Ampullary carcinoma: Treatment and prognosis

AUTHORS: Harvey Mamon, MD, PhD, Carlos Fernandez-del Castillo, MD
SECTION EDITOR: Kenneth K Tanabe, MD
DEPUTY EDITOR: Sonali M Shah, MD

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INTRODUCTION

Periampullary tumors are neoplasms that arise in the vicinity of the ampulla of Vater. Neoplasms that arise in this site can originate from the pancreas, duodenum, distal common bile duct (CBD), or the structures of the ampullary 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 confluence of the distal common bile duct and the pancreatic duct (figure 2).

This topic review will cover the treatment and prognosis of ampullary carcinomas. The epidemiology, biologic behavior, clinical manifestations, and diagnosis and staging are covered separately. (See "Ampullary carcinoma: Epidemiology, clinical manifestations, diagnosis and staging".)

TREATMENT FOR LOCALIZED DISEASE

The only potentially curative treatment for ampullary carcinoma is surgical resection. Complete tumor resection with negative margins (R0 resection) is a prerequisite for cure.

It can be difficult to distinguish a primary ampullary carcinoma from other periampullary tumors preoperatively. However, true ampullary cancers have a better prognosis than periampullary malignancies of pancreatic or bile duct origin. Resectability rates are higher, and five-year survival rates are approximately 30 to 50 percent in patients with limited lymph node involvement. By contrast, less than 10 percent of patients with completely resected node-positive pancreatic cancer are alive at two years. Thus, an aggressive approach to diagnosis and treatment of periampullary tumors is needed to ensure that patients with these comparatively favorable cancers are treated optimally.

Current trends for locally advanced, borderline and categorically unresectable pancreatic cancer are to administer upfront (neoadjuvant) chemotherapy, with or without radiation therapy, prior to exploration. How initial treatment with chemoradiotherapy or with aggressive chemotherapy regimens such as FOLFIRINOX (leucovorin plus short-term infusional fluorouracil plus oxaliplatin and irinotecan) will affect the prognosis of cancers in the periampullary region that turn out to be ampullary and not pancreatic head cancers at the time of resection is not known. At least some data suggest potential benefit for neoadjuvant therapy in a subset of patients with ampullary cancer [1], but the selection of appropriate candidates is not established. (See "Initial chemotherapy and radiation for nonmetastatic, locally advanced, unresectable and borderline resectable, exocrine pancreatic cancer".)

Pancreaticoduodenectomy — Pancreaticoduodenectomy (Whipple operation) is considered the standard approach for ampullary cancer (figure 3). This can be done as a pylorus-preserving procedure or as a conventional pancreaticoduodenectomy, which includes an antrectomy (figure 4). Although some authors claim advantages of a pylorus-preserving procedure because of a shorter operative time and less intraoperative blood loss [2], this is based on European variations of the technique, which require creation of a Roux-en-Y to anastomose separately the gastric from the pancreatic and biliary anastomosis. Otherwise, there are no differences in long-term survival, and some series have shown higher incidence of delayed gastric emptying with the pylorus preservation. The impact of a pylorus-preserving procedure on long-term gastrointestinal function is less certain. Some studies suggest an improved nutritional state (as reflected by faster weight gain in the first postoperative year), but results have been inconsistent. (See "Pylorus-preserving pancreaticoduodenectomy" and "Overview of surgery in the treatment of exocrine pancreatic cancer and prognosis".)

Surgical outcomes from pancreaticoduodenectomy for ampullary cancer have improved over time. In contemporary single-institution series, rates of potentially curative resection have increased from approximately 80 to over 90 percent [3-7]. Long-term survival is possible after

pancreaticoduodenectomy, even for patients with lymph node metastases or invasion beyond the duodenal wall (T3 disease (table 1)) [8]. (See 'Prognosis' below.)

Although pancreaticoduodenectomy has been associated with high perioperative morbidity and mortality rates in the past, contemporary series show that in experienced hands, perioperative (30-day) mortality rates are between 0 and 5 percent [3-7,9-12]. Perioperative morbidity rates are between 20 and 40 percent, with the most common problems being anastomotic (pancreatic) leak, delayed gastric emptying, and intra-abdominal infection [13,14]. (See 'Complications' below.)

These improved outcomes have been attributed to better operative technique and postoperative care. One of the most important reasons for this is the greater experience of a limited number of surgeons who perform the procedure regularly in high-volume institutions [15-17]. Good outcomes have been described even in patients older than 80 years in such centers. However, even within high-volume hospitals, operative mortality rates from pancreaticoduodenectomy vary considerably depending on the experience of the individual surgeon [18].

Preoperative biliary drainage — The most common presenting symptom of ampullary carcinoma is obstructive jaundice (80 percent) caused by obstruction or compression of the distal bile duct by the tumor. (See "Ampullary carcinoma: Epidemiology, clinical manifestations, diagnosis and staging".)

The role of preoperative biliary drainage in patients with periampullary tumors is controversial. Because obstructive jaundice can impair hepatic, renal, and immune function, it was hoped that preoperative relief of jaundice would correct these defects and decrease postoperative morbidity and mortality rates from pancreaticoduodenectomy. However, the available data from randomized trials of preoperative drainage versus no drainage are conflicting. Furthermore, three meta-analyses examining the benefit of preoperative biliary drainage for patients with obstructive jaundice have come to different conclusions, with one finding neither an adverse nor a favorable impact of preoperative stenting on the incidence of postoperative morbidity or mortality, another finding an overall adverse impact of stenting on the postoperative complication rate, and the third, significantly fewer postoperative complications in the stented group but no impact on postsurgical mortality. (See "Surgical resection of lesions of the head of the pancreas", section on 'Conventional versus modified pancreaticoduodenectomy' and "Overview of surgery in the treatment of exocrine pancreatic cancer and prognosis", section on 'Role of preoperative biliary drainage'.)

In the specific setting of ampullary cancer, the benefit of preoperative biliary drainage was addressed in a retrospective series of 82 patients undergoing potentially curative surgery at a single hospital in Singapore; 35 were drained preoperatively and 47 were not [19]. Preoperative drainage was associated with a significantly reduced incidence of postoperative wound infection (3 versus 26 percent), but there was no favorable impact on other postoperative complications or survival.

Uncertainty as to the benefit of preoperative drainage has led to differing approaches. Some surgeons routinely decompress jaundiced patients with an endoscopically placed stent prior to surgery. However, others reserve biliary decompression for selected patients in whom surgery will be delayed or those with debilitating pruritus or a clinical picture of cholangitis with fever and leukocytosis.

In practice, the majority of patients who present with obstructive jaundice will have been stented by a gastroenterologist before the diagnosis is established and it is known whether or not the patient is a surgical candidate; the surgeon usually has little influence on the decision. For those who are not stented, our preference is to proceed with endoscopic retrograde cholangiopancreatography (ERCP) and stenting only when there is high-grade jaundice (>15 mg/dL of bilirubin) and surgery will not take place within the following week.

The prognostic implication of obstructive jaundice at presentation on prognosis is discussed below. (See 'Obstructive jaundice' below.)

Complications — The most frequent treatment-related complication of pancreaticoduodenectomy is pancreatic fistula, and the rates are higher for patients with ampullary cancer than for pancreas cancer because the pancreatic parenchyma is typically normal in ampullary carcinoma. Other complications include delayed gastric emptying, hemorrhage, sepsis, bile leaks, and postoperative diabetes as a result of pancreatic resection. (See "Surgical resection of lesions of the head of the pancreas", section on 'Perioperative morbidity and mortality'.)

Local resection — Many patients with ampullary cancer are older adults and have significant comorbidities. This has generated interest in less aggressive surgical options, such as local resection or ampullectomy for selected patients.

Experience with this approach is limited to small published series, in which most of the patients were considered high-risk candidates for surgery [3,20-30]. Comparison of these studies with each other is limited by different eligibility criteria for ampullectomy and the fact that the extent of surgery (eg, "ampullectomy" versus "local resection") has not always been clearly specified.

In the aggregate, the available data indicate that local resection is associated with lower morbidity than pancreaticoduodenectomy, but at the expense of higher recurrence rates and inferior survival, at least in the setting of invasive disease [13,23,25,31-35].

The largest series included 37 patients who were planned for ampullectomy rather than pancreaticoduodenectomy at Memorial Sloan-Kettering Cancer Center because of significant comorbidity or a small ampullary lesion (median 1.5 cm, range 0.4 to 4.2 cm) that was thought to represent a benign adenoma after a preoperative biopsy [33]. Intraoperatively, eight cases were converted from ampullectomy to pancreaticoduodenectomy because of disease extent or a frozen-section finding of invasive tumor. Eight of the 29 patients treated by ampullectomy alone had invasive tumor on the final histology; seven recurred, and only one was alive at last follow-up. By contrast, of the 91 patients undergoing pancreaticoduodenectomy during the same time period for invasive adenocarcinoma, 68 were still alive at the end of the study period, 49 without recurrence.

Early, low-grade tumors — In contrast to pancreaticoduodenectomy, ampullectomy does not accomplish removal of the regional lymph nodes. Because of the low rate of nodal metastases (less than 4 percent in most series), some have suggested that local resection is a reasonable approach for well-differentiated small (<6 mm) tumors that do not penetrate through the ampullary musculature (ie, Tis, T1 (table 1) [8]) [30,36-39].

However, the majority of the patients reported in these series had ampullary adenomas, and few had carcinomas. A major concern is the inferior cancer-specific survival following local resection of small ampullary invasive carcinomas in the analysis from Sloan-Kettering described above [37]. Furthermore, in other series, 45 percent of patients with pathologically confirmed T1 invasive ampullary adenocarcinomas had lymph node metastases [40].

Thus, while local ampullary excision could be considered for high-risk patients with well-differentiated T1 ampullary cancers that are <6 mm based on endoscopic ultrasound (EUS), a more aggressive surgical approach is preferred by most surgeons for invasive tumors, including well-differentiated T1 lesions, as long as the patient is a reasonable candidate for pancreaticoduodenectomy.

In our view, local resection (ampullectomy with lymph node sampling) is a reasonable alternative to pancreaticoduodenectomy for selected patients with noninvasive (pTis) tumors (table 1). However, pancreaticoduodenectomy is preferred for any invasive adenocarcinoma, if the patient can tolerate this approach.

Recommendations for management of ampullary carcinoma are not included in published guidelines from either the National Comprehensive Cancer Network (NCCN) [41] or the

European Society for Medical Oncology (ESMO) [42].

Minimally invasive nonsurgical therapies — Minimally invasive nonsurgical therapies for ampullary carcinoma include endoscopic snare resection, Nd:YAG laser ablation, and photodynamic therapy. While potentially curative in the setting of ampullary adenomas, all three modalities of nonsurgical treatment provide palliative rather than curative benefit for patients with ampullary carcinoma. These methods are appropriate only for patients who are not operative candidates and those who refuse surgery.

The literature on these techniques in the setting of ampullary carcinoma is limited to single-case reports and small series.

- Endoscopic snare resection (papillectomy) is an effective means of treating ampullary adenomas. (See "Ampullary adenomas: Management".)

  Endoscopic papillectomy has been attempted in early stage (Tis, T1) well-differentiated ampullary cancers without angiolymphatic invasion [37]. However, acceptance of this method for definitive treatment is hampered by the inadequacy of biopsy in terms of correct pathologic characterization of the lesion (and therefore its risk of harboring lymph node metastases) and the inability to predict successful, margin-negative endoscopic resection [22,43-46].

  Endoscopic debulking has been used mainly preoperatively to permit stent insertion and decompression of the biliary tree. The controversy surrounding the need for preoperative biliary decompression is discussed above. (See 'Preoperative biliary drainage' above.)

