Cholangiocarcinoma
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Cholangiocarcinoma is a neoplasm originating from the intra- or extra-hepatic bile duct epithelium [1]. Historically, it was first described by Durand-Fardel in 1840 [2]. It was not until 1911 that primary liver neoplasias were distinguished based on their cellular origin into “hepatomas” and “cholangiomas” or “hepatocellular carcinomas” and “cholangiocarcinomas” [3,4]. Hilar cholangiocarcinoma as a specific entity was first described by Klatskin in 1965, and cholangiocarcinomas arising at this anatomic site are often referred to as Klatskin tumors [5]. Cholangiocarcinomas may be considered rare tumors comprising only 3% of gastrointestinal tumors; however, they are the second most common primary hepatic tumors, and their incidence is increasing. Surgical resection or liver transplantation is the only potentially curative therapeutic option. Photodynamic therapy can be palliative for unresectable but localized cancer. In the future, targeted therapies have the potential to extend life for patients with advanced metastatic disease.

Classification

Cholangiocarcinomas are classified according to their anatomic location as intrahepatic and extrahepatic (Fig. 1A). The extrahepatic type including cancers involving the confluence of the right and left hepatic ducts accounts for 80% to 90% and the intrahepatic type for 5% to 10% of all cholangiocarcinomas. The anatomic margins for distinguishing intra- and extrahepatic cholangiocarcinomas are the second order bile ducts. Extrahepatic cholangiocarcinomas can further be subdivided according to the Bismuth classification into types I to IV (type I, tumor involves the common hepatic...
duct distal to the biliary confluence; type II, tumor involves the biliary confluence; type IIIa, tumor involves the biliary confluence plus the right hepatic duct; type IIIb, tumor involves the biliary confluence plus the left hepatic duct; type IV, multifocal or tumor involves the confluence and both the right and left hepatic ducts) (Fig. 1B). Further subclassification of extra- and intrahepatic cholangiocarcinomas has been defined based on their macroscopic appearance. Extrahepatic cholangiocarcinomas display a sclerosing, nodular, and papillary phenotype of which the sclerosing or periductal infiltrating type is the most common. It is characterized by annular bile duct thickening due to infiltration and fibrosis of periductal tissues. Intrahepatic cholangiocarcinomas are subclassified into mass forming, periductal infiltrating, mass forming plus periductal infiltrating, and intraductal; this classification has been shown to correlate with prognosis [6]. Histologically, adenocarcinoma is the most common pathologic form, comprising 90% of cases. Other histologic types include papillary adenocarcinoma, intestinal type adenocarcinoma, clear cell adenocarcinoma, signet-ring cell carcinoma, adenosquamous carcinoma, squamous cell carcinoma, and oat cell carcinoma [7].

**Epidemiology**

Cholangiocarcinoma accounts for less than 2% of all human malignancies [8]; however, it is the second most common primary hepatic malignancy...
after hepatocellular carcinoma, accounting for 10% to 15% of primary hepatic malignancies. Its prevalence is geographically heterogeneous, with the highest rates in Asia, especially Southeast Asia\cite{9}. In Western Europe and the United States, the incidence and mortality have increased over the last 4 decades.

