, with a sensitivity of 82 percent and a specificity of 100 percent [68].

Role in staging — EUS is the most accurate modality available to assess the T stage of ampullary tumors, which is critical for planning surgical intervention. Multiple series consistently document primary T staging accuracies of 70 to 90 percent [7,59,61,64,69-75]. Accuracy may be decreased in the presence of an endobiliary stent [63]. EUS is less helpful for N staging.

EUS is capable of obtaining images of the distal biliary and pancreatic ducts, permitting assessment of local intraductal tumor extension. EUS also accurately demonstrates tumor penetration into the duodenum by demonstrating obliteration of the interface between the tumor and the muscularis propria of the duodenum (a feature that upstages the tumor to T2).

Tumor extension into the pancreas constitutes T3 disease, while invasion beyond the pancreas signifies T4 disease (image 3).

EUS is less accurate for N staging than it is for T staging. Ampullary cancers drain into two peripancreatic lymph node basins: the retroduodenopancreatic chain and the superior mesenteric chain. Regional lymph nodes also include the lymph nodes along the hepatic artery and portal vein [29]. One study reported sensitivity and specificity rates of 67 and 96 percent, respectively, for EUS detection of nodal metastases when abnormal nodes were seen (defined as those over 1 cm in diameter and located in the above two positions) [75]. Another series found sensitivity and specificity rates of 69 and 38 percent, respectively, when all visualized lymph nodes present around the duodenopancreatic block were presumed to be metastatic, regardless of size or position [74]. However, others have reported sensitivity rates as low as 21 percent for detection of nodal metastases by EUS [76].

EUS-guided FNA of suspicious lymph nodes may further increase the accuracy of nodal staging. This topic is discussed in detail separately. (See "Endoscopic ultrasound-guided fine needle aspiration in the gastrointestinal tract", section on 'Pancreatic lesions'.)

Intraductal ultrasonography — The technical evolution of EUS has led to the development of small-caliber intraductal ultrasound (IDUS) miniprobes (approximately 2 mm), which can be passed through standard endoscopes directly into the bile or pancreatic duct. The small caliber, flexibility, and excellent image quality produced by these catheters make them useful for evaluating a variety of biliary and pancreatic disorders. IDUS accurately visualizes the anatomy of the papilla and is the only procedure that reliably differentiates the sphincter of Oddi muscle from the remainder of the papilla. As a result, IDUS can be useful for diagnosing and assessing the size and extent of papillary tumors. In a study of 40 patients with ampullary neoplasms, 33 of whom had ampullary carcinoma, IDUS was more accurate than EUS for T staging and evaluating ductal invasion, making it useful in selecting cases that might be considered for endoscopic excision [77]. (See "Intraductal ultrasound for evaluating the pancreaticobiliary ductal system".)

Magnification endoscopy with narrow-band imaging — Narrow-band imaging uses optical filters to enhance visualization of microvessels and mucosal surface architecture in gastrointestinal diseases. The technique demonstrates abnormal vessels associated with high-grade dysplasia on the surface of high-grade adenomas and adenocarcinomas. Abnormal vessels have not been identified on the surface of benign ampullary adenomas with hyperplastic or inflammatory histology. Preliminary studies have suggested a potential role for the evaluation of ampullary lesions [78].

Liver biochemical tests — Blood chemistries cannot establish the diagnosis of ampullary carcinoma but may reflect the presence of cholestasis when an ampullary neoplasm results in partial or complete biliary obstruction. Patients generally have a cholestatic pattern of liver biochemical test abnormalities, although aminotransferases may also be elevated [33]. The prothrombin time may be elevated due to impaired absorption of fat-soluble vitamins, including vitamin K [79].

Serum tumor markers — Serum tumor markers are not specific for ampullary carcinomas and have limited diagnostic application. Nevertheless, some ampullary cancers are associated with increased serum levels of carbohydrate antigen 19-9 (CA 19-9) and/or carcinoembryonic antigen (CEA) [16,80], and serial assay of these tumor markers may be useful for post-treatment follow-up. (See "Ampullary carcinoma: Treatment and prognosis", section on 'Post-treatment surveillance'.)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Ampullary neoplasms".)

SUMMARY AND RECOMMENDATIONS

- **Clinical manifestations** – Patients with ampullary cancer most commonly present with jaundice caused by obstruction of the distal bile duct by tumor. (See 'Clinical manifestations' above.)
- **Diagnosis and staging** – Diagnosis and staging are achieved by a combination of endoscopic, radiologic, and histologic features. There are two major considerations: identification of the tumor and distinction from an ampullary adenoma or tumor arising from outside of the ampulla (mainly pancreatic carcinoma or distal cholangiocarcinoma). (See 'Diagnosis and staging' above.)
- **Imaging studies**
  - **Transabdominal ultrasound** – A transabdominal ultrasound is a reasonable first test in patients presenting with obstructive jaundice, but it will generally not show the tumor. (See 'Transabdominal ultrasonography' above.)

- **Abdominal computed tomography** – Multiphase helical abdominal computed tomography (CT) should be obtained to visualize the pancreas and surrounding structures. Although its spatial resolution is inadequate to determine the degree of local tumor invasion, it is the most useful test to exclude the presence of distant metastases. (See 'Abdominal computed tomography' above.)

- **ERCP** – Endoscopic retrograde cholangiopancreatography (ERCP) is the single most useful endoscopic study since it permits identification of the tumor, biopsy, and decompression, if needed. (See 'Endoscopic retrograde cholangiopancreatography' above.)

  We do not routinely employ endoscopic ultrasound (EUS) for the diagnosis and staging of ampullary carcinoma. While EUS is as sensitive as ERCP and superior to CT and transabdominal ultrasound for detecting small ampullary tumors, it is typically not required for diagnosis. It may have a role in preoperative staging but may result in overstaging. (See 'Endoscopic ultrasonography' above.)