- Laser ablation offers the potential for control of local tumor growth in patients who are unfit for more aggressive therapy. In one such series of 12 patients with ampullary cancer, duodenal obstruction was relieved in one, and the longest survival was 36 months (median 21 months) [47].

- Compared with laser ablation, photodynamic therapy (PDT) eradicates local tumor with less surrounding tissue destruction. PDT uses a photosensitizing drug (a hematoporphyrin derivative, Photofrin), which is disproportionately retained by malignant tissue after intravenous administration. Irradiation with visible light via a light-transmitting catheter (light-guide) placed through an endoscope and targeted at the tumor energizes the photosensitizing molecule within the tumor and catalyzes oxygen free-radical generation leading to cell death [48]. The major side effect of PDT is prolonged cutaneous photosensitivity after the procedure, requiring the patient to avoid sunlight and wear appropriate clothing to protect the skin for several weeks after treatment.

In the largest series of PDT involving 10 patients with ampullary cancer, remission was achieved for 8 to 12 months in three patients who had small tumors confined to the ampulla [49]. Tumor bulk was greatly reduced in four additional patients, while little effect was observed in the remaining three.

PROGNOSIS

The outcome of resected ampullary cancer depends on the extent of local invasion, status of the surgical margins, and the presence or absence of nodal metastases [6,13,50-52]. Five-year survival rates following pancreaticoduodenectomy range from 64 to 80 percent for patients with node-negative disease, and from 17 to 50 percent for node-positive disease [3,5,9-13,15,20,31,32,53-58].

Survival curves from one retrospective single-institution series, stratified according to surgical stage (as defined by the 2017 American Joint Committee on Cancer [AJCC]/Union for International Cancer Control [UICC] staging system (table 1)) are illustrated in the figure (figure 5).

Outcomes tend to be somewhat worse in population-based analyses. As an example, five-year survival rates stratified by stage at presentation from a series of 1301 patients with ampullary cancer reported to the National Cancer Institute SEER (Surveillance, Epidemiology, and End Results) database between 1988 and 2003 are presented in the table (table 2) [52].

These survival data are better than similar presentations for pancreatic cancer, particularly for those with node-positive disease. It is unclear whether this represents a true difference in biology or earlier presentation of ampullary cancers due to earlier biliary obstruction. (See "Ampullary carcinoma: Epidemiology, clinical manifestations, diagnosis and staging", section on 'Epidemiology and biologic behavior'.)

Prognostic factors — The following sections will summarize the available data on predictors of recurrence.

Histology and histomolecular phenotype — In addition to depth of tumor invasion (the T stage (table 1)) and nodal status, high-grade histology and positive surgical margins are associated with a worse prognosis [3,7,11,13,20,56,57,59-67]. Whether there is a correlation between prognosis and morphologic type (ie, intestinal versus pancreaticobiliary) is unclear; the available data are conflicting, with some suggesting no difference, and others, a worse prognosis for the pancreaticobiliary type [67-71].

Contemporary data suggest that adenocarcinomas of the ampulla of Vater can be subdivided according to histologic subtype, immunohistochemical staining pattern, and molecular features into distinct subsets with differing biologic behavior:

- In a retrospective study of a cohort of 72 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), median survival 16 versus 116 months [70]. When histomolecular phenotype was combined with the lymph node status, three subsets of ampullary adenocarcinomas emerged with significantly different survival outcomes:

  - Patients with a node-negative, non-pancreaticobiliary histomolecular phenotype tumor 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.

- In another study, 146 resected "ampullary carcinomas" were carefully evaluated using stringent pathologic criteria to exclude distal bile duct and pancreatic cancer cases [71]. The authors ended up with 97 "true" ampullary carcinomas, the majority of which (72 percent) were intestinal, and the remainder either pancreatobiliary (23 percent) or mixed (5 percent). The median overall survival for this cohort was remarkably good (101 months), and the five-year survival was significantly better for the intestinal phenotype compared with pancreatobiliary/mixed phenotype (73 versus 56 percent). Genotyping was performed in 75 cases, and the majority (67 percent) were wild-type for KRAS. Tumors with a KRAS G12D mutation had a worse median survival (62 months) compared with other KRAS mutations or the wild-type genotype (145 and 155 months, respectively).

- However, others have failed to find a significant overall survival difference between the intestinal and pancreaticobiliary subtypes of ampullary cancer [72].

Given the conflicting data, the most recent 2017 Tumor, Node, Metastases (TNM) staging classification of the AJCC/UICC did not include histomolecular phenotype as a component of its prognostic stage groups (table 1) [8].

Whether and how this information could be used to individualize treatment decisions, particularly with regard to adjuvant therapy, is unclear. The impact of adjuvant therapy on outcomes according to histomolecular phenotype could not be addressed in the Australian study since only a minority of patients (64 of 208) in all three cohorts received adjuvant chemotherapy, and it was not randomly assigned [70]. The same was true in the Massachusetts General Hospital study, where only 31 percent of patients received additional postsurgical treatment [71]. 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 [73]. However, prospective study of treatment selection based on histomolecular phenotype is needed before conclusions can be drawn as to the utility and clinical significance of histomolecular phenotype [74]. At present, adjuvant therapy recommendations for patients with ampullary cancer follow guidelines established for pancreatic cancer rather than intestinal cancer. (See 'Adjuvant therapy' below.)

Nodal metastases — The presence of nodal involvement portends a worse prognosis. However, among patients with nodal metastases, the number of affected nodes, particularly compared with the total number of examined nodes, is also of prognostic importance [7,75-78].

The number of involved nodes divided by the total number of examined nodes is referred to as the lymph node ratio (LNR). One study evaluated the utility of using the LNR for predicting recurrence and survival in 90 patients who underwent resection of ampullary carcinoma [75]. The median number of resected nodes was 16, and patients with 16 or more examined nodes had a significantly lower recurrence rate and better five-year survival (81 versus 45 percent) than patients whose pathology material contained 16 or fewer nodes. Five-year survival was also predicted by the LNR:

- LNR = 0 – 75 percent
- LNR >0 to ≤0.2 – 49 percent
- LNR >0.2 to ≤0.4 – 38 percent
- LNR >0.4 – 0 percent

Given these data, in the 2017 revision of the TNM staging system, which went into effect in the United States on January 1, 2018, the number of involved regional lymph nodes influences N

stage (table 1) [8]. The relevance of the new T and N stage designations and stage groupings on prognosis is outlined in the figure (figure 5) [79]. (See "Ampullary carcinoma: Epidemiology, clinical manifestations, diagnosis and staging", section on 'TNM staging system'.)

The implications of these data on the extent of lymph node dissection (ie, whether there is a role for extended lymphadenectomy) are unclear. A prospective, randomized study of 62 patients who underwent resection of ampullary carcinoma found no difference in the five-year survival in the group undergoing standard versus extended lymphadenectomy (56 versus 60 percent) [80]. The authors concluded that the added morbidity of extended lymphadenectomy could not be justified by the better oncologic outcomes. We agree with this conclusion, and do not routinely perform extended lymphadenectomy in these patients. The surgeon and pathologist should aim to dissect and analyze at least 12 lymph nodes.

Obstructive jaundice — Patients who present with obstructive jaundice tend to have a worse prognosis. In one study, 5- and 10-year survival rates were 70 and 49 percent, respectively, in patients who did not present with obstructive jaundice versus 34 and 29 percent, respectively, in patients who were jaundiced at presentation [81]. These data could be interpreted as demonstrating that early detection of ampullary carcinoma prior to the onset of obstructive jaundice is associated with a better oncologic outcome. The role of preoperative biliary drainage in patients who present with obstructive jaundice is addressed above. (See 'Preoperative biliary drainage' above.)

Intraoperative blood transfusion — In a systematic review, patients who required intraoperative transfusion of more than three units of red blood cell units had worse outcomes than those requiring less blood [82]. However, patients who require transfusion tend to be sicker as a group (or their tumors are more advanced, requiring more intraoperative dissection) than those who do not require transfusion. Therefore, the independent contribution of intraoperative blood transfusion to outcomes remains uncertain.

Tumor marker elevation — Elevated preoperative levels of the serum tumor markers CA 19-9 (carbohydrate antigen 19-9, also called cancer antigen 19-9) and carcinoembryonic antigen (CEA) are associated with a poorer prognosis relative to individuals with normal values [54,83]. In one study, the optimal cutoff levels of CA 19-9 to stratify risk for disease recurrence was >150 units/mL in non-jaundiced patients and >300 units/mL in the presence of cholestasis [83]. (See "Ampullary carcinoma: Epidemiology, clinical manifestations, diagnosis and staging", section on 'Serum tumor markers'.)

Prognostic nomograms — Prognostic nomograms for disease-specific survival have been developed for patients with non-metastatic ampullary cancer such as age, tumor size and depth

of invasion, lymph node ratio, and histology [84]. Whether models such as these are better at predicting prognosis as compared with AJCC stage grouping (figure 5), is not clear.

Patterns of recurrence — In many series, recurrences are approximately evenly split between locoregional recurrence and distant spread [12,85], although others note a predominance of distant metastases [54,64]. The risk factors for locoregional and distant recurrence are slightly different. This was shown in a series of 127 patients who underwent pancreaticoduodenectomy with regional lymphadenectomy for ampullary carcinoma [12]. The median time to recurrence was 11.4 months, and the risk factors for locoregional recurrence were the presence of pancreatic invasion and tumor size. By contrast, lymph node metastasis was the sole risk factor for distant recurrence. Both pancreatic invasion and lymph node involvement were significant predictors of inferior survival.

The most common site of distant spread is the liver, but other sites include peritoneum, bone, supraclavicular lymph nodes and lung [12,54,85].

ADJUVANT THERAPY

Our recommended approach — The results of clinical trials are not definitive, and there is no consensus regarding the optimal management of patients after resection of an ampullary cancer. Recommendations for management of ampullary carcinoma are not included in published consensus-based guidelines from either the National Comprehensive Cancer Network (NCCN) [86] or the European Society for Medical Oncology (ESMO) [42].

Many clinicians do not recommend adjuvant chemoradiotherapy or chemotherapy for resected ampullary cancers, citing the more favorable prognosis of ampullary as compared with other biliary tract cancers [60,87] and the lack of data from randomized trials proving a survival advantage. However, we suggest that these patients be managed in a manner similar to the approach used for resected pancreatic cancer, even for those who have the intestinal histomolecular phenotype. (See 'Histology and histomolecular phenotype' above.)

Eligible patients should be encouraged to enroll in clinical trials evaluating the potential benefits of chemotherapy and/or chemoradiotherapy, as well as new therapies. If protocol therapy is not available or declined, the approach differs outside of and within the United States:

- Most European clinicians advocate chemotherapy alone, emphasizing the survival benefit of chemotherapy in the German CONKO-001 trial [88], the lack of a significant survival benefit with chemoradiotherapy in an early European Organisation for Research and Treatment of Cancer (EORTC) trial [89], and the detrimental impact of chemoradiotherapy

on survival seen in the European Study Group for Pancreatic Cancer (ESPAC)-1 trial [90]. Similarly, the Japanese approach also includes chemotherapy alone.

If chemotherapy alone is chosen, for patients with an excellent performance status who are able to tolerate it, we suggest modified FOLFIRINOX (oxaliplatin plus irinotecan with leucovorin and short-term infusional fluorouracil [FU] (table 3)), rather than gemcitabine alone, based on results from the Canadian/Unicancer/PRODIGE group demonstrating improved survival with FOLFIRINOX compared with gemcitabine in the adjuvant setting for pancreatic cancer. We also prefer this regimen over gemcitabine plus capecitabine. (See "Treatment for potentially resectable exocrine pancreatic cancer", section on 'Modern combination regimens (FOLFIRINOX and gem-nabpaclitaxel)'.)

