Ampullary Adenocarcinoma, Version 1.2023

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ABSTRACT

Ampullary cancers refer to tumors originating from the ampulla of Vater (the ampulla, the intraduodenal portion of the bile duct, and the intraduodenal portion of the pancreatic duct), while periampullary cancers may arise from locations encompassing the head of the pancreas, distal bile duct, duodenum, or ampulla of Vater. Ampullary cancers are rare gastrointestinal malignancies, and prognosis varies greatly based on factors such as patient age, TNM classification, differentiation grade, and treatment modality received. Systemic therapy is used in all stages of ampullary cancer, including neoadjuvant therapy, adjuvant therapy, and first-line or subsequent-line therapy for locally advanced, metastatic, and recurrent disease. Radiation therapy may be used in localized ampullary cancer, sometimes in combination with chemotherapy, but there is no high-level evidence to support its utility. Select tumors may be treated surgically. This article describes NCCN recommendations regarding management of ampullary adenocarcinoma.

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The complete NCCN Guidelines for Ampullary Adenocarcinoma are not printed in this issue of JNCCN but can be accessed online at NCCN.org.

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Disclosures for the NCCN Ampullary Adenocarcinoma Panel

At the beginning of each NCCN Guidelines Panel meeting, panel members review all potential conflicts of interest. NCCN, in keeping with its commitment to public transparency, publishes these disclosures for panel members, staff, and NCCN itself.

Individual disclosures for the NCCN Ampullary Adenocarcinoma Panel members can be found on page 782. (The most recent version of these guidelines and accompanying disclosures are available at NCCN.org.)

The complete and most recent version of these guidelines is available free of charge at NCCN.org.
Ampullary cancers are defined as tumors originating from the ampulla of Vater (formed by 3 anatomic components: the ampulla, the intraduodenal portion of the bile duct, and the intraduodenal portion of the pancreatic duct), while periampullary cancers may arise from locations encompassing the head of the pancreas, distal bile duct, duodenum, or ampulla of Vater. Although relatively rare, accounting for only 0.2% of gastrointestinal malignancies and 6% of all periampullary cancers, ampullary adenocarcinoma is an important entity given the pathologic variations and associated prognosis. The 5-year overall survival (OS) for ampullary cancer is between 35% and 50%; however, prognosis can vary greatly based on a variety of factors such as patient age, TNM classification, differentiation grade, and treatment modality received. For example, the 5-year OS for AJCC 7th Edition stage I, stage II, and stage III + IV ampullary cancers is 64%, 27%, and 17%, respectively. Similar to other malignancies, distant metastatic disease bodes a particularly poor prognosis for ampullary cancer. Regardless, ampullary tumors generally have a more favorable outcome compared with other periampullary malignancies. In a single-institutional review of 2,564 periampullary cancers, the median survival for ampullary cancer was 47 months compared with 19, 23, and 54 months for pancreatic, biliary, and duodenal cancer, respectively. Early detection might partially contribute to this prognostic pattern.

The ampulla of Vater is an anatomically complex region, and distinction of periampullary tumors based on site of origin is particularly challenging, especially for large tumors that have invaded surrounding organs at presentation. The ampulla of Vater is comprised of 2 mucosal tissue types: pancreatobiliary ductal mucosa and intestinal mucosa. Therefore, ampullary cancer can be divided into 2 histologic subtypes: pancreatobiliary subtype and intestinal subtype, a classification system initially developed by Kimura et al. The proportion of each subtype varies widely between study populations. CDX2 and MUC1 are useful biomarkers to distinguish the 2 subtypes (pancreatobiliary subtype: CDX2 negative, MUC1 positive; intestinal subtype: CDX2 positive, MUC1 negative) and have been shown to be independent prognostic factors in multiple studies. Other biomarkers that have been proven useful in making this distinction are MUC2 and CK20. The utility of these biomarkers, however, is limited by staining method (hematoxylin and eosin vs immunohistochemistry), staining positivity threshold, and subjective pathologists’ assessment. It should be noted that a significant proportion of ampullary
adenocarcinomas may be of mixed phenotype. Thus, the NCCN panel recommends reporting of histologic subtypes as pancreatobiliary, intestinal, or mixed, with the predominant pattern noted in the pathology report for the mixed subtype (see “Pathologic Analysis: Specimen Orientation, Histologic Sections, and Reporting” in AMP-D, available in these guidelines at NCCN.org). It has been postulated for all periampullary cancers that histologic subtype is at least as important a prognostic factor as tissue of origin. Each ampullary cancer subtype seems to resemble its periampullary counterpart in terms of biologic behavior and prognosis, with the pancreatobiliary subtype demonstrating higher lymph node involvement and worse survival than the intestinal subtype. In a retrospective study of 95 ampullary cancers and 206 matching periampullary cancers, the OS of pancreatobiliary subtype was comparable to that of pancreatic cancer (25 vs 14 months; \( P = .123 \)), but worse than that for intestinal subtype (25 vs 98 months; \( P < .001 \)).

Systemic therapy is used in all stages of ampullary cancer. This includes neoadjuvant therapy for resectable or borderline resectable disease (albeit used more rarely compared with pancreatic cancer), adjuvant therapy, and first-line or subsequent-line therapy for locally advanced, metastatic, and recurrent disease. Data for systemic therapy in ampullary cancer are very limited; the only phase III randomized trial to date that enrolled a relatively large number of patients with ampullary cancer was ESPAC-3, which tested 5-fluorouracil (5-FU) + leucovorin versus gemcitabine in the adjuvant setting. Thus, the NCCN recommendations for systemic therapy options in ampullary cancer are frequently extrapolated from data in the setting of pancreatic cancer, colorectal cancer, and biliary tract cancer, as well as panel members’ clinical experience. Often, systemic therapy recommendations for pancreatobiliary/mixed type are derived from pancreatic or biliary tract cancer, whereas those for intestinal type are derived from colorectal cancer (see NCCN Guidelines for Colon Cancer and NCCN Guidelines for Small Bowel Adenocarcinoma, available at NCCN.org). Many regimens are put forth as likely options; however, their potential utility in individual patients must be carefully evaluated by the treating physicians based on interpretation of original trial data and drug risk/benefit profile (see “Principles of Systemic Therapy” in AMP-E, page 765).

Radiation therapy (RT) is another treatment modality that can be used in localized ampullary cancer, sometimes in combination with chemotherapy, but no high level evidence exists to support its utility. The goal of RT is to sterilize vessel margins, enhance the likelihood of a margin-
negative resection, and/or provide adequate local control to prevent or delay progression or prevent local disease recurrence while minimizing the risk of RT exposure to surrounding organs at risk (see “Principles of Radiation Therapy” in AMP-F, page 771). Finally, palliation and supportive care are warranted to prevent and ameliorate suffering while ensuring optimal quality of life for patients with end-stage disease who have run out of options (see “Principles of Palliation and Supportive Care” in AMP-G, page 776). For both of these modalities, recommendations are derived from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Pancreatic Adenocarcinoma (available at NCCN.org), which can serve as an additional source of reference. Brieﬂy, opioids with or without neurolysis or endoscopic ultrasound (EUS)-guided celiac plexus neurolysis can be used for pain management in ampullary cancer. Palliative RT with or without chemotherapy or high-intensity focused ultrasound can also be used for severe pain refractory to analgesic therapy, although the recommendation for high-intensity focused ultrasound is only supported by a small number of observational studies.43

