



Cholangiocarcinoma: a site-specific update on the current state of surgical management and multi-modality therapy

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Abstract: Biliary tract cancers (BTC) are rare, heterogeneous malignancies that include cholangiocarcinoma and gallbladder cancer (GBC). Cholangiocarcinoma subtypes differ by anatomic location and molecular profile. Currently, resection with lymphadenectomy is the only curative treatment of locally advanced cholangiocarcinoma. Given the high risk of recurrence, multi-modality therapy spanning surgery, chemotherapy, and radiation therapy should be considered. Current data is discordant and there is limited prospective data to support an optimal treatment regimen, though recent studies have demonstrated the utility of adjuvant chemotherapy and chemoradiation in specific settings and patient populations. There is a potential role for neoadjuvant chemotherapy in patients with resectable disease or chemoradiation in select patients with unresectable, locally advanced disease. Randomized clinical trials are necessary to establish the effectiveness of therapies specific to disease sites, especially with the emerging role of immunotherapy and targeted therapy to actionable mutations.

Keywords: Cholangiocarcinoma; intrahepatic; hilar; perihilar; surgery; chemotherapy; radiation therapy; chemoradiation

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Introduction

Biliary tract cancers (BTC) encompass a broad spectrum of malignancies which include cholangiocarcinoma and gallbladder cancer (GBC). Based on anatomic location, cholangiocarcinoma is further stratified into intrahepatic cholangiocarcinoma (IHCC), and extrahepatic cholangiocarcinoma (EHCC), which is further subdivided into hilar or perihilar cholangiocarcinoma (PHCC) and distal cholangiocarcinoma (DCC). Notably, tumors that involve the bifurcation of the ducts are known as Klatskin tumors. IHCC comprise approximately 20–30%, PHCC comprise 50%, and DCC comprise 10–30% of all cholangiocarcinomas (1,2).

Cholangiocarcinoma has differences in growth pattern

and can present as mass-forming, periductal-infiltrating, or intraductal. Mass-forming growth patterns are more commonly seen in IHCC, peri-ductal-infiltrating growth in PHCC, while intraductal growth can occur at any location (3).

It is important to note that although these subtypes all arise from the biliary system, there are differences in disease progression, molecular profile, and response to therapy. In this review we focus on the multidisciplinary approach to the management and treatment of cholangiocarcinoma, encompassing surgical and multi-modality therapies.

Epidemiology

Cholangiocarcinoma is a rare malignancy, accounting for 3% of all gastrointestinal cancers and 10–15% of cancers

of the hepatobiliary system (4). Global incidence of cholangiocarcinoma in 2013 was approximately 186,000 (5). The incidence of IHCC is increasing, while the incidence of EHCC is decreasing, though the latter remains the most common (6,7). Known risk factors for cholangiocarcinoma include cholelithiasis, choledochal cysts, primary sclerosing cholangitis, hepatitis B and C, and liver fluke infections (8,9).

Cholangiocarcinoma is characterized by significant geographic variation. Cholangiocarcinoma is more prevalent in eastern Europe, Asia, and Latin America, while it is more rare in western Europe and the United States (10). IHCC has increased incidence in Western countries in recent years, compared to the incidence of EHCC, which has remained stable (11). These variable incidence rates are likely attributable to genetic and environmental differences.

Cholangiocarcinoma is characterized by early lymph node invasion and distant metastasis. These malignancies often present at an advanced stage and are often inoperable resulting in poor prognosis with a 5-year overall survival (OS) ranging from 5–15% (6,12,13). The 5-year OS survival rates for resected IHCC, PHCC, and DCC are 32.7%, 24.2%, and 39.8%, respectively (14,15). Only approximately 10–30% of patients are deemed to have resectable disease at the time of diagnosis (16,17).

Distinct sites of disease

Though cholangiocarcinomas predominantly arise from the epithelial cells of the biliary tree, there is increasing data to support differences in tumor biology that impact clinicopathologic outcomes. Cholangiocarcinomas have discernible gene heterogeneity based on anatomic location and the use of histopathologic and molecular diagnostic techniques suggests variable tumor microenvironment and stroma between the subtypes. Whole genome sequencing performed by the International Cancer Genome Consortium revealed distinct mutations that affect prognosis (18). Broadly, BTCs have clusters of mutations in known oncogenes (*KRAS*, *p53*, *ERBB2/HER2/NEU*) and tumor suppressor genes (*SMAD-4*, *BCL-2*, *p16*, and *p53*) (19,20).