If FOLFIRINOX is deemed too toxic for the patient, then adjuvant therapy with gemcitabine plus capecitabine as per the ESPAC-4 trial (table 4) is a reasonable approach. (See "Treatment for potentially resectable exocrine pancreatic cancer", section on 'Other gemcitabine and FU-based approaches'.)

Therapy with gemcitabine alone (table 5) or, where available, S-1 alone is also a reasonable option, particularly for patients with a borderline performance status or a comorbidity profile that precludes combination chemotherapy. (See "Treatment for potentially resectable exocrine pancreatic cancer", section on 'Other gemcitabine and FU-based approaches'.)

When chemoradiotherapy is not given, we suggest six months of adjuvant chemotherapy.

- The American approach differs with regard to chemoradiotherapy. For most patients with resected ampullary cancer stage T2N0 or higher (table 1), we suggest the addition of concurrent infusional FU-based chemoradiotherapy to adjuvant chemotherapy. However, the benefit of adjuvant radiation therapy (RT) remains controversial, and this approach is not typically chosen outside of the United States. (See "Treatment for potentially resectable exocrine pancreatic cancer", section on 'Does chemoradiotherapy add benefit to chemotherapy?'.)

  As with pancreatic cancer, the optimal way to sequence FU-based chemoradiotherapy and systemic chemotherapy is unclear. When chemoradiotherapy is planned, our preferred approach is four months of chemotherapy followed two to four weeks later by six weeks of concurrent RT with either infusional FU (250 mg/m^2 daily) or capecitabine (825 mg/m^2 twice daily, five days per week during RT).

Benefit from adjuvant therapy — Despite the high rate of potentially curative resections in contemporary series, more than one-half of patients die from recurrent disease, suggesting the need for effective adjuvant therapy. There are few published data to guide the use of adjuvant therapy in patients with resected ampullary cancer.

Chemoradiotherapy — Benefit from postoperative chemoradiotherapy in patients with completely resected disease has been suggested in several uncontrolled series [59,91-97]. In one of the largest reports from the Mayo Clinic, 29 of 125 patients who underwent definitive surgery for an ampullary cancer received adjuvant RT with concurrent FU, while the remainder received no adjuvant therapy [91]. In multivariate analysis, lymph node status emerged as the only significant predictor of outcome. Overall survival rates at one, three, and five years in the adjuvant therapy group were 91, 54, and 48 percent, compared with 66, 22, and 11 percent in the control group. Within the high-risk node-positive subgroup (n = 54), the 24 patients who received adjuvant therapy survived significantly longer than the 30 who did not receive it.

On the other hand, other retrospective comparisons [98,99], and the only phase III randomized trial that included a substantial number of patients with ampullary carcinoma have failed to show a benefit for postoperative chemoradiotherapy. In a trial from the EORTC, 218 patients with resected pancreatic or other periampullary cancers were randomly assigned to postoperative RT (40 Gy in split courses) plus concurrent FU (25 mg/kg per day by continuous infusion) or observation [89]. For the 104 periampullary cancers (which included cancers of the ampulla, distal common bile duct or duodenum), there was no difference in the two-year survival rate (67 versus 63 percent) or in the incidence of locoregional recurrence in the treated patients compared with controls. (See "Treatment for potentially resectable exocrine pancreatic cancer", section on 'Fluorouracil-based approaches'.)

Even the results of meta-analyses are discordant:

- A year 2016 meta-analysis of 10 retrospective reports totaling 3361 patients who either received adjuvant chemoradiotherapy or no adjuvant therapy after resection of an ampullary carcinoma concluded that despite the fact that more patients had locally advanced disease or nodal metastases in the treated group, adjuvant chemoradiotherapy significantly reduced the risk of death (hazard ratio [HR] 0.75, 95% CI 0.6-0.94) [100]. However, there was significant heterogeneity between studies, mainly attributed to the two series that reported the largest benefit from adjuvant RT [91,97].

- On the other hand, a later analysis of 14 studies of adjuvant therapy in periampullary adenocarcinoma (including six randomized trials, the remainder retrospective reports) concluded that there was no survival benefit for any adjuvant strategy (adjuvant

chemoradiotherapy or chemotherapy) for treatment of periampullary cancers [101]. However, there were few T3 or T4 tumors in the analysis, and the data are most compelling for benefit of adjuvant therapy in this subgroup.

Chemotherapy alone — A benefit for adjuvant chemotherapy has been suggested in retrospective analyses [102,103], but has been difficult to prove in randomized trials:

- The benefit of adjuvant chemotherapy for resected ampullary adenocarcinomas was directly studied in the international ESPAC-3 trial, in which 428 patients with periampullary malignancies (297 ampullary, 96 bile duct, 35 other) were randomly assigned to one of three arms: observation alone, leucovorin-modulated FU (six courses of leucovorin 20 mg/m^2 IV bolus followed by FU 425 mg/m^2, daily for five days, once per month), or single-agent gemcitabine (1000 mg/m^2 weekly for three of every four weeks for six months) [73]. A complete (R0) resection was achieved in 84 percent of patients, and 59 percent had node-positive disease.

  The use of adjuvant chemotherapy was associated with a potentially meaningful overall survival advantage but it was not statistically significant (median 43 versus 35 months, HR 0.86, 95% CI 0.66-1.11). Although of a greater magnitude, the difference in median survival between gemcitabine-treated and observed patients was still not statistically significant (median 46 versus 35 months, HR 0.77, 95% CI 0.57-1.05). However, in secondary multivariate analysis adjusting for predefined prognostic variables, there was a statistically significant survival benefit for any chemotherapy (HR for death 0.75, 95% CI 0.57-0.98) and for gemcitabine alone (HR 0.70, 95% CI 0.51-0.97). Furthermore, when the analysis was restricted to patients with ampullary cancer, those treated with gemcitabine had a median survival that was almost twice as long as those in the observation group (median 71 versus 41 months); the median survival in the FU/leucovorin group was 57.8 months. Post hoc analysis did not show differential treatment responsiveness based on histologic subtype.

  There was no difference in overall survival between the chemotherapy arms, but grade 3 or 4 stomatitis (11 versus 0 percent) and diarrhea (14 versus 4 percent) were significantly more common with leucovorin-modulated FU, and there were more serious adverse effects in the FU group as well.

- The only other randomized trial that addressed the benefit of adjuvant chemotherapy was a multicenter randomized trial from Japan that compared surgery with and without postoperative chemotherapy (two courses of mitomycin plus infusional FU, followed by prolonged oral administration of FU until tumor progression) in 508 patients with pancreaticobiliary tract cancer (56 with ampullary cancer) [104]. A significant survival

benefit for adjuvant chemotherapy was seen in the patients with gallbladder cancer (five-year survival 26 versus 14 percent), but not in those with ampullary cancer (five-year survival 28 versus 34 percent in the chemotherapy and control groups, respectively).

- As noted above, a meta-analysis of 14 studies of adjuvant therapy in periampullary adenocarcinoma (including the two randomized trials discussed above) concluded that there was no survival benefit for any adjuvant strategy (adjuvant chemoradiotherapy or chemotherapy) for treatment of periampullary cancers; however, the benefits of adjuvant chemotherapy were not analyzed separately from those of chemoradiotherapy [101]. Also, as noted above, there were few T3 or T4 tumors in the analysis, and the data are most compelling for benefit of adjuvant therapy in this subgroup.

POST-TREATMENT SURVEILLANCE

Post-treatment surveillance to detect recurrent or persistent disease is performed at regular intervals, although the optimal surveillance strategy is undefined [41]. National Comprehensive Cancer Network (NCCN) guidelines are not available. Many clinicians follow patients every six months for five years and annually thereafter. Follow-up visits usually include history and clinical examination, and serum tumor markers (typically CEA and CA 19-9). The utility of periodic computed tomography (CT) scan of the abdomen is unclear.

While the need for endoscopic surveillance is universally accepted, most published recommendations are similar to those reported after local resection of ampullary adenomas. A reasonable approach is surveillance endoscopy every six months for two years, then annually for an additional three to five years. (See "Ampullary adenomas: Management".)

CHEMOTHERAPY FOR ADVANCED DISEASE

Choice of therapy — Limited data exist to guide physicians in the choice of chemotherapy, largely because of the rarity of this disease. Much of the data on chemotherapy for advanced ampullary cancer are in combined series that include patients with small bowel, pancreatic, and ampullary adenocarcinomas, or more commonly, ampullary plus biliary tract cancers. However, particularly because of advances in treatment of advanced disease, the distinction as to a periampullary tumor is of intestinal, biliary, or pancreatic origin is particularly important for the selection of the treatment approach. (See "Treatment of small bowel neoplasms", section on 'Metastatic disease' and "Systemic therapy for advanced cholangiocarcinoma" and "Initial systemic chemotherapy for metastatic exocrine pancreatic cancer".)

For true ampullary cancers, there is no consensus on the best management for patients with metastatic disease. Patients with ampullary cancer were included in the ABC trial of gemcitabine with and without cisplatin, although they represented a small minority [105]. There was a significant survival advantage to the combination both in terms of progression-free and overall survival, compared with gemcitabine alone. Many consider this to represent the standard regimen for advanced ampullary as well as biliary tract cancers. (See "Systemic therapy for advanced cholangiocarcinoma" and "Treatment of advanced, unresectable gallbladder cancer", section on 'Palliative systemic chemotherapy'.)

However, others disagree, treating these patients more like those with advanced pancreatic cancer or small bowel adenocarcinoma [106]. (See "Initial systemic chemotherapy for metastatic exocrine pancreatic cancer" and "Treatment of small bowel neoplasms", section on 'Metastatic disease'.)

Importance of somatic and germline genomic testing — All patients who might be candidates for systemic targeted therapy should undergo next generation sequencing of tumor tissue, and be referred for germline genomic testing. DNA mismatch repair deficiency (dMMR)/ high levels of microsatellite instability (MSI-H), and other potentially actionable germline and somatic (tumoral) genetic alterations found in ampullary cancers more often than in pancreatic or biliary tract cancers [107-110]. These molecular alterations may identify patients for whom molecularly targeted therapy (eg, pembrolizumab for dMMR/MSI-H) may be an option. (See "Tissue-agnostic cancer therapy: DNA mismatch repair deficiency, tumor mutational burden, and response to immune checkpoint blockade in solid tumors".)

SUMMARY AND RECOMMENDATIONS

- **Surgical versus nonsurgical treatment**
  - We recommend pancreaticoduodenectomy rather than local resection for most patients with invasive ampullary carcinomas (**Grade 1B**). (See 'Pancreaticoduodenectomy' above.)
  - We suggest local ampullary excision rather than pancreaticoduodenectomy for patients with noninvasive ampullary tumors (pTis (table 1)) (**Grade 2B**).

    Ampullectomy is also a reasonable approach for poor surgical candidates who have a well-differentiated T1 tumor (table 1) that is <6 mm in size (based on endoscopic ultrasound [EUS]). However, a more aggressive surgical approach is preferred for

patients who are candidates for pancreaticoduodenectomy because of better outcomes. (See 'Local resection' above.)

- Nonsurgical treatment modalities (ie, endoscopic snare resection, laser ablation, photodynamic therapy) provide palliative rather than curative benefit for patients with ampullary carcinoma. These methods should be restricted to patients who are not operative candidates and those who refuse surgery. (See 'Minimally invasive nonsurgical therapies' above.)

- **Adjuvant therapy** – We offer adjuvant therapy to all patients with resected ampullary cancer stage T2N0 or higher (table 1). (See 'Adjuvant therapy' above.)

  - For patients with an excellent performance status who are able to tolerate it, we suggest modified FOLFIRINOX (oxaliplatin plus irinotecan with leucovorin and short-term infusional fluorouracil [FU] (table 3)), rather than a gemcitabine-based regimen (**Grade 2C**). (See "Treatment for potentially resectable exocrine pancreatic cancer", section on 'Modern combination regimens (FOLFIRINOX and gem-nabpaclitaxel)'.)