Genetics of Ampullary Cancer

At the genomic level, important similarities and differences between ampullary cancer and other periampullary cancers exist. For example, the frequency of KRAS mutations seems to be comparable between ampullary cancer44,45 and duodenal cancer46,47 but is much lower in either cancer than in pancreatic cancer (~30%–40% vs ~90%48). KRAS mutations have been suggested to be predictive of outcomes in ampullary cancer; however, their prognostic value over histologic subtype is questionable.44,45,49 The distribution of KRAS mutations across ampullary cancer subtypes is also unclear, because present studies include very small numbers of patients, but they appear more frequent in pancreatobiliary subtypes.50–52 Other somatic alterations that have been reported in ampullary cancer include mutations in APC, TP53, CDKN2A, DPC4, ELF3, PIK3CA, and SMAD4, HER2 amplifications, and microsatellite instability (MSI).51,53–60 Pathogenic mutations reported include BRCA1/2, ATM, RAD50, and MUTYH.57,61 A recent genomic classification study using a large data set of 3,411 patients with peri-ampullary cancers found high concordance between histologic ampullary cancer subtypes and their respective genomic categories. Specifically, the pancreatobiliary subtype corresponds to pancreatic adenocarcinoma genomic signature, which is characterized by a high incidence of KRAS mutations. The intestinal subtype corresponds to colorectal adenocarcinoma genomic signature, which is
characterized by mutations in APC and PI3KCA, higher tumor mutational burden (TMB), and DNA mismatch repair deficiency (dMMR). However, there was significant genomic heterogeneity within each histologic subtype.52

Many targeted agents are currently approved by the US FDA for a variety of cancers or that are under clinical development and testing. Future investigations into the genomic landscape of ampullary cancer might have great implication in the selection of appropriate candidates for targeted therapy.

Clinical Presentation and Workup

The workup for patients presenting with clinical suspicion of ampullary neoplasm consists of pancreatic protocol CT (abdomen and pelvis; see “Principles of Diagnosis, Imaging, and Staging” in AMP-A, page 761), followed by esophagogastroduodenoscopy with or without EUS with biopsy and colonoscopy (if not previously performed according to established guidelines). The workup for patients diagnosed with noninvasive ampullary neoplasms, with or without high-grade dysplasia, should be similar to those with periamppullary duodenal adenomas.

Endoscopic biopsies of ampullary adenocarcinoma have shown poor diagnostic accuracy, with high false-negative rates reported in the literature (~20%-40%). The presence of adenocarcinoma within an adenoma can be missed by endoscopic biopsies, as adenocarcinoma foci have been reported in the final pathologic analysis of what was initially diagnosed as ampullary adenomas.62–72 EUS and CT are commonly used imaging techniques in the initial diagnosis and subsequent staging of ampullary neoplasms, with EUS noted as the more specific and sensitive modality in several small, single-institution, prospective studies.63,70,72–82

Ampullary Adenocarcinoma

Patients presenting with ampullary adenocarcinoma should receive further workup consisting of chest CT, pancreas protocol CT of abdomen/pelvis, liver function tests, and detection of baseline CA 19-9 and CEA. Endoscopic retrograde cholangiopancreatography/percutaneous transhepatic cholangiography can be considered as clinically indicated. The NCCN Guidelines for Ampullary Adenocarcinoma derive their pancreatic cancer radiology reporting template from the NCCN Guidelines for Pancreatic Adenocarcinoma (available at NCCN.org). Endoscopic retrograde cholangiopancreatography/percutaneous transhepatic cholangiography has been used frequently in the further evaluation of ampullary neoplasms and can provide additional diagnostic capability.
albeit with increased morbidity and even mortality, beyond what esophagogastroduodenoscopy/EUS and CT can offer. An elevated CA 19-9 level may be indicative of ampullary adenocarcinoma, although normal levels have been reported in 37% of patients. Genetic testing for inherited mutations can be considered, with the same recommendations as those found in the NCCN Guidelines for Pancreatic Adenocarcinoma. Specifically, genetic testing for inherited mutations is recommended for any patient with confirmed ampullary cancer, using comprehensive gene panels for hereditary cancer syndromes. Genetic counseling is recommended for patients who test positive for a pathogenic mutation (ATM, BRCA1, BRCA2, CDKN2A, MLH1, MSH2, MSH6, PALB2, PMS2, STK11, and TP53) or for patients with a positive family history of cancer, especially pancreatic/ampullary cancer, regardless of mutation status (see NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic, available at NCCN.org). Multidisciplinary consultation is also warranted, with the same considerations as those found in the NCCN Guidelines for Pancreatic Adenocarcinoma. Specifically, multidisciplinary review should consider involving expertise from diagnostic imaging, interventional endoscopy, medical oncology, radiation oncology, surgery, pathology, geriatric medicine, genetic counseling, and palliative care (see “Principles of Palliation and Supportive Care” in AMP-G, page 776). Consultation with a registered dietitian should be considered (see NCCN Guidelines for Older Adult Oncology and NCCN Guidelines for Palliative Care, both available at NCCN.org).

Following the workup previously noted, patients with no metastatic disease should receive MRI to evaluate indeterminate liver lesions as clinically indicated. PET/CT may be used when MRI cannot be performed (eg, pacemaker-dependent patient). Histologic subtyping of the tumor as pancreatobiliary, intestinal, or mixed should also be performed, if possible. Patients with metastatic disease should receive biopsy confirmation, preferably from a metastatic site. Core biopsy is recommended, if possible, to obtain adequate tissue for molecular testing.

Molecular profiling of tumor tissue should be performed with the same considerations as those found in the NCCN Guidelines for Pancreatic Adenocarcinoma. Specifically, tumor/somatic molecular profiling is recommended for patients with locally advanced/metastatic disease who are candidates for anticancer therapy to identify uncommon mutations. Specifically testing for potentially actionable somatic findings including, but not
limited to fusions (ie, ALK, NRG1, NTRK, ROS1, FGFR2, RET), mutations (ie, BRAF, BRCA1/2, KRAS, PALB2), amplifications (HER2), MSI, dMMR, or TMB via an FDA-approved and/or validated next-generation sequencing–based assay is recommended. Testing on tumor tissue is preferred; however, circulating tumor DNA testing can be considered if tumor tissue testing is not feasible.

Treatment of Ampullary Adenoma

Ampullary adenomas are benign tumors that can arise sporadically or in the setting of hereditary polyposis syndromes such as familial adenomatous polyposis. Ampullary adenomas can undergo malignant transformation and result in ampullary adenocarcinomas; however, the exact course and rate of transformation are still unclear.85–87

Patients presenting with ampullary adenoma can be treated with endoscopic removal (preferred), surgical ampullectomy, or pancreaticoduodenectomy (see “Principles of Surgical Technique” in AMP-C, page 764). Patients with negative margins after endoscopic removal or surgical ampullectomy should undergo endoscopic surveillance, whereas after pancreaticoduodenectomy, patients do not need to undergo surveillance. Patients with positive margins after endoscopic removal can undergo re-excision, ampullectomy, or pancreaticoduodenectomy. Patients with positive margins after ampullectomy can undergo pancreaticoduodenectomy.

Since foci of occult adenocarcinoma have been found in ampullary adenoma, and the exact timeline and rate of malignant transformation from adenoma to adenocarcinoma is not known, there is some debate regarding the optimal management of these lesions. A few studies have attempted to put forth criteria for endoscopic removal of benign ampullary neoplasms.88,89 The NCCN panel recommends that ampullary adenomas up to 20 mm in diameter be safely removed endoscopically, including those with high-grade dysplasia. Depending on the size and extent of invasion, ampullary adenomas might require multiple rounds of resection and more than one surgical technique for complete removal.72,90,91 All 3 techniques—endoscopic resection,62–64 surgical ampullectomy,65,69,92 and pancreaticoduodenectomy65,69,84 have been shown to be effective in removing ampullary adenomas in retrospective, heterogeneous studies. In particular, endoscopic resection, also interchangeably referred to as endoscopic papillectomy or endoscopic ampullectomy in the literature, has been shown to be effective and safe in patients with ampullary adenomas. The reported recurrence rates are between 6% and 40% with varying lengths of follow-up; most recurrences are
successfully resected endoscopically. Commonly reported complications include hemorrhage, perforation, and pancreatitis. Endoscopic resection is the NCCN-preferred treatment modality for ampullary adenomas. The NCCN panel recommends endoscopic removal of ampullary adenomas to be performed at a high-volume center.

