Distal Cholangiocarcinoma

Paxton V. Dickson, MD, Stephen W. Behrman, MD*

KEYWORDS

• Cholangiocarcinoma • Pathophysiology • Surgery • Adjuvant therapy

KEY POINTS

- Cancer of the distal common bile duct (distal cholangiocarcinoma) is a rare malignancy that often clinically presents similar to pancreatic cancer; however, it has a distinct set of risk factors indicating a unique pathophysiology relative to other periampullary neoplasms.
- Patients with primary sclerosing cholangitis (PSC) have a markedly increased risk for cholangiocarcinoma (CC) and should undergo rigorous surveillance to preempt malignant transformation.
- Patients with imaging and endoscopy suggesting only locoregional disease, and of adequate performance status, should undergo exploration for possible pancreaticoduodenectomy.
- Once resected, surgeons and pathologists should work together to mark the critical margins of the surgical specimen. Positive resection margins and lymph node metastases have consistently been shown to lead toward poor prognosis after pancreaticoduodenectomy.
- There are limited data to support adjuvant chemotherapy after potentially curative resection for distal cholangiocarcinoma. Institutional series suggest a potential benefit from postoperative chemoradiation, particularly in patients with R1 resection or positive nodes.
- For patients with unresectable or metastatic disease, palliative systemic chemotherapy usually includes gemcitabine and cisplatin; however, median survival in these patients is less than 1 year.

Cholangiocarcinoma (CC) involving the distal common bile duct (distal cholangiocarcinoma [DCC]) is a periampullary neoplasm less common than, but often difficult to distinguish from, pancreatic adenocarcinoma (PDA). Although the prognosis and cure rate of DCC is improved over that of PDA, it remains a highly lethal disease. Although the diagnostic and therapeutic management of DCC is not dissimilar from PDA, the pathophysiology is, in many instances, distinctly different. Certain patient populations demand close surveillance for the development of DCC and, in some instances, preemptive surgical extirpation of a diseased biliary tree before the development of frank carcinoma is necessary. Furthermore, recent work has elucidated aberrant molecular and inflammatory mediators that might predispose to the development of DCC and offer the potential

Division of Surgical Oncology, Department of Surgery, University of Tennessee Health Science Center, 910 Madison Avenue, Suite 329, Memphis, TN 38163, USA
* Corresponding author.
E-mail address: sbehrman@uthsc.edu

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for a more targeted approach toward this challenging disease. Current neo/adjuvant management schemes are suboptimal, and in many instances extrapolated from those of intrahepatic and hilar CC, and PDA and other periampullary neoplasms.

EPIDEMIOLOGY

It is difficult to determine the exact incidence of DCC because studies often collectively include intrahepatic, hilar, and distal CC, and gallbladder carcinoma. However, trends in the United States and other countries indicate the incidence of extrahepatic CC (hilar and distal) is stable or in some instances decreasing. This is in contradistinction to intrahepatic CC, which is rising in incidence worldwide. These epidemiologic trends suggest a biologic difference relative to the anatomic location of these tumors.[1,2] Although there have been no epidemiologic studies specifically analyzing the incidence of distal disease, this is important going forward because DCC is, in many aspects, a vastly different disorder than hilar CC and gallbladder carcinoma. CC, regardless of anatomic location, is more common in Asia than in Western countries.[3]

RISK FACTORS FOR DCC

Approximately 80% of all patients diagnosed with CC in any anatomic location have no identifiable risk factor for the development of the disease. In contrast, there are well-described conditions leading to chronic biliary inflammation that have a clear association with the development of CC. Recent work has accelerated knowledge of the molecular pathways and genetic aberrations that may contribute toward the development of cholangiocarcinogenesis. For the purposes of this discussion, only the pathophysiology most often encountered specific to DCC is presented.

Clinical: Social

Although population-based analyses have found smoking and alcohol consumption common among patients with CC, there are no data to clearly link these factors with disease development. Interestingly, a recent meta-analysis suggests that diabetes may significantly increase the risk of CC including extrahepatic CC.[4,5]

Clinical: Disease Specific

Primary sclerosing cholangitis

Primary sclerosing cholangitis (PSC) is an autoimmune disease that can affect the entire biliary tree. PSC confers a lifetime risk for the development of CC of 9% to 31% or a 1500-fold increase over that of the general population. Moreover, the risk of PSC-associated CC increases in those with concomitant ulcerative colitis.[6] PSC is isolated to the extrahepatic biliary tree in 10% to 20% of patients, frequently presents as an isolated high-grade stricture, and has been demonstrated on pathologic examination of Whipple specimens performed for suspected malignant disease.[7,8] Furthermore, the development of CC in the residual native bile duct has been described following orthotopic hepatic transplantation for PSC.[9,10] Currently, there is no single test identifying CC in the setting of PSC; therefore, an aggressive surveillance program for these individuals is mandatory. Findings that may indicate the development of CC in a patient with PSC include a rising carbohydrate antigen (CA) 19-9 and/or carcinoembryonic antigen (CEA), the emergence of a dominant stricture, clinical and biochemical deterioration of liver function, weight loss, jaundice, and the presence of bile duct dysplasia on brush cytology. Diagnostically, endoscopic retrograde cholangiopancreatography (ERCP) in conjunction with endoscopic intraductal ultrasound and cholangioscopic biopsy has proved most accurate in establishing