    For less fit patients, gemcitabine plus capecitabine (table 4) or gemcitabine plus nabpaclitaxel (table 6) are reasonable alternatives. (See "Treatment for potentially resectable exocrine pancreatic cancer", section on 'Other gemcitabine and FU-based approaches'.)

    We reserve gemcitabine alone (table 5) or, where available, S-1 alone for patients with a borderline performance status or a comorbidity profile that precludes combination chemotherapy.

    When chemoradiotherapy is not given, we suggest six months of adjuvant chemotherapy.

  - We also suggest adding concurrent chemoradiotherapy to systemic chemotherapy for patients with resected ampullary cancers stage T2N0 or higher (table 1), rather than chemotherapy alone (**Grade 2C**). (See 'Our recommended approach' above.)

    During the concurrent chemoradiotherapy portion, we prefer infusional FU, but oral capecitabine is an acceptable alternative.

    The optimal way to sequence FU-based chemoradiotherapy and systemic chemotherapy is unclear. Our preferred approach is to administer all of the chemotherapy initially. For patients who have no evidence of metastatic disease, we recommend four months of systemic chemotherapy, followed by six weeks of

chemoradiotherapy using concurrent infusional FU (250 mg/m^2 daily) beginning two to four weeks after finishing chemotherapy. This is the same approach we use for resected pancreatic cancer. (See 'Adjuvant therapy' above.)

- **Patients with metastatic disease**

  - The optimal regimen for systemic therapy of true ampullary tumors has not been established. Based on the results of the ABC trial, the combination of gemcitabine plus cisplatin is a reasonable approach for patients who are able to tolerate it. Others use single-agent gemcitabine initially (table 7) followed by an oxaliplatin-based regimen, or vice versa, in a manner similar to treatment of pancreatic cancer. (See 'Chemotherapy for advanced disease' above.)

  - All patients who might be candidates for systemic targeted therapy should undergo somatic and germline genomic testing for potentially actionable molecular alterations. DNA mismatch repair deficiency (dMMR)/ high levels of microsatellite instability (MSI-H), and other potentially actionable germline and somatic (tumoral) genetic alterations are more frequently found in ampullary cancers than in pancreatic or biliary neoplasms, and they may identify patients for whom molecularly targeted therapy (eg, pembrolizumab for dMMR/MSI-H) may be an option. (See 'Importance of somatic and germline genomic testing' above.)

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Topic 2506 Version 43.0

GRAPHICS

Sphincter of Oddi in relation to the ampulla of Vater

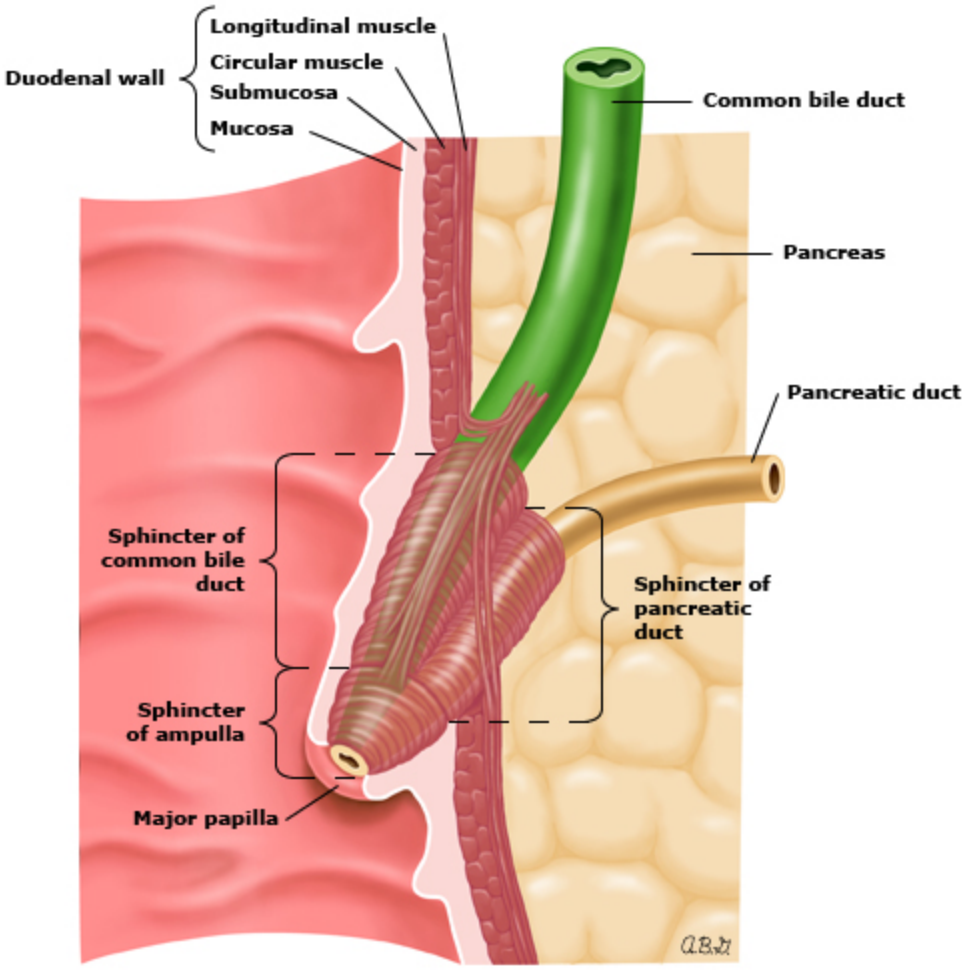
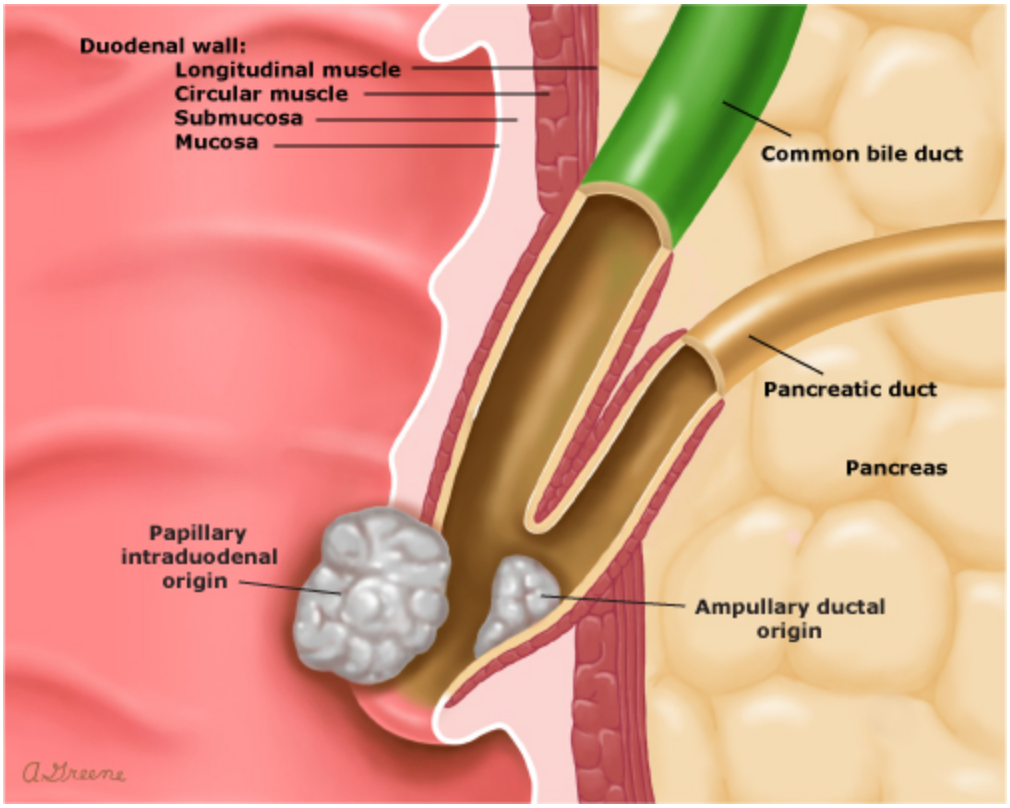


Diagram of the anatomy of the sphincter of Oddi and ampulla of Vater. The muscle fibers of the sphincter of Oddi surround the intraduodenal segment of the common bile duct and the ampulla of Vater. A circular aggregate of muscle fibers, known as the sphincter choledochus (or sphincter of Boyden), keeps 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.