**Incidence**

In the United States, the age-adjusted incidence of intrahepatic cholangiocarcinoma has increased by 165% from 0.32/100,000 in 1975 to 1979 to 0.85/100,000 in 1995 to 1999; between 1985 and 1993, the incidence rate increased dramatically\cite{10,11}. An increasing incidence has also been observed in other regions around the globe. Estimated incidence rates in Crete, Greece, have increased from 0.998/100,000 in 1992 to 1994 to 3.327/100,000 in 1998 to 2000\cite{12}. In Japan, the frequency of intrahepatic cholangiocarcinoma diagnosed at autopsy increased from 0.31% to 0.58% between 1976 to 1977 and 1996 to 1997\cite{13}. Although it was reported that the incidence rates for extrahepatic cholangiocarcinoma decreased by 14% from 1.08/100,000 to 0.82/100,000 in 1998\cite{9}, these numbers are not accurate because the majority of the epidemiologic studies misclassified hilar cholangiocarcinoma as intrahepatic cholangiocarcinoma. This systematic mistake was due to a misclassification of these tumors in the ICD-O coding system derived data form for the Surveillance, Epidemiology, and End Results program. Welzel and colleagues\cite{14} addressed this issue and reevaluated incidence rates of intra- and extrahepatic cholangiocarcinoma after correction of this misclassification. They reported that 91% of hilar tumors were misclassified as intrahepatic, resulting in an overestimation of intrahepatic cholangiocarcinoma by 13% and an underestimation of extrahepatic cholangiocarcinoma by 15%. Nevertheless, reevaluation of incidence rates in the United States between 1978 and 2000 still identified a significant increase of intrahepatic cholangiocarcinomas, while no significant change in the incidence of extrahepatic cholangiocarcinomas was noted. The cause of the global increase in the incidence rates for intrahepatic cholangiocarcinomas is unclear. The etiopathogenesis for most patients with cholangiocarcinoma remains obscure.

**Gender, age, and other factors**

Worldwide, the average age at presentation is 50 years. In Western nations, most instances of cholangiocarcinomas are diagnosed at 65 years of age or older and only rarely before the age of 40 years\cite{9}. In the general population, 52% to 54% of cholangiocarcinomas are observed in male patients; however, mortality data show a higher estimated annual percentage change (EAPC) in females when compared with males, with an EAPC of $6.9 \pm 1.5$ for males and $5.1 \pm 1.0$ for females\cite{15}. Differences in the prevalence of cholangiocarcinoma have been reported globally as well as
between different racial and ethnic groups [16]. Globally, the highest prevalence has been described in Southeast Asia. Within the United States, a comparison of the 10-year prevalence between 1990 and 2000 showed a high age-adjusted prevalence of 1.22/100,000 for intrahepatic cholangiocarcinomas in Hispanics. Interestingly, within this group, the prevalence was higher in females. The lowest prevalence was described in African Americans, with a prevalence of 0.5/100,000 for males and 0.17/100,000 for females. Asian Pacific Islanders and Caucasians had prevalence rates ranging between these two groups.

Etiology

In most patients, cholangiocarcinoma has developed without an identifiable etiology; however, certain risk factors for cholangiocarcinoma have been established. One of the most commonly recognized risk factors is primary sclerosing cholangitis. The prevalence of cholangiocarcinoma in patients who have primary sclerosing cholangitis is 5% to 15% [17]. The annual incidence rate for cholangiocarcinoma in the setting of primary sclerosing cholangitis is 0.6% to 1.5% [17,18]. In most patients, cholangiocarcinomas are diagnosed within the first 2.5 years after the diagnosis of primary sclerosing cholangitis, and prospective studies have reported that 37% of patients developing cholangiocarcinoma will do so within the first year following the diagnosis of primary sclerosing cholangitis [17,18]. Hepatobiliary flukes are another risk factor for cholangiocarcinomas. A strong association has been shown with the species Opisthorchis viverrini and Clonorchis sinensis and the development of cholangiocarcinoma [19]. Especially in East Asia, one of the regions with the highest prevalence of cholangiocarcinoma, these flukes are endemic. They are ingested with undercooked fish and infest the bile ducts and occasionally the gallbladder. Increased incidence rates of cholangiocarcinomas in liver fluke–infected patients have been shown in several case-control studies, and the correlation has been confirmed in animal models [20–22]. Another risk factor for cholangiocarcinoma that is more common in Asian than Western countries is hepatolithiasis. Cholangiocarcinoma incidence rates of 10% in patients who have hepatolithiasis have been reported [23–25]. Additional risk factors for cholangiocarcinoma include Caroli’s syndrome, congenital hepatic fibrosis, and choledochal cysts, all of which carry a 10% to 15% risk for cholangiocarcinoma [26–28].