the diagnosis of CC in the setting of PSC.[11] Resected CC for a dominant stricture resulting from unsuspected PSC in the absence of other objective criteria for the diagnosis remains exceptional.[8]

Choledochal cyst

Choledochal cysts are congenital cystic dilations of the intrahepatic and/or extrahepatic biliary tree. Although this disorder is most commonly recognized in infancy, the disease may go unrecognized until adulthood. Patients may present with symptoms related to associated choledocholithiasis, such as nausea, vomiting, and epigastric pain. Elevated liver function tests and jaundice are not uncommon. The pathophysiology of extrahepatic cysts is believed to result from an anomalous junction of the pancreatic and biliary ducts resulting in a long common channel thereby allowing reflux of pancreatic enzymes into the biliary tree with resultant cystic degeneration from chronic inflammation. Type I (solitary extrahepatic) and type IV (extrahepatic and intrahepatic dilation involving the bile duct confluence) cysts have the highest lifetime risk of CC with an incidence up to 30%.[12] When discovered, types I and IV choledochal cysts, even if asymptomatic, should be resected as a measure of prophylaxis against malignant degeneration. This typically involves resection of the extrahepatic biliary tree to the level of the ductal confluence and reconstruction with Roux-en-Y hepaticojejunostomy. Even after resection, this population remains at higher risk for the development of CC relative to the general population, especially if the entirety of the biliary tree at risk is not removed.[4,13]

Parasitic Infections

Biliary infestation with the liver flukes *Opisthorchis viverrini* and *Clonorchis sinensis*, both of which are prevalent in Southeast Asia, is associated with the development of CC. Chronic inflammation of the biliary epithelium by these parasites is believed to increase the susceptibility to cholangiocarcinogenesis.[14] Both hospital- and population-based case-control studies from Thailand and Korea examining infection with liver flukes by *O viverrini* antibody titers and the presence of *C sinensis* in stool have noted a strong association with the development of CC, irrespective of anatomic location within the biliary tree.[15–17] Limited data suggest that all areas of the biliary tree including extrahepatic locations are prone to carcinoma.[17] Because infestation is linked to poor sanitation, therapeutic intervention has focused on prevention. Treatment with anthelmintic agents is important if infection is documented.

BIOLOGIC BASIS OF CHOLANGIOCARCINOGENESIS

Inflammatory Mediators

Cholestasis, regardless of cause, results in abnormal exposure of the biliary epithelium to bile acids. Deoxycholic acid, a derivative of bile acids, has been shown to activate epidermal growth factor receptor and serve as a neoplastic stimulus by promoting cellular proliferation and attenuating apoptosis in cholangiocytes.[18,19] The cytokine interleukin-6 is upregulated in CC relative to normal biliary tract cells and is regarded as a growth factor for its propagation.[20] Interleukin-6 has also been shown to desensitize CC to normal apoptotic cell death.[21] Furthermore, interleukin-6 induces increased expression of progranulin in CC in contrast to nonmalignant cholangiocytes. Progranulin expression is found in multiple tumor types and is associated with high tumorigenecity.[22] Cyclooxygenase-2, a prostaglandin, is overexpressed in CC and premalignant conditions, such as PSC. Cyclooxygenase-2 accumulation results in cellular proliferation and inhibition of apoptosis in CC, a process reversed by the administration of the cyclooxygenase-2 inhibitor celecoxib.[5,23]

Growth Factors

Human CC cell lines express high levels of vascular endothelial growth factor leading to angiogenesis and cancer growth. Inhibition of vascular endothelial growth factor reduces cell proliferation and leads to apoptosis in tumor tissue.[7,24] Epidermal growth factor receptor is a mediator of cholangiocarcinogenesis as previously noted. Epidermal growth factor receptor has been detected in more than one-third of samples obtained from patients with CC.[25]

Stromal Alterations

In common with pancreatic carcinoma, CC exhibits an epithelial-mesenchymal transition that results in a desmoplastic stroma predominantly composed of cancer-associated fibroblasts surrounding glandular structures. As opposed to tumors with epithelial expression, those exhibiting the mesenchymal phenotype have been associated with the development of chemoresistance in pancreatic cancer and tumor progression in CC.[26,27] Furthermore, CC is associated with increased levels of matrix metalloproteinases, which break down the extracellular matrix to allow tumor spread.[28]

Genetic Aberrations

A mutation of the p53 tumor suppressor gene is seen in 20% to 61% of patients with CC, resulting in inhibition of the normal cellular apoptotic response.[29] Mutations of many other genes in CC have been identified and offer the potential for future targeted therapy.[30] miRNAs are single-strand noncoding RNA products that may have tumor suppressor or oncogenic activity. Aberrant regulation of miRNA has been described in CC resulting in cancer cell proliferation and survival.[31] Manipulation of dysregulated miRNA may offer a potential avenue for CC treatment.