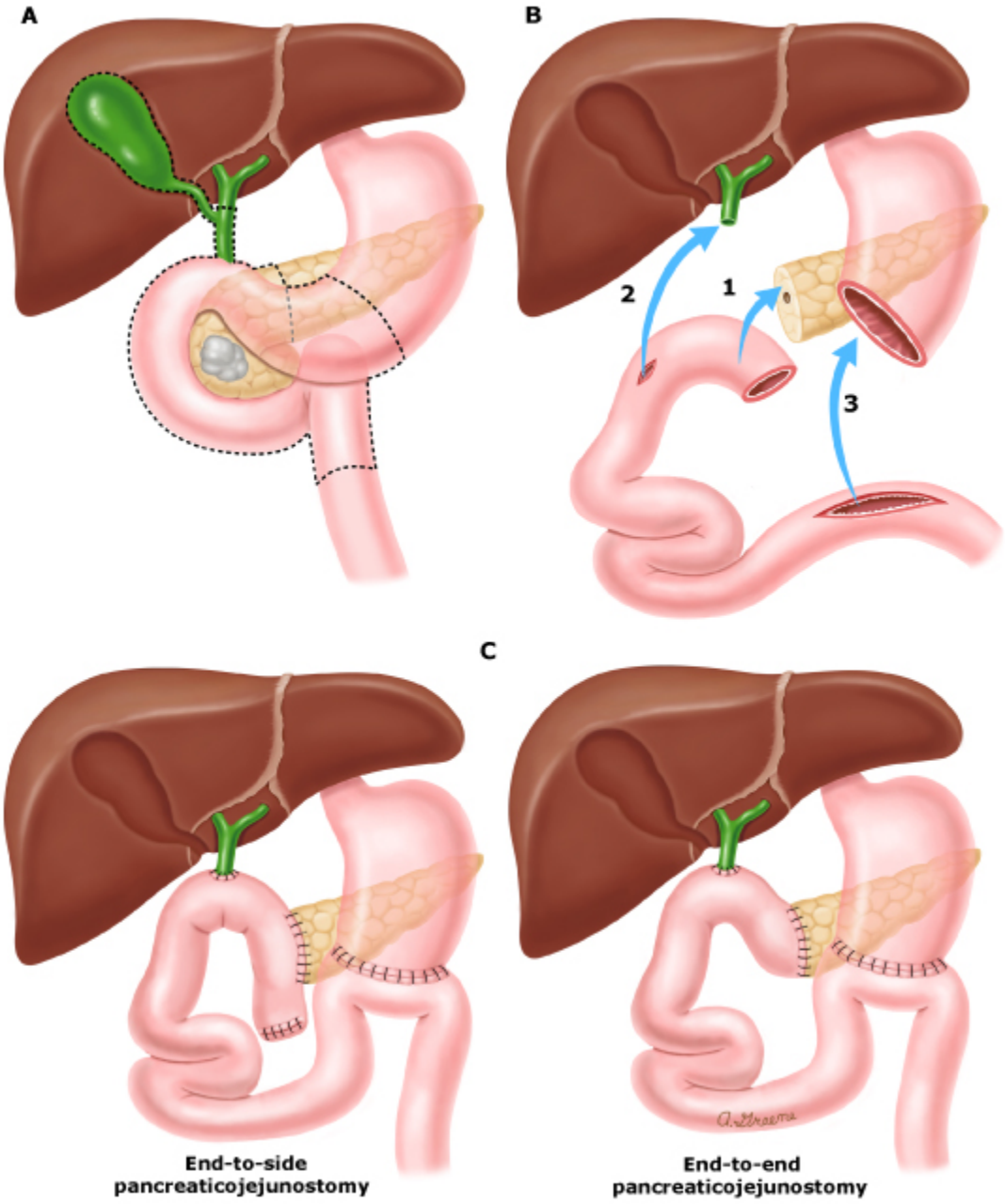
Graphic 78786 Version 4.0

Locations ampullary tumors



Graphic 53240 Version 1.0

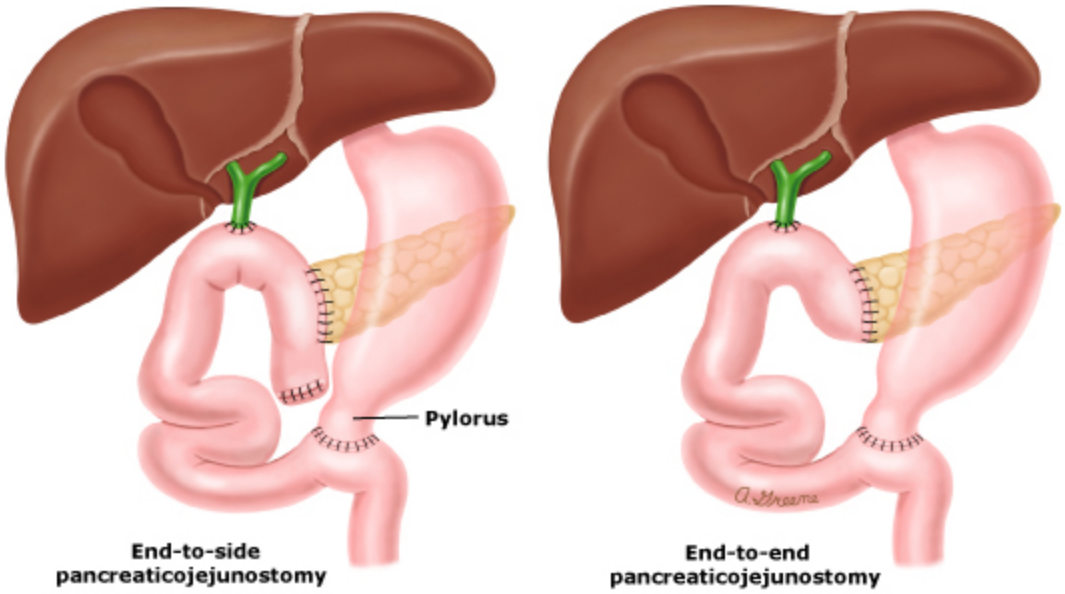
Conventional pancreaticoduodenectomy (Whipple procedure; Polya)



Polya refers to the style with which the gastrojejunostomy is constructed.

Graphic 82519 Version 3.0

Pylorus-preserving pancreaticoduodenectomy



Graphic 60689 Version 2.0

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

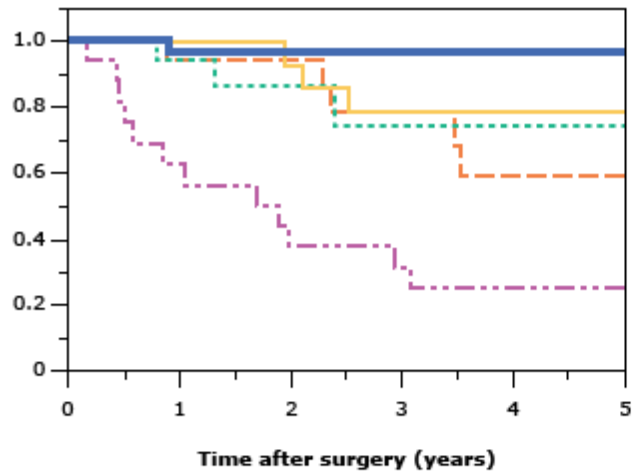
TNM: tumor, node, metastasis; AJCC: American Joint Committee on Cancer; UICC: Union for International Cancer Control.

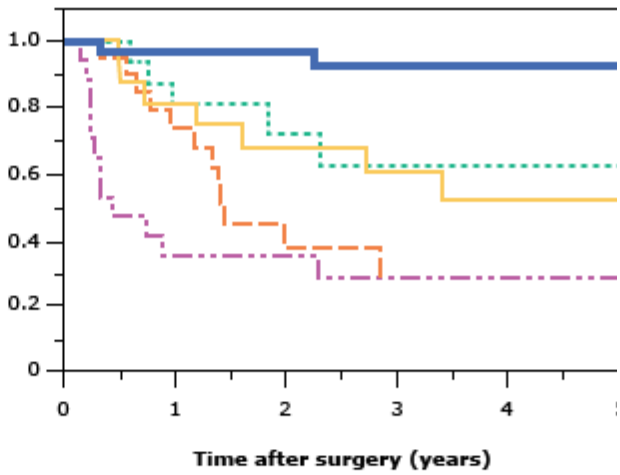
Used with permission of the American College of Surgeons, Chicago, Illinois. The original source for this information is the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer International Publishing. Corrected at 4th printing, 2018.

Graphic 110872 Version 8.0

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

A

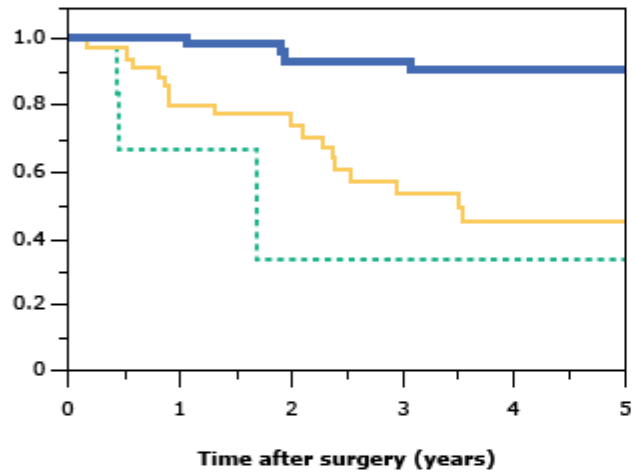


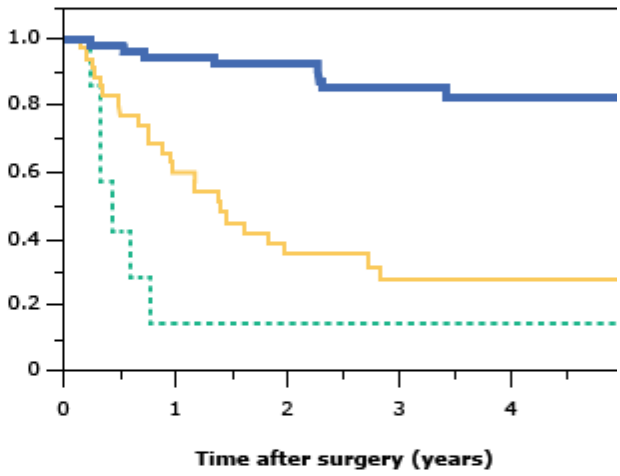


Number at risk						
T1a	33	27	24	20	16	11
T1b	16	15	13	10	9	7
T2	18	15	9	5	2	0
T3a	20	16	12	9	6	5
T3b	17	10	6	5	4	4

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

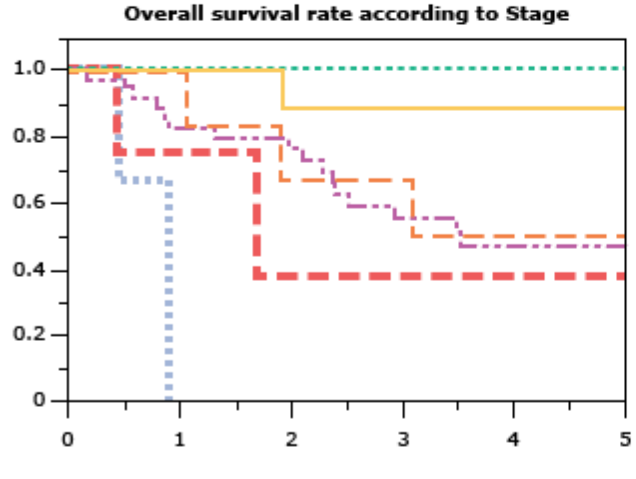


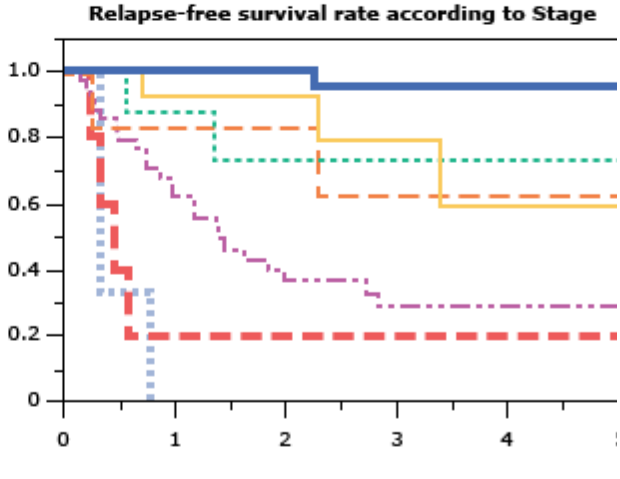


Number at risk						
N0	61	53	41	33	26	19
N1	36	29	22	15	10	7
N2	7	3	1	1	1	1

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

Five-year survival in a series of 1301 patients with ampullary cancer reported to the SEER* registry between 1988 and 2003

Stage at presentation	N	Five-year survival percent	
		OS	CSS
Ia	218	60	74
Ib	255	57	66
IIa	252	30	41
IIb	483	22	30
III	38	27	34
IV	15	0	0
N stage			
N0	518	48	59
N1	749	21	28

OS: overall survival; CSS: cause-specific survival.

* SEER: Surveillance, Epidemiology and End Results database of the National Cancer Institute.

Modified from: O'Connell, et al. Ann Surg Oncol 2008; 15:1820.

Graphic 76691 Version 1.0

Modified FOLFIRINOX chemotherapy for pancreatic cancer[1,2]

Cycle length: 14 days.

Drug	Dose and route	Administration	Given on days
Oxaliplatin¶	85 mg/m^2 IV	Dilute in 500 mL D5W$^\Delta$ and administer over two hours (prior to leucovorin). Shorter oxaliplatin administration schedules (eg, 1 mg/m^2 per minute) appear to be safe.[3]	Day 1
Leucovorin◇ §	400 mg/m^2 IV	Dilute in 250 mL NS or D5W$^\Delta$ and administer over two hours (after oxaliplatin).	Day 1
Irinotecan¥	150 mg/m^2 IV	Dilute in 500 mL NS or D5W$^\Delta$ and administer over 90 minutes. Administer concurrent with the last 90 minutes of leucovorin infusion, in separate bags, using a Y-line connection.	Day 1
Fluorouracil (FU)	2400 mg/m^2 IV	Dilute in 500 to 1000 mL 0.9% NS or D5W$^\Delta$ and administer as a continuous IV infusion over 46 hours. To accommodate an ambulatory pump for outpatient treatment, can be administered undiluted (50 mg/mL) or the total dose diluted in 100 to 150 mL NS.$^\Delta$	Day 1

Pretreatment considerations:

Emesis risk	▪ HIGH (greater than 90% frequency of emesis).‡ ▪ Refer to UpToDate topics on prevention of chemotherapy-induced nausea and vomiting in adults.
Prophylaxis for infusion reactions	▪ Although infusion reactions have been reported with oxaliplatin, there is no recommended standard premedication for this regimen. ▪ Refer to UpToDate topics on infusion reactions to systemic chemotherapy.
Vesicant/irritant properties	▪ Oxaliplatin and FU are irritants, but oxaliplatin can cause significant tissue damage; avoid extravasation. ▪ Refer to UpToDate topics on extravasation injury from chemotherapy and other non-antineoplastic vesicants.