ACKNOWLEDGMENT

The editorial staff at UpToDate acknowledge A James Moser, MD, who contributed to an earlier version of this topic review.

REFERENCES

1. Benhamiche AM, Jouve JL, Manfredi S, et al. Cancer of the ampulla of Vater: results of a 20-year population-based study. Eur J Gastroenterol Hepatol 2000; 12:75.
2. Albores-Saavedra J, Schwartz AM, Batich K, Henson DE. Cancers of the ampulla of vater: demographics, morphology, and survival based on 5,625 cases from the SEER program. J Surg Oncol 2009; 100:598.
3. Goodman MT, Yamamoto J. Descriptive study of gallbladder, extrahepatic bile duct, and ampullary cancers in the United States, 1997-2002. Cancer Causes Control 2007; 18:415.
4. Van Dyke AL, Shiels MS, Jones GS, et al. Biliary tract cancer incidence and trends in the United States by demographic group, 1999-2013. Cancer 2019; 125:1489.
5. Brennan MF. Surgical management of peripancreatic cancer. In: Atlas of Surgical Oncology, Bland KL, Karakoukis CP, Copeland, EM (Eds), WB Saunders Company, Philadelphia 1995. p. 473.

6. Palazzo L. Staging of ampullary carcinoma by endoscopic ultrasonography. Endoscopy 1998; 30 Suppl 1:A128.
7. Quirk DM, Rattner DW, Fernandez-del Castillo C, et al. The use of endoscopic ultrasonography to reduce the cost of treating ampullary tumors. Gastrointest Endosc 1997; 46:334.
8. Talamini MA, Moesinger RC, Pitt HA, et al. Adenocarcinoma of the ampulla of Vater. A 28-year experience. Ann Surg 1997; 225:590.
9. Jagelman DG, DeCosse JJ, Bussey HJ. Upper gastrointestinal cancer in familial polyposis. Lancet 1988; 332:1139.
10. Church J, Simmang C, Standards Task Force, et al. Practice parameters for the treatment of patients with dominantly inherited colorectal cancer (familial adenomatous polyposis and hereditary nonpolyposis colorectal cancer). Dis Colon Rectum 2003; 46:1001.
11. Xue Y, Balci S, Aydin Mericoz C, et al. Frequency and clinicopathologic associations of DNA mismatch repair protein deficiency in ampullary carcinoma: Routine testing is indicated. Cancer 2020; 126:4788.
12. Monson JR, Donohue JH, McEntee GP, et al. Radical resection for carcinoma of the ampulla of Vater. Arch Surg 1991; 126:353.
13. Nakase A, Matsumoto Y, Uchida K, Honjo I. Surgical treatment of cancer of the pancreas and the periampullary region: cumulative results in 57 institutions in Japan. Ann Surg 1977; 185:52.
14. O'Connell JB, Maggard MA, Manunga J Jr, et al. Survival after resection of ampullary carcinoma: a national population-based study. Ann Surg Oncol 2008; 15:1820.
15. Morris-Stiff G, Alabraba E, Tan YM, et al. Assessment of survival advantage in ampullary carcinoma in relation to tumour biology and morphology. Eur J Surg Oncol 2009; 35:746.
16. Smith RA, Ghaneh P, Sutton R, et al. Prognosis of resected ampullary adenocarcinoma by preoperative serum CA19-9 levels and platelet-lymphocyte ratio. J Gastrointest Surg 2008; 12:1422.
17. Sommerville CA, Limongelli P, Pai M, et al. Survival analysis after pancreatic resection for ampullary and pancreatic head carcinoma: an analysis of clinicopathological factors. J Surg Oncol 2009; 100:651.
18. Woo SM, Ryu JK, Lee SH, et al. Recurrence and prognostic factors of ampullary carcinoma after radical resection: comparison with distal extrahepatic cholangiocarcinoma. Ann Surg Oncol 2007; 14:3195.

19. Ruemmele P, Dietmaier W, Terracciano L, et al. Histopathologic features and microsatellite instability of cancers of the papilla of vater and their precursor lesions. Am J Surg Pathol 2009; 33:691.
20. Kadmon M, Tandara A, Herfarth C. Duodenal adenomatosis in familial adenomatous polyposis coli. A review of the literature and results from the Heidelberg Polyposis Register. Int J Colorectal Dis 2001; 16:63.
21. Howe JR, Klimstra DS, Cordon-Cardo C, et al. K-ras mutation in adenomas and carcinomas of the ampulla of vater. Clin Cancer Res 1997; 3:129.
22. Perrone G, Santini D, Zagami M, et al. COX-2 expression of ampullary carcinoma: correlation with different histotypes and clinicopathological parameters. Virchows Arch 2006; 449:334.
23. Ang DC, Shia J, Tang LH, et al. The utility of immunohistochemistry in subtyping adenocarcinoma of the ampulla of vater. Am J Surg Pathol 2014; 38:1371.
24. Chang DK, Jamieson NB, Johns AL, et al. Histomolecular phenotypes and outcome in adenocarcinoma of the ampulla of vater. J Clin Oncol 2013; 31:1348.
25. Schueneman A, Goggins M, Ensor J, et al. Validation of histomolecular classification utilizing histological subtype, MUC1, and CDX2 for prognostication of resected ampullary adenocarcinoma. Br J Cancer 2015; 113:64.
26. Zimmermann C, Wolk S, Aust DE, et al. The pathohistological subtype strongly predicts survival in patients with ampullary carcinoma. Sci Rep 2019; 9:12676.
27. Perkins G, Svrcek M, Bouchet-Doumenq C, et al. Can we classify ampullary tumours better? Clinical, pathological and molecular features. Results of an AGEO study. Br J Cancer 2019; 120:697.
28. Shaib WL, Sharma R, Brutcher E, et al. Treatment utilization and surgical outcome of ampullary and duodenal adenocarcinoma. J Surg Oncol 2014; 109:556.
29. Herman JM, Pawlik TM, Merchant NB, et al. Ampulla of Vater. In: AJCC Cancer Staging Manu al, 8th ed, Amin MB (Ed), AJCC, Chicago 2017. p.327.
30. Overman MJ, Zhang J, Kopetz S, et al. Gene expression profiling of ampullary carcinomas classifies ampullary carcinomas into biliary-like and intestinal-like subtypes that are prognostic of outcome. PLoS One 2013; 8:e65144.
31. Neoptolemos JP, Moore MJ, Cox TF, et al. Effect of adjuvant chemotherapy with fluorouracil plus folinic acid or gemcitabine vs observation on survival in patients with resected periampullary adenocarcinoma: the ESPAC-3 periampullary cancer randomized trial. JAMA 2012; 308:147.
32. Smith RC. Surgical treatment for ampullary carcinoma. Aust N Z J Surg 1999; 69:170.