Pathophysiology

The previously described etiologic factors create an environment of chronic inflammation predisposing biliary epithelium to malignant transformation. Chronic inflammation and cholestasis have been linked to carcinogenesis in cholangiocarcinoma. Together, both conditions can promote the
four major cancer phenotypes: (1) autonomous cell proliferation; (2) inva-
sion/metastases; (3) escape from senescence; and (4) evasion of cell death
[29,30]. A variety of molecular alterations have been described in these
carcinogenic phenotypes [29–32]. Chronic inflammation results in the
expression of multiple cytokines and chemokines by cholangiocytes and
inflammatory cells [29,33]. One of the key cytokines in cholangiocarcinoma
carcinogenesis is interleukin-6 (IL-6) [29,34–36]. It mediates cholangiocarcinoma
cell survival by up-regulation of the potent anti-apoptotic protein
Mcl-1 [37–39]. Cellular Mcl-1 protein levels are further enhanced by bile
acid–induced epidermal-derived growth factor receptor activation [40,41].
IL-6 mediates escape from senescence by the induction of telomerase [42].
Further damage is mediated by cytokine induction of inducible nitric oxide
synthase (iNOS) in inflammatory cells and epithelial bile duct cells. Increased iNOS expression has been observed in cholangiocytes in primary
sclerosing cholangitis and cholangiocarcinoma, and elevated serum nitrate
concentrations have been identified in patients with liver fluke infection
[43]. Increased expression of iNOS results in increased generation of nitric
oxide which inhibits DNA repair proteins and apoptosis by nitrosylation
of base excision repair enzymes (eg, OGG1) and caspase-9, respectively
[43,44]. Several additional molecular alterations have been reported, result-
ing in the activation of growth factors and proto-oncogenes as well as
inhibition of tumor suppressor genes [29,45]. In addition, alterations in
genes coding for adhesion molecules and anti-angiogenic factors have
been described, mediating tumor invasion and spread [29,45].

Diagnosis

The diagnosis and staging of cholangiocarcinoma require a multimodality
approach involving laboratory, radiologic, endoscopic, and pathologic anal-
ysis. Despite the variety of techniques used, determining the extent of dis-
ease still poses a challenge and is often underestimated. The diagnostic
modalities described in the following sections, in combination and in the
appropriate clinical context, are useful to help achieve diagnostic accuracy.

Clinical, endoscopic, and radiologic diagnosis

Extrahepatic and intrahepatic cholangiocarcinomas present with distinct
clinical signs that translate into their clinical and radiologic presentation.

Clinical presentation

Most cholangiocarcinomas remain clinically silent until the advanced
stages. Once patients become symptomatic, the clinical presentation is dom-
inated by the anatomic location of the tumor. The predominant clinical fea-
ture of extrahepatic cholangiocarcinoma is biliary obstruction resulting in
painless jaundice, with which 90% of patients initially present [7,46].
Intrahepatic cholangiocarcinoma presents in most cases as an intrahepatic mass causing right upper abdominal quadrant pain and other tumor-related symptoms such as cachexia and malaise. Approximately 10% of patients present with cholangitis [7].

**Ultrasonography**

Ultrasound is one of the first-line imaging modalities chosen for the evaluation of cholestasis or liver dysfunction. For the identification of cholangiocarcinoma, it has only limited value [46]. Findings include unspecific signs such as intrahepatic bile duct dilatation with an abrupt change in bile duct caliber in cases of extrahepatic and hilar cholangiocarcinoma. Extrahepatic cholangiocarcinoma tumor masses are seldom identified by ultrasound [47,48]. Intrahepatic cholangiocarcinomas are identified as a non-specific intrahepatic mass. Doppler ultrasonography can be helpful for detecting compression and tumor encasement of the portal vein or hepatic artery. Overall, the sensitivity and specificity of ultrasound is poor in the diagnosis of cholangiocarcinoma, and staging generally relies on other imaging modalities [49,50].