Infection prophylaxis	▪ Primary prophylaxis with G-CSF is not warranted. However, given the risk of grade 3 or 4 neutropenia (46%[1]), primary prophylaxis with G-CSF is used at many institutions, especially when this regimen is used in the adjuvant setting.[2] ▪ Refer to UpToDate topics on use of granulocyte colony stimulating factors in adult patients with chemotherapy-induced neutropenia and conditions other than acute leukemia, myelodysplastic syndrome, and hematopoietic cell transplantation.
Dose adjustment for baseline liver or renal dysfunction	▪ A lower starting dose of oxaliplatin and irinotecan may be needed for severe renal insufficiency.[4,5] A lower starting dose of irinotecan and FU may be needed for patients with hepatic impairment.[5,6] ▪ **NOTE:** We do not recommend administration of FOLFIRINOX unless serum bilirubin is normal. ▪ Refer to UpToDate topics on chemotherapy hepatotoxicity and dose modification in patients with liver disease, conventional cytotoxic agents; chemotherapy hepatotoxicity and dose modification in patients with liver disease, molecularly targeted agents; and chemotherapy nephrotoxicity and dose modification in patients with renal insufficiency, conventional cytotoxic agents.
Maneuvers to prevent neurotoxicity	▪ Pharmacologic methods to prevent/delay the onset of oxaliplatin-related neuropathy are controversial due to the absence of large clinical trials proving benefit. Counsel patients to avoid exposure to cold during and for approximately 48 hours after each infusion.[4] Prolongation of the oxaliplatin infusion time from two to six hours may mitigate acute neurotoxicity. ▪ Refer to UpToDate topics on overview of neurologic complications of platinum-based chemotherapy.
Cardiac issues	▪ QT prolongation and ventricular arrhythmias have been reported after oxaliplatin. ECG monitoring is recommended if therapy is initiated in patients with heart failure, bradyarrhythmias, coadministration of drugs known to prolong the QT interval, and electrolyte abnormalities. Avoid oxaliplatin in patients with congenital long QT syndrome. Correct hypokalemia and hypomagnesemia prior to initiating oxaliplatin. ▪ Cardiotoxicity observed with FU includes myocardial infarction/ischemia, angina, dysrhythmias, cardiac arrest, cardiac failure, sudden death, electrocardiographic changes, and cardiomyopathy.
Monitoring parameters:	
▪ CBC with differential and platelet count prior to each treatment.	
▪ Electrolytes (especially potassium and magnesium) and liver and renal function prior to each treatment.	

- Irinotecan is associated with early and late diarrhea, both of which may be severe.[5] For patients who develop abdominal cramping and/or diarrhea within 24 hours of receiving irinotecan, administer atropine (0.3 to 0.6 mg IV) and premedicate with atropine during later cycles. Patients must be instructed in the early use of loperamide for late diarrhea. Patients who develop diarrhea should be closely monitored and supportive care measures (eg, fluid and electrolyte replacement, loperamide, antibiotics, etc) should be provided as needed.
- Refer to UpToDate topics on enterotoxicity of chemotherapeutic agents.

- Assess changes in neurologic function prior to each treatment.

Suggested dose modifications for toxicity:

Myelotoxicity

- Do not retreat unless neutrophil count is ≥1500/microL and platelets are ≥75,000/microL. The following dose reduction guidelines for hematologic toxicity are recommended; several of these are based upon recommendations in the original FOLFIRINOX protocol.[7]
- **Neutropenia**
  - If day 1 treatment delayed for granulocytes is <1500/microL or febrile neutropenia or grade 4 neutropenia >7 days: Reduce irinotecan dose to 120 mg/m^2. For second occurrence: Reduce oxaliplatin dose to 60 mg/m^2. If nonrecovery after a two-week delay, or if there is a third occurrence of granulocytes <1500/microL on day 1, discontinue treatment. For grade 4 neutropenia >7 days **during** treatment or febrile neutropenia, reduce oxaliplatin dose to 60 mg/m^2 and the infusional FU dose to 75% of the original dose. For the second occurrence, reduce dose of irinotecan to 120 mg/m^2 and the dose of infusional FU an additional 25%. Discontinue treatment for third occurrence.
- **Thrombocytopenia**
  - If day 1 treatment delayed for platelet count <75,000/microL, reduce oxaliplatin dose to 60 mg/m^2 and reduce the continuous infusion FU to 75% of original doses. For second occurrence, reduce irinotecan dose to 120 mg/m^2. If nonrecovery after a two-week delay, or if there is a third occurrence of platelets <75,000/microL, discontinue treatment. For grade 3 or 4 thrombocytopenia **during** treatment, reduce oxaliplatin dose to 60 mg/m^2 and the infusional FU dose to 75% of the original dose. For the second occurrence, reduce dose of irinotecan to 120 mg/m^2 and the dose of infusional FU an additional 25%. Discontinue treatment for third occurrence.

Diarrhea

- Do not retreat with FOLFIRINOX until resolution of diarrhea for at least 24 hours without antidiarrheal medication. For diarrhea grade 3 or 4, or diarrhea with fever and/or grade 3 or 4 neutropenia, reduce irinotecan dose to 120 mg/m^2. For second occurrence, reduce the oxaliplatin dose to 60 mg/m^2 and the continuous FU dose to 75% of original dose. Discontinue treatment for third occurrence.

	▪ **NOTE:** Severe diarrhea, mucositis, and myelosuppression after FU should prompt evaluation for DPD deficiency. ▪ Refer to UpToDate topics on enterotoxicity of chemotherapeutic agents.
Mucositis or hand-foot syndrome	▪ For grade 3 to 4 toxicity, reduce dose of infusional FU by 25%.
Pulmonary toxicity	▪ Oxaliplatin has rarely been associated with pulmonary toxicity. Withhold oxaliplatin for unexplained pulmonary symptoms until interstitial lung disease or pulmonary fibrosis is excluded. ▪ Refer to UpToDate topics on pulmonary toxicity associated with antineoplastic therapy, cytotoxic agents.
Neurologic toxicity	▪ For persistent grade 3 paresthesias/dysesthesias or transient grade 2 symptoms lasting >7 days, decrease oxaliplatin dose by 25%.[4] Discontinue oxaliplatin for grade 4 or persistent grade 3 paresthesia/dysesthesia. ▪ There is no recommended dose for resumption of FU administration following development of hyperammonemic encephalopathy, acute cerebellar syndrome, confusion, disorientation, ataxia, or visual disturbances; the drug should be permanently discontinued.[6]
Cardiotoxicity	▪ Cardiotoxicity observed with FU includes myocardial infarction/ischemia, angina, dysrhythmias, cardiac arrest, cardiac failure, sudden death, ECG changes, and cardiomyopathy. There is no recommended dose for resumption of FU administration following development of cardiac toxicity, and the drug should be discontinued.[6]
Other toxicity	▪ Any other toxicity ≥grade 2, except anemia and alopecia, can justify dose reduction if medically indicated. ▪ For other nonhematologic toxicities, if grade 2, hold treatment until ≤grade 1; if grade 3 or 4, hold treatment until ≤grade 2.[5]
If there is a change in body weight of at least 10%, doses should be recalculated.	

This table is provided as an example of how to administer this regimen; there may be other acceptable methods. This regimen must be administered by a clinician trained in the use of chemotherapy, who should use independent medical judgment in the context of individual circumstances to make adjustments, as necessary.

IV: intravenous; D5W: 5% dextrose in water; NS: normal saline; G-CSF: granulocyte colony-stimulating factors; QT: time between the start of the Q wave and the end of the T wave (heart electrical cycle); ECG: electrocardiogram; CBC: complete blood count; DPD: dihydropyrimidine dehydrogenase.

¶ Many centers routinely infuse oxaliplatin via central venous line because of local pain with infusion into a peripheral vein.

Δ Diluent solutions should not be modified without consulting a detailed reference due to potential incompatibility(ies).

◇ Leucovorin dose is given for d,l-racemic mixture.[8] Use half the dose for LEVOleucovorin (l-leucovorin).

§ In the setting of advanced (metastatic) disease, day 1 leucovorin, which was not administered in one of the supporting studies,[1] is optional.[5] Whether a reduced starting dose is needed in patients who are homozygous for the UGT 1A1*28 allele (Gilbert syndrome) and whether testing for this allele should be carried out prior to starting irinotecan is controversial. Refer to UpToDate topic on "Enterotoxicity of chemotherapeutic agents".

¥ A lower initial dose of irinotecan may be considered for patients with poor performance status, prior pelvic or abdominal radiotherapy, or increased bilirubin levels.

‡ At many institutions, regimens that combine oxaliplatin with irinotecan on day 1 are considered highly emetogenic, warranting the use of a neurokinin-1 receptor antagonist on day 1. The National Comprehensive Cancer Network considers this and similar regimens as moderately emetogenic.

References:

1. *Ozaka M, et al. Cancer Chemother Pharmacol 2018; 81:1017.*
2. *Conroy T, et al. J Clin Oncol 2018; ASCO #LBA4001. (Abstract available online at meetinglibrary.asco.org/record/159164/abstract, accessed on June 15, 2018).*
3. *Cercek A, et al. J Oncol Pract 2016; 12:e459.*
4. *Oxaliplatin injection. United States Prescribing Information. US National Library of Medicine. (Available online at dailymed.nlm.nih.gov, accessed on August 22, 2016).*
5. *Irinotecan hydrochloride injection. United States Prescribing Information. US National Library of Medicine. (Available online at dailymed.nlm.nih.gov, accessed on August 22, 2016).*
6. *Fluorouracil injection. United States Prescribing Information. US National Library of Medicine. (Available online at dailymed.nlm.nih.gov, accessed on August 22, 2016).*
7. *Conroy T, et al. N Engl J Med 2011; 364:1817.*
8. *Leucovorin Calcium injection. United States Prescribing Information. US National Library of Medicine. (Available online at dailymed.nlm.nih.gov, accessed on August 22, 2016).*

Graphic 109546 Version 16.0

Gemcitabine and capecitabine (GemCap) for adjuvant therapy of pancreatic cancer[1]

Cycle length: 28 days.
Duration: 6 months.

Drug	Dose and route	Administration	Given on days
Gemcitabine	1000 mg/m^2 IV	Dilute in 250 mL NS* (concentration no greater than 40 mg/mL) and administer over 30 minutes.	Days 1, 8, and 15
Capecitabine¶	830 mg/m^2 per dose by mouth	Twice daily (total dose 1660 mg/m^2 per day). Swallow whole with water within 30 minutes after a meal, with each dose as close to 12 hours apart as possible. Do not cut or crush tablets.Δ	Days 1 through 21

Pretreatment considerations:

Emesis risk	▪ LOW. ▪ Refer to UpToDate topics on prevention of chemotherapy-induced nausea and vomiting in adults.
Infection prophylaxis	▪ Primary prophylaxis with G-CSF is not indicated based on a low risk for febrile neutropenia with this regimen.[1] ▪ Refer to UpToDate topics on prophylaxis of infection during chemotherapy-induced neutropenia in high-risk adults.
Dose adjustment for baseline renal dysfunction	▪ A lower starting dose of gemcitabine may be needed for patients with liver impairment. A lower starting dose of capecitabine may be needed for patients with moderate renal impairment.[2] ▪ Refer to UpToDate topics on chemotherapy hepatotoxicity and dose modification in patients with liver disease, conventional cytotoxic agents; chemotherapy hepatotoxicity and dose modification in patients with liver disease, molecularly targeted agents; and chemotherapy nephrotoxicity and dose modification in patients with renal insufficiency, conventional cytotoxic agents.