IHCC uniquely has FGFR1–3 fusion gene mutation rates of 11–17% and IDH1/2 mutation rates of 5–36% (21,22). The frequency of *KRAS* and *p53* mutations is 40–50% and 2.4–44.4%, respectively (23). EHCC have *ERBB2/HER2/NEU* overexpression frequencies of 5–10%, *KRAS* mutation rates of 8.3–42%, *SMAD4* mutation rates 21%, and *PIK3CA* mutation rates of 7% (24). IDH1/2 mutations

are seen at much lower rates of 0–7% compared to IHCC. *ERBB2/HER2/NEU* overexpression is not seen in IHCC (24).

Given the variable molecular landscape of cholangiocarcinoma, there is increased interest in genetic profiling and the application of targeted therapies. Ongoing clinical trials are evaluating the use of FGFR kinase inhibitors (NCT02924376, NCT02150967), IDH1 inhibitors (NCT02989857), and PDL1 immune checkpoint inhibitors (NCT02628067).

Surgical principles

Currently, resection is the mainstay of treatment for patients who present with resectable disease. The operative strategy is based on the anatomic location of the tumor. For IHCC, a negative-margin resection offers patients the best chance for prolonged survival (25,26). For resectable IHCC, a non-anatomic or anatomic segmental or major hepatic resection with concurrent portal lymphadenectomy is recommended. Extended resections, major vascular resections and reconstructions, and *en bloc* resections of contiguous organs have been reported with acceptable patient outcomes, though the possibility of curative resection must be tailored to each patient's presentation and comorbidities (27,28). Perihilar tumors often pose a technical challenge given their location at the central portion of the liver. As a result, surgical management includes a formal bile duct resection, major hepatic resection with the possibility of a caudate lobe resection, *en bloc* porta hepatis lymphadenectomy, and a biliary drainage procedure, such as a Roux-en-Y hepaticojejunostomy. The Bismuth-Corlette staging system can aid in operative planning, though this system does not account for vascular or lymph node involvement (29). The surgical management of DCC is classically a pancreatoduodenectomy (Whipple procedure) (30,31).

Determining “resectability”

Both technical and oncologic considerations must be taken into account when evaluating a patient for resection. First, the patient must be medically fit and able to tolerate a major operation. During the preoperative evaluation, ultrasound, endoscopic ultrasound (EUS), and cross-sectional imaging are useful modalities. Specifically, magnetic resonance imaging (MRI) with magnetic resonance cholangiopancreatography (MRCP) helps define the extent of resectability, nodal disease burden, and

level of biliary obstruction. In select patients, preemptive biliary stenting and/or catheterization can be considered. Endoscopic retrograde cholangiopancreatography (ERCP) with or without cholangioscopy aids in delineating bile duct morphology, particularly the level of strictures. There is the added benefit of obtaining additional diagnostic information via brush cytology or fine needle aspiration (FNA) if a tissue diagnosis is needed prior to resection or the delivery of preoperative therapy. Positron emission tomography (PET) and diagnostic laparoscopy can further define the extent of the tumor burden and assess for disseminated disease to aid in the determination of oncologic appropriateness (32,33). Resection rates for IHCC, PHCC, and DCC were noted to be 56%, 60%, and 91% in a retrospective series of 294 patients over a 23-year period (25).

Criteria for resection includes the absence of extrahepatic organ invasion, paraceliac and retropancreatic nodal metastasis, distant liver metastasis, disseminated disease, and extensive vascular invasion of the portal vein and hepatic artery (34). Significant vascular involvement of the portal vein or hepatic artery may preclude patients from undergoing surgery as this poses a significant risk factor for disease recurrence and increases postoperative morbidity (35,36). Major vascular resection, however, has been successfully performed in select patients to ensure negative margins and should be discussed in patients with a favorable response to pre-operative therapy (37,38).

Lymphadenectomy

Lymph node metastasis is a strong negative prognostic indicator (39,40). Portal lymphadenectomy should be performed in all patients with IHCC as up to 30% of patients will have evidence of lymph node metastasis (41). Lymph node metastasis for IHCC portends reduced survival (24 months for N1, 30 months for N0, $P=0.03$) (41). The 8th edition of the AJCC recommends the removal of at least 6 lymph nodes to adequately stage the extent of nodal disease (42). Given the nature of the operations for PHCC and DCC, a regional lymphadenectomy is inherently included in the procedure. Removal of distant lymph nodes, outside the porta hepatis, has not reproducibly been shown to be associated with improved survival.