CLINICAL PRESENTATION AND EVALUATION

Patients with DCC typically present with painless jaundice and experience pruritus, clay colored stools, and tea-colored urine, similar to patients with PDA or other periampullary malignancies. Although biliary obstruction rarely results in cholangitis, patients may begin to experience right upper quadrant discomfort and a bloating sensation. Laboratory assessment most frequently reveals elevated bilirubin, alkaline phosphatase, γ-glutamyl transpeptidase, and the eventual elevation of hepatic transaminases.

The diagnostic evaluation of a patient with suspected DCC or periampullary neoplasm generally involves a combination of radiographic and endoscopic studies aimed at trying to define the local extent of disease, evaluate for potential metastases, and obtain tissue confirmation if the diagnosis is unclear. For patients who present with jaundice, transabdominal ultrasound is often the initial imaging modality and is very sensitive for identifying intrahepatic and extrahepatic ductal dilation, the presence of a choledochal cyst, cholelithiasis or choledocholithiasis, and potential mass lesions.[32,33] This is often followed by cross-sectional imaging with either computed tomography or magnetic resonance imaging. Patients with DCC (and other periampullary neoplasms) often have a finding of a distended gallbladder with dilated extrahepatic and intrahepatic ducts. Conversely, perihilar CC has dilated intrahepatic ducts with a normal-sized common bile duct and possibly a contracted gallbladder. A mass lesion may or may not be identified on computed tomography or magnetic resonance imaging but both studies are helpful in identifying a choledochal cyst. Contrast-enhanced triple-phase computed tomography allows for evaluation of critical vascular

anatomy, regional lymph node basins, and potentially identifies distant metastases.[34] DCC may result in biliary dilation alone but not uncommonly results in the classic double-duct sign found with PDA.

When imaging findings are suggestive of a periampullary mass or distal bile duct stricture, endoscopic evaluation is usually the most appropriate next step if the diagnosis is uncertain, the lesion appears borderline resectable, metastatic disease is suggested, or deep jaundice is present requiring preoperative surgical decompression.[35] This may include ERCP, endoscopic ultrasound (EUS), and/or cholangioscopy. ERCP permits accurate visualization of the biliary tree, allows for tissue sampling for possible diagnosis, and placement of preoperative or palliative endobiliary stents. When a tissue diagnosis is necessary for treatment planning, transampullary biopsy has been shown to have a higher sensitivity than bile sampling or brush cytology.[36–38] EUS with fine-needle aspiration biopsy is another modality useful in evaluation and potential diagnosis of biliary malignancy and, unlike ERCP, does not require cannulation of the biliary tree.[39] EUS not only allows for biopsy of biliary strictures or masses, but also permits evaluation of regional lymph nodes and vascular structures. Recently, peroral cholangioscopy has evolved as a technique that allows direct visualization of biliary epithelium and accurate targeting for biopsies.[40] The combined ability to visualize mucosal abnormalities and obtain directed biopsies potentially offers improved diagnostic yield over ERCP or EUS[41] and is most helpful in those with PSC. Certainly, the endoscopic modality of choice is largely driven by institutional expertise and the nature of individual cases.

The tumor markers CA 19-9 and CEA have been used in patients with biliary tract malignancies.[42,43] These markers have marginal sensitivity in diagnosing CC, and may often be elevated in benign inflammatory or stricturing processes of the biliary tree. For patients with PSC, serial measurements of CA 19-9 and/or CEA should be a component of surveillance for possible malignant transformation.[44] Another use of these markers is for monitoring of possible recurrence or response to therapy in patients with a confirmed diagnosis of CC.

PRINCIPLES OF SURGICAL TECHNIQUE

The diagnosis of DCC cannot always be definitively ascertained either preoperatively or intraoperatively because the tumor may infiltrate the pancreatic head and lead to a desmoplastic reaction often difficult to distinguish from PDA. Similar to other periampullary neoplasms, it is imperative that surgical extirpation of DCC focus on the achievement of R0 resection because margin positivity is associated with poor long-term survival.[45] Pancreaticoduodenectomy for DCC must focus on meticulous medial perivascular dissection of tissue off the superior mesenteric artery (SMA) and vein and a careful regional lymphadenectomy.