Monitoring parameters:

- CBC with differential and platelet count weekly during treatment.
- Assess basic metabolic panel (including serum creatinine) and liver function tests every three weeks prior to each new cycle and otherwise as indicated during treatment.

- Monitor for diarrhea and palmar-plantar erythrodysesthesias during treatment.
- **NOTE:** Severe diarrhea, mucositis, and myelosuppression after capecitabine should prompt evaluation for dihydropyrimidine dehydrogenase deficiency.
- Refer to UpToDate topics on enterotoxicity of chemotherapeutic agents and cutaneous side effects of conventional chemotherapy agents.

- More frequent anticoagulant response (INR or prothrombin time) monitoring is necessary for patients receiving concomitant capecitabine and oral coumarin-derivative anticoagulant therapy.

- Cardiotoxicity observed with capecitabine includes myocardial infarction/ischemia, angina, dysrhythmias, cardiac arrest, cardiac failure, sudden death, electrocardiographic changes, and cardiomyopathy. These adverse reactions may be more common in patients with a prior history of coronary artery disease.
- Refer to UpToDate topics on cardiotoxicity of nonanthracycline cancer chemotherapy agents.

Suggested dose modifications for toxicity:

Myelotoxicity	▪ Dose modifications were not presented with the abstract.[1] Other studies using gemcitabine plus capecitabine have suggested dose modifications for hematologic toxicity.[3] Do not initiate a new cycle unless neutrophils are ≥1500/microL and platelets are ≥100,000/microL. Reduce the day 8 (or day 15) gemcitabine dose by 25% for an absolute neutrophil count of 500 to 1000/microL or a platelet count of 50,000 to 100,000/microL. Decrease gemcitabine by 25% for subsequent cycles for febrile neutropenia, grade 4 hematologic toxicity lasting for more than seven days, or bleeding-associated thrombocytopenia.
Nonhematologic toxicity (including hepatotoxicity)	▪ Grade 2: For the first, second, and third occurrence, hold capecitabine therapy.[2] After resolution to grade 1 or less, resume treatment (first occurrence, no dosage adjustment; second occurrence, 75% of the starting dose; third occurrence, 50% of the starting dose).[2] For the fourth occurrence of a grade 2 toxicity, discontinue capecitabine therapy. ▪ Grade 3: For the first and second occurrence, hold capecitabine therapy. After resolution to grade 1 or less, resume treatment at a reduced dose (first occurrence, 75% of the starting dose; second occurrence, 50% of the starting dose). For the third occurrence of a grade 3 toxicity, discontinue capecitabine therapy. ▪ Grade 4: Discontinue capecitabine therapy. Alternatively, hold capecitabine therapy, and begin next treatment at 50% of the starting dose when toxicity resolves to grade 1 or less; discontinue treatment for first recurrence of grade 4 toxicity. ▪ Gemcitabine is commonly associated with a transient rise in serum transaminases, but these are seldom of clinical significance. There is insufficient information from clinical studies to allow clear dose recommendations in these patients.

	▪ Patients with grade 3 or 4 hyperbilirubinemia may resume capecitabine once toxicity has reduced to ≤grade 2, but at a reduced dose.[2] ▪ Refer to UpToDate topics on chemotherapy hepatotoxicity and dose modification in patients with liver disease, conventional cytotoxic agents and chemotherapy hepatotoxicity and dose modification in patients with liver disease, molecularly targeted agents. ▪ Hold gemcitabine for other ≥grade 3 nonhematologic toxicity that is likely related to gemcitabine until it decreases to ≤grade 1.[4] Restart gemcitabine with a 25% dose reduction.
Pulmonary toxicity	▪ A variety of manifestations of pulmonary toxicity have been reported in patients treated with gemcitabine. Discontinue gemcitabine immediately and permanently. ▪ Refer to UpToDate topics on pulmonary toxicity associated with antineoplastic therapy, cytotoxic agents.
Thrombotic microangiopathy	▪ Thrombotic microangiopathy (TMA, also sometimes called thrombotic thrombocytopenic purpura [TTP] or hemolytic uremic syndrome [HUS]) has been associated with gemcitabine in individuals who have received a large or small cumulative dose.[4] Consider the possibility of TMA if the patient develops Coombs-negative hemolysis, thrombocytopenia, renal failure, and/or neurologic findings. Management consists of drug discontinuation and supportive care, without plasma exchange, as long as there is high confidence in a drug-induced etiology rather than TTP. ▪ Refer to UpToDate topics on drug-induced thrombotic microangiopathy.
Omitted capecitabine doses for toxicity are not replaced or restored. Resume treatment with the planned next cycle.	
If there is a change in body weight of at least 10%, doses should be recalculated.	

This table is provided as an example of how to administer this regimen; there may be other acceptable methods. This regimen must be administered by a clinician trained in the use of chemotherapy, who should use independent medical judgment in the context of individual circumstances to make adjustments, as necessary.

IV: intravenous; NS: normal saline; G-CSF: granulocyte colony stimulating factor; CBC: complete blood count; INR: international normalized ratio; DPD: dihydropyrimidine dehydrogenase.

* Diluent solutions should not be modified without consulting a detailed reference due to potential incompatibility(ies).

¶ Capecitabine is contraindicated in patients with known DPD deficiency. No capecitabine dose has been shown to be safe in patients with complete DPD deficiency, and data are insufficient to recommend a dose in patients with partial DPD activity.

Δ Extemporaneous compounding of liquid dosage forms is possible, but not routinely recommended.

References:

1. *Neoptolemos JP, et al. J Clin Oncol 2016 34:(suppl; abstr LBA4006).*
2. *Capecitabine. United States Prescribing Information. US National Library of Medicine. (Available online at https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/020896s044s045s046s047s048s049s050s051lbl.pdf, accessed on December 20, 2022).*
3. *Knox JJ, et al. J Clin Oncol 2005; 23:2332.*
4. *Gemcitabine injection. United States Prescribing Information. US National Library of Medicine. (Available online at dailymed.nlm.nih.gov, accessed on August 29, 2016).*

Graphic 109104 Version 11.0

Gemcitabine for nonmetastatic pancreatic and biliary cancer[1]

Cycle length: 4 weeks.

Drug	Dose and route	Administration	Given on days
Gemcitabine	1000 mg/m^2 IV	Dilute in 250 mL normal saline (concentration no greater than 40 mg/mL) and administer over 30 minutes.	Weekly for three weeks followed by one week of rest

Pretreatment considerations:

Emesis risk	▪ LOW. ▪ Refer to UpToDate topics on prevention of chemotherapy-induced nausea and vomiting in adults.
Infection prophylaxis	▪ Primary prophylaxis with granulocyte colony stimulating factors not indicated (risk of neutropenic fever <1%). ▪ Refer to UpToDate topics on use of granulocyte colony stimulating factors in adult patients with chemotherapy-induced neutropenia and conditions other than acute leukemia, myelodysplastic syndrome, and hematopoietic cell transplantation.
Dose adjustment for baseline liver or renal dysfunction	▪ A lower starting dose may be needed for patients with liver impairment. ▪ Refer to UpToDate topics on chemotherapy hepatotoxicity and dose modification in patients with liver disease, conventional cytotoxic agents and chemotherapy hepatotoxicity and dose modification in patients with liver disease, molecularly targeted agents.

Monitoring parameters:

- CBC with differential and platelet count weekly during treatment.
- Assess basic metabolic panel (including serum creatinine) and liver function prior to each cycle and otherwise as indicated during treatment.

Suggested dose modifications for toxicity:

Myelotoxicity	▪ This regimen should not be initiated unless the white blood cell count is >3500 cells/microL and platelets are ≥100,000/microL.[1] During therapy, the dose of gemcitabine should be decreased by 25% if the absolute neutrophil count decreases to <1000 cells/microL but ≥500 cells/microL, or the platelets decrease to <100,000/microL and ≥50,000/microL.[2] The United States Prescribing Information recommends holding gemcitabine for an absolute neutrophil count <500 cells/microL or platelets <50,000/microL.[2]

Hepatotoxicity	▪ Gemcitabine is commonly associated with a transient rise in serum transaminases, but these are seldom of clinical significance. There is insufficient information from clinical studies to allow clear dose recommendations in these patients.
Thrombotic microangiopathy	▪ Thrombotic microangiopathy (TMA, also sometimes called thrombotic thrombocytopenic purpura [TTP] or hemolytic uremic syndrome [HUS]) has been associated with gemcitabine, in individuals who have received a large or small cumulative dose.[2] Consider the possibility of TMA if the patient develops Coombs-negative hemolysis, thrombocytopenia, renal failure, and/or neurologic findings. Management consists of drug discontinuation and supportive care, without plasma exchange, as long as there is high confidence in a drug-induced etiology rather than TTP. ▪ Refer to UpToDate topics on drug-induced thrombotic microangiopathy.
Pulmonary toxicity	▪ A variety of manifestations of pulmonary toxicity have been reported. Discontinue gemcitabine immediately and permanently. ▪ Refer to UpToDate topics on pulmonary toxicity associated with antineoplastic therapy, cytotoxic agents.
If there is a change in body weight of at least 10%, doses should be recalculated.	

This table is provided as an example of how to administer this regimen; there may be other acceptable methods. This regimen must be administered by a clinician trained in the use of chemotherapy, who should use independent medical judgment in the context of individual circumstances to make adjustments, as necessary.

IV: intravenous; CBC: complete blood count.

References:

1. *Oettle H, et al. JAMA 2007; 297:267.*
2. *Gemcitabine hydrochloride injection. United States Prescribing Information. US National Library of Medicine. (Available online at dailymed.nlm.nih.gov, accessed on November 28, 2011).*

Graphic 81436 Version 21.0

Gemcitabine plus nanoparticle albumin-bound paclitaxel (nabpaclitaxel) for advanced pancreatic and biliary cancer[1,2]

Cycle length: 4 weeks.

Drug	Dose and route	Administration	Given on days
Nabpaclitaxel*	125 mg/m^2 IV	Administer undiluted over 30 minutes.	Days 1, 8, and 15¶
Gemcitabine	1000 mg/m^2 IV	Dilute in 250 mL NSΔ (concentration no greater than 40 mg/mL) and administer over 30 to 60 minutes, after nabpaclitaxel.	Days 1, 8, and 15¶

Pretreatment considerations:

Emesis risk	▪ MODERATE. ▪ Refer to UpToDate topics on prevention of chemotherapy-induced nausea and vomiting in adults.
Vesicant/irritant properties	▪ Nabpaclitaxel can cause significant tissue damage; avoid extravasation. ▪ Refer to UpToDate topics on extravasation injury from chemotherapy and other non-antineoplastic vesicants.
Prophylaxis for infusion reactions	▪ Premedication to prevent hypersensitivity reactions is generally not needed. Premedication may be needed in patients who have had a prior hypersensitivity reaction to nabpaclitaxel. ▪ Refer to UpToDate topics on infusion reactions to systemic chemotherapy.
Infection prophylaxis	▪ The incidence of febrile neutropenia with this regimen is 3%.[1] Primary prophylaxis with G-CSF is not indicated. ▪ Refer to UpToDate topics on use of granulocyte colony stimulating factors in adult patients with chemotherapy-induced neutropenia and conditions other than acute leukemia, myelodysplastic syndrome, and hematopoietic cell transplantation.
Dose adjustment for baseline liver or renal dysfunction	▪ A lower starting dose for gemcitabine and nabpaclitaxel may be needed for patients with liver impairment. **Do not administer nabpaclitaxel to patients with pancreatic cancer and moderate to severe liver impairment (AST <10 times the ULN and total bilirubin >1.5 times the ULN OR AST >10 times the ULN OR bilirubin >5 times the ULN).** ▪ Refer to UpToDate topics on chemotherapy hepatotoxicity and dose modification in patients with liver disease, conventional cytotoxic agents and chemotherapy hepatotoxicity and dose modification in patients with liver disease, molecularly targeted agents.