33. Tsukada K, Takada T, Miyazaki M, et al. Diagnosis of biliary tract and ampullary carcinomas. J Hepatobiliary Pancreat Surg 2008; 15:31.

34. Herman JM, Pawlik TM, Merchant NB, et al. Ampulla of Vater. In: AJCC Cancer Staging Manu al, 8th ed, Amin, MB (Eds), AJCC, Chicago 2017. p.327. Corrected at 4th printing, 2018.

35. Imamura T, Yamamoto Y, Sugiura T, et al. The Prognostic Relevance of the New 8th Edition of the Union for International Cancer Control Classification of TNM Staging for Ampulla of Vater Carcinoma. Ann Surg Oncol 2019; 26:1639.

36. Camp ER, Vogel SB. Blind Whipple resections for periampullary and pancreatic lesions. Am Surg 2004; 70:6.

37. Qiao QL, Zhao YG, Ye ML, et al. Carcinoma of the ampulla of Vater: factors influencing long-term survival of 127 patients with resection. World J Surg 2007; 31:137.

38. Skordilis P, Mouzas IA, Dimoulios PD, et al. Is endosonography an effective method for detection and local staging of the ampullary carcinoma? A prospective study. BMC Surg 2002; 2:1.

39. Bakkevold KE, Arnesjø B, Kambestad B. Carcinoma of the pancreas and papilla of Vater: presenting symptoms, signs, and diagnosis related to stage and tumour site. A prospective multicentre trial in 472 patients. Norwegian Pancreatic Cancer Trial. Scand J Gastroenterol 1992; 27:317.

40. Lee M, Kim MJ, Park MS, et al. Using multi-detector-row CT to diagnose ampullary adenoma or adenocarcinoma in situ. Eur J Radiol 2011; 80:e340.

41. Rivadeneira DE, Pochapin M, Grobmyer SR, et al. Comparison of linear array endoscopic ultrasound and helical computed tomography for the staging of periampullary malignancies. Ann Surg Oncol 2003; 10:890.

42. Ryan DP, Schapiro RH, Warshaw AL. Villous tumors of the duodenum. Ann Surg 1986; 203:301.

43. Posner S, Colletti L, Knol J, et al. Safety and long-term efficacy of transduodenal excision for tumors of the ampulla of Vater. Surgery 2000; 128:694.

44. Clary BM, Tyler DS, Dematos P, et al. Local ampullary resection with careful intraoperative frozen section evaluation for presumed benign ampullary neoplasms. Surgery 2000; 127:628.

45. Beger HG, Treitschke F, Gansauge F, et al. Tumor of the ampulla of Vater: experience with local or radical resection in 171 consecutively treated patients. Arch Surg 1999; 134:526.

46. Yamaguchi K, Enjoji M, Kitamura K. Endoscopic biopsy has limited accuracy in diagnosis of ampullary tumors. Gastrointest Endosc 1990; 36:588.

47. Sauvanet A, Chapuis O, Hammel P, et al. Are endoscopic procedures able to predict the benignity of ampullary tumors? Am J Surg 1997; 174:355.
48. Domagk D, Wessling J, Reimer P, et al. Endoscopic retrograde cholangiopancreatography, intraductal ultrasonography, and magnetic resonance cholangiopancreatography in bile duct strictures: a prospective comparison of imaging diagnostics with histopathological correlation. Am J Gastroenterol 2004; 99:1684.
49. Ponchon T, Berger F, Chavaillon A, et al. Contribution of endoscopy to diagnosis and treatment of tumors of the ampulla of Vater. Cancer 1989; 64:161.
50. Bourgeois N, Dunham F, Verhest A, Cremer M. Endoscopic biopsies of the papilla of Vater at the time of endoscopic sphincterotomy: difficulties in interpretation. Gastrointest Endosc 1984; 30:163.
51. Shemesh E, Nass S, Czerniak A. Endoscopic sphincterotomy and endoscopic fulguration in the management of adenoma of the papilla of Vater. Surg Gynecol Obstet 1989; 169:445.
52. Park SH, Kim YI, Park YH, et al. Clinicopathologic correlation of p53 protein overexpression in adenoma and carcinoma of the ampulla of Vater. World J Surg 2000; 24:54.
53. Sato T, Konishi K, Kimura H, et al. Adenoma and tiny carcinoma in adenoma of the papilla of Vater--p53 and PCNA. Hepatogastroenterology 1999; 46:1959.
54. Takashima M, Ueki T, Nagai E, et al. Carcinoma of the ampulla of Vater associated with or without adenoma: a clinicopathologic analysis of 198 cases with reference to p53 and Ki-67 immunohistochemical expressions. Mod Pathol 2000; 13:1300.
55. Younes M, Riley S, Genta RM, et al. p53 protein accumulation in tumors of the ampulla of Vater. Cancer 1995; 76:1150.
56. Chung CH, Wilentz RE, Polak MM, et al. Clinical significance of K-ras oncogene activation in ampullary neoplasms. J Clin Pathol 1996; 49:460.
57. Irie H, Honda H, Shinozaki K, et al. MR imaging of ampullary carcinomas. J Comput Assist Tomogr 2002; 26:711.
58. Jang KM, Kim SH, Lee SJ, et al. Added value of diffusion-weighted MR imaging in the diagnosis of ampullary carcinoma. Radiology 2013; 266:491.
59. Cannon ME, Carpenter SL, Elta GH, et al. EUS compared with CT, magnetic resonance imaging, and angiography and the influence of biliary stenting on staging accuracy of ampullary neoplasms. Gastrointest Endosc 1999; 50:27.
60. Mukai H, Nakajima M, Yasuda K, et al. Evaluation of endoscopic ultrasonography in the pre-operative staging of carcinoma of the ampulla of Vater and common bile duct. Gastrointest Endosc 1992; 38:676.