Future liver remnant (FLR)

IHCC and PHCC sometimes pose a unique technical dilemma as a major hepatectomy may be indicated. The

surgeon must determine if the FLR has adequate inflow, outflow, and biliary drainage. For carefully selected patients with IHCC and PHCC, portal vein embolization (PVE) is a viable option to optimize FLR function.

The liver has a remarkable regenerative capacity for functional recovery after hepatectomy. In patients with healthy, non-cirrhotic livers, 70–80% of the volume can be removed and still allow for meaningful recovery (43,44). Due to segmental anatomic differences across patients, the implementation of preoperative volumetric analysis aids in predicting FLR function. This can be done using predictive mathematical models or cross-sectional imaging, including CT and 3D CT volumetry (45,46). Though traditionally used in liver transplant patient candidates, functional assessments including the MELD score and the Child-Turcotte-Pugh (CTP) score have been applied to patients being evaluated for oncologic resections as well (47).

PVE is a strategy to maximize the safety of liver surgery and expand the patient population eligible for resection. By occluding the branch of the portal vein on the intended specimen, PVE allows for hypertrophy of the FLR. PVE has been shown to increase the FLR volume an average of 12% and allow 60% of patients previously deemed unresectable due to liver capacity limitations to proceed with surgery (43,48-50). Although the application of PVE is not yet the standard of care, prior studies have shown no adverse effect on morbidity and mortality following hepatectomy (51-55). PVE is a worthwhile option for patients where FLR is the only precluding factor for hepatic resection.

Negative margin resection (R0)

For resections at any site, an R0 resection has been shown to be superior to non-operative management and margin-positive resections demonstrating an improvement in OS (56,57). PHCC patients who received an R0 resection and hepatectomy with curative-intent demonstrated improved disease-specific survival (DSS) and OS compared to those undergoing an R1 resection (58,59). A prospective study in 2012 by Ribero *et al.* demonstrated a median OS of 39 months and a 5-year OS rate of 39.8% for patients with PHCC undergoing an R0 resection (60). For DCC, patients with an R0 resection have a median OS of 48 months, compared to 9 months in patients with an R1 resection ($P=0.042$) (61). The projected ability to achieve an R0 resection is a major determinant of “technical resectability”.

Evaluation of biliary tree involvement is necessary to develop an operative plan for tumor-free margins

and for potential biliary drainage procedures. Cross-sectional imaging allows for visualization of tissue planes. Cholangiography can also be utilized to further characterize bile duct anatomy and to determine the extent of proximal bile duct involvement (62). Historically, for patients who underwent curative intent resections, R0 margins were achieved in approximately 30% of PHCCs and 50% of DCCs (63). As the understanding that PHCC required a major hepatectomy in addition to a bile duct resection to achieve an R0 resection became commonly accepted, a 2001 series demonstrated a 78% rate of R0 resection for PHCC (59). In a retrospective review of 225 patients with PHCC who underwent resection, the importance of an R0 resection is further emphasized as a microscopic margin was associated with early disease recurrence ($P=0.04$) (64). A retrospective review from 2001 to 2012 also compared 96 PHCC patients who received an R0 *vs.* an R1 resection (65). In this study, a median OS difference (33 *vs.* 19 months, $P=0.002$) was noted, favoring an R0 resection. Given the importance of a negative margin, in instances where the margin is positive on intra-operative frozen section analysis, some have advocated for taking an additional resection margin to obtain an R0 margin if technically feasible (66-68). Obtaining negative bile duct margins significantly decrease the probability for locoregional recurrence (66,69,70).

Adjuvant chemotherapy

Until recently, administration of adjuvant therapy after resection was not standard of care. Furthermore, the optimal regimen had not been well established given conflicting studies that included retrospective series limited by inherent study design and small sample size. Recently completed prospective randomized controlled trials have shaped the consensus guidelines for delivering adjuvant therapy after resection of cholangiocarcinoma.

The initial first-line systemic therapy for advanced disease was established by the ABC-02 trial, a phase III randomized control trial that compared patients with locally advanced or metastatic cholangiocarcinoma, GBC, and ampullary cancer receiving gemcitabine alone to patients receiving gemcitabine plus cisplatin. Gemcitabine plus cisplatin was associated with an increased median OS (11.7 *vs.* 8 months, $P<0.001$) and progression free survival (8 *vs.* 5 months, $P<0.001$) (71,72). It is important to note the treatment arms were comprised of a heterogeneous cohort of patients with biliary tract malignancies.