**Computed tomography**

CT can be helpful in the staging, preoperative planning, and evaluation of vascular encasement. Intrahepatic cholangiocarcinoma can present as an irregular shaped mass with delayed and peripheral enhancement during the portovenous phase of the study. Hilar and extrahepatic cholangiocarcinomas may present as a mass, ductal thickening, or nonunion of the right and left hepatic duct with or without ductal thickening. As is true for ultrasound, hilar tumor masses are difficult to visualize by CT. Intrahepatic bile duct dilatation in a single small lobe and hypertrophy of the contralateral lobe signify the atrophy-hypertrophy complex seen with lobar duct obstruction frequently plus ipsilateral portal vein encasement [51]. Evaluation of intraductal spread and detection of lymph node and peritoneal metastases by CT are also suboptimal. The sensitivity for N2 metastases detection by CT has been reported to be 50% and the overall accuracy in the assessment of resectability 60% to 75%.

**Magnetic resonance imaging and magnetic resonance cholangiopancreatography**

At present, MRI with magnetic resonance cholangiopancreatography (MRCP) is the best available imaging modality for cholangiocarcinoma [46]. It provides information regarding tumor extent, biliary and hepatic parenchymal anatomy, and intrahepatic metastases. Cholangiocarcinoma is characterized on MRI as a hypointense structure on T1-weighted images and a hyperintense structure on T2-weighted images (Fig. 2). Central hypointensity on T2-weighted MRI corresponds to central fibrosis. In dynamic contrast-enhanced MRI, cholangiocarcinoma is usually recognized...
by delayed moderate peripheral enhancement. Involved bile ducts are identified by irregular ductal narrowing with proximal dilatation [52]. The imaging quality of cholangiocarcinoma can be enhanced significantly by the use of ferumoxide, a routine adjunct for MRI at the authors’ center [53,54].

**Cholangiography**

Cholangiography is one of the most important tests in the evaluation of cholangiocarcinoma [46,55]. It allows early diagnosis and can help evaluate the proximal and distal intraductal extent of the tumor. Cholangiography can be done by performing endoscopic retrograde cholangiopancreatography (ERCP), MRCP, or transcutaneous cholangiography (PTC). MRCP has the advantage of being noninvasive and the possibility of obtaining additional information about other intra- and extrahepatic anatomic structures, whereas ERCP and PTC have the advantage of allowing bile duct sampling for diagnostic analysis as well as the possibility of relieving biliary obstruction by the insertion of stents. The choice of the imaging modality depends also on location of the tumor; distal extrahepatic cholangiocarcinoma is optimally evaluated by ERCP. At times, hilar cholangiocarcinomas can only be stented by the percutaneous route.

**Endosonography with fine-needle aspiration**

Endosonography allows further evaluation of regional lymph nodes and the biliary tree, thereby obtaining further information for staging. In addition, it allows ultrasound-guided, fine-needle aspiration of lymph node tissue for pathologic analysis. The use of this technique for obtaining tissue
from a suspicious hilar lesion is not advised because it can result in tumor spread with peritoneal tumor seeding [45].

**Positron emission tomography**

As seen in other malignancies, cholangiocarcinoma cells may accumulate $^{18}$F-2-deoxy-glucose (FDG), thereby depicting cholangiocarcinomas as “hot spots” [46]. Mucinous cholangiocarcinomas are an exception because they have been shown not to accumulate FDG [49]. In a recent study with a limited number of patients, a sensitivity of 92% and specificity of 93% for detecting the primary lesion were described [56]; however, the sensitivity for detecting distant metastases and regional lymph node metastases was only 67% and 13%, respectively. In addition, false-positive results can be generated in the setting of chronic inflammation, and negative results do not exclude malignancy [57]. In a larger number of patients, CT/PET scanning of cholangiocarcinoma was associated with a lower sensitivity, especially for extrahepatic cancer [58].

**Other imaging modalities**

Other imaging techniques include intraductal ultrasound, endoscopic/percutaneous flexible cholangioscopy, and radiolabeled imaging. These techniques are not part of the routinely performed diagnostic work-up.

**Laboratory analysis**

Laboratory-based analysis for the diagnosis of cholangiocarcinoma is restricted to serum, bile, bile duct brush cytology, and lymph node pathology. Percutaneous biopsy of the primary tumor is not advised due to an increased risk of tumor spread.