Medial dissection of the pancreatic head/uncinate process is crucial because this margin is typically closest to the epicenter of the tumor and most difficult to maximize. Adequate extirpation requires completely skeletonizing the right anterolateral aspect of the SMA down to the level of the adventitia and mobilization of the uncinate process off this vessel. This enhances pancreatic tissue yield while broadening the medial (retroperitoneal) margin relative to the carcinoma (**Fig. 1**). As detailed next, portal or superior mesenteric vein resection or reconstruction is occasionally required.[46,47]

The liberal use of partial or complete vein resection when tumor infiltration is suspected during pancreaticoduodenectomy has been extensively studied with respect to PDA and it would be reasonable to extrapolate these findings to DCC.[48–50] On evaluation of excised specimens in patients undergoing vein resection, only 60% to 70%

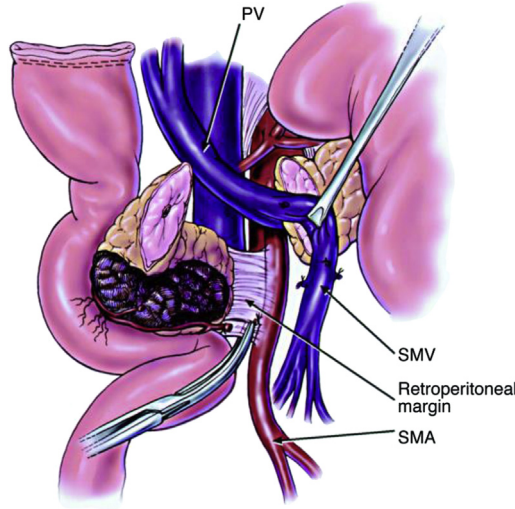

Fig. 1. Complete mobilization of the superior mesenteric (SMV) and portal veins, and separation of the specimen from the right lateral border of the superior mesenteric artery (SMA). PV, portal vein. (*From* Wayne JD, Abdalla EK, Wolff RA, et al. Localized adenocarcinoma of the pancreas: the rationale for preoperative chemoradiation. Oncologist 2002;7(1):34–45.)

had histologic evidence of frank tumor involvement and R0 resections were still not obtainable in 10% to 30%. However, if an R0 resection is obtained with vein excision, longevity seems similar to those with R0 resections without venous involvement, with no significant increase in morbidity and mortality. These data support an aggressive approach to partial or complete vein excision if tumor infiltration is suspected, although acceptance of this concept is not universal. Although the numbers are more limited, similar findings have been noted with respect to arterial resection and reconstruction and judicious use of this technique seems to be reasonable in select populations.[50,51] A recent meta-analysis reviewing vascular resection suggests that the safety and survival outcome of patients having vascular resection during a Whipple procedure is equivalent to those having standard resection alone if performed at high-volume centers.[52]

Lymphadenectomy should include a thorough dissection of regional nodes. Specific to DCC, all nodes surrounding the common bile duct and porta hepatis should be carefully excised as potential draining basins from distal common bile duct cancers. Hepatic artery nodes should be considered for resection if there is clinical suspicion of involvement because these basins have been shown to have prognostic implications in PDA and possibly also could in CC.[53]

PATHOLOGIC ANALYSIS

Specimen Orientation and Margin Assessment

The primary purpose of pathologic analysis of the Whipple specimen is to determine the pathologic stage of the tumor by evaluating the type, grade, size, and extent of the cancer. The National Comprehensive Cancer Network® (NCCN®) panel for pancreatic adenocarcinoma has proposed guidelines for pathologic analysis to bring uniformity to reporting to allow consistent interpretation from institution to institution.[54] These recommendations are most appropriate for DCC.

Specimen orientation, margin identification, and inking should involve pathologist and surgeon because this helps ensure accurate assessment of the size and extent of the tumor and proximity concerns of the malignancy to the margins assessed. One of the impediments to comparison of data across institutions is the variability in the names given to various margins. Definitions of the margins and uniformity of nomenclature are critical to ensure accurate reporting. The NCCN® recommends the following margins be inked and assessed separately (Fig. 2).[54]

SMA (Retroperitoneal/Uncinate) Margin

The most important margin is the ragged, soft tissue directly adjacent to the proximal 3 to 4 cm of the SMA. In common with other margins assessed, radial rather than en face sections are recommended and more clearly demonstrate how closely this margin is approached by tumor. The simple step of palpating the specimen can help guide the pathologist as to the best location along the SMA margin to select for sampling.

Posterior (Retroperitoneal) Margin

This margin is from the posterior caudad aspect of the pancreatic head that merges with the uncinate margin and that appears to be covered by loose connective tissue.