Given these positive findings with utilizing a doublet

regimen consisting of gemcitabine and platinum, the PRODIGE 12-ACCORD 18 (UNICANCER GI) study was conducted in the adjuvant setting, which was a phase III randomized control study of 194 patients with localized BTC (IHCC, PHCC, DCC, and GBC) who underwent a R0 or R1 resection and were randomized to adjuvant chemotherapy with gemcitabine-oxaliplatin (GEMOX) or surveillance alone. Despite a clinically significant difference between groups, no statistically significant difference in OS was noted between the study and control arms (75.8 *vs.* 50.8 months, $P=0.74$), and this trial was deemed a negative trial (73). The Bile Duct Cancer Adjuvant Trial (BCAT) is a randomized phase III trial comprised of patients with resected bile duct cancer comparing adjuvant gemcitabine *vs.* observation (74). The study determined there was no significant difference in median OS (62.3 *vs.* 63.8 months, $P=0.96$) or RFS (36 *vs.* 39.9 months, $P=0.69$) between the adjuvant gemcitabine and observation cohorts. Notably, the study was under-powered as it did not accrue the planned number of patients.

The BILCAP trial was the first randomized controlled, phase III multicenter trial of 447 patients with IHCC, PHCC, muscle-invasive GBC, and lower bile duct cholangiocarcinoma that demonstrated an OS benefit of adjuvant chemotherapy with capecitabine over surveillance alone. Though there was no significant difference in OS in the intent-to-treat analysis, patients who received adjuvant capecitabine in the per-protocol analysis had an increased median OS of 51 months compared to 36 months in the placebo observation group ($P=0.028$) (75). The BILCAP trial has largely informed current consensus guidelines favoring adjuvant chemotherapy with 6 months of capecitabine for resected biliary tract malignancies.

There are other ongoing trials to further elucidate the optimal adjuvant chemotherapy regimen. The Japanese S-1 *vs.* placebo JCOG1202 is a randomized phase III trial of 350 patients with biliary tract adenocarcinoma or adenosquamous carcinoma (IHCC, EHCC, GBC, or ampulla of Vater cancer) comparing adjuvant S-1 therapy *vs.* observation alone in resected BTC with a primary end-point of median OS (UMIN000011688) (76). The German Adjuvant Chemotherapy with Gemcitabine and Cisplatin Compared to Standard of Care after Curative Intent Resection of Biliary Tract Cancer (ACTICCA-1) phase III randomized controlled trial includes 781 patients diagnosed with IHCC, PHCC, EHCC, and muscle invasive gallbladder carcinoma comparing adjuvant cisplatin and gemcitabine to standard of care (curative intent resection)

with the endpoint of DFS (NCT02170090). The standard-of-care arm was revised to include adjuvant capecitabine in light of the data from the BILCAP trial (77).

The ASCO Clinical Practice Guideline offers treatment recommendations for patients with resected BTCs. The current standard of care is to offer adjuvant capecitabine chemotherapy for 6 months based on the data in the BILCAP trial (75,78). Continued patient enrollment in clinical trials is highly encouraged to further define the optimal regimen.

Adjuvant radiation therapy

There is limited data available to support adjuvant radiation in IHCC after resection (12). For patients with EHCC, including both PHCC and DCC, the selective use of adjuvant chemoradiation may be warranted, particularly in the setting of an R1 resection (79,80).

A retrospective study by Shinohara and colleagues demonstrated the potential utility of adjuvant radiation therapy for IHCC. Patients who underwent surgery and received adjuvant radiation therapy had a median OS of 11 months, compared to 6 months for patients that underwent surgery alone, and 7 months for patients that received radiation alone as their primary therapy ($P=0.013$) (79). In a retrospective review of 92 patients with unresectable and advanced IHCC, Kim *et al.* demonstrated that patients who received chemoradiation had improved OS and PFS compared to patients that received chemotherapy alone (OS 9.1 *vs.* 6.2 months, $P<0.05$ and PFS 4.3 *vs.* 1.9 months, $P=0.001$) (81). Importantly, this study included patients with locally advanced disease that did not undergo resection. There is a need for randomized control trials to determine the role of chemoradiation for locally advanced, non-resectable IHCC compared to chemotherapy alone. Unfortunately, one such trial recently closed due to poor accrual.