61. Rösch T, Braig C, Gain T, et al. Staging of pancreatic and ampullary carcinoma by endoscopic ultrasonography. Comparison with conventional sonography, computed tomography, and angiography. Gastroenterology 1992; 102:188.
62. Tio TL, Mulder CJ, Eggink WF. Endosonography in staging early carcinoma of the ampulla of vater. Gastroenterology 1992; 102:1392.
63. Chen CH, Tseng LJ, Yang CC, et al. The accuracy of endoscopic ultrasound, endoscopic retrograde cholangiopancreatography, computed tomography, and transabdominal ultrasound in the detection and staging of primary ampullary tumors. Hepatogastroenterology 2001; 48:1750.
64. Midwinter MJ, Beveridge CJ, Wilsdon JB, et al. Correlation between spiral computed tomography, endoscopic ultrasonography and findings at operation in pancreatic and ampullary tumours. Br J Surg 1999; 86:189.
65. Müller MF, Meyenberger C, Bertschinger P, et al. Pancreatic tumors: evaluation with endoscopic US, CT, and MR imaging. Radiology 1994; 190:745.
66. Howard TJ, Chin AC, Streib EW, et al. Value of helical computed tomography, angiography, and endoscopic ultrasound in determining resectability of periampullary carcinoma. Am J Surg 1997; 174:237.
67. Snady H, Cooperman A, Siegel J. Endoscopic ultrasonography compared with computed tomography with ERCP in patients with obstructive jaundice or small peri-pancreatic mass. Gastrointest Endosc 1992; 38:27.
68. Defrain C, Chang CY, Srikureja W, et al. Cytologic features and diagnostic pitfalls of primary ampullary tumors by endoscopic ultrasound-guided fine-needle aspiration biopsy. Cancer 2005; 105:289.
69. Kubo H, Chijiiwa Y, Akahoshi K, et al. Pre-operative staging of ampullary tumours by endoscopic ultrasound. Br J Radiol 1999; 72:443.
70. Buscail L, Pagès P, Berthélemy P, et al. Role of EUS in the management of pancreatic and ampullary carcinoma: a prospective study assessing resectability and prognosis. Gastrointest Endosc 1999; 50:34.
71. Mitake M, Nakazawa S, Tsukamoto Y, et al. Endoscopic ultrasonography in the diagnosis of depth invasion and lymph node metastasis of carcinoma of the papilla of Vater. J Ultrasound Med 1990; 9:645.
72. Tio TL, Tytgat GN, Cikot RJ, et al. Ampullopancreatic carcinoma: preoperative TNM classification with endosonography. Radiology 1990; 175:455.

73. Mukai H, Yasuda K, Nakajima M. Tumors of the papilla and distal common bile duct. Diagnosis and staging by endoscopic ultrasonography. Gastrointest Endosc Clin N Am 1995; 5:763.
74. Tio TL, Sie LH, Kallimanis G, et al. Staging of ampullary and pancreatic carcinoma: comparison between endosonography and surgery. Gastrointest Endosc 1996; 44:706.
75. Itoh A, Goto H, Naitoh Y, et al. Intraductal ultrasonography in diagnosing tumor extension of cancer of the papilla of Vater. Gastrointest Endosc 1997; 45:251.
76. Shoup M, Hodul P, Aranha GV, et al. Defining a role for endoscopic ultrasound in staging periampullary tumors. Am J Surg 2000; 179:453.
77. Ito K, Fujita N, Noda Y, et al. Preoperative evaluation of ampullary neoplasm with EUS and transpapillary intraductal US: a prospective and histopathologically controlled study. Gastrointest Endosc 2007; 66:740.
78. Uchiyama Y, Imazu H, Kakutani H, et al. New approach to diagnosing ampullary tumors by magnifying endoscopy combined with a narrow-band imaging system. J Gastroenterol 2006; 41:483.
79. Khan SA, Davidson BR, Goldin R, et al. Guidelines for the diagnosis and treatment of cholangiocarcinoma: consensus document. Gut 2002; 51 Suppl 6:VI1.
80. Todoroki T, Koike N, Morishita Y, et al. Patterns and predictors of failure after curative resections of carcinoma of the ampulla of Vater. Ann Surg Oncol 2003; 10:1176.