**Tumor markers**

The most studied serum tumor markers are the carbohydrate antigen 19-9 (CA 19-9), carcinoembryonic antigen (CEA), and carbohydrate antigen 125 (CA-125). CEA and CA-125 are unspecific and can be elevated in the setting of other gastrointestinal or gynecologic malignancies or other bile duct pathology such as cholangitis and hepatolithiasis [59]. CA 19-9 was first described in 1979 and is currently the most commonly used tumor marker for cholangiocarcinoma [60,61]. Nevertheless, CA 19-9 has certain limitations which need to be considered when using it as a tumor marker. First, CA 19-9 serum concentrations depend on the Lewis phenotype. As many as 10% of the population have been found to be Lewis negative, resulting in undetectable CA 19-9 levels [62,63]. Second, CA 19-9 can also be elevated in other gastrointestinal or gynecologic malignancies and in the setting of bacterial cholangitis [64–66]. The use of a CA 19-9 level cutoff value of greater than 129 U/mL was shown to result in a sensitivity of 78.6% and a specificity of 98.5%, and a change in CA 19-9 of 67.3 U/mL over time provided a sensitivity of 90% and specificity of 98% [67].
Cytologic analysis

A tissue diagnosis is usually obtained by brush cytology or bile duct biopsy during ERCP. In the setting of primary sclerosing cholangitis, interpretation of cytology can be challenging due to reactive changes by inflammation [68]. The sensitivity and specificity for conventional brush cytology are reported to be 37% to 63% and 89% to 100%, respectively [69–71]. The limitations of conventional cytology relate to the typically desmoplastic structure of this cancer and limited access to the biliary system. To improve diagnostic accuracy for the diagnosis of cholangiocarcinoma, new advanced cytologic techniques have been introduced, including digital image analysis and fluorescence in situ hybridization (FISH). Both techniques identify aneuploidy. In digital image analysis, DNA content relative to normal ploidy is quantitated. A comparison of digital image analysis with cytology in patients with suspicious biliary strictures demonstrated a sensitivity of 39.3% with digital image analysis compared with 17.9% by cytology. The specificity was 77.3% with digital image analysis compared with 97.7% with cytology [72]. Evaluation of digital image analysis in patients who had primary sclerosing cholangitis, 20% of whom had cholangiocarcinomas, demonstrated a sensitivity and specificity of 43% and 87%, respectively. In patients who had primary sclerosing cholangitis with negative cytology, a sensitivity and specificity of 14% and 88% were described [73]. FISH allows the detection of chromosomal amplifications by fluorescence and is interpreted as positive if five or more cells display gains of two or more chromosomes (polysomy) [73]. In patients who had primary sclerosing cholangitis, polysomy detected by FISH had a sensitivity of 47%, a specificity of 100%, a positive predictive value of 100%, and a negative predictive value of 88% in the detection of cholangiocarcinomas. In the setting of neither positive nor suspicious cytology, the sensitivity was 20% and the specificity 100%; the positive predictive value was reported to be 100% and the negative predictive value 88% [74]. FISH remarkably increases the yield of brush cytology for the diagnosis of cholangiocarcinoma without compromising specificity.