Studies directly comparing the 3 resection techniques are scant and of retrospective nature. A study comparing all 3 modalities with surveillance found that endoscopic resection was associated with higher residual and recurrent tumor rates than pancreatoduodenectomy (27.6% vs 0% and 17.2% vs 0%, respectively) but fewer adverse events (AEs) (10.2% vs 29%). This study contained too few surgical ampullectomies to be able to draw any meaningful conclusions regarding this modality. Another study directly comparing endoscopic resection and surgical ampullectomy reported no difference in mortality, margin positivity, and reoperation between the 2 procedures. Endoscopic resection, however, was associated with significantly lower morbidity (18% vs 42%; P=.006) and readmission rates (16% vs 34%; P=.03). Overall, endoscopic resection seems to lead to more recurrences, but is generally safer than surgical procedures. In a study including 180 patients with ampullary adenomas, endoscopic resection was associated with a greater risk of recurrence than operative resection (32% vs 3%; P=.006) but a lower rate of complication (58% vs 29%; P<.001). A meta-analysis that included 5 studies and a total of 466 patients with ampullary adenomas concurred that surgical treatment had lower recurrence rate (risk difference, 0.10; 95% CI, −0.01 to 0.19) than endoscopic resection; however, no difference in complication rates was found (risk difference, −0.15; 95% CI, −0.53 to 0.23).

Treatment of Ampullary Adenocarcinoma

Treatment of Localized Disease

The first line of treatment of localized ampullary adenocarcinoma usually involves surgery, primarily pancreatoduodenectomy. Specimens are obtained at this point for pathologic analysis to determine the pathologic stage of the tumor, completeness of resection, and other histopathologic features that impact prognosis and clinical management. Decisions about diagnostic management and resectability should involve multidisciplinary consultation at a high-volume center with reference to appropriate high-quality imaging studies to evaluate the extent of disease (see “Principles of Surgical Technique” and

9 Tumor/somatic molecular profiling is recommended for patients with locally advanced/metastatic disease who are candidates for anti-cancer therapy to identify uncommon mutations. Consider specifically testing for potentially actionable somatic findings including, but not limited to: fusions (ie, ALK, NRAS1, NTRK, ROS1, FGFR2, and RET), mutations (ie, BRAF, BRCAY2, KRAS, and PALB2), amplifications (HER2), MSI, dMMR, or TMB via an FDA-approved and/or validated NGS-based assay. RNA sequencing assays are preferred for detecting RNA fusions. Testing on tumor tissue is preferred; however, cell-free DNA testing can be considered if tumor tissue testing is not feasible. See Discussion.

1 Principles of Systemic Therapy (AMP-E).

2 Principles of Radiation Therapy (AMP-F).

3 Defined as ECOG 0–1, with good biliary drainage and adequate nutritional intake.

4 Principles of Palliation and Supportive Care (AMP-G).

5 Serial imaging as indicated to assess disease response. See Principles of Diagnosis, Imaging, and Staging (AMP-A).

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Pathologic Analysis: Specimen Orientation, Histologic Sections, and Reporting

Decisions about diagnostic management and resectability should involve multidisciplinary consultation at a high-volume center with reference to appropriate high-quality imaging studies to evaluate the extent of disease. Resections should be done at institutions that perform a large number (at least 15–20) of pancreatic resections and/or endoscopic and surgical ampullectomy annually.

High-quality dedicated imaging of the ampullary region should be performed at presentation (even if standard CT imaging is already available), preferably within 4 weeks of surgery, and following neoadjuvant treatment to provide adequate staging and assessment of resectability status. Imaging should be done prior to stenting, when possible.

Imaging should include dedicated pancreatic CT of abdomen (preferred) or MRI with contrast.

- Multidetector CT (MDCT) angiography, performed by acquiring thin, preferably submillimeter, axial sections using a dual-phase pancreatic protocol, with images obtained in the pancreatic and portal venous phase of contrast enhancement, is the preferred imaging tool for dedicated pancreatic imaging.² Scan coverage can be extended to cover the chest and pelvis for complete staging as per institutional preferences. Multidetector reconstruction is preferred as it allows precise visualization of the relationship of the primary tumor to the mesenteric vasculature as well as detection of subcentimeter metastatic deposits. MDCT Pancreatic Adenocarcinoma Protocol, AMP-A (3 of 8).
- MRI is most commonly used as a problem-solving tool, particularly for characterization of CT-indeterminate liver lesions or when contrast-enhanced CT cannot be obtained (as in cases with severe allergy to iodinated Intravenous [IV] contrast material). This preference for using MDCT as the main imaging tool in many hospitals and imaging centers is mainly due to the higher cost and lack of widespread availability of MRI compared to CT. MRI Pancreatic Adenocarcinoma Protocol, AMP-A (4 of 8).

The decision regarding resectability status should be made by consensus at multidisciplinary meetings/directors following the acquisition of dedicated ampullary imaging including complete staging. Use of a radiology staging reporting template is preferred to ensure complete assessment and reporting of all imaging criteria essential for optimal staging, which will improve the decision-making process.² Pancreatic Cancer Radiology Reporting Template, AMP-A (5 of 8). This template can also be used for ampullary tumors.

Biliary stent placement is not routinely recommended prior to planned surgery; however, a stent may be considered for symptoms of cholangitis/fever or severe symptomatic jaundice (intense pruritus), or if surgery is delayed for any reason, including neoadjuvant therapy (see “Principles of Stent Management” in AMP-B, page 763).

Neoadjuvant systemic therapy can be considered, particularly in patients at high risk, with or without subsequent chemoradiation. High-risk features include imaging findings, markedly elevated CA 19-9, markedly elevated CEA, large primary tumors, large regional lymph nodes, excessive weight loss, and extreme pain. There is limited evidence to recommend specific neoadjuvant regimens off-study, and practices vary with regard to the use of chemotherapy and chemoradiation. After neoadjuvant therapy and stent placement, pancreatic protocol CT or MRI is recommended, followed by surgery in case of resectable disease. Unresectable disease should be managed with the same systemic therapy regimens as metastatic disease.

All resected ampullary cancers can receive postoperative adjuvant treatment. The initiation of adjuvant systemic therapy is recommended within 12 weeks of surgery if the patient is medically fit. The optimal duration of treatment is 4 to 6 months. The NCCN recommendations for each disease stage are as follows: (1) stage I disease, systemic therapy or observation; (2) stage II disease, systemic therapy with or without chemoradiation or observation; and (3) stage III disease, systemic therapy with or without chemoradiation.

After adjuvant therapy, patients should undergo surveillance every 3 to 6 months for 2 years, then every 6 to 12 months for up to 5 years or as clinically indicated. During surveillance, history and physical examination should take place, as should chest CT and CT or MRI of the abdomen and pelvis with contrast. CEA and/or CA 19-9 levels should also be measured.

Surgical Techniques

Pancreatodudenumectomy is the primary surgical technique for the removal of primary ampullary adenocarcinoma, with reported postoperative 5-year survival of 32%–78%.⁶⁻⁸,¹⁰,¹³,¹⁹,²⁴,²⁵,¹⁰⁰⁻¹⁰² The reported morbidity and mortality for this procedure are 27%–59% and 2%–10%, respectively.⁶⁻⁸,¹²⁻¹⁵,⁶⁹,⁷³,⁸⁴,¹⁰⁰⁻¹⁰² It should be noted that most studies are small, retrospective, contain heterogeneous populations, and combine results for benign and malignant ampullary neoplasms or combine results for

“Pathologic Analysis; Specimen Orientation, Histologic Sections, and Reporting” on AMP-D, available at NCCN.org. Biliary stent placement is not routinely recommended prior to planned surgery; however, a stent may be considered for symptoms of cholangitis/fever or severe symptomatic jaundice (intense pruritus), or if surgery is delayed for any reason, including neoadjuvant therapy (see “Principles of Stent Management” in AMP-B, page 763).