Topic 655 Version 28.0

GRAPHICS

Sphincter of Oddi in relation to the ampulla of Vater

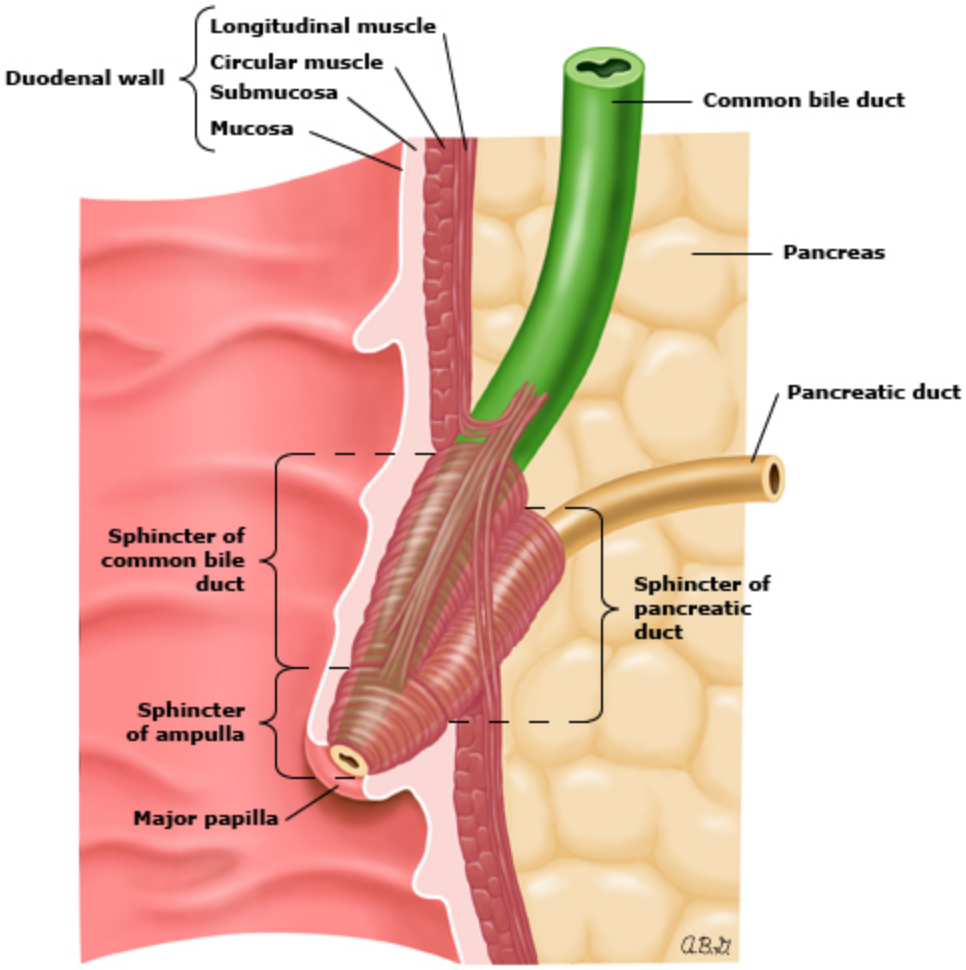
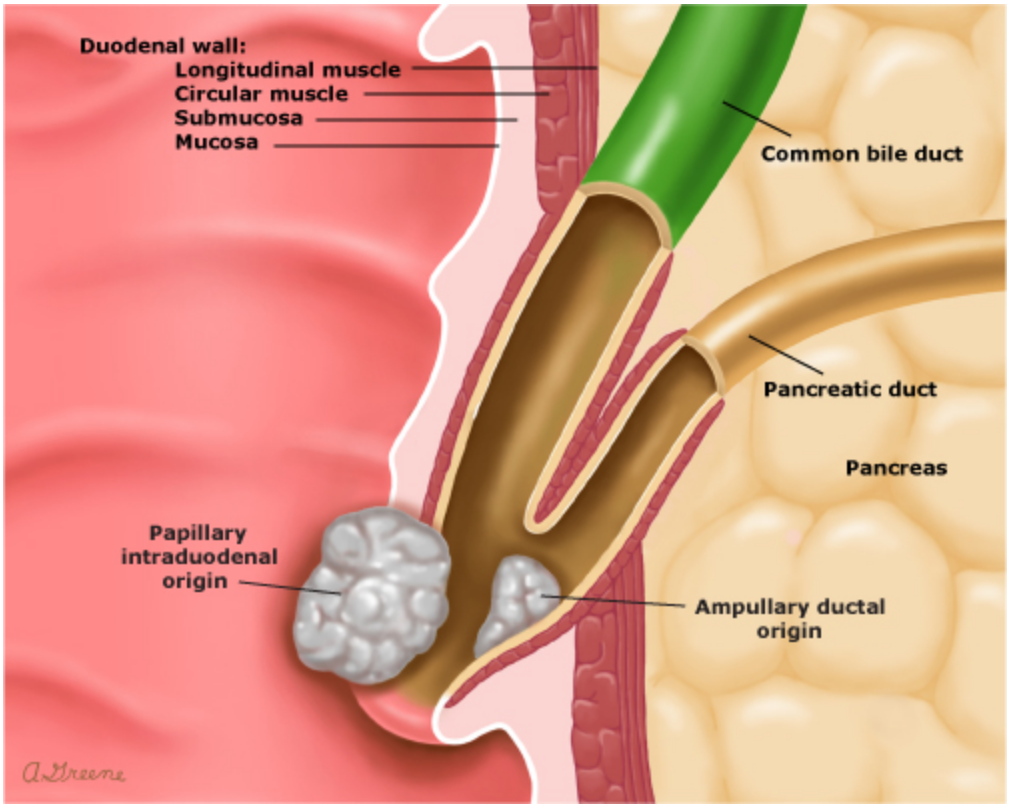


Diagram of the anatomy of the sphincter of Oddi and ampulla of Vater. The muscle fibers of the sphincter of Oddi surround the intraduodenal segment of the common bile duct and the ampulla of Vater. A circular aggregate of muscle fibers, known as the sphincter choledochus (or sphincter of Boyden), keeps resistance to bile flow high and thereby permits filling of the gallbladder during fasting and prevents retrograde reflux of duodenal contents into the biliary tree. A separate structure, called the sphincter pancreaticus, encircles the distal pancreatic duct. The muscle fibers of the sphincter pancreaticus are interlocked with those of the sphincter choledochus in a figure-of-eight pattern.