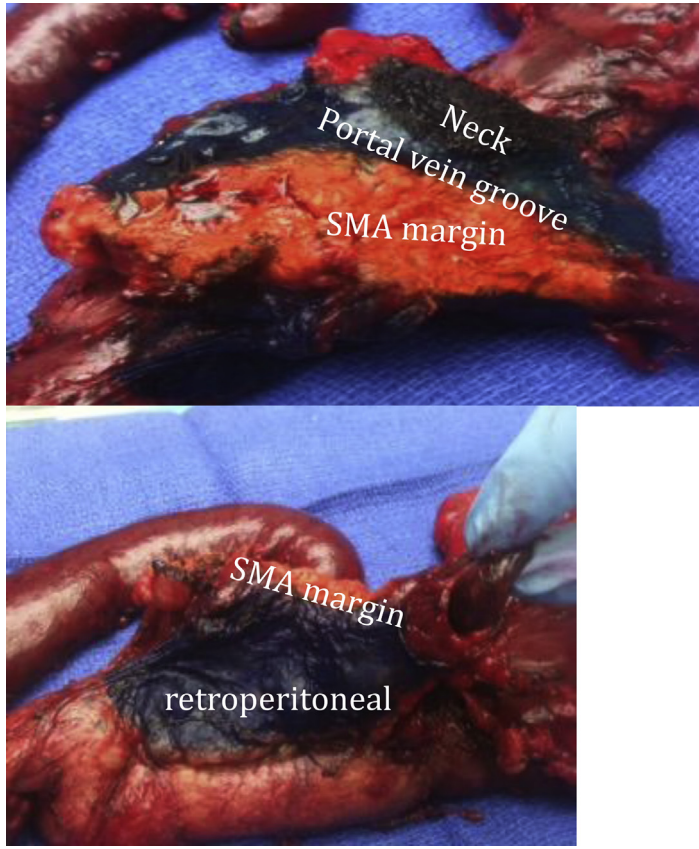

Fig. 2. The surgeon and pathologist should collaborate to appropriately mark/ink the critical margins including the pancreatic neck, superior mesenteric, and portal vein groove.

In some instances this margin can be included in the same section as the SMA margin section.

Portal Vein Groove Margin

This is the smooth-surfaced groove on the posterior surface of the pancreatic head that rests over the portal vein. As is true for the posterior margin, in some instances this margin can be included in the same section as the SMA section.

Pancreatic Neck (Transection) Margin

This is the en face section of the transected pancreatic neck. The section should be placed into the cassette with true margin facing up so that the initial section into the block represents the true surgical margin. For purposes of frozen section analysis in the operating room, the authors recommend assessment 5 mm from the transected pancreatic neck. This eliminates any cautery artifact that may impede the pathologist's assessment for cancer on frozen section. Furthermore, this ensures a minimum of a 5-mm clearance of tumor from this particular margin. If tumor is found on microscopic assessment, resection of further pancreas to achieve an R0 resection can be easily accomplished.

Bile Duct Margin

In common with the pancreatic neck and particularly relevant to DCC the authors recommend assessment of the entirety of the portion of bile duct submitted for frozen section analysis intraoperatively because further excision of the extrahepatic biliary tree can be accomplished readily to maximize tumor clearance. Moreover, when there is clinical suspicion or pathologic confirmation of DCC, the stump of the distal common bile duct demands specific scrutiny. Specifically, the circumferential soft tissue sheath or radial periductal margin around the distal common bile duct should be assessed.[55]

Other margins analyzed in Whipple specimens include the proximal and distal enteric margins (en face sections) and anterior surface (closest representative). The anterior surface is not a true margin, but identification and reporting of this surface when positive may portend a risk of local recurrence, and so should be reported in all cases.[56] Collectively, these pancreatic tissue surfaces constitute the circumferential radial margin. Designating the various specific margins with different colored inks allows recognition on microscopy.

Specimen Grossing Technique and Extent of Tissue Sampling

The approach to histologic sectioning of a Whipple specimen has unfortunately been based on institutional or pathologist preference and experience and has not been uniformly applied between centers of excellence. Options include (1) axial slicing through a plane perpendicular to the second portion of the duodenum; (2) bivalve or multivalve sectioning, bisecting the pancreas along probes placed in the bile and pancreatic ducts and then serially section along each half of the pancreas; or (3) breadloafing technique whereby the specimen is sectioned perpendicular to the neck of the pancreas (**Fig. 3**).[56]

The bivalve technique does not allow a satisfactory three-dimensional perspective of the carcinoma relative to the entire specimen. The breadloafing technique becomes difficult in the region of the duodenum and may distort the relationship of the tumor to the ampulla and the insertion of the pancreatic and bile ducts. In contrast to other techniques, axial slicing (**Fig. 4**) provides an overall assessment of the epicenter of the tumor relative to the ampulla, bile duct, duodenum, and pancreas, and all of the