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ampullary cancers and other periampullary cancers. Reported prognostic factors for survival and recurrence outcomes include lymphovascular invasion, perineural invasion, tumor size and stage, ulceration, differentiation, presence and extent of lymph node metastasis, resection margin status, and CEA and CA 19-9 levels. However, data vary widely across studies on each of these parameters. For example, perineural invasion is not always documented on the pathology report and thus is not included in many analyses. Many studies that included perineural invasion, however, found that it has a significant impact on recurrence and/or survival, at least on univariate analyses if not multivariate analyses. Bettchart et al12 (n=70) reported a median survival of 18.7 vs 51.9 months for cancers with and without perineural invasion, respectively (P=.001). Regarding 5-year survival, Song et al107 (n=89) reported rates of 36.8% versus 72.1% in those with and without perineural invasion, respectively (P<.001). CEA and CA 19-9 levels are 2 other features that have not been consistently measured and documented for ampullary cancer. Studies have reported an inverse association between CA 19-9 level and recurrence/survival, an association for CEA but not CA 19-9, an association for CA 19-9 on univariate but not multivariate analyses, or no association between either marker with recurrence and/or survival. Therefore, the prognostic utility of these markers remains controversial.

The impact of histologic subtype on surgical outcome is, perhaps, even more understudied. According to Park et al106 (n=93), among patients who developed early recurrence (defined as within 6 months of surgery; disease-free survival = 4.2 months), the pancreatobiliary subtype recurred early compared with the intestinal subtype (71.4% vs 28.6% early recurrences; P=.001); however, this might be due to more advanced T stage and lymph node metastases in the pancreatobiliary subtype. A multivariate analysis from this study also showed that pancreatobiliary subtype was associated with very early recurrence after surgery. Bolm et al108 reported median OS after pancreatoduodenectomy to be 118 versus 156 months for pancreatobiliary/mixed subtype versus intestinal subtype, respectively, with statistical significance on univariate (P=.003) but not multivariate analysis. Evidence thus far is not definitive on whether histologic subtypes are independent prognostic factors for outcomes.

Studies have reported lymph node positivity in 30%–67% of patients with ampullary adenocarcinomas undergoing pancreatoduodenectomy. For optimal staging, a minimum of 17 lymph nodes in
pancreatoduodenectomy specimens is recommended. As mentioned earlier, the presence and extent of lymph node involvement is predictive of outcome in ampullary cancer. Except for the results from 2 small single-institution studies, each including fewer than 100 patients, it was uniformly demonstrated that survival was significantly better for node-negative versus node-positive disease. In particular, a large population-based study that included 1,301 patients who underwent resection for ampullary cancer reported significantly higher 5- and 10-year disease-specific survival for node-negative versus node-positive disease (59.4% vs 28.4%; P<.001 and 54.1% vs 21.9%; P<.001, respectively). Furthermore, an increased number of positive lymph nodes diminishes survival, as the cumulative 5-year survival rates were reported in a small study (n=34) to be 85% with 0 positive nodes, 63% with 1 to 3 positive nodes, and 0% for ≥4 positive nodes (P<.0001). Factors such as tumor size, histologic grade, perineural invasion, microscopic vessel invasion, depth of invasion, and morphology have been associated with lymph node invasion. In particular, one study (n=450) noted that the risk of lymph node invasion increased with T stage (T1, 28.0%; T2, 50.9%; T3, 71.7%; T4, 77.3%; P<.001). Another study (n=259) reported similar results, with lymph node positivity rates at 11.3%, 28.4%, 43.8%, and 100% for T1, T2, T3, and T4 tumors, respectively.

Very few studies directly compare pancreatoduodenectomy and surgical ampullectomy. One larger study (n=450, pancreatoduodenectomy = 435, ampullectomy = 15), which did not separate results for ampullary adenomas and ampullary adenocarcinomas, reported no statistically significant difference in morbidity (52.2% vs 33.3%) or mortality (2.1% vs 0%) between the 2 procedures. The number of ampullectomies in this study, however, was too small to make any meaningful conclusion. A more recent, albeit smaller, study (63 pancreatoduodenectomies, 26 ampullectomies) demonstrated that pancreatoduodenectomy led to more postoperative complications, specifically significantly higher mean blood loss, longer operative time, and more pancreatic fistula. There were also 3 deaths with pancreatoduodenectomy versus no deaths with ampullectomy. It was noted that patients treated with pancreatoduodenectomy in this study tended to present more frequently with jaundice, gross morphology, and large tumor size. No difference was found in 5-year OS (65.6% vs 64.6%), but pancreatoduodenectomy resulted in longer disease-free survival (median ~85 vs 40 months—estimated from Kaplan-Meier curves; P=.025). Overall and as expected, ampullectomy seems to result in lower morbidity and mortality but is associated with a higher recurrence rate. A few studies have attempted to
establish standard indications for ampullectomy in patients with ampullary cancer; however, the specific criteria remain to be determined.

Recently, laparoscopic and robotic pancreatoduodenectomies have become more widespread due to their potential for quicker recovery and shorter hospital stays; however, how they compare with open pancreatoduodenectomy remains a question under investigation.

Postoperatively, the rates of recurrence and time to recurrence vary widely across studies. Recurrences have been reported as early as less than 6 months and as late as 22.5 months after surgery.

The goals of surgical extirpation of carcinoma of the ampulla of Vater focus on the achievement of an R0 resection, as a margin-positive specimen is associated with poor long-term survival. Achievement of a margin-negative dissection must focus on meticulous peripancreatic and perivascular dissection of the tumor and surrounding tissues, ensuring vascular resection and reconstruction, complete resection of tumor nodules, and complete mobilization of the PV and SMV from the surrounding tissue. Tethering of the carcinoma to the lateral wall of the PV, or the presence of frank venous occlusion noted on preoperative imaging, the need for lateral venorrhaphy or complete portal or SMV resection and reconstruction to achieve an R0 resection may be suggested but is often not known until division of the pancreatic neck has occurred. Tethering of the carcinoma to the lateral wall of the PV while uncommon, requires careful dissection to free the vein from the pancreatic head if it is possible to do so. Differentiation of tumor infiltration into the vein wall from tumor-related desmoplasia is frequently impossible to ascertain. Data support an aggressive approach to partial or complete vein excision if tumor infiltration is suspected.

Neoadjuvant Therapy

Very few studies have investigated the use of neoadjuvant therapy in ampullary cancer. Overall, the use of neoadjuvant therapy is low, varying between 1% and 4% of patients undergoing surgery across studies. In the biggest and most recent study on this topic with a total of 8,688 patients with ampullary cancer, 175 of whom received neoadjuvant therapy, no difference in OS was found between the neoadjuvant and the surgery-first groups (43 vs 33 months, respectively; \( P = 0.401 \) on univariate and 0.416 on multivariate analysis). It was noted in this study that patients who received neoadjuvant therapy tend to be younger and more likely to have nodal metastases. This result was recapitulated by 2 other studies, one that included 3,762 patients, 94 of whom received neoadjuvant therapy, and another smaller study with 142 patients, 43 of whom received neoadjuvant therapy. Despite little proven advantage in improving survival, neoadjuvant therapy led to downstaging (15%–67% of tumors across studies) and was associated with decreased use of adjuvant chemotherapy or chemoradiation. These studies emphasize the need for careful selection of patients who might benefit from neoadjuvant therapy.
cancer include FOLFIRINOX, gemcitabine + cisplatin, gemcitabine + capcitabine, and gemcitabine + albumin-bound paclitaxel. The NCCN-recommended neoadjuvant therapy options for intestinal type ampullary cancer include FOLFOXIRI, FOLFOX, and capecitabine (CapeOx). All of these regimens can be potentially followed by chemoradiation based on multidisciplinary tumor board recommendation.