Graphic 78786 Version 4.0

Locations ampullary tumors



Graphic 53240 Version 1.0

Ampulla of Vater cancer TNM staging AJCC UICC 8th edition

Primary tumor (T)	
T category	**T criteria**
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma *in situ*
T1	Tumor limited to ampulla of Vater or sphincter of Oddi or tumor invades beyond the sphincter of Oddi (perisphincteric invasion) and/or into the duodenal submucosa
T1a	Tumor limited to ampulla of Vater or sphincter of Oddi
T1b	Tumor invades beyond the sphincter of Oddi (perisphincteric invasion) and/or into the duodenal submucosa
T2	Tumor invades into the muscularis propria of the duodenum
T3	Tumor directly invades the pancreas (up to 0.5 cm) or tumor extends more than 0.5 cm into the pancreas, or extends into peripancreatic or periduodenal tissue or duodenal serosa without involvement of the celiac axis or superior mesenteric artery
T3a	Tumor directly invades pancreas (up to 0.5 cm)
T3b	Tumor extends more than 0.5 cm into the pancreas, or extends into peripancreatic tissue or periduodenal tissue or duodenal serosa without involvement of the celiac axis or superior mesenteric artery
T4	Tumor involves the celiac axis, superior mesenteric artery, and/or common hepatic artery, irrespective of size
Regional lymph nodes (N)	
N category	**N criteria**
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph nodes metastasis
N1	Metastasis to one to three regional lymph nodes
N2	Metastasis to four or more regional lymph nodes
Distant metastasis (M)	
M category	**M criteria**
M0	No distant metastasis
M1	Distant metastasis

Prognostic stage groups			
When T is…	**And N is…**	**And M is…**	**Then the stage group is…**
Tis	N0	M0	0
T1a	N0	M0	IA
T1a	N1	M0	IIIA
T1b	N0	M0	IB
T1b	N1	M0	IIIA
T2	N0	M0	IB
T2	N1	M0	IIIA
T3a	N0	M0	IIA
T3a	N1	M0	IIIA
T3b	N0	M0	IIB
T3b	N1	M0	IIIA
T4	Any N	M0	IIIB
Any T	N2	M0	IIIB
Any T	Any N	M1	IV

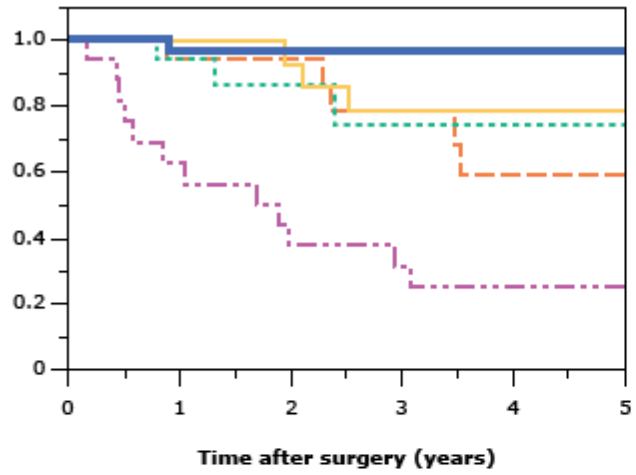
TNM: tumor, node, metastasis; AJCC: American Joint Committee on Cancer; UICC: Union for International Cancer Control.

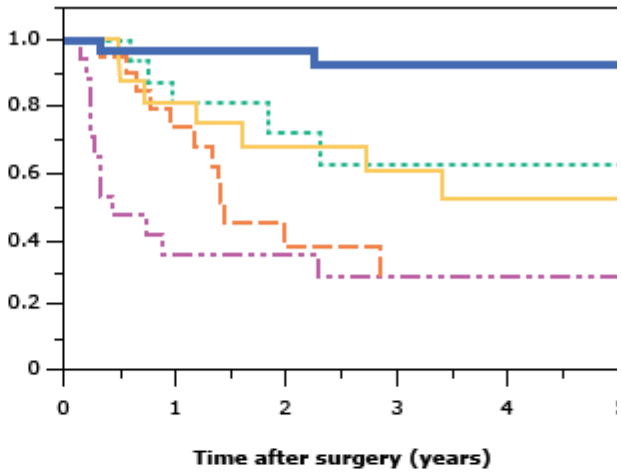
Used with permission of the American College of Surgeons, Chicago, Illinois. The original source for this information is the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer International Publishing. Corrected at 4th printing, 2018.