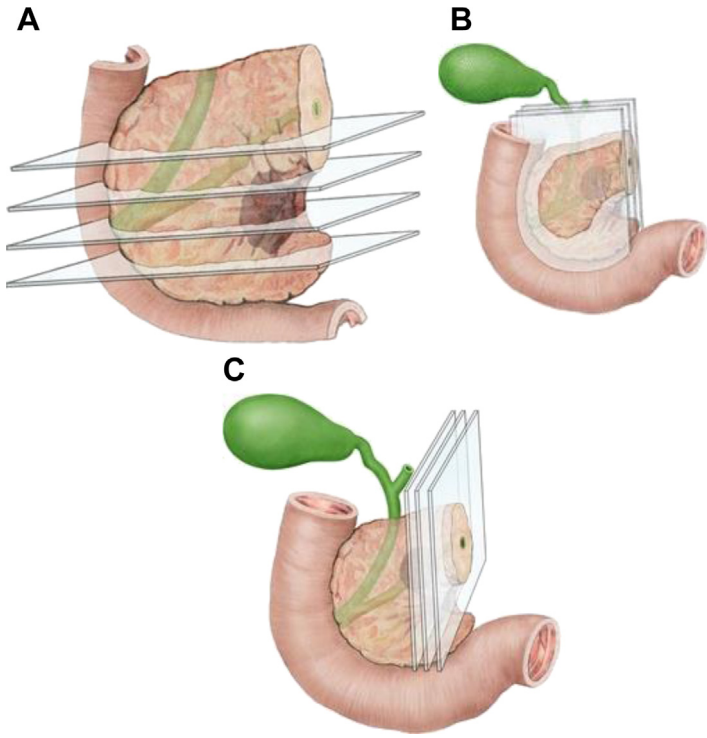

Fig. 3. The approach to histologic sectioning of a Whipple specimen. (*A*) Axial slicing through a plane perpendicular to the second portion of the duodenum. (*B*) Bivalve or multivalve sectioning, bisecting the pancreas along probes placed in the bile and pancreatic ducts and then serially sectioning along each half of the pancreas. (*C*) Bread loafing technique whereby the specimen is sectioned perpendicular to the neck of the pancreas. (*From* Verbeke CS. Resection margins and R1 rates in pancreatic cancer: are we there yet? Histopathology 2008;52(7):787–96; with permission.)

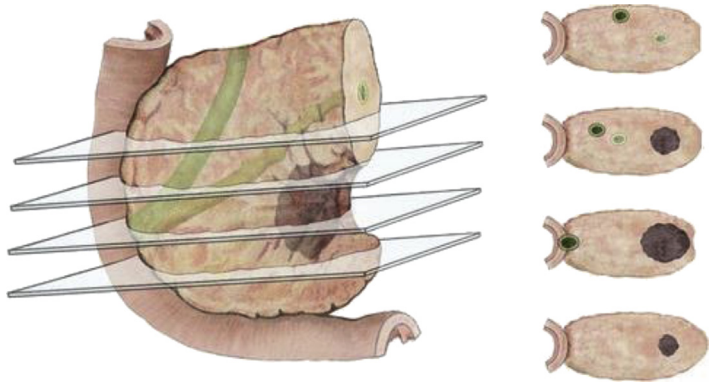

Fig. 4. Axial slicing of the Whipple specimen provides an overall assessment of the epicenter of the tumor relative to the ampulla of Vater, bile duct, duodenum, and pancreas, and all pancreatic circumferential tissue margins. (*From* Verbeke CS. Resection margins and R1 rates in pancreatic cancer: are we there yet? Histopathology 2008;52(7):787–96; with permission.)

pancreatic circumferential tissue margins mentioned previously. In addition, axial slicing correlates with preoperative computed tomography or magnetic resonance imaging. Achievement of a large number of thin slices (>12) is possible by this technique allowing a dogmatic assessment of the primary tumor relative to the margins of resection.[55]

Although the NCCN favors axial slicing there is no one correct way to dissect a Whipple specimen. The most important aspects of dissection are clear and accurate assessment of the margins.[54] It is currently unknown what constitutes an adequate margin in DCC resection specimens. The authors strongly recommend reporting tumor clearance in millimeters for all pertinent margins described previously to allow prospective accumulation of these important data for future analysis.