For pancreatobiliary/mixed type ampullary cancer, the recommendations for FOLFIRINOX or modified FOLFIRINOX (mFOLFIRINOX), gemcitabine + cisplatin, gemcitabine + capcitabine, and gemcitabine + albumin-bound paclitaxel are derived from the NCCN Guidelines for Pancreatic Adenocarcinoma and NCCN Guidelines for Biliary Tract Cancers, with the addition of gemcitabine + capcitabine based on panel members' clinical experience. It should be noted that there are no prospective randomized phase III data supporting these recommendations. The available evidence is derived from prospective phase II or randomized phase II studies as well as from retrospective studies. For more information on these studies, see the discussion sections of the NCCN Guidelines for Pancreatic Adenocarcinoma and the NCCN Guidelines for Biliary Tract Cancers (available at NCCN.org).

For intestinal type ampullary cancer, all 3 recommendations are derived from the NCCN Guidelines for Colon Cancer and the NCCN Guidelines for Small Bowel Adenocarcinoma. These recommendations are based on high-level evidence, phase III randomized data from the neoadjuvant FOxTROT trial (FOLFOX, CapeOx) in localized colon cancer, data from the TRIBE and TRIBE2 trials (FOLFOXIRI) for metastatic disease, and data from one phase II study with neoadjuvant FOLFOXIRI for localized colon cancer. For more information on these studies, see the discussion section of the NCCN Guidelines for Colon Cancer (available at NCCN.org).

Adjuvant Therapy
Adjuvant therapy is frequently used after curative resection in ampullary cancer, most often in the form of chemotherapy. RT can also be used in the adjuvant setting, often in combination with chemotherapy. Most of the literature on adjuvant therapy in ampullary cancer is retrospective in nature. In a recent large analysis of National Cancer Database data (n = 4,190), both adjuvant chemotherapy (n = 880) and adjuvant chemoradiation (n = 670) were found to be associated with improved OS compared with observation (n = 2,640). In the first analysis, median OS for the adjuvant chemotherapy group and the
observation group were 47.2 and 35.5 months, respectively (hazard ratio [HR], 0.82; \(P = .01\)). In the second analysis, median OS for the adjuvant chemoradiation group and the observation group were 38.1 and 31.0 months, respectively (HR, 0.84; \(P = .02\)). Patients who are at high risk, such as those with higher T- and N-stage disease, seemed to benefit more from both adjuvant chemotherapy and adjuvant chemoradiation.136 Two large meta-analyses, one that included 71 studies and 8,280 patients,16 and the other that included 10 studies and 3,361 patients,137 together with many smaller retrospective studies, agree on the benefit of adjuvant therapy, whether chemotherapy, RT, or chemoradiation for resected ampullary cancers.108–110,125,138–140 Some studies have also documented the usefulness of adjuvant therapy specifically for patients with lymph node involvement.111,139,140 Narang et al111 (n = 186) showed that, for patients with node positive disease, adjuvant chemoradiation compared with observation led to longer OS (median OS, 32.1 vs 15.7 months; 5-year OS, 27.5% vs 5.9%; HR, 0.47; \(P = .004\)). In this study, adjuvant therapy was more likely used for higher T-stage, lymph node involvement, and close or positive margins. Kamarajah et al (n = 1,106) showed the benefit of adjuvant RT for N2 disease in improving both disease-specific survival (median, 27 vs 19 months; \(P = .0044\)) and OS (median, 23 vs 17 months; \(P = .0091\)).139 An interesting finding was reported by Bolm et al108 (n = 214), in which adjuvant therapy (gemcitabine, gemcitabine + oxaliplatin, capecitabine, FOLFOX, chemoradiation, or unknown regimen) was beneficial for the pancreatobiliary subtype (improved median OS, 85 vs 65 months for observation; \(P = .005\)) but not the intestinal subtype. According to the NCCN panel, chemotherapy should be given before administration of chemoradiation, if chemoradiation is being considered due to positive or close margins.

Despite many positive reports on the benefit of adjuvant therapy, an equal amount of literature exists showing no effect of adjuvant therapy on recurrence and survival outcomes.6,7,14,22,84,101,141–148 It was shown in almost all of these studies that adjuvant therapy was more commonly used in patients with more advanced disease (poorly differentiated, higher T/N stage). In a recent retrospective study by Kang et al144 (n = 475), no benefit was noted with adjuvant 5-FU + leucovorin-based chemotherapy over observation in terms of both OS and recurrence-free survival, even after stratification by TNM stage. However, there seemed to be a particular benefit of this regimen versus observation for the intestinal subtype (5-year OS, 83.7% vs 33.2%; \(P = .015\); and recurrence-
free survival, 46.5% vs 24.9%; \( P = 0.035 \), but not for the pancreatobiliary/mixed type. Winter et al.\(^8\) reported no benefit of adjuvant chemoradiation (5-FU plus 50.4 Gy) versus observation overall, but found a slight improvement in survival for patients with cancers with perineural invasion (30.4 vs 12.5 months; \( P = 0.08 \)).

The NCCN-recommended adjuvant therapy options for pancreatobiliary/mixed type ampullary cancer are gemcitabine (category 1), 5-FU + leucovorin (category 1), gemcitabine + capcitabine, gemcitabine + cisplatin, FOLFOX/CapeOx, capcitabine, and mFOLRINOX. Based on the same data, the NCCN-recommended adjuvant therapy options for intestinal type ampullary cancer include 5-FU + leucovorin (category 1), FOLFOX/CapeOx, and gemcitabine.

The recommendations for 5-FU + leucovorin and gemcitabine are based on results of the ESPAC-3 trial.\(^9\) In this phase III, randomized, open-label trial, patients with ampullary, bile duct, or other periampullary cancers were randomized to 5-FU + leucovorin, gemcitabine, or observation. A total of 297 patients with ampullary cancer were randomized, with 100, 92, and 105 patients in each arm, respectively. The median survival for each arm was 57.8, 70.8, and 40.6 months, respectively. Statistical comparisons between treatment arms were not reported for individual cancer types. When data for all 3 cancer types were combined, no significant difference was found in survival between treatment arms, but the HR for chemotherapy compared with observation was significant (\( P = 0.03 \)). The authors mentioned that there was no significant difference in survival between the pancreatobiliary subtype and the intestinal subtype in response to treatment; however, these data were not reported. The rate of treatment-related serious AEs was higher in those receiving 5-FU + leucovorin than in those receiving gemcitabine (49% vs 30%; \( P = 0.002 \)). Based on the high level of evidence presented in this study, the NCCN panel assigned a category 1 designation to gemcitabine and 5-FU + leucovorin for the adjuvant treatment of resected ampullary cancers. Gemcitabine is also used in the adjuvant setting in pancreatic cancer, based on data from CONKO-001.\(^149\)

The recommendation for gemcitabine + capcitabine is based on extrapolation of data from ESPAC-4.\(^150\) ESPAC-4 was a phase III, randomized, open-label trial that tested gemcitabine monotherapy or gemcitabine in combination with capcitabine for the adjuvant treatment of resected pancreatic cancer. A total of 730 patients were included in the final analysis, 366 in the gemcitabine arm and 364 in the gemcitabine + capcitabine arm. The
The median OS was 25.5 months and 28 months in the gemcitabine and gemcitabine + capecitabine arms, respectively \((P = .032)\). While 54% of patients in the monotherapy group experienced any grade 3–4 AEs, this rate was 63% in the combination arm.