A 2007 study of 75 patients with PHCC demonstrated that patients who received adjuvant radiation therapy after an R1 or R2 resection had improved OS compared to observation alone (82,83). There was no association between radiation and OS in those who achieved an R0 resection. Accordingly, in instances where there are positive margins after surgery for patients with EHCC, there may be a role for salvage radiation therapy to address residual disease.

A 2003 retrospective review by Heron *et al.* demonstrated increased median OS for 221 patients with proximal EHCC who underwent surgery and received adjuvant radiation,

compared to radiation alone (24 *vs.* 13 months, $P=0.007$), again demonstrating the importance of resection for this disease (84). SWOG0809 is a prospective, phase II, single-arm trial of 79 patients with resected EHCC and GBC who received adjuvant capecitabine and gemcitabine followed by concurrent radiation and capecitabine. Median OS was 35 months (85). Given the single-arm study design, it is unclear whether this survival benefit is from chemotherapy or radiation therapy. Importantly, patients with an R1 resection had similar survival as those with an R0 resection, suggesting the potential utility of radiation in margin positive resections.

There are no prospective trials investigating the role of adjuvant therapy specifically for DCC. Current retrospective data is mixed and is often extrapolated from pancreatic cancer studies. At this time, there is a lack of strong data to support the use of adjuvant radiation therapy for DCC, unless considering the circumstance of an R1 resection.

Current ASCO clinical practice guidelines are largely based on SWOG0809, recommending chemoradiation for patients with hilar cholangiocarcinoma and DCC with positive surgical margins (R1 or R2 resection) (78). Given current study limitations and paucity of definitive data, further investigation is needed to determine the utility of adjuvant radiation or chemoradiation for locoregional control, particularly for patients with IHCC.

Neoadjuvant therapy

There are no formal recommendations for neoadjuvant therapy in the NCCN guidelines or ASCO clinical practice guidelines. Given the overall dismal outcomes for cholangiocarcinoma and similarity to pancreas cancer, it inherently follows that efforts should be directed at determining the role of neoadjuvant therapy prior to resection. The heterogeneity and unique challenges associated with each disease site mandate a separate discussion for each anatomic location of cholangiocarcinoma.

IHCC

Le Roy *et al.* conducted a retrospective study of 186 patients between 2000 and 2013 with resectable IHCC comparing neoadjuvant chemotherapy, upfront surgery, and chemotherapy alone (86). Median OS was 24.1 months in the neoadjuvant chemotherapy and surgery cohort,

25.7 months in the surgery-only cohort, and 7.8 months in the chemotherapy-only cohort. There was no significant difference between the neoadjuvant chemotherapy and the upfront surgery group. There may, however, be a role for neoadjuvant treatment in patients with resectable but oncologically high-risk IHCC including large lesions >5 cm, multifocal tumors or satellite lesions confined to the same lobe of the liver as the dominant lesion, the presence of major vascular invasion, and suspicious or involved regional lymph nodes (N1 disease). There is an ongoing phase II trial to determine the feasibility of neoadjuvant gemcitabine, cisplatin, and abraxane (nab-paclitaxel) in this patient population with primary outcomes of preoperative/operative therapy completion and incidence of adverse events (NCT03579771). Others have suggested that there may be an advantage from chemoradiation to down-stage the tumor burden and increase the likelihood of resectability in patients who present with locally advanced unresectable disease (87,88). The Le Roy *et al.* study discussed above also demonstrated 50% conversion from unresectable to resectable disease with the use of neoadjuvant chemotherapy, supporting its use alone without radiation.

PHCC

A definitive tissue diagnosis for PHCC is often difficult to obtain prior to resection, thus making delivering neoadjuvant therapy a challenging therapeutic strategy. The armamentarium to make a diagnosis includes cholangiography (either endoscopic or percutaneous), spy glass cholangioscopy, and fluorescence in situ hybridization (FISH). Brushings via cholangiography allows for tissue sampling, though the sensitivity is highly variable, ranging from 20–50% (89–91). Spy glass cholangioscopy is another modality that provides direct visualization of the biliary system. Cholangioscopy has increased sensitivity and specificity (90% and 95.8%, respectively) when compared to ERCP (92,93). FISH has been shown to increase the sensitivity of cholangiography to 35–60% as well (94). A retrospective review from 1983 to 1996 of 81 patients with EHCC did not show a mean OS difference in patients who received neoadjuvant chemoradiation, post-operative chemoradiation, post-operative radiation therapy, or surgery alone, though it is worth noting 100% of the patients who received neoadjuvant chemoradiation underwent an R0 resection ($P<0.001$). A more recent retrospective review of 57 patients with PHCC comparing neoadjuvant radiation

to surgery alone had similar findings (95). Despite negative margin resections, however, there was no statistically significant difference in median DFS or OS ($P=0.91$, $P=0.26$, respectively).