The NCCN Pancreatic Adenocarcinoma Panel currently supports pathology synoptic reports from the College of American Pathologists.[57] The proposal included herein is an abbreviated *minimum* analysis of pancreatic cancer specimens from the College of American Pathologists recommendations that we believe should be used for DCC (**Table 1**). In addition to the standard TNM staging, other variables are included, all of

Table 1
Proposed pathologic analysis of DCC

Tumor size (obtained from careful gross measurement of the largest dimension of the tumor in centimeters)
Histologic grade (G [x-4])
Primary tumor extent of invasion (T [x-4])
Regional lymph nodes (N [x-1])
Number of nodes recovered
Number of nodes involved
Metastases (M [0-1])
Margins (involvement should be defined and surgical clearance measured in millimeters)
Whipple resection
SMA (retroperitoneal/uncinate) margin
Posterior margin
Portal vein groove margin
Pancreatic neck (transection) margin
Bile duct margin
Enteric margins
Anterior surface
Distal pancreatectomy
Proximal pancreatic (transection) margin
Anterior (cephalad) peripancreatic (peripheral) surface (optional)
Posterior (caudad) peripancreatic (peripheral) margin
Lymphatic (small vessel) invasion (L)
Vascular (large vessel) invasion (V)
Perineural invasion (P)
Additional pathologic findings
Pancreatic intraepithelial neoplasia
Chronic pancreatitis
Final Stage: G, T, N, M, L, V, P.

which have prognostic implications in the evolution of pancreatic carcinoma that might be important in DCC.[58,59]

STAGING AND PROGNOSIS

The median survival of patients who undergo resection for DCC is approximately 2 years with a 5-year survival of 20% to 40% depending on the extent of disease.[60] Several institutional series have identified prognostic factors for patients who undergo resection for DCC, helping to form the framework for the current staging classification. In the seventh edition of the American Joint Commission on Cancer Staging Manual, distal bile tumors are classified as lesions arising between the junction of the cystic duct–common bile duct and the ampulla of Vater and are staged separately from perihilar and intrahepatic CC (previous editions had staged perihilar and distal CCs together).[60] The current staging classification schema is shown in **Table 2**.

DeOliveira and colleagues[61] reported on more than 500 patients with CC treated at the Johns Hopkins hospital, including 239 individuals with distal tumors. In this series,

Table 2
Seventh edition American Joint Commission on Cancer staging for distal bile duct tumors

Primary Tumor			
Tx Primary tumor cannot be assessed			
T0 No evidence of primary tumor			
Tis Carcinoma in situ			
T1 Tumor confined to the bile duct histologically			
T2 Tumor invades beyond the wall of the bile duct			
T3 Tumor invades the gallbladder, pancreas, duodenum, or other adjacent organs without involvement of the celiac axis, or the superior mesenteric artery			
T4 Tumor involves the celiac axis, or the superior mesenteric artery			
Regional Lymph Nodes			
NX Regional lymph nodes not assessed			
N1 No regional lymph node metastases			
N2 Regional lymph node metastases			
Distant Metastasis			
M0 No distant metastases			
M1 Distant metastases			
Staging Classification			
Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage III	T4	Any N	M0
Stage IV	Any T	Any N	M1

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5-year overall survival for patients with DCC was 23%. On multivariate analysis, resection margin status (R0 vs R1/R2), lymph node status (positive vs negative), tumor size (< or >2 cm), and degree of tumor differentiation were all found to significantly impact survival among this group of patients. Similarly, Murakami and colleagues[62] found margin status and lymph node status to significantly impact survival in patients who underwent resection for CC. In a follow-up series from this same institution, specifically examining 43 patients with distal bile duct tumors, resection margin status and lymph node status were again identified as important prognostic factors for survival[63] with 5-year survivals of 8% and 60% for patients with positive and negative margins, respectively, and 5-year survivals of 18% and 46% for patients with positive and negative nodes, respectively. Other factors shown to be predictive of poor prognosis include perineural invasion, lymphovascular invasion, pancreatic invasion, and depth of tumor invasion.[64,65]

POSTOPERATIVE THERAPY FOR LOCOREGIONAL DISEASE

The role of adjuvant therapy in patients with DCC after potentially curative resection is ill defined. Data evaluating the use of adjuvant chemotherapy for CC are limited, and for the most part, combine patients with intrahepatic and extrahepatic CC, gallbladder cancer, and ampullary and pancreatic cancer. In a phase III trial evaluating surgery followed by treatment with 5-FU and mitomycin-C versus surgery alone in patients with bile duct, gallbladder, pancreatic, or ampullary cancer, postoperative chemotherapy offered no benefit in overall or disease-free survival in patients with bile duct carcinoma, regardless of resection margin status.[66] The European Study Group for Pancreatic Cancer-3 periampullary trial, which randomized patients to postoperative observation or 6 months of chemotherapy with either 5-FU/leucovorin or gemcitabine, included 96 patients with bile duct carcinoma.[67] Subset analysis of this group did not demonstrate any improvement in median survival between those randomized to 5-FU/leucovorin (18.3 months) or gemcitabine (19.5 months) versus observation (27.2 months). Given results observed in these trials, there is a general lack of support for the use of adjuvant chemotherapy after R0 resection of bile duct carcinoma.