The recommendation for gemcitabine + cisplatin is extrapolated from data from a phase II randomized trial that enrolled 410 patients with advanced biliary tract cancer.\(^{151}\) Ampullary cancers were included, but the exact number was not reported. Patients with locally advanced or metastatic disease were randomly assigned to receive either gemcitabine + cisplatin \((n = 204)\) or gemcitabine alone \((n = 206)\). The median OS and median progression-free survival \((PFS)\) were significantly longer in the combination group versus the single-agent group \((OS, 11.7 \text{ vs } 8.1 \text{ months}; P < .001 \text{ and PFS, } 8.0 \text{ vs } 5.0 \text{ months}; P < .001, \text{ respectively})\). The rates of any grade 3–4 AEs were similar between the 2 arms \((70.7\% \text{ vs } 68.8\% \text{ for combination and single agent, respectively})\). Gemcitabine + cisplatin was not tested in the adjuvant setting in this trial, but other smaller trials tested adjuvant gemcitabine + cisplatin after surgery for biliary cancers.\(^{152,153}\)

The recommendation for CapeOx is extrapolated from data from a phase II trial that enrolled 31 patients with advanced small bowel and ampullary cancers, 12 of whom had ampullary cancer.\(^{154}\) All patients had metastatic or unresectable tumors and no prior systemic chemotherapy. Everyone received CapeOx. The overall response rate was 50%, and the median OS was 20.4 months. The NCCN panel deems FOLFOX a reasonable alternative to CapeOx based on clinical experience with these agents in periampullary cancers. CapeOx was not tested in the adjuvant setting in this trial. In addition, the recommendation of FOLFOX/CapeOx adjuvant therapy for intestinal type ampullary cancers is also derived from adjuvant FOLFOX/CapeOx chemotherapy trials in colon cancer.\(^{155,156}\)

The recommendation for capecitabine is based on extrapolation of data from BILCAP, a phase III randomized trial that enrolled 447 patients with biliary tract cancer (cholangiocarcinoma or muscle-invasive gallbladder cancer).\(^{157}\) In this study, patients were randomly assigned to capecitabine \((n = 223)\) or observation \((n = 224)\) after surgery. After a median follow-up of 60 months, the median OS was statistically similar between the 2 arms \((51.1 \text{ vs } 36.4 \text{ months in the capecitabine vs observation groups, respectively}; P = .097)\). Serious AEs were observed in 21% of patients in the capecitabine group and 10% of patients in the observation group. In addition, the recommendation for capecitabine adjuvant therapy for
intestinal type ampullary cancers is derived from the X-ACT study in colon cancer.\textsuperscript{158}

The recommendation for mFOLFIRINOX is based on extrapolation of data from the PRODIGE 24/CCTG PA.6 phase III randomized trial in resected pancreatic cancer.\textsuperscript{159} In this study, 493 patients with pancreatic cancer were randomly assigned to receive mFOLFIRINOX (n=247) or gemcitabine (n=246) postoperatively. The median PFS and median OS were significantly longer in the mFOLFIRINOX group compared with the gemcitabine group (21.6 vs 12.8 months; \textit{P}<.001; and 54.4 vs 35.0 months; \textit{P}=.003, respectively). The rate of grade 3–4 AEs was higher in the mFOLFIRINOX group (75.9% vs 52.9%).

Chemosradiation

The NCCN recommendations for chemosradiation in ampullary cancer are similar to those in the NCCN Guidelines for Pancreatic Adenocarcinoma, NCCN Guidelines for Biliary Tract Cancers for pancreatobiliary ampullary cancers, and NCCN Guidelines for Small Bowel Adenocarcinoma for intestinal type ampullary cancers (all available at NCCN.org). The preferred options for pancreatobiliary, mixed, and intestinal types are capecitabine + concurrent RT and 5-FU + concurrent RT, while gemcitabine + concurrent RT is recommended for pancreatobiliary type only. All 3 regimens have been reported in the literature, mostly in the adjuvant setting; however, these studies are usually small, retrospective, single-institutional, and heterogenous.\textsuperscript{16,109,111,125,136,137,140,148} The most commonly used chemoradiation regimen in these studies is 5-FU–based. In a large analysis of data from the National Cancer Database, in which 870 patients received adjuvant chemotherapy and 669 patients received adjuvant chemoradiation, it was observed that adjuvant chemotherapy use increased (9%–32% between 2004–2005 and 2012–2013) during the same time that adjuvant chemoradiation use decreased (20%–12% during the same time period).\textsuperscript{136} As described in the previous section on adjuvant therapy, the literature is split regarding the usefulness of adjuvant chemoradiation in patients with ampullary cancer.\textsuperscript{16,109,111,125,136,137,140,148} A systematic review and meta-analysis of large databases was conducted using 10 retrospective studies including 3,361 patients with ampullary cancer. Adjuvant RT was delivered with concurrent chemotherapy, mostly 5-FU, in all institutional studies. The results demonstrated that adjuvant chemoradiation significantly reduced the risk of death (HR, 0.75; \textit{P}=.01).\textsuperscript{137} Several studies are in agreement that adjuvant chemoradiation seems...
to particularly benefit patients who are node positive, as mentioned in the previous section on adjuvant therapy.111,137,140 A phase III, randomized EORTC trial tested adjuvant chemoradiation with 5-FU versus observation alone after surgery in patients with pancreatic head and periampullary cancers. Of the 103 patients assigned to the observation arm, 57 had pancreatic cancer, 44 had periampullary cancer, and 2 were unknown; of the 104 patients assigned to the treatment arm, 55 had pancreatic cancer, 48 had periampullary cancer, and 1 was unknown. However, it was not specified how many patients had ampullary cancer in this study. Regardless, the final results were not in favor of chemoradiation, showing no significant difference in median duration survival or 2-year survival rates between the 2 arms.160 There is more high-level evidence on chemoradiation in the setting of pancreatic cancer, such as data from ESPAC-1, which can be extrapolated to ampullary cancer.161 For more information on these studies, see the discussion section of the NCCN Guidelines for Pancreatic Adenocarcinoma (available at NCCN.org).

**Treatment of Metastatic Disease**

Patients diagnosed with metastatic ampullary adenocarcinomas should receive genetic testing for hereditary mutations and molecular profiling of tumor tissue, if not previously done. Those with good performance status (PS; defined as ECOG 0–1 with good biliary drainage and adequate nutritional intake) can receive systemic therapy. Chemoradiation may be used for palliative indications. For select patients with oligometastatic disease and response/stable disease to systemic therapy, local-directed therapy to liver or lung metastases may be considered after review in a multidisciplinary tumor board. Patients with poor PS should receive palliative and best supportive care and be considered for systemic chemotherapy, targeted therapy based on molecular profiling as clinically indicated, or for palliative RT (see “Principles of Radiation Therapy” and “Principles of Palliation and Supportive Care” in AMP-F and AMP-G, pages 771 and 776, respectively). For specific systemic therapy regimen recommendations, see “Principles of Systemic Therapy” in AMP-E (page 765).

**First-Line Systemic Therapy**

For pancreatobiliary/mixed type ampullary cancer with good PS, the recommendations for FOLFIRINOX/mFOLFIRINOX, gemcitabine + albumin-bound paclitaxel, gemcitabine + cisplatin, gemcitabine + cisplatin + durvalumab, and gemcitabine + capecitabine are derived from the NCCN Guidelines...
for Pancreatic Adenocarcinoma and the NCCN Guidelines for Biliary Tract Cancers (available at NCCN.org), with the addition of FOLFOX based on panel members’ clinical experience. Most of these recommendations are based on phase II/III randomized data (FOLFIRINOX/ mFOLFIRINOX, gemcitabine + albumin-bound paclitaxel, gemcitabine + cisplatin, gemcitabine + cisplatin + durvalumab, and gemcitabine + capecitabine). For more information on these studies, see the discussion sections of the NCCN Guidelines for Pancreatic Adenocarcinoma and NCCN Guidelines for Biliary Tract Cancers. For pancreatobiliary/mixed type ampullary cancer with poor PS, simplified formulations of the same regimens for patients with good PS are recommended, with the goal of reducing toxicity. Although gemcitabine, capcitabine, and 5-FU + leucovorin are appropriate for these patients, those with ECOG PS 2 can receive multiagent regimens such as FOLFOX or gemcitabine + albumin-bound paclitaxel.