Neoadjuvant radiation therapy confers unique challenges during the operation itself. The creation of new anastomoses with tiny, irradiated ducts may prove technically difficult. This may lead to an increased bile leak rate. A retrospective review of 28 patients with locally advanced gallbladder carcinoma who received neoadjuvant chemoradiation demonstrated a leak rate of 43% (96). At this time, there is no reported data on bile leak rates for patients with cholangiocarcinoma who received neoadjuvant radiation or chemoradiation (97,98). The utilization of liver transplantation for patients with unresectable PHCC provides the largest experience with neoadjuvant therapy for cholangiocarcinoma. Patients who meet the strict inclusion criteria for transplant are treated with combination neoadjuvant chemoradiation prior to liver transplantation. During transplant, the entire biliary apparatus is removed and replaced, thus eliminating the risk of biliary reconstruction after radiation seen with resection. A protocol developed at the Mayo Clinic highlights the efficacy of neoadjuvant chemoradiation and liver transplantation *vs.* resection for patients with Klatskin tumors. In their original report, 38 patients received a liver transplant and 54 patients underwent a hepatic resection. The 5-year OS rate for the transplant cohort was 82%, compared to 21% in the resection group ($P=0.022$) (99). A retrospective study of 287 patients by Darwish Murad *et al.* had a RFS of 78% and 65% at 2 and 5 years ($P<0.001$), respectively (100). A prospective study by Loveday and colleagues demonstrated a 2-year post-transplant OS of 55.6% in 6 patients (101). Based on these data, neoadjuvant chemoradiation prior to liver transplantation should be considered in patients with unresectable PHCC that meet the strict inclusion criteria.

DCC

It is difficult to differentiate DCC from pancreatic ductal adenocarcinoma (PDAC) in the head of the pancreas preoperatively given the often-indistinguishable imaging findings. In addition, there are no known proteins that are differentially expressed by malignant cells of the biliary tract compared to pancreas cancer. Consequently, there is no immunohistochemical (IHC) marker for biliary epithelium. Though cytokeratin-7 is suggestive of pancreato-biliary

origin, it is not specific to cholangiocarcinoma (102). Gross evaluation of the resection specimen is needed for a definitive diagnosis. Thus, developing neoadjuvant protocols specifically for DCC is challenging because of the inability to accurately identify the study population in the preoperative setting. In a limited retrospective analysis by McMasters *et al.*, 9 patients from 1983 to 1996 received neoadjuvant chemoradiation for EHCC (5 PHCC, 4 DCC) followed by surgery. An R0 resection margin was obtained at a rate of 100% for patients who received neoadjuvant therapy, compared to 54% in patients who did not ($P < 0.01$) (98). These data support the role of neoadjuvant therapy in increasing the likelihood of achieving an R0 resection. Larger prospective studies are needed, but are limited by the logistical constraints outlined above.

Conclusions

BTC is comprised of a heterogeneous group of malignancies spanning cholangiocarcinoma and GBC. Subtypes of cholangiocarcinoma differ in anatomic location and molecular profiles, thus presenting unique opportunities for actionable targets. Localized cholangiocarcinoma is amenable to curative-intent resection and should be accompanied with a regional lymphadenectomy. Given the high risk of recurrence, multi-modality therapy encompassing surgery, chemotherapy, and radiation therapy should be discussed in the context of a multidisciplinary team. There is limited prospective data at present to define the optimal therapy for cholangiocarcinoma. Despite this, recent trials and pooled data support the use of adjuvant capecitabine after resection of biliary tract malignancies. There may be a role for the selective use of adjuvant radiation in patients with positive margins. For patients with high-risk features, neoadjuvant chemotherapy should be considered, but needs to be studied. Additional prospective, randomized control trials are needed to ascertain the effectiveness of therapies specific to the different disease sites. There is an ongoing need for continued cooperation and international collaboration to continue to improve patient outcomes. The future is promising with the expanded focus on clinical trial enrollment, particularly with the emerging role of precision medicine and immunotherapy.

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Footnote

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