Because local recurrence presents an obstacle in curing patients with DCC, several investigators have examined the use of radiation therapy in the adjuvant setting. Hughes and colleagues[68] reported on 34 patients with DCC treated with pancreaticoduodenectomy and adjuvant chemoradiation at the Johns Hopkins Hospital. Actuarial 5-year overall survival was 35% and local control was 70%. When compared with historical control subjects from the same institution (patients managed with surgery alone)[69] the addition of chemoradiation seemed to confer a survival benefit (36.9 vs 22 months; $P<.05$). Nelson and colleagues[70] reported similar 5-year actuarial survival (33%) and local control rates (78%) among 45 patients with extrahepatic CC treated at Duke University with surgery and either neoadjuvant or adjuvant chemoradiation. In each of these institutional reviews, most patients had disease recurrence at distant sites, leading investigators to conclude that chemoradiation offers a local control benefit for resected extrahepatic CC. In a retrospective review of 65 patients from the M.D. Anderson Cancer Center with extrahepatic CC, there was no difference in locoregional recurrence or 5-year survival rates between patients who underwent R0 resection and had negative nodes (N0) and received no adjuvant therapy and patients who had either R1 resection and/or positive nodes (N1) and were treated with postoperative chemoradiation.[71] These results suggest a benefit of postoperative chemoradiation in individuals with features that place them at high risk of recurrence.

Finally, Lim and colleagues[72] examined outcomes in 120 patients with extrahepatic bile duct carcinoma treated with radical resection followed by chemoradiation or chemoradiation and subsequent systemic chemotherapy. In this study, postoperative chemoradiation followed by systemic chemotherapy resulted in significantly improved 3-year disease-free and overall survival compared with patients treated with postoperative chemoradiation alone. Although limited by small sample size and their retrospective nature, collectively these data suggest that postoperative chemoradiation with or without systemic chemotherapy may offer improved local control and possible survival benefit after resection for extrahepatic CC, particularly in patients with R1 resection and/or node-positive disease. For patients who undergo R0 resection and have node-negative disease, current NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) recommend observation, enrollment in a clinical trial, consideration of chemoradiation, or consideration of fluoropyrimidine or gemcitabine chemotherapy.[35] For patients with positive resection margins and/or node-positive disease these guidelines recommend consideration of chemoradiation followed by chemotherapy or chemotherapy alone. Clearly, there is a need for randomized prospective trials to better define the appropriate adjuvant therapy in patients who undergo potentially curative resection for DCC.

PALLIATION FOR PATIENTS WITH UNRESECTABLE DISEASE AND/OR DISTANT METASTASES

For patients who have locally advanced, unresectable disease or distant metastases, the prognosis is very poor. Several chemotherapy regimens have been evaluated in the management of these patients.[73] An analysis of clinical trials evaluating chemotherapy for patients with advanced biliary tract cancer suggested that a combination of gemcitabine and platinum-based agents confers the greatest survival benefit.[74] The Advanced Biliary Cancer 02 Trial was a randomized, controlled, phase 3 study comparing cisplatin plus gemcitabine with gemcitabine alone in patients with metastatic or locally advanced biliary tract malignancy.[75] Patients randomized to receive cisplatin-gemcitabine demonstrated a significant improvement in median overall (11.7 vs 8.1 months; $P<.0001$) and progression-free (8 vs 5 months) survival. Based on these data, doublet chemotherapy with cisplatin-gemcitabine is considered standard first-line chemotherapy for patients with locally advanced unresectable or metastatic CC (NCCN Guidelines®). Before initiation of systemic therapy, a definitive tissue diagnosis should be confirmed, and adequate biliary drainage should be achieved.

SUMMARY

DCC is a rare malignancy that often clinically presents similar to pancreatic cancer; however, it has a distinct set of risk factors indicating a unique pathophysiology relative to other periampullary neoplasms. In particular, patients with PSC have a markedly increased risk for CC and should undergo rigorous surveillance to preempt malignant transformation. Patients with imaging and endoscopy suggesting only locoregional disease, and of adequate performance status, should undergo exploration for possible pancreaticoduodenectomy. Once resected, surgeons and pathologists should work together to mark the critical margins of the surgical specimen. Positive resection margins and lymph node metastases have consistently been shown to lead toward poor prognosis after pancreaticoduodenectomy. There are limited data to support adjuvant chemotherapy after potentially curative resection for DCC. Institutional series suggest a potential benefit from postoperative chemoradiation, particularly in patients with R1 resection or positive nodes. For patients with unresectable or

metastatic disease, palliative systemic chemotherapy usually includes gemcitabine and cisplatin; however, median survival in these patients is less than 1 year. It is hoped that investigation into the biologic and genetic basis of this disease will lead toward a targeted approach to treatment that might offer improved survival.

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