For intestinal type ampullary cancer, all recommendations are derived from the NCCN Guidelines for Colon Cancer (available at NCCN.org). Most of the recommendations are based on phase II/III, randomized data (FOLFOXIRI ± bevacizumab, FOLFIRI ± bevacizumab, and CapeOx ± bevacizumab). Whereas all of these options are appropriate for patients with good PS, 5-FU + leucovorin and capcitabine are considered appropriate options for those with poor PS, with the same rationale of reducing toxicity. With the exception of FOLFOXIRI ± bevacizumab, all other regimens for good PS can also be used in select patients with ECOG PS 2. These patients can additionally receive 5-FU ± bevacizumab and capcitabine ± bevacizumab. For more information on these studies, see the discussion section of the NCCN Guidelines for Colon Cancer (available at NCCN.org).

Due to the controversial role of anti-EGFR therapies in KRAS wild-type small bowel cancers or for right-sided colon cancers, the panel members do not recommend using anti-EGFR therapies for KRAS wild-type ampullary adenocarcinomas of intestinal subtype. Data regarding anti-EGFR–targeted therapies in ampullary adenocarcinomas are scant. Due to no data with tipiracil/tipifarnib ± bevacizumab or with regorafenib in small bowel cancers or intestinal subtype ampullary carcinomas, these agents are not recommended.

In addition to chemotherapy recommendations, pembrolizumab is a recommended option for all ampullary tumors with MSI-high (MSI-H), dMMR, or high TMB...
(TMB-H) (≥10 mut/Mb), and nivolumab + ipilimumab is a recommended option for MSI-H, dMMR intestinal type ampullary cancers. Patients can also receive larotrectinib or entrectinib if the tumors test positive for NTRK gene fusion. These options are applicable regardless of PS. With the exception of nivolumab + ipilimumab, the rationale for which comes from the metastatic colorectal cancer setting, the other 4 regimens are supported by basket trials that included many different cancer types. No ampullary cancer and a very small number of periampullary cancers were included in these studies. Therefore, cautious extrapolation of data from these studies to the ampullary cancer setting is prudent.

The recommendation for pembrolizumab is supported by data from the phase II KEYNOTE-518 study, in which a total of 233 patients representing 27 tumor types were treated with pembrolizumab after failure with prior therapy. The objective response rate was 34.3%, median PFS was 4.1 months, and median OS was 23.5 months. The rate of grade 3–5 treatment-related AEs was 14.6%. No patient with ampullary cancer was enrolled, although the trial included 24 patients with gastric cancer, 22 patients with cholangiocarcinoma, 22 patients with pancreatic cancer, and 19 patients with cancer of the small intestine.

The recommendation for nivolumab + ipilimumab is based on data in the metastatic colorectal cancer setting, hence its suitability only for intestinal type ampullary cancer. In the phase II CheckMate 142 study, patients with no prior treatment received nivolumab + ipilimumab until disease progression. The objective response rate was 69%, and 2-year PFS and 2-year OS were 74% and 79%, respectively. The rate of grade 3–4 treatment-related AEs was 22%. This trial also included a cohort of previously treated patients. In this group (n=119), the objective response rate was 55% and the 1-year PFS and 1-year OS were 71% and 85%, respectively. The rate of grade 3–4 treatment-related AEs was 32%.

The recommendations for larotrectinib and entrectinib are supported by data from 2 phase I–II basket trials. The first enrolled 55 patients, including 4 with colon cancer, 2 with cholangiocarcinoma, and 1 with pancreatic cancer, who were treated with larotrectinib. The overall response rate was 75%, and neither the median duration of response nor the median PFS was reached after a median follow-up of 9.9 months. The second basket trial enrolled 54 patients, including 4 with colorectal cancer, 3 with pancreatic cancer, and 1 with cholangiocarcinoma. Objective response was noted in 57% of patients, and the median PFS and median OS were 11 months and
21 months, respectively.177 Patients in both of these trials had received prior systemic therapy.

Based on the recent FDA approvals, dabrafenib + trametinib can be used as a treatment option for BRAF V600E-mutated ampullary adenocarcinomas with good or poor PS. This recommendation is based on data from 2 clinical trials.178,179 NCI-MATCH Subprotocol H was an open-label study that evaluated dabrafenib + trametinib in patients with solid tumors, lymphomas, or multiple myeloma whose tumors harbored a BRAF V600E mutation. Overall, the response rate was 37.9% (n=29), with a median duration of response of 25.1 months. With a median follow-up of 23 months, median OS was 28.6 months; median PFS was 11.4 months.178 ROAR was a phase II, open-label basket trial in patients with BRAF V600E-mutated rare cancers. In 43 patients with BRAF V600E-mutated biliary tract cancer, the response rates by investigator and independent reviewer assessment were 51% and 47%, respectively. Median OS was 14 months and median PFS was 9 months.179

Treatment for Disease Progression

Patients with disease progression and good PS should preferably be enrolled in clinical trials. Alternative options are systemic chemotherapy, or possibly targeted therapy based on molecular profiling as clinically indicated, or palliative RT for severe pain refractory to analgesic therapy. The second line of treatment includes palliative and best supportive care or clinical trial enrollment. Patients with disease progression and poor PS should receive palliative and best supportive care and be considered for systemic therapy, targeted therapy based on molecular profiling as clinically indicated, or palliative RT (see “Principles of Radiation Therapy” and “Principles of Palliation and Supportive Care” in AMP-F and AMP-G, pages 771 and 776, respectively). For specific systemic therapy regimen recommendations, see “Principles of Systemic Therapy” in AMP-E (page 765). For anyone receiving therapy for disease progression, serial imaging is recommended as indicated to assess disease response.

The recommendation for selpercatinib is supported by data from a phase I/II basket trial in RET fusion-positive solid tumors other than lung and thyroid tumors (LIBRETTO-001).180 Among 41 patients with solid tumors, including pancreatic, biliary tract, and colorectal cancers, the overall response rate was 43.9% and the median duration of response was 24.5 months. The median PFS was 13.2 months. Among 11 patients with pancreatic cancer, the response rate was 54.5% and the median...
duration of response was not reached. The FDA approved selpercatinib as a treatment option for locally advanced or metastatic RET fusion-positive solid tumors.

Subsequent-Line Systemic Therapy

For subsequent therapy for disease progression, the rule of thumb is that any regimen other than the one used in the first-line setting is a possible option. In patients with good PS and pancreatobiliary/mixed type ampullary cancer previously treated with a gemcitabine-based regimen, a fluoropyrimidine-based regimen is recommended for subsequent-line therapy. FOLFIRINOX\(^1\) or mFOLFIRINOX and FOLFOX\(^1\) can be used, as well as modifications to these regimens including 5-FU + leucovorin + liposomal irinotecan,\(^1\) CapeOx,\(^2\) and 5-FU + leucovorin.\(^3\) Vice versa, in patients with good PS and pancreatobiliary/mixed type ampullary cancer previously treated with a fluoropyrimidine-based regimen, a gemcitabine-based regimen is recommended for subsequent-line therapy. Gemcitabine + albumin-bound paclitaxel and gemcitabine + capecitabine can be used, as can modifications to these regimens including gemcitabine. In addition, FOLFIRI\(^4\) or 5-FU + leucovorin + liposomal irinotecan\(^5\) can be tried in case of no progression on prior irinotecan. In patients with poor PS and pancreatobiliary/mixed type ampullary cancer, gemcitabine,\(^6\) capecitabine,\(^7\) or 5-FU + leucovorin\(^8\) can be used for disease progression, depending on the first-line regimen used. For patients with ECOG PS 2, multiagent regimens such as FOLFOX and gemcitabine + albumin-bound paclitaxel are options, as are CapeOx and FOLFIRI based on panel members’ clinical experience.