Graphic 110872 Version 8.0

Prognostic stratification of ampullary cancer according to the 8th edition of th classification (2017)

A

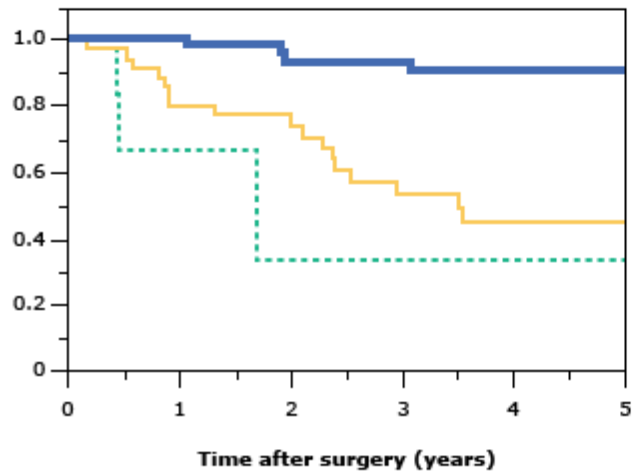


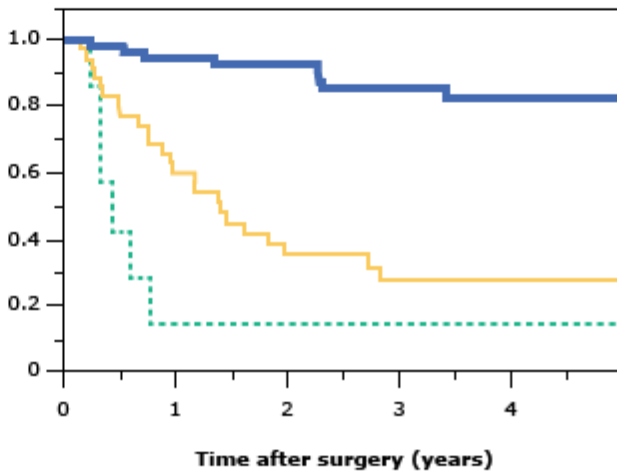


Number at risk						
T1a	33	27	24	20	16	11
T1b	16	15	13	10	9	7
T2	18	15	9	5	2	0
T3a	20	16	12	9	6	5
T3b	17	10	6	5	4	4

Number at risk						
T1a	33	27	24	19	15	1
T1b	16	13	9	7	5	
T2	18	13	8	5	1	
T3a	20	13	5	3	3	
T3b	17	6	4	4	4	

B

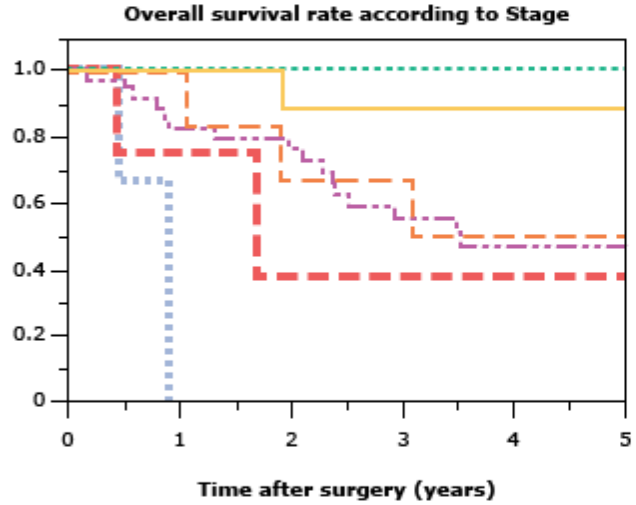


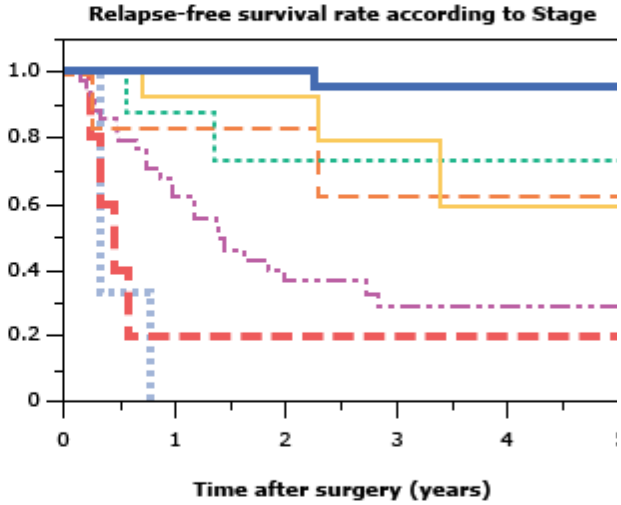


Number at risk						
N0	61	53	41	33	26	19
N1	36	29	22	15	10	7
N2	7	3	1	1	1	1

Number at risk						
N0	61	50	40	30	23	
N1	36	21	10	7	4	
N2	7	1	1	1	1	

C





Number at risk						
IA	32	27	24	20	16	11
IB	14	13	8	5	3	2
IIA	9	7	5	4	4	3
IIB	6	5	4	4	3	3
IIIA	34	18	22	15	10	7
IIIB	5	3	1	1	1	1
IV	4	0	0	0	0	0

Number at risk						
IA	32	27	24	19	15	1
IB	14	12	8	5	2	
IIA	9	6	4	3	3	
IIB	6	5	4	3	3	
IIIA	34	21	10	7	4	
IIIB	5	1	1	1	1	
IV	4	0	0	0	0	

(A) Significant differences in OS were found between T1 and T2 (p = 0.0499) and T3a and T3b (p = 0.0189), bu between T1b and T2 (p = 0.6286) or T2 and T3a (p = 0.8889). Significant differences in RFS were found betwe T1b (p = 0.0030), but not between T1b and T2 (p = 0.9313), T2 and T3a (p = 0.0732), or T3a and T3b (p = 0.211