Monitoring parameters:	
▪ CBC with differential and platelets weekly during treatment.	
▪ Assess comprehensive metabolic panel prior to each cycle or when clinically indicated during treatment.	
▪ Monitor for infusion reactions.	
▪ Monitor for extravasation.	
▪ Sensory neuropathy occurs frequently with nabpaclitaxel; assess for changes in neurologic function prior to each treatment cycle.	
▪ Monitor for signs and symptoms of pneumonitis.	
Suggested dose modifications for toxicity:	
Myelotoxicity	▪ **Do not administer** nabpaclitaxel and gemcitabine on day 1 of each new cycle unless ANC is >1500/microL and platelet count is >100,000/microL.[2,3] For patients who develop neutropenic fever OR ANC <500/microL for >7 days or delay of next cycle by >7 days or thrombocytopenia, withhold treatment until counts recover to an ANC of at least 1500/microL and platelet count of at least 100,000/microL on day 1, or to an ANC of at least 500/microL and platelet count of at least 50,000/microL on days 8 or 15 of the cycle.[2,3] Upon resumption of therapy, reduce both drugs by 20 to 25% upon the first occurrence, an additional 20 to 25% on the second recurrence, and discontinue treatment for a third occurrence.
Sepsis	▪ Sepsis has occurred in patients with or without neutropenia (risk factors are biliary obstruction or presence of a biliary stent). Initiate broad-spectrum antibiotics in the presence of fever, even if not neutropenic. Interrupt nabpaclitaxel and gemcitabine until sepsis resolves and, if neutropenic, until neutrophils are at least 1500/microL, then resume at lower doses.[3]
Thrombotic microangiopathy	▪ Thrombotic microangiopathy (TMA; also sometimes called thrombotic thrombocytopenic purpura [TTP] or hemolytic uremic syndrome [HUS]) has been associated with gemcitabine in individuals who have received a large or small cumulative dose.[4] Consider the possibility of TMA if the patient develops Coombs-negative hemolysis, thrombocytopenia, renal failure, and/or neurologic findings. Management consists of drug discontinuation and supportive care, without plasma exchange, as long as there is high confidence in a drug-induced etiology rather than TTP. ▪ Refer to UpToDate topics on drug-induced thrombotic microangiopathy.
Peripheral neuropathy	▪ For days 1,8, and 15: withhold nabpaclitaxel for grade 3 or 4 neuropathy.[2,3] Resume nabpaclitaxel at 20 to 25 percent reduced doses when peripheral neuropathy improves to grade ≤2 or completely resolves. Upon

	resumption of therapy, reduce nabpaclitaxel by 20 to 25% for the first occurrence of grade 3 or 4 peripheral neuropathy, and an additional 20 to 25% for the second occurrence.[3] Discontinue treatment for a third occurrence.[3] For grade 2 peripheral neuropathy, decrease nabpaclitaxel dose by 20 to 25%.[2]
Hepatotoxicity	▪ Gemcitabine is commonly associated with a transient rise in serum transaminases, but these are seldom of clinical significance. There is insufficient information from clinical studies to allow clear gemcitabine dose recommendations in these patients. ▪ Reduced starting doses of nabpaclitaxel are recommended for individuals with pre-existing moderate to severe hepatic impairment; the need for further dose adjustments in subsequent courses based upon ongoing hepatotoxicity should be based on individual tolerance and clinician judgment.[3] ▪ One protocol recommends the following:[2] on days 1, 8, and 15, for serum bilirubin elevations ≥grade 2, withhold both drugs until toxicity resolves to grade ≤1; resume treatment at the same dose as before. If not resolved, discontinue therapy. ▪ Refer to UpToDate topics on chemotherapy hepatotoxicity and dose modification in patients with liver disease, conventional cytotoxic agents and chemotherapy hepatotoxicity and dose modification in patients with liver disease, molecularly targeted agents.
Pulmonary toxicity	▪ A variety of manifestations of pulmonary toxicity have been reported with gemcitabine. Pneumonitis has occurred with the use of nabpaclitaxel in combination with gemcitabine. Permanently discontinue treatment with both agents.[3] ▪ Refer to UpToDate topics on pulmonary toxicity associated with antineoplastic therapy, cytotoxic agents.
Other toxicity	▪ On days 1, 8, and 15: for grade 3 cutaneous toxicity, hold both drugs until recovered to ≤grade 2, and reduce nabpaclitaxel dose by 20 to 25% and gemcitabine dose by 20%.[2] For grade 3 mucositis or diarrhea, withhold therapy until it improves to ≤grade 1, then resume with reduction of nabpaclitaxel dose by 20 to 25% and gemcitabine dose by 20%.
If there is a change in body weight of at least 10%, doses should be recalculated.	

This table is provided as an example of how to administer this regimen; there may be other acceptable methods. This regimen must be administered by a clinician trained in the use of chemotherapy, who should use independent medical judgment in the context of individual circumstances to make adjustments, as necessary.

IV: intravenous; NS: normal saline; G-CSF: granulocyte colony-stimulating factors; AST: aspartate aminotransferase; ULN: upper limit of normal; CBC: complete blood count; ANC: absolute neutrophil count.

* Do not substitute paclitaxel for nabpaclitaxel.

¶ If a dose held or missed because of treatment-related toxicity was to be given on day 1 of the next cycle, the next cycle will not start until the day the next dose is given. Held doses of either drug on days 8 or 15 are considered omitted.

Δ Diluent solutions should not be modified without consulting a detailed reference due to potential incompatibility(ies).

References:

1. *Von Hoff DD, et al. N Engl J Med 2013; 369:1691.*
2. *Sahai V, et al. JAMA Oncol 2018; 4:1707.*
3. *Abraxane for injectable suspension (paclitaxel protein-bound particles for injectable suspension) (albumin-bound). United States Prescribing Information. US National Library of Medicine. (Available online at dailymed.nlm.nih.gov, accessed April 24, 2013).*
4. *Gemcitabine hydrochloride injection. United States Prescribing Information. US National Library of Medicine. (Available online at dailymed.nlm.nih.gov, accessed April 24, 2013).*

Graphic 89668 Version 26.0

Gemcitabine for metastatic pancreatic and biliary tract cancer[1]

Cycle length: 8 weeks for first cycle, then 4 weeks.

Drug	Dose and route	Administration	Given on days
Gemcitabine*	1000 mg/m^2 IV	Dilute in 250 mL normal saline (concentration no greater than 40 mg/mL) and administer over 30 to 60 minutes.	Weekly for seven weeks followed by one week of rest in the first cycle, then weekly for three weeks followed by one week of rest in all subsequent cycles

Pretreatment considerations:

Emesis risk	▪ LOW. ▪ Refer to UpToDate topics on prevention of chemotherapy-induced nausea and vomiting in adults.
Infection prophylaxis	▪ Primary prophylaxis with granulocyte colony stimulating factors not indicated (incidence of neutropenic fever <1%[1-4]). ▪ Refer to UpToDate topics on use of granulocyte colony stimulating factors in adult patients with chemotherapy-induced neutropenia and conditions other than acute leukemia, myelodysplastic syndrome, and hematopoietic cell transplantation.
Dose adjustment for baseline liver or renal dysfunction	▪ A lower starting dose may be needed for patients with liver impairment. ▪ Refer to UpToDate topics on chemotherapy hepatotoxicity and dose modification in patients with liver disease, conventional cytotoxic agents and chemotherapy hepatotoxicity and dose modification in patients with liver disease, molecularly targeted agents.

Monitoring parameters:

- CBC with differential and platelet count weekly during treatment.
- Assess basic metabolic panel (including serum creatinine) and liver function tests prior to each cycle and otherwise as indicated during treatment.

Suggested dose modifications for toxicity:

Myelotoxicity	▪ This regimen should not be initiated unless the white blood cell count is >3500 cells/microL and platelets are ≥100,000/microL.[1] During therapy, the dose of gemcitabine should be decreased by 25% if the absolute neutrophil count decreases to <1000 cells/microL but ≥500 cells/microL, or the platelets decrease to <100,000/microL and ≥50,000/microL.[5] The United States Prescribing Information recommends holding gemcitabine for an absolute neutrophil count <500 cells/microL or platelets <50,000/microL.[5]
Hepatotoxicity	▪ Gemcitabine is commonly associated with a transient rise in serum transaminases, but these are seldom of clinical significance. There is insufficient information from clinical studies to allow clear dose recommendations in these patients.
Thrombotic microangiopathy	▪ Thrombotic microangiopathy (TMA, also sometimes called thrombotic thrombocytopenic purpura [TTP] or hemolytic uremic syndrome [HUS]) has been associated with gemcitabine, in individuals who have received a large or small cumulative dose.[5] Consider the possibility of TMA if the patient develops Coombs-negative hemolysis, thrombocytopenia, renal failure, and/or neurologic findings. Management consists of drug discontinuation and supportive care, without plasma exchange, as long as there is high confidence in a drug-induced etiology rather than TTP. ▪ Refer to UpToDate topics on drug-induced thrombotic microangiopathy.
Pulmonary toxicity	▪ A variety of manifestations of pulmonary toxicity have been reported. Discontinue gemcitabine immediately and permanently. ▪ Refer to UpToDate topics on pulmonary toxicity associated with antineoplastic therapy, cytotoxic agents.
If there is a change in body weight of at least 10%, doses should be recalculated.	

This table is provided as an example of how to administer this regimen; there may be other acceptable methods. This regimen must be administered by a clinician trained in the use of chemotherapy, who should use independent medical judgment in the context of individual circumstances to make adjustments, as necessary.

IV: intravenous; CBC: complete blood count.

* In the original protocol, the gemcitabine dose could be increased by 25% up to, but not exceeding, a dose of 1250 mg/m^2 after the first cycle, provided the absolute neutrophil count and platelets exceed 1500 cells/mm^3 and 100,000/mm^3, respectively, and nonhematologic toxicity was less than or equal to WHO Grade 1.[1]

References:

1. Burris HA, et al. J Clin Oncol 1997; 15:2403.

2. Oettle H, et al. Ann Oncol 2005; 16:1639.

3. Stathopoulos GP, et al. Br J Cancer 2006; 95:587.

4. *Herrmann R, et al. J Clin Oncol 2007; 25:2212.*
5. *Gemcitabine hydrochloride injection. United States Prescribing Information. US National Library of Medicine. (Available online at dailymed.nlm.nih.gov, accessed on November 28, 2011).*

Graphic 60330 Version 24.0

Contributor Disclosures

Harvey Mamon, MD, PhD Consultant/Advisory Boards: Merck Scientific Advisory Board [Esophageal cancer]. All of the relevant financial relationships listed have been mitigated. **Carlos Fernandez-del Castillo, MD** No relevant financial relationship(s) with ineligible companies to disclose. **Kenneth K Tanabe, MD** Patent Holder: EGF SNP to determine risk for HCC [Cirrhosis, hepatocellular carcinoma]; Use of EGFR inhibitors to prevent HCC [Cirrhosis, hepatocellular carcinoma]. Consultant/Advisory Boards: Cancer Expert Now [GI cancers, melanoma]; GSK [GI Cancers]; Imvax [GI cancers]; Leidos [Melanoma, GI cancers]; Teledoc [GI cancers, melanoma]. Other Financial Interest: American Cancer Society [Honoraria as editor of Cancer]. All of the relevant financial relationships listed have been mitigated. **Sonali M Shah, MD** No relevant financial relationship(s) with ineligible companies to disclose.

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