In addition to these agents, gemcitabine + cisplatin for known BRCA1/2/PALB2 mutations is recommended for patients with good PS in the subsequent-line setting. This recommendation is supported by data from a phase II randomized trial in which 50 patients with previously untreated pancreatic cancer with germline BRCA/PALB2 mutations were randomly assigned to gemcitabine + cisplatin or gemcitabine + cisplatin + veliparib. The response rate was 74.1% and 65.2% for each arm, respectively; median PFS was 10.1 months and 9.7 months, and median OS was 15.5 months and 16.4 months, respectively.\(^9\)

Similar to recommendations for the first-line setting, all of the recommendations for the subsequent-line setting are derived from phase II/III data in pancreatic cancer or biliary cancer, with the exception of the reference for FOLFIRINOX, which is an exploratory analysis of the
MPACT trial. For more information on these studies, see the discussion sections of the NCCN Guidelines for Pancreatic Adenocarcinoma and NCCN Guidelines for Biliary Tract Cancers (available at NCCN.org).

For patients with good PS and intestinal type ampullary cancer, FOLFIRI + bevacizumab is a possible subsequent-line option for those previously treated with an oxaliplatin-based regimen. FOLFOX + bevacizumab or CapeOx + bevacizumab can be used for patients previously treated with an irinotecan-based regimen. For patients with poor PS and intestinal type ampullary cancer, the same recommendations as those in the first-line setting apply (5-FU + leucovorin; for those with ECOG PS 2: capecitabine + bevacizumab, 5-FU + bevacizumab, FOLFOX + bevacizumab, FOLFIRI + bevacizumab, and CapeOx + bevacizumab). Similar to recommendations in the first-line setting, all of the recommendations for the subsequent-line settings are derived from phase II/III data in colon cancer. For more information on these studies, see the discussion section of the NCCN Guidelines for Colon Cancer (available at NCCN.org).

Targeted therapy regimens recommended in the first-line setting are also possible options in the second-line setting: pembrolizumab, nivolumab + ipilimumab, larotrectinib, entrectinib, selpercatinib, and dabrafenib + trametinib. As explained in the previous section, trials demonstrating the efficacy of these regimens included all or a portion of patients who had received and experienced progression on prior systemic therapy. Furthermore, dostarlimab-gxly is recommended for good and poor PS in tumors with MSI-H or dMMR. This recommendation is based on results of a phase I basket study in which a total of 209 patients, including 99 with gastrointestinal cancer (69 with colorectal cancer) received dostarlimab-gxly until disease progression or discontinuation. The objective response rate was 41.6%. HER2 overexpression occurs in 13% of ampullary cancers, and HER2 targeting is relevant. HER2-targeted therapy is included in the NCCN Guidelines for Biliary Tract Cancers (applies to pancreatobiliary subtype; available at NCCN.org). The FDA also recently approved tucatinib + trastuzumab for pretreated colorectal cancer. In the MY PATHWAY basket trial, among 114 patients, trastuzumab + pertuzumab conferred an overall response rate of 26%, and responses occurred in pancreatic (22%), biliary (29%), and colorectal (38%) cancers with HER2 amplifications, supporting the use of this combination in HER2-amplified ampullary carcinomas. Of note, the NCCN panel currently does not recommend HER2-targeted therapy as a treatment option for ampullary adenocarcinoma.
Ampullary cancers are rare gastrointestinal malignancies, and prognosis varies greatly depending on a number of factors. Surgery is generally the first line of treatment for localized ampullary adenocarcinoma. Although a number of neoadjuvant therapy recommendations are included in the NCCN Guidelines, very few studies have investigated the use of neoadjuvant therapy in ampullary cancer. Adjuvant systemic therapy is often used after curative resection in ampullary cancer. First-line systemic therapy options for metastatic disease are largely extrapolated from the NCCN Guidelines for Pancreatic Adenocarcinoma, NCCN Guidelines for Biliary Tract Cancers, and NCCN Guidelines for Colon Cancer (all available at NCCN.org). For subsequent therapy for disease progression, any regimen other than the one used in the first-line setting is a reasonable option. There are a number of targeted agents currently available, as well as under clinical development and testing. Future investigations into the genomic landscape of ampullary cancer may have impact on the selection of appropriate candidates for targeted therapy.

References


### Individual Disclosures for the Ampullary Adenocarcinoma Panel

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<td>Al S. Benzon, II, MD</td>
<td>ARI ImmunoTech; Astellas Pharma US, Inc.; Biocartis (Biomarker); Bristol-Myers Squibb Company; GSK; Mirati Therapeutics, Inc.; Novartis Pharmaceuticals Corporation; Pfizer Inc.; PATHCOLD, UCI, Temple, Yaman; Theravisc</td>
<td>Theravisc; Amgen; Bristol-Myers Squibb Company; Janssen Oncology; Nektar; Pfizer Inc.; Hospira Inc.</td>
<td>None</td>
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<td>Dara B. Carp, MD</td>
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<td>None</td>
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<td>AADI; BiMed Valley; Bioplos; Buxhiringer Ingehelm GmbH; Braf; Fibricon; Glaxo; Novartis; Inc.; Loxo; Merck &amp; Co., Inc.; Novartis Pharmaceuticals Corporation; Roche Laboratories, Inc.</td>
<td>Amgen Pharma US, Inc.; Bristol-Myers Squibb Company; Foundation; Eli Therapeutics; GM Biosciences; Ipsen; Merus; Pfizer Inc.</td>
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<td>Jared A. Christensen, MD</td>
<td>None</td>
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<td>None</td>
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<td>Brian Coto, MD</td>
<td>Galera Pharm</td>
<td>None</td>
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<td>Marco Del Chiaro, MD, PhD</td>
<td>Boston Scientific Corporation; Haemuvacs, Inc.</td>
<td>None</td>
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<td>Mary Dillhoff, MD, MS</td>
<td>None</td>
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<td>None</td>
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<td>Christos Fourtoulis, MD</td>
<td>Becterum; Angen Inc.; Awarix, Inc.; Astellas Pharma US, Inc.; AstraZeneca Pharmaceuticals LP; AVID Pharmaceuticals, Inc.; CS Pharmaceuticals; Cura Inc.; Department of Defense; Dragony Therapeutics; Genentech, Inc.; Hosier Oncology Group; Inova Corporation; Ipsen; IVA Therapeutics; Kadmon; Kisa Pharmaceuticals; Medimmune Inc.; Merck &amp; Co., Inc.; Merati Therapeutics; Novacor; Pelcon Pharmaceuticals, Pfizer Inc.; Seattle Genetics, Inc.; Sirna Therapeutics; Synta Pharmaceuticals; Taiho Pharmaceuticals Co., Ltd.; TransThera Biosciences</td>
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<td>John W. Kurtzman, MD, MHS</td>
<td>None</td>
<td>Legal consulting: drafting opinions, unrelated to pancreatic cancer</td>
<td>None</td>
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<td>Nicole L. Chu, MD</td>
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<td>Bayer HealthCare; Fourt; Kinnate; Stela Biotech</td>
<td>Bluewater Genomics, Fibrogen</td>
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<td>Arman Inc.; AstraZeneca Pharmaceuticals LP; Eli Lilly and Company; Genentech, Inc.; Giotrion; Hoxon Network; Ipsen; Merck &amp; Co., Inc.; Novocare; Seattle Genetics, Inc.; Taiho Pharmaceuticals Co., Ltd.</td>
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<td>Cassandra Moretti</td>
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<td>Eric K. Nakamura, MD</td>
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<td>Anil K. Narang, MD</td>
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<td>Jorge O'Brien, MD</td>
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<td>Patricio M. Polanco, MD</td>
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<td>Sushanth Reddy, MD</td>
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<td>Marsha Reynolds, MD, PhD</td>
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<td>Courtney Swede, MD</td>
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<td>Pathology</td>
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<td>Medical oncology; Hematology/Hematology oncology</td>
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<td>Mark J. Truty, MD, MS</td>
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<td>None</td>
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<td>Celgene Corporation; Grail; Mirati Therapeutics, Inc.</td>
<td>None</td>
<td>Medical oncology</td>
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</table>

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Robert A. Wolff, MD, McGraw-Hill