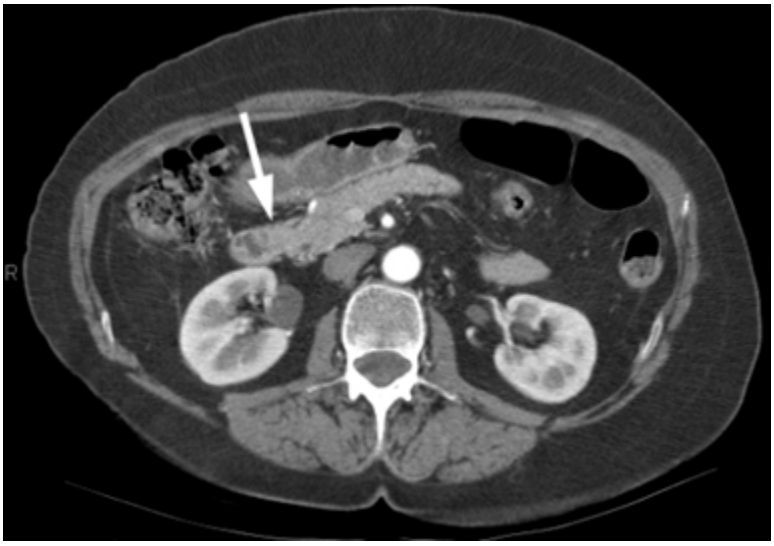
(B) Significant differences in OS were found between N0 and N1 (p <0.0001), but not between N1 and N2 (p = Significant differences in RFS were found between N0 and N1 (p <0.0001) and N1 and N2 (p = 0.0259).

(C) Significant differences in OS were not found in any intergroup; however, significant differences in RFS we between stages IA and IB (p = 0.0175), but not between the other subgroups.

UICC: Union for International Cancer Control; AJCC: American Joint Committee on Cancer; OS: overall surviva recurrence-free survival.

Graphic 129939 Version 4.0

Ampullary carcinoma



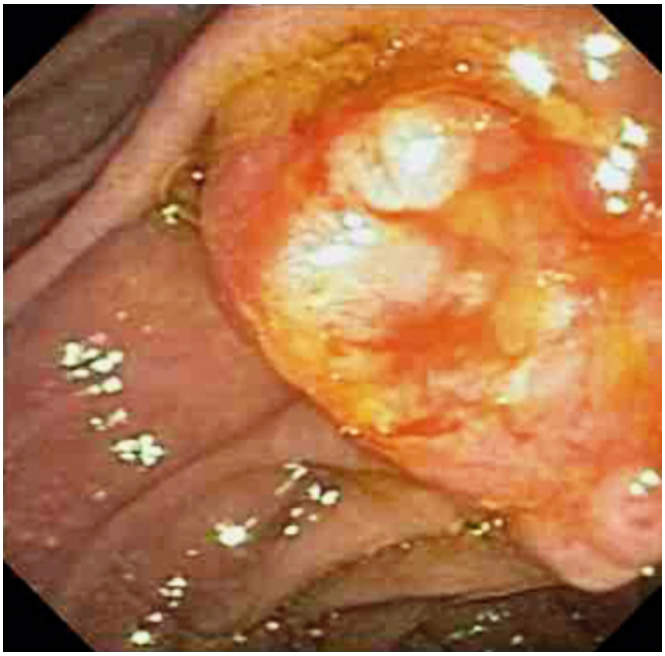
Spiral abdominal CT scan showing a small ampullary mass (arrow) in a 74-year-old woman with occult gastrointestinal blood loss. Note that the pancreatic head appears uninvolved.

CT: computed tomography.

Courtesy of A James Moser, MD.

Graphic 63759 Version 3.0

Ampullary cancer endoscopy

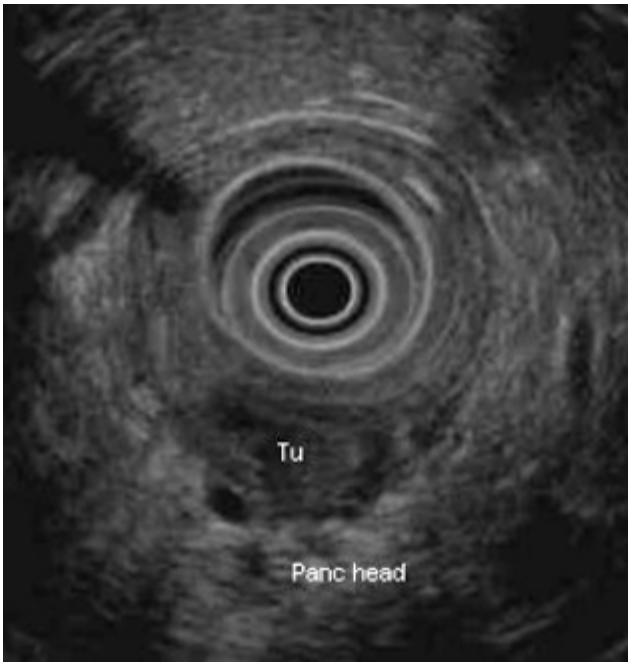


Endoscopic view of an ampullary carcinoma. Note the nodular appearance of the tumor.

Courtesy of David Carr-Locke, MD.

Graphic 70689 Version 2.0

Ampullary carcinoma



Endosonographic image obtained during endoscopic ultrasound showing invasion of an ampullary lesion into the pancreatic head (T3). The tumor clearly penetrates the muscularis propria.

Courtesy of A James Moser, MD.

Graphic 72481 Version 3.0

Contributor Disclosures

John A Martin, MD No relevant financial relationship(s) with ineligible companies to disclose. **Douglas A Howell, MD, FASGE, FACG** No relevant financial relationship(s) with ineligible companies to disclose. **Tracy Jaffe, MD** No relevant financial relationship(s) with ineligible companies to disclose. **Sonali M Shah, MD** No relevant financial relationship(s) with ineligible companies to disclose. **Shilpa Grover, MD, MPH, AGAF** No relevant financial relationship(s) with ineligible companies to disclose.

Contributor disclosures are reviewed for conflicts of interest by the editorial group. When found, these are addressed by vetting through a multi-level review process, and through requirements for references to be provided to support the content. Appropriately referenced content is required of all authors and must conform to UpToDate standards of evidence.

Conflict of interest policy

→