Therapy

Surgery

Resection

Surgical resection with curative intent is the treatment of choice for extrahepatic cholangiocarcinoma. Although the rate of resectability has been reported to be as high as 65%, curative resection or margin-free resection (R0) rates are less than 50% [75]. Criteria for unresectability of cholangiocarcinomas include bilateral involvement of the hepatic ducts to the level of the secondary biliary radicals, atrophy of one liver lobe with encasement of the contralateral portal vein branch, or atrophy of one liver lobe with
contralateral secondary biliary radical involvement [76,77]. Bilateral portal vein branch encasement or involvement of the major portal vein is also a classic contraindication to surgical resection. Likewise, bilateral hepatic artery encasement would be a contraindication. Intrahepatic metastases are associated with such a poor outcome that most surgeons consider these patients unresectable. Lymph node involvement is more controversial. The outcome has not been reported to be influenced by local lymph node involvement [78]; therefore, many surgeons will pursue resection despite local lymph node metastases. Distant lymph node metastases are a contraindication to surgery. Comorbidities including significant liver disease, cirrhosis, and cardiovascular or other systemic diseases as well as the patient’s performance status have to be taken into consideration in the decision to proceed with surgery. Solitary intrahepatic cholangiocarcinomas are resected by hepatic lobectomy or segmentectomy. This strategy has reported to achieve 5-year survival rates of 23% to 63% [79–81]. With R0 resection, overall 5-year survival rates of 30% to 41% for hilar tumors, 31% to 63% for intrahepatic tumors, and 27% to 37% for extrahepatic cholangiocarcinomas have been reported [78,81–85]. Mortality rates of resection are 5% to 10% in major referral centers and mostly due to infections; liver failure is unusual as a cause for postoperative mortality [78]. The perioperative morbidity rate is between 31% and 85% [86–88].

The goal of neoadjuvant treatment options is to increase resectability rates and decrease recurrence rates after resection. Neoadjuvant strategies include chemotherapy, radiation, combined radiochemotherapy, and photodynamic therapy. Studies evaluating the treatment effects have demonstrated only limited effects, have been nonrandomized, have been conducted in only limited numbers of patients, and report only short-term follow-up [89,90]. Currently, no adjuvant therapy can be recommended. Preoperative portal vein embolization before extended complex hepatectomy with the goal of decreasing postoperative liver dysfunction was first described by Makuuchi and colleagues [91]. Liver resection is restricted to a postsurgical remnant liver volume of 25% to 30% [92]. The rationale behind portal vein embolization is a compensatory hypertrophy of the nonembolized hepatic segments, thereby allowing extended hepatectomy with minimal postoperative liver dysfunction. Increased resectability after portal vein embolization was shown in a subset of patients who otherwise would have been marginal candidates for resection due to low remnant liver volumes [93]. A recent study in 150 patients undergoing extended hepatectomy for cholangiocarcinoma failed to show a significant difference in 5-year survival [94].

Transplantation

Initial results with liver transplantation for extrahepatic cholangiocarcinomas were disappointing, with 5-year survival rates of 23% to 26% and recurrence rates of 51% to 59% [95–97]. Based on the observed outcomes, liver transplantation was discouraged as a therapeutic option for extrahepatic
cholangiocarcinomas. Promising results were achieved with a new neoadjuvant strategy including external beam radiation concomitant with fluorouracil (5-FU) followed by brachytherapy and then venous infusion of 5-FU before liver transplantation for extrahepatic cholangiocarcinomas [98]. Further evaluation of this strategy with a modification of the chemotherapy regimen resulted in significantly improved outcomes after liver transplantation in patients with perihilar cholangiocarcinomas [99]. Pretransplant treatment consisted of external beam radiation with 4500 cGy in 30 fractions with concomitant chemotherapy with 500 mg/m²/d of 5-FU for the first 3 days of radiation. Chemoradiotherapy was followed by brachytherapy with 2000 to 3000 cGy of iridium 192. Upon completion, patients were treated with 2000 mg/m²/d of capecitabine 2 of every 3 weeks until transplantation. Patients with surgically confirmed stage I or II disease were approved for liver transplantation. Five-year recurrence rates were 12%, and the overall 5-year survival rate in intention-to-treat analysis was 58% and 81% in patients who underwent liver transplantation. The results were compared with retrospective data from patients who had undergone potentially curative resection at the same institution between 1993 and 2004. The 5-year survival rate in the resection group was 21% and the 5-year recurrence rate 58%. Risk factors for tumor recurrence in patients treated with this neoadjuvant chemoradiotherapy approach followed by transplantation in a Cox regression analysis were older age, a level of CA 19-9 greater than 100 U/mL on the day of transplantation, prior cholecystectomy, a mass on cross-sectional imaging, residual tumor greater than 2 cm in explant, tumor grade, and perineural invasion in explant [100].

A similar protocol involving brachytherapy with 6000 cGy of iridium 192 and chemotherapy of 300 mg/m²/d of 5-FU but no external beam radiation was evaluated at the University of Nebraska [101]. Long-term disease-free survival was reported in 45% of transplanted patients; however, histopathologic analysis of explants showed the inclusion of stage III tumors in 46% of transplanted patients. The results of these studies show the importance of careful patient selection based on thorough surgical staging as well as the feasibility of a neoadjuvant chemoradiotherapeutic strategy (Box 1). If these requirements are met, excellent results can be achieved in patients with unresectable, localized, and regional lymph node–negative perihilar cholangiocarcinomas [102]. In contrast to the excellent outcomes with liver transplantation for extrahepatic perihilar cholangiocarcinomas, liver transplantation for intrahepatic cholangiocarcinomas is still fraught with disease recurrence and cannot be advocated.

Local palliative therapy

Photodynamic therapy

Photodynamic therapy includes the application of a photosensitizing agent followed by exposure to light at a wavelength corresponding to the
absorption spectrum of the photosensitizer. Illumination initiates a type II photochemical reaction resulting in the generation of reactive oxygen species [103]. The antiproliferative effect is mediated by cell death induced by reactive oxygen species as well as thromboses within the tumor-supplying vessels, with ischemia as well as tumor-specific immune reactions [104–106]. The most commonly used compound is porfimer, a hematoporphyrin derivative that is activated at a wavelength of 630 nm and shown to cause cell death at a tissue depth of 4 to 6 mm [107]. Several studies have evaluated the effects of photodynamic therapy in patients with unresectable cholangiocarcinomas [108–110]. The results of these studies indicate a reduction in tumor thickness and an improvement of cholestasis and life quality [110,111]. Several studies also show a trend toward improved survival [111–115]. Two studies also evaluated photodynamic therapy as neoadjuvant or adjuvant treatment [90,116]; however, neither one was a controlled study. A recent study evaluating photodynamic therapy in patients with mostly Bismuth type III and IV cholangiocarcinoma found on multivariate analysis that a visible mass on imaging, low serum albumin levels, and a prolonged time between diagnosis and photodynamic therapy were predictors of poorer survival [117]. Photodynamic therapy is a reasonable approach for palliation in cholangiocarcinomas [118]. Its role as a neoadjuvant or adjuvant treatment requires further study.

**Box 1. Criteria for liver transplantation**

**Diagnostic criteria**
- Positive (transluminal) biopsy
- Positive conventional cytology on brush cytology
- Stricture plus FISH polysomy
- Mass lesion on cross-sectional imaging
- Malignant appearing stricture and persistent CA 19-9 >100 U/mL in the absence of cholangitis

**Exclusion criteria**
- Prior radiation or chemotherapy
- Uncontrolled infection
- Intrahepatic metastases
- Extrahepatic or distal lymph node metastases
- Other malignancy within 5 years of cholangiocarcinoma diagnosis
- Age <18 or >65 years
- Comorbidities forbidding chemo- or radiotherapy or liver transplantation
- Hilar mass on cross-sectional imaging with a radial diameter of >3 cm
Radiotherapy

Other techniques for local ablation include radiotherapy, radiofrequency ablation, and transcatheter ablation. There are two main administration modes for radiotherapy for cholangiocarcinomas—external beam radiotherapy and intraluminal iridium 192 brachytherapy. Several uncontrolled studies have evaluated radiotherapy in the adjuvant, neoadjuvant, and palliative setting [119–121]. In the palliative setting, survival benefits in a subset of patients without metastases were described [122]; however, the studies were uncontrolled, the results mixed, and the radiation had significant morbidity including gastrointestinal bleeding, strictures, small bowel obstruction, and even hepatic decompensation [123]. The authors do not employ postoperative external beam radiotherapy as an adjuvant strategy at their center.

Systemic therapy

There are no randomized controlled studies evaluating the effect of chemotherapy in cholangiocarcinoma. Existing data are derived from case reports or small clinical studies with insufficient statistical power to allow definitive conclusions. Several different chemotherapeutic drugs have been evaluated. In general, tumor response to these drugs was poor. The most commonly studied chemotherapeutic drugs include 5-FU and gemcitabine. 5-FU has been studied extensively as a monotherapeutic agent as well as in combination with other chemotherapeutic agents such as doxorubicin, epirubicin, cisplatin, lomustine, mitomycin C, paclitaxel, and other drugs (eg, interferon-α) [124–133]. These studies were limited in the number of patients studied, nonrandomized, and noncontrolled, and were not able to demonstrate significant tumor responses or significant prolongation of life. More recent studies have focused on gemcitabine, which was approved in 2002 by the US Food and Drug Administration for cholangiocarcinoma [134]. Studies evaluating gemcitabine as a monotherapeutic agent or in combination with other chemotherapeutic agents such as cisplatin, oxaliplatin, docetaxel, mitomycin C, and 5-FU/leukovorin reported up to 60% response rates [135,136]. Nevertheless, there are no randomized controlled studies evaluating gemcitabine in cholangiocarcinoma; therefore, its impact on survival is unclear.

Targeted chemotherapy

We are rapidly entering the era of targeted chemotherapy for solid malignancies. For example, antiangiogenic therapies and targeted inhibition of receptor tyrosine kinases are now approved for several malignancies. Such therapies have not yet been thoroughly exploited for the treatment of cholangiocarcinoma. Targeted inhibition of the epidermal growth factor receptor has been reported with a suggestion of benefit [137,138]. Potential therapies in the future may include targeted inhibition of IL-6, blockade
of Mcl-1 expression/function, and employment of the death ligand agonist, tumor necrosis factor–related, apoptosis-inducing ligand (TRAIL). It is hoped that such trials can be developed for cholangiocarcinomas.

**Palliation of cholestasis**

The main cause of morbidity in cholangiocarcinoma is cholestasis and its complications including cholangitis and pruritus. Several treatment options for restoration of biliary drainage exist, including endoscopic treatment via ERCP, surgical, or percutaneous approaches. Surgical drainage is achieved by choledochojejunostomy or hepaticojejunostomy and radiologic treatment by PTC with stent placement. A comparison of endoscopic stent placement with surgical biliary bypass showed similar efficiency in the treatment of malignant cholestasis but lower mortality, treatment-related early complications, and shorter hospital stay with endoscopic treatment [139–141]; therefore, endoscopic restoration of biliary drainage is generally preferred. In complete biliary obstruction, percutaneous or surgical methods can be unavoidable. A comparison between unilateral and bilateral hepatic duct drainage showed that unilateral stent placement achieved similar rates of successful drainage as bilateral stenting [142]. Plastic stents require exchange in 2- to 3-month intervals because they tend to become occluded by a biofilm of bacteria and proteinacious material, but they are preferred in patients with expected survival of less than 6 months or those awaiting planned surgery [143]. Metal stents are superior in stent patency and more cost effective in patients with anticipated survival of greater than 6 months [144].

**Summary**

Cholangiocarcinoma is a highly malignant tumor and the second most common form of primary hepatic carcinoma. Its incidence has increased within the last 3 decades without clear etiologic explanations for the increase. Its prognosis is devastating, and the only curative therapy is surgical; however, significant progress has been achieved in our understanding of the etiology and molecular pathogenesis of this malignancy. Also, progress has occurred in diagnosis and therapy. With the increasing arsenal of diagnostic modalities, patients can potentially be diagnosed at earlier stages, thereby making them amenable to curative therapies. With the increase in aggressive surgical management, the results of resection have improved as reflected in better overall outcomes. For patients with unresectable perihilar cholangiocarcinomas, impressive 5-year survival rates can be achieved with liver transplantation combined with neoadjuvant chemoradiotherapy in highly selected patients. With the increasing knowledge of the molecular pathogenesis of this disease, there is hope for nonsurgical alternatives in the future, especially targeted therapies.
References


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